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The Year in Cardiology 2018: Arrhythmias and Cardiac Devices

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Introduction

As in the previous years (1), numerous relevant contributions on cardiac arrhythmias and devices were presented and published. For this traditional look back on the past year, the authors identified a selected group of studies, abstracts and articles with potential impact in daily practice.

Cardiac arrhythmias, AF and AF ablation

During 2018, a number of important trials have been presented or published that concern the important topic of atrial fibrillation (AF) and catheter ablation of AF.
After its presentation at ESC 2017, the long awaited CASTLE-AF study was finally published in 2018 (2). As previously discussed,1 CASTEL-AF randomized a total of 363 patients to AF ablation vs. conventional care (of the 3'013 screened patients). Only heart failure patients (LVEF ≤35%, all with an ICD or CRT) with both paroxysmal and persistent AF were included The primary composite endpoint of all-cause death or worsening heart failure was reduced by 38% in the ablation compared to the conventional group (HR: 0.62, 95% CI: 0.43–0.87; P=0.007). Both components of the primary endpoint were significantly reduced by AF ablation, i.e. worsening heart failure (HR: 0.56 (95% CI: 0.37–0.83); P=0.004) as well as all-cause mortality (HR: 0.53 (95% CI: 0.32–0.86); P=0.011). LVEF improved by 7% after 12 months in the ablation-group compared to the conventional treatment group, and ablated patients were twice as likely to be free from AF as individuals in the conventional group over the 5 year duration of the trial. On the downside, 1.7% pericardial effusion were observed in the ablation group (2).
The most anticipated presentation this year was the presentation of the results of the CABANA trial at the Heart Rhythm Society Meeting in May 2018 (3). While the manuscript has not been published as of the time this article was written, most of the results are available. The CABANA trial was a prospective randomized clinical trial that compared the outcomes of catheter ablation versus medical therapy in 2204 patients >65 years of age or less than 65 years of age with one or more stroke risk factor. The primary endpoint was a composite endpoint of death, disabling stroke, serious bleeding, or cardiac arrest. The mean patient age was 67.5 yrs, 43% had paroxysmal AF, 47% had persistent AF and 10% had long standing persistent AF. In the pre-specified intention to treat analysis the primary outcome did not differ in the two groups (8% for ablation versus 9.2% for drugs, P=NS). Secondary endpoints included all-cause mortality, which also did not differ (5.2 vs. 6.1% respectively, P=NS) and the composite of death or CV hospitalization which favored ablation (51.7% vs. 58.1%, P=0.001). Ablation was associated with a 47% reduction in AF with 60% of patients in the

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ablation arm free of AF. The major complication rate of catheter ablation was 9% as compared with 4% in the drug arm. At the end of the day this was a negative trial. However, intention to treat analysis was influenced by high rate of cross overs (27.5% of subjects in medical therapy arm actually underwent catheter ablation and 9.2% of patients in ablation arm did not have catheter ablation). In any case, the results do not negate the clinical value of AF ablation. The 2017 AF Ablation Consensus Document as well as the ESC and ACC AF Guidelines make it clear that the primary indication for AF ablation is for improvement of quality of life (4–6). The results of CASTLE-AF and CABANA support these guideline recommendations, but no not fully defense the concept that catheter ablation of AF lowers the composite of death, disabling strike, serious bleeding, or cardiac arrest. However, while waiting for the results of the pending final outcome study (EAST), evidence is accumulating which indicates that AF may in fact play a much more causal role rather than that of a "nuisance bystander" in the pathophysiology of cardiovascular diseases and, as a result, AF ablation may possibly serve more than just symptomatic relief (1).

Another study to be aware of examined temporal trends in AF recurrence after ablation between 2005 and 2014, based on the nationwide Danish cohort study (7). Five thousand four hundred twenty five patients undergoing a first time AF ablation were included The rates of AF recurrence at one year post ablation fell from 45% in 2005–2006 to 31% in 2013–2014. Factors associated with a higher recurrence rate of AF included AF duration > 2 years, female gender, hypertension, and cardioversion within one year of ablation. These findings are not surprising, they are important as they provide a "real world" look at the efficacy of AF ablation and how it continues to improve over time.

The POWDER AF Trial (8) was a prospective randomized clinical trial that examined the clinical value of continuing or stopping antiarrhythmic drug therapy three months post AF ablation. AF recurrence post the 3 month blanking period occurred markedly less frequently when antiarrhythmic drugs were continue (2/74, 2.7%) vs those patients in which antiarrhythmic drug therapy was stopped at 3 months (16/73, 16.9%). These data support the view that etiopathogenesis of AF is complex and catheter ablation itself may not control all the mechanisms.

And the final trial to draw your attention to is the Race 3 Trial (9). This trial randomized patients with early persistent AF and mild to moderate heart failure to targeted therapy of underlying conditions or conventional therapy. Both groups received rhythm control therapy. In the intervention group additional therapies that were started included mineralocorticoid receptor antagonists, statins, ACE inhibitors, and cardiac rehabilitation including physical activity, dietary restrictions, and counseling. The primary endpoint was sinus rhythm on a 7 day Holter monitor at one year. At one year sinus rhythm was present in 89 (75%) of the intervention group versus 79 (63%) in the conventional group (P=0.042). This study is important as it calls attention to the chorus of voices and data worldwide emphasizing the importance of risk factor modification in patients with AF.

Anticoagulation in AF – Stroke prevention and beyond

At the European Society of Cardiology Meeting 2009 in Barcelona, the first trial investigating a modern Novel Oral Anticoagulant (NOAC) in AF was presented (10). What followed was a paradigm shift in the prevention of stroke in AF with similar (if not better) efficacy as well as safety (particularly regarding the most feared complication of intracranial hemorrhage). In order to answer questions arising during daily clinical practice the European Heart Rhythm Association (EHRA) "Practical Guide" was realized by Hein Heidbüchel and co-workers in 2013 (11), followed by an update in 2015 (12). A fully reworked and expanded version of the EHRA practical guide was presented and published in March 2018 was initiated and ultimately published in March 2018 (13).

Some good examples of situations without evidence in the beginning which were essentially solved over the years were those of perioperative management of NOACs around cardioversion, cardiac device implantations as well as AF ablation. For cardioversion, latest evidence from the EMANATE trial indicates that also with apixaban, the risk of stroke and systemic embolism is very low (0/753 patients, vs. 6/747 with heparin/VKA) with equally very low risk of major bleeding events (14). Those findings are much in line with the X-Vert and Ensure-AF study using rivaroxaban (15) and edoxaban (16), respectively, as well as with findings from the Re-LY trial using dabigatran (17). Taken together, these findings indicate that cardioversion can safely be performed with NOACs provided the necessary prerequisites are met (comparable to those with VKA) (13).

For AF ablation, uninterrupted (or only a brief interruption) had been demonstrated to be the therapy of choice for dabigatran (18) and rivaroxaban (19), which was this year supplemented by the AXAFA study with apixaban *(Fig. 1)* (20). Indeed, also for apixaban, uninterrupted NOAC therapy resulted in a low number of ischemic and bleeding events in 674 patients receiving either continuous apixaban or warfarin (composite of death, stroke, or BARC 2-5 bleeding: 6.9% vs. 7.3%). A substudy of 335 subjects examined the impact of these two anticoagulation strategies on asymptomatic cerebral emboli detected by MRI. There was no difference in the primary outcome, being observed in 22 of 318 patients randomized to apixaban versus 23/315 randomized to VKA. There were two strokes or TIAs in the trial,

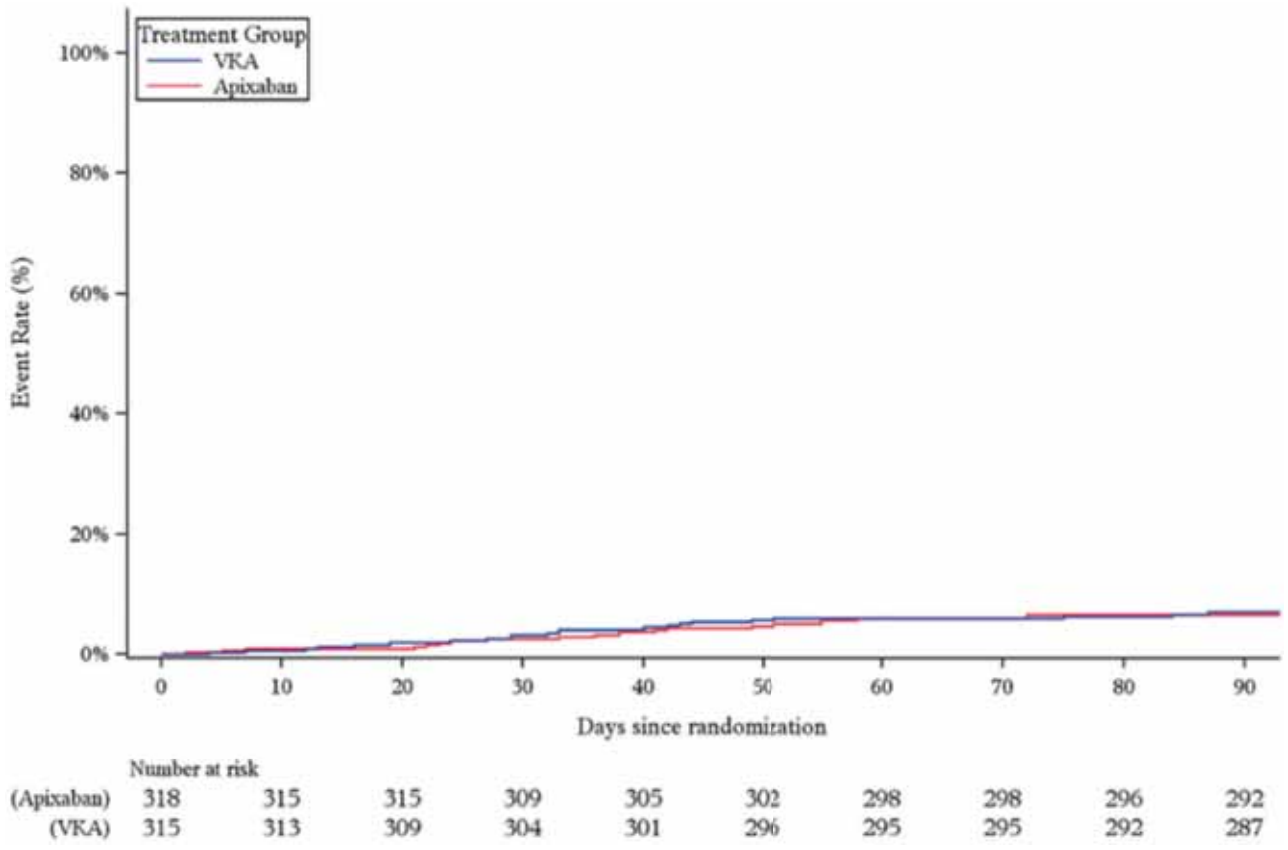

FIGURE 1. Main outcome of the AXAFA trial (20). Cumulative primary outcome since randomiza-tion until 90 days after randomization. VKA, vitamin K antagonist therapy. Reproduced from (20)

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both in the apixaban arm. Major bleeding was observed in 3.1% of patients receiving apixaban versus 4.4% on VKA therapy (P=NS). The incidence of asymptomatic cerebral emboli lesions also did not differ based on the anticoagulation strategy. This study further supports the safety and efficacy of performing AF ablation on uninterrupted NOAC therapy.

In the BRUISE CONTROL-2 study, both uninterrupted (median time from last intake to operation=12 hours) as well as interrupted (median time from last intake to operation=72 hours) NOAC therapy resulted in a low number of bleeding and even fewer ischemic events, indicating that either strategy may be employed in peri-operative management of these patients 821).

Another notable study examined the relationship between dementia and oral anticoagulation in patients with AF. This was a retrospective study based on the large Swedish National Registry (22). The study included 444 106 patients with a hospital diagnosis of AF and no prior history of dementia. During over 1.5 million years of follow-up, patients on anticoagulant therapy at baseline had a 29% lower risk of dementia than patients without anticoagulation treatment. While this study is by no means definitive, it does support the hypothesis that anticoagulation of AF patients reduces risk of dementia. NOACs have revolutionized the management of stroke prevention in AF, based on the randomized clinical trials and “real world” evidence. When interpreting the wealth of information stemming from the latter it is important to keep in mind which type of data sources should be used to answer which type of research questions – and where to be careful due (23). Has the update of NOAC translated into measurable effects? In English national databases, the number of patients with known AF increased linearly from 692 054 to 983 254 (prevalence 1.29% vs. 1.71%) from 2006–2016. At the same time, hospital episodes of AF-related stroke/100 000 AF patients increased from 80/week in 2006 to 98/week in 2011 and declined to 86/week in 2016 (2006–2011 difference 18.0, 95% confidence interval (CI) 17.9–18.1, 2011–2016 difference −12.0, 95% CI: −12.1 to −11.9). In parallel, anticoagulant use in at-risk patients (CHA_2DS_2-VASc ≥2) increased from 48.0% to 78.6% and anti-platelet use declined from 42.9% to 16.1%, especially in the period from 2011–2016. These data indicate that the introduction of the NOACs, its inclusion in official

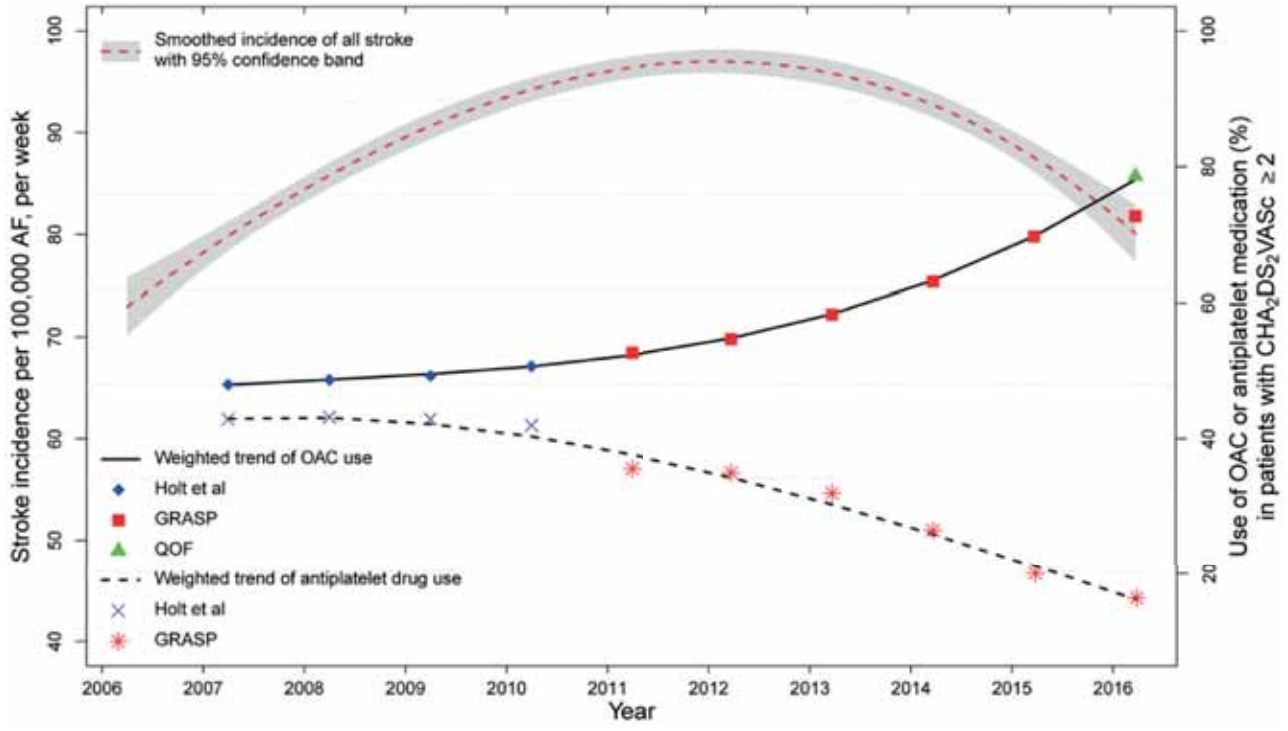

FIGURE 2. Atrial fibrillation-related stroke in England and its association with uptake of oral antico-agulation (24). Temporal trend in finished consultant episodes of atrial fibrillation-related stroke per 100'000 patients with atrial fibrillation and uptake of oral anticoagulants and anti-platelet drugs for pa-tients with atrial fibrillation and a CHA_2DS_2-VASc score ≥2 (24). The anticoagulant timeline is a weighted trend derived from Holt et al., GRASP AF, and Quality and Outcomes Framework (24). Reproduced from (24)

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guidelines (5), and the substantial increase in teaching activities and awareness were indeed paralleled by a reduction in hard clinical endpoints *(Figure 2)* (24). Conversely, the authors predict that if the use of anticoagulants had remained stable at the levels of 2009, 4068 (95% CI: 4046–4089) more strokes would have occurred in 2015/2016. A great example of a successful joint effort "to reduce the burden of cardiovascular disease" – the official ESC mission.

How can we increase adherence to NOACs even more? Telemonitoring-based feedback may be the answer, according to an innovative Belgian pilot study in 48 patients (25). Whether this also holds true in larger sample sizes as well as the question of cost-effectiveness in a larger scale setting remains to be proven.

Prevention of sudden cardiac death

Since the two landmark studies (DINAMITE and IRIS) demonstrated no reduction of mortality with ICD within first 40 days after acute MI, a strategy of bridging this time period with wearable cardioverter defibrillator (WCD) has been introduced. To evaluate the efficacy of this approach, the large, randomized VEST (Vest Prevention of Early Sudden Death Trial) trial screened 13,774 patients between 2008 to 2017, of whom 2302 with acute MI and left ventricular ejection fraction (LVEF) ≤35% were 2:1 randomized within 7 days of hospital discharge to open-label WCD or usual care (26). During a median follow-up of 84 days, 1.6% of the WCD group and 2.4% of the control group experienced the primary end point of sudden cardiac death or death from ventricular arrhythmia (HR: 0.67; 0.37 – 1.21; P= 0.18). Of 1,524 patients in the WCD arm, 20 patients (1.3%) received an appropriate shock, of which 14 survived to 90 days. Nine patients experienced an inappropriate shock, and 70 patients had aborted shocks. Surprisingly, all-cause death occurred more frequently in the control arm (4.9%, mainly due non-sudden death) as compared to 3.1% in treatment arm (P=0.04). The overall mortality difference of 36% was announced as a positive trial documenting significant benefit of WCD. However, since the trial did not meet its primary end-point, the results – overall – did not demonstrate a clinically meaningful reduction of

arrhythmic mortality, and in the light of significant cost of the technology, it remains questionable in whom the use of a WCD early after myocardial infarction is justified.

Recent studies suggested that complex evaluation of apparently unexplained cardiac arrests has a substantial potential to unmask specific etiology (27). A large ongoing prospective registry of sudden cardiac arrest in the Paris area was used to describe characteristics of patients with a diagnosis of idiopathic ventricular fibrillation and evaluate the completeness of investigations in this population. Investigations performed during the index hospitalization or planned after hospital discharge were recorded to evaluate the completeness of assessment of unexplained cardiac arrest. Out of 18,622 cases of out-of-hospital cardiac arrests in a period from 2011 to 2016, 717 survivors at hospital discharge fulfilled the definition of sudden cardiac arrest. Among them, 88 (12.3%) remained unexplained after initial investigation using ECG, echocardiography and coronary angiography. Magnetic resonance imaging and other investigations yielded the diagnosis in additional 39 patients (5.9%). Genetic testing and family screening, recommended in ESC guidelines, were initiated in only 9 (18.4%) and 12 (24.5%) cases, respectively. These findings emphasize the importance of referring victims of cardiac arrest to expert centers offering a comprehensive assessment – something still substantially underused in many clinical scenarios and areas today, and clearly a call for action.

Ventricular tachycardia ablation

Catheter ablation has become current state-of-the-art strategy for management of VT resistant to antiarrhythmic drugs. With the advent of electro-anatomical mapping, various strategies of substrate mapping have been developed with different procedural endpoints and outcomes. The recent meta-analysis included 6 studies for the comparison of standard ablation of stable VT vs. substrate modification, with a total of 396 patients (mean age 63±10 years, 87% males) (28). In addition, 7 studies were selected to assess the impact of complete vs. incomplete substrate modification, with a total of 391 patients (mean age 64±years, 90% males). The results suggested that substrate modification is associated with decreased composite VA recurrence/all-cause mortality compared to standard ablation of stable VTs [risk ratio (RR) 0.57, 95% confidence interval (CI) 0.40–0.81]. Complete substrate modification was associated with decreased VA recurrence as compared to incomplete substrate modification (RR: 0.39, 95% CI: 0.27–0.58). Needless to say that different strategies of substrate modification may be combined together to provide even better benefit.

Another question is about the role of percutaneous support for VT ablation. Recently, multicenter observational, real world data from experienced centers, comparing 105 pts on hemodynamic support with 1,650 VT ablations without the support, were published (29). As expected, subjects with mechanical support were sicker, had lower LVEF and more co-morbidities. Their outcome (procedural success, complications, in hospital mortality or 12 mortality) was worse than in patients ablated without the support. When matched cohort of patients with LVEF <20% and NYHA functional class III and IV was analyzed, there was no significant difference in clinical outcomes when compared with no hemodynamic support. These results do not support the widespread use of percutaneous mechanical support in such sick population. Current substrate-based ablation strategies allow substantial modification of a substrate even without a need for induction of VT or without general anesthesia, the strategy predominantly used in Europe.

Despite improving results of catheter ablation for VT, critical parts of the arrhythmia substrate may not be accessible. A fascinating alternative has been suggested recently – noninvasive radiation of arrhythmogenic substrate (30). Radiosurgery was applied in 5 subjects who had either at least one traditional invasive ablation procedure that failed or a contraindication to ablation procedures. All underwent a combined anatomical imaging study and non-invasive body surface mapping. VT was inducible in four to identify more precisely VT exit points. This information together with data from previous electroanatomic mapping was used for location of the target volume for radiotherapy. Over 46 patient-months following a blanking period of 6 weeks, a marked reduction in total VT burden was noted from the baseline in all subjects (99.9%). In addition to these dramatic reductions in VT, the short-term safety profile was encouraging. More data in this respect have been provided by very recent publication of the ENCORE-VT trial from the same author group (31). This was a prospective, phase I/II trial of noninvasive cardiac radioablation in adults with treatment-refractory episodes of VT or cardiomyopathy related to premature ventricular contractions. Nineteen patients were enrolled (17 for VT) and body-surface mapping was used to identify the target for ablation. Radioablation was associated with markedly reduced ventricular arrhythmia burden (median number of VT episodes reduced from 119 to 3; P<0.001) with modest short-term risks (2 patients developed a treatment-related serious adverse event - heart failure exacerbation and pericarditis). It allowed reduction in antiarrhythmic drug use and improvement in quality of life. Taken together, this strategy opens new therapeutic horizons for high-risk patients or those with inaccessible myocardial substrate. Obviously the safety and efficacy have to be carefully evaluated in further studies.

Implantable Cardiac electronic devices – His Bundle, Multipoint Pacing and other

The quest for optimal pacing methodology continues; both regarding standard bradycardia pacing as well as for cardiac resynchronization therapy (CRT). In a randomized phase 1 study – More Response on Cardiac Resynchronization Therapy with MultiPoint Pacing (MORE-CRT MPP) – presented at the EHRA meeting 2018 in Barcelona, 1921 patients were prospectively enrolled and followed for 6 months. Patients with a reduction in LVESV <15% were then randomized to MPP vs. traditional biventricular pacing. While there was no difference in conversion from non-response to responder status between the two groups (31.8% with MPP vs. 33.8% in the conventional biventricular arm, P=0.65), the responder rate was much greater in those patients with optimal MPP programming. Additional studies are required to further delineate the usefulness of MPP to reduce non-responder rates. On another note, this study once more emphasizes the importance of adequate expert device programming – an aspect frequently overlooked in daily clinical practice, but which nonetheless should represent a core expertise of every cardiologist taking care of these patients.

Is His Bundle pacing the solution? Some single center non-randomized studies surfacing over the year of 2018 indicate that this may be the case. But, like last year, we have to conclude that until results from adequately powered randomized clinical trials are available these studies have to be viewed with caution. Particularly for cardiac pacing/resynchronization therapy, experience has taught us that such data have to be viewed as “hypothesis generating” until a randomized clinical trial can show a clear benefit (32, 33). Several such studies are underway, and hopes are high that His bundle pacing may turn out to be an important weapon in our armamentarium.

Another question is about the role of AV nodal ablation with implantation of CRT device for rate control of AF in elderly population. The results of the multicenter randomized APAF-CRT trial further support for this strategy (34). The study population consisted of 109 subjects with symptomatic permanent AF, narrow QRS ≤110 ms and at least one hospitalization for heart failure in previous year. Finally, 50 patients were analyzed in intention to treat analysis in AV junction ablation arm and 52 in drug treatment arm. Besides significant improvement in symptoms, the study showed significant 62% reduction in primary endpoint (death or hospitalization due heart failure or worsening of heart failure) in favor of AV junction ablation with implantation of CRT device (0<0.01). The difference between treatment arms was even more pronounced in patients with LVEF ≤35% (82% reduction of primary endpoint, p<0.005).

Conflict of Interest Statements

Josef Kautzner: Dr Kautzner reports personal fees from Bayer, Biosense Webster, Boehringer Ingelheim, Boston Scientific, EPIX, Medtronic, Merck Sharp & Dohme, Liva Nova (MicroPort CRM) and St. Jude Medical (Abbott) for participation in scientific advisory boards. He has received speaker honoraria from Bayer, Biosense Webster, Biotronik, Boehringer Ingelheim, Boston Scientific, Daiichi Sankyo, Medtronic, Merck Sharp & Dohme, Mylan, Pfizer, ProMed sro, and St. Jude Medical (Abbott)

Hugh Calkins: Dr. Calkins reports consultancy to Medtronic, Abbott, and Biosense Webster; honoraria from Boehringer Ingelheim, Biosense Webster, and Medtronic; and research support from Boston Scientific.

Jan Steffel: Dr. Steffel has received consultant and / or speaker fees from Abbott, Amgen, Astra-Zeneca, Atricure, Bayer, Biosense Webster, Biotronik, Boehringer-Ingelheim, Boston Scien-tific, Bristol-Myers Squibb, Daiichi Sankyo, Medscape, Medtronic, Merck/MSD, Novartis, Pfizer, Sanofi-Aventis, WebMD, and Zoll. He reports ownership of CorXL. *Dr. Steffel* has received grant support through his institution from Abbott, Bayer Healthcare, Biosense Webster, Biotronik, Boston Scientific, Daiichi Sankyo, and Medtronic.

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