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EDITORIAL

The shocking lack of evidence for implantable cardioverter defibrillators for heart failure; with or without cardiac resynchronization

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This editorial refers to 'Very long-term survival and late sudden cardiac death in cardiac resynchronization therapy patients', by S. Barra *et al.*, doi:10.1093/eurheartj/ehz238.

Clinical research has transformed the lives and expectations of many patients with heart failure, especially for those aged <75 years with symptomatic, clinically stable, chronic heart failure and a reduced left ventricular ejection fraction.[1,2] The median survival for such patients with moderate or severe symptoms in the 1980s was <5 years. Life expectancy has more than doubled for those who now receive contemporary specialist care. This change in prognosis has been brought about both by slowing or reversing ventricular dysfunction and congestion and by reducing the risk of sudden (presumed arrhythmic) death.[1,3] Many patients are keen to hear this more optimistic view rather than the previous doom-laden message so common in the heart failure literature.[1] However, a possible consequence of greater longevity is more frailty and senescence, which are becoming increasingly important limitations to the benefits of treatments for heart failure but may potentially also constitute important new therapeutic targets.[4] Clinical trialists need to be aware of this evolution in the natural history of heart failure when designing future research.

One of the great advances in care for heart failure is cardiac resynchronization therapy pacemakers (CRT-Ps) that may also have an implantable cardioverter defibrillator (ICD) function (CRT-D). Improvement in battery life, which may now exceed 10 years, means that these devices now often outlive their hosts. CRT was designed to optimize the sequence of atrial and bi-ventricular contraction, thereby reducing functional mitral regurgitation, improving left ventricular performance, preventing ventricular tachy- and bradyarrhythmias, improving well-being, and prolonging life.[5] Selection for CRT is relatively straightforward and should be considered for many patients with heart failure, a reduced left ventricular ejection fraction (HFrEF) in sinus rhythm, and a QRS duration >130 ms.[6] Although guidelines also recommend CRT for patients with atrial fibrillation, this seems somewhat premature.[7] For patients with atrial fibrillation and HFrEF, no randomized controlled trial has specifically investigated the benefits of pulmonary vein ablation and CRT over and above guideline-recommended pharmacological management, although this might have accounted for some of the benefit observed in trials such as CASTLE-AF.[7] Only one small randomized trial (n = 102) has investigated bi-ventricular pacing with atrioventricular node ablation compared with avoiding pacing altogether.[7] Several trials do show that bi-ventricular pacing is superior to right ventricular pacing in patients with atrial fibrillation and HFrEF, but this may reflect the deleterious effects of right ventricular pacing rather than any assumed benefit of bi-ventricular pacing that does not also deliver atrioventricular resynchronization.[7]

The ICD was designed to terminate malignant ventricular tachyarrhythmias, either by delivering a shock or with overdrive pacing and, incidentally, also by preventing lethal bradycardia. There are serious doubts about the utility of ICD in patients with heart failure, especially in older patients, who often have other life-shortening conditions such as diabetes, lung disease, or kidney disease.[3,7–9] Randomized trials suggest that ICDs might only be effective in patients with a left ventricular ejection fraction <30% and QRS duration >120 ms but with few or no symptoms of heart failure or co-morbid conditions.[10,11] Patients with grossly elevated plasma concentrations of natriuretic peptides are likely to die of progressive heart failure and do not appear to benefit from an ICD.[12] Patients with low plasma concentrations of natriuretic peptides may not benefit because they have a good prognosis without device intervention.[13] Basically, ICDs are most effective at preventing sudden arrhythmic death for patients who have some increased risk of arrhythmias but, more importantly, are otherwise at low risk (*Figure 1*). Rather than trying to identify patients at high risk of sudden death, clinicians should be selecting

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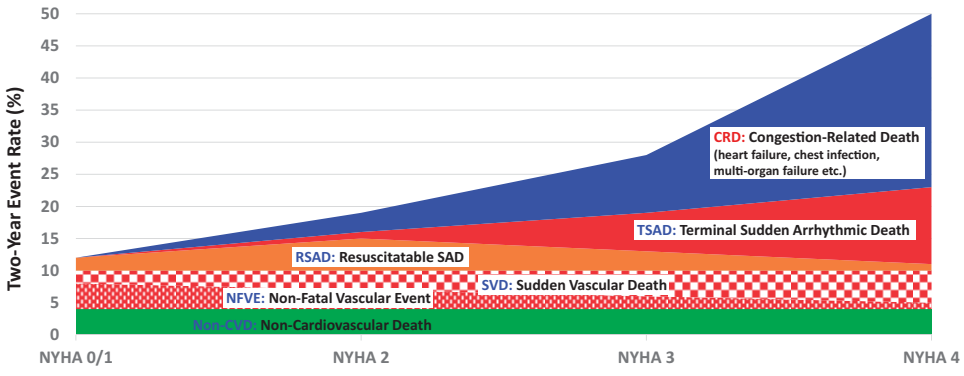

	NYHA 0/1		NYHA 2		NYHA 3		NYHA 4	
	Absolute Rate	% of Deaths	Absolute Rate	% of Deaths	Absolute Rate	% of Deaths	Absolute Rate	% of Deaths
CRD	0%	0%	3%	16%	9%	32%	27%	54%
TSAD	<1%	<1%	1%	5%	6%	21%	12%	24%
RSAD	2%	17%	5%	26%	3%	11%	1%	2%
SVD	2%	17%	3%	16%	4%	14%	5%	10%
NFVE	4%	33%	3%	16%	2%	7%	1%	2%
Non-CVD	4%	33%	4%	21%	4%	14%	4%	8%

Figure 1 Two-year cause-specific mortality and non-fatal vascular events for patients with cardiovascular disease according to New York Heart Association (NYHA) class. Numbers and proportions are a conceptual representation of absolute and relative risk and are not strictly evidence-based. Note that for patients in NYHA Class 4, interventions for sudden arrhythmic death may be ineffective or fail to lead to a meaningful prolongation of life because the patient is likely soon to die of worsening heart failure. CRD, congestion-related death, otherwise called death due to worsening heart failure; NFVE, non-fatal vascular event (e.g. myocardial infarction and stroke; note that events are more likely to be suddenly fatal as heart failure progresses); Non-CVD, non-cardiovascular death; RSAD, resuscitatable sudden arrhythmic death; SVD, sudden vascular death; TSAD, terminal (non-resuscitatable) sudden arrhythmic death.

patients at low risk of death for any other reason. In clinical practice, only a minority of patients use their ICD during the lifetime of the device. The decision to implant an ICD is often problematic for clinicians and often a difficult discussion with patients.

Advances in pharmacological therapy and CRT have improved ventricular function, which has reduced overall mortality; both sudden death and due to worsening heart failure. However, it is not clear that the proportion of sudden deaths compared with overall mortality has fallen over the last 20 years; it remains ~35% of all deaths and almost 50% of cardiovascular deaths.[14] For patients with HFrEF who are unlikely to die of cancer, progressive heart failure, or some other problem within the next 10 years, for every 100 ICDs implanted, one or two lives will be meaningfully prolonged each year and 10–20 lives over a decade. Treatments that prolong life and reduce the risk of dying from progressive heart failure, including CRT, should increase the time alive after ICD implantation and therefore increase the chances of a successful ICD intervention. However, there is a paucity of evidence that CRT-D improves survival compared with CRT-P.

In this issue of the *European Heart Journal*, Barra *et al.*[15] describe the long-term outcome of 534 people who had received CRT-P and 1241 who had received CRT-D and had survived the first 5 years after device implantation. After adjusting for age and other factors, there was no difference in all-cause mortality or sudden death between those who had received CRT-D rather than CRT-P. Importantly, only 15 patients assigned to CRT-D and 14 to CRT-P died suddenly [adjusted hazard ratio 1.0, 95% confidence interval (CI) 0.45–2.44]. Progression of heart failure and non-cardiovascular disease, which are unlikely to be reduced by an ICD, accounted for two-thirds of deaths.

This was not a randomized trial. The mean age at implantation of CRT-P was 70 years compared with just 64 years for those who received CRT-D, about half of the patients had ischaemic heart disease, >40% had a history of atrial fibrillation, and >60% had a QRS duration >150 ms. Statistical methodologies may not adequately adjust for observed differences and cannot account for unmeasured confounders. The results might also have been biased by differences in mortality and cause of death prior to the 5-year post-implant baseline. This analysis included only 1775 of the 5782 patients initially enrolled. We are not told what happened to the other 4007 (69%) patients; >2000 had probably died, some will have been lost to follow-up, and some may have been followed for <5 years. In the largest of the component cohorts, CERTITUDE (n = 1705),[16] after adjusting for differences in patient characteristics, more deaths had occurred at 2 years of follow-up amongst those selected to receive CRT-P rather than CRT-D [adjusted relative risk (aRR) 1.54, 95% CI 1.07–2.21; P = 0.02] but there was no substantial increase in sudden death (aRR 1.21, 95% CI 0.45–3.29, P = 0.70). Amongst those who received CRT-P, annual unadjusted rates for sudden death, death due to heart failure, and non-cardiovascular death were, respectively, 1.2%, 7.5%, and 3.2% and for CRT-D, respectively, 0.8%, 3.3%, and 2.0%.

Current guidelines leave the decision regarding CRT-D or CRT-P to the treating physician. Not surprisingly there is huge international variation in the preference for CRT-D and CRT-P.[17,18] In view of the difference in cost and complications between CRT-P and CRT-D,

and the lack of evidence of a difference in efficacy, randomized trials are required to quantify the benefits and risks for each device to help patients and physicians to make the best decisions about treatment. By preventing death from worsening heart failure, CRT may increase the opportunity for an effective ICD intervention. However, CRT might reduce the arrhythmia substrate by improving ventricular function and preventing long pauses, making the ICD function redundant, especially for people who are at high risk of dying from problems other than an arrhythmia.

The RESET-CRT (https://clinicaltrials.gov/ct2/show/NCT03494933) has begun to enrol patients in Germany, and a similar study is planned in the UK. Both aim to enrol ~2000 patients, and both have a primary outcome of all-cause mortality. Importantly, the investigators for each trial are in dialogue rather than competition, and intend, in due course, to share results.

Conflict of interest: J.G.F.C. has received grants, personal honoraria, and non-financial support from Medtronic, and personal honoraria from Abbott/St Jude. G.H. reports research grants from Abbott, Biotronik, Boston Scientific, and Medtronic to his institution (Heart Center Leipzig) without personal financial benefits, and is Chief Investigator of the RESET-CRT trial. M.P. has no conflicts to declare.

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