Adverse outcomes after primary PCI

Renicus Suffridus Hermanides

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Ongewenste uitkomsten na primaire pci

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Copromotores:	dr. A.W.J. van ’t Hof dr. J.P. Ottervanger
Beoordelingscommissie:	Prof. dr. R.J. de Winter Prof. dr. H. Boersma dr. P.P.T. de Jaegere

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Introduction and outline of the thesis

STEMI

Coronary heart disease is still an important cause of death in the Western countries.(1,2) ST-Elevation Myocardial Infarction (STEMI) is a dangerous manifestation of this disease, mostly caused by an acute occlusion of a major coronary artery usually due to disruption of an atherosclerotic plaque with subsequent formation of an occluding thrombus.(3)

Effective and rapid restoration of blood flow to ischemic myocardial tissue is the most important initial goal in the treatment of patients with STEMI. Primary percutaneous coronary intervention (PCI) is the preferred strategy for reperfusion in the treatment of STEMI when feasible and when performed in a timely matter.(4,5) Primary PCI has been shown to be superior to fibrinolytic therapy.(6-8) However, during or after primary PCI, unfavourable events, like bleeding and sub-optimal angiographic results may occur, which can influence the prognosis negatively.

Bleeding

Concomitant use of anti-thrombotic drugs during primary PCI promotes sustained vessel patency and tissue perfusion by reducing acute vessel closure and preventing distal embolization.(9) However, with the increasing use of antiplatelet and antithrombotic agents, concern has grown with regard to the negative side effects of these drugs, especially bleeding.

Although bleeding during or after primary PCI was long considered as inherent to the modern therapeutic approach, it is currently seen as the most common non-cardiac complication in patients treated for STEMI. Bleeding complications are associated with worse clinical outcomes and adverse events such as myocardial infarction, stroke, stent thrombosis, and death, see figure 1.(10-12)

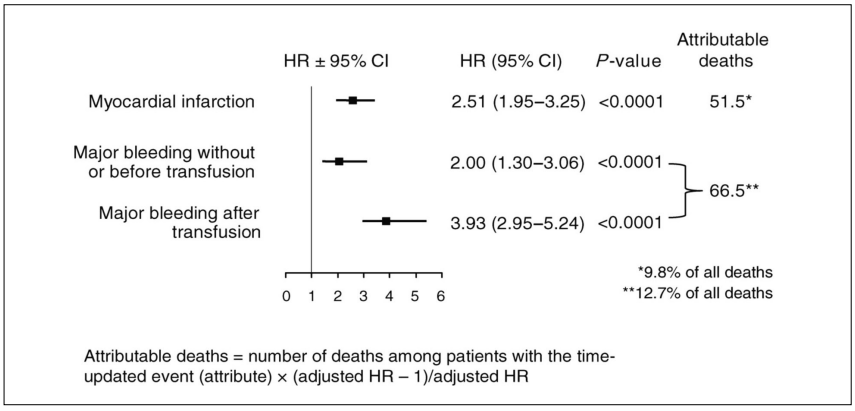

Figure 1: Influence of major bleeding and myocardial infarction in the first 30 days on the risk of death over 1 year in the ACUITY trial. Mehran R, et al. Eur Heart J Suppl 2009;11:C4-C8. It can be appreciated that bleeding during the first 30 days after myocardial infarction has a significant negative impact on prognosis.

There are modifiable and non-modifiable risk factors for bleeding. The choice, dose, and combination of antithrombotic and antiplatelet drugs is probably the most readily modifiable risk factor. The complexity of these medical agents from which to choose is increasing with regard to the number of agents, regimens used, potency, mechanisms of action, and duration of therapy. Research on the effect of newer and potentially safer antiplatelet and antithrombotic agents has focused on optimizing efficacy without increasing the risk of bleeding. The clinical effect of these agents are usually expressed as "NACE" (net adverse clinical events) including the composite of major adverse cardiac events and non CABG-related major bleeding complications.
During the last decade many studies were performed regarding the efficacy and safety of glycoprotein IIb/IIIa inhibitors in STEMI. Glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban) block the final pathway of platelet aggregation, and are recommended for STEMI patients who are candidates for primary PCI. (13) The Ongoing Tirofiban In acute Myocardial infarction Evaluation (On-TIME 2) trial has shown that routine pre-hospital initiation of high-dose bolus tirofiban in addition to aspirin, heparin and high-dose clopidogrel improves PCI success in STEMI.(14,15) However, whether tirofiban also leads to an important increase of bleeding is unknown. Furthermore, there is limited information about safety in patients with a high risk of bleeding and elderly patients who are pre-treated with tirofiban.

Sub-optimal angiographic outcome

Although primary PCI is the most effective reperfusion strategy for STEMI, it fails to restore optimal myocardial reperfusion in some patients, mostly due to a failure to cross the culprit lesion, the occurrence of coronary dissection, distal embolization or no-reflow. These sub-optimal angiographic results remain the "Achilles heel" of primary PCI, and are associated with an increased incidence of worse outcome. (16-18)
No-reflow refers to a state of myocardial hypoperfusion in the presence of a patent epicardial coronary artery. Although it is clear that abnormalities at the level of the microvasculature cause the no-reflow phenomenon, the exact mechanism is uncertain.(19) Attributable factors may include endothelial swelling, myocyte edema, tissue compression, and neutrophil infiltration. Embolization of athero-thrombotic material during primary PCI is also considered to be an important contributor to the no-reflow phenomenon. The incidence of distal embolization after primary PCI ranges from 6-15%.(20,21) and it's occurrence has been associated with excessive manipulation of the epicardial coronary bed, treatment of the right coronary artery, large thrombus burden, length, and diameter of the infarct-related-artery.(22)
The presence of distal embolization on the coronary angiogram is associated with

worse myocardial blush grade and Thrombolysis In Myocardial Infarction (TIMI) graded flow, less ST-segment resolution, higher incidence of new Q-waves, higher enzyme levels, and a higher incidence of re-infarction at 1 year after PCI.(21)
During the last decade, multiple strategies have been shown to reduce the occurrence of sub-optimal angiographic results including performing primary PCI within 120 minutes of first medical contact(23), the use of (primary) stenting(24), thrombus aspiration(25), and the liberal use of adjunctive therapies such as intravenous glycoprotein IIb/IIIa inhibitors or bivalirudin.(26-29) One potential improvement may be the administration of pre-hospital glycoprotein IIb/IIIa inhibitors (tirofiban), as part of a triple antiplatelet therapy (aspirin, high dose clopidogrel and tirofiban).

Outline of this thesis

As mentioned, bleeding and sub-optimal angiographic results are unfavourable events of primary PCI. The aim of this thesis was to identify patients at risk for these complications, to improve risk stratification with regard to bleeding enabling a more tailored anti-thrombotic regiment and to optimise pharmacological therapy to reduce the risk of these adverse events after primary PCI These research questions were assessed by using data from a large cohort registry of STEMI patients treated with primary PCI, by performing sub-analyses of the randomised On-TIME 2 study, and by a randomised controlled clinical trial about access-site closure devices in patients with high risk of bleeding.

In **Chapter 2**, the current treatment of ST-elevation myocardial infarction is described.
Part one of this thesis focuses on the incidence, predictors and prevention of bleeding in patients who underwent primary PCI.
Chapter 3 describes the incidence, predictors and prognostic importance of bleeding after primary PCI for STEMI in a prospective, large single-centre, observational cohort study of consecutive STEMI patients who presented in our hospital (Zwolle STEMI registry). In **Chapter 4, 5 and 6** data are presented of sub-analyses of the On-TIME 2 trial, a prospective, double-blind, placebo-controlled, international, randomized controlled trial investigating the efficacy of pre-hospital use of high dose tirofiban in STEMI patients who are candidates for primary PCI. **Chapter 4** addresses the risk of bleeding after pre-hospital administration of tirofiban, on top of aspirin, clopidogrel and heparin, in STEMI patients planned to undergo primary PCI. In **chapter 5 and 6** we determined the efficacy and safety of tirofiban in high risk bleeding subgroups. **Chapter 5** focuses on the net clinical benefit of early pre-hospital initiation of tirofiban in patients at high risk of bleeding, using the CRUSADE bleeding risk score. The treatment interaction of age on effects of pre-hospital administration of tirofiban before primary PCI for STEMI is described

in **chapter 6**. In **chapter 7**, we describe the effects of a pre-hospital fixed heparin bolus on activated clotting time in consecutive patients with STEMI (Zwolle STEMI registry).
In **chapter 8** we described the results of the ANGIOCARE trial, a prospective, single-centre, randomized comparison of manual compression versus a closure device, to prevent access-site related bleeding complications in patients who underwent (primary) PCI, and who had a high risk of bleeding.

Part two of this thesis focuses on the incidence and pharmacologic mechanisms to prevent sub-optimal procedural outcome during primary PCI. **Chapter 9** addresses the influence of early pre-hospital use of tirofiban in reducing PCI related complications during or after primary PCI in STEMI patients. **Chapter 10** describes the beneficial effect of early, upfront tirofiban use as compared to bail-out use, in a large unselected patient population undergoing primary PCI. The effect of early pre-hospital treatment with tirofiban on angiographic outcome is outlined in **chapter 11**. Finally, the impact of elevated LDH on admission as predictor of sub-optimal angiographic- and clinical outcome in STEMI patients is addressed in **chapter 12**.

References

1. Lloyd-Jones D, Adams RJ, Bron TM, et al. Heart disease and stroke statistics-2010 update: a report from the American Heart Association. Circulation 2010;121:e46-e215.
2. Widimsky P, Wijns W, Fajadet J, et al. Reperfusion therapy for ST elevation myocardial infarction in Europe: description of the current situation in 30 countries. Eur Heart J 2010;31:943-956.
3. Libby P. Current concepts of the pathogenesis of the acute coronary syndromes. Heart 2000;83:361-366.
4. Simes RJ, Topol EJ, Holmes DR, et al. Link between the angiographic substudy and mortality outcomes in a large randomised trial of myocardial reperfusion. Importance of early and complete infarct artery reperfusion. Circulation 2005;91:1923-1928.
5. Ross AM, Coyne KS, Moreyra E, et al. Extended mortality benefit of early postinfarction reperfusion: Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries Trial. Circulation 1998;97:1549-1556.
6. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet 2003;361:13-20.
7. Zijlstra F, de Boer MJ, Hoorntje JC, Reiffers S, Reiber JH, Suryapranata H. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. N Engl J Med 1993;328:680-684.
8. Grines CL,Browne KF, Marco J, et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1993;328:673-679.
9. Antman EM, Hand M, Armstrong PW, Bates ER, Green LA, Halasyamani LK, Hochman JS, Krumholz HM, Lamas GA, Mullany CJ, Pearle DL, Sloan MA, Smith Jr SC. 2007 Focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: A report of the ACC/AHA Task Force on Practice Guidelines. J Am Coll Cardiol 2008;58:210-247.
10. Eikelboom JW, Metha SR, Anand SS, et al. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. Circulation 2006;114:774-782.
11. Manoukian SV, Feit F, Mehran R, et al. Impact of major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary syndromes: an analysis from the ACUITY trial. J Am Coll Cardiol 2007;49:1362-1368.
12. Rao SV, O'Grady K, Pieper KS, et al. Impact of bleeding severity on clinical outcomes among patients with acute coronary syndromes. Am J Cardiol 2005;96:1200-1206.
13. Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization. The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2010;31:2501-2555.
14. van 't Hof AW, ten Berg JM, Heestermans AA, et al. Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial. Lancet 2008;372:537-546.
15. ten Berg JM, van 't Hof AW, Dill T, et al. On behalf of the Ongoing Tirofiban In Myocardial infarction Evaluation (On-TIME) 2 study group. Effect of early, pre-hospital initiation of high-bolus dose tirofiban in patients with ST-segment elevation myocardial infarction on short and long-term clinical outcome. J Am Coll Cardiol 2010;55:2446-2455.
16. Morishima I, Sone T, Mokuno S, et al. Clinical significance of no-reflow phenomenon observed on angiography after successful treatment of acute myocardial infarction with percutaneous transluminal coronary angioplasty. Am Heart J 1995;130:239-243.
17. Morishima I, Sone T, Okumura K, et al. Angiographic no-reflow phenomenon as a predictor of adverse long-term outcome in patients treated with percutaneous transluminal coronary angioplasty for first acute myocardial infarction. J Am Coll Cardiol 2000;36:1202-1209.
18. Ndrepepa G, Tiroch K, Fusaro M, et al. 5-year prognostic value of no-reflow phenomenon after primary percutaneous coronary intervention in patients with acute myocardial infarction. J of Am Coll Cardiol 2010;55:2383-2389.
19. Rezkalla SH, Kloner RA. No-reflow phenomenon. Circulation 2002;105:656-662.
20. Henriques JP, Zijlstra F, Ottervanger JP, de Boer MJ, van 't Hof AW, Hoorntje JC, Suryapranata H. Incidence and clinical significance of distal embolisation during primary angioplasty for acute myocardial infarction. Eur Heart J 2002;23:1112-1117.
21. Fokkema ML, Vlaar PJ, Svilaas T, Vogelzang M, Amo D, Diercks GF, Suurmeijer AJ, Zijlstra F. Incidence and clinical consequences of distal embolization on the coronary angiogram after percutaneous coronary intervention for ST-elevation myocardial infarction. Eur Heart J 2009;30:908-915.
22. Napodano M, Ramondo A, Tarantini G, et al. Predictors and time-related impact of distal embolization during primary angioplasty. Eur Heart J 2009;30:305-313.
23. van der Werf F, Bax J, Betriu A, et al. ESC committee for practice guidelines (CPG). Management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2008;29:2909-2945.
24. Stone GW, Grines CL, Cox DA, et al. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. N Engl J Med 2002 28;346:957-966.

25. Svilaas T, Vlaar PJ, van der Horst IC, et al. Thrombus aspiration during primary percutaneous coronary intervention. N Engl J Med 2008;358:557-567.
26. Antoniucci D, Rodriguez A, Hempel A, Valenti R, Migliorini A, Vigo F, Parodi G, Fernandez-Pereira C, Moschi G, Bartorelli A, Santoro GM, Bolognese L, Colombo A. A randomized trial comparing primary infarct artery stenting with or without abciximab in acute myocardial infarction. J Am Coll Cardiol 2008;42:1879-1895.
27. De Luca G, Suryapranata H, Stone GW, Antoniucci D, Tcheng JE, Neumann FJ, Van de Werf F, Antman EM, Topol EJ. Abciximab as adjunctive therapy to reperfusion in acute ST-segment elevation myocardial infarction: a meta-analysis of randomized trials. JAMA 2005;293:1759-1765.
28. Montalescot G, Antoniucci D, Kastrati A, et al. Abciximab in primary coronary stenting of ST-elevation myocardial infarction: a European meta-analysis on individual patient's data with long-term follow-up. Eur Heart J 2007;28:443-449.
29. Stone GW, Witzenbichler B, Guagliumi G, et al. HORIZONS-AMI trial investigators. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med 2008;358:2218-2230.

2

Treatment of ST-elevation myocardial infarction (STEMI) - a review

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R.S. Hermanides, J.P. Ottervanger

Abstract

In patients with ST segment elevation myocardial infarction (STEMI), timely and adequate treatment may improve the prognosis dramatically. Restoration of the infarct vessel patency is one of the cornerstones of initial treatment. Compared to fibrinolytic therapy, primary percutaneous coronary intervention (PCI) results in higher short-term and long-term survival, a lower incidence of recurrent infarction and a better left ventricular function. Although (drug-eluting) stents may reduce restenosis, effects on mortality are less clear. Administration of glycoprotein IIb/IIIa antagonists may further reduce periprocedural coronary complications, but possibly bivalirudin gives similar effects with less bleeding.

Beta-adrenergic blockers, angiotensin-converting-enzyme inhibitors and statins should be initiated in all patients with STEMI, although cautious use of beta-blockers is advised in patients at risk of cardiac shock. Patients with diabetes should receive optimal glucose control. High-risk patients, particularly those with low ejection fraction, should receive an Implantable Cardioverter Defibrillator (ICD) after 30 days, although it is not clear whether patients after primary PCI also have benefits, particularly if they have no signs of heart failure.

Introduction

Of the patients with an acute coronary syndrome (ACS), particularly those with ST elevation myocardial infarction (STEMI) should be treated fast and aggressive, because if they are treated not or not well, they have a very bad prognosis. Treatment has been changed during the last decades, and prognosis has improved subsequently during this time period (figure 1). We review current treatment of STEMI.

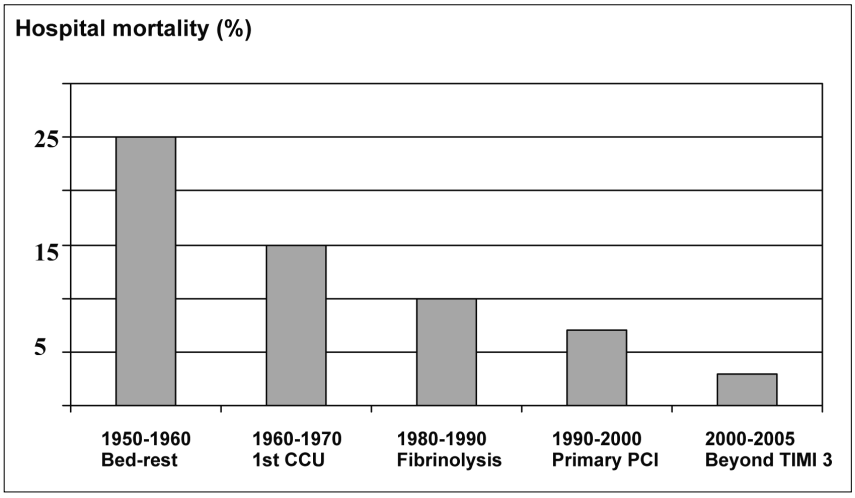

Figure 1: Hospital mortality in patients admitted for myocardial infarction in Zwolle in different time periods.

Rapid diagnosis

Treatment starts with a fast diagnosis of STEMI, and all patients with suspected myocardial infarction should have rapid ECG recording and interpretation. Guideline door-to-balloon-times are more often achieved when trained paramedics independently triage and transport patients directly to a designated primary PCI center than when patients are referred from emergency departments.(1)

Reperfusion therapy

Reperfusion therapy (either mechanical or pharmacologic) is indicated for patients with chest pain with a duration of 12 hours or less in association with ST-segment elevation greater than 0.1 mV in two or more contiguous electrocardiographic leads or a new (or presumed new) left bundle-branch block. Early, effective and sustained reperfusion of the culprit artery is needed to salvage myocardium, maintain left ventricular function, and reduce mortality. A decision must be made as soon as possible as to whether reperfusion will be achieved with either fibrinolysis or primary PCI.(2)

Fibrinolytic therapy

In comparison with conservative management (medical treatment without reperfusion therapy), fibrinolytic therapy improves left ventricular systolic function and survival in patients who present within 12 hours of symptom onset and who have no contraindications for fibrinolyis (as history of intracranial haemorrhage or ischemic stroke within the past 3 months, active bleeding or previous allergic reaction to fibrinolytics). Fibrinolysis can be considered in patients who present to a facility without the capability for prompt intervention with primary PCI within 90 minutes of first medical contact and in patients who present to a facility in which the relative delay necessary to perform primary PCI (the expected door-to-balloon time minus the expected door-to-needle time) is greater than one hour. The time interval from first patient contact to initiation of fibrinolysis should be less than 30 minutes.(2,3)

Rescue PCI should be considered for patients in whom reperfusion fails to occur after fibrinolytic therapy because event-free survival after failed thrombolytic therapy is significantly higher with rescue PCI than with repeated thrombolysis or conservative treatment.(4,5)

Facilitated PCI might be performed as a reperfusion strategy in higher-risk patients when primary PCI is not immediately available and bleeding risk is low.(2) A combined approach with a quickly started clot-dissolving drug (thrombolysis and / or glycoprotein IIb/IIIa) followed by later PCI of the culprit lesion (lyse now, stent later) has therefore some attractiveness.(6) The ASSENT-4 trial was prematurely interrupted because of higher in-hospital mortality after full dose tenecteplase followed by PCI compared with primary PCI alone.(7) However, the recent CARESS-in-AMI trial showed that after treatment with a combination of half-dose reteplase plus abciximab, urgent transfer for immediate PCI is a better strategy than standard therapy with clinically indicated rescue PCI.(8)

Primary PCI

If high-quality PCI is available, multiple randomized trials have shown enhanced survival compared to fibrinolysis with a lower rate of intracranial haemorrhage and recurrent myocardial infarction (MI).(9) According to ACC / AHA guidelines for the treatment of STEMI patients, the time from medical contact to PCI (door-to-balloon time) should be 90 minutes.(10)

Compared to fibrinolysis, primary PCI restores more often angiographically normal flow, including optimal TIMI 3 flow and blush, and has additional importance in patients with a contraindication for fibrinolysis.(11-15) Moreover, about a quarter of patients receiving fibrinolytic therapy has reocclusion of the infarct-related artery within 3 months after the myocardial infarction, with a recurrent infarction, which

is very rare after primary PCI.(16) Therefore, primary PCI is preferable, even if the "door-to-balloon" interval exceeds 90 minutes, in patients with a contraindication to fibrinolytic therapy, a high risk of bleeding with fibrinolytic therapy and those, with signs of heart failure.(17,18)

Not surprisingly, primary PCI is associated with an improved left ventricular systolic function and a higher long-term survival. The benefits of stenting are almost entirely due to treatment of dissection in the acute phase and a lower need for repeat ischemia-driven revascularization.(19,20) The CADILLAC study showed that the incidence of clinical end points, including ischemia-driven revascularization of the target vessel, is significantly lower with stenting compared to balloon angioplasty.(21) As compared with bare-metal stents, drug-eluting stents may further reduce restenosis within 12 months after primary PCI.(22,23,24) Especially if drug-eluting stents are used, dual antiplatelet therapy (aspirin and clopidogrel) should be given for at least 12 months to decrease the occurrence of subacute stent thrombosis.

Antithrombotic medication

Dual-antiplatelet therapy with aspirin and a thienopyridine is a cornerstone of treatment to prevent thrombotic complications in STEMI patients(25), particularly after it has been determined that emergency bypass surgery is not required. As adjunctive to aspirin, a 3-month-regimen of moderate-intensity coumarin may reduce reocclusion and recurrent events after successful fibrinolysis.(26) Recently, the TRITON trial showed that prasugrel compared to clopidogrel was associated with significantly reduced rates of ischemic events, including stent thrombosis, but with an increased risk of major bleeding, including fatal bleeding in ACS patients with scheduled PCI.(27) Among patients treated with fibrinolytic therapy who have subsequent PCI, enoxaparin has been associated with a reduced risk of death or recurrent MI without difference in the risk of major bleeding.(28) Unfractionated heparin has several limitations, including unpredictable pharmacokinetics, inhibition by plasma proteins, and the potential to activate platelets.(29) Considerable reductions in periprocedural complications have been achieved with administration of glycoprotein IIb/IIIa antagonists (abciximab, tirofiban, eptifibatide) in addition to heparin.(30)

An alternative for heparin is bivalirudin, a direct thrombin inhibitor. Recently, the HORIZONS trial reported that bivalirudin compared with unfractionated heparin plus glycoprotein IIb/IIIa inhibitors resulted in similar efficacy with less bleeding in patients with STEMI treated with primary PCI.(31) Data from the HORIZONS trial in STEMI patients and REPLACE-2 trial in elective PCI, make a strong case for the use of bivalirudin rather than unfractionated heparin plus glycoprotein IIb/IIIa in the great majority of STEMI patients, with the possible exception of patients with cardiogenic shock or stent thrombosis, and patients with a large thrombus burden

or no re-flow following PCI. In the latter case, platelet glycoprotein IIb/IIIa inhibitors would be used as a bail-out strategy.(32)
Primary PCI is sometimes limited by distal embolization and risk of no reflow phenomenon. Distal embolization after primary PCI is related to more extensive myocardial damage and a poor prognosis.(33,34) Thrombus aspiration before primary PCI results in better myocardial reperfusion and clinical outcomes than conventional PCI and has been associated with lower enzyme release, and a lower risk of distal embolization and no-reflow.(35)

Coronary artery bypass graft surgery

Coronary artery bypass graft surgery (CABG) is infrequently performed in patients with STEMI, but may be life saving in patients with failed primary PCI, particularly in patients with a large size of myocardium at risk. Also patients with left main or three-vessel disease but with restoration of blood flow either spontaneous or after balloon PCI may benefit of short-term CABG.

Medication after reperfusion

Beta-adrenergic blockers(36,37) and angiotensin-converting-enzyme inhibitors(38) should be initiated in all patients, provided that the patient has no contraindications and is hemodynamically stable. Beta-blockers have indisputably been demonstrated to be clinically useful, but administration should be deferred or given carefully in patients with signs of heart failure, hypotension or shock during the first days.(39,40) The increase in risk in hemodynamically compromised patients is consistent with current recommendations from the ACC/AHA.(2,10)
Especially early metoprolol administration during acute coronary occlusion increases myocardial salvage.(41) Patients with obstructive lung disease may receive less often beta blockers.(42) However, although these patients should be treated with caution, the majority of these patients can safe use beta blockers.(43)
Chronic therapy with an ACE inhibitor (unless contraindicated) for all patients after an STEMI is recommend. An angiotensin II receptor blocker (ARB) is an alternative for patients who do not tolerate an ACE inhibitor, usually due to cough. ARB's appear to be as effective as ACE inhibitors in reducing atherosclerotic events, even when used in addition to other secondary preventive treatments.(44) ACE inhibitors/ARB's are most important in patients with heart failure, a LVEF less than 40 percent, diabetes, or hypertension. The optimal approach is less clear in asymptomatic, normotensive, nondiabetic patients with no or minimal impairment in left ventricular function. Statin therapy at discharge is associated with a significant reduction in 1-year mortality after primary PCI and is recommended for all patients.(45,46) Patients with signs of heart failure may benefit of aldosterone antagonists.(47)
The identification of major modifiable risk factors for coronary heart disease

(CHD) (dyslipidemia, hypertension, smoking, obesity, inactivity, and diabetes) is a prerequisite to the implementation of preventative interventions. Risk factor modification by therapeutic lifestyle changes, as well as drug therapies can decrease morbidity and mortality in such patients.

Diabetes

Patients with diabetes have an adverse prognosis after ST-segment elevated myocardial infarction, after either fibrinolysis or primary PCI.(48) Also after primary PCI, diabetes is independently associated with both incomplete ST-segment resolution and reduced myocardial blush grade (MBG). There are several mechanisms that can explain these findings, including microvascular disease and a higher degree of platelet aggrebility and adhesiveness.(49,50,51) Diabetic patients have better outcomes with primary PCI compared to fibrinolysis.(52) Whether meticulous regulation of DM and glucose levels, prior or following restoration of epicardial flow, improves myocardial reperfusion is unclear and further investigations are warranted. Changes in lifestyle after discharge may prevent or delay the occurrence of type 2 diabetes in patients with impaired glucose intolerance.(53)

Additional revascularisation

After either primary PCI or fibrinolysis, (additional) revascularisation should be considered if ischemia is documented by non-invasive imaging. The ACC/AHA guidelines recommend exercise stress with imaging using radionuclide myocardial perfusion imaging (MPI) or echocardiography for patients who are able to exercise and vasodilator (adenosine or dipyridamole) MPI or dobutamine echocardiography for patients who cannot.

Re-stenosis rates of the infarct related vessel are considerably higher in more complex lesion subsets, such as small vessels, long lesions, and bifurcations, and these patients should be monitored intensively, to detect myocardial ischemia.

Patients with multivessel disease (MVD), have often an unfavorable clinical outcome, with also less improvement of LV function after the infarction. Possibly, additional revascularisation may be of benefit in these patients, with probably no mortality difference between patients treated by PCI or CABG during long-term follow-up. (54,55)

Various single center registries also reported the efficacy of DES for multivessel disease (56,57), but randomized trials should confirm this approach. CABG is compelling for patients with left main disease or more diffuse coronary disease or specific high-risk patient subgroups (ie, multivessel disease with left ventricular dysfunction and diabetics), whereas patients with less diffuse disease and focal lesions are good candidates for PCI.(58,59)

ICD implantation

Primary prevention of sudden cardiac death after myocardial infarction by an Implantable Cardioverter Defibrillator (ICD) was particularly studied in MADIT II and DINAMIT.(60,61) MADIT II demonstrated that in patients with a history of myocardial infarction who had reduced LV function (ejection fraction lower than 30%) there was a significant mortality reduction after implantation of an ICD. In DINAMIT, patients were randomised 6-40 days after myocardial infarction, in those with signs of reduced LV function and impaired autonomic tone. Although in DINAMIT a significant reduction of arrhythmogenic death was observed in patients randomised to ICD (HR 0.42, 95% CI 0.22-0.83), risk of non-arrhythmogenic death was increased in these patients, resulting in the absence of a significant mortality difference between the treatment groups. Current guidelines advise to give an ICD after 30 days in those patients who have an ejection fraction lower than 30%.

Guidelines

According to the guidelines of the American College of Cardiology and American Heart Association, primary PCI is a class I indication in patients with myocardial infarction with ST-segment elevation who can undergo the procedure within 12 hours after the onset of symptoms. Similarly, the European Society of Cardiology considers primary PCI the preferred reperfusion strategy for patients with myocardial infarction with ST-segment elevation (as a class I indication).(62) Also other recommendations of the guidelines, including those on ICD, additional revascularisation and drugs are in accordance of our review.

Future Perspectives

Although treatment of STEMI has improved during the last decades, in several fields additional improvement should be achieved. Regional strategies should be applied for reducing time to diagnosis, reducing time from diagnosis to arrival in a PCI center and decreasing door-to-balloon time in all patients. Additional randomized trials should demonstrate the most optimal combination of medical treatment given before arrival in the hospital. In patients with primary PCI, bleeding should be further decrease, possibly by use of agents as bivalirudin rather than heparin combined with glycoprotein IIb/IIIa inhibitors. It should be clarified for how long agents as clopidogrel must be used to prevent risk of stent thrombosis, particularly in patients with drug eluting stents. After reperfusion therapy, much more patients should receive appropriate medication, including beta blockers, ACE inhibitors and statins and in those with multivessel disease, non-invasive ischemia detection should be applied. Before discharge, more intensive strategies for long-term life style modification should be initiated, including smoking cessation and weight reduction by both diet and physical exercise.

References

1. Le May MR, Derek Y. S, Dionne R, et al.: A citywide protocol for primary PCI in ST-segment myocardial infarction. N Engl J Med 2008;358:231-240.
2. Antman EM, Anbe DT, Armstrong PW, et al.: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction. Available at: www.acc.org/qualityandscience/clinical/statements.htm (accessed August 24, 2006).
3. Menon V, Harrington RA, Hochman JS, et al.: Thrombolysis and adjunctive therapy in acute myocardial infarction: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126:549S-575S.
4. Ross AM, Lundergan CF, Rohrbeck SC, et al.: Rescue angioplasty after failed thrombolysis: technical and clinical outcomes in a large thrombolysis trial. J Am Coll Cardiol 1998;31:1511-1517.
5. Gerschlick AH, Stephens-Lloyd A, Hughes A, et al.: Rescue angioplasty after failed thrombolytic therapy for acute myocardial infarction. N Engl J Med 2005;353:2758-2768.
6. Verheugt FW.: Lyse now, stent later: the grace of GRACIA. Lancet 2004;364:1014-1015.
7. van der Werf F, Ross A, Armstrong P, et al.: Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomized trial. Lancet 2006;367:569-578.
8. Di Mario C, Dudek D, Piscione F, et al.: Immediate angioplasty versus standard therapy with rescue angioplasty after thrombolysis in the combined abciximab reteplase stent study in acute myocardial infarction (CARESS-in-AMI): an open, prospective, randomized, multicentre trial. Lancet 2008;371:559-568.
9. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet 2003;361:13-20.
10. Antman EM, Hand M, Armstrong PW, et al.: 2007 focused update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Group to Review New Evidence and Update the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction). Available at: www.acc.org/qualityandscience/clinical/statements.htm (accessed September 18, 2007).
11. Grines CL, Cox DA, Stone GW, et al.: Coronary angioplasty with or without stent implantation for acute myocardial infarction. N Engl J Med 1999;341:1949-1956.
12. Stone GW, Brodie BR, Griffin JJ, et al.: Prospective, multicenter study of the safety and feasibility of primary stenting in acute myocardial infarction: in-hospital and 30-day results of the PAMI stent pilot trial. J Am Coll Cardiol 1998;31:23-30.
13. Juliard J-M, Himbert D, Golmard J-L, et al.: Can we provide reperfusion therapy to all unselected patients admitted with acute myocardial infarction? J Am Coll Cardiol 1997;30:157-164.
14. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. N Engl J Med 1993;329:1615-1622.
15. Anderson JL, Karagounis LA, Becker LC, et al.: TIMI perfusion grade 3 but not grade 2 results in improved outcome after thrombolysis for myocardial infarction: ventriculographic, enzymatic, and electrocardiographic evidence from the TEAM-3 Study. Circulation 1993;87:1829-1839.
16. Gibson CM, Karha J, Murphy SA, et al.: Early and long-term clinical outcomes associated with reinfarction following fibrinolytic administration in the Thrombolysis in Myocardial Infarction trials. J Am Coll Cardiol 2003;42:7-16.
17. Antman EM, Anbe DT, Armstrong PW, et al.: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction -- executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). Circulation 2004;110:588-636.
18. Ahmed S, Antman EM, Murphy SA, et al.: Poor outcomes after fibrinolytic therapy for ST-segment elevation myocardial infarction: impact of age (a meta-analysis of a decade of trials). J Thromb Thrombolysis 2006;21:119-129.
19. Thune JJ, Hoefsten DE, Lindholm MG, et al.: Simple risk stratification at admission to identify patients with reduced mortality from primary angioplasty. Circulation 2005;112:2017-2021.
20. Hochman JS, Sleeper LA, Webb JG, et al.: Early revascularization in acute myocardial infarction complicated by cardiogenic shock. N Engl J Med 1999;341:625-634.
21. Stone GW; Grines CL; Cox DA, et al.: Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. N Engl J Med 2002 28;346:957-966.
22. 22. Valgimigli M, Percoco G, Malagutti P, et al.: Tirofiban and sirolimus-eluting stent vs abciximab and bare-metal stent for acute myocardial infarction: a randomized trial. JAMA 2005;293:2109-2117.
23. Spaulding C, Henry P, Teiger E, et al.: Sirolimus-eluting versus uncoated stents in acute myocardial infarction. N Engl J Med 2006;355:1093-1104.
24. Laarman GJ, Suttorp MJ, Dirksen MT, et al.: Paclitaxel-eluting versus uncoated stents in primary percutaneous coronary intervention. N Engl J Med 2006;355:1105-1113.
25. Chen ZM, Jiang LX, Chen YP, et al.: Addition

of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 2005;366:1607-1621.
26. Brouwer MA, van den Bergh JP, Aengevaeren, WR, et al.: Aspirin Plus Coumarin Versus Aspirin Alone in the Prevention of Reocclusion After Fibrinolysis for Acute Myocardial Infarction. Results of the Antithrombotics in the Prevention of Reocclusion In Coronary Thrombolysis (APRICOT)-2 Trial Circulation 2002;106:659-665.
27. Wiviot SD, Braunwald E, McCabe CH, et al.: Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001-2015.
28. Gibson MC, Murphy SA, Montelascet G, et al.: Percutaneous Coronary Intervention in patients receiving Enoxaparin or Unfractionated Heparin After Fibrinolytic Therapy for ST-Segment Elevation Myocardial Infarction in the ExTRACT-TIMI 25 Trial. J Am Coll Cardiol 2007;49:2238-2246.
29. Eitzman DT, Chi L, Saggin L, et al.: Heparin neutralization by plateletrich thrombi: role of platelet factor 4. Circulation 1994;89:1523-1529.
30. Lincoff AM, Califf Rm, Topol EJ. Platelet glycoprotein IIb/IIIa blockade in coronary artery disease. J Am Coll Cardiol 2000;35:1103-15.
31. Stone GW, Witzenbichler B, Guagliumini G, et al.: Comparison of bivalirudin to unfractionated heparin and glycoprotein IIb/IIIa inhibitors during primary percutaneous coronary intervention in acute myocardial infarction. N Engl J Med (in press).
32. Brodie B. What anti-thrombotic therapy is best with primary PCI for acute ST elevation myocardial infarction: How should the HORIZONS trial change current practice? Cath Cardiovasc Int 2008;71:816-821.
33. Weitz JL, Hudoba M, Masel D, Maraganore J, Hirsch J. Clot-bound thrombin is protected from inhibition by heparin-antithrombin III but is susceptable to inactivation by antithrombin III independent inhibitors. J Clin Invest 1990;86:385-391.
34. Henriques JPS, Zijlstra, F, Ottervanger JP, et al.: Incidence and clinical significance of distal embolization during primary angioplasty for acute myocardial infarction. Eur Heart J 2002;23:1112-1117.
35. Svilaas T, Vlaar PJ, van der Horst IC, et al.: Thrombus aspiration during primary percutaneous coronary intervention. N Engl J Med 2008;358:557-567.
36. Halkin A, Grines CL, Cox DA, et al.: Impact of intravenous beta-blockade before primary angioplasty on survival in patients undergoing mechanical reperfusion therapy for acute myocardial infarction. J Am Coll Cardiol 2004;43:1780-1787.
37. Kernis SJ, Harjai KJ, Stone GW, et al.: Does beta-blocker therapy improve clinical outcomes of acute myocardial infarction after successful primary angioplasty? J Am Coll Cardiol 2004;43:1773-1779.
38. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. Lancet 1995;345:669-685.
39. Hjalmarson A, Olsson G. Myocardial infarction: effects of beta-blockade. Circulation 1991;84:VI-101–VI-107.
40. Ibanez B, Prat-González S, Speidl WS, et al.: Early metoprolol administration before coronary reperfusion results in increased myocardial salvage. Circulation 2007;115:2909-2916.
41. Everly MJ, Heaton PC, Cluxton RJ Jr. Beta-blocker underuse in secondary prevention of myocardial infarction. Ann Pharmacother 2004;38:286-293.
42. Salpeter S, Ormiston T, Salpeter E. Cardioselective beta-blockers for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2005;(4):CD003566.
43. Chen ZM; Pan HC; Chen YP; et al.: Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 2005;366:1622-1632.
44. McMurray J, Solomon S, Pieper K, et al.: The effect of Valsartan, Captopril, or both on atherosclerotic events after acute myocardial infarction: an analysis of the valsartan in acute myocardial infarction trial (VALIANT). J Am Coll Cardiol 2006;47:726-733.
45. Cannon CP, Braunwald E, McCabe CH, et al.: Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350:1495-1504.
46. De Luca G, Suryapranata H, Ottervanger JP, et al.: Impact of statin therapy at discharge on 1-year mortality in patients with ST-segment elevation myocardial infarction treated with primary PCI. Atherosclerosis 2006;189:186-192.
47. Pitt B, Remme W, Zannad F, et al.: Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003;348:1309-1321.
48. Timmer JR, Ottervanger JP, Thomas K, et al.: Long-term cause specific mortality after myocardial infarction in Diabetes. Eur Heart J 2004;25:926-931.
49. Prasad A; Stone GW; Stuckey TD, et al.: Impact of diabetes mellitus on myocardial perfusion after primary angioplasty in patients with acute myocardial infarction. J Am Coll Cardiol 2005;45:508-514.
50. Timmer JR, van der Horst IC, de Luca G, et al.: Comparison of myocardial perfusion after successful primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction with versus without diabetes mellitus. Am J Cardiol 2005;95:1375-1377.

51. Colwell JA, Nesto RW. The platelets in diabetes: focus on prevention of ischemic events. Diabetes Care 2003;26:2181-2188.
52. Timmer JR, Ottervanger JP, de Boer MJ, et al.: Primary percutaneous coronary intervention compared with fibrinolysis for myocardial infarction in diabetes mellitus: Results From the Primary Coronary Angioplasty vs Thrombolysis-2 Trial. Arch Intern Med 2007;167:1353-1359.
53. Tuomilehto J, Lindstrom J, Eriksson JG, et al.: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001;344:1343-1350.
54. Serruys PW, Unger F, Sousa JE, et al.: Comparison of coronary artery bypass surgery and stenting for the treatment of multivessel disease. N Engl J Med 2001;344:1117-1124.
55. SoS Investigators. Coronary artery bypass surgery versus percutaneous coronary intervention with stent implantation in patients with multivessel coronary artery disease (the Stent or Surgery trial): A randomized controlled trial. Lancet 2002;360:965-970.
56. Ong AT, Serruys PW, Aoki J, et al.: The unrestricted use of paclitaxel versus sirolimus-eluting stents for coronary artery disease in an unselected population—One Year Results of The Taxus-Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) Registry. J Am Coll Cardiol 2005;45:1135-1141.
57. Orlic D, Bonizzoni E, Stankovic G, et al.: Treatment of multivessel coronary artery disease with sirolimus-eluting stent implantation: Immediate and mid-term results. J Am Coll Cardiol 2004;43:1154-1160.
58. Yang Z, Shen W, Zhang R, et al.: Coronary artery bypass surgery versus percutaneous coronary intervention with drug-eluting stent implantation in patients with multivessel coronary disease. J Interven Cardiol 2007;20:10-16.
59. Javaid A, Steinberg DH, Buch AN, et al.: Outcomes of coronary artery bypass grafting versus percutaneous coronary intervention with drug-eluting stents for patients with multivessel coronary artery disease. Circulation 2007;116:I-200 – I-206.
60. Moss AJ, Zareba W, Hall WJ, et al.: Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877-883.
61. Hohnloser SH, Kick KH, Dorian P, et al.: Randomized trial of prophylactic implantable cardioverter defibrillator after acute myocardial infarction. N Engl J Med 2004;351:2481-2488.
62. Van de Werf F, Ardissino D, Betriu A, et al.: Management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2003;24:28-66.

Part 1

Bleeding: incidence, predictors and influence of treatment

3

Incidence, predictors and prognostic importance of bleeding after primary PCI for ST-Elevation Myocardial Infarction

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R.S. Hermanides, J.P. Ottervanger, J.H. Dambrink, M.J. de Boer, J.C. Hoorntje, A.T. Gosselink, H. Suryapranata, A.W. van 't Hof, on behalf of the Zwolle myocardial infarction study group

Abstract

Aims: To investigate incidence, predictors and prognosis of bleeding in ST-Elevation Myocardial Infarction (STEMI) patients who underwent primary percutaneous coronary intervention (PCI).

Methods and results: A large scale, prospective, observational study was performed between 1991 and 2004 in a single teaching hospital in the Netherlands including all consecutive STEMI patients who underwent primary PCI. The independent association between both major and minor bleeding and one-year mortality was evaluated using Cox proportional Hazard models.
A total of 5030 patients were included, of whom 109 patients (2%) had cardiac surgery within 48 hours. Data on bleeding <48 hours were available in 4717 patients (96%). Of these, 80 (1.6%) had a major bleeding, whereas minor bleeding was observed in 266 patients (5.6%). Independent predictors of minor bleeding were advanced age, multivessel disease, Killip class ≥2 on admission, anterior MI location and TIMI 0 flow before PCI. Killip class ≥2 on admission was an independent predictor of major bleeding. Major bleeding (HR 3.5 (95% CI 2.3-5.4)) was associated with an increased risk of death at one year.

Conclusion: After primary PCI, the incidence of major bleeding is less than 2%. Although relatively infrequent, major bleeding complications are strongly and independently related to short- and midterm mortality.

Introduction

In patients with an acute coronary syndrome (ACS), including ST-Elevation Myocardial Infarction (STEMI), who undergo percutaneous coronary intervention (PCI), a number of antithrombotic and antiplatelet drugs are used.(1-3) A major limitation of these drugs is the increased risk of bleeding with particularly an increased risk in older patients, females, and those with renal failure, diabetes or heart failure.(4) In fact, bleeding may currently be the most common non-cardiac complication of therapy in patients with acute coronary syndromes, and anemia can develop or worsen during hospitalization even in the absence of overt bleeding.(5,6) An increased short-term and long-term mortality after bleeding complications have been demonstrated in a number of studies in patients with ACS.(7-10) Not surprisingly, research to the effect of newer and potentially safer antithrombotic agents have focused on the prevention of bleeding.(3,11,12) Although it is quite clear from randomised trials that primary PCI results in higher survival rates and less bleeding compared to fibrinolysis(13-15), bleeding may still occur after primary PCI. There is, however, limited information about the incidence, predictors and prognostic importance of bleeding in patients who have primary PCI for STEMI. The aim of the present study was to evaluate the incidence and predictors of bleeding in patients undergoing primary PCI and whether bleeding is related to prognosis.

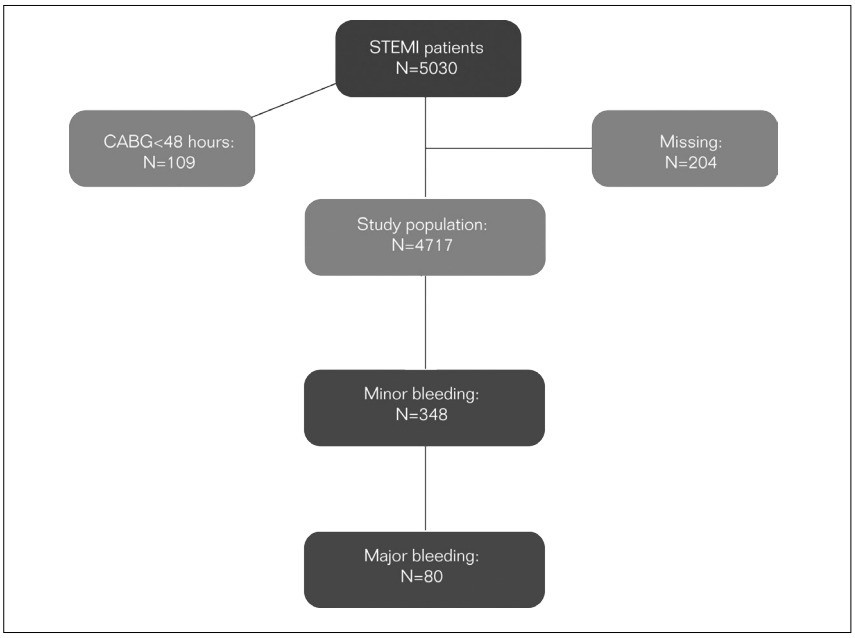

Figure 1: Flow chart of the study population

Population

From January 1991 to December 2004, individual patient data from all patients with admission diagnosis of STEMI admitted for primary PCI at the Isala klinieken (Zwolle, the Netherlands) were prospectively recorded. To avoid double inclusion of patients, only the first recorded admission for STEMI during the study period was used. Before the primary PCI procedure all patients received 300-500 mg of aspirin intravenously, and 5000-10.000 IU intravenous heparin. In addition to aspirin and heparin, clopidogrel was given 300mg orally since 1999. Primary PCI was performed with standard techniques if the coronary anatomy was suitable for angioplasty. Success of the PCI was determined by the classification system of the Thrombolysis in Myocardial Infarction (TIMI) trial (16), in which a grade 3 blood flow indicates normal flow within the vessel, in combination with a myocardial blush grade 2 or 3.(17) Additional treatment with glycoprotein IIb/IIIa inhibitors (12.5μg/kg bolus tirofiban) or stents was left to the discretion of the treating cardiologist. In those who had treatment with glycoprotein IIb/IIIa inhibitors, only a half dose of unfractionated heparin was given. All patients were treated with optimised drug-therapy including angiotensin-converting enzyme inhibitors, β-blockers and lipid-lowering drugs where appropriate.

Measurements (end points, definitions)

The frequency of bleeding during the first 48 hours was defined and classified according to the TIMI criteria.(18) Major bleeding was defined as either intracranial bleeding or overt bleeding with a decrease in hemoglobin ≥5 g/dl (≥ 3.1 mmol/L) or a decrease in hematocrit ≥15% within 48 hours after admission. Minor bleeding was defined as observed bleeding with decrease in hemoglobin ≥3 g/dl (≥1.9 mmol/L), or >10% decrease in hematocrit. If a bleeding site was not identified: >4 g/dl decrease in the hemoglobin concentration or >12% decrease in hematocrit within 48 hours after admission or intracranial bleeding within 48 hours.

Patients were diagnosed with STEMI if they had chest pain of > 30 minutes duration and ECG changes with ST segment elevation > 2 mm in at least 2 precordials and > 1 mm in the limb leads. Recurrent myocardial infarction was diagnosed when there was a 50 percent decrease of creatine kinase-muscle-brain fraction (CK-MB) from a previous peak value, followed by a subsequent rise to a level exceeding the upper limit of normal.

Protocol-specified blood sampling for CK and CK-MB levels was performed at baseline and at 8 hours, 16 hours and 24 hours after PCI. Measurement of serum total CK and CK-MB levels was performed according to local hospital standards. A large enzymatic infarct size was defined as patients who had a CK release (peak CK) in the highest tertile of the study population. Peak CK and peak CK-MB are

comparable independent predictors of LV function and one-year mortality in STEMI patients after primary PCI.(19) Left ventricular ejection fraction was measured before discharge by radionuclide ventriculography or by echocardiography if the patient had atrial fibrillation. Radionuclide ventriculography was performed by using the multiple gated equilibrium method following the labelling of red blood cells of the patient with 99mTc-pertechnate. A General Electric 300 gamma camera with a low-energy all-purpose parallel-hole collimator was used. Global ejection fraction was calculated by a General Electric Star View computer using the fully automatic PAGE program. In patients with atrial fibrillation, standard 2-dimensional and Doppler imaging was performed and stored in cineloop format by well-trained echocardiographists and reviewed by experienced cardiologists who estimated the ejection fraction by visual assessment.

Data collection and follow-up

We collected the following variables from the patient files: age, gender, history of hypertension, diabetes, hyperlipidemia, smoking, previous myocardial infarction, Killip class on admission, angiographic variables, laboratory measurements, pre-discharge LV function and discharge medication. Follow-up information was obtained from the patient's general physician or by direct telephone interview with the patient. Study approval was obtained from the medical ethic committee of our hospital.

Statistical Analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 12.0.1. Continuous data were expressed as mean ± standard deviation and categorical data as percentage, unless otherwise denoted. Differences between continuous data were performed by students t test and the chi-square or Fisher's exact test was used as appropriate for dichotomous data. Multivariable logistic regression analysis was performed to test the independent association between baseline characteristics and bleeding. Separate analyses were performed according to potential influence of glycoprotein IIb/IIIa inhibitors, since data on its use were only collected from 2000 to 2004.

Significant variables analyzed are reported with their respective odd ratios and 95% confidence intervals. Cox proportional-hazards regression models were used to estimate hazard ratios of bleeding with regard to survival at one year. Survival was represented by Kaplan-Meier curves. For all analyses, statistical significance was assumed when the two-tailed probability value was < 0.05.

Results

Baseline characteristics

During the study period 5030 patients were included, of whom 109 patients (2%) had cardiac surgery within 48 hours. Mean age was 61.2±11.9 years (range 19-94 years) and 24% of those were female. Data on bleeding were available of 4717 patients (96%), and these patients compromised the study population (figure 1). Data on use of glycoprotein IIb/IIIa inhibitors were collected from 2000, and were available in 2032 patients (87% of 2330 patients admitted after 2000). A total of 80 patients (1.6%) had major bleeding, 75 patients with significant Hb decrease, and 5 patients with intracranial bleeding. Minor bleeding was observed in 266 patients (5.6%).

Predictors of bleeding

Differences of the baseline characteristics between patients with and without major bleeding are summarized in table 1 and the differences between patients with and without minor bleeding are summarized in table 2. There was a significant increase in major bleeding compared to no bleeding when glycoprotein IIb/IIIa inhibitors during primary PCI were used. Patients with bleeding (both major and minor) had a significantly higher Killip class ≥2 on admission compared with patients with no bleeding (39% and 29.3% vs. 10%, p=0.001). Duration of ischemic time was significantly longer for patients with major bleeding compared with those without bleeding (5.5 hrs vs. 4.8 hrs, p=0.04).

After multivariable analyses, adjusting for all variables that were statistically significant in univariable analyses only Killip class ≥2 on admission (OR 2.3 95% CI 1.7-2.9) remained a significant independent predictor of major bleeding. Independent predictors of minor bleeding were age (OR 1.03 per year, 95% CI 1.01 – 1.04), multi vessel disease (OR 1.5 95% 1.1 – 2.1), Killip class ≥2 on admission (OR 2.1 95% CI 1.8 – 2.4), anterior MI location (OR 1.3 95% CI 1.1 – 1.6) and TIMI 0 flow before PCI (OR 1.5 95% CI 1.1 – 2.1). Separate multivariable analyses revealed that use of GP IIb/IIIa was neither an independent predictor of major nor minor bleeding.

Bleeding and clinical outcome

Clinical outcome of the patients is summarized in table 3 and 4. Patients with major bleeding had a significantly larger enzymatic infarct size (p<0.001) and a lower LV ejection fraction (P=0.04) (table 3). Also the prevalence of a severely depressed LV ejection fraction (< 30%) was much higher in those with major bleeding compared to patients without major bleeding (27% vs. 13%, p=0.02). The mean hospital stay was significantly longer in patients with major bleeding (p<0.001). Unlike re-infarction, both stroke (p<0.001) and mortality (p<0.001) after 30 days as well

Table 1: General characteristics according to major bleeding in 4717 patients who were admitted for primary PCI for ST-elevation MI

Variables	No bleeding N=4371	Major bleeding N=80	P value
Age	60.9 ± 11.9	62.3 ± 11.8	0.28
Female gender	23	38	<0.001
History of			
MI	12	20	0.18
CABG	3	5.1	0.15
PCI	6.1	8.8	0.85
Stroke	3.3	3.8	0.28
Hypertension	29	39	0.20
Diabetes	10.0	7.5	0.16
Anterior location	50	38	<0.001
Ischemic time (hr)	4.7 ± 5.7	5.3 ± 3.8	0.49
Killip ≥2 on admission	8	39	<0.001
Coronary angiography			
Multi vessel disease	51	71	0.001
TIMI o flow pre-PCI	62	63	0.83
Initial treatment			
Glycoprotein IIb/IIIa inhibitor *	59	80	0.05
No PCI performed	8	20	<0.001
TIMI 3 flow post-PCI	89	71	<0.001

% or mean ± SD, * data available from 2000, of 2032 patients.
MI=myocardial infarction. CABG=coronary artery bypass graft. PCI=percutaneous coronary intervention. TIMI=thrombolysis in myocardial infarction.

Table 2: General characteristics according to minor bleeding in 4717 patients who were admitted for primary PCI for ST-elevation MI

Variables	No bleeding N=4371	Minor bleeding N=266	P value
Age	60.9 ± 11.9	65.3 ± 11.6	<0.001
Female gender	23	34.6	<0.001
History of			
MI	12	13.6	0.85
CABG	3	3.8	0.85
PCI	6.1	4.9	0.71
Stroke	3.3	4.9	<0.001
Hypertension	29	30.1	0.92
Diabetes	10.0	16.2	<0.001
Anterior location	50	37.6	<0.001
Ischemic time (hr)	4.7 ± 5.7	5.5 ± 6.8	0.0.6
Killip ≥2 on admission	8	29	<0.001
Coronary angiography			
Multi vessel disease	51	66.5	<0.001
TIMI o flow pre-PCI	62	64.7	0.001
Initial treatment			
Glycoprotein IIb/IIIa inhibitor *	59	67.6	0.13
No PCI performed	8	9.4	0.01
TIMI 3 flow post-PCI	89	70.7	<0.001

% or mean ± SD; * data available from 2000, in 2032 patients

as 1 year were significantly higher in those with major bleeding compared to those without major bleeding. Similar to major bleeding, those with minor bleeding had a significantly larger enzymatic infarct size (p<0.001) and a lower LV ejection fraction (p=0.04) (Table 4).

A total of 191 patients (4%) died within 30 days and 318 (6.7%) died within one year after admission. Both major bleeding, HR 7.0 (95% CI 4.7 – 10.5) and minor bleeding, HR 2.5 (95% CI 1.8 – 3.5) were associated with increased one-year mortality. Survival curves of patients with and without major or minor bleeding are depicted in figures 2 and 3.

After adjusting for differences in age and gender both major bleeding, HR 6.0 (95% CI 4.0 – 8.9) and minor bleeding, HR 1.8 (95% CI 1.3 – 2.6) were associated with increased one-year mortality. In the final survival multivariable model, adjustments were made for age, gender and for variables that were statistically significant different between those with and without bleeding in the multivariable analyses. Again, however only major bleeding, HR 3.5 (95% CI 2.3 – 5.4) was associated with increased one-year mortality.

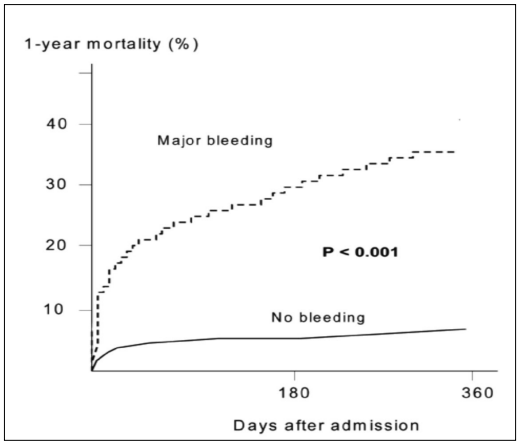

Figure 2: One-year mortality in patients with (N=80) and without (N=4371) major bleeding

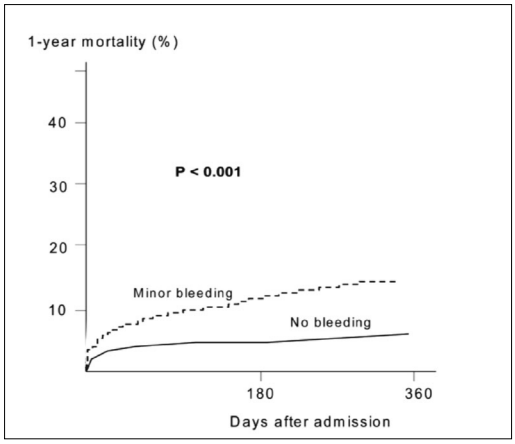

Figure 3: One-year mortality in patients with (N=266) and without (N=4371) minor bleeding

Discussion

In this large registry, the incidence of major bleeding within 48 hours after primary PCI was low, 1.6%. The incidence of minor bleeding was 5.6%. Major bleeding was an independent predictor of mortality.

Previous studies

Periprocedural bleeding is the most frequently reported non-cardiac complication

Table 3: Outcome according to major bleeding in 4717 patients who were admitted for primary PCI for ST-elevation MI

Variables	No bleeding N=4371	Major bleeding N=80	P value
Mean LVEF (%)	45 ± 12	41 ± 13	0.03
LVEF <30%	13	27	0.02
Peak CK	2362 ± 2210	4392 ± 6708	<0.001
Mean hospital stay (days)	4.7 ± 6.1	9.1 ± 8.8	<0.001
Mortality			
30 days	3.2	27.5	<0.001
One year	5.8	32.5	<0.001
Stroke			
30 days	0.3	6.3	<0.001
One year	0.8	7.5	<0.001
Re-MI			
30 days	2.8	3.8	0.60
One year	4.9	3.8	0.64

% or mean ± SD
LVEF=left ventricular ejection fraction CK=creatine kinase.

Table 4: Outcome according to minor bleeding in 4717 patients who were admitted for primary PCI for ST-elevation MI

Variables	No bleeding N=4371	Minor bleeding N=266	P value
Mean LVEF (%)	45 ± 12	43 ± 13	0.04
LVEF <30%	13	12.4	0.01
Peak CK	2362 ± 2210	3962 ± 5215	<0.001
Mean hospital stay (days)	4.7 ± 6.1	10.2 ± 8.0	<0.001
Mortality			
30 days	3.2	10.5	<0.001
One year	5.8	13.9	<0.001
Stroke			
30 days	0.3	0.8	0.13
One year	0.8	1.1	0.63
Re-MI			
30 days	2.8	4.1	0.19
One year	4.9	4.5	0.79

% or mean ± SD
LVEF=left ventricular ejection fraction CK=creatine kinase.

after PCI for ACS. The incidence of major bleeding in patients with ACS as reported in randomized trials varied, depending on bleeding definition, clinical presentation and treatment. An incidence of major bleeding of 4.1% was observed in the TIMI II trial (20), whereas an incidence as high as 15% was reported in the TIMI I trial. (16) The GUSTO IV-ACS trial reported low rates of both major bleeding (1.2%) and minor bleeding (2.8%) in ACS patients treated with abciximab without early revas-

cularization.(21) The GRACE study reported an incidence of major bleeding of 4.8% in STEMI patients, which was higher than in patients with NSTEMI and unstable angina.(4)

In the OASIS 5 trial (12), investigating patients with ACS, major bleeding was 0.6% in the fondaparinux group versus 1.4% in the enoxaparin group. Possibly, incidence of major bleeding may decrease after use of fondaparinux. The ACUITY trial reported a higher rate of major bleeding in ACS patients treated with heparin plus glycoprotein IIb/IIIa inhibitors (5.7%) versus bivalirudin monotherapy (3.0%). (10)

Predictors of bleeding

In our study, Killip class ≥2 on admission was independently associated with an increased risk of major bleeding.

Independent predictors of minor bleeding were advanced age, multi vessel disease, Killip class ≥2 on admission, anterior MI location and TIMI 0 flow before PCI. An increased risk of minor bleeding among patients of older age was also observed in previous studies.(4,22-24)

Patients with Killip class≥2 were more at risk for developing bleeding post-PCI, probably due to a more invasive therapy in these hemodynamically unstable patients. Both multivessel disease (more extensive coronary artery disease) and TIMI 0 flow pre-PCI may have been associated with more difficult PCI procedures, with longer procedure times.

In contrast to prior studies, our study showed that the use of glycoprotein IIb/IIIa inhibitors is not an independently predictor of major bleeding or minor bleeding. This may be explained by our use of only half-dose heparin when glycoprotein IIb/IIIa inhibitors were administered. Furthermore until 2006 we used half-dose bolus glycoprotein IIb/IIIa inhibitors (12.5μg/kg bolus tirofiban).

Prognostic importance of bleeding

A prognostic risk score for major bleeding in patients undergoing PCI via the femoral approach has been developed.(25) Although this combined clinical and procedural model may be useful to determine which patients are at greatest risk after PCI, STEMI patients however, were excluded and for these patients it is not useful.

Our study found that bleeding is an important independent predictor of prognosis in STEMI patients who underwent primary PCI. Major bleeding was associated with increased one-year mortality. Recently, Ndrepepa et al,(26) also reported an independent relationship between bleeding early after PCI and mortality at one year in patients with unstable angina and NSTEMI.

Several potential mechanisms might underlie the association between bleeding and deterioration of prognosis. Bleeding might lead to early cessation of dual antiplatelet therapy, which might result in ischemia, hemodynamic decompensation, stent

thrombosis, recurrent myocardial infarction or death.(27,28) Next, bleeding with hypovolemia and impaired oxygen carrying capacity might precipitate a hyper-adrenergic state, hypotension and heart failure. Furthermore, bleeding leads to blood transfusions that might themselves lead to increased cardiovascular risk.(7) Transfusion may induce microcirculatory disorder, nitric oxide, 2,3-DPG depletion and immunologic effects which may also affect long-term outcome.(29) Moreover, bleeding leads to a prolonged and complex hospital stay and might require invasive monitoring. The impact of bleeding on outcome varies with the initial severity. The more severe the bleed, the greater the impact on outcome.(30)

Study strengths and limitations

During the 13 years of inclusion, techniques of PCI and drug treatment (afterwards) have (been) changed. This may have affected outcome, but seems unlikely to have affected our principal conclusions. Our follow-up period was only one year, we had no data on death causes or data of medication changes during follow-up, clopidogrel was not included as a variable in analysis because of missing data during the first years. Also we recorded bleeding for just 48 hours after primary PCI. More important, this study period was before the era of routine measuring activated clotting time (ACT). We had no data on body weight, anticoagulant agents employed in-hospital, situation requiring systemic anticoagulation, previous history of bleeding, rate of transfusion, location and cause of bleeding and timing and method of sheath removal (manual or with closure device). Finally, no data on use of IABP or duration of primary PCI procedure were collected.

Conclusion

After primary PCI for STEMI, the incidence of major bleeding is less than 2%. Although relatively infrequent, major bleeding complications are strongly and independently related to short- and midterm mortality.

Trials on concomitant medication during primary PCI should pay much attention to the risk of bleeding complications.

References

1. Collet JP, Montelascot G, Lison L, Choussat R, Ankri A, Drobinski G, Sotirov I, Thomas D. Percutaneous coronary intervention after subcutaneous enoxaparin pretreatment in patients with unstable angina pectoris. Circulation 2001;103:658-663.
2. Ferguson JJ, Antman EM, Bates ER, Cohen M, Every NR, Harrington RA, Pepine CJ, Theroux P. Combining enoxaparin and glycoprotein IIb/IIIa antagonists for the treatment of acute coronary syndromes; finale results of the National Investigators Collaborating on Enoxaparin-3 (NICE-3) study. Am Heart J 2003;146:628-634.
3. Ferguson JJ, Califf RM, Antman EM, Cohen M, Grines CL, Goodman S, Kereiakes DJ, Langer A, Mahaffey KW, Nessel CC, Armstrong PW, Avezum A, Aylward P, Becker RC, Biasucci L, Borzak S, Col J, Frey MJ, Fry E, Gulba DC, Guneri S, Gurfinkel E, Harrington R, Hochman JS, Kleiman NS, Leon MB, Lopeze-Sendon JL, Pepine CJ, Ruzyllo W, Steinhubl SR, Teirstein SR, Toro-Figueroa L, White H. Enoxaparin vs. unfractionated heparin in high risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: primary results of the SYNERGY randomized trial. JAMA 2004;292:45-54.
4. Moscucci M, Fox KA, Cannon CP, Klein W, Lopez-Sendon J, Montelascot G, White K, Goldberg RJ. Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). Eur Heart J 2003;24:1815-1823.
5. Tahnk-Johnson ME, Sharkey SW. Impact of thrombolytic therapy on hemoglobin change after acute myocardial infarction. Am J Cardiol 1993;71:869-872.
6. Jan KM, Chien S, Bigger JT jr. Observations on blood viscosity changes after acute myocardial infarction. Circulation 1975;51:1079-1084.
7. Rao SV, Jollis JG, Harrington RA, Granger CB, Newby LK, Armstrong PW, Moliterno DJ, Lindblad L, Pieper K, Topol EJ, Stamler JS, Califf RM. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. JAMA 2004;292:1555-1562.
8. Segev A, Strauss BH, Tan M, Constance C, Langer A. Predictors and 1-year outcome of major bleeding in patients with non-ST-elevation acute coronary syndromes: insights from the Canadian Acute Coronary Syndrome Registries. Am Heart J 2005;150:690-694.
9. Eikelboom JW, Metha SR, Anand SS, Xie C, Fox KA, Yusuf S. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. Circulation 2006;114:774-782.
10. Manoukian SV, Feit F, Mehran R, Voeltz MD, Ebrahimi R, Hamon M, Dangas GD, Lincoff AM, White HD, Moses JW, King SB 3rd, Ohman EM, Stone GW. Impact of major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary syndromes: an analysis from the ACUITY trial. J Am Coll Cardiol 2007;49:1362-1368.
11. Lincoff AM, Bittl JA, Harrington RA, Feit F, Kleiman NS, Jackman JD, Sarembock IJ, Cohen Dj, Spriggs D, Ebrahimi R, Keren G, Carr J, Cohen EA, Betriu A, Desmet W, Kereiakes DJ, Rutsch W, Wilcox RG, de Feyter PJ, Vahanian A, Topol EJ. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. JAMA 2003;289:853-863.
12. Mehta SR, Granger CB, Eikelboom JW, Bassand JP, Wallentin L, Faxon DP, Peters RJ, Budai A, Afzal R, Chrolavicius S, Fox KA, Yusuf S. Efficacy and safety of fondaparinux versus enoxaparin in patients with acute coronary syndromes undergoing percutaneous coronary intervention results from the OASIS-5 Trial. J Am Coll Cardiol 2007;50:1742-1751.
13. Zijlstra F, de Boer MJ, Hoorntje JC, Reiffers S, Reiber JH, Suryapranata H. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. N Engl J Med 1993;328:680-684.
14. Grines CL, Browne KF, Marco J, Rothbaum D, Stone GW, O'Keefe J, Overlie P, Donohue B, Chelliah N, Timmis GC A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. The Primary Angioplasty in Myocardial Infarction Study Group. N Engl J Med 1993;328:673-679.
15. Zijlstra F, Hoorntje JC, de Boer MJ, Reiffers S, Miedema K, Ottervanger JP, van 't Hof AW, Suryapranata H. Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1999;341:1413-1419.
16. The TIMI Study Group. The Thrombolysis In Myocardial Infarction (TIMI) trial. N Engl J Med 1985;31:932-936.
17. van 't Hof AW, Liem A, Suryapranata H, Hoorntje JC, de Boer MJ, Zijlstra F. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction: myocardial blush grade. Circulation 1998;97:2302-2306.
18. Rao AK, Pratt C, Berke A, Jaffe A, Ockene I, Schreiber TL, Bell WR, Knatterud G, Robertson TL, Terrin ML. Thrombolysis in Myocardial Infarction (TIMI) Trial - phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. J Am Coll Cardiol 1988;11:1-11.
19. Nienhuis MB, Ottervanger JP, de Boer MJ, Dambrink JH, Hoorntje JC, Gosselink AT, Suryapranata H, van 't Hof AW. Prognostic importance of creatinine kinase and creatine kinase-MB after primary PCI for ST elevation myocardial infarction. Am Heart J 2008;155:673-679.

20. Bovill EG, Terrin ML, Stump DC, Berke AD, Frederick M, Collen D, Feit F, Gore JM, Hillis LD, Lambrew CT. Hemorrhagic events during therapy with recombinant tissue-type plasminogen activator, heparin, and aspirin for acute myocardial infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI), Phase II Trial. Ann Intern Med 1991;115:2562-65.
21. Lenderink T, Boersma E, Ruzyllo W, Widimsky P, Ohman EM, Armstrong PW, Wallentin L, Simoons ML. Bleeding events with abciximab in acute coronary syndromes without early revascularization: an analysis of GUSTO IV-ACS. Am Heart J 2004;147:865-873.
22. Kinnaird TD, Satbile E, Mintz GS, Lee CW, Canos DA, Gevorkian N, Pinnow EE, Kent KM, Pichard AD, Satler LF, Weissman NJ, Lindsay J, Fuchs S. Incidence, predictors, and prognostic implications of bleeding and blood transfusion following percutaneous coronary interventions. Am J Cardiol 2003;92:930-935.
23. Fox KA, Mehta SR, Peters R, Zhao F, Lakkis N, Gersh BJ, Yusuf S. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) Trial. Circulation 2004;110:1202-1208.
24. Collet JP, Montelascot G, Agnelli G, Van de Werf F, Gurfinkel EP, Lopez-Sendon J, Laufenberg CV, Klutman M, Gowda N, Gulba D. GRACE investigators. Non-ST-segment elevation acute coronary syndromes in patients with renal dysfunction: benefit of low-molecular-weight heparin alone or with glycoprotein IIb/IIIa inhibitors on outcome. The Global Registry of Acute Coronary Events. Eur Heart J 2005;26:2285-2293.
25. Nikolsky E, Mehran R, Dangas G, Fahy M, Na Y, Pocock SJ, Lincoff AM, Stone GW. Development and validation of a prognostic risk score for major bleeding in patients undergoing percutaneous coronary intervention via the femoral approach. Eur Heart J 2007;28:1936-1945.
26. Ndrepepa G, Berger PB, Mehilli J, Seyfarth M, Neumann FJ, Schomig A, Kastrati A. Periprocedural bleeding and 1-year outcome after percutaneous coronary interventions: appropriateness of including bleeding as a component of a quadruple end point. J Am Coll Cardiol 2008;51:690-697.
27. Eisenstein EL, Anstrom KJ, Kong DF, Shaw LK, Tuttle RH, Mark DB, Kramer JM, Harrington RA, Matchar DB, Kandzari DE, Peterson ED, Schulman Califf RM. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. JAMA 2007:297:159-168.
28. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M, Michev I, Corvaja N, Briguori C, Gerckens U, Grube E, Colombo A. Incidence, predictors and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005;293:2126-2130.
29. Rao SV, O'Grady K, Pieper KS, Granger CB, Newby LK, Mahaffey KW, Moliterno DJ, Lincoff AM, Armstrong PW, Van de Werf F, Califf RM, Harrington RA. A comparison of the clinical impact of bleeding measured by two different classifications among patients with acute coronary syndromes. J Am Coll Cardiol 2006;47:809-816.
30. Rao SV, Eikelboom JA, Granger CB, Harrington RA, Califf RM, Bassand JP. Bleeding and blood transfusion issues in patients with non-ST segment elevation acute coronary syndromes. Eur Heart J 2007;28:1193-1204.

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Risk of bleeding after prehospital administration of high dose tirofiban for ST-Elevation Myocardial Infarction

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R.S. Hermanides, J.P. Ottervanger, J.H. Dambrink, T. Dill,
K.G. Houwelingen, J.M. ten Berg, J.J. Kolkman, C. Hamm,
A.W. van 't Hof, on behalf of the On-TIME 2 trial investigators

Abstract

Background: In most patients with ST-elevation myocardial infarction (STEMI), antiplatelet drugs are already administrated in the ambulance, before hospital admission. We investigated the safety of prehospital initiation of a high dose of the glycoprotein IIb/IIIa inhibitor tirofiban on top of aspirin, clopidogrel and heparin.

Methods: It concerns a sub-analysis of the On-TIME 2 trial. 1398 patients were enrolled and 1275 patients (91.2%) had clinical follow up. Non CABG-related bleeding was defined according to the TIMI criteria. Logistic regression was used to determine predictors of 30-day bleeding. The independent association between bleeding and mortality (30-day and 1-year) was evaluated using Cox proportional Hazard models.

Results: Bleeding (major or minor) was observed in 47 patients (3.7%), with only 13 patients (1%) with major bleeding. The strongest independent determinants of bleeding were age (OR 1.05, 95% CI 1.01–1.08, p=0.011), Killip class >1 at admission (OR 2.5, 95% CI 1.2–5.3, p=0.020) and intra aortic balloon pump (IABP) use (OR 4.2, 95% CI 1.6–11.1, p=0.003). High dose tirofiban was not an independent predictor of bleeding (OR 1.7, 95% CI 0.9–3.2, p=0.116). Bleeding was associated with an increased risk of 30-day mortality (HR 5.5, 95% CI 1.6–7.8, p<0.001) and one-year mortality (HR 3.2, 95% CI 1.4–7.2, p=0.005).

Conclusion: Prehospital use of high dose tirofiban is safe and associated with a low risk of bleeding. Age, Killip class >1, IABP use, but not high dose tirofiban are independent determinants of bleeding in STEMI patients. Bleeding is independently associated with 30-day and 1-year mortality.

Introduction

Antithrombotic and antiplatelet drugs reduce mortality and other major adverse cardiac events (MACE) in patients with primary coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI).(1-5) However, this benefit may be accompanied by an increased risk of (peri-procedural) bleeding, particularly with the use of glycoprotein IIb/IIIa inhibitors (GPI).(6,7) Bleeding is currently the most common non-cardiac complication in patients treated for STEMI, and is associated with worse outcomes.(8-10) The choice, dosage and duration of antithrombin and/or antiplatelet therapy are perhaps the most readily modifiable risk factors for bleeding. For this reason, research on the effect of newer and potentially safer antithrombotic agents have focused on the prevention of bleeding.(11-13)

Routine prehospital initiation of high-dose bolus tirofiban (HDT) in addition to aspirin, heparin and high-dose clopidogrel improves PCI success in STEMI(14), but whether HDT also leads to an important increase of bleeding is unknown. Therefore, the aims of the present study were to evaluate the safety of prehospital initiation of HDT and to determine the predictors of bleeding in STEMI patients undergoing primary PCI. Furthermore, we investigated whether bleeding was related to prognosis.

Methods

Study design

It concerns a sub-analysis of the On-TIME 2 trial (N=984) and it's open label run-in phase (N=414). The On-TIME 2 trial was a prospective, multicentre, placebo-controlled, randomised, clinical trial investigating the effect of pre-hospital administration of HDT on top of aspirin, clopidogrel and heparin in STEMI patients treated with primary PCI. The On-TIME 2 trial is registered, number ISRCTN06195297. The rationale, design, primary- and 1-year results of the study have been described previously.(14-16)

Ethics

Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

Procedures

Patients were randomly assigned to prehospital treatment with HDT (25 μg/kg bolus and 0.15 μg/kg/min maintenance infusion for 18 h) or placebo (bolus plus infusion) by blinded sealed kits with study drug. In the ambulance or referring centre, 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 (ACT) was less than 200 seconds. Coronary angiography and PCI were done according to each institution's guidelines and standards. Patients who underwent coronary artery bypass grafting (CABG) <30 days were excluded from analysis.

Measurements (end points, definitions)

The primary efficacy endpoint was to assess the safety of HDT and to determine the predictors of (major or minor) bleeding. The key secondary endpoint was to determine if bleeding was related to prognosis. Another secondary endpoint was to compare clinical outcome in patients with access-site bleeding versus non access-site related bleeding.

30-day bleeding (non CABG-related) was assessed and adjudicated using the thrombolysis in myocardial infarction (TIMI) scale.(17) Major bleeding was defined as either intracranial bleeding or overt bleeding with a decrease in hemoglobin ≥5 g/dl (≥ 3.1 mmol/L) or a decrease in hematocrit ≥15% within 30 days after admission. Minor bleeding was defined as identified bleeding with decrease in hemoglobin ≥3 g/dl (≥1.9 mmol/L), or >10% decrease in hematocrit. If a bleeding site was not identified, a >4 g/dl (≥ 2.4 mmol/L) decrease in the hemoglobin concentration or >12% decrease in hematocrit within 30 days after admission would be the criteria. Anemia was defined using World Health Organization criteria (hemoglobin <13 g/dl (8.0 mmol/L) in men and <12 g/dl (7.5 mmol/L) in women.(18) A blinded, independent clinical endpoint committee adjudicated all clinical endpoints including bleeding. Follow-up information was derived from outpatient clinic visits or via contact by telephone at 30 days and 1 year.

Statistical Analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 15.0.1. All analyses were done according to the intention-to-treat principle. All p values were two-sided. For all analyses, statistical significance was assumed when the two tailed probability value was <0.05. Continuous data were expressed as mean ± standard deviation and categorical data as percentage, unless otherwise denoted. Differences between continuous data were performed by student's t test or Mann Whitney U test and the chi-square or Fisher's exact test was used as appropriate for dichotomous data. Multivariable logistic regression analyses were performed to identify independent determinants of bleeding. Backward stepwise selection was used selecting baseline variables with entry/stay criteria of $p<0.10$. Variables entered into the model included age (per year increment), female gender, previous CVA, Killip class > 1, TIMI risk score > 3 and intra-aortic balloon pump (IABP) use, and randomisation to

HDT. Significant variables analyzed are reported with their respective odd ratios and 95% confidence intervals. Cox proportional-hazards regression models were used to estimate hazard ratios of bleeding with regard to survival at 30 days and 1 year follow-up, selecting baseline variables with entry/stay criteria of $p<0.10$. Variables entered into the model included age, female gender, renal insufficiency, Killip class > 1, three vessel disease, IABP use and non CABG-related (major or minor) bleeding. Survival was represented by Kaplan-Meier curves.

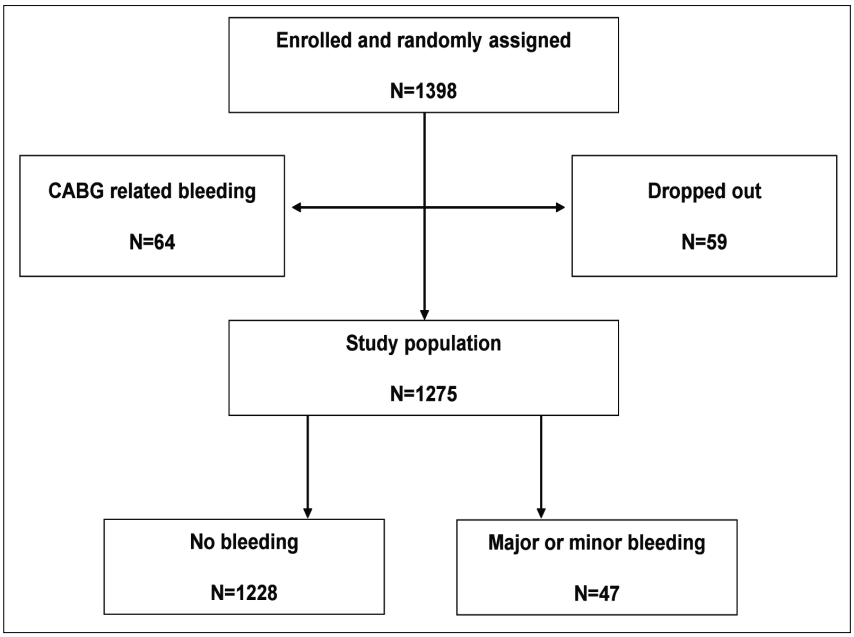

Figure 1: Sub-analysis profile

Results

Baseline characteristics

Figure 1 shows the sub-analysis profile. Of the 1275 patients who had 30-day clinical follow-up (91.2%), 47 patients developed a (major or minor) bleeding (3.7%). 13 patients developed a major bleeding (1.0%) and 34 patients a minor bleeding (2.7%). Of the 47 patients with bleeding, 47% were access site related, 6% retro-peritoneal bleeding, 17% gastro-intestinal bleeding and 30% other. Of the 1275 patients, 632 were randomly assigned to HDT and 643 to no HDT or placebo. The incidence of non CABG-related bleeding was not significantly different in patients randomised to HDT and no HDT or placebo (4.4% vs 3.0%, p=0.198). Differences of baseline and angiographic characteristics between patients with and without bleeding are summarized in table 1 and 2. Bleeding patients were significantly older, more often female, and had a higher rate of renal failure. Furthermore, patients with bleeding

Table 1: Baseline characteristics of patients with and without bleeding

Baseline	No bleeding N=1228	Bleeding N=47	P value
Age	61.4 ± 12.0	68.6 ± 9.8	<0.001
Female gender	23.9	42.6	0.004
BMI	26.8 ± 3.8	27.0 ± 3.8	0.768
Hypertension	33.3	48.9	0.027
Smoking	48.7	25.5	0.002
Hypercholesterolemia	24.9	36.2	0.082
Family history	40.1	42.6	0.740
Diabetes Mellitus	10.7	12.8	0.596
Previous MI	8.5	12.8	0.307
Previous PCI	7.7	17.0	0.022
Previous CABG	2.0	2.1	0.934
Previous CVA	1.3	4.3	0.092
Anemia*	14.5	15.0	0.933
Renal insufficiency	14.8	40.0	<0.001
TIMI risk > 3	27.9	65.2	<0.001
Killip > 1	11.6	26.1	0.003
Systolic BP (mmHg)	131.8 ± 24.6	130 ± 30	0.672
Diastolic BP (mmHg)	77.9 ± 15.6	73 ± 16	0.020
Ischemic time (min)	167 (128 – 243)	159 (130 – 289)	0.602
Time SO to diagnosis (min)	76 (45 – 145)	81 (46 – 177)	0.635
Study medication angio	55 (43 – 70)	60 (43 – 75)	0.430
Randomised to Tirofiban	50.0	59.6	0.198

Data are n/N (%) or mean (SD), or median (IQR). BMI=body mass index. MI=myocardial infarction. PCI=percutaneous coronary intervention. CABG=coronary artery bypass grafting. GFR= glomerular filtration rate. BP=blood pressure. Renal insufficiency= creatinine clearance <60 ml/min (as calculated by MDRD). SO=symptom onset.
* Only recorded in the double-blind phase.

had a significantly higher rate of Killip class >1 on admission and more often a TIMI risk score >3. However, randomisation to prehospital HDT was not significantly different between the groups.

Angiographic and laboratory characteristics

Patients with bleeding had more often left main stenosis. Furthermore, bleeding patients had a significantly higher rate of IABP use, temporary pacemaker use, a longer time to sheath removal and more often manual compression as compared to closure devices to achieve hemostasis. The occurrence of thrombocytopenia was associated with a higher risk of bleeding.

Table 2: Angiographic and laboratory outcomes of patients with and without bleeding

Baseline	No Bleeding N=1228	Bleeding N=47	P value
Three vessel	15.3	19.1	0.469
Left main stenosis	0.3	2.1	0.030
Anterior infarction	42.2	46.3	0.601
Angio performed	98.7	100	0.431
TIMI flow at initial angiography			0.276
0,1	46.7	58.7	
2	33.2	26.1	
3	20.1	15.2	
ACT (sec)*	179 ± 64	194 ± 69	0.201
Extra UFH (2500IU)*	72.5	73.2	0.922
Overdose UFH**	58.4	68.1	0.187
Overdose Tirofiban***	0.9	4.4	0.074
PCI done	89.6	100	0.001
PCI immediately after CAG	99.3	95.7	0.011
- Rescue thrombosuction	10.8	8.5	0.612
- IABP	0.4	14.9	<0.001
- Temporary pacemaker	0.4	4.3	0.001
Distal embolisation after PCI	6.5	8.8	0.585
TIMI 0/1 flow or distal embolisation	9.7	13.0	0.251
Time sheath removal (min)	41 (28 – 101)	271 (71 – 1175)	< 0.001
Hemostasis*			
-Closure device	73.1	34.2	< 0.001
Angio-Seal	92.2	84.6	0.275
-Manual compression	26.9	65.8	
Laboratory outcomes			
Hb baseline*	9.5 ± 7.1	9.0 ± 2.4	0.667
Hematocrit*	0.4 ± 0.0	0.4 ± 0.04	0.081
Thrombocytes*	250 ± 70	257 ± 83	0.510
Thrombopenia at 72-96 hr****	8.2	24.3	0.005

Data are n/N (%) or mean (SD). TIMI=thrombolysis in myocardial infarction. ACT=activated clotting time. UFH=unfractionated heparin. PCI=percutaneous coronary intervention. CAG=coronary angiography. IABP=intra aortic balloon pump. MBG=myocardial blush grade. Hb=hemoglobin.

* Only recorded in the double-blind phase.

** More than weight adjusted UFH dosage (60 IU/kg)

*** Patients with GFR<30 should get half dose Tirofiban (12.5 µg/kg bolus)

**** Thrombocytes<150x109/L

Table 3: Clinical outcomes in patients with and without bleeding

Baseline	No bleeding N=1228	Bleeding N=47	P value
LVEF < 30%	6.0	10.3	0.295
Peak CK	1721 ± 1701	2571 ± 2865	0.037
Mean hospital stay	4.4 ± 5.0	8.8 ± 10.0	<0.001
30 day Outcome			
Death	2.8	14.9	<0.001
Recurrent MI	2.0	8.5	0.003
Death or recurrent MI	4.6	23.4	<0.001
Urgent TVR	3.1	10.6	0.005
- Urgent CABG	0.2		0.734
- Urgent PCI	2.9	10.6	0.003
MACE	6.1	25.5	<0.001
Stroke	0.6	6.4	<0.001
1 year Outcome	**N=1219**	**N=46**	
Death	4.3	17.4	<0.001
Recurrent MI	2.6	13.0	0.002
Death or recurrent MI	6.7	30.4	<0.001

Data are n/N (%) or mean (SD). LVEF=left ventricular ejection fraction. CK=creatine kinase. MACE=major adverse cardiac event. TVR=target vessel revascularisation. MI=myocardial infarction.

Independent determinants of bleeding

After multivariate analyses, adjusting for all variables that were statistically significant in univariable analyses, age (odds ratio (OR) 1.05, 95% CI 1.01 – 1.08, p=0.011), Killip class > 1 at admission (OR 2.5, 95% CI 1.2 – 5.3, p=0.020) and IABP use (OR 4.2, 95% CI 1.6 – 11.1, p=0.003) were independent determinants of bleeding. Randomisation to HDT was not an independent predictor of bleeding (OR 1.7, 95% CI 0.9 – 3.2, p=0.116).

Clinical outcome

Table 3 shows all clinical outcomes. Patients with bleeding had a significant higher mean peak creatine kinase level and a longer mean hospital stay. Thirty days mortality was significantly higher in the bleeding group (14.9% vs 2.8%, p=0.005, figure 2). There were however no significant differences of 30-day mortality or 30-day MACE between patients with access site- and those with non access site related bleeding. Patients with bleeding had a significant higher rate of stroke within 30 days after admission (6.4% vs 0.6%, p<0.001) and also a significant increased rate of 30-day MACE (25.5% vs 6.1%, p<0.001, table 3).

A total of 61 patients (4.8%) died within one year after admission and this was

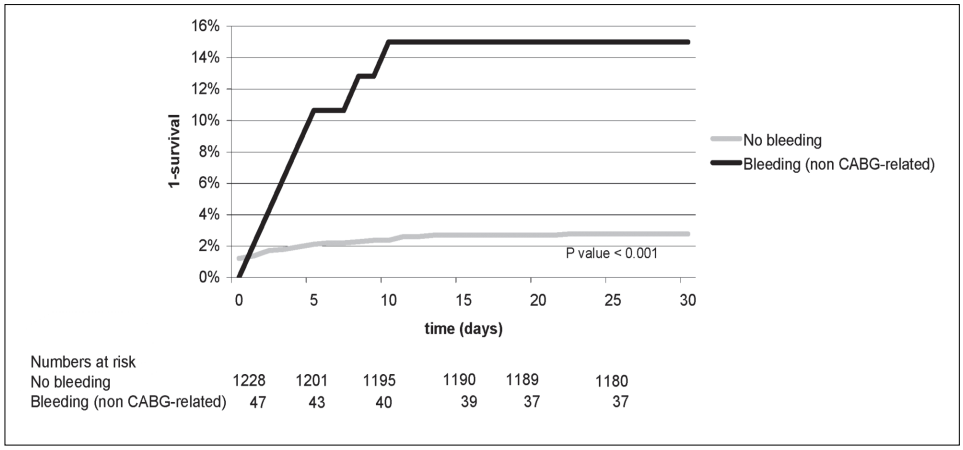

Figure 2: 30-day mortality

significantly higher in the bleeding group (17.4% vs 4.3%, p<0.001). After adjusting for variables that were statistically significantly different in univariate analysis, bleeding was associated with both increased 30-day mortality (HR 5.5, 95% CI 1.6 – 7.8, p<0.001) and one-year mortality (HR 3.2, 95% CI 1.4 – 7.2, p=0.005).

Comparison of outcomes in both study phases

We compared patients in the open label phase with those in the blinded phase. There were no important differences in baseline characteristics between the two groups. Also, there were no important differences regarding the association between risk factors for bleeding in the two phases, although of course because of the smaller sample size, the statistical significance was less clear.

Furthermore, in all study phases, randomisation to tirofiban was not significant different in patients with- or without bleeding. In the open label phase, tirofiban was associated with a relative risk of 0.79 (0.58 – 1.75) on bleeding, whereas in the blinded phase this relative risk was 0.84 (95% CI 0.67 – 1.14). In both groups, bleeding was significantly associated with increased 30-day and 1-year mortality.

Discussion

Our analysis shows that prehospital use of HDT in the ambulance is safe and associated with a low risk of bleeding in patients treated with primary PCI for STEMI. Age, Killip class >1 and IABP use are independent determinants of (major or minor) bleeding. Bleeding is independently associated with short-term and long-term adverse outcomes.

Occurrence of bleeding: comparison with previous studies

Comparison of bleeding rates between different studies is difficult due to various antithrombotic regimens, differences of inclusion/exclusion criteria and the used definition of bleeding.(19)

The HORIZONS-AMI trial revealed that anticoagulation with bivalirudin alone, as compared with heparin plus GPI, reduced major bleeding, but observed a much higher incidence of (non-CABG related) TIMI bleeding in the heparin plus GPI group (9.6%) compared to our analysis (4.4%).(13) Although in- and exclusion criteria were identical in HORIZONS-AMI and On-TIME 2, and the patients comparable, HORIZONS-AMI used a different heparin protocol (heparin was given both before [76%] and during [99%] the procedure, with target ACT around 250 seconds), while in the On-TIME 2 trial heparin was dosed before [100%] and during [72.6%] the procedure with target ACT around 180 seconds. Furthermore, in HORIZONS-AMI not tirofiban but abciximab (52%) and eptifibatide (47%) were used.

In the ADMIRAL trial, the prevalence of 30-day TIMI overall bleeding (major or minor) in the abciximab group was 12.8%, mainly driven by minor bleeding.(20) In the FINESSE trial, the prevalence of TIMI overall bleeding (major or minor) at discharge in the abciximab facilitated PCI group was 10.1%.(21) These trials also showed a higher prevalence of bleeding as compared to our analysis, but in these trials also CABG-related bleeding were included.

Predictors of bleeding

There is debate whether GPI are independent associated with bleeding.(22-24) In our analysis, prehospital use of HDT was not an independent predictor of bleeding, but the incidence of bleeding in our population was low, and therefore conclusions should be made cautiously.

Our analysis confirmed that advanced age, Killip class >1 and IABP use are associated with an increased risk of bleeding.(10,24,25) Early IABP removal, if possible, may decrease the risk of access site related complications.(26)

Because baseline prediction of bleeding risk can modify medical strategies, possibly also in STEMI the CRUSADE bleeding score, which was introduced for NSTEMI, can be used.(27) Also a recently reported bleeding risk score for acute coronary syndrome can be used.(28) Additional studies should clarify how use of these bleeding risk scores should modify (antiplatelet) medical therapy.

Impact of bleeding

Our analysis confirms previous observations (8,9,10,24,54,29) that bleeding is an independent determinant of both short- and long-term mortality.

Potential explanations for the high mortality after bleeding include hemodynamic disturbances caused by the bleeding, premature cessation of antiplatelet therapy and liberal use of blood transfusion.(9-11,23,24,30,31)

Limitations

Limitations of the On-TIME 2 trial have been described.(14) ACT measurement and hemostasis with manual compression or closure device were only recorded in the double-blind phase of the On-TIME 2 trial and thus were not included as a variable in analysis of the combined group. In the present study, we pooled the results from the double-blind study phase with 414 patients from the open-label phase who were randomised to high dose tirofiban or no tirofiban in the ambulance. Although the treatment in the open-label phase was not blinded, it is important to note that the study protocol for the 2 phases only differed with regard to trial design: open-label versus blinded. The pooled analysis was pre-specified in the final protocol and statistical plan for the study, and there was no difference in baseline characteristics or in the effect of high dose tirofiban on the primary endpoint between the 2 phases of the study.

Furthermore, we described a pre-specified sub-analysis with limited patient numbers, randomisation (high dose tirofiban or no high dose tirofiban/placebo) was not powered to demonstrate differences in bleeding, and only 47 patients (3.7%) had a non CABG-related (major or minor) bleeding. Because of these circumstances, the safety of high dose tirofiban has to be interpreted with some caution.

Conclusion

In patients with STEMI, prehospital administration of high dose tirofiban is safe and associated with a low risk of bleeding. Age, Killip class >1 and IABP use are strong, independent determinants of bleeding. Bleeding remains an independent predictor of 30-day and 1-year mortality.

References

1. Collet JP, Montalescot G, Lison L, et al. Percutaneous coronary intervention after subcutaneous enoxaparin pre-treatment in patients with unstable angina pectoris. Circulation 2001;103:658-663.
2. Ferguson JJ, Antman EM, Bates ER, et al. Combining enoxaparin and glycoprotein IIb/IIIa antagonists for the treatment of acute coronary syndromes; final results of the National Investigators Collaborating on Enoxaparin-3 (NICE-3) study. Am Heart J 2003;146:628-634.
3. Ferguson JJ, Calif RM, Antman EM, et al. Enoxaparin vs. unfractionated heparin in high risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: primary results of the SYNERGY randomized trial. JAMA 2004;292:45-54.
4. Stone GW, Mc Laurin BT, Cox DA, et al. Bivalirudin for patients with acute coronary syndromes. N Engl J Med 2006;355:2203-2216.
5. Grines CL, Bonow RO, Casey DE Jr, et al. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: a science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. J Am Dent Assoc 2007;138:652-655.
6. The EPIC investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. N Engl J Med 1994;330:956-961.
7. ESPRIT investigators. Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrillin Therapy. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. Lancet 2000;356:2037-2044.
8. Eikelboom JW, Metha SR, Anand SS, et al. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. Circulation 2006;114:774-782.
9. Manoukian SV, Feit F, Mehran R, et al. Impact of major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary syndromes: an analysis from the ACUITY trial. J Am Coll Cardiol 2007;49:1362-1368.
10. Rao SV, O'Grady K, Pieper KS, et al. Impact of bleeding severity on clinical outcomes among patients with acute coronary syndromes. Am J Cardiol 2005;96:1200-1206.
11. Lincoff AM, Bittl JA, Harrington RA, et al. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. JAMA 2003;289:853-863.
12. Mehta SR, Granger CB, Eikelboom JW, et al. Efficacy and safety of fondaparinux versus enoxaparin in patients with acute coronary syndromes undergoing percutaneous coronary intervention results from the OASIS-5 Trial. J Am Coll Cardiol 2007;50:1742-1751.
13. Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med 2008;358:2218-2230.
14. van 't Hof AW, ten Berg JM, Heestermans AA, et al. Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial. Lancet 2008;372:537-546.
15. van 't Hof AW, Hamm C, Rasoul S, et al, on behalf of the On-TIME 2 investigators. Ongoing tirofiban in myocardial infarction evaluation (On-TIME) 2 trial: rationale and study design. EuroInterv 2007;3:371-380.
16. ten Berg JM, van 't Hof AW, Dill T, et al. On behalf of the Ongoing Tirofiban In Myocardial infarction Evaluation (On-TIME) 2 study group. Effect of early, pre-hospital initiation of high-bolus dose tirofiban in patients with ST-segment elevation myocardial infarction on short and long-term clinical outcome. J Am Coll Cardiol 2010;55:2446-2455.
17. Rao AK, Pratt C, Berke A, et al. Thrombolysis in Myocardial Infarction (TIMI) Trial — phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. J Am Coll Cardiol 1988;11:1-11.
18. World Health Organization. Nutritional anaemias: report of a WHO scientific group. World Health Organ Tech Rep Ser 1968;405:5-37.
19. Rao SV, Eikelboom JW, Steg PG, et al, on behalf of the Academic Bleeding Consensus multidisciplinary working group. Am Heart J 2009;158:881-886.
20. Montalescot G, Barragan P, Wittenberg O, et al. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. N Engl J Med 2001;344:1895-1903.
21. Ellis SG, Tendera M, de Belder MA, et al. Facilitated PCI in patients with ST-elevation myocardial infarction. N Engl J Med 2008;358:2205-2217.
22. Valgimigli M, Biondi-Zoccai G, Tebaldi M, et al. Tirofiban as adjunctive therapy for acute coronary syndromes and percutaneous coronary intervention: a meta-analysis of randomized trials. Eur Heart J 2010;31:35-49.
23. Spencer FA, Moscucci M, Granger GB, et al. Does comorbidity account for the excess mortality in patients with major bleeding in acute myocardial infarction? Circulation 2007;116:2793-2801.
24. Feit F, Voeltz MD, Attubato MJ, et al. Predictors and impact of major hemorrhage on mortality following percutaneous coronary intervention from the REPLACE-2 trial. Am J Cardiol 2007;100:1364-1369.

25. Kinnaird TD, Satbile E, Mintz GS, et al. Incidence, predictors, and prognostic implications of bleeding and blood transfusion following percutaneous coronary interventions. Am J Cardiol 2003;92:930-935.
26. Ferguson JJ III, Cohen M, Freedman RJ Jr, et al. The current practice of intra-aortic balloon counterpulsation: results from the Benchmark registry. J Am Coll Cardiol 2001;38:1456-1462.
27. Subherwal S, Bach RG, Chen Ay, et al. Baseline risk of major bleeding in Non-ST-elevation myocardial infarction. Circulation 2009;119:1873-1882.
28. Mehran R, Pocock SJ, Nikolsky E, et al. A risk score to predict bleeding in patients with acute coronary syndromes. J Am Coll Cardiol 2010;55:2556-2566.
29. Mehran R, Lansky AL, Witzenbichler B, et al. Bivalirudin in patients undergoing primary angioplasty for acute myocardial infarction (HORIZONS-AMI): 1-year results of a randomised controlled trial. Lancet 2009;374:1149-1159.
30. Wang TY, Xiao L, Alexander KP, et al. Antiplatelet therapy use after discharge among acute myocardial infarction patients with in-hospital bleeding. Circulation 2008;118:2139-2145.
31. Rao SV, Jollis JG, Harrington RA, et al. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. JAMA 2004;292:1555-1562.

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Net clinical benefit of pre-hospital glycoprotein IIb/IIIa inhibitors in patients with ST-Elevation Myocardial Infarction and high risk of bleeding

Submitted

R.S. Hermanides, J.P. Ottervanger, J.M. ten Berg, A.T. Gosselink, K.G. van Houwelingen, J.H. Dambrink, P.R. Stella, C. Hamm, A.W. van 't Hof, on behalf of the On-TIME 2 trial investigators

Abstract

Aims: Aim of this sub-analysis was to assess the net clinical effect of pre-hospital administration of tirofiban in STEMI patients with high risk of bleeding.

Methods and results: This is a retrospective sub-analysis of the On-TIME 2 trial, a multicentre, controlled randomised trial of the effects of high bolus dose tirofiban given in the ambulance in STEMI patients. Tirofiban was given on top of aspirin, heparin, and clopidogrel. According to CRUSADE, patients with a moderate to very high baseline risk of bleeding were defined as high risk and patients with a very low- or low risk baseline bleeding risk were defined as low risk. Primary endpoint was net adverse clinical events (NACE) at 30 days (defined as the combined incidence of death, recurrent myocardial infarction, urgent target vessel revascularization, stroke, or non-CABG related major bleeding). Of 1309 patients, a high bleeding risk was present in 291 patients (22.2%). In these high risk bleeding patients tirofiban significantly improved post-percutaneous coronary intervention (PCI) ST segment resolution. Administration of tirofiban in high risk bleeding patients showed no difference in 30-day major adverse cardiac events (MACE) (9.4% vs 13.0%, p=0.330, RR 0.72, 95% CI 0.37 – 1.39). However, pre-treatment with tirofiban was associated with a non-significant increase in non CABG-related bleeding (8.6% vs 3.6%, p=0.082, RR 2.38, 95% CI 0.90-6.39). The net clinical effect (30-day NACE) of tirofiban in this group was balanced (11.5% vs 15.2%, p=0.365, RR 0.76, 95% CI 0.41-1.38).

Conclusion: Pre-hospital use of tirofiban in ST-Elevation Myocardial Infarction patients with high risk of bleeding improves post-PCI ST segment resolution but increases non-significantly the risk of non-CABG related bleeding. The net result is a balanced effect on 30-day NACE. Additional studies should clarify how use of bleeding risk scores should modify medical (antiplatelet) therapy.

Introduction

Pre-hospital initiation of high bolus dose (HBD) tirofiban in addition to aspirin, heparin and high-dose clopidogrel improves clinical outcome(1,2), and is associated with a low risk of bleeding.(3) However, bleeding is currently the most common non-cardiac complication in patients treated for ST-elevation myocardial infarction (STEMI), and has emerged as an independent predictor for subsequent mortality in patients with acute coronary syndromes (ACS).(4-9) Therefore, in patients with a high risk of bleeding, the benefits of tirofiban may be counterbalanced by bleeding complications, resulting in less benefit or even an increased risk of mortality after administration of tirofiban.

It is currently unknown whether pre-hospital HBD tirofiban in high risk bleeding patients is beneficial. The aim of this study was to assess the net clinical benefit of early initiation of HBD tirofiban in STEMI patients with high risk of bleeding, using data of the On-TIME 2 trial.

Methods

Study design

It concerns a retrospective pooled sub-analysis of the On-TIME 2 trial (N=984) and it's open label run-in phase (N=414). The On-TIME 2 trial was a prospective, multicentre, placebo-controlled, randomised, clinical trial investigating the effect of pre-hospital administration of HBD tirofiban on top of aspirin, clopidogrel and heparin in STEMI patients treated with primary PCI. The On-TIME 2 trial is registered, number ISRCTN06195297. The rationale, design, primary- and 1-year results of the study have been described previously.(1,2,10)

Procedures

Patients were randomly assigned to prehospital treatment with HBD tirofiban (25 μg/kg bolus and 0.15 μg/kg/min maintenance infusion for 18 h) or no HBD tirofiban [phase 1] or placebo (bolus plus infusion) by blinded sealed kits with study drug [phase 2]. In the ambulance or referring centre, all patients also received a bolus of 5000 IU of unfractionated heparin (UFH) intravenously together with aspirin 500 mg intravenously and a 600 mg loading dose of clopidogrel orally. Before PCI, additional UFH (2500 IU) was only given if the activated clotting time (ACT) was less than 200 seconds. Coronary angiography and PCI were done according to each institution's guidelines and standards.

Measurements (end points, definitions)

The primary efficacy endpoint of this retrospective pooled analysis was to assess the net clinical benefit of early initiation of HBD tirofiban in STEMI patients with a high

bleeding risk. Net clinical benefit was defined as net adverse clinical events (NACE) at 30 days (defined as the combined incidence of death, recurrent myocardial infarction (MI), urgent target vessel revascularization, stroke, or non-CABG related major bleeding).

30-day major or minor bleeding (non CABG-related) was assessed and adjudicated using the thrombolysis in myocardial infarction (TIMI) scale.(11) As because of the low incidence of major- and minor bleeding, both bleeding definitions were combined. Major bleeding was defined as either intracranial bleeding or overt bleeding with a decrease in hemoglobin ≥5 g/dl (≥3.1 mmol/L) or a decrease in hematocrit ≥15% within 30 days after admission. Minor bleeding was defined as identified bleeding with decrease in hemoglobin ≥3 g/dl (≥1.9 mmol/L), or >10% decrease in hematocrit. If a bleeding site was not identified, a >4 g/dl (≥ 2.4 mmol/L) decrease in the hemoglobin concentration or >12% decrease in hematocrit within 30 days after admission would be the criteria. Another secondary endpoint was the composite of major adverse cardiac events (MACE, defined as the combined incidence of death, recurrent myocardial infarction or urgent target vessel revascularisation) at 30 days.

Renal clearance of creatinine was calculated with the Cockcroft-Gault formula. (12) The definition of prior vascular disease (prior stroke and/or peripheral artery disease) was adopted by the CRUSADE registry. The definitions of death, recurrent MI, early recurrent MI, and urgent target vessel revascularisation have been described previously.(1) A blinded, independent clinical endpoint committee adjudicated all clinical endpoints except for death. Follow-up information was derived from outpatient clinic visits or via contact by telephone at 30 days and 1 year.

CRUSADE bleeding score

The CRUSADE bleeding score(13) was developed by assigning a weighted integer to each independent predictor on the basis of its coefficient in the final model. The eight predictors of in-hospital major bleeding were: baseline hematocrit, estimated creatinine clearance, baseline heart rate, baseline systolic blood pressure, female sex, signs of congestive heart failure on presentation, prior vascular disease, and diabetes mellitus. This score was found to perform consistently across the post admission treatment subgroups (eg, invasive care, use of antiplatelet and/or anticoagulants) in patients with NSTEMI. A point score for each patient was calculated by summing the weighted integers (range 1 to 100 points) and the bleeding score was divided into quintiles: very low risk (20), low risk (21 to 30), moderate risk (31 to 40), high risk (41 to 50), and very high risk (>50).

According to CRUSADE, patients with a moderate to very high baseline risk of bleeding in this sub-analysis were defined as high risk and patients with a very low- or low risk baseline bleeding risk were defined as low risk.

Statistical Analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois, USA) version 15.0.1. All analyses were done according to the intention-to-treat principle. All p values were two-sided. For all analyses, statistical significance was assumed when the two tailed probability value was <0.05. Continuous data were expressed as mean ± standard deviation and categorical data as percentage, unless otherwise denoted. Differences between continuous data were performed by student's t test or Mann Whitney U test and the chi-square or Fisher's exact test was used as appropriate for dichotomous data.

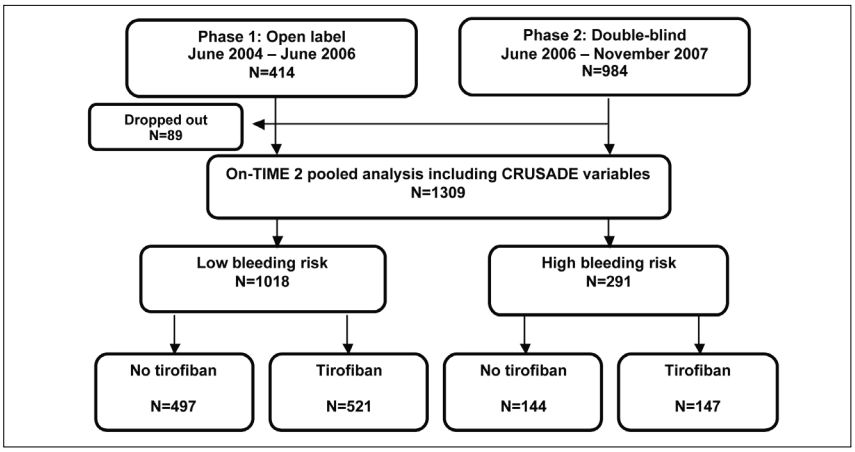

Figure 1: Study flow-chart

Results

In 1309 patients (93.6%) all 8 CRUSADE variables could be assessed and a high bleeding risk was present in 291 patients (22.2%, figure 1). The distribution of the CRUSADE bleeding risk quartiles are depicted in figure 2. Of the 1309 patients, complete 30-day follow-up was observed in 1261 patients (96.3%).

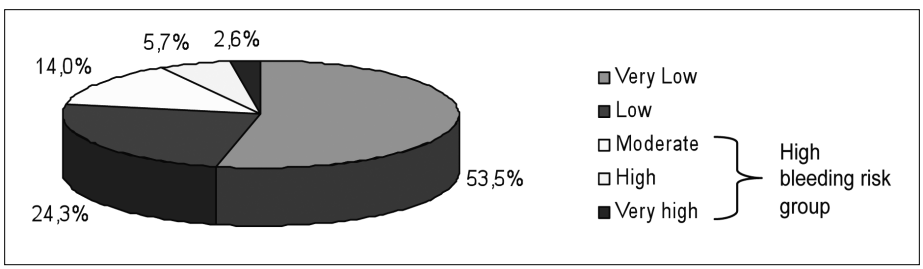

Figure 2: CRUSADE bleeding risk distribution in On-TIME 2

Table 1: Baseline and angiographic characteristics of patients with high- and low CRUSADE bleeding risk

Baseline	Low risk N=1018	High risk N=291	P value
Age	59.1±10.9	71.2±9.6	<0.001
Female gender	86.3	40.9	<0.001
BMI	27.2±3.6	25.6±3.8	<0.001
Hypertension	29.2	51.2	<0.001
Smoking	51.3	30.9	<0.001
Hypercholesterolemia	24.0	32.0	0.006
Family history	42.4	34.0	0.011
Diabetes Mellitus	8.6	20.3	<0.001
Previous MI	8.1	11.7	0.057
Previous PCI	8.1	9.3	0.505
Previous CABG	1.9	2.4	0.561
Previous CVA	0.8	4.5	<0.001
Anemia*	10.3	31.4	<0.001
Renal insufficiency	1.9	61.9	<0.001
TIMI risk > 3	18.6	67.0	<0.001
Killip > 1	8.5	24.7	<0.001
Ischemic time (min)	164 (126 – 246)	184 (138 – 236)	0.004
Time SO to diagnosis (min)	75 (44 – 145)	88 (51 – 156)	0.052
Time study medication to angiography (min)	55 (43 – 70)	60 (46 – 75)	0.003
Randomised to tirofiban	51.2	50.5	0.842
Angiography performed	99.5	99.3	0.655
Anterior infarction	43.1	39.1	0.247
Three vessel disease	14.8	28.0	<0.001
Extra UFH (2500IU)*	74.3	69.1	0.148
Overdose UFH**	51.5	82.5	<0.001
PCI immediately after CAG	99.5	98.0	0.041
- Thrombus aspiration	10.9	8.6	0.276
- IABP	3.9	8.6	0.001
Time sheath removal (min)	40 (28 – 107)	50 (30 – 360)	0.003
Hemostasis*			
-Closure device	72.8	60.6	0.001
Tirofiban 12-24 hr after PCI	24.6	26.6	0.470
Bail-out study medication*	24.7	21.8	0.391

Data are n/N (%) or mean (SD), or median (IQR). BMI=body mass index. MI=myocardial infarction. PCI=percutaneous coronary intervention. CABG=coronary artery bypass grafting. CVA=cerebro vascular accident. Renal insufficiency= creatinine clearance <60 ml/min (as calculated by Cockgroft-Gault). TIMI=thrombolysis in myocardial infarction. SO=symptom onset. HBD=high bolus dose. UFH=unfractionated heparin. PCI=percutaneous coronary intervention. CAG=coronary angiography. IABP=intra aortic balloon pump.

* Only recorded in the double-blind phase.

** More than weight adjusted UFH dosage (60 IU/kg)

Comparison between low risk- and high risk bleeding patients

The baseline- and angiographic characteristics between high risk bleeding patients and low risk bleeding patients were, as expected, different (table 1). High risk bleeding patients were older, more often male, had more often a previous history of diabetes mellitus, hypertension and renal insufficiency. Furthermore, high risk

Table 2: Location of non CABG-related major or minor bleeding in patients with high-and low CRUSADE bleeding risk

	No HBD tirofiban N=18	HBD Tirofiban N=27
Gastro intestinal	22.2	11.1
Retro-peritoneal	5.6	7.4
Access site	44.4	51.9
Other	27.8	29.6

	Low risk N=28	High risk N=17
Gastro intestinal	17.9	11.8
Retro-peritoneal	3.6	11.8
Access site	32.1	53.0
Other	46.4	23.5

Data are n/N (%).

bleeding patients had more often a TIMI risk score >3 and a Killip class >1 on admission as compared to low risk bleeding patients. Randomisation to tirofiban was not significantly different in both groups.

High risk bleeding patients had significantly more often three vessel disease and use of an intra-aortic balloon pump (IABP) as compared to low risk bleeding patients.

Furthermore, high risk bleeding patients had more often an overdosage of UFH (82.5% vs 51.5%, $p<0.001$) and a higher mean activated clotting time (ACT) (189±68 vs 177±60, $p=0.015$) as compared to low risk bleeding patients, whereas treatment with additional UFH on cathlab was not different in both groups.

As expected, high risk bleeding patients had a significantly higher rate of non CABG-related bleeding as compared to low risk patients (6.1% vs 2.9%, $p=0.009$, RR 2.16, 95% CI 1.2 - 3.9). However, in contrast to low risk bleeding patients, the

localisation of bleeding in these high risk patients was mostly access-site related (53.0% vs 32.1%, table 2).

These 'vulnerable' high risk bleeding patients had a significantly higher rate of 30-day all cause mortality (7.2% vs 0.6%, p<0.001, RR 12.2, 95% CI 5.2 – 29.3) and 30-day MACE (11.2% vs 4.3%, p<0.001, RR 2.6, 95% CI 1.7 – 4.1) as compared with low risk bleeding patients.

Table 3: Electrocardiographic- and angiographic outcome in patients with high- and low CRUSADE bleeding risk

	No HBD tirofiban N=619	HBD Tirofiban N=642	P	RR	95% CI
ST deviation >3 mm baseline					
Low risk	461/476 (96.8)	486/502 (96.8)	0.974	1.00	0.98 – 1.02
High risk	135/139 (97.1)	136/139 (97.8)	0.702	1.00	0.98 – 1.04
ST deviation >3 mm 1 h post-PCI					
Low risk	179/437 (41.0)	170/456 (37.3)	0.260	0.91	0.77 – 1.07
High risk	73/124 (58.9)	52/120 (43.3)	0.015	0.74	0.57 – 0.94
Initial TIMI 3 flow					
Low risk	85/461 (18.4)	109/473 (23.0)	0.083	1.25	0.97 – 1.61
High risk	29/137 (21.2)	29/135 (21.5)	0.950	1.01	0.64 – 1.60
TIMI 3 post-PCI					
Low risk	413/441 (93.7)	404/454 (89.0)	0.013	0.95	0.92 – 0.99
High risk	108/126 (85.7)	110/120 (91.7)	0.142	1.07	0.98 – 1.15
MBG 3 post-PCI					
Low risk	175/414 (42.3)	189/428 (44.2)	0.580	1.05	0.90 – 1.22
High risk	50/115 (43.5)	54/114 (47.4)	0.554	1.09	0.82 – 1.45

TIMI=thrombolysis in myocardial infarction. MBG=myocardial blush grade.

Effect of tirofiban in both bleeding risk groups on angiographic- and clinical outcomes

Table 3 shows the angiographic- and clinical outcomes. Early initiation of tirofiban in the high risk bleeding group significantly decreases ST deviation >3mm 1 hour post-PCI (43.3% vs 58.9%, p=0.015, RR: 0.74, 95% CI 0.57 – 0.94) whereas no significant difference was found on ST segment deviation in the low risk bleeding group. There was no significant difference in initial TIMI 3 flow, final TIMI 3 flow and myocardial blush grade (MBG) between the study medication groups in the high risk bleeding group, whereas in the low risk bleeding group final TIMI 3 flow was less often established in patients with tirofiban pre-treatment.

Pre-treatment with tirofiban in high risk bleeding patients had no significant impact on 30-day net adverse clinical events (NACE) (11.5% vs 15.2%, p=0.365, RR: 0.76, 95% CI 0.41 – 1.38). However, tirofiban significantly reduced the rate of 30-day

NACE in low risk bleeding patients (table 4). Although, pre-hospital administration of tirofiban in high risk bleeding patients reduced 30-day mortality with 50% it had no significant impact on 30-day all cause mortality (5.0% vs 10.1%, p=0.108, RR: 0.50, 95% CI 0.21 – 1.16) as well as on 1-year all cause mortality (9.4% vs 13.2%, p=0.309, RR: 0.71, 95% CI 0.36 – 1.37). However, in low risk bleeding patients early treatment with tirofiban significantly reduced 30-day- and 1-year mortality (table 4). There were no significant differences in 30-day MACE in patients treated with tirofiban compared to no tirofiban for both bleeding risk groups. In contrast to low risk bleeding patients, high risk bleeding patients who were treated with tirofiban showed a strong trend toward a higher incidence of non CABG-related bleeding as

Table 4: Clinical outcome in patients with high- and low CRUSADE bleeding risk

30-day	**No HBD tirofiban N=619**	**HBD Tirofiban N=642**	**P**	**RR**	**95% CI**
Mortality					
Low risk	6/481 (1.2)	0/503 (0.0)	0.012	0.00	0.00 – 0.61
High risk	14/138 (10.1)	7/139 (5.0)	0.108	0.50	0.21 – 1.16
Re-MI					
Low risk	11/481 (2.3)	6/503 (1.2)	0.188	0.52	0.20 – 1.35
High risk	2/138 (1.4)	5/139 (3.6)	0.255	2.48	0.56 – 11.0
Urgent TVR					
Low risk	20/481 (4.2)	14/503 (2.8)	0.238	0.67	0.35 – 1.29
High risk	4/138 (2.9)	6/139 (4.3)	0.527	1.49	0.46 – 4.86
MACE					
Low risk	26/481 (5.4)	16/503 (3.2)	0.084	0.59	0.32 –1.07
High risk	18/138 (13.0)	13/139 (9.4)	0.330	0.72	0.37 –1.39
Non CABG-related bleeding					
Low risk	13/481 (2.7)	15/503 (3.0)	0.792	1.11	0.53 – 2.31
High risk	5/138 (3.6)	12/139 (8.6)	0.082	2.38	0.90 – 6.39
CABG-related bleeding					
Low risk	17/497 (3.4)	26/521 (5.0)	0.213	1.46	0.81 – 2.64
High risk	9/144 (6.2)	10/147 (6.8)	0.849	1.09	0.47 – 2.55
NACE					
Low risk	32/481 (6.7)	19/503 (3.8)	0.042	0.57	0.33 – 0.98
High risk	21/138 (15.2)	16/139 (11.5)	0.365	0.76	0.41 – 1.38
1-year					
Mortality					
Low risk	12/477 (2.5)	4/497 (0.8)	0.036	0.32	0.11 – 0.93
High risk	18/136 (13.2)	13/139 (9.4)	0.309	0.71	0.36 – 1.37

Data are n/N (%). Re-MI=recurrent myocardial infarction. Urgent TVR=urgent target vessel revascularization. MACE=major adverse cardiac event (the combined incidence of death, recurrent MI, urgent TVR). NACE=net adverse clinical event (the combined incidence of death, recurrent MI, urgent TVR, stroke, or non-CABG related major bleeding)

compared to those without tirofiban pre-treatment (8.6% vs 3.6%, p=0.082, RR: 2.38, 95% CI 0.90 – 6.39).

Discussion

Our results show that pre-hospital tirofiban for primary PCI in patients with a high risk of bleeding 1) improves post-PCI ST segment resolution, 2) shows no difference in 30-day MACE, and 3) is associated with a non-significant increase of non CABG-related bleeding, mostly access-site related. The net result is a balanced effect on 30-day NACE.

The On-TIME 2 trial recently demonstrated that the glycoprotein IIb/IIIa inhibitor (GPI) tirofiban, when given in the ambulance, resulted in an improvement of ST-segment resolution (primary endpoint) as a marker for myocardial perfusion and an improved clinical outcome in patients with STEMI undergoing primary PCI.(1,2) Consistent with these findings, several other trials showed a greater benefit for patients who received early GPI treatment after the onset of symptoms.(14-17) However, not all studies have demonstrated such clinical benefits from (early) GPI use.(18-21)

Impact of antiplatelet and antithrombotic agents in patients with high risk of bleeding

Bleeding is an independent determinant of both short- and long-term mortality.(3-7,22) Potential explanations for the high mortality after bleeding include a hemodynamic disturbance caused by the bleeding, premature cessation of antiplatelet therapy and liberal use of blood transfusion.(5,7,8,23-26) Therefore, in patients with high risk of bleeding, the potential benefits of GPI's may be less clear and use of these agents may be even harmful in these patients. In our study, patients at high risk of bleeding did have benefit from tirofiban as shown by an improved ST deviation post PCI, at the cost of a (non-significant) increase in bleeding. Effect on clinical outcome was a non-significant reduction in 30-day (and 1-year) all cause mortality after tirofiban. Explanation for this trend toward improved clinical outcome may be that bleeding occurred mostly at the access site (table 4), which has in general a good prognosis.(27,28) So, pre-treatment with high dose tirofiban may be considered in high risk bleeding patients. However, the net clinical benefit of tirofiban can be further improved in this group. Possibly, a radial approach in these high risk bleeding patients will decrease bleeding, with more pronounced benefits of tirofiban. However, there is a need for further research to support this approach. Furthermore, excess dosing of (post-PCI) heparin may contribute to the increased incidence of bleeding, particularly in the high-risk bleeding group.(29) Improved heparin dosing may also increase net clinical effect of tirofiban in these patients.

HORIZONS-AMI demonstrated that bivalirudin alone as compared to UFH and GPI in STEMI patients improved clinical outcome and reduced bleeding.(20) However, in this

study bleeding in the UFH/GPI group was very high. Additional studies should clarify how use of these bleeding risk scores should modify medical (antiplatelet) therapy.

Bleeding risk score

Baseline prediction of bleeding risk can complement ischemic risk prediction, and optimise medical- or invasive strategies for ACS. The CRUSADE bleeding risk score has been generally validated and found to be useful in another cohort of NSTEMI patients.(30) However, recently, another bleeding risk score has been developed to predict 30-day non CABG-related major bleeding in ACS patients.(31) Because of the novel finding of a higher white blood count predicting major bleeding in this risk score, which first deserves further investigation, and absence of Killip class in this risk score, which is a strong independent predictor of bleeding, we only used the CRUSADE bleeding risk score for predicting bleeding risk.

Limitations

Several limitations of the present analysis should be considered. First of all, data from the two phases of the On-TIME 2 trial with different design (open label and double-blind) were combined. However, both study phases had identical inclusion and exclusion criteria and there was no difference in baseline characteristics between the two phases of the study. The included STEMI patients in On-TIME 2 were obviously not low risk patients, because 29.4% of the patients (table 1) were identified as high ischemic risk according to the TIMI risk score.(32) Although the data were collected prospectively, this was a post-hoc analysis with a relative small sample size, and the study was not powered to demonstrate benefits of tirofiban in our subgroups. Furthermore, primary PCI was performed in all patients by the femoral approach. Finally, the CRUSADE bleeding risk score was developed for and validated in NSTEMI patients to predict in-hospital major bleeding, whereas we used it for STEMI patients to determine whether patients had a low- or high bleeding risk.

Conclusion

Pre-hospital use of tirofiban in ST-Elevation Myocardial Infarction in patients with high risk of bleeding improves post-PCI ST segment resolution, has no impact on 30-day MACE, but increases non-significantly the risk of non-CABG related bleeding. The net result is a balanced effect on 30-day NACE. Additional studies should clarify how use of bleeding risk scores should modify medical (antiplatelet) therapy.

References

1. van 't Hof AW, ten Berg JM, Heestermans AA, Dill T, Funck RC, van Werkum W, Dambrink JH, Suryapranata H, van Houwelingen G, Ottervanger JP, Stella PR, Giannitsis E, Hamm C. Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial. Lancet 2008;372:537-546.
2. ten Berg JM, van 't Hof AW, Dill T, Heestermans AA, van Werkum JW, Mosterd A, van Houwelingen KG, Koopmans PC, Stella PR, Boersma E, Hamm C. On behalf of the Ongoing Tirofiban In Myocardial infarction Evaluation (On-TIME) 2 study group. Effect of early, pre-hospital initiation of high-bolus dose tirofiban in patients with ST-segment elevation myocardial infarction on short and long-term clinical outcome. J Am Coll Cardiol 2010;55:2446-2455.
3. Hermanides RS, Ottervanger JP, Dambrink JH, Dill T, van Houwelingen KG, ten Berg JM, Kolkman JJ, Hamm C, van 't Hof AW. Risk of bleeding after pre-hospital administration of high dose tirofiban for ST-Elevation Myocardial Infarction. International Journal of Cardiology 2010 [Epub ahead of print].
4. Kinnaird TD, Satbile E, Mintz GS, Lee CW, Canos DA, Gevorkian N, Pinnow EE, Kent KM, Pichard AD, Satler LF, Weissman NJ, Lindsay J, Fuchs S. Incidence, predictors, and prognostic implications of bleeding and blood transfusion following percutaneous coronary interventions. Am J Cardiol 2003;92:930-935.
5. Rao SV, O'Grady K, Pieper KS, Granger CB, Newby LK, Van de Werf F, Mahaffey KW, Califf RM, Harrington RA. Impact of bleeding severity on clinical outcomes among patients with acute coronary syndromes. Am J Cardiol 2005;96:1200-1206.
6. Eikelboom JW, Metha SR, Anand SS, Xie C, Fox KA, Yusuf S. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. Circulation 2006;114:774-782.
7. Feit F, Voeltz MD, Attubato MJ, Lincoff AM, Chew DP, Bittl JA, Topol EJ, Manoukian SV. Predictors and impact of major hemorrhage on mortality following percutaneous coronary intervention from the REPLACE-2 trial. Am J Cardiol 2007;100:1364-1369.
8. Manoukian SV, Feit F, Mehran R, Voeltz MD, Ebrahimi R, Hamon M, Dangas GD, Lincoff AM, White HD, Moses JW, King SB 3rd, Ohman EM, Stone GW. Impact of major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary syndromes: an analysis from the ACUITY trial. J Am Coll Cardiol 2007;49:1362-1368.
9. Ndrepepa G, Berger PB, Mehilli J, Seyfarth M, Neumann FJ, Schömig A, Kastrati A. Periprocedural bleeding and 1-year outcome after percutaneous coronary interventions: appropriateness of including bleeding as a component of a quadruple end point. J Am Coll Cardiol 2008;51:690-697.
10. van 't Hof AW, Hamm C, Rasoul S, Guphta S, Paolini JF, ten Berg JM, on behalf of the On-TIME 2 investigators. Ongoing tirofiban in myocardial infarction evaluation (On-TIME) 2 trial: rationale and study design. EuroInterv 2007;3:371-380.
11. Rao AK, Pratt C, Berke A, Jaffe A, Ockene I, Schreiber TL, Bell WR, Knatterud G, Robertson TL, Terrin ML. Thrombolysis in Myocardial Infarction (TIMI) Trial — phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. J Am Coll Cardiol 1988;11:1-11.
12. Cockgroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31-41.
13. Subherwal S, Bach RG, Chen Ay, Gage BF, Rao SV, Newby LK, Wang TY, Gibler WB, Ohman EM, Roe MT, Pollack CV Jr, Peterson ED, Alexander KP. Baseline risk of major bleeding in Non-ST-elevation myocardial infarction. Circulation 2009;119:1873-1882.
14. Goto S, Tamura N, Ishida H. Ability of anti-glycoprotein IIb/IIIa agents to dissolve platelet thrombi formed on a collagen surface under blood flow conditions. J Am Coll Cardiol 2004;44:316-323.
15. Montalescot G, Barragan P, Wittenberg O, Ecollan P, Elhadad S, Villain P, Boulenc JM, Morice MC, Maillard L, Pansiéri M, Choussat R, Pinton P, for the ADMIRAL Investigators. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. N Engl J Med 2001;344:1895-1903.
16. Ortolani P, Marzocchi A, Marrozzini C, Palmerini T, Saia F, Taglieri N, Baldazzi F, Dall'Ara G, Nardini P, Gianstefani S, Guastaroba P, Grilli R, Branzi A. Long-term effectiveness of early administration of glycoprotein IIb/IIIa agents to real-world patients undergoing primary percutaneous coronary interventions: results of a registry study in an ST-elevation myocardial infarction network. Eur Heart J 2009;30:33-43.
17. Huber K, Holmes Jr DR, van 't Hof AW, Montalescot G, Aylward PE, Betriu GA, Widimsky P, Westerhout CM, Granger CB, Armstrong PW. Use of glycoprotein IIb/IIIa inhibitors in primary percutaneous coronary intervention: insights from the APEX-AMI trial. Eur Heart J 2010;31:1708-1716.
18. The EPIC investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. N Engl J Med 1994;330:956-961.
19. ESPRIT investigators. Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrillin Therapy. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. Lancet 2000;356:2037-2044.
20. Ellis SG, Tendera M, de Belder MA, van Boven

AJ, Widimsky P, Janssens L, Andersen HR, Betriu A, Savonitto S, Adamus J, Peruga JZ, Kosmider M, Katz O, Neunteufl T, Jorgova J, Dorobantu M, Grinfeld L, Armstrong P, Brodie BR, Herrmann HC, Montalescot G, Neumann FJ, Effron MB, Barnathan ES, Topol EJ. FINESSE investigators. Facilitated PCI in patients with ST-elevation myocardial infarction. N Engl J Med 2008;358:2205-2217.

21. Stone GW, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, Kornowski R, Hartmann F, Gersh BJ, Pocock SJ, Dangas G, Wong SC, Kirtane AJ, Parise H, Mehran R; HORIZONS-AMI Trial Investigators. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med 2008;358:2218-2230.
22. Mehran R, Lansky AL, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, Kornowski R, Hartmann F, Gersh BJ, Pocock SJ, Wong SC, Nikolsky E, Gambone L, Vandertie L, Parise H, Dangas GD, Stone GW; HORIZONS-AMI Trial Investigators. Bivalirudin in patients undergoing primary angioplasty for acute myocardial infarction (HORIZONS-AMI): 1-year results of a randomised controlled trial. Lancet 2009;374:1149-1159.
23. Lincoff AM, Bittl JA, Harrington RA, Feit F, Kleiman NS, Jackman JD, Sarembock IJ, Cohen DJ, Spriggs D, Ebrahimi R, Keren G, Carr J, Cohen EA, Betriu A, Desmet W, Kereiakes DJ, Rutsch W, Wilcox RG, de Feyter PJ, Vahanian A, Topol EJ; REPLACE-2 Investigators. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. JAMA 2003;289:853-863.
24. Spencer FA, Moscucci M, Granger GB, Gore JM, Goldberg RJ, Steg PG, Goodman SG, Budaj A, FitzGerald G, Fox KA; GRACE Investigators. Does comorbidity account for the excess mortality in patients with major bleeding in acute myocardial infarction? Circulation 2007;116:2793-2801.
25. Wang TY, Xiao L, Alexander KP, Rao SV, Kosiborod MN, Rumsfeld JS, Spertus JA, Peterson ED. Antiplatelet therapy use after discharge among acute myocardial infarction patients with in-hospital bleeding. Circulation 2008;118:2139-2145.
26. Rao SV, Jollis JG, Harrington RA, Granger CB, Newby LK, Armstrong PW, Moliterno DJ, Lindblad L, Pieper K, Topol EJ, Stamler JS, Califf RM. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. JAMA 2004;292:1555-1562.
27. Rao SV, Eikelboom J, Steg PG, Lincoff AM, Weintraub WS, Bassand JP, Rao AK, Gibson CM, Petersen JL, Mehran R, Manoukian SV, Charnigo R, Lee KL, Moscucci M, Harrington RA; Academic Bleeding Consensus Multidisciplinary Working Group. Standardized reporting of bleeding complications for clinical investigations in acute coronary syndromes: A proposal from the Academic Bleeding Consensus (ABC) Multidisciplinary working group. Am Heart J 2009;158:881-886.
28. Verheugt FW, Steinhubl SR, Hamon M, Darius H, Steg PG, Valgimigli M, Marso SP, Rao SV, Gershlick AH, Lincoff AM, Mehran R, Stone GW. Incidence, prognostic impact, and influence of antithrombotic therapy on acces and nonaccess site bleeding in percutaneous coronary intervention. JACC Cardiovasc Interv 2011;2:191-197.
29. Alexander KP, Chen AY, Roe Mt, Newby LK, Gibson CM, Allen-LaPointe NM, Pollack C, Gibler WB, Ohman EM, Peterson ED; CRUSADE Investigators. Excess dosing of antiplatelet and antithrombin agents in the treatment of non-ST-segment elevation acute coronary syndromes. JAMA 2005;294:3108-3116.
30. Abu-assi E, Gracia-Acuna JM, Ferreira-Gonzalez I, Pena-Gil C, Gayoso-Diz P, Gonzalez-Juanatey JR. Evaluating the performance of the can rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the ACC/AHA Guidelines (CRUSADE) bleeding score in a contemporary Spanish cohort of patients with Non-ST segment elevation acute myocardial infarction. Circulation 2010;121:2419-2426.
31. Mehran R, Pocock SJ, Nikolsky E, Clayton T, Dangas GD, Kirtane AJ, Parise H, Fahy M, Manoukian SV, Feit F, Ohman ME, Witzenbichler B, Guagliumi G, Lansky AJ, Stone GW. A risk score to predict bleeding in patients with acute coronary syndromes. J Am Coll Cardiol 2010;55:2556-2566.
32. Morrow DA, Antman EM, Charlesworth A, Cairns R, Murphy SA, de Lemos JA, Giugliano RP, McCabe CH, Braunwald E. TIMI risk score for ST-elevation myocardial infarction: a convenient, bedside, clinical score for risk assessment at presentation: an intravenous nPA for treatment of infarcting myocardium Early II trial substudy. Circulation 2000;102:2031-2037.

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The impact of age on effects of pre-hospital initiation of high bolus dose of tirofiban before primary angioplasty for ST-elevation myocardial infarction

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R.S. Hermanides*, K.G. Houwelingen*, J.P. Ottervanger, M.J. de Boer,
T. Dill, C. Hamm, P.R. Stella, E. Boersma, J.M. ten Berg,
A.W. van 't Hof, for the On-TIME 2 trial investigators
* contributed equally

Abstract

Purpose: Glycoprotein IIb/IIIa inhibitors are favourable in ST-elevation myocardial infarction (STEMI) patients, and the additional value of early pre-hospital high bolus dose tirofiban has recently been established. The aim of this study was to determine the impact of age on myocardial reperfusion and clinical outcomes of pre-hospital administration of high bolus dose tirofiban.

Methods: This is a pre-specified sub-analysis of the multicentre, double-blind, placebo-controlled, randomised On-TIME 2 trial and it's open label phase.
The primary endpoint was mean residual ST segment deviation 1 hour after primary PCI and was evaluated in three age groups.

Results: Of the 466 patients in the highest tertile (≥68 years), median age was 74.4 years (IQR 71.3–78.6 years) and 231 (50%) were randomised to tirofiban.
Mean residual ST segment deviation 1 hour after PCI was significantly lower in elderly patients pre-treated with tirofiban compared to elderly patients without tirofiban pre-treatment (4.2±5.2 mm vs 6.4±7.5 mm, p=0.001). Furthermore, elderly patients pre-treated with tirofiban had a non-significantly higher rate of 30-day major or minor bleeding compared to elderly patients without tirofiban pre-treatment (14.2% vs 9.0%, p=0.088). 30-day net adverse clinical events in elderly patients with- or without tirofiban was not significantly different (11.9% vs 15.2%, p=0.300).

Conclusion: The effect of pre-hospital initiation of high bolus dose tirofiban on myocardial reperfusion, as determined by ST-segment resolution is highest in the elderly patients. However, this was associated with a trend towards more bleeding complications, resulting in a balanced clinical effect after 30-day follow-up. Future studies should evaluate whether the elderly STEMI patient may benefit from highly effective and safer anti-platelet therapy

Introduction

Although primary percutaneous coronary intervention (PCI) is beneficial, elderly patients with ST-elevation myocardial infarction (STEMI) still have a worse prognosis, including worse myocardial reperfusion, as compared to younger patients.(1-4) Glycoprotein IIb/IIIa inhibitors (GPI's) are favourable in STEMI patients(5,6), and the additional value of early pre-hospital high bolus dose tirofiban has recently been established(7,8), but combined antithrombin and GP IIb/IIIa inhibitor regimens have also been associated with a higher risk of bleeding.(9,10) A sub-analysis of the CADILLAC trial showed that abciximab administration was not of major benefit in elderly patients.(11) However, whether elderly patients will have improvement of myocardial reperfusion and subsequently improvement of clinical outcome with routine pre-hospital triple antiplatelet therapy is yet unknown. Therefore, the aim of this pre-specified sub-analysis of the On-TIME 2 trial was to determine the impact of age on myocardial reperfusion and clinical outcomes of pre-hospital administration of high bolus dose tirofiban.

Methods

Study design and patients

It concerns a pre-specified sub-study of the pooled analysis of the Ongoing Tirofiban In Myocardial infarction Evaluation 2 trial. The On-TIME 2 trial consisted of 2 phases: an open-label phase, followed by a double-blind, placebo-controlled phase. STEMI patients were randomized to either high bolus dose tirofiban or no tirofiban (phase 1) or placebo (phase 2) in addition to aspirin, heparin, and high-dose clopidogrel. The rationale, design, primary- and 1 year results of the study have been described previously.(7,8,12) Age has been stratified into tertiles and this sub-analysis is based on data of all 1398 randomised patients.

Procedures

Patients were randomly assigned to pre-hospital treatment with tirofiban (25 μg/kg bolus and 0.15 μg/kg/min maintenance infusion for 18h) or no tirofiban or placebo (bolus plus infusion) by blinded sealed kits with study drug. In the ambulance or referring centre, 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 2500 IU unfractionated heparin was only given if the activated clotting time was less than 200 seconds. Coronary angiography and PCI were done according to each institution's guidelines and standards.

Measurements (end points, definitions)

The primary efficacy endpoint was the extent of residual ST-segment deviation at 1 hour after PCI, as described previously.(13,14) The secondary (safety) endpoint was 30-day major or minor bleeding.

30-day bleeding (CABG-related or non CABG-related) was assessed and adjudicated using the thrombolysis in myocardial infarction (TIMI) scale.(15) Major bleeding was defined as either intracranial bleeding or overt bleeding with a decrease in hemoglobin ≥5 g/dl (≥3.1 mmol/L) or a decrease in hematocrit ≥15% within 30 days after admission. Minor bleeding was defined as identified bleeding with decrease in hemoglobin ≥3 g/dl (≥1.9 mmol/L), or >10% decrease in hematocrit. If a bleeding site was not identified, a >4 g/dl (≥ 2.4 mmol/L) decrease in the hemoglobin concentration or >12% decrease in hematocrit within 30 days after admission would be the criteria.

A blinded, independent clinical endpoint committee adjudicated all clinical endpoints apart from death. Follow-up information was derived from medical hospital records, outpatient clinic visits or via contact by telephone at 30 days and at 1 year.

Ethics

The investigation conforms with the principles outlined in the Declaration of Helsinki. The study was approved by the Committee on Research Ethics of our hospital.

Statistical analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 16.0.1. All analyses were done according to the intention-to-treat principle. All p values were two-sided. For all analyses, statistical significance was assumed when the two tailed probability value was <0.05. Continuous data were expressed as mean ± standard deviation or as median with 25th and 75th percentiles and categorical data as percentage, unless otherwise denoted. Differences between continuous data were performed by student's t test and the chi-square or Fisher's exact test was used as appropriate for dichotomous data.

To evaluate whether treatment with tirofiban on ST deviation >3mm 1 hr post-PCI, 30-day mortality, 30-day (major or minor) bleeding, and 30-day net adverse clinical events (NACE) was different over the three age groups, interaction analyses were performed. For the interaction analysis a significance level p<0.10 was used.(16)

Results

Figure 1 shows the trial profile. Of the 466 patients in the highest tertile (≥68 years), 231 (50%) were randomised to tirofiban. 30-day clinical follow-up was achieved in 219 patients (95%) assigned to tirofiban and 223 patients (95%) to no tirofiban.

Comparison of elderly patients vs younger patients

Baseline characteristics of the study population stratified by age are summarized in table 1. The elderly patients studied in this analysis presented with a higher prevalence of several comorbid conditions including diabetes, hypertension, and previous myocardial inarction (MI). They had also more often multivessel disease, a higher TIMI risk score and a longer ischemic time as compared to younger patients. Table 2 summarizes the angiographic- and electrocardiographic findings according to age group. A gradual decline of ST resolution and residual ST deviation was found with increasing age. The rate of PCI did not differ significantly between the age groups. However, post-procedural TIMI 3 flow and a myocardial blush grade 3 were achieved less often in the elderly group. Table 3 shows the clinical outcome. Short-term (30-day mortality, 30-day MACE) and long-term clinical outcome (1-year mortality) was also worse in the elderly population. Furthermore, thirty-day major or minor bleeding and non CABG-related major or minor bleeding were significantly higher in the elderly patients. This was confirmed by hemoglobin decrease and transfusion rate, which was highest in the elderly patients.

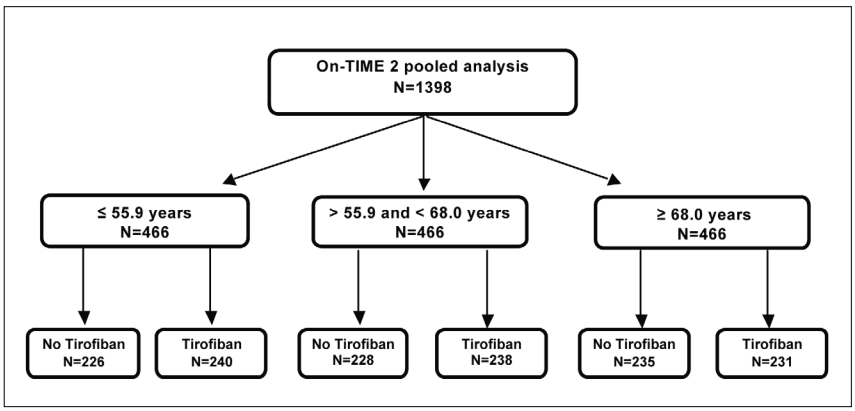

Figure 1: Flow chart of the study

Comparison of tirofiban vs no tirofiban in the elderly

Baseline characteristics between the elderly groups were comparable, with the exception of the rate of previous myocardial infarction, which was significantly higher in elderly patients not pre-treated with tirofiban (10.5% vs 17.0%, p=0.045).

Table 1: Baseline characteristics

Characteristics	≤ 55.9 yr	> 55.9 and < 68.0 yr	≥ 68.0 yr	P
	N=466	N=466	N=466	
Female gender	18.2	20.4	33.3	<0.001
Hypertension	22.3	33.5	46.4	<0.001
Smoking	70.4	46.5	24.3	<0.001
Diabetes Mellitus	7.7	10.5	15.3	0.001
Previous MI	8.0	5.4	13.8	<0.001
Previous PCI	8.6	5.4	10.3	0.019
Previous CABG	0.6	2.1	3.4	0.011
Killip > 1	12.3	12.5	12.3	0.996
TIMI risk score > 3	6.1	17.8	65.8	<0.001
Randomised to tirofiban	51.5	51.1	49.6	0.826
Ischemic time (min)	158 (122 – 230)	162 (124 – 247)	183 (136 – 274)	<0.001
Time SO to diagnosis (min)	73 (41 – 129)	72 (43 – 150)	94 (51 – 172)	<0.001
Time SO to study medication (min)	83 (55 – 138)	90 (59 – 165)	105 (63 – 180)	<0.001
Three vessel disease	9.3	17.9	25.6	<0.001
Angiography performed	98.9	99.4	97.2	0.017

Data are n/N (%) or mean (SD), or median (IQR). BMI=body mass index. MI=myocardial infarction. PCI=percutaneous coronary intervention.
CABG=coronary artery bypass grafting. SO=symptom onset.

Table 2: Angiographic-, electrocardiographic outcomes

Characteristics	≤ 55.9 yr	> 55.9 and < 68.0 yr	≥ 68.0 yr	P
	N=466	N=466	N=466	
Angiographic outcome				
PCI performed	85.6	89.2	86.0	0.195
Initial TIMI 3 flow	24.2	20.4	18.3	0.099
TIMI flow 3 post-PCI	92.6	90.7	87.1	0.033
MBG 3 post-PCI	49.0	45.1	37.2	0.004
Thrombus aspiration	10.1	10.9	9.6	0.810
IABP	3.6	4.4	7.1	0.046
Electrocardiographic outcome				
ST resolution diagnosis before coronary angiography				0.002 (trend)
Complete	23.0	15.1	12.1	
Partial	17.2	19.6	21.2	
No	59.9	65.3	66.8	
ST resolution diagnosis 1 h after PCI				<0.001 (trend)
Complete	66.6	65.7	55.1	
Partial	22.0	24.0	25.1	
No	11.4	10.2	19.7	
Residual ST deviation > 3mm 1 hr after angiography/PCI	37.3	40.7	47.9	0.007
Residual ST deviation 1 hr after angiography/PCI	3.6 ± 5.3	3.8 ± 4.9	5.3 ± 6.6	<0.001

Data are n/N (%) or mean (SD), or median (IQR). TIMI=thrombolysis in myocardial infarction. MBG=myocardial blush grade.
PCI=percutaneous coronary intervention. IABP=intra aortic balloon pump.

Median age in the highest tertile was 74.4 years (IQR 71.3 – 78.6 years). The primary endpoint, mean residual ST-segment deviation 1 hour after PCI, was significantly lower in elderly patients who were pre-treated with tirofiban compared to elderly patients without tirofiban pre-treatment (4.2 ± 5.2 vs 6.4 ± 7.5, p=0.001, figure 2). In contrast to elderly patients, tirofiban pre-treatment had no significant impact on the primary endpoint in the youngest patients (tertile 1, 3.5 ± 5.9 vs 3.6 ± 4.7, p=0.676). There was a significant interaction between randomisation (tirofiban or no tirofiban) and the three age groups with respect to ST deviation >3mm 1 hour post-PCI (p for interaction 0.026, figure 2). Furthermore, complete ST-segment resolution 1 hour after PCI was more often accomplished in elderly patients who had tirofiban pre-treatment (60.5% vs 50.0%, p for trend 0.005). Also after changing the cut-off point to the age of >65 years of age, mean residual ST-segment deviation 1 hour after PCI, was significantly lower in elderly patients who were pre-treated with tirofiban compared to elderly patients without tirofiban pre-treatment (4.1 ± 5.2 vs 6.1 ± 7.1, p=0.001).

The incidence of thirty-day major or minor bleeding was higher in elderly patients who were pretreated with tirofiban as compared to elderly patients without

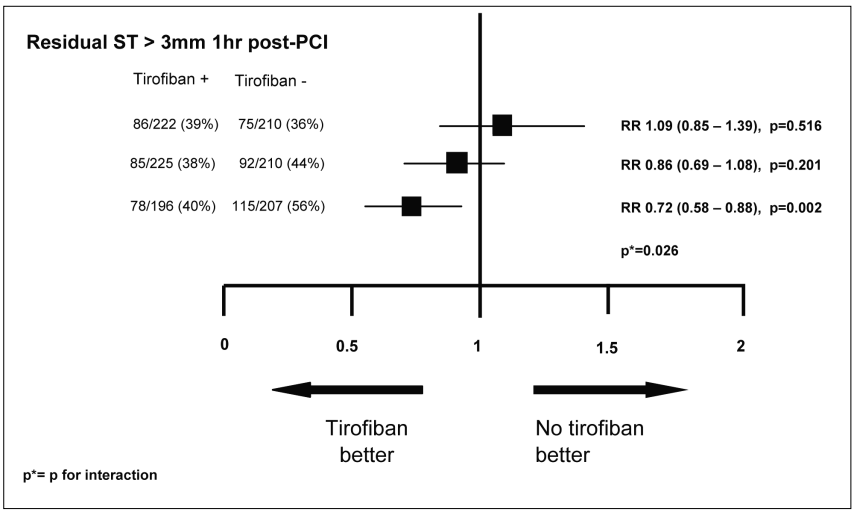

Figure 2: Risk ratios of the primary endpoint (extent of residual ST-segment deviation 1 h after PCI) according to the stratified age subgroups

tirofiban pre-treatment (14.2% vs 9.0%, p=0.088, figure 3). Thirty-day major bleeding was significantly higher in elderly patients with tirofiban pre-treatment (6.8% vs 2.7%, p=0.040). Transfusion rates (5.8% vs 3.7%, p=0.311) and decrease in hemoglobin from baseline to 96 hours after admission (-0.35 ± 5.83 vs -1.33 ± 6.71, p=0.464) were not significantly different in both groups. Thirty-day NACE was not significantly different in elderly patients with- or without tirofiban pre-treatment

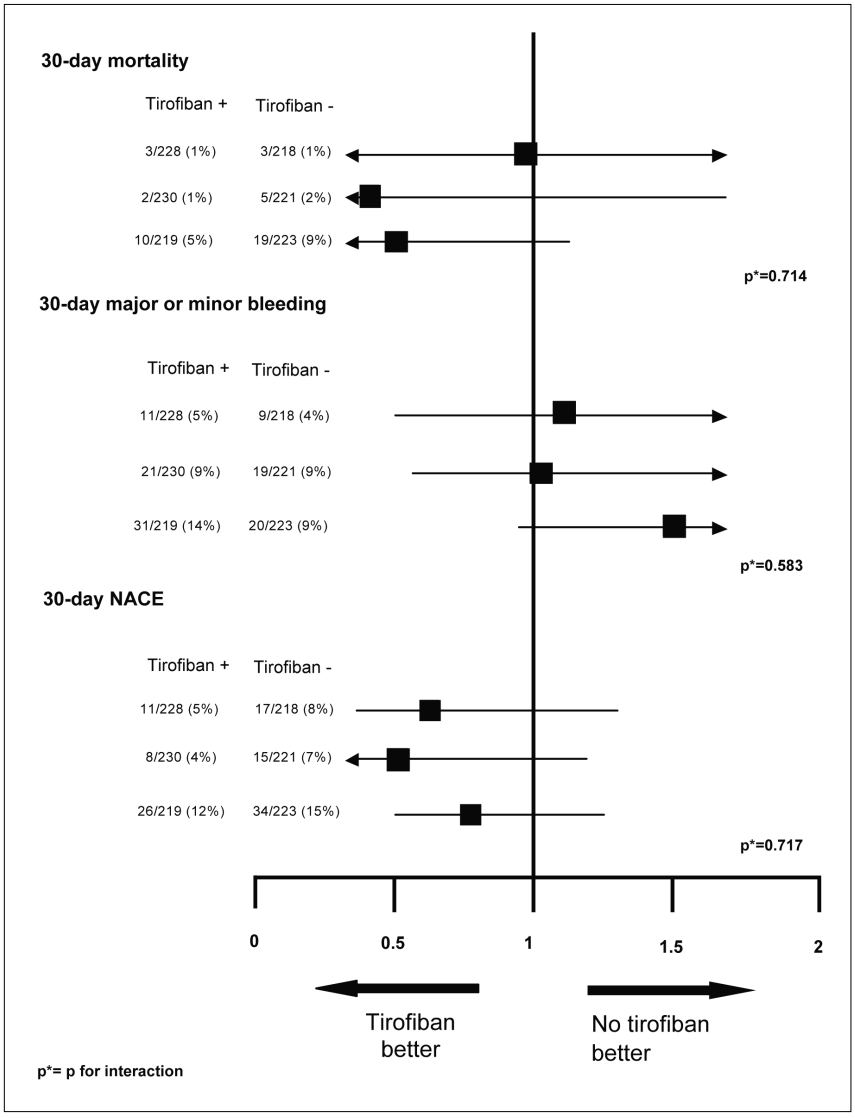

Figure 3: Risk ratios of 30-day mortality, 30-day major- or minor bleeding, and 30-day NACE according to the stratified age subgroups

(11.9% vs 15.2%, p=0.300, figure 3). We found a trend towards a lower rate of 30-day mortality (4.6% vs 8.5%, p=0.093, figure 3) as well as a lower rate of 1-year mortality (7.9% vs 12.2%, p=0.091) in elderly patients pre-treated with tirofiban. Furthermore, there were no significant differences in medication use at 30-days post-PCI between the elderly groups.

Table 3: Clinical outcomes

Characteristics	≤ 55.9 yr	> 55.9 and < 68.0 yr	≥ 68.0 yr	P
Peak CK	1769 ± 1841	1734 ± 1729	1686 ± 1682	0.802
30 day Outcome	**N=446**	**N=451**	**N=442**	
Death	1.3	1.6	6.6	<0.001
Cardiac	1.1	1.6	5.9	<0.001
Non-cardiac	0.2	0.0	0.7	0.085
MACE	5.6	4.4	11.5	<0.001
30 day Safety				
Major or minor bleeding	4.5	8.9	11.5	<0.001
Major bleeding	2.7	2.0	4.8	0.049
Non CABG-related major or minor bleeding	1.6	2.9	6.1	0.001
Non CABG-related major bleeding	1.1	0.2	1.6	0.107
Hb decrease Baseline – 18-24 hr	-0.50 ± 1.04	-0.78 ± 5.43	-0.67 ± 2.65	0.153
Hb decrease Baseline – 72-96 hr	-0.61 ± 1.36	-0.83 ± 5.81	-0.82 ± 6.28	0.004
Transfusion	1.8	2.3	4.7	0.026
Thrombocytopenia	5.7	8.3	15.9	<0.001
NACE	6.3	5.1	13.6	<0.001
1 year Outcome	**N=441**	**N=448**	**N=437**	
Death	2.3	2.0	10.1	<0.001
Cardiac	1.6	1.6	7.3	<0.001
Non-cardiac	0.7	0.4	2.7	0.004

CK=creatine kinase. MI=myocardial infarction. TVR=target vessel revascularization. MACE=major adverse cardiac events.
CABG=coronary artery bypass grafting. Hb=hemoglobin. NACE=net adverse clinical events (the combined incidence of death,
recurrent MI, urgent TVR, stroke, or non-CABG related major bleeding).

Discussion

Our analysis showed that in elderly patients with STEMI, routine pre-hospital treatment with high bolus dose tirofiban in addition to aspirin, heparin, and high-dose clopidogrel has marked benefit on myocardial reperfusion, as determined by ST-segment resolution. However, this was associated with a higher incidence of 30-day bleeding, resulting in a balanced clinical effect after 30-days follow-up.

The elderly patients studied in this analysis presented with a higher prevalence of several comorbid conditions as compared to younger patients. Our results confirmed the results from other trials showing that elderly patients have less effective myocardial reperfusion, reflected by ST segment resolution, as compared to their younger counterparts.(17) The major finding of our study was that the effect of routine pre-hospital treatment with tirofiban on ST resolution (the primary end point of the On-TIME 2 trial) was most marked in elderly STEMI patients. This is an important finding, because the degree of ST-segment resolution after primary PCI is strongly associated with preservation of left ventricular systolic function and with improved prognosis.(14,18) This may have even more consequences, since a previous published post-hoc analysis suggested that the impact of ST-segment resolution on mortality is greater in elderly patients than younger patients.(17) Possibly this is the explanation for the (non-significantly) beneficial effect of tirofiban on 1-year cardiac mortality in elderly patients, as observed in our analysis.

A subgroup-analysis of the ADMIRAL trial showed that the 30-day and 6-month composite endpoints of death, reinfarction, or urgent target vessel revascularization were significantly lower in patients ≥ 65 years of age who received a GPI compared with placebo.(19) The beneficial effects of tirofiban in elderly patients in our study, as determined by improvement of ST-segment resolution and a trend towards a decrease in (cardiac) mortality, can partly be neutralized by a higher risk of bleeding, as has been demonstrated for NSTE-ACS patients.(20) Additionally, in a pre-specified subgroup analysis of the ACUITY trial, the benefit of bivalirudin monotherapy over combined therapy with GPI's in terms of the number needed to treat to prevent 1 bleeding event was particularly high in patients older than 75 years of age.(21) Bleeding is associated with worse short-term and long-term outcomes.(22-24) Antithrombotic therapy itself is an independent predictor of bleeding and overdose in susceptible patients, like elderly patients and those with renal insufficiency, may add additional risks.(25) However, the CADILLAC trial suggested that abciximab as an adjunct to primary PCI in elderly patients may be safe.(11) In our analysis, routine treatment of tirofiban in elderly patients when compared to elderly patients without tirofiban pre-treatment showed a non-significant increase of 30-day bleeding. Although, this has not been confirmed by transfusion rate and hemoglobin decrease, elderly patients at high risk of bleeding might not be treated with a GPI. Thus, despite the small patient numbers, our data suggest that high dose tirofiban is effective and should be considered in elderly STEMI patients with a low to moderate bleeding risk. However, whether newer antithrombotic drugs, as ticagrelor, are more effective in elderly patients, and especially in those with a high bleeding risk, should be confirmed.(26)

Furthermore, a radial approach for PCI in elderly patients (≥75 years) seems effective in reducing bleeding complications.(27) A recently published meta-analysis of radial versus femoral approach revealed that the greatest absolute benefit for radial approach appeared in the setting of primary angioplasty for STEMI.(28) However, in the On-TIME 2 trial, primary PCI was performed in all patients by the femoral approach.

Limitations

Limitations of the On-TIME 2 trial have been described(7); the patients enrolled in this study were derived from a randomised trial and may not be representative of the general population. Primary PCI was performed in all patients by the femoral approach. Cut-off values may influence results. We stratified age into tertiles and found that tirofiban had the highest efficacy in older patients. However, with increasing subgroups, the number of patients in the groups becomes smaller, and because of lack of robustness of the analysis, the conclusions of the current study should be seen as hypothesis generating. Although only the TIMI bleed score was

used for defining bleeding, transfusion rates and decreases in hemoglobin were also assessed. Finally, patients older than 85 years were excluded, and our results can only be extrapolated to these patients with caution.

Conclusion

The effect of pre-hospital initiation of high bolus dose tirofiban on myocardial reperfusion, as determined by ST-segment resolution is highest in the elderly patients. However, this was associated with a trend towards more bleeding complications, resulting in a balanced clinical effect after 30-day follow-up. Future studies should evaluate whether the elderly STEMI patient may benefit from highly effective but more safe antiplatelet therapy.

References

1. Barakat K, Wilkinson P, Deaner A, Fluck D, Ranjadayalan K, Timmis A. How should age effect management of acute myocardial infarction? A prospective cohort study. Lancet 1999;353:955-959.
2. Batchelor WB, Anstrom KJ, Muhlbaier LH, Grosswald R, Weintraub WS, O'Neill WW, Peterson ED. Contemporary outcome trends in the elderly undergoing percutaneous coronary interventions: results in 7,472 octogenarians. J Am Coll Cardiol 2000;36:723-730.
3. Graham MM, Ghali WA, Faris PD, Galbraith PD, Norris CM, Knudtson ML. Survival after coronary revascularization in the elderly. Circulation 2002;105:2378-2384.
4. Maggioni AP, Maseri A, Fresco C, Franzosi MG, Mauri F, Santoro E, Tognoni G. Age-related increase in mortality among patients with first myocardial infarctions treated with thrombolysis. N Engl J Med 1993;329:1442-1448.
5. Antman EM, Anbe DT, Armstrong PW, Bates ER, MD, Green LA, Hand M, Hochman JS, Krumholz HM, Kushner FG, Lamas GA, Mullany CJ, Ornato JP, Pearle DL, Sloan MA, Smith Jr SC. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). Circulation 2004;110:588-636.
6. Antman EM, Hand M, Armstrong PW, Bates ER, Green LA, Halasyamani LK, Hochman JS, Krumholz HM, Lamas GA, Mullany CJ, Pearle DL, Sloan MA, Smith Jr SC. 2007 Focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: A report of the ACC/AHA Task Force on Practice Guidelines. J Am Coll Cardiol 2008;58:210-247.
7. Van 't Hof AW, Ten Berg JM, Heestermans AA, Dill T, Funck RC, van Werkum JW, Dambrink JH, Suryapranata H, van Houwelingen KG, Ottervanger JP, Stella PR, Giannitsis E, Hamm C. Ongoing Tirofiban In Myocardial infarction Evaluation (On-TIME) 2 study group. Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial. Lancet 2008;372:537-546.
8. ten Berg JM, van 't Hof AW, Dill T, Heestermans AA, van Werkum JW, Mosterd A, van Houwelingen KG, Koopmans PC, Stella PR, Boersma E, Hamm C. On behalf of the Ongoing Tirofiban In Myocardial infarction Evaluation (On-TIME) 2 study group. Effect of early, pre-hospital initiation of high-bolus dose tirofiban in patients with ST-segment elevation myocardial infarction on short and long-term clinical outcome. J Am Coll Cardiol 2010;55:2446-2455.
9. Boersma E, Harrington RA, Moliterno DJ, White H, Theroux P, van der Werf F, de Torbal A, Armstrong PW, Wallentin LC, Wilcox RG, Simes J, Califf RM, Topol EJ, Simoons ML. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. Lancet 2002;359:189-198.
10. Lincoff AM, Bittl JA and Harrington RA, Feit F, Kleiman NS, Jackman JD, Sarembock IJ, Cohen DJ, Spriggs D, Ebrahimi R, Keren G, Carr J, Cohen EA, Betriu A, Desmet W, Kereiakes DJ, Rutsch W, Wilcox RG, de Feyter PJ, Vahanian A, Topol EJ. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. JAMA 2003;289:853-863.
11. Guagliumi G, Stone GW, Cox DA, Stuckey T, Tcheng JE, Turco M, Musumeci G, Griffin JJ, Lansky AJ, Mehran R, Grines CL, Garcia E. Outcome in elderly patients undergoing primary coronary intervention for acute myocardial infarction: results from the controlled abciximab and device investigation to lower late angioplasty complications (CADILLAC) trial. Circulation 2004;110:1598-1604.
12. van 't Hof AW, Hamm C, Rasoul S, Guphta S, Paolini JF, ten Berg JM, on behalf of the On-TIME 2 investigators. Ongoing tirofiban in myocardial infarction evaluation (On-TIME) 2 trial: rationale and study design. EuroInterv 2007;3:371-380.
13. De Luca G, Maas AC, Suryapranata H, Ottervanger JP, Hoorntje JC, Gosselink ATM, Dambrink JH, de Boer MJ, van 't Hof AW. Prognostic significance of residual cumulative ST-segment deviation after mechanical reperfusion in patients with ST-segment elevation myocardial infarction. Am Heart J 2005;150:1248-1254.
14. van 't Hof AW, Liem AL, de Boer MJ, Zijlstra F, on behalf of the Zwolle myocardial Infarction Study Group. Clinical value of 12-lead electrocardiogram after successful reperfusion therapy for acute myocardial infarction. Lancet 1997;350:615-619.
15. Rao AK, Pratt C, Berke A, Jaffe A, Ockene I, Schreiber TL, Bell WR, Knatterud G, Robertson TL, Terrin ML. Thrombolysis in Myocardial Infarction (TIMI) Trial — phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. J Am Coll Cardiol 1988;11:1-11.
16. Assmann SF, Pocock SJ, Enos LE, Kasten LE. Subgroup analysis and other (mis)uses of baseline data in clinical trials. Lancet 2000;355:1064-1069.
17. Prasad A, Stone GW, Aymong E, Zimetbaum PJ, McLaughlin M, Mehran R, Garcia E, Tcheng JE, Cox DA, Grines CL, Gersh BJ. Impact of ST-segment resolution after primary angioplasty on outcomes after myocardial infarction in elderly patients: An analysis from the CADILLAC trial. Am Heart J 2004;147:669-675.
18. Matetzky S, Novikov M, Gruberg L, Freimark

D, Feinberg M, Elian D, Novikov I, Di Segni E, Agranat O, Har-Zahav Y, Rabinowitz B, Kaplinsky E, Hod H. The significance persistent ST elevation versus early resolution of ST-segment elevation after primary PTCA. J Am Coll Cardiol 1999;34:1932-1938.

19. Montalescot G, Barragan P, Witternberg O, Ecollan P, Elhadad S, Villain P, Boulenc JM, Morice MC, Maillard L, Pansiéri M, Choussat R, Pinton P; ADMIRAL investigators. Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-term follow-up. New Engl J Med 2001;344:1895-1903.
20. Hernandez AV, Westerhout CM, Steyerberg EW, Ioannidis JP, Bueno H, White H, Theroux P, Moliterno DJ, Armstrong PW, Califf RM, Wallentin LC, Simoons ML, Boersma E. Effects of platelet glycoprotein IIb/IIIa receptor blockers in non-ST segment elevation acute coronary syndromes: benefit and harm in different age subgroups. Heart 2007;93:450-455.
21. Lopez RD. Alexander KP, Manoukian SV, Bertrand ME, Feit F, White HD, Pollack CV Jr, Hoekstra J, Gersh BJ, Stone GW, Ohman EM. Advanced age, antithrombotic stategy, and bleeding in non-ST-segment elevation acute coronary syndromes: results from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial. J Am Coll Cardiol 2009;53:1021-1030.
22. Eikelboom JW, Metha SR, Anand SS, Xie C, Fox KA, Yusuf S. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. Circulation 2006;114:774-782.
23. Manoukian SV, Feit F, Mehran R, Voeltz MD, Ebrahimi R, Hamon M Dangas GD, Lincoff AM, White HD, Moses JW, King SB 3rd, Ohman EM, Stone GW. Impact of major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary syndromes: an analysis from the ACUITY trial. J Am Coll Cardiol 2007;49:1362-1368.
24. Rao SV, O'Grady K, Pieper KS, Granger CB, Newby LK, Van de Werf F, Mahaffey KW, Califf RM, Harrington RA. Impact of bleeding severity on clinical outcomes among patients with acute coronary syndromes. Am J Cardiol 2005;96:1200-1206.
25. Alexander KP, Chen AY, Roe MT, Newby LK, Gibson CM, Allen-LaPointe NM, Pollack C, Gibler WB, Ohman EM, Peterson ED; CRUSADE investigators. Excess dosing of antiplatelet and antithrombin agents in the treatment of non-ST-segment elevation acute coronary syndromes. JAMA 2005;294:3108-3116.
26. Cannon CP, Harrington RA, James S, Ardissino D, Becker RC, Emanuelsson H, Husted S, Katus H, Keltai M, Khurmi NS, Kontny F, Lewis BS, Steg PG, Storey RF, Wojdyla D, Wallentin L. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. Lancet 2010;375:283-293.
27. Achenbach S, Ropers D, Kallert L, Turan N, Krähner R, Wolf T, Garlichs C, Flachskampf F, Daniel WG, Ludwig J. Transradial versus transfemoral approach for coronary angiography and intervention in patients above 75 years of age. Catheter and Cardiovasc Intervent 2008;72:629-635.
28. Jolly SS, Amlani S, Hamon M, Yusuf S, Phil D, Mehta SR. Radial versus femoral access for coronary angiography or intervention and the impact of major bleeding and ischemic events: a systematic review and meta-analysis of randomized trials. Am Heart J 2009;157:132-140.

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Sub-optimal anticoagulation with pre-hospital heparin in ST-elevation myocardial infarction

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R.S. Hermanides, J.P. Ottervanger, J.H. Dambrink, M.J. de Boer,
J.C. Hoorntje, A.T. Gosselink, H. Suryapranata, F. Zijlstra, A.W. van 't Hof

Abstract

This is a prospective, observational study performed in all consecutive STEMI patients who had activated clotting time (ACT) measurement on arrival in the cathlab before coronary angiography. We studied the therapeutic effects of a pre-hospital fixed heparin bolus dose in consecutive patients with ST-elevation myocardial infarction (STEMI).

A total of 1533 patients received pre-hospital administration of aspirin, high dose clopidogrel (600mg) and a fixed bolus dose of 5000 IU unfractionated heparin (UFH), according to the national ambulance protocols. Some patients were also treated with glycoprotein IIb/IIIa inhibitors (GPI) in the ambulance. A therapeutic ACT range was defined according to the ESC guidelines as 200-250 seconds when patients had GPI pre-treatment and 250-350 seconds when no GPI pre-treatment.

Of the 1533 patients, 216 patients (14.1%) had an ACT within the therapeutic range, 82.3% of the patients had a too low ACT, whereas 3.5% of the patients had a too high ACT. After multivariable analysis, the only independent predictor of a too low ACT was increasing weight (OR 1.02/kg, 95% CI 1.01–1.03, p=0.001). Patients with a too low ACT had less often an open infarct related vessel (initial TIMI flow 2,3) as compared to patients with an ACT in range (36.5% vs 45.9%, p=0.013).

In only a minority of patients with ST-elevation myocardial infarction, pre-hospital treatment with a fixed bolus dose unfractionated heparin is within the therapeutic ACT range. Increased weight is an independent determinant of a too low ACT. We strongly recommend weight adjusted administration of unfractionated heparin in the ambulance.

Introduction

Since the first primary percutaneous coronary intervention (PCI), intravenous unfractionated heparin (UFH) has been the cornerstone of antithrombotic therapy during primary PCI for ST-elevation myocardial infarction (STEMI) to prevent acute vessel closure due to thrombus.(1) It is recommended to perform the procedure under an activated clotting time (ACT) of 250-350 seconds (200-250 seconds if glycoprotein IIb/IIIa inhibitors (GPI) are used).(2) Inadequate heparin dosing has been associated with an increased risk of re-infarction.(3) UFH overdose is related with bleeding(4), and bleeding is strongly associated with poor prognosis.(5,6) Many trials and registries suggested to use a weight adjusted UFH protocol in the ambulance.(2,7-10) We evaluated this in several local ambulance protocols of the Netherlands, Belgium, Germany and United Kingdom and found however, that all give a fixed bolus dose of 5000 IU UFH in the ambulance in STEMI patients in daily clinical practice, possibly resulting in under- or overtreatment. Therefore, the aim of this study was to investigate the effects of a pre-hospital fixed heparin bolus dose on therapeutic ACT range in consecutive patients with ST-elevation myocardial infarction.

Material and methods

Population

From January 2006 to December 2009, individual patient data from all patients with diagnosis of STEMI admitted for primary PCI at the Isala klinieken (Zwolle, the Netherlands) and had ACT measurement were prospectively recorded. To avoid double inclusion of patients, only the first recorded admission for STEMI during the study period was used. Patients were diagnosed with STEMI if they had chest pain of >30 minutes duration and ECG changes with ST segment elevation >2 mm in at least 2 precordials and >1 mm in the limb leads. In addition, we did not restrict our population to those presenting within 12 hr of symptom onset but included those presenting at any time with ongoing symptoms or clinical instability and an indication for primary PCI.

Procedure details and adjunctive medical therapy

According to protocol all patients received 500mg of aspirin intravenously, high loading dose of clopidogrel (600mg orally) and a fixed bolus dose of 5000 IU UFH intravenously. After bolus initiation in the ambulance or referral centre ACT was measured on arrival in the cathlab before device activation and this measurement was defined as the index ACT.

According to institutional guidelines additional UFH was administered only in cases were the ACT was less than 200 seconds, if the procedure lasted more than 1

hour or at the discretion of the operator if complications appeared. All ACT's were measured locally by using a Hemochron device (International Technidyne, Edison, New Yersey, USA).(11-15)
In some patients additional treatment with GPI's (25μg/kg bolus tirofiban) was given in the ambulance or referral centre. Primary PCI was routinely performed by femoral access using 6 French sheaths with selective thrombus aspiration and stent implantation where appropriate.

Endpoint

The primary endpoint of this study was the effect of a fixed bolus dose of UFH on therapeutic ACT range in consecutive STEMI patients. A therapeutic ACT range was defined according to the ESC guidelines as 200-250 seconds when patients had GPI pre-treatment and 250-350 seconds when no GPI pre-treatment.(2)

Data collection and follow-up

Baseline clinical characteristics, laboratory measurements, angiographic characteristics, and procedural details were collected in a case record form. Follow-up information was obtained from the patient's general physician or by direct telephone interview with the patient.

Ethics

The investigation conforms with the principles outlined in the Declaration of Helsinki. The study was approved by the Committee on Research Ethics of our hospital.

Statistical Analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 16.0.1. Continuous data were expressed as mean ± standard deviation and categorical data as percentage, unless otherwise denoted. Differences between continuous data were performed by students t test or Mann-Whitney test and the chi-square or Fisher's exact test or Kruskal Wallis test was used as appropriate for dichotomous data. Multivariable logistic regression analysis was performed to test the independent predictors of a too low ACT, selecting baseline variables with entry/stay criteria of $p<0.10$. Variables entered into the model for a too low ACT included age (per year increment), gender, length (per cm increase), weight (per kg increase), and time from UFH administration to ACT measurement. Significant variables analyzed are reported with their respective odd ratios and 95% confidence intervals. For all analyses, statistical significance was assumed when the two-tailed probability value was <0.05.

Results

Baseline characteristics

During the study period ACT was measured in 1533 STEMI patients, mean age was 62.9 ± 12.4 years, weight was 82.3 ± 14.5 kg, 13.2% had a GFR <60 ml/min and 25.5% were females. The median ACT was 185 seconds (interquartile range 163 - 207), whereas the mean was 191 ± 47 seconds.

Patients with a too low ACT as compared to patients with an ACT in range were younger, had more weight, had a longer time between UFH administration to ACT measurement, and as expected received more often additional UFH in the cathlab prior to coronary angiography, see table 1.

Table 1: General characteristics

Characteristics	Too low ACT	ACT in range	P
	N=1261	N=216	
Age	62.4 ± 12.2	64.6 ± 12.8	0.010
Male gender	75.8	71.8	0.200
BMI	26.9 ± 4.1	26.4 ± 3.7	0.156
Weight	83.1 ± 14.7	78.5 ± 13.1	<0.001
Hypertension	33.5	35.8	0.516
Smoking	41.2	38.0	0.374
Hypercholesterolaemia	20.5	26.1	0.068
Family history	39.8	42.1	0.515
Diabetes Mellitus	10.6	7.4	0.146
Previous MI	9.2	10.2	0.658
Previous PCI	9.1	11.1	0.341
Previous CVA	3.4	4.2	0.580
Renal insufficiency	12.2	18.7	0.012
Killip > 1	5.3	6.0	0.672
Time from UFH administration to ACT measurement (min)	82 (63 – 109)	74 (60 – 91)	< 0.001
Ischemic time (min)	200 (145 – 320)	197 (139 – 291)	0.322
Aspirin pre-treatment	92.8	94.4	0.383
Clopidogrel pre-treatment	88.5	87.0	0.512
Tirofiban pre-treatment	34.0	67.1	<0.001
Median ACT (sec)	178 (159 – 195)	223 (209 – 259)	<0.001
Initial TIMI 2,3 flow	36.5	45.9	0.013
Final TIMI 3 flow	92.4	89.7	0.208
Non CABG-related bleeding 30 days	3.4	3.3	0.942

Data are n/N (%) or mean (SD), or median (IQR). BMI=body mass index. MI=myocardial infarction. PCI=percutaneous coronary intervention.
CABG=coronary artery bypass grafting. CVA=cerebrovascular accident. UFH=unfractionated heparin. ACT=activated clotting time. TIMI=thrombolysis in myocardial infarction.
Renal insufficiency=GFR (glomerular filtration rate) <60 (according MDRD).

14.1% of the patients had an ACT within the therapeutic range, 82.3% of the patients had a too low ACT, whereas 3.5% of the patients had a too high ACT. Of the 608 patients (39.7%) who had GPI pre-treatment, 23.8% had an ACT within the therapeutic range, 70.6% of the patients had a too low ACT, whereas 5.6% of the patients had a too high ACT. Of the 925 patients without GPI pre-treatment, 7.7% of the patients had an ACT within the therapeutic range, 89.9% of the patients had a

too low ACT, whereas 2.4% of the patients had a too high ACT.
Patients with a too low ACT had less often an open infarct related vessel (initial TIMI flow 2,3) as compared to patients with an ACT in range (36.5% vs 45.9%, p=0.013).

Predictors of a too low ACT (<200 seconds for GPI pre-treatment and <250 seconds for no GPI pre-treatment)

After multivariable analyses, adjusting for all variables that were statistically significant in univariate analyses, only weight (per kg increase) (OR 1.02, 95% CI 1.01 – 1.03, p=0.001) remained an independent predictor of a too low ACT. Furthermore, the finding that weight was an important predictor of a too low ACT was supported after stratifying weight into quartiles (p<0.001, figure 1). There were no independent predictors of a too high ACT.

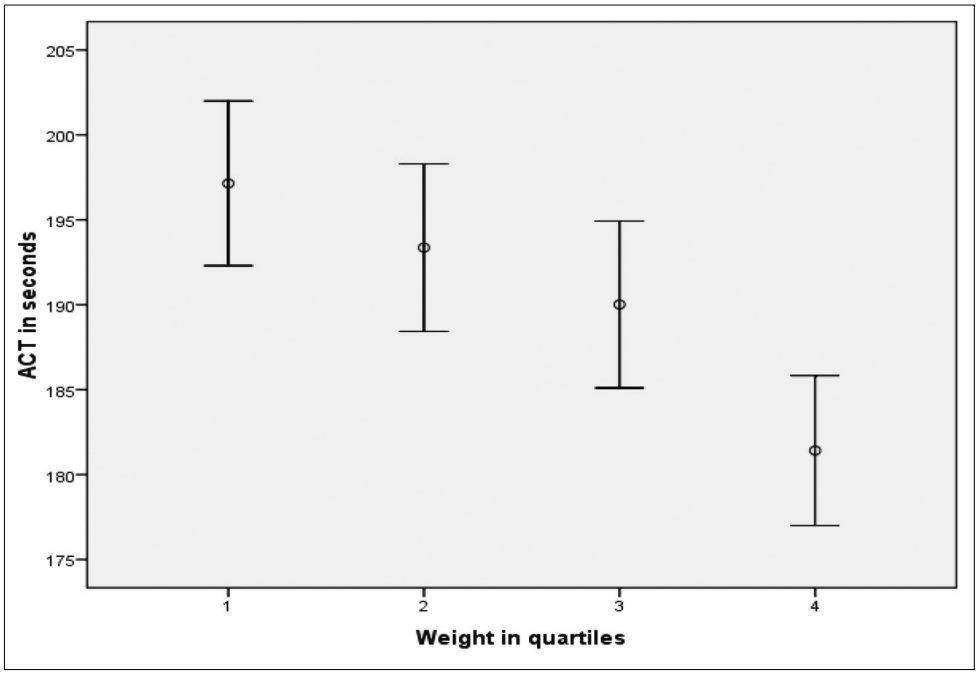

Figure 1: Impact of weight on activated clotting time in seconds after stratifying weight into quartiles. Error plot with mean ACT in seconds and 95% CI, Kruskal Wallis test: p<0.001

Discussion

To our knowledge, this is the first large study in non-selected primary PCI patients which determines the effects of a fixed bolus dose of unfractionated heparin in the ambulance or referral centre on therapeutic ACT range. The major finding of

the present study is that only 14.1% of the STEMI patients had an ACT within the therapeutic range.
Of those who had GPI pre-treatment, 23.8% had an ACT within the therapeutic range. Of the patients with no GPI pre-treatment only 7.7% had an ACT within the therapeutic range. Furthermore, increased weight is an independent determinant of a too low index ACT.

In univariate analyses there were significantly more patients in the ACT-in-range-population who had pre-hospital administration of high dose tirofiban. Possibly this is in part an effect of tirofiban since it has been demonstrated that GPI use on top of heparin leads to a prolongation of the ACT.(17)

Therapeutic efficacy of heparin

Despite the fact that evidence for supporting UFH in primary PCI is limited, use of UFH for primary PCI in STEMI is widely supported.(18) However, heparin has a number of limitations, including a narrow therapeutic window of adequate anti-coagulation without bleeding, heparin induced thrombocytopenia, reduced ability to inactivate thrombin bound to fibrin as well as factor Xa bound to activated platelets within a thrombus, and a highly variable dose-response relation requiring laboratory monitoring. According to the ESC guidelines, UFH should be given at a dose able to maintain an ACT of 250-350 seconds (200-250 seconds if GPI's are used).(2)
Greater peak ACT values have been associated with a greater incidence of bleeding and vascular complications.(19-21) Four randomized trials of heparin dosing in patients undergoing PCI, consistently found that lowering the dose of heparin reduced minor, but not major, bleeding rates(22-25), which is in accordance with the results of the recently published FUTURA/OASIS-8 trial.(26) With the introduction of GPI's, stenting, and clopidogrel treatment, post hoc analyses of large clinical trials have suggested that a reduction of the UFH dose would reduce the risks of bleeding without compromising the ischemic risks.(27,28) However, pooled data suggested a U-shaped curve for ischemic and bleeding complications after PCI and UFH-only therapy, whereas with abciximab, the U-shape relation was no longer present.(17)
In a more recent post hoc analysis of 4 PCI trials with UFH doses of 65 to 90 IU/kg, the previously described U-shaped curve for ischemic events could not be not reproduced, however, a modest association was still found between greater ACT values and bleeding complications.(27) This was confirmed by a sub-analysis of the ESPRIT trial.(28)
Our analysis revealed that patients with a too low ACT had less often an open infarct related vessel, as compared with patients with an ACT within the range, but we can not prove a causal relationship with UFH.

Recommendations for improvement

Optimising heparin dose

The current ESC guidelines recommend for STEMI patients who are candidates for primary PCI an i.v. UFH bolus with a starting dose of 100 IU/kg weight (60 IU/kg if GPI's are used).(2) However, we observed after reviewing ambulance protocols from different countries, including the Netherlands, Belgium, Germany and UK, that in daily clinical practice a fixed bolus dose of UFH in the pre-hospital setting is used, probably due to practical reasons. Our results confirm that a weight adjusted dosing of UFH may improve anticoagulation level. However, because of the individual variation, also after weight adjusted administration of UFH, ACT on admission should be measured in every patient. Furthermore, in the ESC guidelines there are no references for the optimal therapeutic ACT range. Therefore, further analyses are warranted to determine the optimal therapeutic ACT range when using UFH weight adjusted.

Alternatives for UFH

Use of LMWH in patients with STEMI may result in a higher frequency of anticoagulation within the therapeutic range, possibly resulting in a reduction of ischemic events.(7,29)

The HORIZONS-AMI trial showed beneficial clinical effects with bivalirudin and provisional GPI as compared to UFH and GPI.(8) Because of a low variable dose response relation, there is no therapeutic range required for bivalirudin. Whether pre-hospital treatment with bivalirudin will further improve net clinical benefit, should be awaited from the ongoing EUROMAX trial (9). We have summarized our recommendations in table 2.

Table 2: Recommendations for treatment of STEMI patients, based on these findings

1. Adjust UFH according to weight in the pre-hospital setting, as recommended in the European guidelines
2. Record the time of administration of UFH in the ambulance or referral center
3. Measure the ACT on arrival in the cath lab, administer additional heparin if necessary, and repeat ACT measurement at the end of the procedure
4. Re-define therapeutic ACT range
5. Renew European guidelines regarding newer antithrombotic agents for use in the pre-hospital setting

UFH=unfractionated heparin. ACT=activated clotting time.

Study strengths and limitations

This is a prospective observational study with known limitations. This study has only focussed on the effects of a fixed bolus dose of UFH given in the ambulance or referral centre on the index ACT. To demonstrate a potential association between sub-optimal ACT and clinical outcome is more difficult in an observational study, particularly because ACT measurements influence administration of additional heparin. Because of inherent differences in the measurement of ACT by different ACT devices and to be consistent, we used only one point-of-care assay ACT device. (13,14) However, it should be noted that biological factors can influence the response to UFH in STEMI patients. Furthermore, the ACT at the end of the PCI procedure, before sheath removal, was not measured.

Conclusion

In only a minority of patients with ST-elevation myocardial infarction, pre-hospital treatment with a fixed bolus dose unfractionated heparin is within the therapeutic ACT range. Increased weight is an important independent predictor of a too low ACT. We strongly recommend weight adjusted administration of unfractionated heparin in the ambulance

References

1. Popma JJ, Weitz J, Bittl JA, et al. Antithrombotic therapy in patients undergoing coronary angioplasty. Chest 1998;114:728S.
2. Wijns W, Kolh P, Danchin N, et al. The task force on myocardial revascularization of the European Society of Cardiology (ESC) and the European Association of Cardio-Thoracic Surgery (EACTS). Guidelines on myocardial revascularization. Eur Heart J 2010;31:2501-2555.
3. Cheng S, Morrow DA, Sloan S, et al. Predictors of initial nontherapeutic anticoagulation with unfractionated heparin in ST-segment elevation myocardial infarction. Circulation 2009;119:1195-1202.
4. Alexander KP, Chen AY, Roe MT, et al; CRUSADE Investigators. Excess dosing of antiplatelet and antithrombin agents in the treatment of non-ST-segment elevation acute coronary syndromes. JAMA 2005;294:3108-3116.
5. Eikelboom JW, Metha SR, Anand SS, et al. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. Circulation 2006;114:774-782.
6. Manoukian SV, Feit F, Mehran R, et al. Impact of major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary syndromes: an analysis from the ACUITY trial. J Am Coll Cardiol 2007;49:1362-1368.
7. Montalescot G, Cohen M, Goldstein P, et al, for the ATOLL investigators. Acute STEMI Treated with primary angioplasty and intravenous enoxaparin Or UFH to Lower ischemic and bleeding events at short- and Long-term follow-up trial. ESC, Stockholm, August 30 2010, Hotline session.
8. Stone GW, WItzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med 2008;358:2218-2230.
9. Steg PG, Hamm C, Goldstein P, et al, for the EUROMAX investigators. European Ambulance Acute Coronary Syndrome Angiox Trial: EUROMAX. http://clinicaltrials.gov/ct2/show/NCT01087723
10. Ellis SG, Tendera M, de Belder MA, et al, for the FINESSE Investigators. Facilitated PCI in patients with ST-elevation myocardial infarction. New Engl J Med 2008;358: 2205-2217.
11. Chia S, Van Cott EM, Raffel OC, et al. Comparison of activated clotting times obtained using Hemochron and Medtronic analysers in patients receiving anti-thrombin therapy during cardiac catheterisation. Thrombosis and Haemostasis 2009:101:413-603.
12. Voyce SJ, Weiner BH, Becker RC. ACT monitoring: current applications in the angioplasty suite. Cardiology 1993;10:6-9.
13. Rath B, Bennett DH. Monitoring the effect of heparin by measurement of activated clotting time during and after percutaneous transluminal coronary angioplasty. Br Heart J 1990;63:18-21.
14. Avendano A, Ferguson JJ. Comparison of Hemochron and Hemotec activated coagulation time target values during percutaneous transluminal coronary angioplasty. J Am Coll Cardiol 1994;23:907-910.
15. Doherty TM, Shavelle RM, French WJ. Reproducibility and variability of activated clotting time measurements in the cardiac catheterization laboratory. Catheter Cardiovasc Interv 2005;65:330-337.
16. Himber J, Burcklen L, Steiner B. Effects of GP IIb/IIIa receptor antagonists on the activated clotting time of heparinized blood. Blood 2000;95:2189-2190.
17. Moliterno DJ, Califf RM, Aguirre FV, et al. Effect of platelet glycoprotein IIb/IIIa integrin blockade on activated clotting time during percutaneous transluminal coronary angioplasty or directional atherectomy (the EPIC trial). Am J Cardiol 1995;75:559-562.
18. Kushner FG, Hand M, Smith SC Jr, et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update) a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2009;54:2205-2241.
19. Chew DP, Bhatt DL, Lincoff AM, et al. Defining the optimal activated clotting time during percutaneous coronary intervention: Aggregate results from 6 randomized controlled trials. Circulation 2001;103:961-966.
20. Blankenship JC, Balog C, Sapp SK, et al. Reduction in vascular access site bleeding in sequential abciximab coronary intervention trials. Catheter Cardiovasc Interv 2002;57:576-483.
21. Popma JJ, Satler LF, Pichard AD, et al. Vascular complications after balloon and new device angioplasty. Circulation 1993;88:1569-1578.
22. The EPILOG investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. N Engl J Med 1997;336:1689-1696.
23. Vainer J, Fleisch M, Gunnes P, et al. Low-dose heparin for routine coronary angioplasty and stenting. Am J Cardiol 1996;78:964-966.
24. Lincoff AM, Tcheng JE, Califf RM, et al. PROLOG investigators. Standard versus low-dose weight adjusted heparin in patients treated with the platelet glycoprotein IIb/IIIa receptor antibody fragment abciximab (c7E3 fab) during percutaneous coronary revascularization. Am J Cardiol 1997;79:286-291.
25. Boccara A, Benamer H, Juliard JM, et al. A randomized trial of a fixed high dose vs a weight-adjusted low dose of intravenous heparin during coronary angioplasty. Eur Heart J 1997;18:631-635.
26. Steg PG, Jolly SS, Metha SR, et al. Low-dose vs standard dose unfractionated heparin for percutaneous coronary intervention in acute

coronary syndromes treated with fondaparinux. JAMA 2010;304:1339-1349.

27. Brener SJ, Moliterno DJ, Lincoff AM, et al. Relationship between activated clotting time and ischemic or hemorrhagic complications: analysis of 4 recent randomized clinical trials of percutaneous coronary intervention. Circulation 2004;110:994-998.
28. Tolleson TR, O'Shea JC, Bittl JA, et al. Relationship between heparin anticoagulation and clinical outcomes in coronary stent intervention: observations from the ESPRIT trial. J Am Coll Cardiol 2003;41:386-393.
29. Brieger D, Collet JP, Silvain J, et al. Heparin or enoxaparin anticoagulation for primary percutaneous coronary intervention. Catheter Cardiovasc Interv 2011;77:182-190.

8

Closure device or manual compression in patients undergoing percutaneous coronary intervention: a randomised comparison

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R.S. Hermanides, J.P. Ottervanger, J.H. Dambrink, M.J. de Boer, J.C. Hoorntje, A.T. Gosselink, H. Suryapranata, A.W. van 't Hof, on behalf of the Zwolle Myocardial Infarction Study Group

Abstract

Aims: Although closure devices may be comfortable for patients, the clinical benefits in patients with moderate to high risk of bleeding are not yet clear.
We compared a closure device with manual compression in moderate to high risk bleeding patients undergoing percutaneous coronary intervention (PCI).

Methods and results: A randomised study was performed to compare a closure device (Angio-Seal, St. Jude Medical, Inc) with manual compression in 627 patients treated with aspirin, clopidogrel, a glycoprotein IIb/IIIa inhibitor and heparin during PCI. Primary endpoint was the in-hospital combined incidence of 1) severe hematoma >5cm at the puncture site or groin bleeding resulting in prolonged hospital stay, transfusion and/or surgical intervention at the puncture site, 2) arteriovenous fistula formation and/or surgical intervention at the puncture site.
A total of 313 patients (49.9%) were randomised to the closure device and 314 patients (50.1%) to manual compression. The combined primary endpoint was 2.6% in the closure device group compared to 4.5% in the manual compression group (p=0.195). In the pre-defined subgroup of patients with a history of hypertension, however, the combined primary endpoint (0.8% vs. 7.2%, p=0.008) was significantly reduced after use of the closure device.

Conclusion: This trial did not show the superiority of using a closure device over manual compression in patients, treated with triple antiplatelet therapy, who underwent PCI. The fact that patients with a history of hypertension had a benefit from a closure device merits further investigation.

Introduction

Vascular complication rates after cardiac catheterization or percutaneous coronary intervention (PCI) range from 1.5% to 9%, and 20% to 40% of patients who experience such complications require surgical intervention.(1,2) The identified risk factors for femoral puncture site complications include age >75 years, female gender, hypertension, diabetes mellitus, low body mass index, location of puncture site, sheath size, duration of the procedure and intensive use of antithrombotic drugs.(3-9)

Because both manual compression after removal of the catheter sheath and bed rest are associated with discomfort to the patient and may have cost implications, arterial puncture closing devices have been developed to avoid manual compression and shorten bed rest. However, although it was shown that use of a closure device resulted in less reported pain(10), two meta-analyses concluded that many of the randomized trials had a limited sample size and were of poor methodological quality, and that there is only marginal evidence that closure devices are more effective than manual compression.(11,12) Furthermore, although some reports showed very low bleeding risks with the use of a closure device in patients treated with intensive antiplatelet medication, this has not been evaluated in a randomised clinical trial. (13,14) The aim of the present study was to compare a closure device with manual compression in moderate to high risk bleeding patients undergoing PCI.

Methods

Study design

The ANGIO-Seal or manual Compression After coRonary intervention Evaluation (ANGIOCARE) study was a single centre, prospective, randomised trial which compared the Angio-Seal closure device with manual compression in a moderate to high-risk patient population. The randomization was 1:1 to receive or not a closure device. All patients were treated with aspirin, high dose clopidogrel, glycoprotein IIb/IIIa inhibitor (GPI) and unfractionated heparin or low molecular weight heparin during PCI.

Data concerning primary and secondary endpoints were analyzed for subgroups defined by age >75 years, female gender, history of hypertension and duration of the procedure. The study was registered, with number ISRCTN22655249 (www.controlled-trials.com). Written informed consent was obtained from all patients. Study approval was obtained from the medical ethic committee of our hospital.

Procedures

A modified Seldinger technique was used to canulate the common femoral artery. (15) Vascular access sheaths were used in every patient. All angiograms were made

with 6F guiding catheters in a standardized fashion. Randomization was performed by means of a computer program in blocks (randomly changing block size) to achieve a balanced allocation. The randomization was done after arterial puncture of the femoral artery.

After the PCI, the sheath in the femoral artery was removed immediately. Closure device deployment (6 F) was performed without routine fluoroscopy of the femoral artery according to the protocol on cath-lab and nursing department (bandage for 4 hours followed by immediate ambulation). Manual compression was performed also on cath-lab, immediate after the procedure, by compression for at least 15 minutes until leakage had stopped, with further treatment according to our local nursing protocol (bandage for 6 hours, ambulation after 8 hours). During bandage the patient was instructed to lie in bed, with the leg remaining straight.

Population

Inclusion criteria were PCI via femoral artery and treatment with aspirin, clopidogrel (600mg pre-loading dose), unfractionated heparin and a glycoprotein IIb/IIIa inhibitor. Patients routinely received weight adjusted unfractionated heparin (60 U/kg) and tirofiban (25 μg/kg bolus and 0.15 μg/kg/min maintenance infusion) according to the guidelines.(16) In patients pre-treated with unfractioned heparin in the ambulance, additional heparin was only given when the activated clotting time was below 200 seconds. When patients were pre-treated with low molecular weight heparin, additional heparin during PCI was only given when the time from the last gift of low molecular weight heparin exceeded 8 hours.

Use of other cardiac medication was left at the discretion of the cardiologist.

Exclusion criteria were: age <18 years, serious comorbidity such as cancer, advanced cerebrovascular disease, unwilling or unable to sign the consent form for participation, females of childbearing age not using medically prescribed contraceptives and unsuitable access site (severe peripheral vascular disease, poor location). It concerned an intention to treat analysis. Patients might have a cross-over according to the decision of the physician. All cases of cross-over were documented.

Measurements (end points, definitions)

The primary endpoint was the combined incidence of 1) severe hematoma >5cm at the puncture site or groin bleeding resulting in prolonged hospital stay, transfusion and/or surgical intervention at the puncture site, 2) arteriovenous fistula formation at the puncture site and/or surgical intervention at the puncture site. The indication for transfusion was defined according to our local hospital protocol as a measured Hb lower than 8.8 g/dl. All puncture sites were examined, 12-24 hours after sheath removal, by research nurses who were blinded for type of treatment. Ultra

sonography was only performed if the patient had pain at the puncture site, there was a hematoma or there were signs of arteriovenous fistula. Secondary endpoints were the decrease of hemoglobin, 1 day after inclusion, and hospital admission duration. Pre-defined subgroups were age >75 years, female gender, history of hypertension and prolonged procedure time. History of hypertension was defined as patients who used antihypertensive drugs for the indication hypertension or with blood pressure more than 140/90 mmHg on more than two occasions prior to the PCI.

Data collection and follow-up

We collected the following variables from the patient files: age, gender, history of hypertension, diabetes, previous myocardial infarction, length, weight, angiographic variables, laboratory measurements, procedure variables and hospital duration. Clinical data were collected prospectively by research nurses. Follow-up information was obtained from medical hospital records, the patient's general physician and by direct telephone interview with the patient. A blinded independent clinical endpoint committee adjudicated all clinical end points.

Statistical Analysis

The sample size was calculated to demonstrate increased efficacy of the use of a closure device compared to manual compression. The estimated incidence of the primary endpoint was 7% in the manual compression group based on the occurrence of bleeding in our previous large single-center observational study in consecutive STEMI patients who underwent primary PCI.(17) A sample size of 614 patients, with 307 patients in each treatment group was planned. A trial of this size has an 80% power at an alpha level of 0.05 to show a decrease in the incidence of the primary endpoint of 7% in the manual compression group compared to 2% in the closure device group.

All analyses were by intention to treat. An interim analysis was performed according to the probability stopping rules of Snapinn after inclusion of 430 patients.

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 15.0.1. Continuous data were expressed as mean ± standard deviation and categorical data as percentage, unless otherwise denoted. Differences between continuous data were performed by student's t test and the chi-square or Fisher's exact test was used as appropriate for dichotomous data. For all analyses, statistical significance was assumed when the two-tailed probability value was <0.05.

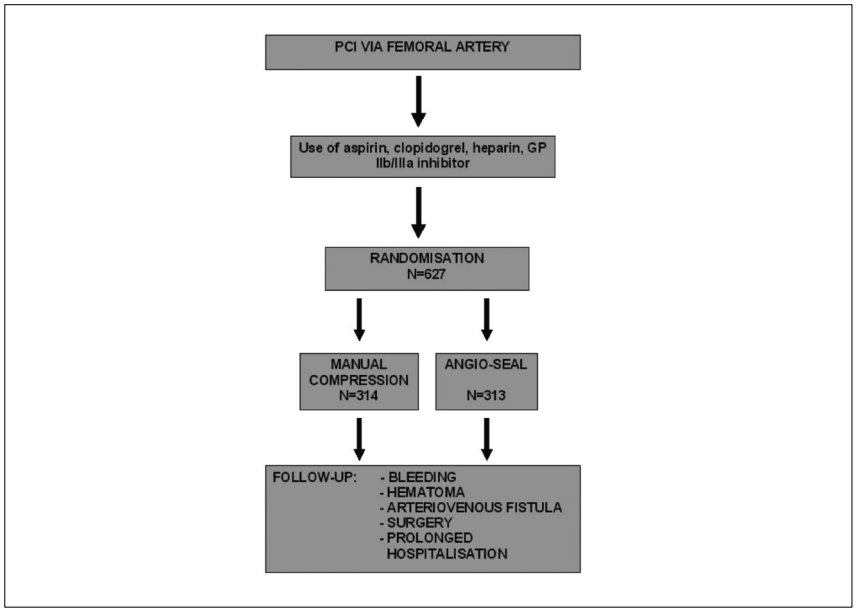

Figure 1: The trial profile

Table 1: Baseline characteristics

Variables	Closure device N=313	Manual compression N=266	P value
Age	64.5 ± 11.3	64.0 ± 11.0	0.635
Age > 75 year	22.0	15.9	0.051
Male gender	76.0	76.1	0.982
Weight (kg)	83.9 ± 14.5	84.9 ± 14.4	0.411
BMI (kg/m2)	27.5	27.6	0.707
BMI (kg/m2) <25	26.5	25.6	0.800
History of			
CABG	19.2	13.4	0.047
PCI	23.1	29.9	0.052
Hypertension	41.3	44.3	0.460
Diabetes	18.2	19.1	0.773
First recorded invasive systolic blood pressure (mmHg)	133 ± 25	134 ± 25	0.376
Systolic blood pressure >140 mmHg	32.4	33.2	0.820
First recorded invasive diastolic blood pressure (mmHg)	72 ± 12	73 ± 12	0.333
Medication			
LMWH before PCI	33.2	30.0	0.390
Unfractionated heparin during PCI	81.4	79.9	0.643

% or mean ± SD. CABG=coronary artery bypass graft. PCI=percutaneous coronary intervention. LMWH=low molecular weight heparin.

Results

Baseline characteristics

Figure 1 shows the trial profile. A total of 627 patients were enrolled in the study between 2006 and 2008, 313 patients were randomly assigned to a closure device and 314 patients to manual compression (no closure device). Baseline characteristics of the patients were comparable between the groups, except for previous CABG which was higher in the closure device group, whereas previous PCI tended to be higher in the manual compression group (table 1).

There were no significant differences in medication use (LMWH, UFH) before or during procedure between both groups. In 3 patients the closure device could not be placed. One patient was randomized to manual compression, but a closure device was placed.

Table 2 shows all clinical outcomes and serious events. There were no significant differences in death, bleeding and transfusion between the both groups. The rate of (retroperitoneal) bleeding was very low in both groups. The combined rate of groin bleeding, hematoma, arteriovenous fistula, surgical intervention, need for transfusion and prolonged hospitalization due to puncture site problems was 2.6% in the closure

Table 2: Procedures and clinical outcome in-hospital

Variables	Closure device N=313	Manual compression N=266	P value
Times			
Procedure time (min)	32.1 ± 15.9	33.5 ± 16.2	0.279
Hb values			
Hb before PCI (g/dL)	14.0 ± 1.5	14.2 ± 1.5	0.257
Hb 24 hours after PCI (g/dL)	13.7 ± 1.6	13.7 ± 1.8	0.697
Hb decrease (g/dL)	0.3 ± 0.8	0.5 ± 0.8	0.186
Death	0	0.3	1.000
Bleeding	2.2	1.9	0.775
Transfusion	0.6	0.6	1.000
Severe hematoma at puncture site	1.6	3.5	0.134
Arteriovenous fistula at puncture site	0.3	0.6	1.000
Surgical intervention at puncture site	0	0.3	1.000
Prolonged hospitalisation for any reason	15.4	15.0	0.884
Primary endpoint	2.6	4.5	0.195

% or mean ± SD. Hb=hemoglobin.

device group compared to 4.5% in the manual compression group (p=0.195). A trend was found towards a lower incidence of severe hematoma at the puncture site in the closure device group compared to the manual compression group (1.6% vs. 3.5%, p=0.134). Duration of hospital admission (secondary end point) and hemoglobin decrease were not significantly different between the groups. The frequency of the primary end point in the 4 pre-defined subgroups age >75 years, female gender, history of hypertension and prolonged procedure time are summarized in figure 2 and table 3. In patients with history of hypertension, the closure device group was associated with a significant larger benefit with regard to the combined primary endpoint. Aggregation of the pre-specified subgroups did not show a significant difference for the primary endpoint between both groups, see table 3.

Discussion

This trial, the largest randomised comparison of a closure device versus manual compression in patients treated with antiplatelet/antithrombotic therapy, including aspirin, clopidogrel, UFH and GPI, shows that a closure device did not reduce the combined primary endpoint significantly. Therefore, the main advantage of a closure device may be patient comfort with shorter bed rest and immobilization. However, in patients with a history of hypertension the combined primary endpoint was significantly reduced and this finding derives further investigation.

Table 3: Subgroup analyses

Variables	Closure device	Manual compression	P value
Age >75 years	**N=69**	**N=50**	
Hb decrease (g/dL)	0.45 ± 1.1	0.61 ± 0.92	0.544
Primary endpoint	4.3	12.0	0.163
Female gender	**N=75**	**N=75**	
Hb decrease (g/dL)	0.42 ± 0.98	0.81 ± 0.87	0.015
Primary endpoint	9.3	8.0	0.772
History of hypertension	**N=129**	**N=139**	
Hb decrease (g/dL)	0.32 ± 0.84	0.53 ± 0.92	0.085
Primary endpoint	0.8	7.2	0.008
*Procedure time longer than median value**	**N=139**	**N=147**	
Hb decrease (g/dL)	0.47 ± 0.89	0.48 ± 0.82	0.978
Primary endpoint	3.6	4.1	0.831

% or mean ± SD

* Procedure time (min) Mean ± SD 32.8 ± 16.1
Median (Q1-Q3) 30 (20-40)
Min-Max 5-108

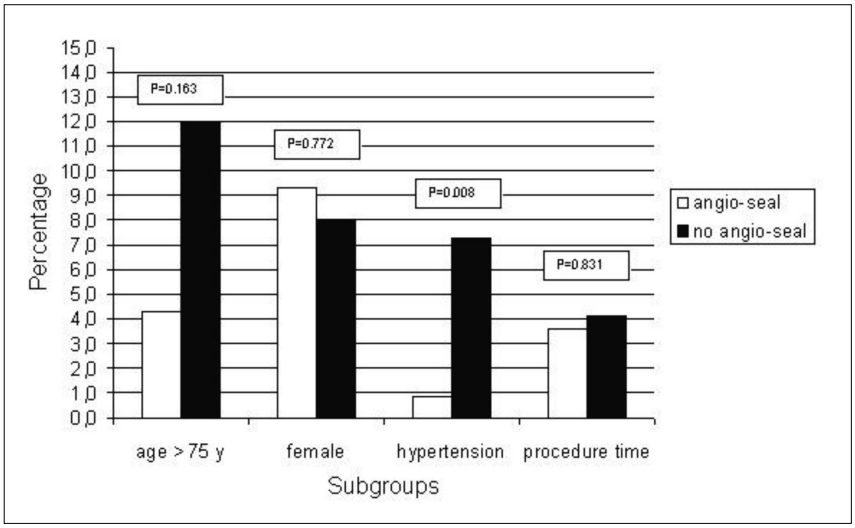

Figure 2: Primary endpoint in the pre-defined subgroups

Previous studies

Exaire et al, showed no difference in bleeding between manual compression and suture-based (Perclose) or collagen-based (Angio-Seal, Vasoseal) closure devices in patients treated with aspirin, clopidogrel and GPI's, who underwent PCI.(13) However, this study was not randomized and the patient groups were not balanced, with a lower risk in the closure device group. Two other large studies revealed also similar risks of access-site related complications between closure devices (Angio-Seal and Perclose) and manual compression in moderate to high risk bleeding patients. (18,19) However, retroperitoneal hemorrhage occurred significantly more often among patients treated with closure devices.(18) A meta-analysis by Nikolsky et al, showed a similar risk of access-site related complications for closure devices (Angio-Seal, Perclose, Vasoseal) compared with manual compression, although in the PCI setting, the Vasoseal device had more complications.(20) Limitations of several studies included in this meta-analysis were evaluation of first generation devices, significant baseline differences in patients characteristics, inclusion of very selected patients and limited operator and institutional experience with device use. Chevalier et al, reported a superior safety and efficacy of an 8 F Angio-Seal device in a population at high bleeding risk compared to manual pressure.(21) This was mainly related to a dramatic decrease of prolonged compression requirement. In our study, all procedures were performed by cardiologists with a lot of experience with Angio-Seal deployment (>500 Angio-Seals per cardiologist) before start of the trial.

Procedures and clinical outcome

Inappropriate location of the femoral artery puncture may influence occurrence of

complications.(22) However, routine fluoroscopy prior to sheath placement, does not reduce complications(23), and is therefore not routinely performed in our hospital. Also because there has been a long debate regarding the merits of femoral artery angiography prior to sheath removal, guidelines are unclear.(24-26)

Little evidence exists regarding the activated clotting time level allowing arterial sheath removal, or the optimal duration of bed rest following sheath removal.(27,28) We removed the sheath immediately after PCI at the cath-lab, partly because of referral facilitation.

Our trial showed lower than anticipated access site complications as compared to an other previous trial.(9) Potential reasons may be smaller guiding catheters (6 F instead of 7 F or 8 F) or weight adjusted heparin bolus (60 U/kg) instead of standard dose.(19) Also, we could have missed complications because duplex sonography to identify arteriovenous fistula or false aneurysms was not routinely performed.

According to the protocol, we analyzed 4 pre-specified subgroups (known risk factors for vascular complications). Our study revealed that patients with a history of hypertension had a significant decrease of the primary endpoint when a closure device was used. Possibly, antihypertensive medication may be protective in preventing access site complications.(29) Also a trend towards benefit for the use of a closure device was found in elderly patients. These observations derive further investigation. Furthermore, the rate of bleeding was higher in females compared to the total population, however, no beneficial effect for the use of a closure device was found in females.

Study strengths and limitations

The study could not be blinded. However, the primary end point was objective (as need for transfusion or need for surgery). Our follow-up period was till discharge and we recorded bleeding for only 24 hours after PCI. We had no data on previous history of bleeding, numbers of prior PCI's, other medication that could have influenced bleeding or renal failure and ACT measurement and blood pressure at the time of sheath removal. We observed only a non-significant difference of the primary endpoint between the two treatment groups. Possibly, with a larger sample size we might have found a significant difference. Efficacy of a closure device in non-selected patients is unknown and should require a much larger trial to assess its efficacy.

Conclusion

This trial did not show the superiority of using a closure device over manual compression in patients, treated with triple antiplatelet therapy, who underwent PCI. The fact that patients with a history of hypertension had a benefit from closure device placement merits further investigation.

References

1. Resnic FS, Blake G, Ohno-Machado L, et al. Vascular closure devices and the risk of vascular complications after percutaneous coronary intervention in patients receiving glycoprotein IIb-IIIa inhibitors. Am J Cardiol 2001;88:493-496.
2. Omoigui N, Califf R, Pieper KS, et al. Peripheral vascular complications in the Coronary Angioplasty Versus Excisional Artherectomy Trial (CAVEAT-I). J Am Coll Cardiol 1995;26:922-930.
3. Oweida SW, Roubin, GS, Smith RB 3rd, Salam AA. Postcatheterization vascular complications associated with percutaneous transluminal coronary angioplasty. J Vasc Surg 1990;12:310-315.
4. McCann Rl, Schwartz LB, Pieper KS. Vascular complications of cardiac catheterization. J Vasc Surg 1991;14:375-381.
5. Muller DW, Shamir KJ, Ellis SG, Topol EJ. Peripheral vascular complications after conventional and complex percutaneous coronary interventional procedures. Am J Cardiol 1992;69:63-68.
6. Lenderink T, Boersma E, Ruzyllo W, et al: GUSTO IV-ACS investigators. Bleeding events with abciximab in acute coronary syndromes without early revascularization: An analysis of GUSTO IV-ACS. Am Heart J 2004;147:865-873.
7. Ellis SG, Elliot J, Horrigan M, et al. Low-normal or excessive body mass index: newly identified and powerful risk factors for death and other complications with percutaneous coronary intervention. Am J Cardiol 1996;78:642-646.
8. Waksman R, King SB, Douglas JS, et al. Predictors of groin complications after balloon and new-device coronary intervention. Am J Cardiol 1995;75:886-889.
9. Dangas G, Mehran R, Kokolis S, et al. Vascular complications after percutaneous coronary interventions following hemostasis with manual compression versus arteriotomy closure devices. J Am Coll Cardiol 2001;38:638-641.
10. Juergens CP, Leung DY, Crozier JA, et al. Patient tolerance and resource utilization associated with an arterial closure versus an external compression device after percutaneous coronary intervention. Catheter Cardiovasc Interv 2004;63:166-170.
11. Koreny M, Riedmuller E, Nikfardjam M, et al. Arterial puncture closing devices compared with standard manual compression after cardiac catheterization. JAMA 2004;291:350-357.
12. Vaitkus PT. A meta-analysis of percutaneous vascular closure devices after diagnostic catheterization and percutaneous coronary intervention. J Invasive Cardiol 2004;16:243-246.
13. Exaire JE, Dauermann HL, Topol EJ, et al, for the TARGET investigators. Triple antiplatelet therapy does not increase femoral access bleeding with vascular closure devices. Am Heart J 2004;147:31-34.
14. Boccalandro F, Assali A, Fujise K, et al. Vascular access site complications with the use of closure devices in patients treated with platelet glycoprotein IIb/IIIa inhibitors during rescue angioplasty. Catheter Cardiovasc Interv 2004;63:284-289.
15. Rapaport S, Sniderman KW, Morse SS, et al. Pseudoaneurysm: a complication of faulty technique in femoral arterial puncture. Radiology 1985;154:529-530.
16. Silber S, Albertsson P, Avilés FF, et al. ESC guidelines for percutaneous coronary interventions. The task force for percutaneous coronary interventions of the European Society of Cardiology. Eur Heart J 2005;26:804-847.
17. Hermanides RS, Ottervanger JP, Dambrink JH, et al. Incidence, predictors and prognostic importance of bleeding after primary PCI for ST-elevation myocardial infarction. EuroIntervention 2010;6:106-111.
18. Cura FA, Kapadia SR, L'Allier PL, et al. Safety of femoral closure devices after percutaneous coronary interventions in the era of glycoprotein IIb/IIIa platelet blockade. Am J Cardiol 2000;86:780-782.
19. Applegate RJ, Grabarczyk MA, Little WC, et al. Vascular closure devices in patients treated with anticoagulation and IIb/IIIa receptor inhibitors during percutaneous revascularization. J Am Coll Cardiol 2002;40:78-83.
20. Nikolsky E, Mehran E, Halkin A, et al. Vascular complications associated with arteriotomy closure devices in patients undergoing percutaneous coronary procedures; A Meta-Analysis. J Am Coll Cardiol 2004;44:1200-1209.
21. Chevalier B, Lancelin B, Koning R, et al; HEMOSTASE trial investigators. Effect of a closure device on complication rates in high local risk patients: results of a randomized multicenter trial. Catheter Cardiovasc Interv 2003;58:285-291.
22. Sherev DA, Shaw RE, Brent BN. Angiographic predictors of femoral access site complications: implication for planned percutaneous coronary intervention. Catheter Cardiovasc Interv 2005;65:196-202.
23. Jacobi JA, Schussler JM, Johnson KB. Routine femoral head fluoroscopy to reduce complications in coronary catheterization. Proc (Bayl Univ Med Cent) 2009;22:7-8.
24. Turi ZG. It's time to seal every artery but…comparing apples and oranges in the vascular sealing literature. Catheter Cardiovasc Interv 2001;53:443-444.
25. Eggebrecht H, Erbel R. Recommendations for future trials in the field of access site closure: focusing on clinically significant endpoints. Catheter Cardiovasc Interv 2002;55:525-526.
26. Turi ZG. Ooze you lose: II, are we really getting better all the time? Catheter Cardiovasc Interv 2002;57:484-485.
27. Niederstadt JA. Frequency and timing of activated clotting time levels for sheath removal. J Nurs Care Qual 2004;19:34-38.
28. Narins CR, Zareba W, Rocco V, McNitt S. A prospective, randomized trial of topical hemostasis patch use following percutaneous coronary and peripheral intervention. J Invasive Cardiol 2008;20:579-584.
29. Dumont CJ. Blood pressure and risks of vascular complications after percutaneous coronary intervention. Dimens Crit Care Nurs 2007;26:121-127.

Part 2

Sub-optimal procedural results

9

High-dose tirofiban reduces the need for bail-out study medication in patients with ST-segment elevation myocardial infarction: results of a subgroup analysis of the On-TIME 2 trial

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R.S. Hermanides, A.A. Heestermans, J.M. ten Berg, A.T. Gosselink, J.P. Ottervanger, K.G. van Houwelingen, J.J. Kolkman, P.R. Stella, T. Dill, C. Hamm, A.W. van 't Hof, on behalf of the On-TIME 2 investigators

Abstract

Objective: We investigated the outcome of patients who received bail-out study medication and evaluated whether high dose tirofiban (HDT) pre-treatment may reduce the need for bail-out study medication.

Design: This is a pre-specified analysis of the multicentre, double-blind, placebo-controlled, randomised On-TIME 2 trial. Bail-out use of study medication was pre-defined and part of the combined clinical endpoint.

Setting: Multiple coronary intervention hospitals in different countries.
Patients: 984 patients were randomised to HDT or placebo. In the subgroup of patients who received blinded bail-out treatment, we compared patients who were pre-treated with placebo and received bail-out high dose tirofiban (HDT bail-out) to those who were pre-treated with HDT and received bail-out placebo (Placebo bail-out).

Interventions: Routine pre-hospital initiation of HDT versus bail-out use of HDT.

Main outcome measures: Electrocardiographic- and clinical outcome.

Results: Blinded bail-out use of study medication was used in 24% (237/980) of patients, with a higher rate in patients pre-treated with placebo: 29% (140/492) versus 20% (97/488), p=0.002. Bail-out versus no bail-out use of study medication was associated with more residual ST deviation (5.5±7.2 vs 3.7±4.8mm, p=0.005), and worse clinical outcome (MACE 30 days 12.2% vs 5.6%, p<0.001), mainly due to poor outcome in the patients who received HDT bail-out. In patients who were pre-treated with HDT but received placebo bail-out study medication, residual ST deviation and clinical outcome did not differ significantly compared to patients who did not receive bail-out medication (4.0±4.6 vs.3.7± 4.8mm, p=0.703, MACE 7.2% vs 5.6%, p=0.535).

Conclusions: Routine pre-hospital treatment with HDT significantly reduced the use of blinded bail-out study medication. The need for bail-out therapy was associated with a less favorable outcome, mainly due to poor outcome in patients pre-treated with placebo. This analysis suggests that routine pre-treatment is superior to provisional use of high dose tirofiban in patients with STEMI.

Introduction

Primary percutaneous coronary intervention (PCI) in patients evolving ST-segment elevation myocardial infarction (STEMI) decreases infarct size and the rates of recurrent ischemia, re-infarction and stroke and improves survival, as compared with fibrinolytic therapy.(1,2) Since atherothrombosis plays a crucial role in the pathogenesis of STEMI(3), antithrombotic and antiplatelet drugs are an essential complement to primary PCI.(4) However, despite successful progression in mechanical reperfusion(5) and pharmacological improvements,[6-8] suboptimal reperfusion or pharmacological resistance(9) may occur, resulting in unfavourable outcome.(10,11) Current guidelines recommend the use of glycoprotein IIb/IIIa inhibitors (GPI's) in addition to aspirin and clopidogrel in patients with STEMI undergoing primary PCI.(12,13)These guidelines are based on studies who all evaluated the efficacy of GPI's when given routinely before PCI.(14,15) However, because of cost restraints, the use of GPI is often restricted to bail-out situations. No study has evaluated GPI versus placebo in this setting. The On-TIME 2 trial compared routine pre-hospital initiation of high dose tirofiban (HDT) to provisional use of HDT in a randomised placebo controlled design. Bail-out use of study medication was pre-defined and part of the combined clinical end-point. Using this unique design, we performed a subgroup analysis and compared patients who were routinely pre-treated with tirofiban and received placebo bail-out to those who received tirofiban bail-out after pre-treatment with placebo.

Methods

Study design and patients

This is a pre-specified analysis of the multicentre, double-blind, placebo-controlled, randomised On-TIME 2 trial (N=984). The rationale, design and primary results of the On-TIME 2 trial have been described previously.(15,16) The On-TIME 2 trial compared routine pre-hospital initiation of high dose tirofiban (HDT) to provisional use of HDT in a randomised placebo controlled design. Bail-out use of study medication was pre-defined and part of the combined clinical end-point. Within the group of patients who received blinded bail-out treatment, we compared the patients pre-treated with placebo who received bail-out tirofiban (HDT bail-out) to those who were pre-treated with HDT and received bail-out placebo (Placebo bail-out).

Procedures

Patients were randomly assigned to pre-hospital treatment with tirofiban (25 μg/kg bolus and 0.15 μg/kg/min maintenance infusion for 18 h) or placebo (bolus plus infusion) by blinded sealed kits with study drug. In the ambulance or referring

centre, all patients also received a bolus of 5000 IU of unfractionated heparin (UFH) intravenously together with aspirin 500 mg intravenously and a 600 mg loading dose of clopidogrel orally. Before PCI, additional UFH (2500 IU) was only given if the activated clotting time was less than 200 seconds. Coronary angiography and PCI were done according to each institution's guidelines and standards.

Bail-out protocol

Before, during, or after PCI, bail-out study medication could be given for the following pre-defined indications: decrease in thrombolysis in myocardial infarction (TIMI) flow grade (TIMI flow grades of 0–2 or slow reflow), dissection with decreased flow, distal embolisation, side-branch closure, abrupt closure of the culprit vessel, clinical instability and prolonged ischemia. HDT bail-out was also given as the high-bolus dose (25 μg/kg bolus). We included blinded bail-out bolus vials in the medication kit to maintain blinding of the initial treatment assignment and to match with the content of the primary infusion. When bail-out treatment was required, the bail-out kit boluses were administered and the study drug infusion was replaced by open-label HDT maintenance infusion up to 12-24 hours. Detailed information regarding the timing and rationale for bail-out was collected on the case report forms.

Measurements (end points, definitions)

The primary efficacy endpoint was the extent of residual ST-segment deviation at 1 h after PCI, as described previously.(17,18) The key secondary endpoint was the composite of major adverse cardiac events (MACE, defined as the combined incidence of death, recurrent myocardial infarction or urgent target vessel revascularisation) at 30 days.

A blinded, independent clinical endpoint committee adjudicated all clinical endpoints except for death. Follow-up information was derived from outpatient clinic visits or via contact by telephone at 30 days and 1 year.

Statistical Analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 16.0.1. All analyses were done according to the intention-to-treat principle. All p values were two-sided. For all analyses, statistical significance was assumed when the two tailed probability value was < 0.05. Continuous data were expressed as mean ± standard deviation or as median with 25th and 75th percentiles and categorical data as percentage, unless otherwise denoted. Differences between continuous data were performed by Kruskal Wallis test or student's t test and the chi-square or Fisher's exact test was used as appropriate for dichotomous data. Multivariate Cox proportional-hazards regression analyses were performed to determine the independent association of

HDT bail-out and 30-day MACE, selecting baseline variables with entry/stay criteria of p<0.10. Variables entered into the model included age, gender, hypertension, smoking, previous myocardial infarction, previous PCI, previous CVA, TIMI risk score > 3, Killip class > 1, HDT bail-out use and placebo bail-out use. Time-to-event outcomes, determined with Kaplan-Meier methods, were compared by means of the log-rank test.

Results

The main results of the On-TIME 2 trial showed that early, pre-hospital initiation of HDT improved ST resolution both before and after PCI in 984 patients planned to undergo primary PCI.(15) Ninety-six percent of patients were included and randomised in the ambulance at a median time of 76 minutes after the onset of symptoms [interquartile range (IQR) 35 – 150]. Importantly, no significant increase in the rate of major bleeding was found.

Four patients died before or during angiography and no data on the use of bail-out medication was available (figure 1). These patients were excluded from the current analysis.

Blinded bail-out use of study medication was used in 24.2% of patients, with a significant higher use in patients pre-treated with placebo 29% (HDT bail-out) vs 20% (placebo bail-out), p=0.002).

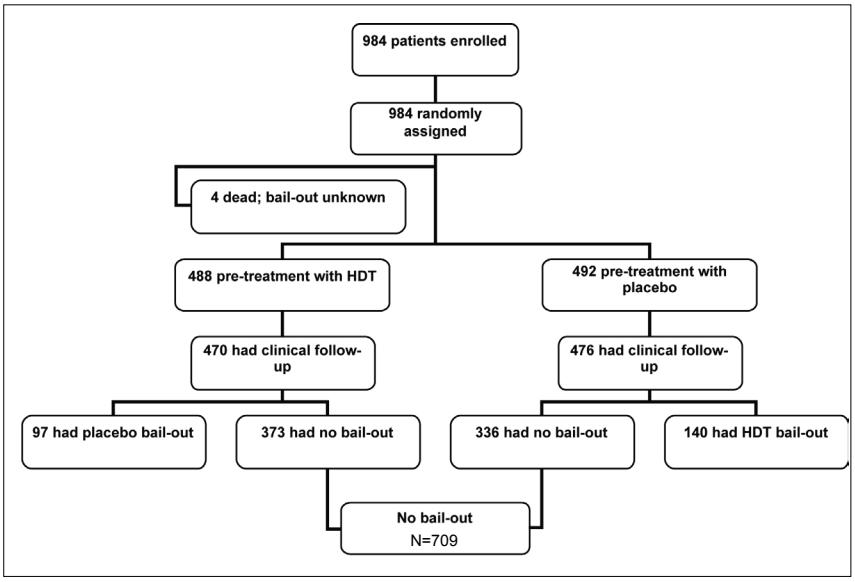


Figure 1: Sub-analysis profile

Comparison of Bail-out versus no Bail-out use of study medication

Baseline characteristics between patients with and without bail-out study medication are summarized in table 1. Bail-out patients had a higher rate of family history of coronary artery disease (p=0.002) and a significantly lower heart rate (p=0.023) and systolic- and diastolic blood pressure (both p=0.001) on admission.

Table 1: Baseline characteristics

Characteristics	No bail-out N=743	Bail-out N=237	P value	HDT bail-out N=140	Placebo bail-out N=97	P value
Age	61.8 ± 12.0	61.7 ± 11.8	0.891	62.5 ± 11.7	60.6 ± 12.0	0.271
Female gender	23.4	26.2	0.390	22.9	30.9	0.165
BMI	26.8 ± 3.7	26.8 ± 3.8	0.920	26.6 ± 4.0	27.0 ± 3.4	0.634
Hypertension	35.0	31.6	0.344	32.1	30.9	0.843
Smoking	47.4	46.0	0.702	47.9	43.3	0.489
Hypercholesterolaemia	26.2	28.7	0.447	27.9	29.9	0.733
Family history	36.2	47.3	0.002	48.6	45.4	0.626
Previous MI	8.4	8.4	0.977	5.7	12.4	0.070
Previous PCI	8.9	8.4	0.833	7.1	10.3	0.389
Previous CABG	1.6	2.1	0.575	2.1	2.1	1.000
Previous CVA	1.5	2.5	0.266	3.6	1.0	0.405
Renal insufficiency	15.4	13.5%	0.499	16.3	9.6	0.144
Anemia	15.1	12.6%	0.351	11.8	13.8	0.643
Systolic BP (mmHg)	133 ± 24	127 ± 24	0.001	125 ± 25	128 ± 23	0.495
Diastolic BP (mmHg)	78 ± 15	74 ± 16	0.001	73 ± 16	76 ± 14	0.131
Heart rate (beats/min)	76 ± 16	74 ± 21	0.023	75 ± 23	73 ± 18	0.559
ACT (sec)	179 ± 63	185 ± 64	0.487	189 ± 64	181 ± 65	0.271
Ischemic time (min)	244 ± 305	239 ± 239	0.319	257 ± 268	214 ± 188	0.204
Time SO to diagnosis	143 ± 216	139 ± 200	0.158	142 ± 208	134 ± 187	0.972
Killip > 1	11.2	15.8	0.064	19.6	10.4	0.059
Three vessel	16.5	20.3	0.189	20.0	20.6	0.907
Anterior infarct	43.3	38.9	0.258	38.9	38.8	0.987
Angio performed	98.5	100	0.075	100	100	
RCA	45.6	46.6	0.790	47.9	44.8	0.643
LAD	41.1	42.8	0.656	41.4	44.8	0.608
CX	12.2	9.3	0.229	9.3	9.4	0.982
LM	0.4	0	0.572	0	0	
Graft	0.6	1.3	0.385	1.4	1.0	1.000

Data are n/N (%) or mean (SD), or median (IQR). BMI=body mass index. MI=myocardial infarction.
PCI=percutaneous coronary intervention.
CABG=coronary artery bypass grafting. BP=blood pressure. ACT=activated clotting time. SO=symptom onset.
IRV=infarct related vessel.
LAD=left anterior descending artery. RCX=ramus circumflex artery. RCA=right coronary artery.
Anemia=defined using World Health Organization criteria (hemoglobin <13 g/dl (<8mmol/L) in men and <12 g/dl (<7.5mmol/L) in women.
Renal insufficiency=GFR (glomerular filtration rate) <60 ml/min (according to MDRD).

Table 2 shows angiographic-, electrocardiographic- and clinical outcomes. Bail-out patients had a lower rate of TIMI 3 flow pre-PCI (p=0.001), myocardial blush grade (MBG) 3 post-PCI (p=0.002) and TIMI 3 flow post-PCI (p<0.001) compared to no bail-out patients. Residual ST deviation 1 hour after PCI, was significantly higher in bail-out patients (p=0.003), despite a higher use of rescue thrombus aspiration. Bail-out use of study medication was associated with worse clinical outcome (MACE 30 days 12.2% vs 5.6%, p<0.001) and a significant higher rate of net adverse clinical events (NACE 30 days, 14.8% vs 6.5%, p<0.001) as compared to no bail-out treatment.

Table 2: Angiographic-, electrocardiographic- and clinical outcomes

Characteristics	No bail-out N=743	Bail-out N=237	P value	HDT bail-out N=140	Placebo bail-out N=97	P value
Angiographic outcome						
TIMI 3 flow pre-CAG	155/664 (23.3)	30/234 (12.8)	0.001	19/140 (13.6)	11/94 (11.7)	0.675
MBG 3 post-PCI	283/596 (47.5)	70/208 (33.7)	0.001	44/125 (35.2)	26/83 (31.3)	0.563
TIMI flow 3 post-PCI	603/635 (95.0)	177/219 (80.8)	<0.001	113/134 (84.3)	64/85 (75.3)	0.098
PCI performed	639/743 (86.0)	221/237 (93.2)	0.003	135/140 (96.4)	86/97 (88.7)	0.019
PCI immediately after CAG	635/639 (99.4)	219/221 (99.1)	0.650	134/135 (99.3)	85/86 (98.8)	1.000
Rescue thrombus aspiration	64/732 (8.7)	69/237 (29.1)	<0.001	42/140 (30.0)	27/97 (27.8)	0.718
IABP	25/732 (3.4)	20/237 (8.4)	0.001	14/140 (10.0)	6/97 (6.2)	0.299
Electrocardiographic outcome						
ST resolution 1 h after PCI			0.081			0.337
Complete	419/652 (64.3)	131/224(58.5)		73/133 (54.9)	58/91 (63.7)	
Partial	152/652 (23.3)	52/224(23.2)		32/133 (24.1)	20/91 (22.0)	
No	81/652 (12.4)	41/224(18.3)		28/133 (21.1)	13/91 (14.3)	
Residual ST deviation > 3mm 1 h after angiography/PCI	269/678 (39.7)	108/228(47.2)	0.041	68/134 (50.7)	40/94 (42.6)	0.223
Residual ST deviation 1 h after PCI			0.003			0.109
Normalised ST segment	222/678 (32.7)	70/228 (30.7)		37/134 (27.6)	33/94 (35.1)	
1-3 mm	187/678 (27.6)	50/228 (21.9)		29/134 (21.6)	21/94 (22.3)	
4-6 mm	139/678 (20.5)	38/228 (16.7)		21/134 (15.7)	17/94 (18.1)	
>6 mm	130/678 (19.2)	70/228 (30.7)		47/134 (35.1)	23/94 (24.5)	
Residual ST deviation 1 h after PCI	3.7±4.8	5.5 ± 7.2	0.005	6.6 ± 8.4	4.0 ± 4.6	0.031
30 day Outcome (N=946)						
Death	17/709 (2.4)	10/237 (4.2)	0.145	7/140 (5.0)	3/97 (3.1)	0.533
Recurrent MI	16/709 (2.3)	11/237 (4.6)	0.056	9/140 (6.4)	2/97 (2.1)	0.207
Urgent TVR	19/709 (2.7)	19/237 (8.0)	<0.001	17/140 (12.1)	2/97 (2.1)	0.005
Death or recurrent MI	33/709 (4.7)	19/237 (8.0)	0.049	14/140 (10.0)	5/97 (5.2)	0.177
MACE	40/709 (5.6)	29/237 (12.2)	<0.001	22/140 (15.7)	7/97 (7.2)	0.050
30 day Safety (N=946)						
Major or minor bleeding	61/709 (8.6)	22/237 (9.3)	0.613	15/140 (10.7)	7/97 (7.2)	0.362
Major bleeding	22/709 (3.1)	11/237 (4.6)	0.502	7/140 (5.0)	4/97 (4.1)	1.000
Non CABG-related major bleeding	9/709 (1.3)	7/237 (3.0)	0.140	4/140 (2.9)	3/97 (3.1)	1.000
Stroke	5/709 (0.7)	3/237 (1.3)	0.421	3/140 (2.1)	0/97	0.272
NACE	46/709 (6.5)	35/237 (14.8)	< 0.001	26/140 (18.6)	9/97 (9.3)	0.047
1 year Outcome (N=933)						
Death	25/707 (3.5)	13/226 (5.8)	0.142	9/133 (6.8)	4/93 (4.3)	0.289
Recurrent MI	21/707 (3.0)	10/226 (4.4)	0.288	8/133 (6.0)	2/93 (2.2)	0.203
Death or recurrent MI	46/707 (6.5)	20/226 (8.8)	0.232	14/133 (10.5)	6/93 (6.5)	0.289

Data are n/N (%) or mean (SD). TIMI=thrombolysis in myocardial infarction. MBG=myocardial blush grade. PCI=percutaneous coronary intervention. IABP=intra aortic balloon pump. Ck=creatine kinase. LVEF=left ventricular ejection fraction. MI=myocardial infarction. TVR=target vessel revascularisation. MACE=major adverse cardiac event (death, recurrent infarction, urgent TVR). NACE=Net adverse clinical events=the combined incidence of death, recurrent MI, urgent TVR, stroke, or non CABG-related major bleeding.

Comparison of HDT Bail-out versus Placebo Bail-out

The indication for bail-out use of study medication was mostly distal embolisation or no-reflow after PCI and did not differ between the groups except for abrupt closure of the culprit vessel which occurred significantly more often in the HDT bail-out compared to placebo bail-out (7.9% vs 1.0%, p=0.031, table 3). However, even after the exclusion of (sub) acute closure of the infarct related vessel requiring urgent repeat PCI, MACE and NACE at 30 days was still highest in the HDT bail-out group (10.1% vs 6.3%, p=0.307 and 13.2% vs 8.3%, p=0.508).

Table 3: Indications for bail-out according to the operator

Characteristics*	HDT bail-out N=140	Placebo bail-out N=97	P value
Dissection with decreased flow	6/140 (4.3)	5/97 (5.2)	0.763
Distal embolism	58/140 (41.4)	44/97 (45.4)	0.548
Side branch closure	4/140 (2.9)	3/97 (3.1)	1.000
Abrupt closure of culprit vessel	11/140 (7.9)	1/97 (1.0)	0.031
Clinical instability	15/140 (10.7)	13/97 (13.4)	0.528
Prolonged ischemia	4/140 (2.9)	4/97 (4.1)	0.719
TIMI flow grade 0-2 or slow reflow	45/140 (32.1)	29/97 (29.9)	0.714

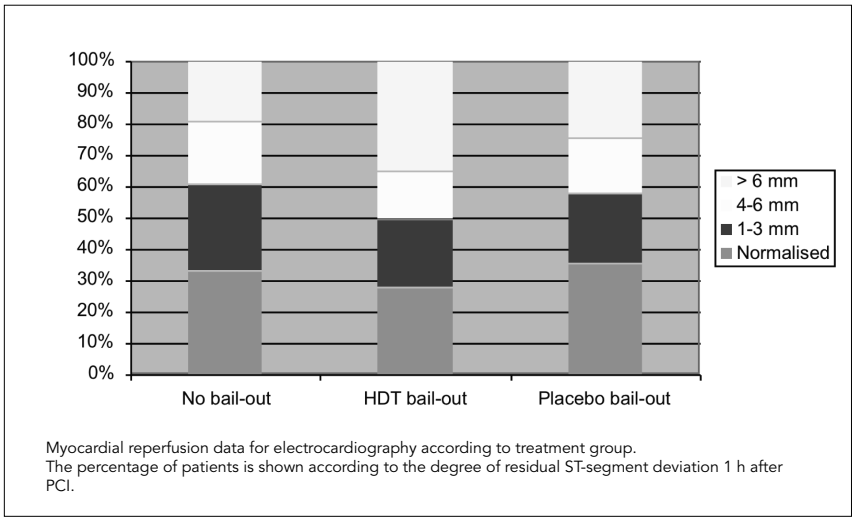
* As reported by the (blinded) operator. Data are n/N (%) or mean (SD). TIMI=thrombolysis in myocardial infarction

The median time from angiography to blinded bail-out use did not differ between both groups (33 [20 – 52] vs 30 [15 – 50], p=0.420).

The primary endpoint, residual ST deviation 1 hour after PCI, was significantly higher in the HDT bail-out group compared to the placebo bail-out group (6.6 ± 8.4 vs 4.0 ± 4.6mm, p=0.031, table 2, figure 2). HDT bail-out patients had a significantly worse clinical outcome (MACE 15.7% vs 7.2%, p=0.049) as compared to placebo bail-out patients (figure 3, Kaplan Meier). After multivariate analysis, only HDT bail-out use remained an independent determinant of 30 day MACE (HR 2.5, 95% CI 1.4 – 4.3). Cardiac death at 1 year (figure 4) was significantly higher and overall bleeding rate was highest in HDT bail out patients.

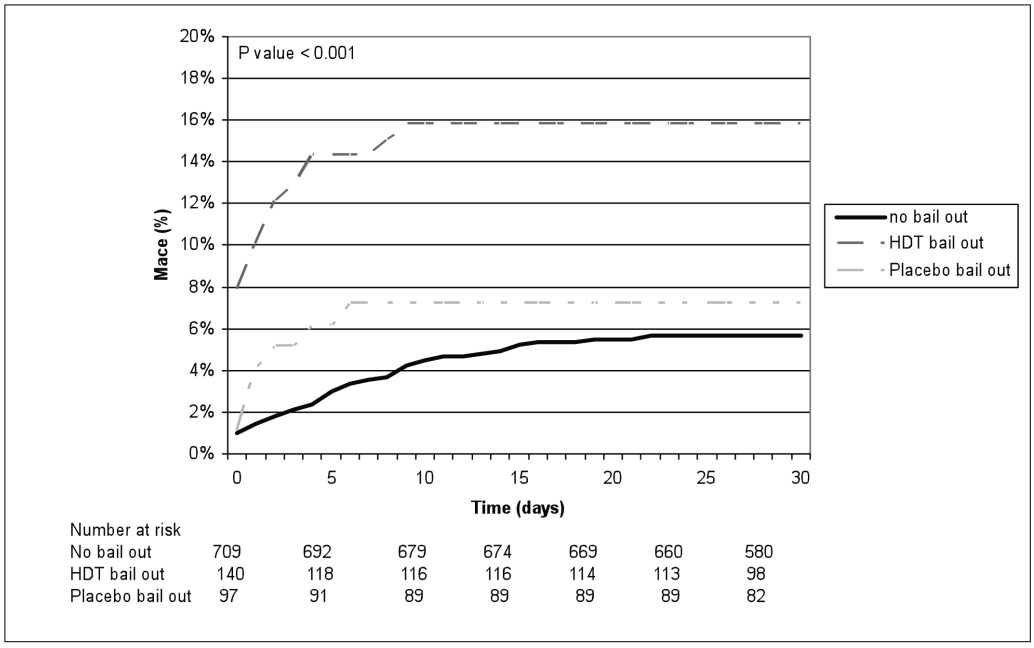
Despite a low rate of final TIMI 3 flow (75.3%) and a high use of rescue thrombus aspiration in the placebo bail-out group, residual ST deviation and clinical outcome in the bail-out group, who were routinely pre-treated with HDT, was not different as compared to patients who did not receive bail-out medication (4.0 ± 4.6 vs.3.7 ± 4.8mm, p=0.703, MACE 7.2% vs 5.6%, p=0.535, table 3).

Figure 2: Primary endpoint for no bail-out vs HDT bail-out and Placebo bail-out



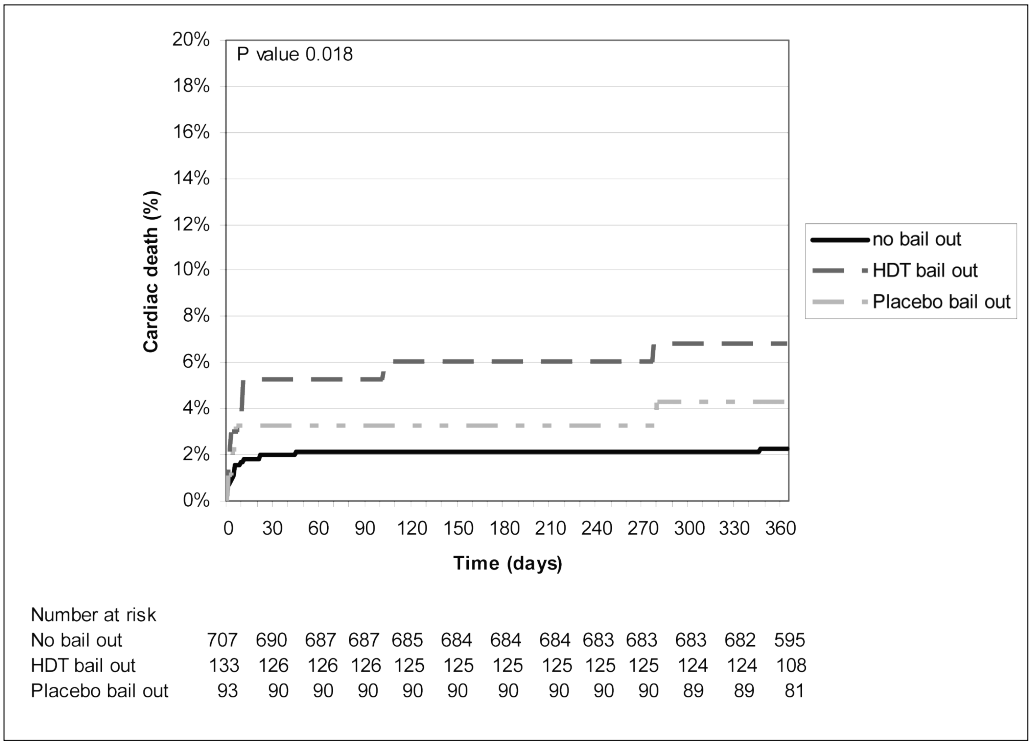
Myocardial reperfusion data for electrocardiography according to treatment group.
The percentage of patients is shown according to the degree of residual ST-segment deviation 1 h after PCI.

Figure 3: Time to event curves (Kaplan-Meier) for 30-day MACE in the 3 groups



Number at risk							
No bail out	709	692	679	674	669	660	580
HDT bail out	140	118	116	116	114	113	98
Placebo bail out	97	91	89	89	89	89	82

Figure 4: Time to event curves (Kaplan-Meier) for 1-year cardiac death in the 3 groups



Number at risk													
No bail out	707	690	687	687	685	684	684	684	683	683	683	682	595
HDT bail out	133	126	126	126	125	125	125	125	125	125	124	124	108
Placebo bail out	93	90	90	90	90	90	90	90	90	90	89	89	81

Discussion

The On-TIME 2 trial showed that routine pre-hospital treatment with high dose tirofiban significantly reduced the incidence of complications requiring the use of blinded bail-out study medication, particularly abrupt closure of the culprit vessel. This analysis shows that patients who were routinely pre-treated with HDT and received placebo bail-out, had quite favorable final ST resolution and clinical outcome despite a low rate of final TIMI 3 flow (75.3%) and a high rate of no-reflow or distal embolisation. A possible explanation of this finding is that, in contrast to epicardial flow, myocardial flow as represented by residual ST deviation 1 hr after PCI, was significantly lower in the placebo bail-out group compared to the HDT bail-out group. This might be related to the higher platelet aggregation inhibition in patients pre-treated with HDT which might be associated with improved myocardial reperfusion, despite epicardial slow or no-reflow.

In the group of patients who were routinely pre-treated with placebo, the use of bail-out study medication (HDT bail-out) was associated with poor outcome: a high rate of MACE, cardiac death and bleeding. This again emphasizes that routine pre-treatment is preferred over provisional use of high dose tirofiban in patients with STEMI.

Routine GPI

Insufficient inhibition of platelet aggregation at the time of PCI correlates with increased likelihood of major cardiovascular adverse events after PCI procedure.(9) The most effective timing of administration of antiplatelet and antithrombotic regimens in STEMI patients is a matter of debate.(15,19)

Although several randomised trials have demonstrated the efficacy of GPI's in the setting of primary PCI for STEMI, large registries have shown that in many countries the use of GPI in this setting is sometimes restricted to patients who develop complications during the procedure (bail-out situation).(20,21)

This strategy is probably driven by attempts to minimize the costs and risk of bleeding associated with these agents. Outcomes after provisional administration of GPI's for complicated or sub-optimal procedural results after primary PCI have not been well characterized. A trial which would randomise patients to GPI or placebo in bail-out situations is difficult to perform.

Subgroup analysis of studies on the use of GPI in primary PCI are therefore important. A previous analysis from the CADILLAC trial already showed that the outcome after complicated or sub-optimal primary PCI is poor despite bail-out GPI use.(22) However, bail-out study medication was not randomized in this trial. The unique double-blind design of the On-TIME 2 study provides an exclusive opportunity to evaluate the outcomes of patients requiring bail-out, both with and without HDT pre-treatment.

Our data confirm a sub-analysis of the ESPRIT trail which revealed a poor clinical outcome in patients requiring bail-out (eptifibatide) after pre-treatment with placebo.(23) These study results, which all report poor outcome and high rate of bleeding despite bail-out use of GPI's highly question whether this provisional use is effective at all. Only a trial in which patients are randomised to GPI or placebo in case of a bail-out situation can answer this question, but it is unlikely that such a study will be performed.

Timing of GPI administration

The On-Time 2 trial was performed in the pre-hospital setting and showed benefit of early versus provisional GPI administration.(15) The FINESSE trial showed no clinical benefit of early (pre-hospital) versus late (cath-lab) administration of GPI(24), however in both arms all patients routinely received GPI. Because of the different trial designs a comparison of these results is not possible.

Previous research as well as the results from On-TIME 2 trial show that GPI's should routinely be given to all STEMI patients prior to primary PCI. However, whether early administration of GPI as compared to late administration results in clinical benefit remains to be evaluated.

Limitations

This is a sub-analysis of the On-TIME 2 trial. Although the indication for using bail-out study medication was pre-defined, the decision to use bail-out therapy in this trial was left to the discretion of the treating cardiologist.

Conclusion

Routine pre-hospital treatment with high dose tirofiban significantly reduced the use of blinded bail-out study medication. The need for bail-out therapy was associated with a less favorable outcome, mainly due to poor outcome in patients pre-treated with placebo. This analysis suggests that routine pre-treatment is superior to provisional use of high dose tirofiban in patients with STEMI.

References

1. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet 2003;361:13-20.
2. Schömig A, Neumann FJ, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. N Engl J Med 1996;334:1084-1089.
3. Libby P. Current concepts of the pathogenesis of the acute coronary syndromes. Circulation 2001;104:365-372.
4. Steinhubl SR, Berger PB, Mann JT III, et al. CREDO investigators. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA 2002;288:2411-2420.
5. Svilaas T, Vlaar PJ, van der Horst IC, et al. Thrombus aspiration during primary percutaneous coronary intervention. New Engl J Med 2008;358:557-567.
6. Montalescot G, Wiviot SD, Braunwald E, et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. Lancet 2009;373:723-731.
7. Stone GW, Witzenbichler B, Guagliumi G, et al; HORIZONS-AMI trial investigators. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med 2008;358:2218-2230.
8. Montalescot G, Antoniucci D, Kastrati A, et al. Abciximab in primary coronary stenting of ST-elevation myocardial infarction: a European meta-analysis on individual patient's data with long-term follow-up. Eur Heart J 2007;28:443-449.
9. Matetzky S, Shenkman B, Guetta V, et al. Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction. Circulation 2004;109:3171-3175.
10. De Luca G, van 't Hof AW, Ottervanger JP, et al. Unsuccessful reperfusion in patients with ST-segment elevation myocardial infarction treated by primary angioplasty. Am Heart J 2005;150:557-562.
11. De Luca G, Ernst N, van 't Hof AW, et al. Predictors and clinical implications of early reinfarction after primary angioplasty for ST-segment elevation myocardial infarction. Am Heart J 2006;151:1256-1259.
12. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). Circulation 2004;110:588-636.
13. Antman EM, Hand M, Armstrong PW, et al. 2007 Focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: A report of the ACC/AHA Task Force on Practice Guidelines. J Am Coll Cardiol 2008;58:210-247.
14. De Luca G, Gibson CM, Bellandi F, et al. Early glycoprotein IIb/IIIa inhibitors in primary angioplasty (EGYPT) cooperation: an individual patient data meta-analysis. Heart 2008;94:1548-1558.
15. Van 't Hof AW, ten Berg JM, Heestermans AA, et al. Ongoing Tirofiban In Myocardial infarction Evaluation (On-TIME) 2 study group. Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial. Lancet 2008;372:537-546.
16. van 't Hof AW, Hamm C, Rasoul S, et al, on behalf of the On-TIME 2 investigators. Ongoing tirofiban in myocardial infarction evaluation (On-TIME) 2 trial: rationale and study design. EuroInterv 2007;3:371-380.
17. De Luca G, Maas AC, Suryapranata H, et al. Prognostic significance of residual cumulative ST-segment deviation after mechanical reperfusion in patients with ST-segment elevation myocardial infarction. Am Heart J 2005;150:1248-1254.
18. van 't Hof AW, Liem AL, de Boer MJ, et al, on behalf of the Zwolle Myocardial Infarction Study Group. Clinical value of 12-lead electrocardiogram after successful reperfusion therapy for acute myocardial infarction. Lancet 1997;350:615-619.
19. Sejersten M, Loumann Nielsen S, Engstrom T, et al. Feasibility and safety of prehospital administration of bivalirudin in patients with ST-elevation myocardial infarction. Am J Cardiol 2009;103:1635-1640.
20. Budaj A, Brieger D, Steg PG, et al. GRACE investigators. Global patterns of use of antithrombotic and antiplatelet therapies in patients with acute coronary syndromes: insights from the Global Registry of Acute Coronary Events (GRACE). Am Heart J 2003;146:999-1006.
21. Mandelzweig L, Battler A, Boyko V, et al; Euro Heart Survey Investigators. The second Euro Heart Survey on acute coronary syndromes: characteristics, treatment, and outcome of patients with ACS in Europe and the Mediterranean Basin in 2004. Eur Heart J 2006;27:2285-2293.
22. Ashby DT, Aymong EA, Tcheng JE, et al. Outcomes following bail-out abciximab administration during primary intervention in acute myocardial infarction (The CADILLAC Trial). Am J Cardiol 2003;92:1091-1094.
23. Cantor WJ, Madan M, O'Shea JC, et al. Bailout use of platelet glycoprotein IIb/IIIa inhibition during coronary stent implantation: Observations from the ESPRIT trial. J Invasive Cardiol 2005;17:360-364.
24. Ellis SG, Tendera M, de Belder MA, et al. Facilitated PCI in patients with ST-elevation myocardial infarction. N Engl J Med 2008;358:2205-2217.

High-dose tirofiban reduces the need for bail-out study medication in patients with ST- segment elevation myocardial infarction: results of a subgroup analysis of the On-TIME 2 trial. Response to a letter: the authors reply

Heart 2011;97:1026

R.S. Hermanides, A.W. van 't Hof

We thank Dr Lin and colleagues for their comments regarding the outcomes of 30-day major adverse cardiac events (MACE) in the pre-defined subgroup analysis of the Ongoing Tirofiban In Myocardial infarction Evaluation 2 trial (On-TIME 2).(1) There are different aspects of their comments that can be addressed.

First, although pre-hospital use of high dose tirofiban reduces the use of bail-out study medication, and need for bail-out study medication was associated with a less favourable 30-day MACE, the 30-day MACE rates in those without bail-out study medication was not significantly different (6.9% in the tirofiban group vs 5.1%, instead of 5.3% described by Lin, in the placebo group). This shows that the benefit of early initiation of tirofiban is mainly preventing complications in patients at high risk of thrombotic events by opening the occluded vessel during transportation(2) and by reducing periprocedural thrombotic complications.(3)

The double-blind On-TIME 2 trial phase was not powered to detect a significant difference in clinical end points (MACE), however in the pooled analysis of the two study phases it was shown that pre-hospital use of tirofiban was safe and associated with a significantly lower incidence of 30-day MACE as compared to placebo (5.8% vs 8.6%, p=0.043).(4) Another aspect which should be mentioned is the possible biases that may affect the death rates in On-TIME 2, as suggested by Lin, et al. Selection bias for procedure choice (urgent PCI or urgent CABG) in case of urgent TVR is not an issue in the On-TIME 2 trial, as treatment allocation was blinded for both the physician and the patient.(5)

We agree that the benefit of pre-hospital treatment with tirofiban to reduce MACE may outweigh the hazard of bleeding for high ischemic risk STEMI patients.

In summary, timing of glycoprotein IIb/IIIa inhibitors, like tirofiban, as well as the level of risk plays a significant role in the benefit offered by this drug in STEMI patients. On-TIME 2 has shown that early pre-hospital administration of high dose tirofiban, in addition to dual antiplatelet therapy and heparin, improves outcome after primary PCI in patients with acute STEMI, especially in early presenters, without a significant increased risk of major bleeding.

References

1. Hermanides RS, Heestermans AA, Ten Berg JM, Gosselink AT, Ottervanger JP, van Houwelingen KG, Kolkman JJ, Stella PR, Dill T, Hamm C, van 't Hof AW. High-dose tirofiban pretreatment reduces the need for bail- out study medication in patients with ST-segment elevation myocardial infarction: results of a subgroup analysis of the On-TIME 2 trial. Heart 2011;97:106-111.
2. Heestermans T, Suryapranata H, ten Berg JM, Mosterd A, Gosselink AT, Kochman W, Dill T, van Houwelingen G, Kolkman JJ, van Werkum JW, Zijlstra F, Hamm C, van 't Hof AW. Facilitated reperfusion with prehospital glycoprotein IIb/IIIa inhibition: predictors of complete ST-segment resolution before primary percutaneous coronary intervention in the On-TIME 2 trial: correlates of reperfusion before primary PCI. J Electrocardiol 2001;44:42-48.
3. Heestermans AA, van Werkum JW, Hamm C, Dill T, Gosselink AT, de Boer MJ, van Houwelingen G, Hoorntje JC, Koopmans PC, ten Berg JM, van 't Hof AW. Marked reduction of early stent thrombosis with pre-hospital initiation of high-dose Tirofiban in ST-segment elevation myocardial infarction. J Thromb Haemost 2009;10:1612-1618.
4. ten Berg JM, van 't Hof AW, Dill T, Heestermans AA, van Werkum JW, Mosterd A, van Houwelingen KG, Koopmans PC, Stella PR, Boersma E, Hamm C. On behalf of the Ongoing Tirofiban In Myocardial infarction Evaluation (On-TIME) 2 study group. Effect of early, pre-hospital initiation of high-bolus dose tirofiban in patients with ST-segment elevation myocardial infarction on short and long-term clinical outcome. J Am Coll Cardiol 2010;55:2446-2455.
5. van 't Hof AW, ten Berg JM, Heestermans AA, Dill T, Funck RC, van Werkum JW, Dambrink JH, Suryapranata H, van Houwelingen KG, Ottervanger JP, Stella PR, Giannitsis E, Hamm C. Ongoing Tirofiban In Myocardial infarction Evaluation (On-TIME) 2 study group. Pre-hospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial. Lancet 2008;372:537-546.

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A comparison between upfront high dose tirofiban versus provisional use in primary PCI in the real world of non selected STEMI patients: Insights from the Zwolle acute myocardial infarction registry

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A.A. Heestermans, R.S. Hermanides, A.T. Gosselink, M.J. de Boer, J.C. Hoorntje, H. Suryapranata, J.P. Ottervanger, J.H. Dambrink, E. Kolkman, J.M. ten Berg, F. Zijlstra, A.W. van 't Hof

Abstract

Background: Despite the proven benefit of glycoprotein IIb/IIIa blockers in patients with acute ST-segment elevation myocardial infarction (STEMI), there is still debate on the timing of administration of these drugs and whether all or only a selection of patients should be treated.
We evaluated the effect of routine upfront versus provisional use of high dose tirofiban (HDT) in a large real world population of non-selected STEMI patients.

Methods: Consecutive STEMI patients were registered in a single centre dedicated database. Patients with upfront HDT therapy before first balloon inflation were compared with patients who received the drug on a provisional basis, after first balloon inflation. Initial TIMI flow of the infarct related vessel and enzymatic infarct size and 30-day clinical outcome were assessed.

Results: Out of 2679 primary PCI patients HDT was given upfront in 885 (33.0%) and provisional in 812 (45.3%). Upfront as compared to provisional HDT showed higher initial patency (22.3% vs. 17.9%, p=0.006), smaller infarct size (1401 IU/L (IQR 609 – 2948) vs. 1620 (753 – 3132), p=0.03) and a lower incidence of death or recurrent MI at 30 days (3.3% vs. 5.1%, p=0.04) without an increase in TIMI bleeding (p=0.24). Upfront HDT independently predicted initial patency (Odds Ratio (OR) 1.47, 95% Confidence Interval (CI) 1.15 – 1.88, p=0.02), enzymatic infarct size (OR 0.70, 95% CI 0.56 – 0.86, p=0.001) and 30-day death or recurrent MI (OR 0.59, 95% CI 0.37 – 0.95, p=0.03).

Conclusion: Our findings support the use of upfront potent antiplatelet and antithrombotic therapy in STEMI patients and encourage further clinical investigations in this field.

Introduction

Despite the proven benefit of glycoprotein IIb/IIIa blockers in patients with acute ST-segment elevation myocardial infarction (STEMI), there is still debate whether these drugs should be given to all patients before primary percutaneous coronary intervention (PCI) or only to a selected group with complications during PCI as bail-out therapy.(1,2) In addition, the timing of administration of these drugs might be debated. The Zwolle acute myocardial infarction (AMI) registry provides a unique opportunity to evaluate upfront versus provisional use of high dose tirofiban (HDT) in a large real world population of non-selected STEMI patients.

Methods

The Zwolle AMI registry is a dedicated database, which registers all consecutive STEMI patients presented for primary PCI at our institution. The institutional review board approved our registry, and all patients gave informed consent.

Procedural details and adjunctive medical therapy

According to protocol all patients received 500 mg of aspirin (Aspegic®), 5000 IU unfractionated heparin intravenously and a loading dose of clopidogrel. HDT therapy consisted of tirofiban (25 μg/kg bolus and 0.15 μg/kg/min maintenance infusion for 12 hours). According to institutional guidelines additional unfractionated heparin was administered only in cases were the activated clotting time was less then 200 seconds. Primary PCI was performed by standard techniques using the femoral approach in most cases. Detailed data of adjunctive medical therapy and procedural details were collected.

Clinical and angiographic variables

Baseline clinical characteristics and outcome data were collected in a case record form. Detailed data on angiographic characteristics and procedural details of the primary PCI were collected. Initial as well as final TIMI flow of the infarct related vessel were assessed using the Thrombolysis in myocardial infarction (TIMI) criteria by the performing operator and all data including the procedural characteristics were entered into a dedicated database.

Follow up and determination of myocardial infarct size

Enzymatic myocardial infarction size was estimated by peak creatinine kinase (CK) and CK-MB in IU/L in the first 48 hours after the acute event, as previously described. (3) Clinical outcome was assessed at 30 days follow-up. Criteria for recurrent myocardial infarction (MI) consisted of a new episode of chest pain with ischemic electrocardiographic changes and increase of cardiac biomarkers. Bleeding was defined according to the TIMI criteria.(4) Death was defined as all cause mortality.

Statistical analysis

Patients who were treated with routine upfront HDT were compared with patients who received the drug on a provisional basis. The use of HDT was classified into upfront or provisional according to the timing of administration of the HDT bolus relative to the time of balloon inflation (upfront: HDT bolus before balloon inflation and provisional: no HDT or HDT bolus after balloon inflation).

Categorical variables were compared using the chi-square test or Fisher's exact test or, the chi-square for trend for ordinal variables, and the Mann-Whitney U test was used for continuous variables. Multivariate analyses of predictors for initial patency, enzymatic infarct size and the combined incidence of recurrent myocardial infarction and mortality were done using logistic regression models. All p-values were two-sided with significance level $p<0.05$. All statistical analyses were performed with SPSS for Windows (Rel. 16.0.1.1. 2007. Chicago: SPSS Inc.).

Results

From January 2004 to January 2009, 3943 consecutive STEMI patients were presented with STEMI at our centre. Patients included in the Ongoing Tirofiban in Myocardial infarction Evaluation (On-TIME) 2 trial (n= 732) and patients who did not receive primary PCI (n=510) were excluded for this analysis (figure 1).(5) Of the 2701 STEMI patients who were treated with primary PCI the timing of administration of HDT in relation to first balloon inflation was known in 2679 patients (99.2%) and these patients form the basis of this report. Eight hundred and eighty five patients (33.0%) were routinely treated upfront with HDT. In the other 1794 patients HDT was given in 812 patients (45.3%) mostly as bailout therapy. Baseline characteristics of the patients are described in table 1. Patients who received upfront HDT treatment were of younger age, more often had undergone prior revascularization or had suffered from a prior MI. Of interest is that patients with upfront HDT treatment were more often diagnosed in a referring centre and that symptom onset to arrival at our PCI centre, door to balloon time and total ischemic time were significantly longer as compared to patients who received HDT therapy on a provisional basis.

Timing of administering of high dose tirofiban

The median pre-treatment time before balloon inflation in patients with upfront HDT treatment was 94 (IQR: 63-130) minutes. In the 812 patients who were treated with HDT in the provisional HDT group the median time of administering HDT was 37 (IQR: 17-62) minutes after balloon inflation.

Effect on initial patency, enzymatic infarct size and outcome

The effect of upfront HDT therapy on initial patency, enzymatic infarct size and

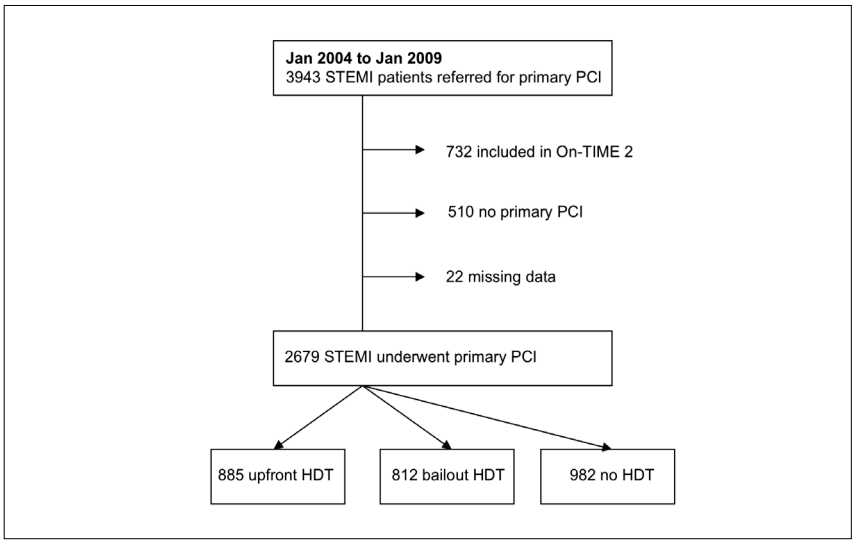

Figure 1: Flow chart Zwolle STEMI registry

Table 1 Baseline characteristics

Variable	Upfront HDT*	Provisional HDT†	p value
	N=885	N=1794	
Age, mean ± SD	62.51 ± 12.34	63.38 ± 12.54	0.09
Female gender, n (%)	236 (26.7)	506 (28.3)	0.38
Hypertension, n (%)	328 (37.1)	625 (35.1)	0.30
Smoking, n (%)	383 (44.1)	762 (43.6)	0.82
Hypercholesterolemia, n (%)	210 (24.0)	352 (19.9)	0.02
Family history of CAD, n (%)	342 (39.9)	693 (41.0)	0.59
Previous PCI, n (%)	101 (11.4)	146 (8.2)	0.006
Previous CABG, n (%)	41 (4.6)	42 (2.3)	0.001
Previous MI, n (%)	103 (11.7)	163 (9.1)	0.04
Previous stroke, n (%)	26 (2.9)	52 (2.9)	0.96
Diabetes mellitus, n (%)	107 (12.1)	199 (11.1)	0.46
TIMI risk score > 3, n (%)	304 (35.8)	591 (37.1)	0.53
Infarct related artery, n (%)			
RCA	332 (37.6)	731 (40.9)	0.10
LAD	384 (43.5)	771 (43.2)	0.88
CX	141 (16.0)	259 (14.5)	0.32
Left main	2 (0.2)	12 (0.7)	0.16
Single-vessel disease, n (%)	465 (52.8)	932 (52.4)	0.82
Three-vessel disease, n (%)	148 (16.8)	326 (18.3)	0.34
Symptom-onset to diagnosis, min (IQR)	116 (57-255.5)	100 (56-193)	0.04
Time from symptom-onset to arrival PCI centre, min (IQR)	180 (112-326)	165 (110-262.5)	0.02
Total ischemic time, min (IQR)	248.5 (166-431.25)	215 (160-328)	< 0.001
Door to balloon time, min (IQR)	51 (32-85)	45 (29-71)	< 0.001
Ischemic time < 180 min, n (%)	248 (28.6)	608 (34.9%)	0.001
Door to balloon time < 45 min, n (%)	363 (41.8)	850 (49.1%)	< 0.001
Diagnosis in ambulance, n (%)	369 (41.7)	931 (51.9%)	< 0.001
Diagnosis in referring centre, n (%)	469 (53.1)	781 (43.6%)	< 0.001
Diagnosis in PCI centre, n (%)	46 (5.2)	81 (4.5%)	0.43

HDT=high dose tirofiban, CAD=coronary artery disease, PCI=percutaneous coronary intervention, CABG=coronary artery bypass grafting, MI=myocardial infarction, TIMI=thrombolysis in myocardial infarction, RCA=right coronary artery, LAD=left anterior descending coronary artery, RCX=ramus circumflex coronary artery

*Upfront HDT: HDT bolus before balloon inflation. †Provisional HDT: no HDT or HDT bolus after balloon inflation.

outcome is shown in table 2. Initial patency (TIMI 3 flow) of the infarct related vessel was significantly higher in patients with upfront HDT therapy as compared to those who received HDT on a provisional base (22.3% vs. 17.9%, p=0.006). Data on enzymatic infarct size were available in 97% of patients. Median enzymatic infarct size was 1550 IU/L (700 – 3066) overall and was significantly smaller in patients routinely treated with upfront HDT therapy. We found no significant difference in stroke as shown in table 2. The rate of TIMI bleeding was similar with routine upfront HDT therapy as compared to provisional use (TIMI major bleeding 2.9% vs. 3.4%, p=0.50 and TIMI major or minor bleeding 6.2% vs.7.5%, p=0.24). The combined incidence of 30-day death or recurrent MI occurred less often in patients with upfront HDT as compared to patients with provisional HDT use (3.3% vs. 5.1%, p=0.04). Survival free of death or recurrent MI at 1-year is shown in figure 2.

Table 2 Angiographic outcome, infarct size and clinical outcome at 30 days

Variables	Upfront HDT*	Provisional HDT†	P value
	N=885	N=1794	
TIMI 3 flow IRV before PCI, n (%)	197 (22.3)	320 (17.9)	0.006
TIMI 3 flow IRV after PCI, n (%)	817 (92.5)	1660 (92.7)	0.88
CK max IU/L, (IQR)	1401 (609-2948)	1620 (753-3132)	0.03
Death, n (%)	20 (2.3)	60 (3.5)	0.12
Recurrent MI, n (%)	10 (1.2)	30 (1.7)	0.27
Death or recurrent MI, n (%)	28 (3.3)	88 (5.1)	0.04
Stroke, n (%)	0 (0.0)	5 (0.3)	0.18
TIMI major or minor bleeding, n (%)	53 (6.2)	129 (7.5)	0.24
TIMI major bleeding, n (%)	25 (2.9)	59 (3.4)	0.50

HDT=high dose tirofiban, TIMI=thrombolysis in myocardial infarction, PCI=percutaneous coronary intervention, CK=creatinine kinase, MI=myocardial infarction

*Upfront HDT: HDT bolus before balloon inflation. †Provisional HDT: no HDT or HDT bolus after balloon inflation.

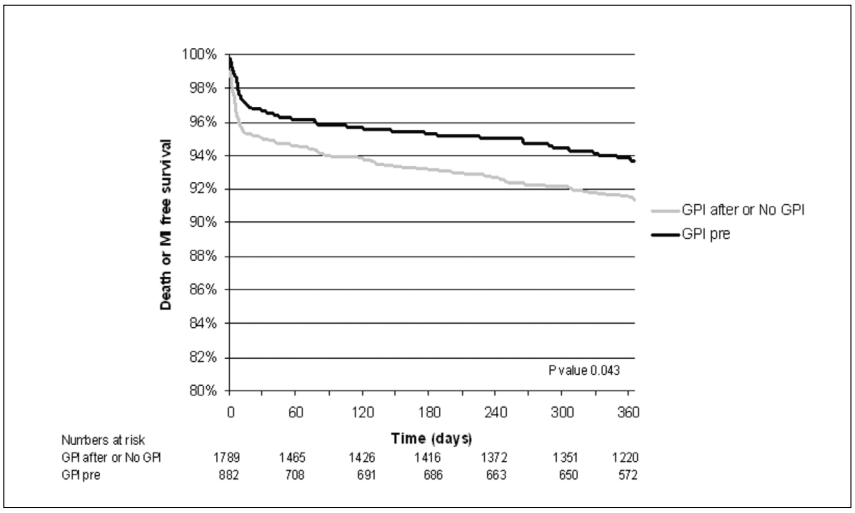

Figure 2: Kaplan Meier survival free of death or recurrent myocardial infarction at 1-year

Multivariate analysis of predictors for initial patency, enzymatic infarct size and outcome

Independent predictors for initial patency (TIMI 3 flow) of the infarct related artery (IRA) were upfront HDT therapy (Odds Ratio (OR) 1.33, 95% Confidence Interval (CI) 1.06 – 1.67, p=0.02), single vessel disease (OR 1.37, 95% CI 1.1 – 1.70, p=0.01), TIMI risk score > 3 (OR 0.76, 95% CI 0.60 – 0.97, p=0.03) and male gender (OR 0.67, 95% CI 0.53 – 0.84, p=0.001).

The independent predictors of a larger median enzymatic infarct size (CK max > 1550 IU/L) were a TIMI risk score > 3 (OR 1.66, 95% CI 1.26 – 2.19, p<0.0001), male gender (OR 0.72, 95% CI 0.56 – 93, p=0.01), upfront HDT therapy (OR 0.70, 95% CI 0.56 – 0.86,p=0.001 and previous CABG (OR 0.47, 95% CI 0.25 – 0.88, p=0.02).

For the combined incidence of death or recurrent MI at 30-days independent predictors after multivariate analyses were TIMI risk score > 3 (OR 3.0, 95% CI 1.76 – 5.28, p<0.0001) and upfront HDT (OR 0.59, 95% CI 0.37 – 0.95, p=0.03).

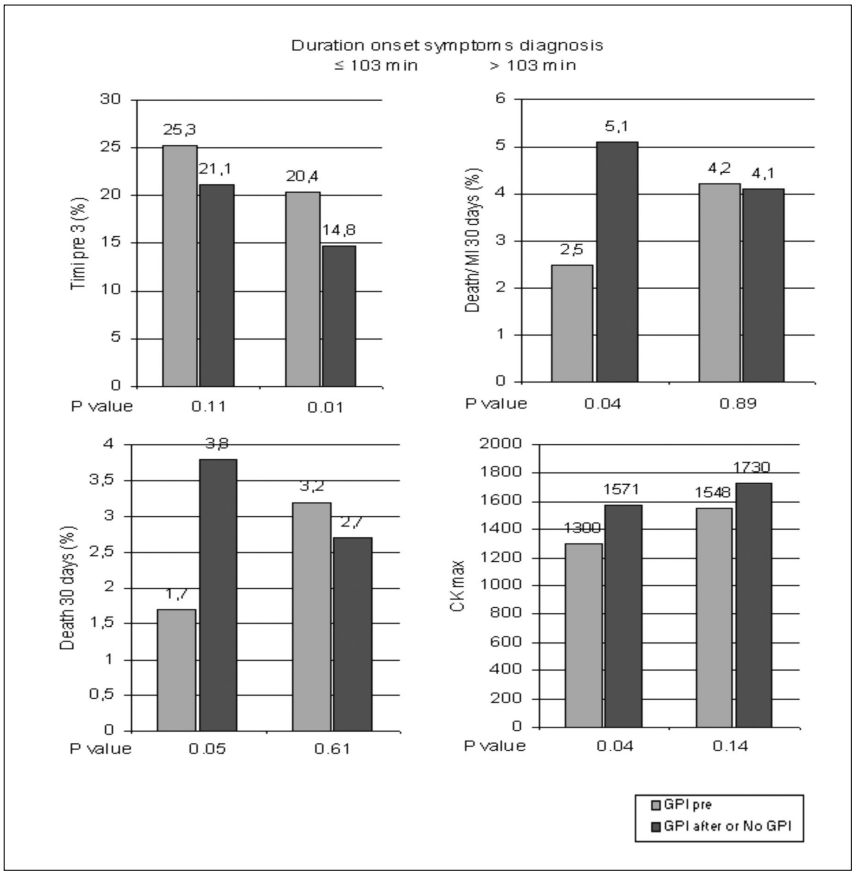

Figure 3: Efficacy of high dose tirofiban in relation to time from symptom onset to STEMI diagnosis

Efficacy of high dose tirofiban in relation to time from symptom onset to STEMI diagnosis

The median (IQR) time of symptom onset to the time of STEMI diagnosis was 103 min. The effect of upfront HDT on initial patency, enzymatic infarct size and outcome was related to the time from symptom onset to first diagnosis as shown in figure 3. In patients with early diagnosis (less than the median time from symptom onset to diagnosis) upfront HDT therapy reduced enzymatic infarct size (CK max 1300 IU/L (IQR 449 – 2860) vs. 1571 (751 – 3129), p=0.04), 30-day mortality (1.7% vs. 3.8%, p=0.05) and reduced the combined incidence of 30-day death or recurrent MI (2.5% vs. 5.1%, p=0.04) as compared to provisional use. However, in patients with longer delay to diagnosis (symptom onset to diagnosis more than 103 minutes) no effect on enzymatic infarct size (CK max 1548 (726 – 2980) vs. 1730 (806 – 3197), p=0.14), 30-day mortality (3.2% vs. 2.7%, p=0.61) or the combined incidence of death or recurrent MI (4.2% vs. 4.1%, p=0.89) was found.

Discussion

In this registry of non-selected primary PCI patients, upfront high dose tirofiban (HDT) improved initial patency of the infarct related vessel, reduced myocardial infarct size and improved clinical outcome as compared to a strategy of provisional use after PCI. Importantly, we found no differences in major bleeding complications between upfront versus provisional use of HDT.

ESC guidelines recommend the administration of glycoprotein IIb/IIIa blockers in STEMI since the reported reduction of 30-day mortality of up to 32% without affecting the risk of hemorrhagic stroke or TIMI major bleeding.(2,6) However, large registry studies show that in real-world practice, glycoprotein IIb/IIIa blockers are given to only 30-50% of patients with STEMI, often for bail-out situations.(7,8) In our registry, 63% of patients were treated with a glycoprotein IIb/IIIa blocker (885 patients upfront before PCI and 815 patients on a provisional basis during or after PCI) reflecting real world practice. It also shows that in routine daily practice, delays to reperfusion are longer and consequently pre-treatment times with potent antithrombotic and antiplatelet drugs when given upfront are longer. The 94 minutes of pre-treatment time is much longer than the 55 minutes of pre-treatment time as seen in the On-TIME 2 trial.(5)

The results of this analysis confirms the results of the On-TIME 2 trial which demonstrated improved ST-segment resolution and clinical outcome with pre-hospital initiated HDT therapy on top of dual antiplatelet therapy (aspirin/clopidogrel) as compared to provisional IIb/IIIa therapy.(5,9) These results may not be compared to studies comparing routine early versus routine late IIb/

IIIa therapy. Results from these studies show conflicting results. The Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events (FINESSE) trial failed to demonstrate benefit from upfront IIb/IIIa blocker administration as compared to the routine administration in the cath-lab.(10) However, a recent meta-analysis showed improved initial patency and ST resolution in patients with upfront IIb/IIIa blockers.(11) Recently other studies found a beneficial effect of early initiation of a glycoprotein IIb/IIIa blocker as well. Ortolani and co-workers found that pre-treatment with an IIb/IIIa blocker in patients referred to a PCI center was associated with a better clinical outcome.(12) The same was found by Hassan et al(13), where the early administration of abciximab was associated with a 26% incidence of aborted myocardial infarction. Upstream administration before primary PCI however, is not supported by the current ESC guidelines. From the above mentioned studies, one may conclude that in STEMI patients, routine administration is superior to provisional administration and that earlier administration might have some advantages as well, however, this need to be confirmed in larger trials.

Our analysis was not a randomised comparison of routine versus provisional use of HDT in STEMI patients. Upfront HDT treatment occurred less often in the ambulance and patient delay, door to balloon time and total ischemic time were significantly longer as compared to patients who received HDT therapy on a provisional basis. All these parameters are related to worse outcome and therefore, the effect of upfront HDT became more pronounced after correction for these differences. The reported reduced incidence of acute stent thrombosis with pre-hospital initiation of HDT(14), although not an endpoint in this analysis, might contribute to a reduced incidence of recurrent MI partly explaining the beneficial effect of upfront HDT on clinical outcome in our registry.

In the present analysis upfront HDT therapy was especially effective in the early hours after symptom onset. This finding of higher efficacy in the early hours of acute myocardial infarction is consistent with the findings of (pre-hospital) thrombolytic therapy, where highest efficacy was found in patients who received lytic therapy within the so called 'golden hour'.(15)

Our findings emphasize that potent antiplatelet and antithrombotic treatment should be given routinely in all STEMI patients planned to undergo primary PCI and not only in patients with complications.

In the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial routine IIb/IIIa therapy was compared to the direct thrombin inhibitor, bivalirudin.(16) This trial showed a significant reduction in major bleeding with bivalirudin and was associated with a reduced 30-day mortality. However, acute stent thrombosis occurred more frequently. In HORIZONS-AMI, a relatively high rate of major bleeding in the glycoprotein IIb/IIIa group was found and this might partly be due to a less strict heparin protocol

with target activated clotting time around 250 seconds. In addition, IIb/IIIa therapy was given relatively late thereby losing the opportunity to have a significant effect on initial patency, infarct size and outcome. In contrast to the findings in the HORIZONS-AMI trial, a recent meta-analysis did not report an increase in TIMI major bleeding with routine administration of IIb/IIIa therapy.(17)

Limitations

There are several aspects of this analysis that merit careful consideration. First, the timing of and dosage of clopidogrel changed in the years from in low dose in the cathlab to high dose in the ambulance. Bioavailability of clopidogrel is known to be significantly impaired in STEMI patients and the magnitude of clopidogrel induced platelet inhibition of clopidogrel is lower and delayed in this clinical setting.(18) These differences in timing and dosage of clopidogrel are probably of minor impact in relation to the impact that upfront versus provisional HDT therapy has. Secondly, this is a post-hoc analysis of a registry of non-randomized patients, introducing potential bias.

In conclusion, in this registry of non-selected primary PCI patients, upfront high dose tirofiban improved initial patency of the infarct related vessel, reduced myocardial infarct size and improved clinical outcome as compared to a strategy of provisional use after PCI. Importantly, we found no increased bleeding rate with routine upfront therapy. Our findings support further clinical investigations for the use of upfront potent antiplatelet and antithrombotic therapy in STEMI patients, preferably in the ambulance.

References

1. Stone GW, Grines CL, Cox DA, Garcia E, Tcheng JE, Griffin JJ, et al. Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) Investigators. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. N Engl J Med 2002;346:957-966.
2. De Luca G, Suryapranata H, Stone GW, Antoniucci D, Tcheng JE, Neumann FJ, et al. Abciximab as adjunctive therapy to reperfusion in acute ST-segment elevation myocardial infarction: a meta-analysis of randomized trials. JAMA 2005;293:1759-1765.
3. Nienhuis MB, Ottervanger JP, de Boer MJ, Dambrink JH, Hoorntje JC, Gosselink AT, et al. Zwolle Myocardial Infarction Study Group. Prognostic importance of creatine kinase and creatine kinase-MB after primary percutaneous coronary intervention for ST-elevation myocardial infarction. Am Heart J 2008;155:673-679.
4. Chesebro JH, Knatterud G, Roberts R, Borer J, Cohen LS, Dalen J, et al. Thrombolysis In Myocardial Infarction (TIMI) trial, phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. Circulation 1987;76:142-154.
5. van 't Hof AW, ten Berg JM, Heestermans T, Dill T, Funck RC, van Werkum JW, et al. Ongoing Tirofiban In Myocardial infarction Evaluation (On-TIME) 2 study group. Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial. Lancet 2008;372:537-546.
6. Van de Werf F, Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. Eur Heart J 2008;29:2909-2945.
7. Budaj A, Brieger D, Steg PG, Goodman SG, Dabbous OH, Fox KA, et al. GRACE Investigators. Global patterns of use of antithrombotic and antiplatelet therapies in patients with acute coronary syndromes: insights from the Global Registry of Acute Coronary Events (GRACE). Am Heart J 2003;146:999-1006.
8. Mandelzweig L, Battler A, Boyko V, Bueno H, Danchin N, Fillippatos G, et al. Euro Heart Survey Investigators. The second Euro Heart Survey on acute coronary syndromes: characteristics, treatment, and outcome of patients with ACS in Europe and the Mediterranean Basin in 2004. Eur Heart J 2006;27:2285-2293.
9. ten Berg JM, van 't Hof AW, Dill T, Heestermans T, van Werkum JW, Mosterd A, et al. on behalf of the Ongoing Tirofiban In Myocardial infarction Evaluation (On-TIME) 2 study group. Effect of Early, Pre-Hospital initiation of high-bolus dose tirofiban in patients with ST Elevation Myocardial Infarction on short and long-term clinical outcome. J Am Coll Cardiol 2010;55:2446-2455.
10. Ellis SG, Tendera M, de Belder MA, van Boven AJ, Widimsky P, Janssens L, et al. FINESSE Investigators. Facilitated PCI in patients with ST-elevation myocardial infarction. N Engl J Med 2008;358:2205-2217.
11. De Luca G, Gibson CM, Bellandi F, Murphy S, Maioli M, Noc M, et al. Early glycoprotein IIb-IIIa inhibitors in primary angioplasty (EGYPT) cooperation: an individual patient data meta-analysis. Heart 2008;94:1548-1558.
12. Ortolani P, Marzocchi A, Marrozzini C, Palmerini T, Saia F, Taglieri N, et al. Long-term effectiveness of early administration of glycoprotein IIb/IIIa agents to real-world patients undergoing primary percutaneous interventions: results of a registry study in an ST-elevation myocardial infarction network. Eur Heart J 2009;1:33-43.
13. Hassan AK, Jukema JW, van der Laarse A, Hasan-Ali H, Wolterbeek R, van der Kley F, et al. Incidence, patient characteristics and predictors of aborted myocardial infarction in patients undergoing primary PCI: prospective study comparing pre- and in-hospital abciximab pretreatment. EuroIntervention 2009;4:662-668.
14. Heestermans AA, Van Werkum JW, Hamm C, Dill T, Gosselink AT, De Boer MJ, et al. Marked reduction of early stent thrombosis with pre-hospital initiation of high-dose Tirofiban in ST-segment elevation myocardial infarction. J Thromb Haemost 2009;7:1612-1618.
15. Boersma E, Maas AC, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. Lancet 1996;348:771-775.
16. Stone GW, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, et al. HORIZONS-AMI Trial Investigators. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med 2008;358:2218-2230.
17. Valgimigli M, Biondi-Zoccai G, Tebaldi M, van't Hof AW, Campo G, Hamm C, et al. Tirofiban as adjunctive therapy for acute coronary syndromes and percutaneous coronary intervention: a meta-analysis of randomized trials. Eur Heart J 2010;31:35-49.
18. Heestermans AA, van Werkum JW, Taubert D, Seesing TH, von Beckerath N, Hackeng CM, et al. Impaired bioavailability of clopidogrel in patients with a ST-segment elevation myocardial infarction. Thromb Res 2008;122:776-781.

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The effect of pre-hospital glycoprotein IIb/IIIa inhibitors on angiographic outcome in STEMI patients who are candidates for primary PCI

Catheter and Cardiovasc Interventions; accepted

R.S. Hermanides, J.W. van Werkum, J.P. Ottervanger, N.J. Breet, A.T. Gosselink, K.G. van Houwelingen, J.H. Dambrink, C. Hamm, J.M. ten Berg, A.W. van 't Hof, on behalf of the On-TIME 2 investigators

Abstract

Objectives: Aim of this study was to assess the effect of early initiation of high bolus dose tirofiban on top of dual antiplatelet therapy on angiographic outcome before and after primary percutaneous coronary intervention (PCI) in ST-elevation myocardial infraction patients.

Background: Glycoprotein IIb/IIIa inhibitors are effective inhibitors of platelet aggregation, and have shown to reduce thrombotic complications in patients undergoing PCI.

Methods: This is a pre-specified angiographic analysis of the On-TIME 2 trial (N=984) and its open label run-in phase (N=414). All angiographic parameters, including quantitative coronary angiography (QCA) were performed in an independent angiographic corelab.

Results: Of the 1398 patients, 709 patients (50.7%) were randomised to pre-hospital tirofiban. An open infarct related vessel (TIMI 2 or 3 flow) at initial angiography was more often present in the tirofiban group as compared to the no tirofiban group (58.3% vs 49.7%, p=0.002). Tirofiban also reduced initial thrombus burden (p for trend=0.035) as well as thrombus grade 5 (46.9% vs 54.3%, p=0.016) and showed a trend toward a reduction in large thrombus burden (LTB) (69.4% vs 74.5%, p=0.055). After PCI, a trend towards a lower corrected TIMI frame count (cTFC) in the tirofiban group was found. A significant interaction was found with time of initiation of study drug, with highest efficacy of tirofiban when given within 76 minutes after symptom onset, with a significantly lower cTFC after PCI (21.9 ± 17.6 vs 23.9 ± 18.5, p=0.008, p for interaction p=0.006).

Conclusion: In patients undergoing primary PCI, pre-hospital administration of tirofiban reduces initial thrombus burden and improves initial patency of the infarct related vessel before PCI. Initiation of tirofiban seems to be most effective when given very early after the onset of symptoms, however, this finding needs confirmation in other studies.

Introduction

Primary percutaneous coronary intervention (PCI) with stent implantation is the preferred reperfusion strategy for ST-segment elevation myocardial infarction (STEMI) if performed by experienced operators in a timely manner.(1) Initial reperfusion with medical therapy before primary PCI is associated with improved short- and long-term clinical outcome.(2)

Angiographic presence of coronary thrombus at PCI is associated with a lower procedural success rate, reflected by a lower post PCI thrombolysis in myocardial infarction (TIMI) flow, lower myocardial blush grade (MBG), less myocardial salvage and worsened short- and long-term prognosis.(3,4) Optimal platelet inhibition during PCI, achieved by dual antiplatelet therapy, has been proposed to potentially prevent the post-procedural myocardial ischemic complications and improve outcome. Glycoprotein IIb/IIIa inhibitors (GPI) are effective inhibitors of platelet aggregation, even when administered additional to aspirin and clopidogrel and have shown to reduce thrombotic complications in patients undergoing PCI.(1,5) The additional value of pre-hospital administration of tirofiban on ST segment resolution and clinical outcome in STEMI patients has recently been demonstrated.(6,7) However, the beneficial effect of pre-hospital initiation of tirofiban on top of aspirin and high-dose clopidogrel on thrombus burden and on initial and final reperfusion in STEMI patients has not been established. It is known that the efficacy of thrombolytic therapy is highly time dependent with the highest efficacy when given within the so-called golden hour.(8) The aim of this study was to investigate the effect of early initiation of high bolus dose tirofiban on angiographic outcome before and after primary PCI in STEMI patients and to establish whether this is also time dependent.

Methods

Patient population

This is a pre-specified angiographic analysis of the Ongoing Tirofiban In Myocardial infarction Evaluation (On-TIME 2) trial (N=984) and its open label run-in phase (N=414). The On-TIME 2 trial was a prospective, multicentre, placebo-controlled, randomised, clinical trial investigating the effect of pre-hospital administration of high bolus dose tirofiban on top of aspirin, clopidogrel and heparin in STEMI patients treated with primary PCI. The On-TIME 2 trial is registered as number ISRCTN06195297. The rationale, design, primary- and 1-year results of the study have been described previously.(6,7,9) For the present analysis, data from the open label randomised phase and the double-blinded randomised phase were combined (N=1398), as described previously.(7)

Randomisation and treatment

Patients were randomly assigned to pre-hospital treatment with high bolus dose tirofiban (25 μg/kg bolus and 0.15 μg/kg/min maintenance infusion for 18 h) or no tirofiban [phase 1] or placebo [phase 2]. Each participating ambulance or referral center was supplied with sealed study kits in blocks of 4, containing either open-label tirofiban or saline solution vials (phase 1) or blinded study medication (phase 2). In the ambulance or referring centre, 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 seconds. 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.

Angiographic analysis

The culprit lesion was identified on the basis of the ECG leads that showed the ischemic ST-T changes and/or the details of the coronary anatomy, particularly the morphology of the lesion(s), such as presence of thrombus, stenosis severity, and other abnormalities of the luminal surface. Each culprit lesion was described qualitatively in terms of anatomic location(10), perfusion characteristics(11), morphological features, and intraluminal thrombus. Presence of coronary thrombus was angiographically determined (before cross-wiring) and classified in 6 grades as described previously.(12) In brief, in thrombus grade 0 (G0), no cine-angiographic characteristics of thrombus are present; in thrombus grade 1 (G1), possible thrombus is present, with such angiography characteristics as reduced contrast density, haziness, irregular lesion contour or a smooth convex meniscus at the site of total occlusion, suggestive but not diagnostic of thrombus; in thrombus grade 2 (G2), there is definite thrombus, with greatest dimensions ≤1/2 the vessel diameter; in thrombus grade 3 (G3), there is definite thrombus but with greatest linear dimension ≥1/2 but ≤ 2 vessel diameters; in thrombus grade 4 (G4), there is definite thrombus, with the largest dimension ≥2 vessel diameters; and in thrombus grade 5 (G5), there is a total thrombotic occlusion. After classification of thrombus burden grades, thrombus burden was stratified in 2 categories, scored as a small thrombus burden (STB) for thrombus grade ≤G3 and a large thrombus burden (LTB) for thrombus grade G4 or G5. All angiographic endpoints, including quantitative coronary angiography (QCA), were assessed and adjudicated by an independent core laboratory. Thrombolysis In Myocardial Infarction (TIMI) flow and myocardial blush grade (MBG) were assessed as previously reported.(11,13) The corrected TIMI frame count (cTFC) was determined pre- and post-PCI as previously described.(14) Distal embolisation was defined as migration of a filling

defect to distally occlude the infarct-related vessel or one of its branches, or a new abrupt cut-off of the distal vessel/branch.(15) No-reflow was defined as reduced antegrade flow (TIMI 2 or 3 during PCI and TIMI 0-1 after PCI) in the absence of a flow limiting dissection. Angiographic success for an interventional procedure was defined as a residual stenosis of < 50% and achievement of TIMI 3 flow.

Endpoints

The primary endpoint of this study was the effect of early initiation of high bolus dose tirofiban on angiographic outcome before (TIMI flow, cTFC) and after (TIMI flow, cTFC, MBG) primary PCI in STEMI patients. The key secondary endpoint of this study was to determine the impact of large thrombus burden on angiographic outcome. The clinical secondary endpoint was to assess 30-day mortality and 30-day major adverse cardiac events ((MACE), as defined by the composite of death, recurrent myocardial infarction (MI), or urgent target vessel revascularization), according to thrombus grade. A blinded independent Clinical Endpoint Committee adjudicated all clinical endpoints. Death, recurrent MI, and urgent target vessel revascularization were defined as previously described.(6)

Ethics

The investigation conforms with the principles outlined in the Declaration of Helsinki. The study was approved by the Committee on Research Ethics of our hospital.

Statistical analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois, USA) version 15.0.1. All analyses were done according to the intention-to-treat principle. All p values were two-sided. For all analyses, statistical significance was assumed when the two tailed probability value was < 0.05. Continuous data were expressed as mean ± standard deviation and categorical data as percentage, unless otherwise denoted. Differences between continuous data were performed by student's t test or Mann Whitney U test and the chi-square or Fisher's exact test was used as appropriate for dichotomous data. Also, a post-hoc analysis for the primary endpoint was performed in a pre-specified subgroup (early versus late presenters). Early presenters were defined as patients with a time from symptom onset to diagnosis (in the ambulance) < 76 minutes, based on the median value of symptom onset to diagnosis.(7) To evaluate whether treatment with high dose tirofiban on LTB, initial TIMI 3 flow, final TIMI 3 flow and cTFC < median was different in early- vs late presenters, interaction analyses were performed. For the interaction analysis a significance level p<0.10 was used.(16) A proportional odds model was used to compare the distribution of thrombus grades in the two groups. In this model, the odds of thrombus with tirofiban relative to no tirofiban or

placebo are assumed to be constant regardless of the grouping of individual grades. Therefore, the model analyzed general trends toward more severe thrombus burden in 1 treatment group as compared to the other. Thrombus grade was not normally distributed, therefore a complementary log-log function was used.

Results

Of the 1398 On-TIME patients, 709 patients (50.7%) were randomised to pre-hospital tirofiban. Coronary angiography was performed in 1377 patients (98.5%) and primary PCI in 1203 patients (86.1%). A flow chart of the study is depicted in figure 1.

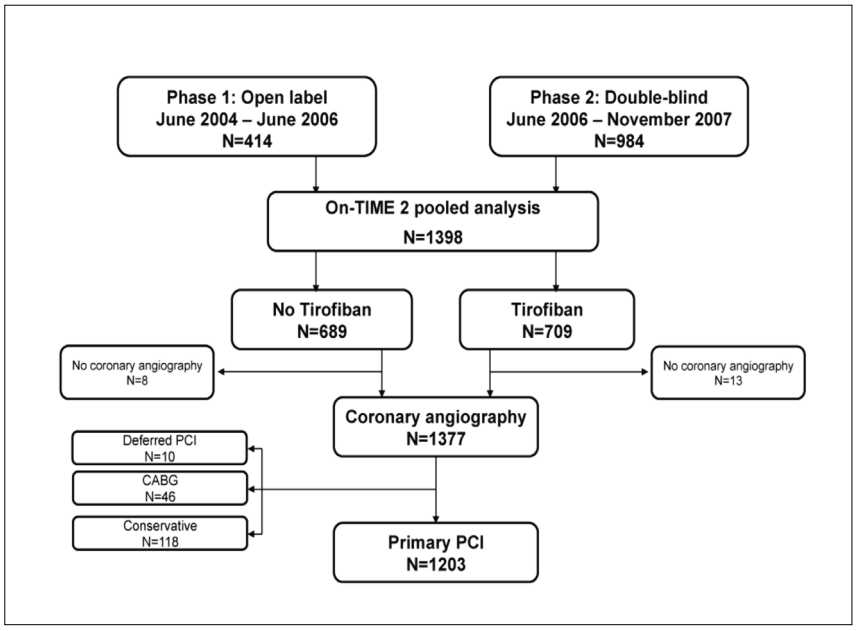

Figure 1: Flow chart. Quantitative coronary angiography analysis was performed in all patients who underwent coronary angiography and/or primary PCI.
PCI=percutaneous coronary intervention. CABG=coronary artery bypass grafting.

Baseline characteristics

Baseline demographic and procedural characteristics of the population according to randomisation of study medication are presented in table 1. There were no differences in the angiographic characteristics of the infarct related artery lesions between both groups.

Table 1: Baseline clinical, Angiographic, and Procedural Characteristics

	No Tirofiban N=689	Tirofiban N=709	P value
Age	62.0 ± 12.1	61.6 ± 11.9	0.529
Male gender	75.5	76.6	0.625
BMI	26.7 ± 3.9	26.9 ± 3.7	0.471
Current smoker	48.7	45.8	0.269
Diabetes	10.6	11.7	0.510
Hypertension	34.4	33.8	0.829
Hypercholesterolemia	25.0	26.4	0.545
Family history	39.5	40.4	0.732
Previous MI	9.2	8.9	0.892
Previous PCI	7.3	8.9	0.257
Previous CABG	2.5	1.7	0.313
Previous CVA	1.7	1.4	0.626
Killip > 1	13.8	11.0	0.107
Ischemic Time (min)	166 (128 - 257)	166 (128 - 239)	0.636
Time SO – diagnosis (min)	80 (46 - 151)	74 (44 - 145)	0.311
Time study medication – angio (min)	55 (43 - 70)	55 (44 - 70)	0.589
Single vessel disease	47.9	51.1	0.224
Two vessel disease	29.2	24.6	0.051
Three vessel disease	17.5	17.7	0.923
IRV			
LAD	41.4	42.0	0.815
RCX	11.6	12.5	0.590
RCA	45.3	44.2	0.685
Graft	1.3	0.8	0.381
Left main	0.5	0.5	1.000
Stent placement	89.7	89.8	0.984
Drug eluting stent	24.2	28.6	0.102
Bare metal stent	76.7	73.2	0.188
Additional devices	17.7	15.1	0.197
Thrombus aspiration	11.7	8.7	0.077
IABP	5.2	4.9	0.826

Data are n/N (%) or mean (SD), or median (IQR). BMI=body mass index. MI=myocardial infarction. PCI=percutaneous coronary intervention. CABG=coronary artery bypass grafting. CVA=cerebro vascular accident. SO=symptom onset. IRV=infarct related vessel. LAD=left anterior descending artery. RCX=ramus circumflex artery. RCA=right coronary artery. IABP=intra-aortic balloon pump.

Angiographic outcome pre-PCI

An open infarct related vessel (TIMI 2 or 3 flow) at initial angiography was more often present in the tirofiban group as compared to the no tirofiban group (58.3% vs 49.7%, p=0.002, table 2). These data were confirmed by QCA analyses which showed a significant reduction in diameter stenosis (82.5 ± 19.0 vs 85.9 ± 17.9, p=0.012) and an increase of minimal luminal diameter (0.49 ± 0.57 vs 0.40 ± 0.52, p=0.020) before PCI in the tirofiban group. Furthermore, tirofiban pre-treatment as compared with no tirofiban pre-treatment reduced initial thrombus burden (p for trend=0.035) as well as thrombus grade 5 (46.9% vs 54.3%, p=0.016) and showed a trend toward a reduction in LTB (69.4% vs 74.5%, p=0.055, table 2).

Table 2: Angiographic outcome pre-PCI

	Total N=1398	No Tirofiban N=689	Tirofiban N=709	P value
Initial TIMI flow				0.008*
TIMI 0,1	584/1270 (46.0)	319/634 (50.3)	265/636 (41.7)	
TIMI 2	420/1270 (33.1)	192/634 (30.3)	228/636 (35.8)	
TIMI 3	266/1270 (20.9)	123/634 (19.4)	143/636 (22.5)	
cTFC	78.3 ± 33.1	79.8 ± 31.7	76.7 ± 34.4	0.119
cTFC < median (100)	33.6	31.6	35.6	0.153
Thrombus grade**				0.035*
Thrombus grade 0**	11/1180 (0.9)	4/591 (0.7)	7/589 (1.2)	
Thrombus grade 1**	61/1180 (5.1)	20/591 (3.4)	41/589 (7.0)	
Thrombus grade 2**	49/1180 (4.2)	20/591 (3.4)	29/589 (4.9)	
Thrombus grade 3**	210/1180 (17.8)	107/591 (18.1)	103/589 (17.5)	
Thrombus grade 4**	252/1180 (21.4)	119/591 (20.1)	133/589 (22.6)	
Thrombus grade 5**	597/1180 (50.6)	321/591 (54.3)	276/589 (46.9)	
LTB**	849/1180 (71.9)	440/591 (74.5)	409/589 (69.4)	0.055
MLD (mm)	0.45 ± 0.55	0.40 ± 0.52	0.49 ± 0.57	0.020
Percent diameter stenosis	84.1 ± 18.5	85.9 ± 17.9	82.5 ± 19.0	0.012
Reference diameter (mm)	2.8 ± 0.59	2.9 ± 0.59	2.8 ± 0.60	0.249

Data are n/N (%) or mean (SD). TIMI=thrombolysis in myocardial infarction. cTFC=corrected TIMI frame count. LTB=large thrombus burden (thrombus grade 4-5). MLD=minimal lumen diameter.
* P value for trend
** only recorded in patients who underwent primary PCI

Angiographic outcome post-PCI

Pre-treatment with tirofiban was associated with a trend toward a lower cTFC post-PCI as compared to no pre-treatment with tirofiban (24.4 ± 19.5 vs 25.4 ± 20.0, p=0.054). There were no differences in final TIMI flow, MBG, distal embolisation, no-reflow, percentage diameter stenosis, and minimal lumen diameter after PCI between the groups (table 3).

Angiographic outcome in early presenters (symptom onset to diagnosis < 76 minutes)

Pre-treatment with tirofiban in patients who presented early resulted in a better initial TIMI 3 flow (27.7% vs 19.9%, p=0.022, figure 2) and a significant reduction in LTB (64.3% vs 73.6%, p=0.013, figure 2) as compared to no tirofiban pre-treatment. Although there was no difference in final TIMI flow (p for trend 0.287), cTFC after PCI was significantly lower in patients who were pre-treated with tirofiban as compared to those without tirofiban pre-treatment (21.9 ± 17.6 vs 23.9 ± 18.5, p=0.008, figure 2). There was a significant interaction between randomisation (tirofiban or no tirofiban) and the early- vs late presenter groups with respect to cTFC (p for interaction 0.006), initial TIMI 3 flow (p for interaction 0.031), and LTB (p for interaction p=0.097), figure 2. Furthermore, pre-treatment with tirofiban resulted in a trend toward a lower MBG as compared with no tirofiban pre-treatment (p for trend 0.072). In patients who presented late, tirofiban had no effect on all angiographic outcomes (figure 2).

Table 3: Angiographic outcome post-PCI

	Total N=1398	No Tirofiban N=689	Tirofiban N=709	P value
Angiographic succes	1120/1202 (93.2)	559/600 (93.2)	561/602 (93.2)	0.988
TIMI flow post-PCI				0.065*
0	25/1197 (2.1)	17/599 (2.8)	8/598 (1.3)	
1	15/1197 (1.3)	6/599 (1.0)	9/598 (1.5)	
2	78/1197 (6.5)	31/599 (5.2)	47/598 (7.9)	
3	1079/1197 (90.1)	545/599 (91.0)	534/598 (89.3)	
cTFC	24.9 ± 19.7	25.4 ± 20.0	24.4 ± 19.5	0.054
cTFC < median (19.2)	47.3	44.6	49.9	0.108
MBG				0.123*
0,1	252/1127 (22.4)	115/561 (20.5)	137/566 (24.2)	
2	382/1127 (33.9)	205/561 (36.5)	177/566 (31.3)	
3	493/1127 (43.7)	241/561 (43.0)	252/566 (44.5)	
Distal embolisation	61/968 (6.3)	36/489 (7.4)	25/479 (5.2)	0.170
TIMI 0,1 flow or distal embolisation post-PCI	101/1197 (8.4)	59/599 (9.8)	42/598 (7.0)	0.079
No-reflow	22/1203 (1.8)	12/601 (2.0)	10/602 (1.7)	0.664
MLD(mm)	2.3 ± 0.61	2.3 ± 0.63	2.3 ± 0.60	0.436
Percent diameter stenosis	15.2 ± 18.8	15.1 ± 19.3	15.3 ± 18.2	0.477
Reference diameter (mm)	2.8 ± 0.53	2.8 ± 0.52	2.7 ± 0.55	0.685

Data are n/N (%) or mean (SD). TIMI=thrombolysis in myocardial infarction. MBG=myocardial blush grade. cTFC=corrected TIMI frame count. MLD=minimal lumen diameter.
* P value for trend

Angiographic outcome in patients with a large thrombus burden

Patients with a LTB less often had initial TIMI 3 flow, a higher cTFC pre-PCI, and a reduced final TIMI 3 flow and MBG 3 as compared to patients with a STB, see table 4. Furthermore, patients with a LTB had a significantly higher rate of distal embolisation (7.4% vs 3.8%, p=0.040) and no-reflow (2.5% vs 0.3%, p=0.013).

30-day clinical outcome according to thrombus grade

Higher thrombus grade was associated with increased 30-day mortality (OR 2.7, 95% CI, 1.2 – 6.1) and 30-day MACE (OR 1.5, 95% CI, 1.0 – 2.3), see table 5.

Table 4: LTB and angiographic- and clinical outcomes

	Total N=1180	STB N=331	LTB N=849	P value
Initial TIMI 3 flow	216/1165 (18.5)	158/326 (48.5)	58/839 (6.9)	<0.001
cTFC pre-PCI	38.7 ± 26.7	36.3 ± 23.6	43.6 ± 31.7	0.017
Angiographic success	1098/1179 (93.1)	317/331 (95.8)	781/848 (92.1)	0.025
TIMI 3 post-PCI	1052/1167 (90.1)	307/326 (94.2)	745/841 (88.6)	0.004
cTFC post-PCI	21.5 ± 11.8	20.3 ± 11.7	21.9 ± 11.9	0.068
MBG 3 post-PCI	481/1102 (43.6)	185/299 (61.9)	296/803 (36.9)	<0.001
Distal embolisation	61/950 (6.4)	10/264 (3.8)	51/686 (7.4)	0.040
No-reflow	22/1180 (1.9)	1/331 (0.3)	21/849 (2.5)	0.013

Data are n/N (%) or mean (SD). TIMI=thrombolysis in myocardial infarction. PCI=percutaneous coronary intervention. MBG=myocardial blush grade. cTFC=corrected TIMI frame count.

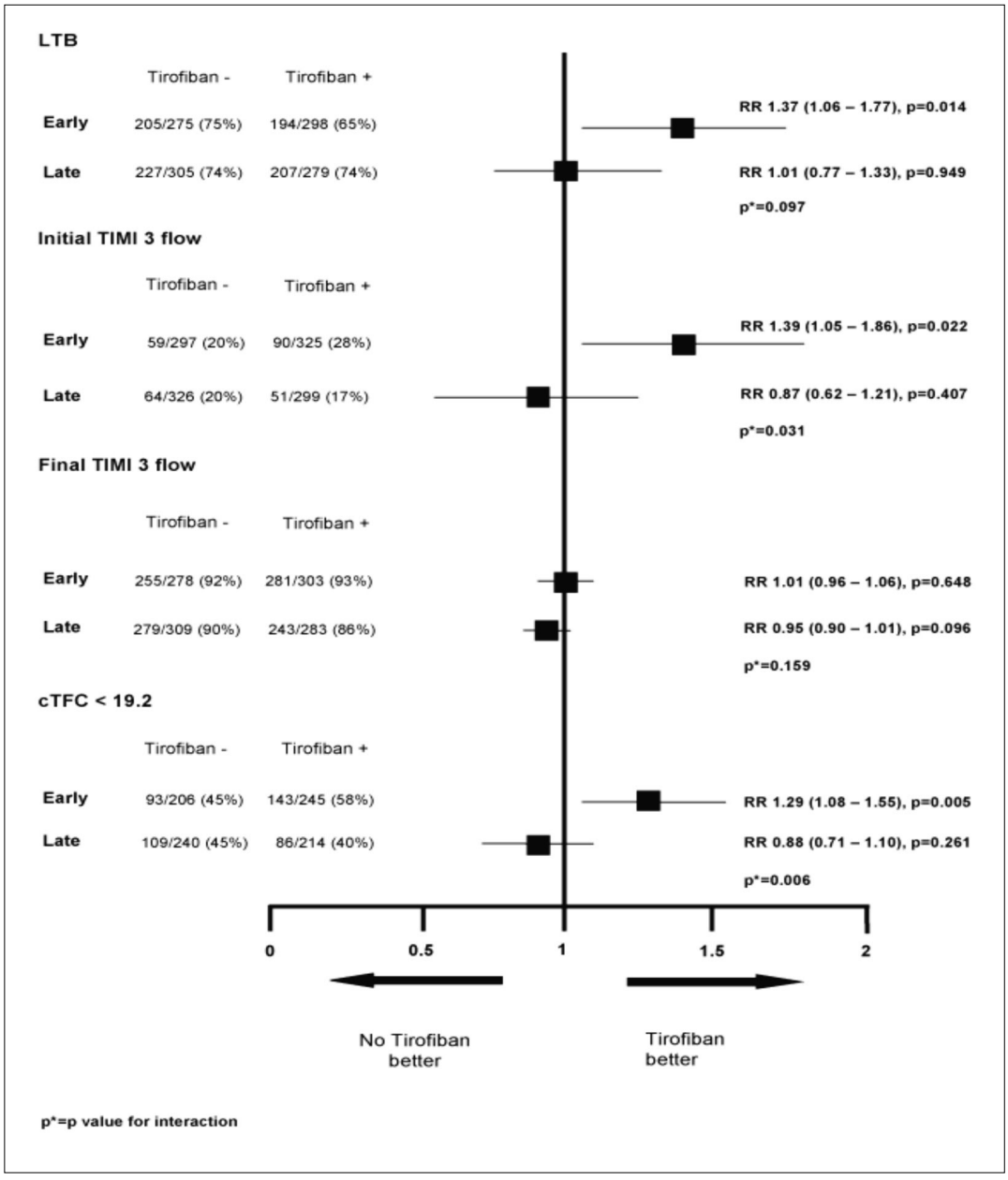

Figure 2: Risk ratios of angiographic outcomes, as measured by quantitative coronary angiography analysis, in early- vs late presenters.
LTB=large thrombus burden. cTFC=corrected TIMI frame count.

Table 5: 30-day clinical outcome according to thrombus grade

N-1146	G 0 N =11	G 1 N=56	G 2 N=48	G 3 N=204	G 4 N=247	G 5 N=580	OR (95% CI)	p-value
MACE	0	3.6	2.1	5.4	4.9	7.8	1.5 (1.0 – 2.3)	0.032
Death	0	0	0	2.0	0.8	3.6	2.7 (1.2 – 6.1)	0.014
MI	0	0	2.1	2.0	2.8	1.7	0.9 (0.5 – 1.7)	0.811
Urgent TVR	0	3.6	2.1	2.9	4.5	4.1	1.2 (0.7 – 1.8)	0.502
Stent thrombosis	0	2.1	2.3	2.2	4.5	4.1	1.3 (0.8 – 2.1)	0.339

Data are (%) MACE=major adverse cardiac events. MI=myocardial infarction. TVR=target vessel revascularisation.

Discussion

This angiographic study shows that pre-hospital initiation of high bolus dose tirofiban reduces initial thrombus burden, improves initial patency of the infarct related vessel but does not improve angiographic reperfusion after PCI. However, in patients who presented early after symptom onset, tirofiban administration also seems to improve angiographic outcome after PCI. Furthermore, a large thrombus burden is an important determinant for adverse angiographic outcome. Finally, the level of thrombus grade is related to clinical outcome: the highest thrombus grade has the worst 30-day clinical outcome.

GPI and angiographic outcome pre-PCI

This study reveals that, after pre-hospital diagnosis in the ambulance, early administration of aspirin, high dose clopidogrel and heparin (control group) is associated with a high initial patency rate (50%). However, pre-hospital use of high bolus dose tirofiban on top of these agents further improves initial patency to a level of 58%. These findings are in accordance with the results of the recently published angiographic substudy of the FINESSE trial.(17)

Although fibrinolytic agents are more effective in inducing initial patency (70-80%), the cocktail of antithrombotic and antiplatelet agents have a better safety profile as compared to lytic agents. This is a major point of concern for lytic therapy as part of a pharmaco-invasive approach, especially due to the increased risk of intracranial bleeding.

GPI and angiographic outcome post-PCI

In primary PCI for STEMI, it is of great importance to obtain rapid and complete restoration of epicardial and myocardial blood flow, as assessed by TIMI 3 flow and MBG 3, because this is associated with better survival.(18,19) Although in our study pre-treatment with tirofiban showed a trend toward a lower corrected TIMI frame count after PCI, it did not significantly influence final TIMI flow and MBG. With regard to these angiographic endpoints, it should be noted that their assessment derives from a single time point sampling of a dynamic phenomenon and that these snapshot

measurements cannot fully explore the integrity of the microvessel network.(20) TIMI flow and MBG might be not sensitive enough to detect differences in the (very) early setting after tirofiban administration.(11,13) Moreover, the differences in corrected TIMI frame count could be explained due to a more quantitative and objective measure with corrected TIMI frame count compared to the semi-quantitative TIMI flow scale.

Impact of GPI on angiographic outcome is time dependent

The additional effect of tirofiban on top of aspirin and high dose clopidogrel on angiographic outcome was highly dependent on the time from symptom onset to diagnosis, with the highest efficacy on angiographic outcome before and after PCI in patients who were diagnosed early after symptom onset. This might be related in the composition of thrombus in early presenters which consists of more fresh newly formed platelet-rich thrombi, more susceptible for strong antiplatelet therapy like GPI.(21) Another argument might be the incomplete effect of clopidogrel loading on platelet aggregration in early presenters.

Recently, a pooled analysis of the On-TIME 2 trial demonstrated reduced mortality with tirofiban pre-treatment.(7) This effect on mortality was more prominent in patients who received tirofiban shortly after symptom onset and patients who received primary PCI.

GPI and thrombus burden in ACS

A large thrombus burden is associated with distal embolisation, which in turn is associated with impaired myocardial reperfusion and poor outcome.(22) Furthermore, a large thrombus burden is an independent predictor of MACE and infarct-related artery stent thrombosis in patients treated with drug-eluting stents for STEMI.(23) In addition, it has recently been revealed that pre-hospital initiation of high-dose tirofiban reduces the 30-day incidence of stent thrombosis in STEMI patients treated with primary PCI and stenting.(24)

Strategies like thrombus aspiration and GPI administration have been shown to decrease thrombus grade before stent deployment. In the setting of unstable angina and NSTEMI, two angiographic sub-studies from the PRISM-PLUS(25) and CAPTURE trials(26) have described a reduction in thrombus burden in patients treated with GPI who underwent PCI.

In our trial, early administration of tirofiban showed a significantly decrease in initial thrombus burden and a strong trend toward a reduction in LTB. A LTB was associated with a decreased angiographic outcome. The presence of 30-day mortality or 30-day MACE was associated with increased odds of reporting higher thrombus burden. Therefore, it is essential to identify and stratifying thrombus, because it has prognostic value.

Limitations

Several limitations of the present analysis should be considered. First, data from the two phases of the On-TIME 2 trial with different design (open label and double-blind) were combined. However, both study phases had identical inclusion and exclusion criteria and there was no difference in baseline characteristics between the two phases of the study. We performed a post-hoc analysis for the primary endpoint in early- vs late presenters. Early administration of tirofiban has the highest efficacy on angiographic outcome before and after PCI in patients who were diagnosed early after symptom onset. These findings are hypothesis generating and needs to be confirmed in larger studies. The data on LTB were only recorded in patients who underwent primary PCI and were available in 98.1% (1180/1203) of the patients. Finally, coronary angiography has inherent limitations for assessing thrombus burden, and there is no gold standard method to be compared with.

Conclusion

In patients undergoing primary PCI, pre-hospital administration of tirofiban reduces initial thrombus burden and improves initial patency of the infarct related vessel. Early initiation of tirofiban has the highest efficacy, including angiographic outcome after PCI, when given shortly after symptom onset, however, this finding needs confirmation in other studies.

A large thrombus burden is associated with poor angiographic- and clinical outcome.

References

1. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, Hochman JS, Krumholz HM, Kushner FG, Lamas GA, Mullany CJ, Ornato JP, Pearle DL, Sloan MA, Smith SC jr, Alpert JS, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). Circulation 2004;110:588-636.
2. Stone GW, Cox D, Garcia E, Brodie BR, Morice MC, Griffin J, Mattos L, Lansky AJ, O'Neill WW, Grines CL. Normal flow (TIMI 3) before mechanical reperfusion therapy is an independent determinant of survival in acute myocardial infarction. Circulation 2001;104:636-641.
3. White CJ, Ramee SR, Collins TJ, Escobar AE, Karsan A, Shaw D, Jain SP, Bass TA, Heuser RR, Teirstein PS, Bonan R, Walter PD, Smalling RW. Coronary thrombi increase PTCA risk. Angioscopy as a clinical tool. Circulation 1996;93:253-258.
4. Singh M, Berger PB, Ting HH, Rihal CS, Wilson SH, Lennon RJ, Reeder GS, Bresnahan JF, Holmes DR Jr. Influence of coronary thrombus on outcome of percutaneous coronary angioplasty in the current era (the Mayo Clinic experience). Am J Cardiol 2001;88:1091-1096.
5. Antman EM, Hand M, Armstrong PW, Bates ER, Green LA, Halasyamani LK, Hochman JS, Krumholz HM, Lamas GA, Mullany CJ, Pearle DL, Sloan MA, Smith Jr SC. 2007 Focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: A report of the ACC/AHA Task Force on Practice Guidelines. J Am Coll Cardiol 2008;58:210-247.
6. van 't Hof AW, ten Berg JM, Heestermans AA, Dill T, Funck RC, van Werkum JW, Dambrink JH, Suryapranata H, van Houwelingen KG, Ottervanger JP, Stella PR, Giannitsis E, Hamm C. Ongoing Tirofiban In Myocardial infarction Evaluation (On-TIME) 2 study group. Pre-hospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial. Lancet 2008;372:537-546.
7. ten Berg JM, van 't Hof AW, Dill T, Heestermans AA, van Werkum JW, Mosterd A, van Houwelingen KG, Koopmans PC, Stella PR, Boersma E, Hamm C. On behalf of the Ongoing Tirofiban In Myocardial infarction Evaluation (On-TIME) 2 study group. Effect of early, pre-hospital initiation of high-bolus dose tirofiban in patients with ST-segment elevation myocardial infarction on short and long-term clinical outcome. J Am Coll Cardiol 2010;55:2446-2455.
8. Boersma E, Maas AC, Deckers JW, Simoons ML. Early thrombolytic therapy in acute myocardial infarction: reappraisal of the golden hour. Lancet 1996;348:771-775.
9. van 't Hof AW, Hamm C, Rasoul S, Guphta S, Paolini JF, ten Berg JM, on behalf of the On-TIME 2 investigators. Ongoing tirofiban in myocardial infarction evaluation (On-TIME) 2 trial: rationale and study design. EuroInterv 2007;3:371-380.
10. Principal investigators of CASS and Associates. National Heart, Lung, and Blood Institute Coronary Artery Surgery Study. Circulation 1981;63(suppl I):I-1-I-139.
11. TIMI study group. The Thrombolysis In Myocardial Infarction (TIMI) trial. Phase I findings. N Engl J Med 1985;312:932-936.
12. Gibson CM, de Lemos JA, Murphy SA, Marble SJ, McCabe CH, Cannon CP, Antman EM, Braunwald E. Combination therapy with abciximab reduces angiographically evident thrombus in acute myocardial infarction: a TIMI 14 substudy. Circulation 2001;103:2550-2554.
13. van 't Hof AW, Liem A, Suryapranata H, Hoorntje JC, de Boer MJ, Zijlstra F. Angiographic assessment of myocardial infarction in patients treated with primary angioplasty for acute myocardial infarction: myocardial blush grade. Zwolle Myocardial Infarction Study Group. Circulation 1998;97:2302-2306.
14. Gibson CM, Cannon CP, Daley WI, Dodge JT Jr, Alexander B Jr, Marble SJ, McCabe CH, Raymond L, Fortin T, Poole WK, Braunwald E. The TIMI frame count: a quantitative method of assessing coronary artery flow. Circulation 1996;93:879-888.
15. Henriques JP, Zijlstra F, Ottervanger JP, de Boer MJ, van 't Hof AW, Hoorntje JC, Suryapranata H. Incidence and clinical significance of distal embolisation during primary angioplasty for acute myocardial infarction. Eur Heart J 2002;23:1112-1117.
16. Assmann SF, Pocock SJ, Enos LE, Kasten LE. Subgroup analysis and other (mis)uses of baseline data in clinical trials. Lancet 2000;355:1064-1069.
17. Prati F, Petronio S, van Boven AJ, Tendera M, de Luca L, de Belder MA, Galassi AR, Imola F, Montalescot G, Peruga JZ, Barnathan ES, Ellis S, Savonitto S. Evaluation of infarct-related coronary artery patency and microcirculatory function after facilitated percutaneous primary coronary angioplasty: the FINESSE –ANGIO (Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events-Angiographic) study. JACC Cardiovasc Interv 2010;3:1284-1291.
18. Henriques JP, Zijlstra F, van 't Hof AW, de Boer MJ, Dambrink JH, Gosselink AT, Hoorntje JC, Suryapranata H. Angiographic assessment of reperfusion in acute myocardial infarction by myocardial blush grade. Circulation 2003;107:2115-2119.
19. Constantini C, Stone GW, Mehran R, Aymong E, Grines CL, Cox DA, Stuckey T, Turco M, Gersh BJ, Tcheng JE, Garcia E, Griffin JJ, Guagliumi G, Leon MB, Lansky AJ. Frequency, correlates,

and clinical implications of myocardial perfusion after primary angioplasty and stenting, with and without glycoprotein IIb/IIIa inhibition, in acute myocardial infarction. J Am Coll Cardiol 2004;44:305-312.

20. Tan WA, Moliterno DJ. TIMI flow and surrogate end points: what you see is not always what you get. Am Heart J 1998;36:570-573.
21. Collet JP, Montalescot G, Lestly C, Mishal Z, Soria J, Choussat R, Drobinski G, Soria C, Pinton P, Barragan P, Thomas D. Effects of abciximab on the architecture of platelet-rich clots in patients with acute myocardial infarction undergoing primary coronary intervention. Circulation 2001;103:2328-2331.
22. Fokkema ML, Vlaar PJ, Svilaas T, Vogelzang M, Amo D, Diercks GF, Suurmeijer AJ, Zijlstra F. Incidence and clinical consequences of distal embolization on the coronary angiogram after percutaneous coronary intervention for ST-elevation myocardial infarction. Eur Heart J 2009;30:908-915.
23. Sianos G, Papafaklis MI, Daemen J, Vaina S, van Mieghem CA, van Domburg RT, Lampros KM, Serruys PW. Angiographic stent thrombosis after routine use of drug-eluting stents in ST-segment elevation myocardial infarction. J Am Coll Cardiol 2007;50:573-873.
24. Heestermans AA, van Werkum JW, Hamm C, Dill T, Gosselink AT, de Boer MJ, van Houwelingen KG, Hoorntje JC, Koopmans PC, ten Berg JM, van 't Hof AW. Marked reduction of early stent thrombosis with pre-hospital initiation of high-dose tirofiban in ST-segment elevation myocardial infarction. J Thromb Haemost 2009;10:1612-1618
25. Zhao XQ, Theroux P, Snapinn SM, Sax FL. Intracoronary thrombus and platelet glycoprotein IIb/IIIa receptor blockade with tirofiban in unstable angina or non-Q-wave myocardial infarction: angiographic results from the PRISM-PLUS trial (platelet receptor inhibition for ischemic syndrome management in patients limited by unstable signs and symptoms. Circulation 1999;100:1609-1615.
26. van den Brand M, Laarman GJ, Steg PG, de Scheerder I, Heyndrickx G, Beatt K, Kootstra J, Simoons ML. Assessment of coronary angiograms prior to and after treatment with abciximab, and the outcome of angioplasty in refractory unstable angina patients. Eur Heart J 1999;20:1572-1578.

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In patients with STEMI, Lactate DeHydrogenase (LDH) elevation may occur early after symptom onset and is associated with poor outcome

Submitted

R.S. Hermanides, J.P. Ottervanger, J.H. Dambrink, J.G. Krabbe, R.J. Slingerland, M.J. de Boer, J.C. Hoorntje, A.T. Gosselink, H. Suryapranata, F. Zijlstra, A.W. van 't Hof

Abstract

Objectives: The aim of the study was to evaluate the relationship between elevated lactate dehydrogenase (LDH) on admission and time from onset of symptoms in patients with ST-elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI). In addition, the association between elevated LDH and angiographic and clinical outcome was assessed.

Background: Elevation of LDH on admission is often used as a sign of late presentation, however, only few studies evaluated the relationship between LDH elevation and time of presentation. In addition, the impact of elevated LDH before primary PCI on angiographic- and clinical outcome is unknown.

Methods and results: A large scale, prospective, observational single-centre study was performed between 16 October 2005 and 31 December 2009 in all consecutive STEMI patients who underwent primary PCI. LDH was measured upon arrival in the PCI centre. Patients who had LDH measurement >1 hour after admission were excluded. The independent association between elevated LDH on admission and 30-day- and 1-year mortality was evaluated using Cox proportionals Hazard models. Results: Elevated LDH was present in 20.0% (491/2453) of patients. In patients with less than 2 hours and 30 minutes of symptoms, LDH was elevated in 14.6% of patients. Patients with elevated LDH were older, more often female, had a higher TIMI risk score and Killip class on admission. Elevated LDH on admission was associated with poor angiographic and clinical outcome (TIMI 3 flow post-PCI 85.5%, no-reflow in 14.5%, 30-day mortality 13.5%). At multivariate analyses, elevated LDH on admission remained a strong predictor of 30-day (HR 6.3, CI 95%, 3.6 – 11.1) and 1-year mortality (HR 3.4, CI 95%, 2.3 – 5.0) independent of time from the onset of symptoms.

Conclusion: Elevation of LDH may occur early after the onset of symptoms in patients with STEMI who are planned to undergo primary PCI and is associated with poor angiographic and clinical outcome, irrespective of time from symptom onset. Elevated LDH on admission is a strong and independent predictor of short and long-term mortality. The mechanism why patients with LDH elevation on admission have a worse outcome remains to be determined.

Introduction

The improvement in the management of patients with ST-elevation myocardial infarction (STEMI) characterised by early diagnosis and treatment of the acute event, improved management of complications, and general availability of pharmacologic and mechanical therapies has significantly reduced cardiac mortality.(1-5) In daily practice, the treatment of STEMI is often based on the duration of symptoms before hospital arrival. The administration of thrombolytic therapy is often considered in patients presenting early after the onset of symptoms. However, the time from symptom onset is often difficult to assess and not always reliable. Elevation of lactate dehydrogenase (LDH) on admission is often used as a sign of late presentation, however, only few studies evaluated the relationship between LDH elevation and time of presentation. In addition, the impact of elevated LDH before primary percutaneous coronary intervention (PCI) on angiographic and clinical outcome is unknown.

The aim of the study was to evaluate the relationship between elevated LDH on admission and time from onset of symptoms in patients with STEMI treated with primary PCI. In addition, the association between elevated LDH and angiographic and clinical outcome was assessed.

Methods

Population

From 16 October 2005 to 31 December 2009, individual patient data from all consecutive patients with admission diagnosis of STEMI admitted for primary PCI at the Isala klinieken (Zwolle, the Netherlands) were prospectively recorded. To avoid double inclusion of patients, only the first recorded admission for STEMI during the study period was used. Patients were diagnosed with STEMI if they had chest pain for >30 minutes and ECG changes with ST segment elevation >2 mm in at least 2 precordials and >1 mm in the limb leads. All patients presenting within 6 hours from symptom onset or between 6 and 24 hours if they had continuous symptoms and signs of ischemia (persistent or recurrent chest pain and/or persistent elevation or re-elevation of ST-segment) were included. Patients who had LDH measurement >1 hour after admission were excluded.

According to the protocol all patients received 500 mg of aspirin intravenously, 600 mg clopidogrel orally and 5000 IU intravenous unfractionated heparin (UFH). In some patients additional treatment with glycoprotein IIb/IIIa inhibitors (GPI) (25μg/kg bolus tirofiban) was given in the ambulance or referral centre. All patients were directly transported to the cath-lab on arrival and acute coronary angiography was performed with subsequent primary PCI when indicated as part of routine treatment for all STEMI patients in our hospital. Primary PCI was routinely performed

by femoral access using 6 French sheaths with selective thrombus aspiration and stent implantation where appropriate. All patients were treated with optimised drug-therapy including angiotensin-converting enzyme inhibitors, β-blockers and lipid-lowering drugs where appropriate. Patients were stratified into elevated LDH and normal LDH on admission. Baseline characteristics, angiographic outcome and clinical outcome were compared between the groups.

Measurements (end points, definitions)

The primary endpoint was the relationship between elevated LDH on admission and time from onset of symptoms. The key secondary endpoint was the association of elevated LDH on admission and angiographic (including no-reflow) and clinical outcome. No-reflow was defined as TIMI 2 or 3 flow during PCI and TIMI 0-2 flow after PCI. Enzymatic myocardial infarction size was estimated by peak CK in IU/L in the first 48 hours after the acute event, as previously described.(6)

Serum marker analysis

Blood samples were drawn on admission. Heparin plasma LDH concentrations were analysed with the Elecsys 2010 system (Roche Diagnostics, Almere, The Netherlands). LDH activity was determined enzymatically on a Roche/Modular automatic analyzer according to the International Federation of Clinical Chemistry (IFCC) recommendation at 37oC.(7) LDH was elevated when its value was above 250 U/L, based on the reference interval in healthy individuals. Protocol-specified blood sampling for CK levels was performed at baseline and at 8 hours, 16 hours, 24 hours and 48 hours after PCI. Measurement of serum total CK levels was performed on the Modular system (Roche Diagnostics).

Angiographic and Electrocardiographic analysis

All angiograms have been reviewed by two experienced investigators who were blinded to all data apart from the coronary angiogram. TIMI flow grades and myocardial blush grade (MBG) were assessed after the PCI procedure, as previously described.(8,9) Residual stenosis was assessed visually. Procedural success was defined as postprocedural TIMI 3 flow in the infarct related vessel in combination with a myocardial blush grade 2 or 3 and a residual stenosis less than 50%.

The sum of ST-segment deviation in all 12 leads was measured 20 ms after the end of the QRS complex with a caliper. We calculated both residual ST segment-deviation on the single ECG after PCI and ST-segment deviation resolution from paired ECGs. Patients were divided into four groups of residual ST-segment deviation (0 mm: normalised ST segment and no residual ST-segment deviation; 1–3 mm; 4–6 mm; and >6 mm) and into three groups of ST-segment deviation resolution (complete: >70% resolution; partial: >30% but <70% resolution; and no resolution: <30% resolution), as described previously.(10)

Data collection and follow-up

Patient characteristics were prospectively acquired on admission using either case record forms or using a computer-based database and patients were followed up for one year by use of hospital records, questionnaire and telephone contact. For patients who died during follow-up, hospital records and necropsy data were reviewed. Follow-up was performed by independent research nurses not involved in patient treatment. Study approval was obtained from the medical ethic committee from our institution and all patients gave informed consent.

Statistical Analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 16.0.1. Continuous data were expressed as mean ± standard deviation and categorical data as percentage, unless otherwise denoted. Differences between continuous data were performed by student's t test and the chi-square or Fisher's exact test was used as appropriate for dichotomous data. Multivariate Cox proportional-hazards regression analyses were performed to determine the independent association of elevated LDH on admission and 30-day- and 1-year mortality, selecting baseline variables with entry/stay criteria of $p<0.10$. Variables entered into the model included age, gender, diabetes mellitus, renal insufficiency, anterior infarction, Killip class >1, symptom onset to arrival PCI centre >6 hrs, three vessel disease, and elevated LDH on admission. Kaplan-Meier curves were constructed for 1-year mortality. For all analyses, statistical significance was assumed when the two-tailed probability value was <0.05.

Results

Baseline characteristics

During the study period 3393 patients were included, of whom 940 patients had LDH measurement >1 h after admission. The remaining 2453 patients form the basis of this report (figure 1). Of the 491 patients (20.0%) with elevated LDH on admission, CK-MB and troponin T were also positive in 72.1% and 85.7% of the patients. Baseline characteristics of the study group stratified by admission LDH are listed in table 1. Patients with elevated LDH were older, more often female, had a higher TIMI risk score and Killip class on admission. In the normal LDH group the diagnosis of STEMI was made more often in the ambulance compared to the elevated LDH group (75,1% vs 63,1%, $p<0.001$).

Elevated LDH was associated with a longer time from symptom onset to arrival PCI centre, and a longer ischemic time. However, in patients with less than 2 hours from symptom onset to arrival PCI centre, LDH was elevated in 14.6% of patients. The prevalence of elevated LDH on admission according to symptom onset to arrival PCI centre is depicted in figure 2.

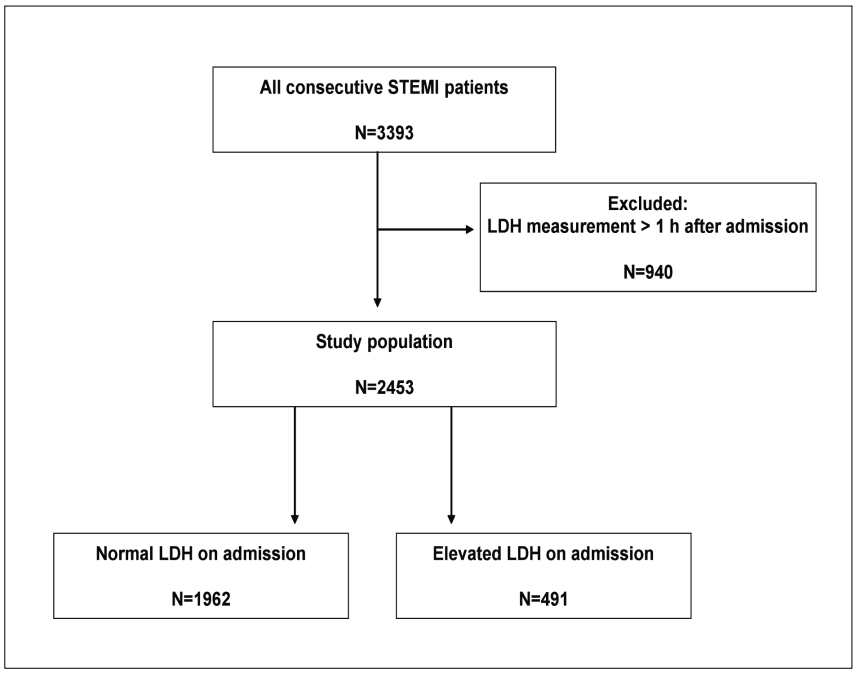

Figure 1: Flow-chart of the study population
Elevated LDH= LDH≥250 U/L.

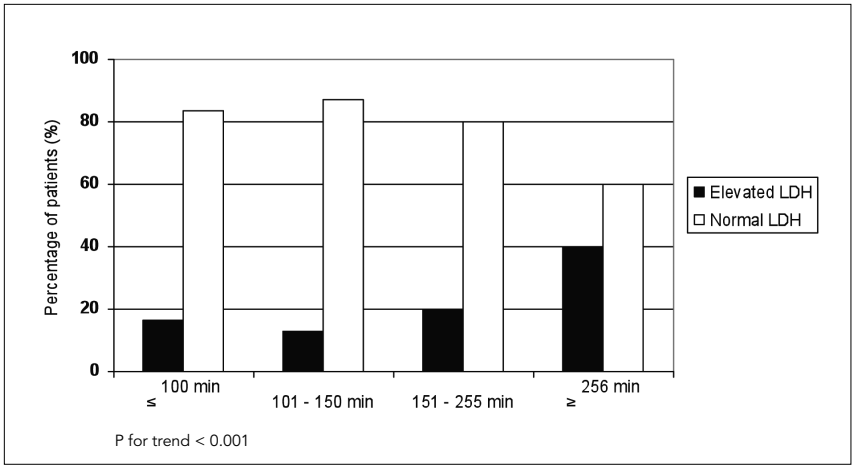

Figure 2: Distribution elevated/normal LDH on admission according to time from symptom onset to arrival PCI centre in quartiles

Table 1: Baseline characteristics of patients with and without elevated LDH

Baseline	Normal LDH N= 1962	Elevated LDH N= 491	P value
Age	63.1 ± 12.4	66.2 ± 12.9	<0.001
Female gender	483/1962 (24.6%)	167/491 (34.0%)	<0.001
Hypertension	681/1956 (34.8%)	201/490 (41.0%)	0.011
Smoking	794/1938 (41.0%)	174/488 (35.7%)	0.032
Diabetes Mellitus	226/1958 (11.5%)	69/490 (14.1%)	0.123
Previous MI	207/1955 (10.6%)	43/491 (8.8%)	0.231
Previous PCI	200/1956 (10.2%)	36/491 (7.3%)	0.052
Renal insufficiency	307/1959 (15.7%)	135/491 (27.5%)	<0.001
Timi risk > 3	603/1928 (31.3%)	267/485 (55.1%)	<0.001
Killip > 1 on admission	89/1959 (4.5%)	93/491 (18.9%)	<0.001
Diagnosis in ambulance	1471/1959 (75.1%)	310/491 (63.1%)	<0.001
SO to diagnosis, min (IQR)	83 (45 – 154)	144 (62 – 497)	<0.001
SO to arrival PCI centre, min (IQR)	140 (99 – 220)	217 (120 – 590)	<0.001
SO to arrival PCI centre > 6 hrs	172/1527 (11.3%)	154/436 (35.3%)	<0.001
Ischemic time, min	192 (145 – 296)	299 (183 – 734)	<0.001
Ischemic time > 180, min	886/1591 (55.7%)	275/366 (75.1%)	<0.001
Door to balloon time (min)	44 (29 – 70)	52 (35 – 88)	<0.001
Q wave on diagnosis ECG	440/1338 (32.9%)	176/308 (57.1%)	<0.001
Cum ST deviation on diagnosis ECG	13.3 ± 9.2	14.5 ± 11.9	0.093
GP IIb/IIIa pre-PCI	947/1934 (49.0%)	200/488 (41.0%)	0.002
Bail-out GP IIb/IIa	406/1934 (21.0%)	98/488 (20.1%)	0.658

Data are n/N (%) or mean (SD), or median (IQR). BMI=body mass index. MI=myocardial infarction. PCI=percutaneous coronary intervention. CABG=coronary artery bypass grafting. GFR= glomerular filtration rate. BP=blood pressure. SO=symptom onset. GP=glycoprotein. Renal insufficiency= creatinine clearance <60 ml/min (as calculated by MDRD).
Elevated LDH= LDH≥250 U/L

Table 2: Angiographic, electrocardiographic- and laboratory outcomes of patients with and without elevated LDH

Baseline	Normal LDH N=1962	Elevated LDH N=491	P value
Three vessel disease	351/1928 (18.2%)	96/458 (21.0%)	0.174
RCA	773/1827 (42.3%)	140/442 (31.7%)	<0.001
LAD	748/1827 (40.9%)	226/442 (51.1%)	<0.001
RCX	268/1827 (14.7%)	57/442 (12.9%)	0.340
Angiography performed	1937/1961 (98.8%)	461/491 (93.9%)	<0.001
Initial TIMI flow			0.013*
0,1	1056/1713 (23.1%)	265/389 (68.1%)	
2	261/1713 (15.2%)	54/389 (13.9%)	
3	396/1713 (23.1%)	70/389 (18.0%)	
PCI immediately after CAG	1641/1681 (97.6%)	372/391 (95.1%)	0.008
Thrombus aspiration	346/1921 (18.0%)	89/466 (19.1%)	0.585
IABP	107/1921 (5.6%)	82/466 (17.6%)	<0.001
TIMI post-PCI			<0.001*
0	25/1677 (1.5%)	8/387 (2.1%)	
1	6/1677 (0.4%)	9/387 (2.3%)	
2	65/1677 (3.9%)	39/387 (10.1%)	
3	1581/1677 (94.3%)	331/387 (85.5%)	
TIMI 0-2 (no-reflow)	96/1677 (5.7%)	56/387 (14.5%)	<0.001
MBG			<0.001*
0	32/1211 (2.6%)	20/223 (9.0%)	
1	111/1211 (9.2%)	50/223 (22.4%)	
2	415/1211 (34.3%)	68/223 (30.5%)	
3	653/1211 (53.9%)	85/223 (38.1%)	
MBG 0-1	143/1211 (11.8%)	70/223 (31.4%)	<0.001
Electrocardiographic			
ST resolution diagnosis 1 h after PCI			<0.002
Complete	306/544 (56.3%)	35/95 (36.8%)	
Partial	140/544 (25.7%)	33/95 (34.7%)	
No	98/544 (18.0%)	27/95 (28.4%)	
Residual ST deviation 1 h	4.8 ± 6.3	6.7 ± 5.7	<0.001

Partial	140/544 (25.7%)	33/95 (34.7%)	
No	98/544 (18.0%)	27/95 (28.4%)	
Residual ST deviation 1 h after angiography/PCI	4.8 ± 6.3	6.7 ± 5.7	<0.001
Residual ST deviation > 3mm 1 h after angiography/PCI	433/959 (45.2%)	137/205 (66.8%)	<0.001
Laboratory outcomes			
First CK positive**	480/1962 (24.5%)	377/491 (76.8%)	<0.001
First CK-MB positive***	403/1962 (20.5%)	354/491 (72.1%)	<0.001
First trop T positive****	700/1925 (36.4%)	372/434 (85.7%)	<0.001

Data are n/N (%) or mean (SD). TIMI=thrombolysis in myocardial infarction. ACT=activated clotting time. UFH=unfractionated heparin. PCI=percutaneous coronary intervention. CAG=coronary angiography. IABP=intra aortic balloon pump. MBG=myocardial blush grade. Hb=hemoglobin. CK=creatine kinase. CK-MB=creatine kinase myocardial band.
*=p for trend
** First CK positive= >200
*** First CK-MB positive= >6% of CK, when CK>200
**** First trop T positive= >0.05
Elevated LDH= LDH≥250 U/L

Angiographic- and electrocardiographic outcome

In table 2 angiographic and electrocardiographic outcome is shown. Post-PCI TIMI 3 flow and MBG 3 were both significantly lower in patients with elevated LDH (85.5% vs 94.3%, p<0.001 and 38.1% vs 53.9%, p<0.001). No-reflow occurred significantly more often in patients with elevated LDH on admission compared to patients with normal LDH (14.5% vs 5.7%, p<0.001). Furthermore, the admission ECG showed a higher degree of ST elevation and more often showed the presence of Q waves in patients with elevated LDH on admission. After PCI, the extent of residual ST segment deviation was also higher in this group.

Clinical outcome

Clinical outcome is summarized in table 3a. Elevated LDH was associated with a larger infarct size (median (IQR): 1899 (76 – 3640) vs 1150 (447 – 2460), p<0.001) and a higher 30-day MACE rate (18.6% vs 5.0%, p<0.001) as compared to patients with normal LDH on admission. Thirty day as well as 1-year mortality was significantly higher in patients with elevated LDH compared to patients with normal LDH on admission (30-day: 13.5% vs 1.7%, p<0.001, 1-year: 21.3% vs 4.4%, p<0.001).

Table 3a: Clinical outcomes in patients with and without elevated LDH

Baseline	Normal LDH N=1962	Elevated LDH N=491	P value
Peak CK	1150 (447 – 2460)	1800 (763-3640)	<0.001
30 day Outcome			
Death	32/1907 (1.7%)	64/474 (13.5%)	<0.001
Recurrent MI	28/1907 (1.5%)	10/474 (2.1%)	0.319
Death, recurrent MI or stroke	63/1907 (3.3%)	74/474 (15.6%)	<0.001
Urgent TVR	57/1907 (3.0%)	27/474 (5.7%)	0.004
MACE	95/1907 (5.0%)	88/474 (18.6%)	<0.001
30 day Safety			
Major or minor bleeding*	51/1907 (2.7%)	37/474 (7.8%)	<0.001
Major bleeding*	24/1907 (1.3%)	17/474 (3.6%)	<0.001
Minor bleeding*	27/1907 (1.4%)	20/474 (4.2%)	<0.001
Stroke	8/1907 (0.4%)	3/474 (0.6%)	0.466
1 year Outcome			
Death	74/1694 (4.4%)	88/413 (21.3%)	<0.001
Recurrent MI	43/1694 (2.5%)	12/413 (2.9%)	0.675
Death and/or MI	111/1694 (6.6%)	97/413 (23.5%)	<0.001

Data are n/N (%) or median (IQR). CK=creatine kinase.
TVR=target vessel revascularisation. MI=myocardial infarction. MACE=major adverse cardiac event.
* Non CABG-related bleeding
Elevated LDH= LDH≥250 U/L

Early Presenters

In those patients who presented within 2.5 hours (150 minutes, median time from onset of symptoms), admission LDH was elevated in 14.6% of patients. Also these early presenting patients had a significantly higher 30-day- and 1-year mortality as compared to the group of early presenters with normal LDH (16.1% vs 1.7%, and 23.0% vs 5.1%,both p<0.001, table 3b and figure 3).

Multivariate predictors of 30-day and 1-year mortality

In the multivariate analysis (table 4), adjustments were made for age, gender, diabetes mellitus, renal insufficiency, time from symptom onset to arrival PCI centre >6 hrs, Killip class >1, anterior infarction, three vessel disease, and elevated LDH on admission. Independent predictors of 30-day mortality were age (HR 1.04, 95% CI

Table 3b: Clinical outcomes in patients with and without elevated LDH according from symptom onset (SO) to arrival PCI centre

	SO - arrival PCI centre > median			SO - arrival PCI centre ≤ median		
	Normal LDH N=667	Elevated LDH N=289	P value	Normal LDH N=860	Elevated LDH N=147	P value
30 day Outcome						
Death	1.7%	12.1%	<0.001	1.7%	16.1%	<0.001
Recurrent MI	0.8%	1.4%	0.467	2.0%	3.5%	0.384
Death, recurrent MI or stroke	2.3%	13.1%	<0.001	3.6%	20.3%	<0.001
Urgent TVR	2.0%	5.3%	0.007	3.5%	7.0%	0.046
MACE	3.6%	16.3%	<0.001	5.9%	23.1%	<0.001
1 year Outcome						
Death	4.3%	20.7%	<0.001	5.1%	23.0%	<0.001
Recurrent MI	2.1%	2.5%	0.771	3.2%	3.2%	1.000
Death and/or MI	5.9%	22.3%	<0.001	8.0%	25.4%	<0.001

Median=150 minutes.
Data are n/N (%) or median (IQR). TVR=target vessel revascularisation. MI=myocardial infarction. MACE=major adverse cardiac event.
Elevated LDH= LDH≥250 U/L. SO=symptom onset.

Table 4: Independent determinants of 30-day mortality

Univariate:

	Hazard rate	95% CI	P value
Age	1.04	[1.02 – 1.07]	0.002
Female gender	0.59	[0.32 – 1.06]	0.076
Killip > 1	2.65	[1.47 – 4.76]	<0.001
Three vessel disease	1.82	[1.07 – 3.11]	0.028
Diabetes Mellitus	1.19	[0.61 – 2.34]	0.605
Renal insufficiency	2.20	[1.25 – 3.86]	0.006
Elevated LDH	6.28	[3.55 – 11.12]	<0.001
Anterior infarction	0.98	[0.58 – 1.66]	0.944
SO-arrival > 6 hrs	0.54	[0.26 – 1.12]	0.10

Multivariate:

	Hazard rate	95% CI	P value
Age	1.07	[1.05 – 1.09]	<0.001
Female gender	1.21	[0.78 – 1.87]	0.395
Killip > 1	8.24	[5.45 – 12.46]	<0.001
Three vessel disease	2.87	[1.81 – 4.53]	<0.001
Diabetes Mellitus	1.75	[1.05 – 2.92]	0.032
Renal insufficiency	5.25	[3.52 – 7.84]	<0.001
Elevated LDH	8.51	[5.57 – 13.01]	<0.001
Anterior infarction	1.21	[0.76 – 1.91]	0.430
SO-arrival > 6 hrs	1.55	[0.93 – 2.59]	0.093

Elevated LDH= LDH≥250 U/L. SO=symptom onset.

Table 5: Independent determinants of 1-year mortality

Univariate:

	Hazard rate	95% CI	P value
Age	1.07	[1.06 – 1.09]	<0.001
Female gender	1.27	[0.91 – 1.77]	0.162
Killip > 1	5.85	[4.15 – 8.25]	<0.001
Three vessel disease	2.73	[1.93 – 3.87]	<0.001
Diabetes Mellitus	1.85	[1.25 – 2.73]	0.002
Renal insufficiency	4.15	[3.04 – 5.66]	<0.001
Elevated LDH	5.44	[3.99 – 7.41]	<0.001
Anterior infarction	1.19	[0.84 – 1.68]	0.329
SO-arrival > 6 hrs	1.61	[1.08 – 2.38]	0.018

Multivariate:

	Hazard rate	95% CI	P value
Age	1.06	[1.01 – 1.04]	0.001
Female gender	0.65	[0.43 – 0.99]	0.046
Killip > 1	2.42	[1.54 –3.80]	<0.001
Three vessel disease	2.04	[1.39 – 3.00]	<0.001
Diabetes Mellitus	1.28	[0.80 – 2.05]	0.309
Renal insufficiency	2.01	[1.35 – 3.01]	0.001
Elevated LDH	3.42	[2.33 – 5.01]	<0.001
SO-arrival > 6 hrs	0.85	[0.53– 1.39]	0.524

Elevated LDH= LDH≥250 U/L. SO=symptom onset.

1.02 – 1.07), Killip class >1 (HR 2.7, 95% CI 1.5 – 4.8), renal insufficiency (HR 2.2, 95% CI 1.3 – 3.9), three vessel disease (HR 1.8, 95% CI 1.1 – 3.1) and elevated LDH on admission (HR 6.3, 95% CI 3.6 – 11.1). Furthermore, elevated LDH was also an independent predictor for 1-year mortality (HR 3.4, CI 95%, 2.3 – 5.0) (table 5).

Discussion

The major finding of this analysis is that elevation of LDH may occur early after the onset of symptoms in patients with STEMI who are planned to undergo primary PCI. In addition, it was found that patients with elevated LDH on admission have worse angiographic (including no-reflow) and clinical outcome. Elevated LDH on admission was a strong and independent predictor of 30-day and 1-year mortality, despite timely primary PCI. Our data show that this occurs, irrespective whether they present early or late. To the best of our knowledge, these findings have not been published in previous reports.

Mechanism for worse outcome

Elevated LDH patients presented with a higher prevalence of several comorbid conditions including diabetes, hypertension and renal failure. They more often presented with signs of heart failure (Killip class >1), a higher TIMI risk score and a longer ischemic time than patients with normal LDH on admission. These clinical variables have a strong influence on outcome. However, after correction for these differences in baseline characteristics by multivariate analysis, elevated LDH on admission remained the strongest independent predictor of 30-day- and 1-year mortality.

Time dependence and elevated LDH

Patients with elevated LDH on admission have a worse outcome, irrespective whether they present early or late, as is shown by the Kaplan-Meier survival curve (figure 3).

The higher incidence of Q waves on presentation suggest that infarctions are older in the group with elevated LDH on admission, despite short standing symptoms: (14.6% of patients with elevated LDH presented within 2 hours and 30 minutes from symptom onset). However, Q waves were also present in 33% of patients who presented without elevation of LDH. This confirms the finding that also the presence of Q waves might occur early after the onset of symptoms as was found in a recent study(11) and confirms that a short duration of symptoms is not always associated with good outcome.

Another finding is that patients with elevated LDH on admission have a greater area at risk: they have a higher cumulative ST elevation on the admission ECG, more often have an anterior MI and more often present with heart failure. The larger the area at risk, the earlier the washout of cardiac enzymes will start, as was previously demonstrated.(12) All these characteristics are predictive of a reduced effectivity of myocardial reperfusion. De Luca and co-workers previously found that these patients have reduced myocardial blush and/or ST resolution despite successful epicardial revascularization.(13) This suggest that LDH elevation on admission is a simple marker predictive of poor reperfusion and consequently clinical outcome.

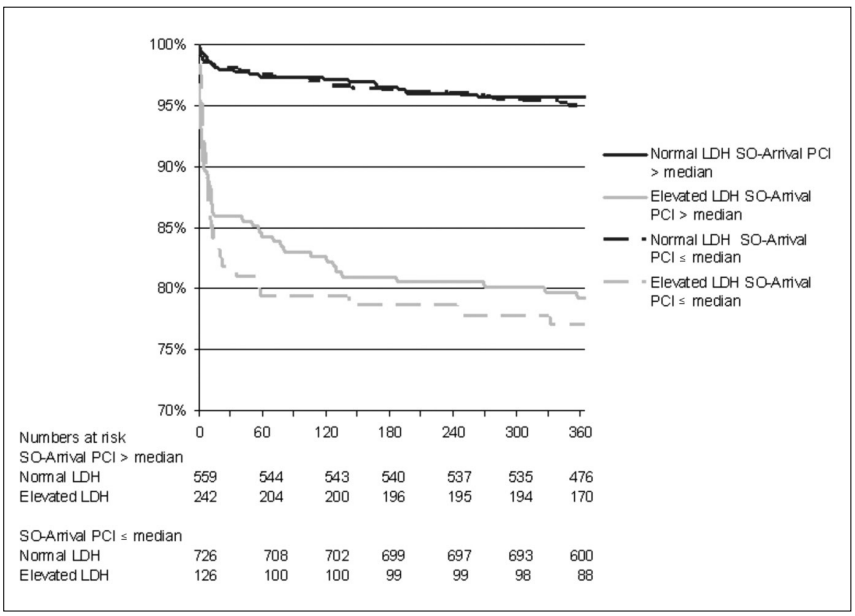

Figure 3: Time to event curves (Kaplan-Meier) for 1-year mortality in the 2 groups adjusted for symptom onset to arrival PCI centre >2 hours and 30 minutes (median).

Another explanation for the elevated cardiac enzymes despite relatively early presentation might be the fact that plaque instability occurred several days or weeks before occlusive coronary thrombosis. Repetitive embolization of activated thrombus might have induced small area's of necrosis before full coronary occlusion. Therefore one may speculate that patients who present with recent onset of symptoms but with already elevated LDH might have had episodes of plaque instability before coronary occlusion, as was shown previously by work from Rittersma and co-workers.(14) The same group also found that thrombus composition and thrombus age (>1 day) were associated with clinical outcome.(15)

Limitations

This study is a post hoc observational analysis of all consecutive STEMI patients enrolled at our institution, and therefore represents daily clinical practice. First, baseline characteristics between the two groups were not similar for all variables: this probably reflects a true difference between patients with and without elevated LDH on admission. Second, our study shows that time from symptom onset to arrival PCI centre is less important for the outcome of the patient than characteristics such as elevated LDH and hemodynamic variables. Furthermore, our data show that time from symptom onset is unreliable in STEMI patients. The onset of symptoms does not always represent the start of the infarction. So, symptom onset should be a less important criterion for decision-making-strategy in STEMI patients. However, some of the important consequences of time, such as early out-of-hospital death, are not represented in our data. Third, electrocardiographic outcomes were available in only 34% of the patients. Finally, LDH is slightly cardiospecific, however, in respectively 72.1% and 85.7% of the patients with elevated LDH on admission, CK-MB and troponin T were positive on admission.

Conclusion

Elevation of LDH may occur early after the onset of symptoms in patients with STEMI who are planned to undergo primary PCI. Irrespective of time from symptom onset to arrival PCI centre, STEMI patients with elevated LDH on admission have a poor angiographic and clinical outcome. Elevated LDH on admission was a strong and independent predictor of 30-day- and 1-year mortality. The exact mechanism why patients with LDH elevation on admission do much worse remains to be determined.

References

1. Ryan TJ, Antman EM, Brooks NH, Califf RM, Hillis LD, Hiratzka LF, Rapaport E, Riegel B, Russell RO, Smith EE 3rd, Weaver RD, Gibbons RJ, Alpert JS, Eagle KA, Gardner TJ, Garson A Jr, Gregoratos G, Smith SC Jr. 1999 update: ACC/AHA guidelines for the management of patients with acute myocardial infarction: executive summary and recommendations: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). Circulation 1999;100:1016-1030.
2. Grines CL, Browne KF, Marco J, Rothbaum D, Stone GW, O'Keefe J, Overlie P, Donohue B, Chelliah N, Timmis GC. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction: the Primary Angioplasty in Myocardial Infarction study group. N Engl J Med 1993;328:673-679.
3. Zijlstra F, Hoorntje JC, de Boer MJ, Reiffers S, Miedema K, Ottervanger JP, van 't Hof AW, Suryapranata H. Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1999;341:1413-1419.
4. Suryapranata H, van 't Hof AW, Hoorntje JC, de Boer MJ, Zijlstra F. Randomized comparison of coronary stenting with balloon angioplasty in selected patients with acute myocardial infarction. Circulation 1998;97:2502-2505.
5. Stone G, Grines CL, Cox AD, Garcia E, Tcheng JE, Griffin JJ, Guagliumi G, Stuckey T, Turco M, Carrol JD, Rutherford BD, Lansky AJ for the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) Investigators, Comparison of angioplasty with stenting with or without abciximab, in acute myocardial infarction. N Engl J Med 2002;346:957-966.
6. Nienhuis MB, Ottervanger JP, de Boer MJ, Dambrink JH, Hoorntje JC, Gosselink AT, Suryapranata H, van 't Hof AW; Zwolle Myocardial Infarction Study Group. Prognostic importance of creatine kinase and creatine kinase-MB after primary percutaneous coronary intervention for ST-elevation myocardial infarction. Am Heart J 2008;155:673-679.
7. Schumann G, Bonora R, Ceriotti F, Clerc-Renaud P, Ferrero CA, Ferard G, Franck PF, Gella FJ, Hoelzel W, Jorgensen PJ, Kanno T, Kessner A, Klauke R, Kristiansen N, Lessinger JM, Linsinger TP, Misaki H, Panteghini M, Pauwels J, Schimmel HG, Vialle A, Weidemann G, Siekmann L. IFCC Primary Reference Procedures for the Measurement of Catalytic Activity Concentrations of Enzymes at 37°C - Part 3. Reference procedures for the measurement of catalytic concentrations of lactate dehydrogenase. Clin Chem Lab Med 2002;40:643-648.
8. TIMI study group. The Thrombolysis In Myocardial Infarction (TIMI) trial. Phase I findings. N Engl J Med 1985;312:932-936.
9. van 't Hof AW, Liem AL, Suryapranata H, Hoorntje JC, de Boer MJ, Zijlstra F. Angiographic assessment of myocardial infarction in patients treated with primary angioplasty for acute myocardial infarction: myocardial blush grade. Zwolle Myocardial Infarction Study Group. Circulation 1998;97:2302-2306.
10. van 't Hof AW, Liem AL, de Boer MJ, Zijlstra F, on behalf of the Zwolle Myocardial Infarction Study Group. Clinical value of 12-lead electrocardiogram after successful reperfusion therapy for acute myocardial infarction. Lancet 1997;350:615-619.
11. Armstrong PW, Fu Y, Westerhout CM, Hudson MP, Mahaffey KW, White HD, Todaro TG, Adams PX, Aylward PEG, Granger CB. Baseline Q-waves surpasses time from symptom onset as a prognostic marker in ST-segment elevation myocardial infarction patients treated with primary coronary intervention. J Am Coll Cardiol 2009;53:1503-1509.
12. Rasoul S, Nienhuis MB, Ottervanger JP, Slingerland RJ, de Boer MJ, Dambrink JH, Ernst NM, Hoorntje JC, Gosselink AT, Suryapranata H, Zijlstra F, van 't Hof AW. Predictors of elevated cardiac troponin T on admission in ST-segment elevation myocardial infarction. Ann Clin Biochem 2006;43:281-286.
13. de Luca G, van 't Hof AW, de Boer MJ, Hoorntje JC, Gosselink AT, Dambrink JH, Ottervanger JP, Zijlstra F, Suryapranata H. Impaired myocardial perfusion is a major explanation of the poor outcome observed in patients undergoing primary angioplasty for ST-segment elevation myocardial infarction and signs of heart failure. Circulation 2004;109:958-961.
14. Rittersma SZ, van der Wal AC, Koch KT, Piek JJ, Henriques JP, Mulder KJ, Ploegmakers JP, Meesterman M, de Winter RJ. Plaque instability frequently occurs days or weeks before occlusive coronary thrombosis: a pathological thrombectomy study in primary percutaneous coronary intervention. Circulation 2005;111:1160-1165.
15. Kramer MC, van der Wal AC, Koch KT, Ploegmakers JP, van der Schaaf RJ, Henriques JP, Baan J Jr, Rittersma SZ, Vis MM, Piek JJ, Tijssen JG, de Winter RJ. Presence of older thrombus is an independent predictor of long-term mortality in patients with ST-elevation myocardial infarction treated with thrombus aspiration during primary percutaneous coronary intervention. Circulation 2008;118:1810-1816.

Summary, conclusions, and future perspectives

Nederlandse samenvatting

Summary and conclusions

This thesis addresses two important unfavourable events (bleeding, and sub-optimal procedural results) during and after primary PCI in STEMI patients. The goals of this thesis were to identify patients who are at risk for these complications, to call attention for better bleeding risk stratification and to search for improvements of (pharmacological) therapy to prevent them from these complications.

In **chapter 1**, a brief introduction about the subject and the background of the thesis is given. Bleeding is currently seen as the most important non-cardiac complication of primary PCI. Sub-optimal angiographic result remains the "Achilles heel" of primary PCI. Since bleeding and sub-optimal angiographic results are associated with poor short- and long-term adverse outcomes, it is explained that more research is mandatory in trying to prevent these complications.

In **chapter 2**, the current treatment of STEMI is summarized. In patients with STEMI, timely and adequate treatment, after a fast diagnosis, improves the prognosis dramatically. Restoration of the infarct vessel patency is one of the cornerstones of initial treatment. Compared to fibrinolytic therapy, primary PCI results in an improved short-term and long-term survival, a lower incidence of recurrent infarction and a better left ventricular function. Although (drug-eluting) stents reduce re-stenosis, effects on mortality are less clear. Additional randomised trials should determine the most optimal combination of antithrombotic and antiplatelet agents given pre-hospitally in the ambulance, during primary PCI and the duration of antiplatelet therapy after primary PCI.

The first part of this thesis describes the incidence, predictors and prevention of bleeding in patients who underwent primary PCI.
In **chapter 3** the incidence, predictors and prognostic importance of bleeding after primary PCI is assessed in a prospective, large single-centre, observational cohort study. 80 patients (1.6%) had a major bleeding, whereas minor bleeding was observed in 266 patients (5.6%). Killip class >1 on admission was an independent predictor of major bleeding. Major bleeding (HR 3.5 (95% CI 2.3 – 5.4)) was associated with increased one-year mortality. This study emphasizes that, although relatively infrequent, major bleeding complications during or after primary PCI are strongly and independently related to short- and midterm mortality.

Additional studies on bleeding where performed, using sub-analyses of the Ongoing Tirofiban in Myocardial Infarction (On-TIME 2) trial, which was conducted to assess potential benefit of pre-hospital initiated high dose tirofiban on top of a loading dose of aspirin, high dose clopidogrel and heparin.

Chapter 4 addresses the risk of bleeding after pre-hospital administration of tirofiban, on top of aspirin, clopidogrel and heparin, in STEMI patients planned to undergo primary PCI. Bleeding (major or minor) was observed in 47 patients (3.7%), with 13 patients (1%) having a major bleeding. Strong independent determinants of bleeding were age (OR 1.05, 95% CI 1.01 – 1.08, p=0.011), Killip class >1 on admission (OR 2.5, 95% CI 1.2 – 5.3, p=0.020) and intra aortic balloon pump (IABP) use (OR 4.2, 95% CI 1.6 – 11.1, p=0.003).
High dose tirofiban was not an independent predictor of bleeding (OR 1.7, 95% CI 0.9 – 3.2, p=0.116). Bleeding was associated with an increased risk of 30-day mortality (HR 5.5, 95% CI 1.6 – 7.8, p<0.001) and one-year mortality (HR 3.2, 95% CI 1.4 – 7.2, p=0.005).
These findings show that pre-hospital use of high dose tirofiban is safe and associated with a low risk of bleeding. Age, Killip class >1, IABP use, but not high dose tirofiban are independent determinants of bleeding in STEMI patients. Bleeding is independently associated with 30-day and 1-year mortality.

It is yet not clear whether high dose tirofiban in STEMI is also beneficial and safe in patients with a high risk of bleeding. Therefore, in **chapter 5**, an additional analysis of the On-TIME 2 trial evaluated the net clinical benefit of early pre-hospital initiation of tirofiban in patients at high risk of bleeding, using the CRUSADE bleeding risk score.
It concerned a retrospective sub-analysis of the On-TIME 2 trial. According to CRUSADE, patients with a moderate to very high baseline risk of bleeding were defined as high risk and patients with a very low- or low risk baseline bleeding risk were defined as low risk. Primary endpoint was net adverse clinical events (NACE) at 30 days. Of 1309 patients, a high bleeding risk was present in 291 patients (22.2%). In these high risk bleeding patients, tirofiban significantly improved ST segment resolution after primary PCI. Administration of tirofiban in high risk bleeding patients did not affect the 30-day incidence of major adverse cardiac events significantly (MACE) (9.4% vs 13.0%, p=0.330, RR 0.72, 95% CI 0.37 – 1.39). However, pre-treatment with tirofiban was associated with a non-significant increase in non CABG-related bleeding (8.6% vs 3.6%, p=0.082, RR 2.38, 95% CI 0.90 – 6.39). The net clinical effect (30-day NACE) of tirofiban in this group was balanced (11.5% vs 15.2%, p=0.365, RR 0.76, 95% CI 0.41 – 1.38).
It is concluded that pre-hospital use of tirofiban in STEMI patients with high risk of bleeding results in a balanced effect of 30-day NACE.

Chapter 6 describes the impact of age on effects of pre-hospital administration of tirofiban before primary PCI. Of the 466 patients in the highest tertile (≥68 years),

median age was 74.4 years (IQR 71.3–78.6 years) and 231 (50%) were randomised to tirofiban.
Mean residual ST segment deviation 1 hour after PCI was significantly lower in elderly patients pre-treated with tirofiban compared to elderly patients without tirofiban pre-treatment (4.2±5.2 mm vs 6.4±7.5 mm, p=0.001). Furthermore, elderly patients pre-treated with tirofiban had a non-significantly higher rate of 30-day major or minor bleeding compared to elderly patients without tirofiban pre-treatment (14.2% vs 9.0%, p=0.088). 30-day net adverse clinical events in elderly patients with- or without tirofiban was not significantly different (11.9% vs 15.2%, p=0.300).
It is concluded that the effect of pre-hospital initiation of high bolus dose tirofiban on myocardial reperfusion is highest in the elderly patients. However, this was associated with a trend towards more bleeding complications, resulting in a balanced net clinical effect after 30-day follow-up.

The therapeutic effects of a pre-hospital fixed heparin bolus dose in consecutive patients with STEMI on activated clotting time is addressed in **chapter 7**. Of the 1533 patients, 216 patients (14.1%) had an ACT within the therapeutic range, 82.3% of the patients had a too low ACT, whereas 3.5% of the patients had a too high ACT. After multivariable analysis, the only independent predictor of a too low ACT was increased weight (OR 1.02 / kg, 95% CI 1.01 – 1.03, p=0.001). Patients with a too low ACT had less often an open infarct related vessel (initial TIMI flow 2,3) as compared to patients with an ACT in range (36.5% vs 45.9%, p=0.013).
This study shows that in only a minority of patients with STEMI, pre-hospital treatment with a fixed bolus dose unfractionated heparin is within the therapeutic ACT range. Increased weight is an independent determinant of a too low ACT. This study strongly recommends weight adjusted administration of unfractionated heparin in the ambulance.

In **chapter 8** we performed a randomised comparison between a closure device and manual compression to prevent access-site related bleeding in patients who underwent (primary) PCI, and had a high risk of bleeding. A total of 313 patients (49.9%) were randomised to the closure device and 314 patients (50.1%) to manual compression. The combined primary endpoint was 2.6% in the closure device group compared to 4.5% in the manual compression group (p=0.195). However, in the pre-defined subgroup of patients with a history of hypertension the combined primary endpoint (0.8% vs. 7.2%, p=0.008) was significantly reduced after use of the closure device. This trial does not show the superiority of using a closure device over manual compression in patients, treated with triple antiplatelet therapy, who underwent PCI.

The second part of this thesis focuses on the incidence, and pharmacologic mechanisms to prevent sub-optimal procedural outcome during primary PCI. **Chapter 9** addresses the outcome of patients who received bail-out study medication and evaluated whether early pre-hospital use of tirofiban may reduces PCI complications (need for bail-out study medication during or after primary PCI) in STEMI patients.

This was a pre-specified analysis of the On-TIME 2 trial. 984 patients were randomised to high dose tirofiban (HDT) or placebo. In the subgroup of patients who received blinded bail-out treatment, we compared patients who were pre-treated with placebo and received bail-out high dose tirofiban (HDT bail-out) to those who were pre-treated with HDT and received bail-out placebo (Placebo bail-out). Blinded bail-out use of study medication was used in 24% (237/980) of patients, with a higher rate in patients pre-treated with placebo: 29% (140/492) vs 20% (97/488), p=0.002. Bail-out versus no bail-out use of study medication was associated with more residual ST deviation (5.5±7.2 vs 3.7±4.8mm, p=0.005), and worse clinical outcome (MACE 30 days 12.2% vs 5.6%, p<0.001), mainly due to poor outcome in the patients who received HDT bail-out. In patients who were pre-treated with HDT but received placebo bail-out study medication, residual ST deviation and clinical outcome did not differ significantly compared to patients who did not receive bail-out medication (4.0±4.6 vs.3.7± 4.8mm, p=0.703, MACE 7.2% vs 5.6%, p=0.535).

It is concluded that routine pre-treatment is superior to provisional use of high dose tirofiban in patients with STEMI.

Chapter 10 describes upfront versus provisional (bail-out) use of high dose tirofiban in a large real world population of non-selected STEMI patients. Patients who were treated routinely upfront with high dose tirofiban before first balloon inflation were compared with patients who received the drug on a provisional basis, after first balloon inflation. Intitial patency was higher in patients with routine upfront tirofiban therapy (22.3% vs 17.9%, p=0.006). Enzymatic infarct size was smaller (1401 IU/L (IQR 609-2948) vs 1620 (753-3132), p=0.03) and the combined incidence of death or recurrent myocardial infarction at 30 days occurred less often in the routinely treated group (3.3% vs 5.1%, p=0.04). After multivariate analysis, upfront high dose tirofiban was an independent predictor of initial patency (OR 1.47, 95% CI 1.15-1.88, p=0.02), enzymatic infarct size (OR 0.70, 95% CI 0.56-0.86, p=0.001) and 30-day death or recurrent myocardial infarction (OR 0.59, 95% CI 0.37-0.95, p=0.03). This registry of non-selected primary PCI patients demonstrates that routine upfront tirofiban therapy improves initial patency of the infarct related vessel, reduces myocardial infarct size and improves clinical outcome as compared to a strategy of provisional use after primary PCI.

The effect of early initiation of high bolus dose tirofiban on top of dual antiplatelet therapy on angiographic outcome before and after primary PCI in STEMI patients is outlined in **chapter 11**. This was a pre-specified angiographic analysis of the On-TIME 2 trial (N=984) and its open label run-in phase (N=414). All angiographic parameters, including quantitative coronary angiography (QCA) were performed in an independent angiographic corelab.

Of the 1398 patients, 709 patients (50.7%) were randomised to pre-hospital tirofiban. An open infarct related vessel (TIMI 2 or 3 flow) at initial angiography was more often present in the tirofiban group as compared to the no tirofiban group (58.3% vs 49.7%, p=0.002). Tirofiban also reduced initial thrombus burden (p for trend=0.035) as well as thrombus grade 5 (46.9% vs 54.3%, p=0.016) and showed a trend toward a reduction in large thrombus burden (LTB) (69.4% vs 74.5%, p=0.055). After PCI, a trend towards a lower corrected TIMI frame count (cTFC) in the tirofiban group was found. A significant interaction was found with time of initiation of study drug, with highest efficacy of tirofiban when given within 76 minutes after symptom onset, with a significantly lower cTFC after PCI (21.9 ± 17.6 vs 23.9 ± 18.5, p=0.008, p for interaction p=0.006). This study demonstrates that in patients undergoing primary PCI, pre-hospital administration of tirofiban reduces initial thrombus burden and improves initial patency of the infarct related vessel before PCI. Initiation of tirofiban seems to be most effective when given very early after the onset of symptoms, however, this finding needs confirmation in other studies.

The impact of elevated lactate dehydrogenase (LDH) on admission on angiographic- and clinical outcome in STEMI is addressed in **chapter 12**. Elevation of LDH on admission is often used as a sign of late presentation, however, only few studies evaluated the relationship between LDH elevation and time of presentation.

The aim of this large scale, prospective, observational single-centre study was to evaluate the relationship between elevated LDH on admission and time from onset of symptoms in patients with STEMI treated with primary PCI. In addition, the association between elevated LDH and angiographic and clinical outcome was assessed. LDH was measured upon arrival in the PCI centre. Elevated LDH was present in 20.0% (491/2453) of patients. In patients with less than 2 hours and 30 minutes of symptoms, LDH was elevated in 14.6% of patients. Patients with elevated LDH were older, more often female, had a higher TIMI risk score and Killip class on admission. Elevated LDH on admission was associated with poor angiographic and clinical outcome. At multivariate analyses, elevated LDH on admission remained a strong predictor of 30-day (HR 6.3, CI 95%, 3.6–11.1) and 1-year mortality (HR 3.4, CI 95%, 2.3–5.0) independent of time from the onset of symptoms.

This study shows that elevation of LDH may occur early after the onset of symptoms

in patients with STEMI who are planned to undergo primary PCI and is associated with poor angiographic and clinical outcome, irrespective of time from symptom onset. Elevated LDH on admission is a strong and independent predictor of short and long-term mortality.

Future perspectives and directions to prevent bleeding

Bleeding risk score

Baseline prediction of bleeding risk can complement ischemic risk prediction, and optimise medical- or invasive strategies for ACS by making judicious treatment selections, and carefully dose antithrombotic medications use. The CRUSADE bleeding risk score to predict in-hospital major bleeding has been generally validated in NSTEMI patients(1), and found to be useful in another cohort of NSTEMI patients.(2) This score was found to perform consistently across the post admission treatment subgroups (eg, invasive care, use of antiplatelet and/or anticoagulants) in patients with NSTEMI. However, the CRUSADE bleeding risk score to predict in-hospital major bleeding has not been validated in STEMI patients yet.

Bleeding definition

The varying definitions of bleeding used in clinical studies to date have made it difficult to compare the safety of available agents. The recent Bleeding Academic Research Consortium standardized approach to capturing bleeding information represents a first step in closing the knowledge gap, which will need prospective validation in future studies.(3)

Antithrombotic therapy

Antithrombin agents and glycoprotein IIb/IIIa inhibitors are frequently overdosed in elderly patients, patients with renal failure and in women with ACS.(4) This overdosing is in turn associated with increased bleeding. Bivalirudin and fondaparinux are anticoagulants that are associated with less bleeding compared with unfractionated heparin and enoxaparin with or without glycoprotein IIb/IIIa inhibitors, and are noninferior with respect to ischemic outcomes when used for the management of ACS.(5) Fondaparinux is associated with an improved survival in NSTEMI,(6) and bivalirudin alone as compared to UFH and GPI in STEMI patients improved clinical outcome and reduced bleeding.(7) However, in this study, bleeding in the UFH/GPI group was very high. Whether pre-hospital treatment with bivalirudin will further improve net clinical benefit, should be awaited from the ongoing EUROMAX trial.(8)

Use of LMWH in patients with STEMI may result in a higher frequency of anticoagu-

lation within the therapeutic range, possibly resulting in a reduction of ischemic events.(9,10)

Recommendations for improvement when using unfractionated heparin

The current ESC guidelines recommend for STEMI patients who are candidates for primary PCI an i.v. UFH bolus with a starting dose of 100 IU/kg weight (60 IU/kg if GPI's are used) (2). However, we observed after reviewing ambulance protocols from different countries, including the Netherlands, Belgium, Germany and UK, that in daily clinical practice a fixed bolus dose of UFH in the pre-hospital setting is used, probably due to practical reasons. Our results confirm that a weight adjusted dosing of UFH may improve anticoagulation level.

Antiplatelet therapy

High on-treatment platelet reactivity, despite dual antiplatelet therapy, is associated with atherothrombotic events following coronary stent implantation.(11)
Clopidogrel has an important interindividual variability in efficacy, especially in STEMI patients.(12) Therefore, new P2Y12 antagonists (prasugrel and ticagrelor), are beneficial as compared to clopidogrel, due to a faster, and less variable and more complete platelet inhibition.(13,14) However, an important side effect of potent platelet inhibition with these agents may be bleeding. Possibly, by using a POPular risk score a more 'tailored' medical antiplatelet therapy can be given in patients who underwent PCI.(15)

Radial approach

For STEMI patients who undergo PCI as a revascularization strategy, a significant proportion of bleeding events is related to the vascular access site. A recently published meta-analysis of radial versus femoral approach revealed that the greatest absolute benefit for radial approach appeared in the setting of primary angioplasty for STEMI.(16) This is confirmed lately in a subgroup of STEMI patients in the RIVAL study.(17)
Furthermore, a radial approach for PCI in elderly patients (≥75 years) seems effective in reducing bleeding complications.(18) Whether a radial approach in high risk bleeding patients will decrease bleeding, is unknown. However, the femoral approach is still preferred in hemodynamic unstable patients who need an IABP or Impella. Another consideration is the radiation dose exposure for the operator, which is increased when using a radial approach as compared to a femoral approach.(19) So there is a need for further research to support this approach in these patients.

Closure device

Several trials, including our ANGIOCARE trial, showed that a closure device did not

reduce the access-site related (bleeding) complications. Therefore, the main advantage of a closure device may be patient comfort with shorter bed rest and immobilization. However, with regard to the safety of the puncture procedure, there is still debate about the possible adjunctive role of fluoroscopy or an echographic-guided puncture for obtaining arterial access to reduce local vascular access complications.
Furthermore, red cell transfusion should be used judiciously until further randomized data are available.

Future perspectives and directions to prevent sub-optimal procedural results

Timely reperfusion

Primary PCI can guarantee restoration of antegrade flow, but can not avoid myocardial necrosis. Thus the aim in the treatment of STEMI would be to improve the rate of abortion of STEMI and to reduce the extension of myocardial necrosis, by a fast diagnosis (primary PCI should be implemented within 120 minutes of first medical contact), and early drug administration and transportation to a primary PCI centre. (20)
Despite the high rate of TIMI 3 flow that can be achieved with mechanical reperfusion, myocardial perfusion is sub-optimal in some patients. All efforts should be aimed at reducing ischemia-reperfusion damage and protecting microcirculation from distal embolization, to prevent dissection and no-reflow.

Embolic protection devices

The use of combined proximal embolic protection and thrombus aspiration during primary PCI did not translate into a clinically relevant smaller infarct size and less impairment of the left ventricular function at follow-up.(21) Recent data did not show any benefit of the use distal embolic protection devices in patients with STEMI on surrogate end points, intermediate or clinical outcomes.(22,23)

Thrombus aspiration

Recent data revealed the benefit of the use of a thrombus aspiration device (Export, Medtronic, Santa Rosa, CA, USA) in the setting of STEMI.(24) Certain subgroups of patients with STEMI have been identified to benefit from thrombus aspiration (eg. high thrombus burden, right coronary artery-related STEMI), however, maybe other patients subsets, may also benefit from thrombus aspiration. Future randomised trials should confirm this.

Timing of administration of antiplatelet drugs

The TRITON-TIMI 38 study demonstrated a significant reduction in primary outcome with prasugrel (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) as compared with clopidogrel in patients with STEMI referred for primary PCI.(25) Ticagrelor, a reversible ADP receptor antagonist, is fast acting and provides high inhibition of platelet aggregation. A subgroup analysis of PLATO showed a significant reduced primary endpoint (cardiovascular death, myocardial infarction or stroke) in patients with STEMI who received ticagrelor compared to clopidogrel. (26) Neither TRITON-TIMI 38 nor PLATO employed a clopidogrel regimen which included a loading dose higher than 300mg, and the vast majority of patients were administered the loading dose during PCI. Further clarity is necessary concerning the comparative effectiveness of prasugrel and ticagrelor alongside higher doses of clopidogrel. Triple antiplatelet therapy including GPI's initiated just prior to PCI is currently recommended by the ESC and ACC/AHA guidelines.

Early pre-hospital GPI or bivalirudin use and Bail-out use of GPI

This thesis clearly shows that bail-out use of GPI is associated with poor outcome and has never been shown to improve outcome, whereas it may increase bleeding complications. Antiplatelet therapy should be given routinely before PCI and should not be reserved for treatment of complications post-PCI.

Based on the findings of the BRAVE-3 trial and FINESSE trial, pre-hospital administration of GPI's is not recommended by the current ESC guidelines. However, as demonstrated by On-TIME 2, which has been confirmed by the results of the EGYPT meta-analysis(27), and a sub-analysis of FINESSE(28), there is a trend in support of early pre-hospital administration of GPI versus late GPI administration (pre-PCI).

Instead of early use of GPI combined with UFH, early use of bivalirudin might be an alternative. As mentioned, bivalirudin alone as compared to UFH and GPI in STEMI patients improved clinical outcome and reduced bleeding.(7) However, in this study, bleeding in the UFH/GPI group was very high. Whether pre-hospital treatment with bivalirudin will further improve net clinical benefit, should be awaited from the ongoing EUROMAX trial.(8)

References

1. Subherwal S, Bach RG, Chen Ay, Gage BF, Rao SV, Newby LK, Wang TY, Gibler WB, Ohman EM, Roe MT, Pollack CV Jr, Peterson ED, Alexander KP. Baseline risk of major bleeding in Non-ST-elevation myocardial infarction. Circulation 2009;119:1873-1882.
2. Abu-assi E, Gracia-Acuna JM, Ferreira-Gonzalez I, Pena-Gil C, Gayoso-Diz P, Gonzalez-Juanatey JR. Evaluating the performance of the can rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the ACC/AHA Guidelines (CRUSADE) bleeding score in a contemporary Spanish cohort of patients with Non-ST segment elevation acute myocardial infarction. Circulation 2010;121:2419-2426.
3. Steg PG, Huber K, Andreotti F, et al. Bleeding in acute coronary syndromes and percutaneous coronary interventions: position paper by the Working Group on Thrombosis of the European Society of Cardiology. Eur Heart J 2011; doi:10.1093/eurheartj/ehr204.
4. Alexander KP, Chen AY, Roe MT, et al. Excess dosing of antiplatelet and antithrombin agents in the treatment of non-ST segment elevation acute coronary syndromes. JAMA 2005;294:3108-3116.
5. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction): developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. Circulation 2007;116:e148-304.
6. Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators, Yusuf S, Mehta SR, Chrolavicius S, et al. Comparison of Fondaparinux and Enoxaparin in Acute Coronary Syndromes. N Engl J Med 2006;354:1464-76.
7. Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med 2008;358:2218-30.
8. Steg PG, Hamm C, Goldstein P, et al, for the EUROMAX investigators. European Ambulance Acute Coronary Syndrome Angiox Trial: EUROMAX. http://clinicaltrials.gov/ct2/show/NCT01087723
9. Montalescot G, Cohen M, Goldstein P, et al, for the ATOLL investigators. Acute STEMI Treated with primary angioplasty and intravenous enoxaparin Or UFH to Lower ischemic and bleeding events at short- and Long-term follow-up trial. ESC, Stockholm, August 30 2010, Hotline session.
10. Brieger D, Collet JP, Silvain J, et al. Heparin or enoxaparin anticoagulation for primary percutaneous coronary intervention. Catheter Cardiovasc Interv 2011;77:182-190.
11. Breet NJ, van Werkum JW, Bouman HJ, et al. Comparison between platelet function tests in predicting clinical outcome in patients undergoing coronary stent placement. JAMA 2010;303:754-762.
12. Heestermans AA, van Werkum JW, Taubert D, et al. Impaired bioavailability of clopidogrel in patients with a ST-segment elevation myocardial infarction. Thromb Res 2008;122:776-781.
13. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001-15.
14. Wallentin L, Becker RC, Budaj AJ, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045-1057.
15. Breet NJ, van Werkum JW, ten Berg, et al. Nieuwe opties in antiplaatjestherapie. Hart Bulletin 2011;3:55-61.
16. Jolly SS, Amlani S, Hamon M, Yusuf S, Phil D, Mehta SR. Radial versus femoral access for coronary angiography or intervention and the impact of major bleeding and ischemic events: a systematic review and meta-analysis of randomized trials. Am Heart J 2009;157:132-140.
17. Jolly SS, Yusuf S, Cairns J, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. Lancet 2011;377:1409-1420.
18. Achenbach S, Ropers D, Kallert L, Turan N, Krähner R, Wolf T, Garlichs C, Flachskampf F, Daniel WG, Ludwig J. Transradial versus transfemoral approach for coronary angiography and intervention in patients above 75 years of age. Catheter and Cardiovasc Intervent 2008;72:629-635.
19. Lange HW, von Boetticher H. Randomized comparison of operator radiation exposure during coronary angiography and intervention by radial or femoral approach. Catheter Cardiovasc Interv 2006;67:12-16.
20. van der Werf F, Bax J, Betriu A, et al. ESC committee for practice guidelines (CPG). Management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2008;29:2909-2945.
21. Haeck JD, Koch KT, Bilodeau L, et al. Randomized comparison of primary percutaneous coronary intervention with combined proximal embolic protection and thrombus aspiration versus primary percutaneous coronary intervention alone in ST-segment elevation myocardial infarction: Proximal Embolic Protection in Acute myocardial infarction and Resolution of ST-Elevation (PREPARE). JACC Cardiovasc Interv 2009;2:934-943.
22. Cura FS, Escudero AG, Berrocal D, et al. Protection

of distal embolization in high-risk patients with acute ST-Segment Elevation Myocardial Infarction (PREMIAR). Am J Cardiol 2007;99:357-363.
23. Kelbaek H, Terkelsen CJ, Helqvist S, et al. Randomized comparison of distal pretection versus conventional treatment in primary percutaneous intervention: the drug elution and distal protection in ST-elevation myocardial infarction (DEDICATION) trial. J Am Coll Cardiol 2008;51:899-905.
24. Svilaas T, Vlaar PJ, van der Horst IC, et al. Thrombus aspiration during primary percutaneous coronary intervention. New Engl J Med 2008;358:557-567.
25. Montalescot G, Wiviott SD, Braunwald E, et al. TRITON-TIMI 38 investigators. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38: double-blind, randomised controlled trial). Lancet 2009;373:723-731.
26. Steg PG, Comparison of ticagrelor, the first reversible oral P2Y12 receptor antagonist, with clopidogrel in patients with acute coronary syndromes: results from the platelet inhibition and patient outcomes (PLATO) trial. Paper presented at: American Heart Association (AHA) 2009 Scientific sessions, 15 November 2009, Orlando.
27. de Luca G, Gibson CM, Bellandi F, et al. Early glycoprotein IIb-IIIa inhibitors in primary angioplasty (EGYPT) cooperation: an individual patient data meta-analysis. Heart 2008;94(12):1548-1558.
28. Prati F, Petronio S, van Boven AJ, Tendera M, de Luca L, de Belder MA, Galassi AR, Imola F, Montalescot G, Peruga JZ, Barnathan ES, Ellis S, Savonitto S. Evaluation of infarct-related coronary artery patency and microcirculatory function after facilitated percutaneous primary coronary angioplasty: the FINESSE –ANGIO (Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events-Angiographic) study. JACC Cardiovasc Interv 2010;3:1284-1291.

Nederlandse samenvatting

Dit proefschrift behandelt 2 belangrijke ongewenste complicaties (bloeding en sub-optimale procedurele uitkomst) tijdens en na primaire PCI bij STEMI patiënten. De doelen van dit proefschrift zijn om patiënten te identificeren die een hoog risico hebben op deze complicaties, aandacht te vragen voor een betere bloedingsrisico stratificatie en te zoeken naar verbetering in farmacologische therapie om deze patiënten te behoeden voor deze complicaties.

In **hoofdstuk 1** wordt een introductie van het onderwerp en de achtergrond van dit proefschrift gegeven. Bloedingen zijn tegenwoordig de belangrijkste niet cardiale complicatie van primaire PCI en sub-optimale procedurele resultaten blijven de 'achilleshiel' van de primaire PCI. Zowel bloedingen als sub-optimale procedurele resultaten zijn geassocieerd met een slechte korte- en lange-termijns uitkomst. Meer onderzoek is nodig om te beoordelen of het aantal complicaties kunnen worden verminderd in de toekomst.

In **hoofdstuk 2** wordt een samenvatting gegeven van de huidige behandeling van STEMI patiënten. Adequate behandeling na een snelle diagnose stelling verbetert in STEMI patiënten de prognose aanzienlijk. Hierbij speelt tijdig herstel van de doorbloeding van het infarct gerelateerde kransslagvat, door primaire PCI of thrombolyse, een sleutelrol. Primaire PCI, vergeleken met thrombolyse, resulteert in een verbetering van korte- en lange-termijns overleving, reduceert van het aantal hernieuwde infarcten, en verbetert de linker ventrikel functie. Verder onderzoek zal moeten bepalen wat de meest optimale combinatie zou moeten zijn van anti-thrombotica en plaatjesaggregatie therapie voorafgaand aan, rondom en na de primaire PCI.

Het eerste deel van dit proefschrift beschrijft de incidentie, voorspellers and preventie van bloedingen in patiënten die een primaire PCI ondergaan.

In **hoofdstuk 3** worden de incidentie, de voorspellers en de gevolgen voor prognose van een bloeding tijdens of na primaire PCI weergegeven in een prospectieve, grote single-center, observationele cohort studie. 80 patiënten (1.6%) had een majeure bloeding, en 266 patiënten (5.6%) had een mineure bloeding. Acuut hartfalen (Killip class >1) tijdens opname bleek een onafhankelijke voorspeller van een majeure bloeding. Een majeure bloeding (HR 3.5 (95% CI 2.3 – 5.4)) was geassocieerd met een toegenomen 1-jaars mortaliteit. Deze studie laat zien dat, hoewel relatief zeldzaam, een majeure bloeding tijdens of na primaire PCI sterk en onafhankelijk gerelateerd is aan een korte- en lange-termijns mortaliteit.

Hoofdstuk 4 beschrijft het risico op een bloeding na pre-hospitale toediening van tirofiban, bovenop aspirine, clopidogrel en ongefractioneerde heparine, in STEMI patiënten die werden ingestuurd voor primaire PCI. Een bloeding werd waargenomen in 47 patiënten (3.7%), waarvan 13 patiënten (1.0%) een majeure bloeding had. Sterke onafhankelijke voorspellers van een bloeding waren leeftijd, (OR 1.05, 95% CI 1.01 – 1.08, p=0.011), killip class >1 tijdens opname (OR 2.5, 95% CI 1.2 – 5.3, p=0.020) en gebruik van een intra-aortale ballon pomp (IABP) (OR 4.2, 95% CI 1.6 – 11.1, p=0.003). Hoge dosis tirofiban bleek geen onafhankelijke voorspeller van een bloeding (OR 1.7, 95% CI 0.9 – 3.2, p=0.116). Een bloeding bleek geassocieerd met een toegenomen risico op 30-daagse mortaliteit (HR 5.5, 95% CI 1.6 – 7.8, p<0.001) and 1-jaars mortaliteit (HR 3.2, 95% CI 1.4 – 7.2, p=0.005).
Deze bevindingen laten zien dat pre-hospitale toediening van hoge dosis tirofiban veilig is en geassocieerd met een laag bloedingsrisico. Leeftijd, killip class >1 tijdens opname, en IABP gebruik zijn, in tegenstelling tot hoge dosis tirofiban, zijn onafhankelijke voorspellers van een bloeding in STEMI patiënten. Een bloeding is onafhankelijk geassocieerd met 30-dagen mortaliteit en 1-jaars mortaliteit.

Het is tot op heden nog niet duidelijk of hoge dosis tirofiban in STEMI patiënten ook gunstig en veilig is in patiënten met een hoog bloedingsrisico. Daarom werd, beschreven in **hoofdstuk 5**, een aanvullende analyse van de On-TIME 2 studie verricht waarbij het netto klinische voordeel van pre-hospitale toediening van tirofiban werd onderzocht in patiënten met een hoog bloedingsrisico, daarbij gebruikmakend van de CRUSADE bloedingsrisicoscore.
Volgens de CRUSADE score, werden patiënten met een matig tot hoog baseline risico op een bloeding gedefinieerd als hoog risico en patiënten met een erg laag tot laag bloedingsrisico gedefinieerd als laag risico. Het primaire eindpunt was het netto klinische effect, gedefinieerd als netto onverwachte klinische uitkomsten na 30 dagen. Van de 1309 patiënten, hadden 291 patiënten (22.2%) een hoog bloedingsrisico. Pre-hospitale toediening van tirofiban in deze groep leidde tot een significante verbetering in ST segment resolutie 1 uur na primaire PCI. Toediening van pre-hospitale tirofiban in patiënten met een hoog bloedingsrisico had geen effect op de 30-daagse incidentie van een majeure onverwachte cardiale uitkomst (9.4% vs 13.0%, p=0.330, RR 0.72, 95% CI 0.37 – 1.39). Echter, pre-hospitale toediening van tirofiban bleek geassocieerd met een niet-significante toename in niet CABG-gerelateerde bloedingen (8.6% vs 3.6%, p=0.082, RR 2.38, 95% CI 0.90 – 6.39). Het netto klinische effect na 30 dagen van tirofiban in deze groep bleef in balans (11.5% vs 15.2%, p=0.365, RR 0.76, 95% CI 0.41 – 1.38). Geconcludeerd kan worden dat pre-hospitale toediening van tirofiban in STEMI patiënten met een hoog risico op bloeding resulteert in een gebalanceerd netto klinisch effect na 30 dagen.

Hoofdstuk 6 beschrijft de impact van leeftijd op de effecten van pre-hospitale toediening van tirofiban voorafgaand aan primaire PCI. In het hoogste tertiel (≥68 jaar) waren 231 patiënten (50%) van de 466 patiënten gerandomiseerd naar tirofiban en de gemiddelde leeftijd bedroeg 74.4 jaar.
De mediane residuele ST segment deviatie 1 uur na PCI was significant lager in oudere patiënten die waren voorbehandeld met tirofiban vergeleken met oudere patiënten die geen voorbehandeling hadden gehad. Verder bleek dat oudere patiënten die waren voorbehandeld met tirofiban, een niet-significant hoger percentage van 30 dagen mineure en majeure bloeding hadden (14.2% vs 9.0%, p=0.088) vergeleken met oudere patiënten die niet waren voorbehandeld met tirofiban. De 30-daagse netto onverwachte klinische effecten waren niet significant verschillend tussen beide groepen (11.9% vs 15.2%, p=0.300). Deze analyse laat zien dat het effect van pre-hospitale toediening van tirofiban ten aanzien van myocardiale reperfusie het grootst is in oudere patiënten. Echter, dit is geassocieerd met een trend naar meer bloedingscomplicaties, uiteindelijk resulterend in een gebalanceerd netto klinisch effect na 30 dagen.

De therapeutische effecten van een pre-hospitaal gefixeerde bolus ongefractioneerde heparine in STEMI patiënten op de activated clotting time (ACT) is onderzocht in **hoofdstuk 7**. Van de 1533 patiënten, hadden 216 patiënten (14.1%) een ACT binnen de therapeutische range, 82.3% van de patiënten had een te laag ACT, en 3.5% een te hoog ACT. Na multivariate analyse bleek dat een toegenomen gewicht de enige onafhankelijke voorspeller was van een te lage ACT (OR 1.02 / kg, 95% CI 1.01 – 1.03, p=0.001). Patiënten met een te lage ACT hadden verleken met patiënten binnen de therapeutische ACT range, significant minder vaak een open infarct gerelateerd kransslagvat (initiële TIM flow 2,3) (36.5% vs 45.9%, p=0.013). Deze studie laat zien dat in een klein deel van de patiënten, pre-hospitale toediening van een gefixeerde bolus ongefractioneerde heparine binnen de therapeutische ACT zitten. Toename van gewicht is een onafhankelijke voorspeller van een te lage ACT. Deze studie beveelt dan ook aan om ongefractioneerde heparine in de ambulance te geven welke gecorrigeerd is voor het gewicht van de patiënt.

In **hoofdstuk 8** rapporteren we de uitkomsten van een gerandomiseerde studie tussen een closure device (plug) en handmatig afdrukken om locatie gebonden complicaties te voorkomen in patiënten, met verhoogd bloedingsrisico, die een (primaire) PCI ondergaan. 313 patiënten (49.9%) werden gerandomiseerd naar een plug en 314 patiënten (50.1%) werden gerandomiseerd naar handmatig afdrukken. Het gecombineerde primaire eindpunt werd bereikt in 2.6% in de groep die een plug had gekregen en in 4.5% in de groep die manuele compressie had ondergaan. Echter in de vooraf gedefinieerde subgroep van patiënten bekend met hypertensie

bleek dat het gecombineerde primaire eindpunt significant lager lag in de groep mensen die een plug had gekregen (0.8% vs 7.2% p=0.008).
Deze studie laat zien dat na dotteren een plug in de lies plaatsen om locale hemostase te bewerkstelligen niet beter is dan handmatig afdrukken met betrekking tot optreden van liescomplicaties, behalve bij de groep van patiënten met hypertensie.

Het tweede deel van dit proefschrift richt zich op de incidentie en farmacologische mechanismen om sub-optimale procedurele uitkomsten tijdens primaire PCI te voorkomen.

In **hoofdstuk 9** wordt de uitkomst beschreven van patiënten die bail-out studiemedicatie hebben gekregen en tevens werd geëvalueerd of vroegtijdig gebruik van tirofiban in de ambulance zou resulteren in een afname van primaire PCI gerelateerde complicaties. Het betrof een vooraf gedefinieerde sub-analyse van de On-TIME 2 trial. 984 patiënten werden in de ambulance gerandomiseerd naar hoge bolus tirofiban of placebo. In de subgroep van patiënten die 'geblindeerd' bail-out studiemedicatie ontvingen, vergeleken wij patiënten die waren voorbehandeld met placebo en bail-out tirofiban (HDT bail-out) kregen met patiënten die waren voorbehandeld met tirofiban en bail-out placebo (placebo bail-out) kregen. In 24% van de patiënten (237/980) bleek een indicatie voor bail-out studiemedicatie. Het geven van bail-out studiemedicatie was vaker noodzakelijk in de groep die was voorbehandeld met placebo: 29% (140/492) vs 20% (97/488), p=0.002. Bail-out versus geen bail-out gebruik van studiemedicatie bleek geassocieerd met een toename van residuele ST-segment deviatie, en een slechtere klinische uitkomst na 30 dagen, vooral door de slechte uitkomst in de patiënten die waren voorbehandeld met placebo en tirofiban bail-out studiemedicatie kregen.
In patiënten die waren voorbehandeld met tirofiban en placebo bail-out studiemedicatie ontvingen werd in vergelijking met patiënten die überhaupt geen bail-out studiemedicatie ontvingen geen significant verschil gezien in residuele ST-segment deviatie na PCI of in klinische uitkomst.
Geconcludeerd kan worden dat het routinematig toedienen van tirofiban superieur is aan het eventueel toedienen van tirofiban op indicatie in STEMI patiënten.

Hoofdstuk 10 beschrijft het routinematig gebruik van tirofiban voorafgaand aan de primaire PCI versus het eventuele gebruik na primaire PCI in een grote populatie van niet-geselecteerde patiënten met een acuut hartinfarct. Patiënten die routinematig voorbehandeld werden met tirofiban voorafgaand aan primaire PCI werden vergeleken met patiënten die tirofiban tijdens primaire PCI of geen behandeling met tirofiban ontvingen. De incidentie van initiële normale doorbloeding van de kransslagader was hoger in patiënten welke routinematig

waren voorbehandeld met tirofiban (22.3% vs 17.9%, p=0.006). De enzymatische infarct grootte was kleiner (1401 IU/L (IQR 609 – 2948) vs 1620 (753 – 3132), p=0.03) en het voorkomen van dood of recidief hart infarct na 30 dagen was lager in de routinematig voorbehandelde groep (3.3% vs 5.1%, p=0.04). In multivariate analyse was routinematige voorbehandeling met tirofiban een onafhankelijke voorspeller van initiële normale doorbloeding (OR 1.47, 95% CI 1.15 – 1.88, p=0.02), enzymatische infarct grootte (OR 0.70, 95% CI 0.56 – 0.86, p=0.001) en dood of recidief hartinfarct na 30 dagen (OR 0.59, 95% CI 0.37 – 0.95, p=0.03). Deze analyse van niet-geselecteerde patiënten welke een primaire PCI hebben ondergaan vanwege een hartinfarct laat zien dat routinematige voorbehandeling met tirofiban een toename geeft van normale doorbloeding van de betrokken kransslagader voorafgaand aan de primaire PCI, een verlaging van de enzymatisch infarct grootte en de klinische uitkomst verbetert in vergelijking met een strategie zonder tirofiban of pas ten tijde van de primaire PCI.

Het effect van pre-hospitale toediening van een hoge bolus tirofiban, bovenop aspirine en clopidogrel, op angiografische uitkomsten voor en na primaire PCI in STEMI patiënten is onderzocht in **hoofdstuk 11**. Het betreft een vooraf gedefinieerde sub-analyse van de On-TIME 2 studie (N=984) en de open label inloop fase (N=414). Van de 1398 patiënten waren 709 patiënten (50.7%) naar pre-hospitale toediening van tirofiban gerandomiseerd. Een open infarct gerelateerd kransslagvat (TIMI 2 of 3 flow) bij initiële angiografie werd vaker gezien in patiënten die waren voorbehandeld met tirofiban vergeleken met patiënten die niet met tirofiban waren voorbehandeld (58.3% vs 49.7%, p=0.002). Voorbehandeling met tirofiban reduceerde eveneens de initiële trombus burden en de trombus gradering klasse 5 en liet daarnaast een lager percentage 'grote trombus burden' zien. Voorbehandeling met tirofiban liet een trend zien van betere coronaire doorbloeding na primaire PCI. Daarnaast werd een significante interactie gevonden met het tijdstip van toediening van tirofiban, waaruit naar voren kwam dat de hoogste effectiviteit van tirofiban werd gevonden wanneer toegediend binnen 76 minuten na ontstaan van klachten. Deze studie laat zien dat pre-hospitale toediening van tirofiban de initiële trombus burden reduceert, en de initiële doorbloeding van het aangedane kransslagvat voorafgaand aan primaire PCI in STEMI patiënten verbetert. Het toedienen van tirofiban is het meest effectief indien dit vroegtijdig na ontstaan van klachten wordt gegeven, echter deze bevinding zal (nog) moeten worden bevestigd in andere studies.

In **hoofdstuk 12** wordt de impact van een verhoogd lactaat dehydrogenase (LDH) bij binnenkomst op angiografische- en klinische uitkomsten in STEMI patiënten beschreven. Een verhoogd LDH bij binnenkomst wordt vaak gezien als een teken

van late presentatie, echter slechts enkele studies hebben de relatie tussen een verhoogd LDH bij binnenkomst en duur van klachten onderzocht. Het doel van deze studie was om de relatie tussen een verhoogd LDH bij binnenkomst en het tijdstip van ontstaan van klachten in STEMI patiënten te onderzoeken. Daarbij werd gekeken naar de invloed van een verhoogd LDH bij binnenkomst op angiografische en klinische uitkomsten. LDH werd bepaald bij binnenkomst in het PCI centrum. Een verhoogd LDH was in 20.0% (491/2453) van de patiënten aanwezig. Bij patiënten die zich binnen 2 en een half uur na ontstaan van klachten presenteerden, werd bij 14.6% van hen een verhoogd LDH gevonden. Patiënten met een verhoogd LDH bij binnenkomst waren ouder, vaker van het vrouwelijk geslacht, hadden een hoger ischemische risico score en vaker tekenen van hartfalen (killip class>1) bij binnenkomst. Een verhoogd LDH bij binnenkomst was geassocieerd met een slechte angiografische en klinische uitkomst. In multivariate analyse was een verhoogd LDH bij binnenkomst een sterke voorspeller van 30-dagen (HR 6.3, CI 95% 3.6–11.1) en 1-jaars mortaliteit (HR 3.4, CI 95% 2.3–5.0) onafhankelijk van de duur van klachten. Deze studie toont aan dat een verhoogd LDH bij binnenkomst reeds kan worden waargenomen vroegtijdig na het ontstaan van klachten in STEMI patiënten. Een verhoogd LDH bij binnenkomst is geassocieerd met een slechte angiografische- en klinische uitkomst, onafhankelijk van de duur van klachten.

List of publications
Dankwoord
Curriculum Vitae

List of publications

Original papers

1. Hermanides RS, Ottervanger JP. Treatment of ST-elevation myocardial infarction (STEMI)- a review
Future Cardiol 2008;4:391-397.

2. Hermanides RS, Ottervanger JP, Elvan A, Ramdat Misier AR. Life-threatening perforation of a defibrillation lead.
Neth Heart J 2009;3:113-114.

3. Hermanides RS, Ottervanger JP, Dambrink JH, de Boer MJ, Hoorntje JC, Gosselink AT, Suryapranata H, van 't Hof AW. Incidence, predictors and prognostic importance of bleeding after primary PCI for ST Elevation Myocardial Infarction.
EuroIntervention 2010;6:106-111.

4. Hermanides RS, Ottervanger JP, Dambrink JH, Dill T, van Houwelingen KG, ten Berg JM, Kolkman JJ, Hamm C, van 't Hof AW. Risk of bleeding after pre-hospital administration of high dose tirofiban for ST-Elevation Myocardial Infarction.
Int J Cardiol. 2010 Dec 29. [Epub ahead of print]

5. Hermanides RS, Ottervanger JP, Dambrink JH, de Boer MJ, Hoorntje JC, Gosselink AT, Suryapranata H, van 't Hof AW. Closure device or manual compression in patients undergoing percutaneous coronary intervention: a randomized comparison.
Journal of Invasive Cardiology 2010;22:562-566.

6. Heestermans AA, Hermanides RS, Gosselink AT, de Boer MJ, Hoorntje JC, Suryapranata H, Ottervanger JP, Dambrink JH, Kolkman JJ, ten Berg JM, Zijlstra F, van 't Hof AW. A comparison between upfront high dose tirofiban versus provisional use in primary PCI in the real world of non selected STEMI patients: Insights from the Zwolle acute myocardial infarction registry.
Neth Heart J 2010;18(12):592.

7. Dambrink JH, Hermanides RS, Beuving D, Nibbering E. Op zoek naar late complicaties.
Medisch Contact 2010;31:1536-1539.

8. Hermanides RS, Heestermans AA, ten Berg JM, Gosselink AT, Ottervanger JP, van Houwelingen KG, Kolkman JJ, Stella PR, Dill T, Hamm C, van 't Hof AW. High-dose tirofiban reduces the need for bail-out study medication in patients with ST-segment elevation myocardial infarction: results of a subgroup analysis of the On-TIME 2 trial. A

sub-analysis of the On-TIME 2 trial.
Heart 2011;97:106-111.

9. Hermanides RS, van 't Hof AW. High-dose tirofiban reduces the need for bail-out study medication in patients with ST-segment elevation myocardial infarction: results of a subgroup analysis of the On-TIME 2 trial. A sub-analysis of the On-TIME 2 trial. Response to a letter; the authors' reply
Heart 2011;97:1026.

10. Hermanides RS*, van Houwelingen KG*, Ottervanger JP, de Boer MJ, Dill T, Hamm C, Stella PR, Boersma E, ten Berg JM, van 't Hof AW. The impact of age on effects of pre-hospital initiation of glycoprotein 2b/3a inhibitors before primary angioplasty for ST-elevation myocardial infarction.
Cardiovasc Drugs Ther 2011 Jul 12. [Epub ahead of print]

11. Hermanides RS, Ottervanger JP, Dambrink JH, de Boer MJ, Hoorntje JC, Gosselink AT, Suryapranata H, Zijlstra F, van 't Hof AW. Therapeutic efficacy of a pre-hospital fixed heparin bolus for STEMI.
Thromb Haemost 2011;11:106(4). [Epub ahead of print]

12. Hermanides RS, van Werkum JW, Ottervanger JP, Breet NJ, Gosselink AT, van Houwelingen KG, Dambrink JH, Stella PR, Hamm C, ten Berg JM, van 't Hof AW. The effect of pre-hospital glycoprotein IIb/IIIa inhibitors on angiographic outcome in STEMI patients who are candidates for primary PCI.
Catheter Cardiovasc Interv.; accepted

13. Hermanides RS, Ottervanger JP, ten Berg JM, Gosselink AT, van Houwelingen KG, Dambrink JH, Stella PR, Hamm C, van 't Hof AW. Net clinical benefit of early pre-hospital initiation of a glycoprotein 2b/3a blocker in patients at high risk of bleeding: results of a sub-analysis of the On-TIME 2 trial using the CRUSADE bleeding.
Submitted

14. Hermanides RS, Ottervanger JP, Dambrink JH, Krabbe JG, Slingerland RJ, de Boer MJ, Hoorntje JC, Gosselink AT, Suryapranata H, Zijlstra F, van 't Hof AW. In patients with STEMI, Lactate DeHydrogenase (LDH) elevation may occur early after symptom onset and is associated with poor outcome.
Submitted

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Curriculum Vitae

Rik Hermanides werd geboren op 10 januari 1983 te Jirnsum. Na het behalen van zijn atheneum diploma op het Piter Jelles College te Leeuwarden in 2001, studeerde hij Geneeskunde aan de Rijks Universiteit Groningen (2001-2007).

Zijn wetenschappelijke stage deed hij bij de cardiologie in het Universitair Medisch Centrum Groningen alwaar hij onderzoek deed naar het effect van neurostimulatie bij therapie refractaire angina pectoris patiënten. Na afronding van zijn keuze co-schap cardiologie in de Isala Klinieken te Zwolle behaalde hij in november 2007 zijn graad tot arts, waarna hij gedurende 10 maanden gewerkt heeft als arts-assistent cardiologie niet in opleiding. Van 1 september 2008 tot 1 april 2011 heeft hij gewerkt in een AGIKO traject (klinische werkzaamheden in combinatie met wetenschappelijk onderzoek) wat uiteindelijk geresulteerd heeft in dit proefschrift. Op 1 april 2011 is hij in het kader van de opleiding cardiologie (opleider dr A.R. Ramdat Misier) gestart met de vooropleiding interne geneeskunde in de Isala klinieken te Zwolle (opleider dr P.H.P. Groeneveld).