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MEDICATION ERRORS ASSOCIATED WITH DIRECT ACTING ORAL ANTICOAGULANTS IN ADULT PATIENTS

BY
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Abstract

Direct oral anticoagulants (DOACs) are effective therapeutic and/or prophylactic agents for thromboembolic events, such as deep venous thrombosis (DVT), pulmonary embolism (PE), and atrial fibrillation (AF). However, DOACs are also recognised as one of the most commonly concerned drug classes in relation to safety incidents. The purpose of this thesis was to determine the epidemiology of errors and explore the factors contributing to medication errors associated with DOACs from the perspectives of healthcare professionals and patients.

The thesis consisted of three main parts: a systematic review and meta-analysis; two retrospective studies, and three in-depth qualitative interview studies. The systematic review and meta-analysis were conducted to determine the prevalence of medication errors associated with DOACs in clinical practice and to identify factors associated with DOACs in adult patients using published literature. Data related to error causation were synthesised using the Reasons Accident Causation Model. The systematic review and meta-analysis were conducted through searching 11 databases, including Medline, Embase and CINHAL, between January 2008 to September 2020. Thirty-two studies were included in the review. The proportion of the study population who experienced either prescription, administration, or dispensing error ranged from 5.3 to 37.3%. The pooled percentage of patients experiencing prescribing error was 20% (95% CI 15-25%; I^2 = 96%; 95% PrI 4-43%). Prescribing error constituted the majority of all error types with a pooled estimate of 78% (95%CI 73-82%; I^2=0) of all errors. The commonly reported causes were active failures, including wrong drug, and dose for the indication. Mistakes such as non-consideration of renal function, and error-provoking conditions, such as lack of knowledge, were common contributing factors.

The second part of this thesis involved two retrospective evaluations undertaken using national and local hospitals' incident reporting databases in Saudi Arabia and through using a national safety incident reporting database in the United Kingdom (UK). The purpose of this phase was to investigate the types of medication errors and contributory factors associated with DOACs. Using three datasets, including the National Food and Drug Authority (Saudi FDA) database, a total of 199 medication error incidents were analysed. The prescribing error was the most common error type representing 81.4% of all errors. Apixaban was the most frequent drug associated with error reporting, with 134 (67.3%) incidents, followed by rivaroxaban (18.6%), and dabigatran (14.1%). In the UK, using the National Reporting and Learning System (NRLS) database, a total of 15,730 incident reports received by the NRLS between 01 January 2017 to 31 December 2019 were analysed. A total of 25 deaths were reported, with a further 270 and

55 incidents leading to moderate and severe harm, respectively. A further 8.8% (n=1381) of incidents were associated with a low degree of harm.

The third part of this thesis consisted of three theory-driven qualitative studies exploring the views, experiences, and contributory factors related to DOACs medication errors from the perspectives of physicians (n=20), nurses (n=14), pharmacists (n=23), and patients (n=9) in Saudi Arabia. The participants were recruited from three different hospitals setting and regions. The analysis identified several themes: factors related to healthcare professionals (e.g., knowledge, lack of communication with other HCPs, confidence and access to guidelines, patient counselling); factors related to patients (e.g., comorbidity, polypharmacy, lack of knowledge of DOACs, using inappropriate sources of information and communication barriers with HCPs); factors related to the organisation (e.g., guidelines, safety culture and incidents reporting system); factors related to the DOACs medications (e.g., lack of availability of antidotes and dosing issues); and strategies for error prevention/mitigation and promote DOACs safety from staff and patient perspectives (e.g., empowering the role of pharmacists, patient education, opportunities for risk assessments, multidisciplinary working and enforcement of clinical guidelines and needed professional training and routine medication review).

The data provided revealed convincing evidence in relation to the prevalence of errors and actual harm caused by such errors when prescribing, dispensing, and administrating DOACs. The key strategies to minimise errors associated with DOACs can be providing interventions to improve education and training of healthcare providers, developing local clinical guidelines, involving pharmacists to lead anticoagulation clinics, improving communication, and adhering to evidence-based strategies.

Synopsis

The purpose of this thesis was to investigate epidemiology and contributory factors in relation to medication errors with direct oral anticoagulants (DOACs).

The programme of work involved mixed-methods including systematic review and meta-analysis of 32 studies published between 2008 and 2020, two quantitative studies of incident reporting databases, and three in-depth qualitative interview studies. Data related to error causation were synthesised using the Reasons Accident Causation Model.

The systematic review and meta-analysis showed that approximately 20% of DOACs prescriptions involved prescribing errors. A total of 15,730 incident reports related to DOACs were identified in the UK National Reporting and Learning System (NRLS) database, with 270, 55, and 25 incidents leading to moderate, severe harm, and death, respectively. Similarly, prescribing errors with potential for patient harm were identified through the analysis of Saudi incident reporting database.

Qualitative studies with patients and healthcare professionals in Saudi Arabia identified factors related to healthcare professionals, patients, organization, and DOACs medications that could lead to errors. The keys to promoting patient safety while using DOACs, as suggested by study participants, included empowering the role of pharmacists in anticoagulation clinics and implementing routine medication review, exercising professional training and patient education, improving communication, performing risk assessments, working in collaborative multidisciplinary team-based, and practicing based on the evidence-based clinical guidelines.

Dedication

This long journey, although challenging at times, has been much more rewarding than I ever anticipated. Several people have supported me throughout this journey, and without their help, support, and kindness, I would not have reached my destination.

I dedicate this thesis first to my parents and my brother, Eng. Mohammed Alrowily and uncle Dr. Mansour Alrowily. I couldn't have done any of this work without their love, prayers, and support.

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EXTERNAL OUTPUT

The doctoral research has resulted in the following outputs to date.

Published peer-reviewed papers

1. Al Rowily A, Jalal Z, Price MJ, et al. Prevalence, contributory factors and severity of medication errors associated with direct-acting oral anticoagulants in adult patients: a systematic review and meta-analysis. European Journal of Clinical Pharmacology. 2022 Apr; 78(4):623-645. doi: 10.1007/s00228-021-03212-y

2. Alrowily A, Jalal Z, Abutaleb MH, Osman NA, Alammari M, Paudyal V. Medication errors associated with direct-acting oral anticoagulants: analysis of data from national pharmacovigilance and local incidents reporting databases. Journal of Pharmaceutical Policy and Practice. 2021 Oct; 1;14(1):81. doi: 10.1186/s40545-021-00369-w

3. Haque H, Alrowily A, Jalal Z, et al. Direct oral anticoagulant-related medication incidents and pharmacists' interventions in hospital in-patients: evaluation using reason's accident causation theory. International Journal of Clinical Pharmacy.2021 Dec ;43(6):1693-704. doi: 10.1007/s11096-021-01302-6.

4. Al Rowily A, Aloudah N, Jalal Z, et al. Views, experiences and contributory factors related to medication errors associated with direct oral anticoagulants: a qualitative study with physicians and nurses. Int J Clin Pharm, 2022. 44(4): p. 1057-1066. doi: 10.1007/s11096-022-01448-x.

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3. Alrowily A, Jalal Z, Paudyal V. Medication Errors Associated with Non-vitamin K antagonist oral anticoagulants (NOACs) In Adult Patients: quantitative study (a poster presentation at the 1ST PHARMACY RESEARCH DAY, King Abdulaziz Medical City - MNG-HA, Riyadh, January 2021.

4. Alrowily A, Jalal Z, Abutaleb M, Al Ammari M, Paudyal V. Exploring medication errors and contributory factors associated with direct acting oral anticoagulants. the e-presentations for UoB Research Poster Conference 2021(Award third-best oral presentation).

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I (Abdulrhman Alrowily) was awarded BSc. in General Pharmaceutical Science in 2005 from King Saud University, College of Pharmacy, Riyadh, Saudi Arabia. After completing this degree, I worked as a pharmacist at King Fahad Military Medical Complex, Dhaharan, Saudi Arabia for seventeen years, which involved working in the outpatient pharmacy and inpatient pharmacy and IV Admixture preparation. In 2013, I worked as Coordinator of Eastern Pharmacovigilance Recorder side effects of medication at the Saudi Food and Drug Authority. In 2016, I enrolled in the programme of Master of advanced clinical pharmacy practice with placement at the College of Pharmacy at Hertfordshire University in the UK. I was awarded the degree with distinction in 2017. After that, I embarked on my PhD programme in pharmacy practice at the University of Birmingham. I have published four peer-reviewed papers and presented at several scientific conferences during my PhD journey.

Contents

Contents..... x
List of Figures..... xix
List of Tables..... xxi
List of Abbreviations..... xxii
Chapter 1. Introduction..... 1
1.1 Physiology of blood coagulation..... 2
1.2 Thromboembolic events..... 5
1.2.1 Venous thromboembolism..... 5
1.2.2 Arterial thromboembolism..... 6
1.3 Impact of thromboembolic event in cardiovascular diseases..... 7
1.4 Atrial fibrillation..... 8
1.4.1 Disease overview..... 8
1.4.1 Management of AF..... 9
1.4.2.1 Guidelines for the use of oral anticoagulants to prevent strokes in patients with atrial fibrillation..... 10
1.4.2 Risk assessment of AF..... 11
1.5 Management of DVT and PE..... 14
1.6 Anticoagulants..... 15
1.6.1 Historical development..... 16
1.6.2 Vitamin K antagonists..... 17
1.6.3 Direct oral anticoagulants..... 18
1.6.4 Evidence bases for use of oral anticoagulants in patients with atrial fibrillation, deep vein thrombosis and pulmonary embolism..... 22
1.6.4.1 Clinical trials..... 22
1.6.4.2 Meta-analyses and observational studies..... 25
1.6.4.3 Parenteral anticoagulants..... 27
1.7 Treatment with anticoagulant drugs..... 27
1.7.1 Treatment indications, duration, and choice of drug..... 27

1.7.2 Medicine related problems 29
1.7.3 Medication Errors prevalence, economic burden, and classification 31
1.7.4 Medication Errors Associated with Direct Oral Anticoagulant 34
1.8 Cardiovascular disease in Saudi Arabia 35
1.9 Healthcare Systems in the Saudi Arabia and the United Kingdom 36
1.9.1 Saudi Arabia's Healthcare System 36
1.9.2 United Kingdom's Healthcare System 38
1.10 Aim of the thesis 40
1.11 Objectives of this thesis 40
1.12 Research Questions 40
1.13 References 41
Chapter 2. Methodology 56
2.1 Introduction 57
2.2 Theoretical framework 59
2.3 Human error theory 63
2.3.1 Person approach of human error 63
2.3.2 System approach of human error 65
2.4 The 'Swiss Cheese' accident causation model (SCM) 65
2.5 Study design 68
2.5.1 Systematic literature review 68
2.5.2 Qualitative, Quantitative research and mixed methods 70
2.6 Qualitative methodology 73
2.6.1 Recruitment of participants 74
2.6.2 Data collection and analysis 74
2.6.3 Reliability and Validity in Qualitative Research 76
2.7 Quantitative methodology 76
2.7.1 Reliability and Validity in Quantitative Research 80
2.8 Research utilizing healthcare/error incident reporting databases 82
2.9 Summary of the chapter 84
2.10 References 85
Chapter 3. Prevalence, contributory factors, and severity of medication errors associated with direct-acting oral anticoagulants in adult patients: a systematic review and meta-analysis…… 90

3.1 Abstract 92
3.2 Introduction 93
3.3 Methods 96
3.3.1 Search Strategy 96
3.3.2 Types of studies 97
3.3.3 Types of participants 97
3.3.4 Outcomes 97
3.3.5 Study selection and data extraction 97
3.3.6 Assessment of methodological quality 98
3.3.7 Data synthesis and statistical analysis 98
3.4 Results 99
3.4.1 Search and study selection 99
3.4.2 Study Characteristics 101
3.4.3 Study quality 113
3.4.4 Study design and data collection 114
3.4.5 Adopted definitions of medication errors 114
3.4.6 Prevalence of errors 114
3.4.7 Prescribing errors and contributory factors 114
3.4.8 Administration errors 117
3.4.9 Dispensing errors 119
3.4.10 Subgroup analyses 119
3.4.11 Consequences, severity of errors 119
3.4.12 Contributory factors 120
3.5 Discussion 120
3.5.1 Prevalence of errors 121
3.5.2 Severity of errors 121
3.5.3 Implications for practice 121
3.5.4 Implications for research 123
3.5.5 Study strengths and limitations 123
3.6 Conclusions 124
3.7 Acknowledgements 125
3.8 Conflict of Interest 125

3.9 Data statement 125
3.10 References 126
Chapter 4. Medication errors associated with direct-acting oral anticoagulants: analysis of data from national pharmacovigilance and local incidents reporting databases 131
4.1 Abstract 133
4.2 Introduction 134
4.3 Methods 135
4.3.1 Study design 135
4.4 Results 137
4.4.1 Medication errors related to specific DOAC and indication 139
4.4.2 Errors as per the stages of medication journey 140
4.4.3 Errors classified as per specific DOAC and their indications 142
4.4.4 Errors classified as per specific DOAC and stages of medication journey 143
4.5 Discussion 145
4.6 Conclusion 148
4.7 References 149
Chapter 5. Contributory factors and patient harm including deaths associated Direct Acting Oral Anticoagulants (DOACs) medication incidents: evaluation of real world data reported to the National Reporting and Learning System 152
5.1 Abstract 154
5.2 Introduction 155
5.3 Methods 157
5.3.1 Study design 157
5.3.2 Data Source and inclusion criteria 157
5.3.3 Data Analysis 158
5.3.4 Ethical approval 158
5.4 Results 159
5.4.1 Degree of harm 160
5.4.2 Incidents leading to deaths 161
5.4.3 Incidents leading to severe to moderate harm 166
5.4.4 Medications involved and indication 170
5.4.5 Indication for medication use 170
5.4.6 Incidents per stage of medication use process 171

5.4.7 Safety incidents per medication error category 171
5.4.8 Patient age 174
5.4.9 Safety incidents per care setting 174
5.5 Discussion 174
5.5.1 Statement of key findings 174
5.5.2 Interpretation of findings 175
5.5.3 Strengths and limitations 176
5.6 Conclusion 176
5.7 Expert opinion 176
5.8 Funding 178
5.9 Declaration of interest statement 178
5.10 Author contribution 178
5.11 Data availability 179
5.12 References 180
Chapter 6. Views, experiences and contributory factors related to medication errors associated with direct oral anticoagulants: a qualitative study with physicians and nurses ... 183
6.1 Abstract 185
6.2 Introduction 186
6.3 Aim 187
6.4 Ethics approval 187
6.5 Method 188
6.5.1 Study design 188
6.5.2 Participants and settings 188
6.5.3 Data collection 188
6.5.4 Data analysis 190
6.6 Results 190
6.6.1 Factors related to healthcare professionals 193
6.6.1.1 Knowledge of HCPs 193
6.6.1.2 Communication and collaboration amongst HCPs 194
6.6.1.3 HCPs confidence in prescribing and administering DOACs 195
6.6.2 Factors related to patients 196
6.6.3 Organizational factors 198

6.6.4 Factors related to DOACs 199
6.6.5 Suggested strategies for prevention/mitigation of errors 201
6.7 Discussion 203
6.7.1 Statement of key findings 203
6.7.2 Interpretation 204
6.7.3 Strengths and weaknesses 205
6.7.4 Future research 206
6.8 Conclusion 206
6.9 Acknowledgements 206
6.10 Funding 207
6.11 Conflict of interest 207
6.12 References 208
Chapter 7. Medication errors in relation to direct-acting oral anticoagulants: a qualitative study of pharmacists' views and experiences 211
7.1 Abstract 213
7.2 Introduction 214
7.3 Aim 215
7.4 Ethics approval 215
7.5 Method 215
7.5.1 Study design 215
7.5.2 Participants and Setting 216
7.5.3 Data collection 216
7.5.4 Data analysis 218
7.6 Results 219
7.6.1 Theme one: Enablers and barriers faced by pharmacists in promoting the safe utilisation of DOACs 222
7.6.1.1 Pharmacists as a facilitator for DOACs safety 222
7.6.1.2 Barriers faced by pharmacists in promoting the safe utilisation of DOACs 223
7.6.2 Theme two: Factors related to other healthcare professionals (HCPs) and related to the patients 225
7.6.2.1 Factors associated with other HCPs 225
7.7 Discussion 231
7.7.1 Statement of key findings 231

7.7.2 Interpretation 232
7.7.3 Strengths and weaknesses 233
7.7.4 Further research 233
7.8 Conclusion 234
7.9 Acknowledgments 234
7.10 Funding 234
7.11 Conflicts of interest 235
7.12 References 235
Chapter 8. Patients' views and experiences on the use and safety of directly acting oral anticoagulants: a qualitative study 238
8.1 Abstract 240
8.2 Introduction 241
8.3 Materials and methods 242
8.3.1 Participants 242
8.3.2 Procedure 243
8.3.3 Ethics approval 243
8.3.4 Materials 244
8.3.5 Data Analysis 244
8.3.6 Rigor and trustworthiness 245
8.4 Results 245
8.4.1 Theme 1: Factors affecting DOACs Safety from patients view 248
8.4.1.1 Knowledge 248
8.4.1.1.1 Lack of knowledge on DOACs 248
8.4.1.1.2 Source of information 249
8.4.1.2 Side effects 250
8.4.1.3 Communication 250
8.4.1.3.1 Lack of communication with HCPs 250
8.4.1.4 Access to DOACs 251
8.4.1.5 Monitoring 251
8.4.2 Theme 2: Barriers to DOACs adherence 252
8.4.2.1 Memory 252
8.4.2.2 Availability of DOACs 252

8.4.2.3 Timely access to hospitals and pharmacies 253
8.4.3 Theme 3: Strategies to promote DOACs safety 254
8.4.3.1 Reminders 254
8.4.3.1.1 Use the medication box to remember/ mobile alarm/caregivers 254
8.4.3.1.2 Following advice from HCPs 254
8.4.3.2 Education 255
8.4.3.2.1 Availability of a health educator in a hospital 255
8.4.3.3 Intensive monitoring and follow up 256
8.4.3.4 Reinforcing adequate communications with HCPs 256
8.5 Discussion 257
8.5.1 Strengths and Limitations 259
8.5.2 Future Plans 259
8.6 Conclusion 259
8.7 Author Contributions 260
8.8 Funding 260
8.9 Acknowledgments 260
8.10 Conflicts of Interest 260
8.11 References 261
Chapter 9. Overall discussion and conclusion 263
9.1 Introduction 264
9.2 Summary of main findings in all studies 264
9.3 Overall interpretation of results 266
9.4 Implication for practice in Saudi Arabia 271
9.4.1 The need to address knowledge gap 272
9.4.2 The need for local clinical protocols and guidelines 273
9.4.3 The need for establishing unified protocols and guidelines 273
9.4.4 The need to improve communication and documentation 273
9.4.5 Pharmacy anti-coagulation clinics and reconciliations services 275
9.4.6 Use of medicine taking reminders and health educators 275
9.5 Implication on Saudi healthcare quality standards and policy 276
9.6 Key strengths and limitations of the research program 276
9.7 Recommendation for future research 277

9.8 Conclusion 278
9.9 References 280
Supplementary Materials 284
Appendices… 302

List of Figures

Figure 1.1 Simplified coagulation pathway and targets for oral anticoagulation....4
Figure 1.2 Antithrombotic pharmacological targets....15
Figure 1.3 Anticoagulant medication timeline.....16
Figure 1.4 Absorption and metabolism of the different direct oral anticoagulants....20
Figure 1.5 Relationships between MEs, ADE and ADR....31
Figure 1.6 Evolution and relationship of medication safety concept....31
Figure 1.7 The classification of medication errors....33
Figure 1.8 Depicts the current organization of the healthcare sectors in Saudi Arabia....37
Figure 1.9 A new healthcare framework in the United Kingdom 39
Figure 2.1 Structure of methodology....57
Figure 2.2 A classification of types of medication errors 64
Figure 2.3 The Yorkshire contributory factors framework to patient safety incidents....61
Figure 2.4 The organisational accident causation model (adopted from Reason, 2005)....66
Figure 2.5 The Swiss Cheese model 67
Figure 2.6 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram....69
Figure 3.1 PRISMA flowchart describing systematic review search and study selection....100
Figure 3.2 Quality assessment of studies included in the review....113
Figure 3.3 Forest plot Meta-analysis of the prevalence of prescribing errors amongst all patients prescribed DOACs....115
Figure 3.4 Forest plot meta-analysis of the prevalence of prescribing errors amongst all medication errors associated with DOACs 116
Figure 3.5 Forest plot Meta-analysis of the prevalence of administration errors amongst all medication errors associated with DOACs 118
Figure 4.1 Proportions of direct acting anticoagulants (DOACs) associated with medical errors 139
Figure 4.2 Different indications of direct oral anticoagulants (DOACs) in the medication error reports....140
Figure 4.3 Different types of medication errors reported with direct oral anticoagulants (DOACs)....141

Figure 4.4 Sub-types of medication errors associated with direct oral anticoagulants (DOACs) 142
Figure 5.1 National Reporting and Learning Dataset used for the evaluation of incidents related to directly-acting oral anticoagulants 159
Figure 6.1 An overview of themes and subthemes emerged during data analysis 192
Figure 7.1 An overview of themes and subthemes emerged during data analysis 221
Figure 8.1 An overview of themes and subthemes emerged during data analysis 247

List of Tables

Table 1.1 Summary of treatment guidelines for the prevention of stroke in patients with atrial fibrillation 10

Table 1.2 Stroke risk by CHADS2 and CHA2DS2-VASc risk scores 13

Table 1.3 Stroke and bleeding risk assessment scores in patients with atrial fibrillation. 13

Table 1.4 Comparison of randomised clinical trials on prevention of stroke in patients with atrial fibrillation 23

Table 2.1 The Yorkshire contributory factors framework to patient safety incidents 62

Table 2.2 The differences between quantitative v.s qualitative research 70

Table 2.3 shows how the researchers address the criteria for trustworthiness during each phase of TA 82

Table 3.1 Study characteristics with Classification of medication error contributory factors. 102

Table 4.1 Characteristics of Medical Errors Reports included in the study 137

Table 4.2 Drug indication and the status of dose appropriateness of DOAC in the Medical Errors Reports 143

Table 4.3 Phases and types of reported medication errors associated with direct oral anticoagulants (DOAC) in the Medical Errors Reports 144

Table 5.1 Detailed descriptions of incidents leading to deaths with the assigned medication process stage, error type and nature of contributing factors 161

Table 5.2 Examples of incidents associated with severe harm 167

Table 5.3 Examples of incidents associated with moderate harm 169

Table 5.4 Proportion and examples of safety incidents per stage of medication error category 172

Table 6.1 Participants characteristics 191

Table 7.1 participants characteristics 220

Table 8.1 participants characteristics 246

List of Abbreviations

ACS	Acute coronary syndrome
ADE(s)	Adverse Drug Event(s)
ADR(s)	Adverse Drug Reaction(s)
AF	Atrial Fibrillation
AKI	Acute kidney injury
BID	Twice daily
BNF	British National Formulary
BNI	British Nursing Index
CASP	Critical appraisal skills programme
CBAHI	Saudi Central Board for Accreditation of Healthcare Institutions
CENTRAL	Cochrane Central Register of Controlled Trials
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CI	Confidence interval
COREQ	The Consolidated criteria for reporting qualitative research
COVID	Corona virus infection disease
CrCl	Creatinine Clearance
DDI	Drug-Drug interaction
DOACs	Direct oral anticoagulants
DVT	Deep Vein Thrombosis
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration
GP	General practitioner
HCPs	Health care professionals
IOM	Institute of Medicine
IPA	International Pharmaceutical Abstract
ISMP	Institute for Safe Medication Practices
IQ	Interquartile range
JCI	Joint commission international
KAIMRC	King Abdullah International Medical Research Center
KFMMC	King Fahad Military Medical Complex
LASA	Look Alike Sound Alike
MD	Mean difference
MEQI	Medication Error Quality Initiative
MUE	Medication Utilization Evaluation
NG	Nasogastric

NOACs	Non-vitamin K antagonist oral anticoagulants
NCC MERP	National Coordinating Council for Medication Error Reporting and Prevention
NHS	National Health System
NICE	National Institute for Health and Care Excellence
NPSA	National Patient Safety Agency
NRLS	National Reporting and Learning System
NVAF	Non-valvular atrial fibrillation
NSTEMI	Non-ST elevation myocardial infarction
OAC	Oral Anticoagulants
OD	Once daily
PIS	participants' information sheet
PrI	Prediction interval
PE	Pulmonary embolism
RF	Renal failure
RCTs	Randomised controlled trials
SCM	Swiss Cheese' accident causation model
SC	Subcutaneous
SD	Standard deviation
SFDA	Saudi Food and Drug Authority
PRISMA-P	Referred Reporting Items for Systematic Review and Meta-Analysis Protocols
TSOAC	Target Specific Oral Anticoagulants
TTO	To take out
TDF	Theoretical Domains Framework
UK	United Kingdom
USA	United States of America
VTE	Venous thromboembolism
VKA	Vitamin-K antagonists
KSA	Kingdom of Saudi Arabia
WHO	World Health Organization

Chapter 1. Introduction

Chapter overview: The aim of this chapter is to provide a general overview of the clinical subject of this thesis. This chapter describes the physiological process of blood coagulation, followed by thromboembolic events caused by disruption of this process, such as venous thromboembolism (VTE), atrial fibrillation (AF), and stroke. The chapter also provides an overview of anticoagulant medications and discusses current clinical guidelines for anticoagulant treatment, with a special emphasis on the usage of direct-acting oral anticoagulants (DOACs) to treat patients with AF and VTE.

1.1 Physiology of blood coagulation

The coagulation process was first introduced in the 19th century. More research has recently focused and examined the coagulation process in some detail. In order to prevent excessive bleeding following tissue damage or trauma, the blood coagulates in a process involving numerous proteins and several cofactors. Injury to a blood vessel due to tissue damage or trauma triggers a coagulation cascade, which involves numerous proteins and cofactors. Activating these coagulation factors in the presence of activated blood platelets successively results in an insoluble fibrin clot, which seals the damaged vessel.(1)

Eleven coagulation factors, differing in their importance, are involved in this process in addition to platelets, vitamin K, calcium, and other essential elements.(2) Each factor is assigned a roman numeral, followed by the letter 'a' if it is activated.(3) Some are more commonly designated by names such as fibrinogen (Factor I), fibrin (Factor Ia), prothrombin (Factor II), thrombin (Factor IIa) and tissue factor (Factor III). The precise roles of certain factors and their interactions remain to be fully clarified.(1, 4, 5)

The simplified illustration of the coagulation cascade shown in Figure 1.1 depicts two alternative pathways: intrinsic when the internal surface of a blood vessel is damaged and extrinsic in the case of external trauma. Each of these pathways leads via a different series of factors to the activation of factor X, which has a pivotal role in the transformation of prothrombin into thrombin, thus facilitating the availability of fibrin.(2)

Haemostasis is maintained under normal physiological conditions by the fact that naturally occurring coagulant and anticoagulant factors are in balance, but this delicate equilibrium may be disturbed in a number of ways, potentially resulting in excessive or insufficient coagulation. The latter can cause haemorrhage, which may be serious in the case of certain haemophilic disorders, for example, whereas a possible outcome of too much coagulation is a thromboembolic event.(1)

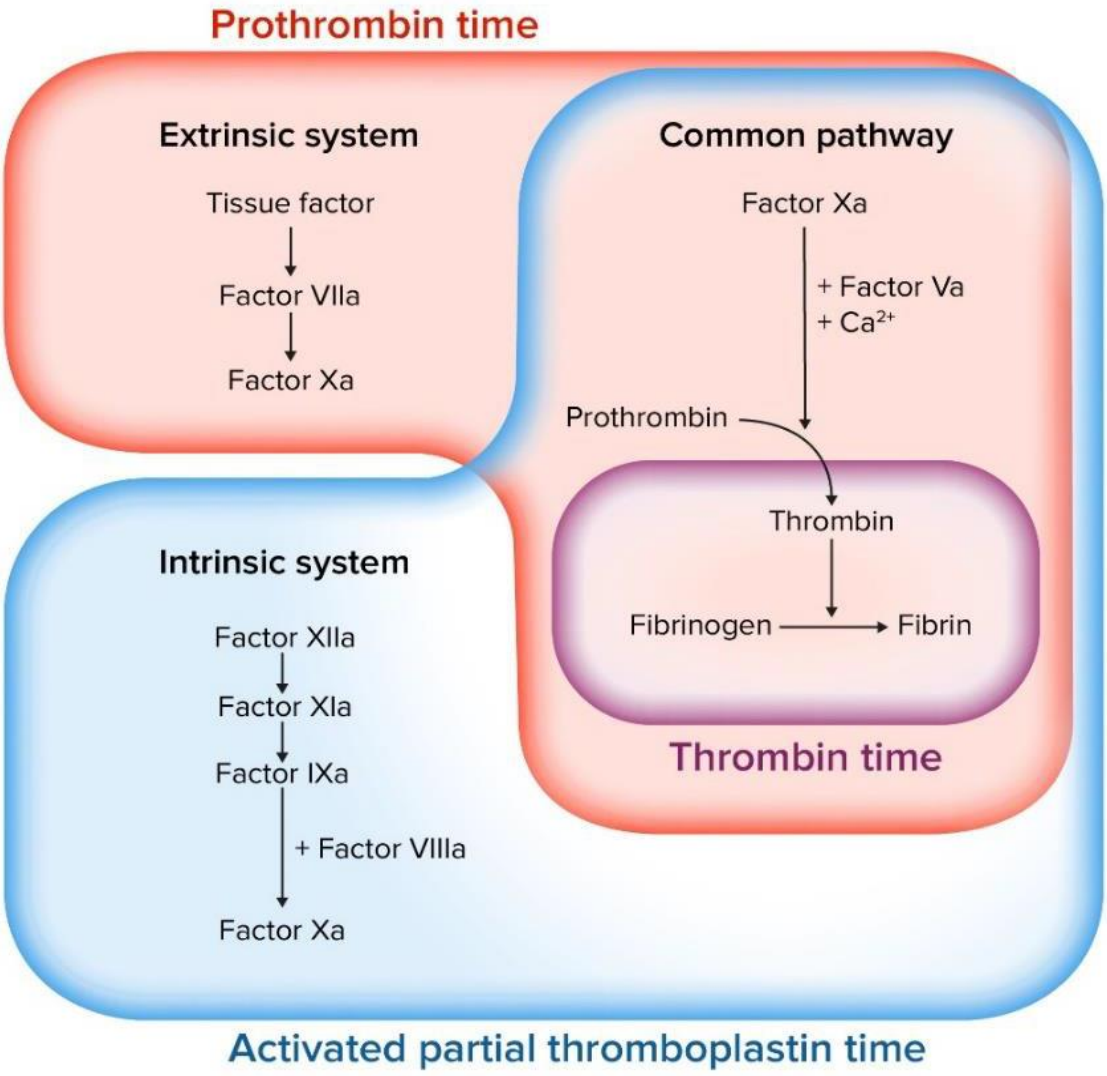


Figure 1.1 Simplified coagulation pathway and targets for oral anticoagulation (6). It is reproduced with permission from https://www.lecturio.com/concepts/coagulation-studies, Copyright Lecturio.

1.2 Thromboembolic events

In order for thrombosis to occur, haemostasis must be disturbed by pathophysiological conditions, originally characterised by the so-called pathogenic triad, comprising vessel damage, venous stasis, and hypercoagulability. Disruption of the flow of the blood or alteration of its composition enables intravascular clots to develop and potentially to block a vessel, whether as a thrombus at the place of origin or as an embolism elsewhere in the body following mobilisation and transportation of the clot through the blood circulation.(1)

A thrombus could be either arterial or venous. Thrombi also differ in their composition: venous thrombi tend to have a high fibrin content, while arterial thrombi have a greater number of platelets.(1, 2) It is debatable whether this is an oversimplified categorisation because of the role of inflammatory processes that contribute to the development of all kinds of thrombi.(7-9)

1.2.1 Venous thromboembolism

There are two distinct types of venous thromboembolism (VTE): deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT is the development of thrombi throughout a deep vein, usually in the extremities, while PE is a potentially fatal complication of DVT whereby a venous thrombus is dislocated and goes on to obstruct an artery in the lungs.(10)

The incidence of VTE in the UK is around 1–2 per 1000 people annually.(11, 12) In the US, for instance, there are between 100 and 200 cases of VTE per 100,000 population,(10, 13) while in Europe, the respective incidence rates of DVT and PE are 148 and 95 per 100,000, respectively.(14) VTE is most often associated with major surgery and lengthy immobilisation, but a number of other conditions are also associated with it. The most important risk factors for

VTE are old age, obesity, cancer, pregnancy, and a previous history of VTE or stroke.(15, 16) PE is reported to be among the most important causes of hospital mortality, the majority of deaths occur among those with PE, as an estimated 20%–25% of all PE cases present as sudden death.(2, 10, 17) Despite a lack of accurate data, a substantial proportion of cases develop in a hospital setting, although around two-thirds of diagnoses are made after discharge in primary care.(14, 18) DVT sometimes has no early symptoms and often has unspecific ones, although patients may complain of pain and swelling, while those with PE may report dyspnoea or chest pain.(17, 19, 20)

1.2.2 Arterial thromboembolism

Unlike venous thrombi, arterial thrombi do not usually result from immobilisation or imbalanced coagulation factors; they can often be attributed to underlying conditions, including atherosclerosis and arrhythmia. The behavioural risk factors for arterial thromboembolism include alcohol consumption, smoking, and inadequate physical activity, while the pathophysiological ones include comorbidities, such as obesity, diabetes, and hypertension.(1)

Vital organs, including the brain and heart, can be affected by arterial emboli, resulting in many hospital admissions and overall deaths.(1) A stroke is an alteration in the blood supply affecting brain function; the majority of strokes (estimated as around 60% to over 80% in some countries) are termed ischaemic, meaning that intracranial blood flow is reduced by blood vessels in the brain being obstructed.(21) Most emboli that cause ischaemic strokes begin with the development of atherosclerotic plaques in large arteries, although emboli can also originate within the heart.(22) Such cardiac emboli frequently arise as a complication of AF or another heart condition or from the presence of a mechanical heart valve; a thrombus may form in AF

because blood stagnates within the left atrium, while the metallic surface of mechanical valves may be directly prothrombotic.(1) AF is discussed further in section 1.4.

1.3 Impact of thromboembolic event in cardiovascular diseases

Cardiovascular disease (CVD) is widespread throughout the world, constituting the most common cause of death. Its forms include disorders of the blood vessels supplying the heart (coronary heart disease), the brain (cerebrovascular disease) and the extremities (peripheral arterial disease), as well as congenital malformations of the heart, damage to its valves and muscles arising from bacterial infection (rheumatic heart disease) and VTE.(23)

Thromboembolic indeed events constitute a particularly heavy burden of disease in developed countries.(24, 25) In 2021, cardiovascular disease and stroke came as the third and fourth leading causes of death among all age groups in the UK, after dementia and Alzheimer's disease and COVID-19.(26) Besides, there is an association between COVID-19 and acute stroke that could be attributed to multiple factors, including hypercoagulable status, inflammation, changes in the vascular endothelium, and platelet activation.(27) A recent systematic review and meta-analysis indicated that stroke was independently associated with an increased risk of mortality in COVID-19 patients.(28)

1.4 Atrial fibrillation

1.4.1 Disease overview

Atrial fibrillation (AF), which is the most frequently occurring arrhythmic disorder, is either paroxysmal (self-terminating), persistent (not self-terminating, but sinus rhythm can be restored), or permanent (sinus rhythm cannot be restored). Some patients have no symptoms, while others report palpitations, dyspnoea, or chest pain.(29) AF increases the risk of stroke up to fivefold, and thus is an independent risk factor.(30) It also negatively affects a patient's prognosis after having a stroke, increasing the risk of disability and death. AF is often associated with cardiovascular conditions, including heart failure, coronary heart disease and hypertension, and various other diseases such as diabetes, chronic pulmonary disease, and obesity.(31, 32)

It is estimated that roughly 1.4 million people in the UK have AF.(33) This is equal to 2.5% of the population. AF prevalence is higher in males (2.9%) than in females (2.0%). AF prevalence increases with age; total estimated AF in the whole population is likely to occur in people aged under 45 is about 2.8%,16.6% in people aged 45-65, and 80.5% in people aged over 65. In developed countries, approximately 2% of the general population is affected by AF, and prevalence is significantly higher among the elderly, exceeding 10% in patients aged over 79.(32) Recent estimates revealed that AF affects at least 1.8% of the population of Scotland and more than 6% of people aged over 65.(34) These prevalence rates can be underestimations because of the common nonspecific nature of AF symptoms and the lack of routine screening. Prevalence is predicted to rise substantially in coming decades as population ages, awareness of AF Increases, and treatment options improve.(35, 36) AF and associated conditions, including stroke, thus constitute a substantial and potentially growing burden on healthcare systems.

1.4.2 Management of AF

The National Institute for Health and Care Excellence (NICE) guideline for atrial fibrillation: diagnosis and management (NG196), NICE (2019) aims at ensuring the best care provided to this patient population, including the assessment and the management of the risks of stroke and bleeding.(37)

Initial management depends on the type of AF and its symptoms, including cardioversion that contains rate control, rhythm control, and catheter ablation. Rate control (via beta-blockers and calcium channel blockers- diltiazem or verapamil) is appropriate for patients who are asymptomatic or have an underlying cause for the arrhythmia or in cases where rhythm control has failed, whereas in symptomatic patients with recurrent paroxysmal and persistent AF, antiarrhythmic drug treatment (via, e.g., amiodarone or flecainide) is recommended. For recent-onset AF, an alternative to oral antiarrhythmic treatment is to restore sinus rhythm by means of cardioversion, either electric or pharmacological (an antiarrhythmic drug given intravenously), while in low-risk patients with paroxysmal AF, catheter ablation may be recommended to restore sinus rhythm.(35) A crucial recommendation in AF patients with additional risk factors is to prevent strokes by administering DOACs. Risk assessment is explained in more detail in the following section, while anticoagulant therapeutics are discussed further in Sections 1.4.2.1.

1.4.2.1 Guidelines for the use of oral anticoagulants to prevent strokes in patients with atrial fibrillation

Updated clinical guidelines for stroke prevention in AF patients often include the use of DOACs and warfarin. The British, Scottish, European, and American guidelines all recommended the use of DOACs in non-valvular AF, with differences in patients' prescribing criteria based on stroke risk assessment and gender. Table 1.1 summarizes different guidelines and recommendations for DOAC use and criteria for patients who are anticoagulation candidates.

Table 1.1 Summary of treatment guidelines for the prevention of stroke in patients with atrial fibrillation

Region	Patient group	Recommendation	Warfarin	DOACs	Comments
EU (European Society of Cardiology) (Camm et al., 2012)	CHA_2DS_2-VASc = 0 (male) or 1 (female)	No antithrombotic therapy			Choice of drug based on patient characteristic and preferences
	CHA2DS2-VASc ≥ 1 (male)	Oral anticoagulant should be considered	✓	✓	First choice: DOACs. Antiplatelet therapy should be considered when patients refuse OAC therapy or cannot tolerate anticoagulants for reasons other than bleeding
	CHA_2DS_2-VASc ≥ 2	Oral anticoagulant	✓	✓	Choice of drug based on patient characteristic and preferences
UK (NICE) (NICE, 2014a)	CHA_2DS_2-VASc = 0 (male) or 1 (female)	No antithrombotic therapy			
	CHA2DS2-VASc ≥ 1 (male)	Oral anticoagulant should be considered	✓	✓	Consider DOACs for patients with labile INRs
	CHA_2DS_2-VASc ≥ 2	Oral anticoagulant	✓	✓	
Scotland (SIGN) (SIGN, 2014)	CHA_2DS_2-VASc = 0 (male) or 1 (female)	No antithrombotic therapy			Choice of drug based on patient characteristic and preferences
	CHA2DS2-VASc ≥ 1 (male)	Oral anticoagulant should be considered	✓	✓	First choice: warfarin. Antiplatelet therapy should be considered when patients refuse OAC therapy or cannot tolerate anticoagulants for reasons other than bleeding
	CHA_2DS_2-VASc ≥ 2	Oral anticoagulant	✓	✓	
US (AHA & American	CHA_2DS_2-VASc = 0 (male) or 1 (female)	No antithrombotic therapy			Choice of drug based on patient characteristic and preferences

College of Cardiology) (January et al., 2014)	CHA2DS2-VASc ≥ 1 (male)	No treatment, OAC, or aspirin may be considered	✓	✓	No drug of choice
	CHA_2DS_2-VASc ≥ 2	Oral anticoagulant	✓	✓	For patients with kidney disease, reduced dose of DOACs can be considered.
	Patients with moderate to severe CKD		✓	✓	Patients with end-stage kidney disease, warfarin is the drug of choice.
	Patients with end-stage renal diseases or on hemodialysis			✓	DOACs recommended for patients with labile.
AHA – American Heart Association; CKD – chronic kidney disease; DOAC – direct oral anticoagulant; INR – International Normalised Ratio; NICE – National Institute for Health and Care Excellence; OAC – oral anticoagulant; SIGN – Scottish Intercollegiate Guidelines Network					

1.4.3 Risk assessment of AF

Although AF is an independent risk factor for stroke, and oral anticoagulants have proved efficacious in preventing strokes in AF patients, DOACs treatment will not necessarily be the best option for every patient. DOACs can have severe side effects, and patients differ in their risk of experiencing a stroke depending on additional risk factors. The risks of strokes and bleeding events should be balanced against each other, hence the introduction of various risk assessment scores.

The two scores most commonly used to predict the risk of stroke in AF patients are the CHADS2 score and its derivative, the CHA2DS2-VASc score, developed in 2001 and 2009, respectively. Both combine a variety of cardiovascular risk factors and are used in clinical practice to stratify patients as at low, medium, or high risk and to determine their need for oral anticoagulant treatment.(38) The CHADS2 score is mainly concerned with the independent risk factors of congestive heart failure, hypertension, diabetes mellitus, and prior stroke, with scores ranging from 0 to 6; a validation study revealed that stroke risks among AF patients, stratified by CHADS2 ranged from 1.9 (score 0) to 18.2 (score 6) per 100 patient-years.(39) According to NICE

guidelines (2017), the CHA2DS2-VASc score ranges from 0 to 9, includes the additional factors of vascular disease and sex, and gives greater emphasis to age to better identify patients with a truly low risk of stroke; the validation study estimated annual stroke rates ranging from 0% for patients with a CHA2DS2-VASc score of 0, to 15.2% for those with a score of 9.(40) Table 1.2 lists stroke risks by risk score based on these validation studies.

The tool most widely used to assess bleeding risk in AF patients is the HAS-BLED score.(41, 42) The HAS-BLED score was initially proposed in 2010, and has been derived and validated in the EuroHeart survey population. The HAS-BLED score has since been validated with multiple independent populations, where it performed as good as (and sometimes better than) the more complex HEMORR2HAGES score. It combines a variety of medical conditions known to increase bleeding risk, including hypertension, abnormal liver and kidney function, and prior strokes and bleeding, with information about age and drug and alcohol use, generating a score from 0 to 9. HAS-BLED, which is proven to be effective in predicting major bleeding, including intracranial haemorrhage, is recommended by some current clinical guidelines, in combination with CHA2DS2-VASc, to decide among OAC therapy options (see Table1.2 and Table 1.3).(35)

Table 1.2 Stroke risk by CHADS2 and CHA2DS2-VASc risk scores (43)

$CHADS_2$ (For Assessment of stroke risk in AF patients)	**CHA_2DS_2-VASc (For Assessment of stroke risk in AF patients)**	**HAS-BLED (For Assessment of bleeding risk in AF patients)**
Congestive heart failure	Congestive heart failure	Hypertension
Hypertension	Hypertension	Abnormal liver/renal function
Age ≥ 75 years	Age ≥ 75 years	Prior stroke
Diabetes	Diabetes	Prior bleeding or predisposition
Prior stroke	Prior stroke	Labile INR (if on warfarin)
	Vascular disease	Age ≥ 65 years, or frail condition
	Age 65 – 74 years	Drugs (e.g., NSAIDs)
	Sex (i.e., female gender; only in the presence of other risk factors)	Alcohol excess/abuse
One point for each risk factor, except for prior stroke, which is worth two points	One point for each risk factor except for age ≥ 75 years & prior stroke, worth 2 points.	One point for each risk factor, two for abnormal function if liver and kidneys are both affected
Risk stratification according to total score (overall range 0–6)	**Risk stratification** according to total score (overall range 0 –9):	**Risk stratification** according to total score (overall range 0 – 9):
0 = low risk	0 = truly low risk	≥ 3 = high risk of major bleeding; indicates that further measures need to be taken (e.g., modify risk factors, if possible)
1-2 = moderate risk	1 = moderate risk	
≥ 3 = high risk	≥ 2 = high risk	

Table 1.3 Stroke and bleeding risk assessment scores in patients with atrial fibrillation

	$CHADS_2$		CHA_2DS_2-VASc
Score	*Stroke rate (per 100 patient years)*	*Score*	*Stroke rate (% per year)*
0	1.9	0	0.0
1	2.8	1	1.3
2	4.0	2	2.2
3	5.9	3	3.2
4	8.5	4	4.0
5	12.5	5	6.7
6	18.2	6	9.8
		7	9.6
		8	6.7
		9	15 2

1.5 Management of DVT and PE

Anticoagulants treatment for patients diagnosed with DVT or PE has two purposes. First, it is the cornerstone for anticoagulation used for treating the thrombotic event to prevent the extension of the thrombus in future, permitting the fibrinolytic system to resolve the thrombus. This process could take around six weeks to resolve it. Second, it prevents, to an enormous extent, the development of additional thrombi. Therefore, for thrombus resolution, anticoagulation is essential for three months or more, according to the patient clinical conditions. Whether to discontinue anticoagulants at three months, the therapy indefinitely is determined by the risk of recurrence and is affected by bleeding risk and patient preferences.(44) Therefore, anticoagulants therapy for VTE has been categorised into three stages: initial therapy, long-term therapy, and extended anticoagulation.

For the period of the beginning of warfarin therapy, overlapping (bridging) therapy with rapid-onset injectable anticoagulants (e.g., low molecular weight heparin or unfractionated heparin) is recommended because warfarin's onset of action is slow.(45) Nevertheless, with the DOACs, which have recently been presented for clinical use, bridging therapy is not necessary owing to their quick onset of anticoagulant effect. The use of new oral anticoagulants is recommended as long-term anticoagulant treatment over warfarin, according to current antithrombotic therapy for venous thromboembolism disease guidelines published in February 2016.(46) Further detailed information on DOACs is provided later in this chapter, in section 1.6.3.

1.6 Anticoagulants

Anticoagulants can prevent thromboembolic events, such as stroke and DVT, by interacting with the physiological mechanisms that trigger blood coagulation (e.g., the coagulation cascade described in Section 1). They differ from antiplatelet drugs, including low-dose aspirin, clopidogrel, dipyridamole, prasugrel and ticagrelor, which affect platelet aggregation. They can prevent myocardial infarction and other conditions arising largely from atherosclerosis. Furthermore, some conditions involve the combined use of platelet inhibitors and oral anticoagulants because of different mechanisms of action (see Figure 1.2) to decrease thromboembolic events.

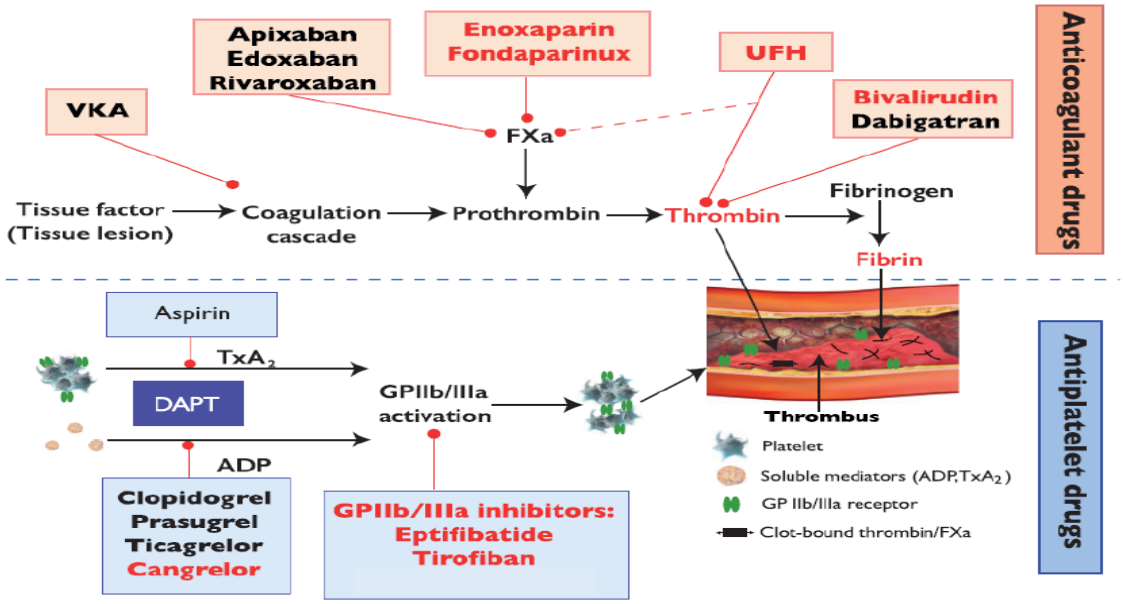
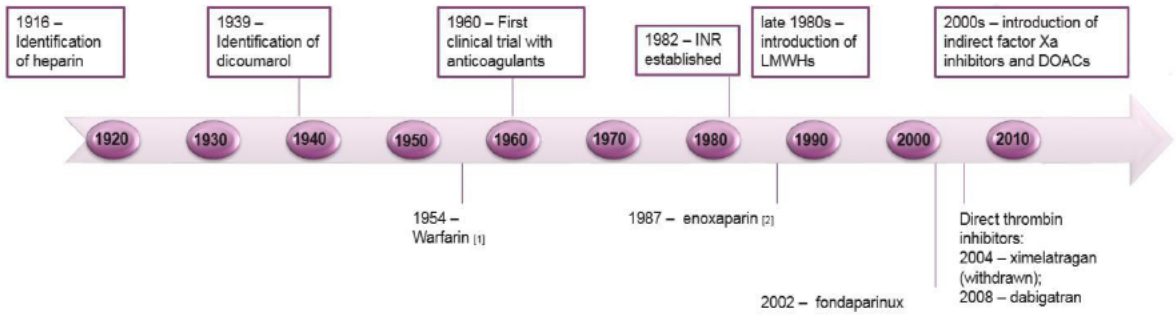


Figure 1.2 Antithrombotic pharmacological targets. Note: Drugs with oral administration are shown in black letters and drugs with preferred parenteral administration in red. ADP=adenosine diphosphate; DAPT=dual antiplatelet therapy; FXa=factor Xa; GP=glycoprotein; TxA2=thromboxane A2; UFH=unfractionated heparin; VKA=vitamin K antagonist (47)

Anticoagulant drugs are usually classified based on the route of administration as oral or parenteral drugs. Further, they are characterised by their mechanism of action (i.e., how they interact with specific components of the coagulation cascade to prevent the formation of blood clots). Although a wide range of different factors are involved in blood coagulation, anticoagulants do not actively target all of them; instead, most current anticoagulant drugs focus either on factor IIa (thrombin) or on factor Xa (directly or indirectly), with the exception of vitamin-K antagonists (VKAs), which are less specific in their range of targets (see Figure 1.2).

1.6.1 Historical development

Anticoagulant drugs have a long history, and the first two to be marketed for medical purposes, heparin and warfarin, are still in clinical use. However, many new drugs have been developed during the last two decades, and the high burden of disease attributable to thromboembolic events means that more are very likely to be developed in future (see Figure 1.3 for a brief overview).



[1] Other vitamin K-antagonists are now available, e.g., phenprocoumon; [2] other LMWHs are now available e.g., dalteparin. INR – International normalised ratio; LMWH – low molecular weight heparin; DOAC – direct oral anticoagulant

Figure 1.3 Anticoagulant medication timeline (48, 49)

The first anticoagulant to become available was heparin, discovered in 1916 at John Hopkins Medical School and first commercialised in 1924, despite observable toxic side effects remaining unresolved. These problems were resolved after the identification of its chemical

structure in 1926 and enhancements to its purification in 1933, allowing an improved form of the drug free of such side effects to be used in humans for the first time in 1937, following surgery.(50) Low-molecular-weight heparins (LMWHs) have been developed since the 1990s and have largely replaced unfractionated heparin, despite their higher costs, because they are easier to administer and monitor.(51, 52)

Warfarin was introduced in 1948 as an improvement on dicoumarol, which was first synthesised in 1940 after being identified in 1939 as the agent causing the lethal bleeding condition of sweet clover disease in cattle eating mouldy sweet-clover hay.(53) Warfarin was originally sold as a rat poison, but was soon used to treat human patients because, unlike other drugs available at that time, it can be administered orally and has a reversible anticoagulant effect.(54) In 1982, a method to measure and standardise warfarin treatment, which is the international normalised ratio (INR) (further described in the next section), was implemented upon the recommendation of the WHO.(55)

Research and development in this century have focused on anticoagulants, which directly target individual coagulation factors and are designed specifically for oral bioavailability. Such direct oral anticoagulants (DOACs), including apixaban, dabigatran etexilate, edoxaban and rivaroxaban, had been approved in various countries for a range of indications, although ximelagatran, an oral direct thrombin inhibitor, was withdrawn after reports of liver damage.(56, 57)

1.6.2 Vitamin K antagonists

While the best-known vitamin K antagonist (VKA) is warfarin, other coumarin derivatives, including acenocoumarol and phenprocoumon, can be used therapeutically.(58) These compounds have the same mechanism of action and are used to treat similar conditions,

although they differ slightly in their pharmacological properties, especially in elimination half-life.

Coagulation factors II, VII, IX and X share a dependence on the availability of vitamin K, which facilitates the γ-carboxylation that is needed for their anticoagulant activity to be expressed. VKAs including warfarin inhibit these vitamin-K dependent factors indirectly via inhibition of the enzyme vitamin K epoxide reductase. This limits the availability of vitamin K, thus suppressing the carboxylation of anticoagulation factors, which results in reducing the anticoagulation effect.(2)

Warfarin is taken orally, and its half-life of around 24 to 58 hours is relatively long. It is highly bioavailable, absorbed quickly, bound mainly by plasma proteins, and metabolised by the liver. If loading doses are used, the onset of action can be rapid, but the full therapeutic effect often occurs only after several days; correspondingly, when the administration is discontinued, observable anticoagulant activity will tend to persist for a further two to five days.(58, 59) The resultant differences within and between individuals require dosing schemes to vary considerably, and careful INR monitoring is essential because VKAs have a narrow therapeutic window: an overdose of warfarin carries the risk of severe bleeding complications (60), whereas if the dose is too low, there is an increased risk of thromboembolism.(61) Warfarin has many drug and food interactions.(60, 62, 63) Besides, noncompliance with the medication could significantly impact the INR level and the treatment outcomes.(64)

1.6.3 Direct oral anticoagulants

Direct oral anticoagulants (DOACs) are categorised either as direct thrombin inhibitors or as direct factor Xa inhibitors, according to the drug target. Since both types interact with

coagulation factors that are active towards the end of the coagulation cascade, they block both the intrinsic and extrinsic blood coagulation pathways.(2)

Direct thrombin inhibitors prevent fibrin clots from forming by inhibiting thrombin, the enzyme, which is responsible for transforming fibrinogen into fibrin, is an important platelet activator.(65) Ximelagatran, having been withdrawn from the market, only one oral direct thrombin inhibitor, dabigatran is currently available.(56)

Dabigatran is not orally active itself, so the agent used is a non-active pro-drug, dabigatran etexilate, which is formulated with tartaric acid because its rapid absorption depends on an acid environment. Even so, its bioavailability after oral administration is only around 7%. The average time to onset of action is 1.5 hours, and the mean half-life is about 8 to 10 hours. About 20% of dabigatran is excreted via the biliary system after being metabolised, and the majority being eliminated unchanged via the kidneys. It is assumed that the potential for drug-drug interactions is low, and that food ingredients have little effect.(58, 66)

Various direct factor Xa inhibitors are being developed in addition to the currently available rivaroxaban, apixaban, and edoxaban. The mechanism by which direct factor Xa inhibitors block the coagulation cascade is the selective and reversible inhibition of factor Xa.(2, 58)

As shown in Figure 1.4., while these three drugs have a rapid onset of action, and their elimination half-lives are shorter than warfarin, they differ in bioavailability and excretion pathways.(58, 67, 68) Broad estimates have been made with the potential of direct factor Xa inhibitors to interact with drugs inhibiting or inducing liver enzymes, yet there is currently little understanding of their potential interactions with food ingredients.(66)

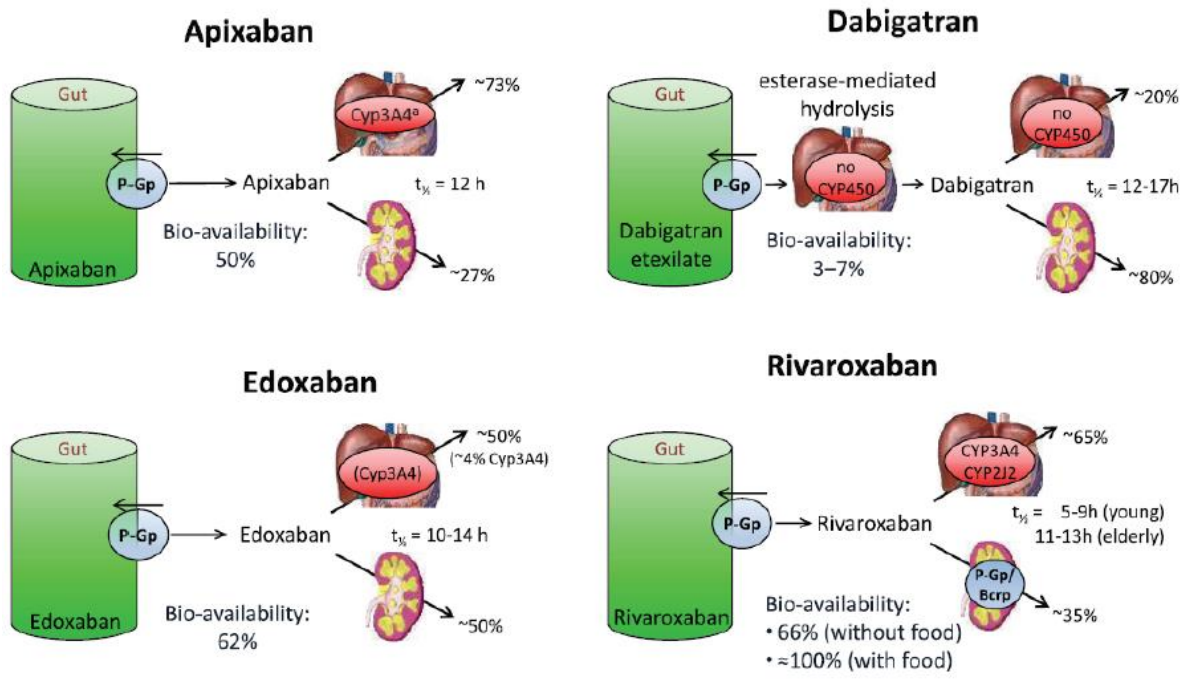


Figure 1.4 Absorption and metabolism of the different direct oral anticoagulants (69)

A number of countries around the world have approved the use of DOACs for a range of conditions, but local prescribing practice may vary substantially where treatment guidelines allow their prescription only to patients in whose warfarin use is contraindicated, experience labile INRs, or are unwilling to use VKAs. Despite being associated with incremental costs (£14,437 for rivaroxaban and £20,101 for apixaban) per quality-adjusted life year, a recent real-world study found that rivaroxaban and apixaban are considered cost-effective from an NHS perspective.(70) Another nationwide English study found that nearly one million additional DOAC prescriptions in the period from 2014-2017 were associated with reduced incidence of AF-related stroke and an incremental per-patient saving of £289.(71) A variety of contextual factors can influence DOACs relative costs, including local health care costs, drug adherence, population risk, and health behaviours like health literacy and self-care. These factors can vary and require further study to determine how they relate to DOACs' costs.

Although treatment with DOACs is associated with various challenges, the most significant is insufficient published data in special patients' populations (e.g., paediatric, renal impairment, hepatic impairment, pregnancy, and lactation) to allow the potential extent of comorbidity or concomitant medication problems to be determined. Some drugs may be contraindicated for certain patients, such as those having severe liver or kidney disease, because of pharmacological issues like elevated renal excretion (especially dabigatran) and liver metabolism (e.g., apixaban).(72, 73) There may also be drug-drug interactions, which represent challenges similar to (if much less severe than) those of warfarin treatment.(74-76) While some interactions have been included in recommendations for DOAC usage and dosing, these are not all proven,(77) and there remains inconclusive evidence of adverse events, particularly on the incidence of bleeding related to the use of DOACs compared with VKAs,(78-82) and on the potentially higher risk of myocardial infarction.(83, 84)

A particular challenge is the lack of specific antidotes to direct factor Xa inhibitors, which requires non-specific reversal therapies with rivaroxaban, apixaban, or edoxaban to be administered in emergencies, despite the failure so far to establish the safety or indeed the efficacy of these methods in relation to DOACs.(85-87) Work is, however, in progress to develop target-specific antidotes for DOACs,(88) and if they do become widely available, this will improve clinical outcomes of bleeding events associated not only with treatment but also with trauma and unplanned surgery.(86)

Another issue is the poor availability of specific, validated tools to sufficiently and precisely monitor the effects of DOAC therapy. It is not recommended to routinely monitored anticoagulation status, but it might be desirable or necessary in certain circumstances; however, such monitoring can be challenging because routine warfarin monitoring tests are inapplicable or unreliable, while any drug-specific assays currently available are either impractical or

potentially inaccurate, or they rely on calibration methods which, while commercially available, have not been scientifically approved.(86, 89)

Further attention should also be given to the adherence to DOACs treatment. Although non-compliance carries similar risks to those applicable to warfarin regimes, such as inadequate protection against major bleeding events, including stroke and the lack of routine monitoring, DOACs have the advantage over warfarin for wider therapeutic window, but their rapid onset of action and relatively short half-life, unwanted treatment outcomes are possible.(67) Clinical data on adherence rates among AF patients have until recently been unavailable and remain limited in scope; DOAC treatment seems to have better short-term adherence than warfarin, but predictions as to long-term use are not warranted by current data.

Finally, the uptake and understanding of DOACs use are currently restricted due to the lack of clinical trials that compare DOACs directly.(90) Possible reasons for this lack of comparative research concern intellectual property rights, the cost of such trials, and their feasibility since it would be unethical to test anticoagulants against placebo in human subjects. As a result, deciding to adopt particular medication regime is more subject to prescribers' and patients' preferences than robust clinical evidence.

1.6.4 Evidence bases for use of oral anticoagulants in patients with atrial fibrillation, deep vein thrombosis and pulmonary embolism

1.6.4.1 Clinical trials

Approval for the use of DOACs to prevent stroke in AF patients has relied largely on four substantial multicentre studies: RE-LY,(91) ROCKET-AF,(92) ARISTOTLE,(93) and ENGAGE AF-TIMI 48,(94) which investigated the efficacy and safety for this indication of dabigatran,

rivaroxaban, apixaban, and edoxaban, respectively, by comparison with warfarin. All four were designed as non-inferiority trials, and they found that DOACs reduced the risk of strokes at least to the same degree as warfarin, with similar risks of major bleeding (see Table 1.4).

Table 1.4 Comparison of randomised clinical trials on prevention of stroke in patients with atrial fibrillation (95)

Study	RE-LY	ROCKET-AF	ARISTOTLE	ENGAGE AF- TIMI 48
Intervention	**Dabigatran** 110 mg or 150 mg twice daily, blinded, vs warfarin, dose-adjusted, unblinded	**Rivaroxaban** 20 mg once daily, blinded, vs warfarin, dose-adjusted, blinded	**Apixaban** 5 mg twice daily, blinded, vs warfarin, dose-adjusted, blinded	**Edoxaban** 30 mg or 60 mg once daily, blinded, vs warfarin, dose-adjusted, blinded
Control	warfarin	warfarin	Warfarin	Warfarin
Method	unblinded	blinded	Blinded	Blinded
Study population		14,264 participants in 45 countries	18,201 participants in 40 countries	21,105 participants in 46 countries
Patient baseline characteristics	mean age 71.5 years; 36.8% female; mean CHADS2 score 2.2	median age 73 years; 39.7% female; mean CHADS2 score 3.48	median age 70 years; 35.5% female; mean CHADS2 score 2.1	median age 72 years; 37.9% female; mean CHADS2 score 2.8
Median follow-up period:	2 years	1.9 years	1.8 years	2.8 years
Primary outcome:	stroke or systemic embolism; relative risk with dabigatran 0.91 (110 mg) / 0.66 (150 mg)	stroke or systemic embolism; relative risk with rivaroxaban 0.79 (per protocol) / 0.88 (intention-to-treat (ITT))	stroke or systemic embolism; relative risk with apixaban 0.79	stroke or systemic embolism; relative risk with edoxaban 1.07 (30 mg) / 0.79 (60mg) per protocol, 1.13 (30 mg) / 0.87 (60 mg) ITT

Safety outcome:	major bleeding; relative risk with dabigatran 0.81 (110 mg) / not significantly different (150 mg)	Relative risk of intracranial haemorrhage with rivaroxaban 0.71. Combined major and non-major, clinically relevant bleeding risk is not significantly different to warfarin.	major bleeding; relative risk with apixaban 0.69	major bleeding; relative risk with edoxaban 0.47 (30 mg) / 0.80 (60 mg)

Although these four trials were similar, the RE-LY and ARISTOTLE trials included mostly AF patients with a moderate stroke risk, whereas participants in both the ROCKET-AF and ENGAGE AF-TIMI 48 studies had much higher average CHADS2 scores. Patients with active liver disease were excluded from the RE-LY trial, but not from the other studies, while thresholds for excluding patients with renal insufficiency also differed. The studies differ crucially in outcome definitions: the ROCKET-AF trial, for example, combines major and non-major haemorrhages, whereas the other three take account only of major bleedings as a primary safety point; as to secondary safety outcomes, these are specifically defined only in the ARISTOTLE and ENGAGE AF-TIMI 48 trials.(91-94)

More recently, there have been RCTs investigating the use of potential antidotes to DOACs. Idarucizumab has been approved for the reversal of dabigatran etexilate, based on the RE-VERSE AD trial,(96) while the ANNEXA-A and ANNEXA-R studies have provided preliminary evidence that andexanet alfa can reverse the anticoagulant effect of direct factor Xa inhibitors; this agent is now subject to a phase III trial.(97, 98)

1.6.4.2 Meta-analyses and observational studies

Numerous reviews of clinical trials have evaluated the use of oral anticoagulants in AF patients, including meta-analyses and systematic reviews conducted under the auspices of the Cochrane Collaboration. These systematic reviews and meta-analyses indicated that oral anticoagulants generally reduce the risk of stroke while increasing the risk of major bleeding; odds ratios and relative risks differed, such as and rivaroxaban 20 mg once daily (0.88, 0.74 to 1.03), Apixaban 5 mg twice daily (odds ratio 0.79, 95% confidence interval 0.66 to 0.94), dabigatran 150 mg twice daily (0.65, 0.52 to 0.81), edoxaban 60 mg once daily (0.86, 0.74 to 1.01), reduced the risk of stroke or systemic embolism compared with warfarin. Reviews

have been generally supportive of the routine use of warfarin(99, 100) and of DOACs(101-103) although evidence for the latter is considered less conclusive; multiple scholars have identified knowledge gaps and called for further research, especially into the treatment of patients in clinical practice.(101, 103-105)

The comparisons of DOACs made to date, based on systematic reviews and meta-analyses of clinical trials, have concluded broadly that all DOACs are similarly safe and efficacious for stroke prevention for patients with AF.(106, 107) Potential differences between individual drugs have nonetheless been identified: dabigatran appears to carry a slightly increased risk of (especially gastro-intestinal) bleeding compared to factor Xa inhibitors in general and apixaban in particular, while dabigatran and apixaban seem to be more efficacious than rivaroxaban in preventing strokes.(108-110) These results, however, should be interpreted cautiously since no direct comparisons between individual DOACs have been made and the RCTs having not been designed to do so; given trial protocols have differed, for instance, they have potential implications for the validity and accuracy of any comparative findings.(108, 109)

Observational studies to evaluate the safety and effectiveness of DOACs in clinical practice are have recently become available although the number of published studies based on real-world data remains limited. Major large-scale studies published so far have been conducted either in the US or in EU, and all have used warfarin as a comparator. The lack of long-term safety and effectiveness data is also being addressed by several ongoing registry studies, including the Global Registry on Long-term Oral Antithrombotic Treatment in patients with Atrial Fibrillation (GLORIA-AF), the Global Anticoagulant Registry in the Field (GARFIELD-AF), the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF), and the Dresden DOACs registry.(111-114)

1.6.4.3 Parenteral anticoagulants

The use of parenteral anticoagulants in the United Kingdom, such as indirect anticoagulants, unfractionated heparin (UFH), low-molecular-weight heparins (LMWHs), fondaparinux, is normally restricted to hospital settings. They are sometimes used as a preventive measure in outpatients; LMWHs, for instance, can be administered once daily or bid by subcutaneous injection, without coagulation monitoring,(115) but generally only in the short term because of difficulties associated with the route of administration.

1.7 Treatment with anticoagulant drugs

1.7.1 Treatment indications, duration, and choice of drug

Depending on the indication, anticoagulation therapy can be given in the short term (up to around three months) or the long term. Short-term treatment, which is common in secondary care, often involves parenteral administration, whereas in long-term treatment, mostly provided in primary care, drug therapy is usually administered orally. More careful adaptation to circumstances is required for long-term treatment because patients who have left hospital care need to be more actively involved.

Short-term anticoagulation therapy is most commonly recommended for primary perioperative prophylaxis of thromboembolic events, the current standard of care being LMWHs (e.g., enoxaparin), or fondaparinux.(116-118) For patients undergoing hip or knee replacement surgery, In adult patients, using DOACs, such as dabigatran, rivaroxaban, apixaban, and edoxaban, are recommended in the UK by The National Institute of Health and Clinical Excellence (NICE) for prevention of stroke and P.E in patients with non-valvular AF and treatment and prevention of recurrent DVT and PE.(40) However, only dabigatran, rivaroxaban, and apixaban

are recommended as prophylactic agents against thromboembolism in adults after elective hip or knee replacement surgery. While treatment usually ends at discharge, an extension of prophylaxis for up to five weeks following discharge is recommended.

In high-risk patients, especially those who have had hips or knees replaced(117, 118), LMWHs are also often used to prevent DVTs during pregnancy and for up to six weeks post-delivery, but administration is suspended during the course of labour.(119) Given the availability of alternatives, such as anti-embolism stockings, only those patients whose risk of developing a DVT is medium or high are given pharmacological thromboprophylaxis, with a decision on the use of anticoagulant drugs being based on the assessment of VTE and bleeding risk.(117, 118)

In the short term, patients with VTEs may also receive initial treatment with LMWHs or fondaparinux, followed after discharge by three to six months' oral anticoagulant treatment to prevent a recurrence, usually with warfarin, although DOACs are also now recommended for this.(46, 118, 120) Treating acute or recurrent VTE with warfarin may require high-intensity therapy with a target INR of 3.0 to 4.0, especially if another event occurs during treatment at a standard therapeutic level.(2)

Long-term anticoagulant therapy is recommended primarily for two major cardiovascular conditions, namely artificial heart valves and AF, both of which can disrupt regular blood flow, making cardiac thrombi more likely to develop and thus significantly increasing the risk of thromboembolic events, including stroke.(17)

In patients with mechanical heart valves, warfarin is the drug of choice; anyone having heart valve replacement surgery is considered to be eligible for thromboprophylaxis medication.(17) These patients, like those with recurrent VTEs, may need higher target INRs, depending on the type and position of the implant.(121) Such treatment is usually permanent. A phase II clinical

trial comparing dabigatran to warfarin found that dabigatran should not be used for this indication.(122) The trial RE-ALIGN was prospective and terminated prematurely after the enrolment of 252 patients because of an excess of thromboembolic and bleeding events among patients in the dabigatran group, and a P value of 0.05 or less was considered to indicate statistical significance. (123) or have oral direct factor Xa inhibitors been approved for this indication.

By contrast, warfarin and all DOACs have been approved for both primary and secondary prevention of stroke in AF patients, and such treatment may—in certain circumstances—be lifelong. As it is true for DVT prevention, anticoagulant therapy in AF patients depends on the assessment of risk factors using particular scoring tools,(115, 124-126) designed to justify or exclude the initiation of anticoagulation.(127) Stroke and bleeding risks are optimally assessed, then if the patient's score exceeds a certain threshold, he/she is considered eligible for treatment (see Section 1.4.3).

1.7.2 Medicine related problems

Medicine-related problems (MRP) or drug-related problems (DRP), are an essential topic to address, cause considerable patient harm, morbidity, and mortality, as well as increase health organisation and hospital care costs.(128) An MRP is defined by Pharmaceutical Care Network Europe Foundation as "an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes".(129) Therefore, Al Hamid et al., 2016 (130) stated that three subtypes are considered a medicine-related problems:

- Adverse Drug Events (ADEs).
- Adverse Drug Reactions (ADRs).
- Medication Errors (ME).

The simplest definition of adverse drug events (ADE) was described by Edwards and Aronson (2000),(131) as *"an adverse outcome that occurs while a patient is taking a drug, but is not or not necessarily attributable to it*". Therefore, ADE is related to issues, such as drug interactions with other medicine, disease, or food. It also indicates that a medicine error can lead to ADE that might cause an ADR.

The Directive 2010/84/EU (2010) defined ADR as "a response to a medicinal product that is noxious and unintended.",(132) while European Medicines Agency (EMA) in UK defines medication errors as *"unintended mistakes in the prescribing, dispensing and administration of a medicine that could cause harm to a patient.".*(133) The National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP) in the USA defines medication errors as:

"Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems, including prescribing; order communication; product labelling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.".(134)

Effects resulting not only from the authorised use of a medicinal product at normal doses, but also from medication errors and uses outside the terms of the marketing authorisation, including the misuse, off-label use, and abuse of the medicinal product. This definition builds upon the medication safety experts and the World Health Organization (1972),(135) and others such as Edwards and Aronson (2000).(131) Nevertheless, not all medication errors are considered MRPs if there are no potential risk effects on the patient.(136) There are interactions between these subtypes, and Figure 1.5 shows the relationship between ADEs, ADRs and ME. Figure 1.6

illustrates this relationship and the research evolution of these concepts over time.

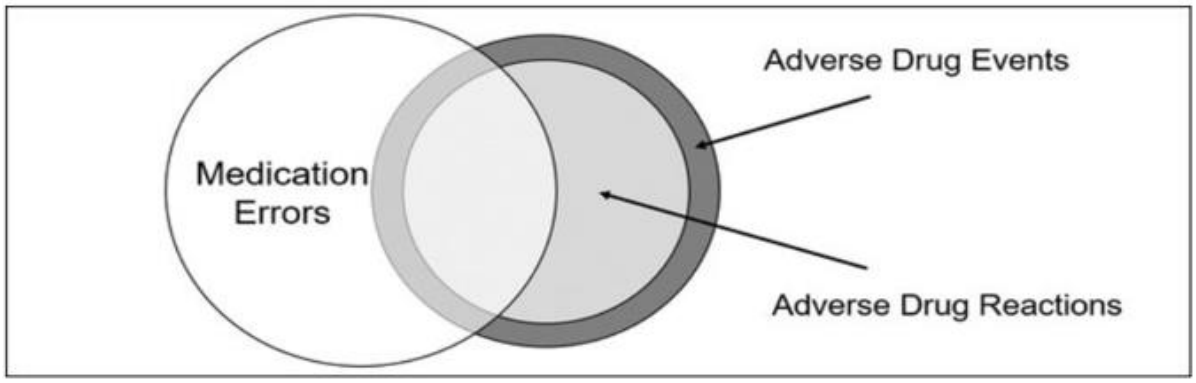


Figure 1.5 Relationships between MEs, ADE and ADR.(137)

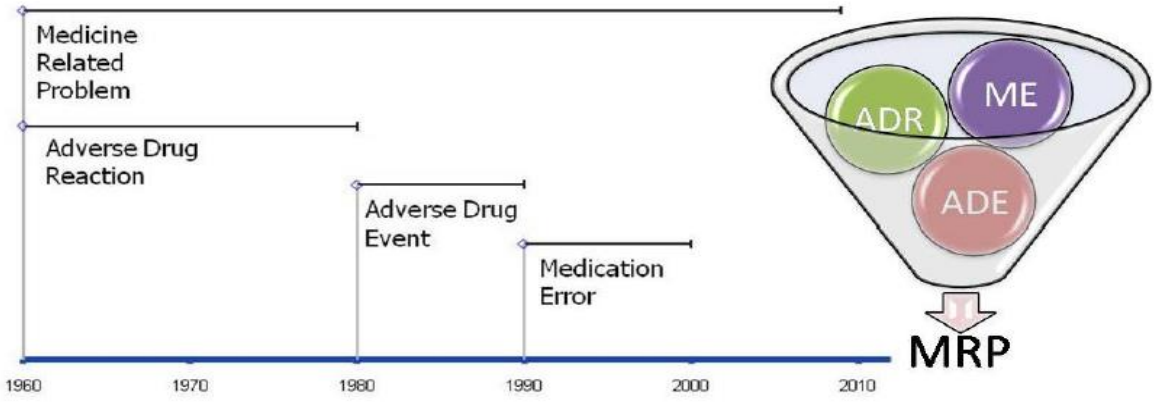


Figure 1.6 Evolution and relationship of medication safety concept (138)

1.7.3 Medication Errors prevalence, economic burden, and classification

Medication error definitions are broad and suggest that errors are preventable at different levels. Cousins et al. (2012) indicate that the highest patient safety incidents reported in healthcare institutions are MEs.(139) In the UK, after reviewing the incidents submitted to the National Reporting and Learning System (NRLS), the former National Patient Safety Agency(140) reported that about 15% of the patient safety incidents in 2004 were medication errors.(141)

Estimating the prevalence of medication errors is challenging due to the varying definitions and classification systems employed. In England and Wales, the National Reporting and

Learning System (NRLS) received about 80,000 preventable medication errors were reported by NHS organisations between 1st October 2013 to 31st March 2014 and cost more than £750 million each year.(139, 142) In addition, preventable medication errors cost the USA approximately $20 billion annually,(143) meaning medication errors are a global issue.

Different approaches can be used to classify medication errors. [144] Classifying medication errors can be based on a psychological theory (see Figure 1.7).(144) Based on the psychological approach, human errors are categorised into mistakes, slips, and lapses.(145) Mistakes are errors in planning actions resulting due to deficiency in the required knowledge or not paying attention to the general rules. Slips are lapses occur during the execution of appropriately planned actions. Slips are action-based errors, while lapses are memory-based errors.

Another approach is to base the classification on the stage in the order of medication use process, such as prescribing, transcribing, dispensing, administration, or monitoring. The further approach reflects the specific types of errors during the stage in the order of medication use process, such as prescribing wrong dose, frequency, or administration route.

Errors may also be classified according to their level of severity as mild, moderate, severe harmful, or lethal errors.

These approaches are not mutually exclusive, and there is no strong evidence to support particular methods of defining or categorising errors, particularly in primary care.(146) The approach taken depends on the setting and the purpose of the classification.

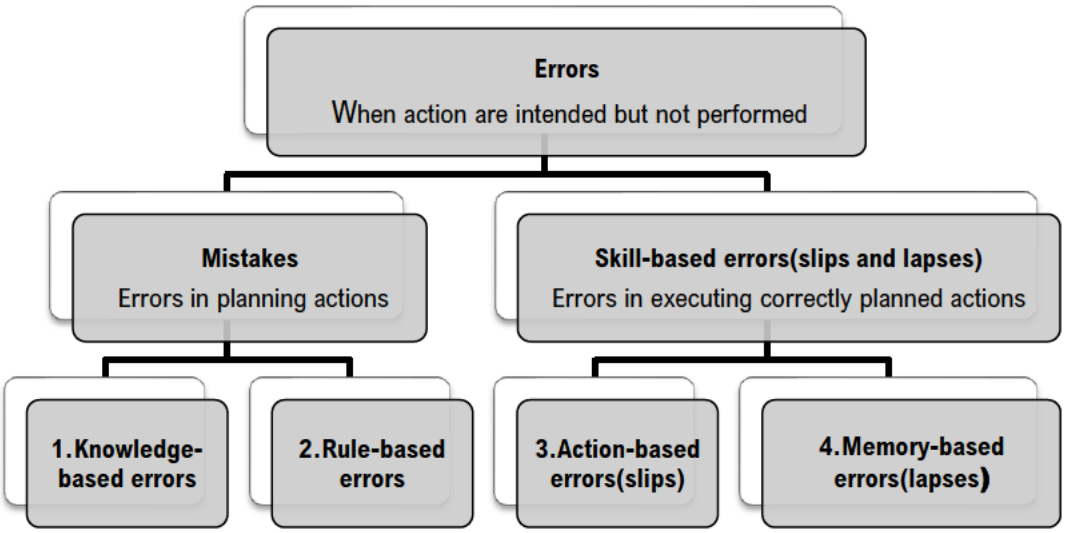


Figure 1.7 The classification of medication errors [146]

1.7.4 Medication Errors Associated with Direct Oral Anticoagulant

Direct oral anticoagulants (DOACs) have been recognised as one of the most commonly concerned drug classes in adverse drug events.(147) The new oral anticoagulant has been linked with potentially preventable adverse events that result in or extend hospital stays.(148) Institute for safe medication practices (ISMP) has published many studies on risks associated with the use of DOACs, such as written duplicate medicine or prescribing, accidental stoppage of therapy, concurrent therapy, dosing errors during the transition of care, and monitoring problems.(149) ISMP has classified DOACs as a high-alert medications that could cause heightened risk or sentinel events and significant harm to the patients if used in error. Thus, the reasons and incidence of errors should be further investigated and no systematic reviews have been conducted to address such serious issue.

A previous study showed that the most recognised type of DOACs medication error in this trust was omitted medicine, which was estimated for about 33% of all incidents, followed by an extra dose as a remote second with 13%. Wrong drug dose and documentation errors were 12% and 9%, respectively.(150)

In a retrospective, hospital-specific, five-year study, Pizza et al. (2011) found that 48.8% (n = 226) of all adverse drug events involved new oral anticoagulant-related medication errors.(147) Missed doses or omitted medicine were the most common in the Piazza's results, with 24.4%. However, it was the second most common error in Cousins & Harris's (2006) study, with about 27% of doses that were reported to be missed.(151) Moreover, a rapid response was issued by the National Patient Safety Agency (NPSA) after reports from the NRLS showed that 21,383 omission incidents occurred between September 2006 to June 2009, of which 23 DOACs omission errors caused death or severe harm, from a total of 95 omissions of other medications that cause serious harm and death.(152)

The findings revealed that prescribing and administrating incidents share the same most common type of error, which is omitted medicine, followed by wrong dose and extra dose for prescribing, besides extra dose and unauthorized drug for administration errors. In the literature review, studies that investigated anticoagulant medication errors did not report the frequency of the types of errors by the stage of medication process.(147, 151, 153, 154) Since most errors were omitted medicine and duplication, the problems are more likely related to medication use process rather than the anticoagulants itself.

Previous studies conducted in the UK indicated that medication errors are frequently encountered with DOAC prescriptions, including inappropriate monitoring, inappropriate dosing, and co-prescribing with LMWH.(155, 156) Similarly, previous studies conducted in Saudi Arabia found significant incidences of underdosing, especially in geriatrics. other findings include inappropriate renal dose adjustments, off-label uses, and high potential drug interactions.(157-159) Such causes of medication errors in Saudi Arabia might be due to the high prevalence of cardiovascular diseases and factors related to the healthcare systems in Saudi Arabia. The following two sections elaborate on both issues.

1.8 Cardiovascular disease in Saudi Arabia

Cardiovascular disease risk factors are prevalent among the Saudi population, including a sedentary lifestyle, obesity, unhealthy diet, dyslipidaemia, hypertension, diabetes, and smoking.(159) Consequently, cardiovascular diseases are among the major causes of mortality in Saudi Arabia. Ischemic heart disease in 2019 was the first leading cause of death among the Saudi population, while stroke was the third one.(160) For stroke, a systematic review estimated its incidence in the Saudi population to be 29 cases for every 100,000 people, while the prevalence was reported to be 186 per 100,000.(161, 162) The prevalence of stroke is significantly lower

in the Saudi population compared to other developed counties, including US and UK, which can be due to the higher percentage of young adults in Saudi Arabia.(163) Despite the relatively lower prevalence, stroke is still among the leading causes of death in the Saudi population, which highlights possible areas of improvement in stroke patients' care in the Saudi health system. For atrial fibrillation, Alamri et al. reported the incidence of atrial fibrillation to be 13.45% among Saudi stroke patients, which is comparable to the findings of previous studies, in which the AF incidence in stroke patients ranged between 11.5% and 23.7%.(164, 165) For thromboembolic events in the COVID-19 era, a recent Saudi study reported the incidence of pulmonary embolism among COVID-19 patients who underwent CT scans to be 22%.(166) These epidemiological data provide an idea about the clinical significance of DOACs use in the Saudi population, considering DOACs place in the pharmacotherapy of non-valvular AF and thromboembolic events as described in section 1.4.2.1.

1.9 Healthcare Systems in the Saudi Arabia and the United Kingdom

1.9.1 Saudi Arabia's Healthcare System

The WHO ranks the Saudi Arabia healthcare system 26th out of 191 healthcare systems.(160) Healthcare services in Saudi Arabia are given free of charge to Saudi nationals and are controlled by the government's Ministry of Health, which is in charge of policy formation and implementation in its institutions, besides auditing the services provided by the private sector. Additionally, the Ministry of Defence, the Ministry of the Interior, the National Guard, and the Ministry of Education provide healthcare services to their personnel.(161) In contrast, the private sector contributes to the provision of healthcare services in Saudi Arabia for a charge or through private medical insurance companies. Healthcare services are classified into three levels: primary care, provided by primary healthcare centres; secondary care, provided in

general hospitals; and tertiary care, provided in speciality institutions such as cardiac, oncology, and organ transplant centres. (163) Figure 1.8 depicts this healthcare setup.

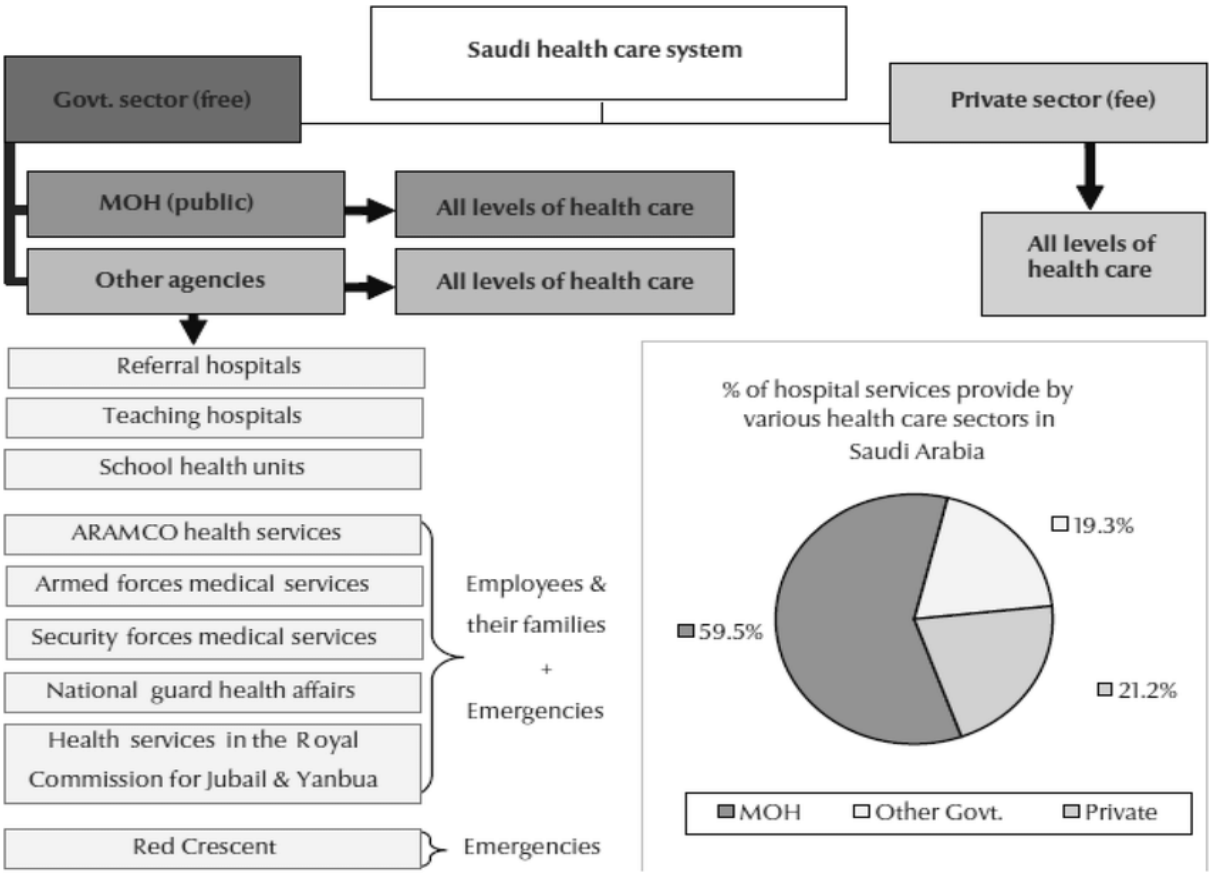


Figure 1.8 Depicts the current organization of the healthcare sectors in Saudi Arabia (163).

For coordination, cooperation, and standardization of practice among different Saudi healthcare sectors, the government established the Council of Health Services, which is led by the Minister of Health and includes representatives from various government health sectors as well as the private sector.(163) The Saudi healthcare system has several obstacles, including a paucity of local healthcare workers and a lack of unified computerized national health information systems.(163) Furthermore, during the Hajj or Umrah season, the Ministry of Health offers healthcare services to millions of tourists and pilgrims worldwide.(164)

The Ministry of Health in Saudi Arabia distributes free medications through pharmacies in hospitals, while primary care centres' prescriptions are dispensed free of charge through private community pharmacies.(165) The Pharmaceutical Care Department in each regional Health Affairs supervises the Ministry of Health-affiliated pharmacies in their jurisdiction.

1.9.2 United Kingdom's Healthcare System

The UK's healthcare system is one of the most well-known healthcare systems in the world, with the WHO ranking it 18th out of 191 nations.(160) The Commonwealth Fund evaluated 11 industrialized nations' healthcare systems based on health system quality, efficiency, access to treatment, equity, and healthy lives and named the UK healthcare system the best among ten other developed nations in 2013.(166) However, healthcare in the United Kingdom is a devolved topic, which means that England, Northern Ireland, Scotland, and Wales each have their own healthcare systems due to distinct regional policies and goals.(167) In 1948, the National Health Service (NHS) was formed in order to give free healthcare to those who did not have the resources to pay for themselves.(168)

Currently, all inhabitants of England are entitled to free healthcare. In contrast, around 13% of the population has private medical insurance, which mostly offers access to acute elective treatment in the private sector. (169) The Department of Health (DOH) is the principal government department in charge of developing and implementing NHS policy. (169, 170)

Since 2013, a new healthcare system has been developed in the UK; all NHS trusts are intended to become foundation trusts by 2014. (171) Some organizations, such as Primary Care Trusts (PCTs) and strategic health authorities (SHAs), have been replaced with the new Clinical Commissioning Groups system (CCGs). CCGs have taken over many of the functions of SHAs and PCTs, as well as some new ones. The Care Quality Commission is in charge of improving patient safety and analyzing and judging the level of safety and quality of care given by health

and social care providers. The primary goal of the new healthcare system is to enhance quality and healthcare outcomes, which should result in increased patient safety. Figure 1.9 depicts the framework of the new healthcare system in the UK.(172)

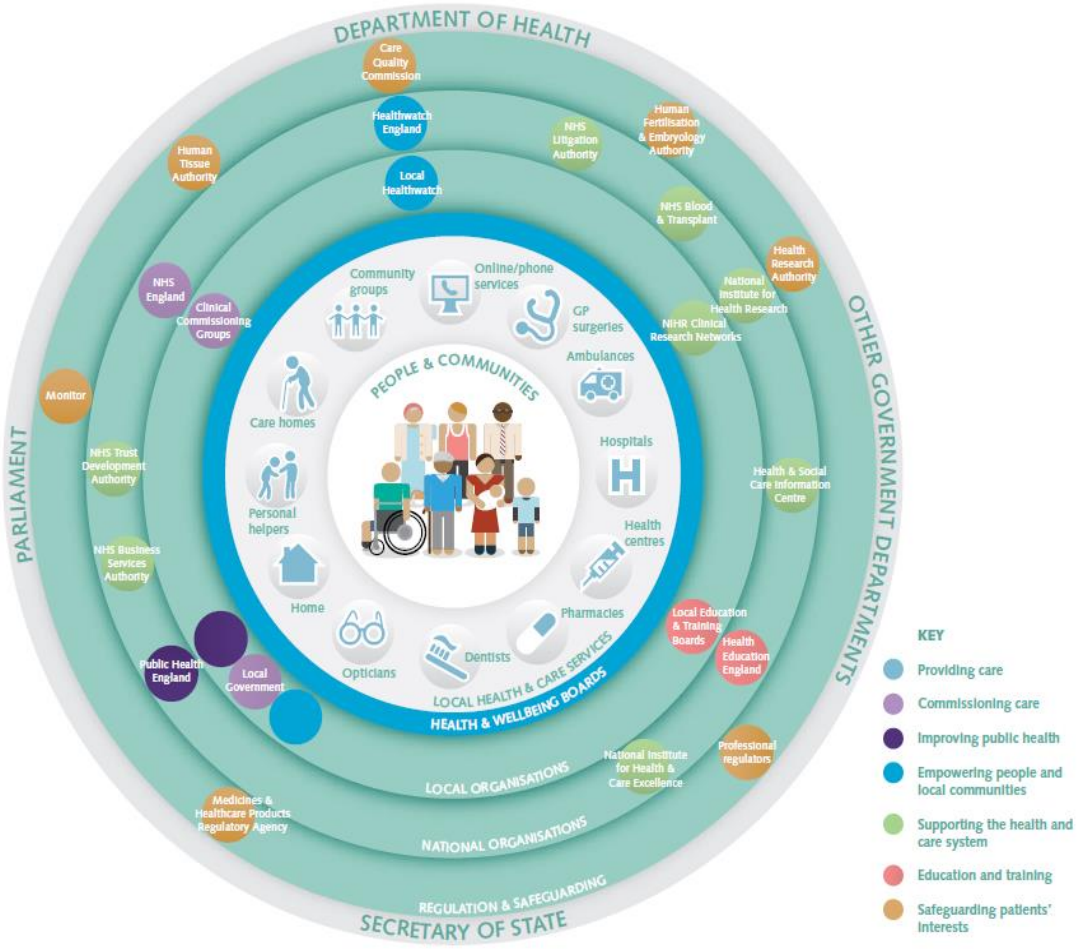


Figure 1.9 A new healthcare framework in the United Kingdom (172)

1.10 Aim of the thesis

The overall aim of this thesis is to explore the epidemiology and contributory factors related to medication errors associated with DOACs.

1.11 Objectives of this thesis

1. Identify the epidemiology (incidence and/ or prevalence) of medication errors associated with DOACs along with their factors contributing to errors associated with DOACs.
2. Review the use of theoretical frameworks in research related to identifying causative factors and interventions to minimise medication errors associated with DOACs.
3. Explore views, experiences, and contributory factors related to DOACs medication errors from the perspectives of healthcare professionals and patients.

1.12 Research Questions

1. What is the prevalence of medication errors associated with novel oral anticoagulants in adult patients?
2. What are the key factors associated with errors while using novel oral anticoagulants in adult patients?
3. What are the views, experiences, and contributory factors related to DOACs medication errors from the perspectives of healthcare professionals and patients?

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Chapter 2. Methodology

Chapter overview: This chapter describes and provides an overview of the theoretical and methodological approaches utilised for this PhD. In addition, it describes and justifies the study designs and research methods used to answer the research questions.

2.1 Introduction

Methodological techniques applied to address the research questions along with the justifications and ethical issues are explained in this chapter. The structure of the methodology for this project is illustrated in Figure 2.1.

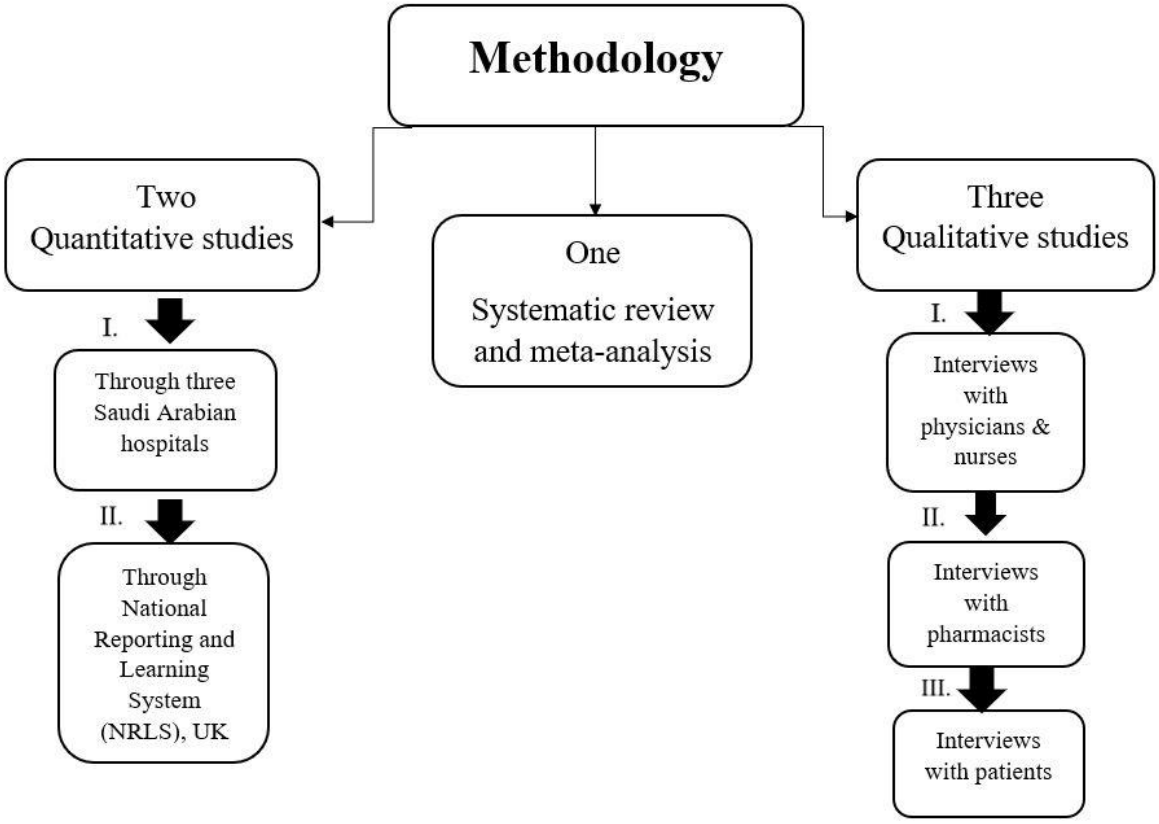


Figure 2.1 Structure of methodology

In this thesis, mixed-methods approach using series of quantitative and qualitative studies was utilised to explore the extent as well as the experiences, behaviours, and perspectives of the healthcare professionals (HCPs), and patients around medication errors associated with DOACs.

Before conducting the mixed-method studies, a systematic review and meta-analysis was performed to estimate both the prevalence of medication errors in clinical practice and to identify the contributory factors associated with DOACs in adult patients employing the reason's accident causation model. The search of scientific literature was conducted between January 2008 up to September 2020.

The systematic review and meta-analysis were followed by part two of the thesis, which consisted of two quantitative studies: the first one aimed to analyse data from secondary care of hospitals in Saudi Arabia for the last 10 years, while the second study aimed to analyse the incident reported data from the National Reporting Learning system (NRLS) in UK between 01 January 2017 to 31 December 2019. Part three of the thesis involved three qualitative studies. The first study involved semi-structured interviews with healthcare professionals, including physicians and nurses who have a role in the management, prescriptions, and administration of DOACs medications. The second study included semi-structured interviews with pharmacists to explore the factors contributing to medication errors. Finally, the third qualitative study included semi-structured interviews with adult patients aged over 18 years old to investigate the nature of causes and factors contributing to medication errors associated with DOACs by semi-structured interviews via Zoom videoconferencing.

The researchers obtained ethical approval from the University of Birmingham Research Ethics Committee (ERN_20-0551) on 6/11/2020 (Appendices 2.1). In addition, three ethical approvals from all of the three participating hospitals: National Guard Hospital in Riyadh (SP20/212/R)

(Appendices 2.2), King Fahad Military Medical Complex in Dhahran (AFHER-IRB-2020–015) (Appendices 2.3) and King Fahad Central Hospital in Jazan (164/2020) (Appendices 2.4) were obtained on 3/06/2021. All participants signed informed consent before the study enrollment (Appendices 2.6 and 2.7).

The following section reviews the perspectives on human error and analyse the theories and methods developed and applied over the years. These theories and methods have sought to improve the understanding of what human error is and how and why it occurs to facilitate the prediction of errors and use these to support patient safety.

2.2 Theoretical framework

There are several human error frameworks relevant to the study of medication safety. The Software, Environment, and Liveware (SHEL) model, for example, is the conceptual model of human factors used to study safety in aviation.(1, 2) Furthermore, the SHEL model has been used to understand and promote safety in operating theatres or emergency rooms.(3) The SHEL model components include: the software, including procedures, protocol, and training; the hardware, including machines and medical instruments; the environmental factors that can influence errors microsystems, including an operating theatre, wards, and consultation room; and the liveware including human factors: doctor, nurse, and other health care professional or patient.(3) The SHEL model can assist in identifying and examining an individual's relevant psychological and behavioural elements (Human Factors) and the interactions between an individual and other components in the system.

Furthermore, the Systems Engineering Initiative for Patient Safety (SEIPS) is another model suggested to be relevant to human factors. This model was designed by the US Institute of

Medicine (IOM) with the application of systems engineering concepts and human factors. It was used to provide a comprehensive view of the whole system instead of focusing on one aspect of the work system. The model is used to frame the design and analysis of the research,(4) for example, the SEIPS model has been applied to healthcare delivery settings, including paediatric hospitals, intensive care units (ICUs), cardiac operating rooms, primary care clinics, outpatient surgery centres, and home health care nursing, and to evaluate multiple health information technologies, such as the computerized provider order entry (CPOE), bar-coded medication administration, electronic health records (EHRs), smart infusion pumps, and virtual ICU technology.(5) The model has been criticized as being too descriptive and does not offer researchers specific guidance on how to use it.(6)

Another model is the Yorkshire Contributory Factors Framework (YCFF), a tool that was developed by Lawton et al. in 2012 to be specific to the healthcare domain. The YCFF is used for optimizing, learning, and addressing the causes of patient safety incidents, as well as to help the clinicians, risk managers, and patient safety officers in the identification of the contributing factors of incidents. (7) The YCFF includes sixteen evidence-based domains and is classified into four main categories; active failures, local conditions, situational factors and latent factors (Figure 2.2 and Table 2.1).

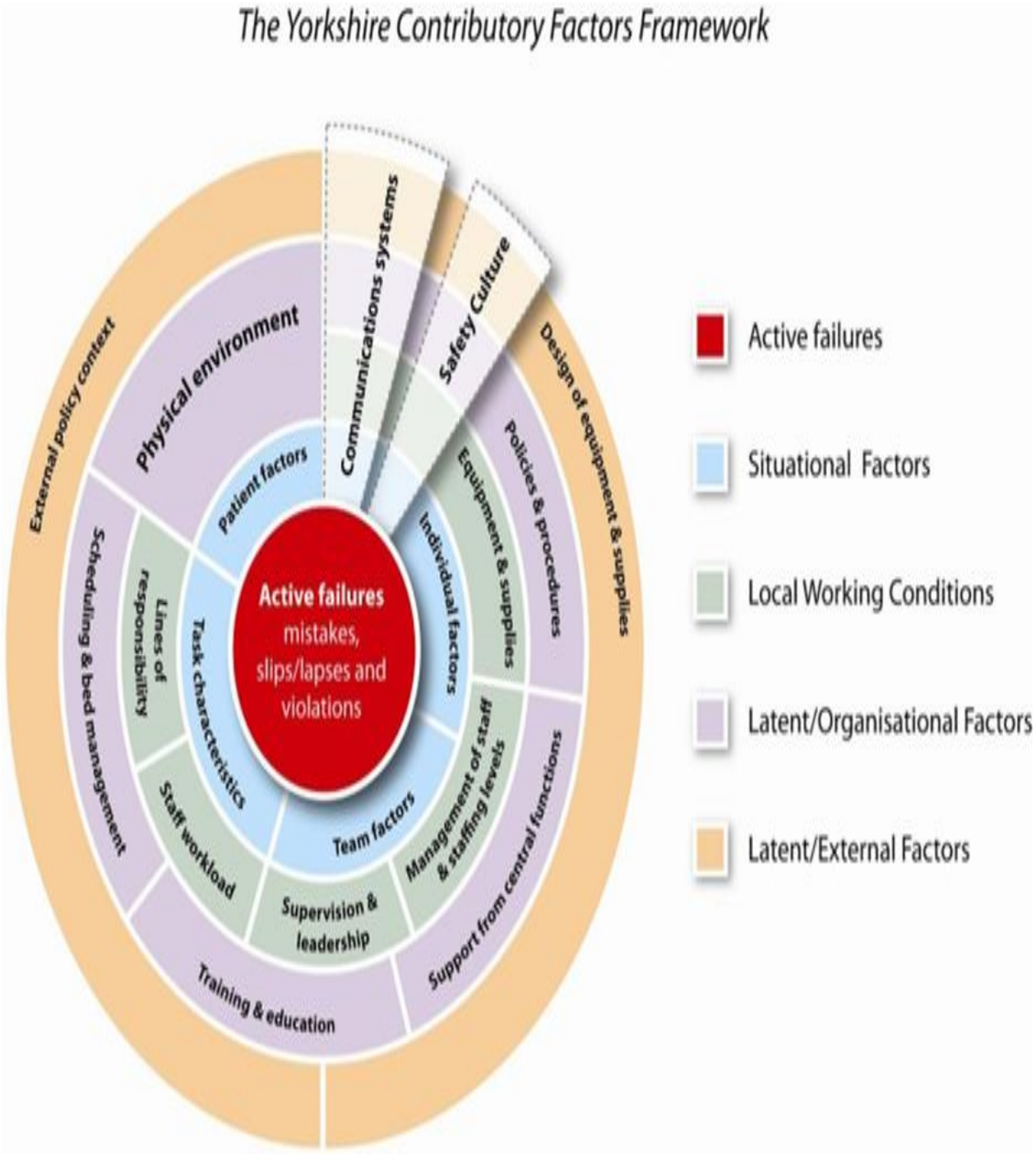


Figure 2.2 The Yorkshire contributory factors framework to patient safety incidents(7).

Table 2.1 The Yorkshire contributory factors framework to patient safety incidents (7).

Factor	Definition
Active failures	Any failure in performance or behaviour (eg, error, mistake, violation) of the person at the 'sharp-end' (the health professional)
Communication systems	Effectiveness of the processes and system in the place for the exchange and sharing of information between staff, patients, groups, departments, and services. This include both written (e.g., documentation) and verbal (e.g., handover) communication systems
Equipment and supplies	Availability and functioning of equipment and supplies
External policy context	Nationally driven policies/directive that impact on the level and equality of resources available to hospitals.
Design of equipment and supplies	The design of equipment and supplies to overcome physical and performance limitations
Individual factors	Characteristics of the person delivering care that may contribute in some way to active failures. Example of such factors include inexperience, stress, and personality attitudes.
Lines of responsibility	Existence of clear lines of responsibility clarifying accountability of staff members and delineating the job role
Management of staff and staffing levels	The appropriate management and allocation of staff to ensure adequate skill mix and staffing levels for the volume of work
Patient factors	Those features of the patient that make caring for them more difficult and therefore more prone to error. These might include abnormal physiology, language difficulties, personality characteristics (e.g, aggressive attitude)
Physical environment	Features of the physical environment that help or hinder safe practice. This refers to the layout of the unit, the fixtures and fittings and level of noise, lighting, temperature
Policy and procedures	The existence of formal and written guidance for the appropriate conduct of the work tasks and processes. This can also include situations where procedures are available but contradictory, incomprehensible or of otherwise poor quality
Safety culture	Organizational value, beliefs and practices surrounding the management of safety and learning from error
Scheduling and bed management	Adequate scheduling to manage patient throughout minimise delays and excessive workload
Staff workload	Level of activity and pressure on time during a shift
Supervision and leadership	The availability and equality of direct and local supervision and leadership
Support from central function	Availability and adequacy of central services in support the functioning of ward/unit. This might include support team from information technology and human resources, portering services, estates or clinically related services such as radiology, phlebotomy, pharmacy.
Task characteristics	Factors related to specific patient related tasks which may make individuals vulnerable to error
Team factors	Any factors related to the working of different professionals within a group which they may be able to change to improve patient safety
Training and education	Access to correct, timely and appropriate training both specific (e.g., task related) and general (e.g., organization related)

2.3 Human error theory

This section provides an overview of the concept of errors, types of errors, and theories of human errors in healthcare.

Errors were classified as active failures and latent failures. The active failures are associated with slips, lapses, mistakes, and violations. The latent failures are related to the environment and work conditions that could facilitate the failures. As per this model, active failures do not arise in isolation but occur as result of error producing condition, that developed at various level within the system. In the clinical settings, this can be a part of the patients, the tasks, team, individual healthcare professional, or even the environment.(7)

The theory of human error can help researchers and the healthcare professionals to understand why medication errors could occur and develop prevention strategies. Human error theory allows for understanding human errors from a person approach or a system approach.(8) Human error is defined as any action or misconduct by human who fails to complete or accomplish the task as anticipated. Taking into account the reasons and the origins of human error, human errors can be classified into three levels, conceptual, contextual, and behavioural. (9) Additionally, if errors are not intended but result from a deviation from safe practice, it is termed a violation. Furthermore, types of errors are classified as active and latent. An active error is the event that results in harm and causes catastrophe, and the latent error is the one that is inherent in the system, such as administrative decisions, system design, quality of equipment and supplies.(10)

The limitation of human error can be viewed into two approaches: the person approach focuses on individual errors, and the system approach focuses on the conditions under which individuals work.(9)

2.3.1 Person approach of human error

The person-centred approach focuses more on how individual errors occur by humans who are limited by cognitive aspects, such as weakness and forgetfulness.(11) According to the reason accidental causation model, the approach focused on unsafe acts, such as slips, lapses, errors, and procedural violations of people at the sharp end, like nurses and physicians (Figure 2.3).(9) It views these unsafe acts as arising from aberrant mental processes, such as forgetfulness, inattention, poor motivation, carelessness, negligence, and recklessness. Reason's model suggests that errors occur from unsafe acts and individual errors, not from the system environment.(9)

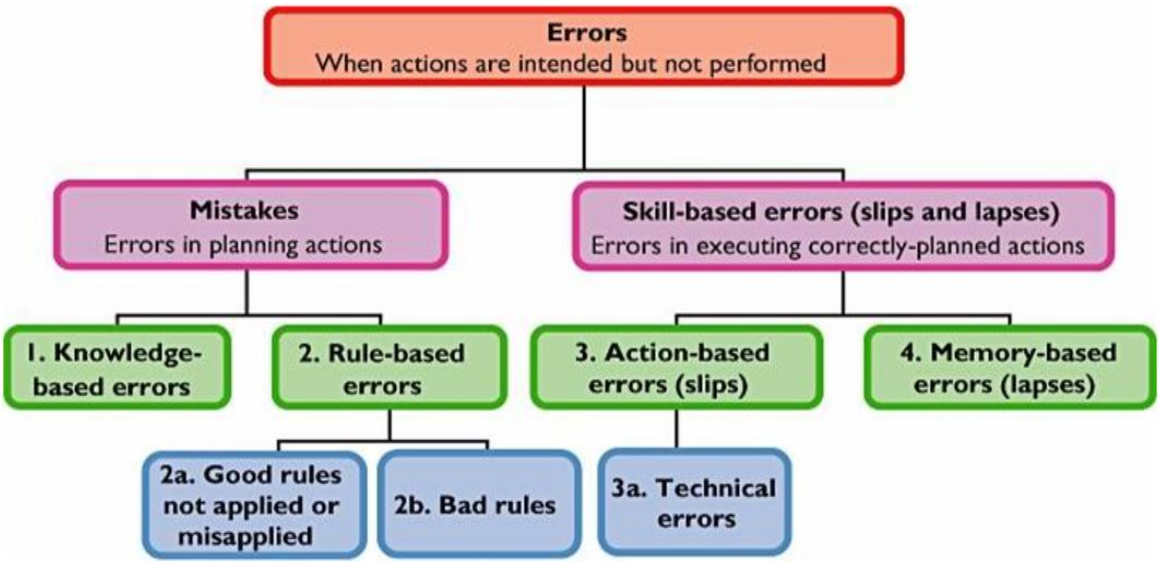


Figure 2.3 A classification of types of medication errors (Adopted from Aronson et al, 2009)

2.3.2 System approach of human error

This approach describes the environment under which an individual work, and attempts to build hinders, and explains how and why the barriers fail.(9) Reason's system approach indicates that errors might happen as a consequence rather than a cause, meaning we cannot change the human conditions, but we can change the environment and the conditions under which human work.(9)

2.4 The 'Swiss Cheese' accident causation model (SCM)

Furthermore, the 'Swiss Cheese' accident causation model (SCM) was first developed by James Reason, and it was used in healthcare system during the examination of health care errors and its management.(12) This model illustrates the cause, process, and consequences of an accident; furthermore, it provides an analysis of the development of an accident. The SCM suggests that in the development of such accidents, three stages are developed: (1) the organizational factors, which includes strategic decisions, managing and auditing; (2) the local workplace factors, which includes insufficient training, poor communications, and unworkable procedures; (3) the unsafe acts. All three stages are illustrated in Figure 2.4.(13)

- **Explanation and justification for choice of "theoretical framework".**

Reason's accident causation model has been very commonly used by previous studies to inform investigation on the causes of medication errors (14). This model stresses on the criticality of safety procedures in the organisation including staff training, automated systems including warning systems, unsafe acts, such as active failures, unsafe conditions, as well as the latent and organisational failures to be studied in the context of medication errors (15). This model

focuses on the system or environment in which the errors occur rather than the practitioners (16). This model is a constructive way to identify the causes of adverse events and strengthen the study's theoretical underpinning support. Application of this model and subsequent identification of incident causes can stimulate the basis for future interventions in minimising medication incidents. For this reason, this was chosen for the research.

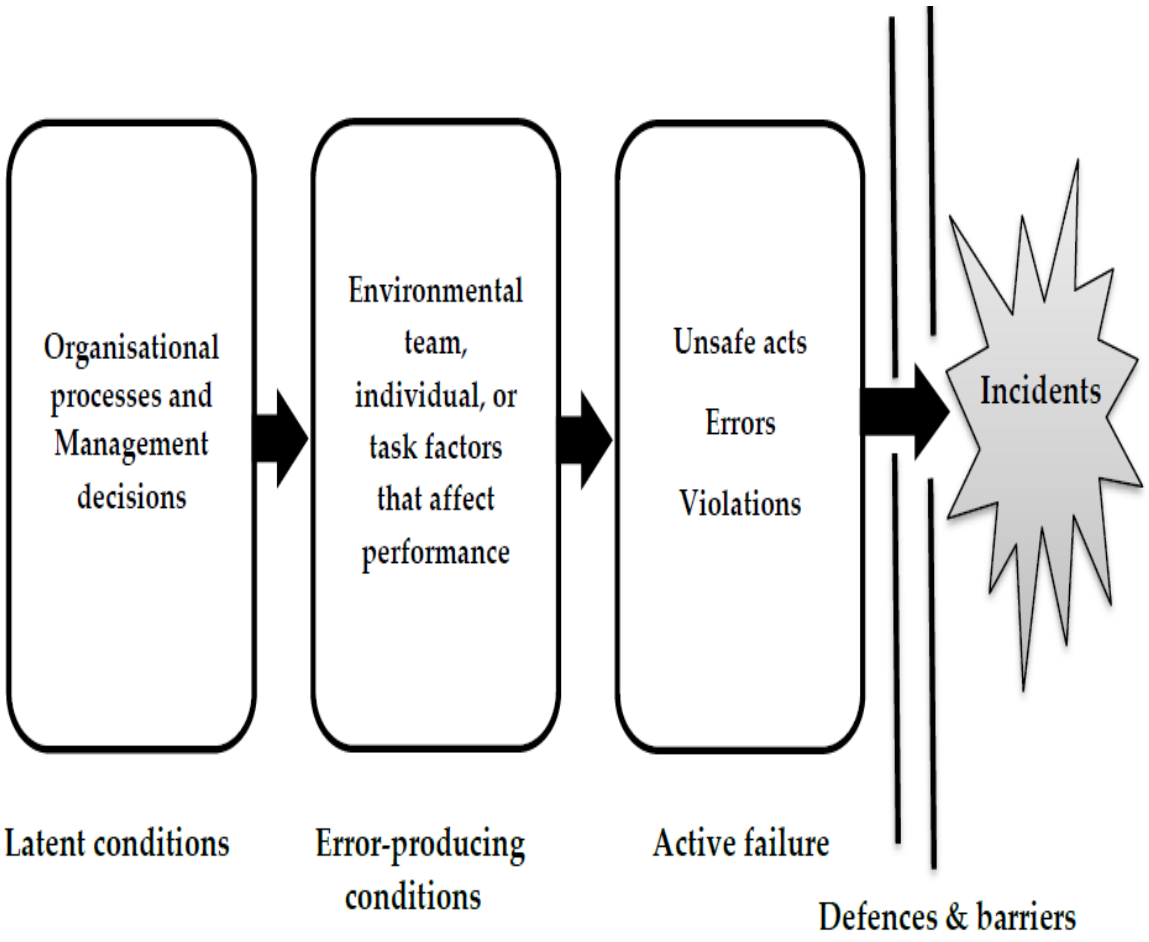


Figure 2.2 The organisational accident causation model (adopted from Reason, 2005) (13).

The SCM assists in understanding both active failures and latent conditions (Figure 2.5). The principle is based on multiple layers or slices of Swiss cheese representing the barriers of the errors and the gaps representing the active failures (unsafe acts) and latent conditions. Active failures or unsafe acts committed by humans who are in direct contact with patients or system, which can be in the form of slips, lapses, fumbles, mistakes, and procedural violations.(17) The latent condition are the potential contributing factors occur at any level of the organization or system, and it is difficult to detect, such as lack of training, poor design, and inadequate supervision, unnoticed defects in manufacturing.

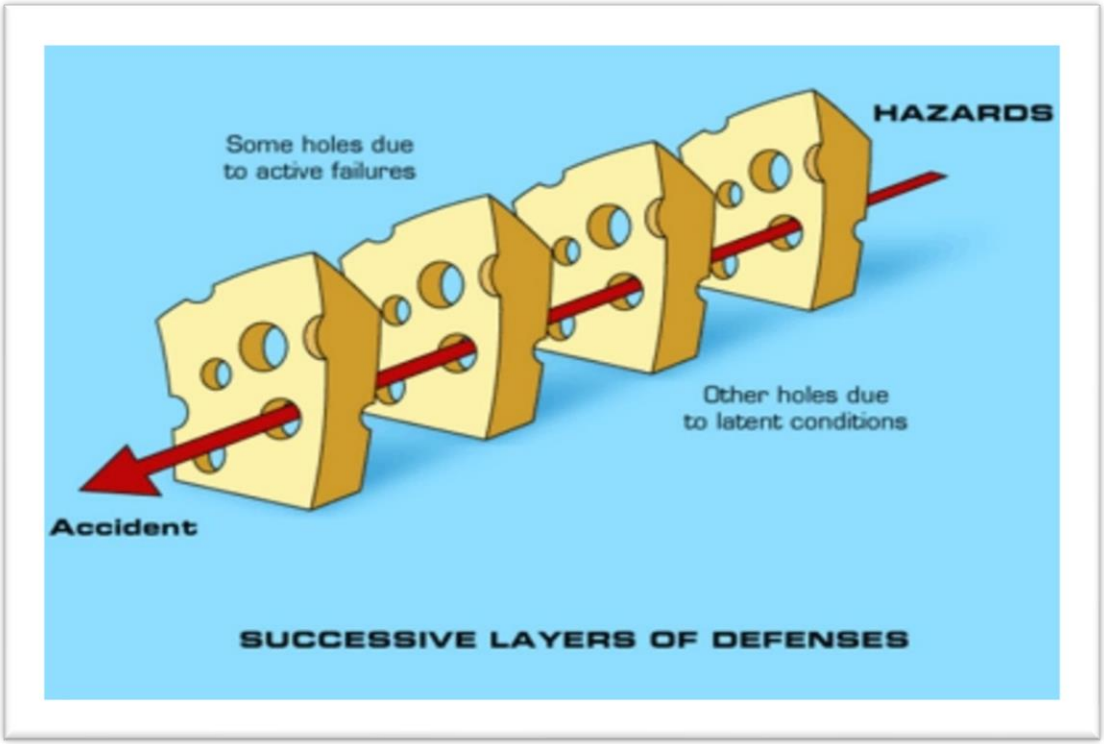


Figure 2.3 The Swiss Cheese model (Adopted from Reason, 2008) (17).

2.5 Study design

2.5.1 Systematic literature review

A systematic literature review is a systematic approach to collecting, critically evaluating, integrating, and presenting findings from multiple research studies on a research question, or topic of interest.(18) It evaluates the quality level and the magnitude of existing evidence on a research question or topic of interest. The systematic literature review should adhere to standardized methodologies or guidelines in systematic searching, filtering, reviewing, critiquing, interpreting, synthesizing, and reporting the findings from multiple articles on a topic or domain of interest.(18)

The main step to conduct systematic literature review is posing a research question based on framework such as PICOS or SPIDER. The research question can be framed in terms of the PICO system, including (P) population, (I) intervention, (C) comparator and (O) outcomes of the studies included in the review. The results are presented in a PRISMA flowchart diagram, as shown in Figure 2.6.(18) This is followed by setting a clear inclusion/exclusion criterion, identifying the relevant work by doing an electronic search with selected databases, study selection, data extraction, assessing the quality of studies, and summarizing the evidence, and interpretations of the findings. Specifying the methods in advance and minimizes the risk of bias.(19)

Cochrane Collaboration guides researchers on how to conduct systematic reviews that are more useful to stakeholders, whether policy decision makers, consumers, or health professionals. The Cochrane Handbook for Systematic Reviews of Interventions introduces the Cochrane approach and informs the reader with a step-by-step guide on how to plan and prepare a

systematic review and offers more in-depth description of the meta-analytical methodology, including the question and inclusion criteria development (questions should be describing participants, interventions, comparisons, and outcomes), the search, the data collection, and the data analysis.(20)

To ensure methodological rigor and quality for the systematic literature review, an evidence-based guide called Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) was created by the international network of health-based collaborators and provides the framework for systematic literature review. It consists of a checklist and flowchart intended to be used as tools for authors seeking to write systematic literature review and meta-analyses. This research aims to address the gap.

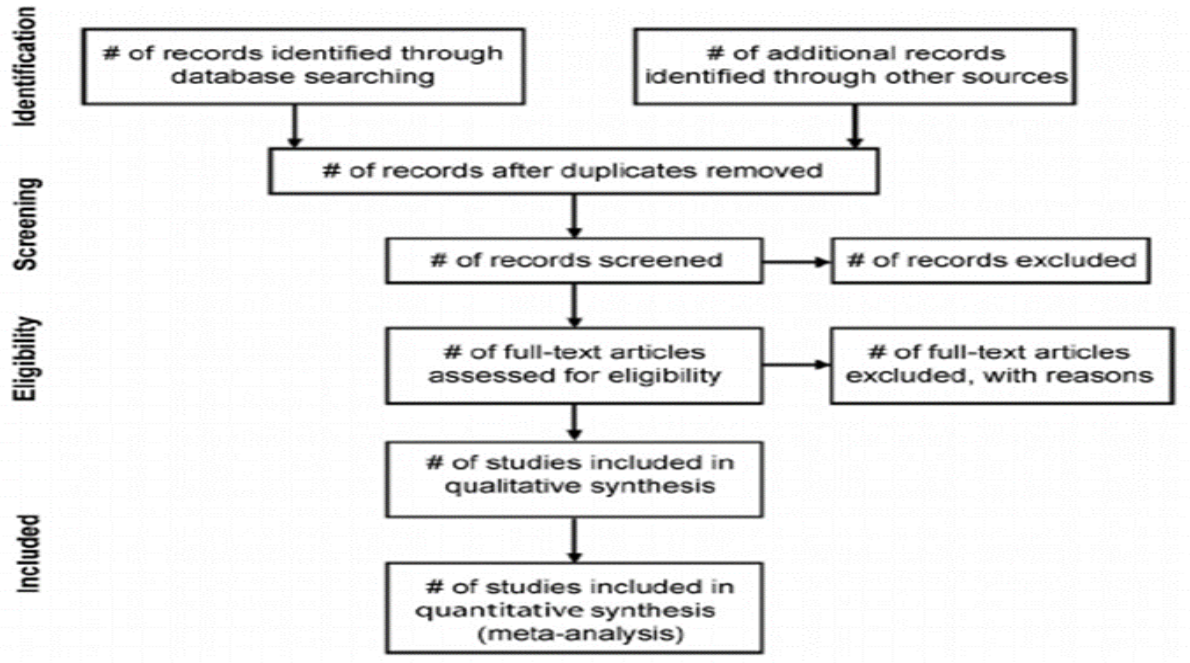


Figure 2.4 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram (21).

2.5.2 Qualitative, Quantitative research and mixed methods

Methodology textbooks classify research designs into three main categories: qualitative, quantitative, and mixed-methods. Qualitative research aims to understand experiences and attitudes of study participants, including patients, the community, or healthcare workers. The methods answer the questions of 'what, 'how' or 'why' of a phenomenon rather than 'how many' or 'how much', which are answered by quantitative methods.(22) It mainly generates texts as data for analysis rather than numbers.(22)

Quantitative research methods aim to examine the connotation between the independent variable and a dependent or consequence variable in a population. The research design can be either a descriptive study, which establishes only the relations between variables, or experimental, which establishes interconnection.(23)

There are stringent criteria to ensure reliability and validity in quantitative research. This also includes statical methods of analysis to check measures of validity and reliability. The qualitative research, however, adopts a more flexible approach. Some strategies used to maximise validity and reliability in qualitative research includes triangulation, audit trail, member check, respondent validation, reflexibility, contextualization, and thick description.(24) Sometimes, both qualitative and quantitative approaches can be adopted in a mixed-methods study. Mixed-methods studies combine a number of data collection methods.(25) Table 2.2 shows the main difference between quantitative and qualitative research studies.

This thesis adopted both quantitative and qualitative methods to explore the epidemiology, experiences, behaviors, and perspectives of the participants involved in the medication errors associated with DOACs at the study site. The first quantitative data included the evaluation of

routinely collected data from three hospitals in Saudi Arabia, which contained data from Saudi Food and Drug Authority pharmacovigilance database and local incidents reporting system from two tertiary care hospitals. The errors were reported between January 2010 and December 2020, and the hospital-based data were retrieved from an electronic medical record system to analyse all the DOACs associated with medication errors. The second quantitative study included evaluating all the routinely collected retrospective patient safety incident reports through the NRLS in the UK between 01 January 2017 and 31 December 2019 at all clinical settings to analyse all the DOACs associated with medication errors. It collates the occurrence of all events that have resulted in or have the potential to result in patient safety incidents.(26) Qualitative studies were undertaken as part of this PhD study to identify the views, experiences, and contributory factors related to DOACs medication errors from the perspectives of healthcare professionals and patients. These included qualitative data from tertiary care hospitals in three different regions in Saudi Arabia through the analysis of semi-structured interviews of online videoconferencing with healthcare stakeholders, including physicians, nurses, and pharmacists who work at the research site. Semi-structured interviews with patients were also conducted. The questions included views, experiences, and perceived factors contributing to medication errors. Interviews were transcribed verbatim and analysed thematically using MAXQDA Analytics Pro 2020 (VERBI Software).

Table 2.2 The differences between quantitative versus qualitative research (adopted from Johnson,2008)(27).

Criteria	Quantitative Research	Qualitative Research
Purpose	To test hypotheses, look at cause & effect, & make predictions.	To understand & interpret social interaction.
Group studies	Larger & randomly selected.	Smaller & not randomly selected.
Variables	Specific variables studied.	Study of the whole, not variables.
Type of data collected	Numbers and statistics.	Words, images, or objects.
Form of data collected	Quantitative data based on precise measurements using structured & validated data-collection instruments.	Qualitative data such as open- ended responses, interviews, participant observations, field notes, & reflections.
Type of data analysis	Identify statistical relationships.	Identify patterns, features, themes.
Objectivity and Subjectivity	Objectivity is critical.	Subjectivity is expected.
Role of Researcher	Researcher biases are not known to participants in the study, & participant characteristics are deliberately hidden from researcher (double blind studies).	Researcher biases may be known to participants in the study, & participant characteristics may be known to the researcher.
Results	Generalizable findings that can be applied to other populations.	Particular or specialized findings that is less generalizable.
Scientific Method	Confirmatory or top-down: the researcher tests the hypothesis and theory with the data.	Exploratory or bottom–up: the researcher generates a new hypothesis and theory from the data collected.
View of Human Behaviour	Regular & predictable.	Dynamic, situational, social, & personal.
Most Common Research Objectives	Describe, explain, & predict.	Explore, discover, & construct.
Focus	Narrow-angle lens; tests a specific hypotheses.	Wide-angle lens; examines the breadth & depth of phenomena.
Nature of Observation	Study behaviour under controlled conditions; isolate causal effects.	Study behaviour in a natural environment.
Nature of Reality	Single reality; objective.	Multiple realities; subjective.
Final Report	Statistical report with correlations, comparisons of means, & statistical significance of findings.	Narrative report with contextual description & direct quotations from research participants.

2.6 Qualitative methodology

Qualitative research focuses on understanding the research query as an idealistic or humanistic approach and depends on the participants to provide in-depth responses to questions about how they have constructed or understood their experience. It is based upon non-numeric data in form of words, including all types of textual analyses, such as content, conversation, discourse, and narrative analyses. This method is used to understand people's beliefs, attitudes, experiences, interactions, and behaviour.(28)

Interviews are the commonly used method of collecting data in qualitative research; in-depth interviews enable researchers to explore the individual perspective and analyse the participants' needs, predicaments, experiences, expectations, and understandings.(29, 30)

The data collection in qualitative research involves conversations between the researcher and interviewee, which have an overall purpose prompted by the research purposes but are strongly guided by the interviewee's perceptions, experiences, and opinions.(31)

The design of semi-structured interviews includes interview guide development, recruitment of participants, participant information sheet (PIS) (Appendices 2.8 and Appendices 2.9), and obtaining consent form. In my qualitative study, participants were provided with a participant information sheet and consent forms to be read and signed. Once the consent forms are returned, the researcher arranged for a suitable date and time for the interviews. The semi-structured interviews were conducted virtually by Zoom videoconferencing as a platform due to limitations caused by the COVID-19 pandemic. At the beginning of each interview, the researcher provided a general brief information about the study and the nature of the questions.

2.6.1 Recruitment of participants

Participants were interviewed by the primary researcher (AA), who took the field notes to ensure the context of the discussions was recorded. The interviewer introduced himself and conducted the interview to identify current practices and experiences. The interviews were guided by topic guides specifically designed for the purpose (HCPs interview topic guide version 0.1 & patients' interview topic guide version 0.1). Questions were supplemented with several prompts to trigger discussions with the interviewees. Each interview was conducted for 30 minutes up to 45 minutes. The interviews were recorded and transcribed verbatim.

The researcher prepared an interview topic guide based on the current literature and validation in the research team and collaborators. It included a list of questions and topics that needed to be covered during the conversation in a particular order. Pilot interviews were conducted to validate the interview questions and make any amendments when necessary.

Once the consent forms were returned, the researcher arranged for a suitable date and time for the interviews to take place. Interview schedules were reviewed by experts including healthcare professionals and patient representatives to ensure that they met the objectives.

2.6.2 Data collection and analysis

The audio recordings were transcribed verbatim, anonymised, and cross-checked against the recording and the researcher's written notes. A sample of transcripts were read and cross-checked against the recordings by two of the supervisors (VP) and (ZJ) who advised for any required changes to the transcripts to ensure that all recordings were accurately transcribed.

- **Explanation and justification for the choice of the thematic analysis**

Data were analysed using the thematic framework method. Thematic analysis is widely recognised as a unique and valuable method, alongside other more established qualitative approaches like grounded theory, narrative analysis, or discourse analysis. Thematic analysis is an accessible, flexible, and increasingly popular qualitative data analysis method (32). Thematic analysis can be utilised in systematically identifying, organising, and offering insight into patterns of meaning (themes) across a dataset (33). By focusing on meaning across a dataset, thematic analysis allows the researcher to make sense of collective or shared meanings and experiences. Thematic analysis is a flexible method that enables the researcher to focus on the data in numerous different ways. With thematic analysis, one can legitimately focus on analysing meaning across the entire dataset or in-depth examine one particular aspect of a phenomenon. Researcher can also examine the latent and underlying meanings, presumptions, and concepts behind what is explicitly stated or report the overt or semantic meanings in the data. Thematic analysis can take on a variety of shapes, making it suitable for a wide range of research questions and topics. For this reason, this was chosen for the research.

Transcripts of the first few interviews were coded into different codes, and each section of the text was assigned to the relevant code. These codes were refined by analysing the rest of the interviews. To avoid ignoring any data, add an ‘other’ code under each theme for any data that did not fit with any code. To facilitate the coding process, the data was analysed using MAXQDA Analytics Pro 2020 (VERBI Software) for qualitative analysis. The pilot interviews were not included in the analysis. Before producing the report, the analysis was validated by the supervisor (VP) to check the main researcher's coding and verify the outcomes and any disagreements will be discussed and resolved.

Generated codes were gathered into themes and a coding framework and used for summarising emerging themes. This coding framework was further refined by analysing the rest of the interviews.

An iterative process of data analysis was used to identify and categorize concepts into key themes and their relationships with each other. The textual material was coded in terms of these categories. The primary researcher (AA) coded the transcribed data for further processing and pattern identification, followed by duplicate sample analysis by the study supervisors (VP, ZJ). Disagreements about coding were resolved through discussion.

Reporting the results of all previous stages was the final stage of data analysis. This stage was considered "the final opportunity of data analysis in thematic analysis", where the extracted data from the interviews was interpreted and linked back to the research objectives and literature.(34)

The reporting of this study was followed by the Consolidated criteria for reporting qualitative research (COREQ). It covers 32 items checklist with three domains developed by reviewing and identifying items from other tools and checklists for qualitative studies. It was also developed to promote explicit and comprehensive reporting of interviews and focus groups.(35)

2.6.3 Reliability and Validity in Qualitative Research

The use of reliability and validity is common in designing a study, analyzing the results, and judging or testing its quality.(36) Reliability is the extent to which results are consistent over time and an accurate representation of the total population under study, and if the results of the study can be reconducted under a similar methodology, then the research instrument is considered reliable.(37)

Validity is defined as the state of being justifiable, logical, relevant, meaningful, confirming to accepted principles or the quality of being sound, just, and well-founded.(37) It determines if the research truly measures what it was intended to measure or how truthful the research results are. In other words, does the research instrument allow the researchers to hit "the bull's eye" of the research object? Researchers determine the validity by asking a series of questions, and they often look for the answers in the research of others.(37)

In 1980, from the crucial work of Lincoln and Guba's, reliability and validity were replaced with the concept of trustworthiness.(38) It refers to the quality, truthfulness, and authenticity of findings, the degree of confidence in data, interpretation, and methods used in qualitative research to ensure the quality of a study.(39) Therefore, examining trustworthiness is crucial to ensure reliability in qualitative research.

Qualitative research trustworthiness criteria were introduced by Lincoln and Guba (1985) and accepted by many qualitative researchers. These criteria include credibility, transferability, dependability, and confirmability.(38) These are defined as follows: credibility is defined as the confidence that can be placed in the truth of the research findings. Lincoln and Guba have suggested a number of techniques to address credibility, including some activities, such as prolonged engagement, persistent observation, data collection triangulation, and researcher triangulation. Transferability refers to the generalizability of the inquiry.(40) According to Bitsch [36], the researcher facilitates the transferability judgment by potential users through the thick description and purposeful sampling. Dependability refers to the stability of findings over time.(41) Confirmability indicates that the interpretations and findings are derived from the data, requiring the researcher to demonstrate how the conclusions and the interpretations have been reached.(40) This is established when credibility, transferability, and dependability are all

achieved.(42) Previous studies have suggested that confirmability of qualitative inquiry can be achieved through an audit trial, reflexive journal, and triangulation.(43, 44)

To analyse the qualitative data, a method called thematic analysis (TA) was applied to identify and analyse the patterns of meaning (themes) and constitutes the cost-effective and flexible tool for exploratory research.(45)

The thematic analysis is presented as a linear, six-phased method, an iterative and reflective process that develops over time with constant moving back and forward between phases (Table 2.3).(46)

In this project, to ensure high reliability and validity of data, before starting the study, AA and the collaborators attended a course about a qualitative study called comprehensive qualitative course. They also attended one-week training about how to use MAXQDA PRO for data analysis. Before the interviews, the topic guide was revised by two supervisors, pharmacists, physicians, and nurses by an expert panel of the specialized team who had an extensive experience and knowledge about DOACs.

The interviews conducted by the primary researcher who was trained and qualified for this purpose, and the transcribed interviews were validated by members of the research group to assure quality of transcribing. The interview was performed by using Zoom digital recording. The reporting of this study was followed by the Consolidated criteria for reporting qualitative research (COREQ). In addition, to improve rigour and trustworthiness, each interview was ended by a summary to be validated by the participants and to check for any ambiguity. After each interview, the two researchers (AA and NA) met and reflected on the information received. Memos such as reporting interviewee's facial expressions or hesitancy to answer specific questions adequately, and journaling was recorded during the interviews and utilized throughout

data collection and analysed using MAXQDA memos. Data collection continued until interviewers noticed saturation (no more new data revealed by the interviewees) in each group of participant HCPs. Data from interviews were kept secure. The inclusion and exclusion criteria and appropriate data sampling were employed to ensure the research data were reliable and valid.

To enhance the validity of the results, the coding assessed by two independent researchers undertook the coding of the interview. In the end, the two independent researchers' team examined the analysis.

2.7 Quantitative methodology

Quantitative research is a scientific, objective, formal, empirical, and systematic process to generate statistical or numerical data. The data are explained and measured by using descriptive figures and numerical data to produce findings, and the results are tested and analysed in relation to a cause-effect relationship using statistical methods.(25) Therefore, quantitative research deals with measurement and makes the assumption that the phenomena being studied can be quantified. The quantitative approach can be applied to studies involving human research.(27) This approach uses more objective measures than the qualitative approach, which depends on subjectivity.(47) It aims to describe events or concepts, new situations, examine relationships between variables, and determines the effectiveness of interventions on selected health outcomes.(48)

According to Sukamolson [44], quantitative research methods can be categorized into: correlational research, survey research, experimental research, and causal-comparative research. Each type of research is explained as follows:

Correlational research determines whether and to what degree the relationship exists between two or more variables within the sample, and the degree of the relationships is expressed by correlation coefficients. Survey research encompasses the use of a sampling method with a designed questionnaire to measure a given population's characteristics by the utilization of statistical methods. In experimental research, the researcher investigates the treatment of an intervention in the study group and then measures the outcomes of the treatment, such as using randomized controlled trials.(49) In causal-comparative research (Ex-Post Facto research), the researcher tries to determine the cause, or reason, for pre-existing differences in groups of individuals.(49)

In this study, quantitative research was applied to identify patient safety incidents, causes, and the factors contributing to medication errors in relation to DOACs through NRLS reports in the UK and Saudi Arabia hospitals. Errors reported from January 2010 to December 2020 were also included.

2.7.1 Reliability and Validity in Quantitative Research

In quantitative research, reliability and validity are two indispensable features that need to be tested individually to ensure the research quality. The concept of reliability and validity are closely related; however, they express different properties of the measuring instrument. For instance, the instrument can be measured to be reliable without being valid.(50)

According to Joppe [46], reliability is defined as the extent to which the results are consistent or repeatable over time with an accurate representation of the total population under study. In other words, it is the ability to measure an instrument to produce similar results when applied at different times.(51)

The most frequently applied methods to test the reliability of the scales are test-retest reliability, alternative forms, and internal consistency tests. To test and prove the research instrument repeatability and internal consistency, three different ways can be applied; split-half, item-total correlations, and alpha reliability coefficient, which is the most preferred internal consistency tests.(50)

Validity is defined as truth or examines whether the results measure what it set out to measure and how applicable it is for the wider population.(52) For quantitative research to be valid, it requires evidence and trustworthiness. Different types of validity including external validity, content validity, internal validity, face validity, and criterion validity.(53)

In this project, to ensure high reliability and validity in the NRLS databases, it was revised by a team and then two members (AA and VP) familiarized themselves by reading the incident-free text description. The extracted data were revised and cleaned for any duplications, and all variables were compiled in an excel file for analysis.

To ensure reliability and validity for databases collected from Saudi Arabia, the data was revised by local collaborators who are expert clinical pharmacists to obtain the required medication error reports. The data were retrieved electronically from the institutions' reporting systems using drug names as the search terms. The extracted data were revised and cleaned for any duplications, and all variables were compiled in an excel file for analysis.

Table 2.3 shows how the researchers address the criteria for trustworthiness during each phase of TA(33).

Phases of Thematic Analysis	Means of Establishing Trustworthiness
Phase 1: Familiarizing yourself with your data.	Prolong engagement with data, triangulate different data collection modes, document theoretical and reflective thoughts, document thoughts about potential codes/themes, store raw data in well-organized archives, keep records of all data field notes, transcripts, and reflexive journals
Phase 2: Generating initial codes	Peer debriefing, researcher triangulation, reflexive journaling, use of a coding framework, audit trail of code generation, documentation of all team meeting and peer debriefings.
Phase 3: Searching for themes	Researcher triangulation Diagramming to make sense of theme connections Keep detailed notes about development and hierarchies of concepts and themes.
Phase 4: Reviewing themes	Researcher triangulation Themes and subthemes vetted by team members Test for referential adequacy by returning to raw data.
Phase 5: Defining and naming themes	Researcher triangulation Peer debriefing Team consensus on themes Documentation of team meetings regarding themes Documentation of theme naming.
Phase 6: Producing the report	Member checking, peer debriefing, describing process of coding and analysis in sufficient details, thick descriptions of context, description of the audit trail, report on reasons for theoretical, methodological, and analytical choices throughout the entire study.

2.8 Research utilizing healthcare/error incident reporting databases

The incident reporting system is a system and mechanism by which many healthcare organisations use to identify MEs and ADEs.(54, 55) In England and Wales, the National Reporting and Learning System (NRLS) is considered the national repository and the central database of patient safety incident reports from health organisations, (56, 57) and the largest patient safety database in the world.(58)

The reporting of incidents to NRLS is voluntary but since from April 2010, the reporting has become mandatory for all the incidents with severe harm or death.(57) In regards to the NRLS database, healthcare professionals are responsible for the reporting of any patient safety incidents involving medication-related incidents to their local incident management system in

anonymous form and then analysed to be submitted to the NRLS in either batches or via online submission.(57)

In each report, the main information involved is the date, the incident's location, the patient's demographics and the reporter's perception of the severity of harm, followed by a free text field in which the incident described by the reporter, what are the potential contributory factors to its occurrence, and how the incidents can be prevented in the future.(57) After that, the NRLS may use these incidents to identify trends and share them with other patient safety organisations to help with the development of patient safety resources.(57) For instance, harmful or death-related incidents are reviewed by NHS improvement clinicians, but sometimes it can be shared with other national patient organisational bodies, such as the Medicines and Healthcare products Regulatory Agency (MHRA), NHS England and CQC.(57) This provides the opportunities to learn from the patient safety incidents across both local and national levels in order to improve patient safety.(59) The database of NRLS is also an essential source of qualitative data that allows for an in-depth understanding of contextual factors associated with medication incidents' occurrence. Other countries like Canada also have an incident reporting system under the name British Columbia Patient Safety and Learning System.(60)

In the current project, an evaluation of all medication incidents reported by hospitals to NRLS between 01 January 2017 and 31 December 2019 in the UK was conducted to identify the contributory factors associated with DOACs.

In Saudi Arabia, the incident reporting system follows a similar pattern as in the UK. The second quantitative and qualitative study used the incidents reporting databases from two healthcare institutions and the pharmacovigilance database called Saudi Food and Drug Administration (SFDA). From January 2010 up to December 2020, the hospital-based data were retrieved from

the electronic medical record system for all errors reported from the year of such medications became available in Saudi Arabia, including patients' demographic data, such as age, gender, weight, and height, drug name and its indication, comorbidities, dosing regimen and duration of treatment, type of medication error, such as prescribing, administration, and dispensing, and renal function test results. In SFDA, the Pharmacovigilance Electronic Reporting Service in an online spontaneous reporting system, which reports all side effects, medication errors, and any defect in the quality of pharmaceutical preparations. It also allows sending and submitting communications to report a drug shortage by health practitioners, pharmacies, health institutions, companies, and community members. It also receives voluntary reports of safety concerns from health practitioners and patients. The two quantitative studies were conducted in two different countries (UK and Saudi Arabia) due to the lockdown and limitations of the COVID-19 Pandemic.

2.9 Summary of the chapter

The research used a variety of research designs, including systematic review and meta-analysis, quantitative methodology, and qualitative methodology to identify epidemiology and factors associated with medication errors in relation to DOACs. Given the range of objectives involved in this programme of work, it was appropriate to adopt a wide range of research methods to enable holistic understanding of how errors occur and how to mitigate them. In the next chapter, a systematic review and meta-analysis study is presented to determine the prevalence of medication errors associated with DOACs.

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Chapter 3. Prevalence, contributory factors, and severity of medication errors associated with direct-acting oral anticoagulants in adult patients: a systematic review and meta-analysis

Chapter overview: This chapter presents a systematic review and meta-analysis to determine the prevalence of medication errors associated with DOACs in clinical practice and to identify contributory factors associated with DOACs in adult patients using the Reasons Accident Causation Model.

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Citation: Al Rowily A, Jalal Z, Price MJ, et al. Prevalence, contributory factors and severity of medication errors associated with direct-acting oral anticoagulants in adult patients: a systematic review and meta-analysis. Eur J Clin Pharmacol. 2021;1–23.

Authors contribution: This study relates to AA's PhD research. VP and ZJ supervised AA for his PhD. All authors co-designed the study. Literature search performed by AA and verified by MA and MHA. Literature retrieving, screening, summarising, data extraction, and quality assessment were undertaken by AA, MHA, MA, and HA. Meta-analysis was conducted by MP and AA and reviewed by VP, ZJ, and MHA. The first manuscript draft was written by AA. All authors reviewed and approved for submission.

3.1 Abstract

Purpose: This study aimed to estimate the prevalence, contributory factors and severity of medication errors associated with DOACs.

Methods: A systematic review and meta-analysis were undertaken by searching 11 databases, including Medline, Embase, and CINHAL, between 1/2008-9/2020. The pooled prevalence of errors and predictive intervals were estimated using random-effects models using Stata software. Data related to error causation were synthesised using the Reason's Accident Causation Model.

Results: From the 5205 titles screened, 32 studies were included, which were mostly based in hospitals and included DOAC treatment for thromboembolism and atrial fibrillation. The proportion of study population who experienced either prescription, administration, or dispensing error ranged from 5.3 to 37.3%. The pooled percentage of patients experiencing prescribing error was 20% (95% CI 15-25%; I2 = 96%; 95% PrI 4-43%). Prescribing error constituted the majority of all error types with a pooled estimate of 78% (95%CI 73-82%; I2=0) of all errors. The common reported causes were active failures including wrong drug, and dose for the indication. Mistakes such as non-consideration of renal function, error-provoking conditions like lack of knowledge were common contributing factors. Adverse events such as potentially fatal intracranial haemorrhage or patient deaths were linked to the errors, but causality assessments were often missing.

Conclusions: Despite their favourable safety profile, DOAC medication errors are common. There is a need to promote multidisciplinary working, guideline- adherence, training and education of healthcare professionals and the use of theory-based and technology-facilitated interventions to minimise errors and maximise the benefits of DOACs usage in all settings.

3.2 Introduction

Direct-acting non-vitamin K antagonist oral anticoagulants (DOACs) including direct thrombin-inhibitor dabigatran, and two-factor Xa inhibitors rivaroxaban and apixaban have become the preferred choice in clinical practice for the primary and secondary stroke prevention in patients with atrial fibrillation, prevention and treatment of venous thromboembolism (VTE), and thromboprophylaxis in patients undergoing total hip or knee arthroplasty. Depending on indications, anticoagulation therapy can be given for a short term (up to around three months) or long term. Short-term anticoagulation therapy is most commonly indicated for primary perioperative prophylaxis of thromboembolic events, such as those undergoing hip or knee replacement surgery. Long-term anticoagulant therapy with DOACs is recommended primarily for major cardiovascular conditions, such as non-valvular atrial fibrillation (NVAF).(1)

DOACs have the advantage over Vitamin-K antagonists (VKA) for a much wider therapeutic window. While the relative ease of prescribing DOACs compared to VKAs makes them more commonly prescribed, healthcare professionals need to be aware of unwanted treatment outcomes associated with medication errors and suboptimal prescribing.[1] DOACs' relatively shorter history of use precludes the current availability of long-term safety data. In addition, pharmacokinetic profiles and drug interactions are not fully understood.

A risk and benefit profiling should be carefully considered/conducted before the prescribing of DOACs. The NICE guideline on atrial fibrillation recommends that bleeding risk, estimated using the HAS-BLED score, should be taken into account when offering anticoagulation.(1) The HAS-

BLED score estimates the risk of bleeding on a 9-point scale. Dose adjustments are often recommended with DOACs for renal creatinine clearance including contraindications for severe renal impairment.(2)

Evidence of adverse events, particularly the incidence of bleeding related to the use of DOACs compared with vitamin-K antagonists in real-life patients have recently emerged.(3) Previous systematic reviews of randomised controlled trials (RCTs) and observational studies have demonstrated the clinical benefits of DOACs compared to VKAs. DOACs significantly reduce the risks of intracranial haemorrhage, gastrointestinal, and major bleeding.(4) However, no direct head-to-head comparisons have been reported for each medicine of DOACs class. This leads to difficulty in the choice of drugs and dosage. A particular challenge is also the lack of availability of specific antidotes for all DOACs, and the lack of clear guidelines around treatment options for patients with intracranial bleeding and gastrointestinal bleeding under DOAC therapy.(5)

Considering the aforementioned factors, DOACs are known to be one of the most common drug classes that are associated with adverse drug events (ADEs).(6) The lack of long-term clinical experiences and the need for careful consideration of risk and benefit profiles makes DOACs candidates for medication errors, particularly prescribing errors which are often responsible for such ADEs.(6)

To date, there exists no systematic reviews and meta-analysis that synthesise the prevalence of medication errors associated with DOACs, including the prevalence of different types of medication errors. In addition, it is imperative to synthesise the contributory factors reported in

the literature. Theoretical models are useful in identifying and interpreting factors that contribute to errors and to enable future interventions that can be effective in minimising such errors.(7)

Reasons Accident Causation Model classifies errors into three different categories including a) active failures which are unsafe acts committed by persons who are in direct contact with the patient or system and includes slips and lapses (errors in task execution), mistakes (errors in planning) and procedural violations (rule breaking); b) error-provoking conditions within the workplace (e.g., time pressure, understaffing, inadequate equipment, fatigue and inexperience) and c) latent failures which arise from decisions made by policy makers, leaders, and top-level management.(8) This model has been widely adopted in research identifying the prevalence and causes of medication errors.(9)

The purpose of this systematic review was to determine the prevalence of medication errors associated with DOACs in clinical practice and to identify contributory factors associated with DOACs in adult patients using the Reasons Accident Causation Model. Results can enable healthcare professionals in diverse settings including primary, secondary, ambulatory care as well as those in the interface, such as community pharmacy, to understand and mitigate common errors and associated consequences on patients and health systems.

3.3 Methods

The systematic review protocol was developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines and registered with the International Prospective Register of Systematic Reviews (PROSPERO code is CRD42019122996) (Appendices 1). The review is reported according to the PRISMA guidelines (10) and MOOSE statements (supplementary material Table S 3.1).

3.3.1 Search Strategy

A systemic search of the literature was undertaken using electronic databases: *Medline, Embase, and Cumulative Index of Nursing and Cumulative Allied Health Literature (CINAHL), British Nursing Index (BNI), International Pharmaceutical Abstract (IPA), Cochrane Central Register of Controlled Trials (CENTRAL)*; and grey sources including *Institute for Safe Medication Practices (ISMP), The FDA Safety Information and Adverse Event Reporting Program (FDA MedWatch), and Google Scholar databases* from 2008 to September 2020. The search terms used included Medical Subject Headings and Natural Language Keywords for DOACs namely: *dabigatran, rivaroxaban betrixaban, apixaban and edoxaban and medication errors (specifically prescribing, and dispensing), and administration errors*. Besides, each database search was restricted to English published studies (supplementary material Table S 3.2) and conducted using the Boolean operators (AND, OR and/or NOT). In addition, reference lists of included studies were screened to identify any additional relevant studies (ancestral research).

3.3.2 Types of studies

We included studies which reported or investigated the rate of prescribing, administration, or dispensing errors associated with DOACs. Studies of adverse drug events that are not classified as errors were excluded, as were review articles, letters, opinion papers, and editorials.

3.3.3 Types of participants

Adult patients (≥18 years) prescribed DOACs were eligible for inclusion.

3.3.4 Outcomes

The primary outcome was the prevalence of medication errors associated with DOACs. Prevalence data on each error type i.e., prescribing, dispensing and administration error was obtained by calculating the number of patients for whom an error was identified amongst the total number of patients included during the data collection period. The errors included in this study were those identified from the following source: chart review, medication review, and those reported to the error reporting systems. The secondary outcomes included the nature of causes, contributory factors, and severity of medication errors associated with DOACs.

3.3.5 Study selection and data extraction

Two reviewers (AA and MHA) independently screened the titles and abstracts of all potentially relevant papers based on the selection criteria. This was followed by a full-text screening using Rayyan QCRI (a web and mobile app for a systematic review screening that facilitates collaboration between different reviewers for inclusion and exclusion of studies).(11) Any

disagreement about study inclusion was resolved through discussion with a third reviewer (VP). Duplicate independent extraction of data was undertaken by researchers working in pairs (AA, MHA, VP, ZJ). The data extracted included: authors, year of publication, country and setting, study design, error prevalence, the nature of errors, error severity and contributory factors. Also, the data on study characteristics, error prevalence, and error causes were extracted. A meta-analysis was performed using Stata/IC 15.1 Software (StataCorp, College Station, TX, USA).

3.3.6 Assessment of methodological quality

Quality assessment was conducted by two independent reviewers (AA and MA) with disagreements resolved by consensus or referred to two other reviewers (HA, VP) as required using the critical appraisal skills programme (CASP) checklist.(12)

3.3.7 Data synthesis and statistical analysis

The meta-analyses were performed on the prevalence of medication errors associated with DOACs by a statistician [MP]. A random-effects model was used to synthesise the data due to the expected heterogeneity between included studies, and the results obtained were presented using forest plots. Heterogeneity was described using I^2 statistics and reporting of 95% prediction intervals.(13) The statistical significance of I^2 was tested with Chi-square test, and P-value level < 0.05 was set as the level of statistical significance. The effect size was calculated as the mean difference (MD) with 95% confidence interval (CI).

Data on error causation were synthesized using Reason's Accident Causation model,(14) as a theoretical framework as per the classification of active failures, error-producing conditions and latent failures.

3.4 Results

3.4.1 Search and study selection

The initial search resulted in 5205 titles search results across all the databases accessed shows the PRISMA flow diagram for this study. The duplicate results and studies that did not meet the inclusion criteria were identified and excluded. Overall, 408 articles were assessed for eligibility, of which 32 studies fulfilled the inclusion criteria for full-text review (Figure 3.1).(15-46)

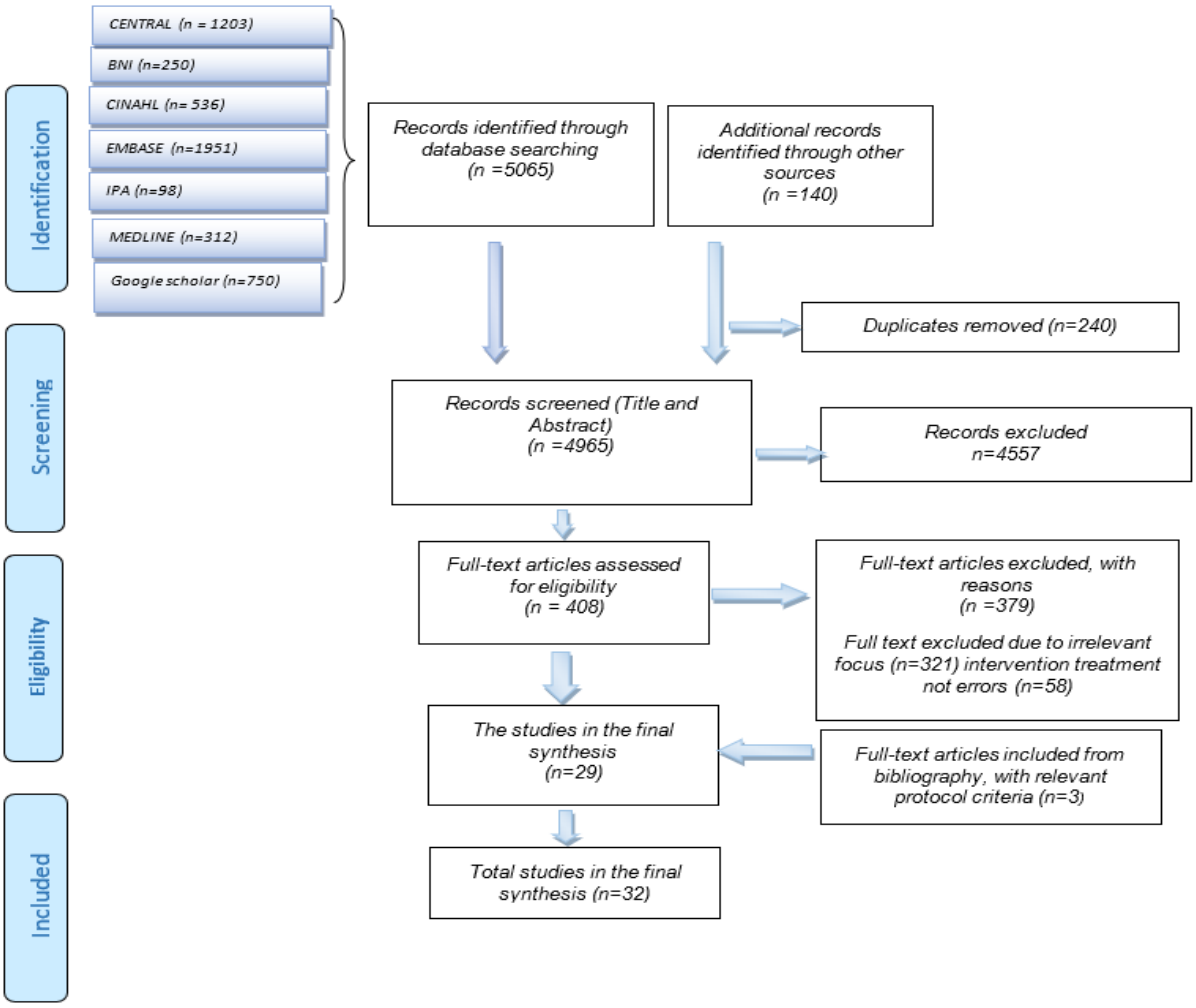


Figure 3.1 PRISMA flowchart describing systematic review search and study selection

Abbreviation:

ISMP: Institute for safe medication practice. FDA: Food and drug authority in the USA. MEDWATCH: The FDA Safety Information and Adverse Event Reporting Program. CENTRAL: Cochrane Central Register of Controlled Trials. BNI: British Nursing Index. CINAHL: Cumulative Index of Nursing and Cumulative Allied Health Literature. IPA: International Pharmaceutical Abstract. MEDLINE is the National Library of Medicine's premier bibliographic database of life sciences and biomedical information. Embase (Excerpta Medica Database) is a biomedical and pharmacological database. MEDLINE is the National Library of Medicine's premier bibliographic database

3.4.2 Study Characteristics

Of the 32 studies included, 12 (40.7%) were conducted in the USA,(15, 19, 20, 24, 33, 35, 37-40, 42, 44) three each in the UK (11.1%),(22, 34, 45) and France,(18, 30, 46) two each in Belgium,(31, 36) Greece,(27, 28) Australia,(23, 41) Ireland,(29, 32) and one each in the Netherlands,(21), Spain,(43) Turkey,(17) Israel,(16) Denmark,(25) and United Arab of Emirates.(26) Studies were conducted in university-affiliated or academic/teaching hospitals,(15, 16, 18, 23, 25, 28-31, 34, 36, 37, 39, 41, 43, 45, 46) tertiary care non-teaching hospitals,(24, 26, 33, 35, 38, 42) primary healthcare Centre's,(22, 43) nursing home,(19) private general hospital,(27) pharmacist managed anticoagulation clinic,(20) central medication registration,(21) poison control system, (40) single center,(32) and patient safety reporting system.(44)

Table 3.1 Study characteristics with Classification of medication error contributory factors

Author (s) Year	Country	Study design, Methods used to identify medication errors	Study setting	Study population	Sample size patient	Sample size (errors)	Types of medication error and data collection method	DOACs drug errors listed or investigated	indications	Results	Classification of contributory factors as per Reason's Accident Causation model		
											Active Failure*	Error Provoking Condition**	Latent Condition***
Bruneau et al 2019 [18]	France	observational prospective study: multicentre	University hospitals	Elderly ≥65 years received and discharged on DOAC and Admitted to acute unit between February and July 2018	157		Prescribing error; retrospective review of medical records	Dabigatran Rivaroxaban Apixaban	AF, VTE, and Others	Prior to admission, (30.6%) had an inappropriate prescription. At discharge, (22.4%) had an inappropriate prescription; The nature of the inappropriateness was under- or overdosing (21.7%)	NR	NR	NR
Dreijer et al 2019 [21]	The Netherlands	a cross-sectional study	Central Medication incidents Registration reporting System (CMR)	Medication error reported to Central Medication incidents Registra ion reporting system. Between December 2012 and May 2015	1000 medication error report		Prescribing error Administration error; errors reported to a national reporting system	Dabigatran Rivaroxaban Apixaban	AF	DOACs were the least frequently type of anticoagulant involved in the reports 3% Most anticoagulant medication errors were reported as prescribing errors (37.1%), followed by administering errors (29.8%). The majority of errors made in the prescribing phase arose from incomplete prescriptions. Omission errors were responsible for the highest percentage of errors in the administering phase	NR	NR	NR

Angel et al. 2019[16]	Israel	Retrospective cohort study	University Hospital	-	4,427	1,237	Inadequate treatment; retrospective review of medical records	Apixaban, Rivaroxaban, Dabigatran	AF	Among the 1,237 patients with inadequate treatment, the most common types of errors were DOAC under-dosing (n=578; 46.7%), VKA when DOAC was indicated (n=258; 20.9%), DOAC despite contraindication to DOAC (n=166; 13.4%), and DOAC over-dosing (n=124; 10.0%).	Mistake: wrong dose	NR	NR
Valentine et al. 2018[44]	USA	Retrospective reviewed database	Pennsylvania Patient Safety Reporting System database	Pennsylvania Patient Safety Reporting System database	1,811	1,546	Duplicate therapy; errors reported to a reporting system	Rivaroxaban, edoxaban, Apixaban, Dabigatran	AF, DVT, and PE	Of the 1,811 reports, 14.6% (n = 265) were considered ADEs and 85.4% (n = 1,546) were medication errors without harm.	NR	NR	NR
Sennesael et al. 2018[36]	Belgium	Prospective observational study in the emergency departments	Teaching hospitals	Patients admitted with a thrombotic or bleeding event while under DOAC	46	38	Prescribing issues and inadequate monitoring; prospective medication review	Rivaroxaban, apixaban, dabigatran	NVAF, VTE	For the 46 patients taking DOAC, 38 adverse events were evaluated as serious ADRs. Among hese, 20 ADRs (53%) were considered to be (potentially) preventable. Prescribing was the main stage of medication process involved in medication error (n = 16), followed by compliance (n = 5).	NR	Inadequate monitoring	NR
Moudallel et al. 2018[31]	Belgium	Retrospective cohort study	University hospital	hospitalized patients aged ≥60 years with at least one DOAC intake during hospital stay	772	193	Prescribing errors, inappropriate dosing; retrospective review of medical records	dabigatran, rivaroxaban, and apixaban	AF, VTE	Inappropriate dosing occurred in 25.0% of hospitalizations with 23.4, 21.9, and 29.7% for dabigatran, rivaroxaban, and apixaban, respectively (p = 0.084). Under dosing was most prevalent for apixaban (24.5%) compared to dabigatran (14.0%)	NR	NR	NR

										and rivaroxaban (12.8%), p < 0.001. In 67.1% (apixaban), 26.7% (dabigatran), and 51.2% (rivaroxaban) of underdosed DOAC case			
Lafon et al. 2018[30]	France	Prospec ive observational study:	Universit y Hospital	All subjects wi h DOAC admitted to the Limoges University Hospital ED	198	-	prescribing errors (incorrect dosage according to age, renal function, co-medications); prospective observation of prescribing records	Rivaroxaban, dabigatran, apixaban	NVAF, VTE	In 16.2 % of the cases, the treatment was not in according to the guidelines: 78 % for prescribing errors (incorrect dosage according to age, renal function, co-medica ions) and 22 % for wrong initial indication	Mistake—wrong dose	Lack of experie nce •Insuffic ient educati on/train ing.	NR
Ioannidis et al. 2018[27]	Athens, Greece	Prospec ive study: clinical pharmacists documented all cases where DOACs were prescribed	Private General Hospital	Private General Hospital	370	42	Prescribing errors (calculated DOACs dosage based on renal function); prospective observation of prescribing records	Rivaroxaban, dabigatran	AF, VTE, PE	A significant amount of patients (11.4%) received DOACs in a way that contradicts the product label guidelines.	•Mistake: wrong dose •violation: doctor not writing the order not in time	NR	NR
Suknate et al., 2018[41]	Australia	Retrospective review: The relevant data were collected by review of medical records by pharmacists	Teaching hospital	Teaching hospital	200	45	Prescribing error (the most common prescription error was under-dosing and overdosing; retrospective review of medical records	Rivaroxaban, apixaban, dabigatran	AF, VTE, PE	Inappropriate prescription of DOACs appears common, although not associated with complications. The prescription was deemed inappropriate in 45 patients (22.5%). The most common prescription error was under-dosing (for age, weight and renal function, or the indication), which was seen in 23 patients (11.5%). Overdosing was seen in seven (3.5%).	• NR	Lack of knowle dge and experie nce	Lack of medicat ion reconcil iation service

Pharithi et al. 2018 [32]	Irland	Single centre, retrospective observational cohort study	Teaching hospital	AF patients who had received at least one dose of any of the NOACs	348	-	Prescribing error; retrospective review of medical records	Dabigatran Rivaroxaban Apixaban	AF		NR	NR	NR
Kartas 2018 [28]	Greece	Cross sectional study; Data extracted from MISOAC-AF registry	Tertiary care hospital	Adult patients with non-valvular AF or atrial flutter	768	-	Prescribing error; discharge medication review	Dabigatran Rivaroxaban Apixaban	AF	Off-label dosing (28.9%) was relevant to more than a quarter of NOAC users, while (23.8%) were underdosed and 21 (5.1%) were overdosed wi h NOAC	NR	NR	NR
Sheikh-Taha et al. 2019 [38]	USA	A retrospective study	Tertiary care center	Adult patients on NOAC between March 1 and June 30, 2017 Huntsville Hospital, Huntsville, Alabama, USA	909	-	Prescribing error; chart review	Dabigatran Rivaroxaban Apixaban edoxaban	AF, DVT, PE	Almost 23.9% of the patients received doses inconsistent with the package labelling; 13.2% of patients received lower than recommended dosing, while 10.7% received higher than recommended dosing. The prevalence of inappropriate dosing was signifcantly more frequent among older patients, taking NOACs for AF(30.3%) compared to those using it for DVT/PE treatment (13%) The prevalence of inappropriate dosing was significantly higher in those with lower CrCl, and taking high number of medications	NR	NR	NR
Sharma et al. 2017[37]	USA	Retrospective study: retrospectively reviewed electronic medical records of 41 patients. A clinical pharmacist	Teaching hospital	Community based hospital	41	10	Prescribing error; chart review	Rivaroxaban, apixaban	AF, VTE, PE	Patients were dosed with 15 mg daily of rivaroxaban for DVT prophylaxis, Which were corrected to 20 mg daily dose.	Mistake-wrong dose due to lack of renal dose adjustment and lack of	NR	NR

		collected this data.									initiation of anticoagulation		
Viprey et al. 2017[46]	France	cross-sectional study: Retrospective review; using data from medical records system of the Lyon teaching hospitals	University teaching hospitals	Hospitalised patients	1188	100	Prescribing errors- The appropriateness of the dosage of the drug; retrospective chart review	Dabigatran and Rivaroxaban	AF,DVT and PE	The highest prevalence of DRPs was found among patients who received rivaroxaban for atrial fibrillation (14·6%; 95% CI, 10·7-18·5). A too low drug dose was the most frequent DRP (n = 56; 4·7%), followed by a too high drug dose (n = 37; 3·1%), contraindication (n = 5; 0·4%), and pharmacokinetic problem requiring dose adjustment (n = 2; 0·2%).	Mistake: wrong dose	NR	NR
Henriksen et al. 2017[25]	Denmark	Descriptive study: retrospective review; Three independent specialists in clinical pharmacology evaluated the severity of incident outcomes	University teaching hospitals	Reports to the Patient Safety Database; University Hospital	Not stated	147	Prescribing errors: excess or insufficient dosing; retrospective review	Dabigatran, Rivaroxaban	AF	Dabigatran: Total number within the subgroup (%);30 (21%); potentially Serious (%)-19 (63%)	Mistake: Excess or insufficient dosing	System errors	NR
Alghadeer et al. 2017[15]	USA	Retrospective review	University teaching hospitals	patients that were prescribed dabigatran, rivaroxaban, or apixaban;	113	10	Prescribing error: Lack of renal dose-adjustment in patients with reduced renal function was the most common reason for inappropriate use (for specific indication, renal function, age and/or	Dabigatran, rivaroxaban, and apixaban	STROKE, VTE	The dose of DOACs was unadjusted (for specific indication, renal function, age and/or weight) in 8.8% (n = 10) of patients collectively. All cases were due to unadjusted doses in patients with renal impairment and occurred in 9.2% (n = 6) of patients receiving dabigatran, 8.8% (n = 3) of patients receiving rivaroxaban, and	Mistake: duplicate therapy and wrong dose	failure staff to follow policy and procedure. Inadequate laboratory results	NR

							weight); retrospective chart review			7.1% (n = 1) of patients receiving apixaban.			
Hussain et al. 2017 [26]	UAE	Retrospective cross-sectional analysis	tertiary care hospital	Patients who received dabigatran	61	28	Prescribing errors; retrospective review of medical records	dabigatran	NVAF	Inappropriate dose was administered in 7 of the 61 patients prescribed dabigatran.	NR	Inadequate knowledge off label indication	NR
Ghai et al. 2017[22]	UK	Retrospective review: Data was collected from two GP prac ices in BognorRegis.	primary care hospital	Patients with NVAF who prescribed DOACs	73	-	Documentation error and prescribing and monitoring errors; retrospective review of medical records	Rivaroxaban,	NVAF	12 patients despite having impaired renal function (CrCl<50) were prescribed the higher dose. Patients with impaired renal function (CrCl<60) did not have their renal function monitored more frequently as is suggested by NICE	Mistake: wrong dose	•Lack knowledge of how to adjust dose CrCls •Poor communica ion between team members	Lack of training
Basaran et al. 2017[17]	Turkey	Prospec ive, observational study: patients with NVAF were screened for OAC prescription	University teaching hospitals	patients with NVAF; outpatient cardiology clinics,	148	24	Inappropriate prescribing; prospective review of prescribing records	Dabigatran, rivaroxaban	NVAF	Inappropriate drug use is frequent among patients with DOACs.	Mistake: wrong dose	NR	NR
Roberts et al. 2017 [34]	UK	Prospec ive observational study:	University teaching hospitals	Patients attending AF clinics, acute medical and cardiology wards; teaching hospital	190	41	Prescribing errors (incorrect dosage according to age, renal Function); prospective review of prescribing records	Rivaroxban, apixaban, edoxaban	AF	Apixaban had the highest rate of inappropriate dosage. As most prescribing errors involved inappropriate dose reduction	•Slips and lapse-memory •Mistake-wrong dose	NR	NR
Victoria et al. 2016[45]	UK	Retrospective review : The data was collected for all DATIX system-reported incidents by clinical pharmacists	University teaching hospitals	-	-	25	Prescribing errors(missed dose, wrong dose for indication, incorrect dosage according to age, renal Function);	Rivaroxaban , apixaban, dabigatran, edoxaban	AF	Patients were prescribed the wrong dose for indication e.g. AF dose of Apixaban for PE. DOACS were often not available on the ward and patients went as long as 48	Slips—memory lapses •Lapse: wrong correct label	Lack of knowledge and familiarity with DOACs	NR

							incident reporting system			hours without anticoagulation			
Keohane et al. 2016 [29]	Ireland	Cross-sectional data was collected from inpatients over a 3 week period	University teaching hospitals	Internal medicine and cardiology wards)	30	-	Prescribing errors (inappropriate dose, indication); review of medical records	Rivaroxaban, apixaban and dabigatran	AF	Out of 70% of the patients, almost 10% were on a NOAC for an inappropriate indication and 11% on an inappropriate dose for the CrCl - Potential drug interactions were common, with 63% of patients concomitantly taking a cautioned or contraindicated medication.	Mistake-prescribing for wrong indica ion and lack of dose adjustment	NR	NR
Glendinning et al. 2015[23]	Australia	Retrospective review: Hospital pharmacy provided a list of patients dispensed either Apixaban or Rivaroxaban; The medication charts and progress notes of these pa ients were reviewed for prescribing errors and the presence of any subsequent complications	University teaching hospitals	-	250	-	Prescribing error, documenta io n error; medical charts and progress notes	Rivaroxaban, apixaban	VTE	19.5% of medication charts prescribing D OACs contained erro rs	NR	NR	NR
Tellor et al. 2015[42]	USA	Retrospective review	Tertiary community hospital	Patients received at least one treatment dose of rivaroxaban,	714	445	Prescribing errors: inappropriate dose; retrospective chart review	Rivaroxaban	NVAF, PE DVT	Of the 445 patients evaluated, 36·9% of patients treated for NVAF and 12·4% treated for VTE were on an inappropriate regimen. The most common errors in the rivaroxaban regimen for VTE treatment were an inappropriate dose (8 patients, 5.7%)	NR	NR	NR
Simon et al. 2015[39]	USA	Retrospective review: a search of the electronic health record	Academic medical centre	Patients seen in outpatient clinics	395	249	Inappropriate prescribing, patient-	Apixaban, dabigatran, rivaroxaban	NVAF, PE DVT	Of contacted patients taking	Mistake-wrong dose and	NR	NR

		(EHR) was conducted					reported inappropriate use; retrospective chart review			rivaroxaban, 24 (23%) reported taking it inappropriately without food, and of contacted patients taking dabigatran, six patients (14%) endorsed inappropriate storage of dabigatran. Ten patients (6%) reported missing at least one TSOAC dose per week.	failure to give rivaroxaban without food		
Greenberg-Schwartz et al. 2015[24]	USA	Retrospective review	Community hospital	-	-	-	Errors included inaccurate renal and hepatic dosing adjustments, incorrect dosage based on indication and duplication of anticoagulation agents; retrospective review of medical records	Rivaroxaban	NVAF, PE DVT	Errors included inaccurate renal and hepatic dosing adjustments, incorrect dosage based on Indication and duplication of anticoagulation agents. Educational program "LEARN" reduced the error from 31.7% to 22%	Slips-acronym errors •Lapse—duplicate therapy	NR	Insufficient education/training opportunities
Stevenson et al. 2014[40]	USA	A retrospective review and prospective observational case series; Data for cases were collected by different poison system staff members	Poison Control Center	Dabigatran, rivaroxaban exposures into the California Poison Control System	Not stated	49	Therapeutic error: patient mistakenly ingested or was given another individual's medication; retrospective and prospective review of medical records	Dabigatran and rivaroxaban	DVT	There were 7 cases of dabigatran accidental extra dosing. The excess doses ranged from 75mg to 750mg	NR	NR	NR

Troncoso et al. 2014[43]	Spain	Observational study: Retrospective review; electronic clinical records	Primary healthcare centers	Patients with AF who have been prescribed dabigatran and rivaroxaban	2,324	197	inappropriate prescribing; retrospective chart review	Dabigatran, rivaroxaban	AF	Some patients had not been prescribed dabigatran or rivaroxaban even though they were potentially suitable candidates for these drugs.	Slips-wrong dose and wrong choice dose	NR	NR
Donaldson et al. 2013[20]	USA	began as a retrospective review of patients on dabigatran therapy and continues as a prospective, intention-to-treat analysis, completed by a pharmacist-managed anticoagulation clinic	Anticoagulant clinics	Patients on dabigatran therapy; pharmacist managed anticoagulation clinic	221	54	Prescribing errors; retrospective chart review	Dabigatran	VTE, PE STROKE	Of the 54 patients experiencing an ADE, five patients (9.3%) should have been on a lower dose based on renal function and/or concurrent drug interactions.	NR	NR	NR
Schwartz et al., 2013[35]	USA	Retrospective review	Community hospital	-	-	-	Prescribing errors (incorrect dosage according to age, renal function) Inappropriate indication -inappropriate time of administration (dietary interactions); retrospective review of medical records	Dabigatran	AF	Educational activities “CARE” reduce prescribing error from 40% to 28%.	NR	NR	NR

Desai et al. 2013[19]	USA	Cross-sectional: retrospective review; The medication error reports in MEQI are collected by healthcare professionals	Nursing Home	individual medication error incidents reported by North Carolina nursing homes to the MEQI	Not stated	1623	Prescribing, documenting or Monitoring errors; retrospective chart review	Dabigatran	AF	Anticoagulant errors were more likely to be associated with patient harm (2% vs 1%, p = 0.001) compared to all other errors.	Slip and lapse-pharmacy dispensing issue and drug name confusion, incorrect transcription.	•Inadequate knowledge •Lack communica ion •Distraction, •Work overloa •failure staff to follow policy and procedure and inadequate information •Shift change	NR

Piazza et al. 2011[33]	USA	Retrospective review: physicians, pharmacists, and a hospital patient safety officer reviewed all reported anticoagulant-related events	Tertiary care Hospital	Inpatient anticoagulant-associated medication errors;	Not stated	226	Transcription errors: missed medication doses; retrospective chart review	Not stated	AF, DVT	Of 463 anticoagulant-associated ADEs, 226 were medica ion errors (48.8%), 141 were ADRs (30.5%), and 96 (20.7%) involved both a medication error and ADR	Slips and lapse: transcription errors Mistakes: wrong medication prescribed for the indica ion	NR	NR

Abbreviations: ADEs: Adverse Effect Events; ADR: Adverse Drug Reaction' AF: Atrial Fibrillation; CrCl: Creatinine Clearance; DOACs: Non-Vitamin K Antagonist Oral Anticoagulants; DRP: Drug Related Problem; DVT: Deep Vein Thrombosis; MEQI: Medication Error Quality Initiative; NR: Not reported; NVAF: Non-Valvular Atrial Fibrillation; OAC: Oral Anticoagulants; TSOAC: Target Specific Oral Anticoagulants; VKA: Vitamine K Antagonist; VTE: Venous Thromboembolism.

*Active failures are unsafe acts committed by people who are in direct contact with the patient or system. They take a variety of forms including slips and lapses (errors in task execution), mistakes (errors in planning) and procedural violations (rule breaking).

**Error-producing conditions within the workplace (e.g., time, pressure, under staffing, inadequate equipment, fatigue and inexperience)

***Latent failures which arise from decisions made by policy makers, leaders and top-level management

3.4.3 Study quality

The quality of the included studies varied. Out of the 32 studies, only two studies (6%) met the eleven CASP-related quality assessment criteria for observational studies, while one study met 10 criteria. The key limitations centred on the lack of justification for the method of sampling and sample size, and exposures characteristics which include drugs and associated comorbidities were often poorly described (Figure 3.2).

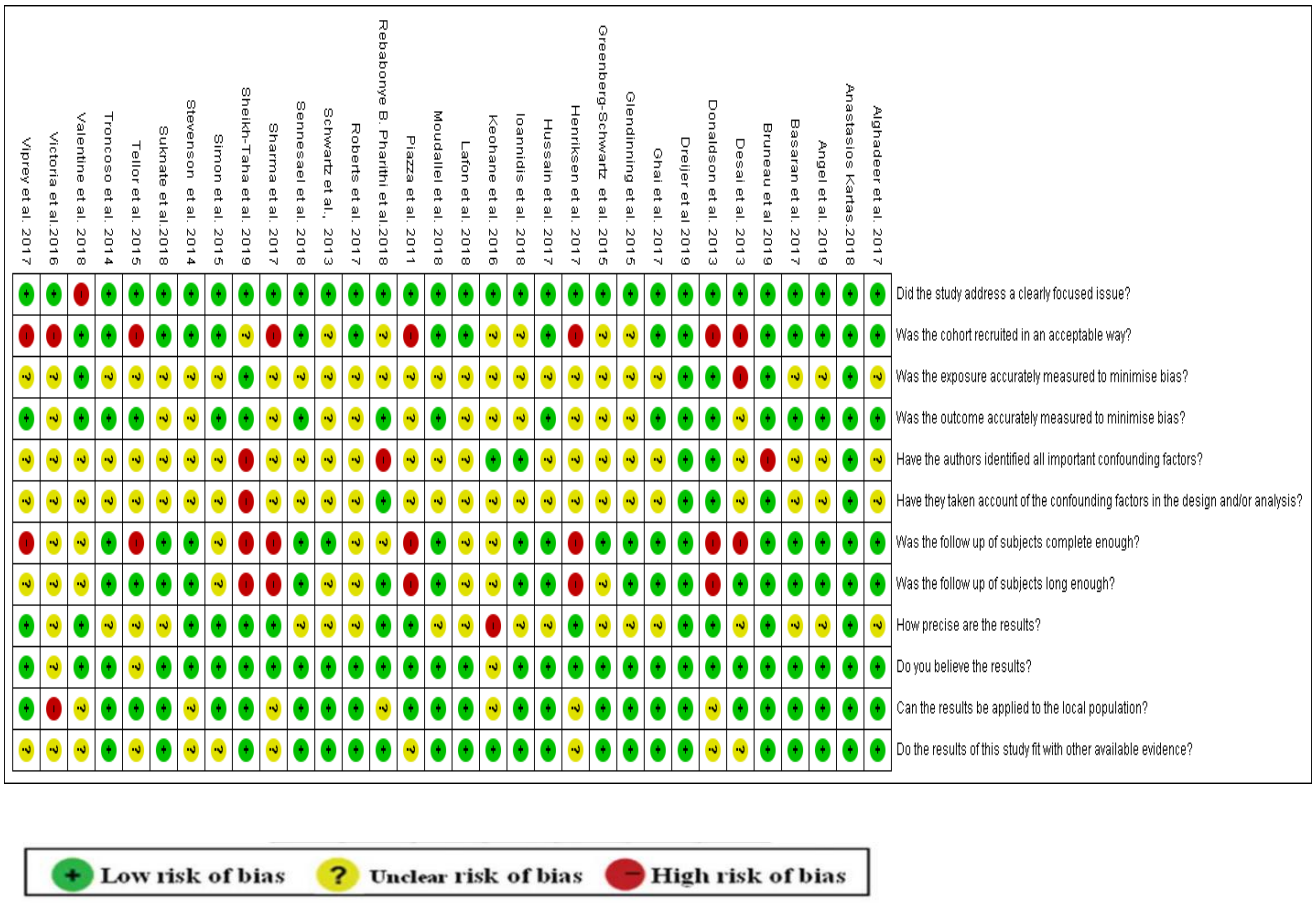


Figure 3.2 Quality assessment of studies included in the review

3.4.4 Study design and data collection

About three quarter of the studies (n= 24) used retrospective routinely collected data,(15, 16, 19, 21-26, 29, 31-35, 37-40, 42-46) six used prospective observational design,(17, 18, 27, 30, 34, 36) while two studies used mixed study design, which were combined with a retrospective chart review, prospective observational data, and clinical trial design.(20, 28) (see Table 3.1)

3.4.5 Adopted definitions of medication errors

Although a clear definition of medication error was not provided in most of the included sample studies (n=30), two studies used established definitions used by: North Carolina's Medication Error Quality Initiative (MEQI), and National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP).(19, 37)

3.4.6 Prevalence of errors

Proportion of patients who experienced either prescribing, dispensing, or administration errors across the studies ranged from 5.3% to 37.3%. The variability in the rates of errors was often contributed to the range of DOACs being indicated, types of DOACs agent used in the study settings, and consideration of either certian type of error or range of errors across the different stages of medication use process (Table 3.1).

3.4.7 Prescribing errors and contributory factors

Eighteen studies reported the number (proportion) of patients amongst the study population where prescribing errors were identified. The overall proportion of patients experiencing

prescribing error was found to be 20% (95%CI 15-25%) with a 95% prediction interval (95% PrI) between 4% and 43% (Figure 3.3).

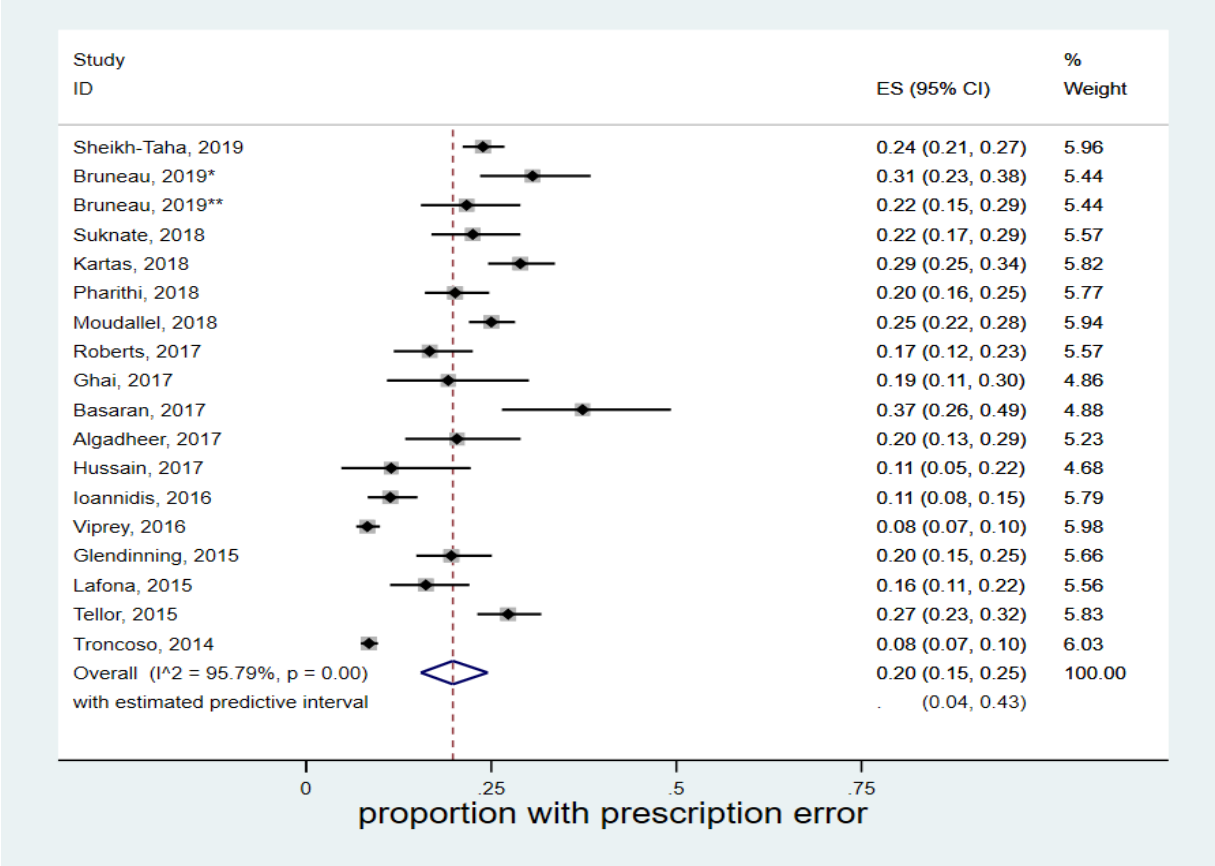


Figure 3.3 Forest plot Meta-analysis of the prevalence of prescribing errors amongst all patients prescribed DOACs

Note: * Pre-admissions; ** At discharge; ES (95% CI): proportion with 95% confidence interval (CI), p-value is from a Chi-square test for heterogeneity

Prescribing errors was the most commonly reported error types. The proportion of prescribing errors as a proportion of all error types ranged from 70 to 78%. The pooled estimate of error rate was 78% (95%CI 73%-82%; $I^2 = 0$, 95%PrI 68%-87%) (Figure 3.4).

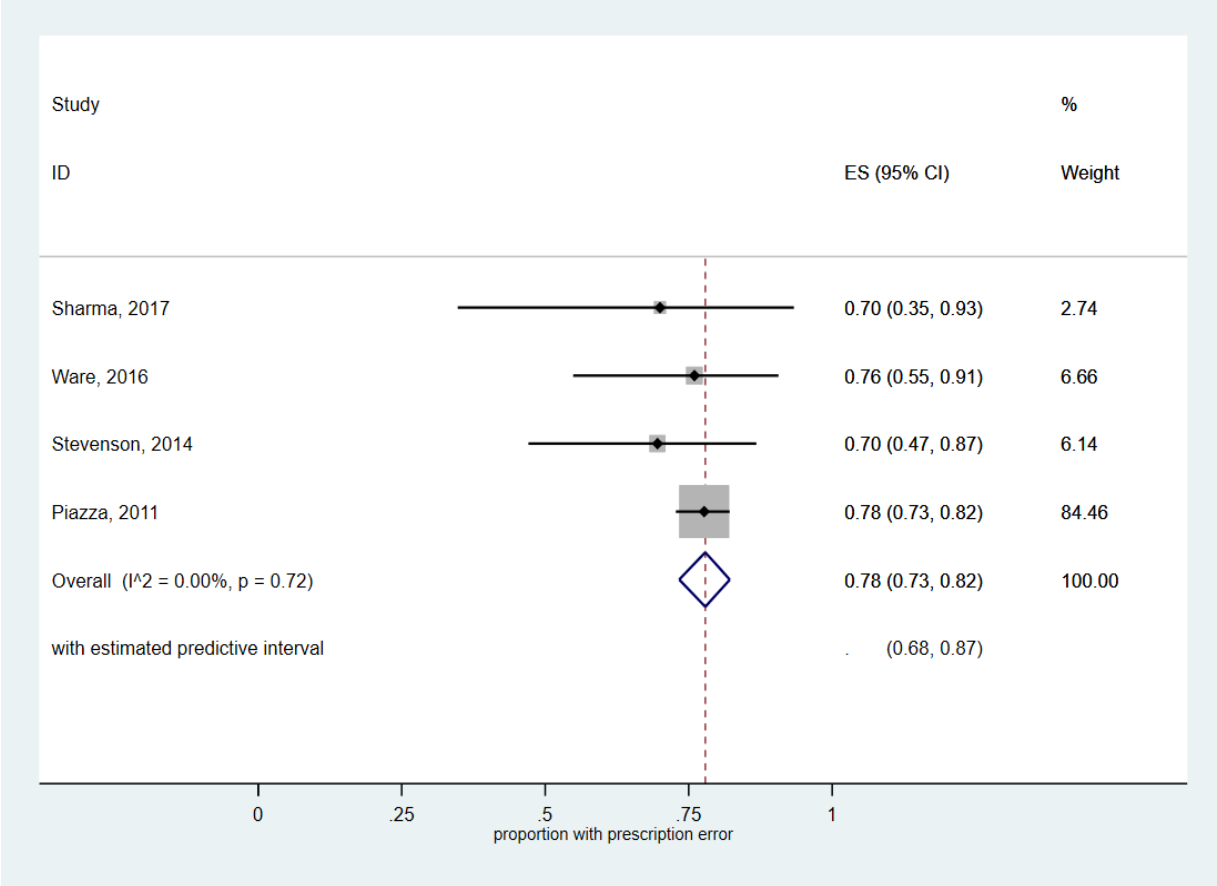


Figure 3.4 Forest plot meta-analysis of the prevalence of prescribing errors amongst all medication errors associated with DOACs

Note: ES (95% CI): proportion with 95% confidence interval (CI), p-value is from a Chi-square test for heterogeneity

Prescribing errors detected in the included studies were over or under dosing (15), missed medication doses,(18) and inappropriate prescribing in the context of indication, altered renal function (particularly creatinine clearance), advanced age, altered weight, concomitant medications, and prescribed contraindication based on product label guidelines (Table 3.1). Studies also reported duplicate therapy from different DOAC agents as one of the common prescribing errors.

A study conducted in a tertiary care community hospital in the USA reported that over a third of patients (n=92, 35.4%) who received rivaroxaban had an inappropriate dose ordered. Forty-one of these patients were considered too low, while 51 were considered too high based on the patient's renal function at the initiation of rivaroxaban.(42) A UK study showed that 12 (16.4%) of the included patients were prescribed the full dose despite having impaired renal function (CrCl<50). (33) In a study conducted in Ireland, an inappropriate dose according to CrCl was found in 11%. (29) The study conducted in a community hospital by Tellor et al. to evaluate the appropriateness of rivaroxaban's dosing, indication and safety reported that 36.9% of patients treated for NVAF, and 12.4% treated for VTE were on an inappropriate regimen.(42) Furthermore, 20 patients (7.7%) were treated for NVAF with an unapproved 10 mg dose of rivaroxaban, whereas two patients (0.8%) had an inappropriately high dosing frequency of twice daily. Although rivaroxaban is only approved for NVAF, six patients (2.3%) were treated for atrial fibrillation as off label use.(42)

3.4.8 Administration errors

Only two studies reported the rate of administration errors amongst all types of medication errors associated with DOACs. Heterogeneity was low ($I^2 = 0$), though there were little data to estimate between-study variance. The pooled estimate gave a prevalence of errors to be 5% (95% CI 2%- 7%). However, nearly all of the weight in the meta-analysis was given to one study.(33) Therefore, there were insufficient studies to calculate a prediction interval (Figure 3.5).

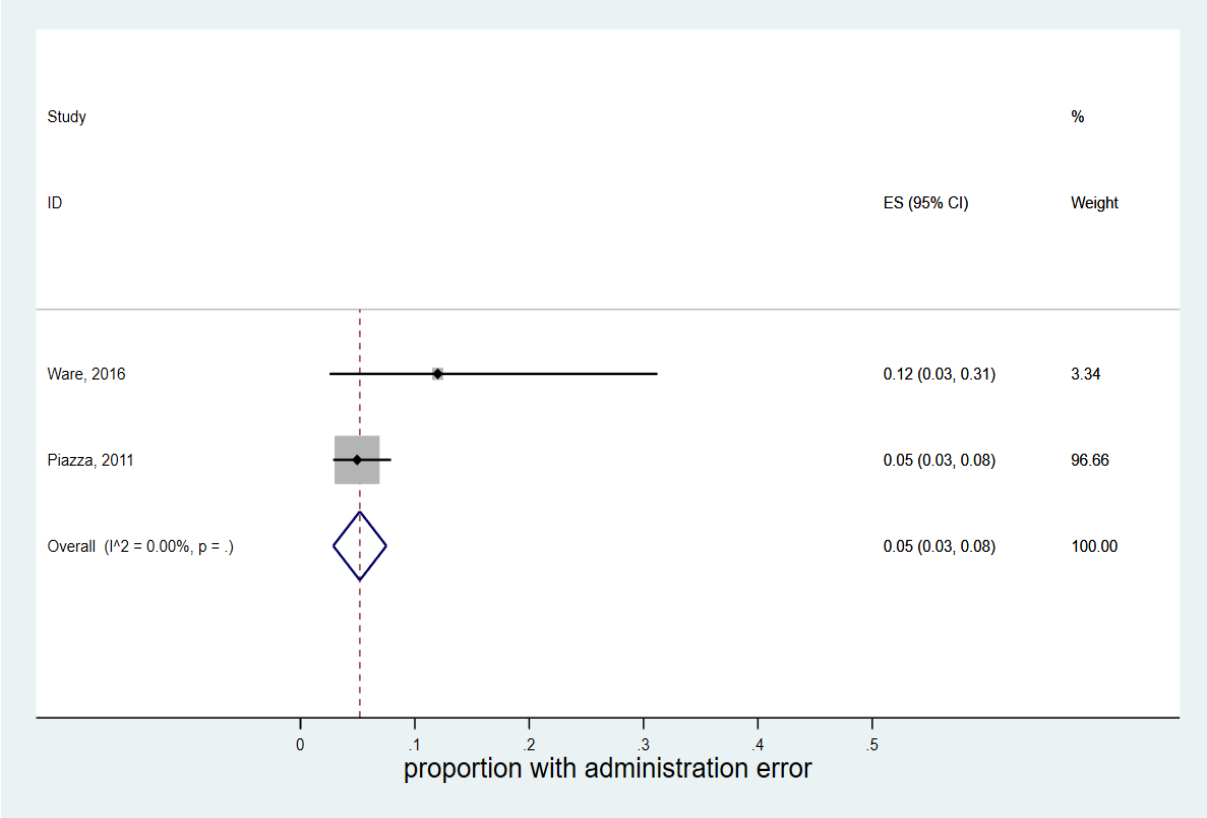


Figure 3.5 Forest plot Meta-analysis of the prevalence of administration errors amongst all medication errors associated with DOACs. Note: ES (95% CI): proportion with 95% confidence interval (CI), p-value

is from a Chi-square test for heterogeneity

A prospective study conducted at a private general hospital in Greece reported that Apixaban was the most frequent DOACs agent to be erroneously administered (13 of 76 cases, 17.1%), followed by rivaroxaban (28 of 257 cases, 10.9%) and dabigatran (one of 37 cases. 2.7%).(27) One study reported that DOACs were often unavailable on the ward, and patients went as long as 48 hours without anticoagulation while admitted.(45) Another study reported that 24 patients (23%) were taking rivaroxaban inappropriately without food, and six patients (14%) endorsed inappropriate storage of dabigatran.(39) A study by Stevenson et al described an administration

error related to dabigatran, in which patients mistakenly ingested the drug or were given another patient's medication.(40)

3.4.9 Dispensing errors

The prevalence of dispensing errors amongst all medication errors associated with DOACs was described in one study. This study reported that out of 25 total prescribing errors associated with DOACs, only 2 (8%, 95% CI= 0-18.6%) were identified as dispensing errors.(45)

3.4.10 Subgroup analyses

Subgroup analyses of error prevalence across various indications and study settings are provided in (supplementary material subgroup analysis 1-4 Figure S 3.3).

3.4.11 Consequences, severity of errors

Only four included studies,(15, 25, 40, 44) assessed the severity of harm associated with the error. Haemorrhage was the most frequently reported adverse event associated with the errors, especially in patients with lower CrCl and older age. In a US study, for example, haemorrhage occurred in 70.2% of the included subjects and of whom, almost 40% of the patients were 80 years or older, and mortality was reported in two patients in this study.(44) However, detailed causality assessment linking errors with adverse events was missing. In another study in Danish, patients prescribed dabigatran, two incidents of potentially fatal outcomes were also reported.(25)

3.4.12 Contributory factors

Of the 32 studies, only 27 reported contributory factors associated with medication errors related to DOACs, yet none of these 27 studies used any theory (e.g., behavioural or organisational) in their methodolgy or data collection or analysis. The results from these studies were categorised according to Reason's Accident Causation model and showed in Table 3.1. The most commonly reported contributing factors were active failures and mistakes, which included failure to consider risk factors of creatitine clearance, age or weight when prescribing such medicines. In addition to the inexperience and lack of knowledge of the prescriber, lack of inter-professional collaboration and poor communications with other healthcare providers or with the patients, as well as staffing and workload issues were also reported as contributory factors that lead to medication errors associated with DOAC (Table 3.1).

3.5 Discussion

Oral anticoagulants are currently among the most widely prescribed medications in clinical practice, with DOACs becoming more and more utilized over VKAs. DOACs have more predictable pharmacokinetic profiles, lower bleeding risks, and fewer drug interactions than warfarin.(47) Complexity of patients' conditions and polypharmacy therapeutics on the other hand, can increase the risk of adverse events. The popularity of DOACs and their associated adverse events made them of interest to investigate errors and identify their contributing factors. The purpose of this study was to systematically review the prevalence of medication errors associated with DOACs and its contributory factors. Studies reported a wide prevalence rates

were often influenced by the method used for error definition and detection, drugs being investigated for errors, and the patient population.

3.5.1 Prevalence of errors

This systematic review revealed that prescribing errors, particularly the dose-related, was the most prevalent type of errors associated with DOACs. Although DOACs are given in fixed doses and not requiring routine coagulation monitoring, dosing varies based on drug used, indication, renal function, age, and body weight, as well as concurrent medications.(48-52) The nature of errors identified in the systematic review were reflective of these factors.

3.5.2 Severity of errors

The severity of medication incidents reports may help identify possible areas for improvement in reporting the adverse events and types of errors related to DOACs. Few studies had reported the severity of adverse events associated with medication errors. New thrombotic and bleeding events risks are found to be associated with suboptimal prescribing,(53) while the likelihood of hospitalisation and mortality increases with overdosing. Detailed causality assessments were often missing in the included studies as to whether the errors primarily contributed to the adverse events.

3.5.3 Implications for practice

There are several risk reduction strategies relevant to minimise and avoid harm related to medications errors with DOACs. Development of novel-theory based, and technology-enabled interventions can improve patient safety. Educating the healthcare professionals through training

sessions and adopting anticoagulant stewardship programme can be effective. Secondly, undertaking medication reconciliation on admission and discharge as well as upon care transfer in combination with medication reviews.

The relative ease of prescribing and monitoring DOACs compared to VKAs makes them the first prescribing choice for many indications like a non-valvular atrial fibrillation and VTE. Such prescribing preference could lead to increased incidence of different types of prescribing errors. Each DOAC has a different dosing schedule and dose adaptations, mostly reductions, depending on one or more patient-specific factors including age, weight, renal function, indication, and concomitant medications. As seen in the included studies, one of the reasons for overdosing DOACs was failing to adjust the dose of DOACs for specific indication, renal function, age and/or weight(31)(31). Similarly, elderly patients who are at high risk of developing stroke are often likely to be underdosed. Amongst the included studies, which reported nearly fatal or fatal adverse events linked to prescribing errors, severe incidents most commonly occurred during sector change, such as admissions, discharge, or undergoing surgery.[25, 44] It is imperative that additional precautions be applied during patient transitions across sectors as well as prior to and after surgical procedures.

This review has revealed that the contributing factors to medication errors with DOACs are multifactorial. These factors include inappropriate drug selection and lack of dose adjustments consideration due to failure to approach patients holistically by assessing, for instance, renal function, medical or medication histories or demographics. Inexperience, poor communication, and lack of inter-professional collaborative practice together with non-compliance to clinical

guidelines also contributed to their inappropriate prescribing. Therefore, adopting inter-professional team-based clinical practice and leaning as well as pharmacist-led anticoagulant stewardship program are likely to minimise errors. A recent meta-analysis showed that including a pharmacist in clinical rounds alongside educational interventions and prescription reviews can significantly reduce prescribing errors by as much as three quarters.[54]

3.5.4 Implications for research

Future studies should expand on the current research to determine techniques that reduce the occurrence of the more prevalent errors associated with DOACs. Behavioural frameworks, such as the Theoretical Domains Framework (TDF), are useful in identifying target behaviours and future interventions. (55) Future studies should consider data from non-hospital settings and undertake rigorous causality assessment to investigate the link between errors and adverse outcomes.

3.5.5 Study strengths and limitations

To the best of our knowledge, this is the first systematic review and meta-analysis that aim to review the prevalence of DOACs associated errors and its contributed factors. A wide range of databases was used including grey literature. However, the current review was limited to the literature published in English language. Overall, the review endorsed the variability of clinical implications and consequences of errors based on patients characteristics such as age, co-morbidities, and concomitant of drug therapy.

Furthermore, this review used Reason's Accident Causation model to analyse the data related to the error causation. This model focuses on the system or the environment in which the error occurred, rather than the individual that caused the error, and the random rather than intentional act. However, it is important to note that classifying errors based on this model could be subject to the researchers' interpretation bias, particularly when the conditions of the error were not thoroughly described. Therefore, mutually exclusive classification of the documented medication errors is not always possible. In addition, well-known causes of medication errors under-reporting, such as perceived fears of blame, punishment, or indemnity either by patients, clinicians or administration, consequences of reporting protocol, heavy workload, and lack of time will impede estimating the true prevalence of actual errors reported in the included studies.[56] Therefore, studies that rely on incident reporting databases to identify error rates are likely to provide underestimation of true prevalence.(57)

3.6 Conclusions

This systematic review and meta-analysis suggest that despite their favourable safety profile and relative ease of use compared to VKAs, medication errors with DOACs are common. Future studies should consider data from non-hospital settings and undertake rigorous causality assessment to investigate the link between errors and adverse outcomes. There is a need to promote multidisciplinary working, guideline- adherence, training and education of healthcare professionals and the use of theory-based and technology facilitated interventions to minimise errors and maximise the benefits of DOACs usage in all settings.

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3.8 Conflict of Interest

The author declares no conflicts of interests.

3.9 Data statement

All data generated or analysed during this study are included in this manuscript.

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Chapter 4. Medication errors associated with direct-acting oral anticoagulants: analysis of data from national pharmacovigilance and local incidents reporting databases

Chapter overview: This chapter presents the study aimed to explore the types of medication errors and contributory factors associated with DOACs in hospital settings in Saudi Arabia using national and local hospital datasets.

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Authors contribution: This study relates to AA's PhD research. VP, ZJ supervised AA for his PhD. All authors co-designed the study. Search was performed by AA and verified by NO and MHA. The data analysis and interpretation were conducted by AA and reviewed by VP, ZJ and MA. The first manuscript draft was written by AA. All authors read and approved the final manuscript

4.1 Abstract

Background: For more than a decade, direct oral anticoagulants (DOACs) have been approved in clinical practice for multiple indications such as stroke prevention in non-valvular atrial fibrillation treatment of deep vein thrombosis and pulmonary embolism. This study aimed to explore the nature and contributory factors related to medication errors associated with DOACs in hospital settings.

Methods: Analysis of error reports using data from a) Saudi Food and Drug Authority pharmacovigilance database and b) local incidents reporting system from two tertiary care hospitals were included. Errors reported from January 2010 to December 2020 were also included. Statistical analyses were performed using IBM (SPSS) Statistics Version 24.0 software.

Results: A total of 199 medication error incidents were included. The mean (range) age of affected patients was 63.5 (19-96) years. The mean reported duration of treatment when incidents happened was 90 days, with a very wide range from one day to 12 months. The prescribing error was the most common error type representing 81.4% of all errors. Apixaban was the most frequent drug associated with error reporting with 134 (67.3%) incidents, followed by rivaroxaban (18.6%), and dabigatran (14.1%). The majority of the patients (n=188, 94.5%) showed comorbidities in addition to the conditions related to DOACs. Polypharmacy, an indication of treatment and duration of therapy were amongst the important contributory factors associated with errors.

Conclusions: This observational study demonstrates the nature of DOAC errors in clinical practice. Developing risk prevention and reduction strategies using the expertise of clinical pharmacists is imperative in promoting patient safety associated with DOAC use.

4.2 Introduction

Direct oral anticoagulants (DOACs), or the non-vitamin K antagonist oral anticoagulants (NOACs) includes dabigatran, rivaroxaban, edoxaban, apixaban, and betrixaban. In Saudi Arabia, clinicians follow recommendations of a recently published clinical pathway for DOACs by the Saudi Society of Clinical Pharmacy.(1) The Saudi Food and Drug Authority approved rivaroxaban in 2011, apixaban in 2014 edoxaban in 2018 and dabigatran in 2009 for stroke prevention in NVAF, and treatment or prevention of venous thromboembolism (VTE).(2) Rivaroxaban also has other indications, such as indefinite anticoagulation, stable coronary arterial disease or peripheral arterial disease, VTE prophylaxis in acutely ill medical patients and in total hip or knee arthroplasty. Apixaban and dabigatran also have approval for VTE prophylaxis in total hip or knee arthroplasty.(1)

DOACs have gained popularity in clinical practice because they have fixed dosing and do not need frequent monitoring, have fewer drug and food interactions, and offer less risk of bleeding compared to warfarin.(3-9) These characteristics have made them an attractive choice for the management of conditions requiring anticoagulation therapy.(10) They are labelled as high-risk medications due to the risk of causing significant patient harm if used inappropriately.(11)

DOACs can cause bleeding if overdosed or exacerbate thromboembolic events if a therapeutic failure occurs, and it could further increase mortality.(12) Factors that could lead to inappropriate prescribing of DOACs could range from inaccurate dosing due to renal dysfunction, non-consideration of patients' body weight or age or concomitant polypharmacy.(13) Currently, there is a lack of research about medication errors associated with DOACs in Saudi Arabia.(14)

Identifying DOACs most commonly involved with errors, type of errors, contributory factors, and patient characteristics that are linked with frequent occurrence of errors can enable identifying appropriate strategies to improve patient safety. This study aims to explore the types of medication errors and contributory factors associated with DOACs in hospital settings in Saudi Arabia using national and hospital local datasets. Specific objectives were: a) Identifying the DOACs most commonly involved in the medication errors and b) identifying the stages in the medication journey where the errors occurred in order to understand the contributory factors.

4.3 Methods

4.3.1 Study design

The design of this study was a retrospective observational using incidents reporting databases from two healthcare institutions and the pharmacovigilance database of a national regulatory body, the Food and Drug Administration (FDA) in Saudi Arabia.

The hospital-based data were retrieved from the electronic medical record system for all errors reported from the year of such medications became available in Saudi Arabia, January 2010 to December 2020. They included patients' demographic data (age, gender, weight, and height), drug name and its indication, comorbidities, dosing regimen and duration of treatment, type of medication error (prescribing, administration, and dispensing), and renal function test results.

The Pharmacovigilance Electronic Reporting Service in the Saudi FDA is an online spontaneous reporting system for reporting side effects, medication errors, and any defect in the quality of

pharmaceutical preparations. It also allows sending and submitting communications to report a drug shortage by health practitioners, pharmacies, health institutions, companies, and community members. It receives voluntary reports of safety concerns from health practitioners and patients.

All reports associated with DOACs errors in adult population generated from 2010-2020 were included in the study for the final analysis. Reports without drug names or not related to DOACs were excluded. The local collaborators at the main centres in Saudi Arabia communicated with the respective departments to obtain the required medication error reports for the said period. The data were retrieved electronically from the institutions' reporting systems using drug names as the search terms. The extracted data were cleaned for any duplications, and all variables were compiled in an excel file.

Statistical analyses were performed using IBM (SPSS) Statistics Version 24.0 software. Quantitative data (age in years) were described using median, range, and Interquartile range after data distribution exploration normality using Kolmogorov–Smirnov (K–S test) and Shapiro tests. Descriptive analysis was utilised to describe numbers and proportions. For all statistical tests, a significance level was determined below 5%. Monte-Carlo Exact test was used for comparing the categorical variables instead of the Chi-Square test because the assumptions of conducting a chi-square test were violated [> 20 % of the cells had an expected count less than 5].

This study was reviewed and approved by a research ethics committee in the University of Birmingham (ERN_20-0551). Approvals were also obtained from King Abdullah International

Medical Research Center (KAIMRC) at Ministry of National Guard, Saudi Arabia (SP/212/R), and from KFMMC (AFHER-IRB-2020-015), as well as from Saudi Food and Drug Authority (SFDA).

4.4 Results

After reviewing the reported safety incidents of medication errors in all involved Saudi Arabia institutions, the database revealed that a total of 199 medication error incidents were found related to direct oral anticoagulants (DOAC); 109 errors were reported from the hospitals, and 90 errors reported from Saudi Food and Drugs Authority (SFDA) from January 2010 to December 2020. Table 4.1 illustrates patients' characteristics with the reported incidents.

Table 4.1 Characteristics of Medical Errors Reports included in the study

Sample Characteristics (n=199)	n (%)
Number of reported medical error /setting: - Hospitals - SFDA	 109 (54.8%) 90 (45.2%)
Age in years: Median (IQ Range)	63.5(48.0–76.0)
Gender: n= 198 Male Female	 99 (50.0%) 99 (50.0%)
Weight in Kg: Median (IQ Range)	75(63.0 – 89.0)
Height in Cm: Median (IQ Range)	161(154.0–169.0)
Comorbidities:	188 (94.5%)
DOAC type: Apixaban Dabigatran Rivaroxaban	 134 (67.3%) 28 (14.1%) 37 (18.6%)

Indications for DOAC:	
Atrial Fibrillation (AF)	113 (56.8%)
Deep Vein Thrombosis (DVT)	55 (27.6%)
Pulmonary Embolism (PE)	20 (10.1%)
Cerebral Venous Thrombosis (CVT)	2 (1.0%)
Others	9 (4.5%)
DOAC dose at the incidence day: (Only for the hospitals dataset)	
Not reported	2 (1.8%)
Under-dose	40 (36.7%)
Optimum dose	47 (43.2%)
Over-dose	6 (5.5%)
++Over- dose	14 (12.8%)
Medication Error type: Prescribing Dispensing Administration Monitoring Storage	 162 (81.4%) 21 (10.6%) 9 (4.5%) 4 (2.0%) 3 (1.5%)
Medication Error Subtype:	
Medication duplicate therapeutic category	33 (16.6%)
Wrong patient	25 (12.6%)
Incorrect dose	44 (22.1%)
Incorrect frequency	29 (14.6%)
Incorrect quantity	30 (15.1%)
Incorrect duration	11 (5.5%)
Incorrect medication	9 (4.5%)
Delay preparation	4 (2.0%)
Improper / lack of documentation	4 (2.0%)
Side effects	2 (1.0%)
Contraindicated drug/drug interactions	8 (4.0%)
Duration of DOAC when incidence happened (days): Median (IQ Range)	90 (30 – 180)
e-GFR at the day of incidence (only for the hospitals) Mean ± SD Range	 78.61 ± 33.21 (0 - 173)

Note: *SD: Standard deviation **IQ: Interquartile range

4.4.1 Medication errors related to specific DOAC and indication

Medication errors were reported for three DOAC drugs; the higher incidents were reported with apixaban (67%), followed by rivaroxaban (19%) and dabigatran (14%) as shown in Figure 4.1.

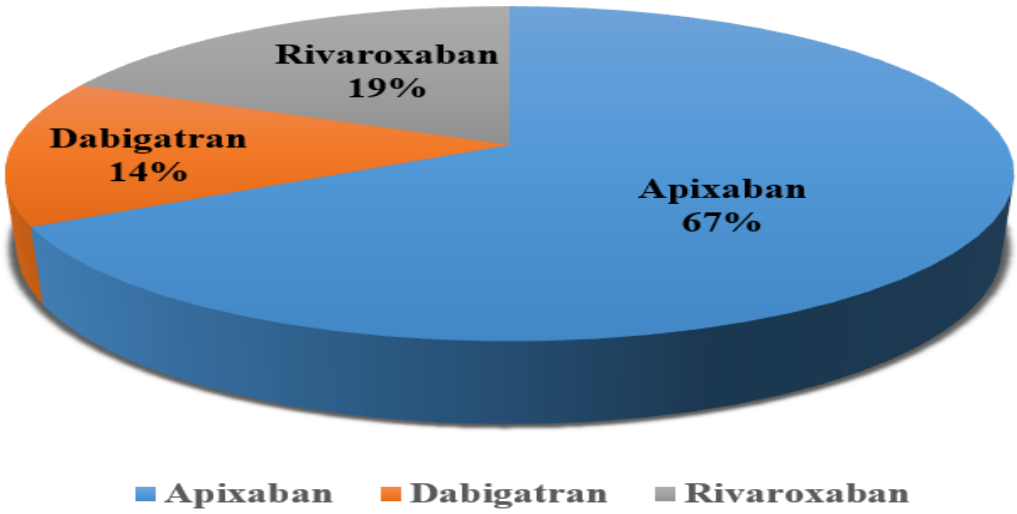


Figure 4.1 Proportions of direct acting anticoagulants (DOACs) associated with medical errors

Most of the indications for DOACs were found to be related to atrial fibrillation at (56.8%), followed by deep vein thrombosis at (27.6%), pulmonary embolism at (10.1%), cerebral venous thrombosis at (1.0%), and others at (4.5%) as shown in Figure 4.2.

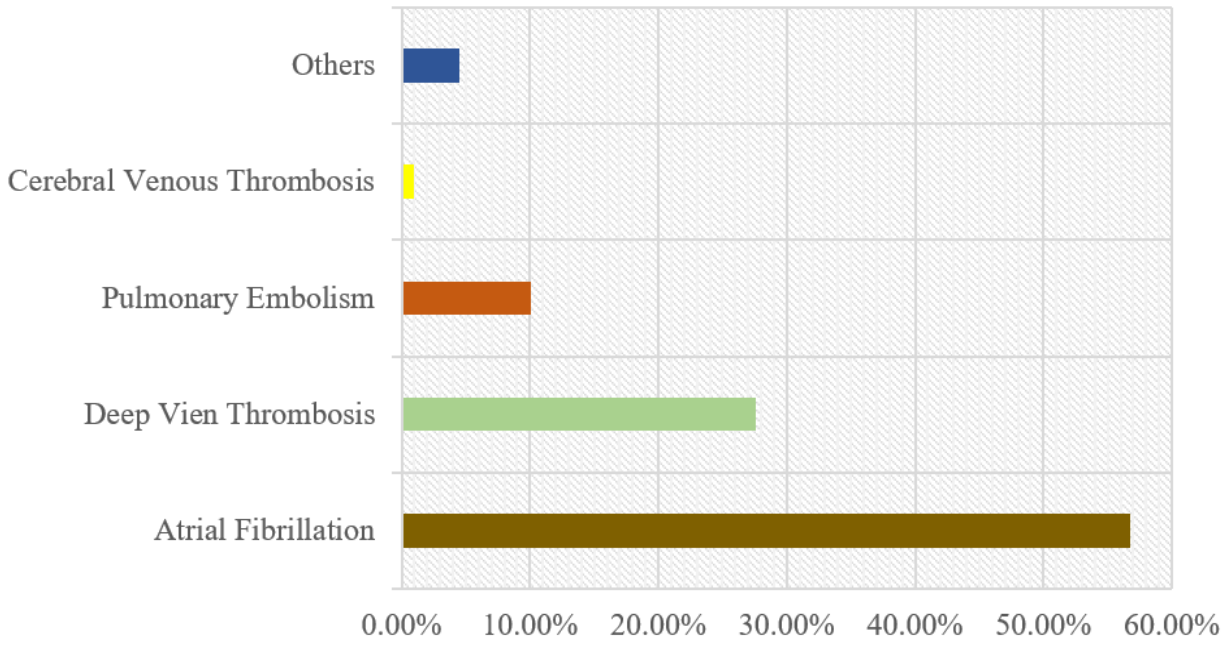


Figure 4.2 Different indications of direct oral anticoagulants (DOACs) in the medication error reports

4.4.2 Errors as per the stages of medication journey

The most commonly identified sub-type of prescribing errors related to prescribing incorrect dose accounting for 44 incidents (22.1%), followed by 33 (16.6%) incidents of duplicate prescribing, 30 (15.5%) incidents of dispensing incorrect quantity, prescribing incorrect frequency with (n=29, 14.6%), 25 (12.6%) incidents of dispensing to the wrong patient, and 11 (5.5%) incidents of prescribing an incorrect duration.

Figure 4.3 shows incidents of medication errors related to the stages of the medication use process.

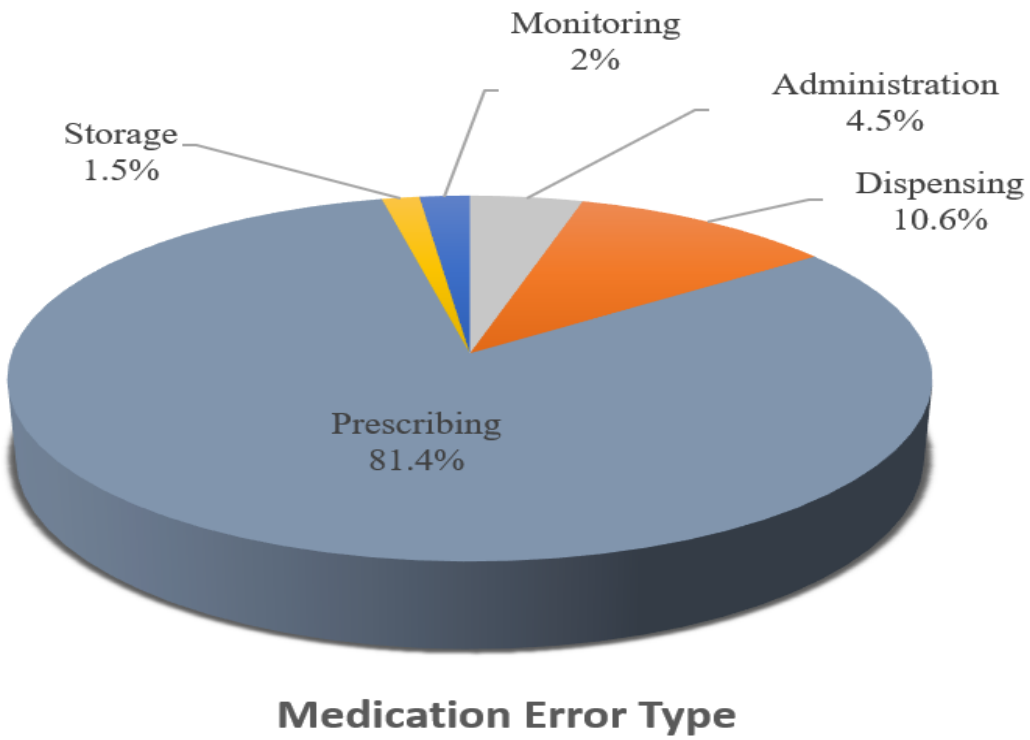


Figure 4.3 Different types of medication errors reported with direct oral anticoagulants (DOACs)

The other sub-types represented minimal incidents (less than 5%), such as delayed preparation, improper or lack of documentation. Figure 4.4 summarises the percentages for all the identified types of medication errors.

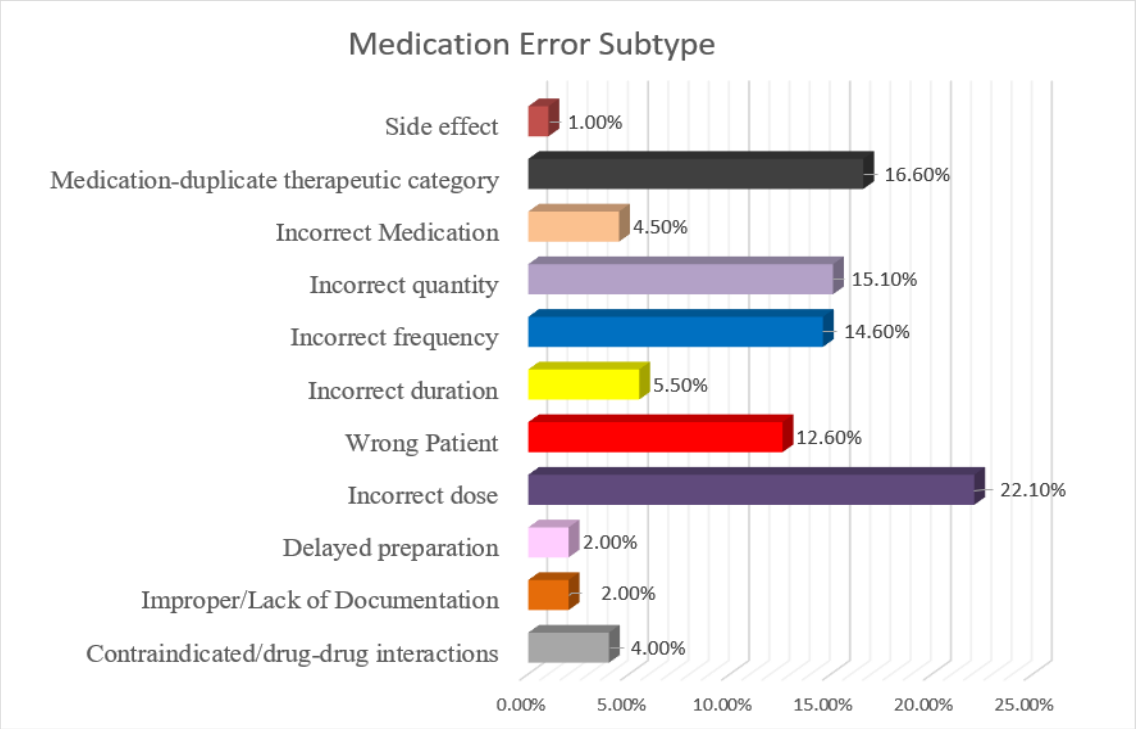


Figure 4.4 Sub-types of medication errors associated with direct oral anticoagulants (DOACs)

4.4.3 Errors classified as per specific DOAC and their indications

Whilst analysing the indication of the DOAC drugs among the collected reports, it was found that apixaban was mainly prescribed for atrial fibrillation (n= 73, 54.5%). It was also prescribed to the cases of deep vein thrombosis (n= 34, 25.4%), pulmonary embolism (n= 17, 12.7%), cerebral venous thrombosis (n= 2, 1.5%), and others such as hip or knee replacement surgery representing about (6%). Likewise, rivaroxaban was mainly prescribed for atrial fibrillation (n= 27, 73%), deep vein thrombosis (n= 8, 21.6%), and pulmonary embolism (n= 2, 5.4%). Dabigatran was prescribed equally for atrial fibrillation and deep vein thrombosis (n= 13, 46.4%, each), and it was prescribed to single cases of pulmonary embolism and others, as shown in table 4.2.

Table 4.2 Drug indication and the status of dose appropriateness of DOAC in the Medical Errors Reports

Drug Indication	DOAC type			Statistical test*	p
	Apixaban (n = 134)	Dabigatran (n = 28)	Rivaroxaban (n = 37)		
Atrial Fibrillation	73 (54.5%)	13 (46.4%)	27 (73.0%)		
Deep Vein Thrombosis	34 (25.4%)	13 (46.4%)	8 (21.6%)		
Cerebral Venous Thrombosis	2 (1.5%)	0 (0.0%)	0 (0.0%)	12.883	0.115
Pulmonary Embolism	17 (12.7%)	1 (3.6%)	2 (5.4%)		
Others	8 (6.0%)	1 (3.6%)	0 (0.0%)		

4.4.4 Errors classified as per specific DOAC and stages of medication journey

Whilst analysing the phases and types of medication errors associated with the three DOAC drugs, it was found that 103 (76.8%) of apixaban incidents occurred during the prescribing phase, 20 (15.0%) during the dispensing phase, 7 (5.2%) occurred during the administration phase, 3 (about 2.3%) occurred during the storage process, and only one incident (about 0.7%) reported during the monitoring phase. For dabigatran, almost all the errors (n= 27, 96.7%) were within the prescribing phase, with only one reported incident during the dispensing phase. For rivaroxaban, the majority of errors (n= 32, 86.5%) occurred during the prescribing phase, with 3 (8.1%) incidents during the monitoring phase, and two incidents (5.4%) during the administration phase. There was a statistically significant difference in the percentage of medication errors among the three reported drugs during the prescribing phase (p = 0.001), while the other phases did not exert statistical significance, as shown in table 4.3.

Table 4.3 Phases and types of reported medication errors associated with direct oral anticoagulants (DOAC) in the Medical Errors Reports

Medication Error Type		DOAC type			Statistical test*	p
		Apixaban (n = 134)	Dabigatran (n = 28)	Rivaroxaban (n = 37)		
Prescribing (n=162, 81.4%)	Medication-duplicate therapeutic category	26 (19.4%)a	1 (3.6%)b	0 (0.0%)b		
	Incorrect dose	17 (12.7%)a	5 (17.8%)a	11 (29.7%)a		
	Wrong Patient	9 (6.7%)a	3 (10.6%)a, b	8 (21.6%)b		
	Incorrect frequency	23 (17.2%)a	2 (7.2%)a	3 (8.1%)a		
	Incorrect quantity	11 (8.3%)a	9 (32.1%)b	9 (24.3%)b	46.262	0.001*
	Contraindicated/drug-drug interactions	6 (4.4%)a	1 (3.6%)a	0 (0.0%)a		
	Incorrect duration	5 (3.8%)a	4 (14.3%)a	1 (2.7%)a		
	Incorrect medication	2 (1.4%)a	2 (7.2%)a	0 (0.0%)a		
	Improper/Lack of Documentation	3 (2.2%)a	0 (0.0%)a	0 (0.0%)a		
	Side effect	1 (0.7%)a	0 (0.0%)a	0 (0.0%)a		
Total per DOAC type		103 (76.8%)	27 (96.4%)	32 (86.5%)		
Dispensing (n=21, 10.6%)	Medication-duplicate therapeutic category	1 (0.7%)	0 (0.0%)	0 (0.0%)		
	Incorrect dose	5 (3.8%)	0 (0.0%)	0 (0.0%)		
	Wrong Patient	5 (3.8%)	0 (0.0%)	0 (0.0%)		
	Incorrect quantity	1 (0.7%)	0 (0.0%)	0 (0.0%)	21.000	0.140
	Contraindicated/drug-drug interactions	0 (0.0%)	1 (3.6%)	0 (0.0%)		
	Incorrect medication	5 (3.8%)	0 (0.0%)	0 (0.0%)		
	Delay preparation	3 (2.2%)	0 (0.0%)	0 (0.0%)		
Total per DOAC type		20 (15.0%)	1 (3.6%)	0 (0.0%)		
Administration (n=9, 4.5%)	Medication-duplicate therapeutic category	5 (3.8%)	0 (0.0%)	0 (0.0%)		
	Incorrect dose	1 (0.7%)	0 (0.0%)	1 (2.7%)		
	Incorrect duration	0 (0.0%)	0 (0.0%)	1 (2.7%)	6.107	0.168
	Side effect	1 (0.7%)	0 (0.0%)	0 (0.0%)		
Total per DOAC type		7 (5.2%)	0 (0.0%)	2 (5.4%)		
Monitoring	Incorrect dosage form	1 (0.7%)	0 (0.0%)	2 (5.4%)		
	Incorrect frequency	0 (0.0%)	0 (0.0%)	1 (2.7%)	4.00	0.504
Total per DOAC type		1 (0.7%)	0 (0.0%)	3 (8.1%)		
Storage (n=3, 1.5%)	Incorrect dose	1 (0.7%)	0 (0.0%)	0 (0.0%)		
	Delay preparation	1 (0.7%)	0 (0.0%)	0 (0.0%)	------	------
	Improper/Lack of Documentation	1 (0.7%)	0 (0.0%)	0 (0.0%)		
Total per DOAC type		3 (2.3%)	0 (0.0%)	0 (0.0%)		

Abbreviations:

**Monte-Carlo Exact test: all phases were valid for conducting the analysis except for the storage phase because the dataset in the other phases was available for only one drug.
**Post-hoc pairwise comparison using z- test was submitted: Each subscript letter (a, b) denotes a subset of DOAC type categories whose column proportions differ significantly from each other on basis of medication error subtype with adjusted p value (< 0.167).

4.5 Discussion

DOACs are considered high-risk medication and have the potential to cause harm when used erroneously.(15) This study for the first time explored the reported medication errors related to the three approved DOAC medications in the Kingdom of Saudi Arabia. Previous studies from outside the Kingdom provide evidence of improper utilization associated with DOACs and potentially inappropriate prescribing leading to adverse events.(15, 16) In retrospective study, medication errors were identified as a common root cause in 40% of anticoagulation-related adverse events.(12)

In Saudi hospitals, several quality measures have been put in place at institutional levels, including restricting prescribing DOAC to certain specialities (e.g., cardiology, haematology, internist, and through clinical pharmacy involvement). In addition, institutional guidelines have been developed based on different international guidelines, including American Heart Association and Chest guidelines. Furthermore, the pharmacy department and pharmacoeconomic centre monitor Medication Utilization Evaluation (MUE) of all DOAC listed in the hospital formulary. It is important that prescribers and healthcare professionals responsible

for dispensing and administration of drugs are aware of the up-to-date guidelines and embrace additional safety practices when dealing with DOACs.

Among three DOACs drugs, apixaban was the most frequently prescribed anticoagulant, thus associated with a higher number of errors. In our study, we were limited to the type of data that could be retrieved from the institutional safety reporting system, and this limited further investigation and follow up for the seriousness of the reported medication errors. Previous studies have found that anticoagulants are often associated with underdosing and overdosing.(17) In one study, approximately a third of the patients received inappropriate dose including lower doses at (18%) and higher doses at (15%).(18)

This study also showed that DOACs associated medication errors were most often reported during the prescribing phase. Most of these errors were typical and included wrong dose, medication, frequency, and duration. These results are in line with prior studies that found most reported medication errors occur in the prescribing stage. Raccah et al. found that prescribing errors with DOACs occur in nearly a third of the patients with AF.(19) Dreijer et al. reported that errors with anticoagulant therapy were most often seen during prescribing and administration phases.(20) In our study, the least type of errors reported were administration error (e.g., apixaban 5.2% and rivaroxaban 5.4%), which usually occurs during the administration of drugs by nurses in hospitals or by patients at home. In France, a prospective nationwide cohort study in primary care reported that 39% of the patients received at least one inappropriate DOAC prescription, mostly were inappropriate under-dosing.(21) Another cross-sectional study of oral

anticoagulant use in patients with AF showed under-dosing in 13.1% of prescriptions, and unfortunately 39.4% of their patients had not prescribed an indicated DOACs.(22)

This observational study is limited due to its retrospective design and the small number of variables available to undertake detailed evaluation of the nature and causes of errors. The sample size was limited despite including both national and local datasets suggesting the extent of under-reporting of medication errors. Furthermore, the consequences, including clinical, humanistic, and cost-related outcomes of these errors, could not be estimated from the available data. Pharmacists and nurses are the main healthcare professionals reporting these prescribing errors in the institution, yet we do not have clear data on the reporting proportion.

4.6 Conclusion

Further development and standardization of risk preventive measures is crucial to minimize the harm from medication errors with DOACs. Most of the reported DOACs associated medication errors relate to prescribing stage, characteristically in the form of inappropriate dose, the inappropriate agent chosen, frequency, and duration. It is critical to educate the healthcare professionals about the safe and effective use of DOACs and the importance of medication error reporting. Pharmacists can play an integral role in minimizing medication error incidents through the development of safe and effective pharmacotherapeutic plans at the initial assessment and prescribing phase. Safety issues can also be identified and addressed during medicines reviews, medicines reconciliation, and patient counselling. Healthcare professionals' awareness and the need to have clear prescribing guidelines is imperative for safe DOACs prescribing.

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Chapter 5. Contributory factors and patient harm including deaths associated Direct Acting Oral Anticoagulants (DOACs) medication incidents: evaluation of real world data reported to the National Reporting and Learning System

Chapter overview: This chapter investigates and reports the nature, severity of harm, and types of all medication incidents related to DOACs submitted through all clinical settings across England and Wales to the NRLS database. An in-depth evaluation of all incidents associated with severe harm and deaths were conducted.

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Authors contribution: The authors confirm contribution to the paper as follows: study conception and design: Abdulrhman Alrowily, Zahraa Jalal and Vibhu Paudyal; data collection: Abdulrhman Alrowily and Vibhu Paudyal; The primary author (Abdulrhman Alrowily) was responsible for cleaning up of data and applying the inclusion/exclusion criteria. A sample of 10% of these data was validated by two other authors Vibhu Paudyal and Zahraa Jalal. Analysis and interpretation of results: Abdulrhman Alrowily, Zahraa Jalal; Draft manuscript preparation: Abdulrhman Alrowily. All authors reviewed the results and approved the final version of the manuscript prior to submission.

5.1 Abstract

Introduction: Direct oral anticoagulants (DOACs) are considered high risk medicines; however, they are frequently associated with medication errors. Nature of incidents and associated outcomes of such incidents are poorly understood.

Areas covered: Using a national patient safety reporting database- the National Reporting and Learning System (NRLS), this study aimed to report the contributory factors and outcomes including severe harm and deaths related to all safety incidents involving DOACs reported to the in England and Wales between 2017 and 2019. Reason's accident causation model was used to classify the incidents.

Expert opinion: A total of 15,730 incident reports were analysed. A total of 25 deaths were reported with a further 270 and 55 incidents leading to moderate and severe harm, respectively. A further 8.8% (n=1381) of incidents were associated with low degree of harm. The majority of the incidents involved active failures (n=13776; 87.58) including duplication of anticoagulant therapies, patients being discharged without DOACs, non-consideration of renal function, and lack of commencement of DOACs post-surgery. This study showed that medication incidents involving DOACs, thus have the potential to cause severe harm and deaths; therefore, there is a need to promote guideline adherence through education, training, and decision support technologies.

5.2 Introduction

Direct oral anticoagulants (DOACs) have been recognized as one of the most commonly concerned drug classes in relation to safety incidents.(1, 2) The lack of long-term clinical experiences and the need for careful consideration of risk and benefit profiles make DOACs more likely candidates for medication errors, particularly prescribing errors.(3) A recent published systematic review of 32 studies concluded that one in five prescriptions of DOACs have errors in prescribing [pooled prescribing error rate of 20% (95% CI 15–25%; I2 = 96%; 95% PrI 4–43%)].(4) However, the review identified that data on circumstances, contributory factors and likelihood of harm were scant.

Medication errors can be detrimental to patient safety, yet they are a common occurrence in clinical practice.(5) A recent estimate suggested that 66 million out of 237 million medication errors which occurred in England annualy are potentially clinically significant.(6) The WHO 'Global Patient Safety Challenge: Medication Without Harm' had set a global challenge which aimed to reduce severe avoidable medication-related harm by 50% by 2022.(7) Errors can occur throughout the medication use processes including storage, distribution, prescribing, compounding, preparing, dispensing and administration and during monitoring.(8)

The National Health Service (NHS) England aims to promote safety culture and to monitor spontaneously reported safety incidents by healthcare professionals (HCPs) or patients through the National Reporting and Learning System (NRLS).(9) The NRLS allows safety incidents in relation to healthcare and healthcare interventions to be reported from all healthcare settings from England and Wales, collated and analyzed to prevent future incidents and promote patient

safety. The NRLS database offers excellent opportunity to identify circumstances and contributory factors in relation to medication errors involving DOACs.

The NRLS defines a 'patient safety incident' as 'any unintended or unexpected incident, which could have or did lead to harm for one or more patients receiving health care'.(10) This paper focused on patient safety incidents that were specifically related to DOACs use. Incidents are likely to occur due to errors in the process of prescribing, preparing, dispensing, administering, monitoring, or through suboptimal advice. Safety incidents also include near misses and never events. Near misses are defined as prevented medicines-related patient safety incidents, which could have led to patient harm, while 'never events' are serious, largely preventable patient safety incidents that should not occur if healthcare providers have implemented existing national guidance or safety recommendations as in case of administration of medication by the wrong route and overdose of high-risk medication despite the published policy.(10)

The purpose of this study was to analyze and report the nature, severity of harm, and types of all medication incidents related to DOACs submitted through all clinical settings across England and Wales to the NRLS database. An in-depth evaluation of all incidents associated with severe harm and deaths were conducted.

5.3 Methods

5.3.1 Study design

This study constitutes a mixed-methods analysis of NRLS data in relation to DOACs safety incidents, contributory factors, degree of harm, and prevention strategies as recommended by organizations responsible for reporting of errors.

5.3.2 Data Source and inclusion criteria

The NRLS is presently managed by NHS Improvement, which receives over three million patient safety incident reports each year.(11) Incidents reported to NRLS from 01 January 2017 to 31 December 2019 were included. Five DOACs that are licensed and used in the NHS in England and Wales were considered for inclusion namely: dabigatran, rivaroxaban, edoxaban, apixaban, and betrixaban. Reports without drug name or not related to DOACs were excluded. A complete list of search terms is available in (supplementary material Table S 5.1). The data of incident reports included patients age, drug name, indication, severity, type and sub-type of medication errors, and location as well as free-text data usually describing “what happened,” “apparent causes” and “actions preventing reoccurrence”.

Data on severity resulting from harm as entered by the reporter in the database were classified as- ‘no harm occurred’; to ‘low’, ‘moderate’, or ‘severe harm’, which respectively caused minimal, temporal, or permanent harm to one or more persons or fatal incidents, respectively.(11) The primary author (AA) checked all entries for completeness, accuracy of

descriptions around severity of harm and applying the inclusion/exclusion criteria. A sample of 10% of these data was validated by two other authors (VP and ZA).

5.3.3 Data Analysis

Frequency tables were generated to report incidents including drug name, age, care setting of occurrence, description of what happen, medication use process stage, medication error category, and degree of harm. The narrative descriptions of contributory factors and prevention strategies in relation to all incidents resulting in moderate harm, severe harm, or death of the patient were analyzed based on Reason's model. Reason's Accident Causation model is a theoretical framework and is most commonly used to inform investigation on the nature and causes of incidents.(12) Incidents can be classified into active failures (such as slips or lapses), those caused by error-producing conditions and latent failures (or system related).(12) Two members of the research team (AA and VP) familiarized themselves by reading the incident free-text description. Incidents were considered irrelevant if the error was not directly associated with DOACs. All free texts data related associated with medication safety incidents involving death, severe and moderately harm were thematically analyzed.

5.3.4 Ethical approval

The University of Birmingham's Ethics Committee reviewed and approved this study (ERN_20-0551) (Appendices 2.1). NHS Improvement granted approval to share the NRLS data with University of Birmingham (Ref:5199/10 December 2020) (Appendices 2.5).

5.4 Results

A total of 24,322 incident reports were identified from the search. During the data cleaning phase, 8592 incidents were excluded as they were duplicate, irrelevant, or insufficient as shown in Figure 5.1.

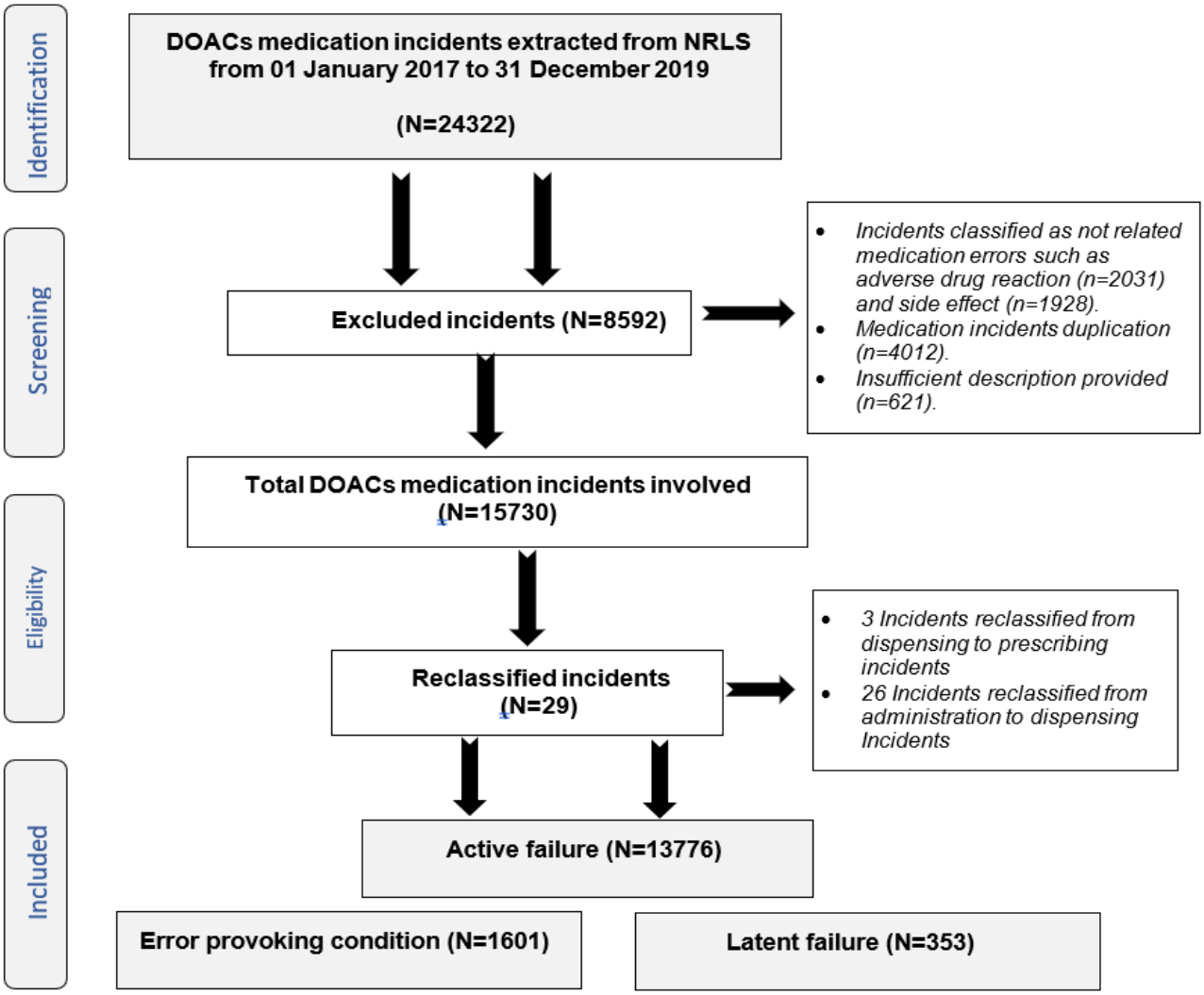


Figure 5.1 National Reporting and Learning Dataset used for the evaluation of incidents related to directly-acting oral anticoagulants

A total of (n=15,730; 64.7%) anonymized DOACs medications incident reports were quantitatively analyzed and categorized according to Reason's accident causation model into

active failures that constituted the majority (n=13776; 87.58%) of causes of safety incidents reported, followed by error-provoking conditions (n=1601; 10.18%) and latent failures (n=353; 2.24%) as shown in (supplementary material Table S 5.2). The majority (n=13776; 87.58%) of these active failures was related to mistakes (n=6286; 45.63%). For instance, “Patient was prescribed Apixaban 25 mg BD. The dose was supposed to be 2.5 mg instead of 25 mg”. Error-provoking conditions contributed to the over a tenth of incidents (n=1601; 10.18%) and within this category, poor documentation constituted the highest reasons (n=704; 43.97%). For instance, “nurse mentioned that 6 doses of dabigatran had not been signed in anticoagulant chart since admission…missed doses?” Latent failure constituted 2.24% of incidents (n=353) mainly owing to the lack of training (n=203; 57.51%). For instance, “The patient was prescribed Apixaban, but dalteparin still continued because … trainings of anticoagulants medication a bit lacking”.

5.4.1 Degree of harm

The NRLS definition of harm is provided in (supplementary material Table S 5.3), and the results of the quantitative analysis for the degree of harm are demonstrates in (supplementary material Table S 5.4). While the majority of the incidents (n=13999; 89%) were associated with no harm and low degree of harm (n=1381; 8.8%), a total of 325 incidents related to moderate or severe harm [moderate: 270 incidents (1.70%) and 55 (0.30%) severe harm]. A further 25 (0.20%) incidents led to deaths.

The majority incidents known to have caused either moderate, severe harm, or deaths occurred in age category 76 to 85 years (104; 29.7%). In total, 44.6% (n=156) were reported to relate to

prescribing, followed by administration (80; 22.8%) and dispensing of medication (60; 17.1%). Wrong omission of medication (70; 20%), followed by contra-indication to the use of the medicine in relation to drugs or conditions (52; 15.4%) and wrong/unclear dose or strength (43; 12.5%) were the three most common types of medication error reported among these incidents.

5.4.2 Incidents leading to deaths

The majority of the 25 incidents leading to deaths were reported to be resulted by active failures caused by mistakes (n=13; 52 %). Free text data in relation to every incident leading to death were analyzed and presented in table 5.1. For example, a physician prescribed apixaban to a patient (who was 56 – 65 years old) only on the drug chart and wrote 'see anticoagulation chart' without writing the same order on the anticoagulation chart. This mistake in prescribing was assumed to have led to death because of the omitted medicine used by the patient before admission.

Table 5.1 Detailed descriptions of incidents leading to deaths with the assigned medication process stage, error type and nature of contributing factors

Incident information	Incident description	Remedial actions proposed
Error type: Wrong / unclear dose or strength **Degree of harm:** Death **Patient age (years)**: 76 to 85 **Medication process**: Dispensing **Drug name**: Apixaban **Accident causation model**: Active failure (Slips)	A patient had Apixaban 5mg tablet twice daily was prescribed a box of Apixaban 5mg. A box of Apixaban 2.5mg was dispensed by mistake.	- Avoid active failure/slips. - Double verification by two pharmacists before dispensing.
Error type: Wrong /transposed/omitted medicine label **Degree of harm:** Death **Patient age (years)**: 76 to 85 **Medication process**: Monitoring **Drug name**: Apixaban **Accident causation model**: Active failure (Lapses)	Discharge medication dispensed for patient, when checking the patient own medication cupboard, a box of Apixaban was found that had a different patient name on and was labelled from hospital	- Avoid active failure/lapses. -Double check labelling information including patient and drug names especially in high alert medications before dispensing. - Monitor proper medication use.

Error type: Omitted medicine **Degree of harm:** Death **Patient age (years)**: 56 to 65 **Medication process**: Prescribing **Drug name**: Apixaban **Accident causation model**: Active failure (Mistakes)	Patient admitted and usually takes Apixaban twice daily, however has only had it administer once daily, Apixaban was prescribed on meds chart and not on the blue anticoagulation chart on the prescription chart it is written saying see anticoagulation chart however there was no chart seen.	- Avoid active failure/mistakes in prescribing. - Ensure proper prescribing in both medication and blue anticoagulation chart. - Ensure conformity between both charts. - Ensure immediate escalation and proper communication between the nurse and the physician before drug administration.
Error type: Contra-indication to drugs or condition **Degree of harm:** Death **Patient age (years)**: 56 to 65 **Medication process**: Administration **Drug name**: Apixaban **Accident causation model**: Active failure (Lack knowledge)	Patient received Dalteparin and Rivaroxaban on the same day failure to cancel Dalteparin prescription when commencing DOACs therapy, patient had severe bleeding and died.	- Avoid active failure/Improve knowledge - - Nurses to receive proper education regarding administration, starting, stopping anticoagulants. - Nurses to communicate with the physician regarding administering such drugs together.
Error type: Contra-indication to drugs or condition **Degree of harm:** Death **Patient age (years)**: 46 to 55 **Medication process**: Monitoring **Drug name**: Rivaroxaban **Accident causation model**: Error provoking condition (Patient condition)	Elderly Patient prescribed rivaroxaban by secondary care. Elderly frail patient with eGFR: 19 unsuitable for rivaroxaban. Secondary care alerted and rivaroxaban changed to Warfarin but unfortunately, patient had severe bleeding and died.	- Avoid error provoking condition. - Monitor kidney function (eGFR) in elderly frail patients before prescribing rivaroxaban or any DOACs.
Error type: Wrong drug/ medicine **Degree of harm:** Death **Patient age (years)**: 26 to 35 **Medication process**: Dispensing **Drug name**: Apixaban **Accident causation model**: Error provoking condition (LASA)	Dispensing 2 days of Apixaban instead of Aripiprazole issued as a TTO. Patient had felt unwell and admitted, CT scan show recently brain injury and haemorrhage finally, patient had coma and died.	- Avoid error provoking condition. - Segregate and double check LASA before dispensing. - Double checking/verification for orders by two pharmacists before dispensing.
Error type: ADRs (when used as intended) **Degree of harm:** Death **Patient age (years)**: 66 to 75 **Medication process**: Monitoring **Drug name**: Apixaban **Accident causation model**: Error provoking condition (Patient condition)	A patient suffered from very fast AF. After stabilization the patient was taken for a CT scan of the head, which revealed significant bleeding. On review of notes and drug chart it was noticed that the patient was on apixaban for AF, but this was not stopped despite a very low platelet count of 3 and 2 in the last 24 to 48 hours. The patient deteriorated and died.	- Avoid error provoking condition. - monitor the blood count and platelet level before/after commence treatment.
Error type: ADRs(when used as intended) **Degree of harm:** Death **Patient age (years)**: 76 to 85 **Medication process**: Prescribing **Drug name**: Apixaban **Accident causation model**: Latent failure (Lack of training)	Junior doctor (trainee) admitted one patient with chest pain diagnosed as ACS "NSTEMI". Treated with medication aspirin, ticagrelor, fondaparinux and bisoprolol. However, the patient was already on Apixaban for AF not taken any for 7 days prior to admission. The patient did not have any Apixaban on the	- Avoid latent failure. - Double checking/verification for diagnosis and identify patient history before order any medication. Ensure proper training for junior doctor.

	evening but did have a dose on the morning. However, the patient had sudden deterioration and reduced level of consciousness with l sided weakness and inattention. She was intubated for CT scan which showed a large Intracerebral haemorrhage.	
Error type: Unknown **Degree of harm:** Death **Patient age (years)**: 66 to 75 **Medication process**: Prescribing **Drug name**: Rivaroxaban **Accident causation model**: Active failure (Mistakes)	Patient prescribed double dose of rivaroxaban for AF. Patient admitted with heavy epistaxis and nose packed. Arrested over night. Cause of death patient had haemopericardium, ruptured left ventricle, mitral valve, and coronary artery disease.	- Avoid active failure/mistake - Avoid mistakes while prescribing. - Double checking/verification of orders by doctor and pharmacists.
Error type: Omitted medicine / ingredient **Degree of harm:** Death **Patient age (years)**: 76 to 85 **Medication process**: Administration **Drug name**: Dabigatran **Accident causation model**: Active failure (Slips)	- Patient was prescribed dabigatran for AF but it wasn't given for 2 days before the patient suffered a large ischaemic stroke, clexane treatment dose is indicated when there is no availability of the oral tablets. When she was found with reduced responsiveness by the nursing staff patient was transferred from ward, but patient quickly deteriorated and died.	- Avoid active failure/slips - Ensure drug available in the ward and proper administration anticoagulants by nurses. - Double checking/verification of orders before administer drug.
Error type: Contra-indication to drugs or condition **Degree of harm:** Death **Patient age (years)**: unknown **Medication process**: Prescribing **Drug name**: Apixaban **Accident causation model**: Active failure (Mistakes)	Patient was prescribed enoxaparin at night after his surgery and his usual on apixaban dose was restarted today morning. The patient received enoxaparin on evening and then apixaban on morning. Apixaban should have been restarted on evening when clexane dose was due. The Patient pass away unfortunately.	- Avoid active failure /mistake - Ensure and double check when should resume DOACs after surgery.
Error type: Wrong / unclear dose or strength **Degree of harm:** Death **Patient age (years)**: 56 to 65 **Medication process**: Prescribing **Drug name**: Apixaban **Accident causation model**: Active failure (Mistakes)	patient on rivaroxaban 15mg OD was prescribed on admission. Nurse saw the chart there was a piece of paper attached to the prescription chart saying that in patients dose rivaroxaban was 15mg BD. It seems that based off of this, someone has circled a second daily dose of rivaroxaban (the dose for treatment of embolism, which was not her diagnosis) without signing or dating this change or questioning the dose and the patient's current dose was found to be 20mg OD once investigated .The wrong dose and timings of DOACs drug was prescribed due to an error.	- Avoid active failure/mistake - Ensure and double check when should DOACs after surgery.
Error type: other **Degree of harm:** Death **Patient age (years)**: Over 85 **Medication process**: Administration **Drug name**: Rivaroxaban	Nurse had failed to administer for medication due at certain time. Rivaroxaban written on medication chart for another patient.	- Avoid active failure/slips - Ensure and double check which DOACs commence for right patient.

Accident causation model: Active failure (Slips)		
Error type: Omitted medicine / ingredient **Degree of harm:** Death **Patient age (years)**: unknown (Frail elderly) **Medication process**: Prescribing **Drug name**: Apixaban **Accident causation model**: Active failure (Mistakes)	Patient admitted with PE. VTE risk assessed no pharmaceutical prophylaxis given. Stockings correctly prescribed but patient declined. Patient should start apixaban 2.5mg BID. However, apixaban appears never to have been prescribed or given. She died in hospital on cause of death PE.	-Avoid active failure/mistake - Ensure council patient of risk not wear the stocking and risk if declined. -Ensure commence and administer the drug to patient. -
Error type: Contra-indication to drugs or condition **Degree of harm:** Death **Patient age (years)**: 56 to 65 **Medication process**: Prescribing **Drug name**: Rivaroxaban **Accident causation model**: Active failure (Mistakes)	Patient prescribed tinzaparin and rivaroxaban concurrently and had been administered medication by nursing staff for 3 days. Doctor reports no clear reason as to why both tinzaparin and rivaroxaban prescribed. Doctor reports it being a busy night shift - this may have been a contributing factor.	-Avoid active failure/mistake - Ensure and double check which DOACs commence for patient. -Mitigate night duty for staff and ensure enough staff not short.
Error type: Contra-indication to drugs or condition **Degree of harm:** Death **Patient age (years)**: 66 to 75 **Medication process**: Prescribing **Drug name**: Edoxaban **Accident causation model**: Active failure (Mistakes)	Patient admitted from other hospital with view to surgical intervention. Doctor documented that apixaban omitted 5 days before intervention. Drug chart showed was given at previous hospital.	- Avoid active failure/mistake - Ensure and double check when DOACs commence for patient prior to transfer and listing for surgery.
Error type: other **Degree of harm:** Death **Patient age (years)**: 76 to 85 **Medication process**: Dispensing **Drug name**: Apixaban **Accident causation model**: Active failure (Slips)	The patient was given her medication for discharge, but in her bag was other medication rivaroxaban intended for another patient (with a similar looking name).	- Avoid active failure/slips - Ensure and double check medication for right patient name and address before discharge patient.
Error type: Omitted medicine / ingredient **Degree of harm:** Death **Patient age (years)**: Over 85 **Medication process**: Dispensing **Drug name**: Rivaroxaban **Accident causation model**: Active failure (Slips)	The nurse was counselling a patient and noticed the apixaban 5mg wasn't in the bag. she went on pharmacy to see if they had dispensed or not, but it had not dispensed yet.	- Avoid active failure/slips - Ensure and double check medication before discharge patient. -Engage with all clinical pharmacist to actively monitor and ensure high standards in the clinical check process.
Error type: Contra-indication to drugs or condition **Degree of harm:** Death **Patient age (years)**: 76 to 85 **Medication process**: Prescribing **Drug name**: Apixaban **Accident causation model**: Active failure (Mistakes)	A patient transfer to the ward (B) from ward (A) on the evening shift and was given apixaban twice daily as well as tinzaparin at evening. The apixaban and tinzaparin had been prescribed together in 1st ward several days ago and the nurses on ward (B) did not administer the tinzaparin as the patient was on apixaban and they were aware not to give the two together. The nurses on ward (A) gave the apixaban and the	-Avoid active failure/Mistake -Double checking/verification for orders by Pharmacists and nurse before administering drug. -Inform to the nurse in charge and explained that nurses should be aware of the need to be vigilant whenever they are giving medication. -inform nurses staff not supposed to be prescribed together and

	tinzaparin until it was spotted the following morning by the pharmacist.	significantly increase the risk of bleeding if given together.
Error type: Omitted medicine / ingredient **Degree of harm:** Death **Patient age (years)**: Over 85 years **Medication process**: Prescribing **Drug name**: Apixaban **Accident causation model**: Active failure (Mistakes)	patient admitted overnight post AF ablation procedure. Morning medication round noted only apixaban and insulin prescribed. Checked only apixaban 8 tablet oral medications plus insulin.	-Avoid active failure/Mistake - Ensure and double check right DOACs for patient prior procedure. - Patients admitted for overnight care should have all their usual medications prescribed as well as those required post procedure.
Error type: Omitted medicine / ingredient **Degree of harm:** Death **Patient age (years)**: 56 to 65 **Medication process**: Prescribing **Drug name**: Rivaroxaban **Accident causation model**: Active failure (Mistakes)	Patient usually takes apixaban BID. However, has only had it administered OD for the last 3 days. Apixaban was prescribed on medication chart and not on the blue anticoagulation chart. On the prescription chart it is written saying see anticoagulation chart however there was no chart seen.	-Avoid active failure/Mistake - Ensure and double check right DOACs dose for patient in all related chart. -Nurses staff should ensure that if drug chart says this we escalate immediately as to not cause any delay / omission of treatment - Doctors also need to be ensuring that there is an anticoagulant chart prescribed if needs to be so nurses can give correct DOACs.
Error type: Other **Degree of harm:** Death **Patient age (years)**: 76 to 85 **Medication process**: **Drug name**: Apixaban **Accident causation model**: Active failure (Mistakes)	Patient had admitted with stroke. Apixaban were stopped whilst on surgery may be planned for spinal abscess. Planned to hold apixaban. On the after day noted no need for surgery but apixaban were not recommended. patient had severe stroke . patient still made no improvement, severely disabled and deteriorated his case then died.	-Avoid active failure/Mistake - Ensure and double check when stop/resume DOACs for patient prior procedure.
Error type: Other **Degree of harm:** Death **Patient age (years)**: 36 to 45 **Medication process**: Prescribing **Drug name**: Apixaban **Accident causation model**: Active failure (Mistakes)	Patient admitted with PE. and prescribed apixaban 10mg BID for 7 days then 5mg BID long term by junior doctor. chart shows the apixaban 10mg BID for 7 days but not written for the 5mg BID for long term.	-Avoid active failure/Mistake -Ensure training Junior doctor for how to prescribe drugs following a initial week long loading dose. - Improve supervision for junior physicians. -Ensure pharmacy provided education for the juniors and seniors are aware how this prescription should be prescribed. - Reenforced with medical team that daily drug chart review is mandatory for all patients -Pharmacy explore an alert can be introduced on system to prompt the doctors when a loading dose regime is present without a maintenance dose.

Error type: Other **Degree of harm:** Death **Patient age (years)**: 36 to 45 **Medication process**: Prescribing **Drug name**: Apixaban **Accident causation model**: Active failure (Mistakes)	Senior Doctor admitted Patient and diagnosed with AF and prescribed apixaban BID, 2nd day patient assessed with thrombosis team and prescribed apixaban OD. Patient still in wrong frequency for many days. Patient had severe bleeding and deteriorated.	-Avoid active failure/Mistake -Ensure good communication between HCPs team. - Engage all clinical pharmacist to actively monitor and ensure high standards in the clinical check process.
Error type: Contra-indication to drugs or condition **Degree of harm:** Death **Patient age (years)**: Over 85 **Medication process**: Prescribing **Drug name**: Apixaban **Accident causation model**: Active failure (Mistakes)	Patient with AKI and planed for discharge. Although medicines reviewed for nephrotoxic drugs it was not identified that apixaban contraindicated as in AKI (eGFR deteriorated from 31 to 19, CrCl would have been closer to 15). Patient developed haemorrhage into left kidney causing pain, worsening AKI and deteriorated his case then died.	-Avoid active failure/Mistake -Ensure all Junior doctor be aware of the medicines safety update sent and informing Apixaban now contraindicated in AKI patients. -Doubled check of renal function before commencing apixaban.

Abbreviations:

* LASA: Look Alike Sound Alike; TTO: To take out; DOAC: Direct Oral Anti-Coagulant; eGFR: Estimated glomerular filtration rate; AKI: Acute kidney injury; ACS: Acute coronary syndrome; OD: Once daily; BID: Twice daily; Crcl: Creatinine clearance; AF: Atrial fibrillation; ; PE: Pulmonary embolism; VTE: Venous thromboembolism, NSTEMI: Non-ST elevation myocardial infarction; HCPs: Health care professionals.

5.4.3 Incidents leading to severe to moderate harm

Qualitative analysis of examples of severe errors are depicted in table 5.2 and represent slips, mistakes, and latent failures. One of the examples documented in the database related to lack of experience and training of cardiologist staff in regard DOACs causing latent failure because of contra-indication to drugs or condition. In this case, the patient (who was 66 – 75 years old) was admitted with chest pain and was on apixaban for managing previous stroke. The patient received fondaparinux to treat ACS while already on apixaban. Afterwards, the patient was readmitted with haemorrhagic stroke because of the errors in prescriptions due to the lack of experience from the cardiologists. Further examples are presented in table 5.2.

Table 5.2 Examples of incidents associated with severe harm

Incident information	Incident description	Remedial actions proposed
Error type: Omitted medicine **Degree of harm:** Severe **Patient age (years)**: Over 85 **Medication process**: Administration **Drug name**: Edoxaban **Accident causation model**: Active failure (Slips)	Edoxaban prescribed on admission but not administered for 3 days (two days on ward 1, one day on ward 2), Patient developed sudden loss of vision due to embolic central retinal artery occlusion. Very likely that this was the direct result of omission of edoxaban	- Avoid Active failure/Slips. - Ensure proper and timely administration of prescribed anticoagulants by nurses.
Error type: Wrong quantity **Degree of harm:** Severe **Patient age (years)**: Over 85 **Medication process**: Prescribing **Drug name**: Apixaban **Accident causation model**: Active failure (Mistakes)	Patient dose of apixaban was not reduced in spite of the advanced age (96 years) and deteriorating renal function. Creatinine 199. Patient was discharged later that day.	- Avoid Active failure/mistakes. - Consider dose adjusting based on kidney function tests before prescribing such drugs. - Introduce alerts for performing kidney function tests before prescribing such drugs. - Add it to the AF management guidelines and improve physicians' knowledge regarding these issues.
Error type: Wrong drug/medicine **Degree of harm:** Severe **Patient age (years)**: 66 to 75 **Medication process**: Prescribing **Drug name**: Apixaban **Accident causation model**: Active failure (Mistakes)	patient was on rivaroxaban and was not told to stop this before surgery. Was documented that he bleed easily, on rivaroxaban but omitted to mention previous DVT	- Avoid active failure/mistakes in prescribing. - Ensure deprescribing of rivaroxaban before surgery.
Error type: Others **Degree of harm:** Severe **Patient age (years)**: Over 85 **Medication process**: Advice **Drug name**: Apixaban **Accident causation model**: Error provoking condition (poor communication)	Patient was referred to Social for ongoing support with this, they visited patient to assess. The patient declined their input, so they did not continue to visit, patient did not have understanding of risks associated with declining support & had been compliant with Social. Health dept were not aware of this and therefore patient missed his evening dose of rivaroxaban.	- Avoid error provoking condition. - Improve communication with patients and provide proper patient education.
Error type: Contra-indication to drugs or condition **Degree of harm:** Severe **Patient age (years)**: 66 to 75 **Medication process**: Prescribing	Patient admitted with chest pain, patient was on apixaban for previous stroke, received ACS treatment including fondaparinux. He received fondaparinux while the patient already on apixaban. Patient	- Avoid latent failure/lack of training. - Ensure proper training. - Improve awareness regarding updated guidelines.

Drug name: Apixaban **Accident causation model**: Latent failure (Lack of training)	readmitted with Haemorrhagic stroke.	
Error type: Wrong drug/ medicine **Degree of harm:** Severe **Patient age (years)**: 66 to 75 **Medication process**: Prescribing **Drug name**: Apixaban **Accident causation model**: Latent failure (Supervisory issues)	Emergency admission of patient with thrombosed mechanical valve, Patient with mechanical mitral valve had warfarin discontinued and apixaban prescribed instead by Cardiology team. apixaban does not work on mechanical valves and is not licenced for that use	- Avoid latent failure/lack of training. - Ensure proper training of cardiology team. - Improve supervision for junior physicians.

Most of the incidents leading to moderate harm (84.8%, 229) were caused by active failure of which the majority were caused by mistakes (49.3 %; n=113). Poor documentation was the most prevalent reason in relation to error provoking conditions (35.1 %; n=35). Heavy workload and lack of training contributed equally (n=2) and were linked to occurrence of the latent failures. For example, patient received co-administration of dalteparin with apixaban for evening dose, and this was reported to have happened because of the heavy workload of the nurses that led to losing concentration in managing the patient's medications and lack of consulting the physician after prescribing dalteparin while the patient was already on apixaban. Further examples are demonstrated in table 5.3.

Table 5.3 Examples of incidents associated with moderate harm

Incident information	Incident description	Remedial actions proposed
Error type: Wrong / unclear dose or strength **Degree of harm:** Moderate **Patient age (years)**: 66 to 75 **Medication process**: Prescribing **Drug name**: Apixaban **Accident causation model**: Active failure (Slips)	Patient admitted with PE On the discharge summary it states: apixaban 10mg OD last dose. Then 5mg OD in 3 months. apixaban dose should be 10mg BID for 1 week followed by reducing dose of 5mg BID until follow up in haematology clinic. Patient has the potential to extend the PE if the dose is OD.	- Avoid active failure/Slips. - Avoid mistakes in dosing while prescribing. -Avoid Loss of concentration and fatigue
Error type: Wrong drug / medicine **Degree of harm:** Moderate **Patient age (years)**: Over 85 **Medication process**: Prescribing **Drug name**: Apixaban **Accident causation model**: Active failure (Mistakes)	Patient was switched from rivaroxaban to apixaban. Rivaroxaban was clearly marked as stopped on the system, however when the community pharmacy requested rivaroxaban the medication was restarted by a GP. The patient did not take the rivaroxaban as they were aware the medication was meant to be changed to apixaban.	- Avoid active failure. - Avoid mistakes in prescribing. - Avoid prescribing stopped drugs.
Error type: Omitted medicine **Degree of harm:** Moderate **Patient age (years)**: 76 to 85 **Medication process**: Administration **Drug name**: Apixaban **Accident causation model**: Active failure (Violations)	Patient on enoxaparin for VTE prophylaxis. She refused to administer 16 doses in different days within a month and had multiple PE. She was then treated with higher dose of enoxaparin for one week. Afterwards, it was switched to apixaban twice a day dosing, and over the weekend, the patient had refused both the evening doses. This was the second time in this patient's admission she had refused a critical medicine, and there was no referral to the medical team.	- Avoid active failure/Violations. - Improve patients' education towards proper medication administration. -Proper education and counselling for patient
Error type: Mismatching between patient and medicine **Degree of harm:** Moderate **Patient age (years)**: 76 to 85 **Medication process**: Prescribing **Drug name**: Apixaban **Accident causation model**: Error provoking condition (Patient condition)	Patient with past medical history including stroke, hypertension, AF and recurrent UTIs. He was on Apixaban and stopped by GP due to recurrent haematuria. Apixaban changed to clopidogrel by GP. Patient arrived to ward with diagnosis of PE.	- Avoid Error provoking condition. - Assess Patient condition thoroughly before deprescribing/prescribing medications. -Double check patient comorbidities

Error type: Wrong drug / medicine **Degree of harm:** Moderate **Patient age (years)**: 36 to 45 **Medication process**: Dispensing **Drug name**: Apixaban **Accident causation model**: Error provoking condition(LASA)	Rivaroxaban 20mg tablets were supplied in error instead of rosuvastatin 20mg tablets.	- Avoid error provoking condition. - Segregate and double check LASA before dispensing. - Improve awareness of such incidences. - Double checking/verification of orders by two pharmacists before dispensing.
Error type: Contra-indication to drugs or conditions **Degree of harm:** Moderate **Patient age (years)**: 36 to 45 **Medication process**: Prescribing (**Administration??**) **Drug name**: Apixaban **Accident causation model**: Latent failure (Heavy workload)	Dalteparin given with apixaban for evening dose. Staffing pressures and workload versus junior nurses not aware and lost in concentration dealing with managing a patient medication.	- Avoid latent failure/Heavy workload. - Improve staff education. - Balancing heavy workload - Reducing staff stress

5.4.4 Medications involved and indication

Apixaban represented the highest number of reported incidents accounting for the majority of the incidents (n=8127; 52.0%) followed by rivaroxaban (n=5658; 36.0 %), edoxaban (n=937; 6.0%), dabigatran (n=787;5.0 %) and unspecified of DOACs (n=221; 1.0 %) as shown in (supplementary material Figure S 5.1).

5.4.5 Indication for medication use

Atrial fibrillation showed the highest number related to the medication incidents (59.50%; n=9340), followed by deep vein thrombosis (DVT) (n=4625; 29.40%), pulmonary embolism (PE) (n=1510; 9.60%) and other conditions (n=255; 2.0%) as shown in (supplementary material Figure S 5.2).

5.4.6 Incidents per stage of medication use process

The highest number of medication incidents were reported to occur during the prescribing stage (n=6614; 42.0%). The second highest category of reported medication incidents was reported to involve administration stage (n=4581; 29.10%), followed by medication dispensing (n=2557; 16.30%), monitoring/follow up (n=571; 3.60%) and advice (n=357; 2.30%), and the least number was reported in the supply stage or OTC drugs use stage (n=48; 0.30%). A total of 6.4% (n=1002) incidents were categorized as 'other' which included storage, response to treatment, order communication, product labelling and packaging. Detailed data and examples of incidents per stage of medication use process are provided in (supplementary material Table S 5.5 and Table S 5.6).

5.4.7 Safety incidents per medication error category

The most common errors resulting in an incident were omission (n=3437; 21.90%), followed by contra-indication to the use of the medicine in relation to drugs or conditions (n=2223; 14.1%), followed by wrong / unclear dose or strength (n=2188; 13.90%), wrong drug / medicine (n=1714; 10.9%). Table 5.4 presents a proportion of safety incidents per stage of medication error category with some examples.

Table 5.4 Proportion and examples of safety incidents per stage of medication error category

Medication Error Category	N (%)	Examples
Omitted medicine / ingredient	3437(21.9%)	'TTO was dispensed for patient. A nurse on the ward realised that anticoagulant medicines (Apixaban 2.5mg tablets) was missing from the TTO, and the nurse phoned pharmacy about the missing medication.'
Contra-indication to the use of the medicine in relation to drugs or conditions	2223(14.1%)	'Patient received rivaroxaban 20mg and dalteparin sodium 5000 units for 2 weeks. Patient should not have been receiving both medicines.'
Wrong / unclear dose or strength	2188(13.9%)	'Inappropriate dose of rivaroxaban had been prescribed for a patient with reduced renal function for treatment of DVT. The patient was prescribed 15mg BID for 21 days, followed by 20mg OD maintenance dosing. The patients' renal function was 41mL/min; therefore, she should have been prescribed maintenance dose of 15mg OD.'
Wrong drug / medicine	1714(10.9%)	'Cardiology registrar prescribed 110mg rivaroxaban by mistake 110mg is the normal dose of dabigatran.'
Wrong frequency	993(6.3%)	'Patient prescribed edoxaban 60mg BID. Asked doctor to change it to once daily.'
Mismatching between patient and medicine	707(4.5%)	'Patient was given wrong drug. two patients with the same surname on ward. The wrong patient was given rivaroxaban 15mg and already taken these medications.'
Wrong quantity	602(3.8%)	'Prescription required for one month supply of rivaroxaban 20mg tablets. But unfortunately, only 2weeks supply.'
Wrong method of preparation / supply	229(1.5%)	'Patient prescribed 2.5 mgs of apixaban BID. the pharmacy supplied 5 mgs. the Label written 2.5 mgs take one tablet BID. There are 6 tablets missing from the box.'
Wrong / omitted verbal patient directions	167(1.1%)	'Patient was discharged on apixaban without receiving the relevant counselling. Doctor stated on the discharge letter that he had been counselled about the use and side effects of apixaban and he has been given information.'
Wrong / transposed / omitted medicine label	131(0.8%)	'Care home telephoned because patient had been discharged at the weekend with an unlabelled packet of apixaban tablets. They are unable to use it as it is unlabelled.'

Wrong storage	86(0.5%)	'During a check for discharge planning, I found in the current patient drug locker a box of opened rivaroxaban 20mg tablets that belonged to a previous patient on the ward.'
Adverse drug reaction (when used as intended)	73(0.5%)	'Patient on apixaban 5mg BID and been prescribed clarithromycin. Manufacturer of apixaban advises to rather avoid taking apixaban while on clarithromycin.'
Wrong formulation	66(0.4%)	'Patient given rivaroxaban and apixaban at the same time and they belong in the same group of drugs.'
Wrong / omitted / passed expiry date	51(0.3%)	'Patient prescribed rivaroxaban with passed expiry date'
Wrong / omitted patient information leaflet	36(0.2%)	'Patient attended for a colonoscopy. Patient had taken apixaban as usual and not received any information on when must be stopping apixaban before procedure.'
Patient allergic to treatment	26(0.2%)	'Patient prescribed rivaroxaban for DVT. Pharmacy had supplied medication. The medication was listed as an ' allergy' for patient on drug chart.'
Wrong route	17(0.1%)	'Rivaroxaban and enoxaparin 4mg SC OD concomitantly administered. Rivaroxaban administered via NG tube and its not suitable for NG administration.'
Unknown	249 (1.6%)	'Patient had been discharged with rivaroxaban 10mg for VTE prophylaxis from nursing staff and also dabigatran 110mg from pharmacy for VTE prophylaxis. patient reported had been taking both medications on discharge.'
Other	2735(17.4%)	'Patient initiated on apixaban for AF. Prophylactic enoxaparin not discontinued when apixaban initiated so patient received concomitant apixaban and enoxaparin for 2 consecutive days.'
Total	15730(100%)	

5.4.8 Patient age

The majority of incidents (28.53%; n=4487) involved patients aged 76 to 85 years followed by patients above 85 years old (22.38%; n=3520) as shown in (supplementary material Figure S 5.3).

5.4.9 Safety incidents per care setting

Cardiology wards in the hospitals had the highest proportion of medication reports for DOACs incidents (n=7346; 46.70%), followed by acute medical ward (n=3311; 21.10%). Community pharmacies had also a relatively high rate of error report (n=1696; 10.80%). Results are provided in (supplementary material Table S 5.7).

5.5 Discussion

5.5.1 Statement of key findings

To our knowledge, this is the first study evaluating the medication incidents relating to DOACs using a large national reporting dataset. Of the 15,730 incidents analyzed, a total of 11% incidents were associated with some degree of harm including severe and moderate harm and contributing to deaths. The present study revealed that apixaban and rivaroxaban were amongst the medications most associated with safety incidents. The majority of all incidents (68%) involved patients aged 66 years and above and occurred in cardiology and acute medical wards in hospitals.

5.5.2 Interpretation of findings

This study supports the widespread use of apixaban and rivaroxaban and showed the preference of apixaban prescribing especially in elderly population. This finding is consistent with previously published data which support apixaban preference due its lower rates of both major and gastrointestinal bleeding than rivaroxaban.(13-15) However, prescribing errors are common. A retrospective cohort analysis investigated the appropriateness of DOACs utilization in outpatient clinics over 4-year and found that apixaban was the most inappropriately prescribed drug.(16)

The findings of our study supports the results of other studies around DOAC errors. A study conducted in a large university academic hospital in the West Midlands of England reported prescribers' active failure contributed to the majority of DOAC-related incidents.(17) Another retrospective study investigated severe medication errors (MEs) reported to the National Supervisory Authority for Welfare and Health (Valvira) in Finland and conveyed similar results as most of the errors occurred in prescribing, administration, and monitoring phases of the medication process due to mainly active failure causes.(18) Omission error had the highest prevalence among medication errors category in the present study, similar to other studies conducted in tertiary care hospitals in England, Wales, and India.(19, 20) Despite most of the errors reported in this study were of no or minimal harm, the drug omitted remained the most persistent cause of all errors including those associated with death or severe harm. This may be triggered by the other factors identified in the study such as poor documentation and communication.

5.5.3 Strengths and limitations

This study has the advantages of using a big national database with extensive information on safety incidents. Availability of free-text description of the safety incidents added value to our study through qualitative analysis. However, researchers noted a lack of a systematized way of narrative reporting. Due to the voluntary nature of the error reporting system, errors are likely to have been under-reported.

5.6 Conclusion

The findings from this large-scale study involving a national incident reporting dataset suggests that medication incidents involving DOACs are a common occurrence and have led to severe harm and deaths. Most of the DOACs- incidents related to active failures such as slips and mistakes followed as well as through poor documentation and communication, and lack of training. Given their proven effectiveness and ease of use, it is imperative to promote safer prescribing and use of DOACs. Health organizations should invest in the continuous professional development, promoting guideline adherence and interventions that have been shown effective in minimizing medication and specifically DOAC related errors.

5.7 Expert opinion

DOACs related incidents are common in healthcare settings, and this study shows that the incidents can lead to fatal outcomes as well as various degrees of harm. Based on Reason's accident causation model, the present study also indicated that the majority of DOACs-pertaining

safety incidents were due to active failures of slips and mistakes, followed by poor documentation and communication, and lack of training. Examples include missed doses, duplication of anticoagulant therapies, patient being discharged without DOACs, and lack of commencement or adjustment of DOACs post-surgery. There is a need to promote guideline adherence through education, training, and decision support technologies given the majority of DOAC errors related to active failures.

Many of the reported incidents leading to harm related to lack of dose adjustments as per renal function. Dose adjustments is key to optimizing treatment and reducing the risk of bleeding. Creatinine clearance (CrCl) instead of eGFR can determine dosage adjustments for DOACs.(21) Mandating renal functions in prescriptions,(22) as well as multifaceted interventions involving the use of clinical pharmacists in ward rounds, technological and educational support can be effective in reducing errors.(23, 24)

This study could guide policymakers, safety professionals as well as the clinical practitioners to pay more attention to omission errors and contraindications while prescribing, dispensing, and administering DOACs. Given the significant impact that such incidents can have on patient related outcomes, some of the omissions or delays of DOACs could provoke significant patient harm that necessitate further and expensive healthcare. Health organizations should focus on training their clinicians on DOACs pharmacotherapy and on human factors associated with medication errors, such as mistakes in prescribing and encourage clinician to follow evidence-based clinical guidelines or pathways to improve prescribing practice of such medications. It is also important to perform clinical audits of reported safety incidents and disseminate recommendations for clinical practice improvements. Pharmacists can play an important role

in ensuring safety practice of such medication, such as implementing medication reviews and medication reconciliation upon admission, care transfer, and on discharge. In addition to implementing anticoagulation stewardship and providing anticoagulation management, pharmacist-based ambulatory care anticoagulation clinics can also promote patient safety.(25)

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5.9 Declaration of interest statement

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

5.10 Author contribution

The authors confirm contribution to the paper as follows: study conception and design: Abdulrhman Alrowily, Zahraa Jalal and Vibhu Paudyal; data collection: Abdulrhman Alrowily and Vibhu Paudyal; The primary author (Abdulrhman Alrowily) was responsible for cleaning up of data and applying the inclusion/exclusion criteria. A sample of 10% of these data was validated

by two other authors Vibhu Paudyal and Zahraa Jalal. Analysis and interpretation of results: Abdulrhman Alrowily, Zahraa Jalal; Draft manuscript preparation: Abdulrhman Alrowily. All authors reviewed the results and approved the final version of the manuscript prior to submission.

5.11 Data availability

All data corresponding to this work are provided with the manuscript.

5.12 References

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Chapter 6. Views, experiences and contributory factors related to medication errors associated with direct oral anticoagulants: a qualitative study with physicians and nurses

Chapter overview: This chapter reports the views, experiences, and contributory factors related to medication errors associated with direct oral anticoagulants. The study was conducted using semi-structured interviews with physicians and nurses.

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Authors contribution: This study relates to Abdulrhman Alrowily, PhD research. VP and ZJ supervised Abdulrhman Alrowily for his PhD. MB, AA, MA co-authors have made substantial contributions to the conception and design of the study. NA revised results (codes and themes) and Abdulrhman Alrowily was responsible for the acquisition of data, analysis, first interpretation of data and first drafting the manuscript. All authors revised it critically for important intellectual content, reviewed, and approved for submission.

6.1 Abstract

Background: Direct oral anticoagulants (DOACs) have become preferable for the management of thromboembolic events. Recent publications have, however, identified high volume of medication errors related to DOACs. There is limited literature on why and how such errors occur or happen in clinical practice.

Aim: This study aimed to explore views, experiences, contributory factors related to DOACs medication errors from the perspectives of healthcare professionals.

Method: Semi-structured interviews using online videoconferencing were conducted with physicians and nurses from tertiary care hospitals in three different regions in Saudi Arabia. Questions included views, experiences, and perceived factors contributing to errors. Interviews were transcribed verbatim and were thematically analyzed using MAXQDA Analytics Pro 2020 (VERBI Software).

Results: The semi-structured interviews (n=34) included physicians (n=20) and nurses (n=14) until data saturation was achieved. The analysis identified five themes: factors related to healthcare professionals (e.g., knowledge, confidence and access to guidelines); factors related to patients (e.g., comorbidity, polypharmacy, medication review, and communication barriers); factors related to organization (e.g., guidelines, safety culture and incidents reporting system); factors related to the DOACs medications (e.g., lack of availability of antidotes and dosing issues); and strategies for error prevention/mitigation (e.g., the need for professional training and routine medication review).

Conclusion: Healthcare professionals identified errors in relation to DOACs as multifactorial including their own and patient lack of knowledge, lack of clinical guidelines and organizational factors including safety culture. Medication review and reconciliation on discharge were key strategies suggested to reduce DOACs related errors. These strategies support the role of pharmacists as direct patients care providers to minimize DOACs errors.

6.2 Introduction

Anticoagulants are first line therapeutic and/or prophylactic regimens for thromboembolic events, such as deep venous thrombosis (DVT) and pulmonary embolism (PE).(1) Their indication also includes prevention of stroke in atrial fibrillation (AF) patients.(2) In addition, patients who cannot tolerate conventional warfarin therapy are usually prescribed direct oral anticoagulants (DOACs) among many other uses. DOACs are also commonly known as novel oral anticoagulants and sometimes called Non-Vitamin-K-antagonist Oral Anticoagulants (NOACs).(3, 4) DOACs are orally administered in fixed doses with no need for prothrombin time (PT) or international normalized ratio (INR) monitoring. Such practical advantages including less food and drug interactions have led to their increased utilization in clinical settings.(5) Their preferential use extends to vulnerable populations including elderly,(6) chronic kidney diseases, (7) and in morbidly obese patients.(8)

A recent systematic review and meta-analysis of 32 studies showed approximately 1 in 5 patients prescribed DOACs experience a prescribing error [pooled prevalence of errors 20% (95% CI 15–25%; I2 = 96%; 95% PrI 4–43%).(9) Common prescribing errors included over or under dosing, contraindications, missed doses and duplicate therapy.(9) However, contributory factors were rarely reported in the included studies, and there was a lack of utilising theory to identify contributing factors.(9) Approaching medication errors using theories and models is important for efficient identification, development and implementation of interventions.(10)

A previous study conducted in Saudi Arabia using error reports submitted to pharmacovigilance datasets revealed that prescribing error was the most common error type representing 81.4%

of all errors.(11) Increased patient age, concurrent comorbidity and polypharmacy, indication and duration for anticoagulation were related to higher incidence of errors.(11, 12) However, there is limited literature on "why and how" such errors occur or happen in clinical practice.

6.3 Aim

This study aimed to explore views, experiences, and contributory factors related to DOACs medication errors from the perspectives of healthcare professionals in Saudi Arabia.

6.4 Ethics approval

The researchers obtained ethical approval from University of Birmingham Research Ethics Committee (ERN_20-0551) on 6/11/2020 (Appendices 2.1). In addition, three ethical approvals from all of the three participating hospitals: National Guard Hospital in Riyadh (SP20/212/R) (Appendices 2.2), King Fahad Military Medical Complex in Dhahran (AFHER-IRB-2020-015) (Appendices 2.3) and King Fahad Central Hospital in Jazan (164/2020) were obtained on 3/06/2021 (Appendices 2.4). All participants signed an informed consent before enrollment in the study (Appendices 2.6).

6.5 Method

6.5.1 Study design

This study used a qualitative design through in-depth interviews. The Consolidated criteria for reporting qualitative research (COREQ) was followed in the reporting of this study (supplementary material Table S 6.1).

6.5.2 Participants and settings

Semi-structured interviews were conducted with HCPs from three different regions in Saudi Arabia: Riyadh, Dhahran, and Jazan. One tertiary hospital in each of the three regions were chosen. Hospitals were selected based on the presence of a cardiology department with at least 2 consultant cardiologists. Purposive sampling was used for the recruitment of participants. Participant inclusion criteria were physicians and nurses who had experiences with DOACs prescribing and treatment.

6.5.3 Data collection

An invitation e-mail was sent to the hospitals to recruit participants into the study. In each hospital, a local collaborator sent the invitation to eligible healthcare professionals. The collaborators also further explained the study objectives to the participants during face-to-face meetings before obtaining their consent to enroll in the study. All participants were provided with participants' information sheet (PIS) (Appendices 2.8), and consent forms were distributed to be read and signed by the participants before conducting the interviews.

A topic guide including all questions to ask the interviewees (supplementary material Table S 6.2) was also designed to help interviewers be consistent with all participants in the different centres. Literature review conducted by the study authors including systematic review and meta-analysis and primary research around the extent of DOACs errors was helpful in developing the abovementioned guide,(9, 13) and in identifying Reason's Accident Causation Model theory.(14) Reason's model categorizes human failure in three pathways: active failures (or person approach) and latent failures (or system approach), and error provoking conditions. Active failures are known to have immediate adverse outcomes compared to latent failures. Questions used in the interviews were mainly focusing on the experience in dealing with DOACs, concerns raised during their utilization in their institution, the level of knowledge about these drugs, the perceived safety culture regarding their use, in addition to having guidelines and policies in place to maximize DOACs effectiveness and to reduce their errors. Moreover, additional questions about the factors associated with errors happening with these drugs and the participants' views regarding prevention of such errors. The questions were revised by the study team who included experts in qualitative research and research collaborators in study sites. The topic guide was further reviewed by five physicians and five nurses. The interviews were conducted in English (as the common language used in the hospitals, and many of the HCPs are English speakers), recorded and transcribed verbatim by a professional transcriber.

The semi-structured interviews were conducted virtually using Zoom videoconferencing as a platform due to limitations caused by the COVID-19 Pandemic. The interview took place from September to THE end of November 2021 and lasted between 40 to 60 minutes in duration.

6.5.4 Data analysis

Interviews were thematically analyzed using MAXQDA Analytics Pro 2020 (VERBI Software)(15). Each transcript was independently analyzed by two authors (AA, NA), a third author checked both versions (VP) for disagreement. Disagreements were resolved by discussions. As the semi-structured interviews progressed, data were analyzed after each interview to develop initial codes and to identify important and new emerging information.

To improve rigor and trustworthiness, each interview was ended by a summary to be validated by the participants and to check for any ambiguity. After each interview, the two researchers (AA and NA) met and reflected on the information received. Memos (such as reporting interviewee's facial expressions or hesitancy to answer certain questions adequately) and journaling were recorded during the interviews and utilized throughout data collection and analysis using MAXQDA memos. Data collection continued until interviewers' noticed saturation (no more new data revealed by the interviewees) in each group of participant HCPs. Data from interviews were kept secure.

6.6 Results

The semi-structured interviews (n=34) included physicians (n=20) and nurses (n=14). Participant's characteristics are presented in Table 6.1.

Table 6.1 Participants characteristics

Participants' Characteristics (n= 34)		
Participants Characteristics:	**Physicians (n=20)**	**Nurses (n=14)**
Gender		
Female	2	13
Male	18	1
Training background qualifications (in years of experience)		
<5	5	6
5-10	12	5
11-15	0	2
16-20	1	0
>20	2	1
DOACs experience (in years)	**prescribing**	**Administer**
<5	12	3
5-10	6	1
11-15	0	8
16-20	1	0
>20	1	2
Specialty or department		
Cardiology	10	2
Internal Medicine	9	1
Unspecialized	0	5
Others*	1	6
Current job title		
Consultant	5	
Registrar	10	
Resident	5	
Nursing		9
Manager of department		5
* Others include any specialist for physicians, and for nursing practitioners in medical wards or medical isolation wards, respiratory department, and critical care unit.		

Saturation of the data collection was achieved after 32 interviews with HCPs and further two interviews were conducted to confirm it.

The analysis of the interviews identified factors associated with medication errors that were categorized under five themes: (1) factors related to healthcare professionals (HCPs); (2) factors related to patients; (3) factors related to organization; (4) factors related to the DOACs as medications; and (5) strategies for improvement. An overview of themes and subthemes emerged during data analysis as shown in Figure 6.1.

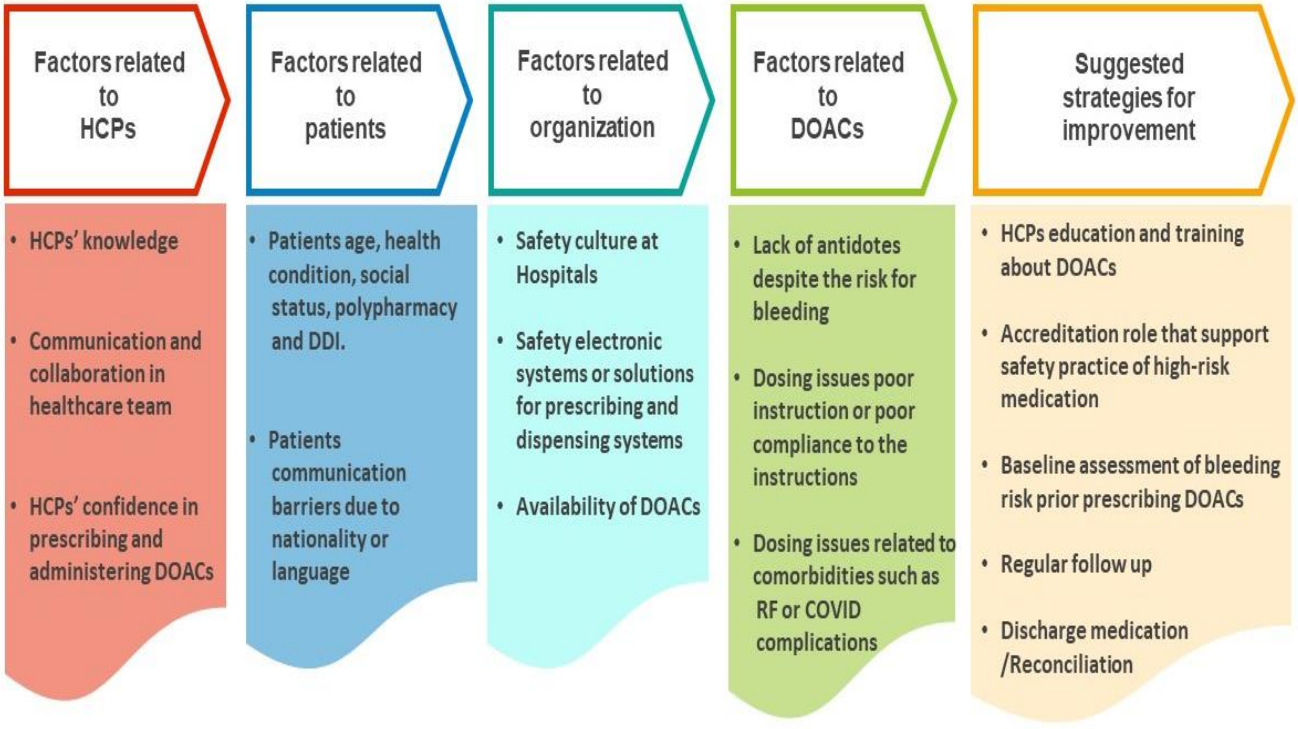


Figure 6.1 An overview of themes and subthemes emerged during data analysis

Abbreviation: HCPs: Healthcare professionals, DOACs: Direct oral anticoagulants, DDI: Drug-Drug interaction, RF: Renal failure, COVID: corona virus infection disease.

The following sections describe each theme accordingly with the aid of illustrative quotations.

6.6.1 Factors related to healthcare professionals

Four sub-themes were identified under factors related to HCPs: HCPs' knowledge, Communication and collaboration in the healthcare team, and HCPs' confidence in prescribing and administering DOACs. Below is a description of each subtheme and the supportive quotations.

6.6.1.1 Knowledge of HCPs

The participants' reported knowledge gaps as factors that contribute to the DOACs medication errors. The physicians pointed out that lack of knowledge about the dose, adverse effects, and contraindications were mostly causing such errors:

"..the challenge ……, do you prescribe accordingly, do you adjust the dose? do you overshoot? do you undershoot, do you undertreat duration? ..and I think that something that needs to be done, …" ***Participant 7, physician (Riyadh)***

In addition, nurses added that their limited knowledge regarding the medications and their reliance on physicians for education.

"We don't have the knowledge … so, first; the physicians will educate us about this type of medication when they start to give…" ***Participant 10, Nurse (Jazan)***

When referring to clinical guidelines, some participants reported not having access to any structured guidelines or protocols.

" No, … we don't have a written guideline protocol. We had a meeting, discussion but nothing written." ***Participant 4, physician (Dhahran)***

6.6.1.2 Communication and collaboration amongst HCPs

The participants mentioned that good communication among the multidisciplinary team was important to improve DOACs safety.

"…when you prescribe medication, you will discuss first with your team, …… So, the team dynamic and the team in our hospital affect the safety of medication very nicely, in a good way". ***Participant 6, physician (Dhahran)***

Some participants mentioned that they often did not agree with DOACs choice selection or the dosage and were concerned with the risk but were hesitant to speak up their concerns to the prescribing physician. And when they did, they were not able to convince the prescribing physician:

"…sometimes worried when It was newly started prescribe DOACs because the risk of bleeding and I have spoken with other colleagues by phone to discuss this case and he was not convinced". ***Participant 3, physician (Dhahran)***

Nurses felt more comfortable to speak with the consultants:

"…. the thing is they are listening to each other [consultants], except for the residents who will not listen … if I have a problem I will talk to the consultant because they are listening to us". ***Participant 9, Nurse (Riyadh)***

Physicians and nurses advocated the role of clinical pharmacists especially in multidisciplinary ward's rounds in preventing medication errors:

"Actually, I found like having a clinical pharmacist in our unit is very very very helpful. To be honest with you, I always depend on them on reviewing the medications of the patients and the interactions" ***Participant 1, physician (Riyadh)***

6.6.1.3 HCPs confidence in prescribing and administering DOACs

Some HCPs reported confidence in prescribing and administering DOACs. Participants outlined the importance of careful history taking prior to prescribing of these medications is important to ensure their safe use, as this physician describes

"Anticoagulation are not like any, like, for example, antibiotic or, yeah, anticoagulation I have really concentrate. I have to review all the medication of the patient. I have to go back again to the patient, ask him about the, past history of, and if he has any bleeding before,. So, it's not like any medication, anticoagulation, yes, yeah." ***Participant 1, physician (Jazan)***

The importance of having accurate diagnosis at the time of prescribing was also needed for prescriber confidence.

"The physicians in general are becoming more confident in using DOACs when they are clear diagnosis and confirmed clear diagnosis with A thrombosis team" ***Participant 5, physician (Dhahran)***

Physicians' adherence to standardized prescribing protocols (or systems) and availability of a clinical pharmacist to check before the prescription reached patients were key to improving prescriber confidence and reducing errors:

"Yeah. the good thing in our hospital that they use a well-structured prescribing medication system for the physician to prescribed any medication, it should be approved by pharmacist first and to be reviewed very well regarding if the patient has any side effect or contraindication to use this agent or contraindication to use this does, the error will be anywhere but it is very uncommon we have in our hospital?" ***Participant 5, physician (Riyadh)***

6.6.2 Factors related to patients

Participants reported that the health condition and age of the patient affected how patients understood the information given to them.

"We took in consideration the risk factors and the comorbidities of the patient that effect understanding the instruction how to use apixaban the age of patient special the elderly and the cognitive disorder such as Alzheimer disease as well." ***Participant 2, physician (Riyadh)***

Some participants expressed that patients' socio-economic status and acceptability of the patient for convincing them also affected the safety of the use of DOACs:

"Some patients are refusing the new medication or even they are receiving it, they are not convinced that they should take. So, I think social factor is one of the most important." ***Participant 5, physician (Dhahran)***

Some physician participants expressed that some of the errors related to DOACs can be attributed to poor patient understanding of the dosing instructions of these medications, or their poor adherence to the instructions.

"…. patient will take by mistake double the dose, he will, he will take half the dose, he will take it three times instead of one time. …. the problem will come with non-compliance or, the prescriber error in dosing." ***Participant 3, physician (Dhahran)***

Further HCP participants mentioned that they do assess patients' interest and ability to understand DOACs before prescribing it.

Effective communication with patients was deemed key to promoting DOACs safety. However, some of the interviewed nurses were non-Arab nationalities and mentioned that they often face language barriers that might contribute to higher errors with DOACs:

"..I believe that one problem that could cause certain errors is, number one, is the language because, sometimes, we're finding it hard, difficult to educate or to inform our patient, especially the elderly… almost all of our patient, we don't have any sitters available at the bedside to help us communicate with the elderly. so, I think that can cause us problems." ***Participant 8, Nurse (Riyadh)***

Some participants attributed errors related to the use of DOACs to poly-pharmacy or inadequate medications reconciliation while receiving healthcare at different healthcare facilities:

"The most factor is that sometimes the patient may come to a different clinic and to my clinic, and then ask for medication, and then he want to have a refill for the whole…. and then he'll

have big stock, you know, and I think, this way, the patient might be mistakenly taking the dose in the wrong way, you know" ***Participant 4, physician (Jazan)***

Some physicians reported that the safest approach is the one that involved the patient, the family and the pharmacist while prescribing DOACs in a shared decision-making process:

"Our system is very nice and organized…, First of all before we start … we discuss with the family or the patient himself, we explain for them the side effects and the dose and duration and everything, if we are not sure about the dose .. we have our clinical pharmacist to guide us for the dose..." ***Participant 2, physician (Riyadh)***

6.6.3 Organizational factors

Participants discussed the importance of organization's patient safety culture and electronic prescribing systems on DOACs medication errors. Although most of the participants expressed feeling safe due to the quality and nature of safety measures adopted in their healthcare organizations, some flagged that DOACs errors were still occurring:

"……so I think we have an excellent system however we still have significant DOACs medication error that I am not happy about" ***Participant 8, physician (Riyadh)***

There were differences in participant perceptions around quality and adequacy of safety policies depending on the regions participants belonged to.

"Yes, we don't have a clear medication safety policy, which is not clear used by all our physicians, and those who are concerned with treatment in, in cases of thrombosis from particulates." ***Participant 4, physician (Jazan)***

Participants described that electronic prescribing systems can promote safe use of DOACs:

"So, essentially, we have a very helpful electronic healthcare system in organization and all medications are ordered through this system, so actually within this system, there is an extremely sensitive drug interaction, alert system that picks up any interaction, so in this system is exceptionally helpful in monitoring these interactions." ***Participant 9, physician (Riyadh)***

However, the unavailability of several DOACs choices of medications within the hospital caused some frustration and challenges for some participants. Having only one choice would put the treating physician in a situation to hesitate to prescribe.

"Okay, availability of the medications. So, sometimes, I feel this anticoagulant is better than this so, for example, I feel Apixaban is better than, for example, Dabigatran but, it's not available. So, the availability also of the medication." ***Participant 1, physician (Jazan)***

6.6.4 Factors related to DOACs

Participants indicated that lack of antidotes to counteract the risk of bleeding that may result from DOACs can affect patients' safety while receiving these medications and the non-availability could lead to physicians prescribing underdosing.

"If the patient unfortunately has bleeding, there is no antidote for direct oral anticoagulant, that's the main concern for us if the patient has a bleeding so, the bleeding is the main issue for us as physician." ***Participant 1, physician (Riyadh)***

Participants stressed concerns regarding the difficulty they encounter in monitoring these agents due to their lack of experience in their use as compared to warfarin:

"…monitoring of anticoagulant affects these agents is problematic … in comparison to warfarin which is essentially universal." ***Participant 9, physician (Riyadh)***

Workload was deemed to impact on DOACs safety. In particular, many participants described having seen their workload increase as a result of the emergence of COVID-19 pandemic:

"...one of it is the workload factor because we are working in COVID-19 area, so the thing is that most of the nurses, can be handling 3 patients, the workload itself is sometimes (a problem) …" ***Participant 9, Nurse (Riyadh)***

COVID-19 was deemed to have impacted patients' response to DOACs efficacy:

"…if we have a patient with corona (COVID-19), and for discharge, we, we keep him on anticoagulant, apixaban, for two weeks at home, as a prophylaxis only. This is not actually, this is not international guideline but, this is local guidelines based on our observation. We have, we have seen many cases, we discharge them, and they come back within like five, ten days with deep venous thrombosis (DVT) or pulmonary embolism (PE)." ***Participant 1, physician (Jazan)***

6.6.5 Suggested strategies for prevention/mitigation of errors

Participants provided several suggestions to help minimize errors related to the use of DOACs.

Educational initiatives and training opportunities could enhance their understanding and prescribing practices of DOACs:

"… I think we need more education and lectures, .. we are developed …. our institute is one of the leading institutes that come into medication safety in particular, but as I said are we perfect? No, we are not" ***Participant 4, physician (Riyadh)***

A few highlighted the positive impact of the healthcare accreditation process on the safe use of medications in general and high-risk medications including the DOACs. Most physicians clearly stated the role of medications by joint commission international (JCI) and the Saudi Central Board for Accreditation of Healthcare Institutions (CBAHI), which is the official agency authorized to grant accreditation certificates to all healthcare facilities operating in Saudi Arabia. This accreditation process even includes the pharmacy and high alert medications, their prescription, dispensing and counselling associated with the dispensing process in order to improve their effectiveness and safety.

"We have JCI [joint commission international] and CBAHI [the Saudi Central Board for Accreditation of Healthcare Institutions] so, regarding the pharmacy, regarding the prescription, electronic prescription, this is, will minimize the DOACs medication errors really, even if you, the system by default, if you write apixaban, by default it will come twice daily (BID)" ***Participant 6, physician (Dhahran)***

HCPs stated that paying careful attention to the baseline assessment of patients' risk of bleeding prior prescribing DOACs was a helpful strategy to avoid accidental bleeding from these agents as described by this physician:

"I'm using, a score to check the bleeding risk for my patient. I have application on my smart phone and then I check the risk of bleeding and I classify my patient, if my patient at high risk of bleeding, I discuss with the patient, or patient relative and, I, you know, I make a balance between if it is strongly indicated and then we make a shared decision between me and a patient" ***Participant 1, physician (Jazan)***

Another physician described the importance of carefully balancing the risk benefit profile prior to DOACs initiation would promote safety and minimize errors:

" first of all you have to review the indication, before starting even the prescribing or thinking about it, what is the indication ok? What is the risk and benefit and then taking the patient's factors like patient preference, patient risk factors, patient comorbidities?" ***Participant 6, physician (Jazan)***

Most participants agreed on the need for regular monitoring of the patients receiving DOACs to ensure the efficacy and safety of these medications:

Participants stressed on the need for adequate patient education and implementation of the medication reconciliation prior to patient's discharge from hospital to support the safe use of medications:

"We usually before discharge the patient with this agent, we sit with them and explain very clearly to the patients, when to stop this and when to stop that and when you come to us again, we explained that." ***Participant 7, physician (Riyadh)***

HCPs reported that confidence in prescribing and administering DOACs is not harming the patients relied on proper patient education:

".. I'm confident to administer this medication to our patient, as long as they will be educated on..." ***Participant 8, Nurse (Riyadh)***

6.7 Discussion

6.7.1 Statement of key findings

This study explored the perception of HCPs about DOACs medication errors. A range of factors related to HCPs, patients, and healthcare organizations and opportunities was identified.

Many participants described that they did not have sufficient knowledge about DOACs. Lack of local protocols, clinical guidelines, information resource were described. Implementation of an educational intervention approach that provides HCPs with the knowledge and training about DOACs and encouraging a discussion about the DOACs medication errors might help to improve safe use of DOACs.(16) Furthermore, our study showed a lack of participant access to national and/or institutional guidelines on the use of DOACs.

Participants in this study emphasised that effective interprofessional collaboration and effective communication among HCPs can play a huge role in promoting DOACs safety. Previous evidence

refers to effective communication and teamwork as core elements for providing safe care.(17-19) Communication failures are an extremely common cause of inadvertent patient harm.(19) Using structured communication tools through digital applications and multidisciplinary team meetings can be effective such as using teleconferences and the digital Walkie-talkie mobile.(20)

6.7.2 Interpretation

Our results revealed that participants' confidence in prescribing DOACs to patients were boosted if they collaborated with clinical pharmacists. Studies have shown that involvement of pharmacists in the appropriate selection of DOACs doses decreased errors.(21, 22) Additionally, pharmacists were able to reduce DOACs errors through medications reviews conducted during the hospital stay, at the clinics and through medication reconciliation.(21, 22)

Patient-centered care was identified to be important in reducing medication errors. Physicians reported that patient and family involvement in a shared decision-making process when prescribing DOACs (especially if replacing warfarin for DOACs) was crucial. Studies have shown that patient engagement and adherence to treatment are essential to achieving optimal treatment outcomes with DOACs.(23)

Participants of this study revealed factors associated with DOACs errors, such as patients age, health condition, socio-economic status, and polypharmacy. Studies have shown that physicians might underdose and/or misdose patients who are elderly or taking a lot of medications.(24-27) HCPs require guidance when managing complex patients as most clinical guidelines focus on single disorders.

The participants of this study also highlighted the importance of safety culture in healthcare organisations. Medication safety programmes have been introduced in many hospitals to minimize the likelihood of harm associated with the use of medication, and maximize the benefits for patients.(28) Adopting facets like medication safety policy, multidisciplinary team policy, double checking policy as well as adopting electronic prescribing system are common safety practices activated in hospitals.(29)

Hospital accreditation standards were deemed effective to improve the safety culture and minimise errors. Since 2006, the Ministry of Health created an accreditation certification for central hospitals across Saudi Arabia to assess hospital performance against an explicit set of standards that included 30 indicators focusing on safety and quality improvement of clinical practice in Hospitals. The Ministry executed vocational and educational programmes to spread the safety culture among HCPs through training.

6.7.3 Strengths and weaknesses

Involvement of participants from different regions with diverse patient populations, variable healthcare practice enhances the transferability of the findings to other regions in Saudi Arabia. In addition, many of the factors identified including organisational, patient, and prescriber related factors are likely to be applicable internationally as evidenced by other publications described in the discussion section. However, differences in organizational and quality of health care such as staffing levels, workload and availability of advanced electronic prescribing systems can impact the transferability of findings to other settings within Saudi Arabia and beyond and this warrants further explorations of the same issue in other regions.

6.7.4 Future research

Qualitative studies consisting of semi-structured interviews of patients and pharmacists to further explore causes and ways to minimise DOACs medication incidents are needed. Future studies may aim to extend the scope of this study to incident severity and its impact on patient health outcomes. Development and evaluations of interventions to minimise errors are needed. Research should be extended to non-hospital settings.

6.8 Conclusion

Our study highlighted important contributory factors to medication errors related to DOACs from the perspective of HCPs. A gap in knowledge and training when dealing with DOACs requires standard guidelines and educational initiatives to support optimal utilization of DOACs. Furthermore, attention should be drawn to the prescribing process being a vital step that requires multi-disciplinary collaboration. Involvement of pharmacists at the prescribing, monitoring and follow-up was identified as a key strategy that can increase physicians' and nurses' confidence and minimize errors.

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6.11 Conflict of interest

Dr. Vibhu Paudyal, who is an Associate editor of the International Journal of Clinical Pharmacy had no role in handling the manuscript, specifically the processes of editorial review, peer review and decision making" There are no other conflicts of interest to declare.

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Chapter 7. Medication errors in relation to direct-acting oral anticoagulants: a qualitative study of pharmacists' views and experiences

Chapter overview: This chapter reports the views, experiences, and contributory factors related to medication errors associated with direct oral anticoagulants. The study was conducted using semi-structured interviews with pharmacists.

Notes for plagiarism check: This section is under review in a peer-reviewed journal with the citation below.

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Authors contribution: This study relates to Abdulrhman Alrowily, PhD research. VP and ZJ supervised Abdulrhman Alrowily for his PhD. MB, AA, MA co-authors have made substantial contributions to the conception and design of the study. NA revised results (codes and themes) and Abdulrhman Alrowily was responsible for the acquisition of data, analysis, the first interpretation of data, and first drafting of the manuscript. All authors revised it critically for important intellectual content, reviewed and approved for submission.

7.1 Abstract

Background: Despite their effectiveness and ease of use, medication errors have been reported to be highly prevalent with direct-acting oral anticoagulants (DOACs).

Aim: This study aimed to explore pharmacists' views and experiences on contributory factors and mitigation strategies around medication errors in relation to DOACs.

Method: This study used a qualitative design and employed in-depth semi-structured interviews with hospital pharmacists from Saudi Arabia. The interview topic guide was developed based on previous literature and Reason's Accident Causation Model. All interviews were transcribed verbatim, and MAXQDA Analytics Pro 2020 was used to thematically evaluate the interviews (VERBI Software).

Results: Twenty-three participants representing a range of experiences participated. The analysis recognised three major themes: a) enablers and barriers faced by pharmacists in promoting safe utilisation of DOACs, such as opportunities to conduct risk assessments and offer patient counselling; b) factors related to other healthcare professionals (HCPs) and patients, such as opportunities for effective collaborations and patient health literacy; and c) effective strategies to promote DOACs safety, such as empowering the role of pharmacists, patient education, opportunities for risk assessments, multidisciplinary working, and enforcement of clinical guidelines and enhanced roles of pharmacists.

Conclusion: Pharmacists believed that enhanced education of healthcare professionals and patients, development and implementation of clinical guidelines, improvement of hospitals' clinical and incident reporting systems, and multidisciplinary team working could be effective strategies to reduce DOACs-related errors. Future research should utilize multifaceted interventions to reduce error prevalence.

7.2 Introduction

Direct-acting oral anticoagulants (DOACs) are an effective treatment option in nonvalvular atrial fibrillation (NVAF) and the prevention and treatment of thromboembolic conditions.(1) They offer advantages over vitamin K antagonists such as warfarin in several aspects, including the need for less intense monitoring and reduced probability of drug-drug and drug-food interactions.(2, 3) Despite their effectiveness and ease of use, a high prevalence of medication errors has been reported with DOACs.(4) A recent systematic review and meta-analysis demonstrated that approximately 20% of DOACs prescriptions have at least one error.(5) DOACs are classified as high-alert medication per the institute for safe medication practices (ISMP), with the potential to cause severe bleeding episodes or even death if used in error.(6) Pharmacists' roles in preventing and mitigating medication errors have been previously emphasised.(5-9) A recent (unpublished) study suggested that errors due to DOACs are linked to severe harm, including deaths. A total of 25 incidents were linked to deaths, with a further 270 and 55 incidents leading to moderate and severe harm, respectively, out of a total of 15,730 DOACs-related incidents reported to the National Reporting and Learning Systems (NRLS).(10)

Understanding contributory factors associated with DOACs-related errors is essential to promote safe utilisation in clinical practice.(5, 6, 8) To identify these contributory factors, the Reason's Accident Causation model offers a theoretical ground to investigate such factors and provide strategies for their mitigation. The model allows safety incidents systematic investigation and identification of various contributory factors.(11) This helps establish potential causality and identify areas of improvement for patient safety.(12) Reason's accident causation model

distinguishes active failures, such as human mistakes and violations, from latent failures associated with system-related factors, such as lack of resources. A previous study identified a lack of adequate knowledge and training of physicians and nurses about DOACs, a lack of confidence and a lack of access to clinical guidelines as critical factors related to DOACs errors.(12) However, pharmacists' perspectives on DOACs related errors and effective strategies to mitigate the contributory factors have not yet been investigated.

7.3 Aim

This study aimed to explore pharmacists' views and experiences on contributory factors and mitigation strategies around medication errors in relation to DOACs.

7.4 Ethics approval

Ethical approval was obtained from the University of Birmingham Research Ethics Committee (ERN_20-0551) (Appendices 2.1). Ethical approvals from individual hospitals were also obtained (164/2020; SP20/212/R; AFHER-IRB-2020-015) (Appendices 2.2, 2.3 and 2.4). Informed consent (Appendices 2.6) was obtained prior to the study enrolment.

7.5 Method

7.5.1 Study design

This phenomenological qualitative study used in-depth interviews. The findings were reported using the consolidated criteria for reporting qualitative research (COREQ) (supplementary

material Table S 7.1).(13) The COREQ checklist includes thirty-two items that enable researchers to appropriately report essential aspects of qualitative research teams, methodology, setting and context, results, analysis, and interpretation.(13)

7.5.2 Participants and Setting

Using purposive sampling technique, pharmacist participants were recruited from tertiary hospitals with cardiology and internal medicine departments with at least two consultant cardiologists (i.e., larger centres) from three different cities in Saudi Arabia: Riyadh, Jazan, and Dhahran. Pharmacists who had experiences in anticoagulation pharmacy stewardship programs or at least an extensive experience in DOACs medication ordering, reviewing, and dispensing were included. Pharmacists in two different rankings as per the Saudi Commission for Health Specialities pharmacists classification system were included. These included the Senior level consultant pharmacists who had graduated with a PhD or postgraduate-year 2 (PGY2) specialized residency program with three years of practice experience after graduation. The junior-level clinical pharmacists included those who have an accredited degree and expertise in clinical pharmacy (e.g., Master, residency, or PhD), but they do not meet the eligibility criteria to be consultants.

7.5.3 Data collection

Hospitals received an invitation e-mail to recruit research participants. A local collaborator invited all pharmacists in each hospital and outlined inclusion criteria. During pharmacy team meetings, collaborators also conveyed research objectives to potential participants. Those who replied to

the invitations were given a participants' information sheet (PIS) (Appendices 2.8) and requested to sign consent forms.

A topic guide was developed based on previous literature and Reason's Accident Causation Model theory to explore DOACs errors.(8, 12, 14, 15) The majority of the interview questions (supplementary material Table S 6.2) focused on eliciting the participants' knowledge and experience with DOACs, concerns around DOACs-related errors, availability of DOACs use guidelines and other information resources in their institutions, their views about healthcare professionals' roles in improving DOACs safety, and their understanding around contributory factors and mitigation strategies. The questions for the interview schedule were drafted by the first author (AA) and further refined by the research team based on advice from research collaborators at study locations. Seven other pharmacists examined the topic guide to improve its clarity. The interviews were conducted in English (since English is commonly used in hospitals in Saudi Arabia and because many of the pharmacists were English speakers), recorded, and transcribed verbatim by an expert transcriber. Prior to the interviews, the study researcher described the purpose of the study and offered the participants to ask any questions.

Due to COVID-19 pandemic restrictions, the semi-structured interviews were undertaken via Zoom videoconferencing as a platform. The study was conducted during September through November 2021. The researcher was supported by a second member of the research team as a note-taker during the interviews.

7.5.4 Data analysis

Thematic analysis of interviews was performed using MAXQDA Analytics Pro 2020. (VERBI Software).(16) Two authors (AA, NA) separately analysed each transcript, while a third author (VP) examined both versions for discrepancies. Any disagreements were discussed with the research team prior to their agreements. As the semi-structured interviews progressed, transcripts and notes from each session were examined to establish initial codes and to detect emergent information.

To increase rigour and credibility, each interview concluded with a verbal summary developed by the interviewer. This summary was discussed, modified when necessary, and finally confirmed with the interviewees to ensure their agreement with the recorded interview content. The two researchers (AA and NA) met after each interview and discussed the data collected. During the interviews, memos (such as noting an interviewee's facial expressions or reluctance to answer specific questions effectively to notice the need for prompting and further stimulate the participants for discussion), and journaling were recorded utilising MAXQDA memos. Interviews were conducted until data saturation had been reached. Data Saturation was achieved when redundant responses to interview questions were observed without any new information. At this point, the codes resulting from the data collected from the interviews were stabilized, and no additional themes emerged from the collected data. Besides, the investigators had the impression that the collected data was sufficient to reach a robust perception of the points raised by the study participants.

7.6 Results

Saturation of the data collection was achieved after 20 interviews, and three further interviews were conducted for assurance. The semi-structured interviews (n=23) were carried out as per the study plan. The median duration for the interviews was 32 minutes, ranging from 19 to 44 minutes. The characteristics of the participants are presented in Table 7.1. As only those who responded to the invitation were recorded, there was no opportunity to record non-response.

Table 7.1 participants characteristics

Participants' Characteristics (n= 23)	
Participants Characteristics:	**Pharmacists (n=23)**
Gender	
Female	9
Male	14
Training background years of experience	
<5	2
5-10	15
11-15	5
16-20	1
>20	0
Years of experience with DOACs orders (in years) *	
<5	14
5-10	2
11-15	4
16-20	2
>20	1
Specialty or department	
Cardiology	2
Internal Medicine	14
Unspecialized	6
Others*	1
Current job title	
Consultant pharmacists	12
Clinical Pharmacists	11

*Others include any specialist for pharmacist: drug information

* Years of experience with DOACs orders (in years): Any experience with dispensing, checking, order handling or monitoring DOACs.

The data analysis identified three main themes: (1) enablers and barriers faced by pharmacists in promoting the safe utilisation of DOACs; (2) factors related to other healthcare professionals (HCPs) and the patients; (3) strategies to promote DOACs safety. Figure 7.1 represents an overview of the themes and subthemes.

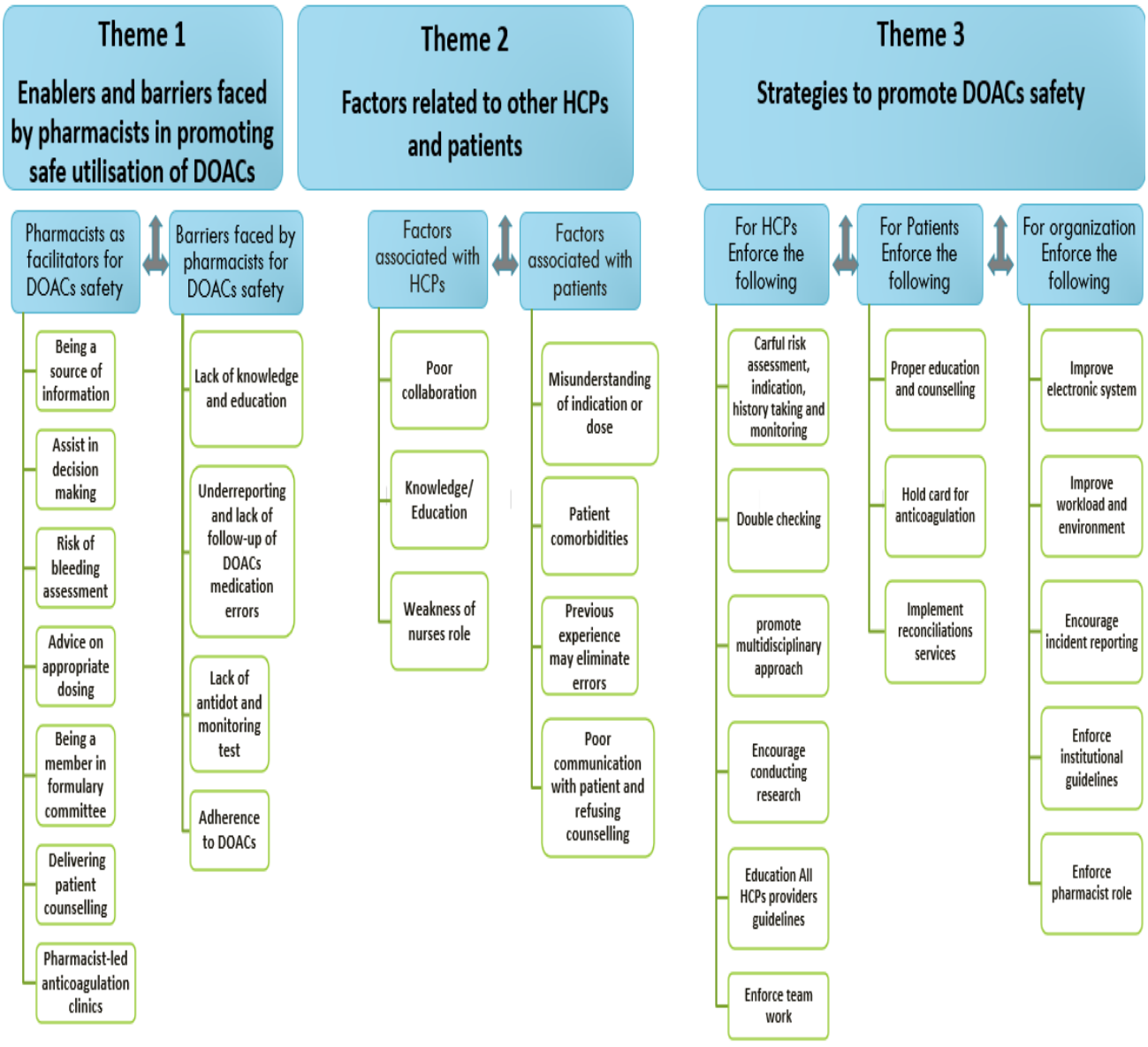


Figure 7.1 An overview of themes and subthemes emerged during data analysis

7.6.1 Theme one: Enablers and barriers faced by pharmacists in promoting the safe utilisation of DOACs

7.6.1.1 Pharmacists as a facilitator for DOACs safety

Participants described pharmacists acting as a source of DOACs information. Besides, they highlighted providing recommendations to assist other HCPs in decision-making (switching from warfarin to DOACs, other elements of prescribing, and administration), participating in bleeding risk assessment, and leading anticoagulation clinics amongst many diverse ranges of roles described (Figure 7.1).

In addition, clinical and drug information pharmacists support formulary decisions that impact the use of DOACs and their safety.

> *"Mainly drug information pharmacist so, I deal with mostly questioned related to DOACs and also was involved in formulary decisions related to DOACs. Those are my main two encounters so, questions received in the drug information centre and, during discussion for formulary addition."* ***Participant 8, pharmacist (Riyadh)***

Participants further illustrated conducting appropriate risk assessments to help improve safe DOACs prescribing.

> *"Again, you have to conduct a reasonable risk assessment, bleeding versus thrombosis risk assessment, based on the patient's scenario, I think you can't prescribe DOACs*

safely without this assessment, which is absent in many cases I've seen, they never do it." ***Participant 2, pharmacist (Dammam)***

Many participants described the assessment of renal functions among the roles of clinical pharmacists to support the decisions around the continuation, adjustment, or discontinuation of DOACs.

“One of our roles as clinical pharmacists is to usually get questions like renal dose adjustments, when can we minimise, the dose based on creatinine clearance (CrCl)and when to hold and when to resume and how to dose based on indication” ***Participant 8, pharmacist (Riyadh)***

Participants also described the patient counselling process as one of the pharmacists' crucial roles, especially during patients’ discharge. In addition, pharmacists provided information on the proper use of DOACs drugs and how to deal with missing doses.

7.6.1.2 Barriers faced by pharmacists in promoting the safe utilisation of DOACs

Pharmacists identified a lack of knowledge of dosing guidelines and other prescribing information related to DOACs as key barriers that might lead to errors while using this class of high-alert medications.

"Honestly, I'm unfamiliar with all DOACs dosing (information), unfortunately but, in some cases I need to be more careful and DOACs dosing in some cases are not mentioned in the guidelines" ***Participant 9, pharmacist (Riyadh)***

Many participants reported that effective medication error reporting, investigation, and follow-up systems were lacking. From some participants' point of view, factors such as lack of time, workload, being bored, or just careless attitude were common reasons for underreporting of DOACs-related safety issues.

> *"Regarding documenting incidents through the occurrence variance reporting (OVR) system in our hospital, to be honest, I don't do it. Why I didn't do that? because don't have time, or sometimes I feel lazy to do this, to be honest."* ***Participant 4, pharmacist (Riyadh)***

Some pharmacists believed that, unlike warfarin, DOACs lack monitoring tools or criteria for dosing. Moreover, the availability of antidotes to antagonize the overdoses of these drugs was another problem that hindered the safe use of DOACs.

> *"I am feeling high responsibilities but, it is not like warfarin. Why? because there is no monitoring criteria for test unlike "INR" for warfarin."* ***Participant 1, pharmacist (Jazan)***

Lastly, participants discussed the impact of patient education on adherence to DOACs and medication errors.

7.6.2 Theme two: Factors related to other healthcare professionals (HCPs) and related to the patients

7.6.2.1 Factors associated with other HCPs

While many described experiences of effective multidisciplinary working, some participants described that physicians do not accept pharmacists' recommendations after medication order review.

> *"… other thing, the resistance from the physician side, when we contact him, he refuses to keep this medication as discontinued so, I feel under pressure if I will review that order, maybe the nurse will give it to the patient, or if I will not review it, maybe also the patient get harm if this medication not administered to him"* ***Participant 3, pharmacist (Riyadh)***

Participants further identified that knowledge regarding the local clinical protocols and guidelines was sometimes lacking, particularly among physicians.

> *"Yeah, some of the physicians do not collaborate with pharmacists, especially upon catching dosing error …They should follow the local hospital protocol and guidelines, and not any other reference."* ***Participant 7, pharmacist (Riyadh)***

Participants further illustrated that the nurses' role should be further empowered. Education and training about identifying adverse events of these drugs were deemed necessary as nurses closely monitor the patients on DOACs.

7.6.2.2 Factors associated with the patients:

Pharmacists discussed that DOACs-related errors could be severe or fatal if patients do not understand dosing information. In addition, there was a risk that patients continued administering two anticoagulants when switched from one to the other.

"so, sometimes the patient, when we shift him from one anticoagulant to another, he continues to use both." ***Participant 2, pharmacist (Riyadh)***

Pharmacists identified that medical history should be clear to avoid prescribing DOACs to those who have comorbidities or contraindications to these drugs.

> *"Wrong patient criteria, for example, patient has advanced liver disease and was prescribed DOAC."* ***Participant 2, pharmacist (Riyadh)***

Many noted that patients often develop knowledge of DOACs through their own user experiences.

> *"Yeah, of course, if patient were more experienced with the medication, this will minimize the risks of error. if the patient has used DOACs for long time and he/she knew what is that medication used for and what side effects may happen."* ***Participant 2, pharmacist (Riyadh)***

Pharmacists discussed the importance of effective communication with patients in minimising errors. However, they reported that it was difficult in some situations, where pharmacists could not effectively communicate with patients. Because of many reasons, including mental health disorders, cognition impairing diseases, and being stressed by pain, in addition to illiteracy and

language barriers. Some also noted that some patients were reluctant to discuss medication-related issues with a pharmacist.

7.6.3 Theme three: Strategies to promote DOACs safety

Study participants reported that reviewing medications by a clinical pharmacist, dose adjustment according to indication and renal function, careful assessment after taking patient history, risk assessment for bleeding tendencies, providing patient education and continuous monitoring for patients after receiving the drugs could be effective strategies to promote DOACs safety.

Furthermore, pharmacists also believed that nurses could play a major role in the prevention of errors by independently double-checking DOACs orders. Finally, they emphasized that the five rights of medication administration (the right patient, the right drug, the right dose, the right route, and the right time) should also be evaluated for users of DOACs before administration.

> *"The nurse should perform independent double checking, it* is very important, especially for this high alert medication," ***Participant 2, pharmacist (Riyadh)***

Participants believed that HCPs should work collaboratively in multidisciplinary teams to decide about patients' suitability to receive DOACs therapy.

> *"I think, forcing the implementation of the multidisciplinary approach is the number one goal to minimise the prescribing errors."* ***Participant 2, pharmacist (Riyadh)***

Pharmacists indicated that research is important to generate evidence regarding DOACs prescribing for new patient population, such as COVID-19 patients. Having strong evidence for prescribing such drugs is essential before using them.

> "*Sometimes physicians don't have any strong evidence (to support their practices with regard to DOACs, e.g: the doctors prescribe DOACs for post-COVID patients. But they don't have any strong evidence regarding this thing."* ***Participant 2, pharmacist (Jazan)***

Participants discussed that identifying patients on DOACs by having specific cards to inform healthcare providers about patients' DOAC therapy can allow delivery of appropriate anticoagulation care and minimize medication errors. Participants also described medication reconciliation as another high-priority strategy that pharmacists should use to combat this problem. This can help identify patients at risk and DOACs associated medication errors and prevent them.

> *"I believe the reconciliation is a very high priority when it comes to catching these kinds of errors. So, if we have proper reconciliation upon patients' admission and, discharge, you make sure that the patient has been… (looked after to avoid errors)."* ***Participant 8, pharmacist (Riyadh)***

Interviewees stated that implementing clinical decision support systems could be an effective strategy to promote DOACs' safety, not only for prescribing error reduction but also for dispensing and administration errors.

Pharmacists stressed on the importance of improving the working environment and decreasing the workload to provide enough time for more patient attention and care. Heavy-duty shifts and busy locations in the pharmacy can negatively affect those patients' safety. In addition, the

participants indicated that encouraging HCPs to report errors associated with DOACs is needed. They emphasised that just the reporting culture should be augmented, and the reporting system should be simplified to save time and facilitate reporting.

Furthermore, interviewees identified that improving awareness and enforcing strict audits for institutional guidelines implementation would help HCPs during the whole medication management cycle, especially if such audits could be supported by a hospital information system (HIS).

> *"Well, I believe that, first, there should be strict protocols and guidelines, and this should be disseminated to all care providers, so they would know what the policy and educational activities is should be also done to them so they will know what's the policy."* ***Participant 7, pharmacist (Riyadh)***

Participants indicated that empowering clinical pharmacists to perform their daily tasks in dealing with these high-alert medications is critical. They exemplified that pharmacists run the anticoagulation clinics, contribute to identifying major adverse effects of these drugs, communicating their recommendations to other healthcare providers in the team, follow up of patients and readjust doses based on the patients' kidney function could also help in minimizing potential DOACs-related errors. Therefore, clinical pharmacist order review before dispensing was deemed crucial to promote DOACs' safety.

7.7 Discussion

7.7.1 Statement of key findings

This study investigated pharmacists' views and experiences about contributory factors and mitigation strategies relevant to DOACs medication errors. Our study findings revealed that pharmacists believe that they could play a vital role in improving DOACs' safety when they are provided with appropriate training and reliable information sources. These results support previous studies' findings which have highlighted the positive impact of pharmacists' interventions in the reduction of DOACs related medication errors.(8) Pharmacists could assist in clinical decision-making, perform bleeding risk assessment, help in dose adjusting, participate in formulary decisions, and provide patient counselling in addition to running specialized anticoagulation clinics.(17)

The data gathered suggested that barriers to DOACs' safety included poor communication with patients, lack of knowledge and training of HCPs, underreporting of errors, and lack of follow-up of patients receiving DOACs.

The study further highlighted several patient-related factors, such as misunderstanding of indications and proper doses, having multiple comorbidities, and lack of prior experience with DOACs increased the likelihood of errors. Pharmacists suggested that careful assessment of cases during history taking, better monitoring, double-checking of orders by pharmacists, multidisciplinary management, research, improving healthcare providers' awareness regarding guidelines and enforcing multidisciplinary teamwork could improve DOACs safety. Moreover,

pharmacists recommended appropriate education and counselling of patients, availability of patient cards indicating the use of DOACs, improving clinical decision support systems, reducing workload for healthcare providers, encouraging error reporting empowering pharmacists' roles, and updating institutional guidelines in order to prevent medication errors caused by DOACs.

7.7.2 Interpretation

A recent study conducted in Qatar corroborated our findings in supporting the positive role of well-trained, experienced pharmacists in promoting DOACs safety. The study authors reported that clinically experienced pharmacists (i.e., those who have board certification or clinical involvement in DOACs prescribing or dispensing) had better awareness and experience in DOACs prescriptions management compared to other pharmacists.(18)

Our study findings are concordant with the results of previously published studies that highlighted the importance of pharmacist-led clinics or services in reducing DOACs errors, as reported by participating pharmacists in our study.(5, 19) Moreover, our study participants revealed that the clinical pharmacist role was vital to improving patients' care especially for patients with chronic disease, comorbidities, and receiving polypharmacy. Physicians and nurses in our previous study also emphasized pharmacists' involvement in care with other HCPs.(12) Physicians' views highlighted the pivotal results of multidisciplinary teamwork to prevent medication errors.(20) Similar to the findings in this study, other literature also suggested pharmacists face similar challenges while reporting incidents of medication errors.(21) Time limitations, heavy workload, and difficulty in dealing with the reporting system

were identified by pharmacists as key barriers to error reporting in our current study and the published literature.(21)

Pharmacists in our study reported that improving healthcare providers' awareness and education is vital for identifying and preventing medication errors. Implementing education and training programs while focusing on reflective learning might reduce medication errors.(21)

7.7.3 Strengths and weaknesses

This study provides an in-depth understanding and detailed factors, reasons and solutions in relation to contributory factors to DOACs errors from pharmacists' perspectives. Although our study is not generalizable- being a qualitative designed study with limited sample size, involvement of participants from different regions in Saudi Arabia with diverse staffing level, patient populations, and variable healthcare practice enabled and enhanced the transferability of the findings to other settings.

7.7.4 Further research

Our study findings provided experience-driven insights for HCPs and policy makers regarding pharmacist views about factors that could hinder DOACs' safety; the study results recommended several strategies to reduce DOACs-related errors. Effective and theory-based interventions to improve knowledge and minimize errors to target gaps illustrated by our findings need to be developed. Multifaced interventions that combine education and technology are required. Implementation and evaluation of pharmacist DOAC prescribing, anticoagulation clinics, and anticoagulation stewardship programs are required. Future research should

investigate the efficacy of proposed DOACs risk mitigation strategies. Future research findings could help prioritise these strategies based on their measured impact on promoting DOACs safety.

7.8 Conclusion

As per the study finding, pharmacist participants of this study believed that DOACs safety could be improved through educating patients and healthcare professionals, developing and implementing clinical guidelines, and improving hospitals' clinical and reporting systems. Furthermore, they highlighted the need to empower a multidisciplinary healthcare team working. Future research should utilise multifaceted interventions to reduce error prevalence and assess the impact of such interventions.

7.9 Acknowledgments

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7.11 Conflicts of interest

As the associate editor of the International Journal of Clinical Pharmacy Dr. Vibhu Paudyal had no role in the management of the submission, including editorial assessment, peer review, and decision-making. There are no other conflicts to declare.

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Chapter 8. Patients' views and experiences on the use and safety of directly acting oral anticoagulants: a qualitative study

Chapter overview: This chapter reports the views, experiences, and contributory factors related to medication errors associated with direct oral anticoagulants. The study was conducted using semi-structured interviews with patients.

Notes for plagiarism check: This section is under review in a peer-reviewed journal with the citation below.

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Authors' contribution: This study relates to Abdulrhman Alrowily, PhD research. VP and ZJ supervised Abdulrhman Alrowily for his PhD. MB, AA, MA co-authors have made substantial contributions to the conception and design of the study. NA revised results (codes and themes) and Abdulrhman Alrowily was responsible for the acquisition of data, analysis, first interpretation of data and first drafting the manuscript. All authors revised it critically for important intellectual content, reviewed and approved for submission.

8.1 Abstract

Direct oral anticoagulants (DOACs) are considered high risk medications and used to prevent thromboembolic events and stroke. This study aimed to examine patients' views and experiences of DOACs use and factors that can promote safety associated with DOACs. In-depth interviews were conducted with adult patients recruited from tertiary care hospitals in Saudi Arabia. Data was analysed thematically. A total of nine participants were recruited. Three major themes were identified: (1) factors affecting DOAC's safety from the patients view; (2) barriers to adherence to DOACs, and (3) strategies to promote the safety of DOACs. Lack of knowledge of DOACs, using inappropriate sources of information, lack of communication with HCPs, difficulty in having access to DOACs and lack of monitoring were the main factors affecting the safe use of DOACs. The unavailability of the drugs and difficulty in time getting to hospitals affected adherence. Patients acknowledged difficulties communicating with healthcare professionals, timely access to anticoagulation clinics and obtaining their DOACs on time. There is a need to develop and evaluate theory-based interventions to promote patient knowledge, understanding and shared decision-making to optimise DOACs use and improve their safety.

8.2 Introduction

Direct oral anticoagulants (DOACs) are extensively prescribed for prevention of stroke and thromboembolism in patients with non-valvular atrial fibrillation (NVAF). NVAF is becoming highly prevalent in the population, with risk estimates reaching about 1 in 3 in white individuals and 1 in 5 for black individuals.(1) Moreover, patients with these conditions are often associated with long-term co-morbidity, polypharmacy, frequent hospitalisation, reduced quality of life and poorer physical function, thereby increasing the likelihood of errors.(2, 3)

The safety and effectiveness of DOACs are highly dependent on safe prescribing as well as the ability of patients to manage and take the medicines. Medication errors associated with DOACs pose significant health risks to patients. A recent systematic review and meta-analysis conducted by the study researcher showed that 20% of patients prescribed DOACs experienced some sort of prescribing error.(4) In another study, it was reported that 62% of all DOACs errors caused patient harm, of which 5.2% caused severe harm, and 0.8% were fatal errors.(5) Most of the fatal errors were due to wrong dose errors, while the most severe harm errors were due to medication omissions. In another study, DOACs were most commonly associated with severe harm, including 25% of all fatal errors, making it the most harmful therapeutic area in the reported incidents.(5) Other studies have shown that medication errors associated with DOAC's resulted in high mortality and morbidity and caused extended stays in the hospital.(6, 7) A retrospective study by Piazza et al. identified medication errors as the common root cause in 40% of anticoagulation-related adverse events.(8)

Suggested strategies to improve medication safety and prevention of medication errors from occurring include the provision of a clinical pharmacist within the clinical team. In addition, it is important to strengthen the communication between healthcare professionals and patients.(9) Despite the high prevalence of errors associated with DOACs, there is a dearth of research looking into patient perspectives on the use of DOACs from the patient perspectives.

Patient participation in research is considered a key component for enhancing the safety and quality of healthcare services. It is important for patients to make informed decisions about their treatment. Lack of patient engagement in the prevention and management of cerebrovascular disorders has previously been previously flagged.(10)

Therefore, this study aimed to examine patients' views and experiences of DOACs use and factors that can promote safety associated with DOACs.

8.3 Materials and methods

8.3.1 Participants

In-depth interviews were conducted with adult patients recruited from tertiary care hospitals in Riyadh, Dhahran, and Jazan regions of Saudi Arabia. Online videoconferencing was used. One tertiary hospital in each of the three Saudi regions was chosen. Hospitals were eligible to participate in the study based on the presence of a cardiology department with at least two consultant cardiologists. Purposive sampling was undertaken for the recruitment of participants. A maximum variation sample was undertaken, including those taking high/low DOAC's use years

and sex. Patients were interviewed until data saturation was achieved and no new code emerged. Saturation of the data collection was achieved after seven interviews with patients, and two further interviews were conducted to confirm it.

8.3.2 Procedure

An invitation e-mail was sent to the anticoagulation clinic through the cardiology department in the hospitals for participants' recruitment. In each hospital, a local collaborator identified the patients from the anticoagulant clinic list and contacted eligible participants. The collaborator explained the study objectives and provided the Arabic language information sheet to the participants during a face-to-face meeting and if agreed (Appendices 2.9), the consent was signed by the collaborator (Appendices 2.7).

8.3.3 Ethics approval

Ethical approval was obtained from the University of Birmingham Research Ethics Committee (ERN 20-0551) (Appendices 2.1). Moreover, three ethical approval was obtained from the three hospitals: National Guard Hospital in Riyadh (SP20/212/R) (Appendices 2.2), King Fahad Military Medical Complex in Dhahran (AFHER-IRB-2020-015) (Appendices 2.3), and King Fahad Central Hospital in Jazan (164/2020) (Appendices 2.4). prior enrolment in the study, all participants signed an informed consent form (Appendices 2.7).

8.3.4 Materials

A topic guide was created by the main researcher (AA) after a literature review of the extent of DOACs errors from the patients' view.(4, 11) Questions focused on the experience in taking DOACs, concerns raised during their use, the perceived level of knowledge they have about these drugs, and the perceived safety culture (Supplementary material Table S 8.1). Specific questions about the factors associated with errors and their prevention were also asked. The questions were revised by the research team and the collaborators, including physicians and pharmacists, who included experts in both qualitative research and DOAC's use. The interviews were conducted in Arabic, recorded, transcribed into Arabic language and translated into the English language in the final stage of analysis when emerged themes and subthemes and choosing the quotes.

8.3.5 Data Analysis

The interviews were systematically analyzed using a thematic content approach using the software program MAXQDA Analytics Pro 2020 (VERBI Software). (5) Each transcript was independently analyzed by two authors (AA, NA), and a third author checked both versions (VP) for discrepancies. Disagreements were resolved by discussions. As the semi-structured interviews progressed, data were analyzed after each interview to develop initial codes and to identify important and new emerging information. The final themes and related quotations were translated into the English language.

Semi-structured interviews were conducted virtually using Zoom videoconferencing as a platform due to limitations caused by the COVID pandemic. The study was conducted from

September 2021 till the end of November 2021, and interviews lasted between 30 to 45 minutes in duration.

8.3.6 Rigour and trustworthiness

To improve rigour and trustworthiness, each interview was ended by a summary to be validated by the participants and to check for any ambiguity. After each interview, the two researchers (AA and NA) met and reflected on the information received. Memos (such as reporting interviewee's facial expressions or hesitancy to answer certain questions adequately) and journaling were recorded during the interviews and utilized throughout data collection and analysis using MAXQDA memos. Data from interviews were kept secure in computers with a secured password. This study was reported in accordance with the Consolidated criteria for reporting qualitative research (COREQ).

8.4 Results

A total of nine participants were recruited. Most of the patients were male (n=6) and had a Bachelor of Science as their degree (n=5). Table 8.1 summarizes participant characteristics.

Table 8.1 participants characteristics

Participants' Characteristics (n= 9)	
Participants Characteristics:	**Patients (n=9)**
Gender	
Female	3
Male	6
Experience of DOACs uses	
<6 months	4
6-12 months	2
1-2 years	1
2-3 years	1
>3 years	1
Education	
Undergraduate degree	5
Complete school aged 18	3
Not disclosed	1
Current job title	
Fully retired from work	3
Unemployed	3
Not disclosed	3

The analysis of the interviews identified three themes: (1) factors affecting DOACs safety from the patients' view; (2) barriers to adherence to DOACs; and (3) strategies to promote the safety of DOACs. Figure 8.1 represents an overview of themes and subthemes that emerged during data analysis.

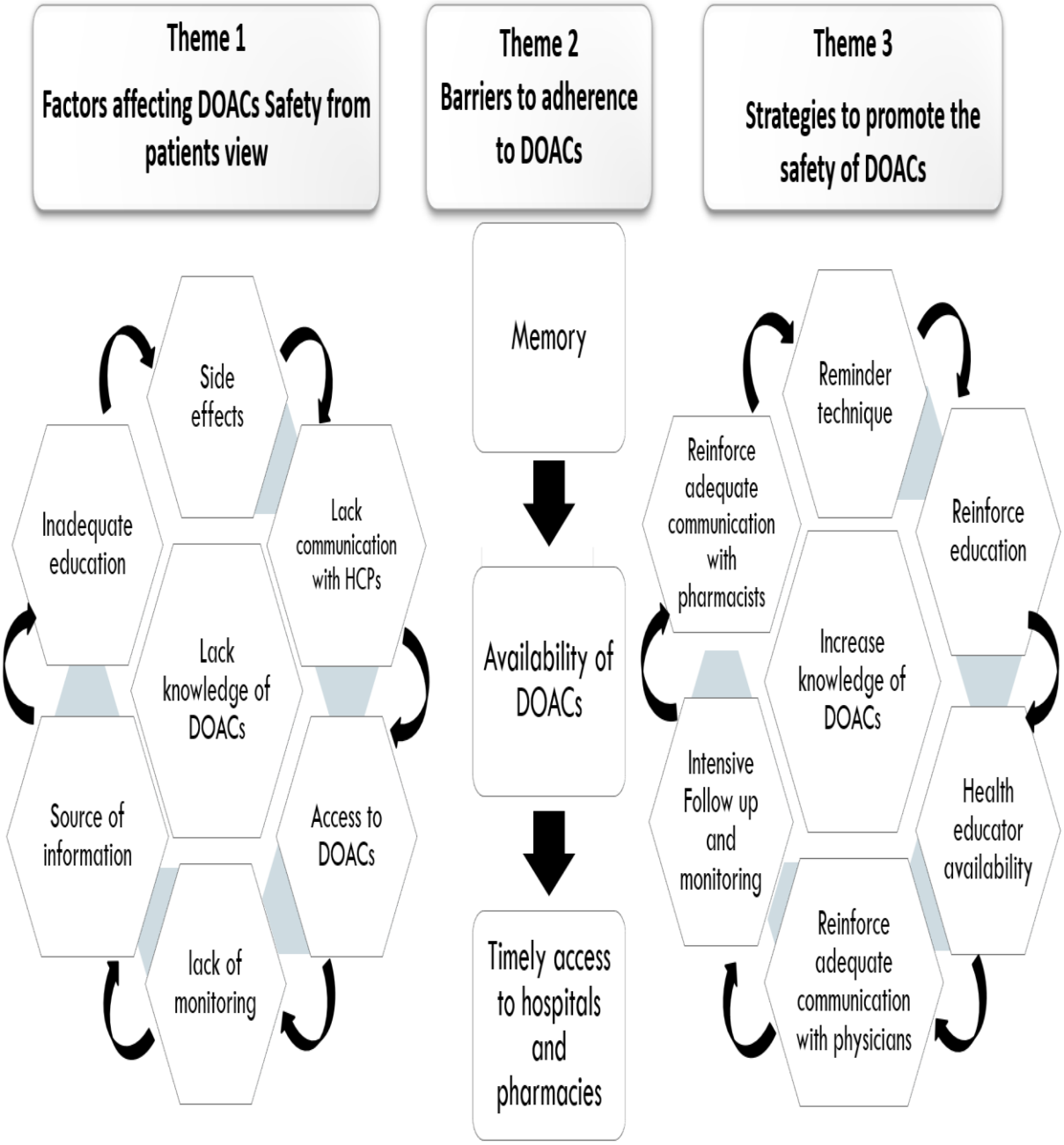


Figure 8.1 An overview of themes and subthemes emerged during data analysis

8.4.1 Theme 1: Factors affecting DOACs Safety from patients view

8.4.1.1 Knowledge

8.4.1.1.1 Lack of knowledge on DOACs

Most participants described having inadequate knowledge in regard to dose, drug-drug interactions, duration, and side effects. They described a lack of adequate time spent with the doctors to answer these queries. Many doctors often refer patients to the pharmacy to request further information about the prescribed DOACs.

> "*….I am not aware of all the information regarding the medication prescribed by the doctor? What I know about him is that he only "blood thinner", And when I am in the clinic with the doctor, he does not give me enough time to find out about the disease and the treatment. He only tells me to go to the pharmacy to take the medicine, and I have other patients, waiting their appointment please*." ***patient 1 (Riyadh)***

Many described a lack of opportunities and busy schedule in the clinics as well as in pharmacies that prevented patients obtaining the information that they needed.

> *"In fact, it is difficult to communicate. I tried to talk to him and explain more to me on the grounds that it was the first time I took the medicine. I talk about how I take medicine. He said to me: You use the medicine as it is written on the prescription, and when I went to the pharmacy they gave me the medicine, but I went back to the clinic asking the doctor. The clinic was crowded, and I was unable to communicate with him"* ***patient 3 (Dammam)***

Other patient participants reported that pharmacists do not offer adequate time to counsel patients and often refer patients to the instructions in the patient information leaflet.

> *"…When I go to the pharmacy to dispense the prescription, the pharmacist dispenses the medications to me and does not explain anything he said all instruction written in the label. as you know the pharmacy is crowded patients, just pack a bag and go home"* ***patient 3 (Dammam)***

8.4.1.1.2 Source of information

Most participants agreed that healthcare professionals only rarely provided them with educational information about DOACs. They stated that they often had to rely on relatives and friends or use untrusted sites accessed through Google to find information regarding DOACs.

> *"….Of course, this medicine was previously taken by one of my relatives, and frankly, I always ask him about the medicine, is taking two doses better than one? When I gave my mother the wrong dose, it caused her to bleed for about five days, and she is in the intensive care unit in the hospital; after this case; I mean I learn it must be very careful with these drugs. If they exceed the normal limit or the required limit, they will have more harm than good. Therefore, in case of forgetfulness or doubt, It is preferable to ask the doctor and pharmacist, or use a leaflet of drug, or enter the Internet to give you general information"* ***patient 2 (Riyadh)***

8.4.1.2 Side effects

Most participants described being unaware of the side effects, including very common side effects such as bleeding. Yet again, the lack of counselling from healthcare professionals was described.

> *"Yes, I have side effects while taking the medicine, so I decided to stop the medicine. The first thing I felt was a pain in the knees, so it is, and I woke up from sleep, my mouth and gums were a little bloody. In fact, I felt worried, as the doctor did not tell me about the side effects of the drug"* ***patient 1 (Riyadh)***

8.4.1.3 Communication

8.4.1.3.1 Lack of communication with HCPs

Lack of communication with HCPs was deemed a key factor compromising patient safety. Many patients indicated the physician did not engage patients in informed decision-making for choosing DOACs anticoagulants.

> *"Frankly, I am like many other patients, had many diseases such as clots, diabetes, hypertension, and high cholesterol. So sometimes I neglect the use of medicines because they are many and I miss monitor them especially since I live alone and another thing the doctor not share us when choose the drug to make a decision what is suitable for me and what available drug or frequency of dose once or twice daily."* ***patient 6 (Riyadh)***

Lack of information often led the patients not knowing how to manage their medicines on a daily basis.

> *"..Sometimes it is very difficult to communicate with the doctor or pharmacist, especially if I did not take the medicine for example if I forgotten. I do not know whether to take the medicine immediately or wait for the next day at the same time of the dose"* ***patient 3 (Dammam)***

8.4.1.4 Access to DOACs

Some patients indicated that the lack of drug delivery services in the hospital affected the accessibility to medications and led to patients not receiving their medicines. for instance, during the COVID-19 pandemic, transportation was deemed challenging.

> *"Yes, the reason is that the hospital is far from housing, and the hospital does not have drug delivery services from the pharmacy if we need refill drug, and we were afraid to go to the hospital to refill medication, especially during the times of the Corona pandemic."* ***patient 7 (Dammam)***

8.4.1.5 Monitoring

Lack of monitoring, especially in the anticoagulation clinic, was deemed a key factor compromising patient safety. Many patients described difficulty obtaining appointments in the anticoagulation clinic. Other participants reported not attending the anticoagulation clinic due to their own carelessness.

"...Sometimes it is very difficult to attend an anticoagulation appointment with the doctor, especially if you forget the day that I have to attend the anticoagulation clinic and sometimes basically the doctor himself forgets to give us an appointment to follow up with him at the clinic" ***patient 3 (Dammam)***

8.4.2 Theme 2: Barriers to DOACs adherence

Under this theme, participants described factors associated with adherence to DOACs and administration errors.

8.4.2.1 Memory

Some patients were described as been prescribed multiple medications. In addition, due to polypharmacy, many patients would often forget to take their DOACs.

"True, to be honest, a lot. I forget to use medicines because I suffer from high blood pressure, diabetes, and heart problems. I have more than 10 medicines that I use. I forget to take medicines, frankly." ***patient 4 (Riyadh)***

8.4.2.2 Availability of DOACs

The availability of DOACs was identified as a major barrier to adherence. One patient indicated that if the drug was not available in the hospital, it would cause the patient to miss doses; and some patients reported that if the drug was not available in the pharmacy, the patient would feel dissatisfied. Dissatisfaction was also expressed by many patients who expressed the drug's high costs when they wanted to purchase it.

"The big problem with edoxaban the availability of drug. I really hope that it is available for free in government pharmacies because most of the time it is not available. The worst is that its price is a little expensive, and every month need one pack is required; For a period of thirty days, it contains 28 tablets and cost is 240 SAR; Sometimes it means in some people cannot pay this price, what I can do, especially if they more than 2 drug out of stock." ***patient 5 (Riyadh)***

8.4.2.3 Timely access to hospitals and pharmacies

Some participants described difficulty accessing DOACs mainly due to barriers in timely getting to hospitals and dispensing pharmacies.

"Patient's daughter: Eliquis particularly rare if it is available in the hospital, due to what we spent a lot of time to go in the same hospital in the same area. However, the hospital is a far away from our town and we had some difficulties to reach the hospital." ***patient 7 (Dammam)***

8.4.3 Theme 3: Strategies to promote DOACs safety

Patients' participants suggested numerous ideas to help minimize errors related to the use of DOACs.

8.4.3.1 Reminders

8.4.3.1.1 Use the medication box to remember/ mobile alarm/caregivers

In order to reduce suboptimal use and minimise administration errors, patients reported using multicompartmental compliance aids and digital app reminders. These were particularly deemed effective where carer support was not always available.

> *"I am so careful I use it that I use the medication at the right time. So I made a schedule for myself and also a mobile alarm, because I have no one from the family to alert me, only my son is present, and sometimes he alerts me and sometimes not; I have diabetes, and I have hypertension, so I set a schedule for me and when do I take the doses so that I do not forget to take them, in a paper I have a morning What should I take in the evening and what should I take in the evening?"* ***patient 2 (Riyadh)***

8.4.3.1.2 Following advice from HCPs

Some patients described that the safe and effective use of DOACs requires patients to follow instructions provided by healthcare professionals.

*"The best way to safely use the drug so that there are no errors; The most important thing is to follow the doctor's instructions no matter what, as well as the pharmacist's question, you go and ask, in such and such, but it is always better and better to refer to the medical source, which is the doctor "**patient 9 (Jazan)***

8.4.3.2 Education

8.4.3.2.1 Availability of a health educator in a hospital

Some patient participants wished that there was a health educator in the hospitals that they could talk to about their medicines. Such health educators would fulfil the roles of education providers that they often expect from their doctors and pharmacists. Participants also referred to pharmacists not undertaking the roles of information providers.

*".... I wish there is a clinic that educates about this medicine, frankly, the doctor and the pharmacist are always busy, I mean, they don't give me enough information. The doctor says, "Take this medicine first thing in the morning and go home, and the pharmacist doesn't explain enough because the label is on the medicine. I wish there was a health educator." He sits with me and teaches me, what should I do if I forget to take the medicine, what if I have certain symptoms, what should I do. And so on" **patient 2 (Riyadh)***

*"We need to have a health educator after receiving the medicines explaining to us the reasons for using this medicine and the pros or cons of the medicine. Frankly, we have medical consultations for them with a special number, so I can call them. But this is not enough because sometimes they are not available." **patient 3 (Dammam)***

"I stress that there should be a medical educator who sits with the patient, talks to the patient, and teaches him about what are the symptoms, if for example something happened to me or if I felt a certain symptom, what is should I and should not do it?" ***patient 4 (Riyadh)***

8.4.3.3 Intensive monitoring and follow up

Regular follow-up to the clinic was identified as another strategy to promote the optimal use of DOACs. In addition, they described that intensive follow-up could help identify patients at risk and medication errors associated with DOACs to mitigate them.

"One of the good things and makes me feel comfortable going to the coagulation clinic, they give me an appointment every three months, about a year every three months. Then they put it every 6 months, then every eight months. On this visit, the doctor was checking an electrocardiogram and making sure of blood thinner tests I advise all patients to commit to visiting the liquidity clinic regularly" ***patient 6 (Riyadh)***

8.4.3.4 Reinforcing adequate communications with HCPs

Patient participants stressed on the need for adequate communication with health care providers outside clinic hours to answer, confirm and support the patient with any inquiries about the safe use of medicines

"I hope there is a way to communicate with the doctor outside the coagulation clinic. This will make it easier for me to identify all my inquiries, especially if side effects occur. Also,

with regard to medication, I hope that communication with the pharmacist is available and easy when we need it" ***patient 8 (Jazan)***

8.5 Discussion

This study aimed to explore patient views and experiences factors contributing to DOACs safety from patients' perspective. The factors recognised by participants in the study were categorized into three themes including factors affecting DOACs safety and strategies to promote DOACs safety. Our study findings showed that the discontinuation of DOACs due to non-availability of drug, suboptimal adherence, and lack of monitoring were key barriers to ensuring optimal use and patient safety. In addition, lack of information, communication with physicians and pharmacists, and inadequate education aware other factors associated with safe and effective use. Participants reported that improving patients' awareness and knowledge, reinforcing education, enhancing accessibility to and communication with healthcare providers, using reminder techniques, in addition to intensifying follow-up activities are the perceived strategies to improve DOACs safety.

There is a dearth of studies looking into patient perspectives on their prescribed DOACs though it is important to assess patients' perspectives and get them involved in initiatives to improve optimal DOACs use and their safety. To the best of our knowledge, this is the first study of its kind to examine patients' perspectives in relation to DOACs using in-depth qualitative analysis. A study conducted in 2014 by Sarrazin et al to determine patients' experience and perception regarding dabigatran using online discussion forums (468 posts), interestingly reported

preference of dabigatran due to the lack of monitoring and dietary restrictions; however, the lack of an antidote was a safety concern.(12)

The link between suboptimal adherence and safety concerns has been reported in previous studies.(13) Patients' forgetfulness was found to be associated with DOACs medication incidents.(13, 14) Patient adherence to such medications is of paramount importance, as missing doses may lead to higher risks of thromboembolism.(15)

Another important factor identified in this study was the availability of drugs. It is important to ensure seamless access to high-risk medications such as DOACs & their generics. Our patients' concerns regarding drug availability and the high cost that makes affordability and adherence challenging are consistent with previous studies findings.(15, 16)

The lack of adequate communication with healthcare professionals, including pharmacies, was particularly concerning. Patients in our study reported that lack of proper communication with healthcare providers was a key factor in compromising their safety. It is important to ensure optimal communication between patients and their healthcare professionals.

Recommendations to promote DOACs safety from patient perspectives identified in this study provide an opportunity to improve the safe and effective use of DOACs. Regular follow-up in the anticoagulation clinic and the availability of health educators were examples of strategies to promote safety. Given that most patients who are users of DOACs are of advanced age, both patients and carers need to be involved, educated, and communicated to promote safety as also recommended by previous studies.(12)

8.5.1 Strengths and Limitations

Having patients actively participate in the decision-making process in their care is critical for improving the quality of care. Patients usually get overlooked, and studies assessing their perspectives regarding this important health-related issue are lacking. Our study, therefore, adds to the dearth in the literature. Despite data saturation being achieved, these results should be interpreted with caution, especially for generalization purposes. Future studies could undertake a survey of patients utilising a larger sample size with questionnaire tools developed based on the findings of this qualitative study.

8.5.2 Future Plans

Future studies could undertake a survey of patients utilising a larger sample size with questionnaire tools developed based on the findings of this qualitative study.

8.6 Conclusion

Patient knowledge regarding DOACs, optimal adherence, adequate communication between healthcare professionals and patients, and timely access to clinics and medicines are key strategies to promote optimal utilisation and safety of DOACs from the patient's point of view. There is a need to develop and evaluate theory-based interventions to promote patient knowledge, understanding, and shared decision-making.

8.7 Author Contributions

This study relates to Abdulrhman Alrowily, PhD research. VP and ZJ supervised Abdulrhman Alrowily for his PhD. MB, AA, MA co-authors have made substantial contributions to the conception and design of the study. NA revised results (codes and themes), and Abdulrhman Alrowily was responsible for the acquisition of data, analysis, the first interpretation of data, and the first drafting of the manuscript. All authors revised it critically for important intellectual content, reviewed and approved for submission.

8.8 Funding

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8.9 Acknowledgments

We would like to thank the collaborators in three different settings for their assistance in identifying and recruiting participants for the study. We also want to thank the study participants.

8.10 Conflicts of Interest

The authors declare no conflict of interest.

8.11 References

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Chapter 9. Overall discussion and conclusion

9.1 Introduction

The overarching objective of this thesis was to investigate medication errors associated with the use of DOACs in hospitals and to explore the contributing factors to such errors. Identifying these factors is expected to help develop mitigation and prevention strategies from the perspectives of healthcare providers and patients. Patients' perspectives regarding DOACs use and how to avoid errors associated with them have long been overlooked in many studies in that regard. However, in our research projects, patients and their safety were at the centre of our investigations. Diversification of the research methodologies used in our projects increases the validity of our results. Such studies are needed to inform the policy and provide data-driven insights for the decision-makers to improve DOACs utilisation and safety.

9.2 Summary of main findings in all studies

The systematic review study conducted at the beginning of my PhD was an opportunity to identify the most prevalent types of medication errors associated with DOACs in the literature. The previous studies revealed that prescribing errors linked to doses were widespread. Active failures and lack of dose adjustment based on kidney function were common contributory factors and causes of medication errors in DOACs. Pharmacists' role as a part of multidisciplinary teams and trainers for other healthcare providers, availability of clinical guidelines, and pharmacist-led anticoagulation clinics were the most common mitigation strategies in the published literature. The dearth of studies from developing countries

encouraged us to investigate the same issue in Saudi Arabia. As shown by the study that used reports data from the Saudi FDA pharmacovigilance database, in addition to data obtained from local incidents reporting from two hospitals in Saudi Arabia, revealed that the majority of DOACs-related medication errors were identified at the prescribing stage. Most of the reported errors were inappropriate drug selection and inappropriate dosage regimen (dose, frequency & duration). Recommendations to reinforce education and training for physicians, in addition to emphasising the importance of reporting incidents of medication errors, are suggested. Furthermore, it is suggested to empower pharmacist's role to minimise medication errors through conducting initial assessment followed by developing a safe and effective pharmaceutical care plan to assist prescribers to take the safer decisions. Medicines reviews and reconciliation plus patient counselling can further aid in identifying and diminishing safety concerns in a timely manner.

Developed countries are no exception when it comes to DOACs associated medication errors. Similar to the situation in Saudi Arabia, prescribing errors and inappropriate dosing were the most prevalent incidents in reports submitted to the national patient safety reporting database- the National Reporting and Learning System (NRLS). Active failure, poor documentation, poor communication, and lack of training were commonly detected in the incident reporting database. Missed doses, duplication of anticoagulant drugs, patients discharged without DOACs, ignoring renal function, and lack of commencement or adjustment of DOACs post-surgery were common causes of DOACs-related errors. After further investigating the same issue using a qualitative approach with Saudi healthcare providers and patients, results revealed that a knowledge gap

exists among physicians and nurses, lack of clinical guidelines, lack of drug information specialists in addition to poor communication were the most common causes of DOACs errors.

On the other hand, patients reported a lack of counselling and communication with healthcare providers leading to discontinuation of medication use. The stakeholders (physicians, nurses, and pharmacists) have agreed on interprofessional collaboration, better communication, developing local clinical guidelines, and allowing pharmacists to lead anticoagulation clinics. Finally, patients suggested that using mobile alarms and medicine boxes and enhancing communication with their healthcare providers would be essential to reduce DOACs-related errors.

9.3 Overall interpretation of results

This PhD thesis commenced through an in-depth search of databases for a systematic review and meta-analysis, followed by research utilising routinely collected incident databases and multiple primary research studies. These projects utilised different methodologies ranging from retrospective evaluation of routinely collected data and analyses of safety incidents reported in hospitals or national databases in two different countries (Saudi Arabia and UK), qualitative interviews with many stakeholders who have been involved in prescribing, dispensing, and administration of DOACs such as physicians, pharmacists, and nurses as well as patients themselves who use these medicines and experience their errors and consequences. This research used the Reason's Accident Causation model, a widely used theoretical framework,

which helps with identifying and understanding the contributing factors to errors and the nature of interventions related to addressing these factors.

The overall findings of all these research projects concluded that DOACs errors are still common despite their favourable safety profile compared to other traditional anticoagulants, such as warfarin or parenteral anticoagulation derivatives. The systematic review, which used extensive literature search methods in 11 databases, including Medline, Embase, and CINHAL, between January 2008 and September 2020 found 32 studies involved a total of more than 10,000 patients in hospitals who experienced DOACs-related errors when it was prescribed for management of thromboembolism or atrial fibrillation. This systematic review confirmed that amongst the most prevalent types of errors associated with DOACs were prescribing errors, particularly dose-related ones that were most prevalent. The pooled percentage of patients experiencing prescribing errors was 20% (95% CI 15–25%; I2 = 96%; 95% PrI 4–43%), which was estimated using random-effects models, and the proportion for those who experienced all types of errors ranged from 5.3 to 37.3%. Active failures (e.g., wrong dosing) were the most common causes, with contributing factors, such as mistakenly non-consideration of renal function or lack of such knowledge as an error-provoking condition. The systematic review revealed that prescribers should be aware of prescribing accurate dosing as it should be customised based on the used DOAC drug, indication, renal function, age, weight, and concurrent intake of drugs taking in consideration the lack of routine dose-adjustment coagulation monitoring for DOACs.[48–52]

While investigating the strategies used in mitigating the error-related factors, the systematic review results further promote pharmacists' role in multidisciplinary, inter-professional and guideline-guided clinical practice as well as their roles in training and educating other healthcare professionals. These findings came in parallel with other literature that revealed the positive impact of pharmacist-led anticoagulant clinics or stewardship programs in improving DOACs' utilisation and minimising related errors.(1-10) It also endorsed the role of technology-facilitated interventions to minimise errors and maximise the benefits of DOACs usage in all settings.(11, 12)

During the systematic review, very few studies had been found on reporting medication incidents and the severity of medication errors associated with DOACs in either developing or developed countries. Therefore, the second study in this thesis attempted to utilise national pharmacovigilance and hospitals' incident reporting databases in Saudi Arabia. This study aimed to retrospectively audit the types of errors and the contributory factors associated with DOACs-related errors in hospital settings from the first year DOACs medicines became available in the Saudi Arabia market frrom January 2010 until December 2020. There were 199 incident reports identified from the databases: 67% pertain to apixaban, 19% to rivaroxaban, and 14% to dabigatran. Prescribing errors comprised the majority type of errors (n=162, 81.4%), with the most identified sub-type of prescribing errors being inappropriate dose prescribing (22.1%), followed by duplicate medicine prescribing (16.6%), and incorrect frequency prescribing and incorrect quantity (15% for each).

This study also acknowledged inappropriate dosing prescribing of DOACs as one of the main sources associated with DOACs' medication errors. These findings supported prior studies' results.(13-16)

Another study aimed to assess the nature, severity, and types of DOACs indicated that in the UK, there was also retrospectively conducted using the NRLS database for incidents reported between January 2017 and December 2019. In this study, a total of 15,730 incident reports related to DOACs were quantitatively analysed and categorised according to Reason's accident causation model. Active failures constituted the vast majority (87.58%) of safety incidents, followed by error-provoking conditions (10.18%) and latent failures (2.24%). Like the study conducted in KSA, prescribing errors were the most cause of safety incidents reports (42.0%), mainly due to inappropriate dose prescribing, omission errors or prescribing errors, while it was contra-indicated. Similarly, apixaban represented the most reported medicine (52.0%), followed by rivaroxaban (36.0 %), edoxaban (6.0%) and dabigatran (5.0 %). The majority of the errors occurred due to active failures of slips and mistakes, followed by poor documentation and communication, and lack of training. This national database also offered the opportunity of studying the severity of harm produced by DOACs errors. There were 355 reports that described the degree of harm during the safety incident. This showed 270 reports, with 76% relating to moderate harm, 55 relating to severe harm, while 25 incidents were linked to death (7.0%). The majority of these harmful incidents occurred in elderly people age aged 77 years or more.

The findings from this large-scale study involving a national incident reporting dataset suggested that medication incidents involving DOACs were common with consequences consistent with previously published studies.(3, 17-23)

The systematic review, along with the previously mentioned retrospective quantitative studies using databases in KSA and the UK, revealed many contributing factors related to DOACs errors, including lack of knowledge amongst prescribers, lack of experience with DOACs prescribing, lack of proper training, poor documentation and communication, and with noncompliance to the therapeutic guidelines.

Consequently, further investigation of these causes from the perspectives of healthcare practitioners and patients was necessary. Therefore, qualitative studies exploring opinions, experiences, and contributing factors regarding medication errors associated with DOACs were conducted with physicians, nurses, pharmacists, and patients. Healthcare practitioners in tertiary care hospitals in three different regions in Saudi Arabia (Riyadh, Dhahran, and Jazan) were approached for semi-structured interviews using online zoom video conferencing with the PI. Interviews were transcribed verbatim and analysed thematically using MAXQDA Analytics Pro 2020 (VERBI Software). A topic guide including questions for the interviewees was designed to be consistent with all participants in the different centres based on the literature review and relevant studies about Reason's Accident Causation Model theory.(24-26) A total of 57 interviews were completed with HCPs as follows: 20 physicians, 14 nurses, and 23 pharmacists. Data saturation was achieved in the last four interviews.

Physicians and nurses' interviews identified the following themes associated with DOACs errors: factors related to patients and healthcare professionals, factors pertaining to DOACS, factors related to organisation and strategies for improvement. Similarly, pharmacists' interviews revealed enabling and hindering factors related to pharmacists, factors associated with the impact of patients and other healthcare professionals, and strategies to promote DOACs' safety. At the same time, patients perceived the three themes. They first expressed their concerns regarding DOACs' safety due to inadequate instruction, unavailability of the health educator in the hospital, and lack of appropriate communication with HCPs. The second theme expressed the barriers to adherence to DOACs, such as causes to forget to take their medications the availability of DOACs; and in the third theme, they suggested strategies to promote the safety of DOACs and minimise errors related to DOACs use. Implications for improving patient safety based on common factors identified from database study as well as the qualitative interviews of doctors, nurses, pharmacists, and patients are discussed below.

9.4 Implication for practice in Saudi Arabia

The results obtained from these studies are essential for practice and policy as they highlight the high rate of medication errors and the type of errors. Furthermore, the factors of the medication errors and the strategies to mitigate include: the need for improving the education and training of healthcare providers, developing local clinical guidelines, involving pharmacists in leading anticoagulation clinics, improving communication and adherence to be the best evidence-based strategies associated with DOACs.

9.4.1 The need to address knowledge gap

Both physicians and nurses acknowledged a gap in their knowledge and training when dealing with DOACs as factors contributing to the DOACs' medication errors. The physicians pointed out that lack of knowledge about the dose, adverse effects, and contraindications were mostly causes of their prescribing errors. Nurses expressed their reliance on the physician's knowledge when administering DOACs without applying further precautions regarding bleeding risk, for example. Due to their limited knowledge about DOACs' choice selection or the dosage, they were hesitant to speak up to the prescribing physician when they noted safety concerns; and when they did, they lack the ability to convince the prescribing physician. Hospital pharmacists also recognised that lack of knowledge, especially regarding the dosing issues for each DOACs with comorbidities, which could lead to making errors. They also stated that nurses' role should be further emphasised. They perceived the importance of educating nurses about these drugs' side effects as they always closely monitor the patients.

Most patients reported that inadequate counselling about the type of DOACs, dose, frequency, duration, and other details affected their understanding of the proper use of these drugs. For instance, when a patient experiences an adverse effect such as bleeding, they usually stop using it. There is, therefore, a need to develop educational and training programs for all healthcare providers to help them improve their knowledge regarding DOACs selection, dosage regimen adjustments, considering renal and hepatic functions and enhancing communication and monitoring DOACs users.

9.4.2 The need for local clinical protocols and guidelines

Many doctors and nurses acknowledged difficulty in having access to national and/or institutional guidelines or protocols or appropriate information resource. They also asked for training and educational intervention to promote its implementation in clinical practice. Pharmacists perceived that knowledge regarding the protocols and guidelines was sometimes lacking, and the skills required to reach these credible resources were required, especially for physicians. Drug information pharmacists have been viewed as a valuable source for ensuring the proper use of DOACs for HCPs and patients. Their skills are valued in answering questions and maintaining a formulary management system.

9.4.3 The need for establishing unified protocols and guidelines

There is also a need for unified clinical protocols or standard guidelines and educational initiatives to support the optimal utilisation of DOACs. Physicians' adherence to standardised prescribing protocols (or systems) and the availability of a clinical pharmacist to check before the prescription reached patients were crucial for improving prescriber confidence and reducing errors.

9.4.4 The need to improve communication and documentation

Patients found communication with HCPs challenging, which led them to stop taking medication earlier. Furthermore, patients experience errors or misuse of DOACs when they rely on instructions from relatives, friends, or untrusted websites such as Google, especially when

pharmacists do not appropriately educate them on how to use the medications after dispensing, arguing that the drug instructions are written in the label. Pharmacists, on the other hand, expressed concern about dispensing prescriptions for patients unable or unwilling to communicate with them because of pain or depression, or illiteracy, as in the elderly or upon patients' request to avoid extended waiting time. Pharmacists indicated that patient pertinent data and medical history should be clear to avoid prescribing DOACs to those who have contraindications to these drugs.

There is also a need to improve communication with healthcare providers and patients. As mitigating strategies to prevent errors occurrence, physicians and nurses declared their interest in pharmacists' collaboration at the prescribing, monitoring and follow-up as a key strategy that can increase physicians' and nurses' confidence and minimise errors.

Effective interprofessional collaboration and effective communication among HCPs to promote DOACs' safety were emphasised. Physicians and nurses advocated the role of clinical pharmacists, especially in multidisciplinary ward rounds in preventing medication errors. They also mentioned that good communication among the multidisciplinary team is important to improve DOACs safety. This recommendation supports previous published experience that highlighted the importance of multidisciplinary rounds in reducing anticoagulation errors.(27) Pharmacists acknowledged the importance of multidisciplinary teams in minimising errors. For example, when a nurse double-checks DOACs orders, this would prevent administration errors. Pharmacists also claimed that sometimes physicians do not accept their recommendations to adjust doses or proceed with their orders ignoring pharmacists' advice after medication reviews

were conducted. Both HCPs and patients stressed the need for adequate communication between them and the patients, especially outside the clinics, to answer, confirm and support their needs with any inquiries to ensure the safe use of medicines. Some patients also endorse physicians' instructions to the pharmacist to help improve their compliance with the instructions.

9.4.5 Pharmacy anti-coagulation clinics and reconciliations services

Pharmacists in this study acknowledged their ability and expertise in reviewing medications, making dose adjustments according to indication and kidney function tests, assessing risk for bleeding tendencies, providing patient education and continuous monitoring for patients after receiving the drugs and viewed them as invaluable strategies to minimise errors associated with DOACs use. Pharmacists also identified medication reconciliation as another high-priority strategy they should be conducted to combat this problem. This can help identify patients at risk and DOACs associated medication errors and prevent them. Patients also considered visiting the anticoagulation clinic regularly as one of their high priorities, as it helps identify risks and errors earlier and be able to mitigate them.

9.4.6 Use of medicine taking reminders and health educators

Patients using the medicine box and mobile alarms can contribute to proper medication use. A recently published systematic review highlighted the positive clinical outcomes associated with using such mobile applications.(28) Some patient participants in this study expressed their need for health educators due to the short time given by physicians and pharmacists.

9.5 Implication on Saudi healthcare quality standards and policy

The latest edition of the Saudi central Board of accreditation of healthcare institutions (CBAHI) standards did not address the anticoagulation stewardship programs.(29) Being high-alert medications, the future standards should consider addressing the implementation of such programs with clear evidence-based criteria. Besides, detailed national guidelines should be developed addressing the best scenarios for these programs' structures, processes, and outcome measurements.(30) Quality audits for hospital accreditations should periodically evaluate such programs and identify their areas of improvement based on national quality standards and guidelines.

9.6 Key strengths and limitations of the research program

One of the strength points of this PhD thesis is using multiple mixed-methods and conducting research using different databases or populations of patients and healthcare practitioners from two different countries at the difficult time of the COVID-19 pandemic. Large databases in the UK and Saudi Arabia were used to comprehensively identify diverse causes of medication error incidents from two different countries, in addition to identifying suggestions to reduce DOACs risks from the perspectives of all stakeholders, including patients. In addition, we have conducted the first systematic review and meta-analysis in relation to errors plus expert search of databases and conducting a comprehensive qualitative study incorporating all relevant stakeholders to generate a panoramic review for the problems and their possible solutions.

However, there still are some limitations that must be considered during the interpretation of our findings. These include the limited number of study participants in the qualitative studies, but this was compromised by the saturation that took place during data collection in the interviews. Therefore, further research with involving large number of hospitals and relying on their internal medication error reporting systems data could be more valid in investigating the incidence, categories, and causes of DOACs-related errors in Saudi Arabia, as the Saudi FDA system should obviously be an underreported issue. Nonetheless, this PhD thesis gave insights into the current practice and utilisation of DOACs in the target countries.

9.7 Recommendation for future research

Future research studies are warranted to explore further the reasons behind the incidents and the strategies required to tackle them. In addition, more research is needed on patients, and their voices should be represented in research as they are the most important stakeholders in drug utilisation studies. There are only a few studies that investigated the patient's beliefs about DOACs therapy, and the majority of them were conducted at the introduction of the DOACs.(31)

Future researchers who want to investigate the real-life clinical and economic effectiveness of DOACs should consider prescribing safety and use databases that contain adverse events/incidents reports. There are still limited studies that investigated the clinical and economic impact of clinical support systems in DOAC therapy. (32)

Randomised controlled trials are also recommended to evaluate pharmacist interventions and to support their role as mitigating strategies for improving DOAC safety. The need for such studies for other mitigating strategies was also highlighted in the recently published systematic review and meta-analysis (33).

Further explorations for incidents severity should be added to the scope of future research in this area in addition to exploring these problems and their possible solutions in non-hospital settings. Research on better communication practices between prescribers and patients and between pharmacists and healthcare providers from one side and patients from the other side is also warranted to inform about the best ways of timely and effective communication styles.

Pharmacists demonstrated that research is essential to generate evidence regarding DOACs prescribing for special patient populations, such as COVID-19 patients.(34) Having strong evidence for prescribing such drugs is critical before using them. This recommendation came in with the recently published Cochrane review that highlighted uncertainties in the evidence of using DOACs in the COVID-19 populations and the need for further research.(35)

9.8 Conclusion

In conclusion, these studies have shed light on identifying and documenting the causes of medication errors associated with DOACs use. The main findings of this project highlighted the high global prevalence of prescribing errors, especially those associated with dosage regimens. In addition, the inability to adjust or customise doses based on kidney function tests contributed

to medication errors. Active failures, poor documentation, and communication, lack of clinical guidelines and proper training, lack of patient counselling, and lack of adherence to proper medication are key contributory factors to DOACs related errors.

Medication errors linked to DOACs can be minimised by empowering pharmacists to run anticoagulation clinics, engage in multidisciplinary teams, and enhance communication with patients and other healthcare providers, in addition to developing local guidelines and participating in broader healthcare providers' training. Counselling and educating patients and empowering them with adherence-provoking tools would also be another solution to promote the safe utilisation of DOACs.

9.9 References

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Supplementary Materials

Chapter 3 supplementary materials

Table S 3.1 The review is reported according to the MOOSE statements.

MOOSE (Meta-analyses Of Observational Studies in Epidemiology) Checklist

A reporting checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Reporting Criteria	Reported (Yes/No)	Reported on Page No.
Reporting of Background		
Problem definition	Yes	Background
Hypothesis statement	Yes	Background
Description of Study Outcome(s)	Yes	Background
Type of exposure or intervention used	Yes	Background
Type of study design used	Yes	Background
Study population	Yes	Background
Reporting of Search Strategy		
Qualifications of searchers (eg, librarians and investigators)	Yes	Method
Search strategy, including time period included in the synthesis and keywords	Yes	Method
Effort to include all available studies, including contact with authors	Yes	Method
Databases and registries searched	Yes	Method
Search software used, name and version, including special features used (eg, explosion)	Yes	Method
Use of hand searching (eg, reference lists of obtained articles)	Yes	Method
List of citations located and those excluded, including justification	Yes	PRISMA checkl
Method for addressing articles published in languages other than English	No	Not applicable
Method of handling abstracts and unpublished studies	Yes	Method
Description of any contact with authors	No	Not applicable
Reporting of Methods		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Yes	Method
Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Yes	Method
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	Yes	Method
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate	Yes	Quality assessn

Reporting Criteria	Reported (Yes/No)	Reported on Page No.
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Yes	Methods, resul
Assessment of heterogeneity	Yes	Methods, resul
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Yes	Methods, resul
Provision of appropriate tables and graphics	Yes	Results
Reporting of Results		
Table giving descriptive information for each study included	Yes	Tables
Results of sensitivity testing (eg, subgroup analysis)	No	Not undertake
Indication of statistical uncertainty of findings	Yes	Results/Discus
Reporting of Discussion		
Quantitative assessment of bias (eg, publication bias)	No	Not applicable
Justification for exclusion (eg, exclusion of non–English-language citations)	Yes	Method
Assessment of quality of included studies	Yes	Method, result
Reporting of Conclusions		
Consideration of alternative explanations for observed results	Yes	Discussion
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Yes	Discussion
Guidelines for future research	Yes	Discussion
Disclosure of funding source	Yes	Title page

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.

Table S 3.2 Search strategy (Search terms used for databases searches).

Database: Ovid MEDLINE(R) <1946 to September Week 3 2020>

Search Strategy:

1 exp Medication Errors/ (17416)	30 exp ANTITHROMBINS/ (23147)
2 exp Anticoagulants/ or new oral anticoagulants.mp. (222093)	31 exp THROMBIN/ (26681)
3 prescribing error*.mp. (615)	32 thrombin direct inhibitor*.mp. (2)
4 dispensing error*.mp. (246)	33 thrombin inhibitor*.mp. (4385)
5 drug error*.mp. (327)	34 direct thrombin inhibitor*.mp. (2190)
6 treatment error*.mp. (371)	35 NOAC*.mp. (1768)
7 drug mistake*.mp. (5)	36 NOA*.mp. (6509)
8 therapeutic error*.mp. (278)	37 DOAC*.mp. (1528)
9 drug mishap*.mp. (3)	38 TSOAC*.mp. (42)
10 medication mistake*.mp. (14)	39 SODA*.mp. (4245)
11 medication mishap*.mp. (12)	40 exp DABIGATRAN/ (3146)
12 administration mistake*.mp. (3)	41 exp RIVAROXABAN/ (3319)
13 dispensing mistake*.mp. (3)	42 apixaban.mp. (2926)
14 prescribing mistake*.mp. (1)	43 edoxaban.mp. (1217)
15 wrong drug*.mp. (185)	44 betrixaban.mp. (145)
16 wrong dose*.mp. (176)	45 direct oral anticoagulant*.mp. (2197)
17 incorrect drug*.mp. (70)	46 target specific oral anticoagulant*.mp. (95)
18 incorrect dose*.mp. (145)	47 specific oral direct anticoagulant*.mp. (0)
19 medication incident*.mp. (116)	48 novel oral anticoagulant*.mp. (980)
20 preventable adverse drug event*.mp. (152)	49 new oral anticoagulant*.mp. (1393)
21 report prescribing error*.mp. (1)	50 Non-vitamin K antagonist oral anticoagulants.mp. (636)
22 omission error*.mp. (552)	51 NON-WARFARIN ORAL ANTICOAGULANTS.mp. (1)
23 transcription error*.mp. (254)	52 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 (58114)
24 discrepancy*.mp. (37482)	53 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 (253928)
25 near miss*.mp. (1966)	54 52 and 53 (697)
26 exp Medication Errors/ (17416)	55 limit 54 to yr="2019 -Current" (35)
27 exp Anticoagulants/ (222027)	
28 exp Factor X/ or exp Factor Xa Inhibitors/ (12869)	
29 oral direct inhibitor*.mp. (33)	

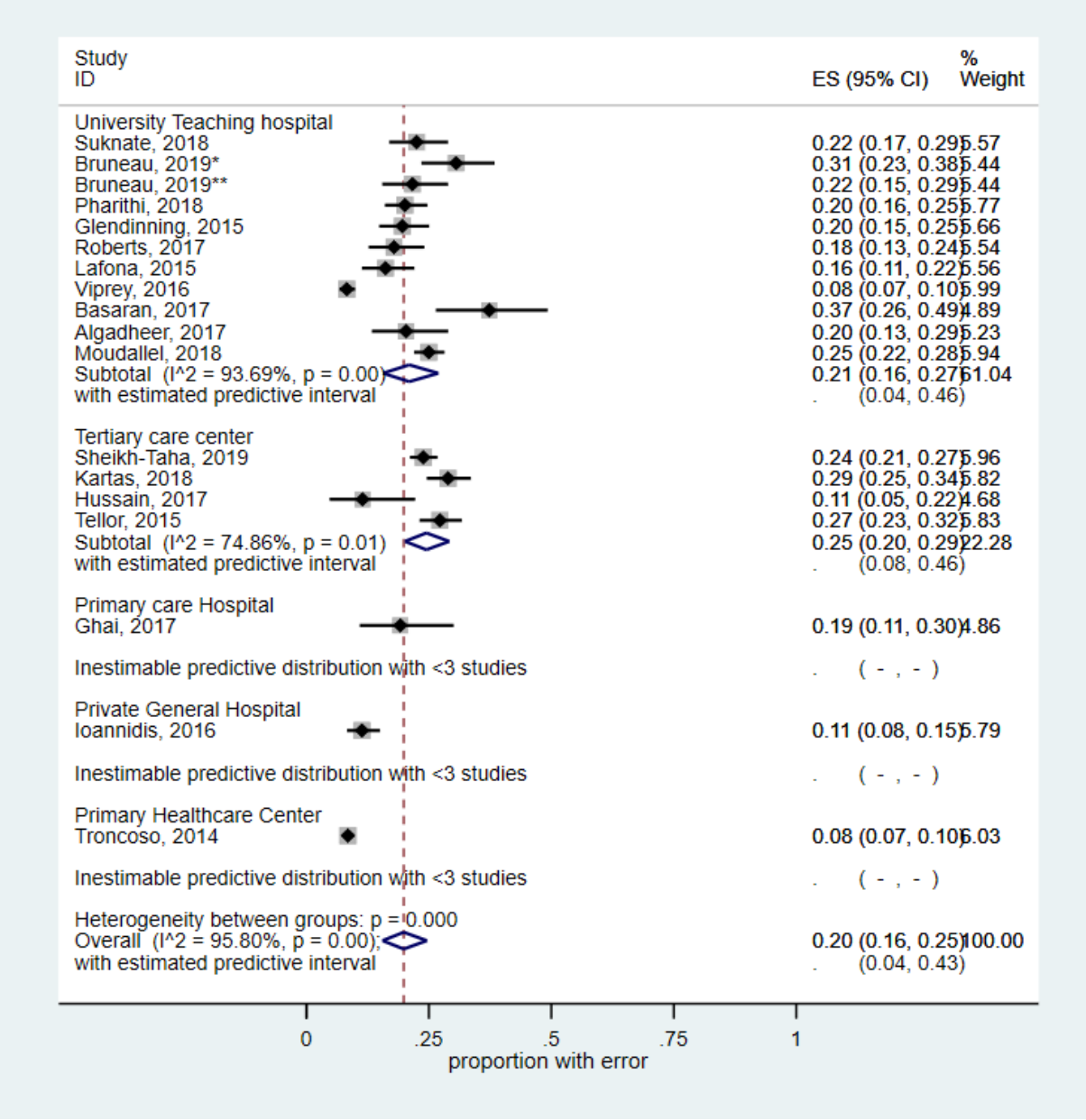


Figure S 3.3 Subgroup analysis 1: Prescribing error for all indication by setting

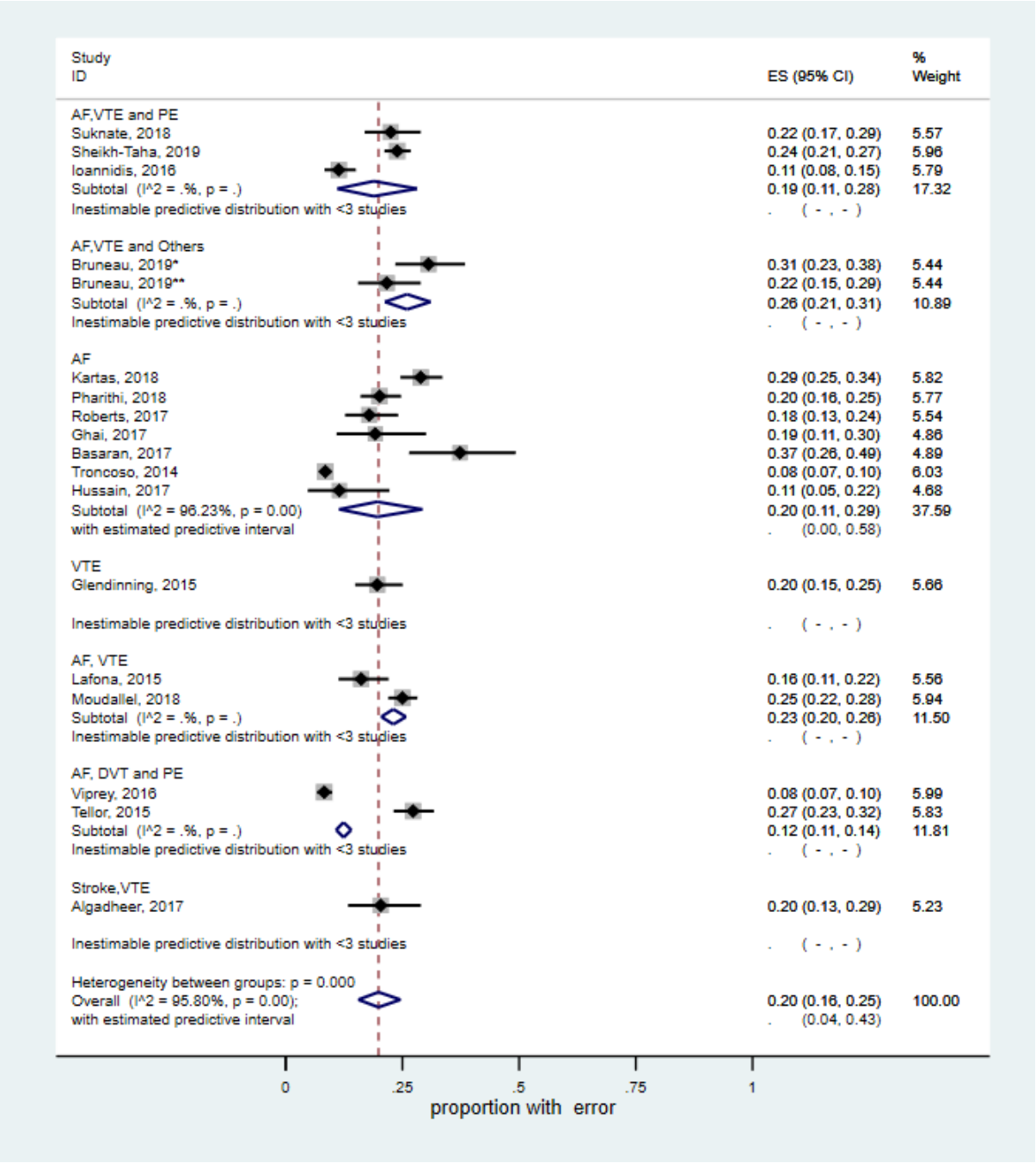


Figure S 3.3 Subgroup analysis 2: Prescribing errors as per indication

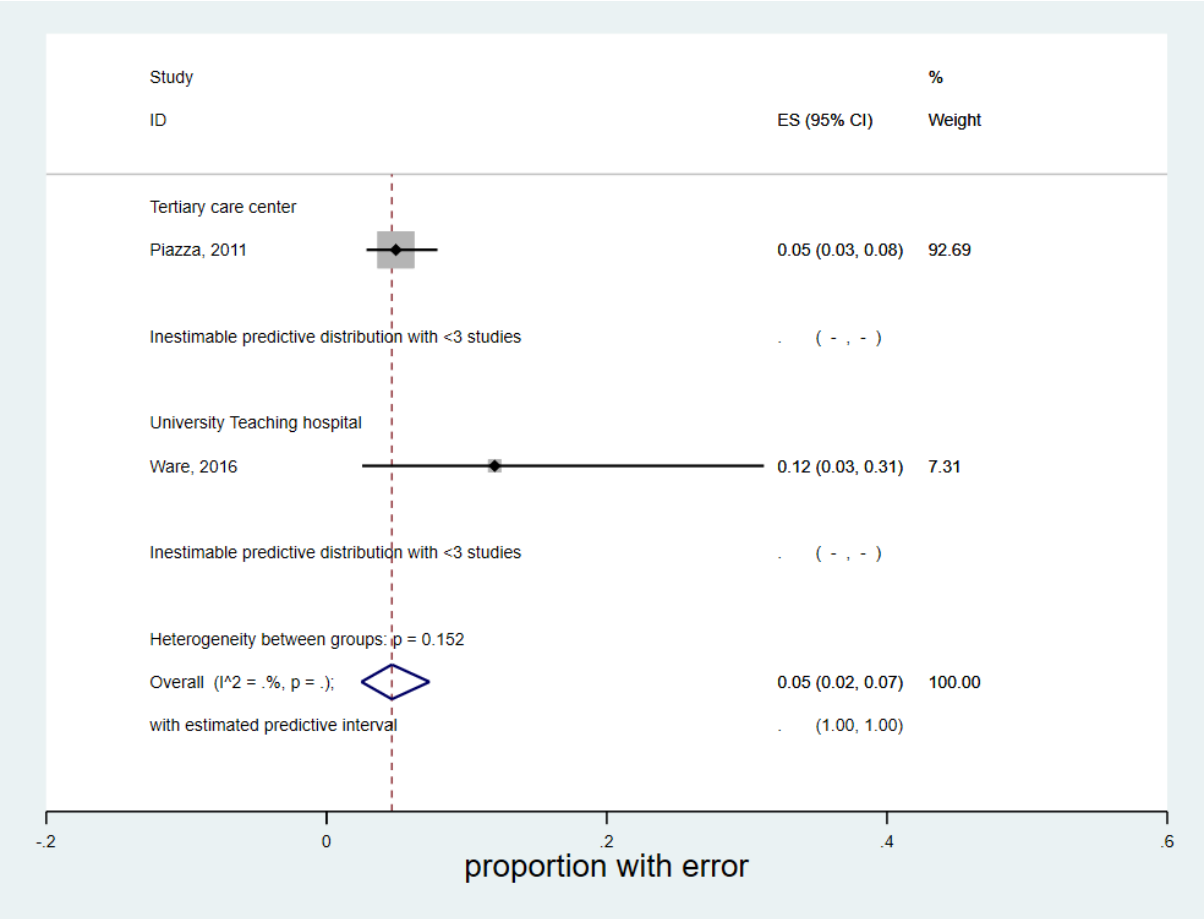


Figure S 3.3 Subgroup analysis 3: Administration error by setting

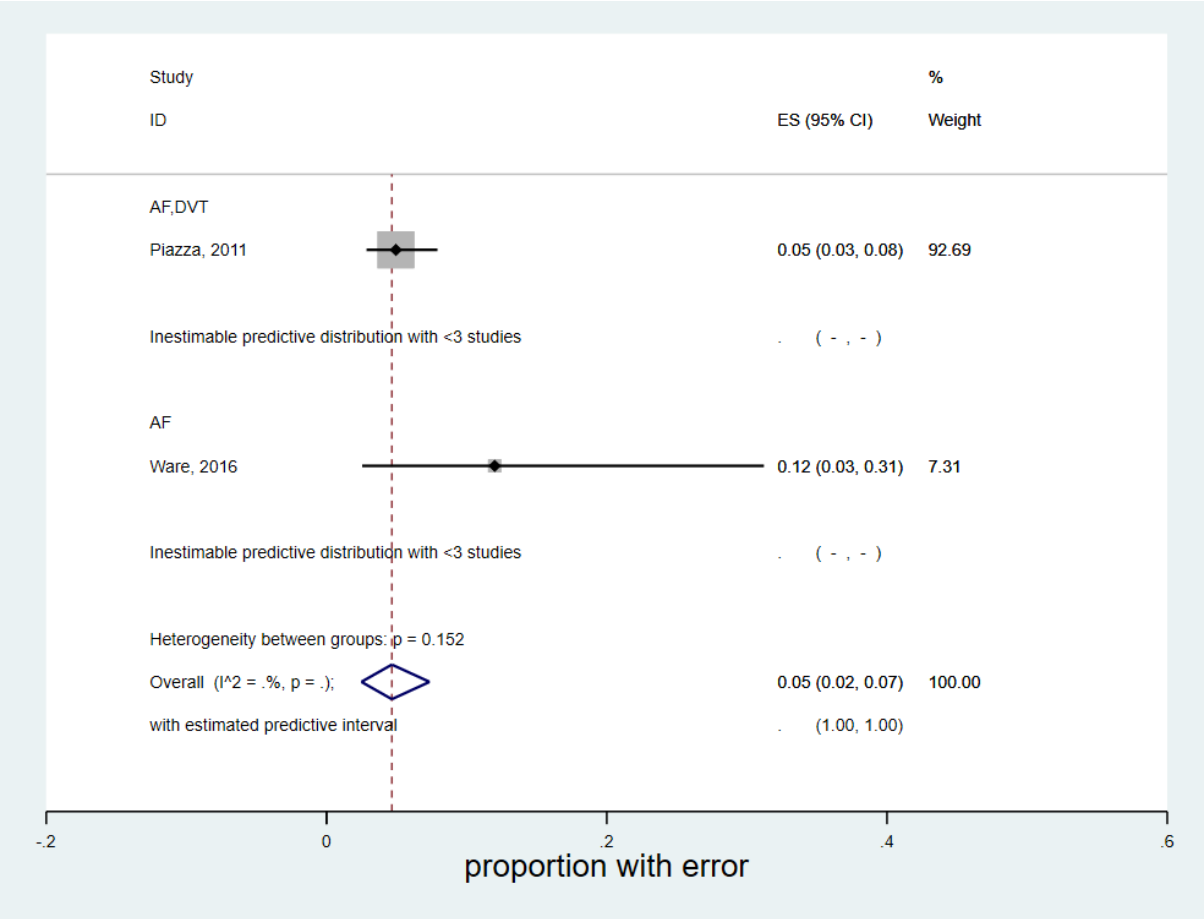


Figure S 3.3 Subgroup analysis 4: Administration error by indication

Chapter 5 supplementary materials

Table S 5.1 Search terms (A complete list of search terms).

novel oral anticoagulants	NOAC/NOACs	novel oral anti-coagulants
new oral anti-coagulants	direct-acting oral anticoagulants	direct oral anticoagulants
novel oral anticoagulants	TSOAC/ TSOACs	target-specific oral anticoagulant
ORAL ANTICOAGULANTS	DOAC/DOACs	non-VKA oral anticoagulants
non-vitamin K antagonist oral anticoagulants	dabigatran	edoxaban
apixaban	Pradaxa	rivaroxaban
Xarelto	Eliquis	Lixiana
Savaysa	Xaban	

Table S 5.2 Medication incidents related to direct oral anticoagulants (DOACs) categorized as per the Reason's accident causation model

Active failures	N	%
Slips	5903	42.85%
Lapses	970	7.04%
Mistakes	6286	45.63%
Violations	358	2.60%
Lack of knowledge	259	1.88%
Total	13776	87.58%
Error provoking conditions	**N**	**%**
Insufficient staff	28	1.75%
Patient condition(s)	145	9.06%
Poor communication	215	13.43%
Lack of experience	27	1.69%
Distractions	94	5.87%
Look alike drugs	378	23.61%
Poor documentation	704	43.97%
Illegible orders	10	0.62%
Total	1601	10.18%
Latent failures	**N**	**%**
Heavy workload	86	24.36%
Lack of training	203	57.51%
Organization factors	27	7.65%
Blame culture	10	2.83%
Supervisory issues	6	1.70%
Organizational policy issues	12	3.40%
Information resource issues	9	2.55%
Total	353	2.24%
Total Errors	**15730**	**100%**

Table S 5.3 The NRLS definition of harm

Degree of harm	Definition
No harm	A situation where no harm occurred: either a prevented patient safety incident or a no harm incident.
Low harm	Any unexpected or unintended incident that required extra observation or minor treatment and caused minimal harm to one or more persons.
Moderate harm	Any unexpected or unintended incident that resulted in a moderate increase in treatment, possible surgical intervention, cancelling of treatment, or transfer to another area, and which caused significant but not permanent harm to one or more persons receiving NHS-funded care.
Severe harm	Any unexpected or unintended incident that appears to have resulted in permanent harm to one or more persons.
Death	Any unexpected or unintended incident that directly resulted in the death of one or more persons.

*Source: NHS Improvement guidance (2017)[10], NHS: National health system.

Table S 5.4 Proportion of DOACs safety incidents classified as per the degree of harm and contributory factors as per Reasons' accident causation model

	Deaths		Severe harm		Moderate harm	
Active failures	**N**	**%**	**N**	**%**	**N**	**%**
Slips	5	23.8%	24	50.0%	85	37.1%
Lapses	2	9.5%	1	2.1%	20	8.7%
Mistakes	13	61.90%	19	39.58%	113	49.34%
Violations	0	0	2	0.0417	7	0.0306
Lack of knowledge	1	4.8%	2	4.2%	4	1.7%
Total (within category)	21	100%	48	100%	229	100%
Error Provoking conditions	**N**	**%**	**N**	**%**	**N**	**%**
Insufficient staff	0	0.0%	0	0.0%	1	2.7%
Patient condition(s)	2	66.7%	1	20.0%	6	16.2%
Poor communication	0	0.0%	1	20.0%	8	21.6%
Lack of experience	0	0.0%	0	0.0%	1	2.7%
Distractions	0	0.0%	0	0.0%	0	0.0%
Look alike drugs (LASA)	1	33.3%	2	40.0%	8	21.6%
Poor Documentation	0	0.0%	1	20.0%	13	35.1%
Illegible orders	0	0.0%	0	0.0%	0	0.0%
Total (within category)	3	100%	5	100%	37	100%
Latent failures (LF)	**N**	**%**	**N**	**%**	**N**	**%**
Heavy workload	0	0%	0	0%	2	50%
Lack of training	1	100%	1	50%	2	50%
Organisation factors	0	0%	0	0%	0	0%
Blame culture	0	0%	0	0%	0	0%
Supervisory issues	0	0%	1	50%	0	0%
Organisational policy issues	0	0%	0	0%	0	0%
Information resource issues	0	0%	0	0%	0	0%
Total (within category)	1	100%	2	100%	4	100%
Total (n)	25		55		270	

Table S 5.5 Proportion of safety incidents per stage of medication use process

Medication use Process	N	%	
Prescribing	6614	42.0%	6614 (42.0%)
Dispensing	2557	16.3%	2557 (16.3%)
Administration	4581	29.1%	4581 (29.1%)
Monitoring/ follow-up of medicine use	571	3.6%	571 (3.6%)
Advice	357	2.3%	357 (2.3%)
Supply or use of over-the-counter (OTC) medicine	48	0.3%	48 (0.3%)
Other	1002	6.4%	1003 (6.4%)

Table S 5.6 Examples of incidents per stage of medication use process

Stage of medication use process	Examples
Prescribing	"Prescription chart rewritten as Apixaban 2.5mg po OD - previously 2.5mg po BD".
Dispensing	"Patient was prescribed Apixaban 2.5mg tablets twice a day, However Apixaban 5mg tablets were dispensed with the 2.5mg label on it in error"
Administration	"Rivaroxaban not signed for on drug chart and not given to patient"
Monitoring/ follow up	"Patient started on apixaban. Chart not seen by pharmacist that day and so apixaban not ordered for this patient by pharmacy . Brought to my [a doctor] attention on Monday that the patient had been given enoxaparin and apixaban Friday , Saturday and Sunday"
Advice	"Patient attended for a colonoscopy; patient had not received information on when should stopping Apixaban"

Table S 5.7 Proportion of safety incidents per location of medical error

Location of Medical Error	N	%	N(%)
Hospital/ Cardiology ward	7346	46.7%	7346(46.7%)
Hospital/ Acute medical Ward	3311	21.1%	3311(21.1%)
Community pharmacy	1696	10.8%	1696(10.8%)
Hospital/Accident/ minor injury unit	1019	6.5%	1019(6.5%)
Hospital/ Pharmacy	727	4.6%	727(4.6%)
GP Surgery room	698	4.4%	698(4.4%)
Hospital/ Mental health service	336	2.1%	336(2.1%)
Hospital/ Ambulatory care treatment centre	255	1.6%	255(1.6%)
Hospital/ Intensive care unit	201	1.3%	201(1.3%)
Hospital/ Residence / Private home	95	0.6%	95(0.6%)
Hospital/ Anticoagulation clinic	21	0.1%	21(0.1%)
Hospital/ Dental surgery room	7	0.0%	7(0.0%)
Rehabilitation centre	8	0.0%	7(0.0%)
Hospital/ Anaesthetic room	4	0.0%	4(0.0%)
Ambulance service (including call / control centre)	2	0.0%	2(0.0%)
Hospital/ oncology ward	2	0.0%	2(0.0%)
Hospital/ orthopaedic ward	2	0.0%	2(0.0%)
Total	15730	100%	

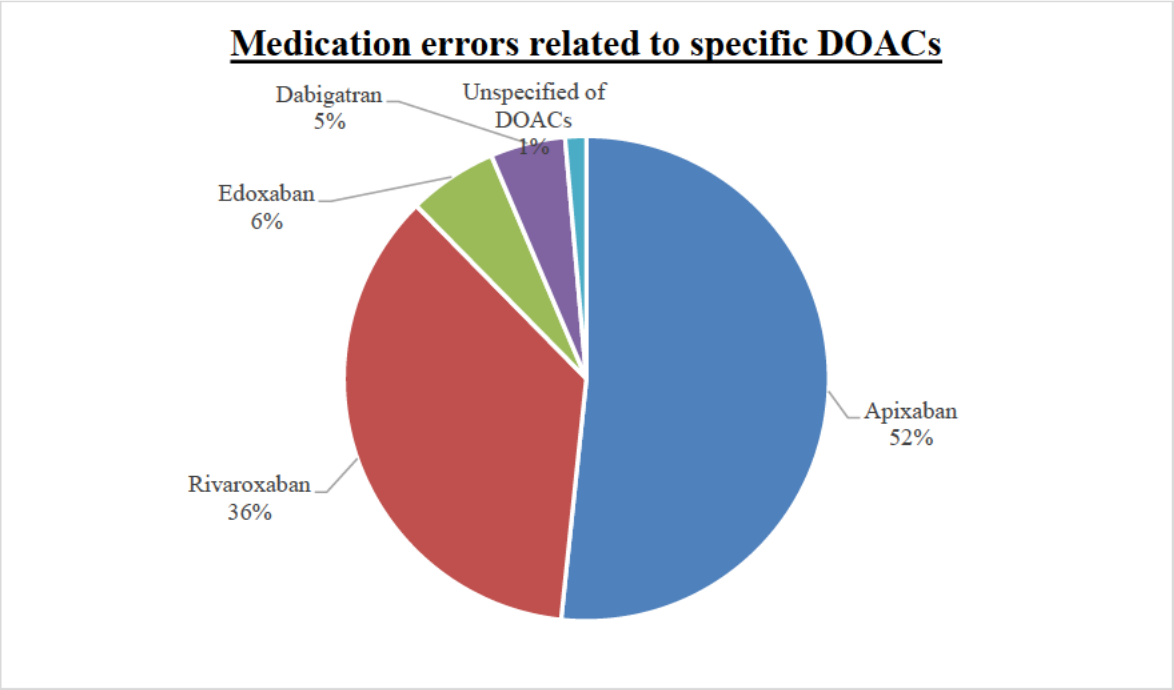


Figure S 5.1 Direct oral anticoagulants (DOACs) involved in the incident reports

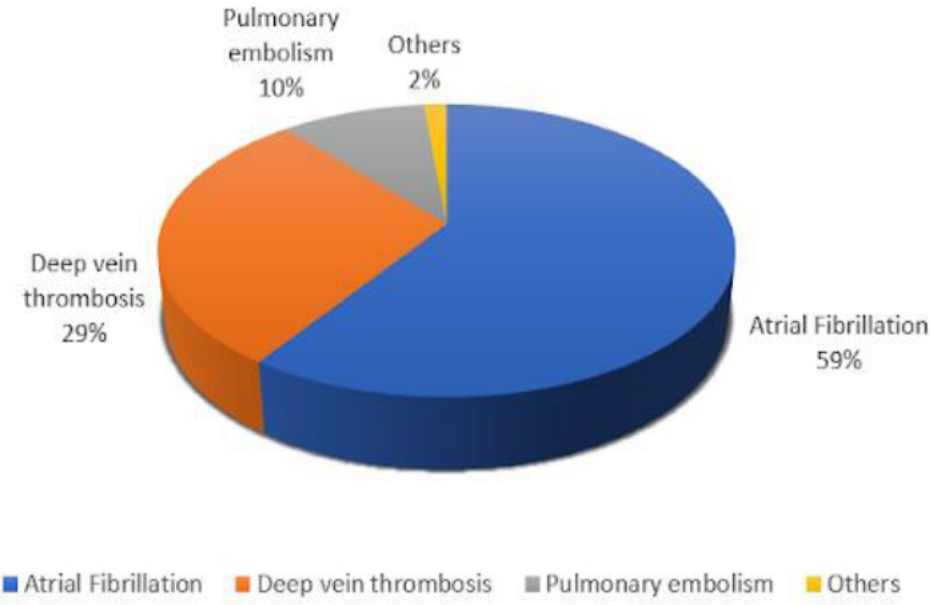


Figure S 5.2 Indications of direct oral anticoagulants (DOACs) involved in the incident reports

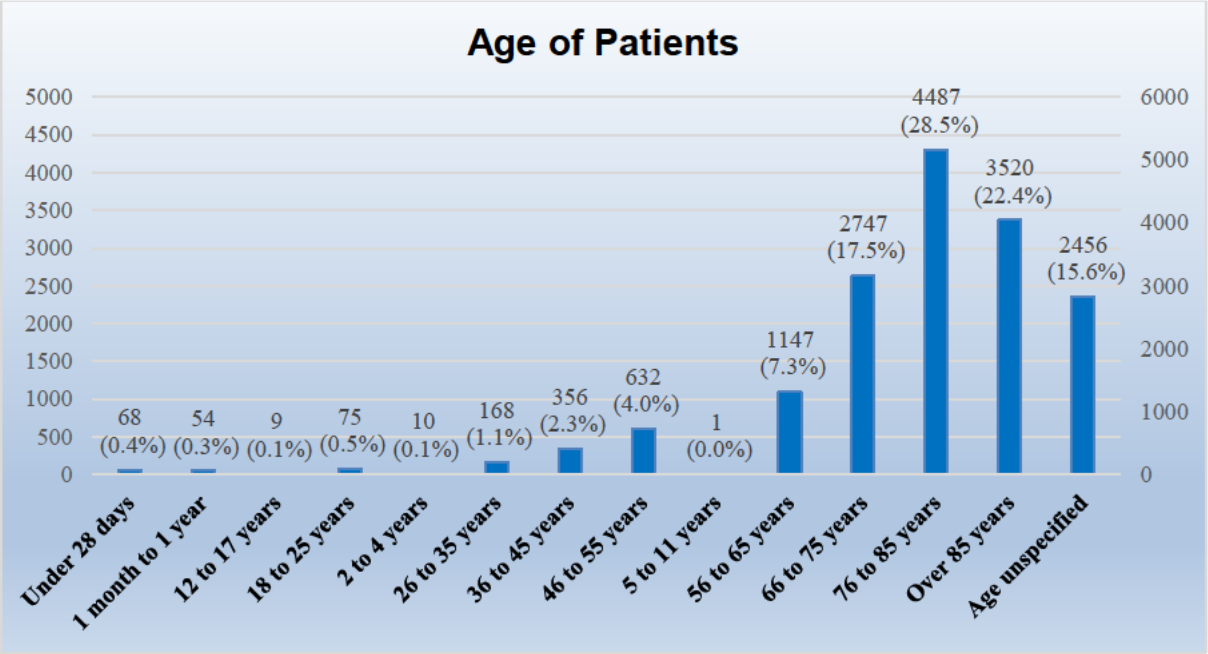


Figure S 5.3 Proportion of safety incidents per patient's age category

Chapter 6 supplementary materials

Table S 6.1 The Consolidated criteria for reporting qualitative research (COREQ)

COREQ (COnsolidated criteria for REporting Qualitative research) Checklist

A checklist of items that should be included in reports of qualitative research. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Topic	Item No.	Guide Questions/Description	Reported on Page No.
Domain 1: Research team and reflexivity			
Personal characteristics			
Interviewer/facilitator	1	Which author/s conducted the interview or focus group?	6
Credentials	2	What were the researcher's credentials? E.g. PhD, MD	1
Occupation	3	What was their occupation at the time of the study?	1
Gender	4	Was the researcher male or female?	6
Experience and training	5	What experience or training did the researcher have?	6
Relationship with participants			
Relationship established	6	Was a relationship established prior to study commencement?	8
Participant knowledge of the interviewer	7	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	7
Interviewer characteristics	8	What characteristics were reported about the inter viewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	7
Domain 2: Study design			
Theoretical framework			
Methodological orientation and Theory	9	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	7,8
Participant selection			
Sampling	10	How were participants selected? e.g. purposive, convenience, consecutive, snowball	8
Method of approach	11	How were participants approached? e.g. face-to-face, telephone, mail, email	8
Sample size	12	How many participants were in the study?	9
Non-participation	13	How many people refused to participate or dropped out? Reasons?	0
Setting			
Setting of data collection	14	Where was the data collected? e.g. home, clinic, workplace	6
Presence of non-participants	15	Was anyone else present besides the participants and researchers?	6
Description of sample	16	What are the important characteristics of the sample? e.g. demographic data, date	9
Data collection			
Interview guide	17	Were questions, prompts, guides provided by the authors? Was it pilot tested?	7
Repeat interviews	18	Were repeat inter views carried out? If yes, how many?	0
Audio/visual recording	19	Did the research use audio or visual recording to collect the data?	6
Field notes	20	Were field notes made during and/or after the inter view or focus group?	7
Duration	21	What was the duration of the inter views or focus group?	7
Data saturation	22	Was data saturation discussed?	9
Transcripts returned	23	Were transcripts returned to participants for comment and/or	0

Topic	Item No.	Guide Questions/Description	Reported on Page No.
		correction?	
Domain 3: analysis and findings			
Data analysis			
Number of data coders	24	How many data coders coded the data?	9,10
Description of the coding tree	25	Did authors provide a description of the coding tree?	9
Derivation of themes	26	Were themes identified in advance or derived from the data?	5
Software	27	What software, if applicable, was used to manage the data?	7
Participant checking	28	Did participants provide feedback on the findings?	0
Reporting			
Quotations presented	29	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	10-20
Data and findings consistent	30	Was there consistency between the data presented and the findings?	10-20
Clarity of major themes	31	Were major themes clearly presented in the findings?	9
Clarity of minor themes	32	Is there a description of diverse cases or discussion of minor themes?	10-20

Developed from: Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007. Volume 19, Number 6: pp. 349 – 357

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.

Table S 6.2 The topic guide (Qualitative interview schedule)

Qualitative interview schedule

1. What is your experience in dealing with DOAC (prescribing, dispensing (processing), or administration)
    - Prompts (This might include, number of years, being involved in formulary selection, mortality& morbidity committee, patients counselling, educational campaign..
2. What are the key concerns with the use of DOACs from your perspective at your institution?
3. How knowledgeable are you in terms of prescribing/dispensing/administring DOACs?
    - Prompting (what about your colleagues, the doses and frequency, when to stop before procedures, side effects, drug pharmacokinetics, indications, and contraindications, safety in pregnancy and lactation, possible drug and food interactions (ask for examples)
4. Do you think that medication use process (MUP) (add more simpler terms about the process as prompting words)is safe at your institution? The perceived safety culture of the hospital).
    - In general, from your prospective how safe is prescribing, dispensing and administration practice of medicines at your institution? Prompting (Do you have medication safety policy, or DOACs guidelines at your institution? Are you familiar with it?
5. Do you have guidelines to follow? What guidelines are you following when you deal with DOAC in adult population with different clinical conditions
6. Does these guidelines address your needs to deal with DOAC patients?
    - Answer this question if the previous question is answered
7. What other information sources (in addition to the guidelines) you use when you deal with DOACs?
8. How skilful do you feel about prescribing/dis/admins of DOACs?
9. Have you had any training or Continuing Medical Education (CME) opportunities to ensure safe practice of DOACs? And if yes, what are they?
    - How common are medication errors associated with DOACs?
    - Have you been involved in medication errors, related to DOACs? If yes, please describe prompting (What was the medication error type? how old was the patient? happened during the shift? was the patient admitted to the hospital or the length of stay prolonged? does the patient required medical intervention to reverse the harm?

From your perspective in this error, what was the contributory factors at that incidence?

    - Contributory factors (What are the potential factors from the error theories?
    - What could have been done differently to minimise the errors?
10. What can be done to minimise errors associated with these medicines, generally speaking?
11. What preventive safety measures should be implemented to minimize medication error associated with DOAC before prescribing, at your institution? How often are patients assessed for their needs based on their clinical circumstances in your setting before being prescribed DOACs?
12. How often are patients assessed for risks of bleeding based on their clinical circumstances in your setting before being prescribed DOACs?
13. How motivated do you think to assess risks in patients?
14. Whose role is it to monitor patients for risks of bleeding and other adverse events in relation to DOACs?

15. Do you think that the current policies and procedures or guidelines at your institution are efficient to maintain patient safety when using DOAC? If no why and what barriers are existing to hender applying these policies by HCW

Overall, what do you think are the most important strategies for preventing prescribing, dispensing, and administration errors in the current practice?

Additional prompts for the researcher to discuss contributory factors

- **Patient characteristics** [prompt: what factor relating to the patient contribute to errors such as seriousness and complexity of their conditions, communication challenges or social factors.]
- **Knowledge of the patient** [prompt: does familiarity with patient make errors more or less likely?]
- **Your therapeutic knowledge and prescribing, dispensing, administer skills**[prompt: how familiar are you with drug, how do you feel about your knowledge of therapeutics and skills]
- **Your information sources and technology** [prompt: what information do you use to help guide you and how useful is this in preventing error?]
- **Task factors** [prompt: is there anything about the way in which prescribing, dispensing, administer task are organised and structured in your practice that might lead to increased risk of errors. E.g: available information on the patient and drug at the point of decision making, competing priorities for time during consultation, interruptions, lack protocol for safe prescribing, dispensing, administer including repeat prescribing and refill]
- **Your working environment** [prompt: what do you think of the working environment within your working day? To what extent(and how) does it contribute to the occurrences of (or prevention of) prescribing, dispensing and administer errors like possible factors including staffing levels and skills mix, workload and shift pattern, design, availability and maintenance of equipment, administrative and managerial support]
- **Team factors** [prompt: what do you think of the team factors within your working day? To what extent do teamwork, team structures and communication contribute to the prescribing, dispensing and administer drug errors, or prevent them for happening? Like possible related factors include verbal communication, written communication, supervision and seeking help]
- **Organisation and management factors** [prompt: to what extent do you think the organisation and management within the practice contribute to prescribing, dispensing and administer or preventing them? What do you think of the safety culture within the practice like possible related factors including financial resources and constraints, organisational structure, policy standards, goals and priorities]
- **Individual factors** [prompt: are there any personal strategies you have for helping to prevent medication errors? Conversely, do you feel there are sometimes individual factors that put you at increased risk of making errors?]
- **Are there any other factors** that you think may important in preventing prescribing, dispensing and administer errors with DOACs? [Prompt: can you describe the factors that you feel interfere with your ability to safely prescribe, dispense and administer drug error?

- **Imagine that you have to teach a doctors, pharmacists and nurse** how to safely administer DOACs. What information would you consider essential for the doctors, pharmacists and nurse to know for preventing errors?

Closing:

A. Is there anything else you did not tell me yet but think may be of interest?
B. Is there anything that you would like to go back and talk about?
C. Switch off tape recorder. Thank the participants.

Chapter 7 supplementary materials

Table S 7.1 The Consolidated criteria for reporting qualitative research (COREQ)

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Field notes	20	Were field notes made during and/or after the inter view or focus group?	6
Duration	21	What was the duration of the inter views or focus group?	6
Data saturation	22	Was data saturation discussed?	6
Transcripts returned	23	Were transcripts returned to participants for comment and/or	6

Topic	Item No.	Guide Questions/Description	Reported on Page No.
		correction?	
Domain 3: analysis and findings			
Data analysis			
Number of data coders	24	How many data coders coded the data?	6
Description of the coding tree	25	Did authors provide a description of the coding tree?	22
Derivation of themes	26	Were themes identified in advance or derived from the data?	7
Software	27	What software, if applicable, was used to manage the data?	6
Participant checking	28	Did participants provide feedback on the findings?	8
Reporting			
Quotations presented	29	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	8
Data and findings consistent	30	Was there consistency between the data presented and the findings?	8
Clarity of major themes	31	Were major themes clearly presented in the findings?	9
Clarity of minor themes	32	Is there a description of diverse cases or discussion of minor themes?	9

Developed from: Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007. Volume 19, Number 6: pp. 349 – 357

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.

Chapter 8 supplementary materials

Table S 8.1 The topic guide (Qualitative interview schedule- Arabic language)

Version 0.3 | Interview Topic Guide for Patients. | 15/09/2020

MENOAC: Qualitative patient interview: Arabic version

Abdulrahman Al Rowily

عزيزي المريض:

فريق البحث بقيادة د/عبدالرحمن الرويلي من جامعة برمنجهام بالمملكة المتحدة، يتقدم لك بخالص الشكر للمساهمة في هذه الدراسة البحثية والتي تهدف بشكل رئيسي إلى إستيضاح وجهة نظرك عن تجربة إستخدام الدواء المسيل للدم. المقابلة ستستغرق ما يقارب خمسة واربعون دقيقة على أعلى تقدير، موافقتك في هذه المرحلة ستعتبر إقرارا من طرفكم بالمشاركة في الدراسة والقيام بتسجيل هذه المقابلة على آلة التسجيل تجهيزا لتحليل بياناتها. لك كامل الحق في التوقف أثناء إجراء المقابلة والإنسحاب منها ولن يؤثر ذلك سلبا في الرعاية المقدمة لك من أي قسم في المنشأة.

محاور المقابلة تتمحور حول:

- المعلومات الدوائية لإستخدام الدواء المسيل للدم
- مصادر معلومات إستخدام الدواء المسيل للدم
- تقنيات الوقاية من المضاعفات الجانبية للأدوية المسيلة للدم

أ- **المعلومات الدوائية لإستخدام الدواء المسيل للدم**

a. هل أنت على دراية بجميع ما يتعلق بإستخدام الدواء المسيل للدم الموصوف لك؟
   i. التأكد من إسم الدواء وجرعته، توقيت الجرعه[بعد الاكل/قبل الاكل] ,دواعي الإستخدام، طريقة التخزين، إستخدام أدوات للتنبيه للجرعات مثل منبه الجوال أو صندوق حفظ الأدوية)
b. هل عانيت من أي أعراض جانبية من إستخدام الدواء المسيل للدم؟
   i. نزيف حاد، نزيف بسيط، كدمات، تجمع دموي داخلي أو خارجي، هبوط حاد في الدورة الدموية، الحاجة لنقل دم، حرقان وألم بالمعدة
c. إذا كان قد سبق لك التوقف عن إستخدام المسيل للدم لمدة يوم أو أكثر، فماذا كان السبب؟
d. ما الإجراء الذي تتبعه في حال أخذت جرعة مضاعفة أو نسيت جرعة أو أكثر من مسيل الدم؟

ب- **مصادر معلومات إستخدام الدواء المسيل للدم**

a. من أين أستقيت معلومات الدواء وكيفية إستخدامه؟
   i. طبيب، صيدلي، ممرض، مثقف صحي، انترنت، وسائل التواصل الاجتماعي,نشره الدواء.
b. هل كان الشرح المعلوماتي الذي تلقيته بخصوص الأدوية المسيلة للدم كافي؟ وعلى ماذا كان يشمل؟ وممن تلقيته؟
c. هل كانت المعلومات التي تلقيتها كافية؟ وإن لم تكن كذلك فماهي أهم المعلومات التي كنت تود الحصول عليها من الطاقم الطبي (طبيب/صيدلي/ممرض)؟

ج- **تقنيات الوقاية من الاخطاء الدوائية للأدوية المسيلة للدم**

a. هل شاركت في صنع القرار في الخطة العلاجية المتعلقة بإستخدام هذا النوع من الأدوية المسيلة للدم؟
b. هل تتناول أي دواء آخر بدون وصفة طبية لأي سبب عارض؟
   a. مسكنات، فيتامينات، مكملات غذائية
c. خلال السنة، كم عدد المرات التي تزور فيها العيادة المختصة بمسيلات الدم أو الطبيب المختص؟
d. كيف تقيم طريقة شرح الطبيب المعالج لك لأهمية الفحوصات/التحاليل المطلوبة لمسيلات الدم وهل تعلم ماهي هذه التحاليل؟
e. هل يتم مناقشتك في الادويه الاخرى التي تتناولها وتأثيرها على الدواء الذي تستخدمه/التداخلات الدوائية /نتائج الفحوصات/التحاليل معك من قبل الطبيب المختص لمسيلات الدم؟ ماهي طبيعة التساؤلات التي تكون لديك عادة على هذه النتائج؟
f. كيف تتواصل مع أي من أعضاء الفريق الطبي المشرف على علاجك بمسيلات الدم؟
   a. طبيب/صيدلي/ممرض/مثقف صحي
g. ما الذي تقترحه لجعل إستخدام المرضى للأدوية المسيلة للدم استخداما آمنا في هذه المنشأة؟

Appendices

Appendices 1 (Chapter 3)

International prospective register of systematic reviews (PROSPERO)

Dear Dr. Paudyal,

Thank you for submitting details of your systematic review "Medication errors associated with non-vitamin K antagonist oral anticoagulants (NOACs) in adult patients" to the PROSPERO register. We are pleased to confirm that the record will be published on our website within the next hour.

Your registration number is: [redacted]

You are free to update the record at any time, all submitted changes will be displayed as the latest version with previous versions available to public view. Please also give brief details of the key changes in the Revision notes facility. You can log in to PROSPERO and access your records at https://www.crd.york.ac.uk/PROSPERO

Comments and feedback on your experience of registering with PROSPERO are welcome at: [redacted]

Best wishes for the successful completion of your review.

Yours sincerely,
PROSPERO Administrator
Centre for Reviews and Dissemination
University of York
York YO10 5DD
[redacted]
www.york.ac.uk/inst/crd
PROSPERO is funded by the National Institute for Health Research and produced by CRD, which is an academic department of the University of York.

Email disclaimer: https://www.york.ac.uk/docs/disclaimer/email.htm

Appendices 2.1 (Chapter 2, Chapter 5, Chapter 6, Chapter 7 and Chapter 8)

University of Birmingham Ethical Approval

Abdulrhman Alrowily (PhD Pharmacy FT Non-Lab (B230))

From: [redacted]
Sent: 06 October 2020 15:55
To: Abdulrhman Alrowily (PhD Pharmacy FT Non-Lab (B230))
Cc: [redacted]
Subject: RE: "MENOACs" University ethics approval ERN_20-0551

Dear Abdulrhman,

My apologies for the delay in responding. Thank you for sending these documents across. I am pleased to confirm that the chair is willing to accept you external ethics reviews in lieu of a UoB review. It was noted that one approval is still pending; please send a copy of this approval across once it is granted.

While we are happy to accept the external ethics review, please note that the Universities RAMP process must be followed for all overseas work (details available at: https://intranet.birmingham.ac.uk/hr/wellbeing/worksafe/policy/Research-Risk-Assessment-and-Mitigation-Plans-RAMPs.aspx) and travel should be done in line with Universities guidance on Covid (https://www.birmingham.ac.uk/coronavirus/travel.aspx). This must be followed prior to the start of the project. Please ensure all approvals are in place. Please note that to travel to Red FCO zones will require additional approvals as mentioned in the link above and will most likely require sign off by your head of college/school. I would recommend you contact your local school health and safety officer in the first instance for help with this (https://intranet.birmingham.ac.uk/hr/wellbeing/worksafe/coords/hscoordinators.aspx).

A few points were raised which it may be helpful for the team to consider in terms of ethics. Please note that we do not need a response to these as we are accepting your external ethics however, we felt that passing on the below may be helpful in terms of points for the research team to consider prior to commencing the project:

- It was suggested, where possible the data collection is done online to minimise face-to-face contact given the current pandemic.
- Please note the consent form for HCP's currently mentions focus groups (it was assumed this should be interviews)
- How would it be handled if a HCP identified an ongoing safety concern within their own/someone else's practice. Or, if they admit to an error which has not previously been reported on? Do you have a duty to disclose this information?
- If a patient does answer a question incorrectly (e.g. taking extra doses, storage etc) how will this be handled? If it's clear they are misinformed, could the researchers encourage them to speak to a doctor for example?

I look forward to receiving your final IRB approval; please send this across once it is available.
Best wishes
Sam

[redacted]
Research Ethics Officer
Research Support Group
C Block Dome (room 137)
Aston Webb Building
University of Birmingham
Edgbaston B15 2TT
[redacted]

1

Please remember to submit a new Self-Assessment Form for each new project. Click Ethical Review Process for further details regarding the University's Ethical Review process.

Click Research Governance for further details regarding the University's Research Governance and Clinical Trials Insurance processes, or email researchgovernance@contacts.bham.ac.uk with any queries

Notice of Confidentiality:
The contents of this email may be privileged and are confidential. It may not be disclosed to or used by anyone other than the addressee, nor copied in any way. If received in error please notify the sender and then delete it from your system. Should you communicate with me by email, you consent to the University of Birmingham monitoring and reading any such correspondence.

From: [redacted]
Sent: 03 September 2020 10:42
To: aer-ethics@contacts.bham.ac.uk
Cc: [redacted]
Subject: "MENOACs" University ethics approval

Dear Research Ethics Officer

Hope you are well during this difficult time,

Kindly, could you please find attached files in regard University ethical approval for my project " Medication error associated with non vitamine k antagonist in adult patients mixed method quantitative and qualitative studies" and all associated material files related my project.

Looking to hear from you soon.

Regard

Abdulrhman Alrowily

Appendices 2.2 (Chapter 2, Chapter 6, Chapter 7 and Chapter 8)

National Guard Hospital in Riyadh Ethical Approval

Kingdom of Saudi Arabia
Ministry of National Guard - Health Affairs

المملكة العربية السعودية
وزارة الحرس الوطني - الشؤون الصحية

King Abdullah International Medical Research Center (KAIMRC)
IRB NCBE Registration No.: H-01-R-005

(84) 94456 1515 94466 irb@ngha.med.sa

IRB Office Memo Ref.No. IRBC/1343/20 E-CTS Ref. No. RYD-20-419812-80592

Study Number: **SP20/212/R**
Study Title: **Medication Errors Associated with non-vitamin K antagonist oral anticoagulants In Adult Patients (MENOACs): A Mixed Method (Quantitative and Qualitative Study).**
Study Sponsor: **Non grant**
IRB Approval Date: **12 August 2020**
IRB Review Type: ■ **Expedited Review** ☐ **Full Board**
Study site(s): **Central Region**

Dear **Dr. Hind Almodaimegh**
Associate Professor, College of Pharmacy, King Saudi Bin Abdulaziz University for Health Sciences
Ministry of National Guard – Health Affairs

Sub-investigator/s: ABDULRHMAN SARRAH R ALROWILY
After reviewing your submitted research proposal/protocol and related documents, the **IRB has APPROVED** the submission. The approval includes the following related documents:

Document/Title	Version	Date
Research Proposal	01	12 August 2020
Data Collection Form	01	12 August 2020
Inform Consent Form	01	12 August 2020

The approval of the research study is valid for **one year** from the above approval to expiration date.

Terms of Approval:

- **Annual Reports:** An Annual report must be submitted for approval to avoid termination/suspension of your research.
- **Financial report:** If your study is funded project, details financial report should be submitted with the scientific report.
- **Final Report:** After completion of the study, a final report must be forwarded to the IRB.
- **Retention of original data:** The PI is responsible for the storage and retention of original data pertaining to the project for a minimum of five years.
- **Reporting of adverse events or unanticipated problems:** The PI is responsible to report any serious or unexpected adverse events or unanticipated problems, which could involve any risk to participants or others, or any event on incidents that may have impact on the research or participants.
- **Biological samples:** No biological samples to be shipped out of the Kingdom of Saudi Arabia without prior IRB approval.
- **Participant incentives:** No financial compensation or gifts to be given to participants without prior IRB approval.
- **Storage of biological samples:** All biological samples collected for the purpose of this research must be stored in the KAIMRC related repository.
- You will need to resubmit the proposal to the IRB for review and re-approval before implementing any changes to the approved proposal.
- It is possible that the IRB may decide that the proposed new changes may exclude the proposal from being accepted for exempt review.
- It is your responsibility to safely store the data collected.
- Please note that phone based surveys are not permitted.
- If your approved proposal requires access to Bestcare, please write to the IRB informing them of the name of the designated data collector and exactly define the period requested for collecting data. Do not start the data collection until an approval memo is issued from the IRB giving permission to that collector to start accessing Bestcare for the duration of the project and after signing a confidentiality agreement.

18 AUG 2020

Prof. Abdullah Al Sayyari
Chairman, Institutional Review Board (IRB)
Ministry of National Guard - Health Affairs

AS/AQ/AJ

P.O. Box 22490, Riyadh 11426
Tel. 8011111
Telex : 403450 NGRMED SJ
(ORACLE 29795)
HA . Printing Press 17 / 137

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تلفون : ٨٠١١١١١
تلكس ٤٠٣٤٥٠

Appendices 2.3 (Chapter2, Chapter 6, Chapter 7 and Chapter 8)

King Fahad Military Medical Complex in Dhahran Ethical Approval

Armed Forces Hospitals Eastern Province
Institutional Review Board (IRB)

اللجنة الدائمة لأخلاقيات البحث العلمي
P PSMCHS, P.O. Box 33048, Dammam 31148, Eastern Region, Saudi Arabia, Tel. 013.8405487/8405490
KACST Registration HA-05-DH-075

IRB Protocol No.	**AFHER-IRB-2020-015**		
Protocol Title	**Medication Errors Associated with Non-vitamin K Antagonist Oral Anticoagulants in Adult Patients (MENOACs): A Mixed Method (Quantitative and Qualitative Study)**		
Principal Investigator	**Abdulrhman S. Alrowily**	**Co-Investigators**	Dr. Abdulrhman Alhusil, Dr. Mozon Alotaibi
Institution	King Fahad Military Medical Complex	**Department**	Pharmacy
IRB Review Date	May 17, 2020	**Effective Date**	June 4, 2020
IRB Review Action	**APPROVED**	**Expiration Date**	June 3, 2021

Thank you for submitting your application to the Armed Forces Hospitals Eastern Region Institutional Review Board (IRB).

The IRB has determined that your proposed project employs retrospective-prospective observational (quantitative and qualitative) study that pose less than minimal risk to the participants. The information will be obtained in such a way that one's responses will not be linked to one's identify or identifying information. The application was reviewed and approved.

Approval is given for one year from the date of approval. Projects, which have not commenced within one year of the original approval, must be re-submitted to the Institutional Review Board (IRB) Committee. If you are unable to complete your research within the validation period, you will be required to request an extension from the IRB Committee**.** *Please note that the approval of this protocol will lapse on 03-June-2021.*

On completion of the research, the Principal Investigator is required to advise the Institutional Review Board if any changes are made to the protocol, a revised protocol must be submitted to the Institutional Review Board for reconsideration. If an unexpected situation or adverse event happens during your investigations, please notify the AFHER IRB as soon as possible. Please refer to the IRB Protocol number denoted above in all communications related to your application and this approval.

Approval is given on the understanding that the "KACST Implementing Regulations of the law of Ethics of Research" are adhered to. Where required, a signed written consent form must be obtained from each participant in the study group. **Accordingly, the principal investigator must submit progress/final report to the IRB Office once you completed your study**. The IRB extend their best wishes for the successful completion of this study.

MOHAMMED D. ALAHMARI, PhD, FAARC, FCCP
Chairman of the Institutional Review Board

Armed Forces Hospitals-EP
HA - ٠٥ - DH - ٠٧٥

Cc: IRB File

King Fahad Military Medical Complex in Dhahran Ethical Approval

MINISTRY OF DEFENSE
MEDICAL SERVICES DIVISION
ARMED FORCES HOSPITALS
EASTERN REGION INSTITUTIONAL
REVIEW BOARD

وزارة الدفاع والطيران
الإدارة العامة للخدمات الطبية

FORM: Departmental Approval for Undertaking a Research Study
موافقة القسم على إجراء دراسة بحثية

Number	Date	Page No.
IRB-FORM-005	03 May 2020	Page 1 of 1

Title of the Proposal: *Medication Errors Associated with non-vitamin K antagonist oral anticoagulants In Adult Patients (MENOACs):*

A Mixed Method (Quantitative and Qualitative Study

Investigator's Name: Abdulrhman S. Alrowily
Co- Investigator: Dr.Abdulrahman Al Husil

To: Chairman of Institutional Review Board

Greetings,

We consent for the above-mentioned research study to be conducted in our department.

The department council has reviewed the submitted study proposal and confirms that (please check all):

- ☒ The study objectives are important and in line with the department's research scope.
- ☒ The study justification is robust and scientifically plausible.
- ☒ The design, sampling technique, procedures and data analysis are justified, accurate and based on recently published literature.

Best regards.

Department: Cardiac Center

Department Head: Brig.Gen./Dr.Khalid Al Faraidy

Signature:

Date: 03 May 2020

عنوان البحث المقترح:

الأخطاء الدوائية المرتبطة بمضادات التخثر الفموية المضاده لفيتامين ك في المرضى البالغين

منهج مختلط (دراسة كمية ونوعية)

أسم الباحث: عبدالرحمن الرويلي

باحث مشارك: عبدالرحمن الحسيل

إلى: رئيس لجنة أخلاقيات البحث

السلام عليكم ورحمة الله وبركاتة:

نود إفادتكم بموافقتنا على إجراء الدراسة البحثية المذكورة أعلاه في القسم التابعة لنا.

راجع مجلس القسم بروتوكول الدراسة المقدم ويؤكد أنه (يرجى مراجعة الكل):

☒ أهداف الدراسة مهمة وتتوافق مع المجال البحثي بالقسم.

☒ مبرر الدراسة قوي ومقبول علمياً.

☒ التصميم و أسلوب أختيار العينات والإجراءات وتحليل البيانات مبرر ودقيق ويستند إلى المؤلفات المنشورة حديثًا.

وتقبلوا تحياتنا.

القسم: قسم أمراض القلب

رئيس القسم: عميد/طبيب خالد الفرائضي

التوقيع: 3 مايو 2020

3-5-2020 IRB-FORM-005-Departmental Approval New_030520

Appendices 2.4 (Chapter 2, Chapter 6, Chapter 7 and Chapter 8)

King Fahad Central Hospital in Jazan Ethical Approval

صحة جازان
Jazan Health

Directorate of Health Affairs
JAZAN RESEARCH ETHICS COMMITTEE
(IRB Reg. # H-10-Z-073)

April 14, 2020G
Shaban 21, 1441H

To: **Dr. Abdurahman S. Alrowily**
Primary Investigator
School of pharmacy, University of Birmingham

Re: **JREC Feedback on Research Proposal**

Dear Dr. Alrowily,

This is in reference to the Research Proposal entitled **"Medication errors associated with non-vitamin K antagonist oral anticoagulants in adult patients (MENOACs)". (Registry # 164/2020)**

The committee has approved your proposal (**Approval no. 015-2020**). As per policy, the Research & Ethics Committee will be following the progress of your study from the time it commences through to its conclusion. Please note the following conditions:

1. **You are required to submit a progress report/update every 6 months from the date of commencement of your research.**
2. **It is required then that you submit to us a report once your research has concluded .**

Enclosed is the Approval Form (Form #06) which you have to fill out for the final phase of the process. Kindly send back to us duly signed accordingly.

Regards,

DIVINE C. QUIAPO
HOSPITAL COMMITTEES CO-ORDINATOR
K.F.C.H., JAZAN

Dr. Ali Hussein Al Mudeer
Chairman
Jazan Research Ethics Committee

cf: File

JHREC Corr Research Proposal Reply/ 164-2020

www.jazanh.gov.sa | 937 | jazan_health | jazan health | jazanh | jazanhealth

King Fahad Central Hospital in Jazan Ethical Approval

صحة جازان
Jazan Health

RESEARCH ETHICS COMMITTEE **FORM 06**

FORM FOR APPROVAL OF RESEARCH PROPOSAL

(JHREC USE ONLY)

A. Investigator/s

	Name	Signature
Principal	**Dr. Abdurahman S. Alrowily**	_____

Title: **"Medication errors associated with non-vitamin K antagonist oral anticoagulants in adult patients (MENOACs)"**

Corresponding address & Bleep no / Phone no.

School of pharmacy, University of Birmingham
00441214142538

B. Institutional notation:

DIRECTOR	**REPRESENTATIVE**
Name _____	Name _____
Signature _____	Signature _____
Date _____	Date _____

☐ Recommended ☐ Not Recommended (explain)

_____

Supervisors/Co-authors
Name: **Co-author/s:**

Dr. Mohammed Abutaleb
Consultant Clinical Pharmacist
King Fahd Central Hospital – Jazan

C. Ethical Review
Merit / Methods
√ Approved ☐ Rejected ☐ For Revision Reasons for Rejected/Revision: _____

D. FINAL APPROVAL
Registry no. **164/2020** Approval no. **015/2020**
Committee meeting of **Notification by Chair via email**
Communication **193**
Applicant Informed: **Email** Date: **April 16, 2020**

DR. ALI AL MUDEER
JREC Chairperson

Appendices 2.5 (Chapter 5)

Data Agreement Sheet Between NHS Improvement and University of Birmingham Ref:5199

(1) **NHS Improvement**

- and -

(2) **THE UNIVERSITY OF BIRMINGHAM**

Data Sharing Agreement

Ref: 5199

1

This Agreement is made on the day of DECEMBER 2020

BETWEEN:

(1) Monitor and the NHS Trust Development Authority, both of Wellington House, 133-155 Waterloo Road, London SE1 8UG (together "NHS Improvement").

(2) THE UNIVERSITY OF BIRMINGHAM whose office is Edgbaston, Birmingham, West Midlands, B15 2TT ("ExOrg").

WHEREAS:

(A) Under the National Health Service Development Authority (Directions and Miscellaneous Amendments etc.) Regulations 2016, NHS Improvement is responsible for the operation of systems for collecting and analysing information relating to the safety of health services and making that information available to such persons as it considers appropriate.

(B) In exercise of its functions, NHS Improvement operates the National Reporting and Learning System ("NRLS") through which providers of NHS funded health care services submit information about patient safety incidents arising in the course of providing health care services.

(C) ExOrg wishes to obtain incident level patient safety data gathered through the NRLS in order to contribute to national or local patient safety learning.

(D) NHS Improvement wishes to provide information gathered through NRLS to ExOrg on the terms and conditions outlined in this Agreement in consideration for ExOrg making its analysis findings available to NHS Improvement.

IT IS AGREED:

1. Definitions and interpretation

In this Agreement::

1.1. "Applicable Laws" means the Data Protection legislation which includes (i) General Data Protection Regulation ((EU) 2016/679) ("GDPR"), (ii) the Data Protection Act 2018, and (iii) all applicable law about the processing of personal data and privacy, including where applicable the guidance and codes of practice issued by the Information Commissioner and any other relevant national authority;

1.2. "Certificate of Destruction" means a certificate in the form set out in Annex D signed by an authorised representative of ExOrg which certifies that the Data and all hard and soft copies thereof held by ExOrg have been securely and permanently destroyed by ExOrg;

1.3. "Commencement Date" means the date this Agreement is signed by both parties;

1.4. "Confidential Information" means:

1.4.1. the Data provided to ExOrg under this Agreement in order to carry out the Purpose; and

1.4.2. any other information which ExOrg receives or obtains in connection with this Agreement the release of which is likely to prejudice the business interests, functions or activities of NHS Improvement or any other Third Party; whether conveyed in writing or orally to ExOrg; but does not include information which:

1.4.3. is publicly available at the time of disclosure under this Agreement;

1.4.4. becomes publicly available following disclosure under this Agreement (other than as a result of disclosure by ExOrg or any other person contrary to the terms of this Agreement);

1.4.5. was lawfully in ExOrg's possession prior to disclosure under this Agreement (as can be demonstrated by ExOrg's written records or other reasonable evidence) free of any restriction as to its use or disclosure prior to its being so disclosed;

1.4.6. following disclosure under this Agreement becomes available to ExOrg (as can be demonstrated by ExOrg's written records or other reasonable evidence) from a source other than NHS Improvement, which source is not bound by any obligation of confidentiality to NHS Improvement in relation to such information; or

1.4.7. is required to be disclosed as a matter of law, or any professional or regulatory obligation;

1.5. "Data" means the data that is provided by NHS Improvement to ExOrg under this Agreement, the details of which are outlined in Annex A. The data is derived from the NRLS but may not be identical to that submitted to NHS Improvement, having undergone anonymisation to remove Identifiers;

1.6. "Data Loss Event": means any event that results, or may result, in unauthorised access to personal data and/or actual or potential loss and or destruction of data in breach of this agreement, including any personal data breach.

1.7. "Identifier" means any information relating to an individual which when combined with other information is capable of identifying an individual and/or becomes Personal Data;

1.8. "Intellectual Property Rights" means all intellectual property rights including copyright, database rights, trademarks and trade mark names, patents, design rights, trade secrets, know-how and all rights of a similar nature or having similar effect which subsist anywhere in the world whether or not any of them are registered and applications for registration of any of them;

1.9. "Personal Data" means any information relating to an identified or identifiable natural person ('data subject').

1.10. "Personnel" means all employees, agents and contractors of ExOrg who may have access to the Confidential Information;

1.11. "Publication" means any paper, report or document derived from the Confidential Information to be Published;

1.12. "Published" means to make available to Third Parties in any form, including the production of hard copy materials, soft and/or electronic copies, emails and posting online;

1.13. "the Purpose" means the purpose for obtaining the Data as described in Annex A;

1.14. "Third Party" means any party other than NHS Improvement and ExOrg; and

1.15. words denoting the singular include the plural and vice versa and words denoting any gender include all genders.

2. Sharing of data

2.1. NHS Improvement agrees to make the Data available to ExOrg solely for the Purpose and only in accordance with the terms of this Agreement. Data will be transferred via nhs.net in encrypted files or via secure FTP as outlined in Annex A.

3. ExOrg responsibilities

3.1. ExOrg shall:

3.1.1. only use the Data for the Purpose unless NHS Improvement gives it prior written consent to such Data being used for some other purpose;

3.1.2. not share the Data with any person or organisation not referred to in Annex A without the prior written consent of NHS Improvement;

3.1.3. maintain an up to date record of the names and job titles of all individuals with access to the Data, which shall be made available to NHS Improvement as soon as reasonably practicable, upon request;

3.1.4. process the Data only in accordance with the terms of this Agreement;

3.1.5. ensure that Personnel with access to the Data are suitably trained and made aware of their responsibilities in handling the Data and Confidential Information;

3.1.6. on termination of this Agreement for any reason, permanently destroy/delete or erase the Data, together with all hard or soft copies of the same and certify the destruction to NHS Improvement using a Certificate of Destruction, within fourteen (14) days of the date of the termination of this Agreement unless agreed otherwise in Annex A or in writing with NHS Improvement;

3.1.7. report to NHS Improvement NHSI.ig@nhs.net within twenty-four (24) hours, any actual or suspected or anticipated instances of a data loss event or a breach of any terms of this Agreement;

3.1.8. take all necessary precautions to ensure that access to the Data is given only to such Personnel engaged to advise it in connection with the Purpose and only to the extent necessary for the performance of the Purpose;

3.1.9. not combine the Data with any other data held by ExOrg or use or manipulate the Data in any way that re-identifies any individual from the Data other than in accordance with Annex A or as agreed in writing with NHS Improvement;

3.1.10. NHS Improvement acknowledges and accepts that the results obtained through use of the Data shall belong to ExOrg. If requested by NHS Improvement, provide NHS Improvement with a copy of the analysis carried out on the Data, the analysis findings and any other related information;

3.1.11. ensure that any Publication does not contain the Data or any information which when combined with other information could lead to the identification of any person, unless agreed in writing with NHS Improvement;

3.1.12. ensure that any Publication complies with all Applicable Laws and the following guidance:

3.1.12.1.Anonymisation Standard for Publishing Health and Social Care Data: http://www.isb.nhs.uk/library/standard/128; and

3.1.12.2.Anonymisation: managing data protection risk code of practice: https://ico.org.uk/media/1061/anonymisation-code.pdf;

3.1.12.3. The Data Use Principles outlined in Annex C;

3.1.13. provide NHS Improvement with a copy and abstract of any proposed Publication at least fourteen (14) days prior to the date it is proposed to be Published and if NHS Improvement reasonably requests, make any amendments to the Publication to ensure it meets the requirements of this Agreement and any Applicable Laws;

3.1.14. before undertaking any Publication using the Data or any derived information, ExOrg must undertake an appropriate risk assessment exercise to ensure compliance with the requirements in paragraph 3.1.11 above;

3.1.15. not assign, transfer or sub-contract any right or obligation under this Agreement other than in accordance with Annex A or as agreed in writing with NHS Improvement;

3.1.16. develop appropriate systems and/or processes to ensure that it complies with the terms of this Agreement and Applicable Laws;

3.2. If ExOrg is required to respond to a request under the Freedom of Information Act 2000 and a request is received regarding the Data, ExOrg must consult with NHS Improvement prior to any release of the Data or Confidential Information. NHS Improvement will respond to ExOrg within five (5) days after receiving ExOrg's notice if that notice requests NHS Improvement to provide information to assist ExOrg to determine whether or not an exemption to the Freedom of Information Act applies to the information requested under that Act.

3.3. ExOrg shall comply with the data security requirements outlined in Annex B of this Agreement.

4. Data Protection

4.1. NHS Improvement will use all reasonable endeavours to fully anonymise the Data before transferring it to ExOrg and will notify ExOrg if it identifies any Identifiers or Personal Data in the Data already provided.

4.2. Notwithstanding clause 4.1 above, the Parties acknowledge that if any Identifiers and/or Personal Information are incorporated into the Data, ExOrg agrees to:

4.2.1. notify NHS Improvement as soon as reasonably practicable and in any event within forty-eight (48) hours, if any such information is identified as contained within the Data and provide details of the relevant unique incident number and field(s) concerned (but not in any circumstances quote any Personal Data identified);

4.2.2. as soon as reasonably practicable and in any event within forty-eight (48) hours, permanently delete any Identifiers and any Personal Data identified in the Data from any electronic copy of the Data held whether identified by ExOrg or NHS Improvement;

4.2.3. as soon as reasonably practicable and in any event within forty-eight (48) hours, permanently destroy or return to NHS Improvement any hard copies of the Data identified as containing Identifiers and/or Personal Data; and

4.2.4. as soon as reasonably practicable and in any event within forty-eight (48) hours, recall any copies of the Data provided to a Third Party which contain Identifiers and/or Personal Data and deal with it in accordance with the steps outlined in 4.2.2 and 4.2.3 above.

4.3. If, and to the extent that, any Identifiers becomes Personal Data in the hands of ExOrg, ExOrg shall be the controller for that information.

4.4. ExOrg will comply at all times with the common law duty of confidentiality and all Applicable Laws.

4.5. ExOrg shall have regard to the Code of Practice on Confidential Information published by the Health and Social Care Information Centre when processing the Data.

4.6. In the event of any change in Applicable Laws subsequent to the date of signature of this Contract, ExOrg shall take such steps as may be requested by NHS Improvement to ensure the processing by ExOrg of the Data complies with Applicable Laws at the time of processing.

4.7. ExOrg shall not transfer the Data outside of the European Economic Area except with the prior written consent of NHS Improvement and only in circumstances when such transfer is permitted under, and complies with the requirements of, the GDPR.

4.8. ExOrg shall notify NHS Improvement about any notice, request or complaints received relating to the Data, including any individual claiming that their Personal Data is contained in the Data; and shall not respond without NHS Improvement's approval.

4.9. ExOrg shall cooperate with NHS Improvement in relation to any notice, request or complaint received in relation to the Data.

4.10. ExOrg must maintain complete and accurate records and information to demonstrate compliance with GDPR (accountability).

4.11. ExOrg must maintain records of its processing activities which meet the requirements of Article 30 of the GDPR.

4.12. ExOrg must designate a data protection officer if required by the data protection legislation

5. Confidentiality

5.1. ExOrg shall:

5.1.1. treat all Confidential Information provided under, or obtained in connection with, this Agreement as confidential and safeguard it accordingly;

5.1.2. not, other than in accordance with Annex A, disclose any Confidential Information to any other person without the prior written consent of NHS Improvement; and

5.1.3. make no commercial use of the Confidential Information or any part thereof.

5.2. ExOrg shall be responsible for any unauthorised disclosure or use of the Data made by any of its Personnel and shall take all reasonable precautions to prevent such unauthorised disclosure or use.

5.3. The confidentiality obligations contained in this Agreement shall continue for a period of five (5) years following termination or expiry of this Agreement.

5.4. Where ExOrg is required as a matter of law to disclose any Confidential Information ExOrg shall notify NHS Improvement.

5.5. On the written request of NHS Improvement, ExOrg will return immediately all Confidential Information provided to ExOrg and all copies of it.

6. Preservation of rights

Nothing in this Agreement shall transfer to ExOrg any right or interest whatsoever in any intellectual property belonging to NHS Improvement.

7. Invalidity

If any provision of this Agreement is held to be void or declared illegal, invalid or unenforceable for any reason whatsoever, that provision shall be divisible from this Agreement and shall be deemed to be deleted from it and the validity of the remaining provisions shall not be affected. If any such deletion materially affects the interpretation of this Agreement, NHS Improvement and ExOrg shall use their best endeavors to negotiate in good faith with a view to agreeing a substitute provision as closely as possible reflecting the commercial intention of the parties.

8. Audit and specific rights

8.1 NHS Improvement and its agent shall be entitled at any time during the term of this Agreement to audit ExOrg's use and storage of the Data (including spot checks should NHS Improvement have any concerns about compliance with the terms of this Agreement).

8.2 ExOrg shall provide such information as NHS Improvement or its agents shall reasonably requests in order to verify its compliance with the terms of this Agreement.

9. Warranties

9.1. ExOrg warrants that:

9.1.1. it has the full right and authority to enter into this Agreement; and

9.1.2. it shall use the Data in accordance with all Applicable Laws.

9.2. NHS Improvement does not warrant the accuracy or completeness of the Data, nor that the Data does not infringe the Intellectual Property Rights of any third party, nor does it undertake that the Data will meet the requirements of, or be fit for purpose of, ExOrg.

10. Liability

10.1. Subject to clause 10.2, the liability of any party excludes all liability arising from, or in connection with, this Agreement, regardless of form of action and whether in contract, tort (including negligence or breach of statutory duty) or otherwise, including:

10.1.1. any loss of profits, revenue, opportunity, contracts, sales, turnover, anticipated savings, goodwill, reputation, business opportunity, production, or loss to or corruption of data (regardless of whether any of these losses or damages are direct, indirect or consequential); and

10.1.2. any indirect or consequential loss or damage whatsoever.

10.2. Nothing in this Agreement shall limit or exclude either party's liability for:

10.2.1. death or personal injury resulting from negligence;

10.2.2. fraud or fraudulent misrepresentations; or

10.2.3. any other liability that cannot be excluded or limited as a matter of law.

11. Indemnity

11.1. ExOrg shall indemnify NHS Improvement up to the value of £500,000 against any liabilities, costs, expenses, damages and losses suffered or incurred arising out of or in connection with:

11.1.1. any loss of the Data by ExOrg;

11.1.2. unauthorised or unlawful use of the Data beyond the Purpose by ExOrg; and

11.1.3. any breach of this Agreement by ExOrg.

11.2. ExOrg shall indemnify NHS Improvement against any liabilities, costs, expenses, damages and losses suffered or incurred arising out of or in connection with any monetary penalty notice imposed on NHS Improvement by the Information Commissioner under the GDPR as a result of ExOrg's breach of this Agreement.

12. Insurance

12.1. ExOrg shall effect and maintain with a reputable insurance company a policy or policies of insurance providing an adequate level of cover in respect of the risks which may be incurred by ExOrg arising out of, or in connection with, this Agreement, including loss of Data and unauthorised or unlawful use of the Data by ExOrg beyond the Purpose. Such insurance shall be maintained for so long as ExOrg may have any liabilities under the Agreement.

13. Remedies

13.1. The rights and remedies provided by the Agreement are cumulative with and not exclusive of any rights or remedies provided by law.

13.2. Without prejudice to any other rights or remedies of the parties, the parties acknowledge that damages might not be an adequate remedy for any breach of the provisions of this Agreement and that, accordingly, they shall be entitled without proof of special damage to the remedies of injunction and specific performance and other equitable remedies for any threatened or actual breach of the provisions of this Agreement.

14. Term and termination

14.1. This Agreement shall commence on the Commencement Date and shall remain in force, unless terminated earlier in accordance with this Clause 14, for the period outlined in Annex A. Both parties must agree in writing to any extension of this Agreement.

15. Notices

15.1. Unless specified otherwise elsewhere in this Agreement. all notices and communications sent pursuant to this Agreement shall be in writing and shall be deemed to have been duly given:

15.1.1. when delivered, if delivered by hand;

15.1.2. on the second working day after mailing, first class postage pre-paid.

15.2. Notices shall be addressed to the following addresses or such other addresses as the parties may notify in writing from time to time:

15.2.1. NHS Improvement: Patient Safety, NHS Improvement, Skipton House, 80 London Road, London SE16LH; nrls.datarequests@nhs.net

15.2.2. ExOrg: Director of Research Support Services, The University of Birmingham, Edgbaston, Birmingham, B15 2TT.

16. Dispute Resolution

16.1. In the event of a dispute arising under this Agreement, authorised representatives of ExOrg and NHS Improvement will discuss and meet as appropriate to try to resolve the dispute within thirty (30) days of being requested in writing by ExOrg or NHS Improvement to do so. If the dispute remains unresolved, it will then be referred to a senior manager from each of the Parties who will use all reasonable endeavours to resolve the dispute within a further thirty (30) days.

17. Governing law and jurisdiction

This Agreement shall be governed by and construed in accordance with English law and shall be subject to the exclusive jurisdiction of the courts of England and Wales.

18. Entire agreement

This Agreement constitutes the entire agreement and understanding between the parties in respect of the Data and supersedes all previous agreements, understandings and undertakings in such respect.

19. Counterparts

This Agreement may be executed in one (1) or more counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument. A signed copy of this Agreement delivered by e-mailed portable document format file or other means of electronic transmission shall be deemed to have the same legal effect as delivery of an original signed copy of this Agreement.

20. A person who is not a party to this Agreement shall not be entitled to benefit or have any rights to enforce any of its provisions and the Contracts (Rights of Third Parties) Act 1999 shall not apply.

SIGNATURES

SIGNED by

(Printed name)

for and on behalf of **NHS Improvement**

Organisational role National Director of Patient Safety

(PLEASE COMPLETE IN CAPITALS)

(Signature)

(Date)

SIGNED by

(Printed name)

for and on behalf of **NHS Improvement SIRO**

Organisational role DIRECTOR OF CORPORATE OPERATIONS

(PLEASE COMPLETE IN CAPITALS)

.....

(Signature)

(Date)

SIGNED by

Amelia Petch (Printed name)

for and on behalf of THE UNIVERSITY OF BIRMINGHAM

Organisational role Head of Research Contracts

(PLEASE COMPLETE IN CAPITALS)



(Signature)

10 December 2020

(Date)

Annex A

1. Details of ExOrg	
(a) Name and job title	Dr Vibhu Paudyal Senior Lecturer in Clinical Pharmacy
(b) Organisation - Please also provide the name of your Data Protection Officer, where the data protection legislation requires you to have one, and your organisation's ICO data protection registration number and expiry date	Nicola Cardenas Blanco, The University of Birmingham
(c) Address	School of Pharmacy Sir Robert Atkins Institute of Cancer Research Building Edgbaston, Birmingham B15 2TT
(d) Email address	[redacted]
(e) Telephone number	[redacted]
(f) Please outline names and job titles of all individuals who will have access to the Data. Where the Data will be accessed by a team of individuals, it is sufficient to outline a description of that team (including the name and the size of the team) provided a list of named individuals in that team is maintained in accordance with paragraph 3.1.3 above.	Dr Vibhu Paudyal Senior Lecturer in Clinical Pharmacy Dr Zahraa Jalal Lecturer in Clinical Pharmacy Mr Abdulrhman Alrowily PhD student
2. How is the data going to be used?	
(a) What is the purpose?	The data will be analysed to identify patient safety incidents in relation to the novel oral anticoagulant medicines.
(b) Please explain how your work will contribute to national or local patient safety learning. Please highlight any benefits to the NHS or wider health community, and if your work will be shared with NHS Improvement.	The direct acting novel oral anticoagulants have provided revolutionary treatment to patients requiring anticoagulation treatment. However, there is a lack of experience associated with these medicines compared to the historically used anticoagulant, Warfarin. The

	analysis of the data will allow us to identify relevant safety related incidents in relation to these medicines. The outcome will help identify where do such safety incidents mostly occur, why do they occur and what can we do to prevent them. We aim to undertake the analyses of safety incidents and submit for publication in a peer reviewed journal by June 2020.
(c) How and to whom do you intend to disseminate the analysis? Please explain your specific methods of communications (e.g. journal papers, articles, internal reports), expected timescales and any intention to combine the data with other data.	The report will consist of a dissertation of PhD study of AA. It will also be submitted for a peer reviewed publications in drug safety journals. We will also share the findings with NHS improvement and disseminate in national and international conferences to promote awareness of the safety issues in relation to these medicines.
3. How will you ensure the security of the data?	
(a) Premises where Data will be stored	All data will be stored in password protected computers at University of Birmingham. Only members of the research team will have access to the data. All data files will be encrypted with password.
(b) Storage of electronic Data (e.g. file encryption, network security, password protection of assets, etc.) **Please note: File level encryption is requested in most instances.**	As above. All data will be stored in password protected computers at University of Birmingham. Only members of the research team will have access to the data. All data files will be encrypted with password.
(c) Access to physical resources for accessing the Data (e.g. swipe card/keypad restricted building/computer access, storage of CDs, etc.)	The University of Birmingham buildings are protected with swipe card access. Computer accesses are restricted to the University staff and students.
(d) Management of paper copies of the Data (Please note: the Data should not be routinely managed via paper copies, use only for exceptional circumstances)	We will not use papers to manage or analyse data. All activities will be conducted electronically.
4. Details of data transfer	

Please note: Data is transferred via nhs.net, encrypted files or via secure FTP (SFTP) via AES 256-bit encryption protected with a 10 character password comprising upper and lower case alphanumeric and special characters (@, $,* etc) communicated to ExOrg via telephone. **If the preferred option is SFTP please supply your IP address for this purpose. Your IT department might have to change firewall rules to enable the secure FTP. Please note that NHS Improvement cannot offer support in the configuration of the secure FTP. NHS Improvement will provide the username, password and server IP address needed to access the SFTP server.**	
IP Address	Regular automated outputs will not be required. Therefore encrypted files will be okay.
5) Third Party Access	
Please note: NHS Improvement data should not be shared or be accessible by any third party without NHS Improvement's prior written consent. Please describe if data will be stored on third party data hosting service, or a contractor will be involved in analysis **(a)** Name of third party organisation, and name all individuals who may have access to the Data. (If none please state 'None')	None
(c) In what capacity/service?	NA
(d) What vetting measures are in place?	NA
6) Destruction of data	
By signing this Agreement, you agree to destroy the data after use. How will you destroy the Data?	We use Blancco File Erasure to securely delete sensitive files. Blancco has multiple erasure algorithm including HMG, Higher Standard.

(specifically specialist software to erase all copies of the Data and/or specialist media used to hold the Data) **Please note: Deletion of files does not adequately remove data from the system. We require deletion compliant with HMG IA (Her Majesty's Government Information Assurance) Policy No.5**	
Application has been approved for: **Expiry date:**	
7) Please describe (in words) which data you require	
8) Outline of the data schedule	
Please note: **(a)** The date of incident is default date searched **(b)** It is also possible to search by the date the incident has been received by Patient Safety **(c)** A combination of the above dates can be used to provide consistent data if you require regular searches as incidents are not reported or processed chronologically **(d)** All Trusts were connected to the NRLS database in 2005 - the default earliest date is therefore 01/01/2005 **(e)**Please give details including consideration of frequency of data release: Weekly Monthly Quarterly Annually Consecutive periods Rolling periods Snapshots Full datasets with historic updates	1. We would like to access all patient safety incident reports for the last 3 years (most recent) from all settings that mention the following medications listed 2. We would like to request all patient safety incident reports for the last 3 years (most recent) from all settings that mentions the following treatment and procedure novel oral anticoagulant NOAC [include plural search NOACs) novel oral anti-coagulant [please include plural search] new oral anti-coagulant [please include plural search] direct-acting oral anticoagulant [please include plural search] direct oral anticoagulant [please include plural search] DOAC [please include plural search DOACs] TSOAC [please include plural search] target-specific oral anticoagulant [please include plural search] novel oral anticoagulant [please include plural search]

	non-VKA oral anticoagulant [please include plural search] new oral anticoagulant [please include plural search] non-vitamin K antagonist oral anticoagulant [please include plural search] apixaban dabigatran edoxaban rivaroxaban Pradaxa Xarelto Eliquis Savaysa Lixiana Xaban
An analyst from the NRLS team may contact you to discuss the next three questions and will fill them on your behalf	
9) Which geographic areas do you require?	
All geographic areas	
10) Which filters do you require?	
none	
11) Please list any free text keywords to be used	
Listed above	

Annex B: Information Security Requirements

Information security

1. Without prejudice to ExOrg's other obligations in respect of information security, ExOrg shall:
   1.1 Ensure protective measures are in place which means appropriate technical and organisational measures which may include: psuedonymisation and encrypting personal data, ensuring confidentiality, integrity, availability, and resilience of systems and service, ensuring that availability of and access to personal data can be restored in a timely manner after an incident, and regularly assessing and evaluating the effectiveness of such measures adopted by it.

   1.2 Having taken account for (i) the nature of data to be protected; (ii) harm that might result from a data loss event; (iii) state of technological developments; (iiii) cost of implementing any measures.

   1.3 The ExOrg must ensure it adopts a data protection by design and default approach in regards to implementation of appropriate technical and organizational measures.

   1.4 ensure that its security arrangements for the Data comply with the following information security standards:
      1.4.1 ISO 27001;
      1.4.2 NHS Digital's Data Protection and Security Toolkit;
      1.4.3 Cabinet Office's "Government Security Classifications" policy, April 2014 with a protective marking level of "UK OFFICIAL – PERSONAL" for the Data ;
      1.4.4 Cyber Essentials Scheme available at https://www.cyberstreetwise.com/cyberessentials/ and the 10 steps to Cyber Security available at: https://www.cesg.gov.uk/10-steps-cyber-security;

   1.5 store the data on a secure network drive with security controls such as role based access control or equivalent in place to limit access to the Data to authorised Personnel;

   1.6 ensure the Data is encrypted either individually or at folder level;

   1.7 not make any paper or physical copies of the Data unless agreed in writing with NHS Improvement;

   1.8 not store the Data on any portable media device;

   1.9 store the FTP server URL and the credentials required to download the data via FTP in a secure (encrypted) repository; and

   1.10 not transfer the Data from the premises of ExOrg outlined in Annex A unless agreed in writing with NHS Improvement

Annex C: Data Use Principles

1. Background and Purpose

The purpose of the National Reporting and Learning System (NRLS) is to enable learning from patient safety incidents. This document sets out the circumstances under which NRLS data is the appropriate data source to be used and describes its appropriate use.

These principles emphasise the purpose and characteristics of the NRLS data, and promote consistency across NRLS data users. It is essential to abide by these principles to ensure we continue to successfully learn from patient safety incident reports.

2. Applies to
These principles apply to all stakeholders, including NHS Improvement staff using NRLS data.

3. The Principles
What does NRLS data tell us?

I. **NRLS data reflects the safety reporting culture in an organisation.**
II. **NRLS data shows the most frequent types of patient safety reported incidents at national, regional and local levels.**
III. **NRLS data shows which types of patient safety incidents are reported as most harmful, at national, regional and local levels.**
IV. **NRLS data helps to understand how patient safety incidents happen.**
V. **NRLS data shows how incident reporting pattern change over time by degree of harm, by topic and by care setting or organisation.**

What doesn't NRLS data tell us?

VI. **It does not provide the actual number of patient safety incidents occurring in the NHS or in a particular organisation.**
VII. **It does not provide information on the full history and characteristics of patients involved in patient safety incidents.**
VIII. **It does not tell us if an organisation is safe or unsafe.**
IX. **It does not show organisations' level of compliance with safety guidelines.**
X. **It does not measure the efficacy of specific safety initiatives.**

4. Key Data Notes
Further key data notes to consider when using NRLS data:

4.1 Total numbers

The NRLS is a largely voluntary scheme for reporting patient safety incidents, and therefore it does not provide the actual number of patient safety incidents occurring in the NHS.

Under-reporting and uneven reporting frequency patterns amongst organisations are the main constraints on the use of NRLS data for statistical purposes. Another limitation can be due to changes to reporting requirements, often resulting in changes to data series over time.

Careful consideration should be given to the dates of changes in mandatory reporting requirements, as these may have a 'one-off' impact, affecting reporting patterns in a specific time frame. Organisational change should also be borne in mind, as newly created and newly merged organisations take time to mature and set up their systems and processes.

Consequently, patient safety incidents reported to the NRLS are simply just that – incidents reported to the NRLS. They should not be presented as the number of incidents actually occurring in an organisation.

4.2 Dynamic database

The NRLS is a dynamic reporting system and the number of incidents reported as occurring at any point in time may increase as more incidents are reported.
Incident classification can also change as local investigations progress and incidents are updated. Therefore, the date of the data extraction always should be included on tables and chart references.

4.3 Trends over time

When comparing NRLS data across time periods, it is important to compare data to the same time period in the previous year(s). This is to take into account known 'seasonality' in the data. There are at least two causes of seasonality in the reporting of patient safety incidents to the NRLS: 'administrative seasonality' and incident seasonality.

'Administrative seasonality'

There are large spikes in the reporting of patient safety incidents to the NRLS every six months (at the end of May and the end of November), as organisations upload batches of data in order to meet the cut-off dates for submission to the NRLS for inclusion in the UK Official Statistics data set.

Incident seasonality

Research suggests rates of morbidity and mortality relate to the time of year which may affect incident reporting.

Therefore, when reviewing changes over time, it is recommended that:

- proportions or percentages are used rather than actual numbers
  (to allow for the differences in the underlying numbers of incidents and the underlying activity of the NHS);
  and
- either the same time period in the previous year, or a full year's worth of data are used
  (in order to take seasonality into account);
  and
- checks are made that any 'change/difference' is not an artefact due to either new/amended national mandatory reporting requirements, or organisational restructuring.

4.4 Timeliness of reporting

Organisations are encouraged to report patient safety incidents to the NRLS at least once a month, and the CQC guidance for the reporting of serious incidents recommends reporting "without delay".
However, in practice there is usually a delay between an incident occurring and it being reported to the NRLS. As this delay is well known, we always allow a minimum of two months lag in analysing data based on the date of the incident (occurring date). This also provides sufficient opportunity for organisations to update incidents, if appropriate.

5. Further support

Detailed guidance on handling NRLS data can be found on:
http://nrls.nhs.uk/resources/?entryid45=135546

If you are unsure about one or more principles, you wish to discuss an analytical methodology, or explore new ways of using NRLS data you should contact NRLS.DATAREQUESTS@NHS.NET .

Annex D: Certificate of Destruction



The Data Sharing Agreement you have with NHS Improvement has expired, in accordance with the terms of your agreement you are requested to confirm that all data provided has been destroyed, this should include the original data plus any copies.

Please refer to your original agreement which will state how you should delete the data.

In accordance to the Records Management Code of Practice for Health and Social Care 2016

Destruction
Paper: paper records can be destroyed to an international standard. They can be incinerated, pulped or shredded (using a cross cut shredder) under confidential conditions. Do not use the domestic waste or put them on a rubbish tip, because they remain.

Digital media: destruction of digital information is more challenging. Records management is concerned with accounting for information so any destruction of hard assets, like computers and hard drives and backup tapes, must be auditable in respect of the information they hold. An electronic records management system will retain a metadata stub which will show what has been destroyed.

The ICO has indicated that if information is deleted from a live environment and cannot be readily accessed then this will suffice to remove information for the purposes of the GDPR. Their advice is to only procure systems that will allow permanent deletion of records to allow compliance with the law.

CERTIFICATE OF DESTRUCTION

AGREEMENT REFERENCE NUMBER

DATE OF DESTRUCTION

METHOD OF DESTRUCTION
(Certificate of Destruction to be sent to NHS Improvement)

SIGNATURE OF DATA RECIPIENT

DATE

NAME

DESIGNATION EMAIL

Please return to: nhsi.ig@nhs.net

Abdulrhman Alrowily (PhD Pharmacy FT Non-Lab (B230))

From: [redacted]
Sent: 28 January 2021 10:18
To: [redacted]
Subject: FW: Ref 5199 V Paudyal - NOACS (Community Pharmacy) Data set
Attachments: Ref 5199 - V Paudyal - NOACS (Community Pharmacy) -(PWP).xlsx

Follow Up Flag: Flag for follow up
Flag Status: Flagged

Dear Abdulrhman
Great news that we have the NRLS data. Please have a look and we should discuss your analysis plan soon.
I will send you password in your mobile text. Please send me the number.

Please save this in your University password protected computer and don't download anywhere else or we will be in trouble.
Many thanks for your patience.

Regards.
Vibhu.

Dr Vibhu Paudyal BPharm, MSc, PhD, SRPharmS
Senior Lecturer in Clinical Pharmacy
School of Pharmacy
College of Medical and Dental Sciences
Sir Robert Aitken Institute for Medical Research
University of Birmingham
Edgbaston, Birmingham
B15 2TT

[redacted]

From: NRLS, Datarequests (NHS ENGLAND & NHS IMPROVEMENT - T1520) [mailto:nrls.datarequests@nhs.net]
Sent: 28 January 2021 10:02
To: Vibhu Paudyal (Pharmacy); NRLS, Datarequests (NHS ENGLAND & NHS IMPROVEMENT - T1520)
Subject: Ref 5199 V Paudyal - NOACS (Community Pharmacy) Data set

A password protected attachment has been sent to you. Please note that the message could not be scanned for malware/viruses due to the message being password protected.

For your security it is highly recommended to confirm the sender's email address and details before attempting to open and extract the file contents.

This is an informational warning from the NHSmail Team.

Good Morning Vibhu,

Please find your data request attached. This file is password protected and the password will be sent separately as agreed.

Please confirm when you receive this email and the password,

1

Many thanks and kind regards Neil

Neil Christopher Barnaby
Oversight & Business Support Officer
NHS England and NHS Improvement
w: www.england.nhs.uk and www.improvement.nhs.uk
Skipton House, 80 London Road, London SE1 6LH

Please note my regular working hours are Monday-Friday, 08:00hrs to 16:00hrs

****
****

This message may contain confidential information. If you are not the intended recipient please inform the
sender that you have received the message in error before deleting it.
Please do not disclose, copy or distribute information in this e-mail or take any action in relation to its contents. To do so is strictly prohibited and may be unlawful. Thank you for your co-operation.

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For more information and to find out how you can switch, https://portal.nhs.net/help/joiningnhsmail

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This message may contain confidential information. If you are not the intended recipient please inform the
sender that you have received the message in error before deleting it.
Please do not disclose, copy or distribute information in this e-mail or take any action in relation to its contents. To do so is strictly prohibited and may be unlawful. Thank you for your co-operation.

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For more information and to find out how you can switch,
https://portal.nhs.net/help/joiningnhsmail

Appendices 2.6 (Chapter 2, Chapter 6, Chapter 7)

Healthcare Professional Consent Form

Version 0.3 Participant Information Sheet 12/04/2020

MENOAC
MEDICATION ERRORS ASSOCIATED WITH NON-VITAMIN K ORAL ANTICOAGULANTS IN ADULT PATIENTS

Healthcare professional consent form

Research project title: Medication Errors Associated with non-vitamin K antagonist oral anticoagulants In Adult Patients (MENOACs): A Qualitative Study

Please initial each box

- I have read the participant information sheet version number_____dated_____and had the opportunity to ask questions and discuss this study ☐
- I agree to take part in this study ☐
- I agree to keep any discussion within the focus group confidential ☐
- I agree the interview will be audio recorded ☐
- I agree for non-identifiable quotes from the focus group to be published ☐
- I understand that I am free to withdraw from the study at any time, Without having to give a reason ☐
- I understand that the data collected during the study may be accessed researchers from BUH Hospital or from regulatory authorities ☐

Name of participant	**Date**	**Signature**
Name of person taking consent	**Date**	**signature**

Contact and further information: If you want any further information about this particular study, you can contact the researcher team.

Abdulrhman Alrowily
Phone: [redacted]
Email: [redacted]

Dr Vibhu Paudyal
Phone: [redacted]
Email: [redacted]

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1

Appendices 2.7 (Chapter 2 and Chapter 8)

Patients Consent Form





نموذج إقرار بالإشتراك في الدراسة

الأخطاء الدوائية المرتبطة بمضادات التخثر الفموية التي لا تحتوي على فيتامين ك في المرضى البالغين

دراسة نوعية

نسخة المريض

الباحث الدكتور/ عبد الرحمن الرويلي يقدرموافقتكم بالمشاركة بدراسة يقوم بها لنيل درجة الدكتوراه من جامعة برمنجهام تحت إشراف الملحقية الثقافية بالمملكة المتحدة، الدراسة متعلقة ب" الأخطاء الدوائية المرتبطة بمضادات التخثر الفموية التي لا تحتوي على فيتامين ك لدى المرضى البالغين". في هذه الدراسة ، نود أن نستكشف آرائكم التي ستساهم بمساعدة فريق البحث على فهم الأسباب المحتملة والعوامل المساهمة في حدوث الأخطاء الدوائية المرتبطة بمضادات التخثر الفموية غير المحتوية على فيتامين ك في المرضى البالغين. سيتم في البداية تقديم نموذج إقرار بالدراسة الذي حال توقيعك عليه، سوف بمقدورك الإطلاع على جميع المعلومات المتعلقة بالدراسة وسيتاح لك الفرصة لطرح جميع الإستفسارات ومناقشتها مع الأخذ بعين الإعتبارتمام سرية الحوار الذي سيدار في هذه الجلسة التي ستسجيل صوتيا وعدم تأثرخطتك العلاجية أو برنامجك الطبي في المنشأة بأي نتائج تصدر من هذا البحث. اذا كانت لديك أي نقاط تود إستيضاحها قبل بدء التسجيل يرجى التفضل بمناقشتها.

- ☐ لقد أطلعت على جميع المعلومات المتعلقة بالدراسة وأتيحت لي الفرصة لطرح جميع الإستفسارات التي لدي ومناقشتها
- ☐ أوافق على المحافظة على سرية الحوار الذي سيدار في هذه الجلسة
- ☐ أوافق على تسجيل هذه المحادثة صوتيا
- ☐ أوافق على أن يتم الإقتباس من الحديث المسجل ليتم نشره في أي من الأوراق العلمية
- ☐ أنا مدرك بأن لي الحق في الإنسحاب من الدراسة والمقابلة في أي وقت بدون إبداء الأسباب
- ☐ أنا مدرك أن جميع البيانات التي تم جمعها خلال هذه الدراسة سيطلع عليها فريق البحث العلمي من جامعة برمنجهام أو أي سلطة أكاديمية أخرى.
- ☐ أوافق على المشاركة في هذه الدراسة

الرقم التسلسلي للمشارك:		
إسم الباحث:	التوقيع	التاريخ

Qualitative interview (Approximately 45-60 min)

Medication Errors Associated with non-vitamin K antagonist oral anticoagulants in Adult Patients (MENOACs): A Qualitative Study

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Background information:

Invite interviewee to briefly tell about him/herself: general information about the background mostly about their experience with about safety concerns associated with NOACs utilization in adult patients used NOACs medications

Please fill in the info below

Gender	
Training background	
Years qualified	
Years of experience	
Speciality	
Current job title	
Years of experience	
Are you involved in another research study?	

Appendices 2.8 (Chapter 2, Chapter 6 and Chapter 7)

Healthcare Professional Information Sheet Form

MENOACs
MEDICATION ERRORS ASSOCIATED WITH NON-VITAMIN K ORAL ANTICOAGULANTS IN ADULT PATIENTS

Healthcare professional Information sheet: interview

Research project title: Medication Errors Associated with non-vitamin K antagonist oral anticoagulants In Adult Patients (MENOACs): A Qualitative Study

We would like to invite you to take part in our research study. Before you decide, we would like to explain what the study is about, and what joining the study will involve. The researcher, Abdulrhman Alrowily, will go through the information sheet with you and answer any questions you have. First, my name is Abdulrhman Alrowily. I am undertaking a PhD study at the University of Birmingham on the Medication Errors Associated with non-vitamin K antagonist oral anticoagulants In Adult Patients. Thank you for showing an interest in our study.

What is the purpose of the study?

The aim of the study to explore your views and gain a more accurate understanding the causes and contributory factors and natures of Medication Errors (MEs) Associated with non-vitamin K antagonist oral anticoagulants (NOACs) In Adult Patients. So please could you consider one or more errors or near misses that occurred whilst you were (prescribe, dispense, administer or monitor that medication. Could you please tell me about these errors during interview?

Here are some information below on the study. Please do not hesitate to contact us using details provided overleaf.

Who is organising the research?

This project is funded by the Saudi Arabian cultural bureau as it is part of a PhD thesis for Abdulrhman Alrowily. The study is being managed by University of Birmingham and University Hospitals Birmingham NHS Foundation Trust (UHB).

Why am I being invited to take part?

We are looking for individuals who fulfil the following criteria:

- Aged ≥18
- Taking any drugs called new oral anticoagulants

We are writing to primary healthcare professionals (physicians, pharmacists and nurses) involved in the care of patients taking NOACs experience.

What does participation involve?

Participation in this study will involve taking part in an interview. The interview should not last more than 45 minutes. The interviews will be conducted by the primary researcher and they will take place at confidential place at your setting (e.g. meeting rooms), or we can modify it according to your needs (e.g. by telephone).

At the day of the interview, you will be asked to complete a short anonymous questionnaire (demographic questionnaire; this will take around 5 minutes). This questionnaire is intended to collect your demographic data including job title, clinical speciality etc. Before the interview begin, we will ask for your permission to record the interview.

Do I have to take part?

No. Participation in this study is voluntary and you may withdraw at any time. If you change your mind after you have taken part, you can still withdraw at any time without given any reason. We will destroy all data, recording and your consent forms. To inform us about your change of mind after the interview,

simply let the researchers on site know if they are available or emailing axa1320@student.bham.ac.uk or contact Dr Vibhu Paudyal at 01214142538. If at any point during interview you feel uncomfortable or unable to continue, the interview will be ceased immediately.

How do I benefit from participation?

There is no direct benefit to you from participation in this study. However, it is possible that by sharing your thoughts and experiences with us, you will be helping our research team (MENOACs) and University of Birmingham to better understand the possible causes and contributory factors of medication errors in people taking NOACs medications in the Saudi Arabia hospital.

What are the possible risks and disadvantages of taking part in the study?

We do not believe that there are risks involved in taking part in the study. We think this should take about 45 minutes in total including consent process. If you have any concerns about the study or some points were unclear in the leaflet, please discuss any concerns with a member of the research team in the first instance.

Will my taking part in the study be kept confidential?

Your participation in the study will be anonymised and you will not be identified in any reports. We will not share your data with any third party. All data will be stored, processed and analysed as per the Data Protection Act 2018.

Non identifiable paper-based data will be stored in a locked filling cabinet in the primary researcher's office. You will be assigned a unique study ID and research data will be stored using this unique ID number, so data will only be identified by this code and their personal information will not be used so that no one will be able to identify you.

Non identifiable electronic-based data will be stored on a password protected computer for analysis purposes located at the University of Birmingham. Data will only be accessed by the primary researcher and the members of the research team. In line with the University's guidelines on records management,

research data will be retained intact for a period of 10 years from the date of collection.

Your name will be deleted from the documents (informed consent and screening questionnaire) and you will be provided with unidentifiable study ID. Other identifiable data (e.g. contact details) that will provided as electronic form including recruitment tool, will be stored as encrypted file and stored in a UoB computer, which will be password protected and it's located at the university and hence the data will be stored securely on the UoB network.

In case you withdraw from the study within 14 days of the interview, your research data will be destroyed, and subsequently your data will not be included in any publications. In case a transcript was submitted for publication and you decided to withdraw from the study, we can destroy all your documents and your personal data will be destroyed as appropriate.

What will happen to the results of the research?

The full findings of the study may be published in a health care journal and presented at a conference and as an academic thesis for the researcher's PhD. You will not be identified in any report.

Who has reviewed and approved this study?

This study was reviewed and approved by xxx research ethics committees.

What do I do next?

If you feel you would like to be involved in our study, please send the consent form back using the pre-paid envelope provided.

Contact and further information: If you want any further information about this particular study, you can contact the researcher team.

Abdulrhman Alrowily
Phone: [redacted]
Email: [redacted]
Dr Vibhu Paudyal
Phone: [redacted]
Email: [redacted]

For further questions or complaints, please contact the Head of Research Governance and Ethics at UoB:

Dr. Birgit Whitman,

Email: researchgovernance@contacts.bham.ac.uk

Appendices 2.9 (Chapter 2 and Chapter 8)

Patients Information Sheet Form

MENOAC
MEDICATION ERRORS ASSOCIATED WITH NON-VITAMIN K ORAL ANTICOAGULANTS IN ADULT PATIENTS

Patients' Participant Information Leaflet: interview

Research project title: Medication Errors Associated with non-vitamin K antagonist oral anticoagulants In Adult Patients (MENOACs): A Qualitative Study

Dear Participant,

My name is Abdulrhman Alrowily. I am undertaking a PhD study at the University of Birmingham on on the Medication Errors Associated with non-vitamin K antagonist oral anticoagulants In Adult Patients. Thank you for showing an interest in our study. In this study we would like to explore your views on the causes and contributory factors and natures of Medication Errors (MEs) Associated with non-vitamin K antagonist oral anticoagulants (NOACs) In Adult Patients. Here are some information below on the study. Please do not hesitate to contact us using details provided overleaf.

Who is organising the research?

The project is being conducted as part of my PhD studies funded by the Saudi Arabian cultural bureau. The study is being managed by University of Birmingham.

Who can take part?

We are looking for individuals who fulfil the following criteria:

- Aged ≥18
- Taking any drugs called new oral anticoagulants which is mean newer blood thinner agent designed to reduce the chance of blood clots forming such as: Dabigatran, rivaroxaban, Apixaban and Edoxaban

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What does participation involve?

Participation in this study will only involve taking part in an interview, and that should not last more than 45 minute. The interviews will be conducted by the researcher and they will take place at Hospital .

At the day of the interview, you will be asked to complete a short anonymous questionnaire (demographic questionnaire; this will take around 5 minutes). This questionnaire is intended to collect your demographic data including your age, employment status, current medication etc. Before the interview begin, we will ask for your permission to record the interview.

Do I have to take part?

No. Participation in this study is voluntary and you may withdraw at any time. If you change your mind after you have taken part, you can still withdraw at any time without given any reason. We will destroy all data, recording and your consent forms. To inform us about your change of mind after the interview, simply let the researchers on site know if they are available or by calling Abdulrhman Alrowily on 07401823717 or through email axa1320@student.bham.ac.uk within 14 days of the interview. Alternatively, you could also phone your GP practice or pharmacy from where you were asked to take part. Your relationship with the practice or the researcher won't be affected by decision to withdraw your contribution. If at any point during interview you feel uncomfortable or unable to continue, the interview will be ceased immediately.

How do I benefit from participation?

By sharing your thoughts and experiences with us, you will be helping our research team (MENOACs) and University of Birmingham to better understand the possible causes and contributory factors of medication errors in people taking NOACs medications in the Saudi Arabia.

What are the possible risks and disadvantages of taking part in the study?

We do not believe that there are risks involved in taking part in the study. We think this should take about 45 minutes in total. If you have any concerns about the study or some points were unclear in the leaflet, please discuss any concerns with a member of the research team in the first instance.

Will my taking part in the study be kept confidential?

Yes, you will be asked to complete online eligibility questionnaire. If you were eligible to participate in the study, we will be collecting some personal data such as contact details for tracking purposes. All your data records cannot be traced back to you as you will be given unidentifiable study ID, which it will be known only for the research team. We will not share your data with any third party. Even If you did not fulfil the criteria your records will be destroyed appropriately; according to the University Data Protection Act 2018. We will not share your data with any third party.

What happens to my information?

Non identifiable paper-based data will be stored in a locked filling cabinet in the primary researcher's office. You will be assigned a unique study ID and research data will be stored using this unique ID number, so data will only be identified by this code and their personal information will not be used so that no one will be able to identify you.

Non identifiable electronic-based data will be stored on a password protected computer for analysis purposes located at the University of Birmingham. Data will only be accessed by the primary researcher and the members of the research team. In line with the University's guidelines on records management, research data will be retained intact for a period of 10 years from the date of collection.

Your name will be deleted from the documents (informed consent and screening questionnaire) and you will be provided with unidentifiable study ID. Other identifiable data (e.g. contact details) that will provided as electronic form including recruitment tool, will be stored as encrypted file and stored in a UoB computer, which will be password protected and it's located at the university and hence the data will be stored securely on the UoB network.

As for identifiable data that will obtained in paper documents (informed consent), will be stored only as paper-based data in a locked filling cabinet in the researcher's office located at the University of Birmingham. Access to them will be restricted to the primary researcher only. These data will be used only to contact you for the interviews. Documents containing identifiable data (consent forms, demographic questionnaires) will be stored separately from other documents in the chief investigator' office at the University. When necessary, representatives from UoB and regulatory authorities will be able to access the information for audit and compliance purposes.

In case you withdraw from the study at any time after the interview, your research data will be destroyed, and subsequently your data will not be included in any publications.

What will happen to the results of the research?

The full findings of the study may be published in a health care journal, as an academic thesis and presented at a conference. You will not be identified in any report.

Who has reviewed and approved this study?

This study was reviewed and approved by research ethics committees.

What do I do next?

If you feel you would like to be involved in our study, please send the consent form with your contact details using the prepaid envelope provided. You may contact Abdulrhman Alrowily on the following email: axa1320@student.bham.ac.uk. The researcher will call you or arrange to meet you at your convenient time for the interview.

Contact and further information: If you want any further information about this particular study, you can contact the researcher team.

Abdulrhman Alrowily
Phone: [redacted]
Email: [redacted]
Dr Vibhu Paudyal
Phone: [redacted]

Email: [redacted]

For further questions or complaints, please contact the Head of Research Governance and Ethics at UoB:

Dr Birgit Whitman,

Email: researchgovernance@contacts.bham.ac.uk

Saudi Food and Drug Authority Data Collection Request

Abdulrhman Alrowily (PhD Pharmacy FT Non-Lab (B230))

From: NPC.Drug@sfda.gov.sa
Sent: 01 October 2020 07:10
To: Abdulrhman Alrowily (PhD Pharmacy FT Non-Lab (B230))
Cc: [redacted]
Subject: استخراج بيانات لغرض بحثي خارجي
Attachments: ME Reports.xlsx; (DOACs) AEs.xlsx

عزيزي الباحث
تحية طيبة ،،

إشارة الى طلبكم الحصول على البيانات الخاصة بالأعراض الجانبية والاخطاء الدوائية للمجموعة الدوائية drugs directly acting anticoagulants لغرض استخدامها في بحث علمي عليه تجدون في المرفقات البيانات المطلوبة.
للاطلاع والاحاطة ،،

الإدارة التنفيذية للتيقظ الدوائي
Pharmacovigilance Executive Directorate
+966112038222
npc.drug@sfda.gov.sa
K.S.A Riyadh - Hittaen Dist
Northern Ring Branch Road

الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority
الإدارة التنفيذية للتيقظ الدوائي
Pharmacovigilance Executive Directorate



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1