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The year in cardiology 2017: arrhythmias and cardiac devices

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Preamble

This traditional overview looks back at the year 2017, summarizing a selection of important and clinically relevant new developments in the fields of cardiac arrhythmias. From new data for the ablation of atrial fibrillation and ventricular tachycardias, over the most recent developments in anticoagulation, to the most recent advances in risk stratification and prevention of sudden cardiac death, we summarize the key findings of relevant studies and put them into perspective for the practicing cardiologist.

Introduction

Once more, numerous relevant contributions on cardiac arrhythmias and devices were presented and published in the year 2017. For the present manuscript the authors identified a selected group of articles with potential impact in daily practice for the readers.

Cardiac arrhythmias and catheter ablation

A great loss

In early January of 2017, one of the electrophysiology's greatest pioneers, *Mark E. Josephson*, passed away at the age of 72 (1). *Dr. Josephson (Figure 1*) had a marked influence on both electrophysiology itself, pioneering in various diagnostic and therapeutic interventions, as well as on countless physicians worldwide through his superb educational activities and personal mentorship. One of his last articles, published in print in April 2017, brings him back to the roots of electrophysiology: The first randomized comparison of drug treatment vs. ablation for atrioventricular nodal re-entrant tachycardia (AVNRT). Not surprisingly, AVNRT ablation (one of the most frequently performed ablations worldwide) turned out to be by far superior to antiarrhythmic drug therapy (2). Another important article in the list of innumerable landmark papers through which Mark left a lasting impression in the field of Cardiology. He will be missed.

Figure 1. Mark E. Josephson (1943–2017) (1)

Indeed, also in daily clinical practice, SVT ablation seems safe and effective, as shown in a prospective German Ablation Quality Registry (3). Success rate of AVNRT ablation was 98.9%; no doubt it needs to be considered standard therapy for this arrhythmia.

Diagnosis and implications of atrial **fibrillation – more than meets the eye**

What do we call atrial fibrillation (AF)? How long does an atrial arrhythmia at a high rate need to be present, detected by which type of device, until we refer to it as AF? It is astonishing how badly evidence is lacking to answer this arguably simple question. Modern implantable cardiac devices such as pacemakers, implantable cardioverter defibrillators (ICD), and cardiac resynchronization therapy devices (CRTs) are capable of detecting and storing any type of atrial high rate episodes from few seconds to days and weeks. But from which time point on do we refer to it as AF and, more importantly, when does stroke risk increase in these patients? Data from the ASSERT trial published this

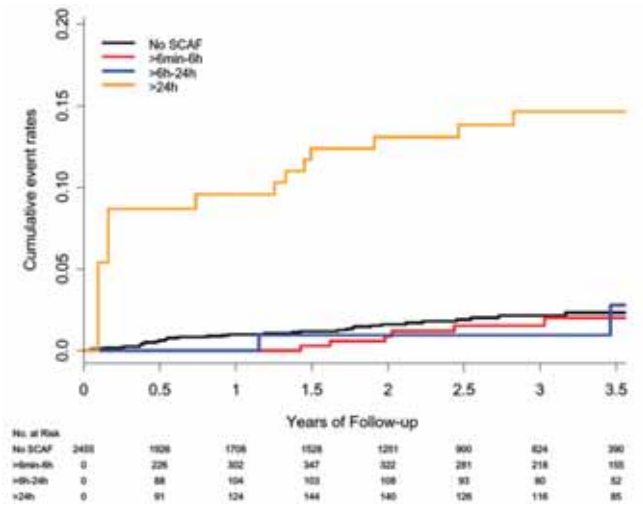

Figure 2. How much atrial fibrillation does it need? Data from ASSERT indicating the risk of stroke to be elevated in patients with device-detected atrial fibrillation >24 h, but not below (4). SCAF, subclinical atrial fibrillation

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year shed some new light on this topic, indicating that episodes longer, but not shorter than 24 h were associated with an increased risk of stroke *(Figure 2)* (4). The REVEAL-AF trial (presented at HRS 2017) investigated the prevalence of AF in 385 patients screened with an insertable loop recorder for a median of 22.5 months. The rate of AF detection was 6.2% at 30 days, increasing to 33.6% by 24 months, similar to the figures observed in the CRYSTAL-AF trial of patients post-cryptogenic stroke (5). Conversely, however, if both patients with and without previous stroke show a similar rate of such short episodes, these findings again raise the question of the importance of short duration "AF" as a predictor of stroke and, consequently, the need for anticoagulation. What to do hence with patients of shorter duration "AF"? Currently, the best answer in a device patient would be to enroll them in any of the ongoing studies investigating exactly this question – the ARTESiA or the NOAH trial (6, 7). These studies focus on device-detected subclinical atrial fibrillation (SCAF) of short duration and studies if a non-vitamin K antagonists oral anticoagulant (NOAC) (apixaban in ARTESiA, edoxaban in NOAH) will be superior in reducing stroke and thrombo-embolic risk compared to control therapy. Until the results of these studies are available, initiation of anticoagulation remains without strong evidence base in such patients.

In addition to the duration of AF, the overall risk of the patients as indicated by the CHA_2DS_2VASc-Score (8) as well as certain biomarkers (9, 10) will likely play a role in identifying patients at increased risk of events and, ultimately, eligibility for anticoagulation. Also here, prospective randomized studies are required to answer this question at the required highest level of evidence.

How to stay in sinus rhythm – is upstream therapy the clue?

Life style modification is about to become a cornerstone in atrial fibrillation therapy. The open studies from Australia – LEGACY (11) and CARDIO FIT (12) – showed that rigorous exercise and weight loss programs on top of risk factor management reduced re-occurrence of atrial fibrillation in overweight [body mass index (BMI) > 27 kg/m^2] patients with paroxysmal or persistent atrial fibrillation patients whether on antiarrhythmic drugs or post-AF ablation.

The RACE 3 investigators (*van Gelder et al.* presented at ESC 2017) took this concept further and focused on patients with symptomatic early persistent atrial fibrillation and early heart failure diagnosed <3 months. The main hypothesis was that early and intense or "upstream therapy" would prevent or delay atrial remodeling and thereby prevent reoccurrence of atrial fibrillation compared to conventional therapy. Exclusion criteria were patients already on mineralocorticoid receptor antagonists (MRA) and a left atrium >50 mm in diameter, NYHA IV and LVEF < 25%. From 2009 to 2015, 119 patients were included in the upstream arm and 126 in the conventional arm. Upstream rhythm control included angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers, MRA, statins, cardiac rehabilitation therapy, and intensive counselling on dietary restrictions, exercise maintenance, and drug adherence. The control arm of conventional rhythm control consisted of rhythm control therapy without cardiac rehabilitation therapy and intensive counselling. Following 3 weeks in each arm patients underwent cardioversion. After 1 year, 75% in the upstream arm and 63% in the conventional study arm were still in sinus rhythm (P = 0.02) with a benefit from upstream therapy across all sub-groups. A significant drop in blood pressure, NT pro-BNP and LDL was also seen in the study arm whereas LVEF or LA-volume did not change. With only a 1 year follow-up, it is not surprising that the composite of CV morbidity/mortality was low and did not differ between the upstream group = 16% and the conventional = 17% groups.

Atrial fibrillation ablation "down the rabbit hole"

The prevalence of AF increases with age and many patients are severely symptomatic. Pharmacologic therapy is problematic, as again evidenced by the possibly detrimental effect of drugs previously used in large scale in AF such as digoxin in a sub study of the ARISTOTLE trial (*Lopes et al.*, presented at ACC 2017). As such, AF ablation has long been hailed as the solution of the problem. According to ESC EHRA guidelines, the indication for AF ablation is to improve quality of life (8). The European AF ablation registry reported an impro-

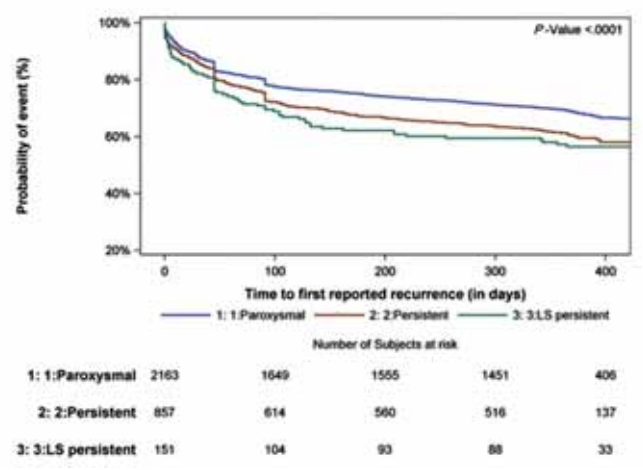

Figure 3. Arrhythmia-free survival by type of atrial fibrillation in the ESC-EHRA atrial fibrillation ablation long-term registry (13)

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ved EHRA score following AF ablation, with good success of the procedure even in long-standing persistent AF *(Figure 3)* (13).

In the landmark MANTRA-PAF trial (14), patients were randomized to antiarrhythmic drug therapy vs. radiofrequency catheter ablation (RFA) as the first therapeutic intervention for atrial fibrillation. The pre-specified long-term results demonstrated after 5 years a lower occurrence and burden of any AF and symptomatic AF in the RFA compared to the AAD group (15). Using 7 days of Holter recordings, 86% of patients in the RFA group were free from AF. Also, quality of life scores were higher in the former compared to the latter group, a signal that was present after 2 years and that persisted during the years thereafter. But also in the control arm a high proportion of patients were in sinus rhythm at the end of follow-up reflecting the early intervention. These results may question very early RF ablation procedures and favour life style modification and risk factor treatment.

However, quality of life had not been studied in a randomized controlled study – nor have hard endpoints (16). This changed when at ESC 2017 the long-awaited CAPTAF (Blomström et al., presented at ESC 2017) and CASTLE AF trial (*Marrouche et al.*, presented at ESC 2017) were presented.

In the CAPTAF, general quality of life assessed by SF 36 was studied after 12 months in 79 patients randomized to RF ablation and 76 to antiarrhythmic drug therapy. All patients had implantable loop recorders enabling comparison of AF burden prior to and post-study start. The results indicate an improvement in quality of life in both groups but with a significantly greater improvement in the ablation group. Specifically, general health – the dimension of the SF 36 for which the study was powered – was improved by 10.5 units or 15% in the ablation group. EHRA score (which ranges between I and IV) improved by on the average 0.5 ($P < 0.01$). Serious adverse events were reported in 11% in the ablation arm and 23% in the control arm which included need for pacemaker-implantation. While there was no statistical difference in AF burden, ablated patients did show only half the AF burden compared to the non-ablated group. It is reasonable to believe that the superior improvement in quality of life in ablated patients was related to absence of AA drugs but also the reduction in AF burden may have had a positive impact. Yet, the discrepancy between maintenance of sinus rhythm and symptom relief remains. Furthermore, the results indicate that OAC indication remains beyond 1 year also in ablated patients.

Atrial fibrillation often accompanies heart failure with a greater proportion with increasing HF severity. Many cardiologists may have felt reluctant to refer such patients for AF ablation for fear of less success rate and clinical benefit. Such clinical practice may however, change following the results of the CASTLE-AF study. In this study a total of 363 patients were randomly assigned to either undergo AF ablation or receive conventional care. To be included patients had to have persistent or paroxysmal AF and LVEF ≤ 35%. All patients had an implantable CRT, ICD, or CRTD enabling monitoring of atrial fibrillation. Of the 3013 screened individuals, 397 were enrolled and randomized 5 weeks later: 179 to the AF ablation group and 184 to the conventional therapy group. The primary composite endpoint of worsening heart failure or all-cause death was reduced by 38% in the ablation compared to the conventional group (HR: 0.62, 95% CI: 0.43–0.87; $P = 0.007$). This was driven by a reduction in both components of the combined endpoint, i.e. worsening heart failure [HR: 0.56 (95% CI: 0.37–0.83); $P = 0.004$] which occurred instantly and all-cause mortality [HR: 0.53 (95% CI: 0.32–0.86); $P = 0.011$] which was evident after a few years. Cardiovascular hospital admissions (HR: 0.72, 95% CI: 0.52–0.99; $P = 0.041$) and cardiovascular mortality (HR: 0.49, 95% CI: 0.29–0.84; $P = 0.009$) was also significantly reduced in the ablation compared to the conventional therapy arm. At the same time, ejection fraction improved by 7% after 12 months in the ablation-group compared to the conventional treatment group, hence offering a potential mechanism through which these impressive effects were obtained. Over the 5 year duration of the trial, ablated patients were twice as much free from AF as non-ablated. As expected, RF ablation of AF was not free from complications with 3.9% strokes/transient ischemic attack (TIA), 1.7% severe acute bleeding, and 1.7% pericardial effusion. In the conventional arm, stroke/TIA was reported in 6.9%. Will these results change the way we see AF ablation in heart failure patients? Will it change the way we treat these patients? It is always difficult to infer a change in daily practice from a comparatively (!) small trial such

as CASTLE AF, with its specific inclusion, and exclusion criteria as well as the dependence on few events and subsequent risk of type I error. This notwithstanding, CASTLE AF does represent a landmark trial in that it indeed represents the first evidence that AF ablation may not simply be a symptomatic procedure but may affect hard clinical outcomes in our patients – and, as a result, may in fact play a causal role rather than that of a 'nuisance bystander' in the pathophysiology of the disease process. Hopefully, the pending randomized controlled trials (RCTs) with similar focus such as the CABANA and RAFT-AF study, as well as the EAST-AF-NET 4 trial (17) will add more evidence.

The question on how to best anticoagulated patients at and around AF ablation on the other hand seems answered. Like for Vitamin K antagonists (VKA), uninterrupted anticoagulation turned out to be both safe and effective also with NOACs. After the first randomized trial using rivaroxaban in this indication had shown no difference in the rate of events (VENTURE-AF) (18), the larger Re-CIRCUIT study confirmed these results in 635 patients undergoing AF ablation randomized to either uninterrupted dabigatran or warfarin. Major bleeding events post-ablation, although overall low, occurred even significantly less with Dabigatran compared to Warfarin (1.6% vs. 6.9%; $P < 0.001$) with no difference in ischemic events. Finally, also apixaban performed well in the AEIOU trial, in which 300 patients were randomly assigned to apixaban uninterrupted or to the morning dose withheld prior to catheter ablation (presented at HRS 2017). When matched to a retrospective uninterrupted warfarin cohort, major bleeding events were similar in both groups and overall occurred in <2% in both arms. The ongoing AXAFA-AFNET 5 study is comparing apixaban to uninterrupted VKA and will be reporting in early 2018 (19). For edoxaban, a recent subanalysis of the ENGAGE AF-TIMI 48 trial demonstrated a similar risk of ischemic and bleeding events in 193 catheter ablation procedures, although only a minority of patients were left on study drug for the procedure (20). A dedicated study, ELIMINATE-AF is underway investigating the efficacy and safety of uninterrupted edoxaban peri-ablation. Overall, the message seems to be emerging in a rather clear fashion that neither withholding (for more than the morning dose) nor bridging seems to be warranted and that a strategy of uninterrupted anticoagulation is the treatment of choice also for NOACs in the peri-AF ablation setting.

In a similar way, it is currently unclear how long before ordinary surgical procedures NOACs need to be discontinued. Recent data from a French multicentre registry indicate that 3 days cessation of therapy predicted NOAC concentrations <30 ng/mL with 91% specificity (21). However, plasma levels are surrogate endpoints; and these data do not deliver proof that stopping NOACs for 72 h is required for all procedures (22). Similar to the perioperative management in the VKA era, bridging with LMWH was performed for years before, ultimately, evidence accumulated that this practice not only does not protect patients from events but may in fact lead to a higher bleeding propensity than uninterrupted warfarin (23, 24). Very recent evidence from the BRUISE-CONTROL 2 study (*Birnie et al.,* presented at AHA 2017) go in a similar direction: In 662 patients with a CHA_2-DS_2-VASc score ≥ 2 randomized to either continuing NOAC therapy (last intake the evening before the procedure) or interruption for at least 2 days, bleeding as well as other endpoints (including mortality and stroke) was rare and occurred to the same extent in both groups. While other studies are underway assessing a similar question in other surgical settings (e.g. the PAUSE trial; NCT02228798), these data for the first time indicate that continuing NOACs (or at least limiting the time of interruption) may be a safe way to proceed for some interventions.

Stroke prevention in atrial fibrillation

The 2016 ESC guidelines clearly put anticoagulation with NOACs as the preferred therapy for stroke prevention in AF (8). Could improvements in warfarin therapy such as genotype-guided dosing tip this balance (25, 26)? So far, the evidence is conflicting. In contrast, however, evidence is accumulating that even patients with well controlled INRs are not at zero risk of events. On the contrary, a recent sub-analysis from ARISTOTLE indicated that the vast majority of intracranial haemorrhages (78.5%) occurred at a therapeutic INR (<3.0) (27). As such, NOACs remain the standard due to the consistent results observed in the four landmark randomized clinical trials with apixaban, dabigatran, edoxaban, and rivaroxaban in a total of >70,000 patients. There are, however, certain differences between the four NOACs that we are only in the process of understanding. Meticulous analyses of existing RCTs as well as new studies shed new light on these differences and improve individualization of NOAC therapy.

One remaining problem is that of inappropriate use of the "reduced" dose of NOACs. Data from insurance claims analyses indicate a rate of up to 40% and more of "reduced dose" use, particularly of apixaban, which does not compare to the 4.7% of patients receiving 2 × 2.5 mg of apixaban in the ARISTOTLE trial (28). Importantly, the effect of using the reduced dose of apixaban or rivaroxaban in patients without the respective dose-reduction criteria leads to completely unpredictable results as this has never been properly studies in a randomized controlled fashion and can hence not be recommended. In contrast, a "lower dose" regimen was studied specifically in the Re-LY as well as in the ENGAGE AF-TIMI 48 trial with dabigatran and edoxaban, respectively (29, 30). Assessment of the proportion of patients taking the lower dose and/or reduced dose of NOACs in daily clinical practice is one strength of insurance claims database research; indeed, the results serve to remind us

to keep up and increase our educational efforts to alert physicians and patients that reproduction of the positive RCT results will only be possibly by using the investigated dosing regimens. In contrast, the assessment of clinical outcomes in the so-called "Real World" research, particularly with insurance claims databases, needs to be viewed with great caution. Independent of statistical methods for adjustment, residual confounding is substantial, severely limits any interpretation of outcomes, and essentially makes assessment of any causal effect impossible, particularly in questions that have never been assessed in an RCT (31).

The same is true for the use of other modalities for stroke prevention in AF, particularly percutaneous as well as surgical left atrial appendage occlusion. Several registry data surfaced in 2017, including the 1-year outcomes of the EWOLUTION registry which demonstrated a low-stroke rate in over 1000 patients undergoing implantation with the Watchman device (*Boersma et al.*, presented at Europace 2017). However, at the same meeting, data from a French registry indicated a high prevalence (6.1%) of device occluder thrombi in 377 consecutive patients implanted with various LAA occluder systems (*Fauchier et al.*, presented at Europace 2017). At the end of the day, the place of the LAA occlude still remains to be determined, even >8 years since publication of the PROTECT-AF study. In view of the available evidence, the current 2016 guidelines appropriately assign a Class IIb recommendation to LAA occlusion for stroke prevention in AF (8). Further registries are unlikely to change this level of recommendation – this will only be possible with new results from well-designed RCTs. Some trials (CLOSURE-AF, ASAP-TOO) in high-risk patients are now underway; others, particularly comparing LAA occlusion to the current (!) standard of therapy, i.e. NOACs, are urgently required. Similarly, a strategy of combining LAA occlusion with low-level NOAC anticoagulation has never been properly explored but has the potential to strike the golden bridge between the seemingly "opposing", but in fact complementary concepts of anticoagulation and LAA occlusion. Unfortunately, so far, interest and motivation from the industry to sponsor such a trial has been limited.

Ventricular tachycardia ablation

Ablation of ventricular tachycardias (VT) has so far been primarily a domain of idiopathic VTs (particularly outflow tract, fascicular VT) and tachycardias with known structural abnormalities (ischemic VT, post-myocarditis etc.). In 2017, *Pappone et al.* (32) reported of the largest series of patients with Brugada syndrome who successfully underwent ablation of an epicardial arrythmogenic substrate in the RVOT – hence in a channelopathy population previously not deemed amenable for ablation. During a median follow-up of 10 months after ablation, elimination of the Brugada ECG phenotype was achieved in 133 of 135 patients undergoing ablation. Will ablation hence become standard therapy for Brugada patients? Will all patients with Brugada syndrome, possibly even "only" with Brugada pattern benefit? What is the natural course of the disease after successful ablation? Many questions remain open, but these results certainly open the door to yet another frontier for ablation therapy in previously believed to be unsuitable patients.

Indeed, the RVOT harbours not only "idiopathic" VT, but has been recognized in other entities including Brugada (as mentioned above) as well as early manifestation of ARVC as well as certain forms of exercise-induced arrhythmogenic remodeling (33). In 57 consecutive patients with scar-related right ventricular VT, the group of *Dr. Zeppenfeld* identified an isolated subepicardial right ventricular outflow tract scar in high-level endurance athletes which was successfully treated by ablation. Furthermore, the scar pattern observed in this exercise-induced arrhythmogenic remodelling demonstrated significant differences compared to that in ARVC and post-inflammatory cardiomyopathy (33). As with the ablation approach suggested for Brugada, the approach appears attractive, but confirmation in larger series as well as long-term outcomes are eagerly awaited.

Indeed, even in "typical" VT ablation patients – those with a "structural" VT – success is far from 100%. In a large cohort, *Tzou et al.* (34) compared patients undergoing a repeat procedure to those with a first VT ablation. Not surprisingly, the former individuals more frequently presented with non-ischemic VT, ICD shocks, and amiodarone treatment. Even though the procedural success was similar between the two groups (93% vs. 92%), complications trended to be higher (especially for pericardial effusion and venous thrombosis) and survival was worse (67% vs 78%, $P = 0.003$). As with virtually all EP procedures – and as a matter of fact, virtually all procedures in Cardiology – such high-end interventions need to be concentrated at specialized centres to allow for maximum efficacy and safety of the procedure.

Sudden cardiac death – risk prediction and prevention

In 2016, the DANISH trial demonstrated no overall benefit of primary prophylactic ICD implantation in 556 patients with non-ischemic heart disease (35). Few studies on cardiac devices have been debated as intensely over the last decade. In a recent meta-analysis of 8567 patients of 11c RCTs (including 3128 patients without ischemic heart disease – IHD), primary prevention ICD implantation reduced the occurrence of all-cause mortality both in patients with ($n = 5439$) as well as in those without ischemic heart disease ($n = 3128$) by 24% (36). Is the question answered then? By far not. As elegantly eluted to in an accompanying editorial by *Lars Kober* (at the same time the principal investigator of the DA-

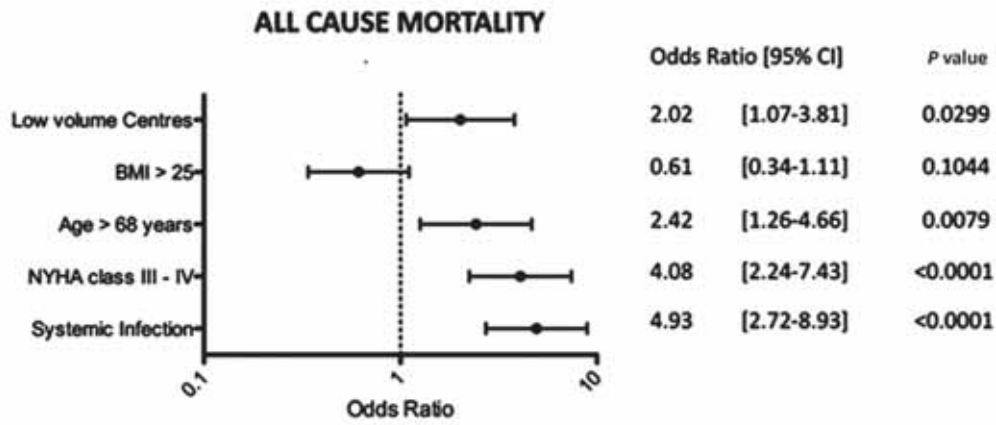

Figure 4. Predictors of overall mortality after lead extraction (41). BMI, body mass index; CI, confidence interval; NYHA, New York Heart Association

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NISH trial) to the aforementioned meta-analysis: "ICDs work – now it is time to find out that needs them" (37). Indeed, as in the DANISH trial, the question is not as black or white as sometimes presented; what is the role of concomitant CRT? What is the use of CRT in elderly patients and in those with relevant comorbidities (including severe heart failure)? Does the impact of defibrillators on survival become less over time? Indeed, these questions are not only valid for ICD in patients with non-ischemic cardiomyopathies, which were included in DANISH. Therefore, the aim of the EHRA initiated "RESET-SCD" trial is to test primary prophylactic ICD implantation in patients with ischaemic heart disease and compromised ejection fraction and will deliver urgently needed new data for this important population. And, on another level: Are we at the best that we can do regarding risk stratification of patients at risk of SCD? Indeed, left ventricular ejection fraction – in spite of being the best documented method for primary prevention ICD eligibility – has important shortcomings. Accumulating evidence indicate that imaging, particularly by MRI, may be helpful. In 399 patients with late gadolinium enhancement (LGE) and an EF≥40% had an over nine-fold increased risk of SCD or aborted SCD than those without LGE (38). The incremental value of using multiple ECG parameters in SCD prediction was tested in the community-based Oregon Sudden Unexpected Death Study (39). When heart rate, LV hypertrophy, QRS transition zone, QRS-T angle, QTc, and Tpeak-to-Tend interval were added to traditional risk factors, the c-statistics improved significantly from 0.625 to 0.753 ($P<0.001$). This was externally validated in the Atherosclerosis Risk in Communities (ARIC) Study. In the accompanying editorial, *Bob Myerburg* rightfully states that although encouraging, the long-term predictive value of these ECG markers will require assessment in a carefully designed randomized clinical trial (40).

Implantable cardiac electronic devices – moving further away from intravascular leads and other "unshakable" paradigms

Both permanent pacemakers as well as ICDs and CRT devices have time after time revolutionized the way that brady- and tachyarrhythmic disorders can be treated. This notwithstanding these systems do come along with the potential of morbidity as patients get older, mostly related to the presence of intravascular leads. Indeed, lead fractures and particularly infection may result in the necessity for lead extraction, which per se is associated with significant morbidity as well as mortality – as demonstrated most recently in the European Lead Extraction ConTRolled Registry (ELECTRa), a prospective registry of consecutive transvenous lead extractions conducted by the European Heart Rhythm Association (EHRA) (41). In 3510 patients undergoing lead extraction at 73 centres in 19 European countries between November 2012 and May 2014, the primary endpoint of in-hospital procedure-related major complication rate occurred in 1.7% (95% CI: 1.3–2.1%) (58/3510 pts), which included a mortality of 0.5% (95% CI: 0.3–0.8%) (17/3510 pts). On the flipside, complete clinical and radiological success rates were high with 96.7% (95% CI: 96.1–97.3%) and 95.7% (95% CI: 95.2–96.2%), respectively (41). Importantly, both efficacy and safety were significantly better in high- vs. low-volume centres *(Figure 4)* – as with almost any other type of procedure, including AF ablation, ICD implantation, and even pacemaker implantation. Food for thought for policy makers and stakeholders of our health care systems, both regarding optimal patient treatment and cost.

Leadless pacemakers have recently been introduced to avoid lead-related problems in pacemaker patients. While both currently available systems performed well in clinical trials, evidence from daily clinical practice

was so far missing. An interim analysis of the ongoing, prospective Micra Post Market Registry now indicated for the first time that the system is also safe and effective if used outside the clinical trial arena (42). While the device was successfully implanted in 792/795 attempts, major complications were rare {13 major complications in 12 patients [1.51% (95% CI: 0.78%–2.62%)]}, including one cardiac effusion/perforation and one micro device dislodgement. This compares well and even exceeds the already low complication rate observed in the landmark clinical trial (43), in spite of the majority of implanters (>87%) not being part of the initial clinical trial. These results also demonstrate the importance of a dedicated structured training program prior to implantation of the system. Some unresolved issues remain, including the feasibility (but also necessity) of extraction, particularly after years of implantation; as well as possible long-term issues that may only surface after years such as the recently discovered premature battery depletion in the SJM/Abbott Nanostim leadless pacemaker (44).

On the tachycardia side, the subcutaneous ICD is gaining momentum for the prevention of sudden cardiac death particularly due to the lack of an intravascular electrode and the associated problems (45). This year, the mid-term results of the global Evaluation oF FactORs ImpacTing CLinical Outcome and Cost EffectiveneSS of the S-ICD (EFFORTLESS S-ICD) registry were published indicating not only fulfilment of the pre-defined endpoints for efficacy and safety but also a low rate of system extraction due to need for antitachycardia pacing, brady pacing, or CRT (46). Prospective studies including PRAETORIAN and UNTOUCHED are currently ongoing and will need to confirm these positive results. However, given the likely reduced morbidity compared to conventional transvenous systems, treatment of patients at lower risk of SCD than 'conventional' ICD recipients appears to be an attractive option. To this end, MADIT-SICD was launched last year, investigating the efficacy and safety of the S-ICD (compared to the current standard of best medical therapy) in post-myocardial infarction diabetes patients ≥65 years with an LVEF 36–50% (47). In addition to improving our ways and means of risk stratification for SCD, reducing the morbidity of systems protecting patients from SCD seems to be a logical step to tackle the challenges of the Myerburg-Paradox (45). While both leadless pacing as well as the S-ICD hence likely represent a glimpse of what the device field will be moving towards in the future, comparative analyses with existing systems (as indicated) are mostly still ongoing. In addition, the higher cost of these systems may be an obstacle in some health care settings preventing the larger volume use of these devices – which, however, is likely to change over the coming years as with every newly introduced therapy.

One other concern about cardiac devices seems to be lessened latest since last year, that is the "risk" of MRI in non-MRI-conditional devices (at least in none high-risk patients undergoing 1.5 T MRI). Using a specific standardized protocol for patient selection, programming, observation during MRI and reprogramming, the investigators of the MAGNA-SAFE registry demonstrated no deaths, lead failures, losses of capture, or ventricular arrhythmias during MRI in 1000 pacemakers and 500 ICDs (48). Whether this is also true for higher risk patients (e.g. pacemaker dependent ICD recipients) remains to be determined. Preliminary data for one such high-risk subgroups appears encouraging: two studies presented at HRS 2017 (*Padmanabhan et al.* and *Brunker et al.*) indicate that MRI seems to be safe and feasible in patients with abandoned leads, i.e. patients previously thought to be absolutely contraindicated to undergo MRI scanning. Further studies are required to substantiate these findings, but given the totality of recently provided data, several paradigms seem to be tumbling in this previously uncharted area of MRI scanning in implantable devices.

Cardiac resynchronization therapy – between guidelines, reality, and alternatives

Although standard therapy in heart failure, CRT remains unevenly implemented in ESC countries according to the 2016 EHRA Whitebook (49). The ESC EHRA HFA CRT Survey II included data on 10 088 new CRT implantations across 42 ESC countries collected between October 2015 and December 2016 (Normand et al., presented at ESC 2017). The results indicate that like in the previous survey (50) doctors go beyond guidelines (51) recommendations when selecting patients for CRT. The most common deviation was to give CRT in LVEF > 35% in 12%, narrow QRS < 120 ms in 8% and NYHA class I in 3%. Of implantations 43% were in patients with a Class I indication according to guidelines, Class II in 21% and Class III meaning implantation is contraindicated in 8%. The results also imply important differences in between countries and centres. The present CRT Survey II is sufficiently big to permit meaningful benchmarking between countries.

His Bundle pacing has resurrected over the last years as a possible alternative to CRT in some settings (52, 53). In a study of 95 patients with an indication for CRT, His bundle pacing was used as a rescue strategy in for failed LV lead or non-response to conventional biventricular pacing (Group I) or as an alternative to the latter for individuals with AV block, bundle branch block, or high ventricular pacing burden. Both groups demonstrated a significant reduction in QRS width, increase in LVEF [30 ± 10% to 43 ± 13% (P = 0.0001)] and improvement in NYHA class (52). Still, many questions remain. Will this be safe and effective also outside specialized centres with great expertise in this technique? Will this also work in patients requiring ICD therapy? And, most importantly, will it turn out to be as effective in reducing hard clinical endpoints (morbidity and mortality) as conven-

tional CRT has been demonstrated to be. Again, randomized clinical trials assessing these open questions will be required, some of which are already ongoing.

Conflict of interest

C.L. has consultant and/or speaker fees from Medtronic, Biotronik, St Jude Medical, Novartis and Vifor. She has received grant support through her institution from Astra Zeneca, Stockholm city council and Heart Lung foundation. J.S. has received consultant and/or speaker fees from Amgen, Astra-Zeneca, Atricure, Bayer, Biosense Webster, Biotronik, Boehringer-Ingelheim, Boston Scientific, Bristol-Myers Squibb, Cook Medical, Daiichi Sankyo, Medtronic, Novartis, Pfizer, Sanofi-Aventis, Sorin, St. Jude Medical/Abbott and Zoll. He reports ownership for CorXL. He has received grant support through his institution from Bayer Healthcare, Biosense Webster, Biotronik, Boston Scientific, Daiichi Sankyo, Medtronic, und St. Jude Medical/Abbott.

References

1. Shenasa M. Mark E Josephson MD. Eur Heart J 2017; 38: 1355–1356.
2. Katritsis DG, Zografos T, Katritsis GD, et al. Gatheter ablation vs. antiarrhythmic drug therapy in patients with symptomatic atrioventricular nodal re-entrant tachycardia: a randomized, controlled trial. Europace 2017; 19: 602–606
3. Brachmann J, Lewalter T, Kuck KH, et al. Long-term symptom improvement and patient satisfaction following catheter ablation of supraventricular tachycardia: insights from the German ablation registry. Eur Heart J 2017; 38: 1317–1326.
4. Van Gelder IC, Healey JS, Crijns H, et al. Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT. Eur Heart J 2017; 38: 1339–1344.
5. Sanna T, Diener HC, Passman RS, et al. CRYSTAL AF Investigators. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med 2014; 370: 2478–2486.
6. Lopes RD, Alings M, Connolly SJ, et al. Rationale and design of the apixaban for the reduction of thrombo-embolism in patients with device-detected sub-clinical atrial fibrillation (ARTESiA) trial. Am Heart J 2017; 189: 137–145.
7. Kirchhof P, Blank BF, Calvert M, et al. Probing oral anticoagulation in patients with atrial high rate episodes: rationale and design of the non-vitamin K antagonist oral anticoagulants in patients with atrial high rate episodes (NOAH-AFNET 6) trial. Am Heart J 2017; 190: 12–18.
8. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016; 37: 2893–2962.
9. Hijazi Z, Oldgren J, Lindback J, et al. The ABC risk score for patients with atrial fibrillation – authors' reply. Lancet 2016; 388: 1980–1981.
10. Hijazi Z, Oldgren J, Lindback J, et al. A biomarker-based risk score to predict death in patients with atrial fibrillation: the ABC (age, biomarkers, clinical history) death risk score. Eur Heart J 2017.
11. Pathak RK, Middeldorp ME, Meredith M, et al. Long-term effect of goal-directed weight management in an atrial fibrillation cohort: a long-term follow-up study (LEGACY). J Am Coll Cardiol 2015; 65: 2159–2169.
12. Pathak RK, Elliott A, Middeldorp ME, et al. Impact of cardiorespiratory fitness on arrhythmia recurrence in obese individuals with atrial fibrillation: the CARDIO-FIT study. J Am Coll Cardiol 2015; 66: 985–996.
13. Arbelo E, Brugada J, Blomstrom-Lundqvist C, et al. on the behalf of the ESC-EHRA Atrial Fibrillation Ablation Long-term Registry Investigators. Contemporary management of patients undergoing atrial fibrillation ablation: in-hospital and 1-year follow-up findings from the ESC-EHRA atrial fibrillation ablation long-term registry. Eur Heart J 2017; 38: 1303–1316.
14. Cosedis Nielsen J, Johannessen A, Raatikainen P, et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. N Engl J Med 2012; 367: 1587–1595.
15. Nielsen JC, Johannessen A, Raatikainen P, et al. MANTRA-PAF Investigators. Long-term efficacy of catheter ablation as first-line therapy for paroxysmal atrial fibrillation: 5-year outcome in a randomised clinical trial. Heart 2017; 103: 368–376.
16. Zakeri R, Van Wagoner DR, Calkins H, et al. The burden of proof: the current state of atrial fibrillation prevention and treatment trials. Heart Rhythm 2017; 14: 763–782.
17. Kirchhof P, Breithardt G, Camm AJ, et al. Improving outcomes in patients with atrial fibrillation: rationale and design of the early treatment of atrial fibrillation for stroke prevention trial. Am Heart J 2013; 166: 442–448.
18. Cappato R, Marchlinski FE, Hohnloser SH, et al. VENTURE-AF

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Investigators. Uninterrupted rivaroxaban vs. uninterrupted vitamin K antagonists for catheter ablation in non-valvular atrial fibrillation. Eur Heart J 2015; 36: 1805–1811.
19. Di Biase L, Callans D, Hæusler KG, et al. Rationale and design of AXAFA-AFNET 5: an investigator-initiated, randomized, open, blinded outcome assessment, multi-centre trial to comparing continuous apixaban to vitamin K antagonists in patients undergoing atrial fibrillation catheter ablation. Europace 2017; 19: 132–138.
20. Steffel J, Ruff CT, Hamershock RA, et al. First experience with edoxaban and atrial fibrillation ablation—insights from the ENGAGE AF-TIMI 48 trial. Int J Cardiol 2017; 244: 192–195.
21. Godier A, Dincq AS, Martin AC, et al. Predictors of pre-procedural concentrations of direct oral anticoagulants: a prospective multicentre study. Eur Heart J 2017; 38: 2431–2439.
22. Auer J, Huber K, Granger CB. Interruption of non-vitamin K antagonist anticoagulants in patients undergoing planned invasive procedures: how long is long enough? Eur Heart J 2017; 38: 2440–2443.
23. Douketis JD, Spyropoulos AC, Kaatz S, et al. for the Bridge Investigators. Perioperative bridging anticoagulation in patients with atrial fibrillation. N Engl J Med 2015; 373: 823–833.
24. Birnie DH, Healey JS, Wells GA, et al. BRUISE CONTROL Investigators. Pacemaker or defibrillator surgery without interruption of anticoagulation. N Engl J Med 2013; 368: 2084–2093.
25. Gage BF, Bass AR, Lin H, et al. Effect of genotype-guided warfarin dosing on clinical events and anticoagulation control among patients undergoing hip or knee arthroplasty: the gift randomized clinical trial. JAMA 2017; 318: 1115–1124.
26. Kimmel SE, French B, Kasner SE, et al. COAG Investigators. A pharmacogenetic versus a clinical algorithm for warfarin dosing. N Engl J Med 2013; 369: 2283–2293.
27. Lopes RD, Guimaraes PO, Kolls BJ, et al. Intracranial hemorrhage in patients with atrial fibrillation receiving anticoagulation therapy. Blood 2017; 129: 2980–2987.
28. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011; 365: 981–992.
29. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361: 1139–1151.
30. Giugliano RP, Ruff CT, Braunwald E, et al. ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013; 369: 2093–2104.
31. Rosendaal FR, Reitsma PH. Brave real world. J Thromb Haemost 2016; 14: 2091.
32. Pappone C, Brugada J, Vicedomini G, et al. Electrical substrate elimination in 135 consecutive patients with Brugada syndrome. Circ Arrhythm Electrophysiol 2017; 10: e005053.
33. Venlet J, Piers SR, Jongbloed JD, et al. Isolated subepicardial right ventricular outflow tract scar in athletes with ventricular tachycardia. J Am Coll Cardiol 2017; 69: 497–507.
34. Tzou WS, Tung R, Frankel DS, et al. Outcomes after repeat ablation of ventricular tachycardia in structural heart disease: an analysis from the International VT Ablation Center Collaborative Group. Heart Rhythm 2017; 14: 991–997.
35. Køber L, Thune JJ, Nielsen JC, et al. DANISH Investigators. Defibrillator implantation in patients with nonischemic systolic heart failure. N Engl J Med 2016; 375: 1221–1230.
36. Shun-Shin MJ, Zheng SL, Cole GD, et al. Implantable cardioverter defibrillators for primary prevention of death in left ventricular dysfunction with and without ischaemic heart disease: a meta-analysis of 8567 patients in the 11 trials. Eur Heart J 2017; 38: 1738–1746.
37. Thune JJ, Kober L. Defibrillators work: now it is time to find out who needs them. Eur Heart J 2017; 38: 1747–1748.
38. Halliday BP, Gulati A, Ali A, et al. Association between midwall late gadolinium enhancement and sudden cardiac death in patients with dilated cardiomyopathy and mild and moderate left ventricular systolic dysfunction. Circulation 2017; 135: 2106–2115.
39. Aro AL, Reinier K, Rusinaru C, et al. Electrical risk score beyond the left ventricular ejection fraction: prediction of sudden cardiac death in the Oregon sudden unexpected death study and the atherosclerosis risk in communities study. Eur Heart J 2017; 38: 3017–3025.
40. Myerburg RJ. Signalling the risk of sudden cardiac death: the ECG and beyond. Eur Heart J 2017; 38: 3026–3028.
41. Bongiorni MG, Kennergren C, Butter C, et al. Investigators oboE. The European lead extraction controlled (ELECTRa) study: a European Heart Rhythm Association (EHRA) registry of transvenous lead extraction outcomes. Eur Heart J 2017; 38: 2995–3005.
42. Roberts PR, Clementy N, Al Samadi F, et al. A leadless pacemaker in the real-world setting: the micra transcatheter pacing system post-approval registry. Heart Rhythm 2017; 14: 1375–1379.
43. Reynolds D, Duray GZ, Omar R, et al. Micra Transcatheter Pacing Study Group. A leadless intracardiac transcatheter pacing system. N Engl J Med 2016; 374: 533–541.
44. Lakkireddy D, Knops R, Atwater B, Neuzil P, Ip J, Gonzalez E, Friedman P, Defaye P, Exner D, Aonuma K, Doshi R, Sperzel J, Reddy V. A worldwide experience of the management of battery failures and chronic device retrieval of the nanostim leadless pacemaker. Heart Rhythm 2017; 14: 1756–1763.
45. Steffel J. The subcutaneous implantable cardioverter defibrillator. Eur Heart J 2017; 38: 226–228.
46. Boersma L, Barr C, Knops R, et al. Implant and midterm outcomes of the subcutaneous implantable cardioverter-defibrillator registry: the EFFORTLESS study. J Am Coll Cardiol 2017; 70: 830–841.
47. Kutyifa V, Beck C, Brown MW, et al. Committee MSIE. Multicenter automatic defibrillator implantation trial-subcutaneous implantable cardioverter defibrillator (MADIT S-ICD): design and clinical protocol. Am Heart J 2017; 189: 158–166.
48. Russo RJ, Costa HS, Silva PD, et al. Assessing the risks associated with MRI in patients with a pacemaker or defibrillator. N Engl J Med 2017; 376: 755–764.
49. Raatikainen MJ, Arnar DO, Merkely B, Camm AJ, Hindricks G. Access to and clinical use of cardiac implantable electronic devices and interventional electrophysiological procedures in the European Society of Cardiology Countries: 2016 report from the European Heart Rhythm Association. Europace 2016; 18: iii1–iii79.
50. Bogale N, Priori S, Cleland JG, et al. Scientific Committee, National Coordinates, and Investigators. The European CRT survey: 1 year (9–15 months) follow-up results. Eur J Heart Fail 2012; 14: 61–73.
51. Ponikowski P, Voors AA, Anker SD, et al. Members ATF. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016; 37: 2129–2200.
52. Sharma PS, Dandamudi G, Herweg B, et al. Permanent his bundle pacing as an alternative to biventricular pacing for cardiac resynchronization therapy: a multi-center experience. Heart Rhythm 2017; pii: S1547-5271(17)31310–3.
53. Ajijola OA, Upadhyay GA, Macias C, et al. Permanent his-bundle pacing for cardiac resynchronization therapy: initial feasibility study in lieu of left ventricular lead. Heart Rhythm 2017; 14: 1353–1361.