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PERCUTANEOUS CORONARY INTERVENTION IN PATIENTS WITH ATRIAL FIBRILLATION:

A study of factors affecting outcome, with a special
emphasis on periprocedural antithrombotic treatment

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To my family

ABSTRACT

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PERCUTANEOUS CORONARY INTERVENTION IN PATIENTS WITH ATRIAL FIBRILLATION: A STUDY OF FACTORS AFFECTING OUTCOME, WITH A SPECIAL EMPHASIS ON PERIPROCEDURAL ANTITHROMBOTIC TREATMENT

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Antithrombotic treatment of patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI) is a delicate balancing between the risk of thromboembolism and the risk of bleeding.

The purpose of this dissertation was to analyze current antithrombotic treatment strategies at the periprocedural stage and report outcomes in-hospital and at 1-month follow-up, and to evaluate the effect of renal impairment and predictive values of various bleeding scores on 1-year outcome after PCI in patients with AF.

The first article was based on retrospective data from 7 Finnish hospitals between 2002–2006 (n=377), while the others were based on a prospective 17-center European register (AFCAS) gathered between 2008–2010 (n=963).

The main findings in patients with AF undergoing PCI were: The use of glycoprotein IIb/IIIa inhibitors during PCI was associated with a four- to five-fold increase in the risk of major bleeding (I). Uninterrupted warfarin treatment did not increase perioperative complications and seemed to decrease bleeding complications compared to heparin bridging (II). Already mild renal impairment (eGFR 60–90mL/min) was associated with a 2.3-fold risk of all-cause mortality during the 12 months following PCI (III). Major adverse cardiac events occurred in 4.5% and bleeding complications in 7.1% of patients in the AFCAS register by 1-month follow-up (IV). In a study of patients in AFCAS register, all currently used bleeding risk scores were poor predictors of bleeding complications by 1-year follow-up (V).

The findings will help improve treatment strategies for this fragile patient population with a high risk of bleeding and thrombotic complications.

Keywords: atrial fibrillation, anticoagulation, antithrombotic, PCI, CKD, bleeding, thrombosis, risk stratification

TIIVISTELMÄ

Heli Lahtela

ETEISVÄRINÄPOTILAIDEN PALLOLAAJENNUSTOIMENPITEET JA HOITOTULOKSIIN
VAIKUTTAVAT TEKIJÄT

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Eteisvärinäpotilaiden antitromboottinen hoito sepelvaltimoiden pallolaajennustoimenpiteiden (PCI) yhteydessä on haasteellista tasapainoilua, jonka pyrkimyksenä välttää sekä tromboottiset komplikaatiot että verenvuodot.

Tutkimuksen tarkoituksena oli analysoida tämänhetkisiä eteisvärinäpotilaiden antitromboottisia hoitokäytäntöjä PCI-toimenpiteen yhteydessä ja raportoida tulokset sekä sairaalavaiheesta, että kuukauden seurannasta. Lisäksi työn tarkoituksena oli arvioida munuaisten vajaatoiminnan vaikutuksia tässä potilasryhmässä, sekä erilaisen vuotoriskiä arvioivien pisteytysten osuvuutta vuoden seurannassa. Laajoja satunnaistettuja tutkimuksia näistä aiheista ei ole saatavilla.

Ensimmäinen artikkeli pohjautui retrospektiiviseen monikeskustutkimukseen (n=377), jossa mukana oli 7 suomalaista sairaalaa vuosina 2002 - 2006. Muut tutkimukset perustuivat prospektiiviseen monikeskusaineistoon, AFCAS-rekisteriin, jossa oli mukana 17 eurooppalaista sairaalaa vuosina 2008 - 2010 (n= 963).

Tutkimusten tärkeimmät löydökset olivat: PCI:n aikaiseen glykoproteiini IIb/IIIa estäjien käyttöön liittyi 4-5-kertainen riski vakaviin verenvuotoihin (I). PCI:n aikainen keskeytyksetön varfariinihoito ei suurentanut komplikaatoriskiä ja näytti jopa laskevan verenvuotoriskiä vertailussa hepariinilla toteutettuun siltahoitoon 451 potilaalla (II). Lievä munuaisten vajaatoiminta (eGFR 60-90mL/min) todettiin 37 %:lla 781 potilaasta ja jopa siihen liittyi 2.3-kertainen kuolemanvaara vuoden seurannassa PCI:n jälkeen (III). Yhteensä 4.5 %:lla AFCAS-rekisterin 963 potilaasta ilmeni jokin merkittävä sydän- tai verenkiertoperäinen komplikaatio kuukauden seurannassa (IV). Kaikki käytössä olevat vuotoriskitaulukot todettiin huonoiksi ennustamaan vuotokomplikaatioita vuoden seurannan aikana PCI:n jälkeen (V).

Tämän tutkimuksen löydökset auttavat parantamaan tämän hauraan ja korkeassa tromboosi- ja vuotoriskissä olevan potilasryhmän hoitokäytäntöjä.

Avainsanat: eteisvärinä, antikoagulaatio, tromboosi, verenvuoto, munuaisten vajaatoiminta

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ABBREVIATIONS

ACS	acute coronary syndrome
AF	atrial fibrillation
ARR	absolute risk reduction
ASA	acetylsalicylic acid
BMS	bare metal stent
BT	bridging therapy
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CHADS ₂	risk-score (Congestive heart failure, Hypertension, Age≥75years, Diabetes mellitus, prior Stroke or TIA or thromboembolism)
CHA ₂ DS ₂ -VASc	risk score (Congestive heart failure, Hypertension, Age≥75years, Diabetes mellitus, prior Stroke or TIA, Vascular disease, Age 65-74 years, Sex category)
CI	confidence interval
CKD	chronic kidney disease
CVD	cardiovascular disease
DAPT	dual antiplatelet therapy
DES	drug-eluting stent
eGFR	estimated glomerular filtration rate
GI	gastrointestinal
GPI	glycoprotein inhibitors IIb/IIIa
HAS-BLED	bleeding score (hypertension, abnormal renal/liver function, prior stroke, prior bleeding, labile INR, age >65 years, drugs/alcohol)
HR	hazard ratio
IAC	interrupted anticoagulation
IQR	Interquartile range
INR	international normalized ratio
LMWH	low-molecular-weight heparin
MACCE	major adverse cardiac and cerebrovascular event

MACE	major adverse cardiac event
MI	myocardial infarction
NKF	National Kidney Foundation
NNT	number needed to treat
NOAC	new oral anticoagulants
NSTEMI	non-ST-elevation myocardial infarction
OAC	oral anticoagulation
OR	odds ratio
PCI	percutaneous coronary intervention
PPI	proton-pump inhibitor
ROC	receiver operating characteristic curve
RR	relative risk
SAPT	single antiplatelet drug therapy
SD	standard deviation
ST	stent thrombosis
STEMI	ST-elevation myocardial infarction
TIA	transient ischemic attack
TLR	target lesion revascularization
TT	triple therapy
TVR	target vessel revascularization
UAC	uninterrupted anticoagulation
UFH	unfractionated heparin
VKA	vitamin K antagonist

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by Roman numeral.

- I Heli Lahtela, Pasi P Karjalainen, Matti Niemelä, Saira Vikman, Kari Kervinen, Antti Ylitalo, Marja Puurunen, Pekka Porela, Kai Nyman, Susanna Hinkka-Yli-Salomäki, K.E. Juhani Airaksinen: Are glycoprotein inhibitors safe during percutaneous coronary intervention in patients on chronic warfarin treatment? *Thrombosis and Haemostasis* 12/2009; 102(6):1227-33.
- II Heli Lahtela, Andrea Rubboli, Axel Schlitt, Pasi P Karjalainen, Matti Niemelä, Saira Vikman, Marja Puurunen, Michael Weber, José Valencia, Fausto Biancari, Gregory Y H Lip, K.E. Juhani Airaksinen: Heparin Bridging vs. Uninterrupted Oral Anticoagulation in Patients with Atrial Fibrillation Undergoing Coronary Artery Stenting. Results from the AFCAS registry. *Circulation Journal* 03/2012; 76(6):1363-8
- III Heli Lahtela, Tuomas Kiviniemi, Marja Puurunen, Axel Schlitt, Andrea Rubboli, Antti Ylitalo, José Valencia, Gregory Lip, K.E. Juhani Airaksinen for the AFCAS Study Group: Renal impairment and prognosis of patients with AF undergoing PCI - The AFCAS trial. Submitted for publication.
- IV Axel Schlitt, Andrea Rubboli, Gregory Y.H. Lip, Heli Lahtela, Jose`Valencia, Pasi P. Karjalainen, Michael Weber, Mika Laine, Paulus Kirchhof, Matti Niemelä, Saira Vikman, Michael Buerke, K.E. Juhani Airaksinen for the AFCAS (Management of Patients with Atrial Fibrillation Undergoing Coronary Artery Stenting Study Group). The Management of Patients with Atrial Fibrillation Undergoing Percutaneous Coronary Intervention with Stent Implantation: In-Hospital-Data from the Atrial Fibrillation undergoing Coronary Artery Stenting Study. *Catheterization and Cardiovascular Interventions* 12/2013;82(7):E864-70. Epub 2013 Aug 28
- V Tuomas Kiviniemi, Marja Puurunen, Axel Schlitt, Andrea Rubboli, Pasi Karjalainen, Saira Vikman, Matti Niemelä, Heli Lahtela, Gregory Y.H. Lip, and K.E. Juhani Airaksinen: Performance of Bleeding Risk-Prediction Scores in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention. *Am J Cardiol* 6/2014;113(12):1995-2001. Epub 2014 Apr 1

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1 INTRODUCTION

Atrial fibrillation (AF) impairs quality of life and independently increases mortality and morbidity, mainly due to stroke, thromboembolism, and congestive heart failure. It is estimated that up to 30% patients with AF also have coronary artery disease (CAD). Percutaneous coronary intervention (PCI) is a common procedure among AF patients, and approximately 5–10% of patients undergoing PCI require long-term oral anticoagulation (OAC), mainly due to AF [1-3]. The long-term prognosis of warfarin-treated PCI patients is unsatisfactory, irrespective of the periprocedural or postprocedural drug combinations used. The periprocedural phase requires balancing between the risk of thromboembolism and the risk of bleeding, combined with the need for combination antithrombotic treatments. Thromboembolism leads to an increased risk of stroke, recurrent myocardial infarction (MI) and stent thrombosis (ST), while bleeding is also associated with an unfavorable prognosis and is an independent predictor of mortality. The management of this growing patient group is challenging, and at present it is not possible to draw firm conclusions on the relative efficacy and safety of different management strategies, since there is a lack of randomized controlled studies as well as high variability in the contemporary management of these patients.

Current guidelines recommend glycoprotein IIb/IIIa inhibitors (GPIs) in high-risk patients undergoing PCI while underscoring the importance of assessing the patient's individual bleeding risk [4, 5]. The interruption of oral anticoagulation and bridging therapy (BT) with unfractionated heparin (UFH) or low-molecular-weight-heparin (LMWH) has also been recommended [6]. However, neither randomized trials nor large prospective datasets have compared different strategies for managing patients on long-term OAC during PCI. Data from recent observational studies suggest that uninterrupted OAC (UAC) could replace heparin bridging in OAC patients undergoing PCI, striking a favorable balance between bleeding and thrombotic complications. Performing PCI during therapeutic anticoagulation (international normalized ratio [INR] 2.0–3.0) is currently regarded as an alternative strategy [7, 8].

Also, assessments of the true efficacy and safety of a triple therapy (TT) combination of vitamin K antagonist (VKA), aspirin, and clopidogrel are incomplete [9, 10]. There is no available data of use of newer P2Y₁₂ receptor inhibitors (prasugrel, ticagrelol) as a part of triple therapy. Finally, limited information exists on the effects of periprocedural variables – such as the vascular access site, the adoption of bridging anticoagulation strategies, and the use of GPIs – on the risk of in-hospital hemorrhagic events [11, 12].

Chronic kidney disease (CKD) has become an increasing problem, affecting up to 16% of the global population [13]. Several studies have established that, in the general population, moderate and severe CKD is associated with increased risk of

cardiovascular morbidity and mortality and increased prevalence of AF [14-21]. According to its traditional definition (eGFR <60mL/min/1.73 m²), CKD has also been associated with an increased risk of post-PCI ischemic and bleeding complications in various patient groups [22-26]. Even the early stage of disease (eGFR 60-89mL/min) seems to increase cardiovascular risk, irrespective of the levels of traditional cardiovascular disease risk factors [27, 28], indicating a need to pay attention to this group of higher-risk AF patients.

The hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio (INR), elderly, drugs/alcohol (HAS-BLED) [29]; anticoagulation and risk factors in atrial fibrillation (ATRIA) [30]; modified Outpatient Bleeding Risk Index (mOBRI) [31, 32]; and reduction of atherothrombosis for continued health (REACH) [33] schemes are validated bleeding risk-prediction tools, but their predictive performance in this frail patient subset remains unknown. We sought to compare the predictive performance of bleeding risk-estimation tools for bleeding events and mortality in a cohort of patients with AF undergoing PCI.

In general, patients with AF have a worse prognosis and require longer in-hospital treatment than patients without AF. AF, then, represents a burden on public health in the form of higher health-care costs, suggesting safe and effective treatment strategies are needed. The aim of this dissertation is to compare various periprocedural antithrombotic treatment strategies from an observational registry and assess the impact of baseline risk factors on short- and long- term outcomes.

2 REVIEW OF LITERATURE

2.1 Atrial fibrillation (AF)

AF is the most common sustained cardiac arrhythmia, affecting 1–3.2% of the general population [34, 35]. As the population ages, it is estimated that AF prevalence will increase among Europeans by at least 2.5-fold over the next 50 years[36]. The calculated lifetime risk for the development of AF is approximately 1 in 4 for persons ≥ 40 years [37, 38], with a slightly higher risk for men [39].

2.1.1 Predisposing factors and co-morbidities

AF is a chronic, progressive disease. It often starts with short, rare, silent, paroxysmal episodes, progresses to longer and more frequent persistent episodes, and finally ends in permanent AF [40]. The development of AF is strongly associated with age, with the risk doubling every decade after 50 years of age [38]. The prevalence of AF increases from 0.5% at 40–50 years to 5–15% at 80 years [34, 39, 41, 42]. The mean age of AF patients has been approximately 75 years [43], but has steadily risen to the current average of 75–85 years [44].

AF commonly coexists with other cardiovascular risk factors and disorders. Over 70% of AF patients have another heart disease or predisposing factor for arrhythmia, and almost 60% of new-onset AF is attributed to common cardiovascular risk factors [45]. The most common contributing factors are heart failure (50%), coronary artery disease (CAD) (30%), hypertension (84%), valvular disease (64%), and cerebrovascular disease (30%). In addition, chronic kidney disease (CKD), diabetes, obesity and lung diseases are known risk factors for AF [37, 38, 44, 46-48].

2.1.2 AF as a risk factor

AF is a complex, heterogeneous disorder with comorbidities significantly modulating disease progression and prognosis. It is associated with increased mortality and morbidity, especially stroke and heart failure [39, 49-51]. The complications have a strong association with increasing age [52].

2.1.2.1 Mortality

AF doubles mortality independently of any other known predictors [41, 53-56]. Several studies have reported 1.5–2.0-fold increases in the mortality rate for males and a corresponding 1.9–2.2-fold increase for females [36, 41], while the relative risk of all-cause mortality is reported to be almost 5-fold in females < 65 years and 3-fold in males during the first year after AF diagnosis [57]. The combination of AF and heart

failure carries an increased risk of mortality compared to those with preserved systolic function [58, 59].

2.1.2.2 Stroke

AF is an independent risk factor for stroke and thromboembolism [49], with a 4–5-fold increase of stroke risk [60, 61]. All types of AF (paroxysmal, persistent, and permanent) seem to carry a similar risk of ischemic stroke [59, 62–65]. On the other hand, up to 20% of all stroke events are thought to be attributable to AF [66] [67]. The absolute risk of stroke averages 3–4% per year in patients with AF, but the risk varies largely depending on patient age and other clinical features [68, 69]. In patients with newly diagnosed AF without any other risk factors, the risk of stroke starts to rise after the age of 65, with a 1.5-fold increase per decade [70].

The mechanisms underlying the increased thrombogenesis appearing during AF are only partly understood. It has been hypothesized that a complex and synergistic combination of pathophysiological changes in endothelial function, blood flow, coagulation factors, platelet function, and fibrinolysis (Virchow's triad) results in a prothrombotic or hypercoagulable state [71–73]. Most AF-related strokes are caused by embolization of a thrombus formed in the left atrial appendage, which causes embolic occlusion of a main cerebral artery or its branches and a large area of cerebral infarction [71], leading to substantial neurologic disability. AF-associated strokes lead to greater disability, higher rates of stroke recurrence, and higher mortality compared to strokes in patients without AF [74].

Several large population-based cohorts have shown the association between female gender and higher risk for stroke [75–79]. Women suffer cardioembolic strokes more frequently than other types of strokes, increasing the risk of early death, with a 1-month case fatality of 24.7% compared with 19.7% in men [80, 81].

2.1.3 Renal impairment and atrial fibrillation

Chronic kidney disease (CKD) has become an increasing problem, affecting up to 16% of the global population [13]. National Kidney Foundation guidelines define 5 stages of CKD (Table 1) based on estimated glomerular filtration rate (eGFR). CKD is defined as kidney damage or eGFR < 60 mL/min per 1.73 m² of body-surface area for 3 months or longer [27]. Even the early stage of disease (eGFR 60–89 mL/min) seems to increase cardiovascular risk, irrespective of levels of traditional cardiovascular disease risk factors [27, 28].

The reported prevalence of CKD in AF patients is 18–25%, with higher figures for those > 70 years of age [14, 20, 82]. These rates are up to 2–3 times higher than in the general population [14]. In a recent review, Kirchhof et al. reported that 12.9% of AF patients have eGFR ≤ 90 mL/min [83].

2.1.3.1 Pathophysiological changes behind the elevated risk of cardio- and cerebrovascular diseases

CKD and the risk of CVD is explained by a range of myocardial and vascular insults, including malignant ventricular remodeling; low-grade inflammation; endothelial dysfunction; derangements in electrolytes, metabolic compounds, and the autonomic nervous system; and calcification and loss of arterial compliance in small and large arteries [84-87]. In patients with AF and CKD, these pathophysiological changes lead to an increased risk of cardiovascular events, stroke, or systemic thromboembolism, but also an increased risk for bleeding [88-91], resulting in increasing periods of hospitalization and cardiovascular morbidity and mortality [14-21]. The adjusted risk for death has been reported to be 1.2–5.9-fold, depending on the stage of CKD [18]. Renal insufficiency has been established as a predictor of stroke in the general population as well as in AF patients [20, 92, 93].

Despite the confirmed risk of all types of CVD, patients with CKD often do not receive the same appropriate treatment as patients with normal renal function [94]. Patients with AF and renal disease also have many other comorbidities, increasing the complexity of managing care, as many common treatments are less used or less effective. Evaluating the risk–benefit balance of anticoagulation for this patient group is a difficult process [95]. However, in a recent large observational study, warfarin treatment was associated with a lower 1-year risk for the composite outcome of death, MI, and ischemic stroke without being associated with a higher risk of bleeding, and this association was not related to the severity of concurrent CKD [96].

Table 1. National Kidney Foundation (NKF) classifications and action plans for the various stages of chronic kidney disease (CKD), modified from the Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines for CKD [28].

Stage	Description	eGFR, mL/min per 1.73 m ²	Action at preceding stages
—	At increased risk	≥60 (with CKD risk factors)	Screening; CKD risk reduction
1	Kidney damage with normal or increased eGFR	≥90	Diagnosis and treatment; treatment of comorbid conditions; slowing progression; CVD risk reduction
2	Kidney damage with mildly decreased eGFR	60–89	Estimating progression
3	Moderately decreased eGFR	30–59	Evaluating and treating complications
4	Severely decreased eGFR	15–29	Preparation for kidney replacement therapy
5	Kidney failure	<15 or dialysis	Kidney replacement (if uremia present)

CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate. CKD is defined as either kidney damage or GFR < 60 mL/min per 1.73 m² for 3 or more months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

GFR is estimated from serum creatinine measurements using the Modification of Diet in Renal Disease study equation, which is based on age, sex, race, and calibration for serum creatinine. For stages 1 and 2, kidney damage is estimated using untimed urine samples to determine albumin–creatinine ratios; a ratio of > 17 mg/g in men or > 25 mg/g in women during two separate measurements indicates kidney damage. The proportion of persons at increased risk for CKD has not been estimated accurately.

2.2 Management of AF

Marked changes in the management of AF have taken place in the past years, and current European (ESC) [44, 97, 98], US (ACC/AHA) [99] and Canadian [100] guidelines, including the Current Care Guideline in Finland [101], have been recently updated. The availability of new oral anticoagulants (NOACs) [102-104] and better knowledge of catheter ablation techniques, along with improved understanding of patient selection for successful procedures, have changed recommendations [105, 106]. The role of new antiarrhythmic drugs in clinical practice has also been defined more clearly [107-109].

2.2.1 Assessment of stroke risk

An individual risk assessment based on stroke prevention with appropriate thromboprophylaxis is the cornerstone of the comprehensive management of AF. Two systematic reviews have confirmed stroke risk factors for AF [68, 110]. Out of 43 predictors of stroke in AF patients, previous stroke/transient ischemic attack (TIA) (relative risk (RR) 2.5), hypertension (RR 2.0), increasing age (RR 1.5 per decade), and diabetes mellitus (RR 1.7) have been identified as the strongest independent predictors of stroke [68, 110].

The identification of various clinical stroke risk factors has led to the publication of stroke risk scoring schemes, which categorize stroke risk into 'high', 'moderate', and 'low' risk strata. The simplest risk assessment scheme is the CHADS₂ score, (Cardiac failure, Hypertension, Age, Diabetes, Stroke) [111]. An updated version, CHA₂DS₂-VASc, was published in 2010 (Table 2) [78]. The principle of these risk stratification schemes is to identify truly low-risk patients who do not need antithrombotic therapy [91, 112, 113]. In addition, the rates of mortality, heart failure, MI, stroke, and gastrointestinal (GI) bleeding increase with higher CHADS₂ scores [114].

Table 2. CHA₂DS₂VASc risk score [78] and adjusted stroke risk %/year [115].

Acronym	Risk Factor	Points		Total Score	Stroke risk %/year
C	Congestive heart failure	1		0	0 %
H	Hypertension	1		1	1.3 %
A ₂	Age ≥ 75 years	2		2	2.2 %
D	Diabetes	1	Score indicating risk of stroke ⇒	3	3.2 %
S ₂	Stroke or TIA	2		4	4.0 %
V	Vascular disease	1		5	6.7 %
A	Age 65–74 years	1		6	9.8 %
Sc	Sex category female ≥ 65 years	1		7	9.6 %
				8	6.7 %
				9	15.2 %

TIA= transient ischemic attack

Despite the known association between CKD and thromboembolism, this association has not been included in any of the current risk stratification schemes. Lip has suggested that the small *c* in the CHA₂DS₂-VASc scoring scheme could also be used to denote “CKD” [116]. Another risk assessment scheme, R₂CHADS₂ (the patient’s CHADS₂ score, plus 2 points if creatinine clearance <60 mL/min [R2]), has been derived from a clinical trial population and identifies renal dysfunction as a potent predictor of stroke in patients with AF [93].

2.2.2 Assessment of bleeding risk

Bleeding poses a major challenge in the therapeutic use of OACs. Many risk factors for bleeding are also risk factors for stroke, which makes bleeding risk stratifications complex. Unfortunately, there is no bleeding risk score in clinical use that includes all notable risk factors. The risk of bleeding should be assessed together with the risk of thromboembolism prior to beginning OAC therapy, and current guidelines recommend the use of the HAS-BLED risk score (Table 3) [117] [98, 100, 118, 119]. A HAS-BLED score of ≥3 indicates that caution is warranted and regular review is recommended, as well as efforts to correct the potentially reversible risk factors for bleeding [44]. However, a high HAS-BLED score per se should not be used to exclude patients from OAC therapy, as a net clinical benefit of OAC treatment has been observed even in patients with high HAS-BLED scores [98, 119]. Other validated bleeding risk-prediction tools include the **Anticoagulation and Risk factors in AF (ATRIA)** [30] (Table 4.), **modified Outpatient Bleeding Risk Index (mOBRI)**[31, 32] (Table 5.), and **Reduction of Atherothrombosis for Continued Health (REACH)** [33](Table 6.) schemes.

Table 3. HAS-BLED score. The risk percentage is modified from the major bleeding within 1 year in patients with atrial fibrillation enrolled in the Euro Heart Survey [117].

Acronyms	Clinical characteristics	Points		Total Score	Risk of major bleeding %
				0	1.13
H	Hypertension	1		1	1.02
A	Abnormal renal and/or liver function	1 or 2 (1 point each)		2	1.88
S	Stroke	1		3	3.73
B	Bleeding (cancer, anemia, thrombocytopenia, thrombotic disorder, prior bleeding)	1	Score indicating risk of bleeding	4	8.7
L	Labile INRs	1	⇒	5	12.5
E	Elderly (e.g. age >65 years)	1		6	.*
D	Drugs and/or alcohol	1 or 2 (1 point each)		7	.*
HAS-BLED score ≥3 high risk of bleeding				8	.*
				9	.*

*Not determined due to lack of available data (0–2 patients/group).

Table 4. Bleeding risk score ATRIA (**A**nticoagulation and **R**isk factors in **A**trial fibrillation).

A	anemia hemoglobin <13 g/dl in men and <12 g/dl in women	3	Patients with scores ≥ 4 are considered to be at intermediate/high bleeding risk.
T	renal impairment (estimated glomerular filtration rate [eGFR] <30 or dialysis treatment)	3	
R	hypertension and	1	
I	previous bleeding episode	1	
A	age ≥ 75 years	2	

Table 5. Bleeding risk score mOBRI (**m**odified **O**utpatient **B**leeding **R**isk **I**ndex).

mOBRI	Age ≥ 65 years	1	Patients with ≥ 1 mOBRI points are at intermediate/high bleeding risk
	Previous stroke	1	
	Gastrointestinal tract bleeding within 2 weeks	1	
	Recent myocardial infarction diabetes or	1	
	Hematocrit <0.30 or		
	Creatinine >1.5 mg/dl, or 133 mmol/L).		

Table 6. Bleeding risk score REACH (**R**eduction of **A**therothrombosis for **C**ontinued **H**ealth)

REACH	Points	
Age groups		REACH scores >10 points are considered intermediate/high for the risk of bleeding.
45 to 54	0	
55 to 64	2	
65 to 74	4	
≥ 75	6	
Peripheral arterial disease	1	
Diabetes	1	
Hypercholesterolemia	1	
Congestive heart failure	2	
Hypertension	2	
Oral anticoagulant	4	
Aspirin	1	
Other antiplatelet	2	
Combination of 2 antiplatelet drugs	4	
Former smoking	1	
Current smoking	2	

2.2.3 Oral anticoagulation (OAC)

OAC is the established mainstay treatment for the prevention of stroke [44, 98]. Approximately 80–90% of patients with AF have an indication for OAC [47, 83]. A risk stratification-based OAC treatment strategy is shown in Figure 1.

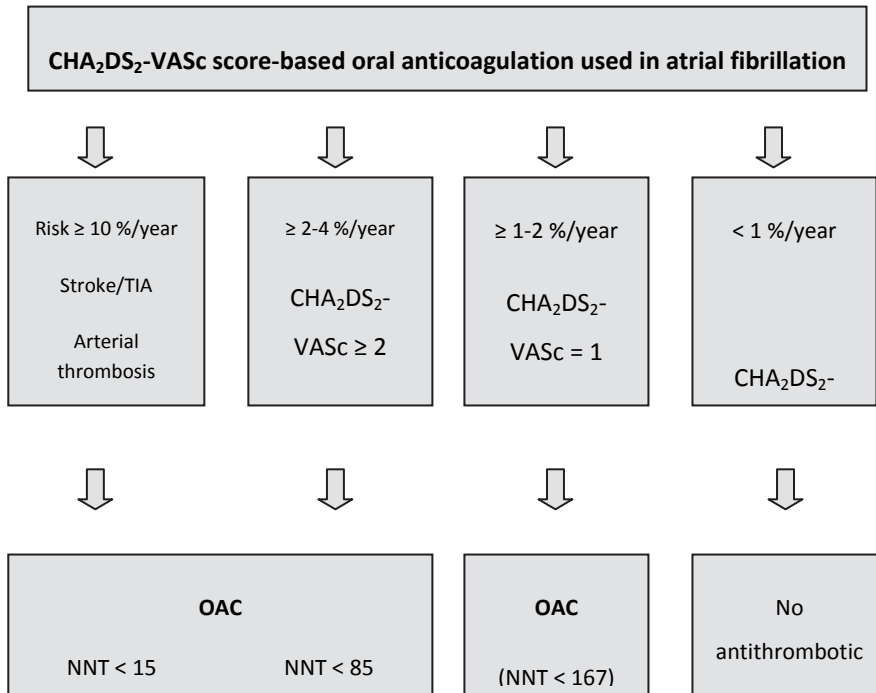


Figure 1. Oral anticoagulation based risk stratification [101]. NNT=Number Needed to Treat, the average number of patients who need to be treated to prevent one additional bad outcome. OAC=oral anticoagulation, TIA=transient ischemic attack

2.2.3.1 Vitamin K antagonist: Warfarin

Vitamin K antagonists (VKAs; warfarin, acenocoumarol, phenprocoumon) have been the most frequently used oral anticoagulants for over 60 years. Their effectiveness has been established in large clinical trials for primary and secondary prevention of stroke in AF [120].

Adjusted-dose warfarin in patients with AF has shown a significant, up to 64%, reduction in the relative risk of ischemic stroke or systemic embolism compared to placebos and up to a 30% reduction in all-cause mortality [121, 122]. Secondary prevention is more efficient with absolute risk reduction (ARR) for stroke (8.4%/year; NNT for 1 year to prevent one stroke of 12 vs primary prevention 2.7%/year; NNT 37). However, with warfarin, the risk of bleeding increases and the rate of major extracranial hemorrhage has been reported to be ≤0.3% per year [123]. In a recent nested case-control analysis, patients with AF have nearly twice (RR: 1.71) the risk of stroke in the first 30 days after initiation of warfarin treatment than those not on warfarin, after which their relative risk decreases (RR 0.50) [124]. A systemic review of the the Cochrane Database, anticoagulants are not more efficacious in the

prevention of recurrent ischemic stroke presumed to be of arterial origin (non-AF stroke) than antiplatelet therapy [125].

2.2.3.2 Novel oral anticoagulants (NOACs)

In 2012, updated guidelines for the management of AF incorporated NOACs, which act by directly and selectively inhibiting key coagulation factors such as thrombin (i.e. dabigatran) and factor Xa (i.e. rivaroxaban and apixaban) [44]. These agents are effective in inhibiting stroke in AF patients, but at the time of study these were not in clinical use. However, very limited data is available on their use in AF patients undergoing PCI, but these new drugs are gradually changing the treatment practices also in patients undergoing PCI.

2.2.4 Antiplatelet therapy

2.2.4.1 Aspirin

Acetylsalicylic acid, i.e. aspirin, irreversibly inhibits the synthesis of thromboxane A₂, resulting in inhibition of platelet function. The antiplatelet effect appears within 1 hour and persists for at least 4 days after cessation of therapy.

In placebo-controlled trials, aspirin has reduced strokes in AF by 20% [126], but this effect was not seen in the elderly (> 80 years) [127]. Aspirin reduced the occurrence of strokes categorized as noncardioembolic significantly more than it did those categorized as cardioembolic [128]. Many randomized trials confirm that aspirin is inferior to OAC for stroke prevention, and the risks of bleeding associated with aspirin are not significantly different from those associated with OAC, especially among the elderly [129-131]. The effect of aspirin on stroke reduction in patients with AF might simply be the effect of aspirin on atherosclerotic vascular disease, which is a very common comorbidity with AF [73]. In primary prevention of AF patients, aspirin has been shown to decrease stroke risk by 33%, while in secondary prevention, reduction has been evaluated to be only 11% [126].

2.2.4.2 P2Y₁₂ receptor inhibitor

Clopidogrel, ticlopidine and prasugrel irreversibly inhibit the platelet surface P2Y₁₂ adenosine diphosphate receptors, leading to irreversible inhibition of platelet aggregation. Ticagrelor affects the same platelet receptor, but its binding is reversible. There is no data comparing clopidogrel or other antagonists to warfarin in the prevention of stroke in AF.

2.2.4.3 Dual antiplatelet therapy (DAPT)

DAPT with aspirin and clopidogrel is less effective for the prevention of stroke in AF patients than adjusted-dose warfarin, with no difference in the occurrence of major bleeding [132, 133]. In a randomized, controlled ACTIVE W trial, investigators

showed that OAC was 40% more effective than the combination of aspirin and clopidogrel in reducing stroke [133]. DAPT with aspirin and clopidogrel is more effective than aspirin alone, but the increased risk of bleeding leads to a reduced net benefit [132]. There is no data available on DAPT with aspirin and prasugrel or ticagrelor for stroke prevention.

2.3 Atrial fibrillation and percutaneous coronary intervention

2.3.1 Prevalence of AF patients undergoing PCI

Approximately 5–8% of patients referred for PCI have an indication for OAC, with nearly 70% of this due to AF [1, 2, 9, 134]. CAD coexists in up to 30% of AF patients who have an indication for OAC [1, 56, 58, 59]. The combination of AF and CAD is associated with significantly higher mortality rates [135]. Both the peri- and postprocedural management of antithrombotic therapy is challenging, with a need to balance the risk of bleeding against that of thromboembolism, stent thrombosis (ST), and adverse cardiac events. The development of stents and novel adjunctive medications have improved PCI outcomes, and the survival advantage of coronary artery bypass (CABG) surgery has been lost in many patient groups [136, 137]. The decision between PCI and CABG surgery should also be guided by technical improvements in cardiology and surgery, local expertise, and patient preference [138, 139]. There is limited data on the outcome of CABG in patients with AF or OAC [140, 141].

2.4 Antithrombotic management of AF patients undergoing PCI

Acute coronary syndrome (ACS) with plaque rupture or local damage in the coronary endothelial surface and/or PCI with stent implantation triggers a prothrombotic and proinflammatory reaction. In patients with AF, these changes occur in addition to the existing prothrombotic state induced by the arrhythmia itself [142, 143]. However, the mechanisms of thrombus formation differ in AF and CAD or ST. Coagulation factors are more important in the development of thromboembolic events during AF, whereas platelet-mediated thrombosis is the dominant pathophysiological mechanism behind the atherothrombotic events [144]. Therefore, in AF patients undergoing PCI, anticoagulant therapies are more effective for prevention of thromboembolism and antiplatelet agents are of greater benefit in the prevention of ischemic events, including ST.

2.4.1 Periprocedural management

At the periprocedural stage, avoiding the formation of a thrombus in the catheters and at the site of balloon-induced plaque rupture requires effective anticoagulation through the use of UFH, LMWH, or uninterrupted oral anticoagulation (UAC) in combination with effective antiplatelet therapy in the form of ASA and thienopyridines. In patients with ACS, the use of UFH or LMWH is recommended in addition to warfarin [1].

2.4.1.1 Periprocedural anticoagulation

There are two main treatment strategies for AF patients receiving OAC in elective PCI: either continuing OAC throughout PCI (UAC) or interrupting OAC (IAC) prior to PCI, with or without UFH or LMWH (i.e. enoxaparin) bridging (bridging therapy, BT). Existing guidelines for the management of patients with AF contain only limited mentions of long-term OAC at the periprocedural stage of PCI, and in many cases, there is no mention of it at all (Table 7). Until 2010, the general recommendations appearing in the guidelines suggested the interruption of VKA with or without BT, depending on individual risk assessment. These recommendations have been based mostly on circumstantial evidence and expert consensus (evidence level C).

The use of individual risk stratification has been endorsed in all guidelines (Table 7). The main differences in the current recommendations lie in the choice of periprocedural antithrombotic medication (UAC vs. LMWH) and the duration of TT (VKA, ASA and clopidogrel) or other combination therapy (Table 7).

Despite these guidelines, there is a lack of consensus among clinicians on the appropriate periprocedural anticoagulation treatment strategy, which tends to be based on clinical judgment as well as the personal opinion of the attending physician. Another challenge for the near future will be the implications of NOACs and novel antiplatelet agents on currently recommended antithrombotic combination strategies.

Table 7. Recommendations for periprocedural management of atrial fibrillation patients based on recent guidelines.

Guideline	Year	Periprocedural anticoagulation	Stent	GPI	Access site	Post-PCI
EHRA/EAPCI [9]	2010	Moderate-high risk of thromboembolism: UAC	BMS prior to elective PCI; DES only in limited clinical situations	Not recommended	Radial	Triple (DAPT)* at 2-4wk, up to 6mo (INR 2-2.5), then OAC
ESC and the European Association for Cardio-Thoracic Surgery (EACTS) Guidelines on Myocardial Revascularization [145]	2010	No mention	No specific mention	No specific mention	Radial	Triple (DAPT)* at 2-4wk up to 6mo (INR 2-2.5), then OAC
North American consensus [10]	2011	No mention	BMS prior to elective PCI; DES only in limited clinical situations	Take risk of bleeding into account	Radial	Triple (DAPT)* from 1-6mo (INR 2-2.5), then VKA+AP up to 12mo, then OAC
ACCF/AHA Practice Guidelines [146]	2011	No mention with AF	BMS; DES in special clinical situations	In specific situations	Radial	No mention
ESC Guideline on Atrial Fibrillation [44]	(2010) 2012	Moderate-high risk of thromboembolism: UAC	BMS prior to elective PCI; DES only in limited clinical situations	No mention	Radial	Triple (DAPT)* at 2-4wk, up to 6mo (INR 2-2.5), then OAC
ACCP: Perioperative Management of Antithrombotic Therapy [147]	2012	Patient with OAC indication: bridging	-	-	-	-
Canadian Cardiovascular Society Guideline [100]	2012	CHADS ≥3 +low bleeding risk: UAC or bridge High both: bridge CHADS ≤ 2 + low bleeding risk: UAC CHADS ≤ 2 + high bleeding risk: IAC	BMS; DES is secondary	No mention	Radial	CHADS>1: TT at 1mo then VKA+AP (Clop/ASA) to 12mo, then OAC (VKA: INR 2-3)
ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction [148]	2013	No mention	BMS; avoid DES	No specific recommendation	Radial	Triple (DAPT)* at 2-4wk up to 6mo (INR 2-2.5), then VKA + AP up to 12mo, then OAC

* = Triple therapy or double antiplatelet therapy based on individual risk stratification according to risk score; GPI=glycoprotein inhibitors IIb/IIIa

EHRA=European Heart Rhythm Association; EAPCI=European Association of Percutaneous Cardiovascular Interventions; ESC=European Society of Cardiology; ACCF/AHA=The American College of Cardiology Foundation and the American Heart Association; ACCP= American College of Chest Physicians

2.4.1.1.1 Treatment strategies with warfarin

In the past few years, several studies have shown a net benefit due to UAC therapy, but in the absence of randomized trials, the use of any antithrombotic strategy during PCI in AF patients is based on consensus [9, 149, 150]. In the light of the available data, the incidence of thromboembolic complications may even increase when VKA is temporarily interrupted. Nor has BT shown any advantage over UAC; rather, it prolongs hospitalization, increases costs [151, 152], and may delay interventions in ACS [6].

The common recommendation is to discontinue warfarin 5 days prior to PCI, based on the estimated 2–5-day anticoagulant effect of a single dose of warfarin [153]. Shorter interruption periods have also been used [150]. When warfarin is interrupted for over 2 days, it is estimated to take approximately 9 days for patient INR to return to therapeutic levels [154]. An IAC strategy might delay the procedure in warfarin-treated patients with ACS, and they are also less likely to undergo PCI [155]. In addition, since warfarin is known to increase activated coagulation time in a predictable fashion [156], it is reasonable to consider the possibility of replacing LMWH with therapeutic OAC, and that this might be as effective as periprocedural heparin treatment.

Recent data has confirmed that even brief interruptions in warfarin treatment are associated with a substantially increased risk of embolic events [104, 157]. On the other hand, warfarin re-initiation may cause a transient prothrombotic state due to the suppression of proteins C and S; the associated elevated risk of thrombosis has been reported to persist for one month [6, 158, 159]. It is also worth noting that if INR is at a therapeutic level <65% of the time, OAC has no advantage over DAPT in reducing vascular events [160]. Warfarin resumption-related INR fluctuations, with the attendant increased risks of bleeding, are also well documented [119]. Several studies have shown an increased risk of bleeding complications in VKA-treated patients receiving additional periprocedural BT, while the reported risk of thromboembolic events appears to be similar compared to non-bridged patients [7, 8, 161-164]. However, clinically significant bleeding events and thromboembolic events are rare when either UAC or BT is used as a treatment strategy [165]. More details from these trials are listed in Table 8.

Table 8. Uninterrupted VKA in patients undergoing PCI.

Author	No. of patients	Average age	Procedure	Femoral %	UAC %	INR mean	GPI %	Major bleed %	Access bleed %	MACE
ten Berg 2001 [166]	530 (AF NR)	60	PCI	100	100	2.1-4.8	-	1.3	1.9	3.2
Jessup 2003 [167]	23 (AF 48%)	72	CA/PCI	100	100	2.4	0	0	0	0
Hildick-Smith 2003 [168]	66 (AF NR)	67	CA	0	100	2.0-4.5	-	0	1.5	0
El-Jack 2006 [154]	59 (AF 68%)	68	CA	100	100	2.3	2.0	0	7.0	0
Lo 2006 [169]	28 UAC (AF 89%)	60	CA	100	100	2.5	-	0	0	0
Annala 2008 [164]	258 (AF 73%)	66	CA	44	69	2.3	0	0	1.7	0
Karjalainen 2008 [8]	241 (AF 71%)	69	PCI	78	100	2.2	18	1.2	5.0	5.4
Helft 2009 [163]	50 (AF 62%)	68	PCI	0	100	2.2	12.0	0	0	0
Gilard 2009 [12]	125 (AF 63%)	71±9	PCI	34	100	2.15	6.0	1.6	4.8	0

AF= atrial fibrillation; NR= not reported; Femoral=femoral access site; UAC=uninterrupted oral anticoagulation; GPI=glycoprotein inhibitors IIb/IIIa; MACE=Major Adverse Cardiac Events; PCI=percutaneous coronary intervention; AC=coronary angiography

2.4.1.1.2 Periprocedural unfractionated heparin (UFH) and low-molecular-weight heparins (LMWH)

According to American (ACCF/AHA) and European (ESC) guidelines, the recommend choices for anticoagulants used during catheterization or PCI are UFH, LMWH, or bivalirudin [145, 146]. Periprocedural treatment has traditionally been performed with UFH to minimize acute thrombotic complications during PCI. The anticoagulant response to UFH varies among patients, and more recently LMWHs or direct thrombin inhibitors have been introduced. Enoxaparin is the most widely used LMWH; it is easy to manage, owing to a predictable dose-effect relationship and a longer dose-independent half-life, and may provide benefits over UFH in primary PCI [170-172] without any increase in bleeding [171, 173]. Importantly, procedural switching from UFH to enoxaparin and vice versa may increase the risk of bleeding and should be avoided [174, 175].

2.4.1.1.3 Fondaparinux

Fondaparinux inhibits the activated clotting factor Xa selectively via antithrombin. Fondaparinux shares all the advantages of LMWH over UFH, but it is not recommended as the sole anticoagulant without UFH to support PCI, owing to the reported increase in catheter thrombosis [176]. There is no data on the use of fondaparinux in AF patients with OAC.

2.4.1.1.4 Bivalirudin

Bivalirudin does not induce or directly affect platelet activation or aggregation, but blocks thrombin-mediated platelet aggregation [177]. Bivalirudin is being increasingly used for anticoagulation during PCI for ACS. Large-scale studies have demonstrated that bivalirudin reduces bleeding and thrombocytopenia compared to UFH with GPI, while resulting in similar rates of ischemic events in patients with stable angina and UAP undergoing PCI or non-STEMI patients undergoing PCI [178-182]. There is only limited data on the use of bivalirudin in AF patients with OAC [183].

2.4.1.2 Procedural antiplatelet therapy in patients with OAC

2.4.1.2.1 Dual antiplatelet therapy (DAPT) with aspirin and clopidogrel

The pathogenesis of coronary thrombosis among patients with CAD and those undergoing PCI is considered to be largely platelet driven [184]. Considering this, DAPT is the cornerstone of pharmacological post-PCI ischemia prevention. DAPT reduces the incidence of periprocedural ischemic complications in OAC patients as well [145, 185-189].

The combination of clopidogrel and aspirin has long been the standard for DAPT [145, 146, 186]. Because of the common resistance to clopidogrel, more potent and rapid P2Y₁₂ receptor inhibitors like prasugrel and ticagrelor have been developed. Both are more effective than clopidogrel but are not currently recommended as part of TT due to the increased risk of bleeding, while they do not significantly differ from clopidogrel regarding the combined ischemic secondary endpoint [190, 191]. For this reason, as well as a lack of data, combining prasugrel and ticagrelor with NOACs is not recommended either [145, 146].

2.4.1.2.2 Glycoprotein IIb/IIIa receptor inhibitors (GPIs)

Glycoprotein IIb/IIIa receptors mediate platelet aggregation, representing the final common pathway of platelet-mediated thrombosis [192]. Despite the proven efficacy of GPIs in primary PCI, high bleeding rates remain a concern [193], and there has been a downgrade in the level of their recommendation. At present, the preference is to use GPIs only in 'bail-out' situations (thrombus, slow flow, vessel closure, and very complex lesions) with general patients [145, 146, 194-196].

Warfarin-treated patients have been excluded from all randomized clinical GPI trials. In real-world practice, warfarin-treated patients are seldom treated with GPIs, and bleeding complications seem to represent a significant limitation to the effectiveness of GPIs [8, 164, 197-200]. The guidelines recommend the use of GPIs only in special situations [9, 201]. No data is available regarding the combination of GPIs and NOACs, and therefore such a combination should generally be avoided.

2.4.2 Antithrombotic management in patients with AF post-PCI

The latest recommendations suggest careful decision-making based on individual risk stratifications, by using CHA₂DS₂-VASc and HAS-BLED scores to identify patient subsets at risk of recurrent ischemic events or bleeding (Tables 2-4). Post-procedural combination antithrombotic therapy needs to be carefully weighed against the increased risk of thromboembolism associated with the withdrawal of OAC and the risk of ST associated with abstention from DAPT [202].

Overall, there is an apparent consensus on TT; however, the current recommendations are based on limited evidence. Accordingly, most of these recommendations are graded IIa (uncertain benefit over risk) with a level of evidence of C (experts' consensus or small studies or observational registries) (Table 7). Post-PCI treatment strategies are based on risk stratifications (Tables 4-7,9-10).

2.4.2.1 Triple therapy vs. other treatment strategies for AF patients after PCI

A TT of OAC, aspirin, and clopidogrel is recommended for AF patients undergoing ACS and/or PCI, but lack of randomized multicenter studies leave the grade of evidence at level C in European and US guidelines (Table 7). Recommendations strongly emphasize individual risk stratification balancing thrombotic risks and the risk of bleeding. In a recent open-label, randomized WOEST trial, researchers compared an antithrombotic therapy of VKA and clopidogrel to TT and reported fewer incidents of MACCE (HR 0.6, p=0.025) and bleeding (HR 0.36, p<0.0001) and a trend to decreasing of TIMI major bleeding (HR 0.56, p=0.159) with the VKA + clopidogrel alternative at one-year follow-up [203].

Table 9. Absolute risk of thromboembolism based on clinical indications of oral anticoagulation (OAC).

Risk	OAC indication	Incidence/year (%)
High	AF (CHA ₂ DS ₂ VASc score ≥4) Previous cardiogenic stroke/systemic embolism Mechanical heart valve Biological mitral or tricuspid valve (<3 months from implantation) Intracardiac thrombus Recent VTE (<3–6 months) Recurrent VTE Thrombophilia	4–10 and above
Moderate	AF (CHA ₂ DS ₂ VASc score 2–3) Previous VTE (6–12 months) *	2–3
Low	AF (CHA ₂ DS ₂ VASc score 1) Previous VTE (>12 months)*	<2

AF = atrial fibrillation; CHA₂DS₂VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, Stroke, associated Vascular disease, Age 65–74 years, Sex category; VTE = venous thromboembolism; *in the absence of risk factors for recurrence (unprovoked, recurrent episodes, thrombophilia, cancer).

Table 10. Timeline for antithrombotic medications in atrial fibrillation patients after PCI, reproduced from Lip et al. [1].

Haemorrhagic risk	Clinical setting	Stent implanted	Recommendations
Low or intermediate	Elective	Bare metal	1 month: TT (warfarin:INR 2.0–2.5 + aspirin clopidogrel + PPI) Lifelong: Warfarin (INR 2.0-3.0) alone.
	Elective	Drug-eluting	3 (-olimus group) to 6 (paclitaxel) months: TT (warfarin (INR 2.0–2.5) + aspirin + clopidogrel) Up to 12 months: Warfarin (INR 2.0–2.5) + clopidogrel/(aspirin) Lifelong: Warfarin (INR 2.0-3.0)
	ACS	Bare metal/ drug-eluting	6 months: TT (warfarin (INR 2.0–2.5) + aspirin + clopidogrel) Up to 12 months: Warfarin (INR 2.0–2.5) + clopidogrel /(or aspirin); Lifelong: Warfarin (INR 2.0–3.0) alone.
High	Elective	Bare metal*	2 to 4 weeks: TT (warfarin (INR 2.0–2.5) + aspirin + clopidogrel) Lifelong: Warfarin (INR 2.0–3.0) alone.
	ACS	Bare metal*	4 weeks: TT (warfarin (INR 2.0–2.5) + aspirin + clopidogrel) Up to 12 months: Warfarin (INR 2.0–2.5) + clopidogrel /(or aspirin) Lifelong: Warfarin (INR 2.0–3.0) alone.

PCI = percutaneous coronary intervention; TT= Triple therapy; PPI= Proton-Pump Inhibitor; *= Drug-eluting stents should be avoided. INR = international normalized ratio; PPI = proton pump inhibitors; ACS = acute coronary syndrome

2.5 Prognosis and adverse events

The main challenge for peri- and postprocedural management of PCI is to find the balance between the risks of major adverse cardiac and cerebrovascular events (MACCE: death, myocardial infarction, need for re-revascularization, stent thrombosis, stroke) and bleeding complications in AF patients on OAC

2.5.1 Mortality

AF has been reported as an independent predictor of 30-day mortality after PCI [204], and the risk has been estimated to be up to four times greater compared to non-AF patients [204-206]. From the periprocedural stage up to the 30-day follow-up, the estimated mortality risk is 0.3–9.9%, depending on the study population and antithrombotic strategy (Tables 11 and 13). AF has been found to be an independent predictor of 1-year mortality in AMI patients, with up to a 3-fold higher risk compared to patients in sinus rhythm [206-208]. This prognosis is worse regardless treatment strategies [209-212].

At 6–24-month follow-up, the estimated mortality in patients treated with TT is 4.4–27.8%; in patients with DAPT, 1.2–17.8%; and in patients with VKA and a single

antiplatelet drug, 2.5-10.9% (Tables 13, 14). Ruiz-Nodar et al. found that OAC reduced the risk of death at 12 months after PCI, even if 71% of the patients had a HAS-BLED score of ≥ 3 ($\text{CHA}_2\text{DS}_2\text{-VASc} \geq 1$) [213]. Caballero et al. reported similar results in octogenarian AF patients undergoing PCI with a mean HAS-BLED of 3.05 [214].

2.5.2 Major adverse cardio- and cerebrovascular events (MACCE/MACE)

AF is a strong independent predictor of adverse cardiovascular events [215, 216]. The rate of in-hospital MACE was 1.7-2.7% (Table 11). In long-term follow-up (6–24 months), the reported prevalence of MACE being 5.8%–26.5% in patients using TT, 1.2%–38.7% in patients using DAPT, and 0.0%–21.0% in patients using VKA and a single antiplatelet drug (Tables 12, 13). Also, new-onset AF after PCI has been associated with higher rates of ischemic events by 3-year follow-up [215, 216].

2.5.2.1 Stroke

The stroke rate in the general PCI population is low: 0.4% [217]. AF is a significant risk for stroke [135], with a tendency towards increased stroke rate in the group in which OAC therapy was interrupted [12]. The estimated risk of stroke from the periprocedural stage to 30-day follow-up is estimated at 0.3–4.2% (Tables 11- 12). At 6–24 month post-PCI follow-up, the reported rates is 1.0–2.8% in patients using TT; 0.7–8.8% in patients using DAPT; and 0.0–4.5% in patients using VKA and a single antiplatelet drug (Tables 12-13).

Table 11. Prognosis of patients with atrial fibrillation undergoing PCI.

Author	Follow-up	Patients	Mortality		MACE		Stroke		Bleeding	
			In-hospital and/or ≤30 days	≥ 12 months	In-hospital and/or ≤30 days	≥ 12 months	In-hospital and/or ≤ 30 days	≥ 12 months	In-hospital and/or ≤ 30 days	≥ 12 months
El-Omar 2003 [218]	in-hospital; 12 mo	SR 9391 AF 426 (VKA 40.8%)	0.7 1.9	5.9 10.3	2.1 1.9	23.4 22.3	1.8 4.2	-	5.5 9.8	-
Karjalainen 2007 [198]	in-hospital; 12 mo	non-OAC 227 219 OAC/ AF (70%)	0.4	1.8	1.3	11.0	0	2.2	0	2.6
Ruiz-Nodar 2008 [215]	median 595 days	426 AF	1.4	8.7	2.7	21.9	0.5	3.2	1.8	8.2
Sambola 2009	6 months	405 OAC AF 68%	-	6.2/ 6 mo	-	7.4/ 6 mo	-	0.7/ 6 mo*	-	Major 12.3 Minor 11.0
Gilard 2009 [12]	in-hospital; 12 mo	359 OAC/AF (69%)	0.3	6.4	1.7**	13.1**	0.3	2.2	All 9.2 Major 1.9	16.7 3.6
Lip 2010 [1]	12 mo	review 18 publications OAC/AF (67.7%)	-	12.0	-	ST 2.0 MI 7.0	-	4.0	-	6.0
Chan 2012 [204]	in-hospital; 30 days	SR 3145 AF 162	-2.2 -9.9	-	-5.5 -13.0	-	0.2/- 0.6/-	-	2.1/- 5.0/-	-
Sarafoff 2013	24 mo***	515 OAC AF (78%)	-	11.8	-	15.9	0.4	2.5	Major 1.0 Minor 8.0	Major 2.1 Minor 8.0
Rubboli 2013 [219]	in-hospital, 5.0 ± 4.9 days	411 OAC/ AF (79%) UAC (43%)	1.7	-	2.7	-	0.7	-	Major 2.1 Minor 4.8	-

PCI= Percutaneous coronary intervention; MACE= Major Adverse Cardiac Events; ST= stent thrombosis; MI= myocardial infarction; * =all embolisms; **=including mortality, ACS, stroke; *** = 41% post-PCI DAPT

Table 12. Trials comparing triple therapy (TT) and double antiplatelet therapy (DAPT) after PCI.

Name/author	Design	Comparison (AF%)	Follow-up Month	EFFICACY		BLEEDING				
				MACCE	Stroke	TT	DAPT	TT	p-value	
Sarafoff 2008 [220]	Prospective, single-center	515 (78%) 306 TT (67%) 209 DAPT (93%)	24	MACCE	14.1	18.0	NS	Major 1.4	3.1	NS
				Death	10.7	13.5	NS	Minor 7.7	8.4	NS
				MI	3.7	2.5	NS			
				Stroke	1.1	3.9	NS			
Ruiz-Nodar 2008 [215]	Retrospective, 2-center	373 (100%) 195 TT 178 DAPT	20	MACE	26.5	38.7	0.01	Major 14.9	9.0	NS
				Death	27.8	17.8	NS	Minor 12.6	9.0	NS
				MI	6.5	10.4				
				Embolism	1.7	6.9				
Rossini 2008 [155]	Prospective multicenter	204 102 TT (67%) 102 DAPT	18	MACE	5.8	4.9	NS	Major 2.9	2.0	NS
							Minor 7.8	2.9	NS	
Ho 2013 [221]	Retrospective, single-center	602 (100) 382 TT, 220 DAPT	6	Death	1.6*	5.3*	NS	Major 10.6	9.6	NS
					11.4**	10.0**	NS	10.6*	8.7*	
				Stroke	1.0*	0.7*		10.4**	11.4**	
					1.0**	1.4**				

PCI= Percutaneous coronary intervention; AF % = a part of patients with atrial fibrillation; * = patients with CHADS₂ ≤2; ** = patients with CHADS₂ >2; MACCE/MACE=Major Adverse Cardiac and Cerebrovascular Events; NS= not significant

Table 13. Clinical data on patients with coronary stent implantation and indication for anticoagulation; **Triple therapy (TT)** vs. double antiplatelet therapy (DAPT) and VKA and single anti-platelet (VKA+AP)

Author	Design	Comparison (AF%)	Follow-up mo	EFFICACY			BLEEDING			p-value		
				TT	DAPT	VKA+AP	p-value	TT	DAPT		VKA+AP	
Karjalainen 2007 [198]	Retrospective, multicenter	478 (on VKA/70%) 106 TT 214 DAPT 78 VKA+AP ^{a,b}	12	ST MI Stroke	1.9 8.5 2.8	5.9 5.5 8.8	15.2 ^a /0 ^b 18.2 ^a /11.1 ^b 3.0 ^a /0 ^b	- - -	Major 6.6	11.8	6.1 ^a 11.1 ^b	- -
Nguyen 2007 [222]	Prospective, multicenter	231 (100%) 156 TT 75 VKA+AP ^{f,g} (ASA ¹ /thienop. ^g)	6	Death MI re-PCI Stroke	5.8 2.2 8.8 0	- - - -	7.7 ^f /5.4 ^g 4.0 ^f /5.1 ^g 17.2 ^f /7.9 ^g 4.5 ^f /2.2 ^g	NR NR NR NR	n=580 ^h Major 5.9 (in-hospital)	-	4.6 (in-hospital)	NS NS
Manzano-Fernandez 2008 [200]	Retrospective single-center	104 (100) 51 TT 53 Non-TT ¹	12	MACE	25.5%	-	21%	NS	Early major 5.8 Later major 21.6	-	11.3 3.8	NS p=0.006
Gilard 2009 [12]	Prospective, multicenter	359 125 TT (63%) 234 DAPT/TT (73%)	12	Death ACS Stroke	8.0 5.0 0.8	- - -	5.6 4.3 3.0	NS NS NS	Major 5.6	-	2.1	0.04
Sambola 2009 [223]	Prospective, multicenter	405 (68%) 278 TT 81 DAPT 46 OAC+AP ^d	6	MACCE Death Embolism	7.9 6.8 0.3	1.2 1.2 1.2	15.2 10.9 2.2	p=0.013	Major 4.3	1.2	6.5 13.0	NS p=0.020
Baber 2010 [224]	Retrospective, single-center	454 170 TT (45%) 284 modif. TT ^e (60%)	12	MACCE Death MI	11.8 5.9 1.8	- - -	11.3 5.3 0.7	NS NS NS	Major 1.1 All 4.7 (in-hospital)	-	1.4 3.5 (in-hospital)	NS NS NS
Gao 2010 [225]	Prospective, single-center (DES)	622 (100%) 142 TT 355 DAPT 125 OAC+AP ^c	12	MACCE Death MI Stroke	8.8 4.4 2.9 0.7	20.1 9.0 5.4 3.6	14.9 5.8 5.8 0.8	p=0.010 NS NS NS	Major 2.9	1.8	2.5 7.4	NS p=0.038
Dewilde 2013 [203]	Open-label, prospective, randomized multicenter	573 (69%) 284 TT 279 VKA+AP ^b (VKA+clop.)	12	MACCE Death MI Stroke	17.6 6.3 4.6 2.8	- - - -	11.1 2.5 3.2 1.1	p=0.025 p=0.027 NS NS	Major 5.6 Severe GUSTO 3.5 All: 44.4	Major TIMI 5.6	3.2	NS NS NS p<0.0001

^a = VKA + ASA; ^b = VKA + clopidogrel; ^c = VKA + clopidogrel (87%), VKA+ASA (13%); ^d = VKA + clopidogrel (80%), VKA+ ASA (13%), LMWH + clopidogrel (4%), LMWH + ASA (2%); ^e = VKA+DAPT (daily aspirin and every other day clopidogrel); ^f = VKA+ASA (49%); ^g = VKA+ thienopyridine (clopidogrel or ticlopidine)(51%); ^h = Of all n=800 (AF 40%); ¹ = VKA interrupted mean 22±31 days, DAPT continues, then TT; ² = VKA+ASA/clopidogrel,

Table 11. Meta-analysis and registry data comparing triple therapy (TT) and double antiplatelet therapy (DAPT) and VKA + antiplatelet therapy (VKA+AP).

Name/author	Design	Comparison (AF%)	Follow-up month	EFFICACY	TT	DAPT	VKA+AP	p-value	BLEEDING TT	DAPT	VKA+AP	p-value
Hansen 2010 [226]	Registry	118,606 (100%) 1261 TT 2859 DAPT 18,345 VKA+ASA ^b 1430 VKA+clop. ^a 47,541 ASA 3717 clop. 50,919 Monotherapy VKA (reference)	40	Stroke	1.45 (0.84– 2.52)	1.56 (1.17–2.10)	0.70 ^a (0.35–1.40) 1.27 ^b (1.14–1.40)		Fatal 0.2% 1.11 (0.16–7.94)	0.6% 1.16 (0.43–3.15)	0.4 ^b /0.6% ^a 1.96 ^b (1.50–2.57) 2.45 ^a	
Gao 2011 [227]	Meta-analysis (9 trials)	5181 (40-100%) TT n = - 1446 DAPT n = - 3671	1–18	Mortality MI Stroke	OR 1.20 (0.63– 2.27) OR 0.84 (0.57– 1.23) OR 0.29 (0.15– 0.58)			P = 0.0004 NS NS	Major OR 2.00 (1.41–2.83)			0.0001
Zhao 2011 [228]	Meta-analysis (9 trials)	1996 (43-100%) TT n = 528-814 DAPT n = 448-707	3	MACE Mortality Stroke	8.8% OR 0.60 (0.42– 0.86) 6.5% OR 0.59 (0.39– 0.90) 0.8% OR 0.38 (0.12– 1.22)	13.9% 9.7% 3.3%		0.005 0.01 NS	Major 4.1% OR 2.12 (1.05–4.29) Minor 9.9% OR 1.74 (0.90–3.35)	1.9% 6.5%		0.04 NS

Name/ author	Design	Comparison (AF%)	Follow- up month	EFFICACY	TT	DAPT	VKA+AP	p-value	BLEEDING	TT	DAPT	VKA+AP	p-value	
Lamberts 2013 [229]	Registry	12,165 (100) 3590 DAPT (reference) 1896 TT 1504 VKA + ASA ^b 548 VKA+ clop ^a (single rest)	12	Death	8.9 OR 0.61 (0.68– 1.00)	17.5	15.6 0.91 ^b (0.77–1.08) 7.1 0.54 ^a (0.35–0.76)		All 14.3 OR 2.08 (1.64–2.65)	6.9 ref.	9.7 1.44 ^b (1.14–1.83) 10.9 1.63 ^a (1.15–2.30)			
				MI+CV Death	16.2 OR 0.83 (0.68– 1.00)	21.3 ref.	17.7 ^b /9.6 ^a 0.56 ^a (0.40–0.79) 0.78 ^b (0.66–0.91)		Fatal 0.9 OR 4.80 (1.64–14.02)	0.3 ref.	0.8 3.90 ^b (1.43– 10.66) 0.5 2.73 ^a (0.54– 13.70)			
				Stroke	4.1 OR 0.67 (0.46– 0.98)	6.3 ref.	5.6 0.81 ^a (0.61–1.08) 0.51 ^b (0.28–0.95)							

VKA= Vitamin K antagonist; AF %= part of patients with atrial fibrillation; MI= myocardial infarction; MACE=Major Adverse Cardiac Event; CV=Cardiovascular;
^a=VKA+clopidogrel; ^b= VKA+ASA

2.5.3 Bleeding

2.5.3.1 Antithrombotic treatment strategies and bleeding after PCI

AF patients on combination antithrombotic treatment are at increased risk of bleeding (Tables 12–16). From the in-hospital stage to the 30-day follow-up, the rate of major bleeding varies 1.8%–9.8%, depending on treatment strategy (Table 11). Bleeding events are highly dependent on the patients' individual characteristics and the procedural treatment strategy used, including access site and choice of antithrombotic, but AF has been evaluated as a significant risk for moderate or severe bleeding [135].

The increased risk of bleeding is linked to a concurrent use of TT and has been well documented in large retrospective studies (Tables 13–16). TT is associated with a 2- to 5-fold increase in the risk of major bleeding compared with non-triple antithrombotic regimens [228] (Tables 15–16). In a large meta-analysis, the risk of major bleeding was 8.5%–15.7% in patients using TT, 3.7%–7.4% in patients using DAPT, and 5.1%–9.5% in patients using VKA and a single antiplatelet drug (Table 16). TT is associated with a 1.6-fold risk of in-hospital major bleeding, this risk growing to 2.4-fold at the 30 day follow-up and 4.6-fold at the 6-month follow-up (Table 15).

The rate of bleeding events seems to increase, even with good control of OAC and time in the therapeutic INR range (TTR) [230]. The most frequent site of serious bleed in patients on TT is the gastrointestinal tract [231, 232]. Age, cerebrovascular disease, CKD, peptic ulcer disease, diabetes, and bleeding during the index myocardial infarction are independent predictors of future bleeding [233].

The adoption of the transradial route for PCI in patients with STEMI is associated with significant reduction in the risk of bleeding in comparison with procedures performed through the femoral route [234, 235]. Proton pump inhibitors somewhat diminish the risk of gastrointestinal bleeding during TT [9, 10, 236].

Table 15. Pooled estimates of bleeding outcomes in post-PCI triple therapy in review by Andrade et al [237]

Time period	Any bleeding, % (95% CI)	Major bleeding, % (95% CI)
In-hospital (6 studies)*	—	1.59 (0.43-4.01)
30 days (14 studies)**	8.28 (5.62-10.94)	2.38 (0.98-3.77)
6 months (9 studies)***	11.92 (5.46-18.38)	4.55 (0.56-8.53)

CI = confidence interval; DES = drug-eluting stent; PCI = percutaneous coronary intervention; VKA = vitamin K antagonist.

*Encompassing only patients receiving uninterrupted VKA therapy. **Encompassing only larger studies (>90 patients). ***Encompassing only patients receiving DES.

Table 16. Major bleeding risk, %, comparison of antithrombotics.

Study	No. of Patients	Follow-up, years	Clopidogrel				OAC+A		TT
			ASA	rel	DAPT	OAC	SA	OAC+clopido grel	
Buresly 2005 [233]	21443*	1.8 [^]	3.2	NA	6.8	5.9	8.3	NA	8.5
Sørensen 2009 [238]	40,812*	1.3 [^]	2.6	4.6	3.7	4.3	5.1	12.3	12.0
Hansen 2010 [226]	118,606°	3.3 [^]	3.7	5.6	7.4	3.9	6.9	13.9	15.7
Lamberts 2012 [239]	11,480**	1.0 [#]	7.0	6.6	7.0	7.0	9.5	10.6	14.2

AF = atrial fibrillation; DAPT = dual antiplatelet therapy; MI = myocardial infarction; NA = not applicable; OAC = oral anticoagulant; PCI = percutaneous coronary intervention; TT = triple oral antithrombotic therapy. *Following acute MI; **Following acute MI or PCI; ° Following first diagnosis of AF. [^] Rates expressed as incidence of bleeding events resulting in hospitalization per patient-year or person-year; [#] Rates expressed as incidence of nonfatal and fatal bleedings resulting in hospitalization per 100 person-years.

2.6 AF patients with CKD undergoing PCI

Patients with renal impairment and AF have a higher risk of ischemic stroke and thromboembolism than patients with normal renal function [21, 93, 240, 241]. Renal impairment also increases the risk for bleeding, along with a strong association for increased cardiovascular morbidity and mortality [16, 242, 243].

CKD has been generally defined as kidney damage or an eGFR < 60 mL/min per 1.73 m² of body-surface area. Using this definition, CKD has been associated with an increased post-PCI risk of ischemic and bleeding complications in various patient groups [22-26]. Patients with CKD often have multivessel or left main disease and make sub-optimal use of guideline-recommended therapies [244-246].

In the light of limited evidence available, myocardial revascularization procedures and cardiovascular medications may significantly improve survival of patients with CKD [247]. ESC guidelines note that for patients with mild ($60 \leq \text{GFR} < 90$ mL/min/1.73 m²) or moderate ($30 \leq \text{GFR} < 60$ mL/min/1.73 m²) kidney disease, there is consistent evidence supporting CABG as a better treatment than PCI, particularly when diabetes is the cause of the CKD, but in the subsets of patients with severe or end-stage CKD (GFR <30 mL/min/1.73 m²) or in hemodialysis, the benefits of CABG over PCI are less consistent. Surgery confers a better event-free survival in the long term than PCI, but in-hospital mortality and complication rates are higher. Individual risk stratification, including the patient's general condition and life expectancy, guide the selection of the most appropriate revascularization strategy, but the least invasive approach is more appropriate for the most fragile and compromised patients. In considering whether or not to perform PCI, only weak evidence suggests that DES is superior to BMS in terms of reduced recurrence of ischemia [145, 195].

3 AIMS OF THE STUDY

The specific aims were:

- I To assess the safety of glycoprotein inhibitors during PCI in patients on chronic warfarin treatment (I).
- II To compare the safety and feasibility of heparin bridging vs. uninterrupted oral anticoagulation in patients with AF undergoing PCI by using the data from the AFCAS (Atrial Fibrillation undergoing Coronary Artery Stenting) registry (II).
- III To assess the effect of renal impairment for prognosis of patients with AF undergoing PCI by using the data from AFCAS registry (III).
- IV To evaluate in-hospital clinical outcomes in patients with AF undergoing PCI (IV).
- V To compare the predictive performance of bleeding risk-estimation tools for bleeding events and mortality in a cohort of patients with AF undergoing PCI (V).

4 MATERIALS AND METHODS

4.1 Study design, subjects and follow-up

4.1.1 Study I

The first substudy was part of a wider protocol in progress to assess thrombotic and bleeding complications related to cardiac procedures carried out in western Finland. The retrospective cohort analysis is based on computerized PCI databases from 7 Finnish hospitals. We analyzed all consecutive patients (N = 523) on chronic warfarin therapy referred for PCI in the participating hospitals in the period 2002–2006.

In this analysis, we focused on patients with non-valvular AF, which was the most frequent indication for warfarin (N=377). Patients with other indications for OAC were not included in this analysis. The medical records of the eligible patients were reviewed in order to determine the perioperative antithrombotic treatments used and the incidence of major bleeding or access site complications and/or major adverse cardio- or cerebrovascular events (MACCE) during hospitalization.

4.1.2 Studies II-V

Papers II-V are based on data from an observational, multicenter, prospective registry: AFCAS (Management of patients with Atrial Fibrillation undergoing Coronary Artery Stenting). AFCAS includes patients with paroxysmal, persistent, or permanent AF who were referred for either elective or emergent PCI. Between December 2006 and February 2010, 963 consecutive patients with AF undergoing PCI were included the AFCAS registry at 17 centers in 5 European countries: Finland, Germany, Italy, Spain, and the UK. Because of the observational design of the study, the only exclusion criteria were unwillingness/inability to participate in the study or to give written informed consent. At each participating center, patients were treated according to local policies and followed up for 12 months (phone call or visit at 1, 3, 6, and 12 months) after PCI. Patients were asked about their clinical outcomes, hospitalizations, and medications. Any additional information has been obtained by contacting one of the patient's physicians, other health care professionals, or from death certificates. The study complied with the Declaration of Helsinki.

Paper II focused on the periprocedural treatment of patients from the AFCAS registry with long-term OAC (N= 529). Patients were treated with different strategies, including treatment with interrupted OAC with or without heparin bridging therapy (BT), uninterrupted OAC with or without procedural heparin bolus (UAC), and uninterrupted OAC plus LMWH with normal therapeutic dosing. The UAC group (N= 290) was defined as the patients for whom OAC was continued throughout the

hospitalization and no more than bolus heparin (i.e. no BT) was administered during PCI. The patients for whom OAC was interrupted before PCI and replaced by therapeutic LMWH treatment formed the BT group (N=161). This report presented data on the in-hospital phase and the 30-day follow-up.

In paper III, patients from the AFCAS registry (n= 781) with available information on pre-PCI creatinine levels were included. According to the Cockcroft-Gault formula, a total of 195 (25%) patients had normal eGFR (≥ 90 mL/min), 290 (37%) mild renal impairment (eGFR 60–89), 263 (34%) moderate renal impairment (eGFR 30–59), and 33 (4%) severe renal impairment (eGFR < 30). We analyzed outcome events at the 12-month post-PCI follow-up.

All 963 patients from the AFCAS register (70.1% male, mean age 73.0 ± 68.2) were included in paper IV. We evaluated data on the efficacy and safety profiles of the various antithrombotic treatment strategies during the periprocedural and post-discharge stages. We also analyzed the use of risk stratifications and contemporary PCI guidelines in the choice of treatment strategies. We reported outcomes for the in-hospital phase and the 30-day post-PCI follow-up.

Paper V included 929 (70.3% male, median age 74 [IQR 11.0]) patients at 1-year follow-up. HAS-BLED, ATRIA, mOBRI, and REACH bleeding risk scores were calculated for each patient based on the definitions used in their validation cohorts. We sought to compare the predictive performance of these bleeding risk-estimation tools in predicting bleeding events and mortality in a cohort of patients with AF undergoing PCI.

4.2 Percutaneous coronary intervention (PCI)

In papers I–IV, coronary angiography and PCI were performed using either the radial or the femoral approach for arterial access and hemostasis was achieved according to local practices. Lesions were treated using contemporary interventional techniques. LMWH, UFH, bivalirudin and GPIs were administered entirely at the operator's discretion. Medication at discharge was at the treating physician's discretion.

4.3 Endpoint definitions

In paper I, MACCE was defined as the occurrence of any of the following during hospitalization: death, Q-wave or non-Q-wave myocardial infarction, revascularization of the target vessel (emergency or elective coronary-artery bypass grafting or repeated coronary angioplasty), stent thrombosis, or stroke. Myocardial infarction (MI) was diagnosed when a rise in the myocardial injury marker level (troponin I or T) was detected together with symptoms suggestive of acute myocardial ischemia. For the diagnosis of myocardial re-infarction, a new rise to $> 50\%$ above the baseline injury marker level was required. Periprocedural infarction

was not routinely screened for, but if suspected, a troponin level $>3x$ the normal 99th percentile level was required for the diagnosis. Target vessel revascularization (TVR) was defined as a re-intervention driven by any lesion located in the stented vessel. Stent thrombosis (ST) was based on angiographic evidence of either thrombotic vessel occlusion or thrombus within the stent, or discovered during autopsy.

Major bleeding was defined as a decrease in blood haemoglobin level of more than 4.0 g per decilitre, the need for the transfusion of ≥ 2 units of blood, the need for corrective surgery, the occurrence of an intracranial or retroperitoneal hemorrhage, or any combination of these. Vascular access site complications included pseudoaneurysms or arteriovenous fistulae, the occurrence of retroperitoneal hemorrhage, and the need for corrective surgery. A decrease in blood hemoglobin level of > 4.0 g per decilitre or the need for the transfusion of ≥ 2 units of blood, or prolongation of index hospitalization because of access site bleeding were also considered access site complications.

In paper II, the primary endpoints were major adverse cardiac and cerebrovascular events (MACCE) and bleeding complications at 30 days follow-up after stenting.

MACCE was defined as the occurrence of any of the following at 30 days after PCI: death, myocardial infarction, revascularization of the target vessel (emergency or elective CABG or repeated PCI), stent thrombosis or stroke. MI was diagnosed when a rise in the myocardial injury marker level was detected together with symptoms suggestive of acute myocardial ischemia. For the diagnosis of myocardial re-infarction, a new rise $>50\%$ above the baseline injury marker level was required. TVR was defined as a re-intervention driven by any lesion located in the stented vessel. ST was defined according to Academic Research Consortium Classification as definite and probable.

Bleeding complications were classified as major bleeding according to Thrombolysis In Myocardial Infarction (TIMI) classification and non-major bleeding complications.

In paper III, the endpoints were 1) all-cause mortality; 2) a composite of MACCE that included all-cause mortality, myocardial infarction, non-elective repeat revascularization (PCI or coronary bypass surgery), ST, transient ischemic attack (TIA), stroke, or other arterial embolism; and 3) bleeding during the 12-month follow-up period.

Periprocedural MI was not routinely screened for, but if suspected, a troponin level of $>3x$ of the normal 99th percentile level was required for the diagnosis. For the diagnosis of myocardial re-infarction, a new rise to $>50\%$ above the baseline injury marker level was required. ST was defined according to the Academic Research Consortium (ARC) classification as definite and probable. TIA was defined as a transient ($<24h$) focal neurological deficit adjudicated by a neurologist, while stroke was defined as a permanent focal neurological deficit adjudicated by a neurologist

and confirmed by computed tomography or magnetic resonance imaging. Systemic embolism was defined as signs/symptoms of peripheral ischemia associated with a positive imaging test. Acute kidney injury was defined as $>26.5 \mu\text{mol/l}$ increase of creatinine.

Bleeding complications were defined according to ARC bleeding criteria (BARC) as any (BARC 1–5), minor (BARC 2), and major bleeding complications (BARC 3a, 3b, 3c, and 5)(Table 17).

Table 17. Bleeding Academic Research Consortium (BARC) Definition for Bleeding.

Type 0:	no bleeding
Type 1	bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional
Type 2	any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation
Type 3	
Type 3a	Overt bleeding plus hemoglobin drop of 3 to $<5 \text{ g/dL}^*$ (provided hemoglobin drop is related to bleed)
Type 3b	Any transfusion with overt bleeding Overt bleeding plus hemoglobin drop $\geq 5 \text{ g/dL}^*$ (provided hemoglobin drop is related to bleed) Cardiac tamponade
Type 3c	Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) Bleeding requiring intravenous vasoactive agents Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal) Subcategories confirmed by autopsy or imaging or lumbar puncture Intraocular bleed compromising vision
Type 4	CABG-related bleeding Perioperative intracranial bleeding within 48 h Reoperation after closure of sternotomy for the purpose of controlling bleeding Transfusion of $\geq 5 \text{ U}$ whole blood or packed red blood cells within a 48-h period† Chest tube output $\geq 2\text{L}$ within a 24-h period
Type 5	Fatal bleeding
Type 5a	Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
Type 5b	Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

CABG= coronary artery bypass graft; *Corrected for transfusion (1 U packed red blood cells or 1 U whole blood= 1g/dL hemoglobin).

In paper IV, outcome measures included major adverse cardiovascular events (MACE) including cardiovascular death, stroke/systemic embolism, need for urgent revascularization, and major and non-major bleeding, at discharge, 1, 3, 6, and 12 months.

Cardiovascular death was defined as death due to cardiac causes or stroke. Stroke was defined as permanent focal neurological deficit adjudicated by a neurologist and

confirmed by computed tomography or magnetic resonance imaging. Systemic embolism was defined as signs/symptoms of peripheral ischemia associated with a positive imaging test. TVR was defined as any (surgical or percutaneous) re-intervention to treat a stenosis occurring in the same coronary vessel treated at the index procedure, within and beyond the target lesion limits.

Major bleeding was defined as intracranial bleeding, bleeding requiring a blood transfusion or surgical/endoscopic treatment, or bleeding leading to long-term disability or death, while non-major bleeding was bleeding requiring no treatment or leading to ambulatory management with no surgical/endoscopic treatment.

In paper V, the primary endpoints were all-cause mortality and bleeding complications defined according to the bleeding academic research consortium (BARC) criteria as any (BARC 2, 3a, 3b, 3c, and 5) or major bleeding (BARC 3a, 3b, 3c, and 5) (Table 17.) [248].

4.4 Statistical analysis

In paper I, continuous variables are presented as means \pm standard deviations (SD) and the study groups were compared using a Student's unpaired t-test. Categorical variables are presented as counts (percentages) and were compared by chi-square or Fisher's exact test where appropriate.

In order to identify the independent predictors of major bleeding, access site complications, and MACCE during hospitalization, at first univariate and then multivariable logistic regression (backward Wald method) were applied. Age, sex, diabetes, ACS, history of MI and heart failure, access site, warfarin pause, use of LMWHs, and total stent length were included in the multivariable analyses. The results are reported as adjusted odd ratios (OR) with 95% confidence intervals (CI). For logistic models, age was categorized into four classes consisting of the age groups 38–59, 60–69, 70–79, and 80–88 years, because of the non-linear relation of age and logit function. The fit of the logistic regression models was adequate according to Hosmer-Lemeshow goodness-of-fit tests. This data was analyzed using SPSS for Windows 16.0 software (SPSS Inc., Chicago, IL, USA).

Propensity scores were used to adjust for potential bias in the comparison between non-randomized study groups. Using logistic regression, they were calculated as the predicted probability that the patient was treated with GPIs as opposed to without GPIs. Baseline clinical characteristics and procedural variables were included in the statistical models. Group differences in outcome variables were compared after adjustment for propensity scores (linear term) by using logistic regression. The results of the logistic regression are presented using ORs and their 95% CIs. A two-sided p-value of <0.05 was required for statistical significance. These analyses were

performed using the SAS System for Windows version 9.2 (SAS Institute Inc., Cary, NC, USA).

In paper II, continuous variables are presented as means \pm SD and study groups were compared using unpaired t-tests. Categorical variables are presented as counts (percentages) and were compared using a chi-square or Fisher's exact test.

In order to identify the independent predictors for bleeding complications and MACCE, first univariate and then multivariate logistic regression was applied. Only the variables significantly associated with dependent variables ($p < 0.05$) during univariate analysis were included in multivariate analysis. Because of the non-linear relation of age and logistic function, age was categorized into four classes – consisting of the age groups 38–59 years, 60–69 years, 70–79 years, and 80–88 years – for the logistic models. The fit of the logistic regression models was adequate according to the Hosmer-Lemeshow goodness-of-fit test.

Propensity scores were used to adjust for potential bias in the comparison between non-randomized BT and UAC groups. The propensity score was calculated as the predicted probability that the patient was treated by UAC as opposed to BT using logistic regression. Baseline clinical characteristics and procedural variables with a p-value of < 0.2 during univariate analysis were included in the backward stepwise logistic regression model. The discrimination of propensity score was tested on a receiver operating characteristics (ROC) curve.

A propensity score was used for risk adjustment as well as for one-to-one propensity score matching. One-to-one propensity score matching between study groups was done between each patient in the UAC and BT groups according to a propensity score difference of < 0.005 . Propensity score stratification analysis was not performed because of the small size of the present series.

The results of the logistic regression are presented using odds ratios (OR) and their 95% confidence intervals (CI). A two-sided p-value of < 0.05 was required for statistical significance. All data was analyzed using PASW version 18 (IBM SPSS, Chicago, IL, USA) and SAS System for Windows version 9.1 (SAS Institute, Cary, NC, USA).

In paper III, continuous variables with normal distribution are reported as means \pm SD and skewed variables are reported as medians and interquartile ranges (IQR) and tested using ANOVAs (Bonferroni) for normally distributed data and using non-parametric tests (Kruskal-Wallis one-way analysis of variance) in other instances. Categorical variables are presented as percentages and chi-square tests were used for comparisons. A p-value of < 0.05 was considered statistically significant.

Kaplan-Meier analyses were used to construct survival plots of time to death, MACCE, and bleeding events after PCI. Multivariate analysis of survival rates was carried out

using Cox models incorporating a backward Wald test. Variables with a p-value of <0.05 in univariate analysis were entered into a stepwise ascending multivariate analysis. All computations were carried out using SPSS software (V20.0, SPSS Inc., Chicago, Illinois, USA).

In paper IV, continuous variables are reported as mean \pm SD, skewed variables as median (IQR) 25/75, and categorical variables as percentages. Student's t-tests, Mann-Whitney U-tests, and chi-square tests were used for comparison of continuous, skewed, and categorical variables respectively. To investigate the influence of variables on the occurrence of MACCE and bleeding events, two logistic regression models were applied. The results of the logistic regression are presented as hazard ratios (HR) with a 95% confidence interval (CI). A p-value of <0.05 was considered statistically significant. All computations were carried out using SPSS software (V11.5 and V19, SPSS, Chicago, IL).

In paper V, data is presented as means \pm SD, medians (IQR) and frequencies (%), as appropriate. Continuous variables were analyzed using independent samples t-tests. Categorical variables were analyzed using chi-square tests.

Independent determinants of any bleeding complication were assessed using univariate modeling, and those associated with any bleeding event at a p-value of <0.10 were entered into a stepwise backward logistic regression analysis. Bleeding risk scores were analyzed in 3 ways: (1) as continuous variables and (2) dichotomous variables (low vs. intermediate/high risk), with a (3) Cox proportional hazard analysis applied to each separately assessed score. Receiver-operating characteristic curves and c-indexes were constructed for any bleeding and for major bleeding endpoints. Significance was set at a p-value of <0.05. Analysis was performed using SPSS version 16.0 (SPSS Inc., Chicago, Illinois).

5 RESULTS

5.1 Are glycoprotein inhibitors safe during percutaneous coronary intervention in patients on chronic warfarin treatment? (I)

In patients with AF and OAC (n=377, male 71%, mean age 70) a total of 111 patients (29%) received periprocedural GPIs, with wide inter-hospital variation in their use (range 3–68%). The use of GPIs increased with the severity of the disease presentation, and 49% of STEMI patients received GPIs. GPIs were used more often with diabetics (40% vs. 26% for non-diabetics) and with patients with interrupted warfarin treatment (71% vs. 48%). Tirofiban was the most often (62%) used GPI, followed by eptifibatide (24%) and abciximab (14%).

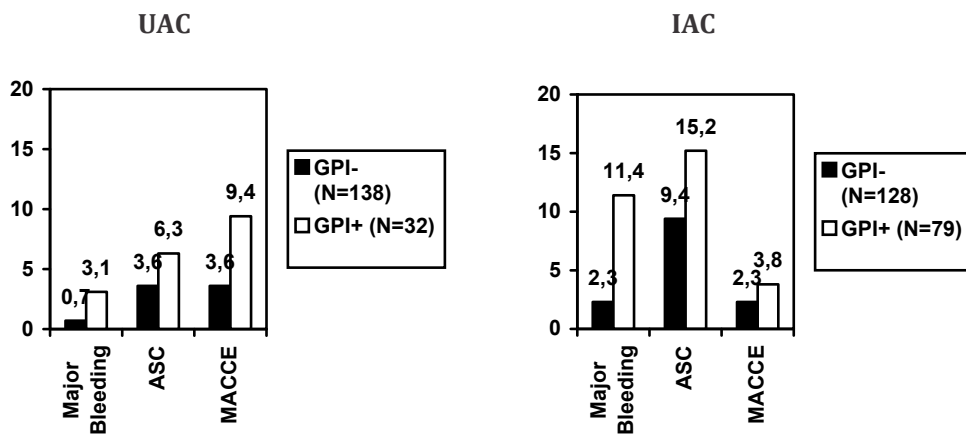
Femoral access was used in the majority of patients in both groups, and closure devices were used in one third of the patients in both groups. Visible intracoronary thrombus was more common in the GPI group.

Warfarin therapy was interrupted before the procedure (mean 3 days) in 71% of patients in the GPI group, and their mean periprocedural INR was 1.89 (range 1.1–3.3). LMWHs were used as a BT or due to subtherapeutic OAC more often in the GPI group than among those patients not taking GPIs (80% vs. 51%, $p < 0.001$). TT was the most often used combination in both groups (56% and 55%). Warfarin was replaced by DAPT after PCI more often (27% vs. 14%, $p = 0.003$) in the GPI group.

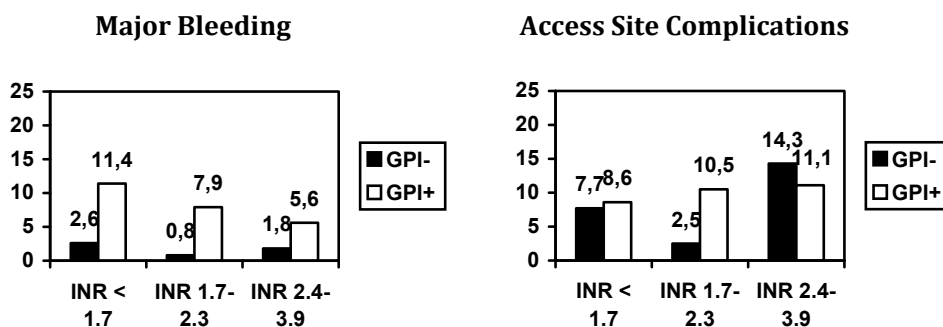
The in-hospital rates of adverse events in the two groups are presented in Table 18. Interruption of warfarin (IAC) treatment tended to increase major bleeding compared to uninterrupted warfarin (UAC) treatment (Figure 2). In-hospital major bleeding events, MACCE or access site complications were not significantly related to INR levels (Figure 3).

Table 18: Outcome events during hospitalization.

	GPI- N= 266	GPI+ N = 111	p-value
MACCE, n (%)	8 (3)	6 (5)	0.37
Death	6 (2)	1 (1)	
Myocardial infarction	4 (2)	5 (5)	
Target vessel revascularization	1 (0.4)	3 (3)	
Stent thrombosis	1 (0.4)	1 (1)	
Stroke	1 (0.4)	0	
Major bleeding, n (%)	4 (1.5)	10 (9.0)	0.001
Patients with access site complications, n (%)	17 (6)	14 (13)	0.06



Figures 2: Interruption of warfarin (IAC) treatment tended to increase major bleeding compared to uninterrupted warfarin (UAC) treatment. GPI+/- = Glykoprotein inhibitor IIb/IIIa used/not used; ASC= Access site complications



GPI- (n)	78	118	56	GPI- (n)	78	118	56
GPI+ (n)	35	38	18	GPI+ (n)	35	38	18

Figure 3. In-hospital major bleeding events, MACCE or access site complications were not significantly related to INR levels (Figure 3). GPI+/- = Glykoprotein inhibitor IIb/IIIa used/not used.

In multivariable analysis, the use of GPIs (OR 5.1, 95%CI 1.3–20.6, $p = 0.02$) and old age (OR 1.2, 95%CI 1.0–1.3, $p = 0.02$) remained the only independent predictors of major bleeding. Also, after adjusting for propensity score, GPIs remained a significant predictor of major bleeding (OR 3.8, 95%CI 1.03–14.1, $p = 0.045$). ACS (OR 5.4, 95%CI 1.1–25.8, $p = 0.03$) and history of heart failure (OR 3.9, 95%CI 1.2–12.6, $p = 0.02$) and total stent length (OR 1.05, 95%CI 1.0–1.09, $p = 0.04$) were independent predictors for MACCE.

5.2 Comparing heparin bridging and uninterrupted oral anticoagulation in patients with atrial fibrillation undergoing coronary artery stenting (II)

In AF patients (N=529) the UAC group (N= 290, male 71.0%, mean age 73.2±7.8) and BT group (N=161, male 71.4%, mean age 73.1±8.0) did not differ at baseline in terms of gender, age or CHADS₂ score. In the BT group, there were more patients with diabetes and hypertension, and the indication for stenting was less frequently stable angina pectoris (30.4% vs. 50.3%).

Femoral access was more common (86.3% vs. 56.6%, p<0.001) in the BT group. There was no difference in the use of DES between the groups. In the BT group, OAC was interrupted for a median of 5 days (before PCI, median 3 days). A total of 116 patients (72%) received LMWH ≥4 days. Antithrombotic treatments are shown in Table 19.

Table 19. Periprocedural antithrombotic treatment and antithrombotic treatment at discharge in patients with uninterrupted anticoagulation (UAC) or patients with bridging therapy (BT).

	UAC (n = 290)	BT (n=161)	p-value
Periprocedural antithrombotic treatment			
Periprocedural INR	2.3±0.5	1.8±0.6	<0.0001
UFH/LMWH procedural bolus	140 (48.3)	112 (69.6)	<0.0001
Bivalirudin	19 (6.6)	2 (1.2)	0.009
Glycoprotein IIb/IIIa inhibitor	20 (6.9)	42 (26.1)	<0.0001
Vitamin K (dose 2–10mg)	-	13 (8.1)	-
Antithrombotic regimens at discharge			
Aspirin + clopidogrel + VKA and/or LMWH	262 (90.3)	123 (76.4)	<0.0001
Clopidogrel + VKA and/or LMWH	16 (5.5)	20 (12.4)	0.011
Aspirin + clopidogrel	1 (0.3)	12 (7.5)	<0.0001
VKA monotherapy	2 (0.7)	0	0.54

INR=International Normalized Ratio; VKA= Vitamin K-antagonist; UFH=Unfractionated heparin; LMWH=Low molecular weight heparin

The length of post-PCI hospitalization was longer in the BT group both in elective and in acute patients (3.2 ± 2.9 vs. 1.9 ± 4.6 days and 7.0 ± 10.4 vs. 5.3 ± 6.3 days, respectively; p<0.05 for both).

The rates of adverse events during the 30-day post-PCI follow-up in the two groups are provided in Table 20. There were no significant differences in the occurrence of MACCE or major bleeding events between the groups. Thromboembolic complications were very rare; there was only 1 stroke in the UAC group. During the index hospitalization, all bleeding events, including access site complications, were more common in the BT group (14.9% vs. 6.6%, p<0.01), but this difference was not significant at 30-day follow-up (18.6% vs. 12.1%, p=0.07) (Table 21). One patient in each group had a fatal intracerebral hemorrhage. In the UAC group, 1 patient underwent gastroscopy and 1 patient underwent bronchoscopy due to bleeding

events. There was no need for corrective surgery and there were no pericardial tamponade incidents in either group. Hematuria, hemoptysis and GI bleeding events were rare in both groups (BT: 2.4% vs. UAC: 1.3%). Bleeding events, access site complications, or MACCE were not related to INR levels in either group.

Table 20. Summary of outcome events

	Overall series			Propensity score matched pairs		
	UAC (n = 290)	BT (n=161)	p-value	UAC n=114	BT n=114	p-value
MACCE, n (%)	11 (3.8)	10 (6.2)	0.25	6 (5.3)	8 (7.0)	0.58
Death	6 (2.1)	4 (2.5)	0.73	5 (4.4)	4 (3.5)	1.00
Myocardial infarction	3 (1.0)	3 (1.9)	0.67	0	0	-
Re-revascularization*	2 (0.7)	4 (2.5)	0.19	0	3 (2.6)	0.25
Stent thrombosis	6 (2.1)	2 (1.2)	0.72	1 (0.9)	0	1.00
definite	2 (0.7)	0	-	0	0	-
probable	4 (1.4)	2 (1.2)	-	1 (0.9)	0	-
Stroke, n (%)	1 (0.3)	0	1.0	0	0	-
All bleeding events	35 (12.1)	30 (18.6)	0.07	18 (15.8)	17 (14.9)	1.00
Major bleeding	4 (1.4)	4 (2.5)	0.25	3 (2.6)	3 (2.6)	1.00
Blood transfusion	3 (1.0)	1 (0.6)	1.0	3 (2.6)	1 (0.9)	0.62
Access site bleeding	16 (5.5)	18 (11.2)	0.030	10 (8.8)	10 (8.8)	1.00

UAC = uninterrupted anticoagulation; BT = bridging therapy; MACCE = number of patients with major adverse cardiac and cerebrovascular events, including death, myocardial infarction, target vessel revascularization, stent thrombosis, and stroke.

Adjusting for propensity score did not identify any significant association between BT and any bleeding complications (OR 1.38, 95%CI 0.77–2.48, $p=0.28$), MACCE (OR 1.16, 95%CI 0.44–3.05, $p=0.76$), repeat revascularization (OR 2.57, 95%CI 0.40–16.48, $p=0.32$) or death (OR 1.00, 95%CI 0.23–4.29, $p=1.00$) during the follow-up. The proportions of MACCE and bleeding events were similar in the propensity-matched groups (Table 20).

Multivariate analysis (Hosmer-Lemeshow test: $P=0.80$) showed that femoral access (OR 2.68, 95%CI 1.35–5.33, $p=0.005$), ACS (OR 1.75, 95%CI 1.01–3.04, $p=0.048$), and history of bleeding (OR 3.10, 95%CI 1.00–9.55, $p=0.049$) were independent predictors of bleeding complications, and that ACS was the only independent predictor for MACCE (OR 3.76, 95%CI 1.22–11.53, $p=0.021$). Baseline INR was not associated with either bleeding complications or MACCE.

5.3 Prognostic impact of renal impairment in patients with atrial fibrillation undergoing coronary artery stenting (III)

In the third study, data on pre-PCI creatinine levels was available for 781 patients (69.7 % male, median age 74 years, age range 45–92). At baseline, patients with severe renal impairment were older, more often female, and more often presented

with ACS as an indication for PCI (Table 21). There were no significant differences in DES use, access site, perioperative medications, or other procedural characteristics between the groups. The use of evidence-based cardiac medications was comparable between the study groups at discharge, with the exception of lipid-lowering agents, which were less often used in patients with severe renal impairment.

Table 21. Baseline characteristics of the study population

All N=781 (100%)	eGFR ≥90 n=195 (25%)	eGFR 60-89 n=290 (37%)	eGFR 30-59 n=263 (34%)	eGFR <30 n=33 (4%)
Male	164 (84.1)	209 (72.1)**	151 (57.4)**	20 (60.6)**
Age (year)	65.5±7.7	73.4±6.7**	77.7 ±5.4**	77.0 ±6.7**
eGFR prePCI	120±28	74±9**	47±8**	21±6**
CHA ₂ DS ₂ - VASc ≥2	188 (96.4)	288 (99.3)*	262 (99.6)*	33 (100)
HAS-BLED (median)	3.0 (1.0)	3.0 (0.25)**	3.0 (1.0)**	4.0 (1.0)**:
Indication for PCI				
Stable angina	95 (48.7)	138(47.6)	108 (41.1)	8 (24.2)*
ACS	100 (51.3)	152 (52.4)	155 (58.9)	25 (75.8)*
Length of hospitalization (days)	4.2±5.2	4.2±6.2	5.9±8.2**	8.8±6.7**

PCI=percutaneous coronary intervention; ; CHA₂DS₂VASc-score = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, Stroke, associated Vascular disease, Age 65–74 years, Sex category; HAS-BLED-score=: Hypertension [uncontrolled, >160 mmHg systolic), Abnormal renal/liver function, Stroke, Bleeding history or predisposition [anemia], Labile INR, Elderly (>65) and Drugs/alcohol concomitantly drugs; ACS=Acute coronary syndrome; P-value < 0.05 = *, p value < 0.01 = **, all values are compared with eGFR ≥90 ml/min/1.73 m² group. Data is reported as number and percentage or mean ± SD or median (IQR); eGFR = estimated glomerular filtration rate

In the overall cohort, TT consisting of a vitamin K antagonist, clopidogrel, and aspirin was used in 72% of the patients after PCI. The use of TT tended to decrease along with decreasing renal function (77.4% vs. 72.8% vs. 68.1% vs. 63.6% across the patient categories). The duration of clopidogrel use was comparable in all eGFR groups.

Outcome events at the 12-month follow-up are presented in Table 22. Overall, the rates of stroke and stent thrombosis were low.

Table 22. Outcome events at 12-month follow-up.

All N=781	eGFR ≥90 n=195	eGFR 60-90 n=290	eGFR 30-60 n=263	eGFR <30 n=33
MACCE				
12 months	25 (12.8)	58 (20.0)*	70 (26.6)**	19 (57.6)**
30 days	7 (3.6)	17 (5.9)	25 (9.5)*	6 (18.2)**
In-hospital	5 (2.6)	11 (3.8)	14 (5.3)	3 (9.1)
DEATH				
12 months	8 (4.1)	26 (9.0)*	39 (14.8)**	15 (45.5)**
30 days	2 (1.0)	10 (3.4)	17 (6.5)**	5 (15.2)**
In-hospital death	2 (1.0)	5 (1.7)	8 (3.0)	2 (6.1)*
Myocardial infarction	4 (2.1)	10 (3.4)	18 (6.8)*	5 (15.2)**
Re-revascularization	13 (6.7)	28 (9.7)	22 (8.4)	4 (12.1)
Stent thrombosis	1 (0.5)	5 (1.7)	6(2.3)	0
Stroke/TIA	4 (2.1)	11 (3.8)	6 (2.3)	2 (6.1)
All thromboembolism	4 (2.1)	11 (3.8)	10 (3.8)	3 (9.1)*
All bleeding (BARC 1-5)				
12 months	41 (21.0)	80 (27.6)	86 (32.7)**	15 (45.5)**
In-hospital	20 (10.3)	29 (10.0)	34 (13.0)	7 (21.2)
BARC>2				
12 months	17 (8.7)	27 (9.3)	33 (12.5)	5 (15.2)

eGFR= estimated Glomerular filtration rate; MACCE= Major Adverse Cardiac and cerebrovascular events; TIA= transient ischemic attack; BARC=bleeding definitions 1-5

The degree of renal impairment remained an independent predictor of mortality and MACCE in a Cox regression model that included ACS, female gender, and age as covariates. Patients with mild renal impairment had a higher risk of all-cause mortality (HR 2.26, 95%CI 1.02–5.00, $p=0.04$) and MACCE (HR 1.63, 95%CI 1.02–2.60, $p=0.04$) compared to those with normal eGFR. Patients with moderate renal impairment had a higher risk of all-cause mortality (HR 3.66 95%CI 1.71–7.83 $p=0.001$) and MACCE (HR 2.22 95%CI 1.40–3.50, $p=0.001$) compared to those with normal eGFR. Patients with severe renal impairment had a very high risk of all-cause mortality (HR 11.21, 95%CI 4.73–26.58, $p<0.001$), with 45% total mortality. The risk of MACCE (HR 5.40, 95%CI 2.96–9.85, $p<0.001$) was also higher among those patients with renal impairment than those with normal renal function.

In multivariate analysis, the risk of bleeding events increased with a decline in renal function (HR 2.01, 95%CI 0.97–4.19, $p=0.06$ for mild; HR 2.38, 95%CI 1.05–5.40, $p=0.04$ for moderate; and HR 6.47, 95%CI 2.41–17.34, $p<0.001$ for severe), compared to those with eGFR ≥90 mL/min including ACS, female gender, and age were included as covariates in a Cox regression model.

Post-procedural creatinine levels were available for 465 (59.5%) of the 781 patients. Acute kidney injury occurred in 35 (7.5%) of 465 patients after PCI affecting 4.7% of patients with normal renal function; 3.8% with mild; 10.5% with moderate; and 22.2% with severe renal impairment, respectively. In a Cox regression model adjusting for age, gender and acute coronary syndrome as an indication for PCI, acute kidney injury was an independent predictor of all-cause mortality (HR 2.91, 95%CI

1.47-5.76, $p=0.002$) and MACCE (HR 2.25, 95%CI 1.28-3.95, $p=0.005$) with a trend to effect on bleeding events (HR 1.63, 95%CI 0.97- 2.73, $p=0.07$) compared to patients with no significant impairment in renal function.

5.4 In-hospital management and outcomes in patients with atrial fibrillation undergoing percutaneous coronary intervention with stent implantation (IV)

In the study IV, at baseline, about one half of 963 patients (70.1% male, mean age 73.0 ± 8.2) with AF undergoing PCI exhibited permanent-pattern AF; 71.8% had a CHADS₂ score of ≥ 2 . The indication for PCI was an ACS – either STEMI or non-STEMI – in 56.5% of cases.

Of the total patients, 71.4% received procedural VKA. Heparin, either LMWH or UFH, was given to the majority of patients. Use of GPIs was limited to about 20% of patients. In 72.6% of cases, PCI was carried out through the femoral route; the radial approach was significantly more often used in patients with ongoing VKA treatment. BMS was the most frequent (56.4%) stent type implanted.

Table 23. Ongoing antithrombotic treatment before PCI.

Ongoing antithrombotic regimen	n (%)
Single antiplatelet therapy (aspirin or clopidogrel)	145 (15.6)
DAPT (aspirin + clopidogrel)	49 (5.1)
VKA only	326 (33.8)
VKA + single antiplatelet therapy	260 (27.0)
Triple therapy (VKA + aspirin + clopidogrel)	82 (8.5)

DAPT=Double antiplatelet therapy; VKA=Vitamin K-antagonist

The overall occurrence of in-hospital MACE was 4.5%, consisting of cardiovascular death in 1.9%, stroke/systemic thromboembolism in 0.6%, and urgent revascularization in 1.5% of patients (Figure 4). Additionally, 4 patients (0.4%) died for other than cardiovascular reasons.

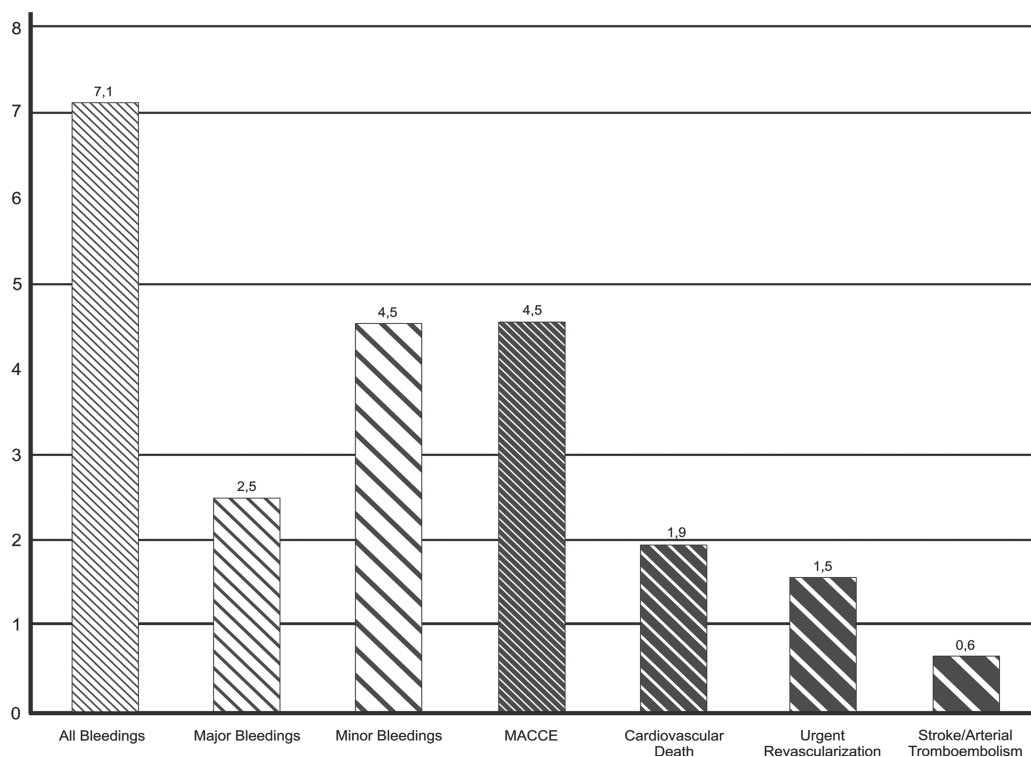


Figure 4. In-hospital adverse events (%) post PCI. MACCE=Major Adverse Cardiac and Cerebrovascular Events

Univariate predictors for in-hospital cardiovascular death were low left ventricular ejection fraction (EF) ($36.3 \pm 11.7\%$ vs. $49.6 \pm 14.0\%$, $p < 0.001$), ACS as the indication for PCI (2.9% ACS vs. 0.8% other, $p = 0.006$), previous treatment with VKAs (3.1% vs. 1.2%, $p = 0.047$) and in-hospital treatment with LMWH (2.7% vs. 0.7%; $p = 0.02$). In a logistic regression analysis including potential confounders, only LMWH treatment (HR 5.551, 95%CI 1.8034–13.3187, $p = 0.012$) and EF as a continuous variable (HR 0.932, 95%CI 0.885–0.981, $p = 0.008$) were related to in-hospital death.

Upon logistic regression analysis, the occurrence of MACE was significantly predicted by the use of GPIs (HR 8.06, 95%CI 1.14–56.96) and female gender (HR 9.18, 95%CI 1.13–74.16, $p = 0.037$), whereas treatment with clopidogrel significantly decreased the likelihood of MACE (HR 0.017, 95%CI 0.001–0.538, $P = 0.021$).

In-hospital bleeding complications occurred in 7.1% of patients (Figure 4). In 2.5% of cases, bleeding was graded as major. ACS as indication for PCI (3.6% vs. 1.0%; $p < 0.01$) and use of GPIs (5.1% vs. 1.9%; $p < 0.01$) were significantly more frequent in patients who experienced major bleeding as compared to those who did not. Of note, GPIs were significantly more often used in patients not on VKA at time of PCI (34.2% vs. 13.3%, $p < 0.001$), but higher INR and ongoing treatment with VKA were not related to bleeding events. Major bleeding was mostly of GI origin (1.3%). Intracerebral

bleeding occurred in 1 patient, severe lung bleeding in 2 patients, and cardiac tamponade after PCI-S in 2 patients. In a stepwise logistic regression analysis, no variables were significantly associated with major bleeding events.

Non-major bleeding mostly occurred at the vascular access site (2.4%). The femoral approach was associated with an increased incidence of bleeding, which reached statistical significance for minor (5.5% vs. 0.8%; $p=0.001$) but not major (3.0% vs. 1.2%; $p=0.11$) bleeding events.

The antithrombotic regimens prescribed at discharge are reported in Table 24.

TABLE 24. Antithrombotic Regimens Prescribed at Discharge: overall population and according to CHADS₂-Score

Combinations at discharge	All n=963	CHADS ₂ score=0 n=46	CHADS ₂ score=1, n=214	CHADS ₂ score≥2 n=665
Triple therapy (%)	71.8 (n=691)	68.2	68.3	73.2
VKA+aspirin+clopidogrel (%)	60.9 (n=586)	66.0	60.8	60.6
LMWH+aspirin+clopidogrel (%)	10.9 (n=105)	2.1	7.5	12.6
DAPT (%)	17.2 (n=166)	19.1	21.5	15.7
VKA+single antiplatelet therapy (%)	10.0 (n=96)	12.7	8.9	10.2
VKA+clopidogrel (%)	8.3 (n=80)	10.6	6.1	8.9
VKA+aspirin (%)	1.7 (n=16)	2.1	2.8	1.3

CHADS₂= Congestive Heart Failure, Hypertension, Age > 75 years, Diabetes, Prior Stroke or transient ischemic attack (TIA); VKA = vitamin K-antagonists; LMWH = low-molecular weight heparin; DAPT = dual antiplatelet therapy.

TT was significantly less often prescribed in patients who did not experience major bleeding in-hospital (47.8% vs. 72.6%; $p=0.009$). The risk of stroke, as evaluated by the CHADS₂ score, did not influence the antithrombotic regimen prescribed at discharge, as no significant differences in the prescription of any regimen were observed. Adherence to VKA therapy was high, as 559 out of the 639 patients (86.9%) on VKA at admission were confirmed as being on VKA at discharge ($p<0.001$). PPI was prescribed in 344 patients (37.4%).

5.5 Performance of bleeding risk-prediction scores in patients with atrial fibrillation undergoing percutaneous coronary intervention

In study V, baseline characteristics according to any bleeding event versus no bleeding event at 1-year follow-up are listed in Table 25.

Table 25. Baseline characteristics according to any bleeding event versus no bleeding event at 1-year follow-up

Variable	Whole Cohort (n = 929)	Bleeding Yes (n = 168)	No (n = 761)	p Value
Median age	75.0 [9.0]	74.0[11.0]	74.0 [11.0]	0.04
Women	276 (29.7%)	61 (36.3%)	215 (28.3%)	0.04
Stable angina pectoris	399 (42.9%)	55 (32.7%)	344 (45.2%)	0.003
DES	227 (25.0%)	35 (21.2%)	192 (25.8%)	0.23
Femoral sheath	663 (71.4%)	137 (81.5%)	526 (69.1%)	0.001
Medication at discharge				
Triple therapy	679 (73.1%)	119 (70.8%)	560 (73.6%)	0.50
Dual antiplatelet	162 (17.4%)	33 (19.6%)	129 (17.0%)	0.43
VKA and clopidogrel	73 (7.9%)	12 (7.1%)	61 (8.0%)	0.87
VKA and aspirin	15 (1.6%)	4 (2.4%)	11 (1.4%)	0.33
Proton pump inhibitor	335 (36.1%)	68 (40.5%)	267 (35.1%)	0.32

DES=drug eluting stent; VKA= Vitamin K-antagonist

At 12 months, the rates of any (BARC 2, 3a, 3b, 3c, and 5), BARC 3, and major (BARC 3a, 3b, 3c, and 5) bleeding events were 18.1%, 9.1%, and 10.4%, respectively. Most bleeding events occurred early within the first month after the index PCI. The mean INR level at the time of the first bleeding event was 1.8 ± 0.6 (range 1.0–3.0).

Increasing age (OR 1.03, 95%CI 1.01–1.06, $p=0.009$), previous peptic ulcer (OR 2.32, 95%CI 1.12–4.84, $p=0.024$), and femoral access site (1.86, 95%CI 1.17–2.97, $p=0.009$) remained independent predictors of any bleeding event in a multivariate logistic regression model including also renal impairment (eGFR <60), gender, body mass index, ACS versus stable angina as an indication for PCI, previous transient ischemic attack/stroke, and the use of GPIs during the index procedure.

Table 26. Cox regression analysis of the HAS-BLED, ATRIA, mOBRI, and REACH scores for the outcomes of any bleeding (BARC 2 to 5), major bleeding (BARC>2), and all-cause mortality

	Any Bleeding		Major Bleeding		All-Cause Mortality	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
HAS-BLED Score	1.04 (0.84-1.28)	0.72	1.10 (0.84-1.45)	0.49	1.26 (0.97-1.63)	0.08
Low <3 vs high ≥ 3	0.87 (0.62-1.23)	0.43	0.89 (0.56-1.40)	0.61	1.18 (0.74-1.88)	0.50
ATRIA Score	1.08 (0.98-1.18)	0.11	1.10 (0.97-1.24)	0.14	1.24 (1.10-1.39)	<0.001
Low <4 vs high ≥ 4	1.24 (0.86-1.78)	0.25	1.62 (1.01-2.61)	0.047	1.99 (1.24-3.17)	0.005
mOBRI Score	1.12 (0.91-1.39)	0.28	1.22 (0.92-1.61)	0.16	1.51 (1.16-1.97)	0.002
Low 0 vs High ≥ 1	1.17 (0.86-1.58)	0.32	1.38 (0.93-2.06)	0.11	1.74 (1.18-2.57)	0.005
REACH Score	1.01 (0.95-1.07)	0.83	0.99 (0.92-1.07)	0.76	1.09 (1.01-1.18)	0.02
Low <11 vs high ≥ 11	1.00 (0.73-1.36)	0.99	0.86 (0.57-1.28)	0.46	1.34 (0.89-2.01)	0.16

For each score, HRs were calculated as a continuous variable (per 1 unit of change) and as a dichotomous low vs. high score. CI = confidence interval; HR = hazards ratio.

Figure 5 shows receiver- operating characteristic curves for the outcomes of any bleeding and major bleeding. Low bleeding risk, as determined by HAS-BLED scores of 0–2, ATRIA scores of 0–3, a mOBRI score of 0, and REACH scores of 0–10, were detected in 23.7%, 73.0%, 7.8%, and 5.7% of patients of the cohort, respectively.

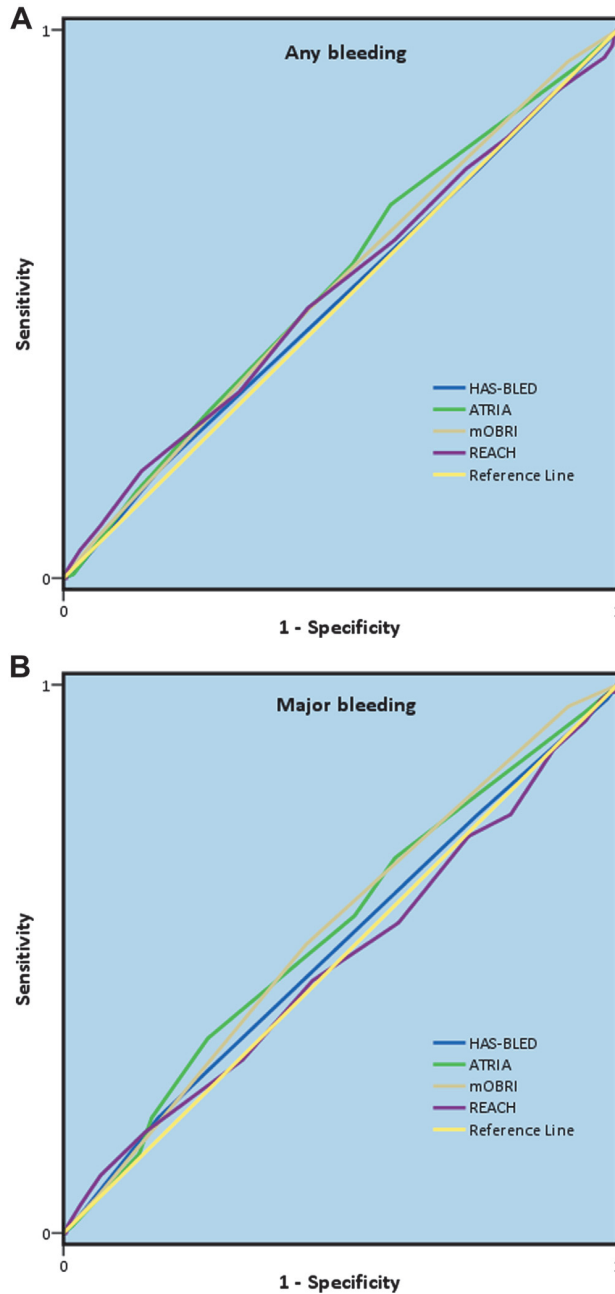


Figure 5. ROC curves according to HAS-BLED, ATRIA, mOBRI, and REACH scores for the outcomes of (A) any bleeding and (B) major bleeding. ROC = receiver operating characteristic.

Figure 6 shows the incidence of any bleeding during various antithrombotic treatment regimens according to the HAS-BLED, mOBRI, ATRIA, and REACH categories of low bleeding risk vs. intermediate/high bleeding risk. TT was associated with a higher absolute rate of any bleeding events compared with other regimens, regardless of the bleeding risk. None of the established bleeding-risk prediction tools performed well in the detection of intracranial bleeding (BARC 3c) as reflected by poor C indexes 0.42, 0.35, 0.58, and 0.41 for HAS-BLED, ATRIA, mOBRI, and REACH scores, respectively.

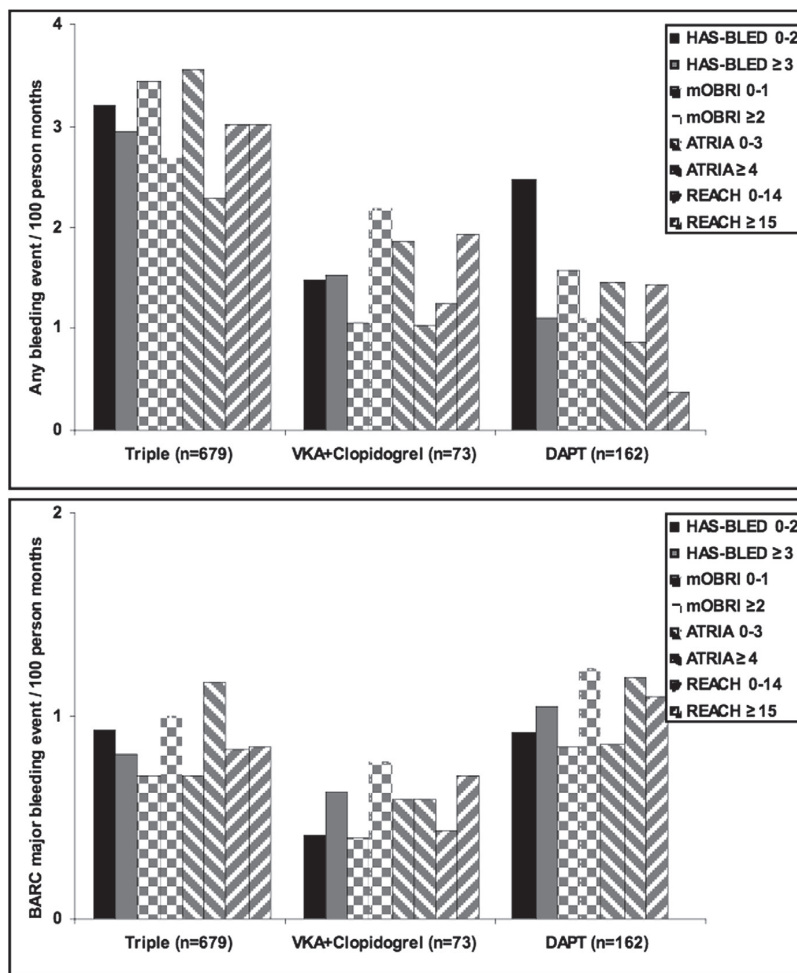


Figure 6. Incidence (number of events per 100 months of treatment with clopidogrel) of any bleeding (upper panel) and BARC major bleeding (lower panel) during various antithrombotic treatment regimens according to the HAS-BLED, mOBRI, ATRIA, and REACH categories of low bleeding risk vs. intermediate/high bleeding risk. Triple = vitamin K antagonist + aspirin + clopidogrel; DAPT = clopidogrel + aspirin; VKA = vitamin K antagonist.

6 DISCUSSION

6.1 Safety of GPIs in patients with AF undergoing PCI (I)

There are no large-scale randomized or observational studies to support the guidelines that exist on treatment of patients with AF undergoing PCI. The first study of this thesis focused on outcomes of patients treated with GPIs during PCI, based on the most comprehensive multicenter data at the time with real-world insight into the periprocedural strategies for managing AF patients on chronic warfarin treatment.

In light of the missing recommendations, it was not a surprise that the survey revealed an over-20-fold inter-hospital difference in the use of GPIs. The clinical characteristics of the patients could not explain the observed differences in management strategy. The use of GPIs was associated with a 5-fold increase in risk of major bleeding, but the bleeding events or MACCE were not related to INR levels when the latter did not exceed the therapeutic range.

Current guidelines recommended that, even without GPIs, warfarin should be discontinued a few days prior to coronary intervention and the periprocedural INR level should not exceed 1.5-1.8 [249, 250]. BT with heparins is recommended in patients considered to be at high risk of thromboembolism. Most patients were treated according to this recommendation, but we could not discern even a trend towards increase of bleeding risk during UAC, and most of the major bleeding events occurred during BT (Figure 2).

Randomized trials have shown a modest increase (2.4% vs. 1.4%) in bleeding risk associated with GPI use [193]. Unfortunately, there was no safety data from clinical trials on warfarin-treated patients, since this patient group has been excluded from all randomized studies of GPIs. In real-world practices, bleeding risk may be increased and bleeding complications may represent a significant limitation to the effectiveness of GPIs as shown by the present and earlier data [251, 252]. Moreover, it is well known that major bleeding has a significant negative prognostic effect [253]. In the CRUSADE registry [252], the use of GPIs was associated with increased in-hospital risk of major bleeding (13.8% vs. 9.0%) and transfusions (10.8% vs. 9.1%) in the patients taking warfarin at home. Our data adds important new information to these findings, since only one third of the warfarin-treated patients from the CRUSADE registry underwent PCI. Of interest is the fact that the incidences of major bleeding and need for transfusions were lower than in the CRUSADE registry, despite the fact that all patients underwent PCI. Furthermore, the registry did not provide any information on, e.g., indications or interruptions of warfarin administration, intensity of anticoagulation, type of GPI used, or access site.

6.2 Heparin bridging vs. UAC in patients with AF undergoing PCI (II)

The second study was based on comprehensive prospective multicenter data on patients with AF undergoing PCI in 2010: the AFCAS register. The main finding in comparison to periprocedural antithrombotic treatment strategies was the detection of the simple strategy of uninterrupted OAC (UAC) as an appealing alternative to bridging therapy (BT). The incidence of severe adverse events was similar for both strategies, and the excess of minor bleeding and access site complications in the BT group was driven mainly by the common use of the femoral route in these patients, whereas bleeding events and MACCE are not related to INR levels. The present findings support the view that therapeutic OAC can replace other modes of periprocedural anticoagulation with a favorable balance between bleeding and thrombotic complications and may lead to considerable cost savings compared with the conventional BT, owing to the significantly reduced length of hospitalization.

In AF patients on OAC, effective anticoagulation is necessary during PCI. The safety and efficacy of BT has been questioned in patients undergoing coronary angiography, pacemaker implantations, or pulmonary vein ablation [164, 254-256]. BT offered no advantages in any of these studies and might even increase bleeding events [256]. It might also delay the invasive treatment in OAC-treated patients with acute coronary syndromes [197] and prolong hospitalization [197, 257].

Current guidelines included limited guidance on long-term OAC during the peri-PCI period and some even ignored this complicated issue [258-260] (Table 4). While the majority of the US guidelines (American College of Chest Physicians/American College of Cardiology/American Heart Association) recommend BT use in conjunction with invasive procedures and even recommend that optimal peri-procedural INR of <1.5 [259, 261], the European Society of Cardiology (ESC) guidelines for the management of valvular heart disease recommend continuation of OAC at modified doses for the majority of patients who undergo cardiac catheterization [260]. Only in the consensus paper of the Working Group on Thrombosis of the ESC, endorsed by the European Heart Rhythm Association (EHRA) and European Association of Percutaneous Cardiovascular Interventions (EAPCI), is the uninterrupted OAC strategy recommended as the preferred strategy for AF patients at moderate to high risk of thromboembolism [262]. The difference between guidelines is due to lack of randomized trials comparing different strategies. In the only small randomized study, therapeutic OAC treatment and warfarin withdrawal (≥ 48 hours) resulted in a similar outcome in patients undergoing coronary angiography, but it took a median of 9 days for INR to return to the therapeutic level [257]. In earlier non-randomized studies, this simple UAC strategy was at least as safe as that of more complicated interrupted OAC, but the low methodological quality of those studies precludes any definitive conclusions [263].

In addition to effective anticoagulation, OAC patients undergoing PCI require potent antiplatelet treatment during the peri-procedural period for effective stent thrombosis prevention. Current guidelines recommend that both aspirin and clopidogrel be administered in the peri-PCI period and continued for 1-12 months, depending on the type of stents and indication of the procedure (Table 7) [264]. While the brevity of the follow-up period in the study (30 days) precludes solid conclusions, the widespread use of a triple therapy of OAC, aspirin, and clopidogrel in the vast majority of our patients may have played a major role in the rather low incidence of MACCE in such a vulnerable patient group. Despite the reported high incidence of bleeding complications with triple therapy, in our population the absolute major bleeding rate was lower than in earlier studies. Variability in definitions of bleeding may partly contribute to this finding.

6.3 Renal impairment in patients with AF undergoing PCI (III)

Renal impairment and AF are two well-known independent high-risk factors for complications in patients undergoing PCI. In Study III, the outcomes of these patients with both of these risk factors – often excluded from clinical trials – were analyzed for the first time by using the data from prospective multicenter real-world registry (AFCAS). We showed that 75% of these patients have CKD according to the current criteria. Importantly, one third of the patients had mild renal impairment (eGFR 60-89mL/min) often unrecognized because the creatinine levels typically lie within the normal range. The principal novel finding is that even this early renal impairment is clinically important and results in an increase in mortality and MACCE.

Although the major impact of renal impairment on the outcome following PCI has long been recognized, less is known about the impact of mild renal impairment. Compared to those with normal renal function, the effect of mild renal impairment on survival and major adverse cardiac event rate was recently reported to be negligible in the general PCI population²⁷. However, it was a significant predictor of worse prognosis in patients presenting with ST-elevation myocardial infarction²⁸. In addition, Reinecke et al. reported that mildly elevated creatinine levels were associated with a twofold increase in total mortality and a 10% reduction in cumulative survival over three years in the general PCI population²⁹. A similar phenomenon was observed by Gibson et al. who found that eGFR < 90 mL/min remained independently associated with increased mortality in non-ST-segment elevation ACS patients³⁰.

Cardiovascular events are the most common cause of death in patients with renal impairment. Explanations of this interaction include the greater frequency of risk factors, such as hypertension and diabetes mellitus. In addition, factors associated with renal disease such as uremic toxins, inflammation, hyperparathyroidism, elevated calcium-phosphate product, fluid overload, and anemia contribute to the severity and extent of the coronary atherosclerosis as well as the higher adverse

event rates in this high risk population. Adverse events may also be related to other conditions than epicardial coronary artery disease such as uremic cardiomyopathy, metabolic derangements, and microvascular disease. Nevertheless, the presence of significant coronary artery stenosis has been reported to worsen the prognosis dramatically ²⁷.

Reflecting this background, patients in the AFCAS study with severe renal insufficiency had more often high-risk baseline characteristics such as multivessel and left main disease and underwent more often emergency PCI due to acute coronary syndrome. In our study, patients with severe renal impairment had an extremely poor prognosis with almost 50% mortality within 12 months.

A dose-dependent effect of worsening renal function was observed on thrombotic and bleeding events in this high-risk patient group. In an earlier smaller study, Manzano-Fernades et al. reported nearly 2.5-fold increase in the risk of PCI associated major bleeding in patients with mild renal impairment and AF ¹⁴. Our study extends these findings showing that decreased eGFR values were associated with an increased risk of any BARC bleeding in patients with AF undergoing PCI, but only a trend in clinically significant bleeding events. In multivariate analysis, patients with mild stage of CKD had a non-significant trend to increased bleeding events, whereas patients with moderate and severe renal impairment had clearly elevated risks. Of clinical interest, thrombotic and thromboembolic events were more common than clinically significant bleeding events suggesting that the prothrombotic risk outweighs the bleeding risk in most patients. Clinical implication of this finding is that potent antithrombotic therapy after PCI should be considered also in patients with impaired renal function without overt fear for bleeding complications.

Acute kidney injury is a frequent complication of PCI especially in patients with acute coronary syndrome and seems to be associated with increased risk of in-hospital morbidity and mortality ³¹. In line with this experience, acute kidney injury occurred in a total of 7.5% after PCI and was an independent predictor of mortality and MACCE in the present study emphasizing the importance of its prevention with adequate hydration and restricted use of contrast agent.

Repeat revascularization rates were relatively low in all eGFR groups when compared to previous studies and especially those evaluating restenosis by repeat angiography ³². This might be explained by the older age and high prevalence of co-morbidities including AF, which might have favoured medical treatment over re-intervention in patients with recurrent angina after PCI. Moreover, no angiographic follow-up was performed, and all target vessel revascularizations procedures were ischemia-driven. It is known that ischemia-driven target vessel revascularizations tend to underestimate the actual rates of restenosis. In addition, the absence of symptoms of restenosis in patients with renal impairment may lead to silent ischemia and contribute to the high risk of subsequent cardiac events. The rate of stent thrombosis

was relatively low in all eGFR groups, and the low number of events precludes comparison between the groups.

6.4 In-hospital and 30-day follow-up data from AFCAS register treatment strategies and outcomes (IV)

The main findings of our study, which is to date the largest prospective dataset on patients with AF undergoing PCI, are (a) most patients are at moderate–high risk of stroke, (b) PCI management is only partially adherent to current recommendations, (c) the in-hospital incidence of MACE and major bleeding is lower than expected, and (d) antithrombotic regimens prescribed at discharge include TT in most cases, although do not appear to be properly matched to a patient’s individual stroke risk.

The large majority of procedures were carried out through the femoral route. The restrictive use of GPIs and the preferential use of BMS were, on the other hand, in accordance with current recommendations [10, 262].

The in-hospital occurrence of MACE was less frequent than in earlier reports [12] and mostly accounted for by cardiovascular death. We suggest that these results may be a consequence of modern treatment options in centers experienced in the management of patients with AF undergoing PCI. However, this event was predicted by a low left ventricular ejection fraction and the use of LMWH, which identify a population at higher risk rather than supporting a correlation with periprocedural variables.

In-hospital major bleeding was rare compared with earlier reports [11, 12], which may also be related to the fact that experienced practitioners treated these high-risk patients. However, a 2.5% rate of major bleedings should be anticipated.

Owing to the highest prevalence of patients at moderate–high risk of stroke, the most frequent prescription of TT as antithrombotic therapy at discharge was anticipated. The fact that individual stroke risk, as evaluated by CHADS₂ score, did not predict the prescribed antithrombotic regimen underscores the need for dedicated efforts in further acquiring and disseminating knowledge on the management of these patients.

6.5 Performance of bleeding risk-prediction scores in patients with atrial fibrillation undergoing percutaneous coronary intervention (V)

Previously, bleeding risk prediction through REACH or ATRIA scores has not been tested in patients with AF undergoing PCI and receiving multiple antithrombotic medications. In the AFCAS registry, the discriminatory capacity of HAS-BLED, ATRIA, mOBRI, and REACH bleeding risk prediction tools were weak, as demonstrated through relatively low C indexes. Overall, despite including many clinically important

determinants in the scores, bleeding risk prediction is complicated, as confirmed by low C indexes in the original validation studies [29-31, 33].

In the study, increasing age, femoral access site, and previous peptic ulcer were independent determinants of bleeding. Compared with radial route, the femoral access site was associated with a 1.9-fold risk of bleeding complications, which mainly occurred during the in-hospital phase. The risk of bleeding was 2.3-fold in those with a previous peptic ulcer. Strikingly, mean INR levels at the time of bleeding events were subtherapeutic, and the maximal INR level was 3.0. This indicates that clinically relevant bleeding events may occur, even at therapeutic INR levels, in these patients receiving multiple antithrombotic medications. The clinical implication of our findings is that bleeding risk cannot be reliably anticipated with these established bleeding risk prediction tools in patients receiving multiple antithrombotic medications due to AF and PCI.

In a study by Ruiz-Nodar et al. [213], the rate of major bleeding was slightly lower than that in the AFCAS registry at 1 year (7.8% vs. 10.4%, respectively), probably reflecting a difference in bleeding definition [271]. A recently published WOEST trial used the same BARC definition of bleeding events [203] as our analysis. In patients on triple therapy, the rate of BARC 3 major bleeding events was higher in the WOEST trial.

In the AFCAS cohort, HAS-BLED, ATRIA, and mOBRI scores did not influence the choice among TT, DAPT, or VKA+clopidogrel treatments, as these were used similarly in patients with low versus intermediate/high scores. In contrast, patients with a low REACH score very seldom were on TT compared to those with an intermediate/high risk score. Nevertheless, no differences in the BARC bleeding rates were noted between patients with low versus intermediate/high REACH scores.

ACS appeared to increase risk of bleeding. One plausible explanation is that patients with ACS, especially ST-elevation myocardial infarction, have more aggressive antithrombotic/anticoagulation treatment during the index procedure compared to stable elective patients. In contrast, the use of DES was 25% in the cohort and was not associated with increased rates of bleeding events. Nevertheless, it seems that clinical evaluation by experienced physicians may be at least as effective as using these scoring schemes. In addition, it seems that the prothrombotic risk outweighs the bleeding risk in most patients, even when the bleeding risk scores are high. Higher mortality rates have been previously reported in patients with intermediate/high mOBRI scores [32] and HAS-BLED scores [213]. However, in the AFCAS cohort, ATRIA appeared a better predictor of mortality than HAS-BLED, mOBRI, or REACH. Overall, the ATRIA score was a better predictor of mortality rather than bleeding. Major bleeding and mortality are endpoints known to be closely related in populations on anticoagulation therapy [32, 213].

6.6 Combined discussion

At the time of performing this study there were no large-scale randomized or observational studies to support the existing guidelines on treatment of patients with AF undergoing PCI. The dissertation is based on two large comprehensive multicenter studies giving a real-world insight into the procedural strategies for managing AF patients on chronic warfarin treatment. These research findings provide valuable guide to the clinical decision making in the treatment of this patient group.

The clinical assessment of patients prior PCI is based on well-known risk-factors including also mild stage of renal impairment. In AF patients on OAC, effective anticoagulation is necessary during PCI and the simple strategy of uninterrupted OAC is an appealing alternative to heparin bridging with favourable balance between bleeding and thrombotic complications and shorter hospitalization. The use of radial route has shown to be safer in these patients with high risk of bleeding. The use of GPIs should be avoided because of a 5-fold increase in the risk of major bleeding.

6.7 Limitations

Study I carries all the inherent limitations of a retrospective study. On the other hand, the strength of our analysis is that we could identify and include all consecutive warfarin-treated patients from the records and avoid the selection bias of prospective studies. In addition to the differences in the perioperative use of GPIs, other differences in management strategies and patient selection not covered by multivariable models or propensity score analyses may modify our results.

Studies II-V, based on the AFCAS register, carry all of the inherent limitations of prospective non-randomized studies, including individual risk-based decision-making in treatment choices for a heterogeneous AF population. The choice of stent and antithrombotic treatment was entirely at the treating physician's discretion. In addition to the differences in the perioperative use of OAC, other differences in management strategy and patient selection may have modified the present results, all of which may not be covered by propensity and/or multivariate analyses. Although the study was the largest and the most comprehensive so far, patient heterogeneity was notable and subgroups analyses were limited.

Study II was slightly underpowered to cover small but clinically significant differences in bleeding and thrombotic complications between the two strategies investigated. If the rate of all bleeding events was assumed to be 10% for UAC, enrollment of at least 160 patients per group would have yielded >80% power to detect non-inferiority of a strategy for the outcome of bleeding events (1-sided α significance level = 0.05). Of note, preoperative INR levels were high in the bridging group, because vitamin K was seldom used in acute patients.

The bleeding risk scores in study V were calculated on a post hoc basis, because HAS-BLED, ATRIA, and REACH scores were published after the enrollment of the patients. Comprehensive information on liver function or labile INR was not available, and thus, they were omitted in the calculation of the “modified” HAS-BLED score. This may diminish the value of applying HAS-BLED to this population. However, the lack of knowledge of labile INR levels probably did not have a major impact on the results, because the mean INR was only 1.8 (range 1.0–3.0) at the time of the first bleeding event, and thus the majority of bleeding events was not caused by supratherapeutic INR levels. Moreover, the number of patients with significant liver failure are likely to be very low, because for many of them, the decision to undergo PCI with stenting would be deferred due to presumed high bleeding risk. GFR values were not available in 181 patients due to the lack of information on creatinine level, and therefore, an ATRIA score was unavailable for these patients. Nevertheless, C indexes and Cox proportional hazard ratios for HAS-BLED, mOBRI, or REACH scores were no different when only patients with GFR were included (data not shown). Bleeding outcomes were defined according to the latest BARC definition [248].

In spite of these limitations, the present data is of value in guiding the treatment of patients with AF undergoing PCI, and would be helpful in planning future prospective studies on this topic. The strength of our study is the inclusion of “real-world” patients with PCI. This is the largest dataset so far analyzing patients with AF undergoing PCI and also including a substantial number of patients with ACS. Endpoints were defined according to recommendations and could be determined in several ways, as the registry also included descriptive information. The centers participating in the AFCAS registry mainly enrolled consecutive patients, with the only exclusion criteria being unwillingness/inability to participate in the study. In this sense, the population represents “real-world” PCI patients with AF.

During the recent years, radial approach has become the recommended route for PCI and the use of GPIs has diminished in clinical practice. NOACs were not in clinical use at time of the study and these results cannot be directly applied to patients using these drugs.

6.8 Future

Prospective, randomized studies are needed to compare different periprocedural strategies in patients on long-term warfarin therapy undergoing PCI. NOACs are probably gradually superseding warfarin in patients with AF undergoing PCI and future research is focusing on the use of NOACs with various antiplatelet combinations.

7 CONCLUSION

Glycoprotein inhibitors IIb/IIIa increases the risk of major bleeding events irrespective of periprocedural INR levels and should be used with caution in patients with AF. (I).

PCI during uninterrupted anticoagulation appears not to be associated with an increase in the risk of bleeding or MACCE when compared to heparin bridging (BT). This simple UAC strategy may lead to considerable cost savings compared with conventional BT, owing to the significantly reduced length of hospitalization (II).

Even mild renal impairment was associated with an increase in all-cause mortality and MACCE with a trend towards increased bleeding events. Patients with severe renal dysfunction and AF have a very poor prognosis, with a high MACCE rate and mortality within the first year after PCI (III).

The majority of AF patients undergoing PCI are at high stroke risk, and therefore VKA treatment should not be withdrawn and combined anticoagulant and antiplatelet treatment is warranted. This is in accordance with current recommendations, thus accounting for the limited occurrence of in-hospital adverse ischemic and bleeding events (IV).

In patients with AF undergoing PCI, increasing age, femoral access site, and previous peptic ulcer were significant predictors of BARC bleeding events. The accuracy of HAS-BLED, ATRIA, mOBRI, and REACH scores in predicting bleeding complications was negligible (V).

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