Vascular Medicine: Intensifying the Focus and Optimizing Care

Diseases of the vasculature affect tens of millions of patients and are a significant source of disability and death. At many medical centers, vascular disease is addressed by a range of medical specialists, not necessarily working in concert. The recent arrival of Joshua Beckman, M.D., ushers in a new era of integrated vascular care at Vanderbilt. Dr. Beckman is the founding Director of the Section of Vascular Medicine. Offering a comprehensive range of consultative and imaging services, Vascular Medicine will provide a true synergistic partnership with Vascular Surgery and other specialties to optimize the care of patients with vascular disease.

Vascular disease can take many forms. Common manifestations include vasospastic disease, like Raynaud’s and acrocyanosis, thermal disease like pernio, and thoracic outlet disease that may cause arterial, venous, or neurologic manifestations. The most common manifestations of vascular disease are claudication related to peripheral atherosclerosis and venous thromboembolism. Not only is quality of life impaired, survival is also compromised. The goal of Vanderbilt’s Vascular Medicine program is to organize the care of patients with all forms of vascular disease, ranging from stable disease to conditions of higher acuity or complexity, to optimize outcomes.

Dr. Beckman has recently begun offering outpatient vascular medicine consultation at the Vanderbilt Heart and Vascular Institute, and the section is actively recruiting additional faculty. The Section of Vascular Medicine will extend the current medical vascular services provided at Vanderbilt, improve the organization and linkage among experts in this field, and foster the development of new methods to care for these patients.

Appointments for Vascular Medicine consultation can be arranged by calling 615-322-2318.

Editors’ Note

In 2015, the Vanderbilt Heart and Vascular Institute (VHVI) saw continued growth in its clinical and academic programs. We recruited several nationally renowned physicians to assume leadership roles in VHVI, including JoAnn Lindenfeld, M.D., (President, Heart Failure Society of America), Joshua Beckman, M.D., (past President, Society for Vascular Medicine), and Ashish Shah, M.D., (previously Surgical Director of Heart Transplant and Mechanical Circulatory Support at Johns Hopkins). Detailed profiles of these new faculty members are provided on page 11.

This issue of Vanderbilt Heart highlights several new programs for patients with heart disease. Above, we describe the new Section of Vascular Medicine, directed by Dr. Beckman. Javid Moslehi, M.D., discusses the emerging field of Cardio-oncology, and describes the clinical and research activities of the Vanderbilt Cardio-oncology Program. Quinn Wells, M.D., details Vanderbilt’s national leadership role in several new precision medicine initiatives.

Vanderbilt also continues to serve a growing number of patients with advanced heart failure. In 2015, 53 adult heart transplants and 72 LVAD implantations were performed. In her article, Dr. Lindenfeld discusses several recently approved therapies for chronic heart failure that are now available at Vanderbilt Heart.
In the age of precision medicine, research is a team sport, and Vanderbilt Heart and Vascular Institute (VHVI) faculty continue to play a prominent role. The recognition that each person’s unique genetic makeup influences the development of disease and response to therapy has opened the possibility that treatments can be tailored in a way that maximizes benefit and minimizes harm for specific patients. Because important genetic variants can be rare or cause subtle effects, few individual centers have sufficient numbers of subjects to explore relationships between genetic variation and drug response. The scope and complexity of modern genomic research necessitates large, multi-institutional collaborations dedicated to making precision medicine a reality.

Vanderbilt University Medical Center researchers are now participating in two large national networks to better understand how patients respond to drugs and how that information can be incorporated into medical care. These initiatives are led by Dan Roden, M.D., an electrophysiologist specializing in genetic diseases and Assistant Vice Chancellor for Personalized Medicine. Dr. Roden is also a member of the National Human Genome Research Institute’s Advisory Council.

Vanderbilt is one of only three organizations nationwide to receive a “P50” grant from the NIH. The grant supports the vision of the NIH Pharmacogenomics Research Network (PGRN), and provides nearly $13 million over five years for the creation of specialized research centers for pharmacogenomics and personalized medicine. These centers of discovery are intended to comprehensively investigate mechanistic questions about drug responses. Vanderbilt’s multidisciplinary team, led by Roden, Denny and Phillips, will use a variety of techniques including stem cells, cellular immunology and immunogenetics, and large-scale data mining in electronic health record (EHR) data to explore inter-individual variation in drug response and toxicity. The program also includes outreach activities to enhance public understanding of pharmacogenomics.

Roden and Denny also lead Vanderbilt’s participation in the Electronic Medical Records and Genomics (eMERGE) network, a national collaboration supported by the National Human Genome Research Institute, part of the NIH. Participating institutions link large DNA biorepositories, such as Vanderbilt’s BioVU DNA bank, and EHR data to conduct large-scale genetic studies. The current focus of the eMERGE network is to understand the clinical impact of genetic variation in approximately 100 medically-relevant genes. Further, eMERGE investigators are developing protocols to return genetic information to patients and clinicians and to develop best practices for decision support. The network will also address cost-effectiveness, and important issues related to the ethical, legal, and social implications of incorporating genetic information into the medical record.

Providing personalized care requires an integrated, patient-centered medical system, and Vanderbilt is part of two large...
collaborative efforts to improve health care delivery. The Mid-South Clinical Data Research Network (CDRN), led by Vanderbilt investigators, is linking sites of health care delivery across the Southeast USA to create a large research network to support pragmatic trials and comparative effectiveness research. The CDRN was established in 2014 by a grant from the Patient-Centered Outcomes Research Institute (PCORI), and was one of only 11 centers selected during the first round of funding.

The CDRN includes sites from the Vanderbilt Health Affiliated Network (VHAN), which includes more than 45 community hospitals and 350 practices in the Mid-South region, Greenway Health, with access to 1,600 clinics in the national PrimeResearch network, and the Carolinas Collaborative, which consists of the University of North Carolina at Chapel Hill, Duke University, and Health Sciences South Carolina (Clemson University, Medical University of South Carolina, University of South Carolina, and 7 other health systems). More information can be found at midsouthcdrn.mc.vanderbilt.edu/about. Ongoing research includes a PCORI-funded pragmatic trial on aspirin dosing.

In September 2015, Vanderbilt University was awarded a four-year, $28 million contract from the Centers for Medicare and Medicaid Services (CMS) to participate in the Transforming Clinical Practice Initiative. One of 39 sites, the Mid-South Transforming Clinical Practice Initiative (Mid-South PTN) is a partnership between Vanderbilt, VHAN, and the Safety Net Consortium of Middle Tennessee. It is using informatics tools developed at Vanderbilt to help over 4,000 clinicians “transform” their practice by improving quality outcomes and reducing unnecessary testing. A major goal of the Mid-South PTN is to reduce unnecessary testing or treatments by 5 percent and hospital readmissions by 20 percent.

Fully realizing the potential of precision medicine requires not only identification of clinically important variants and rigorous study of underlying mechanisms, but also translation into clinical practice – including a framework for engaging providers and patients and providing quality care. Vanderbilt is joining with institutions from across the country to create networks of research teams to address these challenges. The goals of this new model of team science, based on more structured collaboration and sharing of best practices, are to accelerate the pace of discovery and to make the promise of precision, patient-centered care a reality.
The treatment of patients with heart failure is complex and multi-disciplinary, and comprehensive care for these patients integrates established interventions with emerging therapies. Contemporary programs for advanced heart failure need to provide patients with rapid access to novel heart failure therapies when they are approved. After a several-year drought in new therapies, the FDA recently approved three new therapies for heart failure—two drugs and one device.

Sacubitril/valsartan (Entresto™) is a combined neprilysin inhibitor and angiotensin II receptor blocker (Angiotensin Receptor-Neprilysin Inhibitor, ARNI) that is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction. Neprilysin degrades several endogenous vasoactive peptides, including natriuretic peptides, bradykinin, and adrenomedullin. Inhibition of neprilysin raises the levels of these substances, countering the deleterious neurohormonal overactivation that occurs in heart failure. Sacubitril/valsartan was approved based on a single, international trial (PARADIGM HF) that randomized 8,442 patients with NYHA Class II-IV and a left ventricular ejection fraction of ≤40% to receive either enalapril (10 mg bid) or sacubitril/valsartan (200 mg bid). To be randomized, subjects had to complete a single blind run-in phase to demonstrate tolerance to enalapril 20 mg bid and a second single blind run-in phase to ensure an acceptable side effect profile with the ARNI. Excluded subjects were those with a systolic blood pressure <95 mg Hg, history of angioedema, estimated GFR < 30 ml/min, potassium > 5.2 mmol/L, or failure to complete either run-in phase of the trial. Sacubitril/valsartan was associated with a 20% reduction in the primary endpoint of death from cardiovascular causes or hospitalization for heart failure.1 All-cause mortality was decreased by 16% and cardiovascular mortality by 20%. All subgroups showed a similar benefit. Interestingly, in the OVERTURE trial published in 2002, omapatrilat (a combination of neprilysin inhibitor and an angiotensin-converting enzyme (ACE) inhibitor) failed to show a reduction in the primary endpoint of death or hospitalization for heart failure compared with ACE inhibitor alone.2 The potentially greater benefit observed with sacubitril/valsartan could be attributable to angiotensin receptor blockade, given the increase in angiotensin II that occurs with neprilysin inhibitors. There is substantial excitement about sacubitril/valsartan because of the significant mortality benefits when added to standard heart failure therapies.

Ivabradine (Corlanor™) inhibits the sinus node If channel to produce a dose-dependent bradycardia without negative inotropy. It is indicated “to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤35% who are in sinus rhythm with resting heart rate ≥70 beats per minute and either are on maximally indicated doses of beta-blockers or have a contraindication to beta-blockers.” Because beta blockers reduce mortality, and the data for reduction in mortality with ivabradine are less certain,
Ivabradine should be used only after careful attempts to increase beta blockers have failed to lower the heart rate to < 70 beats per minute.

The approval of ivabradine was based on two large randomized trials (BEAUTIFUL and SHIFT) conducted primarily in Europe. After European approval of this drug, it was widely expected that the FDA would convene a Cardiorenal Advisory panel to consider the drug, but the drug was approved without a full panel discussion. Controversy remains about whether beta-blocker titration was adequately attempted in BEAUTIFUL and SHIFT, and about the safety of the drug in patients with activity-limiting angina and heart failure (due to the results of SIGNIFY). SIGNIFY was a recent, large randomized trial evaluating ivabradine in 19,102 patients who had both stable coronary artery disease without clinical heart failure and a heart rate of ≥70 beats per minute. Subjects were randomly assigned to placebo or ivabradine, at a dose of up to 10 mg twice daily, with the dose adjusted to achieve a target heart rate of 55 to 60 beats per minute. The primary endpoint was a composite of death from cardiovascular causes or nonfatal myocardial infarction. After a median follow-up of 27.8 months, there was no significant difference between the ivabradine group and the placebo group in the incidence of the primary endpoint (6.8% and 6.4%, respectively; P=0.20), nor were there significant differences in the incidences of death from cardiovascular disease or nonfatal myocardial infarction. Ivabradine was associated with an increase in the incidence of the primary endpoint among patients with activity-limiting angina but not among those without activity-limiting angina (P=0.02 for interaction). The incidence of bradycardia was higher with ivabradine than with placebo (18.0% vs. 2.3%, P<0.001). Ivabradine should not be used in patients taking strong cytochrome P450 3A4 inhibitors, in those with a heart rate < 60 beats per minute, or in those who are pacemaker-dependent.

CardioMEMS Heart Failure System

In May 2014, the FDA approved the CardioMEMS™ Heart Failure System “to reduce heart failure readmissions in patients with chronic heart failure.” The system became available in fall 2014, and has been clinically available since then. The system consists of an implantable pulmonary artery monitor.
(PA) sensor, delivery system, and Patient Electronics System. The implantable sensor is permanently placed in the pulmonary artery during an outpatient right heart catheterization procedure. Patients must be able to take aspirin and clopidogrel (Plavix) for one month following implantation. The PA sensor is about the size of a small paper clip and has a thin, curved wire at each end (Figure 1). The sensor does not require any batteries or wires. The Patient Electronics System includes the electronics unit, antenna, and pillow. The patient lies down on a pillow each day to wirelessly transmit PA pressures which are then downloaded by health care providers. The pattern of increases (or decreases) in PA pressures allows health care providers to adjust medications to normalize PA pressures with diuretics or vasodilators.

After an FDA panel rejection of CardioMEMS in December 2011, a second FDA advisory committee in early 2014 narrowly recommended approval (6 votes to 4). The approval was based largely on an open-label study conducted with patients enrolled in the CardioMEMS pivotal trial (CHAMPION). In the CHAMPION study, the PA pressure sensor was implanted in 550 NYHA class III heart-failure patients (both reduced and preserved ejection fraction) with a history of decompensation. Control subjects had the device implanted but pressures were not transmitted to health care providers. The system was associated with a 30% reduction in hospitalizations compared with standard care. There was a 39% reduction in heart-failure-related hospitalization in the treatment group compared with the control group at 6 months.

The CardioMEMS System is now available at Vanderbilt. For questions or evaluation of patients for the CardioMEMS system please contact Connie Lewis, N.P., Kelly Schlendorf, M.D., Daniel Lenlihan, M.D., or JoAnn Lindenfeld, M.D. Patients implanted with the CardioMEMS device will be monitored by the Heart Failure team.

References:
Cardio-oncology: A Rapidly Evolving Discipline
Javid Moslehi, M.D., Assistant Professor of Medicine and Director, Cardio-oncology Program

Patient Case: JR is a 52-year-old mother of four who was diagnosed with chronic myelogenous leukemia (CML) in 2002. Over the last 13 years, she has been treated with a number of tyrosine kinase inhibitors (TKI), which have kept her cancer at bay. However, since she was switched to a new TKI, called nilotinib (Tasigna), she has developed diabetes and now presents with claudication in her left leg. She is referred to the Cardio-oncology clinic for management of her cardiovascular issues. The referring oncologist also wants to know whether her most recent treatment is responsible for her cardiovascular problems.

Cardio-oncology (the cardiovascular care of cancer patients) has emerged as a new discipline in medicine in part due to the explosion of novel oncologic therapies, which have dramatically changed the natural course of cancers and have introduced survivorship as a new theme in oncology care. Many of these therapies can have side effects on the heart and vasculature. In addition, since cardiovascular disease is prevalent in the general population, cardiac disease represents a major burden for cancer survivors (15 million Americans in 2015).

Cardio-oncology is not a new field. Forty years ago, cardiovascular issues were observed in patients, particularly children, treated with anthracyclines and radiation. However, these treatments were nonspecific and cytotoxic. The advent of more selective, mechanism-based therapies more than a decade ago led to hopes for an improved safety profile. An early example was trastuzumab (Herceptin), the first drug targeting the erbB2/Her2 signaling pathway, which is overexpressed in a subset of breast cancers. However, despite trastuzumab’s oncologic success, a significant percentage of treated patients developed heart failure. Bevacizumab (Avastin), which targets a signaling pathway important for angiogenesis, has been highly successful in the treatment of some cancer types but is associated with hypertension, thrombosis, and cardiomyopathy.

The Vanderbilt Cardio-oncology Program
The Vanderbilt Cardio-oncology Program brings together clinicians and researchers who collaborate to understand the complications associated with traditional and new cancer therapies. This multidisciplinary program has several current anticancer therapies that can have cardiovascular toxicity.

Current Cardio-oncology Research at Vanderbilt:

- Effects of TKI on the cardiovascular system
- Mechanisms of toxicities for newer cancer drugs
- Genetic changes that modify the cardiovascular effects of cancer therapies
- Risk factors that predispose individuals to both cancer and cardiovascular disease

Javid Moslehi, M.D.
components, including cardiovascular care of cancer patients, basic and translational research, and training of the next generation of cardio-oncologists.

In the past, heart failure was thought to be the main complication associated with cancer therapies, but recent drugs have been associated with vascular complications (including hypertension), metabolic derangements, thrombosis, and arrhythmia. As a result, our clinical program consists of clinicians with varied expertise. Daniel Lenihan, M.D., and JoAnn Lindenfeld, M.D., are interested in cardiomyopathies that arise in cancer patients. Dr. Lenihan also directs the Vanderbilt Amyloidosis Multidisciplinary Program (VAMP), a comprehensive clinical program providing care for patients who have suspected or confirmed amyloidosis. David Slosky, M.D., and Javid Moslehi, M.D., are investigating vascular and metabolic complications that arise in cancer patients.

In addition, the Vanderbilt Cardio-oncology thrombosis center has a special interest in thrombotic disorders in oncology patients. Finally, recognizing the importance of cardiovascular health in cancer survivors, our group has developed a cancer survivorship program. One component of the program is an innovative approach known as the “ABCDEs,” described by Moslehi and colleagues.4

A distinguishing feature of the Vanderbilt Cardio-oncology Program is close interaction between clinicians, physician-scientists, and researchers. Thomas Force, M.D., is a physician-scientist and past president of the Heart Failure Society of America who is an international authority on cell signaling in the heart. Dr. Force has defined the roles of kinases in the cardiovascular system and how specific TKI, used for cancer therapy, perturb this system. Dr. Moslehi is interested in the mechanism of toxicities for newer
drugs, including ones that target the protein degradation machinery of the cell. In addition, Drs. Moslehi and Lenihan have a number of ongoing clinical studies designed to translate these basic research findings into clinical practice. Cardio-oncology investigators are also leveraging Vanderbilt’s BioVU, the largest biorepository at a single academic medical center worldwide, to explore genetic changes that modify the cardiovascular effects of cancer therapies.

Research efforts are also directed toward understanding mechanisms by which common risk factors can predispose patients to both cancer and cardiovascular disease. Emerging data suggest that traditional cardiac risk factors, such as hyperlipidemia, diabetes, and obesity predispose patients to cancer as well. Indeed, obesity has been called the most important risk factor for cancer. At Vanderbilt, we are studying the underlying mechanisms and how specific interventions such as statins or exercise may reduce cardiovascular and cancer risk in the survivor population.

For additional information on the Vanderbilt Cardio-oncology Program, we encourage you to contact the author at: javid.moslehi@vanderbilt.edu.

References:
New Faculty Profiles

JoAnn Lindenfeld, M.D.
Professor of Medicine
Director, Heart Failure and Transplantation Program

Dr. Lindenfeld began her career investigating the role of anemia in the regulation of cardiac output, which subsequently led her to develop the heart failure and transplant program at the University of Colorado. She has extensive experience in the direction and oversight of large multicenter randomized clinical trials in heart failure, heart transplantation, and mechanical circulatory support, and has served on steering committees, data and safety monitoring committees, and endpoint committees of numerous national and international multicenter trials. Dr. Lindenfeld is currently a member of the steering committees of COAPT, FIX-HF, Parachute, and CAT-HF. She has served on the FDA Cardiorenal Advisory Panel for 8 years and the Cardiovascular Devices Panel for 4 years, and continues to be an ad hoc member of both panels. She was chair of the Heart Failure Society of America Clinical Practice Guidelines published in 2006 and 2010, served as vice-president of the Heart Failure Society of America from 2012 to 2014, and is currently the president of the Heart Failure Society of America. As Director of the Heart Failure and Transplantation Program, she currently leads the clinical and research efforts of the group, which is reorganizing advanced heart failure and transplantation services within the Division of Cardiovascular Medicine to improve delivery of all types of treatment for patients with heart failure.

Ashish Shah, M.D.
Professor of Cardiac Surgery
Surgical Director, Vanderbilt Heart Transplant And Mechanical Circulatory Support

Ashish Shah, M.D., Professor of Cardiac Surgery, comes to Vanderbilt from Johns Hopkins, where he was Surgical Director of the Heart Transplant and Mechanical Support Program and Associate Director of the Division of Cardiac Surgery. Shah earned his medical degree from the University of Pittsburgh School of Medicine and then did his internship, residency, and research fellowship at Duke University Medical Center. His clinical interests are end stage heart disease and end stage organ failure. His goal for the heart transplant program is “smart growth” and understanding where ventricular support and transplant technology fit in terms of serving the Vanderbilt and Mid South communities. Vanderbilt is on schedule to reach 1,000 heart transplants within three years.
Joshua Beckman, M.D., MSc.
Professor of Medicine
Director, Vascular Medicine

Joshua Beckman, M.D., MSc., is the Director of Vanderbilt’s newly formed Section of Vascular Medicine within the Division of Cardiovascular Medicine. He is a translational researcher whose work focuses on how diabetes causes vascular disease, specifically the mechanisms that cause endothelial dysfunction and susceptibility to atherosclerosis. Dr. Beckman’s research program includes ongoing investigations that seek to understand how various forms of insulin resistance impact endothelial cell signaling and vasomotor function, whether atherosclerosis causes insulin resistance and vascular dysfunction, and how oxidative stress impacts cardiac, vascular, and renal function. At Vanderbilt, he is creating a Section of Vascular Medicine that provides the non-surgical care for patients with a range of conditions including peripheral artery disease, venous thromboembolism, vasculitis, hypertension, and aortic disease. Beckman earned his medical degree at New York University and his MS degree in Epidemiology from the Harvard School of Public Health. Following an internship, residency, and fellowship at Presbyterian Hospital in New York, he completed a fellowship in vascular medicine at the Brigham and Women’s Hospital. He served as Director of the Cardiovascular Fellowship Program at the Brigham from 2006 to 2013. Beckman, who was an Associate Professor of Medicine at Harvard Medical School prior to coming to Vanderbilt, has received numerous teaching accolades including the W. Proctor Harvey, M.D., Young Teacher Award and the Eugene Braunwald Teaching Award. He is the past President of the Society for Vascular Medicine, and currently chairs the AHA’s Council on Peripheral Vascular Disease.

Editors

Robert N. Piana, M.D.
Thomas J. Wang, M.D.
Quinn S. Wells, M.D., PharmD, MSCI