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META-ANALYSIS

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Arianna Morena [1,2], Federico Giacobbe [1,2], Lorenzo Candido-Todesco [1,2], Andrea Moretti [1,2], Andrea Saglietto [2], Pier Paolo Bocchino [2], Jérôme Garot [3], Matteo Anselmino [1,2], Marco Merlo [4], Gianfranco Sinagra [4], Ibrahim El-Battrawy [5,6,7], Fabrizio D'Ascenzo [1,2], Federico Ferraris [2], Charles Guenancia[8], Robin Nijveldt [9], Davide Castagno [1,2], Moshe Rav Acha [10], Chee Yuan Ng [11], Giulia De Lio [2], Filippo Angelini [2], Simone Frea [2], Claudia Raineri[2], Guglielmo Gallone [1,2], Kristian Hay Kragholm [12], Francesco Ravera [1], Florent Huang [13,14], Mathieu Kerneis [13,14], Gemma Pelargonio [15], Maria Lucia Narducci [15], Massimo Imazio [16], Gaetano Maria De Ferrari [1,2], and Veronica Dusi [1,2]*

[1]Department of Medical Sciences, University of Turin, Turin, Italy; [2]Division of Cardiology, Cardiovascular and Thoracic Department, Città della Salute e della Scienza, Turin, Italy; [3]Institut Cardiovasculaire Paris Sud (ICPS), CMR Department, Hôpital Privé Jacques Cartier, Ramsay Santé, Massy, France; [4]Center for Diagnosis and Treatment of Cardiomyopathies, Cardiovascular Department, Azienda Sanitaria Universitaria Giuliano-Isontina (ASUGI), University of Trieste, Trieste, Italy; [5]Department of Cellular and Translational Physiology, Institute of Physiology, Ruhr University, Bochum 44801, Germany; [6]Department of Molecular and 2-Experimental Cardiology Ruhr-University Bochum, Institut für Forschung und Lehre (IFL), Bochum 44791, Germany; [7]Department of Cardiology and Rhythmology, St.Josef-Hospital, UK RUB, Ruhr University Bochum, Bochum 44791, Germany; [8]Université Bourgogne Europe—CHU DIJON, service de cardiologie—PEC2 UFR Sciences de Santé, Dijon, France; [9]Department of Cardiology, Radboud University Medical Center, Nijmegen, The Netherlands; [10]Integrated Heart Center, Shaare Zedek Hospital, Hebrew University, Jerusalem, Israel; [11]Cardiac Arrhythmia Center, Massachusetts General Hospital, Harvard University, Boston, MA, USA; [12]Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark; [13]ACTION Study Group, Sorbonne Université, Assistance Publique-Hôpitaux de Paris, La Pitié-Salpêtrière Hospital, Department of Cardiology, Paris, France; [14]Sorbonne Université, Assistance Publique-Hôpitaux de Paris, La Pitié-Salpêtrière Hospital, Medical Intensive Care Unit, Paris, France; [15]Department of Cardiovascular Sciences, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy; and [16]Department of Medicine, University of Udine; Cardiothoracic Department, University Hospital Santa Maria della Misericordia, ASUFC, Udine, Italy

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Aims Long-term arrhythmic risk after myocarditis remains uncertain, and optimal management is debated. We aimed to assess the incidence and predictors of major arrhythmic events (MAEs) after myocarditis.

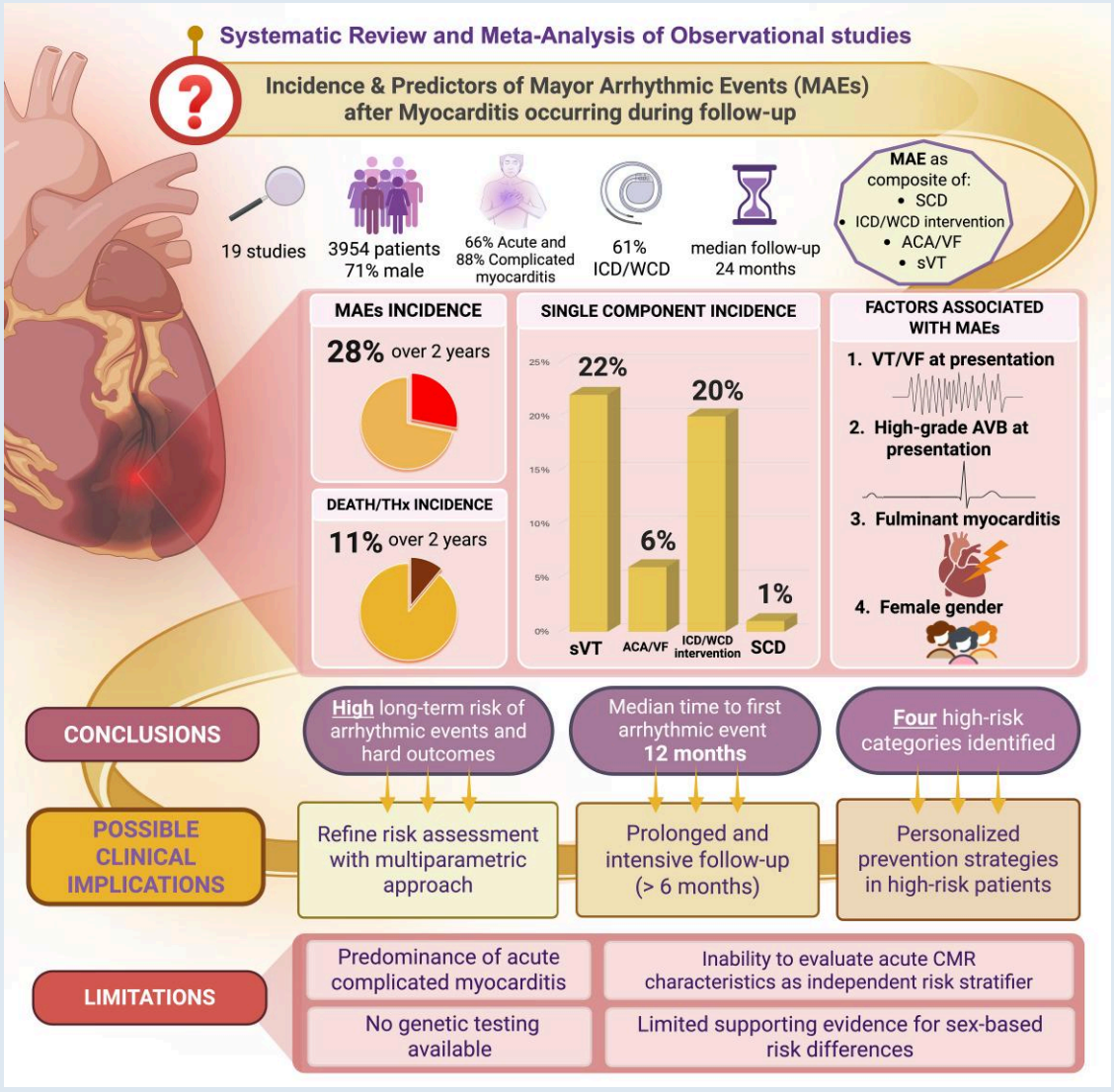
Methods and results We conducted a systematic literature review and meta-analysis including 19 observational studies on myocarditis and MAEs during follow-up. Major arrhythmic events were defined as a composite of sudden cardiac death (SCD), ventricular fibrillation (VF), aborted cardiac arrest (ACA), sustained ventricular tachycardia (sVT), and appropriate implantable cardioverter defibrillator (ICD) or wearable-cardioverter defibrillator (WCD) intervention. The primary outcome was the incidence of MAEs after discharge; secondary outcomes included occurrence of each component of MAEs and the composite of all-cause mortality or heart transplantation (HTx). Three thousand nine hundred and fifty-four patients (71% male, 67% acute, 88% complicated myocarditis) were included. At presentation, 15% had high-grade atrioventricular block (AVB), 31% heart failure, 38% MAEs. At a median

* Corresponding author. Tel: +390116336022, *E-mail address*: veronica.dusi@unito.it

follow-up of 24 months (interquartile range 19–57), 28% suffered MAEs, with a median time of presentation of 12 months. The incidence of sVT, ACA/VF, appropriate ICD/WCD intervention, and SCD were 22%, 6%, 20%, and 1%, respectively. The combined rate of all-cause mortality/HTx was 11%. At meta-regression analysis, high-grade AVB, MAEs at presentation, and fulminant myocarditis were associated with higher risk of MAEs during follow-up, while male gender resulted as a protective factor.

Conclusion The incidence of MAEs after a complicated acute myocarditis can be high over time. Further prospective studies are needed to better stratify high-risk patients, identify those with an underlying arrhythmogenic cardiomyopathy, and guide antiarrhythmic strategies.

Graphical Abstract



The upper part of the figure describes patients characteristics (n=3954 from 19 studies, 61% with ICD/WCD at discharge) and outcomes, together with the four identified factors associated with MAEs after discharge, namely VT/VF at presentation, high-grade AV block, fulminant myocarditis, and female gender. The lower part contains the conclusions of the study, highlighting the high long-term risk of arrhythmic events post-discharge, the possible clinical implications and specifically the importance of refining risk assessment with multimodal approaches, implementing targeted long-term surveillance and considering a personalized approach for high-risk patients and finally the limitations of the study, mostly represented by the lack of genetic testing data, limited evidence for sex-based differences and potential confounding in observational design. Complicated myocarditis was defined by the presence of at least one of the following at presentation: (1) HF at presentation (2) MAEs, or (3) high grade AVB. AVB, atrioventricular block; ACA, acute

cardiac arrest; CMR, cardiac magnetic Resonance; ICD, implantable cardioverter defibrillator; MAE, major adverse event; SCD, sudden cardiac death; sVT, sustained ventricular tachycardia; VF, ventricular fibrillation; WCD, wearable cardioverter defibrillator.

Keywords Myocarditis • Ventricular arrhythmias • Implantable cardioverter defibrillator

What's new

- The risk of arrhythmic events after the acute phase of a myocarditis and the predictors of increased arrhythmic risk during follow-up are still controversial topics.
- This systematic review and meta-analysis shows that the incidence of major arrhythmic events after myocarditis is not trivial in the studied population (mostly complicated cases) and is particularly associated with a severe presentation and the female sex.
- These findings highlight the urgent need for improved patient phenotyping after a first myocarditis, particularly when complicated, to identify those who would most benefit from antiarrhythmic drugs and early implantation of implantable cardioverter defibrillators.

Introduction

Myocarditis is a complex inflammatory disease of the myocardium secondary to infective and non-infective triggers, resulting in heterogeneous clinical manifestations.[1] Some patients are asymptomatic or mildly symptomatic, while others develop severe complications like heart failure (HF), cardiogenic shock (CS), or life-threatening ventricular arrhythmias (VAs) such as sustained ventricular tachycardia (sVT) and ventricular fibrillation (VF).[2] Ventricular arrhythmias can eventually manifest as electrical storms or clustered events, which are particularly challenging to manage and may necessitate acute haemodynamic support[3,4] Notably, myocarditis remains an under-recognized cause of sudden cardiac death (SCD) in some populations, with post-mortem prevalence estimates from 9% to 44% and 2% to 12% of SCDs in young adults.[5,6] In addition, major arrhythmic events (MAEs) can occur during the acute inflammatory phase and in the chronic post–myocarditis period, posing ongoing SCD risk beyond initial presentation.[7,8] As an expression of active inflammation in an otherwise normal heart, acute or sub-acute phase MAEs may lack long-term prognostic value if managed properly[9] and without signs suggesting an underlying arrhythmogenic cardiomyopathy (ACM, hot phase). Conversely, MAEs that arise in the chronic phase[10] may result from persistent inflammation, that in turn might indicate an underlying ACM, and/or from the presence of a post-inflammatory scarring that can be assessed as late gadolinium enhancement (LGE) at cardiac magnetic resonance (CMR) imaging. These findings are associated with long-term occurrence of MAEs even in patients without MAEs at presentation.[1,11,12] Additionally, awareness that acute myocarditis can be an initial manifestation of a genetic cardiomyopathy is a relatively recent development. In the 2024 American Consensus Decision Pathway[13] on myocarditis diagnosis and management, a novel four-stage classification is proposed from stage A (at risk of myocarditis) to stage D (advanced myocarditis). Notably, Stage D includes pathogenic gene variants linked to dilated cardiomyopathy (DCM) and ACM, with emphasis on desmoplakin and titin, as well as associated neuromuscular disorders.

Previously, the 2022 European guidelines on VAs as well as the 2022 American guidelines on HF supported implantable cardioverter defibrillator (ICD) implantation, apart from HF common indications, only as secondary prevention measure regardless of the underlying substrate, such as ejection fraction impairment, LG distribution or presence of high-risk genes mutations.[14,15] Recently, the first focused European guidelines for managing myocarditis and pericarditis was released. Along with (Class IIa, Level C) support for wearable cardioverter-defibrillator (WCD) use for 3–6 months in patients with sustained VTs during the acute phase of myocarditis as a bridge to recovery (recognizing that some of these patients may not need a permanent ICD), clinicians may (Class IIb, Level C) consider ICD implantation 3–6 months after the acute episode in patients with persistent risk factors for ventricular arrhythmias.[16] Nonetheless, WCD usage across European countries is still extremely variable depending on national regulatory and reimbursement policies, as stressed by a recent comprehensive meta-analysis.[17]

In this context, the optimal management and therapeutic approaches for MAEs as well as SCD prevention during myocarditis follow-up, including early ICD implantation, remain a topic of ongoing debate since the predictors of MAEs following myocarditis are still undefined. Accordingly, the 2023 Lancet Commission on Sudden Cardiac Death has highlighted myocarditis, inflammatory cardiomyopathies, and arrhythmic risk stratification as key strategic priorities for the coming decade.[18]

To address this knowledge gap, we conducted a systematic literature review and meta-analysis focusing on the incidence and predictors of MAEs in long-term follow-up of patients experiencing myocarditis.

Methods

Search strategy

This meta-analysis was conducted according to Cochrane Collaborations and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements and was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD420251009444). Pubmed, Ovid Embase, and Scopus were searched up to 31 December 2024 for available studies on myocarditis and MAEs by two investigators (A.M., An.M.) without restrictions relevant to the publication status. An additional reviewer (FG) was involved in reaching a consensus when discrepancies occurred and checking the extracted data for accuracy. Research results were first screened at title/abstract levels; listed studies were then retrieved in full text.

The search strategy included the keywords 'myocarditis' or 'inflammatory cardiomyopathy', 'arrhythmias', 'ventricular tachycardia', 'ventricular fibrillation', 'sudden cardiac death', 'wearable cardioverter defibrillator', 'implantable cardioverter defibrillator', or 'appropriate ICD therapy'. The full electronic Pubmed search strategy is provided in the Supplementary material online, Appendix. As a meta-analysis of previously published observational studies, institutional review board approval was not required.

Selection criteria

We sought after original studies that included patients with a myocarditic presentation leading to hospitalization and reported any

clinical adverse outcomes during ≥3 months follow-up after discharge encompassing VAs, appropriate ICD interventions, SCD, aborted cardiac arrest (ACA), cardiovascular deaths, all-cause deaths, and heart transplantation (HTx). Major arrhythmic events and outcomes occurring during the index hospitalization were not included in the analysis.

The eligible population included patients with either acute or chronic myocarditis leading to hospitalization, mostly confirmed by endomyocardial biopsy (EMB—according to the Dallas criteria, supplemented, when appropriate, by immunohistochemistry and molecular biology),[19] or by CMR imaging based on the original or revised Lake Louise Criteria.[20,21] The distinction between acute and chronic myocarditis, when reported, was based on symptoms duration (less or more than 1 month) and histological findings, with the common ground being the index hospitalization where the diagnosis was initially established.

For each included study, data with the longest follow-up duration was selected. Animal studies, abstracts, case reports, meta-analyses, conference presentations, editorials, expert opinions, studies involving only paediatric patients and immune-mediated myocarditis, including immune checkpoint inhibitor-driven myocarditis as well as Covid 19-related myocarditis were excluded. Each full text study was reviewed twice before inclusion. Reference lists of articles were also searched to identify other relevant studies.

Presentation assessment (definitions used for the present meta-analysis)

Major arrhythmic event at presentation: a combined definition was used including sVT, VF and ACA.

Heart failure at presentation: when reported, the definition varied widely across studies, ranging from initial congestion/haemodynamic deterioration to CS. Accordingly, we maintained this broad definition.

Complicated myocarditis: again, a working definition was used, defined as the presence of at least one of the following at presentation: (1) HF at presentation, (2) MAEs, or (3) high-grade atrioventricular block (AVB).

Fulminant myocarditis: to address heterogeneity and incomplete reporting across included studies, we used a working definition, as already proposed by Ammirati *et al.*,[2] characterized by the presence of either primary haemodynamic compromise (CS) or haemodynamic deterioration due to MAE (including cardiac arrest).

Outcomes assessment

The pre-specified primary outcome of our analysis was the incidence of MAEs, defined as the composite of SCD, ACA, or ventricular fibrillation (VF), sustained ventricular tachycardia (sVT), and appropriate ICD or wearable cardioverter defibrillator (WCD) interventions occurred after discharge and only during follow-up. Secondary endpoints included the incidence of each component of MAEs, along with the incidence of the composite of HTx or all-cause deaths. In case of multiple events in the same patient, only the first event was considered. Furthermore, to identify the significant predictors of MAEs, a pooled analysis of odds ratio (OR) of the main predictors reported at multivariable analysis in our study cohort was conducted. Additionally, a meta-regression analysis of the primary outcome was performed to assess whether the incidence of MAEs was influenced by prespecified study-level factors.

Due to high heterogeneity in our cohort, a leave-one-out sensitivity analysis was performed to assess the robustness of the pooled estimates for the primary outcome: each study was sequentially removed, and the meta-analysis was recalculated to evaluate the influence of individual studies on the overall results. Additionally, targeted single-study exclusion analyses were conducted to explore the impact of specific studies that showed either methodological concerns, high risk of bias, or outlier effect estimates. Finally, another analysis was conducted by considering only studies encompassing patients with ICD implanted after myocarditis presentation, to exclude potential bias given by the invasive monitoring.

Internal validity and quality appraisal

The quality of the included studies was independently appraised by two unblinded reviewers (L.C.-T., An.M.), on prespecified electronic forms with divergences resolved after consensus. We modified the MOOSE item list to incorporate the specific characteristics of the included studies. This involved separately abstracting and appraising aspects such as study design, setting, data source, and statistical methods for multivariable analysis. Consistent with The Cochrane Collaboration's approach, we also assessed the risk of biases, including analytical, selection, adjudication, detection, and attrition biases. This was expressed as low, moderate, or high risk of bias, and incomplete reporting leading to inability to ascertain the underlying risk of bias. The Cochrane Risk of Bias in non-randomized controlled trials ROBIN I tool was used to assess quality for adjusted observational studies.[22] Study quality assessment is represented in Supplementary material online, *Figure S1* in Supplementary material online, Appendix. Small study bias was appraised by graphical inspection of funnel plots and Egger's test.

Statistical analysis

Continuous variables are reported as mean (standard deviation, SD) or median [first (Q1) and third quartile (Q3) range; interquartile range (IQR)]. Categorical variables are expressed as *n* (%). Statistical pooling for incidence estimates and for OR of predictors of studies at multivariate analysis was performed according to a random-effects model with generic inverse-variance weighting, computing risk estimates with 95% confidence intervals (CIs), using STATA v18 (StataCorp, College Station, TX, USA). Univariate meta-regression analysis was performed via linear mixed-effects models with the STATA 'metareg' package.

Hypothesis testing for superiority was set at the two-tailed 0.05 level. Hypothesis testing for statistical homogeneity was set at a two-tailed 0.10 level and based on the Cochran Q test, with I^2 values of 25%, 50%, and 75% representing mild, moderate, and extensive statistical inconsistency, respectively. Given variability in trial duration, event rates were used instead of raw event counts.

Results

Search results

Our search strategy identified 7414 records, of which 2817 were duplicates. Four additional studies were identified using backward and forward snowballing techniques. Titles and abstracts of 4597 papers were evaluated, and a total of 66 full-text articles were retrieved and assessed for eligibility. Of these, 47 studies did not meet the inclusion criteria and were excluded; thus, 19 studies were included in the final meta-analysis.[7,23–40] The PRISMA flowchart is reported in ***Figure 1***. All studies were observational: 16 (84.2%) were retrospective and 3 were prospective.

Risk bias assessment results

ROBIN-I risk of bias assessment for included studies is shown in Supplementary material online, *Figure S1*. Five studies[26,27,29,32,39] had a serious risk of bias in a maximum of one domain each, primarily in D2 (participant selection, 4/5 cases), and in one instance in D7 (result selection reporting). Across all studies and domains, 2[29,38] and 7[7,24–26,30,33,39] out of 19 studies were considered to have a serious and moderate risk of bias, respectively. This results in an overall serious bias risk of 10.5% and a moderate or serious bias risk of 47%.

Study population and baseline characteristics

A total of 3954 patients [71% male, median age: 46 (IQR 43–51) years old] were included in the final analysis. The individual

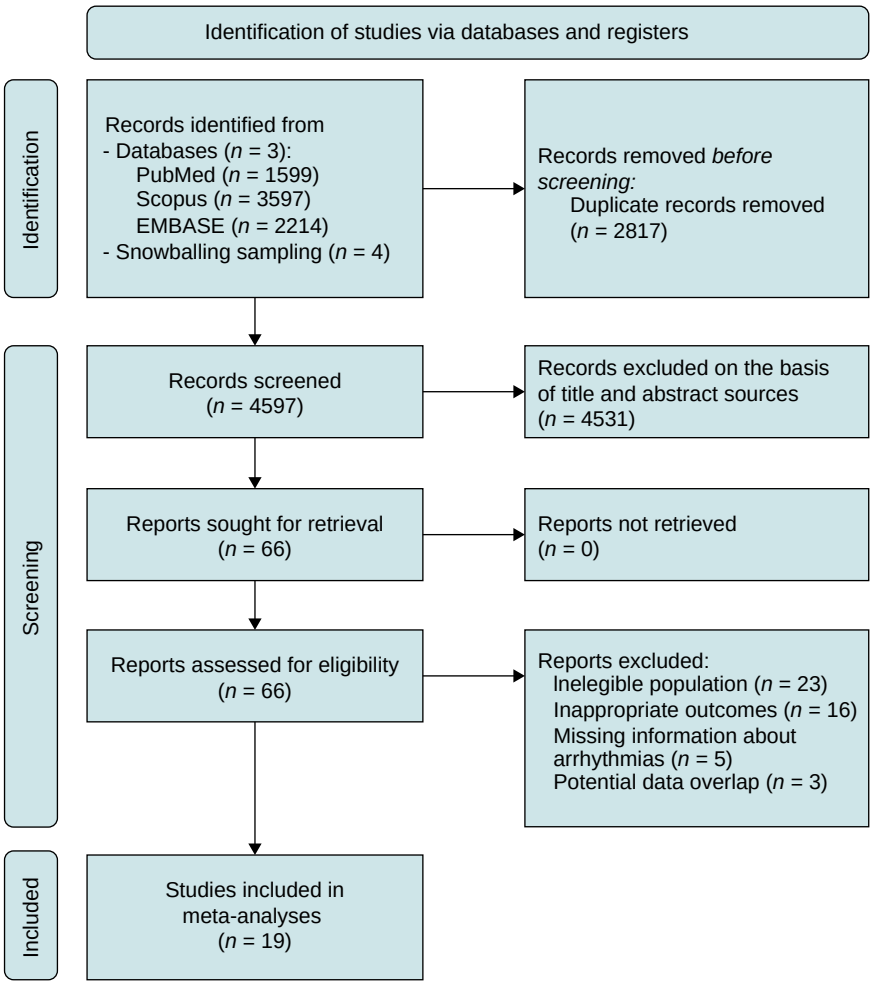


Figure 1 PRISMA flow diagram. PRISMA, Preferred Reporting Items of Systematic Reviews and Meta-Analysis.

study definitions of MAE and the characteristics of each included study are shown in *Table 1*.

Overall, 12 studies focused on the arrhythmic risk following myocarditis, all the studies reported on the incidence of SCD, sVT, VF (or ACA) and, when available, ICD/WCD appropriate interventions. Notably, three studies[30,31,34] focused on the use and potential benefit of WCD devices at discharge among myocarditis with reduced left ventricular ejection fraction (LVEF) or in secondary prevention. Comprehensive data on the included studies and the populations' baseline characteristics are reported in *Table 2*.

The population was primarily affected by acute myocarditis (66.5%) while the remaining were chronic ones. Additionally, 12 (63.2%) studies focused on complicated myocarditis (see methods for the definitions) of which 6 (31.6%) included only myocarditis with arrhythmic presentation. Overall, 88% of patients (IQR 51.2–100%) presented with complicated myocarditis.

The main presenting clinical manifestations were high-grade AVB (15.1%; IQR 3.3–25.5%), HF (30.5%; IQR 21.9–44.7%), and MAEs (38.1%; IQR 21.2–63.7%), namely sVT (27.6%; IQR 18.6–44.6%) and VF (12.5%; IQR 3.9–25.6%). Median LVEF at presentation was 47% (IQR 38–50%).

In most studies, myocarditis diagnosis had to be confirmed by either EMB or CMR imaging (see Supplementary material online, *Table S1*). Of 19 studies, 8 (42%) required biopsy for diagnosis,[24,25,30,32–34,37,38] 3 (16%) required CMR,[28,35,36] and 1 (5%) required both.[40] Among the remaining 7 studies, 4 (21%) required either CMR or biopsy,[23,26,27,39] while 3 (16%) relied on clinical diagnosis,[7,29,31] although CMR was often performed in two of these. Overall, EMB was available in 83.5% (IQR 56–100%) cases. The most common histological subtype was lymphocytic myocarditis (55.8%; IQR 0–92.3%) and almost 7% had giant cells myocarditis (6.8%; IQR 0.6–100%), the latter coming mainly from four studies[23,32,36,38] focusing on this specific subtype. Cardiac magnetic resonance was performed in 79% (IQR 54.8–97.8%) of the total population, and overall LGE was present in most cases (89.4%; IQR 77.9–100%).

Medical therapy, genetic analysis, and ICD at discharge

Considering studies reporting data on antiarrhythmic drugs at discharge, most patients were discharged on beta-blocker (84.6%; IQR 74.8–93.6), albeit with a great variability across studies (from 30% to 100%) and only 10.8% (IQR 8.8–15.0%)

Table 1 Summary of studies characteristics

Study (year)	Study design	Population size (*n*)	Age, median or mean (IQR or SD)	Arrhythmic presentation definitions	HF at presentation, *n* (%)	ICD/WCD implantation at discharge, *n* (%)	Follow-up in months (median (IQR or range))	Inclusion criteria	MAEs definition	Primary endpoints
Gentile (2021)	OR	156	44 (33–55)	VF and sVT	–	93 (59.6)	23 (7–60)	AM with life-threatening VAs at presentation, alive at discharge and without occurrence of HTx or LVAD implantation during the index hospitalization.	SCD or successfully defibrillated VF, sVT requiring ICD therapy or synchronized external cardioversion.	Recurrence of MAEs after discharge as composite of SCD, successfully defibrillated VF, documented sVT requiring synchronized external cardioversion or ICD therapy.
Ekström (2016)	OR	51	52 (±12)	VF, sVT and distal AVB	20 (39.2)	31 (60.8)	19	Giant cell myocarditis diagnosed by EMB or surgical myocardial biopsies, autopsy or after transplantation.	SCD or successfully defibrillated VF by ICD or DC shock, VT requiring ICD therapy or DC shock.	SCD (fatal or aborted)
Pelargonio (2020)	OR	56	51	VF and sVT	25 (44.6)	56 (100)	65	EMB proven myocarditis who received an ICD for either primary or secondary prevention.	VAs causing haemodynamic instability (VF, sVT, nsVT).	Occurrence of cardiac death or appropriate ICD-delivered therapy, either ATP or shock.
Rav-Acha (2024)	OR	69	44 (36–56)	MMVT, sVT, VF, and nsVT	31 (45)	24 (34.8)	66	AM (verified by CMR or EMB) with documented VAs during acute phase illness.	Sustained MMVT, sustained polymorphic VT/VF, and nsVT.	Sustained VA or all-cause mortality.
Kahle (2022)	OR	76	41.5 (±2.5)	MMVT, VF, PVC	–	43 (56.6)	24 (±3)	Myocarditis (verified by CMR or EMB) with or without arrhythmic presentation.	Recurrent VA, as MMVT, VF, and PVC.	Characteristics and prognostic relevance of VA in patients with myocarditis.

Continued

Table 1 *Continued*

Study (year)	Study design	Population size (*n*)	Age, median or mean (IQR or SD)	Arrhythmic presentation definitions	HF at presentation, *n* (%)	ICD/WCD implantation at discharge, *n* (%)	Follow-up in months (median (IQR or range))	Inclusion criteria	MAEs definition	Primary endpoints
Peretto (2020)	OP	185	44 (±15)	VF, sVT, nsVT, grade ≥2 PVC (Lown's classification), advanced AVB	46 (24.8)	78 (42.2)	27 (±7)	Myocarditis (verified by CMR and EMB) and VA at index hospitalization.	sVT, VF, or appropriate ICD therapy.	Predictors of malignant VA (including VT, VF, or appropriate ICD therapy) in patients with myocarditis at different inflammatory stages.
Kragholm (2021)	OR	2523	49 (30–69)	VT, sVF, atrial fibrillation or flutter, AVB	324 (12.8)	40 (1.6)	3	Myocarditis, either as primary or secondary diagnosis with a primary diagnosis of HF, sVT/VF/arrest, ICD Implantation or AF.	Major VAs (sVT, VF, cardiac arrest) and ICD implantation.	90-day risks of all-cause mortality.
Tscholl (2021)	OR	59	46 (±14)	sVT and VF	–	59 (100)	24 (±22)	Carriers of WCD for SCD prevention for the diagnosis of myocarditis with LVEF < 50% and/or arrhythmias.	sVT and VF.	Composite of sustained VA and overall mortality during follow-up.
El-Battrawy (2023)	OR	124	51.6 (±13.4)	VT and VF	34 (27.4)	124 (100)	3	Carriers of WCD due to myocarditis and reduced LVEF or prior VA.	Major VAs, including VT, VF, appropriate WCD/ICD shock.	Predicting or identifying patients with myocarditis at risk for SCD due to VT/VF.
Sasko (2021)	OR	51	43 (30–56)	VF or unstable VT	16 (30)	51 (100)	56.4 (12–144)	Biopsy proven viral myocarditis with VF or haemodynamic unstable VT at presentation, LGE at CMR, preserved LVEF and ICD implantation for secondary prevention.	VT and VF.	VT/VF recurrence and predictors of recurrences.

Continued

Table 1 *Continued*

Study (year)	Study design	Population size (*n*)	Age, median or mean (IQR or SD)	Arrhythmic presentation definitions	HF at presentation, *n* (%)	ICD/WCD implantation at discharge, *n* (%)	Follow-up in months (median (IQR or range))	Inclusion criteria	MAEs definition	Primary endpoints
Rosier (2020)	OR	68	47	VT/VF treated with ICD either ATP or shock	–	65 (100)	36	Carriers of ICD for sVT/VF during acute phase of myocarditis or as myocarditis sequelae.	ICD appropriate interventions on either VT or VF.	Occurrence of a MAE.
Kandolin (2013)	OR	32	50	sVT, VF, and distal AVB	10 (31)	18 (69.2)	15	Histologically verified giant cell myocarditis.	sVT or VF.	Occurrence of HTx or death.
Blaschke (2021)	OR	39	47.5 (±14.7)	nSVT and sVT	–	39 (100)	3	Carriers of WCD in clinically suspected myocarditis.	sVT in patients wearing WCD.	Occurrence of VA (sustained and non-sustained) in myocarditis compared to DCM patients, both wearing WCD.
Vos (2022)	OR	162	40 (27–54)	VF (with or without ICD shock), unstable VT, or sVT with ICD shock and high-grade AVB	–	–	66 (26.4–99.6)	CMR proven acute myocarditis.	Major VAs such as VF (with or without ICD shock), haemodynamic unstable VT, or sVT with ICD shock.	Occurrence of MACE: all-cause mortality, HTx, HF hospitalizations, and life-threatening VAs.
Sanguineti (2015)	OP	203	42.7 (±16.5)	sVT and VF	10 (5)	–	18.9 (±8.2)	CMR-based diagnosis of AM.	Occurrence of SCD, ACA, sVT.	Occurrence of MACE such as SCD or aborted SCD, HTx, documented sVT, HF, recurrence of AM, and the need for hospitalization for cardiac causes.

Continued

Table 1 *Continued*

Study (year)	Study design	Population size (*n*)	Age, median or mean (IQR or SD)	Arrhythmic presentation definitions	HF at presentation, *n* (%)	ICD/WCD implantation at discharge, *n* (%)	Follow-up in months (median (IQR or range))	Inclusion criteria	MAEs definition	Primary endpoints
Maleszewski (2015)	OR	26	54.6 (±14.1)	VAs	15 (57.7)	15 (57.6)	57.6 (12–199.3)	Biopsy proved GCM survived for >1 year without heart transplantation.	Occurrence of VAs.	Rates of recurrent HF, VAs, renal failure and infectious complications.
Narducci (2021)	OP	31	42 (±14)	sVT, VF, and/or appropriate ICD interventions	–	13 (41.9)	19 (14–32)	Unexplained complex VAs and clinical suspected myocarditis with LVEF >40%.	Occurrence of sVT, VF, and/or appropriate ICD interventions.	Incidence of sustained VAs, defined as sVT, VF, and/or appropriate ICD interventions.
Anzini (2016)	OR	15	37 (25–65)	sVT or VF	2 (13)	10 (67)	58 (38–108)	AM EMB or CMR proved presenting with sVT.	SCD or appropriate ICD intervention on SVT (ATP or ICD shock)	Recurrence of MAE such as SCD or appropriate ICD intervention on sVT (ATP or ICD shock).
Nordenswan (2021)	OR	28	58 (±10)	nsVT, sVT, VF, and high-grade AVB	13 (46)	13 (46)	–	Clinical or post-mortem diagnosis of either cardiac sarcoidosis or GCM.	SD, aborted SCD (VF terminated successfully either by an ICD or by external defibrillation).	Recurrence of MACE: cardiac death, aborted SCD, and HTx.

AM, acute myocarditis; ACA, aborted cardiac arrest; AVB, atrioventricular block, ATP, antitachycardia pacing; CMR, cardiac magnetic resonance; EMB, endomyocardial biopsy; ICD, implantable cardiac defibrillator; GCM, giant cell myocarditis; VF, ventricular fibrillation; MACE, major adverse cardiovascular events; MAE, major arrhythmic events; MMVT, monomorphic ventricular tachycardia; nsVT, non-sustained ventricular tachycardia; PVC, premature ventricular contractions; SCD, sudden cardiac death; SD, sudden death; sVT, sustained ventricular tachycardia; VA, ventricular arrhythmias; WCD, wearable cardioverter defibrillator; HTx, heart transplantation; HF, heart failure; OR, observational retrospective; OP, observational prospective.

Table 2 Summary of clinical and instrumental characteristics of the cohorts included in the meta-analysis

	Patient's characteristics, %				Myocarditis type, %						Presentation, %						CMR*, %		Therapy at discharge, %			
Study (year)	Male	HP	DM	EMB	Lymphocytic	Giant cells	Eosinophilic	Sarcoidosis	Acute	Chronic	High-grade AVB	HF	VF / sVT	VF	sVT	\colorbox{red}{\quad} LVEF	CMR	LGE	BBs	Amiodarone	ICD	WCD
Gentile (2021)	77	–	–	62.8	55.8	3.2	2.6	1.3	–	–	–	–	100	33.3	66.6	50	75	80.3	93	–	59	0.6
Ekström (2016)	31.4	–	–	100	0	100	0	0	–	–	27	39.2	22	7.8	13.7	–	47.1	100	–	–	60.8	0
Pelargonio (2020)	56	–	–	100	100	0	0	0	46.4	53.6	–	44.6	40	12.5	26.7	42	62.5	–	84	8	100	0
Rav-Acha (2024)	66.7	17.6	7.6	40.6	23.2	8.7	7.2	1.4	100	0	–	45	55	18.8	36.2	41	82.6	–	78.2	9	34.8	0
Kahle (2022)	74.3	–	–	64.5	–	–	–	–	31.6	9.2	–	–	42.1	14.5	27.6	47	90.8	73.7	73.7	10.5	30.3	26.3
Peretto (2020)	69	18	8	61.1	61.1	0	0	0	66.5	–	17	24.8	36.2	4.3	31.8	49	100	100	84.9	–	42.2	0
Kragholm (2021)	67.7	31.9	7.7	3.9	–	–	–	–	–	–	1.4	12.8	1.8	–	–	–	8.5	–	30.2	–	1.6	0
Tscholl (2021)	81.4	33.9	18.6	100	76.3	6.8	3.4	1.7	–	–	–	–	18.6	3.4	15.2	32	0	–	94.9	–	0	100
El-Battrawy (2023)	74.2	38	16.4	–	–	–	–	–	–	–	–	27.4	40	–	–	30	79	88.8	91.4	11.1	0	100
Sasko (2021)	72.5	–	0	100	100	0	0	0	100	0	–	30	100	–	–	50	100	100	84.3	25.5	100	0
Rosier (2020)	83.8	19.1	4.4	0	–	–	–	–	41.2	58.8	–	–	89.7	32.4	57.3	–	95.6	100	93.8	21.5	100	0
Kandolin (2013)	26.9	–	–	–	0	100	0	0	100	0	31.2	31	25	3.1	21.8	38	28.1	–	96.1	–	69.2	69.2
Blaschke (2021)	87.2	41	10.3	100	92.3	–	–	7.7	10.3	89.7	–	–	5.1	0	5.1	25.6	–	–	100	12.8	0	100
Vos (2022)	75	16	3	13	9.2	1.2	1.2	–	100	0	0.6	–	–	–	–	51	100	90	–	–	–	–
Sanguineti (2015)	76	–	–	–	–	–	–	–	–	–	–	5	6	–	–	57	100	100	–	–	–	–
Maleszewski (2015)	35	–	–	100	0	100	0	0	100	–	–	57.7	–	–	–	–	–	–	73	–	57.6	0
Narducci (2021)	–	–	–	100	100	–	–	–	25.8	74.1	–	–	35.5	–	–	55	–	39	62	7	41.9	0
Anzini (2016)	60	–	–	67	–	–	–	–	–	–	–	13	100	47	53	–	73	73	–	–	67	0
Nordenswan (2021)	32	21	7	100	0	100	0	–	–	–	21	46	–	–	–	–	–	100	–	–	46	0

AVB, atrioventricular block; CAD, coronary artery disease; CRM, cardiac magnetic resonance; DM, diabetes mellitus; EMB, endomyocardial biopsy; HF, heart failure; ICD, implantable cardiac defibrillator; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; HP, hypertension; VF, ventricular fibrillation; SVT, sustained ventricular tachycardia; WCD, wearable cardioverter defibrillator. *During the index hospitalization.

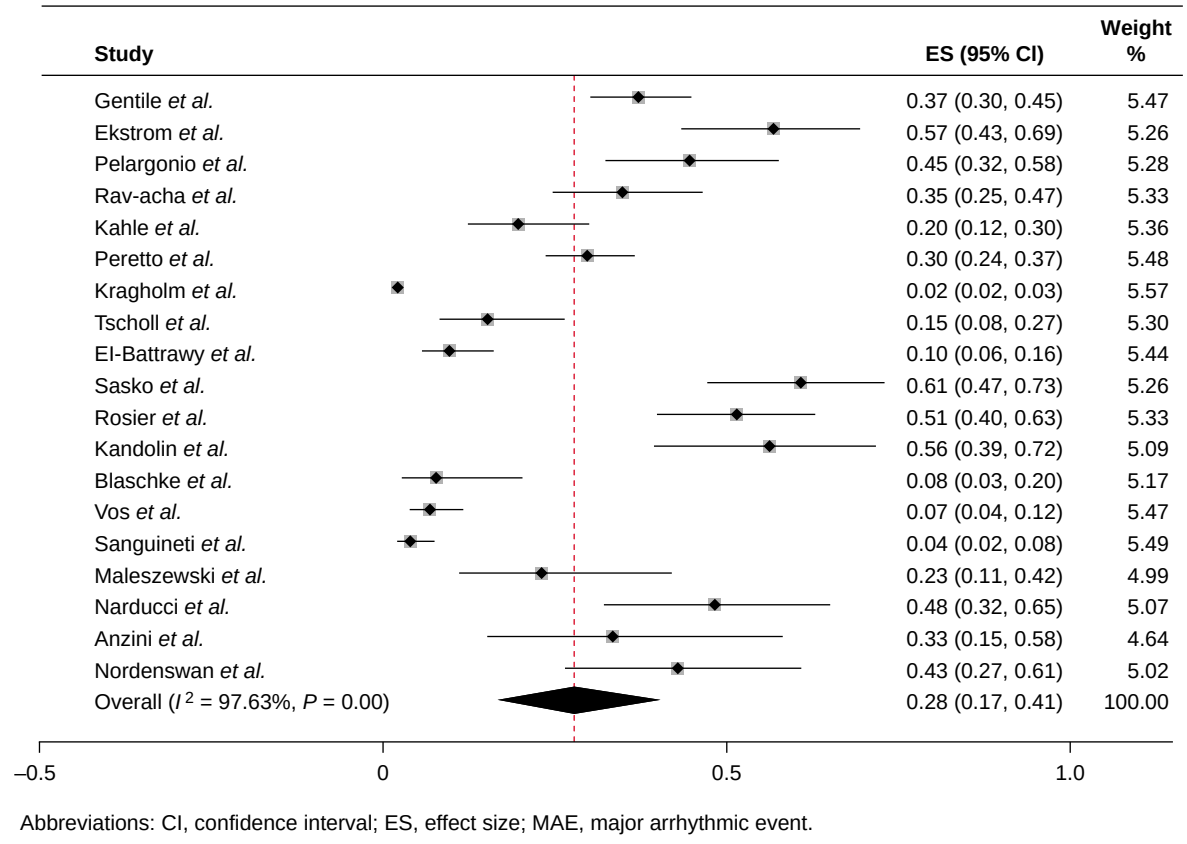


Figure 2 **Primary endpoint. Incidence of MAEs during follow-up in the overall population.** CI, confidence interval; ES, effect size; MAE, major arrhythmic event.

on amiodarone. The type and dose of beta-blocker were not reported. Implantation of an ICD or prescription of a WCD was performed at the time of discharge in more than half of the population (60.8%; IQR 46.0–100.0%).

In six studies,[7,25,30–32,34] ICD implantation or WCD prescription at discharge was 100%. The majority of WCD carriers derived from three studies[30,31,34] focused on these specific devices. In none of the included studies, patients were reported to have undergone genetic analysis to exclude an underlying cardiomyopathy at onset.

Primary and secondary outcomes and predictors of MAEs

At a median follow-up of 24 months (IQR 19–57), the pooled proportion of patients who experienced a MAE was 28% (95% CI 17–41%) with high heterogeneity among studies (I^2 98%). ***(Figure 2)***. The median time of MAE presentation was 12 months (IQR 10–19).

Only 12 SCDs were reported over 2 years, with an overall incidence of 1% (95% CI 0–4%). Appropriate ICD/WCD interventions were registered in 20% of cases (95% CI 9–34%). ACA/VF and sVT had an incidence of 6% (95% CI 0–15%) and 22% (95% CI 10–37%), respectively; ultimately, the combined incidence of all-cause mortality and HTx was 11% (95% CI 6–18%). All secondary outcomes results are represented in *Figures 3*, *4*, and *5*.

At meta-regression analysis, high-grade AVB at presentation (β coefficient 0.125, $P = 0.003$), VF/sVT at presentation (β coefficient 0.020, $P = 0.022$), and fulminant myocarditis (β coefficient 0.020, $P = 0.032$) were identified as study-level variables associated with a higher incidence of MAEs during follow-up. Heart failure at presentation, heterogeneously defined and reported across studies, showed a borderline-significant trend towards higher MAE risk (β coefficient 0.005, $P = 0.052$), while male gender showed a statistically significant inverse association (β coefficient −0.005, $P = 0.042$). On the contrary, the presence of LGE at CMR, histological subtype, LVEF <35%, and acute or chronic phenotype at EBM were not associated with MAE incidence during follow-up. All meta-regression results are presented in ***Table 3*** and shown through the bubble plot in ***Figure 6***. Ultimately, due to the limited number of MAEs predictors found in the individual studies, the pooled analysis of ORs could not be performed.

Sensitivity analyses

A leave-one-out sensitivity analysis was performed to assess the robustness of the pooled incidence estimate of MAEs. The exclusion of individual studies did not significantly alter the overall pooled estimate, with incidence values ranging from 27% to 31% as shown in Supplementary material online, *Table S2*. This indicates that no single study disproportionately impacted the overall result, supporting the stability and reliability of the findings.

After that, a targeted single-study exclusion was performed by excluding the study of Kragholm *et al.*,[29] which encompassed the majority of patients of our study cohort, so as to prevent any possible dominance bias of this study. In addition, its short median

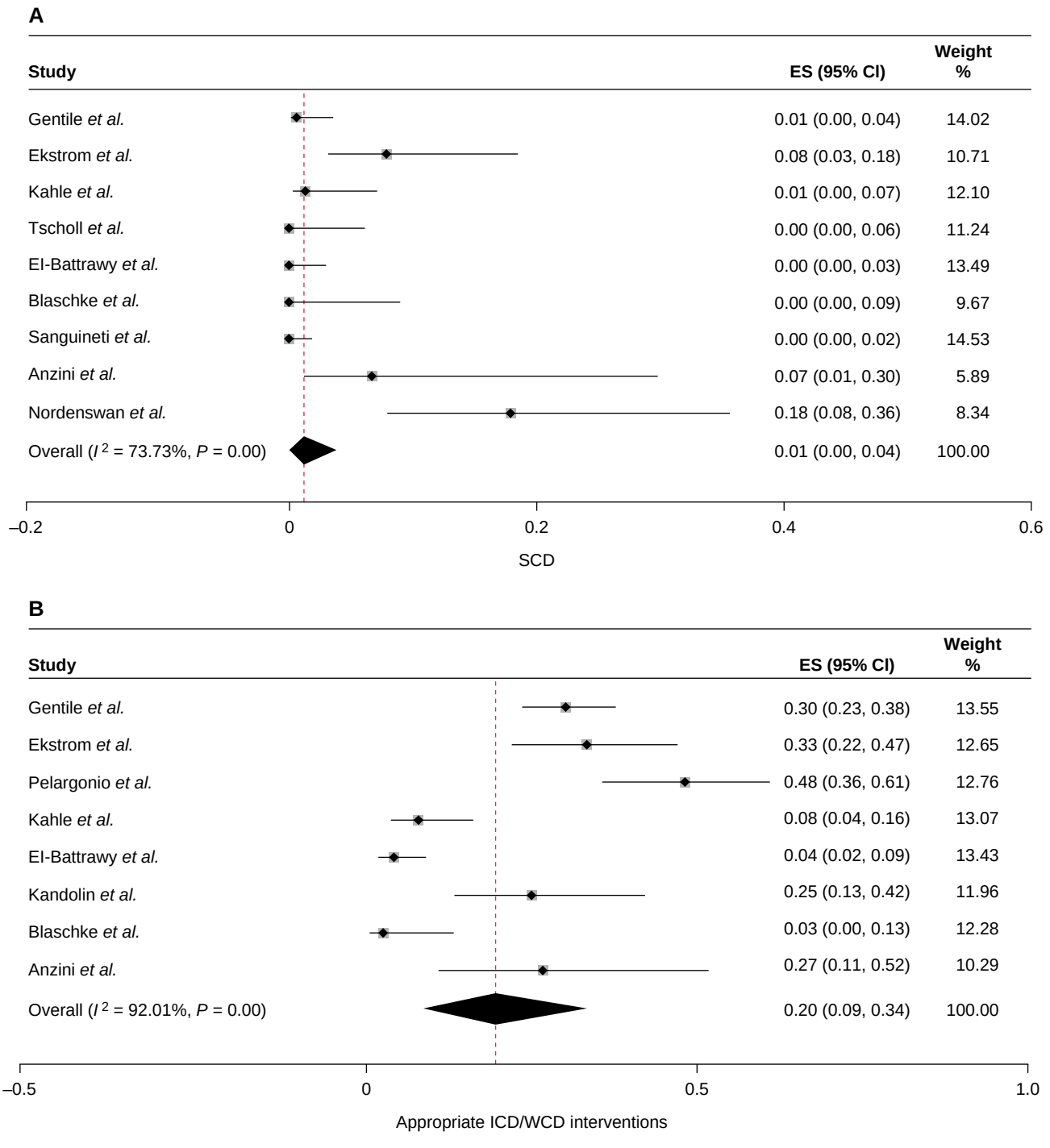


Figure 3 Secondary endpoints. Incidence of SCD (A) and of appropriate ICD/WCD Interventions (B) during follow-up. ICD, implanted cardioverter defibrillator; SCD, sudden cardiac death.

follow-up duration (3 months) and the very low rate of ICD implantation at discharge (1.6%) may justify the lower detection rate of MAEs, which showed the lowest incidence (2.1%) among all included studies. The sensitivity analysis was conducted only on total MAEs and all-cause mortality/HTx. As expected, the revised pooled incidence of MAEs was higher at 31% (95% CI 23–40%) as well as the composite of death/HTx at 12% (IQR 4.5–22%) as reported in Supplementary material online, *Figures S2 and S3* in Supplementary material online, Appendix.

After excluding this study, the results at meta-regression analysis did not differ from the previous ones, as shown in Supplementary material online, *Table S3* and Supplementary material online, *Figure S3* of the Appendix, supporting the robustness and reproducibility of our results.

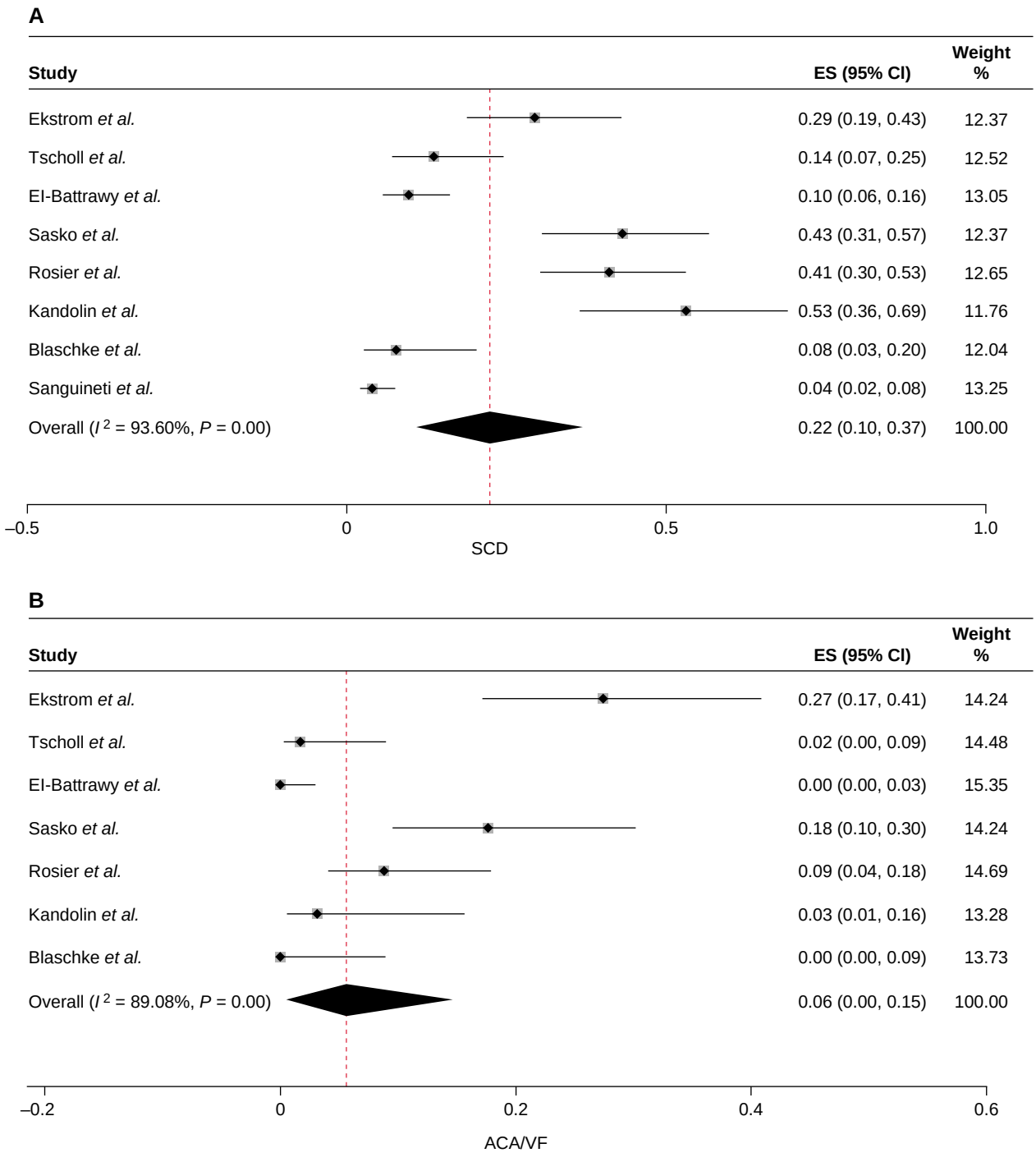


Figure 4 Secondary endpoints. Incidence of sVT (A) and ACA/VF (B) during follow up. ACA, aborted cardiac arrest; sVT, sustained ventricular tachycardia; VF, ventricular fibrillation.

An additional sensitivity analysis, limited to the 6 studies in which all patients had an ICD/WCD at discharge (Figure 7), showed an incidence of MAEs of 29% (95% CI: 12–50%, I^2 = 94%) over a median follow-up of 30 months. Notably, in this subgroup, no SCDs occurred and the incidence of all-cause death/HTx was lower (5% vs. 11%), Figure 8. Supplementary material online, *Table S4* details the incidence and type of MAEs across these six studies. Post-discharge MAE rate ranged 5–51%, higher in combined ICD (52%) than WCD (6%) recipients ($P < 0.0001$). This difference likely reflects variations in follow-up duration (longer in ICD recipients) and patient heterogeneity across studies. Among 80 patients from 5 of 6 studies with available VAs type details, VTs were the predominant treated VA (80% vs. 20% VF), suggesting a primary mechanism related to anatomical scar. The percentage of patients with treated VF episodes did not significantly differ between ICD

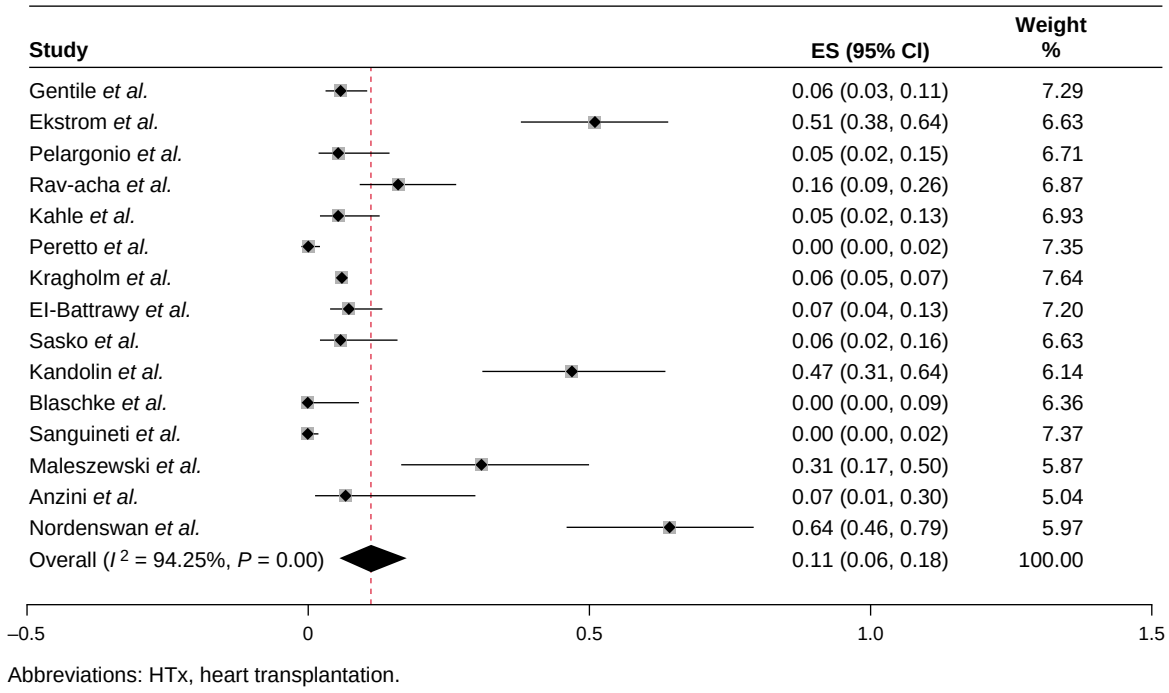


Figure 5 Secondary endpoints. Incidence of all-cause death/HTx during follow-up in overall population. HTx, heart transplantation.

Table 3 Meta-regression of the study-level effect modifiers of MAE incidence after myocarditis

	Study arms, *n*	β coefficient	*P* value	I^2, %	R^2, %
Male	19	−0.0310	**0.046**	100	16.9
Age, y	19	0.0056	0.553	97	−3.4
CAD	6	−0.0140	0.147	96	32.0
Lymphocytic myocarditis	13	−0.0053	0.783	63	−18.9
Giant cells myocarditis	11	0.0013	0.300	94	3.9
Acute myocarditis	11	0.0009	0.614	94	−8.6
Chronic myocarditis	9	−0.0019	0.935	68	−18.4
High-grade AVB at presentation	6	0.1254	**0.003**	98	89.1
VF/sVT at presentation	17	0.0208	**0.022**	100	26.2
HF at presentation	12	0.0500	0.052	100	26.6
LVEF <35% at presentation	3	0.1158	0.267	68	74.1
LGE at CMR	14	0.0033	0.863	96	−7.7
Fulminant myocarditis	18	0.0207	**0.032**	100	21.1

AVB, atrioventricular block; CAD, coronary artery disease; CMR, cardiac magnetic resonance; HF, heart failure; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; VF, ventricular fibrillation; sVT, sustained ventricular tachycardia. Bold values are significant at $P < 0.05$.

(23%, 15/66) and WCD recipients (7%, 1/14, $P = 0.1882$), likely due to patient heterogeneity across studies.

Discussion

In this systematic review and meta-analysis, we aimed to determine the incidence of MAEs in patients with a prior myocarditis requiring hospitalization, mainly with a complicated presentation, and to identify clinical features linked to arrhythmic events during long-term post-discharge follow-up. The main findings and related potential implications can be summarized as follows (*Graphical abstract*):

(1) In this selected population mostly presenting with complicated acute myocarditis, the pooled incidence of MAE during a median 2-year follow-up was 28%, including a 1% incidence of SCD.

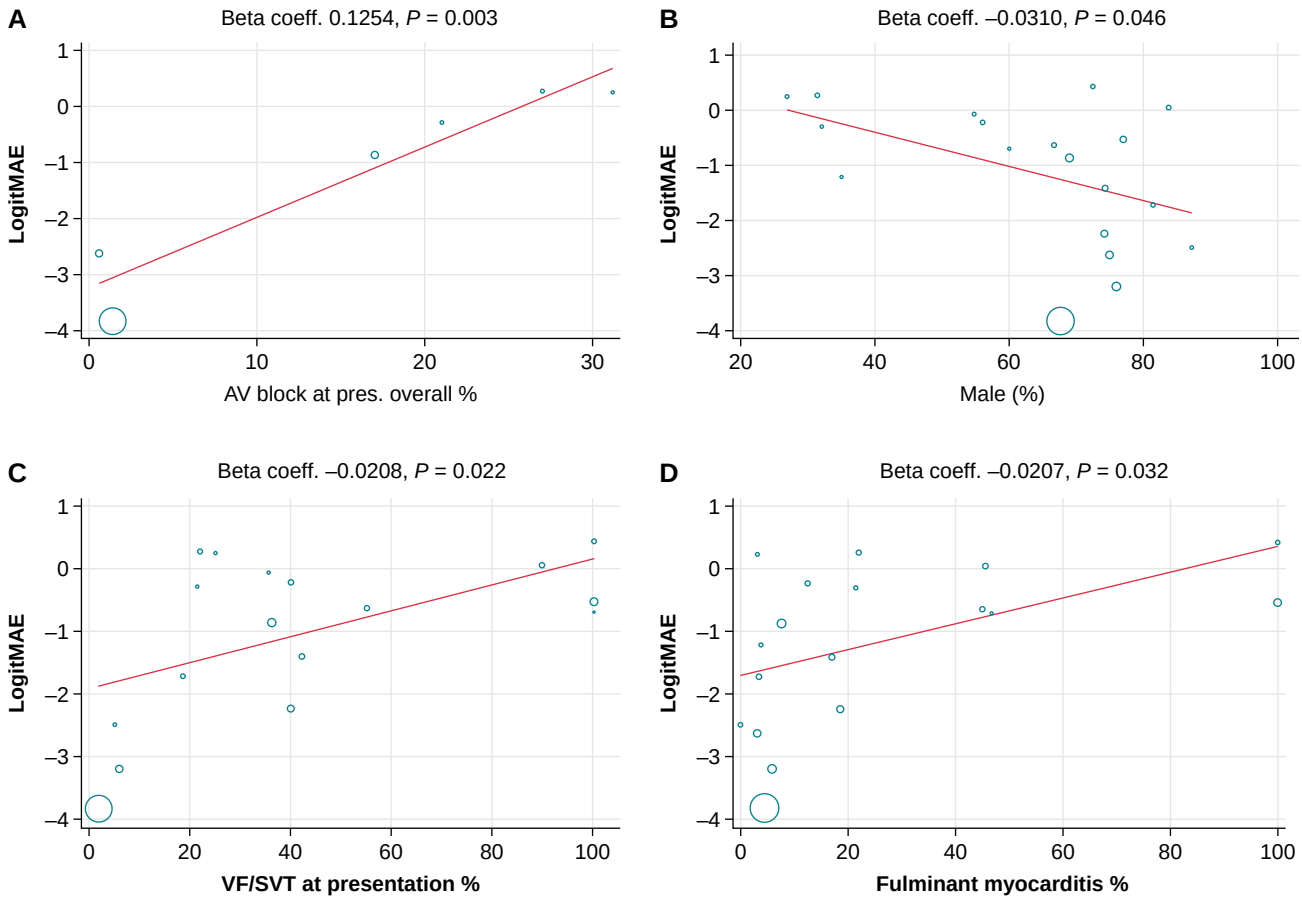
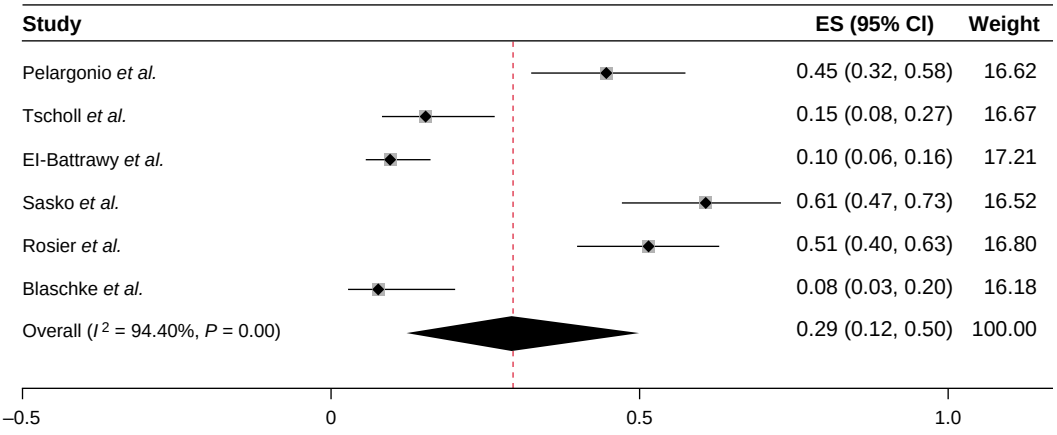
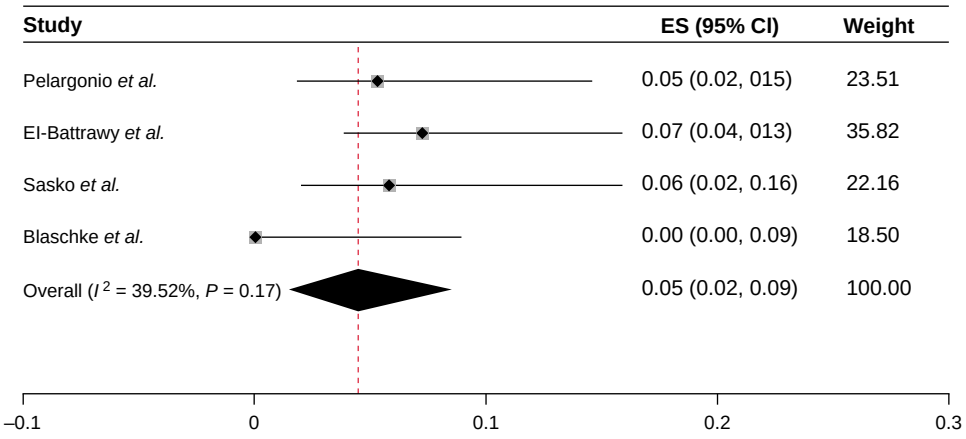


Figure 6 **Study-level statistical significant variables of MAEs. Bubble plot.** AV, atrioventricular; MAE, major arrhythmic event; sVT, sustained ventricular tachycardia; VF, ventricular tachycardia.



Abbreviations: ICD, implanted cardioverter defibrillator; MAE, major arrhythmic event; WCD, wearable cardioverter-defibrillator.

Figure 7 **Sensitivity analysis focused only on studies with full ICD/WCD carriers at discharge. Incidence of MAEs during follow-up.** ICD, implanted cardioverter defibrillator; MAE, major arrhythmic event; WCD, wearable cardioverter-defibrillator.



Abbreviations: HTx, heart transplantation; ICD, implanted cardioverter defibrillator; WCD, wearable cardioverter-defibrillator.

Figure 8 Sensitivity analysis focused only on studies with full ICD/WCD carriers at discharge. Incidence of death/THx during follow-up. HTx, heart transplantation; ICD, implanted cardioverter defibrillator; WCD, wearable cardioverter-defibrillator.

(2) The median time to MAE occurrence was 12 months after the index myocarditis event.
(3) The sensitivity analysis restricted to studies with ICD/WCD carriers revealed a comparable MAE incidence of 29%, but with a significantly lower rate of all-cause death or HTx (5% vs. 11%) and no SCDs.
(4) Clinical characteristics at presentation suggestive of complicated myocarditis such as high-grade AVB at presentation, VF/VT at presentation, and fulminant myocarditis, as well as female sex, were associated to higher long-term MAEs incidence whereas this did not occur for LGE at CMR or LVEF during the index hospitalization.
(5) The composite incidence of all-cause mortality and HTx was 11% at 2 years.
(6) The occurrence of sVTs, ACAs/VF, and appropriate ICD/WCD interventions during the same follow-up were 22%, 6%, and 20%, respectively. None of the included studies reported genetic analysis to exclude an underlying ACM at onset.

To date, managing arrhythmic risk and preventing SCD after myocarditis remains controversial due to limited evidence. Long-term follow-up has documented life-threatening arrhythmias after acute myocarditis, with incidences reported from 28% to 61%.[7,41] Variations arise from differences in study populations, patient characteristics, detection methods, discharge therapy, and follow-up length.[42] A recent meta-analysis of five studies on myocarditis with arrhythmic presentation showed higher VA recurrence (41% over 2 years) than our findings.[41] Without systematic genotyping, many MAEs at presentation may reflect a hot phase of a genetically determined cardiomyopathy rather than classical myocarditis.[43] Another meta-analysis of 586 patients found a pooled prevalence of pathogenic/likely pathogenic (P/LP) variants in cardiomyopathy genes of 4.2% (uncomplicated) and 21.9% (complicated presentations).[44] Another important yet underexplored issue is how discharge antiarrhythmic therapy,[45] especially beta-blocker type and dose (often unreported), affects MAEs. Reported beta-blocker use was highly heterogeneous across studies and may have influenced MAEs.[46]

Although our study population more closely reflects real-world practice than Narducci *et al.*[41] meta-analysis, we still observe a higher prevalence of complicated cases than the historical 25%.[47] This includes patients with acute haemodynamic deterioration and other severe cases that may carry dangerous genetic variants, potentially explaining the high rate of sequelae during follow-up and limiting generalizability. The high prevalence of ICD/WCD use (median 60.8%) in the included studies suggests clinical concern in this setting. Although ICD/WCD use may enable earlier detection and treatment of VAs (including potentially asymptomatic or self-terminating events), the similar MAE incidence between the overall cohort and those with ICD/WCD suggests that the arrhythmic burden is not solely due to detection bias (enhanced monitoring). Instead, it supports the idea that arrhythmic risk remains inherently elevated after complicated myocarditis. The significant reduction in all-cause mortality, the complete absence of SCDs, and the notable 20% rate of appropriate ICD/WCD interventions in the device-monitored subgroup highlight on one side, the potential protective benefits of ICDs/WCDs in carefully selected patients, on the other side, the predominance of haemodynamically tolerated sVT over not tolerated arrhythmias leading to ACA. However, the lack of a control group in our analysis limits the conclusiveness of these observations.

Importantly, the median time to first MAE was 12 months, highlighting the need for long-term surveillance. Delayed arrhythmic risk challenges the idea that WCD use is only needed early post-discharge. Some studies[48,49] and the latest European guidelines[18] have proposed WCD as a bridge during recovery; however, our findings urge against stopping monitoring too soon, especially in high-risk patients. In short, most events occur during initial hospitalization, but substantial residual risk of major VA persists late after the index event.

Regarding predictors of MAEs, our analysis confirms that specific clinical features at presentation may help identify patients at higher risk.[47] Patients presenting with major VAs had a higher risk of recurrence, consistent with previous evidence[7,26] and suggesting that initial arrhythmias often portend a more arrhythmogenic substrate. High-grade AV block, although less common, was also associated with higher risk, likely reflecting widespread myocardial inflammation affecting the conduction

system,[50] as observed in giant cell myocarditis. Fulminant presentation similarly portends a worse arrhythmic prognosis, likely due to more extensive myocardial injury.[51]

Interestingly, male sex emerged as a protective factor against arrhythmic outcomes in our analysis. This result should be interpreted with caution: while myocarditis is more common in young men,[47,52] prior analyses have not consistently shown a gender difference in long-term arrhythmic risk.[41] Therefore, our finding may reflect either unique aspects of our pooled cohort or a true biological disparity. Potential mechanisms could include hormonal influences, differences in immune response, an underlying genetic cause for the myocarditis such as the presence of a P/LP variant in cardiomyopathy-associated genes or virus tropism, warranting further investigation to refine risk stratification strategies. Despite female sex and hot phases had been identified as strong predictors of VAs in desmoplakin variant carriers,[53] with the former not being confirmed in a latest large international cohort[54], genetic analysis is still not routinely recommended after a first myocarditis episode without other indicators of underlying cardiomyopathy.[55] Confirmation of our findings would suggest lowering the threshold for genetic analysis in female patients experiencing a first myocarditis episode complicated by arrhythmias or fulminant onset, potentially also including out of hospital cardiac arrests with a myocarditis substrate.[56,57,58]

During follow-up, sVTs occurred more often (22%) than ACAs/VF (6%), underscoring the central role of scar-related substrate—re-entry or focal circuits—in arrhythmogenesis.[23,59]

However, our meta-analysis found no significant association between LGE on CMR during the index hospitalization and MAEs, which is only in apparent contrast to prior evidence from multimodal imaging including electroanatomical mapping[60,61] that suggests an association between stabilized substrate extension/characteristics and later arrhythmic risk. For example, in the largest CMR myocarditis study to date (Gräni C *et al.*, $n = 670$), only 23% of patients had recent myocarditis (≤3 weeks), which was more common in those with LGE (28%) than without (19%). Our findings likely reflect the exam's early timing (during index hospitalization), resulting in a higher prevalence (nearly 90%), greater extent and lower prognostic power of LGE, including segments with reversible oedema that do not carry the same arrhythmogenic risk as chronic, stable LGE. Indeed, various aspects of LGE characterization (location, extent, pattern) do not carry the same arrhythmogenic risk,[48,62,63] but many studies lacked detailed LGE data, limiting targeted analysis. In a recent Italian study,[63] oedema resolved and LGE stabilized within 3 months after acute myocarditis presentation, with LGE at 3 and 12 months (but not at presentation) linked to persistent VAs.

We also found no strong effect of histology (e.g. lymphocytic vs. giant-cell) or LVEF on arrhythmic outcomes in the pooled data. This may reflect that the sickest patients underwent HTx or died before discharge and that the included studies' methodologies varied, potentially missing in-hospital events. Moreover, the fact that a significant percentage of patients included in the studies had a complicated form of myocarditis with a high percentage of LGE on acute CMR and low LVEF at onset weakened the predictive power of these factors. Sensitivity analyses showed consistent results, supporting reproducibility of our findings.

Possible clinical implications and future directions

The 2025 European guidelines on myocarditis are less conservative than the 2022 ones on VAs. They permit temporary protection during the acute myocarditis phase complicated by VAs using WCD instead of immediate permanent ICD implantation. Implantable cardioverter defibrillator implantation for primary prevention may be considered after the acute phase if persistent risk factors are documented, though definitive evidence is still needed. The 2023 Japanese guidelines on myocarditis treatment suggest a similar approach.[4] The latest 2017 American Guidelines on VAs,[64] constrained by limited evidence, offered permissive recommendations, with a IIb indication for ICD implantation only in acute giant cell myocarditis complicated by VAs. Finally, the latest 2020 Canadian guidelines on VAs[65] also did not provide specific indications for ICD implant in myocarditis. In current clinical practice, the decision to implant a permanent ICD is often deferred beyond 3–6 months after the index event, when the patient has reached a chronic 'stable' condition.[13] Given the high rate of arrhythmic events acutely and chronically, and the median time to MAEs of 12 months, myocarditis follow-up should extend beyond the initial months, even with LVEF improvement. Until further evidence is available, beta-blocker therapy should be considered at discharge for most patients, and primary prevention ICD implantation may be appropriate for selected high-risk individuals. Further research is needed to determine the true protective effects, type, and optimal dosage of beta-blockers in this setting. The limited predictive value of CMR during the acute phase and EMB in this context suggests that no single modality is sufficient to accurately stratify post-myocarditis arrhythmic risk. Promising avenues being explored include invasive electroanatomic mapping to quantify scar-related electrical instability,[25] genetic susceptibility,[10,57] and therefore timing and indication to genetic analysis with the potential, supported by our work, of gender specific differences, and repeated CMR at follow-up to quantify myocardial healing through oedema or LGE extent evolution and left ventricle functional parameters.[7,66,67] Indeed, improved risk stratification strategies by multiparametric assessment are warranted.

Study limitations

This meta-analysis has several limitations that are intrinsic with the characteristics of the included studies. First, the included studies showed marked heterogeneity and selection biases, particularly in the types of myocarditis (e.g. acute vs. chronic and complicated vs. not complicated) evaluated, clinical characteristics at presentation, arrhythmic endpoint definitions, treatment strategies, and in the length of follow-up, which was relatively short in some cohorts. The main selection bias is that the included cohorts mostly represent acute complicated myocarditis, as also reflected by the high rate of ICD/WCD implantation at discharge, therefore limiting generalizability to the broader myocarditis population. Second, finding male gender as a protective factor in our current combined population provides only a partial explanation given the current limited supporting evidence and potential confounding factors. There is a possibility that some patients, especially women, carried a P/LP cardiomyopathy variant and experienced hot phases that could affect later arrhythmia risk. The evidence is limited, coming from observational, mostly retrospective studies. Treatment approaches varied; device use (e.g. WCD) may have been biased towards higher-risk patients and was not standardized. Predictors were inconsistently reported. Outcome data often lacked VA cycle lengths, hindering differentiation between haemodynamically tolerated and non-tolerated events. Major arrhythmic event definitions were generally consistent, but

some studies counted non-sustained VT, adding to heterogeneity. Finally, from a statistical standpoint, meta-regression with only 19 studies risks overfitting. Also, apart from the timing of CMR, the fact that a significant percentage of patients included in the studies had a complicated form of myocarditis with a high percentage of LGE on acute CMR and low LVEF/high HF prevalence at presentation weakened the predictive power of these factors and precluded the assessment of the role of imaging and CMR in conditioning decision-making.[68,69]

Nonetheless, our study offered valuable insights into the predictors of arrhythmic risk in patients with myocarditis and highlights the necessity of future prospective studies to improve risk stratification on this important topic.

Conclusions

This meta-analysis of existing literature on post-myocarditis MAE risk reveals a sustained high incidence of events throughout at least the first year in the studied population, implying a need for extended and close monitoring also in the chronic phase. The main variables found to be associated with higher MAEs incidence were presentation characteristics of complicated myocarditis and female sex.

Further prospective studies are needed to refine patients' characterization (including indication to first line genetic analysis to exclude the onset of an underlying genetically determined cardiomyopathy), risk stratification strategies, long-term management, and life-threatening arrhythmias prevention, by identifying patients who may benefit from a more aggressive monitoring approach and early ICD implantation.

Supplementary material

Supplementary material is available at *Europace* online.

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None.

Conflict of interest: None declared.

Data availability

The data underlying this article are available in the article and in its online supplementary material.

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