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Clinical Cardiology [ALERT]

Critical analysis of the latest clinical research in cardiovascular medicine

ABSTRACT & COMMENTARY

# Late-breaking Clinical Trials From the European Society of Cardiology Congress, August 2017

*By Joshua D. Moss, MD*

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**Dr. Moss reports no financial relationships relevant to this field of study.**

SYNOPSIS: Late-breaking findings of several important clinical trials in atrial fibrillation management were presented as part of the "Hot Line" sessions at this year's European Society of Cardiology Congress in Barcelona, Spain. A selection particularly relevant to the general cardiology community is presented here.

SOURCE: European Society of Cardiology Congress 365. Available at: http://bit.ly/2yrygxe. Accessed Oct. 16, 2017.

**Catheter Ablation versus Standard conventional Treatment in patients with LEft ventricular dysfunction and Atrial Fibrillation (CASTLE-AF) (Marrouche NF, et al.)**

In this prospective, randomized, controlled study at 31 sites in nine countries, 179 patients with left ventricular (LV) dysfunction and heart failure randomly underwent ablation for atrial fibrillation (AF), and 184 patients received conventional therapy. Ablation consisted of pulmonary vein isolation plus additional lesions at the discretion of the operator. After a standing blanking period, an additional ablation procedure also could be performed. Conventional therapy was administered based on the 2006 American College of Cardiology/American Heart Association/European Society of Cardiology guidelines. About two-thirds of patients were treated with a rate-control strategy, targeting goal heart rates of 60-80 beats per minute at rest and 90-115 beats during moderate exercise. Mean age at enrollment was 64 years, and mean ejection fraction (EF) was about 32%, with almost all patients exhibiting New York Heart Association class II or III heart

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failure symptoms. Arrhythmia burden was assessed via implantable cardioverter-defibrillator remote monitoring.

The burden of AF based on memory from the implanted devices was substantially lower after ablation over a median follow-up of 38 months, comprising about 25% of the time in the ablation group compared with > 50% of the time in the conventional therapy group. At both one year and five years, the mean EF improved significantly more from baseline in the ablation group than in the conventional therapy group. Patients undergoing catheter ablation were 38% less likely to experience the primary composite endpoint (mortality and worsening heart failure admissions), 47% less likely to die, and 44% less likely to require heart failure hospitalization. Reassuringly, serious complication rates were low in the ablation group, including a rate of stroke or transient ischemic attack that was lower than that of the conventional therapy group.

■ COMMENTARY

Several smaller trials, non-randomized studies, and anecdotal data have suggested a benefit to rhythm control via catheter ablation of AF in patients with LV dysfunction and heart failure. Improved quality of life and EF have been mostly consistent findings. This relatively large randomized trial makes a strong case for offering heart failure patients with AF an ablation procedure to significantly reduce their risk of mortality and heart failure hospitalization. Patients with paroxysmal, persistent, and long-standing persistent AF were included, and results were largely conserved across pre-specified subgroups. Patients with EF ≥ 25% demonstrated substantially better improvement with ablation, while those with EF < 25% exhibited more equivalent outcomes with ablation or conventional therapy. Ablation also appeared more favorable in younger patients, those with less severe heart failure, and men. However, there was no subgroup in which conventional therapy was significantly superior, and the potential benefits of ablation for AF should be considered early in the management of patients with heart failure.

**Catheter Ablation compared with optimized Pharmacological Therapy for Atrial Fibrillation (CAPTAF) (Blomstrom-Lundqvist C, et al.)**

In another prospective, multicenter, randomized trial of ablation vs. medical therapy for AF, 155 patients with symptomatic AF first received an implantable cardiac monitor for a two-month run-in period prior to therapy. The implantable monitor was used to rigorously assess arrhythmia burden. The primary endpoint was the change in general health, as measured by the 36-Item Short Form Survey, from baseline to 12 months.

In this trial, the proportion of time in AF was reduced more in the ablation group than in the group treated with antiarrhythmic drugs, but the difference was not statistically significant. Nevertheless, after 12 months of follow-up, the general health score had improved significantly more in the ablation group than in the drug group. The complication rate between treatment groups was similar.

■ COMMENTARY

In patients without LV dysfunction, the main indication for AF ablation is to provide symptom relief. However, this is the first trial to use change in quality of life as the primary endpoint while simultaneously monitoring arrhythmia burden with an implantable cardiac monitor. Despite a non-significant reduction in overall AF burden at one year with ablation compared with antiarrhythmic drug therapy, patient quality of life improved significantly. The evidence continues to build that the concept of choosing rate vs. rhythm control for patients with symptomatic AF is overly simplistic, as rhythm control with ablation represents a superior option to rhythm control with drugs.

**Apixaban compared with parenteral heparin and/or vitamin K antagonist in patients with nonvalvular atrial fibrillation undergoing cardioversion: Rationale and design of the EMANATE trial (Ezekowitz MD, et al.)**

In the large randomized trials of the novel oral anticoagulants dabigatran, rivaroxaban, apixaban, and edoxaban vs. a vitamin K antagonist (VKA), there were low event rates of stroke, systemic

embolism, and major bleeding after cardioversion procedures. However, the patients in those trials typically logged longer periods of anticoagulation prior to the cardioversion.

The goal of the EMANATE trial was to compare outcomes in patients who underwent < 48 hours of anticoagulation with either apixaban or heparin/VKA prior to cardioversion. Patients with mitral stenosis or previous valve surgery, as well as those on dual antiplatelet therapy, were excluded. Overall, 753 patients were randomized to apixaban and 747 to heparin/VKA. In the apixaban arm, cardioversion could be performed as little as two hours after initiation of anticoagulation if a loading dose of 10 mg was administered (5 mg if the patient exhibited two of three standard criteria for reduced apixaban dosing). The mean $CHA_2DS_2$-VASc score was 2-3, and most patients demonstrated preserved EF.

Over 30 days follow-up after cardioversion, there were six events in the heparin/VKA group (five ischemic strokes and one hemorrhagic stroke) and none in the apixaban group ($P$ = 0.016). There were three major bleeds and 11 clinically relevant non-major bleeds in the apixaban group, and six major bleeds and 13 clinically relevant non-major bleeds in the heparin/VKA group.

In an additional analysis, 61 of 840 patients who underwent TEE imaging prior to cardioversion had thrombus present. All except one patient remained on their assigned anticoagulant regimen. For those who underwent repeat imaging, at a mean of 37 days later, 11 of 23 patients on apixaban still had thrombus. For those on heparin/VKA, eight of 18 still had thrombus, a similar ratio.

### ■ COMMENTARY

The results of EMANATE further support the use of apixaban for thromboembolic prophylaxis prior to cardioversion, even when anticoagulation is started as little as two hours pre-procedure. The convenience of avoiding heparin/VKA is likely to be significant to both caregivers and patients, although actual differences in costs were not reported. ■

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ABSTRACT & COMMENTARY

# Patent Foramen Ovale Intervention Rises to Occasion in Cryptogenic Stroke

***By Jeffrey Zimmet, MD, PhD***

*Associate Professor of Medicine, University of California, San Francisco; Director, Cardiac Catheterization Laboratory, San Francisco VA Medical Center*

**Dr. Zimmet reports no financial relationships relevant to this field of study.**

SYNOPSIS: After years of uncertainty, three large randomized trials have shown a benefit to patent foramen ovale closure in reducing recurrence after cryptogenic stroke in the right patients.

SOURCES: Saver JL, Carroll JD, Thaler DE, et al. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. *N Engl J Med* 2017;377:1022-1032.

Mas JL, Derumeaux G, Guillon B, et al. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. *N Engl J Med* 2017;377:1011-1021.

Søndergaard L, Kasner SE, Rhodes JF, et al. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. *N Engl J Med* 2017;377:1033-1042.

Patent foramen ovale (PFO) is a common condition in the general population, with autopsy studies estimating a prevalence of more than 25%. Prior studies of contrast echocardiography diagnosing PFO placed it between roughly 10% and 30% of patients. Retrospective studies have long drawn an association between PFO and cryptogenic stroke, particularly in patients with larger shunts or with atrial septal aneurysm (ASA), but until very recently randomized evidence supporting PFO closure in these patients has been lacking. The first of three negative contemporary trials, CLOSURE I in 2012 found a clearly negative result with a device known as the STARFlex. Although it has been noted that this trial included lower-risk patients, as well as patients with lacunar strokes who would not be expected to benefit from PFO closure, this information could not prevent the downfall of its parent company. Two subsequent trials published the following year, the PC trial and the RESPECT trial, both used the Amplatzer PFO

Occluder. The PC trial investigators randomly assigned cryptogenic stroke patients to PFO closure or to medical therapy, which likewise failed to show a significant treatment effect of PFO intervention.

The results of the largest of these studies, RESPECT, were more nuanced. Enrollment was much slower than expected, taking eight years to complete. Patients in the medical therapy arm were more likely to withdraw from the study (in many cases to seek intervention). In the intention-to-treat analysis, although there were half as many strokes in the closure arm compared with medical therapy, this difference did not meet statistical significance ($P = 0.08$). More than four years later, Saver et al conducted an analysis of the extended follow-up from this trial, increasing the median duration of follow-up to 5.9 years (vs. 2.2 years in the original trial). During that period, the number of patients experiencing recurrent stroke increased to 18 in the closure group and 28 in the medical therapy group, yielding the all-important significant *P* value for the difference between groups ($P = 0.046$). The authors reported a relative risk reduction of 35% and a number needed to treat of 43 to prevent one recurrent stroke at five years.

The results of the CLOSE trial and the Gore REDUCE trial also showed that PFO closure resulted in reduced rates of recurrent stroke compared to medical therapy. As an investigator-initiated study, the CLOSE trial was about the strategy of PFO closure rather than a particular device. Eleven different devices ultimately were used, which reflects the greater availability of devices outside the United States. More important was the stringent inclusion criteria of this trial, which required either an ASA or a large interatrial shunt to qualify, presumably to increase the odds that the PFO was causative in the original event. Strikingly, CLOSE reported no recurrent strokes at all in the PFO closure group, whereas stroke occurred in 14 of the 235 patients in the antiplatelet therapy group ($P < 0.001$).

In terms of patient selection, REDUCE represents a middle ground between CLOSE and earlier trials. Although > 80% of patients in each group in REDUCE presented with moderate or large shunts, small shunts also were included, and such enrollees were not required to exhibit other risk factors such as ASA. Nonetheless, closure was associated with a lower likelihood of recurrent stroke, with a relative risk of 0.51 (95% confidence interval, 0.29-0.91; $P = 0.04$). In each trial, procedural success rates were high, while serious procedural complications were uncommon. As in previous reports, the procedure was associated with a small but significant increase in episodes of atrial fibrillation, which in most cases were self-limited. In these three randomized trials comparing interventional to medical therapy for PFO in the setting of cryptogenic stroke, the primary conclusions were similar. In younger patients with cryptogenic stroke and PFO, closure of the PFO was associated with lower rates of recurrent stroke compared with medical therapy consisting primarily of antiplatelet medication.

## ■ COMMENTARY

After so many years without clear supportive data, there are three positive, independently performed, randomized, controlled trials, which truly represent a tipping point for PFO closure in cryptogenic stroke. Before applying these data to average stroke patients, it is worthwhile to review several key points.

First, the patients in these trials were not all-comers with stroke. The patients included in these trials were younger overall, with average ages in the low-to-mid-40s. None of the trials enrolled patients > 60 years of age. Cryptogenic stroke is defined primarily by what is not found, rather than by what is present.

This means that the event is not the result of small-vessel occlusive disease (a lacunar stroke, which is recognized as unlikely to be of embolic origin), and that imaging has excluded proximal arterial stenosis and alternate cardioembolic sources, including atrial fibrillation. Before being considered for PFO closure, the average patient should undergo not only basic brain imaging for stroke but also MRI or CT angiography of the intracranial arteries, cervical arteries, aortic arch, TEE, and screening for atrial fibrillation.

Most strokes are not caused by PFO, and PFOs are very common. The more risk factors a patient exhibits for run-of-the-mill atherosclerotic or embolic stroke, the less likely it is that closing a PFO will be effective. On the other hand, it should be clear from this discussion that not all PFOs are created equally regarding magnitude of the interatrial shunt, presence of atrial septal aneurysm, and their potential role in the etiology of a stroke.

Some have argued that young stroke patients undergoing PFO with a large shunt and otherwise negative complete screening no longer should be labeled as cryptogenic and should be treated accordingly.

Based on the available evidence, PFO closure is now a viable option for U.S. patients who have suffered a cryptogenic stroke. It is essential that potential candidates are screened appropriately so that patients who are most likely to benefit are targeted for therapy. ■

ABSTRACT & COMMENTARY

# Can Medical Therapy Improve Functional Mitral Regurgitation?

***By Van Selby, MD***

*Assistant Professor of Medicine, University of California, San Francisco, Cardiology Division, Advanced Heart Failure Section*

**Dr. Selby reports no financial relationships relevant to this field of study.**

SYNOPSIS: Among patients who presented with heart failure with reduced ejection fraction and severe functional mitral regurgitation, mitral regurgitation improved in 38% of patients with medical management. Improvement in mitral regurgitation was associated with increased survival.

SOURCE: Nasser R, Van Assche L, Vorlat A, et al. Evolution of functional mitral regurgitation and prognosis in medically managed heart failure patients with reduced ejection fraction. *JACC Heart Fail* 2017;5:652-659.

In heart failure with reduced ejection fraction (HFrEF), functional mitral regurgitation (FMR) develops because of left ventricular (LV) dilation and dysfunction. The resulting tethering of the structurally normal mitral leaflets causes failure to coapt. Development of FMR is associated with worse prognosis. Medical therapy for HFrEF, including ACE inhibitors and beta-blockers, improves outcomes and is associated with improvements in LV remodeling. Whether medical management of HFrEF can reduce the severity of FMR and improve prognosis has not been well studied.

Nasser et al studied 163 patients with HFrEF treated at an academic medical center in Belgium. About half the patients had ischemic cardiomyopathy. MR severity was assessed by echocardiography at baseline and follow-up. All patients were treated with maximally tolerated doses of standard medical therapy for HFrEF (ACE inhibitors, beta-blockers, and aldosterone antagonists). Median follow-up was 50 months. Improvement in FMR was defined as a reduction from severe to nonsevere MR, and worsening MR was defined as an increase from nonsevere to severe MR. The primary endpoint was a composite of all-cause death, heart transplant, or hospitalization for HF or arrhythmia.

At baseline, 31% of patients demonstrated severe FMR. Patients with severe FMR were older and exhibited larger LV volumes and lower EF. During the study period, 38% of patients with severe FMR improved to nonsevere FMR, while 18% of those with nonsevere FMR at baseline progressed to severe FMR. Patients with sustained severe FMR or those who progressed to severe FMR received a significantly worse prognosis compared to those who improved or remained nonsevere ($P < 0.0001$). In multivariate models, the presence of severe FMR at follow-up was the single strongest predictor of both the primary endpoint and mortality (odds ratio, 2.5). On the other hand, severity of FMR at baseline was not associated with worse prognosis.

Patients with severe FMR at follow-up exhibited more LV enlargement and were more likely to demonstrate a restrictive LV filling pattern compared to those with nonsevere FMR. The authors concluded that severe FMR can be treated successfully with medical therapy in nearly 40% of patients, with associated improvements in LV remodeling and prognosis.

## ■ COMMENTARY

In multiple studies of HFrEF, FMR is associated with an increased risk of adverse outcomes, including death. The negative effect of FMR often is attributed to progressive LV remodeling because of the increased volume overload caused by MR. This creates a vicious cycle whereby the worsening LV remodeling leads to increased FMR and more LV volume overload. There is growing interest in repair of FMR, whether surgically or percutaneously. However, current medical therapy for HFrEF can improve LV remodeling and theoretically reduce the severity of FMR. Understanding the effect of medical therapy on FMR and identifying which patients will improve with medical therapy alone is crucial for appropriate patient selection for surgical or percutaneous treatment of FMR.

Nasser et al showed that in a subset of patients with HFrEF and severe FMR, the degree of MR can improve with aggressive medical therapy for heart failure. Patients in whom FMR improves are less likely to show increasing LV volumes. Perhaps most importantly, patients in whom FMR improved during the study period showed significantly better survival and lower rates of the composite endpoint compared to those in whom FMR remained severe. These

findings suggest an initial course of aggressive medical therapy may be indicated for most, if not all, patients with HFrEF and FMR before considering invasive valve repair.

The authors highlighted the importance of targeting volume status to prevent the progression of FMR. Patients with improvement in FMR severity during the study period were more likely to show improvement in the LV filling pattern, reflecting improvement in volume status. In the study population, diuretics were up-titrated aggressively as needed to keep patients euvolemic, and extensive education regarding dietary sodium and fluid restriction was provided. Although this association does not prove more aggressive, diuretic use can improve FMR. Given the proposed pathophysiology of FMR, it would make sense that reducing LV volume overload would help improve FMR severity.

This was a relatively small, single-center study. Only 50 patients presented with severe FMR at baseline, so, ideally, the findings should be replicated in a larger cohort to confirm the observed rate of improvement, and, hopefully, identify clinical predictors of FMR improvement. The study by Nasser et al provides helpful insight into the clinical course of patients with HFrEF and FMR who are managed medically. However, many important questions remained unanswered. First, how can clinicians identify those patients with FMR who will improve with medical therapy alone? Second, how should clinicians manage those patients who will not improve with medical therapy alone, or those in whom severe FMR persists despite maximally tolerated therapy? Percutaneous mitral valve repair has gained significant interest in recent years, but its utility in FMR is unproven. The creators of the Cardiovascular Outcomes Assessment of the Mitra-Clip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial randomized patients with severe FMR to MitraClip vs. medical therapy. The results are expected in late 2018. Until then, clinicians should use maximally tolerated medical therapy for HFrEF, including use of diuretics and salt restriction, to optimize each patient's volume status. ■

ABSTRACT & COMMENTARY

# Transcatheter Mitral Valve Replacement as an Alternative to Other Surgical Options

***By Michael H. Crawford, MD, Editor***

SYNOPSIS: A large registry study of transcatheter mitral valve replacement (TMVR) in patients with degenerated mitral valve bioprostheses or failed mitral annuloplasty repairs who were at high risk for repeat surgery showed that TMVR can be performed successfully. However, the initial and long-term results are better in the degenerated bioprothesis group.

SOURCES: Yoon SH, Whisenant BK, Bleiziffer S, et al. Transcatheter mitral valve replacement for degenerated bioprosthetic valves and failed annuloplasty rings. *J Am Coll Cardiol* 2017; 70:1121-1131.

Webb JG, Cheung AW, Dvir D. Transcatheter mitral valve replacement when mitral surgery fails. *J Am Coll Cardiol* 2017;70:1132-1134.

In the 21st century, there has been a shift toward bioprosthetic surgical mitral valve replacements compared to mechanical prosthesis, which has been fueled partially by the availability of transcatheter valves to treat the inevitable bioprosthetic mitral valve degeneration or failure of a mitral annular ring and repair. However, there are few data on this application of transcatheter valve deployment. Thus, investigators created an international registry of patients undergoing transcatheter mitral valve replacement (TMVR) for degenerated mitral bioprostheses or failed annuloplasty rings and repairs. The primary endpoints were all-cause mortality at 30 days and one year. Other clinical events were secondary endpoints. A total of 248 patients with previous mitral valve surgery underwent TMVR at 25 centers, most for degenerated bioprosthesis (71%). The rest underwent failed repairs with annuloplasty rings. Women made up 57% of the patients. Their mean age was 73 years. Surgical risk scores were high (STS = 9, EuroSCORE = 27). Mitral stenosis was more common in the degenerated valve group and mitral regurgitation in the failed repair group. Two-thirds had undergone a transapical access procedure, with almost all the rest transseptal access. Compared to the bioprosthetic group, the annular ring patients experienced a lower technical success rate (83% vs. 96%; $P = 0.001$). Mean mitral gradients were 6 mmHg in both groups, but the annuloplasty ring group exhibited more post-procedure moderate or more mitral regurgitation (19% vs. 7%; $P = 0.003$). Also, the ring group demonstrated more life-threatening bleeding (8% vs.2%; $P = 0.03$) and acute kidney

injury (11% vs. 4%; $P = 0.03$). The one-year all-cause mortality also was higher in the ring group (29% vs. 13%; $P = 0.01$). The authors concluded that TMVR is a reasonable alternative to surgery in high-risk patients with degenerated mitral bioprostheses or failed annuloplasty repairs, but the latter group demonstrated higher procedural complications and one-year mortality rates.

## ■ COMMENTARY

Once an alternative to surgery is available, off-label use is bound to happen because patients in general would rather not undergo surgery. In some cases, it makes sense for other reasons, such as degenerated mitral bioprostheses or failed repairs, because repeat surgery in patients who may be a decade older often is high risk. Therefore, it is not surprising that TMVR has been deployed in such patients. These multicenter registry data on the outcomes is welcome. Admittedly, this is not common. In this report spanning eight years of experience, each of the 25 sites in Europe and North America averaged eight procedures over the eight years of the study.

The major findings of this study are that the results are acceptable in such high-risk-for-surgery patients, and degenerated mitral bioprostheses produced better outcomes than failed annuloplasty repairs. In fact, the one-year mortality was more than two times higher in the latter patient group. Part of this was because of reduced technical success and higher early complications (bleeding, renal injury), but further problems also occurred in the ring patients. The need for re-intervention was higher with rings (17% vs. 7%; $P = 0.03$) and left ventricular ejection fraction was lower (44% vs. 53%; $P < 0.001$). Significant post-procedure MR was higher with flexible rings compared to the semi-rigid ones. Interestingly, 30-day mortality, stroke, and immediate conversion to surgery occurred at very low rates and were not different in the two groups. Finally, the access site did not affect the success of the procedure, but the transseptal approach required closure of the resulting atrial septal defect in 12%. The accompanying editorial suggested reserving TMVR for those who are not surgical candidates. Also, the editorialists noted that oral anticoagulants should be administered for at least the first three months post-TMVR since patients in this trial so treated demonstrated no mitral valve thrombi, whereas only three of the 84 treated with antiplatelet drugs demonstrated thrombi. At this time, the SAPIEN 3 valve has been approved for TMVR use. Hopefully, this will encourage the development of specific equipment for TMVR that will reduce the need for the apical approach and eliminate the need to repair the intra-atrial system with the transseptal approach. ■

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## CME/CE INSTRUCTIONS

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## CME/CE QUESTIONS

1. **Intense medical therapy for systolic heart failure in patients with severe functional mitral regurgitation (MR) can:**

   a. reduce MR in almost all patients.

   b. eliminate MR in most patients.

   c. reduce MR in one-third or more of patients.

   d. eliminate MR in one-third or more of patients.

2. **Which of the following is recommended before deciding a stroke is cryptogenic and may benefit from patent foramen ovale closure?**

   a. Stroke characterization imaging

   b. Angiographic imaging of proximal aorta and head and neck vessels

   c. Screening for atrial fibrillation

   d. All of the above

3. **Recent studies of catheter ablation in atrial fibrillation compared to medical therapy have shown:**

   a. improved left ventricular ejection fraction in systolic heart failure patients.

   b. reduced morbidity and mortality in systolic heart failure patients.

   c. improved quality of life in patients with normal left ventricular ejection fraction.

   d. All of the above

4. **Transcatheter mitral valve replacement is appropriate for symptomatic patients:**

   a. with severe mitral valve prolapse.

   b. with a degenerated mitral bioprothesis.

   c. who are low-risk surgical candidates who present with failed mitral valve repairs.

   d. with severe mixed rheumatic mitral valve disease.

## CME/CE OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss the most current information related to cardiac illness and the treatment of cardiac disease;
- explain the advantages and disadvantages, as well as possible complications, of interventions to treat cardiac illness;
- discuss the advantages, disadvantages, and cost-effectiveness of new and traditional diagnostic tests in the treatment of cardiac illness; and
- discuss current data regarding outpatient care of cardiac patients.