Original Article

Left Ventricular Thrombus and Subsequent Thromboembolism, Comparison of Anticoagulation, Surgical Removal, and Antiplatelet Agents

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Aim: Left ventricular (LV) thrombus is one of the risk factors for systemic thromboembolism. The aims of this study were to compare the long-term clinical outcomes of LV thrombus using current therapeutics, anticoagulation, operative treatment, and antiplatelet agents and to identify independent predictors of systemic thromboembolism.

Methods: We screened 86,374 patients for intracardiac thrombus in the electronic medical records and imaging databases. Records of 62 patients with LV thrombus, diagnosed between May 2003 to November 2011, were comprehensively reviewed regarding baseline characteristics, imaging data and thrombus outcomes, thromboembolic events and treatment complications by treatment group.

Results: The majority (80.6%) had ischemic etiology. Systemic thromboembolism developed in 18 patients; 8 (45%) were post-treatment thromboembolisms while 10 events occurred before treatment began. No post-treatment thromboembolism occurred in the operative treatment group; in contrast, 7 post-treatment thromboembolisms occurred in anticoagulation group (17%) (Log rank $p=0.175$). Independent predictors of post-treatment thromboembolism were dilated cardiomyopathy (HR 61.30, $p=0.001$), previous cerebrovascular events (HR 7.06, $p=0.042$), female gender (HR 7.11, $p=0.031$), and echocardiographic left ventricular end-diastolic diameter (HR 1.15, $p=0.047$).

Conclusions: In this study, the rate of post-treatment thromboembolism was not significantly different among the treatment groups; however, operative treatment tended towards less post-treatment thromboembolism than other treatment groups.

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Key words, Acute myocardial infarction, Dilated cardiomyopathy, Ischemic cardiomyopathy, Intracardiac thrombus, Left ventricular thrombus

Introduction

Left ventricular (LV) thrombus formation is a frequent complication of ischemic heart disease, particularly in acute myocardial infarction (MI), even

after successful revascularization¹. At least 5% of patients develop LV thrombus after acute MI². Various other conditions, including idiopathic dilated cardiomyopathy (DCMP), stress-induced cardiomyopathy and valvular heart disease-induced severe LV dysfunction, are known risk factors for LV thrombus formation^{3,4}.

The clinical relevance of LV thrombus is the association with increased risk of systemic arterial thromboembolism⁵⁻⁷. It is known that anticoagulation therapy with warfarin reduces both the risk of LV thrombus formation and subsequent thromboembo-

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Fig. 1. Flow of Participants Diagram.

TTE denotes trans-thoracic echocardiography, TEE trans-esophageal echocardiography, MRI magnetic resonance imaging, CT computed tomography.

Abbreviations: LA, left atrium; LV, left ventricle; RA right atrium; RV right ventricle.

lism, but increases the risk of bleeding⁷⁻⁹). Current ACC/AHA guidelines recommend anticoagulation with warfarin for patients with LV thrombus or cardioembolic stroke (class I, level of evidence: b)¹⁰; however, chronic anticoagulation has inevitable bleeding complications.

Moreover, the long-term consequences and frequency of systemic thromboembolism after conventional anticoagulation for LV thrombus have not been sufficiently investigated. Evidence of the superiority of conventional anticoagulation relative to surgical removal or antiplatelet agents is scarce, as are studies of independent predictors of systemic thromboembolism. The aims of this study were to investigate long-term clinical outcomes for LV thrombus, including the rate of systemic thromboembolism and complications of current therapeutics (conventional anticoagulation, operative treatment, antiplatelet agents) and to identify independent predictors of systemic thromboembolism.

Materials and Methods

Patient Population and Data Collection

All patients with LV thrombus, diagnosed by two-dimensional echocardiography, cardiac magnetic

resonance imaging (MRI) or coronary computed tomographic (CT) angiography were included as study subjects. From May 2003 to November 2011, we performed 75,936 two-dimensional transthoracic echocardiographies (TTEs), 1,100 cardiac MRIs and 9,338 coronary CT angiographies (CTAs). The respective imaging databases were screened for intra-cardiac thrombus; 69 patients were found with LV thrombus. After 7 of these patients, whose transesophageal echocardiography (TEE) confirmed no intra-cardiac thrombus, were excluded from this analysis, 62 patients remained as study patients (**Fig. 1**).

A comprehensive review of each patient's clinical data was performed using the electronic medical record system to identify baseline characteristics and medications at the time of LV thrombus diagnosis. Medical records were also evaluated for echocardiographic parameters, morphology of the LV thrombus in three imaging modalities, treatment of the LV thrombus, initial anticoagulation, details of the operative procedure, events of systemic thromboembolism, cardiac or all-cause mortality and complications of treatment including major or minor bleeding.

Decisions regarding the treatment strategy for LV thrombus were made by the patient's primary physi-

cian. All patients who were anticoagulated with warfarin were evaluated by the Anticoagulation Service in our institution at least 1 or 2 times a month to maintain a stable prothrombin time (PT) international normalized ratio (INR) value between 2 to 3. If the patients were treated with an antiplatelet agent only, the reasons for no anticoagulation were determined by medical record review and consultation with the patient's primary physician. An attempt was made to contact and interview, via telephone, all patients who were lost to follow-up. Except for 9 patients, including 4 deceased patients and 5 follow-up losses, all patients are currently being followed. This study was approved by the institutional review board.

Imaging Modalities

Two-Dimensional Echocardiography

Two-dimensional echocardiographic examinations were performed using three different commercially available systems (Vivid E9, GE Healthcare, Wilmington, MA, USA; Sonos 7500, Philips Medical Systems, Eindhoven, The Netherlands; Sequoia C512, Siemens Medical Solutions, Erlangen, Germany) and standard techniques in accordance with the guidelines of the American Society of Echocardiography¹¹. LV thrombus was defined as an echo-dense mass within the ventricular cavity with 1) a marked delineation toward the lumen and 2) a structural texture different from the myocardium and that 3) could be separated from the underlying endocardium by an endocardial lining; 4) was visible throughout the entire cardiac cycle; and 5) could be demonstrated in at least two different views as previously described⁸. Any suspected diagnosis of LV thrombus with TTE was confirmed by TEE using the same equipment (Vivid E9; GE Healthcare). Thrombus shape was classified as pedunculated (with demonstration of pendulations apart from those mediated by myocardial contraction) or sessile; thrombus mobility was defined as mobile or mural. A mobile thrombus, including pedunculated or multiple thrombi, was categorized as a high-risk LV thrombus. The left ventricular ejection fraction and left atrial size were calculated by volumetric methods, which were measured in both apical 4-chamber and 2-chamber views. Every echocardiographic finding was confirmed at the time of examination by the staff of our institution, who specialize in cardiovascular imaging.

Cardiac MRI and Coronary CT Angiography

Cardiac MRI was performed with a 1.5 Tesla MR system (Philips Medical System). The imaging protocol included cine-MRI, T2-weighted imaging,

early gadolinium enhancement and late gadolinium enhancement imaging. All subjects underwent coronary CTA with retrospective ECG gating on a 64 channel Multi-Detector CT scanner (Brilliance iCT; Philips Medical System, Boston, USA). Detailed imaging protocol of cardiac MRI and coronary CTA is presented in Supplementary Materials.

Definitions and Outcome Analysis

The conventional anticoagulation group was defined as patients who were prescribed warfarin, regardless of antiplatelet agent use. If the patient had undergone surgical removal of LV thrombus, the patient was classified into the operative treatment group, regardless of medication status. The antiplatelet agent group included patients who had received neither warfarin nor operative treatment for LV thrombus and who were taking one or more antiplatelet agents. In our study, many systemic thromboembolisms had occurred before treatment of LV thrombus began. Thus, we separated thromboembolic events as pre-treatment or post-treatment events. Embolic events that developed before the initiation of LV thrombus treatment were defined as pre-treatment. In contrast, embolic events that developed after the initiation of anticoagulation, antiplatelet agents or operative treatment were defined as post-treatment thromboembolism.

The primary outcome of the main analysis was the rate of post-treatment thromboembolism that included embolic cerebral infarction, transient ischemic attack and peripheral embolism. For cerebral infarction, the events were classified as embolic if the criteria, previously reported by Hart *et al.*¹², were met. Transient ischemic attack was defined as any focal neurologic deficit of sudden onset that lasted < 30 min and lacked abnormal findings on brain MRI. Peripheral thromboembolism was defined as a combination of signs and symptoms of end organ ischemic damage that was confirmed by conventional angiography or CTA.

The cause of death was classified as cardiac or non-cardiac, defined according to Academic Research Consortium definitions¹³. Bleeding events were defined according to the Thrombolysis in Myocardial Infarction (TIMI) criteria¹⁴. Major bleeding was defined as any intracranial hemorrhage, more than a 5 g/dL decrease in the hemoglobin concentration or more than a 15% absolute decrease in the hematocrit.

Outcomes related to thrombus morphology and changes of the maximum size were also evaluated. Follow-up echocardiography was performed in 48 patients (77.42%). Resolution of LV thrombus and the follow-

up size of the thrombus were abstracted from the database. Thrombus resolution was strictly defined as complete resolution, that is, no evidence of LV thrombus on follow-up echocardiography. Width and thickness of the thrombus were recorded; maximum thrombus size was defined as the greatest value among all widths and thicknesses.

Statistical Analysis

Categorical variables are presented as numbers and relative frequencies (percentages) and were compared using the χ^2 test or Fisher's exact test, as appropriate. Normally distributed continuous variables are expressed as the means and standard deviations, and between-group differences were analyzed using the independent sample *t*-test or the Mann-Whitney *U* test as appropriate. The three treatment modalities were compared using the Kruskal-Wallis test for continuous variables and χ^2 test for categorical variables. Pairwise comparisons between two groups were performed as post-hoc analysis using the Bonferroni corrected *p* value. The change in LV thrombus size, before and after treatment, was evaluated with the Wilcoxon signed rank sum test. Kaplan-Meier analysis was used to calculate the cumulative incidence of the primary outcomes (post-treatment thromboembolism) and the log rank test or Breslow test was used to compare the differences in event-free survival among the groups, as appropriate.

A Cox proportional hazard regression model was used to evaluate the adjusted hazard ratio (HR) of each clinical variable and to identify independent predictors of pre-treatment or post-treatment systemic thromboembolism. Variables were included as covariates in multivariate analyses if they were distributed differently among the treatment groups, were associated with the primary outcome in univariate analyses or were generally accepted as potential confounders. The adjusted covariates are shown in **Supplementary Table 1**. Since there were differences in important baseline characteristics, such as the proportion of mobile or multiple thrombi and the maximum thrombus size among the three treatment groups, particularly between the anticoagulation group and antiplatelet agent group, we performed two 1:1 matched analyses without replacement (one compared the anticoagulation and operative treatment groups, the other compared the anticoagulation and antiplatelet agent groups) using a propensity score. The log-odds of the probability that a patient was treated with surgical removal or antiplatelet agents was modeled as a function of the confounders. A caliper width of 0.6 SDs was used because this value has been shown to elimi-

Supplementary Table 1. Independent Variables Analyzed using the Cox Proportional Hazard Regression Model

Variables	Measure
Baseline characteristics and risk factors	
Age	Continuous
Sex (M/F)	Nominal
Hypertension	Nominal
Diabetes mellitus	Nominal
Current smoking	Nominal
Dyslipidemia	Nominal
Chronic renal failure	Nominal
Atrial fibrillation (permanent or paroxysmal)	Nominal
Malignancy	Nominal
Previous myocardial infarction	Nominal
Previous cerebrovascular accident	Nominal
Underlying Heart Conditions	
Cardiac arrest	Nominal
Severe aortic stenosis	Nominal
Ischemic CMP	Nominal
Hypertrophic CMP	Nominal
Stress-induced cardiomyopathy	Nominal
Dilated CMP	Nominal
Medications	
Acetylsalicylic acid	Nominal
Clopidogrel	Nominal
Cilostazole	Nominal
Triflusal	Nominal
Warfarin	Nominal
Beta-adrenergic receptor blockers	Nominal
ACEI or ARB	Nominal
Digoxin	Nominal
Diuretics	Nominal
Statin	Nominal
Calcium-channel blocker	Nominal
Echocardiographic parameters	
LVEDD	Continuous
LVESD	Continuous
Ejection fraction	Continuous
Left atrial size	Continuous
Anteroapical aneurysm	Nominal
Others	
Thrombus mobility	Nominal
Maximum size	Continuous
Operation before embolism	Nominal
Dor operation, aneurysmectomy, or thrombectomy	Nominal

* Data are expressed as the means $\pm$ SD or as counts (%).

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CMP, cardiomyopathy; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension.

Table 1. Baseline Characteristics of Patients with Left Ventricular Thrombus ($n=62$)*

Characteristics		Total ($n=62$)	Embolism (–) ($n=44$, 71.0%)	Embolism (+) ($n=18$, 29.0%)	<i>p</i> value
Baseline Characteristics	Age	63.61 ± 13.94	64.95 ± 13.42	60.33 ± 15.04	0.239
	Male	50 (80.6%)	35 (79.5%)	15 (83.3%)	0.732
	BMI	19.26 ± 2.90	19.35 ± 2.59	19.06 ± 3.54	0.725
	Diabetes mellitus	18 (29.0%)	14 (31.8%)	4 (22.2%)	0.450
	Hypertension	36 (58.1%)	29 (65.9%)	7 (38.9%)	0.087
	Dyslipidemia	38 (61.3%)	27 (61.4%)	11 (61.1%)	0.985
	Current smoker	18 (29.0%)	12 (27.3%)	6 (33.3%)	0.759
	Atrial fibrillation [†]	2 (3.2%)	1 (2.3%)	1 (5.6%)	0.500
	CRF	5 (8.1%)	4 (9.1%)	1 (5.6%)	>0.999
	eGFR [‡]	74.42 ± 26.85	71.51 ± 23.72	81.39 ± 32.89	0.193
	Malignancy	3 (4.8%)	3 (6.8%)	0 (0%)	0.550
	Prior myocardial infarction	25 (40.3%)	17 (38.6%)	8 (44.4%)	0.778
	Prior CAD	29 (46.8%)	21 (47.7%)	8 (44.4%)	0.814
	Prior CVA	9 (14.5%)	6 (13.3%)	3 (17.6%)	0.696
	STEMI	21 (33.9%)	18 (40.9%)	3 (16.7%)	0.082
Underlying Heart Conditions	Ischemic CMP	50 (80.6%)	36 (81.8%)	14 (77.8%)	0.732
	Dilated CMP	5 (8.1%)	2 (4.5%)	3 (16.7%)	0.141
	Apical HCM ^P	2 (3.2%)	2 (4.5%)	0 (0%)	>0.999
	Stress-induced CMP	3 (4.8%)	3 (6.8%)	0 (0%)	0.550
	Severe AS	1 (1.6%)	1 (2.3%)	0 (0%)	>0.999
	Cardiac arrest due to Brugada syndrome	1 (1.6%)	0 (0%)	1 (5.6%)	0.290
Medications	Acetylsalicylic acid	45 (72.6%)	33 (75.0%)	12 (66.7%)	0.541
	Clopidogrel	22 (35.5%)	18 (40.9%)	4 (22.2%)	0.243
	Cilostazole	1 (1.6%)	1 (2.3%)	0 (0%)	>0.999
	Triflusal	2 (3.2%)	1 (2.3%)	1 (5.6%)	0.507
	Warfarin	45 (72.6%)	28 (63.6%)	17 (94.4%)	0.014
	Digoxin	6 (9.7%)	3 (6.8%)	3 (16.7%)	0.344
	ACEI or ARB	41 (66.1%)	30 (68.2%)	11 (61.1%)	0.768
	Diuretics	23 (37.1%)	16 (36.4%)	7 (38.9%)	0.852
	β-blockers	36 (58.1%)	26 (59.1%)	10 (55.6%)	0.798
	Calcium channel blockers	6 (9.7%)	3 (6.8%)	3 (16.7%)	0.344
	Nitrates	4 (6.5%)	3 (6.8%)	1 (5.6%)	>0.999
	Statins	36 (58.1%)	26 (59.1%)	10 (55.6%)	0.798
	Others [§]	4 (6.5%)	3 (6.8%)	1 (5.6%)	>0.999
Thrombus Morphology	Maximum size	17.44 ± 7.48	16.51 ± 7.22	19.66 ± 7.83	0.137
	Apical location	62 (100%)	44 (100%)	18 (100%)	NS
	Mobile/Multiple	9 (14.5%)	4 (9.1%)	5 (27.8%)	0.058
	Mural/Sessile	53 (85.5%)	40 (90.9%)	13 (72.2%)	0.058
Echocardiographic Parameters	LVEDD	53.55 ± 8.75	52.72 ± 8.58	55.54 ± 9.08	0.147
	LVESD	39.22 ± 11.85	38.47 ± 11.58	41.00 ± 12.63	0.256
	LVEF	40.23 ± 14.29	39.74 ± 12.56	41.40 ± 18.13	0.498
	LA Size	41.18 ± 9.35	40.16 ± 9.80	43.63 ± 7.88	0.033
	LAVI	39.14 ± 20.48	39.61 ± 21.48	37.46 ± 17.80	0.500
RWMA	None	2 (3.2%)	1 (2.3%)	1 (5.6%)	0.500
	Anteroapical akinesia	48 (77.4%)	35 (79.5%)	13 (72.2%)	0.739
	Global hypokinesia/akinesia	11 (17.7%)	7 (15.9%)	4 (22.2%)	0.715
	Apical aneurysm	18 (29.0%)	13 (30.2%)	5 (27.8%)	0.848

*Data are expressed as the means ± SD or as counts (%).

[†]Atrial fibrillation included both permanent and paroxysmal atrial fibrillation.[‡]Estimated glomerular filtration rate (mL/min/1.73 m²) was calculated by MDRD (Modification of Diet in Renal Disease) equation.[§]Others included coronary vasodilators (nicorandil) or metabolic agents (vastatin).Abbreviations: AS, aortic stenosis; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CMP, cardiomyopathy; CRF, chronic renal failure; CVA, cerebrovascular accident; eGFR, estimated glomerular filtration rate; HCM^P, hypertrophic cardiomyopathy; LA, left atrium; LAVI, left atrium volume index; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; RWMA, regional wall motion abnormality; STEMI, ST segment elevation myocardial infarction.

Table 2. Diagnostic Modalities of 62 Cases of Left Ventricular Thrombus

Diagnostic Modality	Number of Examinations	Patients with (+) result	Detection Rate *
TTE	61	48	78.7%
MRI	13	13	100%
CT angiography	12	12	100%

*Detection rate (%) was defined as the proportion of positive results per number of diagnostic examinations performed.

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging, TTE, transthoracic echocardiography.

nate almost 90% of the bias in the observed confounders¹⁵⁾. All probability values were two-sided and p -values < 0.05 were considered statistically significant. In case of Bonferroni correction, p -values < 0.017 were considered statistically significant. The statistical package SPSS, version 18.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism, version 5 (GraphPad Software Inc., La Jolla, CA, USA) were used for statistical analyses.

Results

Patient Population and Baseline Characteristics

Among 86,374 patients who underwent two-dimensional echocardiography, cardiac MRI, or coronary CTA from May 2003 to November 2011, 62 patients had documented LV thrombus (**Fig. 1**). Mean age was 63.61 ± 13.94 years, the majority were male (80.6%) and had ischemic heart disease (80.6%) including acute MI (**Table 1**). Twenty-one patients (33.9%) were admitted due to acute ST segment elevation MI (STEMI) that was treated with primary percutaneous coronary intervention within 90 minutes of door-to-balloon time (19 patients, 90.5%) or thrombolysis within 30 minutes of door-to-needle time (2 patients, 9.5%). All patients with STEMI had anterior wall myocardial infarction.

Eighteen of 62 patients (29%) developed systemic thromboembolism, with pre-treatment and post-treatment thromboembolism combined. There were no significant differences in baseline characteristics or medication history between patients with or without thromboembolism except for warfarin. Most patients (72.6%) were taking low-dose acetylsalicylic acid (100 mg/day) and 35.5% of patients were taking clopidogrel.

None of the study patients had hypo- or hyperthyroidism or a medical or familial history of congenital thrombophilic disorders, for example, protein C, S

Supplementary Fig. 1. Diagnostic Modalities for Left Ventricular Thrombus.

This Venn diagram depicts the diagnostic modality that definitely diagnosed LV thrombus. In the study population, 61 patients underwent trans-thoracic echocardiography (TTE). Among them, LV thrombus was found in only 48 patients by TTE. Thirteen of the 14 patients, who were diagnosed with LV thrombus through cardiac MRI or coronary CT angiography, did not show LV thrombus on their TTE.

or antithrombin deficiency or antiphospholipid antibody syndrome. In addition, no patient had both LV thrombus and ventricular non-compaction, which has been associated with systemic thromboembolism¹⁶⁾.

Thrombus Characteristics and Echocardiographic Parameters

All of the LV thrombi were located in the cardiac apex and most had mural attachment and sessile morphology (53 patients, 85.5%) (**Table 1**). High-risk thrombi (mobile thrombi including pedunculated or multiple thrombi) were more frequent in patients with thromboembolism (9.1% vs. 27.8%, $p = 0.058$). Patients with or without thromboembolism had similar echocardiographic parameters, excepting that the LA size was larger in patients with thromboembolism (**Table 1**). Using the aforementioned analysis, several variables, including thrombus mobility, maximum thrombus size, echocardiographic parameters and medication history, were selected as covariates for multivariate analysis to elucidate independent predictors of systemic thromboembolism (**Supplementary Table 1**).

Table 3. Comparison of Treatment Groups for Left Ventricular Thrombus*

	Anticoagulation (<i>n</i> =42, 67.7%)	Operative Treatment (<i>n</i> =8, 12.9%)	Antiplatelet Agent (<i>n</i> =12, 19.4%)	<i>p</i> value
Interval to treatment (days)	0 (IQR 0-13.75)	5.0 (IQR 2-11)	0 (IQR -4-0)	0.924
Treatment duration (days)	327.0 (IQR 56.0-1016.8)	947.5 [‡] (IQR 150.0-1736.8)	460.5 (IQR 131.5-1269.5)	0.304
Baseline Characteristics				
Age	63.90 ± 14.07	60.50 ± 14.56	64.67 ± 14.04	0.790
Male	33 (78.6%)	6 (75.0%)	11 (97.7%)	0.617
BMI	19.20 ± 2.92	18.97 ± 3.50	19.80 ± 2.49	0.818
Diabetes mellitus	11 (26.2%)	3 (37.5%)	4 (33.3%)	0.759
Hypertension	24 (57.1%)	4 (50.0%)	8 (66.7%)	0.743
Dyslipidemia	27 (64.3%)	5 (62.5%)	6 (50.0%)	0.667
Current smoker	13 (31.0%)	3 (37.5%)	2 (16.7%)	0.537
Atrial fibrillation [†]	2 (4.8%)	0 (0%)	0 (0%)	0.611
CRF	4 (9.5%)	0 (0%)	1 (8.3%)	0.662
eGFR [§]	75.54 ± 25.98	71.31 ± 33.60	72.44 ± 27.42	0.890
Prior myocardial infarction	15 (35.7%)	3 (37.5%)	7 (58.3%)	0.365
Prior CAD	17 (40.5%)	4 (50.0%)	8 (66.7%)	0.271
Prior CVA	4 (9.5%)	1 (12.5%)	4 (33.3%)	0.117
STEMI	15 (35.7%)	2 (25.0%)	4 (33.3%)	0.835
Underlying Heart Condition				
Ischemic CMP	32 (76.2%)	7 (87.5%)	11 (91.7%)	0.426
Dilated CMP	5 (11.9%)	0 (0%)	0 (0%)	0.274
Apical HCMP	2 (4.8%)	0 (0%)	0 (0%)	0.611
Stress-induced CMP	2 (4.8%)	0 (0%)	1 (8.3%)	0.696
Severe AS	0 (0%)	1 (12.5%)	0 (0%)	0.032
Cardiac arrest due to Brugada syndrome	1 (2.4%)	0 (0%)	0 (0%)	0.785

* Data are expressed as counts (%), unless otherwise indicated. Days are presented as the median value and interquartile range.

[†] Atrial fibrillation included both permanent and paroxysmal atrial fibrillation.

[‡] Treatment duration in operative treatment group defined as postoperative duration in days.

[§] Estimated glomerular filtration rate (mL/min/1.73 m²) was calculated by MDRD (Modification of Diet in Renal Disease) equation.

Abbreviations: AS, aortic stenosis; CAD, coronary artery disease; CMP, cardiomyopathy; CRF, chronic renal failure; CVA, cerebrovascular accident; eGFR, estimated glomerular filtration rate; HCMP, hypertrophic cardiomyopathy; IQR, interquartile range; STEMI, ST segment elevation myocardial infarction.

Diagnostic Modalities

TTE was performed in 61 of the 62 study patients; however, LV thrombus was diagnosed only in 48 patients (78.7%) (Table 2). In the remaining 13 patients, LV thrombus was recognized by cardiac MRI or coronary CTA, as shown in Supplementary Fig. 1.

Treatment Groups for the LV Thrombus

Each patient was treated for LV thrombus with one of three treatment options according to the primary physician's decision; 42 (67.7%) were treated with conventional anticoagulation, 8 (12.9%) with operative treatment and 12 (19.4%) only with antiplatelet agents (Table 3). There were no significant differences in baseline characteristics except for 1 patient with severe aortic valve stenosis in the operative treatment group.

In the anticoagulation group, adequate ranges of PT INR were maintained and the mean PT INR value was 2.75 ± 0.43 during the treatment period (median 327 days). In 18 (42.9%) patients, anticoagulation was discontinued due to complete resolution of thrombus, based on follow-up echocardiography, (11 patients, 61.1%), bleeding (major bleeding: 1 patients, 11.1%; minor bleeding: 3 patients, 16.7%), death (2 patients including 1 death due to major bleeding, 11.1%) and refusal by the patient (1 patient, 5.6%). None of the 11 patients who discontinued warfarin after TEE showed complete resolution of LV thrombus had post-treatment thromboembolism. Follow-up TEE did not detect recurrence of LV thrombus when performed in 4 patients after resolution of the thrombus (median duration of follow-up echocardiography: 456 days (IQR 193.75-888.50 days).

Supplementary Table 2. Detailed Descriptions of Operative Treatment of LV Thrombus

Patient	Indication and pre-operative condition	OP	OP type	Complications	Discharge date (Postoperative)
M/78	3VD with LV thrombus, Ambulatory	CABG + Dor	Elective	None	9 days
M/47	3VD with LV thrombus, Ambulatory	CABG + Dor	Elective	None	15 days
F/83	3VD with LV thrombus, Cardiogenic shock under IABP	CABG + Thrombectomy	Emergency	None	10 days
M/68	3VD with LV thrombus, Ambulatory	CABG + Thrombectomy	Elective	None	4 days
M/41	Severe AS with LV thrombus, Cardiac arrest under ECMO	Bentall OP + Thrombectomy	Emergency	ECMO wound infection	49 days
M/54	3VD with LV thrombus, Cardiac arrest under ECMO	CABG + Dor	Elective	None	18 days
M/57	3VD with LV thrombus (High-risk thrombus with small embolic stroke), Bed-ridden	CABG + Dor	Urgent	RITA harvest site bleeding*	15 days
M/57	3VD with LV thrombus (High-risk thrombus with multiple embolic strokes and hemorrhagic conversion [†]), Bed-ridden	CABG + Dor + Craniotomy and hematoma evacuation	Emergency	None	Admission for postoperative rehabilitation

*This patient developed postoperative hemothorax; re-do sternotomy found bleeding at the RITA harvest site. The bleeding focus was successfully controlled. This event counted as a TIMI major bleeding event.

[†]This patient developed hemorrhagic conversion of an embolic cerebral infarction during infusion of unfractionated heparin preoperatively. Thus, we did not count this event as a TIMI major bleeding event in the operative treatment group.

Abbreviations: AS, aortic stenosis; CABG, coronary artery bypass grafting; Dor, Dor operation; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; LV, left ventricle; OP, operation; RITA, right internal thoracic artery; 3VD, three-vessel coronary artery disease.

All but one patient in the operative treatment group were diagnosed with 3-vessel disease, which required coronary artery bypass grafting (CABG). One patient had been diagnosed with severe aortic stenosis due to a bicuspid aortic valve (**Supplementary Table 2**). The median interval from thrombus detection to operation was 5 days (**Table 3**).

The 12 patients that were treated only with antiplatelet agents had at least one reason that precluded anticoagulation (**Supplementary Fig. 2**). The most frequent reason for preclusion was a high risk for bleeding (7 patients).

Thrombus Outcomes

The frequency of high-risk thrombi did not differ among the treatment groups; however, the maximum thrombus size was significantly smaller in the antiplatelet agent group (**Table 4**). The relative size decrease was significantly greater in the anticoagulation and operative treatment groups than in the anti-

platelet agent group (**Table 4** and **Fig. 2A**). Moreover, follow-up echocardiography showed complete resolution of thrombus in all patients in the operative treatment group (**Fig. 2B**). In the antiplatelet agent group, follow-up size of the thrombus was not significantly different from the initial size (**Fig. 2A**).

Clinical Outcomes

Ten (55.0%) of the 18 thromboembolism events occurred before the treatment began (pre-treatment thromboembolism). Post-treatment thromboembolism developed in 17.1% of the anticoagulation group, 0% of the operative treatment group and 8.3% of the antiplatelet agent group, without statistically significant differences (**Table 4**). Thromboembolism-free survival of the treatment groups, depicted in **Fig. 3A**, showed a tendency towards longer survival in the operative and antiplatelet agent groups than in the anticoagulation group, which was not significantly different. During the median follow-up of 24 months,

Supplementary Fig. 2. Reasons for not using Anticoagulation in the Antiplatelet Agent Group.

Twelve patients were treated with one or more antiplatelet agents only. The reason that precluded anticoagulation with warfarin is depicted. Seven patients were considered at high risk for bleeding for the following reasons: recurrent gastrointestinal tract bleeding due to benign peptic ulcer disease or inflammatory bowel disease, 4 patients; receiving intraocular treatment for medically intractable glaucoma, 1 patient and liver cirrhosis Child class B to C with PT prolongation, 2 patients. Three patients, who had advanced dementia and lacked care-givers, were considered to be unable to keep comply with the details of warfarin anticoagulation and required regular follow-up.

no post-treatment thromboembolism event occurred in the operative treatment group; in contrast, such events occurred in the anticoagulation group and antiplatelet agent group.

Major and minor bleeding events developed more frequently in the anticoagulation group than in the operative treatment group; however, one patient in the operative treatment group developed postoperative bleeding from a right internal thoracic artery harvesting site (Table 4). Notably, the two major bleeding events in the anticoagulation group consisted of intracranial bleeding that resulted in permanent neurologic sequelae and massive gastrointestinal tract bleeding that resulted in death. All three minor bleeding events occurred in the anticoagulation group. All the bleeding events precluded further maintenance of anticoagulation.

There were 4 deaths (Table 4). In the anticoagu-

lation group there were 2 cardiac deaths (one cardiogenic shock due to non-ST segment elevation myocardial infarction and one sudden cardiac death due to ventricular tachycardia) and one death due to massive gastrointestinal bleeding. One patient in the antiplatelet agent group died of septic shock.

Clinical Outcomes in Propensity Score Matched Groups

Post-treatment thromboembolism showed a tendency towards a lower rate in the operative and antiplatelet agent groups than in the anticoagulation group (Fig. 3A); however, the frequency of high-risk thrombi and thrombus maximum size were lower in the antiplatelet agent group. In addition, the treatment groups differed in baseline characteristics including medications and thrombus profiles (Table 3 and 4). Because of such differences, we performed propensity score matching, which yielded 8 pairs for each comparison, anticoagulation versus operative treatment and anticoagulation versus antiplatelet agents. Matching produced more balanced groups, particularly with respect to medications and thrombus profiles (Supplementary Table 3 and 4).

In this comparison of the anticoagulation versus operative treatment groups, two post-treatment thromboembolism events occurred, both in the anticoagulation group (Supplementary Table 3). In addition, survival curves showed more prominent differences in the event-free survival (Fig. 3B) compared with that of unmatched analysis (Fig. 3A).

In contrast, one patient in each group suffered post-treatment thromboembolism in the matched pairs of the anticoagulation and antiplatelet agent groups (Supplementary Table 4). The tendency towards lower post-treatment thromboembolism in the antiplatelet agent group in the survival curve, which was found in the unmatched analysis (Fig. 3A), disappeared in the propensity score-matched analysis (Fig. 3C).

Clinical Outcomes According to the Underlying Heart Condition

The treatment groups were inhomogeneous with respect to the underlying heart condition, and ischemic etiology was found in 32 (76.2%), 7 (87.5%) and 11 (91.7%) of patients treated with anticoagulation, operative treatment and antiplatelet therapy, respectively (Table 3). Among patients with non-ischemic etiology, 10 patients were treated with anticoagulation, 1 patient with operation, and 1 patient with antiplatelet therapy. Among all study subjects, only 5 (8.1%) patients had DCMP; all were treated with anticoagulation. Therefore, we performed further

Table 4. Clinical Outcomes According to Treatment Group*

Outcome	Anticoagulation (n = 42, 67.7%)	Operative Treatment (n = 8, 12.9%)	Antiplatelet Agent (n = 12, 19.4%)	p value
Thrombus Morphology				
High-risk thrombus [†]	6 (14.3%)	2 (25.0%)	1 (8.3%)	0.648
Maximum size	18.37 ± 7.31	18.36 ± 5.75	13.23 ± 8.32	0.019
Thrombus Outcomes				
Follow-up echo	32 (76.2%)	8 (100.0%)	8 (66.7%)	0.193
Interval to echo [‡]	354.0 (IQR 55.0-790.5)	55.0 (IQR 13.0-254.0)	392.5 (IQR 184.8-1159.0)	0.068
Resolution	21 (65.6%)	8 (100.0%)	2 (25.0%)	0.006
Follow-up size	6.11 ± 9.87	0.00	11.56 ± 11.44	0.018
Size decrease (mm)	- 12.16 ± 11.30	- 18.36 ± 5.75	- 2.13 ± 5.56	0.007
Size decrease (%)	- 67.69 ± 49.76%	- 100.0%	- 12.00 ± 41.82%	0.002
Clinical Outcomes				
Any embolism	15 (35.7%)	2 (25.0%)	1 (0%)	0.202
Pre-treatment	8 (19.5%)	2 (25.0%)	0 (0%)	0.152
Post-treatment	7 (17.1%)	0 (0%)	1 (8.3%)	0.618
CVA	11 (26.2%)	2 (25.0%)	1 (8.3%)	0.422
TIA	2 (18.2%)	0 (0%)	0 (0%)	>0.999
Stroke	9 (81.8%)	2 (100%)	1 (100%)	>0.999
Neurologic sequela	7 (63.6%)	2 (100%)	1 (100%)	0.670
Peripheral embolism	4 (9.5%)	0 (0%)	0 (0%)	0.753
Bleeding event [§]	5 (11.9%)	1 (12.5%) [¶]	0 (0%)	0.539
Major	2 (4.8%) [#]	1 (12.5%) [¶]	0 (0%)	0.423
Minor	3 (7.1%)	0 (0%)	0 (0%)	>0.999
Cardiac death	2 (4.8%)	0 (0%)	0 (0%)	>0.999
Death due to bleeding	1 (2.4%)	0 (0%)	0 (0%)	>0.999
All Cause death	3 (7.1%)	0 (0%)	1 (8.3%)	>0.999

* Data are expressed as the means ± SD or as counts (%).

[†] High-risk thrombus was defined as either a mobile thrombus, including pedunculated thrombus, or multiple left ventricular thrombi.

[‡] Interval to follow-up echocardiography, data are expressed as median and interquartile range.

[§] Bleeding events were defined according to the Thrombolysis in Myocardial Infarction (TIMI) criteria. Major bleeding was defined as any intracranial hemorrhage, more than a 5 g/dL decrease in the hemoglobin concentration or more than a 15% absolute decrease in the hematocrit.

[¶] One patient in the operative treatment group developed postoperative bleeding from the right internal thoracic artery harvest site. The patient was successfully treated with re-do sternotomy and bleeding control.

[#] These two major bleeding events included one death due to massive hematemesis and subsequent hypovolemic shock.

Abbreviations: Echo, echocardiography; IQR interquartile range; TIA, transient ischemic attack.

analyses according to the underlying etiology, ischemic versus non-ischemic and DCMP versus no DCMP (**Supplementary Table 5**).

Post-treatment thromboembolism developed in 2 patients (40%) with DCMP. In univariate analysis, DCMP was associated with a 5.6-fold increased risk for post-treatment thromboembolism (OR, 5.67; 95% CI 0.78-41.01; $p=0.059$). After adjustment for potential confounders, DCMP remained a strong and significant independent predictor of post-treatment thromboembolism (**Table 5**). In contrast, ischemic cardiomyopathy was not associated with post-treatment thromboembolism in univariate (OR, 0.68; 95% CI, 0.12-3.89; $p=0.665$) or in multivariate anal-

yses (OR, 0.05; 95% CI, 0.00-1227.12; $p=0.977$).

Independent Predictors of Thromboembolism

Using a Cox proportional hazard regression model with the aforementioned multiple covariates (**Supplementary Table 1**), independent predictors of pre-treatment thromboembolism were cardiac arrest and mobile or multiple thrombi. Independent predictors of post-treatment thromboembolism were female gender, a previous cerebrovascular event, DCMP and large left ventricular end-diastolic diameter (LVEDD) (**Table 5**). Treatment modalities (anticoagulation, operative treatment, or antiplatelet agents) were not independent predictors of systemic thromboembolism.

Fig. 2. Changes of LV Thrombus Size and Resolution Rate According to the Treatment Groups.

A) Changes of LV thrombus size (mm). B) Thrombus resolution rate based on follow-up echocardiography. The resolution rate was significantly different among the three groups. The resolution rate was significantly higher in the operative treatment group than in the antiplatelet agent group (100.0% vs. 25.0%, Bonferroni corrected $p = 0.007$). However, there was no significant difference in the relative size change and resolution rate between anticoagulation group and operative treatment group in the post-hoc analysis. The results of Wilcoxon signed rank sum test for the analyses of the change of LV thrombus size before and after the treatment are presented. Post-hoc analyses with Bonferroni corrected p value are also presented. Asterisk denotes a statistically significant p value.

Univariate analysis of the subgroup with non-ischemic etiology ($n = 12$) without indications for open heart surgery, found that LVEDD and the proportion of mobile or multiple thrombi were greater in those

with post-treatment thromboembolism, with marginal statistical significance (**Supplementary Table 6**); however, we could not build a model for multivariate analysis in this subgroup due its small size.

Fig. 3. Kaplan-Meier Curves for Thromboembolic Event Free Survival According to the Treatment Groups (Post-treatment Embolism Only).

Clinical outcomes analyses were performed only with post-treatment embolism. A) Kaplan-Meier Curves show a comparison of event-free survival among the three treatment groups. Log rank p values are presented. B) Thromboembolic event-free survival in propensity score matched pairs, comparison between anticoagulation and operative treatment groups. C) Thromboembolic event-free survival in propensity score matched pairs, comparison between anticoagulation and antiplatelet agent groups. Because the survival curves crossed, the Breslow p value was determined.

Discussion

The current study measured the long-term outcomes of treatment strategies during a median follow-up of 24 months. The overall risk of systemic thromboembolism during 2 years was 29.0%. Over one-half of the systemic thromboembolisms (55.0%) occurred before the detection of LV thrombus (pre-treatment thromboembolisms). The rate of post-treatment thromboembolism was not significantly different among the three treatment groups.

The operative treatment group had no post-treatment thromboembolisms and the highest resolution rate and decrease of LV thrombus size. The conventional anticoagulation group had the highest rate of post-treatment embolism (7 of 8 events, 87.5% occurred in this group), despite a larger decrease in thrombus size than in the antiplatelet agent group. Notably, post-treatment thromboembolism even occurred during adequate maintenance of the target PT INR.

Supplementary Table 3. Propensity Score Matching between the Anticoagulation and Operative Treatment Groups*

	Anticoagulation (n = 8)	Operative Treatment (n = 8)	p value
Medications			
Acetylsalicylic acid	6 (75.0%)	7 (87.5%)	>0.999
Clopidogrel	2 (25.0%)	2 (25.0%)	>0.999
Dual antiplatelet agents (Aspirin and Clopidogrel)	2 (25.0%)	2 (25.0%)	>0.999
Warfarin	8 (100.0%)	3 (37.5%)	0.315
Thrombus Morphology			
High-risk thrombus [†]	3 (37.5%)	2 (25.0%)	>0.999
Maximum size	19.88 ± 9.72	18.36 ± 5.75	0.916
Thrombus Outcomes			
Follow-up echo	6 (75.0%)	8 (100.0%)	0.467
Resolution	3 (50.0%)	8 (100.0%)	0.055
Follow-up size	10.47 ± 12.08	0.0	0.031
Clinical Outcomes			
Post-treatment	2 (25.0%)	0 (0.0%)	0.467
CVA	0 (0%)	1 (12.5%)	>0.999
Peripheral embolism	1 (12.5%)	0 (0%)	>0.999
Bleeding event [‡]	2 (25.0%)	1 (12.5%)	>0.999
Minor	1 (12.5%)	0 (0%)	>0.999
Major	1 (12.5%)	1 (12.5%)	>0.999

*Data are expressed as the means ± SD or as counts (%).

[†]High-risk thrombus was defined as mobile or multiple left ventricular thrombi.

[‡]Bleeding events were defined according to the Thrombolysis in Myocardial Infarction (TIMI) criteria. Major bleeding was defined as any intracranial hemorrhage, more than a 5 g/dL decrease in the hemoglobin concentration or more than a 15% absolute decrease in the hematocrit.

Abbreviations: CVA, cerebrovascular accident; echo, echocardiography.

Embolic Risk of Conventional Anticoagulation

Regarding the efficacy of anticoagulation, two previous meta-analyses found that the relative risk of embolism in anticoagulated patients with LV thrombus after myocardial infarction was 0.3 (95% CI 0.1-0.5) and 0.14 (95% CI 0.04-0.52)^{7, 9}; however, these studies only compared the efficacy of anticoagulation with that of no anticoagulation. Moreover, these meta-analyses did not evaluate dual antiplatelet agents (acetylsalicylic acid and clopidogrel), which are common current therapeutics for patients with acute myocardial infarction. Prior studies reported various rates of post-treatment thromboembolism (from 0% to 33.3%) even with adequate anticoagulation. The rate of post-treatment embolism of these studies is as follows: Nihoyannopoulos *et al.*¹⁷ (none of 21 patients), Weinreich *et al.*¹⁸ (none of 25 patients), Stratton *et al.*⁶ (2 of 23 patients, 8.7%), Visser *et al.*¹⁹ (7 of 46 patients, 15.2%), Keren *et al.*²⁰ (6 of 38 patients, 15.8%), Jugdutt *et al.*²¹ (27 of 115 patients, 23.5%), Haugland *et al.*⁵ (5 of 16 patients, 31.3%) and Johanssen *et al.*¹ (5 of 15 patients, 33.3%). The overall rate of post-treatment thromboembolism in our anticoagulation group was 17.1%, consistent with previous

studies. The reported resolution rate of thrombus with anticoagulation is also variable, ranging from 48% at 6 months follow-up to 65-85% at 24-month follow-up^{9, 17, 20, 21}. Similarly, the resolution rate of the thrombus in our study was 65.6% in the anticoagulation group. The remaining chronic thrombus also confers a substantial risk of systemic thromboembolism^{5, 19}. These prior studies support our findings that conventional anticoagulation is not able to eliminate the risk of systemic thromboembolism, even with adequate maintenance of anticoagulation, unless the LV thrombus has completely disappeared.

Outcomes of Operative Treatment

Even though we failed to detect a statistically significant difference in event-free survival between the anticoagulation and operative treatment groups, this tendency towards longer survival in the operative treatment group increased after imbalances in baseline covariates were corrected with propensity score matching. It is noteworthy that the clinical severity of the operative treatment group was greater than that of the other groups. Three of eight patients in the operative treatment group had undergone surgery with mechan-

Supplementary Table 4. Propensity Score Matching between the Anticoagulation and Antiplatelet Agent Groups*

	Anticoagulation (<i>n</i> = 8)	Antiplatelet agent (<i>n</i> = 8)	<i>p</i> value
Medications			
Acetylsalicylic acid	7 (87.5%)	8 (100%)	>0.999
Clopidogrel	3 (37.5%)	6 (75.0%)	0.315
Dual antiplatelet agents (Aspirin and Clopidogrel)	3 (37.5%)	6 (75.0%)	0.315
Thrombus Morphology			
High-risk thrombus [†]	2 (25.0%)	1 (12.5%)	>0.999
Maximum size	16.63 ± 5.55	15.06 ± 9.17	0.342
Thrombus Outcomes			
Follow-up echo	6 (75.0%)	6 (75.0%)	>0.999
Resolution	3 (50.0%)	1 (16.7%)	0.545
Follow-up size	10.27 ± 12.21	13.77 ± 12.25	0.806
Clinical Outcomes			
Post-treatment	1 (12.5%)	1 (12.5%)	>0.999
CVA	0 (0%)	1 (12.5%)	>0.999
Peripheral embolism	1 (12.5%)	0 (0%)	>0.999
Bleeding event [‡]	1 (12.5%)	0 (0%)	>0.999
Minor	1 (12.5%)	0 (0%)	>0.999

*Data are expressed as the means ± SD or as counts (%).

[†]High-risk thrombus was defined as mobile or multiple left ventricular thrombi.

[‡]Bleeding events were defined according to the Thrombolysis in Myocardial Infarction (TIMI) criteria. Major bleeding was defined as any intracranial hemorrhage, more than a 5 g/dL decrease in the hemoglobin concentration or more than a 15% absolute decrease in the hematocrit.

Abbreviations: CVA, cerebrovascular accident; echo, echocardiography.

ical circulatory support (intra-aortic balloon pump or extracorporeal membrane oxygenation) and 2 of 8 patients (25%) had highly mobile or multiple thrombi which embolized preoperatively. Theoretically, complete resolution or treatment of thrombus will eliminate the possibility of systemic thromboembolism. Reports of operative treatment of LV thrombus have been scarce; most such reports are confined to case reports or case series. Previously Nili, M *et al.* reported 4 cases of surgical removal of LV thrombus; these patients did not develop post-treatment thromboembolism after thrombectomy with or without CABG, similar to our findings²². All other reports were case reports of successful removal of an LV thrombus through thrombectomy or video-assisted transaortic removal with excellent postoperative results²³⁻²⁵.

Bleeding Risk of Conventional Anticoagulation

Conventional anticoagulation is known to confer about a 20% risk of bleeding⁶; the bleeding rate of our study was 11.9%, including 2 major bleeds, with 1 death due to bleeding. The most serious bleeding complication, intracranial hemorrhage, causes approximately 90% of deaths and most of the permanent disability in patients with warfarin-associated bleeding²⁶. Anticoagulation with warfarin increases the risk

of intracranial hemorrhage by 2-5-fold^{27, 28}. Furthermore, the known propensity of major bleeding to increase mortality is supported by several clinical trials, including the REPLACE-2 trial²⁹ and the TRITON-TIMI 38 trial³⁰. The overall hazard ratio of bleeding, including major and minor bleeding, was 5.84 (95% CI 4.11-8.29) in the TRITON-TIMI 38 trial³⁰. In our study, the risks of major bleeding and mortality associated with bleeding were considerable. Meticulous risk stratification regarding bleeding and systemic thromboembolism should be considered before starting anticoagulation.

Predictors of Embolism

To facilitate treatment that is more individualized than routine anticoagulation, it is important to establish selection criteria for patients at high-risk of systemic thromboembolism. Through Cox proportional hazard regression modeling, we found that mobile or multiple thrombi were independent predictors of pre-treatment thromboembolism, as previously reported^{1, 5, 6, 19, 21}. Initial presentation with cardiac arrest was also a significant independent predictor of pre-treatment embolism. Severe LV dysfunction due to chronic myocardial infarction or symptomatic heart failure is a well-known risk factor for cerebral infarc-

Supplementary Table 5. Baseline Characteristics and Clinical Outcomes According to the Underlying Heart Condition (Ischemic Etiology versus Non-ischemic Etiology)*

		Ischemic Etiology (n = 50, 80.6%)	Non-ischemic Etiology (n = 12, 19.4%)	p value
Baseline Characteristics	Age	64.18 ± 12.28	61.25 ± 19.98	0.936
	Male	41 (82.0%)	9 (75.0%)	0.582
	Diabetes mellitus	15 (30.0%)	3 (25.0%)	0.732
	Hypertension	34 (68.0%)	2 (16.7%)	0.001
	Dyslipidemia	36 (72.0%)	2 (16.7%)	0.001
	Current smoker	16 (32.0%)	2 (16.7%)	0.293
	Atrial fibrillation	2 (4.0%)	0 (0%)	>0.999
	CRF	3 (6.0%)	2 (16.7%)	0.246
	Prior myocardial infarction	25 (50.0%)	0 (0%)	0.001
	Prior CAD	29 (58.0%)	0 (0%)	<0.001
	Prior CVA	9 (18.0%)	0 (0%)	0.185
	STEMI	21 (42.0%)	0 (0%)	0.005
Echocardiographic Parameters	LVEDD	52.35 ± 7.53	58.45 ± 11.71	0.082
	LVESD	36.95 ± 9.93	48.48 ± 14.79	0.008
	LVEF	41.98 ± 13.49	33.08 ± 15.83	0.047
	LA Size	41.31 ± 8.82	40.67 ± 11.68	0.757
	RWMA			
	None	1 (2.0%)	1 (8.3%)	0.352
	Anteroapical akinesia	43 (86.0%)	5 (41.7%)	0.003
Thrombus Morphology	Global hypokinesia/akinesia	5 (10.0%)	6 (50.0%)	0.004
	Apical aneurysm	17 (34.7%)	1 (8.3%)	0.089
	High-risk thrombus [†]	7 (14.0%)	2 (16.7%)	0.814
	Maximum size	16.68 ± 6.88	20.53 ± 9.24	0.144
Treatment Group	Anticoagulation	32 (64.0%)	10 (83.3%)	0.306
	Operative treatment	7 (14.0%)	1 (8.3%)	0.690
	Antiplatelet agent	11 (22.0%)	1 (8.3%)	0.431
Thrombus Outcomes	Follow-up echo	40 (80.0%)	8 (66.7%)	0.442
	Interval to echo [‡]	354.0 (IQR 55.0-790.5)	55.0 (IQR 13.0-254.0)	0.014
	Resolution	26 (65.0%)	5 (62.5%)	0.893
	Follow-up size	5.68 ± 9.63	7.60 ± 10.88	0.691
	Size decrease (mm)	-10.88 ± 10.10	-15.81 ± 13.87	0.387
	Size decrease (%)	-64.72 ± 51.41%	-65.73 ± 48.56%	0.947
Clinical Outcomes	Anticoagulation	32 patients	10 patients	
	Any Embolism	11 (34.4%)	4 (40.0%)	0.746
	Pre-treatment	6 (18.8%)	2 (20.0%)	0.930
	Post-treatment	5 (15.6%)	2 (20.0%)	
	Operative treatment	7 patients	1 patients [¶]	0.746
	Any Embolism	2 (28.6%)	0%	>0.999
	Pre-treatment	2 (28.6%)	0%	>0.999
	Post-treatment	0%	0%	
	Antiplatelet agent	11 patients	1 patient [#]	-
	Any Embolism	1 (9.1%)	0%	>0.999
	Pre-treatment	0%	0%	-
	Post-treatment	1 (9.1%)	0%	>0.999

*Data are expressed as the means ± SD or as counts (%). Non-ischemic cardiomyopathy included 5 patients with dilated cardiomyopathy, 3 with stress-induced cardiomyopathy, 2 with hypertrophic cardiomyopathy, and 2 patients with severe aortic stenosis and Brugada syndrome, respectively.

[†]High-risk thrombus was defined as either a mobile thrombus, including pedunculated thrombus, or multiple left ventricular thrombi.

[‡]Interval to follow-up echocardiography, data are expressed as the median and interquartile range.

[¶]One patient with severe aortic stenosis with LV thrombus was treated with operative treatment (aortic valve replacement with LV thrombectomy).

[#]One patient with stress-induced cardiomyopathy was treated only with antiplatelet agent.

Abbreviations: CAD, coronary artery disease; CRF, chronic renal failure; IQR, interquartile range; LA, left atrium; LAVI, left atrium volume index; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; RWMA, regional wall motion abnormality; STEMI, ST segment elevation myocardial infarction.

Table 5. Independent Risk Factors for Systemic Thromboembolism

Variables	Adjusted HR	95% CI	<i>p</i> value
Pre-treatment embolism			
Cardiac arrest	82.28	4.51-1502.53	0.003
Mobile/Multiple thrombi	13.75	1.36-138.27	0.026
Post-treatment embolism			
Female	7.11	1.19-42.35	0.031
Prior CVA	7.06	1.08-46.24	0.042
DCMP	61.30	5.10-736.11	0.001
LVEDD (per 1 mm)	1.15	1.00-1.31	0.047

Abbreviations: CVA, cerebrovascular accident; CI, confidence interval; DCMP, dilated cardiomyopathy; HR, hazard ratio; LVEDD, left ventricular end-diastolic dimension.

tion³¹). Myocardial dysfunction, including severe LV dysfunction or symptomatic heart failure, is a common manifestation in survivors of cardiac arrest³²; therefore, cardiac arrest might be the precipitating cause of embolic cerebral infarction.

Since pre-treatment embolism is difficult to prevent, it is more important to identify predictors of post-treatment embolism. In this study, a prior cerebrovascular accident, idiopathic DCMP and large LVEDD were found to be independent predictors of post-treatment embolism. Recently, Sharma *et al.* reported that LVEDD was significantly associated with the development of LV thrombus but not with systemic thromboembolism, and predictors of systemic thromboembolism were ischemic cardiomyopathy and low EF⁴). In contrast, in the current study, idiopathic DCMP (but not ischemic cardiomyopathy) was the most powerful predictor of systemic thromboembolism. However, DCMP and a previous history of cerebral infarction or transient ischemic attack are already known to be strong risk factors for cardiogenic embolism and cerebral infarction³³). All patients with DCMP were treated with anticoagulation; this uneven distribution of treatment modality could be one of the reasons that DCMP was found to be an independent predictor; however, DCMP remained an independent predictor of post-treatment thromboembolism after adjusting for the treatment modality and underlying heart condition.

Interestingly, female gender was also an independent predictor of post-treatment thromboembolism. In the literature, there is no clear explanation of why female gender was associated with increased thromboembolic risk. Recently, female gender was reported to be associated with an increased risk for clopidogrel hypo-responsiveness^{34, 35}). Gender-specific differences exist in the activity of CYP enzymes³⁶). Men have increased CYP1A2 activity, while women have

increased CYP3A4 activity. Warfarin undergoes extensive metabolism by the cytochrome P450 isoforms. CYP2C9 is responsible for the metabolism of S-warfarin, while R-warfarin is metabolized by CYP1A2, CYP2C19 and CYP3A4³⁷). Enhanced activity of CYP3A4 in women would increase warfarin clearance compared to in men. Furthermore, differences in the hormonal status (menopause) could influence thrombogenicity. Taken together, differences in CYP enzyme activity and the hormonal status might affect the response to clopidogrel and warfarin use in women. Of note, sex differences in ischemic stroke or postoperative stroke after carotid endarterectomy were frequently described^{38, 39}).

These aforementioned high-risk patients for post-treatment embolism need to be more aggressively treated and closely followed.

Limitations

Some important limitations of this study should be considered. First, this study was performed using a single center database with a relatively small number of patients, which might have lacked statistical power to detect differences in the primary outcome among treatment groups. Second, this study was a retrospective, descriptive study that could not control for unmeasured confounders. Even though we used propensity score matching and Cox proportional hazard regression modeling to minimize the influence of potential confounders, the possible influences of uncontrolled and unknown confounding factors should be considered. In addition, there were no data regarding the presence of thrombophilia, for example, protein C, S or antithrombin deficiency or antiphospholipid antibody syndrome, because thrombophilia evaluation is not routinely performed in our hospital. However, obesity and impaired renal function, which

Supplementary Table 6. Baseline clinical and thrombus characteristic in patients with non-ischemic etiology*

Characteristics	Total (n = 12)	Embolism (–) (n = 10, 83.3%)	Embolism (+) (n = 2, 16.7%)	p value
Baseline Characteristics				
Age	61.25 ± 19.98	64.20 ± 20.43	46.50 ± 10.61	0.237
Male	9 (75.0%)	8 (80.0%)	1 (50.0%)	0.455
Diabetes mellitus	3 (25.0%)	8 (80.0%)	1 (50.0%)	0.455
Hypertension	2 (16.7%)	2 (20.0%)	0%	>0.999
Dyslipidemia	2 (16.7%)	2 (20.0%)	0%	>0.999
Current smoker	2 (16.7%)	1 (10.0%)	1 (50.0%)	0.318
Atrial fibrillation [†]	0%	0%	0%	–
CRF	2 (16.7%)	2 (20.0%)	0%	>0.999
eGFR [‡]	69.87 ± 40.95	75.07 ± 42.83	43.85 ± 17.75	0.197
Malignancy	1 (8.3%)	1 (10.0%)	0 (0%)	>0.999
Prior myocardial infarction	0%	0%	0%	–
Prior CAD	0%	0%	0%	–
Prior CVA	0%	0%	0%	–
Underlying Heart Conditions				
Ischemic CMP	0%	0%	0%	–
Dilated CMP	5 (41.7%)	3 (30.0%)	2 (100.0%)	0.152
Apical HCMP	2 (16.7%)	2 (20.0%)	0 (0%)	>0.999
Stress-induced CMP	3 (25.0%)	3 (30.0%)	0 (0%)	0.550
Severe AS	1 (1.6%)	1 (10.0%)	0%	>0.999
Cardiac arrest due to Brugada syndrome	1 (1.6%)	1 (10.0%)	0%	>0.999
Thrombus Morphology				
Maximum size	20.53 ± 9.24	8.79 ± 2.78	15.56 ± 11.00	>0.999
Apical location	62 (100%)	44 (100%)	18 (100%)	NS
Mobile/Multiple	9 (14.5%)	4 (9.1%)	5 (27.8%)	0.058
Mural/Sessile	53 (85.5%)	40 (90.9%)	13 (72.2%)	0.058
Echocardiographic Parameters				
LVEDD	58.45 ± 11.71	52.72 ± 8.58	74.15 ± 12.52	0.053
LVESD	48.48 ± 14.79	44.80 ± 12.59	66.90 ± 12.87	0.133
LVEF	33.08 ± 15.83	35.60 ± 16.11	20.50 ± 8.36	0.196
RWMA				
None	1 (8.3%)	1 (10.0%)	0 (0%)	>0.999
Anteroapical akinesia	5 (41.7%)	5 (50.0%)	0 (0%)	0.470
Global hypokinesia/akinesia	6 (50.0%)	4 (40.0%)	2 (100.0%)	0.455
Apical aneurysm	1 (8.3%)	1 (10.0%)	0 (0%)	>0.999

* Data are expressed as the means ± SD or as counts (%).

[†] Atrial fibrillation included both permanent and paroxysmal atrial fibrillation.

[‡] Estimated glomerular filtration rate (mL/min/1.73 m²) was calculated by MDRD (Modification of Diet in Renal Disease) equation.

Abbreviations: AS, aortic stenosis; CAD, coronary artery disease; CMP, cardiomyopathy; CRF, chronic renal failure; CVA, cerebrovascular accident; eGFR, estimated glomerular filtration rate; HCMP, hypertrophic cardiomyopathy; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; RWMA, regional wall motion abnormality.

are also associated with enhanced thrombogenesis^{40, 41}, were evaluated as independent predictors of post-treatment thromboembolism; we did not find a notable association with post-treatment thromboembolism. Third, the limited sensitivity of TTE for the detection of LV thrombus may have underestimated the recur-

rence of LV thrombus. Fourth, the uneven distribution of the patients among the treatment groups and possible allocation bias should be considered. All patients with dilated cardiomyopathy were treated with anticoagulation; hence, this study could not compare treatment modalities for this subgroup. All

patients in the operative treatment group had another absolute indication for open heart surgery, i.e. 3-vessel disease requiring CABG or severe aortic stenosis requiring aortic valve replacement. While the operative treatment group had the potential for improvement of their left ventricular function, most of the patients in the conventional anticoagulation group had low potential for improvement of their left ventricular function.

All statements about the possible superiority of operative treatment should be taken as hypothesis generating. In fact, it is difficult to recommend open-heart surgery to patients whose only indication is LV thrombus; however, our study reflects the current management of LV thrombus. Nonetheless, in patients with a high-risk profile, surgical removal might reduce the incidence of thromboembolism more than anticoagulation therapy. It is unknown whether the reduction in post-treatment thromboembolism outweighs the risk of surgery related morbidity and mortality. Nevertheless, to the best of our knowledge, the current study is the first report to compare the long-term efficacy and consequences of anticoagulation, operative treatment, and antiplatelet agents for the treatment of LV thrombus. We expect that these limitations will be more appropriately addressed in future randomized trials comparing anticoagulation with operative treatment in patients with LV thrombus.

Conclusion

The rate of post-treatment thromboembolism did not differ significantly among the three treatment groups. Nonetheless, we observed a tendency towards a lower rate of post-treatment embolism in the operative treatment group. Given the risk of bleeding and insufficient resolution rate with anticoagulation, alternative or additive treatment, especially for patients at high risk for systemic thromboembolism should be considered. Further prospective randomized controlled studies are needed to clarify these issues.

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Conflict of Interest

None.

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Supplementary Materials

Detailed Imaging Protocols of Cardiac MRI and Coronary CT angiography

Cardiac MRI

The imaging protocol included the following techniques/pulse sequences: 1) LV mass and function: Balanced steady-state free precession (SSFP) gradient echo cine loops were acquired in both two-chamber and four-chamber views. Parameters were TR 3.54 ms, TE 1.77 ms, flip angle 60, FoV 350 mm×350 mm, matrix 192×190, in-plane resolution: 1.82 mm×1.84 mm, 30 phases per cardiac cycle, and number of signal average 1.00. Slice thickness was 8 mm without an interslice gap. 2) T2-weighted imaging: Triple-inverted fast spin echo images were acquired in short axis orientation (TR, 1714.29 ms; TE, 100.00 ms; TI, 550 ms and slice thickness 8 mm without an interslice gap) using the cardiac coil. 3) Early gadolinium enhancement: Axial T1-weighted fast spin echo images (TR, 2.68 ms; TE, 1.34 ms; flip angle 50°; FoV 335×360; matrix 128×121 and in-plane resolution 2.61 mm×2.97 mm) were obtained before and during the first 4 min immediately after administration of 0.1 mmol/kg Gadolinium-DTPA (OMNIS-CAN; GE Healthcare, Waukesha, WI, USA). The cardiac coil was used for signal acquisition. 4) Late gadolinium enhancement (LGE): After testing different inversion times (180-350 ms) for optimal suppression of the myocardium, contiguous stacks of long- and short-axis DE inversion recovery-prepared fast low angle shot gradient echo images were obtained 10-15

min after administration of a second bolus of contrast agent (0.1 mmol/kg). Parameters were TR 4.63 ms, TE 1.50 ms, flip angle 15, and number of signal average 3.00. Slice thickness was 8 mm on long axis and short axis images.

Coronary CT Angiography

All subjects underwent coronary CTA with retrospective ECG gating on a 64-channel Multi-Detector Computed Tomography (MDCT) scanner (Brilliance iCT; Philips Medical System, Boston, MA, USA). Anteroposterior and lateral topograms were followed by prospectively ECG-triggered unenhanced calcium scoring acquisition. A bolus tracking method was routinely used. Then, 50-70 mL of a mixture of iomeprol (Iomeron 400; Bracco, Milan, Italy) nonionic IV contrast medium and saline (4:6 ratio) was administered through a triphasic bolus power injector (Stellant; Medrad, (city, state?) USA) at a rate of 4 mL/s. The scan delay for each patient was determined with an automatic bolus tracking system with a threshold of 200 HU at the descending thoracic aorta. Coronary CTA acquisition was performed with a scan delay of peak plus 8.2 seconds with the following parameters: gantry rotation time, 0.27 seconds; slice thickness, 0.9 mm; interval, 0.45 mm; kVp/mAs 120/800; image matrix 512×512 and pitch, 0.18. We used ECG modulation for all patients (100% peak tube current in mid-diastole, up to 80% reduction during systole) to reduce radiation exposure. The images were post-processed at a workstation (Extended Brilliance Workspace, Version 4.0; Philips Medical System).