Innovation and expansion define the Vanderbilt Heart and Vascular Institute (VHVI) in 2020.

Since the last VHVI newsletter, the world has changed. The COVID-19 pandemic has challenged us to figure out how to care for this new illness, while continuing to provide exceptional care for patients made vulnerable by cardiovascular disease. Vanderbilt has met that challenge in numerous ways — by being a leader in testing capabilities, by innovating and deploying new techniques in the care of hospitalized COVID patients, and by furthering the discovery science that may one day render this virus tamed. As COVID-focused efforts continue, so too do our mission-critical efforts to improve the care of patients with cardiovascular disease. In this issue of our newsletter, we are excited to share some of those key efforts with you.

Our cardiac transplant program has spearheaded efforts to expand the pool of eligible donors by developing protocols to include those with hepatitis C. Utilizing these novel approaches to narrow the gap between organ supply and demand, in 2019 VHVI achieved the distinction as the largest (tied) cardiac transplant program in the nation by volume.

The portfolio of structural heart disease interventions continues to grow at VHVI as well. Transcatheter aortic valve replacement was originally reserved for extreme-or high-risk patients. Here we review the extension of this intervention to intermediate- and even low-risk patients with aortic stenosis. In parallel, we continue to advance transcatheter interventional techniques for the mitral, pulmonary and tricuspid valves. The continued growth of the Adult Congenital Heart Disease program also reflects the depth and breadth of expertise at VHVI, which is built on a foundation of interdisciplinary collaboration. VHVI continues to achieve national recognition as a center of excellence in genomics research designed to personalize the treatment of cardiac disorders. The eMERGE network presented here reflects one of these national initiatives: Vanderbilt has been an eMERGE site since 2007, and was very recently selected to continue in the network for a further five years during which polygenic risk scores will be the major focus. The pace of discovery will certainly escalate further in this new decade. VHVI is positioned extremely well to continue to lead locally and nationally in this exciting new era.

Be well, stay safe, and thank you for your partnership.
The mission of the Vanderbilt Adult Congenital Heart Disease Program is to provide the highest-quality specialized cardiac care to the emerging adult congenital heart disease (ACHD) population in Tennessee and the Southeastern United States. As the ACHD population grows, there is increasing need for ACHD cardiologists and ACHD programs that provide comprehensive care to care to this complex population. Vanderbilt’s ACHD program is a collaboration between Vanderbilt Heart and Vascular Institute and Pediatric Heart Institute offering complete ACHD care including general ACHD care, general and advanced cardiac imaging, electrophysiology, interventional cardiology, pregnancy care, advanced heart failure and transplantation, pulmonary hypertension and congenital heart surgery. Treatment of complex patients requires long-term planning with individualized, coordinated care. Tetralogy of Fallot and transposition of the great arteries are two forms of congenital heart disease (CHD) that highlight the ability of the Vanderbilt’s Adult Congenital Heart Program to offer multidisciplinary, creative and coordinated care.

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart defect. The first surgical palliations of the “blue babies” with TOF were performed in the 1940s and the first repairs of TOF were performed in the 1950s as the field of cardiac surgery rapidly advanced. Surgical relief of obstruction to blood flow to the lungs leaves many TOF patients with chronic leakage of their pulmonary valves.

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<td>ACHD Cardiac Catheterizations (&gt;= 18 years old)</td>
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<td>Percutaneous pulmonary valve replacements</td>
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<td>ACHD EP studies with ablation</td>
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<td>ACHD Transplantation (&gt;= 18 years old)</td>
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<td>ACHD Transplant Evaluations</td>
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<td>ACHD Cardiac MRI (&gt;= 18 years old)</td>
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<td>Tetralogy of Fallot</td>
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<td>Transposition of Great Arteries</td>
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Often benign for decades, pulmonary valve insufficiency can cause the right heart to gradually enlarge and can cause exercise intolerance. In addition, there is increased risk of sudden death related to arrhythmia even long after repair. Caring for adult TOF patients is a multidisciplinary process with evaluations that can involve...
echocardiography, cardiac MRI, exercise testing and electrophysiology studies. Some TOF patients will require pulmonary valve replacement as adults either with a traditional surgical approach or with newer catheter-based approaches, which have emerged as alternatives to surgery in certain patients, even those who have never previously undergone valve replacement. At Vanderbilt University Medical Center (VUMC), we implant nearly 20 transcatheter pulmonary valves each year in patients with CHD. Vanderbilt’s Adult Congenital Program approaches valve replacement in an innovative way by integrating valve replacement with heart rhythm management. By strategically planning electrophysiology studies, cardiac ablation procedures, and, if indicated, placement of implantable cardioverter-defibrillator (ICD), our team creates a unified plan for each patient to simultaneously treat valve dysfunction function and address the risk of sudden death.

D-Transposition of the great arteries (TGA) is another cyanotic congenital heart defect in which the connections of the ventricles to the great arteries are reversed. Contemporary surgical repair is the arterial switch operation which involves connecting the aorta and the pulmonary artery to the proper ventricle. Many adults with TGA have undergone an older repair strategy called the “atrial switch” with either the Mustard or Senning operation. These surgeries involve constructing atrial baffles that reroute venous blood through the atria to the opposite side of the heart to improve oxygen levels. Adult atrial switch patients are at risk for obstruction or leaks of the atrial baffles, heart rhythm disturbances, and failure of the right ventricle. At Vanderbilt Heart and Vascular Institute (VHVI), our team-based care for atrial switch patients includes subspecialty evaluation with transthoracic and transesophageal echocardiography, cardiac MRI, 3D modeling, cardiopulmonary stress testing and electrophysiology studies. Some patients may require cardiac catheterization to open baffles with stents or close leaks with closure devices, ablation procedures to treat
cardiac arrhythmias, specialized pacemaker or ICD placement, or device lead extraction (Figures 1-3).

Vanderbilt’s ACHD and congenital heart disease surgical programs also work in close collaboration with our high-volume advanced heart failure and transplant program. This collaboration allows for increased access for ACHD patients who develop heart failure — including those with TGA — to evaluation for heart transplantation and mechanical support options.

The population of patients with ACHD continues to grow, and Vanderbilt’s Adult Congenital Heart Program is well positioned to address the broad spectrum of complex challenges these patients face. We will continue efforts to integrate clinical services at VUMC in order to provide the best individualized care to this population.

Figure 4: 3D Echocardiography to guide percutaneous closure of baffle leak in atrial switch patient (A: Wire in position across the leak, B: After deployment of septal occlusion device).
The treatment of severe aortic stenosis (AS) has been revolutionized over the past decade by the introduction of transcatheter aortic valve replacement (TAVR) as a viable treatment option for extreme, high, and intermediate risk AS patients. This transformation continued in 2019 with emergence of new data supporting the extension of TAVR to patients with severe AS at low risk for surgical aortic valve replacement (SAVR).

Aortic stenosis is known as a disease with a long latent period. However, once symptoms (chest pain, shortness of breath, or syncope) occur, there can be rapid progression to death. Death is related to the mechanical obstruction to cardiac output and there is no effective medical therapy. Symptomatic severe AS has therefore long been a class I indication for SAVR in both the European and the U.S. valve guidelines. In reality, however, up to half of severe AS patients have historically either been denied or never considered for SAVR because of advanced age, frailty or other comorbidities. TAVR was initially developed as a potential therapy for this high-risk population frequently denied surgery. Since the initial case report in 2002, TAVR has exploded as a therapeutic option with 300,000 cases performed worldwide.

**Extreme Risk:** The Placement of Aortic Transcatheter Valves (PARTNER) B trial in nonoperative patients was the first and only trial to randomize participants to either TAVR or standard therapy including balloon aortic valvuloplasty. At one year, there was an absolute 20% survival advantage to TAVR with the balloon expandable Edwards SAPIEN heart-valve system (31% vs 51%; p<0.001), and this advantage persisted for the 5-year life of the trial. The CoreValve Extreme Risk Pivotal Trial (self-expanding valve) and The REpositionable Percutaneous Replacement of Stenotic Aortic Valve Through Implantation of Lotus Valve System (Reprise III) trial extreme-risk arm (mechanically expandable valve) both showed similar superiority compared to medical therapy, as well as acceptable safety. Based on these data, the U.S. Food and Drug Administration (FDA) approved TAVR for high-risk and inoperable patients with symptomatic aortic stenosis in November 2011.

**High Risk:** The PARTNER A trial randomized severe AS patients at high risk for SAVR in a 1:1 fashion to either TAVR using the balloon expandable Sapien valve or SAVR. High-risk patients are operative candidates considered by the heart team to have a 30-day surgical mortality of more than 10% based on the Society of Thoracic Surgery predicted risk of mortality (STS PROM). At 30 days and one year, the primary trial end point of all-cause mortality for TAVR vs SAVR was similar in both groups (24.2% vs 26.8%). The high-risk arm of the CoreValve U.S. Pivotal Trial, which randomized participants to either TAVR or SAVR with a primary end point of all-cause mortality at one year, showed fewer events in the TAVR group (14.2% vs. 19.1%; p = 0.04). This is the only randomized trial to show superior survival for TAVR compared to SAVR for the primary powered end point. Additionally, the stroke rates for TAVR vs. SAVR at one year and three years were 8.8% vs. 12.6% (p = 0.10) and 12.6% vs. 19.0% (p = 0.03), respectively, in favor of TAVR.
Intermediate Risk: Intermediate-risk patients assessed by the heart team are considered to have an STS PROM between 3% and 10%. The PARTNER II A trial randomized more than 2,000 participants between SAVR and TAVR with a primary end point of all-cause mortality or disabling stroke at two years. The mean STS PROM was 5.8% in both study arms. After two years, the event rates for TAVR and SAVR were comparable at 19.3% vs. 21.1% (p = 0.25). It should be noted that in the subset of transfemoral (TF) as treated TAVR (76.3%) the primary outcome compared favorably to SAVR (16.3% vs. 20%, p = 0.04). Additionally, there was no difference in neurologic events at any time point. The Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI) trial was a prospective randomized trial comparing TAVR using a self-expanding device (CoreValve or Evolut R) to SAVR in 1,746 patients at intermediate surgical risk. At 24 months, the primary end point of all cause death or disabling stroke occurred in 12.6% of TAVR vs. 14.0% of SAVR participants, demonstrating non-inferiority. A second non-randomized intermediate-risk trial was the continued access arm of the SURTAVI trial, which enrolled 275 patients using SURTAVI risk criteria but without a SAVR arm. The 30-day mortality and disabling stroke rates in this group were 0% and 0.4%.

Low Risk: Given the track record of efficacy in extreme, high, and intermediate risk populations, there has been intense interest in the performance of TAVR in severe AS patients at low surgical risk. The PARTNER 3 trial has now provided compelling data supporting TAVR in the low surgical risk population. PARTNER 3 randomized 1,000 subjects with an STS-PROM of less than 4% (mean STS-PROM score 1.9%) to TAVR with the balloon expandable Sapien 3 device or SAVR. The average age of those treated
was 73.4 years. The primary composite endpoint of death from any cause, stroke and rehospitalization at one year occurred in 8.5% of patients undergoing TAVR and 15.1% of patients treated with SAVR (p < 0.001 for noninferiority; p = 0.001 for superiority). The risk of death or disabling stroke was 1% in the TAVR arm and 2.9% with SAVR, a difference that was statistically significant (HR 0.34; 95% CI 0.12-0.97). In the Evolut Low-Risk trial (self-expanding device), the primary endpoint of all-cause mortality or disabling stroke for TAVR vs. SAVR at 24 months was 5.3% vs. 6.7% (p < 0.05 for noninferiority, p > 0.05 for superiority). At two years, all-cause mortality was similar between groups, but disabling stroke was 1.1% for TAVR vs. 3.5% for SAVR (p < 0.05).

These landmark trials are practice changing. The PARTNER 3 and Evolut-Low Risk trials suggest that low surgical risk patients with severe AS do as well and perhaps even better with TAVR compared with SAVR over the first two years after treatment. Continued follow-up will be essential to understand long-term performance and the risk of structural valve degeneration.

In response to these data demonstrating equivalent or superior outcomes for TAVR compared to SAVR among patients with severe aortic stenosis at low surgical risk, in August of 2019 the FDA approved an new indication for the self-expanded Evolut series and the balloon-expandable Sapien 3 transcatheter heart valves for the treatment of patients with severe aortic stenosis at low risk for surgery. Thus, these valves are now approved across the entire spectrum of risk, including patients deemed ineligible for surgery, those at high or intermediate risk, and now those at low risk.

At the Vanderbilt Heart and Vascular Institute (VHVI) we are offering TAVR to an increasing number of low-risk patients with severe aortic stenosis. In 2019 VHVI treated 185 patients with TAVR: 27 patients (14.5%) were low risk SAVR candidates, with the percentage of low risk patients treated with TAVR rising steadily since approval, now up to 36% of procedures. VHVI continues to advance the field in transcatheter interventions to treat structural heart disease.
Vanderbilt University Medical Center tied for first place as the busiest heart transplant program by volume in the United States in 2019. Led by Medical Director Kelly Schlendorf, M.D., and Surgical Director and Chief of Cardiac Surgery Ashish Shah, M.D., the program performed over 300 heart transplants from 2017 to 2019, more than 1.5-fold the number performed from 2014 to 2016 (Figure 1). Among the key factors driving program growth are expanding partnerships with referring providers and institutions across the Southeast, a state-of-the-art mechanical circulatory support program, and the dedication and hard work of dozens of individuals across multiple disciplines who care for these patients before and after transplant surgery. Equally important has been Vanderbilt’s pioneering role in transplantation of hearts from hepatitis C virus (HCV)-infected donors.

The advent of direct-acting antiviral (DAA) therapies for treatment of HCV has made inclusion of HCV-infected donors, who were previously considered too high risk, an important option to expand the donor pool and thereby narrow the gap between organ supply and demand and reduce wait times for many patients awaiting transplant.

Vanderbilt began accepting HCV-positive donor hearts in the fall of 2016. Since then, the program has transplanted over 100 HCV-positive hearts, more than any other transplant center in the United States. After transplantation, recipients of hearts from HCV-positive donors are treated with standard immunosuppression and those who go on to develop HCV infection are cared for in collaboration with transplant hepatologists who guide HCV treatment (Figure 2).

A report describing the program’s early outcomes, published in the Journal of Heart and Lung Transplantation, was awarded Best Paper of 2018 by the International Society of Heart and Lung Transplantation for its impact on advancing the science of heart transplantation (Figure 3).
Longer term outcomes in a larger cohort of patients were published in December in JAMA Cardiology.

Among recipients of hearts from HCV-positive donors at Vanderbilt, median wait-list time is approximately 4 days, remarkably short relative to national reported median wait-list times ranging from 70 to 535 days. While most patients will go on to develop HCV post-transplant, DAA therapy is well tolerated and highly effective despite immunosuppression, and 1-year survival rates are similar to those of patients transplanted with hearts from HCV-negative donors during the same period. Work is ongoing to shed more light on outcomes at 1-year and beyond.

**Figure 2: Hepatitis C Protocol**

Clinical protocol in patients undergoing heart transplantation from hepatitis C-positive donors.

- **Patient Consent**
  - Education and informed consent

- **Immunosuppression**
  - OHT
  - Triple drug therapy (FK, MMF, steroids)

- **Donors considered HCV-positive if:**
  - HCV antibody positive, or
  - HCV nucleic acid testing positive

- **Surveillance and Treatment**
  - Hepatology consultation

- **dd-HCV infection**

- **HCV genotyping**

- **Data Collection and Analysis**
  - Ongoing

- **DAA Therapy**

**Abbreviations:**
- HCV – hepatitis C virus
- OHT – orthotopic heart transplant
- FK – FK506 (Prograf)
- MMF – mycophenolate mofetil
- dd-HCV – donor-derived hepatitis C virus
- DAA – direct-acting antiviral

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**Figure 3: Best Paper 2018**

The Journal of Heart and Lung Transplantation

The Official Publication of the International Society for Heart and Lung Transplantation (ISHLT)

Early outcomes using hepatitis C-positive donors for cardiac transplantation in the era of effective direct-acting anti-viral therapies

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VANDERBILT HEART

VanderbiltHeart.com
A 43-year-old man with ischemic cardiomyopathy presents with VT storm...

In an increasingly busy referral center like Vanderbilt, we see patients like this every day. As we deal with their immediate problems, we are also becoming increasingly sensitized to the idea that genetic variation plays a big role in how we should be thinking about caring for them and their families. As genetic testing for cardiovascular diseases becomes increasingly common, we are also seeing patients who have variants in key cardiovascular disease genes, but who may not (yet) have symptoms. Vanderbilt Heart and Vascular Institute (VHVI) faculty have been leading a decade-long effort to understand when genetic testing makes sense in patients with disease, and in the broad population, as one goal of the NIH’s electronic Medical Records and Genomics (eMERGE) network.

For the young patient with ischemic cardiomyopathy, an obvious question is whether they have familial hypercholesterolemia (FH), one of the commonest cardiovascular genetic diseases. FH is under-recognized, under-diagnosed, and represents an opportunity to intervene in family members, especially children, to prevent early onset coronary disease. Genetic testing for FH involves sequencing the three common disease genes, LDLR, APOB and PCSK9, to find rare variants that cause the very high LDL cholesterol values typical of FH. Once we find them, we screen other family members to see if they are affected at the genetic level (and whether they have high LDL values). Interestingly, even among patients with very high LDL, for example, >300 mg/dl, those rare variants are found only in a minority. What is the problem in the remaining patients? New research now suggests that in those patients very high LDL results from the combined effects of dozens, hundreds, or even millions of genetic variants, each contributing a tiny amount to risk; some patients are unlucky enough to have inherited many risk variants, and so have very high “polygenic risk scores”.

To try to understand whether genetic testing might be useful in a broad population, eMERGE has just completed a project in which 25,000 patients (2,500 at each of 10 sites, including Vanderbilt) were sequenced in 109 genes known to cause serious diseases: these included genes for FH, arrhythmia diseases like long QT, cardiomyopathies and cancer susceptibility. At Vanderbilt, our 2,500 patients were recruited from adult clinics, and most had no symptoms. Testing like this yields dozens of variants in each participant, but only those designated known or likely pathogenic, a minority, were returned to the patients, their doctors, and their electronic health records (EHRs). We found pathogenic variants in 158 of our participants, and 10 were unfortunate enough to have two pathogenic variants. About half of the identified variants were in cancer genes, and most of the other half in cardiovascular genes: 12 patients had FH, 12 had cardiomyopathies, and eight had arrhythmia variants. The vexing problem, that all genetic medicine is facing, is that some of the patients who carry rare genetic variants that are designated pathogenic nevertheless have no diagnosable disease. One idea is that it is the combination of rare pathogenic variants and a high polygenic risk score that makes people actually get a disease. And that’s where eMERGE will be going next.

VHVI investigators participating in the eMERGE project include Dan Roden who has been PI since we joined the network in 2007, Ben Shoemaker who specializes in the care of patients with genetic arrhythmia disease, and Quinn Wells who specializes in the care of patients with cardiomyopathies.
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