

Too old to shock? Questioning added benefit of ICD in elderly CRT patients

Citation for published version (APA):

Strik, M., Vernooy, K., & Prinzen, F. W. (2018). Too old to shock? Questioning added benefit of ICD in elderly CRT patients. *International Journal of Cardiology*, 263, 65-66.
<https://doi.org/10.1016/j.ijcard.2018.04.036>

Document status and date:

Published: 15/07/2018

DOI:

[10.1016/j.ijcard.2018.04.036](https://doi.org/10.1016/j.ijcard.2018.04.036)

Document Version:

Publisher's PDF, also known as Version of record

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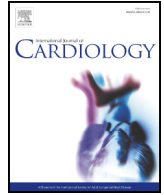
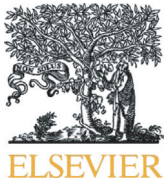
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Editorial

Too old to shock? Questioning added benefit of ICD in elderly CRT patients

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ARTICLE INFO

Article history:

Received 3 April 2018

Accepted 9 April 2018

According to current guidelines, candidates for Cardiac Resynchronization Therapy (CRT) are often also candidates for Implantable Cardioverter Defibrillator (ICD) therapy. The 2013 European Society of Cardiology Clinical Practice guidelines on Cardiac Pacing and Cardiac Resynchronization Therapy offer clinical guidance to the choice of CRT-P or CRT-D [1]. Factors favoring CRT-D are life expectancy of more than one year and the presence of ischemic heart disease. Factors favoring CRT-P are presence of disease which is expected to lead to mortality not related to ventricular arrhythmia such as advanced heart failure (NYHA classes III–IV), severe renal insufficiency, or other major co-morbidities and associated frailty and cachexia. More recently, the PROSE-ICD prospective observational study reported that high-sensitive CRP >9.42, hematocrit $\geq 38\%$, blood urea nitrogen >20 mg/dl and absence of beta blocker therapy are independently associated with higher occurrence of appropriate therapies, suggesting added benefit of CRT-D [2]. Of note, in the PROSE-ICD study 31 appropriate therapies were counted in the 305 patients over a 5 year follow-up period, ventricular fibrillation being the underlying rhythm in only 4 of these cases. These low numbers of appropriate therapy are in line with the decreasing trend in total as well as sudden death in clinical trials (Fig. 1). Therefore, to many it was not surprising that the recently published DANISH trial showed no survival benefit of ICD in general and of CRT-D over CRT-P [3].

The potential added benefit of treating ventricular tachyarrhythmias has been debated since the beginning of the CRT era. One of the first randomized CRT trials (COMPANION) comprised a mix of patients with ischemic and non-ischemic cardiomyopathy and contained a CRT-P and a CRT-D arm [4]. While mortality was significantly lower in the CRT-D arm as compared to the medical treatment arm, there was no significant difference in mortality between CRT-P and CRT-D patients. While the positive results of the COMPANION and other trials paved the way to widespread use of CRT, the discussion of whether to use CRT-D for

primary prevention was recently sparked by the DANISH trial, that included only non-ischemic patients. Subanalysis of this trial, comparing 332 CRT-D and 323 CRT-P patients, did not find a difference in death from any cause (19% versus 20%, $P = \text{NS}$) [3]. Subgroup analysis did show a significant benefit of ICDs in patients younger than 68 years old [3].

Against this background, Döring and colleagues report their retrospective evaluation in this issue of the International Journal of Cardiology [5]. They investigated the impact of ICD-therapy on survival in 177 elderly (>75 years old) CRT recipients, approximately half of them having ischemic cardiomyopathy and about 20% of them having complete AV-block. During a mean follow-up of 26 months, there was no difference in mortality between both patient groups (35% in the CRT-P, and 35% in the CRT-D group, $P = 0.99$). The lack of a significant difference in all-cause mortality was a result of the low risk of sudden cardiac death among included patients. Only 5/97 CRT-D patients (5.2%) had appropriate therapies (shocks in 3 and ATP in 2 patients) and lack of such therapy may not have led to sudden death in all of these patients.

The results of the Döring study as well as the DANISH and PROSE-ICD studies support each other in the sense that they show low incidence of sudden death and shock therapy in patients fulfilling ICD selection criteria (LV EF <35%).

On the other hand, the Döring study has several important limitations. The retrospective design of the study is associated with significant differences in baseline characteristics between CRT-P and CRT-D patients, which may include various risk factors that affect mortality; for instance, CRT-P patients were on average 5 years older and were possibly evaluated to have an expected life expectancy of less than one-year while CRT-D patients had wider QRS duration, wider left ventricular diameters and lower left ventricular ejection fraction. Moreover, due to the small number of patients and even smaller number of deaths and shock therapies, the lack of significance between CRT-P and CRT-D should at best be considered as a “non-inferiority” of CRT-P as compared to CRT-D. The sample size of 177 patients allowed for a 96% power to detect a 20% difference in all-cause mortality between the treatment groups after 2 years of follow-up.

Altogether, the results of the study by Döring and colleagues do not yet warrant the withholding of ICD therapy in elderly CRT candidates. However, the study strongly urges to perform a randomized controlled trial comparing ICD vs. non-ICD (both with and without CRT) in ischemic patients, thus complementing the results of the DANISH study. This study should be powered to also show the effect of age on effectiveness of ICD therapy.

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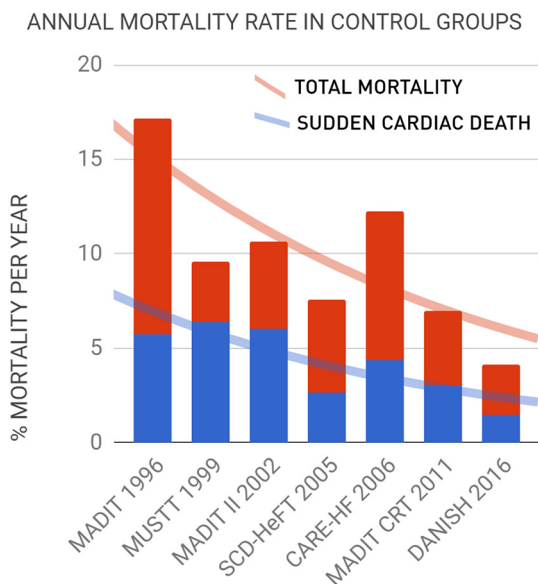


Fig. 1. Total and sudden death in seven major clinical trials over two decades. Blue indicates SCD, red death of all other causes. Data were taken from the control groups in the various studies (reference [3] and: Greenberg et al. *JACC* 2004;43:1459–65; Buxton et al., *NEJM* 1999;341:1882–90; Packer et al. *Circulation* 2009;120:2170–6; Cleland et al. *Eur. Heart J.* 2006;27:1928–32; Barsheshet et al. *JACC.* 2011;57:2416–23; Moss et al. *NEJM* 1996;335:1933–40). Lines are the trend lines fitted through the data, indicating a >60% reduction in sudden cardiac death (blue line) and total mortality (red line) over two decades. This decrease may be explained by the better treatment of heart failure patients as well as the more liberal inclusion criteria.

Importantly, even if a significant difference would be found in such a study, also the number needed to treat for achieving a benefit should be considered. For example, in the younger (<68 years old) DANISH trial patients, ICD therapy significantly reduced all-cause mortality from 21.9 to 15.5% over the 5.5 year follow-up period. Even in this positive scenario, the absolute risk reduction of 6.4% by ICD indicates that it takes implantation of 15 ICDs to prevent one death in a period of 5.5 years. This number should be weighed against the added discomfort

for the patient and the excess health care costs. In the latter respect, a meta-analysis indicated an incremental cost-effectiveness ratio (ICER) of approximately 35,000 euro per life year gained for CRT-D as compared to CRT-P [6]. Of note, this number was derived from studies performed a decade ago. As the figure shows, both total death and sudden death have halved since that time, so currently the actual ICER may have doubled. Therefore, it seems likely that better selection criteria need to be developed for effective ICD implantation. A recent review concluded that microvolt T-wave alternans and cardiac magnetic resonance with late gadolinium enhancement may contribute to a better risk stratification of sudden death [7].

Conflict of interest

MS has no disclosures; K.V. reports consultancy for Medtronic; research grants from Medtronic; speaker fees from Abbott; F.P. reports research grants from Medtronic, Abbott, Biotronik, Sorin, Biosense Webster.

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