European Heart Journal
Acute Cardiovascular Care
EUROPEAN SOCIETY OF CARDIOLOGY®

Original scientific paper

European Heart Journal: Acute Cardiovascular Care
2(3) 280–291

DOI: 10.1177/2048872613483019
acc.sagepub.com
SAGE

Management and outcomes of patients presenting with STEMI by use of chronic oral anticoagulation: results from the GRACE registry

Alvaro Alonso[1,2], Joel M Gore[2], Hamza H Awad[3], Ann L Quill[2], Gilles Montalescot[4], Frans van de Werf[5], Dietrich C Gulba[6], Keith AA Fox[7], Kim A Eagle[8], Christopher B Granger[9], Allison Wyman[2] and Ph Gabriel Steg[10–12]; for the GRACE Investigators

Abstract

Aims: To describe the characteristics, treatment, and mortality in patients with ST-elevation myocardial infarction (STEMI) by use of chronic oral anticoagulant (OAC) therapy.

Methods: Using data from the Global Registry of Acute Coronary Syndromes (GRACE), patient characteristics, treatment, and reperfusion strategies of STEMI patients on chronic OAC are described, and relevant variables compared with patients not on chronic OAC. Six-month post-discharge mortality rates were evaluated by Cox proportional hazard models.

Results: Of 19,094 patients with STEMI, 574 (3.0%) were on chronic OAC at admission. Compared with OAC non-users, OAC users were older (mean age 73 vs. 65 years), more likely to be female (37 vs. 29%), were more likely to have a history of atrial fibrillation, prosthetic heart valve, venous thromboembolism, or stroke/transient ischaemic attack, had a higher mean GRACE risk score (166 vs. 145), were less likely to be Killip class I (68 vs. 82%), and were less likely to undergo catheterization/percutaneous coronary intervention (52 vs. 66%, respectively). Of the patients who underwent catheterization, fewer OAC users had the procedure done within 24 h of admission (56.5 vs. 64.5% of OAC non-users). In propensity-matched analyses (n=606), rates of in-hospital major bleeding and in-hospital and 6-month post-discharge mortality were similar for OAC users and OAC non-users (2.7 and 3.7%, p=0.64; 15 and 13%, p=0.56; 15 and 12%, p=0.47, respectively), rates of in-hospital recurrent myocardial infarction (8.6 and 2.0%, p<0.001) and atrial fibrillation (32 and 22%, p=0.004) were higher in OAC patients, and rates of 6-month stroke were lower (0.6 and 4.3%, p=0.038). Patients in both groups who underwent catheterization had lower mortality than those who did not undergo catheterization.

Conclusions: This is the largest study to describe the characteristics and treatment of STEMI patients on chronic OAC. The findings suggest that patients on chronic OAC are less likely to receive guideline-indicated management, but have similar adjusted rates of in-hospital and 6-month mortality.

Keywords

Acute coronary syndrome, anticoagulant, guidelines, myocardial infarction

Received: 8 May 2012; accepted: 27 February 2013

[1]Tulane University Heart and Vascular Institute, New Orleans, LA, USA
[2]University of Massachusetts Medical School, Worcester, MA, USA
[3]Mercer University School of Medicine, Macon, GA, USA
[4]Centre Hospitalier Universitaire Pitié-Salpétrière, Paris, France
[5]University Hospitals Leuven, Leuven, Belgium
[6]Herzzentrum Ludwigshafen, Ludwigshafen, Germany
[7]University of Edinburgh, Edinburgh, UK
[8]University of Michigan Cardiovascular Center, Ann Arbor, MI, USA
[9]Duke University Medical Center, Durham, NC, USA
[10]INSERM U-698, Paris, France
[11]Université Paris 7, Paris, France
[12]Hôpital Bichat Claude Bernard, AP-HP, Paris, France

Corresponding author:
Joel M Gore, Division of Cardiovascular Medicine, University of Massachusetts Medical School, 55 Lake Avenue North, Worcester, MA 01655, USA.
Email: Joel.Gore@umassmemorial.org

Introduction

The management of patients on chronic oral anticoagulation (OAC) who develop ST-segment elevation myocardial infarction (STEMI) presents a clinical conundrum. Many clinicians withhold or delay effective reperfusion and antithrombotic or antiplatelet therapies because of concerns over a potentially higher risk of bleeding among these patients.

Little is known about the best treatment strategy in this subset of patients when they present acutely. No randomized trials have addressed this question, and guidelines limit their comments on patients on OAC who present with STEMI to statements of caution due to a potentially increased bleeding risk.[1–3] The goal of this study was to describe the characteristics, treatments (reperfusion and associated therapies), and in-hospital and 6-month mortality rates in patients on chronic OAC and presenting with STEMI using data from the Global Registry of Acute Coronary Events (GRACE) and to compare them with patients not on chronic OAC.

Methods

Patients

GRACE was a prospective, multinational, observational registry in patients hospitalized for an acute coronary event (www.outcomes.org/grace). The design and methods have been published previously.[4] Briefly, GRACE included 70,359 patients admitted to 126 hospitals in 14 countries between 1999 and 2007. GRACE was designed to reflect a population representative of patients with acute coronary syndromes (ACS), irrespective of geographical region. Patients entered into the registry had to be ≥18 years old, alive at the time of hospital presentation, admitted with a presumptive diagnosis of ACS, and have one or more of the following: electrocardiographic changes consistent with ACS, serial increases in serum biochemical markers of cardiac necrosis, and documentation of coronary artery disease. The qualifying ACS must not have been precipitated by a significant non-cardiovascular comorbidity such as trauma or surgery. Patients were followed up for approximately 6 months after hospital discharge. The population for this study included 19,094 patients with STEMI, 574 of whom were receiving OAC at the time of hospital admission. Where required, study investigators received approval from their local hospital ethics or institutional review board for the conduct of the study.

Definitions

To characterize the onset of a myocardial infarction (MI) as a hospital outcome, it had to have occurred >24 h after hospital presentation, to have been confirmed by electrocardiographic changes or elevation of cardiac biomarkers, and to have involved one of the following scenarios: (a) patients with an admission diagnosis of unstable angina who developed an MI; (b) patients who were diagnosed with an MI after coronary artery bypass graft surgery (CABG) or a percutaneous coronary intervention (PCI) provided they had qualified for enrolment before the CABG or PCI; or (c) patients who had presented with an MI and were diagnosed as having had recurrent MI.

Patients receiving chronic OAC were defined as those routinely taking a vitamin K antagonist at home and within 7 days of hospital presentation.

All patients in whom cardiac catheterization was performed were included in the catheterization and/or PCI (Cath/PCI) group, regardless of whether a PCI was performed. Hours to Cath/PCI was defined as the time to the earliest procedure. The medical therapy group was defined as those who did not undergo Cath/PCI. Major bleeding in hospital had to be life threatening, require a transfusion of ≥2 units of packed red cells, cause a ≥10% decrease in haematocrit, or result in death. Six-month mortality encompassed all deaths occurring during the 180 days from the time of discharge from hospital.

Statistical methods

Data are presented as frequencies and percentages for categorical data, and as means and standard deviations (SD) for continuous variables. *p*-values are for Fisher's Exact test for binomial variables and the Wilcoxon rank-sum test for continuous variables. All tests were two-sided with $\alpha = 0.05$. All analyses were performed using SAS software version 9.1 (SAS Institute, Cary, NC, USA).

To determine whether there was a relationship between time to Cath/PCI and 6-month mortality in STEMI patients on chronic OAC, Cox proportional hazard models were used, unadjusted and adjusted for other factors potentially associated with death. Candidate variables for adjustment included the GRACE risk score;[5] age; sex; new ST-segment elevation or left bundle branch block after the initial electrocardiogram; country; medical history of congestive heart failure (CHF), hypertension, peripheral artery disease, CABG, transient ischaemic attack (TIA) or stroke, atrial fibrillation, bleeding, coronary artery disease, MI, angina, or renal insufficiency; and chronic use of aspirin, thienopyridine, oral beta-blockers, diuretics, or amiodarone. After step-wise regression, the following significant ($p<0.05$) variables were retained in the model: GRACE risk score, medical history of CHF, and recurrent ST-segment elevation or new left bundle branch block. Complete covariate data were available for 472 patients. Cath/PCI was included in the model as a time-varying covariate to account for the fact that the patient's Cath/PCI status could change during hospitalization.

The proportional hazards assumption was checked for all variables using a covariate-by-time interaction, which

Table 1. Baseline characteristics of GRACE STEMI patients by chronic OAC status.

Characteristic	OAC users (*n*=574)	OAC non-users (*n*=18,520)	*p*-value
Age (years)	73±12	65±14	<0.001
<65	130 (22.7)	9306 (50.4)	<0.001
65–74	144 (25.1)	4439 (24)	0.55
75–84	226 (39.4)	3488 (18.9)	<0.001
≥85	74 (12.9)	1244 (6.7)	<0.001
Male sex	361 (63.1)	13,011 (70.6)	<0.001
Medical history			
Atrial fibrillation	306 (53.7)	783 (4.3)	<0.001
Prosthetic valve[a]	23 (7.0)	30 (0.3)	<0.001
Venous thromboembolism[b]	40 (12.2)	121 (1.2)	<0.001
Stroke/TIA	139 (24.3)	1168 (6.4)	<0.001
Myocardial infarction	253 (44.2)	3459 (18.8)	<0.001
Congestive heart failure	154 (27.1)	1121 (6.1)	<0.001
PCI	123 (21.6)	1689 (9.2)	<0.001
CABG	109 (19.2)	917 (5.0)	<0.001
Diabetes	165 (28.9)	3880 (21.1)	<0.001
Hypertension	383 (67.3)	9773 (53.0)	<0.001
Hyperlipidaemia	248 (44.0)	7068 (38.5)	0.008
Smoking	273 (47.9)	11,179 (60.7)	<0.001
Peripheral arterial disease	101 (17.7)	1225 (6.7)	<0.001
Renal insufficiency	76 (13.3)	1000 (5.4)	<0.001
Major bleeding	7 (1.2)	175 (1.0)	0.51

Values are mean±SD or *n* (%). Exact sample size for a given characteristic may vary slightly due to missing data. Two-sided Wilcoxon rank sum test for continuous variables; two-sided Fisher's Exact test for binomial variables.
[a]Data for ~2002–2007; *n*=10,538.
[b]Data for ~2002–2007; *n*=10,518.
CABG, coronary artery bypass graft surgery; GRACE, Global Registry of Acute Coronary Events; OAC, oral anticoagulation; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischaemic attack.

was violated ($p \leq 0.05$) for time to Cath/PCI, meaning that the effect of Cath/PCI on death changed according to when the Cath/PCI was performed. The time of Cath/PCI was therefore classified into several categories for comparison with those not receiving Cath/PCI.

Propensity-matched analyses. Propensity matching was performed to compare event rates in OAC users and non-users. Multiple logistic regressions were done on a model whose outcome was OAC use or non-use, considering as covariates patient characteristics that showed the greatest difference between the two groups. One-to-one matching of OAC to non-OAC users was done, as the latter had a low probability of receiving OAC and thus had no OAC counterpart, whereas most OAC patients had at least one non-OAC counterpart. The probability of each matched pair's OAC use differed at most by 0.01.

Results

Patient population

Of the overall GRACE population 19,094 patients presented with STEMI, 574 (3.0%) of whom were OAC users. Patients' baseline characteristics are shown in Table 1. OAC users were significantly older and more likely to be female. Rates of atrial fibrillation, prosthetic heart valves, history of stroke/TIA, and history of MI were significantly higher among OAC users, whereas smoking was significantly more frequent among OAC non-users. There was no difference in history of major bleeding.

OAC users had an overall worse Killip class and a higher GRACE risk score compared with OAC non-users (Table 2). Nearly one-third of patients on OAC were in the highest GRACE risk category compared with 16.0% of OAC non-users.

Medications

At admission, OAC users were more likely than OAC non-users to be taking beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB), and statins, whereas aspirin and thienopyridine use was similar in both groups (Table 3).

During hospitalization, fewer of the OAC users received aspirin, beta-blockers, statins, or thienopyridines compared with OAC non-users (Table 3). Vitamin K antagonist therapy was maintained in 52.4% of OAC

Table 2. Clinical characteristics on presentation of GRACE STEMI patients by chronic OAC status.

Characteristic	OAC users (*n*=574)	OAC non-users (*n*=18,520)	*p*-value
Pulse (beats/min)[a]	85±27	80±22	<0.001
SBP (mmHg)[b]	135±33	138±30	0.012
Initial creatinine (mg/dl)[c]	1.3±0.8	1.2±0.8	<0.001
Cardiac arrest	23 (4.1)	600 (3.3)	0.28
Killip class			
I	385 (68.0)	14,845 (81.7)	<0.001
II	115 (20.3)	2304 (12.7)	<0.001
III	56 (9.9)	730 (4.0)	<0.001
IV	10 (1.8)	299 (1.6)	0.74
GRACE risk score[d]			
Overall score	166±35	145±36	<0.001
Risk category			
Low[e]	120 (22.6)	7975 (47.7)	<0.001
Moderate[f]	240 (45.1)	6084 (36.4)	<0.001
High[g]	172 (32.3)	2675 (16.0)	<0.001

Values are mean±SD or *n* (%). Exact sample size for a given characteristic may vary slightly due to missing data. Two-sided Wilcoxon rank sum test for continuous variables; two-sided Fisher's Exact test for binomial variables.
[a]Data available for 566 and 18,185 patients in the two groups.
[b]Data available for 567 and 18,244 patients in the two groups.
[c]Data available for 558 and 17,729 patients in the two groups.
[d]Data available for 532 and 16,734 patients in the two groups.
[e]GRACE risk score <140; risk of death <2.9%.
fGRACE risk score ≥140 and <180; risk of death <9.8%.
[g]GRACE risk score ≥180; risk of death ≥9.8%.
GRACE, Global Registry of Acute Coronary Events; OAC, oral anticoagulation; SBP, systolic blood pressure; STEMI, ST-segment elevation myocardial infarction.

Table 3. Medications of GRACE STEMI patients by chronic OAC status.

Medication	OAC users (*n*=574)	OAC non-users (*n*=18,520)	*p*-value
Prior to admission			
Aspirin	149 (26.1)	4472 (24.2)	0.30
Thienopyridine	25 (4.5)	550 (3.0)	0.06
ACEI/ARB	253 (45.1)	4125 (22.5)	<0.001
Beta-blockers	256 (45.1)	3540 (19.2)	<0.001
Statins	164 (28.7)	2833 (15.4)	<0.001
In hospital			
Aspirin	463 (80.9)	17,471 (94.4)	<0.001
Thienopyridine	222 (39.6)	10,645 (57.7)	<0.001
Glycoprotein IIb/IIIa inhibitors	133 (23.5)	6303 (34.2)	<0.001
Unfractionated/LMW heparin	439 (76.6)	15,984 (86.6)	<0.001
Vitamin K antagonist	301 (52.4)	857 (4.6)	<0.001
ACEI/ARB	416 (73.1)	13,605 (73.8)	0.73
Beta-blockers	451 (79.5)	15,672 (84.9)	<0.001
Statins	317 (55.5)	12,585 (68.2)	<0.001
At discharge[a]			
Aspirin	302 (73.3)	14,386 (93.2)	<0.001
Thienopyridine	181 (44.6)	8848 (57.5)	<0.001
Vitamin K antagonist	269 (65.1)	816 (5.3)	<0.001
ACEI/ARB	303 (74.5)	11,166 (72.6)	0.43
Beta-blockers	302 (73.7)	12,470 (80.9)	<0.001
Statins	250 (60.8)	11,191 (72.7)	<0.001

Values are *n* (%). Exact sample size for a given characteristic may vary slightly due to missing data. Two-sided Fisher's Exact test.
[a]Data available for 413 and 15,448 patients in the two groups.
ACEI/ARB, angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers; GRACE, Global Registry of Acute Coronary Events; LMW, low-molecular-weight; OAC, oral anticoagulation; STEMI, ST-segment elevation myocardial infarction.

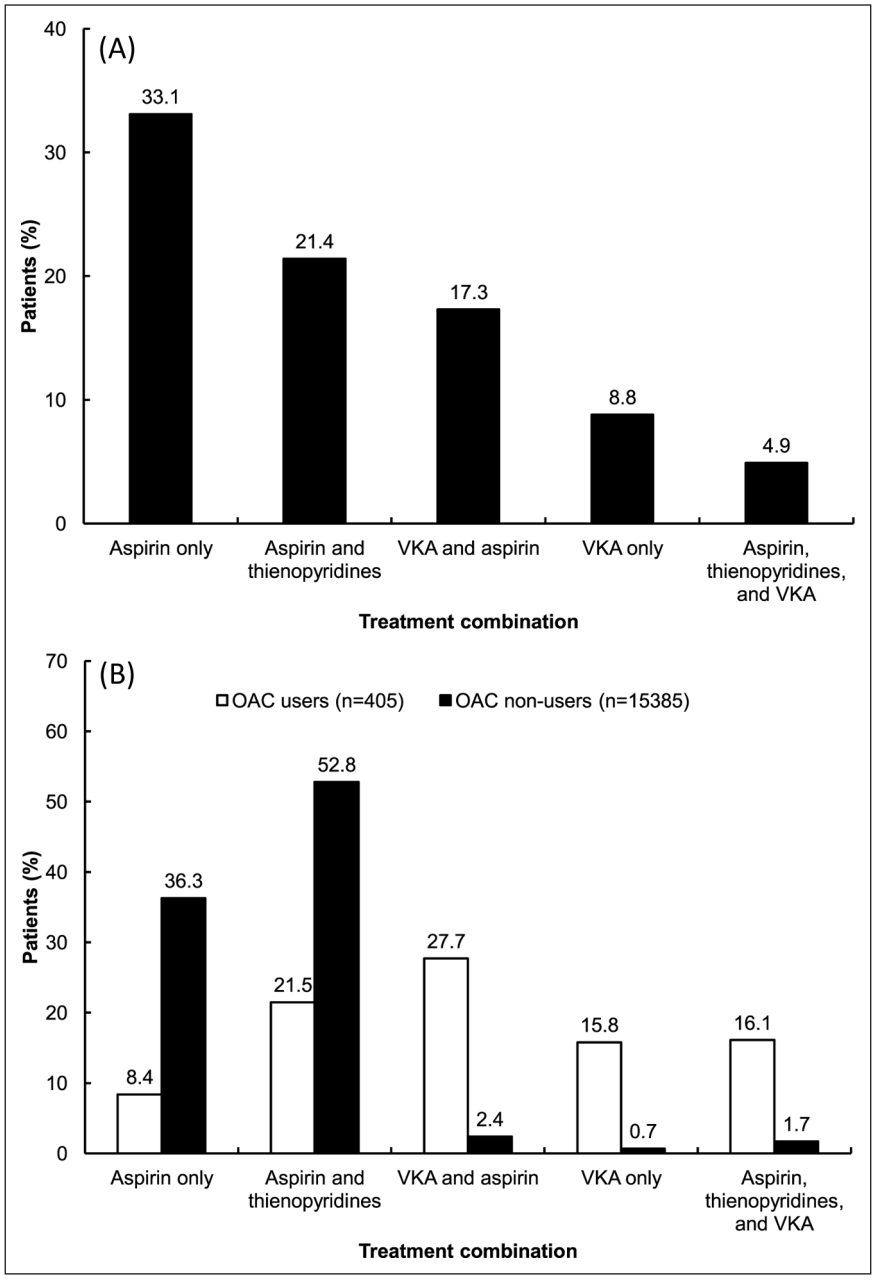

Figure 1. (A) Antiplatelet and anticoagulant agent administration in the first 24 h among 556 STEMI patients on chronic OAC with status known for all three agents. (B) Selected medication combinations at discharge from hospital among STEMI patients with status known for all three medications.
Categories are mutually exclusive.

patients during hospitalization and in 65.1% at discharge, compared with 4.6 and 5.3%, respectively, of OAC non-users. Use of antiplatelet and anticoagulant drugs administered in the first 24 h of admission among OAC users is shown in Figure 1A.

At discharge from hospital, OAC non-users were most likely to be given aspirin and thienopyridines (52.8%) or aspirin alone (36.3%), whereas medical therapy for OAC users was more varied (Figure 1B).

Interventions and clinical outcomes

The rate of Cath/PCI during hospitalization was lower among OAC users than among OAC non-users (Table 4). Of the patients who had a Cath/PCI, just over half of the OAC users had the procedure performed in the first 24 h compared with almost two-thirds of OAC non-users.

Data were available for propensity matching in 319 patients because the strongest covariates associated with

Table 4. In-hospital interventions by chronic OAC status.

Intervention	OAC users (*n*=574)	OAC non-users (*n*=18,520)	*p*-value
Cath/PCI	295 (52.0)	12,014 (66.0)	<0.001
<6 h	130 (45.9)	6080 (53.3)	0.016
6 to <12 h	17 (6.0)	489 (4.3)	0.18
<12 h	147 (51.9)	6569 (57.6)	0.06
12–48 h	37 (13.1)	1774 (15.6)	0.28
>48 h	99 (35.0)	3064 (26.9)	0.004
≤24 h	160 (56.5)	7362 (64.5)	0.007
Stented	168 (29.0)	8373 (45.0)	<0.001
CABG	20 (3.6)	609 (3.3)	0.72
Fibrinolytic	59 (10.4)	5814 (32.0)	<0.001

Values are *n* (%). Exact sample size for a given characteristic may vary slightly due to missing data. Two-sided Fisher's Exact test.
CABG, coronary artery bypass graft surgery; Cath/PCI, cardiac catheterization and/or percutaneous coronary intervention; OAC, oral anticoagulation; the total Cath/PCI not known fo all patients.

Table 5. Propensity analysis: event rates by chronic OAC status.

Event	OAC users (*n*=303)	OAC non-users (*n*=303)	*p*-value
In-hospital			
Major bleeding			
Overall	8 (2.7)	11 (3.7)	0.64
With Cath/PCI	6 (4.3)	5 (3.6)	0.99
Recurrent MI >24 hours after hospitalization[a]	26 (8.6)	6 (2.0)	<0.001
CHF/pulmonary oedema	84 (27.7)	72 (23.8)	0.31
Cardiogenic shock	27 (8.9)	20 (6.6)	0.36
Cardiac arrest/ventricular fibrillation	39 (12.9)	29 (9.7)	0.25
Sustained ventricular tachycardia	18 (6.0)	18 (5.9)	0.99
Atrial fibrillation	97 (32.2)	66 (21.9)	0.004
Renal failure	37 (12.4)	31 (10.3)	0.44
Mortality			
Overall	46 (15.2)	40 (13.2)	0.56
With Cath/PCI	16 (10.3)	10 (6.0)	0.22
With Cath/PCI <12 h	10 (12.2)	10 (10.9)	0.82
6 months after discharge[b]			
Death	30 (14.7)	24 (11.8)	0.47
Myocardial infarction	7 (4.1)	8 (4.3)	0.99
Stroke	1 (0.6)	8 (4.3)	0.038

Values are *n* (%) Exact sample size for a given characteristic may vary slightly due to missing data. Two-sided Fisher's Exact test.
[a]Data for ~2002–2007; *n*=603.
[b]From hospital discharge to 6 months post discharge. Data available for 204 and 204 patients in the two groups.
Cath/PCI, cardiac catheterization and/or percutaneous coronary intervention; CHF, congestive heart failure; OAC, oral anticoagulation; MI, myocardial infarction.

chronic OAC use were available only in the most recent version of the case report form. Non-OAC counterparts with similar model probabilities were found for 303 of these patients. In multiple logistic regression, the three strongest factors associated with chronic OAC use were medical history of atrial fibrillation, venous thromboembolism, and prosthetic valve replacement; other factors included age, presentation in Killip class III, and medical history of transient ischaemic attack, congestive heart failure, percutaneous coronary intervention, coronary artery bypass graft, and diabetes mellitus. The model c-statistic was 0.92.

After propensity matching, the three strongest factors in univariate analysis were similar among OAC users and non-users: 55.1% of OAC users and 55.7% of non-users had a history of atrial fibrillation; 6.3 and 3.6% had a prosthetic valve replacement; and 11.2 and 12.2% had a history of venous thromboembolism (full data not shown). In propensity-matched analyses, there was no significant difference in the overall frequency of in-hospital major bleeding in OAC users and non-users (Table 5), while recurrent MI and atrial fibrillation occurred more frequently in OAC users. Unadjusted in-hospital mortality rates were higher

among OAC users than non-users (15.2 vs. 7.4%, $p<0.0001$; full data not shown), but were similar after propensity matching (15.2 and 13.2%; Table 5). Among discharged patients, OAC users had a higher unadjusted mortality rate at 6 months than non-users (13.4 vs. 4.3%, $p<0.0001$; data not shown), whereas propensity-adjusted differences were not statistically significant (14.7 vs. 11.8%, $p=0.47$; Table 5). Adjusted 6-month stroke rates were lower in OAC users (Table 5). No other adjusted differences were found.

Impact of Cath/PCI in OAC users

OAC users who underwent Cath/PCI during hospitalization were significantly younger, more likely to be male, to be in Killip class I, and have a lower GRACE risk score than OAC users who were treated with medical therapy only, whereas history of CABG did not differ between the two groups (Table 6).

Major bleeding occurred at a higher rate in OAC users who had Cath/PCI compared to those treated medically, but hospital mortality was higher for patients treated medically. Among patients discharged alive from hospital, 20.0% of medically treated patients died within 6 months compared with 6.9% of those who underwent Cath/PCI (Table 6).

Impact of timing of catheterization and use of OAC

The unadjusted Cox model suggested a survival advantage among OAC users undergoing Cath/PCI within 12 h of admission compared with those not undergoing Cath/PCI (Figure 2A). However, the adjusted Cox model did not reveal a significant difference between the Cath/PCI and medical therapy groups regardless of the timing of the Cath/PCI (Figure 2A).

Among OAC non-users, unadjusted and adjusted 6-month mortality was significantly lower among patients undergoing Cath/PCI within 12 h compared with no Cath/PCI (Figure 2B).

Discussion

This study describes the clinical and treatment characteristics of patients on chronic OAC presenting with STEMI, as evaluated in the GRACE registry. Overall, these patients appeared to be less likely to undergo Cath/PCI, to receive antiplatelet and antithrombotic medications, or to receive other evidence-based therapies compared with STEMI patients not on chronic OAC.

Previous studies have highlighted the importance of pre-existing conditions (e.g. valvular disease and cerebrovascular events) in the treatment selection and outcomes of patients presenting with an ACS.[6,7] The use of OAC has been associated with adverse in-hospital events in the non-ST-elevation ACS population. In another GRACE study, patients on chronic OAC were found to have a 6% higher in-hospital adverse event rate than patients not on OAC.[8] In the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the American College of Cardiology/American Heart Association guidelines (CRUSADE) Registry, non-ST-segment elevation ACS patients on OAC at admission (n=7201) were less likely to receive antiplatelet and antithrombotic medications than patients not on OAC (n=93,877).[9] Furthermore, patients on chronic OAC were less likely to undergo diagnostic cardiac catheterization, PCI, or CABG, and waiting times for these procedures were longer.[9] Likewise, the RICO Survey of 2112 STEMI patients showed that the 93 patients on OAC were less likely to undergo reperfusion therapy or receive antiplatelet agents than patients not on OAC, and they experienced a higher incidence of in-hospital death, recurrent MI, and bleeding.[10] Our study shows similar results among the STEMI population. We found that STEMI patients on chronic OAC were also less likely to undergo reperfusion and that, when this was performed, it was seldom within the recommended times.

Choice of reperfusion therapy

An analysis of data from GRACE found that the use of evidence-based therapies and PCI has increased over time in the STEMI population, and this has been matched with statistically significant decreases in the rates of death, cardiogenic shock, and heart failure compared to fibrinolysis.[11] A concern specific to emergency PCI is that of access-site bleeding complications, particularly among patients receiving OAC. We found a significantly higher frequency of major bleeding among patients who underwent cardiac catheterization, but whether this was directly related to the degree of anticoagulation (international normalized ratio, INR) or to the more frequent of use of anticoagulant and antiplatelet therapies in the Cath/PCI group is not known. Overcoagulation is likely to have occurred and may explain these findings.

We analysed the data for either diagnostic catheterization or catheterization followed by a PCI assuming an intention to perform a PCI, because in real life, not all patients who present with STEMI have a coronary anatomy suitable for this procedure. We wanted to emphasize this principle in a challenging population, in which comorbidities and the administration of chronic OAC may have played a significant role in deciding who should undergo Cath/PCI and when it should be performed.

Choice of adjunctive pharmacotherapy and cardiac catheterization access site

With regard to adjunctive pharmacotherapies (e.g. aspirin, thienopyridines, glycoprotein IIb/IIIa inhibitors, heparins, and

Table 6. Characteristics, treatment, and outcomes in OAC patients undergoing Cath/PCI or medical therapy.

Characteristic	Cath/PCI (*n*=295)	Medical therapy (*n*=268)	*p*-value
Age (years)	70±11	76±11	<0.001
Male sex	205 (64.5)	150 (56.4)	0.002
Medical history			
Stroke/TIA	61 (20.7)	74 (27.9)	0.048
PCI	63 (21.6)	58 (21.8)	0.99
CABG	54 (18.6)	51 (19.2)	0.91
Major bleeding	4 (1.4)	3 (1.1)	0.99
Killip class I	220 (75.9)	157 (59.0)	<0.001
GRACE risk score[a]			
Overall score	159±33	174±35	<0.001
High-risk category[b]	61 (22.3)	109 (43.4)	<0.001
In-hospital medication			
Unfractionated/LMW heparin	247 (84.0)	183 (68.3)	<0.001
Glycoprotein IIb/IIIa inhibitor	119 (41)	11 (4.2)	<0.001
Aspirin	268 (91.2)	186 (69.7)	<0.001
Thienopyridine	178 (61.0)	44 (16.8)	<0.001
In-hospital adverse events			
Recurrent myocardial infarction >24 h after hospitalization[c]	12 (7.0)	17 (11.1)	0.24
CHF/pulmonary oedema	61 (20.9)	104 (39.0)	<0.001
Cardiogenic shock	32 (10.9)	24 (9.0)	0.48
Cardiac arrest/ventricular fibrillation	38 (13.0)	38 (14.2)	0.71
Sustained ventricular tachycardia	19 (6.5)	19 (7.1)	0.87
Major bleed/haemorrhagic stroke	18 (6.1)	6 (2.3)	0.035
Death	32 (10.9)	52 (19.4)	0.006
Events within 6 months of discharge[d]			
Death	15 (6.9)	36 (20.0)	<0.001
Myocardial infarction	6 (3.3)	7 (4.9)	0.57
Stroke	2 (1.0)	1 (0.6)	0.99

Values are mean±SD or *n* (%). Exact sample size for a given characteristic may vary slightly due to missing data. Two-sided Fisher's Exact test.
[a]Data available for 251 and 273 patients in the two groups.
[b]GRACE risk score ≥180; risk of death ≥9.8%.
[c]Data for ~2002–2007; *n*=324.
[d]Data available for 180 and 216 patients in the two groups.
CABG, coronary artery bypass graft surgery; Cath/PCI, cardiac catheterization and/or percutaneous coronary intervention; CHF, congestive heart failure; GRACE, Global Registry of Acute Coronary Events; LMW, low-molecular-weight; OAC, oral anticoagulation; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack.

direct thrombin inhibitors) in OAC patients presenting with STEMI, there is no evidence to suggest that one drug is better or safer than another because these patients have traditionally been excluded from clinical trials involving such treatments (Table 7).[12–32] Neither do we know whether different loading or maintenance doses of these drugs should be used.

The same applies to the choice of access site for cardiac catheterization. Two recent trials provide evidence that transradial catheterization is associated with a lower bleeding risk, but they too excluded patients on OAC.[16,24] It would appear reasonable, however, to infer that patients on OAC should preferably undergo transradial catheterization.

In the absence of evidence, the use of anticoagulation in the cardiac catheterization laboratory varies widely for OAC patients with STEMI: while some operators may choose the direct thrombin inhibitor bivalirudin because of its overall lower bleeding risk, others elect to use unfractionated heparin because its effects can be reversed with protamine in the event that bleeding occurs.

Discharge medications and outcomes

Another central problem is the systematic definition of a discharge medication plan for patients who require single or dual antiplatelet therapy in addition to OAC due to their long-term bleeding risk. These patients are treated with great variability. Various retrospective and prospective studies have addressed the role of triple therapy (aspirin plus thienopyridine plus vitamin K antagonist) and bleeding risk.[33–35] A multicentre, randomized, open-label trial is underway to assess whether the combination of OAC and clopidogrel reduces the risk of bleeding and is not inferior

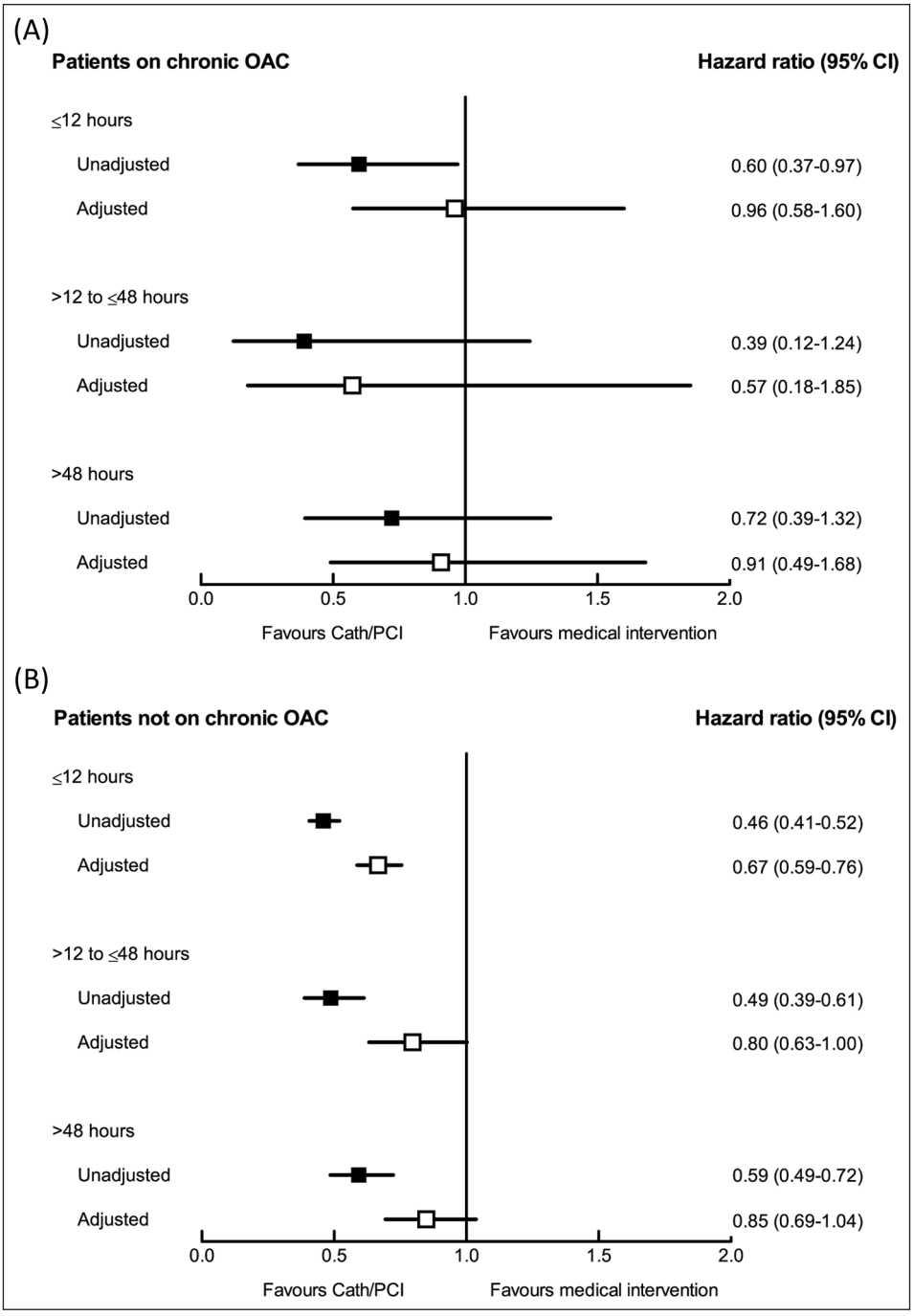

Figure 2. Hazard ratios for 6-month death in cardiac catheterization and/or percutaneous coronary intervention vs. medical therapy in (A) OAC users and (B) OAC non-users.

to triple therapy with respect to the prevention of thrombotic complications after PCI in patients on OAC.[36]

Limitations

There are several limitations to our observational study. Data were not available regarding the degree of anticoagulation of these patients upon presentation, particularly when considering that subtherapeutic INR levels have been reported in 22–43% of patients on OAC.[37,38] It is possible that part of the complex decision making for these patients would be affected by the INR levels, and this may have played a role in selection bias. We could not assess the impact of transradial versus transfemoral access on bleeding complications in the

Table 7. Selected landmark antiplatelet, anticoagulant, interventional, or STEMI management trials excluding patients on OAC.

Study	Intervention	Comments
PLATO[12]	Ticagrelor vs. clopidogrel in ACS	Excluded OAC patients
HORIZONS-AMI[13]	Bivalirudin vs. UFH in STEMI	Excluded OAC patients
TRITON-TIMI 38[14]	Prasugrel in ACS	Excluded OAC patients
CURRENT-OASIS 7[15]	Aspirin and clopidogrel, low vs. high dose in ACS	Excluded OAC patients
RIFLE-STEACS[16]	Radial vs. femoral access in STEMI	Excluded OAC patients
ASSENT-3[17]	Fibrinolytic ± GP IIb/IIa and LMWH or UFH	Excluded OAC patients
ASSENT-4[18]	Facilitated PCI	Excluded OAC patients
BRAVE-3[19]	Abciximab after clopidogrel load in STEMI	Excluded OAC patients
INFUSE-AMI[20]	Intracoronary abciximab, thrombus aspiration, or both in STEMI	Excluded OAC patients
GUSTO V[21]	Fibrinolytic and full- vs. low-dose GP IIb/IIIa in STEMI	Excluded OAC patients
ExTRACT-TIMI 25[22,23]	LMWH vs. UFH in STEMI	Excluded OAC patients
RIVAL[24]	Radial access in ACS	Not specified, but excluded patients with bleeding risk
CLASSICS[25]	ASA + clopidogrel with or without loading dose	Excluded OAC patients
PCI-CURE[26]	Clopidogrel pretreatment for PCI in NSTE-ACS	Excluded OAC patients
COMMIT[27]	Clopidogrel vs. placebo + ASA + fibrinolytic in STEMI	Not reported
CLARITY-TIMI 25[28]	Clopidogrel vs. placebo + ASA + fibrinolytic in STEMI	Not reported
APRICOT[29]	ASA vs. OAC to prevent recurrent ischaemia after fibrinolysis	Excluded patients on prior OAC
On-TIME 2[30]	GP IIb/IIIa-facilitated PCI in STEMI	Not specified, but excluded patients with bleeding risk
FINESSE[31,32]	Facilitated PCI vs. primary PCI	Not specified, but excluded patients with bleeding risk

ACS, acute coronary syndromes; ASA, aspirin; GP, glycoprotein; LMWH, low-molecular-weight heparin; OAC, oral anticoagulant; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; UFH, unfractionated heparin.

Cath/PCI group. It is also possible that certain characteristics and outcomes may not have been detected because of our sample size. Nonetheless, this is the largest study to date to explore the outcomes of STEMI patients on chronic OAC and the only one to portray the practice patterns with respect to this challenging patient population.

Although propensity matching was performed for OAC and non-OAC patients, it is unlikely that our propensity-matched patients randomly received, or did not receive, chronic OAC. Thus, no inference should be made attributing chronic warfarin use in itself to better or worse outcomes. Secondly, because the propensity model was unusually discriminant (c-statistic of 0.92), few patients are left with similar propensities, implying the propensity-matched results pertain to a small subset of patients.

Conclusions

This group of patients has a high comorbidity burden, and the choice and timing of reperfusion and adjunctive therapies were based on clinical judgment. Despite apparent unadjusted differences between OAC users and non-users, the following propensity matching rates of in-hospital major bleeding or death and 6-month death were similar between the two groups. When comparing outcomes in STEMI patients on chronic OAC treated with medical therapy with those who received Cath/PCI, the latter were less likely to die in hospital or by 6 months post-discharge. While these observations could reflect adequate patient selection by the treating physicians, they should be interpreted with caution given their limited power and non-randomized nature and because unmeasured variables may have influenced the treatment choice. Furthermore, there are no randomized data to suggest whether a better treatment strategy actually exists. Bleeding complications also appear to be more frequent among STEMI patients on chronic OAC undergoing Cath/PCI. Certainly, more data are required to better treat this intriguing patient population.

Acknowledgments

We thank the patients, physicians and study coordinators participating in GRACE, and the staff at the Center for Outcomes Research, including Gordon FitzGerald for statistical support, Linda Chase and Sophie Rushton-Smith. Further information about the project, along with the complete list of participants, can be found at www.outcomes.org/grace.

Conflict of interest

Sanofi-Aventis had no involvement in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication. The design, conduct, and

interpretation of GRACE data are undertaken by an independent steering committee. AA, HHA, ALQ and AW declare no conflicts of interest. JMG has received speaker and consulting honoraria and research grant support from Sanofi-Aventis. GM has received speaker and consulting honoraria and research grant support from Sanofi-Aventis and Eli Lilly. FVdeW has received research grant support from Boehringer Ingelheim, Genentech, and Sanofi-Aventis. DCG has received research grant support from Sanofi-Aventis. KAAF and KAE have received speaker and consulting honoraria and research grant support from Sanofi-Aventis and Bristol-Myers-Squibb. CBG has received research grant support from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb Company, GlaxoSmithKline, Eli Lilly, Medtronic, Merck, Novartis, Roche, Sanofi-Aventis, The Medicines Company, and INO Therapeutics. PhGS has received research grants from Servier and consultancy fees/honoraria from Amgen, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo/Eli Lilly alliance, Eisai, GlaxoSmithKline, Medtronic, Merck Sharpe and Dohme, Pfizer, Roche, Sanofi-Aventis, Servier, and The Medicines Company and has equity ownership in Aterovax.

Funding

This work was supported by a grant from Sanofi-Aventis to the Center for Outcomes Research, University of Massachusetts Medical School.

References

1. Lloyd-Jones D, Adams R, Carnethon M, et al.; Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics – 2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2009; 119: e21–e181.
2. Van de Werf F, Bax J, Betriu A, et al.; ESC Committee for Practice Guidelines (CPG). Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology. *Eur Heart J* 2008; 29: 2909–2945.
3. Antman EM, Anbe DT, Armstrong PW, et al.; American College of Cardiology, American Heart Association Task Force on Practice Guidelines, Canadian Cardiovascular Society. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *Circulation* 2004; 110: e82–e292.
4. GRACE Investigators. Rationale and design of the GRACE (Global Registry of Acute Coronary Events) Project: a multinational registry of patients hospitalized with acute coronary syndromes. *Am Heart J* 2001; 141: 190–199.
5. Eagle KA, Lim MJ, Dabbous OH, et al.; GRACE 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.
6. Hasdai D, Lev EI, Behar S, et al. Acute coronary syndromes in patients with pre-existing moderate to severe valvular disease of the heart: lessons from the Euro-Heart Survey of acute coronary syndromes. *Eur Heart J* 2003; 24: 623–629.
7. Hasdai D, Haim M, Behar S, et al. Acute coronary syndromes in patients with prior cerebrovascular events: lessons from the Euro-Heart Survey of Acute Coronary Syndromes. *Am Heart J* 2003; 146: 832–838.
8. Brieger D, Fox KA, Fitzgerald G, et al.; Global Registry of Acute Coronary Events Investigators. Predicting freedom from clinical events in non-ST-elevation acute coronary syndromes: the Global Registry of Acute Coronary Events. *Heart* 2009; 95: 888–894.
9. Wang TY, Chen AY, Peterson ED, et al. Impact of home warfarin use on treatment patterns and bleeding complications for patients with non-ST-segment elevation acute coronary syndromes: observations from the CRUSADE quality improvement initiative. *Eur Heart J* 2008; 29: 1103–1109.
10. Oudot A, Steg PG, Danchin N, et al. Impact of chronic oral anticoagulation on management and outcomes of patients with acute myocardial infarction: data from the RICO survey. *Heart* 2006; 92: 1077–1083.
11. Fox KA, Steg PG, Eagle KA, et al.; GRACE Investigators. Decline in rates of death and heart failure in acute coronary syndromes, 1999–2006. *JAMA* 2007; 297: 1892–1900.
12. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009; 361: 1045–1057.
13. Stone GW, Witzenbichler B, Guagliumi G, et al.; HORIZONS-AMI Trial Investigators. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med* 2008; 358: 2218–2230.
14. Wiviott SD, Antman EM, Gibson CM, et al.; TRITON-TIMI 38 Investigators. Evaluation of prasugrel compared with clopidogrel in patients with acute coronary syndromes: design and rationale for the TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet InhibitioN with prasugrel Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38). *Am Heart J* 2006; 152: 627–635.
15. CURRENT-OASIS 7 Investigators, Mehta SR, Bassand JP, et al. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. *N Engl J Med* 2010; 363: 930–942.
16. Romagnoli E, Biondi-Zoccai G, Sciahbasi A, et al. Radial versus femoral randomized investigation in ST-segment elevation acute coronary syndrome: the RIFLE-STEACS (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) study. *J Am Coll Cardiol* 2012; 60: 2481–2489.
17. ASSENT 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.
18. ASSENT investigators. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. *Lancet* 2006; 367: 569–578.
19. Mehilli J, Kastrati A, Schulz S, et al.; Bavarian Reperfusion Alternatives Evaluation-3 (BRAVE-3) Study Investigators. Abciximab in patients with acute ST-segment-elevation

myocardial infarction undergoing primary percutaneous coronary intervention after clopidogrel loading: a randomized double-blind trial. *Circulation* 2009; 119: 1933–1940.
20. Stone GW, Maehara A, Witzenbichler B, et al.; INFUSE-AMI Investigators Intracoronary abciximab and aspiration thrombectomy in patients with large anterior myocardial infarction: the INFUSE-AMI randomized trial. *JAMA* 2012; 307: 1817–1826.
21. Topol EJ and GUSTO V Investigators. Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: the GUSTO V randomised trial. *Lancet* 2001; 357: 1905–1914.
22. Antman EM, Morrow DA, McCabe CH, et al.; ExTRACT-TIMI 25 Investigators. Enoxaparin versus unfractionated heparin as antithrombin therapy in patients receiving fibrinolysis for ST-elevation myocardial infarction. Design and rationale for the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment-Thrombolysis In Myocardial Infarction study 25 (ExTRACT-TIMI 25). *Am Heart J* 2005; 149: 217–226.
23. Antman EM, Morrow DA, McCabe CH, et al.; ExTRACT-TIMI 25 Investigators. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. *N Engl J Med* 2006; 354: 1477–1488.
24. Jolly SS, Yusuf S, Cairns J, et al.; RIVAL trial group. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. *Lancet* 2011; 377: 1409–1420.
25. Bertrand ME, Rupprecht HJ, Urban P, et al.; CLASSICS Investigators. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: the Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS). *Circulation* 2000; 102: 624–629.
26. Mehta SR, Yusuf S, Peters RJ, et al.; Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) Investigators. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001; 358: 527–533.
27. Chen ZM, Jiang LX, Chen YP, et al.; COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005; 366: 1607–1621.
28. Sabatine MS, Cannon CP, Gibson CM, et al.; CLARITY-TIMI 28 Investigators. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005; 352: 1179–1189.
29. Meijer A, Verheugt FW, Werter CJ, et al. Aspirin versus 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.
30. Van't Hof AW, Ten Berg J, Heestermans T, et al.; Ongoing Tirofiban In Myocardial Infarction Evaluation (On-TIME) 2 study group. Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial. *Lancet* 2008; 372: 537–546.
31. Ellis SG, Armstrong P, Betriu A, et al.; Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events Investigators. Facilitated percutaneous coronary intervention versus primary percutaneous coronary intervention: design and rationale of the Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events (FINESSE) trial. *Am Heart J* 2004; 147: E16.
32. Ellis SG, Tendera M, de Belder MA, et al.; FINESSE Investigators. Facilitated PCI in patients with ST-elevation myocardial infarction. *N Engl J Med* 2008; 358: 2205–2217.
33. Zinn A and Feit F. Optimizing antithrombotic strategies in patients with concomitant indications for warfarin undergoing coronary artery stenting. *Am J Cardiol* 2009; 104: 49C–54C.
34. Sorensen R, Hansen ML, Abildstrom SZ, et al. Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. *Lancet* 2009; 374: 1967–1974.
35. Nguyen MC, Lim YL, Walton A, et al.; GRACE Investigators. Combining warfarin and antiplatelet therapy after coronary stenting in the Global Registry of Acute Coronary Events: is it safe and effective to use just one antiplatelet agent? *Eur Heart J* 2007; 28: 1717–1722.
36. Dewilde W and Berg JT. Design and rationale of the WOEST trial: What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing (WOEST). *Am Heart J* 2009; 158: 713–718.
37. Malik AK and Taylor AJ. Can warfarin randomized trials be reproduced in 'real life'? Adherence to warfarin guidelines for intensity of anticoagulation in a university-based warfarin clinic. *South Med J* 2000; 93: 58–61.
38. Newman DH and Zhitomirsky I. The prevalence of nontherapeutic and dangerous international normalized ratios among patients receiving warfarin in the emergency department. *Ann Emerg Med* 2006; 48: 182–189, 189 e181.