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REVIEW ARTICLE

Single Lead Implantable Cardioverter Defibrillator with a Floating Atrial Dipole: A Systematic Review and Non-Comparative Meta-Analysis

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ABSTRACT

Background: A DX implantable cardioverter defibrillator (ICD) system consists of an ICD and a shock lead equipped with two ring electrodes positioned in the atrium, referred to as the DX-lead. This system allows the collection of atrial signals using a single lead. Multiple studies on the device have been conducted over more than a decade.

Aims: The aim of this study is to summarise these data in a non-comparative meta-analysis.

Methods: A systematic literature review targeting publications on studies including a certain type of ICD, VR-DX ICD, was conducted. Subsequently a meta-analysis of proportions was conducted. Endpoints selected for evaluation included p-wave amplitude (at day 0, <6 months, 6-12 months and >12 months), appropriate and inappropriate shock rates, and all-cause mortality.

Results: One randomised controlled trial, 11 prospective cohort studies and registries, and two retrospective studies were selected for analysis. P-wave amplitudes were consistently in a range where they can support clinical decision making across studies and remained stable over a follow-up of up to two years. Pooled shock incidence was consistent with industry standard for appropriate (10.7%) and inappropriate shocks (2.4%) across studies. All-cause mortality was at an average of 5%, increasing, as expected, with duration of study follow-up. Like shock results, mortality was within the expected range.

Conclusion: This analysis shows that the VR-DX ICD system works reliably and provides an added benefit compared to single chamber ICD in the form of atrial sensing. Atrial view without requiring a second lead provides clinicians with an attractive, hardware-sparing option for the continuous monitoring of atrial activity.

Keywords: DX ICD; implantable cardioverter defibrillator; atrial fibrillation; atrial burden monitoring; atrial dipole

Introduction

Implantable cardioverter defibrillators (ICDs) have been a mainstay of ventricular tachycardia and ventricular fibrillation therapy for decades, as key prevention of sudden cardiac arrest and death. They also enable collection of data from the ventricle directly and, in the case of dual chamber ICDs, also from the atrium to allow for optimisation of therapy through best possible programming. Some patients receive a dual chamber ICD without having an atrial pacing indication, bringing with it the increased risks of adverse events associated with implantation of a second lead. [1] The implantation of an atrial lead potentially could have a significant negative clinical impact, such as an increased risk of hospitalisations, thromboembolic events and death. [2] Additionally, lead extractions, should they become necessary, are associated with a high risk of complications, especially in women. [3] Yet clinicians are rightfully interested in atrial sensing to enhance understanding of cardiac activity, support the diagnosis of atrial tachyarrhythmias, and provide a continuous assessment of the atrial arrhythmia burden. All these ultimately support therapy decision making. This is particularly important as the association between high atrial fibrillation (AF) burden and stroke and development of heart failure is well established. [4] The detection of AF may also be particularly pertinent today as research shows a potential link between a COVID-19 infection and an increased risk of tachyarrhythmias. [5]

VR-DX ICD is a single lead ICD system where an atrial dipole is positioned on the right ventricular shock lead offering atrial sensing. Amplification and filtering of the signal from the atrial dipole is optimized to lead to reliable atrial information, distinguishing it from traditional VDD systems (ICD systems utilizing far-field sensing to sense the atrium), due to the limitations of atrial input stages used in e.g., VDD pacemakers (fixed sensing thresholds). [6] This provides a unique hardware feature for patients where atrial pacing is not required, but information from the atrium is desired to enable early atrial diagnostics. VR-DX ICD has been available for over a decade and a comprehensive body of evidence has been created over this time, but no summary of the available body of data is available. The aim of this research is to summarise the data on key outcomes across a comprehensive number of studies in the form of a meta-analysis (MA). It created a summary of non-comparative outcomes for atrial sensing amplitude over time, appropriate and inappropriate shock rates, and all-cause mortality associated with the VR-DX ICD system.

Methods

SYSTEMATIC LITERATURE REVIEW METHODS

The systematic literature review (SLR) and MA were performed in adherence to the Population, Intervention, Comparison and Outcome (PICO) framework, PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and MOOSE (Meta-analysis of Observational Studies in Epidemiology) checklist on the reporting quality of MAs.

The review considered for inclusion clinical trials and observational studies evaluating VR-DX ICD in adults with a primary or secondary prevention indication for an ICD or adult patients with heart failure requiring cardiac resynchronisation therapy with defibrillator (CRT-D). Case studies or case reports were not considered for inclusion. The search was limited to full-text articles in English published since 2000 and conference abstracts published since 2020 as it was assumed that data presented at older conferences had since been published in peer-reviewed journals. No restriction by geography was applied. Systematic searches were conducted in MEDLINE, EMBASE, Cochrane Databases and the Database of Abstracts of Reviews of Effects on 27th September 2022. Grey literature searches were conducted through targeted searches of relevant conference publications, online publications not indexed in searched databases, reference checking of previously published SLRs and data on file. The search strategy was designed using a combination of medical subject (MeSH in MEDLINE and Emtree in Embase) headings and keywords. Title screening, abstract and full-text review were conducted by two independent reviewers (HEA and NM), with conflicts resolved by a third, senior reviewer (AF). Data from the included studies were extracted into pre-approved extraction templates (HEA and NM), with all extractions validated by a second reviewer (AF). Quality assessment (i.e., risk of bias assessment) of included studies was done using the Mixed Methods Appraisal Tool (MMAT) [7].

META-ANALYSIS METHODS

A feasibility assessment was conducted to determine which studies were eligible to be included in the MA. This assessment focused on the similarity of reported outcomes across studies, which included considerations regarding the definition, measurement, assessment timepoint and/or follow-up durations. Studies were also compared based on their study patient baseline, and treatment characteristics, to identify any significant differences that would preclude their inclusion in the meta-analysis.

Endpoints selected for MA included mean or median p-wave amplitude (at day 0, <6 months, 6-12 months and >12 months), appropriate and inappropriate shock rates, and all-cause mortality. The endpoints were chosen according to their availability across a maximum number of studies to provide an overview of key functions and outcomes of the device. A MA of proportions was employed to generate pooled estimates of relevant outcomes associated with VR-DX ICD system. [8] A random-effects (DerSimonian-Laird method) [9] model was chosen to account for the expected heterogeneity across included studies. [8] All MA were run in the statistical program R (Version 4.0.2).

P-wave amplitude was meta-analysed using mean values (i.e., raw means) and corresponding standard deviations (SDs) in the main analysis. A meta-analysis of the median values was not feasible given the considerable differences in patient populations and follow-up durations across the studies reporting this outcome. Proportional MA of appropriate and inappropriate shocks used the number of patients with an event over a total number of patients with the VR-DX ICD, where the proportional values and corresponding standard errors (SEs) were used to calculate the pooled effect estimates per outcome. Since data on shocked patients were not presented per annum by included studies, analyses per annum were explored, but not considered feasible. The presented analyses of shock rates were thus based on the assessment timepoints reported by the studies. Measures of variability (i.e., 95% confidence intervals [CIs]) were generated based on the SEs and SDs of the proportions and means, respectively. Where studies presented zero events, a zero-correction was applied in the proportional MA in line with the Cochrane Handbook. [8] This means that the denominator was increased by one, and the nominator by 0.5 to avoid biased outcomes.

Levels of heterogeneity (T^2, H^2, I^2 parameter) were identified and measured per outcome. Heterogeneity levels (i.e., I^2 parameter) were assessed based on the thresholds given in the Cochrane Handbook. [8] Sensitivity analyses were conducted to allow evaluation of factors potentially driving heterogeneity. Heterogeneity analyses included removal of studies with lowest quartile of study participants, removal of largest study, removal of retrospective studies and removal of CRT-D study where applicable.

The terminology for 'VR-DX ICD' was chosen throughout this publication to enable clear distinction from standard VDD technology.

Results

EVIDENCE REVIEW

Literature searches yielded 5,525 results from online databases and 20 results from grey literature searches. After removal of duplicates, 3,211 titles were screened, 399 of which were selected for full-text review. The full-texts of two articles could not be retrieved and only 397 records were further assessed for eligibility in line with the selected study requirements. Seventeen studies were selected for inclusion in the SLR, with an additional two records identified from grey literature searches, bringing the total number of included records to 19 (accounting for 17 unique studies). [6,10-25] Selected studies included one randomised controlled trial, 14 prospective cohort studies and prospective registries, and two retrospective studies. Data for one study was partially collected from on file records in the form of a manuscript that had been accepted for publication in a peer reviewed journal. Three of the included articles (Biffi [2017], Biffi [2020] and Niehaus [2003]) [10,16,21] only reported relevant outcome data for sensing amplitude, albeit median instead of mean values. Given considerable differences in patient characteristics, such as the distribution of patients by sex, NYHA stage and underlying heart condition, as well as follow-up durations a meta-analysis of median sensing amplitudes was not considered feasible, resulting in the formal exclusion of the three above mentioned studies from the analysis.

Studies included in the analysis were assessed to be of acceptable quality and reporting standards for inclusion into the study as per MMAT. The selection and review process are described in Figure 1. An overview of the studies included in the final analysis is provided in Table 1.

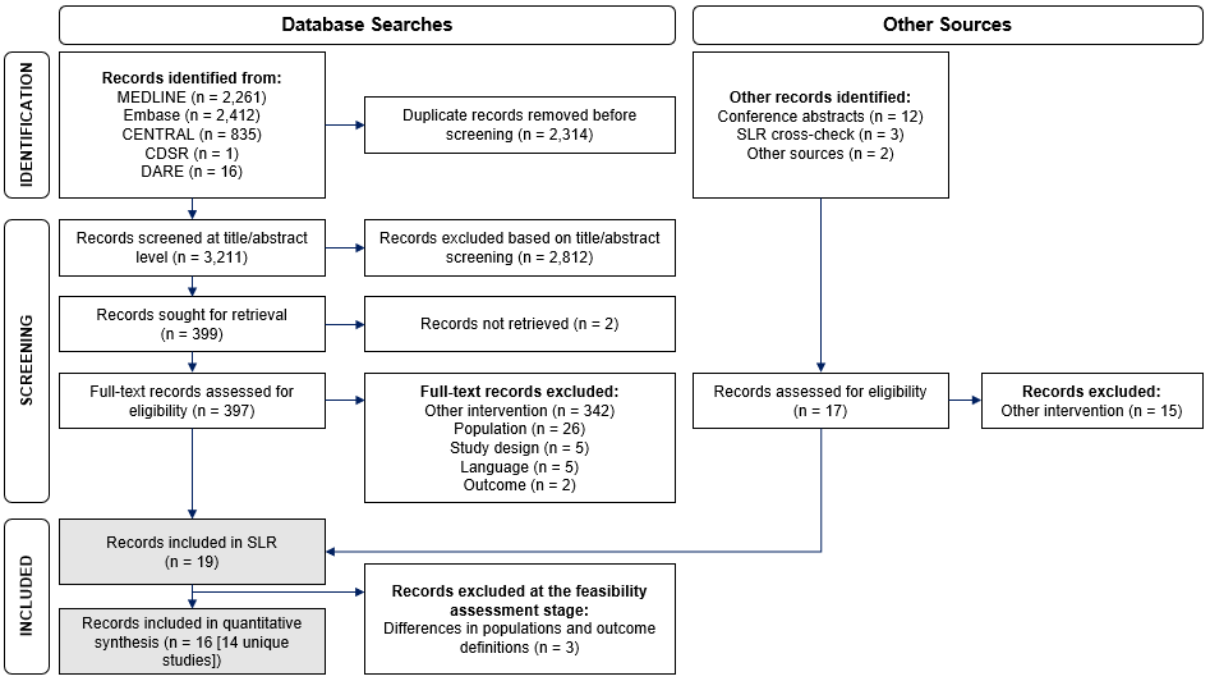


Figure 1. PRISMA flow diagram of systematic literature review selection process [26]

Table 1. Descriptions of studies selected for the meta-analysis [6,11-15,17-20,22-25] (NR – Not reported)

Study	Study Design	# of Patients	Mean/ median follow-up (days)	Country	Population	Data Collection Years
Schuchert (2003)	Prospective, enrolment strategy not reported	15	NR	Germany	Primary or secondary prevention	NR
Sticherling (2011)	Prospective, randomized	265	370 ± 104	Germany, Switzerland	Primary or secondary prevention	NR
Stazi (2012)	Prospective, enrolment strategy not reported	43	384 ± 244	Italy	Primary or secondary prevention	2008-2010
Safak (2013)	Prospective, enrolment strategy not reported	116	150 ± 57 (mean) 171 (median)	International	Primary or secondary prevention	2010
Iori (2014)	Prospective, enrolment strategy not reported	13	200	Italy	Primary or secondary prevention	2013-2014
Worden (2016)	Retrospective, consecutive patient enrolment	35	432 ± 197	US	Primary or secondary prevention	2013-2016
Michalak (2017)	Prospective, consecutive patient enrolment	25	90-180	Poland	Primary or secondary prevention and sinus rhythm	2015-2016
Kurt (2018)	Prospective, comparative, consecutive patient enrolment	212	697 ± 392	Germany	Primary prevention single-chamber ICD (de novo implant or replacement)	2011-2018

Study	Study Design	# of Patients	Mean/ median follow-up (days)	Country	Population	Data Collection Years
Safak (2018)	Prospective, enrolment strategy NR	93	693	Germany	NR	2010-2014
Marai (2019)	Prospective, consecutive patient enrolment	73	360	Israel	Primary or secondary prevention single-chamber ICD	2013-2016
Matrix (2019)	Prospective, enrolment strategy NR	2,054	677 ± 173 (mean) 727 (median)	International	Primary or secondary prevention single-chamber ICD	2013-2018
Thomas (2019)	Prospective, case-control, enrolment strategy NR	450	360	US	Primary or secondary prevention ICD	2014-2017
Shaik (2020)	Retrospective, comparative, enrolment strategy NR	240	468	US	Guideline indication for CRT-D	NR
Gwag (2021)	Prospective, consecutive patient enrolment	86	522 ± 237	South Korea	Primary or secondary prevention ICD	2014-2020

PATIENT CHARACTERISTICS

Patients across trials were predominantly male, as common in trials of cardiac implantable devices, and comparable in age, except for CRT-D trials where patients were older. The same applied to average left ventricular ejection fraction, which averaged 34.9% across non-CRT-D studies. The majority of patients were implanted with a primary prevention indication except in Gwag (2021) [24], where the majority of patients received an implant for secondary prevention. Rates of comorbidities and baseline medication (not displayed) were similar across studies. Patient characteristics are graphically displayed in Figure 2.

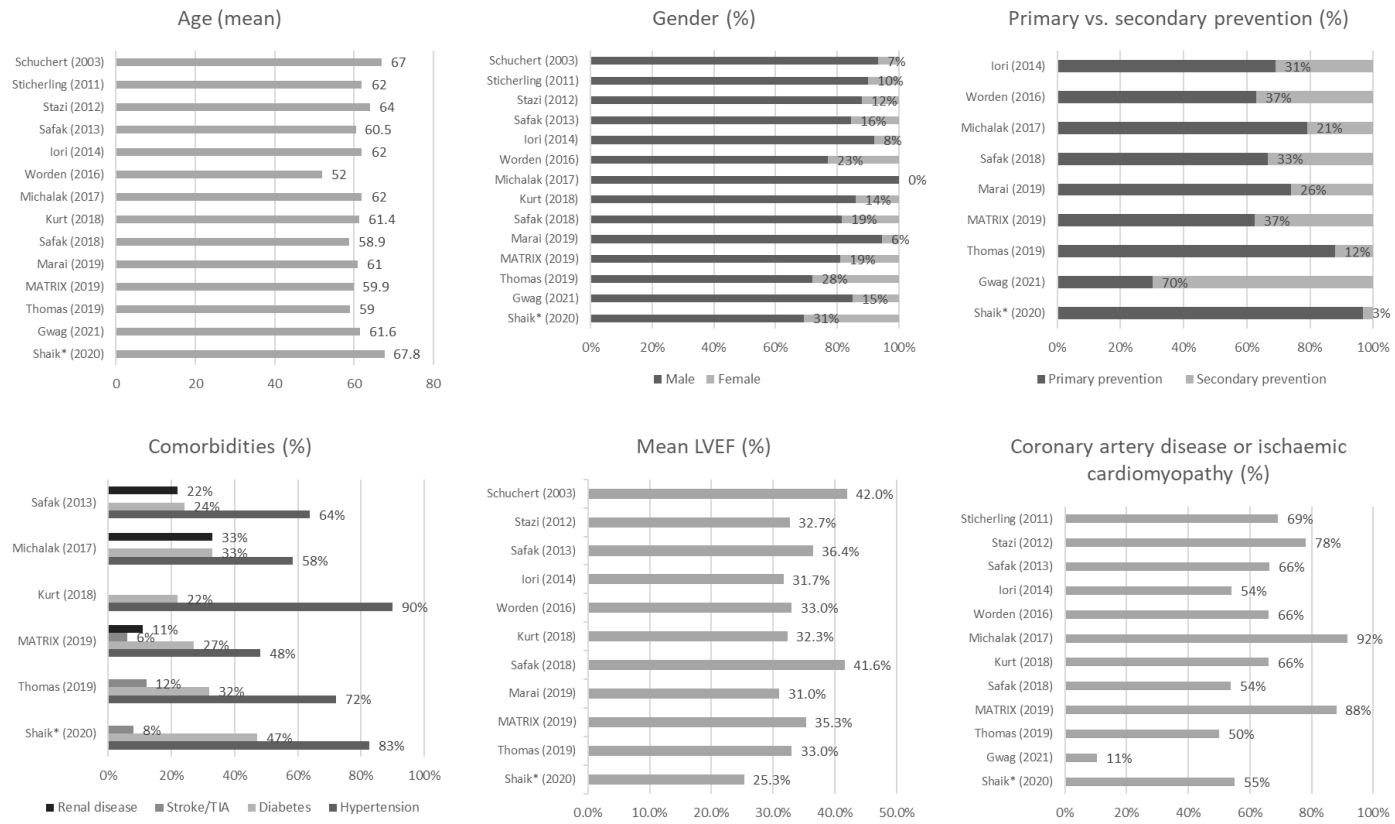


Figure 2. Outline of patient characteristics as reported in the studies. Where data were not reported in a study, the study is not displayed in the respective chart; (*) Indicates study with CRT-D patients; LVEF = left ventricular ejection fraction

P-WAVE AMPLITUDE

In total, the analysis reports pooled results from 14 studies published over 19 years and involving more than 3000 patients. Results for mean p-wave amplitude were gathered from 11 studies reporting values from day 0 (Fig. 3A), months 3-6 (Fig. 3B), 6-12 (Fig. 3C) and >12 months (Fig. 3D). Overall pooled results showed steady atrial sensing at day 0, 6 months, 12 months, and 24 months. P-wave amplitudes were consistent over time across studies, irrespective of the proportion of patients with AF included in the studies. No mean p-wave amplitude reported was lower than 2mV (reported on day 0) [14] and overall p-wave amplitudes converged around a mean of 4-6mV after 6 months and up to 24 months follow-up. P-wave amplitudes showed a trend of being initially lower in male patients (at day 0 and at 3-6 months), however this difference vanished over time. Sensitivity analyses excluding very large studies, retrospective studies, or studies of the smallest quartile (by patients included) did not significantly change results (see Figures 4 to 8).

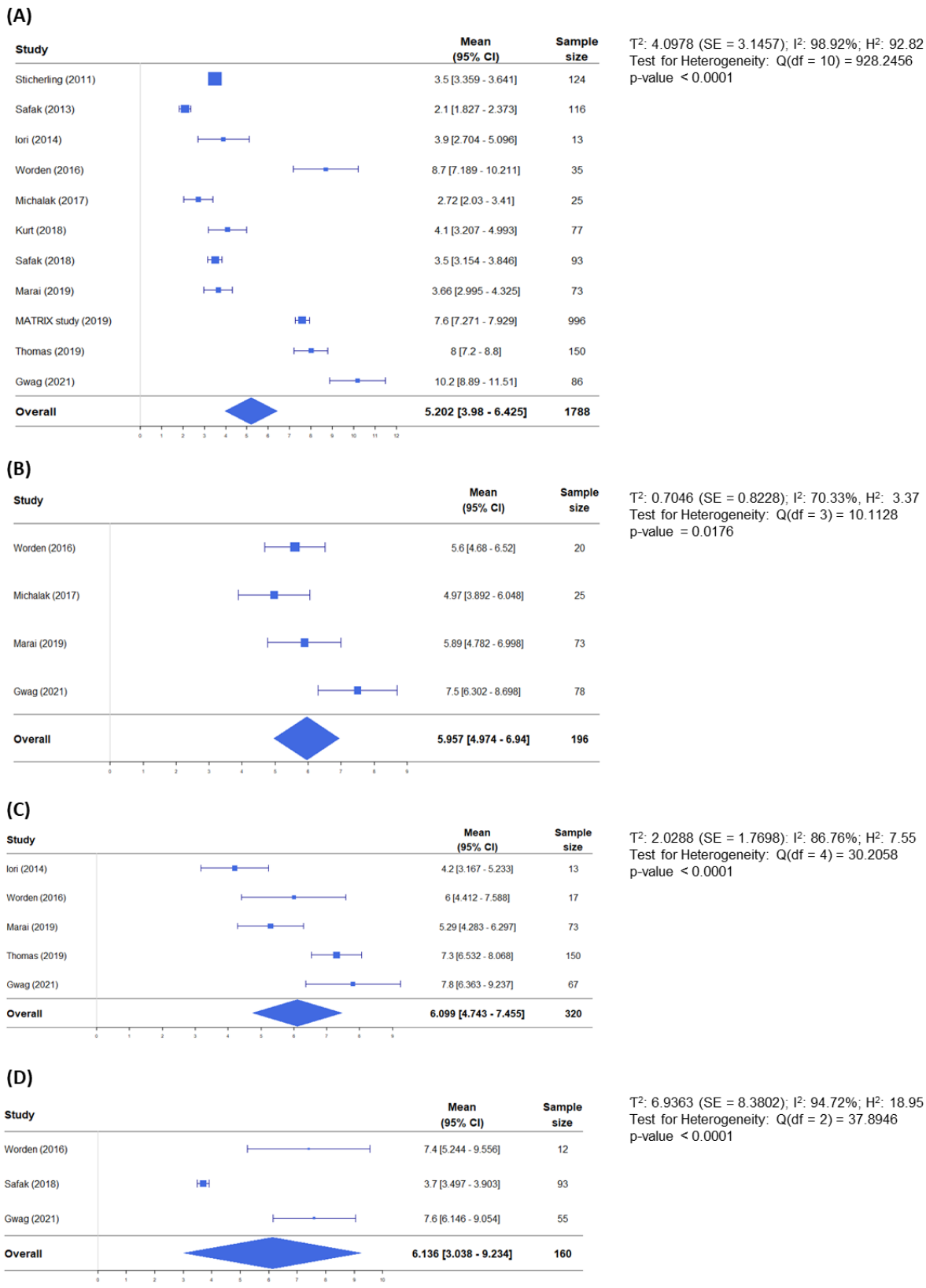
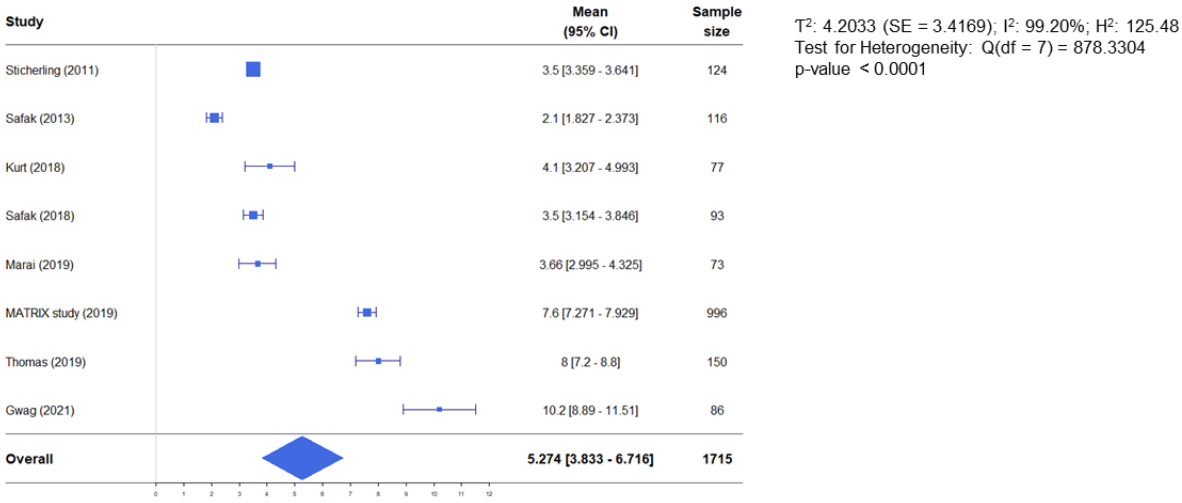


Figure 3. (A) Atrial sensing mean (ASM) day 0, (B) ASM 3-6 mos, (C) ASM 6-12 mos, (D) ASM >12 mos



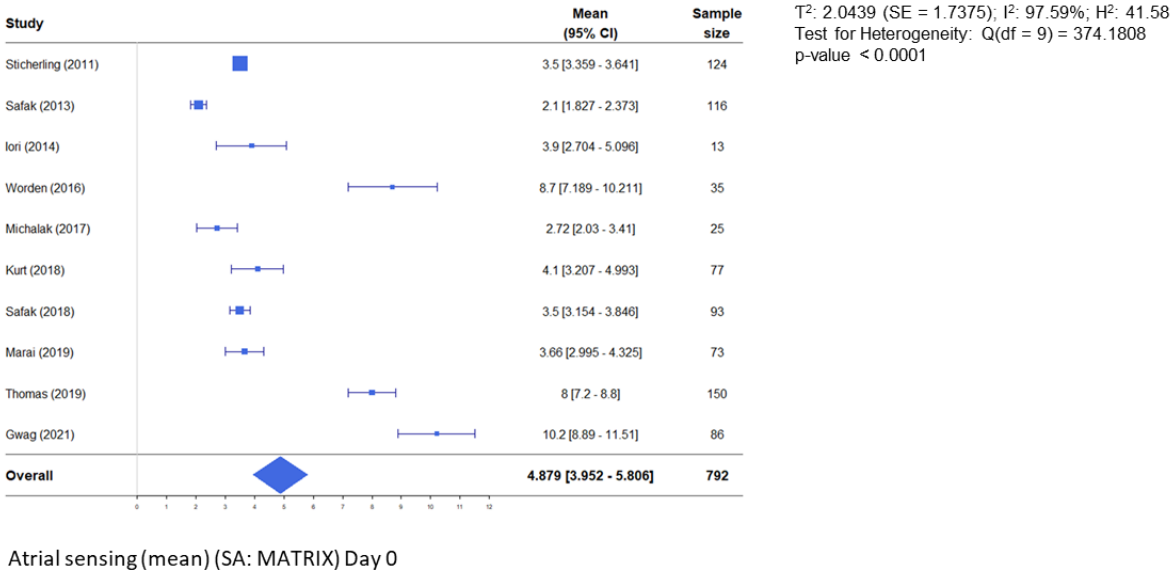
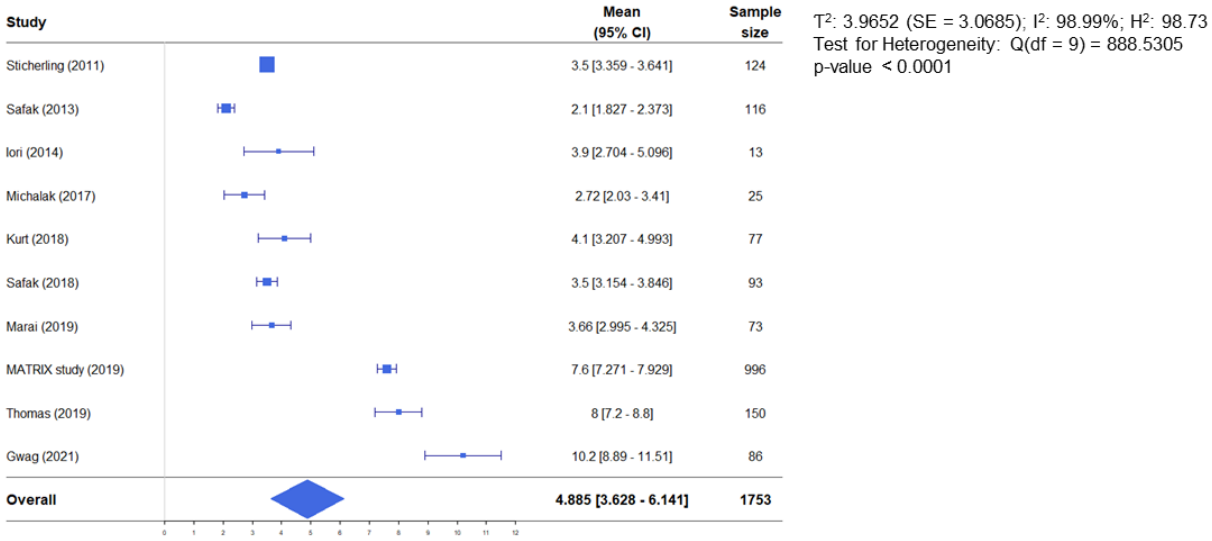
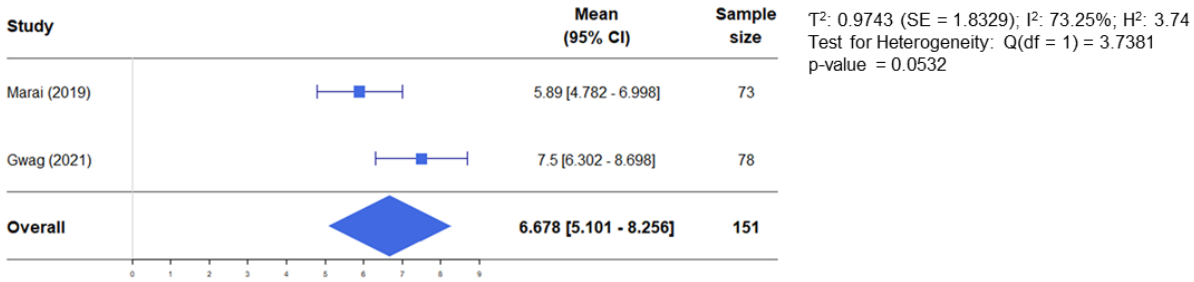


Figure 4. Atrial sensing (AS; mean) on day zero, sensitivity analyses adjusted for sample size (top) and for the MATRIX study (bottom)

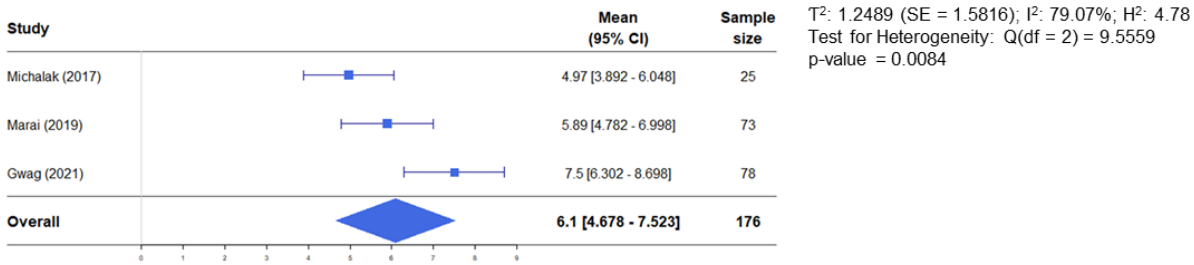


Atrial sensing (mean) (SA: retrospective studies); Day 0

Figure 5. Atrial sensing (mean) on day zero, sensitivity analysis adjusted for retrospective studies



Atrial sensing (mean) (SA: sample size); <6 months (excludes day 0 data)



Atrial sensing (mean) (SA: retrospective studies) <6 months (excludes day 0 data)

Figure 6. Atrial sensing (mean) at less than 6 months, sensitivity analyses adjusted for sample size (top) and for retrospective studies (bottom)

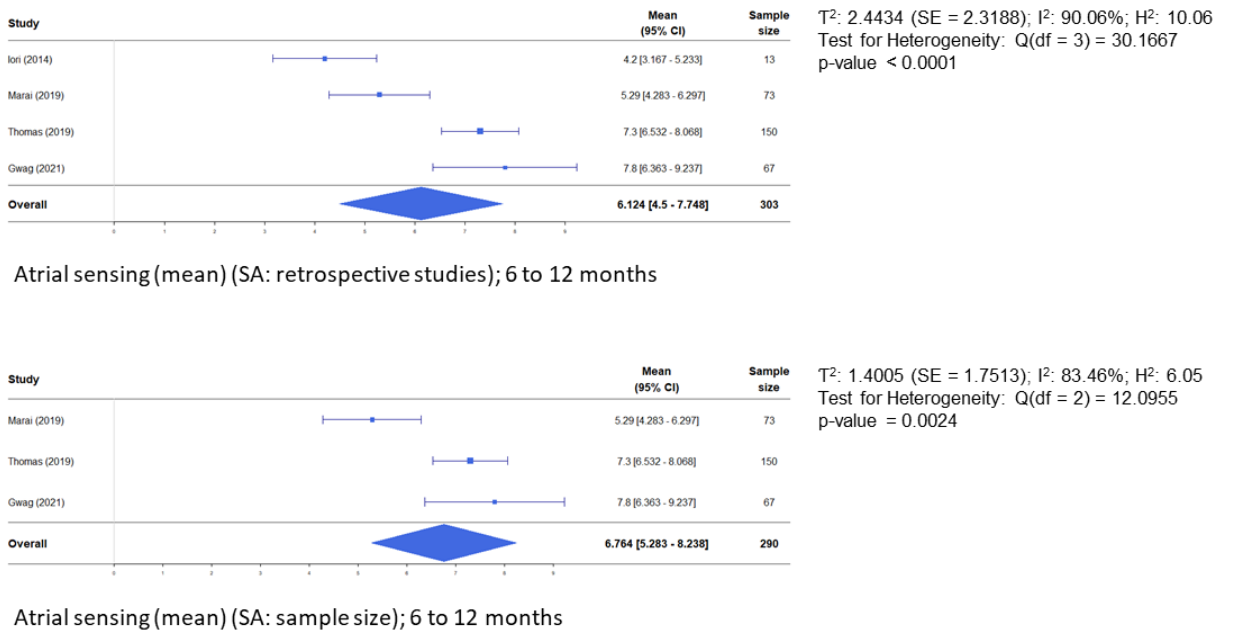


Figure 7. Atrial sensing (mean) at 6-12 months, sensitivity analyses adjusted for retrospective studies (top) and for sample size (bottom)

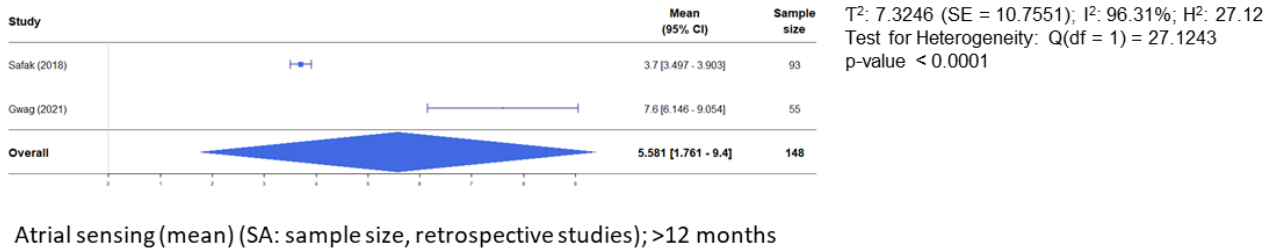


Figure 8. Atrial sensing (mean) at more than 12 months, sensitivity analyses adjusted for sample size and retrospective studies

APPROPRIATE AND INAPPROPRIATE SHOCK RATES

Pooled appropriate and inappropriate shock rates were gathered from up to 10 studies including over 500 patients for appropriate shock and 900 patients for inappropriate shock rates respectively, with a mean follow-up time of 422.5 days and a median follow-up of 384 days (Fig. 9). The analysis comprised the total study population in both analyses. The results show that on average 10.7% of patients included in the studies received appropriate therapy in the form of a shock. Appropriateness of the therapy was adjudicated by a reviewer post-therapy within each study included in this review. Inappropriate shocks administered by the device were assessed as a proportion across studies to evaluate the performance of the device. In total, 2.4% of patients received an inappropriate shock. Sensitivity analyses controlling for sample size, retrospective studies, or CRT-D studies slightly lowered heterogeneity but did not significantly change pooled rates (2.0%-2.7%) (see Figures 10 and 11).

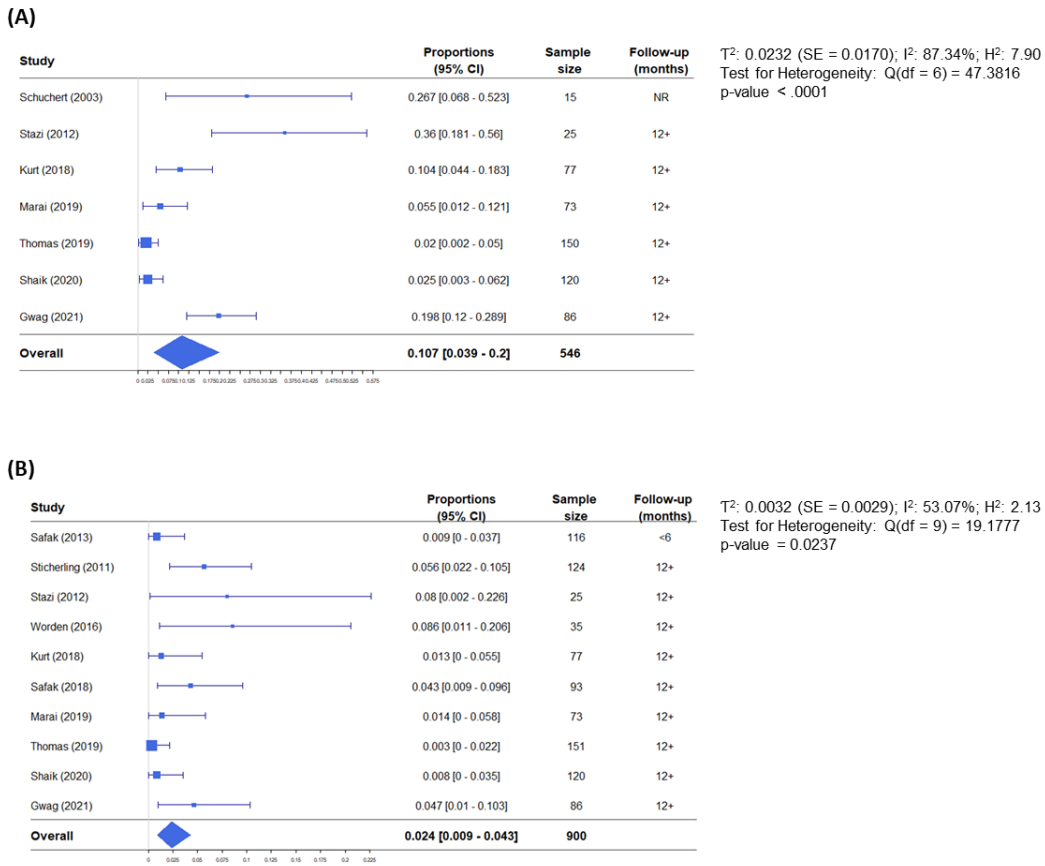
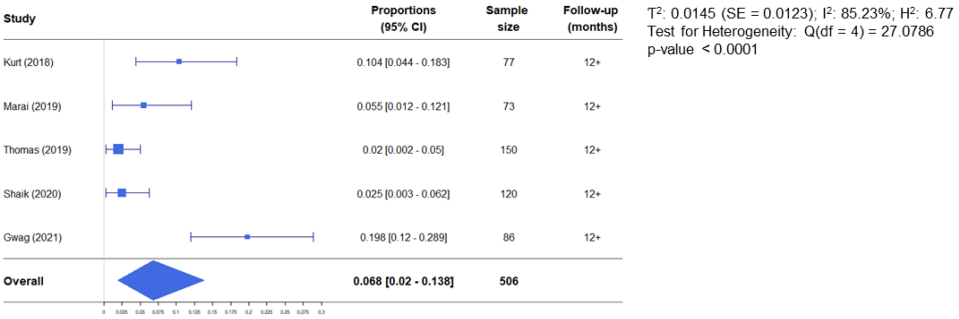
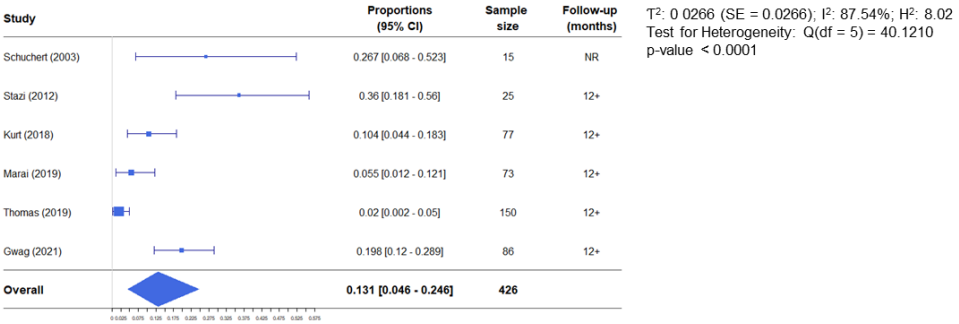


Figure 9. (A) Pooled rate of appropriate shocks, (B) Pooled rate of inappropriate shocks

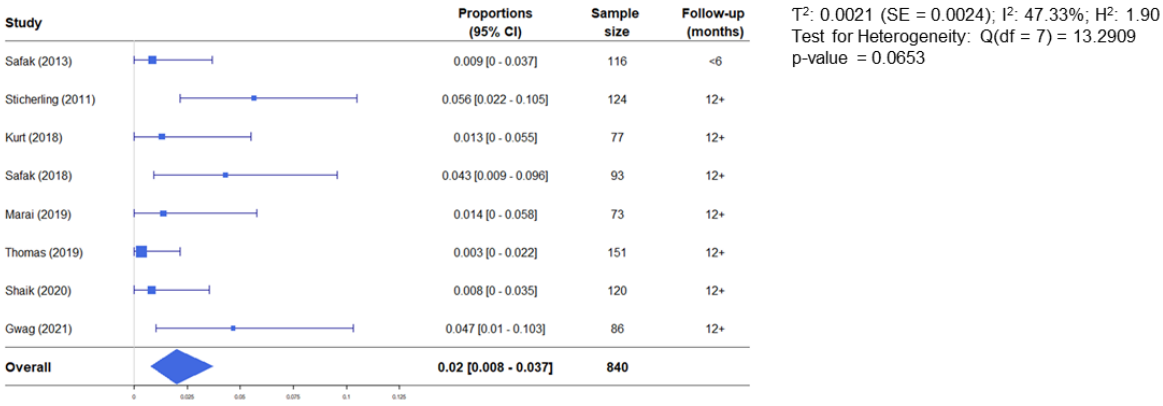


Appropriate shocks (SA: sample size); % of patients with an appropriate shock among the total study sample size

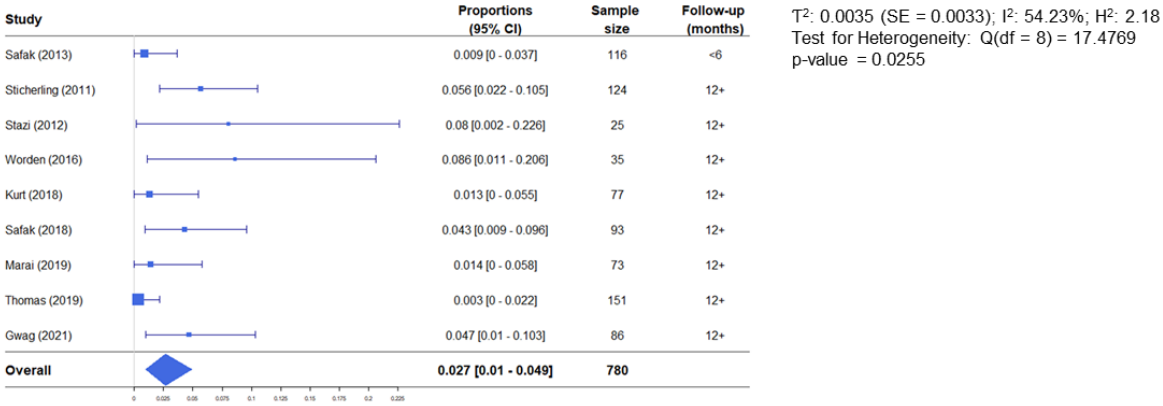


Appropriate shocks (SA: retrospective, CRTD studies); % of patients with an appropriate shock among the total study sample size

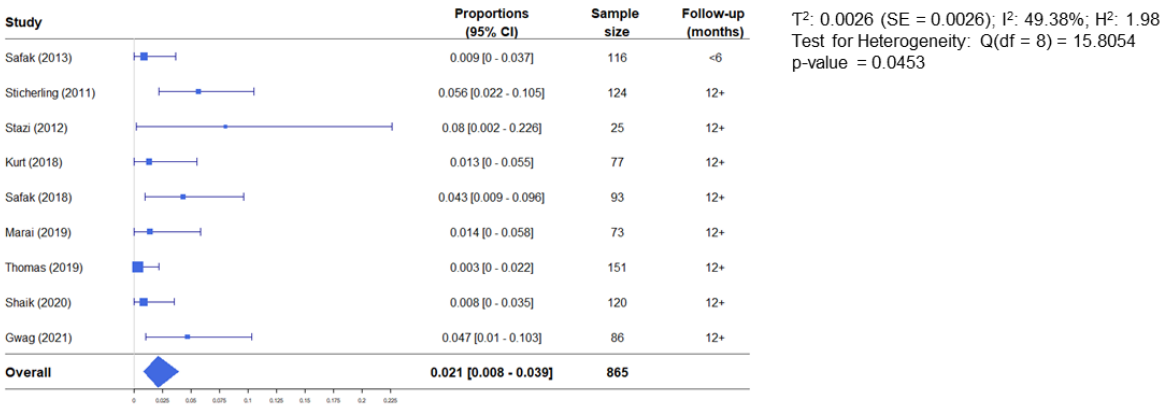
Figure 10. Appropriate shocks (percentage of patients with an appropriate shock among the total study sample size), sensitivity analyses adjusted for sample size (top) and retrospective studies and CRT-D studies (bottom)



Inappropriate shocks (SA: sample size); % of patients with an inappropriate shock among the total study sample size*



Inappropriate shocks (SA: CRTD); % of patients with an inappropriate shock among the total study sample size*



Inappropriate shocks (SA: retrospective studies); % of patients with an inappropriate shock among the total study sample size*

*A zero-correction was applied to the Thomas as this study reported zero events for this particular outcome. This means that the denominator was increased by one, and the nominator by 0.5 to avoid biased outcomes.

Figure 11. Inappropriate shocks (percentage of patients with an inappropriate shock among the total study sample size), sensitivity analyses adjusted for sample size (top), CRT-D studies (middle) and retrospective studies (bottom)

ALL-CAUSE MORTALITY

All-cause mortality was pooled for completeness across 7 studies including 2615 patients and study period spanning more than a decade. Pooled results reveal an average all-cause mortality of 5% over the course of up to 24 months follow-up. As expected, the highest mortality was observed in the study with the longest follow-up, in this case the MATRIX registry (24 months follow-up; NCT01774357) [25]. Upon removal of the MATRIX registry in sensitivity analysis, only including pooled analysis of studies of 6 months to a year follow-up, all-cause mortality decreased to less than 4% with an I^2 of 0.00% (see Figure 12).

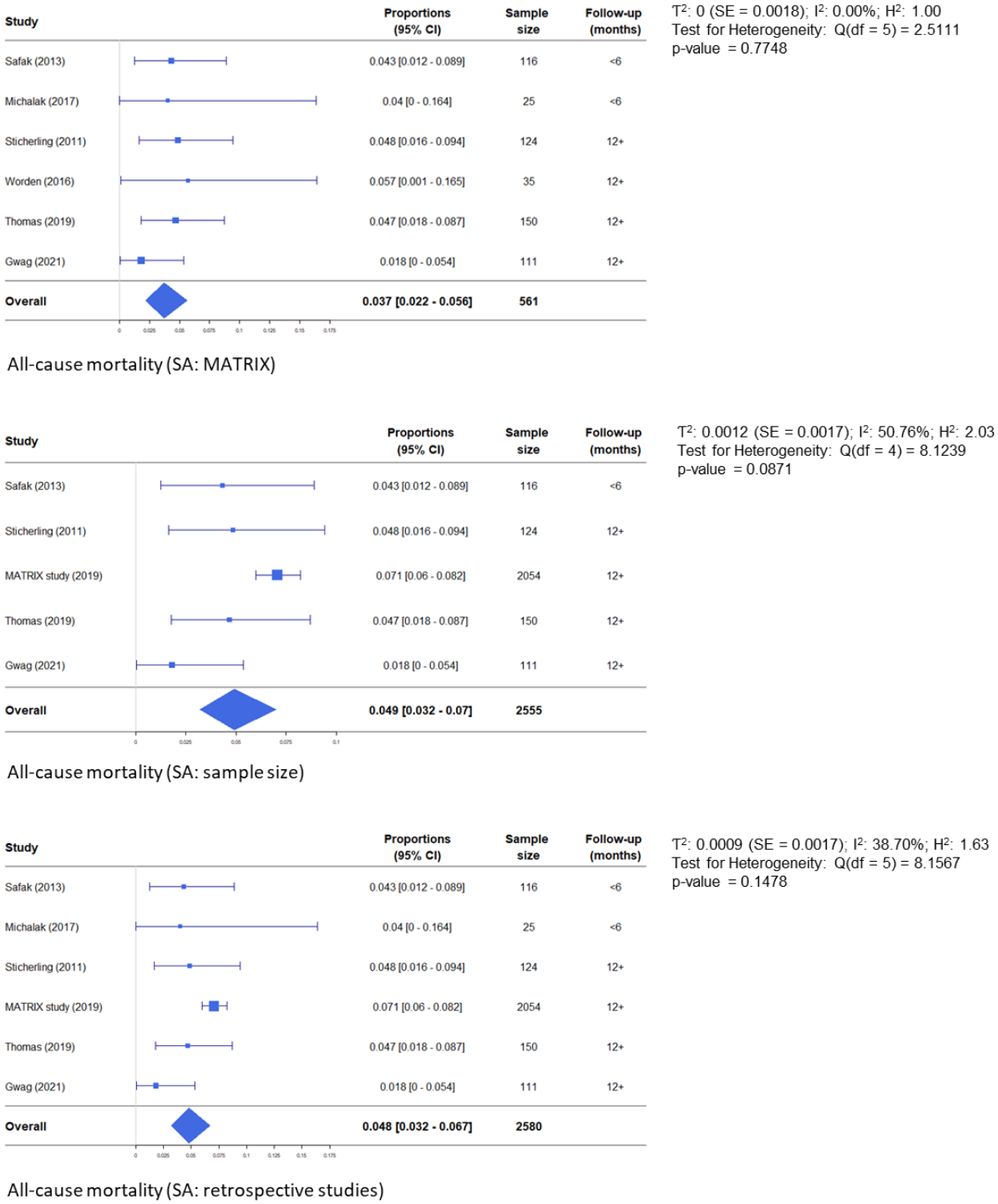


Figure 12. All-cause mortality, sensitivity analyses adjusted for the MATRIX study (top), sample size (middle) and retrospective studies (bottom)

Discussion

This is one of the first publications including MAs of proportions to have been published in the ICD field. Its aim was to summarise key endpoints on VR-DX ICD to enable clinicians' informed decision making by considering technical outcomes of the device over a longer time span and different patient populations. This MA of proportions is complementary in its approach to another MA published by Pung and colleagues [27], which took a comparative point of view with a focus on reliable detection of sub-clinical AF. The analysis here found that the device performs with consistency across several populations, particularly regarding the reliability of the atrial signal and its interpretability.

P-wave indices are consistently in a range where they allow meaningful clinical interpretation and support the detection and monitoring of sub-clinical AF and atrial high-rate episodes, as well as decision making on treatment of AF. This is confirmation of the initial assertion of the study by Stazi in 2012, that the atrial signal quality is consistently amplified to produce an interpretable signal without producing oversensing. [13] High atrial signal quality will support overview of atrial burden and assist clinicians in making appropriate choices on initiation of oral anticoagulation or further therapy. A consistent view of atrial burden is becoming increasingly important since a high atrial burden over a prolonged period has already been well established as an independent risk factor for ischaemic stroke and heart failure. [28] The correlation between increased atrial burden and other clinical outcomes remains under investigation, but may further highlight the importance of a consistent view of the atrial burden. [29] VR-DX ICD can continuously observe this atrial burden as demonstrated in the two-year follow-up of the MATRIX registry. [25] Atrial diagnostics are enhanced through the availability of remote monitoring, which enables continuous observation of atrial activity and improvement of therapy, leading to better long-term outcomes. [30] Long-term atrial sensing stability was also corroborated in the MATRIX registry at 24 months in line with the MA findings presented in this research (2.5 – 6mV at 24 months). [25]

As a point of interest, in Figure 3 (A) (mean atrial sensing on day 0) two relatively distinct clusters of studies can be seen. This cannot be interpreted with certainty; however, it seems likely that this is due to the device generation used. BIOTRONIK ICDs launched since 2013 use a new input stage that result in different, often higher sensing amplitudes. Many of the studies included in the analysis do not exactly list the devices used, but the timing of the enrolment and publication support the assumption that the studies reporting higher atrial sensing amplitudes mainly used devices that use the new input stage.

Pooled shock results demonstrate that rates of appropriate and inappropriate shocks are on par with industry and the performance of other devices reported in major studies or meta-analyses over the past decades. Rates in literature vary between 2% and 30% for inappropriate shocks and 7-10% for appropriate shocks. [31-33] This is irrespective of population characteristics and observed comorbidities. However, studies reporting on shocks per annum would potentially improve clinical interpretation and contextualisation. Further, the pooled results confirm conclusions of individual studies comparing VR-DX ICD to VR and DR ICDs, that DX is superior to single-chamber ICD care in detecting AF [20,34] and equivalent to dual chamber ICD in terms of atrial detection [12]. This analysis was able to show pooled frequency of events crucial to ICD therapy in a VR-DX ICD across a range of studies and cohorts over several decades. While the analysis was not comparative, it enabled inclusion of a broad evidence base allowing for discovery of new patterns and insight into the consistency of performance of VR-DX ICD devices.

All-cause mortality results should be interpreted within the clinical context and the follow-up duration of each individual study. A study in ICD patients from 2021 with 23 months follow-up time suggested an all-cause mortality of 13% in ICD patients [35], which is roughly in line with our findings.

No major differences between male and female patients were found indicating that there are no significant performance differences between sexes. An initial difference in p-wave sensing amplitudes was observed at day 0 and up to 6 months in a sub-group analysis by sex. This may be explained by the difference in heart sizes, i.e., male patients having on average a larger atrium influencing initial sensing amplitudes to be lower. The difference disappeared by 6 months. Given this information, implantation of devices with fewer leads may be preferable. This particularly applies in females, given the known difficulties of lead extraction and higher associated adverse event rates, as well as the increased risk of long-term adverse clinical events as a result of AF and thus a higher need for close observation in female ICD patients. [3,36,37]

The findings of this analysis are of importance, given on one hand the mounting evidence on the importance of early rhythm detection and control, and on the other hand the continuous collection of

data supporting a considerably better safety profile of lead-sparing technology. The EAST-AFNET 4 Trial established a long emerging pattern, that early rhythm intervention for patients with AF is superior to a wait-and-see approach. [38] In the trial, both pharmaceutical and interventional management strategies for early AF control resulted in a reduced morbidity and mortality for patients, although the superiority of early rhythm control over usual care resulted in the trial being stopped early. For these interventions to be implemented early and provide their intended benefit, clinicians require appropriate data to act on, which ICDs with atrial sensing in combination with a remote monitoring system can provide. Most patients receive atrial sensing through a second atrial lead. However, existing evidence, including from a more recent Dutch registry, suggests that the rate of complications increases with each additional implanted ICD lead.[2] [39] The highest complication rate in the Dutch registry was observed with subcutaneous lead approaches, while transvenous single-lead approaches were associated with the best safety and reliability profile. These combined findings may lead clinicians to implant a second lead, accepting related risk, or to give up on monitoring the atrium, by choosing a single-lead device without atrial sensing. A second, separate device which monitors atrial activity may be considered a solution, although it is bound to drive cost or increase error as multiple data sources would have to be integrated. There is a trend for a change in clinician preference away from erring on the side of monitoring and utilizing dual-chamber ICD devices in patients without an atrial pacing indication, as seen in a cross-sectional study from the US. [40] The study included over 260,000 patients and observed implanting practices over roughly a decade, showing centre-based preferences, but an overall inclination to increasingly use lead-sparing ICDs (i.e., single-chamber devices). This is likely an acknowledgment of the importance of the devices' superior safety as well as economic profile. Given the large amount of evidence reviewed in this study, clinicians may want to consider opting for a single-lead device with an atrial dipole and remote monitoring, to enable both early rhythm detection and intervention, as well as comply with best safety practices.

The findings of this study support the discussion undertaken in a review in 2021, assisting in the identification of patients who can benefit from a DX device. [41] In overview this includes patients without an indication for atrial stimulation, but a need for AV sequential pacing or atrial monitoring. The review outlines when patients should receive a DX device, while this research demonstrates that technical performance of the device in just these patients is reliable and can support clinical decision making.

As expected, observed heterogeneity was high, given the study was conducted as an MA of proportions and included studies of diverse design and origin. As the data includes mainly technical endpoints and spans decades, the pooling of data and analysis was still deemed appropriate and desirable. However, as it should be a future goal to increase insight into variables which may drive divergent effects, some key points should potentially be considered for inclusion in future studies, for example the amount of follow-up reprogramming administered to patients with an ICD or a cardiac implantable device of any type.

LIMITATIONS

The studies included in this analysis are largely observational studies and as such inherently carry a higher risk of selection bias, which is likely a key driver of heterogeneity. The 'learning effect', i.e. that implantation and device performance tend to improve with increased proficiency of the implanter over time, is an established confounder in medical device trials and also likely to be the origin of some of the heterogeneity observed in the presented analyses [42]. Unfortunately, it remains a very difficult factor to control for.

The analysis was conducted as an MA and had the goal to be as inclusive as possible. However, this resulted in excess heterogeneity in most analyses. These can be partially explained by the differences between the studies (see Table 1), likely especially differences in primary and secondary prevention. Indications may also change per patient over time within in each study without being captured, as well as different programming of ICDs in line with regional and general practice of the time. Of note, as p-wave amplitude is a technical value where common direction of result and true effect is of limited relevance and rather the lowest value of p-wave amplitude observed is relevant to clinical decision making, heterogeneity measures are of lesser importance to the interpretability of the results.

A conversion of mean shock values to incidence rates was considered, however as follow-up time is also only captured as a mean across studies, this conversion would have been very imprecise and introduced further heterogeneity. As a result, the approach was rejected.

Conclusion

Results show that the VR-DX ICD system is working as a reliable ICD system, supporting patients long-term and providing an added benefit compared to VVI-ICD in the form of atrial sensing. The additional information gained from the atrial view without requiring an additional lead provides clinicians with an attractive option when advanced insight is required but lead-sparing therapy is important.

Conflict of Interest Statement

Authors 1, 3 and 4 were engaged by BIOTRONIK. Authors 2 are employees of BIOTRONIK.

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Consent

Informed Consent/Consent to publish (for case reports/original research): Not applicable

Ethics approval

Not applicable

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