Anticoagulation after Anterior Myocardial Infarction and the Risk of Stroke

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Abstract

Background: Survivors of anterior MI are at increased risk for stroke with predilection to form ventricular thrombus. Commonly patients are discharged on dual antiplatelet therapy. Given the frequency of early coronary reperfusion and risk of bleeding, it remains uncertain whether anticoagulation offers additional utility. We examined the effectiveness of anticoagulation therapy for the prevention of stroke after anterior MI.

Methods and Findings: We performed a population-based cohort analysis of 10,383 patients who survived hospitalization for an anterior MI in Ontario, Canada from April 1, 1999 to March 31, 2001. The primary outcome was four-year ischemic stroke rates compared between anterior and non-anterior MI patients. Risk factors for stroke were assessed by multivariate Cox proportional-hazards analysis. Warfarin use was determined at discharge and followed for 90 days among a subset of patients aged 66 and older (n = 1483). Among the 10,383 patients studied, 2,942 patients survived hospitalization for an anterior MI and 20% were discharged on anticoagulation therapy. Within 4 years, 169 patients (5.7%) were admitted with an ischemic stroke, half of which occurred within 1-year post-MI. There was no significant difference in stroke rate between anterior and non-anterior MI patients. The use of warfarin up to 90 days was not associated with stroke protection after anterior MI (hazard ratio [HR], 0.68; 95% confidence interval [CI], 0.37–1.26). The use of angiotensin-converting-enzyme inhibitors (HR, 0.65; 95% CI, 0.44–0.95) and beta-blockers (HR, 0.60; 95% CI, 0.41–0.87) were associated with a significant decrease in stroke risk. There was no significant difference in bleeding-related hospitalizations in patients who used warfarin for up to 90 days post-MI.

Conclusion: Many practitioners still consider a large anterior-wall MI as high risk for potential LV thrombus formation and stroke. Among a cohort of elderly patients who survived an anterior MI there was no benefit from the use of warfarin up to 90 days post-MI to prevent ischemic stroke. Our data suggests that routine anticoagulation of patients with anterior-wall MI may not be indicated. Prospective randomized trials are needed to determine the optimal antithrombin strategy for preventing this common and serious adverse outcome.

Citation: Udell JA, Wang JT, Gladstone DJ, Tu JV (2010) Anticoagulation after Anterior Myocardial Infarction and the Risk of Stroke. PLoS ONE 5(8): e12150. doi:10.1371/journal.pone.0012150

Introduction

Patients with acute ST-segment elevation myocardial infarction (STEMI) have an elevated risk of stroke, most of which are ischemic in origin [1]. The risk for stroke after myocardial infarction (MI) is estimated to be 44-fold higher within the first 30 days, and remains 2 to 3 times higher than expected during the subsequent 3 years [1]. Longitudinal stroke risk following an MI is estimated to be approximately 1 percent by the first month, 2 percent by one year, and 5 percent by four years [2,3,4].

The association between the size, severity, and location of an MI and risk of developing stroke remains controversial [5–14]; nonetheless, practice guidelines recommend anticoagulation in certain settings [15]. For instance, left ventricular (LV) thrombus formation after an MI poses an increased risk of cardioembolism, which is reduced by anticoagulation [7,14,16–25]. Anterior-wall location of a MI has historically been considered a surrogate marker for potential focal dyskinesia leading to LV aneurysm or thrombus complication, which some estimate occurs in approximately one-third of individuals within the first 2 weeks following an anterior MI [26]. Myocardial infarction treatment patterns and subsequent post-MI complications have evolved dramatically in the past 20 years, particularly with regard to effectiveness and expediency in medication use, revascularization, ventricular imaging, and hospital discharge. As a result, practice patterns vary on whether or not anterior MI alone warrants anticoagulation in an era of early revascularization and coronary artery stent therapy that may reduce LV dysfunction or LV thrombus formation.

The devastating impact of a stroke after an MI, and the increasing number of persons at risk because of improved post-MI...
survival, constitutes an important public health matter for persons with heart disease. Consequently, the effectiveness of anticoagulation therapy after anterior MI for the prevention of stroke warrants further investigation.

**Methods**

**Study Population**

The design of the Enhanced Feedback for Effective Cardiac Treatment (EFFECT) study has been described previously [27,28]. The EFFECT study is a large province-wide initiative designed to improve the quality of acute MI care in Ontario, Canada. In summary, the EFFECT database consists of a large population-based sample of acute MI patients hospitalized throughout Ontario, Canada between April 1, 1999 and March 31, 2001. The hospitals included university-affiliated and community-based institutions from both rural and urban settings. All had admitted more than 30 patients with acute MI during the two years of sampling.

For this study, we excluded patients who had a previously recorded MI admission within the past year, those who sustained a MI as an in-hospital complication (e.g. post-operative), those who were transferred from an outside institution, those younger than 20 or 105 years of age or older, nonresidents of the province of Ontario, and those with invalid health insurance numbers. We also excluded those with a history of warfarin use due to previous atrial fibrillation, valvular disease, carotid endarterectomy, or thromboembolic disease, because these patients may have had other indications (other than an anterior MI) for receiving warfarin post infarction.

For the diagnosis of an acute MI, each patient had to meet the European Society of Cardiology/American College of Cardiology clinical criteria for acute MI [29], and its onset must have occurred before the patient arrived at the hospital.

The records of patients who met the inclusion and exclusion criteria for the study were reviewed by trained cardiology research nurses for abstraction of clinical data and processes of care related to the index MI hospitalization. Random re-abstraction of charts indicated high interrater agreement [30]. A random sample of 125 patients was identified among hospitals treating at least 125 suitable candidates during the study period. For hospitals that treated fewer than 125 suitable candidates during the study period, all charts were reviewed. Among the 104 acute care hospitals eligible for the study, 103 institutions ultimately participated in the study. A total of 11,524 patients with a most-responsible diagnosis of AMI (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9] code 410) were identified using the Canadian Institutes of Health Information (CIHI) hospital discharge abstract database [27,28]. Additional details related to the exclusion/inclusion criteria and validation of the AMI coding have been published elsewhere [27,28,31–33]. Administrative data were linked anonymously using encrypted individual health card numbers.

**Ethics Statement**

The study protocol was submitted to and approved by the research ethics boards at the participating institutions and Sunnybrook Health Sciences Centre. The research ethics boards approved a waiver of informed consent for collecting the study data due to the minimal risk nature of the study [34,35].

**Definitions, Study Outcomes and Data Sources**

We defined a set of clinical and demographic variables that may potentially be associated with stroke after MI that were available from chart review. Patient hospitalizations were identified using ICD-9 and 10 codes in CIHI hospital discharge abstracts to longitudinally characterize subsequent events and co-morbid illnesses (Table S1). We used each patient’s encrypted identification number to link hospital discharge data to the Registered Persons Database (RPDB) in order to calculate mortality. The RPDB provides data on the vital status of residents of Ontario and records both in- and out-of-hospital death. The Ontario Drug Benefits (ODB) database was used to longitudinally identify medications each participant aged 66 and older was dispensed during the observation period, from Ontario’s universal drug benefits plan.

The primary study cohort was those patients who were diagnosed as having an acute anterior-wall MI, with additional analyses conducted using the complete data set of all MI survivors. Anterior location of the MI was defined as a diagnostic electrocardiogram having either Q-waves or ST-elevation greater than 1 mm in leads I and aVL or V_{1+} through V_{6}. A subset of the above cohort (n = 1483), those aged 66 and older, was selected to analyze the effect of out-patient medication use on outcomes.

The primary study outcome was the rate of ischemic stroke (Table S1) among acute anterior-wall MI patients who survived to hospital discharge. Secondary outcomes focused on death from any cause and bleeding-related complications, such as hospitalization for gastrointestinal (GI) or cerebral hemorrhage. We evaluated warfarin use among the entire cohort upon discharge, and continued warfarin use 30, 60, and 90 days after the index MI among those aged 66 and older, as the exposure of interest. We chose to study warfarin use at monthly intervals between discharge and 90 days in order to determine whether there is a significant protective effect of longitudinal warfarin use on the rate of stroke in routine clinical practice among those who take warfarin for any duration, including up to the guideline-recommended three months.

**Statistical Analysis**

The demographic and clinical characteristics of patients with anterior MI and other types of MI were compared. Dichotomous variables were compared by the chi-squared test and continuous variables by the Student’s t-test.

We used Cox proportional-hazards analysis to identify factors associated with an increased risk of ischemic stroke after hospitalization for an anterior MI. Candidate variables were included in the initial Cox regression model if they were associated with stroke in a univariate analysis (P<0.25). Backward variable elimination, with an elimination criterion of a P-value of more than 0.05, was then used to create a parsimonious model for predicting ischemic stroke. We determined that the assumption of proportional hazards was met in all Cox regression models. Survival-free of stroke curves were constructed for warfarin users and non-users among anterior-wall MI patients.

The results are shown as means ± SD unless otherwise indicated. Statistical analysis was performed using SAS version 9.1 (SAS Institute Inc, Cary, NC); a P-value less than 0.05 was considered statistically significant.

**Results**

**Clinical Characteristics**

Among the 11,524 index MI patients assessed for eligibility for this study, 10,383 patients survived to hospital discharge, of which 2,942 (28%) had an anterior-wall MI (50% or 1483 were patients aged 66 or older). The clinical characteristics of the study patients are shown in Table 1. Patients who survived an anterior MI to discharge were younger (65 vs. 67 years, P<0.001), more likely to be...
male (67 percent vs. 65 percent $P = 0.028$), and had a significantly lower incidence of previous MI (20 percent vs. 23 percent $P<0.001$) as compared to those who survived other types of MI. Anterior MI patients were more likely to present with significant left ventricular dysfunction (defined as an LV ejection fraction $<40\%$ or grade 3 or 4, or narrative description of LV function as “moderate” or “severe”) (23 percent vs. 11 percent $P<0.001$) and had a higher likelihood of developing a left ventricular aneurysm, thrombus or ventricular septal defect (5 percent vs. 1 percent $P<0.001$) as a complication of the index MI. Upon discharge from hospital, anterior MI patients were more likely to be prescribed an anticoagulant (22 percent vs. 12 percent; $P<0.001$), including warfarin (14 percent vs. 6 percent; $P<0.001$), an angiotensin-converting-enzyme (ACE) inhibitor (59 percent vs. 52 percent; $P<0.001$) and clopidogrel (6 percent vs. 5 percent; $P = 0.02$), but less likely to be prescribed aspirin (73 percent vs. 77 percent; $P<0.001$), calcium antagonists (22 percent vs. 26 percent; $P<0.001$), and nitrates (38 percent vs. 44 percent; $P<0.001$).

### Total Incidence of Stroke and Secondary Outcomes

The unadjusted rates of stroke, bleeding, and mortality among the entire cohort are summarized in Table 2. One hundred and

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**Table 1. Characteristics of 10,383 Myocardial Infarction Patients Discharged Alive.**

| Variable                          | Total (N = 10,383) | Anterior MI (N = 2,942) | Other MI (N = 7,441) | P-value |
|-----------------------------------|--------------------|-------------------------|----------------------|---------|
| **Patient Demographics**          |                    |                         |                      |         |
| Age                               | 66.46 ± 13.51      | 65.52 ± 13.75           | 66.84 ± 13.39        | <.001   |
| Male                              | 6,805 (65.5%)      | 1,976 (67.2%)           | 4,829 (64.9%)        | 0.03    |
| **Past Medical History**          |                    |                         |                      |         |
| Diabetes mellitus                 | 2,621 (25.2%)      | 707 (24.0%)             | 1,914 (25.7%)        | 0.07    |
| Myocardial infarction             | 2,333 (22.5%)      | 595 (20.2%)             | 1,738 (23.4%)        | <.001   |
| Congestive heart failure          | 418 (4.0%)         | 120 (4.1%)              | 298 (4.0%)           | 0.86    |
| Hypertension                      | 4,692 (45.2%)      | 1,291 (43.9%)           | 3,401 (45.7%)        | 0.09    |
| Previous smoker                   | 2,569 (24.7%)      | 674 (22.9%)             | 1,895 (25.5%)        | 0.007   |
| Previous atrial fibrillation      | 122 (1.2%)         | 26 (0.9%)               | 96 (1.3%)            | 0.08    |
| Previous ischemic stroke          | 133 (1.3%)         | 33 (1.1%)               | 100 (1.3%)           | 0.36    |
| **In-Hospital Findings & Procedures** |                  |                         |                      |         |
| Peak creatine kinase (CK) $>2$ times the upper limit of normal | 6,293 (60.6%) | 1,966 (66.8%) | 4,327 (58.2%) | <.001 |
| Killip class $\geq 3$             | 248 (2.4%)         | 82 (2.8%)               | 166 (2.2%)           | 0.09    |
| LV dysfunction                    | 1,461 (14.1%)      | 679 (23.1%)             | 782 (10.5%)          | <.001   |
| LV aneurysm, thrombus, or ventricular septal defect (VSD) | 226 (2.2%) | 139 (4.7%) | 87 (1.2%) | <.001 |
| ST elevation on any lead groups   | 4,979 (48.0%)      | 2,474 (84.1%)           | 2,505 (33.7%)        | <.001   |
| Reperfusion therapy               | 3,414 (32.9%)      | 1,419 (48.2%)           | 1,995 (26.8%)        | <.001   |
| Discharge systolic blood pressure | 120.42 ± 19.68     | 118.01 ± 19.39          | 121.36 ± 19.65       | <.001   |
| Discharge diastolic blood pressure| 67.89 ± 11.62      | 67.33 ± 12.07           | 68.11 ± 11.43        | 0.002   |
| In-hospital atrial fibrillation    | 620 (6.0%)         | 171 (5.8%)              | 449 (6.0%)           | 0.67    |
| In-hospital ischemic stroke       | 20 (0.2%)          | 7 (0.2%)                | 13 (0.2%)            | 0.51    |
| **Discharge Medications**         |                    |                         |                      |         |
| ACE inhibitors                     | 5,578 (53.7%)      | 1,745 (59.3%)           | 3,833 (51.5%)        | <.001   |
| Angiotensin II receptor blocker (ARB) | 216 (2.1%) | 67 (2.3%) | 149 (2.0%) | 0.38    |
| Antiarrhythmics or digoxin         | 1,232 (11.9%)      | 364 (12.4%)             | 868 (11.7%)          | 0.32    |
| Anticoagulants                     | 1558 (15.0%)       | 640 (21.8%)             | 918 (12.3%)          | <.001   |
| Aspirin                           | 7,877 (75.9%)      | 2,137 (72.6%)           | 5,740 (77.1%)        | <.001   |
| Beta-adrenergic antagonists        | 7,021 (67.6%)      | 2,026 (68.9%)           | 4,995 (67.1%)        | 0.09    |
| Calcium antagonists                | 2,713 (26.1%)      | 645 (21.9%)             | 2,068 (27.8%)        | <.001   |
| Clopidogrel                        | 529 (5.1%)         | 173 (5.9%)              | 356 (4.8%)           | 0.02    |
| Diuretics                          | 2,593 (25.0%)      | 725 (24.6%)             | 1,868 (25.1%)        | 0.63    |
| Low molecular weight heparin (LMWH) | 237 (2.3%) | 60 (2.0%) | 177 (2.4%) | 0.30    |
| Nitrates                           | 4,346 (41.9%)      | 1,102 (37.5%)           | 3,244 (43.6%)        | <.001   |
| Statins                            | 3,453 (33.3%)      | 952 (32.4%)             | 2,501 (33.6%)        | 0.22    |
| Warfarin                           | 870 (8.4%)         | 400 (13.6%)             | 470 (6.3%)           | <.001   |

Data are reported as number (percentage) of patients or mean ± standard deviation (SD) value unless otherwise specified.

doi:10.1371/journal.pone.0012150.t001
seventy-six (6 percent) of the 2,942 patients discharged alive after an anterior-wall MI were diagnosed within 4 years with an acute ischemic stroke (Table 2). Seven strokes (0.2 percent) occurred in-hospital, leaving 169 (5.7 percent) stroke events following hospital discharge, approximately half of which occurred within the first year of discharge. In univariate analysis, there were no significant differences between anterior-wall MI patients and all other MI patients with regard to one- and four-year ischemic stroke rates, as well as the secondary outcomes of in-hospital, 30-day, 90-day stroke rate, all-cause mortality, and hospitalization for bleeding-related complications after one year. These results were similar after excluding those patients who developed in-hospital atrial fibrillation after one year. The unadjusted characteristics of elderly patients, who developed and did not experience an ischemic stroke after an anterior MI, are shown in Table 3. Patients who had a stroke after anterior MI were more likely to have previous diabetes mellitus (43 percent vs. 25 percent; P<0.001), higher systolic blood pressure upon discharge (126 mmHg vs. 120 mmHg; P=0.006), develop atrial fibrillation (14 percent vs. 8 percent; P=0.023) as a complication of their index anterior MI, and less likely to be prescribed an ACE inhibitor (53 percent vs. 63 percent; P=0.02) and beta-blocker (53 percent vs. 64 percent; P=0.02). There was no significant difference in the rate of warfarin use, at or after discharge, among patients who developed and did not experience an ischemic stroke after an anterior MI.

### Independent Risk Factors for Stroke

To determine risk factors associated with the occurrence of stroke after anterior MI and, in particular, whether longitudinal warfarin use had any significant protective effect on stroke occurrence, an analysis was restricted to those 1,483 patients aged 66 and older, who were eligible for Ontario’s universal drug benefit plan. Compared to the entire cohort of anterior MI patients, elderly patients were less frequently male (55 percent vs. 67 percent, P<0.001), more likely to have prior heart failure (7 percent vs. 4 percent, P<0.01) and hypertension (50 percent vs. 44 percent, P<0.01). Elderly anterior MI patients were less likely to be treated with immediate reperfusion therapy (38 percent vs. 48 percent P<0.001) and had a higher likelihood of developing in-hospital atrial fibrillation (8 percent vs. 6 percent P<0.001) as a complication of the index MI. Upon discharge from hospital, elderly anterior MI patients were more likely to be prescribed an ACE inhibitor (63 percent vs. 59 percent; P<0.01) and antiarrhythmic therapy or digoxin (18 percent vs. 12 percent; P<0.01), less likely to be prescribed a beta-blocker (63 percent vs. 69 percent; P<0.01) and statin (27 percent vs. 32 percent; P<0.01), with similar rates of anticoagulation and aspirin use at discharge.

The unadjusted characteristics of elderly patients, who developed and did not experience an ischemic stroke within 4 years after discharge for an anterior MI, are shown in Table 3. Patients who had a stroke after anterior MI were more likely to have
Table 3. Univariate Analysis of Four-Year Ischemic Stroke Risk among 1,483 Elderly Anterior Myocardial Infarction Patients.

| Variable                             | Stroke   | Non-Stroke | P-value |
|--------------------------------------|----------|------------|---------|
|                                      | N = 118  | N = 1,365  |         |
| Patient Demography                   |          |            |         |
| Age at admission for MI              | 76.77±6.69 | 76.52±6.97 | 0.71    |
| Male gender                          | 58 (49.2%) | 756 (55.4%)| 0.19    |
| Past Medical History                 |          |            |         |
| Diabetes mellitus                    | 50 (42.4%) | 346 (25.3%)| <.001   |
| Myocardial infarction                | 33 (28.0%) | 319 (23.4%)| 0.26    |
| Congestive heart failure             | 8 (6.8%)  | 92 (6.7%)  | 0.99    |
| Hypertension                         | 63 (53.4%) | 677 (49.6%)| 0.43    |
| Previous smoker                      | 32 (27.1%) | 363 (26.6%)| 0.90    |
| Previous atrial fibrillation         | 2 (1.7%)  | 16 (1.2%)  | 0.62    |
| Previous ischemic stroke             | 4 (3.4%)  | 22 (1.6%)  | 0.16    |
| In Hospital Findings & Procedures    |          |            |         |
| Killip class $\geq 3$                | 6 (5.1%)  | 51 (3.7%)  | 0.47    |
| LV dysfunction                       | 27 (22.9%) | 334 (24.5%)| 0.70    |
| LV aneurysm, thrombus, or VSD        | 6 (5.1%)  | 67 (4.9%)  | 0.93    |
| Reperfusion therapy                  | 37 (31.4%) | 525 (38.5%)| 0.13    |
| In-hospital onset of atrial fibrillation | 16 (13.6%) | 104 (7.6%) | 0.02    |
| In-hospital onset of ischemic stroke | 0 (0.0%)  | 5 (0.4%)   | 0.51    |
| Discharge systolic blood pressure    | 126.11±25.59 | 120.47±20.31| 0.006   |
| Discharge diastolic blood pressure   | 67.18±13.42 | 66.39±12.04| 0.51    |
| Discharge Medications                |          |            |         |
| ACE inhibitors                       | 62 (52.5%) | 868 (63.6%)| 0.017   |
| ARB                                  | 2 (1.7%)  | 41 (3.0%)  | 0.42    |
| Antiarrhythmic therapy or digoxin    | 26 (22.0%) | 239 (17.5%)| 0.22    |
| Aspirin                              | 80 (67.8%) | 987 (72.3%)| 0.30    |
| Beta-adrenergic antagonists          | 62 (52.5%) | 868 (63.6%)| 0.02    |
| Calcium antagonists                  | 35 (29.7%) | 335 (24.5%)| 0.22    |
| Diuretics                            | 42 (35.6%) | 476 (34.9%)| 0.88    |
| LMWH                                 | 3 (2.5%)  | 24 (1.8%)  | 0.54    |
| Nitrates                             | 53 (44.9%) | 580 (42.5%)| 0.61    |
| Clopidogrel                          | 7 (5.9%)  | 64 (4.7%)  | 0.54    |
| Statins                              | 29 (24.6%) | 372 (27.3%)| 0.53    |
| Warfarin                             | 15 (12.7%) | 205 (15.0%)| 0.50    |
| Drug Benefit Claims for Warfarin     |          |            |         |
| Within 30-days post discharge        | 11 (9.3%) | 185 (13.6%)| 0.19    |
| Within 90-days post discharge        | 12 (10.2%)| 191 (14.0%)| 0.25    |

Data are reported as number (percentage) of patients or mean ± standard deviation (SD) value unless otherwise specified.

doi:10.1371/journal.pone.0012150.t003

Table 4. Multivariate Model of Four-Year Ischemic Stroke Risk among 1,483 Elderly Patients with Anterior Myocardial Infarction.

| Variable                                | Hazard Ratio (95% CI) | P-value |
|-----------------------------------------|-----------------------|---------|
| Warfarin user for 90 days               | 0.68 (0.37–1.26)      | 0.22    |
| Previous diabetes mellitus              | 2.35 (1.63–3.40)      | <.001   |
| Discharged on antiarrhythmic therapy or digoxin | 1.60 (1.01–2.52) | 0.045   |
| Discharged on an ACE inhibitor          | 0.65 (0.44–0.95)      | 0.025   |
| Discharged on beta-adrenergic antagonists | 0.60 (0.41–0.87)   | 0.008   |

Candidate variables were included in the initial Cox regression model if they were associated with stroke in a univariate analysis (P<0.25) listed in Table 3. Backward variable elimination, with an elimination criterion of a P value of more than 0.05, was then used to create a parsimonious model for predicting ischemic stroke.

doi:10.1371/journal.pone.0012150.t004
significant reduction in ischemic stroke with warfarin use upon discharge or for a further 30-, 60-, or 90 days.

The utility of anticoagulation for the prevention of stroke after anterior MI is unclear. Anticoagulation might prevent the development of LV thrombus, which once detected is considered an established risk factor for embolic stroke [7,14,16–25]. However, previous estimates of anterior MI as an independent risk factor for LV thrombus or stroke have been inconsistent [5–14,16–25], and information on their propensity for development after current standard interventions (e.g. antiplatelet and fibrinolytic therapy) for acute MI is limited [14]. Some studies have suggested that LV dysfunction is a stronger predictor of LV thrombus formation [16,17,21,22] and the development of stroke [4]. Hence, the 2005 American College of Cardiology/American Heart Association practice guidelines [15] recommend those with STEMI complicated by LV dysfunction and extensive regional wall-motion abnormalities or LV mural thrombus noted on an imaging study receive a minimum of 3 months of warfarin for secondary prevention of stroke. There have only been a few small, non-blinded, randomized trials and observational studies of warfarin for established LV thrombus after MI for secondary prevention of systemic emboli, and these have demonstrated inconsistent results [36–39]. All were conducted before fibrinolytic and antiplatelet therapy had become routine. Our data suggests that overall, anterior MI patients do not have a higher risk of stroke, or death, as compared to other types of MI patients.

No prospective randomized controlled trial using warfarin has been conducted to study its efficacy after anterior STEMI in preventing left ventricular thrombus for prevention of stroke. The Fragnin in Acute Myocardial Infarction trial [40] prospectively demonstrated that administration of subcutaneous dalteparin (150 IU/kg body weight every 12 hours) for the duration of hospital stay after anterior MI reduced the risk of LV thrombus formation by 37 percent. But this trial was underpowered to demonstrate a significant effect on stroke and only followed patient outcomes for 11 days. Administration of subcutaneous heparin after thrombolysis for a STEMI [12], or alone in anterior STEMI [41], also did not demonstrate an effect on stroke. In a retrospective analysis [42], warfarin use in patients with heterogeneous causes of chronic left ventricular dysfunction demonstrated improved survival and risk of hospitalization for heart failure, but had no effect on stroke.

Meta-analyses of randomized controlled studies of moderate intensity warfarin with aspirin therapy after acute coronary syndrome (ACS) have demonstrated a relative risk reduction of stroke of approximately 40–46%, representing an absolute risk reduction between 0.5–1.28 percent [43,44]. These studies were conducted before routine use of coronary artery stenting and, as warfarin is not considered adequate for preserving stent patency compared to thienopyridine agents [45,46,47], its use has lost ground to competing antiplatelet and antithrombin regimens. Warfarin use after a MI has not become the standard of practice within North America also due to concerns regarding its cost-effectiveness [48] and potential bleeding complications [49]. Stroke outcomes after MI may still change as practice patterns incorporate new guidelines based on studies that demonstrated benefit in combined cardiovascular endpoints with the use of various antithrombin agents [50,51,52] and newer antiplatelet agents [53,54] throughout the index hospitalization after acute MI.

Patients who developed stroke after MI were older, had previous hypertension, heart failure, diabetes, prior stroke, and LV dysfunction complicating their index MI (Table 6), in keeping with well established risk factors for stroke following MI. These observations reinforce that secondary prevention efforts should focus on identifying and treating these risk factors for stroke, prior to hospital discharge as opposed to routine pre-emptive anticoagulation of all anterior MI patients. For instance, ACE inhibitor [55,56,57,58] and beta-blocker [59,60,61,62] therapy after acute MI complicated by congestive heart failure or LV dysfunction has demonstrated a 15–20% relative risk reduction in mortality and cardiovascular morbidity within stable patients. Whether a specific class of antihypertensive therapy offers additional protection against stroke post-MI, particularly in prevention of atrial fibrillation, has yet to be determined [63].

A major strength of our study was the longitudinal analysis of medication use and consideration of relative indications for
appropriate anticoagulation after index hospitalization, such as atrial dysrhythmia. We also considered relative contraindications to, and complications from, anticoagulation therapy, such as major bleeding that required hospitalization. Our research has some limitations that merit emphasis. Our study was a population-based cohort analysis, and as such has inherent limitations and survival bias associated with its retrospective nature and lack of randomization. As well, the elderly cohort of anterior MI patients who survived to hospital discharge may not represent the general post-MI population. Because we used administrative data to measure stroke outcomes, we were limited in the amount of clinical information regarding the nature of each outcome. For instance, left ventricular ejection fraction data was only available for approximately half of the entire EFFECT cohort. We cannot ascertain data on the development of conditions that did not require hospitalization, such as out-of-hospital atrial fibrillation, stroke or hemorrhage, which may have occurred over the 4 year period, and as such our study may be underpowered due to the limited number of stroke hospitalizations. Ischemic stroke etiologies vary, and may be from causes other than cardioembolism, such as large artery atherosclerosis or small-vessel lacunar disease. In addition, we cannot ascertain the appropriateness of warfarin therapy, intensity of anticoagulation, or compliance in individual patients. For instance, our observation that a significant

Table 5. Characteristics of Patients Diagnosed with Ischemic Stroke among 10,383 Patients within Four Years of Hospital Discharge for Myocardial Infarction.

| Variable                                  | Total   | Stroke  | Non-Stroke | P-value |
|-------------------------------------------|---------|---------|------------|---------|
| **Patient Demographics**                  |         |         |            |         |
| Age at admission of MI                    | 66.35 ± 13.52 | 73.01 ± 13.52 | 65.96 ± 13.52 | <.001   |
| Male gender                               | 6,670 (64.2%) | 307 (53.2%) | 6,363 (64.9%) | <.001   |
| **Past Medical History**                  |         |         |            |         |
| Diabetes mellitus                         | 2,576 (24.8%) | 226 (39.2%)  | 2,350 (24.0%) | <.001   |
| Myocardial infarction                     | 2,273 (21.9%) | 166 (28.8%)  | 2,107 (21.5%) | <.001   |
| Congestive heart failure                   | 410 (4.0%)  | 45 (7.8%)  | 365 (3.7%)  | <.001   |
| Hypertension                              | 4,570 (44.0%) | 319 (55.3%)  | 4,251 (43.4%) | <.001   |
| Previous smoker                           | 2,522 (24.3%) | 144 (25.0%)  | 2,378 (24.3%) | 0.73    |
| Previous atrial fibrillation              | 118 (1.1%)  | 16 (2.8%)  | 102 (1.0%)  | <.001   |
| Previous ischemic stroke                  | 131 (1.3%)  | 24 (4.2%)  | 107 (1.1%)  | <.001   |
| **In Hospital Findings & Procedures**     |         |         |            |         |
| Anterior wall myocardial infarction       | 2,942 (28.3%) | 169 (29.3%)  | 2,773 (28.2%) | 0.60    |
| Peak CK > 2 times the upper limit of normal | 6,148 (59.2%) | 318 (55.1%)  | 5,830 (59.5%) | 0.028   |
| Killip class ≥3                           | 239 (2.3%)  | 18 (3.1%)  | 221 (2.3%)  | 0.182   |
| LV dysfunction                            | 1,392 (13.4%) | 104 (18.0%)  | 1,288 (13.1%) | <.001   |
| LV aneurysm, thrombus, or VSD             | 214 (2.1%)  | 14 (2.4%)  | 200 (2.0%)  | 0.53    |
| In-hospital onset of atrial fibrillation  | 588 (5.7%)  | 52 (9.0%)  | 536 (5.5%)  | <.001   |
| ST elevation on any lead groups           | 4,852 (46.7%) | 236 (40.9%)  | 4,616 (47.1%) | 0.003   |
| Reperfusion therapy                       | 3,300 (31.8%) | 125 (21.7%)  | 3,175 (32.4%) | <.001   |
| Discharge systolic blood pressure         | 120.38 ± 19.62 | 125.12 ± 22.90 | 120.11 ± 19.38 | <.001   |
| Discharge diastolic blood pressure        | 67.88 ± 11.62 | 68.64 ± 12.50 | 67.84 ± 11.57 | 0.12    |
| **Discharge Medications**                 |         |         |            |         |
| ACE Inhibitors                            | 5,449 (52.5%) | 319 (55.3%)  | 5,130 (52.3%) | 0.187   |
| ARB                                       | 213 (2.1%)  | 13 (2.3%)  | 200 (2.0%)  | 0.73    |
| Antiarrhythmic therapy or digoxin          | 1,190 (11.5%) | 105 (18.2%)  | 1,085 (11.1%) | <.001   |
| Aspirin                                   | 7,734 (74.5%) | 385 (66.7%)  | 7,349 (74.9%) | <.001   |
| Beta-adrenergic antagonists                | 6,880 (66.3%) | 337 (58.4%)  | 6,543 (66.7%) | <.001   |
| Calcium antagonists                       | 2,659 (25.6%) | 167 (28.9%)  | 2,492 (25.4%) | 0.065   |
| Diuretics                                 | 2,510 (24.2%) | 213 (36.9%)  | 2,297 (23.4%) | <.001   |
| LMWH                                      | 232 (2.2%)  | 9 (1.6%)   | 223 (2.3%)  | 0.26    |
| Nitrates                                  | 4,245 (40.9%) | 271 (47.0%)  | 3,974 (40.5%) | 0.003   |
| Clopidogrel                               | 511 (4.9%)  | 26 (4.5%)  | 485 (4.9%)  | 0.62    |
| Statin                                    | 3,380 (32.6%) | 131 (22.7%)  | 3,249 (33.1%) | <.001   |
| Warfarin                                  | 850 (8.2%)  | 66 (11.4%)  | 784 (8.0%)  | 0.004   |

Data are reported as number (percentage) of patients or mean ± standard deviation (SD) value unless otherwise specified.

doi:10.1371/journal.pone.0012150.t005
proportion of warfarin users who developed stroke in a univariate analysis (P < 0.05). Backward variable elimination, with an elimination criterion of a P value of more than 0.05, was then used to create a parsimonious model for predicting ischemic stroke. doi:10.1371/journal.pone.0012150.t006

### Table 6. Multivariate Model of Four-Year Ischemic Stroke Risk among 10,383 Myocardial Infarction Patients Discharged Alive.

| Variable                  | Hazard Ratio (95% CI) | P-value |
|---------------------------|-----------------------|---------|
| Discharge on warfarin     | 1.04 (0.78–1.37)      | 0.81    |
| Age at admission of MI    | 1.04 (1.03–1.05)      | <0.001  |
| Discharge diastolic blood pressure | 1.01 (1.00–1.02)     | 0.03    |
| Hypertension              | 1.21 (1.10–1.44)      | 0.04    |
| Previous diabetes mellitus| 1.82 (1.52–2.18)      | <0.001  |
| Previous congestive heart failure | 1.45 (1.04–2.02)    | 0.03    |
| Previous ischemic stroke  | 2.38 (1.45–3.78)      | <0.001  |
| Reperfusion therapy       | 0.80 (0.64–0.98)      | 0.04    |
| LV dysfunction            | 1.27 (1.01–1.59)      | 0.04    |
| Discharge on a statin      | 0.70 (0.57–0.86)      | <0.001  |
| Discharge on a diuretic    | 1.23 (1.01–1.49)      | 0.04    |
| Discharge on aspirin       | 0.73 (0.61–0.89)      | 0.002   |

Candidate variables were included in the initial Cox regression model if they were associated with stroke in a univariate analysis (P < 0.25). Backward variable elimination, with an elimination criterion of a P value of more than 0.05, was then used to create a parsimonious model for predicting ischemic stroke.

### Table S1

| Variable                  | Hazard Ratio (95% CI) | P-value |
|---------------------------|-----------------------|---------|

**Supporting Information**

Conceived and designed the experiments: JAU JT. Performed the experiments: JAU JTW JT. Analyzed the data: JAU JTW DJG JT. Contributed reagents/materials/analysis tools: JAU JTW DJG JT. Wrote the paper: JAU DJG JT.

**Author Contributions**

1. Witt BJ, Brown RD, Jacobsen SJ, Weston SA, Yawn BP, et al. (2005) A community-based study of stroke incidence after myocardial infarction. Ann Intern Med 143: 785–792.
2. Witt BJ, Ballman KV, Brown RD, Meverden RA, Jacobsen SJ, et al. (2006) The incidence of stroke after myocardial infarction: a meta-analysis. Am J Med 119: 354.e1–e9.
3. Hurlen M, Abdelnoor M, Smith P, Eriksson J, Arnesen H (2002) Warfarin, aspirin, or both after myocardial infarction. N Engl J Med 347: 969–74.
4. Loh E, Sutton MS, Wun CC, Rosadeau JL, Flaker GC, et al. (1997) Ventricular dysfunction and the risk of stroke after myocardial infarction. N Engl J Med 336: 251–7.
5. Herlitz J, Holm J, Peterson M, Karlson BW, Evander MH, et al. (2005) Factors associated with development of stroke long-term after myocardial infarction: experiences from the LoWASA trial. J Intern Med 257: 201–7.
6. Tamne D, Reicher-Reiss H, Boyko V, Behar S (1995) Stroke risk after anterior wall acute myocardial infarction. SPRINT Study Group. Secondary Prevention Reinforcement Israeli Nifedipine Trial. Am J Cardiol 76: 825–6.
7. Greaves SC, Zhi G, Lee RTF, Solomon SD, MacFadyen J, et al. (1997) Incidence and natural history of left ventricular thrombus following anterior wall acute myocardial infarction. Am J Cardiol 80: 442–448.
8. Moo T, Eriksson P, Stegmayr B (1997) Ischemic stroke after acute myocardial infarction. A population-based study. Stroke 28: 762–7.
9. Bodenheimer MM, Sauer D, Shareef B, Brown MW, Fleiss JL, et al. (1994) Relation between myocardial infarct location and stroke. J Am Coll Cardiol 24: 61–6.
10. Hess D, D’Cruz IA, Adams RJ, Nichols FT (1993) Coronary artery disease, myocardial infarction, and brain embolism. Neurol Clin 11: 397–411.
11. Konrad MS, Coffer E, Coffer KS, McKinnis R, Massey EW, et al. (1984) Myocardial infarction and stroke. Neurology 34: 1403–9.
12. Muggioni AF, Franzoni MG, Santoro E, White H, Van de Werf F, et al. (1992) The risk of stroke in patients with acute myocardial infarction after thrombolytic and antiplatelet therapy. N Engl J Med 327: 1–6.
13. O’Connor CM, Califf RM, Massey EW, Mark DB, Kerriakes DJ, et al. (1990) Stroke and acute myocardial infarction in the thrombolytic era: clinical correlates and long-term prognosis. J Am Coll Cardiol 16: 535–540.
14. Nayak D, Aronow WS, Sukhija R, McClung TA, Mosen CE, et al. (2004) Comparison of frequency of left ventricular thrombi in patients with anterior wall versus non-anterior wall acute myocardial infarction treated with antiplatelet and antiplatelet therapy or with without coronary recanalization. Am J Cardiol 93: 1529–30.
15. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, et al. (2004) 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 110: e82–292.
16. Vaitkus PT, Barnathan ES (1993) Embolic potential, prevention and management of mural thrombus complicating anterior myocardial infarction: a meta-analysis. J Am Coll Cardiol 22: 1004–9.
17. Keating EC, Gross SA, Schlomowitz RA, Glassman J, Mazur JH, et al. (1983) Mural thrombi in myocardial infarctions: prospective evaluation by two-dimensional echocardiography. Am J Med 74: 809–95.
18. Anouser RW, Mikell FL, Elperger J, Hodges M (1981) Incidence of left-ventricular thrombosis after acute transmural myocardial infarction. Serial evaluation by two-dimensional echocardiography. N Engl J Med 305: 297–302.
19. Reeder GS, Lengyl M, Tajik AJ, Seward JB, Smith HC, et al. (1981) Mural thrombus in left ventricular aneurysm: incidence, role of angiography, and relation between anticoagulation and embolization. Mayo Clin Proc 56: 77–81.
20. Weintraub WS, Ba’alhaki HA (1989) Decision analysis concerning the application of echocardiography to the diagnosis and treatment of mural thrombi after anterior wall myocardial infarction. Am J Cardiol 64: 708–16.
21. Lamas GA, Vaughan DE, Pfeffer MA (1980) Left ventricular thrombus formation after first anterior wall acute myocardial infarction. Am J Cardiol 46: 62–35.
22. Weinrich DJ, Burke JF, Paulotto FJ (1984) Left ventricular mural thrombi complicating acute myocardial infarction: long term follow-up with serial echocardiography. Ann Intern Med 100: 789–94.
23. Vecchio G, Chiaurelli F, Lupi G, Bellotti P, Domenicucci S (1991) Left ventricular thrombus in anterior acute myocardial infarction after thrombolysis. Circulation 84: 512–519.
24. Friedman MJ, Carlson K, Marcus FL, Woolfenden JM (1982) Clinical correlations in patients with acute myocardial infarction and left ventricular thrombus detected by two-dimensional echocardiography. Am J Med 72: 884–8.
25. Danzig JM, Delemarre BJ, Bot H, Visser CA (1996) Left ventricular thrombus in acute myocardial infarction. Eur Heart J 17: 1640–5.
26. Foster V, Halperin JL (1989) Left ventricular thrombi and cerebral embolism. N Engl J Med 320: 392–4.
27. Tu JV, Donovan LR, Lee DS, Austin PA, Ko DT, et al. (2004) Quality of Cardiac Care in Ontario. Toronto/Ontario: Institute for Clinical Evaluative Sciences.
28. Bradshaw PJ, Ko DT, Newman AM, Donovan LR, Tu JV (2006) Validity of the GRACE acute coronary syndrome prediction model for 6-month post-discharge death in an independent data set. Heart 92: 905–909.

29. Kouvaras G, Chronopoulos G, Soufras G, Sofronas G, Solomos D, et al. (1990) Randomized multicenter comparison of conventional anticoagulation versus Warfarin anticoagulation and survival: a cohort analysis from the studies of left ventricular thrombosis early after acute myocardial infarction. Eur Heart J 7: 898–92.

30. Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, et al. (2003) Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. JAMA 290: 2381–2387.

31. Schull MJ, Vermeulen M, Donovan L, Newman A, Tu JV (2005) Can the wrong statistic be bad for health? Improving the reporting of door-to-needle time performance in acute myocardial infarction. Am Heart J 150: 583–587.

32. Kontny F, Dale J, Abildgaard U, Pedersen TR (1997) Randomized trial of low molecular weight heparin in prevention of left ventricular thrombus formation and arterial embolism after patients with stroke. CMAJ 161: 989–96.

33. Miller FG, Emanuel EJ (2008) Quality-improvement research and informed consent. N Engl J Med 358: 763–767.

34. Miller FG, Emanuel EJ (2008) Quality-improvement research and informed consent in the Registry of the Canadian Stroke Network. Impracticality of informed consent in the Registry of the Canadian Stroke Network. N Engl J Med 358: 1414–1421.

35. Al-Khadra AS, Salem DN, Rand WM, Udelson JE, Smith JJ, et al. (1998) Comparison of high-dose with low-dose subcutaneous heparin to prevent left ventricular mural thrombosis in patients with acute transmural myocardial infarction. N Engl J Med 320: 352–7.

36. Graham DJ, Newby DE, Califf RM, Topol EJ (2005) Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 357: 2001–2015.

37. Antman EM, Morrow DA, McCabe CH, Murphy SA, Ruda M, et al. (2006) Fondaparinux: an antithrombin therapy in left ventricular thrombosis after acute coronary syndromes: an updated and comprehensive meta-analysis of 25 307 patients. Eur Heart J 27: 519–26.

38. Bradford PJ, Ko DT, Newman AM, Donovan LR, Tu JV (2006) Validity of the GRACE acute coronary syndrome prediction model for 6-month post-discharge death in an independent data set. Heart 92: 905–909.

39. The OASIS-6 Trial Group (2006) Comparison of fondaparinux and enoxaparin in acute coronary syndromes. N Engl J Med 354: 1464–76.

40. Kontny F, Dale J, Abildgaard U, Pedersen TR (1997) Randomized trial of low molecular weight heparin in prevention of left ventricular thrombus formation and arterial embolism after acute myocardial infarction. N Engl J Med 334: 1084–9.

41. Tu JV, Donovan LR, Austin PC, Ko DT, Newman AM, et al. (2005) Warfarin plus aspirin was superior to aspirin alone after acute myocardial infarction but increased bleeding. ACP J Club 138: 34.

42. Pullicino P, Thompson JL (2003) Warfarin, aspirin, or both after myocardial infarction [Letter]. N Engl J Med 348: 256–7.

43. The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators (2009) Comparison of fondaparinux and enoxaparin in acute coronary syndromes. N Engl J Med 360: 2045–57.

44. Kontny F, Dale J, Abildgaard U, Pedersen TR (1997) Randomized trial of low molecular weight heparin in prevention of left ventricular thrombus formation and arterial embolism after acute myocardial infarction. Am Heart J 134: 1597–603.

45. Leon MB, Baim DS, Popma JI, Gordon PC, Cutille DE, et al. (1998) A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Senta Anticoagulation Restenosis Study Investigators. N Engl J Med 339: 1665–71.

46. Antman EM, Morrow DA, McCabe CH, Murphy SA, Ruda M, et al. (2006) Fondaparinux versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. N Engl J Med 354: 1477–88.

47. Tu JV, Donovan LR, Austin PC, Ko DT, Newman AM, et al. (2005) Warfarin plus aspirin was superior to aspirin alone after acute myocardial infarction but increased bleeding. ACP J Club 138: 34.

48. Wiviott SD, Braunwald E, McCabe CH, Matsulecto G, Ruzyllo W, et al. (2007) Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 357: 2001–2015.

49. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, et al. (2009) Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 361: 1045–1057.

50. The MIAMI Trial Research Group: metoprolol in acute myocardial infarction. N Engl J Med 334: 989–96.

51. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ, et al. (1992) Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial: The SAVE Investigators. N Engl J Med 327: 689–77.

52. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators (1993) Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. Lancet 342: 812–28.

53. The Task Force on Beta-blockers of the European Society of Cardiology (2004) Expert consensus document on β-blocker therapy after myocardial infarction reinfarction in patients with acute ST-segment elevation myocardial infarction. JAMA 295: 1519–50.

54. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, et al. (2009) Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 361: 1045–1057.

55. Fagan JW, McPeek M (2006) Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. JAMA 290: 2381–2387.

56. Kontny F, Dale J, Abildgaard U, Pedersen TR (1997) Randomized trial of low molecular weight heparin in prevention of left ventricular thrombus formation and arterial embolism after acute coronary myocardial infarction: the fragmin in acute myocardial infarction (FRAMI) study. J Am Coll Cardiol 30: 962–969.

57. The FANTASTIC study. Circulation 113: e873–e923.

58. The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators (2006) Comparison of fondaparinux and enoxaparin in acute coronary syndromes. N Engl J Med 357: 2001–2015.

59. The MIAMI Trial Research Group: metoprolol in acute myocardial infarction. N Engl J Med 334: 989–96.

60. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, et al. (2009) Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 361: 1045–1057.

61. The MIAMI Trial Research Group: metoprolol in acute myocardial infarction. N Engl J Med 334: 989–96.

62. The MIAMI Trial Research Group: metoprolol in acute myocardial infarction. N Engl J Med 334: 989–96.