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CLINICAL REVIEW

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Routine DFT testing in patients undergoing ICD implantation does not improve mortality: A systematic review and meta-analysis

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ABSTRACT

Defibrillation threshold (DFT) testing has been an integral part of implantable cardioverter-defibrillator (ICD) implantation to confirm appropriate sensing of ventricular fibrillation and to establish an adequate safety margin for defibrillation. However, there is a lack of evidence regarding benefits of routine DFT testing. Therefore, we performed a meta-analysis to assess its mortality benefit. We searched MEDLINE for studies comparing mortality outcomes in ICD recipients who underwent DFT testing to those who did not. For the second analysis, studies comparing outcomes in patients with high- vs low-energy DFT were included. Odds ratio and standard errors were calculated, and inverse variance method in a random-effect model was used to combine effect sizes. Fifteen studies with 10,975 subjects comparing outcomes in patients who underwent routine DFT testing during ICD implantation and those who did not were included. There was no difference in the group that did not undergo DFT testing with regards to all-cause mortality (OR 0.935; CI 0.725-1.207; P = 0.606), cardiac mortality (OR 0.709; CI 0.385-1.307; P = 0.271), noncardiac mortality (OR 0.921; CI 0.701-1.210; P = 0.554), and arrhythmic mortality (OR 1.152; CI 0.831-1.596; P = 0.396). Percentage of successful appropriate first shocks among the two groups showed no difference. Five studies with 2278 subjects were included in the second analysis comparing patients with low DFT vs high DFT. Patients with high DFT had no significant increase in all-cause mortality compared to patients with low DFT (OR 0.527; CI 0.034-8.107; P = 0.646). Patients requiring higher DFT had no increased all-cause mortality compared to patients with lower DFT. Routine DFT testing during ICD implantation does not confer any significant benefit.

KEYWORDS

defibrillation testing, DFT, ICD, implantable cardioverter defibrillator, mortality

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1 | INTRODUCTION

Implantable cardioverter-defibrillators (ICDs) improve survival in patients with high risk of ventricular arrhythmias and sudden cardiac death.[1-3] Defibrillation threshold (DFT) is defined as the minimal energy required to successfully terminate a ventricular arrhythmia by an ICD. Traditionally, DFT testing had been considered an essential part of ICD implantation, to ensure adequate detection of ventricular fibrillation (VF) or ventricular tachycardia (VT), appropriate verification of system integrity, and the ability of the device to terminate VF/VT with a shock.[4,5] Induction of VF with T-wave shocks and demonstration of a DFT safety margin (DSM) of 10 Joule (J) have been standard practice.[6]

Nevertheless, recent evolution of implant techniques and technology has made deviations from this clinical practice more common. Newer ICDs are much more efficient than in the past, with higher energy devices providing improved safety margin, possessing biphasic shock delivery, active cans, and improved leads.[7,8] DFT testing is not free of inherent complications as well, with one registry reporting death, hemodynamic compromise, emergent intubation, prolonged CPR, strokes, and precipitation of heart failure during and after the procedure.[9] Also, DFT testing under controlled conditions may not replicate the patient's condition during a true, clinical, ventricular arrhythmia resulting from congestive heart failure, ischemia, and electrolyte imbalance, and hence may not be a reliable predictor of outcome.[10]

Although DFT testing has never been reliably shown to improve clinical outcomes, the practice of not performing DFT testing is arbitrary, and its safety is yet unproven given the lack of adequate prospective follow-up studies.[11] While observational studies have shown an increased mortality rate among patients not having DFT testing,[12] several recent studies independently showed that lack of DFT testing was not associated with significant difference in mortality or first shock effectiveness.[13,14] Hence, we performed a systematic review and combined the data using meta-analytical techniques in an attempt to strengthen the level of evidence and provide deeper insight into this issue. In this meta-analysis, we aimed to compare the following: (a) the effect of routine DFT testing in patients undergoing ICD or cardiac resynchronization with defibrillator (CRT-D) implantation vs no DFT testing in the same population on mortality including all-cause, cardiac, arrhythmic, and noncardiac; (b) the effect of high DFT at testing in patients undergoing ICD implantation vs low DFT at testing on all-cause mortality.

2 | METHODS

Our meta-analysis is in accordance with recommendations of the Meta-analysis of Observational Studies in the Epidemiology Group (MOOSE).[15]

2.1 | Inclusion criteria

1. *For meta-analysis comparing mortality in DFT testing vs No DFT testing:* Studies (retrospective and prospective; randomized and nonrandomized) comparing outcomes in patients who received DFT testing to patients who did not receive DFT testing at the time of implant of their ICD, CRT-D, or upgrade were included, if they reported incidence of all-cause, cardiac, noncardiac, and/or arrhythmic mortality. Studies with a mean follow-up duration of at least 12 months to assess mortality were included.
2. *For the secondary meta-analysis comparing mortality in high DFT at testing vs low DFT at testing:* Studies of patients undergoing DFT testing prior to ICD implantation were included, if they reported the incidence of all-cause mortality and compared it between patients requiring high DFT at testing vs low DFT at testing. The arbitrary cutoff for labeling high DFT vs low DFT varied among individual studies with values ranging from 9 to 18 Joules (J) (Table 2).

2.2 | Exclusion criteria

Studies were excluded if they (a) lacked a control group, (b) inadequate data on baseline characteristics, (c) were published only in abstract form, and (d) were non-English studies with no English translation.

2.2.1 | Search strategies

We searched MEDLINE (1966-2015) and Google Scholar using keywords: defibrillation threshold testing, DFT, ICD, implantable cardiac defibrillator, AND mortality, in various combinations. "Related Article" was featured on PubMed, and a manual search of references was also used to identify additional studies. We reviewed the full text of relevant articles. English translations, if necessary, were obtained. Titles and abstracts were independently reviewed by two reviewers (M.A and N.T) and cross-verified for inclusion. Details of the search strategy are reported in Figure 1.

2.2.2 | Data extraction and assessment of study quality

For each included study, all data elements uniformly reported across most studies were extracted by a third reviewer (M.K) and are shown in Tables 1 and 2. The quality of each study was evaluated in accordance with the guidelines of United States Preventive Task Force and the Evidence-Based Management Group.[16,17] The following characteristics were assessed: (a) clear inclusion and exclusion criteria; (b) study sample representative of the population; (c) explanation of sample selection; (d) full specification of clinical and

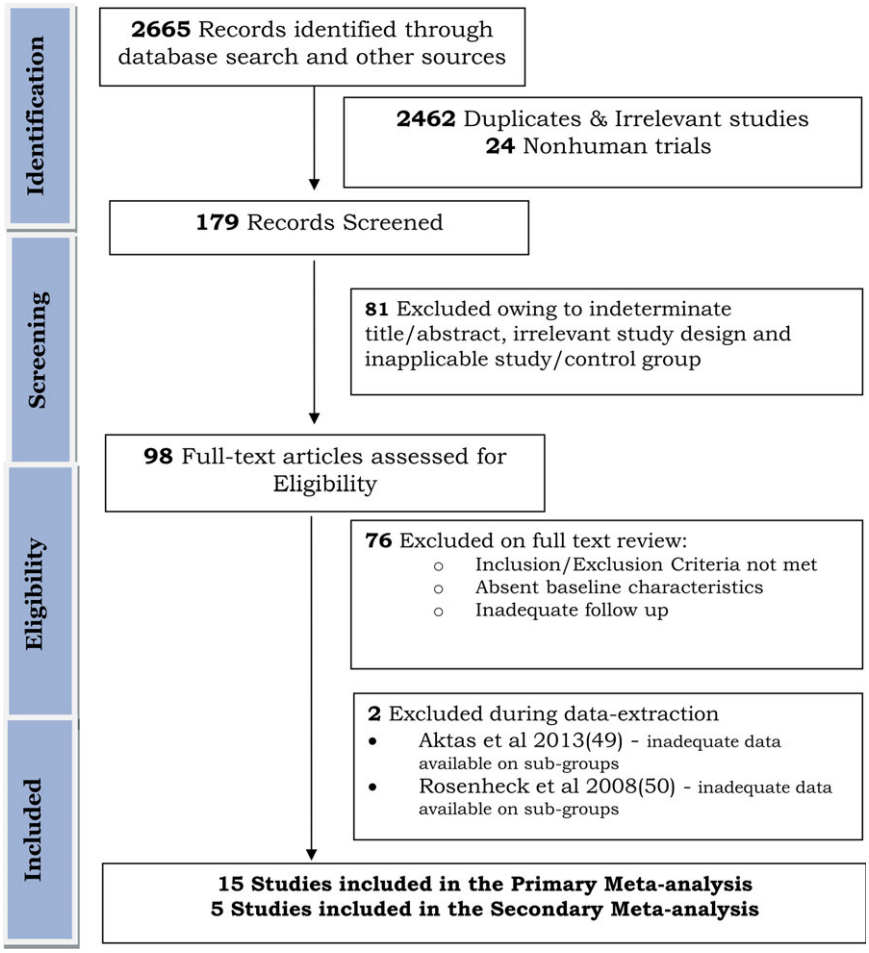

FIGURE 1 Search strategies and screening of studies for inclusion in the meta-analysis

demographic variables; (e) reporting loss of follow-up; (f) clear definition of outcomes and outcome assessment; and (g) adjustment of possible confounders in multivariate analysis. Studies were graded as "poor" if they met 3 or less criteria, "fair" if they met 4-5 criteria, and "good" if they met >5 criteria. The quality assessment of individual studies is reported alongside baseline variables in Tables 1 and 2. All disagreements between reviewers were resolved by consensus.

2.2.3 | Statistical methods

Data were extracted as either odds ratio (OR) or event rate. If hazard ratio was available, it was considered as the best estimate of OR. If both univariate and multivariate analyses were available, data from multivariate analyses were taken. Pooled ORs and 95% confidence intervals (CIs) were calculated using the more conservative DerSimonian and Laird random-effects model.[18] All tests were 2-sided, and a P value <0.05 was deemed significant. Heterogeneity was assessed by the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance. I^2> 50% was considered significant heterogeneity.[19,20] Potential publication bias was assessed by visual inspection of funnel plots, in which standard errors were plotted against log ORs, as well as Eggers regression intercept. All statistical analyses were performed using Comprehensive Meta-Analysis V3 (BioStat Inc., Englewood, NJ).

3 | RESULTS

3.1 | Meta-analysis of DFT Testing vs No DFT Testing

Fifteen studies with 10 975 subjects comparing outcomes in patients who underwent routine DFT testing during ICD/CRT-D implantation and those who did not were included in the primary meta-analysis. Eight studies were retrospective cohort, while remaining seven were prospective with four randomized controlled trials (RCT). Baseline characteristics of the studies included in the primary analysis are shown in Table 1.

The average mean follow-up duration of the studies was 27.6 months. Standard primary and secondary indications for ICD implantation were noted among all studies. Most studies employed a single shock DFT testing protocol where the arbitrary cutoff value was at least 10 J below the maximum output of the implanted

TABLE 1 Baseline characteristics of 15 studies included in the meta-analysis comparing mortality between DFT vs no DFT

Study, year	No. of patients	Study design	Mean follow-up, months	CRT-D, %		Mean age, years		Men, %		Primary prevention, %		LVEF, %		Hyper tension, %		Diabetes mellitus, %		Beta-blockers, %		ACE/ARB, %		Antiarr hythmics, %		DFT Protocol	Quality assessment
				DFT	No DFT	DFT	No DFT	DFT	No DFT	DFT	No DFT	DFT	No DFT	DFT	No DFT	DFT	No DFT	DFT	No DFT	DFT	No DFT	DFT	No DFT		
Arnson et al, 2014[38]	1574	Prospective cohort	12	23	40.3	62.6	64.8	86.5	82.8	55.9	79.4	NA	NA	56.2	60.3	33.3	38.3	84	81	73.4	73.9	26.6	14.6	SS	Good
Ashino et al, 2015[39]	150	Retrospective cohort	111.6	8.2	54.5	55.4	62.5	84.9	88.3	28.7	40.2	53.5	38.8	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SS	Good
Bansch et al, 2015 NORDIC ICD trial[14]	1077	RCT (multicenter)	12	NA	NA	64.9	64.7	82	80.1	81.3	80.8	NA	NA	65	65	34.3	34.1	93.9	93.1	89.8	93.3	13.5	14.7	SS	Good
Bianchi et al, 2009[40]	291	Retrospective cohort	23	NA	NA	69	69	81	90	NA	NA	26	27	NA	NA	NA	NA	72	57	74	76	76	66	SS	Good
Brignole et al, 2012 SAFE-ICD study[11]	2120	Prospective, observational study (multicenter)	24	35	46	66	67	82	79	69	70	32.1	31	44	58	23	28	65	70	66	71	26	23	SS	Good
Calvi et al, 2010[41]	122	Prospective cohort	12	NA	NA	63.9	61.6	83.3	96.3	31	65	31	28	NA	NA	21.2	26	100	100	100	100	NA	NA	SS	Good
Hall et al, 2007[21]	112	Retrospective cohort	17.7	NA	NA	58.8	64.1	84.2	72.2	NA	NA	25.12	20.98	NA	NA	NA	NA	73.7	67.9	78.9	77.4	22.8	29	SD	Good
Healey et al, 2012[42]	145	RCT (multicenter)	24.2	49.3	55.7	65.9	67.9	80	77	95	94	24.7	23.6	57	53	43	27	88	90	NA	NA	17.3	10	SS	Good
Healey et al, 2015 SIMPLE TRIAL[13]	2500	RCT (multicenter)	37.2	29.2	27.9	63	62.6	80.5	81.4	NA	NA	32	31.6	NA	NA	NA	NA	86.8	88	87.2	88.5	15.2	14.6	SS	Good
Kovacevic-Kostic et al, 2013[43]	40	RCT, single center	12	NA	NA	59	56	85	80	NA	NA	26	30	60	60	30	16	100	90	90	80	70	70	SS	Good
Michowitz et al, 2011[44]	256	Retrospective cohort	32	100	100	60	64.3	78	65	76	71.1	23	20.9	40	48	26	33	82	77	86	77	24	29	SS	Good
Pires et al, 2006[12]	332	Retrospective cohort	43.2	NA	NA	64	64.9	80.6	67	NA	NA	26.8	19.8	NA	NA	NA	NA	30.2	56.2	NA	NA	41.9	60.1	SD	Good
Russo et al, 2005[25]	1139	Retrospective cohort	24.5	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SS	Good
Sadoul et al, 2013[45]	904	Retrospective cohort	12	43.7	71.1	61.7	65.4	85.8	81.9	60	79.6	32	26	NA	NA	NA	NA	74.6	63.8	70.4	76.6	26.9	29.8	SS	Good
Codner et al, 2012[46]	213	Retrospective cohort	24	17.5	21.8	61.8	66.9	91.3	84.2	41.3	43.6	29.4	28.8	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SS	Good

LVEF: left ventricular ejection fraction; SS: single shock; SD: step down; DFT: defibrillation threshold.

TABLE 2 Baseline characteristics of 5 studies included in the meta-analysis comparing mortality between low DFT vs high DFT

Study, year	No. of patients	Study design	High DFT cutoff	Mean follow-up, months	Mean age, years		Men, %		LVEF, %		Amiodarone, %		Quality assessment
					Low DFT	High DFT	Low DFT	High DFT	Low DFT	High DFT	Low DFT	High DFT	
Blatt et al, 2008[35]	717	Retrospective analysis of RCT	>10 J	45.5	NA	NA	NA	NA	NA	NA	NA	NA	Good
Roman-Gonzalez et al, 2001[22]	18	Retrospective cohort	>25 J AND DSM <10 J	60	NA	NA	NA	NA	NA	NA	NA	NA	Good
Rubenstein et al, 2013[47]	508	Prospective cohort	>10 J	38.4	60.2	57.15	NA	NA	30	26.8	20.8	21.9	Good
Shukla et al, 2003[36]	968	Retrospective analysis of RCT	≥18 J	6	60.8	60.3	81.7	84.5	38.3	34	27.2	42.7	Good
Theuns et al, 2005[48]	67	Prospective cohort	>9 J	38	60.5	60	34	24	37.4	26.8	13	12	Good

device. Step-down protocol for DFT testing was used only in two studies (Hall et al[21] and Pires et al[12]). Three studies[13,38,39] included patients with hypertrophic cardiomyopathy, while only one study[38] included patients with congenital heart disease. Analysis of the funnel plot for the primary analysis showed no significant publication bias (Figure 1A). In our pooled analysis (Figure 2), we found that patients who did not undergo routine DFT testing prior to ICD implantation had no significant increase in all-cause mortality compared to the patient group that did undergo DFT testing (OR 0.935; CI 0.725-1.207; P = 0.606). A sensitivity analysis of this endpoint including only randomized controlled studies showed a similar result (OR 1.001; CI 0.832-1.204; P = 0.993, data not shown), Also, there was no statistically significant difference among the two groups with regards to cardiac mortality (OR 0.709; CI 0.385-1.307; P = 0.271), noncardiac mortality (OR 0.921; CI 0.701-1.210; P = 0.554), and arrhythmic mortality (OR 1.152; CI 0.831-1.596; P = 0.396) as shown in Figures 3, 4, and 5, respectively. Another subgroup analysis (Figure 2A) comparing the percentage of successful appropriate first shocks among the two groups showed no difference as well (OR 0.611; CI 0.349-1.070; P = 0.948).

3.2 | Meta-analysis of high DFT vs low DFT

Five studies with 2278 subjects were included in the second analysis comparing patients with low DFT at the time of testing vs high DFT. Three studies were retrospective, and two were prospective. Baseline study characteristics are shown in Table 2. Follow-up duration ranged from 6 to 60 months. Individual studies had their own cutoff values for segregating high DFT vs low DFT groups with values ranging from 9 to 18 J (Table 2). Roman-Gonzalez et al[22] is the only study that had its high DFT group labeled as those requiring DFT >25 J along with defibrillation safety margin (DSM) <10 J. Funnel plot for the analysis showed no significant publication bias among the studies (Figure 3A). Our pooled analysis (Figure 6) showed that patients with high DFT at testing had no significant increase in all-cause mortality compared to patients with low DFT (OR 0.527; CI 0.034-8.107; P = 0.646).

4 | DISCUSSION

Our meta-analysis of published prospective and retrospective data shows that patients who did not undergo routine DFT testing during ICD implantation have no evidence of increased all-cause, cardiac, or arrhythmic mortality compared to patients who underwent DFT testing. The results of our analysis that includes two additional studies including a large RCT are consistent with recently published meta-analysis[23] and recent randomized controlled trials[13,14]; wherein, no difference in cardiac mortality was detected. Our meta-analysis also shows for the first time that patients with high DFT at implantation testing have similar outcomes as patients with low DFT.

Defibrillation testing at the time of ICD implantation has been a part of ICD therapy since its inception in 1980. Testing the device

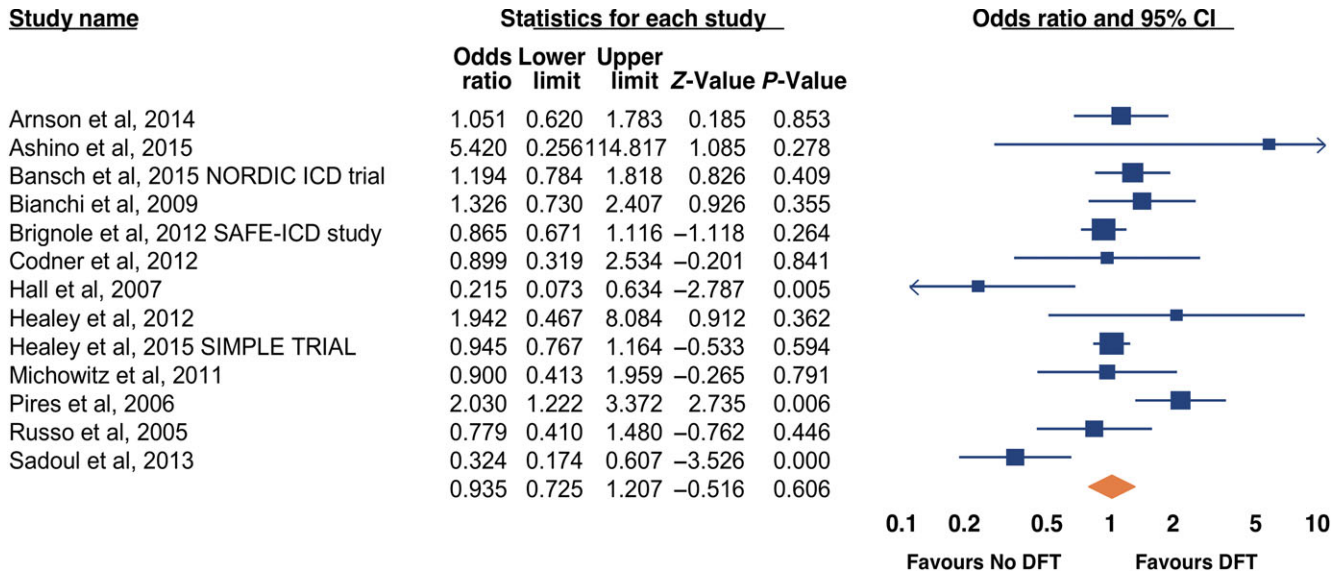

FIGURE 2 Forest plot of all-cause mortality in patients who underwent DFT testing compared to those who did not

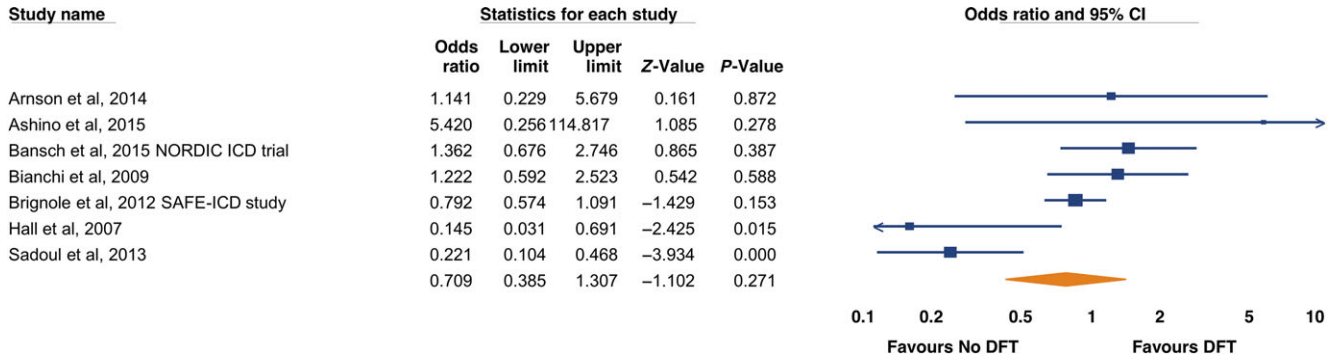

FIGURE 3 Forest plot of cardiac mortality in patients who underwent DFT testing compared to those who did not

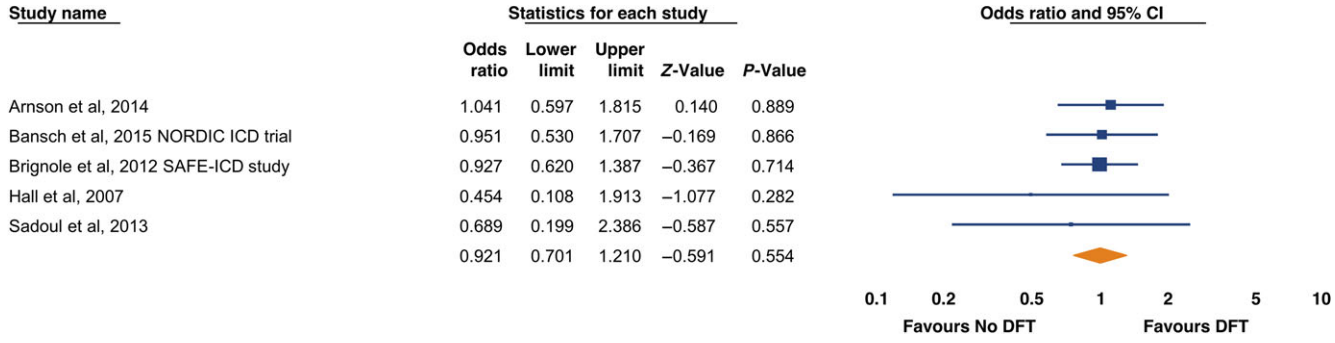

FIGURE 4 Forest plot of noncardiac mortality in patients who underwent DFT testing compared to those who did not

being implanted by confirming that it could detect and terminate ventricular fibrillation seemed reasonable, as the technology was new and the risk of failure was unknown at the time. However, there are no standardized guidelines or high-quality data supporting the fact that DFT testing actually improves mortality or clinical outcomes. Also, with the advent of newer and higher energy devices with active generators and lead refinements over the last three decades, DFT testing is gradually being refrained from. This is evidenced by Stavrakis et al's[24] observation that large retrospective studies are showing an increase in the rate of deferred DFT testing from 5% in the years 1997-2003,[25] to 30% in 2005,[26] and 65% between 2007 and 2010.[27] Common reasons for not performing DFT testing include primary prevention and CRT-D[26,27] atrial fibrillation and oral anticoagulation use,[28] lower ejection fraction,[26,28] and

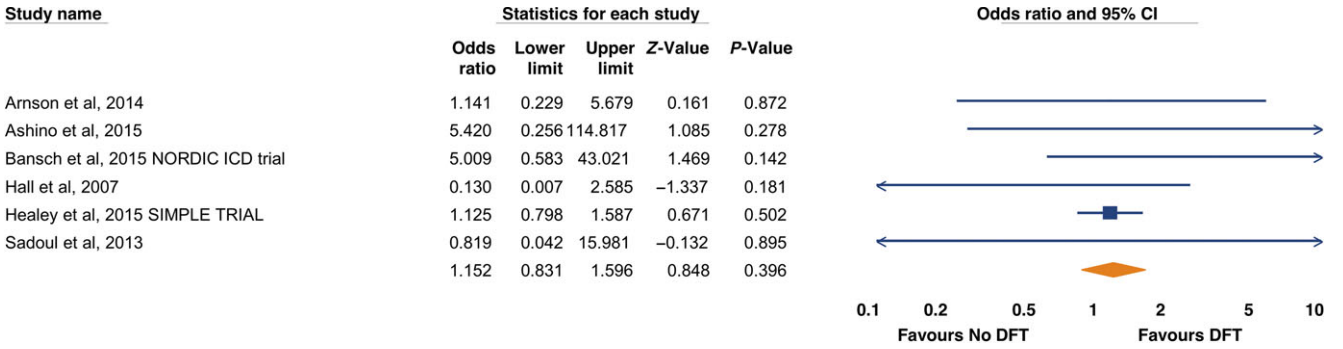

FIGURE 5 Forest plot of arrhythmic mortality in patients who underwent DFT testing compared to those who did not

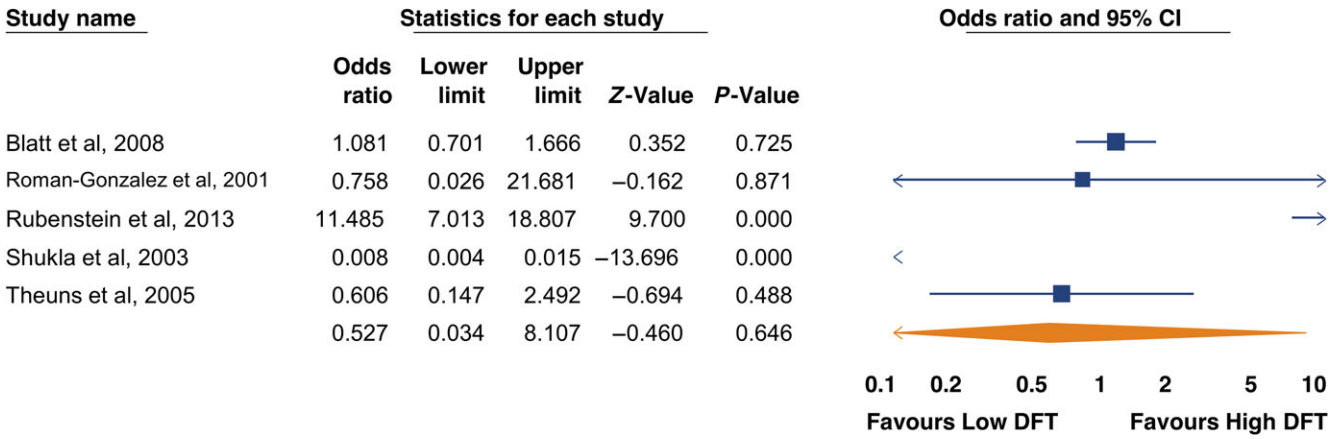

FIGURE 6 Forest plot of all-cause mortality in patients who had high DFT at testing compared to those who had low DFT

center's practice.[27] Furthermore, antiarrhythmic drugs and electrolyte imbalance have shown to influence DFT, making usefulness of routine testing even more challenging. In several previous studies, untested patients appeared to be sicker at baseline than tested patients and may have created a selection bias in the assessment of outcomes of the untested patient groups.[9,12,28]

Some experts have also argued that performing DFT testing is unlikely to reduce sudden cardiac death rate to a value that is clinically relevant (<1%).[11] The reasons for the failure of DFT testing to actually show any improvement in clinical outcomes and mortality are not clear and only speculated at this moment. One common explanation is that ICD shocks per se can lead to adverse cardiovascular outcomes[24] which may counteract any potential benefit of DFT testing. A recent investigation shows that DFT testing is associated with elevated plasma levels of troponin, NT Pro BNP, and markers of apoptosis.[29] This periprocedural acute myocardial damage triggered by DFT test shocks can further be detrimental if more than one shock is required to terminate induced ventricular fibrillation. It is important to note that time interval between these test shocks may be relevant for defibrillation thresholds and any correlation with cardiac damage and overall prognosis needs to be further investigated. Although uncommon, DFT testing has been known to be associated with complications including hemodynamic compromise, stroke, nonresponsive ventricular fibrillation, need for resuscitation, and death.[9,30,31] Another reasoning is that DFT testing under controlled conditions may not replicate the patient's condition during a ventricular arrhythmia (congestive heart failure, ischemia, and electrolyte imbalance) and hence may not be a reliable predictor of outcome.[10] While an argument may be made that even with the current technology, a significant number of patients identifiable by risk scoring systems[32] have high DFT at implantation,[33] given that defibrillation is a probabilistic phenomenon,[34] baseline DFT testing does not have any predictive value on the future shock efficacy.[35] Similar results were found in our study as well where the percentage of successful appropriate first shocks did not differ between groups that underwent DFT testing and did not undergo DFT testing (OR 0.611; CI 0.349-1.070; P = 0.948). There is a paucity of evidence regarding routine DFT testing in patients with hypertrophic cardiomyopathy and congenital heart disease, and the results are contradicting.[51-54] As studies included in this meta-analysis did not have adequate representation of patients with hypertrophic cardiomyopathy and congenital heart disease, it may not be unreasonable to consider DFT testing at the time of ICD implantation in these patients. Nonetheless, the question of whether this particular subset of patients gets any benefit from DFT testing needs to be evaluated by appropriately powered randomized trials.

High DFT at the time of implantation, while associated with a more sicker patient population, may not always be associated with

increased mortality or an increased risk of sudden death.[36] This was confirmed in our study where the group requiring higher DFT at testing had no significant difference in mortality compared to the group requiring lower DFT (OR 0.527; CI 0.034-8.107; $P = 0.646$). With the advances in technology, defibrillation thresholds are lower with good safety margins and remain stable. Even if the safety margin is low, consecutive shocks usually convert the arrhythmia to normal rhythm, and patients are saved from instantaneous arrhythmic death. Low DFT does not guarantee the benefit of a lifesaving shock in case of VF; similarly, high DFT does not always imply a worse prognosis.[37]

4.1 | Limitations

Our finding may have important clinical implications, as it may provide support to the practice of omitting DFT testing, which is becoming increasingly prevalent in real-world practice.[24] However, it should be acknowledged that some of our study designs were observational, retrospective, single-center, and had inherent limitations. In fact, our study highlights the lack of high-quality, randomized controlled trials and warrants one to evaluate the clinical outcomes of DFT testing and further guide the clinician regarding the need for DFT testing in specific populations such as congenital heart disease, hypertrophic cardiomyopathy, and right-sided implants. In such populations, our results should be interpreted with caution and DFT testing can be considered as they were underrepresented in our analysis. Although the indications for ICD/CRT-D implantation were uniformly distributed across studies, a subgroup analysis comparing primary vs secondary prevention could not be performed owing to limited data available. The lack of a standardized DFT protocol across studies in the first analysis and the absence of a particular energy level to segregate high- and low-energy groups in the second analysis are other key limitations to be noted in our study. Furthermore, out of five studies included in the analysis comparing mortality between low and high DFT, only three studies[35,47,48] used more than 9-10J as cutoff value for high DFT which may not reflect a real-life clinical scenario which is another limitation. Finally, the settings in individual studies pertaining to tachyarrhythmia therapy were not uniformly reported and may have been heterogeneous across studies adding to the limitations.

5 | CONCLUSIONS

Patients requiring higher DFT had no increased all-cause mortality compared to patients with lower DFT. DFT testing during ICD implantation does not confer any significant benefit. These results have several potential clinical implications but need to be further explored with large, well-designed prospective randomized trials especially in specific patient populations.

CONFLICT OF INTEREST

Authors declare no conflict of interests for this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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