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Myocardial reperfusion in STEMI and the role of the antithrombotic/antiplatelet therapy

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Myocardial reperfusion in STEMI and the role of the antithrombotic/antiplatelet therapy

Enrico Fabris

Myocardial reperfusion in STEMI and the role of the antithrombotic/antiplatelet therapy

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Myocardial reperfusion in STEMI and the role of the antithrombotic/antiplatelet therapy

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Promotor:	Prof. Dr. A.W.J. van 't Hof
Copromotores:	Dr. E Kedhi (Isala Ziekenhuis, Zwolle) Dr. R.S. Hermanides (Isala Ziekenhuis, Zwolle)
Beoordelingscommissie:	Prof. Dr. H.J.G.M. Crijns (Voorzitter) Prof. Dr. F.W. Prinzen Dr. J.M. ten Berg (St. Antonius Ziekenhuis, Nieuwegein) Prof. Dr. R.J. de Winter (AMC, Amsterdam)

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"Considerate la vostra semenza:
fatti non foste a viver come bruti,
ma per seguir virtute e canoscenza"

"Consider well the seed that gave you birth:
you were not made to live your lives as brutes,
but to be followers of worth and knowledge"

Dante Alighieri, *Divine Comedy, Inf. 26.118-20*

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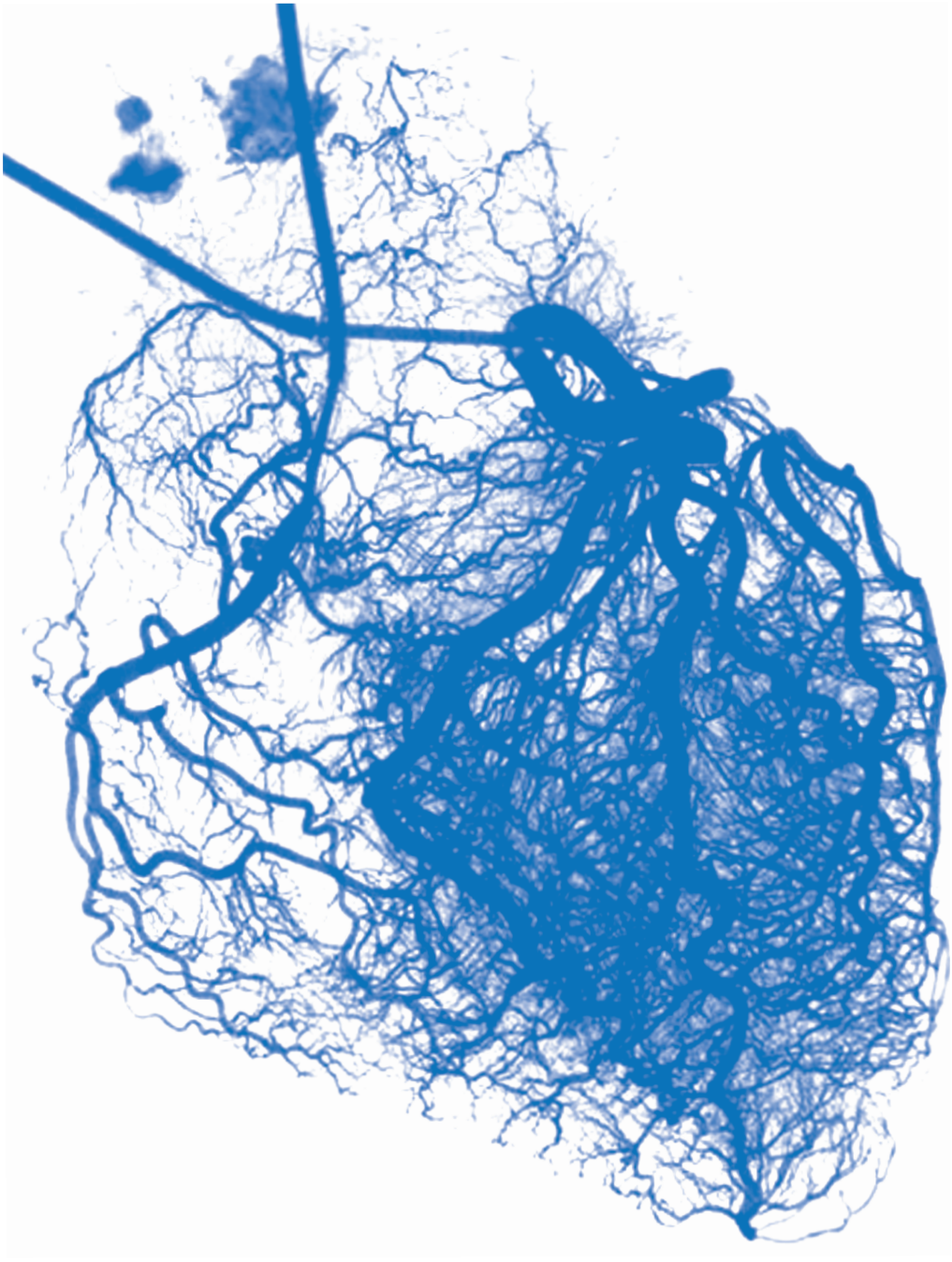

Chapter one

General introduction and Outline of the thesis

General Introduction

Acute ST-segment elevation myocardial infarction (STEMI) is one of the major cause of morbidity, mortality and disability worldwide[1].

Rupture or erosion of an atherosclerotic plaque in the coronary artery circulation is the usual initiating event in STEMI followed by a sudden arterial thrombosis with formation in most cases of an occlusive thrombus and critical reduction in blood flow[2].

Early and complete recanalization of the infarct-related artery and achievement of early myocardial reperfusion is one of the main goals in STEMI patients for improving prognosis, and timely reperfusion with primary percutaneous coronary intervention (PCI) is considered the treatment of choice[1]. Antithrombotic therapy, including anticoagulant and antiplatelet agents, is the cornerstone of pharmacological treatment to optimize clinical outcomes in patients with STEMI undergoing primary PCI[3]. Several classes of anticoagulant and antiplatelet agents targeting mediators and receptors promoting thrombosis are currently available, but finding the optimal cocktail is still a clinical challenge.

The use of intravenous anticoagulant agents is mandatory during primary PCI[1], and different intravenous anticoagulant drugs are available. Dual antiplatelet therapy (DAPT) comprising aspirin and P2Y12 inhibitors, has a pivotal role in the treatment of STEMI patients[1]. Moreover, intravenous antiplatelet drugs as glycoprotein IIb/IIIa inhibitors, may provide immediate strong platelet inhibition until the full antiplatelet effect of oral agents is achieved. Antithrombotic therapy aims to facilitate epicardial reperfusion, to reduce thrombotic burden, to improve microcirculation reperfusion, and to prevent ischemic complications as early stent thrombosis events or recurrent myocardial infarction[4]. Conversely the most common complications of antithrombotic therapy is bleeding which may range from access site hematoma to fatal bleeding[5].

In this perspective finding a balance that minimizes both thrombotic and bleeding risk remains crucial. Potential identification of patients who may (or not) derive the greatest benefit from more aggressive antithrombotic regimen is relevant for a tailored and optimized therapy for STEMI patients. It is important to select the appropriate antithrombotic regime, however also the timing of administration of pharmacological therapy (pre-hospital vs in hospital) as well as the duration after PCI (short vs long period) is fundamental.

Therefore this thesis explores the role of currently available antithrombotic therapies for improving myocardial reperfusion and clinical outcomes in patients with STEMI undergoing primary PCI.

Starting from the importance of angiography and serial electrocardiograms for the assessment of myocardial reperfusion and in particular microvascular and tissue-level reperfusion, we investigate the factors which may influence myocardial reperfusion. We analyse the impact of therapy administration in the pre-hospital setting, and in particular the potential benefit of pre-hospital DAPT administration, of different anticoagulation regimens as well as of adjunctive pharmacological treatment as glycoprotein IIb/IIIa inhibitors. Finally we explore the optimal duration of DAPT after primary PCI with second generation drug-eluting stents, performing a dedicated randomized clinical trial to evaluate the safety of a shorter DAPT regimen.

Outline of the thesis

In chapter **two** we describe the use of angiography and serial electrocardiography for the assessment of coronary reperfusion and identify coronary microvascular obstruction/dysfunction.

In chapter **three** we identify independent predictors of complete ST-segment resolution (STR) pre-primary percutaneous coronary intervention (PCI) in STEMI patients enrolled in the ATLANTIC trial.

In chapter **four** we evaluate the independent predictors of complete STR after primary PCI in STEMI patients enrolled in the ATLANTIC trial.

In chapter **five** we assess the effect of bivalirudin monotherapy compared to a control group receiving unfractionated or low-molecular-weight heparin plus optional glycoprotein IIb/IIIa inhibitors, on 1-year mortality, a pre-specified outcome of the EUROMAX trial.

In chapter **six** we investigate the potential association between early tirofiban treatment and NT-proBNP level after primary PCI.

In chapter **seven** we evaluate the association between baseline NT-proBNP levels and long-term mortality and the effect of pre-hospital tirofiban administration on mortality in relation to NT-proBNP levels.

In chapter **eight** we explore the potential synergy between prehospital ticagrelor administration and thrombus aspiration in patients with STEMI treated with primary PCI.

In chapter **nine** we have designed a non-inferiority randomized trial (the DAPT-STEMI trial) to evaluate the safety of shorter dual antiplatelet therapy (DAPT) duration (6 vs standard 12 months) in STEMI patients treated with second generation drug eluting stents

In chapter **ten** we report the results of the DAPT-STEMI trial and its primary endpoint, a composite of all-cause mortality, any myocardial infarction, any revascularization, stroke, or major bleeding at 2 years after primary PCI.

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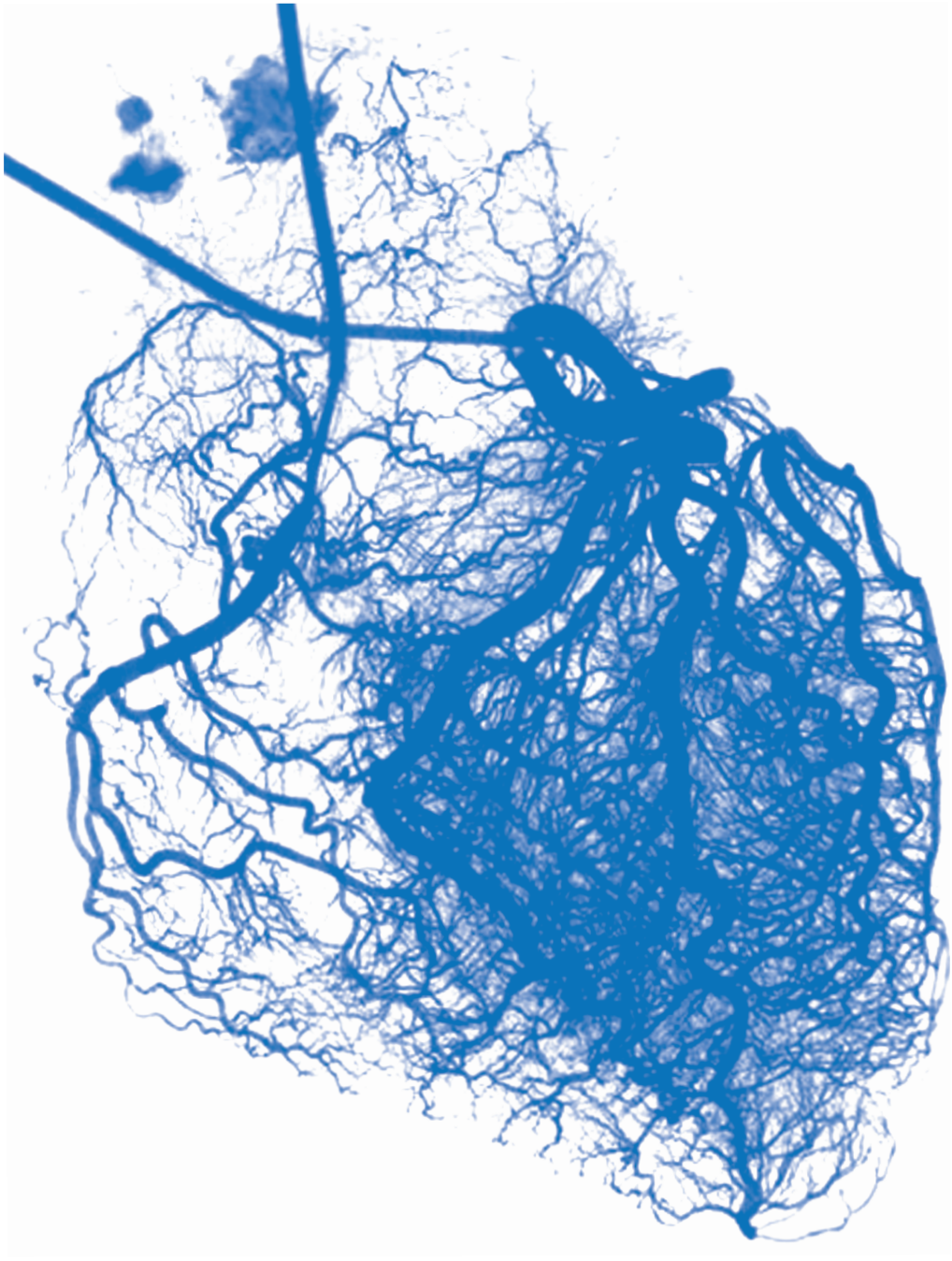
Part one

Myocardial reperfusion before and after primary PCI, diagnosis of microvascular obstruction



Chapter two

Angiography and Electrocardiography for the assessment of coronary microvascular obstruction

Enrico Fabris, Arnoud WJ van 't Hof

Coronary Microvascular Obstruction in Acute Myocardial Infarction

ISBN: 978-0-12-812528-1. Elsevier

Abstract

The achievement of early myocardial reperfusion is one of the main goals in ST elevation myocardial infarction (STEMI) for reducing infarct size and improving prognosis. In the last decade, several observations have shown that angiography and serial electrocardiograms (ECG's) are important for the assessment of reperfusion, in particular the evaluation of microvascular and tissue-level reperfusion, also considering their prognostic value.

In this chapter, we describe the use of angiography and serial electrocardiography for the assessment of coronary reperfusion and identify coronary microvascular obstruction/ dysfunction (CMVO).

Coronary Angiography

Angiographic parameters of coronary microvascular dysfunction and obstruction are represented by thrombolysis in myocardial infarction (TIMI) flow score, TIMI frame count, myocardial "blush" grade.

Thrombolysis in myocardial infarction flow score (TIMI flow score)
In the early era of myocardial reperfusion intravenous fibrinolytic agents were the most widely used means for acute re-establishment of vessel patency. Fibrinolytic efficacy had been evaluated by the Thrombolysis in Myocardial Infarction (TIMI) Study Group, founded in 1983, which designated TIMI flow grade classification[1] to characterizes coronary blood flow in the infarct-related artery, which was usually measured at 60 to 90 minutes after the administration of fibrinolytic therapy[2].

Definitions of perfusion in the TIMI Trial were:

Grade 0 (no perfusion): There is no antegrade flow beyond the point of occlusion.

Grade 1 (penetration without perfusion): The contrast material passes beyond the area of obstruction but "hangs up" and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cineangiographic filming sequence.

Grade 2 (partial perfusion): The contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry of contrast material into the vessel distal to the obstruction or its rate of clearance from the distal bed (or both) are perceptibly slower than its entry into or clearance from comparable areas not perfused by the previously occluded vessel - e.g., the opposite coronary artery or the coronary bed proximal to the obstruction.

Grade 3 (complete perfusion): Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction, and clearance of contrast material from the involved bed as rapid as clearance from an uninvolved bed in the same vessel or the opposite artery.

A simpler description of TIMI flow can be summarized as:

TIMI 0: the absence of any antegrade flow beyond a coronary occlusion

TIMI 1: flow is faint antegrade coronary flow beyond the occlusion, although filling of the distal coronary bed is incomplete.

TIMI 2: flow is delayed or sluggish antegrade flow with complete filling of the distal territory

TIMI 3: flow is normal flow that fills the distal coronary bed completely

Coronary patency expressed as TIMI flow grade has gained wide acceptance for its prognostic value. Indeed, in the angiographic sub-study of GUSTO trial, patients with TIMI grade 3 flow at 90 min after thrombolysis had improved left ventricular function and 30-day mortality rate. In patients with TIMI grade 3 flow the 30-day mortality rate was 4.4% whereas that for patients with TIMI grade 0-1 flow was 8.9%[3] and the two-year mortality for those with TIMI 3 flow was 7.9 % compared to 15.7 percent for those with lesser flow grades[4]. A model was also used to determine whether differences in 90-min patency could predict mortality rates for the entire trial. The results of that model were striking with a correlation between predicted and observed results of 0.97 with R^2= 0.92[5]. The close relation between the predicted and observed 30-day mortality rates supported the concept that an important mechanism for improved survival with thrombolytic therapy was achievement of early, complete perfusion. Moreover TIMI grade 3 flow measured at 60 minutes after thrombolytic administration point appeared to be a valid alternative to that at 90 minutes permitting earlier decisions regarding post-thrombolytic intervention[6].

Survival benefit of maintained TIMI grade 3 perfusion was confirmed by a meta-analysis which included 3,969 patients from five angiographically controlled, prospectively performed studies of thrombolysis in myocardial infarction (MI), demonstrating that early and complete (grade 3) TIMI flow was associated with superior survival and clinical outcome and conversely grade 2 perfusion in poor outcome, closer to that of an occluded than an open artery[7]. Indeed patients with grade 2 flow have indexes of MI (ejection fraction, enzyme peaks, ECG markers, or morbidity index) similar to those in patients with an occluded artery (grades 0 and 1 flow)[8], therefore early achievement of grade 2 flow did not appear to lead to optimal myocardial salvage, and achieving grade 3 perfusion alone was considered, at that time, the goal for the angiographic reperfusion success[9].

Although the reduction in coronary flow may be caused by damage to the epicardial vessels (i.e. dissection), focal spasm of the epicardial vessels, macro embolization etc., coronary flow may be markedly reduced even in patients with re-perfused acute myocardial infarction and without any residual vessel obstruction. In such patients, the reduction in coronary flow may suggest the existence of CVMO. The extreme phenomenon of this concept is the "no-reflow phenomenon": an open epicardial artery without flow into the myocardium. The term "no-reflow", however, has been increasingly used to describe microvascular obstruction and reduced myocardial flow after opening an occluded artery[10]. Indeed if coronary occlusion is prolonged, the microvasculature shows extensive capillary damage and myocardial cell swelling[11], when coronary is re-opened, myocardial reperfusion is achieved only in areas with anatomically preserved microvasculature, whereas reflow does not occur in myocardium with extensive microvascular damage. Contrariwise, adequate myocardial reflow shortly after epicardial coronary reperfusion is an accurate indication of microvascular integrity. Although the mechanism of no-reflow seems to imply many pathways of which probably only a part has been clarified[12], distal embolization of plaque and/or thrombus from the lesion site is a likely mechanism.

Ito et al[13] showed that TIMI 2 flow may reflect advanced CVMO assessed with the use of myocardial contrast echocardiography (MCE). MCE data showed a broad no reflow area in all patients with TIMI grade 2, whereas MCE reflow was obtained in the majority of patients with TIMI grade 3 reflow. Thus, broad and advanced microvascular perfusion abnormality was considered a main cause for postprocedural reduction in the epicardial coronary flow in patients with acute myocardial infarction.

No-reflow therefore can initially be demonstrated by analysis of TIMI flow grade (<3), however it may occur in a sizeable proportion of patients with TIMI flow grade 3 using more specific methods (see next sections). Indeed, the sensitivity of TIMI flow assessment in the detection of myocardial no-reflow is rather low and the patency status of the infarct-related artery does not always indicate the extent of microvascular integrity. The primary objective of reperfusion therapies is not only restoration of blood flow in the epicardial coronary artery expressed by TIMI 3 but also complete and sustained reperfusion of the infarcted myocardium. Indeed it has to be noted that TIMI flow grade describes epicardial instead of myocardial blood flow as confirmed by van't Hof et al. who have shown that a substantial number of patients with TIMI 3 flow have persistent ST-segment elevation on the post-angioplasty ECG, suggesting an impairment of myocardial reperfusion[14].

Thrombolysis in myocardial infarction (TIMI) frame count

Because of the lack of reproducibility of TIMI flow assessment, particularly TIMI 2 flow, Gibson and colleagues[15] have described the corrected TIMI frame count (CTFC), which counts the number of cineangiographic frames required for the injection of contrast to reach a fixed distal point in the infarct artery.

In contrast to the conventional TIMI flow-grade system, the CTFC is quantitative rather than qualitative, and it is a continuous rather than a categorical variable. The normal CTFC for the right coronary artery (RCA) and circumflex vessels is approximately 21 frames; for the left anterior descending artery (LAD) it is 36 frames. The first frame used for TIMI frame counting is the first frame in which dye fully enters the artery. This occurs when three criteria are met: (1) A column of nearly full or fully concentrated dye must extend across the entire width of the origin of the artery; (2) Dye must touch both borders of the origin of the artery; and (3) There must be antegrade motion to the dye[15].

The distal landmark branches are used for analysis: the distal bifurcation of the LAD (ie, the "mustache," "pitchfork," or "whale's tail"); in the circumflex system, the distal bifurcation of the segment with the longest total distance that includes the culprit lesion; and in RCA, the first branch of the posterolateral artery. Since the LAD is usually longer than the other major arteries, the CTFC of LAD is often higher and therefore value is normalized: the CTFC of the LAD is divided by 1.7, the ratio of the unadjusted mean CTFC of LAD to the mean frame count of the other arteries[15]. CTCF is a quantitative assessment of coronary blood flow that varies only a small amount in association with body size, systemic arterial pressure, age, and sex[16] but it depends upon a set acquisition frame-rate of 30 frames per second, standardized guide catheters, and sustained maximal epicardial vasodilatation. However, it should be noted that nitrate use, heart rate, and the phase of the cardiac cycle in which dye is injected had significant effects on the TFC. Therefore these factors need to be considered[17].

CTFC correlates with stenosis severity in the infarct artery after infarction, infarct zone regional wall motion, and creatine kinase levels[18]. Faster (lower) 90-minute CTFCs have been related to improved in-hospital and 1-month clinical outcomes after thrombolytic administration in univariate and multivariate models. Even among those patients classified as having normal flow (TIMI grade 3 flow, CTFC≤40), CTFC identified a subgroup of patients with TIMI grade 3 flow who were at a particularly low risk or higher-risk of adverse outcomes[19].

Moreover CTFC has been shown to be a predictor of long-term outcome: its measurement three weeks after MI was an independent predictor of five-year survival, providing additional prognostic information within TIMI flow grades.[20]

Other angiographic parameters to describe the effectiveness of myocardial reperfusion

Because of the limits of TIMI flow grade in describing myocardial blood flow, other angiographic parameters had been introduced to describe the effectiveness of myocardial reperfusion.

When contrast medium is properly injected and cine acquisition is sufficiently prolonged, the filling of myocardial vasculature appears as an angiographic "blush," or a "ground-glass" appearance. This appearance can be used in the catheter laboratory to visually assess microvascular filling and as marker of microvascular dysfunction and no-reflow[21]. Two simple angiography-derived microvascular perfusion scores describing myocardial opacification with contrast are the myocardial blush grade[22] and TIMI myocardial perfusion grade[23].

Myocardial blush grades

The myocardial blush grade is based on the visually assessed contrast density in the infarcted myocardium after reperfusion therapy[22,24] (Figure 1).

The angiographic myocardial blush grades are analogous to the TIMI grades for flow in the epicardial infarct–related coronary artery and are graded as follow:

Myocardial blush grade 0: no myocardial blush or contrast density;

Myocardial blush grades 1: minimal myocardial blush or contrast density;

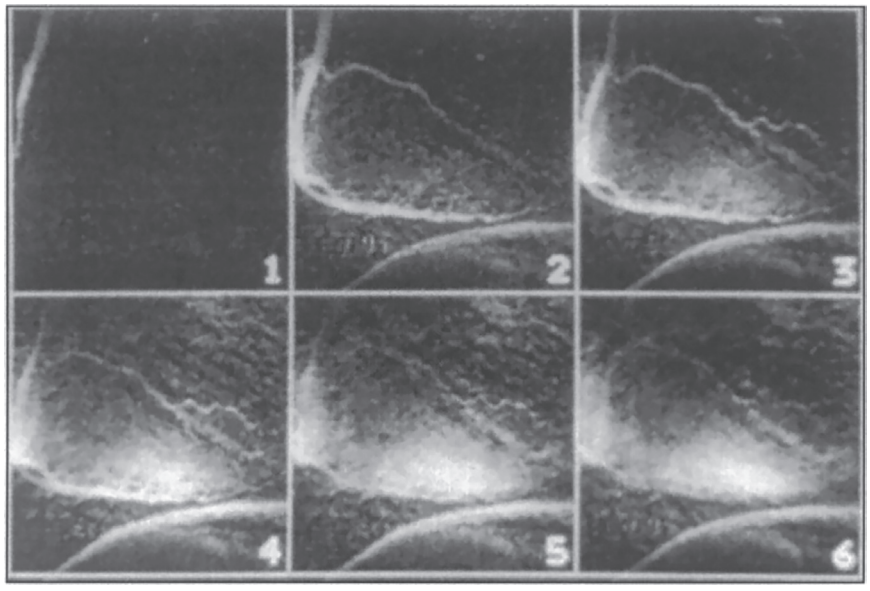
Myocardial blush grades 2: moderate myocardial blush or contrast density but less than that obtained during angiography of a contralateral or ipsilateral non– infarct-related coronary artery;

Myocardial blush grades 3: normal myocardial blush or contrast density, comparable with that obtained during angiography of a contralateral or ipsilateral non–infarct-related coronary artery.

Van 't Hof et al. have shown that myocardial blush grade was related to TIMI flow, however, it was clear that patients with myocardial blush grade <2 could have "normal" TIMI flow[22].

Myocardial blush grade was related to long-term mortality independently of TIMI flow suggesting that the myocardial blush grade is an angiographic variable that takes the extent of myocardial reperfusion into account (including micro vascular tissue), and it was confirmed of additional prognostic value[22] (Figure 2).

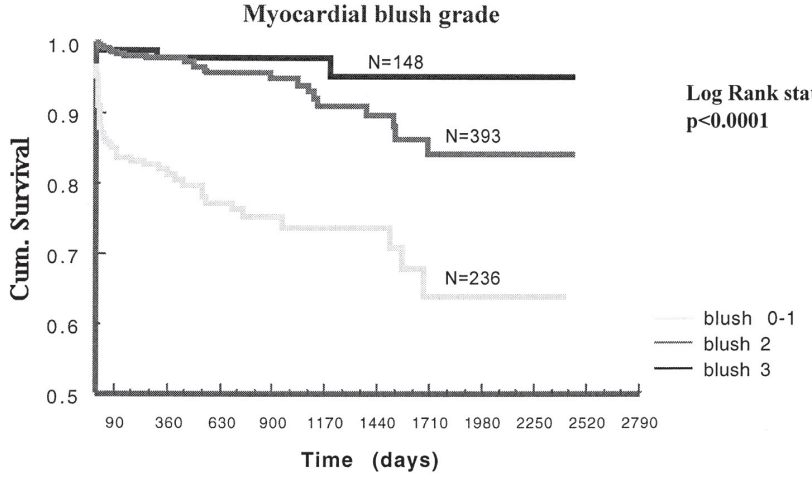
Figure 1. Digital subtraction images of a contrast infection in a right coronary artery



In frame I part of the proximal epicardial vessel is filled; in 2 the entire epicardial artery is filled and some contrast has arrived in the small intramyocardial vessels. On subsequent frames the myocardium perfused by this right coronary artery becomes clearly visible. By comparison with another myocardial territory/perfusion area of another epicardial coronary artery this myocardial 'blush' can be graded visually as 0-absent blush, 1-minimal blush, 2-moderate, less than normal blush 3-normal blush. From Zijlstra et al. Neth Heart J. 2002;10:111-117

Myocardial blush grade has been shown as the best predictor of nonreperfusion defined by MCE and was the invasive parameter with the greatest predictive value for left ventricular function after acute MI[25]. Myocardial blush grade 0 to 1 has been demonstrated to be an independent predictor for long-term mortality (during 22.1 ± 15.6 months of follow-up)[26].

Figure 2. Kaplan-Meier survival curves for 777 patients with known myocardial blush grades



Myocardial blush grade 0 or 1 indicates no or minimal blush or contrast density of myocardium supplied by infarct-related vessel on postangioplasty angiogram. Blush grade 2 indicates moderate blush or contrast density, and blush grade 3 indicates normal blush or contrast density, comparable with blush obtained during angiography of contralateral or ipsilateral non–infarct-related coronary artery.

From van't Hof AW et al. Circulation. 1998;97:2302-2306.

TIMI myocardial perfusion grade

TIMI myocardial perfusion (TMP) grade is a simple semiquantitative classification scheme, that can be used to characterize the filling and clearance of myocardial perfusion from a coronary angiogram and is graded as follow[27]:

TMP Grade 0: Failure of dye to enter the microvasculature. Either minimal or no ground-glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit artery, indicating lack of tissue-level perfusion.

TMP Grade 1: Dye slowly enters but fails to exit the microvasculature. There is the ground-glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit lesion that fails to clear from the microvasculature, and dye staining is present on the next injection (about 30 seconds between injections).

TMP Grade 2: Delayed entry and exit of dye from the microvasculature. There is the ground-glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit lesion that is strongly persistent at the end of the washout

phase (ie, dye is strongly persistent after 3 cardiac cycles of the washout phase and either does not or only minimally diminishes in intensity during washout).

TMP Grade 3: Normal entry and exit of dye from the microvasculature. There is the ground-glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit lesion that clears normally and is either gone or only mildly/moderately persistent at the end of the washout phase (ie, dye is gone or is mildly/moderately persistent after 3 cardiac cycles of the washout phase and noticeably diminishes in intensity during the washout phase), similar to that in an uninvolved artery. Blush that is of only mild intensity throughout the washout phase but fades minimally is also classified as grade 3.

A simpler description of TMP grade can be summarized as:

TMP grade 0: minimal or no myocardial blush;

TMP grade 1: dye stains the myocardium, and this stain persists on the next injection;

TMP grade 2: dye enters the myocardium but washes out slowly so that dye is strongly persistent at the end of the injection;

TMP grade 3: there is normal entrance and exit of dye in the myocardium.

As for myocardial blush, TMP grade, measured at angiography performed at 90 minutes after thrombolytic administration, was a predictor of outcome. A mortality gradient across the TMP grades has been demonstrated[27] , with mortality lowest in those patients with TMP grade 3 (2.0%), intermediate in TMP grade 2 (4.4%), and highest in TMP grades 0 and 1 (6.0%; 3-way P=0.05). Even among patients with TIMI grade 3 flow in the epicardial artery, the TMP grades allowed further risk stratification of 30-day mortality: 0.73% for TMP grade 3; 2.9% for TMP grade 2; 5.0% for TMP grade 0 or 1 (P=0.03 for TMP grade 3 versus grades 0, 1, and 2; 3-way P=0.066). Moreover TMP grade 3 flow was a an independent predictor of 30-day mortality in a multivariate model that adjusted for the presence of TIMI 3 flow (P=NS), the corrected TIMI frame count (OR 1.02, P=0.06), the presence of an anterior myocardial infarction (OR 2.3, P=0.03), pulse rate on admission (P=NS), female sex (P=NS), and age (OR 1.1, P<0.001).

This emphasizes again that impaired perfusion by the use of angiographic parameters which describe the effectiveness of myocardial reperfusion was related to a higher risk of mortality independently of the flow in the epicardial artery. The TMP grade remained predictive of improved survival after a two-year follow-up[28] and the TMP

grade is a sensitive indicator of the efficacy of reperfusion strategies also in patients treated with primary percutaneous intervention (PCI)[29].

Summarizing, angiographic "blush" is a simple, widely available, and virtually costless technique for the immediate diagnosis of microvascular impairment at the time of acute catheterization and the evaluation of myocardial tissue-level perfusion. However important drawbacks complicate the widespread use of this measure. The visual assessment requires an experienced observer, and is associated with marked variability and an intrinsic limited reproducibility[30]. To overcome this issue, automated quantization of myocardial blush using off-line software has become available, with significantly improved inter- and intraobserver variability and good correlation with with long-term prognosis and indexes of myocardial remodelling[31–34].

In conclusion, microvascular obstruction and dysfunction may be consistent when TIMI flow is less than 3 or 3 with an abnormal myocardial blush grade. Therefore the real goal of STEMI perfusion is to obtain TIMI 3 "with evidence of adequate myocardial reperfusion" which can be considered as myocardial blush 2 or 3[22,35].

Electrocardiogram

Although successful recanalization of the epicardial vessel is a necessary condition for obtaining myocardial reperfusion, we have already seen that it is the microvascular flow that most strongly correlates with outcome. In the last decades, ST segment monitoring has been increasingly used in clinical practice and in clinical research for the assessment of myocardial microvascular reperfusion in patients with MI and ST resolution (STR) as tool for the evaluation of the efficacy of reperfusion therapy[36,37].

ST resolution quantification

STR is commonly expressed as the percentage from baseline, thus measuring ST-segment elevations, measured 60 ms after J point, in all leads related to infarct area and resolution of the sum of ST-segment elevation (sum STR) after reperfusion therapy either by fibrinolysis or primary PCI.

Categories of resolution of the sum of ST-segment elevation has been described: complete resolution is defined as ≥70% resolution, partial resolution is defined as <70% to 30% resolution, and no resolution is defined as <30%.[38,39] However, to measure the sum of all the ST- segment elevations means the method not simple for routine practice and also alternative methods have been proposed:

1) "Single-lead STR" measured by comparing one ECG lead with the most prominent ST-segment deviation at baseline and at a given time point after reperfusion[40]. STR obtained in a single lead is an easy and accurate prognosticator of cardiac 30-day mortality in patients with STEMI and is useful for early identification of low- and high-risk subgroups of patients[40].

2) "Max ST elevation (STE)": MaxSTE represents the existing ST-segment deviation in the single ECG lead of maximum ST-segment deviation, which is present at a given time, Max STE is measured as per single-lead STR, but it is not compared with ST-segment deviation on the baseline ECG. In patients with anterior MI max STE is evaluated simply by the maximum ST-segment elevation. In contrast, in patients with inferior infarction, the mirroring aspect of the magnitude of the ST-segment changes needs to be considered. Max STE is measured either by maximum ST-segment elevation on 1 inferior lead or maximum ST-segment depression on a precordial lead V1 to V4, whichever is greater at the time of evaluation. If any bundle branch block is present, only maximum ST-segment elevation is considered[41]. MaxSTE predicts early and medium-term mortality when recorded 90 min after thrombolysis[42].

3) "STE index" (STE-I): this index minimize the effect of the different number of leads involved, indeed the STE sum is divided by the number of the leads presenting STE. STR is therefore considered as the STE-I variation, obtained as the percent reduction after reperfusion of the STE-I. Santoro et al.[43] evaluating STE-i measured at 1, 5, 10, 20, and 30 min after restoration of epicardial blood flow in 37 STEMI patients, showed that STE-I progressively declined (>50%), in patients with TIMI 3 flow whereas no significant change in STE-I was observed in patients with TIMI flow< 3, suggesting that the reduction of STE-I ≤50% at 30 min after myocardial revascularization suggested microvascular obstruction.

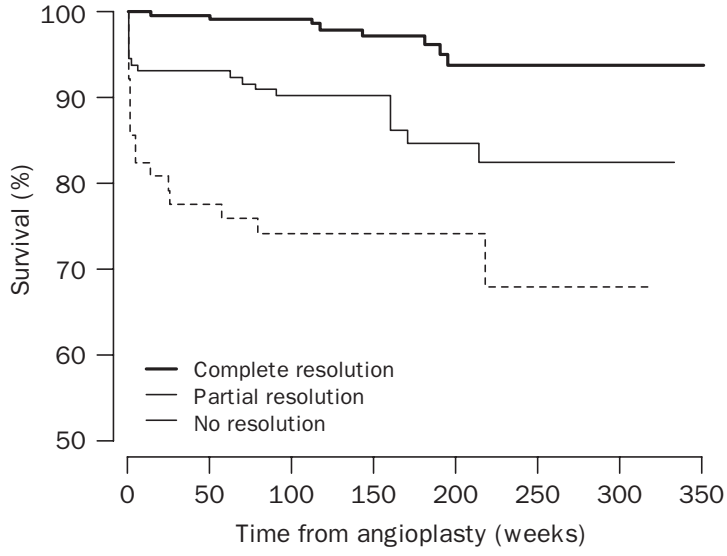
ST-segment elevation resolution and diagnosis of microvascular obstruction

The usefulness of STR for predicting epicardial reperfusion is well established. In the fibrinolitc era Califf et al[44] showed that patients with STR had 90% probability of a patent infarct related artery associated with successful reperfusion at the microvascular level but approximately 50% of patients with no STR presented with a patent epicardial infarct artery. Therefore a complete STR predicts an open infarct artery reasonably well but the absence of STR gives no information about patency[44].

Indeed STR can be considered a surrogate for tissue-level reperfusion[45] and showed a prognostic power that persists even after accounting for the effects of epicardial blood flow[46].

This has been confirmed in the primary PCI era (figure 3), where it has become clear that persistence of ST elevation do not indicate failure to re-canalize the infarct related artery, but rather indicates impaired myocardial perfusion due to microvascular obstruction. Moreover in the primary PCI era the clear relation between the ECG findings, enzymatic infarct size, and left-ventricular function has been demonstrated showing that the extent of STR reflects myocardial salvage[14]. Also STR before PCI is associated with small infarct size, and improved clinical outcome[47–49]. Fast STEMI diagnosis, early prehospital initiation of drug pretreatment, may be predictive of complete reperfusion before primary PCI expressed as STR[47].

Figure 3. Kaplan-Meier survival curve for 398 patients who underwent successful primary angioplasty according to ST segment resolution



The figure shows the survival curves for the three groups according to ST resolution. Normalized ST segment was defined as no residual ST-segment elevation of 0.1 mV or more in any of the 12 leads (complete ST-segment-elevation resolution); improved ST segment was defined as residual ST-segment elevation of less than 70% of that on the first ECG (partial ST-segment-elevation resolution); unchanged ST segment was defined as a residual ST-segment elevation of 70% or more of that on the first ECG (no STsegment- elevation resolution).

From van't Hof AW et al. Lancet 1997;350:615–619.

Correlation of STR with other imaging techniques of MVO

Kim et al[50] demonstrated by using cardiac magnetic resonance imaging (CMRI) at 8.2±8.0 days (early phase) and 3.3±1.1 months (late phase) after successful PCI, that in patients with early STR (≥70%) persistent microvascular obstruction in early-

phase CMRI occurred less frequently compared with patients with no STR, and in patients with no STR late-phase CMRI revealed a significant increase in left ventricle end-diastolic volume and reduced ejection fraction. Also Husser et al[51] also showed that ST-segment changes were related to microvascular obstruction observed by cardiovascular magnetic resonance (CMR) after primary PCI. In particular, microvascular obstruction was associated with a significantly increased sumSTE at all times after revascularization. The difference in the magnitude of STR between infarcts with and without microvascular obstruction was significant 6 h after revascularization and the best predictor of microvascular obstruction was a sumSTE >3 mm 90 min after pPCI.

Moreover in 180 patients with STEMI treated with primary PCI, residual STE, was the only independent predictor of microvascular injury whereas the number of Q waves was the only independent predictor of infarct size and transmural extent of infarction[52].

Finally Weaver et al[53] showed in 41 STEMI patients that persistent single lead maximal residual ST elevation (maxSTE) was higher at each time point after PCI in those with microvascular obstruction but only became statistically significant after 24hours. Moreover measurements at 48 or 72hours after primary PCI provided the best correlation with the combination of infarct size, artery area at risk and intramyocardial haemorrhage[53].

STR is a useful tool to diagnosis microvascular obstruction, however which leads to analyse, the optimal timing of ECG analysis and the best cut-off values of these parameters to achieve the better accurate diagnosis of microvascular obstruction remain uncertain.

Post-procedural residual cumulative ST-segment deviation and ST depression resolution

It should be considered that an high postprocedural ST-segment elevation, even though in the presence of complete resolution, may represent residual ischemia as a consequence of suboptimal reperfusion. Moreover, as described above, the STR analysis, which take in consideration both ECGs and the subsequent ratio, means that the method is not very simple for routine practice.

Indeed in a large cohort of patients studied by De luca et al.[54], the analysis based only on postprocedural ECG (at 3 hours after revascularization) had a larger feasibility in comparison with STR analysis (83% vs 69%). The Authors analysed the sum of ST-segment elevation and deviation [considering both elevation and depression (residual cumulative ST deviation)], measured 20 milliseconds after the end of the QRS

complex. At multivariate analysis, postprocedural residual cumulative ST deviation (combined elevation and depression), but not residual cumulative ST elevation, was an independent predictor of 1-year mortality. Residual cumulative ST-segment deviation provided better prognostic information (area receiver operating characteristic [ROC] = 0.733) than STR (area ROC = 0.636) or ST-segment deviation resolution (area ROC = 0.660) in terms of 1-year mortality. These data were confirmed for both anterior and non-anterior infarct location[54]. A residual cumulative ST-segment deviation of 5 mm was the best threshold in terms of prognostic stratification after primary PCI for STEMI[54]. Thus, it is conceivable that the inclusion of ST-segment depression in the evaluation of myocardial perfusion would give more additional prognostic information in comparison with only ST-segment elevation. Indeed in patients who had postprocedural TIMI grade 3 flow and complete STR, postprocedural incomplete resolution of ST-segment depression (which was observed in 8.2% of a total of 1,548 patients who had STEMI and underwent primary PCI) was associated with larger infarcts and subsequently with a higher mortality rate[55]. Finally when ST depression is present in STEMI patients undergoing primary PCI, ST-depression resolution <50% provided independent prognostic value that is incremental to ST-elevation resolution[56]; indeed in Patients enrolled in the APEX-AMI trial whom failed (16%) to resolve at least 50% of concomitant ST depression experienced over a two-fold increase in 90 day mortality. Moreover patients who failed to resolve ST depression ≥50% less frequently had post-PCI TIMI 3 flow and a tendency for greater myocardial necrosis based on changes in cardiac troponins[56].

Q waves and QRS for prediction of poor microvascular reperfusion

The presence of Q waves at presentation with a first acute STEMI reflects a more advanced stage of the infarction. STR indicating successful myocyte reperfusion may differ according to how far the infarction process has progressed. Indeed in 144 patients with a first acute myocardial infarction treated with streptokinase the presence of Q waves at presentation was a predictor of failure to achieve 50% STR suggesting that the presence of initial Q waves may reflect reduced myocyte reperfusion, even in those with early infarct artery patency[57]. Moreover Uyarel et al[58] in 112 consecutive patients (with first acute STEMI of <12-hour onset who underwent successful-TIMI-3 flow-primary PCI) showed that the presence of high QRS score (>4) measured by modified Selvester QRS-scoring system[59] (which is used to estimate the size of infarction) was an independent predictor of incomplete STR and 30-day major cardiovascular events.

In the baseline ECG of STEMI patients the different grade of distortion of the terminal portion of the QRS[60] [identified as 1) tall symmetric abnormal T waves in the involved leads, without ST elevation or major changes in the terminal portion of the

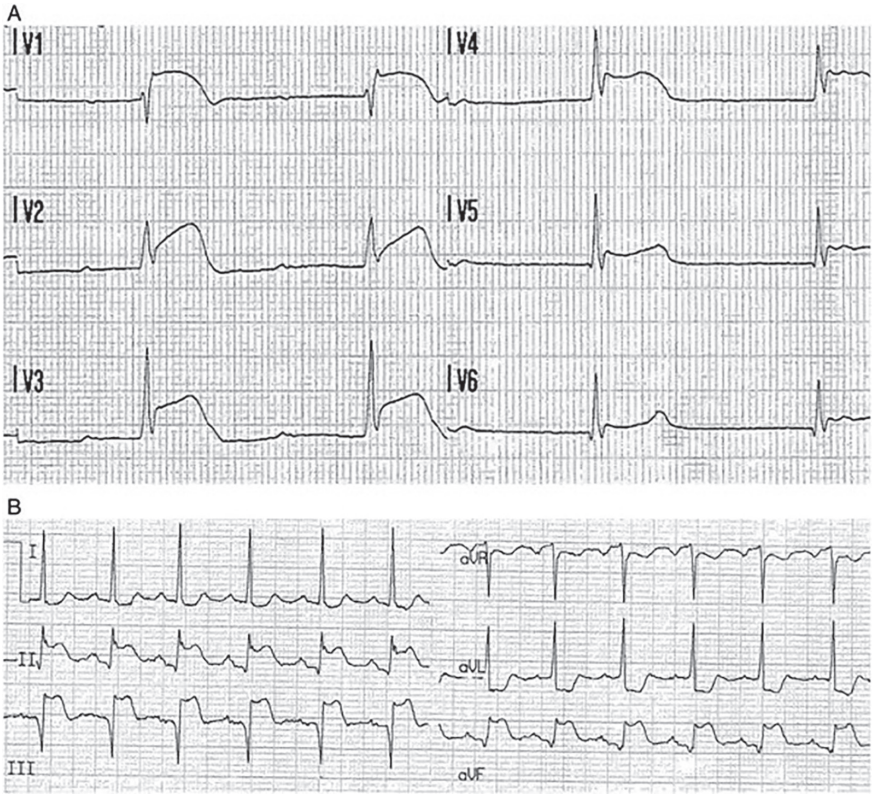
QRS; 2) abnormal T waves and ST elevation (>0.1 mV) in 2 or more adjacent leads, without major changes in the morphology of the terminal portion of the QRS; and 3) abnormal T waves and ST elevation (>0.1 mV), accompanied by distortion of the terminal portion of the QRS complex in 2 or more adjacent leads (emergence of the J point at a level above the lower half of the R wave or disappearance of the S wave in leads with an Rs configuration) was independently associated with a higher hospital mortality rate[60,61].

In a cohort of 1308 STEMI patients with interpretable electrocardiograms the QRS complex-grade 3 ischemia (G3I)[60] (see Figure 4 for example) was associated with high-risk patient criteria (older age, diabetes, TIMI risk score >3, Killip class >1, and anterior myocardial infarction) and one hour post-PCI, residual ST deviation was higher in patients with G3I compared with patients with Grade 2 ischemia (G2I). After multivariate adjustment, G3I was an independent predictor of failure of ST-segment resolution 1 hour post-PCI and 30-day mortality[62]. Moreover STEMI patients with the distortion of the terminal portion of the QRS present more often no-reflow after PCI[63,64].

Among ECG variables, also admission QRS duration was found to be an independent predictor of angiographic no-reflow in an unselected STEMI population treated with primary PCI. The patients in the no-reflow group were found to have longer admission QRS duration when compared to patients in the reflow group (IQR, 80-93 [median, 84] milliseconds vs 60-80 [median, 76] milliseconds, respectively; $P < .001$). Conversely, narrowing of QRS duration was found to be associated with adequate reflow[65].

In conclusion, the words of Gibson reported in an editorial in 2001 "In a time of dizzying advances in diagnostic modalities, it is refreshing to see what a useful, simple, noninvasive, broadly accessible, easily repeatable/applied, and affordable tool the ECG is"[66] seem still very actual considering that also in recent trials of STEMI patients STR resolution is confirmed to be a surrogate marker of clinical outcome[48,67]; thus, STR may be still considered in the modern era of STEMI treatment an useful tool to investigate the impact of new therapies on myocardial reperfusion. Finally, it is important to know that based on a combination of angiographic and electrocardiographic indices, a reasonable estimate of patients who get optimal myocardial reperfusion is about 35%[10]. Accordingly, it is important to identify patients with impaired reperfusion as early as possible, as they might benefit from a more aggressive pharmacological treatment[68].

Figure 4. Diagnostic ECG of a patient with anterior STEMI (A) and an inferior STEMI (B) showing G3I.



There is ST-elevation in lead V1 through V6, and there are no S waves in V2 through V3 (A). There is ST elevation in II, III, and aVF, and the ST J-point amplitude is 50% or greater of the R-wave amplitude in these leads (B). From Postma S et al. J Electrocardiol 2011;44:516–522

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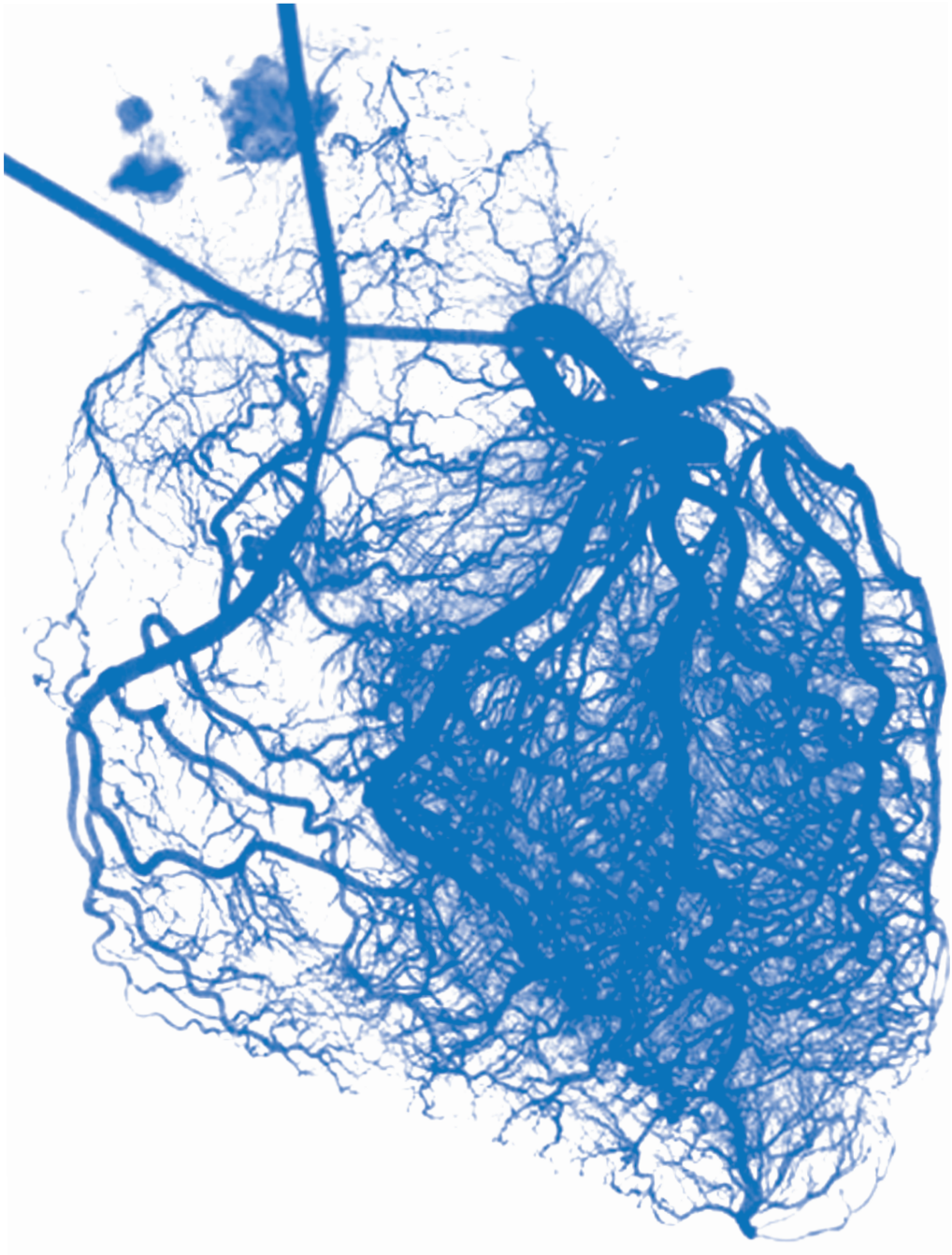

Chapter three

Impact of presentation and transfer delays on complete ST-segment resolution before primary percutaneous coronary intervention: insights from the ATLANTIC trial

Enrico Fabris, Arnoud van 't Hof, Christian W. Hamm, Frédéric Lapostolle, Jens Flensted Lassen, Shaun G. Goodman, Jurriën M. ten Berg, Leonardo Bolognese, Angel Cequier, Mohamed Chettibi, Christopher J. Hammett, Kurt Huber, Magnus Janzon, Béla Merkely, Robert F. Storey, Uwe Zeymer, Warren J. Cantor, Hélène Rousseau, Eric Vicaut, Gilles Montalescot

EuroIntervention. 2017;13:69-77

Abstract

Aims: to identify predictors of complete ST-segment resolution (STR) pre-primary percutaneous coronary intervention (PCI) in patients enrolled in the ATLANTIC trial.

Methods and Results: ECGs recorded at the time of inclusion [pre-hospital (pre-H)-ECG] and in the catheterization laboratory before angiography (pre-PCI-ECG) were analysed by an independent core laboratory. Complete STR was defined as ≥70%. Complete STR occurred pre-PCI in 12.8% (204/1598) of patients and predicted lower 30-days composite MACCE (OR=0.10, 95%CI 0.002-0.57;p=0.001) and total mortality (OR=0.16, CI 0.004-0.95;p=0.035). Independent predictors of complete-STR included the time from index event to pre-H ECG (OR=0.94, CI 0.89-1.00;p=0.035), use of heparins before pre-PCI-ECG (OR=1.75, CI 1.25-2.45;p=0.001) and time from pre-H-ECG to pre-PCI-ECG (OR=1.09, CI 1.03-1.16;p=0.005). In the pre-H ticagrelor group, patients with complete STR had a significantly longer delay between pre-H-ECG and pre-PCI-ECG compared to patients without complete STR [median 53 (44-73) vs 49 (38.5-61) (mins);p=0.001]; however, this was not observed in the control group (in-hospital ticagrelor) [50 (40-67) vs 49 (39-61);p=0.258].

Conclusions: Short patient delay, early administration of anticoagulant and ticagrelor if long transfer delay is expected, may help achieve reperfusion prior to PCI. Pre-H treatment may be beneficial in patients with longer transfer delays allowing the drug to become biologically active.

Introduction

In the randomized, double-blind, placebo-controlled ATLANTIC trial, prehospital (pre-H) administration of ticagrelor in patients with acute ST-segment elevation myocardial Infarction (STEMI) appeared to be safe but did not improve pre-percutaneous coronary intervention (PCI) ST-segment elevation resolution (STR) and/or TIMI 3 flow in the culprit artery[1]. However, it is possible that the brief interval time from study drug administration in the ambulance to catheterization laboratory (cath lab) may have limited the potential benefit of pre-H ticagrelor administration.

Since the identification of factors related to this objective may provide further insights into the optimization of pre-hospital STEMI patient management. Therefore, we undertook an exploratory analysis describing the predictors, and clinical significance, of complete STR before PCI in STEMI patients enrolled in the ATLANTIC trial.

Methods

Study design and procedures

ATLANTIC was an international study that randomized patients presenting with ongoing STEMI to receive double-blind treatment with a 180 mg loading dose of ticagrelor either pre-H (in-ambulance) or in-hospital (in-cath lab), in addition to aspirin and standard of care.

The trial design and main results have been published[1,2]. Briefly, eligible patients were identified by ambulance personnel for inclusion in the study following diagnosis of STEMI of more than 30 minutes' but less than 6 hours' duration, and with expected time from qualifying ECG to first balloon inflation of less than 120 minutes. Randomization and first loading dose of ticagrelor or matching placebo took place immediately after ECG confirmed the diagnosis of STEMI. Patients were then transferred to undergo coronary angiography and PCI, and the second loading dose was administered in the cath lab. All patients then received maintenance treatment with ticagrelor 90 mg twice daily for at least 30 days, up to a maximum of 12 months. In-ambulance use of glycoprotein (GP) IIb/IIIa inhibitors was discouraged, but left to physicians' discretion.

Electrocardiographic analysis, definitions and endpoints used

ST-segment analysis was performed on ECGs recorded pre-H (at the time of inclusion) and in the cath lab before angiography. The degree of STR was assessed by an independent core laboratory (eResearch Technology, Peterborough, United Kingdom) blinded to study treatment. The STR was calculated as the mean ST-segment elevation pre-H minus the mean ST-segment elevation pre-PCI divided by the mean ST-segment

elevation pre-H and expressed as a percentage, i.e. STR = ((STpre-hospital – STpre-PCI) / STpre-hospital) x 100. Complete STR was defined as ≥70% STR.

Clinical endpoints, evaluated up to the date of the last study visit (≤32 days), included composite major adverse cardiovascular clinical events (MACCE, defined as death, myocardial infarction, stroke or urgent revascularization), definite stent thrombosis, and total mortality.

Safety endpoints analysed included major or minor bleeding (excluding coronary artery bypass graft [CABG]-related bleeding) within 48 hours of first dose and after 48 hours and up to the last study visit using the Study of Platelet Inhibition and Patient Outcomes (PLATO); or major, minor and minimal bleeding up to the last study visit using TIMI, and Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention Patients (STEEPLE) definitions[2]. An independent adjudication committee conducted a blinded review of all clinical endpoints (except deaths and minimal bleeding events).

Statistical analysis

For continuous variables, mean, standard deviation and Student's t-test p-value are presented in case of Gaussian distribution, or median, interquartile ranges and Mann-Whitney's p-value in case of non-Gaussian distribution. For categorical variables, number, percent and chi-square test p-value are presented or Fisher's test p-value is presented in case of low numbers of events.

Ischemic endpoints analyses were performed in the modified intention-to-treat population, i.e., those patients who underwent randomization, received at least one dose of the study drug and had complete data for STR pre-PCI. For each endpoint, the two groups (complete STR group and incomplete STR group) were compared with the use of a logistic regression model. The 95% confidence intervals for the odds ratio were calculated and results were also presented as survival curves using Kaplan-Meier estimates.

Potential predictors of complete STR before PCI were first identified as those variables with a p-value <0.10 in univariate analyses; these were then introduced in the multivariate analysis adjusted for baseline characteristics and major determinants of STR, including age, sex, body mass index, diabetes mellitus (DM), prior coronary intervention and prior MI, with a p-value <0.05 threshold for significance.

All tests had a two-sided significant level of 5% and were performed with the use of SAS software, version 9.4 (SAS Institute).

Results

Complete descriptive analysis of patients with pre-PCI complete STR compared to incomplete STR is showed in table 1.

Table 1. Descriptive Analysis

Characteristic	Incomplete STR pre-PCI (<70%) (n=1394)	Complete STR pre-PCI (≥70%) (n=204)	Total (n=1598)	p-value
Age, years; median [q1;q3]	59[52;70]	59[51.5;67]	59[52;69]	0.3685
Age ≥75 years, %	225(16.1)	25(12.3)	250(15.6)	0.1536
Female, n(%)	269(19.3)	41(20.1)	310(19.4)	0.7870
Weight, kg; median [q1;q3]	80[70;89.5]	76[66;88]	80[70;89.5]	**0.0139**
BMI ≥30 kg/m^2, n(%)	279(20.0)	29(14.2)	308(19.3)	**0.0499**
Diabetes mellitus, n(%)	187(13.4)	25(12.3)	212(13.3)	0.6483
TIMI risk score group, n(%)				0.8036
0–2	843(60.5)	128(62.8)	971(60.8)	
3–6	526(37.7)	73(35.8)	599(37.5)	
>6	25(1.8)	3(1.5)	28(1.8)	
Prior cardiac history, n(%)				
Prior MI	105(7.5)	19(9.3)	124(7.8)	0.3744
Prior PCI	86(6.2)	21(10.3)	107(6.7)	**0.0277**
Prior CABG	5(0.4)	3 (1.5)	8(0.5)	0.0705
Prior hemorrhagic stroke	4(0.3)	0(0)	4(0.3)	1.0000
Prior ischemic stroke	10(0.7)	2(1.0)	12(0.8)	0.6583
Prior TIA	19(1.4)	1(0.5)	20(1.3)	0.4997
Other medical history, n(%)				
COPD	56(4.0)	8(3.9)	64(4.0)	0.9481
Chronic renal failure	24(1.7)	3(1.5)	27(1.7)	1.0000
Killip Class I, n(%)	1271(91.2)	187(91.7)	1458(91.2)	0.8171
Location of care at time of randomization, n(%)[a]				0.2642
In ambulance (primary transfer)	1043(74.8)	160(78.4)	1203(75.3)	
In emergency unit before ambulance transfer (secondary transfer)	351(25.2)	44(21.6)	395(24.7)	
Study medication				
1st loading dose	1393(99.9)	204(100)	1597(99.9)	1.0000
2nd loading dose	1354(97.1)	198(97.1)	1552(97.1)	0.9544
Maintenance dose	1224(87.8)	181(88.7)	1405(87.9)	0.7063

Actual pre-H ticagrelor, no morphine	319(22.9)	67(32.8)	386(24.2)	**0.0019**
Actual pre-H ticagrelor, use of morphine	353(25.3)	36(17.7)	389(24.3)	**0.0170**
Actual in-H ticagrelor, no morphine	365(26.2)	47(23.0)	412(25.8)	0.3376
Actual in-H ticagrelor, use of morphine	357(25.6)	54(26.5)	411(25.7)	0.7928
Aspirin use				
Use before Pre-PCI ECG	1114(79.9%)	166(81.4%)	1280(80.1%)	0.6260
Use in the 24 h before index event	418(30.0%)	58(28.4%)	476(29.8%)	0.6503
Other antithrombotic medication for index event				
Use of GP IIb/IIIa inhibitor before pre-PCI ECG	42(3%)	11(5.4%)	53(3.3%)	0.0763
Intravenous anticoagulant during hospitalization	1236(88.7)	192(94.1)	1428(89.4)	**0.0183**
Use of heparin before pre-PCI ECG	870(62.4%)	151(74.0%)	1021(63.9%)	**0.0013**
Time from index event to pre-H ECG (min) [q1;q3]	73[42;140]	66[38;114.5]	71[42;138]	**0.0321**
Time from index event to 1st loading dose (min) [q1;q3]	90[60;159]	85[55;135]	90[60;155]	0.0598
Time from pre-H ECG to pre-PCI ECG (min) [q1;q3]	49[39;61]	52[42;70.5]	49[39;62]	**0.0021**
Time from 1st loading dose to 2nd loading dose (min) [q1;q3]	30[21;42.5]	32[23;48]	30[21;43]	0.1002
Time from 1st loading dose to pre-PCI ECG (min) [q1;q3]	31[22;42]	33.5[25;48]	31[22;43]	**0.0083**
Procedures for index event, n(%)				
Coronary angiography	1382(99.1)	203(99.5)	1585(99.2)	1.0000
Thrombus-aspiration	748(53.7)	86(42.2)	834(52.2)	**0.0021**
PCI	1239(88.9%)	186(91.2%)	1425(89.2)	0.3243
With stent	1166(83.6)	175(85.8)	1341(83.9)	0.4371
Without stent	73(5.2)	11(5.4)	84(5.3)	0.9260
CABG	13(0.9)	8(3.9)	21(1.3)	**0.0028**

MI=myocardial infarction, PCI=percutaneous coronary intervention, CABG=Coronary Artery Bypass Graft, TIA=transient ischemic attack, COPD=chronic obstructive pulmonary disease, GP=glycoprotein,

Pre-H=pre Hospital, In-H=in Hospital.

Patient characteristics

A total of 1598 patients with both pre-H and pre-PCI ECGs available were included in the present analysis. Complete STR pre-PCI occurred in 12.8% (n=204/1598) of patients. Patients with complete STR were less frequently obese (weight: median [q1;q3], 76 [66;88] vs 80 [70;89.5] kg, p=0.014; body mass index (BMI) ≥30 kg/m2, 14.2% vs 20%, p=0.0499) compared with incomplete STR. Patients with a prior PCI had more often complete STR (10.3% vs 6.2%, p=0.028). No other patient demographic characteristics were significantly different between the two groups.

Pre-hospital pharmacological treatment

Use of aspirin before pre-PCI ECG (80.1%) or its use in the 24h before index event (29.8%) as well as the use of GP IIb/IIIa inhibitor before pre-PCI ECG (3.3%) was not different between complete STR and incomplete STR group, conversely the use of heparin (any type) before pre-PCI ECG was more frequent in the complete STR group (74% vs 62.4%,p=0.001).

Moreover, the complete STR group more frequently received pre-H ticagrelor administration without concomitant morphine use, compared with the incomplete STR group (32.8 % vs 22.9 %,p=0.002); conversely, the concomitant use of morphine and pre-H ticagrelor was more frequent in the incomplete STR group compared with the complete STR group (25.3% vs 17.7%,p=0.017). The use of in-H ticagrelor with or without concomitant use of morphine was similar in the complete vs incomplete STR group.

Pre-hospital interval times

Interestingly, the complete STR group exhibited a shorter time interval from the index event to pre-H ECG (mins) (median [q1;q3], 66 [38;114.5] vs 73 [42;140],p=0.032); conversely, a longer time interval from pre-H ECG to pre-PCI ECG (mins) (median [q1;q3], 52 [42;70.5] vs 49 [39;61], p=0.002) and a longer time interval from the first loading dose to the pre-PCI ECG (mins) (median [q1;q3], 33.5 [25;48] vs 31 [22;42], p=0.008).

Clinical significance of pre-PCI complete ST resolution

On logistic regression analysis, complete STR predicted both lower composite MACCE (OR 0.10, CI 0.002-0.57,p=0.001) and total mortality (OR 0.16, IC 0.004-0.95,p=0.035) but not definite stent thrombosis (table 2). Kaplan-Meier curves are shown in figure 1 and 2. There was no association between complete STR and increased bleeding risk, with the exception of minor non-CABG-related bleeding events (PLATO definition) within 48 hours of first dose (table 3).

Figure 1. Composite MACCE Kaplan-Meier curves in relation to complete and incomplete STR

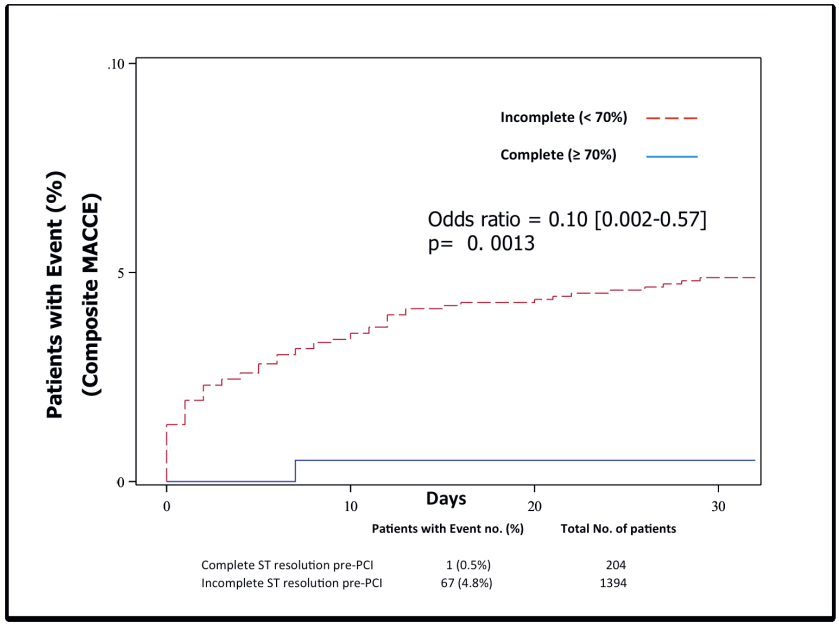

Figure 2. Total mortality Kaplan-Meier curves in relation to complete and incomplete STR

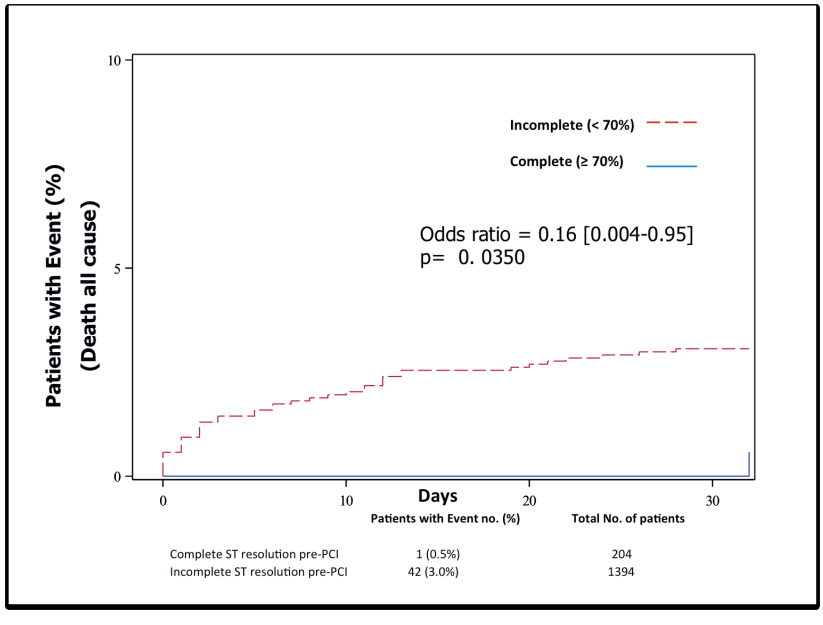

Table 2. ST-segment resolution and ischemic endpoints*, logistic regression analysis.

Ischemic endpoints	Incomplete STR pre-PCI (<70%) (n=1394)	Complete STR pre-PCI (≥70%) (n=204)	Odds ratio†	p-value†
Composite of death, MI, stroke and urgent revascularization– n, (%)	67(4.8%)	1(0.5%)	0.10[0.002;0.57]	**0.0013**
Definite stent thrombosis- n,(%)	11(0.8%)	0(0%)	0.44[0;2.14]	0.3777
Death (all-cause)– n, (%)	42(3.0%)	1(0.5%)	0.16[0.004;0.95]	**0.0350**

*Events occurring up to the date of the last study visit (≤32 days) are included in the table
†exact if n<5 in one group

Predictors of pre-PCI complete ST resolution

On univariate and multivariate analysis of pre-PCI complete STR are presented in table 4. At multivariate adjusted analysis (with age, sex, BMI, diabetes, prior PCI and prior myocardial infarction as variables forced in the model), modifiable independent predictors for complete STR were the time interval (mins) from index event (onset of symptoms) to pre-H ECG (OR=0.94, CI 0.89-1.00, p=0.035), which may represent "patient delay" time, the time from pre-H ECG to pre-PCI ECG (OR=1.09, CI 1.03-1.16,p=0.005), which may represent the transfer delay from ambulance to cath lab, and lastly the use of heparin before pre-PCI ECG (OR = 1.75, CI 1.25-2.45,p=0.001). Further independent predictors, but non-modifiable in relation with patients' early management, were BMI <30 kg/m^2 (OR=1.56, CI 1.02-2.39,p=0.039) and prior PCI status (OR=2.15, CI 1.07-4.35, p=0.033).

Table 3. ST-segment resolution and non-CABG-related bleeding events*, logistic regression analysis

Non-CABG-related bleeding events	Incomplete STR pre-PCI (<70%) (n=1394)	Complete STR pre-PCI (≥70%) (n=204)	Odds ratio [CI]†	p-value†
PLATO definition				
Within 48 h of first dose				
Major	23(1.7)	2(1.0)	0.59 [0.07;2.42]	0.7611
Minor	9(0.7)	5(2.5)	3.87 [1.28;11.66]	**0.0163**
Composite of major and minor	32(2.3)	7(3.4)	1.51 [0.66;3.47]	0.3294
After 48 h and up to 30 days*				
Major	17(1.2)	2(1.0)	0.80 [0.09;3.42]	1.0000
Minor	10(0.7)	1(0.5)	0.68 [0.02;4.84]	1.0000
Composite of major and minor	27(1.9)	3(1.5)	0.76 [0.15;2.49]	1.0000
TIMI and STEEPLE definition Up to 30 days*				
TIMI				
Major	19(1.4)	2(1.0)	0.72 [0.08;3.01]	1.0000
Minor	32(2.3)	6(2.9)	1.29 [0.53;3.12]	0.5724
Minimal	9(0.7)	1(0.5)	0.76 [0.02;5.52]	1.0000
STEEPLE				
Major	37(2.7)	3(1.5)	0.55 [0.11;1.76]	0.4696
Minor	19(1.4)	5(2.5)	1.82 [0.67;4.92]	0.2395
Unknown	4(0.3)	1(0.5)	1.71 [0.04;17.40]	1.0000

*Events occurring up to the date of the last study visit (≤32 days) are included in the table.
†exact if n<5 in one group

Effect of pre-hospital ticagrelor on ST resolution pre-PCI

There was no significant difference between the pre-H group and the in-H group in terms of the proportion of patients who had complete STR before PCI (13.2% vs 12.4%, OR=1.07, CI 0.8-1.44, p=0.63, respectively). In the pre-H ticagrelor group, patients with complete STR had a significantly longer delay between pre-H ECG and pre-PCI ECG (mins) compared to patients without complete STR [median 53 (44-73) vs 49 (38.5-61), p=0.001]; this was not observed in the control group (in-hospital ticagrelor) [50 (40-67) vs 49 (39-61), p=0.258] (table 5).

Table 4. Clinical predictors of complete ST resolution before PCI

		Univariate		Multivariate n=1571		Multivariate adjusted* n= 1571	
Variables[§]	**n**	**Odds ratio[CI]**	**p-value**	**Odds ratio[CI]**	**p-value**	**Odds ratio [CI]**	**p-value**
Time from index event to 1st loading dose	1582		0.0751[¥]				
≤1vs >3 h		1.69[1.07;2.69]					
>1-3 vs >3 h		1.30[0.86;1.99]					
≤1 vs >1-3 h		1.30[0.92;1.83]					
Time from index event to pre-H-ECG (min)	1597	0.95[0.89;1.00]	0.0448[¥]	**0.94[0.89;1.00]**	**0.0354**	**0.94[0.89;1.00]**	**0.0346**
Time from pre-H ECG to pre-PCI-ECG (min)	1598	1.04[1.00;1.09]	0.0554[¥]	**1.09[1.03;1.16]**	**0.0041**	**1.09[1.03;1.16]**	**0.0051**
Sex (female vs male)	1598	1.05[0.73;1.52]	0.7870			1.25[0.84;1.85]	0.2747
Age	1598	0.99[0.98;1.01]	0.3401				
Age (≥65 vs <65 years)	1598	0.85[0.62;1.16]	0.3081			0.80[0.57;1.11]	0.1758
Body mass index (<30 vs ≥30 kg/m^2)	1572	1.53[1.01;2.31]	0.0459[¥]	1.55[1.02;2.35]	0.0406	1.56[1.02;2.39]	0.0389
Prior myocardial infarction (yes vs no)	1598	1.26[0.76;2.11]	0.3751			0.83[0.41;1.71]	0.6190
Prior PCI (yes vs no)	1598	1.75[1.06;2.88]	0.0295[¥]	**1.82[1.08;3.05]**	**0.0241**	**2.15[1.07;4.35]**	**0.0328**
Prior CABG (yes vs no)	1598	4.14[0.64;21.47]	0.0705[¥]				
Diabetes mellitus (yes vs no)	1598	0.90[0.58;1.41]	0.6485			1.00[0.63;1.58]	0.9831
Use of heparin before pre-PCI-ECG (yes vs no)	1598	1.72[1.23;2.39]	0.0014[¥]	**1.72[1.23;2.41]**	**0.0015**	**1.75[1.25;2.45]**	**0.0011**
Use of GP IIb/IIIa inhibitor before pre-PCI-ECG (yes vs no)	1598	1.84[0.93;3.62]	0.0806[¥]				

*The multivariate adjusted analysis is the multivariate analysis with variables forced in the model: Age, sex, BMI, Diabetes, Prior PCI, Prior MI.

[§]variables with p-value <0.10 in univariate analysis or forced in the multivariate adjusted analysis. [¥]variables with p-value <0.10 in univariate analysis

Table 5. Transfer time and ST-segment resolution in in-hospital and pre-hospital ticagrelor groups

Variable	Group	n	Pre-PCI STR	Median [q1;q3]	p-value
Time from pre-H-ECG to pre-PCI-ECG (min)	**In-hospital ticagrelor group**	722	Incomplete (<70%)	49[39;61]	0.2581
		102	Complete (≥70%)	50[40;67]	
	Pre-hospital ticagrelor group	672	Incomplete (<70%)	49[38.5;61]	**0.0013**
		102	Complete (≥70%)	53[44;73]	

Discussion

The ATLANTIC ST-segment resolution sub-study represents, in the primary PCI era, the largest prospective cohort of STEMI patients focusing on early myocardial reperfusion expressed as complete STR during patient transportation for primary PCI.

Because achieving early myocardial reperfusion is the main goal in STEMI patients, this study evaluated the possible factors influencing early coronary reperfusion before primary PCI. The fact that a longer delay during patient transportation (the time from pre-H ECG to pre-PCI ECG) emerged as an independent predictor of complete STR suggests that pre-H antithrombotic treatment may become effective when there is a longer transfer time, allowing drug to become biologically active. Moreover, it was only in the pre-H ticagrelor group that patients with complete STR had a significantly longer transportation delay compared to patients without complete STR; conversely, this was not observed in the control group (in-H ticagrelor), thus suggesting a possible effect of pre-H ticagrelor administration in patients with longer transfer delay. The possible efficacy of pre-treatment with antiplatelet agents should be viewed in the perspective of an early or delayed access to coronary angiography and revascularization[3]. A short medical contact-to balloon times, may explain the absence of a detectable benefit of in-ambulance ticagrelor before the PCI procedure[1]. However, whereas the short time to PCI achieved in the ATLANTIC study[1] represents excellent practice, it may not reflect routine practice. Despite remarkable improvement[4], the timeliness of reperfusion therapy for STEMI patients transferred for primary PCI is often prolonged, with a significant proportion of transferred patients not achieving a guideline-recommended[5,6] door-to-balloon time of less than 90 minutes[4,7]. It is evident, therefore,

that, in the real world, early administration of potent antiplatelet therapy may represent an opportunity for improving pre-PCI myocardial reperfusion[8]. This analysis provides further support for a pre-H ticagrelor strategy in STEMI patients, especially for those who still present with a long transfer time. Although this finding can only be considered as hypothesis-generating, the potential benefit of pre-H ticagrelor administration should not be denied, especially considering its proven safety[1]. This is in line with the last ESC Guidelines which recommend to give P2Y12 inhibitors at "the time of first medical contact"[9], a recommendation which is more specific as compared to the 2013 ACCF/AHA Guidelines which states that P2Y12 inhibitors "should be given as early as possible or at time of primary PCI "[6].

A new opportunity to accelerate the onset of action of the antiplatelet effect could be the use of crushed or chewed rather than whole tablets[10,11]; conversely the use of morphine was shown to delay the absorption and onset of action of ticagrelor[1, 12]; moreover, the possible delay in ticagrelor absorption in the setting of STEMI, cannot be overcome by increasing loading dose regimens[13]. Pre-H administration of a fast-acting antiplatelet agent, such as cangrelor[14], may represent a new strategy to be tested in order to improve pre-PCI reperfusion.

The importance of in-ambulance treatment is also suggested by the fact that early use of heparin (before pre-PCI ECG) was an independent predictor of complete pre-PCI STR. This suggests that the earlier heparin is instituted, the greater the therapeutic benefit. This is in line with current guidelines that strongly recommend, despite the paucity of evidence[15,16], early administration of anticoagulant at the time of diagnosis, and also with the common practice among many European emergency medical services, to give anticoagulant as soon as possible, including in the pre-H setting.

Interestingly, complete STR was more frequent in patients with lower weight and BMI, and BMI <30 kg/m^2 emerged as independent predictor of complete STR. This may reflect the possible influence of BMI on efficacy of antithrombotic therapy[17]; however, ticagrelor efficacy is not influenced by BMI[18].

Another independent predictor of complete STR was short "patient delay" (the time from index event to pre-H ECG). This emphasizes, once more[19,20], that the delay between symptom onset and diagnosis (first ECG) should be minimized as much as possible. The early period after symptom onset represents a golden opportunity for antithrombotic therapy, because the platelet content of the fresh coronary thrombus is maximal and more susceptible to powerful antiplatelet agents[21]; moreover, early reperfusion after symptom onset has the maximal lifesaving potential, through myocardial salvage. Patient education is an important component in reducing this delay[22], and it is

interesting that, in this analysis, prior PCI status was another independent predictor of complete STR. One might speculate that these patients recognised the symptoms of acute myocardial infarction and took timely action to seek medical help.

The ATLANTIC ST-segment resolution analysis highlights the elements that may help to achieve reperfusion before primary PCI. This is particularly relevant considering that this sub-study confirmed[19,23,24] the prognostic importance of electrocardiographic assessments of early reperfusion, showing that pre-PCI complete STR represents a valid surrogate marker for cardiovascular clinical outcomes, namely MACCE and death (figure 1 and 2).

Finally, the reduction in ischemic complications associated with pre-PCI complete STR was not associated with an excess of major bleeding. This result was consistent across all the definitions and types of bleeding adjudicated by the clinical endpoint committee, with the exception of a signal for more early minor bleeding.

Limitations

First, this analysis was a post-hoc analysis and therefore should be viewed as hypothesis generating. Second, continuous ST-segment monitoring was not used, thereby precluding the identification of dynamic changes that may be observed during the acute phase of STEMI. Third, this analysis considered only STR as a marker of myocardial reperfusion and did not consider TIMI 3 flow in the culprit artery. However, patients with STR are likely to have a patent infarct artery[25]; moreover, STR can be considered a surrogate for tissue-level reperfusion[23] and, in the fibrinolytic era STR showed a prognostic power that persists even after accounting for the effects of epicardial blood flow[26]. Overall, there was a small difference between the different time intervals that have been considered; however, this study identified clear independent predictors of outcome with clinical applicability. Finally, the possibility of unaccounted confounding related to the non-randomized administration of heparin cannot be excluded, therefore the potential benefit of early heparin administration requires confirmation in future studies.

Conclusions

Pre-PCI complete STR is a valid surrogate marker for cardiovascular clinical outcomes. Short patient delay, early administration of anticoagulant and ticagrelor if long transfer delay is expected, may help achieve reperfusion prior to PCI. The fact that a longer delay during patient transportation emerged as independent predictor of complete STR suggests that pre-H treatment may be beneficial in patients with longer transfer delays allowing the drug to become biologically active.

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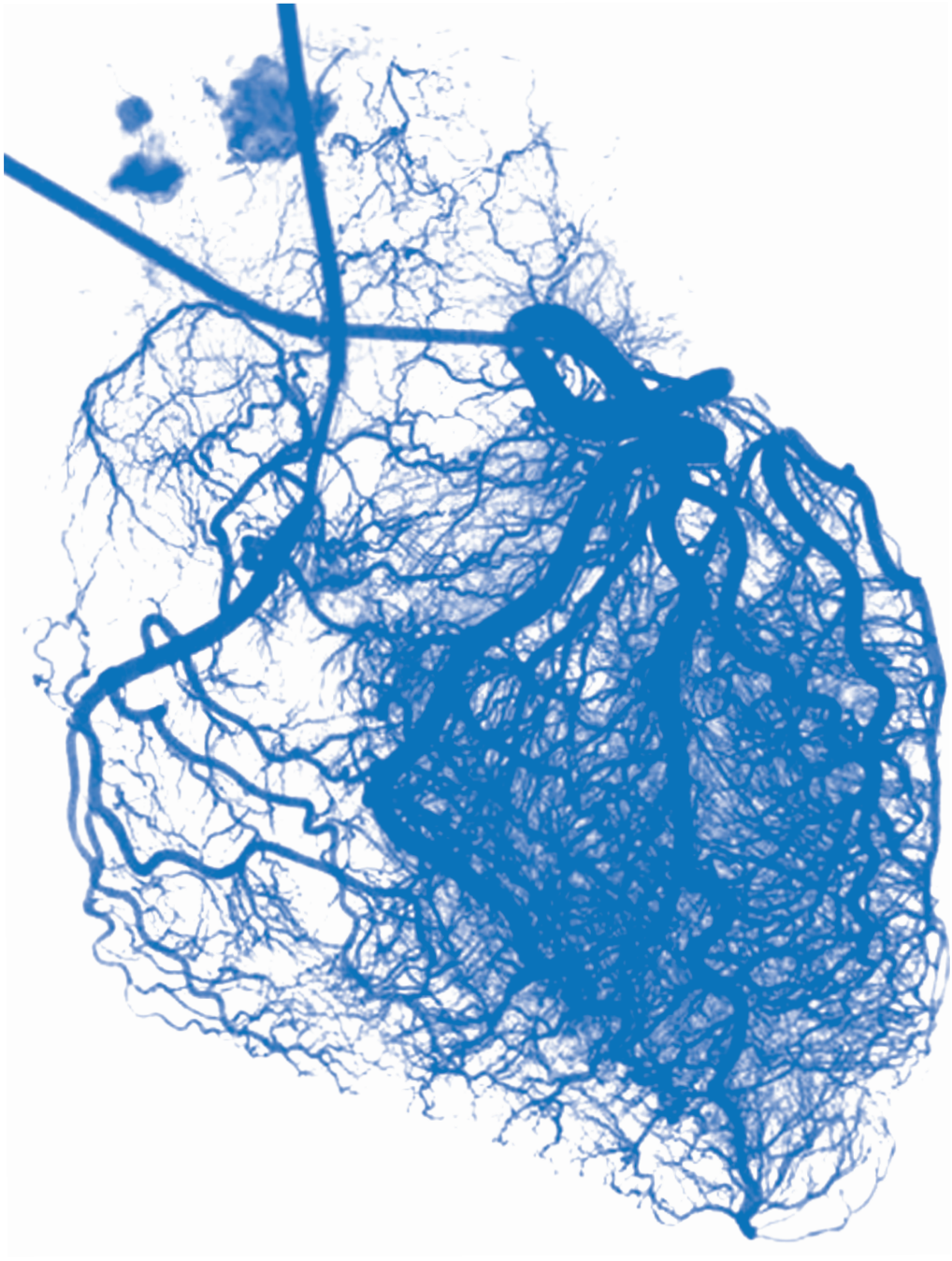

Chapter four

Clinical impact and predictors of complete ST segment resolution after primary percutaneous coronary intervention: a subanalysis of the ATLANTIC Trial

Enrico Fabris, Arnoud van't Hof, Christian W. Hamm, MD, Frédéric Lapostolle, Jens Flensted Lassen, Shaun G. Goodman, Jurriën M. ten Berg, Leonardo Bolognese, Angel Cequier, Mohamed Chettibi, Christopher J. Hammett, Kurt Huber, Magnus Janzon, Béla Merkely, Robert F. Storey, Uwe Zeymer, Warren J. Cantor, Anne Tsatsaris, Mathieu Kerneis, Abdourahmane Diallo, Eric Vicaut, Gilles Montalescot

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Abstract

Background: In the ATLANTIC trial the early use of aspirin, anticoagulation and ticagrelor coupled with very short medical contact-to-balloon times represent good indicators of optimal treatment of ST-elevation myocardial infarction (STEMI) and an ideal setting to explore which factors may influence coronary reperfusion beyond a well-established prehospital (pre-H) system.

Methods: This study sought to evaluate predictors of complete ST-segment resolution (STR) after percutaneous coronary intervention (PCI) in STEMI patients enrolled in the ATLANTIC trial. ST-segment analysis was performed on electrocardiograms (ECGs) recorded at the time of inclusion [pre-H ECG], and 1 hour after PCI (post-PCI ECG) by an independent core laboratory. Complete STR was defined as ≥70% STR.

Results: Complete STR occurred post-PCI in 54.9% (n=800/1456) of patients and predicted lower 30-day composite major adverse cardiovascular and cerebrovascular events (MACCE) (OR 0.35, 95% CI 0.19-0.65; p<0.01), definite stent thrombosis (OR 0.18, 95% CI 0.02-0.88; p=0.03), and total mortality (OR 0.43, 95% CI 0.19-0.97; p=0.04). In multivariate analysis, independent negative predictors of complete STR were the time from symptoms to pre-H ECG (OR 0.91, 95% CI 0.85-0.98; p<0.01) and diabetes mellitus (OR 0.6, 95% CI 0.44-0.83; p<0.01); pre-H ticagrelor treatment showed a favourable trend for complete STR (OR 1.22, 95% CI 0.99-1.51; p=0.06).

Conclusions: this study confirmed that post-PCI complete STR is a valid surrogate marker for cardiovascular clinical outcomes. In the current era of STEMI reperfusion, patients' delay and diabetes mellitus are independent predictors of poor reperfusion and would need specific attention in the future.

Introduction

In the randomized, double-blind, placebo-controlled ATLANTIC (Administration of Ticagrelor in the catheterization laboratory or in the Ambulance for New ST elevation myocardial Infarction to open the Coronary artery) trial, prehospital (pre-H) administration of ticagrelor in patients with acute ST elevation myocardial Infarction (STEMI) appeared to be safe but did not improve coronary or myocardial reperfusion before percutaneous coronary intervention (PCI)[1]. It is possible that the impressive brief interval time from ambulance to catheterization laboratory may explain the absence of a detectable benefit of pre-H administration before PCI, however the effects of pre-hospital ticagrelor became apparent after PCI[2].

In the ATLANTIC trial the frequent early use of aspirin and anticoagulation and the early use of ticagrelor coupled with very short medical contact-to-balloon times represent good indicators of optimal treatment of STEMI patients[3]. Because achieving myocardial reperfusion is the main goal in STEMI patients for improving prognosis, this setting is ideal to explore which factors may influence myocardial reperfusion beyond a well-established pre-H system.

Therefore, we undertook an exploratory analysis describing the predictors, and clinical significance, of complete ST resolution (STR) post PCI in STEMI patients enrolled in the ATLANTIC trial.

Methods

Study design and procedures

ATLANTIC was an international study that randomized patients presenting with ongoing STEMI to receive double-blind treatment with a 180 mg loading dose of ticagrelor either pre-H (in-ambulance) or in-H (in- catheterization laboratory), in addition to aspirin and standard of care.

The trial design and main results have been published[1,4]. Briefly, eligible patients were identified by ambulance personnel for inclusion in the study following diagnosis of STEMI of more than 30 minutes' but less than 6 hours' duration, and with expected time from qualifying ECG to first balloon inflation of less than 120 minutes. Randomization and first loading dose of ticagrelor or matching placebo took place immediately after ECG confirmed the diagnosis of STEMI. Patients were then transferred to undergo coronary angiography and PCI, and the second loading dose was administered in the cath lab. All patients then received maintenance treatment with ticagrelor 90 mg twice daily for at least 30 days, up to a maximum of 12 months. In-ambulance use of glycoprotein (GP) IIb/IIIa inhibitors was discouraged, but left to physicians' discretion.

Electrocardiographic analysis, definitions and endpoints used

ST-segment analysis was performed on ECGs recorded pre-H (at the time of inclusion) and 1 hour after PCI (post PCI ECG). The degree of STR was assessed by an independent core laboratory (eResearch Technology, Peterborough, United Kingdom) blinded to study treatment. The STR was calculated as the mean ST-segment elevation pre-H minus the mean ST-segment elevation post PCI divided by the mean ST-segment elevation pre-H and expressed as a percentage, i.e. STR = ((STpre-hospital – ST post-PCI) / STpre-hospital) x 100. Complete STR was defined as ≥70% STR[5].

Clinical endpoints, evaluated up to the date of the last study visit (≤32 days), included composite major adverse cardiovascular clinical events (MACCE, defined as death, myocardial infarction, stroke or urgent revascularization), definite stent thrombosis, and total mortality.

Safety endpoints analysed included major or minor bleeding (excluding coronary artery bypass graft [CABG]-related bleeding) within 48 hours of first dose and after 48 hours and up to the last study visit using the Platelet Inhibition and Patient Outcomes (PLATO) study definitions; or major, minor and minimal bleeding up to the last study visit using TIMI, and Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention Patients (STEEPLE) definitions[4]. An independent adjudication committee conducted a blinded review of all clinical endpoints (except deaths and minimal bleeding events).

Statistical analysis

For continuous variables, mean, standard deviation and Student's t-test p-value are presented in case of Gaussian distribution, or median, interquartile ranges and Mann-Whitney's or Wilcoxon test p-value in case of non-Gaussian distribution. For categorical variables, number, percent and chi-square test p-value are presented or Fisher's test p-value is presented in case of low numbers of events. Ischemic endpoints analyses were performed in the modified intention-to-treat population, i.e., those patients who underwent randomization, received at least one dose of the study drug and had complete data for STR post-PCI. For each endpoint, the two groups (complete STR and incomplete STR) were compared with the use of a logistic regression model. The 95% confidence intervals for the odds ratio were calculated. Potential predictors of complete STR post PCI were first identified as those variables with a p-value <0.10 in univariate analyses; these were then introduced in the multivariate analysis adjusted for baseline characteristics, with a p-value <0.05 threshold for significance.

All tests had a two-sided significant level of 5% and were performed with the use of SAS software, version 9.4 (SAS Institute).

Results

Complete descriptive analysis of patients with post-PCI complete STR compared to incomplete STR is showed in table 1.

Table 1. Descriptive Analysis

Characteristic	ST resolution post-PCI Incomplete (<70%) (n=656)	ST resolution post-PCI Complete (≥70%) (n=800)	Total (n=1456)	P-value
Age, years; median [Q1;Q3]	61 [52;71]	59 [51;68]	60 [52;69]	**0.0070**
Age ≥75 years, %	113(17.2)	106(13.3)	219(15.0)	**0.0347**
Female, n (%)	122 (18.6)	150 (18.8)	272 (18.7)	0.9408
Weight, kg; median [Q1;Q3]	80 [70;88]	80 [70; 90]	80 [70;90]	0.8466
BMI ≥30 kg/m^2, n (%)	121 (18.5)	164 (20.5)	285 (19.6)	0.3255
Diabetes mellitus, n (%)	108 (16.5)	77 (9.6)	185 (12.7)	**<0.0001**
TIMI risk score group, n (%)				**0.0076**
0–2	379 (57.8)	516 (64.5)	895 (61.5)	
3–6	264 (40.2)	278 (34.8)	542 (37.2)	
>6	13 (2.0)	6 (0.8)	19 (1.3)	
Prior cardiac history, n (%)				
Prior MI	54 (8.2)	56 (7.0)	110 (7.6)	0.3762
Prior PCI	50 (7.6)	49 (6.1)	99 (6.8)	0.2589
Prior CABG	3 (0.5)	4 (0.5)	7 (0.5)	1.0000
Prior hemorrhagic stroke	2 (0.3)	2 (0.3)	4 (0.3)	1.0000
Prior ischemic stroke	9 (1.4)	5 (0.6)	14 (1.0)	0.1462
Prior TIA	9 (1.4)	4 (0.5)	13 (0.9)	0.0784
Other medical history, n (%)				
COPD	30 (4.6)	29 (3.6)	59 (4.1)	0.3613
Chronic renal failure	14 (2.1)	8 (1.0)	22 (1.5)	0.0776
Killip Class I, n (%)	597 (91.0)	736 (92.0)	1333 (91.6)	0.4975

Procedures for index event, n (%)				
Thrombo-aspiration	369 (56.3)	485 (60.6)	854 (58.7)	0.0917
PCI	656 (100)	800 (100)	1456 (100)	
Without stent	41 (6.3)	42 (5.3)	83 (5.7)	0.4129
With stent	615 (93.8)	758 (94.8)	1373 (94.3)	
DES	391 (59.6)	444 (55.5)	835 (57.4)	0.1152
BMS	237 (36.1)	325 (40.6)	562 (38.6)	0.0795
Study medication				
Aspirin use				
Any use	653 (99.5)	797 (99.6)	1450 (99.6)	1.0000
Maintenance dose	641 (97.7)	787 (98.4)	1428 (98.1)	0.3604
Pre PCI ECG use	500 (76.2%)	620 (77.5%)	1120 (76.9%)	0.5639
Use in the 24h before index event	201 (30.6%)	234 (29.3%)	435 (29.9%)	0.5642
Other antithrombotic medication for index event				
GP IIb/IIIa inhibitor	205 (31.3)	262 (32.8)	467 (32.1)	0.5418
Intravenous anticoagulant during hospitalization	584 (89.0)	720 (90)	1304 (89.6)	0.5447
Use of heparin before pre PCI ECG	382 (58.2%)	503 (62.9%)	885 (60.8%)	0.0710
Time from symptoms to Pre-H ECG (Mins)	76 [42;150]	69 [41;122]	71 [42;135]	0.0332
Time from symptoms to 1st Loading Dose (Mins)	96 [60;166]	85 [60;142]	90 [60;151]	0.0195
Time from Pre-H ECG to Pre-PCI ECG (Mins)	50 [39;62]	49 [38;61]	49 [39; 61]	0.5687

Patient characteristics

In the ATLANTIC trial, 1862 consenting patients were randomized to receive either pre-H or in-H ticagrelor. Of these, a total of 1456 patients who underwent PCI and had both pre-H and post-PCI ECGs available were included in the present analysis. Patients received pre-H ticagrelor and in-H ticagrelor in 49% (713) and in 51% (743), respectively. Complete STR post-PCI occurred in 54.9% (n=800/1456) of patients. Patients with complete STR were younger (59 [51;68] vs 61 [52;71 years, p=0.01), were less frequently diabetics (9.6% vs 16.5%, p<0.01) and had lower TIMI risk scores (see table 1) compared with incomplete STR. Patients with complete STR had shorter interval time from symptom onset to pre-H ECG (69 [41;122] vs 76 [42;150] min, p=0.03) or from symptom onset to first loading dose of study medication (85 [60;142] vs 96 [60;166] min, p=0.02). No other patient demographic characteristics were significantly different between the two groups.

The use of heparin (any type) pre-PCI was more frequent in the complete STR group compared with incomplete STR (62.9 vs 58.2%, p=0.07). Use of aspirin (99.6%) was not different between complete STR and incomplete STR group as well as the use of GP IIb/IIIa inhibitors (GPI) (32.1%). It has to be noted that in-ambulance use of GPI was discouraged and GPI was used only in 3.3% during patients' transfer to the catheterization lab.

Effect of pre-hospital ticagrelor on ST resolution post-PCI

Post PCI complete STR occurred in 57.5% of patients in the pre-H ticagrelor group and in 52.5% of patients in the control group (p= 0.055). The degree of STR was significantly greater in the pre-H group (median, 75.0% vs. 71.4%, p= 0.049).

Clinical significance of post-PCI complete ST resolution

On logistic regression analysis, post PCI complete STR predicted both lower 30 days composite MACCE (OR 0.35, IC 0.19-0.65] p<0.01), definite stent thrombosis (OR 0.18, 95% CI 0.02-0.88; p=0.03) and total mortality (OR 0.43, 95% CI 0.19-0.97; p=0.04) (table 2) (figure 1 and 2). Complete STR predicted both lower major (OR 0.31, 0.11-0.88, p=0.03) and a composite of major and minor (OR 0.48, IC 0.24-0.998, p=0.049) non-CABG-related bleeding events according to PLATO definition (table 3).

Table 2. Post PCI ST-segment resolution and ischemic endpoints*, logistic regression analysis

Ischemic endpoints	ST resolution post-PCI Incomplete (<70%) (n=656)	ST resolution post-PCI Complete (≥70%) (n=800)	Odds ratio† [CI]	P-value†
Composite of death, MI, stroke and urgent revascularization - n, (%)	34 (5.2%)	15 (1.9%)	0.35[0.19;0.65]	**0.0008**
Definite stent thrombosis - n, (%)	9 (1.4%)	2 (0.3%)	0.18 [0.02;0.88]	**0.0282**
Death (all-cause) - n, (%)	17 (2.6%)	9 (1.1%)	0.43 [0.19;0.97]	**0.0410**

*Events occurring up to the date of the last study visit (≤32 days) are included in the table.
† exact if n<5 in one group

Figure 1. Total mortality curves in relation to complete and incomplete STR

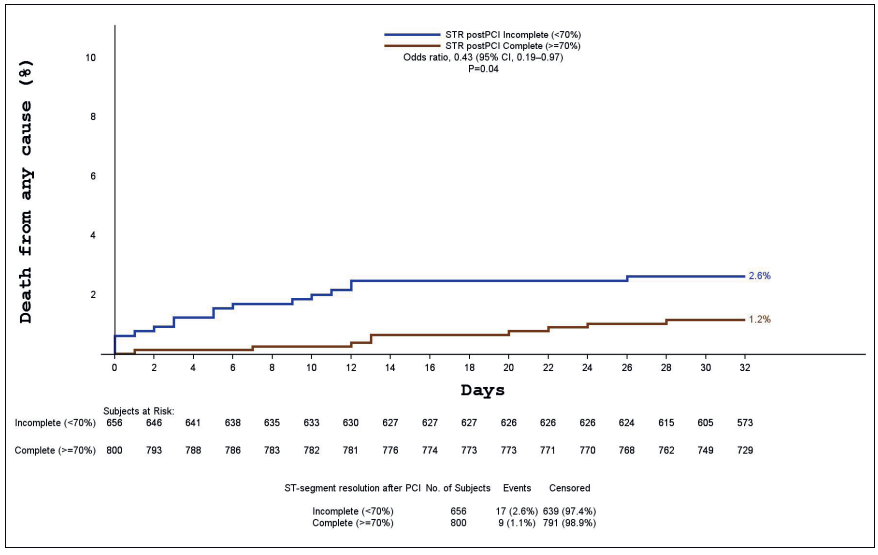

Figure 2. Composite MACCE curves in relation to complete and incomplete STR Post PCI

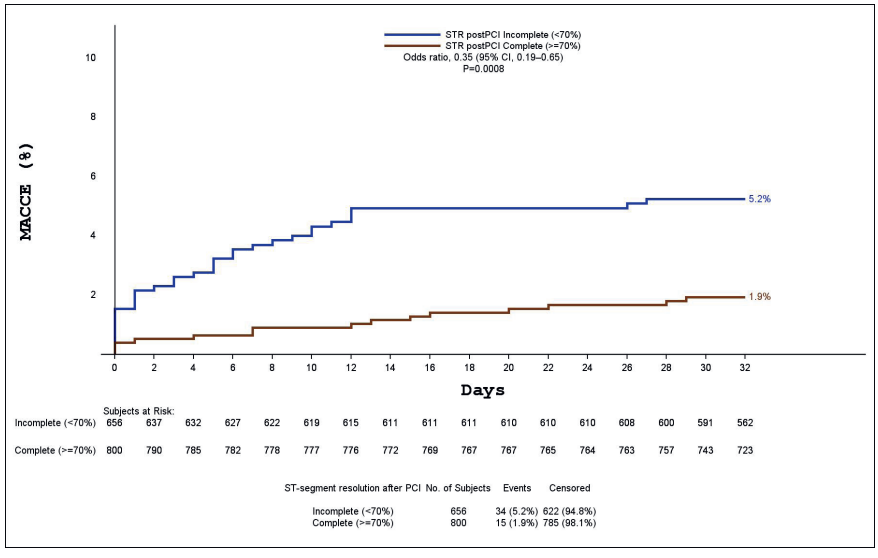

Table 3. Post PCI ST-segment resolution and non-CABG-related bleeding events*, logistic regression analysis

Bleedings events	ST resolution post-PCI Incomplete (<70%) (n=656)	ST resolution post-PCI Complete (≥70%) (n=800)	Odds ratio† [CI]	P-value†
Non-CABG-related bleeding events (PLATO definition)				
Within 48 hours of first dose				
Major	13 (2.0)	5 (0.6)	0.31 [0.11;0.88]	**0.0273**
Minor	7 (1.1)	7 (0.9)	0.82 [0.29;2.35]	0.7091
Composite of major and minor	20 (3.1)	12 (1.5)	0.48 [0.24;0.998]	**0.0494**
After 48 hours and up to 30 days*				
Major	10 (1.5%)	5 (0.6%)	0.41 [0.14;1.20]	0.1017
Minor	4 (0.6%)	7 (0.9%)	1.44 [0.36;6.73]	0.7631
Composite of major and minor	14 (2.1%)	12 (1.5%)	0.70 [0.32;1.52]	0.3657
Non-CABG-related bleeding events up to 30 days* (TIMI and STEEPLE definitions)				
TIMI				
Major	9 (1.4%)	6 (0.8%)	0.54 [0.19;1.53]	0.2493
Minor	20 (3.1%)	16 (2.0%)	0.65 [0.33;1.26]	0.2030
Minimal	4 (0.6%)	3 (0.4%)	0.61 [0.09;3.64]	0.7076
STEEPLE				
Major	21 (3.2%)	10 (1.3%)	0.38 [0.18;0.82]	**0.0133**
Minor	10 (1.5%)	11 (1.4%)	0.90 [0.38;2.13]	0.8121
Unknown	2 (0.3%)	4 (0.5)	1.64 [0.24;18.21]	0.6960

*Events occurring up to the date of the last study visit (≤32 days) are included in the table.
† exact if n<5 in one group

Predictors of post-PCI complete ST resolution

The results of univariate and multivariate analysis of post-PCI complete STR are presented in table 4. At multivariate analysis, independent negative predictors of complete STR were time from symptoms to pre-H ECG (OR = 0.91, 95% CI 0.85-0.98, p<0.01) and diabetes mellitus (OR = 0.6, CI 0.44-0.83, p<0.01); pre-H ticagrelor treatment showed a favourable trend for complete STR (OR 1.22, 95% CI 0.99-1.51; p=0.06).

Table 4. Univariate and Multivariate analysis of predictors of complete ST resolution post PCI

	Univariate Logistic Model*			Multivariate Logistic Model†		
Variables	**N**	**Odds-ratio (95% CI)**	**P-value**	**N**	**Odds-ratio (95% CI)**	**P-value**
Ticagrelor Pre-H vs Ticagrelor In-H	1456	1.22 (1.00;1.51)	0.0547	1455	1.22 (0.99;1.51)	0.0609
Age	1456	0.99 (0.98;1.00)	0.0054			
Age (Group ³75 Years vs <75 Years)	1456	0.73 (0.55;0.98)	0.0352	1455	0.94 (0.66;1.34)	0.7507
Chronic Renal Disease (Yes vs. No)	1456	0.46 (0.19;1.11)	0.0847	1455	0.57 (0.23;1.40)	0.2229
Diabetes Mellitus (Yes vs. No)	1456	0.54 (0.40;0.74)	0.0001	1455	**0.60 (0.44;0.83)**	**0.0018**
Use of heparin before pre PCI ECG (Yes vs. No)	1456	1.21 (0.98;1.50)	0.0711	1455	1.17 (0.95;1.46)	0.1416
Sex (Female vs Male)	1456	1.01 (0.77;1.32)	0.9408			
TIMI Risk Score Category (0-2 vs >6)	1456	2.95 (1.11;7.83)	0.0099	1455	2.32 (0.82;6.50)	0.0851
TIMI Risk Score Category (3-6 vs >6)	1456	2.28 (0.85;6.09)	0.2812	1455	2.01 (0.73;5.50)	0.2985
Time from symptoms to 1st LD (1 vs > 3 hours) (<=1 hours vs >3 hours)	1445	1.36 (0.99;1.86)	0.2299			
Time from symptoms to 1st LD (>1-3 vs >3 hours) (>1-3 hours vs >3 hours)	1445	1.35 (1.03;1.78)	0.1587			
§Time from symptoms to Pre-H ECG (mins)	1455	0.89 (0.83;0.96)	0.0016	1455	**0.91 (0.85;0.98)**	**0.0078**
Transient Ischaemic Attack (Yes vs. No)	1456	0.36	0.0915	1455	0.37	0.1079

* The Univariate Logistic Model † Multivariate Logistic Model: variables with p-value <0.10 in univariate analysis

§ Unit=60 for Time from symptoms to pre-H ECG. Pre-H= pre Hospital; in-H= in Hospital; LD=loading dose

Discussion

This ATLANTIC trial sub-analysis evaluated a large prospective cohort of STEMI patients focusing on myocardial reperfusion expressed as post PCI complete STR. In this cohort of patients who received early antithrombotic treatment and fast transportation to the cath lab we found that patients' delay and diabetes mellitus were independent predictors of reduced myocardial reperfusion after PCI. These findings provide further insights into the potential optimization of STEMI management in the current era of STEMI reperfusion, and are particularly important because they clearly identify patient subtypes who need particular attention.

Interestingly, the time from pre-H ECG to pre-PCI ECG was not different in the 2 groups (complete vs incomplete STR). However, in our study this time was very short, and when time to PCI is as brief as it was in the ATLANTIC Trial, it might blunt the risk associated with patients transfer delay, and at the same time it may suggest that when a well-established prehospital system has optimal performance further efforts to reduce time to PCI time (i.e. the system-of-care-dependent time (system delay)) might not further improve outcomes. Therefore, these data may suggest that other additional strategies are needed to improve outcomes in STEMI population. Indeed, despite the efforts to reduce door-to-balloon time over the past decade, a recent analysis from the Cath-PCI registry[6] questioned the usefulness of decreasing door-to-balloon times in the contemporary era. However, that study did not collect information regarding the ischaemic time determined by the time from symptom onset to ECG thus suggesting that also additional factors need to be targeted in the contemporary treatment. Indeed the prognostic importance of short ECG-to-PCI times[7,8] is likely to be modulated by the duration of ischaemia until diagnostic ECG is performed[9]. This is relevant considering that still a significant proportion of patients continue to delay seeking medical care voluntarily or not[10]. Moreover, considering that the education profile of patients is an important component to reduce delay[11], still considerable efforts should be made to educate the general public about the positive effects of an early and adequate first emergency call.

Patient delay is crucial, in fact, the early period after symptom onset represents a golden opportunity for antithrombotic therapy[12], because the platelet content of the fresh coronary thrombus is maximal and more susceptible to powerful antiplatelet agents[13]; and early reperfusion has the maximal lifesaving potential, through myocardial salvage.

Although a slight decrease in patient delay during the years has been reported, effort should be done especially in those at higher risk of prolonged patient delays

as elderly patients, diabetics, female and those who have symptoms presentation during the night [14,15].

Although the known worse outcome observed in diabetic patients may be partially related due to the longer time-delay to presentation, diabetes has been associated with abnormal coronary endothelial function, diminished coronary flow reserve, and impaired ischemic preconditioning[16-18], all of which may result in abnormal myocardial perfusion. This study confirmed that diabetes is an independent predictor of impaired myocardial perfusion after primary PCI[19-21]. Indeed, these patients may cumulate both the additional risk of being diabetic and a longer delay from chest pain to emergency call due a higher pain threshold or a more atypical clinical presentation. Additional research is required to develop further approaches to enhance microcirculatory function after primary PCI[22], which may improve clinical outcomes. This should be considered a high priority because diabetes is continuing to be an increasing international health burden and its prevalence continues to rise[23].

Interestingly, myocardial reperfusion rates numerically favoured pre-H ticagrelor treatment, and although pre-H treatment did not reach statistical significance as independent predictor of myocardial reperfusion, pre-H ticagrelor showed a favourable trend. The possible efficacy of pre-treatment with antiplatelet agents should be viewed in the perspective of an early or delayed access to coronary angiography and revascularization, and pre-H ticagrelor administration may help to achieve early (pre-PCI) myocardial reperfusion in patients with longer transfer delays[24] and may help to reduce ischemic endpoints, over the first 24 hour[2]. This may be particularly pertinent in patients who do not receive pre-H opiate treatment, which might counteract the time advantage of pre-H administration of oral $P2Y_{12}$ inhibitors[25]. Although the routine pre-H initiation of high-bolus dose of GPI has been showed to improve STR[26], in this analysis GPI did not emerge as predictor of STR; however in the ATLANTIC trial in ambulance use of GPI was discouraged and therefore GPIs were used in a very small percentage during patients' transfer (3.3%) and were frequently used for bailout situations. Thus this setting may conceal the potential effect of GPIs administration.

Pre-H administration of a fast-acting antiplatelet agent, such as cangrelor, may represent a new strategy to be tested in order to improve myocardial reperfusion. Because cangrelor is administered intravenously and has rapid onset, it could offer particular advantages in the STEMI primary PCI setting, especially where there is little opportunity for pretreatment as in patients who are intubated or in cardiogenic shock or those experiencing nausea and vomiting. In a pooled analysis of patient-level data from the three CHAMPION trials[27], cangrelor compared to control (clopidogrel or

placebo), reduced PCI periprocedural thrombotic complications, at the expense of increased bleeding, however only 12% of STEMI where included in these studies[27].

This analysis highlighted the key factors that in the current era of STEMI treatment may influence reperfusion post primary PCI expressed as STR. This is relevant considering that this study confirmed the prognostic importance of electrocardiographic assessments of early reperfusion[28], showing that post-PCI complete STR still represents a valid surrogate marker for cardiovascular clinical outcomes at 30 days. Finally, the lower ischemic complications associated with post-PCI complete STR was associated with lower major non-CABG-related bleeding events according to the PLATO and STEEPLE definitions. This could be related to the fact that patients with early optimal reperfusion may require less frequently the use of more potent post-PCI antithrombotic regimens, including prolonged GPIs administrations, however it is also possible that patients with complete STR were at lower risk of bleeding because of other factors.

Limitations

This analysis was a post-hoc analysis and therefore should be viewed as hypothesis-generating. This analysis considered only STR as a marker of myocardial reperfusion and did not consider TIMI 3 flow in the culprit artery. However, patients with complete STR are likely to have a patent infarct artery[29]; moreover, STR can be considered as a surrogate for tissue-level reperfusion[30] and, in the fibrinolytic era STR showed a prognostic power that persists even after accounting for the effects of epicardial blood flow[31].

Conclusions

Post-PCI complete STR is confirmed to be a valid surrogate marker for cardiovascular clinical outcomes. In the current era of STEMI reperfusion, patients' delay and diabetes are independent predictors of poor reperfusion and would need specific attention in the future.

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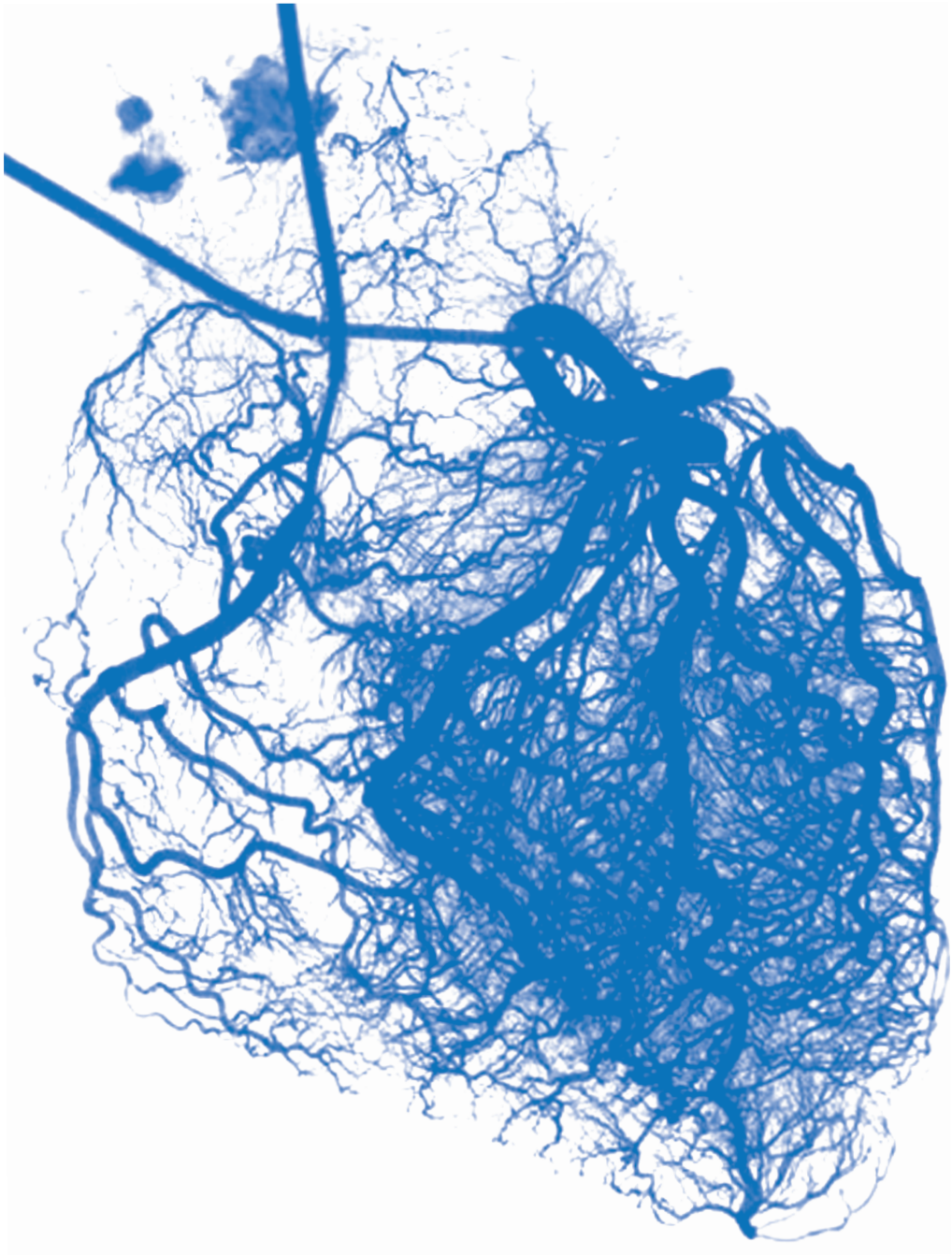
Part two

Therapy to improve myocardial reperfusion and/or to improve outcomes



Chapter 5

One-Year Mortality for Bivalirudin vs Heparins Plus Optional Glycoprotein IIb/IIIa Inhibitor Treatment Started in the Ambulance for ST-Segment Elevation Myocardial Infarction

Enrico Fabris, Sinem Kilic, Arnoud W. J. van 't Hof, Jurrien ten Berg, Ana Ayesta, Uwe Zeymer, Martial Hamon, Louis Soulat, Debra Bernstein, Prodromos Anthopoulos, Efthymios N. Deliargyris, Philippe Gabriel Steg

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Abstract

Importance: uncertainty exists regarding potential survival benefits of bivalirudin compared with heparins with routine or optional use of glycoprotein IIb/ IIIa inhibitors (GPI) in patients with ST-segment elevation myocardial infarction (STEMI) and there are few data regarding long term mortality in the context of contemporary practice, with frequent use of radial access and novel P2Y12 inhibitors.

Objective: assess the effect of bivalirudin monotherapy compared to a control group receiving unfractionated or low-molecular-weight heparin plus optional GPI, on 1-year mortality, a pre-specified outcome of the EUROMAX trial.

Design: international, randomized, open-label trial.

Setting: patients with STEMI being transported for primary percutaneous coronary intervention (PCI).

Participants: 2198 STEMI patients (from March 10, 2010, through June 20, 2013) were randomized (1:1) during transport for primary PCI.

Main Outcomes and Measures: the primary outcome was mortality at 1-year. All deaths were adjudicated as cardiac or non-cardiac by an independent blinded clinical events committee. Mortality at 1-year was assessed and examined across multiple pre-specified subgroups.

Results: Complete 1-year follow up was available for 98.5% (n=2164) of the patients. All-cause mortality at 1-year occurred in 5.4% of the patients. The number of all-cause deaths was the same for both treatment groups (59 deaths in each group, relative risk [RR]=1.02, 95% confidence interval [CI]: 0.72-1.45; p=0.92). No differences were noted in the rates of 1-year cardiac death (44 (4%) for bivalirudin, 48 (4.3%) for the control group, RR=0.93, 95% CI: 0.63-1.39; p=0.74) or non-cardiac death (15 (1.4%) for bivalirudin, 11 (1.0%) for the control group, RR=1.39 CI: 0.64, 3.01 p=0.40). Results were consistent across the pre-specified patient subgroups. The rate of deaths occurring between 30-days and 1-year were also similar 27 (2.5%) in the bivalirudin group, and 25 (2.3%) in the control group, RR=1.10; 95% CI, 0.64-1.88; p=0.73.

Conclusions and Relevance: In patients with STEMI who were being transported for primary PCI, treatment with bivalirudin, or with heparin with optional use of GPI, resulted in similar 1-year mortality. The reduced composite of death/major bleeding at 30 days in the bivalirudin arm of the EUROMAX trial did not translate into reduced cardiovascular or all-cause death at 1-year.

Introduction

There is persistent debate whether heparin or bivalirudin, in patients undergoing primary percutaneous coronary intervention (PCI), results in superior clinical outcomes. Studies comparing bivalirudin with other anti-thrombotic strategies have produced inconsistently lower mortality findings[1-5]. In the EUROMAX trial[1], bivalirudin initiated during transport for primary PCI, improved 30-day clinical outcomes with a reduction in the primary composite of death and major bleeding, which was driven by a marked reduction in major bleeding without obvious difference in 30-day mortality. Major bleedings are strongly associated with an increased risk of subsequent long-term mortality[6]. Long-term follow-up is important to assess potential late benefits of bivalirudin in primary PCI; we therefore assessed the effect of bivalirudin monotherapy compared to a control group receiving unfractionated or low-molecular-weight heparin plus optional glycoprotein IIb/IIIa inhibitor (GPI), on 1-year mortality, a pre-specified outcome of the EUROMAX trial.

Methods

Study design and treatment

The EUROMAX study design and results have been published[1,7]. In brief, patients ≥18 years presenting with STEMI intended for primary PCI within 2 hours of first medical contact were randomized (1:1) to either bivalirudin or intravenous heparin (unfractionated or low molecular weight) with optional use of GPI. All patients received aspirin and P2Y12 inhibitor as early as possible after the first medical contact. Decisions regarding access site, performance of thrombus aspiration, and stent type were left to physician preference.

The trial protocol is provided in the supplementary material.

Study Outcomes

The present analysis aims to evaluate the pre-specified end point of 1-year mortality. All deaths were adjudicated as cardiac or non-cardiac by an independent, blinded Clinical Events Committee. Mortality was examined across multiple pre-specified subgroups. Per protocol, there was no collection of nonfatal outcomes beyond the 30-day period.

Statistical analysis

Analyses were performed in the intention-to-treat (ITT) population, which was defined as all patients who underwent randomization and provided written informed consent.

Categorical outcomes were compared by means of the chi-square test or Fisher exact test. Continuous variables were compared by means of the Wilcoxon rank sum test. Time-to-event outcomes, determined with Kaplan-Meier methods, were compared by means of the log-rank test. For all analyses, a 2-sided $p < 0.05$ was considered statistically significant. All statistical analyses were performed by SAS software, version 9.2.

Results

A total of 2218 patients were enrolled in the trial. Of these patients 2198 provided formal written informed consent and were included in the ITT population. The baseline characteristics of patients were well matched between the two groups, although there were higher rates of diabetes and previous myocardial infarction in the control group (table 1). Treatments and procedures are summarized in e-table 1. One-year follow up was available for 98.5% (2164/2198) of the patients (e-figure 1).

One-year follow up was available for 98.5% (2164/2198) of the patients (e-figure 1).

Death from any cause at 1-year occurred in 59 patients in the bivalirudin group (5.4%) and 59 patients in the control group (5.3%) (relative risk [RR]= 1.02; 95% confidence interval [CI], 0.72 -1.45; p=0.91) (e-table 2). A Kaplan-Meier (KM) curve for all-cause mortality up to 1-year by treatment group is presented in Figure 1 (A). No differences were noted in the rates of 1-year cardiac death, 44 cardiac deaths (4.0%) in the bivalirudin group vs 48 (4.3%) in the control group (RR=0.93, 95% CI: 0.63-1.39; p=0.74), or non-cardiac deaths, 15 (1.4%) vs 11 (1%) (RR=1.39, 95% CI: 0.64-3.01; p=0.40) (e-table 2). KM curves of 1-year cardiac death and non-cardiac death according by treatment group are presented in Figure 1 (B).

Table 1. Baseline Characteristics of the Intention-to-Treat Population*

Characteristic	Bivalirudin (N = 1089)	Control (N = 1109)
Age		
Median (IQR) — yr	61 (52–71)	62 (52–72)
>65 yr — no. (%)	394 (36.2)	434 (39.1)
Female sex — no. (%)	275 (25.3)	248 (22.4)
Cardiac-related history — no. (%)†		
Diabetes‡	127 (11.7)	169 (15.3)
Hypertension	459 (42.2)	504 (45.5)
Hyperlipidemia§	398 (36.6)	417 (37.6)
Current smoker	453 (41.6)	472 (42.6)
Previous myocardial infarction‡	80 (7.4)	113 (10.2)
Previous percutaneous coronary intervention	97 (8.9)	108 (9.7)
Previous CABG	18 (1.7)	29 (2.6)
Killip class II, III, or IV — no./total no. (%)¶	77/996 (7.7)	69/1000 (6.9)
Anemia — no./total no. (%)	129/987 (13.1)	148/989 (15.0)
Creatinine clearance — no./total no. (%)		
≤60 ml/min	147/1001 (14.7)	165/998 (16.5)
>60 ml/min	854/1001 (85.3)	833/998 (83.5)

* There were no significant between-group differences except in the two categories that are noted below. CABG denotes coronary-artery bypass grafting, and IQR interquartile range.

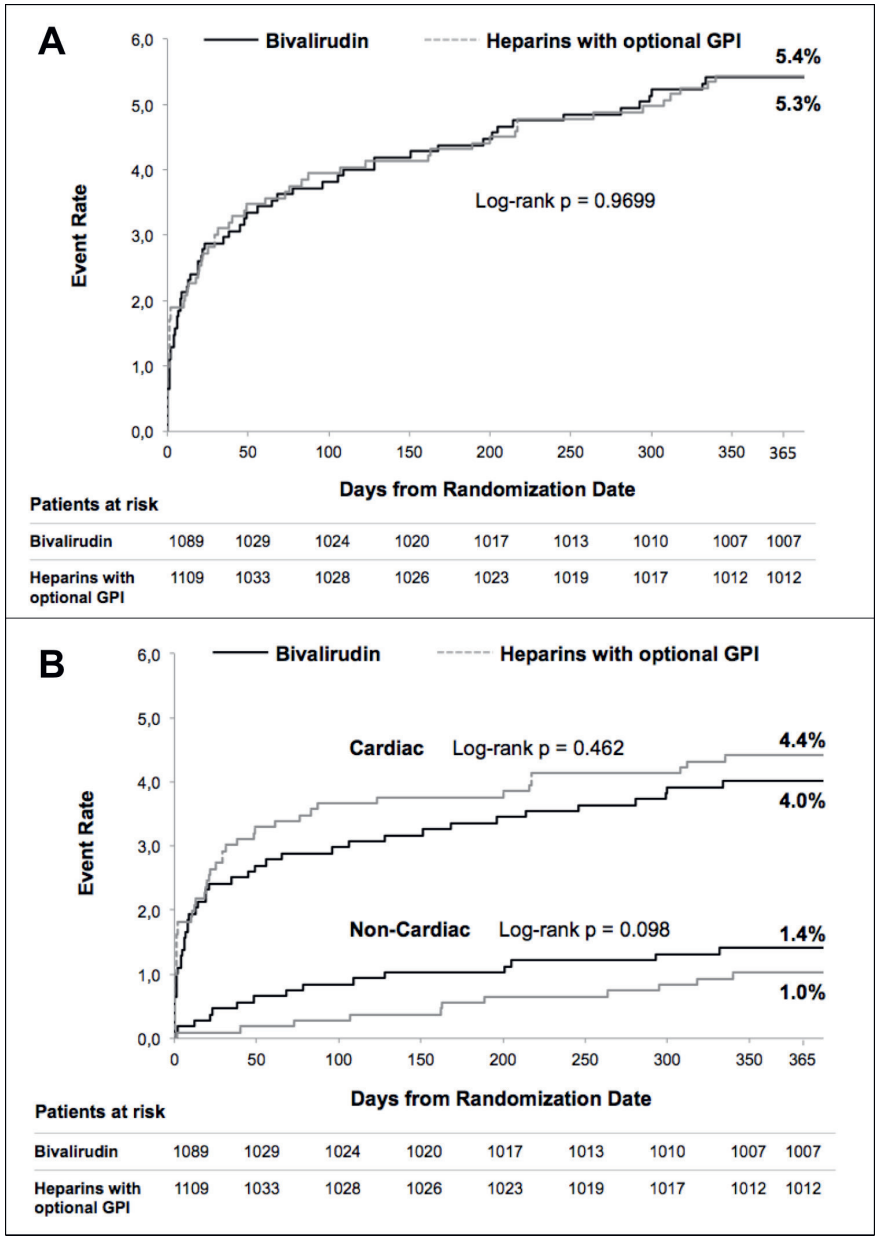
† Data on cardiac-related history were missing for one patient in each study group.

‡ P<0.05 for the between-group comparison.

§ Hyperlipidemia was defined as a diagnosis of hyperlipidemia or the use of lipid-lowering therapy.

¶ Killip classes are as follows: class I, no clinical signs of heart failure; class II, rales or crackles in the lungs, a third heart sound, and an elevated jugular venous pressure; class III, frank acute pulmonary edema; and class IV, cardiogenic shock or hypotension and evidence of peripheral vasoconstriction.

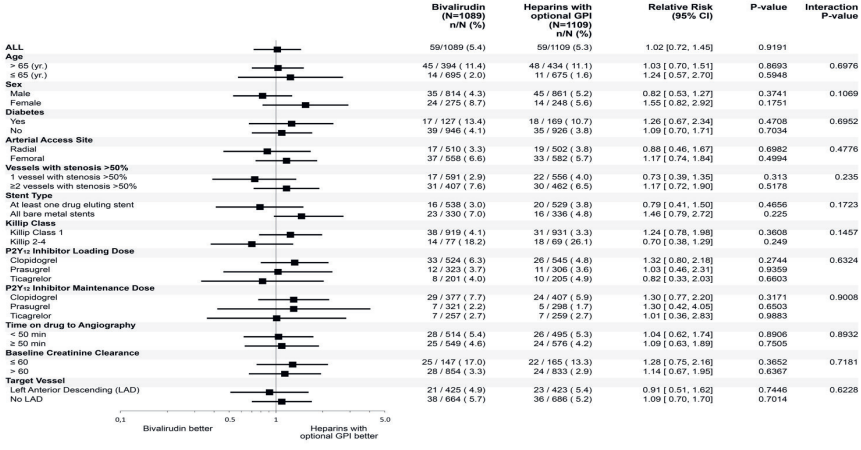
Figure 1. Panel A: Kaplan–Meier Curves of All cause deaths at 1 Year.
Panel B: Kaplan–Meier Curves of Cardiac and Non-cardiac Deaths at 1 Year.



No differences were noted also in the rates of deaths between 30-day and 1-year: 27 deaths (2.5%) in the bivalirudin group and 25 deaths (2.3%) in the control group (RR=1.10; 95% CI: 0.64-1.88; p=0.73); no difference in the rate of cardiac deaths, 17 (1.6%) in the bivalirudin group vs 15 (1.4%) in the control group (RR=1.15, 95% CI: 0.58-2.39; p=0.68), or non-cardiac deaths, 10 (0.9%) vs 10 (0.9%) (RR=1.02, 95% CI: 0.43-2.44; p=0.96) (e-table 3).

An analysis of the effect of bivalirudin in 12 prespecified subgroups, showed no significant interactions with baseline or procedural variables, including the arterial-access site and type of P2Y12 inhibitor that was administered (Figure 2).

Figure 2. Subgroup Analysis of 1-Year Mortality Outcome



Discussion

In this international, randomized, open-label study, bivalirudin, compared with heparins with optional use of GPI, was not associated with a reduction in 1-year all-cause or cardiac mortality, a result that was consistent across multiple subgroups. This information is potentially important given a lack of data regarding long-term outcome of bivalirudin compared with heparin in STEMI patient treated in ambulance, with frequent use of radial access and novel P2Y12 inhibitors.

The HORIZONS-AMI trial had a profound impact on the management of STEMI patients, in part due to its findings of a substantial reduction in cardiac mortality, present at 30 days and maintained over 3 years[2]. However the precise mechanism by which bivalirudin reduced long term mortality in HORIZONS-AMI is uncertain.

The HEAT PPCI trial[3], using GPIs only for bail out, in both the bivalirudin and heparin arms, found no difference in either bleeding complications or 30-day total mortality between the two groups. It has been suggested that the higher bleeding rates seen in prior trials with heparin were due to the routine or high rate use of GPIs in combination with heparin[8]. However in the multicentre Chinese BRIGHT trial, bleeding at 30 days was reduced by bivalirudin compared with both heparin with GPI or heparin without GPI, but despite bleeding reduction there was no clear difference in 30-day mortality between groups[4]. The recent MATRIX[5] trial, the largest trial to explore bivalirudin in modern contemporary care, found a reduction in 30-day all-cause mortality with bivalirudin compared with heparin plus optional GPI (1.7% vs 2.3% respectively, p=0.042), associated with a reduction in bleeding, although the primary outcome of the trial (a composite of death, myocardial infarction, or stroke) did not reach statistical significance. This finding appears to validate the findings of the HORIZONS trial, however long-term data on mortality are still pending (e-table 4).

In EUROMAX[1], bivalirudin reduced the risk of primary composite endpoint of death and non-CABG-related bleeding at 30 days after PCI. However although bivalirudin reduced major bleeding compared with both patients treated with heparin plus bailout GPI and patients treated with heparin and routine GPI[9], no reduction in death rates at 30 days (2.9% vs. 3.1%) was observed. There is evidence that bleeding affects short[10] - and long-term mortality (hazard ratio of 4.2)[6] and that the impact of non-procedural bleeds is greater than that of access site bleeds and greater in the short term than in the long term[10]. In the EUROMAX the achieved substantial reductions in bleeding with bivalirudin were consistent for both access- and non-access site bleeding events[11]. However, this reduction in bleeding did not translate into reduced cardiovascular or all-cause death at 1 year, a result in contrast with HORIZONS-AMI and MATRIX. However in these two trials, patients randomized to the bivalirudin arm had received heparin before randomization, approximately two-thirds of the patients in HORIZON-AMI and one-third of the patients in MATRIX.

A number of important changes have occurred in clinical practice and trial design since the HORIZONS-AMI trial. First, the rates of major bleeding in the heparin arm were lower in the EUROMAX trial (6.0 vs 8.3% in the HORIZONS-AMI[2]), which may be related to the lower rates of use of GPIs (from 98% in the HORIZONS-AMI[2] trial vs 69.1% in EUROMAX[1]). The rate of use of GPI, which was left to physician preference in the heparin group (as either "routine"-started before PCI- or bailout), makes EUROMAX unique, also because the other trials[2-5], have implemented GPI use either as only routine or as only bailout strategy.

Second, the use of the radial access was frequent in EUROMAX but not in HORIZONS. Importantly, the reduction in the primary outcome seen in EUROMAX at 30-day was consistent across radial and femoral access subgroups[12]. Third, in EUROMAX the use of new and more potent antiplatelet agent (ticagrelor and prasugrel), might have altered the balance between ischemic and bleeding risks[13] compared to HORIZONS-AMI. Finally EUROMAX was slightly smaller and with lower statistical power than HORIZONS.

In EUROMAX there was a higher risk of acute stent thrombosis with bivalirudin. Although it is tempting to attribute the similar long-term mortality in the two treatment arms of EUROMAX to contrary and offsetting effects of bivalirudin on bleeding and stent thrombosis, a patient-level analysis of HORIZONS and EUROMAX found that the mortality attributable to early ST was significantly lower after bivalirudin than after heparin plus GPI, possibly related to the timing of stent thrombosis, which occurred earlier in bivalirudin-treated patients[14].

Further studies are needed to find the optimal anticoagulant regimen able to improve long-term mortality outcomes.

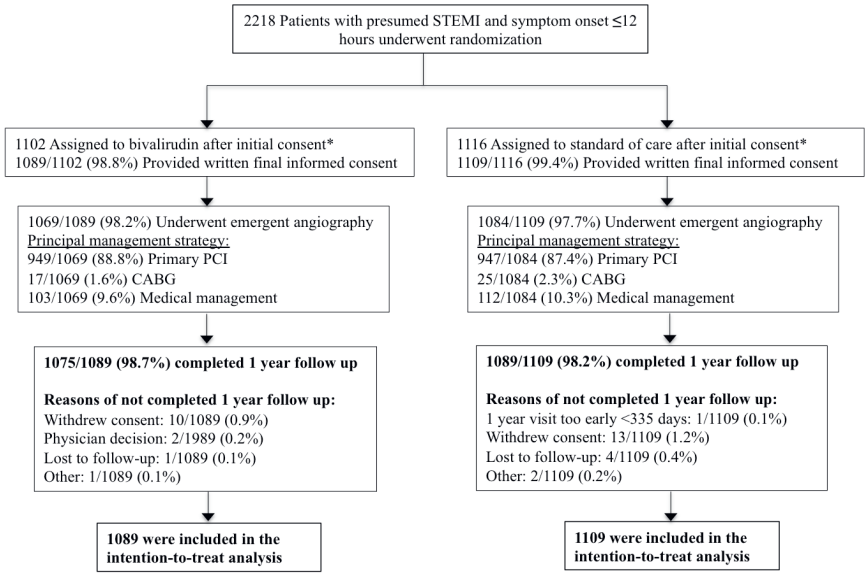
Study limitations

Limitations of the EUROMAX trial has been previously described[1] and some limitations of this study should be taken into consideration. The present analysis was not designed to determine the possible mechanisms underlying death occurrence. Even though this analysis was pre-specified, EUROMAX was not powered to examine 1-year mortality and its cardiac and no cardiac components, accordingly the confidence interval of the hazard ratio for mortality at 1 year cannot exclude a 28% reduction or conversely a 45% increase in mortality with bivalirudin. In that respect, it is noteworthy that there does not appear to be significant heterogeneity between the EUROMAX and HORIZONS-AMI trial when analysed at patient-level[15].

Conclusions

In patients with STEMI treated earlier in ambulance, with frequent use of radial access and novel P2Y12 inhibitors,, bivalirudin, as compared with heparin with optional use of GPI, showed similar long-term mortality outcome. In this specific setting the reduced composite of death/major bleeding at 30 days in the bivalirudin arm of the EUROMAX trial did not translate into reduced cardiovascular or all-cause death at 1-year.

E-Figure 1: Patient Flow Chart.



*Abridged written or oral consent. CABG denotes coronary artery bypass graft, PCI percutaneous coronary intervention, STEMI ST-segment elevation myocardial infarction.

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E-table 2. Procedures and Study Medications in the Intention-to-Treat Population*

Variable	Bivalirudin (N = 1089)	Control (N = 1109)
Randomized in ambulance — no. (%)	1030 (94.6)	1045 (94.2)
Randomized in non–PCI-capable hospital — no. (%)	59 (5.4)	64 (5.8)
Aspirin use — no. (%)	1088 (100.0)	1107 (99.8)
P2Y12 inhibitor loading dose — no./total no. (%)		
Any agent	1048/1066 (98.3)	1058/1083 (97.7)
Clopidogrel	524/1048 (50.0)	545/1058 (51.5)
Ticlopidine	0	2/1058 (0.2)
Prasugrel	323/1048 (30.8)	306/1058 (28.9)
Ticagrelor	201/1048 (19.2)	205/1058 (19.4)
P2Y12 loading dose before angiography — no./total no. (%)	913/1011 (90.3)	923/1010 (91.4)
P2Y12 inhibitor maintenance dose — no./total no. (%)		
Any agent	957/1065 (89.9)	969/1082 (89.6)
Clopidogrel	377/957 (39.4)	407/969 (42.0)
Ticlopidine	2/957 (0.2)	5/969 (0.5)
Prasugrel	321/957 (33.5)	298/969 (30.8)
Ticagrelor	257/957 (26.9)	259/969 (26.7)
Initial anticoagulation — no. (%)		
Bivalirudin	1074 (98.6)	29 (2.6)
Unfractionated heparin	24 (2.2)	997 (89.9)
Enoxaparin	0	94 (8.5)
Median time from initiation of anticoagulation to angiography (IQR) — min	50 (37–67)	50 (37–65)
Glycoprotein IIb/IIIa inhibitor — no./total no. (%)†		
Any	125/1088 (11.5)	766/1109 (69.1)
Routine use	42/1088 (3.9)‡	649/1109 (58.5)
Bailout use§	83/1046 (7.9)	117/460 (25.4)
Arterial-access site — no./total no. (%)		
Femoral	558/1069 (52.2)	582/1084 (53.7)
Radial	510/1069 (47.7)	502/1084 (46.3)
Single-vessel disease — no./total no. (%)	591/1069 (55.3)	556/1083 (51.3)
Left-main-stem disease — no./total no. (%)	82/1069 (7.7)	86/1084 (7.9)

Infarct artery treated with primary PCI — no./total no. (%)		
Left main coronary artery	6/943 (0.6)	13/946 (1.4)
Left anterior descending coronary artery	425/943 (45.1)	423/946 (44.7)
Left circumflex coronary artery	115/943 (12.2)	132/946 (14.0)
Right coronary artery	417/943 (44.2)	412/946 (43.6)
Bypass grafting (venous or arterial)	4/943 (0.4)	10/946 (1.1)
Balloon angioplasty only — no./total no. (%)	48/943 (5.1)	42/946 (4.4)
Implantation of stent — no./total no. (%)		
Any type	868/943 (92.0)	865/946 (91.4)
Drug-eluting	538/943 (57.1)	529/946 (55.9)
Thrombectomy — no./total no. (%)	304/943 (32.2)	298/946 (31.5)
CABG during hospitalization — no. (%)	21 (1.9)	29 (2.6)
Medications at discharge — no. (%)		
ACE inhibitor or ARB	718 (65.9)	709 (63.9)
Aspirin	1000 (91.8)	1012 (91.3)
Beta-blocker	944 (86.7)	957 (86.3)
P2Y12 inhibitor	938 (86.1)	941 (84.9)
Statin	968 (88.9)	997 (89.9)

*ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, PCI percutaneous coronary intervention, and TIMI Thrombolysis in Myocardial Infarction.

† P<0.05 for the between-group comparisons in this category.

‡ The routine use of a glycoprotein IIb/IIIa inhibitor in the bivalirudin group was a deviation from the protocol.

§Data are provided for patients who were eligible for bailout use of a glycoprotein IIb/IIIa inhibitor (i.e., those who did not receive the drug routinely).

E-table 3 Adjudicated Endpoints – up to 1 year (ITT population)

Category	Bivalirudin (N=1089)	Standard Care (N=1109)	Total (N=2198)	Relative Risk [95% CI]	P-value
Death	59/1089 (5.4)	59/1109 (5.3)	118/2198 (5.4)	1.02 [0.72, 1.45]	0.9191
Cardiac	44/1089 (4.0)	48/1109 (4.3)	92/2198 (4.2)	0.93 [0.63, 1.39]	0.7362
Non-cardiac	15/1089 (1.4)	11/1109 (1.0)	26/2198 (1.2)	1.39 [0.64, 3.01]	0.4032

E-table 4 Adjudicated Endpoints – between 30 days and 1 year (ITT population)

Category	Bivalirudin (N=1089)	Standard Care (N=1109)	Total (N=2198)	Relative Risk [95% CI]	P-value
Death	27/1089 (2.5)	25/1109 (2.3)	52/2198 (2.4)	1.10 [0.64, 1.88]	0.7285
Cardiac	17/1089 (1.6)	15/1109 (1.4)	32/2198 (1.5)	1.15 [0.58, 2.30]	0.6833
Non-cardiac	10/1089 (0.9)	10/1109 (0.9)	20/2198 (0.9)	1.02 [0.43, 2.44]	0.9674

E-table 5. Randomized trials comparing heparin and bivalirudin in STEMI/AMI setting

Trial	Pts (n)	BIV Arm (n)	HEP Arm (n)	Age (yr)	Radials (%)	GPI (%) BIV Arm	GPI (%) HEP Arm	MORTALITY								
								30-day follow-up			1-year follow-up			3-year follow-up		
								BIV Arm n (%)	HEP Arm n (%)	p Value	BIV Arm n (%)	HEP Arm n (%)	p Value	BIV Arm n (%)	HEP Arm n (%)	p Value
HORIZONS-AMI	3602	1800	1802	60	5.9%	7.5%	98%	37 (2.1)	56 (3.1)	**0.047**	61 (3.5)	86 (4.8)	**0.037**	102 (5.9)	134 (7.7)	**0.030**
EUROMAX	2198	1089	1109	62	46%	12%	69%	32 (2.9)	34 (3.1)	0.86	59 (5.4)	118 (5.4)	0.91			
BRIGHT*	1925*	655	641	58	79%	4.6%	5.6%	9 (1.4)	13 (2.0)	0.36	12 (1.8)	16 (2.5)	0.41			
		655	629°	58	79%	4.6%	100%	9 (1.4)	14 (2.2)	0.25	12 (1.8)	17 (2.7)	0.29			
HEAT	1812	905	907	63	81%	13%	15%	46 (5.1)	39 (4.3)	0.43						
MATRIX[§]	7213[§]	3610	3603	65	50%	4.6%	25.9%	59 (1.7)	83 (2.3)	**0.04**						

*Only STEMI population considered; ° heparin + GPI group; [§]4010 (55.6%) had STEMI: 2012 (55.7%) in Bivalirudin arm, and 1998 (55.5%) in Heparin arm. Pts= patients, n= number, yr=year; BIV= Bivalirudin, HEP=Heparin, GPI=glycoprotein IIb/IIIa inhibitors

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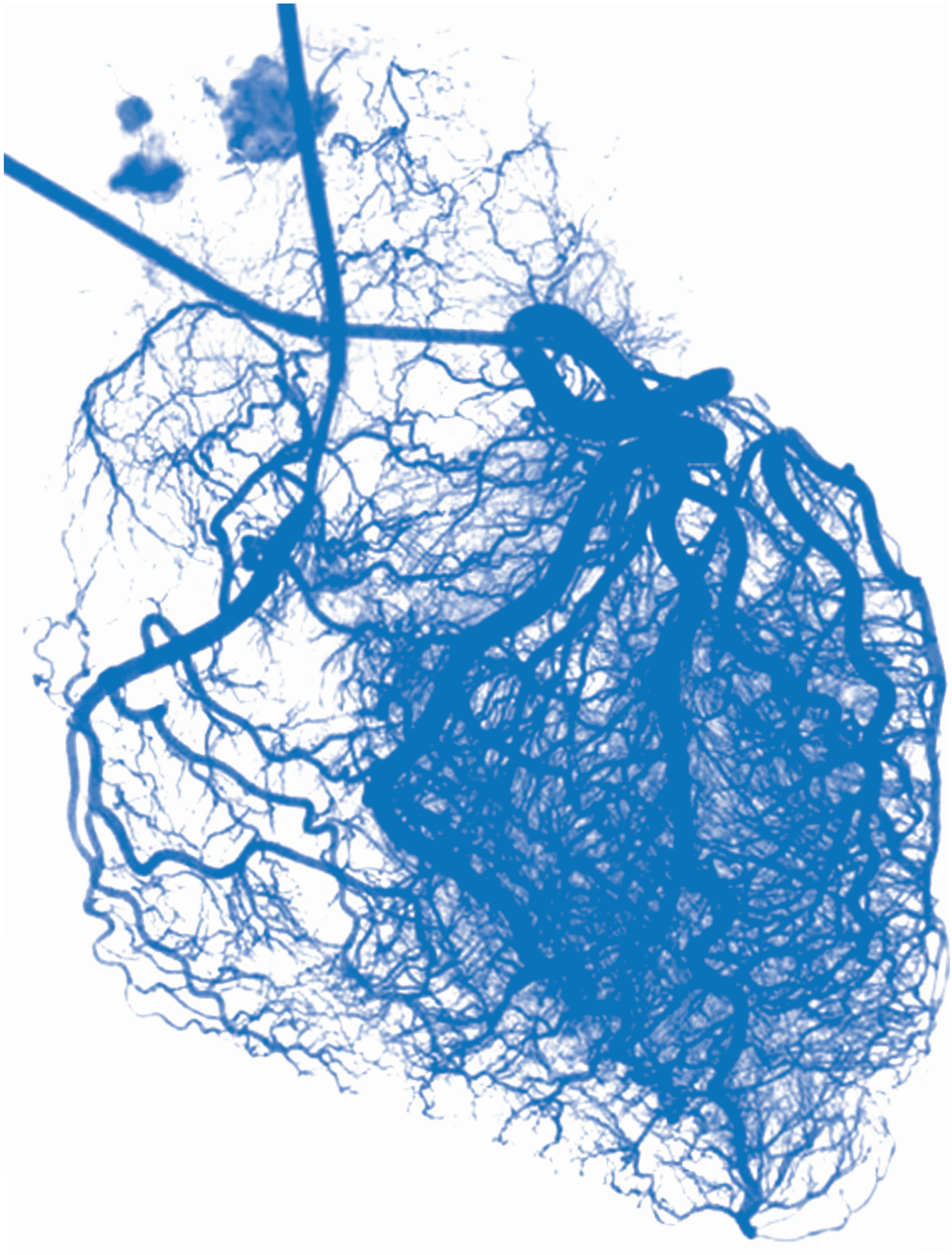

Chapter six

Effect of early tirofiban administration on NT-proBNP level in patients treated with primary PCI

Enrico Fabris, Jan Paul Ottervanger, Renicus S. Hermanides, Jurrien M. ten Berg, Gianfranco Sinagra, Petra C. Koopman, Evangelos Giannitsis, Christian Hamm, Arnoud W. J. van 't Hof

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Abstract

Objective to investigate the potential association between early tirofiban treatment and NT-proBNP level after primary percutaneous coronary intervention (PCI).

Background Whether the use of adjunctive early Glycoprotein IIb/IIIa inhibitors (GPIs) therapy, may affect the level of NTproBNP after primary PCI is poorly studied.

Methods 984 ST-elevation myocardial infarction (STEMI) patients undergoing primary PCI were randomized to either pre-hospital tirofiban administration or placebo. NT-proBNP levels were evaluated on admission before angiography (baseline) and 18-96 hours after PCI.

Results There were 918 (93.3%) patients with NT-proBNP values available at baseline and 865 (87.9%) post-PCI. Post PCI NT-proBNP level dichotomized with median value as cut-off (968.8 pg/ml, IQR 430.9-1970.0) was significantly lower in patients treated with early tirofiban as compared to placebo (45.5% vs 54.2% p=0.011). At multivariate logistic regression analysis, independent predictors of post PCI NT-proBNP level above the median were: NT-proBNP baseline level (OR 5.19; 95% CI, 2.92-9.25, p<0.001), Killip class>I (OR 4.07; 95% CI 1.24-13.36, p=0.021), anterior infarct location (OR 2.61; 95% CI 1.84-3.70, p<0.001), age (years) (OR 1.04; 95% CI 1.03-1.06, p<0.001), Male gender (OR 0.38; 95% CI 0.26-0.57, p<0.001), Prior PCI (OR 0.49; 95% CI 0.27-0.90, p=0.021) and tirofiban administration (OR 0.71; 95% CI 0.51 to 0.99; p=0.045).

Conclusions In a large cohort of STEMI patients, pre-hospital tirofiban administration was independently associate with a lower risk of high NT-proBNP level after primary PCI, supporting the potential benefit of early antithrombotic treatment administration in STEMI patients.

The trial is registered under No. ISRCTN06195297

Introduction

Early recovery of the infarct-related artery blood flow is the goal of treatment for patients with ST-elevation myocardial infarction (STEMI)[1] and adjunctive early pharmacological therapies are potential options to improve myocardial reperfusion[2,3], and clinical outcomes[4] in patients treated with primary percutaneous coronary intervention (PCI). The N-terminal pro-B-type natriuretic peptide (NTproBNP), an established heart failure biomarker, has been shown to liberate from myocardium following acute myocardial infarction[5], and elevated levels have been associated with poor outcomes also in the setting of acute coronary syndrome[4,6-11].

However, whether the use of adjunctive early Glycoprotein IIb/IIIa inhibitors (GPIs) therapy, aimed at improving myocardial perfusion, may affect the level of NTproBNP after primary PCI is poorly studied.

The Ongoing Tirofiban In Myocardial Infarction Evaluation 2 (On-TIME 2) trial[3] randomized patients undergoing primary PCI to pre hospital tirofiban administration vs placebo and measured the levels NT-proBNP in a subgroup of patients on admission before angiography and after primary PCI. Therefore, we undertook a subgroup analysis of the On-TIME 2 trial in order to investigate the potential association between early tirofiban treatment and NT-proBNP levels after primary PCI.

Methods

Study design

The On-TIME 2 trial (ISRCTN06195297) was an international, multicenter, prospective, placebo-controlled, double-blind, randomized trial. The rationale and design of the study have been previously described[12]. The trial randomized patients undergoing primary PCI to pre hospital tirofiban administration vs placebo to investigate the effect of pre-treatment on the extent of residual ST segment deviation 1 hour after primary PCI compared to placebo. The results of the study, showing that early initiation of tirofiban improved ST-segment resolution compared to placebo, have been previously published[3].

In brief, the study population consisted of patients with STEMI who were candidates for primary PCI treatment. Eligible patients were men and women, 21 to 85 years of age, with symptoms of acute myocardial infarction (MI) for >30min but <24 h, and ST-segment elevation of >1 mV in 2 adjacent electrocardiogram leads. Exclusion criteria were known severe renal dysfunction, therapy-resistant cardiogenic shock, persistent severe hypertension, and an increased risk of bleeding. Also excluded were patients

with a left bundle branch block and patients with a life expectancy of <1 year. Written informed consent was obtained by an intensive care nurse in the ambulance or, in a minority of the patients, by a physician in the referral center. The study protocol was approved by all local ethics committees involved.

Randomization and treatment

Patients were randomly assigned to pre-hospital treatment with high dose bolus (HDB) tirofiban (25 mcg/kg bolus and 0.15 mcg/kg/min maintenance infusion for 18 h) or placebo. In the ambulance or referring center, all patients also received a bolus of 5000 IU of unfractionated heparin intravenously together with aspirin 500 mg intravenously and a 600 mg loading dose of clopidogrel orally. Before PCI, additional unfractionated heparin (2500 IU) was only given if the activated clotting time was less than 200 sec. Coronary angiography and PCI were performed according to each institution's guidelines and standards. Additional treatment with thrombus aspiration was left at the discretion of the treating cardiologist.

Subgroup with blood samples for NT-pro BNP measurement

Blood samples were taken on admission before angiography (baseline) and 18-96 hours thereafter (post-PCI). NT-proBNP was measured by a sandwich immunoassay on a fully automated analyzer (NT-pro BNP ELECSYS 2010, Roche Diagnostics, Mannheim, Germany). The NT-proBNP levels were assessed and dichotomized with median value as cut-off, because the NT-proBNP value above the median has been demonstrated to be and independent factor of short and long term clinical outcomes[4].

Statistical analysis

Continuous data were expressed as mean ± SD or median with interquartile range. Categorical data were expressed as percentages. Categorical variables were analyzed with the $\chi 2$ test or Fischer's exact test, and continuous variables with the Mann-Whitney U-test (2 sided). Values of $p<0.05$ were considered statistically significant. We performed univariate and multivariate logistic regression analyses in order to investigate the potential association between early Glycoprotein IIb/IIIa inhibitors (GPIs) administration and NTproBNP levels above the median after PCI.

All analyses were performed according to the intention-to-treat principle. Statistical analysis was performed with PASW Statistics 24 (SPSS Inc, Chicago, Ill).

Results

The On-TIME 2 trial recruited a total of 984 patients who were randomized to either placebo or tirofiban treatment. There were 918 (93.3%) patients with samples available for NT-proBNP at admission (baseline).

There was no significant difference in baseline NT-proBNP levels considered as a binary variable dichotomized with median value as cut-off (median 137, IQR 60.1 - 359.8 pg/ml) in patients randomized to tirofiban compared to patients randomized to placebo (227/464, 48.9% vs. 232/454, 51.1% p=0.51, respectively).

Patients with baseline NTproBNP level above the median value exhibited an higher risk profile compared to patients with level below the median, as presented in table 1.

Table 1 Baseline characteristics of patients with a baseline NTproBNP level ≤ median* versus > median*

	NT-proBNP level ≤ median (N=459)	NT-proBNP level > median (N=459)	p-value
Age (years)	57.3±9.9	66.3±11.8	<0.001
Male gender	384/459 (83.7%)	311/459 (67.8%)	<0.001
Current smoking	246/456 (53.9%)	185/456 (40.6%)	<0.001
Diabetes mellitus	42/458 (9.2%)	64/459 (13.9%)	0.024
Body mass index (kg/m2)	27.2±3.8	26.4±3.6	0.009
Hypertension	113/459 (24.6%)	195/459 (42.5%)	<0.001
Hypercholesterolaemia	111/457 (24.3%)	133/459 (29.0%)	0.109
Killip>I	10/458 (2.2%)	31/458 (6.8%)	<0.001
Prior myocardial infarction	25/458 (5.5%)	52/458 (11.4%)	0.001
Prior CABG	6/459 (1.3%)	11/459 (2.4%)	0.221
Prior PCI	31/459 (6.8%)	52/459 (11.3%)	0.016
Anterior infarct location	164/409 (40.1%)	177/405 (43.7%)	0.297
Time to intervention‡	152 (122-202)	193 (137- 292)	<0.001
Heart rate > 100 bpm	15/456 (3.3%)	35/455 (7.7%)	0.004
Systolic blood pressure < 100 mmHg	32/453 (7.1%)	33/456 (7.2%)	0.919
Randomisation to Tirofiban	237/459 (51.6%)	227/459 (49.5%)	0.509

‡From onset of symptoms to intervention in minutes, median (25th-75th IQR)
***** Median value: 137, IQR 60.1-359.8 pg/ml

Post PCI NT-proBNP level and predictors of NT-proBNP level above the median
There were 865 (87.9%) patients with samples available for NT-proBNP post PCI.

Clinical characteristics of patients according to post PCI NT-proBNP level below or above the median are shown in Table 2. Several characteristics were significantly different in the two patient cohorts. Patients with NT-proBNP level above the median were older, less frequently male, had higher baseline NT-proBNP level and presented higher rate of Killip class > 1, anterior myocardial infarction, heart rate >100 bpm as compared to patient with NT-proBNP levels below the median, which, conversely, were more frequently smokers and had higher rate of prior PCI. Interestingly patients with NT-proBNP level below the median were more frequently randomized to receive tirofiban compared to patient with NT-proBNP levels above the median.

Moreover, the post PCI NT-proBNP level considered as a binary variable dichotomized with median value as cut-off (968.8 IQR 430.9-1970.0) was significantly lower in patients treated with pre-hospital tirofiban as compared to placebo (194/426, 45.5% vs 238/439, 54.2% p=0.011).

At multivariate logistic regression analysis, independent factors associated to higher level of post PCI NT-proBNP (above the median) were baseline NT-proBNP, Killip>I, anterior infarct location and older age (Table 3). Conversely Tirofiban administration was independently associated with a lower risk of high post PCI NT-proBNP level, Odds Ratio (OR) 0.71 (95% CI 0.51 to 0.99; p=0.045) (Table 3). Other independent factors associated with a lower risk of high post PCI NT-proBNP were male gender and history of prior PCI (Table 3).

Table 2 Baseline characteristics of patients with a post PCI NTproBNP level ≤ median* versus > median*

		NT-proBNP level post PCI ≤ median (N=433)	NT-proBNP level post PCI > median (N=432)	p-value
NT-proBNP baseline	N Mean ± SD Median (IQR)	418 163.02 ± 280.87 79.72 (44.48-162.80)	417 995.54 ± 2563.45 259.2 (89.3-789.2)	<0.001
Age (years)		58.7 ± 10.6	64.9 ± 11.8	<0.001
Male gender		364/433 (84.1%)	287/432 (66.4%)	<0.001
Current smoking		233/430 (54.2%)	184/432 (42.6%)	0.001
Diabetes mellitus		42/432 (9.7%)	56/432 (13.0%)	0.133
Body mass index (kg/m2)		27.0 ± 3.4	26.5 ± 4.0	0.008
Hypertension		135/433 (31.2%)	159/432 (36.8%)	0.081
Hypercholesterolaemia		127/433 (29.3%)	105/431 (24.4%)	0.099
Killip>I		5/433 (1.2%)	27/432 (6.3%)	<0.001
Prior myocardial infarction		41/431 (9.5%)	29/432 (6.7%)	0.132
Prior CABG		7/433 (1.6%)	9/432 (2.1%)	0.611
Prior PCI		47/433 (10.9%)	28/432 (6.5%)	0.022
Anterior infarct location		121/433 (31.8%)	201/396 (50.8%)	<0.001
Time to intervention‡		158 (122-221)	178.5 (133-257)	<0.001
Heart rate > 100		16/431 (3.7%)	31/429 (7.2%)	0.023
Systolic blood pressure <100 mmHg		23/430 (5.3%)	35/427 (8.2%)	0.097
Randomisation to Tirofiban		232/433 (53.6%)	194/432 (44.9%)	0.011

‡From onset of symptoms to intervention in minutes, median (25th 75th IQR)

* median value: 968.8, IQR 430.9-1970.0 pg/ml

Table 3 Multivariate logistic model for post PCI NTproBNP > median*

Variables	Univariate model		Multivariate model^	
	OR (95% CI)	p-value	OR (95% CI)	p-value
NT-proBNP baseline	8.54 (4.85-15.03)‖	<0.001	5.19 (2.92-9.25)	<0.001
Age (years)	1.05 (1.04-1.06)	<0.001	1.04 (1.03-1.06)	<0.001
Male gender	0.38 (0.27-0.52)	<0.001	0.38 (0.26-0.57)	<0.001
Current smoking	0.63 (0.48-0.82)	0.001		
Diabetes mellitus	1.38 (0.90-2.11)	0.134		
Body mass index (kg/m2)	0.97 (0.93-1.00)	0.063		
Hypertension	1.29 (0.97-1.70)	0.081		
Hypercholesterolaemia	0.78 (0.57-1.05)	0.100		
Killip Class>I	5.71 (2.18-14.96)	<0.001	4.07 (1.24-13.36)	0.021
Prior myocardial infarction	0.68 (0.42-1.12)	0.134		
Prior CABG	1.29 (0.48-3.51)	0.611		
Prior PCI	0.57 (0.35-0.93)	0.024	0.49 (0.27-0.90)	0.021
Anterior infarct location	2.21 (1.65-2.96)	<0.001	2.61 (1.84-3.70)	<0.001
Time to intervention‡	1.03 (1.00-1.07)¶	0.066		
Heart rate > 100	2.02 (1.09-3.75)	0.026		
Systolic blood pressure < 100	1.58 (0.92-2.72)	0.099		
Randomisation to Tirofiban	0.71 (0.54-0.92)	0.011	0.71 (0.51-0.99)	0.045

‖ per 1000, ‡ From onset of symptoms to intervention, ¶ per hour, * median value: 968.8, IQR 430.9-1970.0 pg/ml, ^Multivariate model (N=750): Criterion all p-values < 0.05 at univariate model

Discussion

In this post-hoc subgroup analysis of the On-TIME 2 trial, we have showed for the first time, in a large cohort of STEMI patients, that early tirofiban administration, was independently associated with a lower risk of high NTproBNP level after primary PCI. This finding has relevant clinical implication because previous studies highlighted that higher levels of NT-proBNP are independently associated with poor short and long term outcomes in the setting of acute myocardial infarction [4,6-11,13,14].

The On-TIME 2 trial showed that early initiation of tirofiban improved ST-segment resolution compared to placebo[3]. Moreover a pre-specified a pooled analysis showed that major adverse cardiac events at 30 days were significantly reduced and there was a strong trend toward a decrease in mortality in patients who were randomized

to tirofiban pretreatment[15]. Additionally, in subgroup analysis of the trial, patients with post PCI NT-proBNP levels above the median showed higher 30-day, 1-year and at 5-year mortality[4].

Thus, in this current analysis, the independent association between early tirofiban treatment and NTproBNP level post PCI may provide further insight into the potential benefit of a GPI-facilitated PCI strategy[15]. Indeed higher biomarker level after primary PCI may be indicative of profound myocardial ischemia and extensive microvascular damage[16,17] and a larger extent of myocardial necrosis[18]. However, early antithrombotic therapy administration, already active and effective at the time of PCI, plays a crucial role in the prevention of microvascular damage and restoration of myocardial tissue reperfusion[3]. The fact that the time course of NT-proBNP level was positively influenced by early tirofiban administration, also compared with placebo, could potentially be dependent on the effectiveness of microvascular reperfusion after PCI, an outcome in which early tirofiban administration has a proven role[3].

Moreover also in large real word STEMI population tirofiban administration prior to primary PCI showed significant improvement in myocardial reperfusion, ST-segment resolution and in-hospital mortality rate[19].

Interestingly, in our analysis, early tirofiban administration effect on NTproBNP level post PCI was independent from baseline NTproBNP level. Indeed, although baseline NT-proBNP level was related to post PCI level and baseline NT-proBNP has been correlated to microvascular obstruction after PCI[20], it has been shown that patients with higher baseline level of NTproBNP may derive particular clinical benefit from early GPIs treatment[4].

Important clinical characteristics associated with higher post PCI NT-proBNP levels include anterior location of myocardial infarction and a Killip class>I. This reflect the ischemic burden of this high-risk population.

In addition, also the female gender and older age where correlated with post PCI NT-proBNP levels above the median highlighting, once more time, as female patients and elderly patients are subgroups that require particular attention in the setting of acute myocardial infarction. Conversely, patients who previously had a PCI were associated with a lower risk of high NT-proBNP level post PCI. One might speculate that these patients, recognizing angina symptoms had taken timely action to seek medical help, thus reducing the "patients delay" and the duration of myocardial ischemia favouring effective myocardial perfusion. Early GPI administration might be also more effective when given shortly after symptom onset[21] probably due

to the lytic effects of GP IIb/IIIa inhibitors on fresh thrombi. Moreover patients with history of prior PCI may already use, before admission, chronic therapies such as aspirin, betablocker or ace-inhibitors and they could have a role on the early course of NT-proBNP level post PCI, however this need to be further explored in future studies.

Finally the potential effect of early tirofiban administration to reduce NT-proBNP levels post PCI is clinically relevant also because a lower level of NTproBNP after primary PCI may identify a low risk population which may be discharged early[22]. The wide spread of STEMI network, and STEMI campaign aimed to increase the number of patients presenting within the early phase of myocardial infarction[23] and therefore suitable for a more aggressive pharmacological approach could contribute to decrease the number of high-risk primary PCI patients worldwide.

Limitations

This is a post-hoc analysis of a randomized trial, therefore, this data should be viewed as hypothesis generating. The baseline NT-proBNP level were similar between tirofiban and placebo group, however the measurement was made at admission (before angiography) when tirofiban was already started; although the time between tirofiban administration and first NTproBNP measurement was very short we cannot exclude a small effect of the drug on the baseline values of NT-proBNP.

Conclusions

In a large cohort of STEMI patients, pre-hospital tirofiban administration was independently associate with a lower risk of high NT-proBNP level after primary PCI, supporting the potential benefit of early antithrombotic treatment administration in STEMI patients.

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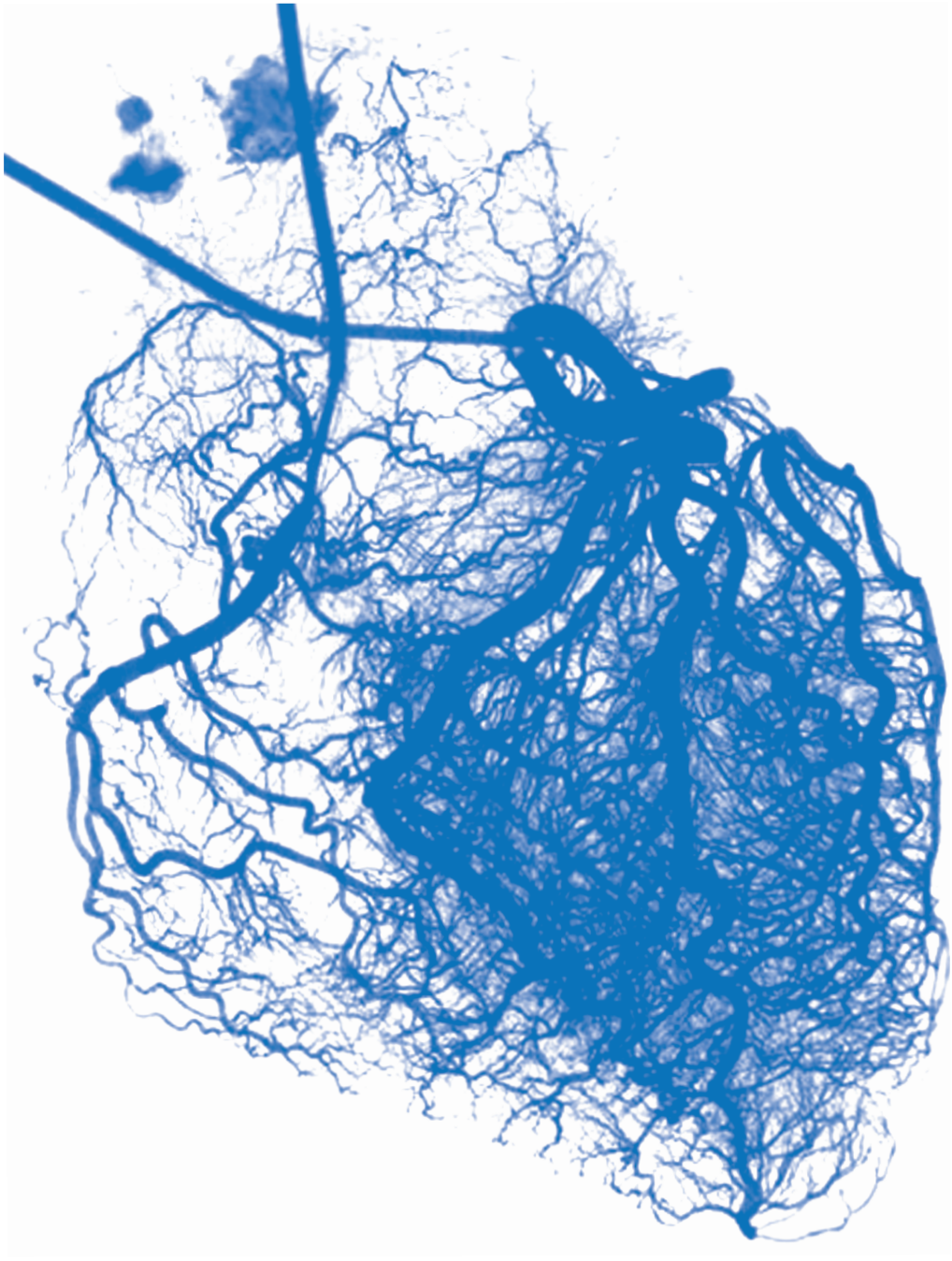


Chapter 7

Long-term mortality and prehospital tirofiban treatment in patients with ST elevation myocardial infarction

Enrico Fabris, Sinem Kilic, Dirk A A M Schellings, Jurrien M ten Berg, Mark W Kennedy, K Gerts van Houwelingen, Evangelos Giannitsis, Evelien Kolkman, Jan Paul Ottervanger, Christian Hamm, Arnoud W J van't Hof

Heart. 2017;103:1515-1520.

Abstract

Objective We undertook a subgroup analysis of the Ongoing Tirofiban In Myocardial infarction Evaluation 2 (On-TIME 2), a placebo-controlled, double-blind, randomized trial, in order to evaluate the association between N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and long-term (5-years) mortality and to investigate the effect of pre-hospital tirofiban administration on mortality in relation NT-proBNP levels.

Methods 984 ST elevation myocardial infarction (STEMI) patients undergoing primary percutaneous coronary intervention (PCI), were randomized to either in ambulance tirofiban or placebo. NT-proBNP levels were evaluated on admission before angiography (baseline) and 18-96 hours thereafter (post-PCI).

Results There were 918 (93.3%) patients with NT-proBNP values available at baseline and 865 (87.9%) post-PCI. Patients with baseline NT-proBNP values above the median (137 pg/ml) had higher 30-day (5.1% vs 0.2%, p<0.001), 1-year (7.0% vs 0.7%, p<0.001) and 5-year (20.3% vs 4.9% p<0.001) mortality as compared to patients with values below the median. Using multivariate cox analysis, NT-proBNP above the median was an independent predictor for 5-year mortality (HR 2.73 (95% CI 1.47 – 5.06; p = 0.002). Patients with values above the median who received early tirofiban treatment had significant lower mortality compared to patients treated with placebo at 30-days (2.7% vs 7.5% p=0.021) and 1-year (4.5% vs 9.4% p=0.043). At 5-years, a lower but non-significant mortality rate was maintained in the treatment group (18% vs 22.4% p=0.265).

Conclusions In STEMI patients, baseline NT-proBNP level independently predict long-term mortality. In patients with baseline NT-proBNP levels above the median, early pre-hospital treatment with tirofiban significantly reduced 30-day and 1-year mortality, suggesting that high-risk patients may derive particular benefit. This finding should be confirmed in other studies.

Introduction

Urgent restoration of perfusion to the myocardium supplied by the infarct-related artery is the primary therapeutic objective in ST-elevation myocardial infarction (STEMI), as it improves survival[1]. Primary percutaneous coronary intervention (PCI) combined with effective antiplatelet therapy is the preferred treatment strategy in STEMI[2]. In order to increase the rates of mechanical reperfusion and so reduce ischemic complications, large interest has focused on adjunctive administration of pharmacological therapy and its timing of administration.

Glycoprotein IIb/IIIa inhibitors (GPIs) are the most powerful class of antiplatelet therapies, and their adjunctive effects have been shown in several randomized trials[3]. In addition, early GPI administration in patients undergoing primary angioplasty for STEMI has been associated with significantly higher rates of pre-procedural epicardial recanalisation and ST-segment resolution[4-8]. However, the benefit of these drugs is less certain in patients at lower risk for ischemic events or those presenting later[9,10] and large randomized trials, conducted to explore the benefits from adjunctive GPIs in addition to clopidogrel administration, showed conflicting results[6,11-13]. Among STEMI patients undergoing primary PCI, the greatest benefit in mortality reduction from GPI usage has been shown in patients with higher-risk profiles[14]. Therefore, identification of additional subgroups of patients who may have particular benefit from GPI administration is of paramount importance to further improve outcomes.

The N-terminal pro-B-type natriuretic peptide (NTproBNP), an established biomarker, has been shown to liberated from myocardium following acute myocardial infarction[15] and elevated levels have been associated with poor outcome in patients with acute coronary syndrome (ACS)[16-21].

The Ongoing Tirofiban In Myocardial infarction Evaluation 2 (On-TIME 2) trial randomized patients undergoing primary PCI to pre hospital tirofiban administration vs placebo to investigate the effect of pre-treatment on the extent of residual ST segment deviation 1 hour after primary PCI compared to placebo. The results of the study showing that early initiation of tirofiban improved ST-segment resolution compared to placebo, have been previously published[6].

We undertook a subgroup analysis of the On-TIME 2 trial with long term follow-up in order to investigate 1) the potential association between NT-proBNP levels and long term mortality, 2) the effect of early tirofiban administration on mortality in relation to NT-proBNP levels in patient with STEMI undergoing primary PCI.

Methods

Study design

The On-TIME 2 trial (ISRCTN06195297) was an international, multicentre, prospective, placebo-controlled, double-blind, randomized trial. The rationale and design of the study have been previously described[22]. In brief, the study population consisted of patients with STEMI who were candidates for primary PCI treatment. Eligible patients were men and women, 21 to 85 years of age, with symptoms of acute myocardial infarction (MI) for >30min but <24 h, and ST-segment elevation of >1 mV in 2 adjacent electrocardiogram leads. Exclusion criteria were known severe renal dysfunction, therapy-resistant cardiogenic shock, persistent severe hypertension, and an increased risk of bleeding. Also excluded were patients with a left bundle branch block and patients with a life expectancy of <1 year. Written informed consent was obtained by an intensive care nurse in the ambulance or, in a minority of the patients, by a physician in the referral center. The study protocol was approved by all local ethics committees involved.

Randomization and treatment

Patients were randomly assigned to pre-hospital treatment with high dose bolus (HDB) tirofiban (25 mcg/kg bolus and 0.15 mcg/kg/min maintenance infusion for 18 h) or placebo. In the ambulance or referring center, all patients also received a bolus of 5000 IU of unfractionated heparin intravenously together with aspirin 500 mg intravenously and a 600 mg loading dose of clopidogrel orally. Before PCI, additional unfractionated heparin (2500 IU) was only given if the activated clotting time was less than 200 sec. Coronary angiography and PCI were performed according to each institution's guidelines and standards. Additional treatment with thrombus aspiration was left at the discretion of the treating cardiologist.

Blood samples for NT-pro BNP measurement

Blood samples were taken on admission before angiography (baseline) and 18-96 hours thereafter (post-PCI). NT-proBNP was measured by a sandwich immunoassay on a fully automated analyzer (NT-pro BNP ELECSYS 2010, Roche Diagnostics, Mannheim, Germany). The NT-proBNP levels were assessed both as continuous values and dichotomized with median value as cut-off.

Mortality outcome

In order to investigate 1) the association between NTproBNP levels and short and long term mortality and 2) the effect of early tirofiban on mortality in relation to NT-proBNP levels, the mortality endpoints of this exploratory study were set at 30 days, 1 year and 5 years. Death was defined as all-cause mortality.

Bleeding outcome

As previously described[6], bleeding was assessed using the TIMI criteria[23]. Major bleeding was defined as clinical overt signs of haemorrhage associated with a decrease in haemoglobin of >5 g/dl (or when haemoglobin assessment is not available, a decrease in haematocrit of >15%). For patients undergoing coronary artery bypass graft surgery, the rate of surgical re-exploration for bleeding and the postoperative volume of blood loss were also evaluated. Follow-up information was derived from visits to the outpatient clinic or from telephone contact at the 30-day follow-up.

Statistical analysis

Continuous data were expressed as mean ± SD or median with interquartile range. Categorical data were expressed as percentages. Categorical variables were analyzed with the $\chi 2$ test or Fisher's exact test, and continuous variables with the Mann-Whitney U-test (2 sided). Values of $p<0.05$ were considered statistically significant. We performed cox multivariate regression analyses on mortality with NT-proBNP below or above the median as the predictor of main interest and baseline characteristics (age, gender, smoking, BMI, diabetes, hypertension, hypercholesterolemia, prior myocardial infarction, prior PCI, admission heart rate, systolic blood pressure, anterior infarct location, ischemic time, post-PCI TIMI flow (less than 3 versus 3), and Killip class (I versus II, III or IV) as confounders. Kaplan–Meier (KM) survival analysis was performed with the use of the log-rank test. All analyses were performed according to the intention-to-treat principle. Statistical analysis was performed with PASW Statistics 18 (SPSS Inc, Chicago, Ill).

Results

Study population

The On-TIME 2 trial recruited a total of 984 patients who were randomized to either placebo or tirofiban treatment. The baseline clinical characteristics for patient receiving placebo or tirofiban were comparable and are reported in Table 1.

Table 1. Baseline characteristics of the patients receiving placebo versus tirofiban

Variable	Placebo (n=454)	Tirofiban (n=464)	p-value
Age (yrs), mean ± SD	62.0 ± 11.8	61.5 ± 11.7	0.504
Male gender	340/454 (74.9%)	355/464 (76.5%)	0.567
Current smoking	223/449 (49.7%)	208/463 (44.9%)	0.152
Diabetes mellitus	51/454 (11.2%)	55/463 (11.9%)	0.760
Body mass index (kg/m2), mean ± SD	26.7 ± 4.0	26.8 ± 3.4	0.506
Hypertension	152/454 (33.5%)	156/464 (33.6%)	0.964
Hypercholesterolemia	112/453 (24.7%)	132/463 (28.5%)	0.195
Killip > I	24/453 (5.3%)	17/463 (3.7%)	0.234
Prior myocardial infarction	34/453 (7.5%)	43/463 (9.3%)	0.331
Prior CABG	9/454 (2.0%)	8/464 (1.7%)	0.772
Prior PCI	36/454 (7.9%)	47/464 (10.1%)	0.245
Anterior infarct location	168/407 (41.3%)	173/407 (42.5%)	0.722
Time to intervention*	167 (128-261)	165 (125-235)	0.371
Heart rate > 100	26/450 (5.8%)	24/461 (5.2%)	0.705
Systolic blood pressure < 100	37/450 (8.2%)	28/459 (6.1%)	0.214

*From onset of symptoms to intervention in minutes, median (25th-75th IQRs). CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention

There were 918 (93.3%) patients with samples available for NT-proBNP at admission (baseline) and 865 (87.9%) post-PCI.

There was no significant difference in NT-proBNP levels between patients randomized to tirofiban or to placebo as a continuous variable (626 ± SD 1850 vs. 646 ± SD 2054 pg/ml, p=0.11, in tirofiban vs placebo group, respectively) nor as a binary variable dichotomized according to the median value (137, IQR 60-360 pg/ml) (48.9% vs. 51.1% p=0.51, in tirofiban vs placebo group, respectively).

Baseline clinical characteristics of patients according to baseline NT-proBNP level below or above the median are shown in Table 2. Several characteristics were significantly different in the two patient cohorts. Patients with baseline NT-proBNP level above the median were older, more frequently female, presented higher rate of diabetes, hypertension, history of myocardial infarction, history of PCI, Killip class > 1, had a higher baseline heart rate and a longer time to intervention as compared to patient with baseline NT-proBNP levels below the median; who conversely had a lower BMI and were less frequently smokers.

Table 2. Baseline characteristics of patients with a baseline NT-proBNP level ≤ median versus > median

Variable	NTproBNP level ≤ median	NTproBNP level > median	p-value
Age (yrs) mean ± SD	57.3 ± 9.9	66.3 ± 11.8	<0.001
Male gender	384/459 (83.7%)	311/459 (67.8%)	<0.001
Current smoking	246/456 (53.9%)	185/456 (40.6%)	<0.001
Diabetes mellitus	42/458 (9.2%)	64/459 (13.9%)	0.024
Body mass index (kg/m$^{2)}$ mean ± SD	27.2 ± 3.8	26.4 ± 3.6	0.009
Hypertension	113/459 (24.6%)	195/459 (42.5%)	<0.001
Hypercholesterolemia	111/457 (24.3%)	133/459 (29.0%)	0.109
Killip > I	10/458 (2.2%)	31/458 (6.8%)	<0.001
Prior myocardial infarction	25/458 (5.5%)	52/458 (11.4%)	0.001
Prior CABG	6/459 (1.3%)	11/459 (2.4%)	0.221
Prior PCI	31/459 (6.8%)	52/459 (11.3%)	0.016
Anterior infarct location	164/409 (40.1%)	177/405 (43.7%)	0.297
Time to intervention*	152 (122; 203)	193 (136; 292)	<0.001
Heart rate > 100	15/456 (3.3%)	35/455 (7.7%)	0.004
Systolic blood pressure < 100	32/453 (7.1%)	33/456 (7.2%)	0.919
Randomization to tirofiban	237/459 (51.6%)	227/459 (49.5%)	0.509

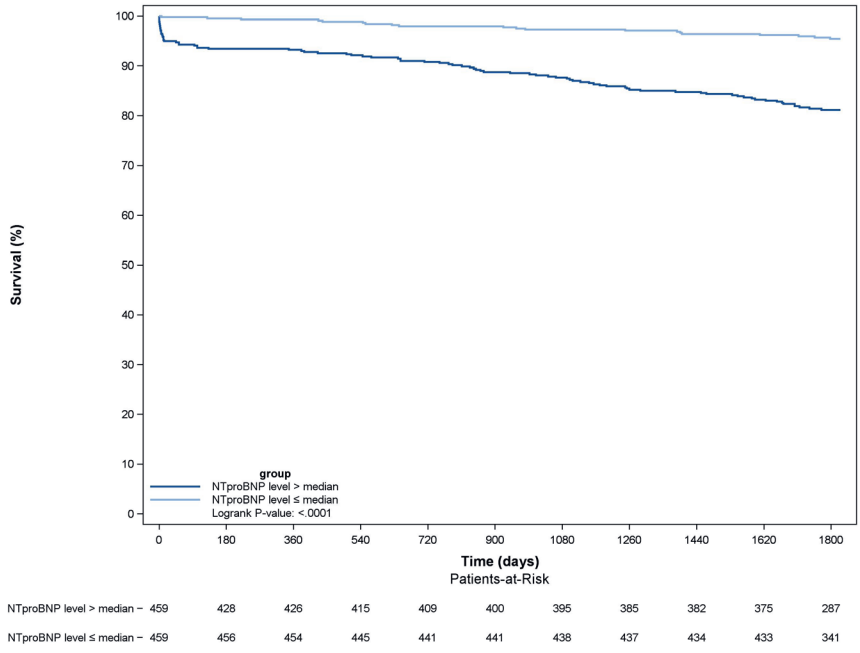
*From onset of symptoms to intervention in minutes, median (25th-75th IQRs). CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention

NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCI, percutaneous coronary intervention

Baseline NT-proBNP and mortality

Patients with baseline NT-proBNP level above the median presented higher 30-day (5.1% vs. 0.2%, p<0.001), 1-year (7.0% vs. 0.7%, p<0.001) and 5-year (20.3% vs 4.9% p<0.001) mortality compared to patients with basal NT-proBNP value below the median. KM curves are showed in figure 1.

Figure 1. Kaplan–Meier survival curves according to admission NT-proBNP levels above or below the median.



The p value, calculated with the use of the log-rank test, is given for the comparison between the two groups at 5 year.

Additionally, NT-proBNP values post-PCI were also strongly related to mortality: patients with NT-proBNP levels above the median post-PCI had a significant higher mortality at 30-days (3.0% vs 0.2% p=0.001), at 1-year (4.8% vs 0.9% p=0.001) and at 5-year (15.5% vs 7.3% p=<0.001); Patients with NT-proBNP levels above the median at admission had a hazard ratio (HR) for 5-year mortality of 4.28 (95% CI 2.47 – 7.41; p < 0.001), and following multivariate cox regression analysis, an HR of 2.73 (95% CI 1.47 – 5.06; p = 0.002).

Effect of early administration of tirofiban on NT-proBNP levels, bleeding and mortality in relation to NT-proBNP level

NT-proBNP

Interestingly in patients treated with pre-hospital tirofiban as compared to placebo, the NT-proBNP levels after PCI tended to be lower when considered as a continuous variable (1732 ± 2866 vs. 2114 ± 5019; p=0.080) and were significantly lower when

considered as a binary variable dichotomized with median value as cut-off (194/426, 45.5% vs 238/439, 54.2% p=0.011) (Table 3).

Table 3. NT-proBNP levels in placebo versus tirofiban groups

	NT-proBNP levels expressed as a continuous variable			NT-proBNP levels dichotomized according to the median value		
	Placebo	**Tirofiban**		**Placebo**	**Tirofiban**	
	Mean ± SD	Mean ± SD	p-value	N/total (%)	N/total (%)	p-value
Admission	646 ± 2054	626 ± 1850	0.108	232/454 (51.1)	227/464 (48.9)	0.509
After PCI	2114 ±2866	1732 ± 5019	0.080	238/439 (54.2)	194/426 (45.5)	0.011

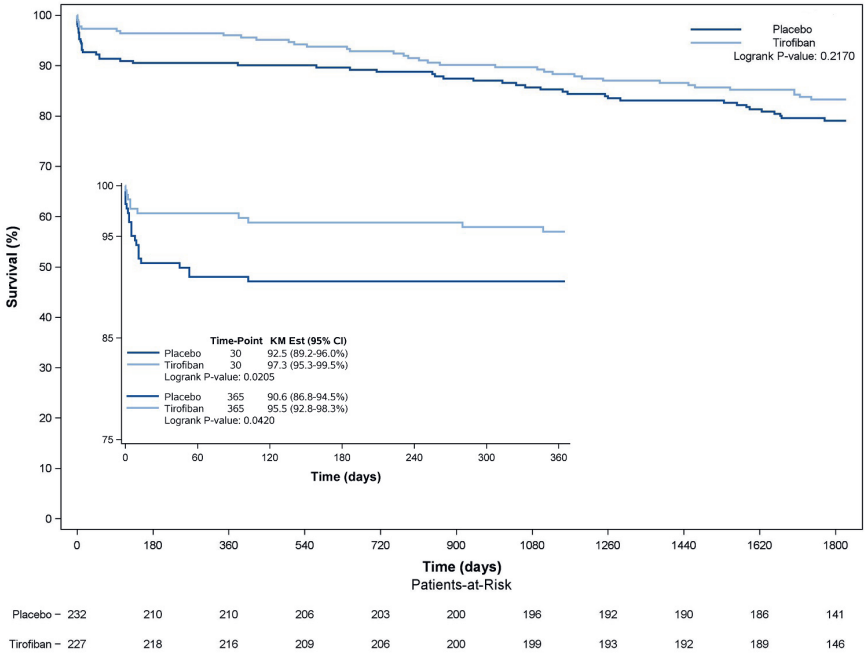
Bleeding

Patients with NT-proBNP levels above the median at admission who received early tirofiban treatment had a similar rate of 30-days major bleeding compared to patients treated with placebo (5.8% vs 3.1%, p= 0.158, for tirofiban vs placebo group, respectively) and of 30 days minor bleeding (7.6% vs 4.4%, p= 0.151).

Mortality

Patients with NT-proBNP above the median at admission who received early tirofiban treatment had a significantly lower mortality at 30-days (2.7% vs. 7.5% p=0.021) and at 1-year (4.5% vs. 9.4% p=0.043) compared to patients treated with placebo (Figure 2). This lower mortality rate in the treatment group was indeed maintained as far as 5-years, although at this point was associated with a non-significant difference (18% vs 22.4% p=0.265). KM curves are showed in figure 2.

Figure 2. Kaplan–Meier survival curves among patients with admission NT-proBNP level above the median, according to treatment group.



The P values, calculated with the use of the log-rank test, is given for the comparison between the two treatment groups at 30 days, 1 year and 5 year months. The inset shows the same data on a magnified scale

Discussion

In this post-hoc subgroup analysis of the On-TIME 2 trial, we have shown in a group of STEMI-only patients that NT-proBNP level above the median is an independent predictor of long term (5-year) mortality outcome. Moreover, we have shown that in patients with baseline NT-proBNP levels above the median early pre-hospital treatment with tirofiban significantly reduces 30-day and 1-year mortality compared to placebo. Furthermore, we have shown that tirofiban, compared to placebo, reduces NT-proBNP levels post PCI. These findings are clinically relevant and novel however they should be considered as hypothesis generating.

We have previously reported the long-term clinical outcomes benefit of a GPI-facilitated PCI strategy[7], however in this current analysis we provide further insight, showing that a high-risk subset of patients, as identified by higher levels of NT-

proBNP upon presentation (Figure 1), represent a subgroup who derive particular benefit from early GPIs treatment in terms of significant mortality reduction up to 1 year (Figure 2). This lower mortality rate was maintained up to 5-years, although at this point with a non-significant difference probably because other factors may influence very long term outcomes.

Previously, a significant relationship between the benefits in mortality reduction from the use of GPIs and patient's risk profile has been suggested[14], and the identification of patients who may incrementally benefit from GPIs administration is important in the ongoing search for a more tailored and optimized therapy for STEMI patients. Therefore, our findings may help to further refine the identification of patients likely to derive the greatest benefit from pre-hospital GPI administration. Importantly the mortality reduction was without a significant increase in either major or minor bleeding complications. However, it should be noted that patients receiving tirofiban had a numerically higher rate of both 30 day major and minor bleeding compare to placebo. Therefore tirofiban should be always used with caution in patients at high bleeding risk.

It is widely believed that the predominant process underlying increased NT-proBNP concentrations is impairment of cardiac function, leading to increased left ventricular wall stretch with resultant synthesis and secretion of NT-proBNP[24]. Ischemic injury due to coronary artery occlusion may first cause diastolic dysfunction, followed by elevation in filling pressures and associated left ventricular wall stretch resulting in the early elevation of serum NT-proBNP levels. However, elevated NT-proBNP concentrations may also result directly from cardiac ischemia, even in the absence of left ventricular dysfunction[25]. Previous studies highlighted that, in STEMI patients, NT-proBNP, drawn within 24 hours of the onset of chest pain, is more accurate in predicting mortality than the Thrombolysis in Myocardial Infarction (TIMI) risk score[26]. Indeed, our group recently revealed that baseline NT-proBNP values predict 30-day mortality in patients with STEMI, treated with PPCI independently and even more strongly than the Zwolle Risk Score alone[27]. However, in STEMI patients the prognostic value of NT-proBNP on long-term, 5-year mortality outcomes to date has never been reported.

NT-proBNP measured before primary PCI has been previously shown to be the strongest, independent predictor of suboptimal microvascular reperfusion[28]. Mechanisms behind the actual association between NT-proBNP and suboptimal reperfusion remain speculative[28]; however biomarker elevation may be the expression of profound myocardial ischemia and extensive microvascular damage leading to relevant ventricular dysfunction, alternatively one could argue that primary microvascular dysfunction, by itself, may influence left ventricular wall stretch

and so BNP values in the setting of acute myocardial infarction. Regardless of the mechanism, patients at risk of suboptimal microvascular reperfusion after PCI, may have particular benefit from adjunctive measures, such as early GPI administration. In fact, it has been shown that an antithrombotic therapy which is already active and effective at the time of PCI, plays a crucial role in the prevention of microvascular damage and restoration of myocardial tissue reperfusion[6].

Interesting, in this study, NT-proBNP level at baseline (before angiography) were not different with respect of the treatment strategy initiated in the ambulance. However, early tirofiban administration significantly reduced the number of patients with an NT-proBNP above the median after PCI. This suggests that the time course of NT-proBNP level may be positively influenced by early tirofiban administration and could potentially be dependent on the effectiveness of microvascular reperfusion after PCI, an outcome in which early tirofiban administration has a proven role[6]. This may be relevant considering that in heart failure patients a change in NT-proBNP, has been recently associated with a change in the subsequent risk of cardiovascular mortality and HF hospitalization[29].

Finally, measurement of NT-proBNP has become easy-to-perform and fast; its early measurement in the ambulance setting, aimed at stratifying patients and guiding early antiplatelet therapy, could represent a possible new strategy to be tested in further studies. Further prospective evaluation of high-risk subgroups identified by elevated NT-proBNP during the acute STEMI phase is warranted.

Limitations

This is a post-hoc analysis of a randomized trial, therefore, our conclusions should be considered as exploratory. NT-proBNP levels were drawn at variable periods after onset of symptoms, therefore it has to be noted that some patients with the highest values of NT-proBNP at admission may include a sub-group of patients with a long ischemia time in which the benefit of early GPI treatment remain uncertain[30]. Despite the fact that the prognostic value of NT-proBNP above the median was independent from ischemia time, further studies are warranted to evaluate the efficacy of early tirofiban administration in subgroup presenting with long ischemia time and high level of NT-proBNP. Moreover this study was performed with clopidogrel, which is not the contemporary guideline-recommended oral therapy for primary PCI. Therefore, the results cannot be directly translated to patients treated with novel P2Y12 inhibitor. Finally, baseline NT-proBNP measurements were made at admission (before angiography) when tirofiban was already started; although the time between tirofiban administration and first NTproBNP measurement was very short we cannot exclude a small effect of the drug on the baseline values of NT-proBNP.

Conclusions

In STEMI patients, NT-proBNP level above the median on admission independently predict long-term (5-year) mortality. Patients with NT-proBNP levels above the median who were treated with pre-hospital treatment with tirofiban, as compared to placebo, had significantly reduced 30-day and 1-year mortality rates. Early tirofiban administration may be particularly effective in reducing mortality in high-risk patients, as identified by higher admission levels of NT-proBNP. This finding should be confirmed in other studies.

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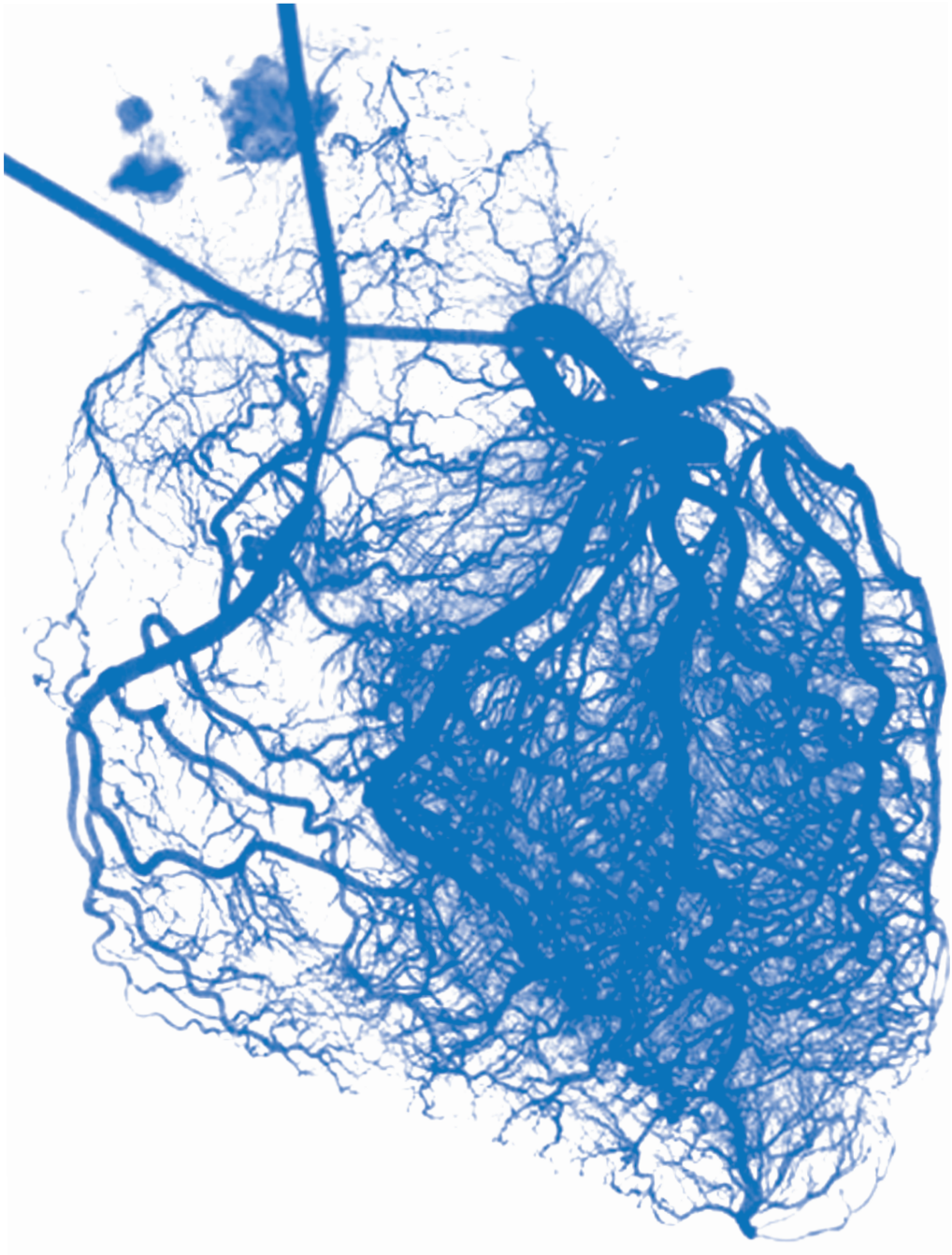

Chapter eight

Thrombus aspiration and prehospital ticagrelor administration in ST-elevation myocardial infarction: Findings from the ATLANTIC trial

Sinem Kilic, **Enrico Fabris,** Arnoud W.J. van 't Hof, Christian W. Hamm, Frédéric Lapostolle, Jens Flensted Lassen, Anne Tsatsaris, Abdourahmane Diallo, Eric Vicaut, Gilles Montalescot

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Abstract

Background: The potential interactions between prehospital (pre-H) ticagrelor administration and thrombus aspiration (TA) in patients with ST-elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI) has never been studied. Therefore, we evaluated the potential benefit of TA and pre-H ticagrelor treatment in patients enrolled in the ATLANTIC trial (NCT01347580).

Methods: This analysis included 1,630 patients who underwent primary PCI. Multivariate analysis was used to explore the potential association of TA and pre-H treatment to clinical outcomes. Potential interactions between TA and pre-H ticagrelor were also explored.

Results: A total of 941 (57.7%) patients underwent TA. In adjusted multivariate logistic model, pre-H ticagrelor treatment was significantly associated with less frequent new MI or definite stent thrombosis (ST) (odds ratio [OR] 0.43, 95% CI 0.20-0.92, p=.031), or definite ST (OR 0.26, 95% CI 0.07-0.91, p=.036) at 30 days. Patients treated with TA had higher frequency of Thrombolysis in Myocardial Infarction (TIMI) flow 0-1 compared with no-TA group (80.7% vs 51.9%, p<.0001). TA when also adjusted for TIMI flow 0-1 showed significant association only for higher bailout use of glycoprotein IIb/IIIa inhibitors (OR 1.72, 95% CI 1.18-2.50, p=.004) and more frequent 30-day TIMI major bleeding (OR 2.92, 95% CI 1.10-7.76, p=.032). No significant interactions between TA and pre-H ticagrelor were present for the explored end points.

Conclusions: TA when left to physicians' discretion was used in high-risk patients, was associated with bailout use of glycoprotein IIb/IIIa inhibitors and TIMI major bleeding, and had no impact on 30-day clinical outcomes. Conversely pre-H ticagrelor treatment predicted lower 30-day rates of ST or new MI without interaction with TA.

Introduction

Acute coronary syndromes are usually precipitated by an acute thrombosis induced by a ruptured or eroded atherosclerotic coronary plaque, causing a sudden and critical reduction in blood flow. The most important treatment for patients with ST-elevation myocardial infarction (STEMI) is early recovery of the infarct-related artery blood flow[1-4]. However, reduced flow due to distal embolization of thrombus is associated with an increased infarct size, reduced recovery of ventricular function, and increased mortality[3,5]. The high frequency of suboptimal myocardial reperfusion after primary percutaneous coronary intervention (PCI) has resulted in the development of devices that evacuate coronary thrombus to limit distal embolization and to protect the microcirculation; moreover, large interest has focused on the prehospital (pre-H) administration of pharmacological therapy.

Clinical trials focusing on manual thrombus aspiration (TA) in primary PCI have generally shown improved myocardial reperfusion. However, no reduction in hard clinical end points was seen when compared with conventional PCI in large clinical trials[3,6].

In the Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery (ATLANTIC) trial, pre-H administration of ticagrelor in patients with STEMI appeared to be safe but did not improve coronary or myocardial reperfusion before primary PCI (4); however, the effects of pre-H ticagrelor became apparent immediately after PCI[7].

Because both TA and pre-H pharmacological treatment are potential options to improve myocardial reperfusion and post-PCI clinical outcomes in patients with STEMI treated with primary PCI, we evaluate the potential benefit of TA and pre-H ticagrelor treatment in patients enrolled in the ATLANTIC trial.

Methods

Study Design and Patients

The ATLANTIC study was an international, randomized, double-blind study (NCT01347580). Patients were randomly assigned to receive either pre-H (in the ambulance) or in-hospital (in the catheterization laboratory) treatment with ticagrelor, in addition to aspirin and standard care. The trial design has been previously published[8].

Study Procedures

In the pre-H group, patients received a 180-mg loading dose of ticagrelor before transfer and then a matching placebo in the catheterization laboratory. Patients in the in-hospital group received a placebo before transfer and then a 180-mg loading dose of ticagrelor in the catheterization laboratory. All the patients subsequently received ticagrelor at a dose of 90 mg twice daily for 30 days, with a recommendation that treatment be continued for a total of 12 months. In-ambulance use of glycoprotein IIb/IIIa inhibitors (GPI) was discouraged but was left to the physician's discretion. In-laboratory use of GPI had to be identified as either a strategy of choice or a bailout treatment during PCI. Coronary angiography was performed via the radial or femoral artery. Manual TA was performed at the discretion of the operator as per the standard protocol followed by conventional PCI to the culprit vessel.

Study end points

Clinical end points, evaluated up to date of the last study visit (≤32 days), included death, new myocardial infarction (MI), stent thrombosis (ST), urgent revascularization, bail-out GPI use, stroke, Thrombolysis in Myocardial Infarction (TIMI) flow grade 3 at the end of the procedure and complete (≥70%) resolution of ST-segment elevation at 60 minutes after PCI. Safety endpoint included major bleeding up to the last study visit using TIMI definitions.

Centralized, blinded reviews of angiographic data and ECG recordings were conducted by Cardialysis Core Laboratory services (Rotterdam, the Netherlands) and eResearch Technology (Peterborough, United Kingdom), respectively. An independent adjudication committee, whose members were unaware of the treatment assignments, reviewed the clinical end points, except deaths and minimal bleeding events

Statistical analysis

Subjects were classified according to TA subgroup. Continuous variables are presented as mean and SD or median (interquartile range), and compared using Student *t* test's P value in case of Gaussian distribution or Mann-Whitney's P value in case of non-Gaussian distribution. Categorical variables are presented as number and percentages and compared using X^2 test P value or Fisher test P value in case of low numbers of events. The association between TA subgroup and clinical end points was assessed by fitting logistic regression model with TA as the only covariate. Odds ratios (ORs) and P values for pre- versus in-hospital ticagrelor were calculated using a logistic regression model with study treatment group as the only explanatory variable. The interaction between TA and study treatment group was tested by using a multivariate logistic regression model. For testing the association between pre-H ticagrelor and

endpoints, a multivariate adjusted analysis was performed with variables forced in the model: age (<75, ≥75 years), sex, body mass index (<30 kg/m^2, ≥30 kg/m^2), prior MI, prior PCI, transient ischaemic attack, nonhaemorrhagic stroke, stent, drug eluting stent, bare metal stent, hypertension, arterial access and GPI before PCI. The same variables forced in the model plus TIMI flow 0-1 were used to evaluate the association between TA subgroup and clinical end points. The 2-sided significance level was fixed at 5%. All tests were performed with SAS version 9.4 (SAS Institute Inc, Cary, NC).

Results

Patient and procedure characteristics

One thousand six hundred thirty patients enrolled in the trial and who underwent primary PCI were included in the analysis.

A total of 941 (57.7%) patients underwent TA. Patients treated with TA were younger (60±12 vs 62 ±12 years, p<.0001), were more frequently men (83% vs 78.4%, p=.019), less frequently had a previous MI (6.6% vs 9.6%, p=.027) or transient ischemic attack (0.4% vs 1.5%, p= .026) and had more frequently radial access (70.4% vs 64.7%, p=.015). Patients treated with TA had higher frequency of TIMI flow 0-1 compared with no-TA group (80.7% vs 51.9%, p<.0001). The rate of bail-out use of GPI was more frequently in the TA group than in the PCI-alone group (37.2% vs. 25.4%, P<.0001). Stenting was lower in the TA group (93.2% vs. 95.6%, P=.036), (table 1).

Table 1. Baseline characteristics and procedural characteristics between patients with and without TA

	TA N=941	No TA N=689	Overall N=1630	p-value
Age mean ± SD	59.9 ± 11.9	62.3 ± 12.1	60.9 ± 12.1	<.0001
Age group (<75, ≥75), n(%) ≥75y	126 (13.4)	132 (19.2)	258 (15.8)	.0016
Sex, n(%) Female	160 (17.0)	149 (21.6)	309 (19.0)	.0187
Weight (kg) mean ± SD	80.8 ± 15.3	79.5 ± 16.1	80.3 ± 15.6	.0797
Body mass index group (kg/m2), n(%) ≥30kg/m^2	193 (20.5)	130 (18.9)	323 (19.8)	.4113
Diabetes Mellitus, n(%)	127 (13.5)	87 (12.6)	214 (13.1)	.6077
TIMI risk score category, n(%)				.0535
0-2	601 (63.9)	400 (58.1)	1001 (61.4)	
3-6	327 (34.8)	276 (40.1)	603 (37.0)	
>6	13 (1.4)	13 (1.9)	26 (1.6)	
TIMI flow grade, n(%)				
0-1	744 (80.7)	349 (51.9)	1093 (68.5)	<.0001
2-3	178 (19.3)	324 (48.1)	502 (31.5)	
Myocardial infarction, n(%)	62 (6.6)	66 (9.6)	128 (7.9)	.0266
PCI, n(%)	55 (5.8)	61 (8.9)	116 (7.1)	.0196
Coronary artery bypass graft, n(%)	4 (0.4)	5 (0.7)	9 (0.6)	.5061
Chronic obstructive pulmonary disease, n(%)	38 (4.0)	27 (3.9)	65 (4.0)	.9030
Chronic renal disease, n(%)	10 (1.1)	14 (2.0)	24 (1.5)	.1085
Hypertension, n(%)	374 (39.7)	303 (44.0)	677 (41.5)	.0868
Congestive heart failure, n(%)	6 (0.6)	7 (1.0)	13 (0.8)	.3963
Hypercholesterolemia, n(%)	328 (34.9)	247 (35.8)	575 (35.3)	.6787
Transient ischemic attack, n(%)	4 (0.4)	10 (1.5)	14 (0.9)	.0265
Hemorrhagic stroke, n(%)	4 (0.4)	0 (0.0)	4 (0.2)	.1425
Nonhemorrhagic stroke, n(%)	6 (0.6)	10 (1.5)	16 (1.0)	.0997
Killip class I, n(%)	857 (91.1)	632 (91.7)	1489 (91.3)	.6427
Arterial access, n(%)				
Radial	659 (70.4)	444 (64.7)	1103 (68.0)	.0154
Femoral	277 (29.6)	242 (35.3)	519 (32.0)	
Stent, n(%) with stent	877 (93.2)	659 (95.6)	1536 (94.2)	.0363
Drug-eluting stent, n(%)	513 (54.5)	433 (62.8)	946 (58.0)	.0008
Bare-metal stent, n(%)	377 (40.1)	240 (34.8)	617 (37.9)	.0315
1st loading dose, n(%)	939 (99.8)	689 (100.0)	1628 (99.9)	.5117
2nd loading dose, n(%)	922 (98.0)	668 (97.0)	1590 (97.5)	.1848
Maintenance dose, n(%)	889 (94.5)	640 (92.9)	1529 (93.8)	.1896
Aspirin use, n(%)	939 (99.8)	685 (99.4)	1624 (99.6)	.2484
GPI before PCI, n(%)	350 (37.2)	175 (25.4)	525 (32.2)	<.0001
Intravenous anticoagulant during hospitalization, n(%)	843 (89.6)	621 (90.1)	1464 (89.8)	.7193

Pre-H treatment and TA as potential predictors of clinical outcomes

At multivariate and adjusted multivariate analysis, pre-H ticagrelor emerged as a predictor of lower incidence of new MI or definite ST (OR 0.43, 95% CI 0.20-0.92, p=.031) , or definite ST (OR 0.26, 95% CI 0.07-0.91, p=.036) at 30 days (table 2).

TA when also adjusted for TIMI flow 0-1 showed significant association only for higher bail-out use of GPI (OR 1.72, 95% CI 1.18-2.50, p=.004) and higher 30-days TIMI major bleeding (OR 2.92, 95% CI 1.10-7.76, p=.032) (table 3).

Importantly TA was not associated with the occurrence of stroke at 30 days. (table 3).

Table 2. Pre- H ticagrelor and study clinical outcomes, adjusted multivariate logistic model

Predictors **Pre-H vs in-hospital ticagrelor**	**Adjusted multivariate logistic model[§]** **N=1622**	
End points	OR (95% CI)	P-value
30-d composite of death/new MI/urgent revascularization and definite ST	1.11 (0.67;1.83)	0.6823
30-d new MI or definite acute ST	0.43 (0.20; 0.92)	0.0307
30-d new MI	0.70 (0.31;1.58)	0.3885
30-d definite ST	0.26 (0.07; 0.91)	0.0357
30-d urgent revascularization	0.82 (0.31;2.16)	0.6899
30-d stroke (ischemic)	3.96 (0.95;16.46)	0.0582
Bail-out use of GPI	0.79 (0.56;1.13)	0.1952
Absence of TIMI flow grade 3 of MI culprit vessel post-PCI	0.89 (0.68;1.16)	0.3812
Absence of ST-segment elevation resolution ≥ 70% post-PCI	0.82 (0.66;1.02)	0.0693
TIMI major bleeding	1.04 (0.41;2.68)	0.9309
TIMI minor bleeding	0.95 (0.54;1.69)	0.8712

§ The multivariate adjusted analysis is the multivariate analysis with variables forced in the model*: age (<75, ≥75), sex, body mass index (<30 kg/m^2, ≥30 kg/m^2), prior MI, prior PCI, transient ischaemic attack, nonhaemorrhagic stroke, stent, DE Stent, BM stent, hypertension, arterial access, and GPI before PCI.

Table 3. TA and study clinical outcomes, adjusted multivariate logistic model

Predictors TA vs NO TA	**Adjusted multivariate logistic Model§ N=1622**	
End points	OR (95% CI)	P-value
30-d composite of death/new MI/urgent revascularization and definite ST	0.84 (0.49;1.44)	0.5334
30-d new MI or definite acute ST	0.92 (0.41;2.07)	0.8488
30-d new MI	0.77 (0.33;1.81)	0.5499
30-d definite ST	1.56 (0.46;5.32)	0.4790
30-d urgent revascularization	0.83 (0.31;2.24)	0.7110
30-d stroke (ischemic)	0.96 (0.23;4.08)	0.9539
Bail-out use of GPI	1.72 (1.18; 2.50)	0.0045
Absence of TIMI flow grade 3 of MI culprit vessel post-PCI	1.09 (0.82;1.46)	0.5390
Absence of ST-segment elevation resolution ≥ 70% post-PCI	0.87 (0.69;1.09)	0.2157
TIMI major bleeding	2.92 (1.10;7.76)	0.0321
TIMI minor bleeding	1.46 (0.79;2.69)	0.2264

§ The multivariate adjusted analysis is the multivariate analysis with variables forced in the model: age (<75, ≥75), sex, BMI (<30 kg/m^2, ≥30 kg/m^2), prior MI, prior PCI, transient ischaemic attack, nonhaemorrhagic stroke, stent, DE Stent, BM stent, hypertension, arterial access, GPI before PCI, and TIMI flow 0-1.

No significant interactions between TA and pre-H ticagrelor were present for the explored end points or composite end points (table 4).

Table 4. Multivariate logistic model for the study clinical outcomes and interaction

		Multivariate logistic model* N=1630	
End points	**Predictors**	**OR (95% CI)**	**P-value**
30-d composite of death/new MI/urgent revascularization and definite ST	Pre-H vs in-hospital ticagrelor	1.04 (0.64;1.68)	0.8741
	TA vs NO TA	0.92 (0.57;1.49)	0.7247
	Interaction†		0.9602
30-d new MI or definite acute ST	Pre-H vs in-hospital ticagrelor	0.39 (0.16;0.95)	0.0375
	TA vs NO TA	1.11 (0.46;2.70)	0.8174
	Interaction†		0.7006
30-d new MI	Pre-H vs in-hospital ticagrelor	0.72 (0.27;1.92)	0.5124
	TA vs NO TA	0.84 (0.32;2.24)	0.7318
	Interaction†		0.8424
30-d definite ST	Pre-H vs in-hospital ticagrelor	0.20 (0.04;1.02)	0.0526
	TA vs NO TA	2.12 (0.42;10.85)	0.3661
	Interaction†		0.5448
30-d urgent revascularization	Pre-H vs in-hospital ticagrelor	0.60 (0.19;1.88)	0.3810
	TA vs NO TA	1.27 (0.41;3.96)	0.6799
	Interaction†		0.3810
30-d stroke (ischemic)	Pre-H vs in-hospital ticagrelor	4.07 (0.45;37.09)	0.2137
	TA vs NO TA	0.95 (0.10;8.63)	0.9609
	Interaction†		0.8516
Bail-out use of GPI	Pre-H vs in-hospital ticagrelor	0.74 (0.52;1.04)	0.0845
	TA vs NO TA	1.86 (1.32;2.63)	0.0004
	Interaction†		0.9113
Absence of TIMI flow grade 3 of MI culprit vessel post-PCI	Pre-H vs in-hospital ticagrelor	0.89 (0.69;1.16)	0.3964
	TA vs NO TA	1.26 (0.96;1.63)	0.0903
	Interaction†		0.6830
Absence of ST-segment elevation resolution ≥ 70% post-PCI	Pre-H vs in-hospital ticagrelor	0.82 (0.66;1.01)	0.0606
	TA vs NO TA	0.84 (0.68;1.04)	0.1076
	Interaction†		0.8163

*Multivariate analysis without covariables testing association between ticagrelor groups, TA groups and clinical endpoint and their interactions. † Interaction between treatment group and TA.

Pre-H treatment and TA as potential predictors of electrocardiographic and angiographic outcomes

TA and pre-H treatment did not emerged as significant predictors of electrocardiographic and angiographic outcomes. No significant interactions between TA and pre-H ticagrelor were present for the explored end points (table 2,3).

Pre-H treatment and TA as potential predictors of bleeding events

TA was strongly associated with TIMI major bleeding (OR 2.92, 95% CI 1.10-7.76, p=.032) (table 3)

Conversely, pre-H treatment showed not significant associations with both major and minor TIMI bleeding (table 2).

Discussion

We evaluated the potential benefit of TA and pre-H ticagrelor treatment in a large cohort of STEMI patients enrolled in the ATLANTIC trial, and for the first time, we evaluated the potential synergy effect of pre-H ticagrelor treatment and TA on post-PCI myocardial reperfusion and clinical outcomes.

Interestingly, TA, when left to physicians' discretion, was not associated with improvement in myocardial reperfusion and clinical outcomes. Conversely, pre-H treatment emerged as an independent predictor of lower incidence of composite 30-day new MI or definite acute ST and definite ST and showed a favorable trend for myocardial reperfusion expressed as complete ST resolution post-PCI, highlighting a potential benefit of pre-H pharmacological treatment in STEMI patients.

Despite the use of pre-H treatment together with the use of TA (aimed to reduce thrombotic burden and to improve coronary flow)[9] and consequently clinical outcomes[10], this analyses showed no significant interactions between TA and pre-H ticagrelor treatment for all the explored end points. However, this analysis showed that TA was frequently used in high risk patients presenting with TIMI flow 0-1 and TA was a strong predictor of bailout use of GPI.

The absence of interaction between pre-H treatment and TA, however, is in line with the INFUSE-AMI trial[11] where patients were randomized in a 2 × 2 factorial design to bolus intracoronary abciximab vs no abciximab and to TA versus no TA. No interaction was present between the 2 randomization groups for the 30-day infarct size end point, although median infarct size was lowest in the intracoronary abciximab plus TA group compared with the other 3 groups combined. However it has to noted

that the INFUSE-AMI trial randomized both GPI and TA, whereas the ATLANTIC trial randomized only pre-H ticagrelor versus in-hospital ticagrelor.

This analysis provided further insights regarding the use of TA in the current era of STEMI reperfusion. Indeed, in STEMI patients who received early antithrombotic treatment and fast transportation to the catheterization laboratory[4], 57.7% received TA treatment; we observed, a lower rate of stenting in patients treated with TA, which may suggest, in some cases, a patency of infarct-related artery after manual TA that enabled the interventional cardiologist to leave the artery unstented. It should be noted that more than half of patients underwent TA despite randomized trials and meta-analyses that tested the effect of TA leading to conflicting results[3,11-23]. Indeed, the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS) trial showed improvement in perfusion indices and significant reduction of mortality and reinfarction after 1 year[14], but this trial has been criticized for lack of statistical power to prove reduced mortality. Conversely, the Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) trial showed no benefit of TA use in 30 day clinical outcomes (all-cause mortality, reinfarction, ST, or revascularization) and follow-up at 1 year did not show increased survival compared with patients who underwent conventional PCI. However, the TASTE trial was powered to demonstrate only a large survival benefit. This shortcoming was addressed in Trial of Routine Aspiration Thrombectomy With Percutaneous Coronary Intervention (PCI) Versus PCI Alone in Patients With ST-Segment Elevation Myocardial Infarction (STEMI) Undergoing Primary PCI (TOTAL) trial. The use of TA in the TOTAL trial showed reduced angiographic distal embolisation and improved ST- segment resolution[3,6], but there was no improvement in outcomes of TIMI flow, myocardial blush grade, or the incidence of no reflow, and the trial showed a neutral result on its primary efficacy outcome (180-day cardiovascular death, recurrent myocardial infarction, cardiogenic shock, or New York Heart Association class IV), and outcomes at 1 year were largely similar[22]. The trial findings, however, raised safety concerns because an increased risk of 30-day stroke was noted with TA with the excess risk already apparent within the first 48 hours after the procedure[24]. Interestingly, in our analysis, TA was not associated with the occurrence of stroke at 30 days, supporting that possibility that the excess risk of stroke could not be fully attributed to TA; indeed, reasonable explanations for increased risk, other than the role of chance associated with the relatively small sample size, are lacking.

Finally TA was associated to increased risk for major TIMI bleeding, whereas pre-H ticagrelor was not. Again, the possible concomitant use of TA and GPI may explain the higher incidence of bleeding events in TA groups. However, there was no interaction between TA and pre-H ticagrelor for bleeding events, suggesting the potential safety of pre-H ticagrelor administration and subsequent use of TA.

Limitations

Several limitations of the present analysis should be considered. This analysis was a post hoc analysis and therefore should be viewed as hypothesis generating. We cannot fully exclude the possibility of confounding as a result of baseline factors that we did not study. The possibility of unaccounted confounding related to the nonrandomized use of TA cannot be excluded; therefore, the potential benefit of TA together with pre-H treatment requires to be evaluated in future studies.

Conclusion

TA when left to physician's discretion was used in high risk patients, was associated with bailout use of GPI and TIMI major bleeding, and was not associated with improvement in 30-day clinical outcome. Conversely, pre-H ticagrelor treatment predicted lower 30-day rates of ST or new MI as well as definite ST without significant interaction with TA.

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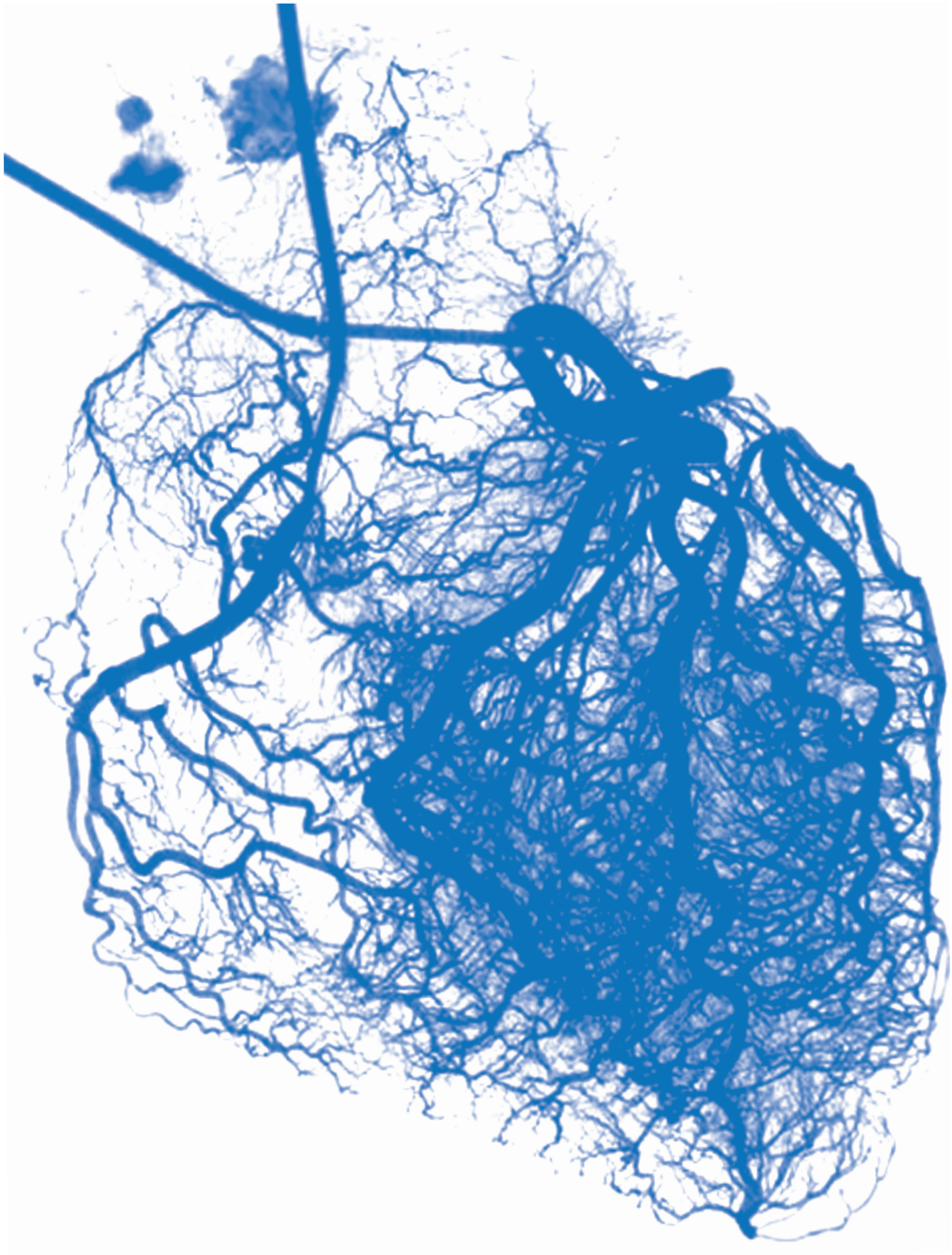
Part three

Duration of dual anti-platelet therapy after primary PCI in STEMI



Chapter nine

A Prospective, Randomized, Open Label Trial of 6 Months vs. 12 Months Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation In ST-elevation Myocardial Infarction: Rationale and design of the "DAPT-STEMI trial"

Elvin Kedhi, **Enrico Fabris**, Martin van der Ent, Mark Kennedy, Pawel Buszman, Clemens von Birgelen, Stéphane Cook, Hans Wedel, Felix Zijlstra

Am Heart J 2017;188:11-17

Abstract

Background: The optimal duration of dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) with second-generation drug eluting stents (DES) is unclear. Because prolonged DAPT is associated with higher bleeding risk and health care costs, establishing optimal DAPT duration is of paramount importance. No other randomized controlled trials have evaluated the safety of shorter DAPT duration in ST elevation myocardial infarction (STEMI) patients treated with second generation DES and latest P2Y12 platelet receptor inhibitors.

Hypothesis: Six months of DAPT after Resolute Integrity stent implantation in STEMI patients is not inferior to 12 months DAPT in clinical outcomes.

Study design: The Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation In ST-elevation Myocardial Infarction (DAPT-STEMI) trial is a randomized, multicentre, international, open label trial, designed to examine the safety (non-inferiority) of 6-month DAPT after Resolute Integrity stent implantation in STEMI patients compared to 12-months DAPT. Event free patients on DAPT at 6-months will be randomized (1:1 fashion) between single (aspirin only) versus DAPT for an additional 6 months and followed until 2 years after primary PCI. The primary end point is a patient oriented composite endpoint of all-cause mortality, any myocardial infarction, any revascularization, stroke and major bleeding (net MACCE) at 18-months after randomization. To achieve a power of 85% for a non-inferiority limit of 1.66, a total of 1100 enrolled patients are required.

Summary: The DAPT-STEMI trial aims to assess in STEMI patients, treated with second-generation DES, whether discontinuation of DAPT after 6 months of event-free survival is non-inferior to routine 12 months DAPT.

Introduction

The optimal duration of dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) with second-generation drug eluting stents (DES) is unclear[1-3]. Because prolonged DAPT is associated with higher bleeding risk and health care costs[4], establishing optimal DAPT duration is of paramount importance. No other randomized controlled trials have evaluated the safety of shorter DAPT duration in ST elevation myocardial infarction (STEMI) patients treated with second generation DES and latest P2Y12 platelet receptor inhibitors. Therefore we have designed a prospective, randomized, open label trial of six months vs. twelve months Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation In ST-elevation Myocardial Infarction: the "DAPT-STEMI" trial, in order to evaluate whether six months of DAPT after Resolute Integrity stent implantation in STEMI patients is not inferior to 12 months DAPT in clinical outcomes.

Study Design

The Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation In ST-elevation Myocardial Infarction (DAPT-STEMI) trial is a prospective, randomized, multicentre, international open label trial testing the hypothesis that 6 months of DAPT after second generation DES implantation in the setting of primary PCI for STEMI is not inferior to 12 months DAPT (non-inferiority hypothesis).

The trial will also incorporate two prospective registries studying:

1) the clinical outcomes after primary PCI with the Resolute Integrity (Medtronic Santa Rosa Ca, USA) stent at 30 days and 6 months (Resolute Integrity in STEMI Prospective Registry).

2) the safety outcomes of Bivalirudin and Ticagrelor or Bivalirudin and Prasugrel combination at 2 and 30 days (Bivalirudin Registry);

Study population, randomization and follow up

The trial population will consist of patients who received a second generation DES during primary PCI. The study flow chart is shown in Figure 1. The inclusion and exclusion criteria are shown in Table 1. Patients that fulfil the inclusion and exclusion criteria will be enrolled after the primary PCI procedure. All patients will be followed during 6 months. At 6 months, patients that fulfil the randomisation criteria (Table 1) will be randomised in a 1:1 fashion to either stop or continue DAPT for an additional 6 months (to a total of 12 months after primary PCI). All randomised patients will be followed for 18 months (or 2 years after primary PCI), while patients that do not

fulfil the randomisation criteria will be excluded from the trial. The randomization will be delivered via sealed envelopes containing a computer-generated sequence produced by the coordinating CRO.

Table 1 Inclusion and Exclusion criteria

INCLUSION CRITERIA ENROLMENT
STEMI patients between 18-85 years, who underwent primary PCI with a second generation drug eluting stent implantation
EXCLUSION CRITERIA ENROLMENT
Intolerance to Aspirin, Prasugrel, Ticagrelor, Clopidogrel, Heparin, Bivaluridin, Zotarolimus or Everolimus
Known bleeding diathesis or known coagulopathy
Planned elective surgical procedure necessitating interruption of dual antiplatelet therapy during the first 6 months after randomization.
History of stent thrombosis
Drug eluting stent in main left coronary artery
Active bleeding, known bleeding diathesis or known coagulopathy.
Oral anticoagulant therapy with Coumadin derivates
Malignancies or other comorbidity with a life expectancy of less than one year or that may result in protocol noncompliance
Pregnancy (present, suspected or planned) or positive pregnancy test (in women with childbearing potential a negative pregnancy test is mandatory)
INCLUSION CRITERIA RANDOMIZATION
Patients that are event-free and on DAPT at 6 months.
EXCLUSION CRITERIA RANDOMIZATION
Occurrence of death, myocardial infarction, stent thrombosis and target vessel or any unscheduled revascularization during the first 6 months after inclusion, with the exception of (scheduled) revascularizations in non-culprit lesions, performed within 45 days from the primary PCI
Stroke or bleeding or surgical procedure requiring discontinuation of DAPT during the first 6 months after inclusion
Oral anticoagulant therapy

STEMI= ST elevation myocardial infarction; DAPT= dual antiplatelet therapy; PCI= percutaneous coronary intervention

Primary endpoints

DAPT- STEMI primary endpoint

The primary endpoint is a composite of all-cause mortality, any myocardial infarction (MI), any revascularization, stroke and TIMI major bleeding[5] (net MACCE) at 18 months after randomization.

Resolute Integrity Registry primary endpoint
The primary end point will be the same as the primary endpoint of DAPT-STEMI, at 30 days and 6 months.

Bivalirudin Registry primary endpoint
The primary end point will be a composite endpoint of all-cause mortality, MI, Stroke, ST and Bleeding (following BARC definition[6]) at 2 and 30 days.

Secondary end points

DAPT-STEMI Secondary end points

The major secondary endpoint will be a composite of all-cause mortality, any MI, stroke, ST and TIMI major bleeding[5] at 9 and 18 months after randomization.

Other secondary endpoints are ST definite/probable (following ARC definition[7]), all-cause mortality, cardiac mortality, any MI, bleeding, stroke, as well as Target vessel MI, target vessel revascularization (TVR), target lesion revascularization (TLR), target vessel failure (TVF), target lesion failure (TLF) evaluated at 9 and 18 months after randomization.

Resolute Integrity Registry secondary endpoints
The secondary endpoints will be identical to those of the secondary endpoints of DAPT-STEMI trial, but measured at 30 days and 6 months.

Bivalirudin Registry secondary endpoints
The secondary endpoints will be ST (following ARC definition[7]), all-cause mortality, cardiac mortality, all MI and target vessel MI evaluated at 2 and 30 days; bleeding (following BARC definitions[6]) at 2 days and Stroke at 2 days.

Procedures and Investigational treatment

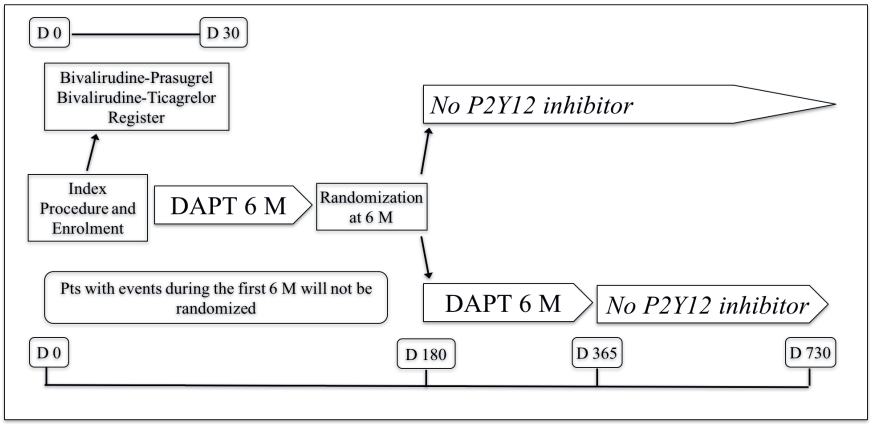
At inclusion all STEMI patients will be treated according to standard clinical practice. Artery puncture site is left to the discretion of the operator, although radial approach is strongly recommended to avoid bleeding complications at the puncture site. Thrombosuction and/or pre-dilation of the lesion are left to the discretion of the operator. If clinically indicated and feasible a PCI with stent implantation will be performed. The recommended stent device will be the Resolute Integrity (Medtronic Santa Rosa Ca, USA). Use of Bivalirudin during primary PCI is strongly recommended. In accordance with revascularization guidelines[8], DAPT, consisting of aspirin (ASA) 150–300 mg per os or 250–500 mg bolus i.v. followed by 75–100 mg daily, and prasugrel 60 mg loading dose, followed by 10 mg daily, or ticagrelor 180 mg loading dose, followed by 90 mg twice daily will be initiated and continued for 6 months. Patients > 75 years and with a body weight of < 60kg will be treated with prasugrel 60 mg loading dose, but followed by 5 mg prasugrel daily. Patient treated with clopidogrel will receive a 600 mg loading dose followed by 75 mg daily for 6 months.

At 6 months patients will be randomized to either discontinue DAPT or continue DAPT for a further 6 months after randomisation (12 months post primary PCI) (Figure 1). Aspirin, 80-100 mg daily will be continued indefinitely in all patients. DAPT compliance, medication use and adverse events will be registered at 6 months (randomisation) and at 24 months after primary PCI. Any interruption or termination, as well as the reason for this, will be documented. Non-compliance will be considered whether the patients voluntary or involuntary stopped the medication without any medical reason. Additional (scheduled) revascularisations in non-culprit lesions, when needed, should be performed within 45 days from the primary PCI, however, even in this case the 6 month follow-up time point is based on the date of the primary PCI.

Ethics and informed consent

This study will be conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO). The patient will be informed of the possible participation in this trial before or during the PCI procedure, but enrolment will only take place after the PCI procedure is completed. Informed consent will be obtained after the PCI procedure in accordance with the Good Clinical Practice guidelines.

Figure 1. Study Flow chart



DAPT= dual antiplatelet therapy, M= months

Statistical analysis

The trial is powered only for the primary endpoint. Analyses will be performed for both the intent-to-treat (ITT) population and per-protocol (PP). The Primary Endpoint will be based on ITT analysis.

The main analysis in this study will be Cox proportional hazards model. The Hazards Ratio (HR) and the upper limit of the two-sided 95%-confidence interval for the HR for the period 0-18 months will be calculated by the Cox model. The hazards ratio over the follow up period will be closely analysed. If the proportional hazards assumption is violated a Poisson model will be used in a secondary analysis.

The upper limit of the two-sided 95%- confidence interval for the HR of 6 months DAPT after STEMI versus the standard of 12 months DAPT will be compared with the non-inferiority limit. If the upper limit of the 95%-confidence interval for the HR is less than 1.66 "Non-inferiority" is declared.

Sample size calculation

The sample size was calculated under the assumption that the alpha value was 0.05 for a two-sided test (0.025 for a one-sided test) with a power of 85% and a non-inferiority limit of 1.66. The non-inferiority limit is chosen to be 1.66 in this study; this limit is similar to or slightly larger than what chosen in other recent trials comparing drugs or devices[9-16]. However we have on purpose chosen a non-inferiority margins based on HR plus the upper 95% CI and not a non-inferiority margin based on an absolute percentage of a pre-specified expected event rate as this implies that this pre-specified event rate should be first reached before non-inferiority can be claimed.

Using a non-inferiority margin based on HR of the observed events avoids this bias. While 1.66 non-inferiority margin might look large it should be noted that this is only the upper limit of the 95%CI of the HR, and if the proportions in both arms were hypothetically exactly equal the upper 95%-confidence limit of the relative risk (or HR) would be 1.33 and the upper 95%-confidence limit for risk difference close to 4%. This illustrates the impact of random fluctuation in a study like DAPT-STEMI.

The endpoint rate at 18 months' post randomisation was assumed to be 15%. This assumption was based on 2 years result of the resolute all-comers trial[17] and Resolute all-comers STEMI subgroup results[18] after excluding the event rates of the first 6 months. The sample size needed for these assumptions is 1000. To compensate for the mortality and non-compliance to dual therapy in the first 6 months (before randomisation) 1100 patients should be enrolled after the PCI procedure.

Data analysis and reporting

Categorical variables will be assessed with the use of $\chi 2$ or Fisher's exact tests, whereas continuous variables will be expressed as mean ± standard deviation or median with range and differences in outcome data will be statistically analyzed using parametric (student t-test) or nonparametric (Wilcoxon rank-sum) tests as appropriate. For the DAPT-STEMI occurrence of the primary endpoint at 18 months after randomization will be used for the main statistical analysis. The results in both groups for the primary endpoint as well as for the secondary endpoints will be presented as time to event curves (Kaplan-Meier).

We have not pre specified an economic analysis as part of the trial, mainly because this is an international trial and health-economics as well as reimbursement strategies are different in different countries. However on the base of the trial result a post hoc analysis of the potential estimation of the cost-benefit of a shorter DAPT duration will be considered.

Discussion

Rationale for shorter DAPT duration after DES

Following concerns of a greater risk of stent thrombosis attributed to delayed stent endothelialisation encountered with first generation DES, DAPT was extended to 12 months after DES implantation on the basis of broad expert consensus[19, 20], irrespective of DES type and despite the absence of evidence-based randomized control trial (RCT) results. However, in the light of significant reduction in thrombotic events achieved from the novel second-generation DESs as compared with the first-generation DESs[21], a shorter duration of DAPT can be contemplated.

Recent RCTs, testing short DAPT duration (≤6 months) after implantation of first- and second generation DES, showed that a short-DAPT strategy versus long-DAPT strategy (≥ 12 months) was non-inferior, in terms of composite primary clinical endpoint[9-11, 22-24]. Interestingly, in the short DAPT arms of these trials, the ischemic and or thrombotic events were similar to the longer DAPT regiment arms, and therefore challenges the notion that 1-year of DAPT is necessary after DES implantation. Finally, recently, several RCTs failed to show survival advantage of prolonging (≥ 12 months) DAPT[25-27]. When considering these trials together, long-term DAPT showed a reduction of stent- and non-stent related thrombotic events but an increase of major bleeding and a trend toward higher risk of all-cause mortality compared with standard regimen[1].

DAPT duration after acute coronary syndrome

The recommendation of 12 months DAPT in patients with acute coronary syndrome (ACS) is based on the CURE[28, 29] and CREDO[30] studies, however the value of long-term treatment with clopidogrel post-PCI isolated from pretreatment was impossible to determine and there was no significant advantage of clopidogrel over placebo after the first weeks following PCI, in terms of death or myocardial infarction[31]. Moreover short term (<12 months) DAPT compared with longer DAPT regimen reduced bleeding without increasing ischaemic complications in studies including patients with high-risk ACS[32], or NSTEMI and STEMI[33]. However, the actual clinical evidence is limited and confounded mainly because those RCTs that enrolled a larger number of ACS patients (range 40 to 75%) did not systematically use a second generation DES.[10, 23, 24, 34], while those that used exclusively second generation DES enrolled only a small proportion of patients with ACS (range 24 to 38%)[9, 11, 22]. Furthermore, the percentage of the STEMI patients enrolled was very low as STEMI was an exclusion criterion in the majority of these trials.[9 10] Finally, none of these trials used the latest generation P2Y12 inhibitors, Prasugrel (Effient®) or Ticagrelor (Brilinta®);

Therefore, in this perspective of the DAPT-STEMI trial results will provide important new information.

DAPT regimen

As already mentioned the recommended DAPT in the study consist of ASA plus prasugrel or ticagrelor as suggested by the guidelines. However, the choice of the P2Y12 inhibitor is left to the physicians in order to reflect the current real world practice in which still a portion of patients receive clopidrogrel for economical and clinical (age, bleeding risk, etc..) reasons. Considering the above mentioned protocol strong recommendation as well as the current guidelines for STEMI treatment, we expect that only a small proportion of patients will be treated with clopidogrel compared to the new P2Y12 inhibitors. Moreover, considering the large size of this

trial, we expect that the percentage of patients receiving different P2Y12 inhibitors in the two arms of the study (short vs 12-months of DAPT) would be well balanced. The potential different outcomes between the newer antiplatelet agents is not the scope of this trial and the trail is not powered for, however we would correct for differences between subgroups might these be observed, in a multivariate analysis.

Finally, as DAPT will be stopped at 12 months even in the in the longer arm as per current guidelines, this study should not be considered as a long term DAPT study.

Anticoagulation

As previously reported the use of Bivalirudin during primary PCI is strongly recommended as suggested by the guidelines[35]. Bivalirudin, has proven safer reducing bleeding and mortality in STEMI treatment, when compared to Heparin and GP IIb/IIIa inhibitors[36, 37], however studies testing combination treatment of Bivalirudin (Angiomax®) with Prasugrel or Ticagrelor showed non-uniform results[38-40] and therefore additional data from the two prospective registers encompassed within the DAPT-STEI trial will enrich the actual knowledge in this setting.

DAPT- STEMI primary endpoint

We chose to follow-up the patients for at least 1 year (18 months in the shorter DAPT arm) after the discontinuation of the DAPT taking into consideration not only stent related thromboembolic events due to the rebound phenomenon after P2Y12 discontinuation but also those events originating from non-infarct related arteries which might also benefit from a longer DAPT. We opted to have a patient oriented primary endpoint and therefore we chose to incorporate also any revascularization as one of the composites of the primary endpoint. Indeed progression of coronary disease has been shown to progress by a repetitive process of atherosclerotic plaque rupture and healing[41] which may manifest as acute coronary syndrome or simply as progression of angina requiring revascularisation; a process that is influenced by multiple factors, including DAPT.

In this sense we could evaluate whether a longer DAPT compared to a short regimen may be able to influence the occurrence of events post DAPT therapy having influenced a possible plaque progression during a prolonged DAPT regimen. On the contrary if this is not true, a similar event rate during the follow up period without DAPT regimen in both arms should be expected.

Resolute Integrity stent

We chose as the recommended stent the Resolute Integrity stent (Medtronic Vascular, Santa Rosa, California), a second-generation thin strut cobalt-chromium stent that

elutes zotarolimus from a three blend composed biocompatible permanent polymer coating with an improved stent frame design. Two large randomised studies have shown non-inferiority for this stent against the golden-standard second-generation DES; the everolimus-eluting cobalt-chromium stent (EES)[42, 43]. Recent data from RCT's and RCT subanalyses have shown that the EES has an excellent safety profile, including in patients with STEMI and shows improved outcomes as compared to BMS as well as first generation DES[44, 45]. Importantly, these studies have shown that STEMI patients treated with EES do not have a higher incidence of stent thrombosis (ST) as compared to the rest of all comer patients as previously believed. Only few data regarding clinical outcomes of STEMI patients treated with this second generation stent are available, however, data from resolute all-comer STEMI population show that this stent is at least as good as EES [18]. In this perspective the prospective register of Resolute Integrity stent for use in STEMI would bring new insights on the outcomes of this new-generation DES in STEMI patient population.

Funding and trial registration

The DAPT-STEMI trial is registered on ClinicalTrials.gov (NCT01459627) and is approved by the local ethics committee. The trial is ongoing at investigative sites in the Netherlands, Norway, Poland and Switzerland. The trial has completed enrolment. August 2017 is the estimated data for final data collection and for primary outcome measure. The trial is funded by Maasstad Cardiovascular Research, Maasstad Hospital, Rotterdam, the Netherlands. The primary investigators and steering committee are solely responsible for the conduct of this study, all study analyses, the drafting and editing of the manuscript and its final contents.

Summary

The *DAPT-STEMI* trial is a prospective, randomized, multicentre, international open label trial which aims to enroll 1100 patients to assess whether restriction of DAPT therapy to 6 months post primary PCI with second generation DES is non inferior to the routine prolongation of such therapy to 12 months after intervention.

Reference:

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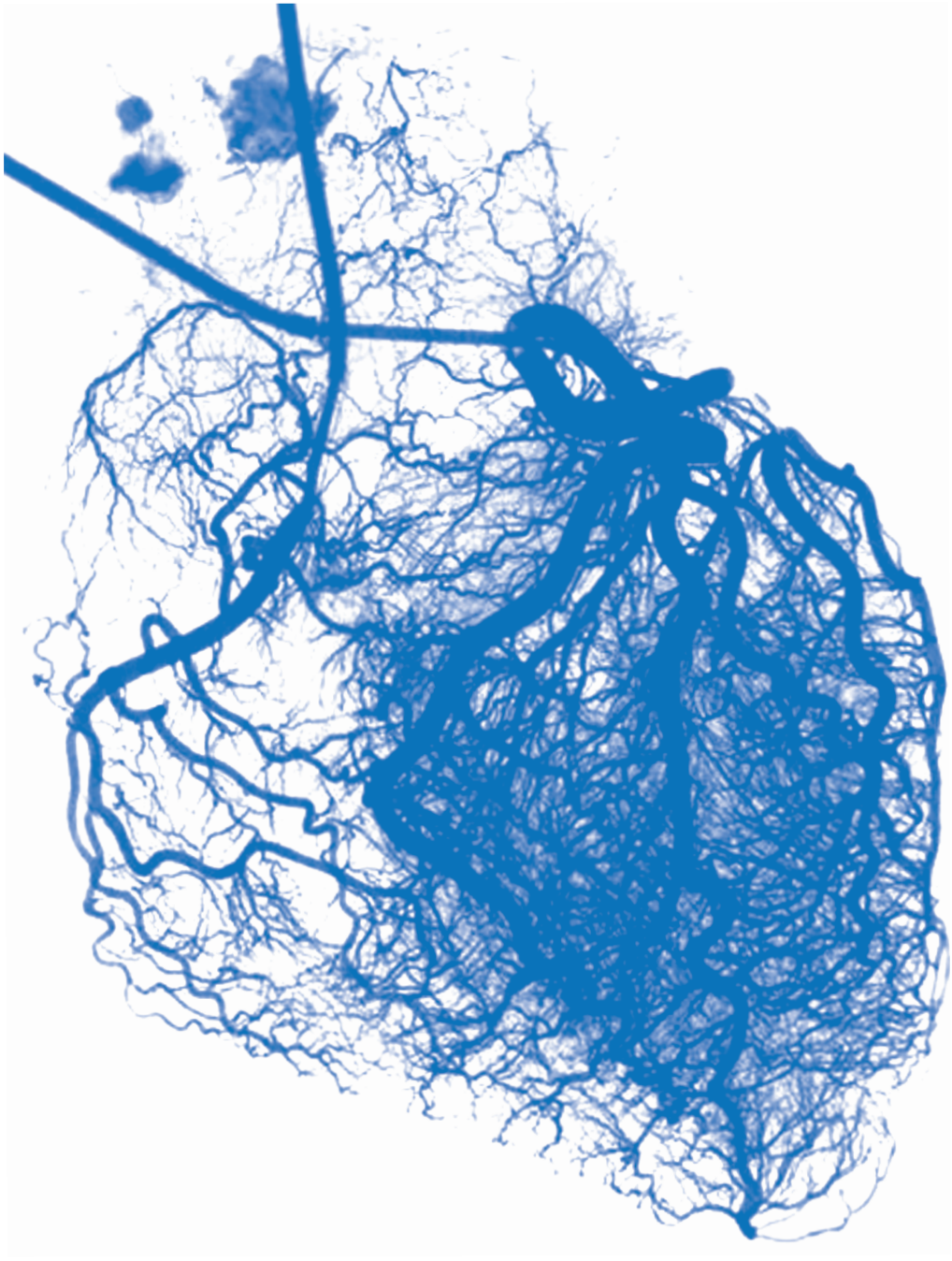

Chapter ten

6 months versus 12 months Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation in ST-Elevation Myocardial Infarction (DAPT-STEMI): a Randomized, Multicenter, Non-Inferiority Trial

Elvin Kedhi, **Enrico Fabris,** Martin van der Ent, Pawel Buszman, Clemens von Birgelen, Vincent Roolvink, Alexander Zurakowski, Carl E. Schotborgh, Jan C. A. Hoorntje, Christian Hasbø Eek, Stéphane Cook, Marco Togni, Martijn Meuwissen, Ria van Vliet, Hans Wedel, Ronak Delewi, Felix Zijlstra

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Abstract

Objectives: To demonstrate that limiting dual antiplatelet therapy (DAPT) duration to 6 months in event-free ST-elevation myocardial infarction (STEMI) patients results in a non-inferior clinical outcome versus a regimen of 12 months DAPT.

Design: Prospective, international, randomized, non-inferiority trial.

Setting: Patients with STEMI treated with primary percutaneous coronary intervention (PCI) and second-generation zotarolimus-eluting stent.

Participants: The trial enrolled STEMI-patients aged 18–85 years who underwent a primary PCI with the implantation of a second generation DES and only event-free patients at six months after primary PCI were randomized at this timepoint.

Interventions: Event-free patients on DAPT at 6-month were randomized in a 1:1 fashion to single antiplatelet therapy (SAPT i.e. aspirin only) or to DAPT for additional 6 months. All randomized patients were then followed for another 18 months (i.e. 2 years after the primary PCI).

Main outcome measures: The primary endpoint (PE) was a composite of all-cause mortality, any myocardial infarction, any revascularization, stroke, or major bleeding at 18 months after randomization.

Results: Between December 19, 2011, and June 30, 2015 a total of 1,100 patients were enrolled in the trial and 870 were randomized: 432 versus 438, in SAPT and DAPT, respectively. The PE occurred in 4.8% versus 6.6 %, in SAPT and DAPT respectively (HR 0.73; 95% confidence interval (CI), 0.41 to 1.27; P=0.26). Noninferiority was met (P for noninferiority =0.004), as the HR upper 95% CI of 1.27 was smaller than the pre-specified noninferiority margin of 1.66.

Between the SAPT and DAPT treatment groups, there was no statistically significant difference in the incidence of all-cause death (0.7% vs. 1.4%, HR 0.51, 95% CI 0.13 to 2.02, P=0.33); death from cardiac causes (0.5% vs. 0.9%, HR 0.51, 95% CI 0.09 to 2.76, P=0.43); MI (1.8% vs. 1.8%, HR 1.02, 95% CI 0.38 to 2.71, P=0.97); stroke (0.7% vs. 0.7%, HR 1.02, 95% CI 0.21 to 5.03, P=0.99); ST (0.7% vs. 0.9%, HR 0.76, 95% CI 0.17 to 3.39, P=0.72); and TIMI major bleeding (0.2% vs. 0.5%, HR 0.51, 95% CI 0.05 to 5.57, P=0.58).

Conclusions: 6-month DAPT duration was non-inferior to 12-month DAPT duration in event-free STEMI patients at 6-month after primary PCI with second generation DES. While optimal duration of DAPT in STEMI patients remains debated, this trial shows that when clinically mandated a shorter DAPT is feasible and safe setting the stage for further dedicated research on DAPT duration in STEMI patients.

Trial Registration: clinicaltrials.gov identifier: NCT01459627

Introduction

Dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) has been used primarily to avoid abruptly thrombotic closure of the vessel after stent implantation[1]. The duration of DAPT has been changed in the last decades, particularly after introduction of the first-generation drug-eluting stents (DES)[2]. The observed high rates of stent thrombosis (ST) with these devices[3] motivated the interventional community to empirically use a longer DAPT regimen up to 12 months, although there was a lack of evidence for this approach. The introduction of second-generation DES has drastically reduced the risk of ST as compared to first-generation and bare metal stents[4–6]. Different trials and meta-analyses have shown that shorter DAPT regimens after PCI with second-generation DES are equally safe; however, the optimal duration of DAPT remains a matter of debate[5,7–9]. Current international guidelines recommend at least 6 months of DAPT after PCI for stable ischemic coronary disease and 12 months in the setting of acute myocardial infarction (MI)[10,11]. For acute coronary syndromes this recommendation is derived from two randomized trials[12,13]. However, the observed benefit was noted only in the first months and may have been biased by the positive influence of upstream preloading with DAPT.

While DAPT reduces the risk of thromboembolic events in general, it is also associated with a higher risk of major bleeding[14] that sometimes can be fatal. The bleeding risk is patient-dependent and not always known before PCI, particularly before primary PCI in setting of an ST-segment elevation MI (STEMI). So far, no trial has shown that continuing DAPT from 6 to 12 months after primary PCI for STEMI is associated with any meaningful improvement of ST and/or other safety outcomes such as myocardial infarction, stroke, or death. As the safety and efficacy profiles of second-generation DES are superior to that of first-generation DES and bare metal stents, and considering the non-fully known bleeding risk prior to primary PCI, it may be appealing to consider a shorter DAPT for STEMI patients treated with second-generation DES.

Therefore, we performed a prospective, randomized trial of 6 versus 12 months of dual antiplatelet therapy after second-generation drug-eluting stent implantation in patients presenting with STEMI (DAPT-STEMI trial) to evaluate whether 6 months of DAPT is noninferior to 12 months of DAPT, in event free patients at 6-month follow-up after primary PCI.

Methods

Study design

The DAPT-STEMI trial (NCT01459627) is a prospective, international, randomized, open label, noninferiority trial designed to compare the clinical outcomes of 6 versus 12 months of DAPT in STEMI patients who underwent primary PCI with a second-generation DES. The trial was conducted at 17 study sites in the Netherlands, Norway, Poland, and Switzerland. The study design has been reported[15]. The trial was conducted in compliance with the International Conference on Harmonisation and the Declaration of Helsinki. The institutional review board of each participating institution approved the study. All the patients provided written informed consent.

Data were reviewed regularly throughout the trial by an independent data and safety monitoring committee. An independent academic clinical-events committee (Diagram), whose members were unaware of the group assignments, adjudicated all endpoints using standard definitions (supplementary material). An independent, blinded core laboratory judged revascularization and ST endpoints. DAPT-STEMI is an investigator driven trial, the trial was sponsored form the Maasstad Cardiovascular Research, Maasstad Hospital, Rotterdam, the Netherlands and from an unrestricted research grant from Medtronic. Statistical design and analysis were performed by statisticians from University of Sahlgrenska Gothenburg, Sweden; University of Amsterdam, Amsterdam, the Netherlands; and Diagram BV (CRO), Zwolle, the Netherlands. The first draft of the manuscript was written by the first two authors and revised based on comments and suggestions of all other co-authors. The corresponding author had full access to the data, and vouches for the integrity of the analyses presented and the adherence of the trial to the protocol (available on-line). All authors had full responsibility for the decision to submit for publication.

Participant Selection

The trial population consisted of STEMI-patients aged 18–85 years who underwent a primary PCI with the implantation of a second-generation DES. Patients who fulfilled the inclusion and exclusion criteria (eTable 1 in the supplementary material) were enrolled after the primary PCI procedure. All patients were followed during the first 6 months; event-free patients at 6-month follow-up who fulfilled the randomization criteria were at this timepoint randomized to either stop or continue DAPT for an additional 6 months. All randomized patients were then followed for another 18 months (i.e. 2 years after the primary PCI). (e-Fig 1)

Interventions

All STEMI patients were treated according to standard clinical practice. The choice of the vascular access route (i.e. radial versus femoral) was left to the discretion of the operator, although radial approach was strongly recommended to avoid bleeding complications at the puncture site. Thrombus aspiration and lesion predilatation were left to the discretion of the operator. The stent device used was the second-generation zotarolimus-eluting stent Resolute Integrity (R-ZES) (Medtronic, Santa Rosa, CA).

In accordance with international revascularization guidelines[10,11], DAPT consisting of: aspirin (ASA) 150-300 mg orally or 250-500 mg bolus intravenously followed by 75-100 mg daily, and prasugrel 60 mg loading dose followed by 10 mg daily or ticagrelor 180 mg loading dose followed by 90 mg twice daily was initiated and continued for 6 months. Patients ≥75 years of age and with a body weight of <60 kg were treated with prasugrel 60 mg loading dose but followed by 5 mg prasugrel daily. Patient treated with clopidogrel received 600 mg loading dose followed by 75 mg daily for 6 months. After 6 months, patients who fulfilled the inclusion and exclusion criteria were randomized, to either discontinue DAPT (i.e. aspirin only) or continue DAPT for another 6 months after randomization (i.e. until 12 months after primary PCI) (e-Figure 1 in Supplementary material). In all patients, aspirin 80-100 mg daily was continued indefinitely.

If required, additional (scheduled) staged revascularizations in non-culprit lesions were performed within 45 days from the primary PCI. However, even in these cases, the time of 6-month follow-up was based on the date of the initial (primary) PCI. All randomized patients were followed for 18 months after randomization (i.e. 2 years after primary PCI).

Outcome Measures

The primary endpoint of this trial is a patient-oriented composite endpoint of all-cause mortality, any myocardial infarction (MI), any revascularization, stroke, or thrombolysis in Myocardial Infarction (TIMI) major bleeding at 18-month follow-up after randomization (i.e. 2 years after primary PCI). The major secondary endpoint was a composite of all-cause mortality, any MI, stroke, ST, or TIMI major bleeding at 18-month follow-up after randomization. Additional clinical endpoints were the individual components of the primary endpoint. Trial endpoint definitions are provided in the Supplementary Material. For the purpose of the primary endpoint, MI were adjudicated based on the ARC definitions [16]. Stroke was defined as any acute neurological event with a duration of at least 24 hours, with focal signs and symptoms and without evidence supporting any alternative explanation, and

confirmed by imaging by computed tomography or magnetic resonance imaging, or by pathological evidence. Bleeding was evaluated based on the TIMI bleeding classification[17].

Sample Size and Statistical Analyses

The trial was designed to test the hypothesis that single therapy with aspirin after 6 months in event-free STEMI patients would be noninferior to DAPT with respect to the primary endpoint. The Hazard Ratio (HR) of the primary endpoint in the treatment and control group were estimated with the use of a Cox proportional-hazards model. A pre-defined noninferiority margin of 1.66 was used in this trial. Non-inferiority of SAPT versus DAPT will be concluded if the estimated 95% confidence interval (CI) of the HR lies entirely below this margin. If the upper limit of the 95% CI exceeds this margin we do not reject the null hypothesis of inferiority. The noninferiority margin chosen in our trial, reflects the knowledge from other trials within cardiology that were available in the literature when this trial was designed [18–21].

The sample size was calculated under the assumption that the α value was 0.05 for a 2-sided test (0.025 for a 1-sided test) with a power of 85%. The endpoint at 18 months after randomization was assumed to be 15%. Taking into account patients non-eligible to randomization due to clinical events in the first 6 months or other exclusion criteria, a total sample size of 1,100 patients was required.

The primary analysis, which was performed on an intention-to-treat basis, included all patients who underwent randomization, regardless of whether they received treatment. The results for the primary endpoint are presented as time to event curves (Kaplan-Meier). The p-values comparing the clinical outcomes in the treatment groups are based on logrank tests. Hazard ratios (HRs) and corresponding 95% CIs were calculated using Cox proportional hazards models. The p-value for non-inferiority was calculated by testing the estimated HR against the non-inferiority HR of 1.66. Indeed, we assume an approximate posterior distribution for the treatment effect based on the estimated HR and its standard error, and use this to derive the probability that the true HR is above 1.66. All tests were two tailed and conducted at a significance level of 0.05. Data for patients who did not have an endpoint event were censored for the analysis of that endpoint at the time of the last known contact or at 18 months (i.e. 2 years after the primary PCI), whichever was earlier. For descriptive purposes, a sensitivity analysis on a per protocol basis for the primary endpoint was performed. Analysis were performed with SPSS version 24 and SAS version 9.4.

Patient and public involvement.

No patients were involved in setting the research question or the outcome measures,

nor were they involved in developing plans for design or implementation of the study. However the central ethical committee (as every committee in the Netherlands) has a special member, the patient committee representative, which task is to look at the design and the implementation of the trial from a patient perspective. The ethical committee could not give a positive advice in case there are still unresolved comments from the patient representative member. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Results

Characteristics of the Study Patients

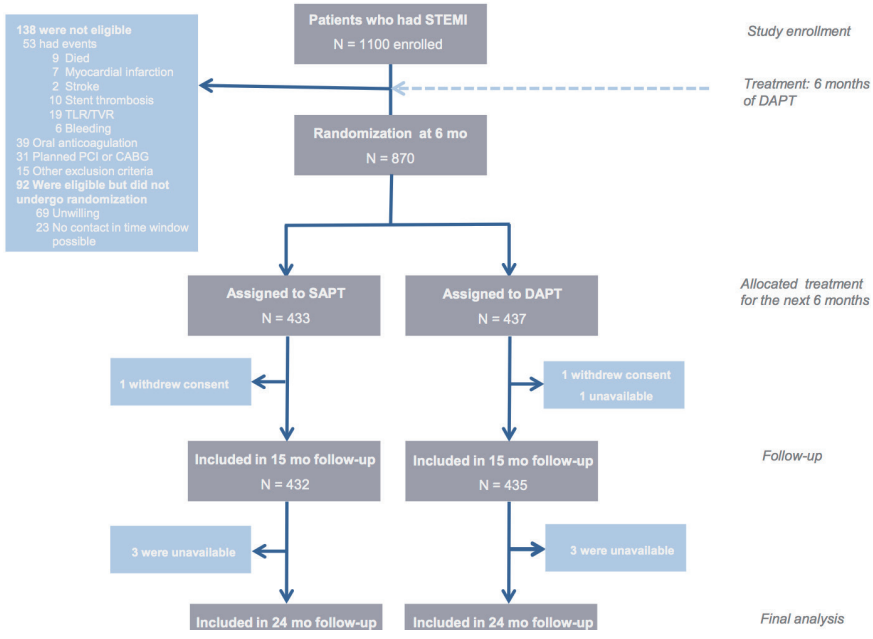
Between December 19, 2011, and June 30, 2015 a total of 1,100 patients were enrolled in the trial. Among these patients, for various reasons, 230 (21.0%) were *not* randomized after 6 months of follow-up (Figure 1). Of these 230 patients, 138 were not eligible for randomization: 55 patients had events during the first 6 months while 83 did not fulfil other randomization criteria. A total of 92 patients were eligible but were not randomized (Figure 1). Among those who were eligible but did not undergo randomization, the most common reason was withdrawal of consent during the 6 months between enrollment and randomization (69). A total of 870 patients were randomized.

Complete information on the primary endpoint was obtained for 99% of the randomized patient population. One patient was lost to follow-up at 15 months, 2 patients withdrew consent, and 6 patients were unavailable for the final 18-month follow-up (i.e. 2 years after the primary PCI), but were known to be alive then (Figure 1).

The two treatment groups were well balanced with respect to baseline characteristics (Table 1). Patients were on average 60 years old, and 76.9% of them were male.

In the trial 6 patients received shorter than 12 months DAPT in the DAPT arm; 2 of these patients had bleeding events while 4 because of poor compliance. Similarly, 14 patients in the SAPT arm received longer than 6 months DAPT of which 4 patients received SAPT with P2Y12 inhibitor, while 10 continued DAPT without evident reason. These crossovers were based on patient or treating physician's preference. None of these patients had major cardiac adverse events.

Figure 1. Enrolment, Randomization, and Follow-up.
Shown is the distribution of patients during enrolment, randomization, and follow up (final follow up 18 months after randomization (i.e. 24 months after the primary PCI). Complete information on the primary endpoint was obtained for 99% of the randomized patient population.



STEMI denotes ST-segment elevated myocardial infarction; MO denotes months; DAPT denotes dual Antiplatelet Therapy; SAPT denotes Single Antiplatelet therapy; PCI denotes percutaneous coronary intervention; CABG denotes coronary artery bypass graft; TLR denotes target lesion revascularization; TVR denotes target vessel revascularization; CAD; coronary artery disease, CABG denotes coronary artery bypass graft; DAPT; dual antiplatelet therapy, LAD; left anterior descending, , RCA; right coronary artery, RCX: right circumflex artery, SAPT; single antiplatelet therapy, STEMI; ST-segment elevated myocardial infarction, TIA: transient ischemic attack

Table 1. Characteristics of the study population

	SAPT (N=433)	DAPT (N=437)
Patient characteristic		
Age – years	59.8 ± 10.7	60.2 ± 10.3
Male gender	337/433 (78%)	332/437 (76%)
Body-mass index	27.8 ± 4.3	27.9 ± 4.5
Medical history		
Prior CABG	8/433 (2%)	2/437 (0.5%)
Prior PCI	29/433 (7%)	18/437 (4%)
Prior myocardial infarction	26/433 (6%)	20/436 (5%)
Stroke or TIA	14/433 (3%)	8/436 (2%)
Peripheral arterial disease	16/433 (4%)	9/436 (2%)
Congestive heart failure	16/433 (4%)	19/436 (4%)
Risk factors		
Diabetes mellitus	54/433 (13%)	61/437 (14%)
Hypertension	193/433 (45%)	195/436 (45%)
Dyslipidaemia	120/433 (28%)	125/436 (29%)
Current cigarette smoker	218/431 (51%)	205/437 (47%)
Family history of CAD	143/431 (33%)	144/436 (33%)
Medication at start of study		
P2Y12 inhibitors		
Clopidogrel	180/433 (42%)	182/437 (42%)
Prasugrel	128/433 (29%)	132/437 (30%)
Ticagrelor	125/433 (29%)	123/437 (28%)
Percutaneous coronary intervention		
TIMI flow		
Baseline TIMI flow <3	355/432 (82%)	355/437 (81%)
Post PCI TIMI flow 3	411/433 (95%)	421/436 (97%)
Infarct related artery		
LAD	169/433 (39%)*	188/437 (43%)
RCA	175/433 (41%)	179/437 (41%)
RCX	89/433 (21%)	70/437 (16%)
Lesion type culprit		
B2	158/428 (37%)	158/433 (36%)
C	108/428 (25%)	101/433 (24%)
Stent type culprit¥		
Zotarolimus-eluting stent	400/432 (93%)	407/436 (93%)
Other	32/432 (7%)	29/436 (7%)
Index procedure		
No. of treated lesions	1.09 ± 0.3	1.10 ± 0.3
No. of treated vessels	1.08 ± 0.3	1.07 ± 0.3
No. of stents total	1.42 ± 0.8	1.48 ± 0.8
Total stent length total – mm	28.5 ± 16	29.8 ± 16
Minimum stent diameter Ω		
< 3 mm	189/613 (31%)	178/645 (28%)
≥ 3 mm	424/613 (69%)	467/645 (73%)
Non culprit lesion intervention	54/433 (12.5%)	62/437 (14%)

valid %

* 1 patient had left main as infarct related artery.

¥ 1 patients received plain old balloon angioplasty without additional stenting

Ω total is number of stent used during index procedure

CAD; coronary artery disease, CABG; coronary artery bypass graft; DAPT; dual antiplatelet therapy, LAD; left anterior descending, PCI; percutaneous coronary intervention, RCA; right coronary artery, RCX: right circumflex artery, SAPT; single antiplatelet therapy, STEMI; ST-segment elevated myocardial infarction, TIA: transient ischemic attack

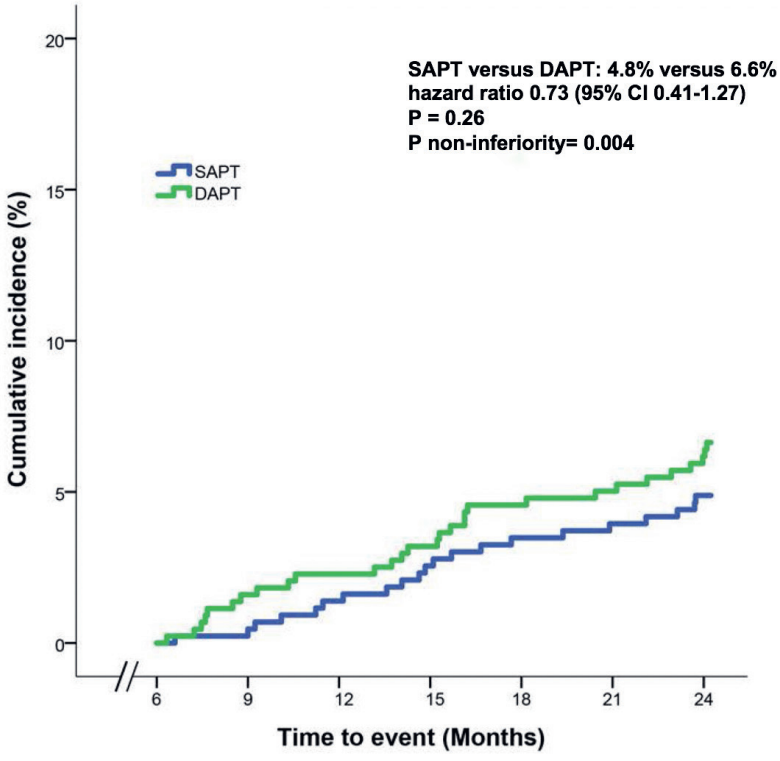
Primary Endpoint

During 18 months after randomization (i.e. 2 years after the primary PCI), the primary endpoint, a composite of all-cause mortality, any myocardial infarction, any revascularization, stroke, or TIMI major bleeding occurred in 4.8% in the single antiplatelet therapy group versus 6.6% in the DAPT group (hazard ratio vs. dual antiplatelet therapy, 0.73; upper 95% confidence interval [CI], 0.41 to 1.27; P=0.26). Noninferiority was met (*P* for noninferiority =0.004), as the upper CI interval of 1.27 is smaller than the pre-specified noninferiority margin of 1.66 (Table 2 and Figure 2).

The per-protocol analysis of the primary endpoint confirmed the result of the main (intention-to–treat) analysis, (hazard ratio 0.74; upper 95% CI 0.42 to 1.30, *P* noninferiority =0.005).

The HR proportionality assumption was examined by graphical checks (e-Figure 2) and by applying supremum tests (e-Figure 3) using the assess statement in Proc PHREG in SAS. Non-inferiority of SAPT vs DAPT calculated across different thresholds of the HR is showed in table 3. As presented in this table the trial could prove the noninferiority not only for the chosen noninferiority margin of 1,66 but for any HR margin above 1.2.

Figure 2. Cumulative incidence of the primary composite endpoint.
Cumulative incidence curves are shown for the primary composite endpoint of all-cause mortality, any myocardial infarction, any revascularization, stroke, and Thrombolysis in Myocardial Infarction (TIMI) major bleeding at 18 months after randomization, in the intention-to-treat population. The number at risk was defined as the number of patients who had not had the event of interest and who were available for subsequent follow-up.



DAPT denotes Dual Antiplatelet Therapy; SAPT denotes Single Antiplatelet Therapy

Table 2. Clinical outcomes at 18 months after randomization

	SAPT (N=433)	DAPT (N=437)	Hazard ratio SAPT vs. DAPT (95% CI interval)	P-Value
Primary endpoint				
Composite of all-cause mortality, any MI, any revascularization, stroke and TIMI major bleeding (net adverse clinical events)	21 (4.8%)	29 (6.6%)	0.73 (0.41 to 1.27)	0.26 0.004 for non-inferiority
Secondary endpoints				
Composite of all-cause mortality, any MI, stent thrombosis, stroke and TIMI major bleeding	14 (3.2%)	19 (4.3%)	0.75 (0.37 to 1.49)	0.40
Death	3 (0.7%)	6 (1.4%)	0.51 (0.13 to 2.02)	0.33
Cardiac	2 (0.5%)	4 (0.9%)	0.51 (0.09 to 2.76)	0.43
Stroke	3 (0.7%)	3 (0.7%)	1.02 (0.21to 5.03)	0.99
Myocardial infarction	8 (1.8%)	8 (1.8%)	1.02 (0.38 to 2.71)	0.97
Stent thrombosis	3 (0.7%)	4 (0.9%)	0.76 (0.17 to 3.39)	0.72
Target lesion failure*	5 (1.2%)	8 (1.8%)	0.63 (0.21 to 1.93)	0.42
Revascularization	13 (3.0%)	17 (3.9%)	0.87 (0.42 to 1.83)	0.72
Urgent	8 (1.8%)	13 (3.0%)	0.83 (0.34 to 1.99)	0.67
Target lesion	4 (0.9%)	4 (0.9%)	1.02 (0.25 to 4.06)	0.98
Target vessel, non-target lesion	2 (0.5%)	5 (1.1%)	0.40 (0.08 to 2.08)	0.28
Non-target vessel	6 (1.4%)	10 (2.3%)	0.76 (0.26 to 2.18)	0.61
Bleeding	3 (0.7%)	5 (1.1%)	0.61 (0.15 to 2.53)	0.49
TIMI major	1 (0.2%)	2 (0.5%)	0.51 (0.05 to 5.57)	0.58
BARC type 3	2 (0.5%)	4 (0.9%)	0.50 (0.09 to 2.75)	0.43
Hospitalization	33 (7.6%)	38 (8.7%)	0.92 (0.58 to 1.48)	0.74
Cardiac	26 (6.0%)	33 (7.6%)	0.84 (0.50 to 1.42)	0.52
Chest pain	11 (2.5%)	13 (3.0%)	0.93 (0.41 to 2.10)	0.85

* Target lesion failure is defined as cardiac death, target lesion revascularization or target lesion myocardial infarction. P-values were calculated with the use of a log rank test.

Data are presented for the intention-to –treat population. Percentages are Kaplan-Meier estimates. P values were calculated with the use of a log-rank test. BARC: Bleeding Academic Research Consortium MI; myocardial infarction, TIMI; Thrombolysis in Myocardial Infarction

Table 3. Non-inferiority of SAPT vs DAPT calculated across different thresholds of the HR

Linear Hypotheses Testing Results				
	Threshold	Wald Chi-Square	DF	Pr > ChiSq
	HR 1.1	2.1037	1	0.1469
	HR 1.2	3.0768	1	0.0794
	HR 1.3	4.1349	1	0.0420
	HR 1.4	5.2536	1	0.0219
	HR 1.5	6.4154	1	0.0113
	HR 1.66	8.3323	1	0.0039

Wald statistic was used to test the estimated parameter against a hypothetical population value. The Wald test was computed as the squared difference of the parameter estimate (B) against the hypothetical value divided by the standard error estimate. In a test for the global null hypothesis the parameter estimate was tested against a value of 0 (HR=1). The other tests tested whether the estimated parameter differs from 0.095 for a HR of 1.1, from 0.182 for a HR of 1.2 etc. The Wald test was performed using Proc PHREG in SAS 9.4.

Secondary Endpoints

The major secondary endpoint, a composite of safety and bleeding at 18 months (i.e. 2 years after the primary PCI),, occurred in 3.2% in the single antiplatelet therapy group versus 4.3% in the DAPT group (hazard ratio 0.75, 95% CI 0.37 to 1.49, P = 0.40). Between the two treatment groups, there was no statistically significant difference in the incidence of all-cause death (0.7% vs. 1.4%, HR 0.51, 95% CI 0.13 to 2.02, P=0.33); death from cardiac causes (0.5% vs. 0.9%, HR 0.51, 95% CI 0.09 to 2.76, P=0.43); MI (1.8% vs. 1.8%, HR 1.02, 95% CI 0.38 to 2.71, P=0.97); stroke (0.7% vs. 0.7%, HR 1.02, 95% CI 0.21 to 5.03, P=0.99); ST (0.7% vs. 0.9%, HR 0.76, 95% CI 0.17 to 3.39, P=0.72); and TIMI major bleeding (0.2% vs. 0.5%, HR 0.51, 95% CI 0.05 to 5.57, P=0.58). (Table 2).

Discussion

Principal findings

This study is the first dedicated randomized clinical trial to compare 6 versus 12 months of DAPT after primary PCI for STEMI. The trial demonstrated that limiting DAPT duration to 6 months' in event free patients resulted in a noninferior clinical outcome, as assessed by the patient-oriented composite clinical endpoint of safety, efficacy, and bleeding, versus the currently recommended regimen of 12 months DAPT. Furthermore, no significant difference was observed with regard to the major secondary composite endpoint of safety and bleeding. In addition, neither statistically significant nor meaningful numerical differences were observed for the components

of the primary endpoint: death, MI, ST, stroke, any revascularisation, or TIMI major bleeding. The primary endpoint, as well as all its individual components showed low event occurrence in both treatment arms, suggesting that event-free patients at 6 months remain at a low risk for further events, irrespective of whether DAPT is continued or not. Our findings are in line with those of other randomized studies which compared 6 versus 12 months of DAPT[22–24]; as a consequence, we feel that they truly represent the low event reality that is seen after PCI with second generation DES. In this perspective, nowadays – in the era of second generation DES – the perception that STEMI patients treated with primary PCI are at a higher risk for stent-related adverse events than patients who underwent PCI for other clinical indications and therefore require longer DAPT is challenged. Another interesting finding which can be observed form the Kaplan-Meier curves is that the discontinuation of DAPT (both in the 6 and 12-month arm) was not associated with a rebound effect on primary endpoint events. This may suggest that DAPT may have no further protective effect beyond these points in time, however further data are needed to explore specifically the potential rebound effect of DAPT discontinuation at different time points.

The low event rates after primary PCI with the second-generation R-ZES might be attributed to the improved design of this device, as compared to first-generation DES. Indeed, thinner stent struts favour a better and homogeneous endothelial strut coverage as compared to the thicker stainless steel struts of the first-generation DES [25], and DES with thin struts have shown a low risk of adverse cardiovascular events in patients with a variety of clinical syndromes[26]. The R-ZES uses a biocompatible durable polymer that enables longer drug elution and has shown to significantly affect the amount of neointima compared with the previous zotarolimus-eluting platform[27]. Moreover the almost complete neointimal coverage within 3 months after the implantation of R-ZES, as observed by optimal coherence tomographic studies, supports a shorter need for DAPT[28,29].

On the other hand, it is well–known that patients presenting with STEMI may have multiple complex coronary plaques, associated with a generally increased risk of adverse cardiovascular events[30], as well as other vulnerable plaques with traits of instability elsewhere in their coronary tree [31]. Nevertheless, nowadays remaining complex "non-culprit" lesions are generally treated after or even during the primary PCI. Regarding the remaining non-significant lesions with traits of "vulnerability", the current understanding is that many of these characteristics may be short–lived, as in most cases these plaques progress through a process of asymptomatic plaque rupture and healing to more stable atherosclerotic lesions while other plaques remain unchanged[32]. Therefore, based on this current understanding of atherosclerosis progression, it is much more likely that these plaques may remain clinically silent or

manifest as stable rather than an acute coronary syndrome. Therefore, while DAPT in setting of secondary prevention may reduce cardiovascular events originating from atherosclerosis progression elsewhere in the coronary tree[33,34], these events are rare and the magnitude of ischemic events reduction may not outweigh the increase in bleeding risk, related to long DAPT duration, as recently shown in the Pegasus[33] and DAPT[35] trials. Major bleeding is an adverse event that is strongly related to mortality[36]. Recent studies have even shown that bleeding is a stronger predictor of non-cardiovascular mortality than thromboembolic and ischemic events[36,37]. Indeed, long DAPT did not impact mortality in the Pegasus trial[33] and OPTIDUAL trial[38], but it was associated with a higher all-cause mortality in the DAPT trial[35]. Therefore the findings of our trial for a combined endpoint of ischemic and bleeding event, is very much in line also with the findings of these trials. Based on this evidence and considering that atherosclerosis is a life-long process, the role of DAPT in secondary prevention remains questionable. While DAPT does not have a major impact on atherosclerosis progression which in large extent is based on rupturing and healing of plaques, it might have some impact on its clinical presentation. In other words: the use of DAPT may result in more patients presenting with stable angina pectoris rather than acute coronary syndromes[39]. As this could influence the need for ischemia-driven revascularization during the treatment period, we incorporated the end point "any revascularisation" into the primary clinical end point of the present trial.

Finally given the potential trade-off between ischaemic vs. bleeding risks for any given DAPT duration, the use of scores might prove useful to tailor DAPT duration[11]. However while the DAPT score[40] estimate ischemic and bleeding risks for DAPT prolongation and the PRECISE DAPT[41] and PARIS[42,43] risk scores provide prediction of bleeding during DAPT supporting clinical decision making for treatment duration, none of these risk prediction models have been prospectively tested in the setting of randomized controlled trial, and even less in STEMI populations, and therefore, their value in improving patient outcomes remains unknown.

Limitations of the study

This study has limitations. The primary endpoint is a combined endpoint of MACCE and bleeding. While this endpoint might not give clear insights for each of these components, considering the bivalent impact of DAPT so much in ischemic as well as bleeding outcomes we believe this endpoint gives better insights to the overall patient outcome. Moreover, individual clinical endpoints were not in opposite directions when comparing DAPT versus SAPT. Excluding the patients with events in the 6-months does indeed introduce a bias of low risk patients, however, rather than being a selection bias, it reflects more the trial design.

In the presented trial the rate of patients enrolment was not high. This may reflect the absence of previous data in this settings and the difficulties to obtain patients consent to the participation in the trial, this was also reflected by the high percentage of consent withdraw at 6 months.

The lower than estimated occurrence of events in both arms, while it might be perceived as another limitation of this trial, it rather reflects the design of this trial: only patients, who were event-free at 6 months, were randomized, which may have excluded a certain proportion of higher risk patients from randomization. Furthermore, the observed event occurrence is in line with previous trials in the field performed with modern DES[23,44]. To avoid the biases that the low event occurrence could introduce to a non-inferiority design based on a fix percentage of the expected event, we chose for a non-inferiority design based on HR. In this model, lower than expected event occurrence would enlarge the confidence intervals and therefore challenge the non-inferiority, however this was not the case in our trial as the HR was 0.73 and the upper CI was 1.27, much lower than the prespecified margin of 1.66. Considering that our endpoint did combine ischemic and bleeding events, we were indeed expecting a numerical benefit for SAPT[23,33,35,44], and therefore we could have chosen a more conservative non-inferiority margin than 1.66, however taking in account a possible chance finding (a numerical benefit in favour of DAPT) we chose a wider margin. It has to be noted that the large non-inferiority margin did not influence the observed non-inferiority as a post hoc analysis showed that the trial would have proved non-inferior even for a much conservative non-inferiority margin of 1,3 (table 3).

Another limitation is that fewer patients than predicted were randomized at 6-month follow-up. The design of the trial in which only event-free patients at 6 months could be randomized contributed to this issue; other reasons were the higher than expected percentage of withdrawal of informed consent as well as the treatment of non-culprit coronary lesions outside the pre-specified accepted time window for staged PCI procedures, which we could not predict when designing the trial. Indeed, the last also explains in part why the number of non-culprit lesion treatment in this trial appears low. However a post-hoc analysis showed that the number of actual versus planned randomised patients had only a minimal influence in the trial power reducing it with only 3 %.

The time from the onset of the pain till revascularization as well as door to balloon time were not recorded in this trial, however considering that the randomization occurred only at 6 months in event free patients such information would not impact importantly the trial outcomes.

Per protocol, the choice of the P2Y12 inhibitor prescribed was at the operators' discretion reflecting the guidelines when this trial was designed. As can be observed in the baseline table, the different P2Y12 inhibitors were similarly distributed between treatment groups. Different P2Y12 inhibitors have different outcomes in safety endpoints and or bleeding[45]; however, potential differences in outcomes between patients treated with different P2Y12 inhibitors can only be appreciated in studies with much larger size than our present trial. Furthermore, because we used a combined (bleeding and MACE) endpoint any possible advantage of Ticagrelor or Prasugrel in ischemic outcomes is counterbalanced from the bleeding outcomes therefore we do not expect that use of clopidogrel did introduce any bias in our results, and if so it would rather underestimate the SAPT benefit. Moreover, according to guidelines when neither of new P2Y12 inhibitors is available, or if they are contraindicated, clopidogrel should be given. Thus the presence of clopidogrel in our trial may still be of importance for those patients that are treated with clopidogrel especially in countries which, for economic reasons, cannot afford the cost of new P2Y12 inhibitors.

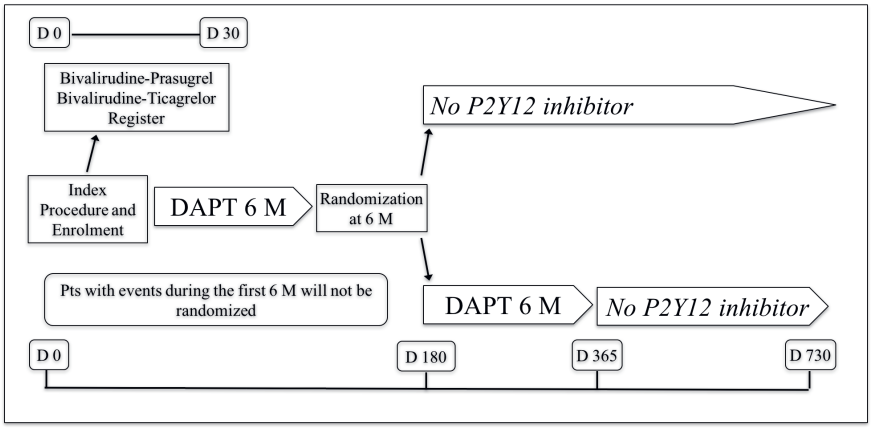
The R-ZES was used in 93% of the patients and thus further studies with other second generation DES are eventually required to establish the extension of this finding. Finally, although cardiogenic shock was not an exclusion criteria for enrollment, patients with overt cardiogenic shock were not enrolled because of their incapability to provide inform consent and therefore the results of the trial cannot apply for these patients as well as for patients with lesions requiring left main stenting who were excluded from the trial.

Conclusions

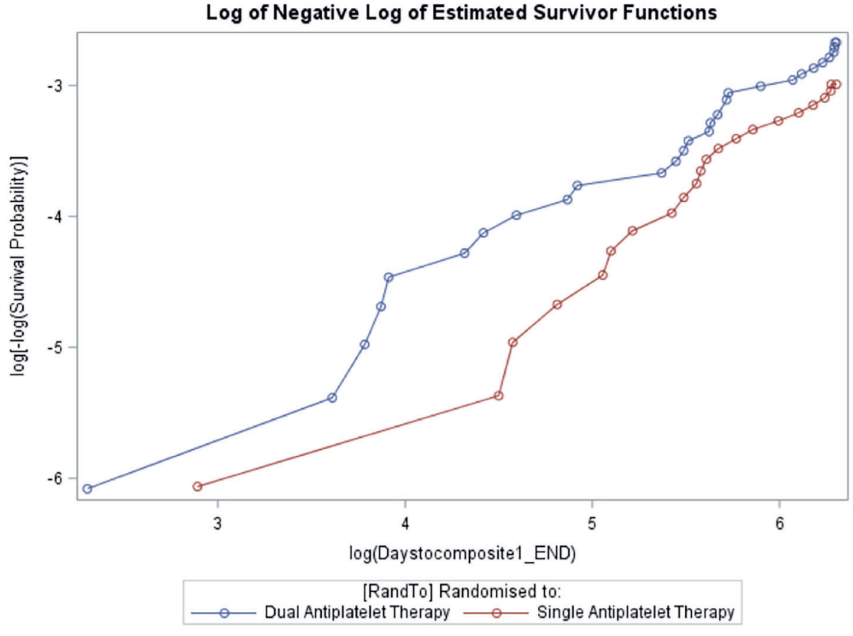
In patients who are event-free 6 months after primary PCI with second generation DES, a 6-month duration of DAPT was associated with outcomes not inferior to those observed after 12 months of DAPT. While larger trials have shown that longer duration of DAPT regimens might be associated with favourable ischemic outcomes, this trial for the first time shows that a shorter DAPT duration is also feasible and safely applicable if clinically required even in STEMI patients, setting the stage for further dedicated research on DAPT duration in this high-risk patient category.

Supplementary figures

E- figure 1. Study Flow chart

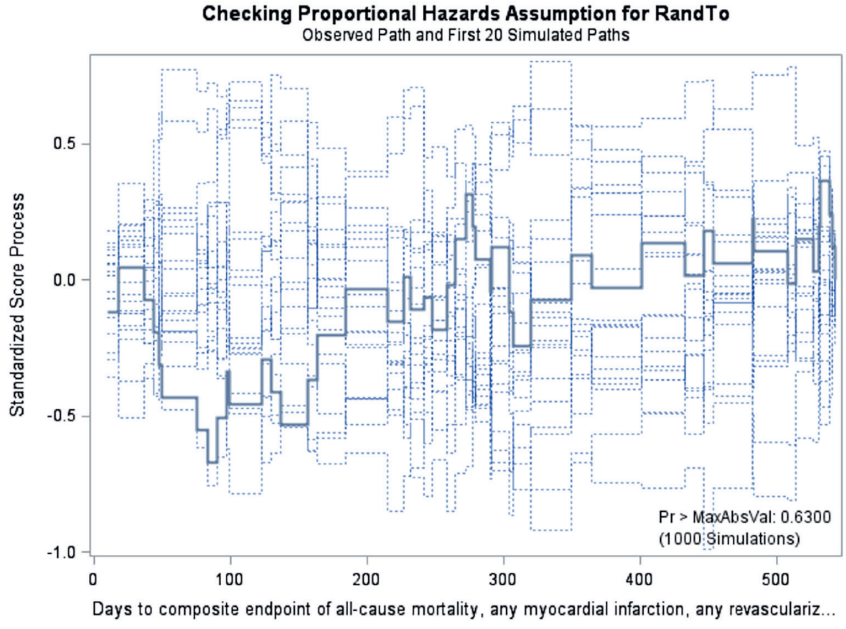


E- figure 2. Graphical checks examining HR proportionality assumption



Graphical checks: If the two lines are parallel, then the hazards can be considered proportional

E-figure 3. Supremum test examining HR proportionality assumption



Supremum Test for Proportionals Hazards Assumption				
Variable	**Maximum Absolute Value**	**Replications**	**Seed**	**Pr > MaxAbsVal**
RandTo	0.6715	1000	1963961059	0.6300

The supremum test p-value of 0.63 indicates that the proportional hazards assumption does hold when comparing SAPT vs. DAPT.

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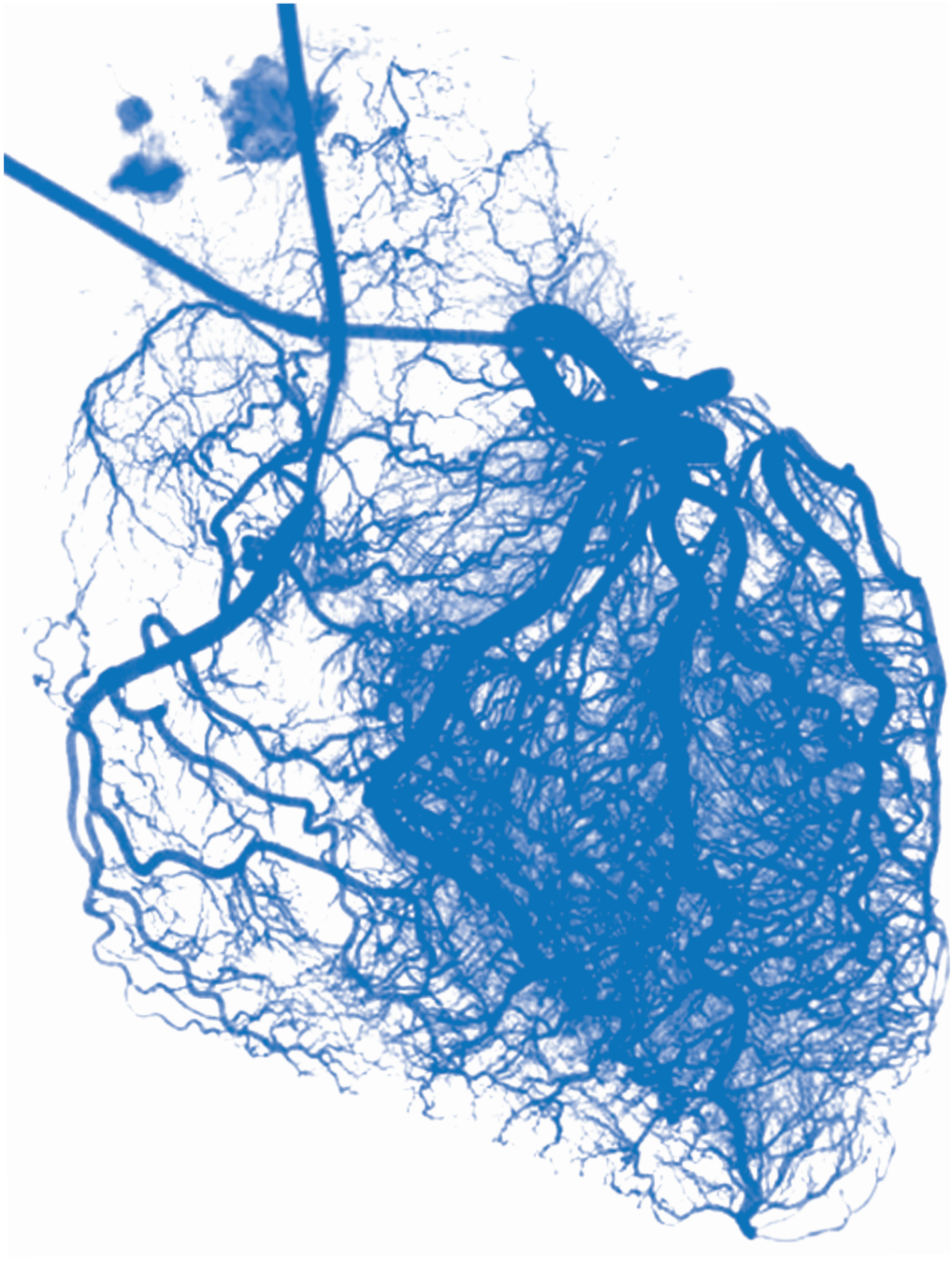

Chapter eleven

Summary, final comments and future perspectives

Summary of this thesis

The achievement of early myocardial reperfusion is one of the main goals in ST elevation myocardial infarction (STEMI) for reducing infarct size and improving prognosis. This thesis investigated the potential factors influencing myocardial tissue reperfusion before and after primary percutaneous coronary intervention (PCI) in the contemporary era of STEMI treatment. Moreover it focused on the role of different antithrombotic/antiplatelet therapies in STEMI patients for improving myocardial reperfusion and clinical outcomes. Finally it evaluated the optimal duration of dual-antiplatelet therapy (DAPT) after primary PCI investigating the safety and efficacy of a short DAPT duration after primary PCI.

In **chapter 2** we described how the angiography and serial electrocardiograms (ECG's) are important for the assessment of reperfusion, and in particular for the evaluation of microvascular and tissue-level reperfusion. The use of some angiographic parameters and ST-segment resolution (STR) are also useful tools to investigate the impact of therapies on myocardial reperfusion and they can be used as surrogate markers of clinical outcomes.

In **chapter 3** we identified the predictors of complete STR pre-primary PCI in patients enrolled in the ATLANTIC trial, a randomized study comparing pre-Hospital (pre-H) vs in-Hospital (in-H) treatment with ticagrelor loading dose in acute STEMI. We showed that complete STR (defined as ≥70%), which occurred pre-PCI in 12.8% of patients, predicted lower 30-days composite MACCE (OR=0.10, 95%CI 0.002-0.57; p=0.001) and total mortality (OR=0.16, CI 0.004-0.95;p=0.035). The independent predictors of complete-STR included the time from index event to pre-H ECG (patients delay) (OR=0.94, CI 0.89-1.00; p=0.035), use of heparins before pre-PCI-ECG (OR=1.75, CI 1.25-2.45; p=0.001) and time from pre-H-ECG to pre-PCI-ECG (OR=1.09, CI 1.03-1.16; p=0.005). Interestingly in the pre-H ticagrelor administration group, patients with complete STR had a significantly longer delay between pre-H-ECG and pre-PCI-ECG compared to patients without complete STR [median 53 (44-73) vs 49 (38.5-61) (mins);p=0.001]; however, this was not observed in the control group (in-hospital ticagrelor) [50 (40-67) vs 49 (39-61);p=0.258]. Therefore this study showed that short patient delay, early administration of anticoagulant and ticagrelor if long transfer delay is expected, may help achieve reperfusion prior to PCI and that pre-H treatment may be beneficial in patients with longer transfer delays allowing the drug to become biologically active.

In **chapter 4** we evaluated the predictors of complete STR after primary PCI in patients enrolled in the ATLANTIC trial. Complete STR occurred post-PCI in 54.9% of

patients and predicted lower 30-day composite MACCE (OR 0.35, 95% CI 0.19-0.65; p<0.01), definite stent thrombosis (OR 0.18, 95% CI 0.02-0.88; p=0.03), and total mortality (OR 0.43, 95% CI 0.19-0.97; p=0.04). Independent negative predictors of complete STR were the time from symptoms to pre-H ECG (OR 0.91, 95% CI 0.85-0.98; p<0.01) and diabetes mellitus (OR 0.6, 95% CI 0.44-0.83; p<0.01); pre-H ticagrelor treatment showed a favourable trend for complete STR (OR 1.22, 95% CI 0.99-1.51; p=0.06). These findings provide further insights into the potential optimization of STEMI treatment, indeed in the current era of STEMI reperfusion characterized by early pre-H drug administration and fast transportation, diabetic patients are still a subgroup who requires further approaches for improving outcomes and additional strategies are needed also to improve patient's delay.

In **chapter 5** we investigated the role of different pre-H hospital anticoagulation regimes. We specifically assessed the effect of bivalirudin compared to heparins with optional glycoprotein IIb/IIIa inhibitors (GPI) on 1-year mortality, a pre-specified outcome of the international, randomized EUROMAX trial. Complete 1-year follow up was available for 2164 patients. All-cause mortality at 1-year occurred in 5.4% of the patients. The number of all-cause deaths was the same for both treatment groups (59 deaths in each group, relative risk [RR]=1.02, 95% confidence interval [CI]: 0.72-1.45; p=0.92). No differences were noted in the rates of 1-year cardiac death (44 (4%) for bivalirudin, 48 (4.3%) for the control group, RR=0.93, 95% CI: 0.63-1.39; p=0.74) or non-cardiac death (15 (1.4%) for bivalirudin, 11 (1.0%) for the control group, RR=1.39 CI: 0.64, 3.01 p=0.40). Thus in patients with STEMI treated earlier in ambulance, with frequent use of radial access and novel P2Y12 inhibitors, bivalirudin, as compared with heparin with optional use of GPI, showed similar long-term mortality outcome.

In **chapter 6** we undertook a subgroup analysis of the On-TIME 2 trial a study that randomized patients undergoing primary PCI to pre-H tirofiban administration vs placebo.

We investigated the potential association between early tirofiban treatment and N-terminal pro-B-type natriuretic peptide (NT-proBNP) level after primary PCI showing that pre-hospital tirofiban administration was independently associate with a lower risk of high NT-proBNP level after primary PCI (OR 0.71; 95% CI 0.51 to 0.99; p=0.045), supporting the potential benefit of early antithrombotic treatment administration in STEMI patients.

In **chapter 7** we explored the association between NT-proBNP levels and long-term mortality and the effect of pre-H tirofiban administration on mortality in relation NT-proBNP levels. NT-proBNP level above the median was an independent predictor

for 5-year mortality (HR 2.73 (95% CI 1.47 – 5.06; p = 0.002) and patients with values above the median who received early tirofiban treatment had significant lower mortality compared to patients treated with placebo at 30-days (2.7% vs 7.5% p=0.021) and 1-year (4.5% vs 9.4% p=0.043). At 5-years, a lower but non-significant mortality rate was maintained in the treatment group (18% vs 22.4% p=0.265). We have shown that a high-risk subset of STEMI patients, as identified by higher levels of NT-proBNP upon presentation, may derive particular benefit from early GPIs treatment in terms of reduced short term and long term mortality. Our findings may help to further refine the identification of patients likely to derive the greatest benefit from pre-hospital GPI administration. Early NT-proBNP measurement aimed at stratifying patients and guiding early antiplatelet therapy, could represent a possible new strategy to be tested in further studies.

In **chapter 8** we investigated the potential interactions between pre-H ticagrelor administration and thrombus aspiration (TA) in patients treated with primary PCI enrolled in the ATLANTIC trial.

A total of 941 (57.7%) patients underwent TA. In adjusted multivariate logistic model, pre-H ticagrelor treatment was significantly associated with less frequent new MI or definite stent thrombosis (ST) (OR 0.43, 95% CI 0.20-0.92, p=0.031), or definite ST (OR 0.26, 95% CI 0.07-0.91, p=0.036) at 30 days. Patients treated with TA had higher frequency of TIMI flow 0-1 compared to no-TA group (80.7% vs 51.9%, p<.0001). TA when also adjusted for TIMI flow 0-1 showed significant association only for higher bail-out use of GPI (OR 1.72, 95% CI 1.18-2.50, p=0.004) and more frequent 30-day TIMI major bleeding (OR 2.92, 95% CI 1.10-7.76, p=0.032). No significant interactions between TA and pre-H ticagrelor were present for the explored endpoints. TA when left to physicians discretion was used in high risk patients and was associated with bail-out use of GPI and TIMI major bleeding but had no impact on 30-day clinical outcomes. Conversely pre-H ticagrelor treatment predicted lower 30-day rates of ST or new MI without interaction with TA.

In **chapter 9** we have designed the Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation In STEMI (DAPT-STEMI) trial, a randomized, multicentre, international, open label trial aimed to examine the safety (non-inferiority) of 6-month DAPT after Resolute Integrity stent implantation in STEMI patients compared to 12-months DAPT. Indeed the optimal DAPT after PCI with second-generation DES is unclear and because prolonged DAPT is associated with higher bleeding risk and health care costs, establishing optimal DAPT duration is of paramount importance.

In the trial event free patients on DAPT at 6-months are randomized (1:1 fashion)

between single (aspirin only) versus DAPT for an additional 6 months and followed until 2 years after primary PCI. The primary end point (PE) is a patient oriented composite endpoint of all-cause mortality, any myocardial infarction, any revascularization, stroke and major bleeding (net MACCE) at 18-months after randomization. To achieve a power of 85% for a non-inferiority limit of 1.66, a total of 1100 enrolled patients are required. No other dedicated randomized controlled trials have evaluated the safety of shorter DAPT duration in STEMI patients.

In **chapter 10** we reported the results of the DAPT-STEMI trial. 1100 patients were enrolled in the trial and 870 were randomized: 432 versus 438, in SAPT and DAPT, respectively. The PE occurred in 4.8% versus 6.6 %, in SAPT and DAPT respectively (HR 0.73; 95% confidence interval (CI), 0.41 to 1.27; P=0.26). Noninferiority was met (P for noninferiority =0.004), as the HR upper 95% CI of 1.27 was smaller than the pre-specified noninferiority margin of 1.66. Limiting DAPT duration to 6 months in event-free STEMI patients resulted in a non-inferior clinical outcome, as assessed by the patient-oriented composite clinical endpoint of safety, efficacy, and bleeding, versus the regimen of 12 months DAPT. This trial for the first time showed that if clinically mandated a shorter DAPT is safe and sets the stage for further dedicated research on DAPT duration in STEMI patients.

Final comments and future perspectives

Ischemic heart disease is a major cause of death and disability in developed countries and accounts for 20% of all deaths in Europe, although with large variations between countries[1]. Although acute and long-term mortality following ST-segment elevation myocardial infarction (STEMI) are decreasing in parallel with greater use of primary percutaneous coronary intervention (PCI) and modern antithrombotic therapy[2], acute STEMI is one of the most life-threatening diseases in the world.

Myocardial reperfusion

Current practice guidelines[3] put a great emphasis on the organization of STEMI networks as central part of STEMI management since they speed transfer to PCI centres and allow the initiation of STEMI treatment at first medical contact once the diagnosis has been set by equipped medical or paramedical staff.

The ATLANTIC (Administration of Ticagrelor in the Cath Lab or in the Ambulance for New STEMI to Open the Coronary Artery) trial was a randomized study comparing pre-Hospital (pre-H) vs in-Hospital (in-H) treatment with ticagrelor loading dose in acute STEMI[4]. In the trial, the frequent early use of aspirin and anticoagulation and the early use of ticagrelor, coupled with very short medical contact-to-balloon times[4],

represent contemporary treatment of STEMI patients and an ideal setting, which has been used in this thesis, to explore potential factors which may influence early coronary reperfusion before and after primary PCI.

Since achievement of early myocardial reperfusion is one of the main goals in STEMI patients for improving prognosis, the identification of factors related to this objective may provide further insights into the optimization of pre-H STEMI patient management. Indeed in this thesis we showed that in patients with STEMI being transported for primary PCI, pre-H treatment with anticoagulant and ticagrelor in addition to aspirin if long transfer delay is expected, may help achieve reperfusion prior to PCI. This provides support for a pre-H strategy treatment for those who still present with a long transfer time. Moreover the potential benefit of pre-H ticagrelor administration should not be denied, especially considering its proven safety.

We showed that "patient delay" should be minimized as much as possible, indeed "patient delay" was independently associate to both pre PCI and post PCI complete ST-resolution. The early period after symptom onset represents a golden opportunity for antithrombotic therapy, because the platelet content of the fresh coronary thrombus is maximal and more susceptible to powerful antiplatelet agents[5], moreover, early reperfusion after symptom onset has the maximal lifesaving potential, through myocardial salvage. Patient education remains an important component in reducing this delay[6] and therefore still considerable efforts should be made to educate the general public about the positive effects of an early and adequate first emergency call. In addition we showed that in an era of rapid STEMI reperfusion treatment with primary PCI and potent antiplatelet therapy, diabetes mellitus remains independently associated with poor myocardial reperfusion and therefore further approaches for the treatment of diabetes mellitus patients are needed.

In the first part of this thesis the ATLANTIC ST-segment resolution analyses highlighted the elements that may help to achieve myocardial reperfusion before and after primary PCI and confirmed the prognostic importance of electrocardiographic assessments of early reperfusion, showing that complete ST-resolution still represents a valid surrogate marker for cardiovascular clinical outcomes.

Pre-H administration of a fast-acting antiplatelet agent, such as cangrelor, may represent a new strategy to be tested in the future in order to improve myocardial reperfusion. Because cangrelor is administered intravenously and has rapid onset, it could offer particular advantages in the STEMI primary PCI setting, especially where there is little opportunity for pretreatment as in patients who are intubated or in cardiogenic shock or those experiencing nausea and vomiting.

Role of the antithrombotic/antiplatelet therapy

Patients with STEMI have acute coronary thrombosis which occludes an epicardial coronary artery and creates a highly prothrombotic milieu for PCI. Therefore, antithrombotic therapy, including a variable cocktail of antiplatelet and anticoagulant drugs, is a key component of the treatment of STEMI. Antithrombotic therapy plays a crucial role in restoration of myocardial tissue reperfusion and in the prevention of microvascular damage. The most effective combination administration of antiplatelet agents and anticoagulants in primary PCI is still uncertain.

Debate persists whether heparin or bivalirudin results in superior clinical outcomes in patients undergoing primary PCI. Studies comparing bivalirudin with other antithrombotic strategies have produced inconsistently lower mortality findings[7–11]. In patients with STEMI treated in the ambulance with frequent use of radial access and novel P2Y12 inhibitors, we showed that patients treated with bivalirudin had similar long-term mortality outcomes compared with heparin and optional Glycoprotein IIb/IIIa inhibitors (GPIs). In this specific context, the reduced composite end point of death and/or major bleeding at 30 days in the bivalirudin arm of the EUROMAX trial did not translate into reduced cardiovascular or all-cause death at 1 year. Additional studies are needed to find the optimal anticoagulant regimen to improve long-term mortality outcomes, however, considering the much higher cost of bivalirudin and no discernible efficacy or substantial safety advantages compared to heparin, like fine wine that never goes out of fashion, heparin currently remains the therapy of choice in patient with STEMI undergoing primary PCI.

Glycoprotein IIb/IIIa inhibitors (GPIs) are the most powerful class of antiplatelet therapies, and their adjunctive effects have been shown in several randomized trials[12]. Among STEMI patients undergoing primary PCI, the greatest benefit in mortality reduction from GPI usage has been shown in patients with higher-risk profiles[12]. Therefore the identification of patients who may particularly benefit from GPIs administration is important in the ongoing research for a more tailored and optimized therapy for STEMI patients. We have shown that pre-hospital tirofiban administration was independently associated with a lower risk of high NT-proBNP level after primary PCI supporting the potential benefit of early antithrombotic treatment administration in STEMI patients. Moreover high-risk subset of patients, as identified by higher levels of NT-proBNP upon presentation, may derive particular benefit from early GPIs treatment in terms of reduced short term and long term mortality, without a significant increase in either major or minor bleeding complications. Therefore our findings may help to further refine the identification of patients likely to derive the greatest benefit from pre-hospital GPIs administration. Moreover early NT-proBNP measurement aimed at stratifying patients and guiding early antiplatelet therapy, could represent a possible new strategy to be tested in further studies.

The high frequency of suboptimal myocardial reperfusion after primary PCI has resulted in the development of devices that evacuate coronary thrombus in order to limit, together with antithrombotic therapy, distal embolization and to protect the microcirculation; clinical trials focusing on thrombus aspiration (TA) in primary PCI have generally shown improved myocardial reperfusion, however, no reduction in hard clinical end points was seen when compared with conventional PCI in large clinical trials[13,14]. For the first time we evaluated the potential synergy effect of pre-H ticagrelor treatment and TA on post-PCI myocardial reperfusion and clinical outcomes in patients enrolled in the ATLANTIC trial. TA when left to physician's discretion was used in high risk patients, was associated with bailout use of GPI and TIMI major bleeding, and was not associated with improvement in 30-day clinical outcome. Conversely, pre-H ticagrelor treatment predicted lower 30-day rates of stent thrombosis (ST) or new MI as well as definite ST without significant interaction with TA.

In the second part of this thesis we highlighted the importance of antithrombotic therapy for the optimisation of clinical outcomes in patients with STEMI undergoing primary PCI. Anticoagulation with unfractionated heparin is an accepted and important therapy for STEMI, especially before and during the PCI procedure. Dual antiplatelet therapy (DAPT) comprising aspirin and P2Y12 inhibitors represents the cornerstone treatment for STEMI and should be given as soon as possible. However, especially in high-risk STEMI patients, more potent antithrombotic treatment strategies may be needed and early GPI administration to tackle an high thrombotic burden should be considered. However, there is still uncertain regarding the role of GPI in the era of new potent P2Y12 inhibitors and the routine use of TA should be discouraged. Adjunctive pharmacotherapy should be tailored to the individual patient, based on assessment of ischaemic and bleeding risk. Finding a balance that minimizes both thrombotic and bleeding risk remains, although difficult, of fundamental importance. Additional research is required to develop further approaches to enhance myocardial perfusion and improve clinical outcomes in high-risk subset of patients. The modulation of inflammatory mechanisms may represent a further future strategy for improving outcomes, indeed also anti-inflammatory therapy has recently showed to significantly reduce the rate of recurrent cardiovascular events[15]. Finally, the presence of endothelial dysfunction, especially in diabetic patients, is implicated in the induction of proatherothrombotic mechanisms[16], thus the development of novel therapeutic approaches targeting endothelial dysfunction could be helpful to ameliorate prognosis in these high risk patients.

Duration of dual anti-platelet therapy

In the third part of thesis we explored the duration of DAPT after primary PCI in STEMI. Over the past few decades, the duration of DAPT has seen drastic changes, most of which have not been driven by evidence, but by expert opinion. DAPT was initially used to reduce thrombotic events after stent implantation and the high rate of ST with first generation drug eluting stents (DES) prompted longer durations of DAPT usage (12 months).

Although a significant reduction in ST has been achieved with second generation DES, the practice of using longer DAPT regimens to reduce overall thromboembolic events in MI patients, independently from ST protection, has gained ground over the past few years. However DAPT usage is strongly associated with a significant increase in bleeding[17,18], including life threatening bleeding. Despite large scale trials evaluating the role of longer DAPT regimens in post MI patients have showed some benefit for longer DAPT in reducing cardiovascular events, these reductions came with a high price in bleeding, which in turn is strongly related to mortality[17]. Therefore because prolonged DAPT is associated with higher bleeding risk and health care costs, establishing optimal DAPT duration is of paramount importance. No other trial has evaluated the safety of DAPT for less than 12 months in patients with STEMI, treated with second generation DES, thus we performed a dedicated randomised clinical trial to compare 6 versus 12 months of DAPT after primary PCI. We showed that limiting DAPT duration to six months in patients with STEMI that are event-free results in a non-inferior clinical outcome, as assessed by a patient-oriented composite clinical endpoint versus 12 months of DAPT. For the first time we showed that a shorter DAPT duration is also feasible and safely applicable if clinically required even in patients with STEMI, setting the stage for further dedicated research on DAPT duration in this category of patients that are at high risk. Based on the results of this trial we are able to keep this research path open for larger randomised trials to take place, which will hopefully establish the optimal duration of DAPT after primary PCI.

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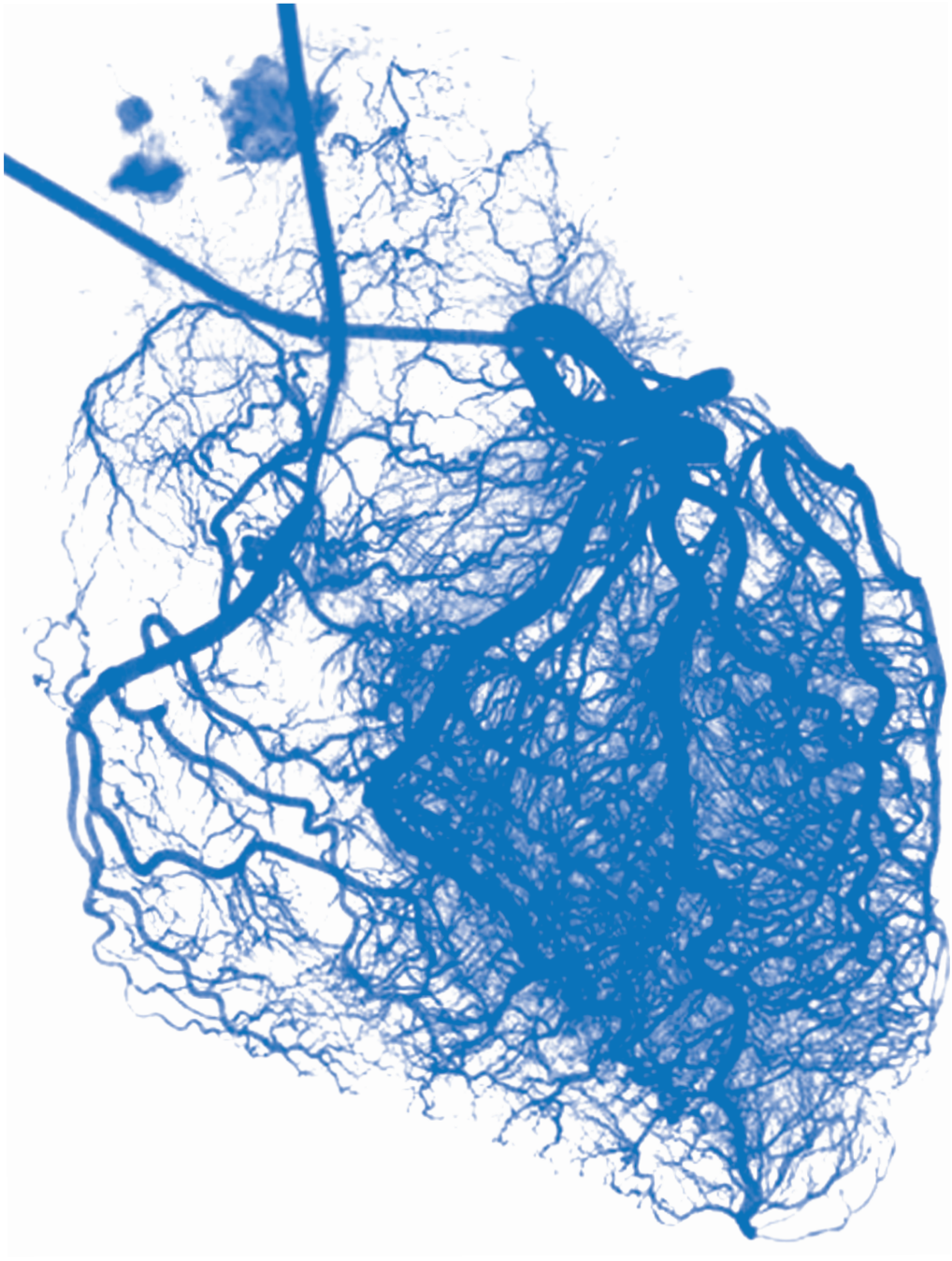

Chapter twelve

List of publications
Curriculum vitae
Acknowledgments

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Curriculum vitae

Enrico Fabris was born on the 1th of May in 1984 in San Dona' di Piave (Venice), Italy.

In 2002 he moved to Trieste where he started his medical training at the University of Trieste and graduated in medicine and surgery, with 110 /110 cum laude (with honours) in 2009.

He started in 2010 the cardiology residency at the University of Trieste (Prof. G. Sinagra). In 2014 during his last year of cardiology training he moved in London, UK, at the Royal Brompton Hospital, Imperial College (Prof C. di Mario) as clinical and research fellow in interventional cardiology where he developed competencies in intracoronary imaging and bioresorbable scaffolds. In 2015 he completed the cardiology residency at the University of Trieste with 50/50 cum laude (with honours). After the cardiology specialization in 2015 he moved to Zwolle, the Netherlands, to complete an interventional cardiology and research fellowship at the Isala Hospital under the supervision of Prof. AWJ van 't Hof and Dr. E. Kedhi which resulted in this thesis. Subsequently he returned to Italy where he currently works as an interventional cardiologist at the University Hospital of Trieste.

Enrico Fabris has served as a reviewer for the following Journals:

British Medical Journal (BMJ), Annals of Internal Medicine, Journal of the American College of Cardiology (JACC), JACC: cardiovascular Intervention, Circulation: Cardiovascular Interventions, Circulation: Cardiovascular Imaging, Heart, European Journal of Heart Failure, European Heart Journal-Cardiovascular Imaging, International Journal of Cardiology, Catheterization and Cardiovascular Interventions, Journal of Cardiovascular Medicine.

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