Title - Who needs an ICD? Controversies and opportunities after DANISH

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The DANISH trial: changing evidence - changing guidelines?

Since the publication of DANISH, the largest ever trial of ICDs in patients with non-ischaemic heart failure (HF), cardiologists are less certain which of their patients should receive an implantable cardioverter defibrillator (ICD)(1). Earlier in the same year (2016) that this trial was presented and published, the European Society of Cardiology Heart Failure Guidelines gave a class IB recommendation for ICDs in non-ischaemic NYHA II/III heart failure with an EF<35%(2). After this large, neutral trial with no reduction in the primary end-point of all-cause mortality is a class 1B recommendation still justified?

How robust was the evidence for ICDs in non-ischaemic HF prior to the DANISH trial? Even before this there had been no randomised trials of ICD versus no ICD in non-ischaemic HF that reported reduced mortality. CAT (n=104),(3) AMIOVIRT (n=103)(4) and DEFINITE (n=458)(5) were all trials of ICDs in non-ischaemic HF that did not show benefit in terms of their primary end-points. The most suggestive previous data was the subgroup analysis of non-ischaemic patients in the SCD-HeFT trial(6). In 792 patients a non-significant trend towards reduced mortality was reported (HR 0.73; CI 0.50-1.07).

Falling rates of sudden death

So why was DANISH neutral? As ICDs can only reduce sudden arrhythmic death, the observation that rates of sudden death have decreased over the last 20 years is likely to be relevant. In a recent analysis of 40,195 patients from 12 pivotal HF trials, rates of sudden cardiac death had reduced by 44% over a 20-year period (trials were conducted from the mid-90s to 2015).(7) This is almost certainly due to major advances in pharmacological therapy for HF. In the DANISH trial rates of sudden death were low; over the 5 years of follow up of 1116 patients only 70 patients had a sudden death. Sudden death occurred in 24 patients (4.3%) in the ICD group and in 46 patients (8.2%) in the control group (hazard ratio, 0.50; 95% CI, 0.31 to 0.82, p = 0.005).(1) While the relative risk reduction is impressive, the absolute reduction in sudden death over more than 5 years of mean follow up was only 3.9%. Sudden death rates have been further reduced by sacubtril/valsartan (which was not available during the DANISH trial) so it could be argued that it is even more difficult in 2018 to reduce sudden death rates.(8)

Can populations which benefit from ICDs be identified?

As ICDs reduce sudden death it is logical to attempt to identify populations at high risk of sudden death. Perhaps ICDs should only be implanted in these groups? There are 2 approaches to identify subgroups at high risk of sudden death. Firstly, by identifying subgroups in previous trials that appeared to benefit and, secondly, to use risk stratification methods (for example using imaging techniques or biomarkers thought to indicate high risk).

Benefit of ICDs in the young?

Subgroup analysis of neutral trials should always be regarded with caution but there does appear to a subgroup that might benefit (more) from ICDs. Younger patients appear to have more to gain. In DANISH there appeared to be greater benefit of ICDs in the young compared to older patients in both continuous and categorical analyses; the younger the patient the greater the apparent benefit.(9) There appeared to be no benefit of ICD implantation in those aged over 70. In this analysis of DANISH, there was a hint of why there is greater benefit of ICDs in the young; sudden death was more common in

younger compared to older patients. If older patients are dying of pump failure and non-cardiovascular causes it should not surprise us that mortality is not reduced by ICDs. DANISH is not alone to report a suggestion of more benefit in the young. For example, in SCD-HeFT, the hazard ratio for those < 65 years of age was 0.68 (95% CI 0.50-0.93) compared to 0.86 (95% CI 0.62-1.18) for those aged over 65 (interaction p value not given).(6) There are causes of non-ischaemic HF that are characterised by very high rates of ventricular arrhythmias (eg Lamin A/C mutations). Intuitively it seems reasonable to prioritise these patients for ICD implantation. Perhaps our increasing knowledge of subtypes of non-ischaemic HF will allow identification of other high-risk groups.

Identifying populations at high risk of sudden death

What about trying to identify a population which stands to gain from ICD therapy by using risk stratifying methods for sudden death? Microvolt T wave alternans had its advocates previously but has not been shown to be a useful tool to select patients for ICD therapy.(10) More recently myocardial scar (late-gadolinium enhancement) detected by cardiac magnetic resonance imaging has been suggested as a means of selecting patients at high risk of sudden death who might benefit from ICDs. This technique is being prospectively tested in a randomised international trial of ICD versus implantable loop recorder with a primary end point of sudden cardiac death or ventricular tachycardia leading to syncope (CMR GUIDE HF [NCT01918215]). The investigators have chosen to study patients with ejection fractions >35% (perhaps surprisingly) of ischaemic or non-ischaemic aetiology but this tool could be used as an entry criterion in trials in patients with ejection fractions of less than 35%. Another technique which is being tested is cardiac metaiodobenzylguanidine (MIBG) scanning. MIBG is a measure of sympathetic cardiac activity; those with greater levels of activity may be at greater risk of sudden death - and therefore be candidates for ICD therapy. ADMIRE-ICD (NCT02656329) is a randomised trial of ICD versus no ICD in 2000 patients with high cardiac MIBG activity and an EF<35% of both ischaemic and non-ischaemic aetiology. The primary end point is all-cause mortality.

Unclear benefit but common complications

What about complication rates of ICDs? If there is marginal or no gain to an invasive therapy, clinicians are mandated to consider any harm that a patient might be exposed to. DANISH reported a substantial complication rate.(1) For example, in the ICD group 3% had a serious device infection, 6% received inappropriate shocks and 2% pneumothoraces. Complication rates in real-world population are even greater.(11) If a patient is to be offered an ICD for non-ischaemic HF he/she should certainly be informed of the cons of ICD implantation before they consent. As older patients (>70 years of age) have more complications than their younger counterparts, this is an additional reason to think carefully before recommending ICD implantation in these patients.(9)

ICDs for HF secondary to coronary artery disease

The evidence for ICDs in non-ischaemic HF has thus been challenged by DANISH. What about primary prevention ICDs for those with an EF<35% secondary to coronary artery disease? For these patients the evidence that resulted in a 1A guideline recommendation by the European Society of Cardiology Heart Failure Guidelines has not changed.(2) But let's think again… SCD-Heft(6) and MADIT 2(12) are the trials that the 1A recommendation are based on. Is it conceivable or likely that if these trials were repeated in the modern era that results would be different? The decline in rates of sudden death is not exclusive to patients with non-ischaemic HF.(7) Medical therapy has improved for those with HF regardless of

aetiology. There is a strong argument for a new primary prevention ICD trial (or trials) in patients on contemporary medical therapy in patients with HF secondary to CAD. Will anyone be brave enough to do this? It is likely that such a trial will be undertaken in the coming years.

Cardiac resynchronisation therapy (CRT) – additional value of ICDs (CRTD)?

What about CRT and ICDs? Who should receive a CRT pacemaker alone (CRTP) and who should receive CRTD? No dedicated trial has addressed this question which arises daily in cardiology units internationally. 2 trials do give a glimpse of the possible additional value of CRTP versus CRTD. COMPANION had a 3-arm randomisation to CRTD, CRTP and optimal medical therapy alone.(13) This trial was not powered to detect a difference between CRTD and CRTP and no difference was seen. 60% of patients in the DANISH trial received CRT so to some extent this was a trial of CRTP versus CRTD. The absence of effect of ICDs in DANISH was similar in those with and without CRT (HR 0.91 95% CI 0.64−1.20 and HR 0.83 95% CI 0.58−1.19, respectively, interaction p value 0.73).(1) A dedicated stand-alone trial of CRTP versus CRTD is undoubtedly necessary.

It should be noted that even with a class 1 indication for ICDs, number of patients receiving these devices has been relatively low (less than 10% of patients even in contemporary clinical trial cohorts(8)). In most countries in the real-world these numbers are even lower. Is this because of financial constraints or because cardiologists and their patients have not been overwhelmed by the absolute risk/benefit ratio?

More questions than answers

Other questions remain: Are the pros and cons of ICDs the same in clinical trials as in real-life? Perhaps the rate of sudden death is higher in real life in patients who are not prescribed or do not tolerate high doses of pharmacological therapy for HF? Perhaps the benefits of ICDs in such patients are greater? What about secondary prevention ICDs? The trials of secondary prevention pre-date modern pharmacological therapy.(14)(15) Randomised controlled trials of secondary prevention ICD versus no ICD seem reasonable. What is the role of subcutaneous ICDs? These have potential benefits as they can be explanted relatively easily if complications arise or myocardial recovery occurs, but they do not offer the bradycardia pacing abilities of transvenous systems. If these are going to be used in patients with HF out with niche indications (for example congenital heart disease or when transvenous access is not possible) randomised trials to assess their efficacy are necessary.

Conclusion - Opportunities for new trials

In summary, the DANISH trial has forced the cardiology community to stop and think about which patients should, and which should not, receive an ICD. In 2018 the unknowns outnumber the shrinking knowns. We do not know who is likely to benefit and who is likely to be harmed. Against this backdrop the logical way forward is to design new prospective randomised trials so that in 10 years we can have informed discussions with patients and their families about the pros and cons of these potentially life-saving devices (Figure 1). New trials are preferable to relying on subgroup analysis and guesswork as to which patients should undergo ICD implantation. Unfortunately, there are hardly any trials that are currently recruiting. Opportunities abound.

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