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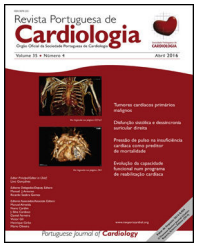

EDITORIAL COMMENT

The implantable cardioverter-defibrillator according to underlying etiology: Why compare apples and oranges?

O cardioversor-desfibrilhador implantável segundo a etiologia subjacente: porque razão comparar alhos com bogalhos?

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Ischemic cardiomyopathy (ICM) is a well-defined entity. A standard definition used in multicenter studies is the presence of systolic dysfunction associated with a history of myocardial infarction or revascularization (coronary artery bypass grafting or percutaneous coronary intervention), ≥75% stenosis of the left main or proximal left anterior descending artery, or ≥75% stenosis of two or more epicardial vessels.[1] Non-ischemic cardiomyopathy (NICM) includes every form of dilated cardiomyopathy without significant coronary disease and is a heterogeneous condition. Idiopathic cardiomyopathy, i.e. the etiology of which is unknown, accounts for up to 50% of cases. There are many potential causes of NICM, including infection, immunologic conditions, toxic injury, genetic factors and tachycardiomyopathy. Determining the prevalence of NICM is made difficult by heterogeneity in definitions and diagnostic criteria, selection bias in study populations, and geographic variation. Likewise, different studies targeting NICM, or comparing these patients with those with ICM, may report different results due to the inclusion of different types of patients.

The study by Marinheiro et al. published in this issue of the *Journal*[2] asks whether defibrillators are less useful in patients with non-ischemic heart disease. This question was raised by the DANISH trial, which suggested that defibrillator implantation is not of significant benefit for primary prevention patients with NICM.[3] The answer is clear in the first sentence of the discussion: ''We found that implantation of an ICD in patients who had heart failure that was not caused by ischemic heart disease did not provide an overall survival benefit, although the risk of sudden cardiac death was halved with an ICD.''[3] Is it in fact reasonable to ask more of an ICD than merely to protect patients against sudden cardiac death (SCD)? This is the only purpose of this type of device, and the reason that it was developed.

The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) began randomizing patients in 1997 and included a total of 2521 subjects, half of whom had NICM. It is the only randomized trial involving patients with NICM in which a significant benefit with regard to all-cause mortality was reported in association with an ICD. However, this benefit was confined to patients in New York Heart Association (NYHA) class II, and this subgroup effect was not anticipated before data analysis.[4] By contrast, in the DEFINITE trial, patients in NYHA class III derived the greatest benefit from ICD therapy,[5] but no significant reduction in all-cause death was found. DANISH was a contemporary prospective randomized multicenter trial performed in a country with an excellent healthcare system, Denmark. All of the country's ICD implantation centers were included and the

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vast majority of patients received optimal medical therapy: target levels of beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and mineralocorticoid receptor antagonists. Furthermore, 58% of patients received cardiac resynchronization therapy (CRT) in accordance with current European guidelines. This represents a major difference between the DANISH and SCD-HeFT trials, as in the latter only 69% and 20% of enrolled patients received beta-blockers and mineralocorticoid receptor antagonists at baseline, respectively, and none received concomitant CRT. It is thus reasonable to state that the results of DANISH may be a more accurate representation of the true benefits of the ICD in this patient population. The management of heart failure patients with medical therapy and CRT has improved substantially over the last two decades, which in turn has led to a reduction in the overall mortality observed in patients with NICM and, as a result, a reduction in the impact of the ICD. Patients with NICM live longer nowadays, and the cumulative burden of their comorbidities may result in a higher percentage of deaths due to non-cardiac or non-SCD rather than SCD.

CRT has undoubtedly been one of the most important advances in the treatment of heart failure patients with prolonged QRS and severe left ventricular dysfunction. This treatment should be considered before implanting an ICD in patients with NICM, as the evidence supporting CRT in these patients appears to be stronger than that supporting the use of an ICD. In a large European cohort of primary prevention patients receiving CRT, Barra et al. assessed the benefit of adding an ICD according to the underlying myocardial substrate.[6] Of a total of 5307 consecutive patients, 4037 (76.1%) received a cardiac resynchronization therapy defibrillator (CRT-D), while the other 1270 (23.9%) received a cardiac resynchronization therapy pacemaker (CRT-P). The population was well balanced between ICM and NICM (2682 patients with ICM and 2625 with NICM). The primary endpoint of the study was all-cause mortality. A secondary cause-of-death analysis was performed, with a focus on SCD vs. non-SCD and an assessment of the percentage excess mortality related to SCD. The authors found that patients with ICM had a more favorable outcome as a group when implanted with CRT-D compared with CRT-P, whereas in patients with NICM there was no significant difference in survival between those receiving CRT-D or CRT-P. In patients with NICM, the excess mortality of CRT-P compared with CRT-D was due to SCD in only 0.4% of cases, compared with 8% in those with ICM.[6] These findings suggest that CRT-D is superior to CRT-P in ICM, but not in NICM. In the latter, the use of CRT-D was not of significant benefit even in CRT patients whose general characteristics best match those of patients who would typically receive CRT-D, that is, younger patients with fewer comorbidities. These results, recently corroborated by Leyva et al.[7], reinforce the need for appropriate patient selection on the basis of the estimated risk of not only SCD but also non-SCD, which is known to correlate with the degree of the patient's comorbidity and frailty.[8] Patient selection on the basis of left ventricular ejection fraction (LVEF) alone is clearly insufficient and, should we choose to rely on this measure only, we will not be selecting the patients most likely to benefit from an ICD.

The PRE-DETERMINE Biologic Markers and Sudden Cardiac Death Study[9] is an ongoing multicenter prospective cohort study of patients with coronary heart disease with a history of myocardial infarction and/or mild to moderate left ventricular dysfunction who do not fulfill consensus guideline criteria for ICD implantation on the basis of their LVEF and NYHA class. Between July 2007 and November 2013, 5761 patients were enrolled in 135 centers in the US and Canada. The preliminary results suggested that a moderately reduced LV function (LVEF 40%-49%) was more strongly associated with sudden/arrhythmic cardiac death, while age and NYHA class II heart failure were more strongly associated with non-sudden death. As in NICM, younger patients should benefit most from an ICD due to a lower prevalence of the competing risk of non-SCD. Although in this study the arrhythmic death risk was continuously and inversely associated with LVEF, the relative risk was higher in patients with an LVEF of 40%–49%.[9] Given that $\geq$70% of individuals experiencing SCD have an LVEF greater than 35%,[10] integration of a more continuous assessment of LVEF into future risk stratification tools may improve prediction of sudden death.

The study by Marinheiro et al.[2] assessed a real-life cohort of 281 patients who received an ICD over a period of ten years. The authors specifically compared the outcome of patients with ICM (66%) with that of patients with NICM (33%). The latter, who represented only one third of the study group, were younger, had less comorbidity and more often received CRT, which could explain why their outcome was generally better. The lack of statistical significance was also the result of an underpowered analysis. Furthermore, these patients were those with NICM who may still benefit from an ICD, as suggested by the subgroup analysis of the DANISH trial. Another criticism of the present study is that appropriate shocks were included in the analysis. Several studies had demonstrated that the occurrence of appropriate shocks is not directly associated with SCD, because most are triggered by ventricular tachycardia episodes that are not always fatal.

Identification of markers that uniquely discriminate sudden arrhythmic death (SAD) from non-SAD will be required to optimize absolute and proportional risk stratification in subpopulations targeted for sudden death prevention.[9]

Hopefully, in the near future more ICDs will be implanted in patients at risk of SCD, but it will always be necessary to take into consideration the patient's comorbidities, which define the underlying risk of non-SCD.

There will probably be an expansion of the indications for ICD implantation in patients with ICM to less severe degrees of LV systolic dysfunction. However, this may not be the case for NICM. The hope is for improvements in knowledge of the underlying pathophysiology, in medical therapy, in selection for CRT and stratification for SCD, possibly by cardiac MRI or other means.

Perhaps an iPhone app will become available that will quickly and easily calculate our patients' risk of SCD.

Conflicts of interest

The author has no conflicts of interest to declare.

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