The Year in Cardiology 2016: arrhythmias and cardiac implantable electronic devices

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Preamble
The year 2016 was characterized by numerous relevant contributions in cardiac arrhythmias. A selected group of articles providing information with potential impact in daily practice has been identified by the authors and is reported in the present article.

Cardiac arrhythmias and catheter ablation

Supraventricular tachycardia: diagnosis and treatment

Supraventricular tachycardia (SVT) continues to be a frequent cause of emergency hospital admission. The REVERT study evaluated the best and most efficient acute treatment strategy for SVT and compared postural modification (leg elevation and supine positioning applied for 15 sec at the end of 15 sec) with standardized strain Valsalva maneuver (i.e. pressure of 40 mm Hg sustained for 15 s by forced expiration measured by aneroid manometer with the target pressure visible to the treating team) (1). The modified treatment was found to terminate SVTs in a significantly larger proportion of patients (43% of 214) than using conventional maneuvers (17% of 214; P<0.0001). As a consequence, significantly less patients in the study arm required adenosine (50% vs. 69%) or emergency anti-arrhythmic treatment (57% vs. 80%) to terminate the incident arrhythmia (1) and no differences in time to discharge from hospital. This finding may considerably affect daily practice and reduce drug-related patient discomfort at time of emergency treatment in patients with SVT. The full scope of up-to-date diagnosis and treatment of SVTs can be reviewed best in 2016 EHRA/ESC consensus document on SVT management (Katritsis et al., EHJ 2016 in press).

Atrial fibrillation: pathophysiology, risks, treatment opportunities, and the new ESC AF guidelines

The intense scientific discussion about the pathophysiology of atrial fibrillation and particularly the drivers for AF progression was enriched and stimulated by a very interesting experimental and clinical study on atrial remodeling (2). It was shown that atrial adipose tissue, which has been previously identified as a strong risk factor for AF development, is progressively replaced by fibrotic tissue that serves as the substrate for AF progression (2). These data may further explain the link between obesity and AF recently described in clinical studies (3). However, those studies also showed a significant reduction of AF burden with weight loss and it is now of particular interest whether or not the reduction in AF burden may coincide with reversed structural remodelling and vice versa (Figure 1). MRI-based fibrosis detection and quantification holds some promise to document the substrate changes over time and may give further insights into this important aspect of AF pathology in the future (Figure 2) (4). However, various methodological hurdles need to yet be overcome, mainly due to the thin wall of the atria, and appropriate protocols are indispensable. Rate control is the most frequent treatment options chosen for and by AF patients world-wide. Data about the best medication to support rate control therapy by symptom relief and reducing
AF-related risks are limited and somewhat controversial (5). A recent nationwide study from Taiwan investigated the long-term effects of beta-blockers, calcium-channel blockers or digitalis given for the rate control in ongoing atrial fibrillation on mortality (6). After adjustment for baseline differences, the risk of mortality was found to be significantly lower in the 43 879 patients receiving beta-blockers and in the 18 466 patients receiving calcium-channel blockers than in a control population of 168 678 patients not receiving any rate-control drug. On the contrary, patients receiving digoxin had a higher risk of mortality. Especially the effects observed for beta-blockers are interesting as a recent meta-analysis on rate control medications did not show such beneficial effects for beta-blockers (7). These findings contribute to the ongoing controversy about the impact of rate-control drugs on the risk of all-cause death in patients with ongoing AF and prompt for the need of future randomized trials to address this relevant question. Patients with aortic stenosis often also have pre-existing AF which may be “silent” or develop AF (so-called “new-onset AF”) early after surgical or transfemoral aortic valve replacement (TAVI). Indeed, when compared with patients in sinus rhythm, patients with AF undergoing surgical or TAVI interventions have been shown to be at higher risk for stroke and bleeding but also for having a higher total mortality (8). A recent clinical update on this topic pointed out that the incidence of new-onset AF may be lower with TAVI as compared with surgical valve replacement (8). However, the optimal treatment strategy of such patients with respect to rhythm or rate control is still unclear. Particularly the role of amiodarone both for the peri-procedural prevention of AF and for classical rhythm control as well as the role of catheter ablation as a rhythm control strategy needs further evaluation in clinical studies and trials. Another field of controversy relates to the optimal anticoagulation regimen especially for TAVI patients: are AF patients after TAVI eligible for NOAC therapy or are vitamin K antagonists the better choice? While there are good arguments in favour of NOACs after TAVI convincing data from specific and large clinical trials are still lacking to answer this important question (9). Catheter ablation of paroxysmal AF: burn it down or freeze it? The comparative effect of catheter-based point-by-point radiofrequency ablation and balloon-based cryo-ablation for the treatment of paroxysmal AF was unknown and had been intensely debate over years.
We now know that both ablation techniques result in the same rhythm outcome and have similar complication rates (10). In the FIRE AND ICE international, multicentre, clinical trial 762 patients with paroxysmal AF were randomly assigned to undergo pulmonary vein isolation with RF-ablation or cryo energy. During 1.5 years of follow-up, no differences were found between the two groups in the incidence of post-ablation clinical failure (i.e. recurrence of AF, occurrence of atrial flutter or atrial tachycardia, use of anti-arrhythmic drugs, or repeat ablation): 34.6% in the cryo-balloon arm and 35.9% in the RF arm. The two techniques also proved similarly safe, with an aggregate incidence of death, cerebrovascular events, or serious treatment-related adverse events of 10.2% and 12.8%, respectively (P=ns). This relatively high incidence of side effects is in line with previous data of prospectively investigated populations. Quality-of-life assessment post-ablation did not differ between the two study arms. In a subsequent study, the same authors reported a lower incidence of repeat ablations, direct-current cardioversions, and all-cause rehospitalization during follow-up in the cryo-balloon study arm (11). Similarly, a non-inferiority of cryo-balloon-assisted vs. RF-assisted ablation was also documented in the Freeze AF study which randomized 315 patients with paroxysmal AF (12). The results of these two studies, which are characterized by a limited adoption in the RF arm of the most recently introduced technologies, will contribute to establish cryo-balloon-assisted ablation as a valuable alternative to RF-assisted ablation of paroxysmal AF. However, it still needs to be evaluated whether substrate-based ablation strategies in patients with paroxysmal AF and low-voltage areas may add benefits with respect to rhythm outcome after RF-based ablation techniques (13).

In patients with persistent AF, the efficacy of catheter-based PVI using RF current was comparatively assessed with that of PVI plus linear ablation and that of PVI plus complex fractionated atrial electrogram (CFAE) ablation in the STAR AF II study (14). In the 589 study patients randomly assigned to the three study arms according to a 1:4:4 randomization ratio, no differences were found in the proportion of patients who were free from recurrent AF after 18-month follow-up (59%, 49%, 46%). These results diverge with those reported in a recent meta-analysis (15) on limited series showing a 51% relative risk reduction in the incidence of recurrent AF in patients receiving linear ablation in addition to PVI when compared with patients receiving PVI only. The discrepancy of findings between these two studies highlights the value of performing randomized studies in order to validate findings from previous studies using less rigorous methodology. Establishing on a large scale the role of antiarrhythmic drugs short-term use after catheter ablation for atrial fibrillation trial, a total of 2038 patients were randomly assigned to antiarrhythmic drug therapy following radiofrequency catheter ablation for paroxysmal, persistent, or long-lasting AF.16 The risk of recurrent atrial tachyarrhythmias was reduced in the antiarrhythmic drug therapy group during the treatment period of 3 months, however without an effect on clinical outcomes at later time points. Does catheter ablation of AF have any effect on stroke rate and/or mortality? In a recent nationwide Swedish Patient Register identifying 361 913 patients, Friberg et
al. evaluated the possible influence of AF ablation on clinical outcome. Using propensity score matching, two cohorts of equal size (2836 patients each) were extracted of which one had received AF ablation and one not. The two cohorts presented similar characteristics in 51 dimensions. After adjustment for known confounders AF ablation was found to be associated with a significantly lower incidence of all-cause mortality (HR=0.50; 95% CI=0.37–0.62) and ischemic stroke (HR=0.69; 95% CI=0.51–0.93). Reduction in the risk of ischemic stroke by means of AF ablation was most pronounced in sub-groups with CHA2DS2VASc score≥2 (HR=0.39; 95% CI=0.19–0.78) and among patients without a new cardioversion beyond 6 months after ablation (HR=0.68; 95% CI=0.48–0.97). These results are encouraging and prompt for the implementation that adequately sized randomized studies may provide to this controversial topic in the next future. Until those trials have arrived and fully reported clinical practice should include continuing life-long anticoagulation after ablation in at risk patients according to the CHADS-VASc Score a point of view which is strongly supported by the 2016 ESC AF management guidelines (5).

The new AF guidelines strengthen a personalized, precision driven approach to patients with atrial fibrillation. Importantly, the role of new AF risk factors and the importance of life style changes for reduction of AF burden and potentially for reduction of AF related risks is intensely described. Moreover, the benefits resulting from integrated AF care, AF heart teams and patient engagement for shared decision-making are presented and specific action is recommended to deliver the best care for AF patients (5).

**Stroke prevention**

An interesting finding referred to as the “obesity paradox” was recently reported in a sub-analysis from the ARISTOTLE trial (18). Out of 17 913 patients enrolled in this study, 7159 were categorized as obese, 6702 overweight and 4052 normal. During 1.8 years follow-up, higher body masses were associated with a lower risk of all-cause mortality (overweight, HR=0.67; 95% CI=0.59–0.78; obese, HR=0.63; 95% CI=0.54–0.74). Such benefit extended to the risk of stroke in the female (P=0.048), but not in the male gender. No measure of adiposity was associated with a different risk of bleeding. Among possible explanations for this finding are an earlier more rigorous use of co-medications and life-style modification (19) and better metabolic reserve (20), which may ultimately affect intermediate-term prognosis in obese patients.

Another interesting finding was observed in a recent sub-analysis from the Engage AF-TIMI 48 trial (21). In this study, a higher degree of protection from all-cause mortality vs. vitamin K antagonist (VKA) therapy was found in the edoxaban 30 mg arm (HR=0.87; 95% CI=0.79–0.96, P=0.006) than in the edoxaban 60 mg arm (HR=0.92; 95% CI=0.83–1.01, P=0.08). This benefit occurred in spite of an evident increased risk of ischemic stroke (HR=1.41; 95% CI=1.19–1.67, P<0.001) at the lower edoxaban dose, which was not found at the higher dose (HR=1.00; 95% CI=0.83–1.19, P=0.97). The fewer total deaths observed with edoxaban were predominantly due to a significantly lower rate of fatal bleeding in the edoxaban groups and particularly in the low dose group. These findings raise our attention on the delicate balance between risk and benefit associated with administration or oral anticoagulants and shift the objective of their use from thromboembolic events to cardiovascular morbidity as a whole. In addition, further subgroup analyses were able to demonstrate a consistent net clinical efficacy and safety of edoxaban in other high risk subgroups such as the elderly22 and patients at increased risk of falls (23), hence establishing the drug as a valuable alternative in our armamentarium for stroke prevention in AF.

A recent randomized controlled study (Ensure AF) (24) showed that oral edoxaban 60 mg once daily presented similar efficacy and safety outcomes as VKAs when administered during the peri-procedural phase on cardioversion of atrial fibrillation. In the 30 days following cardioversion using either an early or delayed strategy, 1095 patients assigned to edoxaban presented a 0.5% incidence of aggregate stroke, myocardial infarction, peripheral embolism or cardiovascular death vs. a 1.0% observed in 1104 patients assigned to VKA therapy (OR 0.46; 95% CI=0.12–1.43). Similarly low incidences of peri-procedural major bleeding (0.3% and 0.5%) were observed in the two arms (OR 0.61; 95% CI=0.09–3.13). These results are similar to those recently reported by Cappato et al. in the X-VeRT trial investigating oral rivaroxaban vs. VKA therapy in the same clinical setting (25). Both trials were not numerous enough to test a non-inferiority hypothesis. However, the high reproducibility of primary efficacy and safety outcomes in the two studies make these NOACs a valuable alternative to VKAs in these patients.

After the authorization for market release of three of the four novel oral anti-coagulants (NOACs) previously investigated in large phase III trials, a number of post-authorization studies have been published providing real-life evidence for efficacy and safety of these new drugs. In a previous registry investigating the real-life efficacy and safety of rivaroxaban, Camm et al. had shown that during about 1-year follow-up, the incidences of major bleeding (2.1 per 100 patient-years) and stroke events (0.7 per 100 patient-years) were low and superimposable to those observed in Rocket AF (26, 27). Most recently, the results from three studies using claims database as data source were reported (28–0). In the REVISIT-US registry (28), a measure of net clinical benefit was inferred by the aggregate estimate of ischemic stroke and intracranial haemorrhage reported in the investigated populations. Real life treat-
Ventricular arrhythmias and sudden cardiac death

Catheter ablation of ventricular tachycardia (VT) is an important technique to manage patients with recurrent VT (Figure 3) (31). However, randomized clinical trials evaluating the potential benefits of catheter ablation as compared with antiarrhythmic drug therapy are scarce. The recently published VANISH trial randomized patients with drug refractory ventricular tachycardia in the setting of ischemic cardiomyopathy and defibrillator protection to VT catheter ablation with continuation of baseline antiarrhythmic medications vs. escalated antiarrhythmic drug therapy (32). In the latter group, amiodarone was initiated if another drug had been used previously. The dose of amiodarone was increased up to 300 mg/day and mexiletine was added thereafter, if clinically required. During 27-month follow-up, significantly more deaths, VT storm events or appropriate ICD shocks were reported in the 127 patients assigned to the escalated therapy arm than in the 132 patients assigned to the ablation arm (69% vs. 59%; HR=0.72; 95% CI=0.53–0.98). However, although such beneficial effects on VT recurrence could be observed in the ablation group there was no difference in overall survival indicating that additional factors such as progression of structural heart disease and progressive heart failure may also play an important role for the prognosis of these patients.

Recurrent ventricular tachycardia in patients with repaired tetralogy of Fallot is a significant risk factor for sudden cardiac death. Treatment with catheter ablation is difficult due to the complex anatomy after surgical repair. However, as recently shown detailed electroanatomical reconstruction and mapping of the conductio

properties in the operated areas effectively identifies critical conduction isthmus that promotes VT (33). In one of the largest patient series of Fallot patients with VT reported so far it could be shown that discrete ablation of the isthmus results in VT termination and rendered VT non-inducible in the majority of patients. In patients with effective ablation VT recurrence was very low proving the benefits of this approach.

In a recent study, Kudenchuck et al. compared parental amiodarone, lidocaine, and saline placebo, along with standard of care, in adults with out-of-hospital cardiac arrest, shock refractory ventricular fibrillation (VF) or pulseless VT after at least one shock (34). Of 3026 enrolled patients, 974 were assigned to amiodarone, 993 to lidocaine and 1059 to placebo. No differences in survival to hospital discharge (24%, 24% and 21%, respectively) or neurologic outcome were found among the three groups. Interestingly, active drug administration was associated with a higher survival rate among patients with by-stander witnessed cardiac arrest (P = 0.05) but not among those with unwitnessed cardiac arrest. These findings offer a serious argument against the administration of intravenous antiarrhythmic therapy.
drugs in unwitnessed out-of-hospital cardiac arrest victims, but leave the door open for their possible use in by-stander witnessed victims.

**Cardiac electronic devices**

**Implantable defibrillator therapy**

Who benefits from an ICD and who does not? The final jury is not out on this ever moving target. In a randomized study of 1116 patients with symptomatic systolic heart failure not caused by coronary artery disease (the DANISH trial), Kober et al. recently showed that implantable cardioverter defibrillator (ICD) therapy in addition to usual care did not confer a significant protection from all-cause mortality as compared with usual care only during long-term follow-up (68 months) (35). In this study, the 50% (highly significant) relative reduction of sudden death risk in patients assigned to an ICD was offset by a larger proportion of patients in this same group presenting with deaths caused by other cardiovascular causes and, above all, by non-cardiovascular death. All time-to-event curves tended to diverge in favour of the ICD population during the first 5 years of follow-up and then to converge. These results contribute significantly to the ongoing debate on the usefulness of ICD therapy for the primary prophylaxis of patients with non-ischemic cardiomyopathy (36, 37). The relatively old age at entry (64 years) and the long duration from time to diagnosis of heart failure to enrolment (19 years) make the investigated population of this study a highly selected one and one with a relatively low life-expectancy (ejection fraction at entry, 0.25). Indeed, a subgroup analysis focusing on patient age revealed a significant statistical interaction, with younger patients (<59 years old) deriving a benefit from ICD in terms of all-cause mortality which...
was not evident in the elderly patients. In addition, the variety of reported cardiomyopathies makes the investigated population rather heterogeneous. Further studies are needed to evaluate the protective efficacy of ICD therapy in patients in whom a non-ischemic dilated cardiomyopathy is diagnosed at a younger age and whose eligibility for primary prophylaxis is raised at a relatively short time interval from diagnosis of heart failure. Previous studies investigating such a population were not numerous enough to test a superiority hypothesis by the ICD system vs. pharmacological therapy only (38). In summary, the results of the DANISH trial are important, but in the end reinforce clinical practice which should ideally already be in place – i.e. to take into consideration competing risk and modes of death, particularly non-cardiovascular as well as pump failure, when deciding to opt for ICD implantation, especially in patients with non-ischemic heart disease. These results are in line with a recent large prospective, multicentre registry of patients with cardiac resynchronization therapy (CRT). In a total of 1705 consecutive patients implanted with either a CRT-P (535 patients) or CRT-D (1170 patients), the adjusted morality hazard ratio 1.54 in CRT-P vs. CRT-D (CI 1.07–2.21, P=0.0209) (39). However, 95% of the excess mortality in CRT-P recipients was due to an increase in non-sudden cardiac death, hence re-iterating the importance of an individualized ‘competing risk’ analysis prior to the right device for each patient.

In a recent report, Vehmemeijer et al. performed a comprehensive review and meta-analysis on the indications, efficacy and safety of ICD therapy in adults with congenital heart disease (40). Overall, 2162 patients (66% males) with a mean age of 37 years at implant were included from 24 studies. The devices were implanted for primary prevention in 53% of patients (95% CI=43.5–62.7%), with non-sustained VT representing the most frequent indication, followed by impaired LV function, inducible VT, syncope, and palpitations or presyncope. The most frequent substrate was tachyarrhythmias of Fallot, followed by transposition of great arteries, congenitally corrected transposition of great arteries, ventricular or atrial septal defects and others. During 3.6-year follow-up, 24% of patients received an appropriate and 22% an inappropriate ICD intervention, inclusive of shock and/or anti-tachycardia pacing. All-cause mortality occurred in 10% of patients. These data offer the rationale for a thoughtful decision process concerning the relatively high rate of complications and inappropriate ICD therapy in these patients.

Subcutaneous implantable cardioverter defibrillators
In a recent study, Friedman et al. evaluated the trends and in-hospital outcomes associated with early adoption of the S-ICD in USA (41). Out of 393 734 ICD implants reported to the National Cardiovascular Data Registry ICD Registry between September 2012 (US Food and Drug Administration S-ICD approval date) and March 2015, the investigators performed a 1:1:1 propensity-matched analysis of 5760 patients to compare in-hospital outcomes among patients with S-ICD with those of patients with single chamber (SC)-ICD and dual chamber (DC)-ICD. The proportion of patients receiving an S-ICD among all ICD patients during the investigated period was 0.9%. Compared with SC-ICD and DC-ICD, patients receiving an S-ICD were younger, more prevalently female, black, undergoing dialysis and survivors of cardiac arrest. Interestingly, many patients presented with a high number of co-morbidities. DFT testing resulted in a successful defibrillation in 99.7% of 2629 patients undergoing induction of ventricular arrhythmias at time of implant. In-hospital complication rates associated with an S-ICD were low (1.1%), similar to those associated with a SC-ICD (1.0%), and lower than those associated with a DC-ICD (1.2, P<0.001). These figures provide an initial perspective of the impact of S-ICD in daily practice and offer an encouraging view on their safety at implant.

Another, preliminary report on the use of a subcutaneous ICD in a limited population of young patients (mean age, 34 years) with congenital heart disease recently showed a 100% success rate of device implant, and a 100% conversion rate with ≤80J of induced arrhythmias (42). Randomized trials are required to confirm these results and evaluate the clinical impact of S-ICD during long-term follow-up (43). The still young technology of the S-ICD is at the same time evolving rapidly. A novel high pass filter (SmartPass, available for Gen 2 and Gen 2.5 of the EMBLEM S-ICD) was introduced this year designed to reduce the risk of T-wave oversensing in S-ICD patients (Theuns et al., presented at HRS 2016). Modelling of inappropriate shock episodes recorded in the large EFFORTLESS registry demonstrated a reduction in inappropriate shocks by 81% compared with the first generation S-ICD.

One of the (perceived) major limitations of current S-ICD systems is the lack of pacing capability, hence limiting its use in patients with known monomorphic VT or an indication for bradycardia pacing. This year it was demonstrated for the first time in an animal model that communication of an S-ICD with a leadless cardiac pacemaker is possible, resulting in adequate termination of a monomorphic VT as well as in normal VVI functionality of the leadless pacer.44 These data are highly encouraging on the way to a further improvement of the current S-ICD system.

Leadless pacemaker
Leadless pacing has taken centre stage in the field of bradycardia pacing for the last years, and important new data surfaced during the year 2016. The primary results of the Micra experience in 725 patients, published in print early in the year (45), demonstrated
favourable electrical values (threshold, sensing, impedance) in 292 of 297 patients with paired 6-month data. About 28 major complications occurred in 25 of 725 patients (4.0%), including 11 (1.9%) cardiac perforation or effusion and 1 death (0.1%). These positive results were reinforced by additional follow-up which were presented at Cardiostim, with an average follow-up duration of 7.7±3.9 months. There was no signal apparent with very few additional clinical events; most importantly, no macro dislodgement and no embolization occurred. With now over 2000 Micra pacemakers implanted, the latter is also mirrored in the ‘real world’ outside the clinical trial, hence reinforcing particularly the safety of the device.

Wearable cardioverter defibrillators

Several studies have documented the efficacy and safety of wearable cardioverter defibrillators (46–48). In a large German registry, 94 patients (1.6%) were treated by the WCD due to ventricular tachyarrhythmias, an incidence of 8.4 (95% confidence interval, 6.8–10.2) per 100 patient-years (German life Vest Circulation 2016). About 112 of the 120 (93%) shocked patients survived 24 h after treatment, whereas asystole was observed in two patients (0.03%) with one resulting death. Taking together the available data, a recent science advisory from the American Heart Association (49), suggested a list of conditions for which this therapy may be recommended, which is in great parts similar to the ESC guidelines for the prevention of sudden cardiac death (50). Among them are the following circumstances:

(i) as a bridging therapy in situations associated with risk of death in which ICDs have been shown to reduce sudden cardiac death but not overall mortality such as within 40 days of myocardial infarction;

(ii) when there is a clear indication for an implantable device accompanied by a transient contraindication or need for interruption in ICD care such as infection;

(iii) when there is concern about a heightened risk of sudden cardiac death that may resolve over time or with treatment of left ventricular dysfunction, e.g. in ischemic heart disease with recent revascularization, newly diagnosed non-ischemic dilated cardiomyopathy in a patient starting guideline-directed medical therapy, or secondary cardiomyopathy (tachycardia mediated and thyroid mediated) in which the underlying cause is potentially reversible;

(iv) as a bridge to more definitive therapy such as cardiac transplantation.

In light of the non-definitive nature of the studies conducted in this field, the authors recognize that their document provides a tentative framework to assist in decision-making of an increasingly used therapy for the protection from sudden cardiac death during a transient clinical phase, but further studies are required to support these recommendations.

Conflict of interest

R.C. has acted as a consultant to Abbott, Bayer, Biosense Webster, Boehringer Ingelheim, Boston Scientific, Daiichi Sankyo, ELA Sorin, Medtronic, Pfizer and St. Jude; participated in speakers’ bureaus for Abbot, BARD, Bayer, Biosense Webster, Boehringer Ingelheim, Boston Scientific, Medtronic, Sanofi and St. Jude; acted as a study investigator for Abbott, BARD, Bayer, Biosense Webster, Cameron Health, Medtronic, Pfizer and Sanofi; received grants from BARD, Biosense Webster, Boston Scientific, ELA Sorin, Medtronic, St. Jude; and holds equity and intellectual property rights in Cameron Health. G.H. Research grants from Biotronik, Boston Scientific and St. Jude Medical through the University Leipzig/Heart Center.

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