A 97-year-old man was referred for assessment to our transcatheter aortic valve implantation (TAVI) team. He had suffered multiple hospitalizations for heart failure with a significantly elevated BNP at 1830 pg/mL. At the time of assessment, he had grade IV New York Heart Association (NYHA) symptoms. Until recently, he had been working actively, but this had subsequently been severely limited by his progressive symptoms. He had a history of bladder cancer and hypothyroidism. He had paroxysmal atrial fibrillation and a low ejection fraction of 23 percent. There was severe aortic stenosis with aortic valve area 0.58 cm² and a peak gradient of 68 mmHg, mean gradient of 40 mmHg. His logistic EuroSCORE was 37 with an STS score of 11.5. He was declined for conventional surgery on the basis of age, risk scores and low ejection fraction.

The patient's symptoms had little improvement after implantation of a biventricular pacemaker defibrillator. The aortic annulus measured 22 mm and iliofemoral vasculature measured 8–9 mm at minimal dimension. He was anatomically and clinically suitable for the Edwards SAPIEN™ transcatheter aortic valve implantation (TAVI) device. Following randomization to TAVI as part of cohort B of the PARTNER trial, this was implanted by transfemoral route in the cardiac cath lab (Fig. 1). His hemodynamics immediately improved, a result we consistently observe after TAVI (Fig. 2). The procedure was uncomplicated and he had a short three-day post-procedural stay. At two weeks’ follow-up, he had a mean gradient of 11 mmHg and an early improvement in ejection fraction to 35 percent. He reported a rapid return to activity with only minor limitation. He continues to be well and enjoys an excellent quality of life more than six months post-procedure.

TAVI offers new hope to patients who cannot be treated by conventional surgery. Recent data from the first randomized controlled trial to assess this technology, the PARTNER trial, has shown both a survival and a quality of life benefit in such patients when compared to conservative management.1 Cedars-Sinai Heart Institute continues to treat patients by this procedure as part of a post-study continued access registry.

The first-in-man TAVI procedure was performed by a former Cedars-Sinai fellow, Alain Cribier, MD, in Rouen, France, in 2002.2 It was a much more complex procedure than it is today, performed by transvenous route and employing a transseptal puncture to deliver the catheter-mounted valve across the mitral valve to the aortic position.

Subsequent iterations to the technology and reduction in device size have facilitated a transfemoral retrograde approach, performed without the need for cardiopulmonary assistance.3 Patients with peripheral vascular disease may be treated by a similarly off-pump antegrade transapical route, or, in selected cases, by alternative innovative approaches such as transaxillary or direct thoracic aortic access.4

**Figure 1:** Deployed TAVI device.  
**Figure 2:** Transcatheter hemodynamics pre- and post-TAVI.  

*Continued on page 4 (see “TAVI”)*
Cytomegalovirus (CMV) infection is the major cause of infectious morbidity and mortality after solid organ transplantation. CMV transmission can occur with transplantation of a seropositive donor organ or can result from blood product transfusion during transplantation. CMV disease can also result from reactivation of a dormant virus in a previously infected recipient. The use of antilymphocyte preparations for induction immunosuppression after transplantation may increase the risk of CMV infection. CMV infection in heart transplant recipients is associated with an increased incidence of allograft rejection, graft atherosclerosis (allograft vasculopathy) and death.1 CMV infection can also lead to host immunosuppression and predispose the patient to opportunistic infections such as fungal and parasitic infections. In one study, CMV disease was associated with significantly decreased survival, with a five-year survival of 68 percent in the non-CMV group compared to 32 percent in the CMV group. The predomi- nant causes of death in the CMV group were infection and graft atherosclerosis.2

**Immunization**

Many strategies to prevent CMV infection in transplanted patients have evolved, including active and passive immunization. Attempts to actively immunize kidney transplant candidates with the immunogenic live attenuated CMV Towne strain vaccine resulted in positive seroconversion, but did not lower the incidence of CMV disease in the patients after transplantation.5-7 However, the vaccinated patients tended to run a milder course of CMV disease than did their non-vaccinated controls.5

**Antiviral therapies**

Ganciclovir has an important role in the prevention of CMV infection and disease after solid organ transplantation. Ganciclovir has excellent *in vitro* activity against all members of the herpes family of viruses. Ganciclovir inhibits DNA polymerase and competes with deoxyguanosine triphosphate to terminate the biosynthesis of the viral DNA strand. In randomized, prospective, double-blind clinical trials, intravenous ganciclovir reduced the incidence of CMV disease to a variable degree in both seropositive and seronegative recipients who were transplanted with hearts from seropositive donors, including recipients treated with antilymphocyte therapy.6,9 Ganciclovir has also been shown to decrease the severity of CMV disease and delay its onset. Oral ganciclovir has been shown to be superior to oral acyclovir in providing CMV prophylaxis after solid organ transplantation.10 Other studies have also shown that sequential prophylaxis with intravenous then oral ganciclovir was more effective than sequential intravenous ganciclovir followed by oral acyclovir in heart transplant recipients.11 However, a disadvantage of oral ganciclovir is its low bioavailability (6%).

Oral valganciclovir is a valine ester prodrug of ganciclovir with a bioavailability of 60 percent. Valganciclovir has replaced oral ganciclovir for prophylaxis and pre-emptive therapy, and has been demonstrated to be as effective as intravenous ganciclovir in the treatment of CMV disease. Oral prophylaxis with valganciclovir is recommended for at least 100 days after heart transplantation.12-15 Recent data suggests 200 days may be superior to 100 days for prophylaxis.

**Intravenous immunoglobulin**

Intravenous immunoglobulin (IVIG) has been shown to reduce the development of donor-specific anti-HLA alloantibodies and appears to be efficacious in the treatment of antibody-mediated allograft rejection.16 In addition to preventing humoral rejection, IVIG has also been used for CMV prophylaxis. IVIG has led to significant reduction of CMV disease and infection in bone marrow and kidney transplant patients.17-19

Furthermore, CMV-specific immune globulin (CMV-IVIG, also known as CMV hyperimmune globulin) has been developed as a means to prevent CMV disease. CMV-IVIG is obtained from fractionation and ultrafiltration of pooled plasma from CMV seropositive donors and standardized for a high titer of CMV antibody. Thus, it has 4- to 8-fold anti-CMV titer compared to unselective immune globulin.20 Possible mechanisms of action for CMV-IVIG include the potentiation of antibody-dependent cell-mediated cytotoxicity response, blockage of cytotoxic T-cell recognition of virus-infected cells and neutralization of CMV.21

The use of CMV-IVIG has been shown to reduce the incidence of serious CMV disease associated with solid organ transplantation. The incidence of virologically confirmed CMV-associated syndromes was reduced to 21 percent in renal transplant patients who were treated with CMV immune globulin versus 60 percent in controls without specific anti-CMV therapy (p<0.01).22 Another study showed that CMV prophylaxis with CMV-specific hyperimmune globulin did not decrease the incidence of CMV infection, but did reduce the severity of subsequent CMV disease.23 In several studies of CMV hyperimmune globulin in heart transplant recipients, the incidence of CMV disease was reduced significantly in the highest risk group of patients.24-26 Variable dosing regimens have been proposed.2

**Combining antivirals and IVIG**

Despite the successes with CMV-IVIG, this therapy alone was inferior to antiviral therapy alone in the prophylaxis of CMV disease. Therefore, the role of combined immune globulin and antiviral therapy has been investigated, with benefit initially shown for combined therapy versus antiviral therapy alone in extrathoracic organ recipients.27,28 Combined CMV-IVIG and ganciclovir was demonstrated to reduce CMV disease and allograft vasculopathy in seronegative recipients with seropositive heart donors.29 Whether CMV-IVIG provides additional benefit in combination with oral ganciclovir is not yet known.

*Continued on page 4 (see “CMV”)*
Visualizing Rupture-Prone Coronary Artery Plaque with Cardiac Computed Tomography

Victor Y. Cheng, MD

Until quite recently, supporters of contrast-enhanced coronary computed tomographic angiography (CCTA) wrestled with the utility of its primary use: detection of anatomically significant coronary artery stenoses. In 2004, mainstream introduction of the 64-detector row scanner made achievement of high-quality coronary artery imaging much more routine, sparking a flood of subsequent accuracy studies that established CCTA as a trustworthy tool for identifying coronary artery stenoses. With the question regarding diagnostic accuracy mostly answered, investigators in the field have redirected attention to novel applications of CCTA that may enhance identification of clinically important coronary artery disease.

Among the most exciting of these new directions is the detailed examination of plaque appearance by CT with the goal of uncovering unique, noninvasively detectable features that typify rupture-prone, or vulnerable, coronary artery plaque. Intravascular ultrasound (IVUS)-based research has implicated specific patterns in plaque appearance as markers for vulnerability. The seminal IVUS-based study by Maniko Ehara, MD, et al. in patients with acute myocardial infarction, unstable angina and stable angina found that plaques responsible for acute myocardial infarction exhibited small calcium inclusions (“spotty calcification”), greater fibro-fatty content and outward vessel wall expansion (“positive remodeling”). These morphologic features may represent increased cellular turnover or metabolic activity within plaque. Dr. Ehara’s findings have been extended by the recently published PROSPECT study, which also found thin-capped fibroatheroma (corresponding in part to a lipid core or high fatty content) and high plaque burden to be predictive of plaques that rupture. While results from Dr. Ehara and PROSPECT have been enlightening, the invasive nature of IVUS leaves its use for risk detection in large populations impractical.

Application of CCTA in large populations is certainly feasible, but can it act as an acceptable substitute for IVUS in detailing plaque? Compared to IVUS, CCTA in expert hands has demonstrated excellent promise in detecting spotty calcification, lipid core (determined on CT by the presence of very low attenuation within the plaque) and positive remodeling (Fig. 1). CCTA also has acceptable performance in quantifying plaque volume. Furthermore, longitudinal studies conducted by Sadako Motoyama, MD, PhD, et al. have shown that plaques displaying lipid core, positive remodeling and large noncalcified plaque volume on CCTA have substantially increased risk of subsequently becoming culprit plaques for acute coronary syndrome. The imaging community has approached these results with controlled enthusiasm, since reproducibility of plaque characterization on CCTA has not been satisfactorily established, and quantification of plaque volume, an important predictor of rupture-prone plaque in PROSPECT, remains labor-intensive. Despite these limitations, it is not likely that CCTA needs to exactly replicate IVUS findings to maintain value in detecting vulnerable plaque.

Concurrent to the excitement for CCTA plaque visualization is the growing interest in radionuclide-based detection of coronary plaque metabolic activity. For most of the research to date, the choice radionuclide has been fluorodeoxyglucose, uptake of which in the coronary artery is seen as evidence of increased macrophage concentration and intra-plaque inflammation. In this experimental application, CCTA takes on the complementary role of creating a precise whole-volume map of the coronary arteries. Fusion of this map to fluorodeoxyglucose positron emission tomography images has been essential in determining whether each detected fluorodeoxyglucose signal truly localizes to a coronary artery.

Detailed coronary plaque imaging pushes the technical boundaries of existing CCTA technology, and challenges await its application in practice. Nevertheless, the opportunity afforded by CCTA to visualize morphologic characteristics of coronary artery plaque in vivo is unique among widely applicable noninvasive tests for coronary atherosclerosis. Early results of this use to identify rupture-prone plaque have been encouraging. Within the cardiac CT community, there is growing optimism that cardiologists may finally have an accessible picture into live coronary plaque biology, one that will ultimately help capture patients at truly elevated risk for myocardial infarction and its dreaded consequences.

References

Dr. Cheng is a cardiologist at the Cedars-Sinai Heart Institute. 
Victor.Cheng@cshs.org
TAVI: continued from page 1

Fundamental to the success of the TAVI procedure is careful patient selection. This comprises a detailed assessment of clinical and anatomical suitability. The patient must have severe symptomatic aortic stenosis and must be evaluated as being at high risk for conventional surgery as assessed by both cardiologists and surgeons. This often employs objective risk scores that have been validated in conventional surgery patients, such as the Society of Thoracic Surgeons score and Logistic EuroSCORE.

The anatomical selection includes a careful measurement of the aortic annulus to appropriately size the TAVI device; this is generally performed by transthoracic echocardiographic screening, with clarification by transesophageal echocardiography if needed. Angiography and CT are used to assess the peripheral vasculature for minimal dimension, extent of calcification and tortuosity for a transfemoral approach. Similar imaging assesses the left ventricular apex for scarring and adhesions in the setting of previous myocardial infarction for a transapical approach.

The PARTNER trial of TAVI employed the Edwards SAPIEN device and had two treatment arms, an inoperable cohort (B) randomized to TAVI or conservative management and a high-risk cohort (A) randomized to conventional surgery or TAVI. Cohort B demonstrated a 30-day mortality for TAVI of 5 percent. Early stroke/TIA was higher with TAVI (6.7% vs. 1.7%) but overall the rate of death or stroke was significantly lower with TAVI at one year (33% vs. 53.3%). The number needed to treat (NNT) for one-year mortality benefit over conservative therapy was five and NNT for mortality or quality of life benefit was only three. Cohort A data was reported in March 2011 at the American College of Cardiology meeting.

The imminent randomized controlled PARTNER II study will compare TAVI to surgery using a smaller profile Sapien XT balloon expandable device in intermediate risk groups, and TAVI using this newer device and the already tested Edwards SAPIEN in higher risk patients. Also planned is an international randomized controlled trial evaluating one of the first fully retrievable and repositionable TAVI devices.

CMV: continued from page 2

Surveillance for CMV infection

An alternative approach to preventing CMV disease in transplant patients involves periodic surveillance for CMV infection prior to the onset of CMV disease. Pre-emptive treatment of heart and lung transplant patients with ganciclovir, based on routine surveillance of CMV antigenemia, has been examined. This study argued that if the risk of CMV disease can be predicted by surveillance of antigenemia, then some patients may not require a mandatory CMV prophylaxis regimen. Cedars-Sinai investigators Stanley Jordan, MD, and Mieko Toyoda, PhD, reported the use of CMV-PCR for monitoring of CMV viremia in renal and cardiac transplant recipients. This appears to be most useful in asymptomatic high-risk patients (seronegative recipients with hearts from seropositive donors), and in patients who have symptoms suggestive of CMV disease after appropriate prophylaxis.

Monitoring with CMV-PCR continues to be useful in detecting CMV viremia, which may occur despite appropriate prophylaxis or treatment, especially in high-risk patients.

Since CMV infection remains a major cause of infectious morbidity and mortality after solid organ transplantation, the early and accurate diagnosis of CMV infection and the development of effective antiviral therapeutic regimens are important to the success of future transplantation.

References
1. Rutman MT et al. JAMA 1989;262;3566-3566.