Risk of Chronic Oral Anticoagulation Therapy in Patients Undergoing Primary Percutaneous Coronary Intervention for ST Elevation Myocardial Infarction – Retrospective Cross-Sectional Study

BY

Subba Reddy Vanga
MBBS, NTR University of Health Sciences, 2002
MS, Northwestern University, 2011

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Chairperson Won Choi

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Edward Ellerbeck

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Paul Kolm

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The Thesis Committee for Subba Reddy Vanga
certifies that this is the approved version of the following thesis:

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Chairperson: Won Sup Choi, PhD, MPH

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Abstract

Background: Although chronic oral anticoagulation therapy reduces mortality and morbidity from thromboembolic diseases, the risk of bleeding and mortality may increase when patients on anticoagulation presents with acute ST elevation myocardial infarction (STEMI) where aggressive antiplatelet and further anticoagulation therapies are warranted.

Objective: To study the characteristics of patients who are on oral anticoagulation therapy (OAC) at the time of presentation with acute STEMI.

Design: Retrospective, cross-sectional study.

Setting: All patients who presented to Christiana Care Health System, Newark, DE with acute ST elevation myocardial infarction with intent of primary percutaneous angioplasty between January 2009 and December 2010.

Outcome Measures: Composite end-point of major bleeding, in-hospital death, cardiogenic shock, and cardiac arrest. Subgroup analysis of major bleeding and in-hospital mortality.

Results: A total of 637 patients were enrolled into the study, the average age of the study population was 61 years, 71% male and 84% Caucasian patients. Of 637 patients, 20 (3.1%) were on OAC at the time of presentation. Both OAC and non-OAC groups differed in baseline characteristics including hypertension, diabetes mellitus, dyslipidemia, peripheral vascular

disease, previous coronary artery disease, and pre procedural laboratory data including hemoglobin and INR (all $p < 0.05$). The groups also differed in the treatment procedures. Patients who were on OAC were more likely to receive bare metal stents and clopidogrel and less likely to be treated with newer antiplatelet agents (prasugrel and ticagrelor) and drug eluting stents (all $p <0.05$). However, the composite endpoint (death, bleeding, and transfusion) was similar in both groups. On multivariable logistic regression analysis, use of anticoagulation and baseline INR were not significant independent predictors of study endpoints. Pre procedural hemoglobin (OR: 0.88, 95%CI: 0.77-0.98, p=0.012) and requirement of IABP (OR: 4.13, 95% CI: 2.25-7.59, $p<0.001$) were independent risk factors for study end points.

Limitations: Overall sample size for patients who were on anticoagulation was limited due to the low (3%) observed prevalence in the study population, however it is similar to other published studies. The inclusion bias resulting from prehospitalization deaths may influence the results.

Conclusions: The contemporary management of acute ST elevation myocardial infarction does not seem to raise the risk of bleeding, in-hospital death, or blood transfusion in patients who are on full anticoagulation.

To

Moukthika

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Introduction

Chronic Oral Anticoagulation

Chronic anticoagulation is widely used to reduce the risk of thromboembolism. The most common indications for use of long-term anticoagulation are atrial fibrillation, venous thromboembolism (e.g.: deep venous thrombosis or pulmonary embolism), and patients with mechanical heart valves. It is estimated that 4 million patients in the US and nearly 7 million patients worldwide are on long-term therapy with oral anticoagulants, primarily warfarin or other coumarin derivatives, for prevention and treatment of venous and arterial thromboembolism [1]. Selected indications and target doses as recommended by the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines 2012 are shown in Table I. Nearly 31 million warfarin prescriptions were filled in 2004 in the USA [2].

Drugs are commonly used to achieve therapeutic anticoagulation by interfering with clotting cascade (Figure 1). Activation of the clotting system ultimately generates fibrin which stabilizes and forms the backbone of a blood clot. There are 3 main classes of drugs suitable for long term oral anticoagulation. Warfarin, the most commonly used of long-term oral anticoagulant, is a vitamin K Antagonist. Warfarin has been used in clinical practice for more than 50 years. Vitamin K antagonists function by inhibiting the enzyme vitamin K epoxide reductase, which uses vitamin K for post-translational modification of several coagulation proteins (factor VII, factor IX, factor X and prothrombin). Dabigatran, a competitive and reversible direct thrombin inhibitor is a second type of the drug that was approved by FDA in October 2010 for use in atrial fibrillation. A third class of medications that were approved for long term oral anticoagulation

are direct Factor Xa inhibitors such as Apixaban and Rivaroxaban. Apixaban was approved by FDA in 2012 reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Rivaroxaban was approved for prophylaxis of DVT in 2011 followed by approval for stroke prevention in patients with non-valvular atrial fibrillation. In 2012 rivaroxaban was also approved for the treatment DVT and PE. Parenteral heparin and low molecular weight heparin are also occasionally used for long-term anticoagulation and to bridge anticoagulation interruption when surgical procedures are required.

Table I: Selected Anticoagulation Recommendations from the 9th Edition of the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.[3]:

Indication	INR Range	Duration (level of evidence)
Antiphospholipid Syndrome	2.0-3.0	indefinite (2B)
DVT and PE		
Transient/reversible risk factor	2.0-3.0	3 months (1B)
Unprovoked	2.0-3.0	at least 3 months (1B) then reevaluate
Second episode of unprovoked	2.0-3.0	extended (1B)
Non-Valvular Atrial Fibrillation/Atrial Flutter		
$CHADS_2$ Score = 0 (low CVA risk)	N/A	no therapy (2B) or aspirin 75-325mg (2B)
$CHADS_2$ Score = 1 (intermediate CVA risk)	N/A	Long-term with dabigatran (2B)
$CHADS_2$ Score $\geq$ 2 (high CVA risk)	2.0-3.0	Long-term, or long-term dabigatran (2B)
With mitral stenosis	2.0-3.0	long-term (1B)
With stable CAD	2.0-3.0	long-term (2C)
Prior to/following cardioversion to sinus rhythm	2.0-3.0	3 weeks/4weeks (1B)
Mechanical Heart Valve		
Aortic	2.0-3.0	long-term (1B)
Mitral	2.5-3.5	long-term (2C)
Bioprosthetic heart valve		
Aortic	N/A	aspirin 50-100mg (2C)
Mitral	2.0-3.0	3 months then switch to ASA (2C)
Cardioembolic Ischemic Stroke	N/A	dabigatran (2B)

CAD: coronary artery disease; $CHADS_2$ Score: a clinical prediction scoring rule for estimating the risk of stroke in patients with non-rheumatic atrial fibrillation which ranges between 0 and 6; DVT: Deep vein thrombosis; INR: international normalized ratio; PE: pulmonary embolism.

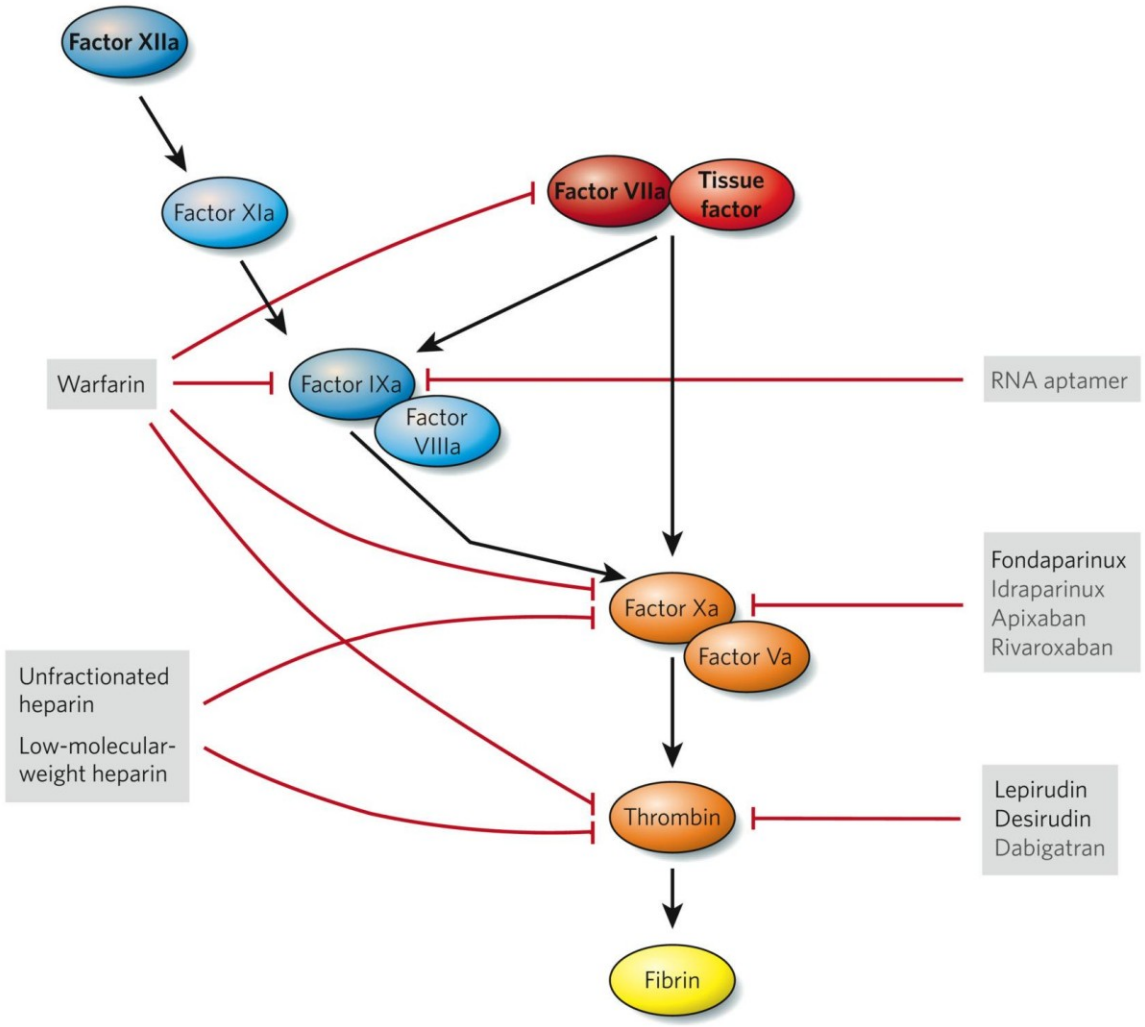

Figure 1: Targets of anticoagulant drugs. When tissue factor is exposed to the blood it binds to the plasma protein factor VIIa (the extrinsic pathway, red). This complex triggers activation of the coagulation cascade through the proteolytic cleavage of both factor X and factor IX and ultimately generates fibrin which on polymerization stabilizes platelet thrombi. The coagulation cascade is amplified by the tenase complex, which consists of factor VIIIa and factor IXa (components of the intrinsic pathway, blue). Factor XIa and factor XIIa might also help to activate the coagulation cascade under pathological conditions. Triggers of thrombosis are shown in bold face. Anticoagulant drugs that are in current use and in development (grey) are listed with their targets (red blocking arrows). Reprinted by permission from Macmillan Publishers Ltd: *Nature* [4], copyright 2008.

Effectiveness of long-term anticoagulation in reducing thromboembolic risk has been well established. In a meta-analysis involving 28,000 patients who have atrial fibrillation, adjusted-dose warfarin was shown to reduce stroke by approximately 60% and death by approximately 25% compared with no antithrombotic treatment [5]. In RE-LY trial, which is a non-inferiority double blind study, patients treated with dabigatran showed rates of stroke and systemic embolism that were similar to those patients who were treated with warfarin (relative risk with dabigatran, 0.91; 95% CI, 0.74-1.11; $P<0.001$ for non-inferiority) [6]. Similarly in ARISTOTLE study, apixaban was shown to be superior to warfarin in reducing stroke in patients with atrial fibrillation (hazard ratio in the apixaban group, 0.79; 95% CI: 0.66 - 0.95; $P<0.001$ for non-inferiority and $P=0.01$ for superiority) [7]. In ROCKET-AF trial, rivaroxaban was also shown non-inferior to warfarin (hazard ratio, 0.88; 95% CI, 0.74 to 1.03; $P<0.001$ for non-inferiority; $P=0.12$ for superiority) [8]. Overall, these studies showed that the average annual risk of stroke in atrial fibrillation is 1.6-1.7 % when treated by warfarin, 1.1% when treated by dabigatran and 1.2 % when treated by apixaban [6, 7].

Atrial fibrillation poses a significant risk for development of stroke and warrants lifelong anticoagulation therapy in a majority of patients. Various risk prediction models have been developed to predict the risk of future stroke in patients with non-valvular atrial fibrillation. The $CHADS_2$ score, is a commonly used tool in the clinical practice, estimates the risk of stroke, which is defined as focal neurologic signs or symptoms that persist for more than 24 hours and that cannot be explained by hemorrhage, trauma, or other factors, or peripheral embolization, excluding transient ischemic attacks [9] . $CHADS_2$ is an acronym for Congestive heart failure, Hypertension, Age>75, Diabetes mellitus, and prior Stroke and the score is calculated by giving

1 point to each condition except stroke which is given 2 points. Therefore $CHADS_2$ score ranges from 0 to 6. A score of 0 is considered low risk, a score of 1 or 2 is considered intermediate risk, and a score ≥3 is considered high risk for stroke. The predicted annual risk of stroke and effect of warfarin in patients with atrial fibrillation is shown in Table II.

Table II: $CHADS_2$ score, thromboembolic risk, and effect of warfarin anticoagulation

$CHADS_2$ score	Events per 100 person-years*		NNT
	Warfarin	No warfarin	
0	0.25	0.49	417
1	0.72	1.52	125
2	1.27	2.50	81
3	2.20	5.27	33
4	2.35	6.02	27
5 or 6	4.60	6.88	44

All differences between warfarin and no warfarin groups are statistically significant except for a trend with a CHADS2 score of 0. NNT: number needed to treat to prevent one stroke per year with warfarin. Data from [9, 10]

Complications of OCA Therapy

The major risk of anticoagulation therapy is bleeding. The FDA's Adverse Event Reporting System indicated that warfarin is among the top 10 drugs with the largest number of serious adverse event reports submitted during the 1990 and 2000 decades. From US death certificates, anticoagulants ranked first in 2003 and 2004 in the number of total mentions of deaths for drugs causing "*adverse effects in therapeutic use*" [2]. Compared to placebo use, warfarin use is associated with a relative risk of 4.8 (95% CI, 2.1-10.8) for fatal bleeding and relative risk of 6.6 (95% CI, 4.0-10.8) for major bleeding. The mean annual frequency of fatal bleeding events was 0.6% (95% CI, 0.4%-0.7%) and major bleeding events were 3.0% (95% CI, 2.6%-3.4%) [2]. Similarly, a population based study has shown that in patients with atrial fibrillation who are on warfarin, the rate of hemorrhage was 3.8% (95% CI 3.8%–3.9%) per person-year [11]. Newer

oral anticoagulation agents had similar bleeding rates that were comparable to warfarin in the initial studies [6-8]. However a meta-analysis of the risk of gastrointestinal bleeding with newer anticoagulant agents showed increased risk with an overall odds ratio of 1.45 (95% CI: 1.07-1.97) and on subgroup analyses the odds ratio for patients with atrial fibrillation was 1.21 (95% CI, 0.91-1.61).

Coronary Artery Disease

Cardiovascular disease is the leading cause of death and a major cause of disability worldwide. In the USA, cardiovascular disease remains the most common cause of death. There has been significant improvement in cardiovascular mortality with cardiovascular related age-adjusted mortality declining from 588.8 deaths per 100,000 in 1950 to 179.1 deaths per 100,000 people in 2010 [12]. The decline in death rate was attributed to various scientific modalities and primary management of coronary artery disease (Fig 2). However, cardiovascular disease and coronary artery disease remain the leading causes of morbidity and mortality.

Clinically coronary artery disease (CAD) represents a spectrum of symptoms and syndromes ranging from asymptomatic clinical finding, chronic stable angina, acute coronary syndromes, and sudden death. Acute coronary syndrome (ACS) is a unifying term representing a common end result, acute myocardial ischemia. ACS itself represents another spectrum of clinical syndromes of acute MI and STEMI represents the most lethal form of ACS, one in which a completely occlusive thrombus results in total cessation of coronary blood flow in the territory of the occluded artery and resultant ST-segment elevation on the ECG.

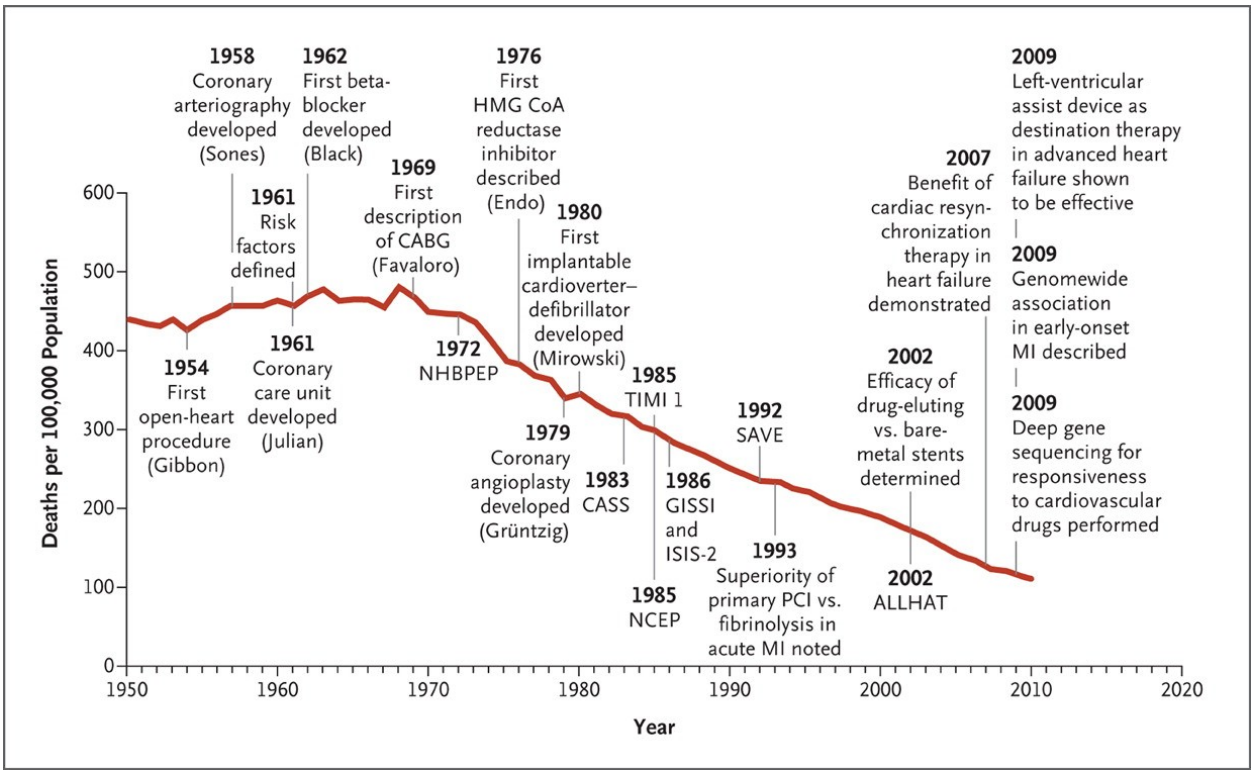

Figure 2: Decline in Deaths from Cardiovascular Disease in Relation to Scientific Advances. The timeline shows the steady decline in cardiovascular deaths over the late 20th and early 21st centuries, along with major advances in cardiovascular science and medicine. ALLHAT denotes Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, CASS Coronary Artery Surgery Study, GISSI Italian Group for the Study of Streptokinase in Myocardial Infarction, HMG-CoA 1-hydroxy-3-methylglutaryl coenzyme A, ISIS-2 Second International Study of Infarct Survival, MI myocardial infarction, NCEP National Cholesterol Education Program, NHBPEP National High Blood Pressure Education Program, PCI percutaneous coronary intervention, SAVE Survival and Ventricular Enlargement, and TIMI 1 Thrombolysis in Myocardial Infarction 1. Reproduced with permission from [13], Copyright Massachusetts Medical Society.

ST Elevation Myocardial Infarction

Although the incidence of CAD was reduced over last few decades, most observational studies have not documented a reduction in the incidence of MI in a variety of time periods [14-17], such as between 1987 and 2006 [18]. Approximately 865,000 new acute myocardial infarctions (AMIs) occur in the United States every year [ref] and nearly 500,000 of them are ST-segment

elevation MI (STEMI) [19]. Of all presentations of ACS, STEMI is associated with the highest mortality.

Further, the accurate and immediate diagnosis of STEMI is of paramount importance for two reasons. First, the diagnosis mandates immediate consideration for reperfusion therapy, either by thrombolytic agents or by mechanical revascularization, most probably PCI. Mortality has been significantly decreased by reperfusion within 12 hours of onset of symptoms in patients with STEMI. However, both pharmacologic and mechanical means of reperfusion have potentially fatal side effects or complications and should not be employed unless the diagnosis is relatively certain. To prevent unnecessary dangers, guidelines were developed.

Treatment, Complications and Prognosis of STEMI

During the last 3 decades, reperfusion therapies have improved progressively by a number of key steps: (1) the development of tissue plasminogen activators, more potent in lysing thrombi than streptokinase; (2) the addition of aspirin and then more potent antiplatelet agents to the fibrinolytic; (3) the use of percutaneous coronary angioplasty following STEMI in place of fibrinolytics; (4) the addition of stents – first bare metal then drug-eluting stents – following intracoronary balloon inflation; and most recently (5) by aspiration thrombectomy prior to coronary stenting. As a consequence of these measures, each of which improved clinical outcomes, in-hospital mortality from STEMI in the general population again declined by half, from 15% to about 7.5% and it is now as low as 3.5% in patients who are enrolled in clinical trials [20] and about 4.8% in large population based registry studies [21]. However, the therapies

are also associated with complications. Non-fatal complications due to acute MI are shown in Table III.

Mortality from complications of acute MI is variable. Mechanical complications are associated with significant mortality while inflammatory complications are usually benign. Patients who developed ventricular septal defect after MI had a 30-day mortality rate of 94% when medically managed and 47% when surgically managed [22]. Papillary muscle rupture resulting in acute mitral regurgitation was found in 7% of patients in cardiogenic shock and contributes to 5% of the mortality after acute MI [23]. However, change in reperfusion strategy from thrombolysis to angioplasty resulted in an 82% decrease in the rate of acute MR, as compared with thrombolytic therapy (0.31% vs 1.73%) [24].

Table III: Non-fatal complications of Acute Myocardial Infarction.

Complication Type	Manifestations	Incidence
Ischemic	Angina, reinfarction, infarct extension	5% - 30%
Mechanical	Heart failure, cardiogenic shock, mitral valve dysfunction, aneurysms, cardiac rupture	VSD: 0.2% MR: 13% to 45% CHF: 7-8%
Arrhythmic	Atrial or ventricular arrhythmias, sinus or atrioventricular node dysfunction	VFib: 2-4%
Embolic	Central nervous system or peripheral embolization	Approx. 2%
Inflammatory	Pericarditis	Approx. 10%

CHF: Congestive heart failure, MR: Mitral regurgitation, VFib: Ventricular fibrillation, VSD: Ventricular septal defect.

Complications of Primary PCI

Complications of primary PCI are similar to those seen during cardiac catheterization, those that occur as a consequence of the specific equipment (e.g., wires) required for the intervention, those related to aggressive antiplatelet and anticoagulant therapies, or those related to the intervention

itself. Most commonly reported complications from primary PCI are mortality, and bleeding. Various risk predictor tools were developed in ACS to identify the patients who are at risk of developing these complications [25-27]. Other reported complications include vascular access site complications, acute kidney injury from iodinated contrast media, peripheral vascular disease, myocardial ischemia, coronary artery injury from the procedure itself.

Outcomes of ACS (Other than STEMI) while on OAC

Results from randomized studies have shown that the annual risk of acute MI in patients treated with warfarin is about 0.64% [28]. In 2004, it was estimated that there were 4 million patients on warfarin therapy and the use of warfarin is increasing [2]. A large national level registry based study using National Cardiovascular Data Registry evaluated the association between home warfarin use and in-hospital mortality and bleeding in patients undergoing PCI [29]. The authors studied 11,173 patients and nearly 3.6% of patients were on home warfarin therapy. In the study, patients taking warfarin were less likely to receive aspirin, theinopyridines, and glycoprotein IIb/IIIa inhibitors during PCI. Unadjusted bleeding rates (elective PCI = 3.2% vs 1.9%; urgent PCI = 8.2% vs 4.8%) and in-hospital mortality (elective PCI = 1.4% vs. 0.6%; urgent PCI = 8.6% vs. 4.5%) were higher among patients taking warfarin. After adjustment for clinical characteristics, the risk of in-hospital mortality was similar with and without previous warfarin use. However, the adjusted risk of bleeding was significantly higher in patients receiving warfarin, for both elective (odds ratio = 1.26, 95% CI 1.09 - 1.46) and urgent PCI (odds ratio = 1.42, 95% CI 1.14 - 1.76). However, the study also included patients who had rescue and facilitated PCI where patients received thrombolytic therapy in addition to PCI. The inclusion of patients who received thrombolytics may have skewed some of the results as thrombolytic

therapy is a well-established risk factor for major bleeding compared to primary PCI patients alone.

Another study using NCDR ACTION Registry®-GWTG™ data studied the early antithrombotic treatment and invasive therapy, and risk of in-hospital major bleeding outcomes of non-STEMI patients by admission international normalized ratio (INR) levels defined as subtherapeutic (INR <2), therapeutic (INR 2-3), and supratherapeutic (INR >3) [30]. Risk of major bleeding was higher among patients with therapeutic (15%, adjusted odds ratio [OR] 1.25, 95% confidence interval [CI] 1.03-1.50) and supratherapeutic anticoagulation (22%, OR 1.60 [1.30-1.97]) compared with the subtherapeutic group (12%). Among patients with admission INR ≥2, 45% were treated with early (within 24 hours) heparin, 35% with early clopidogrel, 14% with early glycoprotein IIb/IIIa inhibitor (GPI), and 36% with early invasive strategy. Early antithrombotic treatment was associated with increased bleeding risk (OR 1.40 (5% CI: 1.14-1.72) for heparin; 1.50 (95% CI: 1.22-1.84) for clopidogrel; 1.82 (95% CI: 1.43-2.32) for GP IIb/IIIa inhibitors); however, an early invasive strategy was not (OR 1.09 (95% CI: 0.86-1.37). No significant interactions were observed between INR level and use of each early treatment in its association with bleeding but early antithrombotic treatment was associated with increased bleeding risk regardless of admission INR level [30].

Prior Literature and Studies on Outcomes of OAC in STEMI

Extensive literature search yielded only limited data in the outcomes of patients who were on anticoagulation at the time of presentation with acute STEMI. Three studied were identified which studied the outcomes of OAC in acute MI and summarized in table IV

Table IV: Summary table of prior literature on the outcomes of acute MI patients who were on OAC at presentation.

Study	Time Period	Type of Study	No. of Patients	Inclusion	Primary aim	OAC use	Bleeding Rate	Mortality Rate	Conclusions	Drawbacks
Oudet et. al. [31]	2001	Population based registry study	2112	Acute MI	To determine the prevalence of OAC among patients with AMI and its impact on management and outcome	4%	8% (OAC Group)	11% (OAC Group)	OR for excess bleeding risk in OAC group is 1.253	Majority of patients were on Fluindione (Only 2% were on warfarin) Only 38% underwent primary PCI and 75% patients had D2B time > 201 min
Vecchio et. al. [32].	2007	Prospective multicenter observational study	116	ACS patients on OAC	To study management techniques and in-hospital outcomes	N/A	11% (STEMI group)	3.7% (STEMI group)	Similar pharmacological and procedural data among groups	No non-OAC was studied for comparison
Mathews et. al. [33].	2007-2008	National level registry based study	103,890	Acute MI (STEMI and NSTEMI only)	Derivation and validation of a model for in-hospital bleeding	5%	10.8% (Overall)	3.7% (Overall)	OR for bleeding risk for OAC group is 1.18	Patients who died within 24 hours of admission were excluded

ACS: Acute Coronary Syndrome; D2B: Door-to-balloon time; NSTEMI: Non-ST Elevation Myocardial Infraction; OAC: oral anticoagulant use; OR: odds ratio; STEMI: ST Elevation Myocardial Infraction.

The first study reported by Oudot et al in 2006 studied 2112 French patients with acute myocardial infarction [31]. The study period was year 2001 which showed nearly 4% of patients were on long term anticoagulation and only 9% of the anticoagulation group received thrombolytic therapy compared to 42% in no anticoagulation group and only 74% of patients had coronary angiogram compared to 93% in no anticoagulation group. The study showed that anticoagulation is not associated with major in-hospital bleed, and long term data was not studied.

In the second study published by Vecchio et al compared the in-hospital outcomes of patients on anticoagulation who presented with STEMI to patients with non-STEMI acute coronary syndromes (non- ST elevation myocardial infarction and unstable angina) from year 2007 [32]. The in-hospital occurrence of death (3.7% vs. 1.1%; OR 3.3; 95% CI: 0.2-56.0), stent thrombosis (3.7% vs. 1.1%; OR 3.3; 95% CI 0.2-56.0) and major bleeding (7.4% vs. 2.2%; OR 3.4; 95% CI 0.4-25.9) were shown to be higher in STEMI patients who underwent primary PCI compared to non STEMI related ACS patients who underwent non-emergent PCI. Most of the patients received unfractionated heparin during the procedure [32].

A large national level registry based study from NCDR ACTION registry showed that warfarin use is predictive of major in-hospital bleeding in patients with STEMI and NSTEMI with an adjusted odds ratio of 1.18 (95% CI: 1.07–1.30) [33]. The data also showed that nearly 5% of the patients in USA are on anticoagulation at the time of presentation with STEMI or NSTEMI. However, the study did not include mortality data or long-term follow-up and also excluded

patients who died within 24 hours of presentation. Further, there was no data on the type of antiplatelet and antithrombotic agents used in the management (Table IV).

Rationale for the study

The direct evidence from existing literature on the outcomes of STEMI patients who were on OAC compared to those who were not on OAC is limited. Moreover, the existing data does not reflect contemporary guidelines in management of STEMI patients undergoing primary PCI [19]. Recent guidelines from ACC/AHA suggests the door-to-balloon time should be less than 90 min for primary PCI which may preclude some patients from receiving anticoagulation reversal agents such as fresh frozen plasma or vitamin K. When anticoagulation reversal agents were not used, further antiplatelet and antithrombotic agents may raise risk of bleeding and or death. When attempts are made to reverse anticoagulation, it may prolong door-to-balloon time and may also result in unfavorable outcomes. It was also shown that risk of bleeding increases significantly when OAC therapy is combined with antiplatelet therapy [34-36]. Antiplatelet therapy forms the cornerstone of management of ACS patients including STEMI. Thus there is clear concern for the safety and outcomes in the particular groups of patients who are on full anticoagulation. Further, no guidelines exist in the management of this subgroup of patients. Given the knowledge gap in the outcomes of the specific group of patients in the contemporary era, we proposed to study the outcomes of the patients in terms of major bleeding and death when presented with STEMI while on long-term anticoagulation.

Study Objectives

The primary aims

1. To determine the prevalence of OAC use in patients OAC use in patients with acute STEMI undergoing primary PCI
2. To describe the process of care of and short-term outcomes of primary PCI in patients with acute STEMI undergoing primary PCI
3. To compare overall outcomes in primary PCI for acute STEMI patients who are on OAC to those who were not on OAC.

Secondary aims:

1. To study whether OAC is an independent predictor of the combined end point of in-hospital death, and major bleeding among patients who presented with acute STEMI.
2. To study whether OAC use is an independent predictor of individual outcomes of major bleeding, and in-hospital mortality in a subgroup analysis.

Methods

Location and subjects

The study was designed a retrospective cross-sectional study involving all patients who had acute ST elevation myocardial infarction and were admitted to Christiana Care Health System, Newark, DE between January 2009 and December 2010 for primary PCI. Locally, door-to-balloon time of less than 90 min in majority of patients with acute STEMI was achieved and maintained since 2009. Similarly, first alternative to warfarin was approved for chronic anticoagulation in October 2010 by FDA and has gained more popularity since 2011. Therefore,

to avoid potential cohort effect, the above time period was chosen. Christiana Care Health System is a large academic community medical center with 1000 beds with an average 53,000 admissions and 165,000 emergency room visits per year. On average, Christiana Care's cardiac catheterization lab performs more than 5,000 diagnostic and 2,000 interventional procedures per year.

At Christiana Care Health System, when a patient suspected of acute MI is encountered, typically a "heart alert" is called in where all personnel and resources required for primary PCI (interventional cardiologist, cardiac catheterization lab and technologist and nursing staff) are immediately alerted. After careful discussion and evaluation of patient, decision to perform emergency cardiac catheterization is usually made within few minutes and a "heart code" will then be called where all the resources are immediately activated and patient is taken to the catheterization lab within few minutes. The details of all heart alerts and heart codes are maintained in an electronic database. Further, cardiac catheterization lab maintains an electronic database where indications, procedural details, complications and outcomes of all patients who had any PCI done. After patient is discharged home, the data is manually verified and updated by a registered nurse and usually a subset of this data is submitted to national level registries as required on quarterly basis.

Inclusion and exclusion criteria

Inclusion criteria:

1. All patients who were aged more than 18 years and were admitted to Christiana Care Health System with the diagnosis of acute ST elevation myocardial infarction within 24

hours after symptom onset and went to cardiac catheterization lab with intent of primary PCI

Exclusion criteria:

1. Patients who had thrombolytics prior cardiac catheterization (ex: salvage or facilitated PCI)
2. Patients who developed STEMI during hospital stay where originally admitted for non-myocardial infarction related problems
3. Acute in-stent thrombosis
4. Acute STEMI after coronary artery bypass surgery (CABG)

Definitions

The definitions used in the study were the standard definitions as describe by ACC NCDR registry. The full lengths of the definitions are given in appendix 1. Briefly, STEMI is defined as acute coronary syndrome of less than 24 hour onset with documented ST elevation on 12-lead surface ECG as per standard definition. Anticoagulation use is defined as the use of full therapeutic dose of any accepted medications (oral warfarin, or oral dabigatran) for at least 4 weeks prior index admission. The laboratory measurement of INR is only included if measured before the beginning of the procedure. Post procedural and INR drawn after administering medications such as heparin were also excluded in the analysis as the mentioned treatments may falsely elevate INR values. In such a situation, INR value is treated as missing.

Data Collection

All eligible patients were identified by electronic query of the cardiac catheterization laboratory database and heart code database. Patients who had the diagnosis of STEMI were identified. The database was also queried for demographic, past medical history and comorbidity, procedural, pre-procedural laboratory, complication and outcomes data. The database lacks information of the home medications and some of the comorbid conditions. Therefore, all medical records of the index admission were reviewed manually by the investigator. The eligibility criteria were reconfirmed by confirming the 12 lead ECG recordings and cardiac catheterization reports as well as physician notes. The data on variables that could not be electronically queried were manually entered into a separate electronic database. The demographic data was compared to United States Social Security Administration's Death Master File updated till March 31, 2013.

Study Approval and Reporting.

The study proposal was reviewed and approved by the Institutional Review Board at Christiana Care Health System, Newark DE (Reference: CCC#33096). A copy of approval is included in the Appendix. The results from the study were written using STROBE guidelines for cross-sectional studies and check list is included in the appendix.

Statistical Analysis

The statistical analysis was performed in the overall STEMI patients, and by grouping subjects in to 2 groups. Group 1 includes those patients who are not on long-term anticoagulation at the time of presentation and group 2 includes those patients who are on full anticoagulation. Initially, all continuous variables were analyzed and confirmed normal distribution. For primary outcome

analysis, the study participants were divided into two groups based on their anticoagulation use. Baseline demographic, medical history, home medications, procedural details and outcomes were analyzed using univariate analyses. All continuous variables were expressed as mean ± standard deviation and Student's t-test was used to compare patients who were on OAC to those who were not on OAC at the time of presentation. Similarly, categorical variables were expressed in percentages and chi-square test or Fisher Exact test were used to compare between the groups.

For secondary outcome analysis, the outcome variables composite end point, mortality and bleeding were analyzed in separate analyses using multivariable logistic regression modeling using stepwise approach. Variables associated with a P-value < 0.2 in the univariate analysis were selected for multivariable analysis and anticoagulation status was retained in the modeling process. The number of variables was limited to 1 per 10 subjects with outcome measure. To avoid confounding, home medications other than warfarin were not used in the modeling as the medication use correlated with the medical history. The final model was tested for goodness-of-fit using Hosmer-Lemeshow test. Results were expressed as odds ratio (OR) with 95% confidence interval (CI). A two-sided P-value <.05 was considered statistically significant for all analyses. All software analyses were conducted using SAS Software version 9.3 (Cary, NC).

Results:

A total of 675 patients cardiac catheterizations were performed on patients with the diagnosis of acute STEMI during the study period. A total of 38 patients were excluded (21 patients had MI while admitted as an in-patient for other medical problems, and 17 patients had acute in-stent thrombosis) (Figure 3). Of the 637 patients analyzed, 20 patients (3.1%) were on full long-term anticoagulation at the time of admission and grouped into group 2 while the remaining 617 (96.1%) were included in group 1. Baseline characteristics, past medical history and medications at the time of admission are shown in table 1. Procedural details are shown in table 2 and outcome details are shown in table 3.

Descriptive Statistics

Patients who were not on anticoagulation were significantly younger than those who were on anticoagulation (61±13 vs 67±12, p= 0.039). Other demographic features including gender (Male 72% vs 55%, p 0.11), BMI (29±6 vs 31±9, p=0.51) and race (Caucasian 83% vs 80%, p=0.88). The prevalence of comorbid conditions was significantly higher in patients who were on anticoagulation compared to those who were not including hypertension, diabetes, dyslipidemia, family history of premature coronary disease, peripheral vascular disease, previous history of MI, prior PCI, congestive heart failure, atrial fibrillation (All p vales < 0.05, see Table 1). Similar to the comorbid conditions, the number of daily medications used by patients who were on anticoagulation are also higher compared to those people who were not on anticoagulation.

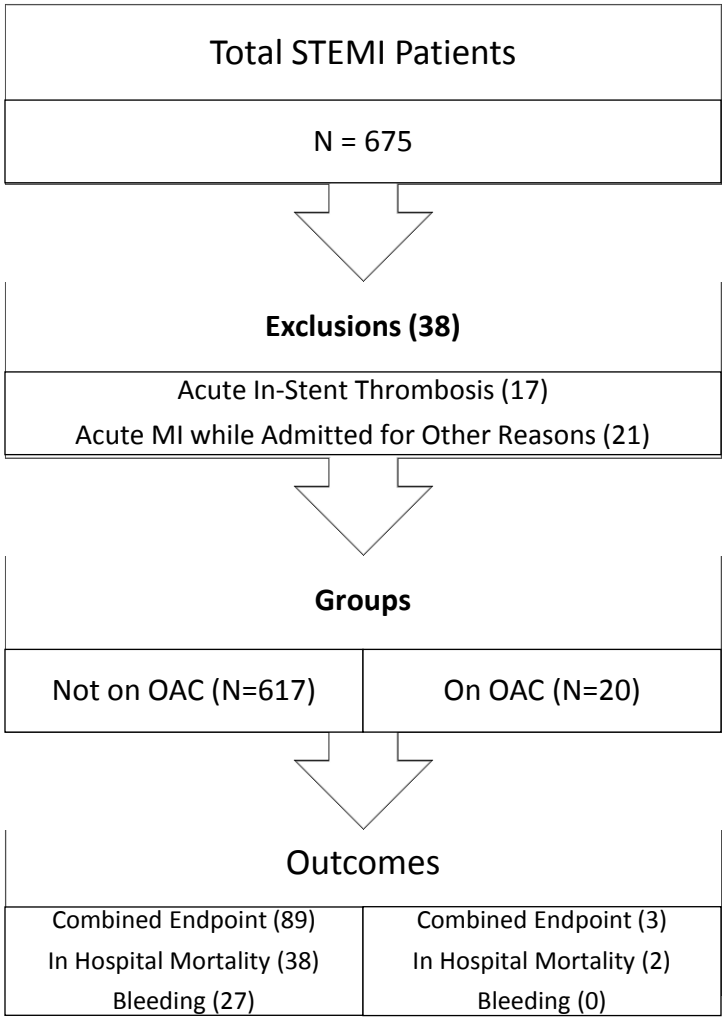

Figure 3: Summary flow chart of study cohort. A total of 675 patients were identified with acute STEMI during the study period. A total of 38 patients were excluded (21 patients developed STEMI during hospital stay while admitted for non-myocardial infarction related reasons and 17 patients developed acute in-stent thrombosis after elective PCI procedure). Group 2 includes 20 patients were on OAC therapy and remaining patients (617) were included in group 1. Summary of outcomes were also included.

There was no difference between the 2 groups in LVEF and initial troponin levels. Patients on anticoagulation had significantly lower hemoglobin levels (12.5 ± 2.3 vs. 14.3 ± 2.1, p =0.001) and higher INR (2.1 ± 1 vs. 1.2 ± 0.3, p<0.001) (Table 2). During procedure, there was no significant difference on the type of arterial access, contrast volume given, fluoroscopy times between both groups. Overall, the majority of patients received aspirin (84%) and bivalirudin

(81%) during the procedure. Nearly 30% of patients received glycoprotein IIb/IIIa inhibitors and heparin based products all of which were not significantly different between both groups (Table 2). However, the majority of patients on anticoagulation received clopidogrel (74% vs 46%, p=0.016) and prasugrel was given to a significantly higher proportion of patients who were not on anticoagulation (34% vs 10%, p=0.03) (Table 2).

All patients were on warfarin in the OAC group. The laboratory measurement of pre-procedural INR was available in 19 (95%) patients who were on OAC. The mean and median IINRs were 2.1 and 2.0 respectively and the range was from 1.2 to 4.7. The INR was subtherapeutic (<2.0) in 9 (47%) Similarly, in the non OAC group, INR data was available in 362 (59%) of patients. The mean and median INR were 1.2 ± 0.3 and 1.1 respectively. The range was from 0.9 to 4.2 and 6 (1.7%) patients had an INR more than 2 from other comorbid conditions such liver disease.

The choice of revascularization methods was different between both groups. Patients who were on anticoagulation received more bare metal stents (75% vs. 33%) and none of them underwent CABG surgery. Nearly 60% of patients received drug eluting stents when not on anticoagulation at admission (p<0.001). Post procedural data shows that the hemoglobin difference remained significant between both groups (non OAC group: 12.1 ± 2.1 vs. OAC group: 10.8 ± 2.1, p<0.001). However, the change in hemoglobin levels was similar among both groups of patients. The OAC group has a drop of 2.2 ± 1.5 gm/dL in hemoglobin (from 14.3 ± 2.1 gm/dL to 12.1 ± 2.1 gm/dL) and OAC group had a drop of 1.8 ± 1 gm/dL in hemoglobin (from 12.5 ± 2.3 gm/dL to 10.8 ± 2.1 gm/dL) (p = 0.13). Post procedural creatinine was significantly higher in patients who were on anticoagulation.

Table 1: Baseline demographics, medical conditions, and home medications of the study population

Variable	*Group 1 (Not on OAC) (N=617)*	*Group 2 (On OAC) (N=20)*	*Total (N=637)*	*P-Value*
Demographics				
Age (years)	60.9 ± 13.1	67.1 ± 13.2	61.1 ± 13.1	**0.039**[1]
BMI (kg/m^2)	28.8 ± 5.9 (N=611)	30.9 ± 8.8	28.9 ± 6.0	0.51[1]
Gender				
Female	175 (28.4%)	9 (45.0%)	184 (28.9%)	0.11[1]
Male	442 (71.6%)	11 (55.0%)	453 (71.1%)	
Race				
Caucasian	508 (82.5%)	16 (80.0%)	524 (82.4%)	0.88[1]
African American	73 (11.9%)	4 (20.0%)	77 (12.1%)	
Baseline Risk Factors and Medical Conditions				
Hypertension	395 (64.0%)	18 (90.0%)	413 (64.8%)	**0.017**[2]
Diabetes Mellitus	132 (21.4%)	8 (40.0%)	140 (22.0%)	**0.048**[2]
Dyslipidemia	382 (61.9%)	19 (95.0%)	401 (63.0%)	**0.0026**[2]
Smoking History	255 (41.3%)	6 (30.0%)	261 (41.0%)	0.31[2]
COPD	43 (7.0%)	3 (15.0%)	46 (7.2%)	0.17[2]
Family History of Premature CAD	22 (3.6%)	7 (35.0%)	29 (4.6%)	**<.0001**[2]
PVD	51 (8.3%)	5 (25.0%)	56 (8.8%)	**0.0093**[2]
Prior MI	122 (19.8%)	8 (40.0%)	130 (20.4%)	**0.027**[2]
Prior PCI	140 (22.7%)	10 (50.0%)	150 (23.5%)	**0.0046**[2]
Prior PCI within 1 Yr	33 (23.6%)	3 (30.0%)	36 (24.0%)	0.65[2]
Prior CABG	48 (7.8%)	3 (15.0%)	51 (8.0%)	0.24[2]
Congestive Heart Failure	32 (5.2%)	5 (25.0%)	37 (5.8%)	**0.0002**[2]
Currently on Dialysis	9 (1.5%)	1 (5.0%)	10 (1.6%)	0.21[2]
Atrial Fibrillation	14 (2.3%)	10 (50.0%)	24 (3.8%)	**<.0001**[2]
Prior History of DVT/PE	6 (1.0%)	6 (30.0%)	12 (1.9%)	**<.0001**[2]
Dilated Cardiomyopathy	0 (0.0%)	1 (5.0%)	1 (0.2%)	**<.0001**[2]
Anemia	17 (2.8%)	2 (10.0%)	19 (3.0%)	0.061[2]
Hypothyroid	28 (4.5%)	2 (10.0%)	30 (4.7%)	0.26[2]
Obstructive Sleep Apnea	20 (3.2%)	1 (5.0%)	21 (3.3%)	0.66[2]
No of CAD Risk Factors	1.9 ± 1.1	2.9 ± 0.7	2.0 ± 1.1	**<.0001**[1]

Home Medications Prior Index Admission				
Aspirin	226 (36.6%)	11 (55.0%)	237 (37.2%)	0.094[2]
Plavix	85 (13.8%)	3 (15.0%)	88 (13.8%)	0.88[2]
ACE Inhibitors/ARB	181 (29.3%)	11 (55.0%)	192 (30.1%)	**0.014[2]**
Beta Blockers	156 (25.3%)	10 (50.0%)	166 (26.1%)	**0.013[2]**
Diuretics	101 (16.4%)	8 (40.0%)	109 (17.1%)	**0.0058[2]**
Calcium Channel Blockers	81 (13.1%)	2 (10.0%)	83 (13.0%)	0.68[2]
Statins	212 (34.4%)	12 (60.0%)	224 (35.2%)	**0.018[2]**
Digoxin	5 (0.8%)	2 (10.0%)	7 (1.1%)	**0.0001[2]**
Vasodilators	24 (3.9%)	1 (5.0%)	25 (3.9%)	0.80[2]
Antiarrhythmics	6 (1.0%)	2 (10.0%)	8 (1.3%)	**0.0004[2]**
Proton Pump Inhibitors	91 (14.7%)	3 (15.0%)	94 (14.8%)	0.98[2]
Thyroid Replacement	39 (6.3%)	2 (10.0%)	41 (6.4%)	0.51[2]
Insulin	42 (6.8%)	5 (25.0%)	47 (7.4%)	**0.0022[2]**
Oral Hypoglycemics	73 (11.8%)	4 (20.0%)	77 (12.1%)	0.27[2]

[1] based on Mann-Whitney U test; [2] based on Fisher's exact test. ACE: Angiotensin converting enzyme, ARB: Angiotensin receptor blocker, BMI: Body mass index, CAD: Coronary artery disease, DVT: Deep vein thrombosis, COPD: Chronic obstructive pulmonary disease, OAC: Oral anticoagulation, PE: Pulmonary embolism, PVD: Peripheral vascular disease.

Table 2: Cardiac catheterization procedural details by Anticoagulation status.

Variable	*Group 1 (Not on OAC) (N=617)*	*Group 2 (On OAC) (N=20)*	*Total (N=637)*	*P-Value*
Pre Procedural Data				
LVEF (%)	45.5 ± 12.3	40.4 ± 12.3	45.4 ± 12.3	0.11[1]
ECG Diagnosis based on				
First ECG	365 (70.7%)	13 (81.3%)	378 (71.1%)	0.58[3]
Subsequent ECG	151 (29.3%)	3 (18.8%)	154 (28.9%)	
Hemoglobin (gm/dL)	14.3 ± 2.1	12.5 ± 2.3	14.2 ± 2.1	**0.001[1]**
Creatinine (mg/dL)	1.1 ± 1.0	1.1 ± 0.4	1.1 ± 1.0	0.44[1]
Troponin T (ng/ml)	0.6 ± 1.7	0.3 ± 0.4	0.5 ± 1.7	0.85[1]
INR	1.2 ± 0.3	2.1 ± 1.0	1.2 ± 0.4	**<.0001[1]**
Procedural Data				
Contrast Volume (ml)	214.5 ± 98.6	192.3 ± 57.2	213.8 ± 97.6	0.36[1]
Fluoroscopy Time (min)	14.8 ± 9.2	13.4 ± 9.3	14.7 ± 9.2	0.28[1]
PCI Delay > 90 min	72 (11.7%)	1 (5.0%)	73 (11.5%)	0.72[3]
Transferred from non-PCI capable Hospital	*87 (14.5%)*	*0 (0.0%)*	*87 (14.1%)*	*0.092[3]*
Arterial Access – Femoral	*529 (92.6%)*	*17 (85%)*	*546 (92.4%)*	*0.25[3]*
Arterial Access – Radial	*42 (7.4%)*	*3 (15%)*	*45 (7.6%)*	
Medications Administered (Immediately Before or During Cardiac Catheterization)				
Aspirin	515 (83.7%)	18 (94.7%)	533 (84.1%)	0.20[2]
Clopidogrel	280 (45.7%)	14 (73.7%)	294 (46.5%)	**0.016[2]**
Prasugrel	210 (34.1%)	2 (10.5%)	212 (33.4%)	**0.032[2]**
Bivalirudin	495 (80.4%)	16 (84.2%)	511 (80.5%)	1.00[3]
GP IIb/IIIa Inhibitor	185 (30.0%)	4 (21.1%)	189 (29.8%)	0.40[2]
LMWH/ Fondaparinux	14 (2.3%)	2 (10.5%)	16 (2.5%)	0.079[3]
Unfractionated Heparin	197 (32.0%)	5 (26.3%)	202 (31.8%)	0.60[2]
Revascularization Methods Used				
Bare Metal Stent	195 (31.6%)	15 (75.0%)	210 (33.9%)	**<0.001[2]**
Drug Eluting Stent	348 (56.4%)	2 (10.0%)	350 (55.4%)	
CABG	24 (3.9%)	0 (0.0%)	24 (3.8%)	
PTCA Only	50 (8.1%)	3 (15.0%)	53 (10.4%)	
Laboratory Findings				
Post Procedural Hemoglobin (gm/dL)	12.1 ± 2.1	10.8 ± 2.1	12.1 ± 2.1	**0.0067[1]**
Post Procedural Creatinine (mg/dL)	1.2 ± 1.2	1.4 ± 0.8	1.2 ± 1.2	**0.025[1]**
Hemoglobin Change (gm/dL)	-2.2 ± 1.5	-1.8 ± 1.0	-2.2 ± 1.5	0.13[1]
Creatinine Change	0.1 ± 0.5	0.3 ± 0.7	0.1 ± 0.5	0.097[1]
Bleeding Complications				
Bleeding in 72 hrs/ Blood	27 (4.4%)	0 (0.0%)	27 (4.2%)	0.41[2]

Transfusion				
Other Complications				
Cardiogenic Shock within 24 Hrs	18 (2.9%)	1 (5.0%)	19 (2.8%)	0.44[2]
Cardiac Arrest within 24 Hrs	32 (5.2%)	0 (0.0%)	32 (5.0%)	0.31[2]
Intra-aortic Balloon pump	61 (9.9%)	3 (15.0%)	64 (10.0%)	0.45[2]
Mortality and Overall Outcomes				
Length of Stay (days)	3.0 ± 4.6	4.1 ± 5.3	3.0 ± 4.7	0.24[1]
Hospital Death	38 (6.2%)	2 (10.0%)	40 (6.3%)	0.36[3]
Mortality at 30 day	41 (6.6%)	2 (10.0%)	43 (6.8%)	0.64[3]
Bleeding/Blood Transfusion/In-Hospital Mortality/Cardiogenic Shock/Cardiac arrest	89 (14.4%)	3 (15%)	92 (14.6%)	1.00[3]

[1] based on Mann-Whitney U test; [2] based on Chi-square test; [3] based on Fisher's exact test
Overall 27 (4.2%) patients developed bleeding complications or required blood transfusion

during the hospital stay. No one in anticoagulation group developed the complication however, the difference was not statistically significant (p=0.41). About 10% of overall patients needed IABP (intraaortic balloon pump) placement and there was no significant difference between both groups (p=0.45). Average length of stay was 3.0 ± 4.7 days which did not differ between both groups (p=0.24). Total number of hospital deaths were 40 (6.3%), 38 (6.2%) died in group 1 and 2 (10%) in group 2 (p=0.36). On composite end point developing bleeding complication, or requiring blood transfusion or in-hospital death or developing cardiogenic shock or arrest was similar between both groups (14.4% vs 15%, p =1.0).

Predictors of composite end point

A total of 92 (14.6%) patients developed the composite endpoint. The unadjusted/univariate and multivariable analyses are shown in table 3. In multivariable model, pre-procedural hemoglobin (OR: 0.88, 95%CI: 0.77-0.98, p=0.012) and requirement of IABP (OR: 4.13, 95% CI: 2.25-7.59,

p<0.001) were found to be significant independent predictors. Hosmer-Lemishow goodness-of-fit statistics for the model was 0.67. For every 1 gm/dL increase at baseline hemoglobin level, the odds of developing bleeding complications was reduced by a factor of 0.88. The use of IABP increases the odds of developing composite endpoint by 4.13 times when other factors remain same. Anticoagulation use and baseline INR were not independent factors for bleeding (Table 3).

Table 3: Predictors of composite end point

Outcome: Composite End Point							
Variable	Univariate analysis			Multivariable analysis			
	OR	95% CI	P value	OR	95% CI	P value	H-L*
Pre procedural Hemoglobin	0.86	0.75 - 0.97	0.02	0.88	0.77 - 0.98	0.012	0.67
IABP	4.09	2.13 - 7.86	<.001	4.13	2.25 - 7.59	<.001	
Anticoagulation	0.62	0.16 - 3.07	0.56				
INR	1.33	0.61-2.89	0.472				
Age	1.02	0.996 - 1.04	0.11				
Gender (Female vs. Male)	0.75	0.43 - 1.32	0.32				
No of CAD Risk Factors	1.18	0.94 - 1.47	0.15				
Bivalirudin	0.83	0.39 - 1.78	0.63				
Glycoprotein IIb/IIIa inhibitor	1.22	0.68 - 2.19	0.50				

*Hosmer-Lemishow goodness of fit statistic. CAD: Coronary artery disease, CI: Confidence interval, IABP: Intraaortic balloon pump, INR: international normalized ratio OR: Odds ratio.

Predictors of bleeding

Overall, 27 (4.2%) patients developed bleeding complication. Univariate and multivariable analyses results were shown in table 4. Revascularization methods, pre procedural hemoglobin (OR: 0.61, 95%CI: 0.5-0.73, p<0.001) and IABP (OR: 5.53, 95%CI: 2.13-14.1, p<0.001) use were strongly associated with increased risk for bleeding, but not anticoagulation use or INR levels or anticoagulation drug of choice (Table 4). Both CABG and DES use were associated

with increased bleeding risk or PRBC transfusion. Due to the significant number of patients who were subtherapeutic in OAC group, INR was used as a continuous variable in the model in place of dichotomous OAC variable to identify any bleeding risk associated with increase in INR. No patient in OAC group had bleeding complication and therefore, univariate analysis on OAC status was not performed. A total of 24 (3.9%) patients in non OAC group had CABG and all of them required blood transfusion. Non-CABG related blood transfusions were only 3 (0.5%) in non OAC group and 0 (0%) in OAC group. CABG seems to be the major cause of blood transfusion accounting for 24 out of 27 (89%) of PRBC blood transfusion.

Table 4: Predictors of bleeding complications

Outcome: Bleeding/PRBC Transfusion							
Variable	Univariate analysis			Multivariable analysis			
	OR	95% CI	P value	OR	95% CI	P value	H-L*
Revascularization CABG vs BMS	7.13	1.53-33.32	0.01	7.11	1.62 -31.2	0.017	0.844
DES vs BMS	1.22	0.43-3.46	0.71	1.34	0.49 - 3.70	0.10	
PTCA Only vs BMS	0.46	0.08-2.48	0.37	0.68	0.14 - 3.26	0.568	
Pre-procedural Hemoglobin	0.60	0.48-0.75	<0.001	0.61	0.50 - 0.73	<0.001	
IABP	4.92	1.77-13.71	0.002	5.53	2.13 - 14.40	<0.001	
INR	1.77	0.50-6.18	0.37				
No of CAD Risk Factors	1.08	0.71-1.63	0.72				
Bivalirudin	1.55	0.39-6.11	0.56				
Glycoprotein IIb/IIIa Inhibitor	0.63	0.22-1.85	0.41				
Age	1.01	0.97 - 1.04	0.75				
Gender (Male)	0.57	0.22-1.46	0.24				

*Hosmer-Lemishow goodness of fit statistic. BMS: Bare metal stent, CABG: Coronary artery bypass grafting surgery, CAD: Coronary artery disease, CI: Confidence interval, DES: Drug eluting stent, IABP: Intraaortic balloon pump, INR: international normalized ratio, PTCA: Percutaneous transluminal coronary angioplasty, OR: Odds ratio.

Predictors of in-hospital mortality

Over all there were (%) deaths in the hospital after admitted with STEMI and underwent primary PCI. The univariate variables were shown in table 5. Male gender and less number of CAD risk factors at baseline seems to be associated with increased risk of mortality but did not achieve statistical significance. On multivariable analysis, Glycoprotein IIb/IIIa use was significant factor, however, the model failed Hosmer-Lemishow goodness of fit test. Therefore, no further analysis was performed.

Table 5: Predictors of in-hospital mortality.

Outcome: In-Hospital Mortality			
Variable	Unadjusted Analysis		
	Odds Ratio	95% CI	P value
Age	0.98	0.96 - 1.01	0.27
Gender (Female vs. Male)	0.47	0.21 - 1.07	0.07
Revascularization CABG vs. BMS	1.14	0.12 - 10.50	0.91
DES vs. BMS	1.86	0.80 - 4.32	0.15
PTCA Only vs. BMS	1.21	0.29 - 5.01	0.79
Anticoagulation	2.67	0.48 - 15.04	0.26
Pre procedural hemoglobin	0.93	0.77 - 1.12	0.44
Pre procedural creatinine	0.90	0.46 - 1.76	0.75
No of CAD Risk Factors	0.74	0.53 - 1.02	0.06
Bivalirudin	2.11	0.74 - 5.98	0.17
Glycoprotein IIb/IIIa Inhibitor	0.62	0.28 - 1.39	0.25
Heparin	1.92	0.71 - 5.18	0.20
IABP	1.72	0.57 - 5.21	0.34

BMS: Bare metal stent, CABG: Coronary artery bypass grafting surgery, CAD: Coronary artery disease, CI: Confidence interval, DES: Drug eluting stent, IABP: Intraaortic balloon pump, PTCA: Percutaneous transluminal coronary angioplasty.

Discussion

Our study showed a prevalence of long-term anticoagulation use of 3.2% in patients with STEMI. Similar portions of OAC or anticoagulation use was noted in the other studies of patients undergoing PCI [29]. Patients who were on long-term anticoagulation are typically older patients and suffer from multiple comorbid conditions. The data is comparable to the previously reported data [15, 18, 19, 25].

Our study also showed that patients on OAC are less likely to receive drug eluting stents. The results may be explained by conscious decision by the operating interventional cardiologist to avoid long-term triple anticoagulation therapy which is associated with increasingly worse long term outcomes including bleeding and mortality [37-43]. Similarly, patients on OAC group are less likely to receive newer antiplatelet agents such as prasugrel where no evidence existed to support their use in combination with warfarin. Although there is significant difference of periprocedural and post procedural difference in hemoglobin levels, both groups of patients had similar drop in hemoglobin levels and PRBC transfusions. Patients who were on anticoagulation had no episodes of major bleeding or required blood transfusion or underwent surgical revascularization with CABG.

Predictors of End Points

Contrary to our expectation, anticoagulation use was not associated with increased risk of combined outcomes. Pre procedural hemoglobin and IABP requirements are independent predictors of the combined outcomes. In our study group, the majority of patients received

bivalirudin. In previous studies which had reported significant increases in bleeding in patients received thrombolytics, heparin or glycoprotein IIb/IIIa inhibitors which may explain some of the differences. However, this postulated beneficial effect of bivalirudin needs to be established in a larger study. The choice of revascularization was also significantly different in both groups. Use of bare metal stents may be associated with less aggressive antiplatelet therapy and might have contributed to lesser events of bleeding. One possible reason for excess use of bare metal stents in patients who were on anticoagulation was to avoid long term dual antiplatelet therapy with warfarin which has shown to increase long term bleeding risk.

Predictors of Bleeding

Interestingly, patients on OAC had no in-hospital bleeding in the study population which was different from previously published data. Studies from a large national level ACTION Registry®-GWTG™ database, the rate of major bleeding after PCI for STEMI and NSTEMI was 11% and home warfarin use was associated with increasing mortality (OR:1.18 and 95% CI:1.07–1.30) [33]. However, more recent data from NCDR CathPCI registry based study showed the average risk bleeding is 5.8% from more than 1 million procedures done nationwide [25]. In our study, over all bleeding risk was only 4.2%.

The paradoxical result may be explained by various reasons. Firstly, physicians are well aware pf the risk of bleeding in patients who are on OAC and probably have taken extra precautions to achieve low bleeding such as careful access site management which were not studied. Secondly, the study cohort has overall less bleeding complications compared to other published studies. For example, overall bleeding risk in STEMI patients was reported as high as 11.5% compared to

4.2% in our study [44]. There is considerable use of bivalirudin in our cohort compared to registry based published data of 40.8% compared to 80.5% in our cohort [44]. Bivalirudin use has shown to reduce bleeding risk from 8.3% to 4.9% when compared to Glycoprotein IIb/IIIa inhibitor use [45]. However, the effect of bivalirudin use in patients who were on OAC was not reported before. Bivalirudin use was not a significant factor in reducing the bleeding on multivariable analysis probably due to small sample size.

Similar to combined end point, the major predictors of bleeding were IABP and lower hemoglobin levels before primary PCI and CABG surgery. Every patient who went for CABG received PRBC infusion which may be expected. Previous studies have shown as high as 27% bleeding risk in patients who had IABP for emergent PCI [46]. Recent updated results from NCDR data shows that pre-procedural hemoglobin is also a risk factor for bleeding after any type of PCI [27]. Our results also support similar findings published in the literature.

Another concern about adherence to INR was identified in the study. Every patient in the group of cohort was on warfarin. The advantage with warfarin compared to other anticoagulants was that the adherence can be easily identified by simple blood test (INR). In the cohort, 47% patients were subtherapeutic defined as INR of less than 2. Previous studies have indicated that subtherapeutic INR in patients who were on anticoagulation were as high as 60% [47-49]. The subtherapeutic INR might have resulted in a bias towards null resulting in OAC use not a significant risk factor for bleeding.

Predictors of Mortality

In-hospital and 30 day mortality in patients with acute STEMI has been reported around 10% over last years and is slowly improving [50-53]. Most contemporary data from NCDR showed the risk-adjusted in-hospital mortality between 2009 and 2011 for STEMI patients who underwent primary PCI was about 5.3% [25], which is similar to our study population. Although there is increased mortality in patients who were on OAC, the statistical significance was not reached due to small sample size and lack of a statistical model. To our knowledge, there were no other direct studies assessing the impact of OAC on mortality in acute STEMI patients.

Generalizability

The study was conducted in a large community academic center reflecting contemporary management patterns in primary PCI. The study shows that there is higher use of bivalirudin, prasugrel use compared to other published literature reflecting contemporary changes in the use of antiplatelet and antithrombotic use. The study also did not exclude patients who died within 24 hours or include those patients who were presenting with a different reperfusion strategy other than primary PCI. The proportion of patients using anticoagulation is similar to most of other published studies. Therefore, the results may be generalizable to all patients who are undergoing primary PCI for STEMI under current guidelines.

Limitations:

Like other retrospective observational studies, there is the potential for unmeasured confounding and selection bias, some STEMI patients might have died before reaching hospital. Relatively small number of patients in the anticoagulation group limits the power the study and no long

term prognostic outcomes were studied. However, the current study provides preliminary data for further exploration of hypotheses using data from large national level registry based databases. Long term outcomes and recurrent hospitalizations and major cardiac events were not studied. A significant number of patients who were on anticoagulation, had sub therapeutic INR on presentation which may underestimate the risk of complications in OAC group.

Conclusions

Overall, 3% of STEMI patients were on long-term anticoagulation at the time of presentation. Despite increase in age, and number of comorbid conditions in patients who were on anticoagulation, the risks of bleeding and in-hospital mortality were similar to those who were not on anticoagulation at the time of STEMI presentation. Patients who were on long term anticoagulation were more likely to receive bare metal stents and clopidogrel. The adjusted risk of bleeding was significantly higher in patients who had lower hemoglobin at presentation and required IABP support or underwent revascularization with CABG. Glycoprotein IIb/IIIa use was associated with increased in-hospital mortality. However, due to small number of patients who were on OAC, the results needs to be confirmed in a large study.

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Appendix

List of Appendices

Appendix 1:
Definitions

Majority of the definitions used are based on NCDR based CathPCI registry standards (Available at www.ncdr.com).

1. **STEMI:** The patient presented with a ST elevation myocardial infarction (STEMI) or its equivalent as documented in the medical record. STEMIs are characterized by the presence of both criteria:

    a. a. ECG evidence of STEMI: New or presumed new ST-segment elevation or new left bundle branch block not documented to be resolved within 20 minutes. ST-segment elevation is defined by new or presumed new sustained ST-segment elevation at the J-point in two contiguous electrocardiogram (ECG) leads with the cut-off points: >=0.2 mV in men or >= 0.15mV in women in leads V2-V3 and/or >= 0.1 mV in other leads and lasting greater than or equal to 20 minutes. If no exact ST-elevation measurement is recorded in the medical chart, physician's written documentation of ST-elevation or Q-waves is acceptable. If only one ECG is performed, then the assumption that the ST elevation persisted at least the required 20 minutes is acceptable. Left bundle branch block (LBBB) refers to new or presumed new LBBB on the initial ECG. ST elevation in the posterior chest leads (V7 through V9), or ST depression that is maximal in V1-3, without ST-segment elevation in other leads, demonstrating posterobasal myocardial infarction, is considered a STEMI equivalent.
    b. Cardiac biomarkers (creatinine kinase-myocardial band, Troponin T or I) exceed the upper limit of normal according to the individual hospital's laboratory parameters a clinical presentation which is consistent or suggestive of ischemia.

    Note: If laboratory data was pending at the time of cardiac catheterization or found out to be normal subsequently but coronary angiogram showing an acute thrombus, patient was included in the study as STEMI patient.

2. **Major Bleeding Complication:** Defined as the patient experienced a suspected or confirmed bleeding event observed and documented in the medical record that was associated with any of the following between start of procedure and 72 hours after procedure:
    a. Hemoglobin drop of >=3 g/dL;
    b. Transfusion of whole blood or packed red blood cells;
    c. Procedural intervention/surgery at the bleeding site to reverse/stop or correct the bleeding (such as surgical closures/exploration of the arteriotomy site, balloon angioplasty to seal an arterial tear, endoscopy with cautery of a GI bleed.

3. **Anticoagulation use:** Defined as chronic use of systemic anticoagulation agents for at least 4 weeks before index hospital admission. The agents that were included in the study are warfarin or dabigatran in oral form and low-molecular weight heparin in subcutaneous form. If a patient is on warfarin and initial INR is less than 1.5, he is not considered on full anticoagulation and treated with other group. If a patient is receiving therapeutic dose of low molecular heparin or dabigatran, then the patient is considered to be on full anticoagulation irrespective of INR. Of note, newer oral antithrombotic agents such as apixaban and rivaroxaban were not included as their use was not approved by FDA during the study period.

4. **In Hospital Mortality:** Obtained from the discharge status of the patient from the registry where it was mentioned as patient died in the hospital. It was confirmed by manual review of medical chart and verifying a copy of death certificate.

Appendix 2

Elements of Data Collection

The following data point were collected by electronic database query of electronic medical records, cardiac catheterization lab database and from the ODS system.

1. Demographics
   a. Age, gender, race and BMI

2. Past medical history (presence of) of the following conditions:

Hypertension
Diabetes
Hyperlipidemia
Current smoking
Family History of premature CAD
COPD
TIA/Stroke
Peripheral vascular disease
Previous Diagnosis of CAD
Previous MI
Previous PCI
Previous CABG
Congestive heart failure
Chronic kidney disease
Pre Procedural left ventricular
ejection fraction
Anemia
Atrial fibrillation
Mechanical heart valve
Previous cardiac embolism
Previous venous thromboembolism
Dilated cardiomyopathy
Obstructive sleep apnea
Malignancy
Previous chemotherapy and radiation
therapy

3. Home medication use at the time of presentation (By classes)

4. Laboratory data
    a. Pre procedure: hemoglobin, INR, creatinine, troponins
    b. Post procedure labs: hemoglobin (lowest in 72 hours) and creatinine (highest)

5. Cardiac cath lab data
    a. Procedural medications used
        Aspirin
        Bivalirudin
        GP IIb/IIIa Inhibitors
        Low Molecular Weight Heparin/ Fondaparinux
        Unfractionated Heparin
        Clopidogrel

    b. Hemodynamic support
        a. IABP
    c. Revascularization
        a. Primary PCI (type of stents drug eluting or bare metal)
        b. CABG (Status and Indication)
        c. PTCA only

6. In-hospital outcomes
    a. Length of stay
    b. Complications including major bleed, minor bleed, stroke
    c. Cardiogenic shock
    d. In-hospital mortality

Appendix 3:

STROBE Checklist

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Checklist
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	✓
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	✓
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	✓
Objectives	3	State specific objectives, including any prespecified hypotheses	✓
Methods			
Study design	4	Present key elements of study design early in the paper	✓
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	✓
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	✓
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	✓
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	✓
Bias	9	Describe any efforts to address potential sources of bias	✓

Study size	10	Explain how the study size was arrived at	✓
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	✓
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	✓
		(*b*) Describe any methods used to examine subgroups and interactions	✓
		(*c*) Explain how missing data were addressed	✓
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	✓
		(*e*) Describe any sensitivity analyses	✓
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	✓
		(b) Give reasons for non-participation at each stage	✓
		(c) Consider use of a flow diagram	✓
Descriptive data	14*	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders	✓
		(b) Indicate number of participants with missing data for each variable of interest	✓
Outcome data	15*	Report numbers of outcome events or summary measures	✓
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	✓

		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	✓
Discussion			
Key results	18	Summarize key results with reference to study objectives	✓
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	✓
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	✓
Generalizability	21	Discuss the generalizability (external validity) of the study results	✓
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	✓

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.