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Arrhythmia Management Devices

New Developments in Cardiac Pacemakers
Panos E. Vardas, MD, PhD; Emmanuel N. Simantirakis, MD, PhD; Emmanuel M. Kanoupakis, MD, PhD

For >50 years, bradycardic patients have enjoyed the benefits of cardiac pacing, a therapy that can improve and, in some instances, prolong their lives. Although initially this unique electric therapy aimed just to maintain an acceptable cardiac output that would support life, contemporary pacemakers mimic the function of the native conduction system of the heart ever more closely while eliminating disturbances of the production and propagation of the electric impulse. Pacemakers nowadays are able to ensure atrioventricular (AV) synchrony and to adapt the heart rate according to the peripheral tissue energy demand while incorporating a large number of useful algorithms. In addition, they have the ability to record and store cardiac electrograms, providing valuable information about other rhythm disturbances such as atrial fibrillation (AF) or ventricular arrhythmias that are not uncommon in paced patients.

At the same time, a better understanding of the natural history of bradyarrhythmias and the recently published results of large, randomized, controlled trials have enabled us to revise older guidelines, to develop new indications for cardiac pacing, and to optimize the selection of the proper pacing mode for each indication on the basis of existing evidence.

Finally, in an attempt to minimize iatrogenic adverse effects caused by pacing from the right ventricular apex (RVA) and right atrial appendage (RAA) and to improve the outcome of cardiac pacing, alternative pacing sites are under evaluation, and leadless pacing and biological pacemakers are among the expectations for the future.

Indications for Cardiac Pacing
Most pacemakers worldwide are implanted because of AV block and sick sinus syndrome (SSS); other indications such as bundle-branch block and neurally mediated syncope are less common. Even more rarely, pacing is done to improve hemodynamics, as in first-degree AV block with a very long PR interval or in hypertrophic obstructive cardiomyopathy, and for indications for specific diseases such as muscular dystrophy or mitochondrial and metabolic disorders. The latest European and American guidelines for cardiac pacing describe all these indications in detail (Table). In this article, we do not repeat the already published guidelines but instead underline some interesting points and cite new data on older indications.

Acquired AV Block and SSS
Patients with complete or Mobitz II AV block are usually highly symptomatic, with syncope, presyncope, dyspnea, and fatigue being the most common symptoms; very rarely are they asymptomatic. However, complete AV block also entails a high risk for cardiac death resulting from heart failure, asystole, or ventricular arrhythmias induced by bradycardia. Old observational and nonrandomized studies clearly showed that cardiac pacing in these patients not only improves symptoms but also reduces mortality. Accordingly, cardiac pacing is recommended for both symptomatic and asymptomatic patients. In patients with Mobitz I AV block, there is some controversy about the usefulness of cardiac pacing. It seems, however, that it should be indicated in symptomatic patients and when the conduction delay is below the AV node. In these cases, progression to complete AV block is common. In terms of pacing in patients with first-degree AV block and a very prolonged PR interval, small studies have shown that dual-chamber cardiac pacing may restore AV synchrony, improving both symptoms and the diastolic mitral valve regurgitation produced by the premature atrial contraction in diastole. In this case, we have to balance the benefit from the restoration of the AV synchrony against the negative effect from the ventricular paced beat.

On the other hand, patients with SSS usually present with syncope, presyncope, or reduced exercise capacity, but their survival is not affected by the syndrome, being similar to that of the general population. In such cases, cardiac pacing aims to alleviate symptoms and should be applied when there is a documented symptom-rhythm correlation. Sometimes, this correlation is difficult to determine, and long-term rhythm monitoring with external or implantable recorders may be useful. In addition, an electrophysiological study may provide information about sinus node function, although its negative predictive value is quite low. Finally, in all cases of AV block or SSS, any transient or reversible cause of bradycardia must be excluded before a decision to implant a permanent pacing system is made.

Syncope in Patients With Bundle-Brunch Block
Several studies have shown that patients with bundle-branch block and severely reduced ejection fraction are at increased risk for sudden cardiac death and are candidates for cardioverter-defibrillator implantation. However, there is still

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a good deal of controversy on the optimal diagnostic and therapeutic strategy in patients with preserved or normal systolic left ventricular (LV) function. In this respect, the use of implantable devices with capabilities for long-term rhythm monitoring has given us important information. The recently published Bradycardia Detection in Bundle Branch Block (B4) study, which included 323 patients with bundle-branch block and a mean ejection fraction of 56±12%, clearly showed that, although the most common cause of syncope was a bradyarrhythmia, mainly AV block, in a substantial number of cases (17.6%), the syncope could be attributed to other causes such as carotid sinus syndrome, ventricular and supraventricular tachycardia, neurally mediated syndrome, orthostatic hypotension, drugs, and pulmonary diseases. In this study, if the initial evaluation, electrophysiological study, and carotid sinus massage were insufficient to establish an etiologic diagnosis, an implantable loop recorder was inserted. With this strategy, an etiologic diagnosis was established in a high percentage (82.7%) of patients. A pacemaker was implanted in 220 patients; a cardioverter-defibrillator was implanted in 19 patients; and radiofrequency catheter ablation was performed in 3 patients. The strategy proved safe; mortality was low (6%) and due mostly to noncardiac and nonarrhythmic causes. In addition, the study confirmed previous findings concerning the high specificity but low sensitivity of an electrophysiological study in such patients. Indeed, in 45% of the patients with a negative electrophysiological study, an arrhythmia was documented by the implantable loop recorder as the cause of syncope. Finally, it must be emphasized that, even with the complete workup used in the B4 study, in ≈17% of patients, the cause of syncope remained unexplained. For such patients, the outcome remains unknown, as does the optimal therapy.

**Reflex Syncope**

The term reflex syncope refers to a spectrum of entities in which an inappropriate response mediated by the autonomic nervous system leads to bradycardia or vasodilatation, with transient cerebral hypoperfusion as a consequence. Syncope, the only symptom that may possibly be ameliorated by
Pacing Mode Selection

After the decision to implant a pacemaker has been made, the next most important step is choosing the pacing mode because it will primarily determine the clinical outcome. This issue is comprehensively addressed in the 2007 European guidelines, the 2008 American guidelines, and a recently published American statement. Obviously, the choice of pacing mode depends on the underlying conduction system disturbance. For SSS and AV block, the 2 most common indications for permanent pacing, the modes should be atrial based and ventricular based, respectively, whereas for reflex syncope, ventricular-based pacing is mandatory.

Pacing Mode in Patients With SSS

The results of 4 randomized studies were in favor of AAIR or DDDR, rather than VVIR, in patients with SSS. These studies showed that patients paced with AAIR or DDDR mode had a significantly lower incidence of AF, stroke, and pacemaker syndrome than those paced with VVI mode. In addition, a single, relatively small trial showed that AAIR mode was associated with significantly lower cardiovascular and total mortality compared with VVI. However, these findings were not confirmed, either by the abovementioned larger randomized trials or by the results of a meta-analysis. Interestingly, until the publication of the Danish Multicenter Randomised Study on AAI Versus DDD Pacing in Sick Sinus Syndrome (DANPACE) trial, no direct comparison between AAIR and DDDR mode had been made. It is known that AAIR pacing preserves the normal ventricular activation but may prolong the spike-R interval, reducing LV filling, whereas DDD pacing ensures optimal AV synchrony but may induce ventricular dyssynchrony, leading in the long term to ventricular remodeling and a reduced ejection fraction. Furthermore, a percentage of patients with SSS (between 0.6% and 1.9% per year) develop AV node disturbances and require a second lead. In the DANPACE trial, 1415 patients with SSS were randomly assigned to AAIR or DDDR pacing and were followed up for a mean of 5.4±2.6 years. No statistically significant difference was found in the primary outcome, which was death from any cause, between AAIR and DDDR pacing. However, AAIR pacing was associated with a higher incidence of paroxysmal AF (28.4% versus 23.0%; hazard ratio, 1.27; 95% CI, 1.03–1.56; P=0.024) and a 2-fold risk of pacemaker reoperation (22.1% versus 11.9%; hazard ratio, 1.99; 95% CI, 1.53–2.59; P<0.001). From the results of the above trials, there is sufficient evidence to support the routine use of DDDR pacing in patients with SSS. However, if there is judged to be a high risk of complications or if venous access does not permit a second lead implantation, AAIR pacing is an acceptable choice. VVI pacing should be limited to backup pacing in patients who require infrequent pacing or in patients in whom atrial-based pacing cannot be achieved.

At this point, 2 other issues related to pacemaker programming are of special importance. First, unnecessary ventricular pacing should be avoided. It is known that unnecessary ventricular pacing may cause AF and deterioration of heart failure. On the other hand, the Search AV Extension and Managed Ventricular Pacing for Promoting Atrioventricular

pacing, usually has a typical clinical presentation, with a trigger responsible for the initiation of the reaction and prodromal symptoms, and the patient’s medical history may establish the diagnosis in most cases. However, more rarely, the presentation is atypical, without prodromal symptoms and triggers, and the diagnosis is based mainly on laboratory tests and the exclusion of structural heart disease. Although patients with various types of reflex syncope (eg, situational syncope) may derive some benefit from cardiac pacing, there is not enough evidence to support such a therapy in general.

The following discussion is limited to our current knowledge of the role of pacing in patients with carotid sinus syndrome and vasovagal syncope. Both are benign conditions that do not affect survival. The goal of therapy is to reduce recurrent syncopal episodes and their consequences.

There is ample evidence to support the postulation that cardiac pacing is highly effective in reducing the syncope recurrence rate in patients with carotid sinus syndrome. A recently published review of the literature reported that, during a follow-up of at least 5 years, the recurrence rate of patients paced because of CCS varied from 0% to 20% as opposed to 20% to 60% for untreated patients. Finally, in a relatively small but well-organized study of 18 consecutive patients who had suspected recurrent, neurally mediated syncope and a positive cardioinhibitory response during carotid sinus massage in whom the diagnosis of cardioinhibitory carotid sinus syndrome was validated by documentation of spontaneous asystolic pauses by an implantable loop recorder, the syncope burden decreased from 1.68 (95% confidence interval [CI], 1.66–1.70) episodes per patient per year before pacemaker implantation to 0.04 (95% CI, 0.038–0.042) after implantation, a 98% reduction in relative risk.

In terms of the role of cardiac pacing in patients with vasovagal syncope, a great deal of confusion has been created by the conflicting results of blinded and nonblinded randomized, controlled trials. The nonblinded trials showed that pacing was effective, whereas the blinded trials found that it was ineffective in managing tilt-induced reflex syncope. Recently, our knowledge has been enriched by the publication of the International Study on Syncope of Uncertain Etiology (ISSUE) studies and the use of implantable loop recorders in the diagnostic evaluation. We have come to realize that the response to a tilting test (bradycardia or vasodilatation) has a weak or no correlation with the response during spontaneous syncope. In ISSUE-3, a randomized, double-blind, controlled trial that included highly symptomatic patients >40 years of age, syncope recurrence rate was 57% (95% CI, 40–74) with the pacemaker off and 25% (95% CI, 13–45) with the pacemaker on (log-rank test, P=0.039, at the threshold of statistical significance of 0.04). The risk of recurrence was reduced by 57% (95% CI, 4–81). The observed statistically and clinically significant reduction in syncope recurrence supports the use of cardiac pacing for the treatment of neurally mediated syncope, with the prerequisite that the patients have clinical characteristics similar to those of patients included in the ISSUE-3 trial.
Conduction (SAVE PACe) trial\(^4\) showed that minimizing ventricular pacing significantly reduces the risk of persistent AF. However, in some cases, a very prolonged AV interval is necessary to avoid ventricular pacing, and this may cause hemodynamic deterioration. In these cases, and especially when there is systolic dysfunction, a biventricular system should be considered.

Second, the sensor for increasing heart rate should not routinely be activated. Although small studies\(^41,42\) have shown a superiority for rate-adaptive pacing in terms of quality of life and exercise capacity, the larger multicenter, randomized Advanced Elements of Pacing Randomized Controlled Trial (ADEPT), involving patients with moderate chronotropic incompetence,\(^43\) did not confirm these results, although a higher rate of hospitalization for heart failure was observed in the patients with rate-adaptive pacing compared with those without rate-adaptive pacing. In addition, an increased risk of AF has been associated with frequent atrial pacing.\(^44\) Thus, rate-adaptive pacing should be reserved for patients with significant and symptomatic chronotropic incompetence.

**Pacing Mode in Patients With AV Block**

In patients with AV conduction disturbances who receive a pacemaker, it is mandatory for the ventricles to be paced. In general, we have to decide among 3 possible choices: single-chamber ventricular rate-adaptive pacing (VVIR) or dual-chamber (DDD) or single-lead (VDD) pacing systems. In contrast to the VVIR mode, which can restore chronotropic competence, the other 2 modes are also able to restore AV synchrony. AV synchrony has an important role in the regulation of cardiac output, mainly at rest and during low levels of exercise, and is especially useful in those patients who depend on optimized ventricular filling such as those with diastolic dysfunction.\(^45,46\)

Many small trials in the past\(^47-49\) have shown that dual-chamber pacing is superior to single-chamber pacing, improving exercise capacity and symptoms and avoiding pacemaker syndrome. Furthermore, the patient preference in most studies is DDD pacing. However, large randomized trials failed to demonstrate any superiority of this mode in terms of harder end points such as morbidity and mortality or in terms of the development of AF and heart failure.\(^50\) At this point, it must be emphasized that in the above randomized trials, most of the patients included were relatively old, whereas there is a lack of data on younger individuals, who are usually more active and do not have significant comorbidities. Nevertheless, and despite the lack of evidence for reducing morbidity and mortality, dual-chamber pacing should be preferred in patients with AV block as a means to avoid pacemaker syndrome and to improve symptoms, whereas VVIR pacing should be restricted to patients with AV and AV block or those in whom the venous access does not permit the implantation of a second lead. As an alternative to DDD pacing, single-lead VDD systems are an acceptable choice in patients with normal sinus node function. Although the procedure time is shorter and the complication rate is lower with these systems, they are not widely used because of atrial sensing problems in the long term and, more important, because they do not have the ability to pace the atrium should sinus node dysfunction develop over time.\(^51,52\)

The usefulness of algorithms to minimize ventricular pacing in patients with AV block is not clear. Although some studies have shown a significant reduction in the percentage of ventricular pacing in patients with intermittent AV block,\(^53,54\) these algorithms should be used with caution because some deleterious effects have been described.\(^55-57\)

Another special issue in patients with AV block is the selection of pacing mode in patients with permanent or long-standing persistent AF for which cardioversion is not planned and in those in whom ablation of the AV node is delivered for rate control. Several studies have shown that VVIR pacing is superior to VVI in terms of exercise capacity, symptoms, and quality of life.\(^58-60\)

**Pacing Mode in Patients With Reflex Syncope**

In patients with carotid sinus syndrome, it seems reasonable, on the basis of the pathophysiology of the syndrome, that DDD should be superior to VVI pacing in reducing syncope recurrence, whereas AAI pacing is ineffective. The results of older studies\(^61-63\) were indeed in favor of DDD pacing compared with VVI; these results, however, were not confirmed by a recently published prospective, randomized, double-blind study.\(^64\) That study made a comparison among VVI, DDDR, and DDDR with a rate-drop response algorithm (rapid pacing after sudden bradycardia detection). The primary end points of syncope or presyncope were significantly reduced after pacemaker implantation in all 3 groups, but no significant differences in the primary outcomes were demonstrated among the 3 pacing modalities. Short Form-36 scores revealed minor benefits of DDDR pacing versus baseline in some categories, but no pacing mode was found to be superior overall. Therefore, given the lack of large randomized trials clarifying the optimal choice of pacing mode, we may conclude that, although DDD pacing should have some priority, VVI pacing could be an acceptable option.

In terms of patients with vasovagal syncope, in most studies evaluating the role of cardiac pacing, DDD pacing with a rate-drop response algorithm was used, but no comparison was made with DDD mode without this algorithm. In any case, AAI pacing should be avoided because asystole may result from complete AV block.

**Alternative Pacing Sites in Patients With Conventional Indications**

The RVA and RAA became the most common sites for permanent cardiac pacing because they are easily accessible and ensure stable pacing and sensing thresholds in the long term. However, during the course of pacing therapy, we have recognized that pacing from these sites may lead to adverse effects that are due mainly to the induction of electric and mechanical dyssynchrony. Various other anatomic sites that have been considered as possible alternatives for pacing are discussed below. However, it should be stressed that they do not represent established modalities and remain investigational.

**Alternative Atrial Pacing Sites**

The sites that have most commonly been studied and compared with the RAA are the high and low interatrial septum,
the Bachmann bundle region, the lateral free wall, and combinations of sites: dual-site right atrial (leads placed in the high right atrium and coronary sinus os) and biatrial (leads placed in the high right atrium and coronary sinus). The concept of pacing from alternating sites is to reduce the total atrial activation time and to improve atrial hemodynamics—and consequently the incidence of paroxysmal and the progression to permanent AF—in patients with a bradycardia indication for pacing and a history of AF.

Although several small studies have indicated that dual-site right atrial pacing and biatrial pacing have an atrial antifibrillatory effect, multicenter, randomized trials failed to show benefit in the long term. Among the alternative single atrial sites, the Bachmann bundle and the low interatrial septum, the most commonly studied sites, have proved feasible and safe, whereas during an intermediate period of follow-up, they seem to prevent AF by reducing interatrial and intra-atrial conduction time. In a randomized study involving 120 patients, Bachmann bundle pacing compared with RAA pacing proved effective in attenuating the progression of AF: Patients with Bachmann bundle pacing had a higher (P<0.05) rate of survival free from chronic AF (75%) at 1 year compared with patients with RAA pacing (47%). In another recently published randomized, controlled study that included 102 patients followed up for 2 years, it was found that, in patients with sinus node disease and intra-atrial conduction delay, low interatrial septum pacing was superior to RAA pacing in preventing progression to persistent or permanent AF. Furthermore, low interatrial septum pacing has been found to significantly improve global and regional atrial mechanical function and to synchronize interatrial electromechanical contraction compared with RAA pacing in patients with sinus node disease and paroxysmal AF. Other studies, however, failed to show any antiarrhythmic effect as a result of pacing from alternative sites. Therefore, results from large, randomized, controlled trials are essential before RAA pacing can be abandoned in favor of alternative atrial pacing sites.

Alternative Ventricular Pacing Sites

It has become clear that RVA pacing leads to ventricular electric and mechanical dyssynchrony and is related to a spectrum of detrimental effects. There have been reports of myocardial perfusion and innervation disturbances, molecular and cellular changes, LV remodeling, and systolic and diastolic dysfunction. Finally, in the long term, RVA pacing is associated with an increased risk of heart failure and AF: Alternative right ventricular pacing sites that have been evaluated in an attempt to attenuate these deleterious effects are the right ventricular outflow tract, interventricular septum, para-hisian regions, and direct His bundle pacing. Although some observational and small randomized studies have shown conflicting results, a systematic review and meta-analysis of 14 randomized, controlled trials found that patients randomized to non-RVA pacing had a greater ejection fraction (4.27%; 95% CI, 1.15–7.40) at the end of the follow-up. However, the benefit was confined to patients with an ejection fraction <45%, whereas there was no significant difference in patients who had preserved systolic LV function. Furthermore, the results were inconclusive in terms of harder end points such as quality of life and survival.

It appears that simultaneous pacing from the right ventricle and LV is clearly superior to pacing from right ventricular sites in preventing the detrimental effects of RVA pacing. Biventricular pacing is an established therapy in patients with heart failure, a wide QRS complex, and severely reduced systolic LV function—even those who do not have a bradycardic indication for pacing—to reduce the progression of the disease, morbidity, and mortality. Patients with similar pathology but with a conventional indication for cardiac pacing seem to derive the same benefit from cardiac resynchronization therapy, although this is less well established. Recently, evidence has emerged that biventricular pacing could be beneficial in patients with moderately reduced or even preserved LV function. In a study that used conductance catheters to assess LV mechanics after AV junction ablation for drug-refractory AF in patients with normal systolic LV function, it was found that LV or biventricular pacing was superior to RVA pacing in terms of contractile function and LV filling. In another randomized study that included 177 patients with an ejection fraction >45% followed up for a mean of 12 months, right ventricular pacing resulted in LV remodeling and a reduced ejection fraction, whereas biventricular pacing prevented these adverse effects. Finally, new horizons for the use of biventricular pacing in patients with AV block, but without an established indication for cardiac resynchronization therapy, have been revealed by the recently presented results of the Biventricular Versus Right Ventricular Pacing in Heart Failure Patients With Atrioventricular Block (Block-HF) trial. This multicenter, prospective, randomized, double-blind trial included 691 candidates for cardiac pacing because of AV block with an ejection fraction ≤50% and mild to moderate heart failure who were randomized to receive either right ventricular or biventricular pacing. Over a mean 36-month follow-up, the biventricular group showed a significant 26% reduction in the primary combined end point of all-cause mortality, heart-failure–related urgent care, and an increase in LV end-systolic volume index. Furthermore, there was a 27% reduction in the relative risk for the composite end point of heart-failure–related urgent care and all-cause mortality.

Pacemaker Diagnostics

The ability of contemporary pacemakers to record and store cardiac electrograms offers paced patients the opportunity for very long-term monitoring of their cardiac rhythm. This is extremely useful for these patients who are known to be at increased risk of developing atrial tachyarrhythmias (AT) or AF (Figure). Asymptomatic AF is common but leads to an increase in the risk of stroke and systemic thromboembolism, just like symptomatic AF. Studies in patients with implanted devices have shown that high-rate episodes detected in patients with sinus node disease doubled the risk of death or stroke, whereas the risk of developing AF was 6 times higher than in those without high-rate episodes. Furthermore, the thromboembolic risk was a quantitative function of the AT/AF burden because an AT/AF burden ≥5.5 hours on any of the 30 prior days appeared to double the thromboembolic risk. The recently published Asymptomatic Atrial Fibrillation and Stroke
Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT) shed more light on the relation between asymptomatic ATs and the risk of stroke and thromboembolic events. This trial enrolled 2580 patients ≥65 years of age with hypertension and no history of AF in whom a pacemaker or defibrillator had recently been implanted. The patients were monitored for 3 months to detect subclinical ATs (episodes of atrial rate >190 bpm for >6 minutes) and followed up for a mean of 2.5 years for the primary outcome of ischemic stroke or systemic embolism. By 3 months, subclinical ATs detected by implanted devices had occurred in 261 patients (10.1%). Subclinical ATs were associated with an increased risk of clinical AF (hazard ratio, 5.56; 95% CI, 3.78–8.1; P<0.001) and of ischemic stroke or systemic embolism (hazard ratio, 2.49; 95% CI, 1.28–4.85; P=0.007). Subclinical ATs remained predictive of the primary outcome after adjustment for predictors of stroke (hazard ratio, 2.50; 95% CI, 1.28–4.89; P=0.008). In another study, newly detected AT/AF episodes (AT/AF >5 minutes on any day) were analyzed in patients with stroke risk factors but without previous stroke or clinical AF who had implantable cardiac rhythm devices. Of 1368 patients enrolled, newly detected AT/AF episodes were identified in 416 (30%) during a follow-up of 1.1±0.7 years. These episodes occurred sporadically, highlighting the difficulty in detecting paroxysmal AT/AF with short-term monitoring. The findings of the ASSERT trial are supported by the results of the Registry of Atrial Tachycardia and Atrial Fibrillation Episodes in the Cardiac Rhythm Management Device Population (RATE), presented during the American Heart Association 2012 Scientific Sessions. In this study, in which 5379 patients were enrolled and followed up for an average of 2 years, it was shown that long episodes of AT or AF are linked to a higher risk of adverse events (including hospitalization for AF, heart failure, ventricular tachycardia, stroke or transient ischemic attack, syncope, or in-hospital cardiac death) in patients with cardiac rhythm management devices. In contrast, patients with only short episodes of AT/AF are at about the same risk for adverse events as otherwise similar patients who never experience an episode of AT/AF. From these findings, it would seem wise for future trials to evaluate whether antithrombotic therapy has any protective role in such patients with silent supraventricular arrhythmias detected by implantable devices and whether devices capable for long-term rhythm monitoring should be used for the primary prevention of stroke in high-risk patients before the development of clinical arrhythmia.

Conclusions
Cardiac pacing is an effective treatment for patients with symptomatic bradycardia, alleviating symptoms and improving quality of life and, in some cases, survival. On the basis of our experience so far, we have come to a better understanding of which patients must be paced and which mode of pacing offers the maximum benefit. Furthermore, new data are expected to clarify the optimal pacing sites for reducing iatrogenic adverse effects. Finally, the improved software of contemporary devices enables long-term cardiac rhythm monitoring, revealing arrhythmias whose appropriate management can be expected to offer pacemaker recipients an even better clinical outcome.

Disclosures
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