# Ventricular tachycardia-inducibility predicts arrhythmic events in post-myocardial infarction patients with low ejection fraction. A systematic review and meta-analysis

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A B S T R A C T

Background: Inducibility of ventricular arrhythmias at electrophysiological study (EPS) has long been suggested as predictive for subsequent arrhythmic events. Nevertheless, the usefulness of EPS in the clinical practice is still unclear. We performed a systematic review and meta-analysis to assess the predictive power of EPS in primary prevention of ventricular arrhythmias in post-myocardial infarction (MI) patients with left ventricular dysfunction.
Methods: MEDLINE and the Cochrane Library databases were systematically searched to identify studies, which analyzed EPS predictive value in post-MI patients with mean EF < 40% for the composite arrhythmic endpoint defined by: sudden cardiac death (SCD), aborted SCD, ventricular tachycardia (VT), ventricular fibrillation (VF), appropriate implantable cardioverter-defibrillator (ICD) interventions.
Results: Nine studies, evaluating 3959 patients with 647 arrhythmic events, were included in the meta-analyses. EPS showed a strong predictive power for the arrhythmic endpoint with a pooled odds ratio (OR) of 4.00 (95% confidence interval [CI]: 2.30–6.96) in the whole set of studies, albeit a high level of heterogeneity among studies. EPS predictive power was higher in studies where VT-inducibility was tested (OR 6.52; 95% CI: 2.30–18.44; sensitivity 0.65, specificity 0.78, and negative predictive value 0.94), versus those assessing VT/VF-inducibility (OR 2.09; 95% CI: 1.34–3.26). VT-inducibility was predictive even when assessed within one month after MI (OR 7.85; 95% CI: 3.67–16.80).
Conclusions: Inducibility of ventricular arrhythmias at EPS is a strong predictor of the arrhythmic endpoint in post-MI patients with impaired EF, particularly when VT-inducibility is tested. EPS could help selecting the patients who can mostly benefit from ICD therapy.

## 1. Introduction

The current guidelines recommend implantable cardioverter-defibrillator (ICD) for primary prevention of sudden cardiac death (SCD) in patients with ischemic cardiomyopathy, based on the values of the left ventricular ejection fraction (EF) [1, 2]. However, EF lacks both sensitivity and specificity for prediction of arrhythmic events. Contemporary real-world data indicate that the majority of patients addressed to ICD therapy by the current guidelines do not have life-saving therapies, while being exposed to ICD side effects [3, 4]. By contrast, several patients who are at risk of SCD are not identified by the EF value, because the main part of SCD patients exhibits just mildly depressed EF [5]. Thanks to the modern pharmacological therapies and wide spread of primary percutaneous coronary interventions (PCIs), a reduction in the risk of SCD has been observed in post-myocardial infarction (MI) patients with impaired EF [6]. This makes particularly urgent to improve, beyond the EF criterion, the selection of patients who can most benefit from an ICD.

In recent years, a great effort has been made to identify additional methods for SCD risk stratification to improve the appropriateness of ICD implantation [5, 7–10]. After MI, a ventricular scar is generally formed, which can act as a predisposing factor to ventricular arrhythmias [11]. The assessment of total scar and border zone extent by late gadolinium enhancement - cardiac magnetic resonance (LGE-CMR) has been demonstrated a promising non-invasive risk marker for arrhythmic events [8]. However, while scar presence is a predisposing factor, arrhythmia inducibility by programmed ventricular stimulation during

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an electrophysiological study (EPS) directly tests the functionality of scar-related circuits, adding significant information to the stratification of arrhythmic risk in post-MI patients. Although some studies have highlighted the predictive power of EPS for arrhythmic events [12, 13], the test is poorly utilized in the current clinical practice and its usefulness is still controversial [1, 14]. To address this question, we performed a systematic review and meta-analysis aiming to assess the predictive power of EPS in post-MI patients with reduced EF.

## 2. Methods

The systematic review and meta-analysis were conducted following the guidelines of the PRISMA Statement [15].

### 2.1. Eligibility criteria

The literature search was performed to identify studies assessing ventricular arrhythmias inducibility by programmed ventricular stimulation during an EPS, in the primary prognostic stratification of ventricular tachyarrhythmias in post-MI patients with mean EF < 40%. Studies presenting endpoints related to ventricular arrhythmic events, such as sudden cardiac death (SCD), aborted SCD, sustained ventricular tachycardia (VT), ventricular fibrillation (VF), appropriate ICD therapy with the inclusion of antitachycardia pacing (ATP), were selected. Additional inclusion criteria were a sample size >50, and a follow-up of at least 1 year. The search was restricted to articles published in English in peer-reviewed journals. Abstracts and session presentations were excluded.

### 2.2. Search strategy, study selection and data collection

MEDLINE and the Cochrane Library electronic databases were systematically searched to identify primary references from January 2000 to December 2017. Studies published before 2000 were not considered to avoid that differences in MI treatment in older studies with respect to the current therapy could introduce bias in the analysis. The search terms used are outlined in the Supplementary material. The database search was followed by a review of the citations from eligible studies by two independent reviewers (MD and MM). Studies were selected based on title and abstract. Selected studies were read thoroughly to identify those suitable for the qualitative and/or quantitative analysis (meta-analysis). The two reviewers independently extracted the demographic and clinical outcome data from the selected studies. When disagreement occurred, they reviewed the papers together to reach joint conclusions. The methodological quality of the studies was evaluated by applying the Newcastle-Ottawa Score (NOS) checklist for non-randomized studies [16], and the Cochrane Risk of Bias Tool for Randomized Controlled Trials for randomized studies [17].

### 2.3. Statistical analyses

Patients' characteristics were conveniently expressed as numbers, percentages, mean ± standard deviation, median (interquartile range), or median [range]. In each study data for the assessed outcomes in patients with positive (EPS+) and negative test (EPS−) were summarized using simple counts. When raw data were not reported, proportions of positive cases, risk ratios, odd ratios (ORs), sensitivity, specificity, positive (PPV) and negative predictive values (NPVs) were used to calculate raw numbers. In one study [18], raw data were estimated from outcome probabilities reported in Kaplan-Meier survival curves at mean follow-up. Binary outcomes were combined by a random effects model using the method by DerSimonian and Laird [19], which estimated pooled ORs with 95% confidence intervals. Pooled ORs were computed for the arrhythmic endpoint, and, where available, for the total mortality endpoint. Where present into the primary studies, adjusted hazard ratios (HR) from Cox multivariate regression models were extracted and meta-analyzed.

Heterogeneity among studies was assessed by chi-squared test, quantified by $I^2$ statistics, and explored by sensitivity analysis, subgroup meta-analyses, and meta-regression.

Statistical measures of performance of a binary classification test, such as annualized event rate (AER) in EPS+ and EPS−, pooled sensitivity, specificity, positive and negative likelihood ratios, PPVs and NPVs were calculated for the overall group of studies and for relevant subgroups [20, 21]. Further details on heterogeneity analyses and computation of diagnostic indices are reported in Supplementary material.

Publication bias was assessed by funnel plot visual inspection and Harbord modified test [22].

All analyses were performed using the Cochrane Collaboration Software Review Manager 5 (version 5.2), and STATA 13.1 Statistics/Data analysis (StataCorp, 4905 Lakeway Drive, College Station, Texas 77845 USA). The 2-tailed statistical significance level was established at 0.05.

## 3. Results

### 3.1. Study selection

The search of Medline and the Cochrane Library databases identified 1125 relevant studies after duplicate removal, which were complemented by seven from the studies' references (Fig. 1S in Supplementary material). 1086 studies were excluded after reading title and abstract, and 46 were retrieved for further evaluation. Of these, 37 studies were excluded, because they did not fulfill all the inclusion criteria. Nine studies, enrolling 3959 patients, were included in the systematic review and meta-analyses. Of these, two were randomized trials (MUSTT (Multicenter Unsustained Tachycardia Trial) [13] and BEST + ICD (BEta-blocker STrategy plus ICD) [23]), one was a post-hoc analysis of a previous randomized trial (MADIT-II (Multicenter Automatic Defibrillator Implantation Trial II)) [18], and six were prospective non-randomized trials [7, 24–28]. The study by Zaman et al. [28] was included despite a partial overlapping (~40%) with that by Kumar et al. [27], given the application of different patients' selection criteria.

### 3.2. Study characteristics

The general characteristics of the nine selected studies are reported in Table 1, while details on the specific EPS protocols applied in each study are outlined in Table 1S in Supplementary material. The studies presented differences in the EPS protocol and timing. In three studies inducibility of sustained monomorphic VT was the main criterion to identify patients with positive test, while in four studies inducibility of either VT or VF was accepted as positive result. In the remaining two studies [18, 26] both criteria were tested and compared. Given these protocol differences, inducibility ranged between 12 and 39% for VT-inducibility and between 24 and 46% for VT/VF-inducibility (Table 1S in Supplementary material). In four studies EPS was performed early after MI (within one month). The quality of the selected studies was generally good, the non-randomized studies yielding NOS scores ranging between 7 and 9, and the randomized studies presenting low risk of bias (Table 1). Demographic and clinical characteristics of the 3959 patients included in the meta-analysis are reported in Table 2. The patients had a mean age of 65 years, and 3304 (83%) were men. In all the studies the mean EF value was ≤ 35%. The average follow-up period ranged from a minimum of 18 months to a maximum of 48 months with a weighted mean of 32 months.

### 3.3. Predictive power of EPS

In the overall group of studies, the patients developed 647 arrhythmic events (16.3%), with an AER of 7% (Table 4S in Supplementary material). The arrhythmic endpoint was reached in 23.4% of patients with positive EPS (AER 10.0%) versus 13.7% of patients with negative EPS (AER 5.8%), with a pooled OR of 4.00 (95% CI: 2.30–6.96,

**Table 1**
Characteristics of the nine studies identified by the systematic review.

| Studies | Year | Study type | Study quality | Patients (n) | Post-MI selection | EPS timing | Inducibility definition | End points | Follow-up (months) |
|---|---|---|---|---|---|---|---|---|---|
| Buxton et al. [13] | 2000 | Randomized | LRB | 1750 | EF ≤ 40%, NSVT | Late | MVT/VF | SCD, aSCD | 40[b] |
| Schmitt et al. [24] | 2001 | Prospective | 4, 2, 2 | 98 | VEB, aHRV, aLP | Early | MVT | SCD, VT, VF[a] | 20 ± 14 |
| Raviele et al. [23] | 2005 | Randomized | LRB | 76 | EF ≤ 40%, VEB, aHRV, aLP | Early | MVT/VF | SCD, VT, VF[a] | 18 ± 12 |
| Daubert et al. [18] | 2006 | Post-hoc | 4, 2, 3 | 593 | EF ≤ 30%, | Late | MVT and MVT/VF | VT, VF[a] | 20 [0.3–53] |
| De Ferrari et al. [25] | 2007 | Prospective | 3, 1, 3 | 106 | EF ≤ 40%, | Late | MVT/VF | SCD, VT, VF[a] | 24 [1–71] |
| Huikuri et al. [26] | 2009 | Prospective | 4, 2, 3 | 282 | EF ≤ 40%, | Late | MVT and MVT/VF | VT, VF | 24 (24–25) |
| Costantini et al. [7] | 2009 | Prospective | 4, 1, 2 | 566 | EF ≤ 40%, NSVT | Late | MVT/VF | SCD, VT, VF[a] | 19 ± 7 |
| Kumar et al. [27] | 2010 | Prospective | 4, 2, 3 | 360 | EF ≤ 40%, | Early | MVT | SCD, VT, VF[a] | 49 ± 29 |
| Zaman et al. [28] | 2014 | Prospective | 4, 2, 3 | 128 | EF ≤ 35%, EF ≤ 30% + HF | Early | MVT | SCD, VT, VF[a] | 32 (24–50) |

Data are numbers (n), mean ± SD or median (interquartile range) or median [range], as available.
Study methodological quality was evaluated by Cochrane Risk of Bias Tool for Randomized Controlled Trials for randomized studies, and by Newcastle-Ottawa Scale for non-randomized studies (Selection, Comparability, Outcome; Range: 0–4, 0–2, 0–3).
aSCD = aborted sudden cardiac death; Early = mean < 1 month after myocardial infarction; EF = ejection fraction; EPS = electrophysiological study; HF = heart failure.
aHRV = abnormal heart rate variability; aLP = abnormal late potentials; Late = mean > 1 month after myocardial infarction; LRB = low risk of bias; MI = myocardial infarction; MVT = monomorphic ventricular tachycardia; NSVT = non-sustained ventricular tachycardia > 3 consecutive beats; SCD = sudden cardiac death; VF = ventricular fibrillation; VPB = ventricular premature beats ≥ 10/h.
  [a] Including ICD appropriate interventions.
  [b] Weighted mean, SD not available.

p < 0.001) (Fig. 1A). Heterogeneity among studies was substantial ($I^2 = 80\%$, p < 0.001), and was subsequently investigated. The funnel plot (Fig. 2S in Supplementary material) showed asymmetry due to the absence of small studies with unfavourable results, and indicated the presence of publication bias, which was testified by the Harbord test (p = 0.002).

Sensitivity analysis showed that the exclusion of any individual study did not significantly affect the association between EPS and the arrhythmic endpoint, nor the level of heterogeneity (Table 2S in Supplementary material). Similar results were obtained when excluding the two studies [13, 26], which performed a specific assessment of SCD and VT/VF (i.e., excluding ICD interventions), and the two studies [27, 28], which used more aggressive stimulation protocols comprising up to four extrastimuli.

Subgroup meta-analyses were performed considering the effects of differences in EPS protocol and timing. As shown in the forest plot of Fig. 1B, the inducibility criteria had relevant effects on the predictive power of the test. The subgroup of studies applying VT-inducibility displayed a higher OR value (6.52; 95% CI: 2.30–18.44) than the studies testing VT/VF-inducibility (2.09; 95% CI: 1.34–3.26). Nonetheless, heterogeneity was just slightly reduced in the two subgroups ($I^2 = 85\%$ and 65%, respectively). Sensitivity analysis showed that heterogeneity in the VT-inducibility subgroup was mainly related to the study by Daubert et al. [18], whose exclusion led to a consistent decrease in heterogeneity ($I^2 = 9\%$, p = 0.35).

As concerns EPS timing, the meta-analysis of the four studies performing an early EPS assessment (Fig. 3S in Supplementary material) pointed out a high predictive power of EPS also in this time frame (OR = 7.85; 95% CI: 3.67–16.80). This subgroup of studies tested mostly VT-inducibility and displayed a non-significant level of heterogeneity ($I^2 = 31\%$, p = 0.23). The subgroup of studies with late assessment displayed instead higher heterogeneity ($I^2 = 74\%$, p = 0.004) with prevalence of VT/VF test, but still testified EPS predictive power (OR = 2.50 [1.50–4.17]).

The meta-regression of the overall data (Fig. 4S and Table 3S in Supplementary material) did not show a significant dependence of EPS predictive power on EF, denying a role of the parameter on the observed heterogeneity.

The meta-analysis performed on the five studies, which reported adjusted HR values with age and EF as main covariates (Fig. 5S in Supplementary material), confirmed the predictive power of EPS with a pooled adjusted HR of 1.98 (95% CI: 1.36–2.88) and a non-significant level of heterogeneity ($I^2 = 56\%$, p = 0.06).

The assessment of EPS diagnostic performance, summarized in Table 3 here and in Table 4S in Supplementary material, showed that test performance was mainly affected by inducibility criteria. All diagnostic indices indicated better performance in studies evaluating VT-inducibility versus VT/VF-inducibility. In particular, in the former group specificity was 0.78 and the NPV, estimated at a median prevalence among studies of 13.1%, was 0.94.

Data on both the arrhythmic and total mortality endpoints were available from four studies [13, 18, 27, 28]. The pooled analysis showed that EPS was a better predictor of arrhythmic events (OR = 2.97; 95% CI: 1.44–6.12) than of total mortality (OR = 1.16; 95% CI: 0.64–2.11), indicating a specific relation of EPS with the arrhythmic endpoint (Fig. 6S in Supplementary material).

**Table 2**
Characteristics of the patients included in the nine studies identified by the systematic review.

| Studies | Age (years) | Males (%) | LVEF (%) | MI (%) | Thrombolysis (%) | PCI (%) | ICD (%) | β-Blocker (%) |
|---|---|---|---|---|---|---|---|---|
| Buxton et al. [13] | 67[a] | 85 | 29[a] | 88 | 21 vs 18[b] | 23 vs 23[b] | 0 | 51 vs 35[b] |
| Schmitt et al. [24] | 58 ± 11 | 82 | 32 ± 8 | 100 | 5 vs 8[b] | 90 vs 92[b] | 95 vs 0[b] | 89 |
| Raviele et al. [23] | 67 ± 9 | 70 | 31 ± 4 | 100 | 44 | 15 | 100 vs 0[b] | 100 vs 100[b] |
| Daubert et al. [18] | 63[a] | 84 | 23[a] | 100 | NA | 44 vs 44[b] | 100 vs 100[b] | 67 vs 64[b] |
| De Ferrari et al. [25] | 61 ± 7 | 95 | 27 ± 7 | 100 | NA | NA | 96 vs 33[b] | 66 vs 68[b] |
| Huikuri et al. [26] | 65 ± 11 | 77 | 35 ± 10 | 100 | 34 | 14 | 100[c] | 89 |
| Costantini et al. [7] | 65 ± 10 | 84 | 28 ± 8 | 75 | NA | 47 | 100 vs 79[b] | 86 |
| Kumar et al. [27] | 59[a] | 79 | 31[a] | 100 | 24 | 69 | 71 vs 6[b] | 90 vs 90[b] |
| Zaman et al. [28] | 58[a] | 84 | 27[a] | 100 | 0 | 94 vs 99[b] | 90 vs 4[b] | 83 vs 96[b] |

Data are numbers (n), percentages (%), mean ± SD, as pertinent.
ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MI = documented acute myocardial infarction (all the patients had coronary artery disease); NA = not available; PCI = percutaneous coronary intervention.
  [a] Weighted mean, SD not available.
  [b] Inducible versus non-inducible patients.
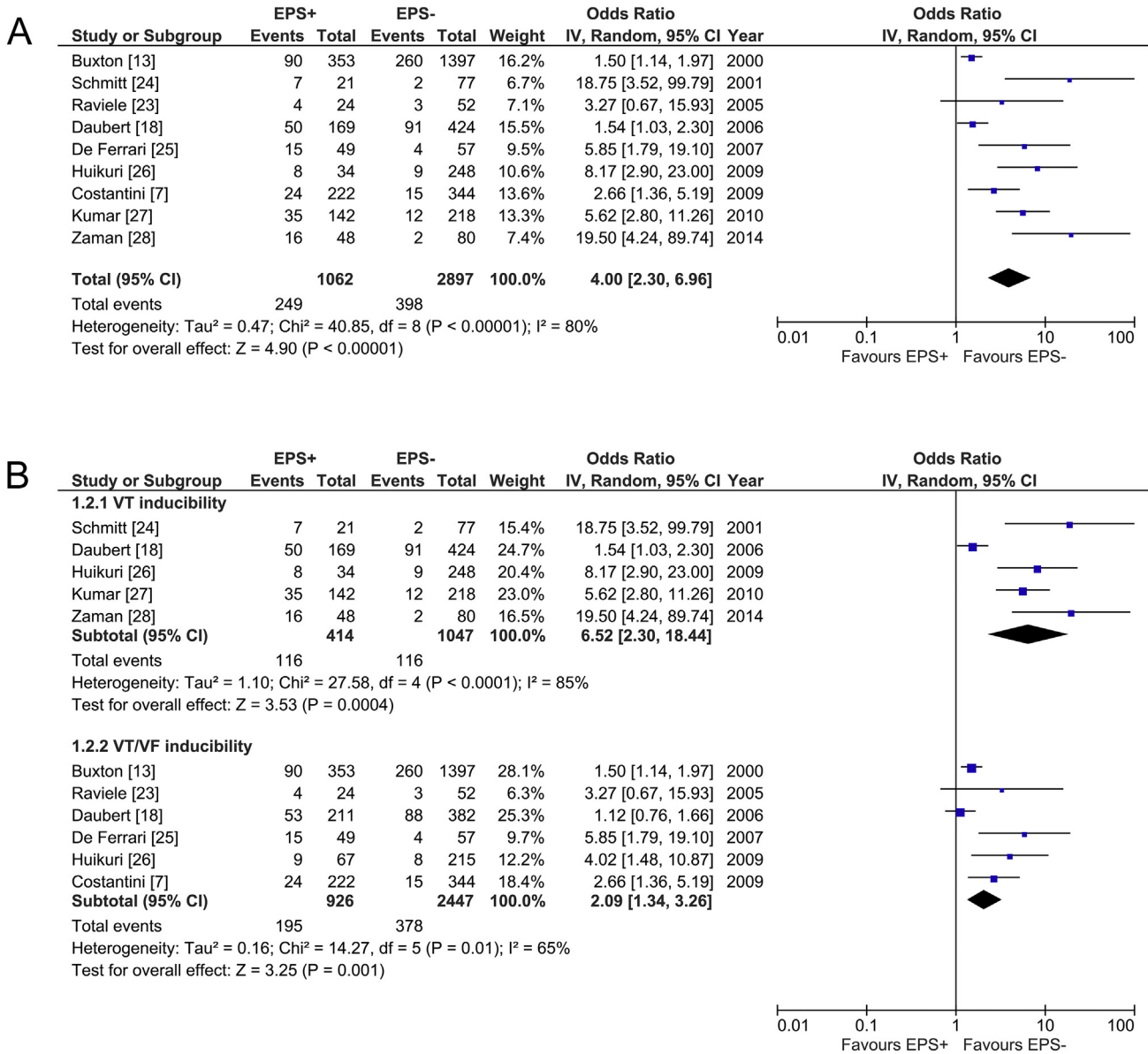  [c] Patients with implantable loop-recorder.

**Fig. 1.** A. Individual and pooled odds ratios (ORs) of the electrophysiological study (EPS) in the overall group of studies. Forest plot comparing the composite arrhythmic endpoint in patients with positive (EPS+) and negative test (EPS−). Reported data in each study pertain to the more predictive induction protocol. B. Individual and pooled ORs of the EPS when different study protocols are applied. Forest plot comparing the composite arrhythmic endpoint in patients with EPS+ and EPS−, when test positivity is associated with inducibility of monomorphic ventricular tachycardia (VT, top) or ventricular tachycardia/ventricular fibrillation (VT/VF, bottom). In two studies [18, 26] both VT and VT/VF induction protocols were tested.

## 4. Discussion

The results of our meta-analysis, including 3959 patients, show that the inducibility of ventricular arrhythmias at EPS is a powerful predictor of subsequent arrhythmic events in post-MI patients with reduced left ventricular EF. The predictive power of EPS was particularly strong when inducibility of sustained monomorphic VT was tested. Finally, differently from other risk stratification markers, such as EF [29], EPS

**Table 3**
Performance of the electrophysiological study test in predicting the composite arrhythmic endpoint in the different subgroups of studies. Pooled sensitivity and specificity were estimated by a bivariate generalized linear mixed model, while positive and negative predictive values were estimated at the median prevalence in each study group using Bayes' rule (see methodological section in Supplementary material).

| Subgroups | Studies (n) | Patients (n) | OR (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) | PPV (95% CI) | NPV (95% CI) |
|---|---|---|---|---|---|---|---|
| Overall | 9 | 3959 | 4.00 (2.30–6.96) | 0.60 (0.43–0.74) | 0.74 (0.67–0.81) | 0.26 (0.23–0.28) | 0.92 (0.91–0.93) |
| VT-inducibility studies | 5[a] | 1461 | 6.52 (2.30–18.44) | 0.65 (0.42–0.82) | 0.78 (0.68–0.86) | 0.31 (0.26–0.35) | 0.94 (0.92–0.95) |
| VT/VF-inducibility studies | 6[a] | 3373 | 2.09 (1.34–3.26) | 0.48 (0.33–0.64) | 0.70 (0.63–0.77) | 0.20 (0.18–0.23) | 0.90 (0.88–0.91) |
| Early assessment studies | 4 | 662 | 7.85 (3.67–16.80) | 0.77 (0.65–0.86) | 0.73 (0.65–0.79) | 0.26 (0.21–0.32) | 0.96 (0.94–0.98) |

CI indicates 95% confidence interval; NPV = negative predictive value; OR = odds ratio; PPV = positive predictive value; VF = ventricular fibrillation; VT = monomorphic ventricular tachycardia.
[a] Two studies tested both VT and VT/VF-inducibility.

displayed a specific relation with arrhythmic events, which may be due to its capability to directly test the presence of viable re-entry circuits in the ventricular scar of post-MI patients.

### 4.1. EPS stimulation protocols

After MI, a more or less extensive ventricular fibrosis appears, which may constitute the substrate for numerous arrhythmias [11]. Programmed ventricular stimulation can identify the presence of conducting channels and reentrant circuits within/around the scar, thus testing its capability to sustain ventricular arrhythmias. Nevertheless, the potential of induced arrhythmias to predict subsequent spontaneous arrhythmic events is significantly affected by the specific EPS protocol applied. In the analyzed studies, substantial variability existed among stimulation protocols, which included differences in the number and location of the applied extrastimuli, the adopted inducibility criteria, comprising type and cycle length of the induced arrhythmias, as well as in EPS timing. In our subgroup meta-analysis we mainly focused on the effects of inducibility criteria on test predictivity. The analysis showed that in studies where the inducibility of sustained monomorphic VT was tested, the OR for subsequent arrhythmic events was 6.52. In contrast, in the studies where the inducibility definition included both VT/VF the OR decreased to 2.09. These general results are confirmed by the two studies, where both inducibility criteria were tested [18, 26]. The higher predictive power of induced monomorphic VT versus VT/VF may be related to the different underlying mechanism of the arrhythmias. While stable and reproducible VT forms are based on the presence of fixed scar-based reentries that the stimulation simply discloses, complex VF forms may be more artefactually-related to the applied stimulation protocol.

Most stimulation protocols included one to three extrastimuli at two right ventricular sites during two drive-cycle lengths. In two recent studies [27, 28], a fourth extrastimulus was used at a single stimulation site, and the authors pointed out that about one third of the patients at risk were not identified when using only three extrastimuli [30]. The more aggressive VT-inducibility protocol, using up to four extrastimuli, seems to have higher sensitivity and NPV for the arrhythmic endpoint without a significant reduction in specificity. Nonetheless, more aggressive protocols can result in an increased inducibility of high rate VTs, more frequent hemodynamic instability and induction of VF [30].

As concerns the prognostic value of the rate of the induced VTs, data are not uniform. While in the MADIT-II trial [18] the induction of VTs with a cycle length ≥240 ms was more predictive than the induction of VTs with shorter cycle lengths, in the study by Zaman et al. [30] there was no prognostic differences between VTs with cycle lengths >230 ms versus higher rate VTs. It should be noticed that in the era of primary PCI, inducible VTs seem as more rapid as earlier revascularization is performed [31, 32].

### 4.2. EPS timing in post-MI patients

In four studies [23, 24, 27, 28] EPS was performed early after MI (within a month), and ventricular arrhythmias-inducibility showed a high predictive power for the subsequent arrhythmic events (OR = 7.85). These data open an important clinical scenario. In the VALIANT trial (Valsartan in Acute Myocardial Infarction Trial) [33], which enrolled 14,609 post-MI patients, SCD rate was higher (1.4% per month) in the first 30 days after MI, exponentially decreasing to 0.5% per month over the first six months, and reaching a steady value of 0.14% per month at two years. Despite the high rate of SCD observed early after MI, the current guidelines do not suggest ICD treatment in this high-risk period [1, 2]. The indication is based on the results of two randomized trials [34, 35], which did not document any ICD benefit on total mortality in patients implanted between 5 and 40 days after MI. Some recent studies in patients treated with primary PCI [27, 28] suggest instead that ICD could be useful even early after MI, when selecting patients based on EPS results. However, the properties of an early arrhythmic substrate and its meaning for prediction of subsequent arrhythmic events need to be further clarified. As well, due to the limited number of studies and the presence of protocol differences between studies performing early versus late assessment, in our meta-analysis we could not quantitatively compare the performance of EPS in the two time frames. Since the electrical-anatomical substrate of arrhythmias may change over time, particularly in the first year after MI, a periodic evaluation of arrhythmic risk may be considered to improve risk stratification.

### 4.3. EPS in patients with low EF value

The major concern to EPS clinical use is the low NPV (0.88) for the arrhythmic endpoint reported by the large MUSTT trial [13], where VT/VF-inducibility was tested in patients with EF ≤ 40%. Such NPV was considered not sufficient to withdraw patients from ICD implantation. The results of the present meta-analysis, including only studies with mean EF < 40%, prospect a different scenario, reporting a pooled sensitivity, specificity and NPV equal to 0.65, 0.78 and 0.94, respectively, when VT-inducibility was tested. Furthermore, as reported above, recent studies showed higher values of sensitivity and NPV of the test with stimulation protocols including up to four extrastimuli [27, 28]. Finally, in the specific range of low EF values we analyzed, the meta-regression did not evidence a significant dependence of the predictive value from the degree ventricular function impairment.

### 4.4. Poly-parametric evaluation

SCD has a multifactorial origin, therefore it is unlikely that a single risk marker could replace the EF value as a predictor of SCD. Probably, only the combination of different markers in a poly-parametric evaluation framework may allow a significant improvement in the stratification of the arrhythmic risk [36]. In four studies of the present meta-analysis [7, 13, 23, 24], EPS was performed in patients pre-selected by non-invasive methods (Table 1). However, differences in study protocols and pre-selection tests hindered the evaluation of the potential prognostic improvement provided by a poly-parametric evaluation including EPS. Indications about this possibility were provided in the ABCD trial (Alternans Before Cardioverter Defibrillator) [7], where the predictive power for arrhythmic events of microvolt T-wave alternans, EPS and their combination was compared in patients with EF ≤ 40%. The AER in patients with two normal tests was approximately three-fold lower than in patients with one abnormal test, and approximately six-fold lower than in patients with two abnormal tests, suggesting the complementarity of the two tests in predicting the arrhythmic outcome. Another promising non-invasive test to be combined with EPS may be LGE-CMR, which was demonstrated highly predictive for arrhythmic events in both patients with EF ≤ 35% and EF > 35% [8]. LGE-CMR non-invasively assesses the ventricular scar that is the probable location of the reentry circuits highlighted by EPS [11]. Indeed, a few studies have shown that LGE-CMR patterns can predict VT-inducibility [37, 38]. As suggested by a recent study [39], the two tests may be combined in a progressive step model, which however needs further evaluation.

EPS clinical use is restrained by its invasiveness, side effects, and costs. Nevertheless, these drawbacks may be overweighted by an improvement in ICD implantation appropriateness. Further indications on the clinical use of EPS may be available upon completion of an ongoing multi-center randomized study, called PROTECT-ICD (Programmed Ventricular Stimulation to Risk Stratify for Early Cardioverter-Defibrillator Implantation to Prevent Tachyarrhythmias following Acute Myocardial Infarction) [40]. The study will randomize >1000 patients with EF ≤ 40% to either EPS-guided early ICD implantation or a control arm with current standard care. A fraction of the trial patients will also undergo LGE-CMR at select centers.

## 5. Limitations

The results of this meta-analysis were mostly based on male patients (a common limitation of SCD, and, more in general, cardiologic studies), with an average age ranging between 58 and 67 years. Thus they can be hardly extended to female and elderly populations. On the other hand, the predictive power of EPS was confirmed in the meta-analysis of adjusted HR, which were mostly corrected for age as covariate.

Except for two randomized trials [13, 23], all the studies included in the meta-analysis were prospective observational or post-hoc analysis studies more open to the risk of bias. Specific tests were performed to evaluate the presence of heterogeneity and publication bias in the overall set of studies, which pointed out the presence of both features. Thus, heterogeneity was thoroughly explored by sensitivity analyses, subgroup meta-analyses, and meta-regression. These further analyses consistently confirmed EPS predictive power, and suggested potential sources of heterogeneity in protocol variability, EPS timing, single study effects and population differences. However, due to the limited number of studies available, we could not fully separate heterogeneity sources and their effects. Finally, the risk of SCD might be overestimated when SCD is assessed by the surrogate endpoint of appropriate ICD intervention [41]. Nevertheless, our sensitivity analysis did not point out major differences when SCD was estimated as a standalone endpoint.

## 6. Conclusions

This meta-analysis showed that the test of ventricular arrhythmia inducibility at EPS had a strong predictive power for arrhythmic events in post-MI patients with low left ventricular EF, provided that inducibility of sustained monomorphic VT was tested. Even early EPS was highly predictive of arrhythmic events, thus opening new therapeutic options in the post-MI phase with the highest arrhythmic risk, which is not covered by current guidelines indications. Based on these data, a more extensive use of EPS could improve the appropriateness of ICD therapy for primary prevention of SCD in post-MI patients.

## Conflicts of interest

None.

## Acknowledgement

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2018.06.002.

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