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Short Communication

Primary Prevention of Sudden Cardiac Death with Implantable Cardioverter-Defibrillators in Patients with Non-Ischemic Dilated Cardiomyopathy

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Abstract

Life-threatening ventricular arrhythmias, including sustained ventricular tachycardia (VT) and ventricular fibrillation (VF) are common in patients with dilated cardiomyopathy and may lead to sudden cardiac death (SCD). Currently, prophylactic implantation of an implantable cardioverter-defibrillator (ICD) is a class I recommendation in patients with HF and left ventricular ejection fraction (LVEF) ≤ 35%. However, all the data available shows a greater benefit in patients with ischemic heart disease than in patients with non-ischemic heart failure. A 2004 meta-analysis of ICD trials done by Desai AS., *et al.* showed a 31% reduction in all-cause mortality with ICD implantation in patients with non-ischemic dilated cardiomyopathy (NIDCM). Although, most of the trials included in this meta-analysis were performed in the early years of the new millennium, the data became and still is the corner stone of the current American College of Cardiology/American Heart Association guidelines for ICD implantation in patients with NIDCM. However, with all the evidence currently available, can we really base our decisions on daily clinical practice in studies conducted over 15 years ago? Were the patients treated in accordance with the current heart failure guidelines at that time? Can we better individualize the patients with NIDCM that would benefit the most? The implantation of an ICD for patients with NIDCM and reduced ejection fraction should be carefully individualized, being more beneficial in young patients, without comorbidities and with an acceptable life expectancy, with a high risk of presenting malignant ventricular arrhythmias and SCD, and in those with the demonstrated MRI presence of myocardial fibrosis.

Keywords: *Non-Ischemic Dilated Cardiomyopathy; Implantable Cardioverter Defibrillator; Heart Failure; Sudden Cardiac Death; Cardiomyopathy*

Introduction

Non-ischemic dilated cardiomyopathy (NIDCM) is mostly characterized by dilatation and altered contraction of one or both ventricles with impaired systolic function and may or may not develop overt heart failure (HF) [1-4]. Most patients present between the ages of 20 and 60, but it is also seen in children and older adults [2]. Symptoms of heart failure such as progressive dyspnea with exertion, impaired exercise capacity, orthopnea, paroxysmal nocturnal dyspnea and peripheral edema are most common.

Life-threatening ventricular arrhythmias, including sustained ventricular tachycardia (VT) and ventricular fibrillation (VF) are common in patients with dilated cardiomyopathy and may lead to sudden cardiac death (SCD). Currently, prophylactic implantation of an implantable cardioverter-defibrillator (ICD) is a class I recommendation in patients with HF and left ventricular ejection fraction (LVEF) ≤ 35% [3,4]. However, the evidence for a benefit is much stronger for patients with ischemic heart disease than it is for patients with heart failure from other causes. A meta-analysis that included both primary and secondary prevention ICD trials performed in 2004 by Desai., *et al*. [5], demonstrated a 31% reduction in all-cause mortality with ICD use in patients with non-ischemic dilated cardiomyopathy (NIDCM).

Although, most of the trials included in this meta-analysis were performed in the early years of the new millennium, the data became and still is the corner stone of the current American College of Cardiology/American Heart Association guidelines for ICD implantation in patients with NIDCM [5]. However, with all the evidence currently available, can we really base our decisions on daily clinical practice in studies conducted over 15 years ago? Were the patients treated in accordance with the current heart failure guidelines at that time? Can we better individualize the patients with NIDCM that would benefit the most? This manuscript will deal and analyze the available contemporary data on this context with these questions in mind. In order to do so, we searched the MEDLINE, PUBMED, and SCOPUS databases using the following keywords: Non-ischemic dilated cardiomyopathy, implantable cardioverter defibrillator, ICD, heart failure, sudden cardiac death, and cardiomyopathy. Over 600 relevant studies were individualized, however we specially analyzed 6 randomized controlled trials that assessed the efficacy of ICD for primary prevention in patients with non-ischemic dilated cardiomyopathy.

Current trials and studies in NIDCM

Recently, the DANISH trial [6] studied the efficacy of ICDs on mortality in patients with non-ischemic systolic HF. It is the largest trial that investigated the effectiveness of the ICD as primary prevention of SCD in NIDCM. Symptomatic patients with New York Heart Association (NYHA) class II or III, or NYHA class IV if cardiac resynchronization therapy (CRT) was planned, and with non-ischemic systolic heart failure (LVEF ≤ 35%), and an increased level (> 200 pg per milliliter) of N-terminal pro–brain natriuretic peptide were eligible for enrolment. A total of 1116 patient were enrolled. A number of 556 patients were randomly assigned to an ICD with guideline-directed optimal medical therapy (OMT) group, and other 560 patients were assigned to the control group, with a median follow-up of 5.6 years [6]. Overall, the two groups were balanced with respect to baseline characteristics. In both groups, 58% of patients received CRT. The majority of patients received target doses of heart failure medication in accordance with the guidelines that were available at the time of the trial, and among the patients with wide left bundle-branch block (QRS duration, ≥ 150 msec), 93% received CRT. Of interest was that the DANISH trial showed that the prophylactic implantation of an ICD in patients with HF of non-ischemic etiology did not decrease total mortality between both groups (23.4% in the control group vs. 21.6% in the ICD group, HR 0.87, 95% CI 0.68 -1.12), despite the fact that a 50% reduction in sudden death was observed with the implantation of the ICD [6].

In 2017 several meta-analyses were published which included patients with NIDCM receiving an ICD for primary prevention of SCD that deserve to be considered. One of them, carried out by Shun-Shin MJ *et al* [7], analyzed patients from 6 randomized controlled trials (CAT, AMIOVIRT, DEFINITE, SCD-HeFT, COMPANION and DANISH). When considering all six trials collectively, it demonstrated a significant benefit of the ICD on all-cause mortality in patients with NIDCM (24% HR compared with medical therapy alone) [7]. Although the meta-analysis by Golwala H., *et al*. [8], included the same 6 trials analyzed in the paper mentioned above by Shun-Shin MJ., et al. they only assessed the efficacy of ICD as primary prevention in NIDCM. Therefore, they identified only 2970 patients with NIDCM whose pooled analysis showed a significant difference of 23% risk reduction in all-cause mortality in the ICD group. Moreover, even after exclusion of trials that had patients with CRT-defibrillator, they observed a significant 24% reduction in all-cause mortality with ICD therapy. When they compared COMPANION and DANISH which were the trials that utilized a good number of CRT patients, they found a tendency to a greater benefit in all-cause mortality in the ICD group compared to the CRT group, although it did not reach a statistically significant difference [8].

Recently, Bansal N., *et al*. [9] examined the association of primary prevention ICDs with mortality and hospitalization in patients who had HF and an LVEF of 40% or less and chronic kidney disease (CKD) with an estimated glomerular filtration rate of less than 60 mL/min/1.73 m2. A total of 5877 CKD patients were studied. Of which 1556 patients had an ICD implantation and the other 4321 did not have an ICD therapy. They not only found that ICD placement was not significantly associated with improved survival, but also that it was associated with greater risk for further hospitalization due to HF symptoms. These data emphasize the fact that not all HF patients would respond alike to ICD therapy, and also stresses the importance of evaluating carefully and individually the potential risks and benefits of ICD implantation in patients with HF and CKD [9]

The importance of the detection of myocardial fibrosis

Another important fact to consider is the presence of myocardial fibrosis which has been associated with a greater risk of ventricular arrhythmias and SCD in patients with dilated cardiomyopathy (Figure 1) [10-19]. The process of fibrosis develops when there is an alteration of the body's natural wound-healing process, which develops an abnormally elevated collagen production by mechanisms poorly understood. The cells from the connective tissue known as fibroblasts become activated and transform into myofibroblasts. They undergo proliferation under normal conditions of wound healing [10]. This in turn causes increased synthesis of collagen protein in the intercellular space. These healing changes begin as an adaptive process that can later on progress to the genesis of excessive myocardial fibrosis [10]. The presence of myocardial fibrosis, identified by late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) imaging, has been associated with a greater risk of ventricular arrhythmias and SCD in patients with dilated cardiomyopathy [20-28]. Recently, a systematic review and meta-analysis, which included 2948 patients from 29 observational studies, assessed the relationship between LGE and ventricular arrhythmias in patients with NIDCM. The analysis concluded that LGE is strongly and independently associated with ventricular arrhythmias or SCD [11]. These findings are understandable knowing that myocardial fibrosis can cause abnormal excitation of the heart resulting in ventricular arrhythmias. Fibrosis is characterized by the proliferation of non-excitable cardiac fibroblasts and an increase in the collagen fibers secreted by these fibroblasts. This results in the presence of un-excitable obstacles for wave propagation causing unidirectional blocks and slow conduction which favors the development of reentry circuits [12-16].

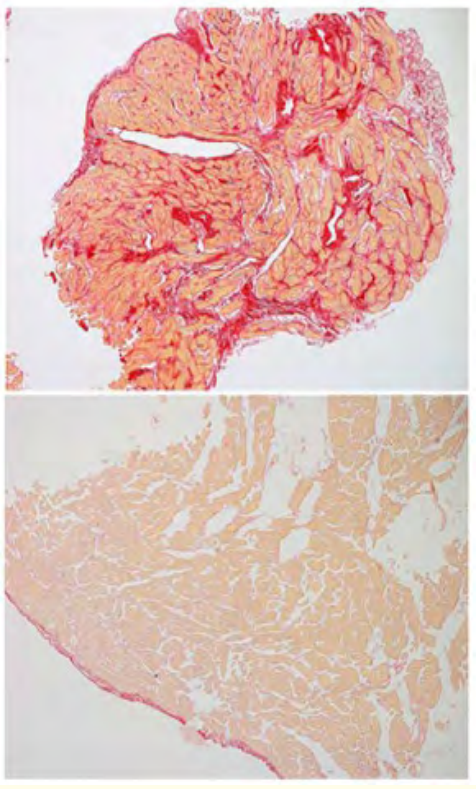

Figure 1: *The upper panel illustrates an example of severe myocardial fibrosis in endomyocardial biopsy detected by picrosirius red staining in a patient with non-ischemic dilated cardiomyopathy and no inducible ventricular arrhythmias. The lower panel depicts the histology of healthy myocardium with a fibrosis area of < 3%. Reprinted with permission from [16].*

Current recommendations for ICD placement based on older studies

Current recommendations for ICD placement as primary prevention of SCD in patients with NIDCM are based on the meta-analysis carried out by Desai., et al. in 2004. The 5 primary prevention trials analyzed were the Cardiomyopathy Trial (CAT) [29], the Amiodarone vs Implantable Cardioverter-Defibrillator Randomized Trial (AMIOVIRT) [30], the Defibrillator in Non-ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) Trial [31], the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) [32], and the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Trial [33]. These are trials that are very difficult to put them all together in the same bag to be analyzed as just one thing since there was substantial qualitative heterogeneity in trial design. The CAT, AMIOVIRT, and DEFINITE trials exclusively enrolled patients with NIDCM, while SCD-HeFT and COMPANION enrolled patients with both ischemic cardiomyopathy and NIDCM. The CAT, AMIOVIRT, and DEFINITE trials randomized patients to ICD or medical therapy in a 2-arm design, but SCD-HeFT and COMPANION had a more complex randomization. Four of the 5 individual primary prevention trials demonstrated a statistically nonsignificant benefit of ICD over medical therapy for all-cause mortality in NIDCM patients. Only the COMPANION trial, which used a device with both cardiac resynchronization and defibrillation capabilities, demonstrated a statistically significant all-cause mortality reduction with ICD over optimal medical therapy. However, in the meta-analysis, the pooled analysis of the 5 primary prevention trials (representing 1854 patients with NICM) demonstrated a statistically significant 31% reduction in all-cause mortality with ICD relative to medical therapy in fixed-effect models.

An important fact to be considered in future guidelines is that, since these above mentioned 5 trials were conducted some 15 years ago, the treatment of patients with HF has changed dramatically. There has been a documented outcome improvement with the introduction of newer pharmacological agents such as angiotensin receptor–neprilysin inhibitors, and the much wider use of mineralocorticoid antagonists, beta-blockers, and statins. These treatments reduce not only total mortality but also specifically the rate of sudden cardiac death. The primary results of a contemporary study the DANISH trial were neutral in all-cause mortality. However, if we consider only the incidence of sudden cardiac death, it was reduced by half with the ICD therapy. The survival benefit with ICD therapy was better in younger patients with NIDCM. Of interest to note is the fact that these results were independent of the utilization of a CRT device. The event rate was lower than that observed in older studies, which reflects the fact that the study population consisted predominantly of outpatients who were in stable condition and who were treated medically in accordance with current HF guidelines, with almost every patient receiving beta-blockers and inhibitors of the renin–angiotensin system and 60% of the patients receiving mineralocorticoid-receptor antagonists. Of all casualties, 31% of deaths were attributed to non-cardiovascular causes. It was observed that higher risk patients may be more likely to benefit from ICD therapy. In addition, those patients who are not expected to die from other causes were found to be good candidates for ICD therapy.

Regarding the meta-analysis results of Shun-Shin MJ., e*t al.* [7], and that of Golwala H., *et al*. [8], we can see again that 5 of the 6 individual trials of primary prevention of sudden death (including DANISH) did not show a significant reduction in total mortality compared to optimal medical treatment. On the other hand, the demonstration of myocardial fibrosis by LGE appears to be a robust predictor of ventricular arrhythmias or SCD across a wide spectrum of patients with dilated cardiomyopathy (Figure 2), including those with mean left ventricular ejection fraction ≥ 35%. Moreover, taking into account the results obtained by Bansal and colleagues, the risks and potential benefits of ICDs should be carefully considered in patients with heart failure and CKD. Therefore, all these findings highlight the need to individualize and clear identify patients who would benefit the most from an ICD implantation.

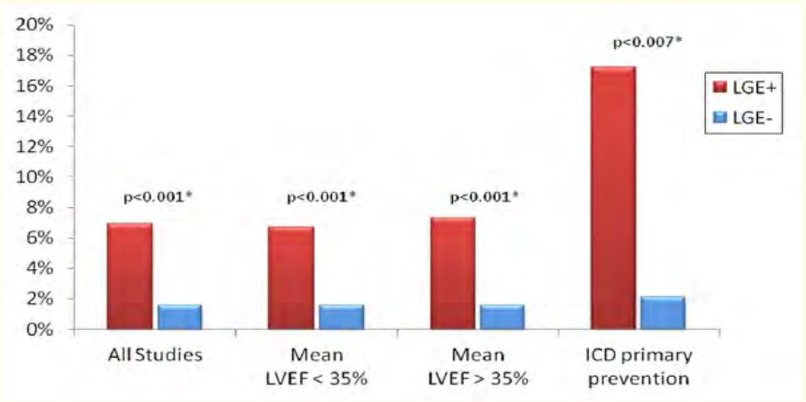

Figure 2: *Annual Rate of the Arrhythmic Endpoint According to Late Gadolinium Enhancement Status The annual event rates were 7.3% of patients with LGE and 1.6% of patients without LGE, respectively (p < 0.001 for weighted risk and rate difference).*
**p values for weighted rate difference. ICD: Implantable Cardioverter-Defibrillator; LGE: Late Gadolinium Enhancement; LVEF: Left Ventricular Ejection Fraction. Reprinted with permission from [11].*

Conclusion

In conclusion, the implantation of an ICD for patients with NIDCM and reduced ejection fraction should be carefully individualized, being more beneficial in young patients, without comorbidities and with an acceptable life expectancy, with a high risk of presenting malignant ventricular arrhythmias and SCD, and in those with the demonstrated MRI presence of myocardial fibrosis.

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