From prescription to bleeding complication: challenges surrounding daily anticoagulant care

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Inappropriate prescriptions of direct oral anticoagulants (DOACs) in hospitalised patients: a narrative review

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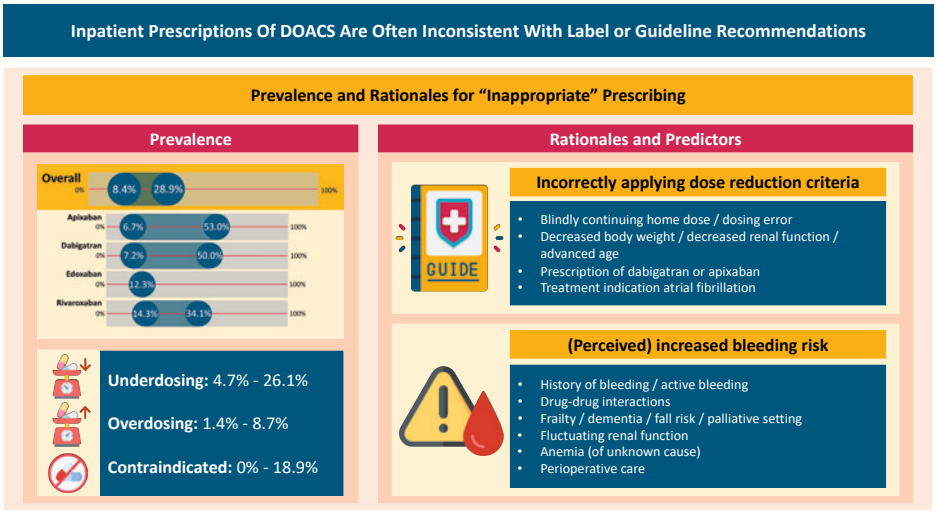
Abstract

Direct oral anticoagulants (DOACs) have become the cornerstone for prevention of thromboembolic events in patients with atrial fibrillation and patients with a history of venous thromboembolism. However, studies show that DOAC prescriptions are commonly inconsistent with guideline recommendations. DOAC dosing in the acutely ill patient could impose an even greater challenge. In this review, we describe the prevalence of inappropriate inpatient prescribing of DOACs and the associated rationales, predictors and clinical consequences. With the aim of promoting appropriate prescriptions of DOACs to hospitalised patients, we further outline DOAC dose reduction criteria justified by various guidelines, illustrating the complexities of appropriate dosing, especially in acutely ill patients. Moreover, we will discuss the impact of anticoagulant stewardship programs and the vital role that pharmacists may play in optimizing inpatient DOAC treatment.



2.1 Introduction

Over the past years, the worldwide proportion of patients with atrial fibrillation (AF) using oral anticoagulation treatment has almost doubled. [1] As a consequence, physicians have to prescribe anticoagulant therapy at or during admission to a hospital more frequently. Direct Oral Anticoagulant (DOAC) prescriptions at hospital level have even quintupled. [2] Worryingly, approximately 8% of inpatient medication errors, which mainly consist of prescription errors, has been suggested to be attributable to any form of anticoagulant therapy. Even though the majority of these errors occurred in low molecular weight heparin (LMWH) and vitamin K antagonists (VKA) prescriptions, a systematic review comprising 162.474 patients showed that almost 25% of DOAC prescriptions were inappropriate too. [3, 4] Despite the assumed advantage of the fixed dosing regimen, a plausible cause for inappropriateness of DOAC prescriptions is the complexity of dose reduction criteria and their application in the acutely ill patient. While underdosing could potentially increase the risk of thromboembolic events, overdosing may lead to bleeding complications. To deal with inappropriate dosing, inpatient multidisciplinary antithrombotic stewardship programs have been developed. These programs resulted in better overall anticoagulant guideline adherence. However, only a minority of patients in these studies were prescribed a DOAC and the introduction of stewardship programs did not lead to a better guideline adherence in DOAC patients. [5]

With the aim of promoting appropriate prescriptions of DOACs to hospitalised patients, this narrative review outlines DOAC dose reduction criteria justified by various guidelines, illustrating the complexities of appropriate dosing, especially in acutely ill patients. Further, we describe the prevalence of inappropriate inpatient prescribing of DOACs and the associated rationales, predictors and clinical consequences. Lastly, we evaluate the literature on the impact of dedicated DOAC stewardship programs.

2.2 Methods

A literature search in the PubMed (MEDLINE), Embase, Web of Science and Cochrane databases was performed from inception to March 3rd 2023 for studies on DOAC prescription appropriateness in hospitalised patients. The search terms were subdivided into three main categories: DOACs, AF or venous thromboembolism (VTE), and inappropriate dosing. A combination of keywords and Medical Subject Heading (MeSH) terms was used for each category. The search terms are available in Supplementary Materials. English or Dutch language studies reporting on dosing appropriateness of DOACs were included, when performed in hospitalised patients, and a DOAC was

prescribed at or during admission. Articles assessing all types of oral anticoagulation, without specifying appropriateness of DOACs, were not considered.

2.3 Dose reduction criteria and guidelines

Dose reduction criteria according to the various product labels and guidelines used by included studies are summarised in **Table 1 and Table 2**. This overview is limited to a prescription indication of AF. Dose reduction criteria vary between the individual DOACs and can be relatively complex. To make it even more complicated, recommendations regarding dose adjustment for each DOAC may differ depending on the product label or guideline used. [6–20] The vast majority of included studies has based the appropriateness of prescribing on the European Medicine Agency's (EMA) Summary of Product Characteristics (SmPC) and Food and Drug Administration (FDA)–approved Prescribing Information. [21–32] Other studies adhered to the Australian Product Information, the Canadian product monographs or the Japanese recommendations of the drug package insert. [16, 33–36] It should be emphasised that the recommended reduced dose for dabigatran is 75 mg twice daily in accordance to FDA, while all other product labels recommend 110 mg twice a day. [11] Similarly, according to the Japanese product information the standard dose of rivaroxaban is 15 mg once daily, and the reduced dose 10 mg once daily instead of 20 mg and 15 mg, respectively. [19]

Other studies adhered to the European Heart Rhythm Association (EHRA) or the Canadian Society of Cardiology (CSC), which provide guidance on anticoagulant treatment as well. [37–40] Dose reduction criteria in those two documents are largely comparable to product label information, except for the addition of a perceived increased bleeding risk as a dose adjustment criterium. In the EHRA Practical Guide, an increased bleeding risk is defined as a history of bleeding or predisposition for bleeding (anaemia, thrombocytopenia), concomitant use of antiplatelet drugs, NSAIDs or systemic corticoids, severe frailty and increased fall risk. [39] Increased risk in the CSC guideline, update 2012, was defined as a HAS-BLED score ≥ 3. [40] The addition of an increased bleeding risk as a dose reduction criterium has been found to significantly alter the assessment of appropriateness, which will be illustrated later in this review.

Table 1. Dose reduction criteria for DOACs in patients with atrial fibrillation as used by the included studies

Guideline	Dose reduction criteria
European Medicine Agency's (EMA)	
Apixaban[6]	When at least two are met:
– Standard dose: 5mg BID	• CrCl 15 – 29 mL/min (or Scr ≥ 1.5 mg/dL / ≥ 133 µmol/L)
– Reduced dose: 2.5mg BID	• Age ≥80 years
	• Body weight ≤60 kg
Dabigatran[7]	• Age ≥80 years
– Standard dose: 150mg BID	• Concomitant use of P-gp inhibitors
– Reduced dose: 110mg BID	Consider dose reduction if: age 75 – 80 years, CrCl 30 – 50 mL/min, patients with gastritis / esophagitis / gastroesophageal reflux
Rivaroxaban[8]	
– Standard dose: 20mg OD	• CrCl 15 – 50 mL/min
– Reduced dose: 15mg OD	
Edoxaban[9]	
– Standard dose: 60mg OD	• CrCl 15 – 50 mL/min
– Reduced dose: 30mg OD	• Body weight ≤60 kg
	• Concomitant use of P-gp inhibitors
Food and Drug Administration (FDA)	
Apixaban[10]	When at least two are met:
– Standard dose: 5mg BID	• Scr ≥ 1.5 mg/dL / ≥ 133 µmol/L, or under dialysis
– Reduced dose: 2.5mg BID	• Age ≥80 years
	• Body weight ≤60 kg
	Concomitant use of strong CYP3A4- or P-gp inhibitors use: avoid
Dabigatran[11]	• CrCl 15 – 30 mL/min
– Standard dose: 150mg BID	• CrCl 30 – 50 mL/min + concomitant P-gp inhibitors use: reduce or avoid
– Reduced dose: 75mg BID	• CrCl <30 mL/min + concomitant P-gp inhibitors use: avoid
Rivaroxaban[12]	• CrCl 15 – 50 mL/min
– Standard dose: 20mg OD	
– Reduced dose: 15mg OD	
Edoxaban[13]	• CrCl 15 – 50 mL/min
– Standard dose: 60mg OD	
– Reduced dose: 30mg OD	
Australian Product Information	
Apixaban[14]	When at least two are met:
– Standard dose: 5mg BID	• Scr ≥ 133 µmol/L / ≥ 1.5 mg/dL
– Reduced dose: 2.5mg BID	• Age ≥80 years
	• Body weight ≤60 kg

Table 1. (Continued)

Guideline	Dose reduction criteria
Dabigatran[14] - Standard dose: 150mg BID - Reduced dose: 110mg BID	• Age ≥75 years • CrCl 30 – 50 mL/min
Rivaroxaban[14] - Standard dose: 20mg OD - Reduced dose: 15mg OD	• CrCl 30 – 50 mL/min
Canadian product monographs	
Apixaban[15] - Standard dose: 5mg BID - Reduced dose: 2.5mg BID	When at least two are met: • Scr ≥ 133 µmol/L / ≥ 1.5 mg/dL • Age ≥80 years • Body weight ≤60 kg
Japanese recommendations of the drug package insert	
Apixaban[16,17] - Standard dose: 5mg BID - Reduced dose: 2.5mg BID	When at least two are met: • Scr ≥ 133 µmol/L / ≥ 1.5 mg/dL • Age ≥80 years • Body weight ≤60 kg • Concomitant use of CYP3A4- or P-gp inhibitors
Dabigatran[16,18] - Standard dose: 150mg BID - Reduced dose: 110mg BID	• Age ≥70 years • CrCl 30 – 50 mL/min • Concomitant use of P-gp inhibitors • History of gastrointestinal bleeding
Rivaroxaban[16,19] - Standard dose: 15mg OD - Reduced dose: 10mg OD	• CrCl 15 – 49 mL/min • Concomitant use of CYP3A4- or P-gp inhibitors
Edoxaban[16,20] - Standard dose: 60mg OD - Reduced dose: 30mg OD	• CrCl 15 – 50 mL/min • Body weight ≤60 kg • Concomitant use of P-gp inhibitors

DOAC: Direct Oral Anticoagulant, BID: twice a day, OD: one a day, Crcl: creatinine clearance, Scr: serum creatinine, P-gp: P-glycoprotein

2.4 Prevalence, rationales and clinical consequences of inappropriate DOAC dosing

2.4.1 Prevalence

The search identified nineteen relevant studies (Table 2). [16, 21–38, 41] The indication for the DOAC was AF in eleven of the studies, AF or VTE in one study, symptomatic

pulmonary embolism in one study, and the remaining 6 studies investigating DOACs for any indication.

In clinical practice, inappropriate prescribing of DOACs in general is reported in 8.4% to 28.9% of hospitalised patients (Table 2). [16, 21, 24-26, 28, 29, 31, 34, 36-38] There is, however, between drug variation. Up to half of the apixaban (6.7% - 53.0%) and dabigatran (7.2% - 50.0%) prescriptions were considered inappropriate while rivaroxaban was inappropriately prescribed in 14.3% to 34.1%, and edoxaban in 12.3% of patients. [22, 24-27, 30, 31, 33-35, 38] Of all prescription errors, underdosing is the most common form and occurred in 4.7% to 26.1% of patients prescribed a DOAC. [16, 21, 23, 24, 26, 28, 29, 33, 34, 36, 37] The highest percentages of underdosing are seen in apixaban prescriptions (9.4% - 40.4%). [22, 24-27, 30, 33-35, 38] Additionally, in up to one in four dabigatran (4.2% – 22.6%) and rivaroxaban (8.4% – 25.1%) prescriptions, the dose was reduced without meeting the dose reduction criteria according to the label or guideline. [24-27, 32, 34, 38] In edoxaban, underdosing was present in 3.6% of users. [24] Overdosing occurred in <10% of prescriptions (DOACs in general 1.4% - 8.3%; apixaban 0.0% - 8.1%; dabigatran 1.0% - 4.7%; rivaroxaban 3.8% - 9.7%; edoxaban 8.7%). [16, 21, 22, 24-30, 33-35, 37, 38] One retrospective study by Lavoie et al., including 500 patients, reported overdosing in 16.2% of patients prescribed dabigatran. [38]

Two studies compared the appropriateness of inhospital DOAC prescriptions as assessed by the EHRA guideline and the product label information. These studies suggest that, when applying the EHRA guideline, prescriptions are more often regarded as underdosed and less often as overdosed, as compared to the EMA-SmPC. [25, 29] For apixaban, one study reported that 67.1% of the underdosed prescriptions when applying EMA-SmPC, would have been considered as appropriate according to EHRA guidelines. [25] The relatively high percentage of overdosing (16.2%) of dabigatran in the study by Lavoie et al., using the CSC guideline, could therefore possibly be explained by the difference in dose adjustment criteria. [38]

In addition to incorrect dosing, DOACs were found to be prescribed in the presence of relative contraindications as well. Percentages between 0% to 18.9% are reported (DOACs in general 0.4% - 2.9%, apixaban 0% - 12.8%, dabigatran 1.0 – 18.9%, rivaroxaban 0% - 10.4%, edoxaban 0%). [21, 24, 26-28, 33, 34] In the majority of these patients, DOAC treatment was relatively contraindicated due to decreased renal function, and to a lesser extent due to drug-drug or drug-disease interactions. [24, 26-28, 33, 34]

Table 2. Prevalence of inappropriate dosing

Study	Study type and population	Type of DOAC	Inappropriate prescription			
			Overall	Underdosed	Overdosed	Contraindicated
Badreldin et al. 2020[30][a]	Single centre retrospective • Saudi Arabia • N = 1271 • Atrial fibrillation	Apixaban	17.5%	9.4%	8.1%	N.A.
Bruneau et al. 2019[21][a]	Multicentre prospective • France • N = 157, aged ≥65 years • All DOAC indications	Overall (apixaban, dabigatran, rivaroxaban)	22.4%	17.1%	4.6%	0.7%
Carlin et al. 2016[33][c]	Single centre retrospective • Canada • N = 47 • Atrial fibrillation	Apixaban	53.0%	40.4%	0%	12.8%
Chua et al. 2022[36][d]	Single centre retrospective • Australia • N = 203 • Atrial fibrillation and VTE	Overall (apixaban, dabigatran, rivaroxaban)	21.7%	13.3%	N.A.	N.A.
Di Micco et al. 2022[32]	Multicentre multinational RIETE registry (179 participating sites; 24 countries across 3 continents) • N = 2066 • Newly diagnosed symptomatic pulmonary embolism	Rivaroxaban	N.A.	8.4%	N.A.	N.A.
Gibson et al. 2018[22][b]	Multicentre retrospective • United States • N = 556 • Atrial fibrillation	Apixaban	13%	12.2%	0.7%	N.A.
Hupfer et al. 2021[23][a]	Single centre observational • Germany • N = 407, aged >85 years • Atrial fibrillation	Overall (apixaban, dabigatran, edoxaban, rivaroxaban)	N.A.	26.1%	N.A.	N.A.

Table 2. (Continued)

Study	Study type and population	Type of DOAC	Inappropriate prescription			
			Overall	Underdosed	Overdosed	Contraindicated
Kartas et al. 2019[37][f]	Cross-sectional • Greece • N = 408 • Atrial fibrillation	Overall (apixaban, dabigatran, rivaroxaban)	28.9%	23.8%	5.1%	N.A.
Lavoie et al. 2016[38][g]	Single centre retrospective • Canada • N = 500 • Atrial fibrillation	Overall Apixaban Dabigatran Rivaroxaban	24% 30.2% 26.4% 19.4%	N.A. 30.2% 10.2% 13.5%	N.A. 0% 16.2% 5.9%	N.A. N.A. N.A. N.A.
Li et al. 2022[34][d]	Multicentre cross-sectional • Australia • N = 1882 • Atrial fibrillation	Overall Apixaban Dabigatran Rivaroxaban	28.9% 28.3% 11.1% 34.1%	22.6% 22.9% 7.1% 25.1%	3.3% 2.6% 2.0% 5.5%	2.9% 2.8% 1.0% 3.4%
Miyazaki et al. 2020[16][e]	Single centre retrospective • Japan • N = 316 (118 in-patients) • Atrial fibrillation	Overall (apixaban, dabigatran, edoxaban, rivaroxaban)	16.1%	12.7%	3.4%	N.A.
Moudallel et al. 2022[24][a]	Single centre cross-sectional • Belgium • N = 1688 • Atrial fibrillation	Overall Apixaban Dabigatran Edoxaban Rivaroxaban	16.9% 18.4% 18.2% 12.3% 20.6%	11.7% 14.2% 11.5% 3.6% 10.9%	8.3% 4.3% 2.7% 8.7% 9.7%	0% 0% 4.1% 0% 0%
Moudallel et al. 2018[25][a]	Single centre retrospective cohort • Belgium • N = 772, aged ≥60 years • All DOAC indications	Overall Apixaban Dabigatran Rivaroxaban	25.0% 29.7% 23.4% 21.9%	N.A. 24.5% 14.0% 12.8%	N.A. 4.5% 4.7% 7.7%	N.A. N.A. N.A. N.A.
Pharithi et al. 2019[26][a]	Single centre retrospective cohort • Ireland • N = 348 • Atrial fibrillation	Overall Apixaban Dabigatran Rivaroxaban	20.4% 22.0% 50.0% 30.1%	19.0% 22.0% 22.6% 16.0%	1.4% 0% 1.0% 3.8%	0% 0% 18.9% 10.4%

Table 2. (Continued)

Study	Study type and population	Type of DOAC	Inappropriate prescription			
			Overall	Underdosed	Overdosed	Contraindicated
Schwartz et al. 2017[27][b]	Single centre retrospective • United States • N = 508 • All DOAC indications	Apixaban Dabigatran Rivaroxaban	18.1% 7.2% 14.3%	15.2% 4.2% 9.4%	2.1% 1.0% 3.5%	0.8% 2.1% 1.4%
Shinoda et al. 2018[35][e]	Single centre retrospective cohort • Japan • N = 120 • Atrial fibrillation	Apixaban	6.7%	6.7%	0%	N.A.
Van Dyke et al. 2022[31][b]	Single centre retrospective • United States • N = 100 • All DOAC indications	Overall Apixaban Rivaroxaban	27% 28% 26%	N.A.	N.A.	N.A.
Viprey et al. 2017[28][a]	Multicentre cross-sectional • France • N = 1188 • All DOAC indications	Overall (apixaban, dabigatran, rivaroxaban)	8.4% AF: 19.9%	4.7% 10.9%	3.1% 7.5%	0.4% 1.6%
Zhang et al. 2020[29][a]	Single centre retrospective • The Netherlands • N = 770 • All DOAC indications	Overall (apixaban, dabigatran, edoxaban, rivaroxaban)	17.4% AF: 23.0%	10.0% 13.0%	7.4% 9.8%	N.A. N.A.

DOAC: Direct Oral Anticoagulant, N: number of patients included, N.A.: not applicable

[a] Appropriateness of prescribing in accordance with EMA Summary of Product Characteristics

[b] Appropriateness of prescribing in accordance with FDA Prescribing Information

[c] Appropriateness of prescribing in accordance with Canadian product monographs

[d] Appropriateness of prescribing in accordance with Australian Product Information

[e] Appropriateness of prescribing in accordance with Japanese package insert

[f] Appropriateness of prescribing in accordance with European Heart Rhythm Association (EHRA) guideline

[g] Appropriateness of prescribing in accordance with Canadian Society of Cardiology (CSC), update 2012

2.4.2 Rationales and predictors

Reported rationales and predictors of inappropriate dosing are shown in **Table 3**. It is reasonable to hypothesize that inappropriateness of prescriptions is a result of unawareness or incorrect application of dose reduction criteria. "Blindly continuing home dose" and "prescribing an erroneous dosage which was corrected later on during admission", two of the rationales and predictors for overdosing reported, support this theory. [22, 24, 25] The complexity and variation in dose reduction criteria for each individual DOAC may play a role in the inter-DOAC variation. In line with this, apixaban and dabigatran were reported to be predictive of inappropriate prescribing. [25, 29] In case of rivaroxaban, there is only one variable that has to be considered (renal function, creatinine clearance (CrCl) 15 – 49 mL/min). [8] However, when prescribing apixaban, age (≥80 years), weight (≤60 kg) and serum creatinine (≥133 µmol/L or ≥1.5 mg/dL) should be taken into account and dose reduction is only justified when two of these factors are present. [6] Increasing serum creatinine, lower body weight and advanced age, all criteria that justify dose reduction in some of the DOACs, were found to be predictors of and rationales for both underdosing and overdosing. [22, 24, 25, 27, 29, 30, 34, 37] Especially when prescribing apixaban, dose reduction in the presence of one instead of two of the criteria results in underdosing, while being unaware of the dose reduction criteria may lead to overdosing in patients with two or more criteria. Additionally, a prescription indication of AF was found to be a predictor of inappropriate dosing. [28, 29, 31] Again, dose reductions are more complex when prescribing a DOAC for AF, especially apixaban, than for other treatment indications, including acute VTE. [6, 10, 14, 15]

Intentional "inappropriate" dosing, especially when dosing lower than recommended, may also be a factor in some cases. A history of bleeding, an (assumed) increased bleeding risk and concurrent use of antiplatelets or other medication that increases bleeding risk were the main reasons or predictors to prescribe a dose lower than guideline recommendations. [22, 24, 30, 33, 35] Previous complications with the appropriate dose was mentioned as a reason for dose adjustment as well. [24, 33] Another reason to prescribe a non-recommended dose was a fluctuating renal function, which is common in the acutely ill patient. [24, 27] In these situations, dosing lower than recommended may be well-considered and entirely appropriate. In other cases, the fear of anticoagulant-related bleeding complications seems to outweigh the possible increased thromboembolic risk due to underdosing. Notably, advanced age, higher serum creatinine levels, decreased body weight, anaemia of unknown cause, falls in the preceding weeks, use of narcotic analgesics and a higher total number of drugs at discharge were identified as reasons or predictors to prescribe a lower than recommended dose. [23, 24, 33, 34] Although none of these factors on its own was a criterium for dose reduction in these specific cases, they do potentially increase the

risk of bleeding complications and physicians may be hesitant to prescribe the regular dose. On the other side, factors that potentially increase bleeding risk (e.g. advanced age, comorbidity) may increase the risk of thrombo-embolic events as well.

Table 3. Reported rationales and predictors for inhospital inappropriate dosing

Inappropriate dosing	Underdosing	Overdosing
History of (minor) bleeding or active bleeding[24,30]	Concurrent use of antiplatelets or other medication that increases bleeding risk[30,33,35]	Dosing error by ordering physician[22]
Concurrent antiplatelet or anticoagulant use[24,30]	History of (minor) bleeding or active bleeding[22,24,30,33,35]	Continuation of home dose[22]
Frailty / dementia / fall risk[24]	Complications with correct dose[33]	Decreased or increased serum creatinine[24,25,30]
Advanced age[22,25,30]	Drop in hemoglobin on correct apixaban dose[33]	(Advanced) age[25,30]
Fluctuating or decreased renal function[22,24,27,29,30,37]	Anaemia of unknown cause combined with history of falls[33]	Body weight <60kg / low BMI[24,30]
Adjusted or decreased body weight[22,24,30]	Perioperatively[33]	
Complications with correct dose[24]	Continuation of home dose / patient is not DOAC-naïve[22,24,34]	
Palliative setting[24]	Perceived increased bleeding risk as deemed by ordering physician[22]	
Dabigatran[25]	Dosing error by ordering physician or pharmacist[22]	
Apixaban[25,29]	Higher serum creatinine[25,34], or decreased serum creatinine[35]	
Continuation of home dose / patient is not DOAC-naive[25]	(Advanced) age[25,34]	
Use of narcotic analgesics[25]	Decreased body weight[24], or increased body weight[25]	
Atrial fibrillation as prescription indication for a DOAC[28,29,31]	Higher total number of drugs at discharge[34]	
Dose-indication mismatch[31]	Use of narcotic analgesics[24]	
Prescription by surgeons versus cardiologists[29]		
History of stroke/TIA[37]		
Higher CHA_2DS_2-VASc score[30]		

2.4.3 Clinical consequences

Inappropriate dosing of DOACs in the general, non-hospitalised, population has been shown to be associated with adverse outcomes (cardiovascular composite outcomes, cardiovascular hospitalisation, all-cause mortality and major bleeding). [42-44] Research on this topic in the inpatient field is far more limited as compared to the outpatient field.

One multicentre retrospective study investigated bleeding and thromboembolic events during hospital admission in 556 patients with AF prescribed apixaban. In total, 15 (2.7%) bleeding events were reported, which all occurred in patients prescribed an appropriate dose or a lower dose than recommended. Among patients prescribed an appropriate dose, 2.3% had a bleeding event, while 5.9% of the underdosed patients experienced a bleeding. The bleeding events consisted of four major bleedings (n = 2 (0.4%) appropriate group, n = 2 (2.9%) underdosed group), four clinically relevant non-major bleedings (n = 2 (0.4%) appropriate group, n = 2 (2.9%) underdosed group), and seven minor bleedings (1.4%, all in the appropriate group). Thromboembolic events did not occur. [22] It may be counterintuitive that bleeding events are more often reported in patients prescribed a lower than recommended dose. It is reasonable to hypothesize that these non-recommended low doses are deliberately, and in retrospect with good reasons, prescribed to patients with an (perceived) increased bleeding risk. This illustrates that deviations from the guideline are not necessarily inappropriate, if well-argued. Nonetheless, another retrospective cohort study consisting of 772 hospitalised patients prescribed any type of DOAC reported twelve bleeding events and two thromboembolic events during admission. All bleeding events occurred in overdosed patients, while the thromboembolic events were observed in underdosed patients. [25]

2.5 Anticoagulant therapy stewardship

Inhospital inappropriate prescribing of DOACs occurs on a regular basis. Even so, the initiation of a DOAC during hospital admission results more frequently in prescriptions consistent with label recommendation, as compared to pre-hospital prescriptions. [16, 25, 34] One study reported that inpatient prescriptions were approximately three times more likely to be appropriate as compared to outpatient prescriptions. [16] Additionally, hospital admission may contribute to correcting prescription errors made prior to hospitalisation. Improvements in the appropriateness of prescribing upon discharge have been reported. [25] New errors are generated during admission as well (4.6%), although the correction rate was clearly higher (37.5%). [21]

Pharmacists may play a vital role in optimizing DOAC treatment in hospitalised patients. For example, one cross-sectional study in a tertiary hospital found that the prescribing physician was contacted by a pharmacist in approximately 80% of inappropriate DOAC prescriptions. The pharmacists' advice was accepted and implemented in 65.5% of cases, yet in 32.7% the physician did not act on the advice. Physicians mainly persisted in underdosing (23.9%), and in a lesser extent to overdosing (8.4%) and contraindicated use (0.4%). Main reasons for continuing prescription inconsistent with the advice of the pharmacist were a history of bleeding or active bleeding; dementia, frailty or an increased fall risk; fluctuating or adjusted renal function, and palliative care or cessation of oral anticoagulant therapy otherwise. [24] In another study, a pharmacist led anticoagulant stewardship program was implemented. All DOAC orders were reviewed by a clinical pharmacist and the prescribing physician was alerted and offered management options in case of a potentially inappropriate prescription. Interference of a pharmacist occurred in one out of three patients prescribed a DOAC, and was more frequent in younger patients and in patients with concomitant use of antiplatelets. Recommendations were accepted in 73% of cases; the highest acceptance rates were seen for the advice to stop concomitant use of antiplatelets (87%), while physicians were less likely to accept the recommendation for drug level monitoring (47%). [45] It should be mentioned that there is limited evidence for DOAC blood level monitoring, and these measurements should only be considered in specific situations. [41]

2.6 Conclusions

Inpatient prescriptions of DOACs are often inconsistent with label or guideline recommendations. Prescribing is complex as dose reduction criteria differ depending on the DOAC prescribed and the drug label or guideline adhered to. Prescribing DOACs to acutely ill hospitalised patients is even more challenging, as fluctuating renal function and factors predisposing to bleeding are more prevalent in this group, e.g. surgical interventions. Inappropriate dosing may be unintentional but also a conscious choice in other cases. Especially underdosing could be appropriate when bleeding risk is high. Even so, when physicians are overly reluctant to adhere to label or guideline recommendations, the risk of thrombo-embolic events and bleeding could potentially be increased. Future studies should focus on rationales for and clinical consequences of inappropriate DOAC prescriptions in hospitalised patients. Moreover, anticoagulant stewardship programs might be beneficial in creating awareness, giving guidance and improving DOAC management.

2.7 References

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Supplementary Material Chapter 2

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((TI=("Atrial Fibrillation" OR "Atrial Fibrillation" OR "Atrial Fibrilation" OR "Atrial Fibrillations" OR "Auricular Fibrillation" OR "Auricular Fibrillations" OR "Venous

Thromboembolism" OR "Venous Thromboembolism" OR "Venous Thrombo embolism" OR "Venous Thromboembol*" OR "Venous Thrombo embol*" OR "VTE" OR "Lung Embolism" OR "Pulmonary Embolism" OR "Lung Embolism" OR "Pulmonary Thromboembolism" OR "Lung Thromboembolism" OR "Pulmonary Thrombo embolism" OR "Pulmonary Thromboembol*" OR "Lung Thromboembol*" OR "Pulmonary Thrombo embol*" OR "Vein Thrombosis" OR "Venous Thrombosis" OR "deep vein thrombosis" OR "Vein Thrombosis" OR "deep venous thrombosis" OR "DVT") OR AK=("Atrial Fibrillation" OR "Atrial Fibrillation" OR "Atrial Fibrilation" OR "Atrial Fibrillations" OR "Auricular Fibrillation" OR "Auricular Fibrillations" OR "Venous Thromboembolism" OR "Venous Thromboembolism" OR "Venous Thrombo embolism" OR "Venous Thromboembol*" OR "Venous Thrombo embol*" OR "VTE" OR "Lung Embolism" OR "Pulmonary Embolism" OR "Lung Embolism" OR "Pulmonary Thromboembolism" OR "Lung Thromboembolism" OR "Pulmonary Thrombo embolism" OR "Pulmonary Thromboembol*" OR "Lung Thromboembol*" OR "Pulmonary Thrombo embol*" OR "Vein Thrombosis" OR "Venous Thrombosis" OR "deep vein thrombosis" OR "Vein Thrombosis" OR "deep venous thrombosis" OR "DVT") OR AB=("Atrial Fibrillation" OR "Atrial Fibrillation" OR "Atrial Fibrilation" OR "Atrial Fibrillations" OR "Auricular Fibrillation" OR "Auricular Fibrillations" OR "Venous Thromboembolism" OR "Venous Thromboembolism" OR "Venous Thrombo embolism" OR "Venous Thromboembol*" OR "Venous Thrombo embol*" OR "VTE" OR "Lung Embolism" OR "Pulmonary Embolism" OR "Lung Embolism" OR "Pulmonary Thromboembolism" OR "Lung Thromboembolism" OR "Pulmonary Thrombo embolism" OR "Pulmonary Thromboembol*" OR "Lung Thromboembol*" OR "Pulmonary Thrombo embol*" OR "Vein Thrombosis" OR "Venous Thrombosis" OR "deep vein thrombosis" OR "Vein Thrombosis" OR "deep venous thrombosis" OR "DVT")) AND (TI=("DOAC" OR "DOACs" OR "Direct Oral Anticoagulant" OR "Direct Oral Anti coagulant" OR "Direct Oral Anticoagulants" OR "Direct Oral Anti coagulants" OR "Direct Anticoagulant" OR "Direct Anticoagulants" OR "NOAC" OR "NOACs" OR "Novel Oral Anticoagulant" OR "Novel Oral Anticoagulants" OR "Novel Oral Anti coagulants" OR "New Oral Anticoagulant" OR "New Oral Anticoagulants" OR "New Oral Anti coagulants" OR "Rivaroxaban" OR "Dabigatran" OR "apixaban" OR "edoxaban" OR "rivaroxaban" OR "Xarelto" OR "dabigatran" OR "Pradaxa" OR "apixaban" OR "Eliquis" OR "edoxaban" OR "Lixiana" OR "Savaysa") OR TS=(("Oral Anticoagulant" OR "Oral Anti coagulant" OR "Oral Anticoagulants" OR "Oral Anti coagulants") AND ("DOAC" OR "DOACs" OR "Direct Oral Anticoagulant" OR "Direct Oral Anti coagulant" OR "Direct Oral Anticoagulants" OR "Direct Oral Anti coagulants" OR "NOAC" OR "NOACs" OR "Novel Oral Anticoagulant" OR "Novel Oral Anti coagulant" OR "Novel Oral Anticoagulants" OR "Novel Oral Anti coagulants" OR "New Oral Anticoagulant" OR "New Oral Anti coagulant" OR "New Oral Anticoagulants" OR "New Oral Anti coagulants" OR "Rivaroxaban" OR "Dabigatran"

OR "apixaban" OR "edoxaban" OR "rivaroxaban" OR "Xarelto" OR "dabigatran" OR "Pradaxa" OR "apixaban" OR "Eliquis" OR "edoxaban" OR "Lixiana" OR "Savaysa"))) AND (TI=("Protocol Compliance" OR "guideline compliance" OR "guideline adherence" OR "guidelines compliance" OR "guidelines adherence" OR "guideline noncompliance" OR "guideline nonadherence" OR "guideline non compliance" OR "guideline non adherence" OR "guidelines non compliance" OR "Institutional Adherence" OR "Institutional Compliance" OR "guidelines discordance" OR "guidelines discordant" OR "guidelines discordance" OR "guidelines discordant" OR "Policy Compliance" OR "Protocol Compliance" OR "Policy Non Compliance" OR "Protocol Non Compliance" OR "Policy Noncompliance" OR "Protocol Noncompliance" OR "Policy Adherence" OR "Protocol Adherence" OR "Policy Non Adherence" OR "Protocol Non Adherence" OR "Policy Nonadherence" OR "Protocol Nonadherence" OR (("guideline" OR "guidelines") NEAR/4 ("compliance" OR "adherence" OR "noncompliance" OR "nonadherence" OR "discordance" OR "discordant")) OR "prescriber compliance" OR "prescriber adherence" OR "prescribers compliance" OR "prescribers adherence" OR "prescriber noncompliance" OR "prescriber nonadherence" OR "prescribers noncompliance" OR "prescribers nonadherence" OR "prescriber non compliance" OR "prescriber non adherence" OR "prescribers non compliance" OR "prescribers non adherence" OR "label adherence" OR "label nonadherence" OR "label non adherence" OR "label compliance" OR (("prescriber" OR "prescribers" OR "prescriber*") NEAR/4 ("compliance" OR "adherence" OR "noncompliance" OR "nonadherence" OR "discordance" OR "discordant")) OR "off-label" OR "Off Label Drug Use" OR "Offlabel" OR "Unlabeled Indication" OR "Unlabeled Indications" OR "Inappropriate Prescribing" OR "inappropriate prescriptions" OR "inappropriate prescription" OR "inappropriate prescribing" OR "inappropriate prescri*" OR "Over Prescribing" OR "Over Prescri*" OR "Under Prescribing" OR "Under Prescri*" OR "Overprescribing" OR "Overprescri*" OR "Underprescribing" OR "Underprescri*" OR "inappropriate dose" OR "inappropriate doses" OR "inappropriate dosage" OR "inappropriate dosages" OR "non recommended doses" OR "nonrecommended doses" OR (("inappropriate" OR "inappropriat*" OR "non recommended" OR "nonrecommended") NEAR/4 ("dose" OR "doses" OR "dosing" OR "dosage" OR "dosages")) OR "Appropriate Dosing" OR "Appropriate Dose" OR "Appropriate Doses" OR "Appropriate Dosage" OR "Appropriate Dosages" OR "Over Dosing" OR "Over Dose" OR "Over Doses" OR "Over Dosage" OR "Over Dosages" OR "Under Dosing" OR "Under Dose" OR "Under Doses" OR "Under Dosage" OR "Under Dosages" OR "Overdosing" OR "Overdose" OR "Overdoses" OR "Overdosage" OR "Overdosages" OR "Overdosaging" OR "Underdosing" OR "Underdose" OR "Underdoses" OR "Underdosage" OR "Underdosages" OR "Underdosaging") OR AK=("Protocol Compliance" OR "guideline compliance" OR "guideline adherence" OR "guidelines compliance" OR "guidelines adherence" OR "guideline noncompliance" OR "guideline nonadherence" OR "guideline

non compliance" OR "guideline non adherence" OR "guidelines non compliance" OR "Institutional Adherence" OR "Institutional Compliance" OR "guidelines discordance" OR "guidelines discordant" OR "guidelines discordance" OR "guidelines discordant" OR "Policy Compliance" OR "Protocol Compliance" OR "Policy Non Compliance" OR "Protocol Non Compliance" OR "Policy Noncompliance" OR "Protocol Noncompliance" OR "Policy Adherence" OR "Protocol Adherence" OR "Policy Non Adherence" OR "Protocol Non Adherence" OR "Policy Nonadherence" OR "Protocol Nonadherence" OR (("guideline" OR "guidelines") NEAR/4 ("compliance" OR "adherence" OR "noncompliance" OR "nonadherence" OR "discordance" OR "discordant")) OR "prescriber compliance" OR "prescriber adherence" OR "prescribers compliance" OR "prescribers adherence" OR "prescriber noncompliance" OR "prescriber nonadherence" OR "prescribers noncompliance" OR "prescribers nonadherence" OR "prescriber non compliance" OR "prescriber non adherence" OR "prescribers non compliance" OR "prescribers non adherence" OR "label adherence" OR "label nonadherence" OR "label non adherence" OR "label compliance" OR (("prescriber" OR "prescribers" OR "prescriber*") NEAR/4 ("compliance" OR "adherence" OR "noncompliance" OR "nonadherence" OR "discordance" OR "discordant")) OR "off-label" OR "Off Label Drug Use" OR "Offlabel" OR "Unlabeled Indication" OR "Unlabeled Indications" OR "Inappropriate Prescribing" OR "inappropriate prescriptions" OR "inappropriate prescription" OR "inappropriate prescribing" OR "inappropriate prescri*" OR "Over Prescribing" OR "Over Prescri*" OR "Under Prescribing" OR "Under Prescri*" OR "Overprescribing" OR "Overprescri*" OR "Underprescribing" OR "Underprescri*" OR "inappropriate dose" OR "inappropriate doses" OR "inappropriate dosage" OR "inappropriate dosages" OR "non recommended doses" OR "nonrecommended doses" OR (("inappropriate" OR "inappropriat*" OR "non recommended" OR "nonrecommended") NEAR/4 ("dose" OR "doses" OR "dosing" OR "dosage" OR "dosages")) OR "Appropriate Dosing" OR "Appropriate Dose" OR "Appropriate Doses" OR "Appropriate Dosage" OR "Appropriate Dosages" OR "Over Dosing" OR "Over Dose" OR "Over Doses" OR "Over Dosage" OR "Over Dosages" OR "Under Dosing" OR "Under Dose" OR "Under Doses" OR "Under Dosage" OR "Under Dosages" OR "Overdosing" OR "Overdose" OR "Overdoses" OR "Overdosage" OR "Overdosages" OR "Overdosaging" OR "Underdosing" OR "Underdose" OR "Underdoses" OR "Underdosage" OR "Underdosages" OR "Underdosaging") OR AB=("Protocol Compliance" OR "guideline compliance" OR "guideline adherence" OR "guidelines compliance" OR "guidelines adherence" OR "guideline noncompliance" OR "guideline nonadherence" OR "guideline non compliance" OR "guideline non adherence" OR "guidelines non compliance" OR "Institutional Adherence" OR "Institutional Compliance" OR "guidelines discordance" OR "guidelines discordant" OR "guidelines discordance" OR "guidelines discordant" OR "Policy Compliance" OR "Protocol Compliance" OR "Policy Non Compliance" OR

"Protocol Non Compliance" OR "Policy Noncompliance" OR "Protocol Noncompliance" OR "Policy Adherence" OR "Protocol Adherence" OR "Policy Non Adherence" OR "Protocol Non Adherence" OR "Policy Nonadherence" OR "Protocol Nonadherence" OR (("guideline" OR "guidelines") NEAR/4 ("compliance" OR "adherence" OR "noncompliance" OR "nonadherence" OR "discordance" OR "discordant")) OR "prescriber compliance" OR "prescriber adherence" OR "prescribers compliance" OR "prescribers adherence" OR "prescriber noncompliance" OR "prescriber nonadherence" OR "prescribers noncompliance" OR "prescribers nonadherence" OR "prescriber non compliance" OR "prescriber non adherence" OR "prescribers non compliance" OR "prescribers non adherence" OR "label adherence" OR "label nonadherence" OR "label non adherence" OR "label compliance" OR (("prescriber" OR "prescribers" OR "prescriber*") NEAR/4 ("compliance" OR "adherence" OR "noncompliance" OR "nonadherence" OR "discordance" OR "discordant")) OR "off-label" OR "Off Label Drug Use" OR "Offlabel" OR "Unlabeled Indication" OR "Unlabeled Indications" OR "Inappropriate Prescribing" OR "inappropriate prescriptions" OR "inappropriate prescription" OR "inappropriate prescribing" OR "inappropriate prescri*" OR "Over Prescribing" OR "Over Prescri*" OR "Under Prescribing" OR "Under Prescri*" OR "Overprescribing" OR "Overprescri*" OR "Underprescribing" OR "Underprescri*" OR "inappropriate dose" OR "inappropriate doses" OR "inappropriate dosage" OR "inappropriate dosages" OR "non recommended doses" OR "nonrecommended doses" OR (("inappropriate" OR "inappropriat*" OR "non recommended" OR "nonrecommended") NEAR/4 ("dose" OR "doses" OR "dosing" OR "dosage" OR "dosages")) OR "Appropriate Dosing" OR "Appropriate Dose" OR "Appropriate Doses" OR "Appropriate Dosage" OR "Appropriate Dosages" OR "Over Dosing" OR "Over Dose" OR "Over Doses" OR "Over Dosage" OR "Over Dosages" OR "Under Dosing" OR "Under Dose" OR "Under Doses" OR "Under Dosage" OR "Under Dosages" OR "Overdosing" OR "Overdose" OR "Overdoses" OR "Overdosage" OR "Overdosages" OR "Overdosaging" OR "Underdosing" OR "Underdose" OR "Underdoses" OR "Underdosage" OR "Underdosages" OR "Underdosaging")) AND LA=(english OR dutch))

- **Cochrane:** https://www.cochranelibrary.com/advanced-search/search-manager

(("Atrial Fibrillation" OR "Atrial Fibrillation" OR "Atrial Fibrilation" OR "Atrial Fibrillations" OR "Auricular Fibrillation" OR "Auricular Fibrillations" OR "Venous Thromboembolism" OR "Venous Thromboembolism" OR "Venous Thrombo embolism" OR "Venous Thromboembol*" OR "Venous Thrombo embol*" OR "VTE" OR "Pulmonary Embolism" OR "Pulmonary Embolism" OR "Lung Embolism" OR "Pulmonary Thromboembolism" OR "Lung Thromboembolism" OR "Pulmonary Thrombo embolism" OR "Pulmonary Thromboembol*" OR "Lung Thromboembol*"

OR "Pulmonary Thrombo embol*" OR "Venous Thrombosis" OR "Venous Thrombosis" OR "deep vein thrombosis" OR "Vein Thrombosis" OR "deep venous thrombosis" OR "DVT"):ti,ab,kw AND ("DOAC" OR "DOACs" OR "Direct Oral Anticoagulant" OR "Direct Oral Anti coagulant" OR "Direct Oral Anticoagulants" OR "Direct Oral Anti coagulants" OR "Direct Anticoagulant" OR "Direct Anticoagulants" OR "NOAC" OR "NOACs" OR "Novel Oral Anticoagulant" OR "Novel Oral Anti coagulant" OR "Novel Oral Anticoagulants" OR "Novel Oral Anti coagulants" OR "New Oral Anticoagulant" OR "New Oral Anti coagulant" OR "New Oral Anticoagulants" OR "New Oral Anti coagulants" OR "Rivaroxaban" OR "Dabigatran" OR "apixaban" OR "edoxaban" OR "rivaroxaban" OR "Xarelto" OR "dabigatran" OR "Pradaxa" OR "apixaban" OR "Eliquis" OR "edoxaban" OR "Lixiana" OR "Savaysa"):ti,ab,kw AND ("Guideline Adherence" OR "guideline compliance" OR "guideline adherence" OR "guidelines compliance" OR "guidelines adherence" OR "guideline noncompliance" OR "guideline nonadherence" OR "guideline non compliance" OR "guideline non adherence" OR "guidelines non compliance" OR "Institutional Adherence" OR "Institutional Compliance" OR "guidelines discordance" OR "guidelines discordant" OR "guidelines discordance" OR "guidelines discordant" OR "Policy Compliance" OR "Protocol Compliance" OR "Policy Non Compliance" OR "Protocol Non Compliance" OR "Policy Noncompliance" OR "Protocol Noncompliance" OR "Policy Adherence" OR "Protocol Adherence" OR "Policy Non Adherence" OR "Protocol Non Adherence" OR "Policy Nonadherence" OR "Protocol Nonadherence" OR "prescriber compliance" OR "prescriber adherence" OR "prescribers compliance" OR "prescribers adherence" OR "prescriber noncompliance" OR "prescriber nonadherence" OR "prescribers noncompliance" OR "prescribers nonadherence" OR "prescriber non compliance" OR "prescriber non adherence" OR "prescribers non compliance" OR "prescribers non adherence" OR "label adherence" OR "label nonadherence" OR "label non adherence" OR "label compliance" OR "off label" OR "Off Label Use" OR "Offlabel" OR "Unlabeled Indication" OR "Unlabeled Indications" OR "Inappropriate Prescribing" OR "inappropriate prescriptions" OR "inappropriate prescription" OR "inappropriate prescribing" OR "inappropriate prescri*" OR "Over Prescribing" OR "Over Prescri*" OR "Under Prescribing" OR "Under Prescri*" OR "Overprescribing" OR "Overprescri*" OR "Underprescribing" OR "Underprescri*" OR "inappropriate dose" OR "inappropriate doses" OR "inappropriate dosage" OR "inappropriate dosages" OR "non recommended doses" OR "nonrecommended doses" OR (("guideline" OR "guidelines") NEAR/4 ("compliance" OR "adherence" OR "noncompliance" OR "nonadherence" OR "discordance" OR "discordant")) OR (("prescriber" OR "prescribers" OR "prescriber*") NEAR/4 ("compliance" OR "adherence" OR "noncompliance" OR "nonadherence" OR "discordance" OR "discordant")) OR (("inappropriate" OR "inappropriat*" OR "non recommended" OR "nonrecommended") NEAR/4 ("dose" OR "doses" OR "dosing" OR "dosage" OR "dosages")) OR "Appropriate Dosing" OR "Appropriate Dose" OR

"Appropriate Doses" OR "Appropriate Dosage" OR "Appropriate Dosages" OR "Over Dosing" OR "Over Dose" OR "Over Doses" OR "Over Dosage" OR "Over Dosages" OR "Under Dosing" OR "Under Dose" OR "Under Doses" OR "Under Dosage" OR "Under Dosages" OR "Overdosing" OR "Overdose" OR "Overdoses" OR "Overdosage" OR "Overdosages" OR "Overdosaging" OR "Underdosing" OR "Underdose" OR "Underdoses" OR "Underdosage" OR "Underdosages" OR "Underdosaging"):ti,ab,kw)