Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Gillinov AM, Bagiella E, Moskowitz AJ, et al. Rate control versus rhythm control for atrial fibrillation after cardiac surgery. N Engl J Med. DOI: 10.1056/NEJMoa1602002

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SUPPLEMENTARY APPENDIX

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Cardiothoracic Surgical Trials Network (CTSN)

The members of the Cardiothoracic Surgical Trials Network (CTSN) involved in this study are as follows:

National Heart, Lung and Blood Institute: Marissa A. Miller, Wendy C. Taddei-Peters, Dennis Buxton, Ron Caulder, Nancy L. Geller, David J. Gordon, Neal O. Jeffries, Albert Lee**;** **National Institute of Neurological Disorders and Stroke:** Claudia S. Moy; **Canadian Institutes of Health Research:** Caroline Wong, Ilana Kogan Gombos, Jennifer Ralph;

Network Chairs: ***Toronto General Hospital,*** Richard Weisel, (Chair); ***Christiana Care Health System,*** Timothy J. Gardner, (Chair-Emeritus); ***Brigham and Women's Hospital,*** Patrick T. O'Gara, (Co-Chair); ***Mount Sinai Health System***, Eric A. Rose, (Vice Chair);

Data Coordinating Center: ***International Center for Health Outcomes and Innovation Research at Icahn School of Medicine at Mount Sinai,*** Annetine C. Gelijns, Emilia Bagiella, Alan J. Moskowitz, Michael K. Parides, Ellen Moquete, Elise Barrow, Helena Chang, Melissa Chase, Edlira Dobrev, Seth Goldfarb, Lopa Gupta, Rami Habas, Katherine Kirkwood, Ron Levitan, Karen O'Sullivan, Jessica Overbey, Cassandra Pineda, Andrea Ratner, Samantha Raymond, Milerva Santos, Kinjal Shah, Hetal Sheth, Nancy Sledz-Joyce, Maria Suprun, Deborah Williams, Paula Williams, Xia Ye;

Clinical Site Investigators: ***Baylor College of Medicine:*** Faisal Bakaeen (PI), ***Baylor Research Institute :*** Michael Mack (PI), Tracine Adame, Natalie Settele, Megan Kolb, Haley Boswell, Lucy Miranda, William Ryan, Robert L. Smith, Paul Grayburn; ***Centre Hospitalier de l'Université de Montréal:*** Louis-Mathieu Stevens (PI), Nicolas Noiseux, Ignacio Prieto, Fadi Basile, Joannie Dionne, Geneviève Péloquin; ***Cleveland Clinic Foundation:*** A. Marc Gillinov (PI), Eugene H. Blackstone, Pamela Lackner, Carrie Geither, Kristen Doud, Michelle Garcia, Roberta Palumbo, Brian Strippy, Robert Wang Randall Starling, Benicio Barzilai, Richard Grimm; *NHLBI Clinical Research Scholars*: Gregory Pattakos, Pamela A. Clarke; ***Columbia University:*** Michael Argenziano (PI), Hiroo Takayama, Lyn Goldsmith, Allan Schwartz; Martin B. Leon, Sowmya Sreekanth; ***Duke University:*** Peter K. Smith (PI), John H. Alexander, Donald D. Glower, Joel Huber, Stacey Welsh, Sarah Casalinova; *NHLBI Clinical Research Scholars:* Brian Englum: ***Emory University:*** Vinod H. Thourani (PI), Robert Guyton, Omar Lattouf, Edward Chen, J. David Vega, Jefferson Baer, Kim Baio, Alexis A. Neill, Tamara Prince; ***Hôpital du Sacré-Coeur de Montréal***: Hugues Jeanmart (PI), Carole Sirois; ***Hôpital Laval:*** Pierre Voisine (PI), Mario Senechal, François Dagenais, Kim O'Connor, Gladys Dussault, Manon Caouette, Hugo Tremblay, Robert Laforce; ***Mission Hospital :*** Mark A. Groh (PI), Oliver A Binns, Stephen W. Ely, Alan M Johnson, John G. Short, Reid D. Taylor, Ralph Mangusan, Tracy Nanney; ***Montefiore-Einstein Heart Center:*** Robert E. Michler (PI), David A. D'Alessandro, Joseph J. DeRose, Jr., Daniel J. Goldstein, Ricardo Bello, Cynthia Taub, Daniel Spevack, Kathryn Kirchoff, Nadia Sookraj, Jon Goldenberg, Juan Garcia, Rebecca Meli; ***Montreal Heart Institute*****:** Louis P. Perrault (PI), Denis Bouchard, Michel Pellerin, Jean François Tanguay, Ismail El-Hamamsy, Céline Odier, Jonathan Lacharité, Sophie Robichaud; ***Mount Sinai Medical Center:*** David Adams (PI), Robin Varghese, Michael Fusilero; ***NIH Heart Center at Suburban Hospital:*** Keith A. Horvath (PI), Philip C. Corcoran, Michael P. Siegenthaler, Greg Kumkumian, Mark Milner, Zurab Nadareishvili, Mandy Murphy, Margaret

Iraola, Ann Greenberg; ***Ohio State University Medical Center:*** Bryan A Whitson (PI), Chittoor Sai-Sudhakar (PI), Ayseha Hasan, Laura Yamakoski, Asia McDavid, Denise Fadorsen; ***University of Alberta Hospital:*** John C. Mullen (PI), Emily Kuurstra, Asvina Bissonauth; ***University of Maryland :*** James S. Gammie (PI), Robert Villanueva, Julia Collins, Stephanie Deasey; ***University of Michigan Health Services:*** Steven F. Bolling (PI), Cathie Bloem, Nicole Gervais ***University of Pennsylvania:*** Michael A. Acker (PI), Steven Messe, James Kirkpatrick, Jesse Raiten, Mary Lou Mayer, Stephen Cresse, Christine Gepty; ***University of Southern California :*** Michael Bowdish (PI), Vaughn A. Starnes, David Shavalle, Amy Hackmann, Craig Baker, Fernando Fleischman, Mark Cunningham, Christi Heck, Edward Lozano, Michelle Hernandez, Sylvia Ramos; ***University of Virginia:*** Irving L. Kron (PI), Gorav Ailawadi, Karen Johnston, John M. Dent, Ravi K Ghanta, John Kern, Leora Yarboro, Michael Ragosta, Brian Annex, Jim Bergin, Sandra Burks, Doug Spaulding; ***University of Wisconsin:*** Shahab A Akhter (PI), Lucian Lozonschi, Takushi Kohmoto, Walter Kao, Maryl Johnson, Ravi Dhingra, Alexandra A. Procak, Jillian Francour;

Protocol Review Committee: David A. Bull (Chair); Patrice Desvigne-Nickens, Executive Secretary; Dennis O. Dixon, Richard Holubkov, Alice Jacobs, Eric M. Meslin, John M. Murkin, John A. Spertus.

Data and Safety Monitoring Board: Frank Sellke (Chair); Cheryl L. McDonald, Executive Secretary; John M. Canty, Jr., Neal Dickert, Dennis O. Dixon, John S. Ikonomidis, David O. Williams, Clyde W. Yancy.

Medical Monitors: James C. Fang, Wayne Richenbacher.

Event Adjudication Committee: Vivek Rao (Chair); Karen L. Furie, Rachel Miller, Sean Pinney, Mary N. Walsh.

Echo Core Lab, Massachusetts General Hospital: Judy Hung, Xin Zeng.

Neurocognitive Core Lab, Duke University Medical Center: Joseph P. Mathew, Jeffrey Browndyke, Yanne Toulgoat-Dubois.

Eligibility Criteria

The study population for this trial consists of adult patients requiring cardiac surgery to treat coronary artery disease, valvular heart disease or a combination of both.

Enrollment Inclusion Criteria

- Age $\geq$ 18 years
- Undergoing heart surgery for coronary artery bypass (on-pump or off-pump CABG) and/or valve repair or replacement (excluding mechanical valves), including re-operations
- Hemodynamically stable

Enrollment Exclusion Criteria

- LVAD insertion or heart transplantation
- Maze procedure
- Transcatheter aortic valve replacement (TAVR)
- History of or planned mechanical valve replacement
- Correction of complex congenital cardiac defect (excluding bicuspid aortic valve, atrial septal defect or PFO)
- History of AF (including AFL)
- History of ablation for AF(including AFL)
- Contraindications to amiodarone
  - PR> 240 ms
  - 2nd or 3rd degree AV block
  - QTc> 480 ms
  - Untreated thyroid disorder
  - AST> 2x upper limit of normal
  - Hepatic cirrhosis
  - Interstitial lung disease
- Contraindications to warfarin
  - Active or recent bleeding
  - High risk of bleeding
  - Liver disease
  - Non-compliance
- Received amiodarone within 6 weeks of index surgery
- Need for long-term anticoagulation
- Concurrent participation in an interventional (drug or device) trial

Randomization Inclusion Criteria

All cardiac surgery patients who meet eligibility criteria will be consented and enrolled. Patients will subsequently be randomized if the following criteria are met:

- AF that persists for > 60 minutes or recurrent (more than one) episodes of AF occurring within 7 days of the surgical date (inclusive, with day of surgery labeled “day 0”) and
- Occurs during the index hospitalization.

Adverse Event Definitions

All serious adverse events (SAE) and all (serious and non-serious) protocol-defined adverse events were collected during the course of the trial. Serious adverse events were defined as any experience that results in a fatality or is life threatening; results in significant or persistent disability; requires or prolongs a hospitalization; results in a congenital anomaly/birth defect; or represents other significant hazards or potentially serious harm to research subjects or others, in the opinion of the investigators. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Non-serious adverse events that were not protocol defined were not collected and are indicated with NA (not applicable) in table 4. If the event was protocol-defined but did not occur we indicated this with a 0 in table 4.

The protocol-defined adverse events are listed below:

Cerebrovascular thromboembolism
A new, temporary or permanent, focal or global neurological deficit ascertained by a standard neurological examination (administered by a neurologist or other qualified physician and documented with appropriate diagnostic tests and consultation note). The examining physician will distinguish between a transient ischemic attack (*TIA*), which is fully reversible within 24 hours (and without imaging evidence of infarction), and a stroke, which lasts longer than 24 hours (or less than 24 hours if there is imaging evidence of infarction). The Modified Rankin Scale and the NIH Stroke Scale (NIHSS) must be administered within 72 hours following the event and at termination of follow up to document the presence and severity of neurological deficits. The Modified Rankin Scale and NIHSS can be found in Appendix I.

Ischemic or Hemorrhagic Stroke
Defined as a neurological deficit that persists beyond 24 hours or less than 24 hours associated with infarction or hemorrhage on an imaging study. Hemorrhagic conversion of an ischemic stroke should be classified as ischemic.

TIA
Defined as an acute neurological deficit that resolves completely within 24 hours with no imaging evidence of infarction or hemorrhage.

Non-cerebral thromboembolism

An acute systemic arterial perfusion deficit in any non-cerebrovascular organ system due to thromboembolism confirmed by one or more of the following:

- Standard clinical and laboratory testing
- Operative findings
- Autopsy findings

This definition excludes central nervous system neurological events.

Bleeding (Mehran, Rao et al. 2011)

Type 1: Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional.

Type 2: Any clinically overt sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that is actionable but does not meet criteria for type 3, type 4 (CABG-related), or type 5 (fatal bleeding) Bleeding Academic Research Consortium (BARC) bleeding. The bleeding must require diagnostic studies, hospitalization, or treatment by a healthcare professional. In particular, the bleeding must meet at least one of the following criteria: First, it requires intervention, defined as a healthcare professional–guided medical treatment or percutaneous intervention to stop or treat bleeding, including temporarily or permanently discontinuing a medication or study drug.

Type 3: Clinical, laboratory, and/or imaging evidence of bleeding with specific healthcare provider responses, as listed below:

- Type 3a bleeding
  - Any transfusion with overt bleeding
  - Overt bleeding plus hemoglobin drop ≥3 to <5 g/dL (provided hemoglobin drop is related to bleeding). Hemoglobin drop should be corrected for intracurrent transfusion in which 1 U packed red blood cells or 1 U whole blood would be expected to increase hemoglobin by 1 g/dL.
- Type 3b bleeding
  - Overt bleeding plus hemoglobin drop ≥5 g/dL (provided hemoglobin drop is related to bleed). Hemoglobin drop should be corrected for intracurrent transfusion in which 1 U packed red blood cells or 1 U whole blood would be expected to increase hemoglobin by 1 g/dL.
  - Cardiac tamponade
  - Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
  - Bleeding requiring intravenous vasoactive drugs
- Type 3c bleeding
  - Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation; does include intraspinal); subcategories confirmed by autopsy, imaging, or lumbar puncture
  - Intraocular bleed compromising vision

Type 4: Coronary Artery Bypass Graft–related bleeding

- Perioperative intracranial bleeding within 48 hours
- Reoperation after closure of sternotomy for the purpose of controlling bleeding

- Transfusion of ≥5 U whole blood or packed red blood cells within a 48-hour period (only allogenic transfusions are considered transfusions for CABG-related bleeds)
- Chest tube output ≥2 L within a 24-hour period

Type 5: Fatal bleeding

Definite or probable bleeding that directly causes death with no other explainable cause. A fatal bleeding event is defined as

- Death due to hemorrhage

NOTE: Hemorrhagic stroke is considered a neurological event and not as a separate bleeding event. Relationship to anticoagulation will be established for all bleeding events.

Cardiac Arrhythmias

Any documented arrhythmia that *results in clinical compromise* (e.g., hemodynamic compromise, oliguria, pre-syncope or syncope) or modification of medical management that requires hospitalization or requires a physician visit, an additional procedure or occurs during a hospital stay. Cardiac arrhythmias are classified as:

1. Sustained ventricular arrhythmia requiring defibrillation, cardioversion or ablation
2. Sustained supraventricular arrhythmia other than AF or AFL requiring drug treatment, cardioversion or ablation
3. Cardiac conduction abnormalities requiring permanent pacemaker
4. QTc prolongation > 500ms

Pericardial Fluid Collection

Accumulation of fluid or clot in the pericardial space that requires surgical intervention or percutaneous catheter drainage. This event will be subdivided into those with clinical signs of tamponade (e.g. increased central venous pressure and decreased cardiac output) and those without signs of tamponade.

Pleural Effusion

Accumulation of fluid or clot in the pleural space documented by chest radiogram or chest CT that requires evacuation with surgical intervention or chest tube placement.

Major Infection

A new clinical infection accompanied by pain, fever, drainage and/or leukocytosis that is treated by anti-microbial agents (non-prophylactic). A positive culture from the infected site or organ should be present unless strong clinical evidence indicates the need for treatment despite negative cultures. The general categories of infection are listed below:

Endocarditis

Signs, symptoms and laboratory findings consistent with endocarditis, including but not limited to fever ≥ 38.0^{o} C, positive blood cultures, new regurgitant murmurs or heart failure, evidence of embolic events (e.g., focal neurologic impairment, glomerulonephritis, renal and splenic infarcts, and septic pulmonary infarcts), and

peripheral cutaneous or mucocutaneous lesions (e.g., petechiae, conjunctival or splinter hemorrhages, Janeway lesions, Osler's nodes, and Roth spots). Echocardiographic evidence of a new intra-cardiac vegetation with or without other signs and symptoms should be considered adequate evidence to support the diagnosis of endocarditis. TEE should be the modality of choice for diagnosis of prosthetic valve endocarditis.

Mediastinitis/Deep Sternal Wound Infection
Signs and symptoms consistent with mediastinitis, include but are not limited to fever, chills, leukocytosis and chest or back pain, *and* mediastinal inflammation documented by diagnostic testing (e.g., chest CT). Information regarding deep sternal wound infections will be collected.

Infectious Pericarditis
Signs and symptoms, including but not limited to fever, leukocytosis and pericardial inflammation, necessitating surgical exploration, drainage and treatment with intravenous antibiotics.

Sepsis
Evidence of systemic involvement by infection, manifested by positive blood cultures and/or hypotension. In addition, we will record systemic antibiotic use for presumptive sepsis.

Localized Infection
Infection localized to any organ system or region other than the mediastinum, pericardium, or endocardium without evidence of systemic involvement (see sepsis definition), ascertained by standard clinical methods and either associated with evidence of bacterial, viral, fungal or protozoal infection, and/or requiring empirical treatment.

Heart Failure

New onset of signs or symptoms of congestive heart failure *or* worsening of pre-existing heart failure by $\geq$ 1 NYHA class.

Myocardial Infarction

Myocardial infarction (MI) should be classified when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions, any one of the following criteria meets the diagnosis for myocardial infarction[1]:

Myocardial Infarction
Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:

- Symptoms of ischemia;
- ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB]);

[1] Joint ESC/ACCF/AHA/WHF Task for the Redefinition of Myocardial Infarction, *Circulation*.2007;116:0-0.

- Development of pathological Q waves in the ECG;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Peri-CABG Myocardial Infarction

For CABG in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases in biomarkers > 5 x 99th percentile URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft of native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related MI.

Sudden unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumed new ST elevation or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or autopsy, with death occurring before blood samples obtained, or at a time before the expected appearance of cardiac biomarkers in blood will be classified as a mortality due to MI.

Renal Events

Three categories of renal events will be identified according to the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group(Bellomo, Ronco et al. 2004):

Risk of Renal Dysfunction

GFR Criteria: Increased SCreat x1.5 *or* GFR decrease > 25%
Urine Output (UO) Criteria: UO < 0.5ml/kg/h x 6 hr

Injury to the Kidney

GFR Criteria: Increased SCreat x2 *or* GFR decrease > 50%
UO Criteria: UO < 0.5 ml/kg/h x 12 hr

Failure of Kidney Function

GFR Criteria: Increase SCreat x3, GFR decrease 75%, *or* SCreat ≥ 4 mg/dl (acute rise ≥ 0.5mg/dl)
UO Criteria: UO < 0.3 ml/kg/h x 24 hr *or* Anuria x 12 hrs

Thyroid Dysfunction

Hypothyroidism

Abnormal thyroid function defined by thyroid stimulating hormone (TSH) levels ≥ 3.04 µIU/L, with or without free T3 levels ≤ 2.3 pg/mL or free T4 levels ≤ 0.8 ng/dL.

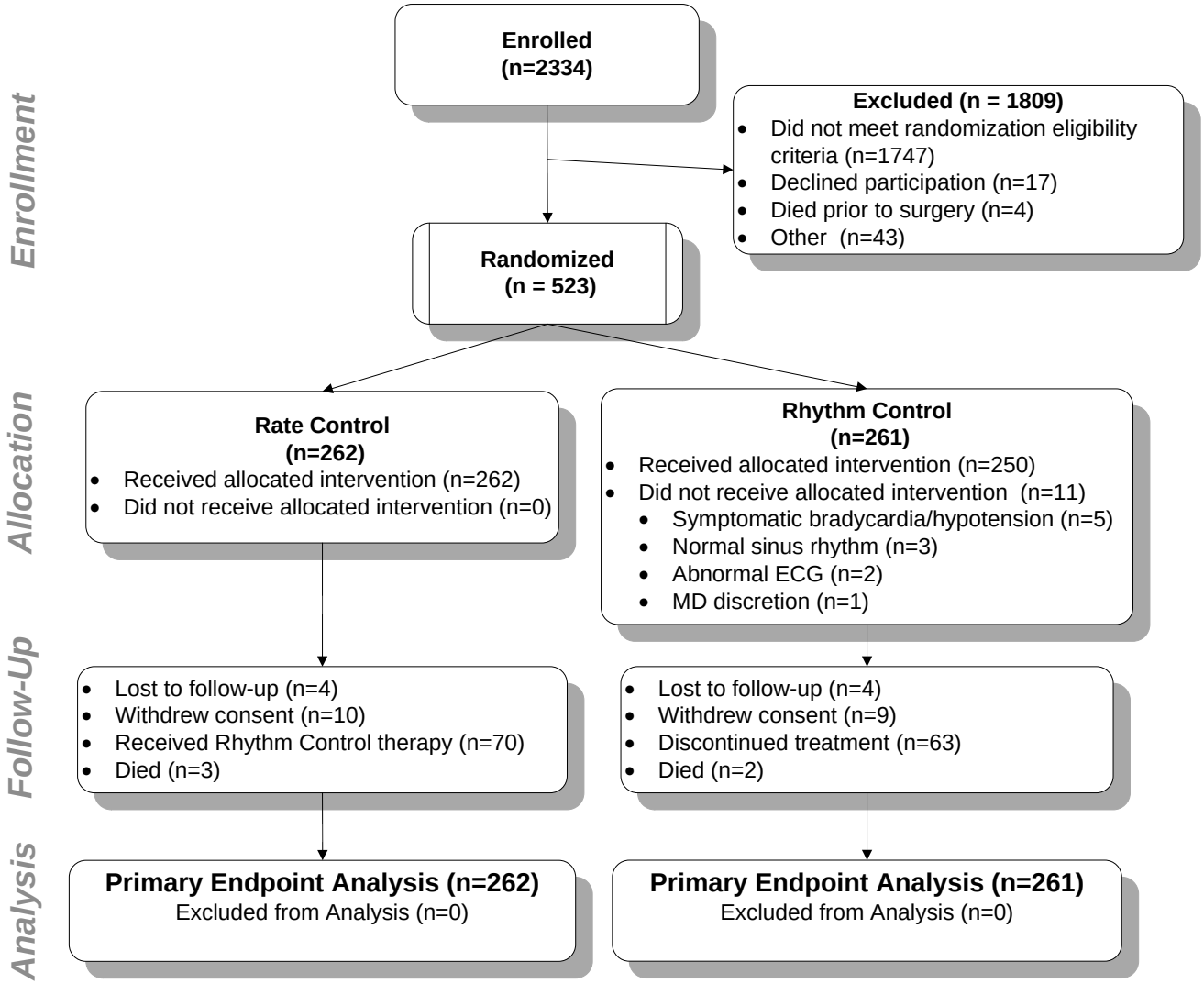
Hyperthyroidism

Abnormal thyroid function defined by thyroid stimulating hormone (TSH) levels ≤ 0.3 µIU/mL, with or without free T3 levels ≥ 4.2 pg/mL or free T4 levels ≥ 1.8 ng/dL.

Other

An event that causes clinically relevant changes in the patient's health, or any event that is life-threatening, results in a fatality, results in permanent disability, requires hospitalization, or prolongs an existing hospital stay.

Figure S1 Consort Diagram



Sensitivity analysis using an instrumental variable

The trial was designed to address the question of whether an *initial* strategy of rate control versus an *initial* strategy of rhythm control leads to differences in the number of days in hospital over the duration of the trial. The intention-to-treat (ITT) analysis directly addresses this well-defined question, and the trial design reflects that patients in each arm would require changes to their randomized assignments for a variety of reasons pre-specified in the trial's protocol (such as adverse effects, intolerance to therapy, or ineffectiveness of therapy). As anticipated, approximately 25% of patients had to switch their randomized assignment for protocol defined reasons. The analytic approach described here addresses the impact that deviations from the randomly assigned therapeutic approach, whether protocol defined or not, may have on the results of the primary (ITT) analysis.

We performed a sensitivity analysis to determine whether non-adherence would influence the study results using an instrumental variable approach. This analysis, using randomization assignment as an instrumental variable for "treatment received" (the therapy to which patients switched, or randomized if not switched) defines an "as treated" analysis of treatment differences. The instrumental variable approach removes much of the bias associated with both known and unknown factors associated with other approaches that either provide a simple estimate of the treatment difference, or adjust only for measured confounders.

We used two- stage linear regression to estimate the causal effect of the predictor T ("treatment received") on the outcome O (total days in hospital, log transformed to reduce skewness)

$$T = \mu_T + \beta_{TR}R + \varepsilon_T \qquad \text{(Stage 1)}$$

$$O = \mu_O + \beta_{OT}T^* + \varepsilon_O \qquad \text{(Stage 2)}$$

In stage 1, regression of the predictor T ("treatment received") on R (randomization assignment) yields predicted values of T (denoted as T*) for each patient, free of confounding. The second stage regression of the outcome O (total days in hospital) on these predicted values provides an estimate of the effect of "treatment received".

The results of these analyses are summarized in the tables below.

Table S1

Instrumental Variable Analysis for total number of days in hospital		
	Parameter Estimate	p-value
Stage 1: Dependent variable Treatment Actually Received (T)		
Randomization Assignment (R)	0.495	<.0001
Stage 2: Dependent Variable log(time in hospital) (O)		
Treatment Actually Received (T*)	0.085	0.505

Table S2

Instrumental Variable Analysis for LOS of index hospitalization		
	Parameter Estimate	p-value
Stage 1: Dependent variable Treatment Actually Received (T)		
Randomization Assignment (R)	0.495	<.0001
Stage 2: Dependent Variable log(time in hospital) (O)		
Treatment Actually Received (T*)	0.043	0.715

The stage 2 analyses confirm no difference between the groups for total number of days in hospital (p=0.51) or for the LOS of index hospitalization (p=0.72).

Table S3 Characteristics of stroke patients

Randomization assignment	Event	Days from surgery to event	Days from randomization to event	Modified Rankin Score 72 hours after event	Modified Rankin Score at termination of follow up	Start of anticoagulation	Total number of days on Warfarin
Rate Control	Stroke	6	4	3	1	After Event	56
Rate Control	Stroke	6	5	2	2	Before Event	58
Rate Control	Stroke	32	29	.	5	Before Event	30
Rate Control	Stroke	31	29	.	1	Before Event	1
Rhythm Control	Stroke	31	27	2	3	After Event	1
Rhythm Control	TIA	1	0	2	1	After Event	58

Stratified analysis by cardiac surgical procedure

We report here the results of the analysis of the primary outcome, total number of days in the hospital from randomization to day 60, stratified by cardiac surgical procedure. Analysis A was performed using the Wilcoxon Rank test to compare the two treatment groups within each cardiac surgery procedure stratum. Analysis B was conducted using a linear regression model on the log-transformed outcome. An interaction term between treatment and surgical procedure was included in the model to evaluate a potential differential effect of the treatment strategy across the three cardiac surgical procedures (isolated CABG, isolated valve and combination of valve and CABG). This interaction was not statistically significant.

Table S4 Analysis A: Results of Wilcoxon Rank test within each cardiac surgery procedure

	Rate Control (N = 262)	Rhythm Control (N = 261)	P value
Total number of days in hospital from randomization to day 60 (Median and Q1,Q3)			
Isolated CABG	4.8 (3.0, 7.7)	5.1 (3.1, 6.8)	0.96
Isolated Valve	5.0 (2.6, 7.1)	4.4 (3.1, 7.0)	0.76
CABG + Valve	5.3 (4.2, 8.4)	7.1 (4.4, 9.7)	0.11

Table S5 Analysis B. Results of the regression model

	B coefficient	Standard Error	p-value
Intercept	1.5	0.07	<.0001
MAIN EFFECTS			
Randomization: Rate control vs Rhythm Control	0.02	0.10	0.84
Surgery: CABG + Valve vs Isolated Valve	0.45	0.12	<.001
Surgery: Isolated CABG vs Isolated Valve	0.11	0.10	0.26
INTERACTION EFFECTS			
Randomization (Rate control) *surgery (CABG + Valve)	-0.22	0.17	0.21
Randomization (Rate control) *surgery (Isolated CABG)	-0.05	0.14	0.71