Circulation Editors’ Picks: Most Read Articles on the Topic of Aortic Disease

The Editors

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Increased Risk of Left Heart Valve Regurgitation Associated With Benfluorex Use in Patients With Diabetes Mellitus: A Multicenter Study

Summary—The aim of this population-based multicenter study was to compare the frequency of left heart valve regurgitations diagnosed by echocardiography in prospectively included diabetic patients who had taken benfluorex for at least 3 months and in matched diabetic control subjects (matched for age, sex, body mass index, smoking, dyslipidemia, hypertension, and coronary artery disease) without previous exposure to the drug. We found a significant increase in the frequency of mild or greater left heart valve regurgitations among patients treated with benfluorex compared with propensity-matched control subjects (31% vs. 13%; P < 0.001). Exposure to benfluorex was associated with a >3-fold increase in the risk of mild or greater left heart valve regurgitations. Furthermore, the risk of benfluorex-induced regurgitations was more important for the aortic valve compared with the mitral valve. Finally, the higher frequency of left heart valve regurgitations among benfluorex-treated patients compared with control subjects was due mainly to an increased frequency of mild regurgitations. The natural history of benfluorex-induced valve abnormalities needs further research.

Conclusions—Our results indicate that the use of benfluorex is associated with a significant increase in the frequency of left heart valve regurgitations in diabetic patients. The natural history of benfluorex-induced valve abnormalities needs further research.

Transcatheter Aortic Valve Replacement for Degenerative Bioprosthetic Surgical Valves: Results From the Global Valve-in-Valve Registry

Summary—In the last decade, bioprosthetic valves have been used more commonly during surgical valve replacements; it is estimated that in subsequent years, many patients will suffer from failed surgical bioprostheses. The Global Valve-in-Valve Registry, which includes in the present analysis 202 patients from 38 centers, is the first large, comprehensive evaluation of transcatheter aortic valve replacement with the use of either Edwards SAPIEN (Edwards Lifesciences, Irvine, CA) or CoreValve (Medtronic, Minneapolis, MN) devices for failed surgically inserted aortic bioprostheses, including 1-year clinical and echocardiographic analyses. According to the registry, the valve-in-valve approach is effective and relatively safe. Improvement in patient functional capacity was clear: 84.1% of treated patients were classified as New York Heart Association class I/II early after the procedure. Clinical and hemodynamic results are maintained in 1-year follow-up. Thirty-day mortality and stroke rates (8.4% and 2%, respectively) are comparable to those in other transcatheter aortic valve replacement cohorts. An efficacy concern involved moderately elevated postprocedural gradients, with predictors in multivariate analysis that include the degree of bioprosthesis stenosis and treatment with an Edwards SAPIEN inside a small bioprosthesis. Safety concerns included ostial coronary obstruction (3.5%) and device malposition (15.3%) resulting in relatively high rates of a need for implantation of another transcatheter aortic valve replacement device (8.4%) and retrieval of a CoreValve (8.9%). Operators of valve-in-valve procedures should be skilled in handling device malposition and related technical maneuvers, if needed. The possible impact on cardiac surgery practice includes referral of patients with failed bioprostheses who are at very high surgical risk to valve-in-valve and selection of valve class during surgery (mechanical versus biologic), in favor of the use of bioprostheses.

Conclusions—The valve-in-valve procedure is clinically effective in the vast majority of patients with degenerated bioprosthetic valves. Safety and efficacy concerns include device malposition, ostial coronary obstruction, and high gradients after the procedure.

Moderate Aortic Enlargement and Bicuspid Aortic Valve Are Associated With Aortic Dissection in Turner Syndrome: Report of the International Turner Syndrome Aortic Dissection Registry

Summary—Aortic dissection and rupture occurs in young women with Turner syndrome. Although this observation is reiterated in case reports, the rarity of its occurrence has limited the availability of information about the natural history and the clinical picture of aortic dissection in Turner syndrome. We estimated that it would require 50,000 patient-years in a prospective longitudinal study to accumulate data similar to the data obtained from the 20 cases we describe from the International Turner Syndrome Aortic Dissection registry. We show that aortic dissection can occur in individuals with Turner
syndrome who have no other documented cardiovascular problems. Pregnancy was associated with 1 of 19 subjects in the International Turner Syndrome Aortic Dissection registry, which is 10 times more common than in the general TS population. Bicuspid aortic valve occurred in 95% of the subjects, but it also occurs commonly in those without aortic dissection. We found that aortic dissection in Turner syndrome occurs at a significantly smaller aortic size than in other genetically triggered aortopathies. Data from 5 individuals with serial echocardiographic measurements obtained before their aortic dissection indicates that a stable ascending aortic size over time may not be a reassuring finding. We conclude that an ascending aortic size index >2.5 cm/m² is a significant risk factor for aortic dissection in those with Turner syndrome.

Conclusions—Aortic dissection in Turner syndrome occurs in young individuals at smaller aortic diameters than in the general population or other forms of genetically triggered aortopathy. The absence of aortic valve or other cardiac malformations appears to markedly reduce the risk of aortic dissection However, aortic dissection can occur in Turner syndrome without cardiac malformations or hypertension. Individuals with Turner syndrome who are >18 years of age with an ascending aortic size index >2.5 cm/m² should be considered for an aortic operation to prevent aortic dissection.  

Long-Term Survival After Aortic Valve Replacement Among High-Risk Elderly Patients in the United States: Insights From the Society of Thoracic Surgeons Adult Cardiac Surgery Database, 1991 to 2007

Summary—We used the Society of Thoracic Surgeons database to examine long-term survival among 145,911 aortic valve replacement patients ≥65 years of age. In-hospital complications and long-term survival were stratified by age, Society of Thoracic Surgeons perioperative risk of mortality, and several comorbidities. We found that long-term survival after surgical aortic valve replacement in the elderly is excellent, although patients with a high Society of Thoracic Surgeons perioperative risk of mortality and those with certain comorbidities (lung disease and renal failure, particularly dialysis-dependent renal failure) carry a particularly poor long-term prognosis. Although the current Society of Thoracic Surgeons perioperative risk of mortality calculator provides reasonable differentiation of long-term survival, a model calibrated to the prediction of long-term risk would be expected to add accuracy. We believe our study is significant in that it examines an area in which there are limited data, namely contemporary long-term outcomes after aortic valve replacement in older individuals. We believe that our findings may improve long-term outcomes for this elderly population by helping to establish best practices in operative and perioperative care.

Conclusions—Long-term survival after surgical aortic valve replacement in the elderly is excellent, although patients with a high Society of Thoracic Surgeons perioperative risk of mortality and those with certain comorbidities carry a particularly poor long-term prognosis.

Determinants and Prognostic Significance of Exercise Pulmonary Hypertension in Asymptomatic Severe Aortic Stenosis

Summary—The management and timing of surgery in asymptomatic patients with severe aortic stenosis remain matters of concern. The risks of aortic valve surgery and late complications of prosthesis in such patients need to be balanced against the possible prevention of sudden death and lowering of cardiac mortality. Hence, early elective surgery could be proposed only to well-selected patients considered at high risk of poor outcome. In the present study, 105 consecutive asymptomatic patients with severe aortic stenosis underwent comprehensive resting and exercise stress echocardiography to evaluate the presence of pulmonary hypertension (PHT). The results showed that 55% of asymptomatic patients may develop exercise PHT. Patients with exercise PHT had significantly lower cardiac event-free survival and a markedly higher rate of death than those without exercise PHT. In addition, exercise PHT was associated with poorer outcome independently of demographic and resting echocardiographic data and exercise-induced changes in mean transaortic pressure gradient. Beyond both resting aortic stenosis severity and systolic pulmonary arterial pressure, the assessment of the presence of exercise PHT provided important incremental predictive value. Even in patients with markedly elevated aortic jet velocity, those with exercise PHT depicted a higher risk of reduced cardiac event-free survival. These results strongly support the use of exercise stress echocardiography in the management of asymptomatic severe aortic stenosis. Early elective aortic valve surgery to prevent irreversible left ventricular myocardial damage, diastolic dysfunction, and symptoms could be advised in patients developing exercise PHT. In contrast, asymptomatic patients with no exercise PHT may be conservatively followed up.

Conclusions—In asymptomatic patients with severe aortic stenosis, the main determinants of Ex-PHT are male sex, resting systolic pulmonary arterial pressure, and exercise parameters of diastolic burden. Moreover, Ex-PHT is associated with a 2-fold increased risk of cardiac events. These results strongly support the use of exercise stress echocardiography in asymptomatic aortic stenosis.

Effects of Phosphodiesterase Type 5 Inhibition on Systemic and Pulmonary Hemodynamics and Ventricular Function in Patients With Severe Symptomatic Aortic Stenosis

Summary—Pressure overload resulting from aortic stenosis causes maladaptive ventricular and vascular remodeling that has deleterious consequences. Patients often present when compensatory mechanisms have been exhausted with advanced heart failure and abnormal hemodynamics characterized by pulmonary venous congestion, pulmonary hypertension, and afterload mismatch. These patients are either inoperable or at increased risk for surgery. Other patients have valve replacement before this clinical decompensation, but their outcomes are worse if there is associated hypertrophic ventricular remodeling and diastolic dysfunction. Existing experimental and clinical studies raise the interesting possibility that phosphodiesterase type 5 inhibition may both favorably alter abnormal hemodynamics and retard or reverse maladaptive remodeling in patients with aortic stenosis. Here, we show that a single dose of a phosphodiesterase type 5 inhibitor is safe in patients with severe symptomatic aortic stenosis and is associated with acute improvements in pulmonary and systemic hemodynamics, resulting in biventricular unloading. Importantly, these data suggest that afterload is not necessarily fixed in patients with aortic stenosis and that reducing vascular afterload may improve hemodynamics in these patients. If it is demonstrated that these hemodynamic benefits can be sustained, perhaps adjunctive medical therapy with phosphodiesterase type 5 inhibition in symptomatic patients with advanced heart failure could serve as a stabilizing bridge to definitive therapy with valve replacement with less risk than a balloon valvuloplasty. Our findings support the need for longer-term studies to evaluate the role of phosphodiesterase type 5.
inhibition as adjunctive medical therapy in patients with aortic stenosis to address these clinical needs.

Conclusions—This study shows for the first time that a single dose of a phosphodiesterase type 5 inhibitor is safe and well tolerated in patients with severe aortic stenosis and is associated with improvements in pulmonary and systemic hemodynamics resulting in biventricular unloading. These findings support the need for longer-term studies to evaluate the role of phosphodiesterase type 5 inhibition as adjunctive medical therapy in patients with aortic stenosis.6

Type 2 Diabetes Mellitus Is Associated With Faster Degeneration of Bioprosthetic Valve: Results From a Propensity Score-Matched Italian Multicenter Study

Summary—Biological prostheses are increasingly implanted to treat disparate cardiac valve diseases. Postoperative structural valve degeneration represents the most relevant drawback of such artificial valves, sometimes leading to substantial leaflet tissue derangement, clinical deterioration and ultimately, reoperation. The causes and pathogenetic mechanisms of artificial valve structural impairment are not yet fully understood. Atherosclerosis-related risk factors have been suggested recently, through analysis of postoperative outcome in limited patient experiences, to play a role in postimplantation bioprosthetic failure. This multicenter retrospective study sought to investigate specifically the early and long-term influence of type 2 diabetes mellitus in terms of composite outcome in patients undergoing bioprosthetic heart valve implantation in the aortic or mitral position. Propensity score analysis enabled a 1:1 match in 2226 diabetic and nondiabetic subjects among 6184 patients submitted to cardiac valve replacement with biological valves during a 21-year period. In this study, type 2 diabetes mellitus was shown to be an independent predictor of unfavorable outcome, either in terms of reduced life expectancy or in terms of structural bioprosthetic valve degeneration, with the insulin-treated subjects showing the most unfavorable postoperative results. Furthermore, diabetes mellitus was shown to negatively affect postoperative tissue valve performance, irrespective of other associated cardiovascular risk factors. Additional studies are needed to disclose the pathogenetic mechanisms by which such a metabolic disorder may affect the structural integrity of tissue valves and to investigate methods to reduce such an adverse event. Meanwhile, strict clinical surveillance is advised on the basis of the currently witnessed higher rate of structural valve degeneration in diabetic patients submitted to cardiac valve replacement with a biological prosthesis.

Conclusions—Patients with type 2 diabetes mellitus undergoing bioprosthetic valve implantation are at high risk of early and long-term mortality, as well as of structural valve degeneration.7

Clinical Implications of Electrocardiographic Left Ventricular Strain and Hypertrophy in Asymptomatic Patients With Aortic Stenosis: The Simvastatin and Ezetimibe in Aortic Stenosis Study

Summary—This is the first study to examine the predictive value of ECG left ventricular strain and hypertrophy during watchful waiting in asymptomatic patients with aortic stenosis. In analyses of 1533 patients with asymptomatic mild to moderate aortic stenosis (aortic peak flow velocity ≥2.5 and ≤4.0 m/s) included in the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study, cardiovascular event rates were considerably higher in those with ECG left ventricular strain or hypertrophy. Despite similar aortic stenosis severity (aortic peak flow velocity ≥3.0 m/s), annual risks of heart failure were ≈1.4% and 0.4% in those with and without ECG strain, respectively. The presence of ECG left ventricular strain and hypertrophy remained significantly associated with poor prognosis also when adjusted by aortic valve area index and mean aortic gradient or when the analyses were updated with annual reexaminations. Thus, low-cost and easily accessible ECG left ventricular strain and hypertrophy data provide valuable tools for risk stratification in patients with aortic stenosis. Whether ECG strain identifies those whose prognosis would be improved by earlier aortic valve replacement merits further study. Finally, treatment with low-dose simvastatin does not influence the progression of ECG left ventricular hypertrophy or strain.

Conclusions—ECG left ventricular strain and left ventricular hypertrophy were independently predictive of poor prognosis in patients with asymptomatic aortic stenosis.8

Health-Related Quality of Life After Transcatheter Aortic Valve Replacement in Inoperable Patients With Severe Aortic Stenosis

Summary—Many patients with severe aortic stenosis do not undergo surgical valve replacement because of prohibitive operative risk. In a cohort of such patients, the Placement of Aortic Transcatheter Valves (PARTNER) trial recently showed that transcatheter aortic valve replacement increased 12-month survival by an absolute margin of 20% but was associated with increased risks of vascular complications and stroke compared with standard therapy, which included balloon aortic valvuloplasty in the majority of subjects. In this trial, quality of life was assessed prospectively with the Kansas City Cardiomyopathy Questionnaire and the Short Form-12 General Health Survey. We found that the overall summary score of the Kansas City Cardiomyopathy Questionnaire, the primary quality-of-life end point, improved 20 to 30 points on a 100-point scale 1, 6, and 12 months after transcatheter aortic valve replacement, whereas the improvement in the control group was 10 to 12 points at 1 and 6 months and only 4 points at 12 months. Similar patterns were observed for the other quality-of-life measures. Thus, during the first year after intervention, quality of life was substantially better in the transcatheter aortic valve replacement group than in the control group in this clinical trial population.

Conclusions—Among inoperable patients with severe aortic stenosis, compared with standard care, transcatheter aortic valve replacement resulted in significant improvements in health-related quality of life that were maintained for at least 1 year.9

Arterial Pulse Wave Dynamics After Percutaneous Aortic Valve Replacement: Fall in Coronary Diastolic Suction With Increasing Heart Rate as a Basis for Angina Symptoms in Aortic Stenosis

Summary—Using the new technique of percutaneous aortic valve replacement in combination with wave intensity analysis, we have identified abnormalities in coronary physiology that are rapidly restored to normal after valve implantation. In addition to being of mechanistic interest, quantification of coronary physiological reserve and in particular its paradoxical reversal may offer a potential way of assessing the severity of aortic stenosis in the presence of comorbidities that may mimic or obscure anginal symptoms. Although currently
Diabetes Mellitus Worsens Diastolic Left Ventricular Dysfunction in Aortic Stenosis Through Altered Myocardial Structure and Cardiomyocyte Stiffness

Summary—In aging populations, diabetes mellitus (DM) and aortic stenosis (AS) are becoming frequent comorbidities. Studies looking at the interaction between DM and AS investigated mainly the progression of sclerocalcific valvular dysfunction. In heart failure (HF), DM raises diastolic left ventricular (LV) stiffness, which adversely affects morbidity and mortality. The DM-related rise in diastolic LV stiffness was observed both in HF with reduced ejection fraction and in HF with normal ejection fraction. In HF with reduced ejection fraction, DM affected myocardial stiffness through excessive fibrosis and arteriolar or capillary deposition of advanced glycation end products, whereas in HF with normal ejection fraction, DM increased myocardial stiffness through elevation of cardiomyocyte F passive. The observed increase in diastolic LV stiffness was shown to result from all 3 aforementioned mechanisms, namely excessive fibrosis, intramyocardial vascular advanced glycation end product deposition, and elevated cardiomyocyte F passive. The latter could be attributed to hypophosphorylation of the stiff isoform of the cytoskeletal protein titin, which is largely responsible for cardiomyocyte F passive. The observed increase in diastolic LV stiffness in patients suffering from both AS and DM. This increase was evident from higher LV end-diastolic pressure at comparable LV end-diastolic volume index. Furthermore, the increase in diastolic LV stiffness was shown to result from all 3 aforementioned mechanisms, namely excessive fibrosis, intramyocardial vascular advanced glycation end product deposition, and elevated cardiomyocyte F passive. The latter could be attributed to hypophosphorylation of the stiff isoform of the cytoskeletal protein titin, which is largely responsible for cardiomyocyte F passive. The observed increase in diastolic LV stiffness in patients suffering from both AS and DM could predispose them to earlier development of heart failure symptoms and an earlier need for aortic valve replacement.

Conclusions—Worse diastolic LV dysfunction in AS-DM predisposes to heart failure and results from more myocardial fibrosis, more intramyocardial vascular advanced glycation end product deposition, and higher cardiomyocyte F passive, which was related to hypophosphorylation of the N2B titin isoform.11

Aortic Valve Replacement in the Elderly: Determinants of Late Outcome

Summary—To identify patient factors related to increased longevity and to assess the potential impact of valve type on overall survival, we analyzed late outcomes of 2890 consecutive patients aged 270 years who had aortic valve replacement (AVR). Our findings may help clinicians in 2 ways. First, we found that several comorbid conditions (eg, renal failure, immunosuppression, concomitant coronary artery disease, history of myocardial infarction, or stroke) were associated with reduced late survival after AVR. These factors, in general, are not modifiable. But the findings that advanced New York Heart Association class predicted poorer late survival emphasizes the importance of not delaying operation unnecessarily in elderly patients. Delaying surgical referral until symptoms progress will not only result in a higher early mortality but will also decrease the likelihood of a satisfactory long-term survival. Second, our data show no important difference in outcome of patients by type of prosthesis. Our data are reassuring in that there is no survival penalty for use of bioprostheses in elderly patients. In addition, our findings demonstrate that the structural deterioration of aortic bioprostheses is a rare event in elderly patients and that redo AVR is rarely necessary.

Conclusions—Survival of elderly patients after aortic valve replacement is influenced by age and preoperative comorbidities; 33% at lowest risk had overall survival similar to that of an age- and sex-matched general population. There was no sufficient evidence that valve type affected survival. Structural deterioration of aortic bioprostheses was rare.12

One-Year Outcomes of Cohort 1 in the Edwards SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) Registry: The European Registry of Transcatheter Aortic Valve Implantation Using the Edwards SAPIEN Valve

Summary—Cohort 1 of the Edwards SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) Registry describes the outcomes at 30 days and 1 year of >1000 consecutive patients undergoing transcatheter aortic valve implantation using the Edwards SAPIEN valve. The 30-day results have previously been published and have established the procedural results of the technique in a large group of patients in a multicenter registry. The 1-year data describe the outcomes in the largest group of transcatheter aortic valve implantation patients at this time point. This combined data will allow the interventional community to adequately consent transcatheter aortic valve implantation patients on the basis of robust data and will also be a benchmark against which future patient groups and any new devices may be measured.

Conclusions—The SOURCE Registry is the largest consecutively enrolled registry for transcatheter aortic valve implantation procedures. It demonstrates that with new transcatheter aortic techniques excellent 1-year survival in high-risk and inoperable patients is achievable and provides a benchmark against which future transcatheter aortic valve implantation cohorts and devices can be measured.13

Bicuspid Aortic Valve Is Associated With Altered Wall Shear Stress in the Ascending Aorta

Summary—This study investigates wall shear stress (WSS) in the thoracic aorta of bicuspid aortic valve (BAV) patients stratified by a specific valve fusion morphology. The main findings of this investigation are that (1) a right-left BAV fusion pattern was associated with significantly and focally elevated WSS in the ascending aorta, (2) this elevation was present both in stenotic and nonstenotic right-left BAV patients, (3) the postvalvular blood flow jet direction was influenced by the position of the fused cusp, and (4) aortic wall/jet impingement positions corresponded to regions of elevated WSS. Evidence is presented showing a mechanism by which impaired cusp mobility may elevate local aortic WSS downstream from the aortic valve. This phenomenon is of interest, given the heterogeneous expression of aortopathy in BAV patients with specific valve fusion patterns and valve lesions. On the basis of previous findings indicating that increased WSS is associated with altered endothelial cell function
and vascular remodeling, the results in this study illustrate WSS patterns as a differentiating characteristic between valve fusion groups beyond genetic predisposition and could be used for risk stratification and clinical decision making. The guidelines for the management of BAV patients with concomitant aortopathy mainly focus on the absolute size of the aorta, the condition of the valve, and the rate of aorta expansion. Information about the hemodynamic forces exerted on the ascending aorta wall as described in this study may help to complement these dimensional measurements and to facilitate more individualized patient management.

Conclusions—The results of this study demonstrate that bicuspid valves induced significantly altered ascending aorta hemodynamics compared with age- and size-matched controls with tricuspid valves. Specifically, the expression of increased and asymmetric WSS at the aorta wall was related to ascending aortic flow jet patterns, which were influenced by the BAV fusion pattern.14

Comparison of the Structure of the Aortic Valve and Ascending Aorta in Adults Having Aortic Valve Replacement for Aortic Stenosis Versus for Pure Aortic Regurgitation and Resection of the Ascending Aorta for Aneurysm

Summary—There is debate whether an aneurysmal ascending aorta should be replaced when associated with a dysfunctioning aortic valve that is to be replaced. We examined this issue by dividing the patients by type of aortic valve dysfunction—either aortic stenosis (AS) or pure aortic regurgitation (AR)—something not done previously. Of the 59 AS patients, 58 (98%) had a congenitally malformed valve and 53 (90%) had only a zero or 1+ aortic medial elastic fiber loss (graded 0 to 4+). In contrast, of the 63 pure AR patients, 38 had a bicuspid valve and 20 of them had zero or 1+ EFL and 18 had 2+ to 4+ EFL; of the 25 with pure AR and tricuspid aortic valves, all 13 with the Marfan syndrome had severe (3+ or 4+) EFL and the 12 without this syndrome had either zero or 1+ EFL. These data strongly suggest that when ascending aortic aneurysm is associated with aortic valve disease, the type of valve dysfunction—AS or pure AR—is very helpful in predicting aortic medial elastic fiber loss.

Conclusions—These data strongly suggest that the type of aortic valve dysfunction—AS versus pure AR—is very helpful in predicting loss of aortic medial elastic fibers in patients with ascending aortic aneurysms and aortic valve disease.15

Coarctation of the Aorta and Coronary Artery Disease: Fact or Fiction?

Summary—Aortic coarctation is reported to predispose to the development of coronary artery disease (CAD). Despite recent advances in surgical and percutaneous management of these patients, recent data indicate that patients with aortic coarctation still die at a much earlier age than the general population. The number 1 cause of death in this population is thought to be CAD. These data raise the question of whether coarctation of the aorta is an independent risk factor for the development of CAD. Our main objectives were to describe the prevalence of CAD among adults with aortic coarctation and to determine whether aortic coarctation is an independent predictor of CAD. Using a population-based congenital heart disease database with longitudinal follow-up of >20 years, we found, not surprisingly, that traditional cardiovascular risk factors independently predicted for the development of CAD in our cohort. However, the presence of aortic coarctation did not independently predict for the development of CAD. To the best of our knowledge, this is the first study to attempt to examine whether coarctation of the aorta is an independent risk factor for the development of CAD. Our results are significant because they are actionable. Our findings suggest that cardiovascular outcomes of patients with coarctation of the aorta may be improved with tighter risk factor control.

Conclusions—Although traditional cardiovascular risk factors independently predicted for the development of CAD, the diagnosis of coarctation of the aorta alone did not. Our findings suggest that cardiovascular outcomes of these patients may be improved with tight risk factor control.16

Identification of a Monocyte-Predisposed Hierarchy of Hematopoietic Progenitor Cells in the Adventitia of Postnatal Murine Aorta

Summary—Leukocytes play diverse and critical roles in vascular biology and disease, including the development and progression of atherosclerosis. The source of leukocytes in the vascular wall has generally been considered to be remote tissues such as bone marrow or spleen via the peripheral circulation. This article presents new evidence that demonstrates that mature murine arteries contain resident stem and progenitor cells that are capable of forming hematopoietic colonies in culture and repopulating different types of blood cells after whole-body irradiation. These hematopoietic populations are strongly skewed toward monocyte/macrophage and lymphocyte lineages and are notably upregulated in proatherogenic mice. They are contained primarily among adventitial cells that express stem cell antigen-1, where they may be resident for prolonged periods, perhaps even constitutively. The presence of such stem and progenitor cells in the arterial adventitia provides a new paradigm to support the local origins of vascular leukocytes, in turn paving the way for a greater understanding of the regulation and involvement of inflammatory cells during vascular responses to acute and chronic injury. Ultimately, defining the role of these cells in human arteries in both health and disease may also provide new therapeutic opportunities to affect the evolution of different vascular disease processes, including atherosclerosis, aneurysm formation, vasculitis, ischemia, and malignancy.

Conclusions—The postnatal murine aorta contains rare multipotent hematopoietic progenitor/stem cells and is selectively enriched with stem cell antigen-1-positive monocyte/macrophage precursors. These populations may represent novel, local vascular sources of inflammatory cells.17

Cost-Effectiveness of Transcatheter Aortic Valve Replacement Compared With Standard Care Among Inoperable Patients With Severe Aortic Stenosis: Results From the Placement of Aortic Transcatheter Valves (PARTNER) Trial (Cohort B)

Summary—In patients deemed ineligible for cardiac surgery, the Placement of Aortic Transcatheter Valves (PARTNER) trial recently demonstrated a 20% absolute survival difference at 12 months when transcatheter aortic valve replacement (TAVR) was compared with standard nonsurgical therapy. The costs and cost effectiveness of this clinical strategy, which would typically be applied to elderly patients, have not been evaluated previously. Empirical data regarding survival,
quality of life, medical resource use, and hospital costs were collected during the PARTNER trial and used to project life expectancy, quality-adjusted life expectancy, and lifetime medical care costs. Average costs for the initial TAVR procedure and hospital stay were $42,806 and $78,542, respectively, but follow-up costs through 12 months were approximately $24,000 lower per patient with TAVR because of higher rates of cardiovascular hospitalization with standard therapy. We projected that over a patient’s lifetime, TAVR would increase life expectancy by 1.9 years (1.6 years after application of a standard 3% discount rate to future costs and benefits) at a discounted lifetime incremental cost of $79,837. The incremental cost-effectiveness ratio for TAVR was thus estimated at $50,200 per year of life gained, or $61,889 per quality-adjusted life-year gained, values generally considered acceptable within the context of the US healthcare system. These estimates were only slightly altered when assumptions about future costs and survival were varied within plausible ranges.

Conclusions—For patients with severe aortic stenosis who are not candidates for surgery, TAVR increases life expectancy at an incremental cost per life-year gained well within accepted values for commonly used cardiovascular technologies.18

Sensitivity of the Aortic Dissection Detection Risk Score, a Novel Guideline-Based Tool for Identification of Acute Aortic Dissection at Initial Presentation: Results From the International Registry of Acute Aortic Dissection

Summary—Acute aortic dissection is known to be an underrecognized condition at presentation, yet the mortality associated with delayed or missed diagnosis is substantial. The American Heart Association, American College of Cardiology, and other professional societies recently published the 2010 thoracic aortic disease guidelines, which include recommendations for the initial bedside screening of at-risk patients. The goal of these recommendations is to improve physician recognition and facilitate prompt diagnostic testing in those at risk. In our study, we modified this guideline-based screening tool to define the aortic dissection detection risk score, which divides patients into low-, intermediate-, and high-risk groups on the basis of historical and examination features. We then tested the aortic dissection detection risk score for sensitivity among 2,538 patients enrolled in the International Registry of Acute Aortic Dissection. Our results indicate that the aortic dissection detection risk score is 95.7% sensitive for the detection of acute aortic dissection and may help to facilitate prompt evaluation if applied at the bedside. Additional studies are needed to determine the specificity of the aortic dissection detection risk score and provide prospective validation.

Conclusions—The clinical risk markers proposed in the 2010 thoracic aortic disease guidelines and their application as part of the acute aortic dissection risk score comprise a highly sensitive clinical tool for the detection of acute aortic dissection.79

Percutaneous Coronary Intervention in Patients With Severe Aortic Stenosis: Implications for Transcatheter Aortic Valve Replacement

Summary—Outcomes of percutaneous coronary intervention (PCI) in patients with severe aortic stenosis (AS) and coronary artery disease are largely unknown. With the advent of transcatheter aortic valve replacement (TAVR), PCI in patients with severe AS warrants a fresh appraisal. In this study, we identified that the risk of PCI in patients with severe AS is similar to that in other high-risk PCI populations. The highest 30-day mortality risk was seen in patients with low ejection fraction (≤30%) and high Society of Thoracic Surgeons score (≥10). These results provide some insight for the management of patients with severe coronary artery disease and AS who present for TAVR. In patients with very low ejection fraction or severe multiple comorbidities, performing TAVR first to improve cardiac hemodynamics and function could be life-saving, although the 12-month mortality of 24% in high-risk but operable TAVR patients in the Placement of Aortic Transcatheter Valve Trial (PARTNER) suggests that there is much to learn about patient selection. In selected patients, PCI may have to be performed before TAVR to improve procedural safety of TAVR. For some patients, combined TAVR and PCI can be considered with or without adjunctive use of support devices. The optimal approach to patients with severe AS and coronary artery disease should be individualized on the basis of the relative impact of coronary artery disease and AS on the clinical presentation and the nature of the comorbidities. We hope that, as the volume of experience in TAVR increases and more data become available, evidence-based treatment strategies for patients with severe AS and coronary artery disease will emerge.

Conclusions—PCI can be performed in patients with severe symptomatic AS and coronary artery disease without an increased risk of short-term mortality compared with propensity-matched patients without AS. Patients with ejection fraction ≤30% and Society of Thoracic Surgeons score ≥10% are at a highest risk of 30-day mortality after PCI. This finding has significant implications in the management of severe coronary artery disease in high-risk severe symptomatic AS patients being considered for transcatheter aortic valve replacement.20

Aortic Regurgitation Quantification Using Cardiovascular Magnetic Resonance: Association With Clinical Outcome

Summary—Timing surgery in patients with significant aortic regurgitation (AR) can be difficult. Currently, surgery is advised for severe regurgitation once symptoms, excess left ventricular (LV) dilation or dysfunction, occur. However, prognosis is already reduced by this stage, and earlier identification of patients suitable for surgery might be beneficial. Accurate quantification of the regurgitation may help, but is difficult with echocardiography. Cardiovascular magnetic resonance can accurately quantify AR and also provides highly accurate measurements of LV volume, but the clinical utility of this has not been established. Our study examined whether quantification of AR and LV volumes with cardiovascular magnetic resonance was associated with the future development of symptoms or other indications for surgery in an initially asymptomatic group with moderate to severe AR. We showed that both severity of AR and LV volumes had significant associations with outcome over the subsequent few years. AR quantification showed a stronger association than LV end-diastolic volume, but the combination of these 2 parameters was better still. Cardiovascular magnetic resonance measurements of AR and LV volumes might enable the identification of potential candidates for early surgery, and this should be tested in a large-scale clinical trial.

Conclusions—High degrees of cardiovascular magnetic resonance (CMR)-quantified AR were associated with the development of symptoms or other indications for surgery. Quantifying AR showed slightly better discriminatory ability than “gold standard” CMR ventricular volume assessment. This could provide a new paradigm for the timing of surgical intervention but requires confirmation in a clinical trial.31
Correlates of Delayed Recognition and Treatment of Acute Type A Aortic Dissection: The International Registry of Acute Aortic Dissection (IRAD)

Summary—An acute aortic dissection is a surgical emergency with a high mortality if left untreated. Given the varied presentations, including similarity to the far more common acute coronary syndromes, diagnosis and appropriate treatment are often delayed. This report evaluates the reasons for delay in the diagnosis of 894 patients in the International Registry of Acute Aortic Dissection Registry. Patients with the most typical presenting signs and symptoms, including abrupt onset of severe chest pain, and those with pulse deficits or hypotension, were diagnosed more quickly. In contrast, patients transferred from referral hospitals had significantly longer times to diagnosis and ultimately to surgery, perhaps related to the physician’s experience with dissection at these hospitals. Delays from diagnosis to surgery also occurred in nonwhites, those with prior cardiac surgery, and those without ongoing shock or hypotension. Education directed at recognition of both typical and atypical presentations of aortic dissection, particularly to those centers with low exposure to aortic emergencies, may be of benefit. The fact that the median times from presentation to diagnosis and from diagnosis to surgery exceeded 4 hours suggests that there is substantial room for improvement. The development of systematic care pathways for diagnosis and management of aortic dissection, similar to those in place for acute myocardial infarction, may be of benefit. The focus of these pathways should include recognition of both typical and atypical presentations, with rapid diagnostic imaging in appropriate candidates and prompt transfer and surgery.

Conclusions—Improved physician awareness of atypical presentations and prompt transport of acute aortic dissection patients could reduce crucial time variables.

Cerebral Protection During Surgery for Acute Aortic Dissection Type A: Results of the German Registry for Acute Aortic Dissection Type A (GERAADA)

Summary—Surgery for acute aortic dissection type A (AADA) requires cerebral protection strategies for aortic arch intervention: Hypothermic circulatory arrest (HCA) alone or with adjunct cerebral perfusion. The optimal strategy is unclear. Through the German Registry for Acute Aortic Dissection Type A (GERAADA), we surveyed the current practice and outcome of cerebral protection during AADA surgery in Central Europe. This is the largest series on this topic published so far. We compared the different cerebral protection strategies: HCA alone, unilateral antegrade cerebral perfusion, and bilateral antegrade cerebral perfusion. Furthermore, we evaluated several technical parameters, eg, perfusion pressures and temperatures within the different strategies. Study end points were mortality and neurological morbidity. The duration of arch intervention turned out to be the major factor influencing the outcome. HCA only appears to be safe for under 30 minutes, whereas antegrade cerebral perfusion doubles the safe time period. Thus, surgery with HCA appears justified only for limited arch interventions. If a more extensive arch reconstruction is required, cerebral perfusion should be initiated immediately. Unilateral and bilateral antegrade cerebral perfusion resulted in equivalent outcomes. We describe parameters that allow the time required for arch reconstruction to be estimated. Referring to our data, we discuss the different cerebral protection strategies and make detailed recommendations on the use of perfusion pressure and other items of clinical importance. This enables the readers to critically reflect and optimize their own practice.

Conclusions—This study reflects current surgical practice for acute aortic dissection type A in Central Europe. For arrest times less than 30 minutes, hypothermic circulatory arrest and antegrade cerebral perfusion (ACP) lead to similar results. For longer arrest periods, ACP with sufficient pressure is advisable. Outcomes with unilateral and bilateral ACP were equivalent.

Atorvastatin, Etidronate, or Both in Patients at High Risk for Atherosclerotic Aortic Plaques: A Randomized, Controlled Trial

Summary—In the present randomized, clinical trial, treatment with atorvastatin plus etidronate, compared with atorvastatin and etidronate monotherapies, showed that atorvastatin could reduce thoracic aortic plaques in which fatty constituents were common and etidronate bisphosphonate could reduce abdominal aortic plaques in which calcified plaques were frequently observed. Treatment with statins reduces serum low-density lipoprotein cholesterol levels and atherosclerotic plaques in the carotid artery, coronary artery, and thoracic aorta. However, it has not been shown to reduce atherosclerotic plaques in the abdominal aorta. To the best of our knowledge, this is the first randomized, clinical trial to demonstrate that the combination therapy of atorvastatin plus etidronate induced the regression of not only thoracic but also abdominal aortic plaques. Bisphosphonates are currently considered the drug of choice for the prevention and treatment of osteoporosis and related fractures. However, accumulating evidence shows that bisphosphonates have the potential to reduce atherosclerotic plaques and vascular calcification. In addition, only first-generation bisphosphonates (etidronate and clodronate) seem to have this ability. It was reported that calcified atherosclerotic plaques in the abdominal aorta were associated with the incidence of cardiovascular events and the independent predictor of coronary heart disease. Therefore, the reduction of calcified atherosclerotic plaques in the abdominal aorta might be beneficial in reducing mortality caused by cardiovascular events.

Conclusions—Atorvastatin plus etidronate combination therapy for 12 months significantly reduced both thoracic and abdominal aortic plaques, whereas atorvastatin monotherapy reduced only thoracic aortic plaques and etidronate monotherapy reduced only abdominal aortic plaques. The effectiveness of combination therapy in reducing atherosclerotic plaques in the abdominal aorta was significantly greater than for both atorvastatin and etidronate monotherapy.

Modeling Supravalvular Aortic Stenosis Syndrome With Human Induced Pluripotent Stem Cells

Summary—Currently, treatment of proliferation-based pathologies relies on drugs like rapamycin that may have a broad impact on patient physiology. Such treatment risks unintended effects in targeted and off-target cell types, potentially initiating new dysfunction. To effectively treat patients, it is critical to root out the mechanisms of proliferative diseases so that treatments can be developed to specifically attack the existing pathology without risking further complications. This study shows for the first time that the hyperproliferation in smooth muscle cells (SMCs) that causes supravalvular aortic stenosis (SVAS) syndrome is, in turn, accompanied by a marked decrease in actin filament bundle formation and an increase in migration. More important, we have shown that treatment with exogenous elastin...
monomers rescues the actin filament bundle formation in supravalvular aortic stenosis cells. With these results taken together, it can be hypothesized that a switch from a contractile to a proliferative phenotype in smooth muscle cells is caused by an elastin deficiency. Induced, pluripotent stem cell models of proliferative diseases such as the one used here should prove valuable in the search for candidate pathways and pharmaceutical agents. As a result, clinical interventions focusing on the enhancement of smooth muscle cell actin filament bundle formation and/or elastin production of affected vessel walls promise higher efficacy and lower risk to the patient than current treatments. There are several avenues through which such interventions can be realizable, but given a candidate drug specific to actin filament bundle formation and/or elastin production, the goal of curing deadly proliferation-based smooth muscle cell diseases appears to be close at hand.

Conclusions—SVAS iPSC-SMCs recapitulate key pathological features of patients with SVAS and may provide a promising strategy to study disease mechanisms and to develop novel therapies.26

Aortic Event Rate in the Marfan Population: A Cohort Study

Summary—Marfan syndrome is a genetic disease usually related to a mutation in the gene coding for FBN1. It is transmitted as a dominant autosomal disease. The genetic nature of the disease allows early diagnosis with familial screening. Progressive aortic dilatation leading to aortic dissection and rupture is the main life-threatening complication associated with the syndrome. Medical management includes β-blocker therapy and prohibition of intensive sports. Regular follow-up visits are crucial to evaluate the aortic diameter with echocardiography and the need for prophylactic aortic surgery. In the present study, the management of 732 patients followed these rules, and the value of 50 mm was our threshold for preventive aortic surgery. Using this strategy, we showed that the risk of aortic event (dissection, rupture, or sudden death) was <0.05%/y in the population with an aortic diameter <50 mm in the absence of known risk factors such as pregnancy, familial history of aortic dissection at a low diameter, or rapid increase in diameter. This risk increases with the diameter of the aorta at the level of the sinuses of Valsalva; this increase was 3-to-4-fold in the patients whose aorta was 50 to 54 mm compared with 45 to 49 mm. The 50-mm threshold at the level of Valsalva appears to be a reasonable threshold for proposing preventive aortic surgery in patients with Marfan syndrome.

Conclusions—Risk of sudden death or aortic dissection remains low in patients with Marfan syndrome and aortic diameter between 45 and 49 mm. Aortic diameter of 50 mm appears to be a reasonable threshold for prophylactic surgery.26

Incidence and Predictors of Early and Late Mortality After Transcatheter Aortic Valve Implantation in 663 Patients With Severe Aortic Stenosis

Summary—Transcatheter aortic valve implantation using the self-expandable CoreValve prosthesis was performed in 663 patients with severe aortic stenosis and high surgical risk in 14 Italian centers. Procedural success was 98% and in-hospital mortality was 0.9%. The mortality rates at 30 days and 1 year were 4% and 15.0%, respectively. Early mortality was acceptably low compared with the anticipated risk calculated by means of the EuroSCORE and was strongly associated with the occurrence of procedural complications. Late mortality continued to occur from 30 days to 1 year after TAVI, primarily as the effect of postprocedural paravalvular aortic regurgitation ≥2+ and nonvalve related comorbidities such as cerebrovascular disease, chronic kidney disease and heart failure. Clinical and hemodynamic benefits observed acutely after TAVI were sustained at 1 year.

Conclusions—Benefit of TAVI with the CoreValve Revalving System is maintained over time up to 1 year, with acceptable mortality rates at various time points. Although procedural complications are strongly associated with early mortality at 30 days, comorbidities and post-procedural paravalvular aortic regurgitation ≥2+ mainly impact late outcomes between 30 days and 1 year.

References


