CONTROVERSY

In Non-ischemic Dilated Cardiomyopathy, the Implantable Cardioverter-Defibrillator Remains the First Choice for Primary Prevention of Sudden Death.

En la miocardiopatía dilatada no isquémica el cardiodesfibrilador implantable sigue siendo la primera elección para la prevención primaria de la muerte súbita

AGONIST

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The indication for implantable cardioverter defibrillator (ICD) for primary prevention of sudden death (SD) in patients with non-ischemic dilated cardiomyopathy (NIDCM) has been supported by multiple randomized studies. (1-5) The development of these complex studies was not simple, and initially those with more patients included ischemic and non-ischemic cardiomyopathy, with fewer non-ischemic patients. Some studies individually showed only a trend toward improved survival with ICD implantation, while others lacked the statistical power to meet their outcomes. (1-3)

The methodology used to address this issue was the meta-analysis.

Desai published one of the first studies that pooled data from the initial five studies on this subject: AMIOVIRT, CAT, DEFINITE, SCD-HeFT and COMPANION. (6) The analysis showed lower all-cause mortality: relative risk (RR) 0.69; 95% confidence interval (95% CI) 0.55-0.87; p = 0.002. The meta-analysis result remained consistent even when excluding the COMPANION study, which included cardiac resynchronization therapy (CRT). These findings, together with others, supported the Class I indication for ICD in primary prevention in both American and European guidelines. (7,8)

However, several important factors weakened this indication: the studies enrolled few patients, follow-up periods were short, and, most importantly, the studies were conducted at a time when therapeutic options for heart failure (HF) were limited, including CRT or subsequent pharmacological advances, which have consistently demonstrated a reduction in cardiovascular mortality. Some reports show a reduction in SD of up to 44% between 1995 and 2014. (9)

The Denmark factor

In 2016, the DANISH study was published. After a 5-year follow-up, it demonstrated a 50% relative risk reduction in SD in the ICD group compared to the control group in NIDCM patients: 4.3% vs. 8.2%; hazard ratio (HR) 0.50; 95% CI 0.31-0.82; p = 0.005, confirming the benefit of ICD in reducing SD. There was a trend toward lower cardiovascular mortality; however, all-cause mortality was similar between the two groups. (10)

Therefore, the DANISH study introduced a wake-up call regarding the previously accepted concept of the benefit of ICD in reducing all-cause mortality. Several factors may account for this finding, namely:

- The population was quite specific, exceptionally treated with a very high rate of drug use that is not replicated in daily clinical practice. The CHAMP HF study, a registry of over 3000 patients with HF, reported that 23%, 33% and 67% of the population were not receiving angiotensin-converting enzyme inhibitors, beta-blockers or aldosterone antagonists, respectively, compared to 4%, 8% and 41% in DANISH. (11)

- In 58% of overall population and in 65% of patients over 70 years old, CRT was implanted, indicating the extensive use of this therapy. In addition, 10% of patients had previous CRT or pacemaker implantation. Studies published at that time, such as PARADIGM-HF and DAPA-HF, reported only 7% of patients with CRT. Even in the OFFICE-IC AR registry of the Argentine Society of Cardiology (SAC) published six years later, 1.8% received CRT and 10.7% CRT with defibrillator (CRT-D), confirming that the DANISH study population was highly selected. (12-14)

Following this reasoning, the proper indication

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for CRT, the prevalence of left bundle-branch block (LBBB) in the DANISH study would be at least twice as high as that reported in other studies: 60% in DANISH vs. 30% in OFFICE-IC AR, which included 644 patients with HF and reduced left ventricular ejection fraction (LVEF). (14)

- With such a high rate of use of CRT, and probably of LBBB as well, it is logical to suggest that much of the observed benefit may have been attributable to this therapy. There are no randomized studies demonstrating superiority in terms of mortality when comparing CRT and ICD. Moreover, as shown in the MADIT CRT study, if resynchronization increases LVEF above 35%, the rate of appropriate ICD therapies is significantly reduced (HR 0.44; 95% CI 0.28-0.68; $p < 0.001$). (15) Although excluding these patients in the DANISH analysis did not change the results, the number of cases is undeniably reduced and, thus, the statistical power to analyze the outcome. In other words, ICD was compared to medical therapy in 40% of the population, while CRT-D was compared to CRT in 60%.

- It is interesting to observe that during the first five years, the mortality curves diverged in favor of ICD but converged in a longer follow-up. The DANISH population was older than that included in the DEFINITE and SCD-HeFT studies. (16,17) Therefore, although ICD may have initially reduced mortality, with longer follow-up in an older population, it is reasonable to observe an increase in non-cardiovascular or HF-related mortality, for which ICD has no effect. Indeed, non-cardiovascular mortality accounted for 31% of deaths in DANISH.

- A *post hoc* analysis of the DANISH study confirmed that patients >70 years of age had a significantly longer history of HF (twice as long), worse functional class , higher levels of NT-proBNP (N-terminal pro-B-type natriuretic peptide), greater renal impairment, and a higher prevalence of atrial fibrillation. (18) These findings help explain why the non-sudden mortality was twice as high compared to patients <70 years of age. It is not surprising, then, that the authors highlighted the benefit of ICD implantation in younger patients, in whom the ICD significantly reduced both sudden and all-cause mortality (HR 0.70; 95% CI 0.51-0.96 ; $p = 0.03$).

However...

Immediately after the publication of the DANISH study, nine meta-analyses were published, all of which included DANISH (Table 1). Using all possible combinations, the result was conclusive: ICD significantly reduced all-cause mortality in NIDCM. (19-27)

- Recent prospective registries, such as BIO-LIBRA—presented this year and including 1,000 patients across 50 sites—continue to report a high rate of ventricular tachycardia/ventricular fibrillation (VT/VF) or death during follow-up in patients with NIDCM receiving ICD with or without CRT in primary prevention. At 3-year follow-up, the rate of VT/VF or death remained high: 28% in men and 17% in women. A lower rate of shock was confirmed in patients with CRT and in women. (28)

Like other studies, DANISH did not consider the etiology of NIDCM. This diagnosis includes heterogeneous populations with potentially distinct clinical courses. Indeed, it is well established that certain conditions are associated with a higher rate of SD, such as arrhythmogenic genetic mutations (e. g., lamin, phospholamban, or filamin) or sarcoidosis. (29) Conversely, ventricular dysfunction due to amyloidosis often leads to death from HF or pulseless electrical activity. It is also worth noting that some forms of dilated cardiomyopathy may be caused or worsened by atrial fibrillation or ventricular ectopic beats, whose progression could be modified with appropriate arrhythmia treatment.

Among the risk markers not evaluated in these studies, the presence of left ventricular fibrosis assessed by cardiac magnetic resonance imaging stands out. Observational studies have shown that this finding is associated with a higher incidence of VT/VF, and it may even help identify patients with lower mortality when treated with CRT-D compared to CRT alone. (30) Therefore, several factors beyond LVEF remain to be assessed to refine patient selection for ICD implantation in the setting of primary prevention.

The risks of implanting an ICD

The complications associated with ICD implantation have become increasingly rare. For instance, with modern programming, the annual rate of inappropriate shocks is now below 2%. Moreover, the advent of subcutaneous ICD—which has no endocardial leads and provides efficacy comparable to conventional ICD—has significantly reduced catheter-related infections and late complications. These advancements further support the consideration of ICD implantation for primary prevention in this patient population.

CONCLUSIONS

The latest guidelines from the American Heart Association (AHA), the American College of Cardiology (ACC), and the Heart Failure Society of America (HFSA) for the management of HF assign a Class I recommendation to ICD implantation for the primary prevention of sudden death in patients with NIDCM, whereas the European and Argentine guidelines classify it as Class IIa. Interestingly, all of these guidelines are based on exactly the same studies. (31- 33)

Given the strong support in both national and international guidelines, primary prevention with an ICD in NIDCM should always be considered as indicated. There is no doubt regarding this indication in patients under 70 years of age, and it should also be considered in those over 70, unless reduced life expectancy, advanced HF or severe comorbidities suggest a higher risk of non-arrhythmic mortality.

Table 1. Meta-analysis of the different studies in primary prevention including patients with non-ischemic dilated cardiomyopathy

Author	Studies	Patients (ICD/MT)	Effect on all-cause mortality	Study conclusion
Al-Khatib et al. 2017 (19)	CAT, DEFINITE, SCD-HeFT, DANISH	1874 (937/937)	HR 0.75 95% CI 0.61-0.93 p = 0.008	PP with ICD is effective in reducing all-cause mortality in NIDCM
Narayanan et al. 2017 (20)	CAT, AMIOVIRT, DEFINITE, SCD-HeWWWFT, COMPANION, DANISH	2347 (962/1385)	RR 0.76 95% CI 0.63-0.91 p = 0.003	Significant decrease in all-cause and sudden mortality in NIDCM
Golwala et al. 2017 (21)	CAT, AMIOVIRT, DEFINITE, SCD-HeFT, COMPANION, DANISH	2970	HR 0.77 95% CI 0.64-0.91	Significant decrease in all-cause mortality in PP in patients with NIDCM
Kołodziejczak et al. 2017 (22).	CAT, AMIOVIRT, DEFINITE, SCD-HeFT, DANISH	2992 (1284/1708)	HR 0 .81 95% CI 072-0.91 p = 0.006	Significant decrease in all-cause mortality in NIDCM
Barakat et al. 2017 (23)	CAT, AMIOVIRT, DEFINITE, SCD-HeFT, DANISH	2573 (1284/1289)	HR. 0.79 95% CI 0.64-0.93 p < 0.001	ICD was associated with significant decrease in all-cause mortality in NIDCM
Stavrakis et al. 2017 (24)	CAT, AMIOVIRT, DEFINITE, SCD-HeFT, COMPANION, DANISH	2967 (1553/1414)	HR. 0.78 95% CI 0.66-0.92 p = 0.003	ICD reduced all-cause mortality by 22% in NIDCM
Romero et al. 2017 (25)	CAT, AMIOVIRT, DEFINITE, SCD-HeFT, DANISH	2573	RR 0.84 95% CI 0.71-0.99 p = 0.03	Significant decrease in all-cause and sudden mortality with ICD in NIDCM
Akel et al. 2017 (26)	CAT, AMIOVIRT, DEFINITE, SCD-HeFT, DANISH	2573	HR 0.80 95% CI 0.67-0.96 p = 0.02	ICD reduced all-cause mortality in NIDCM
Masri et al. 2017 (27)	CAT, DEFINITE, SCD-HeFT, COMPANION, DANISH	2867 (1503/1364)	RR 0.76 95% CI 0.64-0.91 p = 0.002	ICD reduced all-cause and sudden mortality in NIDCM

ICD: implantable cardioverter defibrillator; MT: medical treatment; NIDCM: non-ischemic dilated cardiomyopathy; PP: primary prevention; Remaining abbreviations in the text.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

REFERENCES

1. Bansch D, Antz M, Boczor S, Volkmer M, Tebbenjohanns J, Seidl K, et al. Primary prevention of sudden cardiac death in idiopathic dilated cardiomyopathy: the Cardiomyopathy Trial (CAT). Circulation 2002;105:1453–8. https://doi.org/10.1161/01.CIR.0000012350.99718.AD

2. Strickberger SA, Hummel JD, Bartlett TG, Frumin HI, Schuger CD, Beau SL, et al. Amiodarone versus implantable cardioverterdefibrillator: randomized trial in patients with nonischemic dilated cardiomyopathy and asymptomatic nonsustained ventricular tachycardia—(AMIOVIRT). J Am Coll Cardiol 2003;41:1707–12. https://doi.org/10.1016/S0735-1097(03)00297-3

3. Kadish A, Dyer A, Daubert JP, Quigg R, Estes NA, Anderson KP, et al. (DEFINITE investigators) Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med 2004;350:2151–8. https://doi.org/10.1056/NEJMoa033088

4. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, et al. (Companion Investigators). Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. Engl J Med 2004;350:2140–50. https://doi.org/10.1056/NEJMoa032423

5. Køber L, Thune J, Nielsen JC, Haarbo J, Videbæk L, Korup E, et al. (SCD-HeFT Investigators). Amiodarone or an Implantable cardioverter defibrillator for congestive heart failure. N Engl J Med 2005;352:225-37. https://doi.org/10.1056/NEJMoa043399

6. Desai AS, Fang JC, Maisel WH, Baughman KL. Implantable defibrillators for the prevention of mortality in patients with nonischemic cardiomyopathy: a meta-analysis of randomized controlled trials. JAMA 2004;292:2874–9. https://doi.org/10.1001/jama.292.23.2874

7. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. J Am Coll Cardiol 2009;53:e1-e90.

8. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787-847.

9. Shen L, Jhund PS, PetrieMC, Claggett BL, Barlera S, Cleland JGF, et al. Declining risk of sudden death in heart failure. N Engl J Med

2017;377:41–51. https://doi.org/10.1056/NEJMoa1609758
10. Kober L, Thune JJ, Nielsen JC, Haarbo J, Videbaek L, Korup E, et al. Defibrillator implantation in patients with nonischemic systolic heart failure. N Engl J Med 2016;375:1221–30. https://doi.org/10.1056/NEJMoa1608029
11. Greene SJ, Butler J, Albert NM, DeVore A, Sharma PP, Duffy C, et al. Medical therapy for heart failure with reduced ejection fraction. The CHAMP-HF registry. J Am Coll Cardiol 2018;72:351–66. https://doi.org/10.1016/j.jacc.2018.04.070
12. McMurray JJ, Packer M, Desai A, Gong J, Lefkowitz L, Rizkala A, et al. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. for the PARADIGM-HF Investigators and Committees N Engl J Med 2014;371:993-1004. https://doi.org/10.1056/NEJMoa1409077
13. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. DAPA-HF Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381:1995–2008. https://doi.org/10.1056/NEJMoa1911303
14. Thierer J, Perna E, Marino J, Coronel M, Barisani JL, Brasca GD, y cols. Insuficiencia cardíaca crónica en Argentina. OFFICE-IC AR, un registro conjunto de la Sociedad Argentina de Cardiología y de la Federación Argentina de Cardiología. Rev Argent Cardiol 2022; 90:15-24. https://doi.org/10.7775/rac.es.v90.i1.20480
15. Mathias A, Moss AJ, McNitt S, ZarebaW, Goldenberg I, Solomon SD, et al. Clinical implications of complete left-sided reverse remodeling with cardiac resynchronization therapy: A MADIT-CRT Substudy. J Am Coll Cardiol. 2016;68:1268–76. https://doi.org/10.1016/j.jacc.2016.06.051
16. Kadish A, Dyer A, Daubert JP, Quigg R, Estes NA, Anderson KP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med 2004;350:2151-8. https://doi.org/10.1056/NEJMoa033088
17. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225-37. https://doi.org/10.1056/NEJMoa043399
18. Elming MB, Nielsen JC, Haarbo J, Videbæk L, Korup E, Signorovitch J, et al. Age and outcomes of primary prevention implantable cardioverter-defibrillators in patients with nonischemic systolic heart failure. Circulation 2017;136:1772–80. https://doi.org/10.1161/CIRCULATIONAHA.117.028829
19. Al-Khatib SM, Fonarow GC, Joglar JA, Inoue LYT, Mark DB, Lee KL et al. Primary prevention implantable cardioverter defibrillators in patients with nonischemic cardiomyopathy: a meta-analysis. JAMA Cardiol 2017;2:685-8. https://doi.org/10.1001/jamacardio.2017.0630
20. Narayanan M, Vakil K, Reddy VK, Baskaran J, Deshmukh A, Benditt DG, et al. Efficacy of implantable cardioverter-defibrillator therapy in patients with nonischemic cardiomyopathy. A systematic review and meta-analysis of randomized controlled trials. 2017;3:962–70. https://doi.org/10.1016/j.jacep.2017.02.006
21. Golwala H, Bajaj NS, Arora G, Arora P. Implantable cardioverter-defibrillator for nonischemic cardiomyopathy: an updated metaanalysis. Circulation 2017;135:201–3. https://doi.org/10.1161/CIRCULATIONAHA.116.026056
22. Kolodziejczak M, Andreotti F, Kowalewski M, Buffon A, Ciccone MM, Parati G, et al. Implantable cardioverter-defibrillators for primary prevention in patients with ischemic or nonischemic cardiomyopathy: a systematic review and meta-analysis. Ann Intern Med 2017;167:103–11. https://doi.org/10.7326/M17-0120
23. Barakat AF, Saad M, Elgendy AY, Mentias A, Abuzaid A, Mahmoud AN, et al. Primary prevention implantable cardioverter defibrillator in patients with non-ischaemic cardiomyopathy: a meta-analysis of randomised controlled trials. BMJ Open 2017;7: e016352. https://doi.org/10.1136/bmjopen-2017-016352
24. Stavrakis S, Asad Z, Reynolds D. Implantable cardioverter defibrillators for primary prevention of mortality in patients with nonischemic cardiomyopathy: a meta-analysis of randomized controlled trials. J Cardiovasc Electrophysiol 2017;28:659–65. https://doi.org/10.1111/jce.13204
25. Romero J, Chaudhary R,Garg J, Lupercio F, Shah N, Gupta R, et al. Role of implantable cardioverter defibrillator in non-ischemic cardiomyopathy: a systematic review and meta-analysis of prospective randomized clinical trials. J Int Cardiac Electrophysiol: Int J Arrhythm Pacing 2017;49:263–70. https://doi.org/10.1007/s10840-017-0260-8
26. Akel T, Lafferty J. Implantable cardioverter defibrillators for primary prevention in patients with nonischemic cardiomyopathy: a systematic review and meta-analysis. Cardiovasc Ther 2017;35(3) e12253. https://doi.org/10.1111/1755-5922.12253
27. Masri A, Hammadah M, Adelstein E, Jain S, Saba S. Implantable cardioverter defibrillator in non-ischemic cardiomyopathy: a meta-analysis of randomized controlled trials. Cardiovasc Diagn Ther 2017;7:397–404. https://doi.org/10.21037/cdt.2017.06.06
28. Kutyifa V, Gleva MJ, Rosero SZ, Di Biase L, Prasad K, TorresVI, Aaron B, et al. Contemporary outcomes of non-ischemic cardiomyopathy patients with implanted devices (BIO-LIBRA). Heart Rhythm 2025;20:1082. https://doi.org/10.1016/j.hrthm.2023.04.033
29. Kayvanpour E, Sedaghat-Hamedani F, Amr A, Lai A, Haas J, Holzer DB, et al. Genotype-phenotype associations in dilated cardiomyopathy: meta-analysis on more than 8000 individuals. Clin Res Cardiol 2017;106:127–39. https://doi.org/10.1007/s00392-016-1033-6
30. Leyva F, Zegard A, Acquaye E, Gubran C, Taylor R, Foley PWX, et al. Outcomes of cardiac resynchronization therapy with or without defibrillation in patients with nonischemic cardiomyopathy. J Am Coll Cardiol 2017;70:1216–27.
31. Heidenreich PA, Bozkurt B, Aguilar A, Allen LA, Byun JJ, Colvin M, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2022;145:e895–e1032. https://doi.org/10.1161/CIR.0000000000001073
32. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2022; 24:131. https://doi.org/10.1002/ejhf.2333
33. Fernández A, Thierer J, Fairman E, Giordanino E, Soricetti J, Belziti C,y cols.. Consenso de Insuficiencia Cardíaca 2022. Rev Argent Cardiol 2023;91 (Suplemento 2):1-80. http://dx.doi.org/10.7775/rac.es.v91.s2

ANTAGONIST

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Non-ischemic dilated cardiomyopathy (NIDCM) is defined as a structural abnormality of the myocardium not attributable to coronary artery disease, characterized by impaired contractility and a variable prognosis that includes a varying risk of sudden death (SD). It may result from multiple causes, such as tachycardia-induced cardiomyopathy, postpartum cardiomyopathy, Chagas disease, post-myocarditis, and cardiomyopathies associated with certain genetic variants, among other etiologies.

In many of these conditions, the indication for implantable cardioverter defibrillator (ICD) implanta-

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tion for the prevention of SD is supported by limited evidence, generally arising from observational studies with small patient populations. In most cases, the decision is based on the presence of a left ventricular ejection fraction (LVEF) ≤35% along with other risk factors for SD. In this context, it is worth noting that a high proportion of cases of lymphocytic myocarditis, tachycardia-induced cardiomyopathy and postpartum cardiomyopathy show recovery of ventricular function once the acute phase or the underlying condition resolves.

Beyond these entities, NIDCM is likely the result of a prior viral infection or various genetic variants, although in a large proportion of cases, the etiology remains unknown.

For the purposes of this discussion, focus will be limited to the latter group, which also represents the most prevalent form of the condition.

CLINICAL TRIALS AND EVIDENCE

For the primary prevention of SD in NIDCM, Table 1 summarizes the results of clinical trials comparing the ICD group with the control group. The studies included are AMIOVIRT, CAT, DEFINITE, DANISH, and SCD-HeFT. (1-5) None of them demonstrated a statistically significant reduction in all-cause mortality, which remains the only clinically relevant endpoint.

By contrast, in ischemic cardiomyopathy, the MADIT, MUSTT and MADIT II trials showed statistically significant difference in favor of the ICD group compared to the control group, although the DINAMIT and CABG-PATCH trials yielded neutral results. (6-10)

The SCD-HeFT study, which included patients with ischemic and non-ischemic cardiomyopathy in equal proportions, demonstrated a significant difference in the overall population but not in the subgroups analyzed by etiology. (5)

However, to complete the analysis, two other relevant publications should be considered.

A meta-analysis that included the five studies shown in Table 1 demonstrated a significant difference in favor of ICD implantation: odds ratio (OR) 0.78, 95% CI 0.66-0.93, $p < 0.05$. (11)

The other publication refers to the DEFINITE trial. A substudy demonstrated that, in patients recently diagnosed with NIDCM, ICD significantly reduced mortality at 3 months post-implantation. (12)

These findings do not strengthen but rather weaken the evidence supporting ICD. A meta-analysis based on negative trials does not carry the same clinical relevance as one that includes at least a single positive trial. In the case of DEFINITE, this is a post hoc analysis with limited statistical value, which also contradicts current guideline recommendations that state that ICD implantation should only be considered after at least three months of optimal medical therapy.

GUIDELINES AND RECOMMENDATIONS

Although not mandatory for medical decision-making, guidelines provide essential support for healthcare professionals. In general, guidelines developed by subspecialties, such as those for electrophysiology or cardiac pacing, tend to be more likely to indicate interventions than general clinical guidelines.

Table 2 summarizes the recommendation levels for ICD implantation in NIDCM compared to ischemic cardiomyopathy, according to the guidelines of the Argentine Society of Cardiology (SAC), (13) the European Society of Cardiology (ESC), (14) and a recent consensus of the American societies on the appropriate use criteria for ICD, cardiac resynchronization therapy and pacing. (15)

In summary:

- In NIDCM, the indication for ICD implantation can only be considered after three months from the initial diagnosis, provided the patient has received optimal medical therapy and has a life expectancy greater than one year.
- Unlike ischemic cardiomyopathy, there is no Class I recommendation for NIDCM, either in the SAC consensus or the ESC guideline. In the American consensus document, although ICD is listed as an "appropriate option", the score on the appropriateness scale is lower.
- In patients with LVEF ≤35% and functional class I (FC I), the ESC does not consider ICD implantation, and the SAC assigns it a Class IIb recommendation, which—on the ordinal scale of recommendations—is closer to Class III than to Class I.
- In patients with LVEF ≤35% and FC II/III, the Class IIa recommendation indicates that ICD implantation "*should be considered*", which is far from a Class I recommendation, where the intervention is forcefully stated to be "*indicated*".

FROM GUIDELINES TO DECISION-MAKING

How, then, can the above conclusions be translated into clinical practice?

Table 1. Controlled clinical trials in non-ischemic dilated cardiomyopathy. Result expressed as hazard ratio (ICD vs. control) and 95% confidence interval.

AMIOVIRT (1)	CAT (2)	DEFINITE (3)	DANISH (4)	SCD-HeFT (5)
0.69 (0.48-1.00)	0.81 (0.33-1.91)	0.65 (0.40-1.06)	0.87 (0.68-1.12)	0.73 (0.50-1.07)

Table 2. Comparison of recommendations in non-ischemic dilated cardiomyopathy and ischemic cardiomyopathy according to the guidelines from the Argentine Society of Cardiology (SAC), the European Society of Cardiology (ESC) and the consensus statement from American College of Cardiology/American Heart Association (ACC/AHA) on the appropriate use criteria for ICD, CRT and pacing.

NIDCM	SAC	ESC	ACC/AHA
LVEF ≤35%, FC I	IIb	NC	A7
LVEF ≤35%, FC II/III	IIa	IIa	A8
Ischemic cardiomyopathy	**SAC**	**ESC**	**ACC**
LVEF ≤30%, FC I	I	IIa	A8
LVEF ≤35%, FC II/III	I	I	A9

Note: Members of the consensus panel of the American societies rated each clinical scenario using an appropriateness scale from A1 to A9. Scores A7-A9 indicate an appropriate behavior for the specific indication: reasonable, generally accepted, with benefits outweighing risks, and suitable to be included in the treatment plan, although its necessity depends on clinical judgment and patient preferences. FC: functional class; LVEF: left ventricular ejection fraction; NC: not considered; NIDCM: non-ischemic dilated cardiomyopathy

One possible approach is as follows: in the case of a Class I recommendation, the clinician may ask: "*Is there any reason not to indicate this procedure?*". In contrast, with a Class IIa recommendation, the question is definitely different: "*Is there any additional finding that supports the indication*?

From this perspective, the possible factors to consider in patients with LVEF ≤35% and FC II/III (Class IIa) may include:

- Syncope of unknown cause
- Positive electrophysiological study
- Other clinical conditions indicating a high risk of SD
- Late gadolinium enhancement or high-risk genetic variants

The last three factors require further consideration.

What is referred to as "*high-risk clinical conditions*" stems from post hoc analyses, which carry lower statistical value.

Regarding late gadolinium enhancement on cardiac MRI, although observational studies have shown an association with SD, ICD implantation in these patients did not reduce mortality. (16) This may explain why the guidelines do not consider it. (17)

Finally, in patients with LVEF >35%, certain genetic variants *(LMNA, FLNC-truncating variants, TMEM43, PLN, DSP, RBM20)*, associated with a higher incidence of SD are considered for a Class IIa recommendation only if additional risk factors are present. (17) This conclusion reflects the fact that some variants initially thought to indicate a poor prognosis have since been reevaluated. For example, in the case of sarcomeric variants in hypertrophic cardiomyopathy, their prognostic value was questioned in the ESC guideline, which states: "*Variants classified as malignant or benign have different phenotypic expression and variable prognosis*", *("...multiple sarcomeric variants suggested to be associated with a worse prognosis, other cohorts have not consistently reported this association...")*, which then modified the assumption with respect to previous documents *("Task Force does not recommend the use of the presence of sarcomeric variant (s) to guide decisions around ICD implantation for primary prevention")*. (14) Could a similar change in the original positioning be applied in the near future to genetic variants associated with NIDCM?

CONCLUSION

This antagonistic position regarding the use of ICD implantation in patients with NIDCM does not support the notion of an absolute contraindication; however, it is sufficient to consider the indication as non-systematic. As previously discussed, certain associated factors should be present to justify the recommendation. Moreover, in the absence of such factors or if the complementary studies are unavailable, ICD implantation may not be appropriate.

Finally, a reflection on the indication of ICD tailored to the economic conditions of the Argentine healthcare system.

In necrotic ischemic cardiomyopathy, the SAC consensus states that *"the appropriate indication of ICD... in our setting requires the need to select higher-risk groups in which to use this valuable therapeutic resource"*. (13)

If such a conclusion is reached in the context of ischemic cardiomyopathy—where the level of evidence is higher—then the concept must necessarily be extended and reinforced in the context of NIDCM, where both the evidence and the strength of guideline recommendations are clearly lower.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

REFERENCES

1. Strickberger SA, Hummel JD, Bartlett TG, Frumin HI, Schuger CD, Beau SL, et al. Amiodarone versus implantable cardioverterdefibrillator: randomized trial in patients with nonischemic dilated cardiomyopathy and asymptomatic non sustained ventricular tachycardia - AMIOVIRT. J Am Coll Cardiol 2003;41:1707-12. https://doi.org/10.1016/S0735-1097(03)00297-3

2. Bänsch D, Antz M, Boczor S, Volkmer M, Tebbenjohanns J, Seidl K, et al. Primary prevention of sudden cardiac death in idiopathic dilated cardiomyopathy: The Cardiomyopathy Trial (CAT). Circulation 2002;105:1453-8. https://doi.org/10.1161/01.CIR.0000012350.99718.AD

3. Kadish A, Dyer A, Levine J, Quigg R, Estes NA, Anderson KP, et al. Prophylactic Defibrillator Implantation in Patients with Nonischemic Dilated Cardiomyopathy (DEFINITE). N Engl J Med 2004;350:2151-8. https://doi.org/10.1056/NEJMoa033088

4. Lars K, Thune JJ, Nielsen JC, Haarbo J, Videbæk L, Korup E, et al, for the DANISH Investigators. Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure. N Engl J Med 2016;375:1221-30. https://doi.org/10.1056/NEJMoa1608029

5. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225-37. https://doi.org/10.1056/NEJMoa043399

6. Moss AJ, Hall WJ, Cannon DS, Daubert JP, Higgins SL, Klein H, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. N Engl J Med 1996;335:1933-40. https://doi.org/10.1056/NEJM199612263352601

7. Buxton AE, Lee KL, Fischer JD, Josephson ME, Prystowsky EN, Hafley H. A randomized study of the prevention of sudden death in patients with coronary artery disease. N Engl J Med 1999;341:1882-90. https://doi.org/10.1056/NEJM199912163412503

8. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877-83. https://doi.org/10.1056/NEJMoa013474

9. Hohnloser SH, Kuck KH, Dorian P, Roberts RS, Hampton JR, Hatala R, et al. Prophylactic Use of an Implantable Cardioverter-Defibrillator after Acute Myocardial Infarction. N Engl J Med 2004;351:2481-88. https://doi.org/10.1056/NEJMoa041489

10. Bigger JT. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary artery bypass graft surgery. Coronary artery bypass graft (CABG) patch trial investigators. N Engl J Med 1997;337:1569-75. https://doi.org/10.1056/NEJM199711273372201

11. Akel T, Lafferty J. Implantable Cardioverter Defibrillators for Primary Prevention in Patients with Nonischemic Cardiomyopathy: A Systematic Review and Meta-Analysis. Cardiovasc Ther 2017;35:1-8. https://doi.org/10.1111/1755-5922.12253

12. Kadish A, Schaechter A, Subacius H, Thattassery E et al: Patients With Recently Diagnosed Nonischemic Cardiomyopathy Benefit From Implantable Cardioverter-Defibrillators. J Am Coll Cardiol. 2006;20:1-6.

13. Retik E, Eidelman G, López Diez JC, Acunzo R, Aguinaga L, Cáceres Monié C, et al. Consenso de Cardiodesfibriladores. Sociedad Argentina de Cardiología. Rev Argent Cardiol 2021;89:1-46

14. Tfelt-Hansen J, Winkel BG, de Riva M, Zeppenfeld K. The '10 commandments' for the 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J 2023;44:176-7. https://doi.org/10.1093/eurheartj/ehac699

15. Russo AM, Desai MY, Do MM, Butler J, Chung MK, Epstein AE, et al: ACC/AHA/ASE/HFSA/HRS/SCAI/ SCCT/SCMR2025 Appropriate Use Criteria for Implantable Cardioverter Defibrillators, Cardiac Resynchronization Therapy, and Pacing J Am Coll Cardiol 2025;11:1213-85. https://doi.org/10.1016/j.jacc.2024.11.023

16. Kuruvilla S, Adenaw N, Katwal AB, Lipinski MJ, Kramer CM, Salerno M. Late gadolinium enhancement on cardiac magnetic resonance predicts adverse cardiovascular outcomes in nonischemic cardiomyopathy: a systematic review and meta-analysis. Circ Cardiovasc Imaging 2014;7:250-8. https://doi.org/10.1161/CIRCIMAGING.113.001144

17. Sorella A, Galanti K, Iezzi L, Gallina S, Mohammed SF, Sekhri N, et al: Diagnosis and management of dilated cardiomyopathy: a systematic review of clinical practice guidelines and recommendations. Eur Heart J 2025;11:206–22. https://doi.org/10.1093/ehjqcco/qcae109

AGONIST REPLY

I congratulate Dr. Cagide for his analysis and his excellent role of antagonist in this controversy. I agree with several of the points raised, particularly those highlighting the need to identify clinical risk factors that may support or not the decision to indicate an ICD. Non-ischemic dilated cardiomyopathy represents a final common pathway for many conditions, each associated with a different risk of SD. Genetic testing is likely to play a more important role as it becomes more accessible, as highlighted in the latest European guideline recommendations. Although not yet conclusive, myocardial fibrosis analysis may provide more insight in the future.

I believe that the suspected ventricular dysfunction caused by arrhythmias should always be considered by clinical cardiologists. There are reports of LVEF above 35% after ablation of frequent ventricular ectopic beats and atrial fibrillation AF, excluding the patient from the formal indication for ICD implantation.

It is also essential to evaluate the relevant causes of SD, i.e., many patients present with comorbidities or advanced heart failure, making it clear that ICD implantation would not alter the overall prognosis. In this regard, the impact of advanced age in NIDCM is particularly noteworthy, as highlighted by the DANISH study.

Finally, I agree with your comment: "In NIDCM, the indication for ICD can only be considered after three months from the initial diagnosis, provided that the patient has received full medical treatment and life expectancy exceeds one year", to which I would add: after a clinical assessment that weighs other potential risk factors for SD and comorbidities affecting overall prognosis.

Carlos Labadet

ANTAGONIST REPLY

A common point emerging from the arguments presented throughout this document is that the recommendation for ICD implantation for the primary prevention of SD in NIDCM is weaker than in ischemic cardiomyopathy, reflecting a definitively lower level of evidence.

In recent years, international guidelines have incorporated, alongside the strength of recommendation and level of evidence, the concept of cost-effectiveness, based on the economic impact of the proposed intervention on healthcare system. These considerations have recently prompted editorials and updates in specialty journals. In our setting, this issue is undoubt

edly even more relevant.

However, if we now combine both conclusions, it becomes clear that routinely recommending ICD implantation for all patients with NIDCM is clearly unsustainable in our country.

Thus, the conclusion of the Argentine Society of Cardiology guidelines is once again reaffirmed when it recommends "adjusting" the indication for ICD implantation in primary prevention in ischemic cardiomyopathy. This leads us to apply the same reasoning in NIDCM, where, as repeatedly noted, the level of evidence is even lower.

Arturo Cagide