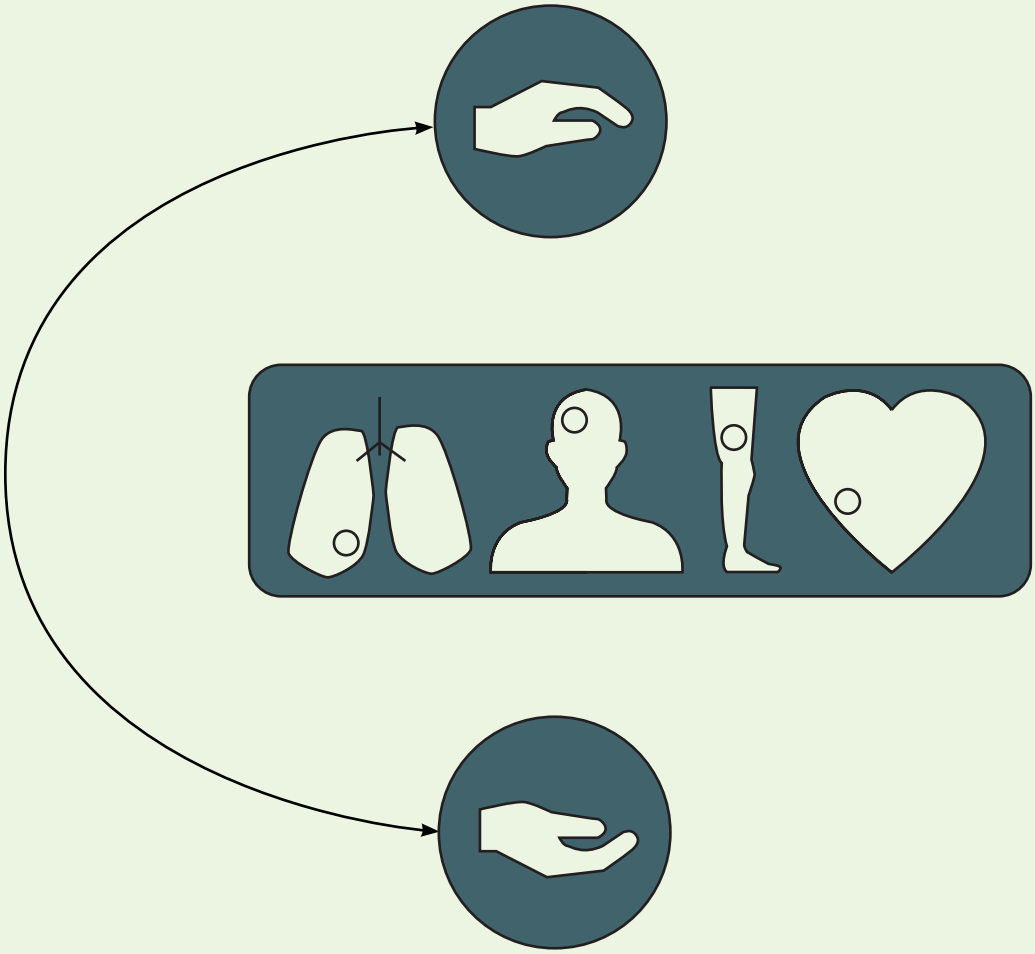
Safety of antithrombotic care in Dutch hospitals



Marco Moesker

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SAFETY OF ANTITHROMBOTIC CARE IN DUTCH HOSPITALS

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de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
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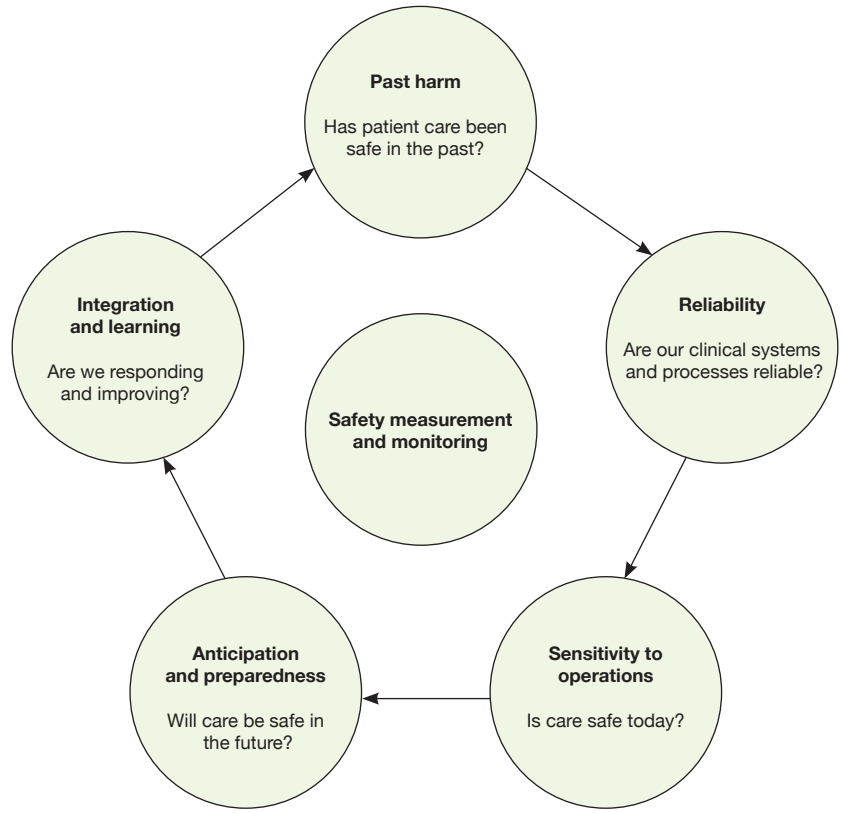
CHAPTER 1 General introduction



1.1 A delicate balance

Antithrombotic drugs belong to the most used medications in healthcare. In the Netherlands, a about one in ten inhabitants received antithrombotic drugs in 2011.[1, 2] However, antithrombotic drug use is not risk free.

Antithrombotic drugs act on the physiological process, known as haemostasis, responsible for managing the formation of blood clots in case of injury. Under normal conditions within the human body, haemostasis maintains a balance between clot formation and clot solvation (Figure 1.11, a).[3] When this delicate balance is disturbed, patients are exposed to increased risks for thrombotic and/or bleeding events such as pulmonary emboli or cerebral haemorrhaging (Figure 1.11, b and c). Maintaining this balance within safe boundaries is therefore of utmost importance to prevent comorbidity and mortality.

Antithrombotic drugs are typically used in case of a pro coagulant imbalance caused by underlying pathologies such as atrial fibrillation or venous thromboembolism. The drugs mitigate the risk for a thrombotic complication at the cost of a small increase in the risk for a bleeding complication. Often, this trade-off is clear cut and favours antithrombotic use. However, if the dosage is too high or certain comorbidities are not recognized this trade-off can quickly become a relevant risk. If this is not recognized and acted upon in time, adverse events (AE) can occur.

In the past two decades, reports of antithrombotic drug related adverse events in Dutch hospitals became more prevalent and have resulted in increased awareness for antithrombotic drug safety. At the same time the exact magnitude of this possible threat to patient safety is still unknown due to limited availability of empirical evidence.

This thesis aims to reduce this gap by systematically measure the safety of antithrombotic care provided in Dutch hospitals. Before introducing the researchquestions and providing the outline of this thesis, several general concepts regarding patient safety and quality of care will be introduced and a general introduction regarding antithrombotic care will be provided.

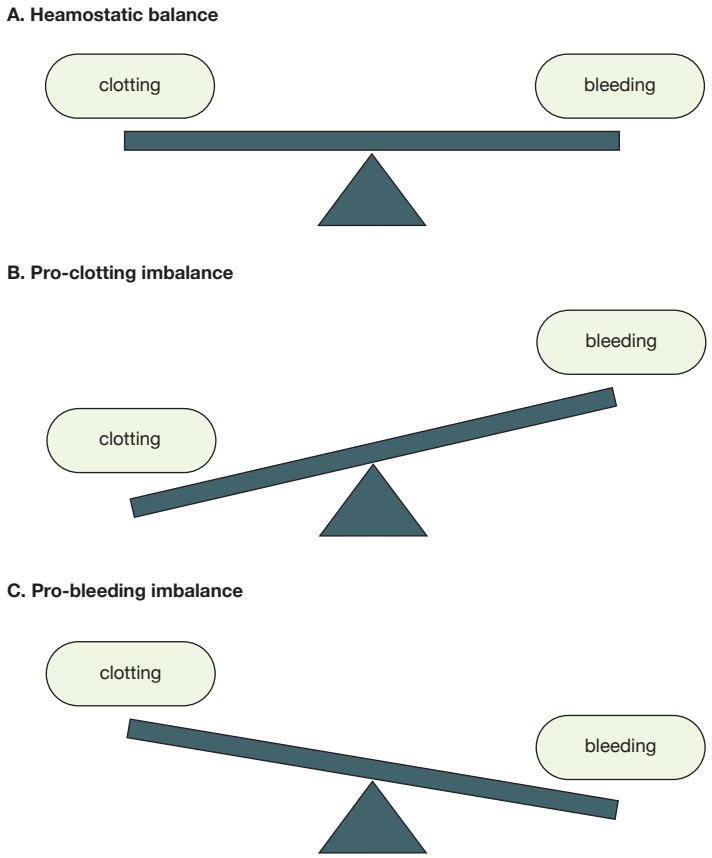


Figure 1.11. Graphical representation of haemostatic balance (a) and imbalanced haemostatic states i.e., pro-clotting (b) and pro-bleeding (c) states.

1.2 Adverse events in healthcare

An AE is defined in literature as “an unintended injury that results in temporary or permanent disability, death or prolonged hospital stay and that is caused by health care management rather than by the patient’s underlying disease process.”[4] The golden standard to reliably study AEs in healthcare is by performing a patient record review. Following on the publication: “To err is human” by the institute of Medicine in 2000, which referenced a comprehensive patient record review study called the Harvard Medical Practice Study, many countries followed this example and started measuring patient safety using this method.[5, 6]

This initial study reported AEs in 3.7% of hospitalized patients, where 27.6% of these were classified as caused due to negligence.[6] More recent studies report AE incidences of 8.4% to 12.3% with preventability rates from 30% up to 70%.[7-13]

In the Netherlands repeated nationwide AE record review studies have been perfor-

med every four years since 2004. Potentially preventable in-hospital deaths decreased from 4.1% in 2004 to 3.1% in 2015/2016.[14-17] The earlier editions of these AE monitors were the starting point for initiating a nationwide patient safety campaign aiming to reduce the number of AEs in Dutch hospitals. This campaign titled: “Prevent harm, work safely” ran from 2008 until 2012.[18] This programme proliferated the implementation of safety management systems in hospitals (VMS).

The effects of this national patient safety programme were evaluated by comparing AEs before and after. Overall, AE rates remained unchanged between 2008 and 2012. However, the proportion of preventable AEs reduced by 30% during the same period. Furthermore, improvement was observed in several specific populations targeted by the patient safety programme themes such as elderly and the surgical population.[19, 20]

Regardless of these encouraging results, new areas for improvements were advocated for after the publication of the third national AE study in 2011/2012. One of these areas was the use of antithrombotic drugs in hospitals.[16]

1.2.1 Antithrombotic related adverse events.

Referring back to the first national AE study in the Netherlands in 2004, antithrombotic drugs were commonly mentioned in the AE summaries that made up the appendix of the report.[14] However, they were not aggregated and reported on separately. In the two subsequent reports, attention for the potential role of antithrombotic drugs in AEs grew. First, in 2008 recommendations advocated to increase the awareness for the anticoagulation intensity and dosing in general and specifically during perioperative processes.[15]

Then, in 2011/2012 the AE report explicitly quantified AEs that involved antithrombotic drugs for the first time. Relative to all medication related AEs, anticoagulants and antiplatelets were involved in 21.0%. Furthermore, 32.0% of the anticoagulant related AEs were potentially preventable.[16] Henceforth, the 2011/2012 report recommended to explore if anticoagulation should be targeted individually as a future national patient safety programme theme. Up until then, antithrombotic drug use had not been targeted specifically by the national patient safety programme (VMS).[18]

Internationally, antithrombotic related adverse events have been studied with different methodologies. Although this hampers comparison, antithrombotic drugs are consistently identified as drugs with considerable risk of AE in European countries such as the United Kingdom, Spain, France, Swiss, Belgium and Denmark.[21-26]

In the United States, the Agency for Healthcare Research and Quality (AHRQ) was able to report longitudinal development of the involvement of antithrombotic drugs in the occurrence of hospital acquired conditions (HACs) using a large nationwide database.

In 2014 per 1000 discharges 16,07 (HACs) were due to antithrombotic drugs. Relative to all medication related HACs this was just under 50%. Preliminary figures from 2017 indicate a reduction to 9.14 antithrombotic related HACs per 1000 discharges and a proportion of just over 37% relative to all medication related HACs. [27]

Details regarding the aetiology and circumstances of AEs involving antithrombotic drugs are often unavailable in literature. This limits these studies’ value to signalling a threat to patient safety. Information on how to deal with this threat is specifically of value when designing interventions aimed to increase patient safety.

Nevertheless, patient safety regarding anticoagulant therapy gained national attention in some countries. In the UK a patient safety alert was broadcasted in 2007 by the national patient safety agency of the NHS.[28] The alert listed nine recommendations to be implemented by NHS and independent healthcare institutions in 2008. Recommendations included knowledge dissemination, procedure documentation, auditing, anticoagulant intensity

monitoring, awareness of co-medication and standardization. In 2018 the recommendations were updated to be applicable for newly marketed anticoagulants too.

Similarly, in the US the Joint Commission accrediting organisation instituted a National Patient Safety Goal regarding anticoagulant therapy to be effective from July 1, 2019, for Joint Commission accredited organizations. The patient safety goals’ focus lies in the implementation of guidelines for a selection of anticoagulant therapy topics that are very similar to the NHS patient safety alert.[29] The Joint Commission has explained her focus towards anticoagulant safety as a response to literature findings that anticoagulant related adverse drug events increased and prescription errors involving anticoagulants are a common cause.[30-33]

1.3 Antithrombotic treatment

The treatment of thrombosis can roughly be divided in treatments targeting venous thrombosis or arterial thrombosis (Figure 1.31).

1.3.1 Venous thrombosis

Venous thrombi are mostly formed in the slow flowing blood of large veins in the legs.[34] The underlying physiology of how such thrombi are formed was described for the first time by the nineteenth-century scientist Rudolf Virchow. Virchow described three factors of influence. 1) Damage to the vessel wall can alter the dynamic of the blood flow and present a vessel wall site at which a thrombi can start forming.[35] 2) Venous stasis is a state in which blood flow is reduced. It is thought that thrombi are formed more easily in slower flowing blood. Stasis occurs in patients who for example are bedridden or undergo surgery.[35] 3) A hypercoagulable state can be defined as the tendency of blood to clot as a result of a variety of prothrombotic factors such as thrombophilia’s, increasing age, smoking, obesity, pregnancy, oral contraceptive use, metabolic syndrome, cancer, long distance travel, immobility, surgery and trauma.[36, 37]

These three factors, commonly referred to as Virchow’s Triad, contribute to the initiation of the coagulation cascade. The coagulation cascade involves a complex set of chain reactions involving around 30 different proteins, known as coagulation factors, reacting with each other.[38] This reaction results in the conversion of soluble fibrinogen in to insoluble strands of fibrin that captures blood cells to form a thrombus. Thrombi that are formed in veins are rich in fibrin and trapped red blood cells and hence are often called red clots.

A pathological manifestation resulting from venous thrombi is deep venous thrombosis (DVT), recognizable as redness, pain and swelling of the leg. A serious and potential lethal complication of DVT occurs when (part of) the thrombus is dislodged and carried away in the blood stream. Often these thrombi get stuck in pulmonary arteries causing a pulmonary embolism.

1.3.2 Arterial thrombosis

Arterial thrombosis is primarily triggered by the rupture of an atherosclerotic plaque that has developed over time due to the accumulation of lipids in the artery wall.[34] Common sites of atherosclerotic plaques are the coronary arteries or the main arteries leading up to the brain. After the rupture, platelets are rapidly recruited to the site of injury to form a primary haemostatic plug. Hereafter specific receptors of the platelets become activated and stimulate additional binding of more platelets (platelet aggregation) resulting in

rapid growth of the thrombus.[34] Because the coagulation cascade also operates in arterial thrombosis, fibrin strands are formed, further strengthening the thrombus. Since arterial thrombi are rich in platelets they are often referred to as white clots.

Arterial thrombosis is the cause of common arterial pathologies such as myocardial infarction or ischaemic cerebral stroke. Both are lethal conditions resulting from the (partial) blockage of oxygen rich blood flows to downstream heart or brain tissue.

1.3.3 Treatments

The different composition of venous and arterial thrombi is reflected by different antithrombotic therapies. In broad terms, venous thrombosis is treated with drugs targeting coagulation cascade proteins involved in fibrin formation. These drugs are known as anticoagulants. Arterial thrombosis is treated with drugs that target platelets (Figure 1.31). They aim to inhibit platelet aggregation and hence are referred to as platelet inhibitors or simply antiplatelets. A third category used in the acute treatment of both kinds of thrombosis are called thrombolytics. They are used for dissolving formed thrombi but will not be discussed in detail in this thesis.

Type of thrombosis	Thrombus characteristics	Common pathologies	Antithrombotic treatment
Venous	Fibrin rich	- Deep vein thrombosis - Pulmonary embolism	Anticoagulants: - Vitamin K antagonist - Heparins
Arterial	Platelet rich	- Myocardial infarction - Ischaemic stroke	Platelet inhibitors: - Aspirin (acetylsalicylic acic) - $P2Y_{12}$ inhibitor

Figure 1.31. Rough distinction between venous and arterial thrombosis, characteristics, pathologies, and treatments.

1.3.3.1 Anticoagulants

Anticoagulants interfere with the coagulation cascade and prevent or limit fibrin strands from forming. Traditional anticoagulants such as heparin and a predecessor of warfarin were discovered almost a century ago and have been used effectively for preventing clot formation since the 1940s.[39] Both these drugs indirectly inhibit several coagulation factors.[40] Nowadays warfarin, together with other anticoagulants such as acenocoumarol and phenprocoumon are classified as vitamin k antagonists (VKAs). VKAs require careful monitoring of the anticoagulation intensity and subsequent dose adjustments to remain within a safe therapeutic range.

From the 1980s onwards the introduction of low-molecular weight heparins (LMWHs), which have the advantage of a more predictable dose response curve, limited the need for intensity monitoring where otherwise unfractionated heparin (UFH) would be used. [41, 42] Common LMWHs are dalteparin, nadroparin and enoxaparin and are, just as UFH, administered parenterally.

More recently, novel oral alternatives to VKAs have become available. They are most referred to as novel or direct oral anticoagulants (NOACs or DOACs). These anticoagulants

differ from VKAs and heparins in that they directly inhibit coagulations factors involved in the coagulation cascade. Comparable with LMWHs, DOACs have more predictable pharmacokinetics and hence require less frequent anticoagulant intensity monitoring.[43]

1.3.3.2 Platelet inhibitors

Platelet inhibitors interact with platelets and can mitigate the aggregation of platelets. They are especially prescribed for primary or secondary prevention of arterial thrombotic events such as myocardial infarction or ischaemic stroke.

Originally extracted from willow trees in ancient times to treat pain and fever, aspirin is nowadays a well-known platelet inhibitor that is still widely used.[44] Aspirin prevents platelet aggregation by irreversibly blocking the COX-1 enzyme inside the platelets.[45] This is however not the only way platelets can be activated, requiring additional agents to establish a full antithrombotic function.[46] To achieve this, agents such as clopidogrel, prasugrel and ticagrelor are available since the late 1990s. These agents inhibit the $P2Y_{12}$ receptors of platelets which plays a central role in platelet aggregation and thrombus formation.[47] Hence, these agents are called $P2Y_{12}$ inhibitors. The combined use of aspirin and a $P2Y_{12}$ inhibitor is referred to as dual antiplatelet therapy (DAPT) which is standard treatment for patients after acute coronary syndromes with medical treatment or percutaneous coronary intervention.[46]

Inherent to the antithrombotic effects, antithrombotic drugs increase the risk for bleeding complications. Often this risk does not outweigh the benefits of the antithrombotic effect and thrombosis prevention. However, the balance between thrombotic and bleeding risk is not always as unambiguous. Clinical guidelines can be of aid in these situations and promote a well-informed decision.

1.4 Guidelines for antithrombotic care

The medical management of patients with antithrombotics is described in clinical practice guidelines (CPGs). These evidence based documents include evidence based recommendations for patient care.[48] CPGs provide clinicians with means to weigh the risks and benefits for particular treatments based on the individual characteristics of their patients. This allows the healthcare provider to select the most appropriate care for an individual patient based on the literature and his or her preference.[48]

Several CPGs for antithrombotic care are relevant for this thesis. First of all, the 'Antithrombotic Therapy and Prevention of Thrombosis, 9th edition' from the American College of Chest Physicians[49] (ACCP) provides recommendations for a plethora of clinical scenarios involving antithrombotic care such as (perioperative) anticoagulant management, prevention, diagnosis, and therapy of VTE and therapy for cardiovascular diseases. The ACCP aims to update and publish this guideline every four year. The 2016 update though, was limited several specific topics.[50]

In the Netherlands the ACCP antithrombotic care guidelines serve as an important basis for adapting the recommendations in a Dutch context and formulate a national CPG. Until 2016 the 'Guideline for Diagnostics, Prevention and Treatment of Venous Thromboembolism and Secondary Prevention of Arterial Thrombosis' released by the former Dutch Quality Institute for Healthcare [51] (CBO) in 2008 was the leading guideline regarding

antithrombotic care. However, this guideline was an adaption from two ACCP versions ago, the 7th ed. published in 2004. Hence, it can be expected to have at least partially reflected outdated evidence in the final years leading up to its replacement in early 2016. At this time a renewed Dutch guideline titled: 'Guideline Antithrombotic Policy' was published and endorsed to guide antithrombotic use in the Netherlands.[52]

1.4.1 Implementation and adherence of antithrombotic guidelines

Since CPGs synthesize large amounts of evidence in one comprehensive body of evidence, they reduce the need of individual clinicians to keep up with all individual publications regarding their specialisation. However, presenting such bodies of evidence does not spontaneously change clinical practice accordingly. Even if clinicians are aware and willing to implement CPG recommendations, changing well established patterns of care is difficult.[53] Hence, to successfully change clinical practice and improve patient care, implementation of CGPs entails much more than just passive distribution of the CPG documentation. Often, barriers to a successful implementation should be identified and tackled.

Due to these challenges, heterogeneous levels of CPG adoption in practice can be observed. This can result in unwanted practice variation between or even within hospitals. Measuring guideline adherence can quantify guideline implementation and practice variation. Expressed as the percentage of patients receiving guideline recommended care, this is a common reported metric.

Two specific themes in antithrombotic care that gained attention internationally regarding guideline implementation and adherence are:

I. Venous thromboembolism prophylaxis
This entails the prevention of VTE in hospitalized patients by administering pharmacologic or mechanical interventions known to reduce the risk of VTE formation and pulmonary embolism.

II. Perioperative management of antithrombotic drugs.
This entails the management of (long term) antithrombotic drug use in patients requiring a surgical procedure.

The first theme practically involves every patient admitted to the hospital. Many of the risk factors for VTE are related to hospitalization such as surgery, trauma, immobilisation, cancer, and inflammation. Since pulmonary embolism remains the leading cause of in-hospital death which can be prevented, insufficient implementation of VTE prophylaxis can have a significant effect on preventable adverse event rates.[54] A large scale multi-national study evaluating VTE prophylaxis use, reported guideline adherent VTE prophylaxis being used in 39.5% and 58.5% of at risk non-surgical patients and at risk surgical patients respectively.[55]

The second theme is only applicable to a relatively small subset of patients using antithrombotic drugs, i.e., those that require surgery. However, these patients provide clinicians with particularly challenging scenarios. That is, what to do with the antithrombotic drug(s) in question? Quitting likely reduces the risk of a bleeding complication but reintroduces the risk for a thrombotic event. Hence, CPGs adopted specific recommendations and means for risk stratification to support the decision making in these clinical situations. The implementation of these recommendations in practice has not been evaluated as extensively as for VTE prophylaxis.

1.5 Safety measurement and monitoring

As stated in the first paragraph, this thesis aims to add insights to the safety of antithrombotic care provided in Dutch hospitals. Yet, what is exactly referred to when defining safety of healthcare organizations? Referring to the calls to action from the NHS and Joint Commission, the amount and frequency of harm reaching the patient was a leading measure when issuing the calls. These two examples clearly demonstrate the responsiveness of a healthcare system to unsatisfying safety within its organizations providing antithrombotic care.

According to Vincent et al. (2014) this assessment of past harm reaching the patient is only the first of five dimensions when evaluating safety in healthcare organizations.[56] Subsequent dimensions in his safety measurement and monitoring framework involve reliability, sensitivity to operations, anticipation and preparedness and integration and learning (Figure 1.51). To obtain a holistic impression, these remaining dimensions should also be taken into account when evaluating the safety of antithrombotic care in Dutch hospitals. The remaining dimensions are now briefly introduced.

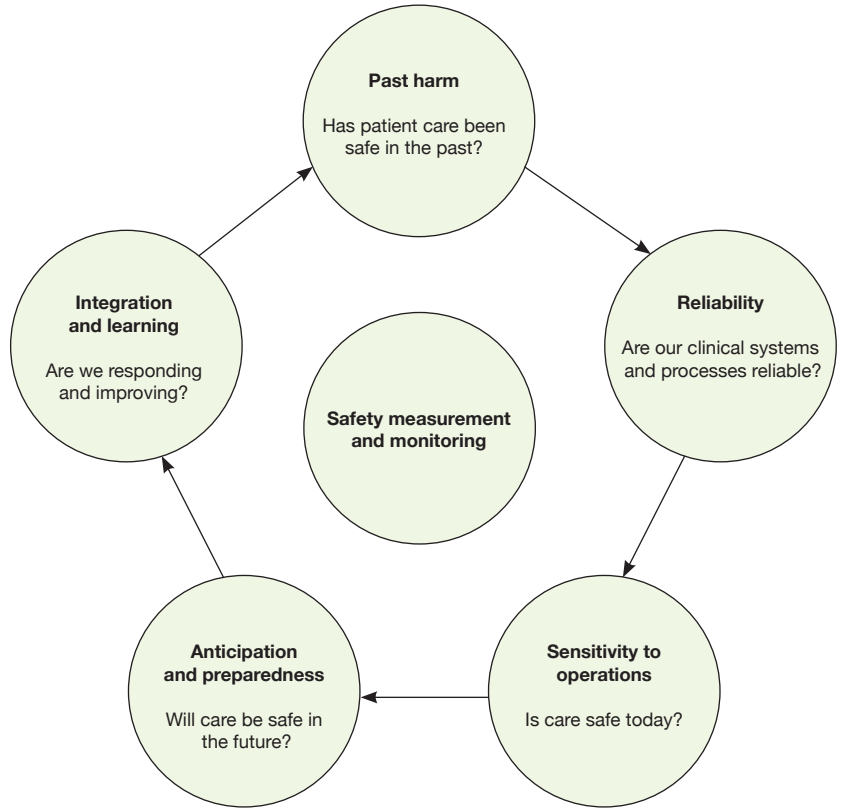


Figure 1.51. The safety measurement and monitoring framework.[56]

1.5.1 Reliability

The reliability dimension is defined as the failure-free operation over time. Vincent et al. (2014) argue that the concept of reliability is applicable to relatively standardised aspects in healthcare. For example, applying hand hygiene, ordering diagnostic tests, or administering antibiotics preoperatively.[56] Thinking in terms of reliability of a certain process is relatively uncommon in healthcare organizations compared with e.g., aviation or other safety critical sectors. Some parallels, however, can be observed in the surgical theatre, where the use of the surgical safety checklist was inspired by aviation checklist usage.[57, 58]

1.5.2 Sensitivity to operations

The sensitivity to operations reflects the healthcare organizations' ability to cope with day-to-day variation and to what extent this influences safety.[56] E.g., how does a sudden rise of patient admissions or an increased sick leave of personnel affect the safety? Mechanisms that support the sensitivity to operations, include safety walk-rounds, briefings, and informal conversations. Furthermore, interviewing patients, to obtain their perspective of perceived day to day safety can be a vital source of information.[56] The concept of sensitivity to operations of a healthcare organisation shows similarities with the new patient safety-II approach.[59] Whereas the patient safety-I approach gains insights by studying what went wrong, and consequently tries to prevent the error from happening again, the patient safety-II approach aims to study and learn from performance that usually goes right. The safety-I and safety-II concepts are further introduced in paragraph 1.6.

1.5.3 Anticipation and preparedness

The anticipation and preparedness dimension is conceptually similar to its preceding dimension, but it applies to a broader horizon reaching into the future. It requires the organization to anticipate on future events and situations that can have a negative impact on safety and will need acting on.

1.5.4 Integration and learning

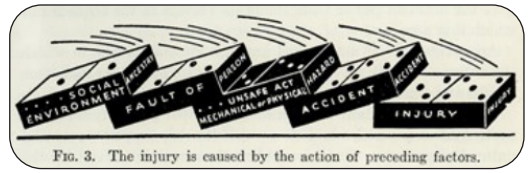
Lastly the integration and learning dimension covers the healthcare organizations' strategy to synthesize and analyse all the various information sources regarding safety and to what extent findings are incorporated in practice. Possible data sources might originate from efforts undertaken regarding any previous dimensions and include incident reports, patient safety indicators, complaint, claims, audits, observations and conversations with patients, families, and staff.[56]

1.6 Safety-I and safety-II

In this thesis, the methods are predominantly applied from a safety-I perspective. However, as introduced earlier, Vincent's third dimension (sensitivity to operations) provides the opportunity to apply methods from a safety-II perspective.

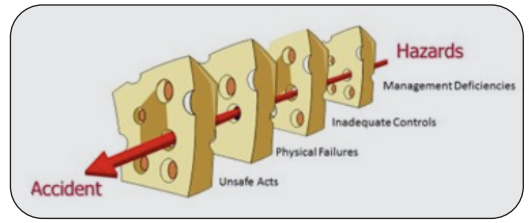
The safety-I perspective is mostly based on the mechanism that adverse events happen because something went wrong, due to a specific cause and once this cause is found it can be taken care of to prevent the event from occurring again. This causality concept is applied in models such as root cause analysis and the domino model (Figure 1.61 a).[59, 60] By assuming a simple linear relationship between cause and effect, analysts try to re-

verse engineer the occurrence of adverse events.[59] With increasing complexity of our socio-technical systems over the last few decades, also in healthcare, this simple linear thinking will not always suffice.[59] Reason's "Swiss Cheese" Model, while still a linear model, explains adverse events as the result of a combination of active failures and latent conditions, allowing for more complexity (Figure 1.61 b).[61]



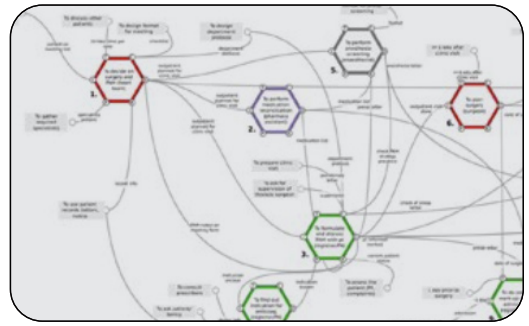
A. Linear models

The domino model of accident causation, as depicted by H. Heinrich in the 1950 edition of his book Industrial Accident Prevention: A Scientific Approach



B. Complex Linear models

James Reason's "Swiss Cheese" Model of Accident Causation (1990)



C. Non-linear models

Hollnagel's Functional Resonance Analysis Method (FRAM) model (2012)

Figure 1.61 Progression of models used in safety research

Both the Domino and Swiss Cheese Models are built on the assumption that the systems in which they are applied are decomposable into meaningful constituent parts which can either be functioning or failing. This decomposable bimodal approach should be able to precisely locate where a system failed.[59] However, in many processes observed variability is hard to explain in a bimodal manner because of both human and organizational involvement. In this case, non-linear models, such as Hollnagel's FRAM model to analyse processes (Figure 1.61 c) might be more suitable to explain the performance in a multimodal manner.[62] FRAM models are increasingly used in safety-II approaches in healthcare. Safety-II embraces the idea that everyday performance is variable. In healthcare it is difficult to describe how work should be carried out in all possible situations, due to some level of unpredictability. As a result, performance adjustments and variability will always be observed, because healthcare personnel are able to (and should) adjust their work to continuously changing circumstances. In safety-II, it is acknowledged that both acceptable outcomes and adverse events emerge from a common basis, i.e. these everyday perfor-

mance adjustments.[59] By studying why care usually goes right, insights are obtained that can explain why occasionally something goes wrong.[59]

Because of the complex nature of antithrombotic care and associated risks, we extended our research by a process analysis study based on safety-II principles.

1.7 Research questions and Thesis outline

Although antithrombotic drugs are used widely and increasingly, little is known about the quality and safety of antithrombotic care. ARAE rates and circumstances are unknown as well as the reliability and daily variations of antithrombotic care processes. Hence, this thesis addresses the safety of antithrombotic care in a broad perspective to inform daily practice, policy makers and future research. We focussed on the two specific clinical antithrombotic processes introduced earlier i.e.: venous thromboembolism prophylaxis and perioperative management of antithrombotic drugs. Our research questions can be categorized within the first three dimensions of the safety measurement and monitoring framework as depicted in Figure 1.51:

Past harm: has patient care been safe in the past?

1) How common are (preventable) antithrombotic related adverse events in Dutch hospitals and what are the circumstances in which they occur?

Corresponding with the first dimension in the safety measurement and monitor framework, the extent of past harm related to antithrombotic related adverse events is studied in **chapter 2**. This chapter describes the results of a post-hoc analysis of 10.917 patient records included in the three most recent national adverse event studies from 2008, 2011/2012 and 2015/2016. Patient records with AEs identified by nurses and physicians, were subjected to further analysis to estimate the incidence of antithrombotic related AEs. In order to explore the circumstances of unsafe care, antithrombotic type, the clinical context, and care delivery factors regarding the identified ARAEs were analysed to see if patterns could be distinguished that can inform future interventions.

Reliability: are our clinical systems and processes reliable?

2) How reliable is perioperative antithrombotic management and administering VTE prophylaxis in Dutch hospitals?
2a) Can we observe variation between hospitals?
2b) Can predictors of unreliable care be identified?

The reliability of systems and processes regarding antithrombotic care, i.e., the safety measurement and monitoring framework's second dimension, is evaluated in **chapters 3 and 4.** In these chapters the reliability is operationalised as the adherence of clinical practice with relevant CPG recommendations. **Chapter 3** studies the reliability of perioperative anticoagulant management in 13 Dutch hospitals. Seven process steps were identified from CPG recommendations and adherence was measured using patient record reviews. Comparative analyses between individual hospitals' reliability were performed to help answer

question 2a; can we observe variation between hospitals?

Chapter 4 zooms in on one step in the perioperative anticoagulant management process: the postoperative use of bridging anticoagulation. Using predictive analysis on patient and provider characteristics, predictors for postoperative bridging and non-compliant postoperative bridging were identified to help answer question 2b; can predictors of unreliable care be identified?

Chapter 5 describes the intrinsic implementability characteristics of recommendations from two major CPGs regarding VTE prophylaxis. Using a panel of experts and the guideline implementability appraisal instrument (GLIA)[63], barriers and facilitators for implementation are identified which can aid interpreting the reliability of antithrombotic processes as studied in the previous 2 chapters.

Sensitivity to operations: is care safe today?

3) How is perioperative antithrombotic management conducted in everyday practice (work-as-done) and how does this relate to predefined procedures (work-as-imagined)?

In **chapter 6** a novel analysis method, the functional resonance analysis method (FRAM), is used to investigate why everyday perioperative antithrombotic management usually goes right. This analysis was applied in an Australian and Dutch cardiothoracic surgery department. The analyses give insight in the day-to-day responsiveness of involved teams and allows to anticipate on vulnerabilities within the systems, corresponding with the third and fourth dimension within the safety measurement and monitoring framework.

Finally, in **chapter 7** the research findings are summarized, and the research questions will be answered. Furthermore, we will discuss the methodological considerations and give our future perspectives regarding quality improvement of antithrombotic care. To conclude we propose our recommendations for clinical practice, healthcare policy and further research.

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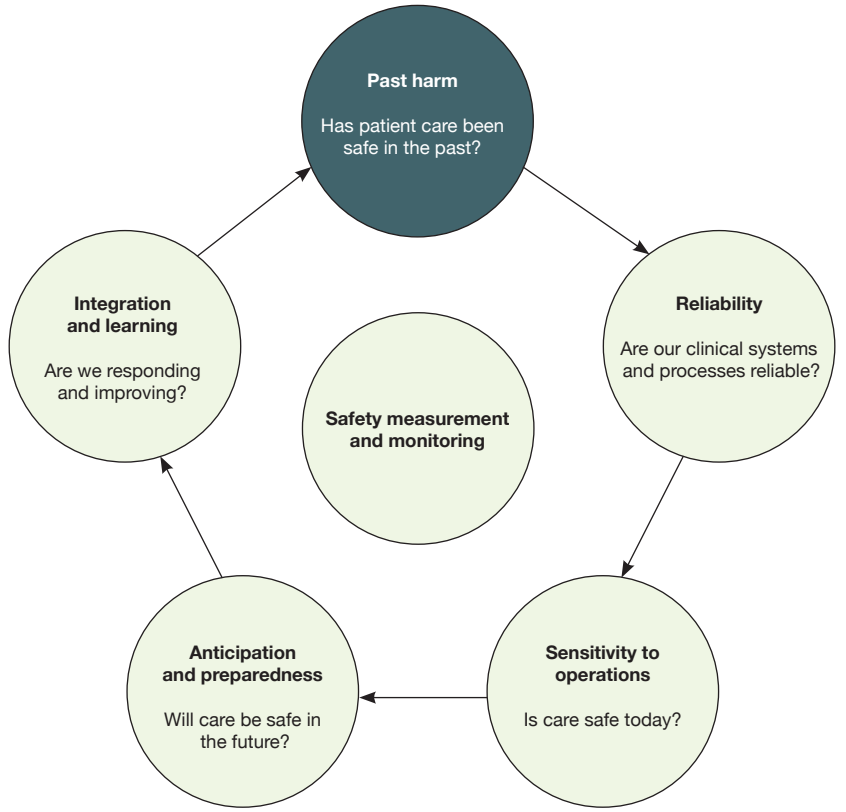
CHAPTER 2

Occurrence of antithrombotic related adverse events in hospitalized patients: incidence and clinical context between 2008 and 2016



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Abstract

Objectives

Antithrombotic drugs are consistently involved in medication-related adverse events (MRAEs) in hospitalized patients. We aimed to estimate the antithrombotic-related adverse event (ARAE) incidence between 2008 and 2016 and analyse their clinical context in hospitalized patients in The Netherlands.

Design and setting

A post-hoc analysis of three national studies, aimed at adverse event (AE) identification, was performed. Previously identified AEs were screened for antithrombotic involvement. Crude and multi-level, case-mix adjusted ARAE and MRAE incidences were calculated. Various contextual ARAE characteristics were analysed.

Results

ARAE incidence between 2008 and 2016 decreased significantly in in-hospital deceased patients from 1.20% (95% confidence interval (CI): 0.63–2.27%) in 2008 to 0.54% (95%CI: 0.27–1.11%) in 2015/2016 (p = 0.02). In discharged patients ARAE incidence remained stable. By comparison, overall MRAE incidence remained stable for both deceased and discharged patients. Most ARAEs involved Vitamin-K antagonists (VKAs). Preventable ARAEs occurred more during weekends and with increasing multidisciplinary involvement. Antiplatelet and combined antithrombotic use seemed to be increasingly involved in ARAEs over time.

Conclusions

ARAE incidence declined by 55% in deceased patients between 2008 and 2016. Opportunities for improving antithrombotic safety should target INR monitoring and care delivery aspects such as multidisciplinary involvement and weekend care. Future ARAE monitoring for the involvement of antiplatelet, combined antithrombotic and direct oral anticoagulant (DOAC) use is recommended.

2.1 Introduction

Antithrombotic drugs are widely used for the treatment and prevention of numerous cardiovascular conditions.[1, 2] Antithrombotic drugs include both anticoagulants (i.e., vitamin-k antagonists (VKA), direct oral anticoagulants (DOAC) and unfractionated (UFH) and low molecular weight heparin (LMWH) as well as antiplatelet agents (i.e., aspirin, clopidogrel). Additionally, double or even triple antithrombotic therapy with a combination of an anticoagulant and one or two antiplatelet agents is indicated for specific patient populations.[3, 4]

Antithrombotic therapy is not without risk. Concomitant to the antithrombotic effect of these agents is an increased risk for bleeding complications which can be fatal or result in severe comorbidity.[5-7] Therefore, efforts to safely use antithrombotic drugs include both thrombotic risk assessment as well as bleeding risk assessment to make the best-informed decisio.[8, 9] However, clinicians are challenged by a plethora, of circumstances complicating antithrombotic use. This includes narrow therapeutic windows requiring regular monitoring of anticoagulants such as VKA and UFH, dietary habits, comorbidities, drug-drug interactions and patient adherence, influencing the antithrombotic effect.[10, 11] Clinical activities requiring temporary interruption of antithrombotic therapy, such as invasive procedures, add to further complexity.[12]

Given this complexity, the use of antithrombotic agents increases patients' susceptibility to adverse events (AE). Over the past decades, antithrombotic drugs were consistently identified as drugs involved in medication-related adverse events (MRAEs).[13-15] However, highly variable study settings and definitions prevent a direct comparison of reported antithrombotic related adverse event (ARAE) incidence. ARAEs further increase comorbidity in an already vulnerable population or can result in patient death.[16-18] Besides the consequences for individual patients, ARAEs also merit attention from a healthcare budget point of view. Recently, a study estimated a 45% increase in hospital admission costs related to an ARAE.[19]

In an effort to reduce medication errors in general, several promising interventions such as computerized physician order entry systems and barcode technology have been implemented.[20, 21] However, a recent study focusing on antithrombotic drugs confirmed that ARAEs still occur regularly.[15]

In the Netherlands, special attention to in-hospital medication safety was embedded in the national Patient Safety program that took place from 2008–2012. While this program showed signs of a positive impact on patient safety, preventable adverse events related to medication did not decrease.[22] The effects of this program for anti-thrombotic care in relation to ARAEs is not known. Therefore, this study will investigate the occurrence of ARAEs in the hospitalized patient population over time using data from three large adverse event studies in the Netherlands. By studying the clinical context of ARAEs we aid the interpretation of ARAE aetiology.

Our aims were to (1) estimate the incidence of ARAEs in the hospitalized patient population from 2008 until 2016, (2) compare this with overall MRAE incidence and (3) quantitatively and qualitatively describe the clinical context of ARAEs. Additionally, longitudinal shifts in incidence and circumstances of ARAEs between 2008 and 2016 will be analysed.

2.2 Materials and Methods

2.2.1 Design and Setting

This study uses a post-hoc analysis of data from three large retrospective patient record review studies aimed at identifying AEs, including medication AEs, in Dutch hospitals. These studies were performed in 2008, 2011/2012 and 2015/2016 using the same standardized methodology.[22-24] These studies aimed to estimate the AE incidence on a national level. Therefore, the hospital and patient sampling was adjusted to be representative of the whole Dutch patient population. For the 2008 and 2011/2012 studies, a random sample of 20 hospitals was studied. In 2015/2016 a random sample of 19 hospitals was selected. The samples were stratified for type of hospital (university, tertiary teaching and general hospitals) and location. In 2008 and 2011/2012 200 admission records per hospital were randomly selected for review, 100 records of discharged patients, and 100 records of in-hospital deceased patients. The 2015/2016 study was limited to records of 150 in-hospital deceased patients per hospital. Within all studies, only one admission per patient was included. Psychiatric, obstetric and paediatric admissions under one year of age were excluded.

To summarize, AEs were identified in two phases. In phase one, trained nurse reviewers screened the records for triggers indicating the presence of AEs. If found, a trained medical specialist reviewer performed an in-depth review of the records in phase two. Patient records of both the index-hospital admission were reviewed as well as records of admissions within one year before and after the index admission. AEs were eligible for inclusion if they occurred during the index admission or if the AE was related with another admission in the same hospital within one year preceding the index admission. An AE was defined according to three criteria:

1. An unintended physical or mental injury
2. The injury resulted in prolongation of hospital stay, temporary or permanent disability or death
3. The injury was caused by healthcare management rather than the patient's underlying disease

The medical specialist followed a standardized procedure to determine the presence and preventability of AEs. Two 6-Point Likert scales were used for this. Likelihood scores greater or equal to 4 indicated a greater than 50% chance of AE presence and the AE being potentially preventable. The reliability of the AE and potential preventability assessment was ascertained by double reviewing 10% of the records in both phases.

All study protocols were approved by the ethical review board of the VU University Medical Center in Amsterdam (protocol numbers: 2005.146, 2009.130, 2016.282).

2.2.2 Identification of Antithrombotic Related Adverse Events

For the post-hoc analysis in the current study, all identified AEs from the previous studies were analysed for the involvement of medication and specifically antithrombotic drugs. AEs for which 'medication' was indicated as the main cause of the AE were classified as primary MRAE, whereas AEs for which 'medication' was indicated as a sub cause of the AE were classified as secondary MRAE.

Then, using free-text fields in the dataset, such as the medication name involved and the AE description and circumstances, one nurse researcher (M.J.M) identified the ARAEs. ARAEs included both AEs occurring due to the intake of antithrombotics and AEs due to wrongfully withholding antithrombotics.

After ARAE identification, the antithrombotic drugs involved were classified as: VKA,

UFH, LMWH, antiplatelet, DOAC or a combination. Other antithrombotic therapies, i.e., intravenous direct thrombin inhibitors and fondaparinux are less common in the Netherlands and were not captured. The ARAEs were then classified on the specific clinical situation in which the ARAE occurred. This was a data-driven classification based on open-text variables describing the ARAE. Categories included: Elevated international normalized ratios (INR), venous thromboembolism (VTE) prophylaxis, perioperative/periprocedural antithrombotic management, disputed antithrombotic indication, adverse drug reaction and patient related. A second nurse researcher (B.C.F.M.S) verified the ARAE classification. Discrepancies were discussed to reach consensus.

2.2.3 Outcomes

Our primary outcomes were the incidence of MRAEs and ARAEs within the deceased hospital population in the years 2008, 2011/2012 and 2015/2016 and within the discharged population in the years 2008 and 2011/2012. Additionally, the incidence of ARAEs among all patients exposed to antithrombotic drugs during admission was determined. This was limited to the 2015/2016 population due to unavailability of antithrombotic exposure status for all included patients in the 2008 and 2011/2012 samples.

Secondary outcomes include variables on ARAE level to describe the clinical context. These variables included the antithrombotic drug(s) used, the specific clinical situation, the ARAE type (bleeding event/thromboembolic event), the responsible medical speciality, number of medical specialities involved, admission department (surgical/non-surgical) and whether the ARAE originated during a weekend or holiday.

Supplementing this quantitative analysis of ARAE clinical context, we provide a qualitative summary of several ARAEs and discuss these in a narrative way.

2.2.4 Statistical Analyses

Descriptive characteristics were calculated separately for discharged and deceased patients for each study period. During the analyses, all proportions were weighted for hospital type to account for the overrepresentation of university hospitals in our samples. In our samples, about 20% of the hospitals were university hospitals whereas in reality this is about 10%. Therefore, we weighted our 20% back to the actual 10%.

Next, we calculated crude MRAE and ARAE incidence weighted for hospital type but not corrected for clustering on hospital level or differences in the patient mix between the years. Then, standardised ARAE and MRAE incidence adjusted for clustering at the hospital level was calculated using multilevel logistic regression analysis. A three-level structure was used: Patients were clustered in hospital departments that were clustered in hospitals. The outcome measures were if a patient experienced an MRAE or ARAE or not.

To correct for patient mix changes between the years of interest, terms were added to the model for sex, age, non-elective admission (yes/no), admission department (surgical/non-surgical) and invasive procedure (yes/no). All variables in the model were standardised to reference values for Dutch hospital admissions in the corresponding year. We performed Wald tests to assess whether differences exist after patient mix corrections in MRAE and ARAE incidence between the years.

For 2015/2016 only and using the same model structure, we calculated standardised adjusted ARAE incidence within the deceased patient population exposed to antithrombotic drugs. To estimate the risk of experiencing an ARAE for antithrombotic drugs used, adjusted odds ratios were calculated for different antithrombotic drugs used.

The clinical context of ARAEs was analysed by pooling all ARAEs. Therefore, additional weigh-

ting procedures were required to account for the oversampling of deceased patients. The samples were weighted back to the actual percentage of deceased patients in the corresponding years.

Lastly, changes over time for ARAE clinical context category, an antithrombotic drug used, and combined use of antithrombotic drugs were analysed and statistically tested.

For all analyses, a p-value less than 0.05 was considered significant. Multilevel analyses were performed in MLwiN version 3.00 (Centre for Multilevel Modelling, Bristol, UK). All other statistical analyses were performed in Stata version 14 (StataCorp, College Station, TX, USA).

2.3 Results

2.3.1 Study Population

In total, 10,917 admission records were included in the three study periods (Figure 1). Table 1 displays the population characteristics of the three study periods included. The most apparent changes over time in patient mix were found in the deceased population. Between 2008 and 2011/2012, patients' age increased (Mann-Whitney U; $p = 0.047$), length of stay decreased (Mann-Whitney U; $p < 0.001$), non-elective admissions were more prevalent ($\chi 2$; $p = 0.024$), and admission departments ($\chi 2$; $p < 0.001$) and main ICD-9 diagnoses ($\chi 2$; $p = 0.003$) changed. Between 2011/2012 and 2015/2016 the length of stay decreased further (Mann-Whitney U; $p < 0.001$), invasive procedures were less common ($\chi 2$; $p = 0.001$) and ICD-9 diagnoses changed ($\chi 2$; $p < 0.001$). Within the discharged population, only the length of stay reduced (Mann-Whitney U; $p < 0.001$) and the distribution of ICD-9 diagnoses changed between the study periods ($\chi 2$; $p = 0.011$).

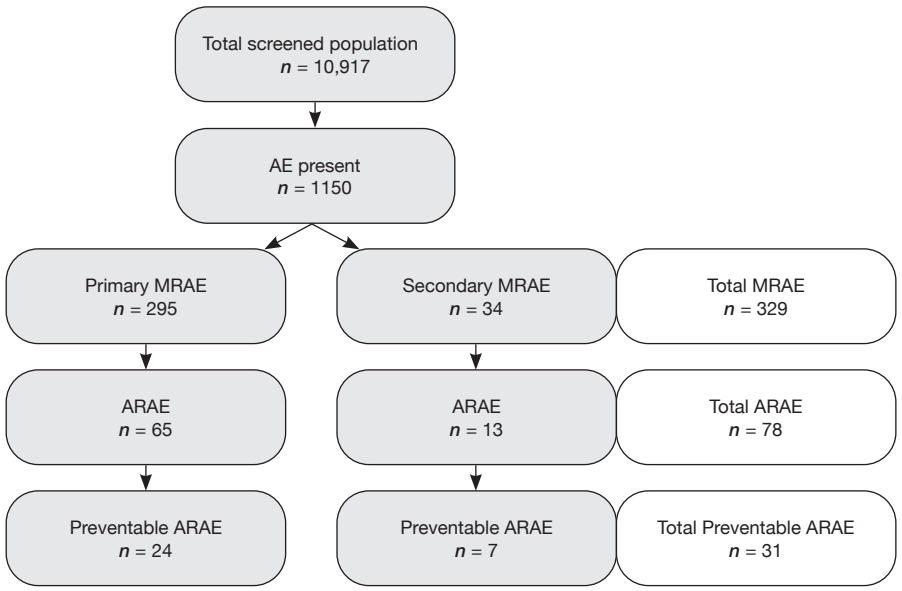


Figure 1. Overview of the total screened population and adverse events identified. MRAE: Medication related adverse event; AE: Adverse event; ARAE: Antithrombotic-related adverse event.

Table 1. Patient characteristics and adverse events per study period and discharge status.

Study Period and Discharge Status					
	Discharged		Deceased		
Hospital Characteristics	**2008**	**2011/2012**	**2008**	**2011/2012**	**2015/2016**
Number of admissions, *n*	2016	2023	2007	2025	2846
General hospital, *n* (%)	1013 (50.25)	794 (39.25)	1015 (50.57)	813 (40.15)	1197 (42.06)
Tertiary teaching hospital, *n* (%)	608 (30.16)	822 (40.63)	593 (29.55)	820 (40.49)	1052 (36.96)
University hospital, *n* (%)	395 (19.59)	407 (20.12)	399 (19.88)	392 (19.36)	597 (20.98)
	Discharged [a]		**Deceased** [a]		
Patient Characteristics	**2008**	**2011/2012**	**2008**	**2011/2012**	**2015/2016**
Male sex, %	49.69	50.09	53.26	52.12	53.27
Age (years), median (IQR)	62 (47–75)	63 (48–75)	77 (67–84)	77 (68–84) [b]	77 (68–85) [b]
1–65, %	56.08	55.44	22.84	21.13	19.80
66–79, %	28.29	28.87	37.13	37.23	36.39
80 and older, %	15.63	15.70	39.95	41.64	43.78
Length of stay (days): median (IQR)	4 (2–8)	3 (2–7) [b]	7 (3–14)	6 (2–13) [b]	4 (1–11) [b c]
Non-elective admission, %	52.44	53.36	86.21	88.50 [b]	88.64 [b]
Department of admission, %				[b d]	[b d]
Surgery	23.98	23.53	13.75	11.55	11.23
Cardiology	15.09	13.68	15.37	12.35	12.85
Internal medicine	17.98	17.62	29.41	29.36	31.59
Orthopaedics	11.57	11.62	1.50	1.38	1.10
Neurology	7.48	6.66	11.16	9.55	9.54
Lung diseases	5.75	6.52	13.33	15.26	12.87
Urology	5.34	5.36	0.87	1.32	0.86
Other	12.8	15.02	14.61	19.23	19.96
Underwent surgical procedure, %	45.48	45.17	20.52	19.04	15.07 [b c]
ICD 9 main diagnostic groups, %		[b d]		[b d]	[b c d]
Infection and parasitic diseases	1.40	3.37	3.31	5.44	4.90
Neoplasms	11.76	11.15	19.06	19.16	12.44
Endocrinic	2.17	2.42	2.61	1.25	1.17
Heart and vascular diseases	19.93	17.20	33.64	29.69	24.14
Respiratory diseases	8.24	8.54	15.2	13.52	15.49
Gastrointestinal diseases	10.87	9.97	7.19	7.34	6.55
Urogenital diseases	6.41	6.30	2.81	2.59	3.43

Signs and symptoms ill defined	6.33	5.31	4.89	4.44	5.02
Injury and poisoning	9.67	9.17	5.94	6.12	6.68
Other	22.48	21.29	4.91	5.00	3.68
Missing	0.74	5.30	0.45	5.46	16.5
Adverse event presence					
Adverse event present, *n* (%)	152 (7.57)	144 (6.92)	315 (15.60)	246 (11.93) [b]	293 (9.86) [b c]
MRAE present, *n* (%)	35 (1.76)	36 (1.72)	84 (4.08)	73 (3.62)	101 (3.44)
ARAE present, *n* (%)	8 (0.51)	9 (0.46)	28 (1.35)	16 (0.79)	17 (0.54) [b]

IQR Inter Quartile Range; ICD 9 International Statistical Classification of Diseases and Related Health Problems 9th edition; MRAE Medication Related Adverse Event; ARAE Antithrombotic Related Adverse Event; [a] Percentages are weighted for hospital type; [b] Significant change ($p < 0.05$) compared with 2008; [c] Significant change ($p < 0.05$) compared with 2011/2012; [d] Variable treated as categorical.

2.3.2 Antithrombotic Related Adverse Event Incidence.

Of the 1150 patients who experienced at least one AE, 329 experienced MRAEs and 78 experienced ARAEs (Figure 1). Regarding the MRAE incidence, no significant changes were observed in the deceased population (4.08% in 2008 to 3.44% in 2015/2016, $\chi 2$; $p = 0.24$) and the discharged population (1.76% in 2008 to 1.72% in 2011/2012, $\chi 2$; $p = 0.92$).

Considering ARAEs however, the incidence within the deceased population decreased significantly from 1.35% in 2008 to 0.54% in 2015/2016 ($\chi 2$; $p = 0.002$) while no change was seen in the discharged population (0.51% in 2008 to 0.46% in 2011/2012, $\chi 2$; $p = 0.83$).

To correct for patient mix differences between the years and clustering of our data we applied multilevel analyses to see if changes in MRAEs and ARAEs between years persisted. Figure 2 displays the development of MRAE and ARAE incidence over time. The MRAE incidence reduction in deceased patients was still non-significant from 3.79% (95% CI: 2.75–5.20%) in 2008 to 2.93% (95% CI: 2.07–4.12%) in 2015/2016 (Wald; $p = 0.12$). However, the ARAE incidence reduction in deceased patients remained significant from 1.20% (95% CI: 0.63–2.27%) in 2008 to 0.54% (95% CI: 0.27–1.11%) in 2015/2016 (Wald; $p = 0.020$). The decline within this period was not equal, 42% of the reduction occurred between 2008 and 2011/2012 and 13% between 2011/2012 and 2015/2016.

In discharged patients, the corrected, standardized MRAE and ARAE incidence remained stable (Figure 2). All model parameters are provided in Table S1.

Among the total 2015/2016 deceased population exposed to antithrombotic drugs (n = 1772), 16 patients experienced ARAEs (Table 2). No ARAEs were observed in patients using either DOACs or UFH. While correcting and adjusting for patient mix and clustering of data, the incidence of ARAEs was highest for patients using VKA followed by antiplatelet agents and LMWH. Corresponding odds ratios for experiencing an ARAE were significant for patients using VKAs (6.06; 95% CI: 2.02–18.14) and antiplatelet drugs (4.21; 95% CI: 1.41–12.57) indicating that these drugs were associated with the highest risk for experiencing an ARAE.

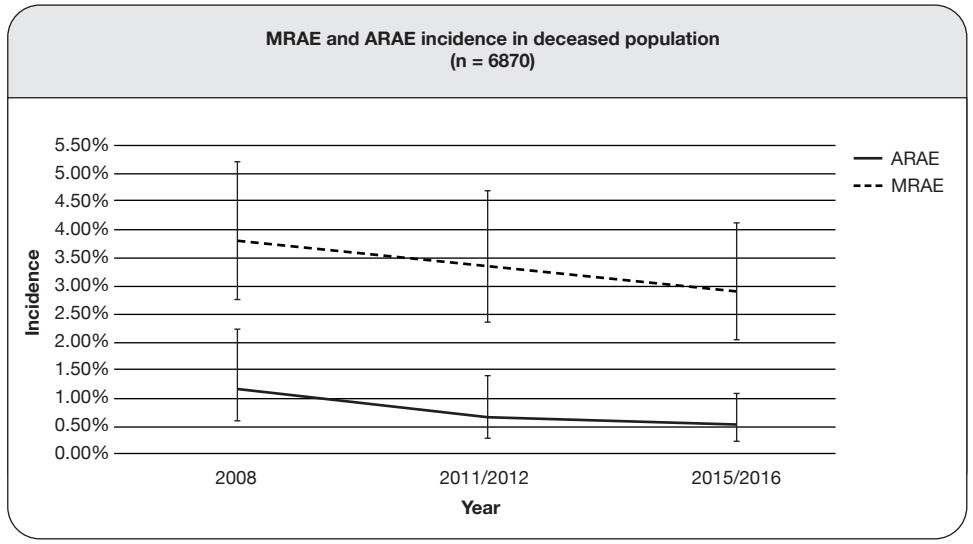


Figure 2. Adjusted standardized MRAE and ARAE incidence in deceased and discharged populations between 2008 and 2015/2016.

Table 2. Antithrombotic use and occurrence of antithrombotic related adverse events in the 2015/2016 deceased hospital population.

Antithrombotic Used During Admission [c]	Patients Exposed to Antithrombotic Drugs During admission (*n* = 1772) *n* (%, weighted) [a]	Patients with ARAE (*n* = 16) *n*	ARAE Incidence, % (95% CI) [b]	Odds Ratio ARAE (95% CI) [b]
VKA	476 (27.59)	9	0.61 (0.14–2.61)	6.06 (2.02–18.14)
LMWH	1162 (65.01)	5	0.14 (0.03–0.74)	1.37 (0.46–4.08)
Antiplatelet	650 (36.95)	6	0.43 (0.09–2.00)	4.21 (1.41–12.57)
UFH	170 (8.43)	0	-	-
DOAC	35 (1.73)	0	-	-

ARAE: Antithrombotic Related Adverse Event; VKA: Vitamin-K Antagonist; LMWH: Low Molecular Weight Heparin; UFH: Unfractionated Heparin; DOAC: Direct Oral Anticoagulant; a Weighted for hospital type; b Adjusted for clustering on hospital and department level and adjusted and standardized for sex, gender, elective admission, admission department, invasive procedure; c Use of multiple antithrombotic drugs is possible.

2.3.3 Clinical Context of Antithrombotic Related Adverse Events

To better understand the clinical context of ARAEs, we pooled all ARAEs over three years and analysed their characteristics. In total, 79 ARAEs were found in 78 patients, of which 32 (28.54%) were classified as potentially preventable during the second phase of the record review. Table 3 displays the clinical context characteristics of the identified ARAEs.

Overall, ARAEs mostly occurred in tertiary teaching hospitals in patients using VKAs and antiplatelet agents. No ARAEs were found for patients using DOACs. Regarding the specific clinical situation, the majority of the ARAEs occurred due to elevated INRs (34.6%) followed by disputed antithrombotic indications (19.0%) and perioperative/periprocedural antithrombotic management (14.5%). ARAEs in the context of VTE prophylaxis, adverse drug reactions and patient-related factors were less common.

Furthermore, ARAEs were almost always bleeding events (91.7%), occurred primarily during the responsibility of a non-surgical specialty (78.4%) and often during a weekend or holiday (40.3%).

Regarding preventable ARAEs, a slightly different clinical context profile was visible. First of all, almost all preventable ARAEs occurred during VKA (77.0%) or LMWH/UFH (44.2%) use and almost none during antiplatelet (2.5%) use. Second, elevated INRs and disputed indications make up 93.8% of preventable ARAEs. Third, surgical specialties are more often responsible during preventable ARAEs (43.0%) and preventability increased when more medical specialists were involved in treatment. Lastly, 59.2% of preventable ARAEs occurred during weekend and holidays, more than overall ARAEs did.

Table 3: Clinical context of (preventable) antithrombotic related adverse events between 2008 and 2015/2016

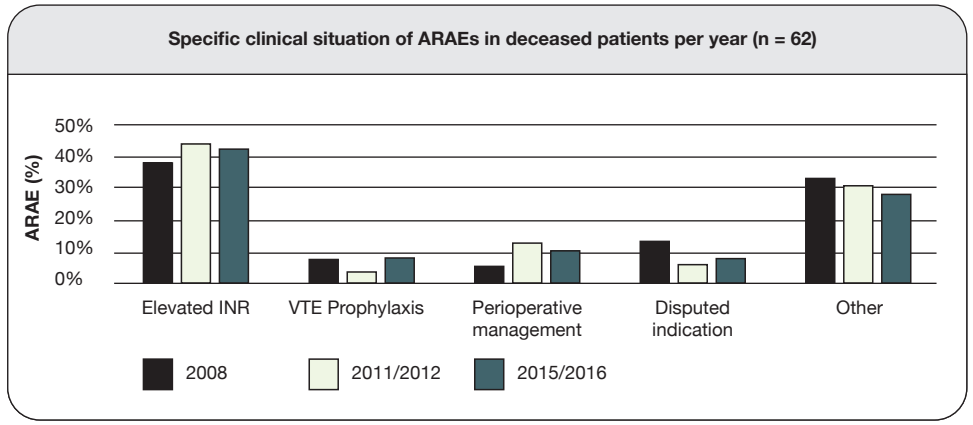
	All ARAEs (*n* = 79) %, weighted [a b]	Preventable ARAEs (*n* = 32) %, weighted [a b c]
Hospital type		
General hospital	29.2	29.3
Tertiary teaching hospital	66.4	69.3
University hospital	4.4	1.4
VKA use	50.5	77.0
LMWH/UFH use	23.5	44.2
DOAC use	0	-
Antiplatelet use	45.0	2.5
Combined antithrombotic use (2 or more)	29.3	23.7
Antithrombotic administered or omitted		
Administered	98.5	97.3
Omitted	1.5	2.7
Specific clinical situation		
Elevated INR	34.6	50.6
VTE prophylaxis	1.0	-
Perioperative/periprocedural antithrombotic management	14.5	2.6
Disputed antithrombotic indication	19.0	43.2
Adverse drug reaction	6.6	-
Patient related	0.3	-
Other	24.1	0
Type		
Bleeding event	91.7	95.7
Thromboembolic event	1.6	3.6
Other	6.8	-
Medical specialty responsible for treatment during ARAE occurrence		
Surgical speciality	21.6	43.0
Non-surgical specialty	78.4	57.0

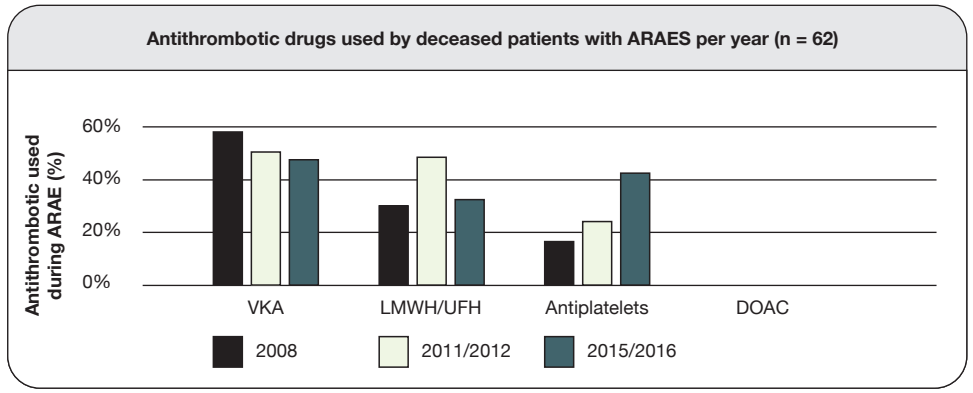
Number of medical specialists involved in treatment		
1	36.2	2.7
2	36.0	64.9
≥3	27.8	32.4
Admission department		
Surgery	6.0	0.7
Cardiology	18.8	6.7
Internal medicine	28.8	24.4
Orthopaedics	0.9	-
Neurology	7.2	0
Lung diseases	16.6	23.6
Urology	19.8	40.0
Other	1.8	3.0
ARAE onset during weekend/holiday	40.3	59.2

ARAE: Antithrombotic Related Adverse Event; INR: International Normalized Ratio; VTE: Venous Thromboembolism; VKA: Vitamin-K Antagonist; LMWH: Low Molecular Weight Heparin; UFH: Unfractionated Heparin; DOAC: Direct Oral Anticoagulant; [a] ARAE presented on adverse event level; [b] Weighted for hospital type; [c] No preventability is given if overall ARAE numbers were smaller than 5.

2.3.4 Changes in the Clinical Context of Antithrombotic Related Adverse Events

To evaluate whether specific clinical situations and antithrombotic drugs involved in ARAEs, changed over the years, we analysed their development within the deceased hospital population. Results are displayed in Figure 3. No significant changes were found for the distributions of the clinical situation or the antithrombotic used. However, antiplatelet use and combined antithrombotic use, show an increasing trend worth further monitoring ($\chi 2$; $p = 0.05$ and $p = 0.09$ respectively).





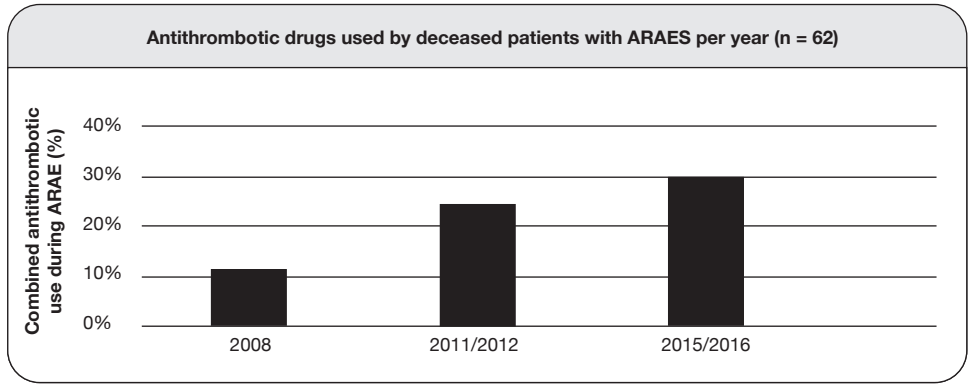


Figure 3. Longitudinal overview of clinical context and antithrombotic drugs involved in ARAEs in deceased patients.

2.3.5 Qualitative Antithrombotic Related Adverse Event Summaries

To further illustrate the various clinical contexts, we summarized several example ARAEs for each specific clinical situation category (Table S2).

Regarding elevated INRs, various factors were identified leading up to the AE. For example, co-medication interacting with the VKA in case 12 (Norfloxacin), case 9 (Amoxicil-

lin) and case 4 (Ceftriaxone) or adding bleeding risk in case 8 (Prednisone), case 5 (NSAID) and case 13 (Acetylsalicylic acid and Clopidogrel). Also, comorbidities known to influence the anticoagulant effect were identified such as in case 16 and case 10 (liver cirrhosis). In several other cases, factors related to the response to and reversal of the elevated INR values possibly added to the AE occurring. For example, the response was delayed by 36 and 72 h respectively in case 2 and case 11. Problems with the INR reversal itself were: Not administering the prescribed reversal agent in case 3 and case 15, insufficient reversal in case 6 or overdosing the reversal, resulting in a sub-therapeutic INR (<1) followed by a transient ischaemic attack in case 14. Lastly, several external factors were identified that possibly added to the AE such as a fall incident in case 1 or radiotherapy in case 7.

ARAEs related to VTE prophylaxis were all pulmonary emboli occurring when no (cases 17, 18, 19) or insufficient (case 20) VTE prophylaxis was administered. Periprocedural antithrombotic management ARAEs involved bleeding events in the context of both inadequately interrupted (cases 21, 27 and 25) and adequately interrupted antithrombotic drugs (cases 22 and 24). Thromboembolic ARAEs regarding periprocedural antithrombotic management occurred in the context of inappropriate interruption of antithrombotic drugs in case 23 or forgoing LMWH bridging during acenocoumarol interruption in a patient with a previous ischaemic cerebrovascular accident (CVA) in case 26.

Disputed antithrombotic indications according to the medical specialist reviewers were either due to questionable indications for (cases 28 and 29), or present contraindications against (cases 30 and 31) antithrombotic use.

Adverse drug reactions and patient-related ARAEs were uncommon and are therefore not specifically discussed, but are included in Appendix A2.

Finally, the “other” clinical context category ARAEs occurred, among others, in the context of continuous venovenous hemofiltration in case 42 and after antithrombotic therapy initiation for cardiac (cases 36, 38) or neurologic (cases 44, 39) indications.

2.4 Discussion

2.4.1 Main Findings

We analysed nearly 11,000 patient records from three large national adverse event studies in the Netherlands for the presence of antithrombotic related adverse events. Adjusted ARAE incidence in the deceased population decreased significantly between 2008 and 2015/2016 by 55%, with the largest decline occurring between 2008 and 2011/2012. Compared with a non-significant reduction of 23% of overall MRAEs in the same population, the relative reduction in ARAEs was larger. This is a positive development given the ageing population under study.

If and how much of the reduction in ARAEs can be attributed to improved quality of care due to the national patient safety program between 2008 and 2012 is difficult to conclude for various reasons. First of all, the safety program was not targeted specifically at antithrombotic drugs. Nonetheless, two improvement modules within the program were aimed at medication in general, including medication reconciliation at admission and discharge and administering of high-risk parenteral medication. These modules have been evaluated twice and found increasing trends in adherence rates.[25] Medication reconciliation at admission is especially likely to improve antithrombotic drug safety since it ensures awareness at admission. Second, other interventions outside the safety program, such as

computerized physician order entry systems or bar code technology that are increasingly common in practice could have positively contributed. Third, patient mix differences between the years were especially present in the deceased hospital population. Although we adjusted our models accordingly for most characteristics, we could not adjust for all variation, such as the differences in ICD-9 main diagnostic groups.

Another explanation of the decrease in ARAEs would be a declining use of antithrombotic medication within the population. Since we did not have information on antithrombotic use of all patients in our sample we could not correct for this. However, on a national level, other sources available reported increasing use of VKAs between 2008 and 2014 after which a decline sets in 2015 and 2016 due to DOAC substitution.[26] Similarly, for antiplatelet agents, an increase in the use of clopidogrel and ticagrelor is reported at the expense of acetylsalicylic acid since 2014.[27] Given the representativeness of our sample for the Dutch population, we believe it is unlikely that the decline in ARAE incidence was caused by an unobserved decline in antithrombotic use in our sample.

We also were able to study the clinical context of ARAEs. Several noticeable characteristics and contextual properties of ARAEs were identified. First of all, half of all ARAEs involved VKAs and correspondingly elevated INRs made up one-third of all ARAEs, often being preventable. This corroborates the complexity of managing patients using these drugs and stresses the importance of careful monitoring during hospitalisation. In our qualitative VKA related ARAE summaries, co-medication and comorbidities were regularly identified as a potential source of the excess anticoagulation. These and other interactions with VKAs are well known and described in the literature.[10, 11, 28] Moreover, they have been identified as the most common reason for excess anticoagulation during admission.[29] However, VKA interactions are plentiful, requiring extensive pharmacologic knowledge. Increasing awareness, standardizing and more frequent INR monitoring during admission, and use of electronic interventions supporting drug interaction detection and INR monitoring are likely candidates for initiating improvement. On the other hand, VKA use is expected to decline in the coming years due to the transitioning to DOACs for indications such as atrial fibrillation and venous thromboembolism, partially alleviating the difficulties with VKA monitoring. It is encouraging that, although DOAC use is still upcoming and not widely used yet in the Netherlands, no DOAC ARAEs were identified in the current study. Future monitoring of DOAC safety is required to infer with more confidence in DOAC safety.

Secondly, one-fifth of all ARAEs and almost half of preventable ARAEs occurred while the indication for antithrombotic use was disputed by the reviewing specialist. Either because of the presence of contraindications against, or no clear indication for antithrombotic use. Guidelines primarily support clinicians in prescribing antithrombotic drugs based on risk profiles. However, risk profiles change over time due to disease and co-medication warranting a more continuous evaluation of clinical characteristics, risk assessments and review of medications used. The recent development of deprescription guidelines might aid in this effort.[30, 31]

Third, several clinical context characteristics related to the delivery of care appeared to be related to ARAEs. First of all, ARAEs and especially those that were preventable occurred often during the weekend or holidays. Assuming equal distributions of patient load and staff, around 30% of ARAEs is to be expected to occur during such days. We found this to be 40% and 59% for overall and preventable ARAEs, respectively. This finding might indicate that antithrombotic drugs and their management are susceptible to the so-called weekend effect due to reduced staffing ratios and experience.[32] Additionally, preventable ARAEs almost always occurred in patients managed by more than one medical specialist,

hinting towards possible difficulties in the coordination of care for patients with antithrombotic drugs. Warranting antithrombotic vigilance in these scenarios should be a main concern for quality improvement initiatives.

The final noticeable findings in ARAE clinical context reflects the development over time in deceased patients. Over the years, the specific clinical situations of ARAEs did not appear to have changed. So, although we found a decline in overall ARAE incidence in deceased patients, the clinical context of ARAEs remained the same. This supports the hypothesis that the patient safety program and its medication modules, might have benefitted the overall antithrombotic medication safety, and that they were not targeted to improve specific clinical processes related to ARAEs. Furthermore, antiplatelet agents and combined use of antithrombotic drugs warrant future monitoring since, although insignificant, a possible upwards trend in ARAE involvement might be present.

Putting our results in a broad international perspective is restricted by serious heterogeneity in study design and setting with other studies. However, a comparable US study performed in 2007 reported an anticoagulant-associated adverse drug event ratio of 5.8%.[19] This was observed within patients exposed to anticoagulants, which is a similar approach with our sub-analysis for the 2015/2016 population. Nevertheless, we observed substantially lower AE rates, that is, between 0.14% and 0.61% depending on the specific antithrombotic. By contrast, in 2004 a Swiss study reported a 0.15% adverse drug event rate within patients exposed to antithrombotics, which is similar to our observations. [33] Regarding the clinical context of ARAEs our findings somewhat corroborate those of a 2017 Danish patient safety database study. VKAs were most often involved with ARAEs (65%), similar to our observations. However, ARAEs that were related with INR monitoring were less common (15%) compared with our study, and 25% of the ARAEs were related with DOACs, where we observed none.[34]

2.4.2 Strengths and Limitations

Several limitations regarding the retrospective chart review require consideration. Among this is hindsight bias introduced by having access to all relevant information at the time of review compared with the gradual gathering of information during the actual admission of the patient. Also, information bias introduced by the dependency of recorded care compared with actual care delivered during the admission could have occurred. At the same time, the method of AE detection by retrospectively reviewing patient records is still seen as the gold standard by many for detecting and analyzing AEs. The strength of our study is that nearly 11,000 patient records were included in three periods of time. Absolute numbers of ARAEs were relatively small. Since the original studies were powered for overall AEs, our post-hoc analyses on ARAE level suffered from power restrictions.

2.4.3 Conclusions.

Adjusted ARAE incidence decreased by 55% in patients who died in the hospital between 2008 and 2016 (1.20% to 0.54%). The ARAE decrease was larger than the decline in overall MRAEs within the same period. In discharged patients, the ARAE and MRAE incidence remained stable between 2008 and 2012. Although the decline in ARAEs is encouraging, several opportunities to further increase antithrombotic safety should be investigated. Among these are INR monitoring in VKA patients, continuous risk assessments during antithrombotic use, and care delivery aspects including vigilance in multidisciplinary involvement and weekend care.

While large gains were made, future ARAE monitoring is recommended to study the involvement of antiplatelet agents, combined antithrombotic drugs use and upcoming DOACs.

2.5 Acknowlegdements

We wish to acknowledge all participating hospitals and their personnel for facilitating the record reviews. Furthermore we wish to acknowledge all physician and nurse record reviewers for their time and effort.

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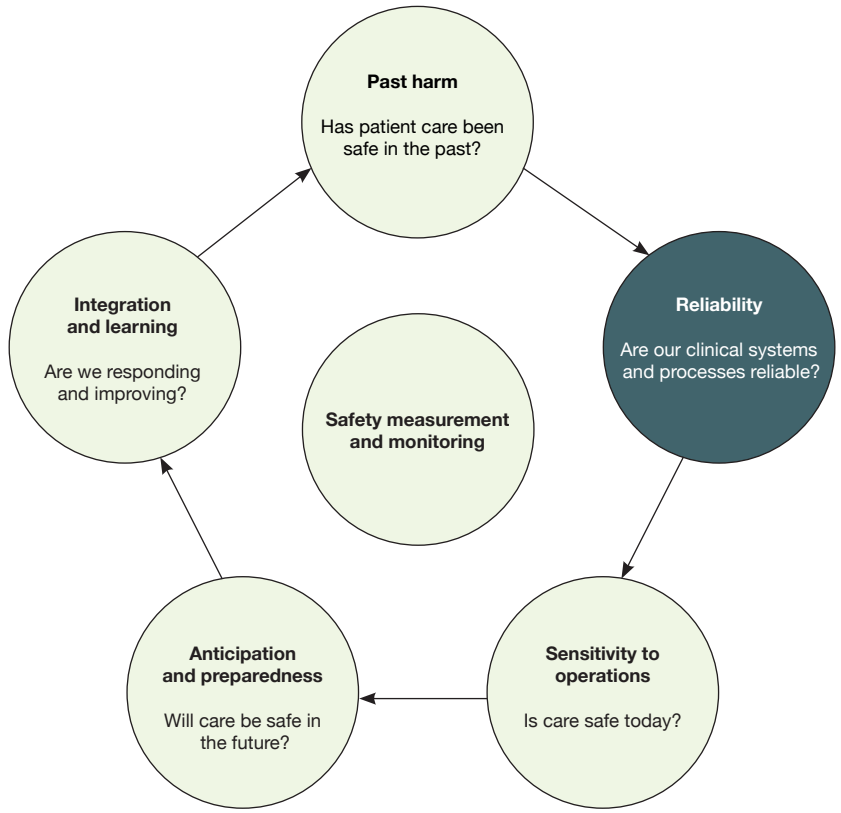
CHAPTER 3

How reliable is perioperative anti-coagulant management? Determining guideline compliance and practice variation by a retro-spective patient record review



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Abstract

Objectives

Surgery in patients on anticoagulants requires careful monitoring and risk assessment to prevent harm. Required interruptions of anticoagulants and deciding whether to use bridging anticoagulation add further complexity. This process, known as perioperative anticoagulant management (PAM), is optimised by using guidelines. Optimal PAM prevents thromboembolic and bleeding complications. The purpose of this study was to assess the reliability of PAM practice in Dutch hospitals. Additionally, the variations between hospitals and different bridging dosages were studied.

Design

A multicentre retrospective patient record review.

Setting and participants: Records from 268 patients using vitamin-K antagonist (VKA) anticoagulants who underwent surgery in a representative random sample of 13 Dutch hospitals were reviewed, 259 were analysed.

Primary and secondary outcome measures: Our primary outcome measure was the reliability of PAM expressed as the percentage of patients receiving guideline compliant care. Seven PAM steps were included. Secondary outcome measures included different bridging dosages used and an analysis of practice variation on the hospital level.

Results

Preoperative compliance was lowest for timely VKA interruptions: 58.8% (95% CI 50.0% to 67.7%) and highest for timely preoperative assessments: 81% (95% CI 75.0% to 86.5%). Postoperative compliance was lowest for timely VKA restarts: 39.9% (95% CI 33.1% to 46.7%) and highest for the decision to apply bridging: 68.5% (95% CI 62.3% to 74.8%). Variation in compliance between hospitals was present for the timely preoperative assessment (range 41%–100%), international normalised ratio testing (range 21%–94%) and postoperative bridging (range 20%–88%). Subtherapeutic bridging was used in 50.5% of patients and increased with patients' weight.

Conclusions

Unsatisfying compliance for most PAM steps, reflect suboptimal reliability of PAM. Furthermore, the hospital performance varied. This increases the risk for adverse events, warranting quality improvement. The development of process measures can help but will be complicated by the availability of a strong supporting evidence base and integrated care delivery regarding PAM.

3.1 Background

Anticoagulant therapy is effective in preventing arterial thromboembolisms, including cerebral stroke, in patients with atrial fibrillation or a mechanical heart valves as well as preventing venous thromboembolism. Managing anticoagulant therapy is challenging for various reasons. Among these are the narrow therapeutic target ranges for the international normalized ratio (INR), susceptibility to dietary fluctuations and co-medication interactions altering the anticoagulant intensity.[1, 2] This urges careful risk assessments and monitoring of anticoagulants to prevent adverse bleeding and thromboembolic events,[3, 4] both having a potential harmful, everlasting effect on quality of life in a largely elderly patient population. However, in the past decade anticoagulants were identified as having one of the highest occurrence of medication related adverse events.[5-8] Corresponding with the first step in the 'safety measurement and monitoring' framework as proposed by Vincent et al. (2014), these studies confirm that anticoagulants cause harm, jeopardizing patient safety.[9] Consecutive quality improvement initiatives targeted at anticoagulant drugs are there for warranted, and some have already been undertaken.[10-12]

To inform these quality improvement efforts, this framework supports assessing the reliability, defined as 'failure-free operation over time', of standardised clinical systems and processes within healthcare. It applies to processes that healthcare professionals have to carry out reliably.[9]

Anticoagulant management around surgery can be regarded as such a process since international guidelines advise and assist standardization.[13] Surgery itself accounts for 21% of anticoagulant related medication errors as found by Henriksen et al. (2017).[14] Therefore, making it a relevant process for a reliability assessment.

Surgical procedures in anticoagulated patients require specific attention. While reducing the risk of thromboembolic events, uninterrupted anticoagulation increases bleeding risk during and after surgery.[15, 16] Hence, preoperative interruption of anticoagulation is often required.[17] For a select group of high risk patients, short-acting heparins, e.g. low molecular weight heparins (LMWH), are required during the interruption period to reduce the time at risk for thromboembolic complications. This is known as 'bridging anticoagulation' and is considered an off-label use of heparins without consensus on optimal dosing.[13, 18, 19] The process of managing anticoagulants around surgery is referred to as 'perioperative anticoagulant management' (PAM). PAM entails several steps that healthcare professionals should carry out reliably to minimize thromboembolic and bleeding complications.[20-22]

Standardized PAM has been evaluated within study contexts several times and found that it was feasible and associated with a low risk for complications.[19, 21-23] However, the persistent occurrence of anticoagulant related adverse events around the time of surgery, questions the reliability of everyday PAM practice compared with study settings.

Evaluating the reliability of standardized PAM in everyday practice can reveal provider or process vulnerabilities that can help in interpreting adverse events. Studies evaluating PAM in everyday practice are scarce and have limited generalizability due to self-reported PAM practices by physicians, restricted patient populations and single centre based studies.[24-27]

Therefore, as the next step in safety measurement and monitoring, the primary aim of this study was to assess the reliability of everyday PAM practice from planning to patient discharge in a selection of Dutch hospitals. Reliability was assessed by determining the percent of patients receiving guideline compliant care. Our secondary aims were to determine if PAM practice varied between hospitals and which heparin dosages are used for bridging anticoagulation.

3.2 Methods

3.2.1 Study setting, design and participants

Long-term oral anticoagulant care in the Netherlands is characterized by a network of anticoagulant management services (AMS). These specialised services are responsible for monitoring and dosage of vitamin-K antagonist (VKA) anticoagulation outside the hospital setting. During hospitalization this responsibility is temporarily transferred from the AMS to the medical specialist until discharge. Also in case of PAM, a transfer of responsibility takes place. According to a Dutch integrated care standard the surgeon together with the anaesthesiologist set the PAM policy.[28] However, the responsibility for executing the PAM policy depends on whether or not the patient is admitted in the hospital. In case of admitted patients the surgeon is responsible for PAM execution. If patients reside at home, the AMS are responsible. The PAM evaluation in this study was performed from the perspective from the hospital where surgery took place.

Hospitals were invited for participation after being selected through a random sampling procedure which was stratified for hospital type and geographic location (urban/rural). Participation was voluntary. At first nineteen hospitals were invited of which ten agreed to participate. To improve the representativeness of our hospital sample relative to all Dutch hospitals we sampled and invited an additional six hospitals of which three agreed to participate. In total, two university, four tertiary teaching and seven general hospitals participated (supplementary figure 1). When given, official reasons for non-participation were: migrations between electronic health records, staffing shortages for facilitating the research and internal reorganizations.

Twenty records of patients using VKA admitted for surgery between 1 June 2015 and 31 December 2015 were randomly selected and reviewed. Randomization of eligible patient records was performed by hospital or research personnel using a random number generator available in the local spreadsheet application. Patients were only included once per hospital. Inclusion criteria were: age ≥18 years, length of stay ≥24 hours, underwent acute or elective surgical procedure using general and/or spinal/epidural anaesthesia. Exclusion criteria were: psychiatric or gynaecologic/obstetric ward admission, admission from or discharge to other hospitals, trauma other than hip fractures on admission, pregnancy or six weeks postpartum and palliative care admission. In case of an irretrievable required (section of a) health record, a replacement record was randomly selected. This study focusses only on patients with interrupted VKAs. Therefore, we excluded records from analysis if the PAM policy was not recorded or when the VKA was not interrupted (supplementary figure 1).

3.2.2 Reliability assessment of perioperative anticoagulation management

A panel of five experts in the thrombosis and haemostasis field was consulted throughout this study. The panel was involved in both developing case report forms and classification models. We distinguished seven steps in the PAM process for the reliability assessment. Based on guidelines and previous assessments, these steps were seen as critical to a safe execution of PAM:

Step 1. Timing of preoperative patient assessment
Step 2. Preoperative VKA interruption interval
Step 3. Preoperative international normalized ratio (INR) testing

Step 4. Preoperative use of bridging anticoagulation
Step 5. Postoperative use of bridging anticoagulation
Step 6. Postoperative restart time for bridging anticoagulation
Step 7. Postoperative restart time for VKA

Reliability of individual PAM steps was defined as the percentage of patients receiving guideline compliant care. The adequacy of the decision to interrupt the VKA is not subject to evaluation in this study, because of the absence of a validated instrument to determine surgical bleeding risk.

Several relevant guidelines on PAM are available. During our data collection period in 2015 the Dutch Quality Institute for Healthcare (CBO) guideline for Diagnostics, Prevention and Treatment of Venous Thromboembolism and Secondary Prevention of Arterial Thrombosis released in 2008 was the leading PAM guideline.[29] This guideline being an adaption of the ACCP guideline for warfarin patients released in 2004,[30] it became apparent that in 2015 the CBO guideline more than likely reflected outdated evidence regarding PAM and current practice has since moved on. Especially since the ACCP updated its guideline in 2012. To account for this, we employed a hybrid frame of reference of the 2008 and 2012 guideline in assessing PAM reliability. We ensured that our assessment criteria reflected the pharmacologic properties of acenocoumarol and phenprocoumon used in the Netherlands as opposed to warfarin used internationally. Table 1 provides an overview of all PAM steps, assessment criteria and sources used.

3.2.3 Patient record review

Trained research assistants and one researcher (MM) reviewed and extracted the data in all hospitals through standardized case report forms. Both outpatient preoperative patient assessment records and inpatient admission records were retrieved. Data extracted from the preoperative patient assessment records included the planned preoperative anticoagulant management i.e. whether the VKA was to be interrupted with or without bridging anticoagulation, interruption dates, and bridging anticoagulation orders. Data required for the determination of thromboembolic risk were extracted from the medical history records. This included the indication for VKA use and presence of relevant comorbidities. Data extracted from inpatient admission records were INR test results, VKA and heparins administration and discharge orders. Furthermore, general demographic, admission, and surgery characteristics were extracted. The study protocol was approved by the medical ethics committee of the VU University Medical Centre, Amsterdam, The Netherlands and the informed consent was waived because of the use of patient record data only (protocol number: 2015/430).

3.2.4 Primary outcome measures: Compliance of perioperative anticoagulant management

Classification models were constructed for determining guideline compliance for each PAM step. Compliance for step 1 to 4 was not assessed for patients undergoing non-elective or emergency surgery. Step 5 to 7 were assessed for all patients while differentiating between elective and non-elective patients. All PAM evaluation criteria and the distinction between compliance and non-compliance are summarized in table 1. We will discuss several steps in detail.

Step 4 and 5 involve determining the thromboembolic risk in order to evaluate the appropriateness of bridging anticoagulation. Thromboembolic risk was determined based on the ACCP 2012 guideline and is provided in supplementary table 1. The classification of

preoperative bridging anticoagulation was based on patient record annotations indicating towards the use of bridging anticoagulation. Postoperative use of bridging was analysed in more detail and included the dosage. Therapeutic and sub therapeutic dosed heparins were both classified as bridging (supplementary table 2). A minimum of two consecutive days of bridging or a discharge prescription present, was required for a classification of postoperative bridging. The adequacy of the duration of bridging therapy was not subject to evaluation.

Step 6 involves the postoperative restart time for bridging anticoagulation. Based on the CBO recommendations, postoperative bridging anticoagulation restarted on the first day following surgery was classified as compliant. CBO makes an exception for high thromboembolic risk patients, for which restarting bridging on the day of surgery is considered compliant as well.

3.2.5 Secondary outcome measures: Practice variation and bridging dosages

Presence of practice variation between hospitals was analysed by determining the individual compliance per hospital. A minimum of ten records per hospital per step was required to include the PAM step in variation analysis. Differences were statistically tested.

For the analysis of postoperative bridging dosages, a distinction was made between therapeutic and sub therapeutic dosages. Therapeutic dose heparins should be adjusted to the patient's weight.

Based on the patients' weight, bridging dosages were classified as either therapeutic or sub therapeutic using threshold values used in the Netherlands.[31] Threshold values are provided in supplementary table 2. Bridging dosage was determined per patient and differences between patients were tested for elective and non-elective surgery, patients' thromboembolic risk and bodyweight strata.

Table 1. Perioperative anticoagulant management steps with evaluation criteria and source

No.	PAM step	Evaluation criteria		Applicable population	Source
Preoperative					
		Compliant	Non-compliant		
1	Timing of patient assessment	-Assessment performed ≥ 7 days preoperative	-Assessment performed < 7 days preoperative	Elective	ACCP, 2012
2	VKA interruption interval	-Acenocoumarol interruption = 3 days -Phenprocoumon interruption = 5 days	-Acenocoumarol interruption ≠ 3 days -Phenprocoumon interruption ≠ 5 days	Elective	CBO, 2008
3	INR testing	-INR is tested on day of surgery	-INR is not tested on day of surgery	Elective	ACCP, 2012
4	Bridging anticoagulation use	Based on thromboembolic risk: -Low/intermediate risk: no bridging used -Intermediate/high risk: bridging used	Based on thromboembolic risk: -Low risk: bridging used -High risk: no bridging used	Elective	ACCP, 2012
Postoperative					
5	Bridging anticoagulation use	Based on thromboembolic risk: -Low/intermediate risk: no bridging used -Intermediate/high risk: bridging used	Based on thromboembolic risk: -Low risk: bridging used -High risk: no bridging used	Elective Non-elective	ACCP, 2012
6	Restart time for bridging anticoagulation	-Bridging restart day = 1st day after surgery In case high thromboembolic risk: -Bridging restart day = day of surgery or 1st day after surgery	-Bridging restart day ≠ 1st day after surgery In case high thromboembolic risk: -Bridging restart day ≠ day of surgery or 1st day after surgery	Elective Non-elective	CBO, 2008
7	Restart time for VKA	-VKA restart day = 1st day after surgery	-VKA restart day ≠ 1st day after surgery	Elective Non-elective	CBO, 2008

PAM: perioperative anticoagulant management; VKA: vitamin-K antagonist; INR: international normalized ratio; ACCP: American College of Chest Physicians; CBO: Dutch Quality Institute for Healthcare

3.2.6 Statistical methods

To describe the study population and PAM practice characteristics we used descriptive statistics. Compliance was expressed as the percentage of patients receiving guideline recommended care with 95% confidence intervals. Differences in PAM practice characteristics and compliance between various groups were tested. Categorical outcomes were tested with Chi-square or Fisher's exact tests, continuous variables with the Man-Whitney U test due to skewedness of the data.

Overall, practice variation between hospitals was tested with the Chi-square test or, when appropriate, the Fisher-Freeman-Halton exact test. Next, post hoc Chi-square tests between individual hospitals' performance for PAM steps were performed. For all tests a p-value <0.05 was considered statistically significant. Bonferroni correction was applied to control for type I error inflation during post hoc testing. Statistical analyses were performed with SPSS version 22 (IBM, Chicago, IL) and Stata version 14 (StataCorp, College Station, TX).

3.2.7 Patient and Public involvement

Patients and public were not directly involved in the current study.

3.3 Results

3.3.1 Study population

We reviewed 268 patient records in thirteen hospitals. Eleven hospitals used internal PAM protocols. The two remaining hospitals did not share information on protocol use. Nine records were excluded from analysis because of uninterrupted VKA or unclear recording of the PAM. The remaining 259 records (mean records per hospital = 19.9; range = 16-23) were analysed (supplementary figure 1).

Demographic and clinical characteristics are displayed in table 2. The mean age of patients was 74.8 years (SD=10.6), most patients were male (56.4%). Atrial fibrillation was the most common indication for VKA use (66.8%) followed by venous thromboembolism (8.9%) and mechanical heart valve (3.5%). Surgery was elective in 71.0% of patients; orthopaedic (34.4%) and gastrointestinal (20.1%) surgeries were most prevalent.

Table 2 Demographic and clinical characteristics of included patients (N=259)

Table 2 Demographic and clinical characteristics of included patients (N=259)

Age (years), mean (SD)	74.8 (10.6)
Male gender, n (%)	146 (56.4)
Elective surgery, n (%)	184 (71.0)
Length of stay (days), median (IQR)	6.0 (3.0–10.0)
VKA, n (%)	
Acenocoumarol	205 (79.2)
Phenprocoumon	54 (20.8)
Indication for VKA use, n (%)	
Atrial fibrillation	173 (66.8)
Venous thromboembolism	23 (8.9)
Mechanical heart valve	9 (3.5)
Multiple [a]	21 (8.1)
Other	33 (12.7)
Comorbidities, n (%)	
iCVA/TIA	37 (14.3)
Thrombophilia	7 (2.7)
Heart failure	20 (7.8)
Hypertension	132 (51.0)
Diabetes mellitus	63 (24.3)
Active cancer/malignancy	55 (21.2)
Thromboembolic risk, n (%)	
Low	138 (53.3)
Moderate	38 (14.7)
High	40 (15.4)
Unknown [b]	43 (16.6)
Type of surgical procedure, n (%)	
Gastrointestinal	52 (20.1)
Orthopaedic	89 (34.4)
Plastic	3 (1.2)
Cardiac	9 (3.5)
Neurosurgery	5 (1.9)
Breast	6 (2.3)
Vascular	36 (13.9)
Urologic	43 (16.6)
Dental/ENT/HN	2 (0.8)
Other	14 (5.4)

SD: standard deviation; IQR: inter quartile range; VKA: vitamin-K antagonist; iCVA: ischaemic cerebrovascular accident; TIA: transient ischaemic attack; ENT: ear, nose and throat; HN: head and neck.
[a] Combination of two of the following indications: atrial fibrillation, venous thromboembolism and mechanical heart valve
[b] 33 patients used VKA for other indications than AT9 provides TE-risk stratification, 10 patient records provided insufficient information to determine TE-risk

3.3.2 Primary outcome measures: Perioperative anticoagulant management practice and compliance

The PAM practice characteristics and compliance with the guidelines are displayed in tables 3 and 4. The median day of patient assessment (step 1) was nineteen days preoperative (IQR = 8-37) corresponding with a compliance of 80.8% with the recommended minimum of seven days.

Data required for determining the duration of withholding VKA (step 2) was available in 119 (64.7%) of elective patient records. Of these, VKA interruptions were compliant in 58.8% of patients. Acenocoumarol and phenprocouman were interrupted for a median of three days (IQR = 3-3) and five days (IQR = 3-7) respectively.

Preoperative INR was tested (step 3) at the day of surgery in a majority of 60.9% elective patients, which is compliant with the recommendation. However, in 12.0% no recent INR test was performed.

Preoperative bridging policies (step 4) were available in 157 of the reviewed records (85.3%). Among these, bridging was used in 47 (29.9%). Preoperative bridging was used more frequently as the thromboembolic risk profile increased. Overall, preoperative bridging use was compliant in 79.7% of elective patients.

Postoperative bridging (step 5) was used in 107 patients (41.3%), with the highest bridging rate of 57.9% for moderate-risk patients. Postoperative bridging of low-risk patients differed between elective and non-elective patients (29.4% vs. 48.5%; χ^2; p = .044). Overall, the compliance of postoperative bridging was 68.5% and differed significantly between elective and non-elective patients (73.5% vs. 56.5%; χ^2; p = .015).

Bridging was restarted (step 6) at a median of one day (IQR = 0-1) whereas VKAs were restarted (step 7) at a median of two days (IQR = 1-3) corresponding with a compliances of 57.8% and 39.9% respectively. Both the bridging and VKA restart interval compliance did not differ between elective and non-elective patients (χ^2; p=.42 and p=.39 respectively).

3.3.3 Secondary outcome measures: Practice variation and bridging dosages

Variation between hospitals' compliance is displayed in figure 1. Performance varied significantly for the preoperative patient assessment (p<.001), preoperative INR testing (p<.001) and postoperative use of bridging anticoagulation (p=.001). Post-hoc testing identified one significantly lower performing hospital for each of these PAM steps (hospitals 2 and 9) and one hospital performed significantly better with the INR testing (hospital 6).

Lastly, bridging dosages of low molecular weight heparin were studied. 54 of the 107 bridged patients (50.5%) received a sub therapeutic dosage, 45 (42.1%) a therapeutic dosage, four (3.7%) a combination, and for another four (3.7%) patients the distinction between the two dosages could not be established (results not shown in table). The bridging dosages did not vary between elective or non-elective patients (χ^2; p=.30) and for different thromboembolic risk strata (χ^2; p=.39). However, bridging dosages varied between patient weight groups (Fisher's Exact; p<.001). Sub therapeutic bridging dosage use increased as the patient weight increased (supplementary table 3).

Table 3. Perioperative anticoagulant management practice characteristics and compliance for preoperative steps

PAM step	Elective surgery (N=184)
1. Assess the patient at least 7 days before surgery	
Valid records, n (%)	182 (98.9)
Time from preoperative assessment to surgery (days), median (IQR)]	19 (8-37)
Compliance, % (95% CI)	80.8 (75.0-86.5)
2. Preoperative VKA withholding duration: **Acenocoumarol: 3 days** **Phenprocoumon: 5 days**	
Valid records, n (%)	119 (64.7)
Withholding duration acenocoumarol (days), median (IQR)	3 (3-3)
< 3 days, n (%)	13 (13.4)
3 days, n (%)	64 (66.0)
> 3 days, n (%)	20 (20.6)
Withholding duration phenprocoumon (days), median (IQR)	5 (3-7)
< 5 days, n (%)	9 (40.9)
5 days, n (%)	6 (27.3)
> 5 days, n (%)	7 (31.8)
Compliance, % (95% CI)	58.8 (50.0-67.7)
3. Test INR preoperative on the day of surgery	
Valid records, n (%)	184 (100)
Day of most recent preoperative INR test, n (%)	
Surgery day	112 (60.9)
Day before surgery	50 (27.2)
Sooner/none	22 (12.0)
Preoperative INR on surgery day, median (IQR)	1.10 (1.00-1.28)
Preoperative INR on day before surgery, median (IQR)	1.20 (1.10-1.30)
Compliance, % (95% CI)	60.9 (53.8-67.9)
4. Apply or withhold preoperative bridging anticoagulation according to thromboembolic risk	
Valid records, n (%)	157 (85.3)
Applied bridging per thromboembolic risk strata, n (%)	
Low	18 (19.1)
Moderate	8 (38.1)
High	9 (50.0)
Unknown	12 (50.0)
Compliance, % (95% CI)[a]	79.7 (72.9-86.5)

VKA: vitamin-K antagonist; IQR: inter quartile range; INR: international normalized ratio; CI confidence interva Unless otherwise stated, all results are based on valid records only.
[a] Based on valid records and records with known thromboembolic risk

Table 4 Perioperative anticoagulant management practice characteristics and compliance for postoperative steps

PAM step	Elective surgery (N=184)	Non-elective surgery (N=75)	P-value [a]	Total (N=259)
5. Apply or withhold postoperative bridging anticoagulation according to thromboembolic risk.				
Valid records, n (%)	181 (98.4)	75 (100)	-	256 (98.8)
Applied bridging per thromboembolic risk strata, n (%)				
Low	30 (29.4)	16 (48.5)	.044	46 (34.1)
Moderate	16 (59.3)	6 (54.5)	.79	22 (57.9)
High	12 (54.5)	7 (38.9)	.32	19 (47.5)
Unknown	15 (50.0)	5 (38.5)	.49	20 (46.5)
Compliance, % (95% CI)[b]	73.5 (66.5-80.5)	56.5 (44.1-68.8)	.015	68.5 (62.3-74.8)

6. Restart bridging anticoagulation, if ordered, 24 hours after surgery. Restart after 12 hours is allowable for high thromboembolic risk patients [c]				
Applicable records (bridging used), n (%)	63 (36.8)	29 (42.0)		92 (38.3)
Valid records, n (%)	63 (100)	29 (100)		92 (100)
Day of postoperative bridging (re)start, median (IQR)	1 (0-1)	1 (1-2)	.09	1 (0-1)
Surgery day, n (%)	20 (31.7)	6 (20.7)	-	26 (28.3)
First day after surgery, n (%)	34 (54.0)	14 (48.3)	-	48 (52.2)
Second day after surgery, n (%)	4 (6.3)	4 (13.8)	-	8 (8.7)
Third day after surgery or later, n (%)	5 (7.9)	5 (17.2)	-	10 (10.9)
Compliance, % (95% CI)	60.7 (48.4-72.9) [d]	51.7 (33.5-69.9)	.42	57.8 (47.6-68.0)
7. Restart VKA 24 hours after surgery [c]				
Applicable records (VKA restarted), n (%)	161 (94.2)	66 (95.7)	-	227 (94.6)
Valid records, n (%)	136 (84.5)	62 (93.9)	-	198 (87.2)
Day of postoperative VKA restart: median (IQR)	1 (1-3)	2 (1-4)	.14	2 (1-3)
Surgery day, n (%)	13 (9.6)	4 (6.5)	-	17 (8.6)
First day after surgery, n (%)	57 (41.9)	22 (35.5)	-	79 (39.9)

VKA: vitamin-K antagonist; IQR: inter quartile range; CI confidence interval
Unless otherwise stated, all results are based on valid and applicable records only.
[a] $\chi 2$ or Mann-Whitney U test between elective and non-elective surgery populations
[b] Based on valid records and records with known thromboembolic risk
[c] Records of patients who underwent 2nd surgery were omitted (elective surgery n=13, non-elective surgery n=6)
[d] Records of patients with unknown thromboembolic risk and bridging restart at surgery day (n=2) were omitted. Thromboembolic risk is required to determine compliance for these patients

3.4 Discussion

This study aimed to assess the reliability of PAM in everyday, also referred to as "real world", practice in a sample of Dutch hospitals. Deviations from recommended PAM care were common. Depending on the PAM step of interest, deviations occurred in at least 19% of patients to as much as 60% of patients.

3.4.1 Compliance and possible implications for practice

The highest non-compliance was found for the VKA and bridging anticoagulation time of restart (step 6 and 7). Both should be restarted after 24 hours post-surgery. However, the restart of bridging was premature or delayed in 42.2% of patients whereas VKA restart interval deviations were even more common, occurring in 60.1% of patients. The majority of these were attributable to a delayed restart which is similar to the findings of others.[24] Delayed restarts prolong the time patients are at risk for a thromboembolic complication due to suboptimal anticoagulation.

The reason for this low compliance for restart intervals is unclear. Restart postponement is preferred if adequate post-surgical haemostasis has not yet occurred; with the current study design we could not observe the adequacy of this decision. However, allowing a 24 hour restart postponement would increase the compliance figures with a modest 8.7% and 13.1% for bridging and VKA restart respectively. Another explanation, described by Flaker et al. (2016), is a difference in attitudes of clinicians in averting thromboembolic or bleeding complications. Clinicians with a risk averse attitude towards bleeding complications might favour a delayed restart, whereas a risk averse attitude towards thromboembolic complications might result in a premature restart.[32]

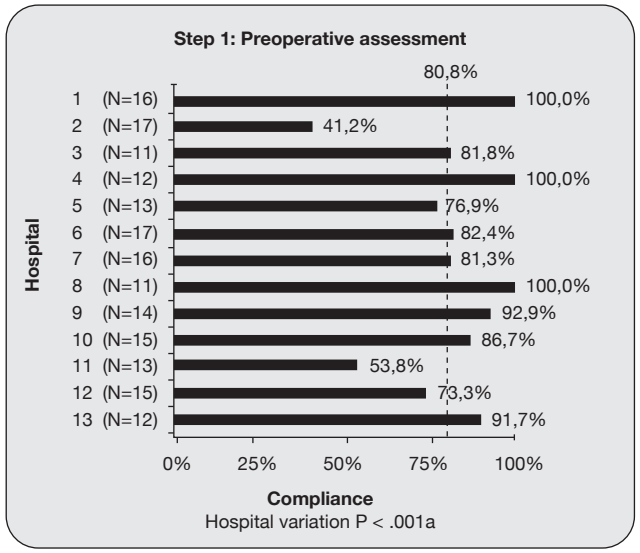
Also, preoperatively the timing of VKA interruption (step 2) appears to be troublesome. An inadequate interruption interval exposes patients to a prolonged thromboembolic risk in case of preliminary VKA interruption. Alternatively, delays or cancellations of surgery can occur in case of delayed VKA interruptions. These situations should be prevented as much as possible since they can increase patients harm, discontent and healthcare costs.

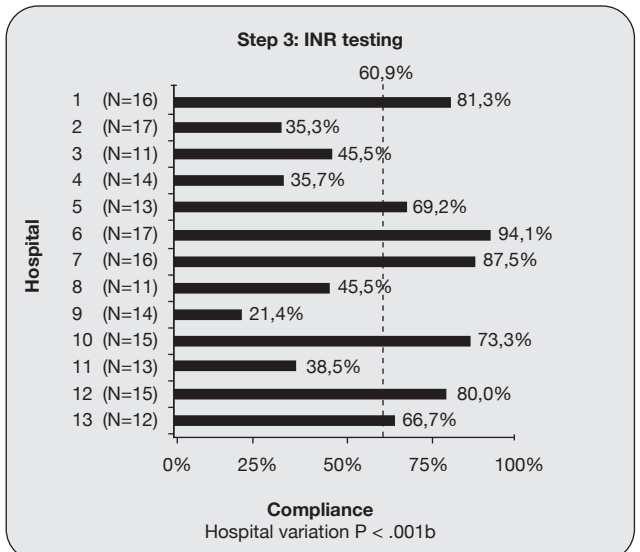
INR testing (step 3) was omitted in 12% of patients. Although not mandated in all guidelines, ensuring INR levels are safe prior to surgery is likely beneficial in preventing adverse bleeding events related to the surgery.

The bridging decision (step 4 and 5) was not in accordance with the guidelines in almost one in three patients. Furthermore, the postoperative performance was significantly lower in non-elective patients due to an overuse of bridging in low risk patients. Emergency surgery settings with less time or priority for assessing the need for bridging anticoagulation, might contribute to this. However, the guidelines are originally aimed at elective patient populations, so our results for non-elective patients should be interpreted accordingly. Regardless of this, the identified difference warrants further investigation of postoperative PAM in non-elective surgery settings. Future guidelines should consider including a statement or recommendation for non-elective surgery patients to inform involved professionals.

Also, the use of sub therapeutic dose bridging in 50% of patients was unexpectedly high given the explicit CBO 2008 recommendation to provide therapeutic dose bridging. Insufficient dose adjustments for bodyweight appeared to be contributing to this observation.

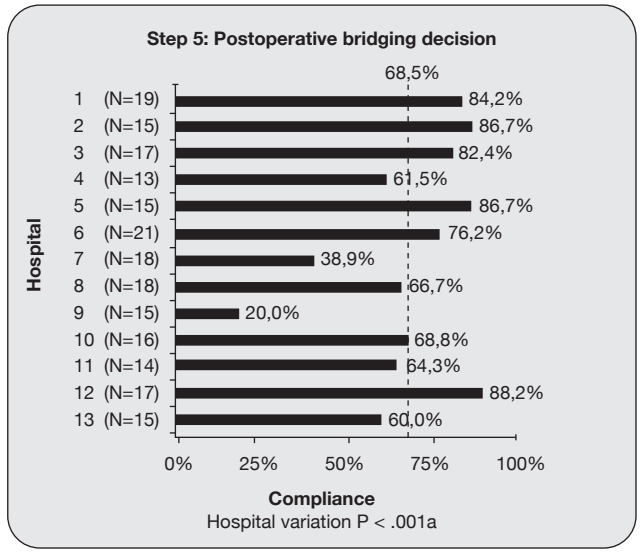
Most cases of non-compliance we observed, directly increase the risk for adverse events. Therefor our study can indirectly explain some of the occurrences of anticoagulant related adverse events that occur around surgery and are reported in other studies.[14, 33]

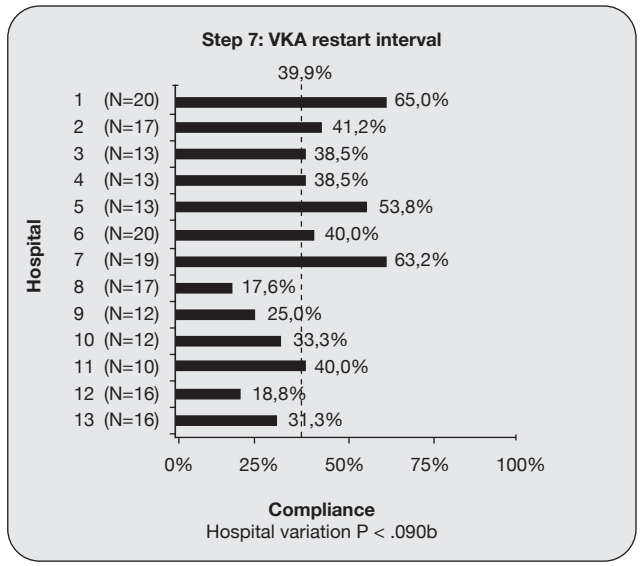




[a] Fisher's exact test
[b] χ^2 test
[c] Hospital's compliance is significantly different. (Post-hoc chi-square test: P < .05, Bonferroni correction applied)

Figure 1. Variation in compliance between individual hospitals for steps 1, 3, 5 and 7. The Dashed vertical line represents the population average





3.4.2 Quality improvement for perioperative anticoagulant management

Our reliability findings inform the development of quality improvement measures for PAM. Since we evaluated the hospitals' performance on the delivery of PAM as oppose to patient outcomes, process measures are most appropriate. Process measures reflect the delivery of care to patients and can inform us of the quality of this care.[34, 35] However, not all PAM steps with corresponding guideline recommendations will be as easily transformed in an effective process measure. For example, the decision whether to use bridging requires a large number of specific risk factors that have to be brought together and comprehended to anticipate on the most favourable outcome for the patient. This will be challenging to include in a single process measure. More straightforward candidates for PAM process measures are the timing of patient assessment or the preoperative INR testing. Supported by modern electronic health record and appointment data, evaluation of these steps should not be problematic. This is confirmed in our study by the amount of valid record entries for these two steps compared with other steps.

Another challenge for quality improvement involves the integrated care aspect of PAM. In the Netherlands 52 anticoagulant management services (AMS) and 121 hospitals are present,[36, 37] indicating heterogeneous service areas and resulting in multiple collaborations. A national integrated anticoagulant care standard aims to align involved healthcare providers and their responsibilities.[28] However, a recent qualitative process analysis of preoperative PAM found a divergent practice pattern regarding the responsibilities of hospitals and AMS during preoperative PAM. Barriers in implementing guidelines at integrated care level, such as a lack of common governance, different logistics, medical oversight and funding, as described by Lang et al. (2012) might be at work here.[38] Implementing a shared responsibility for preoperative PAM might encourage the alignment of involved integrated care providers.

As a final point towards PAM quality improvement, it is worthwhile to note that new evidence for PAM in VKA patients is rapidly emerging. Guidelines are quickly complemented by new evidence, among which is evidence suggesting a relation between early onset (<24 hours) of postoperative bridging anticoagulation and major bleeding complications.[39] Other evidence competes with the effectiveness of bridging anticoagulation. The BRIDGE-trial found that bridging did not reduce thromboembolic complications but increased the risk for bleeding complications compared with non-bridging.[40] This trial was published in the last month of our patient inclusion (December 2015) so its suspected impact in terms of reduced bridging in atrial fibrillation patients had not been translated into clinical practice yet. Since a majority of our study population were atrial fibrillation patients and bridging low-risk patients was the most prevalent form of non-compliance, the BRIDGE-trial findings might have positively influenced the overall bridging compliance from December 2015 onwards. What adds to this expectation is the Dutch national guideline update in April 2016, where the number of thromboembolic risk strata got limited to only two. Most of the patients in the moderate risk stratum are reassigned towards the lower risk stratum for which bridging is not recommended [31]. These developments show that the evidence base is still subject to change rather than well-established, posing an obstacle for quality improvement measure development.[41] Furthermore, long guideline update intervals, delay new evidence to reach practice.[42]

3.4.3 Strengths and limitations

Our study has several strengths and limitations. First of all, the multicentre design with a representative sample of Dutch hospitals provide us with insight in current PAM practice in the Netherlands. Furthermore, the use of patient record data allowed us to evaluate the "real world" PAM practice without risking bias caused by study setting or observation.

At the same time, the dependency on routine patient record data has its own limitations. The PAM registration in the records was not always of high quality. This became apparent for the preoperative VKA interruption, details regarding preoperative bridging, and documentation of postsurgical haemostasis. These were sometimes insufficiently documented. Although this probably introduced some bias to the compliance assessment for these two steps, it is not expected to change conclusions much due to the high prevalence of non-compliance in valid records.

Additionally, the specific agreements between hospitals and involved AMS regarding PAM cooperation were not available for this study. Therefore, we cannot rule out that some of our observed variation is attributable to between-hospital variation regarding such cooperations.

The voluntary participation of hospitals poses as another limitation. In total 25 hospitals were invited to participate, of which only thirteen accepted. Therefor we cannot exclude the possibility of some selection bias at hospital level.

As a final limitation we wish to acknowledge that no clinical outcomes were ascertained, preventing the establishment of a relationship with observed practice patterns.

3.4.4 Conclusions

Based on the unsatisfying compliance with most guideline recommendations, we can conclude that the reliability of the PAM process in the Netherlands is suboptimal. Additionally, PAM varies between hospitals and different dosages of bridging anticoagulation are used due to suboptimal adjustments for patients' weight. These findings confirm that standardized PAM is complex and not straightforward to implement in everyday practice. The observed non-compliance in many cases directly increases the risk for adverse events in individual patients.

Our study informs the development of process measures for PAM aimed at monitoring and quality improvement. Our PAM step approach can be used as a prelude to a future checklist for self-audits or standardization of PAM documentation. However, several challenges have to be overcome also. Among these are: obtaining a stronger evidence base, reducing the knowledge to action gap and alignment of integrated care providers involved in PAM.

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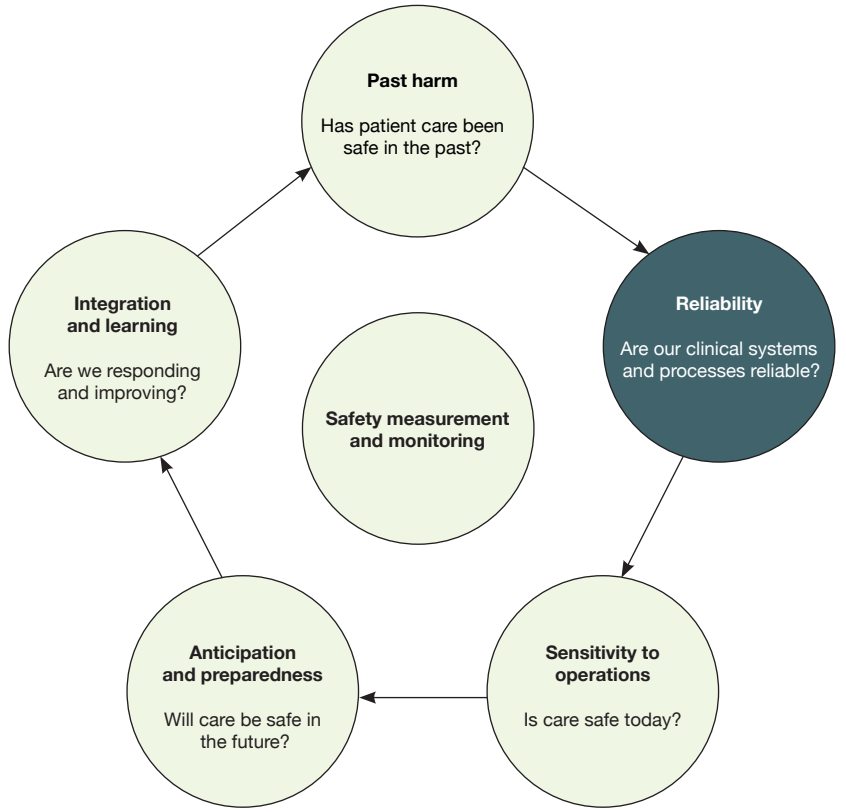
CHAPTER 4 Guideline compliance for bridging anticoagulation use in vitamin-K antagonist patients; practice variation and factors associated with non-compliance



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THROMBOSIS JOURNAL (2019)

Abstract

Background

Bridging anticoagulation is used in vitamin-K antagonist (VKA) patients undergoing invasive procedures and involves complex risk assessment in order to prevent thromboembolic and bleeding outcomes.

Objectives: Our aim was to assess guideline compliance and identify factors associated with bridging and especially, non-compliant bridging.

Methods

A retrospective review of 256 patient records in 13 Dutch hospitals was performed. Demographic, clinical, surgical and care delivery characteristics were collected. Compliance to the American College of Chest Physicians ninth edition guideline (AT9) was assessed. Multilevel regression models were built to explain bridging use and predict non-compliance.

Results

Bridging use varied from 15.0 to 83.3% (mean = 41.8%) of patients per hospital, whereas guideline compliance varied from 20.0 to 88.2% (mean = 68.5%) per hospital. Both established thromboembolic risk factors and characteristics outside thromboembolic risk assessment were associated with bridging use. Predictors for overuse were gastrointestinal surgery (OR 14.85, 95% CI 2.69–81.99), vascular surgery (OR 13.01, 95% CI 1.83–92.30), non-elective surgery (OR 8.67, 95% CI 1.67–45.14), lowest 25th percentile socioeconomic status (OR 0.33, 95% CI 0.11–1.02) and use of VKA reversal agents (OR 0.22, 95% CI 0.04–1.16).

Conclusion

Bridging anticoagulation practice was not compliant with the AT9 in 31.5% of patients. The aggregated AT9 thromboembolic risk was inferior to individual thromboembolic risk factors and other characteristics in explaining bridging use. Therefor the AT9 risk seems less important for the decision making in everyday practice. Additionally, a heterogeneous implementation of the guideline between hospitals was found. Further research and interventions are needed to improve bridging anticoagulation practice in VKA patients.

4.1 Background

Long-term use of oral anticoagulants such as vitamin-K antagonists (VKA) reduces the risk of thromboembolic events in patients with atrial fibrillation, venous thromboembolism or mechanical heart valves.[1-3] When these patients undergo invasive procedures, such as surgery, the anticoagulant therapy often needs interruption to reduce bleeding. This interruption can increase the risk of thromboembolic complications.[4] In an effort to reduce this risk, short-acting low molecular weight heparin (LMWH) or unfractionated heparin (UFH) are temporarily administered. This is known as 'bridging anticoagulation'.[5-7] In general, anticoagulants are consistently identified in adverse event studies as factors involved in preventable adverse events [8, 9], partially occurring in the context of bridging.[10] Due to the risks involved, bridging anticoagulation urges a careful trade-off between thromboembolic and bleeding risk.[11, 12] Consequently, clinicians are required to perform a thorough risk assessment as part of the decision-making in perioperative VKA management. The American College of Chest Physicians' Antithrombotic Therapy and Prevention of Thrombosis, Ninth Edition guideline (AT9) published in 2012 includes recommendations for this risk assessment by classifying patients in low, moderate or high thromboembolic risk.[4] Bridging is only explicitly recommended for high-risk patients, but might be considered for moderate risk patients too based on individual patient and surgical factors. Compliance to the AT9 risk stratification and similar guidelines related to bridging is suboptimal.[13-15] Non-compliant bridging can be differentiated in underuse or overuse of bridging anticoagulation. Underuse refers to withholding bridging anticoagulation in high thromboembolic risk patients and overuse refers to unnecessarily administering bridging anticoagulation in low thromboembolic risk patients (Fig. 1). Underuse exposes patients to a higher risk of thromboembolic complications whereas overuse exposes patients to a higher risk for bleeding complications.[13-16]

	Compliance type	Description[a]	Potential avoidable consequences
Compliance	Compliant use	Not bridging high-risk patients Bridging high-risk patients	n/a
Non-compliance	Overuse	Bridging low-risk patients	Bleeding complications
	Underuse	Not bridging high-risk patients	Thromboembolic complications

[a] Recommendations for moderate-risk patients involve both bridging or not bridging, so both strategies are considered compliant

Figure 1 A typology of guideline compliance in perioperative VKA management based on the American College of Chest Physicians' Antithrombotic

Both bleeding and thromboembolic complications can have serious consequences for patients' mortality and morbidity.[3, 17] Keeping non-compliant bridging strategies at a minimum should therefore be pursued. Which patients are at risk for non-compliant bridging

strategies is relatively unknown. Together with the risks involved around non-compliant bridging, and accumulating evidence reporting up to a 5-fold increased bleeding incidence when bridging is used, identifying patients at risk for a non-compliant bridging strategy is important in reducing preventable mortality and morbidity.[11, 12, 18] Therefore, this study aims to determine guideline compliance of bridging anticoagulation in everyday practice and identify factors associated with bridging use, especially predictors for non-compliant under- and overuse of bridging anticoagulation in Dutch hospitals.

4.2 Methods

4.2.1 Study design and population

Our current study is part of a larger study evaluating the quality of anticoagulant management in Dutch hospitals by retrospectively reviewing patient records.[19] The hospital sample was stratified by type: university, tertiary teaching, and general hospitals. Within these strata a random selection of hospitals was made while accounting for a proper representation of urban and rural based hospitals. In total, 25 hospitals were invited in two waves of which 13 hospitals participated including two university, four tertiary teaching and seven general hospitals (Fig. 2). Twenty records of patients on long-term VKA, admitted in three consecutive months between June to December 2015 were randomly selected for reviewing the bridging anticoagulation policy. Randomisation of eligible patient records was executed by hospital or research personnel using a random number generator available in common spreadsheet applications. In case of the absence of a required (section of a) health record, a replacement was randomly selected instead. Inclusion criteria were: age ≥ 18 years, length of stay ≥24 h, undergoing acute or elective surgical procedure using general and/or spinal/epidural anaesthesia. Exclusion criteria were: psychiatric or gynaecologic/ obstetric ward admission, admission from or discharge to other hospitals, trauma other than hip fractures on admission, pregnancy or six weeks postpartum and palliative care admission. We excluded patients from analysis if the bridging policy was not recorded, preventing the bridging classification or in case of continued VKA during surgery, making bridging unnecessary (Fig. 2).

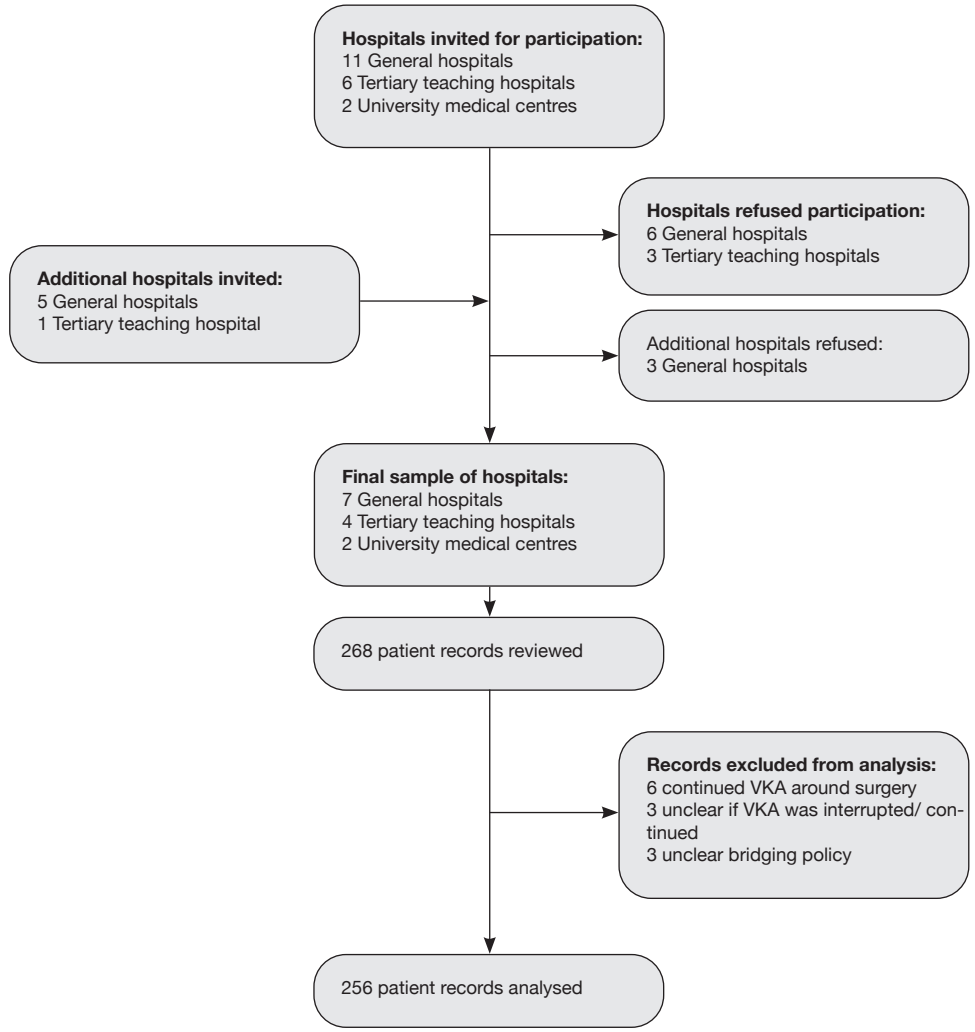

Figure 2 Hospital sample and patient record flowchart

4.2.2 Guideline selection

At the time of data collection in 2015 the Dutch guideline that encompassed bridging anticoagulation in VKA patients was the Guideline for Diagnostics, Prevention and Treatment of Venous Thromboembolism and Secondary Prevention of Arterial Thrombosis released by the former Dutch Quality Institute for Healthcare (CBO) in 2008.[20] This guideline however was an adoption of the ACCP guideline for warfarin patients released back in 2004.[21] During study preparations it became apparent that in 2015, current practice had moved on and the CBO guideline, at least partially, reflected outdated evidence regarding bridging anticoagulation. Especially since the ACCP updated their guidelines in 2008 and 2012. Several hospitals that were included in our study already pointed out that the AT9 recommendations regarding bridging were incorporated in local protocols. Taken altogether, using the AT9 as a frame of reference for the current study was regarded as the most appropriate.

4.2.3 Patient record review and compliance assessment

The patient record review consisted of two phases. Phase one involved the extraction of all data from patient records. Phase two involved the actual bridging anticoagulation evaluation. A panel of five experts in the thrombosis and haemostasis field, all of whom participated in guideline development on antithrombotic care, were consulted throughout the two phases. The panel contributed in developing standardized case report forms for phase one and classification models for determining guideline compliance in phase two.

4.2.3.1 Phase one: data extraction

In phase one, LMWH and UFH administration data was extracted from the patient records. Other data extracted were: demographic, clinical, surgery, and care delivery characteristics (Additional file 1: Tables S2-S3). For demographic characteristics variables such as age, sex and socioeconomic status (SES) were collected. SES was extracted from open source data available from the Netherlands Institute for Social Research and matched with our data using the patients four-digit zip code.[22] Clinical characteristics primarily included risk factors used for determining the AT9 thromboembolic risk classification.[4] These were supplemented with characteristics used in thrombo-prophylaxis risk assessment[23, 24] and patient related risk factors for bleeding as well as surgical bleeding.[25, 26] A previous bleeding event was defined as any bleeding coming to the attention of the treating physician. In absence of an alternative validated instrument, determination of surgical bleeding risk was based on a Dutch expert consensus classification of procedures in low-, medium- or high-risk strata.[27] Other surgical characteristics extracted were: type, duration, whether a second surgery was performed and type of anaesthesia. Lastly, care delivery characteristics based on adverse event studies, such as weekend admission or surgery, were extracted.[28-30] Data extraction took place from January to August 2016. Trained research assistants and one researcher (MM) extracted all patient record data. The study protocol was approved by the medical ethics committee of the VU University Medical Centre, Amsterdam, The Netherlands and the informed consent was waived because of the use of patient record data only (protocol number: 2015/430).

4.2.3.2 Phase 2: classification of guideline compliance

In phase two, patients were classified on thromboembolic risk according to the AT9 (Additional file 1: Table S1) and bridging anticoagulation use. In case of multiple indications for VKA use (e.g. atrial fibrillation and mechanical heart valve), the indication associated with the highest thromboembolic risk was used for determining guideline compliance. The bridging anticoagulation classification was based on postoperative administration of LMWH or use of continuous intravenous UFH infusion. Prophylactic LMWH regimens were not classified as bridging. See Additional file 1: Table S2 for details on LMWH dosages classified as bridging anticoagulation. Compliance with the guideline was defined as withholding bridging anticoagulation in low thromboembolic risk patients and administering bridging anticoagulation in high thromboembolic risk patients. Underuse was defined as not bridging high thromboembolic risk patients. Overuse was defined as bridging low thromboembolic risk patients (Fig. 1). For moderate-risk patients, both bridging and non-bridging were defined as compliant, since the AT9 does not recommend a specific approach for this patient group.

4.2.4 Statistics and model development

To describe the study population regarding demographic, clinical, surgical and care delivery characteristics we used descriptive statistics. Characteristics associated with bridging use were analysed with univariable and multivariable logistic regression. The dependent variable in our first model was: bridging versus no bridging. Independent variables considered for entry in the model were the aforementioned demographic, clinical, surgical and care delivery characteristics. To predict a guideline discordant bridging decision in relation to the AT9 guideline, we created two separate models. One to identify predictors for overuse in the low thromboembolic risk population and one to identify predictors for underuse in the high thromboembolic risk population. Independent variables in this second and third model were slightly different compared to the first model. We excluded variables for which the exposure to the independent variable did not precede the measurement of the dependent variable (admission on critical or cardiac care unit, length of stay, presence of central venous or spinal and epidural catheters, second surgery performed, laboratory tests during admission). Furthermore, the AT9 thromboembolic risk was not considered as an independent variable since thromboembolic risk served as the foundation for the classification of, under and overuse of bridging, therefore not being informative. Univariable logistic regression results are presented as odds ratios (OR) and 95% confidence intervals (95% CI). Results were considered significant if the 95% CI did not intersect unity. Following the univariable analyses, a p value entry level set at < 0.10 was used for a multivariable forward selection procedure. The maximum number of independent variables allowed in the models was based on the 10:1 rule to prevent overfitting.[31] Cases with missing values for independent variables were excluded from the regression analyses. Furthermore, variables with more than 10% missing values were not considered for multivariable modelling. To enable our models to estimate predictor coefficients independent of possible practice variation between hospitals, we applied a multilevel approach in all regression analyses. Because the patient data were clustered within hospitals a random intercept on hospital level was allowed. C-statistics were calculated to evaluate the discriminative power of the models. A c-statistic of 0.5 to 0.7 is interpreted as a low discriminative power, 0.7–0.9 as moderate and > 0.9 as high. Statistical analyses were performed with SPSS version 22 (IBM, Chicago, IL).

4.3 Results

4.3.1 Study population

In total, 268 records were reviewed of which 256 records were eligible for bridging anticoagulation analyses (Fig. 2). The mean age of patients was 74.8 (SD = 10.6) years, 55.9% were male. Other characteristics are displayed in Table 1. Atrial fibrillation was the most common indication for VKA use with (74.2%). Thromboembolic risk was low, moderate or high in 52.7, 14.8 and 15.6% of patients respectively. 33 (12.9%) patients used VKA for other indications than AT9 provides recommendations and could thus not be classified according to AT9 thromboembolic risk. In 10 (3.9%) patients the records provided insufficient information for thromboembolic risk classification.

Table 1 Demographic, clinical and surgical characteristics for the overall population

	Patients N = 256
Demographic characteristics	
Male sex	143 (55.9)
Age (years), mean (SD)	74.76 (10.59)
Clinical characteristics	
AT9 Thromboembolic risk	
Low	135 (52.7)
Moderate	38 (14.8)
High	40 (15.6)
Other VKA indication [a]	33 (12.9)
Risk factors unknown	10 (3.9)
Atrial fibrillation	190 (74.2)
Mechanical heart valve	20 (7.8)
Venous thromboembolism	34 (13.3)
Previous thromboembolic event during VKA interruption	3 (1.2)
iCVA/TIA	37 (14.5)
Thrombophilia	7 (2.7)
Coronary heart disease	74 (28.9)
Heart failure	20 (7.8)
Hypertension	129 (50.4)
Diabetes mellitus	62 (24.2)
Active cancer/malignancy	54 (21.5)
Previous bleeding[b]	13 (5.1)
VKA regimen	
Acenocoumarol	203 (79.3)
Phenprocoumon	53 (20.7)
Length of stay (days): median (IQR)	6 (3–10)
Surgery characteristics	
Elective	181 (70.7)
Type of 1st surgery	
Urologic	40 (15.6)
Orthopaedic	89 (34.8)
Gastrointestinal	52 (20.3)
Vascular	36 (14.1)
Other	39 (15.2)
Surgical bleeding risk	
High	209 (81.6)
Moderate	44 (17.2)
Low	3 (1.2)

Results are expressed as n (%) unless stated otherwise
AT9: Antithrombotic Therapy and Prevention of Thrombosis, Ninth Edition guideline, iCVA: ischaemic cerebrovascular accident, IQR: inter quartile range, SD: standard deviation, TIA: transient ischaemic attack, VKA: vitamin-K antagonist
[a] No AT9 risk classification is available for VKA indications other than atrial fibrillation, mechanical heart valves and venous thromboembolism
[b] Any previous bleeding event annotated in the medical record

Table 2 displays the AT9 thromboembolic risk of the patients for each of the indications for VKA use. The most prevalent thromboembolic risk category was low for atrial fibrillation patients (69%), moderate for venous thromboembolism patients (65%) and high for mechanical heart valve patients (45%).

Table 2 AT9 thromboembolic risk for each of the VKA indication groups

	Indication group: n (column %) [a]		
AT9 Thromboembolic risk	**Atrial fibrillation**	**Mechanical heart valve**	**Venous thromboembolism**
Low	131 (69)	1 (5)	6 (18)
Moderate	19 (10)	4 (20)	22 (65)
High	35 (18)	9 (45)	4 (12)
Unknown [b]	5 (3)	6 (30)	2 (6)

AT9: Antithrombotic Therapy and Prevention of Thrombosis, Ninth Edition guideline; VKA: vitamin-K antagonist
[a] Multiple indications are possible
[b] Insufficient documentation of risk factors in the records, so the AT9 risk could not be determined

4.3.2 Bridging use and guideline compliance

In 107 (41.8%) patients, bridging anticoagulation was used. Bridging rates between hospitals ranged from 15 to 83% of all patients per hospital (Fig. 3a). Based on the AT9 thromboembolic risk recommendations, the decision to apply or withhold bridging anticoagulation was compliant with the guideline in 68.5% of all patients for which the thromboembolic risk could be determined (N = 213). Compliance rates for each AT9 risk and VKA indication strata are given in Table 3. Compliance was lowest for high risk atrial fibrillation patients (46%, N = 35), low risk venous thromboembolism (50%, N = 6) and low risk mechanical heart valve patients (0%, N = 1), however the latter two were very small strata.

Low risk atrial fibrillation patients on the other hand, comprised the largest stratum in our study (51.2% of the total population), with a compliance of 67%.

Table 3 Compliance of postoperative bridging per indication and AT9 thromboembolic risk group

	Compliance of postoperative bridging per indication group: n(%) [a]		
AT9 Thromboembolic risk	Atrial fibrillation	Mechanical heart valve	Venous thromboembolism
Low	88 (67)	0 (0)	3 (50)
Moderate	19 (100)	4 (100)	22 (100)
High	16 (46)	5 (56)	3. (75)

AT9: Antithrombotic Therapy and Prevention of Thrombosis, Ninth Edition guideline; VKA: vitamin-K antagonist
[a] Multiple indications are possible

Comparing hospitals, the compliance rate ranged from 20 to 88% of all patients per hospital (Fig. 3b).

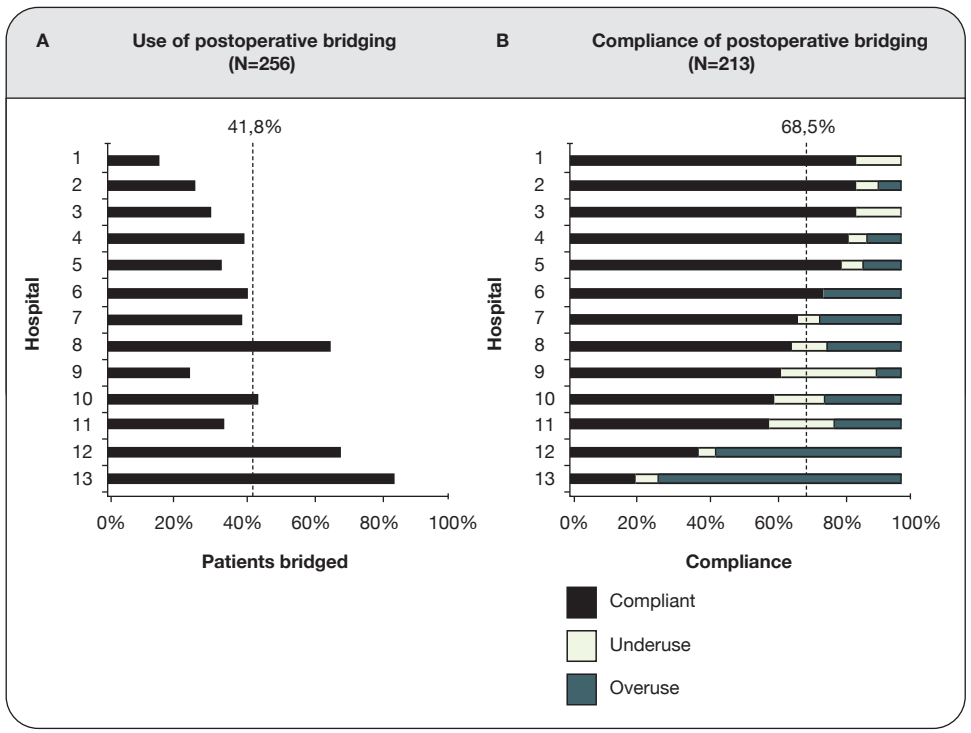

Figure 3 Barcharts displaying the use (a) and compliance (b) of postoperative bridging anticoagulation per hospital and on average. The dashed vertical

4.3.3 Factors associated with use of bridging anticoagulation

Univariable logistic regression results for the application of bridging are presented in Additional file 1: Table S3. Compared to low-risk patients, moderate thromboembolic risk patients had a significant increased odds (OR 3.36, 95% CI 1.52–7.41) and highrisk patients a borderline insignificant increased odds (OR 2.05, 95% CI 0.95–4.21) for receiving bridging anticoagulation. Furthermore, all three main indications for VKA use were significantly associated with bridging: mechanical heart valve (OR 3.69, 95% CI 1.34–10.20) and venous thromboembolism (OR 2.35, 95% CI 1.09–5.07) patients were more likely to receive bridging anticoagulation while atrial fibrillation patients (OR 0.50, 95% CI 0.27–0.92) were less likely to be bridged. Characteristics outside the AT9 thromboembolic risk assessment associated with bridging were length of hospital stay (OR 1.07 per day, 95% CI 1.03–1.11), critical or cardiac care unit admission (OR 3.80, 95% CI 1.80–8.05), second surgery (OR 6.45, 95% CI 1.96–21.21), and admission to a university hospital (OR 3.94, 95% CI 1.16–13.35). Lastly, gastrointestinal (OR 3.83, 95% CI 1.50–9.74), vascular (OR 3.74, 95% CI 1.36–10.29) and other (OR 3.06, 95% CI 1.12–8.39) surgery types were positively associated with bridging. Our multivariable logistic regression analysis included 249 patients and resulted in a model with critical or cardiac care unit admission, second surgery, mechanical heart valve, surgery type, venous thromboembolism, ischeamic CVA or TIA and previous bleeding, as explanatory variables for bridging use. Regression parameters are displayed in Table 4. The model's power to discriminate between bridged and non-bridged patients was moderate (c-statistic 0.85, 95% CI 0.80–0.90).

Table 4 Multivariable logistic regression models for bridging use and overuse of bridging, adjusted for clustering at hospital level

	OR (95% CI)[a]
Model 1, All patients	
Bridging used (reference: no bridging used)	
ICU/CCU stay during admission	4.45 (1.72–11.51)
Second surgery performed	3.21 (0.83–12.49)
Mechanical heart valve	8.10 (2.38–27.50)
Type of 1st surgery (reference category: urologic)	
Orthopaedic	1.10 (0.42–2.91)
Gastrointestinal	3.45 (1.21–9.87)
Vascular	3.21 (1.01–10.21)
Other	3.57 (1.14–11.21)
Venous thromboembolism	3.91 (1.57–9.74)
iCVA/TIA	2.49 (1.02–6.11)
Previous bleedingb	3.59 (0.80–16.17)
Model 2, Low TE risk patients:	
Overuse of bridging (reference: compliant use)	
Type of 1st surgery (reference category: urologic)	
Orthopaedic	3.18 (0.60–16.71)

Gastrointestinal	14.85 (2.69–81.99)
Vascular	13.01 (1.83–92.30)
Other	57.30 (5.27–623.62)
Non-elective surgery	8.67 (1.67–45.14)
Lowest 25th percentile SES	0.33 (0.11–1.02)
VKA reversal agent used	0.22 (0.04–1.16)

CCU: cardiac care unit, ICU: intensive care unit, iCVA: ischaemic cerebrovascular accident, TIA: transient ischaemic attack, SES: Socioeconomic status, VKA: Vitamin-K antagonist
a Adjusted for clustering at hospital level
b Any previous bleeding event annotated in the medical record

4.3.4 Predictors of over- and underuse of bridging anticoagulation

Overuse of bridging anticoagulation occurred in 34.1% of low thromboembolic risk patients and underuse occurred in 52.5% of high thromboembolic risk patients. Univariable logistic regression results for both over- and under use are presented in Additional file 1: Table S4. Within low risk patients, positive associations for overuse of bridging were found for non-elective surgery (OR 2.72, 95% CI 1.03–7.19), gastrointestinal (OR 15.87, 95% CI 3.02–83.42), vascular (OR 9.58, 95% CI 1.49–61.42) and other (OR 27.43, 95% CI 3.49–215.38) surgery types, and admission to a university medical centre (OR 9.01, 95% CI 1.05–77.57). The high risk patient strata was of limited size (40 patients). Hence, the power to capture a significant association for underuse within this population was limited. Only a borderline insignificant effect for surgery duration was observed (OR 0.98 per minute, 95% CI 0.96–1.00). The multivariable logistic regression parameters for predicting overuse of bridging are presented in Table 4.Surgery type and non-elective surgery were positive predictors whereas membership of the lowest 25th percentile SES and VKA reversal agent use were negative predictors for overuse of bridging. The discriminative power for predicting overuse of bridging was high (c-statistic 0.91, 95% CI 0.86–0.97).

4.4 Discussion

4.4.1 Bridging use and guideline compliance

In 31.5% of the patients in our sample the bridging anticoagulation policy was not compliant with the American College of Chest Physicians' Antithrombotic Therapy and Prevention of Thrombosis, Ninth Edition recommendations. Bridging was used during 41.8% of VKA interruptions, lower than reported in existing literature.[13, 14, 16] As a result, the 52.5% underuse of bridging was higher in our study compared with 36.8 and 13.0% reported in other studies.[13, 14] Conversely, the 34.1% overuse of bridging in low risk patients is on the lower side of the spectrum of overuse rates reported by others that ranged between 28.7 and 84.3%.[13-15] However, these low-risk patients represent over 50% of the VKA patient population in our study and are mostly patients with atrial fibrillation. Although the exact number of VKA patients undergoing surgery in the Netherlands is unavailable, there are over 460.000 VKA patients present.[32] Based on our findings, overuse of bridging is likely to occur in a substantial amount. In light of accumulating evidence towards increased bleeding risk among bridged patients this overuse warrants attention. In a meta-analysis of predominantly observational studies, Siegal et al. 2012 found that bridged patients had a 5-fold increased risk for overall, and a 3-fold increased risk for major bleeding.[11, 12] This was confirmed by Douketis et al. in 2015 in the BRIDGE-trial, where the risk of major bleeding was 0.41; 95% CI 0.20–0.78 for non-bridged patients relative to bridged patients.[12] Bleeding complications occurring in bridged patients have been found to increase the risk for reoperation and prolonged hospitalisation.[33, 34] Moreover, the BRIDGE-trial also found that nonbridging was not associated with an increased incidence of thromboembolic complications, which contradicts the rationale behind bridging anticoagulation. Given this evidence and our study results, low risk atrial fibrillation patients undergoing surgery comprise a large group of patients who might benefit the most from improvement efforts to reduce bridging overuse and reduce adverse bleeding outcomes.

4.4.2 Factors associated with bridging anticoagulation, predicting over- and underuse

To understand why current bridging practice is not always in line with guideline recommendations we aimed to identify characteristics associated with bridging use. The associations found for atrial fibrillation, mechanical heart valve and venous thromboembolism patients correspond with the findings of others where most atrial fibrillation patients did not receive bridging and most mechanical heart valve and venous thromboembolism patients were at least at moderate thromboembolic risk justifying bridging anticoagulation use.[14, 35, 36] Regarding, the aggregated AT9 thromboembolic risk strata, the moderate and high risk strata were more likely to receive bridging, which is to be expected. However, the introduction of individual thromboembolic risk factors and other characteristics in our multivariable analysis rendered the association insignificant. Translating this to practice, it can be argued that awareness to the aggregated AT9 thromboembolic risk might be limited to individual risk factors that make up the AT9 risk strata. Also, patient characteristics outside the AT9 thromboembolic risk assessment may be involved in the decision to apply bridging. Our study points to several of these. First, a history of bleeding showed a positive association with bridging. This seems contradictory, and is difficult to explain. One would expect a more conservative approach to using bridging anticoagulation in patients with signs of a previous bleeding. However, only recently the risks of bridging versus uninterrupted anticoagulation were supported with high quality data. Before this, bridging with fast onset and offset heparins seemed the safest option. Second, bridging use and overuse occurred more frequently in gastrointestinal, vascular and other surgery types compared with urologic and orthopaedic surgery. Perceived thromboembolic risks relative to the surgical procedures can play a role. The AT9 thromboembolic risk classification does not formally include this but designates certain high thromboembolic risk procedures.[4] Furthermore, heterogeneous practice and preferences between medical specialties related to the studied surgery types might be responsible for our findings. A recent survey study underscores this. Flaker et al. (2016), found different perioperative management strategies between medical specialties.[37] Third, Intensive or cardiac care unit admission and a second surgery were associated with higher bridging rates. We think this is possibly explained by factors related with the severity of the patient's disease and clinical course that we were unable to correct for, such as the inability to take oral medication. In these cases parenteral heparins are a feasible alternative to oral VKAs. Regarding bridging overuse specifically, primarily surgical characteristics such as type and urgency were predictive for non-compliant use of bridging. Based on these characteristics, the population at which further investigation

and improvement efforts should aim for can be narrowed down. Additionally we found that membership of the lowest 25th percentile socioeconomic status was a significant negative predictor for overuse. Besides socioeconomic status being a well-established determinant for health and access to health services,[38, 39] associations with guideline compliance have also been found before.[40, 41] Altogether, our exploratory analyses indicate that current bridging anticoagulation practice is not explained by the ACCP's thromboembolic risk assessment recommendations alone. Our study therefore confirms the findings of several other studies.[14, 15, 42, 43] Why practice is not in accordance with bridging recommendations is relatively unknown. Whether the other associated clinical and surgical characteristics identified, are the result of a conscious assessment in everyday bridging practice, cannot be concluded based on our results.

4.4.3 Practice variation

Our results also revealed variation between hospitals. Bridging varied from 15 to 83% of patients, similar to a US study where rates ranged from 10 to 88%.[36] Furthermore, hospitals that bridged more frequently had lower compliance rates and higher overuse rates. Thus, higher bridging rates cannot solely be explained by casemix differences regarding thromboembolic risk. More likely, a heterogeneous implementation or embedment of guidelines into local processes and protocols results in variations in practice. For example, differences in responsible professionals in terms of specialty or experience might affect the risk assessment for bridging anticoagulation. The existence of variation like this was endorsed in a Dutch report revealing substantial differences between hospital's adaptations of an integrated anticoagulant care guideline. This guideline predominantly contains recommendations regarding care processes, responsibilities and communication for anticoagulant care. Among others, a major difference observed was the instalment of dedicated anticoagulation committee's or case managers while other hospitals were less progressive.[44]

4.4.4 Strengths and limitations

Our study has several strengths and limitations. Our multi-centre design is a strength and informs us on bridging anticoagulation practice in a variety of hospitals while the entire sample was representative for the Dutch hospital distribution. The voluntary hospital participation can be regarded as a limitation that could have introduced selection bias on hospitals' awareness or priority regarding anticoagulant care. The retrospective approach is another strength in ensuring results not being influenced by carrying out the study but rather reflect everyday care. On the other hand, the dependency of routinely recorded medical data might be a limitation. Although efforts were made to retrieve all required information, some records were found to be too incomplete to include and others were prone to missing information, especially details required for thromboembolic risk classification of mechanical heart valve patients. While this might have introduced some bias to our results, it also stresses the importance of adequate record quality. Additionally, we wish to nuance non-compliance. First, our study was carried out in a transition period between an outdated guideline and the adoption of the AT9. Second, the reasoning behind informed guideline deviations were not collected from the medical records. Hence, we wish to point out that non-compliance with the guidelines does not necessarily reflect poor care. Lastly, the limited amount of high risk patients in our sample prevented a multivariable analysis for bridging underuse.

4.5 Conclusions and implications

In 31.5% of the patients the bridging anticoagulation policy was not in line with the AT9 recommendations. Improvement efforts targeted at low-risk atrial fibrillation patients are expected have the biggest effect on overall compliance and potentially adverse outcomes since these patients represented over 50% of our study population. Bridging was predominantly related with individual clinical and surgical characteristics rather than the aggregated AT9 thromboembolic risk. Overuse of bridging, was the most prevalent form of non-compliance. Gastrointestinal, vascular and non-elective surgery were risk factors for overuse. Underuse of bridging in high-risk patients was less prevalent and no significant risk factors were identified. Our results raise the question whether AT9 risk assessment sufficiently reflects the risks that are perceived in everyday practice or if they are deviant for other reasons. Also a large variation in bridging practice between hospitals was observed, where hospitals with high bridging rates had lower compliance rates and vice versa. Based on our study, several implications can be thought of to improve bridging anticoagulation practice. 1) Qualitative research can inform us on the reasons and mechanisms leading to differences between everyday practice and what is advocated in the guidelines. 2) The characteristics associated with non-compliant bridging, should be taken in to account in interventions aimed at improving decision making in bridging anticoagulation, e.g. electronic decision support systems. 3) Variation between hospitals regarding the implementation and embedment of guidelines in local practice should be studied to identify factors related with practice variation.

4.6 Acknowledgements

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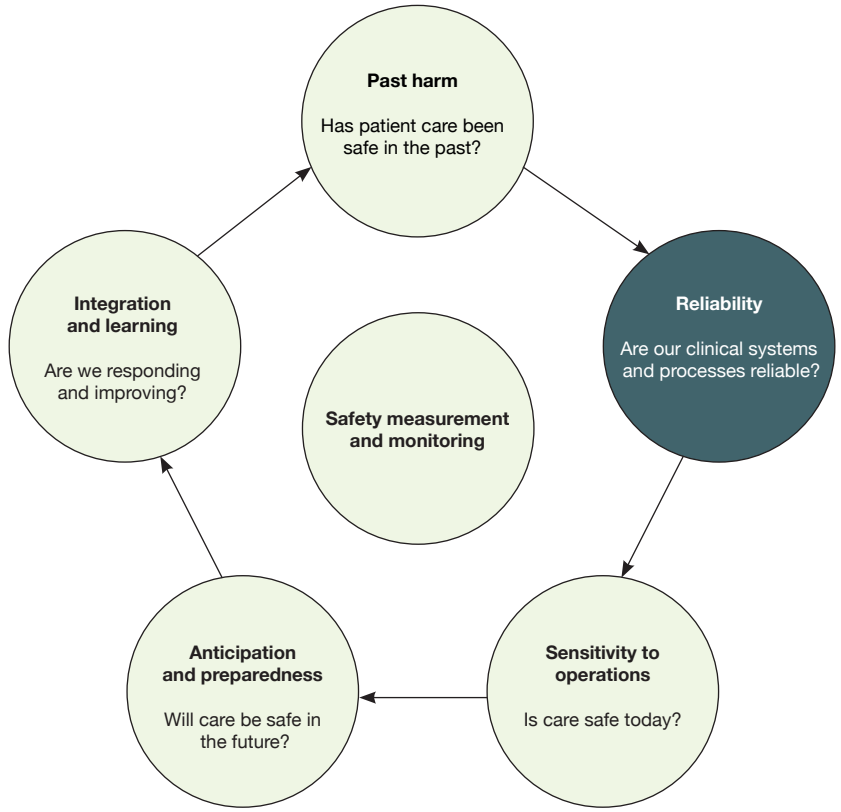
CHAPTER 5

Guidelines' risk assessment recommendations for venous thromboembolism prophylaxis: A comparison and implementability appraisal



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THROMBOSIS RESEARCH (2018)

Abstract

Introduction

Venous thromboembolism (VTE) prophylaxis guidelines for non-surgical patients recommend VTE and bleeding risk assessment to guide prophylactic strategies. These recommendations differ between guidelines and implementation is suboptimal. Assessing a guideline's implementability characteristics helps predicting the ease of implementation and reveals barriers.

Objectives

We aimed to compare guidelines' risk assessment recommendations and critically appraise the implementability characteristics.

Material and methods

Two guidelines, one from the American College of Chest Physicians and one from the National Institute for Health and Care Excellence were selected for comparison. Risk assessment methods and subsequent prophylactic recommendations were compared. Eight experts then appraised the guideline recommendations on intrinsic implementability characteristics using the GuideLine Implementability Appraisal (GLIA) instrument. GLIA identifies barriers and facilitators for guideline implementation in nine dimensions.

Results

Eleven out of 20 individual VTE-risk factors and 2 out of 19 individual bleeding-risk factors used, were present in both guidelines. Additionally, a high VTE- or bleeding risk was defined differently between the two guidelines. The GLIA appraisal identified implementation barriers within all recommendations analyzed. On content level, barriers were identified in recommendations addressing bleeding risk assessment, mechanical prophylaxis and critical care patients. On implementability level, barriers were identified in decidability, flexibility, effect on process of care and computability dimensions.

Conclusion

Depending on the guideline used, VTE-prophylaxis will most likely be provided to different non-surgical patient populations, primarily due to discordance in bleeding risk assessment. Revising the recommendations, taking into account the most apparent implementation barriers, should be considered. However, insufficient evidence to support the recommendations currently complicates this.

5.1 Introduction

Venous thromboembolism (VTE), comprising deep vein thrombosis and pulmonary embolism, is a well-known complication in hospitalized patients, resulting in a significant increase in patient mortality and morbidity.[1, 2] Half to three quarters of all hospital-associated VTE events occur in non-surgical patients.[3, 4] Pharmacological prophylaxis with low molecular weight heparin reduces the incidence of VTE in hospitalized non-surgical patients.[5-7] The use of VTE-prophylaxis is supported by evidence based consensus guidelines available since 1986.[8, 9] These guidelines present ways to support risk assessment of VTE based on numerous risk factors. Patients classified with a high risk for VTE are eligible for prophylaxis. However, multiple guidelines are available for the same clinical problem which leads to guidelines conflicting with each other. As a result guidelines validity is questioned and the clinical decision making is complicated.[10] Few studies addressed this issue for VTE-prophylaxis guidelines. The studies that did, were mainly aimed at surgical patient populations.[11-13] Furthermore, the implementation of VTE-prophylaxis guidelines in hospitalized nonsurgical patients is known to be suboptimal with reported adherence rates ranging from 12.7% to 49%.[14-17] Interventions aimed at improving guideline adherence resulted in improvements averaging around 80%.[18] However, a majority of these interventions require substantial resources to maintain high guideline adherence. Until now, the implementability of VTE guidelines for nonsurgical patients has hardly been studied. The implementability of a guideline can be defined as "a set of characteristics that predict the relative ease of implementation of guideline recommendations".[19] Implementability factors can be categorized as extrinsic or intrinsic. Extrinsic factors can be organizational and provider specific obstacles inherent to a specific healthcare system.[19] Intrinsic characteristics are for example: unambiguity, consistency, and completeness.[20, 21] Identification of these intrinsic factors is especially important because they can, in a majority of cases, be taken care of during the guideline development.[19] Consequently, if improvements are made to these intrinsic characteristics, this could result in improved evidence-based care and outcomes.[22] To our knowledge the implementability of guidelines addressing VTE-prophylaxis for hospitalized non-surgical patients has not been assessed before. Therefore, our aim for this study is twofold.

First, to compare the risk assessment recommendations of two influential international guidelines for VTE-prophylaxis in hospitalized non-surgical patients. Second, to critically appraise the two guidelines on the intrinsic implementability characteristics of their risk assessment recommendations. As a result, inconsistencies between guideline recommendations and possible barriers and facilitators for the guideline implementability will be revealed.

5.2 Materials and Methods

5.2.1 Patient population and guideline selection

This study focuses on non-surgical patients admitted for an acute medical illness. Patients admitted for stroke are outside the study scope, since specific recommendations for VTE-prophylaxis for this group exist.

We aimed to compare two influential original guidelines that were independently developed and not adaptations from other guidelines. Expert opinion was used to determine

the most important original guidelines. In preparation of a Dutch VTEprophylaxis guideline, experts from the 'Knowledge Institute of Medical Specialists' (Kennisinstituut van Medisch Specialisten) Utrecht, The Netherlands designated two original guidelines as most influential. These were "the antithrombotic therapy and prevention of thrombosis, 9th edition" guideline from the American College of Chest Physicians (ACCP) published in 2012 and the "venous thromboembolism in adults admitted to hospital: reducing the risk" guideline from the National Institute for Health and Care Excellence (NICE) published in 2010.[23, 24] Both served as a basis for the Dutch guideline concerning V-prophylaxis.[25]

5.2.2 Aim 1: Comparison of risk assessment recommendations

The recommendations on the use of VTE-prophylaxis typically require a trade-off between patient's VTE- and bleeding risk. When the VTE-risk is elevated, VTEprophylaxis should be considered. However, if the patient's bleeding risk is also elevated, pharmacologic prophylaxis can be contra-indicated, because of its increased risk for bleeding complications. Mechanical forms of VTE-prophylaxis might be more suitable for these patients. Recommendations from both guidelines addressing the following risk assessment components were selected for a comparison on content level:

1. Risk factors included in the VTE-risk assessment
2. Risk factors included in the bleeding risk assessment
3. Criteria for indicating pharmacologic VTE-prophylaxis
4. Criteria for contra-indicating VTE-prophylaxis
5. Criteria for indicating mechanical VTE-prophylaxis

5.2.3 Aim 2: Implementability appraisal

The second aim of this study was to critically appraise the included guideline recommendations on their intrinsic implementability characteristics using a panel of experts. The Guideline Implementability Appraisal (GLIA) instrument was used for this.[19] This instrument collects expert opinion using structured questions to anticipate on guideline implementation barriers. GLIA consists of two parts. The first part includes nine questions on global considerations to be answered for the guideline as a whole. The second part includes 21 questions specifically aimed at the individual guideline recommendations and, as such, must be answered for each individual recommendation. The 21 questions in part two cover eight dimensions relating to intrinsic implementability: executability, decidability, validity, flexibility, effect on process of care, measurability, novelty/innovation and computability. The GLIA instrument is provided in supporting information Table 1. All questions have four response categories: 'yes', 'no', 'not applicable' and 'unsure'. Questions answered with 'no' indicate implementability barriers. Part two of the GLIA instrument, was only applied to recommendations concerning risk assessment and prophylaxis use. The recommendations selected for GLIA appraisal are given in Table 1. When a recommendation referred to other specific information in the guideline, e.g. a table, this information was provided together with the recommendation to the appraisal panel.

Table 1 Recommendations appraised with eGLIA for each guideline

Guideline	Recommendations appraised with eGLIA
ACCP	2.3. For acutely ill hospitalized medical patients at increased risk of thrombosis (Table 2), we recommend anticoagulant thromboprophylaxis with LMWH, LDUH bid, LDUH tid or fondaparinux 2.4. For acutely ill hospitalized medical patients at low risk of thrombosis (Table 2), we recommend against the use of pharmacologic prophylaxis or mechanical prophylaxis 2.7.1. For acutely ill hospitalized medical patients who are bleeding or at a high risk for bleeding (Table 3), we recommend against anticoagulant thromboprophylaxis 2.7.2. For acutely ill hospitalized medical patients at increased risk of thrombosis who are bleeding or at high risk for major bleeding, we suggest the optimal use of mechanical thromboprophylaxis with graduated compression stockings (GCS) or intermittent pneumatic compression (IPC), rather than no mechanical thromboprophylaxis. When bleeding risk decreases, and if VTE-risk persists, we suggest that pharmacologic thromboprophylaxis be substituted for mechanical thromboprophylaxis 3.4.3. For critically ill patients, we suggest using LMWH or LDUH thromboprophylaxis over no prophylaxis 3.4.4. For critically ill patients who are bleeding, or are at high risk for major bleeding (Table 3), we suggest mechanical thromboprophylaxis with GCS or IPC until the bleeding risk decreases, rather than no mechanical thromboprophylaxis. When bleeding risk decreases, we suggest that pharmacologic thromboprophylaxis be substituted for mechanical thromboprophylaxis
NICE	1.1.2. Regard medical patients as being at increased risk of VTE if they: – have had or are expected to have significantly reduced mobility for 3 days or more or – are expected to have on-going reduced mobility relative to their normal state and have one or more of the risk factors shown in box 1 1.1.4. Assess all patients for risk of bleeding before offering pharmacological VTE-prophylaxis. Do not offer pharmacological VTE-prophylaxis to patients with any of the risk factors for bleeding shown in box 2, unless the risk of VTE outweighs the risk of bleeding 1.4.1. Offer pharmacological VTE-prophylaxis to general medical patients assessed to be at increased risk of VTE. Choose any one of: – fondaparinux sodium – low molecular weight heparin (LMWH) – unfractionated heparin (UFH) (for patients with severe renal impairment or established renal failure) 1.4.6. Offer pharmacological VTE-prophylaxis to patients with cancer who are assessed to be at increased risk of VTE (see Section 1.1). Choose any one of: – fondaparinux sodium – LMWH – UFH (for patients with severe renal impairment or established renal failure) Start pharmacological VTE-prophylaxis as soon as possible after risk assessment has been completed. Continue until the patient is no longer at increased risk of VTE. 1.4.7. Do not routinely offer pharmacological or mechanical VTE-prophylaxis to patients with cancer having oncological treatm,nt wh:o are ambulant 1.4.8. Do not routinely offer pharmacological or mechanical VTE-prophylaxis to patients with central venous catheters who are ambulant 1.4.9. Consider offering pharmacological VTE-prophylaxis with LMWH (or UFH for patients with severe renal impairment or established renal failure) to patients with central venous catheters who are at increased risk of VTE (see Section 1.1) 1.4.13. Consider offering mechanical VTE-prophylaxis to medical patients in whom pharmacological VTE-prophylaxis is contraindicated. Choose any one of: – anti-embolism stockings (thigh or knee length) – foot impulse devices – intermittent pneumatic compression devices (thigh or knee length)

1.6.8. Offer VTE-prophylaxis to patients admitted to the critical care unit according to the reason for admission, taking into account:
- any planned interventions
- the use of other therapies that may increase the risk of complications

LMWH: low molecular weight heparin LDUH: low dose unfractionated heparin, GCS: graduated compression stockings, IPC: intermittent pneumatic compression, VTE: venous thromboembolism.

The appraisal was done using the 'eGLIA' electronic version of the GLIA instrument, available at http://nutmeg.med.yale.edu/eglia/.

5.2.3.1 Appraisal process

Our eGLIA appraisal panel comprised four clinical experts in the field of thrombosis and four guideline implementation experts, as was recommended previously.[19] Five of these experts were also involved in the development and implementation of the Dutch Antithrombotic Policy guideline.[26] All appraisers independently completed the appraisal for the selected recommendations and global dimensions. In accordance with previous studies, after finishing the appraisal, each panel member received an overview of their own and other panel members' answers.[27] eGLIA questions for which discrepancy in appraisal existed, defined as less than five appraisals in any of the response categories 'yes', 'no' or 'not applicable', were identified for discussion with the panel. Six appraisers attended a teleconference where discrepancies were discussed. The remaining two appraisers commented by email on the discussion results. Due to the amount of questions for which discrepancy existed, an extensive discussion for every eGLIA question was not feasible. Therefore, only the most important dimensions for guideline implementability, i.e. the executability and decidability dimension, were discussed by phone. If a recommendation is not able to clearly communicate what to do (executability) or when to do it (decidability) it is not fully implementable.[19] Additionally the global considerations were discussed in detail. Discrepancy in the remaining dimensions was discussed by structured emails.

5.2.3.2 Analysis

A priori we defined that the occurrence of at least five 'no' appraisals for a single eGLIA question results in a classification as barrier to guideline implementation for that question. Correspondingly, the occurrence of at least five 'yes' appraisals was defined as a facilitator. If after the discussion, agreement could still not be reached the eGLIA question was marked as a borderline barrier showing the tendency towards the most prevalent response. The proportions of identified barriers per guideline were calculated to enable a comparison between both guidelines on their intrinsic implementability characteristics.

5.3 Results

5.3.1 Comparison of risk assessment recommendations

Table 2 lists the risk assessment components for VTE-prophylaxis together with the guideline's content and recommendations in relation to these components. In the table, seemingly similar risk factors used in the two guidelines are displayed next to each other.

Table 2 Recommendation specifications for the VTE-risk assessment components per guideline

	Guideline	
Risk assessment component	**ACCP**	**NICE**
Risk factors included in the VTE-risk assessment	-Active cancer	-Active cancer or cancer treatment
	-Previous VTE (with the exclusion of superficial vein thrombosis)	-Personal history of VTE
		-First degree relative with a history of VTE
	-Already known thrombophilic condition	-Known thrombophilia's
	-Recent (≤1 month) trauma and/or surgery	
	-Elderly age (≥70 years)	-Age over 60 years
	-Heart failure -Acute myocardial infarction	-Heart disease
	-Respiratory failure	-Respiratory pathologies
	-Acute infection	-Acute infectious diseases
	-Acute rheumatologic disorder	
	-Ischemic stroke	
	-Obesity (BMI ≥30)	-Obesity (BMI ≥ 30)
	-Ongoing hormonal treatment	-Use of hormone replacement therapy
		-Use of oestrogen-containing contraceptives
	-Patients admitted to ICU/CCU	-Critical care admission
		-Inflammatory conditions
		-Metabolic pathologies
		-Endocrine pathologies
		-Dehydration
		-Varicose veins with phlebitis
	-Reduced mobility (anticipated bed rest with bathroom privileges either because of patient's limitations or on physician's order for at least 3 days)	-A significantly reduced mobility (bedbound, unable to walk unaided or likely to spend a substantial proportion of the day in bed or in a chair) for ≥3 days -On-going reduced mobility relative to normal state
Risk factors included in the bleeding risk assessment	-Active gastroduodenal ulcer	
	-Active bleeding	-Active bleeding
	-Bleeding in 3 months before admission	
	-Platelet count $<50 \times 10^9$/L	-Thrombocytopenia (platelets $<75 \times 10^9$/L)
	-Age ≥ 85 years	

	-Hepatic failure (INR > 1.5) -Severe renal failure (GFR <30 mL/min/m2) -ICU or CCU admission -Central venous catheter -Rheumatic disease -Current cancer -Male sex	-Acquired bleeding disorders (such as acute liver failure) -Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with INR higher than 2) -Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 h -Lumbar puncture/epidural/spinal anaesthesia within the previous 4 h -Acute stroke -Uncontrolled systolic hypertension (230/120mmHG or higher) -Untreated inherited bleeding disorders (such as haemophilia and von Willebrand's disease)
Criteria for indicating pharmacologic VTE-prophylaxis	Patients with PADUA score ≥ 4 Patients admitted to ICU/CCU	Patients with or expected to have a significantly reduced mobility for ≥3 days Patients expected to have on-going reduced mobility relative to their normal state and have one or more of the above VTE-risk factors Patients with a cancer and have one or more of the above VTE-risk factors Patients with a central venous catheter and having one or more of the above VTE-risk factors Patients admitted to the critical care unit according to the reason for admission and taking into account: any planned interventions and the use of other therapies that may increase the risk of complications
Criteria for contra-indicating pharmacologic VTE-prophylaxis	Patients who are bleeding Patients with more than one of the above mentioned risk factors	Patients with any of the risk factors for bleeding, unless the risk of VTE outweighs the risk of bleeding

	Patients with active gastroduodenal ulcer Patients with bleeding in 3 months before admission Patients with a platelet count $<50 \times 10^9$/L	
Criteria for indicating mechanical VTE-prophylaxis	Patients classified as having an increased risk of VTE and are bleeding or classified as being at high risk for bleeding	Patients for whom pharmacologic prophylaxis is contra-indicated

VTE: venous thromboembolism, BMI: body-mass index, ICU: intensive care unit, CCU: cardiac care unit, INR: international normalized ratio.

5.3.1.1 Risk factors included in the VTE-risk assessment

Combined, 20 individual VTE-risk factors are listed in the guidelines. Eleven are prevalent in both guidelines with operational differences between the guidelines for: 'age' (≥60 vs ≥70 years), 'cardiac function' (heart failure or myocardial infarction only vs heart diseases in general), 'respiratory function' (respiratory failure vs respiratory pathologies) and 'mobility impairments' (reduced mobility ≥3 days vs reduced mobility ≥3 days or reduced mobility relative to normal state). ACCP reports an additional three VTE-risk factors not found in NICE. Whereas, NICE reports an additional six risk factors.

5.3.1.2 Risk factors included in the bleeding risk assessment

Combined, 19 individual bleeding risk factors are listed in the guidelines. Two of which are prevalent in both: 'active bleeding' and a 'low platelet count/thrombocytopenia'. The threshold value for thrombocytopenia differs between ACCP (<50 x 10^9/L) and NICE (<75 x 10^9/L). ACCP reports ten additional bleeding risk factors of which, 'age', 'ICU/CCU admission', 'central venous catheter', 'rheumatic disease' and 'current cancer' are concomitantly used as VTE-risk factors in ACCP or NICE. NICE reports seven additional bleeding risk factors, of which 'acute stroke' is a VTE-risk factor in ACCP.

5.3.1.3 Criteria for indicating pharmacologic VTE-prophylaxis

Recommendations on when pharmacologic prophylaxis is recommended differ between ACCP and NICE. ACCP adopted the PADUA-score and recommends pharmacologic prophylaxis for patients with a score of at least 4.[28] 'Active cancer', 'previous VTE', 'reduced mobility' and 'thrombophilic conditions' score 3 points. Following NICE's recommendations, mobility impairments must be present in order to justify the use of pharmacologic prophylaxis. Furthermore, NICE has a separate recommendation for cancer patients, recommending pharmacologic prophylaxis if one or more other VTE-risk factors are present. This emphasis on mobility impairments and cancer is shared with ACCP's recommendations since these risk factors correspond with 3 PADUA points, requiring only 1 more to reach the threshold value for VTE-prophylaxis.

Both guidelines also recommend the use of prophylaxis in critically ill patients (NICE) or patients admitted to the ICU or CCU (ACCP). Lastly, NICE has a separate recommendation for patients with a central venous catheter (CVC).

5.3.1.4 Criteria for contra-indicating VTE-prophylaxis

ACCP's risk factors for bleeding are adopted from the IMPROVE study that identified risk factors at admission associated with in-hospital bleeding.[29] ACCP contra-indicates pharmacologic prophylaxis if any of the risk factors 'active gastroduodenal ulcer', 'bleeding in three months before admission', and 'platelet count below 50 x 10^9 /L' are present. Additionally, pharmacologic prophylaxis is contra-indicated with the presence of two or more bleeding risk factors or if the patient is actively bleeding. NICE contra-indicates pharmacologic prophylaxis if any of the listed risk factors are present, unless the VTE-risk outweighs the risk of bleeding. No recommendation is given on how to proceed with this trade-off between VTE- and bleeding risk.

5.3.1.5 Criteria for indicating mechanical VTE-prophylaxis

Both guidelines recommend mechanical forms of VTE-prophylaxis, such as graduated compression stockings or intermittent pneumatic compression, if pharmacologic VTE-prophylaxis is contra-indicated because of an increased risk for, or an active bleeding.

5.3.2 Implementability appraisal of the guidelines

Fig. 1 (next page) presents the final implementability appraisal results. For the ACCP-guideline, 33 implementation barriers, six borderline barriers and 84 implementation facilitators were identified. For the NICE-guideline, 51 implementation barriers and 144 implementation facilitators were identified. The proportion of implementation barriers within each guideline's total amount of appraised recommendations was 0.262 and 0.258 for ACCP and NICE respectively. All appraised recommendations for both guidelines contained at least one implementation barrier.

5.3.2.1 Facilitators to guideline implementation

Four dimensions were primarily appraised as facilitating the guideline's implementation. First, the executability dimension primarily contains clear descriptions of the recommended actions. However, "the optimal use of mechanical prophylaxis" found in the ACCP was too vague. Additionally, for both guidelines it is unclear when to provide critical patients with prophylaxis. Second, the measurability dimensions consists solely of facilitators, meaning that adherence to, and outcomes of the recommended actions are measurable. Third, the novelty/innovation dimension was mostly facilitating implementation, indicating no new skills are required and recommendation are consistent with existing attitudes. Recommendations for mechanical prophylaxis are an exception to this. Several appraisers argued that its use, requires knowledge and skills not readily available in current practice resulting in borderline barriers found in the ACCP's novelty/innovation domain.

Lastly, the validity dimension was appraised as facilitating for ACCP and to a lesser extent for NICE, mainly because the quality of the evidence that supports the recommendation is not explicitly stated in NICE's recommendations.

5.3.2.2 Barriers to guideline implementation

Barriers to guideline implementation were primarily present in four dimensions. First, decidability barriers were found in ACCP's recommendations addressing the bleeding risk assessment. A clear definition of patients at "high risk for bleeding" is lacking, preventing a consistent implementation. Furthermore, the definitions "critically ill" and "acutely ill" were deemed ambiguous definitions. NICE's decidability barriers occurred in recommendations addressing bleeding risk and critical patients. Vague terminology such as "reason of admission", "planned interventions" and "other therapies" were given as a reason. NICE's recommendation 1.4.6 through 1.4.9 were partially overlapping with recommendation 1.1.2 because all can be applied to cancer patients. Internal consistency (global dimension question 7) was therefore appraised as a barrier. Second, the flexibility dimension was similarly appraised between the guidelines. Question 18: 'the individualization of the recommendations based on patient characteristics' was a barrier for several recommendations due to vague terminology for patient characteristics. Also question 19: 'modification of the recommendations based on practice characteristics' was a barrier for all recommendations in both guidelines.

Third, barriers in the effect on process of care dimension occurred in mechanical prophylaxis recommendations. The use of intermittent pneumatic compression was seen as a workflow disruption due to complexity, time consumption, monetary investments and requiring new skills. Borderline barriers emerged in ACCP's recommendations for VTE- and bleeding risk assessment. Together, information on more than 20 variables is required per patient. Some appraisers believed this disrupts current workflow.

Lastly, the computability dimension contained barriers for electronic implementation of the guidelines. Doubts were expressed on the electronic availability and specificity of all the required patient data for the risk assessments. A majority of the required patient data will only be available in open text fields, hindering the systematic use for risk assessments. Assuming this can be resolved, the recommended actions in both guidelines are specific enough for an electronic execution (questions 29,30). For example issuing an electronic order for prophylaxis.

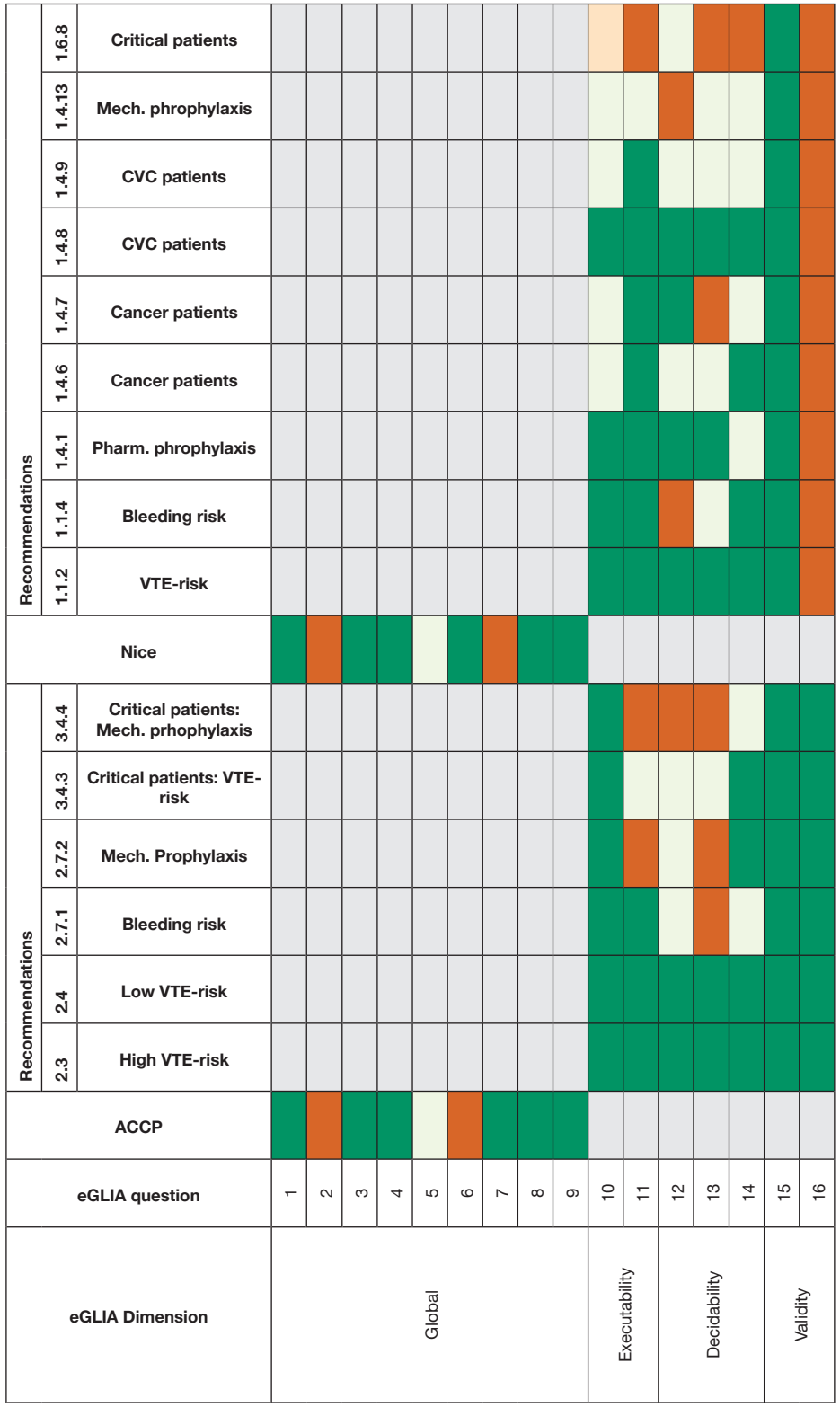
5.4 Discussion

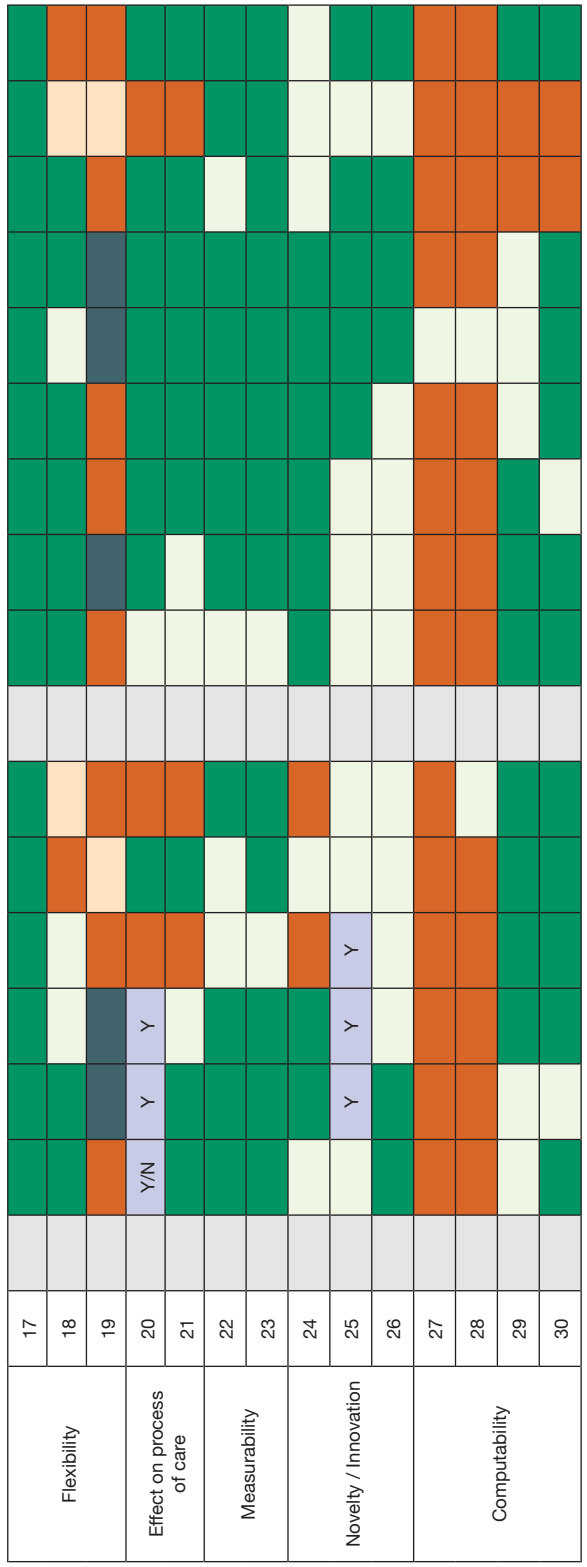
The aim of this study was to compare the risk assessment recommendations for VTE-prophylaxis in hospitalized non-surgical patients used in two influential international guidelines. Secondly, these recommendations were critically appraised by a panel of experts on their implementability characteristics.

5.4.1 Risk assessment comparison

Concerning the identification of patients being at risk for VTE, ACCP and NICE largely correspond with each other. The individual risk factors required in the determination of VTE-risk largely overlap. Critical care admissions, reduced mobility and cancer presence are major components included in VTE risk. This is in agreement with existing literature, since these risk factors are prevalent in most other risk assessment models (RAMs) available for VTE.[30, 31] In general however, VTE RAMs that have been externally validated, including the PADUA-score, show limited performance in guiding the use of VTE-prophylaxis for high risk patient groups.[32]

Bleeding risk assessment differences are more apparent. Just two of the 19 individual bleeding risk factors occur in both the ACCP and NICE. Also, the threshold for contra-indicating pharmacologic prophylaxis differs. In the NICE recommendation, the presence of any of the bleeding risk factors contra-indicates pharmacologic prophylaxis. Whereas, in the ACCP only four of the listed risk factors are absolute contra-indications. This difference might be explained by the limited availability of evidence for bleeding risk assessment, resulting in different approaches within each guideline development group. Only recently the IMPROVE bleeding RAM was externally validated.[33] Approximately 20% of the patients





Facilitator: >6 YES

Facilitator: 5 YES

Barrier: >6 NO

Barrier: 5 NO

Non applicable: >6 N/A

Bordeline barrier: <5 In any category, tendency towards most popular category is given: Y=YES, N=NO

Global question

ACCP American College of Chest Physicians; NICE National Institute for Health and Care Excellence; VTE Venous thromboembolism; CVC Central Venous Catheter

Figure 1. Final eGLIA appraisal results for the ACCP and NICE guideline.

were classified with high bleeding risk. The incidence of bleeding events in this high-risk group was over two-fold higher than in the low-risk group, but the overall performance of the model was poor.

Ideally a combined assessment of both VTE and bleeding risk should be performed prior to using prophylaxis. Interestingly, the ACCP lists three risk factors used in both VTE- and bleeding risk assessment: 'cancer', 'age' and 'ICU/CCU admission.' This suggests a positive relationship between the two risks, complicating the decision making. A recent evaluation of combined risk assessment concluded that the physicians' attitudes on prescribing prophylaxis was more influenced by VTE- than bleeding risk when evaluating patients with both high VTEand bleeding risk.[34]

5.4.2 Implementability of risk assessment recommendations

The assessment of implementability of both guidelines showed that none of the appraised recommendations in any of the guidelines were straightforward to implement. In absence of validated means to quantify and compare guideline implementability between guidelines, we consider the 0.04 difference in proportions of identified barriers a non-significant difference. Nonetheless, the identified barriers and facilitators give us vital information in how guidelines are perceived in their current form and we will touch upon those now.

Clusters of barriers can be identified on recommendation and dimension level. On recommendation level, apparent implementation barriers occur for recommendations regarding mechanical prophylaxis, critical care patients and bleeding risk assessment. Use of mechanical prophylaxis in non-surgical patients is minimal and attitudes towards its use can differ between and within countries.[14, 35] For example, mechanical prophylaxis in non-surgical patients is more common in the United States.[36] This might have influenced the panel's appraisal for mechanical prophylaxis.

The bleeding risk assessment suffered from decidability barriers in both guidelines. ACCP's recommendation lacks a definition of high risk for bleeding and NICE's recommendation lacks a clear description of how to handle the trade-off between VTE- and bleeding risk if both are elevated. These barriers reflect the combined VTE- and bleeding risk assessment issue mentioned before and also the observed variation of the bleeding risk assessment content of the two guidelines.

Critical patients are addressed in separate recommendations. Besides a lacking definition for critical patients, the recommendations do not allow for individualization of the recommended actions based on patient characteristics. This contrasts with recommendations for non-critical patients in which numerous risk factors are involved. Additional ambiguous terminology used by the NICE for critical patients makes implementation of this recommendation uncontrollable.

To overcome these executability and decidability barriers, the formulation of the recommendations should be modified to a structured, concise and more uniform way. The Institute of Medicine suggests that "a recommendation should be articulated in a standardized form detailing precisely what the recommended action is and under what circumstances it should be performed."[37] The implementability of both guidelines is likely to benefit from more explicit distinctions between the affected patient populations and accompanying risk assessment(s).

Several other clusters with barriers were found at the dimension level. First, NICE's recommendations lacked an explicit stating of the quality of the supporting evidence. Strong and supporting evidence was identified as an influencing feature promoting guideline use by others.[38] ACCP's use of the GRADE scheme for quality of the supporting evidence as

well as the strength of the recommendation is a comprehensive way to provide this information to guideline users.

Next, flexibility barriers complicate modification of recommendations based on varying practice characteristics. These characteristics can be very divergent such as a lack of time or the unavailability of certain resources. Although these can be regarded as external factors, a flexible recommendation enables anticipation on such practice or 'real life' variations, increasing the intrinsic implementability of the recommendations and the guideline.

Furthermore, the computability dimension contained barriers. Electronic implementation of guidelines is gaining more and more attention. Various efforts regarding the risk assessment and correct use of VTE-prophylaxis have been made to improve the implementation of guidelines.[18, 39, 40] The main concerns we identified are insufficient patient information in the electronic health records and insufficient specificity of the risk factors for electronic use. Substantial alterations and additions are required in order to allow for electronic implementation of the recommendations. Significant monetary and resource investments are required to facilitate this. Electronic interventions however, are successful in improving guideline implementation and adherence.[18, 39, 40]

The implementability appraisal in this study should not be confused with an overall quality appraisal of guidelines. Appraisal instruments such as the AGREE II also cover many more guideline characteristics.[41] For example, stakeholder involvement or the thoroughness of guideline development. These characteristics are not explicitly involved in eGLIA but have been shown to be predictors of guideline implementation indicating a relation between a guideline's quality and implementability characteristics.[42] AGREE II however, does not solely focus on guideline implementability and hence, does not cover all implementability dimensions as extensively as eGLIA. Moreover, eGLIA assesses the guideline on overall and individual recommendation level, whereas AGREE II assesses the guideline solely on an overall level. Our findings show that the guideline characteristics concerning implementability vary extensively on individual recommendation level underlining the relevance of recommendation level assessment. Consequently, guideline development groups can more accurately target their enhancements on recommendations most needing improvement. A combined assessment with eGLIA and AGREE II seems reasonable, but they are partly overlapping, resulting in duplicate assessment efforts.[43] Merging the two instruments can be beneficial.

5.4.3 Clinical relevance

Besides the relevance for implementation efforts, our findings are also relevant to VTE-prophylaxis risk assessment in clinical practice. Regarding the risk assessment differences, a heterogeneous deployment of VTE-prophylaxis in populations subject to the ACCP or NICE guidance can be expected. Especially the contra-indications for VTE-prophylaxis are perceived very differently. Whether this subsequently influences outcomes for individual patients is not directly known. However, several recent studies established associations between guideline adherence and patient outcomes. Lower adherence with VTE-prophylaxis guidelines was associated with increased mortality, longer length of stay and higher VTE incidence.[44-46] Since, by concept, adherence is based on guideline content, this is evidence for an association between guideline content and patient outcomes. Furthermore, the implementability differences we identified are also likely to influence the ease of implementation and hence the adherence of clinical practice to each of the guidelines. Possibly indirectly influencing patient outcomes.

5.4.4 Limitations

First of all, this study is limited to two international guidelines regarding VTEprophylaxis in non-surgical patients. Including a larger number of guidelines would have broadened our analysis and allowed the identification of certain key risk factors. Key risk factors are expected to be prevalent in most available guidelines whereas, more trivial risk factors will be restricted to a minority of guidelines. Comparisons on this scale however will be complicated by guidelines that are locally adapted versions of other, international, guidelines. For example the Australian and Canadian guidelines are both informed by ACCP guidelines. Given this, and our aim to complement our guideline comparison with the implementability appraisal requiring a significant time investment by appraisers, we limited ourselves to two influential original guidelines.

Second, the majority of the appraisal panel was unfamiliar with the appraisal of guidelines using the eGLIA instrument. By providing the panel with a manual for the appraisal with eGLIA and discussing the results afterwards, any misunderstandings could be resolved. Also, all panel members were experienced in guideline development and/or implementation and hence, were familiar with the constructs in eGLIA. Future applications of eGLIA are likely to benefit from a training session before appraisal commences. This might reduce the time necessary for the appraisal. Third, questions can be raised on the reliability of the eGLIA instrument. Similar recommendations between the two guidelines were appraised differently. E.g. within the novelty/innovation dimension, barriers occurred in ACCP's recommendations concerning mechanical prophylaxis whereas these were not identified in NICE's seemingly similar recommendation. To our knowledge published results of any intraand inter-rater agreement reliability testing of the eGLIA instrument are not available, although plans for doing so were raised shortly after its development in 2005.[19] Reliability testing, preferably on the dimension level, would allow eGLIA users to better frame any identified borderline barriers or other inconsistencies while interpreting the results.

Fourth, the appraisal panel solely consisted of Dutch experts appraising from a Dutch perspective, possibly limiting the generalizability to other healthcare settings.

5.5 Conclusions

We can conclude that depending on the guideline used VTE-prophylaxis will most likely be provided to different non-surgical patient populations. This variation is expected to occur more often because of discordance in bleeding- than in VTE-risk assessment. Difficulties in implementing the guidelines are expected specifically for recommendations concerning bleeding risk assessment, mechanical prophylaxis and critical care patients. Some other issues can arise while trying to implement the risk assessment recommendations electronically and implementing the guidelines in different clinical contexts. The amount of implementation barriers between the two guidelines was comparable. However, the identified barriers were clustered differently between the implementability dimensions.

It is expected that both guidelines will be updated or replaced by newer versions in the coming years. This study incentivizes a more extensive evaluation of intrinsic implementability and reformulation of recommendations with apparent barriers. Specific attention should go to the executability and decidability of individual recommendations. Patient populations, risk factors and threshold values used in RAMs are likely to benefit the most

from more explicit formulations. Both guidelines can improve on this. In order to assure improved implementability characteristics in future guidelines, we recommend guideline developers to consider implementability assessments prior to dissemination. On a final note, we recognize that some of the underlying evidence used in guidelines might be insufficient to support straightforward risk assessments and clear cut trade-offs for VTEprophylaxis in the non-surgical patient population. This will be a challenge in developing guidelines with sufficient intrinsic implementability characteristics.

5.6 Acknowledgements

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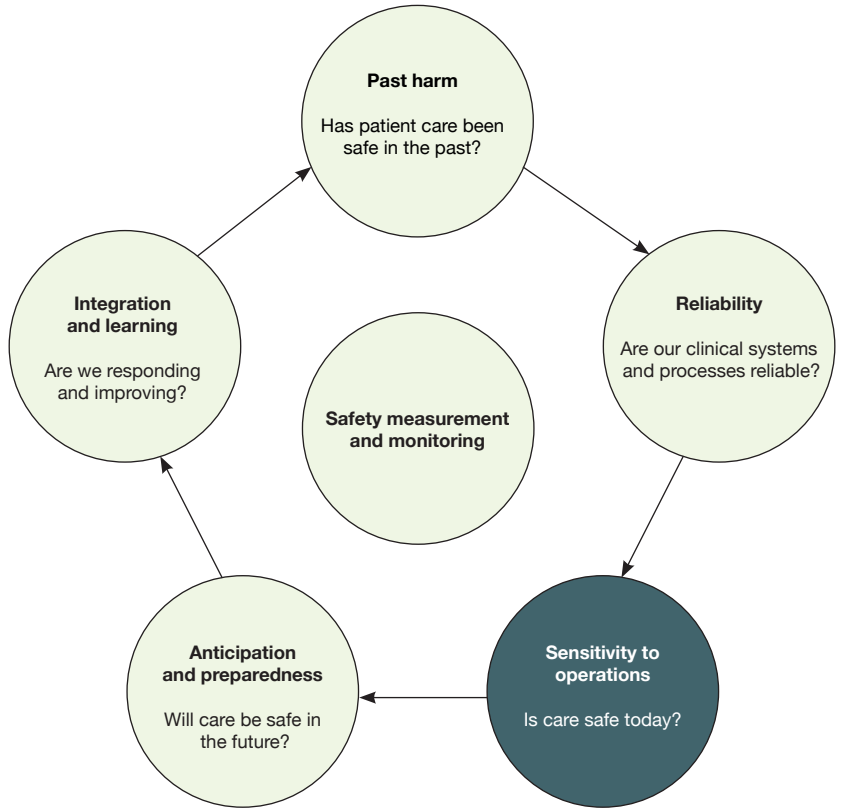
CHAPTER 6

Preoperative Anticoagulation Management in Everyday Clinical Practice: An International Comparative Analysis of Work-as-Done Using the Functional Resonance Analysis Method



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Abstract

Objectives

Preoperative anticoagulation management (PAM) is a complex, multidisciplinary process important to patient safety. The Functional Resonance Analysis Method (FRAM) is a novel method to study how complex processes usually go right at the frontline (labeled Safety-II) and how this relates to predefined procedures. This study aimed to assess PAM in everyday practice and explore the usability and utility of FRAM.

Methods

The study was conducted at an Australian and European Cardiothoracic Surgery Department. A FRAM model of work-as-imagined was developed using (inter)national guidelines. Semi structured interviews with 18 involved professionals were used to develop models reflecting work-as-done at both sites, which were presented to staff for validation. Workload in hours was estimated per process step.

Results

In both centers, work-as-done differed from work-as-imagined, such as in the division of tasks among disciplines (e.g., nurses/registrars rather than medical specialists), but control mechanisms had been developed locally to ensure safe care (e.g., crosschecking with other clinicians). Centers had organized the process differently, revealing opportunities for improvement regarding patient information and clustering of clinic visits. Presenting FRAM models to staff initiated discussion on improvement of functions in the model that are vital for success. Overall workload was estimated at 47 hours per site.

Conclusions

This FRAM analysis provided insight into PAM from the perspective of frontline clinicians, revealing essential functions, interdependencies and variability, and the relation with guidelines. Future studies are warranted to study the potential of FRAM, such as for guiding improvements in complex systems.

6.1 Introduction

Anticoagulation is a common and effective therapy for patients with an increased risk of thromboembolic events (e.g., due to atrial fibrillation or mechanical heart valves)[1, 2] yet also responsible for a substantial proportion of medication-related adverse events.[3-6] Management of anticoagulation therapy is delicate and complex, especially around surgical procedures where it involves a trade-off in decision-making: continuation increases the risk of perioperative bleeding, but interruption increases the risk of thromboembolic events (e.g., stroke).[7, 8] Some patients may temporarily need "bridging therapy" (e.g., low–molecular-weight heparin) during interruption of their anticoagulation therapy. A team of healthcare professionals must coordinate anticoagulation care, including medical specialists, nurses, pharmacists, general practitioners, and, in some countries, anticoagulation services.[9] Communication and coordination issues are common, increasing risks of adverse outcomes.[9-11] While guidelines have been developed to support this process,[12-16] guideline adherence is highly variable, which may expose patients to unnecessary risks of perioperative complications.[17-20]

Rather than continuing the search for guideline non adherence and root causes of complications (labeled as the Safety-I approach[21]), a promising alternative is to increase understanding of this complex process in everyday practice, including the capacities that facilitate safe patient care. This approach, referred to as Safety-II, is linked to other positive approaches to patient safety, such as positive deviance,[22, 23] appreciative inquiry,[24] or learning from excellence.[25] Safety-II seeks to understand how processes usually go right at the front line and how this relates to predefined procedures, such as protocols or process design.[26-28] Analysis of actual practice is also recognized as an important first step when striving to implement improvements.[29] A useful tool for this purpose is the Functional Resonance Analysis Method (FRAM), which has been endorsed by safety experts, such as James Reason,[30] as a promising way forward to improve safety in complex systems. The FRAM has been applied in various settings, including aviation,[31] air traffic management,[32, 33] railway traffic,[34] manufacturing,[35] and construction.[36] Although healthcare is a classic example of a complex system, the uptake of this new approach has been limited in medical research.[37, 38]

This study assessed preoperative anticoagulation management (PAM) using semi structured interviews with frontline clinicians in an Australian and European hospital. The study aimed (1) to obtain a deeper understanding of how PAM is conducted in everyday practice (work-as-done) and how this relates to predefined procedures (work-as-imagined) and (2) to examine the applicability of a Safety-II approach using FRAM for medication management research, as a tool to reconcile work-as-imagined and actual work-as-done.

6.2 Methods

This study was conducted at the cardiothoracic surgery departments of both an Australian and Dutch university hospital. These settings were selected for high incidence of complex surgeries with patients on anticoagulation therapy regimens. In this study, PAM relates to continuing, ceasing, or bridging anticoagulation therapy, including vitamin K antagonists, non-vitamin K antagonists (e.g., dabigatran, rivaroxaban), and platelet ag-

gregation inhibitors (e.g., acetylsalicylic acid, clopidogrel), in patients planned for elective open-heart surgery.

6.2.1 Functional Resonance Analysis Method

The FRAM can be used to describe essential activities that build up a process, visualized in models.[30] In a FRAM model, activities are represented in "functions" depicted as hexagons with 6 different labels or "aspects" (Fig. 1). The models can be based on various sources of information, including guidelines, observations, or interviews with the frontline. To obtain a deeper understanding of a complex process, FRAM requires a targeted, defined scope.[39] Hence, the focus of this study was limited to the preoperative phase. For detailed information on FRAM, we refer to practical instruction guides[40] and previous publications.[37-39] The study investigators attended workshops on the methodology[41, 42] and were supervised by researchers with experience in Safety-II and FRAM (R.C.W. and J.B.).

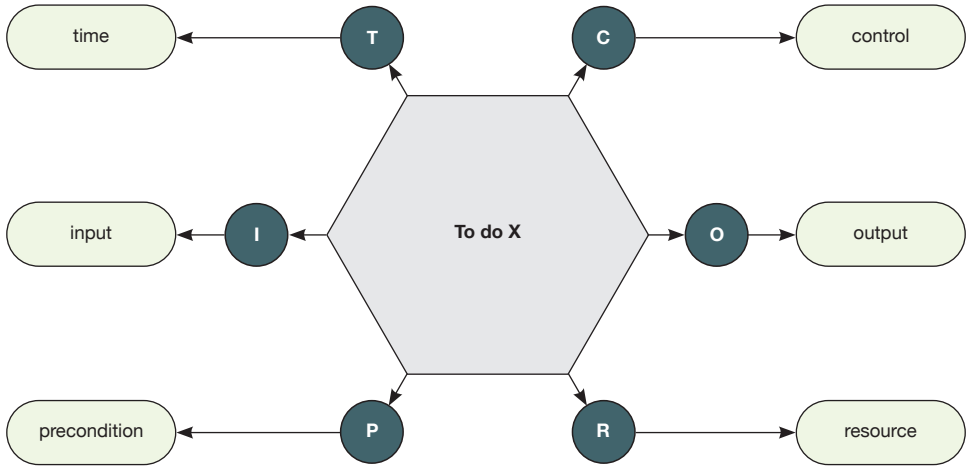

Figure 1 The FRAM function with all aspects

In "To do X," X can represent any activity (e.g., to admit patient). The 6 aspects represent: – input: what the function starts, acts on, or changes; – time: any time constraints that might affect the function (e.g., by which it will be carried out later); – control: how the function is monitored or controlled, work agreements, visions or objectives; – output: the outcome or state change that emerges from the function; – resource: material or people needed to carry out the function, or consumed during the function; – precondition: a condition that must be satisfied before the function can be commenced.

6.2.2 Interviews and Modeling

In accordance with previous FRAM studies,[37, 39] an initial model of PAM "as-imagined" was constructed based on the leading international guideline from the American College of Chest Physicians[43] and a Dutch National Guideline.[44] The Australian Clinical Excellence Commission and Commission on Safety and Quality in Health Care both confirmed that Australia has no common guideline. This initial model provided the basis for semi structured interviews, which were conducted between April and June 2017 with 18 healthcare professionals involved in PAM(Table 1). Interviewees were purposively selected: the director at the Australian hospital and a senior physician assistant (PA) at the Dutch

hospital provided the initial point of approach for recruitment, and additional professionals were recruited through interviewees. Interviews were held individually with 1 interviewer in Australia (N.L.D.) and 2 interviewers in the Netherlands (M.S.d.V./M.J.M.). After written consent, interviews were audio recorded and summarized immediately afterward for the investigators. Interviews were guided by a topic list (Appendix 1, http://links.lww.com/JPS/A165) based on questions of the FRAM method, with minor adaptations made for the specific discipline interviewed.[39, 40] The FRAM models reflecting PAM "as-done" were developed based on the interviews by the investigators who also conducted the interviews. An iterative modeling process was applied with preliminary models developed after each interview and updated versions guiding the following interviews. The "FRAM Model Visualizer" was used to construct the FRAM models.[44] Interviews were conducted until data saturation was reached for the model,[45] defined as 3 consecutive interviews during which no new functions emerged for the model. In both hospitals, a discussion meeting was organized to present the final models to involved staff as a means of validation, and to elaborate on potential clinical implications and recommendations. To examine usability of this novel method (e.g., for quality managers), total workload in hours was estimated per step of the FRAM analysis (excluding study-related work, such as drafting the manuscript).

Table 1 The FRAM Process Steps and Disciplines Interviewed, With Estimated Workload per Site

Process Steps			Time, h†
Work-as-imagined model	Development of model based on international guidelines.		7
Interviewed professionals (n)* including preparations, processing, and iterative model development	*Australia (10):* • Cardiothoracic surgeon (1) • Cardiologist (2) • Nurse case manager (1) • Nurse unit manager (2) • Anesthetist (1) • Preadmission clinic nurses (3)*	*The Netherlands (8):* • Cardiothoracic surgeon (1) • Cardiologist (1) • Cardiothoracic PA (2) • Registrars (2) • Anesthetist (1) • Planning office secretary (1)	20
Work-as-done model	Development of final model based on information gathered in interviews and analysis of potential variability and interdependence.		15
Meeting with frontline (team discussion)	Department meeting gathering all involved staff to present, validate, and discuss the final model (ca., 1–2 hours), with subsequent processing of feedback.		5
Total			47

*Interviewed disciplines differ because of the different disciplines involved in the centers. Australian interviews were conducted in 2 instances within a 2-month timeframe because of time limitations for providers. All were interviewed individually, except for the preadmission clinic nurses who were interviewed together.†Overall workload per site for the analysis carried out by 3 main investigators collaboratively.

6.2.3 Analyses

The FRAM models can be studied by assessing variability and interdependence of functions.[38, 40] Variability can be due to human, organizational, or environmental factors affecting timing or precision of functions. 38 Functions may also be interdependent (known as "coupling") in which case a function impacts later functions ("functional up-

stream-downstream coupling"). This interdependence between functions may allow variability in 1 function to spread through the process, e.g., information omitted in 1 function may impact later functions that use this information. Variability and interdependence were assessed for the "foreground functions," which are the main steps in the process depicted in hexagons, in contrast to "background functions" depicted in grey boxes, which are considered to be more stable and have a less prominent role in analysis.

6.3 Results

The PAM "as-imagined" model reflected guideline recommendations for task division and communications between healthcare professionals. A key role was assigned to anesthetists, who were expected to decide upon a definitive PAM strategy (i.e., to continue, cease, or bridge), after a proposal by treating physicians, and to inform patients and other clinicians (Appendix 2, http://links.lww.com/JPS/A166). Interviews with healthcare professionals about PAM "as-done" lasted between 45 and 60 minutes. Data saturation was reached for the models in both settings (Table 1). Notable differences between the models and time investments are discussed in Tables 1 and 2.

Table 2 Preoperative Anticoagulation Management "as-done" in Australia vs. the Netherlands

Theme	Australia	The Netherlands
Patient visits	2 preoperative hospital visits: 1 with surgeon and afterwards nurse CM, and 1 preadmission clinic visit.	1-day preoperative clinic visit, including pharmacy assistant, PA/registrar, cardiothoracic surgeon, and anesthetist.
Disciplines Multidisciplinary communication	Central role for nurses, including NUM, nurse CM, and clinic nurse. Anesthetist involved in work-up upon admission and in case of abnormalities. NUM might ask questions on PAM strategy during other cardiac group's multidisciplinary meeting.	Central role for PA/registrar and role for planning office secretary. Anesthetist not involved in PAM strategy or in case of abnormalities. Daily heart team meeting with surgeon and cardiologist; preoperative clinic with multiple disciplines at same location.
Decision-making	Surgeons decide on PAM strategy and consider themselves solely responsible for this. However, if surgeons omit this, the nurse CM will remind them to or, if the case is straightforward, select a strategy using her personally developed protocol.	Surgeons and cardiologists consider themselves responsible to select a PAM strategy at their team meeting, but, in practice, the PA/registrar mostly selects an anticoagulation strategy according to the departmental protocol.
Resources Protocols	• Patient records, referral letters, medication list • Booking sheet (also via e-mail) • Preoperative screening results • Preadmission booklet • Instructions by NUM • NUM's notebook, surgery board • Asking patient (upon admission) Surgeons use their knowledge of international guidelines, and nurse CM uses own protocol.	• Patient records, referral letters, medication list (verified by pharmacy assistant) • Heart team meeting form • Preoperative letter • Secretary's patient lists • Asking the patient (clinic, admission). Departmental (2-page) protocol based on guidelines,† used by registrars/PAs and surgeons.

Patient instructions	• Surgeon, nurse CM, and clinic nurses • Prescription (if indicated) • Instruction letter; preadmission booklet	• PA/registrar, and secretary (over phone) • Prescription (if indicated)
Signaling abnormalities* Outpatient setting Inpatient setting Signaling channels (least to most urgent)	If the clinic nurse notices that PAM strategy is unclear (e.g., mixed information), she consults nurse CM. If the NUM signals abnormalities during preadmission checks or admission, she notifies the surgeon or, in case of low platelet levels, the anesthetist. Face-to-face (e.g., ward rounds) > e-mail > texting > phone.	The anesthetist (at clinic) or secretary may notice that a missing, unclear or unusual PAM strategy, and contact the surgeon, registrar or PA. If the PA/registrar signals abnormalities during preparations or upon admission, a proper response will be discussed the surgeon. Face-to-face (e.g., clinic or during afternoon handoffs) > phone.
Individual systems	• NUM developed system for preadmission checks (notebook, surgery board, EHR notes, and mental checklist) • Nurse CM developed protocol for PAM strategy based on local experience.	• Locally developed departmental protocol for PAM based on guidelines • Secretary developed own checklist to list patient information to guide phone calls

*Response to abnormalities is identical at both sites: a reversal agent (e.g., vitamin K) or platelets will be administered to ensure values within an appropriate range for surgery. If not effective or not possible, the surgery is postponed.
†Guidelines include ACCP 2012; ESC/EACTS 2014; ESC 2016.

6.3.1 Australian Model

The Australian model (Fig. 2) consists of the following 8 main functions:

1. **To decide on surgery and PAM:** at the clinic, cardiothoracic surgeons see referred patients to inform them about the treatment as well as PAM strategy and provide them with a "preadmission booklet."
2. **To discuss PAM with the patient:** subsequently, patients see the nurse case manager (CM) who schedules the surgery, further explains the PAM strategy, and checks whether the surgeon noted this on the preadmission booklet. If not, the nurse asks the surgeon or, if straightforward, selects a strategy based on a self-developed protocol. The patient also receives an instruction letter, and prescriptions for bridging therapy if required. Lastly, the nurse e-mails a "booking sheet" with patient, surgery, and PAM details to the preadmission clinic, admission wards, anesthetists, and operating theaters.
3. **To conduct intake at preadmission clinic:** 2 to 3 weeks before surgery, patients visit the hospital again for a preoperative screening with several tests. At this preadmission clinic, a nurse checks whether the patient received and understood the PAM strategy. If unclear, the clinic nurse contacts the nurse CM (function 2) to provide the patient with PAM instructions.
4. **To start selected PAM strategy up until admission:** at home, patients are expected to adhere to the PAM strategy.
5. **To conduct preadmission checks:** in preparation for the following week's surgeries, the nurse unit manager (NUM) of the admission ward retrieves the preoperative screening results from the electronic health record (EHR) and PAM strategies from booking sheets. If the NUM identifies anticoagulation related abnormalities, the surgeon and/or anesthetist will be texted or called. The NUM notes all patient details, including PAM

strategy, in a personal notebook and on the “surgery board” (i.e., white board on the ward). The NUM usually admits patients but provides electronic instructions for colleagues if this is not the case (e.g., weekends).

6. **To perform work-up:** upon patient admission the night before surgery, the NUM determines whether patients adhered to the PAM strategy by asking and by assessing international normalized ratio (INR) and platelet levels.
7. **To conduct an anesthetic work-up:** the work-up of the anesthetist also includes a check of anticoagulation medication and INR.
8. **To respond to abnormalities:** if patients did not adhere to the PAM strategy and/or the INR is not within the appropriate range, the NUM notifies the surgeon (Table 2), who decides whether or not to administer a reversal agent (e.g., vitamin K) or postpone the surgery. If platelet levels are too low, the nurse texts or calls the anesthetist, who can decide on administering extra platelets so that surgery can proceed.

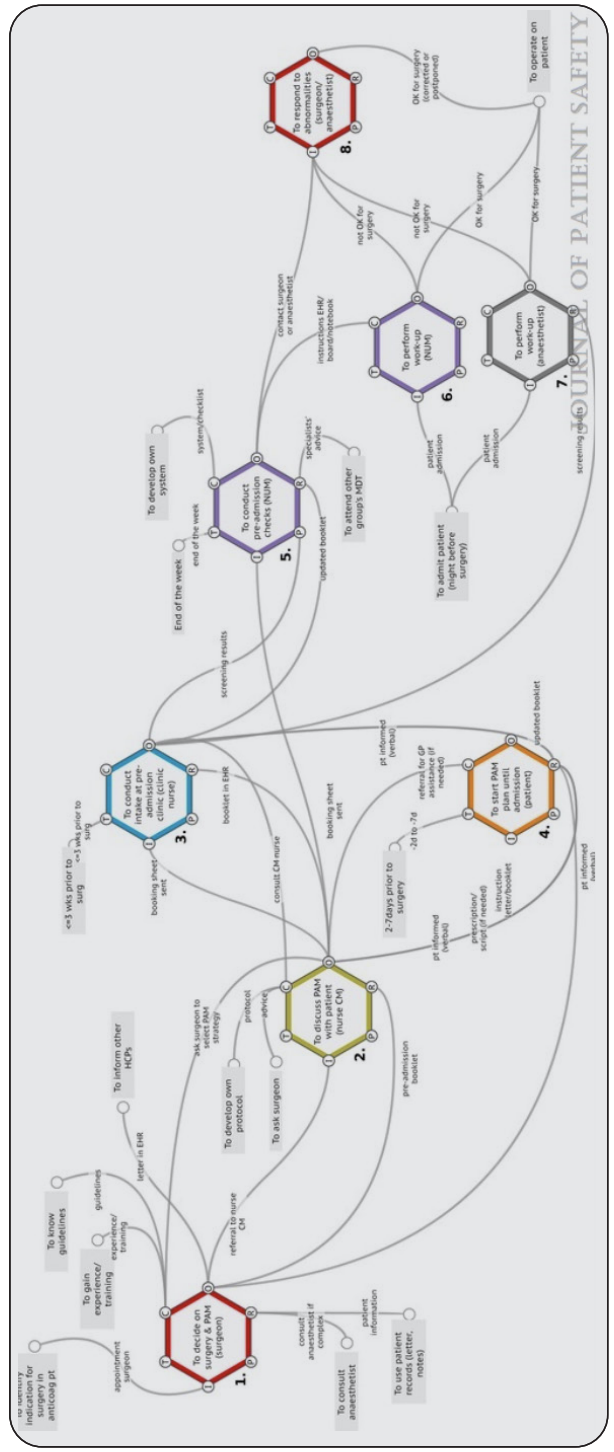

Figure 2 Work-as-done model of PAM in the Australian hospital.

6.3.2 Dutch Model

The Dutch model (Fig. 3) is composed of 10 main functions:

1. **To decide on surgery and PAM:** the cardiothoracic surgeon and interventional cardiologist discuss treatment options for referred patients in a daily "heart team meeting." They document their decisions, including a PAM strategy, in the EHR. Surgical patients are scheduled for a 1-day preoperative clinic visit with various clinicians in a fixed order (functions 2–5).
2. **To perform medication reconciliation:** a pharmacy assistant ensures an up-to-date medication list in the EHR.
3. **To formulate and discuss PAM with the patient:** patients consult a registrar or PA (alternating shifts), who provides them with verbal instructions on the PAM strategy and prescriptions if needed. All required preoperative actions are noted in a "preoperative letter" in the EHR (not provided to patients). Often, no PAM strategy has been selected or documented by the "heart team" (function 1), in which case the registrar or PA selects a strategy according to the departmental protocol and, if needed, supervision from the attending surgeon (Table 2).
4. **To find out the indication for anticoagulation therapy:** to select the appropriate PAM strategy, the registrar or PA revisits the patient's indication for anticoagulation therapy, which can be obtained from the patient, EHR or by consulting the prescribing specialist by telephone or e-mail. Patients subsequently visit the surgeon, but this consult serves to educate patients on the surgery rather than PAM.
5. **To perform pre-anesthesia screening:** the anesthetist conducts a screening and provides patients with a letter that includes a medication list with preoperative instructions. For anticoagulation therapy, however, this is no more detailed than "stop in consultation with surgeon."
6. **To plan surgery:** a surgeon schedules the following week's surgeries and informs the planning office. Surgeries are planned at least 5 days in advance, unless vacant spots have to be filled.
7. **To inform patients:** the planning office informs patients over the phone about their exact date of surgery in the upcoming week and any required preoperative actions, such as a PAM strategy. Phone calls are guided by information in the preoperative letters (function 3) and, if necessary, digital meeting forms (function 1). One of the secretaries developed a checklist to guide this process (Fig. 4). If surgeries are rescheduled, the secretary informs patients in a similar fashion.
8. **To start the selected PAM strategy:** At home, patients are expected to adhere to the PAM strategy.
9. **To perform work-up:** upon admission the day before surgery, the registrar or PA determines whether patients adhered to the PAM strategy and performs appropriate testing (e.g., INR), according to notes in the preoperative letter (function 3) and/or the medication list. Platelet levels are tested at the clinic (function 2) and only repeated if 6 or more weeks have passed.
10. **To respond to abnormalities:** registrars or PAs respond to abnormalities (e.g., elevated INR) after discussing with the surgeon whether or not to administer a reversal agent or to postpone surgery.

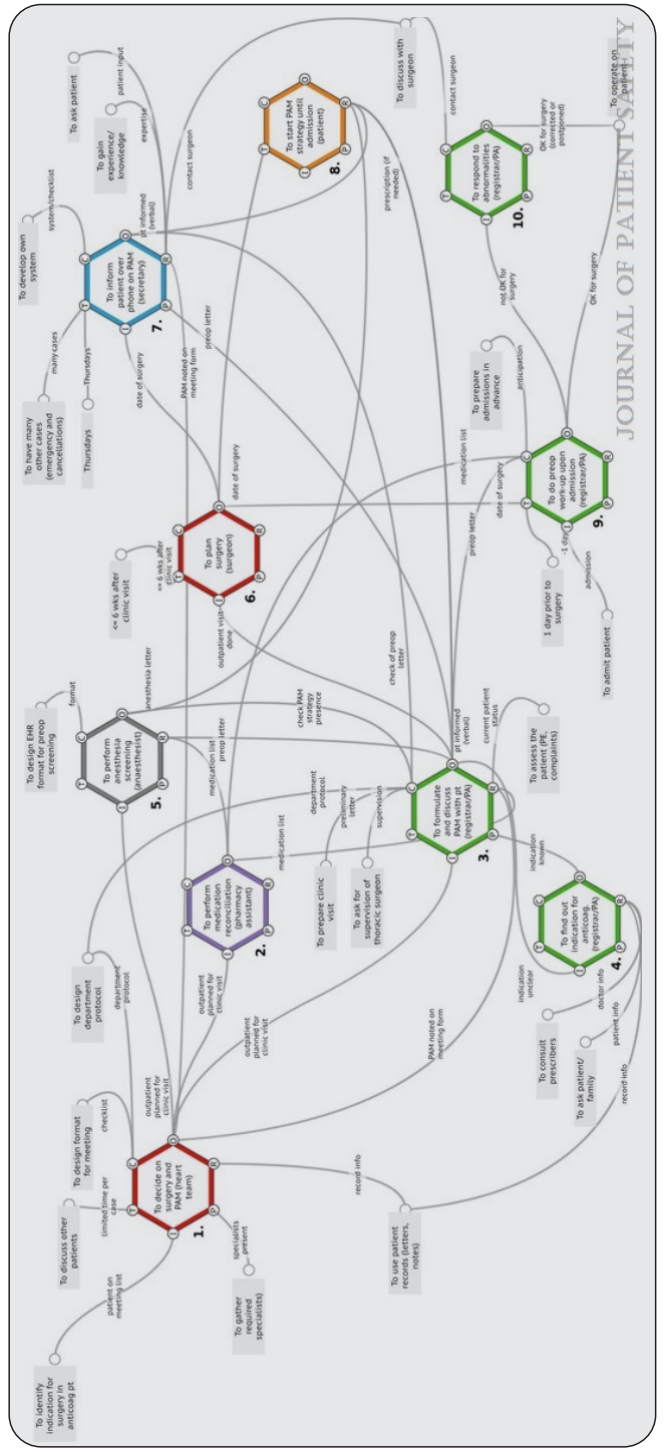

Figure 3 Work-as-done model of PAM in the Dutch hospital.

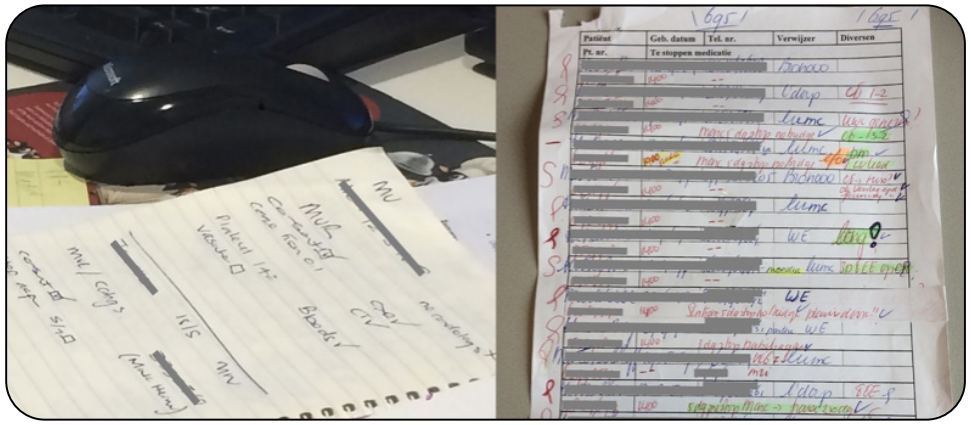

Figure 4 Photographs of naturally developed individual systems of Australian nurse unit manager (left) and Dutch planning office secretary (right).

6.3.3 Variability and Interdependence

In the Dutch setting, variability became particularly apparent for function 1, as registrars and PAs mentioned that he team meeting mostly did not produce a PAM strategy. Similarly, the Australian nurse CM often selected a PAM strategy if the surgeon omitted to note this in the preadmission booklet. In complex cases, the nurse CM would consult the surgeon, which is similar to Dutch registrars/PAs who may ask for supervision from the surgeon.

At both sites, functions 1–3 provided outputs that served as important resources for several "downstream" functions. These functions generated documents that served important roles later on, namely, the Australian booking sheet (output of function 2; input for 3/4) and the Dutch preoperative letter (output of function 3; resource for 5; precondition for 7; control for 9) (Figs. 2, 3).

Both models also included downstream functions that controlled upstream functions. The Australian nurse CM could remind surgeons to fill out a PAM strategy (i.e., function 2 controlling 1), and the clinic nurse consulted the nurse CM if the PAM strategy was unclear (i.e., function 3 controlling 2). Both Dutch anesthetists (function 5) and secretaries (function 7) could signal a missing or incomplete preoperative letter, thereby controlling function 3.

Interdependence was particularly apparent for Dutch function 3, linked to as many as 5 other foreground functions (i.e., 1, 2, 4, 5, and 7) (Fig. 3). Remarkably, there were 2 similar, partially overlapping functions (7 and 8) for work-up upon admission in Australia causing duplicate measurements of INR (Fig. 2).

The functions that represented patients adhering to the PAM strategy (Australian function 5; Dutch function 8) seemed to have no formal "input" or "active agent" to start this function and hence seemed to depend solely on the patient's memory and support from verbal and/or written instructions.

6.4 Discussion

This study was the first to use a Safety-II approach and FRAM in the context of medication management in healthcare. This provided insight into the complex process of PAM "as-done" and "as imagined" in 2 international contexts. This process differed substantially between the study sites, both in practical organization and disciplines involved. While, in both centers, "work-as-done" at the front line differed from "work-as-imagined" in generic guidelines, both had developed control mechanisms to ensure successful PAM, such as critical review of a colleague's decisions and documents, and individual systems to enhance efficiency and thoroughness.

Work-as-done differed from the process "as-imagined" by guidelines, which assumed that physicians, specifically anesthetists, play a central role in PAM. In both centers, however, this was the responsibility of surgical staff rather than anesthesia staff, with key roles assigned to (specialized) nurses or registrars/PAs. This may have practical purposes, because these disciplines also have a central role in inpatient care. Furthermore, in contrast to the national guideline,[46] the Dutch process did not involve anticoagulation services, usually responsible for outpatient anticoagulation management in the Netherlands. Instead, the department temporarily took over this responsibility to enhance clarity for patients. These examples illustrate how studying work-as-done might help identify potential differences between local practices and guidelines but also the pragmatic, practical reasons behind it. Moreover, this study revealed varying perceptions on roles and responsibilities among clinicians involved in anticoagulation management, which aligns with a recent survey study.[9] For example, interviewed surgeons felt responsible for formulating and documenting the PAM strategy, but other staff reported that this was often omitted in which case they made a decision.

6.4.1 Opportunities for Improvement

Although patients received various forms of information, both centers relied on the patient's memory to adhere to the PAM strategy at home. Modern information technology may provide solutions for a more active "input" for this function, such as automated text messages on the day the patient has to stop anticoagulation. Simple written instructions, as used in Australia, could be developed in the Dutch department to offer a useful reminder for patients at home. Learning cuts both ways, as the Australian department might consider limiting the number of information sources as this also increases the risk of conflicting information. In addition, they may consider introducing a single-day multidisciplinary clinic with involvement of a pharmacy assistant, as used in the Dutch setting, to limit the number of hospital visits for patients and ensure accurate medication information.

Inaccuracies in, or unavailability of, documents produced in early functions to record the PAM strategy could negatively affect later steps in the process (e.g., informing the patient). In these situations, the identified control mechanisms may prove their value, e.g., other staff may select a PAM strategy if omitted in function 1. Although this illustrates clinicians' profound adaptive skills, it may also result in habituation to the fact that this information is missing, decreasing use of this resource. Therefore, there should be clear agreements on what can be expected from staff carrying out these functions. Individual staff had

naturally developed some of these control mechanisms, such as a checklist or notebook. Although these are likely to support thoroughness, they may also pose safety risks when key persons are absent or replaced and colleagues are unfamiliar with these methods. To illustrate, the Dutch secretary seemed to view her checklist as a "personal aid" and did not plan on transferring this method to new staff members. Hence, this potentially valuable control mechanism may be jeopardized because of its individual and not structural nature.

6.4.2 Practical Implications and Usability

The FRAM seemed to be a promising tool that can be readily applied to study a multidisciplinary medication management process and identify functions that are important for success. The workload of FRAM collaboratively was estimated to be approximately 47 hours per site (Table 1), which is comparable with the workload associated with traditional methods, such as a root cause analysis.[47] In line with a previous study,[37] clinicians seemed to easily understand the relevance, background, and design of FRAM. Reflection meetings with staff were considered insightful and raised awareness of interdependencies between activities of colleagues. For example, Dutch senior staff questioned whether anesthetists could actually signal a missing or incorrect PAM strategy, but a junior registrar confirmed that he had experienced this occasionally. Staff also used the model to discuss opportunities for improvement, such as the redundancy in the Australian work-up upon admission. This way, FRAM may be used to reconcile and improve the synergy between the world of guidelines and systems design (work-as-imagined) and the world of everyday clinical practice (work-as-done). The FRAM could also be used as a support tool for incident analyses because it allows studying how an event emerged in relation to work-as-done rather than only comparing such events with expectations of a process (e.g., protocols).[39] A unique feature of FRAM is that it does not need to be triggered by an incident, because it can be used proactively to gain understanding of work-as-done. This could potentially respond to recent calls for greater proactivity and a greater focus on what goes right in patient safety improvement.[48] Future studies could seek to combine more quantitative analyses with the qualitative FRAM models, for example, to measure defined outputs of functions with statistical process control[49] or to quantify functions' variability so that probability simulations can be applied.[50]

6.4.3 Study Strengths and Limitations

To our knowledge, this is the first study to study a medication management process "as-imagined" and "as-done." A specific strength of the method is its focus on activities that are responsible for the fact that clinical work usually goes right rather than specific situations where things go wrong. Studying work-as-done offers a way forward for patient safety, which under the traditional Safety-I domain is mainly focused on complications or incidents, which are very important—but also very specific, and often rare.[21, 27] This study has international applicability as it showed that visualization of work-as-done using FRAM can be used to study and compare challenges and strengths in 2 international contexts. While the multicenter context is also an advantage, both sites were cardiothoracic surgery departments at teaching hospitals, which may limit generalizability to other units. More research in other settings is warranted, because PAM is also a common practice for other specialties. Moreover, real practice may still differ from the models developed in this study because we did not use direct observations,[51] and the purposive sampling strategy may introduce the risk of selecting a subgroup or network of professionals, which could be prevented with random samples in future studies. In mitigation, and in accordance with

qualitative research guidelines,[52] we used data saturation to increase the ability to identify the most relevant functions and interdependencies.

6.5 Conclusions

This study provided a deeper understanding of anticoagulation management in practice and in relation to guidelines. The FRAM seemed to be an insightful tool, suitable for studying complex healthcare processes, such as medication management, identifying functions that are important to ensure the process functions as intended, including their interdependence and variability. In addition, this proactive approach revealed the opportunities for improvement and the presence of naturally developed individual systems, which otherwise remained undetected. Future studies are warranted to investigate PAM as well as the applicability of FRAM in other healthcare contexts.

6.6 Acknowledgements

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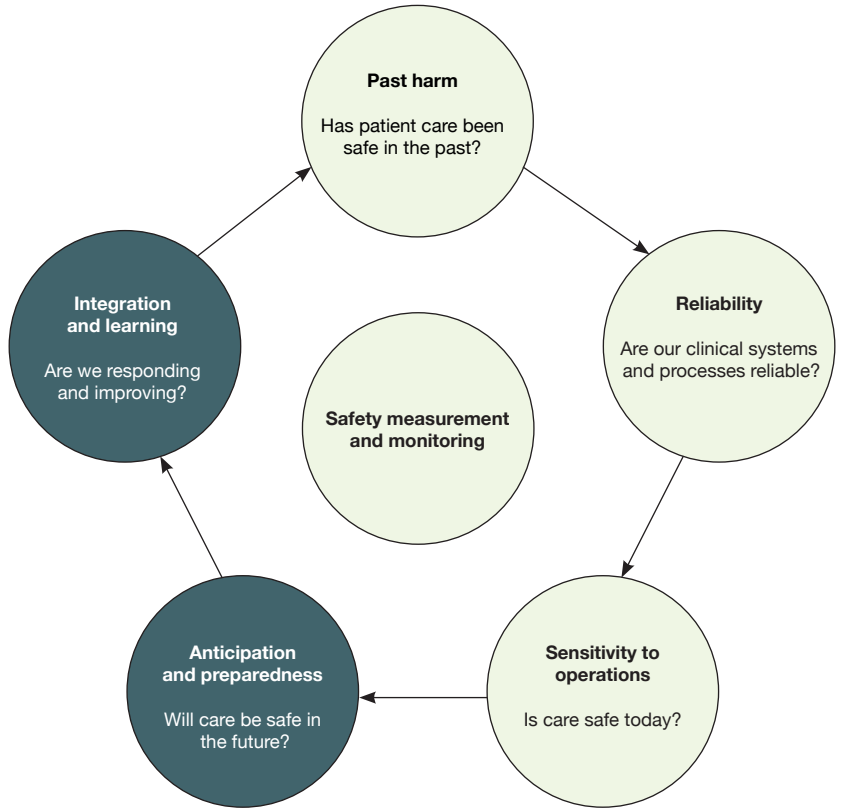
CHAPTER 7 General discussion



This thesis focussed on the safety of antithrombotic care in Dutch hospitals. Since reliable data regarding the safety of antithrombotic care in the Netherlands is sparse, this thesis primarily aimed to add to this knowledge gap. As introduced in chapter 1, the various studies that we have conducted can be classified under the first three dimensions of the "safety measurement and monitoring framework" as proposed by Vincent et al. (2014).[1]

The outline of this concluding chapter is graphically depicted in Figure 71.

At first, we present the main research findings in light of the research questions introduced in chapter 1:

Past harm: has patient care been safe in the past

1) How common are (preventable) antithrombotic related adverse events in Dutch hospitals and what are the circumstances in which they occur?

Reliability: are our clinical systems and processes reliable?

2) How reliable is perioperative antithrombotic management and administering VTE prophylaxis in Dutch hospitals?
2a) Can we observe variation between hospitals?
2b) Can predictors of unreliable care be identified?

Sensitivity to operations: is care safe today?

3) How is perioperative antithrombotic management conducted in everyday practice (work-as-done) and how does this relate to predefined procedures (work-as-imagined)?

Next, we will touch upon several methodological considerations regarding our research. Then, we will discuss our future perspectives on quality improvement of antithrombotic care from the perspective of Vincent's final dimensions: *anticipation and preparedness* and *integration and learning.* To conclude this chapter and thesis, we propose recommendations for clinical practice, healthcare policy and further research.

7.1 Main research findings and implications

7.1.1 How common are (preventable) antithrombotic related adverse events in Dutch hospitals and what are the circumstances in which they occur?

In **chapter 2** we studied over 10.000 Dutch patient records to identify antithrombotic related adverse events (ARAEs) that occurred during hospital admissions. We found that ARAE incidence based on records of deceased patients decreased from 1.20% in 2008 to 0.54% in 2015/2016.

In itself this is an encouraging result, which can indicate that over time, less patients experienced an ARAE. However, there are some other findings that are more concerning.

First of all, the decline was only observed in in-hospital deceased patients and not in discharged patients. Although it has been shown that only studying deceased patients' records is an efficient approach to identify overall adverse events (AEs) in comparison to also studying discharged patients,[2] it is unclear whether this is also the case for the ARAE subpopulation. The fact that we have not observed a decrease in ARAEs in discharged patient records between 2008 and 2011/2012 and could not study this population in 2015/2016

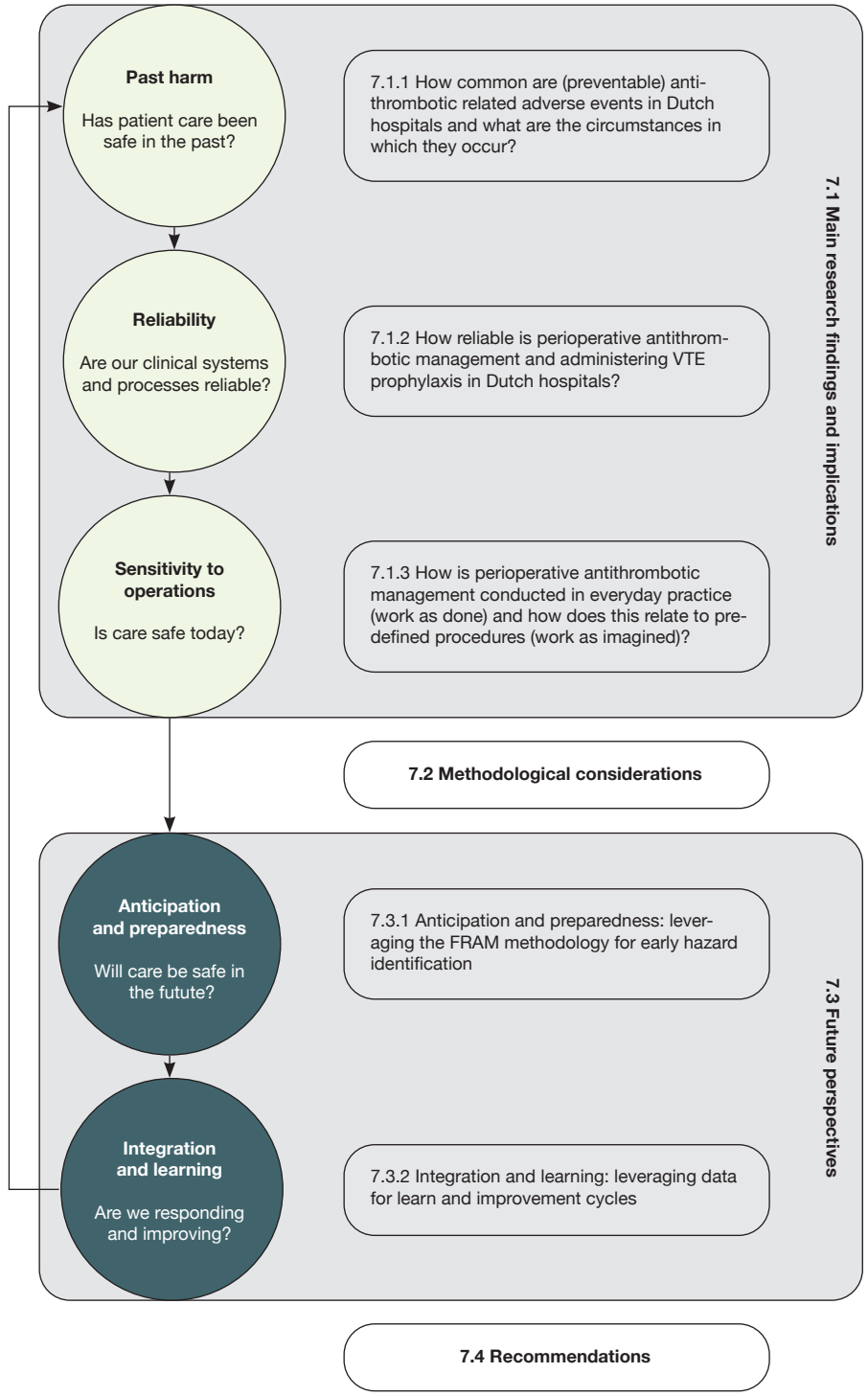


Figure 76.71 Graphical representation of the general discussion in relation to Vincent's safety measurement and monitoring framework

therefore advocates further investigation within this patient population.

Second, the potential preventability of ARAEs was relatively high at 28.54%. Compared with other clinical domains such as non-surgical procedures (10.7%), surgery (17.0%) and overall medication use (21.5%), ARAE preventability is markedly higher.[3] Whether or not this preventability can be reduced remains to be seen. However, experiences from other clinical domains are promising in this regard. For example, between 2008 and 2011/2012 the preventability of AEs in surgical procedures was brought down from 40.1% to 17.0% after elaborating national interventions aimed at the surgical process. These interventions included implementation of pre-, peri- and post-surgical checklists, and increased supervision by the Dutch Health and Youth Care Inspectorate (IGJ). It might be worthwhile to benefit from the lessons learned during this period and adapt them for use in the reduction of ARAE preventability.

Third, we observed increasing trends of the involvement of antiplatelet and combined antithrombotic use in ARAEs. Both were involved in around 10% of the ARAEs in 2008 but over time this rose to 30% and 40% for combined antithrombotic and antiplatelet use respectively in 2015/2016. Although this increase was not statistically significant, the potential implication of this observation warrants attention. An explanation may be found in changes in the prescription patterns over time. For example a study by Hanemaaijer et al. (2015) observed an increased number of patients using only platelet inhibitors, dual antiplatelet therapy (aspirin + $P2Y_{12}$ inhibitor) and triple antithrombotic therapy (dual antiplatelet therapy + anticoagulant) between 2008 and 2013 in the Netherlands.[4] These changes in prescription patterns are supported by clinical practice guidelines (CPGs) for treating patients with acute coronary artery disease where it is acknowledged that dual and triple antithrombotic therapy regimens are associated with increased bleeding risk and that this risk proportionally relates to the duration of therapy.[5, 6] Hence, risk stratification and recommendations are provided which incorporate the time of use as an input variable in order to support the decision making. Whether or not the ARAE rate we observed in “real world”, out of study context is within expected boundaries based on clinical trial evidence should be examined further.

Given these concerns, the observed decline of ARAEs in deceased patients is still a positive development. It could imply that awareness of antithrombotic risks rose over time under the influence of increasing attention in the nationwide AE studies and studies in other care settings such as in primary care. [3, 7-10] Additionally, experts in the field of antithrombotic care initiated various quality improvement efforts aimed at antithrombotic care such as integrated care programmes and clinical practice guideline development.[11, 12] These initiatives could also have influenced the ARAE incidence in a positive way.

7.1.1.1 Circumstances of unsafe care

The second part of our first research question entails the circumstances of ARAEs. In **chapter 2** we identified several circumstances of (preventable) ARAEs that were related with aspects of the care delivery. Among these were care provided during weekends (present in 59.2% of all preventable ARAEs) and/or more than 1 involved medical specialty (present in 97.3% of all preventable ARAEs).

Both these care delivery aspects are known for having a potential negative effect on patient safety whose cause lie in the organisation of care. E.g., staffing levels and skills, and the coordination and transfer of care between wards and specialties. [13, 14] The fact that these two care delivery aspects were identified in light of ARAE occurrence can suggests that improvements can still be made that will benefit antithrombotic safety.

Furthermore, we also observed differences in preventability between clinical specialties. Overall, the vast majority of ARAEs occurred under the responsibility of a non-surgical specialty, i.e., 78.4%, compared with 21.6% of ARAEs during surgical responsibility. Since patients using antithrombotics are generally older and less frequently undergo surgery, this observation was expected. What stands out is that when only referring to preventable ARAEs, surgical and non-surgical specialties exhibit a much more equal distribution of ARAEs. I.e., 43.0% vs. 57.0% respectively. This tells us that although ARAEs in surgical patients are less common, they are more frequently judged as being preventable events compared with non-surgical patients.

Lastly, we found that around one third of all ARAEs and half of all preventable ARAEs were related to an elevated international normalised ratio (INR). From the qualitative analysis in **chapter 2** various causes were identified such as drug-drug interactions, comorbidities, and reversal agent administration errors. These causes have been described before.[15-17] Furthermore, the Dutch federation of anticoagulant management services (FNT) monitors and publishes known vitamin-K antagonist (VKA) interactions since 1999 and provides a web application where healthcare providers can search for interactions. [18, 19] Given this, it is difficult to find an explanation for the rather high representation of elevated INR as the cause for ARAEs. Perhaps a qualitative investigation, e.g., from a safety-II perspective such as presented in chapter 6, of the INR monitoring processes within hospitals can shed light on additional causes. Until these insights become available, promising interventions that can be explored are electronic drug-drug interaction detection, point-of-care INR testing and anticoagulant stewardship.[20-22]

7.1.2 How reliable is perioperative antithrombotic management and administering VTE prophylaxis in Dutch hospitals?

In **Chapter 3** we presented the results of the reliability assessment of perioperative anticoagulant management (PAM) in patients using VKA’s. Patient records from 13 hospitals were studied to assess the reliability of seven profound steps within the PAM process. Deviations with CPG recommendations for these steps were found in a minimum of 19% of the patients up to as much as 60% of patients depending on the specific PAM step of interest.

In the same selection of hospitals, we also evaluated the reliability of venous thromboembolism (VTE) prophylaxis use in hospitalized patients. The results were presented in a Dutch report ‘Antistollingszorg in Nederlandse Ziekenhuizen’ in 2017.[23] Depending on specific subpopulations we found CPG deviations in 75% (spinal surgery), 45% (non-surgical patients), 36% (general surgery) and 6% (orthopaedic surgery) of included patients in the decision whether or not to apply pharmacologic VTE prophylaxis. Deviations in surgical patients were primarily caused by an overuse of VTE prophylaxis whereas in non-surgical patients also underuse contributed significantly to the observed deviation.

Both the PAM process steps as well as the underlying risk assessment for the application of VTE prophylaxis can be interpreted in a similar manner as process quality measures. I.e. they reflect how clinical processes are executed within the hospital rather than measuring organizational characteristics or patient outcomes that characterise structure and outcome quality measures respectively.[24, 25] In the Netherlands many process measures have been defined and evaluated by on a yearly basis by the Health and Youth Care Inspectorate (IGJ). When a process measure is introduced for the first time, it is expected that the results leave room for improvement and considerable variation between hospitals is present. Repeated measuring and benchmarking may than lead to better scores and less variation

between hospitals. E.g. the timeliness of preoperative antimicrobial prophylaxis when first measured in 2013 was adequate in 89.9% and increased to 96.8% in 2018.[26] As of 2019 this measure is no longer evaluated because a further increase is not expected. Similarly, documenting the CHA2DS2-VASc risk score for atrial fibrillation patients increased from 85% in 2016 to 93% in 2018.[26] Compared with these two examples the compliance of the PAM process steps is low.

7.1.2.1 Can we observe variation between hospitals?

Besides studying the overall reliability of the PAM process in Dutch hospitals, we also compared hospitals with each other in **chapter 3**. Doing so, we observed significant practice variation between participating hospitals for several PAM steps. Observed differences between the highest and lowest performing hospitals were as high as just over 70% and post-hoc testing identified both significantly under- and over performing hospitals. If we had been able to include more patients per hospital, this range would most likely be smaller, but still, we believe the observed variation is disturbing and indicative of heterogeneous CPG adoption and reliability of the PAM process. Whether or not this also resulted in different patient outcomes between lower and higher performing hospitals cannot be concluded on our research since we did not have outcome measures for our study. Alternatively, using PAM process measures to infer outcomes might be possible.

Based on literature from other clinical domains, the relationship between process and outcome quality measures is not straightforward. For example, research in other patient populations has found both strong as well as virtually no associations between process and outcome measures for acute coronary syndrome and heart failure respectively.[27, 28] Regarding the PAM process steps, we expect, based on other literature available, that the pre- and postoperative decisions to apply bridging anticoagulation are related with postoperative bleeding complications, and therefore are important process measures. [29, 30] The relationship between the timing of preoperative assessment and VKA interruption and INR testing with common outcome measures such as complications and mortality is less straightforward. Rather we expect these process measures to be associated with other unfavourable events such as postponement of surgery and a longer hospital stay.

7.1.2.2 Can predictors of unreliable care be identified?

In **chapter 4** we extensively studied the use of postoperative bridging as part of PAM. We were interested in predictive parameters non-compliant postoperative bridging. Before we started modelling for this, we developed a model that predicted whether a patient would receive postoperative bridging anticoagulation regardless of whether this was in line with the CPG recommendation.

Besides several expected predictors directly related with an elevated thromboembolic risk, (mechanical heart valve, previous VTE and/or CVA/TIA) we found that several surgery types and indicators of the severity of the disease (ICU/CCU admission, second surgery performed) were positively correlated with the use of postoperative bridging.

As discussed in **chapter 4** the difference between medical specialties might be explained by a different perception of thromboembolic and/or bleeding risk relative to the risks inherent to the surgical procedure. Whether this is the true explanation in our study is unknown. However, other literature points in the same direction.[31] CPGs could try and support the different medical specialties by explicitly including a more elaborate (specialty specific) surgical bleeding and thromboembolic risk assessment in the risk stratification. The correlation of ICU/CCU admission with postoperative bridging is most likely related

with parenteral therapeutic heparin or low molecular weight heparin (LMWH) being the only feasible alternative available due more patients not being able to take oral medication on the ICU. In case of a short-term subsequent surgery, therapeutic dose LMWH administration between surgeries is most likely preferred over restarting VKA which requires INR monitoring and dose adjustments. Both these possible explanations for using therapeutic heparin or LMWH postoperatively should be confirmed by the clinical practice after which it should be considered whether to address these scenarios in PAM guidelines or refer to guidelines for the treatment of the underlying condition for which the anticoagulants are required.

Our model predicting non-compliant overuse of postoperative bridging in low thromboembolic-risk patients also yielded the surgery type as an important predictor. This underlines our recommendation from the previous paragraph to further investigate this between specialty variation and address this in relevant CPGs. Since we also observed between specialty variation in VTE prophylaxis use (chapter 7.1.2), further investigation might be combined. An additional important predictor for overuse that was discovered entails non-elective surgeries. It appears from our study that patients who were urgently operated were more likely to receive postoperative bridging anticoagulation when this was not recommended by the CPG based on their risk profile. However, strictly speaking, current CPGs do not explicitly include non-elective surgery patients in their recommendations regarding bridging and PAM in general. Hence, we should be discrete when drawing conclusions about the deviations we observed.

To our knowledge there is no scientific evidence available that discusses the matter of postoperative bridging after non-elective or emergency surgery. This is surprising since a significant proportion of surgeries in VKA patients are unplanned. In our study this was about 30%. Given that our study sample originated from a random hospital and record selection, we believe that this 30% is a representative figure for the Netherlands. Omitting a statement or recommendation regarding postoperative bridging for such a large proportion can be a risk for the patients involved. Especially since the risks of postoperative bridging became more apparent in recent literature[29, 30] supporting more reluctance regarding bridging. Therefore, we believe PAM CPGs should address this patient group and provide recommendations regarding postoperative bridging while considering possible preoperative reversal agent use.

7.1.3 How is perioperative antithrombotic management conducted in everyday practice (work-as-done) and how does this relate to predefined procedures (work-as-imagined)?

In **chapter 6** we developed FRAM models for the preoperative PAM settings in a Dutch and Australian cardiothoracic surgery setting. We aimed to obtain a deeper understanding of how PAM is conducted in everyday practice (work-as-done) and how this relates to predefined procedures (work-as-imagined). By doing so we would obtain insight in whether PAM is sensitive to daily operations and variation. Focus was laid on how the PAM policy was set and carried out preoperatively.

Although preoperative PAM workup differed markedly between the two sites under investigation, both sites experienced variability in the functions that were to result in an initial PAM policy, i.e., to interrupt, bridge or continue. In both settings the responsible surgeon was identified as the one who should formulate the PAM policy. However, this was often not the case and hence, both sites had organised downstream functions in such a way that a PAM policy was formulated after all.

In the Dutch setting, registrars, and physician assistants (PAs) were responsible for formulating the PAM policy. Both the anaesthetist and department secretary would signal a missing PAM policy during the execution of their respective functions in the FRAM model, effectively controlling the registrars and PAs work. Similarly, in the Australian setting the nurse case-manager serves as a control for the surgeon in case a PAM policy is missing.

Another remarkable finding which is limited to the Dutch context, entails the alignment between the hospital and the anticoagulant management services (AMS), who are, under normal circumstances, responsible for outpatient anticoagulant management. There appeared to be no involvement of AMS. Moreover, the hospital department temporary took over all responsibility by directly instructing the patient how to take their medication in the days leading up to the procedure. This is not in line with the national integrated care standard recommendations[11], however the department argued this increases clarity for patients. Furthermore, it eliminates variability and reduces dependency from having to align PAM care with AMS. Especially given that thoracic surgery departments typically have larger service areas with potentially more AMS to align with. Not having to include the AMS in the Dutch model for this reason, probably benefits the understandability of a model that in itself comes across as complex.

The FRAM models from both cardiothoracic settings had in common that several functions were controlled by self-developed checklists. These aids were only used by their developers and were not transferred to colleagues. On one hand, this is evidence of the resilience of the involved professionals to take action and introduce an extra control mechanism to reduce variability in the controlled function. On the other hand, given that these aids are personal, the control mechanism might disappear quietly in case of an unexpected absence, or other change in staff.

Our FRAM analysis can be positioned in the third dimension of the safety measurement and monitoring framework which addresses the question whether healthcare processes are sensitive to daily operations and variability. Regarding PAM, we believe this is the case for the departments that were under study in the Netherlands and Australia. However, we cannot extrapolate this to other departments and hospitals without question. Therefore, we would need to perform FRAM analyses on a larger scale within the same healthcare system. This will be complicated by the relatively large time investment that was required for developing the FRAM models per department, i.e. 47 hours in our study, which can be regarded as a barrier for large scale application.

Most of the other FRAM applications in healthcare we are aware of, are also limited to a single specific healthcare setting. Hence, domain wide conclusions regarding resilience are difficult to make. The study by Schutijser et al. (2019) can be seen as an exception here, because the FRAM analysis was applied on the process of administering injectable mediation in multiple wards spread over two hospitals from the same healthcare system.[32] Although the included hospitals are still limited in number, valuable insights from comparing the FRAM analyses were obtained.

To conclude, an important barrier or deficiency of FRAM we wish to point out is the lack of an endorsed method for quantifying variation in functions and the influence of variation on downstream functions. Ultimately, a FRAM model is not able to present probabilities of unwanted outcomes such as AEs. This limitation has primarily been recognized by studies from outside the healthcare domain.[33-36] We believe however, that this deficit could prevent a widespread adaptation of FRAM in healthcare and obstruct endorsement by healthcare management and/or policy makers. Not being able to quantify the probability of a FRAM model instance that causes AEs, can come across as elusive and might not be

allocated time and resources for improvement by healthcare management. By combining the FRAM methodology with computational approaches, such as Monte Carlo simulations can help quantifying the sources of variability in a complex system and can help direct focus on functions with the highest variability. This novel addition to FRAM has been proposed by Patriarca et al. (2017) in a study from the air traffic control domain.[34]

7.2 Methodological considerations

In this thesis various quantitative and qualitative methods were used for obtaining our study results. We believe this mixed-methods approach can be regarded as a strength of this thesis. Inspired by the “safety measurement and monitoring framework” from Vincent et al. (2014)[1], we were able to obtain insights in the quality of care of complex antithrombotic processes from various perspectives. Furthermore, our record review studies were performed in hospital samples representative for the Netherlands. Hence, we believe that our findings are also representative for the Dutch context but extrapolating the results outside this context should be done carefully. Especially since the Netherlands has a rather unique organisation of antithrombotic care in which anticoagulant management services (AMS) play an important role.

For measuring the incidence of ARAEs we performed a post-hoc analysis of several repeated record review studies aimed at identifying overall AEs. This Record review studies have been the gold standard for over 20 years for identifying AEs in healthcare.[37] A well-known limitation of this method is hindsight bias from the reviewers perspective by having access to all relevant information during the review. Another limitation is information bias that is introduced by the dependency on a well-documented patient record. These biases should be considered when interpreting the results. A strength of our post study is that we were able to derive relevant insights and detailed contextual information on subgroups of patients with an ARAE that made up only about 7% of the overall AE group. This is indicative of the quality of the original data source and promotes reuse of data for new research questions. The importance and potential of reusing scientific data is increasingly endorsed in the research community.[38]

Another record review study was designed for measuring the reliability of antithrombotic care delivery in hospitals. As opposed to the record review study aimed at identifying AEs, the records were reviewed by researchers and research assistants. Because we primarily extracted information for evaluating process measures this was a feasible alternative. However, it limited us in extracting, and eventually reporting, information about patient outcomes and possible complications. We recommend appointing physician reviewers for this in the future and explore whether automatic natural language processing solutions can help reduce manual labour. In addition, perioperative care delivery agreements were in some cases documented outside the hospital by the AMS, due to collaboration agreements. In future studies this should be accounted for by including AMS records in reviews where necessary.

A qualitative method that we applied for this thesis was the FRAM analysis. Instead of focussing on what goes wrong in antithrombotic care delivery, this study focussed on identifying why antithrombotic care delivery usually goes right by studying the every-day adjustments made by healthcare professionals to account for daily variation. Adopting this alternative perspective allowed us to focus also on activities that are responsible for the

fact that clinical work usually goes right rather than isolated cases where things go wrong. However, we have two concerns regarding this novel approach. First, FRAM analyses are very time consuming and application in a large representative multicentre setting for obtaining nationwide insights is yet to be examined. Second, it is unclear whether FRAM analyses can support quantification of risks for unwanted outcomes for patients, as discussed in paragraph 7.1.3.

7.3 Future perspectives

So far in this thesis we have discussed our research in light of the first three dimensions of Vincent's safety measurement and monitoring framework since most of our research and research questions can be positioned under these dimensions: "past harm", "reliability" and "sensitivity to operations." To conclude the safety measurement and monitoring framework for antithrombotic care in the Netherlands, we now touch upon the last two dimension of the framework: "anticipation and preparedness" and "integration and learning." The last dimension is discussed from our future perspective on continuous data-driven learning and improvement.

7.3.1 Anticipation and preparedness: leveraging the FRAM methodology for early hazard identification

This dimension is all about thinking ahead and trying to identify hazards to patient safety in order to intervene in a timely manner to prevent unwanted outcomes. Vincent et al. (2014) stresses that there are no unambiguous approaches or information sources that are guaranteed to be of aid for this goal. Rather, it requires a certain mind-set that encourages a critical view on and promotes questioning of the course of events in a healthcare department, institution or system.[1] Formal approaches that can be considered for this dimension are human reliability analyses, safety cases and indicators such as safety culture and staffing levels.[1] Ultimately, a healthcare organisation might want to combine all this information in an advanced risk prediction system. However, Vincent et al. (2014) noted that from all five dimensions in the safety measurement and monitoring framework, the "anticipation and preparedness" dimension is the most underdeveloped of all dimensions.[1]

Regarding antithrombotic care, one of our findings described in **chapter 2** indirectly points to a possible effect from staffing levels on ARAE's, i.e., the weekend effect, when fewer staff is available. Hence, underlining the potential of monitoring staffing levels in advance could be an important factor in preventing future AEs. Furthermore, we expect that the application of FRAM models on various antithrombotic care processes will be beneficial for the anticipation of hazards within these local processes. Typically, FRAM models are developed in close collaboration with involved professionals, encouraging them to reflect on individual and team performance and interdependence. Additionally, FRAM models can also be specifically deployed to anticipate on latent hazards and risks in complex socio-technical systems. For example, Rosa et al. (2015) anticipated the risks workers are exposed to when working in construction sites with continuously changing circumstances and demands.[39] Within healthcare however, this approach to FRAM has not gained much consideration. Salehi et al. (2020) found 16 applications of FRAM in healthcare of which only one study performed a FRAM analysis for hazard identification and risk management.[36] Within other domains, hazard identification was a much more prevalent

application, i.e. in 9 out of 36 non-healthcare applications of FRAM.[36] This is indicative of the novelty of using FRAM in healthcare safety research. Going forward, we suggest FRAM applications for hazard anticipation in antithrombotic care and healthcare in general. In addition, as discussed in paragraph 7.1.3, mounting FRAM models with a computational component in an attempt to quantify future risks can be valuable for estimating probabilities of unwanted outcomes.

7.3.2 Integration and learning: leveraging data for learn and improvement cycles

Vincent's fifth and final dimension combines the data sources of preceding dimensions into meaningful and actionable insights to improve the quality and safety of care. In their article Vincent et al. (2014) mention a "safety information reporting system" that should act as "an information, analysis, learning, feedback and action system."[1] Regarding antithrombotic care such a data driven approach can be achieved by integrating data from EHRs such as used in **chapters 2, 3 and 4,** with non-clinical data sources such as e.g. staffing levels, filed complaints and patient reported outcomes. Validation, analysis, and reporting should then be applied for generating reliable, and actionable insights on a continuous basis in order to support learning and improving antithrombotic care.

7.3.2.1 A data driven approach

In chapters 2, 3 and 4 we used clinical data for measuring harm and reliability of antithrombotic care delivery. We believe that both our data source and measures are similar compared with how these are used in clinical registries for measuring process and outcomes quality measures. Since the digitalization of patient records and improved extraction possibilities, clinical registries can more easily be established for data driven learning cycles within and between hospitals.

Given the large reliability variation for PAM between hospitals as presented in **chapters 3 and 4,** process quality measures are obvious candidates for adoption in a first iteration of an antithrombotic care registry. From other clinical registries we have seen that reducing variability by measuring process measures is a successful approach in the Netherlands.[40-42] An important characteristic of these registries is that the "clinical auditing" principle was applied to ensure adoption of the registry within the medical domain of interest.[43]

In clinical auditing a major role is set aside for healthcare professionals working in the clinical domain of interest. They define quality measures, datasets, analyses and provide interpretation.[43] If antithrombotic care processes are integrated in continuous monitoring and feedback cycles we can see, among many minor, two major challenges.

First of all, CPG's. In **chapters 3 and 4** we highlighted several concerns with the CPG's regarding PAM. For a large part these concerned outdated recommendations, urging for quicker updates of the CPG's when new scientific evidence becomes available. Another challenge regarding CPG's entails their implementability as we discussed in **chapter 5** for two influential VTE prophylaxis CPG's. In this study we found several more concerns regarding the evidence base used for CPG development. Interestingly, the two guidelines, used the same evidence and were developed in the same period, but resulted in a different recommendation for the bleeding risk assessment. As a result, the 'decidability' (when to act) was deemed to be barrier for implementation. For several other CPG recommendations, the 'executability' (how to act) was found to be a barrier for implementation. To use CPGs as a foundation for clinical auditing with process quality measures, we believe that both the executability and decidability of individual recommendations should be unambiguous

Second, antithrombotic care can be characterised as highly multidisciplinary and entails a diverse patient population. Although the major indications for antithrombotic therapy are cardiovascular, other specialties must manage this as a comorbidity. For example, INR monitoring and dosage adjustments for VKA patients should continue during any hospitalization. In line with clinical auditing, these healthcare professionals should all be involved in developing quality measures for antithrombotic care. This will be challenging, because potentially all medical specialties are involved. Therefor it has been encouraging to see such a collaboration taken place in the development of two guidance documents, i.e. the national antithrombotic care guideline: 'Richtlijn antitrombotisch beleid' (Antithrombotic care guideline)[12] and the 'Landelijke Standaard Ketenzorg Antistolling' (Dutch national standard integrated antithrombotics).[11] While the former entailed a guideline endorsed by over ten scientific medical associations, the latter describes various critical processes in both primary, secondary and tertiary care settings. Each process is described in detail and responsibilities per discipline are made explicit.

7.3.2.2 Responsibility

Upon overcoming these challenges and obtaining access to a data platform for antithrombotic care as proposed in the previous paragraph, the responsibility for monitoring and adjustments should be clear. It seems evident this should be a multidisciplinary team of professionals involved in antithrombotic care delivery. Referring again to the LSKA standard, the recommended antithrombotic case management, responsible for antithrombotic care delivery within hospitals, could be suitable for this task. However, the implementation of case management for antithrombotic care varies between hospitals.[44]

A comparable approach to antithrombotic case management has already been implemented for antimicrobial drug use in hospitals. In a similar way, antimicrobial drug use is also highly decentralised between departments and disciplines. In addition, patient populations are heterogeneous as well. Hence, some form of central governance of antimicrobial policy was instituted. Referred to as 'Antimicrobial Stewardship' and formalized in organization wide 'A-teams' this effort has reduced antimicrobial use, improved patient outcomes and potentially prevented and/or controlled antimicrobial resistance.[45, 46] In analogy with these 'A-teams', research by Dreijer et al. (2016) focussed on the implementation of 'coagulation teams' or 'stolling-teams' in Dutch. These multidisciplinary teams were tasked with daily medication reviews of patients using antithrombotics, focussing on dosing, interactions, contraindications and perioperative bridging.[47] Compared with usual care, instituting the multidisciplinary 'S-team' was associated with a reduction of anticoagulant complications and all-cause mortality.[22]

Taking these experiences to heart, antithrombotic case management or 'S-teams' can play a major role in data driven integration and learning initiatives and also drive safety-II analyses such as FRAM for various antithrombotic care processes.

7.3.2.3 National improvement initiatives

After the publication of the Dutch AE monitor of 2015/2016, of which the underlying data was used in this thesis, governing bodies involved in hospital care, joint forces and have set goals for further improving patient safety in Dutch hospitals.[48] In this *"Tijd voor verbinding"* programme, Antithrombotic care is listed as the first pillar for improvement.

Over a course of four years, four challenges within antithrombotic care delivery are tackled:

1. Practice variation between hospitals
2. Knowledge of professionals and patients and their carers

3. Cooperation in the networks around patients
4. Complication registration on a regional or national level

Most of these challenges were recognized during our research for this thesis, of which the practice variation between hospitals is the most striking similarity.

Solutions to these challenges include, among others: real-time availability of prescription data, standardized protocols, instituting antithrombotic case managers or 'S-teams', establishing knowledge networks or platforms, apply safety-II analyses on known best-practices and discussing complications in a multidisciplinary setting.

Early 2022 the latest edition of the Dutch AE monitor was published covering patients deceased in hospitals in 2019. In this monitor antithrombotic involvement in medication related adverse events increased to 38.9%. The preventability of these ARAEs reduced to 20.1% compared with the previous monitor.[49] It is recommended to review the implemantation of medication guidelines and apply a combination of safety-I and safety-II methods in a multidisciplinary setting.

7.4 Recommendations

In this thesis we studied ARAE incidence and circumstances together with the reliability and everyday practice of antithrombotic care. Regarding ARAEs, our research showed that the incidence in Dutch hospitals declined in the deceased population. Although this is encouraging, we also observed a lacking decline in discharged patients, a relatively high preventability, a persistent involvement of elevated INRs as ARAE cause and a slightly increasing trend of antiplatelet and/or combined antithrombotic therapy involvement in ARAEs. Regarding antithrombotic care reliability, deviations from recommended care were common and variation between hospitals in delivering recommended care was evident. These findings are supported by our study of everyday antithrombotic care. Work-as-done varied significantly from work-as-imagined for some PAM process steps that we studied. However, downstream functions were present to avert possible harm reaching the patient.

Through this thesis we already proposed and explored several recommendations for the future. In this paragraph they are briefly summarized and integrated with our perspectives on future antithrombotic care. Recommendations are made for clinical practice, healthcare policy and further research.

7.4.1 Recommendations for clinical practice

Monitor antithrombotic care process measures.

In this thesis we found room for improvement concerning the reliability and variation of antithrombotic care processes. Based on this it is recommended to continue the monitoring of these processes by formulating process measures which are evaluated periodically and are compared between hospitals. This will continue to support quantifying and, in time, reduce practice variation.

Use FRAM models in antithrombotic care settings for anticipating on latent hazards.

As discussed in 7.3.1, FRAM models in healthcare are not widely in use yet and those reported in medical literature are often not used for hazard and risk identification. We recommend exploring the additional benefits of FRAM analyses for this purpose in healthcare in general and for antithrombotic care settings especially. For example, can we anti-

cipate what the effect of an expected or unexpected decline in staffing levels has on the quality of antithrombotic care processes?

Continue hospital wide implementation of antithrombotic case-management

In analogy with hospital-wide antimicrobial stewardship, a comparable approach for antithrombotic case-management is recommended. A first proposal in and various implementations have already been attempted based on the LSKA standard. However, widespread institution of antithrombotic case-management in the Netherlands has not been achieved yet.

We envision an important role and responsibility for antithrombotic case-management in progressing towards a data-driven integration and learning cycle in Dutch hospitals.

7.4.2 Recommendations for healthcare policy

Continue measurement of antithrombotic related adverse events

Although the patient safety research community is shifting from a safety-I to a safety-II perspective, we believe that measuring harm should be maintained as an important cornerstone for measuring and quantifying patient safety. Ultimately, safety-II initiatives are also aimed at improving patient safety. By continued monitoring of patient harm, initiatives from both safety perspectives can be evaluated using before and after measurements.

Based on our research, continued measurements to consider should be targeted on the following three topics:

1. INR monitoring in patients taking VKAs
2. Patients taking antiplatelet agents, including double and triple antithrombotic therapy
3. The discharged patient population

In addition, it should be considered to start monitoring ARAE's in patients taking NOACs. NOACs were underrepresented during our data collection period because they were not widely prescribed yet.

Consider evaluating the quality of antithrombotic care by means of a clinical registry

In this thesis and work related to it, we have demonstrated that perioperative anticoagulant management and VTE prophylaxis are both antithrombotic care processes with evident practice variation between hospitals. Repeated audit and feedback cycles are obvious candidates to try and reduce this variation. We believe that by formalizing this in the context of a clinical registry in line with the clinical auditing principle should be considered. If done well, this can result in a widely supported platform for evaluating not only PAM and VTE but potentially other antithrombotic care processes. Antithrombotic case management or similar institution wide antithrombotic advisory bodies can serve as catalysts for local adoption of the clinical registry and interpretation of the resulting insights.

Clinical practice guideline progression

Throughout this thesis, CPG's have played a central role. In several chapters we suggested improvements or additions regarding relevant antithrombotic CPGs. They can be categorized as either concerning CPG content or development:

CPG content

1. Include PAM recommendations for non-elective surgery settings.
2. Include PAM recommendations for multiple short-term consecutive surgeries.
3. Include PAM recommendations for patients unable to take oral medication.
4. Include PAM specialty specific risk stratification for surgical bleeding and thromboembolic risk.

CPG development

1. Faster revisions of recommendations in CPGs when new scientific evidence becomes available.
2. The decidability and executability of CPG recommendations should be unambiguous and endorsed from a multidisciplinary perspective to improve uptake and implementation in clinical practice

7.4.3 Recommendations for further research

Study INR monitoring processes in hospitals

Elevated INRs were responsible for a majority of ARAEs identified in this thesis and this proportion remained stable over time. Underlying mechanisms were not further explored in the context of this thesis. Hence, we recommend future research to focus on the INR monitoring processes in order to design interventions for improvement. We think that a safety-II perspective for such a study is in place, and FRAM analyses should be considered.

In addition, a more technological solution can possibly be found in automatic or continuous INR monitoring similar to devices that are used for continuous glucose monitoring in diabetes patients. Unexpected INR fluctuations will then be recognized faster and can be act upon accordingly.

Explore methodologies to quantify FRAM analyses in healthcare

In the general discussion of this thesis, we briefly elaborated on the possibilities for an additional quantitative approach to the FRAM methodology. We believe that this can help in the comparison of FRAM analyses between various settings and supports the legitimacy of FRAM analyses and its' results, that might otherwise remain elusive to healthcare management.

We recommend studying the applicability and added value of quantitative add-on methods to the FRAM methodology already applied in other risk prone domains.

7.5 References

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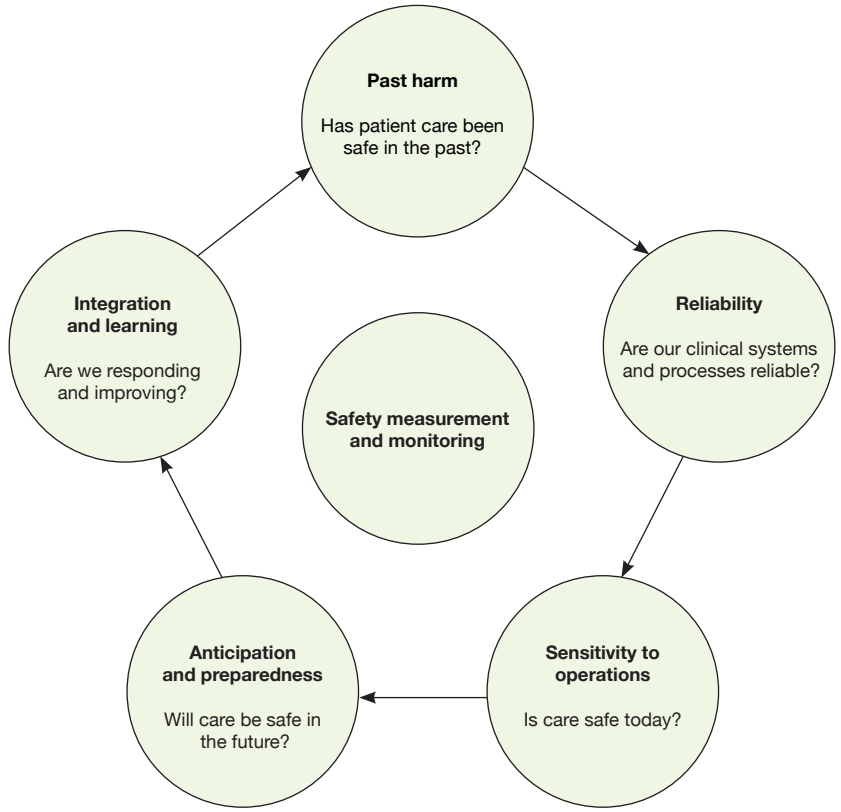
SUMMARY / SAMENVATTING



Summary

Antithrombotic drugs belong to the most used medications in healthcare. About one in ten Dutch inhabitants uses antithrombotic drug.[1, 2] Antithrombotic drugs are used to reduce the risk of clot formation caused by pathologies such as atrial fibrillation or venous thromboembolism. Mitigating this risk comes at the cost of a small increase in the risk of bleeding. Often this trade-off is clear-cut and favours the use of antithrombotic drugs. However, a lot of factors influencing this trade-off can quickly increase the complexity of this trade-off making it less clear-cut. If this is not recognized, this can in some cases result in the occurrence of adverse events related to antithrombotic drug use (ARAEs)

ARAEs gained increasing attention in adverse event studies in the Netherlands in the past two decades but the exact magnitude of this problem remained unknown. Hence, ARAEs were not targeted specifically in national patient safety improvement strategies. [3-6] This thesis aims to systematically measure the safety of antithrombotic care provided in Dutch hospitals to guide future improvement efforts.

The safety measurement and monitoring framework was used as a guiding framework for the studies in this thesis.[7] Research questions were formulated in analogy with the first three dimensions of this framework, i.e.: *Past Harm, Reliability* and *Sensitivity to Operations*. In the general discussion the study findings fed the prospective assessment of the last two dimensions of the framework: *Anticipation and preparedness* and *Integration and Learning*.

The research questions were:

1) How common are (preventable) antithrombotic related adverse events in Dutch hospitals and what are the circumstances in which they occur?

2) How reliable is perioperative antithrombotic management and administering VTE prophylaxis in Dutch hospitals?

3) How is perioperative antithrombotic management conducted in everyday practice (work-as-done) and how does this relate to predefined procedures (work-as-imagined)?

In **chapter 2** we aimed to estimate the antithrombotic-related adverse event incidence between 2008 and 2016 and analyse the clinical context by a post-hoc analysis of three Dutch adverse event (AE) studies. Previously identified AEs were screened for antithrombotic involvement and contextual ARAE characteristics were analysed. Between 2008 and 2016 ARAE incidence decreased significantly in in-hospital deceased patients from 1.20% in 2008 to 0.54% in 2015/2016 (p = 0.02). In discharged patients ARAE incidence remained stable over the years. Most ARAEs involved Vitamin-K antagonists (VKAs) and ARAEs that were classified as potentially preventable occurred more during weekends and when multiple medical specialists were involved. Antiplatelet and combined antithrombotic therapy appeared to be increasingly involved in ARAEs over time. Opportunities for improving antithrombotic safety should target INR monitoring and care delivery aspects such as multidisciplinary involvement and weekend care. Future ARAE monitoring for the involvement of antiplatelet, combined antithrombotic and direct oral anticoagulant (DOAC) use is recommended.

In **chapter** 3 we assessed the reliability of anticoagulant management in patients undergoing surgery. Surgery in patients on anticoagulants requires careful monitoring and risk assessment to prevent harm. This process, known as perioperative anticoagulant management (PAM), is optimised by using clinical practice guidelines (CPG). We assessed the reliability of PAM practice, operationalised as compliance with CPG recommendations, by analysing 259 patient records from 13 hospitals. Additionally, variation between hospitals was studied. We found that preoperative compliance was lowest for timely VKA interruptions (58.8%) and highest for timely preoperative assessments (81%). Postoperative compliance was lowest for timely VKA restarts (39.9%) and highest for the decision to apply bridging (68.5%). Variation in compliance between hospitals was observed for the timely preoperative assessment, INR testing and postoperative bridging. The unsatisfying compliance reflects suboptimal reliability of PAM in practice, which varied between hospitals. This may have increased the risk for ARAEs, advocating quality improvement efforts. Continued measurement and monitoring of these PAM process measures may help.

In **chapter 4** we studied the reliability of postoperative bridging anticoagulation and associated factors. Bridging anticoagulation is used in vitamin-K antagonist (VKA) patients undergoing invasive procedures and involves a complex risk assessment to prevent thromboembolic and bleeding outcomes. By retrospectively reviewing 256 patient records from 13 hospitals, demographic, clinical, surgical and care delivery characteristics were collected. Compliance was assessed by comparing practice with the American College of Chest Physicians ninth edition CPG (AT9) recommendations for bridging. We found that bridging was used in 41.8% of patients, whereas the compliance of bridging was somewhat higher with 68.5%. Both established thromboembolic risk factors and characteristics outside the AT9 thromboembolic risk assessment were associated with bridging use. Overuse of bridging was associated with gastrointestinal and vascular surgery, non-elective surgery, lower socioeconomic status, and use of anticoagulant reversal agents. The combined AT9 thromboembolic risk score was inferior to individual thromboembolic risk factors and other characteristics in explaining bridging use. Therefore, the AT9 risk seemed less important for the decision making in everyday practice.

In **chapter 5** we compared the American College of Chest Physicians and National Institute for Health and Care Excellence guidelines' risk assessment recommendations for venous thromboembolism (VTE) prophylaxis in non-surgical patients. Additionally, we critically appraised their implementability characteristics. VTE prophylaxis CPGs recommend the assessment of VTE and bleeding risk to guide prophylactic strategies. Because their implementation in practice is suboptimal, assessing the implementability characteristics aids implementation. Eight experts, involved in antithrombotic CPG development, appraised the intrinsic implementability characteristics of the CPG recommendations using the Guideline Implementability Appraisal (GLIA) instrument. We found that eleven out of 20 VTE-risk factors and only 2 out of 19 bleeding-risk factors, were present in both CPGs. Furthermore, high VTE- or bleeding risk was defined differently. Implementability barriers were identified in GLIAs decidability, flexibility, effect on process of care and computability dimensions. Revising the recommendations, considering the most apparent implementation barriers, is recommended.

In **chapter 6** we studied the everyday practice of preoperative PAM from a safety-II perspective. This novel perspective aims to learn from complex processes in healthcare and understand why they usually go right. Using the Functional Resonance Analysis Method (FRAM) we assessed everyday PAM (work as done) in relation to predefined procedures for PAM (work as imagined). The study was conducted at an Australian and European Cardiothoracic Surgery Department. The work-as-imagined FRAM model was based on (inter) national CPGs. Two work-as-done FRAM models were developed based on 18 semi structured interviews with professionals involved in PAM from both sites. These were presented to the centre's staff for validation. In both centres, work-as-done differed from work-as-imagined, such as in the division of tasks among disciplines (e.g., nurses/registrars rather than medical specialists), but control mechanisms had been developed locally to ensure safe care (e.g., crosschecking with other clinicians). The centres had organized the PAM process differently, revealing opportunities for improvement regarding patient information and clustering of clinic visits. By using the FRAM as analysis method, we gained insight into PAM from the perspective of frontline clinicians, revealing essential functions, interdependencies and variability, and the relation with CPGs. Future studies are warranted to study the potential of FRAM, such as for guiding improvements in complex systems.

Chapter 7 is the general discussion in which we interpret our main research findings and give our future perspective on antithrombotic care quality improvement.

How common are (preventable) antithrombotic related adverse events in Dutch hospitals and what are the circumstances in which they occur?

In our research we found that ARAE incidence in deceased patients decreased from 1.20% in 2008 to 0.54% in 2015/2016. Although this is an encouraging result, other findings were concerning. These are: a lacking decline of ARAEs in discharged patients, the relatively high preventability of ARAEs (28.54%) and the increasing trend of involvement of antiplatelet and/or combined antithrombotic therapy in ARAEs over time. To lower the preventability of ARAEs, lessons might be learned from the surgical processes in which the preventability of surgical AEs significantly reduced during the past years. Continued monitoring of antiplatelet and combined anticoagulant therapy is recommended to confirm our suspected increase of involvement in ARAEs.

Given these concerns, the observed decline of ARAEs in deceased patients is still a positive development and could imply that awareness of antithrombotic risks rose over time under the influence of increasing attention in the nationwide AE studies. Furthermore, within the field of antithrombotic care various quality improvement efforts were already underway that might have contributed. Regarding circumstances of ARAEs, an important finding was that around one third of ARAEs in general and half of the preventable ARAEs, related to an elevated INR. Causes lie in, among others, drug-drug interactions, comorbidities, and reversal agent administration errors. These causes were already known from existing literature and in practice. We recommend a qualitative safety-II investigation to learn why these well-known causes sometimes still result in an ARAE.

How reliable is perioperative antithrombotic management and administering VTE prophylaxis in Dutch hospitals?

Reliability was operationalised as CPG compliance in this thesis. From our research we can conclude that deviations from antithrombotic CPG recommendations were common. Most of these recommendations can be regarded as process measures. When comparing

them as such with measures from other clinical domains, compliance is low. Additionally, we observed significant variation in compliance, up to 70 percentage points, between hospitals. This is indicative of a heterogeneous adoption of antithrombotic CPG recommendations in practice. Whether or not this is a risk to patient safety cannot be concluded directly from our research, however for some process measures it seems evident that they are related with less favourable outcomes, such as preoperative INR determination. Continued measuring and benchmarking of antithrombotic process measures, e.g., by clinical auditing, should be considered to increase reliability and reduce practice variation.

We also studied whether we could identify factors related with unreliable antithrombotic care. Regarding PAM we found that several surgical characteristics (type, urgency, and multiple surgeries) demonstrated a correlation with the use of bridging therapy or non-recommended bridging therapy. Other literature points to a difference in the perception of embolic and bleeding risk between surgical specialties as an explanation. Regarding the urgency of an operation, CPGs lack explicit recommendations for non-elective bridging therapy. It is recommended to address both between-specialty variation as well non-elective bridging therapy in the next CPG revision.

How is perioperative antithrombotic management conducted in everyday practice (work-as-done) and how does this relate to predefined procedures (work-as-imagined)?

From our FRAM we concluded that preoperative PAM is organised differently in practice than what is described in CPGs and related documents. Especially formulating the preoperative PAM policy was organised differently i.e., registrars and physician assistants (work-as-done) vs. the surgeon (work-as-imagined). Various downstream functions, such as self-developed checklists, were set to signal a missing PAM policy. We can conclude that FRAM analyses can provide valuable insights in how work-as-done is organised at individual hospitals or wards. It can help visualising the ingenuity and resilience of healthcare professionals. A limitation of FRAM is the lack of quantitative measures for the interpretation of a model. This might hinder a widespread adoption of FRAM models in healthcare. Hence, we recommended to explore such methods in healthcare as has been done in other research domains.

After discussing the research questions, **chapter 7** continuous with a prospective assessment of the last two dimensions of the framework.

It is recognized that the anticipation and preparedness dimension is the most underdeveloped dimension of the framework in healthcare organisations. We suggest investigating the use of FRAM methodology for prospective hazard identification. This is a recognized application of FRAM in other research domains but remains relatively underused within the healthcare domain.

Finally, for the integration and learning dimension, we draft our future perspective on progressing towards a data driven platform to support learning and improvement of antithrombotic care. This platform should be founded following the principles of clinical auditing to support adoption and recognition by professionals from relevant medical domains. To get there, barriers concerning unambiguous and conflicting clinical practice guidelines should be tackled and a broad spectrum of medical specialties and domains have to get aligned because antithrombotic medication is used all across the medical domain. An inspiring example of quality improvement within a comparable domain is the antimicrobial medication domain.

We conclude this thesis by making recommendations for clinical practice, healthcare policy and further research.

Regarding clinical practice, we recommend periodical monitoring of process measures, explore the use of FRAM models for hazard anticipation, and the implementation of antithrombotic case-management in analogy with antimicrobial stewardship.

Regarding healthcare policy, we recommend continuing periodical measurement of ARAEs, and to consider the overall quality of care measurement in the context of a clinical registry. Furthermore, we recommend the revision of relevant CPG's and to revise the CPG development process.

Regarding further research, we recommend to further investigate the processes of INR measurement in hospitals, since a majority of ARAE's occurred during out-of-range INR's. Lastly, we recommend exploring additional or additive methodologies that help quantifying the results of FRAM analyses in healthcare.

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Samenvatting

Antitrombotica behoren tot de meest gebruikte medicijnen in de gezondheidszorg. Ongeveer een op de tien Nederlanders gebruikt antitrombotica.[1, 2] Antitrombotica worden gebruikt om het risico op stolselvorming door pathologieën zoals atriumfibrilleren of veneuze trombo-embolie te verminderen. Het verminderen van dit risico gaat ten koste van een kleine toename van het risico op bloedingen. Vaak is deze afweging duidelijk en heeft het gebruik van antitrombotica de voorkeur. Veel factoren die deze afweging beïnvloeden, kunnen de complexiteit van deze afweging echter snel vergroten, waardoor deze minder duidelijk wordt. Als dit niet wordt herkend, kan dit in sommige gevallen leiden tot het optreden van antitrombotica gerelateerde bijwerkingen (AGB's)

AGB's kregen de afgelopen twee decennia steeds meer aandacht in onderzoeken naar bijwerkingen in Nederland, maar de exacte omvang van dit probleem bleef onbekend. Om die reden kregen AGB's geen specifieke aandacht in nationale strategieën voor verbetering van de patiëntveiligheid.[3-6] Dit proefschrift heeft als doel om de veiligheid van antitrombotische zorg in Nederlandse ziekenhuizen systematisch te meten als leidraad voor toekomstige verbeteringsinspanningen.

Het raamwerk voor het meten en monitoren van veiligheid is gebruikt als leidraad voor de onderzoeken in dit proefschrift.[7] Onderzoeksvragen zijn geformuleerd in analogie met de eerste drie dimensies van dit raamwerk, namelijk: *Past Harm, Reliability* en *Sensitivity to Operations*. In de algemene discussie voedden de onderzoeksresultaten de prospectieve beoordeling van de laatste twee dimensies van het raamwerk: *Anticipation and Preparedness* en *Integration and Learning.*

De onderzoeksvragen waren:

1) Hoe vaak komen (te voorkomen) antitrombotica gerelateerde bijwerkingen voor in Nederlandse ziekenhuizen en onder welke omstandigheden treden ze op?

2) Hoe betrouwbaar is de perioperatieve behandeling van antitrombotica en het toedienen van VTE-profylaxe in Nederlandse ziekenhuizen?

3) Hoe wordt de perioperatieve antitrombotische behandeling in de dagelijkse praktijk uitgevoerd (work-as-done) en hoe verhoudt dit zich tot vooraf gedefinieerde procedures (work-as-imagined)?

In **hoofdstuk 2** wilden we de incidentie van antitromboticagerelateerde bijwerkingen tussen 2008 en 2016 schatten en de klinische context analyseren door middel van een post-hoc analyse van drie Nederlandse studies over onbedoelde schade. Eerder geïdentificeerde bijwerkingen werden gescreend op antitrombotische betrokkenheid en de context ronden de AGB werden geanalyseerd. Tussen 2008 en 2016 nam de AGB-incidentie significant af bij in het ziekenhuis overleden patiënten van 1,20% in 2008 tot 0,54% in 2015/2016 ($p = 0,02$). Bij ontslagen patiënten bleef de incidentie van AGB's in de loop der jaren stabiel. Bij de meeste AGB's waren vitamine K-antagonisten (VKA's) betrokken en AGB's die als potentieel vermijdbaar waren geclassificeerd, kwamen meer voor tijdens weekenden en wanneer meerdere medisch specialisten betrokken waren. Bloedplaatjesaggregatieremmers en gecombineerde antitrombotische therapie bleken in de loop van de tijd steeds

meer betrokken te zijn bij AGB's. Mogelijkheden voor het verbeteren van de veiligheid van antitrombotica moeten zich richten op INR-monitoring en zorgverleningsaspecten zoals multidisciplinaire betrokkenheid en weekendzorg. Toekomstige AGB-monitoring voor de betrokkenheid van bloedplaatjesaggregatieremmers, gecombineerd gebruik van antitrombotica en directe orale anticoagulantia (DOAC) wordt aanbevolen.

In **hoofdstuk 3** hebben we de betrouwbaarheid van de behandeling met anticoagulantia onderzocht bij patiënten die een operatie ondergingen. Chirurgie bij patiënten die anticoagulantia gebruiken, vereist zorgvuldige monitoring en risicobeoordeling om schade te voorkomen. Dit proces, dat bekend staat als perioperatief antistollingsbeleid (PAB), wordt geoptimaliseerd door gebruik te maken van klinische richtlijnen. We hebben de betrouwbaarheid van het PAB beoordeeld door de naleving van de richtlijnaanbevelingen voor 259 patiëntendossiers uit 13 ziekenhuizen te analyseren. Daarnaast is er gekeken naar variatie tussen ziekenhuizen. We vonden dat de naleving het laagst was voor de tijdigheid van VKA-onderbrekingen (58,8%) en het hoogst was voor een tijdige preoperatieve beoordeling (81%). De postoperatieve richtlijnnaleving was het laagst voor een tijdige VKA-herstart (39,9%) en het hoogst voor de beslissing om overbruggingstherapie toe te passen (68,5%). Variatie in richtlijnnaleving tussen ziekenhuizen werd waargenomen voor tijdige preoperatieve beoordeling, INR-testen en postoperatieve overbruggingstherapie. De onbevredigende naleving weerspiegelt een suboptimale betrouwbaarheid van PAB in de praktijk, die varieerde tussen ziekenhuizen. Dit kan het risico voor AGB's hebben vergroot, wat pleit voor inspanningen voor kwaliteitsverbetering. Voortdurende meting en monitoring van deze PAB-procesmaatregelen kan helpen.

In **hoofdstuk 4** hebben we de betrouwbaarheid van postoperatieve overbruggingstherapie en geassocieerde factoren bestudeerd. Overbruggende antistolling wordt gebruikt bij patiënten met vitamine K-antagonisten (VKA) die invasieve procedures ondergaan en omvat een complexe risicobeoordeling om trombo-embolische en bloedingscomplicaties te voorkomen. Door retrospectief 256 patiëntendossiers van 13 ziekenhuizen te bekijken, werden demografische, klinische, chirurgische en zorgverleningskenmerken verzameld. Naleving werd beoordeeld door de praktijk te vergelijken met de aanbevelingen van de American College of Chest Physicians, negende editie, richtlijn (AT9) voor overbrugging. We zagen dat er overbrugging werd gebruikt bij 41,8% van de patiënten, terwijl de richlijnnaleving van overbrugging met 68,5% iets hoger was. Zowel vastgestelde trombo-embolische risicofactoren als kenmerken buiten de AT9-trombo-embolische risicobeoordeling waren geassocieerd met overbruggingsgebruik. Overmatig gebruik van overbrugging was geassocieerd met gastro-intestinale en vasculaire chirurgie, niet-electieve chirurgie, een lagere sociaaleconomische status en het gebruik van anticoagulantia. De gecombineerde AT9 trombo-embolische risicoscore was inferieur aan individuele trombo-embolische risicofactoren en andere kenmerken bij het verklaren van overbruggingsgebruik. Daarom lijkt het AT9-risico minder belangrijk voor de besluitvorming in de dagelijkse praktijk.

In **hoofdstuk 5** vergeleken we de risicobeoordelingsaanbevelingen van de American College of Chest Physicians en het National Institute for Health and Care Excellence voor profylaxe van veneuze trombo-embolie (VTE) bij niet-chirurgische patiënten. Daarnaast hebben we hun implementeerbaarheidskenmerken kritisch beoordeeld. Deze richtlijnen bevelen aan om het VTE en bloedingsrisico als leidraad te gebruiken voor profylactische strategieën. Omdat de implementatie van VTE prophylaxe in de praktijk suboptimaal is,

helpt het beoordelen van de implementeerbaarheidskenmerken bij de implementatie. Acht experts, betrokken bij de ontwikkeling van antitrombotische richtlijnen, hebben de intrinsieke implementeerbaarheidskenmerken van de richtlijn-aanbevelingen beoordeeld met behulp van het Guideline Implementability Appraisal (GLIA) instrument. We zagen dat elf van de 20 VTE-risicofactoren en slechts 2 van de 19 bloedingsrisicofactoren overeen kwamen in beide richtlijnen. Daarnaast werd een hoog VTE- of bloedingsrisico anders gedefinieerd. Implementatiebelemmeringen werden geïdentificeerd in de GLIA *decidability, flexibility, effect on process of care* en *computability* dimensies. Het wordt aanbevolen om de aanbevelingen te herzien, rekening houdend met de meest voor de hand liggende implementatiebarrières.

In **hoofdstuk 6** hebben we de dagelijkse praktijk van preoperatieve PAB bestudeerd vanuit een veiligheids-II perspectief. Dit nieuwe perspectief is bedoeld om te leren van complexe processen in de gezondheidszorg en te begrijpen waarom ze meestal goed gaan. Met behulp van de Functional Resonance Analysis Method (FRAM) hebben we de dagelijkse PABM (work as done) beoordeeld in relatie tot vooraf gedefinieerde procedures voor PAB (work as imagined). De studie werd uitgevoerd op een Australische en Europese afdeling cardiothoracale chirurgie. Het work-as-imagined FRAM-model was gebaseerd op (inter)nationale richtlijnen. Op basis van 18 semi-gestructureerde interviews met professionals die betrokken zijn bij PAB van beide vestigingen, werden twee 'work-as-done' FRAM-modellen ontwikkeld. Deze werden ter validatie voorgelegd aan het personeel van het centrum. In beide centra verschilde work-as-done van work-as-imagined, zoals bij de taakverdeling tussen disciplines (bijvoorbeeld verpleegkundigen/arts-assistenten in plaats van medisch specialisten), maar ter plaatse waren controlemechanismen ontwikkeld om veilige zorg te garanderen (bijvoorbeeld kruiscontroles met andere clinici). De centra hadden het PAB-proces anders ingericht, waardoor er verbeterpotentieel geobserveerd werd op het gebied van patiëntinformatie en clustering van kliniekbezoeken. Door de FRAM als analysemethode te gebruiken, hebben we inzicht gekregen in PAB vanuit het perspectief van eerstelijns clinici, waardoor essentiële functies, onderlinge afhankelijkheden en variabiliteit en de relatie met richtlijnen werden onthuld. Toekomstige studies zijn nodig om het potentieel van FRAM verder te bestuderen, bijvoorbeeld voor het begeleiden van verbeteringen in complexe systemen.

Hoofdstuk 7 is de algemene discussie waarin we onze belangrijkste onderzoeksresultaten interpreteren en ons toekomstperspectief geven op kwaliteitsverbetering van antitrombotische zorg.

Hoe vaak komen (te voorkomen) aan antitrombotica gerelateerde bijwerkingen in Nederlandse ziekenhuizen voor en onder welke omstandigheden treden ze op?

In ons onderzoek ontdekten we dat de incidentie van AGB's bij overleden patiënten daalde van 1,20% in 2008 tot 0,54% in 2015/2016. Hoewel dit een bemoedigend resultaat is, waren andere bevindingen zorgwekkend. Te weten: een uitgebleven afname van AGB's bij ontslagen patiënten, de relatief hoge vermijdbaarheid van AGB's (28,54%) en de toenemende trend van betrokkenheid van plaatjesaggregatieremmers en/of gecombineerde antitrombotische therapie bij AGB's in de loop van de tijd. Om de vermijdbaarheid van AGB's te verlagen, kunnen lessen worden getrokken uit de chirurgische processen waarbij de vermijdbaarheid van chirurgische bijwerkingen de afgelopen jaren aanzienlijk is afgenomen. Voortdurende monitoring van plaatjesaggregatieremmers en gecombineerde

anticoagulantiatherapie wordt aanbevolen om onze vermoede toename van betrokkenheid bij AGB's te bevestigen.

Gezien deze zorgen is de waargenomen afname van AGB's bij overleden patiënten nog steeds een positieve ontwikkeling die zou kunnen betekenen dat het bewustzijn van antitrombotische risico's in de loop van de tijd is toegenomen onder invloed van toenemende aandacht in de landelijke onderzoeken maar zorggerelateerde schade. Verder zijn er op het gebied van de antitrombotische zorg al diverse kwaliteitsverbeteringsinspanningen gaande die daaraan zouden kunnen hebben bijgedragen. Wat betreft de omstandigheden van AGB's, was een belangrijke bevinding dat ongeveer een derde van de AGB's in het algemeen en de helft van de te voorkomen AGB's verband hielden met een verhoogde INR. Oorzaken liggen onder meer in interacties tussen geneesmiddelen, comorbiditeiten en fouten bij het toedienen van middelen die de werking van antithrombotica tegengaan. Deze oorzaken waren al bekend uit de bestaande literatuur en in de praktijk. We raden een kwalitatief veiligheids-II-onderzoek aan om te achterhalen waarom deze bekende oorzaken soms toch leiden tot een AGB.

Hoe betrouwbaar is de perioperatieve behandeling van antitrombotica en het toedienen van VTE-profylaxe in Nederlandse ziekenhuizen?

Betrouwbaarheid is in dit proefschrift geoperationaliseerd als richtlijn naleving. Uit ons onderzoek kunnen we concluderen dat afwijkingen van antitrombotische richtlijnaanbevelingen veel voorkomend waren. De meeste van deze aanbevelingen zijn te beschouwen als procesmaatregelen. Wanneer ze als zodanig worden vergeleken met maatregelen uit andere klinische domeinen, is de naleving laag. Bovendien zagen we significante variatie in naleving, tot 70 procentpunten, tussen ziekenhuizen. Dit wijst op een heterogene adaptatie van antitrombotische richtlijnaanbevelingen in de praktijk. Of dit een risico is voor de patiëntveiligheid kan niet direct uit ons onderzoek worden afgeleid, maar voor sommige procesmaatregelen lijkt het evident dat ze samenhangen met minder gunstige uitkomsten, zoals preoperatieve INR-bepaling. Voortdurende meting en benchmarking van antitrombotische procesmaatregelen, bijvoorbeeld door clinical auditing, moet worden overwogen om de betrouwbaarheid te vergroten en praktijkvariatie te verminderen.

We hebben ook onderzocht of we factoren konden identificeren die verband houden met onbetrouwbare antitrombotische zorg. Met betrekking tot PAB vonden we dat verschillende chirurgische kenmerken (type, urgentie en meerdere operaties) een correlatie vertoonden met het gebruik van overbruggingstherapie of niet-aanbevolen overbruggingstherapie. Andere literatuur wijst op een verschil in de perceptie van tromboembolisch- en bloedingsrisico tussen chirurgische specialismen als verklaring. Met betrekking tot de urgentie van een operatie, missen de richtlijnen expliciete aanbevelingen voor ongeplande overbruggingstherapie. Het wordt aanbevolen om zowel variatie tussen specialismen als ongeplande overbruggingstherapie aan te pakken in de volgende richtlijn revisie.

Hoe verloopt de perioperatieve behandeling van antitrombotica in de dagelijkse praktijk (work-as-don) en hoe verhoudt dit zich tot vooraf gedefinieerde procedures (work-as-imagined)?

Uit onze FRAM hebben we geconcludeerd dat preoperatieve PAB in de praktijk anders is georganiseerd dan beschreven in richtlijnen en gerelateerde documenten. Vooral het formuleren van het preoperatieve PAB-beleid was anders georganiseerd, namelijk arts-assistenten en physician assistants (work-as-done) versus de chirurg (work-as-imagined). Verschillende downstream-functies, zoals zelf ontwikkelde checklists, zijn ingesteld om

een ontbrekend PAM-beleid te signaleren. We kunnen concluderen dat FRAM-analyses waardevolle inzichten kunnen opleveren in de manier waarop work-as- done is georganiseerd in individuele ziekenhuizen of afdelingen. Het kan helpen om de vindingrijkheid en veerkracht van zorgprofessionals in beeld te brengen. Een beperking van FRAM is het ontbreken van kwantitatieve maatregelen voor de interpretatie van een model. Dit zou een wijdverbreide acceptatie van FRAM-modellen in de gezondheidszorg kunnen belemmeren. Daarom hebben we aanbevolen om dergelijke methoden in de gezondheidszorg te verkennen, zoals in andere onderzoeksdomeinen is gedaan.

Na bespreking van de onderzoeksvragen vervolgt **hoofdstuk 7** met een prospectieve beoordeling van de laatste twee dimensies van het raamwerk.

Erkend wordt dat de dimensie *anticipation and preparedness* de meest onderontwikkelde dimensie is van het raamwerk in zorgorganisaties. We stellen voor om het gebruik van de FRAM-methodologie te onderzoeken voor het identificeren van potentiële gevaren. Dit is een erkende toepassing van FRAM in andere onderzoeksdomeinen, maar blijft relatief onderbenut binnen het domein van de gezondheidszorg.

Ten slotte, voor de *integration and learning* dimensie, omschrijven we ons toekomstperspectief voor een datagedreven platform om leren en verbeteringen van antitrombotische zorg mee te kunnen ondersteunen. Dit platform dient te worden opgericht volgens de principes van clinical auditing om acceptatie en erkenning door professionals uit relevante medische domeinen te ondersteunen. Om daar te komen, zullen barrières met betrekking tot eenduidige en tegenstrijdige richtlijnen moeten worden aangepakt. Daarnaast moet een breed spectrum van medische specialismen en domeinen op elkaar worden afgestemd, omdat antitrombotische medicatie in het hele medische domein worden gebruikt. Een inspirerend voorbeeld van kwaliteitsverbetering binnen een vergelijkbaar breed domein is antimicrobiële medicatie.

We sluiten dit proefschrift af met aanbevelingen voor de klinische praktijk, het zorgbeleid en verder onderzoek.

Met betrekking tot de klinische praktijk bevelen we periodieke monitoring van procesmaatregelen aan en verdere verkenning van het gebruik van FRAM-modellen voor anticipatie op gevaren. Daarnaast bevelen we de implementatie van antitrombotische case-management aan in analogie met hoe dit ook gerealiseerd is voor antimicrobiele middelen.

Wat betreft zorgbeleid, raden we aan om de periodieke meting van AGB's voort te zetten en te overwegen om dit in de context van een klinische registratie te doen. Verder bevelen wij de herziening van relevante richtlijnen aan alsmede het herzien van het richtlijn ontwikkelingsproces.

Wat verder onderzoek betreft, raden we aan om de processen van INR-meting in ziekenhuizen verder te onderzoeken, aangezien de meeste AGB's plaatsvonden door verhoogde INR's. Ten slotte raden we aan om aanvullende of additieve methodologieën te onderzoeken die helpen bij het kwantificeren van de resultaten van FRAM-analyses in de gezondheidszorg.

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Marco Jeroen Moesker was born on july 26th 1988 in Doetinchem, the Netherlands. After graduation from HAVO at Ulenhof College Doetinchem in 2006, he studied for a bachelor in nursing at Saxion University of applied sciences in Enschede. He graduated in 2011 after which he started working as a registered nurse in clinical psychiatry. In 2012 he continued studying health sciences at the University of Twente in Enschede. He finished his master in health technology assessment in 2014. His master thesis was titled: "*Assessing the cost-effectiveness of point-of-care testing for primary care patients with symptoms suggestive of acute coronary syndrome.*" After finishing his master's, Marco started his PhD project on antithtombotic care in Dutch hospitals. The PhD project was a collaboration between NIVEL (Netherlands Institute for Healthcare Research) in Utrecht and the VU University in Amsterdam. He worked at NIVEL from 2015 till 2017 and at the VU University from 2017 till 2018. After his research, Marco started working at Medical Research Data Management (MRDM) in Deventer. After several other positions, he is now working as data engineer and team lead of a small analytics team.

PhD education

Marco followed several courses during his PhD research. He trained his research skills with the courses research integrity (VUmc Academy), English writing and presenting (Babel), Stata (NIVEL), Epidemiological research (EPIDM) and multilevel analysis (EPIDM). Next to that he followed several workshops to obtain skills in FRAM analysis (FRAMily) and basic didactics (VUmc).

Furthermore, he attended several congresses and scientific meetings. He attended and presented at the conference "*transmulare antistolling*", "*symposium patientveiligheid*" and "*international forum on quality and safety in healthcare*". Marco also supervised education for Bachelor and Master students of the medicine study of VUmc in several subjects like patient safety and confidentiality.

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