The past two decades have witnessed a marked improvement in survival after heart transplantation; approximately 50% of recipients now survive over 13 years despite being older and having more co-morbidities at the time of transplant compared to earlier transplant recipients. Longer survival comes at a price; specifically, more years of exposure to immunosuppressive drugs and the potential associated risks. In the first year after transplant, death is most often due to acute rejection or infection. Although infection remains a significant cause of death after the first year, late deaths are most likely due to cardiac allograft vasculopathy (CAV) and malignancies.

Heart transplant recipients typically require more aggressive immunosuppressive regimens than other solid organ transplants, and this intense immunosuppression is likely responsible for the increased incidence of CAV and malignancy seen in this population. Two recent retrospective studies by the cardiac transplant group at Mayo Clinic in Rochester, Minnesota have addressed the role of immunosuppressive agents, specifically calcineurin inhibitors (CNIs) such as cyclosporine and tacrolimus, and the mammalian target of rapamycin (mTOR) inhibitors such as sirolimus and everolimus, in the development of allograft vasculopathy and late malignancies in heart transplant recipients.

CNIs block the activity of calcineurin in T-lymphocytes, decreasing the production of inflammatory cytokines, and have long been used in immunosuppressive regimens. Troublesome side effects include nephrotoxicity and hypertension. Sirolimus blocks signal transduction pathways in both B and T cells; this action is responsible for its immunosuppressive effect. Additionally, it impairs the proliferative response to cytokines and growth factors by vascular smooth muscle cells.

“Prior to 2006, most heart transplant patients at Mayo Clinic in Rochester, Minnesota received induction therapy consisting of antithymocyte globulin (ATG), with a minority receiving muromonab CD-3 (OKT-3) during the first 5 years after transplant,” says Sudhir S. Kushwaha MD, study author and past medical director of the heart transplantation program in the William J. von Liebig Center for Transplantation and Clinical Regeneration at Mayo Clinic in Rochester, Minnesota. “All patients also received maintenance immunosuppression that included a CNI, an antimetabolite (azathioprine or mycophenolate mofetil), and tapering doses of prednisone. Conversion to sirolimus was prompted by deteriorating renal function attributed to the CNI, biopsy evidence of rejection, or CNI intolerance.”

After 2006, patients received rabbit ATG from transplant until tacrolimus was in the target range in addition to mycophenolate mofetil and ste-
Cardiac Allograft Vasculopathy

CAV is associated with both cell-mediated and humoral responses that result in immune-mediated endothelial damage, vascular inflammation, intimal smooth muscle proliferation, and fibrosis.

The first study evaluated the incidence, progression, and severity of CAV in patients receiving sirolimus for long-term immunosuppression compared to those receiving CNIs. A cohort of 402 patients who were transplanted between 1994 and 2005, were treated with a CNI alone (134 patients) or were converted to sirolimus (268 patients), and had undergone at least 1 intravascular ultrasound (IVUS) examination of their coronary arteries was reviewed. The primary endpoints included progression of CAV by IVUS volumetric assessment, all-cause mortality, CAV-related death, and CAV-related events such as allograft failure. The demographic and clinical characteristics of the group were similar except for age; the sirolimus group was statistically older (54.2 ± 12.5 years vs. 48.9 ± 14.5 years; p=0.001).

At a mean follow-up of 8.9 years from transplant all-cause mortality was lower in the sirolimus group compared to the CNI group, and incidence of fatal and non-fatal CAV-related events was also lower. Further analysis suggested better outcomes in patients with earlier (< 2 years) conversion to sirolimus compared to later (> 2 years) conversion after transplant. The progression in plaque volume and the plaque index were both significantly mitigated in the sirolimus group compared to the CNI group. Conversion to sirolimus-based immunosuppression was associated with similar rates of rejection and without allograft deterioration.

Post-Transplant Malignancy

The reduction in the mortality secondary to CAV-related disease did not fully account for the overall improved survival in transplant patients receiving sirolimus, prompting investigators to consider the role that sirolimus might play in the incidence of post-transplant malignancy.

The intensity and the duration of immunosuppression are associated with the risk of developing cancers, as well as recipient factors such as latent Epstein-Barr virus infection. One of the current challenges in the transplant field is reducing the risk of immunosuppressive-related malignancies, while at the same time suppressing rejection of allograft.

In the second study, 523 heart transplant patients were retrospectively evaluated; of these, 307 were converted to sirolimus and 216 remained on a CNI. Demographic and clinical characteristics were similar between the two groups, although the patients converted to sirolimus were on average slightly older (3.7 years); there was no difference in the rates of Epstein-Barr and cytomegalovirus viremia and the rates of rejection between the two groups. Those patients receiving ATG induction therapy were more likely to convert to sirolimus, while those receiving OKT-3 were more likely to remain on a CNI regimen (p<0.0001). Mean follow-up was 10 years.

“Patients who converted to sirolimus had statistically significant lower overall rates of non-skin malignancies, post-transplant lymphoproliferative disease, and recurrent non-melanoma skin cancer,” says Alfredo L. Clavell MD, one of the study authors and current medical director of cardiac transplantation in the William J. von Liebig Center for Transplantation and Clinical Regeneration at Mayo Clinic in Rochester, Minnesota “Both the 10-year overall survival and the 10-year malignancy-free survival was statistically greater in the sirolimus group compared to the CNI only group. There was no difference in the incidence of de novo non-melanoma skin cancers, although the risk of recurrent skin cancer was significantly reduced in the sirolimus group.”

The dose-dependent increase in associated cancers with CNIs has been attributed to increased levels of growth and angiogenic factors, effects not seen with mTOR inhibitors, and more likely to promote the development of malignant cells. The mTOR inhibitors have antiproliferative and antimigratory effects on vascular smooth muscle cells, reduce extracellular matrix accumulation and fibrosis, and induce nitric oxide production, all resulting in positive remodeling of the vasculature. Thus, early conversion from a CNI-based regimen to sirolimus substitutes a stimulant to malignant transformation for one with a positive remodeling effect on the coronary vasculature, resulting in lower rates of CAV and malignancy. To review the full studies:


HONORS

Naser Ammash MD, cardiologist at Mayo Clinic in Rochester, has been named the chief executive officer of Sheikh Shakhbout Medical City in partnership with Mayo Clinic in Abu Dhabi, United Arab Emirates. Sheikh Shakhbout Medical City includes a 741-licensed-bed hospital that will be fully operational in early 2020.

Veronique Roger MD, has been named one of two 2019 Distinguished Mayo Clinic Investigators. The Distinguished Mayo Clinic Investigator Award is presented to staff whose research careers demonstrate evidence of distinction, high distinguished scholarship, creative achievement, and excellence in education and administrative responsibilities. Dr. Roger, a member of the Department of Cardiovascular Medicine at Mayo Clinic in Rochester, Minnesota, is the Elizabeth C. Lane Ph.D., and M. Nadine Zimmerman Ph.D., Professor of Internal Medicine. Over the last two decades, Dr. Roger’s research has focused on the epidemiology and outcomes of cardiovascular diseases. She has made notable contributions to the understanding of the evolving epidemiology of cardiovascular diseases, specifically in the study and respective outcomes of myocardial infarction, heart failure, and atrial fibrillation.

Garvan C. Kane MD PhD, Cristina Pislaru MD, and Sorin V. Pislaru MD PhD, Department of Cardiovascular Medicine at Mayo Clinic in Rochester, Minnesota are members of a Mayo Clinic team recognized by the American Society of Echocardiography (ASE) as ASE Foundation Top Investigators at the organization’s scientific sessions in June 2019. The team’s abstract was “Prognostic Value of Cardiac Power Output in Patients with Normal Left Ventricular Ejection Fraction Referred for Stress Echocardiography.”

Mayo Clinic in Rochester, Minnesota matriculated 22 cardiovascular fellows at ceremonies in June, 2019. Melissa A. Lyle MD received the Cardiology Outstanding Achievement Award in Clinical Performance. Dr. Lyle is completing an advanced heart failure and transplant fellowship at Emory University in Atlanta, Georgia. Michel Corban MD received the Cardiology Outstanding Achievement Award in Research. Dr. Corban is completing an interventional cardiology fellowship at Mayo Clinic in Rochester, Minnesota. Samuel J. Asivatham MD, electrophysiologist at Mayo Clinic in Rochester, Minnesota, and director of the electrophysiology training program, received the Rick A. Nishimura Teacher of the Year Award.
Earlier Intervention May Improve Outcomes in Patients with Aortic Valve Regurgitation

The treatment of cardiovascular disease is increasingly guideline-driven, gleaned from data collected in clinical trials. Technological advances and changing clinical practice require that these guidelines be periodically revisited and updated. The 2014 American Heart Association/American College of Cardiology (AHA/ACC) valvular heart disease guidelines updated recommendations previously reviewed in 2006. These guidelines included recommendations regarding timing of surgical intervention in severe aortic regurgitation (AR). While the studies used to formulate the updated recommendations were the best available, they were nonetheless based upon patient populations evaluated more than 20 years ago. Moreover, these prior studies did not routinely include non-surgical patients or uniformly control for the effects of concomitant coronary artery disease. Additionally, echocardiographic parameters to quantitate aortic valve function and ventricular diastolic function were not yet standardized. Furthermore, over the decades the pathophysiology of AR has changed, and surgical experience and the technical aspects of valve repair have evolved. A recent study led by Patricia A. Pellikka MD, cardiologist at Mayo Clinic in Rochester, Minnesota and director of the Mayo Clinic echocardiography laboratory, addresses these contemporary issues in patients with isolated chronic AR of at least moderate severity in light of the 2014 AHA/ACC guidelines.

Dr. Pellikka and colleagues retrospectively reviewed 748 consecutive patients who underwent comprehensive transthoracic echocardiographic evaluation (TTE) at Mayo Clinic in Rochester, Minnesota between January 2006 and October 2017 and were identified as having isolated, moderate-severe or severe AR (Figure 1). Patients with concomitant aortic or mitral stenosis, mitral regurgitation, endocarditis, aortic dissection, prior mitral or aortic valve surgery, hypertrophic cardiomyopathy, ischemic cardiomyopathy, prior myocardial infarction or coronary artery bypass grafting, or a terminal malignancy were excluded from the review.

Comprehensive TTE with chamber quantification was performed, including measurements of left ventricular chamber dimensions and systolic and diastolic function. An integrated diagnostic approach combining quantitative and semi-quantitative measures (proximal isovelocity surface area-derived regurgitant volume [PISA], vena contracta width, and time-velocity integral of the reversed flow in the descending aorta) was used to determine AR severity. Symptom status was determined by documentation in the electronic health record by the treating cardiologists and cardiovascular surgeons. Surgical indications and class were defined by the 2014 AHA/ACC guideline criteria, including symptoms (Class I), LV ejection fraction < 50% (Class I), surgery for aortic disease (Class I), indexed LV end-systolic dimension > 25 mm/m² (Class IIa), LV end-systolic diameter > 50 mm (Class IIa), and LV end-diastolic dimension >65 mm (Class IIb).

The endpoint was all-cause mortality; cardiac mortality was not used due to the limitations of data derived from death certificates. The observation period was the time between date of qualifying TTE and last evaluation or death. Mean overall observation duration for the group was 4.9 years. The mean age of the group was 58 ± 17 years, and 18% were female. Aortic valve surgery was performed in 48% of patients (and of those almost 90% were within 6 months of contact) and included repair in 27% and replacement in 73% of these; 52% of patients did not have surgery.

Importantly, this study demonstrated that the decision to pursue surgical intervention in these patients with AR of at least moderately-severe degree was driven largely by the presence of class I indications, of which symptoms were by far the most common; class II indications were the only criteria in 14% of patients who went on to surgery. However, the researchers also noted that symptom status was a strong predictor of all-cause mortality, despite the fact that surgical mortality has been reduced to very low levels. Symptomatic patients were older, and had more severe diastolic dysfunction. Over 80% of symptomatic patients did not have guideline-defined LV enlargement, perhaps delaying recognition of clinically significant AR.

Other than aortic valve surgery which was associated with better survival, the LV end-systolic diameter indexed to body surface area was the only objective criterion linked to all-cause mortality (Figure 2). The risk of death clearly began to increase for LV end-systolic diameter index over 20 mm/m², with a 1.5-fold increase in mortality compared to patients with LVESDI < 20 mm/m². This measurement is lower than the threshold of > 25 mm/m² suggested by current guidelines. This variable is likely particularly important in identifying asymptomatic surgical candidates among women and elderly patients with smaller body surface areas who were less likely to have...
The observation in this study that patients had a higher mortality once they developed any symptoms suggests that the presence of class II criteria should prompt consideration of surgical intervention even if the patient has not yet developed symptoms,” says Dr. Pellikka. “Aortic valve surgery was associated with improved outcome and should be considered at an earlier stage of left ventricular enlargement.”

Does Reduction in Red Meat Consumption Improve Health?

The recent compilation of 5 articles in the *Annals of Internal Medicine* regarding the benefits of reducing meat consumption by 3 servings per week was both controversial and surprising. Controversial because it recommended that a person eating processed/red meat should continue their current rate of consumption because reducing intake by 3 servings per week, as the authors concluded, would not lower their risk of cardiovascular disease or cancer. Surprising because this series of studies showed that a lower consumption of processed/red meat was associated with a significant reduction in total mortality, cardiovascular mortality, cancer mortality and incidence of type 2 diabetes mellitus. All 5 studies were authored by the Guideline Recommendations from the Nutritional Recommendations (NutriRECS) Consortium, an international self-organized group with a self-proclaimed goal of producing “rigorous evidence-based nutritional recommendations adhering to trustworthiness standards” (Johnston BC, Zeraatkar D, Han MA et al. Unprocessed red meat and processed meat consumption: Dietary guideline recommendations from the Nutritional Recommendations (NutriRECS) Consortium. Ann Intern Med 2019;171:756–764. doi:10.7326/M19-1621).

The analysis included a large number of studies that included a tremendously large number of subjects: for cardiovascular outcomes (cardiovascular disease, stroke, and myocardial infarction) and type 2 diabetes mellitus, 23 cohort studies with 1.4 million participants; for adverse cancer outcomes, 31 cohorts with 3.5 million participants; for overall lifetime cancer mortality, 17 cohorts with 2.2 million participants; and for the risk of adverse cardiometabolic and cancer outcomes, 70 cohort studies with just over 6 million participants. They assessed the risk for adverse cardiometabolic outcomes on the basis of an average of 10.8 years follow-up, and adverse cancer outcomes over a lifetime. In all groups, a statistically significant reduction was found in the major endpoints when processed/red meat consumption was reduced. This data is consistent with prior studies showing that processed/red meat consumption is associated with increased total and cardiovascular mortality. Some questions persist:

**Why did the authors conclude that reduced consumption of processed/red meat does not improve health?**

The authors explained that their conclusion to not recommend reduction of red meat consumption was based on the following factors: 1) there was a small absolute risk reduction based on a decrease of 3 servings per week, the certainty of evidence for a reduction of adverse health outcomes associated with meat consumption was low, 2) people valued and preferred eating meat, and 3) the panel focused exclusively on health outcomes associated with meat and did not consider animal welfare and environmental issues. Thus, the authors stated that “taken together, these observations warrant a weak recommendation to continue current levels of red meat and processed meat consumption.”

**Is reduction of 3 servings of processed/red meat per week a large amount?**

A reduction of 3 servings a week equals 9 ounces, or 1.3 ounces a day, which may be interpreted as a minimal reduction, equivalent to one less bite of processed/red meat per day. In addition, the analysis did not delineate if the baseline consumption of meat was high or low (e.g. > 14 servings or < 7 servings per week).

**Did these findings include relevant recent randomized trials that assessed benefits of a healthy diet?**

No. These studies excluded 2 randomized trials evaluating the Mediterranean Diet, the Lyon Heart Study in secondary cardiovascular disease prevention, and the PREDIMED Study in primary prevention.

**How do these recommendations potentially affect the environment?**

Recent studies have shown that compared to a typical Western diet, reducing processed/red meat to 3 ounces per day can reduce an individual’s environmental (including land, energy, and water consumption along with gas emission) “footprint” by 72%. (Environ Health 2013 Dec 30;12:118. doi: 10.1186/1476-069X-12-118; United States Department of Agriculture - Economic Research Service).

**Do the findings support the authors’ recommendations?**

The authors meta-analyses of dietary patterns showed that a moderate reduction in processed/red meat consumption by 3 servings per week would not lower their risk of cardiovascular disease or cancer.
red meat consumption was associated with lower total mortality (13%; CI\textsubscript{95%} = [8%, 18%]), lower cardiovascular disease mortality (14%; CI\textsubscript{95%} = [6%, 21%]), lower cancer mortality (11%; CI\textsubscript{95%} = [4%, 17%]), and a lower risk of type 2 diabetes mellitus (24%; CI\textsubscript{95%} = [14%, 32%]). Some may interpret these results as clinically significant although the authors did not.

Almost all nutritional studies are observational; it is impossible to conduct long-term, randomized, blinded dietary trials, making it difficult to formulate exact guidelines. Nevertheless, it would seem prudent based on the totality of trial evidence to continue to adhere to current dietary guidelines. For more information about nutrition, healthy diets, and tips for shopping and cooking, please see:

https://www.mayoclinic.org/healthy-lifestyle/nutrition-and-healthy-eating/basics/nutrition-basics/hv-20049477

**HONORS**

Jeffrey B. Geske MD, cardiologist at Mayo Clinic in Rochester, Minnesota, received the Golden Apple Award from the Mayo Clinic Alix School of Medicine class of 2020. The Golden Apple Award is presented annually to a preclinical educator who displays unique skill and extraordinary dedication in teaching undergraduate medical students. Dr. Geske is an associate professor of medicine in the Mayo Clinic College of Medicine and Science.

Vatsal Ladia MD, second year electrophysiology fellow at Mayo Clinic Arizona won the Electrophysiology Jeopardy Grand Prize at the 2019 Heart Rhythm Society Board Review Course, where he competed against other electrophysiology fellows and recertifying physicians. After graduating in June 2020, Dr. Ladia will be joining Self Regional Medical Center in Greenwood, South Carolina.

Bryan Cannon MD, pediatric electrophysiologist at Mayo Clinic in Rochester, Minnesota, has been elected president of the Pediatric & Congenital Electrophysiology Society (PACES), an international organization of professionals providing care to children and young adults with cardiac rhythm disturbances.

Juan M. Bowen MD, received the 2019 Antoine Marfan Award at the annual Marfan Foundation meeting in Houston, Texas. The award recognizes Dr. Bowen as a relentless champion for the Marfan Foundation and related-conditions community. He has joint appointments in the departments of cardiovascular medicine and community internal medicine at Mayo Clinic in Rochester, Minnesota, and is an assistant professor of medicine in the Mayo Clinic College of Medicine and Science.

**ANNOUNCING NEW WEBINAR SERIES**

**CARDIO-ONCOLOGY: CARDIAC TUMORS WEBINAR**

**MAYO CLINIC CARDIOVASCULAR EDUCATION**

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Mayo Clinic Cardiovascular Digital Education is delighted to announce a new webinar series “Contemporary Cases in Cardiology.” This non-credit program will be offered free of charge, and it will cover a broad range of topics of cross-disciplinary interest. The inaugural webinar on February 10, 2020 is entitled “Cardio-Oncology: Cardiac Tumors”, moderated by Joerg Herrmann MD with presentations from Drs. Kyle Klarich, Phillip Young, and John Stulak. This topic will be of interest to cardiologists, cardiovascular surgeons, oncologists, general internists, radiologists, trainees, and NPs/PAs.

This webinar will:

- Provide an overview of the cardiac masses and how to approach, initial imaging, and management approach.
- Expand on imaging techniques beyond echo and which one to choose based on clinical suspicion, and which other additional techniques can be utilized.
- Elaborate on biopsy and surgical strategies, whether and when to operate, and outcomes and therapeutic risks.

Join us for this webinar on February 10, 2020, 2:00 PM – 3:00 PM Central Time. Please register at our website: https://cveducation.mayo.edu/cardio-oncology
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For additional information:
Web: https://cveducation.mayo.edu/
Email: cvcme@mayo.edu
Phone: 800-283-6296

Ski the Summit @ Copper:
Echo Imaging in Colorado
Copper Mountain, CO March 1-5, 2020

Cardiac Rehabilitation Workshop:
The Mayo Clinic Model
Rochester, MN March 24-26, 2020

Heart Failure Management for NP’s,
PA’s and Primary Care Providers
Lake Buena Vista, FL March 26-28, 2020

Mayo Clinic Extracorporeal Membrane
Oxygenation (ECMO) Symposium
Scottsdale, AZ March 27-28, 2020

Echo Fiesta: An In-Depth Review of Adult Echocardiography for Sonographers and Physicians
San Antonio, TX April 6-9, 2020

Echocardiography Review Course for
Boards and Recertification
Rochester, MN April 17-21, 2020

Basic to Advanced Echocardiography
Hilton Head Island, SC May 13-16, 2020

Foundations in Cardiology Practice –
NEW COURSE!
Scottsdale, AZ May 14-16, 2020

Echo/Imaging New York: State-of-the-Art
New York, NY June 4-7, 2020

Cardiac Rhythm Device Summit: Implantation,
Management, and Follow Up
New York, NY June 18-20, 2020

Heart Failure Up North: Practical Approaches
to the Management of Congestive Heart Failure
Brainerd, MN June 27-28, 2020

Echo Alaska: Frontiers of Multimodality Imaging
Including Echo, Cardiac CT, and MRI
Anchorage, AK July 13-17, 2020

Current Applications and Future of Artificial
Intelligence in Cardiology
San Francisco, CA July 23-25, 2020

Success With Failure: Strategies for the
Evaluation & Treatment of Heart Failure
Whistler, BC, Canada July 26-28, 2020

Cardiovascular Review Course for Initial
Certification and Recertification
Rochester, MN August 22-26, 2020

Echo Focus Session
Rochester, MN August 27, 2020

Internal Medicine Review for Nurse Practitioners,
Physician Assistants & Primary Care Physicians
Rochester, MN September 9-11, 2020

Advanced Catheter Ablation: New Tips, Techniques
and Technologies for Complex Arrhythmias
Boston, MA September 12-15, 2020

Interventional Cardiology Board Review
Rochester, MN September 18-20, 2020

The Genetics of Heart & Vascular Disease
Phoenix, AZ September 24-26, 2020

Challenges in Clinical Cardiology: A Case-Based Update
Chicago, IL September 25-27, 2020

Echocardiography in Pediatric & Adult Congenital Heart Disease Case Studies: Including Multimodality Imaging
Phoenix, AZ October 1-4, 2020

Echo Revolution: Adult Echocardiography for Physicians and Sonographers
Boston, MA October 11-13, 2020

Cases in Echocardiography, Cardiac CT and MRI
Napa, CA October 21-24, 2020

Coronary Artery Disease: Case-Based Learning
Dana Point, CA October 30-November 1, 2020

Cardiovascular Review in Bahrain:
Case-Based Approach
Manama, Bahrain November 4-7, 2020

The Heart Beat of Cardiology:
Practical Application of Echocardiography
Chicago, IL December 10-12, 2020

Echo on Marco Island: Case-Based Approach
Marco Island, FL December 17-20, 2020

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