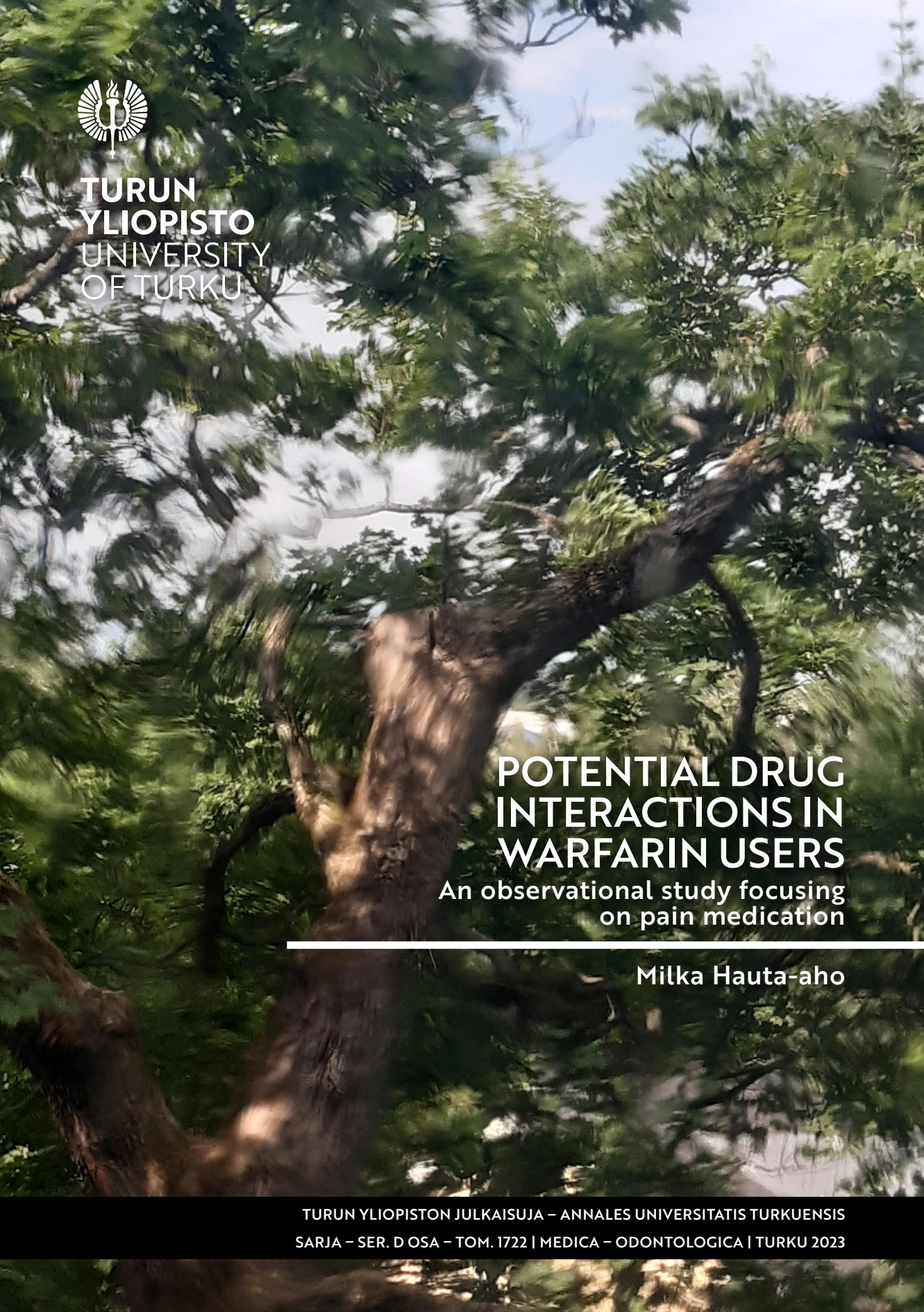

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An observational study focusing on pain medication

Milka Hauta-aho

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Primum non nocere.

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ABSTRACT

Bleeding is a common and potentially serious adverse drug reaction associated with warfarin therapy. Warfarin undergoes several drug interactions with frequently used pain medications, which themselves are recognized as an independent risk factor for bleeding. Furthermore, warfarin and pain medications are commonly used by older persons.

This thesis was conducted as three observational studies utilizing data obtained from real-life clinical care. The purpose of this study was to investigate the frequency and clinical consequences of drug interactions in various patient populations and different phases of warfarin therapy. More specifically, the frequency of co-prescribing potentially interacting pain medications among warfarin users in outpatient and inpatient settings was determined. Moreover, the clinical consequences of co-administration of potentially interacting pain medications among warfarin users in an inpatient setting were investigated. Finally, the effect of warfarin initiation was examined on the use of potentially interacting pain medication in an outpatient setting and among frail and non-frail inpatients.

These studies demonstrate that co-prescribing of warfarin and potentially interacting pain medications was more common in inpatients than in outpatients. Accordingly, an increased bleeding risk associated with potentially interacting pain medication was observed in inpatients. At the time of warfarin initiation, the interaction frequencies differed between pain medication classes. The use of paracetamol increased in warfarin initiators in both outpatient and inpatients excluding frail inpatients, whereas the opposite was seen for the use of NSAIDs.

In conclusion, the frequencies of warfarin drug interactions differed between pain medication classes, settings of care, and phases of warfarin therapy. The increased risk of bleeding due to potential drug interactions still requires attention when pain medications are prescribed to warfarinized patients.

KEYWORDS: Warfarin, non-steroidal anti-inflammatory drugs, paracetamol, tramadol, drug interactions, pain medication, analgesics, frailty, bleeding risk

TURUN YLIOPISTO
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TIIVISTELMÄ

Verenvuoto on varfariinihoidon yleinen, vakavimmillaan kuolemaan johtava haitta, jonka riskiä varfariinin lääkeinteraktiot lisäävät. Varfariinilla on lukuisia lääkeinteraktioita yleisesti käytettyjen kipulääkkeiden kanssa. Sekä varfariinin että kipulääkkeiden käyttö painottuu iäkkäisiin potilaisiin.

Tämä väitöskirjatyö koostuu kolmesta havainnoivasta tutkimuksesta, joissa tutkittiin lääkeyhteisvaikutuksia aiheuttavien kipulääkkeiden käyttöä varfariinihoitoa saavilla potilailla arkielämässä. Tutkimuksen tavoitteena oli selvittää varfariinin ja kipulääkkeiden yhteiskäytön yleisyyttä sairaalapotilailla ja avohoidon potilailla, yhteiskäytön kliinisiä seurauksia sairaalapotilailla sekä varfariinin aloittamisen vaikutusta kipulääkkeiden käyttöön avohoidossa sekä sairaalahoidossa olevilla raihnaisilla ja ei-raihnaisilla potilailla.

Nämä tutkimukset osoittavat, että potentiaalisesti lääkeyhteisvaikutuksia aiheuttavien kipulääkkeiden käyttö oli yleisempää sairaalahoitoa saavilla varfariinin käyttäjillä kuin avohoidon potilailla. Sairaalahoidossa olevilla potilailla kipulääkkeiden ja varfariinin yhteiskäyttöön liittyi kohonnut verenvuotoriski verrattuna pelkkää varfariinihoitoa saaviin potilaisiin. Lääkeinteraktioiden esiintyvyydessä oli eroja kipulääkeryhmien välillä uusilla varfariinin käyttäjillä. Parasetamolin käyttö kasvoi, kun taas tulehduskipulääkkeiden käyttö väheni varfariinihoidon aloittamisen myötä sekä avohoidossa että sairaalahoidossa olevilla potilailla, pois lukien ei-raihnaiset potilaat.

Yhteenvetona todetaan, että varfariinin ja kipulääkkeiden yhteiskäytön esiintyvyydessä on eroja eri kipulääkeryhmien, potilasryhmien ja varfariinihoidon vaiheiden välillä. Yhteiskäyttöön liittyvään haittariskiin tulee edelleen kiinnittää huomiota varfariinihoitoa saaville potilaille kipulääkkeitä määrätessä.

AVAINSANAT: Varfariini, tulehduskipulääkkeet, parasetamoli, tramadoli, lääkeyhteisvaikutus, kipulääkitys, raihnaisuus, verenvuotoriski

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Abbreviations

ADR	Adverse drug reaction
AF	Atrial fibrillation
ANOVA	Analysis of variance
ASA	Acetylsalicylic acid
AS	Activity score
ATC	Anatomic Therapeutic Chemical
CI	Confidence interval
CNS	Central nervous system
COX	Cyclo-oxygenase
CYP	Cytochrome P450
DDD	Defined Daily Dose
DOAC	Direct oral anticoagulant
GGCX	γ-Glutamylcarboxylase
GI	Gastrointestinal
ICD-10	International Classification of Diseases, 10th version
INR	International Normalized Ratio
IQR	Interquartile range
Hb	Hemoglobin
NAPQI	*N*-acetyl-*p*-benzoquininoimine
NSAID	Non-steroidal anti-inflammatory drug
OAC	Oral anticoagulant
OR	Odds ratio
PG	Prostaglandin
PPI	Proton pump inhibitor
SERT	Serotonin transporter protein
SSRI	Serotonin reuptake inhibitor
TTR	Time in the therapeutic range
TXA_2	Thromboxane A_2
VKOR	Vitamin K Epoxide Reductase
VTE	Venous thromboembolism
WHO	World Health Organisation

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Rikala M*, Hauta-aho M*, Helin-Salmivaara A, Lassila R, Korhonen MJ, Huupponen R. Co-Prescribing of Potentially Interacting Drugs during Warfarin Therapy - A Population-Based Register Study. *Basic & Clinical Pharmacology & Toxicology*. 2015;117(2):126–32.

II Hauta-aho M, Tirkkonen T, Vahlberg T, Laine K. The effect of drug interactions on bleeding risk associated with warfarin therapy in hospitalized patients. *Annals of Medicine*. 2009;41(8):619–28.

III Hauta-aho M, Teperi S, Korhonen MJ, Farinola N, Bell JS, Johns S, Shakib S, Huupponen R. Frailty and co-prescribing of potentially interacting drugs in new users of warfarin. *Drugs & Aging*, 2020;37:373–382.

* denotes equal contribution.

1 Introduction

The use of oral anticoagulant (OAC) therapy has steadily increased over the past decades. From the 1950s until recent years, warfarin was the cornerstone of OAC therapy when direct oral anticoagulants (DOAC) were introduced. Although DOACs have been rapidly adopted in clinical use, warfarin is still widely used, and in some indications it remains as the only possible OAC. The indications for OAC therapy, especially stroke prophylaxis in atrial fibrillation (AF), become more common with advancing age and require long-term administration of OACs. The number of over 70 years old people in Finland has increased by almost 400 000 since 1995 (Statistics Finland, 2020b) and simultaneously, the life expectancy has lengthened by approximately five years in both genders (Statistics Finland, 2020a). Along with the growth of aging populations and extending old age, the use of OAC can be predicted to continue to rise (Kornej et al., 2020; Lippi et al., 2021).

Bleeding is an inherent adverse drug reaction linked with warfarin therapy; the risk of bleeding is increased with older age (Hindricks et al., 2021) and there are also known to be several warfarin drug interactions (Wang et al., 2021). Pain medications increase the bleeding risk via a variety of mechanisms. Some drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs), potentiate the bleeding risk by impairing platelet function (Schafer, 1999) and damaging the gastric mucosa (Laine, 1996), others may interfere with the synthesis of coagulation factors (Whyte et al., 2000). Moreover, combining different types of pain medications is an everyday practice to achieve a better response in pain treatment (Pain: Current Care Guidelines, 2017), which may further elevate the bleeding risk. The significance of potential drug interactions becomes emphasized in an older patient population as both pain and the use of pain medications are common, and more importantly, these patients often have several other bleeding risk factors and are susceptible to adverse drug reactions.

The overlapping adverse effects of pain medications and oral anticoagulants challenge pain management in warfarinized patients. However, in order to improve the safety of drug therapy, it is important to study prescribing practices in large-scale populations and real-life settings.

The present study focuses on potential drug interactions with warfarin and commonly used pain medications. It aims at investigating routine prescribing practice, the implementation of this knowledge in different phases of warfarin therapy, and the clinical consequences of drug interactions in real-life patient populations.

2 Review of the Literature

2.1 Warfarin

2.1.1 Clinical pharmacology of warfarin

Warfarin is an oral anticoagulant, which has been in clinical use since the 1950s (Pirmohamed, 2006). In Finland, warfarin was launched in 1967, and for decades, it was the only oral anticoagulant available until direct oral anticoagulants reached the market in the 2000s (FimeaWeb, 2022). Warfarin is indicated in the prevention and treatment of thromboembolic diseases, and it is most commonly used to reduce the risk of cardioembolic stroke in patients with AF (Hindricks et al., 2021; Virjo et al., 2010). There are other indications including the prevention and treatment of venous thrombosis and pulmonary embolism. Currently, warfarin is the only oral anticoagulant indicated for thromboprophylaxis in patients with rheumatic mitral valve disease, mechanical heart valve, or left ventricular thrombus following myocardial infarction, and in children. It is also used to prevent thromboembolism in patients undergoing elective hip or knee replacement with contraindications to DOACs (Heestermans et al., 2022; Warfarin SPC; Deep vein thrombosis and pulmonary embolism: Current Care Guidelines, 2016; Acute myocardial infarction: Current Care Guidelines, 2022).

2.1.1.1 Mechanism of action

Warfarin exerts its anticoagulant effect by interfering with the metabolism of vitamin K and the production of certain coagulation factors. Coagulation factors II, VII, IX, and X are synthetized as precursors which require post-translational carboxylation in order to achieve their procoagulant activity. This reaction is catalyzed by γ-glutamylcarboxylase (GGCX), which requires reduced vitamin K as a cofactor (Stenflo et al., 2003). Warfarin inhibits vitamin K epoxide reductase (VKOR), the enzyme converting the oxidized vitamin K back to its reduced form (Suttie, 1987) (Figure 1). This inhibition results in a depletion of functional coagulation factors, and thereby impaired blood coagulation. Because warfarin affects blood coagulation at the level of protein synthesis, achieving a full anticoagulation response takes two

to seven days, the time during which the functional coagulation factors are eliminated. Warfarin also inhibits the activation of protein C and protein S, two endogenous anticoagulants, which results in a paradoxical procoagulant effect in the early days of warfarin therapy (Hirsh et al., 1998).

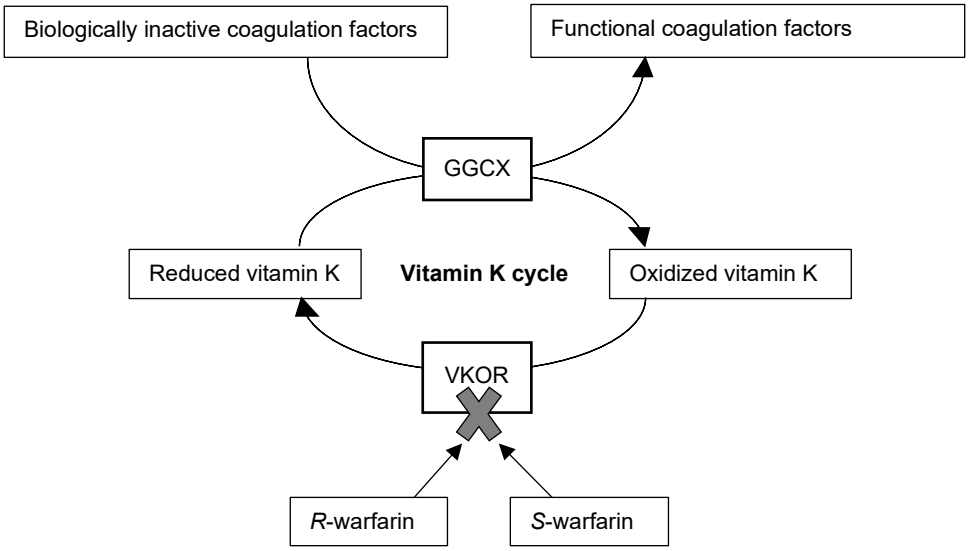


Figure 1. The mechanism of action of warfarin. GGCX, γ-Glutamylcarboxylase; VKOR, Vitamin K epoxide reductase. Adopted from Brunton et al. in Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12 ed. McGraw-Hill Education.

2.1.1.2 Pharmacokinetics

Warfarin is administered as a racemic mixture of *S*- and *R*-warfarin. *S*-warfarin is three to five times more potent than *R*-warfarin contributing 60–70 % of the anticoagulant effect (Breckenridge et al., 1974; Hirsh et al., 1998). The enantiomers differ also in their metabolic pathways. *S*-warfarin is transformed into an inactive metabolite primarily by the cytochrome P450 (CYP) 2C9 isoenzyme (Wadelius et al., 2007), whereas *R*-warfarin is metabolized mainly by CYP3A4 and CYP1A2 isoenzymes (Kaminsky et al., 1997). Orally administered warfarin is fully absorbed in the gut, reaching complete bioavailability (Breckenridge et al., 1973). In plasma, warfarin is strongly protein bound mainly to albumin with a free fraction of under 2 % (Yacobi et al., 1976). The distribution volume of warfarin is as low as 0.14 l/kg (Kaminsky et al., 1997).

2.1.1.3 Warfarin therapy

Warfarin is a cumbersome drug to use for both clinicians and patients. The narrow therapeutic index, the wide variation in dosing requirements, and the risk of bleeding complicate warfarin therapy. In order to achieve safe, yet effective therapy, the intensity of anticoagulation is routinely monitored by blood tests, and the dose is adjusted accordingly. The intensity is expressed as the International Normalized Ratio (INR) value with the target range of 2.0–3.0 for AF patients and 2.5–3.5 for patients with mechanical heart valve (Atrial fibrillation: Current Care Guidelines, 2021). The percentage of time when consecutive INR values are within the therapeutic range indicates the quality of warfarin therapy, and this is expressed as the time in the therapeutic range (TTR) (Rosendaal et al., 1993). The TTR should exceed 80 % (Atrial fibrillation: Current Care Guidelines, 2021) as the stability of the anticoagulation effect throughout the therapy is associated with a lower risk of thrombotic and hemorrhagic adverse events (Lehto et al., 2017; Tiili et al., 2019). In Finnish studies, the median TTR has been reported to vary between 67 and 73 % (Helin et al., 2013; Lehto et al., 2017; Leskelä et al., 2013) and the proportion of patients reaching TTR >70 % in a range between 41.7 and 54.7 % (Hallinen et al., 2014).

In addition to regular laboratory monitoring, well-managed warfarin therapy requires careful patient education and good compliance and adherence (Atrial fibrillation: Current Care Guidelines, 2021). The daily warfarin dose requirement varies between individual patients and may range from less than 0.5 mg up to 20 mg (Wadelius et al., 2007; Puhakka, 2011). The large variation is dependent on the patient's age, gender, weight, and comorbidities, but it is also attributable to genetic and environmental factors. It has been estimated that genetic variants, specifically in genes coding CYP2C9 and vitamin K epoxide reductase complex 1 (VKORC1), explain together with stable nongenetic factors around 50 % of the variation in the warfarin dose requirement (Johnson et al., 2017). Clinically, the most relevant variant alleles of *CYP2C9* are *CYP2C9*2* and *CYP2C9*3*. For *VKORC1*, the most significant single nucleotide polymorphism is -1636G>A (Table 1). Furthermore, several *VKORC1* variants have been identified and linked with warfarin resistance and an exceptionally high dose requirement (Rost et al., 2004; Watzka et al., 2011).

Contrary to the stable effect of genetic factors and stable nongenetic factors, environmental factors cause variations in the warfarin dose at the level of each individual. Specifically, the dietary intake of vitamin K, changes in the individual's health status, such as acute infections or diarrhea, may lead to alterations in the response to warfarin. In addition, concomitant medication may also alter warfarin response by either inducing or inhibiting enzymes metabolizing warfarin or interfering the synthesis of coagulation factors (See Chapter 2.3 Warfarin drug interactions).

Table 1. The major genetic polymorphisms affecting warfarin dose requirements.

Gene, variant allele	Allele frequency	Comments
CYP2C9		
**2* (Arg144Cys)	12 % in Finnish population (Hilli et al., 2007)	Patients homozygous or heterozygous for *CYP2C9*2* and *CYP2C9*3* exhibit impaired metabolism of *S*-warfarin, leading to a longer half-life of the drug, and have a reduced warfarin maintenance dose. With empiric warfarin dosing, individuals with *CYP2C9*2* and *CYP2C9*3* require more time to achieve a stable dose, are at increased risk of over-anticoagulation (INR>4) and risk of bleeding (Johnson et al., 2017).
**3* (Ile359Leu)	7% in Finnish population (Hilli et al., 2007)	See above (*2, Comments)
***VKORC1* intron region**		
-1639G>A	38.9 % in Finnish population (Genome Aggregation Database)	Increased warfarin sensitivity and lower dose requirement (Johnson et al., 2017).

A, adenosine; Arg, arginine; Cys, cysteine; G, guanine; Ile, isoleucine; Leu, leucine.

The variation in dosing requirements is a challenge, especially during the initiation phase of therapy. According to the current practice, warfarin is commenced using a standard dose of 3 or 5 mg daily, mainly depending on the patient's age and weight. The daily dose is adjusted by INR values measured every second or third day over the first week of therapy. The INR value on the 7th day determines the weekly warfarin dose which forms the basis for dosing adjustments. Thereafter, the INR value is measured weekly until stable therapy is achieved and monitoring interval can be extended up to four to eight weeks (Lassila, 2019; Puhakka, 2011).

Algorithms accounting for genetic and patient-related factors have been developed in order to better estimate warfarin dosing and numerous dosing calculators are available online (for example http://www.warfarindosing.org). Utilizing genetic information in estimating the initial warfarin dose has been shown to shorten the time before achieving therapeutic INR, decrease excessive anticoagulation, and increase TTR in variant allele carriers (Arwood et al., 2017; Pirmohamed et al., 2013). However, the utilization of algorithms in everyday clinical care is not well established presumably due to the lack of routine in genotyping practice, and the introduction of alternative OACs to warfarin.

2.1.1.4 Adverse effects

Common adverse effects

Bleeding is the most common adverse effect associated with warfarin therapy; its severity varies from mild bruising, epistaxis, or excessive bleeding after a minor injury, to fulminant hemorrhage requiring urgent hospitalization with even a fatal outcome. The most common location for major bleeding is in the gastrointestinal tract, whereas intracranial hemorrhage (ICH) is associated with the highest fatality with an average 30-day mortality rate of 50 % (Aguilar et al., 2007).

The frequency of bleeding reported in the published literature varies in a range between 10–15 % per person-year for minor hemorrhages (Bahit et al., 2017; Connolly et al., 1991) and between 2–5 % per person-year for major hemorrhages (Table 2). However, it is challenging to estimate the exact bleeding frequency and make a comparison between studies due to variations in definitions and study populations. For example, a commonly used definition for major bleeding requires a visit to a hospital due to any hemorrhage or fatal bleeding, but specific diagnosis codes for bleeding are also utilized. Only some studies follow the definition for major bleeding issued by the International Society for Thrombosis and Hemostasis *i.e.* a hemorrhage causing a significant blood loss, requiring blood transfusion, occurring at a critical site, or resulting in death (Schulman & Kearon, 2005). Furthermore, in randomized trials, the inclusion criteria may be more strict producing a demographically more homogenous study population than in observational studies and potentially excluding the most challenging patient groups in real-life. Moreover, the follow-up in randomized trials may be more intensive with even minor bleeding episodes being observed and recorded, whereas smaller sample sizes may result in the non-occurrence of the less common adverse events in comparison to observational studies with large study populations. Thus, the detection and resulting rates for adverse events depend ultimately on the study design.

Table 2. Bleeding frequencies during warfarin therapy reported in observational studies and randomized controlled trials.

OBSERVATIONAL STUDIES

Study, design	Study population	Bleeding definition	Bleeding frequency
Gomes et al. 2013 cohort study	AF patients initiating warfarin, *n*=125,195 median age 77 years	An emergency visit or hospital admission for hemorrhage based on selected ICD-9 and ICD-10 codes	3.8 % per PY
Gallagher et al. 2014 cohort study	Newly diagnosed AF patients, *n*=16,513 median age 74 years	Hospital admission for hemorrhage based on selected ICD-10 codes	3.8 % per PY during current use
Hansen et al. 2018 cohort study	Newly diagnosed AF patients, *n*=153,682 median age 76 years	Hospital admission for hemorrhage based on selected ICD-8 and ICD-10 codes	cumulative incidence of 3.2–3.9 % during the first year of AF
Wieloch et al. 2011 cohort study	All warfarin users, *n*=18,391 Indications for warfarin use AF (64 %), venous thromboembolism (19%), and heart valve dysfunction (13%) mean age 70 years	Major bleeding according to International Society on Thrombosis and Hemostasis*	2.6 % per PY
Cressman et al. 2015 cohort study	AF patients initiating warfarin, *n*=166,742 median age 78 years	An emergency visit or hospital admission for hemorrhage based on selected ICD-9 and ICD-10 codes	4.8 % per PY
Lindh et al. 2008 cohort study	New warfarin users, *n*=1,523 Indications for warfarin use: AF (51 %), DVT (25 %), PE (12 %) median age 66 years	Severe bleeding according to WHO criteria**	2.6 % per PY

RANDOMISED CONTROLLED TRIALS

Study	Study population	Bleeding definition	Bleeding frequency
Connolly et al. 2009 (RE-LY)	AF patients, *n*=6,002 mean age 71 years	Major bleeding defined as a reduction in the hemoglobin level of at least 20 g per liter, transfusion of at least 2 units of blood or symptomatic bleeding in a critical area or organ	3.36 % per year
Patel et al. 2011 (ROCKET AF)	AF patients, *n*=7,133 median age 73 years	Major bleeding defined as clinically overt bleeding associated with any of the following: a reduction in the hemoglobin level of at least 20 g per liter, transfusion of at least 2 units of blood, symptomatic bleeding in a critical area or organ, permanent disability, or fatal outcome	3.4 % per PY
Granger et al. 2011 (ARISTOTLE)	AF patients, *n*= 6,368 mean age 70 years	Major bleeding according to the International Society on Thrombosis and Hemostasis*	3.09 % per year
Giugliano et al. 2013 (ENGAGE AF-TIMI 48)	AF patients, *n*= 7,036 median age 72 years	Major bleeding according to the International Society on Thrombosis and Hemostasis*	3.43 % per year

*Hemorrhages causing a significant blood loss, requiring blood transfusion, occurring at critical site, or resulting in death (Schulman et al., 2005).
**Lethal, life-threatening, permanently disabling, or leading to hospital admission (excluding emergency room admission), or prolongation of hospital stay (Lindh et al., 2008).
AF, atrial fibrillation; CI, confidence interval; DVT, deep vein thrombosis; ICD-10, International classification of Diseases -10; PE, pulmonary embolism; PY, person-year; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ARISTOTLE, Abixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET AF, The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; ENGAGE AF-TIMI; Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation – Thrombolysis in Myocardial Infarction 48.

Several risk factors for bleeding have been identified. The risk of bleeding increases with advancing age, but depends also on other patient characteristics, co-morbidities, drug and food interactions, and the phase and quality of warfarin therapy (Table 3). Some of the risk factors, such as age, prior bleeding, or genetic factors, cannot be modified, whereas some are potentially modifiable, *e.g.* anemia, thrombocytopenia, or excessive risk of falls, and others, such as elevated blood pressure, INR control, or drug interactions, are modifiable (Hindricks et al., 2021).

Various risk stratification schemes have been developed to aid clinicians in estimating the bleeding risk and the net benefit of warfarin therapy (Beyth et al., 1998; Gage et al., 2006a; Pisters et al., 2010; Fang et al., 2011). Although the performance of risk scores in predicting major bleeding is modest and varies between risk scores (Senoo et al., 2016), they have been claimed to outweigh the clinician's impression (Beyth et al., 1998).

Table 3. Patient- and therapy-related risk factors for warfarin-therapy-associated bleeding. Modified from Hindricks et al. 2021.

Patient characteristics	Comorbidities	Therapy-related factors
Older age	Hypertension (uncontrolled)	Initiation phase of warfarin therapy
Prior bleeding	Congestive heart failure	Supratherapeutic INR
Alcohol abuse	Hepatic or renal impairment	Labile INR
Frailty	Anemia	Drug and food interactions
Excessive fall risk	Reduced platelet count or function	
Genetic factors	Malignancy	
Weak compliance	History of stroke or transient ischemic attack	

The bleeding risk can be decreased by identifying and addressing modifiable risk factors and avoiding additional risk factors, such as drug interactions. Co-morbidities, such as anemia, thrombocytopenia, and if possible, uncontrolled hypertension should be treated prior to warfarin initiation. The greatest risk for excessive anticoagulation (Jaakkola et al., 2017) and bleeding (Gomes et al., 2013; Rikala et al., 2016) occurs during the first months of warfarin therapy. Thus, a well-judged estimation of initial warfarin dose according to the patient's age, gender, body mass index, potential previously used warfarin dose, and *CYP2C9* and *VKORC1* genotype may shorten the time for reaching the stable INR level (Wadelius et al., 2006). Numerous algorithms based on demographic, clinical, environmental

and genetic factors have been developed to better predict warfarin dose requirements, although only a few are externally validated and have been clinically assessed to outweigh fixed dose-initiation approaches (Asiimwe et al., 2021). However, dosing algorithms have not been widely adopted in clinical practice, and warfarin is initiated using a fixed dosing regimen (See Chapter 2.1.1.3). Despite the risk of serious and even fatal adverse drug reactions (Kauppila et al., 2021), the benefits of anticoagulant therapy outweigh the risk of bleeding specifically in older patients with a high risk of stroke (Hart et al., 2007).

Rare adverse effects

Other, although considerably less common ADRs of warfarin therapy are skin necrosis and purple toe syndrome. The ultimate pathophysiological mechanisms behind these conditions are unclear. However, it is hypothesized that skin necrosis is a consequence of the warfarin-induced imbalance in the levels of vitamin K-dependent proteins C, protein S, and coagulation factors II, VII, IX, and X, which results in a transient hypercoagulable state and the pathological formation of occlusive thrombi in the small vessels of skin (Bircher et al., 2006). The speculative mechanism behind the purple toe syndrome is that warfarin induces the embolization of cholesterol crystals from atherosclerotic plaques in large arteries, which occlude the small vessels in the toes and fingers, resulting in ischemia (Vu et al. 2017). The incidence of skin necrosis and purple toe syndrome is at its highest early after warfarin initiation. The treatment involves the cessation of warfarin therapy (Vu et al. 2017).

2.1.2 Trends in the use of warfarin in Finland

The use of OACs has steadily increased in Finland since the 1990s (Figure 2). This growth is largely explained by the rising prevalence and incidence of AF and the introduction of clinical guidelines on the use of OAC therapy in patients with AF. The risk of developing AF increases along with age (Hindricks et al., 2021), and in Finland, the number of persons over 65 years old has grown by at least 100,000 persons each 5-year period since 2005 (Statistics Finland, 2022). Moreover, the rising incidence of AF has been demonstrated in age-adjusted studies, which is considered to reflect the increasing prevalence of risk factors for AF, such as hypertension, diabetes mellitus, obesity, obstructive sleep apnea, and alcohol consumption (Hindricks et al., 2021; Miyasaka et al., 2006). More importantly, the first national current care guideline of AF was published in 2005, and warfarin therapy was recommended for all patients with AF except for patients with lone AF and those younger than 60 years (Atrial fibrillation: Current Care Guideline, 2005).

The new knowledge on the benefits of OAC therapy was rapidly adopted changing the prescribing practice (Virjo et al., 2010).

The Pre-DOAC era

Prior to the era of the DOACs, a handful of population-based studies described the use of warfarin in Finland. In the early 1990s, Fogelholm and colleagues accessed medical records and reported the prevalence of OAC treatment of 1.6 % among over 40 years old people in a primary care setting. They also described a slightly higher prevalence of warfarin use in men than in women and an increasing prevalence in older age groups. The highest prevalence of 5.2 % was detected in men over 80 years of age (Fogelholm et al., 1992). A few years later, Eskola et al. published similar observations on the rapidly increasing prevalence of OAC treatment among individuals over 40 years old (Eskola et al., 1996). They described the highest prevalence of OAC treatment in 75–79 years old men (4.38 %) and 80–84 years old women (4.27 %). Moreover, in the study conducted by Eskola et al., the prevalence of OAC use was 0.7 % in 1992, which had more than doubled to 1.8 % by 2004 when the next study on warfarin use in Finland was conducted by Virjo and colleagues (Virjo et al., 2010). The increasing prevalence of warfarin use based on drug reimbursement data was also reported by Huhtakangas et al; according to these values, the prevalence of warfarin use increased from 0.63 % to 2.28 % between 1993 and 2008 (Huhtakangas et al., 2011).

Along with the increasing prevalence of use, the mean age of warfarin users increased from 68.9 years in 1992 to 72.4 years in 2004 (Eskola et al., 1996; Virjo et al., 2010). In 2009, the mean age of patients who received drug reimbursement on warfarin purchase was 73.7 years and more than half of patients were over 75 years old (Jyrkkä et al., 2011).

A few studies have identified the indications for warfarin treatment; Eskola et al. described AF as the most common main indication for warfarin therapy in 38 % of patients, whereas Virjo et al. reported the same for 60 % of patients twelve years later. The second most common indication was deep vein thrombosis in 9–15 % of warfarin users (Eskola et al., 1996; Virjo et al., 2010). Similar observations on the most common indications for warfarin therapy were reported also by Fogelholm et al. based on a subset of 208 patients in their study population. (Fogelholm et al., 1992).

Little information is available on the comorbidities and co-medications in unselected warfarin user populations from the pre-DOAC era. Jyrkkä et al. described warfarin users based on drug reimbursement registers in 2009. According to special reimbursement register data, approximately 40 % of warfarin users had hypertension, one in four had coronary heart disease, and every fifth user suffered

from diabetes (Jyrkkä et al., 2011). In reality, these and other co-morbidities may be even more common than recognized from the register data.

The DOAC era

The most significant changes in the use of warfarin therapy took place in the 2000s as DOACs were introduced and the selection of OACs expanded with new drugs. Ximelagatran, a direct thrombin inhibitor, was introduced in 2004, but it was withdrawn in two years due to the emergence of hepatotoxicity (McNaughton et al., 2014). Dabigatran and rivaroxaban were authorized in 2008, first with the indication of the prevention of venous thromboembolism in adults undergoing elective hip or knee replacement surgery (Finnish Medicines Agency, 2022; Ilomäki et al., 2015). In 2012, dabigatran was granted an extension of marketing approval with an indication for stroke prophylaxis in patients with non-valvular AF (Ilomäki et al., 2015); this was shortly followed by approvals for rivaroxaban in 2012 and apixaban in 2013 (Aarnio et al., 2020). AF was included in the approval of edoxaban as it was launched into the market (Aarnio et al., 2020). However, the price of DOAC therapy was considerably higher for patients than warfarin, and therefore, warfarin remained as the prevailing OAC for several years after the introduction of DOACs (Figure 2).

The reimbursement status of DOACs and the criteria for entitlement of reimbursement have changed several times in the 2010s. In 2015, DOACs became reimbursable in stroke prevention in patients with non-valvular AF and at least a high risk of stroke without the requirement of failed or contraindicated warfarin therapy (Aarnio et al., 2020). Thereafter, the use of DOACs has increased rapidly and this has been simultaneously accompanied by a decreasing use of warfarin as interpreted from reimbursement statistics (Figure 2). A possible explanation for this change may be that DOACs started to replace warfarin use in AF patients. However, caution is warranted when interpreting reimbursement statistics during the 2010s as the non-reimbursed use of DOACs is not captured which may lead to an underestimation of the user numbers whereas the potential switch between warfarin and DOACs may result in an overestimation of the use of both forms of anticoagulants (Aarnio et al., 2020).

Studies on warfarin use in an unselected population in Finland are scarce in the DOAC era. A recent study based on electronic prescription data described AF as being the most common indication for an OAC prescription for both warfarin and DOACs (26.9 % and 46.1 % of prescriptions, respectively) in 2016 (Aarnio et al., 2020). However, the actual percentages may be considerably higher as in two thirds of warfarin prescriptions, the information on indication was lacking, whereas the same was true in less than one third of DOAC prescriptions. However, studies focusing in the OAC use among AF patients in Finland do exist. Hellman et al.

described the anticoagulant use of outpatients and inpatients with AF between 2015 and 2017. Although during the study period, warfarin was initiated in 100,209 patients and DOAC in 30,832 patients, the number of new warfarin users decreased by 35 %, while the number of new DOAC treatments increased by 62 % (Hellman, 2020). Interestingly, the patients who were using warfarin were older and had more comorbidities than patients using DOACs. Similar observations have been published in other countries (Zhu et al., 2018) as well as in Finland by Rissanen et al. and Leminen et al. (Leminen et al., 2019; Rissanen et al., 2021).

The rapid adoption of DOACs is explained by their certain advantages in clinical use in comparison to warfarin with the most important benefits being the lower incidence of intracranial hemorrhages, fixed dosing, and the fact that routine laboratory monitoring is not needed. However, drawbacks exist as well, such as the price of antidotes and still accumulating experience in reversal practice. On the other hand, warfarin is the only OAC indicated for thromboprophylaxis in patients with a mechanical heart valve, severe mitral stenosis, or severe renal failure, and in children. Furthermore, the quality of warfarin therapy in Finland is generally good (Hallinen et al., 2014; Lehto et al., 2017) and some patients may prefer to continue with warfarin use especially if their long-term INR level remains stable reaching a high TTR. At present, DOACs are recommended as the first line OAC due to their superior compliance and safety compared to warfarin (Atrial fibrillation: Current Care Guideline, 2021). Altogether, DOACs have gained the position as the most commonly used OACs in Finland, whereas warfarin appears to remain as a necessary OAC in situations where DOACs are without indication or contraindicated. Nevertheless, the projected number of persons over 65 years is estimated to exceed 25 % of the Finnish population in 2030, and as the population ages, it is predicted that the prevalence of OAC therapy will continue to increase (Statistics Finland, 2018).

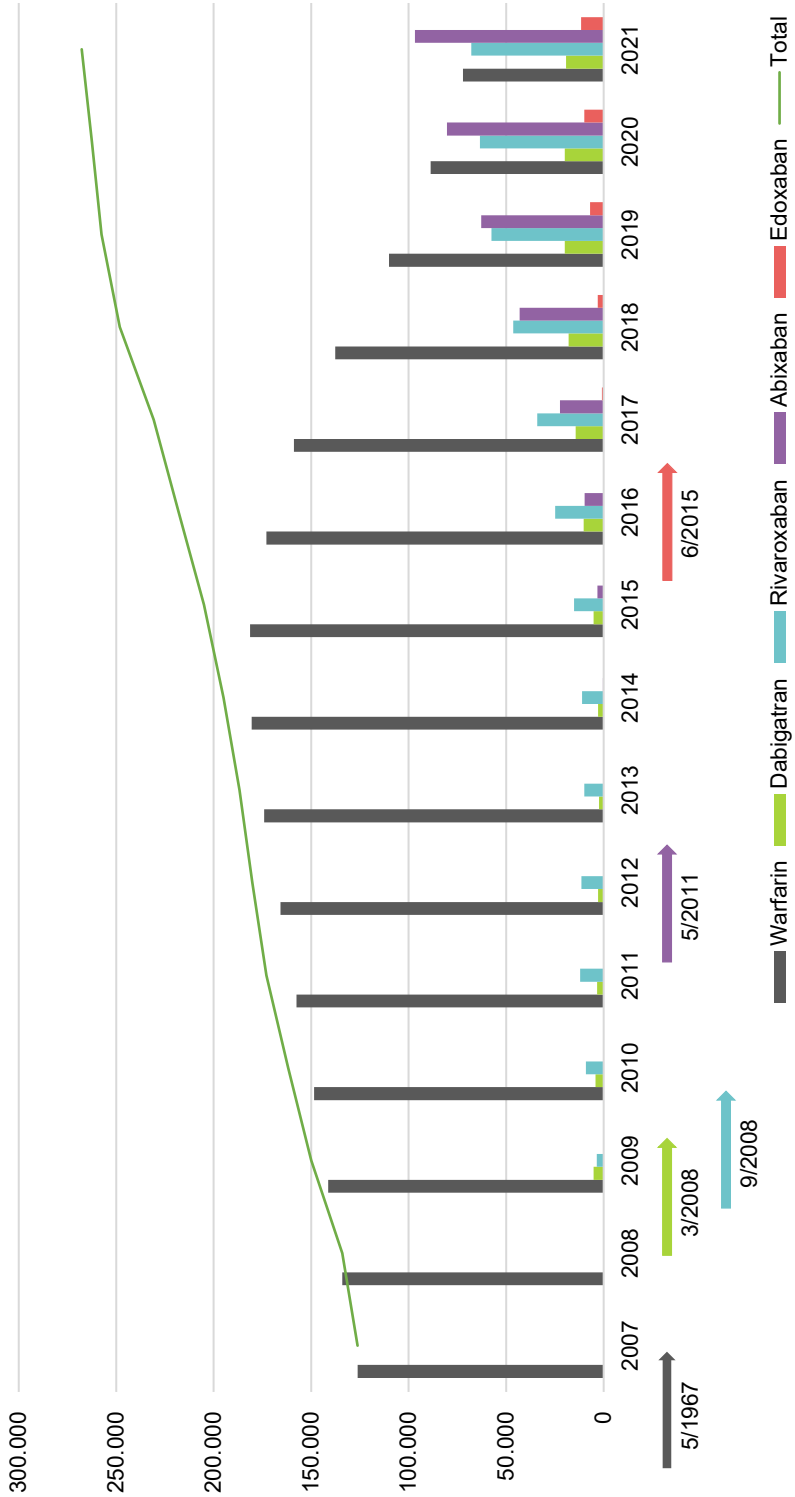


Figure 2. The number of persons receiving reimbursement for oral anticoagulant purchases in 2007–2021 and the time of marketing authorization for each OAC. A person may have received reimbursement for more than one OAC in a particular year. Data source: Prescription Register, Social Insurance Institution.

2.2 Pain medication in older people

Pain is a common and significant health problem. Approximately 20 % of the adult population in Europe suffers from chronic pain (Breivik et al., 2006). In older people, who are commonly referred as persons 60 or 65 years old or older, the prevalence of chronic pain is 2–4-fold higher compared to younger age groups because diseases evoking pain disproportionately affect older adults (Abdulla et al., 2013; Larsson et al., 2017). Chronic conditions affecting musculoskeletal system, such as osteoarthritis, rheumatic diseases, and degenerative disorders, are typical causes of nociceptive pain (Hasselström et al., 2002; Rapo-Pylkkö et al., 2016), whereas neuropathic pain is commonly caused by peripheral diabetic neuropathy, postherpetic neuralgia, post-stroke pain, and compression of spinal nerves (Giovannini et al., 2021). Pain management is of major importance in older people as persistent or inadequately treated pain is associated with numerous adverse outcomes including functional impairment (Ardoino et al., 2020), decreased quality of life (Johansson et al., 2021), depression (Sharpe et al., 2017; Zis et al., 2017), and development of frailty (Lin et al., 2020; Otones Reyes et al., 2019; Sodhi et al., 2020). Pain medications are an essential part of clinical pain management.

Challenges in the use of pain medication in older people

While appropriate pharmacotherapy can reduce adverse outcomes related to pain, the increased risk of adverse drug reactions complicates the use of pain medications in older people. Age-related physiological changes, such as decreased lean body mass and reduced kidney and liver function, may alter pharmacokinetics, and if the drug dose is not reduced, the elevated concentration may result in toxicity. Moreover, potential changes in receptor density, affinity, binding and downstream reactions may modify pharmacodynamic responses. In addition, co-morbidities may limit the selection of pain medications. In polymedicated older persons, the high probability of drug interactions further increases the risk of adverse drug reactions, and the declines in both physiological and homeostatic mechanisms impair the ability of the aged body to compensate for potential adverse effects, this being particularly the case in frail patients. Furthermore, adverse drug reactions may be difficult to distinguish from symptoms that are common in older people, such as slurred speech, confusion, or falls. Attitudes or cognitive impairment may cause underreporting of pain and atypical clinical manifestations of pain and challenge the monitoring of the response to drug therapy (Rastogi et al., 2013; Davies et al., 2015).

Frail older persons comprise a special subpopulation among the aged. Frailty is a syndrome characterized by a decreased reserve and a limited ability to respond to stressors resulting from cumulative declines across multiple physiologic systems and causing a vulnerability to adverse outcomes (Clegg et al., 2013). Approximately one

in ten community-dwelling over 60 years old person is frail (Collard et al., 2012; Ofori-Asenso et al., 2020). Frail patients often present with weight loss, weakness, exhaustion, slowness, and low physical activity; these symptoms have been included in a phenotype-based score developed and validated for objective measuring of frailty (Fried et al., 2001). Furthermore, frailty is characterized by an increased risk of sarcopenia and increased levels of body fat, chronic inflammation, a decreased immune response, overactivation of the coagulation system and a reduction in heart rate variability (Hilmer et al., 2019). Frailty has also been associated with a higher prevalence of pain (Blyth et al., 2008; Shega et al., 2012).

Although frail older adults may be more susceptible to adverse events related to inadequately treated pain, they are at a higher risk of experiencing the adverse events of pain medication because of their reduced resilience (Hilmer et al., 2017). The complexity of pain medication use is amplified in frail older people because of the wide variation in drug disposition and response (McLachlan et al., 2011). In addition, the high prevalence of comorbidities and polypharmacy further increases the risk of adverse events (Gnjidic et al., 2012). Nonetheless, there is only limited evidence on the effect of frailty on the pharmacokinetics and pharmacodynamics of pain medications complicating the dose estimation (Hilmer et al., 2017). The current treatment guidelines recommend ‘a start low and go slow’ approach in dosing (Ickowicz, 2009), which unfortunately may carry a risk of undertreatment of pain (Hanlon et al., 2009).

The use of pain medication in older people

Pain medications are among the most commonly used drugs in older home-dwelling people (Jyrkkä et al., 2009; Wastesson et al., 2018). According to a recent study, more than eight out of every ten of older people had purchased prescription pain medication during a year (Marttinen et al., 2021). In two Finnish surveys, 16–23 % of home-dwelling older persons reported the daily use of prescribed pain medication (Lehti et al., 2021; Pokela et al., 2010). The use of pain medication is more common in the frail in comparison to the non-frail: up to 68 % of frail and 41 % of non-frail individuals reported that they had consumed prescribed or over-the-counter pain medication during the previous two weeks (Koponen et al., 2013). Paracetamol and non-selective non-steroidal anti-inflammatory drugs (NSAID) were the most common pain medications, being used regularly by 11 % and 2 % of older home-dwelling people, respectively (Lehti et al., 2021). Weak opioids were utilized by 3–7 % of older adults (Lehti et al., 2021; Pokela et al., 2010) whereas strong opioids were used by 1 % of older adults (Lehti et al., 2021).

Parallel figures and similar order of pain medication use were reported in a register-based study by Hamina and colleagues. The prevalence of prescription pain

medication use in cognitively intact older home-dwelling people was 33.5 % (Hamina et al., 2017). The highest prevalence *i.e.* 19.0 %, was reported for paracetamol, followed by NSAIDs (17.4 %), mild opioids (6.9 %), and strong opioids (1.1 %). Another register-based study conducted by Taipale et al. reported that 36.4 % of over 90 years old home-dwelling people had purchased prescription pain medications during a 6-month period. Paracetamol was most commonly purchased (24.6 %), followed by NSAIDs and opioids (10.9 % for each) (Taipale et al., 2016).

According to various studies, paracetamol appears to be the most commonly used pain medication, followed by non-selective NSAIDs and opioids. In particular, the use of pain medications is highly prevalent among females and among individuals over 80 years of age (Hamina et al., 2017; Helin-Salmivaara et al., 2003; Pokela et al., 2010).

The consumption of pain medications in Finland

The total consumption of the most commonly used pain medications has doubled in Finland since 1996 (Figure 3). It can be speculated whether the increased number of over 65 years old persons (by 530,000) over the past 25 years (Statistics Finland, 2020b) and the improved pharmacological pain management along with the current care guidelines for pain therapy issued in 2005 (Pain: Current Care Guidelines, 2017) have contributed to this growth. Non-selective NSAIDs have remained the most widely consumed drugs, whereas the consumption of paracetamol has increased considerably, reaching the same levels of consumption as in other Nordic countries (Wastesson et al., 2018). Codeine in combination with paracetamol has kept its position as the most commonly sold opioid throughout this time, although there has been a declining trend in its consumption over the past decade. Instead, the consumption of tramadol has steadily remained in the range of 2–3 DDD/1000 inhabitants/day since the millennium. Oxycodone and buprenorphine are the most widely consumed strong opioids (Finnish Medicines Agency, 2021).

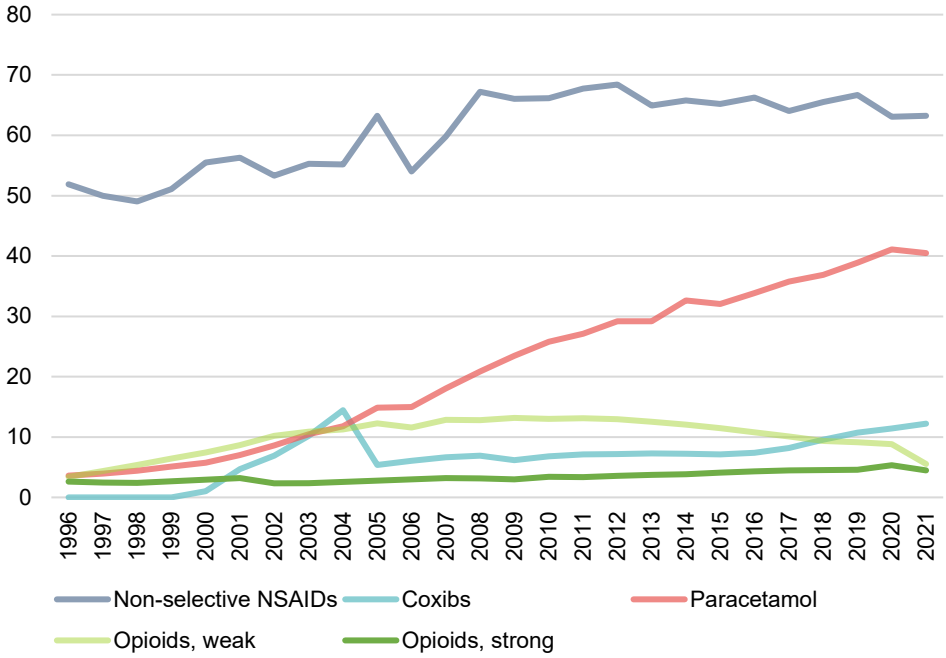


Figure 3. The consumption of pain medications in 1996–2021 measured as DDD/1000 inhabitants per day according to wholesale statistics. The total consumption figures include both prescription and over-the-counter analgesics. Data source: Finnish Medicines Agency, Drug Sales Register.

2.2.1 Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory agents (NSAIDs) are analgesics with anti-inflammatory, antipyretic, and platelet aggregation inhibiting properties. If one examines their chemical structure, then it is apparent that they represent a heterogeneous group of compounds (Crofford, 2013). Although the history of industrially manufactured NSAIDs dates back to the 19th century, several new compounds have been launched in the late 20th and early 21st centuries. Some NSAIDs have later been withdrawn from the market, mostly due to serious adverse effects, such as hepatoxicity as occurred with nimesulide and cardiovascular problems such as the myocardial infarction (MI) linked to the use of rofecoxib (McNaughton et al. 2014). NSAIDs are indicated in the treatment of pain, especially of nociceptive origin, and fever. Unlike other NSAIDs, acetylsalicylic acid (ASA) is used primarily for the prevention of thrombotic events in patients with atherosclerotic diseases.

2.2.1.1 Mechanism of action

NSAIDs exert their actions by inhibiting cyclo-oxygenase (COX) enzymes, which catalyze the production of prostanoids (Vane, 1971). Prostanoids are a diverse group of lipid mediators synthesized from cell membrane-derived arachidonic acid through the action of phospholipase A2. Two major isoforms of cyclo-oxygenases, COX-1 and COX-2, are responsible for the formation of prostaglandins in mammalian cells. The isoforms are encoded by distinct genes, and they differ in terms of their tissue distribution and expression. COX-1 is constitutively expressed and functions as a "housekeeping" enzyme being responsible for the production of various prostaglandins, prostacyclin, and thromboxanes, which are involved in essential physiological functions, such as platelet aggregation, the maintenance of the gastric mucosa, and the regulation of cardiovascular and renal functions (Miller, 2006). In contrast, the expression of COX-2 is primarily induced by inflammatory stimuli and mitogens in various tissues, although some constitutive expression exists in renal tissues (Harris et al., 2004) and in vascular endothelium (Funk et al., 2007). Thus, the analgesic, anti-inflammatory, and antipyretic effects of NSAIDs are primarily mediated through the inhibition of COX-2 in the context of pathological conditions, whereas the adverse effects can be traced to the inhibition of the physiological functions of COX (Miller, 2006).

NSAIDs can be categorized into non-selective NSAIDs and COX-2 inhibitors, *i.e.* coxibs, according to their selectivity towards the two isoenzymes. Non-selective NSAIDs inhibit both COX isoenzymes in therapeutic concentrations, although selectivity towards different isoenzymes varies between the individual NSAIDs (Moore, 2020). In an attempt to avoid the adverse effects related to the blockade of COX-1, in particular gastrointestinal toxicity, coxibs were developed to achieve a selective inhibition of COX-2 (Laine, 2002).

2.2.1.2 Pharmacokinetics

Chemically, NSAIDs are themselves weak acids or are metabolized into weak acids. This similarity explains some of the common pharmacokinetic properties shared by the different NSAIDs (Day et al., 1988). Generally, the absorption of NSAIDs following oral administration is rapid and complete. Most NSAIDs bind highly to plasma proteins and have a low volume of distribution, ranging from 0.1 to 0.3 l/kg. While the majority of NSAIDs are metabolized in the liver, only a few have active metabolites (ASA, diclofenac) or are prodrugs (nabumetone, sulindac). Thus, most NSAIDs are cleared via hepatic metabolism (Davies et al., 2000). The physiological changes attributable to aging as such have only a relatively minor effect on the pharmacokinetics of NSAIDs (Woodhouse et al., 2012). Instead, coexisting hepatic

or renal dysfunction with hypoproteinemia warrants caution in dosing, as with many other drugs.

2.2.1.3 Adverse effects

Due to the wide expression of COX enzymes, the adverse effects of NSAIDs extend to several tissues and organ systems. The gastrointestinal tract is most commonly affected, whereas cardiovascular and renal adverse effects are encountered especially among aged patients with conditions affecting these organs. Rare ADRs of NSAIDs comprise bronchoconstriction (Leuppi et al., 2001), various skin reactions (Marzano et al., 2016), liver toxicity (Bessone, 2010), and even less commonly, bone marrow toxicity (Van Den Bemt et al., 2004).

2.2.1.3.1 Gastrointestinal adverse effects

The gastrointestinal (GI) adverse effects of NSAIDs vary in severity from superficial mucosal injuries to ulceration, which may further evolve into serious complications *i.e.* stricture, perforation, or bleeding (Bjarnason et al., 2018). NSAIDs damage the gastrointestinal mucosa through multiple mechanisms (Figure 4). The decreased synthesis of prostaglandins, especially prostaglandin E_2 (PGE_2), reduces the secretion of mucus and bicarbonate, which protect the mucous membrane from the corrosive effect of hydrochloric acid. Simultaneously, the acid secretion increases enhancing the harmful exposure. Furthermore, the diminished prostaglandin levels decrease mucosal blood flow, a process that impairs the healing of mucosal injuries. In addition, NSAIDs damage the gastric mucosa through a phenomenon called “ion trapping”. Most NSAIDs are weak organic acids, and in the low pH of the stomach lumen, they exist in the non-ionized, lipophilic form. This enables diffusion through the gastric mucus and across plasma membranes into epithelial cells. In the cytoplasm, where pH is neutral, these weak acids become dissociated into the ionized and more lipophobic form, which does not favor the molecule’s diffusion out of the cells. Thereby, hydrogen ions and ionized drug molecules become “trapped” within the cells, and this accumulation can evoke a cellular injury (Laine, 1996; Matsui et al., 2011). Moreover, NSAIDs reduce the hydrophobicity of the gastric mucus, which weakens the defensive barrier of the mucous membrane predisposing it to topical damage (Schoen et al., 1989).

Upper abdominal symptoms, such as dyspepsia or nausea, are presented in 15–60 % of patients using NSAIDs, which often require the discontinuation of therapy. However, there does not seem to be any correlation between the symptoms and actual mucosal injuries. Subepithelial hemorrhages and mucosal erosions, which may cause minor, subclinical bleeding, are seen in endoscopy in approximately 40–

60 % of patients taking non-excessive doses of NSAIDs. The prevalence of gastric or duodenal ulcers in regular users varies between 15 % to 30 %, whereas the annual incidence of NSAID-related ulcers and serious complications is 2.5–4.5 % and about 1–1.5 %, respectively (Laine, 1996; Laine, 2002).

The risk of serious upper GI adverse events *i.e.* bleeding, perforation, and obstruction associated with the use of nonselective NSAIDs is around fourfold as compared to non-users (García Rodríguez et al., 2001). The risk is increased by older age, a history of peptic ulcer, the use of high doses of non-selective NSAIDs for prolonged periods, the concurrent use of another NSAID, antiplatelets, anticoagulants, selective serotonin reuptake inhibitors, or corticosteroids, and *H. pylori* infection (Sostres et al., 2013). The magnitude of risk varies between the individual NSAIDs and is lower for the coxibs than for the non-selective NSAIDs (Castellsague et al., 2012; Massó González et al., 2010; Sostres et al., 2013). The risk of an NSAID-induced GI adverse event can be reduced with gastroprotective agents, such as proton pump inhibitors or, a PGE_2 analog misoprostol (Scheiman, 2013). Moreover, the use of NSAIDs should be limited to the lowest effective dose and the shortest possible treatment time.

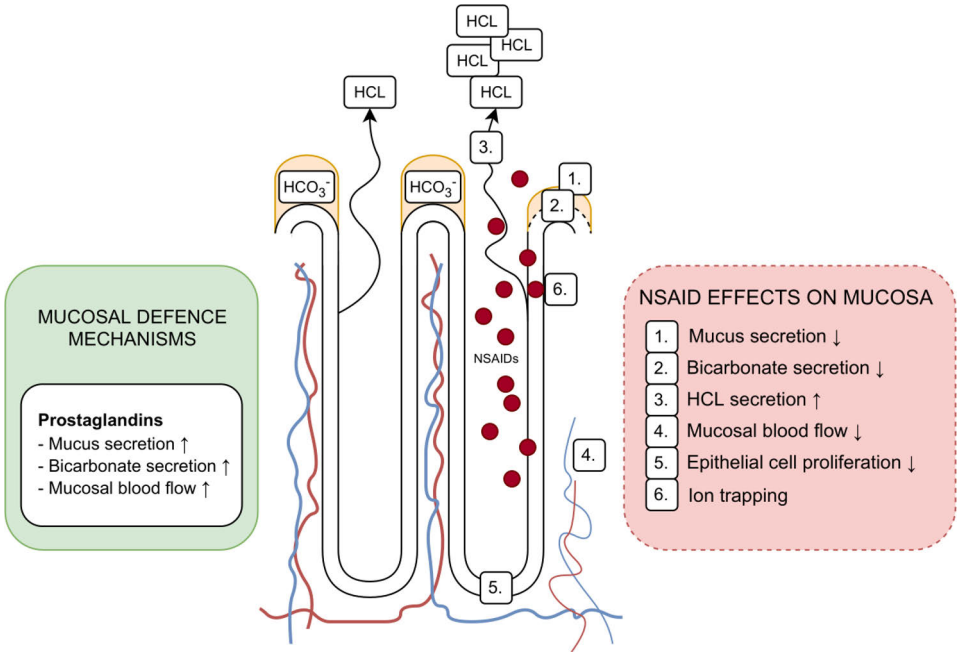


Figure 4. The mechanisms of gastrointestinal mucosal damage of non-selective NSAIDs. Adopted from: Vuolteenaho et al. In: Lääketieteellinen farmakologia ja toksikologia, Duodecim 2022. HCL, hydrochloric acid; HCO_3^-, bicarbonate.

2.2.1.3.2 Antiplatelet effects

The inhibition of platelet COX-1 prevents the formation of thromboxane A_2 (TXA_2) (Jeremy et al., 1985; Parks et al., 1981) which impairs platelet aggregation and prolongs the bleeding time, thus increasing the tendency towards systemic bleeding. ASA differs from the other NSAIDs by covalently acetylating COX-1 in platelets, whereas the other NSAIDs cause a reversible inhibition by competing with the common binding site of COX (Schafer, 1995). Due to the permanent effect on platelet COX-1, ASA is used as a platelet aggregation inhibitor in patients with cardiovascular disease in doses of 50–100 mg per day – a dose considerably lower than when it is administered as an analgesic.

2.2.1.3.3 Cardiovascular adverse effects

The most significant cardiovascular adverse effects of NSAIDs include MI and stroke. The underlying mechanism is proposed to be related to the inhibition of COX-2 and the reduced production of prostacyclin by the vascular endothelium with little or no impact on COX-1-dependent production of TXA_2 in platelets (Minhas et al., 2023). This change in the prostaglandin levels has been proposed to shift the balance towards prothrombotic conditions and potentially result in MI or stroke (Ray et al., 2003; Vane, 2002). The increased risk of MI associated with the use of NSAIDs was first noted in the long-term clinical trial of high doses of rofecoxib where it was observed that the incidence of MI was lower in patients on naproxen as compared to patients on rofecoxib (0.1 % vs. 0.4 %, respectively) (Bombardier et al., 2000). Similar observations on the association of an increased risk of MI with rofecoxib therapy resulted in the withdrawal of rofecoxib in 2004 (Bresalier et al., 2005). Thereafter, also the use of non-selective NSAIDs has been associated with an increased risk of MI (Bally et al., 2017; Helin-Salmivaara et al., 2006) and their use should be avoided in patients with atherosclerotic vascular disease or risk factors for this disease (Pain: Current Care Guideline, 2017).

Other important cardiovascular adverse effects involve blood pressure elevation and heart failure. COX-2 inhibition results in a reduction in the synthesis of both PGE_2 and prostacyclin, i.e. prostanoids which are associated with reduced sodium excretion and a potential increase in systemic vascular resistance, respectively. In patients with pre-existing hypertension, edema, heart failure, or chronic kidney disease, these effects may lead to a worsening of the clinical condition and adverse outcomes (White, 2007).

2.2.2 Paracetamol

Paracetamol *(N*-acetyl-para-aminophenol*, Am.* acetaminophen*)* belongs to the group of anilide analgesics. In addition to its analgetic effect, it has antipyretic and weak anti-inflammatory properties (Anderson, 2008). Paracetamol is recommended as the first-line treatment of mild to moderate pain as monotherapy and in combination with opioid analgesics in older patients (Ickowicz, 2009).

2.2.2.1 Mechanism of action

Despite its wide use, paracetamol's mechanism of action remains unknown. Previously, paracetamol was thought to produce its analgesic effect, an elevation in pain threshold, and an antipyretic action by inhibiting prostaglandin synthesis in the central nervous system (CNS), specifically via COX-2 inhibition (Graham et al., 2005). However, recent studies have suggested that a metabolite of paracetamol, *N*-arachidonoylphenolamine (AM404), acts on the endocannabinoid system with the transient receptor potential vanilloid 1 (TRPV1) channels in the central nervous system also playing a major role on paracetamol-induced analgesia (Ohashi et al., 2020). In addition, the involvement of the serotonergic system, the nitric oxide synthesis pathway, and several other ion channels have also been speculated to contribute to paracetamol's effect (Przybyła et al., 2021). Thus, paracetamol-induced analgesia may result from a synergistic effect between multiple mechanisms on the central nervous system and peripheral sites (Anderson, 2008).

In peripheral tissues, therapeutic concentrations of paracetamol inhibit COX activity when the levels of arachidonic acid and peroxides are low. However, this inhibition appears to be lost when the levels of arachidonic acid and peroxides are high as is typical in severe inflammatory conditions, such as rheumatoid arthritis or platelet activation (Boutaud et al., 2002; Schildknecht et al., 2008). This may explain not only the low anti-inflammatory effect of paracetamol but also the lack of effect on the gastric mucosa.

2.2.2.2 Pharmacokinetics

Paracetamol is readily absorbed from the gastrointestinal tract and it is rapidly and evenly distributed in most tissues including the CNS (Forrest et al., 1982; Moreau et al., 1993). Age does not change its absorption (Divoll et al., 1982), but the volume of distribution and clearance are decreased in older people, especially in frail patients (Mian et al., 2018). Paracetamol is primarily conjugated into glucuronide and sulfate conjugates which are excreted in urine (Prescott, 1980). Between 5–10 % of paracetamol is oxidized mostly by CYP2E1 into *N*-acetyl-*p*-benzoquininoimine (NAPQI), but also isoenzymes CYP1A2, CYP3A4, and CYP2A6 are involved in

oxidation (Chen et al., 1998; Raucy et al., 1989; Thummel et al., 1993). This highly reactive metabolite is immediately conjugated with glutathione and subsequently excreted as cysteine and mercapturate conjugates in urine (Coles et al., 1988; Hodgman et al., 2012).

2.2.2.3 Adverse effects

Liver damage is the most common serious adverse effect of the otherwise well-tolerated paracetamol. The liver toxicity of paracetamol depends on the detoxification of NAPQI by glutathione conjugation. If the rate of NAPQI formation exceeds the rate of glutathione conjugation, the accumulating NAPQI binds covalently to hepatocyte components resulting in a potentially fatal liver injury. The hepatic injuries associated with paracetamol use most commonly result from either intentional or unintentional overdose; for example, a single dose of 10 to 15 g in adults is sufficient to overwhelm the hepatic detoxification capabilities. Other factors contributing to hepatotoxicity are the induction of oxidative enzymes by other drugs, chronic alcohol consumption, or the depletion of glutathione in cases of malnutrition (Larson, 2007). In the presence of these factors, cases of toxicity have been reported occurring even at therapeutic doses of 4 g per day (Eriksson et al., 1992). Due to the risk of hepatotoxicity, liver failure is an absolute contraindication, while hepatic insufficiency and chronic alcohol abuse represent relative contraindications for paracetamol use (Pickering et al., 2011). In order to avoid hepatotoxicity, a maximum paracetamol dose of 2–3 g per day is recommended in older adults for regular use (Finnish Medicines Agency, 2022).

2.2.3 Tramadol

Tramadol is one of the two weak opioids on the market in Finland. It is available only by prescription in various formulations as a single agent and combination preparations with paracetamol or dexketoprofen (Finnish Medicines Agency, 2022). Tramadol differs from codeine in having a monoaminergic action in addition to its opioid properties. It is indicated in the treatment of moderate and severe pain and is commonly used to alleviate the pain associated with osteoarthritis, low back pain, and also in neuropathic pain due to its dual analgesic action (Finnish Medicines Agency, 2022; Grond et al., 2004).

2.2.3.1 Mechanism of action

The dual analgesic action of tramadol is explained by the chirality and prodrug character of the compound. Both enantiomers of the parent compound and their

active metabolites differ in their receptor binding properties (Table 4). The monoaminergic action of tramadol is produced by the enantiomers of the parent drug: (+)-tramadol inhibits serotonin reuptake and increases serotonin efflux while (-)-tramadol is responsible for the inhibition of noradrenaline reuptake (Raffa, 1996; Grond et al., 2004; Lassen et al., 2015). The opioid effect is produced by (+)-tramadol and especially by its active metabolite M1, which binds to the μ-opioid receptor and is several hundred times more potent than its parent compound. The principal mechanism responsible for the analgetic effect of tramadol is opioid agonism, which inhibits the generation of nociceptive stimulus, whereas the monoaminergic effects take part in pain modulation, enhancing the inhibitory descending pathways associated with pain transmission in the CNS (Grond et al., 2004).

Table 4. Comparison of receptor affinities of enantiomers and the active metabolite M1 of tramadol. Adopted from Beakley et al., 2015.

Opioid component	Affinity for opioid receptors	Reuptake inhibition	
	μ	Noradrenaline	Serotonin
(+)-Tramadol	+++	+	++
(-)-Tramadol	+	++	+
M1	++++	-	-

2.2.3.2 Pharmacokinetics

Orally administered tramadol is rapidly and almost completely absorbed after its ingestion. It undergoes first-pass metabolism which reduces the systemic bioavailability to 70 % (Lassen et al., 2015). The distribution volume of 300 l reflects the high tissue affinity of tramadol. The main metabolic pathways of tramadol are *O*- and *N*-demethylation and conjugation with glucuronic acid and sulfate compounds prior to excretion in urine (Grond et al., 2004).

The formation of the active metabolite *O*-desmethyl-tramadol (M1) is catalyzed by CYP2D6. The polymorphism of *CYP2D6* gene causes variations in the response to tramadol (Paar et al., 1997). More than 100 allelic variations of *CYP2D6* gene have been identified including whole gene deletions and copying of genes, which result in lacking, impaired, or amplified function (Pharmacogene Variation Consortium, 2022). The corresponding phenotypic variations are categorized as poor, intermediate, normal, and ultrarapid metabolizers according to their enzyme activity (Caudle et al., 2020; Crews et al., 2021). Ultrarapid metabolizers are exposed

to a stronger opioid effect as the serum concentrations of M1 are approximately 40 % higher than those in poor metabolizers. In contrast to ultrarapid metabolizers, poor metabolizers have a higher concentration of the monoaminergic parent compound and are at risk for adverse effects related to the hyperserotonergic state (Hassamal et al., 2018). Based on the frequencies of variant allele haplotypes in a Finnish population, nearly 90 % of Finns are normal metabolizers, 7 % are ultrarapid metabolizers, while only 3 % and 2 % are intermediate or poor metabolizers, respectively (Pietarinen et al., 2016) (Table 5). Concomitant administration of drugs causing inhibition or induction of CYP enzymes may result in a change in the phenotype, and further, an increased risk of adverse effects or a lack of effect.

Table 5. Relationship of CYP2D6 phenotype, activity score, and the predicted frequencies of CYP2D6 phenotypes in a Finnish population of 857 volunteers.

CYP2D6 phenotype	Poor metabolizer	Intermediate metabolizer	Normal metabolizer	Ultrarapid metabolizer
Activity score (AS) range (Crews et al., 2021)	0	0<AS<1.25	1.25≤AS≤2.25	AS>2.25
Frequency in Finns (predicted) (Pietarinen et al., 2016)	2.3 %	2.5 %	87.7 %	7.5 %

2.2.3.3 Adverse effects of tramadol

The most commonly reported adverse effects of tramadol include the typical adverse effects of opioids: dizziness, nausea, vomiting, somnolence, constipation, and seizures (Grond et al., 2004). A rare, but potentially serious adverse drug reaction related to tramadol's inhibition of serotonin re-uptake is the so-called serotonin syndrome. The risk of suffering the serotonin syndrome is increased particularly when tramadol is administered with other serotonergic medications, CYP2D6 inhibitors, or in high doses alone (Hassamal et al., 2018).

An often unrecognized adverse effect of tramadol is the impairment of platelet function. Upon activation, platelets release serotonin, which plays an essential role in hemostasis by amplifying the stimulative effect of adenosine diphosphate, collagen, and thrombin on platelet aggregation (Skop et al., 1996; Li et al., 1997). However, serotonin is not synthesized by platelets but is harvested from plasma by uptake via the serotonin transport proteins (SERT) (Mercado et al., 2010) which are identical to the SERT system found in the CNS (Lesch et al., 1993). It has been shown that tramadol inhibits serotonin re-uptake by platelets both *in vitro* and *ex*

vivo (Barann et al., 2015). Unlike the situation with selective serotonin reuptake inhibitors, there is rather scarce clinical evidence on the association of tramadol use with bleeding risk (Järnbert-Pettersson et al., 2019).

2.3 Warfarin drug interactions

Warfarin is known to have several hundreds of drug interactions (Holbrook et al., 2005; InxBase 2022; Martins et al., 2011). The large number of drug interactions is explained by the complex mechanism of action and pharmacokinetic properties. Most importantly, warfarin drug interactions are recognized as an independent risk factor for warfarin therapy-related adverse drug reactions, *i.e.* bleeding and stroke, which highlight the significance of these interactions (Holbrook et al., 2005). With respect to the pharmacokinetic drug interactions, the clinically most significant are those affecting warfarin metabolism (Benet et al. 2002; Greenblatt et al. 2005). The concomitant use of drugs inhibiting the CYP2C9 enzyme prevents the inactivating metabolism of *S*-warfarin. This inhibition leads to increased warfarin plasma concentrations and an enhanced intensity of anticoagulation (See Chapter 2.1.1.2). Enzyme inhibition is possible after a single dose, whereas the induction of CYP2C9 enzyme requires repeated dosing of inducing drugs, and the effect is seen after a delay of days to weeks (Hakkola et al., 2020; Pelkonen et al., 2008). Similarly, the inhibition of CYP3A4 and CYP1A2 activity results in the blockade of *R*-warfarin's metabolism. Although *R*-warfarin is the less potent of the two enantiomers, its increased concentration may intensify the anticoagulant effect so that it becomes clinically significant due to its long half-life (Kaminsky et al., 1997). However, the drug interactions occurring in the metabolic phase can be detected and controlled by close INR monitoring and dose adjustments.

The pharmacodynamic drug interactions of warfarin are mediated by various mechanisms affecting hemostasis and bleeding risk. For instance, selective serotonin re-uptake inhibitors and tramadol impair platelet function by causing a depletion of serotonin in platelets (See Chapter 2.2.3.3). Analgesic drugs, not onlythe NSAIDs, but in particular ASA, impair platelet aggregation by inhibiting the synthesis of TXA_2, whereas platelet aggregation inhibitors block the receptors involved in adhesion (See Chapter 2.2.1.3.2). Moreover, as stated above, NSAIDs can cause an ulceration of the gastric mucosa by direct toxicity and by weakening the defensive barrier thereby increasing the risk for gastrointestinal bleeding (See Chapter 2.2.1.3.1). Antibiotics may affect the synthesis of vitamin K via gut microbiota or interfere with the vitamin K cycle thus reducing the synthesis of vitamin K dependent coagulation factors (See Chapter 2.1.1.1). Contrary to pharmacokinetic interactions, pharmacodynamic drug interactions do not affect the INR value apart from some exceptions affecting vitamin K metabolism.

Some warfarin drug interactions include both types of interaction mechanisms. For example, some NSAIDs cause a pharmacokinetic interaction by inhibiting the CYP2C9 enzyme and a pharmacodynamic interaction by impairing platelet function and causing gastric erosion (See Chapter 2.3.1). Therefore, the clinical effect of some warfarin drug interactions may be challenging to predict and control.

2.3.1 Warfarin-NSAID drug interactions

The mechanism of warfarin and NSAID drug interactions is fundamentally pharmacodynamic. NSAIDs increase the risk of bleeding by impairing platelet aggregation, inhibiting the synthesis of gastroprotective prostaglandins and via their direct cytotoxic effects on GI mucosa (See Chapters 2.2.1.3.2 and 2.2.1.3.1) whereas warfarin affects the synthesis of coagulation factors (See Chapter 2.1.1.1). Coxibs were developed to provide a better GI safety profile over non-selective NSAIDs (Goldstein et al., 2001; Scheiman et al., 2004). However, some investigators have suggested that this benefit may well be lost when these drugs are combined with warfarin (Battistella et al., 2005; Delaney et al., 2007; Villa Zapata et al., 2020; Wang et al., 2021) although conflicting results have also been reported (Boyce et al., 2018; Cheetham et al., 2009; Chung et al., 2005).

In addition to the above pharmacodynamic interaction mechanisms, a pharmacokinetic component may also play a role in the interaction. Several NSAIDs, such as ibuprofen, naproxen, diclofenac, meloxicam, and celecoxib, are metabolized by CYP2C9, and this shared metabolic pathway with warfarin may affect drug exposure especially in *CYP2C9* variant allele carriers with decreased or missing enzyme function (Theken et al., 2020). The clinical significance of *CYP2C9* polymorphism in the pharmacokinetic interaction has been studied between other coumarin anticoagulants and NSAIDs (Beinema et al., 2007; Van Dijk et al., 2004; Visser et al., 2005) but its significance in the case of warfarin remains largely unknown (Malhi et al., 2004). Both warfarin and NSAIDs are highly protein binding drugs, but the clinical relevance of protein binding displacement is considered to have been overstated (Benet et al., 2002; Sands et al., 2002).

2.3.2 Warfarin-paracetamol drug interactions

Paracetamol is recommended as the first-line pain medication in patients on warfarin for its low interaction potential and better GI safety profile compared to NSAIDs (Pain: Current Care Guidelines, 2017). However, several case reports and prospective studies have been published revealing that increased INR values are associated with the concomitant use of paracetamol, suggesting that an interaction between warfarin and paracetamol does exist (Fitzmaurice et al., 1997; Hylek et al.,

1998; Kwan et al., 1999; Andrews, 2002; Gebauer et al., 2003; Mahé et al., 2005; Mahé et al., 2006; Dharmarajan et al., 2007; Parra et al., 2007).

Despite the numerous reports for a warfarin-paracetamol interaction, the mechanism to account for the interaction is not fully understood. Initially, a pharmacokinetic interaction mechanism between *R*-warfarin and paracetamol was suggested (Lehmann, 2000), but this hypothesis was abandoned when it was discovered that a paracetamol overdose resulted in decreased coagulation factor levels in the absence of a liver injury (Whyte et al., 2000).

Further investigations demonstrated that the toxic metabolite of paracetamol, NAPQI, inhibits both GGCX and VKOR activities *in vitro* (Thijssen et al., 2004). This mechanism is supported by *in vivo* data from randomized placebo-controlled studies, in which paracetamol exposure in daily doses of 2 to 4 g per day increased the INR value, whereas the plasma concentrations of vitamin K dependent coagulation factors were decreased (Mahé et al., 2006; Parra et al., 2007; Zhang et al., 2011).

Paracetamol has also been suggested to impair platelet function. In an *in vitro* study, paracetamol inhibited platelet COX-1, and when administered to healthy volunteers, it displayed a dose-dependent anti-aggregatory property (Munsterhjelm et al., 2005). The effect was synergistically increased in combination with diclofenac, a non-selective NSAID (Munsterhjelm et al., 2005) but as expected, not with the coxibs (Munsterhjelm et al., 2006). In contrast, paracetamol administration had no effect on platelet adhesion and aggregation properties in warfarinized patients (Mahé et al., 2006).

The clinical significance of the warfarin-paracetamol interaction remains ambiguous. Although the enhancement of anticoagulation has been noted in small randomized controlled trials (Mahé et al., 2005; Mahé et al., 2006; Parra et al., 2007) and in a meta-analysis (Caldeira et al., 2015) data on the effect of interaction on bleeding risk is limited (Launiainen et al., 2010; Shalansky et al., 2007). The magnitude of the INR elevation observed because of concomitant use may not cause a significant increase in bleeding risk. Evidently, a clarification of the effect of paracetamol on platelet function will require further investigation. However, concomitant paracetamol administration at large doses may be sufficient to precipitate overanticoagulation and bleeding in individual patients with other concomitant bleeding risk factors or drug-induced impairment of hemostasis.

2.3.3 Warfarin-tramadol drug interaction

The interaction between warfarin and tramadol was initially observed after several case reports described elevated INR values and signs of bleeding in warfarinized patients receiving tramadol therapy (Dumo et al., 2006; Juel et al., 2013; Sabbe et

al., 1998; Scher et al., 1997; Veltri et al., 2019). Furthermore, a case-control study demonstrated a 3-fold elevated risk (OR 3.1; 95 % CI 1.7–5.4) for hospitalization because of excessive anticoagulation in warfarin users with concomitant tramadol use (Pottegård et al., 2013).

Although the exact interaction mechanism for warfarin-tramadol interaction remains to be fully elucidated, both pharmacokinetic and pharmacodynamic mechanisms have been proposed. The pharmacokinetic interaction most likely originates from the CYP3A4-mediated metabolism of both *R*-warfarin and (±)-tramadol (See Chapters 2.1.1.2 and 2.2.3.1). It has been postulated that the interaction would be attributed to the *CYP2D6* genotype and affect particularly *CYP2D6* variant allele carriers with defective enzyme function. In these patients, the metabolism of tramadol would be shunted to CYP3A4, which would then impair the metabolism of *R*-warfarin. Although *R*-warfarin is less potent than *S*-warfarin, it has a longer half-life, contributing up to 30–40 % of warfarin's effect. Thus, the potential competitive inhibition of CYP3A4 may result in an intensified anticoagulation (Hedenmalm et al., 2004; Subrahmanyam et al., 2001). The pharmacodynamic interaction mechanism involves the inhibition of serotonin reuptake in platelets and the resulting impairment of platelet function (See Chapter 2.2.3.3). However, although the interaction mechanism between warfarin and tramadol can be extrapolated from the better known evidence of the SSRI-warfarin interaction (Dalton et al., 2006; Wallerstedt et al., 2009), more comprehensive research should be conducted to verify the potential pharmacodynamic interaction and the exact mechanism behind the pharmacokinetic interaction.

2.4 Population-based studies on potential pain medication drug interactions in warfarin users

There are rather limited numbers of population-based studies investigating the use of potentially interacting pain medications in warfarin users (Table 6a–c). Only a few studies have investigated the frequency of co-prescribing of paracetamol or tramadol. Although the reported frequencies are of similar magnitude, 13–19 % for paracetamol and 5–7 % for tramadol, the low number of studies and the wide variation in exposure definitions complicate any comparison of the results and evaluating the extent of co-prescribing.

Previous research has tended to focus on the co-prescribing of NSAIDs or more specifically coxibs, in warfarin users. The reported frequencies, however, show extensive variation between studies, 3–22 % for NSAIDs and 2–13 % for coxibs (Table 6a), partly due to the diversity in definitions of exposure and users. In fact, these values may underestimate the current situation as the data in most of the studies were extracted more than a decade ago, and during the time that has elapsed, the use

of both warfarin and the studied pain medications has changed substantially (See Chapters 2.1.2 and 2.2).

The clinical consequences *e.g.* increased risk of bleeding, have attracted even less attention in the present literature. Concerning paracetamol and tramadol, only one study of each has been published describing the increased risk of bleeding associated with concomitant warfarin use (Gasse et al., 2005; Vitry et al., 2011) (Table 6b–c). With respect to the NSAIDs and in some cases only the coxibs, the clinical consequences have been reported in only a few cohort (Cheetham et al., 2009; Olsen et al., 2020; Vitry et al., 2011) and case-control (Battistella et al., 2005; Delaney et al., 2007; Suh et al., 2012) studies - and with conflicting results (Table 6a). Based on the existing literature, the current picture of both the frequency and clinical consequences of co-prescribing pain medications in warfarin users in real-life settings remains ambiguous.

Table 6a. Population-based studies on the frequency of co-prescribing NSAIDs or coxibs and/or associated risk of bleeding in warfarin users.

Study (published) **Design** **Data source**	**Population** **Study period**	**Definition of warfarin exposure**	**a. Definition of interaction exposure** **b. Outcome or case definition (where applicable)** **c. Frequency of co-prescribing** **d. Incidence and/or relative risk of bleeding compared to warfarin only**
Wittkowsky et al. (2004) Cohort study Pharmacy claims database, US	Warfarin users *n*=134,833 Jun 1, 1998–May 31, 1999	≥1 purchase of warfarin	a. Purchase of an interacting drug during warfarin exposure c. Celecoxib 9.3 %, rofecoxib 6.1 %, ibuprofen 1.6 %, diclofenac 1.5 %, naproxen 1.3 %, indomethacin 1.0 %, ketorolac 1.0 %, sulindac, piroxicam, ketoprofen <1.0 %
Battistella et al. (2005) Nested case-control study Ontario Drug Benefit Program, Canada and Canadian Institute for Health Information Discharge Abstract Database, Canada	Warfarin users ≥66 years old *n*(warfarin users) = 98,821 *n*(cases)= 361 *n*(controls)= 1,437 Apr 1, 2000–March 31, 2001	≥1 purchase of warfarin. Exposure deemed discontinued if the time between purchases >120 days. Follow-up 90 days after the last purchase.	a. Purchase of any NSAID or coxib in the 90 days prior to index day b. Hospitalization due to UGIB d. NSAID+warfarin OR 1.9 (95 % CI 1.4–3.7), celecoxib+warfarin OR 1.7 (95 % CI 1.2–3.6), rofecoxib+ warfarin OR 1.9 (95 % CI 1.7–3.6)
Gasse et al. (2005) Cohort study and nested case-control study General Practice Research Database, UK	New warfarin users 40–84 years old *n*=4,152 Jan 1991–Apr 2004	≥1 purchase of warfarin. A fixed 90 days' duration of exposure. Exposure deemed discontinued if the time between purchases >90 days.	a. Purchase of an interacting drug during warfarin exposure. The duration of interaction: number of tablets divided by prescribed daily dose. b. Idiopathic bleeding event during continuous warfarin exposure resulting in hospitalization within 30 days or death within 7 days c. Not reported for cohort patients d. None of non-aspirin NSAIDs episodes involved bleeding events

Study (published) **Design** **Data source**	**Population** **Study period**	**Definition of warfarin exposure**	**a. Definition of interaction exposure** **b. Outcome or case definition (where applicable)** **c. Frequency of co-prescribing** **d. Incidence and/or relative risk of bleeding compared to warfarin only**
Delaney et al. (2007) Case-control study General Practice Research Database, UK	Warfarin users ≥18 years old *n*(cases)=4,028 *n*(controls)=40,171 Jan 1, 2000–Dec 31, 2005	Purchase of warfarin within 90 days before index date	a. Purchase of an interacting drug within 90 days before index date b. The 1st ever GI bleed d. NSAID+warfarin RR 4.79 (95 % CI 2.79–8.21), coxib+warfarin RR 4.62 (95 % CI 1.48–14.43)
Snaith et al. (2008) Cohort study Prescribing data of 321 primary care practices in Scotland, UK	Warfarin users *n*=17,861 Apr 1, 2005–Mar 31, 2006	The time between the first purchase of warfarin and 1 month following the last purchase of warfarin	a. Purchase of an interacting drug during warfarin exposure ('One-off interaction'). 'Repeat interaction' included interacting drugs purchased after warfarin initiation. c. 'One-Off interaction': NSAIDs 5.3 %, coxibs 1.8 %. 'Repeat interaction': NSAIDs 21.0 % and coxibs 2.4 %
Håkonsen et al. (2009) Cohort study Norwegian prescription register, Norway	Warfarin users *n*=103,737 Jan, 1 2004–Dec 31, 2006	The time between the first and last purchases of warfarin during each study year	a. Purchase of NSAID between the first and last purchases of warfarin c. NSAIDs 22.9 % (2004); 17.4 % (2005); 16.0 % (2006) of warfarin users with ≥2 purchases per year
Cheetham et al. (2009) Cohort study Kaiser Permanente Southern California, USA	New warfarin users ≥18 years old *n*=35,548 Jan 1, 2000–Dec 31, 2005	≥ 1 purchase of warfarin. Exposure determined on a daily basis according to instructions of use, amount of tablets dispensed, and days' supply listed in the pharmacy database. Exposure deemed discontinued if the time between purchases >183 days.	a. Exposure to NSAIDs determined on a daily basis according to instructions of use, amount of tablets dispensed, and days' supply listed in the pharmacy database b. GI bleed resulting in hospitalisation c. NSAIDs 17.7 %, coxibs 3.5 % of warfarin courses d. NSAID+warfarin HR 3.58 (95 % CI 2.31–5.55), coxib+warfarin HR 1.71 (95 % CI 0.60–4.84), NSAID+warfarin vs. coxib+warfarin HR 3.69 (95 % CI 1.42–9.60)

Study (published) Design Data source	Population Study period	Definition of warfarin exposure	a. Definition of interaction exposure b. Outcome or case definition (where applicable) c. Frequency of co-prescribing d. Incidence and/or relative risk of bleeding compared to warfarin only
Vitry et al. (2011) Cohort study Australian Department of Veterans' Affairs administrative claims database, Australia	New warfarin users ≥ 65 years old *n*=17,661 Jul 1, 2002–Jun 30, 2006	≥ 1 purchase of warfarin. A fixed 42 days' duration of exposure. Exposure deemed discontinued if the time between purchases > 2 times the duration of exposure.	a. Purchase of an interacting drug yielding overlapping exposure period with warfarin. b. Bleeding-related hospital admission c. NSAIDs 32.2 per 100 person-years, celecoxib 12. per 100 person-years d. NSAIDs: RR 1.19 (95 % CI 0.90–1.59), celecoxib: RR 1.07 (95 % CI 0.69–1.68)
Gavronski et al. (2012) Cohort study Estonian Health Insurance Fund, Estonia	Warfarin users ≥50 years *n*=7,175 Jan 1 – Jun 30, 2008	≥ 1 purchase of warfarin. The duration of exposure defined by the number of DDDs.	a. Purchase of an interacting drug yielding ≥7 days overlapping exposure period with warfarin. The duration of exposure defined by the number of DDDs. c. NSAIDs 14% of warfarin users
Suh et al. (2012) Nested case-control study MedStat MarketScan, US	New warfarin users with AF and ≥18 years old *n*(warfarin users) =7,971 *n*(cases)= 744 *n*(controls)= 2,484 Jan 1, 2005–Jun 30, 2008	≥ 1 purchase of warfarin within 6 months after the initial warfarin purchase	a. Purchase of an interacting drug with ≥ 1 day's overlapping supply with warfarin during the 30-day period before the bleeding event b. Bleeding event (ICH, GIB, other) d. Analgesic+warfarin: OR 1.33 (95 % CI 1.07–2.24) (the class of analgesics in American Hospital Formulary Service Drug Information database)
Lindh et al. (2014) Cohort study Swedish Prescribed Drug Register, Sweden	Warfarin users ≥18 years old *n*=143,729 Aug 15–Dec 15, 2011	≥ 1 purchase of warfarin	a. Purchase of NSAID (incl. coxibs) during the study period c. NSAIDs 3.0% of warfarin users

Study (published) **Design** **Data source**	**Population** **Study period**	**Definition of warfarin exposure**	**a. Definition of interaction exposure** **b. Outcome or case definition (where applicable)** **c. Frequency of co-prescribing** **d. Incidence and/or relative risk of bleeding compared to warfarin only**
Taipale et al. (2015) Cohort study MEDALZ-2005 cohort, Finnish Prescription register, Finland	Warfarin users *n*=3,385 with AD *n*=4,830 without AD Jan 1, 2006–Dec 31, 2009	≥2 purchases of warfarin and continuous use of ≥60 days	a. NSAID (incl. coxibs) exposure period constructed by modelling register data on reimbursed purchases. Concomitant use was defined as ≥30 days of overlapping exposure period with warfarin. c. NSAIDs 12.2 % of warfarin users without AD and 10.3 % of warfarin users with AD
Ilomäki et al. (2015) Cohort study and case-crossover analysis Finnish Prescription Register, Finland	New warfarin users *n*=54,025 Jan 1, 2012–Sept 30, 2013	≥ 1 purchase of warfarin	a. Purchase of NSAID (incl. coxibs) within 3 months' follow-up period c. NSAIDs 2.6 % of warfarin users
Olsen et al. (2020) Cohort study The National Prescription Registry, The Danish National Patient Registry, Denmark	New warfarin users with AF and 39–95 years old Co-prescribing: *n*=21,753 Aug 22, 2011–Jun 30, 2017 Bleeding risk: *n*=16,722 Jan 1, 2012–Dec 31, 2015	≥ 1 purchase of warfarin	a. The exposure to NSAIDs (incl. coxibs) defined by dividing the number of dispensed tablets by the estimated dose. Concomitant use was defined as the time during which patients had both medications available. b. GI bleed resulting in hospitalisation c. NSAIDs 18.3–21.2 % (2011–2017) of warfarin users d. NSAID+warfarin HR 1.95 (95 % CI 1.21–2.69)

AD, Alzheimer's disease; AF, atrial fibrillation, DDD, defined daily dose; GIB, gastrointestinal bleeding; HR, hazard ratio; ICH, intracranial hemorrhage; IR incidence ratio; NSAID, non-steroidal anti-inflammatory drug; OR, odds ratio; PY, patient-years; RR, rate ratio; UGIB, upper gastrointestinal bleeding.

Table 6b. Population-based studies on the frequency of co-prescribing of paracetamol and/or associated risk of bleeding in warfarin users.

Study (published) **Design** **Data source**	**Population** **Study period**	**Definition of warfarin exposure**	**a. Definition of interaction exposure** **b. Outcome or case definition (where applicable)** **c. Frequency of co-prescribing** **d. Incidence and/or relative risk of bleeding compared to warfarin only**
Wittkowsky et al. (2004) Cohort study Pharmacy claims database, US	Warfarin users *n*=134,833 Jun 1, 1998–May 31, 1999	≥ 1 purchase of warfarin	a. Purchase of an interacting drug during warfarin exposure c. 18.52 % of warfarin users
Gasse et al. (2005) Cohort study and nested case-control study General Practice Research Database, UK	New warfarin user 40–84 years old *n*=4,152 Jan 1991–Apr 2004	≥1 purchase of warfarin. A fixed 90 days' duration of exposure. Exposure deemed discontinued if the time between purchases >90 days.	a. Purchase of an interacting drug during warfarin exposure. The duration of interaction: number of tablets divided by prescribed daily dose b. Idiopathic bleeding event during continuous warfarin exposure c. Not reported for cohort patients d. IR 3.8 per 100 patient-years at risk
Håkonsen et al. (2009) Cohort study Norwegian prescription register, Norway	Warfarin users *n*=103,737 Jan 1, 2004–Dec 31, 2006	The time between the first and last purchases of warfarin during each study year	a. Purchase of paracetamol between the first and last purchases of warfarin c. 12.6 % (2004), 14.5 % (2005), and 15.9 % (2006) of warfarin users with ≥2 purchases of warfarin per year
Ilomäki et al. (2015) Cohort study and case-crossover analysis Finnish Prescription Register, Finland	New warfarin users *n*=54,025 Jan 1, 2012–Sept 30, 2013	≥ 1 purchase of warfarin	a. Purchase of paracetamol within 3 months' follow-up period c. 34.2% of warfarin users

IR, incidence rate.

Table 6c. Population-based studies on of co-prescribing tramadol and/or associated risk of bleeding in warfarin users.

Study (published) **Design** **Data source**	**Population** **Study period**	**Definition of warfarin exposure**	**a. Definition of interaction exposure** **b. Outcome or case definition (where applicable)** **c. Frequency of co-prescribing** **d. Incidence and/or relative risk of bleeding compared to warfarin only**
Håkonsen et al. (2009) Cohort study Norwegian prescription register, Norway	Warfarin users *n*=103,737 Jan 1, 2004–Dec 31, 2006	≥ 1 purchase of warfarin during each study year	a. Purchase of tramadol between the first and last purchases warfarin c. 4.7 % (2004), 5.1 % (2005), and 6.0 % (2006) of warfarin users with ≥2 purchases of warfarin per year
Vitry et al. (2011) Cohort study Australian Department of Veterans' Affairs administrative claims database, Australia	New warfarin users ≥65 years old *n*=17,661 Jul 1, 2002–Jun 30, 2006	≥ 1 purchase of warfarin. A fixed 42 days' duration of exposure. Exposure deemed discontinued if the time between purchases > 2 times the duration of exposure.	a. Purchase of tramadol drug yielding overlapping exposure period with warfarin. b. Bleeding-related hospital admission c. 16.6 per 100 person-years d. IR 9.4 per 100 person-years (3.7–23.6), RR 2.37 (95 % CI 0.93–6.01) compared to warfarin only
Lindh et al. (2014) Cohort study Swedish Prescribed Drug Register, Sweden	Warfarin users ≥18 years old *n*=143,729 Aug 15,–Dec 15, 2011	≥ 1 purchase of warfarin	a. Dispensing of tramadol in combination with warfarin, the exact definition not described c. 4.6 % of warfarin users
Taipale et al. (2015) Cohort study MEDALZ-2005 cohort, Finnish Prescription register, Finland	Warfarin users *n*=3,385 with AD *n*=4,830 without AD Jan 1, 2006–Dec 31 2009	≥2 purchases of warfarin and continuous use of ≥60 days	a. Tramadol exposure period constructed by modelling register data on reimbursed purchases. Concomitant use was defined as ≥30 days of overlapping exposure period with warfarin c. 7.0 % of warfarin users without AD and 3.4 % of warfarin users with AD

Study (published) Design Data source	Population Study period	Definition of warfarin exposure	a. Definition of interaction exposure b. Outcome or case definition (where applicable) c. Frequency of co-prescribing d. Incidence and/or relative risk of bleeding compared to warfarin only
Ilomäki et al. (2015) Cohort study and case-crossover analysis Finnish Prescription register, Finland	New warfarin users *n*=54,025 Jan 1, 2012–Sept 30, 2013	≥ 1 purchase of warfarin	a. Purchase of tramadol within 3 months' follow-up period c. 3.0 % of warfarin users

AD, Alzheimer's disease; IR, incidence rate; RR, rate ratio.

3 Aims

Warfarin and pain medications are commonly used drugs especially in aged individuals. Successful oral anticoagulation therapy is effective in preventing morbidity and mortality whereas adequate pain treatment improves several aspects of the quality of life in older people. However, the adverse effects of warfarin and various pain medications are overlapping, and their concomitant use is associated with an increased risk of bleeding when compared to the use of warfarin or pain medications on their own. This study seeks to depict the scale and consequences of their co-prescribing in real-life settings.

The specific aims of the study were as follows:

1. To determine the frequency of co-prescribing of potentially interacting pain medications among warfarin users in outpatient and inpatient settings. (Studies I and II)
2. To investigate the clinical consequences of co-administration of potentially interacting pain medications among warfarin users in inpatient setting. (Study II)
3. To examine the effect of warfarin initiation on the use of a potentially interacting pain medication in outpatients and among frail and non-frail inpatients. (Studies I and III)

4 Materials and Methods

4.1 Data sources

This thesis is based on original studies in which clinical and administrative databases were utilized. These databases and other data sources are described in detail below.

4.1.1 Finnish Prescription register (Study I)

The Prescription register was established in 1994 by the Social Insurance Institution for administrative purposes. It is a nationwide register containing data on reimbursed prescription drug purchases from all Finnish pharmacies. At the time of the study, the recorded data for each purchase contained information on each patient, such as age, gender, and unique person identification number, and on each drug, for example, Anatomical Therapeutic Chemical (ATC) code, pharmaceutical form, strength and package size, the number of dispensed packages, the amount of drug in defined daily doses (DDD), and the dispensing date. However, no structured information was recorded on the prescribed dose, duration of therapy or indication.

The Prescription Register does not include data on drug use in hospitals and public care facilities where drugs are supplied by the service provider. Drugs purchased over-the-counter and non-reimbursable drugs are not registered (Furu et al., 2010; Klaukka, 2001).

4.1.2 Turku University Hospital registers (Study II)

The complete medication information of all patients has been recorded into an electronic medication register in Turku University Hospital since the beginning of 1996 including the wards investigated in Study II. At the time of the study, the register contained individual level data on past and current medication use during hospital admissions and outpatient visits. The data input was performed by physicians and nurses as a part of the routine medical care. Data on drug use could be searched from the database using ATC classification codes. In Study II, the search result included the personal identification number, which enabled identification of

individual patients and made it possible to have linkage to other databases. No other medication record programs were used over the study period.

Similar to the recording of medication information, the results of laboratory tests have been stored in a laboratory database since 1994. Test specific codes could be used to search test results from the database. Data on discharge diagnoses and the dates of admission and discharge at an individual level were collected into a diagnosis register for administrative purposes. The 10th version of International Classification of Diseases (ICD-10) has been utilized in recording data on diagnosis since 1996.

4.1.3 Royal Adelaide Hospital medical records and patient interviews (Study III)

The medical records of Royal Adelaide Hospital (Adelaide, South Australia, Australia) used in routine clinical care were reviewed in order to collect patient data in Study III. The clinical data on patient characteristics and comorbidities were collected from case notes, and the data on home medication (*e.g.* at admission and warfarin initiation) and discharge medications from the medication charts and discharge letters. These data were utilized to calculate bleeding and stroke risk scores and Charlson comorbidity scores (Charlson et al., 1987) (See Appendices 4 and 5).

Patients were interviewed to verify that they had no previous warfarin use as well as to collect information on their alcohol consumption in order to estimate the bleeding risk scores, with their frailty status being determined using the Reported Edmonton Frail Scale (See Chapter 4.2.2).

4.2 Study populations

In all three studies, the study populations consisted of warfarin users. The details of the study populations in the individual studies are described in Table 7.

In Study I, two populations of warfarin initiators and users were formed utilizing Prescription Register data (See Chapter 4.1.1) and using warfarin ATC code (B01AA03) as the search criteria (See Appendix 1). The search identified 204,616 outpatients, who had ≥1 reimbursed warfarin purchase between January 1, 2006 and December 31, 2010. The population of warfarin initiators consisted of 110,290 persons who had their first warfarin purchase between January 1, 2007 and September 30, 2010, and had made no warfarin purchases in the preceding 365 days. The population of warfarin users consisted of 148,536 persons who had at least one warfarin purchase in 2010 including both warfarin initiators and users.

In Study II, a population of warfarin users was formed utilizing the Turku University Hospital medication register data (See Chapter 4.1.2) and the warfarin

ATC code as the the search criteria. The search identified 6,772 patients who had been administered warfarin in 8,615 treatment periods between July 1, 1996 and December 31, 2004.

In Study III, a population of warfarin initiators was formed by recruiting previously warfarin-naïve inpatients aged ≥60 years who were commenced on warfarin for any indication within 14 days of their recruitment. The 151 study participants were further categorised into frail and non-frail individuals according to their frailty status (See Chapter 4.3.5).

Table 7. The study populations, data sources, study periods, and inclusion and exclusion criteria utilized in individual studies.

Study	Participants, *n*	Setting	Data source	Enrollment period	Inclusion criteria	Exclusion criteria
I	Warfarin users, *n*=148,536 Warfarin initiators, *n*= 110,290	Outpatient	Finnish Prescription register	Jan 1 to Dec 31, 2010 Jan 1, 2007 to Sep 30, 2010	≥1 warfarin purchase in 2010 ≥1 warfarin purchase over the enrollment period	N/A Warfarin purchase within 365 days
II	Warfarin users, *n*=6,772 Warfarin treatment periods, *n*=8,615	Inpatient	Turku University Hospital registers on medication, laboratory results, and diagnoses	Jul 1, 1996 to Dec 31, 2004	Treated on the study wards over the enrollment period	N/A
III	Warfarin initiators, *n*=151	Inpatient	Royal Adelaide Hospital medical records Patient interviews	Oct 1, 2012 to Sep 30, 2013	Warfarin initiation for any indication within 14 days of recruitment Age ≥60 years old	Previous warfarin use

4.3 Measures

4.3.1 Warfarin exposure

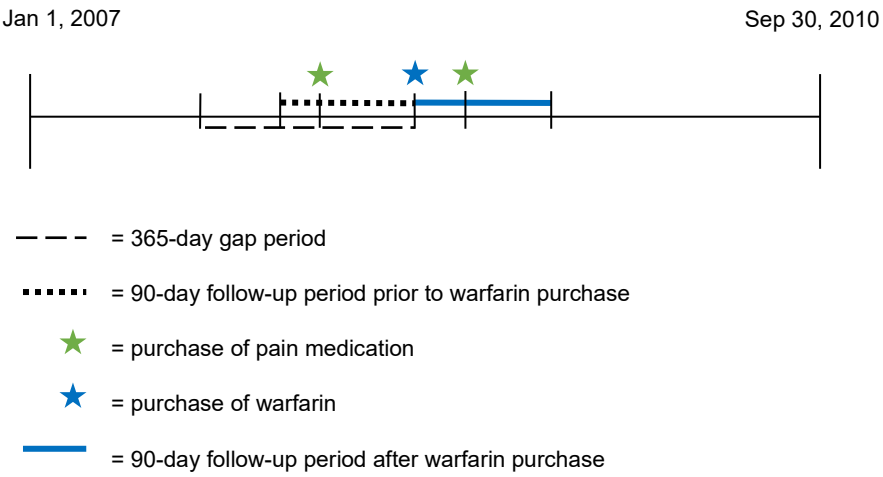
Exposure to warfarin was defined differently in all three studies due to the diverse settings and data sources in each work (Figure 5).

In Study I, warfarin exposure was based on the records of reimbursed warfarin purchases. In the initiator population, warfarin exposure was defined as a fixed 90 days period beginning from the day of warfarin purchase as drugs are reimbursed at a maximum for a 3 months' supply per single transaction. In the warfarin user population, warfarin exposure was defined as a fixed 180 days period starting from the day of warfarin purchase. Warfarin exposure was considered finished if the time between consecutive purchases exceeded 180 days, consistent with the definition used by Gomes and colleagues (Gomes et al., 2013), or in the case of long-term institutionalization, death or the end of the follow-up period in 31 December 2010, which ever occurred first.

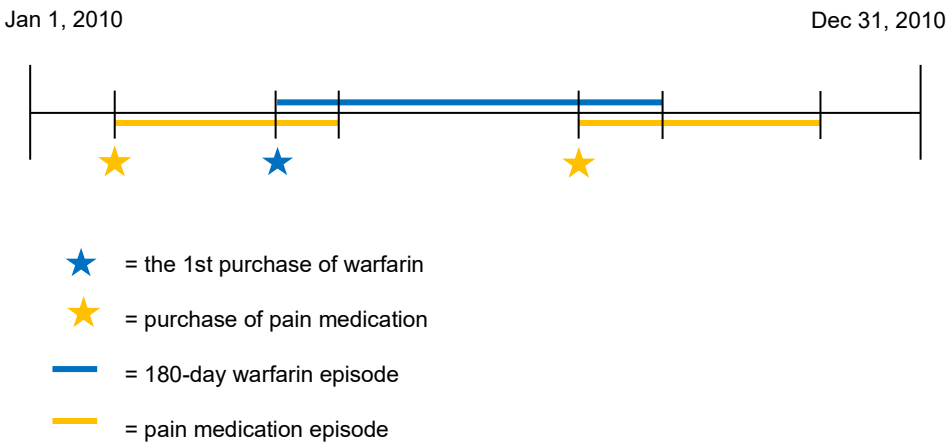
In Study II, warfarin exposure was ascertained by manually reviewing the extracted medication register data. The duration of warfarin exposure was defined utilizing recorded initiation and termination dates of warfarin therapy.

In Study III, warfarin exposure was ascertained by reviewing the patient files and medication charts. Patients were followed from the date of warfarin initiation until the date of discharge from the hospital.

Study I, warfarin initiators



Study I, warfarin users



Study II, warfarin users

= admission

= discharge

= warfarin therapy

= initiation of pain medication

= pain medication episode

Study III, warfarin initiators

= admission, review of home medication

= discharge, review of discharge medication

= initiation of warfarin therapy

= warfarin therapy

= ending of pain medication

= pain medication episode

= initiation of pain medication

Figure 5. Schematic illustrations of warfarin and pain medication exposures in the study populations of Studies I–III.

4.3.2 Selection of and exposure to interacting drugs

The potentially interacting pain medications were selected on the basis of literature and database searches. In Study I, potentially interacting pain medications were searched from the INXBASE® drug-drug interaction database (previously SFINX®) (version March 2014) (Böttiger et al., 2009). Systemically administered pain medications classified as 'to be avoided' and 'special consideration required' *e.g.* possessing the potential for a clinically significant interaction with warfarin were chosen. This list of interacting drugs was updated (version June 2015) and utilized in Study III. In Study II, the interacting drugs were selected on the basis of literature search in the MEDLINE database and the Stockley's Drug Interactions textbook (Stockley, 2002).

In Study I, among warfarin users, exposure to pain medication was defined by the duration of the prescription, which was calculated by dividing the quantity of drug purchased by defined daily dose (DDD). DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults (WHO Collaborating Centre for Drug Statistics Methodology). To allow for non-adherence, the duration of each pain medication prescription was multiplied by 1.5. The exposure was considered continuous if the next prescription was filled within the duration of preceding prescription. At least a 1-day overlap of warfarin and interacting drug prescriptions was considered as an exposure to a drug interaction independent of which of the drugs was prescribed first (Figure 5). Among warfarin initiators, the exposure to the drug interaction was defined as a purchase of a potentially interacting pain medication within the 90-day follow-up period.

In Study II, co-administration of warfarin and pain medication of at least 7 days was regarded as an exposure to an interaction. The duration of the interaction was defined by manually reviewing the medication register data and utilizing recorded initiation and termination dates of drug therapy (Figure 5).

In Study III, the exposure to interacting medication was reviewed at two time points: prior to hospitalization, *e.g*. home medication, when warfarin therapy had not yet been commenced, and at the discharge, when warfarin therapy had been initiated (Figure 5).

4.3.3 Laboratory data and risk scores

Laboratory data were collected in Study II in order to detect anemia as an indicator of subclinical or clinical bleeding and to describe the intensity of anticoagulation effect. Mean hemoglobin (Hb), hematocrit (HCT), erythrocyte count, mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), and thrombocyte count were selected as they are utilized in the clinical diagnostics of anemia. INR value was chosen to describe the anticoagulation effect of warfarin (See

Chapter 2.1.1.3). All laboratory tests were performed in the central laboratory of Turku University Hospital according to laboratory standards. The results were considered as outcome variables and reviewed from the day two after the initiation of interacting medication or warfarin only until day five after the end of the interacting medication or warfarin only. In cases where the first and the last day of the medication were unavailable, laboratory data was collected over the whole study period. In cases where there were multiple laboratory results over a treatment period, an average was calculated for further statistical analysis. In addition, the lowest hemoglobin (Min Hb) values were recorded for each treatment period.

The bleeding and stroke risk scores and Charlson comorbidity score were calculated for the participants in Study III. The characteristics (*i.e.* age and gender) and comorbidities included in the scores (See Appendices 4 and 5) were collected by reviewing case notes at the time of recruitment. Instead of searching for specific diagnosis codes, the past medical history was reviewed for text referring to a diagnosis as these information is used also when various risk scores are calculated in routine clinical practice. The HASBLED score was calculated without scoring 'Labile INR values' and HEMORR2HAGES without information on CYP2C9 *genotype* as reported by previous studies (Lefebvre et al., 2016; Olesen et al., 2011).

4.3.4 Bleeding diagnoses

The clinical consequences of drug interactions were examined in Study II by reviewing the ICD-10 coded bleeding diagnoses (See Appendix 2) over the period of co-administration of warfarin and potentially interacting pain medication or warfarin only. In order to analyse the anatomical location of bleeding, the diagnoses were divided into four subcategories for further analyses: all (including all searched bleeding diagnoses), intracranial, upper gastrointestinal, and lower gastrointestinal bleeding diagnoses (See Appendix 2).

4.3.5 Frailty

In Study III, the frailty status of each inpatient was assessed at the time of the recruitment according to the version of the Edmonton Frail Scale (See Appendix 3) as modified by Hilmer et al. (Hilmer et al., 2009); this has been utilized in several previous studies (Bennett et al., 2014; Perera et al., 2009; Thai et al., 2015). The Edmonton Frail Scale assesses cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence, and functional performance (Rolfson et al., 2006). It has been validated for the assessment of frailty by non-medically trained researchers. In the utilized version, the previous 'get up and go' test has been substituted with a self-report of function

in the two weeks prior to admission in order to avoid confounding by the effects of acute illness (Hilmer et al., 2009). The utilized Edmonton Frail Scale scores define patients' frailty status as follows: 0–5 not frail, 6–7 apparently vulnerable, 8–9 mild frailty, 10–11 moderately frail, and 12–18 severe frailty. In the analysis, the frailty scale was collapsed into two categories because of the low number of patients in the categories of the highest frailty. Patients with a score of ≥8 were considered frail. A similar merging of categories has been conducted in previous publications (Bennett et al., 2014; Hilmer et al., 2009; Perera et al., 2009; Thai et al., 2015).

4.3.6 Covariates

In Study II, the use of concomitant oral glucocorticoid and proton pump inhibitor (PPI) medication with warfarin therapy was considered as a confounding factor. Data on the use of PPI and oral glucocorticoid medication were searched from the medication database (See Chapter 4.1.2) using selected ATC classification codes (See Appendix 1). The concomitant use of warfarin or warfarin and pain medications was determined by manually reviewing the extracted medication register data and utilizing recorded initiation and termination dates of medication therapies.

4.4 Data analyses

In Study I, warfarin users and initiators were analyzed separately. Among warfarin users, the proportions of those who purchased potentially interacting pain medications during the follow-up period in 2010 were computed. Among warfarin initiators, the proportions of those who purchased potentially interacting pain medications within the 90 days' follow-up period after the initiation of warfarin therapy were calculated. The pain medication purchases were further stratified according to pain medication purchases during the 3-month period preceding warfarin initiation.

In Study II, the proportion of those warfarin treatment periods during which non-selective NSAIDs or coxibs were co-administered and which were linked to a bleeding diagnosis were calculated. The distributions of categorizing variables (sex, concomitant exposure to a proton pump inhibitor or oral glucocorticoid medication) were compared between the treatment periods of study groups using binary logistic regression analysis. The correlation between the treatment periods measured from the same patient was accounted for by using generalized estimation equations. A linear mixed model with patients as a random effect was used for comparing the means of continuous variables (age, laboratory values) between the study groups (Brown et al., 1999). Dunnett's method with controls as a comparison group was used for multiple comparisons (Dunnett, 1955).

The risk for bleeding, the risk of an out-of-target range value for Hb (<117 g/l for women and <134 g/l for men), platelet count (<360x10^9/l), and INR value (>3.0) and the differences in these risks between the study groups were tested with binary logistic regression using generalized estimation equations. Analyses were adjusted for age, sex, study ward, and PPI and oral glucocorticoid medication. The warfarin only group was used as a reference group in the logistic models. The results from logistic models were quantified by using odds ratios (OR) with their 95% confidence intervals (CI).

In Study III, continuous variables were characterized using estimated means and standard errors (SE) derived from the statistical model for normally distributed variables and median and interquartile range (IQR) of values for variables that were not normally distributed. The normality of variables was evaluated visually and tested with the Shapiro-Wilk test. Square root transformation was used when necessary to make variables more normally distributed. The main statistical analyses for risk scores were performed using an analysis of variance (ANOVA) model. Sex, age group, AF, and frailty were included in all models. The McNemar test was used to test the statistical significance of the differences in the use of individual drugs between time points, and Fisher's exact test was applied to evaluate the statistical significance of the differences between the frailty groups. More complicated models were not fitted to data on individual drugs due to the small sample size.

The statistical significance level was set at 0.05 in all tests. Statistical analyses were performed using SAS System for Windows, release 9.1 and 9.4 (SAS Institute Inc., Cary, NC).

4.5 Ethical approvals

The data utilized in Studies I and II was recorded as part of routine administrative processes and clinical practice. In Study I, data obtained from Social Insurance Institution was de-identified. The protocol for Study II was approved by authorities of Turku University Hospital responsible the maintenance of the hospital registers. In Studies I and II, patients were not contacted, and therefore, no legal requirements existed for ethics committee approvals and consent information.

In Study III, the study protocol was approved by the ethical committee of Royal Adelaide Hospital. A consent information was obtained from each participant or their carer or next of kin when appropriate prior to recruitment.

5 Results

5.1 The characteristics of study populations

The characteristics of study populations in Studies I-III are described in Tables 8a–c.

Table 8a. The characteristics of warfarin users and initiators in Study I. Data source: Prescription Register, Social Insurance Institution.

	Warfarin users	Warfarin initiators
Patients, *n*	148,536	110,299
Women, %	46.9	48.3
Mean age (SD)	73.2 (12.3)	69.6 (14.2)

SD, standard deviation.

Table 8b. The characteristics of the groups examined in Study II. Data source: Turku University Hospital medical record database, Finland.

	Warfarin + non-selective NSAIDs	Warfarin + coxibs	Warfarin only
Treatment periods, *n* (% of all 8,615)	1,273 (14.8)	246 (2.9)	3,633 (42.2)
Patients, *n* (% of all 6,772)	1,067 (15.8)	222 (3.3)	3,614 (53.4)
Women, %	61.1*	60.8*	47.0
Mean age, (range)	68* (17–97)	68* (24–92)	66 (14–97)
Treatment periods with concomitant exposure to PPI, (% of treatment periods)	353* (27.7)	104* (42.3)	501 (13.8)
Treatment periods with concomitant exposure to oral glucocorticoids, (% of treatment periods)	552* (43.4)	116* (47.2)	54 (1.5)

* $p<0.001$ compared to warfarin only in binary logistic regression analysis.
NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor.

Table 8c. The characteristics of frail and non-frail patients in Study III. Data source: Royal Adelaide Hospital, South Australia.

	Non-frail	Frail
Patients, *n* (% of all 151)	102 (67.5)	49 (32.5)
Women, *n* (%)	34 (33)	23 (47)
Median age (range)	71 (60–93)	74 (61–96)
60–69 years, *n* (%)	46 (45.1)	15 (30.6)
70–79 years, *n* (%)	37 (36.3)	19 (38.8)
≥ 80 years, *n* (%)	19 (18.6)	15 (30.6)
Charlson comorbidity index, estimated mean (SE)	1.4 (0.1)	2.0 (0.1)**
Risk scores, estimated mean (SE)		
OBRI	1.7 (0.1)	1.9 (0.1)*
ATRIA	7.0 (0.2)	7.0 (0.3)
Hemorr2hages	3.2 (0.1)	3.5 (0.2)
HAS-BLED	3.0 (0.1)	3.4 (0.2)
CHADS2	1.1 (0.1)	1.3 (0.1)
CHA2DS2-VASc	2.0 (0.1)	2.5 (0.2)*

*p<0.05, **p<0.001 compared to non-frail category in ANOVA (See Chapter 4.4 for more details). ATRIA, Anticoagulation and Risk Factors; $CHADS_2$ and CHA_2DS_2-Vasc, Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, Stroke, Vascular disease, Female; HAS-BLED, Hypertension, Abnormal renal function, Abnormal liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs concomitantly, Alcohol concomitantly; Hemorr2hages, Hepatic or renal Disease, Ethanol abuse, Malignancy, Older age (age >75 years), Reduced platelet count or function, Hypertension (uncontrolled), Anemia, Genetic factors, Excessive falls risk, Stroke, Prior bleed; OBRI, Outpatient Bleeding Risk Index; SE, standard error.

5.2 The frequency of co-prescribing potentially interacting pain medications among warfarin users in outpatient and inpatient settings (Studies I and II)

A total of 148,536 outpatients purchased warfarin in 2010 corresponding to 2.8 % of the whole population of Finland in 2010. In the tertiary hospital setting, 6,772 inpatients (6.8 % of all inpatients) were administered with warfarin over a total of 8,615 treatment periods (5.4 % of all treatment periods) over the 8.5 years' study period.

In an outpatient setting, paracetamol was by far the most frequently co-prescribed pain medication being purchased by over 40 % of warfarin users (Table 9). NSAIDs and tramadol were both purchased by nearly 5 % of warfarin users. In the inpatient setting, NSAIDs and coxibs were co-administered to 12.4 % and 2.6 % of inpatients, respectively. Ibuprofen was the most commonly used NSAID in both study populations (Tables 9 and 10a). With respect to the coxibs, etoricoxib was the

most commonly co-prescribed coxib among outpatients (Table 9) and rofecoxib among inpatients (Table 10b).

Table 9. The proportion of warfarin users who were co-prescribed with an interacting pain medication of all warfarin users (n=148,536) in an outpatient setting in Finland in 2010. Data source: Prescription Register, Social Insurance Institution.

Non-selective NSAIDs	***n* (%)**	**Coxibs**	***n* (%)**	**Others**	***n* (%)**
Ibuprofen	3,487 (2.4)	Etoricoxib	3,273 (2.2)	Paracetamol	61,958 (41.7)
Diclofenac	1,405 (1.0)			Tramadol	6,648 (4.5)
Naproxen	808 (0.5)				
Meloxicam	956 (0.6)				

Table 10a. The proportion of warfarin treatment periods with co-prescribed non-selective NSAIDs of all warfarin treatment periods and the proportion of single non-selective NSAID treatment periods of all non-selective NSAID-warfarin treatment periods in warfarin users in an inpatient setting in the time period 1996–2004. Data source: Turku University Hospital medical record database, Finland.

	Number of treatment periods	**The proportion of all warfarin treatment periods (*n*=8,615), %**	**The proportion of non-selective NSAID treatment periods (*n*=1,273), %**
Non-selective NSAIDs	1,273	14.8	100
Ibuprofen	355	4.1	27.9
Diclofenac	216	2.5	17.0
Naproxen	201	2.3	15.8
Ketoprofen	164	1.9	12.9
Nimesulide	143	1.7	11.2
Indomethacin	67	0.8	5.3
Meloxicam	50	0.6	3.9
Ketorolac	30	0.3	2.4
Nabumetone	13	0.2	1.0
Tolfenamic acid	13	0.2	1.0
Piroxicam	8	0.1	0.6
Etodolac	4	0.04	0.3
Tenoxicam	3	0.03	0.2
Tiaprofenic acid	3	0.03	0.2
Aceclofenac	2	0.02	0.2
Mefenamic acid	1	0.01	0.1

No co-administration was found for lornoxicam, dexibuprofen, or dexketoprofen.

Table 10b. The proportion of warfarin treatment periods with co-prescribed coxib of all warfarin treatment periods and the proportion of single coxib treatment periods of all coxib-warfarin treatment periods in warfarin users in an inpatient setting in the time period 1996–2004. Data source: Turku University Hospital medical record database, Finland.

	Number of treatment periods	The proportion of all warfarin treatment periods (*n*=8,615), %	The proportion of coxib treatment periods (*n*=246), %
Coxibs	246	2.9	100
Rofecoxib	121	1.4	49.2
Celecoxib	105	1.2	42.7
Etoricoxib	17	0.2	6.9
Valdecoxib	3	0.03	1.2

No co-administration was found for parecoxib.

5.3 The clinical consequences of potentially interacting pain medications among warfarin users in an inpatient setting (Study II)

Altogether 265 warfarin treatment periods (3.1% of all warfarin treatment periods, *n*=8,615) were linked to at least one bleeding diagnosis recorded over the period of co-administration of warfarin and non-selective NSAIDs, coxibs, or warfarin only (*i.e.* control group). The percentages of treatment periods with bleeding diagnoses were 3.5 % and 4.9 % in the non-selective NSAID and coxib groups, respectively, but only 1.5 % in the control group (Table 11).

Co-administration of both non-selective NSAIDs and coxibs was associated with an approximately 3-fold elevated risk for any bleeding compared to warfarin alone (OR 2.6, 95 % CI 1.56–4.23 and OR 3.1, 95 % CI 1.44–6.67, respectively) (Table 11). Co-administration of non-selective NSAIDs and warfarin was associated with a 4-fold increased risk for bleeding in the lower gastrointestinal tract (OR 4.0, 95 % CI 1.13–13.93) whereas no statistical significance could not be demonstrated for other bleeding sites due to the small number of cases.

Table 11. The proportions of warfarin treatment periods linked with a bleeding diagnosis and the bleeding risk associated with co-administration of warfarin and non-selective NSAIDs or coxibs when compared to warfarin only in Turku University Hospital, Turku, Finland, in 1.6.1996–31.12.2004.

	Warfarin + non-selective NSAIDs (*n*=1,273)	**Warfarin + coxibs (*n*=246)**	**Warfarin only (*n*=3,663)**
All bleeding diagnoses			
n (% of treatment periods)	44 (3.5)	12 (4.9)	53 (1.5)
OR (95 % CI)	2.57 (1.56–4.23)	3.10 (1.44–6.67)	1.0
Upper GI bleeding diagnoses			
n (% of treatment periods)	8 (0.6)	2 (0.8)	8 (0.2)
OR (95 % CI)	2.79 (0.88–8.91)	2.91 (0.33–25.79)	1.0
Lower GI bleeding diagnoses			
n (% of treatment periods)	10 (0.8)	1 (0.4)	9 (0.2)
OR (95 % CI)	3.96 (1.13–13.93)	1.73 (0.24–12.51)	1.0
Intracranial bleeding diagnoses			
n (% of treatment periods)	5 (0.4)	0 (0)	8 (0.2)
OR (95 % CI)	1.68 (0.47–6.02)	n/a	1.0

Binary logistic regression adjusted for age, sex, ward, proton pump inhibitor, and oral glucocorticoid medications. Adjustment for ward was impossible in the lower GI and intracranial bleeding categories because the number of diagnoses in some specialties was zero.
CI, confidence interval; GI, gastrointestinal; NSAID, non-steroidal anti-inflammatory drug; OR, odds ratio.

The laboratory values were available for 85–95 % of the treatment periods. The mean hemoglobin and minimum hemoglobin concentrations were significantly lower in both the non-selective NSAID and coxib groups when compared to the warfarin only group ($p<0.001$) whereas no significant difference was observed in mean INR values (Table 12).

Table 12. Selected laboratory values in the study groups. Mean values and range are given. Data source: Turku University Hospital medical record database, Finland.

	Warfarin + non-selective NSAIDs	Warfarin + coxibs	Warfarin only
Hb, g/l (range)	123** (70–171)	124** (85–174)	133 (78–197)
Min Hb, g/l (range)	107** (45–167)	108** (55–173)	121 (42–197)
HCT (range)	0.37** (0.20–0.51)	0.37** (0.24–0.52)	0.39 (0.24–0.57)
Erythrocyte count, x 10^{12}/l (range)	4.05** (2.37–6.46)	4.07** (2.60–5.70)	4.32 (2.49–8.47)
MCH, pg/cell (range)	31 (23–38)	31 (25–38)	31(18–40)
MCV, fl (range)	91 (73–109)	91 (79–110)	91 (59–118)
Thrombocyte count, x 10^{9}/l (range)	250** (29–864)	274 (86–667)	232 (9–1223)
INR (range)	2.4 (0.9–5.2)	2.3 (0.9–4.6)	2.3 (0.8–7.0)

** p <0.01 for comparison to the control in linear mixed model adjusted for age, sex, ward, and concomitant exposure to proton pump inhibitor and oral glucocorticoid medications.
NSAID, non-selective non-steroidal anti-inflammatory drug; Hb, hemoglobin; HCT, hematocrit; MCH, mean cellular hemoglobin; MCV, mean corpuscular volume; INR, international normalized ratio.

The risk (OR) for the mean hemoglobin concentration being below the target range (117 g/l for women, 134 g/l for men) during the treatment period was almost doubled in both interaction groups when compared to the warfarin only group. No elevated risk for INR value above the therapeutic range (2.0–3.0) was observed in the interaction groups (Table 13).

Table 13. The proportions of treatment periods linked with Hb and Min Hb value below the lower limit of normal, Thrombocytes and INR above the upper limit of normal, and the risk of an extra-target range value associated with co-administration of warfarin and non-selective NSAIDs or coxibs when compared to warfarin only in Turku University Hospital, Turku, Finland, in 1.6.1996–31.12.2004.

	Warfarin + non-selective NSAIDs (*n*=1,273)	**Warfarin + coxibs (*n*=246)**	**Warfarin only (*n*=3,663)**
Hb			
n (% of treatment periods)	627 (49.3)	122 (49.6)	1,022 (27.9)
OR (95 % CI)	1.90 (1.60–2.26)	1.91(1.41–2.58)	1.0
Min Hb			
n (% of treatment periods)	934 (73.4)	175 (71.1)	2,619 (71.5)
OR (95 % CI)	2.49 (2.08–2.98)	2.05 (1.46–2.87)	1.0
Thrombocytes			
n (% of treatment periods)	103 (8.1)	88 (6.9)	165 (4.5)
OR (95 % CI)	1.58(1.18–2.12)	1.29 (0.70–2.38)	1.0
INR			
n (% of treatment periods)	92 (7.2)	88 (6.9)	216 (5.9)
OR (95 % CI)	1.07 (0.81–1.42)	1.07 (0.62–1.82)	1.0

Binary logistic regression analysis adjusted for age, sex, ward, and concomitant exposure to proton pump inhibitor and oral glucocorticoid medications.
Hb, hemoglobin; HCT, hematocrit; INR, international normalized ratio; NSAID, non-steroidal anti-inflammatory drug; OR, odds ratio.

5.4 The effect of warfarin initiation on the use of interacting pain medication in an outpatient setting and among frail and non-frail inpatients (Studies I and III)

The outpatient study population comprised 110,299 persons who initiated warfarin therapy between 1 January 2007 and 30 September 2010. The inpatient study population included 98 non-frail and 47 frail inpatients who were initiated on warfarin therapy during their hospital admission in the time period between 1 October 2012 and 30 September 2013 and whose medication data was available before and after warfarin initiation.

Prior to warfarin initiation, NSAIDs were the most commonly used of the studied pain medications in outpatients used by 13.3 % of study population (Table 14). Among inpatients, paracetamol was the prevailing pain medication used by roughly 1/3 of non-frail and 2/3 of frail patients (Table 15). Tramadol was the least widely used drug in both study populations.

After warfarin initiation, the use of NSAIDs decreased in both outpatients and inpatients (Tables 14 and 15). In fact, no use was detected in either the non-frail or

frail inpatients. On the contrary, the use of paracetamol doubled in outpatients. Among inpatients, the use of paracetamol increased in non-frail, but decreased in their frail counterparts so that at discharge nearly half of the patients in both groups were using paracetamol (Table 15). A similar increasing trend in the use of tramadol was observed in outpatients and in both non-frail and frail inpatients (Table 16).

Table 14. The proportion of incident warfarin users who purchased NSAIDs, paracetamol, or tramadol over the 3 months' period preceding (Before) and following (After) warfarin initiation of all incident warfarin users (*n*=110,299) in Finland in 2007–2010. Data source: Prescription Register, Social Insurance Institution.

	Before, *n* (*% of all*)	**After, *n* (*% of all*)**
NSAIDs	14,662 (13.3)	4,417 (4.0)
Paracetamol	11,189 (10.1)	22,452 (20.4)
Tramadol	2,631 (2.4)	3,959 (3.6)

Table 15. The proportions of incident warfarin users who were co-prescribed NSAIDs, paracetamol, or tramadol before (Home) and after (Discharge) warfarin initiation of non-frail and frail inpatients in Royal Adelaide Hospital, South Australia, in 2012–2013.

	Non-frail (*n*=98)		**Frail (*n*= 47)**	
	Home, n (%)	*Discharge, n (%)*	*Home, % (n)*	*Discharge, % (n)*
NSAIDs	9 (9.2)	0 (0.0)**	3 (6.4)	0 (0.0)
Paracetamol	35 (35.6)	48 (49.5)*	30 (64.6)***	25 (53.2)
Tramadol	0 (0.0)	7 (7.1)**	2 (4.3)	4 (8.5)

**p*<0.05 compared to the proportion of users at home within the frailty category in McNemar's test
***p*<0.001 compared to the proportion of users at home within the frailty category in McNemar's test
****p*<0.05 compared to the proportion of users at home in non-frail category in Fisher's exact test

Table 16. The trends in the use of potentially interacting pain medication after warfarin initiation stratified by medication and patient population. Outpatient data source: Prescription Register, Social Insurance Institution, Finland. Inpatient data source: Royal Adelaide Hospital, South Australia.

	Outpatients	**Non-frail inpatients**	**Frail inpatients**
NSAIDs	↓	⁄	⁄
Paracetamol	↑	↑	↓
Tramadol	↑	↑	↑

↓= the use of pain medication of interest decreased compared to the frequency of use before initiation;
↑= the use of pain medication of interest increased compared to the frequency of use before initiation;
⁄= no use detected after warfarin initiation.

In the outpatient population, the use of paracetamol was prevalent also when warfarin initiators were stratified according to the use or non-use of pain medication preceding warfarin initiation (Figure 4). The only subgroup where tramadol was the most commonly used pain medication after warfarin initiation was the strata of those patients who had been using tramadol before warfarin initiation.

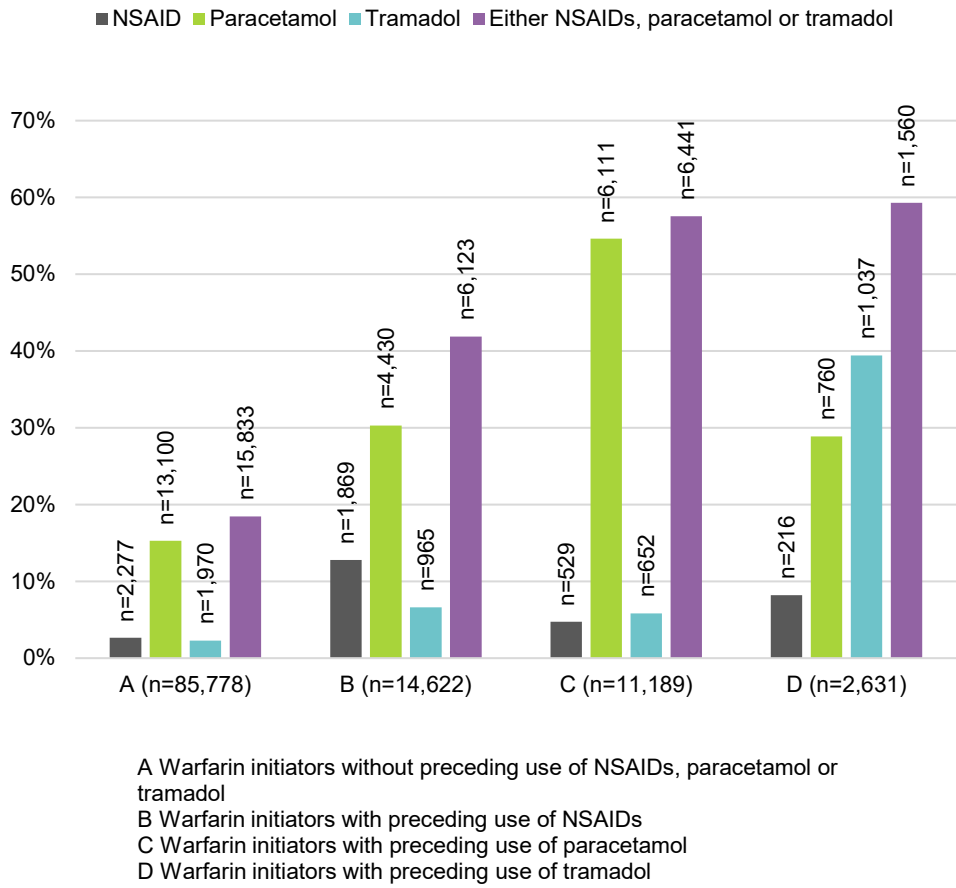


Figure 6. The proportion of warfarin initiators purchasing NSAIDs, paracetamol, or tramadol within 90-day follow-up period stratified according to pain medication use during 90 prior to warfarin initiation in Finland in 2007–2010. Data source: Prescription Register, Social Insurance Institution. Adopted from the original publication (Rikala et al., 2015).

6 Discussion

6.1 General discussion

Older people are a growing part of Western populations. In Finland, almost every fourth person was over 65 years old at the end of year 2022 (Statistics Finland, 2022). Aging is accompanied by chronic conditions which often require the long-term use of medications. Specifically, warfarin and pain medications are used predominantly by older people, and the concomitant use of these drugs is common despite the potential for drug interactions increasing the risk of bleeding. Moreover, older age predisposes patients to bleeding complications, and the presence of other risk factors further elevates the risk of bleeding. Considering the large number of warfarin users exposed to potentially detrimentally interacting pain medications, even a slight increase in the bleeding risk may have significant public health implications. However, although warfarin has been used for decades, the existing literature is limited concerning its use and drug interactions with pain medications in the Finnish population. The analysis of drug prescribing utilizing medical record and register data enables the detection of harmful prescribing practices, and thereby, produces information which can be applied for improving the safety of drug therapies.

Administrative databases and healthcare registers have traditionally been used in pharmacoepidemiological studies on drug utilization, ADRs, and in the recent decades also, on drug interactions. In comparison to randomized controlled trials, register-based studies make possible the inclusion of a large number of patients in the setting of routine care as well as the identification of rare events. More importantly, register studies allow an examination of the safety and efficacy of drugs in typical real-world patients or in specific vulnerable patient groups who would not fulfil eligibility criteria for clinical trials. Moreover, data is available in a relatively straightforward manner (Avorn, 2007). Patients can be followed for long periods and information on drug use is not affected by the participant's recall, which is a common problem in interview- and questionnaire-based studies. Furthermore, register-based studies are the only option for investigating the incidence and magnitude of the adverse effect of a drug combination with a known harmful action as undertaking a randomized setting would not be ethically acceptable.

The limitations inherent in observational studies include the possibility of bias and confounding. However, with careful design and adequate analysis methods, it is possible to mitigate the effect of these threats to validity on the study's outcomes (Strom et al., 2021). Nonetheless, the generalizability of results may be limited due to local practices if for example, a database covers only a single hospital or a geographically restricted area.

In Finland, comprehensive health care registers provide an excellent setting for register-based studies (Furu et al., 2010; Klaukka, 2001; Wettermark et al., 2013). Furthermore, the nation's unique identification number system enables data linkage between various registries and exploring data at an individual level if needed. In addition, data utilization for research purposes is regulated by legislation to ensure privacy protection.

Oral anticoagulation therapy has undergone a remarkable change over the past decade. After six decades in which warfarin was the only oral anticoagulant available in Finland, four new DOACs were launched; this means that until the most recent years, warfarin remained as the predominant OAC (See Chapter 2.1.2). Studying the use of non-reimbursable drugs has not been possible at the population level until the introduction and expansion of electronic prescriptions in the 2010s (Aarnio et al., 2020). For these reasons, warfarin was the only OAC included in the present studies.

6.2 Principal findings

6.2.1 The frequency of co-prescribing potentially interacting pain medications among warfarin users in outpatient and inpatient settings (Studies I and II)

The frequency of co-prescribing the potentially interacting pain medications among warfarin users differed between outpatient and inpatient populations. Among outpatients, paracetamol was co-prescribed to almost every other warfarin user, whereas tramadol, non-selective NSAIDs, and coxibs were prescribed to only 2–5 % of warfarin users. Among inpatients, non-selective NSAIDs and coxibs were co-prescribed more frequently with warfarin; the rates were 16 % and 3 % of inpatients, respectively.

The co-prescribing frequency for NSAIDs in our studies was lower than that described in previous studies investigating outpatients (Cheetham et al., 2009; Gavronski et al., 2012; Håkonsen et al., 2009; Taipale et al., 2015), but similar for coxibs (Cheetham et al., 2009; Snaith et al., 2008) and tramadol (Håkonsen et al., 2009; Lindh et al., 2014; Taipale et al., 2015). It is possible that the differences between the studies may partly be explained by methodological variations (Hughes et al., 2023). However, the low co-prescribing frequency detected in our study

indicates that clinicians have been aware of the potential risks of the drug combination although avoiding concomitant NSAID use was not recommended by the Current care guideline at the time of Study I (The safe use of NSAIDs: Current care guideline, 2003 and 2009).

Among inpatient warfarin users, the frequency of non-selective NSAID use was over 3-fold higher than in outpatients. This may reflect the fact that inpatients were generally more ill and had undergone invasive procedures requiring analgesia with good anti-inflammatory properties. Moreover, at the time of Study II, there were no prescription delivery system integrated interaction databases available, which would have warned about harmful drug combinations. Furthermore, the current care guideline on the safe use of NSAIDs was launched in the midway part of the study period (The safe use of NSAIDs: Current care guideline, 2000), which coincides with the introduction of the first coxib medication (Finnish Medicines Agency, 2022). The data for inpatient and outpatient studies were collected in separate years which may explain some of the differences observed in the co-prescribing frequencies between the study populations, for instance, due to potential changes in prescribing practices. Thus, the frequencies of co-prescribing should be interpreted in the light of prescribing practices and guidelines at that time.

6.2.2 The clinical consequences of co-administration of potentially interacting pain medications among warfarin users in an inpatient setting (Study II)

The co-administration of non-selective NSAIDs or coxibs was associated with an approximately 3-fold elevated risk for any bleeding compared to warfarin only. No difference was observed in the risk for upper gastrointestinal bleeding between non-selective NSAID and coxib groups. Similar results have been reported previously suggesting that coxibs do not provide improved gastrointestinal safety over non-selective NSAIDs in patients taking warfarin (Battistella et al., 2005; Delaney et al., 2007).

The increased bleeding risk observed in the interaction groups was supported by the laboratory data. The significantly lower mean hemoglobin levels in both interaction groups may be a reflection of subclinical gastrointestinal bleeding, and the risk for having the lowest hemoglobin value (Min Hb) below the target range was 2–2.5-fold higher in patients taking concomitant non-selective NSAIDs or coxibs when they are compared to patients receiving warfarin alone. Chronic inflammatory diseases are known to lower the blood hemoglobin concentration and elevate the platelet count (Adamson et al., 2001; Ertenli et al., 2003), which partly contribute to the somewhat higher platelet count and lower mean hemoglobin observed in the non-selective NSAID and coxib groups than in the warfarin only

group. However, the mean INR value did not differ between the groups emphasizing the fact that INR monitoring was unable to detect the increased bleeding risk associated with these pharmacodynamic drug interactions.

The use of proton pump inhibitors and oral glucocorticoids was significantly more common in the interaction groups in comparison to the warfarin only group, and these were taken into account as potential confounders in the statistical analyses. However, not only does the frequent use of PPI suggest that there was an increased gastrointestinal toxicity due to co-administration of warfarin and NSAIDS or coxibs, but it also may be an indication of possible preventive measures being initiated to minimize the bleeding risk (Ray et al., 2016).

6.2.3 The effect of warfarin initiation on the use of potentially interacting pain medication in an outpatient setting and among frail and non-frail inpatients (Studies I and III)

The effect of warfarin initiation on the use of potentially interacting pain medication was principally rather similar in outpatients and among non-frail and frail inpatients. The use of NSAIDs decreased dramatically or was totally abolished after warfarin initiation. Instead, the use of paracetamol increased in outpatients and non-frail inpatients, whereas in frail inpatients, a small decrease was seen in paracetamol use. A slight increase in the use of tramadol was detected in all patient groups.

The observed decrease in the use of NSAIDs is similar to observations previously published in large register-based studies (Ilomäki et al., 2015; Lindh et al., 2014). Although NSAIDs have been among the most common interacting drugs in outpatients on warfarin (Gavronski et al., 2012; Tragni et al., 2013; Vitry et al., 2011), this does not seem to be true anymore.

The avoidance of prescribing NSAIDs may have contributed to the observed increase in the prescribing of paracetamol and tramadol. Similar results of increased use of tramadol and avoidance of NSAIDs were also described in a Swedish register-based study, indicating that the warfarin-tramadol interaction may be poorly recognized by clinicians (Lindh et al., 2014). In the inpatient population, it is possible that tramadol and paracetamol were prescribed for post-operative analgesia as non-frail inpatients had been operated more often than frail inpatients.

In the outpatient population, warfarin initiators were stratified according to the use or no use of pain medications prior to warfarin initiation. Tramadol was the most commonly prescribed pain medication in those patients who had tramadol prescriptions already prior to warfarin initiation, suggesting this subgroup may have consisted of patients with more severe chronic pain. Paracetamol was the most commonly prescribed pain medication in patients who had no pain medication use or had used paracetamol or NSAIDs prior to warfarin initiation. This observation

indicates not only the apparent need for pain medications, but also points to an adherence to the recommendations in clinical practice guideline (Pain: Current Care Guidelines, 2017).

Altogether, these findings suggest that there has been a growing awareness by clinicians of the increased bleeding risk associated with concomitant use of NSAIDs with warfarin. However, neither paracetamol nor tramadol are trouble-free in warfarinized patients due to their effect on hemostasis (Caldeira et al., 2015; Mahé et al., 2006; Pottegård et al., 2013). Paracetamol may potentiate the warfarin response when the daily dose exceeds 2 g (Parra et al., 2007; Zhang et al., 2011). The high frequency of co-prescribing paracetamol and warfarin highlights the need for further research on the clinical significance of the potential interaction (Martín-Pérez et al., 2018).

6.3 Strengths and limitations

6.3.1 Strengths

One of the main strengths of the present studies was the access to comprehensive registers representing drug use in a real-life setting. The use of prescription register data in Study I made it possible to capture a large, nationally representative cohort of warfarin initiators and users in a primary care setting. In Studies II and III, the use of medical record data allowed investigating drug use in an inpatient setting. Although one common uncertainty in register-based studies with clinical outcome is the actual exposure to drugs, nonetheless in Study II, it is likely that the study subjects were truly exposed to the prescribed drugs during the inpatient care. Moreover, retrieving and examining laboratory and diagnosis data over the treatment periods enabled investigating the clinical consequences. Furthermore, as the diagnoses were recorded throughout the treatment periods, potential bleeding outcomes were captured thoroughly. In study III, in addition to using data recorded during routine clinical care, individual level clinical data on patient characteristics was utilized. Approximately two thirds of the patients were recruited and interviewed by the doctoral candidate, who also collected patients' clinical data for the study. In study III, in addition to using data recorded during routine clinical care, individual level clinical data on patient characteristics was utilized.

Other strengths of the present studies are the multifaceted approaches and wide perspective in co-prescribing. The use of various data sources enabled us to incorporate different levels of care spanning from the national level in primary care to the hospital setting and inpatients, and finally to focus on a special risk group. Specifically, data accumulated over inpatient care on hospital level is not commonly utilized in drug interaction studies, which are predominantly based on drug

dispensing or claim data and focusing on prescribing in the outpatient setting. Our studies complement the few previous drug interaction studies based on hospital register data (Laine et al., 2000; Tirkkonen et al., 2004; Tirkkonen et al., 2008; Tirkkonen et al., 2010; Tirkkonen et al., 2013). This approach demonstrates the significance and feasibility of benefiting from hospital register data for large-scale research purposes as reflected in the recent development of data lakes. Moreover, the studies were conducted at the time when data management *e.g.* combining data from various registers, was largely based on manual work and modern tools were unavailable.

Finally, one of the important strengths is that co-prescribing during different phases of warfarin therapy *e.g.* in the initiation phase and during ongoing therapy was studied. In addition, the change in the co-prescribing by comparing prescribing potentially interacting pain medication prior to and after warfarin initiation was investigated. This approach has rarely been used in register-based studies, but produces clinically important information about prescribing practices (Ilomäki et al., 2015).

6.3.2 Limitations

Potential for selection bias

In Study II, the selection procedure based on the warfarin ATC code produced a heterogenous study population including all patients who were administered warfarin during the study period. The study groups may have differed from each other in terms of their baseline bleeding risk as well as in potential confounders, all of which could not be controlled. Furthermore, warfarin initiators and prevalent users were analyzed together, although it is known that the first 3 months of warfarin therapy represent a high risk period for bleeding events, and that the inclusion of prevalent users may have created a survivor bias. Thus, combining these two populations with differing bleeding risks may have exerted an effect on the observed association. However, the direction of this potential bias cannot be estimated.

In Study III, a selection bias may have been introduced by the recruitment process. Consecutive patients were identified from daily INR measurement reports provided by the hospital laboratory. However, at the request of the hospital research ethics committee, the patients were invited to participate in the study by the hospital staff, which may have introduced some variation in the selection of potential participants. As in Study II, the direction or magnitude of potential selection bias in the study results is unknown.

Potential for measurement bias

The main limitation in Study I is the potential underestimation of co-prescribing. As only reimbursed drug purchases are recorded into the Prescription register, detecting the co-prescribing of non-reimbursable pain medications, *i.e.* if the patient purchased small package sizes of NSAIDs or paracetamol, was not possible. However, it is unlikely that non-reimbursable sizes of pain medications were prescribed as small package sizes are available without prescription. Furthermore, although the use of non-prescription drugs is an important cause of drug interactions and a common source of misclassification bias in studies utilizing reimbursement data, the focus in Study I was on prescribing practice rather than on the actual exposure and clinical consequences of drug interactions. In addition, including those prescriptions which were never filled was not possible. However, it is presumable that the extent of non-filled pain medication prescriptions was marginal as purchasing reimbursed pain medications is more inexpensive than the costs of over-the-counter products.

It is possible that in Study I warfarin exposure may have been overestimated, and thereby, the occurrence of co-prescribing by assigning a fixed duration of 180 days for each warfarin prescription. This duration may have been too long for single warfarin prescriptions when the indication was some form of short-term therapy, such as deep venous thrombosis or pulmonary embolism (Deep vein thrombosis and Pulmonary embolism: Current Care Guideline, 2016) or early discontinuers. A similar overestimation may have occurred for pain medications as the calculation of duration of each pain medication prescription was based on DDD. However, the duration of pain medication prescriptions were multiplied by 1.5 to take into account the *pro re nata* use, non-adherence, and delayed refills and thus this diminished the potential risk of overestimation. Moreover, it is possible that the prescribed dose of pain medications may have been higher than the DDD leading to an underestimation of the duration of the prescription. Nevertheless, a sensitivity analysis was performed, which indicated that assigning a shorter duration for either a warfarin or pain medication prescription had only a minor influence on the occurrence of co-prescribing (data not shown).

The overestimation of exposure may have occurred also in Study II, as the exact date for the initiation and termination of long-term medication, specifically warfarin, was often missing. However, the INR values collected indicated current warfarin use during the hospital sojourn. Moreover, the possibility of human errors cannot be excluded in the data entry concerning Studies II and III. Nonetheless, in Studies II and III, the actual exposure to the interacting medication is highly likely to have occurred as drugs were administered during the inpatient care. In Study III, a source of recall error may have affected self-reporting of medication use and health status

prior to admission affecting the frailty classification. In Study II, bleeding episodes that occurred after the individual's discharge from hospital may have been missed.

Potential for confounding

An important limitation inherent to observational studies is confounding. In study II, unmeasured confounding may have exerted an effect on our estimates of the relative risk of bleeding (OR). Although the analyses were adjusted for proton pump inhibitor and oral glucocorticoid use, some important risk factors for bleeding, such as prior bleeding or *H. pylori* infection, were potential confounders, which could not be accounted for. Furthermore, it was not possible to distinguish whether patients with an increased bleeding risk had been prescribed coxibs instead of non-selective NSAIDs, which leads to the possibility for uncontrolled confounding by indication. Potential confounding by indication may have biased the ORs for NSAIDs downwards and those for coxibs upwards.

6.4 Future considerations

The use of warfarin has decreased along with the increasing use of DOACs. This trend can be expected to continue as generic DOAC preparations are expected to emerge in the current decade and antidotes for DOACs have become available (U.S. Food & Drug Administration; European Medicines Agency). In the growing population of OAC users, the fixed dosing and the ease of use are the major advantages that DOACs hold over warfarin. However, DOACs are not suitable for all patients. At the moment, they are contraindicated in patients with a mechanical heart valve. A randomized clinical trial comparing dabigatran and warfarin in patients with mechanical heart valve was terminated prematurely because of an excess of thromboembolic and bleeding events among patients in the dabigatran group (Eikelboom et al., 2013). To date, only one additional clinical trial investigating DOACs in patients with mechanical heart valve has been registered in Clinicaltrials.gov website (www.clinicaltrials.gov, accessed April 19, 2023), but recruiting has not been started as April 19, 2023. Furthermore, DOACs should be used with caution or avoided in patients with advanced renal or liver failure – both often encountered in older people, particularly in frail older people. Moreover, the lack of a simple method for monitoring the intensity of anticoagulation and affordable antidotes for overriding their effect are true drawbacks of DOACs. Also the higher out-of-pocket cost for patients compared to warfarin may limit DOAC use in aged people with a small income. As a result, warfarin will remain in the OAC selection as it cannot be fully replaced with DOACs (Burg, 2022).

As the use of warfarin declines, clinicians' knowledge on managing warfarin therapy may deline making the therapy more challenging. Thus, information on the utilization of warfarin and potentially interacting co-medication in the future user population may become even more important in order to maintain the quality and safety of warfarin therapy. Recent studies have indicated that warfarin is initiated in older and more ill patients than DOACs (Hekkala, 2021; Hellman et al., 2020). In this vulnerable patient population, special consideration in prescribing is required to avoid drug interactions as polypharmacy is common and the bleeding risk is high due to advanced age and comorbid conditions. As for pain medication, although it appears that the adverse effects associated with the concomitant use of NSAIDs and OACs in older patients have been acknowledged, the safety of co-administration of paracetamol or tramadol still requires further investigation in anticoagulated older patients as the interaction mechanism remains unclear. In addition, similar research in the real-world setting is needed relating to the potential drug interactions in DOAC users on all levels of care and in special risk groups (Zhang et al., 2020).

Drug interaction studies have conventionally utilized reimbursement and claims data (The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance, 2022), whereas register-based studies performed in inpatient settings are less common (Laine et al., 2000; Leal Rodríguez et al., 2022; Tirkkonen et al., 2008, 2010, 2013, 2004; Zwart-Van Rijkom et al., 2009). The use of electronic health records registers may provide a new tool for such studies. However, one must be aware of the limitations of these registers. For example, data used for proper patient selection may only partially be available in a structured format which may affect the size and completeness of the population captured (Laaksonen et al., 2020).

The recent establishment of data lakes provides improved facilities for register-based drug interaction studies in hospital and inpatient settings. Data lakes are designed to facilitate efficient, secure, and tailored extracting of selected data from multiple registries simultaneously, and they contain data of medical records and various administrative registers generated in conjunction with routine hospital care. In the outpatient setting in Finland, the establishment of an electronic prescription system has broadened the possibilities of register-based drug research. Currently, all prescriptions must be issued electronically and the information on issued and filled prescriptions are stored in the Prescription Centre in the nationwide Kanta database. This is a major benefit in comparison to Prescription register data, which only contained data on reimbursed drug dispensations. The electronic prescription database makes it possible to examine drugs independently of their reimbursement status or potential changes on reimbursement criteria, but it also provides the opportunity to conduct more specific investigations of prescribing according to

prescriber's location and speciality (Aarnio et al., 2020). For example, Böckerman and colleagues examined the quality of prescribing measured as co-prescribing of warfarin and NSAIDs utilizing electronic prescription data (Böckerman et al., 2020). They demonstrated that the adoption of electronic prescribing and improved information coordination had reduced the probability of co-prescribing warfarin and NSAIDs by 35 % in rural regions where the majority of prescriptions were written by unspecialized physicians. This study indicates the benefits of utilizing electronic prescription data on drug interaction studies. Altogether, these recent developments enable the utilization of more specific and comprehensive data for future research in the currently changing field of OAC therapy.

7 Conclusions

The aim of the studies in this thesis was to study the frequency and clinical consequences of co-prescribing warfarin with potentially interacting pain medications in real-life settings. In Finland, 1.3 % of the population (n=72,081) received reimbursement for warfarin in 2021 comprising more than quarter of all patients receiving reimbursement for oral anticoagulants. Warfarin drug interactions with several pain medications are a recognised risk factor for bleeding. Both warfarin and pain medications are commonly used by older persons who are susceptible to adverse drug reactions. The significance of safe drug treatment has increased as the numbers of aged individuals in the population grow, older age lasts longer, and drug therapies are increasingly provided. Recognising potentially harmful prescribing practices is essential in order to improve the safety of drug therapies in real-life settings.

First, the co-prescribing of potentially interacting pain medications among warfarin users was common, but the frequencies differed between outpatient and inpatient settings. Nearly half of outpatient warfarin users were co-prescribed with the studied pain medications, most commonly paracetamol. This accords with clinical guidelines as does the lower frequency in the co-prescribing of non-selective NSAIDs, coxibs and tramadol. Among inpatients, the co-prescribing of non-selective NSAIDs and coxibs was three times more common than among outpatients. This finding calls for special attention as inpatients are generally more ill and may be at higher bleeding risk due to acute or worsened illness.

Second, the co-administration of potentially interacting pain medication was associated with an increased bleeding risk in hospitalized warfarin users. Coxibs were associated with a similar magnitude of the bleeding risk as non-selective NSAIDs suggesting that coxibs do not provide better gastrointestinal safety in comparison to non-selective NSAIDs in warfarin users. As expected, no increase in the INR value was observed, highlighting the fact that INR monitoring is not sufficient if one wishes to detect the increased bleeding risk associated with pharmacodynamic drug interactions. Instead, a low hemoglobin concentration may be an indication of the presence of subclinical bleeding.

Third, the use of potentially interacting pain medications changed at warfarin initiation in outpatients and in frail and non-frail inpatients. The use of NSAIDs decreased dramatically in outpatients and was totally abolished in inpatients suggesting that physicians are well aware of the risks of this drug combination. The use of paracetamol increased among outpatients and non-frail inpatients as recommended by the clinical guidelines. Instead, paracetamol use decreased in frail inpatients possibly due to more careful medication review or a switch to stronger pain medications. The use of tramadol increased in all warfarin initiators suggesting that the potential drug interaction between warfarin and tramadol may not be well recognised by physicians. Similar observations were made when the effect of warfarin initiation was examined according to pain medication use preceding warfarin initiation in outpatients.

To conclude, the frequencies of warfarin drug interactions differed between pain medication classes, settings of care, and the phases of warfarin therapy. It is evident that the increased risk of bleeding due to potential drug interactions still requires attention when pain medications are prescribed to warfarinized patients.

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Appendices

Appendix 1, ATC codes used in database searches

Study I

Potentially interacting pain medications	ATC code
Indomethacin	M01AB01
Sulindac	M01AB02
Ketorolac	M01AB15
Diclofenac	M01AB55
Meloxicam	M01AC06
Ibuprofen	M01AE01
Naproxen	M01AE02
Ketoprofen	M01AE03
Dexketoprofen	M01AE17
Mefenamic acid	M01AG01
Tolfenamic acid	M01AG02
Celecoxib	M01AH01
Parecoxib	M01AH04
Etoricoxib	M01AH05
Nabumetone	M01AX01
Nimesulide	M01AX17
Piroxicam	M02AA07
Tramadol	N02AX02
Acetylsalicylic acid	N02BA01
Paracetamol	N02BE01

Study II

Potentially interacting pain medications	ATC code
Aceclofenac	M01AB16
Diclofenac	M01AB05, M01AB55
Etodolac	M01AB08
Indomethacin	M01AB01, M01AB51
Ketorolac	M01AB15
Lornoxicam	M01AC05
Meloxicam	M01AC06
Piroxicam	M01AC01
Tenoxicam	M01AC02
Dexibuprofen	M01AE14
Dexketoprofen	M01AE17
Ibuprofen	M01AE01, M01AE51
Ketoprofen	M01AE02
Tiaprofenic acid	M01AE11
Mefenamic acid	M01AG01
Tolfenamic acid	M01AG02
Nabumetone	M01AX01
Nimesulide	M01AX17
Celecoxib	M01AH01
Etoricoxib	M01AH05
Parecoxib (injection)	M01AH04
Rofecoxib	M01AH02
Valdecoxib	M01AH03

PPI and oral glucocorticoid and medications	ATC code
Esomeprazole	A02BC05, A02BD06
Lansoprazole	A02BC03, A02BD02, A02BD03
Omeprazole	A02BC01, A02BD01, A02BD05
Pantoprazole	A02BC02, A02BD04
Rabeprazole	A02BC04
Dexamethasone	H02AB02
Hydrocortisone	H02AB09
Methylprednisolone	H02AB04
Prednisolone	H02AB06
Prednisone	H02AB07

Appendix 2, Bleeding diagnoses searched over the warfarin treatment periods in Study II

ICD-10 code	Bleeding diagnosis	Subcategory
D50.0	Iron deficiency anaemia secondary to blood loss	
D62	Acute posthaemorrhagic anaemia	
D69.9	Haemorrhagic condition, unspecified	
H11.3	Conjunctival haemorrhage	
H21.0	Hyphaema	
H31.3	Choroidal haemorrhage and rupture	
H35.6	Retinal haemorrhage	
H43.1	Vitreous haemorrhage	
H92.2	Otorrhagia	
I23.0	Haemopericardium as current complication following acute myocardial infarction	
I60	Subarachnoid haemorrhage	
I60.0	Subarachnoid haemorrhage from carotid siphon and bifurcation	
I60.1	Subarachnoid haemorrhage from middle cerebral artery	
I60.2	Subarachnoid haemorrhage from anterior communicating artery	
I60.3	Subarachnoid haemorrhage from posterior communicating artery	
I60.4	Subarachnoid haemorrhage from basilar artery	
I60.5	Subarachnoid haemorrhage from vertebral artery	
I60.6	Subarachnoid haemorrhage from other intracranial arteries	
I60.7	Subarachnoid haemorrhage from intracranial artery, unspecified	
I60.8	Other subarachnoid haemorrhage	
I60.9	Subarachnoid haemorrhage, unspecified	
I61	Intracerebral haemorrhage	ICH
I61.0	Intracerebral haemorrhage in hemisphere, subcortical	ICH
I61.1	Intracerebral haemorrhage in hemisphere, cortical	ICH
I61.2	Intracerebral haemorrhage in hemisphere, unspecified	ICH
I61.3	Intracerebral haemorrhage in brain stem	ICH
I61.4	Intracerebral haemorrhage in cerebellum	ICH
I61.5	Intracerebral haemorrhage, intraventricular	ICH

ICD-10 code	Bleeding diagnosis	Subcategory
I61.6	Intracerebral haemorrhage, multiple localized	ICH
I61.8	Other intracerebral haemorrhage	ICH
I61.9	Intracerebral haemorrhage, unspecified	ICH
I62	Other nontraumatic intracranial haemorrhage	ICH
I62.0	Subdural haemorrhage (acute)(nontraumatic)	ICH
I62.1	Nontraumatic extradural haemorrhage	ICH
I62.9	Intracranial haemorrhage (nontraumatic), unspecified	ICH
I85.0	Oesophageal varices with bleeding	UGIB
J94.2	Haemothorax	UGIB
K25	Gastric ulcer	UGIB
K25.0#	Gastric ulcer, acute with haemorrhage	UGIB
K25.2	Gastric ulcer, acute with both haemorrhage and perforation	UGIB
K25.4	Gastric ulcer, chronic or unspecified with haemorrhage	UGIB
K25.6	Gastric ulcer, chronic or unspecified with both haemorrhage and perforation	UGIB
K26	Duodenal ulcer	UGIB
K26.0#	Duodenal ulcer, acute with haemorrhage	UGIB
K26.2#	Duodenal ulcer, acute with both haemorrhage and perforation	UGIB
K26.4#	Duodenal ulcer, chronic or unspecified with haemorrhage	UGIB
K26.6#	Duodenal ulcer, chronic with both haemorrhage and perforation	UGIB
K27	Peptic ulcer, site unspecified	UGIB
K27.0	Peptic ulcer, acute with haemorrhage	UGIB
K27.2	Peptic ulcer, acute with both haemorrhage and perforation	UGIB
K27.4	Peptic ulcer, chronic or unspecified with haemorrhage	UGIB
K27.6	Peptic ulcer, chronic with both haemorrhage and perforation	UGIB
K28	Gastrojejunal ulcer	LGIB
K28.0	Gastrojejunal ulcer, acute with haemorrhage	LGIB
K28.2	Gastrojejunal ulcer, acute with both haemorrhage and perforation	LGIB
K28.4	Gastrojejunal ulcer, chronic or unspecified with haemorrhage	LGIB
K28.6	Gastrojejunal ulcer, chronic with both haemorrhage and perforation	LGIB
K62.5	Haemorrhage of anus and rectum	LGIB

ICD-10 code	Bleeding diagnosis	Subcategory
K66.1	Haemoperitoneum	LGIB
K92.1	Melaena	LGIB
K92.2	Gastrointestinal haemorrhage, unspecified	LGIB
R04	Haemorrhage from respiratory passages	
R04.0	Epistaxis	
R04.1	Haemorrhage from throat	
R04.2	Haemoptysis	
R04.8	Haemorrhage from other sites in respiratory passages	
R04.9	Haemorrhage from respiratory passages, unspecified	
R31	Unspecified haematuria	
R58	Haemorrhage, not elsewhere classified	
T81.0	Haemorrhage and haematoma complicating a procedure, not elsewhere classified	
Y60	Unintentional cut, puncture, perforation or haemorrhage during surgical and medical care	

ICH, intracranial hemorrhage; LGIB, lower gastrointestinal bleeding, UGIB, upper gastrointestinal bleeding.

Appendix 3, Reported Edmonton Frail Scale

Frailty domain	Item	0 point	1 point	2 points
General health status	In the past year, how many times have you been admitted to a hospital?	0	1–2	>2
	In general, how would you describe your health?	Excellent Very good Good	Fair	Poor
Functional independence	With how many of the following activities do you require help? - Meal preparation - Shopping - Transportation - Telephone - Housekeeping - Laundry - Managing money - Taking medications	0–1	2–4	>4
Social support	When you need help, can you count on someone who is willing and able to meet your needs?	Always	Something	Never
Medication use	Are you on five or more different prescription medications on a regular basis?	No	Yes	
	At times, do you forget to take your prescription medications?	No	Yes	
Nutrition	Have you recently lost weight such that your clothing has become looser?	No	Yes	
Mood	Do you often feel sad or depressed?	No	Yes	
Continence	Do you have a problem with losing control of urine when you do not want to?	No	Yes	

Frailty domain	Item	0 point	1 point	2 points
Functional performance	Two weeks ago, were you able to: - Do heavy work around the house like washing windows, walls, or floors without help? - Walk up and down stairs to the second floor without help? - Walk 1 km without help?	 Yes Yes Yes	 No No No	
Cognition	Pre-drawn circle. Add the numbers in the correct positions to make a clock then place the hands to indicate a time of ten past eleven.	No errors	Minor erros	Major errors
Totals /17				

Scoring: 0–5 Not frail, 6–7 Vulnerable, 8–9 Mild frailty, 10–11 Moderate frailty, 12–17 Severe frailty.

Appendix 4, Stroke and bleeding risk scores

Risk scheme	Risk Factors	Risk Category	Points
Outpatient Bleeding Index (Beyth et al. 1998)	Age ≥65 years (1 point) History of stroke (1 point) History of GI bleeding (1 point) Recent MI, haematocrit < 30 %, creatinine >1.5 mg/dl, or diabetes mellitus (1 point if any of these)	Low Intermediate High	0 1–2 3–4
HEMORR$_2$HAGES (Gage et al., 2006a)	Hepatic or renal disease (1 point) Ethanol abuse (1 point) Malignancy (1 point) Older age >75 yrs (1 point) Reduced platelet count or function (1 point) Prior bleed (2 points) Hypertension (1 point) Anemia (1 point) Genetic factors (1 point)* Excessive fall risk or neuropsychiatric disease (1 point) Stroke (1 point)	Low Intermediate High	0–1 2–3 ≥4
HAS-BLED (Pisters et al., 2010)	Hypertension (1 point) Abnormal renal or liver function (1 point each) Stroke (1 point) Bleeding history or predisposition (1 point) Labile INR (1 point) Elderly (>65 years) Drugs or alcohol concomitantly (1 point each)	Low 0–2 High ≥ 3	

Risk scheme	Risk Factors	Risk Category	Points
ATRIA (Fang et al., 2011)	Anemia (3 points) Renal disease (3 points) Age ≥ 75 years (2 points) Prior bleeding (1 point) Hypertension (1 point)	Low 0–3 Intermediate 4 High 5–10	
$CHADS_2$ (Gage et al., 2001)	Congestive Cardiac Failure (1 point) Hypertension (1 point) Age >75 years (1 point) Diabetes Mellitus (1 point) Cerebrovascular Accident or TIA (2 point)	Low 0 Moderate 1–2 High ≥ 2	
$CHADS_2VASc$ (Lip et al., 2010)	Congestive Cardiac Failure (1 point) Hypertension (1 point) Age > 65 years Age 64–75 years (1 point) Age ≥75 years (2 points) Diabetes Mellitus (1 point) Cerebrovascular Accident or TIA (2 points) Vascular Disease (Prior MI, peripheral artery disease, or aortic plaque) (1 point) Female gender when age ≥75 years (1 point)	Low 0 Moderate 1 High ≥ 2	

GI, gastrointestinal; INR, international normalized ratio; MI, myocardial infarction; TIA, transient ischemic attack.

Appendix 5, Charlson comorbidity score

Assigned weights for disease	Conditions
1	Myocardial infarct Congestive heart failure Peripheral vascular disease Cerebrovascular disease Dementia Chronic pulmonary disease Connective tissue disease Ulcer disease Mild liver disease Diabetes
2	Hemiplegia Moderate of severe renal disease Diabetes with end organ damage Any tumor Leukemia Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor AIDS

Assigned weights for each condition that a patient has. The total equals the score. Example: myocardial infarct (1) and diabetes with end organ damage (2) = total score (3). (Charlson et al., 1987).

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