Supplement to

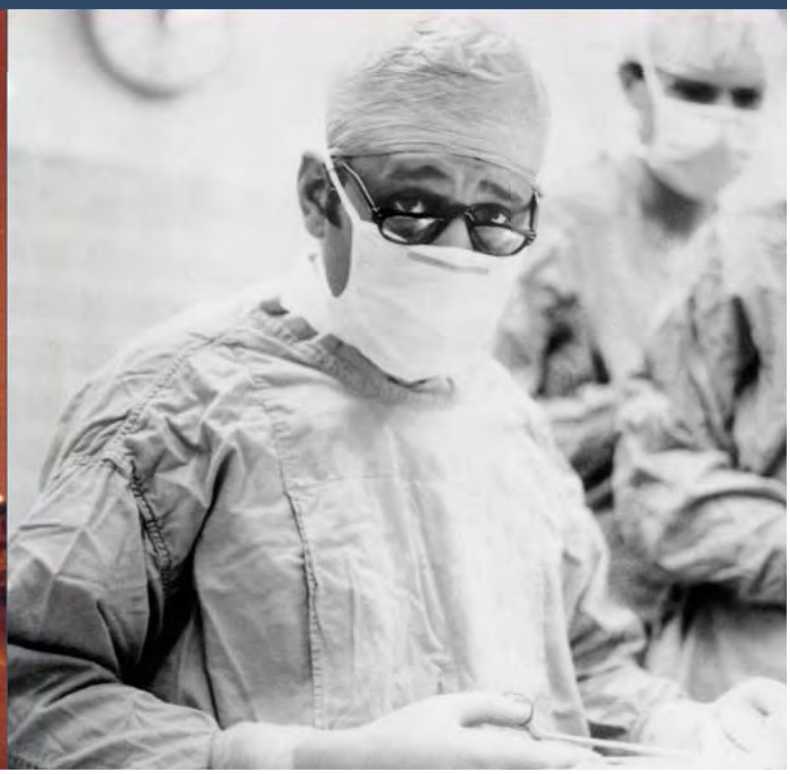
CLEVELAND CLINIC JOURNAL OF MEDICINE

VOLUME 84 | SUPPLEMENT 4 | DECEMBER 2017 | www.ccjm.org

Selected presentations from

Sones/Favaloro Scientific Program

Transforming the delivery of cardiovascular care: Research and innovation in the Heart & Vascular Institute



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Transforming the delivery of cardiovascular care: Research and innovation in the Heart & Vascular Institute

Supplement Editor

Umesh Khot, MD
Heart & Vascular Institute
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Cover art: Cleveland Clinic cardiologist F. Mason Sones, MD, who in 1958 launched the modern era of heart disease diagnosis using coronary angiography (left) and Rene Favaloro, MD, who in 1967 conducted the first documented successful coronary artery bypass surgery using a saphenous vein (right).

Cleveland Clinic Journal of Medicine [ISSN 0891-1150 (print), ISSN 1939-2869 (online)] is published monthly by Cleveland Clinic.

STATEMENTS AND OPINIONS expressed in this supplement to the *Cleveland Clinic Journal of Medicine* are those of the authors and not necessarily of Cleveland Clinic or its Board of Trustees.

SUBSCRIPTION RATES: U.S. and possessions: personal $145; institutional $173; single copy/back issue $20. Foreign: $190; single copy/back issue $20. Institutional (multiple-reader rate) applies to libraries, schools, hospitals, and federal, commercial, and private institutions and organizations. Individual subscriptions must be in the names of, billed to, and paid by individuals.

SUBSCRIPTIONS, EDITORIAL, BILLING/ACCOUNTING, AND PRODUCTION:
Cleveland Clinic Journal of Medicine, 1950 Richmond Road, TR4-04, Lyndhurst, OH 44124
Phone (216) 444-2661 • **Fax** (216) 444-9385 • **E-mail** ccjm@ccf.org • www.ccjm.org

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Results of the GLAGOV trial

ABSTRACT

Statins therapy reduces atheroma in proportion to the reduction of low-density lipoprotein cholesterol (LDL-C). Proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors are a new class of injectable human monoclonal antibodies shown to lower LDL-C when added to statin therapy. In a randomized, double-blind, placebo-controlled study, 968 patients with symptomatic coronary artery disease were treated with statins alone or combined with the PCSK9 inhibitor, evolocumab, and assessed for change in percent, total volume, and regression of coronary atheroma. Treatment with statins plus evolocumab achieved mean LDL-C levels of 36.6 mg/dL, produced atheroma regression with a mean change in percent of atheroma volume of about 1% ($P < .001$), and induced regression in a greater percentage of patients. The clinical benefits of LDL-C as low as 20 mg/dL shown in this trial warrant further investigation.

KEY POINTS

Statin therapy achieves regression of atherosclerosis in proportion to reductions in LDL-C.

PCSK9 inhibitors are a new class of injectable human monoclonal antibodies shown to lower LDL-C when added to statin therapy.

Treatment with statins plus the PCSK9 inhibitor, evolocumab, achieved mean LDL-C levels of 36.6 mg/dL, atheroma regression, and demonstrated clinical benefit for LDL-C as low as 20 mg/dL.

Intravascular ultrasonography (IVUS) has been used for the past 20 years to measure atheromatous plaque in patients with coronary artery disease. The total volume of atherosclerosis in a coronary artery segment can be calculated using IVUS. A rotating transducer produces an image of a single, cross-sectional slice of the artery from which the atheroma area is calculated. A motorized device is used to withdraw the catheter, obtaining a series of cross-sectional slices at 1-mm intervals. The atheroma area for each slice is summated to obtain the total volume of atherosclerosis in the artery.

IVUS has demonstrated that statins slow the progression or even induce regression of coronary atherosclerosis in proportion to the degree of reduction in low-density lipoprotein cholesterol (LDL-C).[1–4] No LDL-C-lowering therapy other than statins has shown regression of atherosclerosis in a trial using IVUS. The lowest LDL-C achieved in prior trials using statins was about 60 mg/dL.[1,3] While this is very low, lower levels have not previously been explored.

Proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors, a new class of drugs, are injectable, fully human monoclonal antibodies that inactivate the PCSK9 protein. PCSK9 inhibitors have been shown to lower LDL-C incrementally when added to statins, achieving very low LDL-C levels.[5,6] However, no data exist describing the effect of low LDL-C levels reached using PCSK9 inhibitors on the progression of atherosclerosis.

THE GLAGOV TRIAL

The Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound (GLAGOV) trial assessed the effect of

This article is based on Drs. Nissen's and Nicholls's presentation at the Sones/Favaloro Scientific Program, "Transforming the Delivery of Cardiovascular Care: Research and Innovation in the Heart & Vascular Institute," held in Cleveland, OH, November 18, 2016. It was also presented at the American Association for Thoracic Surgery. The article was drafted by *Cleveland Clinic Journal of Medicine* and was then reviewed, revised, and approved by Drs. Nissen and Nicholls.

Dr. Nissen reported research/grant support for the Cleveland Clinic Center for Clinical Research to perform clinical trials from AbbVie, AstraZeneca, Amgen, Cerenis Therapeutics, Eli Lilly, Esperion, Pfizer, The Medicines Company, Takeda, and Orexigen Therapeutics. Dr. Nissen is involved with these multicentered clinical trials, but receives no personal remuneration for his participation. Dr. Nissen consults for many pharmaceutical companies but requires them to donate any honoraria or consulting fees directly to charity so that he receives neither income nor a tax deduction. Dr. Nicholls reported research grant support and consulting fees from Amgen, Sanofi, and Regeneron.

doi:10.3949/ccjm.84.s4.01

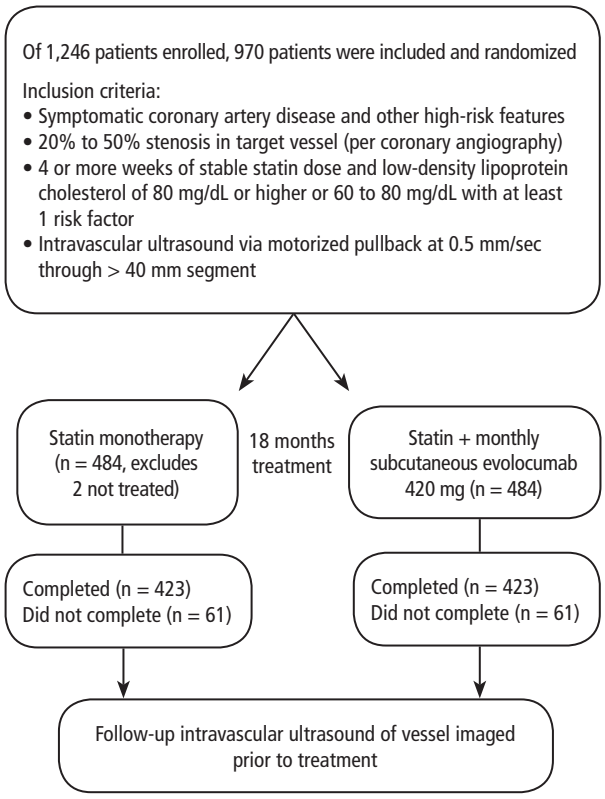


Figure 1. GLAGOV trial design.

Based on information from reference 7.

PCSK9 inhibitor therapy on coronary atheroma.[7] The primary end point was the change in percent atheroma volume (PAV) after treatment, and secondary end points were the change in total atheroma volume and percent of patients with atheroma regression. This randomized, double-blind, placebo-controlled study included 968 patients with symptomatic coronary artery disease and other high-risk features from 197 centers around the world. Patients had a coronary angiogram with a vessel that contained an intermediate stenosis and received statin therapy for at least 4 weeks and had LDL-C levels greater than 80 mg/dL or 60 to 80 mg/dL with additional high-risk features. Following IVUS, patients were randomized for 18 months of treatment with either a statin alone or a statin plus a monthly injection of the PCSK9 inhibitor evolocumab. At the end of treatment, IVUS was performed in the same artery that we imaged at the beginning of the study (**Figure 1**).

Table 1 shows the patients' baseline demographic features and statin use. The average age of patients was 60 and almost all were on statin therapy, with most taking high levels of high-intensity statins. Baseline

TABLE 1
Baseline patient demographics and statin use

Characteristic	Statin monotherapy (n = 484)	Statin plus evolocumab (n = 484)
Age, mean	59.8	59.8
Male gender	350 (72.3%)	349 (72.1%)
BMI mean kg/m^2	29.5	29.4
Diabetes	104 (21.5%)	98 (20.2%)
Smoking	113 (23.3%)	124 (25.6%)
Statin use	476 (98.3%)	478 (98.8%)
High intensity	290 (59.9%)	280 (57.9%)
Moderate intensity	185 (38.2%)	196 (40.5%)
Low intensity	1 (0.2%)	2 (0.4%)
LDL-C, mean mg/dL	92.4	92.6

BMI = body mass index; LDL-C = low-density lipoprotein cholesterol

Based on information from reference 7.

LDL-C was very good at 92 mg/dL to 93 mg/dL, a level that would be considered good control by contemporary standards.

RESULTS

LDL-C levels

After 18 months of treatment, patients receiving statin monotherapy had a mean LDL-C of 93 mg/dL, which was essentially unchanged from the start of the study. Patients receiving statin therapy with the addition of the PCSK9 inhibitor evolocumab had a mean LDL-C of 36.6 mg/dL and a trough level of 29 mg/dL 2 weeks after dosing (**Figure 2**). To our knowledge, these are the lowest LDL-C levels that have ever been achieved in a major trial at the time.

Change in percent atheroma volume

With respect to the primary end point of change in PAV, patients on statin monotherapy had neither progression nor regression, and the percent change from baseline was not statistically significant (**Figure 3**). However, patients receiving the addition of the PCSK9 inhibitor had a statistically significant change in PAV of –0.95% ($P < .001$); they had less plaque at the end of the 18-month trial than at the start.

Polynomial regression analysis was used to evaluate the relationship between the achieved LDL-C levels and the rate of atheroma progression. Starting at an LDL-C of 110 mg/dL to 20 mg/dL, there was a linear

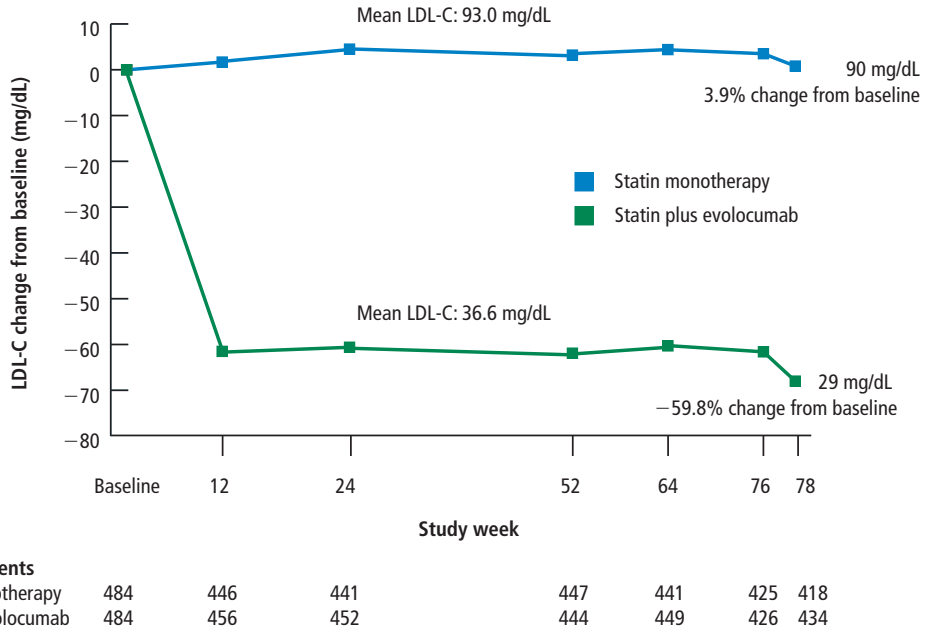


Figure 2. Change in LDL-C for statin monotherapy and statin + evolocumab treatment arms. LDL-C = low-density lipoprotein cholesterol

relationship between lower LDL-C and less atheroma progression (**Figure 4**). This striking relationship was a uniform benefit across the full population and held for virtually every subgroup including by age, sex, baseline non-high-density lipoprotein cholesterol, diabetes presence or absence, and intensity of statin therapy.

Total atheroma volume and percent of patients with atheroma regression

The secondary end point measuring the total atheroma volume in the coronaries showed no change in total volume of atherosclerotic plaque in the statin monotherapy group and a decrease in the statin plus evolocumab group.

An additional secondary end point was the percent of patients with atheroma regression, defined as any decrease in total atheroma volume or PAV. The percent of patients with total atheroma volume regression was greater in the statin plus evolocumab group (61.5%) than in the monotherapy group (48.9%; $P < .001$). PAV regression was also greater in patients in the statin plus evolocumab group (64%) compared with patients in the statin monotherapy group (47%; $P < .001$) (**Figure 5**). It is important to note that atheroma regression cannot occur in all patients, as other factors drive atherosclerotic disease, but the high percentage of patients with manifest coronary disease experiencing regression in this study is encouraging.

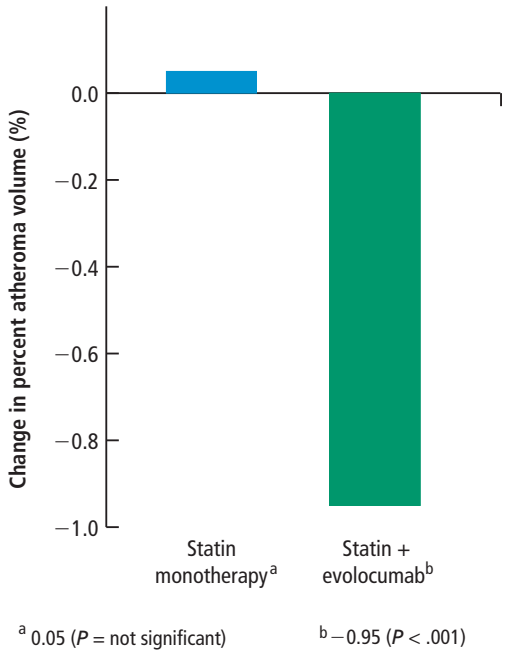


Figure 3. Change in percent atheroma volume from baseline.

Based on information from reference 7.

Patients with LDL-C < 70 mg/dL

A subgroup of patients had a baseline LDL-C below 70 mg/dL, the lowest level recommended by guideline. Patients in this subgroup who received statin

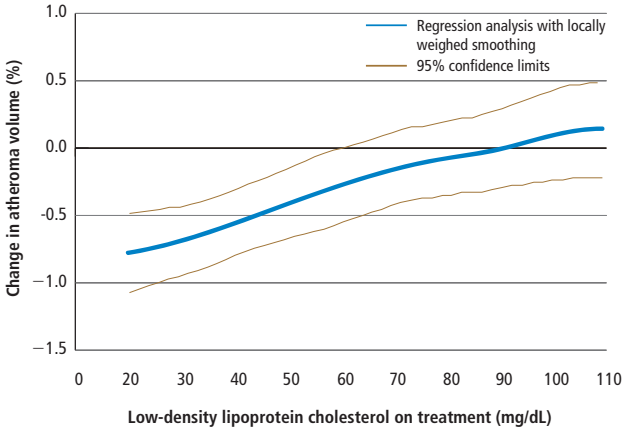
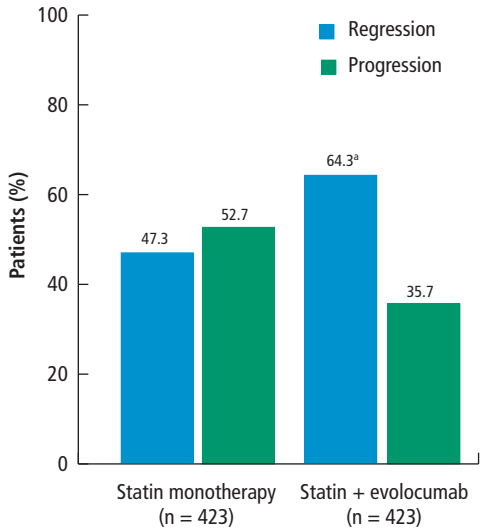


Figure 4. Relationship between achieved low-density lipoprotein cholesterol levels and change in atheroma volume.



[a]*P* < .001 for comparison to statin monotherapy group.

Figure 5. Percent of patients with regression or progression of percent atheroma volume.

Based on information from reference 7.

monotherapy remained at a mean LDL-C of 70 mg/dL whereas patients on statin plus evolocumab achieved a mean LDL-C of 24 mg/dL with a mean 2-week post-dosing trough level of 15 mg/dL, an unbelievably low level of LDL-C. In this subgroup, 81% of patients receiving statin plus evolocumab had atheroma regression, compared with 48% of patients in the statin monotherapy group. The percent of patients with atheroma regression in this subgroup of patients with low LDL-C at baseline was twice that seen in the larger study population (33% vs 17%), revealing profound levels of regression in patients treated with dual therapy.

TABLE 2
Percent of patients with adverse events and safety findings

Event	Statin monotherapy (n = 484)	Statin plus evolocumab (n = 484)
Death	4 (0.8%)	3 (0.6%)
Nonfatal myocardial infarction	14 (2.9%)	10 (2.1%)
Nonfatal stroke	3 (0.6%)	2 (0.4%)
Hospitalized or unstable angina	4 (0.8%)	3 (0.6%)
Coronary revascularization	66 (13.6%)	50 (10.%3)
First major cardiovascular event	74 (15.3%)	59 (12.2%)
Injection site reactions	0	0.4
Antievolocumab binding antibody	NA	1 (0.2%)
Neutralizing antibodies	NA	0
Neurocognitive events	6 (1.2)%	7 (1.4%)
New-onset diabetes	18 (3.7%)	17 (3.6%)
Myalgia	28 (5.8%)	34 (7.0%)

NA = not available

Based on information from reference 7.

Safety

Many people have expressed concerns about adverse effects of very low cholesterol levels. While this study was too small to evaluate morbidity and mortality, the rates of death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, and coronary vascularization trended in a favorable direction (**Table 2**). Essentially, no safety findings of any significance were reported in patients treated to these extremely low LDL-C levels.

Limitations

Like all trials, this one has limitations. The population is very select: these are patients with clinically indicated angiogram, not a primary prevention population. Some study participants dropped out, which is always a limitation. And of course, this is a sur-

rogate measure; it is a measure of disease activity, not a measure of morbidity and mortality. Morbidity and mortality data for this new class of drugs should be available in about a year, though this study suggests that those data will be favorable.

CONCLUSION

High LDL-C is universally accepted as a factor in the formation of arterial plaque and atherosclerosis. Statin therapy reduces LDL-C levels to slow or induce regression of coronary atherosclerosis in proportion to the magnitude of LDL-C reduction as measured by IVUS. However, the question of how far to reduce lipid levels has evolved over the last 4 decades. In the 1970s, a normal total cholesterol was < 300 mg/dL. More recent data that suggest optimal LDL-C levels for patients with coronary artery disease may be much lower than commonly achieved.

In this study, in patients with symptomatic coronary artery disease, treatment with statins and the addition of the PCSK9 inhibitor evolocumab achieved mean LDL-C levels of 36.6 mg/dL, produced atheroma regression with a mean change in PAV of about 1% ($P < .001$), induced regression in a greater percentage of patients, and showed incremental benefit for treatment of LDL-C down to as low as 20 mg/dL. The GLAGOV trial provides intriguing evidence that clinical benefits may extend to LDL-C levels as low as 20 mg/dL; however, the sample size of the trial was modest, providing limited power for safety assessments.

Since this presentation, the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial achieved a median LDL-C of 30 mg/dL and reduced risk of cardiovascular events in patients with atherosclerotic cardiovascular disease treated with evolocumab added to statin therapy.[8] Additional large outcomes trials of PCSK9 inhibitors and their role in reducing LDL-C and regression of coronary atheroma and atherosclerosis are eagerly awaited.

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Trends in cardiovascular risk profiles

ABSTRACT

Outcomes for patients with coronary artery disease (CAD) have improved in the past 20 years likely due to advances in clinical care such as angiotensin-converting enzyme inhibitors, antiplatelet agents, and reduced time to cardiac cauterization procedures. But how have the risk factors for CAD changed in the past 2 decades? Analysis of nearly 4,000 patients with ST-elevation myocardial infarction (STEMI) at a tertiary care center found that patients presenting with acute STEMI are younger and more obese than in the past. The prevalence of smoking, hypertension, and diabetes mellitus is also increasing. Primary and secondary prevention and aggressive efforts to modify risk factors for CAD is essential for further improvement in cardiovascular outcomes.

KEY POINTS

Advances in treatment of CAD have improved patient outcomes over the past 20 years.

Prevalence of risk factors for CAD has increased over the past 20 years in patients presenting with STEMI with patients now more likely to be younger and with higher prevalence of smoking, obesity, hypertension, and diabetes.

Emphasis on primary and secondary prevention to reduce CAD risk factors is needed to improve outcomes and reduce the cost of care.

This article is based on Dr. Kapadia's presentation at the Sones/Favaloro Scientific Program, "Transforming the Delivery of Cardiovascular Care: Research and Innovation in the Heart & Vascular Institute," held in Cleveland, OH, November 18, 2016. The article was drafted by *Cleveland Clinic Journal of Medicine* and was then reviewed, revised, and approved by Dr. Kapadia.

Dr. Kapadia reported no financial interests or relationships that pose a potential conflict of interest with this article.

doi:10.3949/ccjm.84.s4.02

Many clinical improvements in treating patients with acute ST-elevation myocardial infarction (STEMI) have been realized in the past 20 years, including angiotensin-converting enzyme inhibitors, antiplatelet agents, and reduced time to cardiac cauterization procedures for acute myocardial infaction.[1] Presumably, primary and secondary prevention measures have also resulted in changes in coronary artery disease (CAD) risk factors over the past 20 years. We sought to quantify mortality outcomes for patients treated in our catherization laboratory and to investigate trends in cardiovascular risk factors in patients during the same period.[2]

STEMI OUTCOMES

Data from our catherization laboratory database of 3,913 patients treated for STEMI at our tertiary care center from 1995 through 2014 were analyzed. To evaluate outcomes over time, patients were grouped based on years treated in 5-year increments resulting in 4 groups spanning 20 years.[2]

Analysis showed reduced mortality rates for patients with STEMI over the past 20 years: the 30-day mortality rate in patients treated from 2010 to 2014 was 7.8%, nearly half the rate of 14% in patients treated from 1995 to 1999. The trend in reduced mortality rates for patients with STEMI was also noted at 1 year and 3 years (**Figure 1**).[3]

CARDIOVASCULAR RISK FACTORS

A reduction in mortality rates in patients treated for STEMI is to be expected over time, given the improvements in clinical practices and procedures and novel medications developed since 1996. But it is also possible that patients presenting with STEMI are healthier than in the past as a result of primary prevention efforts to minimize CAD risk factors and changes in CAD risk factors over time.

To determine whether CAD risk factors have changed over time, we analyzed the risk factors in

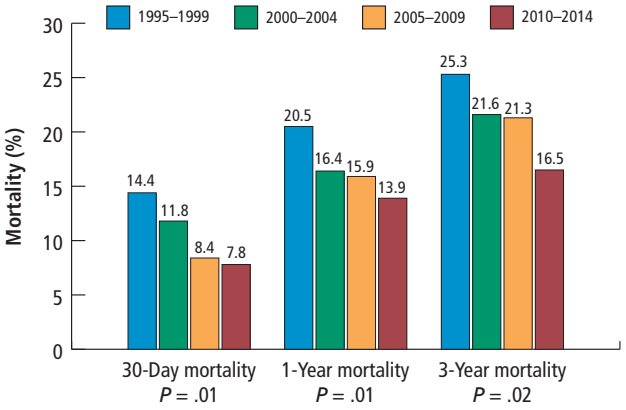

Figure 1. Rates of 30-day, 1-year, and 3-year mortality for patients treated for ST-elevation myocardial infarction.

Reprinted from the American Journal of Cardiology (Mentias A, et al. Effect of shorter door-to-balloon times over 20 years on outcomes of patients with anterior ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. Am J Cardiol 2017; Jul 24. doi:10.1016/j.amjcard.2017.07.006.

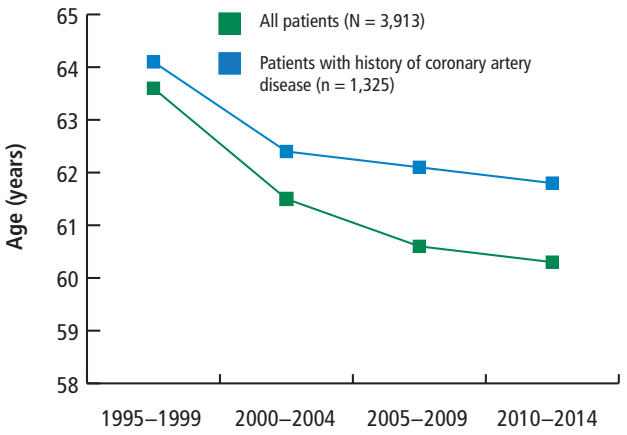

Figure 2. Patient age at presentation with ST-elevation myocardial infarction.

Based on data from reference 2.

the 3,913 patients treated for STEMI in our database. Risk factors included in the analysis were:

- Age
- Sex
- Diabetes mellitus
- Hypertension
- Smoking
- Hyperlipidemia
- Chronic renal impairment (serum creatinine greater than 1.5 mg/dL)
- Obesity (body mass index greater than 30 kg/m^2).[2]

The prevalence of risk factors was determined in the entire cohort as well as in the 34% (n = 1,325) of patients previously diagnosed with CAD. The trend in risk factors in patients previously diagnosed with CAD could indicate the effectiveness of secondary prevention efforts compared with primary prevention in the broader patient population.

Results show that the average age of patients presenting with STEMI has decreased from 64 to 60 over the past 20 years, and the trend is consistent regardless of a history of CAD (**Figure 2**).[2]

The prevalence of the cardiovascular risk factors of tobacco use, obesity, hypertension, and diabetes in patients with STEMI increased from 1995 to 2014, as well as patients with a history of CAD (**Figure 3**).[2]

These data suggest that despite a better understanding of cardiovascular risk factors, the cardiovascular risk profiles of patients with acute STEMI have deteriorated over the past 20 years: patients are younger at presentation and more likely to be obese, to smoke, and to have hypertension and diabetes. These trends hold true in patients with and without a history of CAD, suggesting primary and secondary prevention efforts are ineffective.

TRENDS IN THE UNITED STATES

To evaluate whether geographic or patient population characteristics could have biased our results, we analyzed mortality and risk factor data from the National (Nationwide) Inpatient Sample (NIS) for patients presenting with STEMI (N = 445,319), non-STEMI (N = 915,341), and stroke (N = 937,425) from 2003 to 2013.[4,5]

Mortality rates

Consistent with the trend in our data, the 10-year NIS data showed a lower mortality rate in 2003 compared with 2013 in patients admitted with extreme-severity STEMI (22% vs 18%), non-STEMI (13% vs 8%), and stroke (15% vs 10%), as well as in patients with moderate-severity disease.[4]

Risk factors

NIS data also revealed a reduction in the percentage of patients age 75 and older admitted for STEMI, non-STEMI, and stroke consistent with younger age at presentation and an increased prevalence of CAD risk factors from 2003 to 2013 (**Table 1**).[4] The percentage of female patients admitted is also decreasing, indicating the increasing prevalence of these conditions in males.

Unfortunately, the prevalence of these relatively preventable CAD risk factors is moving in the wrong direction. The prevalence of smoking in patients presenting with non-STEMI, STEMI, or acute stroke is

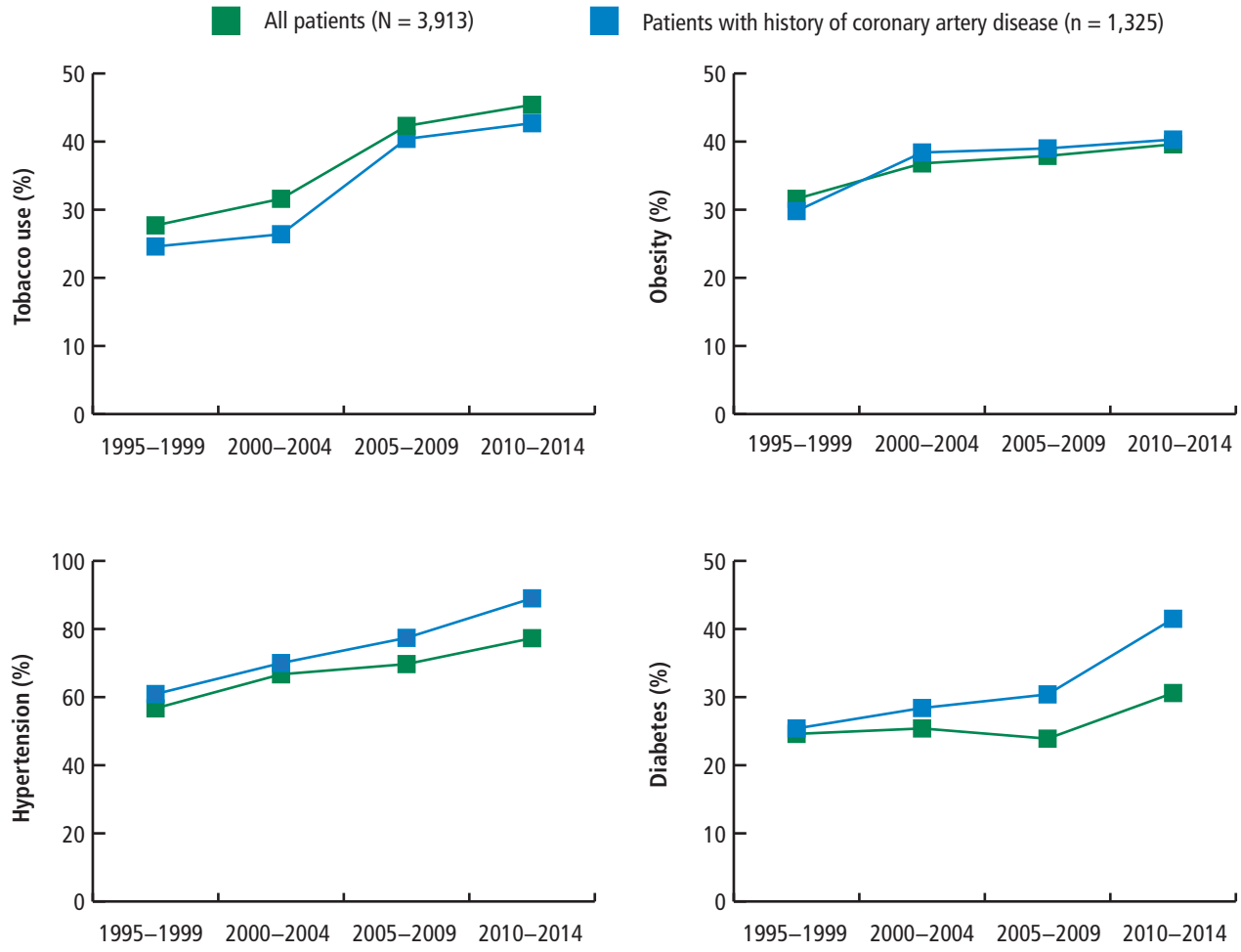

Figure 3. Prevalence of risk factors in patients presenting with ST-elevation myocardial infarction over time.

Based on data from reference 2.

higher than in the past, contrary to the nationwide trend of decreasing rates of smoking.[6] The increased rate of obesity evident in our data and the NSI data is consistent with rising obesity rates in the United States, which went from 30% to 37% in adults and from 14% to 17% in youth from 2000 to 2014.[7] The percentage of adults with diabetes has increased tremendously in the United States, from 4.4% of adults in 1994 to 9.1% of adults in 2015.[8] The rise in diabetes has led to increased rates of CAD, heart disease, and stroke in patients with diabetes.[9]

OPPORTUNITIES AHEAD

Despite improved STEMI outcomes, trends in cardiovascular risk profiles are deteriorating, emphasizing the critical need to educate people about primary and secondary prevention. Folsom et al[10] conducted an analysis of a community-based sample to determine the prevalence of ideal cardiovascular health based on 4 ideal health behaviors (nonsmoking, low body mass index, adequate physical activity, healthy diet) and 3 ideal risk health factors (total cholesterol, blood pressure, and moderate glucose control).[10] Each of the 7 behavior and risk factors was defined by ideal, intermediate, and poor characteristics. Very few study participants (0.1%) had ideal levels for all 7 healthy cardiovascular behaviors and risk factors, and over 82% had poor levels for all 7 behaviors and characteristics. The need to educate and improve cardiovascular health exists for both adults and youth. Measures of cardiovascular health in the United States indicate that 18% of adults age 50 or older and 46% of youth (ages 12 to 19) have 5 or more of the 7 health cardiovascular behaviors and risk factors at ideal levels.[11]

Improvement in primary and secondary prevention measures may also present opportunities to contain or reduce the cost of care. Thus far, according to NIS registry data from 2003 to 2013, the mean adjusted cost of hospitalization for patients with STEMI increased about 14%, remained about the same for patients with non-STEMI, and increased about 3% for patients with stroke.[4]

TABLE 1
Percent of patients admitted in 2003 and 2013 with ST-elevation MI, non-ST-elevation MI, and stroke by age, risk factor, female sex, and uninsured status

	STEMI (N = 445,319)		NSTEMI (N = 915,341)		Stroke (N = 937,425)	
	2003	2013	2003	2013	2003	2013
Age > 75 (%)	28	21	43	37	50	44
Smoking (%)	30	47	20	39	14	31
Obesity (%)	7	15	7	17	4	11
Hypertension (%)	50	65	60	76	72	83
Diabetes (%)	24	29	33	41	30	37
Hyperlipidemia (%)	37	63	36	65	26	57
Female (%)	36	32	44	40	55	51
Uninsured (%)	6	10	3	6	3	5

NSTEMI = non-ST-elevation myocardial infarction (MI); STEMI = ST-elevation myocardial infarction

Data from reference 4.

CONCLUSION

Advances in clinical care have improved outcomes for patients with CAD during the past 2 decades. These gains have come despite a higher prevalence of CAD risk factors in patients. More emphasis on primary and secondary prevention to reduce CAD risk factors may further improve outcomes and possibly lower the cost of care. Aggressive encouragement of risk factor modification is necessary and should go beyond cardiologists to include primary care physicians, preventive clinics, secondary cardiovascular prevention, and population-based efforts.

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Expanding indications for TAVR: The preferred procedure in intermediate-risk patients?

ABSTRACT

Transcatheter aortic valve replacement (TAVR) has steadily replaced surgical aortic valve replacement (SAVR) in symptomatic patients with severe aortic stenosis, primarily those at high risk for surgical complications. As TAVR use increases, spurred by technological advances in valve design and patient preferences for the less-invasive procedure, studies have provided data supporting the efficacy and safety of TAVR. Recently, TAVR has expanded to intermediate-risk patients, increasing the potential patient population. Although emerging evidence supports its use in lower-risk patients, some adverse events may limit its adoption in a wider patient population. These include stroke, paravalvular leak, valve durability, valve thrombosis, and need for pacemaker replacement. Ongoing clinical trials are expected to provide answers.

KEY POINTS

TAVR has become the preferred alternative to SAVR in inoperable and high-risk patients.

The US Food and Drug Administration has approved TAVR valves for use in patients with aortic valve stenosis who are at intermediate risk of morbidity or mortality associated with open-heart surgery.

Initial outcomes support expanding TAVR to intermediate-risk patients, including mortality and stroke data, but concerns exist related to valve durability, valve thrombosis, and rates of permanent pacemaker implantation.

This article is based on Dr. Brown's presentation at the Sones/Favaloro Scientific Program, "Transforming the Delivery of Cardiovascular Care: Research and Innovation in the Heart & Vascular Institute," held in Cleveland, OH, November 18, 2016. The article was drafted by *Cleveland Clinic Journal of Medicine* and was then reviewed, revised, and approved by Dr. Brown.

Dr. Brown reported no financial interests or relationships that pose a potential conflict of interest with this article.

doi:10.3949/ccjm.84.s4.03

Surgical aortic valve replacement (SAVR) started in the 1960s with a porcine aortic valve sutured to a stainless steel frame. The first human transcatheter aortic valve replacement (TAVR) procedure in the United States was in 2002. In the past 15 years, technological advances in heart valve design have made TAVR the preferred alternative in patients at high risk for surgical complications. This article outlines studies comparing balloon-expandable TAVR vs SAVR for patients at extreme, high, and intermediate surgical risk, and presents evidence that supports the expanded use of TAVR in patients at lower surgical risk.

TAVR: THE PREFERRED ALTERNATIVE TO SURGERY

For patients needing aortic valve replacement, the initial step was to show that TAVR recipients have better outcomes than those who receive no treatment. In the Placement of Aortic Transcatheter Valves (PARTNER) trial, investigators evaluated all-cause mortality in patients who needed valve replacement but were not candidates for surgery because of an extreme risk for complications (cohort B) (**Table 1**). In those who were not treated with TAVR, the mortality rate was 50% at 1 year. At 5 years, the mortality rate was 94%. In short, virtually all patients died under conservative medical management. For those undergoing TAVR, mortality rates were significantly lower: 31% at 1 year and 72% at 5 years ($P < .0001$).[1]

Investigators next established TAVR outcomes as being noninferior to SAVR in high surgical risk patients (PARTNER trial cohort A) at 1 year.[2] A midterm follow-up of this study published in 2015 reported comparable rates of all-cause mortality at 5 years in high-risk patients undergoing TAVR vs SAVR, thus confirming the noninferiority of TAVR vs a surgical approach in high-risk patients for the longest duration of follow-up currently available.[3]

For patients, if the results of 2 different procedures are similar, they are typically going to choose the less

invasive option. As a result, use of TAVR has increased: nearly 300,000 procedures have been performed worldwide, and approximately 75,000 were completed in 2016 alone. These numbers are projected to increase fourfold in the next 10 years. In the United States, almost one-third of Medicare-reported aortic valve replacements in 2015 were performed using TAVR.[4]

These data show that TAVR has become the preferred alternative to SAVR in inoperable and high-risk patients.

TAVR IN INTERMEDIATE-RISK PATIENTS

The US Food and Drug Administration (FDA) initially approved TAVR for patients judged to be ineligible for open-chest valve replacement cardiac surgery or at high risk for SAVR. This represents a small percentage of the total patient population needing aortic valve replacement. The Society of Thoracic Surgeons database of aortic valve disease cases during 2002 to 2010 (N = 141,905) shows that just 6.2% were ranked as high risk (ie, population eligible for TAVR in 2016). Most patients (79.9%) were low risk, and 13.9% were intermediate risk.[5]

The PARTNER 2A and PARTNER S3i trials evaluated TAVR in intermediate-risk patients. In PARTNER 2A, 2,032 intermediate-risk patients were randomized to either TAVR or SAVR. Results after 2 years showed no difference between TAVR and SAVR in the primary end point of all-cause mortality or disabling stroke at 24 months (rates 19.3% vs 21.1% for SAVR) (**Figure 1**).[1]

A subanalysis of the transfemoral-access cohort provided additional support for TAVR. It showed that the rate of death and stroke in this cohort began to trend more favorably for TAVR. At 24 months, the difference in the primary end point was statistically significant in favor of TAVR (16.3% vs 20.0% for surgery; $P = .04$).[1]

One potential reason to explain the data in favor of TAVR was the introduction of the Sapien 3 valve midway through the PARTNER 2 trial. The FDA allowed the device to be evaluated in a propensity-score analysis comparing TAVR with the Sapien 3 valve vs results for the surgical arm in the PARTNER 2A trial in intermediate-risk patients.[6] Results showed a 75% lower rate of all-cause mortality at 30 days with TAVR (1.1% vs 4.0% for surgery), which extended out to 12 months (7.4% vs 13.0%). Rates of disabling stroke were similar: 30-day rates were 1.0% for TAVR vs 4.4% for surgery; 12-month rates were 2.3% vs 5.9%. Data for combined mortality and stroke reflected the differences: 3.7% for TAVR vs 9.7% for SAVR at 30 days, and 10.8% vs 18.8% at 12 months (**Figure 2**). Both the noninferiority data and superiority data on the primary end point of mortality and stroke were statistically significant for TAVR vs SAVR ($P < .001$).[6,7]

TABLE 1
Defining surgical risk

Surgical risk is calculated using the Society of Thoracic Surgeons risk-score model, which provides a prediction of a patient's risk for surgical mortality and major complications. Patients are assigned a risk category based on the following scores:

- High risk: > 8%.
- Intermediate risk: 4% to 8%
- Low risk: < 4%.

Based on these data, in August 2016, the FDA approved the Sapien valves for use in patients with aortic valve stenosis who are at intermediate risk of death or complications associated with open-heart surgery. If the differences in outcomes reported during the PARTNER S3i trial are extrapolated to the total number of valve replacement surgeries performed worldwide, the potential number of patients who may benefit from TAVR is substantial.

DOWNSIDE OF TAVR

Although results with TAVR appear promising, there are important issues to address before it can be adopted in a wider patient population (ie, low-risk patients). These primarily focus on the following:

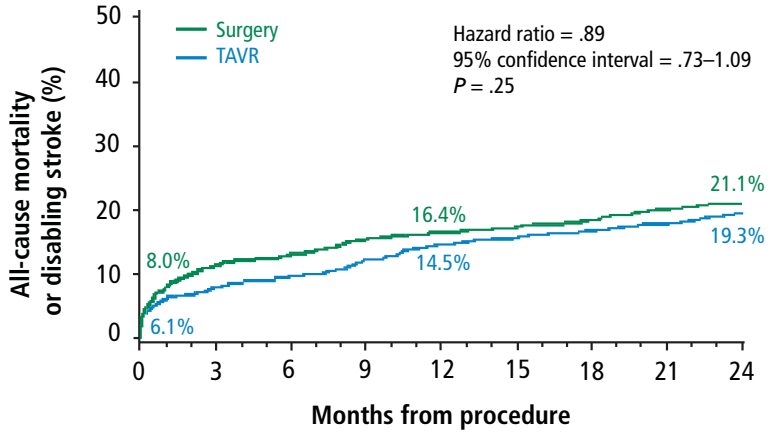
- Stroke
- Paravalvular leak
- Need for pacemaker replacement
- Valve durability
- Leaflet immobility or valve thrombosis.

Stroke

The incidence of stroke associated with TAVR is a concern, but it has decreased with the introduction of the Sapien 3 valve. In the PARTNER 2 trial, the 30-day stroke rate in intermediate-risk patients who received the Sapien 3 valve was 2.6%.[1] This compares with a 5.6% overall rate in the PARTNER 1A trials using the first Sapien valve.[2] The rate of stroke events is expected to decrease further as TAVR is expanded into healthier populations with better vasculature.

Paravalvular leak

Rates of moderate or severe paravalvular leak at 30 days have also decreased with the Sapien 3 valve and were



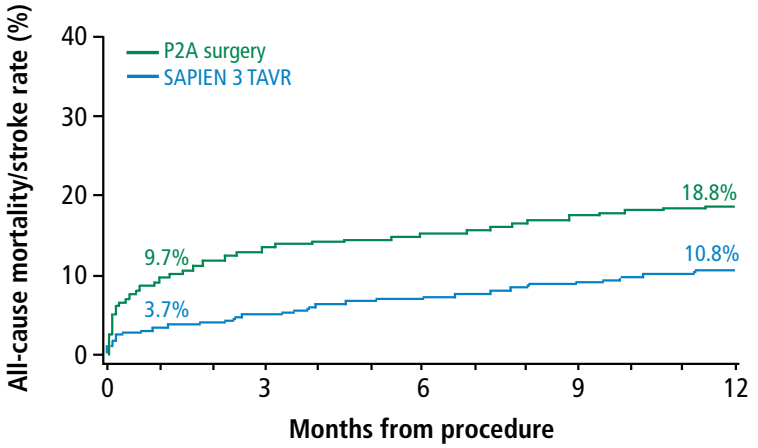
Number at risk:

Surgery	1021	838	812	783	770	747	735	717	695
TAVR	1011	918	901	870	842	825	811	801	774

Figure 1. All-cause mortality or disabling stroke rates for TAVR vs SAVR in intermediate-risk patients during the PARTNER 2A trial showed no statistical difference.

SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement

From Leon MB, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med 2016; 374:1609–1620. Copyright © 2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.



Number at risk:

P2A surgery	944	805	786	757	743
S3i	1077	1012	987	962	930

Figure 2. The 1-year rates for all-cause mortality and all stroke show better outcomes for TAVR vs SAVR.[7]

SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement

4.2% overall in the PARTNER S3i trial.[6] These rates have ranged from 11.5% overall in the PARTNER 1A trial[2] to 4.2% in the PARTNER 2B trial[1] that used the Sapien XT valve for transfemoral-access TAVR.

New pacemakers

The percentage of TAVR procedures that result in a new requirement for a pacemaker increased to about 11% in 2014, up from 6.8% in 2012 to 2013.[8] The requirement for a new pacemaker within 30 days following TAVR appeared to decrease again in the PARTER 2 trial, to 8.5%.[1]

Durability

Evidence is emerging showing the limited durability of bioprosthetic aortic valve. Multiple studies have reportedly shown this, and this is true for all tissue valves, including those surgically inserted. A study assessing data from 357 patients showed that structural valve degeneration begins at 7 years postoperatively. By 10 years, only about 86% of valves were free from degeneration. At 12 years, that dropped to 69%.[9]

A study comparing TAVR vs SAVR showed that under identical loading conditions and with identical leaflet tissue properties, leaflets of valves placed via TAVR sustained higher stresses, strains, and fatigue damage.[10]

Overall, these results provide the possibility that TAVR valves may have reduced valve life compared with SAVR valves. Unknown durability may be an issue to consider when evaluating TAVR for implantation in intermediate- and low-risk patients.

Leaflet immobility and valve thrombosis

In the past 2 years, the problem of potential subclinical valve leaflet thrombosis, on both surgically inserted and TAVR valves, has emerged.[11] The FDA is monitoring these complications because of their potential impact on the safety and efficacy of these valves.

This complication was first reported as an unexpected finding of reduced leaflet motion on 4-dimensional computed tomography, a sign suspicious for valve thrombosis, in a subgroup of patients evaluated 30 days after implantation.[12] A study from

Denmark found a 7% incidence of valve thrombosis in TAVR valves. They reported that warfarin could prevent thrombosis.[13]

At the Heart Hospital Baylor Plano, our TAVR team has identified approximately 50 cases of thrombosis that caused partial valve occlusion. Administering warfarin for 3 months resolved the thrombosis in virtually all cases. In 1 case, a thrombosed valve was surgically explanted with good patient outcome. Pathological analysis confirmed that reduced leaflet motion seen on 4-dimensional CT was valve thrombosis, as suspected by imaging specialists.[14]

IS TAVR APPROPRIATE FOR INTERMEDIATE-RISK PATIENTS?

Although there are ample data supporting the use of TAVR in intermediate-risk patients, SAVR remains the most effective option in certain clinical situations:

- Younger patients who will need valve replacement later in life
- Bicuspid valves with eccentric bulky calcification
- Aortopathy (aortic disease above the valve)
- Small calcified roots
- Severe calcification of left ventricular outflow tract
- Low-lying coronary arteries (typically, ≤ 6 mm from the aortic annulus)
- Severe septal bulging
- Severe mitral regurgitation and/or tricuspid regurgitation
- Conduction system disease that puts the patient at high risk for pacemaker implantation
- Valve replacement in valves with a diameter 20 mm or smaller.

Nevertheless, outcomes seem to support TAVR in intermediate-risk patients. At the Heart Hospital Baylor Plano, 30-day outcomes with the Sapien 3 valve have shown all-cause mortality of 1.1% and all-stroke mortality of 2.6% (1.0% for disabling stroke). Large registries of the Sapien 3 valve have reported similar outcomes at 30 days: mortality 1%, disabling stroke 2%, major vascular complications 2%, and moderate to severe paravalvular leak 2%.[15]

Overall, the rates of major vascular complications and of life-threatening bleeding are 2%, and the need for new pacemakers is 4%. Results from several trials support TAVR as an alternative to surgery in intermediate-risk patients. In patients who are candidates for transfemoral access, TAVR may provide additional clinical advantages. However, questions about long-term durability and new requirements for pacemakers are issues for TAVR use in intermediate- and low-risk patients. More data are needed to answer these questions.

At the Heart Hospital Baylor Plano, the number of TAVR procedures from 2012 to 2015 increased from 49 cases to 215, while the number of SAVR procedures remained constant (166 in 2012 and 162 in 2015). During that time, outcomes improved dramatically: in-hospital mortality rates dropped from 2% to 0% and 30-day mortality dropped from 3% to 0%. There have been 227 consecutive SAVR patients with no in-hospital or 30-day mortality and 261 consecutive TAVR patients with no mortality.

These results support initiating clinical trials of TAVR in low-risk patients. In 2016, the FDA approved TAVR valves for 2 clinical trials in patients with aortic stenosis who are at low risk of surgical mortality. These large clinical trials, each with about 1,200 patients, are expected to provide data that will help determine whether TAVR is a safe and effective option for low-risk patients.

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CABG: A continuing evolution

ABSTRACT

Use of coronary artery bypass grafting (CABG) has had a resurgence, as clinical trial data emerged showing that it remains the standard of care for patients with complex lesions. Debate exists regarding various factors, including endoscopic vs open vein-graft harvesting, single vs bilateral mammary artery grafts, radial artery vs saphenous vein grafts, right internal mammary artery vs radial artery grafts, and on-pump vs off-pump surgery. More recent developments include minimally invasive approaches, robotics, and hybrid revascularization, which are changing the risk-benefit ratio for this patient population.

KEY POINTS

CABG is considered the standard of care for patients with intermediate or high coronary artery disease burden.

Traditional CABG performed via median sternotomy with the use of cardiopulmonary bypass is the technical standard for surgical coronary revascularization.

Suturing the left internal mammary artery directly to the left anterior descending artery is the most effective technique for coronary revascularization.

Minimally invasive approaches to CABG are safe and effective alternatives in select patient populations.

This article is based on Dr. Bakaeen's presentation at the Sones/Favaloro Scientific Program, "Transforming the Delivery of Cardiovascular Care: Research and Innovation in the Heart & Vascular Institute," held in Cleveland, OH, November 18, 2016. The article was drafted by *Cleveland Clinic Journal of Medicine* and was then reviewed, revised, and approved by Dr. Bakaeen.

Dr. Bakaeen reported that he has no financial interests or relationships that posed a potential conflict of interest with this article.

doi:10.3949/ccjm.84.s4.04

The evolution of coronary artery bypass grafting (CABG) has been a key component in significantly reducing the morbidity and mortality associated with occlusive coronary artery disease (CAD). Cleveland Clinic surgeons, through their technical interventions and innovations, have led the evolution in coronary revascularization starting in the 1960s and continuing today. This article provides a brief overview of the evolution and describes the issues associated with current CABG approaches.

EARLY WORK IN RECONSTRUCTIVE CORONARY ARTERY SURGERY

Results from the first large series of venous grafting for CAD were reported in 1970 by Favaloro and colleagues at Cleveland Clinic.[1] They showed the efficacy of grafting in treating CAD, with low associated morbidity and mortality, thus establishing this surgery as the treatment modality for CAD.

The technique of surgical myocardial revascularization was a culmination of developments that began years earlier with the Vineberg procedure, involving suturing of the mammary artery to the muscle rather than a vessel-to-vessel anastomosis. From this followed the coronary patch, end-to-end bypass, and then end-to-side bypass.

In the 1970s, the refinement of suturing the left internal mammary artery (LIMA) directly to the left anterior descending (LAD) artery using magnifying loops was pioneered and popularized at Cleveland Clinic. This later became the cornerstone of future coronary revascularizations.

As a direct result of the successful technical advances and excellent clinical outcomes, the volume of CABG procedures in the United States rose steadily during the 1980s and reached its peak in 1995. It then began a slow decline that continued until 2013, when the trend began to reverse. It was still rising through 2015.

WHY THE RENEWED INTEREST IN CABG?

A key component to continued use of CABG is that it appears to have a clinical edge over other treatments. This has been shown in several high-profile studies:

SYNTAX,[2,3] FREEDOM,[4,5] BEST,[6] and NOBLE.[7] For example, in the SYNTAX trial, which compared CABG vs percutaneous coronary intervention (PCI), the conclusion from both the 1-year[2] and the 5-year[3] results was that CABG should remain the standard of care for patients with complex lesions—those with an intermediate or high burden of CAD.

The 5-year outcomes showed that the rate of major adverse cardiac and cerebrovascular events favored CABG over PCI (26.9% vs 37.3%, respectively; $P < .0001$).[3] All-cause mortality, although not statistically significant, also was better for CABG (11.4% vs 13.9%). This indicates that as the complexity and burden of disease increase, the benefit of CABG over PCI becomes more prominent. In short, the worse the disease, the better the results with CABG.

Why is CABG better?

One rationale is that CABG not only bypasses the culprit-lesion vessel, it also protects against future lesions. An elegant study published in 2010 showed that in most cases of acute myocardial infarction (MI), the culprit coronary lesion is in the first 7 cm of the LAD.[8] With CABG, most distal anastomoses are beyond 7 cm and, thus, are beyond the location of the vast majority of potential future culprit lesions.

An important factor is the modern-day safety record of CABG. According to the Society of Thoracic Surgeons Adult Cardiac Surgery Database,[9] in 2016 the expected operative mortality for CABG was just over 2%. At the Cleveland Clinic, CABG mortality has consistently been below 1% despite the complexity of the cases and the higher percentage of reoperations performed at the Clinic. In addition, the low incidence of major complications after CABG has contributed to its endurance as an important therapeutic option for CAD over the decades.

IMPROVING LONG-TERM CABG OUTCOMES

Improving vein graft patency

The Achilles heel of CABG is the decline of patency of saphenous vein grafts. The occlusion rate of these veins is 6% to 8% at hospital discharge and approximately 10% at 1 year after CABG. By 10 years, half of the vein grafts are diseased or occluded, with progression of atherosclerotic disease over time.

There has been controversy about whether open harvesting of the saphenous vein is better than endoscopic vein harvesting for patency-related outcomes. This arose after the publication of an ad hoc analysis that gave poor marks to endoscopic vein-graft harvesting.[10] Its major finding was that endoscopic vein harvesting had higher rates of vein-graft failure at 12 to 18 months than open vein harvesting (46.7% vs 38.0%, respectively; $P < .001$). At 3 years, endoscopic harvesting was associated with higher rates of death, MI, or repeat revascularization (20.2% vs 17.4%, $P = .04$).

A US Food and Drug Administration-sanctioned Society of Thoracic Surgeons observational study, however, reviewed outcomes from 235,394 patients who underwent CABG from 2003 through 2008 and found no significant increase in 5-year mortality rates with use of endoscopic vein-graft harvesting vs open harvesting.[11] This study showed that the less invasive endoscopic approach is still an option.

In 2015, Taggart and colleagues[12] reported on a pioneering procedure that wraps the saphenous vein graft with a stent. Initial results showed external stenting had the potential to improve vein-graft lumen and reduce intimal hyperplasia at 1 year postoperatively. Surgeons can expect more data on this technology in the future.

COMPARING CONDUIT OPTIONS FOR CABG

Arterial vs venous grafts

The 1986 report by Loop and colleagues from Cleveland Clinic showed that the patency of the mammary artery graft was superior to that of the saphenous vein and that patients receiving a mammary bypass had significantly better 10-year survival (82.6% vs 71.0%, respectively; $P < .0001$).[13] The findings of this landmark study established the LIMA-to-LAD bypass as the technical standard for surgical coronary revascularization.

Single vs bilateral mammary artery grafts

In December 2016, results of the Arterial Revascularization Trial (ART) were published comparing single vs double mammary artery grafts.[14] In this prospective randomized trial, the 5-year results showed no significant difference between these mammary grafts in terms of all-cause mortality, MI, or stroke. Bilateral mammary artery grafts, however, were associated with a higher risk of sternal wound complications (3.5% vs 1.9%, respectively; $P = .005$) and sternal reconstruction (1.9% vs 0.6%; $P = .002$).

Before abandoning bilateral mammary grafts, practitioners should remember that after 5 years, survival rates begin to favor bilateral over single grafts. This is based on the 2004 Cleveland Clinic report[15] of 20-year follow-up data showing that bilateral internal mammary artery grafting was associated with improved survival compared with single artery grafting. In this study, survival rate curves began to diverge 5 years

postoperatively and continued to diverge with time in favor of bilateral artery grafts. Despite the potential long-term benefits, only 5% of CABG surgeries in the US are done with bilateral mammary grafts. Cleveland Clinic policy is to use bilateral mammary grafting in selected patients who stand to benefit from the extended longevity associated with this technique. **Figure 1** shows the sites of bilateral mammary grafting and radial artery bypass.

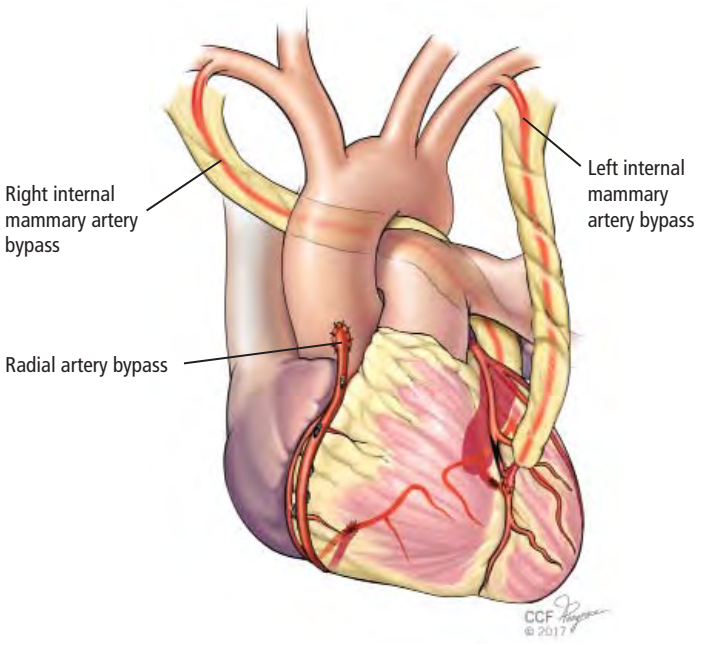

Figure 1. Sites of bilateral mammary grafting and radial artery bypass.

Radial artery vs saphenous vein grafts

In the largest randomized study comparing these two graft options,[16] the 1-year results showed no difference in graft patency; a follow-up analysis is in progress. In contrast, randomized studies from Canada[17] and the United Kingdom[18] suggest that there are potential benefits associated with use of radial artery grafts in terms of patency and clinical outcomes. In addition, observational data from centers experienced in radial artery grafting have demonstrated favorable outcomes. Radial arteries perform best when bypassing totally occluded or severely stenotic vessels in which there is no or little risk of competitive flow from the native circulation.

Right internal mammary vs radial artery grafts

A propensity-matched comparison study looking at multiple studies (N = 15,374 patients) concluded that use of the right internal mammary artery provides better outcomes.[19] It was associated with a 25% risk reduction for late death and a 63% risk reduction for repeat vascularization, both statistically significant vs the radial artery rates. But there is a randomized study showing that the radial artery is as good as or better than the right internal mammary artery. At this point, it is not clear which artery is better as an adjunct for the LIMA-to-LAD bypass.

GUIDELINES FOR GRAFT SELECTION

In 2016, the Society of Thoracic Surgeons published guidelines that encouraged the use of arterial grafts, giving it a class IIa designation, meaning that the evidence indicates it is *reasonable* to consider.[20]

The guidelines note the following:

- The internal mammary artery should be used to bypass the LAD when bypass of the LAD is indicated.
- As an adjunct to the left internal mammary artery, a second arterial graft (the right internal mammary artery or radial artery) should be considered in appropriate patients.
- Use of bilateral internal mammary arteries should be considered in patients who are not at high risk for sternal complications.

COMPARING SURGICAL APPROACHES

Traditional CABG performed via median sternotomy and with the use of cardiopulmonary bypass remains the technical standard in surgical coronary revascularization. However, technologies have allowed surgeons to use different and sometimes less invasive approaches that may have good outcomes in select patients with suitable risk profiles and favorable coronary anatomies.

On-pump vs off-pump CABG

The popularity of CABG without cardiopulmonary bypass ("off-pump") peaked in 2002, when it constituted approximately 23% of CABG procedures and then declined to 17% by 2012.[21] The ROOBY (Veterans Affairs Randomized On/Off Bypass) trial of 2,203 VA patients showed that at 1 year, those in the off-pump group had worse composite outcomes, poorer graft patency, and greater incidence of incomplete revascularization than the on-pump group.[22] However, the use of off-pump CABG was vindicated in two other trials—CORONARY and GOPCABE—in which experienced surgeons in high-volume centers with high-risk patients had no difference in outcomes at 1 and 5 years.[23–25] The recommendation is to tailor

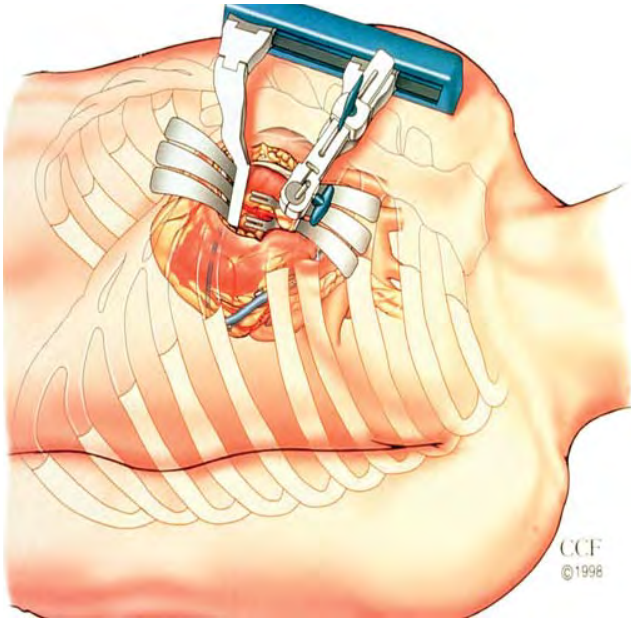

Figure 2. Exposure of the left anterior descending for a minimally invasive direct coronary artery bypass.

the procedure to the patient rather than the patient to the procedure. The best option is always to do what is right for the patient. For example, patients with diseased ascending aortas or liver disease may benefit from an off-pump approach.

MINIMALLY INVASIVE CABG

Minimally invasive direct coronary artery bypass (MIDCAB) is a surgical procedure that revascularizes the LAD without a median sternotomy or cardiopulmonary bypass. **Figure 2** shows the exposure of the LAD for this procedure. Robotics also can be used for harvesting the mammary artery and for performing MIDCAB.

Robotic CABG

This procedure has advantages and disadvantages. The advantages are primarily related to the minimally invasive approach:

- There is no surgeon hand tremor
- It is less invasive
- It provides better cosmetic results
- It is expected to result in less pain, fewer transfusions, fewer complications, and shorter length of hospital stay, although those have not been proven.

Disadvantages include the following:

- Compromised completeness of revascularization—with some "difficult" vessels left unbypassed
- Longer operative times
- Higher cost
- Concern about graft patency with inexperienced surgeons
- Higher-than-expected mortality in some reports.

In 2013, a study of 500 patients treated with robotic totally endoscopic CABG showed that this procedure could be safe and effective, although the best outcomes were achieved in patients with less severe disease requiring fewer bypasses.[26] In other words, it is more appropriate for LIMA-to-LAD suturing and less complex anatomy, and it is best performed with cardiopulmonary bypass with the heart arrested.

Hybrid revascularization

This procedure is a combination of minimally invasive CABG (MIDCAB or robotic CABG) to revascularize the LAD and PCI to treat the remaining vessels in multivessel CAD. The CABG and PCI can be concurrent or staged. The hybrid approach has the attraction of being less invasive and uses the technical standard LIMA-to-LAD approach, but it has the obvious limitation of not incorporating additional arterial grafting and the possibility of a compromised technical outcome in less experienced hands.

A collaborative task force from several cardiovascular medical societies developed evidence-based guidelines to address the hybrid coronary revascularization approach. They give it a class IIa recommendation, indicating that it is a *reasonable* approach to treating patients in whom there are limitations and challenges to traditional CABG. For other patients, they gave it a class IIb recommendation, indicating that it *may be reasonable* to use as an alternative to multivessel PCI or CABG.[27]

THE EVOLUTION CONTINUES: CABG VS PCI

As CABG and PCI continue to evolve, surgical approaches to CAD are becoming more sophisticated with the use of more arterial conduits, less invasive surgical approaches, and development of new types of stents for PCI; however, expect the debate to continue regarding which approach to CAD is best. This is not a battle between surgical and nonsurgical specialties. Rather, the goal should be an amicable, collaborative heart-care team. After all, the most important question is, as always, which therapy is best for the individual patient.

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A new generation of drug-eluting stents: Indications and outcomes of bioresorbable vascular scaffolds

ABSTRACT

Drug-eluting stents (DES) are increasingly being used as a less invasive alternative to coronary artery bypass grafting. Early generation DES had durable polymers that provided acceptable efficacy outcomes but had high rates of stent thrombosis leading to myocardial infarction and death. Second-generation DES have improved outcomes by reducing stent thrombosis and recurrent stenosis. Newer DES with biodegradable polymers have similar efficacy as second-generation DES, but have higher rates of stent thrombosis. This review compares outcomes of bioresorbable scaffolds and looks at stent technology developments that may improve outcomes.

KEY POINTS

Complications with first-generation durable polymer DES—stent thrombosis and restenosis with target lesion revascularization—led to the development of bioresorbable stents.

Bioresorbable and durable polymer metallic DES have similar rates of efficacy and of stent thrombosis.

Bioresorbable DES should be placed in appropriate patient populations and lesion subsets, and limited to arteries larger than 2.25 mm.

This article is based on Dr. Waksman's presentation at the Sones/Favaloro Scientific Program, "Transforming the Delivery of Cardiovascular Care: Research and Innovation in the Heart & Vascular Institute," held in Cleveland, OH, November 18, 2016. The article was drafted by *Cleveland Clinic Journal of Medicine* and was then reviewed, revised, and approved by Dr. Waksman.

Dr. Waksman reported research grant support from Abbott Vascular, Biosensors International, Biotronik, Boston Scientific, Edwards Lifesciences; consulting for Abbott Vascular, Amgen, Biosensors International, Biotronik, Boston Scientific, Corindus, Lifetech Medical, Medtronic Vascular, Philips Volcano, Symetis; and serving on speaker's bureau for AstraZeneca.

doi:10.3949/ccjm.84.s4.05

The development of a new generation of drug-eluting stents (DES) has had a dramatic impact on the number of stents used for percutaneous transluminal coronary angioplasty for the treatment of coronary artery disease (CAD). But even second- and third-generation DES fall short when compared with coronary artery bypass grafting (CABG) with regards to the need for repeat reavascularization. CABG is advantageous because it bypasses the entire disease segment of the vessel. Thus for multivessel complex CAD, it is still considered the best choice. Nevertheless, most patients prefer the less-invasive option of stents, so practitioners need to provide the best stent available.

There are 3 primary criteria for DES selection:

- Efficacy for a broad range of patients and lesion complexities that primarily provides consistency in improving measures of angiographic and clinical efficacy
- Safety as determined by the following:
  - Enable healing and promote endothelialization
  - Permit functional endothelium
  - Obtaining complete apposition
  - Reduction or elimination of late and very late stent thrombosis
  - Minimizing the need for long-term dual antiplatelet therapy
- Performance provided by reliable delivery capabilities to the lesion site.

GREAT EXPECTATIONS

New DES must be shown to be superior to previous generation stents. Although preclinical endothelialization and other mechanistic surrogates are good enough to claim an improvement, the traditional method is to compare clinical outcomes with the new stent versus the existing stent in a randomized clinical trial.

The first-generation DES demonstrated superiority

over bare-metal stents and became the default stent of choice for revascularization. But complications of first-generation stents such as stent thrombosis and late restenosis led to the development of second-generation DES, which demonstrated superiority over the first-generation DES. Although third-generation DES have been introduced with bioresorbable polymers, these have not improved clinical outcomes when compared with second-generation DES. Overall, the outcomes of second-generation DES are good, with low event rates that challenge the ability to demonstrate further improvement or superiority with third-generation DES. Nevertheless, there is an ongoing effort to continue to improve the current stents with thinner struts and more biocompatible polymer, biodegradable polymer, or polymer-free stents. **Table 1** shows the evolution of DES from the nonbiodegradable polymer-based stents to the bioresorbable scaffolds, which are completely eliminated from the body.

TABLE 1
Evolution of drug-eluting stents

First generation

Nonbiodegradable (ie, durable) polymer-based thick strut
Sirolimus- or paclitaxel-eluting stents

Second generation

Nonbiodegradable (ie, durable) polymer-based thin strut
"Limus"-eluting stent (eliminated paclitaxel)

Third generation

Biodegradable polymer-based thick or thin strut
"Limus"-eluting stent

Third generation "B"

Polymer-free strut
"Limus"-eluting stents

Fourth generation

Bioresorbable, thick/thin strut
"Limus"-eluting vascular scaffolds (PLLA or magnesium)

"Limus" drugs: biolimus, everolimus, myolimus, novolimus, sirolimus, zotarolimus.
PLLA = poly-L-lactic acid

PROBLEMS WITH DURABLE POLYMER STENTS

Complications with durable polymer DES have included increased local inflammation and neoatherosclerosis. There are reports of subacute stent thrombosis due to lack of adequate expansion and stent apposition. Also reported was late thrombosis, resulting in increased rates of myocardial infarction and death.

These issues motivated engineers to improve and iterate the DES technology. One important technological change is the decrease in strut thickness from 140 µm to as low as 60 µm. The thickness of the polymer coating also has been reduced. The polymer became thinner, more biocompatible, and in some stents, only abluminal. Further developments were to substitute the durable polymer with a biodegradable polymer and perhaps even design a polymer-free stent.

BIORESORBABLE POLYMERS EMERGE

The time course for resorption of bioresorbable polymers ranges from 2 to 15 months, but they all degrade, which should improve long-term outcomes. A meta-analysis of data from the LEADERS trial and ISAR-TEST 3 and 4 found that the bioresorbable polymer stents were associated with significantly lower rates of target-lesion revascularization (P = .029) and stent thrombosis (P = .015) than durable polymer DES at 4 years after implantation.[1] Those results led to the notion that stents with a biodegradable polymer would result in lower rates of stent thrombosis than durable polymer stents; however, that was not the case when stents with biodegradable polymers were compared with second-generation DES.

In the COMPARE II trial,[2] the rates of stent thrombosis and target-lesion revascularization were not statistically different for the thick-strut biodegradable polymer biolimus-eluting stent (Nobori) compared with the second-generation thin-strut permanent-polymer stents (Xience). In the CENTURY II trial,[3] a third-generation biodegradable sirolimus-eluting stent (Ultimaster) had stent thrombosis rates similar to those of a durable polymer everolimus-eluting stent (Xience) 300 days after insertion (4.36% vs 5.27%, respectively). Target-lesion revascularization rates were also about the same for the stents. In the EVOLVE II trial comparing the thin-strut biodegradable everolimus-eluting stent (Synergy) vs the thin-strut permanent-polymer everolimus-eluting stent (Promus), the 12-month target lesion failure rates for the stents were essentially the same.[4]

THE RATIONALE FOR BIORESORBABLE STENTS

Another approach was to use biodegradable scaffolds that will be eliminating from the vessel wall once it "completes the job." The main bioresorbable materials used were polylactic acid or biodegradable metal-

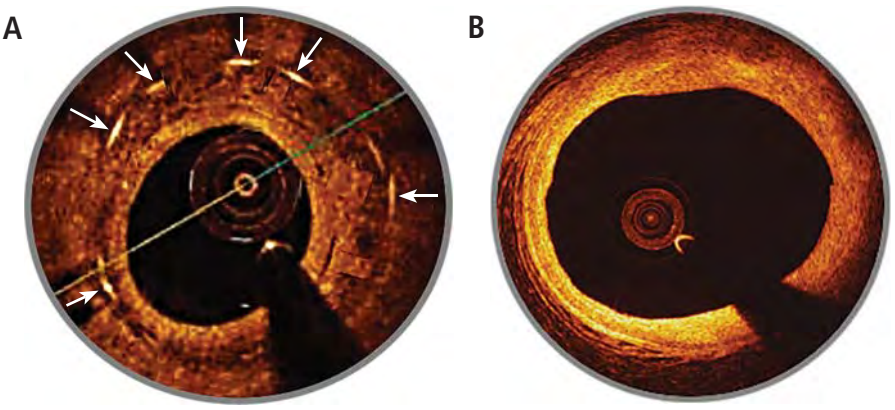

Figure 1. Optical coherence tomographic images show difference in arteries 5 years after implantation of metallic drug-eluting stent (A) and bioresorbable drug-eluting stent (B). Arrows (A) point to remaining stent. In contrast, the bioresorbable stent (B) was completely absorbed.

(A) Reprinted from Atherosclerosis (Kuramitsu S, et al. Long-term coronary arterial response to biodegradable polymer biolimus-eluting stents in comparison with durable polymer sirolimus-eluting stents and bare-metal stents: five-year follow-up optical coherence tomography study. Atherosclerosis 2014; 237:23–29). © 2014 with permission from Elsevier. (B) Courtsey of S. Windecker.

like magnesium. These materials pose a technological challenge. While the biodegradable scaffolds are completely eliminated overtime, they still need to equate the performance of best-in-class drug-eluting stent with respect to efficacy and safety. After the Absorb everolimus-eluting BVS system (Absorb BVS) was launched in Europe, initial studies showed scaffold-related thrombosis rates as high as 3.4%.[5–7] That compares with 0.4% for second-generation DES—a troubling result for a new technology.

Rates of restenosis and stent thrombosis are similar for bioresorbable stents and standard durable polymer stents. But what are the potential added benefits of bioresorbable stents? And will they improve patient outcomes?

Bioresorbable stents certainly appeal to patients who do not want a permanent, rigid, metallic implant. Also appealing are the proposed benefits of restoration of vasomotion, late luminal enlargement, preservation of CABG targets, and relief of angina. Whether bioresorbable stents improve these outcomes has not been established. Currently, there is no long-term evidence of reduced rates of adverse events, although in 1 study, optical coherence tomography images recorded 10 years after implantation of the first bioresorbable stents showed a pristine vessel with no signs of the struts.[8]

Several facts are known about the Absorb BVS:

- Preclinical evidence shows complete resorption and return of vascular function, but this takes 3 to 4 years.
- Imaging data at 5 years from the Absorb cohort B trial show complete resorption of struts, lumen preservation, return of function, and plaque regression.[9]
- In ABSORB III, the pivotal US trial, the stent was within the primary end point showing noninferiority in safety and effectiveness compared with Xience in the first year.[10]
- Absorb clinical trials in Japan and China confirmed ABSORB III results.
- Meta-analysis (> 3,300 patients) confirmed safety and effectiveness of Absorb.[11]
- Real-world Absorb clinical evidence continues to show improving outcomes with optimized implant techniques.
- Absorb stent was approved by the US Food and Drug Administration (FDA) in July 2016; more than 150,000 have been implanted worldwide.

In a 5-year follow-up study, optical coherence tomographic images showed encouraging results (**Figure 1**)[12]: the treated artery healed well, with a large lumen diameter and no remnants of metal. A meta-analysis of 1-year results showed no statistical differences in the patient-oriented composite end point for death, myocardial infarction, or target-lesion revascularization for Absorb vs the durable polymer Xience DES.[11] Stent thrombosis events also were not statistically different, although the numbers numerically were double for Absorb. Numbers also were higher for target-lesion failures, cardiac death, target-lesion myocardial infarction, and ischemic-driven target-lesion revascularization, but, again, they were not statistically significant.

The increased rates of target-lesion revascularization and stent thrombosis were likely attributable to inserting the stents into small-diameter vessels that are probably too small for the Absorb BVS. When small vessels (< 2.25 mm) are eliminated from the analysis, the rates were as follows.

Results for vessels > 2.25 mm:

- Target-lesion revascularization: 6.7 % vs 5.5%
- Stent thrombosis: 0.9% vs 0.6%.

Results for small vessels (< 2.25 mm):

- Target-lesion revascularization: 12.9% vs 8.3%
- Stent thrombosis: 4.6% vs 1.5%.

The lesson is that the Absorb BVS should not be

placed in arteries smaller than 2.25 mm in diameter.

ABSORB II STUDY RESULTS RAISE QUESTIONS

Another concern was uncovered in July 2016 when results were published from the ABSORB II trial on vasomotor reactivity at 3 years.[13] This clinical trial randomized 501 patients in a 2:1 ratio to the Absorb BVS or the Xience DES at 46 sites outside the United States. Assessment for changes in mean lumen diameter between pre- and post-nitrate administration showed no differences between the groups; thus, the Absorb BVS did not achieve a level of superior vasomotor reactivity. There was vasomotor reactivity probably because the surrogate marker was angiographic follow-up and not intravascular ultrasound or tomography.

Further, the coprimary end point of angiographic late luminal loss at 3 years did not meet its noninferiority standard. The Absorb BVS was expected to have lower rates of late lumen loss because the struts are gone and there is less new intimal formation; however, at 3 years, that was not the case.

The rate of acute stent thrombosis also was alarming: 8 cases for Absorb BVS versus none for Xience. This caused alarm, raising the question of why it was happening in these patients 2 to 3 years after implantation.

Animal studies investigating the association of thicker struts and increased thrombogenicity have reported that the 157-µm BVS had much more platelet buildup and thrombogenicity than a 120-µm biomatrix stent. The 74-µm Synergy stent had even lower rates of thrombosis. The reason for increased thrombogenicity with thicker struts requires further study.

Also, an analysis of the secondary cardiac end points at 3 years in ABSORB II found no clinical patient-oriented differences between the Absorb BVS and the Xience stent (20.8% vs 24.0%, respectively; $P = .44$). However, rates of device-oriented clinical end points were significantly higher for Absorb BVS (10.4% vs 4.9%; $P = .043$).[13]

Clearly, the results for Absorb BVS in this study were not positive. One explanation is suboptimal implantation techniques that did not appose the polymer to the wall. A few years ago, focus shifted to an optimal technique for scaffold deployment, which included predilation, appropriate sizing of the scaffold to the size of the vessel, and postdilation with the intention of embedding the polymer in the vessel wall. Multiple studies have reported fewer incidents of stent thrombosis with the implementation of this protocol.[14]

Further studies have continued to report increased rates of late scaffold thrombosis in follow-ups of 30 days to 3 years. This resulted in an advisory letter from the FDA focused on appropriate clinical use of the device and withdrawal of ABSORB from commercial use in Europe and Australia.

TABLE 2
Bioresorbable vascular scaffolds

Name (Marketer)	Strut thickness (µm)	Scaffold	Drug
First generation			
ReZolve (REVA)	228	PolyCarb	SES
ART 18AZ (ART)	170	PDLLA	None
Absorb BVS 1.1 (Abbott)	156	PLLA	EES
Fortitude (Amaranth)	150	PLLA	SES
DeSolve (ELIXIR)	150	PLLA	NES
Magmaris (Biotronik)	150, 120	Mg, PLLA	SES
Second generation			
Fantom (REVA)	125	PolyCarb	SES
Mirage (Manli Cardiology)	125	PLLA	SES
Aptitude (Amaranth Medical)	120	PLLA	SES
DESolve Cx (ELIXIR)	120	PLLA	NES
RENUVIA (Boston Scientific)	≤99		

ART = Arterial Remodeling Technologies; EES = everolimus-eluting stent; NES = novolimus-eluting stent; PDLLA = poly-DL-lactic acid; PLLA = poly-L-lactic acid; PolyCarb = poly-tyrosine-derived polycarbonate; SES = sirolimus-eluting stent

BIORESORBABLE SCAFFOLDS PIPELINE

The field of bioresorbable stents has expanded dramatically (**Table 2**). The first-generation devices range from 228 µm to 120 µm. The hypothesis is that over time, the smaller, resorbable stent scaffold will result in fewer adverse events because no stent or polymer will remain.

This is questionable because one has to believe in the vulnerable plaque theory, which assumes potential eruption of plaques. The Absorb can actually seal a thin cap atheroma and necrotic core over time. It seems that this technology can cause some late lumen enlargement and seal an existing plaque, which may have implications for the future.

SUMMARY

This is the current state of the Absorb BVS:

- More than 150,000 implanted globally
- Received FDA approval in July 2016
- Should not be used in small vessels (ie, lumen diameter < 2.25 mm)
- Thrombosis rates 2 to 3 years after implantation are of concern
- Focusing on appropriate surgical implantation technique can improve outcomes.

Overall, use of bioresorbable stent technology is intriguing. While there is ongoing patient preference for bioresorbable technology, clinical trial results raise the question of whether bioresorbable scaffolds are inferior to best-in-class DES. Improving the scaffold technology and the implantation techniques may equate the short-term outcome of the bioresorbable scaffolds with metallic stents with the hope that over time (when the scaffold is gone), the advantage will be with the bioresorbable scaffolds. Meanwhile, the technology is still seeking its best clinical utility, and a matching performance to the best-in-class DES.

Time will tell whether 5 to 10 years after implantation, BRS technology will outperform durable metallic stents.

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Improving the safety and efficacy of robotically assisted mitral valve surgery

ABSTRACT

To improve outcomes with robotically assisted mitral valve surgery, Cleveland Clinic conducted a study evaluating outcomes in 1,000 consecutive cases. Primary areas of interest were to determine whether increased surgical experience with robotic techniques improved outcomes and to identify opportunities that could improve procedural processes. Results showed that these surgeries were effective and safe in terms of improvements in procedure time, transfusion rates, stroke risk, number of mitral valve replacements, and number of conversions to sternotomy. The development and implementation of a patient-selection algorithm halfway through the study further improved outcomes by refining patient eligibility criteria. This study showed that use of a focused preoperative assessment with an algorithm-driven patient selection process combined with increased technical expertise can enhance outcomes with robotic mitral valve surgery.

KEY POINTS

Surgeon competence with robotic techniques, which can be improved through experience, is a key to improving outcomes.

This patient-selection algorithm provides an evidence-based approach to identifying patients who are the best candidates for the robotic approach.

This study showed that increased surgical competence and improved patient selection improved patient outcomes for the primary end points.

This article is based on Dr. Mick's presentation at the Sones/Favaloro Scientific Program, "Transforming the Delivery of Cardiovascular Care: Research and Innovation in the Heart & Vascular Institute," held in Cleveland, OH, November 18, 2016. It was also presented at the American Association for Thoracic Surgery. The article was drafted by *Cleveland Clinic Journal of Medicine* and was then reviewed, revised, and approved by Dr. Mick.

Dr. Mick reported no financial interest or relationships that pose a potential conflict of interest with this article.

doi:10.3949/ccjm.84.s4.06

In the years since the introduction of robotically assisted mitral valve surgery, surgeons have looked for ways to improve techniques and procedures. A study from Cleveland Clinic presented at the American Association for Thoracic Surgery in 2016 assessed efficacy and safety outcomes associated with 1,000 consecutive robotically assisted mitral valve surgeries at Cleveland Clinic.[1] The purpose of the study was to assess the clinical outcomes from these cases and analyze whether the outcomes changed over time as surgeons became more competent with robotic techniques. This analysis was also designed to identify procedural processes that improved outcomes during the trial.

STUDY METHODS

Data were collected from January 2006 through November 2013. Baseline characteristics showed a relatively young patient population, mostly male, with a reasonably preserved ejection fraction (**Table 1**).

Nearly all cases (96%) were classified as degenerative mitral valve disease (N = 960). Of those, most had posterior leaflet prolapse (68%), about one-third (29%) had bileaflet prolapse, and only 3% had anterior leaflet involvement.

All surgeries were performed through right port incisions and used femoral cannulation for peripheral

TABLE 1
Baseline characteristics

Age	56 (± 10) years
Male	77%
New York Heart Association class I and II	92%
Ejection fraction	60.4% (± 5.1%)
Atrial fibrillation	8.9%
Tricuspid regurgitation ≥ 2	9.5%

TABLE 2
Safety of robotically assisted mitral valve surgery

Event	No. (%)
Death	1 (0.1)
Stroke	
Any stroke	14 (1.4)
Permanent stroke	8 (0.8)
Re-exploration for bleeding	25 (2.5)
Atrial fibrillation	189 (18.9)
Any transfusion	118 (12)
Wound infection	0 (0)

TABLE 3
Cases converted to sternotomy (N = 20)

Mitral etiology	Number	Percentage
Residual mitral valve regurgitation	7	35
Bleeding	6	30
Exposure	4	20
Ischemia	1	5
Aortic valve injury	1	5
Aortic dissection	1	5

bypass. The aorta was occluded with either a Chitwood transthoracic clamp or a balloon.

STUDY RESULTS

It is important to remember that with femoral artery perfusion, the blood flow is opposite to the normal direction; thus, it goes up the aorta into the head vessels, which presents its own risks and challenges. Also, during retrograde perfusion, there is a risk of dislodging atherosclerotic plaque leading to brain embolus and stroke.

Nevertheless, outcomes data showed that these procedures were safe, with just 1 death in the 1,000 cases (**Table 2**). There was an overall 1.4% stroke rate, with a 0.8% permanent stroke rate. Atrial fibrillation occurred in 18.9%, approximately 12% required a transfusion, and 2.5% needed re-exploration for bleeding.

In these 1,000 cases, 997 were planned mitral valve repairs, 2 were mitral valve replacements, and 1 was resection of a mitral valve fibroelastoma. Results for the mitral valve repairs were excellent, with postoperative mitral regurgitation occurring in less than 1% of patients.

There were 20 conversions to sternotomy, mainly during the earlier stages of this study. **Table 3** lists the causes of conversions. Most were from residual mitral valve regurgitation, bleeding, or exposure difficulties.

PROCEDURAL IMPROVEMENTS

A primary point of interest was to identify procedural improvements that occurred during the course of the study. The areas evaluated in robotically assisted mitral valve surgery were the efficacy of the procedure in time, transfusion rates, stroke risk, how many mitral valve replacements occurred, and how many required conversion to sternotomy. These were assessed to determine whether surgical experience resulted in improvement.

Results showed that those efficiencies improved during the study. Cardiopulmonary bypass time decreased from about 140 minutes to 130 minutes. Cross-clamp time improved more dramatically from about 110 minutes to 90 minutes. And the percentage of cases requiring postoperative or intraoperative blood transfusion improved from about 24% to 10%.

PATIENT SELECTION CRITERIA: ALGORITHM

After 500 cases, enough data had been collected to create an algorithm for determining which patients would be eligible for mitral valve repair via the robotic approach vs a sternotomy-based approach. Use of the algorithm (**Figure 1**) relies on results from echocardiography and computed tomography (CT) for most of the selection process. Echocardiography results that indicate a sternal approach would be preferred include significant aortic insufficiency, which complicates cardioplegia delivery, severe mitral annulus calcification, left ventricular dysfunction, and pulmonary hypertension. CT results are important in assessing patients for aortoiliac atherosclerosis, femoral artery diameter, and pectus excavatum. The existence of any of these indicates a patient more appropriate for the sternal approach than the robotic approach.

ALGORITHM IMPACT

What was the effect of this algorithm? In the 500 cases after its implementation, the stroke rate decreased by more than half—from 10 incidents before to 4 incidents after—and mitral replacements dropped from 4 to 0. The rate of conversion from robotic repair to conventional sternotomy in this patient series also

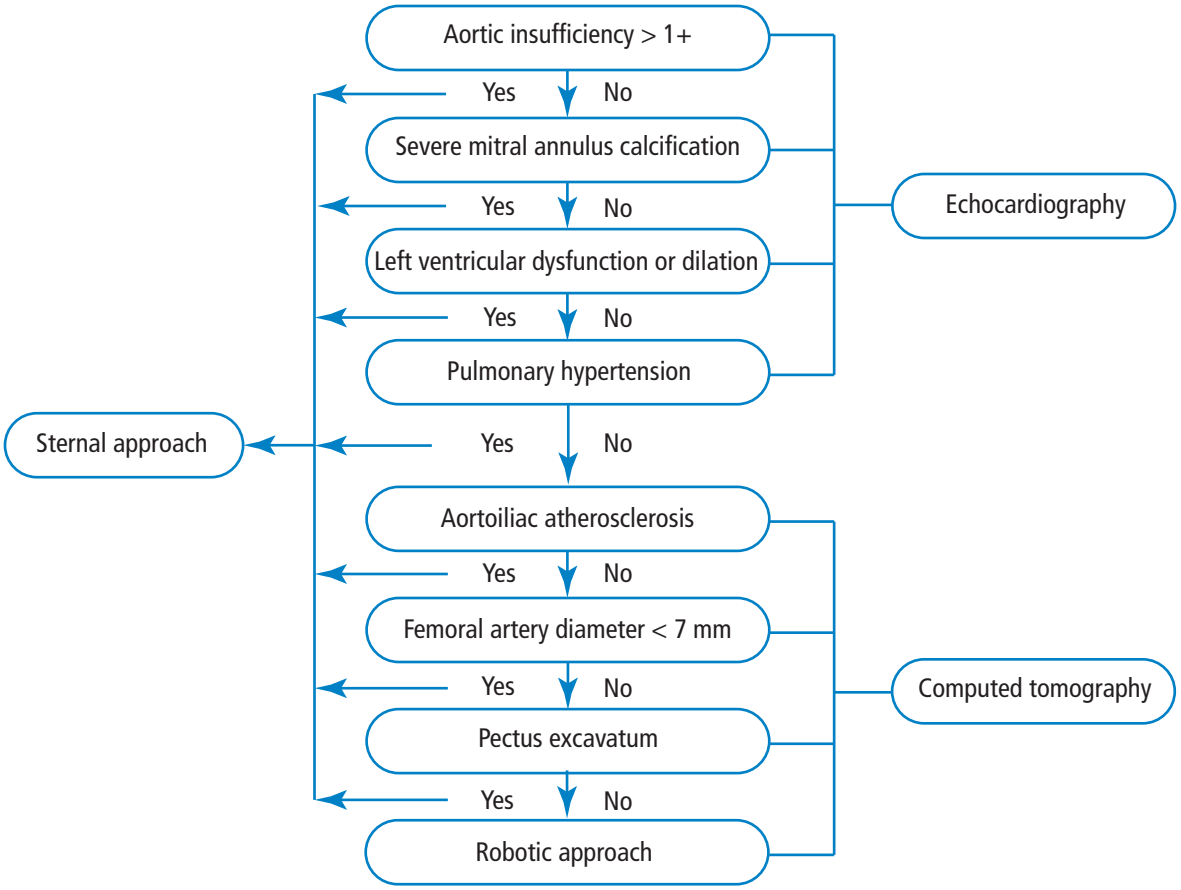

Figure 1. Algorithm for determining patient eligibility for the robotic approach to mitral valve repair.[1]

improved, although this likely reflects surgical experience more than the algorithm. The conversion rate initially increased as surgeons gained experience with the robotic techniques. It rose to 4% during the first 300 to 400 cases, then dropped to 2% at the 500-case mark. It leveled off for the next 300 cases before dropping to 0 toward the end of the series.

Other metrics improved as well, which were attributed to a combination of surgical experience with robotic assistance and use of the patient-selection algorithm. The stroke risk declined to 0.8%, ischemic and cardiopulmonary bypass times declined, and the transfusion rate declined. No mitral replacements were done in the last 500 cases, and the conversion to conventional sternotomy rate declined to 1%.

In conclusion, this Cleveland Clinic study showed that a combination of a focused preoperative assessment using the patient-selection algorithm and increased surgical experience with robotic techniques enhanced clinical outcomes and improved procedural efficiency associated with robotically assisted mitral valve surgery.

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Aortic replacement in cardiac surgery

ABSTRACT

The number of aorta procedures performed annually in the United States has grown substantially during the past decade. Cleveland Clinic is a leader in research on the risk of aortic dissection in patients with a bicuspid or tricuspid aortic valve and associated aneurysm, which has led to changes in the recommendations of when to operate. Safety and efficacy data support more proactive treatment for most patients with thoracic aortic aneurysm and/or dissection with a growing emphasis on the need to provide life-long care to patients with aortic conditions.

KEY POINTS

Adding a proximal thoracic aortic procedure to cardiac surgery does not adversely affect safety and efficacy.

Presence of a bicuspid aortic valve does not significantly affect outcomes of aortic root procedures.

Data support aortic replacement in patients when the aortic root vessels reach 5.5 cm in diameter.

Use of circulatory arrest does not directly affect the stroke risk associated with ascending aortic replacement surgery, but it may be a marker for more serious pathology.

This article is based on Dr. Roselli's presentation at the Sones/Favaloro Scientific Program, "Transforming the Delivery of Cardiovascular Care: Research and Innovation in the Heart & Vascular Institute," held in Cleveland, OH, November 18, 2016. It was also presented at the American Association for Thoracic Surgery. The article was drafted by *Cleveland Clinic Journal of Medicine* and was then reviewed, revised, and approved by Dr. Roselli.

Dr. Roselli reported research grant support from Gore; consulting fees from Bolton, Gore, and Medtronic; and honoraria for speaking/teaching from Vascutek.

doi:10.3949/ccjm.84.s4.07

In 2015, Cleveland Clinic cardiac and vascular surgeons performed more than 1,000 open or endovascular operations involving the thoracic aorta, the most of any US medical center. Cardioaortic operations account for a large volume of the procedures performed annually in the Department of Thoracic and Cardiovascular Surgery at Cleveland Clinic. Of the approximately 4,000 cardiac procedures performed per year at Cleveland Clinic, nearly 1 in 5 includes thoracic aorta replacement.

Providing optimal care to patients with thoracic aortic disease requires a multidisciplinary approach beginning in the preoperative phase and extending through the life of patients and their families. In the Aortic Center at Cleveland Clinic Heart & Vascular Institute, cardiovascular medicine and imaging specialists, geneticists, and cardioaortic and vascular surgeons work in unison to provide the highest quality care. This involves active analysis of outcomes to continuously improve the quality of care provided.

This paper examines trends in the treatment of thoracic aortic disease, describes the different types of therapeutic procedures, and explores details about their safety and efficacy by summarizing the key research findings on cardioaortic procedures published from our Center during the last 2 years.

SEGMENTAL PERSPECTIVE

The thoracic aorta begins in the aortic root, which includes the aortic valve, and it is both anatomically and physiologically different from the ascending aorta (**Figure 1**).

In general, there are 4 types of aortic repair procedures that include the root (**Figure 2**):

1. Modified Bentall procedure with a mechanical composite valve graft (CVG)
2. Modified Bentall procedure with a biologic CVG
3. Homograft, or allograft, root replacement with a human cadaveric aorta
4. Valve-preserving aortic root replacement with a prosthetic graft but which leaves the patient's native aortic valve intact with or without accompanying repair of that valve.

A Cleveland Clinic study published in 2016 analyzed 957 elective aortic root replacement procedures performed from 1995 through 2014.[1] The number of procedures in this study were evenly distributed across these 4 aortic root replacement strategies.

The perioperative mortality rate was 0.73% and the stroke rate was 1.4%. For 3 of the 4 procedure types, 15-year survival rates were excellent: above 80% for mechanical CVG, allografts, and valve-preservation surgery. The survival rate for biologic CVG was lower (57%), reflecting the difference in population, as these were typically older patients.

This study also demonstrated the durability of these operations, with a reoperation rate of approximately 15% at 15 years. Reoperation rates for patients having undergone these operations should be considered in the light of competing risk of death from other causes. As such, the risk of reoperation after mechanical CVG, biologic CVG, and valve-preserving procedures were similar, ranging from 5% to 15%. Allografts had the highest reoperation rates (approximately 30% at 15 years) because they used to be the biologic root replacement of choice for younger patients but have since been found to wear out at a similar rate as other bioprostheses.[2] As a result, they are now used less frequently for elective indications.

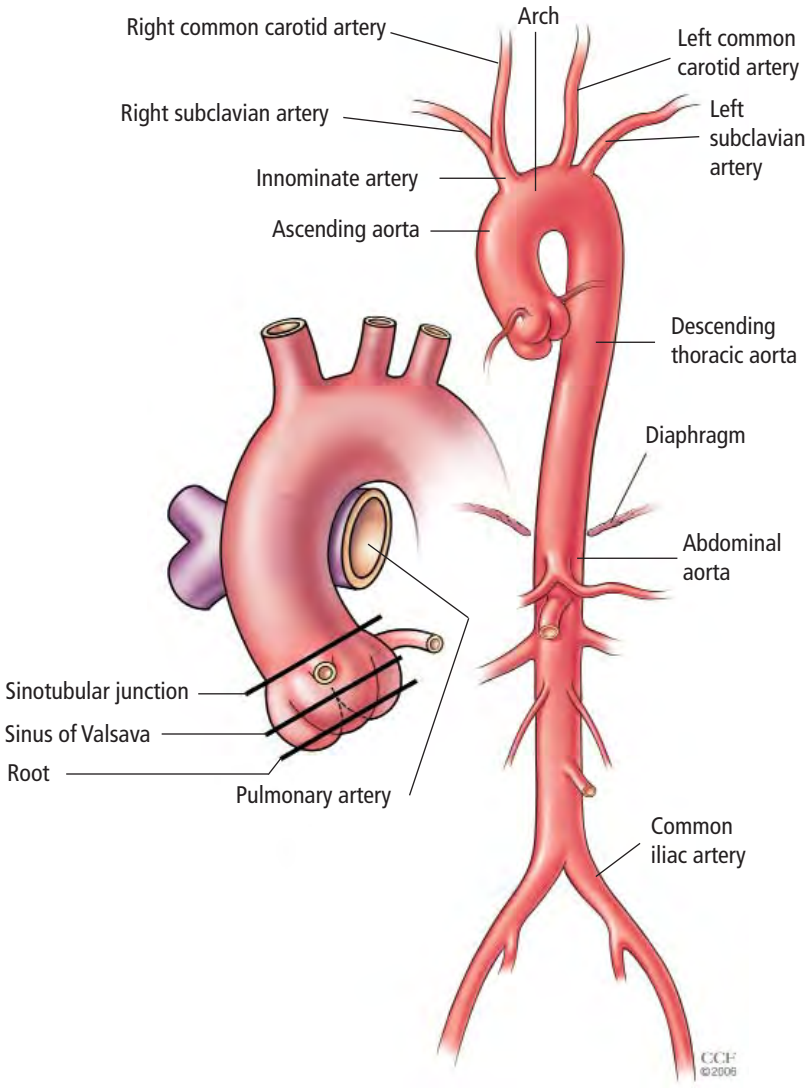

Figure 1. The sections of the aortic root and its position in the aorta.

The trend in choice of aortic root replacement procedures varied greatly during the study (**Figure 3**). The greatest shift was seen for valve-preserving operations, which accounted for about 60% of all root replacement operations in 2014, up from about 9% in 1995. The use of biologic CVG replacement stayed about the same at 30%, while mechanical CVG usage decreased from about 25% to 5%. The most dramatic decrease was in allograft replacements, dropping from nearly 70% in 2000 to about 5% in 2014 for the reasons described above. The use of allografts at our institution remains high, however, at more than 100 per year, mostly for urgent treatment of endocarditis.

Cleveland Clinic practitioners now perform more than 80 valve-preserving root replacement operations per year, approximately 700 overall.

Clinical implications

For patients presenting with aortic root aneurysm, consider the following:

- Valve-preserving aortic root replacement is preferred for patients with root aneurysm and a tricuspid aortic valve without valve stenosis.
- Valve-preserving aortic root replacement with either remodeling or reimplantation is also preferred for patients with a bicuspid aortic valve with a dilated annulus or root aneurysm, but without aortic-associated aortic valve stenosis
- Mechanical CVG is preferred for younger patients with root aneurysm and aortic valve stenosis

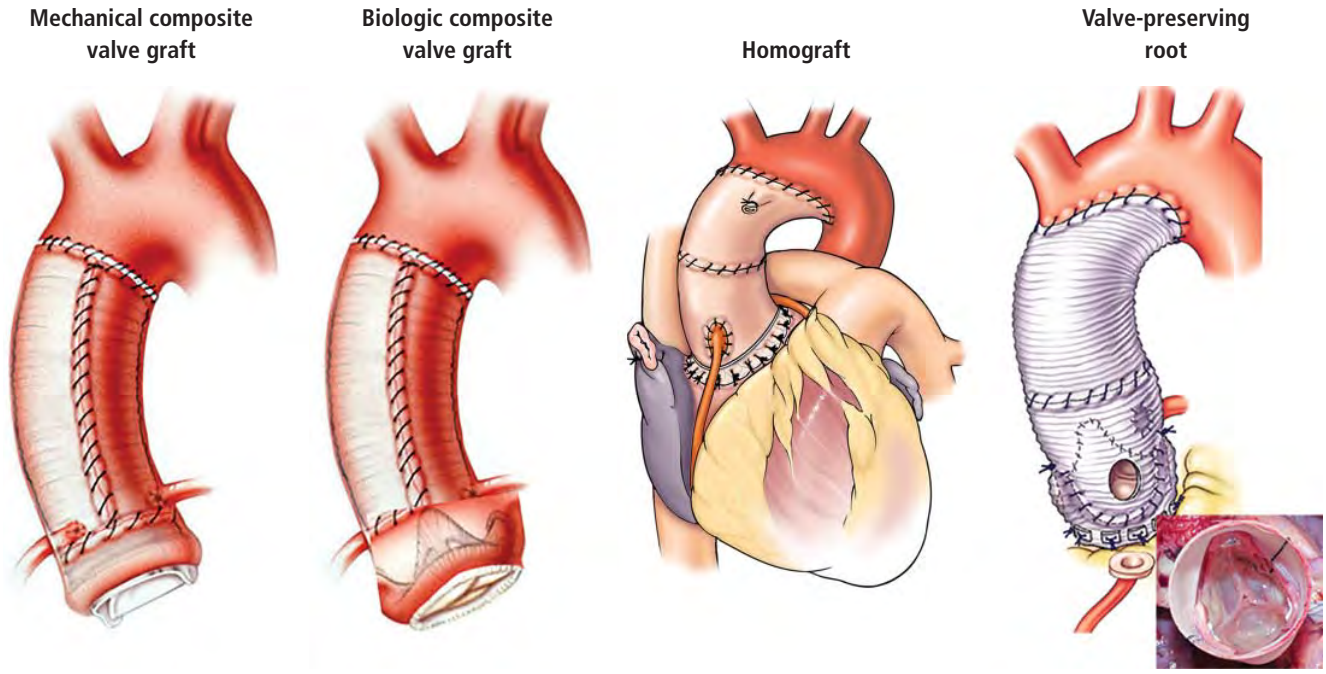

Figure 2. The 4 types of ascending aorta and aortic root replacement surgeries.

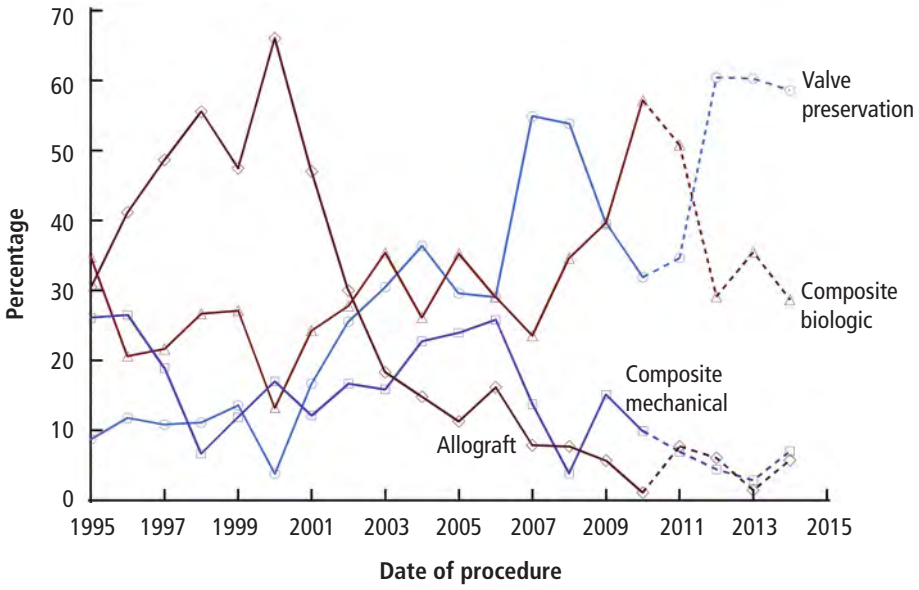

Figure 3. Trends in number of root replacement surgeries at Cleveland Clinic. Note: dotted lines indicate projected trends.

Reprinted from Svensson LG, et al. Long-term survival, valve durability, and reoperation for 4 aortic root procedures combined with ascending aorta replacement. J Thorac Cardiovasc Surg 2016; 151:764–774. © 2016 with permission from The American Association for Thoracic Surgery. http://www.sciencedirect.com/science/journal/00225223.

(usually a bicuspid or unicuspid aortic valve); biomechanical CVG is preferred for older patients with root aneurysm and associated aortic valve stenosis.

- Allografts are now reserved primarily for patients with endocarditis and for older patients with a small aortic root.

WHAT ARE THE RISKS WITH ASCENDING AORTIC REPAIR?

The condition of the patient at presentation has become the strongest predictor of surgical risk. An improved understanding of these associations can improve our prediction of risks and the decision about when to operate. Patients needing aortic replacement can present with a broad spectrum of pathologies. For example, a patient who presents with acute type A dissection is quite different from a patient with an enlarging ascending aneurysm who had a previous aortic valve replacement for bicuspid aortic valve stenosis as a young adult. Further, both are different from the elderly patient with the complex

constellation of coronary disease, multivalve disease, atrial fibrillation, and an ascending aneurysm—an increasingly common presentation.

Guidelines supporting the decision to replace the aorta in patients with chronic asymptomatic aortic disease are limited by a lack of data on surgical risk and long-term effectiveness.

A study from the Society of Thoracic Surgeons database assessed outcomes in patients who had surgical replacement of the ascending aorta, with or without root repair.[3] The operative mortality (either in-hospital or within 30 days of surgery) was 8.3% and ranged from 3.5% for elective surgery to 9.1% for urgent surgery, and 21.5% for emergencies. End-stage kidney disease and reoperation were also shown to be independent predictors of risk in that study.

Outcomes at Cleveland Clinic for elective ascending aortic procedures are much better than these national averages. Outcomes data are important to patients when making a decision about prophylactic surgery. In a study analyzing 1,889 patients undergoing elective ascending replacement at Cleveland Clinic between 2006 and 2010, the operative mortality was only 0.5% for those undergoing isolated ascending replacement and 2% for those requiring a multicomponent operation. In the multicomponent group, 87% included aortic valve replacement, 29% coronary bypass, and 25% underwent more than 2 different combined procedures.[4]

Patient risk factors

A comparison of patient risk factors for the 2 groups showed that the isolated replacement group had larger aortic diameters, more extensive disease with dilated descending aortas, and were more frequently undergoing a reoperation than the multicomponent group.

To further define the risks, we conducted a propensity-matching study of 197 pairs of these patients, comparing 62 variables including aortic morphology data gathered from 3-dimensional analysis of computed tomography scans. Results showed no differences in survival rates between the groups during 4 years of follow-up.[4] A comparison of the risk of other perioperative complications—death, stroke, need for dialysis, respiratory failure, and bleeding—also showed no differences between the groups.

Does adding ascending aortic replacement to other cardiac procedures increase the surgical risk?

To answer this question, we collected data on Cleveland Clinic patients between 2006 and 2011 who had aortic surgery in combination with cardiac surgery (N = 1,677) and compared them against a similar cohort who only had cardiac surgery (N = 12,617).[5] The objectives were to determine the risk of adding aortic surgery to an elective cardiac operation. A second objective was to determine the impact of circulatory arrest on outcomes.

Comparison 1. We identified 1,284 matched pairs from the 2 groups. Data showed a slightly higher risk of stroke in patients who had cardioaortic surgery (2.4%) compared with those who had cardiac surgery alone (1.7%); however, the mortality rate was not significantly different between the groups.

Does circulatory arrest affect the stroke rate?

From the matched pairs of patients who underwent cardioaortic surgery, we identified a subset of patients who had circulatory arrest and compared them with those who did not have circulatory arrest. The circulatory arrest group had worse outcomes. Mortality rates were 4.1% vs 1.0%, respectively, and stroke rates were 3.9% vs 0.9%.

This raised the question of whether circulatory arrest was the cause of the worse outcomes or a marker of patients with more advanced disease.

The decision to use circulatory arrest is primarily based on 2 factors:

- Patient-specific factors, such as those with advanced aortic disease in whom circulatory arrest is unavoidable.
- Surgeon preference/technical decision. For example, in a patient with a bicuspid valve, the surgeon may choose to use a brief period of circulatory arrest instead of clamping the proximal arch.

Comparison 2. To further define the impact of circulatory arrest, we grouped the patients who underwent cardioaortic surgery (N = 1,677) into those who had circulatory arrest (n = 728) or no arrest (n = 949). From those groups, we identified 324 matched pairs of patients and compared the outcomes.

Our results showed no differences associated with the use of circulatory arrest in rates of mortality (1.2% with and 0.6% without) or stroke (1.5% for both groups) when comparing patients with similar disease characteristics. These results suggest that the need for circulatory arrest was probably not the culprit but more likely a marker of patients with more complex disease. It is their more advanced disease that puts them at higher risk.

Comparison 3. To determine whether circulatory arrest has an overall impact on cardiac surgery, we took the population of matched cardioaortic patients from comparison 2 regardless of whether they had circulatory arrest and compared them to the larger group of

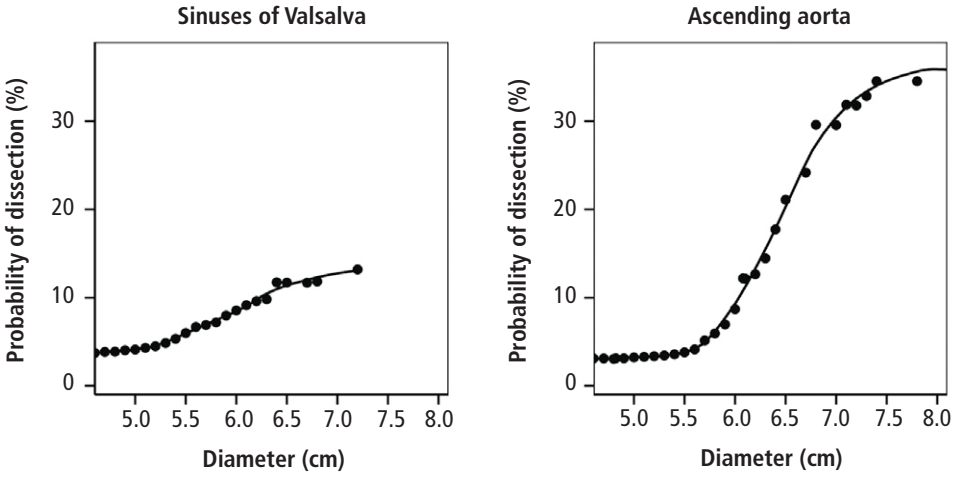

Figure 4. Risk of dissection in patients with bicuspid aortic valve increases more steeply in valves with a diameter larger than 5.5 cm.

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12,617 cardiac surgery-alone patients. Again, results indicated that the addition of aortic surgery had no real impact on outcomes. Both groups had similarly low risks for both mortality (0.9% with aortic replacement vs 0.5% without) and stroke (1.4% with aortic replacement vs 1.1% without).

Clinical implications

This multistepped comparison study found that adding ascending aortic replacement to cardiac surgery had essentially no impact on mortality or stroke. These data provide evidence indicating that cardiac surgeons should be more proactive in deciding whether to add ascending aorta replacement to cardiac surgery when treating a patient with a dilated ascending aorta. It must be noted, however, that patients with more advanced aortic disease are a higher risk population. All of these findings highlight the importance of managing thoracic aortic disease within an experienced multidisciplinary center.

AORTIC DISSECTION RISK IN PATIENTS WITH A BICUSPID AORTIC VALVE AND AORTOPATHY

To help stratify these risks, a Cleveland Clinic study published in 2015 analyzed data from 1,181 patients with bicuspid aortic valve and associated aortopathy. The goal was to determine the risk of aortic dissection based on the diameter of the ascending aorta.[6] Results showed that the probability of dissection increased steeply when the aortic root was 5 cm and the ascending aorta reached about 5.5 cm (**Figure 4**).

These findings provided important evidence supporting the need to be more proactive in the decision to perform aortic replacement. Furthermore, the data prompted the American Heart Association and the American College of Cardiology to publish a clarification statement providing more detail to its thoracic aorta and aortic valve guidelines. This update indicates that in patients with a bicuspid aortic valve, it is reasonable to recommend surgery when the aorta is 5 cm instead of waiting until 5.5 cm in high-volume centers that have demonstrated excellent surgical outcomes. This clarification statement was based on Cleveland Clinic outcomes showing a mortality rate of 0.25% and a stroke rate of 0.75% in a population that included patients undergoing emergency aortic dissection surgery.[6]

This study also analyzed data on patients treated with expectant care with optimal medical management and imaging surveillance (ie, to monitor the dilated aorta). Results from this subset showed that the probability of needing an aortic intervention is about 60% during the next 10 years once the aorta is within the 4.5 cm to 5 cm range.

Another study addressing the correlation between risk and aortic size examined 771 patients with a dilated ascending aorta (≥ 4 cm) and a tricuspid aortic valve.[7] This study confirmed the use of patient height as an important factor for indexing maximum aortic size to patient body size for predicting risk of late complications. Specifically, this study suggested that the risk of complications from aortic aneurysm rises when the maximum aortic area-to-height ratio exceeds 10. This serves as a follow-up to previously published data demonstrating the value of aortic cross-sectional area-to-height ratio as a predictor of risk in patients with bicuspid valves.[8] In general, the results of all 3 studies suggest that we should be more proactive in operating on patients with a dilated ascending aorta to prevent later risk of rupture or dissection when the surgical risk is low.

When making decisions about patients who need

aortic replacement, it is important to assess many patient details: their aortic disease, their other non-aortic comorbidities, and the institution's outcomes. This decision is best made by a dedicated cardioaortic specialist at a dedicated center of excellence.

WHAT IS COMING?

Minimally invasive and endovascular surgery

More ascending aortic surgeries are being done using minimally invasive approaches. At Cleveland Clinic, about 40% of isolated ascending aortic operations are performed through a mini-sternotomy J incision approach. A Cleveland Clinic study published in 2017 evaluated outcomes from this less-invasive technique for proximal aortic surgery compared with full median sternotomy.[9] Results showed it was an effective approach with fewer complications, shorter hospital stays, and lower costs.

Stent grafts

The role for stent-graft devices has continued to expand.[10] At Cleveland Clinic, we have performed more than 40 ascending aortic stent-graft procedures, one of the largest numbers in the world. Having this stent-graft option has enabled us to provide treatment for the patients at exceedingly high risk who previously had few or no options. Industry partners are working to develop dedicated devices for these indications, and we are working with them to bring new device trials to this underserved population of patients.

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