Effect of an Investigational Vaccine for Preventing *Staphylococcus aureus* Infections After Cardiothoracic Surgery

A Randomized Trial

Vance G. Fowler Jr, MD, MHS
Keith B. Allen, MD
Edson D. Moreira Jr, MD, MPH, PhD
Moustafa Moustafa, MD
Frank Isgro, MD
Helen W. Boucher, MD
G. Ralph Corey, MD
Yehuda Carmeli, MD
Robert Betts, MD
Jonathan S. Hartzel, PhD
Ivan S. F. Chan, PhD
Tessie B. McNeely, PhD
Nicholas A. Kartsonis, MD
Dalya Guris, MD
Matthew T. Onorato, BS
Steven S. Smugar, MD
Mark J. DiNubile, MD
Ajoke Sobanjo-ter Meulen, MD, MSc

Importance Infections due to *Staphylococcus aureus* are serious complications of cardiothoracic surgery. A novel vaccine candidate (V710) containing the highly conserved *S aureus* iron surface determinant B is immunogenic and generally well tolerated in volunteers.

Objective To evaluate the efficacy and safety of preoperative vaccination in preventing serious postoperative *S aureus* infection in patients undergoing cardiothoracic surgery.

Design, Setting, and Participants Double-blind, randomized, event-driven trial conducted between December 2007 and August 2011 among 8031 patients aged 18 years or older who were scheduled for full median sternotomy within 14 to 60 days of vaccination at 165 sites in 26 countries.

Intervention Participants were randomly assigned to receive a single 0.5-mL intramuscular injection of either V710 vaccine, 60 μg (n=4015), or placebo (n=4016).

Main Outcome Measures The primary efficacy end point was prevention of *S aureus* bacteremia and/or deep sternal wound infection (including mediastinitis) through postoperative day 90. Secondary end points included all *S aureus* surgical site and invasive infections through postoperative day 90. Three interim analyses with futility assessments were planned.

Results The independent data monitoring committee recommended termination of the study after the second interim analysis because of safety concerns and low efficacy. At the end of the study, the V710 vaccine was not significantly more efficacious than placebo in preventing either the primary end points (22/3528 V710 vaccine recipients [2.6 per 100 person-years] vs 27/3517 placebo recipients [3.2 per 100 person-years]; relative risk, 0.81; 95% CI, 0.44-1.48; *P*=.58) or secondary end points despite eliciting robust antibody responses. Compared with placebo, the V710 vaccine was associated with more adverse experiences during the first 14 days after vaccination (1219/3958 vaccine recipients [30.8%; 95% CI, 29.4%-32.3%] and 866/3967 placebo recipients [21.8%; 95% CI, 20.6%-23.1%], including 797 [20.1%; 95% CI, 18.9%-21.4%] and 378 [9.5%; 95% CI, 8.6%-10.5%] with injection site reactions and 66 [1.7%; 95% CI, 1.3%-2.1%] and 51 [1.3%; 95% CI, 1.0%-1.7%] with serious adverse events, respectively) and a significantly higher rate of multiorgan failure during the entire study (31 vs 17 events; 0.9 [95% CI, 0.6-1.2] vs 0.5 [95% CI, 0.3-0.8] events per 100 person-years; *P*=.04). Although the overall incidence of vaccine-related serious adverse events (1 in each group) and the all-cause mortality rate (201/3958 vs 177/3967; 5.7 [95% CI, 4.9-6.5] vs 5.0 [95% CI, 4.3-5.7] deaths per 100 person-years; *P*=.20) were not statistically different between groups, the mortality rate in patients with staphylococcal infections was significantly higher among V710 vaccine than placebo recipients (15/73 vs 4/96; 23.0 [95% CI, 12.9-37.9] vs 4.2 [95% CI, 1.2-10.8] per 100 person-years; difference, 18.8 [95% CI, 8.0-34.1] per 100 person-years).

Conclusions and Relevance Among patients undergoing cardiothoracic surgery with median sternotomy, the use of a vaccine against *S aureus* compared with placebo did not reduce the rate of serious postoperative *S aureus* infections and was associated with increased mortality among patients who developed *S aureus* infections. These findings do not support the use of the V710 vaccine for patients undergoing surgical interventions.

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INFECTIONS WITH *STAPHYLOCOCCUS aureus* following median sternotomy cause substantial morbidity and mortality.[1-3] A safe vaccine that provides protection against a majority of *S aureus* strains during the postoperative period would address an important unmet medical need.[4,5]

A novel vaccine candidate (V710; Merck Sharp & Dohme Corp) containing the highly conserved *S aureus* 0657nI iron surface determinant B (IsdB) was protective in animal challenge models[6-8] and immunogenic within 14 days after a single dose of either an adjuvanted or nonadjuvanted formulation in healthy volunteers.[9,10] Antibody response to V710 was similar in younger and older partici-

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Author Affiliations are listed at the end of this article.
Corresponding Author: Vance G. Fowler Jr, MD, MHS, Duke University Medical Center, Hanes Bldg, Room 153, Trent Drive, PO Box 102359, Durham, NC 27710 (fowle003@mc.duke.edu).

pants.[9,10] Elevated antibody responses persisted for at least 1 year after vaccination in most patients.[10] The immunogenicity and tolerability of a lyophilized V710 formulation were generally similar to the properties of the original liquid formulation.[10]

The current phase 2b/3 study was initiated to evaluate the efficacy and safety of preoperative vaccination with nonadjuvanted lyophilized V710 in preventing serious *S aureus* infections in patients about to undergo a median sternotomy for cardiothoracic surgery.

METHODS

Objectives

The primary efficacy objective was to demonstrate whether a single dose of V710 vaccine administered between 14 and 60 days prior to cardiothoracic surgery (involving a full median sternotomy) would reduce the proportion of adult patients with postoperative *S aureus* bacteremia and/or *S aureus* deep sternal wound infections through postoperative day 90 by at least 20% relative to placebo. Secondary efficacy objectives included demonstrating a reduction in the proportion of patients who developed any invasive or surgical site infection with *S aureus* through postoperative day 90. The primary safety objective was to evaluate the adverse event profile of a single dose of V710 vaccine administered preoperatively to patients awaiting cardiothoracic surgery. Immunogenicity was also assessed.

Study Design

A sequential-design, multicenter, randomized, double-blind, placebo-controlled trial was conducted internationally to evaluate the safety, efficacy, and immunogenicity of a 60-μg dose of V710 vaccine in patients aged 18 years or older scheduled for cardiothoracic surgery involving a full median sternotomy within 14 to 60 days following vaccination. The protocol was approved by the institutional review boards or ethical review committees at each site and executed in accordance with Good Clinical Practice guidelines. Patients were excluded if pregnant or breastfeeding, febrile (≥38.0°C [100.4°F]) in the previous 48 hours, immunocompromised (including but not limited to human immunodeficiency virus infection or immunosuppressive therapies), unstable, or recently immunized with any other vaccine (except for pneumococcal or influenza vaccines, which were allowed at least 7 days prior to or 15 days after study vaccination). Patients with cirrhosis, bleeding diathesis, renal failure requiring dialysis, or a history of injecting recreational drugs in the last 5 years were also excluded. At screening, specific preoperative variables were assessed to calculate a Society of Thoracic Surgeons score for the risk of major infections following cardiothoracic surgery with higher scores representing greater risk.[11,12] Eligible patients provided written informed consent before any study procedures took place.

The V710 vaccine was provided as a lyophilized formulation without adjuvant stored at 2°C to 8°C (35.6°F to 46.4°F). The 0.45% saline diluent for V710 reconstitution and the placebo solution were kept at room temperature. The vaccine was to be reconstituted immediately before use, resulting in a clear, colorless to slightly yellow liquid, and administered by an unblinded pharmacist or study coordinator not otherwise involved in the patient's subsequent care.

Participants were randomized in a 1:1 ratio (FIGURE) by site using an interactive voice response system to receive a single 0.5-mL injection of either 60 μg of V710 vaccine or 0.9% saline placebo in the deltoid (or thigh) muscle at the time of enrollment. Patients were monitored for evidence of immediate hypersensitivity reactions for 30 minutes after vaccination. The total time in the study for each patient was to be 14 to 60 days from vaccination to cardiothoracic surgery and another 360 days postoperatively; after termination of enrollment, patients still in the study were followed up for at least 90 days after vaccination. Study patients were mandated to receive preoperative antibiotic prophylaxis in addition to other customary preoperative and perioperative measures according to the local standard of care. The protocol offered nonbinding recommendations regarding selection, timing, and duration of prophylactic antibiotics. An independent data monitoring committee reviewed safety data on an ongoing basis and in conjunction with the predefined interim efficacy analyses.

Case Definitions and Adjudication Process

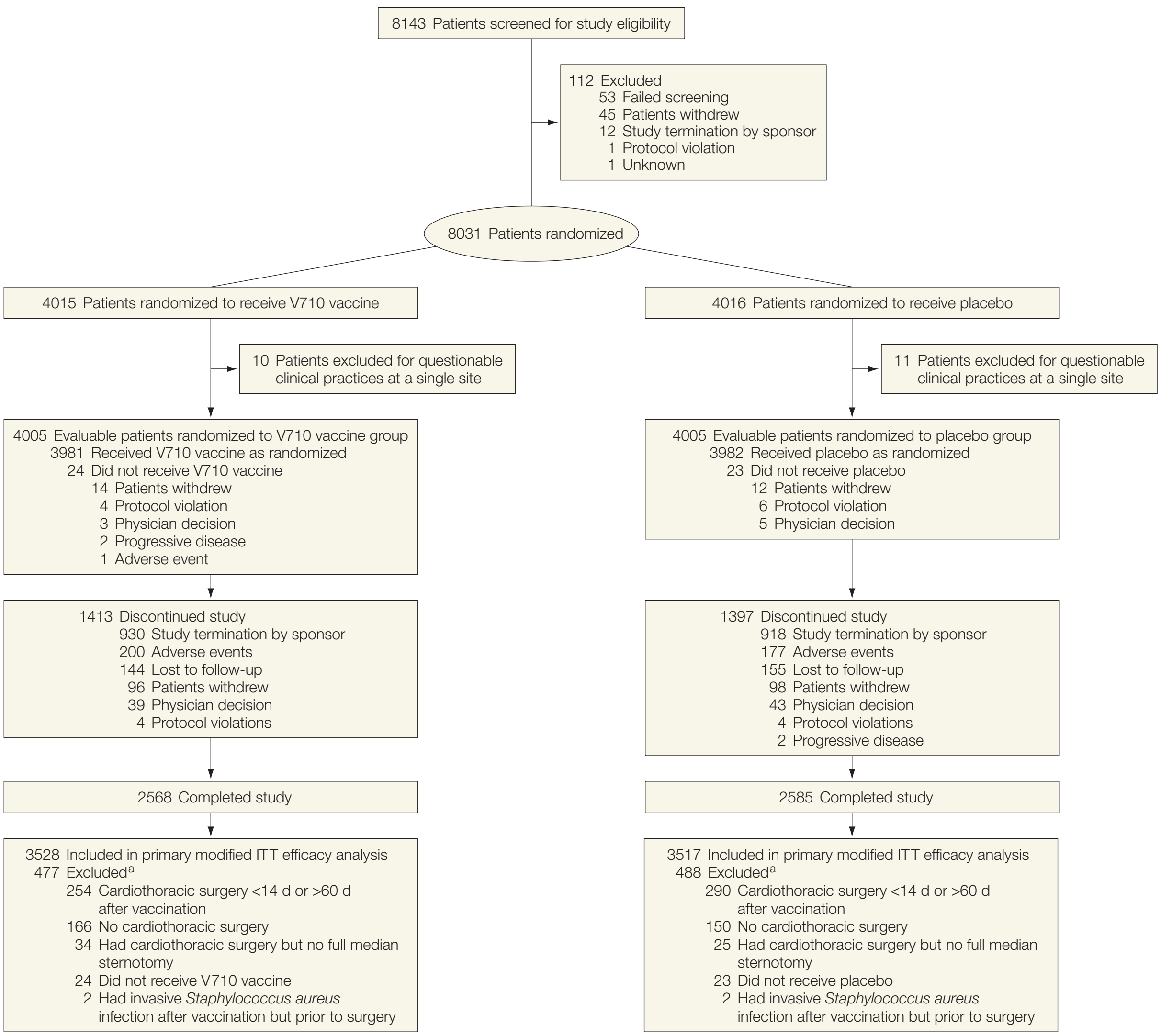
All efficacy end points were assessed through postoperative day 90 and adjudicated by an independent adjudication committee blinded to treatment group using the Centers for Disease Control and Prevention's definitions for nosocomial infections.[13] For the primary end points, bloodstream infection was defined as at least 1 positive blood culture for *S aureus* (regardless of the presence of clinical symptoms) and deep sternal wound infection was defined as postoperative mediastinitis or a surgical site infection involving the sternum or deeper myofascial tissue planes. The secondary efficacy end points were invasive *S aureus* infections (including bacteremia or any deep-seated infection) and superficial or deep surgical site infections (including the sternotomy, vascular harvest, and chest tube sites).

Statistical Analysis

The study was designed to detect at least a 20% reduction in the number of cases based on the prespecified combined end point of *S aureus* bacteremia and/or *S aureus* deep sternal wound infections through postoperative day 90 in V710 recipients compared with placebo recipients (ie, vaccine efficacy >20%). All reported adverse events irrespective of intensity or causality were tabulated for the 14-day period immediately following vaccination; selected serious adverse events continued to be collected for the entire 360-day postoperative length of the study. Patients were handled as randomized for the primary efficacy analysis and as treated for the safety analysis.

The trial was event-driven, using the number of *S aureus* cases rather than number of enrolled patients for measuring trial progress and defining when the trial was complete. Total enrollment was estimated from the expected number of accumulated cases of *S aureus* bacteremia and/or *S aureus* deep sternal wound infections. A group-sequential design with 4 distinct stages (at 24, 48, 77, and 107 primary end point events) was used in the study such that after each threshold of primary end point events was reached, an analysis of futility and/or efficacy was conducted. Group-sequential methods[14] using exact methods for binomial data (which adjusted for the predefined success and futility stopping rules at each stage) were used to calculate the exact power, type I error rate, and confidence intervals for efficacy. Stopping rules for futility were chosen to ensure that the probability of moving forward with a nonefficacious vaccine would be low while controlling the 1-sided type I error rate at 2.5%. Additionally, the stopping rules for success were selected such that if they were met, the resulting lower limit of the con-

Figure. Participant Flow



Participants who discontinued the study could have discontinued at any of the following points: (1) following randomization but prior to vaccination; (2) following vaccination but prior to inclusion in the primary modified intention-to-treat (ITT) efficacy population; or (3) following inclusion in the primary modified ITT efficacy population but prior to completion or termination of the study. The predominant reason for not completing the study was the early termination of the trial, which accounted for 1848 (65%) of the total 2857 patient discontinuations.

[a] Patients may have been excluded from the primary modified ITT efficacy population for more than 1 reason but are included in the total only once.

fidence interval for vaccine efficacy would be greater than 20% (the predefined threshold for study success). Only futility was assessed at the first 2 stages to guarantee that a sufficiently large safety database would be collected prior to potentially stopping for success.

The initial interim review after 24 primary end point events had been accrued was to serve as a safety assessment and futility analysis; the study was to be terminated early if at least 13 *S aureus* cases (of the 24 total cases) occurred in the V710 vaccine group. The second interim analysis, planned once 48 cases had been accrued, was also intended to assess futility, defined as at least 22 cases in the V710 group. The third interim analysis was to include 77 cases to assess both futility and efficacy. Futility was to be declared at the last interim analysis if at least 32 cases occurred in the V710 group. The statistical criterion for success was specified as the lower bound of the exact 95% confidence interval for vaccine efficacy greater than 20% and would be met at this interim analysis if 22 or fewer cases occurred in the V710 group.

If criteria for futility or success were not satisfied during the interim analyses, the trial was to continue enrollment until the final target of 107 *S aureus* cases had been accrued. With 107 cases, an assumed vaccine efficacy of 60%, and a type I error of .05, the study had an overall power of approximately 92% to conclude that the true vaccine efficacy was greater than 20%. An estimated 15 000 patients would be required to accrue the 107 *S aureus* cases necessary for the final analysis. A lower bound of the exact 95% confidence interval for efficacy of V710 relative to placebo of greater than 20% for the primary combined end point would establish that the vaccine was efficacious as predefined by protocol. If the primary hypothesis was satisfied, a vaccine efficacy greater than 0% against a secondary end point would allow the further conclusion that the vaccine was efficacious in preventing the particular end point.

Efficacy Analyses

Study efficacy results were based on a modified intention-to-treat (ITT) approach. Vaccine efficacy was defined by protocol as the relative risk reduction of an end point in vaccine recipients compared with the placebo group. The primary efficacy analysis was conducted in the primary modified ITT population, prespecified as vaccinated patients who underwent full median sternotomy between day 14 and day 60 after vaccination and who did not develop a serious preoperative *S aureus* infection. The primary modified ITT population was denoted as the full analysis set in the protocol. The primary efficacy analysis was supported by a secondary modified ITT analysis and a per-protocol analysis. A secondary modified ITT population included vaccinated patients who subsequently underwent cardiothoracic surgery irrespective of the type of surgical procedure or timing relative to vaccination. Patients who developed serious preoperative *S aureus* infections were retained in the secondary modified ITT population. The per-protocol population included vaccinated patients undergoing full median sternotomy between day 14 and day 60 after vaccination with neither serious preoperative *S aureus* infections nor major protocol violations. Cross-treated patients were analyzed based on the vaccination group to which they were randomized in the primary and secondary modified ITT populations and based on what they actually received in the per-protocol population.

To supplement the estimates of vaccine efficacy stipulated in the protocol and required by regulatory agencies (which were based on the case split without regard to duration of follow-up), relative risks (which accounted for both the number of patients and length of follow-up time) were calculated for the key primary efficacy results.

Safety Analyses

All vaccinated patients with follow-up data were included in the adverse experiences summaries as treated. Adverse experiences reported by the site investigator as possibly, probably, or definitely vaccine-related were tallied as vaccine-related. Injection site reactions and oral temperatures were actively monitored for 5 days after vaccination. All adverse experiences in the 14 days immediately after vaccination were captured using a patient vaccine report card. Serious adverse experiences considered to be vaccine-related, associated with *S aureus* infection, and/or resulting in death were to be reported throughout the entire study. Subsequent to recognition of a safety signal, the incidence of multiorgan failure was retrospectively assessed irrespective of causality or timing. Diagnoses of "multiorgan failure" were accepted verbatim as an adverse event term reported by the site investigators; no definitions or criteria were imposed per protocol because this complication was not anticipated as an issue a priori. Extensive post hoc exploratory analyses were performed to investigate safety concerns. After the decision to terminate the study was made, all vaccinated patients still in the study were to be followed up at least until postvaccination day 90. Due to the potential for differing follow-up times for individual patients, the overall adverse event rate was to be expressed as the number of patients with adverse experiences per 100 person-years of follow-up. Patients developing multiple adverse experiences were counted only once in any given category.

Prior to the early study termination, the primary safety end point had been specified per protocol as the incidence of vaccine-related serious adverse experiences developing at any time after vaccination through postoperative day 180. The point estimate with its corresponding 2-tailed 95% confidence interval for the risk difference between the V710 and placebo groups of developing a vaccine-related serious adverse experience was to be calculated using the method of Miettinen and Nurminen[15] for analysis of Poisson rates accounting for the potential differential follow-up time. Frequencies were also computed for adverse experiences occurring during the 14-day postvaccination period.

Immunogenicity Analyses

Blood samples were to be collected from all patients just before vaccination, at the time of hospitalization for surgery (14 to 60 days after vaccination), and on postoperative days 45 and 90 for exploratory immunogenicity analyses. In a preselected subset of patients, additional specimens were to be obtained on postoperative days 180, 270, and 360 as well. A direct binding assay was developed for the detection of total IgG antibodies to the iron surface determinant of *S aureus* using a Luminex platform.[16] Opsonophagocytic activity was assessed with an investigational assay by the uptake of fluorescently labeled *S aureus* by a human granulocytic cell line in the presence or absence of patient serum, comparing postvaccination to preimmune serum samples.[17]

RESULTS

Patient Accounting and Baseline Characteristics

The study was conducted from December 12, 2007, to August 19, 2011, at 165 sites in 26 countries on 5 continents. No concerns were raised by the data monitoring committee following the initial interim analysis in January 2010. Following the second interim analysis on April 8, 2011, the data monitoring committee recommended suspension of enrollment and vaccination because of concerns about a possibly higher rate of mortality and multiorgan failure in V710 vaccine recipients than in placebo recipients, and the committee requested further analyses. On June 2, 2011, following review of the supplemental results, the data monitoring committee recommended permanently closing the study to enrollment because of continuing safety concerns coupled with the low probability of success. The sponsor followed the recommendations from the data monitoring committee.

When the database was locked on September 13, 2011, 7983 participants had been vaccinated (Figure). Because repeated audits had uncovered irregularities in clinical practices at 1 site, 21 patients from this site were excluded from all analyses before the data were unblinded. Five participants were inadvertently given the wrong injection based on the group to which they had been randomized. Two patients in each group experienced a serious preoperative *S aureus* infection leading to exclusion from the primary efficacy population; none of these 4 patients developed a postoperative *S aureus* infection. Approximately 64% of patients in each study group completed the 360-day safety follow-up. The predominant reason for patients discontinuing the study was the premature study termination by the sponsor in response to the recommendation of the data monitoring committee, accounting for 1848 (65%) of the total 2857 discontinuations.

Baseline characteristics of randomized patients were balanced across groups (TABLE 1). Vaccine and placebo recipients had similar metabolic characteristics, infection risk scores, *S aureus* colonization rates, and types of surgical procedure.

Efficacy

In the primary modified ITT analysis, V710 vaccine was not significantly more efficacious than placebo in preventing the prespecified combined end point (22 adjudicated cases in 3528 evaluable V710 recipients vs 27 adjudicated cases in 3517 evaluable placebo recipients; event rate, 2.6 [95% CI, 1.6-4.0] vs 3.2 [95% CI, 2.1-4.7] per 100 person-years, respectively), yielding a relative risk of 0.81 (95% CI, 0.44-1.48). There was no significant vaccine efficacy (18.5%; 95% CI, −48.6% to 55.8%) (TABLE 2). No significant differences in efficacy between the vaccine and placebo groups were observed at any point during the study (eFigure 1; available at http://www.jama.com). An additional adjudicated case of *S aureus* infection in a V710 vaccine recipient had been excluded from the primary analysis because it had been determined during a quality-assurance audit that the site might have used questionable clinical practices. Inclusion of this additional adjudicated case yielded a nonsignificant vaccine efficacy of 14.8% (95% CI, −54.3% to 53.3%). Two cases from each group were reported after termination of the trial and consequently not adjudicated. Counting all cases, overall vaccine efficacy with respect to the primary end point was also nonsignificant (13.8%; 95% CI, −52.5% to 51.6%).

In the secondary modified ITT analysis, estimates based on adjudicated cases ranged from 12.9% (95% CI, −50.8% to 50.0%) for preventing invasive *S aureus* infections to 29.3% (95% CI, −1.8% to 51.2%) for preventing *S aureus* surgical site infections. The lower number of *S aureus* surgical site infections was driven by fewer superficial lower extremity (usually saphenous vein) donor site infections (13 vs 36 in the V710 and placebo groups, respectively), without a meaningful between-group difference in the infection rate for sternal wounds. However, harvesting techniques, perioperative antibiotic prophylaxis, and other adjunctive measures were not controlled and varied among sites. Combining all end points, vaccine efficacy was 25.3% (95% CI, −3.4% to 46.2%) (eFigure 2).

In a post hoc analysis, estimates of vaccine efficacy were higher in preventing methicillin-susceptible *S aureus* (MSSA) than methicillin-resistant *S aureus* (MRSA) infections for the primary, secondary, and exploratory end points. Infection with MRSA occurred in 23 (34%; 95% CI, 23%-46%) of the 68 V710 vaccine recipients with *S aureus* infection and in 17 (19%; 95% CI, 11%-28%) of the 91 placebo recipients with *S aureus* infection in the primary efficacy population ($P=.04$). *Staphylococcus aureus* infections developed in 3.3% (95% CI, 2.1%-4.9%) and 5.5% (95% CI, 3.9%-7.6%) of nasal carriers compared with 1.6% (95% CI, 1.2%-2.2%) and 1.8% (95% CI, 1.4%-2.4%) of noncarriers in the V710 and placebo groups, respectively ($P=.09$).

Safety

The V710 vaccine was associated with a higher rate of overall adverse experiences during the 14 days following vaccination, predominantly but not exclusively at the injection site (TABLE 3). In this immediate 14-day postvaccination period, vaccine-related injection site adverse reactions were significantly more common among V710 recipients than placebo recipients (19.2% [95% CI, 18.0%-20.5%] vs 9.1% [95% CI, 8.2%-10.0%]; difference, 10.1% [95% CI, 8.6%-11.7%]), whereas rates of vaccine-related systemic adverse experiences (3.1% [95% CI, 2.6%-3.7%] vs 2.8% [95% CI, 2.3%-3.4%]; difference, 0.3% [95% CI, −0.5% to 1.0%]), serious adverse experiences (1.7% [95% CI, 1.3%-2.1%] vs 1.3% [95% CI, 1.0%-1.7%]; difference, 0.4% [95% CI, −0.2% to 0.9%]), serious vaccine-related adverse experiences (0 events in each group), and preoperative deaths (11 deaths [0.3%; 95% CI, 0.1%-0.5%] vs 6 deaths [0.2%; 95% CI, 0.1%-0.3%]; difference, 0.1% [95% CI, −0.1%-0.4%]) did not differ significantly between vaccine and placebo recipients, respectively.

Over the course of the entire study, 1 vaccine-related serious adverse event was reported in each group: *Clostridium difficile* colitis in a V710 vaccine recipient on postvaccination day 53 (postoperative day 37) and lymphoma in a placebo recipient on postvaccination day 237 (postoperative day 222) (Table 3). No statistically significant differences in overall vaccine-related serious adverse events or all-cause mortality were found between the V710 and placebo groups, whereas postoperative multiorgan failure developed more commonly in V710 recipients than placebo recipients (31 vs 17 events, yielding 0.9 [95% CI, 0.6-1.2] vs 0.5 [95% CI, 0.3-0.8] events per 100 person-years, respectively; difference, 0.4 [95% CI, 0.0-0.8] events per 100 person-years; $P=.04$). In no cases were multiorgan failure or death attributed to the vaccine by the site investigator, although the placebo recipient with "vaccine-related" lymphoma later died. All patients with reported multiorgan failure died. A full list of all serious adverse experiences in both V710 and placebo recipients is provided in the eTable.

Significantly more patients with postoperative *S aureus* infections died in the V710 vaccine group (15 deaths) than in the placebo group (4 deaths), yielding respective mortality rates of 23.0

Table 1. Selected Baseline Characteristics of Randomized Patients by Group[a]

Characteristics	V710 Vaccine Group (n = 4005)	Placebo Group (n = 4005)	Total (n = 8010)
Vaccinated	3981 (99)	3982 (99)	7963 (99)
Sex			
Male	2677 (67)	2669 (67)	5346 (67)
Female	1328 (33)	1336 (33)	2664 (33)
Self-identified race			
White	3089 (77)	3062 (76)	6151 (77)
Black	71 (2)	77 (2)	148 (2)
Asian	521 (13)	543 (14)	1064 (13)
Multiracial	311 (8)	311 (8)	622 (8)
Other or unknown	13 (<1)	12 (<1)	25 (<1)
Self-reported ethnicity			
Hispanic or Latino	903 (23)	905 (23)	1808 (23)
Region			
Asia/Pacific (New Zealand)	1977 (49)	1975 (49)	3952 (49)
Europe (including Russia)	523 (13)	529 (13)	1052 (13)
Latin America	731 (18)	733 (18)	1464 (18)
United States	774 (19)	768 (19)	1542 (19)
Age			
Median (range), y	65 (18-91)	66 (19-93)	66 (18-93)
>70 y	1332 (33)	1353 (34)	2685 (34)
Underlying metabolic conditions			
Diabetes mellitus	963 (24)	961 (24)	1924 (24)
BMI >30	1108 (28)	1027 (26)	2135 (27)
Society of Thoracic Surgeons infection risk score, median (range)[b]	6 (0-29)	6 (0-26)	6 (0-29)
Nasal colonization			
Colonized with any *Staphylococcus aureus*	738 (18)	714 (18)	1452 (18)
Colonized with MRSA	72 (2)	65 (2)	137 (2)
Underwent cardiothoracic surgery			
Full median sternotomy	3784 (94)	3807 (95)	7588 (95)
Any cardiothoracic procedure[c]	3815 (95)	3832 (96)	7647 (95)
CABG surgery only	1193 (30)	1241 (31)	2434 (30)
Aortic valve	1037 (26)	991 (25)	2028 (25)
Mitral valve	496 (12)	484 (12)	980 (12)
Tricuspid valve	22 (1)	23 (1)	45 (1)
CABG surgery and valve	313 (8)	357 (9)	670 (8)
Other	754 (19)	736 (18)	1490 (19)
Timing of operation			
Days after vaccination, median (IQR)	24 (18-37)	24 (18-36)	24 (18-37)
Patients in each postvaccination period, d			
<14	26 (1)	41 (1)	67 (1)
14-40	2983 (74)	2982 (74)	5965 (74)
41-60	578 (14)	560 (14)	1138 (14)
61-90	152 (4)	167 (4)	319 (4)
>90	76 (2)	82 (2)	158 (2)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CABG, coronary artery bypass graft; IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*.
[a] Data are expressed as No. (%) of participants unless otherwise indicated. Denominators were not adjusted for missing data. The 21 patients randomized at the site with questionable clinical practices (n=10 to the V710 group and n=11 to the placebo group) have been excluded from this table and all analyses.
[b] Adapted from Fowler et al.[11]
[c] Corresponds to patients included in the secondary (modified intention-to-treat) analysis.

(95% CI, 12.9-37.9) and 4.2 (95% CI, 1.2-10.8) per 100 person-years (difference, 18.8 [95% CI, 8.0-34.1] per 100 person-years) (TABLE 4). In contrast to the placebo group (in which none of the 17 patients with MRSA infections died), the mortality rate in V710 recipients was numerically higher in patients infected with MRSA (8/24 [33%; 95% CI, 16%-55%]) than with MSSA (7/49 [14%; 95% CI, 6%-27%]). Preoperative antibody responses were comparable among V710 recipients with postoperative *S aureus* infection whether they survived or died. In the overall subgroup with staphylococcal infection, 5 deaths were attributed to multiorgan failure, all of which occurred in V710 recipients.

Immunogenicity

Preliminary characterization of the clinical isolates indicated that the *isdB* gene was highly conserved, with more than 95% homology. Anti-IsdB IgG titers at the time of surgery in V710 vaccine recipients were consistently greater than the prevaccination baseline levels, indicating that the vaccine was immunogenic (eFigure 3). Furthermore, the antibody titers after receipt of V710 vaccine were significantly higher than after receipt of placebo. Antibody responses in V710 recipients who developed primary *S aureus* infections were comparable with the titers achieved in V710 recipients who did not develop *S aureus* infection. Geometric mean anti-IsdB IgG levels peaked near postoperative day 45 and then slowly but steadily declined.

The V710 vaccine induced a significant, albeit modest and transient, increase in functional antibodies. The geometric mean increase in antibody titer with opsonophagocytic activity from baseline was 2.5-fold (95% CI, 2.2-2.8) in the subset of 299 V710 recipients evaluated 14 to 60 days after vaccination (just prior to surgery) and 1.9-fold (95% CI, 1.6-2.2) in the 94 V710 recipients evaluated at postoperative day 90, but had decreased to 1.2-fold (95% CI, 1.0-1.3) in the 84 V710 recipients evaluated on postoperative day 360. The corresponding percentages of evaluable V710 recipients achieving at least a 4-fold increase in opsonophago-

Table 2. Primary and Sensitivity Efficacy Analyses of the Composite Primary End Point[a]

	V710 Vaccine Group				Placebo Group					
Prespecified Analyses	Patients With *S aureus* Bacteremia/Deep Sternal Wound Infection, No.	Vaccinated Patients, No.	Follow-up, y[b]	Event Rate (95% CI)[c]	Patients With *S aureus* Bacteremia/Deep Sternal Wound Infection, No.	Vaccinated Patients, No.	Follow-up, y[b]	Event Rate (95% CI)	Relative Risk (95% CI)[d]	Vaccine Efficacy[d]
Secondary modified ITT analysis (vaccinated patients with any cardiothoracic procedure)	23	3815	903.6	2.5 (1.6-3.8)	28	3832	908.5	3.1 (2.0-4.5)	0.83 (0.45-1.49)	17.9 (−47.9 to 54.8)
Primary modified ITT analysis (vaccinated patients with full median sternotomy on postvaccination day 14-60)[e]	22	3528	837.6	2.6 (1.6-4.0)	27	3517	836.6	3.2 (2.1-4.7)	0.81 (0.44-1.48)	18.5 (−48.6 to 55.8)
Supportive per-protocol analysis (vaccinated patients with full median sternotomy on postvaccination day 14-60 without major protocol violations)[e]	19	3456	822.2	2.3 (1.4-3.6)	26	3460	824.1	3.2 (2.1-4.6)	0.73 (0.38-1.38)	26.9 (−37.2 to 61.8)

Abbreviations: ITT, intention-to-treat; S aureus, *Staphylococcus aureus*.
[a] The prespecified primary end points were postoperative *S aureus* bacteremia and/or *S aureus* deep sternal wound infections through postoperative day 90.
[b] Total efficacy follow-up time (years) from date of surgery to the first *S aureus* infection or the end of the protocol-stipulated efficacy window (90 days after surgery).
[c] Absolute rate of *S aureus* bacteremia or deep sternal wound infection per 100 person years = (c/years) × 100, where *c* is the number of patients with *S aureus* bacteremia or deep sternal wound infection.
[d] Vaccine efficacy was calculated as $(1 - c_{V710}/c_{placebo}) \times 100\%$, where *c* is the number of patients with *S aureus* bacteremia or deep sternal wound infection, based on the number of cases in the V710 and placebo groups without regard to length of follow-up, as stipulated in the protocol and by regulatory agencies. To supplement the estimates of vaccine efficacy (which were based on the case split without regard to duration of follow-up), relative risks (which accounted for both the number of patients and length of follow-up time) were retrospectively computed for the key primary efficacy results. Because the length of follow-up was modestly different for the V710 and placebo groups, the relative risk reduction (1 − relative risk) closely approximates but does not exactly match the vaccine efficacy.
[e] Patients experiencing a serious preoperative *S aureus* infection were to be excluded from these analyses. There were 2 such cases in each group, but none of these 4 patients developed a subsequent postoperative *S aureus* end point event during the study.

cytic antibody titer at these 3 points were 29% (95% CI, 24%-35%) at 14 to 60 days, 17% (95% CI, 10%-26%) at 90 days, and 4% (95% CI, 1%-10%) at 360 days. In contrast to the V710 group, the change in baseline geometric mean titer for evaluable placebo recipients was not significantly different from 1 (indicating no meaningful increase) at any of the 3 measurement points, and only 3 (1%; 95% CI, 0%-4%) of the 241 placebo recipients evaluated 14 to 60 days after vaccination had at least a 4-fold increase in titer.

COMMENT

The development of a safe and effective vaccine against serious *S aureus* infections in high-risk populations would represent a major step forward, but continues to present unresolved challenges.[18-20] *Staphylococcus aureus* vac-

Table 3. Types and Frequencies of Adverse Experiences (AEs)

	V710 Vaccine Group (n = 3958)	Placebo Group (n = 3967)	Between-Group Difference (95% CI)[a]
Frequency of preoperative AEs during the 14-d postvaccination period, No. (%) [95% CI] of vaccinated patients with safety follow-up			
With any AE	1219 (30.8) [29.4-32.3]	866 (21.8) [20.6-23.1]	9.0 (7.0 to 10.9)
With vaccine-related AE[b]	821 (20.7) [19.5-22.0]	437 (11.0) [10.1-12.0]	9.7 (8.1 to 11.3)
With febrile reaction[c]	17 (0.4) [0.3-0.7]	29 (0.7) [0.5-1.0]	ND
With vaccine-related febrile reaction AE[b,c]	6 (0.2) [0.1-0.3]	13 (0.3) [0.2-0.6]	ND
With injection site AE[c]	797 (20.1) [18.9-21.4]	378 (9.5) [8.6-10.5]	10.6 (9.1 to 12.2)
With vaccine-related injection site AE[b,c]	760 (19.2) [18.0-20.5]	360 (9.1) [8.2-10.0]	10.1 (8.6 to 11.7)
With non–injection site AE	673 (17.0) [15.8-18.2]	602 (15.2) [14.1-16.3]	1.8 (0.2 to 3.4)
With vaccine-related non–injection site AE[b]	122 (3.1) [2.6-3.7]	111 (2.8) [2.3-3.4]	0.3 (−0.5 to 1.0)
With serious AE	66 (1.7) [1.3-2.1]	51 (1.3) [1.0-1.7]	0.4 (−0.2 to 0.9)
With serious vaccine-related AE[b]	0 [0.0-0.1]	0 [0.0-0.1]	0.0 (−0.1 to 0.1)
Who discontinued because of AE	0 [0.0-0.1]	0 [0.0-0.1]	0.0 (−0.1 to 0.1)
Who died of any cause	11 (0.3) [0.1-0.5]	6 (0.2) [0.1-0.3]	0.1 (−0.1 to 0.4)
Rate (%) [95% CI] per 100 person-years of AEs occurring anytime during the study[d]			
With serious vaccine-related AE[b]	1 (0.0) [0.0-0.2]	1 (0.0) [0.0-0.1]	0.0 (−0.1 to 0.1)
With serious AE who had a *Staphylococcus aureus* infection[e]	49 (1.4) [1.0-1.8]	57 (1.6) [1.2-2.1]	−0.2 (−0.8 to 0.4)
Who developed multiorgan failure[f]	31 (0.9) [0.6-1.2]	17 (0.5) [0.3-0.8]	0.4 (0.0 to 0.8)
Who died of any cause	201 (5.7) [4.9-6.5]	177 (5.0) [4.3-5.7]	0.7 (−0.4 to 1.8)

Abbreviation: ND, not done because per the protocol statistical analysis plan, risk differences not computed when there was less than 1% observed adverse experiences in either group.
[a] Differences (95% CIs) were calculated as the AE rate in the V710 group minus the AE rate in the placebo group, using the method of Miettinen and Nurminen.[15]
[b] Determined by investigator to be possibly, probably, or definitely vaccine-related.
[c] Injection site and febrile reactions were actively solicited for the 5-day period immediately following vaccination. Oral temperatures ≥38.0°C (≥100.4°F) were recorded during this period in 21 (0.6%) and 19 (0.5%) of the V710 and placebo groups, respectively.
[d] The follow-up time represents the number of days from vaccination to the date of either the first event (if the patient had an event) or the last day of study follow-up (if the patient did not have an event).
[e] Associated with (although not necessarily caused by) *S aureus* infection.
[f] Not prespecified per protocol but added after a safety signal was recognized during the second interim review. Nominal *P* value for the V710 group vs placebo group was *P*=.04.

Table 4. Analysis of Mortality and Multiorgan Failure in Patients With Postoperative *Staphylococcus aureus* Infections

	V710 Vaccine Group (n = 3815)				Placebo Group (n = 3832)				
	No. of Events		Total Follow-up Time, Person-Years[a]	Estimated Event Rate per 100 Person-Years (95% CI)[b]	No. of Events		Total Follow-up Time, Person-Years[a]	Estimated Event Rate per 100 Person-Years (95% CI)[b]	Rate Difference, (95% CI) per 100 Person-Years[b]
	Total	MRSA			Total	MRSA			
Patients with *S aureus* bacteremia or deep sternal wound infection	23	11			28	8			
Who died	7	4	19.6	35.7 (14.4-73.6)	2	0	25.7	7.8 (0.9-28.1)	28.0 (2.0-66.7)
Who died with multiorgan failure	3	2	20.2	14.9 (3.1-43.4)	0	0	25.9	0.0 (0.0-14.2)	14.9 (0.0-43.7)
Patients with any *S aureus* infection	73	24			96	17			
Who died	15[c]	8	65.2	23.0 (12.9-37.9)	4	0	94.4	4.2 (1.2-10.8)	18.8 (8.0-34.1)
Who died with multiorgan failure	5	2	65.9	7.6 (2.5-17.7)	0	0	94.5	0.0 (0.0-3.9)	7.6 (3.2-17.8)

Abbreviation: MRSA, methicillin-resistant *S aureus*.
[a] Follow-up time is the number of days from vaccination to the date of either the first event (if the participant had an event) or the last day of study follow-up (if the participant had no event).
[b] Estimated event rate=(total events/person-years)×100.
[c] The 1 additional V710 recipient with *S aureus* infection who died at the excluded site is not tabulated here. Inclusion of this patient would have yielded a mortality rate difference of 20.2 [9.2, 35.7] per 100 person-years.

cine candidates to date have been designed to elicit production of opsonic antibodies, but humoral immunity may be inadequate to prevent *S aureus* infections.[18-22] An earlier vaccine containing *S aureus* types 5 and 8 capsular polysaccharides conjugated to nontoxic recombinant *Pseudomonas aeruginosa* exotoxin A (StaphVAX, Nabi Biopharmaceuticals) appeared to confer limited short-term protection against *S aureus* bacteremia in patients undergoing hemodialysis for approximately 40 weeks after vaccination in a proof-of-concept study[21]; however, a larger clinical trial later failed to demonstrate any benefit.[22]

In our study of adult patients undergoing cardiothoracic surgery, preoperative vaccination with V710 did not significantly reduce the composite incidence of *S aureus* bacteremia and deep sternal wound infection. Because vaccination with V710 resulted in consistent humoral responses, the lack of efficacy was not simply due to failure to boost IgG levels against homologous IsdB. A numerical reduction in the number of end points in the vaccine group relative to the placebo group was seen during the early postoperative period when antibody titers were peaking, but these differences were not statistically significant. In a series of post hoc subgroup analyses uncorrected for multiple comparisons, vaccine efficacy was numerically higher against MSSA than MRSA infections, superficial than deep surgical site infections, and in baseline nasal *S aureus* carriers than in noncarriers, but the wide confidence intervals around these point estimates included zero. Overall mortality also did not significantly differ in the 2 groups. However, further analyses demonstrated that *S aureus*–infected V710 recipients were significantly more likely to die postoperatively than *S aureus*–infected placebo recipients. A higher mortality rate in infected V710 recipients relative to placebo recipients was evident among patients experiencing a primary end point (ie, bacteremia and/or deep sternal wound infection) as well as among patients developing any type of postoperative *S aureus* infection.

In the second planned interim analysis, multiorgan system failure in the postoperative period (as gauged by serious adverse event reporting) appeared to be associated with receipt of V710 vaccine. Since no protocol-prescribed criteria for multiorgan failure were available, the adverse event term could have been applied inconsistently at different study sites. Despite the post hoc nature of the many exploratory analyses, which were unadjusted for multiple comparisons, the consistency of the association between V710 and later development of multiorgan failure across multiple subgroups raises the possibility that the relationship may not simply be the result of chance alone.

A causal relationship linking receipt of V710 vaccine to higher rates of delayed multiorgan failure and mortality among *S aureus*–infected patients in this trial has not been established. MRSA infections, which have been associated with a higher mortality than MSSA surgical site infections,[23,24] were more common in the V710 group than the placebo group and potentially could have contributed in part to the observed higher mortality among V710 recipients. However, a clear mechanism by which the anti-IsdB antibody response induced by preoperative receipt of V710 could have aggravated the outcome of postoperative staphylococcal infections in our patients,[25-27] despite appearing safe and efficacious in the early clinical studies and preclinical models,[6-8] remains to be determined. The paradoxical finding of worse outcomes after receipt of a vaccine has been previously encountered.[28-32]

The role of humoral immunity in protecting against *S aureus* is incompletely understood.[33] For example, the presence of antibodies to the *S aureus* Panton-Valentine leukocidin has been associated with poor outcomes in a murine soft-tissue infection model.[34] Opsonophagocytic antibodies induced by V710 (if not accompanied by bacterial killing) could theoretically permit intracellular survival of *S aureus*,[35] potentially enhancing morbidity and mortality; however, the increase in opsonophagocytic activity observed after V710 administration was generally modest. Subsequent to termination of our study, the potential role of cell-mediated immunity in protection against *S aureus* infections has received increasing attention.[18,19,36-44]

In conclusion, the use of the V710 vaccine against *S aureus* did not reduce the rate of serious postoperative *S aureus* infections compared with placebo and was associated with increased mortality among patients who developed *S aureus* infections. These findings do not support the use of the V710 vaccine for patients undergoing surgical interventions.

Author Affiliations: Duke University Medical Center and Duke Clinical Research Institute, Durham, North Carolina (Drs Fowler and Corey); St Luke's Mid-America Heart and Vascular Institute, Kansas City, Missouri (Dr Allen); Division of Cancer Epidemiology, McGill University, Montreal, Quebec, Canada (Dr Moreira); Associação Obras Sociais Irmã Dulce- Oswaldo Cruz Foundation, Brazilian Ministry of Health, Salvador, Bahia, Brazil (Dr Moreira); South Carolina Nephrology and Hypertension Center, Orangeburg (Dr Moustafa); Academic City Hospital Ludwigshafen, Ludwigshafen, Germany (Dr Isgro); Tufts Medical Center (Dr Boucher) and Beth Israel Deaconess Medical Center (Dr Carmeli), Boston, Massachusetts; University of Rochester School of Medicine, Rochester, New York (Dr Betts); Merck Sharp & Dohme, Whitehouse Station, New Jersey (Drs Hartzel, Chan, McNeely, Kartsonis, Guris, Smugar, DiNubile, and Sobanjo-ter Meulen and Mr Onorato).

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Study concept and design: Fowler, Allen, Hartzel, Chan, Kartsonis, Onorato, DiNubile.
Acquisition of data: Fowler, Allen, Moreira, Moustafa, Isgro, Boucher, Corey, Carmeli, Betts, McNeely.
Analysis and interpretation of data: Fowler, Allen, Moreira, Boucher, Corey, Carmeli, Betts, Hartzel, McNeely, Kartsonis, Guris, Smugar, Onorato, DiNubile, Sobanjo-ter Meulen.
Drafting of the manuscript: Fowler, Allen, Hartzel, Onorato, DiNubile, Sobanjo-ter Meulen.
Critical revision of the manuscript for important intellectual content: Fowler, Allen, Moreira, Moustafa, Isgro, Boucher, Corey, Carmeli, Betts, Hartzel, Chan, McNeely, Kartsonis, Guris, Smugar, Onorato, DiNubile, Sobanjo-ter Meulen.
Statistical analysis: Hartzel, Chan.
Administrative, technical, or material support: Boucher, McNeely, Guris, Onorato, Smugar, DiNubile, Fowler.
Study supervision: Kartsonis, Guris, Onorato, Sobanjo-ter Meulen.
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V710 Protocol 003 Principal Investigators: *Austria:* Martin Grabenwoeger; *Belgium:* Paul Herijgers, Philippe Kolh; *Brazil:* Cely Saad Abboud, Luiz Carlos Bodanese, Renato Kalil, Maria Patelli Lima, Edson Duarte Moreira Jr, Eliana Lima Bicudo dos Santos, Tania Mara Strabelli, Flavio Queiroz Telles; *Chile:* Francisco Arancibia, Michael Howard, Luis Sepulveda; *Colombia:* Alvaro Ignacio Arango, Victor Raul Castillo, Alejandro Escobar; *Denmark:* Peter Skov Olssen; *Finland:* Kalervo Werkkala; *France:* Bernard Albat, Christian Auboyer, Laurent Barandon, Laurent Beydon, Lionel Camilleri, Hervé Dupont, Roland Henaine, Marc Laskar, Jean-Luc Mainardi, Pascal Menestret, Fabrice Vanhuyse; *Germany:* Manju Guha, Gerhard F. Hauf, Christian Hengstenberg, Frank Isgro, Arndt H. Kiessling, Alexandros Paraforos, Ali Peivandi, Gerhard Walterbusch; *Guatemala:* Luis Velasquez; *Ireland:* Mark DaCosta; *Italy:* Elvio Covino, Ruggero DePaulis, Francesco Musumeci, Gian Federico Possati; *Japan:* Shuhei Azuma, Joji Hoshino, Hiroshi Iida, Toshiaki Ito, Hiromi Kurosawa, Hidenori Sako, Kazuyoshi Tajima, Toshifumi Takeuchi, Imun Tei, Fumio Yamazaki, Kenji Yamazaki, Hideo Yoshida; *Korea:* Hyuk Ahn, Byung-Chul Chang, Kun Jik Kim, Kyong Ran Peck; *Malaysia:* Venugopal Balchand, Kui Hian Sim; *Mexico:* Luis Humberto Gomez, Reynaldo Jimenez, Jesus Octavio Martinez-Reding; *New Zealand:* Shay McGuinness; *Norway:* Rune Haaverstad, Asbjørn Karevold; *Peru*: Hector Bedoya, Carlos Cerron, Jaime Ulloa; *Russia:* Olga Barbarash, Vladimir V. Lomivorotov, Natalia G. Mezentseva, Viktor F. Mordovin, Iliya Staroverov, Alexander V. Troitskiy; *Singapore:* Chong Hee Lim; *Spain:* Benito Almirante; Emilio Bouza Santiago, Angel Fernandez Gonzalez, Juan José Goiti-Unibaso, Jose Maria Gonzalez Santos, Jesus Herreros Gonzalez, Eduardo Otero, Jose Luis Pomar, Guillermo Reyes-Copa, Jesus Rodriguez-Bano, Jacobo Silva-Guisasola; *Sweden:* Gunnar Engstrom, Ulf Kjellman, Dan Lindblom, Jan Thorelius; *Taiwan:* Jiun-Yi Li, Chien-Sung Tsai, Shoei-Shen Wang; *United Kingdom*: Christopher Blauth, Frank Y. Lie, Tom J. Spyt, Catherine Sundarshan; *United States*: David Affleck, Lishon Aklog, Edmund Alexander, Keith B. Allen, Michael Argenziano, Joseph S. Auteri, Robert F. Betts, Steven W. Boyce, Emmanouil Brilakis, Martha I. Buitrago, David Caparrelli, Paul Carson, Thomas L. Carter Jr, Alfred Casale, Thomas D. Christopher, Michael Climo, Clarence B. Creech, Harry D'Agostino, Ralph Damiano Jr, Bruce Darrow, R. Duane Davis, Ramzi K. Deeik, Barry Charles Esrig, Michael Firstenberg, Tim Alexander Fischell, James S. Gammie, Mauricio J. Garrido; Ralf E. Gebhard, Eliot W. Godofsky, Kamal M. F. Itani, Paul Kanaly, James Keegan, Junaid Khan, Michael Lazar, Kwan S. Lee, John Lucke, Steven Kent Macheers, Jeffery C. Milliken, Sang (Alex) H. Na, Richard A. Nathan, Rathel L. Nolan, Steven D. Owens, Timothy L. Pansegrau, Brenda Peart, Eric Peck, Chand Ramaiah, John F. Reinhardt, Anthony J. Rongione, Todd Rosengart, Thomas G. Sharp, Patrick J. Simpson, David Spielvogel, Stephen A. Tahta, Antone Tatooles, Richard Thompson, James C. Todd, Jeffery Veluz, Michael Wait, Peter Walts, Daniel R. Watson, John B. Weiss, J. Alan Wolfe, Duane G. Wombolt, James K. Wu, James L. Zellner. *Data Monitoring Committee:* Adolf W. Karchmer, MD (Harvard Medical School), Kyung Mann Kim, PhD (University of Wisconsin–Madison), William Schaffner, MD (Vanderbilt University School of Medicine), Sara E. Cosgrove, MD, MS (Johns Hopkins Medical School). *Efficacy Endpoint Adjudication Committee:* Helen W. Boucher, Ralph Corey, Yehuda Carmeli.

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