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Bastiaan Zwart

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Stent thrombosis and antithrombotic strategies in percutaneous coronary intervention

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CHAPTER

1

Coronary Stent Thrombosis in the current era:

Challenges and Opportunities for Treatment

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Abstract

The introduction of the drug-eluting stent has raised concerns regarding the occurrence of stent thrombosis (ST), particularly late (and very late) thrombosis. This renewed attention shows that ST remains a major concern after implantation of both bare metal and drug-eluting stents. Cardiologists should be aware of this dreadful complication, because it is associated with substantial morbidity and mortality. Numerous clinical, procedural, and angiographic risk factors have been identified. Moreover, the influence of novel determinants, such as high on-treatment reactivity, genetic predisposition, and the stent's direct effects on the (healing of the) vessel wall, now are recognized. Consequently, the pathophysiology of ST has evolved into a complex multifactorial model. This broader understanding of the pathophysiology of ST enables cardiologists to perform extensive risk stratification to identify patients at higher risk and provides clues to important treatment options. The core of primary prevention after stent implantation, as well as secondary prevention after ST, should consist of a) the prevention of modifiable risk factors and b) optimal individualized treatment for each patient. Future developments, such as genetic bedside testing, point-of-care platelet testing, and sophisticated imaging modalities, might aid in this approach.

1.1 Introduction

The treatment of patients with coronary artery disease has changed dramatically since Andreas Grüntzig [1] introduced percutaneous coronary intervention (PCI) in 1977. By means of a simple expanding balloon at the site of coronary narrowing, it was possible to reduce the narrowing and relieve angina pectoris. However, initial treatment with plain-old balloon angioplasty was limited by early elastic recoil, negative remodeling, and intimal hyperplasia, leading to restenosis (35%–45%). The high percentage of acute closures (5%–8%) was another major limitation, although it was drastically reduced by the introduction of coronary stents.

Coronary stenting

Coronary stenting initially was a bail-out indication for treating acute complications of balloon angioplasty. The most important bail-out indications for coronary stent implantation were to provide a mechanical scaffold for the vessel wall, to seal dissections, and to prevent elastic recoil. Studies in the mid-1990s demonstrated that coronary stenting also reduced angiographic restenosis, from the 30% to 40% rate seen with balloon angioplasty to 10% to 20%. However, the broad use of coronary stents introduced a new complication of coronary stent implantation: coronary stent thrombosis (ST).

Coronary stent thrombosis

PCI with stent implantation induces mechanical laceration and fissuring of the atherosclerotic plaque as well as denudation of the arterial endothelium. Hence, it is not surprising that the studies done in the mid-1990s reported ST rates as high as 20% to 25%, because little concomitant anticoagulation was administered[2]. Acute thrombotic closure of the coronary stent results in a life-endangering condition with catastrophic consequences. It usually presents as an acute myocardial infarction or sudden death. Initially, this problem was tackled with complex anticoagulation regimes such as aspirin, heparin, and warfarin therapy; however, these treatments led to unacceptably high rates of major bleeding, vascular complications, and prolonged hospital stays. The development and introduction of new antiplatelet agents, such as the thienopyridines (eg, ticlopidine and clopidogrel) and the glycoprotein IIb/IIIa inhibitors (abciximab, tirofiban, eptifibatide), as well as advances in techniques (eg, application of high-pressure stent dilatation) led to a breakthrough in the general use of coronary stents.

Stent technologies

Improvements in strut configuration and thickness, as well as new materials, enhanced deliverability and reduced vessel damage. These advancements led to the introduction in 2003 of drug-eluting stents (DES), which release drugs that reduce neointimal formation through the arrest of cell proliferation. DES reduced rates of in-stent restenosis significantly.

By that time, it was generally believed that ST occurring after the first month was rare. Nevertheless, soon after the introduction of DES, the interventional community was alarmed by a suspected high incidence rate of late ST (beyond 1 month). Although late ST was not investigated extensively in bare metal stents (BMS), the introduction of DES brought this subject to the attention of cardiologists[3,4]. Consequently, in recent years, renewed attention has been paid to late ST, with experts concluding that ST continues to occur at a stable rate after the first month [5, 6]. Given the fact that ST often has devastating clinical consequences, there has been considerable interest in identifying patients at high risk for this catastrophic event. Multiple studies and registries have investigated the relationships between patient, lesion, and procedural factors and ST, but all have been hampered by methodologic challenges, primarily the low incidence of ST in contemporary patient series[7-10]. Despite these important limitations, several predictors have been found, providing much insight into this complex pathophysiology. The primary aim of this review is to provide a better understanding of the underlying mechanisms responsible for ST and, ultimately, to establish an optimal strategy to reduce this dreadful complication.

1.2 Definition of stent thrombosis

Despite being a quantitatively minor problem, ST has a major clinical impact because of the high risk of myocardial infarction and death. However, the true impact and incidence of ST have been neglected for more than 10 years, partly because its definition has varied greatly among randomized clinical trials and observational registries. To allow a fair comparison (ie, provide consistency across studies) between the true rates of ST across different trials and registries, a new uniform definition of ST was proposed recently by the Academic Research Consortium (ARC), a collaboration of research organizations from Europe and the United States[11]. & ST is classified according to 1) its timing and 2) the level of evidence for its presence. Timing is defined in four categories, implying different pathophysiologic mechanisms (Table 1). The level of evidence is stratified into three categories, indicating varying degrees of certainty: possible, probable, and definite ST (Table 2).

Table 1. Temporal categories of stent thrombosis.

Timing	Time after stent implantation
Acute*	< 24 hours
Subacute*	> 24 hours but <30 days
Late	> 30 days but < 1 year
Very late	> 1 year

* together referred to as ‘early’

Table 2. Definite, probable and possible stent thrombosis.

Category	Description
Definite	• Angiographic confirmation of stent thrombosis: intracoronary thrombus in or <5 mm proximal/distal to the stent AND clinical or biochemical changes compatible with cardiac ischemia, or angiographic thrombus • Pathological confirmation of thrombus (at autopsy or after thrombectomy)
Probable	• Any unexplained death <30 days after coronary stenting • Any MI in the territory of the implanted stent
Possible	• Any unexplained death > 30 days after coronary stenting

1.3 Epidemiology

BMS versus DES

The pivotal trials investigating the safety of DES initially reported on a follow-up of 1 to 2 years. After their use was embraced by interventional cardiologists because of reductions of in-stent restenosis rates, DES came under fire from the US Food and Drug Administration in 2003 because of a supposed surplus of late, and particularly very late, ST accompanying the use of DES [3,4]. & Recently, several reviews and meta-analyses thoroughly addressed this issue [12,13]. Although several confounding factors (eg, off-label use of DES, indications for index PCI, subtypes of stents, and the complexity of lesions treated) varied broadly across the studies, complicating a head-to-head comparison, the following general conclusions can be drawn: 1) mortality rates with BMS and DES are similar, 2) the incidence of early ST is the same for BMS and DES, and 3) the use of BMS might impose a slight excess risk of ST within the first 6 months, whereas DES are associated with a moderate increase in ST after 1 year. However, the latter does not translate into higher mortality rates, which can be explained by the reduced need for revascularization associated with the use of DES. Some authors report even lower mortality rates with DES compared with BMS [14]. & In an important meta-analysis published in 2009, Brar et al. [15] compared DES with BMS in 33,873 patients with myocardial infarction treated with primary PCI. The authors concluded that the use of DES in myocardial infarction appears safe and efficacious and is not associated with an increase in ST. These data were confirmed by a large study from Shishehbor et al. [16].

Incidence of coronary stent thrombosis

In the BMS era, the incidence of ST declined quickly, from initial rates of approximately 24% to only 1% to 5% in the first month. & The incidence of ST beyond 1 month after implantation was not recognized until the publication of case reports of late ST associated with brachytherapy [17,18]. Since then, late BMS thrombosis received researchers' attention, although relatively few studies on the subject were published. These studies reported a yearly incidence of less than 1% for late ST in BMS [5,19]. The aforementioned meta-analyses

estimated the incidence of late ST in both BMS and DES, despite different definitions of ST among the studies. The overall incidence of late and very late ST from registries and trials was estimated at 0.5% to 1.5% during the first year and 0.5% per year thereafter.

Outcome after stent thrombosis

Although several studies addressed the important question regarding clinical outcome after ST, they provided little consistency regarding mortality rates [20-22]. However, recently published studies assessed the outcome in larger cohorts of patients with ST. De la Torre-Hernandez et al. [23] analyzed 23,500 patients after stent implantation, 301 of whom developed definite ST. Mortality at 1 year follow-up was 16%, and recurrent ST occurred in 4.6% of patients. In addition, several risk factors for mortality were identified, including older age, left ventricular ejection fraction less than 45%, nonrestoration of Thrombolysis in Myocardial Infarction (TIMI) flow grade 3, and additional stenting. Van Werkum et al. [24] performed a long-term follow-up in a consecutive cohort of 431 patients with definite ST. After a median follow-up of 27.1 months, the primary end point (a composite of cardiac death and definitive ST) occurred in 111 patients (25.8%), with a cardiac mortality rate of 12.3%.The cumulative incidence rates of definite recurrent ST, definite or probable recurrent ST, any myocardial infarction, and any target vessel revascularization were 18.8%, 20.1%, 21.3%, and 32.0%, respectively. This unexpectedly high recurrence rate was confirmed by another study by Lemesle et al. [25], who reported a recurrence rate of 36% in patients successfully treated for a first ST during a median follow-up of 40 months.

1.4 Pathophysiology and predictors of stent thrombosis

The pathophysiology of ST has evolved from the identification of single causative factors to a complex multifactorial model (Fig. 1). Numerous risk factors have been identified during the past years Historically, these predictors can be classified as clinical, procedural, or lesion related. More recently, researchers recognized the involvement of novel determinants, including a heightened platelet reactivity status despite antiplatelet therapy, impaired responsiveness to antiplatelet therapy, genetic predisposition, and direct effects of the stent on the vessel wall. The many factors contributing to ST are depicted in Fig. 1. Although early and late ST share several common risk factors, the impact of these factors varies. Early and late ST represent unique pathophysiologic characteristics, which are discussed separately.

Early stent thrombosis

Numerous studies have reported the predominance of mechanical and anatomic etiologies underlying early ST, including bifurcation and restenotic lesions, number of stents implanted, small vessels, lesion diameter and complexity (types B and C), undersizing and/or underexpansion of the coronary stent, (residual) dissections, postprocedural TIMI flow grade less than 3, absence of glycoprotein IIb/IIIa inhibitor treatment, and lack of

intravascular ultrasound (IVUS) guidance [7–10•]. Disturbances in coronary flow (increased shear stress) at bifurcations and restenotic lesions may activate platelets and contribute to delays in arterial healing. Moreover, a large number of stents and long total stent length delay the process of endothelialization, which in turn increases the risk of ST. Another very important nonmechanical cause of early ST is premature cessation of clopidogrel therapy, which is associated with hazard ratios up to 90 [20].

Late and very late stent thrombosis

Late ST seems less strongly linked to mechanical factors related to the index PCI procedure. In addition, the influence of clopidogrel cessation on late and very late ST is less well established, and when an association has been found, the risk has been consistently lower than that for early ST [10,21,26-30]. Nevertheless, several clinical predictors are strongly related to late and very ST, including acute coronary syndrome as the indication for the index PCI, active malignancy, diabetes, low ejection fraction, and renal failure [10•,20]. In addition, the stent itself is involved in the development of ST. Several autopsy studies described the histopathologic changes of the vessel wall following stent implantation, presumably as a result of the direct effects of the coronary artery [31]. Chronic inflammation surrounding the stent is found in a substantial number of patients. This phenomenon has been exclusively related to the use of polymers and other components in DES. Within months, this inflammatory process can induce late malapposition and vascular remodeling. Besides the negative influence of this process, DES induce delayed healing and incomplete endothelialization, resulting in impaired coverage of stent struts, even beyond 1 year after stent implantation [32]. These bare stent struts are thought to induce thrombus formation to the vessel wall. Although (the extent of) these findings might be biased by the fact that they are from autopsy studies representing a small and selected patient population, they were reproduced recently in studies using intravascular imaging technologies (eg, IVUS and optical coherence tomography) and histopathologic findings from thrombi obtained with thrombectomy catheters [31–33]. Cook et al. [33] found both histopathologic (thrombus) signs of inflammation and IVUS evidence of vessel modeling. Importantly, histopathologic analysis of harvested thrombus showed infiltration of eosinophils and macrophages following implantation of sirolimus-eluting and paclitaxeleluting stents, respectively, suggesting a hypersensitivity reaction.

The importance of concomitant antithrombotic therapy

Various antithrombotic regimens have been studied for their ability to minimize the incidence of acute and subacute ST while reducing the risks of hemorrhagic complications. Current guidelines recommend dual-antiplatelet therapy (aspirin and clopidogrel) for all patients undergoing coronary stent implantation. Dual-antiplatelet therapy is absolutely necessary to prevent ST, although the optimal duration of this therapy after coronary stent implantation remains unclear. It is hoped that ongoing trials such as Double Randomization of a Monitoring Adjusted Antiplatelet Treatment Versus a Common Antiplatelet Treatment

for DES Implantation, and Interruption Versus Continuation of Double Antiplatelet Therapy (ARCTIC, NCT00827411) and Safety and Efficacy of Six Months Dual Antiplatelet Therapy After Drug-Eluting Stenting (ISAR-SAFE, NCT00661206) will reveal the optimal duration of dual-antiplatelet therapy after DES implantation.

High on-treatment platelet reactivity

Despite the standard "one-size-fits-all" dual-antiplatelet therapy regimen with aspirin and clopidogrel, it has become clear that many patients still suffer from recurrent atherothrombotic coronary events. As a result, the number of studies and papers focusing on this socalled treatment failure has grown exponentially since 2003. Throughout the past few years, multiple studies have demonstrated that the response to a fixed dose of antiplatelet therapy (clopidogrel and aspirin) is highly variable and the responsiveness to clopidogrel, as measured with adenosine diphosphate (ADP)-induced aggregation, follows a bell-shaped gaussian distribution. Consequently, many patients receiving combination therapy with aspirin and clopidogrel fail to obtain the optimal benefit from it. This phenomenon has been termed resistance to antiplatelet therapy in the medical literature. However, the somewhat confusing term resistance implies that these drugs do not reach their pharmacologic target at all, which is not the case in most instances. Hence, the alternative term high ontreatment platelet reactivity was introduced recently. To date, six studies have demonstrated a clear association between the magnitude of ontreatment platelet reactivity and the occurrence of ST. Thus, high ontreatment platelet reactivity has emerged as another important risk factor for ST. Moreover, consistent findings across multiple studies indicate that high on-treatment platelet reactivity is associated particularly with early ST [34,35]. Whether high on-treatment platelet reactivity also is associated with late ST needs to be explored in sufficiently powered studies.

Pharmacogenetics

The pathophysiology of arterial thrombosis is very complex, and multiple factors have been identified as being involved. Nonetheless, these known factors alone do not fully explain an individual's risk profile, and it is likely that multiple genetic polymorphisms are involved. Likewise, there is much interindividual heterogeneity in the response to antithrombotic therapy [36,37,38], and it has been demonstrated clearly that interindividual variations in metabolism, transporters, and drug targets are important determinants of drug efficacy. Because this straightforward principle of pharmacogenetics can affect any step in modulating the pharmacokinetics and pharmacodynamics, this concept might be more relevant than complex genetics leading to the development of cardiovascular diseases [39]. During the past four years, the impact of a genetic mutation related to clopidogrel metabolism has been elucidated. In 2006, Hulot et al. [40] identified the CYP2C19*2 mutation responsible for the biotransformation of the prodrug into its active metabolite. This cytochrome P-450 enzyme is involved in the biotransformation of clopidogrel into its

active metabolite. Carriers of the *2 alleles exhibit higher platelet reactivity [40,41]. Of equal importance, the CYP2C19*2 mutation is not uncommon, with carrier frequencies varying between 20% and 50%, depending on the population and ethnicity. In addition, a dose response is evident: homozygotes for CYP2C19*2/*2 respond even less well to clopidogrel therapy than heterozygotes for CYP2C19*2,who in turn respond less well than wildtype homozygotes. Importantly, several large trials published in 2009 demonstrated that genetic variation has an effect on the pharmacologic and clinical response to clopidogrel. Several studies correlated these genetic variations to clinical outcomes, including cardiovascular death, myocardial infarction, and ST. In their subanalysis of the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel (TRITON)-TIMI 38, Mega et al. [41] found that CYP2C19*2 carriers had a threefold risk of ST. Sibbing et al. [42] found CYP2C19*2 carriers to have a fourfold risk of ST. Other CYP mutations have been associated with high on-treatment platelet reactivity. Harmsze et al. [43] investigated a large cohort of clopidogrel-treated patients undergoing elective PCI and discovered that CYP2C9*3 carriers exhibited higher platelet reactivity and more often were poor responders. These findings represent a major step forward in this field of research and might have important treatment implications. Future trials will have to prove the clinical relevance of genetic testing.

Triggering mechanisms of stent thrombosis

Several superimposing factors have been investigated in myocardial infarction, including time of day, physical exercise, infection, and emotional stress. However, only case reports have been published so far on a possible relationship between triggering mechanisms and ST [44,45]. In our own institutional experience, however, triggering mechanisms seem to play an important role (unpublished data). All consecutive patients with definite ST in our large cohort were interviewed about the possible performance of vigorous physical exercise, the presence of an infection, or the presence of acute emotional stress preceding the onset of symptoms accompanying the ST. In 23% of these patients, a trigger was identified. Importantly, a clear circadian variation with a steep morning peak also was identified [46].

1.5 Treatment

Curative treatment

It should be kept in mind that curative management strategies for patients presenting with ST are mainly empirically based, as only a few studies have evaluated (observationally) the available treatment modalities [5]. Nonetheless, data from numerous registries and casecontrol studies do offer certain guidance for managing patients with ST. For instance, evidence from histopathologic studies indicates that patients in whom ST is highly suspected should be treated with emergent PCI, not thrombolytic therapy [47–49].

Emergent PCI

Because in most cases ST presents as myocardial infarction, or even cardiogenic shock, the credo “time is muscle” is of utmost importance, and patients should be transported immediately to an interventional center upon diagnosis. The diagnosis of ST is confirmed by coronary angiography, although it must be noted that, in general, the identification of a thrombus on a conventional angiogram may be a difficult challenge.

Given the relatively large thrombus load associated with ST, thrombus aspiration might be beneficial in obtaining effective reperfusion [50], although more clinical data are urgently needed. Subsequent balloon dilatation should be performed; if stent malapposition (eg, due to undersizing or late malapposition) is identified, additional balloon dilatation with well-sized balloons and higher balloon pressure is advisable. However, if the stent appears well expanded and no residual dissection is present, another stent should not be implanted, as several studies have demonstrated that implanting an additional coronary stent at the time of the first ST is associated with an increased risk of recurrent ST and even death [23,24]. & The use of glycoprotein IIb/IIIa therapy during emergent PCI for ST is strongly recommended, as two large observational studies indicated protective effects against ST recurrence [5,24].

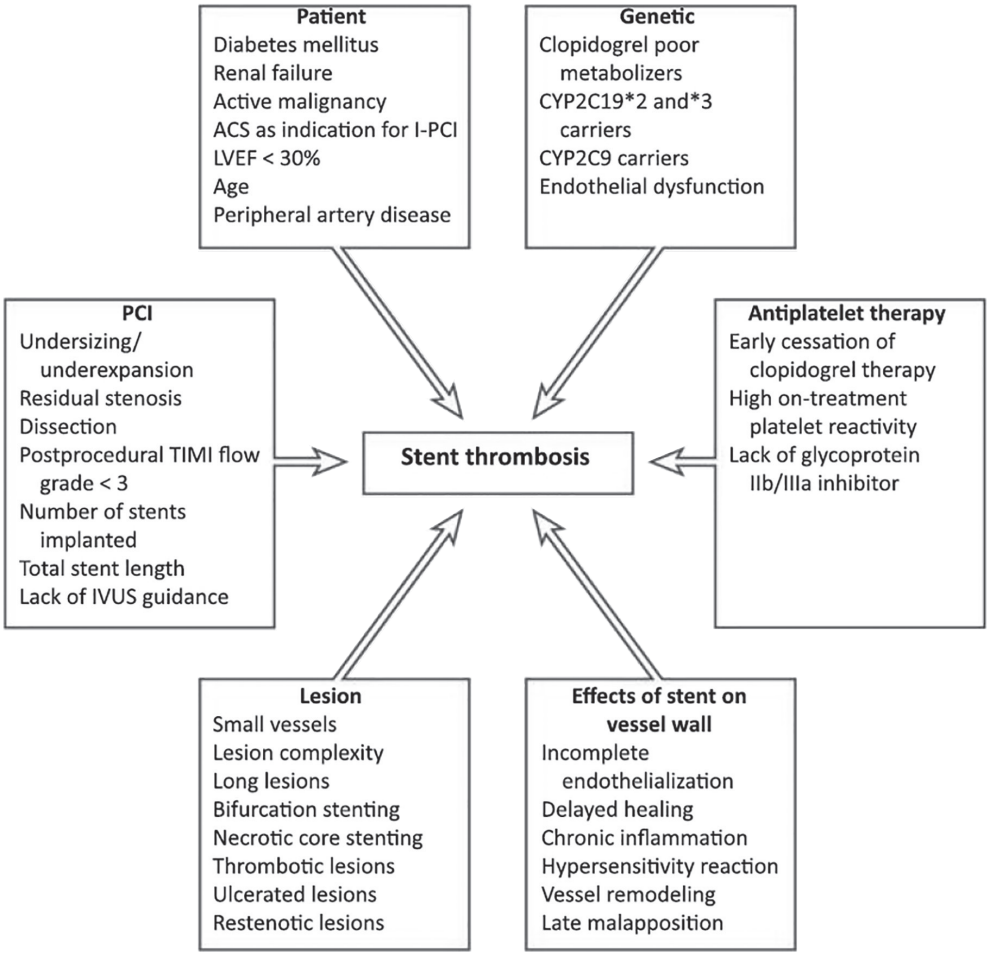

Figure 1. Predictors of stent thrombosis. ACS – acute coronary syndrome; I-PCI – index percutaneous coronary intervention; IVUS – intravascular ultrasound; LVEF – left ventricular ejection fraction; PCI percutaneous coronary intervention; TIMI – Trombolysis in Myocardial Infarction.

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CHAPTER

2

A paradigm shift: from reducing stent thrombosis towards balancing ischaemic versus bleeding risk

Based on:

Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention or after acute coronary syndrome.

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Abstract

The introduction of the drug-eluting stent has raised concerns regarding the occurrence of stent thrombosis (ST), particularly late (and very late) thrombosis. This renewed attention shows that ST remains a major concern after implantation of both bare metal and drug-eluting stents. Cardiologists should be aware of this dreadful complication, because it is associated with substantial morbidity and mortality. Numerous clinical, procedural, and angiographic risk factors have been identified. Moreover, the influence of novel determinants, such as high on-treatment reactivity, genetic predisposition, and the stent's direct effects on the (healing of the) vessel wall, now are recognized. Consequently, the pathophysiology of ST has evolved into a complex multifactorial model. This broader understanding of the pathophysiology of ST enables cardiologists to perform extensive risk stratification to identify patients at higher risk and provides clues to important treatment options. The core of primary prevention after stent implantation, as well as secondary prevention after ST, should consist of a) the prevention of modifiable risk factors and b) optimal individualized treatment for each patient. Future developments, such as genetic bedside testing, point-of-care platelet testing, and sophisticated imaging modalities, might aid in this approach.

2.1 Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention or after acute coronary syndrome.

2.1.1 Introduction

Dual antiplatelet therapy (DAPT) with acetylsalicylic acid in combination with a $P2Y_{12}$-inhibitor is now the standard of care after an acute coronary syndrome (ACS) and after percutaneous coronary intervention (PCI). DAPT is recommended with a class I level of evidence in the current European and American guidelines [1-3].

Since the introduction of second-generation DES, rates of stent thrombosis have decreased by approximately 50% [4]. Current rates of ST are estimated to be approximately 0,5 – 0.8% in the first year [5,6]. Very late ST beyond one year has become a rarity with incidence rates of ST in newer generation DES be estimated at 0.1-0.2 per 100 persons-years [7]. The total ST risk amounts to <1%, even at a follow-up duration of more than five years [5,8].

With the fall in the incidence of stent thrombosis associated with newer generation DES together with the use of stronger $P2Y_{12}$ inhibitors, attention has shifted to the downsides of DAPT. Due to the very action of platelet inhibitors, patients are at increased risk of bleeding. Although premature discontinuation of $P2Y_{12}$-inhihitors has been shown to be the most important risk factor for ST [9-12], the lower complication rates of coronary stents together with an increased awareness of bleeding on DAPT, has led cardiologists to question the optimal duration of DAPT after coronary stenting.

From a mechanical point of view, DAPT is mandatory in the first months after stent implantation until endothelialisation has been completed. Interestingly, two recent studies using a new-generation DES demonstrated that an ultra-short course (1 month) of DAPT was DES was superior to BMS [13,14].

As the risk of (very) late ST is less of a concern with the development of 2nd generation DES, prolonged DAPT is now more aimed at preventing (recurrent) myocardial infarction and other ischemic events not related to the implanted stent. The PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study demonstrated that approximately one-half of events during follow-up after ACS were attributable to nonculprit lesions [15]. Similarly, in the Dual Antiplatelet Study (DAPT Study) 55% of myocardial infarctions beyond one year of stenting were not related to stent thrombosis thus occurred spontaneously [16]. Nevertheless, it is important to realise that ST is associated with very high mortality rates [17] and therefore it is crucial to identify those at increased risk for ST.

Rather than focussing on the stent or the angiogram only, the key to success is to treat the patient's overall thrombotic risk. An example of such an approach is the PEGASUS-TIMI 54 trial [18], which investigated whether patients who had a previous myocardial infarction with additional risk factors could benefit from prolonged DAPT.

In the last five years, multiple studies have been published comparing duration of DAPT after PCI and in ACS patients. While some of these studies investigated whether a shorter DAPT duration might be as safe as the standard regimen, the other studies tried to establish a benefit from prolonged dual antiplatelet therapy.

Although these studies have focused attention on individualised treatment and current ESC guidelines provide backup to individualize treatment, few patients in daily practice are currently being treated with a shorter or prolonged DAPT duration in our experience. This article summarizes the results of relevant studies and meta-analysis and interprets the main findings and differences. Furthermore, we propose a practical approach for the clinician to identify patients who are likely to benefit from an alternative DAPT duration.

2.1.2 Studies on optimal duration of DAPT

At least 18 randomized controlled trials (RCTs) of optimal DAPT duration after PCI have been performed. However, results are not easy to interpret, as length of treatment varied (short course of DAPT varied from 3 to 6 months, standard duration from 6 to 12 months and prolonged from >12 to 48 months). Furthermore, comparison strategies varied (short versus standard DAPT, prolonged vs. standard DAPT and short vs. prolonged) and different definitions were used, as reflected for example by the use of multiple bleeding definitions (TIMI, BARC, STEEPLE, GUSTO). Subsequently, an almost equal number of high quality meta-analyses have been published, often using trial-level data.

Shorter duration

In summary, the results of the RCTs and several meta-analyses after shorter DAPT duration indicate that a shorter DAPT regimen is non-inferior (and thus equally effective) as standard DAPT duration and might even provide a benefit in terms of bleeding. Importantly from a mechanical view point, the OPTIMA-C trial demonstrated favourable stent strut coverage at six months follow-up. [19] However, it must be noted that most studies included low-risk patients and only patients with stable and unstable angina, or a very low proportion of ACS patients (<15%) [20-24].

Details regarding ACS patients must be derived from a few randomised trials and from subanalyses and meta-analyses. The REDUCE trial, a physician-initiated multicentre randomised trial which included 1,500 ACS patients treated with the COMBO-stent, showed

that three months was non-inferior to twelve months of DAPT [25]. However, numerically higher rates of mortality and ST were observed in the three-month DAPT group. The SMART-DATE, a large randomised non-inferiority trial randomised a total of 2712 ACS patients to either 6 or 12 months of DAPT [26]. The authors failed to demonstrate non-inferiority: myocardial infarction occurred more frequently in the 6-month DAPT group than in the 12-month or longer DAPT group (1.8% vs. 0.8%, p=0.02). On the other hand, a pooled analysis of three randomised controlled trials demonstrate that short-duration DAPT (6 months or less) showed a similar incidence of net adverse cardiovascular and clinical events as compared to ³12 months DAPT. Moreover, a 2017 review used individual patient data and compared efficacy of reduced DAPT duration in patients with and without ACS [27] concluded that in ACS patients, 6 month DAPT or less was associated with numerically higher rates of MI and ST as compared to 12 month DAPT. By network meta-analysis, 3 month DAPT, but not 6 month DAPT was associated with higher rates of MI and ST. Three month DAPT was safe in patients with stable CAD undergoing PCI. Short DAPT was associated with lower rates of major bleeding irrespective of clinical presentation. No differences in all-cause mortality were observed.

Another network meta-analysis suggested no increase in ischaemic events with short term DAPT in ACS patients [28].

Two other studies deserve special notion. The LEADERS FREE trial compared a regimen of one month of DAPT in BMS treated patients vs. patients treated with a polymer-free drug-coated umirolimus (a sirolimus analogue) stent among patients with high bleeding risk (defined by meeting at least one out of 13 criteria such as high age, long term oral anticoagulation or hospital admission for bleeding) [13]. The study found that this DES was superior to BMS. The ZEUS trial randomized patients either at high bleeding risk or high ischemic risk to either a second-generation zotarolimus-eluting stent (ZES) or bare-metal stents (BMS). DAPT duration was based on patient based characterics and was similar between the two groups. Two-thirds of patients qualified for a very short (30 day) course of DAPT. Overall, Major Adverse Cardiac event rate was lower in the DES treated group (17.5 vs. 22.1 p=0.011) and definite or probable ST rate was lower as well 2.0% vs. 4.1%; p = 0.019) [14].

Prolonged dual antiplatelet therapy

The majority of RCTs after prolonged DAPT failed to demonstrate a benefit of prolonged treatment or met the non-inferiority hypothesis. Two studies (comparing 6 vs 24 months of DAPT and 12 vs. 18-30 months of DAPT, respectively) even suggested potential harm from prolonged DAPT in terms of increased rates of major bleeding [29,30]. Of note, none of the RCTs has demonstrated an increase in fatal bleeding rates with prolonged DAPT, although interpretability again is hampered by low event rates.

Although no consistent benefit of prolonged DAPT was observed in the individual RCTs for the ischemic end points, most subsequent meta-analyses using pooled data did find a significant benefit of prolonged DAPT, but also more bleeding complications.

Consequently, it is now believed that DAPT after 12 months reduces ischemic events but at the cost of increased bleeding rates. In the American College of Cardiology and American Heart (ACC/AHA) focused update on DAPT it was estimated that prolonged DAPT leads to an absolute decrease in ST and ischemic complications of ≈1% to 2% at the cost of an absolute increase in bleeding complications of ≈1% [2].

Mortality in prolonged DAPT

Several previous studies have raised concerns that serious bleeding events resulting from prolonged DAPT might lead to increased rates of all-cause death, thereby offsetting the reduction in cardiac death and nonfatal ischemic events with prolonged antithrombotic therapy. This suspicion arose in the DAPT study and in some [31-34] but not all meta-analyses[35,36] One meta-analysis suggested higher all-cause mortality in prolonged DAPT as compared to short DAPT in patients treated with 2nd generation DES. [28]

The DAPT study [16] was by far the largest trial demonstrated a benefit of prolonged DAPT (30 vs. 12 months) in reducing ST (0.4 vs 1.4%, p=0.001) and major adverse cardiac and cerebrovascular events (4.3 vs. 5.9%, p=<0.001), but at the cost of significantly more GUSTO moderate or severe bleeding (2.6 vs. 1.6%, p=0.001). An unexpected but important finding was a borderline significant (p=0.05) excess mortality (all-cause death 2.0% in prolonged DAPT vs. 1.5% in placebo treated patients) due to more non-cardiovascular deaths [16,37].

The meta-analysis in the ACC/AHA focused update addressed this topic as well and found "weak evidence" of increased mortality with prolonged thienopyridine-based DAPT in RCTs that successfully achieved their predefined enrolment target [4] Another analysis in this review suggested increased mortality with prolonged DAPT in patients without a prior history of ACS but not in patients with a history of prior ACS.

The mechanisms of this possible association are to date not clear, neither did the studies suggesting increased mortality rates investigate whether this is related to prolonged DAPT in general or specifically with the thienopyridine-based $P2Y_{12}$-receptor antagonists (i.e. clopidogrel, prasugrel) as opposed to ticagrelor which is not a thienopyridine.

Prolonged DAPT after MI

The subgroup of patients who have had an MI are particularly at risk for recurrent ischemic events. Unfortunately, only few studies focused on this specific patient group.

The PEGASUS is a double-blind RCT including 21,162 patients with a previous myocardial infarction and at least one of the following additional -risk factors: age of 65 years or older, diabetes mellitus requiring medication, a second prior spontaneous myocardial infarction, multivessel coronary artery disease, or chronic renal dysfunction, Patients were randomized to prolonged DAPT with ticagrelor at one of two maintenance doses (90 mg or 60 mg twice daily for a minimum of 12 months) or placebo [18]. This study demonstrated an absolute risk reduction of cardiovascular death, myocardial infarction and stroke of 1.3 % at the cost of an equally increased risk of major bleeding. All-cause death did not differ significantly between the groups. Again, the effect of prolonged DAPT in this trial seems to be attributable to the progressive natural course of coronary artery disease rather than to the stent implantation.

Udell et al. analysed in a recent meta-analysis in patients with previous MI either treated medically or managed with PCI whether prolonged DAPT after one year (mean difference in achieved duration of DAPT 30 months) is beneficial and found a reduction in major adverse cardiovascular events including stent thrombosis (6.4 vs. 7.5%; risk ratio, RR 0.78, p = 0.001) and cardiovascular death (2.3 vs. 2.6%; RR 0.85, p = 0.03), but no significant effect on overall mortality (RR of 0.92 (95% CI 0.83-1.03; p = 0.13)(35). An increased rate of major bleeding was observed (1.85 vs. 1.09%; RR 1.73, p = 0.004), but not fatal bleeding. Overall, it is seems that the benefit of prolonged DAPT in reducing future ischemic events is much stronger after MI as compared to stable CAD patients [38].

2.1.3 Interpretation

Conceptually, some of the foregoing conclusions are difficult to interpret. How can shorter-duration DAPT be as effective as the “standard regimen” while on the other hand extended duration DAPT does reduce recurrent ischemic events including stent thrombosis?

Moreover, the paradigm that platelet inhibitors reduce thrombotic risk but increase bleeding still holds true for the various strategies. As this principle was observed in studies after prolonged DAPT duration but not in studies after shorter duration, this observed asymmetrical treatment effect might thus be due to the low number of events, selection of patients or chance.

Indeed, it proves useful to look in detail at these studies. With regard to stent thrombosis, which is an important end point, studies investigating a shorter DAPT duration are hampered by very low event rates. In ISAR-SAFE (6 vs. 12 months), at 9 months only 5 vs. 3 patients with ST were observed; in EXCELLENT (6 vs. 12 months): 6 vs. 1 ST at 12 months; in SECURITY (6 vs. 12 months): 2 vs 3 ST at 12 months, OPTIMIZE (3 vs. 12 months): 4 vs 1 ST at 12 months, in RESET (3 vs. 12 months): 2 vs. 3 ST at 12 months, in REDUCE 6 vs 12 ST [20-25].

Thus none of these studies were powered to detect differences in stent thrombosis rates and in addition, some of these studies enrolled less patients than expected. Therefore, the clinical outcomes of these RCT's investigating shorter DAPT duration should be interpreted with caution with regard to the end point stent thrombosis and for the group of patients with ACS.

With regard to prolonged DAPT, another consideration should be borne in mind. In most RCTs, patients were randomized after the first year and only if they did not have any major bleeding or in some studies did not have any (bleeding neither ischemic) events at all. In these patients, a reduction of ischemic events was observed although at the cost of increased bleeding rates, but it should be noted that this is a highly selected patient group. On the other hand, one can argue that this is a reflection of clinical practice, in which the decision to extend DAPT after a year can be revised at any stage should haemorrhagic or ischemic events occur.

Although in most studies ischemic outcomes are reported next to bleedings or even as a combined end point, it is hard to appreciate how bleeding risks should be weighed against ischemic risks. Clearly, cardiovascular death is more relevant than a non-fatal extracranial bleeding whereas a disabling intracranial haemorrhage is more devastating than an uncomplicated myocardial infarction. The impact of bleeding should however not be underestimated, as it is a strong predictor of mortality – in some studies even greater than mortality associated with myocardial infarction. [36,39]

The ADAPT-DES study [17] has provided important detailed information on this subject. The authors demonstrated that ST (especially early ST) is associated with the highest mortality rates. Although ST was infrequent (incidence of 0.9%), it was associated with very high mortality rates ranging from 15 to 38% (the latter for early ST). Spontaneous (non ST-related) MI was less frequently fatal, although late MI (after 1 year) was more dangerous than early MI (7.5 vs. 5.1 and 0.8% for >365 days, 30-365 and <30 days, respectively). Mortality rates after clinically relevant bleeding were comparable with spontaneous MI with again higher mortality rates when the events occurred later after PCI. An interesting finding of this study was that DAPT discontinuation within 12 months was only slightly more frequent after clinically relevant bleeding. No excess ST or MI was observed in patients with clinically relevant bleeding.

In conclusion, as there is evidence of potential harm associated with prolonged DAPT, it should only be considered in carefully selected patients at substantially high ischaemic risk and low haemorrhagic risk.

Current guidelines

The 2018 European Society of Cardiology (ESC) guidelines on myocardial revascularisation advise to treat patients with stable coronary artery disease undergoing PCI with DAPT for six months, irrespective of stent type (class I level A) [1]. Shorter DAPT duration may be considered after DES implantation in patients with high bleeding risk (IIa, A), whereas the guideline advises that DAPT may be used for more than 6 months in patients at high ischemic risk and low bleeding risk who have tolerated the first course of DAPT without bleeding complications (IIb, A). The latter is remarkable, because the benefit of prolonged DAPT in reducing future ischemic events is much stronger after MI as compared to stable CAD - and might even cause harm in some patients.

The STEMI guidelines, which stem from 2017, advise 12 months of DAPT as default therapy [40]. In patients who are at high risk of severe bleeding complications (not defined), discontinuation of $P2Y_{12}$-inhibitor after 6 months should be considered (IIa, B). The guidelines advise that in high ischaemic-risk patients (criteria according to PEGASUS trial) who have tolerated DAPT without a bleeding complication, extended treatment beyond 12 months may be considered (Class IIB, B)

In patients with NSTE-ACS treated with PCI, standard DAPT duration is recommended for 12 months according to recently updated guidelines [3]. In patients with an excessive bleeding risk, discontinuation after 3 months should be considered (IIa, B) – even though evidence stems predominantly from studies including mostly low-risk patients with stable CAD. The use of bleeding scores (e.g. PRECISE-DAPT score) is encouraged when deciding to reduce DAPT duration. On the other hand, in patients with ACS and high risk for recurrent ischaemic events (defined as complex CAD and at least 1 high risk criterion) and without increased risk of major bleeding (for extensive list of definitions refer to ESC guidelines), continuation of DAPT for more than 12 months may be considered (class IIa).

2.2. The right strategy for the right patient: use of risk scores

2.2.1 Introduction

In conclusion, the aforementioned studies and reviews suggest that a minimum duration of three to six months is effective in low-risk patients with stable coronary artery disease after 2nd generation DES implantation, whereas in ACS patients DAPT duration <12 months should only be considered in patients with excessive bleeding risk. Extension of DAPT beyond 12 months appears to be only beneficial in selected subgroups, most notably patients with prior myocardial infarction who are at higher risk of ST and other recurrent spontaneous atherothrombotic events as well as cardiovascular death.

The large RCTs and high quality meta-analyses do however not support one new standard DAPT duration in all patients. They rather support a personalised treatment in which the duration of DAPT is determined on an individual patient basis, reflecting an accurate trade-off between the individual ischemic and haemorrhagic risks.

2.2.2 Available risk scores

Risk scores may aid in this decision making. Previously, several clinical patient characteristics (e.g. ACS, diabetes, impaired left ventricular function) as well as procedural (e.g. dissection, bifurcation stenting) and angiographic factors (e.g. undersizing of the stent, small stent diameter) have been identified as risk factors for stent thrombosis. [9,41,42]. As was demonstrated in previous studies, however, approximately 50% of recurrent atherothrombotic evens are not related to stent thrombosis [15,16]. Therefore, the patients overall ischemic risk should be considered when it comes to longer duration of DAPT.
Traditionally used scores to assess ischemic risk include the TIMI and GRACE risk score [43,44]. Whereas these risk scores are very useful in the initial assessment of ischemic risk and hence in guiding treatment and timing of coronary angiography, the clinical applicability in the out-patient setting is limited, as the variables focus mainly on patient characteristics at presentation (STT-deviation, cardiac biomarkers). Several other ischemic risk scores have been developed to assess the risk of recurrent atherothrombotic events including stent thrombosis. [45-47]

The DAPT risk score [41] is currently the only risk score which can be used to identify patients benefitting from prolonged DAPT. In the DAPT study, patients free from major bleeding or ischaemic events during the initial course of DAPT, were randomised at 12 months after PCI to receive either prolonged DAPT or placebo. A net clinical model was developed, considering both ischaemic and bleeding risk. The risk score consists of nine variables, including age, smoking, diabetes, MI at presentation, prior PCI or MI, paclitaxel-eluting stent, stent diameter <3 mm, congestive heart failure or left ventricular ejection fraction below 30% and vein graft stenting. A simplified model was constructed. Point were adjudicated to each variable, with the total score ranging from -2 to 10. Patients with a score of ³2 are considered to have a high thrombotic risk and were found to benefit from prolonged DAPT, whereas patients with a DAPT risk score <2 did not derive any benefit or even harm with prolonged DAPT. In conclusion, the DAPT score was able to discriminate patients who were likely to benefit vs. those who were likely to be harmed by prolonged DAPT. Although no prospective validation has to date been performed, several studies have retrospectively evaluated the use of the DAPT score in different external cohorts, which showed fair discriminatory properties. [48,49-51]
The DAPT risk score is believed to a useful tool to guide DAPT duration in event free patients one year after PCI.

Bleeding risk in hospitalised patients is typically assessed by the CRUSADE risk score [52]. However, this risk score is not applicable to ambulant patients undergoing elective PCI for stable angina. In the PRECISE-DAPT trial [53], Costa and co-workers developed a prediction tool for out-of-hospital bleeding in a mixed cohort of 15,000 patients with both stable coronary artery disease and ACS who underwent PCI (and were predominantly treated with clopidogrel). Their model used five items (age, creatinine clearance, haemoglobin, white-blood-cell count, and previous spontaneous bleeding) to predict Thrombosis in Myocardial Infarction (TIMI) major or minor bleeding with fair discrimination (C-index 0.71–0.73)
The performance of the model was subsequently verified in two validation cohorts (including the BernPCI registry, which is representative of the population seen in daily clinical practice) that demonstrated only moderate predictability (C-index 0.65–0.70). The researchers observed significantly more bleeding events in patients with the highest bleeding risk (highest quartile, score >25) who were treated with prolonged DAPT (12–24 months) compared with those treated with a short (3–6 month) duration (absolute risk difference 2.59%, 95% CI 0.82–4.34), but not in patients with very low to moderate bleeding score (0.14%, 95% CI −0.22 to 0.49). Interestingly, the researchers found that prolonged DAPT in patients at high bleeding risk did not reduce the rate of ischaemic events, although no competing-risk analyses had been performed. Similar results were observed in the subset of patients with ACS at the time of PCI. Prospective validation of the risk score is currently being investigated. [54]

Finally, the PARIS [46] score is another risk score, which was developed to predict both bleeding and ischaemic risk. The separate risk scores for bleeding and ischaemic events both contain 6 items. The score have a similar discrimination properties as compared to the PRECISE-DAPT and DAPT risk score, but was not tested in an alternative DAPT regimen and therefore it cannot be used as a clinical decision instrument to guide DAPT duration.

2.2.3. Using risk scores in clinical practice

The 2018 and 2020 ESC guidelines on myocardial revascularization and NSTE-ACS state that the PRECISE-DAPT risk score can be used to select patients eligible for reduced DAPT duration. The DAPT score is not specifically mentioned. The 2017 ESC focused update on DAPT does mention the DAPT score as a risk stratification tool for clinical practice [7].

A difficulty in clinical daily practice is that several risk factors for bleeding and ischemic risk overlap (e.g. renal function, age, malignancies), which complicates the use of a score for one or other risk alone. Interestingly, the DAPT study found that higher age increased bleeding risk more than ischemic risk. [41] On the other hand, the PEGASUS trial, which considered older age and chronic renal dysfunction among others a risk factor for ischemic risk did

convincingly demonstrate a benefit from prolonged DAPT with ticagrelor although at the cost of major but not fatal or intracranial bleeding.

Our own study group recently proposed [55] an algorithm implementing both risk scores. We proposed the consecutive use of PRECISE-DAPT for the in-hospital phase, thereby selecting high bleeding-risk patients (i.e. PRECISE-DAPT score ≥25) in whom a short course of DAPT should be considered. Subsequently, in patients who are treated with standard DAPT duration (i.e. PRECISE-DAPT score <25) and who do not encounter haemorrhagic complications during the first months of DAPT, the DAPT score is calculated. In patients with DAPT score >2, DAPT can be prolonged after the first year (Figure 1).

Implementation in clinical practice

Algorithms like the PRECISE-DAPT and DAPT-scores and, ideally, a consecutive approach using both risk scores, should be tested either in existing patient cohorts and in future prospective studies to prove their validity and applicability. In testing such strategies, it is important to acknowledge a distinction according to clinical presentation: stable coronary artery disease and ACS patients.

We believe in an important advisory role for the interventional cardiologist. As angiographic complexity (including multivessel disease) and procedural results are best known by the doctor who performed the PCI, the interventional cardiologist should be in the lead to determine the *minimum* DAPT duration which has to be incorporated in the PCI report. For patients who are conservatively managed, the treating physician is in the lead.

In all scenario's, it is essential to include the recommended DAPT duration (and preferred $P2Y_{12}$ inhibitor) in the discharge letter. This advice should be communicated to the referring district hospitals if applicable, and to his or her general practitioner. Secondly, patient awareness and patient empowerment is very important. Therefore, we advise to discuss the length of the DAPT duration and considerations with the patient whilst he is in hospital. Finally, DAPT duration is not a static advise and can be revised at any time in the course of the patient's follow-up (e.g. recurrent myocardial infarct, stroke or bleeding complications). This implies an important role for the cardiologist who follows his patient in clinic. At least, the DAPT duration should be rediscussed at the time of the first follow-up visit after discharge and at every yearly follow-up.

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CHAPTER

3

Antithrombotic therapy in patients with atrial fibrillation undergoing percutaneous coronary intervention

3.1 Introduction

Whereas duration of dual antiplatelet therapy (DAPT) has become more complex than before, antithrombotic regimens in patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI) could arguably be even more complex. Illustrating the relevant overlap in clinical practice, approximately 1 in 5 patients with AF undergo PCI at some point in life. From the PCI perspective, 1 in 12 patients undergoing coronary stenting has concomitant AF and an indication for OAC [1,2].

In AF patients with a CHADSVASC score ³1 in males and ≥2 in females, oral anticoagulation (OAC) is warranted to reduce the risk of systemic thromboembolic events including stroke, whereas patients undergoing PCI have an indication for dual antiplatelet therapy consisting of aspirin and a $P2Y_{12}$ inhibitor in order reduce the risk of stent thrombosis or other recurrent atherothrombotic events [2-4]. The combination of dual antiplatelet therapy and OAC is referred to as 'triple therapy' (TAT) and is recommended by current international guidelines and consensus documents for one week and up to one month in patients at high thrombotic risk [4,6,7].

Triple antithrombotic therapy (TAT) confers at least a two times higher risk of bleeding as compared to 'double therapy' (DAT, a combination of OAC and a $P2Y_{12}$ inhibitor, i.e. with the omittance of aspirin) [8,9]. Therefore, it is advised to keep the duration of TAT as short as possible or to consider an alternative regimen of double therapy [3,4].

3.2 Trials investigating triple therapy versus double therapy

Five large randomised controlled trials compared TAT with the combination of (N)OAC and an antiplatelet agent. The WOEST study was the first to investigate a regime of omitting aspirin from the TAT regime in patients treated with vitamin K antagonists (VKA) undergoing PCI [10]. All patients were treated with clopidogrel. The WOEST study showed that DAT was associated with a reduction of bleeding without an increase in thrombotic events, as compared to patients treated with TAT.

Meanwhile, the world of antiplatelet and antithrombotic agents changed with the introduction of more potent $P2Y_{12}$-inhibitors including prasugrel and ticagrelor and with the introduction of the of nonvitamin K oral anticoagulant therapy (NOAC). The use of NOACs (rivaroxaban and dabigatran, respectively) plus a $P2Y_{12}$-inhibitor were compared with a triple therapy strategy including VKA in the PIONEER AF-PCI and RE-DUAL PCI trials [11,12]. Both studies demonstrated a lower risk of bleeding associated with the former regimen, but due to the design of these studies, it was not clear whether this was an effect of omitting aspirin, a benefit of NOAC over VKA or an effect of the lower NOAC dose used in the studies. Surprisingly, the ENTRUST-AF PCI study, which was the most recent trial comparing a DAT

regimen with edoxaban versus VKA-based TAT, failed to show a reduction in bleeding rates and no differences in ischemic outcomes either [13]. Finally, the in 2019 published AUGUSTUS study assessed the efficacy and safety of TAT in a 2 × 2 design, which allowed the independent comparisons of VKA versus NOAC and aspirin versus placebo. [14] This largest study thus far included 4614 patients with ACS or who underwent PCI. The study demonstrated that a combination of full dose apixaban with a $P2Y_{12}$-inhibitor but without aspirin resulted in less bleeding as compared with regimens that included a vitamin K antagonist and/or aspirin. In patients treated with DAT, no significant differences in ischaemic events was observed. First, this study established the benefits of NOAC over VKA which now also holds true in patients with concomitant (dual) antiplatelet therapy. Based on their superior safety profile, NOAC should be preferred over VKA, also in combination with antiplatelet agents. Second, the evidence was strongly in favour of double therapy. However, it must be noted that this study again was not powered for ischemic events and a numerical higher incidence of stent thrombosis was observed in patients not receiving aspirin. Furthermore, it is important to acknowledge that the AUGUSTUS patients were low-risk patients, as the majority of patients (>60% in all treatment arms) underwent either elective PCI or had medically managed ACS.

Several meta-analyses have been published using pooled data from the randomised trials. These meta-analyses demonstrated a relative reduction in bleeding with approximately 40-50% and did not find a significant difference in ischemic outcomes [8,15-19]. Only two meta-analysis of randomised controlled trials signalled a small increase in terms of stent thrombosis (but not spontaneous myocardial infarction) associated with DAT [20,21]. In these two studies, stent thrombosis was significantly reduced with TAT, although incidence rates were low (0.6% vs. 1.0%, p=0.04 and 0.7% vs. 1.1%, p=0.041). Importantly, this effect was counterbalanced by a significantly higher bleeding rate (International Society on Thrombosis and Haemostasis major or clinically relevant nonmajor bleeding 13.5-14.6% vs. 20.3-22.6%,). No significant differences in all-cause death or cardiovascular death were observed.

In conclusion, several trials showed that DAT is associated with a lower rate of bleeding complications (safety) with no increase in thrombotic complications (efficacy) as compared to TAT in AF patients undergoing PCI. However, all trials were underpowered for ischaemic endpoints and, a numerical increase in ischemic events (small absolute numbers) was observed in some trials [11,14,22]. With regard to stent thrombosis, a small was observed in some meta-analyses. It should be kept in mind that in some trials, aspirin was used for several days up to one week during and after PCI [12,14].

3.3 Bleeding and association with adverse outcomes

It was already known that risk of major bleeding is about 1.8-fold higher with DAPT than with aspirin alone and at least 2.5-fold higher when aspirin is combined with VKA [23]. In the aforementioned trials, bleeding risk was associated with a ~1.5 to 2-fold increase in major of clinically relevant bleeding.

So why does bleeding matter? Bleeding is one of the most dreaded iatrogenic complications of antithrombotic treatment, as it is strongly associated with adverse outcomes including a strong link with mortality. When major bleeding occurs, it is associated with an ≤4 fold increase in ischaemic events and up to a 5-fold increase in death [23,24] or even up to a 10-fold mortality risk with GUSTO severe bleeding [25]. In-hospital major bleeding confers a ~5-fold risk of mortality [26]. Spontaneous bleeds might confer a higher risk of mortality as compared to access-site related bleeds. [27,28]

Besides the direct link between bleeding events and increased morbidity and mortality and reflecting in part the effect of interrupting antithrombotic therapy, there appears to be an indirect link between haemorrhagic complications are adverse outcomes. [29]

Other trials showed that bleeding complications confer a similar or even higher risk of mortality as compared to recurrent ischaemic events [30,31].

3.4 Optimal treatment of AF patients undergoing PCI

To summarise, bleeding is very prevalent among patients treated with a combination of anticoagulation and antiplatelet drugs. In AF patients undergoing PCI, TAT is associated with a ~1.5 – 2 fold increase in bleeding rates, which are already very high in these patient group. Bleeding is not a benign side effects as it confers a high-risk of adverse events including death.

With regard to ischaemic outcomes, most reviews and meta-analyses could not show a difference in ischaemic outcomes, although two meta-analyses signalled a small increase in stent thrombosis with DAT. However, in absolute terms, ischaemic events are roughly 10-fold less prevalent in contemporary practice as compared to the bleeding complications [20]. Arguably, net clinical risk of these patients seems to be determined by bleeding risk and not by ischaemic risk.

Therefore, DAT seems a very reasonable strategy in AF patients undergoing PCI and could be the new default strategy. However, to be able to further improve and tailor treatment in these specific group of AF patients undergoing PCI, several questions remain to be answered.

First, is DAT also effective and safe in patients at high ischaemic risk? Some studies described specific sub groups of patients included in the original trials. An analysis of prespecified subgroups in the RE-DUAL trial could not detect differences in outcomes across the subgroups of diabetes, age ≥80 years, or when stratified for indication for PCI. [11] Other subgroup analyses from RE-DUAL, AUGUSTUS and PIONEER AF-PCI trials focusing on patients with ACS or diabetes or with high risk procedural or characteristics suggested no difference in these patients either, although it must be stressed that these studies focused on one parameter only [22,32-34]. Therefore, it remains unknown whether patients with a combination of ischaemic risk factors who are therefore at high risk for recurrent thrombotic events can safely be treated with DAT.

Focusing on bleeding again, another unresolved clinical issue is how we can quantify bleeding risk and identify high-risk patients. Currently, no bleeding model exists for this specific patient population of AF patients undergoing PCI. For ACS patients the CRUSADE risk score is being used, whereas the HAS-BLED score is currently being used to estimate bleeding risk in patients with atrial fibrillation. [35,36] However, neither of these scores is applicable to the specific subset of patients with AF who undergo PCI currently exists. The development of a bleeding score would be a very useful addition to improve the care for these patients in daily practice.

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CHAPTER

4

Aims and outline of this thesis

Part I of this thesis focuses on stent thrombosis. Although many knowledge has been gathered about stent thrombosis, including predictors and treatment modalities, some other area's remain unchartered territory. Triggering mechanisms such as vigorous exercise and emotional stress are known to play a role in luxating spontaneous myocardial infarction (i.e. not stent thrombosis related), but it is unknown whether triggering mechanisms play a role in stent thrombosis as well. In **Chapter 5** the role of triggering mechanisms in provoking stent thrombosis is investigated. **Chapter 6** describes the absolute risk of stent thrombosis when clopidogrel is discontinued early. Finally, **chapter 7** focuses on an antithrombotic strategy to overcome the delayed absorption of $P2Y_{12}$-inhibitors associated with morphine when this is given in STEMI patients before undergoing primary PCI. In **Chapter 8**, three individual patient reports are included to illustrate particularly interesting cases of stent thrombosis.

Part II starts with an overview **(chapter 9)** of the current literature on platelet function testing and discusses the value and possibilities of its use in clinical practice. In **chapter 10**, correlation and agreement of four different platelet function test are discussed and the performance and feasibility of the use of a panel of three combined tests is described.

Part III addresses the subgroup of AF patients who undergo PCI. Currently, these patients are more and more treated with oral anticoagulation and a $P2Y_{12}$-inhibitor but with the omittance of aspirin. **Chapter 11** investigates whether a strategy of so-called "double therapy" is also effective in patients at high thrombotic risk and how to select those patients who might benefit from triple therapy. Finally, in **chapter 12**, the development and validation of a prediction tool to estimate individual patients bleeding risk is described.

CHAPTER

5

Triggering mechanisms of stent thrombosis

B. Zwart, J.W. van Werkum, A.A.C.M. Heestermans, J.C. Kelder, A.C. Zomer, A.W.J. van 't Hof, F.W.A. Verheugt, J.M. ten Berg

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Abstract

Aims:
The aim of this study was to determine the role of potential triggers of stent thrombosis.

Methods and results:
Patients (n =437) with “definite” ST were recruited consecutively in the setting of a large multicentre observational cohort study. Patients were interviewed with validated questionnaires to identify one of the following triggers: I) timing of onset of ST, II) performance of vigorous (S 6 MET) physical activity in the two hours preceding ST, III) presence of emotional stress (experiencing a serious life event in the 14 days preceding the ST or feelings of anger in the 12 hours of ST) and IV) presence of a documented active infection at the time of ST. A total of 363 patients (83.1%) were able to supply adequate information. A significant trigger was identified in 83 patients (22.9%). Analysis of the different categories according to timing of ST revealed a higher prevalence of triggers with an increasing time-interval between index PCI and ST. Analysis of circadian variation showed a steep peak incidence from 7am-12pm.

Conclusions:
Triggering mechanisms such as time of the day, physical exertion, emotional stress and infection may play an important role in a considerable number of patients presenting with ST, in particular in patients with (very) late ST.

Introduction

Stent thrombosis (ST) is a feared complication of percutaneous coronary intervention (PCI) because it is associated with considerable morbidity and mortality.[1-4] Given the devastating clinical consequences of ST, comprehensive risk stratification to identify those patients at high risk for this catastrophic event is mandatory. Previous studies have identified several important clinical, procedural and angiographic predictors that are associated with ST. These include acute coronary syndromes as the indication for PCI, premature discontinuation of clopidogrel therapy, high ontreatment (clopidogrel) platelet reactivity, bifurcation stenting, diabetes mellitus, renal failure, LAD stenting, impaired left ventricle ejection fraction, small stent diameter and long total stent length.[2-9] Nonetheless, it is surprising why only a small subgroup of patients with risk factors for ST will eventually develop ST. Or the other way around, there remains a group of patients experiencing ST that is not characterised by the above mentioned conventional determinants. Consequently, further identification of superimposing mechanisms beyond the currently known risk factors will probably advance our understanding of the pathogenesis of ST.

Although several triggering mechanisms of myocardial infarction have been well established, only anecdotal evidence exists on the association between triggers and stent thrombosis.[10-12] Given a certain degree of similarity in most pathophysiological pathways between ST and myocardial infarction8, we sought to extrapolate the triggering factors that are commonly known for myocardial infarction (such as timing of onset[13-15], vigorous physical exercise[15-19], infection[20-23] and emotional stress[24-28]) to the arena of stent thrombosis.

Methods

The present study is a sub study of the Dutch Stent Thrombosis Registry (DSTR)[1,7]. In brief, the DSTR is a large-scale, multi-centre study conducted in three high-volume centres (>2,500 interventions per centre per year) in The Netherlands. All consecutive patients with an angiographically confirmed stent thrombosis ("definite" according to the ARC-criteria[29]) between January 2004 and February 2007 were enrolled. Stent thrombosis was categorised according to the timing of the event: acute (occurrence within the first 24 h after the index-procedure), subacute (from 24 h to 30 days), late (from 30 days to one year) and very late (>1 year after the index procedure).

Patient interview

All patients enrolled in the DSTR were intensively interviewed using standardised questionnaires about the conditions and activities in the time frame preceding the stent thrombosis. To minimise bias in ascertainment, conditions and circumstances elicited from

patients in response to the open question: “Please describe in detail what you were doing in the hours before the onset of chest pain” were recorded. The open question was followed by a set of predefined, well-validated questions about the hypothesised triggers. The interviewers used a structured data abstraction and questionnaire form for data acquisition.

Timing of onset

The onset of discomfort was used as the onset time for ST. This reported time was checked with PCI-reports. All acute ST’s were excluded from this analysis, to eliminate the influence of PCI-time on the circadian variation.

Physical exercise

Patients were asked whether they had performed any physical activity in the two hours preceding the stent thrombosis. The degree of physical activity intensity was quantified by the Compendium of Physical Activities[30], a coding scheme that classifies physical activity by rate of energy expenditure. This list, developed to enhance comparability of results across studies using self-reports of physical activity, characterises specific physical activities (both daily activities and sports) based on the standard of a metabolic equivalent (MET)[16,30]. The MET is used to estimate the amount of oxygen used during physical activity. One MET correlates with the energy (oxygen) required sitting down quietly. Any activity that burns three to five METs is considered moderate-intensity physical activity. Activity that burns ≥6 METs is considered vigorous-intensity physical activity. Patients were considered to have been engaged in vigorous exertion if they reported a peak MET of six or more in the two hours preceding the ST.

Infection

Patients were asked about any signs and conditions indicating the presence of an infection at the time of ST. All medical records were checked and laboratory charts were screened for inflammatory and infectious parameters indicative for an infection, including positive cultures, antibiotics use, (hs)-C-Reactive Protein (CRP), blood sedimentation rate (BSE), leukocyte count and leukocyte differentiation. Referring hospitals, general practitioners and pharmacies were also contacted to obtain additional information. Only documented infections (confirmed in clinical records) or by means of at least one positive cultures in combination with a Creactive protein level >100 (mg/L).

Emotional stress

To study the impact of emotional stress as a potential trigger, two components of emotional stress were considered relevant: 1) life events and 2) anger.

Life events

To objectify the impact of life events, the Social Readjustment Rating Scale (SRRS) by Holmes and Rahe was used[31,32]. This scale has been designed to assess the cumulative stress of several positive or negative life events, as measured over the last year. The SRRS consists of a list of 43 life events. These items are ranked in order from the most impact (death of spouse, 100 points) to the least impact (minor violations of the law, 11 points). The number of "Life Change Units" that apply to events in the past year of an individual's life are added and the final score will give a rough estimate of how stress affects health.

Because the aim of this study was to determine whether a life event can provoke stent thrombosis, the SRRS was slightly modified. Instead of using the cumulative incidence of life events in the last year, the occurrence of life events in the two weeks prior to the stent thrombosis was recorded. Furthermore, as in our opinion the clinical relevance of the life events is rapidly decreasing towards the bottom of the list, only life events mentioned on the upper half of the SRRS were regarded as potential triggers (i.e., the first 22 of 43 items, corresponding to ≥29 points).

Acute emotional stress

Beside life events, other acute emotions (e.g., anger and extreme anxiety) can also induce stress. Given the subjective character of this category of mental stress, only episodes of anger were recorded as an potential mental stressor, as this emotional trigger has been most intensively investigated[24,33]. The requirement for this acute emotional stressor was the occurrence of anger within 12 hours preceding the stent thrombosis.

Statistical analysis

Continuous variables were reported as medians with 25th and 75th percentiles, and categorical variables were reported as frequencies with percentages. The chi squared test was used to compare categorical variables and for trend in proportions. A p-value <0.05 was considered significant. Descriptive statistics was performed with SAS, version 9.1.3 (SAS Institute Inc., Cary, NC, USA). The number of triggers determined was presented as "number of triggers identified" for the several separate of triggers and as "number of patients in whom a trigger was identified" for the cumulative number of triggers.

Results

A total of 437 patients were enrolled in the DSTR. Of these, 56 (12.8%) patients died before the interview had taken place. Cardiovascular causes (including stent thrombosis) accounted for 88.8% of all deaths. Fourteen (3.2%) patients were lost-to-follow-up and four (0.9%) patients were not able to supply adequate information. These patients were also excluded from the analysis (Figure 1).

The remaining 363 patients (83.1%) were able to supply adequate information. In the majority of cases, data were collected by direct patient interview. In eight cases (2.2%) the partner instead of the patient was interviewed because of communication problems (e.g., language problem, previous history of cerebrovascular accident). The median time between the ST and patient interview was 11 months (25^{th}-75^{th} percentiles: 6-18 months).

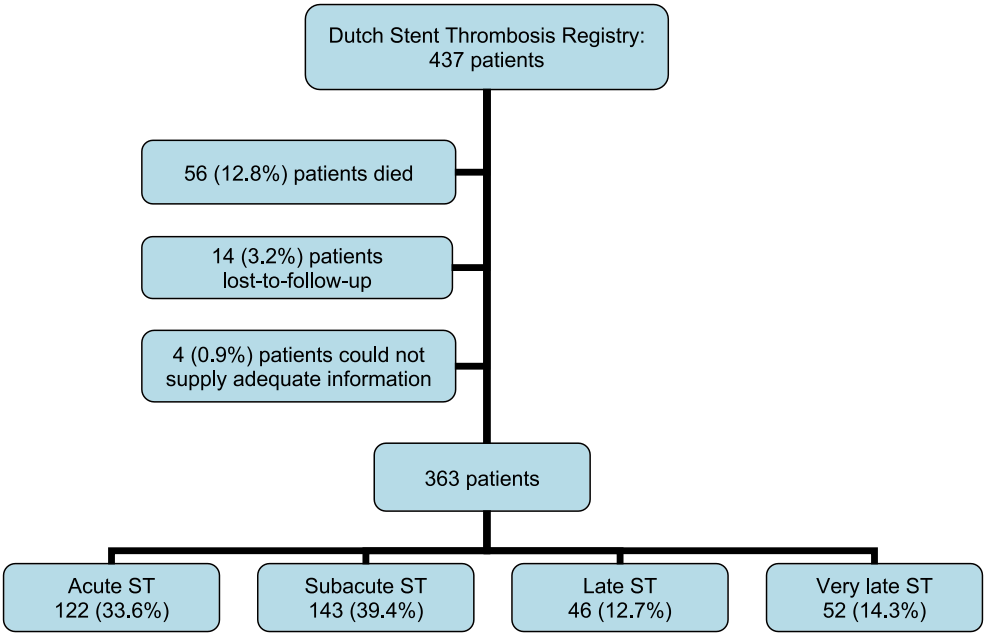

Figure 1: Study design and subject disposition.

Timing of onset

The hourly distribution of the timing of the onset of chest pain is depicted in Figure 2. A marked circadian variation – although less pronounced in patients with late or very late ST – in frequency of symptom-onset was observed with a minimum of events during night hours and a steep increase in events in the morning hours from 07:00 to 12:00 (noon). This six hour time-interval accounted for ~50% of all ST.

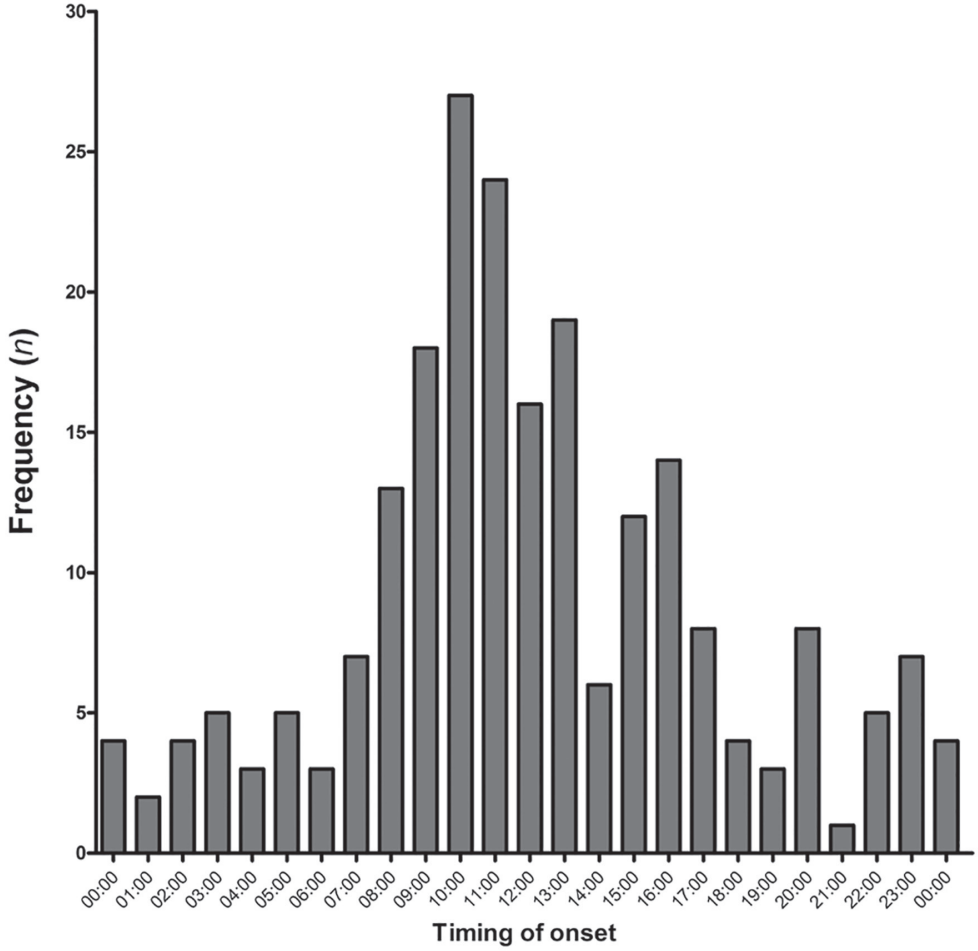

Figure 2: The hourly distribution of the timing of the onset of the chest pain.

Triggering factors

Eighty-three patients (22.9%) reported the presence of at least one triggering event or condition. Four patients reported two different triggers. In two patients both an infection trigger and an emotional trigger were recorded, whereas in two other patients both an infection trigger and a physical exercise trigger was recorded. Figure 3 shows the prevalence of the different triggers preceding the stent thrombosis subdivided in categories according to the timing of ST. The cumulative prevalence of the different triggers in the acute group is fairly low, whereas the prevalence of triggers in the subacute, late and very late group is higher. Analysis of the different categories of ST revealed a higher prevalence of triggers with an increasing time-interval between index PCI and ST (p for trend <0.0001).

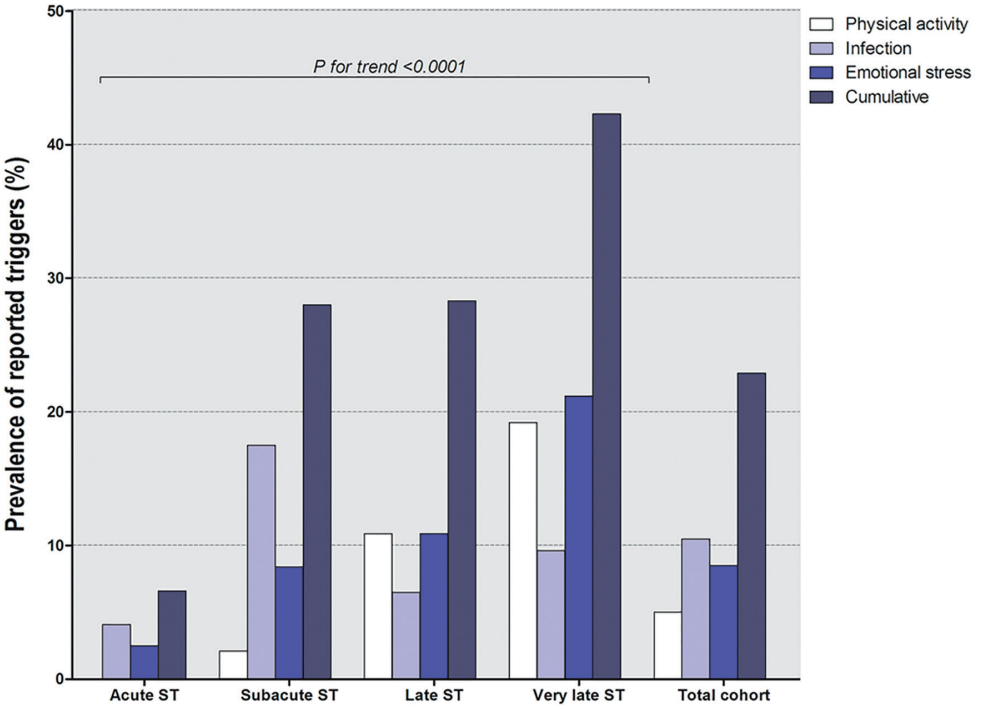

Figure 3: The prevalence of the different triggers preceding the stent thrombosis subdivided in categories according to the timing of ST. Separate triggers displayed as percentage identified triggers; cumulative charts displayed as percentage patients with an identified trigger.

Physical exercise

A total of 28 patients reported that they had performed physical exercise preceding the onset of ST. Of these, in 10 patients the MET was <6 and these patients did not fulfil the requirements for a significant exercise trigger. In the remaining 18 patients (5.0%), vigorous physical exertion (MET S6) was identified as a trigger preceding ST.

Infection

Thirty-eight patients (10.5%) reported the presence of an infection on the day of the stent thrombosis. Review of medical charts, laboratory parameters and cultures confirmed the presence of an active infection in all cases. The different types of infections are summarised in Table 1.

Table 1: Specification of infection focus.

Type of infection	Number of patients
Pneumonia	12
Urinary Tract Infection	10
Gastro-enteritis	3
Focus unknown	3
Bacteraemia	2
Orthopaedic infection	2
Other	6

Emotional stress

A total of 31 patients (8.5%) reported the occurrence of a life event or feelings of anger preceding the stent thrombosis. Twenty-two patients (6.1%) experienced a life event within two weeks prior to the stent thrombosis. According to the SRRS, the mean ± SD score was 52±17 points, ranging from a minimum score of 29 (corresponding with "change of responsibilities at work") to a maximum score of 100 (corresponding with "death of spouse"). Nine patients (2.5%) reported an episode of anger within 12 hours preceding the ST.

Risk factors

The prevalence of risk factors is generally comparable in patients with and without a trigger preceding the stent thrombosis, although patients in whom a trigger was identified are on average three years younger (Table 2). In addition, left ventricular ejection fraction <30% and cessation of clopidogrel at the time of stent thrombosis were more frequently observed in patients with a trigger.

Table 2: Baseline table.

Risk factor	Trigger identified: yes n (%)	Trigger identified: no n (%)	Significance (p-value)
Age	58.1 (mean)	61.0 (mean)	0.052
LAD stenting	53/83 (63.9)	166/280 (59.3)	0.54
Cessation of clopidogrel	38/82 (46.3)	74/280 (26.4)	< 0.001
DES implantation	32/83 (38.6)	102/280 (36.4)	0.82
Diabetes	22/83 (26.5)	54/280 (19.3)	0.21
Bifurcation stenting	43/83 (51.8)	139/280 (49.6)	0.82
Renal failure (MDRD <30ml/min)	0/76 (0.0)	5/262 (1.9)	0.50
LVEF <30%	12/83 (14.5)	19/280 (6.8)	0.049
Stent length >30mm	26/83 (31.3)	78/279 (28.0)	0.65
STEMI as indication for index-PCI	51/83 (61.4)	161/278 (57.9)	0.66

Discussion

The present study is the first exploratory study investigating the relationship between triggering mechanisms and the occurrence of stent thrombosis in a large consecutive cohort of patients with ST, although no causal conclusions could be drawn from these descriptive data.

Substantial experimental and clinical evidence from the 80s and 90s strongly supports a causal relationship between several triggering mechanisms (such as timing of onset, strenuous exercise, presence of an infection and emotional stress) and the occurrence of myocardial infarction. Given the fact that ST and myocardial infarction share some, but not all, pathophysiological mechanisms, it is likely that these triggers may play a role in the pathophysiology of ST as well. However, only anecdotal evidence exists on the role of triggering mechanisms in ST.[10-12]

Despite the absence of a plaque rupture in the initial cascade of events leading to ST, numerous studies have revealed that other relevant physiologic processes are stimulated by several triggering mechanisms and contribute to the formation of an occlusive thrombus in the implanted coronary stent. These processes include increased sympathetic activity and vagal withdrawal, elevation in plasma catecholamines and renin levels, increased thrombin generation, increased heart rate and blood pressure, exercise induced coronary-artery spasm, increased systemic inflammation, increased vascular resistance, increased vessel-wall stress, a heightened platelet reactivity status and a hypercoagulability state[34-38]. These effects are mediated by complex mechanisms, involving □2-adrenergic receptor expression, von Willebrand factor platelet interaction, GPIIb/IIIa interaction, P-selectin expression of platelets and the release of nitric oxide.

With regard to physical exercise, several studies revealed paradoxical effects of moderate exercise and vigorous exercise on platelet function.[39,40], suggesting that moderate exercise suppresses platelet reactivity and increases fibrinolysis. Conversely, vigorous exercise – especially in untrained individuals – enhances both platelet reactivity and coagulation, whereas it promotes fibrinolysis as well. From this perspective, moderate-intensity activity could be considered safe, whereas vigorous exercise might lead to a prothrombotic state ultimately leading to the formation of a thrombus.

In the present study, a surprisingly high percentage (almost 25%) of patients with ST reported a trigger. Analysis of the categories of ST revealed a higher prevalence of triggers with an increasing time interval between index PCI and ST. Interestingly, the prevalence of the studied triggering mechanisms was the highest (42%) in the group of patients presenting with a very late stent thrombosis.

The lowest prevalence of the studied triggering mechanisms was found in patients presenting with acute ST. This observation is in line with previous findings identifying mechanical and procedural factors as the predominant cause of acute stent thrombosis[41,42]. Consequently, the pathophysiology of acute stent thrombosis should be considered distinct from the other categories of stent thromboses.

The identification of potential triggering mechanisms of ST might have important clinical implications related to both prognosis and prevention[26]. From a prognostic perspective, the presence of in particular emotional stress may imply that certain individuals are more vulnerable to stress-induced biological responses than others[35]. Consequently, the presence of emotional stress should be considered as a marker of increased risk. In addition, previous studies found personality to be an important predictor of adverse clinical outcome: type-D personality (patients high in negative affectivity and social inhibition) was independently associated with myocardial infarction and death in patients undergoing PCI with stent implantation.[43] Of even more importance, Denollet et al demonstrated that the interaction effect of negative emotions with social inhibition – more than negative emotions alone – is associated with major adverse cardiac events. These findings might provide additional clues to identification of specific patients at increased risk of stent thrombosis.[44]

In relation to prevention, the ideal approach should involve a range of various strategies for the different types of triggering mechanisms. First, patients undergoing coronary stent implantation should be encouraged to perform moderate physical activity on a regular basis, because the beneficial effects of exercise training in the secondary prevention of coronary artery disease have been well established.[45] In addition, several epidemiological studies demonstrated that the performance of moderate exercise on a regular basis lowers both the baseline risk as well as the relative risk that an episode of heavy physical exertion will trigger myocardial infarction16,19,46. However, caution remains warranted when patients plan to perform vigorous exercise, especially when untrained. According to the guidelines of the ACC/AHA47, patients should undergo an exercise test under supervised conditions, before starting to perform vigorous exercise.

Second, it has been known for several decades that infections (in particularly pneumonia and influenza)[22,23,48] are associated with myocardial infarction. The high prevalence of infection (almost 20%) especially in patients with subacute ST suggests that infection plays an important role in the pathogenesis of subacute ST. Better surveillance and management strategies in order to timely identify the first symptoms of infection in hospitalised patients with a recently implanted coronary stent and strict compliance with current standards for the prevention followed by prompt antibiotic treatment of infections may aid in prevention.

Limitations

The results of our study should be interpreted in the light of the following limitations. First, the substantial period of time between the ST and the patient interview makes this population susceptible to information and recall bias. This may have resulted in both an underestimation as well as an overestimation of the prevalence of some triggering mechanisms (in particular vigorous exercise and emotional stress). However, this cannot explain the high prevalence of triggers found in this study. Moreover, exceptional activities or emotions in the hours preceding the catastrophic event of a ST are easy to remember. In addition, well-documented markers of infection and positive cultures as well as the reported time of performance of the emergent PCI for ST are not subjected to these forms of bias.
Second, the retrospective character of our study did not allow a case-crossover study design (cases serve as their own controls and therefore the design eliminates confounding by stable individual characteristics) because a detailed memory of the daily activities on just an ordinary day in the past (control-day) or a broader period of time is often not very clear. Due to the absence of this control group, a comparison with the prevalence of triggers in an average PCI-cohort cannot be made. Nonetheless, our data reveal a relatively high prevalence of triggering mechanisms in patients with ST as compared to the prevalence of similar triggering mechanisms in myocardial infarction (vigorous physical exercise: 3.8% to 10%[16,28,33,46,49], any emotional stress: 4.4% - 6.8%[26,28,49]) To overcome the aforementioned important limitations, very strict criteria were used to assign the presence of an exercise or emotional trigger. In addition, the interview was always started with an open question. Moreover, well-standardised reference charts and questionnaires from the field of sports medicine and psychology were used.
In conclusion, triggering mechanisms such as time of the day, physical exertion, emotional stress and infection may play an important role in a considerable number of patients presenting with ST. The prevalence of these triggering mechanisms is particularly high in patients with late and very late ST.

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CHAPTER

6

High risk of stent thrombosis in the first 6 months after coronary stenting

B. Zwart, T.C. Godschalk, J.C. Kelder, J.M. ten Berg

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Abstract

Objectives:
To estimate the incidence of stent thrombosis (ST) after early discontinuation of clopidogrel.

Background:
Premature discontinuation of clopidogrel is the strongest risk factor for ST. In contrast, recent studies suggest that shorter dual antiplatelet therapy (DAPT) can be discontinued as soon as 3 months after stenting. However, these studies included very few ACS patients and were not powered for ST. Hence, little is known about the occurrence of ST in high-risk populations when DAPT is discontinued early.

Methods:
This is a subanalysis of The Dutch ST Registry 437 ST cases (mainly first generation DES and BMS). Acute coronary syndrome was the indication for index-PCI in 74% of the patients. Clopidogrel discontinuation rates in ST patients and matched controls were used to calculate the absolute incidence of ST after early clopidogrel discontinuation.

Results:
The overall rate of ST after cessation of clopidogrel was 4.6% (95%CI: 3.9-5.4%), as compared to 1.7% (95%CI: 1.5-1.9%) in patients who did not discontinue clopidogrel. The incidence of ST was 35.4% when clopidogrel was discontinued in the first 30 days after index-PCI declining to 11.7% when clopidogrel was discontinued in the first 180 days.

Conclusions:
This dedicated ST registry shows that ST rates were very high when clopidogrel was discontinued before 6 months after index-PCI and therefore suggests that clopidogrel discontinuation in the first 6 months after ACS should be avoided.

Introduction

Stent thrombosis (ST) is a feared complication of percutaneous coronary intervention (PCI) with stent implantation. Although the incidence in recent studies has declined, it is estimated to occur in 0.5–1% of patients in the first year after stent implantation, falling to 0.5% or less in the following years[1–6].

Dual antiplatelet therapy (DAPT) with acetylsalicylic acid in combination with a P2Y12-inhibitor in order to prevent atherothrombotic events, such as ST, is the standard of care after PCI. DAPT is recommended with a class I level of evidence in current American and European guidelines,[7–9] with a recommended treatment duration of 6-12 months depending on the indication for PCI. Clopidogrel is the most commonly used $P2Y_{12}$-inhibitor and it is still first choice in PCI patients with stable coronary artery disease. Although the stronger P2Y12 inhibitors ticagrelor and prasugrel are recommended in the acute coronary syndrome (ACS) setting,[9] two recent studies showed that clopidogrel is still frequently used in ACS in both the United States and Europe.[10,11]

Premature discontinuation of clopidogrel (discontinuation before the recommended treatment duration) has been shown to be the strongest risk factor for the occurrence of ST.[4,6,12–14] Nevertheless, several recent randomized controlled trials suggest that shorter DAPT duration (3-6 months) might be as safe as the standard regime. However, these studies were underpowered[15] for the endpoint ST with ST numbers of 10 or less per study. In addition, these studies included mainly low-risk patients and no or only small numbers of ACS patients.

Looking from a mechanical view point, the concept of delayed arterial healing in drug-eluting stents (DES) emphasizes the risks of discontinuing clopidogrel in the first months after stenting. Previous studies identified several factors associated with DES, including delayed healing (delayed endothelial regeneration), neoatherosclerosis, and chronic inflammatory response, which typically develop months or even years after stent implantation, leaving DES at persisting risk for atherothrombotic events.[16–21] Although second generation DES have undergone several changes such as thinner stent struts and more biocompatible polymer coatings in order to minimize these problems, it is not clear when arterial healing has been completed and thus when DAPT can be discontinued safely.

As it is currently unknown what the impact of early clopidogrel cessation on the occurrence of ST is, particularly after ACS, we sought to investigate the absolute risk of ST after clopidogrel discontinuation in our Dutch Stent Thrombosis Registry, one of the largest consecutive ST cohorts.[4]

Materials and Methods

The Dutch Stent Thrombosis Registry (DSTR) is a multi-center study conducted in three high-volume centers in the Netherlands (>2500 interventions/center/year). All consecutive patients with an angiographically confirmed (definite) ST were enrolled. Both DES (73% first generation [ie, Taxus or Cypher] and bare-metal stents [BMS]) were used. The recommended duration of clopidogrel therapy was 12 months for ACS patients. For patients undergoing PCI for stable coronary artery disease, the recommended standard DAPT duration was 12 months for DES (3–6 months in selected patients, eg., because of bleeding events) and 1 month for patients undergoing BMS angioplasty. The duration of clopidogrel use as well as aspirin compliance after patient discharge was assessed with telephonic patient interview as well as data from pharmacy records (the date of clopidogrel dispensed and the number of days supplied for each dispense). In case of disagreement, the pharmacy data were used for the analysis.

ST was defined according to the Academic Research Consortium criteria for "definite" ST[22]. Consecutive patients suffering ST were matched in a 1:2 ratio to patients who underwent PCI with stent implantation but without ST during follow-up. Matching criteria included indication for index-PCI (PCI of stent implantation), PCI center, and date of index-PCI, in order to correct for patient or procedure related factors.

To study the impact of discontinuation of clopidogrel, a "virtual ST time" was assigned for the matched controls, which was based on the same duration between index-PCI and ST as in patients with ST (cases). This virtual ST time allowed to calculate the time between clopidogrel discontinuation and the virtual ST date for the matched controls (Figure 1). The study design and methods were published in more detail previously.[4]

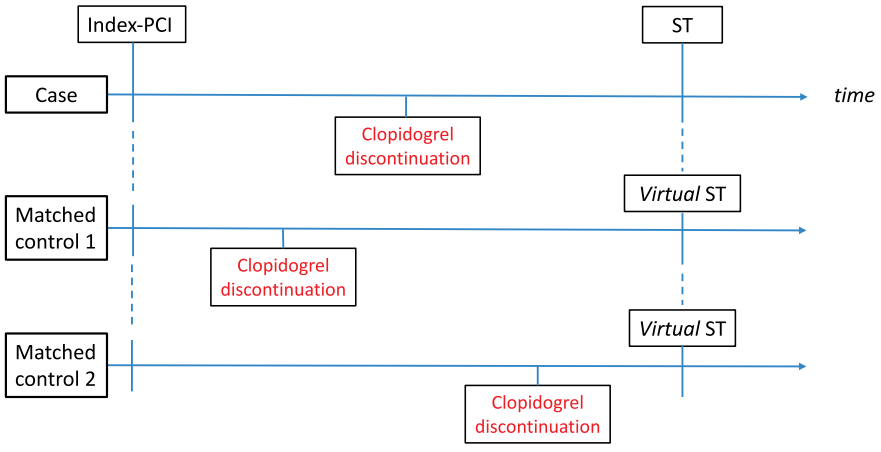

Figure 1: Clopidogrel discontinuation in matched controls.

The aim of the present study was to determine the incidence of ST after cessation of clopidogrel and to calculate this absolute risk for specific time frames (ST ≤30, ≤90, ≤180 days) after index-PCI.

The incidence of ST after clopidogrel discontinuation was calculated by comparing the number of patients suffering ST after discontinuation of clopidogrel to the estimated total number of patients in the PCI registry who discontinued clopidogrel but did not suffer a ST. This total number of patients discontinuing clopidogrel was estimated by extrapolating the discontinuation rate in the matched controls to the total cohort of the PCI registry (Figure 2).

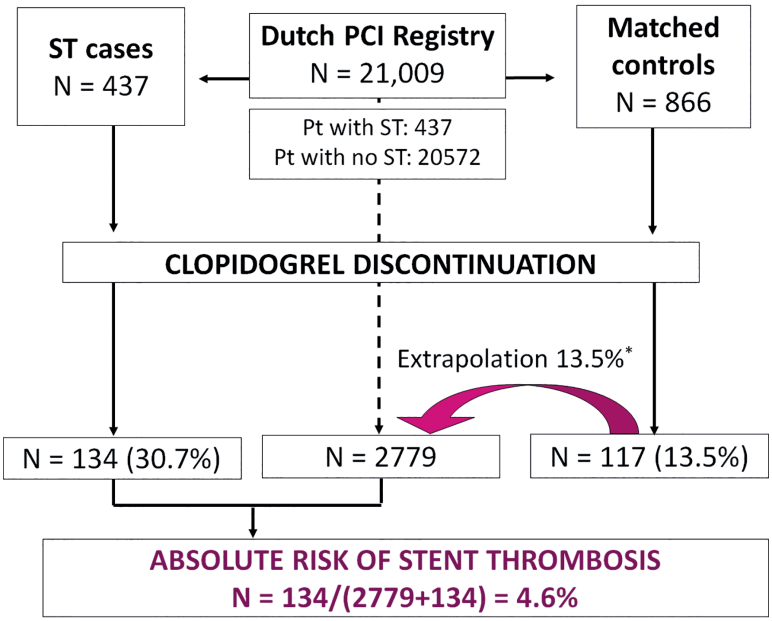

Figure 2: Method of calculation of absolute risk of stent thrombosis.

The absolute risk of ST after clopidogrel discontinuation in specific time frames (ST ≤30, ≤90, and ≤180 days after index-PCI) was calculated in a similar manner (Figure 3). ST cases in the predefined time frames were matched to their controls. The percentage of discontinuation in the matched control patients for this time frame was extrapolated to the total cohort of the registry to estimate the number of patients discontinuing clopidogrel in that same time frame. Subsequently, the absolute risks of ST after clopidogrel discontinuation in different time frames could be calculated (ST cases after discontinuation of clopidogrel in a specific time frame divided by all patients who had discontinued clopidogrel in the same time frame).

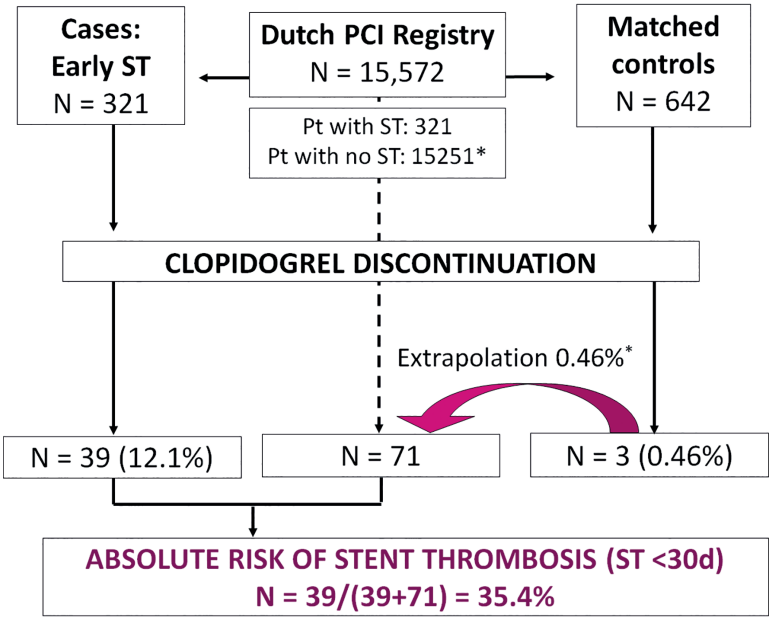

Figure 3: Method of calculation of absolute risk of stent thrombosis in cases with ST ≤30 days after index-PCI.

To assess whether the found association between clopidogrel cessation and the occurrence of ST was likely to be a causal relation, the timing of ST after discontinuation of clopidogrel was assessed. As platelet inhibition is believed to persist for 5-7 days after clopidogrel cessation, we calculated the proportion of patients suffering a ST <7 days after discontinuing clopidogrel. In addition, we calculated the proportion of patients suffering a ST <14 days after clopidogrel cessation, following the findings of the PARIS study that suggested that interruption for 14 days might be safe.[23]

Statistical analysis was performed with SAS v 9.3 (SAS Institute, Inc., Cary, NC). Continuous variables were summarized by means, standard deviations, medians, interquartile ranges, and minimum and maximum values. Categorical variables were summarized by frequencies and percentages.

Results

A total of 437 patients out of 21 009 patients (2.1%) presented with a definite ST during a median follow-up of 30.9 months. Relevant baseline characteristics are shown in Table 1. The majority of patients (74.1%) underwent the index-PCI for the indication unstable angina/ NSTEMI (16.5%) or STEMI (57.7%).

Table 1: Baseline characteristics.

	Cases (n=437)	Matched Control Subjects (n=866)	p Value
Clinical characteristics/total (%)			
Age, yrs	61.0 ± 11.8	62.3 ± 11.7	0.0616
Female/total (%)	108/437 (24.7)	235/862 (27.3)	0.3512
Indication/total (%)			
Stable angina	113/437 (25.9)	242/866 (27.9)	Matched item
UAP/NSTEMI	72/437 (16.5)	124/866 (14.3)	Matched item
STEMI	252/437 (57.7)	500/866 (57.7)	Matched item
Lesion characteristics/total (%)			
ACC/AHA B2 or C	334/437 (76.4)	516/866 (59.6)	0.0001
Bifurcation lesion	228/437 (51.7)	210/866 (24.3)	0.0001
Coronary vessel			
LAD	273/437 (62.5)	375/866 (43.3)	0.0001
RCA	128/437 (29.3)	348/866 (40.2)	0.0001
RCX	65/437 (14.9)	148/866 (17.1)	0.3411
Vein graft	5/437 (1.1)	21/866 (2.4)	0.1435
Procedural characteristics/total (%)			
Stent type			
BMS	270 (61.8)	614 (70.9)	0.0015
DES	152 (34.8)	238 (27.5)	
Mixed stent(s)	15 (3.4%)	14 (1.6)	
Total stent length, mm	27.8 ± 15.2	23.7 ± 14.2	0.0001
Total number of stents	1.5 ± 0.8	1.3 ± 0.7	0.0001
Minimal stent diameter*, mm	3.0 ± 0.4	3.1 ± 0.4	0.0001

A total of 134 out of 437 (30.7%) of patients discontinued clopidogrel prior to suffering ST, as compared to 117/866 (13.5%) patients in the matched controls group (Figure 2). The majority of these patients (88.1%) were on aspirin therapy at the time of ST, whereas the small proportion of patients not started on aspirin were mainly treated with oral anticoagulation (84% of patients).

The absolute risk of ST after discontinuation of clopidogrel therapy was 4.6% (95%CI: 3.9-5.4%) as compared to a rate of 1.7% (95%CI: 1.5-1.9%) in patients who did not discontinue clopidogrel (Figure 2). When stratified for timing after index-PCI, the absolute ST risk when clopidogrel was discontinued was 35.4% for ST in the first 30 days after index-PCI (Figure 3). The ST risk decreased inversely over time but remained high until 6 months after index-PCI, with an absolute ST risk of 19.0% and 11.7% for the first 90 days and first 180 days after index-PCI, respectively (Figure 4).

In patients suffering early ST (ie, ≤30 days after index-PCI), ST occurred within 7 and 14 days after clopidogrel cessation in respectively 84.6% and 92.3% of patients. In patients developing ST within 90 and within 180 days after index-PCI, this proportion was respectively 76.0% and 68.3% within 7 days and respectively 86.0% and 83.3% within 14 days (Table 2).

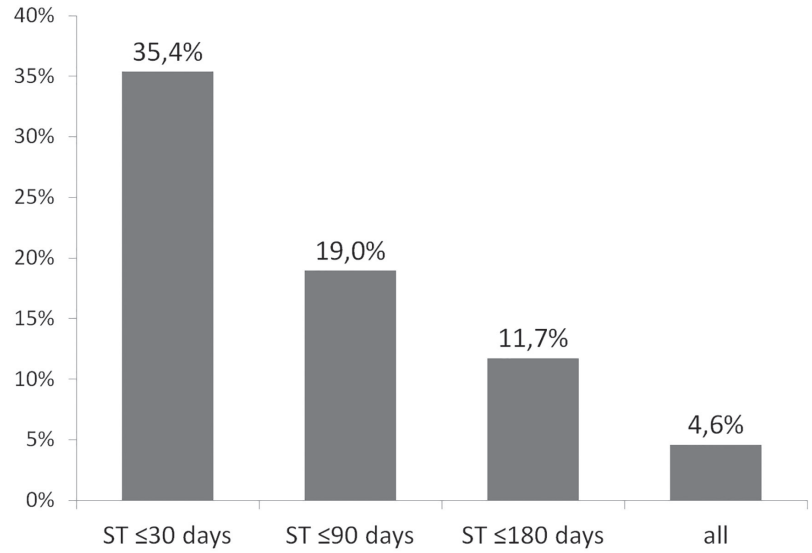

Figure 4: Absolute risk of stent thrombosis after clopidogrel discontinuation.

Table 2: Timing of ST after discontinuation of clopidogrel .

	Duration of clopidogrel discontinuation	
	≤ 7 days	**≤ 14 days**
ST ≤30 days after index-PCI	84.6% (33/39)	92.3% (36/39)
ST ≤90 days after index-PCI	76.0% (38/50)	86.0% (43/50)
ST ≤180 days after index-PCI	68.3% (41/60)	83.3% (50/60)

Discussion

Our study demonstrates that early cessation of clopidogrel was strongly associated with the occurrence of ST. We showed a remarkably high absolute risk of ST when clopidogrel was discontinued in the first 30 days after index-PCI (35.4%) and within 90 and 180 days (19.0% and 11.7%, respectively), which was not reported before. These results apply mainly to ACS patients, as this was the indication for the index-PCI in the majority (74%) of ST patients.

The occurrence of ST should be considered as a serious complication, given the fact that ST presents in nearly all cases as myocardial infarction and given the poor clinical outcome after ST with high rates of recurrent ST and cardiac death (18.2% and 9.5%,respectively) at 1 year in the Dutch Stent Thrombosis Registry.[24]

Until now, information on the absolute incidence of ST after clopidogrel cessation is scarce and relies on smaller studies. Schultz et al. calculated in a prospective cohort study including

73 ST cases that the cumulative incidence of ST in patients who discontinued clopidogrel before 6 months was approximately 12.5%, which is comparable with our study.[25]

Should we shorten the duration of DAPT after ACS?

Recently, several studies have been published, suggesting that a shorter DAPT duration (3-6 months) might be as safe as the standard DAPT of 6-12 months. However, all of these studies are hampered by very low ST rates (ISAR-SAFE: five vs. three patients with ST at 9 months; EXCELLENT: six vs. one ST at 12 months; SECURITY: two vs. three ST at 12 months; OPTIMIZE: four vs. one ST at 12 months; RESET: two vs. three ST at 12 months).[26–30] Most of these studies were not powered to detect differences in ST rates or enrolled less patients than expected. Therefore, the clinical outcomes of these randomized controlled trials regarding ST should be interpreted with caution. Moreover, most of these studies included low-risk patients and a small proportion of ACS patients. However, a recent meta-analysis addressed this question specifically and concluded that 3 months of DAPT after ACS—but not after PCI for stable CAD)—was associated with higher ST and MI rates.[31]

Hence, registries such as the present one are needed to study the risks of low-frequent events such as ST in high-risk patients. The current registry with 437 ST cases enabled us to detect and highlight the risks of early DAPT discontinuation. It might be advisable to be reluctant in reducing DAPT duration in STEMI patients who underwent PCI, although further prospective and randomized studies are needed.

Perioperative interruption of DAPT

In patients undergoing surgery shortly after PCI, the issue whether it is safe to temporarily discontinue clopidogrel is of special importance. Need for surgery is not uncommon as demonstrated by a recent study estimating that 14.3% of patients undergo surgery in the first year after coronary stenting[32]. Current guidelines recommend to discontinue clopidogrel 5 days in advance[33]. However, the risk of ST is distinctively increased in the first week after cessation of clopidogrel therapy[4].

The recently published PARIS registry investigated DAPT interruption, defined as planned cessation of antiplatelet treatment due to surgical necessity with reinstitution of DAPT within 14 days[23]. The authors found an increased overall Major Adverse Cardiac Events risk after brief interruption, but no significant increase in thrombotic events, thereby suggesting that with interruption <14 days of DAPT for surgical procedures might be safe. However, the timing of interruption was not provided and the mean duration of sustained DAPT of 357 days suggested a small number of patients discontinuing DAPT in the first 6 months. Moreover, the overall rate of interruption and adverse events in this study was low, thereby limiting the power of the study. Although this PARIS study provided important insights, no conclusions can be drawn unfortunately with regard to when it is safe to temporarily discontinue DAPT.

The current study, although not specifically addressing patients undergoing surgery, highlights the possible risks of early clopidogrel discontinuation after PCI. The majority of ST occurred within 14 days in this registry and this observation might question the findings in the PARIS study that a brief interruption is safe. However, again prospective studies are needed to address this issue and strategies to minimize the risks in patients undergoing surgery shortly after PCI.

Limitations

The incidence of ST in the Dutch Stent Thrombosis Registry is higher than in more recent studies. This may in part be explained by the high proportion of first-generation DES. As the overall ST incidence has declined, the absolute risk calculations of ST after discontinuation of clopidogrel might be lower in current clinical practice. Of note, the absolute ST rates might be underestimated for the reported time frames, as only information on clopidogrel therapy at the time of ST was used. Consequently, patients discontinuing clopidogrel early but suffering ST in a later time frame were not counted in the former time frame. Secondly, results are shown as aggregate data (rather than separate analyses for STEMI, NSTEMI, and stable patients), as the small patient numbers and the used extrapolation method did not allow for such a sub analysis. However, as the cohort consisted of a mix of unstable/ACS patients (74%) and stable patients (26%), the risks associated with early DAPT discontinuation after ACS might still be underestimated.

Furthermore, current guidelines now recommend the use of stronger $P2Y_{12}$-inhibitors such as ticagrelor and prasugrel over clopidogrel. However, clopidogrel is still widely used in patients with acute coronary syndrome (ACS)[10,11], despite this recommendation. Therefore, we believe the message of our study is still contemporary in endorsing the importance of clopidogrel continuation in the first 6 months after stent implantation.

Finally, ST risk might interfere with the reason of clopidogrel cessation, for example, bleeding or surgery, which might lead to a prothrombotic state and thus adding to ST risk. As the current study is a registry, it is not possible to correct for such factors. However, this is a “real world registry” reflecting the real risks associated with early clopidogrel discontinuation.

Conclusion

The absolute rates of ST in this large registry with a high proportion of ACS patients were very high when clopidogrel was discontinued in the first 6 months after index-PCI. Clinicians should be reluctant in reducing DAPT duration in ACS patients, unless the patient is considered to have an excessive bleeding risk.

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CHAPTER

7

Use of glycoprotein IIb/IIIa antagonists to prevent stent thrombosis in morphine-treated patients with ST-elevation myocardial infarction

B. Zwart, M. Yazdani, K.W. Ow, J.D. Richardson,
J. Iqbal, J.P. Gunn, R.F. Storey

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Abstract

Morphine can delay absorption of $P2Y_{12}$-inhibitors in ST-elevation myocardial infarction (STEMI) patients, which has the potential to expose these patients to increased stent thrombosis risk after primary percutaneous coronary intervention (PPCI). Limited evidence exists for pharmacotherapeutic strategies aiming to mitigate this risk. We evaluated the impact of guideline-driven 'routine' glycoprotein IIb/IIIa antagonist (GPI) use in morphine-treated patients undergoing PPCI. 3224 consecutive STEMI patients undergoing PPCI at a large tertiary cardiac centre between 2012 and 2017 were evaluated. GPI use and outcomes before and after introduction of a local guideline were compared, and rates of definite stent thrombosis were identified at 24 hours and 30 days. GPI use increased from 42.4% to 69.9% after the introduction of the new guideline. Stent thrombosis occurred in 1.3% (26/1947) pre-guideline and 0.6% (7/1244) post-guideline (P = 0.037). Of the 33 stent thrombosis cases, 90% (27/30) had received morphine, of whom 85.2% (23/27) had not received adjunctive GPI. Routine GPI use in morphine-treated STEMI patients undergoing PPCI appears to protect against stent thrombosis. Although hampered by low patient numbers, GUSTO mild to moderate bleeding was more frequently observed in GPI treated patients, whereas differences in GUSTO moderate or severe bleeding were not significantly different. Large-scale studies are needed to establish the overall risk-benefit of GPI therapy in morphine-treated PPCI patients and to assess alternative strategies for preventing acute stent thrombosis in these patients.

Introduction

Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor is the standard of care for the management of acute coronary syndromes (ACS) and for percutaneous coronary intervention (PCI), being recommended in the current international guidelines.[1,2,3,4] In the setting of ST-elevation myocardial infarction (STEMI) and other ACS manifestations, the $P2Y_{12}$ inhibitors ticagrelor and prasugrel are now preferred to clopidogrel as first-line therapy in those without contraindications, except in those requiring oral anticoagulant therapy.[1,24] Morphine is often used in patients with STEMI for analgesia, sedation, anxiolysis and reduction of adrenergic drive, heart rate and myocardial oxygen consumption.[1,2,5] However, morphine has been shown to delay absorption of $P2Y_{12}$-inhibitors in STEMI patients, which has the potential to expose these patients to increased thrombotic risk.[6,7,8,9] Some evidence of a harmful effect comes from the ATLANTIC (Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery) study, which showed a significant interaction between morphine use and the effects of pre-hospital administration of ticagrelor; pre-hospital compared to in-hospital ticagrelor administration appeared to improve resolution of ST-elevation in those who did not receive morphine whereas no apparent benefit was seen in morphine-treated patients.[10] Another study found that morphine-treated STEMI patients exhibited larger infarct size and lower myocardial salvage index[11], although a further observational study found no differences in in-hospital complications or 1-year mortality.[12] Evidence for clinical efficacy of GPI use in morphine-treated patients with STEMI is limited. In a small observational study (32 STEMI patients treated with prasugrel), a bridging strategy with abciximab in morphine-treated patients appeared to ensure adequate platelet inhibition as measured with Multiplate electrode aggregometry.[13] However, no evidence is available regarding clinical outcomes with such a strategy and no data exist about the effect in ticagrelor-treated patients in this setting. The recommendations for GPI use in addition to $P2Y_{12}$ inhibitors in the current guidelines are restricted to specific situations (bail-out strategy, no-reflow or angiographic evidence of a large thrombus).[24] No specific recommendations are given for morphine-treated patients. Although the aforementioned studies suggest that platelet function and clinical outcomes are worse in morphine treated STEMI patients, no accepted strategies exist to overcome this issue. Therefore, an institutional guideline was introduced in our hospital in 2012 with the purpose of improving the outcomes of morphine treated STEMI patients.

The aim of the current observational cohort study was to compare the effect of GPI before and after the introduction of this guideline for morphine-treated STEMI patients in terms of stent thrombosis and mortality, as well as to obtain pilot data on bleeding events.

Methods

Consecutive patients undergoing primary PCI for STEMI at South Yorkshire Cardiothoracic Centre, Sheffield, United Kingdom, between 1 April 2012 and 28 February 2017 were included. This hospital provides a primary PCI service for the surrounding population of approximately 1.8 million people. Standard antithrombotic therapy throughout the observation period consisted of aspirin and ticagrelor (or prasugrel if ticagrelor was not tolerated or cautioned for reasons other than bleeding risk). Heparin was given intravenously or intra-arterially at a dose of approximately 70 units/kilogram. Use of GPI in morphine-treated patients was encouraged after introduction of the local protocol in March 2015, which specifically recommended that "in the absence of contraindication, tirofiban should be considered routinely in patients who have received morphine prior to or shortly after loading dose of $P2Y_{12}$ inhibitor" at an intravenous bolus dose of tirofiban 25 mcg/kg followed by maintenance dose of 0.15 mcg/kg/min for a duration of 6 hours, unless a reduced dose was indicated for renal failure or longer duration was indicated for management of residual thrombus.

GPI use as documented in the procedure information system was collected and compared between the pre-guideline group (April 2012 to February 2015) and the post-guideline group (from March 2015 to February 2017).

A search was performed for patients undergoing a re-PCI within 30 days and PCI reports were reviewed to identify any possible cases of stent thrombosis. Cases that met the Academic Research Consortium criteria for definite stent thrombosis[14] were recorded and additional details regarding morphine were collected for these patients. 30-day vital status was available for all patients from the national register of deaths.

Bleeding rates in local cohort

Bleeding rates and details of in-ambulance morphine use were not available for many patients, partly due to transfer to local hospitals after 12 hours meaning that complete hospital records were not available or due to incomplete records. Consequently, a detailed analysis was performed in a sub-cohort of 374 local STEMI patients in order to provide pilot data on bleeding rates, according to Global Utilization of Streptokinase and tPA for Occluded arteries (GUSTO) criteria for mild, moderate and severe bleeding, in the first 30 days. Bleeding rates were compared between the pre-guideline cohort and the post-guideline cohort, between GPI-treated patients and patients not treated with GPI, and, finally, in patients who received the institutional "guideline-based therapy" (i.e. morphine-treated patients who received GPI or patients who did not receive morphine and did not receive GPI) versus patients not receiving the institutional guideline-based therapy. Patients were excluded if they were transferred after PCI to their local district general hospital. For the

bleeding outcomes, only procedures performed by operators using predominantly radial access at the beginning of the census date (1 April 2012) were included in order to reduce bias from increased adoption of, and skill in using, radial artery access during the second period leading to reduced bleeding risk.[1-2, 15]

Statistical analysis

Categorical variables were summarized by frequencies and percentages and Chi-square tests were used in intergroup comparisons of categorical variables. Fisher's Exact Test was used for low frequency events. Continuous variables were summarized as mean and standard deviation, and values were compared using a standard t-test for normally distributed data. Stent thrombosis rates were compared with Kaplan Meier plots using log ranks test. The primary outcome was definite stent thrombosis at 30 days and secondary outcomes were definite stent thrombosis at 24 hours and all-cause mortality at 30 days.

Results

Study population

3224 consecutive STEMI patients undergoing primary PCI were included. Details of repeat PCI procedures and all-cause deaths within 24 hours and at 30 days were available for all these patients. In the post-guideline cohort, radial access was more common, and patients presented more frequently with cardiogenic shock, whereas peripheral arterial disease was less common (Table 1). Details regarding GPI use were available in 2297/3224 (71.2%) of patients. GPI use increased from 42.4% to 69.9% after the introduction of the new guideline (Table 2).

Table 1: Baseline characteristics.

n (%) unless indicated	Main cohort Pre guideline	Main cohort Post guideline	P value	Local cohort Pre-guideline	Local cohort Post guideline	P value
Age, mean ± SD	62.9 ± 12.7	63.6 ± 12.5	0.10	62.1 ± 12.9	62.6 ± 12.9	0.71
Female sex	547/1973 (27.7)	335/1251 (26.8)	0.59	55/233 (23.6)	32/141 (22.7)	0.79
Diabetes	265/1823 (14.5)	178/1071 (16.6)	0.13	29/212 (13.7)	17/113 (15.0)	0.73
Hypercholesterolaemia	542/1586 (34.2)	253/831 (30.4)	0.06	62/192 (32.3)	30/93 (32.3)	0.99
Hypertension	673/1586 (42.4)	315/831 (37.9)	0.03	74/192 (38.5)	34/93 (36.6)	0.75
Current or ex smoker	1064/1468 (72.5)	507/747 (67.9)	0.02	127/174 (73.0)	56/84 (66.7)	0.30
Radial access	994/1745 (57.0)	810/1119 (72.5)	0.001	142/226 (62.8)	101/125 (80.8)	0.001
Culprit vessel						
LAD	845/1959 (43.1)	511/1235 (41.4)	0.33	86/220 (39.1)	39/125 (31.2)	0.14
CX	305/1959 (15.6)	190/1235 (15.4)	0.89	38/220 (17.3)	24/125 (19.2)	0.29
RCA	895/1959 (45.7)	546/1235 (43.3)	0.21	112/220 (50.9)	69/125 (55.2)	0.44
Peripheral Artery Disease	69/1586 (4.4)	13/831 (1.6)	0.001	8/192 (4.2)	0/93 (0)	0.05
Previous CVA	38/1586 (2.4)	13/831 (1.6)	0.18	3/192 (1.6)	2/93 (2.2)	0.72
History of renal disease (creatinine > 220 umol/l or dialysis)	21/1726 (1.2)	11/1033 (1.1)	0.72	2/199 (1.0)	0/110 (0)	0.29
Previous myocardial infarction	202/1675 (12.1)	136/958 (14.2)	0.12	27/190 (14.2)	12/100 (12.0)	0.60
Previous PCI	161/1861 (8.7)	105/1032 (10.2)	0.17	18/212 (8.5)	7/104 (6.7)	0.59
Previous CABG	32/1867 (1.7)	21/1048 (2.0)	0.57	3/211 (1.4)	1/103 (1.0)	0.74
Cardiogenic shock	93/1886 (4.9)	72/1089 (6.6)	0.054	6/216 (2.8)	4/111 (3.6)	0.74

Table 2: Frequencies of GPI use in primary PCI patients.

Cohort	GPI use pre-guideline n (%)	GPI use post-guidelinen (%)	P value
Main cohort	587/1385 (42.4)	628/898 (69.9)	<0.001
Local sub-cohort	100/232 (43.1)	93/141 (66.0)	<0.001
No Morphine	29/66 (43.9)	16/27 (59.3)	0.18
Morphine	68/160 (42.5)	75/110 (68.2)	<0.001

GPI: glycoprotein IIb/IIIa receptor antagonist (abciximab or tirofiban).

Outcomes

85 of 3224 patients underwent re-PCI within 30 days, in whom 33 cases of definite stent thrombosis were identified (1.0%). 26 stent thrombosis events occurred in the cohort before the introduction of the guideline (26/1973; 1.3%) compared with 7 stent thrombosis events (7/1251; 0.6%) occurring after the introduction of the new guideline (p=0.037, log-rank test)(Figure 1A). The majority of stent thrombosis events (29/33) were acute (i.e. occurring within 24 hours) with fewer events post-guideline compared with pre-guideline (P = 0.037, log-rank test)(Figure 1B). For 30 out of 33 stent thrombosis patients, details on morphine use were available: 27/30 (90%) patients had received morphine, of whom 23/27 (85.2%) had not received adjunctive GPI. No significant difference in 30-day mortality was observed between the pre- and post-guideline group (5.9% vs. 7.3%, p=0.13).

When stratified for GPI use rather than time period, 5/1217 (0.4%) of patients receiving GPI suffered a stent thrombosis vs. 28/1080 (2.6%, p<0.0001) of patients who did not receive GPI (Table 3).

Table 3: 30-day outcomes according to era or use of GPI.

	Pre-guideline group n (%)	Post-guideline group n (%)	P value
Stent thrombosis	26/1973 (1.3)	7/1251 (0.6)	0.037
All-cause mortality	117/1973 (5.9)	91/1251 (7.3)	0.13
	No GPI n (%)	**GPI n (%)**	**P value**
Stent thrombosis	28/1080 (2.6)	5/1217 (0.4)	<0.0001
All-cause mortality	63/1080 (5.8)	88/1217 (7.2)	0.18

P values are derived using log-rank test.

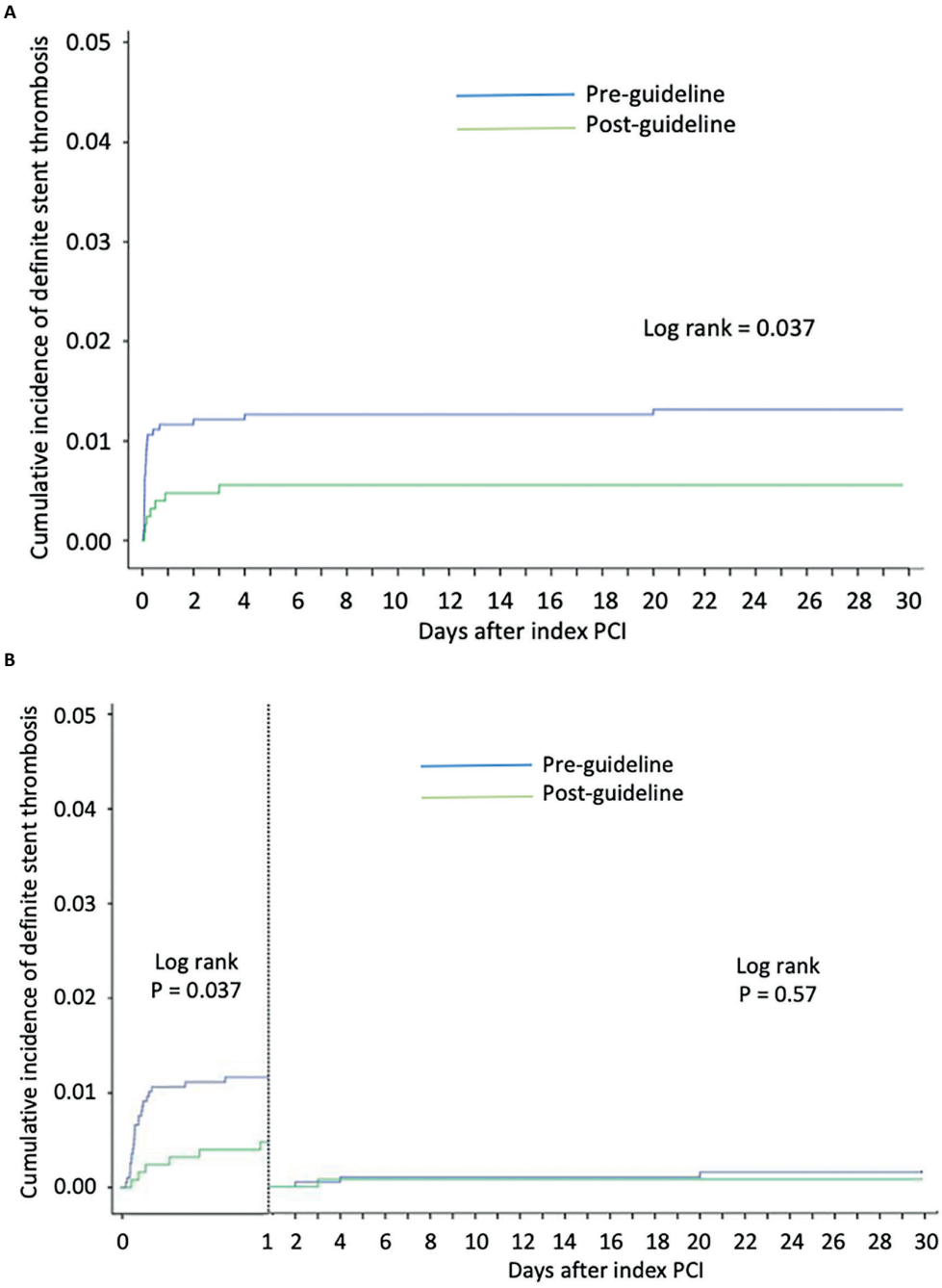

Figure 1: Rates of definite stent thrombosis pre- and post-introduction of local guideline.

Bleeding rates in local subgroup

2387 patients were transferred back to their local hospital following their primary PCI procedure. Of the remaining 937 patients, a total of 374 patients were included in the bleeding analysis (Figure 2). Details regarding GPI use were available in all patients and details regarding morphine use were available in 363 of 374 patients (97.1%). Baseline characteristics were similar to the overall cohort (Table 1). Following introduction of the institutional guideline, GPI use increased from 42.9% to 66.4%. Any GUSTO bleeding occurred in 17.6% of patients pre-guideline and 13.5% of patients post-guideline (p=0.29) and GUSTO moderate or severe bleeding occurred in 1.7% and 2.8%, respectively (p=0.47).

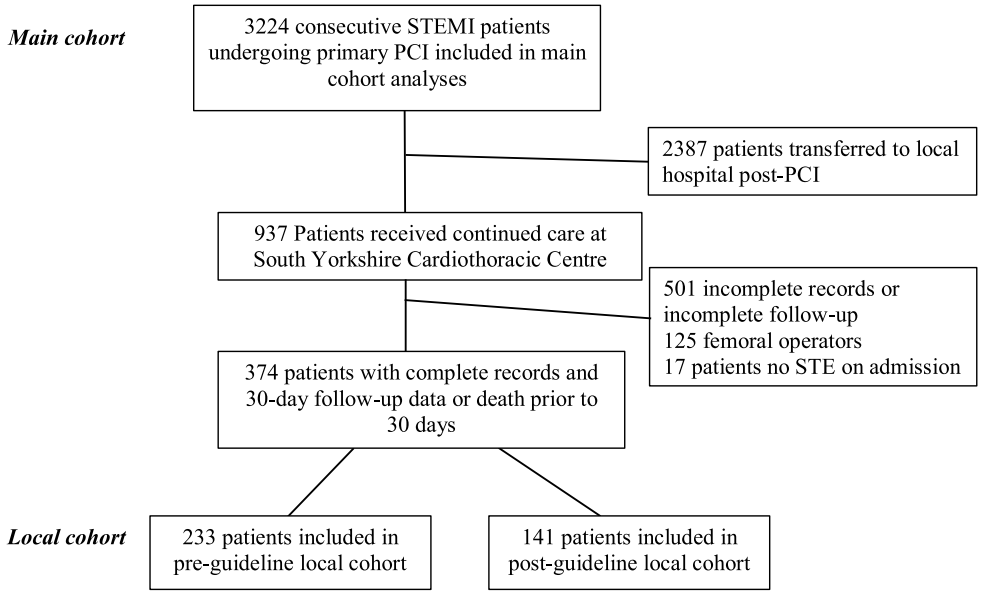

Figure 2: Flow Chart of Patient Selection.

PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; STE, ST elevation.

In GPI-treated patients during either time period, any GUSTO bleeding was more frequently observed compared with patients not treated with GPI (21.8% vs. 10.0%, respectively; p=0.002) but differences in GUSTO moderate or severe bleeding were numerically but not statistically significant (3.1% vs. 1.1%; p=0.29). Despite the aim of limiting differences in radial access use between the two time periods, there was an increase in use of radial access in the post-guideline period (Table 1).

Table 4: Bleeding rates in local sub cohort according to era, GPI use and protocol-guided therapy.

	Pre-guideline group n (%)	**Post-guideline group n (%)**	**P value**
Any GUSTO bleeding	41/233 (17.6)	19/141 (13.5)	0.29
GUSTO moderate or severe bleeding	4/233 (1.7)	4/141 (2.8)	0.47
	No GPI n (%)	**GPI group n (%)**	**P value**
Any GUSTO bleeding	18/180 (10.0)	42/193 (21.8)	0.002
GUSTO moderate or severe bleeding	2/180 (1.1)	6/193 (3.1)	0.29
	Guideline-based GPI use n (%)	**Not guideline-based GPI use n (%)**	**P value**
Any GUSTO bleeding	24/172 (14.0)	33/192 (17.2)	0.40
GUSTO moderate or severe bleeding	2/172 (1.2)	6/192 (3.1)	0.20

Discussion

The introduction of a new guideline in our centre has led to a 65% relative increase of GPI use in patients with STEMI undergoing primary PCI. There was a significant decrease in the number of definite stent thrombosis cases after the introduction of the new guideline. Overall, a significantly lower incidence of stent thrombosis was observed in GPI-treated patients. The majority of patients suffering a stent thrombosis had received morphine but not adjunctive GPI. More bleeding events were observed with GPI use but there was not a statistically significant increase in moderate-to-severe GUSTO bleeding. The increased risk of major bleeding with GPI is well documented and consequently this strategy may not be the optimal means of preventing acute stent thrombosis in morphine-treated primary PCI patients. Indeed, we have recently conducted a pharmacodynamic study to assess the impact of a bolus and 6-hour infusion of enoxaparin in primary PCI patients as an alternative strategy to routine use of GPI in morphine-treated patients and are currently comparing this against a strategy of routine use of tirofiban with unfractionated heparin (NCT03568838)[16]. Cangrelor is a rational option for providing parenteral $P2Y_{12}$ inhibition pending the absorption of an oral $P2Y_{12}$ inhibitor although a standard 2-hour cangrelor infusion may not be sufficient to cover the period of delayed absorption of the oral inhibitor in all patients and care must be taken if clopidogrel or prasugrel is used as the oral inhibitor since cangrelor can block the binding of clopidogrel and prasugrel active metabolites to the $P2Y_{12}$ receptor.[17, 18]

This observational study is the first to describe the feasibility and outcomes of 'routine' GPI use in morphine-treated patients undergoing primary PCI. Overall, the adherence to the protocol was fair. Whereas the use of GPI has substantially increased after the introduction of the new guideline, still not all morphine-treated patients received adjunctive GPI. This could in part be explained by other factors playing a role in clinical practice, such as patient bleeding risk and possible contra-indications. Equally, other patients received GPI without

being treated with morphine, thus a reflection of other perceived indications for GPI use, such as residual thrombus load after PCI.

Limitations

The observational and retrospective nature of this registry, evaluating the effects of the introduction a new local guideline, implies that treatment strategy was not randomised. Patients were not followed up prospectively and so we cannot be certain that events were not missed. However, since our hospital is the only one providing a PCI service to the surrounding population, we considered that re-PCI rates for non-fatal stent thrombosis at our centre are a reasonable reflection of the impact of a change in protocol on event rates.

A further limitation is that details on bleeding outcomes were only available in a local sub-cohort that was relatively small since a substantial number of patients had been excluded, mostly due to repatriation within 12-24 hours of patients to district general hospitals following primary PCI, and so our analyses are not sufficient to evaluate the safety of increased use of GPI. Selection on the basis of geography is unlikely to alter the finding of this registry other than to reduce the sample size. However, the unavailability of a large number of complete records may have biased the findings and further prospective studies are required for more reliable assessment of bleeding rates. The increased use of radial artery access may have attenuated the effect of increased GPI use on bleeding events. As such, the bleeding data are intended only to provide crude pilot data for planning such studies and also do not provide any guide to the safety of increased GPI use when femoral artery access is used.

Finally, over time between the two observation periods, procedural techniques might have changed. Although adjustment for possible confounding variables was not possible, we assume that changes in procedural techniques were limited, as the total time period (<5 years) of this registry was relatively small. Moreover, as illustrated in Table 1, no major differences with regard to baseline clinical and procedural characteristics were observed between the two cohorts.

Conclusions

This observational study is the first to describe the feasibility and outcomes of ‘routine’ GPI use in morphine-treated patients undergoing primary PCI. Our results suggest that GPI use is highly protective for the occurrence of acute stent thrombosis. Further large-scale registries and clinical trials are needed to further establish the overall risk-benefit of GPI therapy in morphine-treated STEMI patients and to assess alternative strategies for preventing acute stent thrombosis in morphine-treated patients.

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CHAPTER

8.1

Vigorous exercise as a triggering mechanism for late stent thrombosis:

a description of three cases

B. Zwart, T.C. van Kerkvoorde, J.W. van Werkum, N.J. Breet, J.M. ten Berg, A.W.J. van 't Hof

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Abstract

Although (very) late coronary stent thrombosis is a rare complication after percutaneous coronary interventions (PCI), its consequences are devastating with a high morbidity and mortality. Previous studies have identified several clinical, procedural and angiographic characteristics that are associated with stent thrombosis but little is known about the underlying mechanisms that induce, provoke or trigger the of stent thrombosis. In the present paper, we describe three patients who suffered from a stent thrombosis immediately after vigorous exercise. Patient 1 suffered a stent thrombosis (ST) after performing an in-hospital bicycle ergometer test, 6 weeks after an acute coronary syndrome. Patient 2 suffered from ST immediately following his first excessive endurance cycling tour, more than 2 years after myocardial infarction. Patient 3 suffered ST while performing vigorous exercise on a bicycle ergometer in a fitness centre. These findings implicate that ST might be triggered by vigorous exercise, especially in untrained patients. Further research after triggering mechanisms of ST is urgently warranted.

Introduction

Stent thrombosis, and in particular late stent thrombosis, is a feared complication of percutaneous coronary intervention (PCI) because it is associated with considerable morbidity and mortality [1-3]. The observed unusual incidence of late and very late stent thrombosis with the first-generation drugeluting stents has alerted the interventional cardiology society. Several research groups have already identified clinical factors, procedural and angiographic characteristics that are associated with the occurrence of stent thrombosis [1,2,4,5]. However, little is known about the superimposing mechanisms that induce, provoke or trigger the stent thrombosis. We describe three patients who suffered from a late stent thrombosis immediately after vigorous exercise.

Case 1

A 47-year old male with a history of hypertension, hypercholesterolemia, smoking and peripheral arterial disease underwent successful PCI of the right coronary artery (RCA) with two bare-metal stents (Vision!, Guidant, Santa Clara, CA, USA): one in the mid-RCA (3.5*18mm) and one in the distal-RCA (3.0*15mm) because of an acute coronary syndrome (ACS) with minimal elevated troponines. The post-procedural Thrombolysis in Myocardial Infarction (TIMI) flow was grade 3. Two days later, the patient was discharged while on aspirin (100 mg/day) everyday, and a statin and clopidogrel (75 mg/day) for 6 months.

During PCI, two lesions in the Left Anterior Descending (LAD) and in the Marginal Obtuse (MO)-branch of the Ramus Circumflex (RCX) were observed. To objective the significance of these lesions, the patient underwent an exercise stress test (estimated Metabolic Equivalent (MET)[6]: 7) with 99mTc-sestamibi single photon emission computed tomography (SPECT) 6 weeks after PCI, while he was still on dual antiplatelet therapy. The patient had not performed strenuous exercise since his PCI. Thirty minutes after this exercise-test, he developed an acute infero-posterior myocardial infarct and underwent a coronary angiography demonstrating a thrombotic occlusion in the proximal stent in the RCA. The occlusion was successfully re-opened with balloon angioplasty and adjunctive abciximab therapy. After the procedure there was a TIMI-III flow. The maximal Creatine Kinase (CK)/ Creatine Kinase isoenzyme MB (CKMB) was 617/ 54 U/L. His systolic ejection fraction after the stent thrombosis remained 450% and 2 days later the patient left the hospital in good clinical condition.

Case 2

A 45-year old man with a history of non-insulin dependent diabetes and a family history of coronary artery disease (CAD) underwent successful PCI of the mid LAD as well as a 80% stenosis in the first diagonal branch with Taxus stents (Boston Scientific, Natick, MA,

USA) (2.75*32 in the mid-LAD, 2.25*12 in the first diagonal branch) because of an acute ST-segment elevated myocardial infarction (STEMI). The TIMI flow was grade 3 and his hospitalization was uneventful. He was discharged on aspirin (for a lifetime), a beta-blocker, oral anti-diabetics and clopidogrel 75mg for the duration of at least 6 months.

More then 2 years later, while he was on single antiplatelet therapy with aspirin, he made his first excessive endurance cycling tour, although he had been training on his bicycle several times before. He travelled 130km within 4,5 hours, corresponding with an average speed of 25–30 km/hour (estimated MET: 7). Fifteen minutes after completion, he experienced chest pain and was presented to an interventional centre. Coronary angiography showed a thrombotic occlusion of the stent in the LAD. The stent thrombosis was successfully treated with balloon angioplasty and adjunctive abciximab therapy and after the procedure there was a TIMI-III flow. The maximal CK/CKMB was 1242/123 U/L. His systolic ejection fraction after the stent thrombosis remained >50%. He was discharged at day 3 on aspirin, beta-blocker, ACE-inhibitor, oral antidiabetics and clopidogrel 75mg daily for a year.

Case 3

A 40-year-old man with a history of insulin dependent diabetes, hypercholesterolemia and a family history of coronary artery disease (CAD) underwent successful PCI of the bifurcation of the mid LAD and the first diagonal branch with a Taxus! stent (3.5–16mm) because of a non-STEMI myocardial infarction. The post procedural TIMI-flow was grade 3 and 2 days later he was discharged with aspirin for a lifetime, a statin, ezetimibe, oral anti-diabetics and clopidogrel 75mg for the duration of at least 6 months.

Approximately 6 months later, his cardiologist agreed to discontinue the clopidogrel according to ACC/AHA guidelines by that time. In addition, he was encouraged to increase the frequency of his weekly exercise. Six days after his clopidogrel cessation, the patient visited a fitness-centre and performed strenuous spinning (indoor cycling on a ergometer, estimated MET: 7) for the first time. He reported having a moderate physical condition at that time. During the final phase of the spinning program (after ±45 minutes) he suddenly experienced chest pain and lost conscience. He was adequately resuscitated by fitness-instructors. Upon arrival of the ambulance, he was diagnosed with ventricular fibrillation and he was successfully defibrillated. He was transferred to our catheterization laboratory by ambulance. Coronary angiography showed a thrombotic occlusion in the first diagonal branch that was successfully treated with balloon angioplasty and adjunctive tirofiban therapy with a post-procedural TIMI-flow was 3 and the maximal CK/CKMB was 870/63 U/L. The systolic ejection fraction after the stent thrombosis remained >50% and 1 day later the patient was discharged on aspirin, a statin, ezetimibe, oral anti-diabetics and clopidogrel 75mg therapy for the duration of one year.

Discussion

Abrupt vessel occlusion caused by a stent thrombosis is a feared complication after PCI and is associated with a considerable high morbidity and mortality. Stent thrombosis is not a rare complication, with an estimated occurrence rate between 2–5%. Given the enormous absolute number of total PCIs performed worldwide, stent thrombosis imposes an enormous risk for a large group of patients, Traditionally, stent thrombosis can be categorized in four different groups according to the time elapsed since implantation. The categories include acute (<24 hours), subacute (>24 hours and <30 days), late- (>30 days and <1 year) and very late stent thrombosis (beyond 1 year) [7]. Recently, there has been much debate about the difference in incidence of in particular late and very late stent thrombosis between different stent types, with the first generation of Drug-Eluting Stent (DES) being the most dreadful ones [8].

Daemen et al. demonstrated that the incidence of DES thrombosis was 1,9% after a mean follow-up period of 3 years [2]. From these patients 60% suffered an early stent thrombosis (<30 days), 24% experienced a late stent thrombosis (51 year) and 16% suffered a very late stent-thrombosis (41 year) after a follow-up of 1180 days. Importantly, late stent thrombosis continued to occur over time with a linear incidence-slope of 0.6% per year.

Similarly, Wenaweser and colleagues demonstrated that the incidence of bare-metal stent thrombosis was 1,6% after a mean follow-up period of approximately 2 years [9]. From all the patients with a Bare Metal Stent (BMS) thrombosis, early stent thrombosis occurred at a rate of 75%, late stent thrombosis at a rate of 23% and very late stent thrombosis at a rate of 2%. Importantly, a linear slope in the cumulative incidence of very late stent thrombosis was not seen.

Multiple studies have already identified several factors that are associated with both BMS and DES thrombosis. These include: acute coronary syndromes as indication for PCI, bifurcation stenting, diabetes mellitus, renal failure, stenting in the proximal LAD, impaired left ventricle ejection fraction, small stent diameter and total stent length [1,2,4,5,10]. Furthermore, several important mechanisms that are associated with late DES thrombosis have recently been revealed, including (1) lack of or delayed endothelialisation, (2) (late) incomplete stent malaposition, (3) polymer/drug hypersensitivity reactions, and (4) premature discontinuation of (dual) antiplatelet therapy [11-15].

Nonetheless, thus far, little is known about the superimposing triggering mechanisms that provoke a stent thrombosis on a certain time point. Several studies in myocardial infarction indicate that a considerable number of these major adverse cardiac events are not random events but rather can be triggered by the daily activities of the patient which ultimately can

cause the rupture of an atherosclerotic plaque. In addition, other factors might play a role, as is reflected by a morning increase in cardiac events. However, very little is known about superimposing factors potent to provoke stent thrombosis. In the present report, which is hypothesis generating in nature, we describe three patients with a late stent thrombosis during or direct after strenuous exercise. Although all three patients were characterized by several major risk factors which definitely puts these patients at an increased a priori risk for the development of stent thrombosis (Case 1: ACS and long total stent length. Case 2: diabetes, ACS, bifurcation-lesion, LAD-lesion, clopidogrel cessation and long total stent-length. Case 3: diabetes, ACS, bifurcation-lesion, clopidogrel cessation and LADlesion), the triggering mechanism causing this acute event seems to be vigorous exercise.

Multiple studies have demonstrated that habitual physical activity reduces the progression of atherosclerosis, decreases platelet reactivity and thus the incidence of atherothrombotic events in patients with coronary artery disease (CAD) [16]. Vigorous exercise, however, might also increases the risk of acute myocardial infarction (AMI) and suddencardiac death (SCD), with or without CAD [17,18].

The pathophysiological background of vigorous exercise provoked stent thrombosis is not yet fully elucidated, but factors include exercise induced coronary-artery spasm, increased heart rate and blood pressure, increased sympathetic activity (including levels of catecholamines) and vagal withdrawal, increased thrombin generation, increased vessel-wall stress and heightened platelet reactivity [19-22].

Several studies investigated the paradoxical effects of moderate exercise and vigorous exercise with regard to platelet function. The opposite effects of these levels of physical intensity have now been well established [23-25]. This evidence suggests that moderate exercise suppresses platelet reactivity and increases fibrinolysis. Conversely, vigorous exercise – especially in untrained individuals – enhances both platelet reactivity and coagulation, whereas it promotes fibrinolysis as well. Aforementioned affects are mediated by several complex mechanisms, including epinephrine, !2-adrenergic receptor expression, von Willebrand factor platelet interaction, GPIIb/IIIa interaction, P-selectin expression of platelets and the release of nitric oxide. From this perspective, moderate-intensity activity can be considered safe, whereas vigorous exercise might lead to a prothrombotic state ultimately leading to the formation of a thrombus.

Remarkably, all patients are relatively young. Although the present report is a series of case reports and thus no general conclusions can be drawn, this observation might be related to more frequent engagement of younger patients in rehabilitation programs and more frequent performance of vigorous physical exercise in general by younger people. Consequently, the question arises whether exercise induced events like stent thrombosis are

unique to young people. However, this is not likely, as several large studies after triggering mechanisms of myocardial infarction do not report this phenomenon. In addition, the young age of these patients is not reflected by their risk profiles and consequent 'biological age'.

Should we discourage exercise for patients with an implanted coronary stent?

The answer to this question is rather difficult and needs to be further nuanced. Regular physical activity is widely advocated in the general population [26], because ample evidence suggests that physical exercise delays the development of atherosclerosis, reduces platelet reactivity and decreases the incidence of coronary heart disease (CHD) events. However, it seems that vigorous exercise – not moderate exercise – can also acutely increase the risk of AMI and SCD. Of special importance in this context is the observation that regular exercise lowers the base-line risk of trigger-induced myocardial infarction [18,27,28].

In our opinion, patients should be encouraged to perform physical activity after myocardial infarction or stent implantation, because the beneficial effects of exercise training in the secondary prevention of coronary artery disease are well established [29]. However, caution is warranted when patients plan to perform vigorous exercise, especially when untrained. According to the guidelines of the American College of Cardiology (ACC)/American Heart Association (AHA) [30], these patients should undergo an exercise test under supervised conditions, before starting to perform vigorous exercise.

Furthermore, physicians play an important role in advising the patients to perform physical exercise after stent implantation, adapted to the individual physical condition of the patient. Physicians and patients might make use of standardized indicators of physical activity (e.g. metabolic equivalent, MET [6]) and mobile devices like heart rate monitors to quantify and compare the intensity activity in order to guide in this complex manner.

In conclusion, vigorous exercise might trigger ST. Further research should be directed towards the relationship between stent thrombosis and possible triggering mechanisms. Until then, patients should undergo a thorough medical evaluation prior to increasing vigorous physical activity. Risk-stratification should be based upon risk factors that are associated with the development of a stent thrombosis as well as the intensity of the activity and the level and frequency of regular exercise.

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CHAPTER

8.2

Time does not heal every wound:

Coronary stent thrombosis of a bare-metal stent more than one decade after its implantation

A.C. Zomer, B. Zwart, J.W. van Werkum, M.J. Suttorp

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Abstract

In the present report, we describe a unique case of very late stent thrombosis with a bare-metal stent that occurred more than a decade after stent implantation. Potential explanations for the late stent thrombosis are non-compliance to aspirin, late acquired malapposition of the stent, progression of atherosclerosis or in-stent restenosis. In our patient, none of these explanations seems to have played a role. Although the occurrence of (very) late stent thrombosis is not uncommon with drug-eluting stent (DES), it is rather unusual with bare-metal stent (BMS). Nevertheless, cardiologists should be aware of the potential complication of late stent thrombosis, even with bare-metal stents.

Introduction

Coronary stent thrombosis is the major downside of percutaneous coronary intervention and is associated with high morbidity and mortality [1–4]. Stent thrombosis is usually classified according to the time elapsed since implantation. Four different categories are routinely used: acute (<24 hours), subacute (>24 hours and <30 days), late- (>30 days and <1 year) and very late stent thrombosis (beyond 1 year) [5].

The introduction of the drug-eluting stents (DES) in 2004 has drastically reduced the incidence of restenosis but recent studies point out that stent thrombosis with DES continues to occur beyond the 1-month time-frame.[4,6] Although DES have proven their safety and efficacy over a longer period (4 years), it appears that late ST occurs more frequently in DES. Despite the controversy regarding the true incremental risk that is associated with late (beyond 30 days) and very late (beyond 1 year) DES thrombosis, it must be noted that little data is available on the (very) long-term safety of BMS. However, several more recent large studies confirm that late ST occurs in BMS as well, but at a lower rate as compared with DES. [7,8] The incidence of bare-metal stent (BMS) thrombosis is estimated to be between 1–2% and it occurs in the majority of cases within the first month after stent implantation. [1,2,7,8]

As we describe in the following case report, even 10 years of uneventful living with a BMS cannot guarantee its patency for a lifetime.

The case

A 55-year-old man with a history of smoking and hypercholesterolemia was admitted to our hospital because of an inferior-posterior myocardial infarction on November 22 1995. He was successfully treated with streptokinase and aspirin, which resulted in a complete resolution of the ST-elevations on the electrocardiogram. The maximal CPK/MB was 502/23 U/l. Echocardiography showed a normal cardiac function and a calculated ejection fraction of 460%. Two weeks later he was brought to the catheterization laboratory because of residual angina pectoris complaints. Coronary angiography revealed a subtotal occlusion of the mid right coronary artery (RCA). Subsequently, he underwent successful PCI of the mid RCA with the implantation of three AVE stents (Medtronic; all 4.0_18 mm). The final result was without residual stenosis or evidence of dissection. The next day, the patient was discharged under aspirin (100 mg/day), acenocoumarol and statin therapy.

The patient remained asymptomatic for the next 10 years while he was on aspirin and a beta-blocker (acenocoumarol was discontinued in April 1996).

In November 2005, he was admitted to our hospital because of an acute onset of chest pain. He was transferred to the cathlab for emergency PCI. Angiography revealed a thrombotic occlusion of the stents in the RCA (Figure 1). The thrombotic occlusion was treated with an aspiration-catheter followed by balloon-angioplasty and concomitant glycoprotein IIb/IIIa therapy. Complete ST-resolution was observed at 30 minutes post-PCI and the maximal CPK/MB-rise was 546/62 U/l (normal CPK 0-175). Echocardiography showed akinesia of the inferior wall and a calculated ejection fraction of 55%. The patient was discharged on day 4. He was prescribed lifelong aspirin, clopidogrel for at least 1 year, a beta-blocker, an ACE inhibitor and a statin.

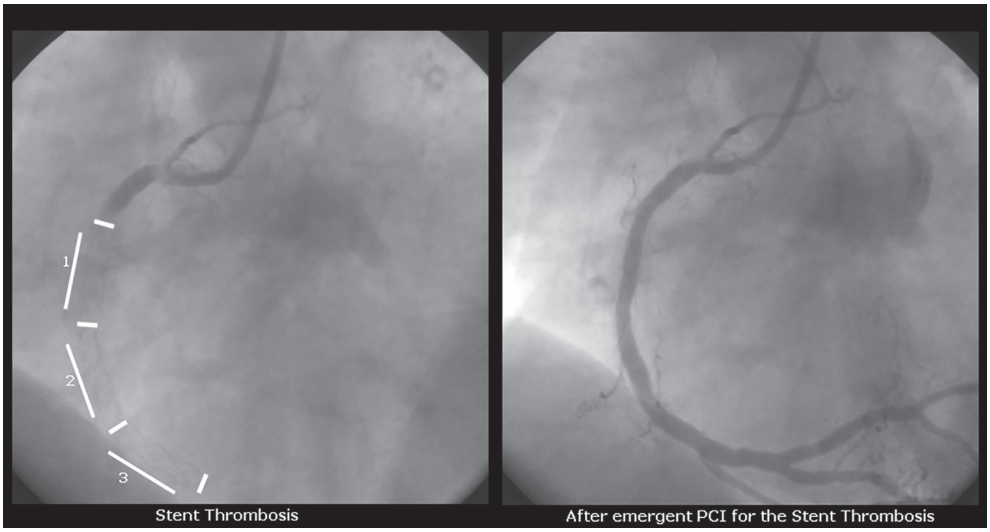

Figure 1:

Coronary angiograms of the patient. The left panel illustrates the right coronary artery (RCA) with the thrombotic occlusion in the AVE stents. The right panel shows the RCA after emergent PCI with aspiration and plain old balloon angioplasty.

Approximately one year later (after cessation of the clopidogrel therapy), the patient was asked to visit our outpatient clinic for a thorough evaluation of his platelet function and his response to aspirin and clopidogrel. Platelet function evaluation was performed by means of ‘‘classical’’ light transmittance aggregometry (using the APACT 4004 aggregometer, LABitec, Germany) before and 6 hours after a 600mg loading dose of clopidogrel. Adenosine diphosphate (ADP; final concentrations: 5 and 20 mmol/L) and arachidonic acid (AA; final concentration: 0.5 mg/L) were used as the agonists. Spontaneous aggregation was also recorded. Remarkably, a heightened residual platelet reactivity despite aspirin and clopidogrel therapy was still present (Figure 2) [9].

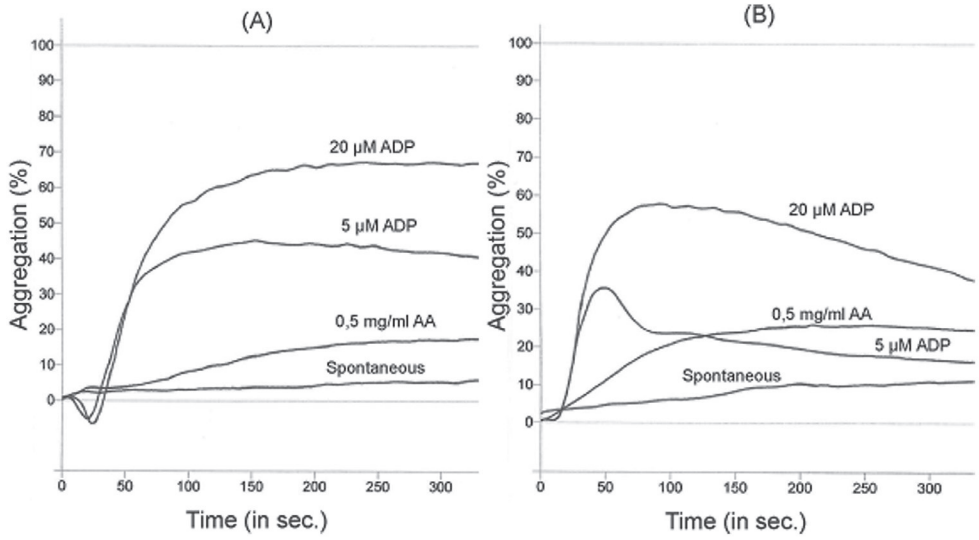

Figure 2:

Light transmission aggregation curves before (left panel) and after (right panel) a 600mg loading dose of clopidogrel. Different agonists (5 mmol/L and 20 mmol/L ADP, 0.5 mg/ml AA) were used to stimulate the platelets. Spontaneous aggregation was also recorded. ADP=adenosine diphosphate. AA=arachidonic acid.

Discussion

Stent thrombosis is a very serious complication following PCI. Multiple determinants may contribute to the occurrence of a stent thrombosis, including clinical factors (such as diabetes mellitus, renal failure, low ventricular ejection fraction), lesion specific factors (such as total occlusions, bifurcation lesions and calcified lesion), and procedural factors (such as long stents, multiple stent implantation, small stent diameter, residual dissection and complex PCI-procedures) [1–3,6,10–12]. Furthermore, stent thrombosis can be the result of (premature) antiplatelet therapy discontinuation and non-responsiveness to platelet inhibitors.[3]

The possible higher occurrence of very late stent thrombosis with DES as compared to BMS has alarmed the interventional community. ‘‘Real world’’ estimates of its incidence derived from unselected cohort registries varies between 1 and 5% and it is obvious that these figures are slightly higher than the incidence that was reported in the initial randomized controlled trials with DES versus BMS [4,6]. This observation could be partly explained by the off-label use of DES and its use for more complex lesions. In addition, several specific – for DES only – pathophysiological mechanisms have been suggested to be responsible for very late DES thrombosis, including:

1. delayed endothelialization [13];
2. (late) incomplete stent malapposition [14];
3. polymer/drug hypersensitivity [15]; and
4. premature discontinuation of (dual) antiplatelet therapy [3,6].

Surprisingly, little data is currently available about the occurrence of very late stent thrombosis with the conventional BMS outside the context of brachytherapy. Moreover, there have been no studies dealing specifically with the incidence of very late bare-metal stent thrombosis.

In the present report, we describe a unique case of very late stent thrombosis with a BMS that occurred more than a decade after the stent implantation. Importantly, no other coronary intervention had taken place in the 10-year interval.

In spite of the heightened platelet reactivity phenotype despite aspirin and clopidogrel, we could not identify any potential explanations for the stent thrombosis in our patient [16–18]. Some data are not available which is a limitation of the present report. Possibly, late acquired malapposition of the stents could have taken place but we did not perform an intravascular ultrasound (IVUS) to exclude or confirm this possibility.

Perhaps, despite overstenting the atherosclerotic lesion, progression of atherosclerosis of the neoendothelium under the BMS could have formed new vulnerable plaques that might have ruptured?

In-stent restenosis is very unlikely to have played a role, as the patient was active and asymptomatic until the acute myocardial infarction occurred. In addition, in-stent neointima proliferation was only moderate on visual estimate (maximal stenosis 30%). The possible reason for this extreme late BMS thrombotic occlusion therefore remains unknown. Nevertheless, this case clearly demonstrates that BMS can also occlude late. Therefore, although very late thrombosis is supposed to occur more frequently after DES placement, it may be unrelated to DES-related substances such as polymers and/or drugs. Proper randomized data from long term follow-up after DES and BMS placement have to demonstrate the true incidence of very late stent thrombosis in patients treated with DES and/or BMS.

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CHAPTER

8.3

3-Dimensional Optical Coherence Tomography Imaging in Early Coronary Stent Thrombosis

K. Teeuwen, B. Zwart, J.W. van Werkum, M. Joner, J.M. ten Berg

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A 45-year-old man presented to our catheterization laboratory with an acute anterior ST-segment elevation myocardial infarction caused by a proximal occlusion of the left descending artery. Two bare-metal stents were implanted with good angiographic results. Besides aspirin and clopidogrel, the patient was treated with abciximab intravenously because of the large thrombus load.

Eight days later, the patient re-experienced severe chest pain, and emergent coronary angiography showed an acute thrombotic occlusion of the recently implanted bare-metal stents. Optical coherence tomography (OCT) was performed after coronary flow was re-established by thrombosuction. The OCT pullback revealed the underlying pathophysiological mechanism that may have caused the subacute stent thrombosis: severe undersizing of the implanted baremetal stents with a large residual thrombus on the naked incomplete apposed stent struts (Fig. 1). After OCT pullback, repeated high-pressure balloon inflations were performed resulting in Thrombolysis In Myocardial Infarction flow grade 3.

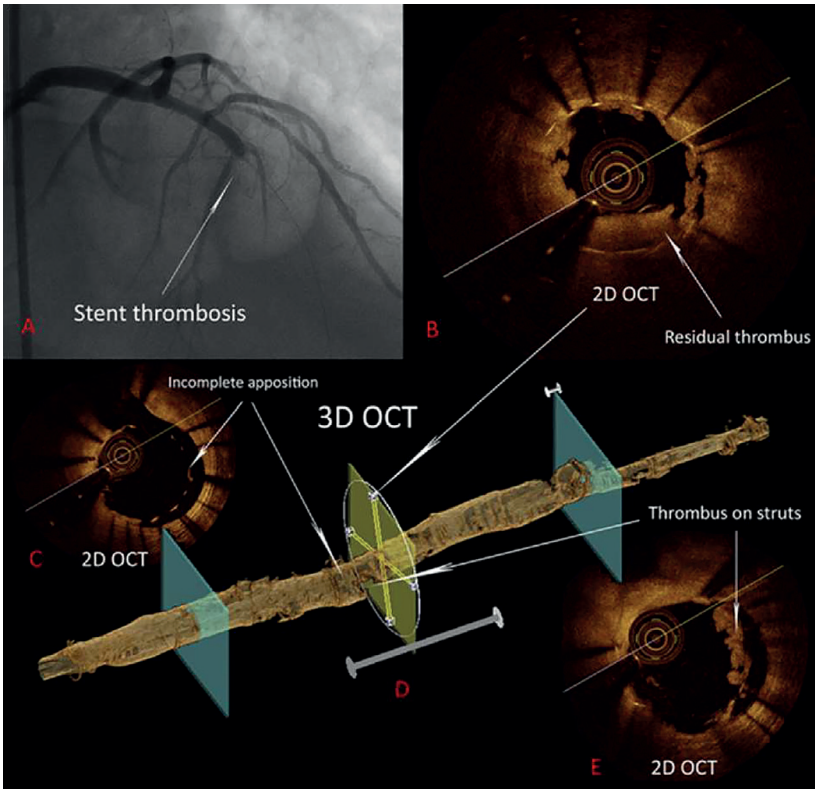

Figure 1: 3D OCT ST.

(A) Coronary angiography: stent thrombosis (ST). **(B)** 2-dimensional (2D) optical coherence tomography (OCT): ST with residual thrombus on stent struts. **(C)** 2D OCT: undersized stent with incomplete stent apposition. **(D)** 3-dimensional (3D) OCT: in the middle, a cavity is seen that correlates to E at 2D OCT. The cavity is caused by laser reflections on the thrombus attached to the incomplete malapposed stent struts. **(E)** 2D OCT: thrombus on stent struts.

Three-dimensional (3D) OCT is a novel technique enabling 3D imaging of the intracoronary lumen. In the present case, the 3D image shows a central cavity, which correlates to thrombus on the incomplete apposed stent struts visualized on 2-dimensional OCT. In the near future, 3D OCT may be a useful tool to guide complex coronary interventions. Further research is imperative to assess the clinical relevance of 3D OCT.

CHAPTER

9

Monitoring antiplatelet therapy in clinical practice:

value and possibilities

Tijdschrift voor Hematologie 2017;14:367-372. Translated from Dutch

Abstract

This paper reviews the concepts of high and low on-treatment platelet reactivity (for aspirin and P2Y12-inhibitors) and its relation with clinical outcomes. The available platelet function tests and the indications for their use are discussed.

Introduction

Aspirin is the oldest antiplatelet drug and is considered as the cornerstone of the treatment of arterial thrombosis. Aspirin prevents platelet activation by irreversibly blocking platelet cyclo-oxygenase 1 (COX1) enzyme and hence preventing synthesis of Thromboxane. Ticlopidine, a P2Y12-inhibitor in the class of thienopyridines was introduced in 1991. It was used as adjuvant treatment modality in acute coronary syndrome (ACS). P2Y12-inhibitors prevent adenosine-diphosphate (ATP) mediated platelet activation by binding to the platelets P2Y12-receptor. Not long after the introduction of ticlopidine, it was succeeded by clopidogrel which had a similar effectivity with fewer side effects. Dual antiplatelet therapy (DAPT) with aspirin and clopidogrel proved to be superior as compared to aspirin monotherapy in preventing atherothrombotic events such as myocardial infarction (MI) and stent thrombosis (ST). Moreover, clopidogrel is now used in the treatment of cerebrovascular accidents and peripheral artery disease.

In the last decade, the P2Y12-inhibitors ticagrelor and prasugrel were introduced, which were both superior to clopidogrel in terms of ischaemic outcomes, but at the cost of a higher bleeding risk. These more potent drugs are now standard care in the treatment of ACS, whereas clopidogrel is still preferred in percutaneous coronary intervention (PCI) for stable coronary artery disease.

The use of more potent P2Y12-inhibitors has illustrated the delicate balance of thrombosis versus bleeding. In recent years, multiple tests have been developed to monitor (residual) platelet reactivity. This review article discusses indications and possibilities for platelet function testing (PFT) in clinical practice.

Available platelet function tests

The pharmacodynamic response to the aforementioned antiplatelet drugs have shown considerable variability in clinical practice resulting in variability in the degree of antiplatelet drug response. An impaired response to the treatment of antiplatelet drugs has been named “resistance” or, more accurately, high on-treatment platelet reactivity (HPR). On the other hand, low residual platelet reactivity (low on-treatment platelet reactivity; LPR) has been described as well and correlates with higher risk of bleeding. Multiple platelet function tests are available and the methods for assessing platelet function vary between these tests. Some tests assess the process of platelet aggregation itself, whereas other tests measure a surrogate for platelet aggregation, such as changes in the P2Y12-receptor-pathway.

An overview will be presented of the most commonly used assays. It must be noted that there is a moderate correlation between the different tests and direct comparisons between

these tests are scarce. In this overview, we will focus on the assays measuring the response to P2Y12-inhibitors, as they are considered most reliable and have been validated well. The following tests will be discussed: light transmittance aggregometry (LTA), VerifyNow©, the Multiplate© and the Vasodilator-Stimulated Phosphoprotein (VASP) Phosphorylation Assay. Commonly used cut-off values have been described in relevant literature, although optimal cut-offs vary between studies and have changed throughout the years. Table 1 provides an overview of the different tests and their characteristics.

Table 1:

Method	Sample type	Correlation with LTA	Practical considerations	Costs
LTA	Plasma	-	Rather complex and labor intensive	Low
VerifyNow	Whole blood	Very good	Very easy to use	High
Multiplate	Whole blood	Good	Easy to use	Moderate
VASP	Whole blood	Good	Rather complex	High

LTA

Classical light transmittance aggregometry (LTA) has been considered the gold standard for measuring platelet reactivity. LTA uses platelet rich plasma and is based on the simple principle of optical detection. As platelet aggregation occurs (in response to an agonist), the sample becomes more translucent and light transmission increases. Platelet aggregation is expressed from 0% to 100% (the latter corresponding to maximal platelet aggregation), or as poor, moderate and good. With the use of various agonists (such as ADP, epinephrine and collagen), various activation pathways can be monitored. The use of different ADP concentrations has been described in previous studies. When testing the efficacy of antiplatelet drugs, it is common not to use the lower ADP concentrations (lower concentrations are used in the diagnostics of bleeding disorders). In clinical practice, either 5µM or 20 µM ADP are used. In the POPular study, comparable results were obtained with using either 5µM or 20µM ADP, although slightly different cut-offs (ROC-AUC 0.63 and 0.62, respectively). One drawback of LTA is the lack of standardization between laboratories. Furthermore, it is a rather complex and therefore a labor-intensive method.

VerifyNow

The VerifyNow system (Accumetrics, San Diego, California, US) is a point-of-care system. Similar to LTA, it is based on light transmittance but uses whole blood. The VerifyNow system is a closed system and therefore does not need additional blood handling. Three cartridges are available in order to test the effect of either aspirin, P2Y12-inhibitors or alpha2b-beta3 (Glycoprotein IIbIIIa antagonists (GPI). The agonists used in each respective assay are arachidon acid, ADP and thrombin activating peptide (TRAP), respectively. Tests results are reported as “reaction units” (aspirin reaction units (ARU), platelet reaction units (PRU) and platelet aggregation units (PAU), respectively) and higher values correspond inversely

to the degree of platelet aggregation. The VerifyNow is considered a reliable test which corresponds well to LTA. Moreover, it is a user-friendly test and therefore very suitable in clinical practice.

Multiplate

The principle of Multiplate is based on impedance platelet aggregometry, i.e. it measures increases in electrical resistance (impedance). Activated platelets attach to two independent sensors in the cuvette, leading to an increase in impedance. Multiplate uses whole blood and, depending on the used agonist, the effect of either aspirin (ASPI-test) or P2Y12-inhibitors (ADP-test) can be monitored. Results are expressed as "arbitrary aggregation units" (AU). Multiplate has been shown to provide valuable prognostic information in clopidogrel treated patients. It correlates well to LTA, but only moderate with the VerifyNow assay. Multiplate requires slightly more skill and training in clinical practice, but at a lower cost than the VerifyNow system.

Vasodilator-Stimulated Phosphoprotein Phosphorylation Assay (VASP)

The vasodilator-stimulated phosphoprotein is an intracellular regulatory protein. Under resting conditions, VASP is not phosphorylated, but when the P2Y12-receptors are activated by ADP, the phosphoprotein becomes phosphorylated which in turn activates the GpIIbIIIa receptor on the platelet surface. Flow cytometry determines the degree of phosphorylation and provides an indirect estimation of the degree of P2Y12-inhibition. As the test is restricted to the use of P2Y12-inhibitors, it can be used even in the presence of GPI. Although the test correlates well to LTA, it demands specific knowledge and specialized staff. Therefore, it use in clinical practice is limited. A specific advantage of the VASP assay is that the test can be executed at a later time point.

Variability in the response to aspirin and clopidogrel

The prevalence of HPR for patients treated with aspirin has been estimated in previous studies to be between 5 and 65%, depending on the used methods and study population. However, many studies assessed predominantly non-COX1-specifix platelet reactivity. However, platelets possess COX2 to a much lesser extent than COX1. Moreover, aspirin primary targets COX1 and targets COX2 only in much higher doses. Monitoring platelet reactivity in aspirin treated patients therefore often yields non-specific results and overestimated the prevalence of aspirin HPR, whereas the assays specifically monitoring COX1 demonstrate a consistent platelet inhibitory effect of aspirin. Therefore, it is now believed that true 'aspirin resistance' is practically non-existent. Consequently, in clinical practice, there is no role for response to aspirin and it is not recommended by the guidelines. Measuring platelet reactivity in aspirin treated patients will therefore no further be discussed.

The variability in the response to clopidogrel, however, has been documented extensively and consistently. The prevalence of HPR is estimated to be around 25% and therefore a substantial proportion of clopidogrel treated patients exhibit HPR. Multiple studies have demonstrated an association with (recurrent) atherothrombotic events in ACS patients and patients who underwent PCI. LPR has been shown to be clinically relevant as well and Sibbing et al. showed a threefold increase associated with LPR in a cohort of 2,533 PCI.

The variability in P2Y12-inhibition with clopidogrel can be explained by the fact that clopidogrel is a prodrug which has to be converted to an active metabolite. This metabolization process takes place in the liver by the cytochrome-P450-system in two steps involving the CYP2C19-enzym. Various genetic polymorphisms have been documented. The 'loss-of-function'-alleles CYP2C19*2 and CYP2C19*3 are most prevalent and these polymorphisms have been independently associated with ischemic outcomes. On the other hand, the 'gain-of-function'-allele CYP2C19*17 is associated with an increased metabolism of clopidogrel and therefore a lower platelet reactivity.

Variability in platelet reactivity with ticagrelor and prasugrel is far less prevalent than with clopidogrel. Although prasugrel is a prodrug as well which needs to undergo CYP-mediated biotransformation, it only needs one activation step. On the other hand, ticagrelor has instantaneous biological antiplatelet activity and does not need transformation. In a recent study in patients who were switched from clopidogrel to prasugrel or ticagrelor, HPR was found in under 15% of patients. On the other hand, LPR according to conventional definitions, appears to be more prevalent than with clopidogrel. Both prasugrel and ticagrelor are more effective in preventing ischaemic events than clopidogrel, but at the cost of an increase in bleeding.

Indications and evidence for the use of platelet function tests in clinical practice

Both HPR and LPR are prevalent and multiple studies have confirmed the prognostic value of platelet function testing (PFT) with ischaemic and bleeding outcomes, although hampered by standardization of cut-offs for HPR and LPR. Based on these strong prognostic associations, it seems reasonable to determine an individual treatment strategy based on PFT, with the aim of balancing the thrombotic and bleeding risk in the individual patient. In studies, this has been referred to as the therapeutic window between HPR and LPR. Several studies in ACS patients and patients undergoing PCI have investigated whether the use of PFT as standard care improves outcomes (in ischaemic and bleeding terms). Although smaller studies initially suggested that individualizing treatment based on PFT could improve (ischaemic) outcomes, subsequent larger and randomized controlled studies could not demonstrate a benefit. Although most studies did show satisfactory results with regard to platelet aggregation, this did not translate into clinical outcomes (Table 2).

Table 2: Overview of large randomised controlled trials after effect of PFT guided treatment.

Study	Number of patients	Study population	Study design and used PFT	Treatment arm	Ischaemic endpoint	Ischaemic outcomes	Bleeding end point	Bleeding outcomes	Limitations
GRAVITAS	2,214	Stable coronary artery disease and ACS	Verifynow assay in all patients (HPR >230 PRU)	Patients with HPR: 1:1 randomisation to clopidogrel 150 mg vs. 75 mg 1dd	Composite of cardiovascular death, non-fatal myocardial infarction or stent thrombosis	HR 1.01 (p=0.97)	Moderate or severe bleeding according to GUSTO criteria	HR 0.59, p=0.10	• clopidogrel double dosing in monitored group (no use of prasugrel) • low proportion of ACS patients • event rate lower than power calculation
TRIG-GER-PCI	423	Stable coronary artery	Verifynow assay in all patients (HPR >208 PRU)	Patients met HPR: 1:1 randomisation to prasugrel 10 mg 1dd vs clopidogrel 75 mg 1dd	Composite of cardiovascular death or myocardial infarction	0 vs 0.5% (0 vs 1 patient)	Non-CABG related major bleeding according to TIMI criteria	1.4 vs. 0.5% (3 vs. 1 patients)	• very low event rate • inclusion of low risk patients
ARCTIC	2,440	Stable coronary artery disease and ACS	1:1 randomisation to standard care vs. PFT monitored therapy with VerifyNow (HPR <235 or ≤15% inhibition; LPR <90% inhibition)	Standard care: clopidogrel (or prasugrel) at discretion of clinician Monitored group: HPR: prasugrel 10 mg or clopidogrel 150 mg. NPR or LPR: clopidogrel 75 mg	Composite of death, myocardial infarction, stent thrombosis, CVA or urgent revascularisation	HR 1.13, p=0.10	STEEPLE major or minor bleeding	HR 0.69, p=0.08	• low proportion of ACS patients • majority of patients in monitored group were treated with double dosed clopidogrel
ANTARCTIC	877	ACS patients aged >75 year	1:1 randomisation to conventional therapy vs. monitored therapy with VerifyNow (HPR ≥208 PRU; LPR ≤85 PRU)	Conventional group: prasugrel 5 mg 1dd Monitored group: Standard care: prasugrel 5 mg 1dd; HPR: prasugrel 10mg 1dd; LPR: clopidogrel 75 mg 1dd	Composite of cardiovascular death, myocardial infarction, CVA, stent thrombosis, urgent revascularisation and bleeding according to BARC definitions	HR 1.0, p=0.98	TIMI, GUSTO, STEEPLE, ISTH bleeding events as separate outcomes	All non-significant	• Prasugrel 5 mg was used in the control group • Low proportion of HPR in monitored group • most conversions in monitored group were switch to clopidogrel in LPR patients

However, these studies yielded some important insights, which at the same time emphasized the limitations of these studies. First, most studies included low-risk patients (PCI for stable angina or with a low proportion of ACS patients), whereas the results suggested that its high-risk patients (e.g. diabetes, three-vessel disease or patients with high bleeding risk) who might benefit most from a personalized strategy. Furthermore, most studies increased clopidogrel dosing if HPR was found, rather than switching patients to the more potent P2Y12-inhibitors prasugrel or ticagrelor, which is nowadays recommended by guidelines.

Hence, routine use of PFT in all patients is not indicated, but individual patients with high bleeding and/or ischaemic risk (or risk of stent thrombosis) might benefit by a PFT guided treatment strategy.

Another patient group in which PFT might be beneficial, is represented by DAPT treated patients undergoing (cardiac) surgery. The TARGET-CABG study showed that PFT guided timing of cardiac surgery yielded a 50% reduction in waiting time for the operation, as compared to standard discontinuation regimes. Although clinical outcomes in these studies were similar, this is an important finding, because these patients can often have instable symptoms and urgent surgery is therefore desirable.

In summary, routine PFT in all patients has not been demonstrated to be beneficial. PFT can, however, be useful in specific patient groups or for specific indications:

- Patients with stent thrombosis or other recurrent thrombotic events while on DAPT treatment
- Patients with significant bleeding while on DAPT treatment
- Patients treated with DAPT with both high ischaemic and high bleeding risk in whom it is desirable to balance these risks
- Patients treated with a P2Y12-inhibitor who need to undergo urgent (cardiac) surgery in whom timing of surgery can be determined by platelet function testing.

Conclusion

High on-treatment platelet reactivity is seen in approximately 25% of clopidogrel treated patients, but to a much lesser extent in patients treated with ticagrelor or prasugrel. On the other hand, low on-treatment residual platelet reactivity is more prevalent with ticagrelor and prasugrel. A consistent relation has been observed between HPR and LPR and adverse ischaemic and bleeding events, respectively. However, no benefit of routine PFT guided adjustment of therapy could be demonstrated. The use of PFT can be useful in selected subgroups such as high risk subgroups and in determining the optimal timing of (cardiac) surgery after interruption of antiplatelet therapy.

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CHAPTER

10

Measuring High on-treatment Platelet Reactivity in clinical practice

Should we use a panel of platelet function tests?

B. Zwart, T.C. Godschalk, K. Zheng, J. Denteneer, J.C. Kelder, J.M. ten Berg

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Abstract

Background:
High on-treatment platelet reactivity (HPR) on P2Y12-inhibitors in patients treated with dual antiplatelet therapy is strongly associated with adverse ischaemic events. Studies have shown conflicting results with regard to the correlation and agreement between the different tests. Several assays are available to establish HPR. A composite advice based on more than one test might be a better way to identify HPR patients.

Objectives:
To compare HPR rates and agreement between individual platelet function tests and a panel of three tests.

Methods:
In our large PCI center, all patients who suffered a stent thrombosis were invited back to a dedicated clinic. Platelet function testing was performed in all patients and matched control patients. HPR rates were compared between individual tests and with a composite comprised of three tests.

Results:
A total of 242 patients were included, of whom in 193 patients all tests were available. HPR rates ranged from 14.6% (VerifyNow cut-off >235 PRU) to 49.7% (VASP). HPR according to the composite advice (≥2 out of 3 tests indicating HPR) was present in 29.8% of patients.
The best correlation with the composite advice was observed with light transmittance aggregometry (kappa=0.78) and VerifyNow (lower cutoff >208 PRU; kappa=0.68). VerifyNow with cutoff >235 PRU identified the smallest proportion of patients with HPR, whereas VASP seemed to “over-identify” HPR.

Conclusions:
In this real life patient cohort, a large variability was observed between four different platelet function tests. The use of a composite advice based on three tests is a promising alternative.

Introduction

High on-treatment platelet reactivity (HPR) on $P2Y_{12}$-inhibitors in patients treated with dual antiplatelet therapy (DAPT) has been demonstrated to be strongly associated with adverse ischaemic events after percutaneous coronary intervention (PCI) or acute coronary syndrome (ACS).[2-4] Several assays are available to establish on-treatment platelet reactivity. Classic light transmittance aggregometry (LTA) is considered as the gold standard. The VerifyNow system is considered a reliable test which is easy to use in clinical practice.[5,6] Other available tests include the Vasodilator-Stimulated Phosphoprotein Assay (VASP) and Multiple Electrode Aggregometry (MEA or Multiplate®).

The results of most randomized controlled trials after tailored P2Y12-therapy have been disappointing. These disappointing results might be a result of poor identification of patients with true "HPR". Of note, all trials used a single platelet function test (VerifyNow assay in the four largest trials).

Studies have shown conflicting results with regard to the correlation between the different platelet function tests[1,7] and even less is known about the degree of agreement between the different tests. The few available studies show that agreement between tests is poor[8,9]. It has been suggested that a composite advice based on more than one test might be a better way to identify patients with HPR.[8] However, no previous studies compared the results of a panel of tests versus individual tests. We therefore investigated the rates of HPR in our cohort of ST patients and matched controls and evaluated correlation and agreement between LTA, VerifyNow, VASP and MEA and a composite advice based on more than one test.

Methods

Since January 2010, all patients who suffered a definite stent thrombosis were invited back to a dedicated stent thrombosis clinic in our center. Patients were invited to visit the outpatient clinic between 30-60 days after ST. $P2Y_{12}$-inhibitors used included either clopidogrel, prasugrel or ticagrelor. Magnitude of on-treatment platelet reactivity was quantified using four platelet function tests in parallel: light transmittance aggregometry with adenosine diphosphate (ADP) 5 and 20 µmol/L as agonist, the VerifyNow P2Y12 assay, Multiplate assay and VASP assay using citrated blood. The following cut-offs for HPR based on the consensus statement were used: LTA ADP peak aggregation >64.5%; VASP >50%; MEA >46 Units (1 Unit = 10 AU*min).[10]. For the VerifyNow, the cut-off used in the composite advice was >235 platelet reactivity units (PRU). For the purpose of this sub analysis, both the cut-off >235 PRU and >208 PRU are reported, as both cut-offs have been used in previous studies. More specifics and the procedure of platelet function testing and considerations for tailored DAPT have been previously described.[11]

A tailored DAPT advice was given based on the LTA, VerifyNow and VASP. When at least two out of three platelet function tests showed HPR, antiplatelet strategy in these patients was changed. Platelet reactivity was also tested with MEA but this was for research purposes only.

Control patients were matched based on the indication (e.g. ST-segment elevation myocardial infarction.) and date of the PCI with stent implantation (±14 days) of the stent thrombosis patients (cases) on a 1:1 ratio. For the current analysis, both cases and control patients were selected.

Data analysis

The distribution of HPR patients across the different tests was depicted using a Venn diagram. In order to compare the performance of the panel of tests versus the different single tests, all individual tests were plotted against the composite advice using a scatter plot. To assess agreement for continuous variables we computed Pearson correlation coefficients along with simple linear regression lines; for categorical variables we computed the Fleiss kappa coefficient.

Results

A total of 242 patients were included, of whom in 193 patients LTA, VerifyNow and VASP were all available, as needed for the composite advice. Baseline characteristics are shown in Table 1. HPR rates ranged from 14.6% (VerifyNow cut-off >235 PRU) to 49.7% (VASP). Separate results stratified for use of either clopidogrel or the stronger $P2Y_{12}$-inhibitors prasugrel and ticagrelor are also shown in Table 2. HPR according to the composite advice based on the panel (≥2 out of 3 tests) was present in 29.8% of patients.

Table 1: Baseline characteristics.

Variable	*n* = 242	
Male sex, n (%)	192	(79.3)
Age, mean(SD)	57.4	(10.4)
BMI	27.1	(3.9)
Current smoking or quit <12 months	117	(48.8)
Diabetes mellitus	33	(13.8)
Hypercholesterolaemia	139	(58.0)
Renal insufficiency	11	(4.6)
Peripheral arterial disease	14	(5.8)
History of ischaemic stroke	4	(1.7)
LV function <45%	47	(20.9)
Previous PCI before index-PCI	49	(20.4)
History of CABG	5	(2.1)
Indication for index-PCI		
Stable angina	64	(26.7)
Unstable angina	32	(13.3)
STEMI	114	(47.5)
NSTE-ACS	21	(8.8)

ACS, acutecoronarysyndrome;CABG,coronaryarterybypassgrafting;LV,left ventricular; NSTE,non-ST-segmentelevation;PCI,percutaneouscoronaryinter- vention; STEMI,ST-segmentelevationmyocardialinfarction.

Table 2: High on-treatment platelet reactivity rates according to the individual tests and according to the composite advice.

HPR, *n* (%)	LTA		VN 235		VASP		VN 208		MEA		Composite (LTA, VN235, VASP)	
Overall	63	(26.2)	35	(14.6)	97	(49.7)	54	(22.5)	47	(25.3)	56	(29.8)
Clopidogrel	50	(40.7)	29	(23.8)	74	(71.8)	45	(36.9)	28	(32.2)	49	(50.5)
Prasugrel orticagrelor	13	(11.1)	6	(5.1)	23	(25.0)	9	(7.63)	19	(19.2)	7	(7.7)

LoHPR, high on-treatment platelet reactivity; LTA, light transmittance aggregometry; MEA, multipl eelectrode aggregometry; VASP, Vasodilator-Stimulated Phosphoprotein Assay; VN, verify now.

Correlation between the different tests and LTA is shown in the Figures 1-3. R-values ranged from 0.33 to 0.53 corresponding to weak or moderate correlation.

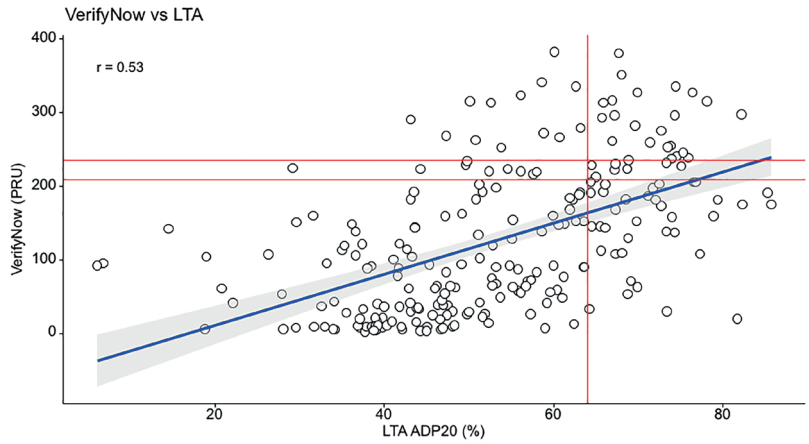

Figure 1: Correlation between Verify Now and light transmittance aggregometry.

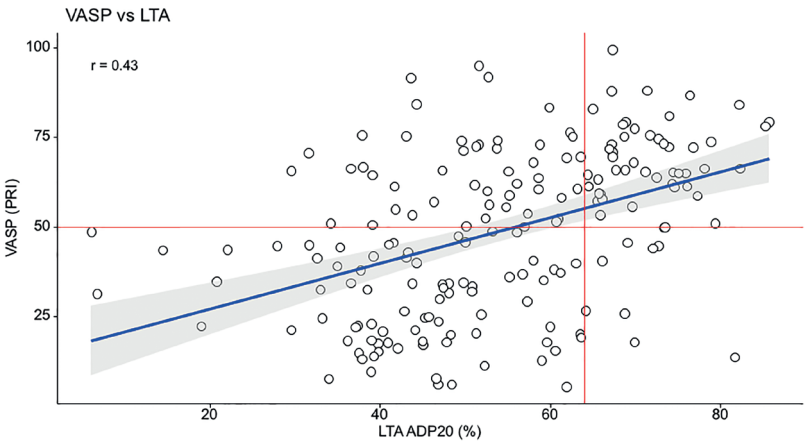

Figure 2: Correlation between Vasodilator-Stimulated Phosphoprotein Assay and light transmittance aggregometry.

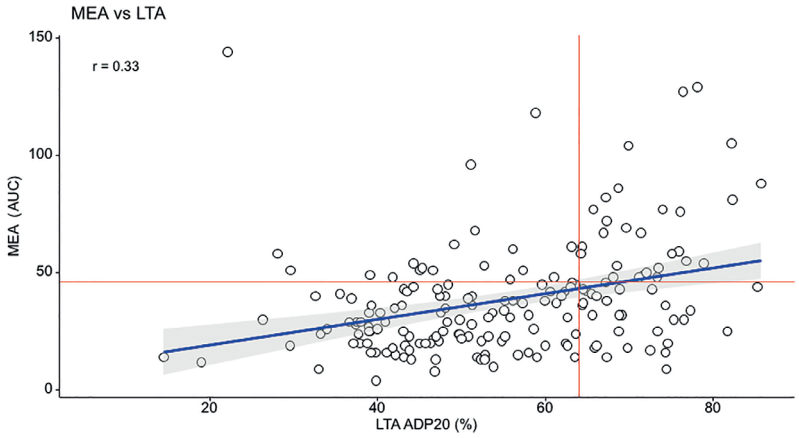

Figure 3: Correlation between multiple electrode aggregometry and light transmittance aggregometry.

The frequency of HPR according to the different tests and the overlap between the tests are shown in Figure 4. Only 10/153 (6.5%) patients were identified with HPR according to all 4 tests, whereas 62/153 (40.5%) patients were identified "good responders" by all four tests.

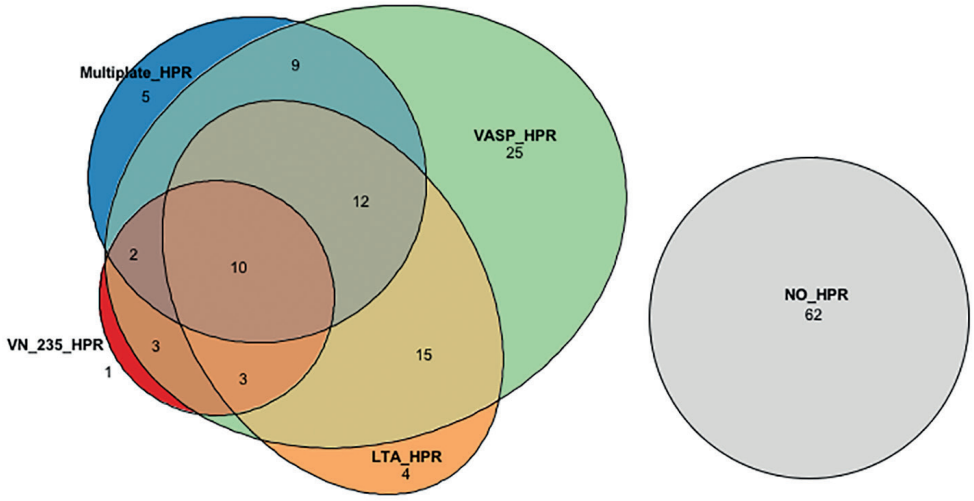

Figure 4: Venn diagram depicting overlap in high on-treatment platelet reactivity rates according to the four tests.

Figures 5 and 6 demonstrate how the composite advice relates to the results of the individual tests. The right hand plot in each figure refers to patients with HPR according to the composite of three tests, whereas the left plot refers to patients with non-HPR. The dots depict individual patients and their platelet function results plotted on the Y-axis. The horizontal line indicates the cut-off for this test. Hence, the right upper and left lower

quadrant indicate that the individual test agrees with the composite advice (HPR and non-HPR, respectively), whereas the left upper and right lower quadrant indicate discordant results.

Figures 5A – 5C depict the tests used at the stent thrombosis clinic (LTA, VerifyNow >235 PRU and VASP, respectively). The composite consists of the total of these three tests, hence the test plotted on the Y-axis is included in the composite. Figure 5D and 5E depict the alternative tests (MEA and VerifyNow with cutoff >208 - both tests were not used in our clinical daily practice) with again the composite including the plotted test.

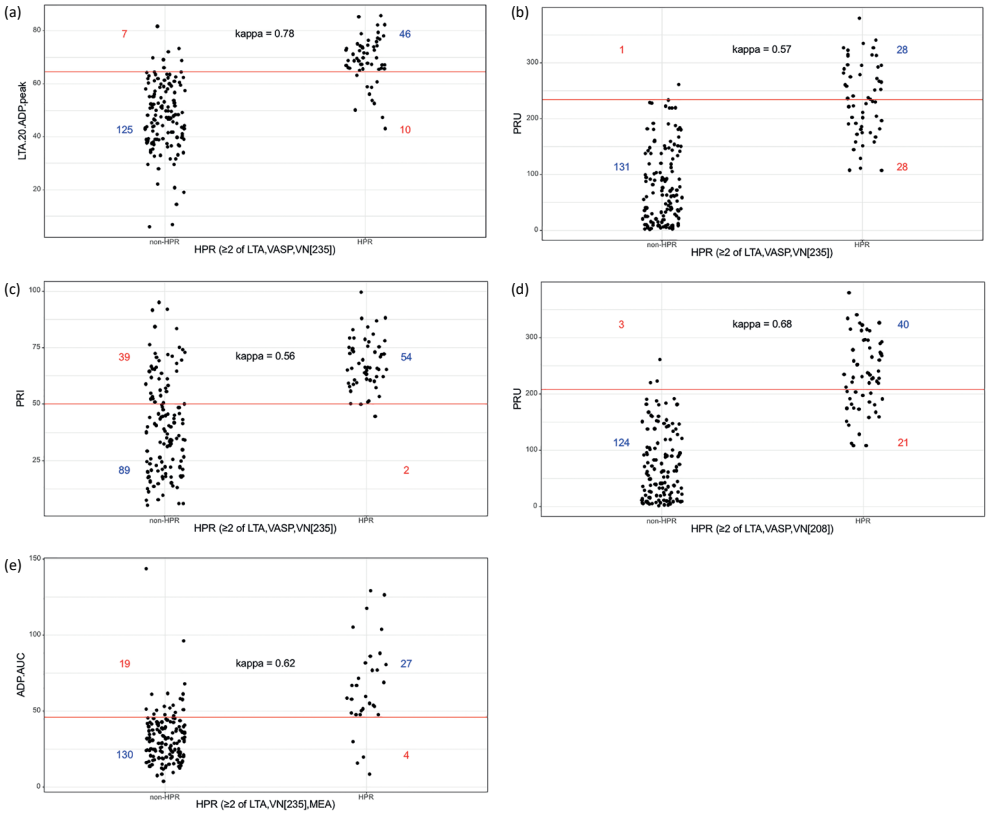

Figure 5: (a–e) Scatter plots depicting association between the individual test and the composite advice used inclinic (light transmittance aggregometry, Verifynow, Vasodilator-Stimulated Phosphoprotein Assay).

In Figures 6A – 6E the test is compared to a composite of three different tests. Hence the test plotted on the Y-axis has not been included in the composite.

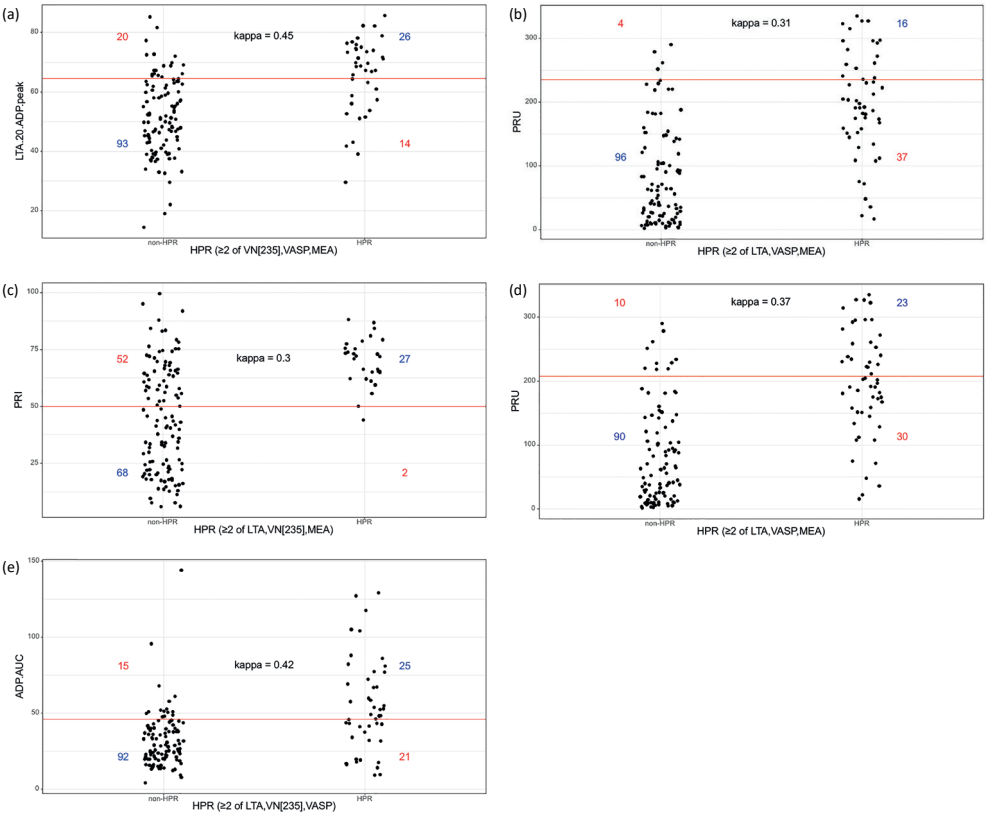

Figure 6: (a–e) Scatter plots depicting association between the individual test and a composite advice using three alternative tests.

As shown in Fig. 5A and 6A, LTA correlates best with the composite advice (kappa = 0.78 and 0.45, respectively) with a low proportion of discordant results (a total of 17/188 (9.0%) or 34/153 (22.2%), respectively). The VerifyNow with cut-off >235 disagreed in only 1/132 (0.8%) or 4/100 (4.0%) with the composite advice when this indicated non-HPR. However, a substantial proportion of patients with HPR according to the panel were not identified by VerifyNow >235 (28/56 (50.0%, Fig 5B or even 37/53 (69.8%, Fig 6B). The VASP, on the other hand, "over-identified" with HPR: in 39/128 (30.4%) or 52/120 (43.3%) patients the test indicated HPR when the panel considered these patients as 'non-HPR' (Fig 5C and 6C). Remarkably, when the lower cut-off was used for the VerifyNow, this test performed substantially better (kappa = 0.68 and 0.37) as compared to VerifyNow >235 with fewer disconcordant results. MEA demonstrated comparable results (kappa = 0.62 and 0.42) with VerifyNow >208 and performed better than both VerifyNow >235 and VASP.

Discussion

The current study demonstrated a considerable variability in HPR rates in a large real-life cohort of high risk ACS patients. Correlation and agreement between the individual tests was found to be weak or moderate at best. The VerifyNow identified the smallest proportion of patients with HPR, whereas the VASP identified an extremely high number of patients with HPR. Heterogeneity was also illustrated by the fact that the four tests agreed in less than half (47%) of all patients. Furthermore, we showed that the VerifyNow >235 PRU and VASP show discordant results in a large proportion of patients when compared to a panel of three tests, whereas LTA, MEA and VerifyNow >208 performed better.

Given the large degree of variability with the individual tests, an advice based on more than one test is promising. Using a panel of three tests, 29% of patients were identified as having HPR, as compared with HPR rates ranging from 14.6% to 49.7% for the individual tests. When using a composite advice, it seems reasonable to use MEA instead of VASP, given the exceptionally high proportion of HPR patients identified by VASP. Alternatively, a different cut-off might be used for the VASP as suggested by some authors.[12]

This is the first study showing the results of using a composite advice based on a panel of platelet function tests and comparing it to the HPR rates of the individual tests. Lemesle et al. compared the performance of three individual platelet function tests in 2013 and already concluded that a sole test might not be sufficient.[13] The authors found that only 31% was identified as normal responders according to all three tests and only 16% as poor responder by all three tests. These figures are in line with the present study.

Previously, four large randomized controlled trials failed to demonstrate a benefit of tailored antiplatelet therapy.[14-17] As suggested before[13], this could be a result of the difficulty of identifying true 'poor responders' with a single test. Interestingly, the VerifyNow which was used in these trials, identifies the smallest proportion of patients with HPR, leaving the possibility that a substantial proportion of poor responders is not identified. In the present cohort, more than twice as many patients were labeled as HPR by the panel of three tests as compared to the VerifyNow >235 as a single test (29.8% vs. 14.6%). Again, speculatively, this could have influenced the results of the trials and might in part explain the non-significant findings of those studies. Therefore, future studies should use a combination of platelet function tests as opposed to one single test.

Limitations

Whereas a composite advice seems promising, no external validation could be performed as a result of lacking a true gold standard. Although intuitively more accurate, the added value of a panel of tests remains therefore speculative. No relation with clinical outcomes was

assessed in this study. In a previous paper, we demonstrated that tailored DAPT in patients who suffered a stent thrombosis reduced the rate of cardiac death and/or recurrent stent thrombosis as compared with a historical cohorts of stent thrombosis patients.[11]

Conclusion

In this real life patient cohort, correlation between the four different platelet function tests was found to be weak with a poor degree of agreement. The VerifyNow assay identified the smallest proportion of HPR patients. We demonstrated that the use of a composite advice based on more than one platelet function test is a feasible alternative. When using a composite advice, MEA rather than VASP should be used given the exceptionally high proportion of patients identified with HPR according to VASP.

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CHAPTER

11

A novel risk score to identify AF patients undergoing PCI at high thrombotic risk

a RE-DUAL PCI secondary analysis

B. Zwart, W.L. Bor, A. de Veer, B.K. Mahmoodi, J.C. Kelder, G.Y.H. Lip, D.L. Bhatt, C.P. Cannon, J.M. ten Berg

** B. Zwart and W.L. Bor contributed equally to this manuscript*

submitted

Abstract

Objectives:
To identify patients at high thrombotic risk who might benefit from triple antithrombotic therapy (TAT) over double antithrombotic therapy (DAT).

Background:
Current guidelines recommend to treat atrial fibrillation (AF) patients who undergo percutaneous coronary intervention (PCI) with TAT up to one month in patients at high thrombotic risk. It is unclear how to select these high-risk patients.

Methods:
This study was a post hoc subanalysis of the RE-DUAL PCI trial. A Cox proportional hazards model was built by stepwise selection of plausible predictor variables for the combined composite endpoint defined as cardiovascular death, myocardial infarction, stent thrombosis or ischaemic stroke. Effect of TAT versus DAT was calculated in the highest proportion of predicted thrombotic risk. Based on beta-coefficients a simplified prediction rule was constructed.

Results:
In 209 patients (7.7%) the combined ischaemic endpoint occurred during the first year. The simplified prediction rule contained 7 variables. In patients with a score ≥5 (N 154, 5.7%), a significant reduction in the composite of myocardial infarction and stent thrombosis was observed with TAT vs. DAT (6.3% vs. 21.0%, p=0.04), without a penalty in terms of bleeding. In patients at low thrombotic risk, a significant increase in bleeding was observed without a reduction of thrombotic events.

Conclusions:
This novel clinical prediction rule was able to identify a subgroup of high-risk patients benefiting from TAT. Our findings support the use of TAT in this small subgroup, while using DAT in the majority of AF patients undergoing PCI.

Introduction

Antithrombotic regimens in patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI) represent one of the most challenging topics for cardiologists in daily practice. In AF patients with a CHA_2DS_2VASc score ³1 in males and ≥2 in females, oral anticoagulation (OAC) is warranted to reduce the risk of systemic thromboembolic events including stroke, whereas patients undergoing PCI have an indication for dual antiplatelet therapy consisting of aspirin and a $P2Y_{12}$ inhibitor in order reduce the risk of stent thrombosis or other recurrent atherothrombotic events [1–3]. Approximately one in five patients with AF undergo PCI at some point in life, illustrating the relevant overlap in clinical practice.[4] From the PCI perspective, one in twelve patients undergoing coronary stenting has concomitant AF and an indication for OAC.[3] The combination of dual antiplatelet therapy and OAC is referred to as triple antithrombotic therapy (TAT). A drawback of TAT is that it confers at least a two-times higher risk of bleeding as compared to double antithrombotic therapy (DAT), i.e. with the omittance of aspirin[5,6].

Current international guidelines and consensus documents recommend TAT for one week and up to one month in patients at high thrombotic risk[2,7,8]. To date, it is unclear how to select patients at high thrombotic risk.

Five randomised controlled trials compared TAT with the combination of (N)OAC and an antiplatelet agent. The WOEST study was the first to investigate a regime of omitting aspirin in anticoagulated patients undergoing PCI.[9] The WOEST study showed that treatment with an VKA and the $P2Y_{12}$ inhibitor clopidogrel (DAT) was associated with a reduction of bleeding without an increase in thrombotic events, compared to patients treated with TAT. Four more recent studies, which used the same approach of TAT versus DAT with NOAC did not show any differences in ischaemic outcomes, whereas all but the ENTRUST-AF PCI study showed a reduction of bleeding complications in patients treated with DAT [10–13].

Although no difference in ischaemic outcomes were observed in the individual trials, it must be noted that all studies were largely underpowered for thrombo-embolic endpoints and the trials included mostly low-risk patients with a small proportion of patients with acute coronary syndrome (ACS) [14,15]. Some meta-analyses suggested a significant but small increase of stent thrombosis in patients treated with DAT [14,16]. A sub analysis of the AUGUSTUS trial pointed to a trade-off in ischaemic vs. bleeding risks. A significant reduction in ischaemic events was observed when TAT was used in the first month after PCI, but at the equal cost of bleeding [17]. After 30 days, TAT continued to increase bleeding without significantly reducing ischemic events. The authors propose a patient-centric decision making on the use of TAT. The recent meta-analysis by Gargiulo et al.[14] supports this concept of a personalised strategy. The authors found evidence for a subgroup of patients who had net benefit of TAT

vs. DAT in favour of reducing ischaemic events; however, they could not provide tools for the identification of this subgroup of patients, nor do international guidelines provide specific guidance for patient selection.

In this study, we sought to find subgroups of patients at high thrombotic risk and to develop a prediction rule to identify high-risk patients who might benefit from TAT.

Methods

Patient cohorts

This study was a post hoc sub analysis of the RE-DUAL trial. The study protocol for this trial has been previously published [18]. In short, in the RE-DUAL PCI trial, the DAT group was treated with dabigatran 110 mg or 150 mg in combination with a P2Y12 inhibitor (clopidogrel in 87% or ticagrelor in 12% of patients). The TAT group consisted of VKA, aspirin and a $P2Y_{12}$ inhibitor (clopidogrel in 90% or ticagrelor in 8% of patients). TAT was given for three months in patients undergoing PCI with DES and for one month in patients receiving a BMS. The study received the proper ethical oversight. The study protocol and any amendments were approved by the ethics committee at each participating center.

Ischemic and Bleeding Endpoints

The combined composite endpoint was defined as cardiovascular death, myocardial infarction (MI), stent thrombosis (definite or probable according to Academic Research Consortium criteria) or ischaemic stroke. The bleeding endpoint was defined as the first Bleeding Academic Research Consortium (BARC) 2, 3 or 5 bleeding within 365 days. For the purpose of a sensitivity analysis, follow-up was truncated after the first event (either thrombotic or bleeding event).

Follow-up

The mean follow-up after PCI was 14 months. For this analysis follow-up was truncated at 365 days to obtain risk estimates for the first year of DAT vs TAT. Groups were compared according to intention-to-treat protocol.

Statistical analysis

Baseline characteristics were compared between patients with and without ischaemic events during the 1-year follow-up by t-test or Chi-square or its nonparametric equivalents as appropriate.

Predictors

Based on clinical plausibility and availability in both trial datasets, variables were considered as candidate predictors. The variables included age, sex, body mass index, hypertension,

hypercholesterolemia, diabetes mellitus including subgroups of insulin dependent diabetes, smoking, alcohol use, medical history (bleeding, MI, PCI, coronary bypass artery grafting, stroke, venous thrombo-embolisms or systemic embolism, renal failure, malignancy, peripheral artery disease, heart failure), MI at presentation, left ventricular ejection fraction, laboratory tests at presentation (haemoglobin, haematocrit, platelet count, leukocyte count, creatinine, estimated glomerular filtration rate by CKD-EPI), and angiographic and procedural characteristics (number of diseased vessels, left main disease, thrombus containing lesion, number of stented vessels, stented vessel/graft, bifurcation PCI, lesion length >30mm and in-stent restenosis stenting). We did not include modifiable factors like medication use, periprocedural heparin use, factors of which reporting might be unreliable like New York Heart Association class classification, and factors with uncertain causal relation like index ECG rhythm and type of atrial fibrillation.

Model development

Since we wanted to characterize the patients' thrombotic risk based on their single clinical features irrespective of receiving DAT or TAT, individual candidate variables for the model were selected from a univariate Cox regression stratified for randomization arm and bare metal stent placement (the latter directly influenced treatment duration). Variables showing P-value <0.30 for the ischemic events model were considered as candidate variables. A Cox model for the combined ischemic endpoint was constructed with forced entry of the stratification variables. Stepwise selection from the candidate variables using a 0.05 significance level was performed. Missing values in the dataset for stepwise model selection were imputed by simple means (overview of missing in table S4). Based on beta-coefficients of the Cox model a point score was constructed using the methods as proposed in the Framingham Study risk scores. [19]

Validation

With the Cox model the expected hazard of the thrombotic end point given the covariates was predicted at 365 days. Also, the point score was calculated for each patient. Predictive accuracy of the model and point score was evaluated by area under the receiver operating curve (c-statistic). The cohort was divided in quintiles, deciles and demi-deciles based on the expected hazards, or grouped by point score to assess calibration. Also, goodness-of-fit was assessed by Hosmer-Lemeshow test.

Observed risks within the different risk categories and risk scores of ischaemic events, bleeding, and mortality were compared between the patients that received TAT or DAT to evaluate if a benefit of TAT over DAT could be found in patients at higher thrombotic risk.
To compare the performance of the new risk score in relation to existing risk scores, c-statistic of the the CHA_2DS_2-VASc for the thrombotic end point in the RE-DUAL cohort was assessed.

External validation was performed in the WOEST2 registry. The WOEST2 registry is a (as yet unpublished) cohort of 885 patients treated with OAC undergoing PCI (mean age 74 years, 31% PCI for ACS, 38% treated with TAT, 94% clopidogrel). Differences in outcomes between TAT and DAT cohorts were not evaluated, as an inherent indication bias exists between the groups due to the observational design of this cohort.

Results

A total of 2725 patients was included in this analysis. In 209 patients (7.7 %) the combined ischaemic endpoint occurred during the first year. Baseline characteristics of patients with and without ischaemic events are depicted in Table 1. Approximately half of the cohort (50.5%) underwent PCI for the indication ACS. Patients with an ischaemic event during follow-up were more likely to have a medical history of MI, heart failure, diabetes, renal failure, peripheral artery disease or prior stroke and were more likely to have presented with ACS. Left ventricular ejection fraction was lower in patients with an ischaemic event during follow-up and multivessel disease was more prevalent. Furthermore, there were significant differences in haemoglobin level, white blood cell count, platelet count and creatinin clearance. BARC 2, 3 or 5 bleedings were documented in 520 patients (19.1%).

Table 1: Baseline characteristics of patients with and without ischaemic events during follow-up.

	Ischaemic end point			
	no	yes	p	test
n	2516	209		
Triple therapy	907 (36.0)	74 (35.4)	0.912	
Age (median [IQR])	71.00 [65.00, 77.00]	71.50 [65.00, 78.00]	0.458	nonnorm
Female sex (%)	611 (24.3)	44 (21.1)	0.334	
Body-mass index (median [IQR])	28.10 [25.30, 31.70]	28.10 [25.10, 31.40]	0.485	nonnorm
Hypertension (%)	2114 (84.1)	180 (86.1)	0.491	
Hypercholesterolemia (%)	1640 (65.2)	130 (62.2)	0.423	
Smoker (%)	310 (12.3)	27 (12.9)	0.888	
Diabetes Mellitus (%)	902 (35.9)	91 (43.5)	0.032	
Insuline dependent DM (%)	248 (9.9)	29 (13.9)	0.089	
Alcohol abuse (%)	1276 (50.7)	99 (47.4)	0.388	
Prior MI (%)	623 (24.8)	76 (36.4)	<0.001	
Congestive heart failure (%)	849 (33.8)	88 (42.1)	0.018	
Prior bleeding (%)	32 (1.3)	0 (0.0)	0.189	
Prior GI bleeding (%)	167 (6.6)	16 (7.7)	0.675	
Stroke (%)	200 (8.0)	26 (12.4)	0.033	
Prior coronary revascularization (%)	951 (37.8)	92 (44.0)	0.089	
History of malignancy (%)	225 (9.1)	16 (7.8)	0.595	
Peripheral artery disease (%)	161 (6.9)	27 (13.8)	0.001	
ACS at baseline (%)	1253 (49.8)	122 (58.4)	0.021	
bl.acstype (%)			<0.001	
STEMI	280 (22.8)	25 (20.8)		
NSTEMI	509 (41.4)	73 (60.8)		
UAP	440 (35.8)	22 (18.3)		
NYHA 3/4 (%)	237 (28.1)	33 (37.5)	0.084	
LVEF at baseline (median [IQR])	54.00 [45.00, 60.00]	47.00 [35.00, 55.00]	<0.001	
Atrial fibrillation or flutter at presentation (%)	1162 (46.2)	103 (49.3)	0.429	

Table 1: Continued

	Ischaemic end point			
	no	yes	p	test
Haemoglobin (mmol/L) (median [IQR])	8.50 [7.76, 9.18]	8.32 [7.51, 8.94]	0.050	
Haematocrit (%) (median [IQR])	41.00 [38.00, 44.00]	40.00 [37.00, 44.00]	0.125	
Platelet count (*10^9.L) (median [IQR])	201.00 [169.00, 243.00]	212.00 [182.00, 252.00]	0.006	
Creatinin (mg/dL) (median [IQR])	1.00 [0.85, 1.19]	1.08 [0.91, 1.22]	0.001	
Creatinin (µmol/L) (median [IQR])	88.00 [75.00, 106.00]	96.00 [80.00, 108.00]	0.001	
eGFR (CKD-EPI) (median [IQR])	76.00 [61.00, 89.00]	68.00 [59.00, 83.00]	<0.001	
White blood cell count (median [IQR])	7.33 [6.09, 8.92]	7.70 [6.45, 9.30]	0.021	
Femoral access (%)	889 (35.6)	83 (40.3)	0.203	
3 vessel disease (%)	418 (17.0)	63 (30.9)	<0.001	nonnorm
Complex procedure (%)	506 (20.1)	43 (20.6)	0.946	
***>2 vessels stenting (%)**	77 (3.1)	9 (4.3)	0.434	nonnorm
***in-stent restenosis stenting (%)**	42 (1.7)	4 (1.9)	1.000	nonnorm
***prior brachytherapy lesion stenting (%)**	2 (0.1)	0 (0.0)	1.000	nonnorm
***unprotected left main stenting (%)**	44 (1.7)	4 (1.9)	1.000	nonnorm
***>2 lesions per vessel stenting (%)**	144 (5.7)	12 (5.7)	1.000	nonnorm
***>30mm stenting (%)**	220 (8.7)	20 (9.6)	0.783	nonnorm
***bifurcation stenting (%)**	88 (3.5)	4 (1.9)	0.308	
***venous graft stenting (%)**	53 (2.1)	5 (2.4)	0.980	
***thrombus containing lesion stenting (%)**	37 (1.5)	6 (2.9)	0.204	
BMS placement (%)	410 (16.3)	40 (19.1)	0.335	
Number of stented vessels (%)			0.123	
1	2016 (81.7)	162 (78.6)		
2	382 (15.5)	33 (16.0)		
3	70 (2.8)	11 (5.3)		
LAD (%)	1191 (47.3)	94 (45.0)	0.559	
LCX (%)	648 (25.8)	69 (33.0)	0.027	
RCA (%)	869 (34.5)	67 (32.1)	0.516	
Graft (%)	68 (2.7)	9 (4.3)	0.260	
Arterial graft (%)	9 (0.4)	2 (1.0)	0.456	
Venous graft (%)	53 (2.1)	5 (2.4)	0.980	
All-cause death (%)	36 (1.4)	77 (36.8)	<0.001	
Composite outcome (%)	0 (0.0)	209 (100.0)	<0.001	
MI or ST (%)	0 (0.0)	158 (75.6)	<0.001	
BARC 2, 3, or 5 bleeding (%)	465 (18.5)	55 (26.3)	0.007	
BARC 3 or 5 bleeding (%)	100 (4.0)	27 (12.9)	<0.001	
Cardiovascular death (%)	0 (0.0)	51 (24.4)	<0.001	
Myocardial infarction (%)	0 (0.0)	110 (52.6)	<0.001	
Stent thrombosis (%)	0 (0.0)	86 (41.1)	<0.001	
Stroke (%)	3 (0.1)	36 (17.2)	<0.001	
Ischemic stroke (%)	0 (0.0)	30 (14.4)	<0.001	
Hemorrhagic stroke (%)	0 (0.0)	6 (2.9)	<0.001	

Table 2 shows results of stratified univariate Cox regression. Strong predictors for ischaemic events were decreased left ventricular ejection fraction, multivessel disease or multivessel stenting, myocardial infarction, diabetes mellitus, peripheral artery disease or stroke and a history of heart failure or renal failure.

Table 2: Univariate analysis for composite ischaemic end point
(* all corrected for treatment arm, study and baremetal stent)

	beta	HR (95% CI for HR)	wald test	p value
LVEF (per % increase)	-0.035	0.97 (0.96-0.98)	41	1.9e-10
3 vessel disease	0.73	2.1 (1.5-2.8)	23	1.3e-06
Number of diseased vessels (per 1 vessel increase)	0.41	1.5 (1.3-1.8)	23	1.7e-06
Myocardial infarction at baseline	0.65	1.9 (1.5-2.5)	22	3.2e-06
History of myocardial infarction	0.52	1.7 (1.3-2.2)	13	0.00028
1 vessel disease	-0.51	0.6 (0.45-0.79)	13	0.00032
Peripheral artery disease	0.74	2.1 (1.4-3.1)	13	0.00037
eGFR (by CKD-EPI, per point increase)	-0.013	0.99 (0.98-0.99)	12	5e-04
Heart failure or LVEF<30%	0.48	1.6 (1.2-2.1)	11	0.00095
Creatinin (per µmol/L increase)	0.0088	1 (1-1)	11	0.00098
Platelet count (per 109/L increase)	0.0032	1 (1-1)	10	0.0016
NYHA classification (per class increase)	0.4	1.5 (1.1-2)	7.5	0.0063
History of renal failure	0.43	1.5 (1.1-2.1)	6.7	0.0095
Heart failure	0.36	1.4 (1.1-1.9)	6.7	0.0099
ACS at baseline	0.36	1.4 (1.1-1.9)	6.6	0.01
History of stroke	0.51	1.7 (1.1-2.5)	5.9	0.015
Graft stenting	0.47	1.6 (0.82-3.1)	1.9	0.17
LCX stenting	0.34	1.4 (1.1-1.9)	5.3	0.021
NYHA class 4	0.89	2.4 (1.1-5.3)	5.1	0.025
Haematocrit (per % increase)	-0.034	0.97 (0.94-1)	4.6	0.032
Diabetes Mellitus	0.29	1.3 (1-1.8)	4.5	0.035
White blood cell count (per 109/L increase)	0.062	1.1 (1-1.1)	4.4	0.035
Haemoglobin (per mmol/L increase)	-0.15	0.86 (0.75-0.99)	4.3	0.038
3 vessels stented	0.62	1.9 (1-3.4)	4	0.046
NYHA class 3/4	0.44	1.5 (1-2.4)	3.9	0.048
Prior coronary revascularization	0.27	1.3 (0.99-1.7)	3.6	0.057
Number of vessels stented (per vessel increase)	0.22	1.3 (0.97-1.6)	2.9	0.088
Insuline dependent diabetes mellitus	0.33	1.4 (0.94-2.1)	2.8	0.095
Body-mass index (per kg/m2 increase)	-0.022	0.98 (0.95-1)	2.5	0.12
Thrombus containing lesion	0.64	1.9 (0.84-4.3)	2.4	0.12
Prior PCI	0.19	1.2 (0.91-1.6)	1.7	0.19
Prior CABG	0.26	1.3 (0.86-1.9)	1.6	0.21
1 vessel stented	-0.21	0.81 (0.58-1.1)	1.5	0.22
Alcohol abuse	-0.17	0.85 (0.64-1.1)	1.4	0.23
Bifurcation stenting	-0.6	0.55 (0.2-1.5)	1.4	0.24
Arterial graft stenting	0.83	2.3 (0.57-9.2)	1.4	0.25
NYHA class 3	0.26	1.3 (0.82-2)	1.2	0.28
Hypercholesterolemia	-0.15	0.86 (0.65-1.1)	1.1	0.3
Female sex	-0.13	0.88 (0.63-1.2)	0.59	0.44
Hypertension	0.14	1.2 (0.78-1.7)	0.5	0.48
Atrial fibrillation or flutter at baseline ECG	0.092	1.1 (0.83-1.4)	0.44	0.51
LAD stented	-0.09	0.91 (0.7-1.2)	0.42	0.52

Table 2: Continued

	beta	HR (95% CI for HR)	wald test	p value
Past or active smoker	0.085	1.1 (0.83-1.4)	0.37	0.54
Hyper coagulable condition	-0.57	0.57 (0.079-4)	0.32	0.57
Prior systemic embolism	-0.54	0.58 (0.081-4.2)	0.29	0.59
History of malignancy	-0.13	0.88 (0.53-1.5)	0.26	0.61
Total stent length >30mm	0.12	1.1 (0.71-1.8)	0.25	0.62
Venous graft stenting	0.14	1.2 (0.47-2.8)	0.10	0.76
In-stent restenosis stenting	0.12	1.1 (0.42-3)	0.06	0.81
STEMI at baseline	0.05	1.1 (0.69-1.6)	0.05	0.82
Prior VTE/SE	-0.083	0.92 (0.43-2)	0.05	0.83
Complex lesion stented	0.038	1 (0.74-1.5)	0.05	0.83
Active smoker	0.028	1 (0.69-1.5)	0.02	0.89
History of venous thromboembolism	-0.047	0.95 (0.42-2.1)	0.01	0.91
>2 lesions per vessel stenting	0.015	1 (0.57-1.8)	0	0.96
Unprotected left main stenting	0.02	1 (0.38-2.7)	0	0.97
Prior major bleeding or predisposition to bleeding	-15	3e-07 (0-Inf)	0	0.99
Prior brachytherapy lesion stenting	-12	6.1e-06 (0-Inf)	0	0.99

After stepwise selection, the multivariable Cox regression model predicting ischaemic events contained left ventricular ejection fraction, number of diseased vessels, MI as indication for index-PCI, thrombocyte count, peripheral artery disease and creatinine clearance. (Table 3). The discriminatory capacity of the ischaemic model was fair (AUC 0.68, CI 0.64-0.72, Figure S1).

Table 3: Cox proportional hazards model.
Analysis stratified for access site, and stent type

Predictor of events	HR (95% CI)	P value
LVEF at baseline (per % increase)	0.973 (0.963-0.984)	<0.001
Number of diseased vessels	1.376 (1.162-1.631)	<0.001
MI as indication for index-PCI	1.693 (1.284-2.233)	<0.001
Platelet count (per 10^9/l increase)	1.003 (1.001-1.005)	0.002
Peripheral artery disease	1.739 (1.152-2.627)	0.008
Creatinin clearance (per ml/min/m^2)	0.990 (0.983-0.998)	0.011

Concordance = 0.688 (se = 0.032)
Rsquare = 0.033 (max possible= 0.634)
Likelihood ratio test = 91.36 on 6 df, p=<2e-16
Wald test = 98.5 on 6 df, p=<2e-16
Score (logrank) test = 100.6 on 6 df, p=<2e-16

Observed ischemic and bleeding outcomes and mortality rates by quintiles for predicted hazards are depicted in Figure 1 and Table S1. Goodness of fit as assessed by Hosmer-Lemeshow test was found to be good (p=1.000). Incidence of ischaemic events ranged from 3.9% for the lowest quintile of thrombotic risk to 15.8% for the highest risk quintile. Comparing high-risk patients to low-intermediate risk patients, significantly more thrombo-embolic events were found in the high-risk patients (15.8% vs. 5.6%, p<0.001, Table S1)

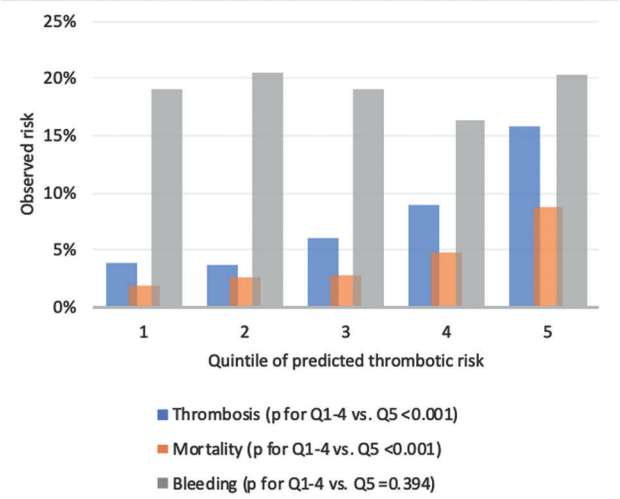


Figure 1:

Observed outcomes with the multivariable model for combined thrombotic end point, BARC 2,3 or 5 bleeding and mortality.

A numerical reduction of the thrombotic end point was observed in patients at the highest thrombotic risk treated with TAT as compared to DAT (Figure 2A). This effect was most pronounced in patients >95th percentile of thrombotic risk (Fig. 2B).

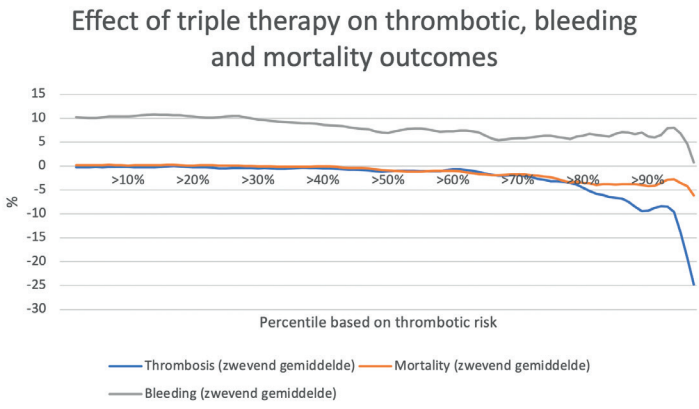


Figure 2:

Absolute risk difference of TAT vs. DAT for thrombotic end point, mortality and BARC 2, 3, 5 bleeding.

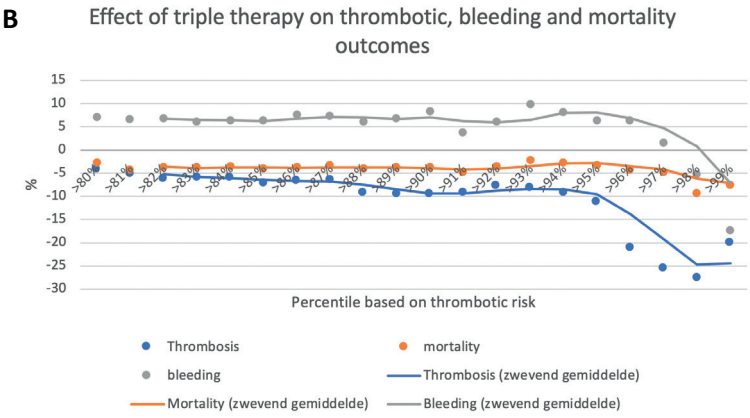


Figure 2: Continued

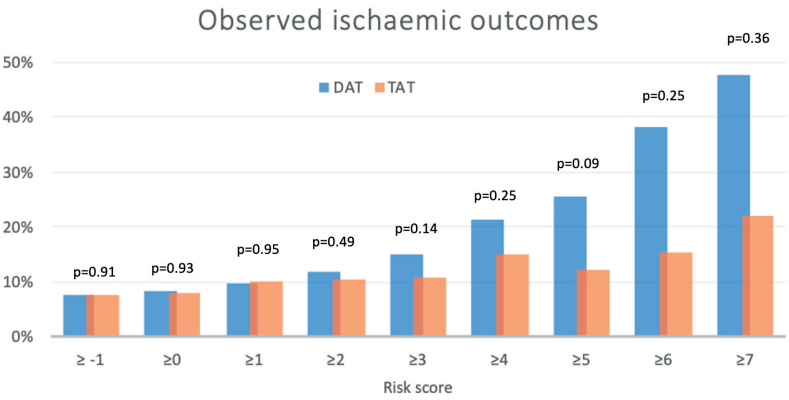
The simplified prediction rule based on the Cox regression model contained 7 variables (Table 4) and retained fair accuracy comparable to the original Cox regression model (AUC 0.66 (0.62-0.69, Fig. S2). The total risk score ranged from -1 points to 8 points. Higher scores were associated with a higher risk of thrombotic events (p_{trend}<0.001). The calibration curve demonstrated excellent calibration for the combined thrombotic end point (Fig S3).

Table 4: Simplified prediction model.

LVEF <30 %	**3**
LVEF 30-50 %	**1**
3-vessel disease	**2**
MI as indication for index-PCI	**2**
Platelet count >400 *109/l	**3**
eGFR >90 ml/min/m2	**-1**
History of peripheral artery disease	**2**

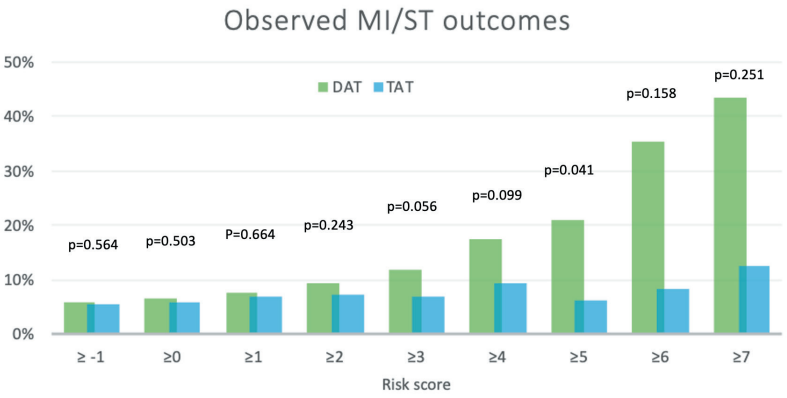
When using a >5 points cut-off, a trend towards a reduction of the composite thrombotic end point in patients treated with TAT as compared to DAT was observed (p=0.09, figure 3A). A significant reduction of myocardial infarction or stent thrombosis was also observed (6.3% vs. 21.0%, p=0.04; Fig. 3B).

A: Observed ischaemic outcomes



	≥ -1	≥0	≥1	≥2	≥3	≥4	≥5	≥6	≥7
No. of events	209	202	165	136	89	54	33	15	13
No. of patients	2725	2449	1655	1211	659	284	154	47	32
	100%	90%	61%	44%	24%	10%	6%	2%	1%

B: Observed MI/ST outcomes



	≥ -1	≥0	≥1	≥2	≥3	≥4	≥5	≥6	≥7
No. of events	158	153	125	103	67	41	25	13	11
No. of patients	2725	2449	1655	1211	659	284	154	47	32
	100%	90%	61%	44%	24%	10%	6%	2%	1%

Figure 3:

Observed Outcomes for DAT vs TAT for different cut-offs of risk score.

C: Observed bleeding outcomes BARC 2+3+5

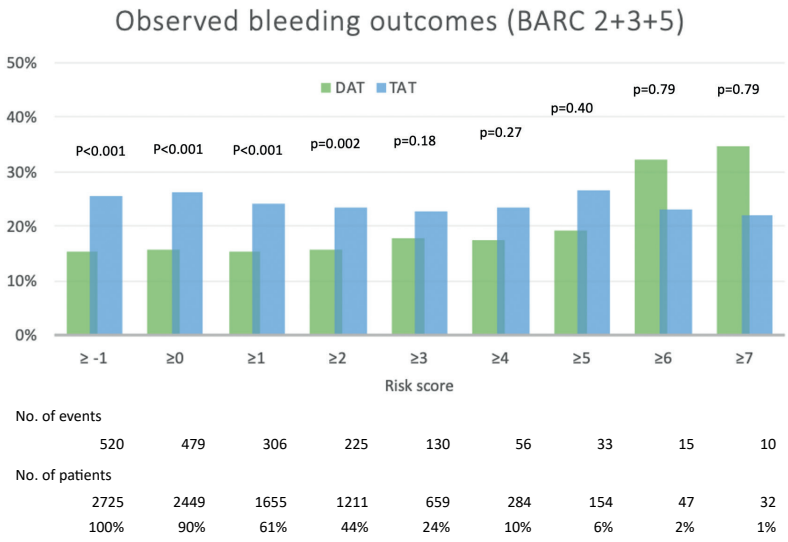


Figure 3: Continued

When considering other outcomes, bleeding events outnumbered ischemic events across all risk categories (Fig. 1) with a significant increase in patients using TAT as compared with DAT (Fig. 3C and S3B) in patients with low thrombotic risk. In patients >95th percentile of thrombotic risk or with a risk score ≥6 the incremental bleeding risk of triple therapy was not found (Fig. 2 and Fig. 3C). A numerical benefit from TAT as compared to DAT with regard to net clinical benefit was found for patients with a risk score cut-off ≥5, whereas in low risk patients treated with TAT a significantly poorer net clinical benefit was observed as compared to patients treated with DAT (Fig. S3).

External validation

The risk score was externally validated in the WOEST 2 registry. Discriminative capacity was similar to the internal validation (C-statistic 0.63, CI 0.56-0.70, Fig. S5).

The score had an excellent overall ability to identify high risk patients with higher scores corresponding to higher risk of thrombotic outcomes (p for trend <0.001, Fig. 4). A score ≥5 identified 11.8% of all patients at high thrombotic risk. Thrombotic risk in these high-risk patients was significantly higher as compared to the remainder of the cohort (16.3% vs 6.7%, p=0.001).

Duration of triple therapy

To study the timing of thrombotic events, a Kaplan Meier curve was constructed (Fig. 5) with separate outcomes for high-risk patients (risk score ≥5) and patients not at high risk (risk score <5). Interestingly, the curves of high-risk patients continued to diverge beyond the first month up to 90 days after PCI. Although this study cannot provide a definitive answer to the question of optimal treatment duration when TAT is given, this observation suggests that a substantial proportion of events continues to take place after the first month in patients treated with DAT but not in those treated with TAT. Therefore, when TAT is prescribed in patients at high thrombotic risk and TAT is well tolerated by the patient in the first month, continuing TAT up to three months might be considered.

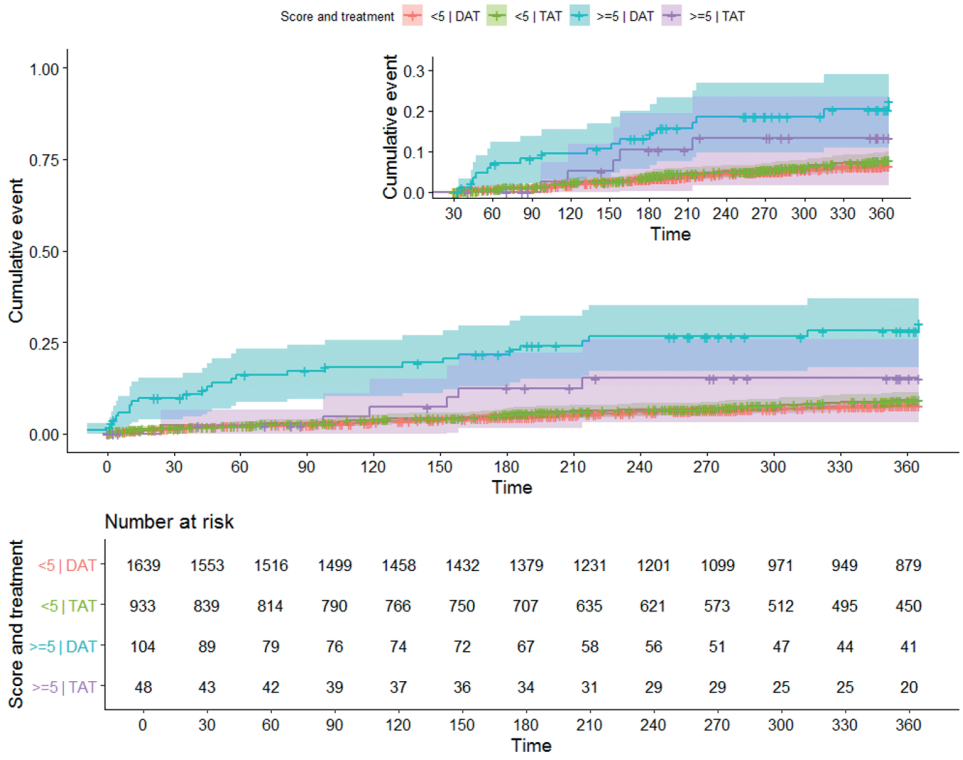


Figure 5:

Kaplan Meier curves for the timing of the combined thrombotic end point (with landmark analysis for events >30 days).

Performance of the CHA_2DS_2-VASc score

When applying the CHA_2DS_2-VASc in the RE-DUAL cohort, it showed only modest accuracy for the combined thrombotic end point (AUC 0.58 (CI 0.54-0.62, Fig. S6).

Discussion

This study sought to identify AF patients undergoing PCI at high risk for recurrent ischemic events who might benefit from TAT. The model was able to identify patients with high thrombotic risk. Triple therapy in these patients at high thrombotic risk was associated with a numerical reduction in thrombo-embolic events as compared to DAT. A simplified prediction rule found a significant reduction in MI/ST with TAT in patients with a risk score >5. Importantly, the lower incidence of ischaemic events with TAT as compared to DAT was outnumbered by an increase in bleeding events in the overall population but not in patients at the highest thrombotic risk.

The observation of a reduction in ischaemic events in high-risk patients is in line with some meta-analysis and subgroup analyses which pointed to a possible benefit of TAT, especially in high risk patients. Two meta-analysis of randomised controlled trials signalled a reduction in terms of stent thrombosis (and a trend for myocardial infarction) associated with TAT[14,16]. Stent thrombosis was significantly reduced, although incidence rates were bvery low, although other meta-analyses did not support this findings [5,20,21].

Our study is the first study to investigate the effect of TAT in patients at high thrombotic risk represented by a combination of high-risk characteristics. Several subgroup analyses of the randomised controlled trials based on single clinical variables (e.g. diabetes, age ≥80 years, ACS patients) could not demonstrated a reduction in ischemic events associated with TAT[22-24], which illustrates the complex and multifactorial aspect of high thrombotic risk which was adequately addressed in the current study by combining multiple patients characteristics.

Further randomised controlled studies will be needed to adequately address the question of TAT vs. DAT, particularly in high-risk patients. Of note, the results of the MASTER DAPT trial are expected this year. This randomised controlled trial (NCT03023020) specifically focuses on the sub group of patients at high bleeding risk [25] in both patients with and without OAC. After a mandatory 30-day DAPT run-in phase, patients with clinically indicated OAC are randomized to up to a total of three months of DAPT vs. single antiplatelet therapy after the first month. The results of the trial, which aims to recruit approximately 4,300 HBR patients from ≥100 interventional cardiology centers globally are to be awaited in 2021.

Clinical implications

Using this prediction rule containing seven clinical, angiographical and procedural parameters, a significant reduction in MI/ST associated with TAT was found in patients at high thrombotic risk undergoing PCI, without a penalty in terms of bleeding. Our findings are an important “proof of concept”, which is in line with general beliefs of many cardiologists with regard to high-risk patients.

On the other hand, for the majority of the population no benefit of TAT was found - and even harm in patients at low thrombotic risk, in whom an increase in BARC3 and 5 bleeding and a poorer net clinical benefit was observed. Therefore, our findings support the utilisation of DAT rather than TAT in the majority of AF patients undergoing PCI, while reserving TAT for a small proportion of patients – as was adapted in the most recent ESC guideline on non-STEMI [7].

Limitations

The TAT arm in this study comprised vitamin K antagonists whereas in contemporary clinical practice NOACs are standard care for its favourable safety profile. In the RE-DUAL trial, DAT including a NOAC was compared to TAT using a VKA, which might have exaggerated bleeding risk in the latter group.

Although an overall increase of bleeding associated with TAT was observed, numerically fewer bleeding events were observed in patients with a risk score of ≥5, which is an interesting observation and could be due to greater degrees of thrombin activation. A similar assymetrical treatment effect was observed in the PRECISE-DAPT bleeding score, in whom patients at high bleeding risk did no longer have a benefit in terms of a reduction in ischaemic events. Alternatively, this observation might be a play of chance or due to low patients numbers.

The performance of the score was good in the WOEST 2 registry which served as an external validation cohort. Although the AUC of 0.63 was modest (and typical of risk scores based on clinical factors), this applies to the overall fit of the risk score and does not necessarily correspond to the ability of the score to identify the patients at the highest risk. Finally, differences between DAT and TAT could not be tested, due to the indication bias inherent to the design of an observational registry. Before adapting this novel risk score into daily clinical practice, further external validation in randomised controlled trials is needed.

Conclusion

A clinical prediction rule was developed to estimate thrombotic risk in AF patients undergoing PCI. The model was able to identify a subgroup of high-risk patients comprising ~ 5% of the patients, in whom a significant reduction in MI/ST was observed with TAT, without a penalty in terms of bleeding. For patients not at high thrombotic risk, no benefit and even harm was found. Our findings support the use of TAT in this small subgroup of high-risk patients, while using DAT in the majority of AF patients undergoing PCI.

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Supplementary material

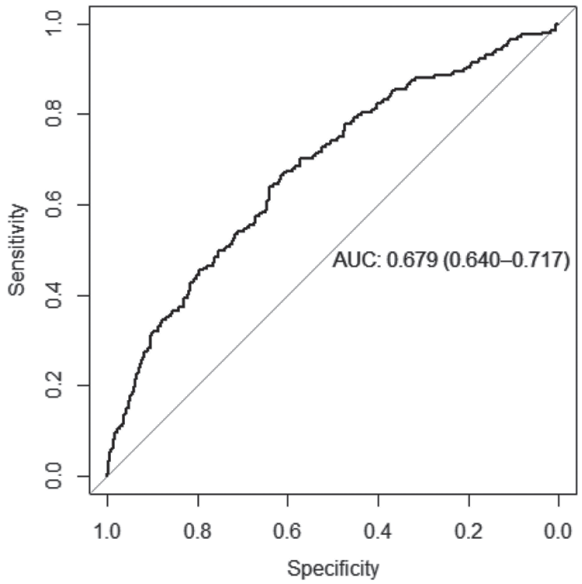


Figure S1:

Predictive accuracy for the combined thrombotic end point.

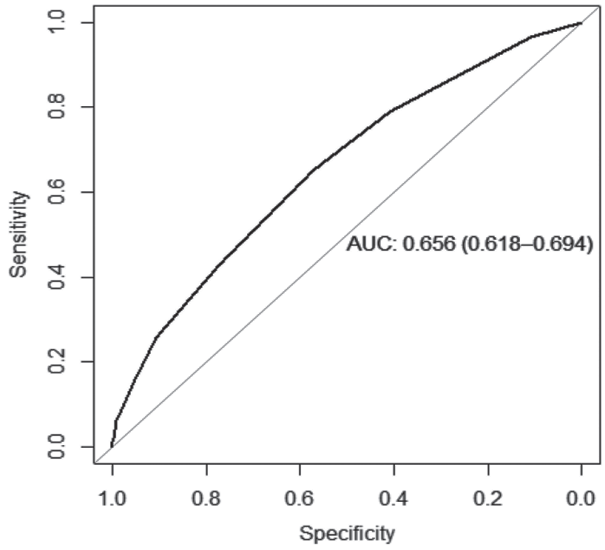


Figure S2:

Predictive accuracy for the combined thrombotic end point for the simplified prediction rule.

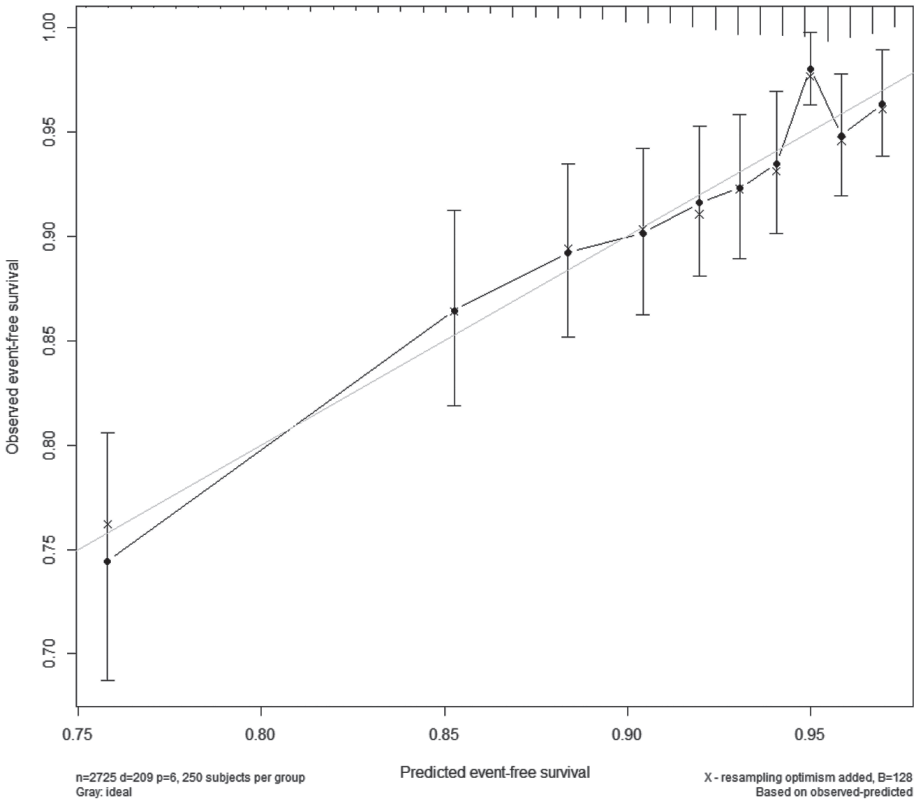
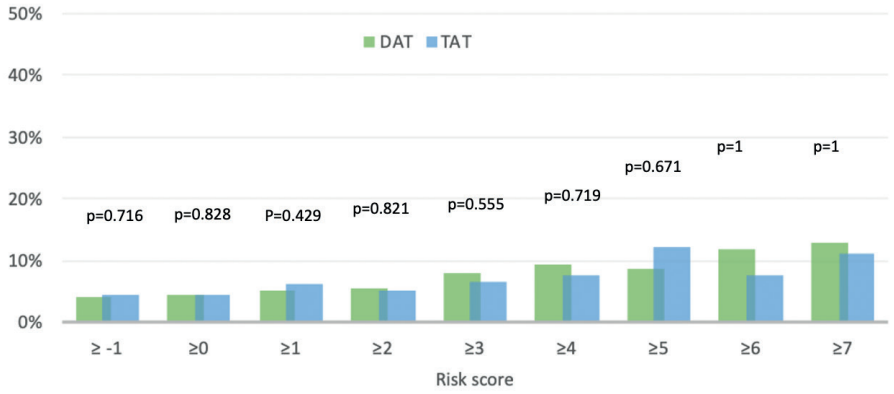


Figure S3:

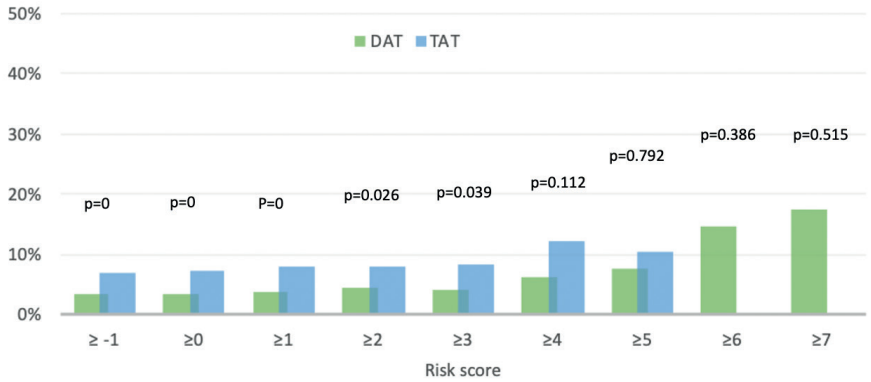
Calibration curve.

A: Observed mortality outcomes



No. of events								
113	109	92	66	50	25	15	5	4
No. of patients								
2725	2449	1655	1211	659	284	154	47	32
100%	90%	61%	44%	24%	10%	6%	2%	1%

B: Observed BARC 3+5 outcomes

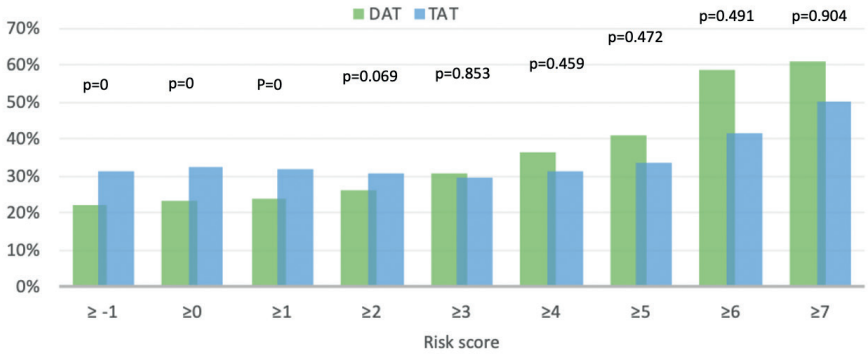


No. of events								
127	122	89	70	37	24	13	5	4
No. of patients								
2725	2449	1655	1211	659	284	154	47	32
100%	90%	61%	44%	24%	10%	6%	2%	1%

Figure S4:

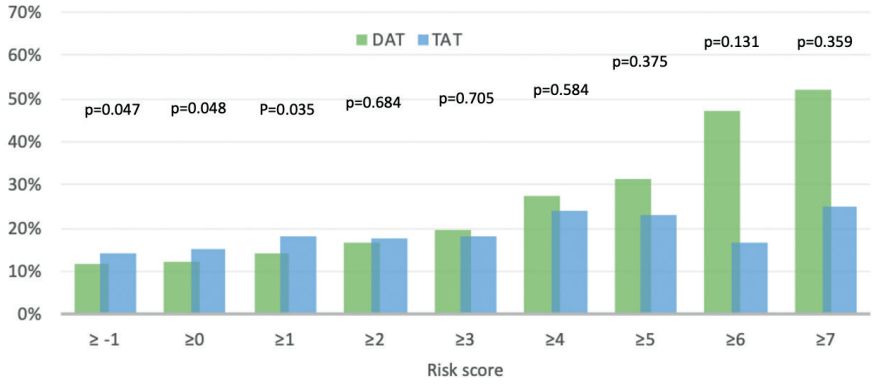
Observed Outcomes for DAT vs TAT for different cut-offs of risk score.

C: Observed net clinical benefit (MI/ST/death/istroke/BARC2+3+5 bleeding) outcomes



No. of events								
696	647	445	336	200	98	59	26	19
No. of patients								
2725	2449	1655	1211	659	284	154	47	32
100%	90%	61%	44%	24%	10%	6%	2%	1%

D: Observed net clinical benefit (MI/ST/death/istroke/BARC3+5 bleeding) outcomes



No. of events								
339	325	256	206	126	74	44	18	14
No. of patients								
2725	2449	1655	1211	659	284	154	47	32
100%	90%	61%	44%	24%	10%	6%	2%	1%

Figure S4: Continued

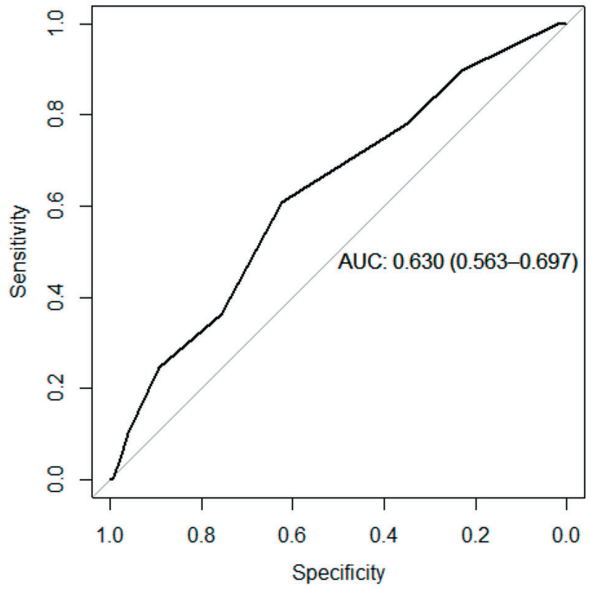


Figure S5:

C-statistic for external validation risk score in WOEST 2.

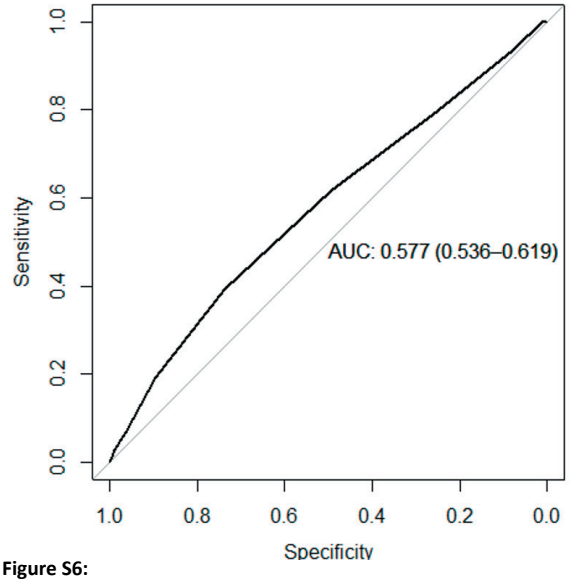


Figure S6:

C-statistic for the CHA2DS2-VASc score in the RE-DUAL cohort for the combined thrombotic end point.

Table S1: Observed outcomes by treatment group, quintiles based on predicted hazards.

	quintiel	N	overall thrombotic end point %	dt thrombotic end point %	tt thrombotic end point %	diff %	p-value	dt bleeding %	tt bleeding %	diff %	p-value	dt mortality %	tt mortality %	diff %	p-value
	1	545	3.85	3.92	3.72	-0.2	1	15.41	26.06	10.65	0.004	1.4	2.66	1.26	0.481
	2	545	3.67	3.52	3.92	0.4	0.995	14.96	29.9	14.94	0	2.35	2.94	0.59	0.885
	3	545	6.06	6.05	6.06	0.01	1	15.27	25.76	10.49	0.004	2.02	4.04	2.02	0.264
	4	545	8.99	7.95	10.88	2.93	0.324	13.35	21.76	8.41	0.016	4.55	5.18	0.63	0.902
high risk	5	545	15.78	17.29	13.13	-4.16	0.246	17.87	24.75	6.88	0.071	9.8	7.07	-2.73	0.356
low-int risk	1 tm 4	2180	5.64	5.37	6.13	0.76	0.52	14.75	25.93	11.18	0	2.58	3.7	1.12	0.176

Table S2: Observed outcomes by treatment group, deciles based on predicted hazards.

deciel	mean predicted hazard	N	overall thrombotic end point %	dt thrombotic end point %	tt thrombotic end point %	diff %	p-value	overall bleeding %	dt bleeding %	tt bleeding %	diff %	p-value	overall mortality %	dt mortality %	tt mortality %	diff %	p-value
1	0.384	273	2.56	2.82	2.08	-0.74	1	19.78	16.38	26.04	9.66	0.079	1.47	0.56	3.12	2.56	0.249
2	0.524	272	5.15	5	5.43	0.43	1	18.38	14.44	26.09	11.65	0.029	2.21	2.22	2.17	-0.05	1
3	0.632	273	1.47	1.15	2.02	0.87	0.959	22.34	17.24	31.31	14.07	0.011	1.47	1.15	2.02	0.87	0.959
4	0.753	272	5.88	5.99	5.71	-0.28	1	18.75	12.57	28.57	16	0.002	3.68	3.59	3.81	0.22	1
5	0.886	273	5.86	4.95	7.69	2.74	0.524	19.41	13.74	30.77	17.03	0.001	3.66	2.2	6.59	4.39	0.139
6	1.029	273	6.23	7.27	4.63	-2.64	0.53	18.68	16.97	21.3	4.33	0.46	1.83	1.82	1.85	0.03	1
7	1.229	272	9.19	7.78	11.43	3.65	0.425	17.28	11.98	25.71	13.73	0.006	5.15	4.79	5.71	0.92	0.957
8	1.515	273	8.79	8.11	10.23	2.12	0.727	15.38	14.59	17.05	2.46	0.73	4.4	4.32	4.55	0.23	1
9	1.948	272	10.66	10.06	11.65	1.59	0.834	17.65	15.38	21.36	5.98	0.276	7.72	8.28	6.8	-1.48	0.832
10	3.449	273	20.88	24.16	14.74	-9.42	0.095	23.08	20.22	28.42	8.2	0.168	9.89	11.24	7.37	-3.87	0.42

Table S3: Observed outcomes by treatment group, demi-deciles based on predicted hazards.

	mean predicted hazard	N	overall thrombotic end point %	dt thrombotic end point %	tt thrombotic end point %	diff %	p-value	overall bleeding %	dt bleeding %	tt bleeding %	diff %	p-value	overall mortality %	dt mortality %	tt mortality %	diff %	p-value
1	0.337	137	3.65	3.53	3.85	0.32	1	18.25	11.76	28.85	17.09	0.022	1.46	0	3.85	3.85	0.277
2	0.431	136	1.47	2.17	0	-2.17	0.823	21.32	20.65	22.73	2.08	0.958	1.47	1.09	2.27	1.18	1
3	0.495	136	5.15	5.21	5	-0.21	1	16.91	15.62	20	4.38	0.712	1.47	2.08	0	-2.08	0.89
4	0.552	136	5.15	4.76	5.77	1.01	1	19.85	13.1	30.77	17.67	0.022	2.94	2.38	3.85	1.47	1
5	0.605	136	2.21	1.15	4.08	2.93	0.61	21.32	18.39	26.53	8.14	0.371	2.21	2.3	2.04	-0.26	1
6	0.658	137	0.73	1.15	0	-1.15	1	23.36	16.09	36	19.91	0.015	0.73	0	2	2	0.778
7	0.719	136	4.41	3.8	5.26	1.46	1	21.32	15.19	29.82	14.63	0.065	3.68	2.53	5.26	2.73	0.709
8	0.787	136	7.35	7.95	6.25	-1.7	0.984	16.18	10.23	27.08	16.85	0.021	3.68	4.55	2.08	-2.47	0.801
9	0.851	136	3.68	2.27	6.25	3.98	0.483	19.12	12.5	31.25	18.75	0.015	2.94	1.14	6.25	5.11	0.248
10	0.92	136	8.09	7.45	9.52	2.07	0.944	19.85	14.89	30.95	16.06	0.053	4.41	3.19	7.14	3.95	0.559
11	0.988	137	3.65	4.6	2	-2.6	0.759	18.98	19.54	18	-1.54	1	2.92	2.3	4	1.7	0.966
12	1.069	136	8.82	10.26	6.9	-3.36	0.706	18.38	14.1	24.14	10.04	0.204	0.74	1.28	0	-1.28	1
13	1.168	136	11.03	8.89	15.22	6.33	0.409	17.65	12.22	28.26	16.04	0.037	7.35	5.56	10.87	5.31	0.438
14	1.291	136	7.35	6.49	8.47	1.98	0.915	16.91	11.69	23.73	12.04	0.104	2.94	3.9	1.69	-2.21	0.81
15	1.432	136	9.56	8.51	11.9	3.39	0.759	13.97	13.83	14.29	0.46	1	3.68	3.19	4.76	1.57	1
16	1.597	137	8.03	7.69	8.7	1.01	1	16.79	15.38	19.57	4.19	0.707	5.11	5.49	4.35	-1.14	1
17	1.787	136	9.56	7.23	13.21	5.98	0.391	21.32	18.07	26.42	8.35	0.345	6.62	6.02	7.55	1.53	1
18	2.108	136	11.76	12.79	10	-2.79	0.833	13.97	12.79	16	3.21	0.792	8.82	10.47	6	-4.47	0.568
19	2.57	136	19.12	21.84	14.29	-7.55	0.396	22.06	18.39	28.57	10.18	0.246	8.82	10.34	6.12	-4.22	0.604
20	4.258	136	22.06	25.56	15.22	-10.34	0.247	24.26	22.22	28.26	6.04	0.572	10.29	11.11	8.7	-2.41	0.888

Table S4: Missing in dataset for the selected variables in the model.

	Missings	%
LVEF	188	6.90%
Number of diseased vessels	63	2.31%
Myocardial infarction at baseline	26	0.95%
Platelet count	3	0.11%
Creatinin clearance	12	0.44%
Peripheral artery disease	179	6.57%

Table S5: Observed Clinical outcomes by subtypes of ischemic events.

quintile	N in quintile	Myocardial infarction N (%)	Stent thrombosis N (%)	Ischemic stroke N (%)	CV death N (%)
1	545	2.39	1.83	0.18	0.92
2	545	2.39	1.28	0.37	0.73
3	545	3.12	2.39	0.92	1.28
4	545	3.85	3.67	1.47	2.02
5	545	8.44	6.61	2.57	4.40

Table S6: Sensitivity analysis: observed thrombotic outcomes as competing risk analysis.

			No competing risk					Competing risk with BARC 2,3, and 5					Competing risk with BARC3 and 5				
deciel	mean predicted hazard	N	overall trombose %	dt trombose %	tt trombose %	diff %	p-value	overall trombose %	dt trombose %	tt trombose %	diff %	p-value	overall trombose %	dt trombose %	tt trombose %	diff %	p-value
1	0.454	545	3.85	3.92	3.72	-0.2	1	3.12	3.08	3.19	0.11	1	3.12	3.08	3.19	0.11	1
2	0.692	545	3.67	3.52	3.92	0.4	0.995	2.94	2.93	2.94	0.01	1	3.49	3.52	3.43	-0.09	1
3	0.957	545	6.06	6.05	6.06	0.01	1	4.59	4.9	4.04	-0.86	0.804	4.77	5.19	4.04	-1.15	0.693
4	1.372	545	8.99	7.95	10.88	2.93	0.324	6.79	6.82	6.74	-0.08	1	7.52	7.1	8.29	1.19	0.739
5	2.7	545	15.78	17.29	13.13	-4.16	0.246	11.56	13.54	8.08	-5.46	0.075	12.66	14.7	9.09	-5.61	0.079

CHAPTER

12

Estimating bleeding risk in AF patients undergoing PCI

Dual or Triple Therapy in AF patients undergoing PCI: the DATA-PCI risk score

B. Zwart, W.L. Bor, B.K. Mahmoodi, A. de Veer, J.C. Kelder, C.P. Cannon, J.M. ten Berg

** B. Zwart and W.L. Bor contributed equally to this manuscript*

Submitted

Abstract

Introduction:
The treatment of patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI) poses a challenge for cardiologists. Patients have an indication for both oral anti-coagulation (OAC) as well as antiplatelet therapy and are therefore at an increased risk of bleeding.

Methods:
We developed a prediction model in the RE-DUAL PCI trial. A Cox model predictive for BARC 2, 3 and 5 bleeding was constructed by stepwise selection from the candidate variables. The expected hazard of bleeding events at 365 days was predicted and compared to observed risk. Based on beta-coefficients of the Cox model a risk score was constructed. External validation was performed in the WOEST trial.

Results:
In 19.1% (520/2725) of patients, a BARC 2, 3 or 5 bleeding was documented. The multivariable Cox prediction model contained age, haematocrit, BMI, a history of malignancy and triple therapy. The discriminatory capacity in the derivation cohort was fair (AUC 0.70). In the simplified risk score, integer points were assigned to the variables. The total risk score ranged from - 5 to +10. Three risk categories could be distinguished: low bleeding risk (score <1 points, 10.7% bleeding risk), intermediate (1-2 points, 17.1%) and high bleeding risk (>2 points, 26.9%). Good discrimination and calibration were found in the WOEST trial.

Conclusion:
We developed a risk score which is able to estimate 1-year bleeding risk specifically for patients on OAC for AF undergoing PCI. As bleeding risk is high in this population, it is essential to identify patients at increased bleeding risk. Moreover, this score can help to estimate bleeding risk with or without triple therapy and thus might aid in (shared) decision making.

Introduction

The treatment of patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI) poses a challenge for cardiologists and other clinicians in daily practice. As these patients have an indication for both oral anti-coagulation (OAC) as well as antiplatelet therapy with a $P2Y_{12}$ inhibitor and/or aspirin, they are therefore at an increased risk of bleeding [1–3]. The combination of dual antiplatelet therapy and OAC (referred to as 'triple therapy') carries at least a two- to three-time risk of bleeding as compared to 'double therapy', a combination of OAC and a $P2Y_{12}$ inhibitor (DAT) [4,5]. However, DAT still carries at least a twofold risk of major bleeding when compared to single antiplatelet therapy(6,7). Several recent trials and meta-analyses have investigated a regimen of double antithrombotic therapy (DAT) against triple therapy (TAT). Most studies suggested an substantially lower rate of bleeding complications associated with DAT, with overall no consistent differences in ischaemic outcomes [8–12]. Current international guidelines and consensus documents recommend TAT for one week and up to one month in patients at high thrombotic risk [1,13,14]. Recently, we developed a risk score to identify this subset of patients at high thrombotic risk (*submitted*). A proportion of ~5% high-risk patients was identified who benefited from TAT.

Bleeding complication associated with antithrombotic therapy outnumber ischaemic event. One review estimated up to a 10-fold difference in contemporary practice [15]. Arguably, net clinical risk of these patients seems to be determined more by bleeding risk than by ischaemic risk. As several studies have shown that bleeding after PCI is strongly associated with adverse outcomes and mortality, it is key to be able to estimate patients' individual risk.

For AF patients in the general population the HAS-BLED score can be used, whereas for patients undergoing PCI the CRUSADE score was developed. To date, no risk tool exists to estimate the bleeding risk in this specific group of patients. In this study, we developed a bleeding risk calculator specifically for AF patients who undergo PCI.

Methods

Patients cohorts

The study was performed in the cohorts from two randomised controlled trials (WOEST trial, RE-DUAL PCI trial) comparing TAT versus DAT in PCI patients. The RE-DUAL cohort served as a derivation cohort and the WOEST cohort served as an external validation cohort.

In the RE-DUAL PCI trial, the DAT group was treated with dabigatran 110 or 150 mg in combination with a $P2Y_{12}$ inhibitor (clopidogrel in 87%, or ticagrelor in 12% of patients). In the WOEST trial DAT consisted of VKA and clopidogrel. In both trials the TAT group consisted

of VKA, aspirin and a $P2Y_{12}$ inhibitor (100% clopidogrel in WOEST, and clopidogrel in 90% or ticagrelor in 8% of patients in RE-DUAL).

Endpoint definitions

The bleeding endpoint was defined as the first Bleeding Academic Research Consortium (BARC) 2, 3 or 5 bleeding within 365 days. Follow-up was truncated after the first event. For instance, a bleeding after a recurrent thrombotic event would not be analysed since antithrombotic management might have been adjusted after the earlier thrombotic event. The composite ischaemic endpoint was defined as cardiovascular death, myocardial infarction (MI), stent thrombosis (definite or probable according to Academic Research Consortium [ARC] criteria) or ischaemic stroke.

Follow-up

The mean follow-up after PCI was 14 months in the RE-DUAL trial and 12 months in the WOEST trial. Groups were compared according to intention-to-treat protocol. For this analysis follow-up was truncated at 365 days to obtain risk estimates for the first year of double versus triple antithrombotic therapy.

Statistical analysis

Baseline characteristics were compared between patients with and without bleeding events during the 1-year follow-up by t-test, or its nonparametric equivalents as appropriate, or Chi-square for categorical variables.

Predictors

Based on clinical plausibility and availability in both trial datasets, variables were considered as candidate predictors. The variables included age, sex, BMI, hypertension, hypercholesterolemia, DM, smoking, alcohol use, medical history (bleeding, MI, PCI, CABG, stroke, VTE or systemic embolism, renal failure, malignancy, PAD, heart failure), MI at presentation, LVEF, and laboratory tests at presentation (haemoglobin, haematocrit, platelet count, leukocyte count, creatinine, eGFR by CKD-EPI). We did not include modifiable factors like medication use.

Model development

Candidate variables for the Cox model were selected by univariate Cox regression stratified for access site and bare metal stent (BMS) placement (as this latter directly influenced treatment duration in RE-DUAL). Variables showing a P-value <0.30 were considered as candidate variables for inclusion in the model. A Cox model (stratified for access site and BMS placement) for the bleeding endpoint was constructed by stepwise selection from the candidate variables using a 0.05 significance level. Missing values in the dataset for stepwise model selection were imputed by simple means (for percentage of missing values

per variable see table S1). Based on beta-coefficients of the Cox model a point score was constructed using the methods as proposed in the Framingham Study risk scores. [16]

Internal validation

With the Cox model the expected hazard of bleeding events given the covariates was predicted at 365 days. Also, the point score was calculated for each patient. Predictive accuracy of the model and point score was evaluated by area under the receiver operating curve. The cohort was divided in quintiles and deciles based on the expected hazards, or grouped by point score to assess calibration. Observed risks of ischaemic events, bleeding, and mortality were compared between the patients that received triple or DAT.

External validation

For every patient in the WOEST trial cohort the point score was calculated. Since malignancy was not recorded in the WOEST database no points were given for malignancy to any patient. Discrimination was evaluated by area under the receiver operating curve. Calibration was evaluated by plotting the observed bleeding risk in decile of the predicted point score. Observed risks of ischaemic events, bleeding, and mortality were compared between the patients that received triple or DAT.

Results

A total of 2725 patients were included in this analysis. In 520 patients, a BARC 2, 3 or 5 bleeding was documented (19.1%). Baseline characteristics of patients with and without bleeding events are depicted in Table 1. Patients with a bleeding event during follow-up in the derivation cohort were more likely to have a history of malignancy or a history of previous PCI, were older and were more often female. In addition, lower BMI and lower haemoglobin and haematocrit were more frequently observed, whereas fewer patients had undergone PCI to a coronary bypass graft or had received a long stent.

Table 1: Baseline characteristics of patients with and without bleeding events during follow-up (REDUAL, derivation cohort).

	BARC 2, 3 or 5 bleeding		
	No (N=2205)	**Yes (N=520)**	**p**
Treatment arm			
Triple therapy (%)	729 (33.1)	252 (48.5)	<0.001
Demographics			
Age (mean (SD))	70.32 (8.63)	72.36 (8.18)	<0.001
Female sex (%)	521 (23.6)	134 (25.8)	0.332
BMI (median [IQR])	28.40 [25.50, 32.00]	27.00 [24.40, 30.40]	<0.001
Comorbidities			
Hypertension (%)	1844 (83.7)	450 (86.5)	0.121
Hypercholesterolaemia (%)	1433 (65.0)	337 (64.8)	0.969

Table 1: Continued

	BARC 2, 3 or 5 bleeding		
	No (N=2205)	**Yes (N=520)**	**p**
Current smoker (%)	278 (12.6)	59 (11.3)	0.474
Diabetes Mellitus (%)	793 (36.0)	200 (38.5)	0.314
Alcohol use (%)	1128 (51.2)	247 (47.5)	0.144
History of myocardial infarction (%)	553 (25.1)	146 (28.1)	0.176
History of heart failure (%)	766 (34.8)	171 (32.9)	0.449
History of GI bleed (%)	140 (6.4)	43 (8.3)	0.141
History of stroke (%)	183 (8.3)	43 (8.3)	1.000
History of renal failure (%)	365 (17.0)	96 (18.9)	0.320
History of PCI (%)	717 (32.5)	195 (37.5)	0.035
History of CABG (%)	227 (10.3)	60 (11.5)	0.454
History of malignancy (%)	175 (8.1)	66 (13.1)	0.001
History of peripheral artery disease (%)	149 (7.2)	39 (8.1)	0.594
History of venous thromboembolism (%)	75 (3.4)	13 (2.5)	0.363
Characteristics at presentation			
Acute coronary syndrome (%)	1117 (50.7)	258 (49.6)	0.698
STEMI (%)	256 (23.4)	49 (19.2)	
NSTEMI (%)	476 (43.5)	106 (41.6)	
Unstable angina (%)	362 (33.1)	100 (39.2)	
LVEF (mean (SD))	51.06 (12.31)	50.92 (13.23)	0.822
ECG of AFib of AFlu (%)	1039 (47.1)	226 (43.5)	0.145
Haemoglobin (mmol/l) (median [IQR])	8.50 [7.82, 9.18]	8.32 [7.57, 9.06]	<0.001
Haematocrit (%)(median [IQR])	41.00 [38.00-44.00]	40.00 [37.00-44.00]	<0.001
White blood cell count (median [IQR])	7.36 [6.12, 8.96]	7.42 [6.12, 8.89]	0.986
Platelet count (median [IQR])	202.00 [171.00, 245.00]	198.00 [168.00, 241.75]	0.296
Creatinin (umol/l) (median [IQR])	88.00 [74.00, 106.00]	88.00 [77.00, 105.00]	0.700
eGFR (CKD-EPI) (median [IQR])	75.00 [61.00, 89.00]	75.00 [60.75, 87.00]	0.159
Procedural characteristics			
Femoral access (%)	775 (35.4)	197 (38.3)	0.249
Heparin use (%)	1855 (84.2)	433 (83.3)	0.664
LMWH use (%)	332 (15.1)	66 (12.7)	0.191
Number of diseased vessels (%)			0.962
1	1130 (52.4)	261 (51.8)	
2	640 (29.7)	150 (29.8)	
3	388 (18.0)	93 (18.5)	
Left main disease (%)	41 (1.9)	7 (1.3)	0.539
Intracoronary thrombus (%)	37 (1.7)	6 (1.2)	0.505
Number of diseased vessels (%)			0.220
1	1758 (81.2)	420 (82.4)	
2	345 (15.9)	70 (13.7)	
3	61 (2.8)	20 (3.9)	
Stent length >30mm (%)	195 (8.8)	45 (8.7)	0.959
LAD stented (%)	1061 (48.1)	224 (43.1)	0.043
LCx stented (%)	580 (26.3)	137 (26.3)	1.000
RCA stented (%)	747 (33.9)	189 (36.3)	0.310
Bypass graft stented (%)	60 (2.7)	17 (3.3)	0.596
Bare metal stent placement (%)	381 (17.3)	69 (13.3)	0.031
Outcomes at 365 days			
Death (%)	74 (3.4)	39 (7.5)	<0.001
Cardiovascular death (%)	32 (1.5)	19 (3.7)	0.002
Myocardial infarction (%)	80 (3.6)	30 (5.8)	0.035
Stent thrombosis (%)	67 (3.0)	19 (3.7)	0.560
Stroke (%)	24 (1.1)	15 (2.9)	0.004
Ischemic stroke (%)	23 (1.0)	7 (1.3)	0.717
Hemorrhagic stroke (%)	0 (0.0)	6 (1.2)	<0.001
BARC 2, 3 or 5 bleeding (%)	0 (0.0)	520 (100.0)	<0.001
BARC 3 or 5 bleeding (%)	0 (0.0)	127 (24.4)	<0.001

Table 2 shows results of stratified univariate Cox regression. Multiple predictors for bleeding events were identified. Strong predictors were triple therapy, history of malignancy, alcohol use, higher age, and lower BMI, haematocrit or haemoglobin.

Table 2: Univariate cox regression for BARC 2,3 and 5 bleeding events.

	Beta	HR (95% CI for HR)	Wald test	p-value
Triple therapy (vs dual therapy)	0.64	1.9 (1.6-2.3)	53	3.9e-13
Age	0.03	1 (1-1)	28	9.5e-08
Haematocrit	-0.046	0.95 (0.94-0.97)	21	4e-06
Body-mass index	-0.039	0.96 (0.94-0.98)	18	2.8e-05
Hx/ Malignancy	0.49	1.6 (1.3-2.1)	14	0.00024
Haemoglobin	-0.16	0.85 (0.78-0.93)	13	0.0013
Alcohol use	-0.19	0.82 (0.69-0.98)	4.7	0.03
Hypertension	0.24	1.3 (0.99-1.6)	3.5	0.062
Female sex	0.16	1.2 (0.97-1.4)	2.6	0.11
Hx/ coronary revascularization	0.14	1.2 (0.97-1.4)	2.5	0.11
Hx/ Vascular disease	0.14	1.2 (0.96-1.4)	2.4	0.13
eGFR	-0.003	1 (0.99-1)	2	0.16
Myocardial infarction as indication for procedure	-0.13	0.88 (0.73-1.1)	1.8	0.18
Hx/ Renal insufficiency	0.14	1.1 (0.92-1.4)	1.5	0.23
Hx/ Myocardial infarction	0.12	1.1 (0.93-1.4)	1.4	0.24
Active smoking	-0.14	0.87 (0.66-1.1)	1	0.31
Hx/ Venous thromboembolism/systemic embolism	-0.2	0.82 (0.5-1.3)	0.61	0.44
Hx/ Peripheral arterial disease	0.13	1.1 (0.82-1.6)	0.57	0.45
Hx/ Diabetes Mellitus	0.067	1.1 (0.9-1.3)	0.55	0.46
Hx/ Hypercholesterolemia	-0.052	0.95 (0.79-1.1)	0.31	0.58
Hx/ Bleeding	0.21	1.2 (0.58-2.6)	0.3	0.58
Left ventricular ejection fraction	-0.0016	1 (0.99-1)	0.2	0.65
Congestive heart failure/ LVEF>30%	-0.024	0.98 (0.81-1.2)	0.06	0.8
Platelet count	-5.8e-05	1 (1-1)	0.01	0.93
Creatinin	0.00012	1 (1-1)	0.01	0.94
Current or past smoker	-0.006	0.99 (0.83-1.2)	0	0.95
Leukocyte count	0.00068	1 (0.96-1)	0	0.97
Acute coronary syndrome as indication for procedure	0.0023	1 (0.84-1.2)	0	0.98
Hx/ Stroke	0.00041	1 (0.73-1.4)	0	1

Corrected for access site and stent type.

The multivariable Cox regression model predicting bleeding events contained triple therapy, age, haematocrit, BMI and a history of malignancy (Table 3). The discriminatory capacity of the bleeding model was fair (AUC 0.704 (CI 0.678-0.730, Figure 1).

Table 3: Cox proportional hazards model predictive of BARC 2, 3 and 5 bleeding.

Predictor of events	HR (95% CI)	P value
Triple therapy	1.808 (1.521-2.149)	< 0.001
Age	1.018 (1.001-1.030)	0.001
Haematocrit	0.967 (0.948-0.986)	0.001
Body-mass index	0.973 (0.955-0.991)	0.003
History of malignancy	1.442 (1.111-1.871)	0.006

Analysis stratified for access site, and stent type.

Concordance = 0.638 (se = 0.02)
Rsquare = 0.038 (max possible = 0.918)
Likelihood ratio test = 104.3 on 5 df, p = <2e-16
Wald test = 105.1 on 5 df, p = <2e-16
Score (logrank) test = 107.3 on 5 df, p = <2e-16

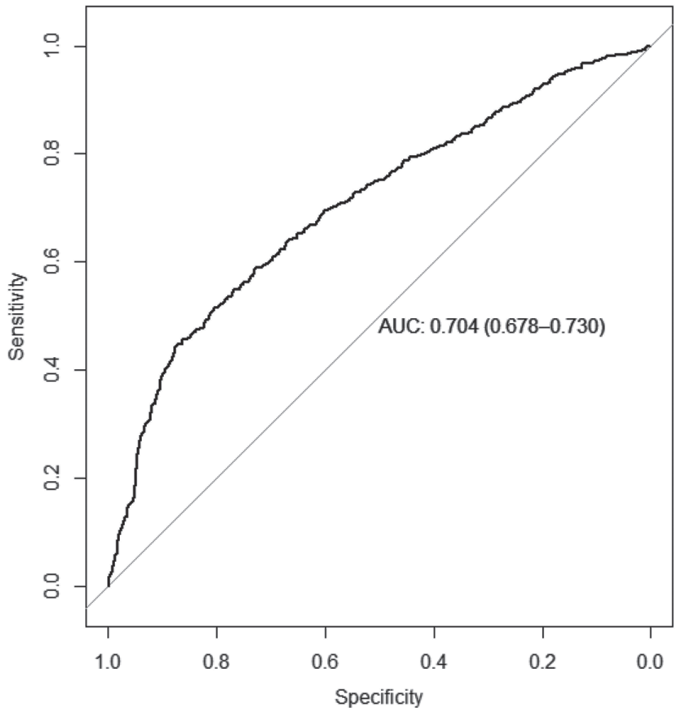


Figure 1: Predictive accuracy for the bleeding end point (RE-DUAL derivation cohort).

In the simplified prediction model, integer points were assigned to the predictors. The following points were assigned: triple therapy +3 points; a history of malignancy +2 points; age +0 for age <60 years ranging to +4 points for age >90; haematocrit -2 to +3 points; BMI -3 to +1 points (Table 4). The total risk score ranged from - 5 to +10. Discrimination of the simplified prediction rule was moderate (AUC 0.64 (0.61-0.66) in the RE-DUAL derivation cohort (Fig. S1).

Table 4: Simplified prediction model.

Age	**<60**	**+0**	Body-mass index	<20	**+1**
	60-70	**+1**		**20-25**	**+0**
	70-80	**+2**		25-30	**-1**
	80-90	**+3**		30-35	**-2**
	>90	**+4**		35-40	**-2**
				>40	**-3**
Haematocrit (%)	<30	**+3**	Malignancy		**+2**
	30-35	**+2**			
	35-40	**+1**	Triple therapy		**+3**
	40-45	**+0**			
	45-50	**-1**			
	>50	**-2**			

Higher scores were associated with higher bleeding rates (Fig. 2 and Table S2). When clustered, a score of <1 points was associated with low bleeding risk (10.7% overall bleeding risk), a score of 1-2 points was associated with intermediate bleeding risk (17.1%), whereas a score of >2 points was associated with high (26.9%) bleeding risk (Table 5).

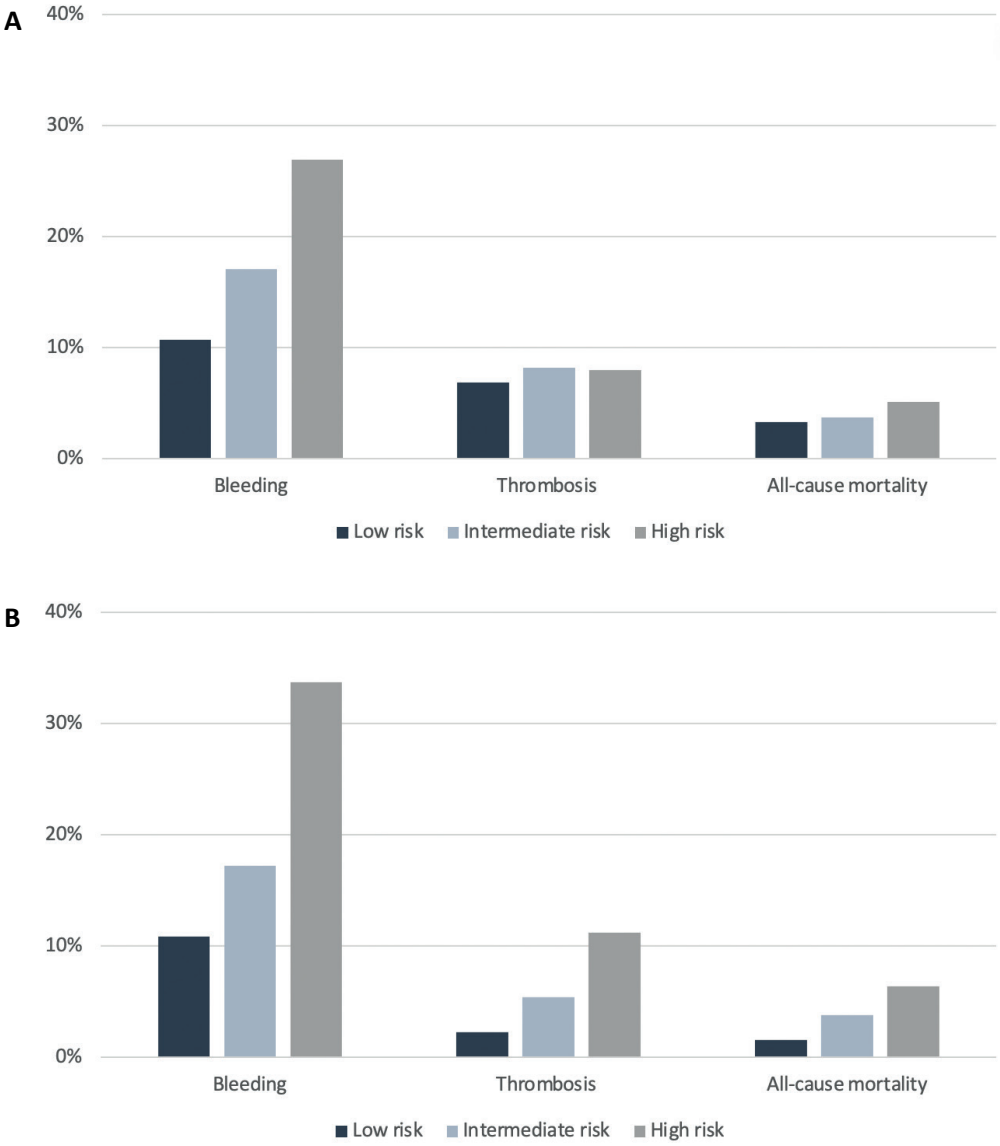


Figure 2: Observed Outcomes in the derivation cohort (A) and in the validation cohort (B).

Low risk: <1 points
Intermediate risk: 1-2 points
High risk: >2 points

Validation cohort

The simplified prediction score was validated in the WOEST study cohort. Discrimination was moderate to fair (AUC 0.66 (0.60-0.71) (Fig. S2). Calibration was similar to the derivation cohort, with bleeding rates varying from 10.9% in low risk, 17.2% in intermediate risk to 33.7% in high-risk patients (Fig 4 and Table S3).

Discussion

This is the first available risk score which was specifically developed to estimate bleeding risk in AF patients undergoing PCI. The prediction model, derived in the RE-DUAL trial and validated in the WOEST trial was able to estimate bleeding risk based on treatment strategy, age, haematocrit, BMI and history of malignancy. Patients were classified to have low bleeding risk (~ 10%), moderate bleeding risk (15-20%) or high bleeding risk (> 25%).

Previous studies have shown that post procedural bleeding confers a major risk of adverse outcomes including mortality [17–19]. Bleeding risk is very high in this particular population treated with a combination of anticoagulation and antiplatelet drugs. To date, no bleeding model existed for this specific patient population of AF patients undergoing PCI. For ACS patients the CRUSADE risk score is being used, whereas the HAS-BLED score is currently being used to estimate bleeding risk in patients with atrial fibrillation. However, these risk scores were developed for different populations. The CRUSADE score was developed for (hospitalised) post-MI patients and is therefore not applicable to patients who undergo PCI for another indication than ACS. The HAS-BLED score was developed in AF patients who were treated with VKA-based OAC.

Implications for clinical practice

AF patients undergoing PCI have a substantially increased bleeding risk due to the combination of both OAC and antiplatelet agents. However, bleeding risk varies considerable between patients. It is essential to identify patients with increased bleeding risk, in order to be able to modifiable factors and to consider modifying the duration of antithrombotic therapy.

Moreover, this score can help to estimate bleeding risk with or without triple therapy in selected patients and thus might aid in (shared) decision making.

Limitations

One limitation of this study is that the triple therapy arm comprised vitamin K antagonists in a substantial proportion of patients. In the RE-DUAL trial, dual therapy including a NOAC was compared to triple therapy using a VKA, which might have exaggerated bleeding risk in the latter group. In WOEST, patients in both the dual and triple therapy received VKA. Indeed, when comparing bleeding rates in the AUGUSTUS trial (its design allowed a comparison for

VKA-based TAT vs. NOAC based TAT), ISTH major or clinically relevant non-major bleeding were higher in VKA based TAT (18.7%) as compared to NOAC-based TAT (13.8%, p-value not provided) (9; supplementary files).

The performance of the bleeding score was modest with a c statistic of 0.70 for the derivation cohort. However, when compared to other risk scores such as HAS-BLED and CRUSADE, discriminatory properties were comparable with AUC's of 0.72 and 0.71, respectively [20,21]. Another more recent bleeding score in AF patients, the biomarker based ABC-score, had a c-index 0.68 which is also similar to our model [22]. The PRECISE-DAPT, a bleeding score used to estimate bleeding risk in PCI patients treated with DAPT, a c-statistic of 0.65-0.70 was observed in the validation cohorts. [23] Of note, the simplified prediction rule in WOEST had a similar performance as compared to the RE-DUAL derivation cohort. This slightly better AUC (although overlapping confidence intervals) in the WOEST is probably a shrinkage effect.

The performance of the HAS-BLED and CRUSADE score could not be tested, due to the fact that not all variables used in these scores were available in the RE-DUAL and WOEST datasets (e.g. heart rate and blood pressure for the CRUSADE and "labile INR's" and bleeding history for the HAS-BLED score).

Conclusion and recommendation

We developed a risk score which is able to estimate 1-year bleeding risk specifically for patients AF patients treated with oral anticoagulation undergoing PCI. Bleeding risk in this population is high, but varies considerable between patients. Therefore it is essential to identify patients with increased bleeding risk. This score can help to estimate bleeding risk with or without triple therapy and thus might aid in (shared) decision making.

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Supplement material

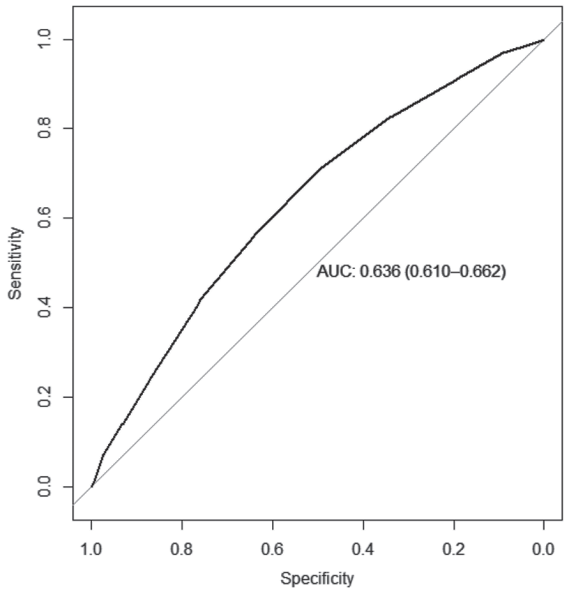

Figure S1: Predictive accuracy for the bleeding end point for the simplified prediction rule (RE-DUAL derivation cohort).

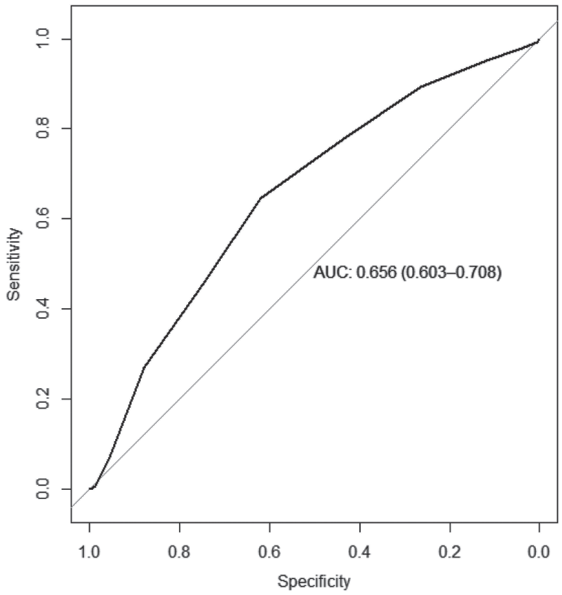

Figure S2: Predictive accuracy for the bleeding end point for the simplified prediction rule (WOEST validation cohort).

Table S1: LBaseline characteristics of patients with and without bleeding events during follow-up (WOEST, validation cohort).

	BARC 2, 3 or 5 bleeding		
	No (N=433)	Yes (N=130)	p
Treatment arm			
Triple therapy (%)	194 (44.8)	90 (69.2)	<0.001
Demographics			
Age (mean (SD))	68.47 (10.61)	68.33 (11.66)	0.901
Female sex (%)	83 (19.2)	32 (24.6)	0.220
BMI (median [IQR])	27.46 [24.78, 30.42]	26.53 [24.57, 28.96]	0.055
Comorbidities			
Hypertension (%)	295 (68.1)	91 (70.0)	0.768
Hypercholesterolaemia (%)	302 (69.7)	94 (72.3)	0.652
Current smoker (%)	48 (11.2)	14 (10.9)	1.000
Diabetes Mellitus (%)	115 (26.6)	25 (19.2)	0.114
History of myocardial infarction (%)	161 (37.2)	35 (26.9)	0.041
History of heart failure (%)	103 (23.9)	38 (29.2)	0.266
History of GI bleed (%)	21 (4.9)	7 (5.4)	0.992
History of stroke (%)	73 (16.9)	26 (20.0)	0.495
History of renal failure (%)	73 (16.9)	26 (20.2)	0.465
History of PCI (%)	154 (35.6)	33 (25.4)	0.038
History of CABG (%)	96 (22.2)	34 (26.2)	0.409
Characteristics at presentation			
Acute coronary syndrome (%)	124 (28.9)	31 (24.2)	0.355
STEMI (%)	12 (9.7)	0 (0)	0.153
NSTE-ACS (%)	112 (90.3)	31 (100.0)	0.153
LVEF (mean (SD))	46.30 (14.23)	45.85 (15.08)	0.795
ECG of AFib of AFlu (%)	155 (35.8)	44 (33.8)	0.762
Haemoglobin (mmol/l) (median [IQR])	8.53 [7.90, 9.20]	8.13 [7.50, 8.90]	0.004
Haematocrit (%) (mean (SD))	40.49 (5.21)	39.26 (5.49)	0.033
White blood cell count (median [IQR])	208.00 [177.00, 244.00]	210.00 [174.00, 247.00]	0.903
Platelet count (median [IQR])	90.00 [75.00, 107.00]	91.00 [75.00, 110.00]	0.775
Creatinin (umol/l) (median [IQR])	75.00 [59.00, 91.00]	75.00 [58.00, 90.00]	0.862
eGFR (CKD-EPI) (median [IQR])	8.53 [7.90, 9.20]	8.13 [7.50, 8.90]	0.004
Procedural characteristics			
Femoral access (%)	322 (74.9)	90 (70.9)	0.429
Heparin use (%)	394 (92.5)	114 (91.2)	0.778
LMWH use (%)	99 (22.9)	35 (27.1)	0.386
Number of diseased vessels (%)			0.551
1	223 (51.7)	65 (50.0)	
2	130 (30.2)	36 (27.7)	
3	78 (18.1)	29 (22.3)	
Left main disease (%)	31 (7.4)	16 (12.6)	0.096
Number of diseased vessels (%)	304 (71.2)	97 (75.2)	0.141
1	102 (23.9)	23 (17.8)	
2	21 (4.9)	8 (6.2)	
3			
Stent length >30mm (%)	104 (24.3)	29 (23.0)	0.859
LAD stented (%)	177 (40.9)	52 (40.0)	0.939
LCx stented (%)	101 (23.3)	34 (26.6)	0.586
RCA stented (%)	126 (29.1)	38 (29.2)	1.000
Bypass graft stented (%)	26 (6.0)	6 (4.6)	0.701
Bare metal stent placement (%)	142 (33.2)	47 (37.6)	0.418

Table S1: Continued

	BARC 2, 3 or 5 bleeding		
	No (N=433)	**Yes (N=130)**	**p**
Outcomes at 365 days			
Death (%)	16 (3.7)	9 (6.9)	0.185
Cardiovascular death (%)	8 (1.8)	2 (1.5)	1.000
Myocardial infarction (%)	17 (3.9)	5 (3.8)	1.000
Stent thrombosis (%)	12 (2.8)	1 (0.8)	0.317
Stroke (%)	5 (1.2)	6 (4.6)	0.032
Ischemic stroke (%)	5 (1.2)	5 (3.8)	0.097
Hemorrhagic stroke (%)	0 (0.0)	1 (0.8)	0.523
BARC 2, 3 or 5 bleeding (%)	0 (0.0)	130 (100.0)	<0.001
BARC 3 or 5 bleeding (%)	42 (9.7)	12 (9.2)	1.000

Table S2: Observed bleeding outcomes, stratified by bleeding score in RE-DUAL cohort.

	Bleeding	**Thrombosis**	**All- cause mortality**
score	***Overall incidence***	***Overall incidence***	***Overall incidence***
<1	10.71%	6.9%	3.33%
N=840	N=90	N=58	N=28
1-2	17.09%	8.16%	3.7%
N=784	N=134	N=64	N=29
>2	26.92%	7.97%	5.13%
N=1092	N=294	N=87	N=56

Low risk: <1 points
Intermediate risk: 1-2 points
High risk: >2 points

Table S3: Observed bleeding outcomes, stratified by bleeding score in the WOEST cohort.

	Bleeding	**Thrombosis**	**All- cause mortality**
score	***Overall incidence***	***Overall incidence***	***Overall incidence***
<1	10.94%	2.34%	1.56%
N=128	N=14	N=3	N=2
1-2	17.2%	5.38%	3.76%
N=186	N=32	N=10	N=7
>2	33.73%	11.24%	6.43%
N=249	N=84	N=28	N=16

Low risk: <1 points
Intermediate risk: 1-2 points
High risk: >2 points

Table S4: Sensitivity analyses for different bleeding definitions with the model developed for BARC 2, 3 and 5 bleeding.

	REDUAL			WOEST		
	BARC 2, 3, and 5	**BARC 3 and 5**	**TIMI major and minor**	**BARC 2, 3, and 5**	**BARC 3 and 5**	**TIMI major and minor**
AUC	0.636 (0.610-0.662)	0.527 (0.481-573)	0.483 (0.443-0.523)	0.656 (0.603-0.708)	0.488 (0.381-0.596)	0.556 (0.441-0.672)
Incidence of bleeding per score						
<1	10.71%	6.55%	8.21%	10.94%	7.81%	7.81%
	N=90	N=55	N=69	N=14	N=10	N=10
1-2	17.09%	5.01%	7.63%	17.2%	5.38%	4.48%
	N=134	N=40	N=61	N=32	N=10	N=9
>2	26.92%	4.88%	7.00%	33.73%	5.22%	4.48%
	N=294	N=53	N=76	N=84	N=13	N=9

CHAPTER

13

Summary and General Discussion

Summary and General Discussion

Stent thrombosis

In part I, the role of triggering mechanisms in provoking stent thrombosis is described. Furthermore, the relation between premature discontinuation of dual antiplatelet therapy (DAPT) and the incidence of stent thrombosis are discussed. Finally, the feasibility of using glycoprotein IIb/IIIa inhibitors in STEMI patients who have been pretreated with morphine is described.

Over the years, many predictors of stent thrombosis have been identified. This includes clinical (e.g. diabetes, LVEF<30%), procedural (e.g. undersizing, edge dissection), angiographic (e.g. TIMI flow grade <3) and genetic risk factors (e.g. carriers of the CYP2C19*2 allele). Furthermore, premature cessation of clopidogrel and high on-treatment platelet reactivity (HPR) are strong predictors of ST. Nonetheless, it is surprising why only a small proportion of patients with risk factors for ST eventually develop ST.

Chapter 5 explored possible triggering mechanisms of ST. In a substantial number of patients (23%), a triggering mechanisms preceding the stent thrombosis was identified. This included vigorous exercise, emotional stress or an active infection at the time of stent thrombosis. In addition, analysis of circadian variation showed a steep peak incidence from 7am-12pm.

These findings are in line with known triggering mechanisms in spontaneous myocardial infarction (i.e. not stent-related). Both physical exercise, timing of onset and emotional stress have all previously been identified as triggering mechanisms for myocardial infarction [1–4]. Stent thrombosis and spontaneous myocardial infarction share many pathophysiological pathways. These processes include increased sympathetic activity and vagal withdrawal, elevation in plasma catecholamines and renin levels, increased thrombin generation, increased heart rate and blood pressure, exercise induced coronary-artery spasm, increased systemic inflammation, increased vascular resistance, increased vessel-wall stress, a heightened platelet reactivity status and a hypercoagulability state. The identification of potential triggering mechanisms of ST might have important clinical implications related to both prognosis and prevention.

First, it should be acknowledged that some patients might be more vulnerable to stress-induced biological responses than others. Second, in relation to prevention, the ideal approach should involve a range of various strategies for the different types of triggering. Patients undergoing coronary stent implantation should be encouraged to perform moderate physical activity on a regular basis, because the beneficial effects of exercise training in the secondary prevention of coronary artery disease have been well

established [5]. Importantly, there is ample evidence that regular moderate exercise lowers both the baseline risk as well as the relative risk that an episode of heavy physical exertion will trigger myocardial infarction [6,7]. However, caution remains warranted when patients plan to perform vigorous exercise, especially when untrained. This supports the current practice of performing an exercise test under supervised conditions in patients who engage in cardiac rehabilitation after a myocardial infarction.

All patients undergoing PCI with stent implantation receive dual antiplatelet therapy (DAPT). Several previous studies have established the relationship between premature discontinuation of clopidogrel and the occurrence of stent thrombosis [8–10]. On the other hand, more recent trials explored a shorter DAPT duration and suggested that a shorter DAPT duration up to 3 months might be as safe as the standard regimen [11,12]. Therefore, the absolute risk of stent thrombosis after early clopidogrel discontinuation was studied in a matched cohort of ST patients (**Chapter 6**). The incidence of stent thrombosis was found to be as high as 35.4% when clopidogrel was discontinued in the first month after PCI and was still 11.7% in case of clopidogrel cessation in the first 180 days. Hence, the risk of stent thrombosis was very high in this cohort of mainly ACS patients, and therefore early clopidogrel cessation should be avoided based on these data.

The absolute incidence of stent thrombosis found in this study seem quite high when compared to contemporary stent thrombosis rates, but is line with other (scarce) data from this era. Schulz et al.[13] found a stent thrombosis rate of ~12% when clopidogrel was discontinued in the first 6 months.

On the other hand, these findings seem to contrast to more recent studies suggesting that a short (3-6 month) regimen could be safe. However, these studies included mostly low-risk patients or were not powered to detected differences in ischaemic outcomes.

The SMART-DATE study was a large randomised trial which assigned a total of 2712 ACS patients to either 6 or 12 months of DAPT [14]. The authors found that myocardial infarction occurred more frequently in the 6-month DAPT group than in the 12-month or longer DAPT group (HR 2.41 (1.15-5.05), p=0.02). A meta-analysis of six randomized controlled trials published in 2017 concluded that in ACS patients, 3 but not 6 months of DAPT was associated with higher ST and MI rates [15]. However, another meta-analysis suggested no increase in ischaemic events with short term DAPT in ACS patients [16].

In conclusion, based on these data, cardiologists should be reluctant in reducing DAPT duration after ACS. However, the characteristics of our patient cohort imply that the conclusions of this study cannot fully be translated to contemporary PCI practice. Most patients received a first generation drug-eluting stents (DES) and patients were treated with

clopidogrel because the more potent P2Y12-inhibitors prasugrel and ticagrelor had not yet been introduced at the time of this registry. Both prasugrel and ticagrelor are associated with a reduction in the rate of ischaemic events, including stent thrombosis [17–20]. While the *prodrug* clopidogrel (i.e. an inactive metabolite) needs to be metabolized into its active form, prasugrel and ticagrelor have a faster onset of action and achieve high levels of platelet inhibition within 1-2 hours [21,22]. Furthermore, ticagrelor and prasugrel have shown more consistent platelet inhibition during maintenance therapy, whereas high-on-treatment platelet reactivity remains a drawback of clopidogrel with inadequate platelet inhibition exposing patients to an increased risk of stent thrombosis [22–24] Ticagrelor and prasugrel have now become the P2Y12-inhibitor of choice in ACS, recommended by international guidelines [26,27].

Chapter 7 discusses the use of an additional anti-thrombotic agent in patients presenting with STEMI who receive morphine before undergoing primary PCI. Morphine is often used in STEMI patients for analgesia, sedation, anxiolysis, and to reduce adrenergic drive, heart rate and myocardial oxygen consumption. However, morphine is also known to delay the absorption of P2Y12-inhibitors, which exposes them to increased risk of ST after primary PCI.

Therefore, in this chapter the effect of concomitant glycoprotein IIb/IIIa inhibitors (GPI) in morphine treated STEMI patients was tested, following the introduction of a new local guideline. 33 cases of stent thrombosis were identified. Overall, a reduction in stent thrombosis associated with GPI was observed (0.4% (5/1217) vs. 2.6% (28/1080), $p < 0.0001$). When looking into detail, 27/30 of stent thrombosis patients in whom morphine use was known had received morphine prior to PCI. The vast majority (85%) of these patients had received morphine but not GPI.

A numerical but statistically not-significant increase in GUSTO moderate-to-severe bleeding was observed, although limited by small patients numbers. The risk of bleeding associated with GPI use is well documented though. Therefore, a strategy of default GPI use in all morphine treated patients might exposes these patients to a high risk of haemorrhagic complications.

However, GPI seems highly effective in preventing stent thrombosis and can be used in selected patients (e.g. complex PCI, edge dissection, low flow state in cardiogenic shock, etc.). Moreover, alternative strategies are needed in order mitigate ST risk in morphine treated STEMI patients, without the downside of high bleeding risk. A recent addition to the portfolio of antithrombotic drugs is the introduction of cangrelor to the market. Cangrelor is an intravenous, reversibly-binding P2Y12-inhibitor. It has an ultra-quick onset and offset of action and is therefore very suitable for use in patients at high thrombotic risk.

Cangrelor is highly potent with a near complete inhibition of platelet aggregation within two minutes after bolus injection.[28] Effectivity of cangrelor in clinical practice was assessed in the *Cangrelor versus standard therapy to achieve optimal management of platelet inhibition* (CHAMPION) trials. In an individual patient meta-analysis of these three trials, cangrelor was found to be effective in reducing myocardial infarction and stent thrombosis.[29] It might be reasonable to administer cangrelor to morphine treated STEMI patients. In addition, use of cangrelor is appealing in other patients at high thrombotic risk undergoing PCI who have not been properly preloaded with a P2Y12-inhibitor (e.g. patients undergoing high risk *adhoc* PCI or STEMI patents presenting with resuscitated cardiac arrest).

In **Chapter 8**, three case descriptions of patients with a particularly interesting case of stent thrombosis are described for illustrative purposes.

Incidence of stent thrombosis anno 2020 and novel insights into pathophysiology

It is estimated that newer generation DES are associated with approximately 50% reduction of stent thrombosis.[30,31] Current rates of ST are estimated to be approximately 0,5 – 0.8% in the first year.[32,33] Very late ST beyond one year has become a rarity with incidence rates of ST in newer generation DES be estimated at 0.1-0.2 per 100 persons-years [34]. The total ST risk amounts to <1% even at a follow-up duration of more than five years [32,35].

Systematic intracoronary imaging together with autopsy studies have provided further detailed insights into the pathophysiology of ST. A Report of the PREvention of Late Stent Thrombosis by an Interdisciplinary Global European Effort (PRESTIGE) Consortium showed that the main findings with optical coherence tomography (OCT) in in acute and subacute ST patients were uncovered struts and underexpansion.[36] In patients presenting with (very) late ST, a more heterogenous etiology was observed, with neoatherosclerosis and uncovered struts as most frequent findings, although underexpansion and severe restenosis were found as well. Neoatherosclerosis is an accelerated form of de-novo atherosclerosis arising within the stent, which typically can develop within months after implantation.[37] Like atherosclerosis in native coronary arteries, plaque disruption or erosion might subsequently cause thrombosis. Another underlying cause of stent thrombosis is positive vessel remodelling, in which a space between the previously placed stent and vessel wall develops over time (i.e. late acquired malaposition). This can also be appreciated with OCT or intravascular ultrasound (IVUS).[38] Moreover, other concepts related to the stent have evolved, such as late luminal loss (which may contribute to late re-stenosis) and vasomotor dysfunction proximal and distal to the stented segment.[31]

Autopsy studies confirmed that the underlying mechanism in many cases was chronic inflammation in combination with a hypersensitivity reactions against the stents polymer.[31,39] This chronic state of inflammation appeared to be the principal cause of the aforementioned

neoatherosclerosis and vessel modelling, as well as impaired endothelialisation and slower strut healing.[39] The stents polymer is an important component of the stent at least partially triggering this state of chronic inflammation.[40]

Introduction of newer generation DES

Improvements in the design of the newest generation DES have been made with regard to the scaffold (i.e. the metal platform, including strut geometry and thickness) and the polymer which carries the antiproliferative drug (e.g. dosing and pharmacokinetic release)[35]. Accordingly, newer generation stents have thinner struts, more biocompatible or even biodegradable coatings and lower doses of antiproliferative drugs.[31]

Newer generation stents such as Resolute, Xience and Synergy are composed of alternative metal alloys such as cobalt–chromium (CoCr) and platinum–chromium (PtCr)[41]. These newer alloys combine reduction in strut thickness with increased radial strength. Stent thickness is of major importance, because thinner struts are associated with faster rates of endothelialisation and lower thrombogenicity.[42] Whereas first generation DES used rather thick struts (120 – 140 um), newer generation DES have a strut diameter of 70-90 um or a strut thickness of even <70um in "ultrathin strut" DES. In addition to strut thickness, it was acknowledged that strut width is an important determinant of blood flow dynamics and manufacturers managed to produce stents with a smaller "footprint" which improved its hemodynamic profile and lowered shear stress.[42]

Another improvement of newer generation DES is the use of polymers with improved biocompatibility and the introduction of biodegradable polymers or even fully polymer-free DES. Some newer-generation DES still use durable (permanent) polymers but managed to improve the biocompatibility (e.g. Xience everolimus-eluting stent (EES), PROMUS Element EES and Resolute zotarolimus-eluting stent (ZES) [42]. These improved polymers reduce platelet adhesion / activation and, importantly, cause less inflammation and improved healing. Other stents such as Synergy EES and Orsiro Sirolimus-eluting stents (SES) use biodegradable polymers. Because the polymer dissolves over time, the exposure of the vessel wall to the polymer-induced vessel wall inflammation is only limited in time and one is essentially left with a BMS after full release of the polymer and drug.[40] Biodegradable DES might have increased long-term safety including stent thrombosis as compared to early generation permanent-polymer DES and comparable results with second-generation (CoCr or PtCr) permanent-polymer DES [39,40].

Although the concept of biodegradable polymers or polymer-free devices is appealing and performance appears to be at par with other newer generation DES, conflicting evidence exists regarding long term *superiority* [39,43–45]. However, more recent studies did show promising results for the ultrathin-strut stent when combined with biodegradable polymers. In the SORT

OUT VII [46], an ultrathin-strut biodegradable polymer stent demonstrated to be superior to a thicker (but also biodegradable polymer) stent with regard to definite stent thrombosis rates. Another very recent and interesting study [47] compared an ultrathin-strut (60 μm) bioresorbable polymer stent with a thin-strut (80 μm) durable-polymer everolimus-eluting stent and showed superiority with regard to target vessel MI and late or very late stent thrombosis. Another study in STEMI patients [48] compared ultrathin-strut biodegradable polymer SES vs. thin strut durable polymer EES and suggested a significant lower rate of target lesion failure at 1 year with the ultra-thin strut biodegradable stent but not stent thrombosis or myocardial infarction. Finally, the BIO-RESORT trial [49] compared two biodegradable very-thin and ultrathin-strut biodegradable polymer stents with a thin-strut durable polymer stent. Although the overall study was negative, sub analyses suggested that the thinner strut-stents may be beneficial in patients with small target vessels and in patients with severely calcified coronary artery disease [50,51].

In conclusion, the combination of (ultra)thin stent struts with a biodegradable polymer coating might be a successful recipe in further improving long-term efficacy and safety in the contemporary generation DES. However, these promising results have yet to be confirmed by more large scale randomized controlled trials.

Tailored therapy based on platelet function testing

Part II addresses platelet function testing. **Chapter 9** is a review paper discussing the prevalence of high (and low) on-treatment platelet reactivity in patients treated with aspirin and P2Y12-inhibitors. An overview of the relationship between high and low on-treatment reactivity with clinical outcomes is given. Furthermore, a summary is provided of studies which sought to establish a benefit of alternative antiplatelet regimens based on platelet function tests. Finally, currently available platelet functions and its indications for clinical use are discussed.

In **Chapter 10**, four platelet function tests are compared in a cohort of stent thrombosis patients. Correlation and agreement between the individual platelet function tests are discussed. Moreover, the feasibility of a composite conclusion based on more than one test is described. HPR rates in this patients cohort ranged from 14.6 for the Verifynow with the commonly used cut-off >235 platelet reactivity units (PRU) to 49.7% for the Vasodilator-Stimulated Phosphoprotein Assay (VASP). HPR according to the composite based on ³2 out of 3 tests was present in 29.8% of patients. Correlation between the different tests was found to be weak to moderate. When comparing the individual tests to the composite based on three other tests, the VerifyNow test (cut-off PRU >235) had a low sensitivity and did not identify 50% of patients who were found to have HPR according to the composite advice (of note, the VerifyNow performed better when the lower cut-off was used). On the other hand,

the VASP assay seemed to "over-identify" HPR: in 43,3% HPR was present according to the VASP assay whereas the panel of tests considered these patients as non-HPR. In conclusion, a considerable variability in HPR rates was found. Agreement between the individual tests and between the individual tests and a panel of three tests was weak to moderate at best. Given the large degree of variability within the individual tests, a conclusion based on a panel of three tests seems a feasible and promising alternative.

So what could be the future of tailoring treatment in patients exhibiting HPR? As discussed in Chapter 8, smaller studies suggested that tailoring treatment based on platelet function testing could improve outcomes [52,53], but larger randomized controlled trials failed to demonstrate a benefit of this individualized treatment [54–57].

Two more recent study rather focused on a strategy of "de-escalating" from the more potent P2Y12-inhibitors back to clopidogrel [58].

The TROPICAL-ACS study randomized 2610 ACS patients to either standard treatment with prasugrel or a strategy of platelet function testing-guided maintenance therapy with clopidogrel or prasugrel from day 14 after hospital discharge (i.e. de-escalation to clopidogrel in patients without HPR)[58]. In the guided de-escalation group, HPR status was established in 511 patients (39%). Platelet function guided de-escalation was found to be non-inferior to standard treatment. No benefit in terms of reducing bleeding complication was found.

The TOPIC trial [59] randomized more than 1200 ACS patients who underwent PCI to a strategy of standard DAPT with prasugrel versus a regimen of de-escalation to clopidogrel in the other study arm (i.e. without platelet function monitoring or selection otherwise). De-escalation was applicable only if the first month post PCI had been uneventful. A de-escalation strategy was superior to an unchanged DAPT strategy in terms of reducing bleeding, whereas no increase in bleeding events was observed.

Other studies individualized treatment based on CYP2C19 polymorphisms rather than on the presence of HPR per se. CYP2C19 is a hepatic enzyme which is involved in the activation of the prodrug clopidogrel. Several genetic polymorphisms have been described, among which the *loss-of-function* alleles CYP2C19*2 and CYP2C19*3 are most relevant in clinical practice. Both alleles have independently been associated with ischaemic events in clopidogrel treated patients.[60]

The recently published POPular Genetics trial randomized patients undergoing primary PCI to a standard regimen of ticagrelor (or prasugrel) versus a so-called genotype-guided group, in which carriers of CYP2C19*2 or CYP2C19*3 alleles received ticagrelor or prasugrel and

noncarriers received clopidogrel [61] Genotype-guided therapy was non-inferior to standard treatment with respect to thrombotic events, but resulted in a lower incidence of bleeding.

The TAILOR-PCI study (NCT01742117, presented ACC 2020 meeting) enrolling more than 5,000 patients undergoing PCI for ACS or stable coronary artery disease randomized patients to either conventional therapy with clopidogrel versus genotype-guided therapy, existing of ticagrelor for carriers of the CYP2C19 loss-of-function allele or clopidogrel for non-carriers. The primary end point occurred in 4% of the genotype-guided group versus 5.9% in the conventional group, although the point of significance was just missed (HR 0.66, p=0.056).

Trials investigating tailored treatment based on genetic testing are promising as well, be it either intensifying treatment in clopidogrel treated patients undergoing PCI or de-escalating treatment in STEMI patients. Obviously, the presence of HPR depends on more than genetic factors alone. Therefore, it is curious why genotype-guided trials seems to be more effective as compared to a platelet function testing based strategy. One can only speculate whether this is either an effect of the large variability in determining HPR with platelet function testing, or a result of trial size or just a matter of chance. However, genotype based testing is an elegant and feasible strategy and might be considered as an alternative to platelet function testing, especially when platelet function testing is not available.

In conclusion, the early randomized controlled trials did not show a benefit of individualizing P2Y12-inhibitor treatment based on platelet function testing with regard to ischaemic end points. More recent studies show that a strategy of de-escalation guided by platelet function testing or genetic testing might be safe and reduce bleeding. Current ESC guidelines recommend to consider de-escalation guided by either platelet function testing or CYP2C19-directed genotyping, especially in patients deemed unsuitable for 12-month potent platelet inhibition [26,27].

Antithrombotic therapy in AF patients undergoing PCI

Part III addresses the subgroup of AF patients who undergo PCI. Currently, these patients are more and more treated with oral anticoagulation and a P2Y12-inhibitor but with the omittance of aspirin. However, most trials comparing so-called double antithrombotic treatment (DAT) with triple antithrombotic therapy (TAT) were underpowered for thrombotic events.

Chapter 11 investigated whether patients at high thrombotic risk might still benefit from a strategy of TAT. In a secondary analysis of the RE-DUAL PCI trial, a Cox proportional hazards model was built to compare effect of TAT versus DAT was calculated in the highest proportion of predicted thrombotic risk. In 209 patients (7.7 %) the combined ischaemic endpoint occurred during the first year. A simplified prediction rule was constructed

containing 7 variables. In patients with a risk score ³5 (N 154, 5.7%), a significant reduction in the composite of myocardial infarction and stent thrombosis was observed with TAT vs. DAT (6.3% vs. 21.0%, p=0.04), without a penalty in terms of bleeding. In patients at low thrombotic risk, a significant increase in bleeding was observed without a reduction of thrombotic events. These findings support the use of TAT in a small subgroup (~5% of patients), while using DAT in the majority of AF patients undergoing PCI.

The observation of fewer ischaemic events in high-risk patients with TAT is in line with some meta-analysis and subgroup analyses which pointed to a possible benefit of TAT, especially in high risk patients. Two meta-analysis of randomised controlled trials signalled a difference in terms of stent thrombosis, although incidence rates were low [62,63]. Interestingly, the meta-analysis by Gargiulo proposed a trade-off on individual patient basis of the number needed to treat for harm (NNTH, i.e. bleeding) and benefit (NNTB, i.e. ischaemic events). They constructed a model calculating the risk between NNTH and NNTB for different risk strata. This highlights the concept that individual risks of bleeding and MI influence the overall risk/benefit ratio of each therapeutic strategy. The model suggested that bleeding risk prevails in most patients, although there might be a smaller sub group of patients who have predominant ischaemic risk with low bleeding risk. The authors do not provide a tool to use in clinical practice but this is rather a theoretical frame work.

The current study is the first study to investigate the effect of TAT in patients at high thrombotic risk represented by a combination of high-risk characteristics. Several subgroup analyses of the randomised controlled trials based on single clinical variables (e.g. diabetes, age ³80 years, ACS patients) could not demonstrated a reduction in ischemic events associated with TAT [64–66], which illustrates the complex and multifactorial aspect of high thrombotic risk which was adequately addressed in the current study by combining multiple patients characteristics.

Our findings are an important “proof of concept”, which is in line with general beliefs of many cardiologists with regard to high-risk patients. Using this prediction rule containing seven clinical, angiographical and procedural parameters, a significant reduction in MI/ST associated with TAT was found in patients at high thrombotic risk undergoing PCI, without a penalty in terms of bleeding. On the other hand, these data suggest to use DAT as default therapy in the majority of patients.

The performance of the score was fair in the WOEST 2 registry which served as an external validation cohort. Differences between DAT and TAT could not be tested in this registry. Before adapting this novel risk score into daily clinical practice, further external validation in an independent randomised controlled trials is needed.

Risk stratification for estimating bleeding risk was investigated in **chapter 12**. The development and validation of a prediction tool to estimate individual patients bleeding risk is described. Based on the RE-DUAL study, a Cox model for Bleeding Academic Research Consortium (BARC) 2, 3 and 5 bleeding was constructed by stepwise selection from candidate variables. Expected hazard of bleeding events at 365 days was predicted. Based on beta-coefficients of the Cox model, a point score was developed. The simplified prediction model contained the following variables: triple therapy, age, haematocrit, BMI and a history of malignancy. Three risk categories could be distinguished: low bleeding risk (~ 10%), moderate bleeding risk (15-20%) and high bleeding risk (>25%).

This is the first available risk score that has been specifically developed to estimate bleeding risk in AF patients undergoing PCI. The prediction model, which was validated in the WOEST study, was able to estimate bleeding risk with fair c-statistics. To date, no other risk scores exists for this patient category. Traditionally used risk scores such as CRUSADE and HAS-BLED scores are not applicable to this specific patient group and cannot be used because different variables are used.

Even when baseline bleeding risk is high in these patients treated with a combination of anticoagulation and (dual) antiplatelet therapy, bleeding risk varies considerably between patients. It is essential to identify patients with increased bleeding risk. This score estimates bleeding risk and helps to balance the antithrombotic benefits and drawbacks of bleeding complications, especially when triple therapy is considered.

Future perspectives

Although the incidence of stent thrombosis has declined by half in the last decade, it is estimated that over three million PCI procedures are performed worldwide, illustrating that the total burden of stent thrombosis still remains significant. Even though overall stent thrombosis risk is low now, specific subgroups of patients deserve attention. Future research should investigate whether morphine pretreated STEMI should receive additional antithrombotic therapy (such as GPI or Cangrelor) by default. Furthermore, studies investigating optimal duration of DAPT after ACS should not only focus on reducing ischaemic events, but also on reducing hemorrhagic complications, given the strong link with adverse outcomes. In an ideal world, a net clinical risk score should be developed that yields a patient-tailored advice on DAPT regimen and duration.

With regard to AF patients undergoing PCI, even more unchartered territory lies ahead. All evidence taken together suggests that DAT should be the default strategy in most AF patients undergoing PCI. We found a small (~5% of patients) subset of patients who seem to benefit from triple antithrombotic therapy. Further external validation in an independent randomised controlled trials is needed. Future studies could shed light on the optimal *duration* when TAT is used in this specific high-risk subgroup (either a short course of one month, either three months or even longer).

Finally, additional risk models are needed that incorporate both bleeding and thrombotic risk. When all randomized trials evaluating TAT vs. DAT in AF patients undergoing PCI were to be pooled, it might be possible to construct a prediction model estimating a patients net clinical risk.

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Appendices

Nederlandse samenvatting

In de inleiding van dit proefschrift wordt het fenomeen stenttrombose geïntroduceerd. Stenttrombose is het optreden van een abrupte afsluiting van een eerder geplaatste kransaderstent door een bloedstolsel. Een kransaderstent (coronaire stent) wordt geïmplanteerd tijdens een dotterbehandeling (percutane coronaire interventie; PCI) om het bloedvat voor de lange termijn open te houden.

In eerdere onderzoeken zijn verschillende risicofactoren voor het optreden van stent trombose geïdentificeerd, zoals diabetes en hartfalen. Daarnaast spelen factoren gerelateerd aan de dotterprocedure een rol, zoals het plaatsen van een te kleine stent, of als tijdens het plaatsen va de stent een dissectie aan de rand van de stent is ontstaan. Ook het (te) vroeg staken van de bloedplaatjesremmende medicijnen is een belangrijke risicofactor en daarnaast zijn genetische factoren zijn van belang: dragers van een afwijkend CYP2C19 gen (dit gen is van belang bij het metabolisme en activeren van de plaatjesremmer clopidogrel) hebben een hoger risico op stenttrombose. Stent trombose presenteert zich meestal als een acuut hartinfarct en is een gevaarlijke complicatie van PCI met een hoge sterfte.

Door de jaren heen zijn stents veel beter geworden en werden bloedplaatjesremmende medicijnen (plaatjesremmers) steeds krachtiger. Daardoor nam het aantal stent tromboses af, terwijl er meer aandacht kwam voor bloedingen als bijwerkingen van plaatjesremmers. Daarnaast werd duidelijk dat niet iedere patiënt dezelfde behandeling hoeft te krijgen. Waar voorheen patiënten na een PCI standaard een jaar behandeld werden met twee plaatjesremmers (dubbele plaatjesremming; DAPT), kunnen sommige patiënten tegenwoordig korter (6 maanden of minder) behandeld, terwijl bepaalde andere patiëntengroepen juist langer behandeld zouden moeten worden. Risicoscores kunnen helpen bij het bepalen van de optimale duur van DAPT.

Het derde onderwerp in dit proefschrift is de behandeling van patiënten met boezemfibrilleren die een PCI ondergaan. Omdat deze patiëntengroep meestal ook al behandeld wordt met orale antistolling, hebben zij een extra verhoogd risico op bloedingen als gevolg van de combinatie van de verschillende bloedverdunners.

Deel I Stenttrombose

In **hoofdstuk 4** van dit proefschrift wordt de rol van uitlokkende factoren bij het optreden van stenttrombose beschreven. Zoals hierboven beschreven, zijn al veel risicofactoren voor stenttrombose bekend. Toch is het opvallend dat slechts een klein deel van de patiënten met bekende risicofactoren uiteindelijk een stent trombose ontwikkeld – en andersom, waarom sommige mensen zonder risicofactoren toch een stent trombose krijgen. In een groot cohort

patiënten met stenttrombose, werd in 23% van de patiënten een uitlokkende factor voor de stenttrombose geïdentificeerd, zoals zware lichamelijke inspanning, emotionele stress of de aanwezigheid van een infectie. Daarnaast werd een duidelijke variatie over de dag gezien, waarbij we hebben kunnen vaststellen dat een stenttromboses meestal in de ochtenduren plaatsvind (piek tussen 7 uur 's ochtends en 12 uur 's middags).

In **hoofdstuk 5** werd het absolute risico op het krijgen van stenttrombose na het stoppen met clopidogrel onderzocht. Clopidogrel is een veelgebruikte P2Y12-remmer en meerdere studies hebben aangetoond dat het vroeg stoppen een belangrijke oorzaak van stent trombose is. Het absolute risico op het krijgen van stenttrombose in een cohort van voornamelijk patiënten met acuut coronair syndroom bedroeg in deze studie 4.6% in vergelijking met 1.7% voor patiënten die clopidogrel niet hadden gestopt. Bij mensen die clopidogrel stopten in de eerste 30 dagen was het risico zelfs 35% en dit percentage was respectievelijk 19% en 12% voor 90 en 180 dagen.

Patiënten met een ST-elevatie myocardinfarct (STEMI) krijgen vaak morfine toegediend, om pijn en angst te verminderen. Daarnaast heeft het een gunstig effect op de adrenaline respons en daardoor op hartfrequentie en zuurstofgebruik van het hart. Een bijwerking van morfine is echter dat het de maaglediging vertraagt en daardoor de opname en werking van P2Y12-remmers, waardoor deze patiënten een hoger risico op stenttrombose hebben. In **hoofdstuk 6** wordt het effect van de plaatjesremmer Glycoproteine-IIb/IIIa-remmers (GPI) bij deze STEMI patiënten die morfine hebben gekregen onderzocht. Als onderdeel van een lokale richtlijn werd deze patiëntengroep standaard behandeld met GPI. In de groep die behandeld werd met GPI werd een significant lager aantal stent tromboses gezien (0.4% (5/1217) vs. 2.6% (28/1080), $p < 0.0001$). Als keerzijde werd een (niet statistisch significant) verschil in bloedingen gezien.

Deel 1 van dit proefschrift wordt afgesloten met drie illustratieve casus van individuele patiënten met een stenttrombose (**hoofdstuk 7**).

Deel II Behandeling op maat met behulp van plaatjesfunctietesten

Hoofdstuk 8 is een overzichtsartikel waarin het voorkomen van zogenaamde hoge plaatjesreactiviteit (*HPR; high on-treatment platelet reactivity*) bij patiënten behandeld met P2Y12-remmers wordt beschreven. Als er sprake is van HPR betekent dat in de praktijk dat plaatjesremmers onvoldoende werkzaam zijn en dat mensen dus een hoger risico op een hartinfarct of stenttrombose hebben. De relatie tussen HPR en klinische uitkomsten wordt beschreven. Daarnaast worden de testen beschreven die beschikbaar zijn voor het meten van plaatjesfunctie. Tenslotte wordt een samenvatting gegeven van studies die op-maat-behandeling gebaseerd op plaatjesfunctietesten hebben onderzocht.

In de praktijk worden vier verschillende plaatjesfunctietesten (assays) gebruikt, maar weinig is bekend over de correlatie tussen de verschillende testen. In **hoofdstuk 9** wordt de correlatie tussen vier testen beschreven. Daarnaast wordt een combinatietest voorgesteld, die gebaseerd is op meer dan 1 afzonderlijke test. In dit onderzoek bleek er een belangrijke variatie te bestaan tussen het voorkomen van HPR volgens de verschillende testen. In een cohort van stenttrombose patiënten varieerde het voorkomen van HPR van 14.6% voor de Verifynow assay (met de veelgebruikte afkapwaarde van >235 PRU) tot 49.7% voor de VASP assay. Correlatie tussen de verschillende testen was zwak – hooguit matig. Wanneer de testen werden vergeleken met een composiet van drie verschillende testen en met lichttransmissie aggregometrie (de 'gouden standaard'), leidde de Verifynow assay met de hoge afkapwaarde tot het onderschatten van het aantal patiënten met HPR, terwijl de VASP assay juist een overschatting gaf.

Deel III Antitrombotische behandeling in AF patiënten die PCI ondergaan

Patiënten met boezemfibrilleren die een PCI ondergaan, worden meestal behandeld met zowel orale antistolling (OAC) als met twee plaatjesremmers (clopidogrel en aspirine). De combinatie van deze drie bloedverdunners (triple therapie; TAT) leidt tot een tweemaal hoger risico op bloedingen. Daarom wordt tegenwoordig meestal dubbele behandeling (DAT) met OAC en clopidogrel gegeven: dit lijkt bij de meeste patiënten veilig.

Aan de andere kant zijn er patiënten met een hoog 'trombotisch risico' die een grote kans hebben op een nieuwe hartinfarcten of andere acute problemen. Deze hoog-risico patiënten zouden wèl baat kunnen hebben bij de zogenaamde triple therapie. Tot op heden was dit niet goed onderzocht. In **hoofdstuk 10** werd daarom onderzocht welke patiënten baat hebben bij de intensievere triple behandeling. Met behulp van een Cox proportioneel model werd een risico score ontwikkeld. In patiënten met een risicoscore van ≥5 (N 154, 5.7% van het cohort) was een significant lager aantal stent tromboses en hartinfarcten te zien als zij met triple therapie werden behandeld, zonder dat het aantal bloedingen toenam. Patiënten met een lagere score hadden helemaal geen baat bij triple behandeling en hadden juist wel meer bloedingen. Deze studie ondersteunt dus het gebruik van triple behandeling bij de kleine groep 'hoog-risico' patiënten, die met behulp van deze score goed kunnen worden geïdentificeerd.

Bloedingen komen frequent voor bij deze patiëntengroep door de combinatie van verschillende bloedverdunners. Het optreden van bloedingen is overigens een gevaarlijke "bijwerking" en geeft een hoog risico op ziekenhuisopnames en overlijden (sommige studies suggereren dat bloedingen een even groot risico op overlijden geven als een hartinfarct). In het laatste hoofdstuk van dit proefschrift, **hoofdstuk 11** wordt de ontwikkeling van een bloedingsscore beschreven. Op basis van een Cox model werd een puntenmodel

ontwikkeld. Deze risicoscore bevatte de items leeftijd, hematocriet, BMI, maligniteit in de voorgeschiedenis en behandeling met triple therapie. Drie risico categorieën konden worden onderscheiden: laag bloedingsrisico (~10%, matig bloedingsrisico (17%) en hoog bloedingsrisico (27%). Dit is de eerste risicoscore die specifiek van toepassing is op patiënten met boezemfibrilleren die een PCI ondergaan. Bij deze groep is het risico op bloedingen dus duidelijk verhoogd, maar onderling blijkt het nog sterk te variëren. Het is daarom essentieel om bij de individuele patiënt het bloedingsrisico in te schatten en vervolgens af te wegen tegen de trombotische risico's.

Verleden, heden en toekomst

In de studies beschreven in dit proefschrift worden de globale ontwikkelingen die de interventiecardiologie de afgelopen tien jaar heeft doorgemaakt beschreven. Door de sterke afname van het probleem stent trombose, is de aandacht nu meer gericht op de afweging tussen voorkomen van trombose en het bloedingsrisico dat gepaard gaan met bloedplaatjesremmers. De uitdagingen aan de horizon zijn om risicoscores verder te verfijnen en om geïndividualiseerde behandeling daadwerkelijk meer in te zetten in de dagelijkse klinische cardiologiepraktijk.

Impact paragraph

In this section, the impact of the research performed in this thesis will be discussed, including a summary of its main findings for non-medical readers, the implications for daily practice and the contribution of this thesis to the scientific field.

Cardiovascular disease is the worldwide leading cause of death. It is estimated that it contributes to 31% of all deaths worldwide, representing 17.9 million people each year. Among these, the vast majority (85%) are due to either heart attacks or stroke. Heart attacks are causes by a blockage in the blood vessels supplying the heart muscle. A heart attack is treated with medication including blood thinners and usually with angioplasty (using a balloon threaded through an artery to unblock the blood vessel). Nowadays, it is standard practice to implant a coronary stent (a small metal tube), which secures long-term patency of the treated blood vessel.

The research described in this thesis comprises two fields of interest related to heart attacks. First, it elaborates on treatment with antiplatelet drugs (blood thinners) in patients with heart attacks or following coronary angioplasty. Second, the subject of stent thrombosis, a feared complication of angioplasty, is discussed. In stent thrombosis, the previously implanted stent is blocked by a thrombus (blood clot), causing a (new) heart attack.

Scientific impact and impact for patients

In the first chapter of this thesis, we showed that the risk of stent thrombosis is high when the blood thinner clopidogrel is discontinued prematurely. This is very relevant for patients, as stent thrombosis is a dangerous condition, which can be lethal. Patients should be careful not to discontinue their medication prematurely after coronary angioplasty. However, some conditions during follow-up, such as undergoing surgery, might necessitate early discontinuation of blood thinners. Patients should be aware of the importance of dual antiplatelet treatment after PCI and are advised to discuss this issue with their cardiologist when early discontinuation is warranted.

Another important finding in this manuscript is the possible beneficial effect of Glycoprotein IIb/IIIa inhibitors (GPI; a class of strong blood thinners) among heart attack patients who are treated with morphine. Morphine is often given to patients suffering heart attacks to alleviate pain and anxiety. However, morphine delays the absorption of blood thinners from the stomach and therefore can compromise its actions. Therefore, these patients have an increased risk of stent thrombosis. We showed that GPI can reduce this risk of stent thrombosis. However, further research is needed as GPI is associated with bleeding complications as well. Therefore, it should be used selectively in clinical practice.

The last part of this thesis concerns the specific group of patients with atrial fibrillation (a heart rhythm condition) who undergo coronary angioplasty. As these patients are already treated with a specific type of blood thinners (anticoagulation), the combination of blood thinners is particularly difficult in this patient group. On the one hand, they tend to have an increased risk of bleeding because of this combination of drugs. On the other hand, it is unknown which combination of medication is optimal both from the perspective of the rhythm disorder and for the angioplasty. In the last part of this thesis, we developed a risk tool able to select high-risk patients who qualify for an intensified course of blood thinners. A second risk calculator was developed aimed at estimating bleeding risk in individual patients. Both risk calculators are very relevant for patients in daily practice, as they enable personalised medicine, in which a specific treatment balancing benefits and risks for an individual patient can be chosen. Moreover, it fosters shared decision making between patient and physician, based on the specific patient characteristics and conditions.

Dissemination of knowledge

In our efforts to share our knowledge with fellow researchers and clinicians, the majority of the research presented in this manuscript was published in peer-reviewed national and international scientific journals. In addition, the results of several studies were presented at international congresses, including the European Society of Cardiology congresses, the Euro Thrombosis conference and the American Heart Association scientific sessions. Finally, chapter two of this thesis is based on a position paper, which was written in order to inform other Dutch cardiologists about current developments in the field of shortening and prolonging treatment with antiplatelet medication.

List of publications

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Curriculum Vitae

Bastiaan Zwart was born in Drachten on the 27th of January 1985. After completing his secondary school (Stedelijk Gymnasium, Leeuwarden), he started studying medicine at the University of Utrecht in 2003. During his study, he spent a research internship at the St. Antonius hospital Nieuwegein, which led to his first oral presentation at the American Heart Association scientific sessions in New Orleans, US. He obtained his medical degree in 2010. After graduating, he started working in the Emergency Department in the Zuwe Hofpoort hospital in Woerden, where he gained skills in acute surgical and medical care. Being particularly interested in design and reimbursement of healthcare systems, he broadened his horizon by working as a consultant with KPMG Advisory for a year. He then realised that working as a clinical doctor should be the foundation of his working practice. In 2013, he started cardiology specialist training at St. Antonius hospital in Nieuwegein under supervision of prof. dr. J.M. Ten Berg. During his cardiology training, he commenced his scientific career, which would result in this thesis. In 2016, he worked as a registrar in the Northern General Hospital in Sheffield, United Kingdom, where he spent much time in the cathlab and started performing PCI's. From 2018-2020 he specialised in interventional cardiology in the Catharina hospital, Eindhoven (under supervision of dr. P.A.L. Tonino). In 2021, he joined the cardiology staff at the Elisabeth-Tweesteden hospital in Tilburg as an interventional cardiologist.