Warfarin for stroke prevention following anterior ST-elevation myocardial infarction

Nicholas I. Buss, Scott E. Friedman, Bruce W. Andrus and James T. DeVries

Objectives **To assess the benefit of vitamin K antagonist (VKA) therapy for prevention of ischemic stroke following anterior ST-elevation myocardial infarction (STEMI) in patients with reduced ejection fraction.**

Methods **A prospective institutional-based registry was used to identify survivors of anterior STEMI with a post-STEMI ejection fraction of 40% or less over a 10-year period. Clinical and procedural characteristics were collected from medical records and vital status from the Social Security Death Index. Outcomes were compared on the basis of VKA use. The primary outcome was a composite of ischemic stroke, death, and clinically relevant bleeding. A secondary analysis examined the effects of low-molecular-weight heparin bridging therapy.**

Results **The primary outcome occurred in 24.7% (40/162) of VKA patients and 20.5% (22/107) of non-VKA patients [adjusted hazard ratio (HR), 1.30; 95% confidence interval (CI), 0.71–2.31]. Ischemic stroke occurred in 2.5 and 0.9% of VKA patients and non-VKA patients, respectively (adjusted HR, 2.81; 95% CI, 0.31–25.1). There was no significant difference in the rate of bleeding or death between groups. The addition of a low-molecular-weight heparin bridge to VKA therapy was associated with increased bleeding events (adjusted HR, 2.55; 95% CI, 1.04–6.24).**

Conclusion **Ischemic stroke was infrequent in the 6 months following anterior STEMI irrespective of VKA treatment status. The routine use of anticoagulation for prevention of stroke following anterior STEMI may not be warranted.** *Coron Artery Dis* **24:636–641** © **2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Keywords: anterior ST-elevation myocardial infarction, Bleeding Academic Research Consortium bleeding, ischemic stroke, left ventricular thrombus, low molecular weight heparin, vitamin K antagonist

Department of Cardiology, The Geisel School of Medicine at Dartmouth/Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, USA

Correspondence to Nicholas I. Buss, MD, Department of Internal Medicine, The Geisel School of Medicine at Dartmouth/Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756, USA
Tel: +1 603 650 7684; fax: +1 603 650 6122;
e-mail: nicholas.i.buss@hitchcock.org

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Introduction

Left ventricular (LV) thrombus is a recognized sequela of anterior ST-elevation myocardial infarction (STEMI). Before the advent of modern revascularization techniques, this complication was frequent, occurring in 20–46% of patients with anterior STEMI [1,2]. Early reperfusion therapies have significantly decreased the incidence of LV thrombus formation [3–8]. Yet, patients with anteroapical STEMI and reduced ejection fraction (EF) are often treated with a vitamin K antagonist (VKA) in hopes of preventing LV thrombus formation [9].

Studies carried out before the percutaneous coronary intervention (PCI) era have shown that anticoagulation with a VKA or low-molecular-weight heparin (LMWH) reduces the incidence of LV thrombus formation following anterior STEMI [10–12]. Although anterior infarcts are associated with LV thrombi, the impact of this finding in predicting adverse events such as stroke and peripheral emboli in the era of early revascularization and widespread dual antiplatelet therapy is not clear [13–15]. Furthermore, the benefit of anticoagulation with a VKA following anterior STEMI in the era of PCI and dual antiplatelet therapy is also uncertain [16]. The adverse consequences of treating this subset of patients with 'triple therapy' (aspirin, clopidogrel, and a VKA) are well understood: the rate of bleeding requiring hospitalization is 15% per year with triple therapy following myocardial infarction (MI) [17]. As a result of this gap in knowledge, the ACC/AHA guidelines do not provide a strong recommendation for VKA use following anterior STEMI (Class IIA, Level of evidence B) [18].

The ambiguity surrounding the risks and benefits of VKA following STEMI leads to wide variations in practice [9,19]. We aimed to determine the net clinical benefit of anticoagulation with a VKA in patients at high risk for LV thrombus formation.

Methods

Study population and data collection

All patients ($N = 761$) presenting to a single medical center between 1/1/2001 and 10/1/2010 with anterior STEMI were identified using an institutional prospective registry (Fig. 1). Only patients at high risk for LV thrombus, on the basis of post-MI LV EF less than or equal to 40%, were included. Patients were excluded if they died during the index hospitalization or underwent emergency coronary artery bypass surgery. In addition, patients with LV thrombus during the index hospitalization were excluded

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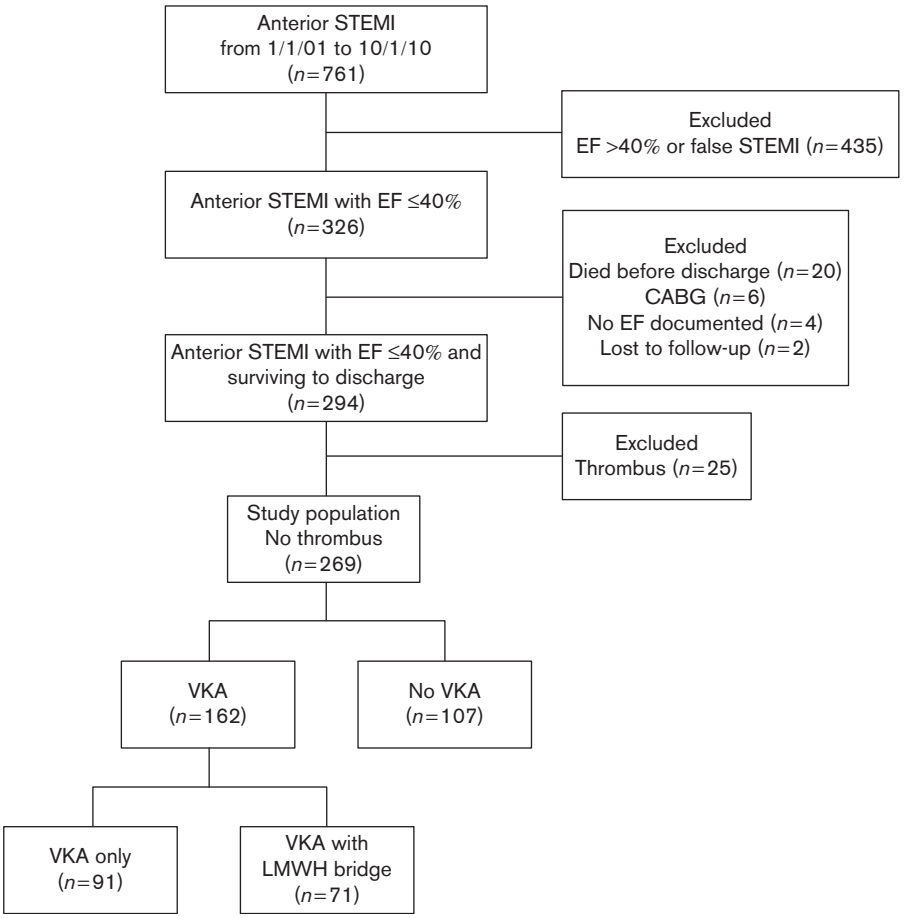
Fig. 1



Overview of study: flow diagram of study design. Reasons for exclusion are listed. CABG, coronary artery bypass graft; EF, ejection fraction; LMWH, low-molecular-weight heparin; STEMI, ST-elevation myocardial infarction; VKA, vitamin K antagonist.

from further analysis as there is consensus that VKA therapy is indicated in these patients [18].

Patients were divided into two groups on the basis of their use of a VKA at the time of discharge from their index hospital stay. The primary outcome measure was a composite of adverse events that included all-cause mortality, ischemic stroke, and clinically relevant bleeding [Bleeding Academic Research Consortium (BARC) 2, 3, or 5] [20]. Bleeding events occurring within 48 h of the STEMI and directly related to thrombolytic therapy or PCI were not included in the analysis. Outcomes were collected for the first 6 months following the index hospitalization.

Patients were indentified through an internal database that has been designed for quality assurance in STEMI care. Blinded ascertainment of bleeding events and ischemic stroke were obtained by review of the electronic medical record. Mortality data were obtained from the Social Security Death Index. Cause of death was determined by review of the medical record and by query of state death records.

Definitions

Anterior STEMI was defined as 1 mm ST elevations in two or more leads V1–V5 or new left bundle branch block and symptoms consistent with a MI with high-grade disease in the left anterior descending artery on coronary angiography. Post-MI EF and the presence of LV thrombus were determined using transthoracic echocardiography during the index hospitalization. LV thrombus was defined as a distinct mass in the LV cavity that was seen throughout the cardiac cycle in at least two different echocardiographic views and was distinguishable from papillary muscles, trabeculae, chordal structures, technical artifact, or tangential views of the LV wall. Anticoagulation was defined as a prescription for a VKA at the time of discharge. An LMWH bridge was defined as two or more doses of enoxaparin at full anticoagulation dosing (1 mg/kg, twice daily). Bleeding outcomes were categorized using the BARC definitions [20].

Statistical analysis

Continuous variables were summarized by mean and SD if normally distributed; median and interquartile ranges

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were used if the distribution was skewed. Patients were stratified by VKA use and their baseline characteristics were compared using a χ^2-test or Fisher exact test for categorical variables and the unpaired *t*-test or the Mann–Whitney–Wilcoxon test for continuous variables. A Cox proportional hazards regression model was used to examine the occurrence of the primary composite outcome as well each of the individual components of the primary outcome on the basis of VKA use. The covariates included in the regression model were age, sex, EF, peak creatinine phosphokinase (CPK), aspirin use, and the presence of apical akinesis on echocardiogram. An exploratory analysis in the subgroup of patients treated with an LMWH bridge in addition to a VKA was carried out to assess for effect modification. Kaplan–Meier curves of the primary endpoint were graphed with time 0 defined as the date of MI. Statistical significance was defined as a two-sided *P*-value less than 0.05.

Table 1 Demographic and index procedure characteristics

	VKA ($n=162$)	No VKA ($n=107$)	*P*-value
Clinical variables			
Mean age (years)[a]	60.4±1.1	67.1±1.5	<0.01
Peak CPK (U/l)[a]	3710±227	2402±243	0.04
Ejection fraction (%)[a]	33.8±0.48	34.0±0.62	0.64
EF subcategories [*n* (%)]			
EF ≤ 20%	10 (6.2)	8 (7.5)	0.80
EF 21–30%	47 (29.0)	31 (29.0)	1.00
EF 31–40%	105 (64.8)	68 (63.5)	0.90
Diabetes [*n* (%)]	40 (24.7)	30 (28.0)	0.54
History of tobacco use [*n* (%)]	76 (46.9)	52 (48.6)	0.78
Previous stroke [*n* (%)]	14 (8.6)	10 (9.4)	0.83
Antiplatelet medications [*n* (%)]			
Thienopyridine	153 (94.5)	105 (98.1)	0.21
Aspirin	162 (100)	102 (95.3)	<0.01
Dual antiplatelet	153 (94.5)	100 (93.5)	0.80
Revascularization methods [*n* (%)]			
Primary PCI	66 (40.7)	50 (46.7)	0.38
Pharmacoinvasive	30 (18.5)	17 (15.9)	0.63
Facilitated PCI	49 (30.2)	29 (27.1)	0.68
Thrombolytics only	9 (5.6)	5 (4.7)	1.00
No revascularization	8 (4.9)	6 (5.6)	0.79
Bleeding related to revascularization	5 (3.1)	6 (5.6)	0.31

CPK, creatinine phosphokinase; EF, ejection fraction; PCI, percutaneous coronary intervention; VKA, vitamin K antagonist.
[a]Data presented as mean value±SD.

Results

Over a 10-year period, 294 patients survived an anterior STEMI and had a post-MI EF of 40% or less (Fig. 1). The median time to echocardiogram from revascularization was 1 day, with a range of 0–6 days after revascularization. LV thrombus was documented during the index hospitalization in 25 (8.5%) patients. These 25 patients were excluded from further analysis, leaving our study cohort at 269 patients. Anticoagulation with a VKA was used in 162 patients (60.2%), whereas 107 patients (39.8%) were not treated with a VKA. An LMWH bridge was used in addition to VKA therapy in 71 patients (26.4%).

Patients receiving VKA therapy were younger (60.4 vs. 67.1 years old; $P = 0.0001$) and had larger myocardial infarcts as judged by peak CPK values (3710 vs. 2402; $P = 0.04$) (Table 1). However, the mean EF of the two groups was similar (33.8 vs. 34.0%; $P = 0.64$). Apical wall motion abnormalities on the initial post-MI echocardiogram were present in almost all patients, with apical akinesis more common in the VKA group and apical hypokinesis more frequent in the non-VKA group (8.4 vs. 1.8%, $P = 0.013$). Aspirin use was more frequent in the VKA group (100 vs. 95.3%, $P = 0.009$). The remaining demographic features, antiplatelet medications, and revascularization parameters were evenly distributed between the two groups.

The primary outcome occurred in 40 (24.7%) patients in the VKA group and 22 patients (20.5%) in the non-VKA group ($P = 0.29$) (Table 2). After adjustment for age, sex, EF, presence of apical akinesis, aspirin use, and peak CPK, there was no significant difference in the primary outcome on the basis of VKA use with a hazard ratio (HR) of 1.30 [95% confidence interval (CI), 0.73–2.31] (see Table 2 for multivariate adjusted HRs).

Stroke occurred in four (2.5%) patients in the VKA group and in one patient (0.9%) in the non-VKA group (HR, 2.81; 95% CI, 0.31–25.10). Clinically relevant bleeding

Table 2 Effect of vitamin K antagonist use following anterior STEMI

	VKA [*n* (%)] ($n=162$)	No VKA [*n* (%)] ($n=107$)	HR	Adjusted HR
Primary composite endpoint	40 (24.7)	22 (20.6)	1.19 (0.71–2.00)	1.30 (0.73–2.31)
Individual components				
Ischemic stroke	4 (2.5)	1 (0.9)	2.81 (0.31–25.10)	3.14 (0.32–30.38)
Clinically relevant bleeding[a]	23 (14.2)	9 (8.4)	1.78 (0.82–3.85)	1.64 (0.73–3.72)
BARC 5 bleeding (fatal)[b]	4 (2.5)	0 (0)	NA	NA
BARC 3 bleeding[b]	10 (6.2)	8 (7.5)	1.89 (0.35–2.26)	0.85 (0.31–2.37)
BARC 2 bleeding[b]	13 (8.0)	6 (5.6)	1.51 (0.57–3.97)	1.13 (0.40–3.15)
Death	14 (8.6)	13 (12.2)	0.71 (0.33–1.52)	1.45 (0.63–3.36)

Results shown for primary outcome (composite of stroke, bleeding, and death) and the individual components. HRs are reported with 95% confidence intervals. Adjusted HRs have been adjusted for age, sex, peak creatinine phosphokinase, ejection fraction, and aspirin use.
BARC, Bleeding Academic Research Consortium; HR, hazard ratio; NA, not available; STEMI, ST-elevation myocardial infarction; VKA, vitamin K antagonist.
[a]BARC 2, 3, or 5 bleeding.
[b]BARC 5 bleeding, fatal bleeding. BARC 3 bleeding, nonfatal 'major' bleeding. BARC 2 bleeding, any clinically overt sign of hemorrhage that is actionable but does not fulfill the criteria for type 3, type 4 (CABG-related), or type 5 BARC bleeding [20].

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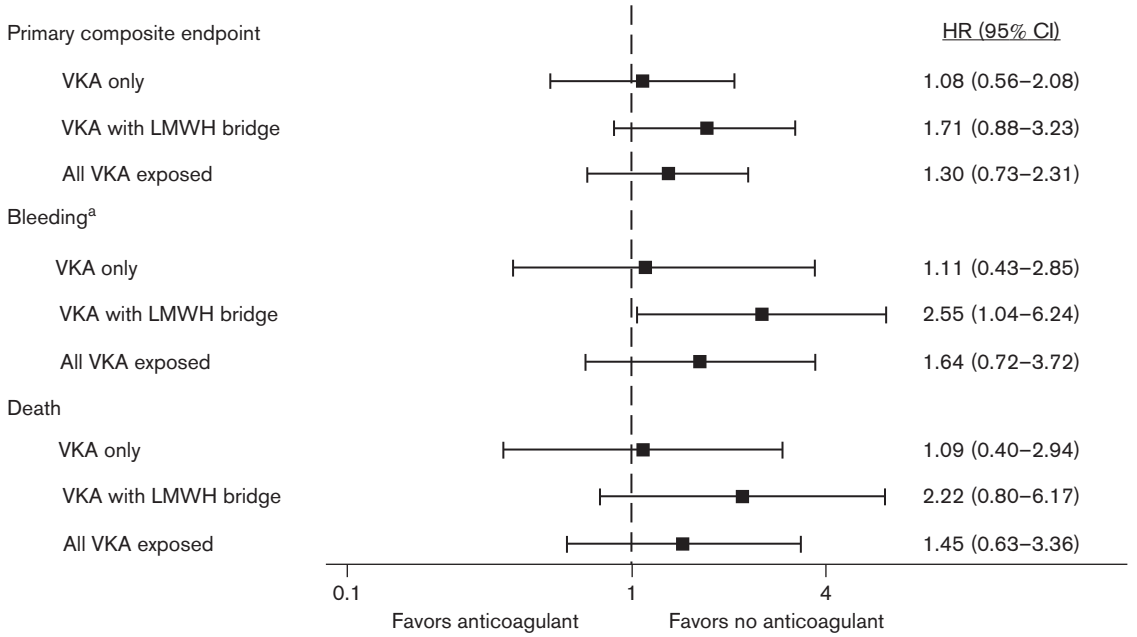
Fig. 2



Adjusted risk of primary and secondary endpoints associated with use of VKA in anterior wall STEMI with EF < 40%. Forest plot for the primary endpoint of death, ischemic stroke, or bleeding and individual endpoints on the basis of the anticoagulation strategy used. Hazard ratios (HRs) with 95% confidence intervals (CIs) are reported. HRs have been adjusted for age, sex, ejection fraction, peak creatinine phosphokinase, aspirin use, and presence of apical akinesis. [a]Bleeding Academic Research Consortium 2, 3, or 5 bleeding [20]. EF, ejection fraction; LMWH, low-molecular-weight heparin; STEMI, ST-elevation myocardial infarction; VKA, vitamin K antagonist.

(BARC 2, 3, or 5) occurred in 23 (14.2%) patients in the VKA group and nine (8.4%) patients in the non-VKA group (HR, 1.78; 95% CI, 0.82–3.85). The four fatal bleeds all occurred in patients receiving a VKA. Death from any cause occurred in 14 (8.6%) patients in the VKA group and in 13 (12.2%) patients in the non-VKA group (HR, 0.71; 95% CI, 0.33–1.52).

Exploratory subgroup analysis showed excess clinically relevant bleeding in the LMWH and VKA group (HR, 2.55; 95% CI, 1.04–6.24, $P = 0.04$). A Forest plot with adjusted HRs for the primary outcome, clinically relevant bleeding, and death is shown in Fig. 2.

The 25 patients found to have LV thrombi during the index hospital stay were followed for 6 months; 24 (96%) were treated with a VKA and 13 (52%) were treated with an LMWH bridge in addition to a VKA. In this group, one patient (4%) had a stroke; this patient was using a VKA at the time of the stroke.

Discussion

In a population at high risk for LV thrombus following anterior STEMI, there was no difference in the primary outcome (stroke, death, or bleed) on the basis of VKA use. In the subgroup treated with an LMWH bridge in addition to a VKA, the incidence of clinically relevant bleeding was increased. Stroke was uncommon, occurring in only 1.9% of the study population over the 6 months following anterior MI. No difference was observed in the rate of stroke on the basis of VKA use.

There are few randomized studies examining the optimal anticoagulation regimen following anterior MI. The FRAMI study prospectively randomized 776 streptokinase-treated patients with anterior STEMI to LMWH (dalteparin) or placebo for an average treatment course of 9 days [10]. Similar to our study, embolic events were rare in the FRAMI study, occurring in only nine (1.1%) patients. Treatment with LMWH did not alter the rate of stroke or systemic embolus, whereas there were more bleeding events in the LMWH group (2.9 vs. 0.3%; $P = 0.006$).

The incidence of stroke following anterior MI in our study is similar to previous estimates [19,21–24]. Udell studied survivors of acute MI in Ontario from 1999 to 2001 and found that 3% of these patients had a stroke in the 12 months following their MI. Interestingly, there was no difference in the rate of stroke on the basis of the anatomic region of the MI (anterior vs. nonanterior MI). In that study, only 20% of the patients with anterior MI were discharged with VKA therapy, which is significantly lower than our rate of VKA use (60%). However, Udell's analysis included all survivors of acute MI, whereas the present study was limited to patients with depressed systolic LV function.

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Bleeding complications increase incrementally when VKA therapy is added to dual antiplatelet therapy. In a nationwide retrospective analysis including all MI survivors in Denmark, triple therapy with aspirin, clopidogrel, and warfarin markedly increased bleeding rates as compared with aspirin monotherapy or dual antiplatelet therapy [17]. A recently published analysis of Horizons-AMI data analyzed ischemic and bleeding outcomes in patients who were treated with triple therapy (aspirin, clopidogrel, and a VKA) as compared with patients treated with dual antiplatelet therapy (ASA and clopidogrel). The indications for VKA therapy in this study were varied and included severely reduced LV EF with a large akinetic area (23.8%), atrial fibrillation (23.8%), and mural thrombus (23.0%). The Horizons investigators found that bleeding was markedly increased in the triple therapy group, whereas ischemic outcomes were similar in both groups [25]. The strong association between bleeding, short-term, and long-term adverse events, including mortality, is well described [26–28]. It is clear that the morbidity and mortality associated with bleeding must be considered when prescribing a VKA or an LMWH for indications with unclear benefits. Our study showed an increased risk of bleeding in patients on 'quadruple therapy' with an LMWH bridge in addition to triple therapy. This finding is intuitive, but the magnitude of excess bleeding risk with this strategy has not been well quantified.

The new antiplatelet agents, prasugrel and ticagrelor, will be used increasingly in the near future. As compared with clopidogrel, these agents exert a more potent antiplatelet effect and are thus associated with higher bleeding rates [29,30]. The use of these newer antiplatelet agents in combination with VKA therapy is untested, but will likely to lead to even higher rates of bleeding.

Ischemic stroke following anterior STEMI was a rare event in this study; thus, the study was underpowered to detect a difference in ischemic stroke on the basis of VKA use. A large study, enrolling ~2400 patients or more, would be required to detect a 50% reduction in stroke with VKA use, assuming a yearly stroke rate of 3% following anterior MI.

The duration and efficacy of VKA therapy is a second concern. The proposed duration of VKA therapy for most patients was 6 months. However, we were unable to verify the actual length of VKA therapy. Furthermore, the amount of time spent in a therapeutic INR range for VKA-treated patients was not available; thus, we cannot make a statement about compliance with VKA therapy. The frequency of bleeding events leading to cessation of VKA therapy or dual antiplatelet therapy could not be assessed from our data. Clinical decision-making around VKA use is difficult to quantify because there are valid reasons for withholding a VKA, such as elevated bleeding risk score or fall risk, which we could not quantify. Finally, this study does not address the optimal anticoagulation regiment for patients with an independent indication for VKA use, such as atrial fibrillation with an elevated CHADS2 score or those found to have a LV thrombus.

Previous studies have shown that most LV thrombi develop within 5 days but can occur up to 14 days after MI. The median time to echocardiogram from revascularization was 1 day in our study; thus, it is possible that LV thrombus developed in some patients after their initial echocardiogram.

In summary, stroke is infrequent following anterior MI and there was no observed benefit to anticoagulation with a VKA in our population. The combination of VKA therapy, dual antiplatelet therapy, and an LMWH bridge leads to an increase in bleeding. The routine use of anticoagulation for prophylaxis against stroke following anterior MI may not be warranted.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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