Putting the future in service of the present:

Risk assessment in acute coronary syndrome patients

Cynthia M. Westerhout

Westerhout, Cynthia M.

Printed by Gildeprint Drukkerijen B.V.

ISBN 978-90-9022330-8

Front cover: Westerhout, Kathleen P; “Buttons & Beads”, Vancouver, Canada, 2007; Permission for use was granted by the artist.

Putting the future in service of the present:
Risk assessment in acute coronary syndromes

De toekomst in dienst van het heden:
Risico evaluatie bij patiënten met een acuut coronair syndroom

Thesis

to obtain the degree of Doctor from the
Erasmus University Rotterdam
by command of the
Rector Magnificus

Prof.dr. S.W.J. Lamberts

and in accordance with the decision of the Doctorate Board
The public defence shall be held on

Wednesday 17 October 2007 at 15:45 hrs
by

Cynthia Mary Westerhout

born in London, Canada

Doctoral Committee

Promoter:	Prof.dr. M.L. Simoons
Other members:	Prof.dr. W.J. van der Giessen Prof.dr. A. Hofman Prof.dr. J.G.P. Tijssen
Copromotor:	Dr. H. Boersma

Financial support by the Netherlands Heart Foundation for the publication of this thesis is gratefully acknowledged.

In memory of Pieter and Joan Westerhout

Table of Contents

Preface

"To be alive at all involves some risk."

~Harold Macmillan (British politician, 1894-1986)

Risk, the possibility of loss or injury, is indeed a fixture in all aspects of our lives, from investing in the stock market to crossing the street. This concept that we now take for granted is in fact relatively novel. Some have argued that the ability to describe, estimate and control risk is a key distinction between past and modern times.[1] In early civilization, the future of human beings was largely thought to be at the whim of the gods. The turning point came during the Renaissance when Chevalier de Méré, a French nobleman with an affinity for gambling and mathematics, challenged the famed French mathematician Blaise Pascal to solve an infamous puzzle: How to divide the stakes of an unfinished game of chance between two players when one of them is ahead.[1,2] Collaboration between Pascal and Pierre de Fermat, a lawyer and a talented mathematician, resulted in a solution and consequently, the theory of probability was born. And it is this concept that is at the heart of modern cardiovascular medicine and research.

In medicine, risk is characterised as the probability of morbidity or mortality as a result of a disease. Subsequent treatment of the disease may also bear some risks along with its benefits, and naturally the medical tradition seeks to mitigate these risks. In part, this has been accomplished over the years through the sophistication of characterising and quantifying risk. Early approaches included case series and anecdotal observations based on physician/institution experience. These provided snapshots of the associations between signs/symptoms/conditions and subsequent events but could not easily be contextualised. The advent of the computer era, the subsequent evolution of statistical methods and the clinical trial movement (i.e., GUSTO-I trial[3], the first mega-trial of over 40,000 AMI patients) are largely responsible for the transformation of risk assessment in cardiovascular medicine as we know it today.

The product of risk assessment is information, which is valuable in guiding physicians, researchers, patients and their families, as well as those involved in resource allocation and health policy. Risk models are designed to provide the probability of a diagnosis or of an outcome occurring in the future, which can then be used to inform medical decision making by identifying low-risk patients for conservative therapy or reserving more aggressive

strategies for high-risk patients. Absolute risk reduction and the number needed to treat to prevent one event provide insights into the evaluation of risk on the larger scale, at the population level. And net clinical benefit and cost-effectiveness are measures commonly considered, especially by administrators, insurance providers and policy makers reviewing new therapies and allocating resources.

Identifying novel risk factors has also enhanced our understanding of the pathophysiology, causal pathways and treatment mechanisms. For instance, the multiple biomarker era has recently been ushered into acute coronary syndromes (ACS) with recognition of markers of myocardial necrosis (e.g., troponin), hemodynamic stress (e.g., brain natriuretic peptide), vascular damage (e.g., creatinine clearance), inflammation (e.g., C-reactive protein (CRP)) and accelerated atherosclerosis (e.g., blood glucose).[4] This information can be used in diagnostic and/or therapeutic development, in tailoring treatment and in the planning and design of future clinical trials by identifying specific risk levels appropriate for study enrolment.

Clinical judgement and statistical methods support the art and science of *putting the future in service of the present*, and this is the common thread woven throughout this thesis. The following eleven chapters are based on various approaches to risk assessment in ACS (including unstable angina, non-ST-elevation myocardial infarction and ST-elevation myocardial infarction) patients enrolled in selected contemporary clinical trials. In addition to the standard risk stratification techniques of logistic regression and survival analysis, several other methods and study designs are highlighted such as pooled/meta-analyses, dynamic risk modelling, multilevel modelling, nested case-control study design and non-inferiority trial design.

Part 1: Approaches to risk prediction in acute coronary syndromes

With the ever-increasing number of new treatments, risk prediction has become the focus of front-line assessment of these patients, and with that is the dominant principle to target more aggressive therapy in higher risk patients. Upon entry of a patient to the health care system, data are collected on their demographics, medical history and initial clinical indicators. In **Chapter 1**, we examine the rich array of patient factors associated with short- and long-term outcomes in 7800 non-ST-elevation ACS patients enrolled in the GUSTO IV ACS trial. Specifically, comprehensive risk models are developed to predict these outcomes and the relative strength of these factors are examined. Simplified risk scores are also presented to illustrate potential clinical applications in these patients.

Typically, risk prediction takes into account the medical history and initial clinical indicators of a patient. However, patients are continually assessed from the first point of entry

into the health care system until discharge and throughout follow-up care. **Chapter 2** introduces a novel approach to risk stratification, which accounts for this evolving nature of risk. Dynamic risk modelling extends beyond the baseline approach by using accumulating information such as post-baseline ECG results, angiographic results, treatment and complications, thereby emulating how a patient's risk can change over time with treatment and/or complications.

In addition to patient factors, the story of risk can be impacted by higher-level factors such as the type of hospital in which a patient was treated or the country or region in which they live. While international differences in the treatment patterns and outcomes of ACS patients are well established, insights into "why" have not been clearly demonstrated. Thus, multilevel modelling is used in **Chapter 3** to quantify the relative contribution of patient-, hospital- and country-level factors on clinical outcomes in patients enrolled in the GUSTO IV ACS trial.

Part 2: Unravelling the pathophysiology of acute coronary syndromes

This second section considers the associations of various co-morbid factors with short- and long-term outcomes in contemporary ACS patients. Insight into these relationships is important to our understanding of the mechanisms of the disease, which may then lead to development of novel therapies and/or improved care and outcomes. The richness of the data collected by large-scale clinical trials provides the ideal environment to pursue questions that were not among the primary objectives of the trial. The GUSTO IV ACS trial, for instance, systematically collected and centrally evaluated electrocardiograms and multiple biomarkers in 7800 non-ST-elevation ACS patients. In **Chapter 4**, these unique data were used to identify electrocardiographic left ventricular hypertrophy as well as to examine its association with long-term mortality and the possible modulation of that relationship by N-terminal pro-brain natriuretic peptide (NT-proBNP) and gender.

While it may not be feasible to collect data on every factor of interest, a case-control study nested within a large clinical trial is an efficient means to this end. Such an approach was taken in **Chapter 5**, which examines the associations between chronic infection with *Chlamydia pneumoniae* and 30-day death or myocardial infarction (MI) and 1-year mortality.

And finally, pooling data from similar clinical trials is an effective approach to examining infrequent but disabling events, such as stroke in ACS patients. By increasing the sample size and thus the power to do so, insights into modifiable (and non-modifiable) factors may lead to improved care and outcomes. **Chapter 6** identifies predictors of stroke within 30 days of an acute coronary event based on a pooled analysis of six major clinical trials testing glycoprotein IIb/IIIa inhibitors

(GPIs) in non-ST-elevation ACS patients.

Part 3: Glycoprotein IIb/IIIa inhibitors in the elderly

Antiplatelet therapy has long been a cornerstone of the treatment of ACS. Advances in the understanding of the pathogenesis of ACS in recent decades have brought about further innovations, namely GPIs. GPIs are now well-established adjunctive agents for patients undergoing percutaneous coronary intervention (PCI), and substantial effort has gone into evaluating this class of agents in those who are not scheduled for early revascularisation. **Chapters 7** and **8** provide a comprehensive review of this literature and an analysis of the risks and benefits associated with these agents, particularly in the elderly. Given that age is an established risk factor in ACS, both relative and absolute benefits (and risks) of GPI therapy across the spectrum of age are relevant. Thus, **Chapter 9** examines this in detail using individual patient data from the six major GPI clinical trials in ACS patients not undergoing early revascularisation.

Part 4: Therapeutic strategies in ST-elevation myocardial infarction

Patients with the most severe of the acute coronary syndromes, that is, ST-elevation acute myocardial infarction (STEMI), present a formidable challenge to those who treat them. Although reperfusion of the occluded epicardial coronary artery is the primary goal, the optimal approach to do so remains quite controversial. Pharmacological and mechanical reperfusion strategies have been developed in parallel, each with their own set of strengths and weaknesses. Given that "time is myocardium", the time elapsed between symptom onset and treatment is one of the key factors in this discussion. In **Chapter 10**, the relative and absolute influence of time to treatment on the efficacy of fibrinolytic therapy versus primary PCI is examined by pooling individual patient data from 22 randomised clinical trials. **Chapter 11** introduces the next step in the evolution of reperfusion therapy through the WEST Study, a Canadian, randomized, feasibility study of 304 STEMI patients featuring a novel regimen of contemporary pharmacologic treatment delivered rapidly paired with a strategy of regimented rescue and routine coronary intervention within 24 hours of initial treatment.

References

1. Bernstein, PL. "Against the gods: the remarkable story of risk." 1996. New York: John Wiley & Sons, Inc.
2. Tannery, Henry, eds. "Oeuvres de Fermat." Vol II, pp.288-314, 1894. Paris.
3. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *New England Journal of Medicine* 1993;329:673-682.
4. Morrow DA, Braunwald E. Future of biomarkers in acute coronary syndromes: Moving towards a multimarker strategy. *Circulation* 2003; 108:250-252.

Chapter One

Short- and Long-Term Risk Stratification in Acute Coronary Syndromes

The Added Value of Quantitative ST-Segment Depression and Multiple Biomarkers

Cynthia M. Westerhout, Yuling Fu, Michael S. Lauer, Stefan James, Paul W. Armstrong, Eyad Al-Hattab, Robert M. Califf, Maarten L. Simoons, Lars Wallentin, Eric Boersma, on behalf of the GUSTO-IV ACS Trial Investigators

OBJECTIVES The purpose of this study was to develop 30-day and 1-year risk stratification models for non–ST-segment elevation acute coronary syndrome (NSTE-ACS) patients that incorporate quantitative ST-segment depression and novel biomarkers.
BACKGROUND Several novel biomarkers have changed the risk profile of ACS; thus, the reassessment of traditional indicators such as ST-segment depression in this new context is warranted.
METHODS Multivariable logistic regression was used to identify significant predictors of 30-day death
and death/myocardial infarction (MI) and 1-year mortality in 7,800 NSTE-ACS patients enrolled in the GUSTO-IV (Global Utilization of Strategies to Open Occluded Arteries-IV ACS) trial between 1998 and 2000.
RESULTS Among all other predictors, the degree of ST-segment depression had the highest prognostic value for 30-day death, 30-day death/MI, and 1-year death. Troponin T (TnT), creatinine clearance, N-terminal pro-brain natriuretic peptide (NT-proBNP), heart rate, and age were also highly influential on adverse outcomes. Unlike TnT and NT-proBNP, C-reactive protein was only predictive of long-term death. In contrast to mortality, the contribution of TnT to predicting 30-day death/MI increased, whereas NT-proBNP's role was attenuated. The discriminatory power was excellent (c-index [adjusted for over-optimism]: 0.82 [30-day death]; 0.72 [30-day death/MI]; 0.81 [1-year]).
CONCLUSIONS In this large contemporary study of NSTE-ACS patients, novel insights into risk stratification were observed—in particular, the utility of quantitative ST-segment depression and multiple biomarkers. Collection of these indicators in future NSTE-ACS populations is recommended to evaluate generalizability and clinical application of these findings.

Demographics, comorbidities, and other classic patient factors have long been the foundation of risk stratification in acute coronary syndromes (ACS)[1–4]. More recently, several biomarkers have also been shown to be associated with the risk for subsequent coronary events, including indicators of myocardial necrosis (troponin), inflammation (C-reactive protein), and hemodynamic

stress (brain natriuretic peptides).

The electrocardiogram (ECG) has continually played an important role in prognosis of ACS patients. ST-segment depression >0.5 mm at baseline, for instance, is associated with poorer prognosis than absence of ST-segment depression. The extent of ST-segment depression, however, is rarely measured or reported even though this refinement substantially improves risk stratification compared with conventional qualitative ECG data (5–8). The prognostic value of combining quantitative ECG data and the extended biomarker profile with classical patient risk factors is unclear. Thus, the systematic collection of quantitative ST-segment depression, cardiac troponin T (TnT), C-reactive protein (CRP), and N-terminal pro-brain natriuretic peptide (NT-proBNP) in 7,800 non–ST-segment elevation acute coronary syndrome (NSTE-ACS) patients enrolled in the GUSTO-IV (Global Utilization of Strategies to Open Occluded Arteries-IV ACS) trial provided a unique opportunity to investigate the relative roles of factors influencing short- and long-term outcomes (9). Risk scores were also developed to illustrate potential clinical applications.

METHODS

Study population. The details of the GUSTO-IV-ACS trial have been previously described (9,10). Briefly, patients over the age of 21 years were eligible if they presented within 24 h after an episode of ischemic chest pain lasting ≥5 min and had either elevated TnT/TnI above the upper limit of normal (ULN) according to the local quantitative or qualitative assays or transient/persistent ST-segment depression (≥0.5 mm) that was not known to be pre-existing and not attributable to a co-existing disorder or medication on the admission ECG. Patients were randomly assigned to abciximab (0.25 mg/kg bolus plus 0.125 μg/kg/min infusion for 24 or 48 h) or placebo. Because abciximab did not reduce the primary or secondary end points, patients from all 3 treatment arms were combined for this analysis. Coronary angiography was not to be performed during or within 12 h after the completion of the study agent infusion. Patients also received aspirin and either unfractionated or low-molecular weight heparin. Other clinically indicated medications were used at the discretion of the treating physician.

ECG analysis. Standard 12-lead baseline ECG data obtained at baseline were centrally evaluated by 2 experienced readers without knowledge of the clinical outcomes in 7,741 patients (99.2%) at the ECG core laboratory (Cleveland Clinic Foundation, Cleveland, Ohio) and were entered and analyzed at the Canadian VIGOUR Centre (University of Alberta, Edmonton, Canada). ST depression was prospectively defined and measured with the aid of a magnifying calliper to the nearest 0.5 mm in all leads except aVR. ST-segment depression was judged to be present if the J point was depressed by 0.5 mm and was followed by a horizontal or down-sloping ST-segment for at least 0.08 s.

Patients were classified as having ST-segment depression if the ST-segment was depressed by ≥0.5 mm in 2 of the limb leads or at least 2 contiguous precordial leads. Patients were categorized into 5 mutually exclusive groups: no ST-segment depression, 0.5-mm, 1- to 1.5-mm, ≥2-mm ST-segment depression, and "confounders." Confounders included left bundle branch block, paced rhythm or ventricular rhythm in 225 patients, or ST-segment elevation on the baseline ECG in 289 patients.

Biomarker analysis. Blood samples were drawn at baseline and analyzed at a core laboratory (Department of Clinical Chemistry, University of Uppsala, Uppsala, Sweden). Details of the assays used have been previously published (11). Baseline levels of TnT, CRP, and NT-proBNP were determined per protocol in all but 685 (8.8%), 692 (8.9%), and 991 (12.7%) patients, respectively. The loss of 500 samples during transport accounts for much of these missing data. Complete data for all 3 biomarkers were available in 6,809 (87.3%) patients. Baseline serum creatinine concentration (mg/dl) was measured at local laboratories in 7,703 of 7,800 patients. To assess renal function, creatinine clearance was calculated with the Cockcroft-Gault equation, which adjusts for age, gender, and weight (12).

End point definitions. The end points of the current study included 30-day death, 30-day death or MI, and 1-year death, as described previously (9). Double counting of patients with more than 1 event was avoided by classifying each patient according to the event with the greatest severity. Thus, a patient with MI who subsequently died was classified as experiencing death but not MI. At 1-year post-randomization, follow-up data on vital status were obtained and were complete in 7,746 patients (99.3%). Possible cases of MI were adjudicated by a clinical end point committee that was not aware of biomarker levels evaluated in the core laboratory (i.e., TnT, CRP, NT-proBNP) or the extent of ST-segment depression on the baseline ECG (9).

Statistical analysis. Baseline characteristics were summarized by frequency and percentage for categorical variables and by median and interquartile range for continuous variables. Creatinine clearance, TnT, CRP, and NTproBNP were categorized into quartiles of their distributions for ease of presentation (11). The choice of TnT over creatine kinase-MB as the preferred marker of myocardial damage was based on established guidelines as well as by an independent analysis of their relative prognostic power (Appendix 1) (13).

Logistic regression evaluated the associations between baseline characteristics and adverse outcomes. Indicators were entered into the full multivariable model if the p value of the univariable association was <0.25. The final multivariable model was constructed by backward stepwise elimination of the least significant factors and the Akaike information criteria. Given that 1-year follow-up was complete

in 99.3% of patients, logistic regression was repeated to determine predictors of 1-year mortality. Unadjusted and adjusted odds ratios and their corresponding 95% confidence intervals are reported. The Hosmer-Lemeshow goodness-of-fit test statistic and calibration of the predicted versus observed event rate according to deciles of predicted risk were calculated to assess model performance. The discriminatory power was estimated by the c-index (i.e., probability of concordance between observed and predicted survival on the basis of pairs of individuals). The models were developed in the entire study population and validated by bootstrapping techniques: 100 bootstrap samples were drawn, with replacement, to estimate the amount of "over-optimism" in the models on the basis of the entire population and quantified by the decrease in the area under the receiver operating characteristic curve (14).

Simplified risk scores were developed to demonstrate the potential for clinical application. The top 5 contributing factors in the model were assigned weights that were equivalent to the logistic regression coefficient multiplied by 10. For patient "i", a weighted risk score was estimated by summing the weighted risk for each variable (risk score= $\sum 10\beta_i x_i$, where ß was the regression coefficient associated with the factor, and x was equal to 1 when the factor was present and 0 when absent). The discriminatory power of the simplified risk scores was also adjusted for over-optimism.

RESULTS

Overall, 301 (3.9%) of the 7,800 enrolled patients died within 30 days after randomization, with an additional 348 patients (4.5%) dying between 30 days and 1 year (Table 1). Of the 659 (8.4%) patients who had an MI or died within 30 days, 358 had a non-fatal MI, 74 had an MI and died, and 227 died without an MI. Patients who experienced an end point were more often older and had a higher frequency of comorbidities and prior cardiac history. Baseline biomarkers (i.e., TnT, NT-proBNP, CRP), heart rate, and the extent of ST-segment depression were significantly higher in patients who died within 30 days or 1 year.

Predictors of 30-day death

Thirteen of 19 possible predictors of 30-day mortality remained statistically significant in the final model. (Table 2) Compared with those without ST-segment depression, the likelihood of 30-day death was twice as high in patients with 1- to 1.5-mm and nearly 4-fold higher with ≥2-mm ST-segment depression, after baseline adjustment ($p < 0.001$). ST-segment depression contributed the most to the model, as indicated by the percentage of the total chi-square (Fig. 1). Creatinine clearance was also strongly associated with 30-day mortality: patients with creatinine clearance ≤58.4 ml/min had a 5-fold increase in the risk of 30-day death relative to >98.6 ml/min ($p < 0.001$). Patients with TnT >0.47 μg/l were more than 3 times as likely to die

Table 1. Baseline Characteristics According to Survival Status at 30 Days and 1 Year After Randomization

	30-Day Death		30-Day Death/MI		1-Yr Death	
	Survived	Died	No	Yes	Survived	Died
n	7,499	301	7,141	659	7,151	649
Age, yrs*	66 (57–73)	74 (69–79)†	66 (56–73)	72 (65–77)†	65 (56–73)	74 (68–79)†
Men, %	62.6	59.5	62.4	63.1	62.7	59.3
Caucasian, %	96.8	96.3	96.8	97.0	96.8	96.5
Hypertension, %	51.8	62.8†	51.5	59.2†	51.3	62.6†
History of hyperlipidemic therapy, %	35.0	39.2	35.1	36.0	34.9	37.3
Diabetes mellitus, %	21.1	33.6†	21.3	27.6†	20.3	35.2†
Current smoker, %	22.9	17.3‡	23.1	18.5†	23.2	16.8†
History of angina pectoris, %	45.4	60.1†	45.2	54.8†	44.5	62.9†
History of MI, %	30.9	50.5†	30.6	43.7†	29.8	52.4†
History of heart failure, %	7.7	23.3†	7.7	14.9†	6.9	23.1†
History of PCI, %	9.9	6.6	9.8	8.6	9.8	8.8
History of CABG, %	9.2	8.6	9.3	8.2	9.1	10.5
History of stroke, %	2.4	7.3†	2.4	5.3†	2.2	6.6†
Body weight, kg*	76 (68–86)	74 (64–83)†	76 (68–86)	75 (66–85)†	76 (68–86)	74 (64–83)†
Heart rate, beats/min	68 (60–79)	75 (65–93)†	68 (60–79)	71 (62–84)†	68 (60–78)	75 (64–90)†
Creatinine clearance, ml/min*	78 (59–99)	55 (39–72)†	78 (60–100)	62 (45–83)†	79 (61–100)	56 (40–73)†
ST-segment depression, mm		†		†		†
None	34.0	13.7	34.5	19.3	34.7	16.6
0.5	27.3	15.3	27.4	20.0	27.6	18.5
1.0–1.5	27.4	35.3	27.1	34.9	27.1	35.1
≥2	5.0	20.3	4.8	13.9	4.7	15.2
Confounders§	6.3	15.3	6.2	11.9	5.9	14.6
Troponin T, μg/l*	0.11 (0.01–0.44)	0.41 (0.08–1.10)†	0.10 (0.01–0.44)	0.23 (0.06–0.68)†	0.10 (0.01–0.43)	0.30 (0.06–0.84)†
NT-proBNP, ng/l*	635 (228–1,724)	2,926 (1,193–7,683)†	622 (223–1,702)	1,560 (529–4,288)†	635 (228–1,723)	2,926 (1,202–7,667)†
CRP, mg/l*	3.90 (1.81–9.40)	6.76 (2.74–24.3)†	3.91 (1.82–9.42)	4.91 (2.15–13.0)†	3.80 (1.78–8.96)	6.97 (2.73–20.3)†

*Median (interquartile range). †$p < 0.001$ (died vs. survived). ‡$p < 0.05$ (died vs. survived). §Confounders include left bundle branch block, paced rhythm, ventricular rhythm, or ST-segment elevation on the baseline electrocardiogram (ECG).

CABG = coronary artery bypass graft; CRP = C-reactive protein; MI = myocardial infarction; NT-proBNP = N-terminal pro-brain natriuretic peptide; PCI = percutaneous coronary intervention.

within the first 30 days than those with TnT ≤0.01 μg/l ($p < 0.001$). Compared with NT-proBNP ≤237 ng/l, the odds of 30-day mortality steadily rose with increasing levels of NT-proBNP, particularly in those >1,896 ng/l, who had nearly a 3-fold increase in the risk of death ($p = 0.012$). Strong prognostic associations were also observed for heart rate and age and, to a lesser extent, histories of MI and heart failure; weight; current smoker; and histories of hyperlipidemic therapy, percutaneous coronary intervention (PCI), and stroke.

Predictors of 30-day death/MI. Among the 8 independent predictors of 30-day death/MI, ST-segment depression and TnT made the greatest contributions. (Table 2, Fig. 1). Compared with patients without ST-segment depression, the odds ratio of 30-day death/MI ranged from 1.2 to 3 as the extent of ST-segment depression increased ($p < 0.001$). Also, patients with TnT >0.47 μg/l were over 2.5 times more likely to experience the composite within 30 days compared with those ≤0.01 μg/l ($p < 0.001$). Creatinine clearance, age, and NT-proBNP were important risk factors, similar to the 30-day mortality model. However, the relative contribution of NT-proBNP was attenuated compared with the mortality models (Fig. 1). Unlike the mortality model, heart rate was not a significant independent predictor of 30-day death/MI.

Predictors of 1-year death. ST-segment depression was the strongest contributor to the model predicting 1-year mortality, similar to the 30-day mortality model (Table 2, Fig. 1). A marked gradient in risk

Table 2. Adjusted OR and 95% CI of Baseline Characteristics Predicting 30-Day Mortality, 30-Day Death/MI, and 1-Year Mortality

	30-Day Mortality			30-Day Death/MI			1-Yr Mortality		
	Adjusted OR (95% CI)	p Value	Chi-Square	Adjusted OR (95% CI)	p Value	Chi-Square	Adjusted OR (95% CI)	p Value	Chi-Square
Age, yrs	1.03 (1.01–1.05)	0.001	10.7	1.02 (1.01–1.03)	0.001	10.9	1.04 (1.02–1.05)	<0.001	29.6
Current smoker	1.60 (1.1–2.3)	0.008	6.7				1.70 (1.3–2.2)	<0.001	15.9
Diabetes mellitus							1.38 (1.1–1.7)	0.001	10.7
History of hyperlipidemic therapy	1.41 (1.1–1.8)	0.009	6.6						
History of angina							1.45 (1.2–1.8)	<0.001	14.7
History of MI	1.46 (1.1–1.8)	0.005	7.9	1.39 (1.16–1.65)	<0.001	10.6	1.59 (1.3–1.9)	<0.001	23.4
History of heart failure	1.56 (1.1–2.1)	0.006	7.1				1.64 (1.3–2.1)	<0.001	16.2
History of stroke	1.80 (1.1–3.0)	0.021	4.8	1.58 (1.07–2.34)	0.023	4.5	1.67 (1.1–2.5)	0.010	6.3
No history of PCI	1.70 (1.05–2.76)	0.034	5.1						
No history of CABG				1.55 (1.14–2.11)	0.006	8.0			
Heart rate, beats/min	1.02 (1.0–1.02)	<0.001	17.1				1.01 (1.0–1.02)	<0.001	24.3
Body weight, kg	1.01 (1.0–1.03)	0.009	6.8	1.01 (1.01–1.02)	0.001	12.0	1.01 (1.0–1.01)	0.007	7.3
Creatinine clearance, ml/min									
>98.6	1	<0.001	39.8	1	<0.001	25.0	1	<0.001	42.9
76.9–98.6	2.17 (1.1–4.1)			1.36 (0.99–1.86)			1.89 (1.3–2.8)		
58.4–76.9	3.61 (1.9–6.8)			1.71 (1.22–2.39)			2.54 (1.7–3.8)		
≤58.4	5.39 (1.1–4.1)			2.39 (1.64–3.49)			3.85 (2.5–6.02)		
ST-segment depression, mm									
No	1	<0.001	45.1	1	<0.001	69.7	1	<0.001	41.0
0.5	1.10 (0.7–1.7)			1.18 (0.91–1.53)			1.05 (0.8–1.4)		
1.0–1.5	1.73 (1.2–2.5)			1.74 (1.38–2.21)			1.37 (1.1–1.8)		
≥2	3.73 (2.4–5.8)			3.14 (2.31–4.26)			2.42 (1.7–3.4)		
Confounders	2.42 (1.5–3.8)			2.27 (1.66–3.11)			2.03 (1.5–2.8)		
Troponin-T, ug/l									
≤0.01	1	<0.001	33.7	1	<0.001	42.2	1	<0.001	23.5
0.01–0.12	2.06 (1.2–3.4)			2.20 (1.61–3.01)			1.31 (0.95–1.8)		
0.12–0.47	2.09 (1.2–3.5)			2.38 (1.74–3.26)			1.60 (1.2–2.2)		
>0.47	3.54 (2.1–5.8)			2.52 (1.83–3.46)			1.99 (1.5–2.7)		
NT-proBNP, ng/l									
≤237	1	0.012	13.7	1	0.041	10.3	1	<0.001	30.0
237–669	1.60 (0.8–3.2)			1.46 (1.04–2.06)			1.33 (0.9–2.1)		
669–1,896	2.00 (1.0–3.9)			1.30 (0.92–1.83)			1.80 (1.2–2.8)		
>1,896	2.72 (1.4–5.3)			1.66 (1.17–2.36)			2.58 (1.7–4.0)		
CRP, mg/l									
≤1.84							1	0.05	8.8
1.84–3.96							1.10 (0.8–1.5)		
3.96–9.62							1.06 (0.8–1.4)		
≥9.62							1.38 (1.0–1.8)		

CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

relative to ST-segment depression was observed, even after baseline adjustment: patients with ≥2 mm were 2.4 times more likely to die within the first year compared with those without ST-segment depression ($p < 0.001$). Other important predictors included creatinine clearance, NT-proBNP, age, heart rate, and TnT. For instance, patients who had ≤58 ml/min creatinine clearance were nearly 4 times more likely to die within the first year compared with >98.6 ml/min. In contrast to 30-day mortality, CRP, diabetes, and prior angina were significant prognostic factors, whereas past use of hyperlipidemic therapy and PCI were no longer significant factors to long-term prognosis. There was also a significant interaction between NT-proBNP and age ($p = 0.006$). In 30-day survivors, the risk profile changed to some extent (Appendix 2, Table A2.1). Whereas TnT was no longer a significant factor, 30-day post-randomization PCI reduced the likelihood of death by 50% ($p = 0.001$).

Model performance. The Hosmer-Lemeshow goodness-of-fit test statistic indicated adequate fit of all models (30-day mortality: chi-square = 4.72 [$p = 0.787$]; 30-day death/MI: chi-square = 11.84 [$p = 0.158$]; 1-year mortality: chi-square = 5.72 [$p = 0.679$]), and calibration was

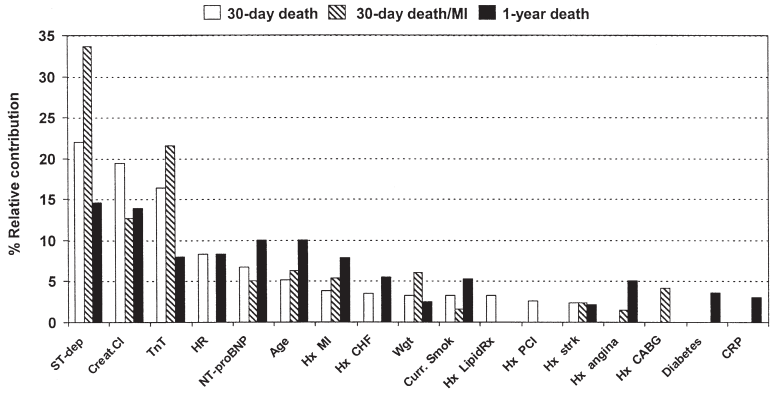


Figure 1. Relative contribution of significant, independent factors to the prediction of 30-day death, 30-day death/myocardial infarction (MI), and 1-year death. Creat. Cl. = creatinine clearance; CRP = C-reactive protein; Curr. Smok. = current smoker; HR = heart rate; Hx Ang = history of angina pectoris; Hx CABG = history of coronary artery bypass graft; Hx CHF = history of congestive heart failure; Hx MI = history of MI; Hx lipidRx = history of hyperlipidemic therapy; Hx PCI = history of percutaneous coronary intervention; Hx strk = history of stroke; NT-proBNP = N-terminal pro-brain natriuretic peptide; ST-dep = ST-segment depression; TnT = troponin T; Wgt = weight.

excellent (Fig. 2). The c-index was 0.83 for the 30-day mortality model, which reflected excellent discriminatory power. The level of over-optimism determined by bootstrapping was 0.01, which reduced the c-index$_{adjusted}$ to 0.82. The model predicting 1-year mortality had comparable discriminatory power of c-index$_{adjusted}$ = 0.81 (over-optimism = 0.01), whereas it was lower for 30-day death/MI (0.72 [over-optimism = 0.01]).

Incremental value of novel risk factors. The incremental value of quantitative ST-segment depression and these biomarkers over "traditional" patient characteristics (e.g., age, comorbidities, history of cardiovascular disease, heart rate) was assessed with 2 approaches. First, the relative contribution of each independent predictor in the model was estimated (Fig. 1). Second, as each of these novel risk factors was added to the model of traditional baseline characteristics, a noticeable increase in the c-index$_{adjusted}$ was observed (Fig. 3).

Simplified risk scores. As shown in Figure 4, the 5-factor risk score ranged from 0 in patients with no risk factors to 51 in those with all (and the most severe degree) of the risk factors for 30-day mortality, from 0 to 39 for 30-day death/MI, and from 0 to 48 for 1-year mortality. The accompanying nomogram translates the risk score into the likelihood of the outcome. The discriminatory power of the risk scores was slightly attenuated but remained reasonably strong (c-index$_{adjusted}$ = 0.78, 0.67, and 0.77, respectively).

DISCUSSION

This large study of contemporary NSTE-ACS patients highlights the striking prognostic value of quantitative ST-segment depression even in the context of an expanded biomarker profile including creatinine clearance, NTproBNP, TnT, and CRP as well as other more traditional baseline risk factors such as creatinine clearance and age.

Electrocardiography has long been

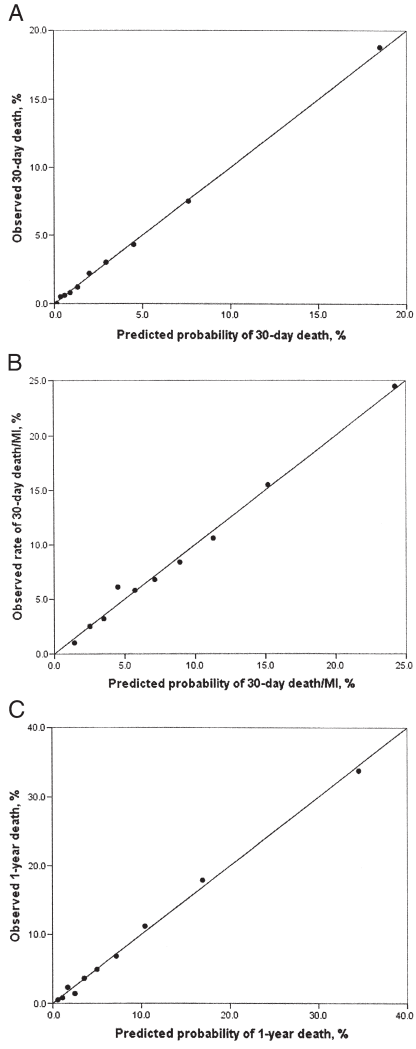


Figure 2. Calibration of risk models: **(A)** 30-day death; **(B)** 30-day death/myocardial infarction (MI); **(C)** 1-year death. **Dots** represent deciles of predicted risk; the **solid line** represents perfect calibration.

an essential clinical tool in the evaluation of ACS as it is inexpensive, readily available, and non-invasive. Numerous studies on the basis of clinical trial and registry samples have also demonstrated that ST-segment depression on the admission ECG is highly influential on short- and long-term outcomes (6,15,16). Although the binary indicator (i.e., presence vs. absence of ST-segment depression) is often used in risk stratification, an increasing body of evidence, including this study, has demonstrated that quantitative ST-segment depression is a substantial refinement (7,8). The PARAGON-A (Platelet IIb/IIIa Antagonism for the Reduction of Acute Global Organization Network) investigators (7) noted a steady increase in 30-day and 1-year mortality as the extent of ST-segment depression rose (30-day mortality: 0.7% [no ST-segment depression], 2.8%[1-mm], and 6.3% [≥2-mm ST-segment depression]; 1-year mortality: 2.0%, 7.8%, and 13.4%, respectively). After baseline adjustment, ST-segment depression made the highest relative contribution to the prediction of 1-year mortality, which was similarly observed in this study.

The quantitative collection of indicators of renal function, myocardial necrosis, hemodynamic stress, and inflammation offered a unique opportunity to explore the pathophysiology of ACS. Abnormal renal function is a well-documented predictor of morbidity and mortality in a wide variety of patients (17). In concert with other ACS studies, lower levels of creatinine clearance were significantly associated with poorer short- and long-term prognosis, even though patients with advanced renal dysfunction were excluded from this trial (9). Impaired renal function might also alter the prognostic value of other serum biomarkers, because their clearance might be inhibited; however, previously published findings dispel

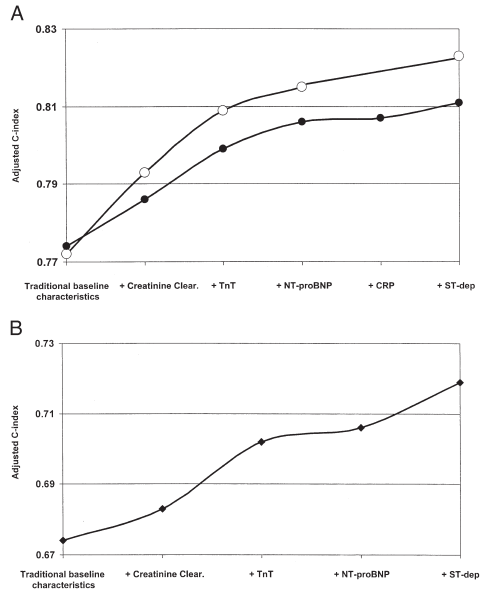


Figure 3. Increase in adjusted C-index as biomarkers and quantitative ST-segment depression are added to the models predicting **(A)** 30-day **(open dots)** and 1-year death **(closed dots)** and **(B)** 30-day death or MI **(closed diamonds)**. Abbreviations as in Figure 1.

this concern (11,18).

In the past, creatine kinase-MB was the reference standard in MI diagnosis, but troponins have replaced creatine kinase-MB with improved sensitivity and specificity (13). In the current study, TnT was ranked second and third among the predictors of 30-day death/MI and 30-day death, respectively, which reflects its role as a highly sensitive marker of myocardial necrosis in the acute phase. Although TnT remained a significant predictor of 1-year mortality (in all-comers), its influence declined over time after the index coronary event.

Elevated levels of BNP have been linked with left ventricular dysfunction and poorer prognosis in patients with heart failure and other associated disorders. Recently, these observations have been extended to ACS patients in whom elevated BNP levels also might be the result of transient ischemia (19–21). As demonstrated previously, increasing quartiles of NT-proBNP were strongly related to an increase in the odds of 30-day and 1-year mortality but not of 30-day MI, after multivariable adjustment (21). Although this relationship remained robust in the current study, it was no longer the top contributor of prognostic information after introducing the extent of ST-segment depression.

The role of inflammation in the pathophysiology of ACS is increasingly important, with CRP as one of the best recognized markers. Although once thought to have a passive role in vascular inflammation, CRP might be an active contributor to atherogenesis, as suggested by recent evidence

Factors	30-day Death	30-day Death/MI	1-year Death
Age (years), <58		0	0
58-65		2	3
66-74		5	8
>74		5	9
Body weight(kg), <69		0	
69-75		1	
76-85		2	
>85		4	
Heart rate(bpm), <61	0		0
61-68	1		1
69-79	3		4
>79	3		5
Creatinine clearance (mL/min), >98.6	0	0	0
76.9-98.6	7	3	6
58.4-76.9	12	5	9
≤58.4	16	9	14
ST-depression(mm), None	0	0	0
0.5	1	2	1
1.0-1.5	6	6	3
≥2	14	12	10
Confounders	10	8	8
Troponin-T(μg/L), ≤0.01	0	0	
0.01-0.12	7	8	
0.12-0.47	7	9	
>0.47	12	9	
NT-proBNP(ng/L), ≤237	0		0
237-669	5		3
669-1896	7		6
>1896	10		10
MAXIMUM SCORE	**51**	**39**	**48**

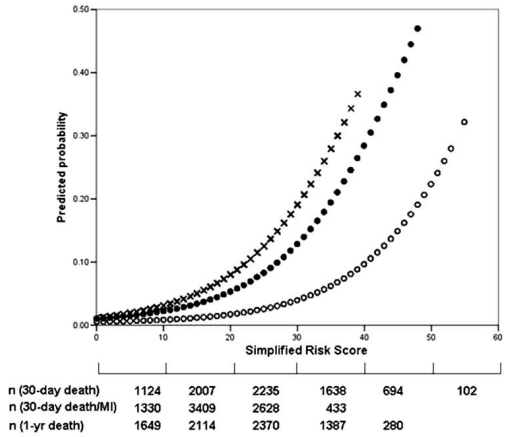


Figure 4. Simplified risk score and nomogram to estimate risk of mortality at 30 days **(open dots)** and 1 year **(closed dots)** and of death or myocardial infarction (MI) at 30 days **(solid x's)**.

(22). Similar to the current study, others observed that the prognostic impact of elevated CRP was not evident early after the coronary event but emerged later as an index of the ongoing evolution of coronary artery disease (23–25).

Classical risk factors such as age and heart rate played a significant role in risk prediction; however, compared with previously published risk models, these factors lost considerable prognostic value in the current study with the inclusion of quantitative ST-segment depression and biomarkers(1,2,26). Heart rate was not an independent predictor of 30-day death/MI, a finding similar to those of other studies, (2).

Clinical implications. Whether risk stratification that defines the optimal management strategy should be driven by non-invasive determinants of ischemia or knowledge of the coronary anatomy remains controversial. Although there is general consensus that patients at highest baseline risk tend to benefit most from early invasive therapy, others have argued that despite risk, invasive angiography and/or revascularization should become the standard of care in virtually all such patients. Higher rates of early invasive treatment, however, do not necessarily translate into improved outcomes in all patients, especially in those without ST-segment changes (27–29). International practice patterns revealed that the use of angiography and angioplasty in NSTE-ACS patients was inversely related to the extent of ST-segment depression (30). Thus, improved risk

assessment as proposed in the current study would better identify patients at increased risk, in whom coronary intervention should be considered, and its implementation might result in the increased efficiency of care. It seems clear that application of this approach depends, to some extent, on what risk one aims to predict and when. As evident in Figure 1, the shorter-term risk of death is strongly influenced by ST-segment depression, renal function, cardiac troponin, and NT-proBNP in addition to traditional risk factors. The relative contribution of ST-segment depression and troponin is actually enhanced as it relates to 30-day death/MI. By 1 year some repositioning occurs such that age, diabetes, prior angina, and CRP appear as factors associated with mortality: whereas the influence of ST-segment depression remains strong, NT-proBNP is strengthened, and troponin is attenuated.

Identifying appropriate treatment strategies might be facilitated through the use of simplified risk models in clinical practice. Several user-friendly risk scores have been developed from clinical trial and registry populations, such as the Thrombolysis In Myocardial Infarction (TIMI) risk score in NSTE-ACS and the recently published risk score from the GRACE (Global Registry of Acute Coronary Events) registry (3,4). However, there are notable limitations.

Although the TIMI risk score contains few factors, its discriminatory power is modest (c index = 0.65), which limits its clinical application. And although the GRACE registry risk score extends beyond the TIMI risk score to include serum creatinine, heart rate, and systolic blood pressure, it is lacking quantitative ST-segment depression, NT-proBNP, and CRP, which were shown to have significant prognostic value in the current study and other studies.

Some limitations of our study should be addressed. First, baseline systolic blood pressure was not available and could have influenced our findings. However, this seems unlikely. An ad hoc analysis of the PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) 30-day death model revealed that if systolic blood pressure was not included, the top 5 predictors (as measured by percent Sigma chi-square) to the model—heart rate(interaction with AMI/UA), age, rales, ST-segment depression (yes/no), and region of enrolment—essentially remained unchanged from the model that included systolic blood pressure (2). Notably, if one of the top indicators, such as heart rate, was not included in the model, the structure of the overall model changed significantly. Second, the extrapolation of these findings to the general ACS population might be in question. According to the protocol, coronary angiography was restricted at least 12 h after the completion of the study drug infusion. Although this might not be routine procedure in many tertiary facilities, it likely is representative of the sizeable proportion of the overall ACS population who do not present

directly to these facilities. And finally, the external validation of these risk models was not provided. To our knowledge, no other clinical trial or population-based cohort possesses the requisite ECG and/or biomarker data required for this task. Validation of clinically meaningful cut points will also be important. Future investigations should incorporate these indicators into their design to achieve this.

In conclusion, the degree of ST-segment depression was the highest contributor to the prediction of 30-day and 1-year mortality and 30-day death/MI in a contemporary sample of 7,800 NSTE-ACS patients. Creatinine clearance, TnT, and NT-proBNP also were significant independent prognostic indicators of adverse outcomes, whereas CRP was only significant in the long-term prediction. The current study provides novel contemporary insights into the risk stratification of NSTE-ACS patients, which might be of particular value in identifying strategies for risk reduction and the planning of future studies.

ACKNOWLEDGMENTS

The authors acknowledge Dr. Wilson W. H. Tang and Dr. Hitinder S. Gurm of the Cleveland Clinic Foundation (Cleveland, Ohio) for their contributions to this manuscript and the collection of heart rate and electrocardiographic data. Dr. Jan-Paul Ottervanger (Hospital De Weezenlanden, Zwolle, the Netherlands) and Dr. Timo Lenderink (Erasmus Medical Center, Rotterdam, the Netherlands) are also thanked for their critical review of earlier drafts of this manuscript. Additional statistical expertise was provided by Dr. Wei-Ching Chang of the Canadian VIGOUR Centre (Edmonton, Alberta, Canada), Dr. Ewout Steyerberg of Erasmus Medical Center (Rotterdam, the Netherlands) and Ms. Karen Pieper of Duke Clinical Research Institute (Durham, North Carolina).

REFERENCES

1. Armstrong PW, Fu Y, Chang WC, et al. Acute coronary syndromes in the GUSTO-IIb trial: prognostic insights and impact of recurrent ischemia. The GUSTO-IIb Investigators. Circulation 1998;98:1860–8.

2. Boersma E, Pieper KS, Steyerberg EW, et al. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients. The PURSUIT Investigators. Circulation 2000;101:2557– 67.

3. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. JAMA 2000;284:835–42.

4. Eagle KA, Lim MJ, Dabbous OH, et al. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month post-discharge death in an international registry. JAMA 2004;291:2727–33.

5. Cannon CP, McCabe CH, Stone PH, et al. The electrocardiogram predicts one-year outcome of patients with unstable angina and non–Q-wave myocardial infarction:

results of the TIMI III Registry ECG Ancillary Study. Thrombolysis In Myocardial Ischemia. J Am Coll Cardiol 1997;30:133– 40.
6. Holmvang L, Luscher MS, Clemmensen P, Thygesen K, Grande P. Very early risk stratification using combined ECG and biochemical assessment in patients with unstable coronary artery disease (a Thrombin Inhibition in Myocardial Ischemia [TRIM] Substudy). The TRIM Study Group. Circulation 1998;98:2004 –9.
7. Kaul P, Fu Y, Chang WC, et al. Prognostic value of ST segment depression in acute coronary syndromes: insights from PARAGON-A applied to GUSTO-IIb. PARAGON-A and GUSTO IIb Investigators. Platelet IIb/IIIa Antagonism for the Reduction of Acute Global Organization Network. J Am Coll Cardiol 2001;38:64 –71.
8. Kaul P, Newby LK, Fu Y, et al. Troponin T and quantitative ST-segment depression offers complementary prognostic information in the risk stratification of acute coronary syndrome patients. J Am Coll Cardiol 2003;41:371– 80.
9. Simoons ML, GUSTO IV-ACS Investigators. Effect of glycoprotein IIb/IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes without early coronary revascularisation: the GUSTO IV-ACS randomised trial. Lancet 2001;357:1915–24.
10. Ottervanger JP, Armstrong P, Barnathan ES, et al. Long-term results after the glycoprotein IIb/IIIa inhibitor abciximab in unstable angina: one-year survival in the GUSTO IV-ACS (Global Use of Strategies To Open Occluded Coronary Arteries IV–Acute Coronary Syndrome) trial. Circulation 2003;107:437– 42.
11. James SK, Lindahl B, Siegbahn A, et al. N-terminal pro-brain natriuretic peptide and other risk markers for the separate prediction of mortality and subsequent myocardial infarction in patients with unstable coronary artery disease: a Global Utilization of Strategies To Open occluded arteries (GUSTO)-IV substudy. Circulation 2003;108: 275–81.
12. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31– 41.
13. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non–ST-segment elevation myocardial infarction—summary article: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee on the Management of Patients With Unstable Angina). J Am Coll Cardiol 2002;40:1366 –74.
14. Schumacher M, Hollander N, Sauerbrei W. Resampling and crossvalidation techniques: a tool to reduce bias caused by model building? Stat Med 1997;16:2813–27.
15. Holmvang L, Clemmensen P, Wagner G, Grande P. Admission standard electrocardiogram for early risk stratification in patients with unstable coronary artery disease not eligible for acute revascularization therapy: a TRIM substudy.

ThRombin Inhibition in Myocardial Infarction. Am Heart J 1999;137:24 – 33.
16. Hyde TA, French JK, Wong CK, Straznicky IT, Whitlock RM, White HD. Four-year survival of patients with acute coronary syndromes without ST-segment elevation and prognostic significance of 0.5-mm ST-segment depression. Am J Cardiol 1999;84: 379 – 85.
17. Ruilope LM, van Veldhuisen DJ, Ritz E, Luscher TF. Renal function: the Cinderella of cardiovascular risk profile. J Am Coll Cardiol 2001;38:1782–7.
18. Aviles RJ, Askari AT, Lindahl B, et al. Troponin T levels in patients with acute coronary syndromes, with or without renal dysfunction. N Engl J Med 2002;346:2047–52.
19. de Lemos JA, Morrow DA, Bentley JH, et al. The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. N Engl J Med 2001;345:1014 –21.
20. Omland T, Persson A, Ng L, et al. N-terminal pro-B-type natriuretic peptide and long-term mortality in acute coronary syndromes. Circulation 2002;106:2913– 8.
21. James S, Armstrong P, Califf R, et al. Troponin T levels and risk of 30-day outcomes in patients with the acute coronary syndrome: prospective verification in the GUSTO-IV trial. Am J Med 2003;115:178–84.
22. Blake GJ, Ridker PM. C-reactive protein and other inflammatory risk markers in acute coronary syndromes. J Am Coll Cardiol 2003;41: 37S–42S.
23. Lindahl B, Toss H, Siegbahn A, Venge P, Wallentin L. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. N Engl J Med 2000;343:1139–47.
24. Heeschen C, Hamm CW, Bruemmer J, Simoons ML. Predictive value of C-reactive protein and troponin T in patients with unstable angina: a comparative analysis. CAPTURE Investigators. Chimeric c7E3 AntiPlatelet Therapy in Unstable angina REfractory to standard treatment trial. J Am Coll Cardiol 2000;35:1535– 42.
25. Lenderink T, Boersma E, Heeschen C, et al. Elevated troponin T and C-reactive protein predict impaired outcome for 4 years in patients with refractory unstable angina, and troponin T predicts benefit of treatment with abciximab in combination with PTCA. Eur Heart J 2003;24:77– 85.
26. Malmberg K, Yusuf S, Gerstein HC, et al. Impact of diabetes on long-term prognosis in patients with unstable angina and non–Q-wave myocardial infarction: results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry. Circulation 2000;102: 1014–9.
27. Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med 2001;344:1879–87.
28. Lagerqvist B, Safstrom K, Stahle E, Wallentin L, Swahn E, FRISC II Study Group. Is early invasive treatment of unstable coronary

artery disease equally effective for both women and men? FRISC II Study Group Investigators. J Am Coll Cardiol 2001;38:41– 8.
29. de Winter RJ, Windhausen F, Cornel JH, et al. Early invasive versus selectively invasive management for acute coronary syndromes. N Engl J Med 2005;353:1095–104.
30. Kaul P, Newby LK, Fu Y, et al. Relation between baseline risk and treatment decisions in non-ST segment elevation acute coronary syndromes: an examination of international practice patterns. Heart 2005;91:876–81.

APPENDIX

For an independent analysis of the relative prognostic power of TnT over creatine kinase-MB as the preferred marker of myocardial damage and adjusted odds ratios and 95% confidence intervals of baseline characteristics in predicting 1-year mortality in 30-day survivors, please see the online version of this article.

Chapter Two

Forecasting mortality: dynamic assessment of risk in ST-segment elevation acute myocardial infarction

Wei-Ching Chang, Padma Kaul, Yuling Fu, Cynthia M. Westerhout, Christopher B. Granger, Kenneth W. Mahaffey, Lars Wallentin, Frans Van de Werf, and Paul W. Armstrong for the ASSENT-3 Investigators

AIMS To demonstrate the feasibility and clinical utility of developing dynamic risk assessment models for ST-segment elevation myocardial infarction (STEMI) patients.
METHODS AND RESULTS In 6066 STEMI patients enrolled in the Assessment of the Safety and Efficacy of a New Thrombolytic-3 (ASSENT-3) trial with complete electrocardiographic data, we assessed the probability of 30-day mortality over the following forecasting periods beginning at day 0 (baseline), 3 h, day 2, and day 5 using multiple-logistic regression. These models were validated and simplified in independent samples of 1622 similar fibrinolytic-treated patients from the ASSENT-3 PLUS trial and in 814 STEMI patients undergoing primary percutaneous coronary intervention in the COMplement inhibition in Myocardial infarction treated with Angioplasty (COMMA) trial. The discriminatory power of these predictive models, from baseline to day 5, was excellent (c-statistics 0.80 to 0.87); and their predictive ability was supported by strong gradients in mortality outcomes as the risk score increased. Dynamic modelling also provided information on the change in prognosis over time which may be used to advise more appropriate therapeutic decisions, e.g. the identification of high-risk patients for possible co-interventions.
CONCLUSION Dynamic modelling for STEMI patients enhances the risk assessment and stratification and should provide valuable ongoing guidance for their management.

By virtue of its nature and the demands of the health care system, medical decision-making in acute coronary syndromes (ACS) is a dynamic process. Patients are continually assessed from the time of entry into the health care system until discharge and throughout the follow-up care. Critical decisions, based in part on the expected outcomes, must be promptly made on admission and over the next several hours and days, as well as at the time of hospital discharge. To help guide patient management and reflect the rapid transition of patient status during hospital stay, we previously introduced the concept of dynamic risk modelling in non-ST-segment elevation ACS patients enrolled in the Global Utilization of Strategies to Open Occluded Arteries- IIb (GUSTO-IIb) trial.[1] Because the short-term morbidity and mortality for ST-segment elevation myocardial infarction (STEMI) patients exceed that of patients without ST-segment elevation, we now extend this concept to provide relevant and timely prognostic information at key decision points for this important population.

As prognostic indices derived from complex models are rarely used in clinical practice,[2] our aim is to further develop simplified and valid risk scores for this dynamic process that can be used at the bedside for risk assessment and clinical management. More specifically, we undertook to: (1) develop a series of prognostic models (dynamic risk models) incorporating clinically relevant information unfolding during the hospital stay; (2) validate these models in independent STEMI patient populations; and (3) generate simplified risk scores and explore their clinical utility.

METHODS

Data sources

Data from the Assessment of the Safety and Efficacy of a New Thrombolytic-3 (ASSENT-3) trial were used to develop a series of dynamic models, which were validated in two independent samples: one with fibrinolytic therapy and the other with primary percutaneous coronary intervention (PCI). The details of these trials have been published previously.[3–5] Briefly, in the ASSENT-3 trial, 6095 STEMI patients presenting ≤6 h of symptom onset were randomly assigned to one of the three treatment groups: full-dose tenecteplase and enoxaparin for a maximum of 7 days, full-dose tenecteplase with weight-adjusted unfractionated heparin for 48 h, or half-dose tenecteplase with weight-adjusted low-dose unfractionated heparin and a 12-h infusion of abciximab. Our study sample consisted of 6066 patients after excluding 29 patients with missing baseline electrocardiographic data.

Our first validation sample consisted of 1622 out of 1639 patients from the ASSENT-3 PLUS trial (after excluding 13 patients who died prior to hospital admission and four patients with missing 30-day mortality data), which enrolled STEMI patients presenting ≤6 h of symptom onset in the pre-hospital setting. Patients were randomly assigned to treatment with tenecteplase and either with enoxaparin or with weight-adjusted unfractionated heparin for 48 h as in the two arms of the ASSENT-3 trial common to ASSENT-3 PLUS.

To broaden the applicability of this approach to patients with primary PCI, we used a second validation sample consisted of 814 STEMI patients enrolled in the COMplement inhibition in Myocardial infarction treated with Angioplasty (COMMA) trial between January 2000 and April 2002, who arrived <6 h of symptom onset with ST-segment elevation ≥2 mm in two contiguous leads or new left-bundle branch block (LBBB). The patients, who were to be treated with primary PCI, were randomly assigned to receive placebo bolus and placebo infusion, 2.0 mg/kg bolus of pexelizumab and placebo infusion for 20 h administered 4 h after the bolus, or 2.0 mg/kg bolus and 0.05 mg/kg/h of infusion of pexelizumab for 20 h.

Categorization of data

We categorized the continuous variables according to the conventions (e.g. age <65, 65–74, 75+; and ST-segment resolution of <30, 30–70, 70+) or the quartiles of

these variables (heart rate, systolic BP, total ST-segment deviation, and QRS scores) as explained subsequently. Given the prognostic importance of the baseline electrocardiogram (ECG) and subsequent ST-segment resolution data in ACS patients,[1,6,7] we incorporated serial ECG data collected after admission to assess the effect of the response to therapy. ECGs were collected in all patients at baseline and at 1 and 3 h after treatment in ASSENT-3 and ASSENT-3 PLUS6 and at baseline, 30 min post-PCI, and 24 h after enrolment in COMMA.5 ECG data were incorporated using three measures: total baseline ST-segment deviation categorized into <12, 12–17, >17 mm; baseline Selvester QRS score[8] categorized into 0–1, 2–4, >4; and ST-segment resolution at 1 and 3 h categorized according to Schroeder's method[9] as complete resolution (≥70%), partial resolution (30–70%), and no ST-segment resolution (<30%). In all trials, however, there were missing or incomplete ECG data/confounders (i.e. without the protocol-defined amount of ST-segment elevation, had LBBB, paced rhythm, ventricular rhythm, or poor quality ECGs) that did not allow for an accurate assessment of ST-segment resolution and QRS scores. Also excluded from the baseline QRS-score assessment were right-bundle branch block (RBBB), Wolff Parkinson White pattern (WPW), left anterior fascicular block (LAHB), left posterior fascicular block (LPHB), left ventricular hypertrophy (LVH), and right ventricular hypertrophy (RVH). The proportion of technically suitable ECGs varied between the time of collection and among trials, as shown in Table 1.

Model development

Our primary endpoint was 30-day all-cause mortality. Four models were developed sequentially in our study (Figure 1), incorporating the information collected at baseline (day 0 model), at 3 h (3 h model), at day 2 (day 2 model), and at day 5 of the hospital stay (day 5 model). These time points were selected to coincide with conventional clinical practice: at baseline to devise an initial assessment/management plan; at 3 h to incorporate the ST-resolution status relating to the success of reperfusion therapy; at the end of day 1 to reassess the early intervention strategies; and at day 4 to further adjust patient management strategies including possible early discharge. The following variables were included in the 30-day mortality models. Day 0 model: Baseline patient data such as demographics (e.g. age, sex, and race), medical histories (e.g. prior MI, hypertension), and presenting characteristics (e.g. Killip class, systolic blood pressure, total ST-deviation, and QRS score). 3 h model: The baseline data plus ST-segment resolution status at 1 and 3 h. Day 2 model: The baseline and 3 h data plus data on revascularization procedures and adverse events that occurred during day 0–1. Day 5 model: The baseline and 3 h data plus data on revascularization procedures and adverse events that occurred prior to day 5.

Table 1 Baseline patient characteristics in the ASSENT-3 trial and the validation samples from the ASSENT-3 PLUS and COMMA trials

	ASSENT-3	ASSENT-3+	COMMA
n	6066	1622	814
Age (years), median (IQR)	61 (52, 70)	62 (53, 72)	60 (51, 71)
≥75 years	14	20	19
Female (%)	24	23	25
Caucasian (%)	85	62	85
Diabetes mellitus (%)	18	15	19
Hypertension (%)	41	36	52
Killip class (%)			
I	89	93[a]	84
II	10	5	13
III–V	2	2	3
Anterior MI (%)	39	42	79
Systolic blood pressure (mmHg), median (IQR)	132 (119, 150)	133 (120, 150)	135 (118, 155)
Heart rate (b.p.m.), median (IQR)	73 (62, 85)	74 (60, 85)	78 (66, 90)
QRS score (%)			
0–1	25	23	26
2–4	28	22	30
>4	22	18	27
Confounders[b]/missing	25	36	17
Total ST-segment deviation (mm) (%)			
<12	46	38	44
12–17	22	26	20
>17	21	24	20
Confounders[b]/missing	11	13	16
ST-segment resolution at 3 h (%)			
No resolution	14	16	10
Partial	25	26	26
Complete	42	39	49
Confounders[b]/missing	20	19	15

b.p.m., beats per minute; MI, myocardial infarction; IQR, interquartile range.
[a]21% of Killip class data were missing in ASSENT-3 PLUS and were excluded in these calculations.
[b]ECG confounders were those without the protocol-defined amount of ST-segment elevation, had LBBB, paced rhythm, ventricular rhythm, or poor quality ECGs that did not allow for an accurate assessment of ST-segment resolution and QRS scores. Also excluded from the baseline QRS-score assessment were RBBB, WPW, LAHB, LPHB, LVH, and RVH.

Multiple-logistic regression procedures for patients who survived to the start of the forecasting period, based on the stepwise, backward variable selection method, were used to develop these models. We assessed the relative contribution of a prognostic factor in the logistic regression model as the proportion of the chi-square value associated with that factor out of the sum of all chi-square values associated with all significant factors. In developing these models, we monitored the use of revascularization [i.e. PCI and coronary artery bypass grafting (CABG)] procedures and the occurrence of serious in-hospital adverse events, defining a broad clinical category of heart failure as a composite of cardiogenic shock, pulmonary edema, or right heart failure and an electrical disorder as a composite of asystole, electro-mechanical dissociation, or ventricular fibrillation after day 1. Missing data were treated either as separate categories or imputed as non-events when they were shown to be associated with the lower 30-day mortality.

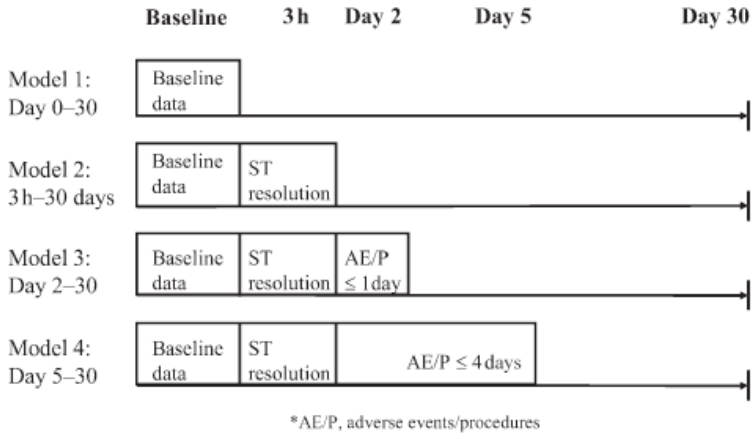


Figure 1 Dynamic modelling of 30-day mortality consisting of four separate models: Model 1 predicts 0–30 day mortality based only on baseline data; Model 2 predicts 3 h to 30 day mortality based on baseline and ST-segment resolution data; Model 3 predicts day 2–30 mortality based also on adverse events and procedures that occurred within 1 day; and Model 4 predicts day 5–30 based on all the data available up to the end of day 4.

Model validation

We evaluated our models based on the discriminatory capacity (i.e. c-statistic) and the model calibration (i.e. concordance between the predicted and the observed outcomes).[10,11] Bootstrapping was performed to estimate the degree of over-optimism associated with c-statistics.12 The validation was performed internally on ASSENT-3 and externally on ASSENT-3 PLUS and COMMA, as noted earlier. In validating these models, we checked the correlation matrices, performed backward stepwise regression, and examined the standard errors of coefficients and interactions among these variables to assess any collinearity and confounding factors.

Simplified risk scores and clinical applications

To illustrate the potential of dynamic risk modelling for bedside use, we further developed and validated simplified risk scores from the day 0, 3 h, day 2, and day 5 models. This was done by assigning points to the coefficients of the most significant (i.e. $x^2 \geq 10$ in Supplementary material online, Table S1) predictors in the models in a 0.5 increment as follows: one point for the coefficient ß = 0.5±0.25, two points for ß = 1.0±0.25, three points for ß = 1.5±0.25, and so on.[13] We then calculated the total risk score for each patient at each period as the sum of the points assigned to the patient's applicable risk factors in the model. These simplified risk scores were validated as for the full models, in terms of both model discrimination and calibration.

To compare our approach with a conventional risk assessment tool,

Table 2 Events and procedures during hospitalization

	Day 0–1 ($n = 6066$)	Day 2 ($n = 5968$)	Day 3–4 ($n = 5879$)	Day 5/disch ($n = 5839$)	Day 0–disch ($n = 6066$)	Median days to event
In-hospital events						
Serious recurrent ischaemia	84 (1.4)	39 (0.5)	29 (0.5)	53 (0.9)	180 (3.0)	2.0
Re-infarction	104 (1.7)	12 (0.2)	27 (0.5)	38 (0.7)	180 (3.0)	1.0
Electrical disorder	132 (2.2)	132 (2.2)	21 (0.4)	46 (0.8)	220 (3.6)	0.0
Heart failure	223 (3.7)	40 (0.7)	28 (0.6)	44 (0.8)	335 (5.5)	1.0
Cardiogenic shock	143 (2.4)	27 (0.5)	14 (0.2)	27 (0.5)	210 (3.5)	1.0
Stroke	61 (1.0)	3 (0.1)	16 (0.3)	14 (0.2)	94 (1.5)	1.0
Major bleeding	51 (0.8)	13 (0.2)	21 (0.4)	106 (1.8)	191 (3.1)	2.0
Death[a]	98 (1.6)	89 (1.5)	40 (0.7)	92 (1.5)	312 (5.1)	2.0
In-hospital procedures						
Percutaneous coronary intervention	662 (10.9)	182 (3.0)	280(4.8)	628 (10.8)	1737 (28.6)	3.0
Bypass surgery	27 (0.4)	17 (0.3)	60 (1.0)	170 (2.9)	274 (4.5)	6.0

Percentage of patients in parentheses. Both fatal and non-fatal events and procedures were included in these figures other than the row labelled as Death.
[a]The number of deaths was 359 (5.9%) in 30 days: 312 (5.1%) in hospital, and 47 (0.8%) between discharge (disch) and 30 days.

we also calculated for each patient a simple Thrombolysis In Myocardial Infarction (TIMI) risk index as follows: (heart rate x $[age/10]^2$) /(systolic blood pressure).[14] This composite index was then used in lieu of the three separate factors of age, heart rate, and systolic blood pressure in our four full models in ASSENT-3 to evaluate the relative contributions of this index to mortality prediction over time. All analyses were performed using SPSS version 13.0 (Chicago, IL, USA) except for bootstrapping, which was performed using STATA version 7 (College Station, TX, USA).

RESULTS

Our ASSENT-3 study sample consisted of 6066 patients whose median age was 61, 24% were women, and 85% were Caucasians. There were some differences in baseline patient characteristics between ASSENT-3 and the validation datasets: patients in ASSENT-3 PLUS were slightly older with fewer Caucasians in the sample, and more patients in COMMA had hypertension and anterior MI as well as higher heart rates (Table 1). Serious in-hospital adverse events among patients in ASSENT-3 were as follows: 3.0% for recurrent ischaemia and also for re-infarction, 3.6% for electrical disorders, 5.5% for heart failure, 1.5% for stroke, 3.1% for major bleeding, and 5.1% for death. Most of these complications occurred within the first few days. In-hospital PCI and CABG procedures were performed on 28.6 and 4.5% of the patients, respectively, with a median of 3 and 6 days to these procedures (Table 2).

Model development

A series of predictive models forecasting 30-day mortality from baseline, 3 h, day 2, and day 5 were developed on the basis of patient characteristics, complications, and procedures acquired up until the beginning of each forecasting period (Tables 1 and 2) and are hereafter referred to as the 'full ASSENT-3 models' (Supplementary material online). As shown in Figure 2A, the three most influential factors in the baseline model were age, systolic blood pressure, and heart rate,

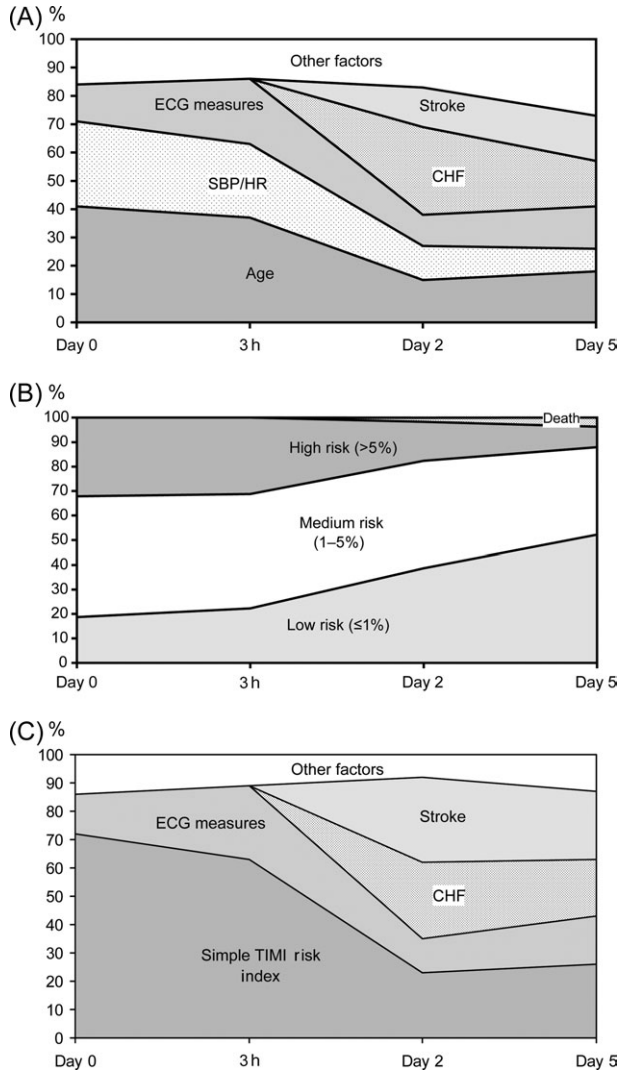


Figure 2 Changing influences of prognostic factors from baseline to day 5 (*A*), and the proportions of patients whose risk of 30-day mortality were assessed as low (≤1%), medium (1–5%), and high (>5%) from baseline to day 5 (*B*). (*A*) is nearly replicated when age, heart rate, and systolic blood pressure were replaced by the simple TIMI risk index composed of these three factors (*C*).

which accounted for 70% of the relative contribution to the mortality prediction. At 3 h, the relative contribution of these factors declined to 63%, and at both day 2 and day 5, it further dropped to 26%. The ECG measures, including the total ST-segment deviation and QRS score at baseline and the ST-segment resolution status at 3 h, accounted

for 13% of the relative contribution at baseline, 23% at 3 h, but attenuated to 11 and 15% at day 2 and day 5, respectively. The in-hospital events of heart failure and stroke were particularly influential and accounted for 45 and 32% of the relative contribution at day 2 and day 5, respectively. Figure 2B depicts the trends in prognosis over time according to low (≤1%), medium (1–5%), and high risk (>5%) of 30-day mortality. Interestingly, the proportion of low-risk patients increased steadily from 18.7% at baseline to 52.2% at day 5, whereas that of high-risk patients declined steadily from 32.1 to 8.4% between baseline and day 5, with an additional 3.7% expiring during that period.

Model validation

As detailed in Supplementary material online, the c-statistics associated with the four full ASSENT-3 models ranged from 0.82 to 0.87, and increased from 0.76 at baseline to 0.84 at day 5 when restricted only to those patients who survived the first four days of hospitalization. The amount of over-optimism was minimal, ranging from 0.004 to 0.005 for the baseline to day 2 models and 0.010 for the day 5 model. None of the Hosmer–Lemeshow statistics for these models was significant, and the Pearson correlation coefficients ranged from 0.997 to 0.999 between the predicted and the observed 30-day mortality probabilities for all models based on the deciles of these probabilities.

The full ASSENT-3 models were then externally validated in ASSENT-3 PLUS and COMMA (Supplementary material online).

The c-statistics ranged from 0.78 to 0.82 when the full ASSENT-3 models were applied to the ASSENT-3 PLUS data, and none of the Hosmer–Lemeshow statistics for these four models was significant. The Pearson correlation coefficients ranged from 0.87 to 0.93 between the predicted and the observed 30-day mortality probabilities for all models based on the deciles of these probabilities. When applied to the COMMA data, the c-statistics ranged from 0.83 to 0.86; and the Pearson correlation coefficients ranged from 0.93 to 0.97 between the predicted and the observed 30-day mortality probabilities, with non-significant Hosmer–Lemeshow statistics for all four models; thus showing the robustness of our ASSENT-3 models. Over-optimism was negligible (<0.001) for all these (full and their simplified) models, because only one predictor variable derived from the ASSENT-3 models was involved in each of these validation models.

Simplified risk scores and clinical applications

The simplified risk scores from the full ASSENT-3 models are detailed in Table 3, and the strong gradients of mortality rates associated with them are depicted in Figure 3. Their discriminatory capacity was also excellent, with the c-statistics ranging from 0.80 to 0.86 (Table 3). A more detailed account of the validation of the simplified models together with their applications to

Table 3 Points assigned to selected factors for developing simplified risk scores[a]

Factor	Day 0	3 h	Day 2	Day 5
Age (years)				
65–74	2	2	2	1
75+	4	4	3	3
Killip class				
II	1	1		
III–IV	3	3		
Heart rate (b.p.m.)				
63–85	1	1	1	
>85	2	2	2	
Systolic BP (mmHg)				
<120	2	2	2	1
120–132	1	1	1	1
Total ST-segment deviation (mm)				
≥12	1	1	1	1
ST-segment resolution				
Partial		0	1	1
No		2	2	2
ECG confounders/missing		2	1	0
In-hospital event (<1 day or 4 days)				
No PCI			2	2
Stroke			8	5
Heart failure			5	4
Electrical disorder			5	3
Maximum possible total score	11	13	32	22
C-index (95% confidence interval)	0.80 (0.77–0.82)	0.80 (0.78–0.82)	0.86 (0.83–0.88)	0.81 (0.77–0.85)

[a]The reference groups are not shown, as the points assigned to them are all set to 0.

individual patients is provided in Supplementary material online.

Dynamic modelling can help identify high-risk patients who should be treated more aggressively. For instance, while the simplified risk score remained unchanged between baseline and 3 h for patients with either complete or partial ST-segment resolution, 97.5% of patients without ST-segment resolution or with an ECG confounder had a higher risk score at 3 h. The rate of in-hospital revascularization in ASSENT-3 was 33.2 and 30.8%, respectively, for those with no ST-segment resolution or an ECG confounder. This was virtually identical to the observed 31.3 and 34.2% for those with partial or complete ST-segment resolution, respectively. The 30-day mortality for those with and without in-hospital revascularization was 5.2 and 10.0% (P = 0.041) among patients without ST-segment resolution and 4.6 and 12.8% (P < 0.001) among those with an ECG confounder. The previous results were unchanged after adjusting for the propensity for in-hospital revascularization. Hence, it is possible that a proportion of the 177 patients who died without complete or partial ST-segment resolution by 3 h but were not revascularized may have been better served by more aggressive treatment.

Our approach is flexible and may also be used to incorporate any traditional prognostic index for predicting clinical outcomes. For instance, when forecasting 30-day mortality in ASSENT-3 based on the simple TIMI risk index in place of individual baseline covariates of age, heart rate, and systolic blood pressure, a similar decline in its influence was also demonstrated (Figure 2C): while this index

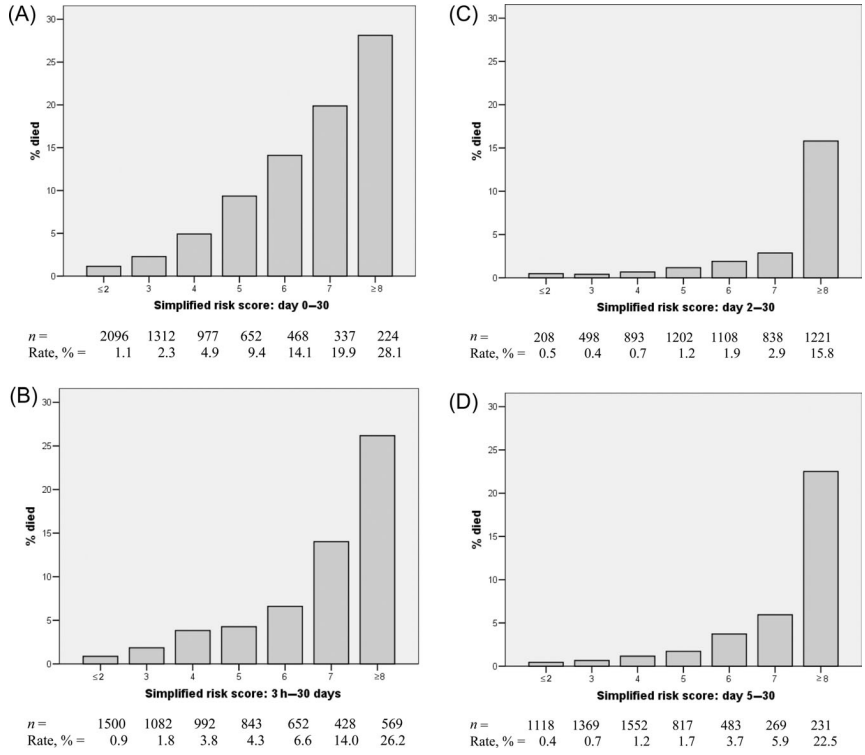


Figure 3 The distribution of mortality rates associated with the risk scores for the day 0 (*A*), 3 h (*B*), day 2 (*C*), and day 5 (*D*) models, showing associations between simplified risk scores and actual mortality rates.

accounted for 72% of the relative contribution to mortality prediction at baseline, that percentage was reduced to 63% at 3 h, and then to 23 and 26% at day 2 and day 5, respectively. Conversely, other factors, such as the ECG measures and in-hospital events, assumed an increasingly greater role and became predominant in mortality prediction and risk stratification in day 2 and day 5 models.

DISCUSSION

Dynamic modelling attempts to capture the texture of clinical risk assessment from the time of first medical contact with acute coronary patients and thereafter, especially during the critical early phase of patient management. As the care of these patients requires prompt and timely adjustments, having implications for both risk-benefit and cost-effectiveness, developing a risk assessment process to reflect this evolutionary process is a worthwhile goal [1,15] and distinguishes our approach from the traditional baseline and discharge models.[16,17]

Several key messages have emerged from our study. First, the dynamic modelling framework enables us to risk-stratify patients at any clinically important time point (e.g. at day 5 for early discharge) as well as over several time points. A

unique strength of dynamic modelling, therefore, is that it captures change in prognosis over time. An advantage of monitoring changes in prognosis is that it is feasible to devise decision rules for patient management, e.g. identifying candidates for early discharge based on the criterion of patients being stable and remaining at a low risk during the first few days of hospitalization.[1] In this paper, we further demonstrated the feasibility of applying simplified risk scores to monitor change in prognosis between baseline and 3 h for identifying opportunities for more aggressive treatment. As factors not available at baseline, such as the ECG tracking of ST-segment evolution and in-hospital events, convey significant prognostic information in addition to baseline values, the performance of these models improved over the traditional baseline model as a result of their inclusion. To illustrate this point, we have used vital signs (i.e. systolic blood pressure, heart rate) collected at both baseline and 24 h in the COMMA trial to recalculate the simple TIMI risk index[14] for each patient at these time points. Logistic regression based on this index alone was performed to predict day 0–30 and day 2–30 mortality, resulting in the c-statistics of 0.85 and 0.92, respectively, when the sample was restricted in both models to those who survived to the start of day 2. A corollary, therefore, is that it is essential to test the optimal methods of collecting significant baseline and in-hospital predictors that can change over time, e.g. heart rate, blood pressure, ECG measures, and biomarkers.[1]

Secondly, a spectrum of models, from very simple to very sophisticated, should be developed and utilized using the dynamic risk modelling framework. For scientific research at tertiary care institutions and academic centres, sophisticated full models should be further developed, tested, and used to provide most valid and reliable answers to clinical questions arising from various health care settings and systems. On the other hand, it is imperative to also develop simplified risk scores, because prognostic indices derived from complex models are rarely used in clinical practice.[2] For rapid, user-friendly bedside use, we developed in this study highly reliable, simplified risk scores (c-statistics 0.80–0.86 after excluding the QRS score) to provide quick risk assessment. The implementation of dynamic risk modelling may be further facilitated through the use of centralized electronic medical records to automatically calculate these probabilities and reduce the burden of data entry to clinicians. Integrating computerized ECG analyses, which could generate standardized ECG measures, into this health information system should also be considered.[18]

Thirdly, our dynamic models are applicable not only to fibrinolytic-treated STEMI patients but also to those undergoing primary PCI. This is important, because an estimated 25–50% of AMI patients currently undergo primary-PCI worldwide.[19] As shown in Supplementary material online, our dynamic models

performed extremely well in both fibrinolytic-treated and primary-PCI patients: the c-statistics for the simplified risk scores ranged from 0.79 to 0.86 in ASSENT-3 PLUS and 0.81 to 0.86 in COMMA; and these scores were strongly and positively associated with mortality rates in all models in both validation datasets. In comparison, the c-statistics for other baseline-risk models were 0.84 for GUSTO-I full model,[20] 0.79 for the (simplified) TIMI risk score,[11] and 0.78 for a simple TIMI risk index (based only on age, heart rate, and systolic blood pressure).[14]

Some limitations of our study should be noted. First, our risk models were developed and validated using specific clinical trials data, which may differ from the general STEMI patient population. It should be noted, however, that over 14% of them were 75 years or more. Although we have validated our models also on an independent sample of primary-PCI patients, further research is warranted to test the generalizability and reproducibility of our results in other settings. Secondly, unlike the probability measures derived from the full models, simplified risk scores are not consistently defined and standardized, and hence may not be strictly comparable, across the forecasting periods. For example, a score of 7 in our study was associated with an observed 30-day mortality rate that changed from 19.8%, through 14.0, 2.9, and 5.9% as it was ascertained at baseline, 3 h, day 2, and day 5, respectively (Figure 3). For tracking change in prognosis over time using simplified risk scores, it is crucial to always refer to the levels of risk associated with these scores (Figure 3) rather than comparing them directly across the periods. Thus, for comparing change in prognosis over time, a better approach may be to use programmable calculators or handheld computers, which can readily compute mortality probabilities for individuals or groups of patients directly from the full models.[1,15]

In conclusion, we have extended the dynamic modelling methodology to STEMI patients receiving either fibrinolytic therapy or primary PCI and demonstrated that this strategy of continuous risk assessment and stratification is feasible and may sharpen evidence-based decision-making in the management of STEMI patients within the critical days after hospital admission.

Supplementary material

Supplementary material is available at European Heart Journal online.

ACKNOWLEDGEMENTS

The ASSENT-3 study was supported by Boehringer Ingelheim, Germany; Genentech, South San Francisco, CA, USA, and Aventis, Bridgewater, NJ, USA. The ASSENT-3 PLUS study was supported by Boehringer Ingelheim, Germany and Aventis, Bridgewater, NJ, USA. The COMMA study was funded by Procter & Gamble Pharmaceuticals and Alexion Pharmaceuticals, Inc.

Conflict of interest: none declared.

REFERENCES

1. Chang W-C, Boersma E, Granger CB, Harrington RA, Califf RM, Simoons ML, Kleinman NS, Armstrong PW, for the GUSTO IIb and PURSUIT Investigators. Dynamic prognostication in non-ST elevation acute coronary syndromes: insights from GUSTO IIb and PURSUIT. Am Heart J 2004;148:62–71.

2. Redelmeier DA, Lustig AJ. Prognostic indices in clinical practice. JAMA 2001;285:3024–3025.

3. Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. Lancet 2001;358:605–613.

4. Wallentin L, Goldstein P, Armstrong PW, Granger CB, Adgey AA, Arntz HR, Bogaerts K, Danays T, Lindahl B, Makijarvi M, Verheugt F, Van de Werf F. Efficacy and safety of tenecteplase in combination with the lowmolecular-weight heparin enoxaparin or unfractionated heparin in the prehospital setting: the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 PLUS randomized trial in acute myocardial infarction. Circulation 2003;108:135–142.

5. Granger CB, Mahaffey KW, WeaverWD, Theroux P, Hochmann JS, Filloon TG, Rollins S, Todaro TG, Nicolau JC, Ruzyllo W, Armstrong PW, for the COMMA Investigators. Pexelizumab, an anti-C5 complement antibody, as adjunctive therapy to primary percutaneous coronary intervention in acute myocardial infarction: the COMplement inhibition in Myocardial infarction treated with Angioplasty (COMMA) trial. Circulation 2003;108:1184–1190.

6. Armstrong PW, Wagner G, Goodman SG, Van de Werf F, Granger C, Wallentin L, Fu Y, for the ASSENT 3 Investigators. ST segment resolution in ASSENT 3: insights into the role of three different treatment strategies for acute myocardial infarction. Eur Heart J 2003;24:1515–1522.

7. Fu Y, Goodman S, Chang W-C, Van de Werf F, Granger CB, Armstrong PW, for the Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) Trial Investigators. Time to treatment influences the impact of ST-segment resolution on one-year prognosis. Insight from the ASSENT-2 Trial. Circulation 2001;104:2653–2659.

8. Hindman NB, Schocken DD, Widmann M, Anderson WD, White RD, Leggett S, Ideker RE, Hinohara T, Selvester RH, Wagner GS. Evaluation of a QRS scoring system for estimating myocardial infarct size: Specificity and method of application of the complete system. Am J Cardiol 1985;55:1485–1490.

9. Schroder R, Wegscheider K, Schroder K, Dissmann R, Meyer-Sabellek W, for the INJECT trial group. Extent of early ST segment elevation resolution: a strong predictor of outcome in patients with acute myocardial infarction and a sensitive measure to compare thrombolytic regimens. J Am Coll Cardiol 1995;26:1657–1664.

10. Morrow DA. New insight into

clinical risk scores for patients with acute coronary syndromes. Am Heart J 2003;146:754–756.
11. 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.
12. Steyerberg EW, Harrell FE Jr, Borsboom GJ, Eijkemans MJ, Vergouwe Y, Habbema JD. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. J Clin Epidemiol 2001; 54:774–781.
13. Moons KGM, Harrell FE. Letter to the Editor: Should scoring rules be based on odds ratios or regression coefficients? J Clin Epidemiol 2002;55:1054–1055.
14. Morrow DA, Antman EM, Giugliano RP, Cairns R, Charlesworth A, Murphy SA, de Lemos JA, McCabe CH, Braunwald E. A simple risk index for rapid initial triage of patients with ST-elevation myocardial infarction: an InTIME II Substudy. Lancet 2001;358: 1571–1575.
15. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, Van de Werf F, Avezum A, Goodman SG, Flather MD, Fox KA, for the Global Registry of Acute Coronary Events (GRACE) Investigators. Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med 2003;163:2345–2353.
16. Newby LK, Hasselblad V, Armstrong PW, Van de Werf F, Mark DB, White HD, Topol EJ, Califf RM. Time-based risk assessment after myocardial infarction. Implications for timing of discharge and applications to medical decision-making. Eur Heart J 2003;24:182–189.
17. Walter LC, Brand RJ, Counsell SR, Palmer RM, Landefeld CS, Fortinsky RH, Covinsky KE. Development and validation of a prognostic index for 1-year mortality in older adults after hospitalization. JAMA 2001;285: 2987–2994.
18. Pelter MM, Adams MG, Drew BJ. Computer versus manual measurement of ST-segment deviation. J Electrocardiol 1997;30:151–156.
19. Ui S, Chino M, Isshiki T. Rates of primary percutaneous coronary intervention worldwide. Circ J 2005;69:95–100.
20. Lee KL, Woodlief LH, Topol EJ, Weaver WD, Betriu A, Col J, Simoons M, Aylward P, Van de Werf F, Califf RM, for the GUSTO-I Investigators. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction. Results from an international trial of 41021 patients. Circulation 1995;91:1659–1668.

Chapter Three

Are international differences in the outcomes of acute coronary syndromes apparent or real? A multilevel analysis

Wei-Ching Chang, William K Midodzi, Cynthia M Westerhout, Eric Boersma, Judith Cooper, Elliot S Barnathan, Maarten L Simoons, Lars Wallentin, E Magnus Ohman, Paul W Armstrong for the GUSTO-IV ACS Investigators

STUDY OBJECTIVE International variation in the outcomes of patients with acute coronary syndromes (ACS) has been well reported. The relative contributions of patient, hospital, and country level factors on clinical outcomes, however, remain unclear, and thus, was the objective of this study.

DESIGN Multilevel logistic regression models were developed for death/(re)infarction (MI) at 30 days and death in one year, with patients (1st level) nested in hospitals (2nd level) and hospitals in countries (3rd level).

SETTINGS The GUSTO IV ACS clinical trial was carried out at 458 hospital sites in 24 countries in 7800 non-ST segment elevation (NSTE) ACS patients.

MAIN RESULTS There were substantial variations among countries in the processes and outcomes of care at 30 days, ranging from 5.4% to 50.0% for percutaneous coronary intervention, 4.3% to 21.2% for coronary artery bypass graft surgery, 5.0% to 13.9% for 30 day death/(re)MI, and 4.9% to 14.8% for one-year mortality. However, the residual inter-country variations in 30 day death/(re)MI and one-year mortality became non-significant and nearly disappeared (p.0.500 for both) after adjusting for key baseline patient characteristics and hospital factors, which became significant (p,0.01 for both). Patient-level factors accounted for 96%–99% of total variation in these end points, leaving the remaining 1% and 4% of variance attributable to hospital level factors.

CONCLUSION The international differences in clinical outcomes in this study of NSTE ACS are primarily accounted for by the patient-level factors, with hospital level factors playing a minor part, and the country-level factors a negligible one. These findings have significant policy and research implications involving international collaboration and comparisons.

Disparities in cardiovascular and other health outcomes across geographical regions are common, and yet not well understood.[1 2] Even after adjustment for baseline patient characteristics, significant variations in clinical outcomes often persist in acute coronary syndrome (ACS) patients.[3–9] Although some studies have not shown mortality differences in either ST segment elevation (STE)[10–16] or non-ST segment elevation (NSTE) ACS patients,[17 18] others have reported better quality of life and mortality outcomes in countries with high revascularisation rates.[3 12 19] Such disparities in

outcomes provide incentives to further investigate the underlying factors, including patient and provider characteristics, socioeconomic and cultural factors, healthcare practices, and other characteristics of healthcare systems.

To our knowledge, however, no study has formally identified and quantified the sources of inter-country variations in the ACS literature, although some have offered opinions on this.[6 8 20] To gauge the amount of variation in outcomes among countries attributable to patient compared with non-patient level factors, we applied multilevel modelling techniques that took into account the hierarchical and correlated nature of healthcare data.[21–24] In such data, findings are generally correlated among patients in the same subgroup, for instance, those cared for at the same hospital or in the same country. Thus, conventional, single level analyses that treat the data as if there were no hierarchical structures violate the assumption of independence of findings required for such methods, and result in suboptimal estimation of the effects of hospital and country level factors.[21–24] Moreover, single level analyses are not designed to assess the components of variation attributable to individual (patient level) compared with contextual (hospital and country level) effects. Thus, our objectives were: (1) to assess the extent of international differences in patient characteristics, care processes, and clinical outcomes, and (2) to determine the extent to which the observed inter-country variations in the composite of 30-day death or post-admission myocardial infarction (MI) and one year all cause mortality can be explained by patient, hospital, and country level factors.

METHODS

Patients and study design

Data from the global utilisation of strategies to open occluded coronary arteries IV acute coronary syndromes (GUSTO IV ACS) were used. The details of this trial have been previously reported.[25 26] Briefly, 7800 patients from the 458 participating hospitals in 24 countries were enrolled between July 1998 and April 2000 (table 1).

Eligible patients were 21 years or older, had at least one episode of angina lasting five minutes or more within the preceding 24 hours without persistent ST segment elevation, and a positive cardiac troponin T or I test (determined using a local qualitative or quantitative assay) or at least 0.5 mm transient or persistent ST segment depression on admission. They were randomly assigned to one of the three treatment groups: abciximab therapy for 24 hours (0.25 mg/kg bolus followed by a 0.125 mg/kg per minute infusion up to 10 mg/kg for 24 hours), abciximab therapy for 48 hours (same bolus and infusion for 48 hours), or matching placebo (bolus and 48 - hour infusion). Coronary angiography was not to be performed during or within 12 hours after the completion of the study agent administration, unless the

Table 1 Number of study sites and patients and selected baseline patient level factors of each country* participating in the GUSTO IV ACS trial

Country	Sites (n)	Patients (n)	Median age	Female (%)	Prior MI (%)	Diabetes (%)	TnT (%)	ST depression (%)	Creatinine clearance (%)	CRP (%)	Enrolment MI (%)
North America											
Canada	31	642	65	31	34	25	46	28	79	59	36
United States	48	462	66	42	33	33	39	36	71	68	34
Western Europe											
Austria	8	78	66	33	30	35	81	32	66	36	13
Belgium	9	163	66	33	31	21	74	43	73	24	36
France	15	197	68	27	26	17	71	29	67	24	25
Germany	32	395	68	34	26	25	75	42	75	29	28
Greece	15	259	66	35	26	31	66	49	73	24	20
Ireland	5	40	64	15	40	10	83	23	78	43	23
Italy	29	486	66	34	30	21	76	42	71	27	27
Netherlands	27	570	66	33	26	11	71	43	83	25	31
Portugal	8	88	68	25	23	19	83	38	75	25	36
Spain	11	362	68	29	20	23	74	40	75	29	40
Switzerland	7	38	65	32	29	11	82	43	76	34	34
UK	15	124	64	30	36	16	77	32	76	29	35
Scandinavia											
Denmark	12	149	66	28	29	10	80	38	80	35	31
Finland	2	79	66	32	34	18	80	42	79	22	28
Norway	10	91	64	42	23	21	84	26	78	23	31
Sweden	28	544	70	34	31	16	88	31	73	22	33
Eastern Europe											
Czech	16	765	69	49	38	31	71	51	66	26	29
Poland	24	1657	65	49	34	17	50	44	81	19	26
Other											
Australia	9	118	66	35	27	14	64	40	64	40	40
Israel	13	265	63	26	35	30	78	39	76	34	27
New Zealand	3	54	61	20	33	13	94	26	80	24	43
South Africa	10	144	60	22	17	19	76	34	80	33	41
All countries	**387**	**7800**	**66**	**38**	**31**	**22**	**66**	**40**	**75**	**31**	**28**

*The actual number of sites from 458 possible sites that had enrolled at least one patient. CRP, C reactive protein >1110 mg/l; creatinine clearance<58.4 ml/min; MI, myocardial infarction; ST segment depression ≥1mm; TnT, troponin T >0.01 μg/l. All missing data were imputed as positive for these indicators.

patient had recurrent or continuing ischaemia at rest associated with ischaemic ST/T segment changes that were not responsive to medical treatment. A clinical end point committee, which was unaware of treatment assignment, adjudicated all possible incidences of MI and, when requested by the Safety and Efficacy Monitoring Committee, also, the cause of death within 30 days. An independent neurologist adjudicated all suspected occurrences of stroke and intracranial haemorrhage. The ethics committees of the participating hospitals approved the protocol, and patients gave informed consent.

Statistical analysis

The primary end point for the GUSTO IV ACS trial (and for this study) was 30-day death/(re)MI, and one-year mortality was a secondary end point. Because no treatment effect was found, the three treatment arms were combined. Biomarkers and renal function were grouped into tertiles to examine their relations with the primary end points: troponin T (TnT) (0.01, 0.01–0.5, and >0.5 mg/l; and C reactive protein (CRP) (4, 4–10, and ≥10 mg/l; creatinine clearance (58.4, 58.4–76.9, and ≥76.9 ml/min; and the extent of ST segment depression into <1 (or no ST segment depression), 1–1.5, and ≥2 mm. For ease of presenting variation among countries, we further dichotomised these data after examining their relations with outcomes, and defined an increased value as follows: >0.01 mg/l for TnT, >1 mm for ST segment depression, >58.4 ml/min for creatinine clearance, and >10 mg/l for CRP. The results were presented in terms of percentages for categorical variables and medians (interquartile ranges) for continuous variables.

Table 2 Use of evidence based drugs before and during hospitalisation according to country

	Aspirin (%)		Clopidogrel (%)		ACE inhibitors (%)		β blockers (%)		Nitrates (%)		Calcium channel blockers (%)	
Country	**Before**	**During**	**Before**	**During**	**Before**	**During**	**Before**	**During**	**Before**	**During**	**Before**	**During**
North America												
Canada	90	98	1	11	27	43	57	86	37	63	29	32
United States	84	96	4	19	28	40	54	83	34	59	26	26
Western Europe												
Austria	78	95	1	22	46	49	63	89	32	39	27	26
Belgium	79	94	0	0	17	25	66	87	25	52	23	22
France	52	96	3	10	18	22	66	81	82	82	41	43
Germany	80	99	4	12	44	72	55	81	35	66	24	15
Greece	69	96	0	0	41	51	49	73	41	85	40	36
Ireland	95	75	0	0	28	38	60	63	25	38	25	30
Italy	66	96	0	0	31	47	45	78	26	70	32	38
Netherlands	71	97	0	4	14	23	57	86	21	56	24	41
Portugal	90	100	0	1	38	63	53	89	50	81	30	18
Spain	89	96	1	4	17	32	34	66	44	74	32	50
Switzerland	87	97	0	37	24	40	68	84	24	37	21	21
UK	90	100	0	9	21	27	60	85	43	56	40	42
Scandinavia												
Denmark	90	98	0	7	17	21	58	86	34	46	33	38
Finland	100	100	0	4	23	35	95	99	54	77	17	17
Norway	92	96	0	1	10	20	70	96	17	44	24	21
Sweden	87	97	1	15	17	28	81	93	34	51	20	24
Eastern Europe												
Czech	81	98	0	0	35	48	53	78	58	79	20	16
Poland	91	98	0	0	48	63	63	84	65	90	25	28
Other												
Australia	95	98	2	11	27	38	59	81	42	53	31	40
Israel	84	99	0	0	29	54	54	83	26	57	24	23
New Zealand	100	100	0	0	26	30	67	85	46	44	35	35
South Africa	71	98	0	0	24	30	31	63	28	44	13	23
All countries	**84**	**97**	**1**	**5**	**31**	**43**	**58**	**83**	**46**	**61**	**26**	**29**

ACE inhibitors, angiotension converting enzyme inhibitor.

To assess the relative contributions of patient and non-patient level factors on outcomes, we began with two level ''null'' models (that is, without containing any independent variables), with patients at the first level and countries at the second. We then developed three level "null" models by including hospitals as an additional level to further identify the variance component attributable to the hospital effects, which has been distributed to both patient and country effects.[28] Thereafter, we developed nested three level models by successively incorporating patient age, other patient baseline characteristics, and the country level percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) rates (as estimated from our dataset). The amount of variance explained was calculated by the proportional change in variance (PCV), or the percentage reduction from the estimated variance in the null model as a result of incorporating a new factor(s) in the model—that is, $PCV=(V_0–V_1)/V_0$, where V_0 is the estimate of the initial (null) variance at the country or hospital level before adjusting for any compositional or contextual factor in the model, and V_1 was the country or the hospital level residual variance after adjusting for covariates.[23] The proportions of total variance related to hospital and country factors were estimated by the intraclass correlation coefficient (ICC) using the formula $V/(V+\pi^2/3)$, where $V=V_0$ or V_1, and $\pi^2/3$ is the fixed variance at the patient level as suggested by Snijders and Bosker.[28] Each model parameter was estimated using the restricted penalised quasilikelihood function in HLM version 6.0 (Lincolnwood, IL, USA) or MLwiN 2.1a (University of London, London, UK), which also

Table 3 Median length of stay and rates of revascularisation (PCI or CABG) and of (re)-myocardial infarction, and/or death at 30 days, and death at one year according to country

Country	Median LOS (days)	30 day CABG (%)	30 day PCI (%)	30 day Revasculation (%)	30 day (re)MI (%)	30 day Death (%)	30 day Death/(re)MI (%)	One year death (%)
North America								
Canada	8	14	25	39	8.4	3.7	5.5	8.1
United States	7	21	27	47	12.6	4.5	9.1	10.6
Western Europe								
Austria	14	5	10	15	8.5	4.2	5.9	11.9
Belgium	11	21	38	58	6.7	3.1	4.1	8.3
France	11	12	36	48	8.6	4.6	4.6	9.1
Germany	15	13	27	40	9.9	5.8	5.6	8.4
Greece	8	6	5	12	6.9	3.1	3.9	7.3
Ireland	15	10	13	20	5.0	5.0	0.0	10.0
Italy	11	16	25	40	9.9	4.5	6.4	8.6
Netherlands	9	12	21	33	6.7	3.7	3.7	7.0
Portugal	10	10	39	49	13.6	8.0	8.0	14.8
Spain	12	8	22	30	8.0	4.4	4.4	8.0
Switzerland	11	11	50	61	7.9	2.6	7.9	7.9
UK	9	7	19	25	8.1	4.8	4.8	10.5
Scandinavia								
Denmark	8	15	18	32	8.7	4.0	5.4	8.1
Finland	9	18	19	35	13.9	2.5	12.7	8.9
Norway	7	10	15	25	6.6	4.4	3.3	7.7
Sweden	8	15	24	39	9.6	2.9	7.9	6.4
Eastern Europe								
Czech	11	4	7	11	11.1	5.4	7.2	12.8
Poland	12	5	7	12	5.9	2.5	4.1	6.9
Other								
Australia	6	8	40	47	10.3	5.1	6.4	6.4
Israel	9	19	40	58	7.5	3.0	5.7	4.9
New Zealand	5	15	11	26	9.3	7.4	1.9	9.3
South Africa	6	21	26	46	6.9	2.8	4.9	5.6
All countries	**10**	**11**	**19**	**30**	**8.4**	**3.9**	**5.5**	**8.3**

CABG, coronary artery bypass graft surgery; LOS, length of stay; PCI, percutaneous coronary intervention; (re)-MI, (re)-myocardial infarction.

provides standard errors and t tests for fixed effects and chi-square tests for random effects. Each variance estimate was presented with a standard error and a p value based on the chi-square test. All other descriptive analyses were performed using SPSS version 11.0 (Chicago, IL, USA).

RESULTS

Variations among countries

The baseline patient characteristics differed significantly among the 24 countries participating in the study (table 1). Variation in other aspects of health care such as the use of evidence-based drugs was also noticeable, and except for calcium channel blockers, their use increased substantially during hospitalisation (table 2).

The diversity was even greater for invasive procedures at 30 days, and there was a threefold variation in the median length of hospital stay (table 3).

Differences in outcomes across countries were also pronounced: 5.0% to 13.9% in 30 day death/(re)MI, 2.5% to 8.0% in 30 day mortality, and 4.9% to 14.8% in one year mortality (table 3).

Sources of variation in 30-day death/(re)MI and in one-year mortality

Table 4 shows the results of our multilevel analyses for 30-day death/(re)MI.

A small but significant intercountry variance of 0.036 (p=0.004) was first shown in the two level null model after factoring out the patient level

Table 4 Analysis of the hospital and country level effects on 30 day death/(re)MI and one year mortality

Variable	Hospital level effects		Country level effects		Intrahospital correlation (%)	Intracountry correlation (%)
	Variance (SE, p)	% Explained	Variance (SE, p)	% Explained		
30 day death/(re)MI						
Two level null model	–		0.0361 (0.024; p=0.004)			1.09
Three level models						
Model 1: null	0.0862 (0.046; p=0.003)		0.0279 (0.023; p=0.072)	22.7	2.53	0.82
Model 2: age only	0.0718 (0.044; p=0.010)	16.7	0.0122 (0.017; p=0.456)	56.3	2.13	0.36
Model 3: all baseline factors*	0.0419 (0.041; p=0.014)	51.4	0.0011 (0.012; p>0.500)	96.1	1.26	0.03
Model 4: Baseline+country level CABG-rate†	0.0462	46.4	0.0001	99.6	1.38	0.00
	0.039; (p=0.032)		(0.001; p>0.500)			
One year death						
Two level null model	–		0.0369 (0.024; p=0.005)			1.11
Three level models						
Model 1: null	0.179 (0.058; p=0.001)		0.0172 (0.022; p=0.312)	46.6	5.13	0.49
Model 2: age only	0.170 (0.059; p=0.002)	4.9	0.0068 (0.018; p>0.500)	60.5	4.91	0.20
Model 3: all baseline factors*	0.124 (0.054; p=0.014)	30.6	0.00002 (0.015; p>0.500)	99.7	3.64	0.00
Model 4: Baseline+country level CABG-rate†	0.103	42.5	0.00023	99.4	3.03	0.01
	(0.050; p=0.008)		(0.001; p>0.500)			

*Adjusted for age, prior myocardial infarction, prior transient ischaemic attacks, prior stroke, prior coronary artery bypass graft surgery, prior use of calcium channel blockers and β blockers, ST segment depression, troponins T, creatinine clearance, and time to randomisation. †Adjusted for country level coronary artery bypass graft surgery (CABG) rate.

effects. To further exclude the hospital level effects that were distributed to both the patient level and country level effects in the two level model, we developed a series of three level models that also included the hospital level factors and showed, first of all, that the intercountry variance was reduced by 22.7% to 0.028 and became non-significant (p=0.072) in the null model (model 1). This variance was further reduced and became negligible (p>0.500) after successively controlling for age, for all baseline patient characteristics, and then also for country level PCI and CABG rates (models 2–4), so that these factors explained nearly all (99.6%) the residual intercountry variation. In contrast, the estimated interhospital variance of 0.086 was significant (p=0.003) in the three level null model, but was only reduced to 0.046 (p=0.032) in the full model (model 4). The reduction in country level variance is depicted in ''caterpillar'' plots for shrunken residuals (logarithmic odds ratios) before and after adjusting for baseline patient factors (fig 1A). Similar plots for hospital level variance are given in figure 1B.

The ICC further shows that 1.09% of the total variation was related to country factors (with the remaining 98.91% related to patient factors) based on the two level null model (table 4). This proportion was reduced in the three level models to 0.82%, 0.36%, 0.03%, and 0.00% in

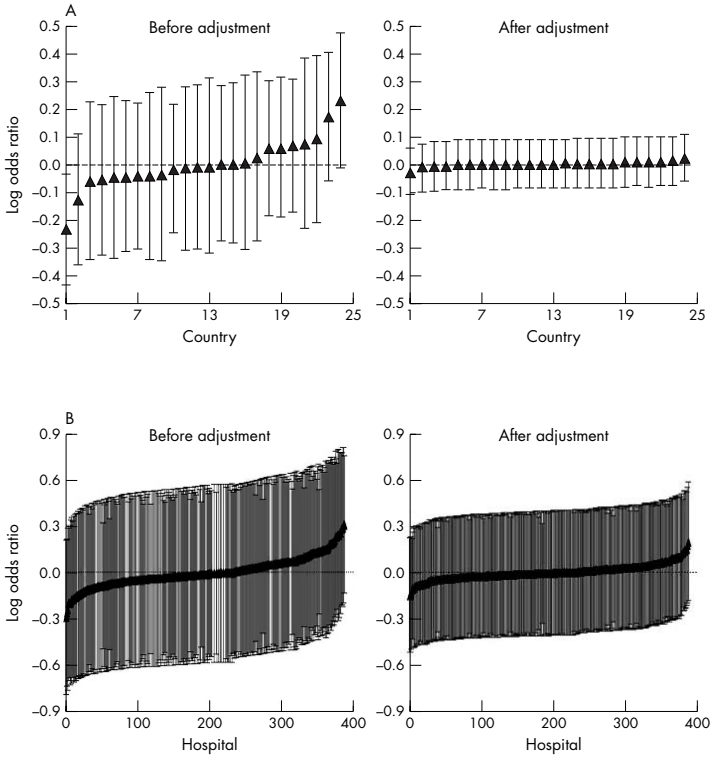


Figure 1 Logarithmic odds ratio and 90% confidence intervals for predicting 30 day death/(re)MI (ranked in ascending order) for each country (A) and for each hospital (B) before and after adjustment for baseline patient level factors.

models 1–4, respectively. By contrast, the intrahospital correlation coefficient was reduced from 2.53% in the three level null model to 1.38% in the full, three level model (model 4). Thus, 3.4% ((0.0279+0.0862)/(0.0279 +0.0862+3.29)) of the total variance was situated at the hospital and country level in the null model (model 1), and as a proportion of the hospital and country variance, 24.5% (0.0279/(0.0279+0.0862)) and 75.5% were at the country and the hospital level, respectively. After adjusting for baseline patient characteristics in model 3, however, such substantial country level effects were reduced from 24.5% to 2.6%. The patient factors, in contrast, accounted for 98.6% of the total variation.

The same multilevel analyses performed for one-year mortality also confirmed that the country level factors, which was significant in the two level null model, played a negligible part (0%) in explaining the intercountry variation in one-year mortality according to the three level models: 97.0% was explained by the patient level factors and the remaining 3% by hospital level factors (model 4, table 4).

DISCUSSION

International comparisons of population health, the incidence and prevalence of disease, and the impact of healthcare organisations and interventions on health outcomes are of great interest.[1 2] The proliferation of large

international clinical trials in cardiovascular and other areas of medicine in the past two decades further stimulated investigation into the variations in practice patterns and outcomes among countries and geographical regions. These variations in health status and treatment outcomes, if real, are of particular concern, as they raise a host of questions concerning the efficacy, effectiveness, efficiency, and equity of the social and healthcare systems as well as the diagnostic and therapeutic procedures used within and among these countries and geographical regions. Identifying the sources of variation in patient outcomes is important, as it may have enormous implications for the design, analysis, and interpretation of such studies. For example, abciximab was not shown to be beneficial in the overall GUSTO IV ACS sample except in North America, where a beneficial effect of a borderline significance was seen. Nevertheless, the Food and Drug Administration (FDA) in the USA has not approved abciximab for frontline medicinal treatment of ACS patients based on the conventional view that subgroup results are less reliable.[27] Our findings of negligible country effects and of comparatively small hospital effects on outcomes in the GUSTO IV ACS trial lend support to the FDA's decision, although the reasons for better performance in North America deserve further investigations. To our knowledge, however, there has not been a rigorous study performed to quantify the sources of intercountry variations in treatment outcomes for ACS patients. In this paper we showed that patient level factors explained 96%–99% of total NSTE ACS outcome variations. Similar findings were obtained in our previous studies of ST segment elevation myocardial infarction (STEMI)[3,29] where significant variations in 30 day and one-year mortality were related mainly to patient characteristics. However, variation in one-year mortality among countries remained highly significant for the STEMI sample even after adjusting for baseline patient characteristics, which was not the case for the NSTE-ACS cohort. Whereas the residual intercountry variation was explained primarily by the country level life expectancy among STEMI patients, the patient and hospital level factors explained that variation in NSTE ACS patients. Such differences may be related to the finding from these studies that variation was greater among countries but smaller among hospitals in STEMI than in NSTE ACS patients, and that life expectancy as a proxy for the state of the nation's health and healthcare system had a greater impact on the outcomes of STEMI than of NSTE ACS. Further research is clearly required on this intriguing contrast.

It is noteworthy that our results are in agreement with those in other NSTE ACS studies.[7 17 18] Although significant international differences persisted in the efficacy and safety of subcutaneous enoxaparin in non-Q wave coronary events (ESSENCE) trial,[8] that study was based on very small samples from the outlier countries. Thus, our

results were aligned with those obtained from a Swedish study that used two level modelling of 30 day mortality after a heart failure,[23] which confirmed that variation among hospitals in mortality after hospitalisation was mainly explained by the differences in baseline patient characteristics. A recent three level analysis of AMI patients in Ontario, Canada further showed that 96.6% of variation in one year mortality was related to patient level factors, leaving 2.8% and 0.6% to physician and hospital level factors, respectively.[21] Similarly, another Ontario study showed that socioeconomic status, although a significant predictor of patient level mortality, had a minimal impact on hospital mortality rates after adjusting for age, sex, and illness severity[30]; as well, a study of social context on heart disease mortality in Texas, USA showed that 95% of the total variance was accounted for by variation at the individual level, leaving the rest to variations in socioeconomic and ethnic factors at the census tract and the county level.[22]

It is also of interest to note that the country level revascularisation rates played a comparatively minor part in further reducing variations among hospitals and countries. Although we also found a negative relation between country level revascularisation and mortality rates, variation among countries remained significant after adjusting for the country level revascularisation rate. It should be noted here that these findings are contextual in nature, and they in no way imply that invasive procedures did not influence the outcomes of ACS at the patient level. To make such an inference is to commit a so-called ecological fallacy, to infer an individual level relation on the basis of group level associations.[31]

As in other NSTE ACS studies,[5 7–9 18 32] we also found significant intercountry differences in drug and procedure use. In particular, in-hospital aspirin use was mandated in the protocol and given at a high rate across all regions (except for Irish patients) as recommended by the 2002 ACC/AHA and ESC guidelines.[33 34] The use of other efficacious drugs such as ACE inhibitors, ß blockers, and long acting nitrates also increased after hospital admission, and their rates were consistent with those found in other studies.[7–9 18] Our finding of significant variations in practice patterns even within the context of rigorously designed clinical trials shows that opportunities exist to increase adherence to practice guidelines.

Several limitations of our study should be noted. Firstly, despite the detailed clinical data that had been collected in the GUSTO IV ACS trial, specific characteristics of hospitals (for example, information of on-site interventional facilities) and physician level data were unavailable.[27 35] Secondly, the GUSTO IV ACS sample may differ from the general population of patients with ACS, as it was not based on a representative sample in participating countries. In particular, coronary angiography was not performed within 12 hours of the

completion of study agent infusion, which is the common practice in most hospitals without interventional facilities in North America and Europe. However, this is unlikely to change the main findings of our study in view of other studies also showing the predominance of patient level factors accounting for clinical outcomes.[21 23] Thirdly, we based our multilevel modelling on a latent variable approach, which assumed an underlying continuous dependent variable.[36] It should be noted that there are other methods of calculating the intraclass correlations and of summarizing contextual level variances, for example, in terms of the median odds ratio.[28 37] However, the use of measures such as the median odds ratios[37] only confirms the findings of this study, and hence is not presented in this paper. Notwithstanding these limitations and considerations, our approach to the analysis of geographical variations has wider applications.

In conclusion, we found that practice patterns as well as patient characteristics differ among countries in a large, contemporary sample of NSTE ACS patients, and that variations in outcomes were related primarily to patient level factors and only small but significant proportions were related to hospital and country level factors. The variation between countries, which was smaller than that between hospitals, became negligible after controlling for patient and hospital effects. Greater attention to collecting data on hospital and physician characteristics in future NSTE ACS international studies and clinical trials, in addition to further exploring and refining patient level data, should provide insights into patient outcomes and optimising care in all healthcare settings.

REFERENCES

1 World Health Organisation. The World Health Report 2000 health systems: improving performance. Geneva: WHO, 2000:21–46.
2 Moise P, Jacobzone S, and the ARD-IHD Experts Group. Outcomes of interventions for IHD. OECD Study of cross-national differences in the treatment, costs and outcomes of ischaemic heart disease. Paris: OECD, 2003:70–9.
3 Gupta M, Chang WC, Van de WF, et al. International differences in inhospital revascularization and outcomes following acute myocardial infarction: a multilevel analysis of patients in ASSENT-2. Eur Heart J 2003;24:1640–50.
4 Giugliano RP, Llevadot J, Wilcox RG, et al. Geographic variation in patient and hospital characteristics, management, and clinical outcomes in ST-elevation myocardial infarction treated with fibrinolysis. Results from InTIME-II. Eur Heart J 2001;22:1702–15.
5 Alexander KP, Peterson ED, Granger CB, et al. Potential impact of evidencebased medicine in acute coronary syndromes: insights from GUSTO-IIb. Global use of strategies to open occluded arteries in acute coronary syndromes trial. J Am Coll Cardiol 1998;32:2023–30.
6 Barbash GI, Modan M, Goldbourt U, et al. Comparative case fatality analysis of the international tissue plasminogen activator/streptokinase mortality trial: variation by country

beyond predictive profile. The investigators of the international tissue plasminogen activator/streptokinase mortality trial. J Am Coll Cardiol 1993;21:281–6.
7 Cohen MG, Pacchiana CM, Corbalan R, et al. Variation in patient management and outcomes for acute coronary syndromes in Latin America and North America: results from the platelet IIb/IIIa in unstable angina: receptor suppression using integrilin therapy (PURSUIT) trial. Am Heart J 2001;141:391–401.
8 Fox KA, Goodman S, Bigonzi F, et al. Inter-regional differences and outcome in unstable angina; analysis of the international ESSENCE trial. Efficacy and safety of subcutaneous enoxaparin in non-Q-wave coronary events. Eur Heart J 2000;21:1433–9.
9 Fu Y, Chang WC, Mark D, et al. Canadian-American differences in the management of acute coronary syndromes in the GUSTO IIb trial: one-year follow-up of patients without ST-segment elevation. Global use of strategies to open occluded coronary arteries (GUSTO) II investigators. Circulation 2000;102:1375–81.
10 Batchelor WB, Peterson ED, Mark DB, et al. A comparison of US and Canadian cardiac catheterization practices in detecting severe coronary artery disease after myocardial infarction: efficiency, yield and long-term implications. J Am Coll Cardiol 1999;34:12–19.
11 Chang WC, Fu Y, Ohman EM, et al. Temporal evolution in the management of acute ST elevation myocardial infarction: the seven-year GUSTO experience from Canada and the United States. The North American GUSTO-I and GUSTO-III investigators. Can J Cardiol 2000;16:1231–9.
12 Mark DB, Naylor CD, Hlatky MA, et al. Use of medical resources and quality of life after acute myocardial infarction in Canada and the United States. N Engl J Med 1994;331:1130–5.
13 Pilote L, Racine N, Hlatky MA. Differences in the treatment of myocardial infarction in the United States and Canada. A comparison of two university hospitals. Arch Intern Med 1994;154:1090–6.
14 Rouleau JL, Moye LA, Pfeffer MA, et al. A comparison of management patterns after acute myocardial infarction in Canada and the United States. The SAVE investigators. N Engl J Med 1993;328:779–84.
15 Tu JV, Pashos CL, Naylor CD, et al. Use of cardiac procedures and outcomes in elderly patients with myocardial infarction in the United States and Canada. N Engl J Med 1997;336:1500–5.
16 Van de WF, Topol EJ, Lee KL, et al. Variations in patient management and outcomes for acute myocardial infarction in the United States and other countries. Results from the GUSTO trial. Global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries. JAMA 1995;273:1586–91.
17 Anderson HV, Gibson RS, Stone PH, et al. Management of unstable angina pectoris and non-Q-wave acute myocardial infarction in the United States and Canada (the TIMI III Registry). Am J Cardiol 1997;79:1441–6.
18 Yusuf S, Flather M, Pogue J, et

al. Variations between countries in invasive cardiac procedures and outcomes in patients with suspected unstable angina or myocardial infarction without initial ST elevation. OASIS (organisation to assess strategies for ischaemic syndromes) registry investigators. Lancet 1998;352:507–14.
19 Kaul P, Armstrong PW, Chang W-C, et al. Long-term mortality of patients acute myocardial infarction in the United States and Canada: comparison of patients enrolled in global utilization of streptokinase and t-PA for occluded coronary Arteries (GUSTO)-I. Circulation 2004;110:1754–60.
20 Akkerhuis KM, Deckers JW, Boersma E, et al. Geographic variability in outcomes within an international trial of glycoprotein IIb/IIIa inhibition in patients with acute coronary syndromes. Results from PURSUIT. Eur Heart J 2000;21:371–81.
21 Austin PC, Tu JV, Alter DA. Comparing hierarchical modeling with traditional logistic regression analysis among patients hospitalized with acute myocardial infarction: should we be analyzing cardiovascular outcomes data differently? Am Heart J 2003;145:27–35.
22 Franzini L, Spears W. Contributions of social context to inequalities in years of life lost to heart disease in Texas, USA. Soc Sci Med 2003;57:1847–61.
23 Merlo J, Ostergren PO, Broms K, et al. Survival after initial hospitalisation for heart failure: a multilevel analysis of patients in Swedish acute care hospitals. J Epidemiol Community Health 2001;55:323–9.
24 Byrk AS, Raudenbush SW. Hierarchical linear models: applications and data analysis methods. Newbury Park, CA: Sage, 1992:1–8.
25 Simoons ML. Effect of glycoprotein IIb/IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes without early coronary revascularisation: the GUSTO IV ACS randomised trial. Lancet 2001;357:1915–24.
26 Ottervanger JP, Armstrong P, Barnathan ES, et al. Long-term results after the glycoprotein IIb/IIIa inhibitor abciximab in unstable angina: one-year survival in the GUSTO IV-ACS (global use of strategies to open occluded coronary arteries IV—acute coronary syndrome) trial. Circulation 2003;107:437–42.
27 O'Shea JC, DeMets DL. Statistical issues relating to international differences in clinical trials. Am Heart J 2001;142:21–8.
28 Snijders TAB, Bosker RJ. Multilevel analysis: an introduction to basic and advance multilevel modelling. London: Sage, 1999:65.
29 Kaul P, Newby LK, Fu Y, et al. International differences in evolution of early discharge after acute myocardial infarction. Lancet 2004;363:511–17.
30 Alter DA, Austin PC, Naylor CD, et al. Factoring socioeconomic status into cardiac performance profiling for hospitals: does it matter? Med Care 2002;40:60–7.
31 Diez-Roux AV. The study of group-level factors in epidemiology: rethinking variables, study designs, and analytical approaches.

Epidemiol Rev 2004;26:104–11.
32 Fox KA, Cokkinos DV, Deckers J, et al. The ENACT study: a pan-European survey of acute coronary syndromes. European network for acute coronary treatment. Eur Heart J 2000;21:1440–9.
33 Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction–2002: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). Circulation 2002;106:1893–900.
34 Bertrand ME, Simoons ML, Fox KA, et al. Management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2002;23:1809–40.
35 O'Shea JC, Fu Y, Chang WC, et al. A tale of two countries: insights from the differences in Canadian/American patterns of care for patients with acute coronary syndromes. Am Heart J 2001;142:14–20.
36 Goldstein H, Browne W, Rasbash J. Partitioning variation in multilevel models.
http://multilevel.ioe.ac.uk/team/materials/pvmm.pdf.
37 Larsen K, Petersen JH, Budtz-Jorgensen E, et al. Interpreting parameters in the logistic regression model with random effects. Biometrics 2000;56:909–14.

Chapter Four

Electrocardiographic left ventricular hypertrophy in GUSTO IV ACS: an important risk marker of mortality in women

Cynthia M. Westerhout, Michael S. Lauer, Stefan James, Yuling Fu, Lars Wallentin and Paul W. Armstrong for the GUSTO IV ACS Investigators

AIM To examine the association of left ventricular hypertrophy (LVH) on admission electrocardiography with adverse outcomes in acute coronary syndrome (ACS) patients.
METHODS AND RESULTS A total of 7443 non-ST-elevation ACS patients in Global Utilization of STrategies to Open occluded arteries (GUSTO) IV ACS trial had admission electrocardiograms analysed at a core laboratory. LVH [≥20 mm Cornell voltage (LV voltage) (women) or ≥28 mm (men) plus strain patterns] was observed in 586 (7.9%) patients, and women accounted for 74%. LVH patients were also older and had more co-morbidities, ST-depression ≥ 0.5 mm, elevated C-reactive protein and N-terminal pro-brain natriuretic peptide (NT-proBNP), and lower troponin T. Invasive procedures occurred less often in LVH patients (cardiac catheterization: 31 vs. 38%, P = 0.001; percutaneous coronary intervention: 12 vs. 20%, P <0.001). Mortality was significantly higher in patients with LVH (30 day: 5 vs. 3%, P = 0.046; 1 year: 14 vs. 7%, P <0.001), whereas 30-day myocardial infarction (MI) and death/MI did not differ. After baseline adjustment including NT-proBNP, LVH remained associated with increased hazard of 1-year mortality in women, but not in men [P-interaction = 0.033; women: adjusted hazard ratio (LVH vs. no LVH): 1.42 (1.04–1.94), P = 0.029].
CONCLUSION Electrocardiographic-LVH identifies an important subset of ACS patients with a higher risk of long-term mortality, particularly among women. These novel findings highlight opportunities to improve treatment and outcome among similar ACS patients.

Although increases in left ventricular (LV) mass can accommodate an increased afterload stress, it may ultimately prove harmful. At that point, left ventricular hypertrophy (LVH) can lead to deleterious cardiovascular effects such as ventricular dysfunction, impaired coronary perfusion, and disturbances in cardiac rhythm.[1] LVH is also a strong precursor of adverse outcomes in a variety of populations ranging from the general population to those with cardiovascular diseases.[2–4] Women with LVH, in particular, have a higher risk of mortality than their male equivalents.[5,6]

Despite recognized unfavourable influence of this condition across the spectrum of coronary artery disease (CAD), LVH is rarely discussed in the realm of acute coronary syndromes (ACS) or cited as a modulator of clinical outcomes in

these patients. In a large cohort of non-ST-elevation (NSTE)-ACS patients enrolled in the Global Utilization of STrategies to Open occluded arteries (GUSTO) IV ACS trial, we examined the prevalence of LVH [as diagnosed on the admission electrocardiogram (ECG)] and hypothesised that LVH would play a role in the likelihood of adverse outcomes. The extent to which gender and/or N-terminal pro-brain natriuretic peptide (NT-proBNP), a marker of haemodynamic stress, may modulate the relationship of LVH with outcomes was also explored.

METHODS

Patient population

Details of the design and primary results of the GUSTO IV ACS trial have been previously described.[7,8] In brief, patients over the age of 21 years were eligible if they presented within 24 h after one or more episodes of ischaemic chest pain lasting at least 5 min. In addition, eligible patients had to have either elevated cardiac troponin T or I above the upper limit of normal according to the local quantitative or qualitative assays, or transient or persistent ST-segment depression (≥0.5 mm) on the admission ECG not known to be pre-existing or not attributable to coexisting disorders (e.g. LVH). Patients were excluded if they had evidence of an acute ST-segment elevation myocardial infarction (MI) or new left bundle branch block, or if percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) was planned within 30 days after enrolment.

Eligible patients were randomly assigned to abciximab (0.25 mg/kg bolus plus 0.125 mg/kg/min continuous infusion for 24 or 48 h) or placebo. All patients were to receive aspirin and either unfractionated or low-molecular-weight heparin. Other clinically indicated medications were used at the discretion of the treating physician.

The primary endpoint of the trial was all-cause death or MI at 30 days. All possible cases of MI were adjudicated by a clinical endpoint committee, which was unaware of the study treatment assignment. Secondary endpoints included 30-day and 1-year death.[7]

Electrocardiogram measurements

Admission ECGs were read independently at the core ECG laboratory at the Cleveland Clinic Foundation (Cleveland, OH, USA) by experienced readers blinded to clinical outcomes. ECG data were then managed and analysed at the University of Alberta (Edmonton, Alberta, Canada). Admission ECGs were available in 7443 (95.4%) of the 7800 patients enrolled in the trial. LVH was identified on the admission ECG defined according to two established criteria: (i) Cornell voltage criteria: the sum of the amplitude of the S-wave in V_3 and R-wave in the aVL lead, ≥28 mm for men and ≥20 mm for women,[9] and (ii) the presence of repolarization abnormalities (strain patterns) classified as ≥1 mm ST-segment depression in lead I and aVL or in v_5 and v_6, or T-wave inversion

Table 1 Patient characteristics according to the presence/absence of left ventricular hypertrophy

	LVH status		*P*-value
	No LVH	LVH	
n	6857	586	
Age, years[a]	66 (56–73)	71 (63–77)	<0.001
Female, *n* (%)	2362 (34.4)	430 (73.4)	<0.001
Caucasian, *n* (%)	6631 (96.7)	569 (97.1)	
Hypertension, *n* (%)	3425 (49.9)	420 (71.7)	<0.001
History of hyperlipidaemic therapy, *n* (%)	2392 (34.9)	219 (37.4)	
Diabetes mellitus, *n* (%)	1347 (19.7)	215 (36.8)	<0.001
Current smoker, *n* (%)	1649 (24.0)	77 (13.1)	<0.001
History of angina pectoris, *n* (%)	3040 (44.3)	348 (59.4)	<0.001
History of MI, *n* (%)	2101 (30.6)	217 (37.0)	<0.001
History of heart failure, *n* (%)	481 (7.0)	89 (15.2)	<0.001
History of stroke, *n* (%)	161 (2.3)	28 (4.8)	<0.001
History of PCI, *n* (%)	667 (9.7)	53 (9.0)	
History of CABG, *n* (%)	604 (8.8)	55 (9.4)	
ACE-inhibitors prior to randomization, *n* (%)	2002 (29.2)	270 (46.1)	<0.001
Beta-blockers prior to randomization, *n* (%)	3970 (57.9)	353 (60.2)	
Aspirin prior to randomization, *n* (%)	5745 (83.8)	498 (85.0)	
Ca channel blockers prior to randomization, *n* (%)	1743 (25.4)	186 (31.7)	<0.001
Factors available upon presentation			
MI upon enrolment, *n* (%)	1952 (28.5)	124 (21.2)	<0.001
Trial entry criteria			<0.001
Positive local troponin I or T only, *n* (%)	1367 (22.7)	54 (10.4)	
ST-segment depression ≥0.5 mm only, *n* (%)	2457 (40.8)	252 (48.6)	
Both positive troponin and ST-segment depression, *n* (%)	2192 (36.4)	212 (40.9)	
Body weight, kg[a]	76 (68–86)	71 (63–77)	<0.001
Heart rate, b.p.m.[a]	68 (60–78)	73 (63–84)	<0.001
Creatinine clearance, mL/min[a]	79 (60–100)	64 (47–86)	<0.001
Central laboratory biomarkers			
Troponin T, μg/L[a]	0.11 (0.01–0.46)	0.07 (0.01–0.38)	
C-reactive protein, mg/L[a]	3.82 (1.81–9.20)	4.67 (2.15–11.6)	<0.001
NT-proBNP, ng/L[a]	605 (219–1641)		<0.001

[a]Median (25th–75th percentile).

in lead I and aVL or in v_5 and v_6.[10]

Laboratory analyses

Details of the central laboratory analyses have been published.[11] Briefly, venous blood samples were collected at the point of randomization, and centrifuged sera were stored at –20•C in aliquots and sent to a central laboratory at the University of Uppsala (Uppsala, Sweden) for the analysis of troponin T, C-reactive protein, and NT-proBNP. A third-generation assay on an Elecsys (Roche Diagnostics) analyser was used to measure the levels of troponin T with a detection limit of 0.01 mg/L. C-reactive protein levels were ascertained using a chemiluminescent enzyme-labelled immunometric assay (Immulite CRP, Diagnostic Product Corp.) with a detection level of 0.1 mg/L. NT-proBNP concentrations were measured with a sandwich immunoassay on an Elecsys 2010 (Roche Diagnostics) analyser with an analytical range of 20–35 000 ng/L and a coefficient of variation at 3.3% at a level of 209 ng/L and 3.0% at a level of 7431 ng/L. Serum creatinine was also measured, and creatinine clearance rate was calculated using the gender-specific Cockcroft and Gault equation.[12]

Statistical analysis

Baseline patient characteristics were presented as numbers and percentages for discrete variables, whereas medians and 25th and 75th percentiles were given for continuous variables. Differences within these baseline characteristics

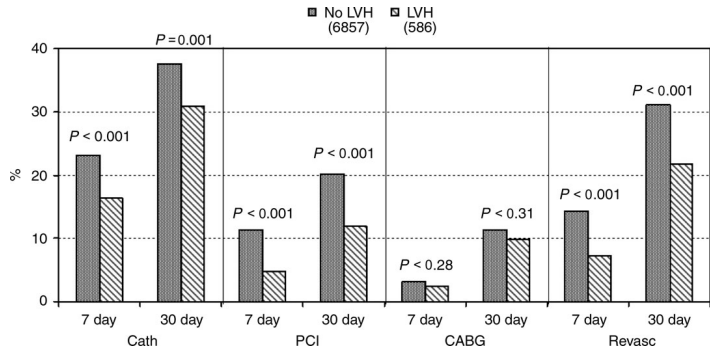


Figure 1 Rates of 7 day and 30 day invasive procedures [i.e. cardiac catheterization (Cath), percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), and revascularization (Revasc)] according to left ventricular hypertrophy status.

according to LVH were tested using the chi-square and Mann–Whitney U tests where appropriate.

We examined the association of LVH status and 30 day PCI and then adjusted for other baseline characteristics using multivariable logistic regression (using stepwise selection). Baseline characteristics were considered if its univariable association with 30 day PCI had a P-value < 0.25, and the final set of covariates included age, gender, histories of angina, MI, CHF, PCI and CABG, heart rate, troponin T (quartiles), and NT-proBNP (quartiles). Interactions among age, gender, and creatinine clearance were tested but did not achieve statistical significance.

The association between LVH and clinical outcomes was examined using Kaplan–Meier estimates and multivariable Cox proportional hazard regression (using stepwise selection). In addition to LVH, other covariates predicting 1 year mortality included age, diabetes, histories of CHF and MI, current smoker, heart rate, ST-depression (none, 0.5 mm, 1–1.5 mm, ≥2 mm), creatinine clearance (quartiles: 25th, 59.2; 50th, 77.8; 75th, 99.1 mL/min), NT-proBNP (quartiles: 25th, 230.5; 50th, 643.7; 75th, 1763 ng/L), and troponin T (quartiles: 25th, 0.01; 50th, 0.111; 75th, 0.452 μg/L).13 Interactions among age, gender, and creatinine clearance did not achieve statistical significance. The likelihood of PCI within 30 days (quintiles) and plausible interaction terms with LVH were also tested (i.e. gender and NT-proBNP). The resulting discriminatory power (adjusted for over-optimism via bootstrapping) was a c-index of 0.805 and an over-optimism factor of 0.01. All tests were two-tailed, and the conventional level of statistical significance (i.e. $P < 0.05$) was used.

RESULTS

Patient characteristics

Of the 7443 patients with available baseline ECG data, LVH was diagnosed in 586 patients [7.9%, 95% confidence interval (CI): 7.3–8.5]. As shown in Table 1, patients with LVH were more often female and older than those without LVH. They were also more likely to have

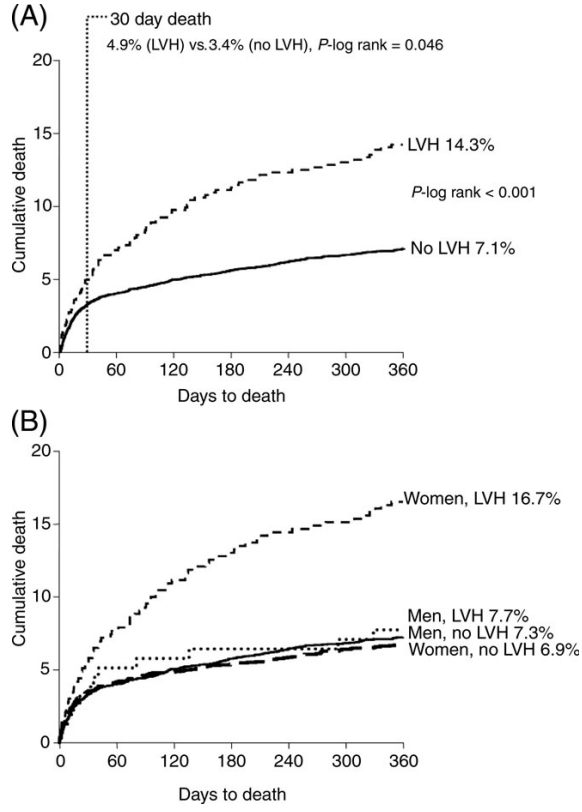


Figure 2 (*A*) Cumulative rates of mortality over 1 year according to left ventricular hypertrophy status. (*B*) Cumulative rates of mortality over 1 year according to left ventricular hypertrophy status and gender. Women with left ventricular hypertrophy had significantly higher rates of 1 year mortality relative to men with left ventricular hypertrophy (*P*-log rank = 0.008) and men and women without left ventricular hypertrophy (*P*-log rank < 0.001, respectively).

hypertension, diabetes mellitus, and a history of cardiovascular diseases including angina pectoris, MI, heart failure, and stroke, but less likely to be a current smoker. The use of medications such as ACE-inhibitors and calcium channel blockers within 1 week prior to randomization was higher in LVH patients, a pattern which continued during the index hospitalization.

Although LVH patients were less likely to present with MI and to have positive quantitative or qualitative troponin I or T, they were more likely to have at least 0.5 mm of ST-segment depression, the second entry criterion of the GUSTO IV ACS trial, than those patients without LVH. This pattern was particularly evident in women with LVH (relative to those without LVH) (data not shown). Median heart rate was significantly higher in LVH patients, whereas renal function as indicated by creatinine clearance was significantly lower in LVH patients

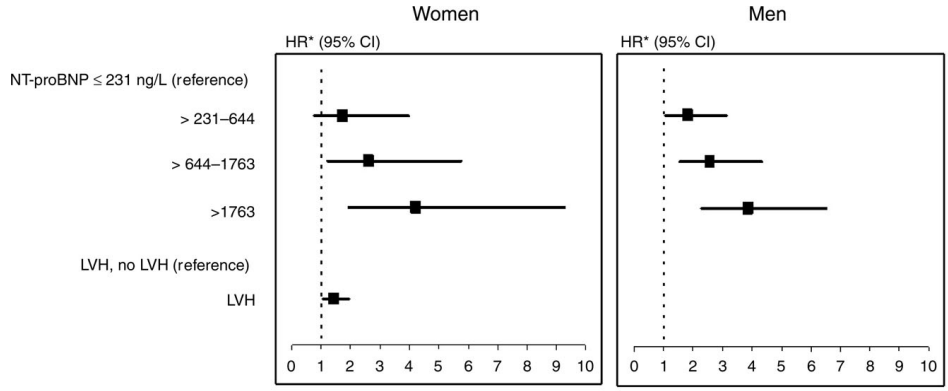


Figure 3 Adjusted hazard ratios (95% confidence interval) for left ventricular hypertrophy and N-terminal pro-brain naturetic peptide in the prediction of 1 year mortality in women (left panel) and men (right panel). *, baseline-adjusted hazard ratios.

than in those without. Median values of C-reactive protein and NT-proBNP assessed in core laboratories were also significantly higher in LVH patients.

Invasive procedures

According to the trial protocol, cardiac catheterization was discouraged during or within 12 h following the completion of the study drug infusion, and patients with PCI or CABG planned within 30 days of randomization were excluded from the trial. Overall, cardiac catheterization occurred in 22.5% of patients within the first 7 days and in 37.0% by day 30. In both the short and long term, patients with LVH underwent fewer catheterizations than those without LVH [7 days: 23.0% (no LVH) vs. 16.4% (LVH), P < 0.001; 30 days: 37.6 vs. 30.9%, P = 0.001] (Figure 1). Similarly, LVH patients were less likely to undergo PCI [7 days: 11.3% (no LVH) vs. 4.8% (LVH), P < 0.001; 30 days: 20.1 vs. 11.9%, P < 0.001]. The likelihood of PCI within 30 days was associated with LVH [adjusted odds ratio (OR): 0.78, 95% CI 0.57–0.98, P = 0.035]. Rates of CABG, however, were not statistically different [7 days: 3.2% (no LVH) vs. 2.4% (LVH), P = 0.28; 30 days: 11.3 vs. 9.9%, P = 0.31].

Clinical outcomes

Rates of 30 day MI and death/MI were similar regardless of LVH [30 day MI: 5.4% (no LVH) vs. 5.1% (LVH), P = 0.92; 30 day death/MI: 8.0% (no LVH) vs. 8.0% (LVH), P = 0.94]. Mortality, however, was significantly higher in LVH patients; 31% higher in LVH patients at 30 days and there was a two-fold increase at 1 year (Figure 2A). And higher rates of 1-year mortality were particularly evident in women with LVH (Figure 2B). After adjustment for various baseline characteristics and propensity for PCI, LVH did not remain a significant predictor of 30-day death or 1-year mortality [30-day mortality: adjusted hazard ratio (HR): 0.84 (0.56–1.26), P = 0.40; 1-year mortality: adjusted HR: 1.22 (0.95–1.56), P = 0.119]. However, a significant interaction between gender and LVH was observed such that LVH remained strongly associated with increased long-term mortality in women, but not in men

(P-interaction = 0.033). Women with LVH had a more than 40% increase compared with those without LVH [adjusted HR: 1.42 (1.04–1.94), P = 0.029] (Figure 3). Notably, NT-proBNP was independently associated with 1-year mortality in both genders.

DISCUSSION

Traditionally, LVH has not been considered in the list of established risk factors in ACS patients.[14–17] A unique opportunity to examine this was possible through the assessment of LVH on the admission ECG in the GUSTO IV ACS trial. In terms of invasive treatment, we found that patients with LVH were less likely to undergo invasive procedures such as cardiac catheterization and PCI within the first week and through to 30 days. LVH was also associated with an increased risk of 1-year mortality, particularly in women, and notably, was independent of NT-proBNP.

Comparisons with other studies

Treatment following an acute coronary event in LVH patients has not been well studied. Similar to our study, however, East et al.[6] showed in a cohort of CAD patients undergoing catheterization that patients with LVH subsequently underwent fewer PCI and CABG procedures. Whether there are opportunities to enhance outcomes of such patients through the utilization of these procedures or other strategies such as more intensive secondary preventative pharmacotherapy is unclear. In our study, an increased likelihood for PCI within 30 days of the initial acute event translated into improved survival in the first year, independent of LVH, which would suggest that increased use of PCI in those with co-existent epicardial coronary disease may also improve their outcomes.

In contrast to its association with invasive therapy, the prognostic implications of LVH to the general population have received more attention. LVH was among the most significant predictors of cardiovascular morbidity and mortality in the general population, as demonstrated by the Framingham Heart Study.[18] Not surprisingly, clinical trials of left ventricular dysfunction, hypertension, and heart failure patients also point to LVH as prominent contributor to adverse outcomes in long-term follow-up.[5] To a lesser extent, the prognostic value of LVH has been recognized in CAD patients.[6,19,20] For instance, East et al.'s study demonstrated that echocardiographic LVH was a significant predictor of long-term mortality after adjustment for other baseline characteristics. There is a dearth, however, in our understanding of the role of LVH in NSTE-ACS patients who do not undergo invasive study.

From the few studies conducted in ACS patients, the presence of LVH appears to confer significant risk of short- and long-term mortality. For instance, in angina patients presenting to the emergency department, a nearly seven-fold unadjusted relative risk of death within the first 48 h was observed in those with LVH.[4] And in a cohort

study of 4720 consecutive AMI patients treated in the coronary care unit in the early 1980s, the 1 year mortality rate was 19.7% in patients with LVH vs. 8.7% in those without (adjusted OR: 1.51, 95% CI 1.09–2.10).[3]

Elevation of brain natriuretic peptides, including NT-proBNP, is commonly observed in patients with heart failure, left ventricular dysfunction, and LVH.[21,22] More recently, through our own work and others, the value of this biomarker has also been recognized in ACS patients.[11,23,24] The novelty of the current study is the opportunity to examine the association between systematically collected NT-proBNP and ECG-diagnosed LVH in NSTE-ACS patients. It seems likely that neurohormonal elevation provides additional indication of left ventricular overload and/or stretch, thereby signalling worse future outcomes in both men and women.

Further interrogation of our findings, however, revealed a major and heretofore unreported difference in the role of gender, as it relates to the prognostic value of LVH in NSTE-ACS. Several studies of CAD-free populations have observed that women have a substantially higher prevalence of LVH and poorer prognosis than men.[18,20,25] These findings were confirmed in our study of ACS patients, with women constituting 38% of the overall GUSTO IV ACS population, yet over 70% of LVH patients. These women had a 1-year mortality more than twice that of men with LVH [16.7% (women) vs. 7.7% (men), P = 0.006]. The underlying nature of their cardiac disease may help to explain, in part, this difference. Coronary perfusion and reserve are compromised in LVH patients, even in those with normal coronary arteries, owing to impaired dilation capacity as a result of structural changes and increased extrinsic coronary resistance.[26,27] Women, in particular, tend to have greater increases in wall thickness and poorer dilation of the LV cavity, which compromises the ability to withstand wall stress and ischaemia.[28] Conversely, the response to wall stress in men is not manifested in wall thickening or loss of dilation. The condition may be further exacerbated in women who have a higher likelihood for microvascular disease and normal coronary arteries, as previously suggested.[7,29,30] Angiographic confirmation of microcirculatory disease in these female patients with LVH and elevated NT-proBNP in GUSTO IV ACS may have provided further insight into this issue.

The current study also highlights that LVH was more prevalent in older patients. Data from the Framingham population and other studies have indicated that LV mass increased with age only in women,[31] whereas more recent data from Olivetti et al.[32] suggested that with ageing, LV mass was preserved in women, but not in men. In particular, their work showed that as men aged, the number of ventricular cardiac myocytes and the proportion of mononucleated and binucleated cells decreased and the size of myocytes increased.

Limitations

Some limitations of our study should be noted. First, the ECG was used in the current study to diagnose LVH, a method that has some inherent weaknesses. While the ECG is often used in large-scale screening programmes, it has established lower sensitive than echocardiography, a higher standard of LV mass detection.[33] Several validation studies have calculated the sensitivity of echocardiography to be in the range of 85–100%, whereas the sensitivity of ECG reached as high as 50% in high-risk cardiovascular disease patient populations and as low as 6–17% in population-based studies. The costs and feasibility associated with the performance of echocardiography, however, make it an impractical option compared with the ECG, which is a simple, universally available test at the point of patient entry. Although echocardiography might have further complemented our findings, we believe that the choice to use the gender-specific Cornell voltage criteria and strain patterns was well founded, as it has been shown to outperform other ECG criteria such as Sokolow–Lyon voltage and Romhilt–Estes point score.[34]

Additional refinement of our results may have been possible through patient attributes such as height (for body-surface area adjustment) and systolic blood pressure, which were not available in GUSTO IV ACS.

A final limitation relates to the usual issue of generalizability of these findings to the global ACS population. Although patients with ST-depression related to pre-existing disorders such as LVH were to be excluded from the GUSTO IV ACS trial, nearly 8% of enrolled patients were diagnosed with LVH on the admission ECG. Since the frequency of LVH in the overall general population is likely greater, our findings deserve exploration in broader patient groups.

CONCLUSION

This study highlights the important association of LVH and long-term prognosis in the ACS patient population. These novel findings should encourage careful assessment of LVH in ACS patients, particularly in females. Investigators should also consider this issue when designing future trials and interrogating population-based registries.

REFERENCES

1. Vasan RS, Levy D. The role of hypertension in the pathogenesis of heart failure. A clinical mechanistic overview. Arch Intern Med 1996;156: 1789–1796.

2. Levy D, Anderson KM, Savage DD, Kannel WB, Christiansen JC, Castelli WP. Echocardiographically detected left ventricular hypertrophy: prevalence and risk factors. The Framingham Heart Study. Ann Intern Med 1988;108:7–13.

3. Behar S, Reicher-Reiss H, Abinader E, Agmon J, Barzilai J, Friedman Y, Kaplinsky E, Kauli N, Kishon Y, Palant A. Long-term prognosis after acute myocardial infarction in patients with left ventricular hypertrophy on the

electrocardiogram. SPRINT Study Group. Am J Cardiol 1992;69: 985–990.
4. Larsen GC, Griffith JL, Beshansky JR, D'Agostino RB, Selker HP. Electrocardiographic left ventricular hypertrophy in patients with suspected acute cardiac ischemia—its influence on diagnosis, triage, and short-term prognosis: a multicenter study. J Gen Intern Med 1994;9:666–673.
5. Vakili BA, Okin PM, Devereux RB. Prognostic implications of left ventricular hypertrophy. Am Heart J 2001;141:334–341.
6. East MA, Jollis JG, Nelson CL, Marks D, Peterson ED. The influence of left ventricular hypertrophy on survival in patients with coronary artery disease: do race and gender matter? J Am Coll Cardiol 2003;41:949–954.
7. Simoons ML, GUSTO IV-ACS Investigators. Effect of glycoprotein IIb/IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes without early coronary revascularisation: the GUSTO IV-ACS randomised trial. Lancet 2001;357:1915–1924.
8. Ottervanger JP, Armstrong P, Barnathan ES, Boersma E, Cooper JS, Ohman EM, James S, Topol E, Wallentin L, Simoons MLGUSTO IVA. Long-term results after the glycoprotein IIb/IIIa inhibitor abciximab in unstable angina: one-year survival in the GUSTO IV-ACS (Global Use of Strategies To Open Occluded Coronary Arteries IV–Acute Coronary Syndrome) Trial. Circulation 2003;107:437–442.
9. Casale PN, Devereux RB, Alonso DR, Campo E, Kligfield P. Improved sex-specific criteria of left ventricular hypertrophy for clinical and computer interpretation of electrocardiograms: validation with autopsy findings. Circulation 1987;75:565–572.
10. Devereux RB, Reichek N. Repolarization abnormalities of left ventricular hypertrophy. Clinical, echocardiographic and hemodynamic correlates. J Electrocardiol 1982;15:47–53.
11. James SK, Lindahl B, Siegbahn A, Stridsberg M, Venge P, Armstrong P, Barnathan ES, Califf R, Topol EJ, Simoons ML, Wallentin L. N-terminal pro-brain natriuretic peptide and other risk markers for the separate prediction of mortality and subsequent myocardial infarction in patients with unstable coronary artery disease: a Global Utilization of Strategies To Open occluded arteries (GUSTO)-IV substudy. Circulation 2003;108: 275–281.
12. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41.
13. Westerhout CM, Fu Y, Lauer MS, James S, Armstrong PW, Al Hattab E, Califf RM, Simoons ML, Wallentin L, Boersma E, GUSTO-IV ACS Trial Investigators. Short- and long-term risk stratification in acute coronary syndromes: the added value of quantitative ST-segment depression and multiple biomarkers. J Am Coll Cardiol 2006;48:939–947.
14. Lee KL, Woodlief LH, Topol EJ, Weaver WD, Betriu A, Col J, Simoons M, Aylward P, Van de Werf F, Califf RM. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction. Results from an international trial of 41,021

patients. GUSTO-I Investigators. Circulation 1995;91:1659–1668.
15. Boersma E, Pieper KS, Steyerberg EW, Wilcox RG, Chang WC, Lee KL, Akkerhuis KM, Harrington RA, Deckers JW, Armstrong PW, Lincoff AM, Califf RM, Topol EJ, Simoons ML. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients. The PURSUIT Investigators. Circulation 2000;101:2557–2567.
16. Malmberg K, Yusuf S, Gerstein HC, Brown J, Zhao F, Hunt D, Piegas L, Calvin J, Keltai M, Budaj A. Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial infarction: results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry. Circulation 2000;102:1014–1019.
17. Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, Van de Werf F, Goodman SG, Granger CB, Steg PG, Gore JM, Budaj A, Avezum A, Flather MD, Fox KAGRACE Investigators. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. JAMA 2004; 291:2727–2733.
18. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med 1990;322:1561–1566.
19. Cooper RS, Simmons BE, Castaner A, Santhanam V, Ghali J, Mar M. Left ventricular hypertrophy is associated with worse survival independent of ventricular function and number of coronary arteries severely narrowed. Am J Cardiol 1990;65:441–445.
20. Liao Y, Cooper RS, Mensah GA, McGee DL. Left ventricular hypertrophy has a greater impact on survival in women than in men. Circulation 1995;92:805–810.
21. Yamamoto K, Burnett JC Jr, Jougasaki M, Nishimura RA, Bailey KR, Saito Y, Nakao K, Redfield MM. Superiority of brain natriuretic peptide as a hormonal marker of ventricular systolic and diastolic dysfunction and ventricular hypertrophy. Hypertension 1996;28:988–994.
22. Suzuki M, Yamamoto K, Watanabe S, Iwata T, Hamada M, Hiwada K. Association between elevated brain natriuretic peptide levels and the development of left ventricular hypertrophy in patients with hypertension. Am J Med 2000;108:627–633.
23. Omland T, Persson A, Ng L, O'Brien R, Karlsson T, Herlitz J, Hartford M, Caidahl K. N-terminal pro-B-type natriuretic peptide and long-term mortality in acute coronary syndromes. Circulation 2002;106:2913–2918.
24. Jernberg T, Lindahl B, Siegbahn A, Andren B, Frostfeldt G, Lagerqvist B, Stridsberg M, Venge P, Wallentin L. N-terminal pro-brain natriuretic peptide in relation to inflammation, myocardial necrosis, and the effect of an invasive strategy in unstable coronary artery disease. J Am Coll Cardiol 2003;42:1909–1916.
25. Thrainsdottir IS, Hardarson T, Thorgeirsson G, Sigvaldason H, Sigfusson N. Survival and trends of

occurrence of left ventricular hypertrophy, gender differences, 1967–92: The Reykjavik Study. J Intern Med 2003;253: 418–424.
26. Strauer BE. Myocardial oxygen consumption in chronic heart disease: role of wall stress, hypertrophy and coronary reserve. Am J Cardiol 1979;44: 730–740.
27. Pichard AD, Gorlin R, Smith H, Ambrose J, Meller J. Coronary flow studies in patients with left ventricular hypertrophy of the hypertensive type. Evidence for an impaired coronary vascular reserve. Am J Cardiol 1981; 47:547–554.
28. Krumholz HM, Larson M, Levy D. Sex differences in cardiac adaptation to isolated systolic hypertension. Am J Cardiol 1993;72:310–313.
29. Roe MT, Harrington RA, Prosper DM, Pieper KS, Bhatt DL, Lincoff AM, Simoons ML, Akkerhuis M, Ohman EM, Kitt MM, Vahanian A, Ruzyllo W, Karsch K, Califf RM, Topol EJ. Clinical and therapeutic profile of patients presenting with acute coronary syndromes who do not have significant coronary artery disease. The Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) Trial Investigators. Circulation 2000;102:1101–1106.
30. Lagerqvist B, Safstrom K, Stahle E, Wallentin L, Swahn EFRISC II Study Group. Is early invasive treatment of unstable coronary artery disease equally effective for both women and men? FRISC II Study Group Investigators. J Am Coll Cardiol 2001;38:41–48.
31. Shub C, Klein AL, Zachariah PK, Bailey KR, Tajik AJ. Determination of left ventricular mass by echocardiography in a normal population: effect of age and sex in addition to body size. Mayo Clinic Proc 1994;69:205–211.
32. Olivetti G, Giordano G, Corradi D, Melissari M, Lagrasta C, Gambert SR, Anversa P. Gender differences and aging: effects on the human heart. J Am Coll Cardiol 1995;26:1068–1079.
33. Devereux RB, de Simone G, Ganau A, Koren MJ, Mensah GA, Roman MJ. Left ventricular hypertrophy and hypertension. Clin Exp Hypertens 1993;15:1025–1032.
34. Devereux RB, Koren MJ, de Simone G, Okin PM, Kligfield P. Methods for detection of left ventricular hypertrophy: application to hypertensive heart disease. Eur Heart J 1993;14(Suppl. D):8–15.

Chapter Five

No prognostic significance of chronic infection with Chlamydia pneumoniae in acute coronary syndromes: Insights from the Global Utilization of Strategies to Open Occluded Arteries IV Acute Coronary Syndromes trial

Cynthia M. Westerhout, Judy Gnarpe, Wei-Ching Chang, Susan FitzPatrick, Elliot S. Barnathan, Eric Boersma, Robert M. Califf, Lars Wallentin, Maarten L. Simoons, and Paul W. Armstrong, on behalf of the GUSTO IV ACS Investigators

BACKGROUND Although relationships between chronic Chlamydia pneumoniae (Cpn) infection and the risk of coronary events in stable coronary artery disease patients have been reported, a similar link in acute coronary syndrome (ACS) patients has not been consistently observed.
METHODS In a nested case-control substudy of the Global Utilization of Strategies to Open Occluded Arteries IV Acute Coronary Syndromes trial, 295 cases (30-day death/myocardial infarction [MI]) were matched by age, sex, baseline creatine kinase–myocardial kinase, and smoking status with 295 control subjects. To test the hypothesis on 1-year mortality, another subset (n = 276) was drawn from the 590-patient cohort; 138 patients who died at 1 year plus the matching controls who survived at 1 year. We measured Cpn IgG and IgA antibody titers in baseline serum with microimmunofluorescence. Conditional logistic regression was used to quantify the prognostic relevance seropositivity (IgG ≥1:32; IgA ≥1:16) and elevated titer levels.
RESULTS The prevalence of Cpn IgG and IgA was similar between cases and controls (30-day death/MI: IgG, 80% vs 85%, P = 0.126; IgA, 45% vs 37%, P = 0.079), and were not statistically significant predictors of 30-day death/MI after baseline adjustment. Likewise, the 1-year death cohort had comparable proportions of Cpn IgG and IgA among cases and controls (86% vs 91% [P = 0.265] and 49% vs 43% [P = 0.334], respectively), and did not add prognostic value.
CONCLUSIONS These findings are in concert with study results suggesting that chronic Cpn infection is not associated with 30-day death/MI or 1-year mortality in non-ST elevation ACS.

Inflammation has emerged as a key contributor to our understanding of the pathophysiology of coronary artery disease. C-reactive protein (CRP), for instance, has been consistently associated with poor outcomes in patients with acute coronary syndromes (ACS), particularly during long-term follow-up.[1-3] Other indicators of inflammation including antibodies of

Chlamydia pneumoniae (Cpn) have received less attention than CRP, but have also been linked to increased risk of events either by initiating or contributing to plaque formation and destabilization.

Infectious particles of Cpn, a common bacterial pathogen known to cause upper and lower respiratory tract infections, are frequently found in atherosclerotic plaques but not in healthy arterial tissues, unlike other organisms such as cytomegalovirus, which has been found in both.[4,5] Hence, Cpn could play a role in the induction and/or progression of atherosclerosis and in the destabilization of plaque leading to thrombosis. If this were the case, the infective status of such patients could prove valuable for risk stratification and subsequent medical decision-making.

To investigate this issue, a nested case-control substudy was conducted in 590 of the 7800 non-ST-elevation ACS patients enrolled in the Global Utilization of Strategies to Open Occluded Arteries IV Acute Coronary Syndromes trial.[6] Associations between Cpn and adverse outcomes at 30 days and 1 year were examined taking into account CRP and other baseline patient characteristics.

METHODS

Study design and subjects

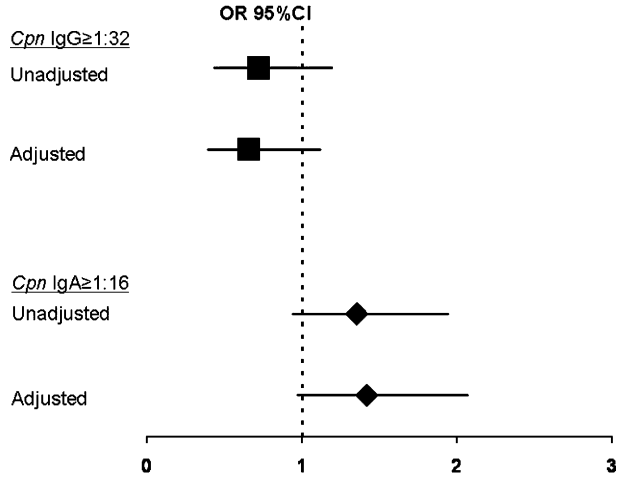
Of the 7800 patients enrolled in the Global Utilization of Strategies to Open Occluded Arteries IV Acute Coronary Syndromes trial, 590 were selected for this nested case-control substudy (Figure 1). The details of this trial have been previously outlined, but briefly, this multicenter randomized clinical trial enrolled ACS patients presenting with either ST segment depression on the admission electrocardiogram or elevated levels of troponin I or T, and tested the efficacy of abciximab (bolus with 24- vs 48-hour infusion) compared to a placebo.[6] The primary end point of the trial was a composite of death or myocardial infarction (MI) within 30 days of randomization, which was observed in 8.4% of 7800 patients. Death at 1 year was a secondary end point and occurred in 8.3% of 7800 patients.[7]

Selection of cases and controls

A sample of 295 patients was chosen at random from the group of patients who had a primary event (i.e., died or had an acute MI within 30 days of randomization). These cases were matched by conventional risk factors including; age (±5 years), sex, smoking status and baseline creatine kinase–myocardial kinase (CK-MB) >2x upper limit of normal with patients who were free of these adverse events at 30 days (controls).[8] The sample size was chosen to afford 96% power to detect an odds ratio (OR) of 2.0 with a correlation between cases and controls of 0.20, a of 5%, and probability of exposure of 50%.

A secondary analysis was preformed to examine the association between Cpn and 1-year mortality given the emerging evidence supporting the long-term prognostic value of inflammatory markers. Thus, a subset of the original case-control study was

Figure 1



Nested case-control study design.

identified (n = 276): 138 patients who died within 1 year and their previously matched partner (Figure 1). Based on our prior assumptions, this substudy had 71% power to detect an OR of 2.0 with a correlation between cases and controls of 0.20, a of 5%, and probability of exposure of 50%.

Blood sample collection and laboratory testing

Serologic analysis of humoral IgG and IgA Cpn antibodies was performed in the Department of Medical Microbiology at the University of Alberta in Edmonton, Canada, according to previously described methods.[9] Plasma samples were diluted 1:16 with phosphate-buffered saline (PBS; pH 7.4) (Sigma, St Louis, MO), then serially diluted with doubling dilutions in PBS (pH 7.4). For IgG determinations, a 1:32 dilution was used for screening, and for IgA a 1:16 dilution. Specimens found to be positive for IgG in the screening test were rediluted in PBS and tested up to a titer of 1:8192. Specimens that were positive for IgA in screening tests were rediluted to a titer of 1:16 using Gullsorb (Gull Laboratories, Salt Lake City, UT) to remove possible interference from IgG, and then serially diluted to a maximum titer of 1:4096 with PBS. All plasma dilutions were incubated on the 21-well antigen slides (Thermobio, Helsinki) for 16 hours at +4•C, then washed 3 times for 5 minutes in PBS to remove excess plasma before adding the rabbit antihuman fluorescein isothiocyanate conjugated IgG or IgA. Further incubation was done for 30 minutes at 37•C, the washing procedure was repeated and the slides finally mounted with buffered glycerol and read using a UV microscope at a

Table I. Baseline characteristics of matched case-control population (n = 590), where a case represents a death or MI within 30 days

	Control (%)	Case (%)	P
n	295	295	
Age (y)*	71 (64-76)	71 (64-76)	1.000
Women*	34.9	34.9	1.000
Whites	97.6	96.3	.474
Body weight (kg)	75 (67-84)	75 (65-85)	.943
Region of enrolment			.211
Western Europe	48.5	46.8	
Eastern Europe	32.2	31.5	
North America	11.9	16.9	
Other†	7.5	4.7	
Hypertension	52.2	62.0	.020
Diabetes mellitus	25.1	29.8	.230
Hyperlipidemia requiring therapy	27.8	38.0	.011
Current smoker*	18.8	18.8	1.000
History of PCI	12.9	9.8	.299
History of CABG	8.8	9.8	.777
History of angina pectoris	53.9	57.6	.407
History of MI	38.6	47.1	.046
History of heart failure	10.8	13.9	.317
History of stroke	4.1	6.8	.203
Prior aspirin use (7 d before randomization)	77.3	75.6	.698
Aspirin use within 48 h of randomization	89.8	85.1	.106
MI diagnosis on enrollment	30.2	32.5	.594
ST segment depression ≥0.5 mm	76.3	85.1	.009
CK-MB >2× ULN*	31.5	31.5	1.000
Troponin T (μg/L)	0.17 (0.01-0.57)	0.21 (0.06-0.59)	.045
CRP (mg/L)	3.49 (1.57-8.94)	4.34 (2.00-14.1)	.042
Cpn IgG ≥1:32	85.4	80.3	.126
Cpn IgA ≥1:16	37.3	44.7	.079

Data are presented in percentages and median (25th, 75th percentile). *CABG,* Coronary artery bypass graft.
*Controls were matched with cases on these factors.
†Other: Australia, New Zealand, Israel, South Africa.

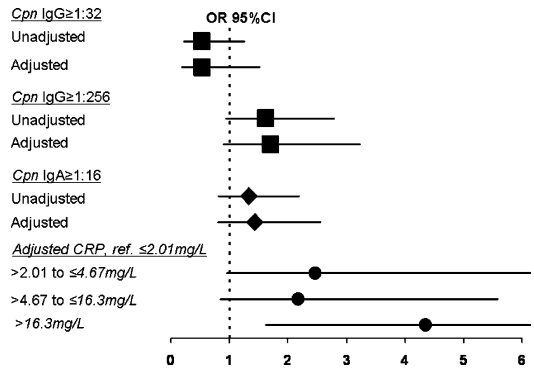
total magnification of 500X). The highest dilution, or titer, giving a homogenous positive reaction with the Chlamydia elementary body antigen was recorded. The investigator was unaware of case/control status during the analysis.

C-reactive protein and troponin T were centrally analyzed by the Department of Clinical Chemistry at the University of Uppsala in Uppsala, Sweden as mandated by the trial protocol. Detailed analytical techniques have been previously published.[3]

Statistical analysis

Frequencies are presented as percentages for categorical data, and the median and 25th and 75th percentiles presented for continuous data. Chi-square and Wilcoxon rank sum tests were applied, as appropriate. Univariable and multivariable associations between baseline patient characteristics and 30-day death/MI were evaluated with conditional logistic regression analysis. Baseline characteristics that had a moderate statistical association with the outcome (i.e., P <0.25) or were clinically plausible were considered in development of the final multivariable model. For example, hypertension, diabetes, hyperlipidemia, histories of angina, MI, congestive heart failure (CHF) or percutaneous coronary intervention (PCI), ST-segment depression ≥0.5 mm, quartiles of troponin T, quartiles of CRP, and Cpn seropositivity were considered in the full model for 30-day death/MI; however, after backward, stepwise selection, history of MI, history of PCI, CRP, and ST-segment depression ≥0.5

Figure 2



Adjusted OR and 95% CI for *Cpn* seropositivity (IgG ≥1:32 or IgA ≥1:16) predicting 30-day death/MI. IgG and IgA were adjusted for history of MI, history of PCI, and ST depression ≥ 0.5 mm.

mm remained in the final model. Cpn seropositivity was forced into the model to calculate adjusted estimates.

These analyses were then repeated for the associations with 1-year death in a subset of patients. Diabetes mellitus, history of CHF, ST depression ≥0.5 mm, and CRP remained as significantly associated with 1-year mortality, and Cpn seropositivity was forced into the model to calculate adjusted estimates.

RESULTS

Baseline patient characteristics are presented in Table I. The median age of the 590 patients included in this nested case-control study was 71 years (25^{th}-75^{th} percentile: 64-76). Nearly 35% of the patients in this study were women, and 23.4% were smokers at the time of enrolment.

Case-control study 1: 30-day death or MI

Baseline characteristic among cases and controls are presented in Table I. Cases had higher rates of hypertension, history of hyperlipidemia requiring therapy, prior MI and ST depression ≥0.5 mm on the baseline electrocardiogram. Cases also had higher median troponin T (P = 0.045) and CRP (P = 0.042). IgA seropositivity (≥1:16) tended to be higher in cases than controls (P = 0.079); however, IgG was comparable (P = .126) (Table I). After adjustment for previous MI, prior PCI and ST depression ≥0.5 mm, seropositive IgG was not a statistically significant predictor of 30-day death/MI (P = 0.126). However, there was a marginal association with seropositive IgA (adjusted OR 1.42, 95% confidence interval [CI] 0.97-2.07, P = 0.074) (Figure 2). Elevated levels of the antibodies were also examined; however, none were significantly associated with 30-day death/MI.

Table II. Baseline characteristics of matched case-control population (n = 276), where a case represents a patient who died within 1 year after randomization

	Control (%)	Case (%)	P
n	138	138	
Age (y)*	75 (69-78)	75 (69-78)	1.000
Women*	37.0	37.0	1.000
Whites	97.8	95.7	.337
Body weight (kg)	74 (66-82.3)	73 (63.8-83.3)	.401
Region of enrolment			.388
Western Europe	44.9	47.1	
Eastern Europe	34.1	36.2	
North America	12.3	13.0	
Other†	8.7	3.6	
Hypertension	56.5	64.5	.218
Diabetes mellitus	24.6	39.9	.010
Hyperlipidemia requiring therapy	29.0	37.7	.160
Current smoker*	15.9	15.9	1.000
History of PCI	12.3	6.5	.148
History of CABG	9.4	11.6	.695
History of angina pectoris	53.6	69.6	.009
History of MI	40.6	56.5	.011
History of heart failure	11.6	23.2	.017
History of stroke	4.3	8.0	.317
Prior aspirin use (7 d before randomization)	74.6	76.8	.779
Aspirin use within 48 h of randomization	86.2	86.2	1.000
MI diagnosis on enrollment	35.5	36.2	1.000
ST-segment depression ≥0.5 mm	71.7	89.9	<.001
CK-MB >2× ULN*	35.5	35.5	1.000
Troponin T (μg/L)	0.20 (0.05-0.76)	0.29 (0.07-0.83)	.255
CRP (mg/L)	4.01 (1.54-9.86)	6.25 (2.40-25.6)	.004
Cpn IgG ≥1:32	90.6	85.5	.265
Cpn IgA ≥1:16	42.8	49.3	.334

Data are presented in percentages and median (25th, 75th percentile).
*Controls were matched with cases on these factors.
†Other: Australia, New Zealand, Israel, South Africa.

Case-control study 2: 1-year death

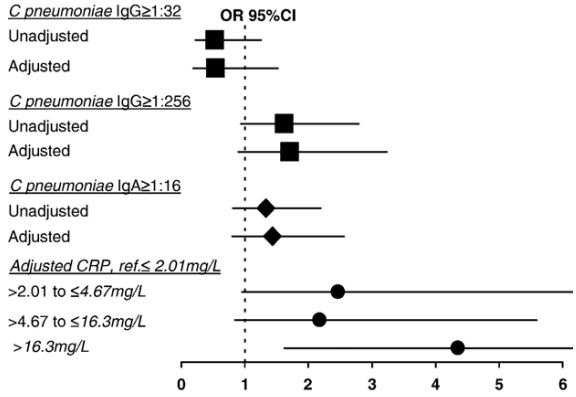
In a secondary case-control study, 138 patients who died within 1 year (case) and their matched pair (control) were selected from the aforementioned cohort (Figure 1). The median age of patients was 75 years, and 37% of the 276 patients were women (Table II). Cases and controls were reasonably matched on baseline characteristics; although patients were more likely to be diabetic, and had histories of angina, MI, and CHF, and ST depression ≥0.5 mm than those who survived through to 1 year (Table II). Median CRP was higher in cases than in controls; there was no significant difference in the prevalence of seropositive Cpn (IgG, P = 0.205; IgA, P = 0.334) or elevated titer levels (data not shown).

One-year mortality was not associated with Cpn seropositivity, even after adjustment with diabetes, history of CHF, ST depression ≥0.5 mm, and CRP (Figure 3). However, patients with elevated Cpn IgG (≥1:256) titer tended to have a nearly 2-fold risk of 1-year death (adjusted OR: 1.7 (0.9-3.24), P = 0.107).

DISCUSSION

The infectious burden of Cpn in our study was high in the overall patient group: 82.9% with IgG ≥1:32 and 41.0% with IgA ≥1:16, which is comparable to healthy, elderly individuals.[10] Cpn IgA is known to have a short half-life in serum in the absence of a continued antigenic stimulus, and continual, elevated levels are indicative of an ongoing or

Figure 3



Adjusted OR and 95% CI for *Cpn* seropositivity (IgG ≥1:32 or IgA ≥1:16) predicting 1-year mortality. IgG ≥1:32, IgG ≥1:256, and IgA ≥1:16 were adjusted for diabetes mellitus, history of CHF, ST depression ≥0.5 mm, and CRP.

chronic infection. Sustained high levels of IgG can also be a reflection of chronic infection, but it is not uncommon to find high titers of IgG in serum several years after a resolved infection.

Although the pathogenic mechanisms responsible for atherosclerotic rupture are not fully understood, ongoing inflammation is thought to be 1 of the major contributors to these clinical events and the infectious agent most often implicated in atherosclerosis is Cpn. Our study, however, did not uncover strong links between Cpn and subsequent adverse events in non-ST-elevation-ACS patients. Despite the signals, Cpn seropositivity did not have statistically significant prognostic value in the short term (i.e., 30-day death/MI) or long term (i.e., 1-year death). Overall, the body of evidence in this area is heterogeneous. Numerous studies in women and men alike have found little to suggest that this infectious agent is a contributor to adverse coronary outcomes,[11-13] whereas others have found the opposite.[14-18] Based on the suggestion that chronic infection is a contributor to poor cardiac outcomes, several large-scale clinical trials tested antibiotic therapy for the secondary prevention of coronary heart disease.[15,19-25] Unexpectedly, no clinical improvement was observed and as a result, [3] diverging conclusions may be drawn: (1) Cpn does not have a role in the progression of atherosclerotic disease; (2) the effects of Cpn infection are irreversible and have already occurred at an earlier stage; (3) Cpn in lymphocytes and monocytes are refractory to antibiotics.[26] There are, however, some notable caveats in these trials that are worth mentioning. The selection of patient groups receiving

antibiotics for putative Cpn infection were in most cases suboptimal and in some of the trials not performed at all, which raises some questions about the validity of many of these trials.[27] Improved criteria are needed to identify patients who may benefit from antimicrobial therapy.

Of note is the possible influence of aspirin on Cpn infection. Previous studies have shown aspirin to inhibit the growth of Cpn, which results in the inhibition of nuclear factor-nB activation and the release of the cytokines IL-6 and IL-8.28 In our study, however, Cpn seropositivity was similar regardless of prior aspirin use (1 week before randomization: IgA 45% [no aspirin] vs 38% [aspirin use], P = 0.22; IgG 83% vs 82%, P = 1.00) or protocol-mandated use (within 48 hours of randomization: IgA 41% vs 39%, P = 0.81; IgG 77% vs 82%, P = 0.52).[29] And although there is little evidence that aspirin decreases CRP values directly, aspirin does lead to a decrease in the amount of inflammation and IL-6, which will inevitably lead to a decrease in CRP production by hepatocytes. Aspirin has been shown to be most effective in individuals who have CRP levels in the upper quartiles.[30]

Limitations

Four limitations of the current study should be noted. First, transient rises in antibody titers, which would verify an active infection, between paired specimens may have occurred, but could not be detected. However, it is very unlikely that many of the patients included would have an acute reinfection and transient high levels of Cpn IgA antibodies.

Second, the timing of Cpn infection could have influenced our findings. A nested case-control study on 600 male US military personnel demonstrated that the risk of AMI was significantly associated with high titers of Cpn IgA (≥1:64), and an increased risk was particularly evident in specimens collected 1 to 5 years before the AMI event.[16] Unfortunately, this level of data was not available in the current study.

The design of this study also has characteristic shortcomings. Case-control studies are generally not considered as the best sources of definitive scientific evidence. However, case-control studies nested within a large, contemporary trial provides cost-effective opportunities for investigations such as this. At the time of study design, only data on 30-day events were available. A subset of the original case-control population was selected later on when 1-year mortality data were available, along with emerging evidence of inflammation's association with long-term adverse events. Hence, there may be concerns with the statistical power of the secondary case-control study.

And finally, the associations between Cpn seropositivity and outcomes were difficult to interpret given the borderline P values. Although there was some suggestion that Cpn seropositivity (i.e., IgA ≥1:16 or IgG ≥1:256) was associated with poor outcomes, the

95% CI crossed the line of unity. We also considered our findings in the context of other studies and design challenges of this study, and as such we concluded that the evidence for an association between Cpn seropositivity and outcomes was not overwhelming.

Future considerations

Additional infectious parameters to capture the "total pathogen burden" should be considered in the future. Other infectious agents may include cytomegalovirus, hepatitis A virus, herpes simplex virus type 1, herpes simplex virus type 2, and Helicobacter pylori. In 2000, Zhu and colleagues[31] demonstrated that the total pathogen burden was significantly associated with CRP levels in 890 coronary artery disease patients. These same investigators were also successful in showing that an increasing pathogen burden was significantly associated with increasing risk of MI or death and was consistent among various CRP levels.[32] The investigators concluded that infection plays an important role in the risk of adverse coronary events and that the risk posed by infection is independently related to the pathogen burden.

CONCLUSIONS

Our study did not provide conclusive evidence for the prognostic role of Cpn infection in this cohort of ACS patients. This does not disprove the theory that Cpn contributes to cardiovascular disease, but may explain why antibiotic treatment of Cpn is not effective in advanced stages of the disease.

REFERENCES

1. Morrow DA, Rifai N, Antman EM, et al. C-reactive protein is a potent predictor of mortality independently of and in combination with troponin T in acute coronary syndromes: a TIMI 11A substudy. Thrombolysis in Myocardial Infarction. J Am Coll Cardiol 1998; 31:1460 -5.

2. Lindahl B, Toss H, Siegbahn A, et al. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. N Engl J Med 2000;343:1139- 47.

3. James SK, Armstrong P, Barnathan E, et al. Troponin and C-reactive protein have different relations to subsequent mortality and myocardial infarction after acute coronary syndrome: a GUSTO-IV substudy. J Am Coll Cardiol 2003;41:916 - 24.

4. Kuo CC, Shor A, Campbell LA, et al. Demonstration of Chlamydia pneumoniae in atherosclerotic lesions of coronary arteries. J Infect Dis 1993;167:841 -9.

5. Jackson LA, Campbell LA, Schmidt RA, et al. Specificity of detection of Chlamydia pneumoniae in cardiovascular atheroma. J Infect Dis 2000;181(Suppl 3):S447 -8.

6. Simoons ML, GUSTO IVA. Effect of glycoprotein IIb/IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes without early coronary revascularisation: the GUSTO IV-ACS randomised trial. Lancet 2001;357:1915- 24.

7. Ottervanger JP, Armstrong P, Barnathan ES, et al. Long-term results after the glycoprotein IIb/IIIa

inhibitor abciximab in unstable angina: one-year survival in the GUSTO IV-ACS (Global Use of Strategies To Open Occluded Coronary Arteries IV-Acute Coronary Syndrome) Trial. Circulation 2003;107:437 - 42.
8. Hahn DL, Golubjatnikov R, Hahn DL, et al. Smoking is a potential confounder of the Chlamydia pneumoniae-coronary artery disease association. Arterioscler Thromb 1992;12:945 -7.
9. Gnarpe J, Sparr A, Naas J, et al. Serological analysis of specific IgA to Chlamydia pneumoniae: increased sensitivity of IgA antibody detection using prolonged incubation and high antigen concentration. APMIS 2000;108:357 - 62.
10. Gnarpe J, Gnarpe H, Gause-Nilsson I, et al. Seroprevalence of antibodies to Chlamydia pneumoniae in elderly people: a twodecade longitudinal and cohort difference study. Scand J Infect Dis 2000;32:177 -9.
11. Ridker PM, Hennekens CH, Buring JE, et al. Baseline IgG antibody titers to Chlamydia pneumoniae, Helicobacter pylori, herpes simplex virus, and cytomegalovirus and the risk for cardiovascular disease in women. Ann Intern Med 1999;131:573 -7.
12. Nieto FJ, Folsom AR, Sorlie PD, et al. Chlamydia pneumoniae infection and incident coronary heart disease: the Atherosclerosis Risk in Communities Study. Am J Epidemiol 1999;150:149 - 56.
13. Ridker PM, Kundsin RB, Stampfer MJ, et al. Prospective study of Chlamydia pneumoniae IgG seropositivity and risks of future myocardial infarction. Circulation 1999;99:1161 -4.
14. Wong BY, Gnarpe J, Teo KK, et al. Does chronic Chlamydia pneumoniae infection increase the risk of myocardial injury? Insights from patients with non-ST–elevation acute coronary syndromes. Am Heart J 2002;144:987 - 94.
15. Cannon CP, Braunwald E, McCabe CH, et al. Antibiotic treatment of Chlamydia pneumoniae after acute coronary syndrome. N Engl J Med 2005;352:1646 - 54.
16. Arcari CM, Gaydos CA, Nieto FJ, et al. Association between Chlamydia pneumoniae and acute myocardial infarction in young men in the United States military: the importance of timing of exposure measurement. Clin Infect Dis 2005;40:1123 - 30.
17. Strachan DP, Carrington D, Mendall MA, et al. Relation of Chlamydia pneumoniae serology to mortality and incidence of ischaemic heart disease over 13 years in the Caerphilly prospective heart disease study. BMJ 1999;318:1035 -9.
18. Siscovick DS, Schwartz SM, Corey L, et al. Chlamydia pneumoniae, herpes simplex virus type 1, and cytomegalovirus and incident myocardial infarction and coronary heart disease death in older adults: the Cardiovascular Health Study. Circulation 2000;102:2335 - 40.
19. Grayston JT, Kronmal RA, Jackson LA, et al. Azithromycin for the secondary prevention of coronary events. N Engl J Med 2005;352:1637 - 45.
20. Muhlestein JB, Anderson JL, Carlquist JF, et al. Randomized

secondary prevention trial of azithromycin in patients with coronary artery disease: primary clinical results of the ACADEMIC study. Circulation 2000;102:1755 - 60.
21. Neumann F, Kastrati A, Miethke T, et al. Treatment of Chlamydia pneumoniae infection with roxithromycin and effect on neointima proliferation after coronary stent placement (ISAR-3): a randomised, double-blind, placebo-controlled trial. Lancet 2001; 357:2085-9.
22. Sinisalo J, Mattila K, Valtonen V, et al. Effect of 3 months of antimicrobial treatment with clarithromycin in acute non-q-wave coronary syndrome. Circulation 2002;105:1555 - 60.
23. Zahn R, Schneider S, Frilling B, et al. Antibiotic therapy after acute myocardial infarction: a prospective randomized study. Circulation 2003;107:1253 -9.
24. Cercek B, Shah PK, Noc M, et al. Effect of short-term treatment with azithromycin on recurrent ischaemic events in patients with acute coronary syndrome in the Azithromycin in Acute Coronary Syndrome (AZACS) trial: a randomised controlled trial. Lancet 2003;361:809 - 13.
25. O'Connor CM, Dunne MW, Pfeffer MA, et al. Azithromycin for the secondary prevention of coronary heart disease events: the WIZARD study: a randomized controlled trial. JAMA 2003; 290:1459- 66.
26. Witherell HL, Smith KL, Friedman GD, et al. C-reactive protein, Helicobacter pylori, Chlamydia pneumoniae, cytomegalovirus and risk for myocardial infarction. Ann Epidemiol 2003;13:170 -7.
27. Wong BY, Gnarpe J. Chlamydia pneumoniae and acute coronary syndrome. N Engl J Med 2005;353:525-8.
28. Tiran A, Gruber HJ, Graier WF, et al. Aspirin inhibits Chlamydia pneumoniae-induced nuclear factor-kappa B activation, cytokine expression, and bacterial development in human endothelial cells. Arterioscler Thromb Vasc Biol 2002;22:1075 - 80.
29. Yoneda H, Miura K, Matsushima H, et al. Aspirin inhibits Chlamydia pneumoniae-induced NF-kappa B activation, cyclo-oxygenase-2 expression and prostaglandin E2 synthesis and attenuates chlamydial growth. Int J Med Microbiol 2003;52:409 - 15.
30. Ridker PM, Cushman M, Stampfer MJ, et al. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997;336:973 -9.
31. Zhu J, Quyyumi AA, Norman JE, et al. Effects of total pathogen burden on coronary artery disease risk and C-reactive protein levels. Am J Cardiol 2000;85:140 -6.
32. Zhu J, Nieto FJ, Horne BD, et al. Prospective study of pathogen burden and risk of myocardial infarction or death. Circulation 2001;103:45 - 51.

Chapter Six

Predictors of stroke within 30 days in patients with non-ST-segment elevation acute coronary syndromes

Cynthia M. Westerhout, Adrian V. Hernandez, Ewout W. Steyerberg, Hector Bueno, Harvey White, Pierre Theroux, David J. Moliterno, Paul W. Armstrong, Robert M. Califf, Lars C. Wallentin, Maarten L. Simoons, and Eric Boersma

AIMS Stroke is an uncommon but serious complication after non-ST-segment elevation acute coronary syndrome (NSTE-ACS). We aimed to identify predictors of stroke within 30 days in patients who suffered NSTE-ACS.

METHODS AND RESULTS We pooled data from six trials (n = 31 402) that randomized NSTE-ACS patients either to platelet glycoprotein (GP) IIb/IIIa receptor blockers or to placebo/control therapy. Potential predictors of stroke included treatment, demographic, and clinical characteristics. We identified predictors using univariable and multivariable logistic models, and their performance was evaluated with calibration (Hosmer–Lemeshow test) and discrimination (c-statistic). We found 228 (0.7%) all-cause strokes: 155 (0.5%) non-haemorrhagic, 20 (0.06%) haemorrhagic, and 53 without computed tomography (CT) confirmation. Patients with any type of stroke had a 30-day mortality of 25%. Randomization to GP IIb/IIIa receptor blockers was not significantly associated with all-cause stroke [OR (95% CI) 1.08 (0.83–1.41)]. Older age [OR per 10-year increase 1.5 (1.3–1.7)], prior stroke [2.1 (1.4–3.1)], and elevated heart rate [per 10-beat increase 1.1 (1.0–1.2)] were the strongest predictors of 30-day all-cause stroke. Similar predictors were found for non-haemorrhagic and haemorrhagic strokes. Smoking, previous myocardial infarction, diabetes, and hypertension were not independent predictors of all-cause stroke. The multivariable model to predict all-cause stroke was well calibrated, but its discrimination was only moderate [c-statistic 0.69 (0.65–0.72)].

CONCLUSION Stroke is a rare complication occurring early after NSTE-ACS, but is associated with high mortality. We found no evidence that GP IIb/IIIa receptor blockers increase stroke risks. A few clinical characteristics predicted higher stroke risks. Thus, incident strokes in NSTE-ACS patients remain largely unexplained.

Non-ST-segment elevation acute coronary syndrome (NSTE-ACS) is a heterogeneous disease. Risk stratification is essential for predicting prognosis, planning treatment strategy, and providing information to patients and relatives.[1,2] Previous papers in patients with NSTE-ACS have evaluated the predictors associated with a range of clinical outcomes at 30 days or 6 months, such as death, cardiovascular death, and cardiovascular death or myocardial infarction (MI).[2–5]

Stroke is an uncommon but severe event in patients presenting with NSTE-ACS. Analyses with a few events in the PURSUIT trial found several clinical predictors of non-

haemorrhagic stroke at 30 days.[6] These patients are also at increased risk for haemorrhagic strokes from polypharmacy anticoagulation. However, the confirmation of the importance of these predictors of stroke with a larger number of patients and events is desirable.

We aimed to identify the baseline clinical and demographic patient characteristics that predict the development of all-cause, non-haemorrhagic, and haemorrhagic strokes within 30 days. We analysed patients with NSTE-ACS from six large international trials. Moreover, we evaluated whether the use of GP IIb/IIIa receptor blockers was associated with an increased risk of stroke.

METHODS

Clinical trials

We used individual patient data from six trials (PRISM, PRISM-PLUS, PARAGON-A, PURSUIT, PARAGON-B, and GUSTO IV-ACS).[7–12] These trials were reported since 1990 with the following characteristics: randomization of patients with NSTE-ACS, comparison of platelet glycoprotein (GP) IIb/IIIa receptor blockers with placebo or control therapy, no-recommendation for early (<48 h) coronary revascularization during study-drug infusion, and enrolment of at least 1000 patients. Heparin was usually begun with 5000 IU and then followed with 1000 IU/h. Heparin was part of the study regimen in the PRISM, PRISM-PLUS, and PARAGON-A trials and was given to all patients in the PURSUIT, PARAGON-B, and GUSTO IV-ACS trials. In addition, all trials excluded patients with thrombocytopaenia (platelets <100 000 cells/mL). Five of the trials excluded patients with renal failure (serum creatinine >2 mg/dL or creatinine clearance <30 mL/min), except the GUSTO IV-ACS trial. All trials excluded patients with a prior stroke: PRISM, PRISM-PLUS, PARAGON-A, and PARAGON-B in the last year; PURSUIT in the last 30 days; and GUSTO IV-ACS in the last 2 years. Further details of the trial designs are available elsewhere.[13] A total of 31 402 patients participated in these trials. Data on 31 387 patients were available for this analysis.

Potential predictors

An electronic database consisting of data from individual patients in all eligible trials was available.[13] These data were checked for completeness, internal consistency of patients' records, and consistency with the published reports. For this analysis, we used available baseline demographic and clinical characteristics, regarded as potential predictors of stroke.[6] Those with almost complete information (<1% of missing values) included age, gender, smoking, weight, and prior history of all the following: hypertension, diabetes, stroke, MI, heart failure, angina pectoris, coronary artery bypass surgery, percutaneous coronary intervention, and use of aspirin. Two variables had 2% of missing values: history of hypercholesterolaemia and ST-depression at baseline.

Other variables had ~20% of missing data: race, heart rate, systolic and diastolic blood pressures, and baseline creatinine kinase MB (CK-MB). Blood pressure and heart rate were not recorded in the GUSTO IV-ACS trial (n = 7800); baseline CK-MB was missing in 7469 patients across different trials. Variables with far more than 20% of missing values were excluded from the analysis, such as prior use of beta-blockers, angiotensin-converting enzyme-inhibitors, nitrates, and calcium antagonists. Troponin levels were systematically collected in only two of the most recent trials (PARAGON-B and GUSTO IV-ACS), in which it was available in 7161 of 13 025 patients. Predictors with ~20% or less of missing values were imputed using the estimated mean procedure in SPSS (SPSS Inc., Chicago, IL, USA, 1999).[14] Atrial fibrillation (AF) and creatinine clearance were not available. The body mass index could not be calculated (i.e. no height was available) and it was not included in the analysis. The use of GP IIb/IIIa receptor blockers was also included as a potential predictor of stroke.

Outcomes

For this analysis, the primary outcomes defined a priori were all-cause stroke, non-haemorrhagic stroke, and haemorrhagic stroke within 30 days of the index ACS. Non-haemorrhagic and haemorrhagic strokes needed CT confirmation. All-cause stroke was missing in 12 patients. Non-haemorrhagic and haemorrhagic stroke was missing in 7434 and 7474 patients, respectively. No formal attempt to impute these outcomes was done.

Statistical analysis

This is a prediction analysis that pools data from six large-scale randomized clinical trials, and it is not a formal meta-analysis. Univariable logistic regression models were used to evaluate the association between each potential predictor and the outcome.

We checked the linearity assumption of continuous variables using restrictive cubic splines. The predictive weight of each variable was expressed as a chi-square statistic, which was calculated on the -2 log likelihood scale. The higher the number, the more important the predictor; a chi-square exceeding 3.84 corresponds to $P < 0.05$ for a predictor with one degree of freedom. All predictors were entered in a multivariable logistic regression model without further selection to properly evaluate their predictive effects while adjusting for the effects of each other predictor.[15] The performance of the multivariable models was studied with respect to discrimination and calibration. Discrimination refers to the ability to distinguish a stroke from no stroke. It was quantified by a measure of concordance, the c-statistic. For binary outcomes, the c-statistic is identical to the area under the receiver operating characteristic curve. The c-statistic lies between 0.5 and 1 and is better if closer to 1.[16] Because the apparent c-statistic is optimistic with low numbers of events, we used a standard

Table 1 Distribution of patient baseline characteristics across stroke types (all-cause, non-haemorrhagic, and haemorrhagic)

Predictor	All-cause strokes $n = 228$			Non-haemorrhagic strokes $n = 155$			Haemorrhagic strokes $n = 20$		
	N	*n* (%)	Deaths (%)[a]	*N*	*n* (%)	Deaths (%)[a]	*N*	*n* (%)	Deaths (%)[a]
Age[b]									
<70 years	20 874	98 (0.5)	20 (20)	15 836	69 (0.4)	10 (15)	15 822	6 (0.03)	4 (67)
≥70 years	10 513	130 (1.2)	36 (28)	8 132	86 (1.1)	17 (20)	8 108	14 (0.17)	9 (64)
Prior stroke[b]									
No	29 890	201 (0.7)	50 (25)	22 777	134 (0.6)	24 (18)	23 744	16 (0.07)	10 (63)
Yes	1 446	27 (1.9)	6 (22)	1 141	21 (1.8)	3 (14)	1 134	4 (0.35)	3 (75)
Heart rate									
<75	16 807	104 (0.6)	18 (17)	12 577	70 (0.6)	11 (16)	12 564	10 (0.08)	5 (50)
≥75	14 580	124 (0.9)	23 (19)	11 391	85 (0.7)	10 (12)	11 364	10 (0.09)	8 (80)
Smoking									
Never	11 499	68 (0.6)	15 (22)	9 516	55 (0.6)	8 (15)	9 511	7 (0.07)	4 (57)
Former	10 429	91 (0.9)	21 (23)	7 577	55 (0.7)	10 (18)	7 557	6 (0.08)	4 (67)
Current	9 307	68 (0.7)	20 (29)	6 768	44 (0.7)	9 (20)	6 753	7 (0.10)	5 (71)
Prior MI									
No	20 648	125 (0.6)	31 (25)	16 345	90 (0.6)	14 (16)	16 317	14 (0.09)	9 (64)
Yes	10 646	103 (1.0)	25 (24)	7 531	65 (0.9)	13 (20)	7 519	6 (0.08)	4 (67)
Diabetes mellitus									
No	24 488	159 (0.6)	43 (27)	18 612	106 (0.6)	18 (17)	18 590	16 (0.08)	11 (69)
Yes	6 860	68 (1.0)	12 (18)	5 317	49 (0.9)	9 (18)	5 299	4 (0.08)	2 (50)
Hypertension									
No	14 417	81 (0.6)	21 (26)	10 908	60 (0.6)	11 (18)	10 891	7 (0.06)	5 (71)
Yes	16 935	147 (0.9)	35 (24)	13 025	95 (0.7)	16 (17)	13 002	13 (0.09)	8 (62)
GP IIb/IIIa RB[c]									
No	13 097	91 (0.7)	21 (23)	9 928	62 (0.6)	9 (15)	9 908	6 (0.06)	2 (33)
Yes	18 290	137 (0.8)	35 (26)	14 040	93 (0.7)	18 (19)	14 020	14 (0.09)	11 (79)

N, number of patients in a defined subgroup; n, number of patients with a stroke within a subgroup, and its percentage of $(n/N) \times 100$.
[a]Deaths within 30 days. The percentage refers to the number of deaths in patients who suffered a stroke.
[b]$P < 0.001$ for the comparison between categories.
[c]Platelet GP IIb/IIIa receptor blocker.

bootstrapping procedure to correct the estimates.[15,16] Calibration refers to whether the predicted risks agree with the observed risk frequencies. Calibration was measured with the Hosmer–Lemeshow goodness-of-fit test.[17] Analyses were performed in SPSS 10.0 and S-PLUS 2000 (Insightful Inc., Seattle, WA, USA).

RESULTS

Patient characteristics

We found 228 (0.7%) all-cause strokes in the study population: 155 (0.5%) were non-haemorrhagic, 20 (0.06%) haemorrhagic, and 53 (0.2%) without CT confirmation. Older patients with a prior stroke, prior MI, diabetes, hypertension, and patients with elevated heart rate had higher risks of all-cause and non-haemorrhagic strokes (Table 1). Smoking was not clearly related with the stroke incidence. Patients with previous percutaneous transluminal coronary angioplasty were at lower risk to develop any stroke. Less clear associations were seen in haemorrhagic strokes, probably due to small numbers. The risks of haemorrhagic stroke due to GP IIb/IIIa receptor blockers were tirofiban 0% (0/5147), lamifiban 0.1% (5/7507), eptifibatide 0.1% (7/10948), and abciximab 0.1% (8/7800). There was no statistical difference among these risks.

A high proportion of patients who suffered a stroke died: 56 (25%) of those with all-cause stroke, 27 (17%) of those with non-haemorrhagic stroke, and 13 (65%) of those with haemorrhagic stroke. The difference in mortality between non-haemorrhagic and haemorrhagic strokes was highly statistically different ($P < 0.001$).

Table 2 Univariable and multivariable OR (95% CI) of predictors of stroke in NSTE-ACS patients

Predictors	All-cause strokes		Non-haemorrhagic strokes		Haemorrhagic strokes	
	Univariable	Multivariable	Univariable	Multivariable	Univariable	Multivariable
Independent						
Age (per 10 years)	1.68 (1.48–1.91)	1.51 (1.31–1.74)	1.59 (1.37–1.86)	1.45 (1.22–1.73)	2.26 (1.41–3.60)	2.17 (1.30–3.64)
Prior stroke	2.81 (1.87–4.21)	2.06 (1.36–3.12)	3.17 (1.99–5.04)	2.36 (1.46–3.80)	5.03 (1.68–15.06)	3.76 (1.21–11.70)
Heart rate (per 10 beats)	1.11 (1.05–1.19)	1.11 (1.04–1.18)	1.13 (1.05–1.20)	1.13 (1.05–1.21)	1.10 (0.95–1.28)	1.15 (0.96–1.37)
Not independent						
Smoking						
Former	1.48 (1.08–2.03)	1.45 (1.05–2.02)	1.26 (0.86–1.83)	1.25 (0.84–1.84)	1.08 (0.36–3.21)	1.75 (0.85–5.65)
Current	1.24 (0.88–1.73)	1.37 (0.98–1.95)	1.13 (0.76–1.67)	1.50 (0.99–2.27)	1.41 (0.49–4.02)	2.48 (0.83–7.40)
Prior MI	1.60 (1.23–2.08)	1.32 (0.99–1.77)	1.57 (1.14–2.16)	1.23 (0.86–1.75)	0.93 (0.36–2.42)	0.82 (0.29–2.38)
Diabetes mellitus	1.53 (1.15–2.04)	1.26 (0.93–1.69)	1.62 (1.16–2.28)	1.35 (0.94–1.93)	0.88 (0.29–2.62)	0.79 (0.26–2.43)
Hypertension	1.55 (1.18–2.03)	1.21 (0.91–1.61)	1.32 (0.96–1.84)	1.00 (0.70–1.40)	1.56 (0.62–3.90)	1.22 (0.46–3.22)

Thirty-day mortality in patients without stroke was 3.4% (1060/31 162), and the difference in mortality between patients with and without stroke was highly significant (chi-square 259, P < 0.00001). No clear relation was observed between predictors and death in patients who suffered any type of stroke (Table 1).

Predictors of stroke

The rate of stroke was 0.8% (137/18 291) among users of GP IIb/IIIa receptor blockers and 0.7% (91/13 099) among non-users of GP IIb/IIIa blockers. There was no difference between users and non-users (chi-square 0.3, P = 0.6). The use of GP IIb/IIIa receptor blockers was not associated with a higher incidence of all-cause [OR (95% CI) 1.08(0.83–1.41)], non-haemorrhagic [1.06 (0.77–1.47)], and haemorrhagic [1.70 (0.65–4.45)] strokes. A subgroup analysis of the 3730 patients with positive troponin levels (>upper limit of normal) was performed. All-cause stroke was observed in 26 patients, and the use of GP IIb/IIIa antagonists was not associated with stroke in the univariate analysis (OR 0.94, 95% CI 0.4–2.1).

The strongest univariable predictors of all-cause stroke were older age (chi-square = 69), prior stroke (chi-square = 19), prior MI (chi-square = 12), hypertension (chi-square = 10), elevated heart rate (chi-square = 9), lighter weight (chi-square = 9), diabetes (chi-square = 8), and smoking (chi-square = 6). The associations are shown in Table 2.
No interactions between predictors were statistically significant. The three most important predictors were older age [OR (95% CI) per 10 years: 1.5 (1.3–1.7)], prior stroke [2.1(1.4–3.1)], and elevated heart rate [per 10 beats: 1.1 (1.0–1.2)]. Smoking, prior MI, diabetes mellitus, and hypertension were not independent predictors of stroke.

The strongest univariable predictors of non-haemorrhagic stroke were older age (chi-square = 38), prior stroke (chi-square = 18), elevated heart rate (chi-square = 9), prior MI (chi-square = 7), and diabetes (chi-square = 7). Lighter weight (chi-square = 4) and hypertension (chi-square = 3) had minor importance. The three most important predictors of non-haemorrhagic stroke had comparable associations as those

described for all-cause stroke. For haemorrhagic strokes, the strongest univariable predictors were older age (chi-square = 12), prior stroke (chi-square = 8), and lighter weight (chi-square = 5). Similarly, the three most important predictors were those of the non-haemorrhagic strokes (Table 2).

Performance of predictive models

The calibration of the predictive model of all-cause stroke was good (Hosmer–Lemeshow test 10.4, P = 0.24), but the discriminative power of this model was moderate [c-statistic (95% CI): 0.69 (0.65–0.72)]. Although the calibration of the predictive models of non-haemorrhagic and haemorrhagic strokes was good, the discriminative power was either moderate [c-statistic 0.67 (0.63–0.71)] or poor [c-statistic 0.58 (0.54–0.63)], respectively.

DISCUSSION

Stroke occurred in 0.7% of patients within 30 days of presenting with NSTE-ACS. Two-thirds of the strokes were non-haemorrhagic. Older age, prior stroke, and elevated heart rate were the strongest predictors of all-cause, non-haemorrhagic, and haemorrhagic strokes. However, the discriminative power of these predictors was moderate and especially poor for haemorrhagic strokes. Thus, it is difficult to accurately predict the incidence of stroke in this population.

The incidence of 30-day all-cause stroke in our patients is comparable with that in similar populations: 0.8% in the GUSTO-IIb trial[18] and 0.5% in the OPUS-TIMI 16 trial.[19] However, in clinical practice, the incidence of 30-day all-cause stroke may be larger, because the in-hospital incidence already reaches 0.7%.[20] In a Spanish nationwide registry (DESCARTES), the incidence of 30-day all-cause stroke was 0.9% (95% CI 0.4–1.3%).[21] For comparison, the incidence of 30-day all-cause stroke in patients with ST-segment elevation-ACS (STE-ACS) treated with thrombolytics was 1.4% (between 1.2 and 1.6%) in the GUSTO-I trial[22] and 0.8% in nine trials from a meta-analysis.[23] The VALIANT registry, including both NSTE- and STE-ACS patients, had 1.5% in-hospital strokes.[24] The proportion of haemorrhagic strokes was ~50% of the total number of strokes in the GUSTO-I trial[22] and 13% in the meta-analysis.[23] Strokes in NSTE-ACS patients were associated with a high mortality rate (25%), which is lower than that observed in STE-ACS patients (41%).[22]

Importantly, the use of GP IIb/IIIa receptor blockers was not clearly associated with an increased incidence of all-cause stroke, non-haemorrhagic stroke, or haemorrhagic stroke. However, it should be recognized that the conclusion regarding the effect of GP IIb/IIIa receptor blockers on haemorrhagic strokes has substantial uncertainty, given the low number of events available and, hence, the limited power of the statistical analysis. The low frequency of haemorrhagic stroke in the overall population, coupled with

lack of clear evidence of increased risk, provides reassurance that fear of intracranial haemorrhage should not be a reason to avoid these drugs. However, when patients receive these drugs on top of more aggressive antithrombotic therapy, the incidence of haemorrhagic strokes increases, as in patients with STE-ACS who received thrombolytics.[25] In our NSTE-ACS patients, predictors associated with the incidence of haemorrhagic stroke were similar to those associated with non-haemorrhagic stroke. In contrast, STE-ACS patients who take oral anticoagulation before admission, with <70 kg, and older than 65 years were at increased risk of haemorrhagic stroke.

Stroke has only been studied as an outcome in a secondary analysis of the PURSUIT trial.[6] Sixty-six non-haemorrhagic strokes in 9461 NSTE-ACS patients were studied. Haemorrhagic strokes were not studied. The strongest predictors were higher heart rate, older age, prior anterior MI, prior stroke or transient ischaemic attack (TIA), and diabetes mellitus. Our analysis of 31 387 patients increased the number of events and the power to find predictors of any type and all-cause stroke. However, the number of haemorrhagic strokes was still limited.

Age was an important predictor of non-haemorrhagic stroke in the PURSUIT6 and GUSTO-I trials.[26] In our analysis, age was the strongest predictor of all-cause, non-haemorrhagic, and haemorrhagic strokes, and its relative importance was slightly higher than the results of the PURSUIT trial. Elderly patients probably have a higher risk of stroke because of multiple co-morbidities associated with older age, such as AF, hypertension, physical inactivity, and asymptomatic carotid stenosis.[27]

Prior stroke has been described as a predictor of stroke in the OPUS-TIMI 16 trial.[28] In this trial, the proportion of 10-month all-cause stroke was 2.9% in 1173 patients with prior extra-cardiac vascular disease (peripheral + stroke + TIA) in comparison with 1.1% in 9108 patients without prior extra-cardiac vascular disease. In the PURSUIT and GUSTO-I trials, 26 prior stroke was analysed in conjunction with prior TIA, and this combined predictor was important. Prior stroke may be a marker of underlying cardiac, carotid, or cerebral vascular disease in ACS patients.

Elevated heart rate was very important in the PURSUIT[6] and GUSTO-I trials.[26] An explanation for the association between elevated heart rate and stroke is not clear.[6] The heart rate may correlate with larger infarctions that predispose patients to a higher likelihood of atrial arrhythmia and left ventricular thrombi. Heart rate is strongly associated with the presentation of AF in patients with NSTE-ACS.[29] AF is a common complication in these patients, occurring in 6.4% of patients enrolled.[30] Moreover, an elevated baseline heart rate may simply be an expression of a prior AF. Unfortunately, our data set did

not provide information over prior or incident AF. Finally, a high heart rate may be an expression of a decompensated heart failure, related to the extent of the MI. Heart failure on admission has been described as an independent predictor of in-hospital all-cause stroke in the VALIANT registry.[24]

Diabetes and prior MI were independent predictors of stroke in the PURSUIT trial,[6] but not in our analysis. Diabetes has a known association with a widespread atherosclerosis, and prior MI is associated with the formation of mural thrombus and emboli. Finally, lighter weight was weakly associated with haemorrhagic stroke. This was probably related to doses of GP IIb/IIIa receptor blockers and anticoagulants that were not reduced in lighter patients, and especially for the elderly.

Our study has some limitations. We had about 7500 patients with missing values for the non-haemorrhagic and haemorrhagic stroke outcomes. The number of non-haemorrhagic strokes was still larger (n = 155) than the largest previously published (n = 66).[6] Although we had a few haemorrhagic strokes (n 1 = 20), regression coefficients of the multiple regression model for haemorrhagic stroke are not biased. Although the performance of the prognostic model may be optimistic, it was internally validated using the bootstrap procedure. We imputed several patient characteristics. Of them, only heart rate remained as a strong predictor, as demonstrated previously.[6]

In conclusion, stroke is an infrequent but serious early complication of patients with NSTE-ACS. Mortality is high, especially for haemorrhagic strokes. Platelet GP IIb/IIIa receptor blockers were not significantly associated with any type of stroke. Three main predictors of stroke were older age, prior stroke, and elevated heart rate. Because the discriminative ability of these patient characteristics was at best moderate, it is difficult to predict which ACS patients will suffer a stroke.

ACKNOWLEDGEMENTS

The data included in this analysis were provided by Merck Inc., White House Station, NJ, USA (sponsor of the PRISM and PRISM-PLUS trials); F. Hoffman-La Roche, Basel, Switzerland (sponsor of PARAGON-A and PARAGON-B trials); COR Therapeutics Inc., San Francisco, CA, USA and Schering-Plough Inc., Kenilworth, NJ, USA (sponsors of the PURSUIT trial); and Centocor Inc., Malvern, PA, USA (sponsor of the GUSTO IV-ACS trial). A.V.H. received support from the Netherlands Organization for Scientific Research (ZON/ MW 908-02-117).

Conflict of interest: D.J.M. is a consultant for Merck, Centocor, and Eli Lilly and has received honoraria from the same, as well as from Roche. H.W. is a consultant for and has received honoraria from Merck. P.T. was a principal investigator and chairman of the Steering Committee for the PRISM-PLUS trial. P.W.A. has received research grants and

honoraria from Eli Lilly and Schering-Plough. R.M.C. has worked with Centocor, Lilly, COR, Schering-Plough, and Merck. M.L.S. is a consultant for Merck, Centocor, and Lilly and has provided paid expert testimony to Schering-Plough.

REFERENCES

1. Marschner IC, Colquhoun D, Simes RJ, Glasziou P, Harris P, Singh BB, Friedlander D, White H, Thompson P, Tonkin A. Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Study. Long-term risk stratification for survivors of acute coronary syndromes. Results from the Long-Term Intervention With Pravastatin in Ischemic Disease (LIPID) Study. J Am Coll Cardiol 2001;38:56–63.

2. Kini AS, Lee PC, Mitre CA, Kim MC, Kamran M, Duffy ME, Marmur JD, Sharma SK. Prediction of outcome after percutaneous coronary intervention for the acute coronary syndrome. Am J Med 2003;115:708–715.

3. Cohen M, Stinnett SS, Weatherley DD, Gurfinkel EP, Fromell GJ, Goodman SG, Fox KA, Califf RM. Predictors of recurrent events and death in unstable coronary artery disease after treatment with combination antithrombotic therapy. Am Heart J 2000;139:962–970.

4. Boersma E, Pieper KS, Steyerberg EW, Wilcox RG, Chang WC, Lee KL, Akkerhuis KM, Harrington RA, Deckers JW, Armstrong PW, Lincoff AM, Califf RM, Topol EJ, Simoons ML. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients. Circulation 2000; 101:2557–2567.

5. Sabatine MS, Januzzi JL, Snappin S, Theroux P, Jang I-K. A risk score system for predicting adverse outcomes and magnitude of benefit with glycoprotein IIb/IIIa inhibitor therapy in patients with unstable angina pectoris. Am J Cardiol 2001;88:488–492.

6. Mahaffey KW, Harrington RA, Simoons ML, Granger CB, Graffagnino C, Alberts MJ, Laskowitz DT, Miller JM, Sloan MA, Berdan LG, MacAulay CM, Lincoff AM, Deckers J, Topol EJ, Califf RM. Stroke in patients with acute coronary syndromes. Incidence and outcomes in the Platelet Glycoprotein IIb/IIIa Inhibitors in Unstable Angina: Receptor Supression Using Integrilin Therapy (PURSUIT) trial. Circulation 1999;99:2371–2377.

7. The PRISM Study Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. N Engl J Med 1998;338: 1498–1505.

8. The PRISM-PLUS Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. Platelet receptor inhibition in ischemic syndrome management in patients limited by unstable signs and symptoms. N Engl J Med 1998;338:1488–1497.

9. The PARAGON Investigators. International, randomised, controlled trial of lamifiban (a platelet glycoprotein IIb/IIIa inhibitor), heparin, or both in unstable angina. Platelet IIb/IIIa antagonism for the

reduction of acute coronary syndrome events in a global organization network. Circulation 1998;97:2386–2395.
10. The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. N Engl J Med 1998;339:436–443.
11. The GUSTO IV-ACS Investigators. Effect of glycoprotein IIb/IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes without early coronary revascularisation: the GUSTO IV-ACS randomized trial. Lancet 2001;357:1915–1924.
12. The PARAGON-B Investigators. Randomized, placebo-controlled trial of titrated intravenous lamifiban for acute coronary syndromes. Circulation 2002;105:316–321.
13. 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 randomized clinical trials. Lancet 2002;359:189–198.
14. Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. Stat Med 1991;10:585–598.
15. Harrell FE Jr. Regression Modeling Strategies with Applications to Linear Models, Logistic Regression and Survival Analysis. New York: Springer; 2001.
16. Steyerberg EW, Harrell FE Jr, Borsboom GJJM, Eijkemans MJC, Vergouwe Y, Habbema JDF. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. J Clin Epidemiol 2001;54:774–781.
17. Hosmer DW, Lemeshow S. Applied Logistic Regression. New York: John Wiley & Sons, Inc.; 1989.
18. The GUSTO IIb Investigators. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. N Engl J Med 1996;335:775–782.
19. Cannon CP, McCabe CH, Wilcox RG, Langer A, Caspi A, Berink P, Lopez-Sendon J, Toman J, Charlesworth A, Anders RJ, Alexander JC, Skene A, Braunwald E. Oral glycoprotein IIb/IIIa inhibition with ortofiban in patients with unstable coronary syndromes (OPUS-TIMI 16) trial. Circulation 2000;102:149–156.
20. Hasdai D, Behar S, Wallentin L, Danchin N, Gitt AK, Boersma E, Fioretti PM, Simoons ML, Battler A. A prospective survey of the characteristics, treatments and outcomes of patients with acute coronary syndromes in Europe and the Mediterranean basin. The Euro Heart Survey of Acute Coronary Syndromes (Euro Heart Survey ACS). Eur Heart J 2002;23:1190–1201.
21. Bueno H, Bardaji A, Fernandez-Ortiz A, Marrugat J, Marti H, Heras M. Management of Non-ST-segment-elevation acute coronary syndromes in Spain. The DESCARTES (Descripcio´n del Estado de los Sindromes Coronarios Agudos en un Registro Temporal ESpan˜ol) Study. Rev Esp Cardiol 2005;58:244–252.
22. Gore JM, Granger CB, Simoons ML, Sloan MA, Weaver WD, White HD, Barbash GI, Van de Werf F,

Ayward PE, Topol EJ. Stroke after thrombolysis: mortality and functional outcomes in the GUSTO-I trial. Circulation 1995;92:2811–2818.
23. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomized trials of more than 1000 patients. Lancet 1994;343:311–322.
24. Szummer KE, Solomon SD, Velazquez EJ, Kilaru R, McMurray J, Rouleau JL, Mahaffey KW, Maggioni AP, Califf RM, Pfeffer MA, White HD; VALIANT Registry. Heart failure on admission and the risk of stroke following acute myocardial infarction: the VALIANT registry. Eur Heart J 2005;26:2114–2119.
25. De Jaegere PP, Arnold AA, Balk AH, Simoons ML. Intracranial hemorrhage in association with thrombolytic therapy: incidence and clinical predictive factors. J Am Coll Cardiol 1992;19:289–294.
26. Mahaffey KW, Granger CB, Sloan MA, Thompson TD, Gore JM, Weaver WD, White HD, Simoons ML, Barbash GI, Topol EJ, Califf RM. Risk factors for in-hospital nonhemorrhagic stroke in patients with acute myocardial infarction treated with thrombolysis: results from GUSTO-I. Circulation 1998;97:757–764.
27. Straus SE, Majumdar SR, McAlister FA. New evidence for stroke prevention. Scientific review. JAMA 2002;288:1388–1395.
28. Cotter G, Cannon CP, McCabe CH, Michowitz Y, Kaluski E, Charlesworth A, Milo O, Bentley J, Blatt A, Krakover R, Zimlichman R, Reisin L, Marmor A, Lewis B, Vered Z, Caspi A, Braunwald E. OPUS-TIMI 16 Investigators. Prior peripheral arterial disease and cerebrovascular disease are independent predictors of adverse outcomes in patients with acute coronary syndromes: are we doing enough? Results from the Orbofiban in Patients with Unstable Coronary Syndromes- Thrombolysis in Myocardial Infarction (OPUS-TIMI) 16 Study. Am Heart J 2003;145:622–627.
29. Kovar D, Cannon CP, Bentley JH, Charlesworth A, Rogers WJ. Does initial and delayed heart rate predict mortality in patients with acute coronary syndromes? Clin Cardiol 2004;27:80–86.
30. Al-Khatib SM, Pieper KS, Lee KL, Mahaffey KW, Hochman JS, Pepine CJ, Kopecky SL, Akkerhuis SL, Stepinska J, Simoons ML, Topol EJ, Califf RM, Harrington RA. Atrial fibrillation and mortality among patients with acute coronary syndromes without ST-segment elevation: results from the PURSUIT trial. Am J Cardiol 2001;88:76–79.

Chapter Seven

Risk-benefit analysis of platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes

Cynthia M Westerhout and Eric Boersma

Four intravenous glycoprotein IIb/IIIa receptor inhibitors (GPIs) (abciximab, eptifibatide, tirofiban and lamifiban) have been tested extensively over the last decade for their efficacy and safety in patients with acute coronary syndromes (ACS). GPIs are well-established adjunct agents for patients undergoing percutaneous coronary intervention, and considerable effort has gone into evaluating these agents in patients who are not scheduled to undergo coronary revascularisation. In the current article, six major randomized clinical trials conducted in the latter patient population are reviewed. Based on a recent meta-analysis of these trials, GPIs reduced the incidence of death or myocardial infarction in patients not scheduled for early revascularisation, with the greatest reduction observed in patients at high risk of thrombotic complications. Major bleeding complications were more frequent in those receiving GPIs, however, the incidences of intracranial haemorrhage and stroke were similar in both treatment groups. Despite these risks, the benefits of GPI therapy in addition to conventional treatment, such as aspirin and heparin, should be considered for these high-risk patients.

Antiplatelet therapy has long been a cornerstone of the treatment strategies available to patients with acute coronary syndromes (ACS). In recent decades, progress in the understanding of the pathophysiology of ACS has brought about innovations in anti-platelet therapy. In particular, an appreciation for the role of platelet aggregation, through the identification of the platelet glycoprotein IIb/IIIa (gp IIb/IIIa) receptor ($\alpha_{IIb}\beta_3$ integrin), has initiated the creation of a new class of pharmaceutical agents, gp IIb/IIIa receptor inhibitors (GPIs) [1].

The blockade of this receptor has proven to be remarkably effective in patients undergoing percutaneous coronary intervention (PCI) by means of a 38% reduction in the incidence of peri-procedural death or myocardial infarction (MI) [2]. However, the efficacy of these agents in patients who are not scheduled for early revascularisation is less certain. In this review, the benefits and risks of GPI therapy in patients suffering from ACS without ST-segment elevation will be evaluated. Specifically, this expert appraisal is based on six large-scale, Phase III, randomised clinical trials, and meta-analyses of these trials, which evaluated intravenous GPIs (abciximab, eptifibatide, tirofiban or lamifiban) against placebo (or standard care) (Table 1).

Pathophysiology of acute coronary syndromes

The acute phase of coronary artery disease represents a spectrum of

Table 1. Glossary of GPI trials for the medical management of ACS patients without ST-segment elevation.

GUSTO-IV-ACS	Global Utilisation of Strategies to Open Occluded Coronary Arteries Trial IV in Acute Coronary Syndromes
PARAGON-A and -B	Platelet gp IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organisation Network-A and -B
PRISM	Platelet Receptor Inhibition for Ischaemic Syndrome Management
PRISM-PLUS	PRISM-in Patients Limited by very Unstable Signs and Symptoms
PURSUIT	Platelet gp IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy

diagnoses ranging from unstable angina (UA) to acute MI (Figure 1). Although further distinctions can be made through the evaluation of the electrocardiogram (ECG) taken at admission and the measurement of serum biomarkers such as creatine kinase-MB isoenzyme (CK-MB) and/or cardiac-specific troponins, a common pathophysiological mechanism unites these acute coronary events [3]. Arterial plaques, characterized by a large lipid core and a thin fibrous capsule, are susceptible to rupture as a result of increased inflammatory activity within the intima. The rupture of the plaque can precipitate thrombus formation, in which case a permanent occlusion may trigger a MI, or a transient occlusion may lead to UA.

Fundamental to the understanding of thrombus formation is an appreciation for the role of the platelet. During haemostasis, platelets are in an antithrombogenic condition and circulate smoothly throughout the vasculature. However, under the conditions of plaque rupture, adhesion molecules on the platelet bind to the highly thrombogenic subendothelial matrix. Subsequently, the platelets enter into an activated state, which is indicated by the activation and expression of approximately 80,000 – 100,000 gp IIb/IIIa receptors on the exterior of the platelet (and even more when accounting for the internal source of these receptors) [4]. These receptors bind fibrinogen, von Willebrand factor and soluble ligands (such as thrombin, ADP or adrenaline); in turn, a dense network of platelets and connecting fibres creates a thrombus [1]. Thus, the blockade of gp IIb/IIIa receptors is central to the inhibition of thrombosis and offers novel opportunities in anti-platelet therapy [5].

Intravenous glycoprotein IIb/IIIa receptor inhibitors

Four intravenous agents have been investigated for their efficacy and safety in ACS patients without ST-segment elevation and who are not scheduled for coronary revascularisation (Table 2). Abciximab is a humanised monoclonal antibody fragment that has a strong affinity for gp IIb/IIIa receptors, vitronectin receptors (on endothelial cells) and MAC-1 (a component of integrins and a member of the leukocyte–integrin adhesion molecule family; otherwise known as CD11b) receptors (on leukocytes). Eptifibatide, tirofiban and lamifiban are smaller in molecular weight than abciximab and inhibit the gp IIb/IIIa receptor via their unique amino acid-binding sequences, which correspond to

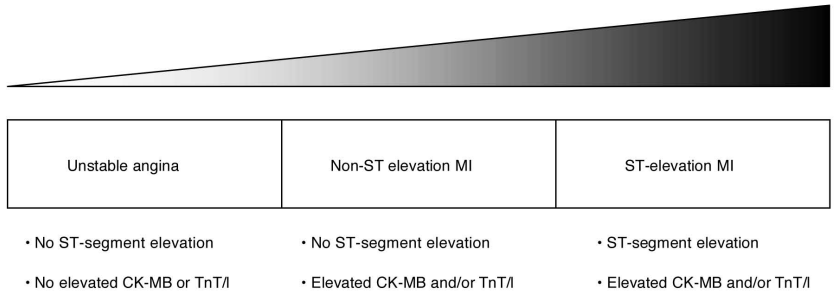


Figure 1. The spectrum of ACS.
ACS: Acute coronary syndrome; CK-MB: Creatine kinase-MB isoenzyme; ECG: Electrocardiogram; MI: Myocardial infarction; TnT/I: Cardiac-specific troponin T or I.

those found in fibrinogen, von Willebrand factor and other ligands of the gp IIb/IIIa receptor [6,7]. Unlike abciximab, the small-molecule GPIs have plasma half-lifes of approximately 2 h and lower binding affinity relative to abciximab. All of these agents, except for lamifiban, have received approval from North American and European regulatory bodies for commercial use.

Efficacy of intravenous glycoprotein IIb/IIIa receptor inhibitors

For patients with high-risk clinical features for whom PCI is not appropriate or available in the early phase of treatment, standard care has included anti-platelet therapy such as aspirin. Although aspirin is a well-established anti-platelet agent, platelet aggregation is not completely inhibited. By preventing the formation of thromboxane A2, aspirin blocks only one of the pathways leading to platelet aggregation. In contrast, GPIs provide more complete inhibition of platelet aggregation through the blockade of fibrinogen-binding receptors (gp IIb/IIIa), otherwise known as the final common pathway. Hence, GPIs were evaluated by six large-scale, randomised clinical trials with the anticipation that GPIs would provide additional benefits over traditional therapy (Tables 1 and 3).

Abciximab

Abciximab was the first GPI agent tested in patients undergoing PCI, and yet is one of the most recently tested agents evaluated in the early medical treatment of ACS. The investigators of the GUSTO-IV-ACS trial compared the effect of two different durations of abciximab infusion (i.e., 24- and 48-h) against a placebo bolus and infusion in ACS patients who were not scheduled to undergo early PCI [8] (Table 3). Enrolled patients also presented with either a positive troponin T or I test according to local laboratory measurements, or transient or persistent ST-segment depression (≥ 0.5 mm). Unlike the investigations of abciximab in patients with unstable refractory angina undergoing PCI [9], no additional benefit from the use of abciximab

Table 2. Characteristics of intravenous GPIs.

	Abciximab	Eptifibatide	Tirofiban	Lamifiban
Trade name (company)	ReoPro™ (Centocor/Eli Lilly)	Integrilin™ (COR Therapeutics/ Schering-Plough)	Aggrastat™ (Merck)	No trade name (Hoffman-La Roche)
Type	Antibody	Cyclic heptapeptide	Peptidomimetic	Non-peptide
Molecular weight (Da)	47,600	832	495	468
Binding to receptor	Irreversible	Competitive	Competitive	Competitive
Plasma half-life (h)	10 – 30 min	2.5	2	2
Approved indications	PCI Refractory UA when PCI is planned within 24 h	PCI ACS (UA and non-Q wave MI)	ACS (UA and non-Q wave MI)	Not approved
Dose regimens	PCI: 0.25 μg/kg bolus + 0.125 μg/kg/min (up to a maximum of 10 μg/min) infusion for 12 h after PCI	PCI: Two boluses of 180 μg/kg given 10 min apart, 2 μg/kg/min infusion for 18 – 24 h started immediately after first bolus ACS: 180 μg/kg bolus + 2 μg/kg/min infusion for 72 – 96 h	ACS: 0.4 μg/kg/min for 30 min + 0.1 μg/kg/min for 48 – 96 h	Not approved

ACS: Acute coronary syndromes; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; UA: Unstable angina.

was observed at 30 days (death or MI at 30 days; 8.0% placebo versus 8.2% 24-h abciximab, p = non-significant; 8.0% placebo versus 9.1% 48-h abciximab, p = non-significant) (Figure 2). A lack of effect was also observed in most subgroups, except for gender. Unexpectedly, women who received the 48-h infusion of abciximab experienced significantly more events at 30 days than those who received placebo.

The reasons for the failure to observe an apparent benefit are unclear, but there are suggestions that the unique patient population, study design, dose regimen of abciximab, or the sample size may have contributed to these unexpected results [8]. Lower rates of revascularisation compared to other GPI trials (PURSUIT) may also explain these data. It is clear, however, that additional investigations are needed to determine the appropriateness of abciximab in the medical management of ACS.

Eptifibatide

In contrast to abciximab, eptifibatide has been successful in reducing ischaemia and adverse clinical outcomes. In the follow-up to the promising results of Schulman's dose-finding trial, the PURSUIT trial investigators tested the hypothesis that eptifibatide could significantly reduce death and MI beyond standard therapy with aspirin and heparin [10,11] (Figure 2; Table 3). A distinguishing feature of this trial is its 'real-world'-based protocol; that is, allowing the physician to make decisions on treatment strategies, including cardiac catheterisation and revascularisation, at their own discretion, thereby providing insight into the use of eptifibatide in actual clinical practice.

The use of eptifibatide in these patients led to a significant reduction in death or non-fatal MI at each time

Table 3. Summary of trials of intravenous GPIs in the medical management of ACS patients.

Trial	Year*	N	Indication	Bolus dose	Infusion	Aspirin?	Heparin?	Primary end point
Abciximab								
GUSTO-IV-ACS	1998	7800	UA, NSTEMI	250 μg/kg	0.125 μg/kg for 24 h	Yes	Unfractionated (or LMWH if enrolled in sub-study)	30-day death or MI
				Placebo	0.125 μg/kg for 48 h			
				Placebo	Placebo			
Eptifibatide								
PURSUIT	1995	10,948	UA, NQMI	180 μg/kg	1.3 μg/kg/min for ≤ 72 h or discharge, 72 – 96 h if PCI (discontinued)	Yes	Recommended	30-day death or non-fatal MI
				180 μg/kg	2.0 μg/kg/min for ≤ 72 h or discharge, 72 – 96 h if PCI			
				Placebo	Placebo			
Tirofiban								
PRISM	1994	3232	UA, NQMI	0.6 μg/kg	0.15 μg/kg for 47.5 h infusion + heparin-placebo	Yes	Part of study regimen	48-h death, MI, or refractory ischaemia
				Placebo	Placebo + heparin			
PRISM-PLUS	1994	1915	UA, NQMI	0.4 μg/kg	0.10 μg/kg/min for 48 – 96 h infusion + dose-adjusted heparin	Yes	Part of study regimen	7-day death, new MI, or refractory ischaemia
				0.6 μg/kg	0.15 μg/kg for 48 – 96 h infusion + heparin-placebo (discontinued)			
				Placebo	Placebo + dose-adjusted heparin			
Lamifiban								
PARAGON-A	1995	2282	UA, NQMI	300 μg	1.0 μg/min for 3 – 5 days and random assignment to heparin or heparin-placebo	Yes	Part of study regimen	30-day death or non-fatal (re)MI
				750 μg	5.0 μg/min for 3 – 5 days and random assignment to heparin or heparin-placebo			
				Placebo	Placebo + heparin			
PARAGON-B	1998	5225	UA, NSTEMI	500 μg	Dose-adjusted lamifiban infusion for ≤ 72 h or until discharge (or 72 – 120 h for PCI) + heparin	Yes	Yes	30-day death, MI or severe, recurrent ischaemia
				Placebo	Placebo + heparin			

*Year: First year of enrolment period.
LMWH: Low molecular weight heparin; MI: Myocardial infarction; NQMI: Non-Q wave MI; NSTEMI: Non-ST-segment elevation MI; PCI: Percutaneous coronary intervention; UA: Unstable angina.

point. A 1.5% absolute reduction was achieved early after the initiation of treatment and was consistently maintained for 30 days (9.6% relative reduction at 30 days compared to those who received the placebo [15.7% placebo versus 14.2% eptifibatide, p = 0.03]) (Figure 2). A favourable treatment effect was noted in all subgroups, with the exception of women (odds ratio [OR] 1.10; 95% confidence interval [CI] 0.91 – 1.34). There appears to be no plausible biological reasoning behind this association and caution should be exercised when interpreting this result, especially in subgroup analyses.

The most dramatic results were

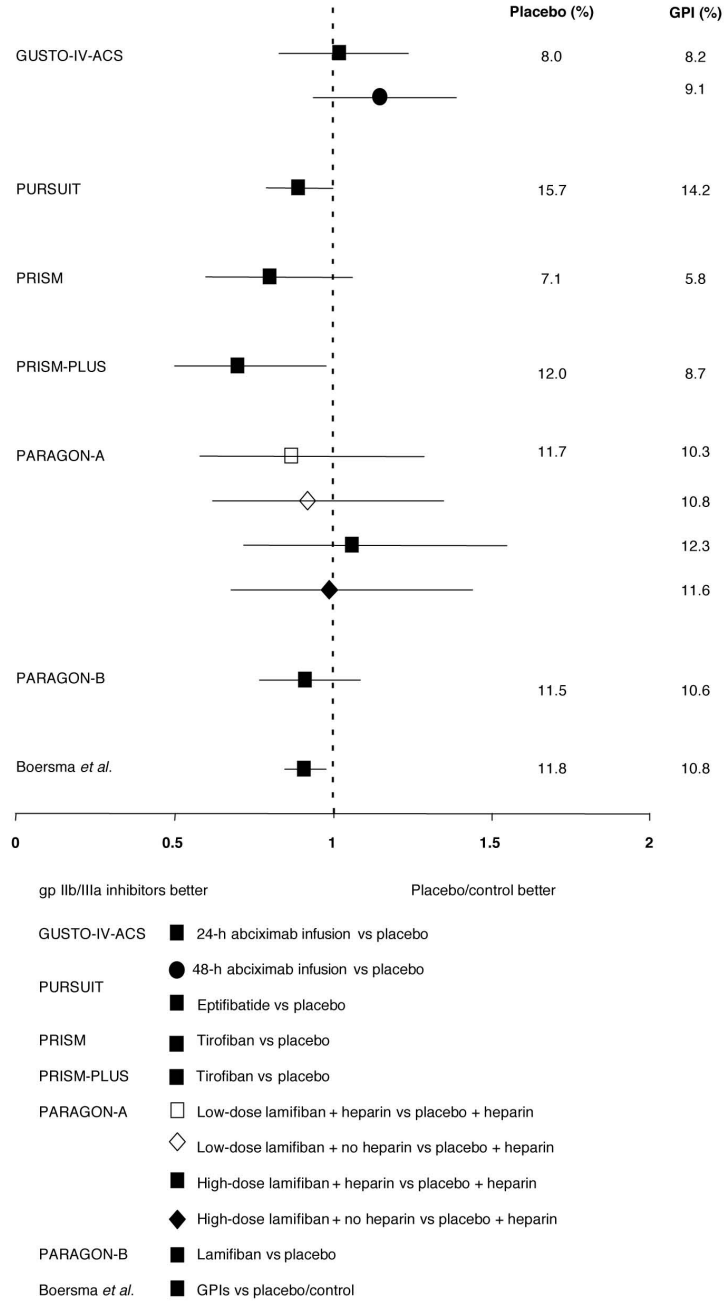


Figure 2. Death or MI at 30 days in trials evaluating GPIs in ACS without ST-segment elevation.
GPI: Glycoprotein IIb/IIIa receptor inhibitor; MI: Myocardial infarction.

realised in those who received eptifibatide and underwent PCI within 72 h after randomisation (31% relative risk reduction in death and non-fatal MI at 30 days [11.6% eptifibatide versus 16.7% placebo, p = 0.01]); whereas, the relative reduction in adverse events experienced by patients not undergoing a procedure was substantially attenuated (7% relative risk reduction; 14.5% eptifibatide versus 15.6% placebo, p = 0.23).

Tirofiban

The use of tirofiban in combination with or in comparison to standard therapies has been evaluated in two major trials, PRISM and PRISM-PLUS [12,13] (Table 3). While a strong body of evidence indicates that aspirin and heparin reduce the incidence of adverse cardiac events, the inconsistent pharmacodynamic response to heparin is cause for some concern. Thus, the intention of the PRISM trial was to evaluate the efficacy and safety of tirofiban against heparin in the medical management of UA patients receiving aspirin [12]. Patients receiving tirofiban benefited from a 32% relative reduction in the composite end point of death, refractory ischaemia or MI at 48 h when treated with tirofiban and aspirin compared to heparin and aspirin (3.8% tirofiban versus 5.6% heparin, relative risk ratio 0.67; 95% CI 0.48 – 0.92, p = 0.01). Although similar reductions in the composite end point were not consistently sustained through follow-up at 7 and 30 days (Figure 2), mortality at 30 days was significantly lower in those receiving tirofiban and aspirin (3.6% tirofiban versus 2.3% placebo; OR 0.62; 95% CI 0.41 – 0.93, p = 0.02).

The PRISM-PLUS investigators compared the efficacy and safety of three treatment arms in patients who were diagnosed with UA or non-Q wave MI and who were also receiving aspirin, tirofiban alone, tirofiban and heparin or heparin alone [13]. At the end of the first interim analysis, the tirofiban-alone treatment arm was terminated due to excess mortality at 7 days. In the remaining patients, tirofiban administered in combination with aspirin and heparin reduced the composite end point of death, MI or refractory ischaemia at 7 days, compared to those who had only received aspirin and heparin (12.9% tirofiban and heparin versus 17.9% heparin, relative risk ratio 0.68; 95% CI 0.53 – 0.88, p = 0.004). The benefits of tirofiban therapy were observed in various subgroups of patients and during long-term (i.e., 30 days and 6 months) follow-up (Figure 2).

Lamifiban

Unlike the previously described agents, lamifiban is not approved for commercial use. The inconclusive results of the two clinical trials, PARAGON-A and -B, may account for the delay in its approval [14,15] (Table 3). Based on promising results from the Canadian Lamifiban Study [16], the PARAGON-A trial was aimed at testing the effects and safety of two doses of lamifiban, with and without heparin, in patients with UA and non-Q wave MI. Unexpectedly, the use of lamifiban did not significantly reduce the

Table 4. Incidences of bleeding complications, intracranial haemorrhage, stroke, and thrombocytopenia in the trials of intravenous GPIs in ACS patients without ST-segment elevation.

Trial	Study drug (number of patients)	Major bleeding (%)	Minor bleeding (%)	Intracranial haemorrhage (%)	Stroke (%)	Thrombocytopenia (%)
GUSTO-IV-ACS	Placebo (2598)	0.3	2.0	< 0.1	0.6	< 0.1
	Abciximab 24-h infusion (2590)	0.6	3.0*	0.2	0.7	2.0*
	Abciximab 48-h infusion (2612)	1.0*	4.0*	0.1	0.5	1.0*
PURSUIT	Placebo (4696)	9.1	7.4	0.1	0.8	< 0.1
	Eptifibatide (4679)	10.6*	12.9	0.1	0.7	0.2
PRISM	Heparin (1616)	0.4	1.9	0.1	-	0.1
	Tirofiban (1616)	0.4	2.0	0.1	-	0.4**
PRISM-PLUS	Heparin (797)	0.8	-	0.0	-	0.3
	Tirofiban + heparin (773)	1.4	-	0.0	-	0.5
PARAGON-A	Placebo + heparin (758)	0.8	-	0.0	0.4	1.1
	Low-dose lamifiban + heparin (377)	0.5	-	0.0	1.1	0.8
	Low-dose lamifiban + no heparin (378)	0.8	-	0.0	1.1	2.1
	High-dose lamifiban + heparin (373)	2.4	-	0.0	0.5	0.8
	High-dose lamifiban + no heparin (396)	1.3	-	0.25	0.8	1.8
PARAGON-B	Placebo (2564)	0.9	11.5	0.1	0.6	0.5
	Lamifiban (2594)	1.3	14.0†	0.1	1.1¶	0.7
Boersma *et al.*	Placebo (13,105)	1.4	-	0.06	0.69	-
	Any GPI (including and excluding heparin) (18,297)	2.4‡§	-	0.09	0.75	-
	Placebo (including heparin) (11,489)	1.4	-	0.05	0.67	-
	Any GPI (including heparin) (15,562)	2.5§	-	0.08	0.73	-
	Placebo (including heparin) (2735)	1.3	-	0.06	0.69	-
	Any GPI (excluding heparin) (3171)	1.8§	-	0.11	0.88	-

primary composite end point of death or non-fatal MI at 30 days (Figure 2); however, the low-dose lamifiban performed better than aspirin and heparin at 6 months (17.9% control, 13.7% low-dose [versus control p = 0.027], 23.5% relative risk reduction, 16.4% high-dose [versus control p = 0.450], 8% relative risk reduction). Overall, it appeared that low-dose lamifiban might have additional value over

Table 4. Incidences of bleeding complications, intracranial haemorrhage, stroke, and thrombocytopenia in the trials of intravenous GPIs in ACS patients without ST-segment elevation *(continued)*.

Trial	Study drug (number of patients)	Major bleeding (%)	Minor bleeding (%)	Intracranial haemorrhage (%)	Stroke (%)	Thrombocytopenia (%)
	Placebo (including heparin) (10,507)	1.0	-	0.07	0.71	-
	Eptifibatide or tirofiban (including and excluding heparin) (13,095)	1.6	-	0.07	0.80	-

Bleeding complications defined by Thrombolysis In Myocardial Infarction (TIMI) study group classification (25) in all trials except for PARAGON-A and -B.
*p < 0.05 for comparison to placebo.
†p = 0.002 for comparison to placebo (intermediate bleeding).
¶p = 0.051 for comparison to placebo.
‡p < 0.001 for comparison to placebo.
§All data excluding GUSTO-IV-ACS.
**p = 0.04 for comparison to placebo.
Definitions of thrombocytopenia differ across trials. Where possible, incidences of severe (< 50,000 platelets per mm^3) or profound (< 20,000 platelets per mm^3) (PURSUIT) thrombocytopenia are reported.
GUSTO-IV-ACS: Major and minor bleedings are non-CABG-related. Actual incidences of intracranial haemorrhage, stroke, and thrombocytopenia were not reported, but the authors stated they were low and no significant differences between abciximab and placebo groups were observed.
PARAGON-A: Rates reported under minor bleeding were classified as intermediate bleeding by trial investigators.
CABG: Coronary artery bypass grafting; GPI: Glycoprotein IIb/IIIa receptor inhibitor.

lamifiban at higher doses. Compared to standard therapy, patients receiving low-dose lamifiban used in combination with heparin experienced the largest reduction in the composite end point at 30 days (12%, non-significant) and at 6 months (30%, p = 0.025).

Several explanations for these unexpected results have been suggested. First, the authors indicated that the statistical power of the PARAGON-A trial might have been inadequate to produce reliable results. Second, a retrospective pharmacokinetic analysis revealed that the study dose regimen was possibly suboptimal. Consequently, PARAGON-B was designed to evaluate the effects of titrated dosing, which were intended to achieve and maintain acceptable plasma levels of lamifiban [15]. Despite these modifications to the dosing regimen, no significant difference in the 30-day or 6-month composite end point of death, MI, or severe recurrent ischaemia was observed (30-day: 12.8% placebo versus 11.8% lamifiban, p = 0.329; 6-month: 15% placebo versus 14% lamifiban, p = 0.284) (Figure 2). Similar to PARAGON-A, the lack of statistical power in this trial should be taken into account when interpreting these results.

Overview of intravenous glycoprotein IIb/IIIa receptor inhibitors

Although there have been no direct comparisons of GPI therapy in this patient population, two comprehensive meta-analyses provide insight into the class effect of these agents [2,17]. Kong *et al*. observed that mortality, at any time point, was not significantly reduced with the use of GPI agents. However, the combined end point of death or nonfatal MI was reduced in those patients receiving GPI therapy at 48 – 96 h (OR 0.77; 95% CI 0.71 – 0.92), 30 days (OR 0.88; 95% CI 0.81 – 0.97) and 6 months (OR 0.88; 95% CI 0.79 – 0.97). With the addition of revascularisation into the

composite end point, similar benefits of GPI therapy were observed [2].

The meta-analysis conducted by Boersma *et al*. [17] provides a contemporary perspective of this class of agents with the inclusion of the PARAGON-B and GUSTO-IV-ACS trials and the exclusion of trials enrolling fewer than 1000 patients [11,16]. Overall, there was a 9% relative reduction in the odds of death or MI at 30 days with the use of GPI agents (p = 0.015) (Figure 2). When the effects of GPI therapy were examined according to prognostically important subgroups, such as age, diabetes mellitus, cardiovascular disease history and condition on admission, improved outcomes with GPI therapy were consistently noted. Significant interactions between allocated study treatment and cardiac troponin levels and gender were observed. In 35% of the 31,402 patients with data on cardiac troponins, patients with positive troponin levels (troponin T or I ≥ 0.1 μg/l) experienced a 15% relative risk reduction of death or MI at 30 days when GPI agents were administered compared to placebo or control (10.3% versus 12.0; OR 0.85; 95% CI 0.71 – 1.03). Conversely, there appeared to be no treatment effect in those patients with negative troponin concentrations (7.0% GPI versus 6.2% placebo/control; OR 1.17; 95% CI 0.94 – 1.44).

With respect to gender, men who received GPI therapy experienced a 19% relative reduction in the risk of death or MI at 30 days compared to placebo or control (10.4% versus 12.6%; OR 0.81; 95% CI 0.75 – 0.89), whereas the use of GPIs in women was associated with a 15% relative risk increase in death or MI at 30 days (11.5% versus 10.4%; OR 1.15; 95% CI 1.01 – 1.30). However, once patients were stratified according to cardiac troponin status, the benefits of GPI therapy were observed in both men and women with elevated troponin levels. Reductions in the risk of death or MI were not observed in men or women with negative troponin levels.

Adverse effects

The pharmacological mechanism behind GPIs acts to influence the restoration of haemostasis and, as such, patients with active bleeding or a history of bleeding disorders including diathesis, gastrointestinal or genitourinary bleeding (within the last 6 months) may be at an increased risk of excessive bleeding complications. Other contraindications include uncontrolled hypertension (≥ 180 mmHg systole and/or ≥ 110 mmHg diastole), severe anaemia and thrombocytopenia [18]. Likewise, patients who have undergone major surgery within the past 3 months, or have a history of stroke or recent trauma, are not recommended for GPI therapy [18].

Even in patients in whom GPI is indicated, bleeding complications may occur and are important safety concerns. Based on the meta-analysis of Boersma *et al*., the use of intravenous GPIs was associated with a 62% relative increase in the incidence of major bleeding

complications, regardless of the use of heparin (OR 1.62; 95% CI 1.36 – 1.94) (Table 4) [17]. As noted by GUSTO-IV-ACS investigators, factors associated with bleeding events include the use of low molecular weight heparin, duration of abciximab infusion, region of enrolment, performance of coronary bypass or PCI, advanced age and female gender [19]. When the incidence of major bleeding complications were compared in men and women in all six trials, women were at slightly higher risk compared to men (women: 3.0% GPI versus 1.4% placebo/control; OR 2.2; 95% CI 1.6 – 2.9; men: 2.1% GPI versus 1.4% placebo/control; OR 1.6; 95% CI 1.3 – 2.0) [18]. However, there was no evidence of heterogeneity (p = 0.10).

Other putative safety concerns of GPI therapy include intracranial haemorrhage (ICH), stroke and thrombocytopenia. The incidence of ICH was low (i.e., < 0.1%) in these trials, and its use with or without heparin was not associated with an increased incidence of ICH (Table 4) [17]. Similarly, the incidence of stroke was also not associated with the use of these agents [17].

Thrombocytopenia is a potential but uncommon adverse effect of GPI therapy. Severe thrombocytopenia (< 50,000 platelets/mm^3) occurs in < 2.0% of patients who receive abciximab and in < 1.0% of patients who receive tirofiban (Table 4). The incidence of profound thrombocytopenia (< 20,000 platelets/mm^3) is estimated to be between 0.3 and 1.0% in patients who receive abciximab and < 0.2% in those who receive eptifibatide [20]. Platelet function should be continually monitored during administration of the GPI agent, and if thrombocyptopenia develops, the cessation of the GPI agent and platelet transfusions (if necessary) should improve platelet function.

Treatment guidelines

Antiplatelet and anticoagulation therapies modulate the progression of coronary artery disease and, as such, they are integral components in the treatment of ACS. Assessing the individual risk of patients provides an opportunity for tailoring these treatment strategies. For patients who have been diagnosed with definite ACS and are experiencing ongoing ischaemia, have high-risk characteristics or will undergo a planned intervention, a combination of aspirin, (unfractionated) heparin and GPIs is recommended by both American and European professional societies [21,101]. Such high-risk features include elevated troponin levels, ST-segment changes, diabetes mellitus, advanced age or recurrent ischaemia. In patients with persistent ischaemia and in whom PCI is not planned, eptifibatide or tirofiban should be administered in combination with aspirin and heparin [101].

These risk criteria are based on the development of comprehensive, yet clinically applicable, risk stratification models [22,23]. Key predictors of death or the composite of death and (re)MI at 30 days in the PURSUIT trial included advanced age, heart

rate, systolic blood pressure, ST-segment depression, signs of heart failure and elevated cardiac biomarkers [22]. The TIMI (Thrombolysis In MI) risk score, which was developed in the unstable angina/non-ST elevation MI patient populations of the TIMI-11B and ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q wave Coronary Events) trials, found a similar array of predictors of death, (re)MI or urgent revascularisation at 14 days [23]. The application of these types of models is valuable in the pursuit of timely and optimal triage of patients.

Conclusion and expert opinion

The use of GPI therapy seems to reduce the incidence of death or MI in patients with ACS who are not scheduled for early revascularisation. These benefits were most evident in patients who were considered to be at high risk for thrombotic complications, e.g., patients with elevated cardiac troponins levels or ST-segment deviations, among others. The risk of major bleeding complications is higher with the use of GPI therapy; however, these risks should not suppress the benefits of this therapy. Therefore, GPI agents should be considered as part of the early medical management of high-risk patients.

REFERENCES

1. Topol EJ, Byzova TV, Plow EF. Platelet GPIIb-IIIa blockers. Lancet 1999;353(9148):227-231.

2. Kong DF, Califf RM, Miller DP et al. Clinical outcomes of therapeutic agents that block the platelet glycoprotein IIb/IIIa integrin in ischemic heart disease. Circulation 1998;98(25):2829-2835.

3. Libby P. Coronary artery injury and atherosclerosis and the biology of atherosclerosis: inflammation, thrombosis, and stabilization. Am. J. Cardiol. 2000; 86(8B):3J-8J.

4. Wagner CL, Mascelli MA, Neblock DS, Weisman HF, Coller BS, Jordan RE. Analysis of GPIIb/IIIa receptor number by quantification of 7E3 binding to human platelets. Blood 1996; 88(3):907-914.

5. Coller BS: The role of platelets in arterial thrombosis and the rationale for blockade of platelet GPIIb/IIIa receptors as antithrombotic therapy. Eur Heart J 1995;16 (Suppl. L):L11-L15.

6. Scarborough RM. Development of eptifibatide. Am Heart J 1999;138(6 Pt 1):1093-1104.

7. Jordan RE, Mascelli MA Pharmacological differentiation of GPIIb/IIIa inhibitors. *Eur Heart J* 1999;1(Suppl. E):E3-E10.

8. Simoons ML. Effect of glycoprotein IIb/IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes without early coronary revascularisation: the GUSTO IV-ACS randomised trial. Lancet 2001; 357(9272):1915-1924.

9. The CAPTURE Investigators: Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE Study. Lancet 1997; 349(9063):1429-1435.

10. Schulman SP, Goldschmidt-Clermont PJ, Topol EJ et al. Effects

of integrilin, a platelet glycoprotein IIb/IIIa receptor antagonist, in unstable angina. A randomized multicenter trial. Circulation 1996;94(9):2083-2089.
11. The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. The PURSUIT Trial Investigators. Platelet glycoprotein IIb/IIIa in unstable angina: receptor suppression using integrilin therapy. N Engl J Med 1998;339(7):436-443.
12. The PRISM Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. Platelet Receptor Inhibition In Ischemic Syndrome Management (PRISM) Study Investigators. N Engl J Med 1998;338(21):1498-1505.
13. The PRISM-PLUS Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. N Engl J Med 1998; 338(21):1488-1497.
14. The PARAGON Investigators. International, randomized, controlled trial of lamifiban (a platelet glycoprotein IIb/IIIa inhibitor), heparin, or both in unstable angina. The PARAGON Investigators. Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network. Circulation 1998;97(24):2386-2395.
15. The PARAGON-B Investigators. Randomized, placebo-controlled trial of titrated intravenous lamifiban for acute coronary syndromes. Circulation 2002;105(3):316-321.
16. Theroux P, Kouz S, Roy L et al. Platelet membrane receptor glycoprotein IIb/IIIa antagonism in unstable angina. The Canadian Lamifiban Study. Circulation 1996;94(5):899-905.
17. Boersma E, Harrington RA, Moliterno DJ et al. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. Lancet 2002; 359(9302):189-198.
18. Bhatt DL, Topol EJ. Current role of platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes. JAMA 2000;284(12):1549-1558.
19. Lenderink T, Boersma E, Ohman EM, Armstrong PW, Wallentin LC, Simoons ML. Bleeding events with abciximab in acute coronary syndromes without early revascularisation: an analysis of the GUSTO-IV-ACS trial. Eur Heart J 2002; Submitted.
20. Lincoff AM, Califf RM, Topol EJ. Platelet glycoprotein IIb/IIIa receptor blockade in coronary artery disease. J Am Coll Cardiol 2000;35(5):1103-1115.
21. Hamm CW, Bertrand M, Braunwald E. Acute coronary syndrome without ST elevation: implementation of new guidelines. Lancet 2001;358(9292):1533-1538.
22. Boersma E, Pieper KS, Steyerberg EW et al.: Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients. The PURSUIT Investigators. Circulation 2000;

101(22):2557-2567.
23. Antman EM, Cohen M, Bernink PJ et al. The TIMI risk score for unstable angina/non-ST elevation MI. A method for prognostication and therapeutic decision
making. JAMA (2000) 284(7):835-842.
24. 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):1-11.
101.http://www.acc.org/clinical/guidelines/unstable/unstable.pdf
Braunwald E, Antman EM, Beasely JW et al. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: a report of the American College of Cardiology/American Heart AssociationTask Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina).

Chapter Eight

Platelet Glycoprotein IIb/IIIa Inhibitors in the Treatment of Non-ST-segment Elevation Acute Coronary Syndromes in the Elderly

Cynthia M. Westerhout and Eric Boersma

The chain of events leading to acute coronary syndromes (ACS), including unstable angina (UA) and non-ST-segment elevation (NSTE) or ST-segment elevation myocardial infarction (STEMI), is triggered by the disruption of an atherosclerotic plaque, which leads to the formation of a platelet-rich thrombus within a coronary artery.[1,2] The inhibition of platelet aggregation is fundamental to the treatment of these patients; however, standard anti-platelet agents such as aspirin do not completely obstruct this activity. Advances in understanding the pathophysiology of ACS have to the recognition of the activation of the glycoprotein IIb/IIIa (Gp IIb/IIIa) receptors on platelets as the final common pathway leading to platelet aggregation. With this target in mind, pharmacological treatment of ACS has been propelled into a new era with agents that completely inhibit platelet aggregation.[3]

In this second of two reviews examining the impact of platelet glycoprotein IIb/IIIa receptor inhibitor (GPI) therapy on patients suffering from ischemic heart disease, the efficacy and safety issues associated with these agents in the medical management of non-ST-segment elevation ACS (NSTE-ACS) will be discussed. Specifically, this appraisal is based on large-scale, phase III, randomized clinical trials and meta-analyses evaluating intravenous (abciximab, eptifibatide, tirofiban and lamifiban) and oral agents (sibrafiban and orbofiban), with particular emphasis on the elderly (as defined in the trials) (Table 1).

Intravenous GPIs

Abciximab

Although it was the first GPI to be tested in patients undergoing percutaneous coronary intervention (PCI), abciximab is one of the most recent to be tested in the front-line medical treatment of NSTEACS. The investigators of the GUSTO-IV ACS (see Table 1 for full trial names) trial compared the effect of two different lengths of abciximab infusion (24-hour and 48-hour) against a placebo bolus and infusion in NSTE-ACS patients who were not undergoing early PCI (Table 2, page 27).[4] In patients with either a positive troponin T or I test, or transient or

Table 1
Glossary of Intravenous and Oral GPI Trials for the Medical Management of NSTE-ACS Patients

GUSTO-IV-ACS	Global Utilization of Strategies to Open Occluded Coronary Arteries Trial IV in Acute Coronary Syndromes
PURSUIT	Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression using Integrilin Therapy
PRISM	Platelet Receptor Inhibition for Ischemic Syndrome Management
PRISM-PLUS	PRISM-in Patients Limited to very Unstable Signs and symptoms
PARAGON -A and -B	Platelet GP IIb/IIIa Antagonist for the Reduction of Acute Coronary Syndrome Events in a Global Organisation Network-A and -B
OPUS TIMI-16	Orbofiban in Patients with Unstable Coronary Syndromes
1st & 2nd SYMPHONY	Sibrafiban versus aspirin to Yield Maximum Protection from Ischemic Heart events post acute coronary syndromes

persistent ST-segment depression (≥ 0.5mm), there was no benefit from the administration of abciximab, regardless of the length of infusion, at 30 days ((death or MI at 30 days) 8.0% placebo versus 8.2% 24-hour abciximab, odds ratio (OR) 1.0, 95% confidence interval (CI) (0.83-1.24); and 9.1% 48-hour abciximab, OR 1.1, 95% CI(0.94, 1.39)). This lack of effect was also evident in both younger (<65 years) and older ((≥ 65 years) patients (Figure 1). Unlike the investigations of abciximab in patients with refractory angina and in those undergoing PCI, it seems that no additional benefit was derived from the use of abciximab in the medical management of NSTE-ACS.

Eptifibatide

On the heels of the success of Gp IIb/IIIa receptor inhibition in patients undergoing PCI, it was suspected that eptifibatide, a small-molecule GPI, could reduce ischemia in UA patients. To follow-up on the promising results of Schulman's dose-finding trial, the PURSUIT trial investigators tested the hypothesis that eptifibatide could significantly reduce death and MI beyond standard therapy, such as aspirin and heparin, in ACS patients without persistent ST-segment elevation (Table 2).[5,6] A unique feature of this trial was its practice-based protocol, which mandated that decisions on treatment strategies, including cardiac catheterization and revascularization, were made at the discretion of the treating physicians.

Overall, the use of eptifibatide in these patients led to a significant reduction in death or non-fatal MI at each time point. On the fourth day after randomization, a 1.5% absolute reduction was achieved and was consistently maintained for 30 days (9.6% relative reduction at 30 days compared to those who received the placebo (15.7% placebo versus 14.2% eptifibatide, p=0.03)). The benefits of eptifibatide therapy were consistent across all age groups (Figure 1).

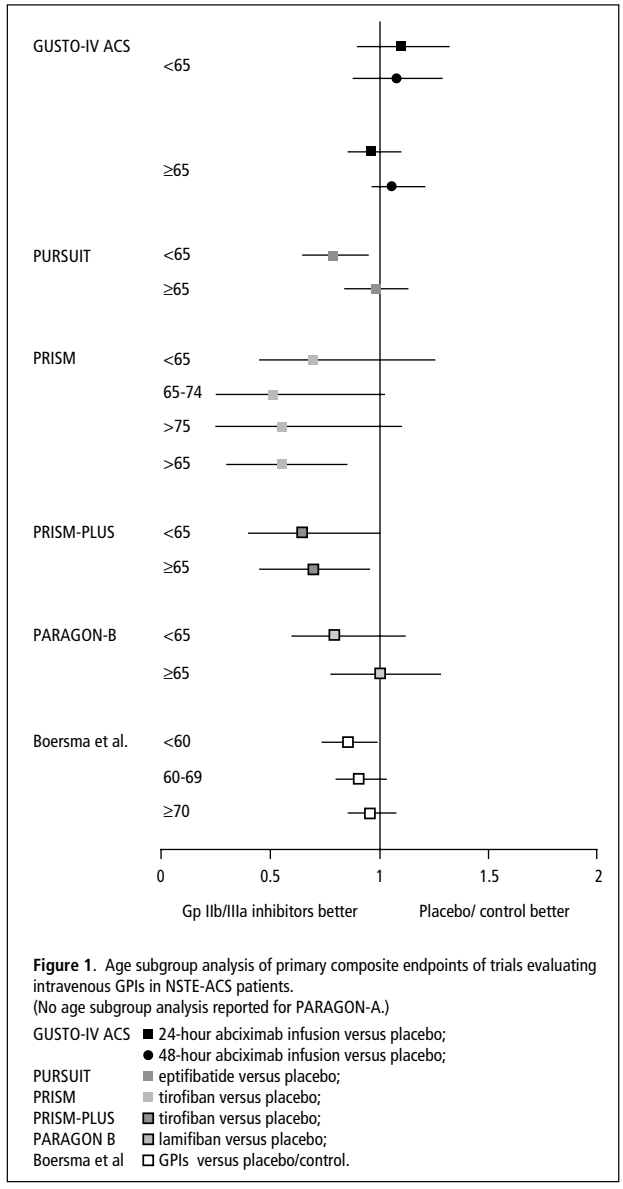


Figure 1. Age subgroup analysis of primary composite endpoints of trials evaluating intravenous GPIs in NSTE-ACS patients.
(No age subgroup analysis reported for PARAGON-A.)

GUSTO-IV ACS ■ 24-hour abciximab infusion versus placebo;
● 48-hour abciximab infusion versus placebo;
PURSUIT ■ eptifibatide versus placebo;
PRISM ■ tirofiban versus placebo;
PRISM-PLUS ■ tirofiban versus placebo;
PARAGON B ■ lamifiban versus placebo;
Boersma et al □ GPIs versus placebo/control.

Interestingly, the incidence of death or nonfatal MI was reduced by 31% (relative) at 30 days in those who received eptifibatide and underwent PCI within 72 hours after randomization (11.6% eptifibatide versus 16.7% placebo, p=0.01), whereas, the relative reduction in patients not undergoing a procedure was substantially attenuated (7% relative risk reduction, 14.5% eptifibatide versus 15.6% placebo, p=0.23).

Tirofiban

In the late 1990s, another small-

Table 2 Summary of Trials of Intravenous GPIs in the Medical Management of NSTE-ACS

Study (Enrolment period)	No. of Patients	Entry Criteria	Study Medication Endpoints	Primary Efficacy
ABCIXIMAB				
GUSTO-IV ACS (1998–2000)	7800	Patients ≥21 years old with NSTE-ACS.	Randomly assigned to: a) abciximab bolus + 24 h infusion (2590) b) abciximab bolus + 48 h infusion (2612) c) Placebo (2598) Abciximab dose: 0.25 mg/kg bolus + 0.125 µg/kg infusion All patients received aspirin, and heparin for non-LMWH-sub-study participants.	Death or MI at 30 days.
EPTIFIBATIDE				
PURSUIT (1995–1997)	10948	Patients with NSTE-ACS.	Randomly assigned to: a) eptifibatide 180 µg/kg + eptifibatide 1.3 µg/kg/min infusion (1487) (terminated at the interim analysis as high-dose eptifibatide proved safe) b) eptifibatide 180 µg/kg + eptifibatide 2.0 µg/kg/min infusion (4722) c) placebo bolus + infusion (4739) Infusion of 72 h or until discharge. All patients received aspirin and were allowed to receive heparin.	Death or non-fatal MI at 30 days.
TIROFIBAN				
PRISM (1994–1996)	3232	Patients with UA.	Randomly assigned to: a) tirofiban 0.6 µg/kg/min for 30 mins + 0.15 µg/kg for 47.5 h infusion + placebo heparin (1616) b) placebo tirofiban + heparin (1616) All received aspirin.	Death, MI, or refractory ischemia at end of 48 h infusion.
PRISM-PLUS (1994–1996)	1915	Patients with NSTE-ACS.	Randomly assigned to: a) tirofiban 0.6 µg/kg/min for 30 mins + 0.15 µg/kg for 48 h infusion + placebo heparin (345) b) tirofiban 0.4 µg/kg/min for 30 mins + 0.10 µg/kg for 48 h infusion + dose-adjusted heparin (773) c) dose-adjusted heparin + placebo tirofiban (797) All received aspirin.	Death, new MI, or refractory ischemia, or re-hospitalization for unstable angina within 7 days.
LAMIFIBAN				
PARAGON A (1995–1996)	2282	Patients with NSTE-ACS.	Randomly assigned to: a) lamifiban 750 µg bolus + 5.0 µg/min infusion for 3–5 days + heparin (373) b) lamifiban 750 µg bolus + 5.0 µg/min infusion for 3–5 days + heparin placebo (396) c) lamifiban 300 µg bolus + 1.0 µg/min infusion for 3–5 days + heparin (377) d) lamifiban 300 µg bolus + 1.0 µg/min infusion for 3–5 days + heparin placebo (378) e) lamifiban placebo + heparin (758) All patients received heparin.	Death or non-fatal (re)MI at 30 days.
PARAGON B (1998–1999)	5167	Patients ≥21 years old with NSTE-ACS.	Randomly assigned to: a) 500 µg bolus lamifiban + dose-adjusted lamifiban infusion ≤ 72 h or until discharge (2597) b) placebo (2570) All patients received aspirin and heparin.	Death, MI or severe, recurrent ischemia at 30 days.

MI, myocardial infarction; NSTE-ACS, non ST-segment elevation acute coronary syndromes; UA, unstable angina.

molecule GPI, tirofiban, was tested for its efficacy in the medical management of NSTE-ACS (Table 2). In the PRISM trial, UA patients benefited from a 32% relative reduction in the composite endpoint of death, refractory ischemia or MI at 48 hours when treated with tirofiban and aspirin compared to heparin and aspirin (5.6% placebo versus 3.8% tirofiban, p=0.01).[7] This relative benefit was homogenous across all age groups (Figure 1). However, these results were not sustained

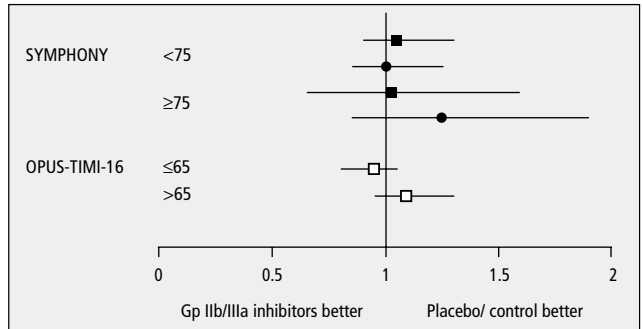


Figure 2. Age subgroup analysis of primary composite endpoints of trials evaluating oral GPIs in NSTE-ACS patients. (No age subgroup analysis reported for the Second SYMPHONY trial.)

SYMPHONY (90-day composite endpoint)
■ low-dose sibrafiban versus placebo;
● high-dose sibrafiban versus placebo;

OPUS-TIMI-16 (10-month composite endpoint)
□ orbofiban versus placebo.

when evaluated at seven and 30 days.

In the second trial, the PRISM-PLUS investigators compared the efficacy of tirofiban alone, tirofiban and heparin in combination, or heparin alone in patients diagnosed with UA or non-Q-wave MI.[8] After the first interim safety analysis, the tirofiban arm was terminated for safety reasons, as excess mortality at seven days was evident in this group. In the remaining patients, tirofiban administered in combination with aspirin and heparin appeared to reduce the incidence of death, MI, or refractory ischemia at seven days compared to those who had only received aspirin and heparin (17.9% heparin alone versus 12.9% tirofiban, p=0.004, 28% relative risk reduction). Longer-term (i.e., 30 days and six months) benefits were also realized. When the composite was analyzed according to subgroups of age, the investigators found that patients who were 65 years or older and were treated with tirofiban and heparin experienced fewer events (death, MI, refractory ischemia or re-hospitalization for unstable angina) at seven days than did those who were treated with aspirin and heparin (17.8% versus 23.5%, 24% relative risk reduction) (Figure 1). Similar benefits were also realized in those less than 65 years of age (8.5% versus 12.4%, 31% relative risk reduction).

Lamifiban

Of the four intravenously administered GPIs, only Lamifiban is commercially unavailable. Inconclusive results of the two large-scale efficacy trials, PARAGON-A and -B, may account for the delay in its approval (Table 2).[9,10] PARAGON-A tested the effects of two doses of lamifiban, with or without heparin and aspirin in UA

Table 3

Summary of Oral GPIs for the Secondary Prevention in Acute Coronary Syndrome Patients

Study (Enrolment period)	No. of Patients	Indication	Study Treatment Arms Endpoint	Primary Efficacy
ORBOFIBAN				
OPUS-TIMI 16 (1997–1998)	10288	Patients ≥18 years old with ACS.	Randomly assigned to: a) 50 mg orbofiban twice daily (3537) b) 50 mg orbofiban twice daily for 30 days +30 mg orbofiban twice daily (3330) c) placebo (3421) All patients received aspirin.	Death, MI, recurrent ischemia at rest leading to rehospitalization or urgent revascularization or stroke at 14 and 30 days, and every 3 months afterwards up until 1 year (6 month minimum).
SIBRAFIBAN				
SYMPHONY (1997–1998)	9233	Patients with ACS.	Randomly assigned to: a) low-dose (weight-adjusted) sibrafiban (3105) b) high-dose (weight-adjusted) sibrafiban (3039) c) aspirin (80 mg twice daily) control (3089)	Death, non-fatal (re)MI, or severe recurrent ischemia at 90 days.
Second SYMPHONY (1999)	6671	Patients with ACS.	Randomly assigned to: a) low-dose (weight-adjusted) sibrafiban + aspirin (80 mg twice daily) (2232) b) high-dose (weight-adjusted) sibrafiban (2174) c) aspirin (80 mg twice daily) control (2231)	Time to death, MI or recurrent ischemia.

ACS, acute coronary syndromes; MI, myocardial infarction.

and non-Q wave MI patients. The use of lamifiban did not significantly reduce ischemic events at 30 days; however, at six months, the low-dose lamifiban performed better than did aspirin and heparin (17.9% control, 13.7% low-dose (versus control p=0.027), 23.5% relative risk reduction, 16.4% high-dose (versus control p=0.450), 8% relative risk reduction). Compared to standard therapy, patients receiving low-dose lamifiban used in combination with heparin experienced the largest reductions in the composite endpoint at 30 days (12%, non-significant) and at 6 months (30%, p=0.025). However, this study was not adequately powered to draw clear conclusions from this data.

Based on retrospective pharmacokinetic analyses of PARAGON-A, it was revealed that a steady-state concentration of 18 to 24 ng/mL lamifiban lead to a significant reduction (40%) in adverse outcomes. A new trial, PARAGON-B, was designed to evaluate the effects of titrated dosing in order to achieve and maintain acceptable plasma levels of lamifiban. Despite these modifications to the dose regime, no significant effect on the 30-day or six-month composite endpoint of death, MI, or severe recurrent ischemia was observed (30-day: 12.8% placebo versus 11.8% lamifiban, p=0.329; six-month: 15% placebo versus 14% lamifiban, p=0.284). A lack of effect was evident in both younger (≤ 65 years) and older (>65 years) patients when

Table 4

Bleeding Complications, Intracranial Hemorrhage and Stroke at 30 days in Patients Enrolled in Trials of Intravenous GPIs in NSTE-ACS Patients

Trial	Study Drug (no. of patients)	Major bleeding (%)	Minor bleeding (%)	Intracranial hemorrhage (%)	Stroke (%)
GUSTO-IV ACS	Placebo (2598)	0.3	2.0	–	–
	Abciximab 24-h infusion (2590)	0.6	3.0*	–	–
	Abciximab 48-h infusion (2612)	1.0*	4.0*	–	–
PURSUIT	Placebo (4696)	9.1	7.4	0.1	0.8
	Eptifibatide (4679)	10.6*	12.9	0.1	0.7
PRISM	Heparin (1616)	0.4	1.9	0.1	–
	Tirofiban (1616)	0.4	2.0	0.1	–
PRISM-PLUS	Heparin (797)	0.8	–	0	–
	Tirofiban + heparin (773)	1.4	–	0	–
PARAGON-A	Placebo + heparin (758)	0.8	–	–	0.4
	Low-dose lamifiban + heparin (377)	0.5	–	–	1.1
	Low-dose lamifiban + no heparin (378)	0.8	–	–	1.1
	High-dose lamifiban +heparin (373)	2.4	–	–	0.5
	High-dose lamifiban + no heparin (396)	1.3	–	–	0.8
PARAGON-B	Placebo (2564)	0.9	11.5	0.1	0.6
	Lamifiban (2594)	1.3	14.0**	0.1	1.1†
Boersma et al.[11]	Placebo (13 105)	1.4	–	0.06	0.69
	Any GPI (incl. & excl. heparin) (18 297)	2.4	–	0.09	0.75
	Placebo (incl. heparin) (11 489)	1.4	–	0.05	0.67
	Any GPI (incl. heparin) (15 562)	2.5	–	0.08	0.73
	Placebo (incl. heparin) (2735)	1.8	–	0.06	0.69
	Any GPI (excl. heparin) (3171)	1.3	–	0.11	0.88
	Placebo (incl. heparin) (10 507)	1.0	–	0.07	0.71
	Eptifibatide or Tirofiban (incl. and excl. heparin) (13 095)	1.6	–	0.07	0.80

Bleeding complications defined by Thrombolysis In Myocardial Infarction (TIMI) study group. (21) *p<0.05 for comparison with placebo; **p=0.002 for comparison with placebo (intermediate bleeding (non-TIMI bleeding classification)). (incl., including; excl., excluding) †p<0.0006 for comparison to placebo.

the primary composite endpoint was evaluated at six months (Figure 2). Similarly to PARAGON-A, the lack of power in this trial should be taken into account when evaluating these results.

Overview of Intravenous GPIs in Elderly Patients

In general, the trials of intravenous GPIs in NSTE-ACS patients revealed significant reductions in adverse cardiac events; however, a problem among some of the trials was inadequate power for the detection of a large treatment effect. To provide a global picture of these agents, a meta-analysis of combined trial data was performed.[11] Overall, GPIs significantly reduced (8% relative) the composite endpoint of death or non-fatal MI at 30 days (11.8% control/placebo versus 10.8% GPIs, OR 0.91, 95% CI (0.85,0.98), p=0.015). Similarly, these benefits were observed in the reduction of the composite endpoint of death or MI in patients of all ages (p (for interaction) = 0.10) (Figure 1). However, reductions in death (3.7% control versus 3.4% GPIs, OR 0.91, 95%CI (0.81, 1.03), p=0.14) and in the composite of death, MI or revascularization (44.3% control versus 42.7% GPIs, OR 0.98 (0.93, 1.02), p=0.33) were not statistically

Table 5

Bleeding Complications, Intracranial Hemorrhage and Stroke at 30 days in Patients Enrolled in Trials of Oral GPIs

Trial	Study Drug (no. of patients)	Major bleeding (%)	Minor bleeding (%)	Intracranial haemorrhage (%)	Stroke (%)
OPUS-TIMI 16	Placebo (3421)	1.20	5.8	0.1	0.4
	Low-dose orbofiban (3537)	2.0**	11.0‡	0.1	0.5
	High-dose orbofiban (3330)	2.3†	11.9‡	0.1	0.7
SYMPHONY	Aspirin (3075)	3.9	12.6	–	0.81
	Low-dose sibrafiban (3083)	5.2§	17.7§	–	0.84
	High-dose sibrafiban (3014)	5.7§	24.6§	–	0.56
Second SYMPHONY	Aspirin (2229)	4.0	10.5	–	0.6
	Low-dose sibrafiban + aspirin (2235)	5.7§	19.9§	–	0.7
	High-dose sibrafiban (2173)	4.6	21.0§	–	0.7

Bleeding complications defined in OPUS-TIMI-16 and the first and Second SYMPHONY trials by Thrombolysis In Myocardial Infarction (TIMI) study group. (21) **p=0.007 for comparison to placebo; †p=0.0006 for comparison to placebo; ‡p<0.0001 for comparison to placebo. 90-day and 7-day safety endpoints evaluated in the first SYMPHONY and Second SYMPHONY trials, respectively. §p<0.05 for comparison to aspirin.

significant with GPI therapy.

Oral GPIs in Elderly Patients

Orbofiban & Sibrafiban

The prolonged use of oral GPIs may extend the benefits of intravenous agents and play a role in secondary prevention. However, the results of the trials on the first generation of oral GPIs, OPUSTIMI-16 (orbofiban) and the first and Second SYMPHONY (sibrafiban) trials did not show significant reductions in clinical events (Figure 2).[12-14] In the older population, those patients receiving the placebo or control experienced fewer events than did those who received the oral GPI. For instance, the administration of orbofiban resulted in an increase in the incidence of the composite endpoint at 10 months in patients over 65 years when compared to those treated with placebo (Figure 2).[12] In addition, in patients over the age of 75 years who were enrolled in the first SYMPHONY trial, those who received high-dose sibrafiban experienced more death, non-fatal (re)-MI or recurrent ischemia at 90 days than did those receiving aspirin (Figure 2).[13]

The next generation of oral agents may find success if the challenges of inter-patient variation in inhibition levels (due to differences in bioavailability or genetics), establishment of titrated doses and development of longer half-lives with higher binding affinities to increase the level of stable inhibition are resolved.[15,16]

Contraindications and Adverse Effects

Patients with active bleeding or a history of bleeding diathesis, gastrointestinal or genitourinary bleeding (within last six months), major surgery within the past three months, a history of stroke and a history of recent trauma are not recommended recipients of this therapy.[17] Other contraindications include uncontrolled hypertension (≥ 180 mmHg systole and/or ≥ 110mmHg diastole), severe anemia and thrombocytopenia.[17]

In general, the use of intravenous GPIs in NSTE-ACS patients was related to an increase in the incidence of major bleeding complications (Table 4).[11] GPI therapy was also a suspected contributor to excess intracranial hemorrhage and stroke; however, the incidence of intracranial hemorrhage (ICH) was rare in the trials of intravenous GPIs in the medical management of NSTE-ACS patients, and its use with or without heparin was not associated with an excess incidence of ICH (Table 4).[11] Similarly, the incidence of stroke was also not associated with this therapy.[11]

Thrombocytopenia is another possible, but infrequent, side effect of this therapy. The incidence of mild thrombocytopenia (< 100 000 platelets/mm^3) was 5% in those receiving 24-hour infusion of abciximab ($p<0.05$ versus placebo) and 7% (48-hour infusion; $p<0.05$ versus placebo) compared to 1% (placebo) in the GUSTO-IVACS trial.[4] When this safety endpoint was evaluated in the PURSUIT trial, eptifibatide was not associated with excess mild thrombocytopenia (6.8% eptifibatide versus 6.7% placebo). However, those receiving eptifibatide were more likely to suffer from severe thrombocytopenia (< 20 000 platelets/mm^3) than were those receiving placebo (0.2% versus <0.1%; relative risk 5.0, 95% CI(1.3, 32.4)).[6] The PRISM and PRISM-PLUS trials also noted that tirofiban was significantly associated with thrombocytopenia (defined as fewer than 90 000 platelets/mm^3), but the number of actual patients affected is quite low.[7,8] When compared to the placebo, the use of lamifiban was not associated with the incidence of thrombocytopenia.[10]

Safety concerns with the use of oral GPIs are minor and are mainly due to gastric bleeding (Table 5). Typically, bleeding was not severe and posed more of an annoyance to patients through bruising and bleeding of the gums, nose, hemorrhoids and menses.

CONCLUSION

Although the age- and sex-standardized mortality due to ischemic heart disease has declined over the past two decades, the incidence of acute coronary syndromes is expected to increase as the proportion of the Canadian population above age 65 increases from 13 to 21% over the next twenty years.[18,19] In addition to advanced age, the clinical profile of these patients often includes comorbidities such as diabetes mellitus and hypertension, which add to the overall complexity of medical decision-making. Despite this, older patients do derive similar relative, and hence, greater absolute benefit from GPI therapy in the medical management of NSTE-ACS compared to their younger counterparts.[20]

The majority of the trials only compare the primary composite clinical endpoint in patients younger than 65 years to those over the age of 65 years. Efforts should be made to report more in-depth, age-specific analyses, particularly on safety endpoints. Future investigations

should specifically address optimal strategies for this rapidly expanding proportion of the population.

REFERENCES

1. Ambrose JA. Plaque disruption and the acute coronary syndromes of unstable angina and myocardial infarction: if the substrate is similar, why is the clinical presentation different? J Am Coll Cardiol 1992; 19:1653-8.
2. Libby P. Coronary artery injury and the biology of atherosclerosis: inflammation, thrombosis, and stabilization. Am J Cardiol 2000; 86:3J-8J.
3. Coller BS. The role of platelets in arterial thrombosis and the rationale for blockade of platelet GPIIb/IIIa receptors as antithrombotic therapy. Eur Heart J 1995; 16 Suppl L:11-5.
4. Simoons ML. Effect of glycoprotein IIb/IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes without early coronary revascularisation: the GUSTO IV-ACS randomised trial. Lancet 2001; 357:1915-24.
5. Schulman SP, Goldschmidt-Clermont PJ, Topol EJ et al. Effects of Integrilin, a platelet glycoprotein IIb/IIIa receptor antagonist, in unstable angina. A randomized multicenter trial. Circulation 1996; 94:2083-9.
6. The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy. N Engl J Med 1998; 339:436-43.
7. Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. Acomparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. N Engl J Med 1998; 338:1498-1505.
8. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISMPLUS) Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. N Engl J Med 1998; 338:1488-97.
9. Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network. International, randomized, controlled trial of lamifiban (a platelet glycoprotein IIb/IIIa inhibitor), heparin, or both in unstable angina. Circulation 1998; 97:2386-95.
10. The PARAGON-B Investigators. Randomized, placebo-controlled trial of titrated intravenous lamifiban for acute coronary syndromes. Circulation 2002; 105:316-21.
11. Boersma E, Harrington RA, Moliterno DJ et al. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. Lancet 2002; 359:189-98.
12. Cannon CP, McCabe CH, Wilcox RG et al. Oral glycoprotein IIb/IIIa inhibition with orbofiban in patients with unstable coronary syndromes (OPUS-TIMI 16) trial. Circulation 2000; 102:149-56.
13. Sibrafiban versus Aspirin to Yield Maximum Protection from Ischemic Heart Events Postacute Coronary

Syndromes Investigators. Comparison of sibrafiban with aspirin for prevention of cardiovascular events after acute coronary syndromes: a randomised trial. Lancet 2000; 355:337-45.
14. The Second SYMPHONY Investigators. Randomized trial of aspirin, sibrafiban, or both for secondary prevention after acute coronary syndromes. Circulation 2001; 103:1727-33.
15. O'Connor FF, Shields DC, Fitzgerald Aet al. Genetic variation in glycoprotein IIb/IIIa (GPIIb/IIIa) as a determinant of the responses to an oral GPIIb/IIIa antagonist in patients with unstable coronary syndromes. Blood 2001; 98:3256-60.
16. Theroux P. Oral inhibitors of platelet membrane receptor glycoprotein IIb/IIIa in clinical cardiology: issues and opportunities. Am Heart J 1998; 135(5 Pt 2 Su):S107-12.
17. Bhatt DL, Topol EJ. Current role of platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes. JAMA 2000; 284:1549-58.
18. Heart and Stroke Foundation of Canada. Heart and Stroke Foundation of Canada: The changing face of heart disease in Canada. 1-107. 1999. Ottawa, Canada, Heart and Stroke Foundation of Canada.
19. Statistics Canada. Population projections for 2001, 2006, 2011, 2016, 2021 and 2026. http://www.statcan.ca/english/Pgdb/People/Population/demo23a.htm . Accessed 28-2-2002.
20. Cannon CP. Elderly patients with acute coronary syndromes: Higher risk and greater benefit from antithrombotic and interventional therapies. Am J Geriatric Cardiol 2000; 9:265-70.
21. Rao AK, Pratt C, Berke Aet 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.

Chapter Nine

Effects of platelet glycoprotein IIb/IIIa receptor blockers in non-STsegment elevation acute coronary syndromes: Benefit and harm in different age subgroups

Adrián V. Hernández, Cynthia M. Westerhout, Ewout W. Steyerberg, John P.A. Ioannidis, Héctor Bueno, Harvey White, Pierre Theroux, David J. Moliterno, Paul W. Armstrong, Robert M. Califf, Lars C. Wallentin, Maarten L. Simoons, Eric Boersma

OBJECTIVE To investigate whether beneficial and harmful effects of platelet glycoprotein (GP) IIb/IIIa receptor blockers in non-ST-elevation acute coronary syndromes (NSTE-ACS) depend on age.

METHODS A meta-analysis of 6 trials of GP IIb/IIIa receptor blockers in NSTE-ACS patients (PRISM, PRISM-PLUS, PARAGON-A, PURSUIT, PARAGON-B, GUSTO IV-ACS; n=31,402) was performed. We applied multivariable logistic regression analyses to evaluate the drug effects on death or non-fatal MI at 30 days, and on major bleeding, by age subgroups (<60, 60-69, 70-79, ≥80 years). We quantified the reduction of death or MI as number needed to treat (NNT), and the increase of major bleeding as number needed to harm (NNH).

RESULTS Subgroups had 11,155 (35%), 9,727 (31%), 8,468 (27%), and 2,049 (7%) patients, respectively. The relative benefit of GP IIb/IIIa receptor blockers did not differ significantly (p=0.5) across age subgroups (odds ratio [95% CI] for death or MI: 0.86 [0.74-0.99], 0.90 [0.80-1.02], 0.97 [0.86-1.10], 0.90 [0.73-1.16]; overall 0.91 [0.86-0.99]). Odds ratios for major bleeding were 1.9 (1.3- 2.8), 1.9 (1.4-2.7), 1.6 (1.2-2.1), and 2.5 (1.5-4.1). Overall NNT was 105, and overall NNH was 90. The oldest had larger absolute increases in major bleeding, but also had the largest absolute reductions of death or MI. Patients ≥80 years had half of the NNT and a third of the NNH in comparison with patients <60 years.

CONCLUSIONS In patients with NSTE-ACS, the relative reduction of death or non-fatal MI with GP IIb/IIIa receptor blockers was independent of patient age. Larger absolute outcome reductions were seen in the elderly, but with a higher risk of major bleeding. A close monitoring of these patients is warranted.

Platelet glycoprotein (GP) IIb/IIIa receptor blockers decrease the risk of death or non-fatal myocardial infarction (MI) at 30 days in patients with non-ST elevation acute coronary syndromes (NSTE-ACS) who are not routinely scheduled for early revascularization [1-4]. Age is an important risk factor for these patients, and if the relative benefits of effective interventions are the

same across age groups, physicians should treat the elderly even more aggressively than the younger, since the absolute benefit may be larger [5]. However, in clinical practice, the utilization of GP IIb/IIIa receptor blockers is lower among elderly patients [6].

Elderly patients may be under-treated because of several reasons: they were underrepresented or excluded from randomized clinical trials (RCTs), clinicians may believe that benefits in younger may not generalize to the elderly, or they may be worried about harmful effects in elderly patients [5].
Researchers have argued that the benefit of GP IIb/IIIa receptor blockers is greater in younger patients [7], similar in old and younger patients [8], or greater in older patients given their higher baseline risk [5, 9].

Yet, it is difficult to determine how the efficacy of GP IIb/IIIa receptor blockers varies among
age subgroups because most trials are not large enough to provide a reliable answer. Individual ACS
trials have been inconclusive or even conflicting regarding the presence or absence of relative differences in drug effects across ages [10-15]. Usually, the patient population was only split in two age groups (e.g. <65 years, ≥65 years) [11, 13-15], and different primary endpoints were considered. An
evaluation of the drug effects across age groups in a meta-analysis using individual data can better define its relative and absolute efficacies in older vs. younger patients.

One more issue is relevant in the interpretation of the effects of GP IIb/IIIa receptor blockers by age groups. The incorporation of harmful major bleeding rates in the evaluation of effects should be considered to further understand the net drug effectiveness across age strata [5, 9, 16].

We investigated whether the relative effects of GP IIb/IIIa receptor blockers were consistent across age subgroups in non-ST-segment elevation ACS patients. Further, we evaluated whether the absolute benefits and harms differed across age subgroups.

METHODS

Trial selection

A meta-analysis of individual patient data was performed, including trials reported since 1990 with the following characteristics: randomization of patients with NSTE-ACS, comparison of a GP IIb/IIIa receptor blocker with placebo or control therapy, no-recommendation for early (<48h) coronary revascularization during study-drug infusion, and enrolment of at least 1000 patients. Six trials met the inclusion criteria -PRISM, PRISM-PLUS, PARAGON-A, PURSUIT, PARAGON-B, and GUSTO IVACS- [10-15] with a total of 31,402 patients. Details of the trial designs are available elsewhere [3].

Patient baseline characteristics

An electronic database consisting of data from individual patients in all eligible trials was available [3]. These data were checked for completeness, for internal

Table 1: Definitions of primary efficacy and harm endpoints across trials

	PRISM	PRISM-PLUS	PARAGON-A	PURSUIT	PARAGON-B	GUSTO ACS-IV
Primary efficacy end point	Death, MI or refractory ischemia at 48 hours	Death, MI or refractory ischemia at 7 days	Death of MI at 30 days	Death or MI at 30 days	Death, MI or severe, recurrent ischemia at 30 days	Death or MI at 30 days
Required level of CK or CK-MB elevation in MI definition	2xULN	2xULN; in relation to PCI: 3xULN	2xULN	1xULN; in relation to PCI: 3xULN; in relation to CABG: 5xULN	2xULN; in relation to PCI: 3xULN; in relation to CABG: 5xULN	3xULN
Primary harm end point: major bleeding	Intracraneal hemorrhage; bleeding leading to decrease in hemoglobin concentration ≥50 g/L; or cardiac tamponade	Intracraneal hemorrhage; bleeding leading to decrease in hemoglobin concentration ≥40 g/L; bleeding requiring transfusion ≥2 units blood; or bleeding requiring surgery	Intracraneal hemorrhage; bleeding leading to hemodynamic compromise requiring intervention	Intracraneal hemorrhage; bleeding leading to hemodynamic compromise requiring intervention	Intracraneal hemorrhage; bleeding leading to hemodynamic compromise requiring intervention	Intracraneal hemorrhage; bleeding leading to decrease in hemoglobin concentration ≥ 50 g/L

MI: myocardial infarction; CK: creatine kinase; CK-MB: creatine kinase fraction MB; ULN: Upper limit of normal; PCI: Percutaneous coronary intervention; CABG: Coronary-artery bypass graft

consistency of patients' records, and for consistency with the published reports. For this analysis, baseline characteristics regarded as important predictors of the outcome for which information was almost complete (i.e. less than 1% missing) were age, gender, diabetes, smoking, previous myocardial infarction [MI], previous heart failure [HF], previous coronary artery bypass surgery (CABG), previous percutaneous coronary intervention (PCI), and ST-segment depression. Other important predictors had more than 20% of missing data: blood pressure and heart rate were not recorded in the GUSTO IV-ACS trial (n=7800, 25%); and baseline creatine kinase MB (CK-MB) was missing in 7469 patients (24%) across different trials. Blood pressure, heart rate and CK-MB were used in addition to the other predictors in secondary analyses that yielded largely similar results.

Endpoints

For this analysis, the primary efficacy endpoint was defined *a priori* as the composite of death of any cause or non-fatal MI at 30 days. MI was part of the composite outcome of all trials. The MI definitions had subtle differences across trials regarding the CK-MB threshold [3] (Table 1). However, all trials had pre-specified definitions of

Table 2. Patient characteristics by age subgroups.

	<60 years (n=11,155)		60-69 years (n=9,727)		70-79 years (n=8,468)		≥80 years (n=2,049)	
	N	%	N	%	N	%	N	%
Gender								
Male	8275	74	6274	65	4841	57	997	49
Diabetes								
Yes	1771	16	2360	24	2269	27	461	23
Smoking								
Never	3931	35	3439	36	3269	39	861	42
Former	3144	28	3537	37	3133	37	621	31
Current	4036	36	2709	28	2015	24	552	27
Previous MI								
Yes	3164	28	3445	36	3162	37	877	43
Previous HF								
Yes	578	5	962	10	1191	14	437	21
Previous CABG								
Yes	1088	10	1305	13	1194	14	185	9
Previous PCI								
Yes	1454	13	1251	13	956	11	162	8
ST depression								
Yes	5096	46	5475	57	5441	65	1403	69
Trial								
PRISM	1274	11	1005	10	781	9	172	8
PRISMPLUS	693	6	603	6	495	6	124	6
PARAGON-A	737	7	728	8	631	8	183	9
PURSUIT	4082	37	3553	37	2763	33	550	27
PARAGON-B	1976	18	1513	16	1374	16	362	18
GUSTO IV	2393	21	2325	24	2424	29	658	32

MI denotes myocardial infarction, HF: heart failure, CABG: coronary artery bypass graft, PCI: percutaneous coronary intervention, y: years. Differences among age subgroups were highly significant ($p<0.001$).

MI [17, 18]. Secondary endpoints were: death; non-fatal MI; coronary artery bypass graft (CABG); percutaneous coronary intervention (PCI); and CABG or PCI. The primary harm endpoint was major bleeding within 30 days. Individual trial definitions of major bleeding had also at most subtle differences, and trial-specific definitions were retained [3]. We should acknowledge that death or non-fatal MI and major bleeding do not have the same utility, and therefore are not comparable events. A few patients with major bleeding die or have an MI within 30 days, and not all of the remaining patients have long-term negative outcomes. Determining the relative weights of these events is largely subjective. A recent review identified that the weight of a major bleeding related to a drug in the context of an acute coronary syndrome was 0.87, in comparison with the weight of death, which was equal to zero [19].

Efficacy analysis by age

We divided the patient data into four subgroups according to age: <60, 60-69, 70-79, and ≥80 years old. The decision to group patients in these intervals was made a priori, and was based on decade intervals of common clinical use. The choice

Table 3. Treatment effect on various endpoints at 30 days according to age subgroups.

	<60y (n=11,155)			60-69y (n=9,727)			70-79y (n=8,468)			≥80y (n=2,049)		
	Events	%	OR* (95% CI)	Events	%	OR (95% CI)	Events	%	OR (95% CI)	Events	%	OR (95% CI)
Death†												
GP IIb/IIIa	70	1.1	0.86	165	2.9	0.98	281	5.6	0.91	115	9.5	0.90
Placebo/Control	58	1.2	(0.61-1.23)	124	3.0	(0.77-1.24)	215	6.2	(0.75-1.09)	88	10.5	(0.67-1.21)
Nonfatal MI‡												
GP IIb/IIIa	372	5.7	0.83	428	7.6	0.85	437	8.8	1.02	112	9.3	0.91
Placebo/Control	316	6.8	(0.72-0.97)	365	8.8	(0.74-0.99)	299	8.6	(0.87-1.19)	85	10.1	(0.68-1.23)
Death or MI												
GP IIb/IIIa	442	6.8	0.86	593	10.6	0.90	718	14.4	0.97	227	18.8	0.90
Placebo/Control	374	8.0	(0.74-0.99)	489	11.9	(0.80-1.02)	514	14.8	(0.86-1.10)	173	20.5	(0.73-1.16)
CABG												
GP IIb/IIIa	828	12.7	1.00	931	16.6	0.92	860	17.2	0.99	102	8.5	1.07
Placebo/Control	590	12.7	(0.90-1.13)	732	17.7	(0.83-1.03)	603	17.3	(0.88-1.11)	67	8.0	(0.77-1.47)
PCI												
GP IIb/IIIa	1839	28.3	0.92	1369	24.4	1.02	894	17.9	0.89	171	14.2	0.90
Placebo/Control	1404	30.1	(0.84-0.99)	991	24.0	(0.93-1.12)	684	19.7	(0.80-1.00)	131	15.6	(0.70-1.15)
CABG or PCI												
GP IIb/IIIa	2618	40.3	0.93	2264	40.4	0.97	1721	34.5	0.93	268	22.2	0.93
Placebo/Control	1960	42.1	(0.86-1.00)	1699	40.8	(0.89-1.05)	1258	36.2	(0.85-1.02)	197	23.4	(0.76-1.15)
Major bleeding												
GP IIb/IIIa	90	1.5	1.90	118	2.3	1.94	174	3.8	1.58	63	5.7	2.46
Placebo/Control	35	0.8	(1.28-2.81)	46	1.1	(1.38-2.74)	80	2.3	(1.21-2.07)	19	2.3	(1.46-4.14)

* Odds ratio of treatment effect between GP IIb/IIIa and Placebo/Control, GP IIb/IIIa denotes platelet glycoprotein IIb/IIIa receptor blockers; †Death within 30 days; ‡ Non-fatal myocardial infarction in patients who survived at least 30 days. Number of patients per age group: <60 y: GP 6496, Placebo/control 4659; 60-69 y: GP 5602, Placebo/control 4125; 70-79 y: GP 4991, Placebo/control 3477; >80 y: GP: 1207, Placebo/control: 842.

of other cut-off points (e.g. quartiles) yielded similar results (not shown). Relative differences between GP IIb/IIIa receptor blockers and placebo/control on the primary endpoint by age subgroups were assessed, within each trial and across all trials. Logistic regression models were used, and odds ratios (OR) and corresponding 95% confidence intervals (95% CI) were calculated. To evaluate GP IIb/IIIa receptor blocker effect modification by age in each individual trial and in all trials, interaction tests were used [20]. These tests also evaluated heterogeneity of effects across trials. The effects of GP IIb/IIIa receptor blockers and the interactions were adjusted for the previously described predictors, for trial, and for potential differences in age-related trends between trials. These effects were combined using random effects calculations [21]. Heterogeneity of interactions across trials was evaluated with the random effects inverse variance model (with trial being the random effect) [22].

Benefit and harm of GP IIb/IIIa receptor blockers by age subgroups

We performed analyses that incorporated the relation among the baseline risk (eBR, proportion of patients in the placebo/control group with the primary efficacy endpoint), the efficacy Odds Ratio (eOR), and the respective number needed to treat [NNT]. The calculation of NNT was done using eBR and eOR, with the formula: [1-eBR(1-eOR)]/ [eBR(1-eBR)(1-eOR)] [22]. The NNT is the number of patients who need to be treated in order to prevent one additional death or non-fatal MI. It is the inverse of the absolute risk reduction (ARR). Further, we looked at the relation among the baseline proportion of the primary harm endpoint in the placebo/control group (hBR), the harm Odds Ratio (hOR), and the respective number needed to harm [NNH]. The NNH was calculated using hBR and hOR,

Table 4. Treatment effects on death or MI at 30 days according to age subgroups, by trial and overall.

	PRISM N=3,232	PRISMPLUS N=1,915	PARAGON-A N=2,282	PURSUIT N=10,948	PARAGON-B N=5,225	GUSTO IV-ACS N=7,800	TOTAL* N=31,402
Age <60 years							
OR (95% CI)	1.13 (0.66-1.96)	0.98 (0.54-1.78)	1.65 (0.83-3.30)	0.72 (0.59-0.88)	0.90 (0.64-1.27)	1.01 (0.65-1.55)	0.86 (0.74-0.99)
Age 60-69 years							
OR (95% CI)	0.86 (0.53-1.38)	0.58 (0.35-0.96)	0.87 (0.55-1.39)	0.93 (0.77-1.20)	0.81 (0.59-1.12)	1.19 (0.85-1.67)	0.90 (0.80-1.02)
Age 70-79 years							
OR (95% CI)	0.63 (0.36-1.09)	1.02 (0.61-1.70)	0.83 (0.53-1.31)	0.91 (0.76-1.11)	1.11 (0.82-1.50)	1.15 (0.88-1.50)	0.97 (0.86-1.10)
Age ≥80 years							
OR (95% CI)	0.45 (0.19-1.07)	0.94 (0.39-2.27)	0.82 (0.37-1.81)	1.27 (0.87-1.86)	0.84 (0.48-1.47)	0.80 (0.52-1.22)	0.90 (0.73-1.16)
All subgroups, adjusted for predictors†	0.80 (0.60-1.06)	0.83 (0.62-1.11)	0.95 (0.72-1.25)	0.88 (0.79-0.98)	0.92 (0.78-1.10)	1.07 (0.90-1.27)	0.91 (0.86-0.99)
Age by GP IIb/IIIa Interaction (p)‡	0.01	0.77	0.15	0.03	0.92	0.52	0.15

* Odds ratios of each age subgroup adjusted for trial.
† Predictors included: age, gender, diabetes, smoking, previous MI, previous heart failure, previous CABG, previous PTCA, ST depression.
‡ Odds ratios adjusted for predictors, and age trend. The interactions age by GP IIb/IIIa are significantly different among trials. p: p-value.

with the formula: [hBR(hOR-1)+1]/[hBR(1-hBR)(hOR-1)] [23]. The NNH is the number of patients who need to be treated in order to cause one major bleeding. It is the inverse of the absolute risk increase (ARI). The NNT and NNH calculations were done overall and by age subgroups.

Role of the funding source

The trials included in this analysis were sponsored by several pharmaceutical companies, which are mentioned in the main trial reports [10-15], and in the acknowledgements. This study was designed, conducted, and interpreted independently of the sponsors. These had the right to review the manuscript, but not censor the findings. No separate industrial grant was obtained for this investigation.

Age subgroups and predictors

Overall, 11,155 (35%) patients were < 60, 9,727 (31%) were 60-69, 8,468 (27%) were 70-79, and 2,049 (7%) were ≥ 80 years-old. Baseline characteristics across age subgroups are shown in Table 2.

The proportion of women and of patients with a history of diabetes, MI or HF, and ST depression increased with age. Further, patients ≥80 years had lower proportions of previous revascularisation procedures than younger patients. The proportion of patients older than 70 years ranged between 30% in the PURSUIT and PRISM trials and 40% in the GUSTO IV-ACS trial.

Endpoints at 30 days by age subgroups

The overall adjusted relative reduction in the odds of death or MI at 30 days was 9% (OR 0.91; 95% CI [0.85-0.99]). There was no difference in the relative benefit of GP IIb/IIIa receptor blockers across age subgroups (p for interaction = 0.5) and this was true also for secondary efficacy endpoints (Table

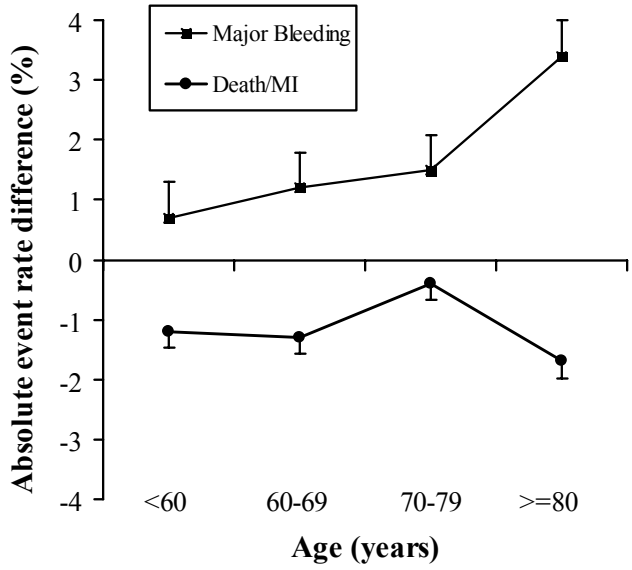


Figure 1. Absolute event rate differences between treatment arms (GP IIb/IIIa vs. placebo/control) by age subgroups in beneficial (death or myocardial infarction) and harmful (major bleeding) endpoints. GP IIb/IIIa denotes platelet glycoprotein IIb/IIIa receptor blockers.

3). Interestingly, the ratio of non-fatal MI over death decreased with increasing age. The overall adjusted relative increase in the odds of major bleeding was 83% (OR 1.83 [1.5-2.2]). This was especially high for patients ≥80 years (OR 2.5 [1.5-4.1]), but there were no significant differences across ages (p for interaction=0.3) (Table 3).

Benefit of GP IIb/IIIa receptor blockers per trial by age subgroups

With regard to the incidence of death or non-fatal MI, two trials showed significantly different relative effects across age subgroups, but in opposite directions (Table 4). The PRISM trial patients had a clear gradient of GP IIb/IIIa receptor blocker effect across ages: older patients had larger odds reductions than younger ones (p for interaction=0.01). Conversely, younger PURSUIT patients had larger odds reductions than the older ones (p for interaction=0.03). The interactions between GP IIb/IIIa receptor blockers and age subgroup were heterogeneous across trials (p=0.002).

Benefit and harm of GP IIb/IIIa receptor blocker across age subgroups The absolute risk of death or MI at 30 days correlated with age, varying from 8% in the youngest (<60 years) to 21% in the oldest group (≥80 years). Major bleeding at 30 days also correlated with age, from 0.8% in the youngest to 2.3% in the oldest. For the overall relative reduction in the odds of death or MI of 9%, the NNT was 105. For the overall relative increase in the odds of major bleeding of 83%, the NNH was 90.

The oldest patients had the largest absolute reductions of death or MI, but also had larger absolute increases in major bleeding. Patients younger than 70 years had higher NNTs and NNHs (149 and 163 for those younger than 60 years, and 105 and 110 for those between 60 and 69 years) than those older than 70 years (87 and 55 for those between 70 and 79 years, and 67 and 56 for those older than 80 years). Figure 1 shows the absolute event rate difference between GP IIb/IIIa receptor blocker and placebo/control arms across age subgroups. We noted a rather larger harm in patients ≥70 years and a somewhat variable benefit across all age subgroups.

DISCUSSION

In patients with ACS without ST elevation, the relative reduction in the odds of death or MI at 30 days with GP IIb/IIIa receptor blockers was largely independent of age. The oldest patients had about 3-fold the baseline risk of the youngest ones, not only for death or MI, but also for major bleeding. In the oldest patients, the use of GP IIb/IIIa receptor blockers yielded larger absolute reductions of death/MI, but also larger absolute increases in major bleeding rates in comparison with the youngest patients.

This meta-analysis had more statistical power than individual trials to explore how the GP IIb/IIIa receptor blocker effects vary by age [7-9, 24]. Individual trials did not report these effects in detail across similar age subgroups [10, 11, 13-15], and they analyzed different endpoints. Previous analyses of the age effects in single trials have yielded inconclusive results [25]. Only the PURSUIT and GUSTO IV-ACS reported the same primary endpoint as we used in this paper. Also, these analyses did not adjust for important predictors of the primary endpoint. We found that the PRISM and the PURSUIT trials showed significant differential relative effects of GP IIb/IIIa receptor blockers across ages, but differences were in the opposite direction. We do not fully understand this phenomenon. We speculate that it could be related to the doses used as well as the duration of the study drug infusion. This might have resulted in different levels of platelet inhibition in the PRISM trial (where the dose was later shown to produce suboptimal platelet inhibition in young patients) as compared to the PURSUIT trial (where the dose was not adjusted for older age or modest renal impairment), which might have had different consequences in younger and older patients.

The effects of other antithrombotics have been evaluated in elderly patients with unstable angina or NSTE-ACS [9]. The low molecular weight heparin enoxaparin, compared with unfractionated heparin, appeared to have greater relative and absolute benefit in patients aged 65 years and older, as compared with younger patients. When comparing clopidogrel plus aspirin to aspirin alone, there was a consistent 20% relative reduction in cardiovascular death, myocardial infarction, or stroke in both elderly and younger patients. For GP IIb/IIIa

receptor blockers, we found an equivalent relative benefit across age subgroups, which translated into a greater absolute benefit in older in comparison with younger patients.

In order to describe the relative gain in primary efficacy end points by age subgroups, we defined a ratio of reduction of non-fatal MIs to reduction of deaths. For instance, a ratio higher than 1 shows a larger benefit in reduction of non-fatal MIs in comparison to reduction of deaths. Given that the ratio of non-fatal MI to death decreased with increased age, the use of GP IIb/IIIa receptor blockers in the oldest likely aborted more deaths than non-fatal MIs.

Most trials, meta-analyses, and systematic reviews have neglected the contribution of major bleeding rates in the evaluation of the net GP IIb/IIIa receptor blocker effectiveness across age subgroups in NSTE-ACS patients [1-4, 10-15, 26-31]. Elderly patients have higher absolute risks of major bleeding [6, 32]. Therefore, the interpretation of the overall GP IIb/IIIa receptor blocker efficacy needs to incorporate this harm. Although there was a trend for increasing bleeding risk with increasing age, this was nowhere close to being statistically significant, and it should be interpreted cautiously given the small number of patients in the highest age category.
An appropriate dosing of GP IIb/IIIa receptor blockers is a requisite to obtain a higher benefit and a lower harm in elderly NSTE-ACS patients. The CRUSADE registry demonstrated that GP IIb/IIIa receptor blockers were underutilized and mis-dosed in elderly patients, who are at higher risk for adverse cardiac events [33]. An essential factor that increases the risk of major bleeding in elderly patients is low renal function, which is associated with higher serum levels of GP IIb/IIIa receptor blockers. Doses used in early trials were more aggressive than currently recommended doses, which are adjusted for renal dysfunction. Thus, elderly NSTE-ACS patients should receive adequate doses of GP IIb/IIIa receptor blockers to obtain the expected clinical benefit, and these doses should be adjusted for their level of renal function to avoid major bleeding events.

A recent decision analysis evaluated the efficacy of an unspecified potential drug on survival in patients with MI and unstable angina [5], and included serious adverse events (fatal complications) as an element of the evaluation of benefit-risk balance by age-related baseline risks. The authors used a registry database, and a hard primary endpoint (mortality at 1 year). The estimate of effectiveness was larger than in our randomized data (relative risk reduction 25%, absolute risk reduction 2%), and the registry population was more heterogeneous in risk (baseline risk of 2.3% in the youngest vs.27% in the oldest). They defined a threshold beyond which the treatment benefit would be outclassed by the treatment harm, and found that the fatal complication rate would have to be sevenfold greater in the oldest compared with the youngest age group to outweigh

the survival benefits associated with treatment. These results need to be interpreted cautiously given that most major events in these patients do not lead to death. Moreover, retrospective observational data may sometimes inflate estimates of treatment efficacy [34].

Some limitations should be acknowledged. First, even with over 30,000 randomised patients, subtle age interactions could have been missed, especially for rare events such as death. We did not see any age interactions for death based on the available data (not reported) and the clinical significance of subtle interactions is debatable. Second, the total number of patients in the ≥80 age subgroup (n=2049) was small, and less than 25% of each of the other three groups (n>8400). Third, a substantial amount of missing values for a few important predictors (blood pressure, heart rate, CK-MB) limited some possibilities of adjusted analysis. However, the results with imputed data yielded similar conclusions (not shown). Fourth, additional research into the appropriate weighting of events is needed, that can allow a more direct comparison between benefits and harms.

A series of nuances should be considered in interpreting these results. The trials included broad populations of patients with ACS. Through analysis of subgroups, it seems evident that higher risk patients, such as those with positive troponins, diabetes, and perhaps ST segment depression, achieve the greatest benefit. Further, it is likely that patients treated with the aggressive revascularisation strategy achieve more benefit than those treated with the conservative strategy. The trials themselves were heterogeneous, as GUSTO IV-ACS showed no benefit and perhaps a detriment of abciximab, and PURSUIT used a very liberal definition of myocardial infarction that minimized the differences between eptifibatide and placebo. Finally, the category of major bleeding overestimates risk relative to the risk of blood transfusion, which is a more direct measure of risk and occurs less frequently (Mahaffey KW et al., Circulation, in press). The EARLY ACS trial is enrolling patients without age limits, it is testing whether the benefit of antithrombotic drugs is similar between elderly and young patients, and it is also addressing each of the above issues [35]. Allowing for these caveats, our analysis provides estimates for NNTs and NNHs by age subgroups that may be used in clinical decision making for the use of GP IIb/IIIa receptor blockers in NSTE-ACS patients.

In conclusion, the relative risk reduction of death or MI with GP IIb/IIIa receptor blocker is independent of age in patients with non-ST-elevation acute coronary syndromes. Larger absolute reductions of death or MI were observed in the oldest in comparison with the youngest patients, as well as larger absolute increases in major bleeding rates. Attention should be given to optimizing the benefit to elderly patients without increasing bleeding, by ensuring that doses

adjusted for renal function are given. Moreover, elderly patients should be monitored more intensively.

ACKNOWLEDGEMENTS

The data included in this subgroup meta-analysis were provided by Merck Inc, White House Station, NJ, USA (sponsor of the PRISM and PRISM-PLUS trials); F. Hoffman-La Roche, Basel, Switzerland (sponsor of PARAGON-A and PARAGON-B trials); COR Therapeutics Inc, San Francisco, CA, USA, and Schering-Plough Inc, Kenilworth, NJ, USA (sponsors of the PURSUIT trial); and Centocor Inc, Malvern, PA, USA (sponsor of the GUSTO IV-ACS trial).

CONFLICT OF INTEREST STATEMENT

D J Moliterno is a consultant for Merck, Centocor, and Eli Lilly, and has received honoraria from the same, as well as from Roche. H White is a consultant for and has received honoraria from Merck. P Théroux was principal investigator and chairman of the Steering Committee for the PRISM-PLUS trial. P W Armstrong has received research grants and honoraria from Eli Lilly and Schering-Plough. R M Califf has worked with Centocor, Lilly, COR, Schering-Plough, and Merck. M L Simoons is a consultant for Merck, Centocor, and Lilly, and has provided paid expert testimony to Schering-Plough.

FUNDING

Dr. Adrián V. Hernández received support from the Netherlands Organization for Scientific Research (ZON/MW 908-02-117).

REFERENCES

1. Lincoff AM, Califf RM, Topol EJ. Platelet glycoprotein IIb/IIIa receptor blockade in coronary artery disease. J Am Coll Cardiol 2000;35:1103-15.

2. Bhatt DL, Topol EJ. Current role of platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes. JAMA 2000;284:1549-58.

3. Boersma E, Harrington RA, Moliterno DJ, et al. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. Lancet 2002;359:189-98.

4. Schulman SP. Antiplatelet therapy in non-ST-segment elevation acute coronary syndromes. JAMA 2004;292:1875-82.

5. Alter DA, Manuel DG, Gunraj N, Anderson G, Naylor CD, Laupacis A. Age, risk-benefit trade-offs, and the projected effects of evidence-based therapies. Am J Med 2004;116:540-5.

6. Avezum A, Makdisse M, Spencer F, et al. Impact of age on management and outcome of acute coronary syndrome: Observations from the Global Registry of Acute Coronary Events (GRACE). Am Heart J 2005;149:67-73.

7. Thompson SG, Higgins JP. Can meta-analysis help target interventions at individuals most likely to benefit? Lancet 2005;365:341-6.

8. Mak KH, Effron MB, Moliterno DJ. Platelet glycoprotein IIb/IIIa receptor antagonists and their use in elderly patients. Drugs Aging 2000;16:179-87.

9. Cannon CP. Elderly patients with

acute coronary syndromes: higher risk and greater benefit from antiplatelet therapy and/or interventional therapies. Am J Geriatr Cardiol 2003;12:259-62.
10. The PRISM Study Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. N Engl J Med 1998;338:1498-505.
11. The PRISM-PLUS Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms. N Engl J Med 1998;338:1488-97.
12. The PARAGON Investigators. International, randomized, controlled trial of lamifiban (a platelet glycoprotein IIb/IIIa inhibitor), heparin, or both in unstable angina. Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network. Circulation 1998;97:2386-95.
13. The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. N Engl J Med 1998;339:436-43.
14. The GUSTO IV-ACS Investigators. Effect of glycoprotein IIb/IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes without early coronary revascularisation: the GUSTO IV-ACS randomised trial. Lancet 2001;357:1915-24.
15. The PARAGON-B Investigators. Randomized, placebo-controlled trial of titrated intravenous lamifiban for acute coronary syndromes. Circulation 2002;105:316-21.
16. Patrono C, Coller B, FitzGerald GA, Hirsh J, Roth G. Platelet-active drugs: The relationships among dose, effectiveness, and side effects. The seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest 2004;126:234S-264S.
17. Early Breast Cancer Trialists'Collaborative Group. Treatment of early breast cancer, vol 1: worldwide evidence 1985-1990. Oxford: Oxford University Press, 1990:12-8.
18. Chan A-W, Hróbjartsson A, Haahr MT, Gøtzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials. Comparison of protocols to published articles. JAMA 2004;291:2457-65.
19. Tengs TO, Wallace A. One thousand health-related quality-of-life estimates. Med Care 2000;38:583-637.
20. Assmann SF, Pocock SJ, Enos LE, Kasten LE. Subgroup analysis and other (mis)uses of baseline data in clinical trials. Lancet 2000;355:1064-9.
21. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.
22. Clarke M, Oxman A, eds. Cochrane reviewers' handbook, version 4.2.0 (updated March 2003). In: The Cochrane Library, issue 4. Chichester: John Wiley & Sons, Ltd, 2003.
23. McQuay HJ, Moore RA. Using numerical results for systematic reviews in clinical practice. Ann Intern Med 1997;126:712-20.

24. Brookes ST, Whitley E, Egger M, Davey Smith G, Mulheran PA, Peters TJ. Subgroup analyses in randomized trials: risks of subgroup-specific analyses; power and sample size for the interaction test. J Clin Epidemiol 2004;57:229-36.
25. Hasdai D, Holmes DR Jr, Criger DA, Topol EJ, Califf RM, Harrington RA, for the PURSUIT trial investigators. Age and outcome after acute coronary syndromes without persistent ST-segment elevation. Am Heart J 2000;139:858-66.
26. Alexander JH, Harrington RA. Recent antiplatelet drug trials in acute coronary syndromes. Clinical interpretation of PRISM, PRISM-PLUS, PARAGON A and PURSUIT. Drugs 1998;56:965-76.
27. Vorchheimer DA, Badimon JJ, Fuster V. Platelet glycoprotein IIb/IIIa receptor antagonists in cardiovascular disease. JAMA 1999;281:1407-14.
28. Casserly IP, Topol EJ. Glycoprotein IIb/IIIa antagonists – from the bench to practice. Cell Moll Life Sci 2002;59:478-500.
29. De Caterina R, Di Gioacchino L. Glycoprotein IIb-IIIa inhibitors in unstable coronary syndromes and percutaneous interventions – a conservative approach. Rev Port Cardiol 2003;22:995-1002.
30. Januzzi JL, Cannon CP, Theroux P, Boden WE. Optimizing glycoprotein IIb/IIIa receptor antagonist use for the non-ST-segment elevation acute coronary syndromes: risk stratification and therapeutic intervention. Am Heart J 2003;146:764-74.
31. Atwater BD, Roe MT, Mahaffey KW. Platelet glycoprotein IIb/IIIa receptor antagonists in non-ST segment elevation acute coronary syndromes. A review and guide to patient selection. Drugs 2005;65:313-24.
32. Ali Raza J, Movahed A. Use of cardiovascular medications in the elderly. Int J Cardiol 2002;85:203-15.
33. Hoekstra JW, Roe MT, Peterson ED, et al. Early glycoprotein IIb/IIIa inhibitor use for non-STsegment elevation acute coronary syndrome: patient selection and associated treatment patterns. Acad Emerg Med 2005;12:431-8.
34. Ioannidis JPA, Haidich A-B, Papa M, et al. Comparison of evidence of treatment effects in randomized and nonrandomized studies. JAMA 2001;286:821-30.
35. Giugliano RP, Newby LK, Harrington RA, et al. The Early Glycoprotein IIb/IIIa Inhibition in Non- ST-Segment Elevation Acute Coronary Syndrome (EARLY ACS) trial: A randomized placebocontrolled trial evaluating the clinical benefits of early front-loaded eptifibatide in the treatment of patients with non-ST-segment elevation acute coronary syndrome—Study design and rationale. Am Heart J 2005;149:994-1002.

Chapter Ten

Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients

Eric Boersma* and The Primary Coronary Angioplasty vs. Thrombolysis (PCAT)-2 Trialists' Collaborative Group

AIMS Although outcomes after acute myocardial infarction (AMI) seemed to be superior with primary percutaneous coronary intervention (PPCI) relative to fibrinolysis (FL), the extent to which treatment delay modulates this treatment effect is unclear.

METHODS AND RESULTS Twenty-five randomized trials (n = 7743) testing the efficacy of PPCI vs. FL were identified in journal articles and abstract listings published between 1990 and 2002. Of these, individual patient data from 22 trials (n = 6763) were pooled, and multi-level logistic regression assessed the relationship among treatment, treatment delay, and 30-day mortality. Treatment delay was divided into 'presentation delay' [symptom onset to randomization; FL: median 143 (IQR: 91–225) min; PPCI: 140 (91–220) min] and hospital-specific 'PCI-related delay' [median time from randomization to PPCI minus median time to FL per hospital; median 55 (IQR: 37–74) min]. PPCI was associated with a significant 37% reduction in 30-day mortality [adjusted OR, 0.63; 95% CI (0.42–0.84)]. Although, there was no heterogeneity in the treatment effect by presentation delay (pBreslow-Day = 0.88), the absolute mortality reduction by PPCI widened over time (1.3% 0–1 h to 4.2% >6 h after symptom onset). When the PCI-related delay was <35 min, the relative (67 vs. 28% pBreslow-Day = 0.004) and absolute (5.4 vs. 2.0%) mortality reduction was significantly higher than those with longer delays.

CONCLUSION PPCI was associated with significantly lower 30-day mortality relative to FL, regardless of treatment delay. Although logistic and economic constraints challenge the feasibility of 'PPCI-for-all', the benefit of timely treatment underscores the importance of a comprehensive, unified approach to delivery of cardiac care in all AMI patients.

'Time is myocardium', a familiar adage in the cardiovascular community, is central to the controversy of the best modality of reperfusion after acute myocardial infarction (AMI).[1,2] Although numerous pharmaceutical and mechanical treatment strategies have helped to further the quest for an absolute 1% mortality reduction after AMI, shortening the time to treatment may make this reduction attainable. Several studies, for example, have established that if fibrinolytic therapy is initiated within 3 h of symptom onset, early mortality can be reduced by 25–30% as compared with conservative therapy. If treated later, only a 15% reduction may be observed.[3–5]

Obtaining and maintaining arterial patency, however, remains a formidable challenge to fibrinolytic therapy.[3,6,7] Whereas normal coronary flow, as measured by Thrombolysis in Myocardial Infarction (TIMI) grade 3, is restored in 29–54% of patients receiving fibrinolysis (FL), primary percutaneous coronary intervention (PPCI) is associated with normal epicardial flow in more than 90% of patients.[7,8] PPCI, however, is not without limitations. Although normal coronary flow may be achieved in the epicardial arteries, flow in the distal microvascular beds may be compromised in a considerable portion of patients by microscopic atherosclerotic debris which becomes dislodged during the procedure.[9,10] Similarly, mechanical reperfusion is also associated with major systemic bleeding in excess of 2% relative to pharmacologic strategies.[11] The treatment delay associated with mobilizing the interventional team and arranging patient transfer to the nearest interventional facility also presents a considerable challenge to timely treatment, especially as most facilities do not operate during 'off-hours'. Under optimal circumstances, this will lead to at least a 30 min treatment-related delay as compared with in-hospital initiation of fibrinolytic therapy.[12] When compared with pre-hospital treatment with FL, this delay may range from 60 to 90 min. Outside of the clinical trial setting, fewer than 30% of PPCI patients had a door-to-balloon time less than 90 min according to findings from the National Registry of Myocardial Infarction (NRMI).[13] Transfers from other institutions lengthened door-to-balloon time considerably, with less than 5% of transfer patients undergoing PPCI within 90 min after first medical contact.[14]

Recent evidence from several large trials suggests that the maximum benefits of either treatment strategy may occur at different time points after symptom onset. With transportation times of up to 2 h, the clinical benefits of PPCI over FL were not modified.[15,16] In contrast, the PRimary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis (PRAGUE)-2 study observed no difference in 30-day mortality between PPCI and FL for patients presenting within 3 h,[17] and the Comparison of Primary Angioplasty and Prehospital Thrombolysis in the Acute Phase of Myocardial Infarction (CAPTIM) trial provided evidence for a better outcome in patients receiving prehospital FL as compared with PPCI, provided that fibrinolytic therapy is initiated within 2 h after symptom onset.[18,19]
Given these recent findings, the aim of the current study was to assess whether the clinical benefit of PPCI compared with in-hospital FL is modulated by the time to treatment in a pooled analysis of randomized clinical trials reported since 1990 (Figure 1).

METHODS

Trial selection

All randomized trials that enrolled at least 50 patients presenting with

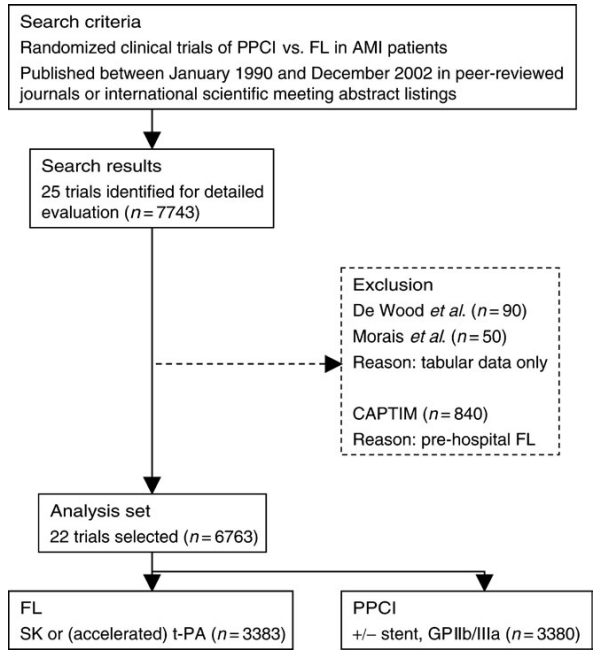


Figure 1 Flowchart of trial search and selection for the pooled analysis.

AMI assigned to treatment with FL or PPCI were considered. Trials published between January 1990 and December 2002 were identified by OVID MEDLINE and ISI Web of Science using a broad range of key words, including '(acute) myocardial infarction', 'FL', 'fibrinolytic', 'thrombolysis', 'thrombolytic', 'streptokinase', 'tissue plasminogen activator', 'accelerated tissue plasminogen activator', 't-PA', 'rt-PA', 'primary', 'angioplasty', 'stent', and 'PCI'. Non-English articles were not excluded. References of identified papers and abstract listings of annual meetings of the American Heart Association (Circulation), American College of Cardiology (Journal of the American College of Cardiology), and European Society of Cardiology (European Heart Journal) were also examined during the same period. Each trial identified in this search was critically and independently evaluated by three investigators (E Boersma, RJ Simes, and CM Westerhout) for patient population, study treatment, protocol, and endpoints. The primary investigators of these studies were contacted for verification and access to individual patient data.

Twenty-five trials, which enrolled 7743 patients, met the abovementioned search criteria (Appendix B, Table B1).[15–18,20–40] Individual patient data were unavailable in two trials (DeWood et al.,[27] n = 90; Morais et al.,[32] n = 50) and the CAPTIM investigators judged that their protocol was incompatible with the other trials included in this pooled analysis,

which excluded an additional 840 patients. Thus, individual patient data from 22 trials (n = 6763) were pooled for the primary analysis. Data were assessed for completeness, internal consistency of patient records, and consistency with published reports. Any discrepancies between analysis of the data provided and previously published results were queried and resolved with the primary investigator of the trial.

Endpoint definition

The primary endpoint of this pooled analysis was all-cause mortality at 30 days. Individually, most trials were not designed (and were underpowered) to evaluate differences in mortality between the treatment strategies; however, pooling these studies provided sufficient power, particularly for subgroup analyses such as those involving time. Other endpoints (i.e. re-infarction and stroke) remained defined according to the original trial-specific criteria.

Statistical analysis

Continuous data were summarized and presented as median values with corresponding IQR, whereas dichotomous data were presented as counts and percentages. Differences in baseline characteristics between subgroups of patients were evaluated by Wilcoxon rank sum tests, Kruskal–Wallis tests or $x2$ tests as appropriate. Time to treatment was categorized into 'presentation delay' (i.e. time from symptom onset to randomization) and 'treatment delay' (i.e. time from randomization to treatment). Patients were further categorized for presentation delays as 0–1, >1–2, >2–3, >3–6, and >6 h, which was determined a priori and based on previously published studies. Unlike presentation delay, the interval between randomization and treatment is influenced by allocated treatment, and analyses that are based on these observations after randomization in individual patients can result in biased estimates of treatment effect. Analyses based on observations at a hospital level may help to overcome this. Thus, the median time between randomization and the start of treatment (i.e. first injection of the fibrinolytic agent or the first balloon inflation) was calculated for each of the 153 hospitals. The hospital-specific difference between these median times was then determined, which is hereafter referred to as 'PCI-related delay', and assigned each patient within that hospital. PCI-related delay was then grouped into quintiles: 0–35, >35–50, >50–62, >62–79, and >79 min. PCI-related delay should be interpreted as the additional time that is needed to start the PCI procedure after treatment with a fibrinolytic agent could have been started.

All analyses were performed according to intention-to-treat principles. Trial-specific outcome data were pooled using the Cochrane–Mantel–Haenszel method, and OR and 95% CI for 30-day death are reported. The Breslow-Day test was applied to examine the statistical evidence of heterogeneity among the trial-

specific ORs. It should be noted that statistical tests for heterogeneity often lack power, and fail to elucidate differences which may be clinically important.[41]

Initially, the influence of presentation delay, as well as PCI-related delay, on the treatment effect at 30 days (i.e. death) was examined using single-level logistic regression. However, given the hierarchical nature of these data (i.e. patients nested within hospitals), multilevel logistic regression was then applied to address random and fixed effects at the patient and hospital levels of the study. At the patient level, age, gender, weight, diabetes mellitus, previous MI, prior revascularization [PCI or coronary artery bypass graft (CABG)], anterior MI at presentation, heart rate, systolic blood pressure, presentation delay, and study treatment (FL or PPCI) were considered fixed effects, and statistical significance was evaluated using the t-ratio.[42] At the hospital level, the average annual PCI volume and PCI-related delay were available at each of the 153 hospitals. The annual PCI volume (on study only) was calculated as the average number of patients randomized to PPCI per year, which was then grouped into tertiles of its distribution (<10, 10–23, ≥24 PPCI/year). At the study level, the likelihood of PCI within 30 days after initial FL, use of stents, use of glycoprotein (GP) IIb/IIIa inhibitors, type of fibrinolytic agent used (streptokinase, t-PA, or accelerated t-PA), single-centred vs. multicentred trial, and the year of publication were considered. When three-level models were tested, there was no variance at the study-level, which provided statistical support that these studies could be pooled for analysis. In addition to these main effects, two interactions were considered: (i) study treatment and presentation delay (patient-level interaction); and (ii) study treatment and PCI-related delay (patient/hospital-level interaction). MLwiN and (version 1.10.0007) statistical software, with residual iterated generalized least squares and pseudoquasi-likelihood model specifications, was used for the multilevel modelling.

Further analyses of the presentation delay treatment association were performed in a priori-selected patient subgroups [<65 vs. ≥65-years-old; female/male; diabetes mellitus; previous MI; anterior vs. non-anterior MI location; systolic blood pressure (<130 vs. ≥130 mmHg); heart rate (<70 vs. ≥70 bpm)], hospital-level average annual PCI volume and study-level type of fibrinolytic agent used.

Two sensitivity analyses, using single-level logistic regression were performed: (i) impact of exclusion of three trials without individual patient data;[18,27,32] and (ii) type of fibrinolytic agent used (i.e. streptokinase, t-PA, accelerated t-PA). Given the 15% reduction in 30-day mortality with 'accelerated' tPA as compared with streptokinase in the GUSTO-I trial, the former has become the 'gold' standard for pharmacological reperfusion therapy.[3] Thus, a sensitivity analysis was performed to evaluate if results of the primary

Table 1 Baseline characteristics of the study population according to study treatment and presentation delay

	FL	PPCI	Presentation delay				
			0–1 h	>1–2 h	>2–3 h	>3–6 h	>6 h
n	3383	3380	747	2000	1712	1640	664
Demographics and co-morbidities							
Age (years)[a]	62 (53–71)	63 (53–71)	60 (52–68)	61 (53–70)	63 (54–71)	65 (55–73)	65 (54–74)[c]
Male (%)	73.2	72.6	76.6	74.8	73.2	69.5	70.6[c]
Diabetes mellitus (%)	12.4	13.5	11.1	9.8	13.1	14.7	20.0[c]
Previous MI (%)	13.2	12.5	14.1	13.5	12.6	11.9	12.5[c]
History of PCI (%)	4.0	3.6	3.5	5.1	3.3	2.9	3.6[d]
History of CABG (%)	2.1	1.2[b]	1.3	2.1	1.5	1.6	1.4
Clinical examination							
Body weight (kg)[a]	79 (75–80)	79 (75–80)	79 (77–82)	79 (75–80)	79 (75–80)	79 (73–80)	79 (72–80)
Systolic blood pressure (mmHg)[a]	133 (120–145)	133 (120–145)	133 (115–140)	133 (120–140)	133 (120–146)	133 (120–148)	133 (120–150)
Heart rate (bpm)[a]	76 (66–82)	76 (66–84)	76 (64–80)	76 (63–80)	76 (67–84)	76 (68–84)	76 (70–90)
Anterior MI (%)	45.8	46.5	49.4	46.2	43.1	44.6	52.4

[a]Continuous data are presented as median values (IQR).
[b]Difference between patients assigned to FL or PPCI, $P < 0.05$.
[c]Difference across subgroups according to time from symptom onset to randomization, $P < 0.05$.
[d]Difference across subgroups according to time from symptom onset to randomization, $P < 0.001$.

analysis were consistent in the studies that compared PPCI with accelerated tPA.

RESULTS

Of 6763 patients, 3383 were randomized to FL and 3380 to PPCI. The distribution of baseline patient characteristics among patients randomized to FL and PPCI was well balanced, with prior CABG as the exception. (Table 1) Younger, male patients and patients with a history of previous MI, or PCI presented earlier, whereas those with diabetes mellitus appeared to have arrived later, especially after 6 h. Patients with an anterior MI tended to present either very early (0–1 h) or very late (>6 h) after symptom onset. In trials with available data, 3.3% of patients randomized to FL actually receive PPCI, whereas 12.1% of patients randomized to PPCI did not receive the assigned treatment.

Overall, the median presentation delay was 142 (IQR: 91–221) min, which did not differ significantly between FL [143 (91–225) min] and PPCI [140 (91–220) min], P = 0.30. Nearly 11% of the 6763 patients were randomized within the first hour after symptom onset, with the majority subsequently randomized between 1 and 3 h after symptom onset (Figure 2). As also shown in Figure 2, the time from randomization to the start of either FL or PPCI was not influenced by the length of time from symptom onset. Given the inherent logistics of the different modalities, the median time to FL was significantly shorter than that of the beginning of PCI [respectively, 19 (10–30) min vs. 76 (61–95) min; P < 0.001], which gave an overall PCI-related delay of 55 (37–74) min.

Thirty-day adverse events and the influence of presentation delay

Overall, 6.6% of 6763 patients died within 30 days of randomization (Table 2). According to randomized treatment, the 30-day death rate was 7.9% of FL patients and 5.3% in those randomized to PPCI (P < 0.001). In patients randomized to FL,

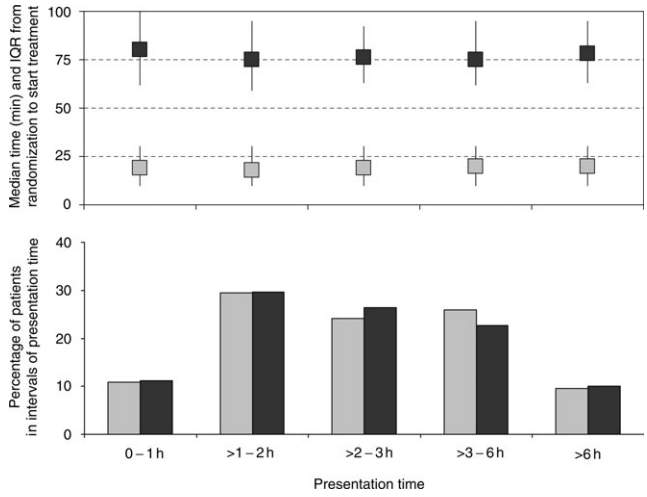


Figure 2 Distribution of patients (bars) and median (25th, 75th percentile) time to treatment [FL (■)] or [PPCI (■)] according to presentation delay and study treatment.

30-day mortality increased two-fold as the presentation delay increased from less than 1 to over 6 h ($P < 0.001$). A similar, yet non-significant trend was observed in patients assigned to PPCI ($P = 0.06$).

Re-infarction occurred in 6.7% of FL patients and in 2.4% of PPCI patients during 30-day follow-up ($P < 0.001$). Among FL patients, re-infarction occurred in 10.4% of patients enrolled within 1 h after symptom onset, and in 6.3% of patients enrolled at more than 6 h after symptom onset ($P = 0.007$). In those randomized to PPCI, there was no difference in the re-infarction rate at 30 days according to presentation delay ($P = 0.5$).

The combined endpoint of 30-day death and re-infarction occurred in 13.5% of FL patients and in 7.3% of PPCI patients ($P < 0.001$). In both treatment groups, there appeared to be an increasing trend in 30-day death or re-infarction with longer presentation delay; however, this was only statistically significant in the FL group ($P < 0.001$).

Treatment, time to treatment, and 30-day mortality

Overall, PPCI patients had a 37% relative lower odds of 30-day mortality than those randomized to fibrinolytic therapy after multi-level covariate adjustment [adjusted OR 0.63; 95% CI (0.42–0.84); $P < 0.001$]. According to presentation delay, the treatment effect consistently favoured PPCI in all the subgroups, and there was no evidence of heterogeneity (pBreslow-Day = 0.9) (Figure 3, left panel). The absolute mortality reduction by PPCI increased from 1.3% in patients randomized in the first hour after symptom onset to 4.2% in those randomized after 6 h. Consequently, with increasing delay,

Table 2 Adverse events at 30 days according to presentation delay

	Overall	Presentation delay				
		0–1 h	>1–2 h	>2–3 h	>3–6 h	>6 h
Fibrinolysis, *n*	3383	368	997	818	876	324
Death (%)	7.9	6.0	6.2	7.3	9.5	12.7[b]
Re-MI (%)	6.7	10.4	4.9	7.4	6.9	6.3[a]
Death or re-MI (%)	13.5	14.9	10.4	13.6	15.0	17.6[a]
Stroke (%)	2.2	4.0	0.8	1.0	5.2	0.0
PPCI, *n*	3380	379	1003	894	764	340
Death (%)	5.3	4.7	4.2	5.1	5.6	8.5[a]
Re-MI (%)	2.4	1.6	2.9	2.3	2.0	3.0
Death or re-MI (%)	7.3	6.1	6.8	7.4	7.2	10.3
Stroke (%)	0.5	0.0	0.8	0.0	1.0	0.0

[a]Difference across subgroups according to presentation delay, $P < 0.05$.
[b]Difference across subgroups according to presentation delay, $P < 0.001$.

the number needed treat to prevent a death, decreased from 77 to 24 patients.

According to quintiles of site-specific PPCI-related delay, the risk of 30-day death was consistently reduced in PPCI patients, and there was evidence of heterogeneity across the quintiles (pBreslow-Day = 0.05) (Figure 3, right panel). In particular, PPCI was associated with a 67% reduction in the odds of 30-day mortality when the PPCI-related delay was less than or equal to 35 min and with a 28% reduction in patients with a longer PPCI-related delay (pBreslow-Day = 0.004 for the comparison of the first quintile with quintiles 2–5).

Subgroup and sensitivity analyses

The relationship between relative treatment effect and presentation delay (less than or equal to/greater than 2 h) were examined within selected patient-, hospital-, and study-level characteristics (Figure 4). In general, treatment with PPCI was consistently favoured over FL in the subgroups considered, regardless of presentation delay. The average annual PCI volume did not influence the relative treatment benefit of PPCI over FL. The relative treatment effect appeared to decline with the use of accelerated t-PA and the year of randomization; however, these trends were not statistically significant.

Ten of the 22 studies (n = 4172) compared PPCI with accelerated t-PA (Appendix B, Table B1). In these trials, PPCI was associated with a 29% relative reduction in mortality [7.4% FL vs. 5.6% PPCI; adjusted OR: 0.71; 95% CI (0.46–0.98)]. Similar to the primary analysis, there was no evidence of heterogeneity in the treatment effect according to presentation delay (pBreslow-Day = 0.9; Figure 5). Also, as seen in the

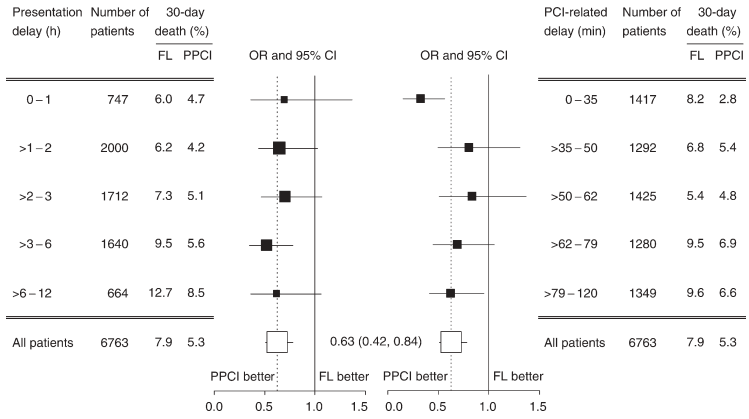


Figure 3 OR and 95% CI for 30-day death in patients randomized to PPCI when compared with FL according to presentation delay (left panel) and PCI-related delay (right panel). OR were adjusted for patient-, hospital-, and study-level covariates.

primary analysis, the treatment effect in favour of PPCI was highest in the first quintile of PCI-related delay. The 95% CI, however, were wide and largely overlapping, resulting in lack of heterogeneity (pBreslow-Day = 0.3).

Although individual patient data for three of the 25 trials originally identified were not available, tabular data for 980 patients were extracted from published reports and analysed for potential bias based on their exclusion.[15,23,28] Overall, a 31% reduction in 30-day death was observed in the PPCI group [7.5% FL vs. 5.3% PPCI; OR: 0.69, 95% CI (0.58–0.83)]. The CAPTIM trial was of particular interest as ~55% of the 840 patients were randomized within the first 2 h after symptom onset. Despite these additional patients, the relative treatment benefit was still in favour of PPCI, regardless of presentation delay (pBreslow-Day = 0.3) (Figure 5). If only accelerated t-PA trials were analysed, the relative benefit was attenuated but still without statistical evidence of heterogeneity (<2 h, OR: 0.98; 95% CI (0.66–1.47); ≥2 h, OR: 0.72; 95% CI (0.54–0.95); pBreslow-Day = 0.21).

DISCUSSION

Overall, PPCI was associated with a 37% relative reduction in the odds of 30-day mortality when compared with in-hospital fibrinolytic therapy, which was slightly attenuated to 28% when only accelerated t-PA trials were considered. Although these findings are not unlike those found in previously published meta- and pooled-analyses,[11,12,43] this analysis extends beyond these by including individual patient data from trials reported since 1997 and focusing on the importance of time to treatment in the reperfusion debate.

The time-sensitivity of fibrinolytic therapy has been well established by the substantial reduction in mortality observed when fibrinolytic treatment is administered within the 'golden hour'.[5] Yet, regardless of the delay in presentation of the current analysis, treatment with PPCI was uniformly associated with lower mortality relative to FL. These

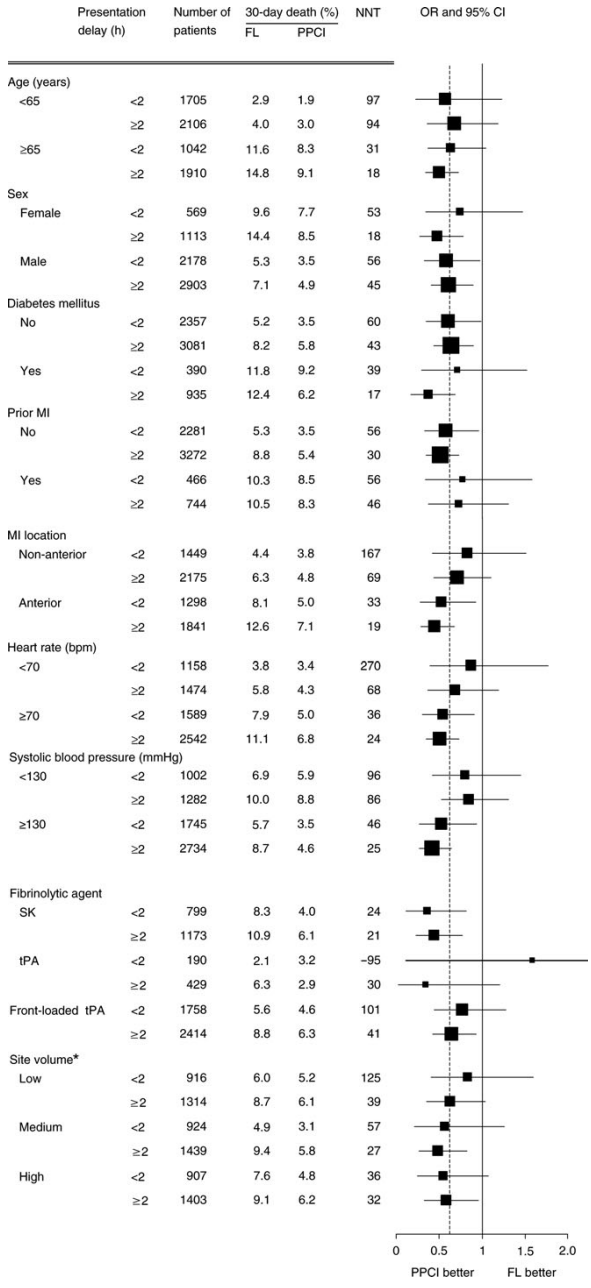


Figure 4 Subgroup analysis of selected patient-, study-, and site-level characteristics. NNT (number needed to treat): the number of patients who need to be treated in order to prevent a death. OR were adjusted for patient-, hospital-, and study-level covariates. *Site volume on-study only, classified by the number of patients randomized to percutaneous transluminal coronary angioplasty per site per year: low, <10 patients/site/year; medium, 10–23 patients/site/year; high, ≥ 24 patients/site/year.

findings were somewhat unexpected given the recently reported evidence. In the CAPTIM trial, for instance, patients randomized within 2 h after symptom onset had a strong trend towards higher 30-day mortality with PPCI when compared with pre-hospital FL [5.7 vs. 2.2%; OR: 2.7; 95% CI (0.94–7.7); P = 0.06].18 Although our sensitivity analysis including the tabulated data from the CAPTIM trial suggests that PPCI provides only a small mortality reduction relative to accelerated t-PA in patients randomized within 2 h, this estimate was not adjusted for potential confounders. Also, from statistical point of view, the estimate of treatment effect in this subgroup did not diverge from the estimate in patients randomized after 2 h. Upon more extensive analysis of the CAPTIM trial, several important details are worth noting. First, this trial was designed to prove the clinical superiority of PPCI over pre-hospital FL. Although, 1200 patients were needed to demonstrate a foreseen 44% relative reduction in the composite endpoint of death, non-fatal myocardial re-infarction and non-fatal stroke, only 67% of the target sample size was achieved. As a result, only a trend towards lower event rates after PPCI was observed (6.2 vs. 8.2% events) and the 95% CI of expected and observed treatment effect were largely overlapping. Thus, the CAPTIM findings should be interpreted with caution and in the context of other pieces of evidence. Finally, over two-thirds of the CAPTIM patients allocated to pre-hospital FL underwent PCI within 30 days, which was notably a strong confounder of treatment effect in our pooled analysis. In fact, the pre-hospital FL treatment strategy of the CAPTIM trial closely approximates the strategy of so-called 'facilitated' PCI in which patients receive adjunctive pharmacologic treatment during transfer for the intervention. Some evidence suggests that such strategy may result in even better patient outcome than the more traditional PPCI approach.[44,45] On the other hand, preliminary analyses of the ASSENT-IV trial demonstrated a higher incidence of major adverse cardiac complications in patients allocated to the strategy of PPCI after pre-treatment with tenecteplase compared with PPCI alone.[46] Several trials such as the Combined Abciximab REteplase Stent Study in acute myocardial infarction (CARESS in AMI),[47] and the Facilitated Intervention for Enhanced reperfusion Speed to Stop ischemic Events (FINESSE) trial are underway to further test this strategy.

The balance of the treatment effect in the current analysis remained with PPCI when its association with PCI-related delay was examined, particularly if the delay was 35 min or less. In 2001, Kent and colleagues[48] presented a 'back-of-the-envelope' calculation for the benefit of PPCI over FL in relation to PCI-related delay. Based on a linear meta-regression on published findings from the first 10 randomized trials of PPCI vs. FL, they concluded that the absolute survival benefit of PPCI compared with FL decreased by 1.7% for every additional 10 min PCI-related delay, and thus, a PCI-

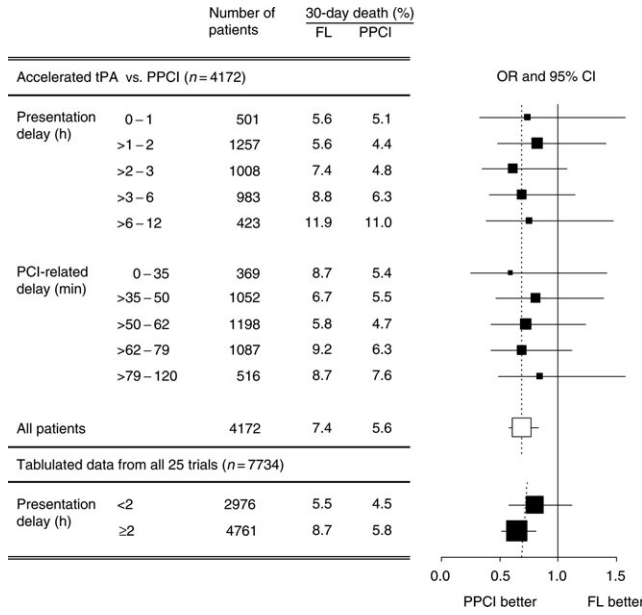


Figure 5 Sensitivity analyses of the use of accelerated t-PA and of the inclusion of trials with tabular data. OR were adjusted for patient-, hospital-, and study-level covariates.

related delay exceeding 50 min would nullify its benefits. Nallamothu and Bates[49] recently repeated the analysis using published data of most of the trials included in our pooled-analysis and reached similar conclusions. Our analysis, however, yielded divergent results which may largely be explained by several methodological differences. First, Kent and Nallamothu presented only absolute treatment effects. Second, the estimated PCI-related delay in their analyses was based on a combination of median and mean values of time-from-onset-to-treatment, time-from-randomization-to-treatment, and time-from-hospitalization-to-treatment, depending on the available data in the separate clinical trial reports. Finally, the results of linear (meta-) regression are susceptible to extreme observations. Although 'back-of-the-envelope' calculations based on tabulated data are relatively straightforward and easy to understand, the caveats of such analyses underscores the importance of pooling individual patient data for these analyses.

PCI-related delay is subject to numerous biases related to the modalities themselves, which are distinct from those influencing presentation delays. These biases are often related to the delivery of these treatment strategies by the healthcare system; and thus, PCI delay was determined at the hospital level in the current analysis. This also has the advantage that PCI delay could be estimated in patients

randomized to PPCI who ultimately did not undergo this procedure. However, these analyses are limited to the extent that they are inadequately powered to demonstrate effects of a delay in treatment. Hence, the observations in relation to presentation delay should be given more weight than those regarding PCI-related delay.

One of the most salient messages of the current study is the importance of timely treatment in AMI patients. Although the relative mortality reduction by fibrinolytic therapy (relative to control) is often highest in patients treated earliest after symptom onset,[5] our data also provides evidence that this is also the case for PPCI, as the relative treatment effects of PCI over FL were not influenced by presentation delay. Secondly, absolute mortality rates in patients undergoing PPCI increased with increasing presentation delay as well as with increasing PCI-related delay. Although we appreciate that these differences may be biased by differences in patient risk profiles, such as the elderly and diabetics who presented later after symptom onset, it is also important to emphasize that time to treatment remained an important outcome determinant after adjustment for baseline characteristics. This observation is consistent with the results from the large (n = 27 080) NRMI registry and a smaller (n = 1791) registry from The Netherlands, and confirms that timely treatment results in improved outcomes.[13,50]

Limitations

Several limitations of this analysis should be addressed. First, the selection of trials may be prone to some bias. As stated earlier, all trials published between January 1990 and December 2002 were considered in the search. Although some time has elapsed since then, to our knowledge, no additional trials have been reported.

Another implication of including trials published since 1990 may be the challenge of generalizability to current practice, given the rapid evolution of therapies and overall cardiac care. Although our analysis revealed no variance across the 22 trials, certain characteristics of recent studies deserve comment. Enrolment in DANAMI-2 and C-PORT, which when combined contributed 30% to the total number of patients in this pooled analysis, was prematurely discontinued owing to better outcomes in patients randomized to PPCI, which were largely driven by high re-infarction rates in FL patients or exclusion of procedure-related re-infarctions. Ideally, a large randomized trial enrolling a broad spectrum of AMI patients would be preferable to meta-analyses. A trial with 80% power would need to enrol 4400 patients (2200 patients in each study arm) to detect a 2% mortality difference.[51] Enrolling large numbers of patients, however, has proven in the past to be a challenge as indicated by the early termination of such recent trials as DANAMI-2 and C-PORT. Thus, meta- and pooled-analyses, such as this one, provide our best estimate of reperfusion

strategies in these patients. Population-based studies such as those from NRMI and others, however, will provide critical evidence as to how the broader AMI population and healthcare system factors will modulate the observations based in the clinical trial setting.

Although the use of individual patient data provided greater analytic flexibility than traditional meta-analyses, additional information on the context of treatment may have been helpful in further elucidating these research questions. Information on the experience (and personal characteristics) of the interventionalist (and/or intervention team), timing of PCI ('business-hours' vs. 'off-hours'), and geographic-, socio-, and economic related barriers to care is rarely collected by clinical trials, but may have profound implications to the generalizability of the findings which comes with confusing aggregate and individual effects, otherwise known the 'ecological fallacy'.[52]

Conclusions and clinical implications

Regardless of the therapeutic strategy, the time expired since the beginning of the coronary occlusion remains central to the reperfusion debate. With this in mind, efforts should be increased to enhance early reperfusion and solutions should involve all stakeholders, from patients to providers to policy-makers.[2] Altering public perception of AMI and the importance of seeking early treatment is a complex undertaking which may be overcome through effective education programming among other behaviour-changing approaches.

The 'real world' poses logistical and economic challenges to the feasibility of a 'PPCI-for-all' approach; however, the benefit of timely treatment as demonstrated in this study underscores the importance of developing a comprehensive and unified approach to improve the delivery of cardiac care in all AMI patients. Unlike the clinical trial setting, disparities in ambulatory care and pre-hospital services, and limited access to tertiary or regional heart centres, both in number of centres and 24-h/7-day capabilities, represent formidable challenges to translating treatment benefit into the general AMI patient population. For example population-based studies have revealed median treatment delays ranging from 42 to 93 min.[53–55] Until these gaps are narrowed, FL still remains a viable treatment strategy when timely PPCI is not available. One treatment does not fit all: time matters.

ACKNOWLEDGEMENTS

This study was supported through a research grant from Boehringer Ingelheim (The Netherlands). The initiation, design and co-ordination of this project, as well as the interpretation and reporting of the findings were entirely independent of this source.

Conflict of interest: none declared in addition to those declared in the primary publications of the individual trials.

APPENDIX A. PCAT-2 Trialists' Collaborative Group

Study Chairs: E Boersma (Erasmus MC, Rotterdam, The Netherlands), RJ Simes (NHMRC Clinical Trials Centre, Sydney, Australia), CL Grines (Beaumont Hospital, Royal Oak, MI, USA).

Writing Committee: E Boersma, CM Westerhout (Rotterdam, The Netherlands; Edmonton, Canada), RJ Simes, WD Weaver (Detroit, MI, USA), HR Andersen (Aarhus, Denmark), PW Armstrong (Edmonton, Canada), C Granger (Durham, NC, USA), CL Grines, F Zijlstra (Groningen, The Netherlands), P Widimsky (Prague, Czech Republic).

Trialists: Zwolle studies: MJ de Boer (Zwolle, The Netherlands), F Zijlstra (Groningen, The Netherlands); E Ribeiro (Sao Paulo, Brazil); L Grinfeld (Buenos Aires, Argentina); F Akhras (London, UK); S Kedev (Skopje, Macedonia); PRAGUE studies: P Widimsky (Prague, Czech Republic); MA DeWood (Spokane, WA, USA); Mayo Trial: RJ Gibbons (Rochester, MN, USA); PAMI and AIR-PAMI: CL Grines (Royal Oak, MI, USA); GUSTO-IIb: CB Granger, R Califf (Durham, NC, USA), PWArmstrong (Edmonton, Canada), and RJ Simes (Sydney, Australia); JIMI: H Aoki (Morioka, Japan); J Morais (Leiria, Portugal); F Ribichini (Cuneo, Italy); E Garcia (Madrid, Spain); LIMI: F Ba¨r (Maastricht, The Netherlands); STAT: MR LeMay (Ottawa, Canada); STOPAMI studies: A Kastrati, A Scho¨mig (Mu¨nchen, Germany); C-PORT: T Aversano (Baltimore, MD, USA); DANAMI-2: HR Anderson, TT Nielsen (Aarhus, Denmark).

Study support: L Barnes, C Pollicino (NHMRC Clinical Trials Centre, Sydney, Australia).

APPENDIX B.

Table B1 Design characteristics and 30-day mortality of the 25 randomized clinical trials (PPCI vs. FL) identified in the literature search

Trial	Patient population	Symptom onset (h)	FL			PPCI			
			Number of patients	Agent	30-day death (%)	Number of patients	Stent used	GP IIb/IIIa used	30-day death (%)
Streptokinase agent									
Zijlstra *et al.*[20]	ST↑, ≤75 years	<6	149	SK	7.4	152	No	No	1.3
Ribeiro *et al.*[21]	ST↑, <75 years	<6	50	SK	6.0	50	No	No	2.0
Grinfeld *et al.*[22]	ST↑	<12	58	SK	9.3	54	No	No	13.8
Zijlstra *et al.*[23]	ST↑, Low risk	<6	53	SK	2.1	47	No	No	1.9
Akhras *et al.*[24]	ST↑	<12	45	SK	0.0	42	No	No	8.9
Kedev *et al.*[25]	ST↑	<12	67	SK	10.4	68	No	No	2.9
Prague-1[16]	ST↑, LBBB	<6	99	SK	14.1	101	Yes	No	6.9
De Boer *et al.*[26]	ST↑, >75 years	<6	41	SK	22.0	46	Yes	No	6.5
Prague-2[17]	ST↑	<12	421	SK	10.0	429	Yes	Yes	6.8
Fibrin-specific agent									
DeWood *et al.*[a 27]	Anterior MI, ST↑, ≤75 years	<12	44	Duteplase	4.5	46	No	No	6.5
Gibbons *et al.*[28]	ST↑, <80 years	<12	56	Duteplase	3.6	47	No	No	4.3
Grines *et al.*[29]	ST↑	<12	200	t-PA	6.5	195	No	No	3.1
GUSTO IIb[30]	ST↑, LBBB	<12	573	t-PA[c]	7.0	565	No	No	5.7
JIMI[31]	ST↑, <80 years	<6	62	t-PA	1.6	59	No	No	1.7
Morais *et al.*[a 32]	Anterior MI, <70 years	<12	25	t-PA[c]	12.0	25	No	No	16.0
Ribichini *et al.*[33]	Inferior/anterior ST↓, <80 years	<6	55	t-PA[c]	5.5	55	No	No	1.8
Garcia *et al.*[34]	Anterior MI	5	94	t-PA[c]	10.6	95	No	No	3.2
LIMI[35]	ST↑, <80 years	<6	75	t-PA[c]	6.7	75	Yes	No	5.3
STAT[36]	ST↑, LBBB	<12	61	t-PA[c]	3.3	62	Yes	Yes	3.2
STOPAMI-1[37]	ST↑	<12	69	t-PA[c]	7.2	71	Yes	Yes	4.2
AIR PAMI[38]	Anterior MI, >70 years	<12	66	t-PA[c]	12.1	71	Yes	Yes	8.5
C-PORT[39]	ST↑	<12	226	t-PA[c]	7.1	225	Yes	Yes	5.3
DANAMI-2[15]	ST↑	<12	782	t-PA[c]	7.8	790	Yes	NA	6.6
STOPAMI-2[40]	ST↑, LBBB	<12	81	t-PA[c]	6.2	81	Yes	Yes	2.5
Pre-hospital FL									
CAPTIM[b 19]	ST↑	<6	419	t-PA[c]	3.8	421	Yes	Yes	4.8

GP, glycoprotein IIb/IIIa inhibitor; LBBB, left bunch branch block; SK, streptokinase; ST↑, ST-segment elevation; ST↓, ST-segment depression.
[a]Excluded from primary analysis because of non-availability of individual patient data.
[b]Excluded from primary analysis because pre-hospital FL.
[c]Accelerated t-PA.

REFERENCES

1. Gibson CM. Time is myocardium and time is outcomes. Circulation 2001;104:2632–2634.
2. Armstrong PW, Welsh RC. Tailoring therapy to best suit ST-segment elevation myocardial infarction: searching for the right fit. CMAJ 2003;169:925–927.
3. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, survival after acute myocardial infarction. N Engl J Med 1993;329:1615–1622.
4. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomized trials of more than 1000 patients. Lancet 1994;343:311–322.
5. 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.
6. Meijer A, Verheugt FW, Werter CJ, Lie KI, van der Pol JM, van Eenige MJ. Aspirin vs. coumadin in the prevention of reocclusion and recurrent ischemia after successful thrombolysis: a prospective placebo-controlled angiographic study.

Results of the APRICOT Study. Circulation 1993; 87:1524–1530.
7. Grines CL. Should thrombolysis or primary angioplasty be the treatment of choice for acute myocardial infarction? Primary angioplasty—the strategy of choice. N Engl J Med 1996;335:1313–1316.
8. Simes RJ, Topol EJ, Holmes DR Jr, White HD, Rutsch WR, Vahanian A, Simoons ML, Morris D, Betriu A, Califf RM. Link between the angiographic substudy and mortality outcomes in a large randomized trial of myocardial reperfusion. Importance of early and complete infarct artery reperfusion. GUSTO-I Investigators. Circulation 1995;91:1923–1928.
9. Kotani J, Mintz GS, Pregowski J, Kalinczuk L, Pichard AD, Satler LF, Suddath WO, Waksman R, Weissman NJ. Volumetric intravascular ultrasound evidence that distal embolization during acute infarct intervention contributes to inadequate myocardial perfusion grade. Am J Cardiol 2003;92:728–732.
10. Henriques JP, Zijlstra F, Ottervanger JP, de Boer MJ, van't Hof AW, Hoorntje JC, Suryapranata H. Incidence and clinical significance of distal embolization during primary angioplasty for acute myocardial infarction. Eur Heart J 2002;23:1112–1117.
11. Keeley EC, Boura JA, Grines CL. Primary angioplasty vs. intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet 2003;361:13–20.
12. Weaver WD, Simes RJ, Betriu A, Grines CL, Zijlstra F, Garcia E, Grinfeld L, Gibbons RJ, Ribeiro EE, DeWood MA, Ribichini F. Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review. JAMA 1997;278:2093–2098.
13. Cannon CP, Gibson CM, Lambrew CT, Shoultz DA, Levy D, French WJ, Gore JM, Weaver WD, Rogers WJ, Tiefenbrunn AJ. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. JAMA 2000;283:2941–2947.
14. Nallamothu BK, Bates ER, Herrin J, Wang Y, Bradley EH, Krumholz HM. Times to treatment in transfer patients undergoing primary percutaneous coronary intervention in the United States: National Registry of Myocardial Infarction (NRMI)-3/4 analysis. Circulation 2005;111:761–767.
15. Andersen HR, Nielsen TT, Rasmussen K, Thuesen L, Kelbaek H, Thayssen P, Abildgaard U, Pedersen F, Madsen JK, Grande P, Villadsen AB, Krusell LR, Haghfelt T, Lomholt P, Husted SE, Vigholt E, Kjaergard HK, Mortensen LS, DANAMI-2 Investigators. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. N Engl J Med 2003;349:733–742.
16. Widimsky P, Groch L, Zelizko M, Aschermann M, Bednar F, Suryapranata H. Multicentre randomized trial comparing transport to primary angioplasty vs. immediate thrombolysis vs. combined strategy for patients with acute myocardial infarction presenting to a community hospital without a catheterization

laboratory. The PRAGUE study. Eur Heart J 2000;21:823–831.
17. Widimsky P, Budesinsky T, Vorac D, Groch L, Zelizko M, Aschermann M, Branny M, St'asek J, Formanek P, 'PRAGUE' Study Group. Long distance transport for primary angioplasty vs. immediate thrombolysis in acute myocardial infarction. Final results of the randomized national multicentre trial—PRAGUE-2. Eur Heart J 2003;24:94–104.
18. Bonnefoy E, Lapostolle F, Leizorovicz A, Steg G, McFadden EP, Dubien PY, Cattan S, Boullenger E, Machecourt J, Lacroute JM, Cassagnes J, Dissait F, Touboul P, of Angioplasty Comparison, Prehospital Thromboysis in Acute Myocardial Infarction study group. Primary angioplasty vs. prehospital FL in acute myocardial infarction: a randomised study. Lancet 2002;360:825–829.
19. Steg PG, Bonnefoy E, Chabaud S, Lapostolle F, Dubien PY, Cristofini P, Leizorovicz A, Touboul P, Comparison of Angioplasty Prehospital Thrombolysis In acute Myocardial infarction (CAPTIM) Investigators. Impact of time to treatment on mortality after prehospital FL or primary angioplasty: data from the CAPTIM randomized clinical trial. Circulation 2003;108:2851–2856.
20. 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.
21. Ribeiro EE, Silva LA, Carneiro R, D'Oliveira LG, Gasquez A, Amino JG, Tavares JR, Petrizzo A, Torossian S, Duprat FR. Randomized trial of direct coronary angioplasty vs. intravenous streptokinase in acute myocardial infarction. J Am Coll Cardiol 1993;22:376–380.
22. Grinfeld L, Berrocal D, Belardi J, Spinetta A, Matas CR, Oberti P, Doval H, Bazzino O, Cagide A. Fibrinolytics vs. primary angioplasty in acute myocardial infarction (FAP). J Am Coll Cardiol 1996;27(suppl.):A222.
23. Zijlstra F, Beukema WP, van't Hof AW, Liem A, Reiffers S, Hoorntje JC, Suryapranata H, de Boer MJ. Randomized comparison of primary coronary angioplasty with thrombolytic therapy in low risk patients with acute myocardial infarction. J Am Coll Cardiol 1997;29:908–912.
24. Akhras F, AbuOusa A, Swann G, Duncan H, ChamsiPasha H, Jabbad H. Primary coronary angioplasty or intravenous thrombolysis for patients with acute myocardial infarction? Acute and late follow-up results in a new cardiac unit. J Am Coll Cardiol 1997;29(suppl.):A235.
25. Kedev S, Petrovski B, Kotevski V, Antov S, Sokolov I, Jovanova S. Primary coronary angioplasty vs. intravenous streptokinase in acute myocardial infarction. J Am Coll Cardiol 1997;29(suppl.):92542.
26. de Boer MJ, Ottervanger JP, van't Hof AW, Hoorntje JC, Suryapranata H, Zijlstra F, Zwolle Myocardial Infarction Study Group. Reperfusion therapy in elderly patients with acute myocardial infarction: a randomized comparison of primary angioplasty and

thrombolytic therapy. J Am Coll Cardiol 2002;39:1723–1728.
27. DeWood MA. Surgical reperfusion vs. rt-PA vs. PTCA as therapy for single vessel LAD anterior myocardial infarction. Circulation 1992;86(suppl.):772.
28. Gibbons RJ, Holmes DR, Reeder GS, Bailey KR, Hopfenspirger MR, Gersh BJ. Immediate angioplasty compared with the administration of a thrombolytic agent followed by conservative treatment for myocardial infarction. The Mayo Coronary Care Unit and Catheterization Laboratory Groups. N Engl J Med 1993;328:685–691.
29. 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.
30. The Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) Angioplasty Substudy Investigators. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acutemyocardial infarction.N Engl J Med 1997;336:1621–1628.
31. Aoki H, Suzuki T, Shibata M, Takino T, Sato N, Mukaida H, Ohira K, Fukami K, Suzuki T, Hiramori K. A prospective randomized trial of intracoronary t-PA vs. coronary angioplasty in acute myocardial infarction: Japanese Intervention trial in Myocardial Infarction (JIMI). Circulation 1997;96(suppl.):3003.
32. Morais J, Faria H, Goncalves F, Brandao V, Calisto J, Goncalves L, Andrade C, Castro G, Freitas M, Providencia L. Primary angioplasty in better than front loaded t-PA to preserve left ventricular function after acute anterior myocardial infarction. Eur Heart J 1997;18(suppl.):P496.
33. Ribichini F, Steffenino G, Dellavalle A, Ferrero V, Vado A, Feola M, Uslenghi E. Comparison of thrombolytic therapy and primary coronary angioplasty with liberal stenting for inferior myocardial infarction with precordial ST-segment depression: immediate and long-term results of a randomized study. J Am Coll Cardiol 1998;32:1687–1694.
34. Garcia E, Elizaga J, Perez-Castellano N, Serrano JA, Soriano J, Abeytua M, Botas J, Rubio R, dS Lopez, Lopez-Sendon JL, Delcan JL. Primary angioplasty vs. systemic thrombolysis in anterior myocardial infarction. J Am Coll Cardiol 1999;33:605–611.
35. Vermeer F, Oude Ophuis AJ, vd Berg EJ, Brunninkhuis LG, Werter CJ, Boehmer AG, Lousberg AH, Dassen WR, Bar FW. Prospective randomized comparison between thrombolysis, rescue PTCA, and primary PTCA in patients with extensive myocardial infarction admitted to a hospital without PTCA facilities: a safety and feasibility study. Heart 1999;82:426–431.
36. Le May MR, Labinaz M, Davies RF, Marquis JF, Laramee LA, O'Brien ER, Williams WL, Beanlands RS, Nichol G, Higginson LA. Stenting vs. thrombolysis in acute myocardial infarction trial (STAT). J Am Coll Cardiol 2001;37:985–991.

37. Schomig A, Kastrati A, Dirschinger J, Mehilli J, Schricke U, Pache J, Martinoff S, Neumann FJ, Schwaiger M. Coronary stenting plus platelet glycoprotein IIb/IIIa blockade compared with tissue plasminogen activator in acute myocardial infarction. Stent vs. Thrombolysis for Occluded Coronary Arteries in Patients with Acute Myocardial Infarction Study Investigators. N Engl J Med 2000;343:385–391.
38. Grines CL, Westerhausen DR Jr, Grines LL, Hanlon JT, Logemann TL, Niemela M, Weaver WD, Graham M, Boura J, O'Neill WW, Balestrini C, Air PAMI Study Group. A randomized trial of transfer for primary angioplasty vs. on-site thrombolysis in patients with high-risk myocardial infarction: the Air Primary Angioplasty in Myocardial Infarction study. J Am Coll Cardiol 2002;39:1713–1719.
39. Aversano T, Aversano LT, Passamani E, Knatterud GL, Terrin ML, Williams DO, Forman SA, Atlantic Cardiovascular Patient Outcomes Research Team. Thrombolytic therapy vs. primary percutaneous coronary intervention for myocardial infarction in patients presenting to hospitals without on-site cardiac surgery: a randomized controlled trial. JAMA 2002;287:1943–1951.
40. Kastrati A, Mehilli J, Dirschinger J, Schricke U, Neverve J, Pache J, Martinoff S, Neumann FJ, Nekolla S, Blasini R, Seyfarth M, Schwaiger M, Schomig A. Stent vs. Thrombolysis for Occluded Coronary Arteries in Patients With Acute Myocardial Infarction (STOPAMI). Myocardial salvage after coronary stenting plus abciximab vs. FL plus abciximab in patients with acute myocardial infarction: a randomised trial. Lancet 2002;359:920–925.
41. Berlin JA, Laird NM, Sacks HS, Chalmers TC. A comparison of statistical methods for combining event rates from clinical trials. Stat Med 1989;8:141–151.
42. Snijders TAB, Bosker RJ. Multilevel Analysis: An Introduction to Basic and Advanced Multilevel Modeling. London: Sage Publications; 1999.
43. Grines C, Patel A, Zijlstra F, Weaver WD, Granger C, Simes RJ, PCAT Collaborators. Percutaneous transluminal coronary angioplasty. Primary coronary angioplasty compared with intravenous thrombolytic therapy for acute myocardial infarction: six-month follow up and analysis of individual patient data from randomized trials. Am Heart J 2003;145:47–57.
44. Ross AM, Coyne KS, Reiner JS, Greenhouse SW, Fink C, Frey M. A randomized trial comparing primary angioplasty with a strategy of shortacting thrombolysis and immediate planned rescue angioplasty in acute myocardial infarction. J Am Coll Cardiol 1999;34:1954–1962.
45. Le May MR, Wells GA, Labinaz M, Davies RF, Turek M, Leddy D, Maloney J, McKibbin T, Quinn B, Beanlands RS, Glover C, Marquis JF, O'Brien ER, Williams WL, Higginson LA. Combined angioplasty and pharmacological intervention vs. thrombolysis alone in acute myocardial infarction (CAPITAL AMI study). J Am Coll Cardiol 2005;46:417–424.

Chapter Eleven

A comparison of pharmacologic therapy with/without timely coronary intervention vs. primary percutaneous intervention early after ST-elevation myocardial infarction: the WEST (Which Early ST-elevation myocardial infarction Therapy) study

Paul W. Armstrong*, WEST Steering Committee

AIMS Uncertainty exists as to which reperfusion strategy for ST-elevation myocardial infarction (MI) is optimal. We evaluated whether optimal pharmacologic therapy at the earliest point of care, emphasizing pre-hospital randomization and treatment was non-inferior to expeditious primary percutaneous coronary intervention (PCI).

METHODS AND RESULTS Which Early ST-elevation myocardial infarction Therapy (WEST) was a four-city Canadian, open-label, randomized, feasibility study of 304 STEMI patients (>4 mm ST-elevation/deviation) within 6 h of symptom onset, emphasizing pre-hospital ambulance treatment and participation of community and tertiary care centres. All received aspirin, subcutaneous enoxaparin (1 mg/kg), and were randomized to one of three groups: (A) tenecteplase (TNK) and usual care, (B) TNK and mandatory invasive study ≤24 h, including rescue PCI for reperfusion failure, and (C) primary PCI with 300 mg loading dose of clopidogrel. Time from symptom onset to treatment was rapid (to TNK for A = 113 and B =130 min and for PCI in C = 176 min). The primary outcome, a composite of 30-day death, re-infarction, refractory ischaemia, congestive heart failure, cardiogenic shock, and major ventricular arrhythmia, was 25% (Group A), 24% (Group B), and 23% (Group C), respectively. However, there was a higher frequency of the combination of death and recurrent MI in Group A vs. Group C (13.0 vs. 4.0%, respectively, P-logrank = 0.021), yet no difference between Group B (6.7%, P-logrank = 0.378) and C.

CONCLUSION These data suggest that a contemporary pharmacologic regimen rapidly delivered, coupled with a strategy of regimented rescue and routine coronary intervention within 24 h of initial treatment, may not be different from timely expert PCI.

Few issues in contemporary cardiovascular medicine have been subjected to more sustained and vigorous debate as the optimal approach to life-saving reperfusion therapy in patients with acute ST-segment elevation myocardial infarction (STEMI). Once thrombotic occlusion of a major epicardial coronary artery was established as the cause of STEMI, parallel developments in pharmacological and mechanical reperfusion strategies occurred. Each has been shown to successfully salvage left ventricular (LV) myocardium, improve LV function, and enhance long-term survival.

The proponents of pharmacologic therapy for STEMI highlight its widespread availability to the broad cross-section of patients worldwide, the lack of dependence on operator experience or institutional resources, and the ability to rapidly apply such therapy in the emergency department or even prior to hospital arrival without the sometimes formidable logistics of transfer to an interventional facility.[1–3] Dissatisfaction with pharmacologic therapy is primarily related to: (i) suboptimal reperfusion rates, (ii) the presence of recurrent ischaemia and re-infarction, and (iii) the risk of intracranial and systemic bleeding complications.[4]

Enthusiasm for primary percutaneous coronary intervention (PCI) has been fuelled in part by a systematic overview indicating that primary PCI was more effective than fibrinolysis in the therapy of STEMI.[5] Although a significant mortality difference was evident favouring PCI, the largest contribution of PCI's advantage over fibrinolysis was a reduction in re-infarction. In addition several methodological concerns have been raised about this report leading some to consider it as hypothesis generating rather than a definitive basis for a change in practice.[1,6]

Given the uncertainty as to which strategy is optimal, and the appreciation of the importance of mechanical co-intervention for patients with failed fibrinolysis, we designed a feasibility study to compare outcomes in patients who underwent expeditious primary PCI with those receiving pharmacologic therapy at the earliest point of care, with an emphasis on pre-hospital randomization and treatment. Also, within the cohort receiving pharmacologic therapy, standard care was applied to half of the group whereas the other half underwent mandatory invasive management within 24 h of enrolment including protocol-specified rescue PCI.

METHODS

Patient population

The Which Early ST-elevation MI Therapy (WEST) study involved four metropolitan Canadian communities (Edmonton, Halifax, Montreal, and Vancouver). Patients with STEMI in whom reperfusion therapy (primary PCI, fibrinolysis or transfer for rescue PCI) was feasible within 3 h of randomization were enrolled. The protocol emphasized expedited care with ECG, randomization and therapy undertaken pre-hospital where possible, and direct communication to PCI teams to enhance their state of readiness.

Eligible patients were male or non-pregnant females (≥18 years) with symptoms presumed secondary to STEMI lasting at least 20 min accompanied by ECG evidence of high risk. These included: ≥2 mm of ST-elevation in two or more contiguous precordial leads or limb leads; or ≥1 mm ST-elevation in two or more limb leads coupled with ≥1 mm ST-depression in two or more contiguous precordial leads (total ST-deviation ≥4 mm) or presumed new left bundle branch block. Patients were excluded if primary PCI was deemed to be available

within 1 h of diagnosis, or if contraindications to fibrinolysis, prior coronary bypass grafting (CABG), or glycoprotein IIb/IIIa antagonist use within 7 days existed.

Study design, treatments, and endpoints

We intended to enrol 100 patients in each of the three treatment arms in this feasibility study. All patients received aspirin (160–325 mg) and subcutaneous enoxaparin (1 mg/kg) at randomization with subsequent use recommended every 12 h for a minimum of 72 h; additional intravenous enoxaparin (0.3–0.5 mg/kg) was permitted during PCI in Group C and its use post-PCI was discretionary. Patients were randomized in open label fashion to one of three treatment groups. Group A received weight-adjusted tenecteplase (TNK) followed by the usual standard of care. Group B also received weight-adjusted TNK but underwent mandatory invasive management within 24 h of enrolment including protocol-specified rescue PCI, if the admission ST-elevation failed to decrease by ≥50% at 90 min after TNK therapy or if haemodynamic or electrical instability occurred. Group C patients underwent primary PCI with a clopidogrel 300 mg loading dose administered along with ASA and enoxaparin on study entry. Abciximab was recommended for Group C and for use in all PCI procedures in each treatment group unless performed within 3 h of fibrinolytic therapy. Clopidogrel use was employed in Groups A and B according to ACC/AHA PCI guidelines.

The primary efficacy endpoint of this study was a 30-day composite of death, re-infarction, refractory ischaemia, congestive heart failure, cardiogenic shock and major ventricular arrhythmia. The individual components were also examined. Definitions are provided in Appendix 2. Two experienced observers blinded to treatment allocation undertook central adjudication of re-infarction, refractory ischaemia, major ventricular arrhythmia, and the indications for rescue PCI.

Secondary efficacy endpoints included 90- and 180 min ST-resolution (according to the Schroeder method) and the infarct size was assessed using the Selvester QRS score and peak creatinine kinase (CK).[7,8] Core laboratories were established where blinded assessments were undertaken for ECG, NT-pro-brain natriuretic peptide (NT-proBNP) and angiographic measurements as noted in Appendix 3.

Safety outcomes included the occurrence of intracranial haemorrhage, disabling stroke, and major systemic bleeding. Finally, we assessed the composite of the primary efficacy and safety endpoints.

The protocol was approved by each institutional Ethics Review Board and a Data and Safety Monitoring Board oversaw the study. WEST was registered at www.ClinicalTrials.gov (identifier NCT00121446) on 13 July 2005.

Statistical analysis

Data were analysed according to intention-to-treat principles and are presented as proportions for categorical variables and as medians and interquartile ranges (IQR) for continuous variables. Data were compared across the treatment groups using chi-square tests, Fisher's exact test, and Kruskal–Wallis tests where appropriate. Repeated measures techniques were used to analyse the variance of NT-proBNP measures across the three collection periods (baseline, 72 h and 30 days).

The WEST study was designed to test the non-inferiority of Groups A and B relative to Group C. In the event of no difference in the primary efficacy composite endpoint between the two fibrinolytic arms, i.e. Groups A and B, we pre-specified a comparison between their combined result and the primary PCI arm, i.e. Group C. Comparisons were undertaken using confidence intervals (CI) with the expectation that a relative minimally important difference (rMID) in the incidence of the primary endpoint of 15% would be considered as evidence for the non-inferiority of pharmacologic therapy relative to primary PCI.

Kaplan–Meier estimates were plotted for the primary efficacy endpoint and 30-day death/re-MI according to the treatment groups. Unadjusted Cox regression with 90% CI was also used in the survival analysis of 30-day death and death/re-MI. Rates of the primary efficacy endpoint were also risk-adjusted to explore the possibility of imbalance of baseline characteristics among the study treatment groups. Using logistic regression techniques, two approaches were applied to develop a model for the primary efficacy endpoint: (i) simplified model based on age, heart rate, systolic blood pressure, Killip class, and anterior MI (top five predictors in the GUSTO I 30-day mortality model);[9] (ii) full model considering all clinically and statistically significant predictors of the outcome. The primary efficacy endpoints were then adjusted by the observed vs. expected ratio.

Pre-specified subgroup analyses included pre-hospital vs. inhospital randomization and time from symptom onset to randomization (≤2 h vs. >2 h).

The data were housed and analysed at the University of Alberta. All analyses were performed using SPSS 13.0 with the exact tests module (SPSS Inc., Chicago, IL, USA).

RESULTS

In Table 1, the baseline characteristics for the three treatment groups are shown. Key baseline characteristics were well balanced across the three treatment groups, although patients in Group B were slightly younger, had fewer anterior MIs and were more frequently in Killip Class I. As illustrated in Table 2 there was excellent adherence to protocol-mandated pharmacotherapy, including near universal use of clopidogrel and 97% use of

Table 1 Baseline patient characteristics according to study treatment groups (intention to treat)

	Intention to treat			All
	Group A	Group B	Group C	
n	100	104	100	304
Age, median (IQR) (years)	58 (51–69)	57 (50–67)	60 (49–71)	58 (50–69)
Gender (female)	25 (25.0)	19 (18.3)	18 (18.0)	62 (20.4)
Hypertension (yes)	37 (37.0)	56 (53.8)*	33 (33.0)	126 (41.4)
Diabetes mellitus, yes (total)	18 (18.0)	8 (7.7)	16 (16.0)	42 (13.8)
Family history of early CAD (yes)	39 (39.0)	44 (42.3)	34 (34.0)	117 (38.5)
History of angina (yes)	25 (25.0)	31 (29.8)	18 (18.0)	74 (24.3)
Previous MI (yes)	14 (14.0)	12 (11.5)	12 (12.0)	38 (12.5)
Previous PCI (yes)	9 (9.0)	8 (7.7)	5 (5.0)	22 (7.2)
Smoking status (current smoker)	45 (45.0)	53 (51.0)	38 (38.0)	136 (44.7)
MI location on Q-ECG (anterior)	42 (42.0)	37 (35.6)	42 (42.0)	121 (39.8)
Killip class				
I	93 (93.9)	99 (97.1)	93 (95.9)	285 (95.6)
II	6 (6.1)	3 (2.9)	4 (4.1)	13 (4.4)
Systolic BP, median (IQR) (mmHg)	140 (12–160)	140 (128–160)	145 (124–160)	141 (124–160)
Diastolic BP, median (IQR) (mmHg)	83 (71–92)	85 (71–98)	80 (70–96)	83 (70–96)
Pulse, median (IQR) (bpm)	75 (65–85)	72 (62–84)	75 (62–88)	74 (63–86)
Weight, median (IQR) (kg)	78 (63–87)	84 (71–97)	80 (67–90)	80 (67–91)
Height, median (IQR) (cm)	169 (162–177)	173 (166–180)	173 (162–178)	173 (163–178)

*$P = 0.006$.

abciximab in the 91 patients undergoing primary angioplasty in Group C. In contrast, 48% of the 91 patients undergoing PCI within 24 h of randomization in Group B received abciximab. In Table 3, median times from symptom onset to protocol-mandated therapy and procedures are shown for the overall population, as well as for those patients randomized pre-hospital (n = 121) vs. in-hospital (n = 183). Once randomization occurred, study drugs were administered expeditiously and the overall median time from symptom onset to PCI in Group C was rapid at 176 min. Group C patients randomized pre-hospital also received their PCI ~1 h earlier than those randomized in hospital.

Of the Group B patients, 102 underwent cardiac catheterization within 24 h, 89 of who received in-hospital revascularization with one additional patient revascularized by 30 days—of these eight patients received CABG. In Group C, 98 patients underwent angiography, 91 underwent in-hospital PCI, and 93 patients had revascularization by 30 days—of these three patients had CABG. Revascularization was also performed in-hospital in 60 Group A patients and by 30 days in 65 patients.

Protocol-mandated rescue angioplasty was undertaken in 28% of Group B patients. An additional nine patients in Group B met the ECG criteria for early rescue: three of these had early angiography without PCI, four had angiography and PCI within the 24 h post-randomization window, and two patients did not undergo angiography. 14 patients (14%) in Group A underwent rescue PCI, a median of 197 min after randomization (IQR 172–280 min). Coronary stents were used in over 97% of all patients undergoing PCI. Initial angiographic findings prior to PCI in Group C patients following ASA, enoxaparin, and 300 mg clopidogrel loading revealed that

Table 2 Summary of protocol-mandated pharmacotherapy

	Group A	Group B	Group C	All
n	100	104	100	304
ASA				
Given within 12 h or at index event	99 (99.0)	104 (100)	98 (98.0)	301 (99.0)
Clopidogrel given instead of ASA	1 (1.0)	0 (0.0)	2 (2.0)	3 (1.0)
Discharged on ASA	91 (91.0)	101 (97.1)	92 (92.0)	284 (93.4)
Discontinued prematurely	7 (7.0)	4 (3.8)	4 (4.0)	15 (4.9)
Enoxaparin				
Given at index event	98 (98.0)	102 (98.1)	98 (98.0)	298 (98.0)
Discontinued prematurely	35 (35.7)	39 (38.2)	13 (13.0)	87 (29.2)
Bleeding [*n* (%) of those discontinued prematurely]	3 (8.6)	5 (12.8)	2 (13.3)	10 (11.2)
Physician discretion	23 (65.7)	24 (61.5)	7 (53.8)	54 (62.1)
Other	9 (25.7)	10 (25.6)	3 (23.1)	22 (25.3)
TNK				
Given at randomization	98 (98.0)	103 (99.0)	–	
Clopidogrel				
Given at index event	–	–	97 (97.0)	

30% had TIMI 2 or 3 flow. In the 90 patients who underwent PCI (with complete angiographic data), 90% had TIMI 3 and 7% had TIMI 2 flow at the conclusion of their procedure. In the 85 Group B patients undergoing PCI, 81% had TIMI 3 and 12% had TIMI 2 flow at the conclusion of their procedure.

In Table 4, the primary efficacy and safety endpoints are shown. No statistically significant differences were observed in the primary composite endpoint or any of its components. The 30-day mortality rate was generally low, particularly in Groups B and C. Group B tended to have lower rates of heart failure and cardiogenic shock, whereas the lowest rate of recurrent MI was in Group C. There were no intracranial haemorrhages, infrequent major systemic bleeding, and no significant safety differences between treatment groups.

Figure 1 demonstrates the Kaplan–Meier curves for the 30-day composite primary efficacy endpoint. Given that there was no significant difference in the primary efficacy endpoint between Groups A and B (25 vs. 24%) these groups were combined when assessing the non-inferiority between fibrinolysis and primary PCI. As shown in Figure 2, the relative difference in the primary efficacy endpoint between Groups A, B and Group C fell within the 15% rMID (Figure 3), however, the 90% confidence limits were broad and hence, this finding is not definitive. The primary efficacy endpoint, risk-adjusted for the only significant predictor i.e. age, was similar across the three treatment groups (Group A: 25.0%; Group B: 24.6%; Group C: 22.5%). No significant mortality difference existed between groups {Group B vs. A: unadjusted hazard ratio (HR) 0.23 [90% CI (0.04–1.46)]; Group C vs. A: 0.25 (0.04–1.54); Group B vs. C: 0.95(0.09–9.7)}. In Figure 3, the composite of 30-day death and recurrent MI is shown. Patients in Group A were significantly more likely to experience a combination of death and recurrent MI than in Group C (Group C vs. A: unadjusted HR 0.29, 90% CI(0.11–0.74); P-logrank = 0.021) whereas there was no difference between Group B and C (Group B vs. C: 1.73 (0.62–4.8); P-logrank = 0.378).

Table 3 Median (IQR) minutes from symptom (Sx) onset to treatment in all patients and according to pre-hospital vs. in-hospital randomization

	Group A	Group B	Group C
Overall ($n = 304$)	100	104	100
Sx onset to randomization	105 (63–158)	114 (67–172)	100 (70–160)
Sx onset to first study drug[a]	113 (74–179)	130 (75–185)	112 (80–164)
Sx onset to PCI	395 (294–3711), $n = 58$	425 (288–1331), $n = 81$[b]	176 (140–280), $n = 91$
Sx onset to rescue PCI	299 (270–325), $n = 14$	277 (213–381), $n = 29$	–
Sx onset to non-rescue PCI	1498 (341–5465), $n = 44$	926 (398–1454), $n = 52$	–
First medical contact[c] to first study drug[a]	51 (37–75)	54 (38–77)	54 (36–69)
First medical contact[c] to PCI	350 (245–3561)	324 (218–1216)	127 (93–159)
Pre-hospital ($n = 121$)	42	42	37
Sx onset to randomization	85 (63–147)	76 (50–114)	72 (49–98)
Sx onset to first study drug	91 (70–156)	91 (57–142)	82 (58–103)
Sx onset to PCI	364 (273–2056), $n = 27$	371 (215–912), $n = 31$	140 (115–171), $n = 33$
Sx onset to rescue PCI	274 (254–351), $n = 8$	217 (193–342), $n = 15$	–
Sx onset to non-rescue PCI	484 (282–3076), $n = 19$	810 (393–1343), $n = 16$	–
First medical contact[c] to first study drug[a]	46 (35–55)	44 (36–57)	41 (32–53)
First medical contact[c] to PCI	331 (223–1720)	245 (196–856)	104 (88–126)
In-hospital ($n = 183$)	58	62	63
Sx onset to randomization	105 (74–160)	135 (91–178)	124 (89–185)
Sx onset to first study drug	119 (86–180)	146 (102–189)	137 (103–201)
Sx onset to PCI	1441 (303–5494), $n = 31$	532 (338–1414), $n = 50$	207 (167–292), $n = 58$
Sx onset to rescue PCI	302 (293–333), $n = 6$	343 (275–419), $n = 14$	–
Sx onset to non-rescue PCI	3216 (376–5547), $n = 25$	1137 (406–1474), $n = 36$	–
First medical contact[c] to first study drug[a]	61 (43–83)	67 (42–92)	61 (40–85)
First medical contact[c] to PCI	1396 (260–5403)	606 (259–1308)	143 (100–169)

[a]First study drug refers to TNK in Groups A and B and to enox in Group C.
[b]Protocol-mandated procedure.
[c]First medical contact refers to ambulance arrival or hospital arrival.

In the nearly 40% of patients randomized to treatment in the pre-hospital setting, 22.3% experienced the primary efficacy endpoint compared with 25.1% in those randomized upon arrival to hospital (P = 0.587). There was no statistically significant difference across the treatment groups in either setting.

As pre-specified, the primary efficacy endpoint occurred in 38 (20.7%) of the 184 patients who were randomized ≤2 h of symptom onset, compared to 35 (29.4%; P = 0.09) of the 119 patients randomized beyond the 2 h mark. This difference was especially evident within Group C patients where there was a two-fold increase in rates in patients randomized beyond 2 h [16.4% (≤2 h) vs. 34.2% (>2 h); P = 0.052].

In Table 5, the ECG data are shown. The baseline sum of ST-deviation was similar across the treatment groups. At 180 min after randomization there was a trend towards more patients achieving complete, i.e. 70% resolution in Group B as compared with Groups A and C. Discharge ECG QRS scores indicated a trend (P = 0.14) towards a higher score i.e. a greater % of LV infarction in Group C. Median peak (IQR) CK data within the three treatment groups revealed IU values of 1199(548–2351), 1590(771–2624), and 1833(852–3649) for Groups A, B, and C respectively, P = 0.045.

Figure 4 illustrates the median NT-proBNP in pg/mL acquired at baseline, 72 h and 30 days. No significant difference in baseline

Table 4 Efficacy and safety endpoints

	Group A	Group B	Group C	All
n	100	104	100	304
Primary efficacy endpoint at 30 days	25 (25.0)	25 (24.0)	23 (23.0)	73 (24.0)
Death	4 (4.0)	1 (1.0)	1 (1.0)	6 (2.0)
Re-MI	9 (9.0)	6 (5.8)	3 (3.0)	18 (5.9)
Heart failure	15 (15.0)	15 (14.4)	18 (18.0)	48 (15.8)
Cardiogenic shock	6 (6.0)	4 (3.8)	7 (7.0)	17 (5.6)
Refractory ischaemia	0 (0.0)	3 (2.9)	0 (0.0)	3 (0.1)
Major ventricular arrhythmias	1 (1.0)	1 (1.0)	1 (1.0)	3 (1.0)
Primary safety endpoint during index hospitalization				
Intracranial haemorrhage	0	0	0	0
Non-haemorrhagic stroke	0	1 (1.0)	1 (1.0)	2 (0.1)
Major systemic bleeding	1 (1.0)	2 (1.9)	1 (1.0)	4 (1.3)
Composite of primary efficacy and safety endpoint	26 (26.0)	26 (25.0)	24 (24.0)	76 (25.0)

median NT-proBNP measures was observed across the three treatment groups. In the repeated measure analysis, which was based on 184 patients with complete NT-proBNP at all 3 collection times, there was a significant trend in the mean NT-proBNP values from baseline to 30 days ($P < 0.001$) such that an increase was observed from baseline to 72 h but then a decline at 30 days. NT-proBNP values were significantly higher in Group C relative to Group A ($P = 0.019$) and to a lesser extent, Group B ($P = 0.092$).

DISCUSSION

Our study of STEMI patients focusing on early reperfusion treatment provides several novel findings. Reperfusion therapy with a contemporary pharmacologic regimen, coupled with a strategy of regimented rescue and routine invasive evaluation within 24 h of treatment, provides an excellent standard of care that is not different from timely expert PCI at experienced centres. We found no difference in the primary composite outcome across the three treatment groups even after adjustment for minor baseline differences. Moreover, there were no intracranial haemorrhages and a small but comparable incidence of non-haemorrhagic stroke and major bleeding.

What might account for our findings that differ from most prior comparisons in larger populations? Our strategy of establishing the diagnosis of STEMI at the first medical contact contributed to expedited randomization with a median time of 105 min from symptom onset. Early diagnosis was followed by expedited treatment, followed by triage and transport in the pre-hospital population. This contributed to the remarkably short times to both fibrinolysis and PCI treatments rarely achieved in prior STEMI clinical trials. The approximate 46 min interval between fibrinolytic treatment in Group B and primary PCI delivery in Group C is well aligned with prior evidence suggesting similar outcomes from both reperfusion methods evaluated in a systematic overview of prior comparisons.[10] Hence, the tendency towards more shock and CHF in Group C is of interest and reminiscent of the findings in the Comparison of Angioplasty and Pre-

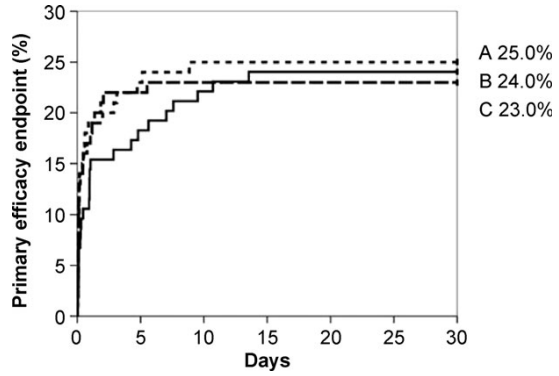


Figure 1 Kaplan–Meier curves of the primary efficacy endpoint according to study treatment groups. Group A ($n = 100$) is represented by the small dashed line; Group B ($n = 104$) by the solid line; Group C ($n = 100$) by the large dashed line.

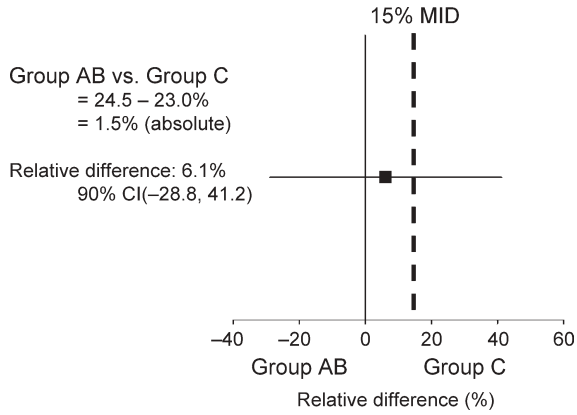


Figure 2 Relative difference in the primary efficacy endpoint between Groups A and B combined and Group C with 90% confidence limits and pre-specified 15% rMID boundary.

hospital Thrombolysis In Acute Myocardial Infarction trial (CAPTIM) where patients treated with fibrinolysis <2 hrs from symptom onset had lower mortality and cardiogenic shock than those randomized to PCI.[11] It is also aligned with the reduced prevalence of cardiogenic shock in the pre-hospital fibrinolysis vs. primary PCI group observed in the French nationwide USIC 2000 Registry.[12] These suggestive clinical trends are further supported by the higher peak CK data, discharge ECG QRS scores and elevated NT-proBNP values at days 3 and 30 found in Group C. Mandatory systematic and timely rescue PCI in Group B performed in 28% of patients may

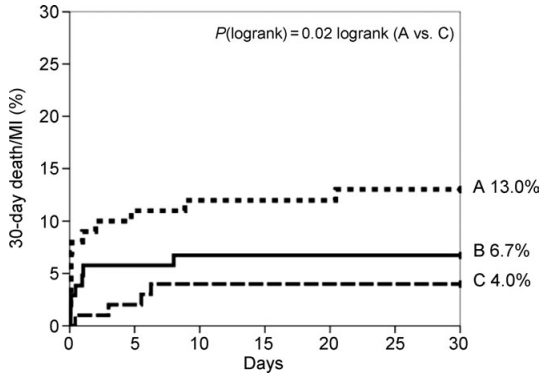


Figure 3 Kaplan–Meier curves of 30-day death/re-MI according to study treatment groups. Group A ($n = 100$) is represented by the small dashed line, Group B ($n = 104$) by the solid line, Group C ($n = 100$) by the large dashed line. Group C vs. A was statistically significant (logrank $P = 0.021$).

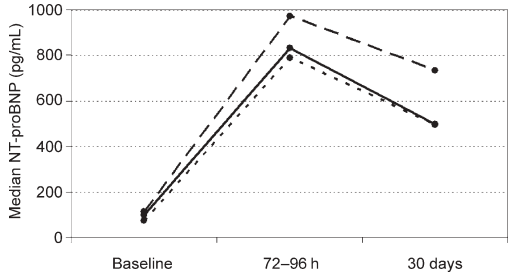


Figure 4 Median NT-proBNP in pg/mL at baseline, 72 h, and 30 days according to study treatment groups. Group A ($n = 72$–84) is represented by the small dashed line; Group B ($n = 75$–83) by the solid line; Group C ($n = 70$–87) by the large dashed line. NT-proBNP values were significantly higher in Group C both at 72 h ($P = 0.03$) and 30 days ($P = 0.007$) relative to Group A.

have further contributed to their favourable outcomes and is supported by the trend towards superior ST-resolution at 180 min.

Our study was not powered to show a definitive impact on mortality or the combination of death and MI. Notwithstanding this, our findings are consistent with the notion that a strategy of early fibrinolysis coupled with routine early invasive management (or timely rescue PCI, if warranted) results in rates of death and re-infarction comparable with those achieved with direct PCI.[11] Whereas prior comparative studies frequently indicate that re-MI constitutes the principal efficacy advantage for PCI this difference is known to be mitigated by the use of enoxaparin, clopidogrel, and timely mechanical co-intervention.[13–16] Interestingly, patients in Group A with later and lower rescue rates and less frequent overall revascularization appeared to fare less well than direct PCI patients, especially relating to the composite of death and re-MI. This finding is consistent with the GRACIA-1 study where patients randomized six hours after fibrinolysis to angiography and intervention within 24 h vs. an ischaemia-guided conservative approach tended to have a reduced

Table 5 Electrocardiographic data: ST-deviation, ST-resolution, and QRS score

	% of LV	Group A	Group B	Group C
Sum of ST-deviation				
n		100	104	100
Baseline		11.8 (7.5–17)	10 (6.5–15.5)	11.3 (7–16.5)
ST-resolution				
90 min				
n		90	97	
≥50% resolution		62 (68.9)	59 (60.8)	
≥70% resolution		39 (43.3)	44 (45.4)	
180 min				
n		79	85	79
≥50% resolution		58 (73.4)	71 (83.5)	62 (78.5)
≥70% resolution		48 (60.8)	59 (69.4)	44 (55.7)
QRS score on discharge ECG				
n		85	92	79
0–1	0–3	20 (20.0)	15 (14.4)	10 (10.0)
2–4	6–12	27 (27.0)	36 (34.6)	22 (22.0)
>4	>12	38 (38.0)	41 (39.4)	49 (49.0)

rate of death or re-infarction.[17] It is noteworthy that coronary interventions in GRACIA-1 occurred a mean of 17 h after fibrinolysis whereas in ASSENT-4 PCI a strategy of immediate PCI (1–3 h) after TNK was associated with higher in-hospital mortality, cardiac ischaemic complications, and stroke as compared with those who received direct PCI alone.[18] Hence, the optimal frequency and timing of co-intervention in patients receiving fibrinolysis remains uncertain but systematic adherence to STEMI rescue guidelines is likely a key factor. Our data are also well aligned with the recently reported REACT study.[16] In that trial, when systematic rescue PCI was employed early after failed fibrinolysis in STEMI patients, their composite outcome of death, re-MI, cerebrovascular accident, and severe heart failure was significantly superior to those receiving repeat fibrinolysis or conservative therapy. Overall times from symptom onset to randomization were well balanced and short in our study, and the expected advantage of pre-hospital randomization was also evident. Hence, our strategy of pre-hospital randomization and treatment not only substantially shortened the time to pharmacologic therapy but also abbreviated the time to PCI by over 1 h by ensuring enhanced readiness at the receiving PCI centres.

Our choice and dosing of enoxaparin deserves discussion given the findings of ASSENT 3 and 3 PLUS.[19,20] We chose to omit the IV enoxaparin bolus and allow for supplemental IV dosing in the setting of PCI. Given the short time lapse from initial dosing of enoxaparin, the time to adequate anticoagulation was likely a more important issue in Group C.[21] However, systematic use of abciximab, known to favourably affect PCI outcomes in such patients was also employed.

Our study has some limitations that should be noted: because a screening log was not maintained and it was unblinded we cannot rule out bias. However the blind adjudication of clinical endpoints as

well as the core assessments of ECG, angiographic, NT-proBNP and CK data conducted without the knowledge of treatment assignment, make this unlikely. Because of the modest sample size, we cannot exclude the play of chance. For us to have reached a definitive non-inferiority conclusion (based on a 15% rMID and 90% CI with a composite endpoint of 24.0% in Group B and 23% in Group C), a trial would need to enrol 1625 patients in each arm or 2578 patients in each arm (based on a similar rMID and a 24.5% composite endpoint in a combined Group A and B vs. 23% in Group C).

In summary, our investigation provides novel data supporting the efficacy, safety and feasibility of a strategic pharmacologic approach that combines fibrinolysis with timely catheter co-intervention for patients who can be assessed early after symptom onset. This strategy is especially relevant to both pre-hospital and community hospital settings and its use in the current study should provide encouragement to regions where an integrated systems approach to the management of STEMI has not yet been undertaken. Although such a strategy requires 24-h/7 day access to interventional facilities, it may provide a more reasonable balance as it relates to the timing and frequency of their use. In the light of the failure of routine immediate intervention after fibrinolytic therapy recently reported in ASSENT-4 PCI coupled with persisting delays in accessing primary PCI, an approach focusing on pre-hospital care and other methods to ensure early treatment and timely and effective post-fibrinolytic rescue seems well positioned to provide a useful therapeutic option deserving of more definitive large-scale investigation.[18,22]

Our findings may particularly assist informing the design of such an initiative.

ACKNOWLEDGEMENTS
We would like to thank the many nurses, paramedical personnel, technical and administrative staff that contributed to WEST and the patients for their volunteer spirit. The study was supported by unrestricted research grants from Hoffman-La Roche and sanofi-aventis Canada and also Eli Lilly Canada.

Conflict of interest: P.W.A. has received speaker honoraria from Hoffman LaRoche and sanofi aventis; I.B. has received speaker honoraria from Hoffman LaRoche; C.B. has received speaker honoraria from Hoffman LaRoche; R.G. has received speaker honoraria from sanofi aventis; B.O. has received speaker honoraria from Hoffman LaRoche; P.T. has received speaker honoraria from Hoffman LaRoche and sanofi aventis; R.W. has received speaker honoraria from Hoffman LaRoche and sanofi aventis.

APPENDIX 1
WEST Steering Committee
Paul W. Armstrong (Chair)
Iqbal Bata
Christopher E. Buller
Edward Cain

James W. Christenson
Richard Gallo
G.B. John Mancini (Director of Core Angiographic Laboratory)
Blair O'Neill
David Petrie
Pierre Theroux (Director of Biomarker Core Laboratory)
Andrew Travers
John Webb
Robert C. Welsh
Biostatistical Analysis: Cynthia M. Westerhout and Wei-Ching Chang
Project Management: Monica Adam and Wanda Sutherland
ECG Core Laboratory: Yuling Fu
Data Management: EPICORE Centre, University of Alberta
Editorial Assistance: Durenda Tremblay

APPENDIX 2

Endpoint definitions

(1) Refractory ischaemia: Symptoms of ischaemia with ST-deviation or definite T-wave inversion persisting for at least 10 min despite medical management while in hospital.

(2) Recurrent MI (myocardial re-infarction): (i) In the first 18 h after randomization: (a) Recurrent signs and symptoms of ischaemia at rest accompanied by new or recurrent ST-segment elevations of ≥0.1 mV in at least two contiguous leads lasting ≥ 30 min.

(ii) After 18 h: (a) New Q-waves (by Minnesota Code Criteria) in two or more leads and/or enzyme evidence of re-infarction: re-evaluation of CK-MB or troponin to above the upper limit of normal and increased by >50% over the previous value.

(b) The total CK must either be re-elevated to two times or more the upper limit of normal and increased by >25% or be re-elevated to >200 U/mL over the previous value.

(1) If re-evaluated to less than two times the upper limit of normal, the total CK must exceed the upper limit of normal by >50% and exceed the previous value by two-fold or be re-elevated to >200 U/mL.

(iii) Re-infarction after PTCA (± stenting):

(a) CK greater than three times the upper limit of normal and 50% greater than the previous value and/or new Q-waves (Minnesota Code) in two or more contiguous leads.

(iv) Re-infarction after CABG surgery:

(a) CK greater than five times the upper limit of normal and ≥50% greater than the previous value and/or new Q-waves (Minnesota Code) in two or more contiguous leads.

(3) Congestive heart failure:

(i) Physician's decision to treat CHF with a diuretic, intravenous inotropic agent or intravenous vasodilator and either

(a) the presence of pulmonary edema or pulmonary vascular congestion on chest X-ray believed to be of cardiac cause or

(b) at least two of the following:

(1) rales greater than one-third up the lung fields believed to be due to CHF.

(2) PCWP >18 mmHg

(3) Dyspnoea, with documented pO_2 less than 80 mmHg on room air or O_2 saturation, 90% on room air, without significant lung disease.

(4) Cardiogenic shock: The manifestation of vascular collapse and shock (SBP < 90 mmHg for at least 30 min or SBP > 90 mmHg

after inotropic or intra-aortic balloon support with a cardiac index <2.2 L/min/m^2 or <2.5 L/min/m^2 inotropic or intraaortic balloon support, peripheral signs of hypoperfusion, and chest X-ray with pulmonary edema.
(5) Major ventricular arrhythmias: Ventricular arrhythmias >6 h after randomization requiring electrical cardioversion/defibrillation.
(6) Major bleeding: Bleeding that causes haemodynamic compromise requiring blood or fluid replacement, inotropic support, ventricular assist devices, surgical intervention, or CPR to maintain a sufficient cardiac output.

APPENDIX 3

NT-proBNP

NT-pro-brain natriuretic samples were allowed to clot for 35–45 min and the blood centrifuged within 1 h of collection for 15 min at 1700 g and shipped in dry ice to a central laboratory (Montreal Heart Institute) where it was stored at -70•C. Samples were acquired at baseline, 72 h after admission, and at 30 days. Samples were batch-analysed at the end of the study by an electrochemiluminescence immunoassay with Roche Elecsys Instrument and Elecsys NT-proBNP Reagent kit (Roche Diagnostics, Indianapolis, USA) with an analytical range of 5–35000 pg/mL and respective intra-assay and inter-assay variability of 8 and 4%.

ECG

ST-segment measurements were acquired manually with magnification and hand-held callipers to the closest 0.05 mV at the J point. Per cent resolution was acquired according to the method of Schroeder. QRS scoring was analysed using the method of Selvester, where each point in the score represents ~3% of the left ventricle.[6,7]

Angiography

All patients in Groups B and C had angiographic analysis undertaken in a core facility to assess culprit coronary artery TIMI flow. These assessments were performed by observers blinded to treatment assignment.

REFERENCES

1. Armstrong PW, Collen D, Antman E. Fibrinolysis for Acute Myocardial Infarction. Circulation 2003;107:2533–2537.
2. Morrison LJ, Verbeek PR, McDonald AC, Sawadsky BV, Cook DJ. Mortality and pre-hospital thrombolysis for acute myocardial infarction: a meta analysis. JAMA 2000;283:2686–2692.
3. Bjorklund E, Stenestrand U, Lindback J. Pre-hospital thrombolysis delivered by paramedics is associated with reduced time delay and mortality in ambulance-transported real-life patients in ST-elevation myocardial infarction. EHJ 2006;27:1146–1152.
4. Grines CL, Serruys P, O'Neill WW. Fibrinolytic therapy. Is it a treatment of the past? Circulation 2003;107:2538–2542.
5. Keeley EC, Boura JA, Grines CL. Comparison of primary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23

randomized trials. Lancet 2003;361:13–20.
6. Antman E, Anbe D, Armstrong PW, Bates E, Green LA, Hand M, Hochman JH, Krumholz H, Kushner FG, Lamas GA, Mullany CJ, Ornato JP, Pearle DL, Sloan MA, Smith SC, Antman EA Jr, Smith SC, Alpert JS Jr, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK, Ornato JP. 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; J Am Coll Cardial 2004;44:671–679; Can J Cardial 2004;20:977–1025.
7. Schroder R, Wegscheider K, Schroder K, Dissmann R, Meyer-Sabellek W. Extent of early ST segment elevation resolution: a strong predictor of outcome in patients with acute myocardial infarction and a sensitive measure to compare thrombolytic regimens. A substudy of the International Joint Efficacy Comparison of Thrombolytics (INJECT) trial. J Am Coll Cardiol 1995;26:1657–1664.
8. Anderson WD, Wagner NB, Lee KL, White RD. Evaluation of a QRS scoring system for estimating myocardial infarct size. VI: identification of screening criteria for non-acute myocardial infarcts. Am J Cardiol 1988;61:729–733.
9. Lee KL, Woodlief LH, Topol EJ, Weaver WD, Betriu A, Col J, Simoons M, Aylward P, Van de Werf F, Califf RM, for the GUSTO-I Investigators. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction. Results from an international trial of 41,021 patients. Circulation 1995;91:1659–1668.
10. Nallamothu BK, Bates ER. Percutaneous coronary intervention vs. fibrinolytic therapy in acute myocardial infarction: is timing (almost) everything? Am J Cardiol 2003;92:824–826.
11. Steg PG, Bonnefoy E, Chabaud S, Lapostolle F, Dubien P-Y, Cristofini P, Leizorovicz A, Touboul P, for the Comparison of Angioplasty Prehospital Thrombolysis In Acute Myocardial Infarction (CAPTIM) Investigators. Impact of time to treatment on mortality after prehospital fibrinolysis or primary angioplasty: data from the CAPTIM randomized clinical trial. Circulation 2003;108:2851–2856.
12. Danchin N, Blanchard D, Steg PG, Sauval P, Hanania G, Goldstein P, Cambou JP, Gueret P, Vaur L, Boutalbi Y, Genes N, Lablanche JM, for the USIC 2000 Investigators. Impact of prehospital thrombolysis for acute myocardial infarction on 1-year outcome. Results from the French nationwide USIC 2000 registry. Circulation 2004;110:1909–1915.
13. Andersen HR, Nielsen TT, Rasmussen K, Thuesen L, Kelbaek H, Thayssen P, Abildgaard U, Pedersen F, Madsen JK, Grande P, Villadsen AB, Krusell LR, Haghfelt T, Lomholt P, Husted SE, Vigholt E, Kjaergard HK, Mortensen LS, for the DANAMI-2 Investigators. A

comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. New Engl J Med 2003;349:733–742.
14. Antman EM, Louwerenburg HW, Baars HF, Wesdorp JCL, Hamer B, Bassand J-P, Bigonzi F, Pisapia G, Gibson CM, Heidbuchel H, Braunwald E, Van de Werf F, for the ENTIRE-TIMI 23 Investigators*. Enoxaparin as adjunctive antithrombin therapy for ST-elevation myocardial infarction: results of the ENTIRE-Thrombolysis in Myocardial Infarction (TIMI) 23 trial. Circulation 2002;105:1642–1649.
15. Sabatine M, Cannon C, Gibson M, Lopez-Sendon J, Montalescot G, Theroux P, Claeys M, Cools F, Hill K, Skene A, McCabe C, Braunwald E, for the CLARITY-TIMI 28 Investigators. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. New Engl J Med 2005;352:1179–1189.
16. Gershlick AH, Stephens-Lloyd A, Hughes S, Abrams KR, Stevens SE, Uren NG, de Belder A, Davis J, Pitt M, Banning A, Baumbach A, Shiu MF, Schofield P, Dawkins KD, Henderson RA, Oldroyd KG, Wilcox R, Rescue angioplasty after failed thrombolytic therapy for acute myocardial infarction. N Engl J Med 2005;353:2758–2768.
17. Fernandez-Avile´s F, Alonso J, Castro-Beiras A, Vazquez N, Blanco J, Alonso-Briales J, Lope´z-Mesa J, Ferna´ndez-Vazquez F, Calvo I, Martinez-Elbal L, San Roman JA, Ramos B, on behalf of the GRACIA (Grupo de Ana´lisis de la Cardiopatı´a Isque´mica Aguda) Group. Routine invasive strategy within 24 h of Thrombolysis vs. ischaemia-guided conservative approach for acute myocardial infarction with ST-segment elevation (GRACIA-1): a randomised controlled trial. Lancet 2004;364:1045–1053.
18. ASSENT 4 Investigators. Primary vs. tenecteplase facilitated percutaneous coronary intervention in patients with ST-elevation acute myocardial infarction: the ASSENT-4 PCI randomized trial. Lancet 2006;367:569–578.
19. Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. Lancet 2001;358:605–613.
20. Wallentin L, Goldstein P, Armstrong PW, Granger C, Adgey AAJ, Arntz HR, Bogaerts K, Danays T, Lindahl B, Ma¨kija¨rvi M, Verheugt F, Van de Werf F. Efficacy and safety of tenecteplase in combination with the lowmolecular weight heparin enoxaparin or unfractionated heparin in the prehospital setting: the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 PLUS randomized trial in acute myocardial infarction. Circulation 2003;108:135–142.
21. Buller CE, Pate GE, Armstrong PW, O'Neill BJ, Webb JG, Gallo R. Welsh RC. Catheter thrombosis during primary percutaneous coronary intervention for acute ST-elevation myocardial infarction despite subcutaneous low-molecular weight heparin, aspirin, clopidogrel

and abciximab pretreatment. Can J Cardiol 2006;22:511–515.
22. Nallamothu BK, Bates ER, Herrin J, Wang Y, Bradley EH, Krumholz HM, for the NMRI Investigators. Times to treatment on transfer patients undergoing primary percutaneous coronary intervention in the United States: National Registry of Myocardial Infarction (NMRI)-3/4 analysis. Circulation 2005;111:761–767.

Summary and Conclusions

William Shakespeare once said "If you can look into the seeds of time, and say which grain will grow and which will not, speak then unto me."; and even today, this desire to foresee the future continues. Throughout this thesis, we characterised various approaches to and purposes of risk assessment in ACS patients with aim of improving patient care and outcomes.

Approaches to risk prediction in acute coronary syndromes

A constellation of factors, both tangible and intangible, can guide the likelihood of an adverse event in an ACS patient. In the first section of this thesis, three approaches to assess this risk were presented, ranging from multivariable logistic regression to methods novel to cardiovascular medicine, dynamic risk modelling and multilevel modelling. Assessing the risk of short- and long-term adverse events in non-ST-elevation ACS patients led to several important findings: namely, the striking prognostic value of quantitative ST-segment depression and multiple biomarkers including NT-proBNP, troponin T and CRP (**Chapter 1**). Whereas demographics, medical history and initial clinical indicators made up the classic risk profile of these patients, the GUSTO IV ACS trial was able to provide strong evidence for the value of these novel indicators. In addition to developing a clinical risk tool based on these factors, our understanding of the disease was also enhanced. In particular, CRP was only predictive of 1-year death, signally the long-term influence of inflammation.

Chapter 2 focused on an innovative approach to risk assessment, dynamic risk modelling. This method extends beyond traditional baseline risk models by forecasting future events based on all data accumulated up until clinically relevant time points. A series of logistic regression models were developed in over 6000 ST-elevation MI patients enrolled in the ASSENT-3 trial to predict 30-day mortality at the following key “forecasting periods”: Baseline, 3 hours, Day 2 and Day 5. A key feature of dynamic modelling is the ability to assess the change in prognostically relevant factors over time. For instance, the relative importance of traditional baseline characteristics, such as age, heart rate and systolic blood pressure was attenuated over time with the occurrence of complications such as stroke and heart failure. This continually updated appraisal of risk may help to advise medical decision making above and beyond what is known initially at hospital admission.

The region or country in which a patient is treated is often cited as having some bearing on the treatment received and/or the risk of adverse events, yet the origins of

these differences are not well characterised. Contextual factors such as provider characteristics, socioeconomic and cultural factors, health care practices and policies may play a role but often these data are not available to perform formal evaluations. To further elucidate the amount of variation in the treatment and outcomes in non-ST-elevation ACS patients due to patient- versus non-patient-level factors, multilevel modelling techniques were applied to the GUSTO IV ACS trial (**Chapter 3**). Across the 24 participating countries, there were significant differences in the processes of care (i.e., revascularisation) and outcomes (i.e., 30-day death/MI and1-year mortality). However, after accounting for key patient- and hospital-level factors, the inter-country differences disappeared; and in fact, patient-level factors were attributable for between 96% and 99% of the total variation in these outcomes. These results point to the potential fallacy in concluding that international differences exist without accounting for the variation related to lower-level factors such as hospital and patient characteristics. Although the hospital-level variation seemed small, it was significant. The collection of data at this level in future studies may help to further explain these differences.

Unravelling the pathophysiology of acute coronary syndromes

The breadth of data collected in large-scale clinical trials provides unmatched opportunity for improving our understanding of ACS. In **Chapter 4**, the quantitative and central assessment of baseline ECGs in the GUSTO IV ACS trial identified patients with electrocardiographic left ventricular hypertrophy (LVH). This condition is not typically considered in the risk profile of ACS; thus, we sought to evaluate its association with mortality and the composite of death or MI, as well as any possible modulation of the effect by gender and/or NT-proBNP, a marker of hemodynamic stress. Of 7443 non-ST-elevation ACS patients, 8% had LVH, with women accounting for three quarters. Long-term survival analysis identified women with LVH as a particularly high-risk subgroup, whom may be targeted with increased vigilance.

Inflammation has been increasingly recognised for its role in the pathogenesis of coronary artery disease based on strong evidence supporting CRP and other inflammatory markers. Chronic infection with *Chlamydia pneumoniae* has in past been linked to the initiation of or contribution to plaque formation and destabilisation, but its relationship with adverse coronary events has yielded conflicting evidence. The findings from our nested case-control study in the GUSTO IV ACS trial did not support this infectious agent as an important risk factor in ACS (**Chapter 5**).

Stroke is an infrequent complication occurring early after non-ST-elevation ACS; however, the ensuing rates of morbidity and

mortality are high. Thus, identification of the factors associated with this event would be helpful in understanding the causes and mitigating these risks. Based on our analysis of six large-scale clinical trials in non-ST-elevation ACS patients, advanced age, prior stroke and elevated heart rate were among the strongest predictors of all-cause stroke within 30 days of randomisation (**Chapter 6**). The risk profile was not altered when predicting specifically non-haemorrhagic or haemorrhagic strokes. Of note, the study treatment, GPIs were not associated with higher risk of stroke. While the identification of these three indicators provides some insight, relying on them to predict the incidence of stroke deserves caution given the modest discriminatory power of the model.

Tailoring treatment in acute coronary syndromes

One of the purposes of risk assessment is to tailor treatment and resources to patients with the best benefit/harm ratio. If a therapy is effective in reducing the relative risk of adverse events uniformly across a broad spectrum of patients, then those at higher absolute risk will have larger absolute risk reductions from the therapy. A meta-analysis of the six large-scale clinical trials on the efficacy of GPIs in ACS addresses this concept relative to age (**Chapter 9**). While we observed a larger absolute risk reduction in death or MI with increasing age, a rise in the absolute risk of major bleeding was also revealed. Given this, we recommended that elderly patients be closely observed to manage these risks.

Although the optimal mechanism of reperfusion therapy remains under much debate, there is little disputing that shorter time to treatment results in improved outcomes in ST-elevation MI patients. Our pooled analysis of 22 clinical trials clearly demonstrated this. Moreover, patients who underwent primary PCI were significantly more likely to survive to 30 days compared to those treated with fibrinolysis, regardless of the treatment delay (**Chapter 10**). However, translating these findings to the 'real world' is a difficult challenge given that this setting is often more complex than the clinical trial environment. As a result, tailoring treatment to fit local or regional settings in favour of minimising the time to treatment should be emphasised. Novel therapeutic strategies, including pre-hospital triage and treatment and regimens combining early pharmacological treatment with timely angiography, are under investigation with this consideration in mind (**Chapter 11**).

CONCLUSIONS

As demonstrated in this thesis, *putting the future in service of the present* can serve a multitude of purposes and can be accomplished using a variety of techniques. While we have made significant progress since the dawn of the modern definition of risk with Pascal and de Fermat, there remains great potential to refine risk assessment. Specifically, risk assessment in ACS will benefit from the exploration of

new measures, statistical techniques and study designs. Innovative approaches to measuring previously unknown or nebulous factors (and/or improving current measures) and addressing more complex research questions will lead to a more comprehensive understanding of risk in these patients.

Although clinical trials are revered for their rich clinical data, they are also limited by select inclusion and exclusion criteria, which challenges the generalisability of the results. Registries and other population-based cohorts, however, have the tremendous potential to forego this limitation through the enhancement of the data collected. Regardless of the cohort under investigation, the serial collection of clinical indicators such as electrocardiograms, biomarkers and vital signs could significantly advance our understanding of the dynamic evolution of risk, and contextual data on institutions, countries and regions could help to complete the global picture of risk.

Finally, the destination of these efforts should focus on the patient. In the past, there has been a challenge in balancing statistical theory and clinical pragmatism, which may have stunted the uptake of risk assessment at the patient level. This gap, however, can be narrowed through fostering a culture of guided risk assessment as well as taking advantage of the technological revolution (e.g., electronic medical records, handheld computers, etc.).

Samenvatting en conclusies

William Shakespeare zei eens "If you can look into the seeds of time, and say which grain will grow and which will not, speak then unto me". Ook vandaag nog bestaat dit verlangen om in de toekomst te kunnen kijken. In dit proefschrift hebben we verschillende methoden en toepassingen van risico-evaluatie in ACS patiënten geschetst, met als doel de patiëntenzorg en uitkomsten te verbeteren.

Methoden van risico voorspelling in het acuut coronair syndroom

Een grote diversiteit aan factoren, grijpbaar en ongrijpbaar, kan bijdragen tot de kans op complicaties bij een ACS patiënt. In het eerste deel van dit proefschrift zijn drie methoden van risico evaluatie weergegeven, variërend van multivariabele logistische regressie tot methoden die nieuw zijn in de cardiovasculaire geneeskunde: dynamische risico modellering en multilevel modellering. Evaluatie van het risico van complicaties op korte en lange termijn in patiënten met non-ST-elevatie ACS, leidt tot diverse belangrijke bevindingen: opvallend was de prognostische waarde van kwantitatieve ST-segment depressie en diverse biomarkers, inclusief NT-proBNP, troponine T en CRP (Hoofdstuk 1). Terwijl het klassieke risicoprofiel van deze patiënten bestaat uit demografische gegevens, medische voorgeschiedenis en klinische indicatoren bij aanvang van de opname, was de GUSTO IV ACS studie in staat om harde bewijzen te leveren voor de waarde van deze nieuwe indicatoren. Naast het ontwikkelen van een klinisch risico-evaluatie instrument gebaseerd op deze factoren, verbeterde ook ons inzicht in de ziekte. In het bijzonder, CRP bleek alleen voorspellend voor 1-jaars sterfte, een aanwijzing voor de lange termijn invloed van ontstekingsprocessen.

Hoofdstuk 2 richt zich op dynamische risico modellering, een innovatieve methode van risico evaluatie. Deze methode gaat verder dan traditionele risico modellen door het voorspellen van toekomstige complicaties, gebruik makend van alle bevindingen tot aan een klinisch relevant tijdstip, dus niet alleen gebaseerd op opnamegegevens.

Een serie van logistische regressie modellen is ontwikkeld, gebaseerd op meer dan 6000 patiënten met ST-elevatie MI, geïncludeerd in de ASSENT-3 studie, om 30-dagen sterfte te voorspellen op de volgende belangrijke “voorspel-momenten”: opname, 3 uur, dag 2 en dag 5. Een cruciaal kenmerk van dynamische modellering, is het vermogen om de verandering in prognostisch belangrijke factoren in de tijd te beoordelen. Bijvoorbeeld, het relatieve belang van traditionele

opnamegegevens, zoals leeftijd, hartfrequentie en systolische bloeddruk, neemt door de tijd heen af door het optreden van complicaties zoals beroerte en hartfalen. De continu bijgestelde evaluatie van risico kan ondersteunend zijn bij het nemen van medische beslissingen, naast de gegevens die bekend zijn aan het begin van de ziekenhuisopname.

Er wordt vaak gezegd dat de regio of het land waar de patiënt behandeld wordt van invloed is op de behandeling en/of de risico's op complicaties, maar de oorzaken van deze verschillen zijn niet duidelijk in kaart gebracht. Contextuele factoren zoals kenmerken van de zorgverleners, sociaal economische en culturele factoren, gezondheidszorgvoorzieningen en -beleid kunnen een rol spelen, maar vaak zijn deze gegevens niet beschikbaar om dit formeel te kunnen onderzoeken. Om de variabiliteit in de behandeling en uitkomsten in patiënten met ST-elevatie ACS ten gevolge van patiënt- versus niet-patiëntgebonden factoren verder toe te lichten, werden multilevel modelleringstechnieken toegepast op de GUSTO IV ACS trial (**Hoofdstuk 3**). Er waren significante verschillen tussen de 24 deelnemende landen, in het zorgproces (bijv. bij revascularisatie) en de uitkomsten (bijv. 30-dagen sterfte / myocardinfarct en 1-jaars sterfte). Echter, de verschillen tussen de landen verdwenen, wanneer gecorrigeerd werd voor belangrijke patiënt- en ziekenhuis gebonden factoren; in feite kon 96% tot 99% van de totale variatie in deze uitkomsten toegeschreven worden aan patiëntgebonden factoren.
Deze resultaten wijzen op de potentiële misvatting dat internationale verschillen bestaan zonder dat gecorrigeerd wordt voor de variatie in relatie tot factoren behorend tot een lager niveau, zoals ziekenhuis- en patiëntgebonden factoren. Hoewel de variatie tussen ziekenhuisgebonden factoren klein leek, was het wel significant. Het verzamelen van gegevens op ziekenhuisniveau in toekomstige studies kan bijdragen tot een verdere verklaring van deze verschillen.

De verklaring van de pathofysiologie van het acuut coronair syndroom

De hoeveelheid gegevens die verzameld zijn in grootschalige patiëntgebonden onderzoeken boden een uitstekende gelegenheid om ons inzicht in ACS te verbeteren. In **hoofdstuk 4**, konden met behulp van kwantitatieve en centrale beoordeling van opname ECG's in het GUSTO IV ACS onderzoek, patiënten worden geïdentificeerd met electrocardiografische linker ventrikel hypertrofie (LVH). Deze aandoening wordt gewoonlijk niet beschouwd als een onderdeel van het risicoprofiel van ACS, dus onderzochten we de associatie met sterfte of het samengestelde eindpunt van sterfte of een myocardinfarct, naast een mogelijke beïnvloeding van het effect van deze associatie door geslacht en/of NT-

proBNP, een kenmerk van hemodynamische stress. Van de 7443 patiënten met non-ST-elevatie ACS, had 8% LVH, hiervan was driekwart vrouw. Lange- termijn overlevingsanalyses lieten zien dat in het bijzonder vrouwen met LVH een hoog risico subgroep vormen, die bijzondere aandacht zou moeten krijgen.

Het is steeds duidelijker geworden dat ontstekingsprocessen een grote rol spelen in de pathogenese van coronaire hartziekten, gebaseerd op harde bewijzen in studies naar CRP en andere ontstekingsmarkers. Chronische infectie door *Chlamydia pneumoniae* is in het verleden geassocieerd met het ontstaan en de progressie van plaquevorming en -destabilisatie. Echter, wat betreft de relatie met complicaties op het gebied van hart- en vaatziekten spreekt de bewijsvoering elkaar tegen. Onze case-control studie, die ingebed was in de GUSTO IV ACS studie, leverde geen bewijs voor deze infectie marker als een belangrijke risico factor in ACS (**Hoofdstuk 5**).
Een beroerte treedt slechts sporadisch op vlak na non-ST-elevatie ACS, maar de complicatie gerelateerde ziekte- en sterftecijfers zijn hoog. Identificatie van de factoren die samenhangen met deze complicatie zouden dus kunnen bijdragen tot het begrijpen van de oorzaken en het verminderen van deze risico's. Uit onze analyse van zes grootschalige studies met patiënten met non-ST-elevatie ACS, bleken oudere leeftijd, een eerder doorgemaakte beroerte en een hogere hartfrequentie de beste voorspellers voor het optreden van een beroerte binnen 30 dagen na randomisatie **(Hoofdstuk 6).**

Het risico profiel veranderde niet door het voorspellen van specifiek niet-bloedige of bloedige beroertes. Het is belangrijk om op te merken dat gebruik van de studiemedicatie, GPIs, niet was geassocieerd met een hoger risico op een beroerte. Hoewel de identificatie van deze drie indicatoren ons enig inzicht geeft, kunnen we hier niet volledig op bouwen om de incidentie van een beroerte te voorspellen, gegeven het bescheiden discriminatieve vermogen van het model.

Behandeling op maat van het acuut coronair syndroom
Een van de doelstellingen van risico evaluatie is om die behandeling en die middelen te geven aan patiënten, die de beste verhouding tussen voor- en nadelen oplevert. Als een therapie effectief is in het verminderen van het relatieve risico op complicaties, op een zelfde manier bij verschillende soorten patiënten, dan zullen patiënten met een hoger absoluut risico een grotere absolute risicoreductie hebben van de therapie. In een meta-analyse van de zes grootschalige patiëntgebonden onderzoeken naar de effectiviteit van GPIs bij patiënten met ACS werd dit concept onderzocht in relatie tot leeftijd. (**Hoofdstuk 9**). Terwijl we een grotere absolute risicoreductie in sterfte of MI observeerden met het toenemen van de leeftijd, was er ook een stijging van het absolute risico op belangrijke bloedingen. Daarom bevelen wij aan dat oudere patiënten

intensief geobserveerd worden om goed met deze risico's om te gaan.

Hoewel er veel discussie blijft over het optimale mechanisme van reperfusie therapie, is er weinig discussie dat een kortere tijd tot de behandeling leidt tot verbeterde uitkomsten bij patiënten met ST-elevatie MI. Onze gepoolde analyse van 22 klinische onderzoeken laat dit duidelijk zien. Bovendien hadden patiënten die een primaire PCI hadden ondergaan een significant betere 30-dagen overleving in vergelijking met degenen die behandeld waren met fibrinolyse, ongeacht de vertraging in de behandeling. (**Hoofdstuk 10**). Echter, vertaling van deze bevindingen naar de dagelijkse praktijk is een moeilijke opgave aangezien deze situatie vaak complexer is dan die van een klinisch onderzoek. Daarom zou, ten behoeve van het minimaliseren van de tijd tot de behandeling, het leveren van maatwerk benadrukt moeten worden, aangepast aan de locale of regionale situatie. In het licht van deze overwegingen worden momenteel nieuwe therapeutische strategieën onderzocht, inclusief prehospitale triage en -behandeling en methoden die vroege medicamenteuze behandeling met tijdige angiografie combineren. (**Hoofdstuk 11**).

Conclusies

Zoals aangetoond in dit proefschrift, kan *de toekomst in dienst worden gesteld van het heden* door gebruik te maken van diverse modellerings-technieken. Hiermee kan een veelvoud aan doelstellingen worden bereikt. Terwijl we belangrijke vooruitgang hebben geboekt sinds de introductie van de moderne definitie van risico door Pascal en de Fermat, bestaat er nog steeds ruimte om risico evaluatie te verfijnen. In het bijzonder zal risico evaluatie in ACS kunnen profiteren van verder onderzoek naar nieuwe methoden, statistische technieken en studie-opzetten. Innovatieve benaderingen om voorheen onbekende of onduidelijke factoren te meten (en/of huidige methoden te verbeteren), en het aanpakken van meer complexe onderzoeksvragen, zullen leiden tot een beter inzicht in het risico van deze patiënten.

Hoewel clinical trials worden gewaardeerd om hun uitgebreide klinische gegevens, zijn zij tegelijkertijd beperkt door hun selecte inclusie en exclusie criteria, hetgeen de generaliseerbaarheid van de resultaten beperkt. Patiënten-registraties en andere populatie-gebaseerde cohorten zijn niet beperkt door selectiecriteria.

Ongeacht het onderzoekscohort kan het herhaaldelijk verzamelen van klinische indicatoren (zoals electrocardiogrammen, biomarkers en vitale functies) een belangrijke verbetering geven van ons begrip van de dynamische ontwikkeling van risico, terwijl contextuele gegevens van instellingen, landen en regio's ons kunnen helpen om het algehele beeld van risico compleet te maken.

Tenslotte, het eindresultaat van deze inspanningen moet zich richten op de patiënt. In het verleden was het een uitdaging om statistische

theorie en klinische realiteit met elkaar in balans te brengen, wat de toepassing van risico evaluatie op patiëntniveau belemmerd kan hebben. Echter, de afstand tussen theorie en praktijk kan verkleind worden door koestering van een cultuur van een model-begeleide risico evaluatie, alsmede door gebruik te maken van de technologische revolutie (bijv. electronische medische dossiers en handcomputers).

Acknowledgements

As my formal education comes to an end, it has become increasingly apparent that this journey has not been unaccompanied. In fact, many people have invested their time, resources and support. This final leg in the journey began with a fateful combination of the Huygens Scholarship, Professor Maarten L. Simoons, Dr. Eric Boersma and Professor Paul W. Armstrong. Soon after my arrival in Rotterdam, I recognised the magnitude of my fortune. Through my promoter, Prof. Simoons and copromoter, Dr. Eric Boersma, I was exposed to a unique combination of clinical and statistical expertise, and had the opportunity to participate in cutting-edge research, as well as access to rich clinical databases. This experience also highlighted the value of local, national and international collaboration; again, putting to rest the notion that science is a solitary process. I also learned that apart from the glamorous aspects of presentations and publications, research takes time and patience. Your enduring encouragement pulled me through those challenging moments and you have strengthened my foundation in research through your expert leadership and guidance. Because of you and this experience, I have been profoundly transformed, both professionally and personally. And for this, I am forever thankful, and I look forward to maintaining our research connection well into the future.

This bridge to the Netherlands could not have been built without a key architect, Professor Paul W. Armstrong. I met him as a green Master's student, and I quickly realized that this was a place to take root and grow. Over the years, I was encouraged to become a well-rounded researcher through exploring every aspect of the research process. I am indebted to you for the opportunities and connections that you have facilitated, and I am honoured to be a part of your research family. You exemplify the gold standard as a researcher and as an individual. You have been (and are) a tremendous mentor, advocate and friend, which have been especially noted during recent times: My deepest gratitude to you.

I would also like to thank the other distinguished members of my committee: Prof. Wim van der Giessen, Prof. Albert Hofman, Prof. Jan Tijssen and Prof. Freek Verheugt for their participation and input into this thesis.

As it is said, "it takes a village to raise a child", it is also true of the novice researcher. I have had the opportunity to work with many talented researchers. In particular, the Research Group at Canadian VIGOUR Centre (CVC) has made a profound impact. Wei-Ching Chang, my first office mate, yoga-buddy and fellow theatre-goer, has been a role model for balance in life and for an

unquenchable thirst for knowledge and wisdom: Many thanks to you, Wei-Ching, for your mentorship and friendship. Padma Kaul, a young researcher who has in many ways been my crystal ball into the future for past several years: Padma, you have been an excellent role model to me, perhaps more than you realize. I am grateful for your insights, both personally and professionally. And my "fashion bar" has been raised on account of your example. Yuling Fu, a dynamic and strong researcher, who also has served as an example of excellence to pursue: Yuling, I have learned a great deal from you, especially your work ethic. And it is so appropriately paired with your quick, sharp wit. Thanks for bringing a smile to so many occasions. Cynthia Yau, my fellow "Cynthia", cubicle- and lunch- buddy, has been a cheerful and valued colleague over the years. My genuine thanks and best wishes to you.

I have also been fortunate to collaborate with gifted researchers at the University of Alberta, including Dr. Judy Gnarpe, Dr. Robert Welsh, Dr. Justin Ezekowitz and Dr. Michelle Graham, and Dr. Christopher Buller from the University of British Columbia.

The members of the clinical operations and administration of CVC also deserve recognition and thanks. I have learned much about the front-end of trials as well as how a research centre functions beyond the presentations and publications of our work. And moreover, this group of individuals has always been blessed with a great sense of humour and warmth.

There have been several key collaborations through the VIGOUR organization that have supported this thesis: in particular, Dr. John Simes and the NHRMC in Sydney, Australia, Prof. Lars Wallentin and Dr. Stefan James in Uppsala, Sweden and Drs. Christopher Granger, Ken Mahaffey and Robert Califf and the DCRI in Durham, NC. I would also like to acknowledge the contribution of Ms. Karen Pieper and Dr. Kerry Lee. And a special thanks to Dr. Michael Lauer (formerly of the Cleveland Clinic, and now NIH-NHLBI). Collaborations through PCAT-2 as well as with other Dutch researchers including Dr. Ewout Steyerberg, Dr. Jan-Paul Ottervanger, Dr. Jorik Timmer and Dr. Timo Lenderink were also valued.

And to my Dutch research family, I extend my heartfelt gratitude for your openness and kindness that made me feel "at home" in my home-away-from-home: Dr. Ron van Domburg, a researcher with great insight and experience which was always accompanied with a kind greeting; Professor Don Poldermans, an energetic and accomplished clinical investigator with a zest for research that is inspiring; Ms. Virginie Poldermans, a tremendously warm person with hearty sense of humour and spirit.

The critical factor to making the Netherlands my second home was the original crew of research fellows in the side-by-side "kamers" on the 5th floor. The brilliant personalities

packed into those cosy offices made me look forward to work each day. I am grateful to Mattie Lenzen, a deep source of thought and perspective with a touch of subtle, dry humour; Esther de Swart, a gal with whom I had many great talks, cups of tea and Friday evening dinners; Anneke de Torbal, a perfect companion both on Dutch soil and beyond (a Friday night diner also, not to mention a memorable trip to Paris!); Miklos Kertai, a sharp clinician-researcher who is destined for greatness and with whom I had many enlightening discussions about research, life as an alien in NL, and life in general; Sanne Hoeks, a keen young researcher with personality to match; Nestor Mercado, a driven clinician with an internal reservoir for medical literature; and to other members of the 5th floor fellowship (i.e., KLEP-groep), my best wishes to Marjo Hordijk-Trion, Maarten Vermuelen, Olaf Schouten, Priya van Vooren, Suzanne Pedersen, Hanneke Takkenberg, John Puvimanusinghe, Chris Jansen, and Arno Ruiter. My thanks also to Adrian Hernandez, a talented colleague with whom I have collaborated, but unfortunately not yet met.

The superb administration of the Thoraxcentrum also deserves recognition: Sarah Fransen, a tremendously helpful and friendly (and quite stylish!) master of Dutch bureaucracy; Wil Barthelemy, for his help and advice with employment matters; Arita Orgers and Ad van Druinen, for processing the financial concerns; and the secretarial group of Prof. Simoons, always armed with a smile. The heartbeat of the KLEP-groep, Cecile Sweers, Jolanda van Wijk and Maria Kamps, was a great source of practical information as well as warm greetings every morning. Hartelijk bedankt!

I would also like to thank the wise gentlemen of the computer group, and in particular, Nico Bruining, Simon Meij, Sebastian de Winter and Stefan Newlan. Thanks for getting me out of the usual computer jams, as well as sharing with me your important research.

My thanks to Dr. Jan Willem de Jong for his assistance through the doctoral degree process. And I am also indebted to Annet Louw for very competently (and cheerfully) guiding me through the final stages of this thesis. Thank you very much, Annet!

Peter van Limbeek and the folks at Gildeprint Drukkerijen in Enschede have been excellent to work with in the final preparations for the printing of this thesis. My thanks for your hard work.

Very special thanks go to three exceptional people in my Dutch experience: Paul Cummins, Wilma Scholte op Reimer, and Colinda Koppelaar. Paul, the resident humorist and entertainment guru stood out early on during my stay in Rotterdam. Whether inside or beyond the doors of the Thoraxcentrum, Paul could always bring about a smile, but more often a hearty laugh and a great story. And if nothing else, my music collection and conference experiences have surely improved on his account. You

have been a great friend, Paul, and my thanks to you for just being you.

Wilma was the first face I saw as I entered the Schiphol arrivals deck, and I could not have asked for a warmer welcome. And her generosity did not end there; she truly has a heart of gold and a lovely family to match. I thank you, my dear friend, for all that you have done. Including me, as part of your family is something I treasure. Wilma, you are a marvellous example of the modern professional woman, and I am honoured that you are one of my paranymphs.

And Colinda, you have a special place in my heart. We became fast friends through your magnetic personality and infectious laugh. And perhaps also for your passion for shopping and wardrobe co-ordination! So many great shopping excursions as well as benefiting from your duties as an internal ambassador: I feel like I have seen more the Netherlands than most residents. You and Ruud have always welcomed me into your home and activities, which meant a great deal. Co, you are on my shortlist of people that I deeply admire and I am honoured to call you my friend. My thanks also for accepting the invitation to be one of my paranymphs.

And finally, there is a group of people who have been by my side from the very beginning of my journey. I have an amazing network of family and friends, originating in Ontario, Alberta and The Netherlands (as well as elsewhere), who have had a hand in shaping me into who I am today. Their impact has been especially felt during the last few years. And in particular, I would like to express my gratitude to the Bosman, Westerhout and Klostergaard families, as well my dear friends Kristi Sargeant-Kerr and Erin Coward.

My most profound gratitude goes to my immediate family. This thesis is appropriately dedicated in the memory of my mother and my father as they were instrumental in encouraging me to realize my potential. They were strong proponents of higher education from an early age, and they always supported my chosen direction. I truly could not have asked for more love or support. Although they cannot be with me in person to celebrate this milestone, I know they are here in spirit. To my brother, Jason, who has taught me many lessons in compassion and humanity. To my sister, Kathleen who has inspired me more than she realizes. She is a courageous and self-aware woman and these attributes will lead her to great success. I am very honoured and proud to use your work for this thesis cover. Kate, my heartfelt thanks to you for your love and support as always. And finally, to Arnold Klostergaard whose unfaltering love has kept me afloat through stormy seas and smiling through good times. Arnie, your kindness, integrity and your love of life are among your best qualities, and I am so very thankful that you have shared them with me over these past few years. My thanks and my love.

Curriculum vitae

Cynthia Mary Westerhout was born on May 22, 1976 in London, Ontario, Canada. She was granted her honours Bachelor degree in Biological Sciences (Bio-Medical Sciences) with Distinction by the University of Guelph in Guelph, Ontario, Canada in 1999. She was also an active member (1996-1999) and Co-President (1998-1999) of the Bio-Medical Sciences Students' Association.

Subsequently, she received her Masters in Medical Sciences (Public Health Sciences-Epidemiology) from the University of Alberta in Edmonton, Alberta, Canada in 2001. She was awarded the *Colin L Soskolne Leadership/Community Participation Award*, and was a Member-At-Large (1999-2000) and the Secretary/Treasurer (2000-2001) of the Public Health Sciences Students' Association. Her thesis was entitled "Utilization and effectiveness of abciximab within one-year of percutaneous coronary intervention in Alberta", which was supervised by Professor Duncan L. Saunders, PhD, Assistant Professor Padma Kaul, PhD and Professor Paul W. Armstrong, MD.

Through the *Huygens Scholarship* awarded by NUFFIC in 2001, she became a research fellow under the guidance of Prof. dr. Maarten L. Simoons and Dr. Eric Boersma at the Thoraxcentrum, Erasmus MC. Since that time, she has pursued her doctoral studies in conjunction with her position as a Research Associate at the Canadian VIrtual coordinating center for Global cOllaborative cardiovascUlar Research (VIGOUR) Centre, directed by Professor Paul W. Armstrong, MD. She also is an editor (2006-present) for the CUBIC! News magazine for PhD students at Erasmus Universiteit Rotterdam, as well as a mentor (2002- present) for the SCIber Mentorship Program, an email mentoring program at the University of Alberta for young girls who have an interest in pursuing a higher education or a career in science.

List of Publications

Peer-Reviewed Publications

1. Buller CE, Welsh RC, Westerhout CM, Webb JG, O'Neill B, Gallo R, Armstrong PW. Guideline adjudicated fibrinolytic failure: Incidence, findings and management in a contemporary clinical trial. *American Heart Journal* (In Press).

2. Kaul P, Chang WC, Westerhout CM, Graham MM, Armstrong PW. Gender differences in admission rates and outcomes among patients presenting to emergency departments with coronary syndromes. *Canadian Medical Association Journal (CMAJ)* (In Press).

3. Westerhout CM, Gnarpe J, Chang W-C, Fitzpatrick S, Barnathan ES, Boersma E, Califf RM, Wallentin L, Simoons ML, Armstrong PW. No prognostic significance of chronic infection with Chlamydia pneumoniae in acute coronary syndromes: Insights from the GUSTO IV ACS trial. *American Heart Journal* 2007;154:306-12.

4. Timmer JR, Ottervanger JP, de Boer MJ, Boersma E, Grines CL, Westerhout CM, Simes RJ, Granger CB, Zijlstra F. Primary coronary intervention compared with fibrinolysis for myocardial infarction in diabetes: Results from the PCAT-2 Collaboration. *Archives of Internal Medicine* 2007;167(13):1353-1359.

5. Westerhout CM, Lauer MS, James S, Fu Y, Wallentin L, Armstrong PW. Electrocardiographic left ventricular hypertrophy in GUSTO IV ACS: An important risk marker of mortality in women. *European Heart Journal* 2007;28:2064-2069.

6. Welsh RC, Gordon P, Westerhout CM, Buller CE, O'Neill B, Armstrong PW. A novel enoxaparin regime for ST elevation myocardial infarction patients undergoing primary percutaneous coronary intervention: A WEST sub-study. *Catheterization and Cardiovascular Interventions* 2007; Online access, published February 12, 2007.

7. Chang WC, Kaul P, Westerhout CM, Graham MM, Armstrong PW. Effects of socioeconomic status on mortality after acute myocardial infarction. *American Journal of Medicine* 2007;120(1):33-39.

8. Hernandez AV, Westerhout CM, Steyerberg EW, Ioannidis JPA, Beuno 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: Benefits and harm in different age subgroups. *Heart* 2007;93(4):450-455.

9. Westerhout CM, Hernandez AV, Steyerberg EW, Beuno H, White H, Theroux P, Moliterno DJ, Armstrong PW, Califf RM, Wallentin LC, Simoons ML, Boersma E. Predictors of stroke within 30 days in patients with non-ST-segment elevation acute coronary syndromes. *European Heart Journal* 2006;27:2956-2961.

10. Westerhout CM, Fu Y, Lauer MS, James S, Armstrong PW, Al-Hattab E, Califf RM, Simoons ML, Wallentin L, Boersma E. Short- and long-term risk stratification in acute coronary syndromes: The added value of quantitative ST-segment depression and multiple biomarkers. *Journal of the American College of Cardiology* 2006;48:939-947.

11. Armstrong PW, WEST Steering Committee. A comparison of pharmacologic therapy with/without timely coronary intervention vs. primary percutaneous intervention early after ST-elevation myocardial infarction: the WEST (Which Early ST-elevation myocardial infarction Therapy) study. *European Heart Journal* 2006;27(13):1530-1538. [CM Westerhout as biostatistical lead]

12. Chang WC, Kaul P, Fu Y, Westerhout CM, Granger CB, Mahaffey KW, Wallentin L, Van de Werf F, Armstrong PW. Forecasting mortality: dynamic assessment of risk in ST-segment elevation acute myocardial infarction. *European Heart Journal* 2006;27(4):419-426.

13. Boersma E, PCAT-2 Collaborators. Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction. *European Heart Journal* 2006;27:779-788. [CM Westerhout as biostatistical lead]

14. Chang WC, Midodzi WK, Westerhout CM, Boersma E, Cooper J, Barnathan ES, Simoons ML, Wallentin L, Ohman EM, Armstrong PW. Are international differences in the outcomes of acute coronary syndromes apparent or real? A multilevel analysis. *Journal of Epidemiology and Community Health* 2005;59(5):427-433.

15. Kertai, MD, Boersma E, Westerhout CM, Klein J, van Urk H, Bax JJ, Roelandt JRTC, Poldermans D. A combination of statins and beta-blockers is independently associated with a reduction in the incidence of perioperatirve mortality and non-fatal myocardial infarction in patients undergoing abdominal aortic aneurysm surgery. *European Journal of Vascular and Endovascular Surgery* 2004;28(4):343-52.

16. Westerhout CM, Saunders LD, Kaul P, Armstrong PW, Knudtson ML, Ghali WA. Inter-institutional variation in the utilization of abciximab for percutaneous coronary intervention. *Canadian Journal of Cardiology* 2004;20(4):405-410.

17. Kertai MD, Boersma E, Westerhout CM, van Domburg R, Bax JJ, Klein J, Poldermans D. Association between long-term statin use and mortality after successful abdominal aortic aneurysm surgery. *American Journal of Medicine* 2004;116(2):96-103.

18. Chang W-C, Kaul P, Westerhout CM, Graham MM, Fu Y, Chowdhury T, Armstrong PW. Impact of sex on long-term mortality from acute myocardial infarction versus unstable angina. *Archives of Internal Medicine* 2003;163:2485-2490.

19. Poldermans D, Bax JJ, Kertai MD, Krenning B, Westerhout CM, Schinkel AF, Thomson IR, Lansberg PJ, Fleisher LA, Klein J, van Urk H, Roelandt JR, Boersma E. Statins are associated with a reduced incidence of perioperative mortality in patients undergoing major noncardiac vascular surgery. *Circulation* 2003;107:1848-51.

Invited Articles

1. Boersma E, Westerhout CM. Intravenous glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: Lessons learned from recently conducted randomized clinical trials. *Current Opinion in Investigational Drugs* 2004; 5(3): 313-9.

2. Westerhout CM, Boersma E. Risk-benefit analysis of platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes. *Expert Opinion in Drug Safety* 2003; 2(1): 49-58.

3. Westerhout CM, Boersma E. Platelet glycoprotein IIb/IIIa inhibitors in the treatment of non-ST-segment elevation acute coronary syndromes in the elderly: Part 2 of 2. *Geriatrics and Aging* 2002; 5(6): 25-32.

4. Westerhout CM, Boersma E. Platelet glycoprotein IIb/IIIa inhibition and percutaneous coronary intervention in the elderly. *Geriatrics and Aging* 2002; 5(5): 30-38.

Invited Presentations

1. Westerhout CM. "Clinical risk prediction: Which risk score to use?" *Invited speaker*: Symposium on Risk Stratification in Acute Coronary Syndromes at the American College of Cardiology Scientific Session 2006, Atlanta, GA, USA (March 13, 2006).

2. Westerhout CM. (i) "Statistical issues in risk stratification: Old issues, new approaches". (ii) "Dynamic risk stratification in ACS". *Invited speaker*: Think tank on "Defining risk in ACS: The gateway to enhancing cardiovascular care" in Washington, DC, USA (June 2-4, 2005).

3. Westerhout CM. "Propensity scores: Reducing bias in outcomes research". *Invited speaker*: Epidemiology Seminars, Department of Public Health Sciences, University of Alberta, Edmonton, AB, Canada (September 20, 2001).

4. Westerhout CM. "Health authority business plans: Beyond the tip of your nose". *Invited speaker*: Epidemiology Seminars, Department of Public Health Sciences, University of Alberta, Edmonton, AB, Canada (February 8, 2001).

Abstracts

1. Westerhout CM, Lee KL, James SK, Van de Werf F, O'Neill WW, Neilsen TT, Weaver WD, Granger CB, Armstrong PW. Dynamic mortality modeling in PCI-treated ST-elevation MI: Implications for clinical decision-making. To be presented at the American Heart Association Scientific Sessions 2007, Orlando, FL.

2. Huber K, Aylward PE, van 't Hof AWJ, Montalescot G, Holmes DR, Betrui AG, Widimsky P, Westerhout CM, Granger CB, Armstrong PW. Glycoprotein IIb/IIIa inhibitors before primary percutaneous coronary intervention of ST-elevation myocardial infarction improve perfusion and outcome: Insights from APEX-AMI. To be presented at the American Heart Association Scientific Sessions 2007, Orlando, FL.

3. Welsh RC, Gordon P, Westerhout CM, O'Neill B, Buller CE, Armstrong PW. Anticoagulation after subcutaneous enoxaparin is time sensitive in STEMI patients treated with TNK. To be presented at the Canadian Cardiovascular Congress 2007, Quebec City, Canada.

4. Brener SJ, Moliterno DJ, Aylward P, van 't Hof AWJ, Ruzyllo W, Ardissino D, Hamm CW, Westerhout CM, Granger CB, Armstrong PW. Predictors of angiographic success and relationship to clinical outcomes during primary PCI for ST elevation acute myocardial infarction: Insights from APEX AMI. To be presented at the European Society of Cardiology Congress 2007, Vienna, Austria.

5. Armstrong PW, Fu Y, Brener SJ, Todaro TG, Moliterno DJ, Holmes D, Adams PX, Westerhout CM, Wagner GS, Granger CB. Myocardial perfusion in STEMI patients following primary PCI: Insights from the ECG/Angiography substudy of APEX AMI. Oral presentation at the American College of Cardiology Scientific Sessions 2007, New Orleans, LA.

6. Fu Y, KW Mahaffey KW, Todaro TG, Van de Werf F, White HD, van 't Hof AWJ, Nielsen TT, Wagner GS, Adams PX, Westerhout CM, Armstrong PW. ST-resolution after primary PCI for STEMI is a strong predictor of outcome. Poster presentation at the American College of Cardiology Scientific Sessions 2007, New Orleans, LA.

7. Ezekowitz JA, Chang WC, Westerhout CM, Armstrong PW. Acute heart failure: What doesn't get admitted may come back to haunt you. Poster presentation at the American Heart Association Scientific Sesssion 2006, Chicago, IL.

8. Buller CE, Welsh RC, Westerhout CM, O'Neill B, Webb J, Bata I, Gallo R, Armstrong PW. Frequency, speed and efficacy of guideline adjudicated rescue percutaneous coronary intervention following contemporary fibrinolysis. Poster presentation at the American Heart Association Scientific Sesssion 2006, Chicago, IL.

9. Bata I, Welsh RC, Westerhout CM, Travers A, Cain E, Christenson JW, Sookram S, Armstrong PW. Pre-hospital recognition of STEMI in WEST: An opportunity not to be denied. Oral presentation at the American Heart Association Scientific Sesssion 2006, Chicago, IL.

10. Hernández AV, Westerhout CM, Steyerberg EW, Ioannidis JPA, Bueno H, White H, Theroux P, Moliterno DJ, Armstrong PW, Califf RM, Wallentin L, 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. Poster presentation made by AV Hernández at the European Society of Cardiology Congress 2006, Barcelona, Spain.

11. Westerhout CM, Hernández AV, Steyerberg EW, Bueno H, White H, Theroux P, Moliterno DJ, Armstrong PW, Califf RM, Wallentin L, Simoons ML, Boersma E. Predictors of stroke within 30 days in patients with non-ST-segment elevation acute coronary syndromes. Oral presentation made by AV Hernández at the European Society of Cardiology Congress 2006, Barcelona, Spain.

12. Welsh RC, Gordon P, Westerhout CM, Buller CE, O'Neill BJ, Cheung PK, Armstrong PW. A novel enoxaparin regime for ST-elevation myocardial infarction patients undergoing primary percutaneous coronary intervention: Intravenous but not subcutaneous enoxaparin achieves adequate anti-Xa levels. Poster presentation made by RC Welsh at the American College of Cardiology Scientific Sessions 2006, Atlanta, GA, USA.

13. Westerhout CM, Chang WC, Fu Y, Goodman SG, van de Werf F, Granger CB, Armstrong PW. Are STEMI outcomes after fibrinolysis worse during "Off-hours"? Insights on circadian rhtythm from ASSENT-2.
    a. Poster presentation made by CM Westerhout at the American Heart Association Scientific Sessions 2005 in Dallas, TX, USA.
    b. Poster presentation made by CM Westerhout at the Canadian Cardiovascular Congress 2005 in Montreal, QC, Canada.

14. Westerhout CM, Graham MM, Chang WC, Kaul P, Armstrong PW. Does sex influence the use of cardiac catheterization after emergency department presentation for suspected coronary artery disease?
    a. Oral presentation made by CM Westerhout at the American Heart Association Scientific Sessions 2005 in Dallas, TX, USA.
    b. Poster presentation made by CM Westerhout at the Canadian Cardiovascular Congress 2005 in Montreal, QC, Canada.

15. Chang WC, Westerhout CM, Kaul P, Fu Y, Armstrong PW. Social deprivation index is a better predictor of mortality after acute myocardial infarction than household income alone.
    a. Oral presentation and press conference made by CM Westerhout at the American Heart Association Scientific Sessions 2005 in Dallas, TX, USA.
    b. Poster presentation made by CM Westerhout at the Canadian Cardiovascular Congress 2005 in Montreal, QC, Canada.

16. Kaul P, Westerhout CM, Chang WC, Armstrong PW. Use of evidence-based medications among elderly patients with acute coronary syndromes: does gender matter? Oral presentation made by CM Westerhout at the Canadian Cardiovascular Congress 2005 in Montreal, QC, Canada.

17. Timmer JR, Ottervanger JP, de Boer MJ, Boersma E, Grines C, Westerhout C, Granger C, Zijlstra F, Klinieken I, Weezenlanden L. Primary percutaneous coronary intervention compared with thrombolysis for acute myocardial infarction in diabetes: Results from randomized trials of the PCAT Collaboration. Poster presentation made by JR Timmer at the American College of Cardiology Scientific Sessions 2005 in Orlando, FL, USA.

18. Boersma E, Simes RJ, Grines CL, Westerhout CM, PCAT-2 Collaborators. Does time matter? Individual patient data-based meta-analysis of primary PCI versus fibrinolysis in acute myocardial infarction randomized trials. Oral presentation made by E Boersma at the American Heart Association Scientific Sessions 2004 in New Orleans, LA, USA.

19. Chang WC, Kaul P, Westerhout CM, Armstrong PW. Unequal access and equalizing effects of revascularization after acute myocardial infarction by socioeconomic group.
    a. Oral presentation made by WC Chang at the American Heart Association Scientific Sessions 2004 in New Orleans, LA, USA.
    b. Oral presentation made by WC Chang at the Canadian Cardiovascular Congress 2004 in Calgary, AB, Canada.

20. Kertai MD, Boersma E, Westerhout CM, Schouten O, Van Domburg R, Klein J, Van Urk H, Poldermans D. Long-term statin use is associated with a reduced mortality after successful abdominal aortic aneurysm surgery. Oral presentation made by MD Kertai at the European Society of Cardiology Congress 2004 in Munich, Germany.

21. Westerhout CM, Gnarpe J, Chang W-C, Barnathan ES, Boersma E, James S, Califf RM, Simoons ML, Armstrong PW. Does chronic infection with *Chlamydia pneumoniae* influence the prognosis of acute coronary syndromes(ACS)? Insights from a nested matched case-control substudy of the GUSTO IV ACS trial. Poster presentation made by CM Westerhout at the American College of Cardiology Scientific Sessions 2004, New Orleans, LA, USA.

22. Kaul P, Westerhout CM, Chang W-C, Armstrong PW. Looking proximally to understand distal outcomes: Gender differences in mortality after acute myocardial infarction. Oral presentation made by P Kaul at the American College of Cardiology Scientific Sessions 2004, New Orleans, LA, USA.

23. Westerhout CM, Lauer MS, James S, Fu Y, Wallentin L, Armstrong PW. Unraveling relationships between left ventricular hypertrophy, NT-proBNP and 1-year mortality in acute coronary syndromes: Insights from GUSTO IV ACS. Oral presentation made by CM Westerhout at the American Heart Association Scientific Sessions 2003, Orlando, FL, USA.

24. Westerhout CM, James S, Fu Y, Lauer MS, Wallentin L, Simoons ML, Armstrong PW. Does quantitative ST-segment depression add value to cardiac biomarkers in the prognosis of short and long-term mortality in acute coronary syndromes? Insights from GUSTO IV ACS.
    a. Oral presentation made by CM Westerhout at the American Heart Association Scientific Sessions 2003, Orlando, FL, USA.
    b. Poster presentation made by CM Westerhout at the Canadian Cardiovascular Congress 2003, Toronto, ON, Canada.
    c. Oral presentation made by CM Westerhout at the Cardiac Sciences Research Day 2003, Division of Cardiology, Department of Medicine, University of Alberta, Edmonton, AB, Canada.

25. Westerhout CM, Fu Y, Lauer MS, Boersma E, Barnathan ES, Wallentin L, Califf RM, Simoons ML, Armstrong PW. Does admission ST depression and troponin impact the use of angiography and revascularisation differently in men and women with acute coronary syndromes (ACS)? Insights from the GUSTO-IV ACS trial. Poster presentation made by CM Westerhout at the European Society of Cardiology Congress 2003, Vienna, Austria.

26. Westerhout CM, Ottervanger JP, Armstrong PW, Hochman JS, James S, Wallentin L, Barnathan ES, Ohman EM, Simoons ML, Boersma E. Predictors of one-year death in men and women: Insights from GUSTO-IV ACS. Poster presentation made by CM Westerhout at the American College of Cardiology Conference 2003, Chicago, IL, USA.