Heart Failure Reviews
https://doi.org/10.1007/s10741-022-10215-z

Is it time to revisit ICD indications?

Amin Yehya[1] · **Jonathan D. Davis**[2] · **Andrew J. Sauer**[3] · **Nasrein E. Ibrahim**[4]

Accepted: 10 January 2022

Keywords ICD · Heart failure · GDMT · Clinical trials

The current ACC/AHA/HFSA 2017 guidelines recommend implantable cardioverter defibrillator (ICD) as primary prevention in patients with left ventricular ejection fraction (LVEF) < 35% despite optimal guideline-directed medical therapy (GDMT) after 90 days to reduce the risk of sudden cardiac death (SCD); however, these recommendations are based on trial data that predate contemporary medical therapy [1]. Published in 1996, the Multicenter Automatic Defibrillator Implantation Trials (MADIT) I trial was the first of these landmark trials (Table 1) [2]. In this trial, patients with history of myocardial infarction (MI) and inducible ventricular tachycardia were randomized to receive ICD versus medical therapy alone. Less than a third of patients were on beta blockers, while approximately 60% on angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blocker (ARB). In 2003, the MADIT II trial demonstrated a 31% reduction in mortality in patients with prior MI and LVEF ≤ 30% in the ICD arm [3]. In the MADIT I and MADIT II trials, only up to 72% of patients were on ACE-I/ARB in MADIT II (compared to only 60% in MADIT I) and only 70% on BB (compared to 26% in MADIT I) [2, 3]. The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) trial in 2005 reported 23% reduction in overall mortality in the ICD group compared to standard therapy alone in patients with ischemic and nonischemic cardiomyopathy [4]. In SCD-HeFT, the use of ACE-I/ARB was higher than that observed in MADIT-II, and the use of digoxin and beta blockers at enrollment and throughout follow-up was similar. As evidenced by the current ACC/AHA/HFSA heart failure treatment guidelines, the clinical trials that led to ICD recommendation enrolled patients with reduced LVEF despite background medical therapy that no longer reflects contemporary standards of optimization.

In this exciting new era of novel drugs and devices in heart failure, there are four pillars of GDMT to reduce morbidity and mortality in patients with heart failure with reduced ejection fraction (HFrEF) [5, 6]. These four pillars are angiotensin receptor-neprilysin inhibitors (ARNI, preferred over ACE-I and ARB), guideline-directed beta blockers, mineralocorticoid receptor antagonists (MRA), and sodium-glucose cotransporter 2 inhibitors (SGLT2i). The development of ARNI and SGLT2i fundamentally changed the management and prognosis of patients with HFrEF [7–9]. A recent analysis of the Prospective Study of Biomarkers, Symptom Improvement, and Ventricular Remodeling During Sacubitril/Valsartan Therapy for Heart Failure (PROVE-HF) trial showed that in ICD-eligible patients, after six and twelve months of therapy with ARNI, EF had improved to > 35% in 32% and 62% of patients, respectively [10, 11]. In another analysis of Prospective Comparison of ARNI [Angiotensin Receptor-Neprilysin Inhibitor] with ACE-I [Angiotensin-Converting Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF), Rohde et al. found that ARNI reduced the risk of SCD independent of ICD use, both in patients with an ICD (HR: 0.49; 95% CI: 0.25 to 0.99) and in those eligible for implantation (HR: 0.81; 95% CI: 0.67 to 0.98) [12]. The benefit was particularly evident in patients eligible for ICD with nonischemic cardiomyopathy ($p < 0.05$). In addition, in a meta-analysis of 34 randomized controlled trials, Fernandes et al. found that SGLT2i use in patients with diabetes was associated with a significant reduction in the risk of SCD (OR: 0.72; 95% CI: 0.54–0.97; P = 0.03) [13]. In patients with HFrEF independent of diabetes, dapagliflozin was found to significantly reduce the risk of SCD

✉ Amin Yehya
amin.yehya@yahoo.com

1 Sentara Heart Hospital, Norfolk, VA, USA

2 San Francisco General Hospital, San Francisco, CA, USA

3 The University of Kansas Health System, Kansas City, KS, USA

4 Inova Heart and Vascular, Falls Church, VA, USA

Published online: 26 January 2022

Table 1 Overview of landmark trials of ICD therapy for primary prevention of SCD: ICM: Ischemic cardiomyopathy, NICM: nonischemic cardiomyopathy, MI: myocardial infarction, LVEF: left ventricular ejection fraction, Hx VT: history of nonsustained ventricular tachycardia, VT: ventricular tachycardia, MedTx: medical therapy.

TRIAL	Patients	ICD + Med Tx	Med Tx alone	Outcome
MADIT I (1996)	ICM (prior MI)	ACE-I/ARB: 60%	ACE-I/ARB: 55%	54% reduction in overall mortality in ICD subgroup
	LVEF < 35%	BB: 26%	BB: 8%	
	Hx VT + induced VT	BB or sotalol: 27%	BB or sotalol: 15%	
	95 ICD: 101 MedTx	Digoxin: 58%	Digoxin: 38%	
MADIT II (2003)	ICM (prior MI)	ACE-I/ARB: 68%	ACE-I/ARB: 72%	31% reduction in overall mortality in ICD subgroup
	LVEF ≤ 30%	BB: 70%	BB: 70%	
	742 ICD: 490 MedTx	Digoxin: 57%	Digoxin: 57%	
DEFINITE (2004)	NICDM	ACE-I/ARB: 97%	ACE-I/ARB: 96%	Reduction in SCD, nonsignificant in all cause mortality
	LVEF <36%	BB: 86%	BB: 84%	
	229 ICD: 229 MedTx	Digoxin: 42%	Digoxin: 42%	
SCD-HeFT (2005)	ICM and NICM	ACE-I/ARB: 94%	ACE-I/ARB: 98%	23% reduction in overall mortality in ICD subgroup
	LVEF ≤ 35%	BB: 69%	BB: 69%	
	847 ICD:829 MedTx: 845 MedTX + Amio	Digoxin: 67%	Digoxin: 70%	
DANISH (2016)	NICDM	ACE-I/ARB: 96%	ACE-I/ARB: 97%	No significant difference in mortality
	LVEF ≤ 35%	BB: 92%	BB: 92%	
	556 ICD: 560 MedTx	MRA: 59%	MRA: 57%	

and ventricular arrhythmias (HR 0.79; 95% CI 0.63–0.99, P = 0.037) [14].

Despite the superior outcomes in patients with HFrEF, most patients are not receiving optimal doses of the medications [15]. In the CHAMP-HF (Change the Management of Patients with Heart Failure) registry of outpatients with HFrEF, less than 1% of eligible patients were receiving target doses of ARNI/ACE-I/ARB, beta blocker, and MRA [16]. Though the recent incorporation of the newest pillar, SGLT2i, increases the complexity of GDMT and may make pharmacologic optimization even more challenging, this "quad therapy" is vastly superior to the traditional BB plus ACE/ARB. Taken in combination, contemporary GDMT—ARNI, BB, MRA, and SGLT2i—as compared to a traditional BB and ACE-I/ARB regimen, has been shown to reduce the risk of heart failure hospitalization (HR 0.32; 95% CI 0.24–0.43), cardiovascular death (HR: 0.50; 95% CI 0.37–0.67), and all-cause mortality (HR 0.53; 95% CI 0.40–0.70) [17]. Contemporary GDMT is estimated to prolong survival, ranging from 6.3 additional years for a 55-year-old to 1.4 additional years for an 80-year-old [17]. The earlier this regimen is initiated, the more benefit patients can accrue. In addition to the survival benefit, GDMT improves LVEF and reduces the incidence of SCD. The benefits are seen within weeks of therapy initiation; thus, the method and timing of initiation should be tailored based on a patient's needs, comorbidities, and preferences to initiate all four pillars and achieve target or maximally tolerated doses most quickly and safely [17]. As we continue to witness new medical therapies that improve outcomes in HFrEF patients, the definition of what constitutes "optimal" GDMT continues to evolve. The current guidelines recommending ICD implantation are founded on data prior to the recent advances in medical management, therefore, a critical reevaluation of the timing and the patients who can benefit from an ICD referral is recommended. We suggest that the current guidelines should revisit baseline GDMT with regard to timing of ICD implantation to reflect the aforementioned changes and advances in GDMT. In the most recent clinical trials including PARADIGM-HF, DAPA-HF, EMPEROR-Reduced only 14%, 26%, 31% of patients had ICD respectively [7–9]. This observation could be due to many reasons, including patients' preference, lack of access or the therapy not being offered, among others. A study to consider is to analyze the subgroups of patients without ICD and on GDMT and propensity-match them with those with ICD and compare their outcomes.

In summary, we do not recommend against ICD use as primary prevention nor are we undermining its pivotal role in helping reduce SCD in patients with HFrEF. We believe that the current advances in medical management might be able to spare patients from an invasive procedure with its known adverse effects and the potential for inappropriate therapies being delivered as well [18].

Funding No funding, grants, or other support was received to assist with the preparation of the manuscript.

Declarations

Conflict of Interest Dr. Yehya received honoraria from Merck, Zoll, Akcea therapeutics and CareDx. Dr. Davis served on an advisory board for Novartis. Dr. Sauer serves as a consultant and has received research support funding from Abbott, Boston-Scientific, Impulse Dynamics, Edwards, Biotronik and Medtronic. Dr. Ibrahim has received honoraria from Cytokinetics, Medtronic, Novartis and Roche and is a consultant for Cytokinetics.

References:

1. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C (2017) 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation 136(6):e137–e161
2. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, Levine JH, Saksena S, Waldo AL, Wilber D, Brown MW, Heo M (1996) Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med 335(26):1933–40
3. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML (2002) Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 346(12):877–83
4. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH (2005) Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 352(3):225–37
5. Al Danaf J, Butler J, Yehya A (2018) Updates on Device-Based Therapies for Patients with Heart Failure. Curr Heart Fail Rep 15(2):53–60
6. Maddox TM, Januzzi JL, Allen LA, Breathett K, Butler J, Davis LL, Fonarow GC, Ibrahim NE, Lindenfeld J, Masoudi FA, Motiwala SR, Oliveros E, Patterson JH, Walsh MN, Wasserman A, Yancy CW, Youmans QR (2021) 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction. J Am Coll Cardiol 77:772–810
7. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR (2014) PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 371(11):993–1004
8. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, Jamal W, Kimura K, Schnee J, Zeller C, Cotton D, Bocchi E, Böhm M, Choi DJ, Chopra V, Chuquiure E, Giannetti N, Janssens S, Zhang J, Gonzalez Juanatey JR, Kaul S, Brunner-La Rocca HP, Merkely B, Nicholls SJ, Perrone S, Pina I, Ponikowski P, Sattar N, Senni M, Seronde MF, Spinar J, Squire I, Taddei S, Wanner C, Zannad F (2020) EMPEROR-Reduced Trial Investigators. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med 383(15):1413–1424
9. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, Böhm M, Chiang CE, Chopra VK, de Boer RA, Desai AS, Diez M, Drozdz J, Dukát A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman CEA, Merkely B, Nicolau JC, O'Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, Verma S, Held C, DeMets DL, Docherty KF, Jhund PS, Bengtsson O, Sjöstrand M, Langkilde AM (2021) DAPA-HF Trial Committees and Investigators. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med 381(21):1995–2008
10. Felker GM, Butler J, Ibrahim NE et al (2021) Implantable Cardioverter-Defibrillator Eligibility After Initiation of Sacubitril/Valsartan in Chronic Heart Failure: Insights From PROVE-HF. Circulation 144(2)
11. Khan MS, Felker GM, Piña IL et al (2021) Reverse Cardiac Remodeling Following Initiation of Sacubitril/Valsartan in Patients With Heart Failure With and Without Diabetes. JACC: Heart Fail 9(2)
12. Rohde LE, Chatterjee NA, Vaduganathan M et al (2020) Sacubitril/Valsartan and Sudden Cardiac Death According to Implantable Cardioverter-Defibrillator Use and Heart Failure Cause. JACC: Heart Fail 8(10)
13. Fernandes GC, Fernandes A, Cardoso R et al (2021) Association of SGLT2 inhibitors with arrhythmias and sudden cardiac death in patients with type 2 diabetes or heart failure: A meta-analysis of 34 randomized controlled trials. Heart Rhythm 18(7)
14. Curtain JP, Docherty KF, Jhund PS et al (2021) Effect of dapagliflozin on ventricular arrhythmias, resuscitated cardiac arrest, or sudden death in DAPA-HF. Eur Heart J 42(36)
15. Sauer AJ, Cole R, Jensen BC, Pal J, Sharma N, Yehya A, Vader J (2019) Practical guidance on the use of sacubitril/valsartan for heart failure. Heart Fail Rev 24(2):167–176
16. Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, Hill CL, McCague K, Mi X, Patterson JH, Spertus JA, Thomas L, Williams FB, Hernandez AF, Fonarow GC (2018) Medical Therapy for Heart Failure With Reduced Ejection Fraction: The CHAMP-HF Registry. J Am Coll Cardiol 72:351–366
17. Vaduganathan M, Claggett BL, Jhund PS, Cunningham JW, Pedro Ferreira J, Zannad F, Packer M, Fonarow GC, McMurray JJV, Solomon SD (2020) Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. Lancet (London, England) 396:121–128
18. Moss AJ, Schuger C, Beck CA, Brown MW, Cannom DS, Daubert JP, Estes NA 3rd, Greenberg H, Hall WJ, Huang DT, Kautzner J, Klein H, McNitt S, Olshansky B, Shoda M, Wilber D, Zareba W (2012) MADIT-RIT Trial Investigators. Reduction in inappropriate therapy and mortality through ICD programming. N Engl J Med 367(24):2275–83