Mexiletine for recurrent ventricular tachycardia in adult patients with structural heart disease and implantable cardioverter-defibrillator – an EHRA systematic review

Short title: Mexiletine in SHD and ICD patients

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Abstract (unstructured)

The aim of the study was to systematically review evidence on the effectiveness and safety of oral mexiletine administered in monotherapy or in combination with other antiarrhythmic drugs for recurrent ventricular arrhythmia (VT/VF) in adult patients with structural heart disease (SHD) and implantable cardioverter-defibrillators (ICD). We systematically searched MEDLINE, EMBASE, and CENTRAL databases from inception to 27 August 2021 for prospective and retrospective studies investigating mexiletine in the target population. The main outcome was the reduction of ICD therapy. The main safety outcome was the presence of any serious adverse events (SAE) leading to mexiletine discontinuation. Study quality was assessed using the Cochrane risk of bias tool or the Newcastle–Ottawa Scale. Four studies comprising 86 mexiletine recipients were included in the review. We also obtained individual data of 50 patients from two studies. Ischemic cardiomyopathy (ICM) was present in 86% of patients. The quality of included studies was moderate/low. A narrative review was undertaken as studies varied widely in terms of study population and treatment. Across studies, mexiletine treatment (with or without amiodarone) seemed to consistently reduce the number of ICD therapies especially in a population where catheter ablation (CA) was unsuccessful or contraindicated. In ICM patients deemed eligible for CA, mexiletine seemed to be inferior to CA. Mexiletine was discontinued in 14% of cases, mainly for gastro-intestinal or neurological SAE. Mexiletine seems to be an option for the long-term treatment of recurrent VT/VF in adult patients with SHD, especially ICM, and ICD in whom catheter ablation was unsuccessful or not suitable.

Keywords:

mexiletine, structural heart disease, implantable cardioverter-defibrillator, shock, arrhythmia, ventricular tachycardia, systematic review

What's new?

- There is a small body of evidence, mainly low-quality observational studies, concerning mexiletine administration in adult patients with structural heart disease, predominantly of ischemic origin, and implantable cardioverter-defibrillator (ICD) and recurrent ventricular arrhythmia (VT/VF).
- Mexiletine seems to be inferior to CA of VT/VF in ischemic cardiomyopathy.
- Mexiletine seems to reduce the number of VT/VF, ICD therapies and electric storm episodes especially when CA was unsuccessful or contraindicated.
- Mexiletine can be effective with or without co-administration of amiodarone.
- Treatment with mexiletine is most often discontinued due to gastro-intestinal and neurological adverse events.

Introduction

Recurrent ventricular tachycardia (VT) in patients with structural heart disease (SHD), defined as ischemic cardiomyopathy (ICM) or non-ischemic cardiomyopathy, and implantable cardioverter-defibrillator (ICD) may lead to repeated shocks, deterioration of quality of life, worsening of heart failure and ultimately to excess mortality.[1-5]

Catheter ablation (CA) of VT is the preferred therapy in case of repeated ICD interventions due to its superior effectiveness and safety over antiarrhythmic drugs (AAD).[1, 4, 6] Nonetheless, CA may be unavailable at the time of the arrhythmia, may not be feasible for particular patient or may fail to control VT. In such cases amiodarone remains the drug of choice.[1, 4, 6] However, sometimes both CA and amiodarone are unsuccessful or contraindicated. In that scenario clinicians must choose between treatment strategies not supported by solid evidence, including other AADs, unconventional ablation techniques (bipolar or alcohol ablation), renal or cardiac sympathetic denervation.[7-12]

Mexiletine is a class Ib AAD sometimes described as an oral form of lidocaine.[12-14] Its antiarrhythmic properties are based on a blockade of the fast sodium channels. By reduction of the phase 0 maximal upstroke velocity of the action potential mexiletine increases the ratio of effective refractory period to action potential duration. Mexiletine has little effect on cardiac intrinsic conduction system, minimal negative inotropic effect, and does not prolong QT interval.[13, 14]

European and North American guidelines indicate intravenous mexiletine as a treatment option for acute suppression of VT and oral mexiletine in the chronic therapy of type 3 long-QT syndrome.[1, 4] However, a few studies in line with clinical practice, suggests its potential usefulness also for the long term treatment of recurrent VT in patients with SHD.[1, 4, 7, 8, 15]

The aim of this study was to systematically review available evidence on the effectiveness and safety of oral mexiletine administered in monotherapy or in combination with other antiarrhythmic drugs for treatment of recurrent ventricular arrhythmia in adult patients with structural heart disease and an implantable cardioverter-defibrillator.

Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[16] The review was conducted by and supervised by members of the Scientific Initiatives Committee of the European Heart Rhythm Association.

Search strategy and selection criteria

MEDLINE (via PubMED), EMBASE and CENTRAL databases were searched from inception to the 27th of August 2021 using the following search string: "mexiletine AND (ventricular (tachycardia OR fibrillation OR arrhythmia) OR (ICD OR implantable cardioverter-defibrillator) OR sudden cardiac death OR torsades de pointes)". Two clinical trials registries (Clinical Trials and International Clinical Trials Registry Platform) were reviewed for ongoing trials. Reference lists of eligible studies and relevant reviews (including systematic reviews comparing CA do AADs) were reviewed for additional information. Full text publications of conference abstracts or registered clinical trials were sought. We also contacted key opinion leaders in the field to guarantee that all relevant studies were identified.

The review included all prospective and retrospective studies with or without a control group. The minimal follow-up was at least 1 month on average for the whole study. Case studies, studies investigating mexiletine for premature ventricular contractions in structurally normal hearts or in an acute setting and studies concerning programmed ventricular stimulation or surface ECG changes after mexiletine administration without long-term follow-up were not eligible for the review. Language was restricted to English.

To be included in the clinical effectiveness assessment, patients had to take mexiletine orally in monotherapy or in combination with other AADs for at least one month on average for the whole study or for each case when individual patient data was available. To capture all important adverse effects of mexiletine, including early complications leading to discontinuation, we decided to include

data from all patients described in the included studies, regardless of their individual observation time.

Two investigators (MF and MK) independently screened and selected potentially eligible studies based on title and abstract. Final eligibility for the review was decided after evaluation of full-text publications. For conference abstracts identified as potentially of interest, the full-text publication was sought. If publication did not occur within 3 years,

All disagreements were resolved via discussion or the involvement of a third referee (RP).

Data extraction and quality assessment

A standardized form was used to extract the following information from each study: 1) study design and methodology, 2) details of mexiletine administration (indication, dose, AAD co-administration), 3) information on the assessment of the main clinical outcome (device interrogation, type of ventricular arrhythmia), including length of follow-up, 4) baseline characteristics of participants (e.g. age, sex, SHD type, treatment before mexiletine administration), 5) outcome and safety measures: ventricular arrhythmia episodes, ICD therapies, electrical storm (ES) episodes, serious adverse events (SAE) which led to drug discontinuation, causes of death during follow-up. In case of missing data on main outcomes, corresponding authors of the original publications were contacted via email. The extraction was done independently by two investigators (MF and MK) and all disagreements were resolved via discussion or the involvement of a third referee (RP). When feasible, corresponding authors of eligible studies were invited to contribute individual patients' data for potential meta-analysis.

The risk of bias in randomized controlled trials (RCTs) was assessed using the Cochrane risk of bias tool [17], while the Newcastle-Ottawa Scale (NOS) was used to assess the quality of non-randomized studies. A trial was considered of high quality if no domains scored as high risk, or low quality if three or more domains scored as high risk. High-quality non-randomized studies were defined as those with a Newcastle-Ottawa score of ≥7. The risk of bias was assessed independently

by two investigators (MF and MK) and all disagreements were resolved via discussion or through the involvement of a third referee (RP).

Outcome measures

The main outcome was the reduction of ICD therapy defined as (i) the sum of shocks and anti-tachycardia pacing episodes on device interrogation or (ii) the number of patients free from any ICD treatment throughout the follow-up in comparison to outcomes reported in the control group or in comparison to the matching time period before mexiletine initiation (only in before-after studies). The main safety outcome was the presence of any serious adverse events (SAE) leading to mexiletine discontinuation. Additional outcome measures included electrical storms and VT/VF episodes. Causes of death and causes of mexiletine discontinuation were also extracted and reported in the review.

Data synthesis and analysis

We obtained patient-level data from the studies of Mugnai et al. and Sobiech et al. and recalculated results in eligible patients and to present study outcomes in a uniform manner. [8, 17] Categorical variables were presented as number of valid observations and proportions. For comparisons Chi square test, or two-tailed Fisher's exact test were used, as appropriate. Continuous variables are presented as a median with quartiles (1st quartile, 3rd quartile) or range and mean with standard deviation in parallel to match reporting the two remaining studies. Due to non-normal distribution comparisons were made using Wilcoxon signed-rank test. Calculations were carried out using STATISTICA 13.3 software package (TIBCO Software Inc., USA). P values of <0.05 were considered statistically significant.

The preplanned meta-analysis of primary and secondary outcomes was not feasible due to high heterogeneity of included studies in terms of population characteristics and indications for mexiletine.

Results

Selection and description of studies

The PRISMA flow diagram in Figure 1 summarizes the study selection process. Primary search identified 1,058 citations. After removal of duplicates, 944 titles and abstracts were independently screened by two investigators. Taking also into account additional searches (reference lists, CA vs AAD systematic reviews), a total of 14 potentially relevant studies were selected for full-text examination. Based on careful analysis of publications we excluded 10 studies, mainly because they were conducted in the acute setting or did not report data of interest (Tab. S1, Supplementary material online).[18-27] One potentially relevant ongoing study in this field was found: Initial Management of Patients Receiving a Single Shock (IMPRESS, NCT03531502). One potentially interesting study was available only as an abstract.[28] The corresponding full-text could not be found despite this study being an abstract presented over 8 years ago.

Finally, four studies were included in the review.[7, 8, 17, 29]

Characteristics of included studies

Studies included in this review included one sub-analysis of a randomized controlled trial (the VANISH trial)[7] and three before-after studies without control group (Table 1) [8, 17, 29]. All studies concerned adult patients, predominantly males with underlying ICM[7, 17] or a mix of ischemic and non-ischemic cardiomyopathy [8, 29]. Before initiation of mexiletine all patients were treated with betablockers and 88% attempted amiodarone.

Having access to individual patient data of Sobiech et al. we excluded four patients from the clinical effectiveness analysis because they either responded well to early CA or percutaneous coronary angioplasty or discontinued the drug due to SAE (two patients), and therefore received mexiletine for less than 1 month (6, 7, 1 and 3 days, respectively). On the other hand, all four were included in the safety analysis. Patient-level data from Mugnai et al. (N=34) was used in the clinical effectiveness analysis, but additional six patients were included in the safety analysis. Those six patients were

reported in the paper to suffer from early SAE leading to mexiletine discontinuation and therefore were eligible for safety but not effectiveness analysis.

Gao et al. enrolled patients with recurrent VT/VF despite AAD but without CA before mexiletine. In the study by Sobiech et al., patients were treated with mexiletine only if the CA had failed, had been contraindicated or the patient still had been on a waiting list for CA. In the included subanalysis of the VANISH trial by Deyell et al. patients on mexiletine without CA were compared to a parallel group of patients without mexiletine but treated with CA. Patients from the study by Gao et al. received relatively low doses of mexiletine but with frequent co-administration of other AAD. In all studies, an ICD interrogation was the basis for the outcome assessment. Apart from the VANISH trial, all studies used a matching time period before mexiletine initiation as the reference for individual patients.

Risk of bias

The risk of bias assessment is summarized in Table S2 (Supplementary material online). Even though the quality of the VANISH trial was considered moderate, Deyell et al. study required further downgrading as it resulted from an unplanned *post hoc* analysis. All three before-after studies scored 4 on the NOS, which is below the established cut-off for high-quality observational studies. They were considered of low quality mainly due to lack of a control group and inclusion of a highly selected population.

Outcomes

Outcomes of the included studies are summarized in Table 2. Access to individual patient data allowed calculation of additional outcomes that were not included in original publications by Mugnai et al. and Sobiech et al. Overall, clinical effectiveness was assessed in a population of 86 patients, of whom 86% had ICM.

All three before-after studies showed that the introduction of mexiletine brings statistically significant benefit in terms of reduction of ICD therapy and recurrent episodes of VT/VF.

Mexiletine vs. catheter ablation

The sub-analysis of the VANISH trial shows inferiority of mexiletine to CA in patients with ICM who failed amiodarone in terms of number of ICD therapies.[7]

Mexiletine when catheter ablation was unsuccessful or contraindicated

Data for this population was derived from the studies by Mugnai et al. and Sobiech et al. Both studies reported reduction in ICD therapies and substantial number of cases without any VT/VF among patients treated with mexiletine.

Mexiletine + amiodarone

Of 27 patients treated with a combination of mexiletine and amiodarone in before-after studies 20 were recruited by Gao et al. (70% of all patients in this study). Without access to individual patient data it is not possible to draw any conclusions about the effect of treatment in this subgroup of patients.

The study shows an overall positive effect of mexiletine on the proportion of patients having electrical storms and a tendency towards lower number of VT/VF episodes per patients. [29]

Safety analysis

All studies intended to report SAE leading to a drug discontinuation (Table 2). The overall proportions of patients experiencing such SAE was 13.5% (13/96), ranging from 0% (0/29, Gao et al.) to 25.0% (4/16, Sobiech el al.) and 27.3% (3/11, Deyell et al.). The reasons for discontinuation were either gastro-intestinal (abdominal pain, nausea or vomiting in 5 cases), neurological (dizziness or ataxia in 6 cases) or mixed (2 cases). Importantly, in 8.3% (8/96) patients SAE resulted in mexiletine withdrawal very early after initiation.

Mexiletine and overall survival

The methodology of included studies does not allow to draw firm conclusions about the effect of mexiletine treatment on overall survival. Of 86 patients treated with mexiletine in all four studies, 20 patients died during the follow-up (Table 2). Two main causes of death were end stage heart failure and cancer.

Discussion

The key findings of our study are: 1. there is a small body of evidence, mainly low quality observational studies, concerning mexiletine administration in adult patients with SHD predominantly of ischemic etiology (86% of all cases), ICD and recurrent VT/VF; 2. mexiletine seems to be inferior to CA of VT/VF in ICM; 3. mexiletine seems to reduce the number of VT/VF, ICD therapies and ES episodes especially when CA was unsuccessful or contraindicated; 4. mexiletine can be effective with or without co-administration of amiodarone; 5. treatment with mexiletine is most often discontinued due to gastro-intestinal and neurological adverse events.

Mexiletine had a long history of clinical use before the ICD and CA era as a antiarrhythmic drug administered both for premature ventricular contractions and SHD VT.[30-33] The drug exhibited mixed effectiveness and considerable adverse effects which appeared to be dosage-related. This systematic review was conducted to summarize contemporary data on the effectiveness and safety of mexiletine, a class Ib AAD, as any line of treatment of recurrent VT/VF in adult patients with SHD and ICD. Due to significant differences in study populations and mexiletine treatment we decided not to meta-analyze the results and present them in a narrative fashion. Studies included in this review were predominantly low quality before-after studies without a control group which probably is a testament to the current position of this drug in this population. Mexiletine is mentioned in guidelines as an option in acute management of VT/VF but for a chronic therapy only LQT3 seems to be recognized as a target population.[1, 4, 15] Mexiletine is also absent from the market in many European countries. Clearly, CA and amiodarone, in this order, are the basis for a long-term VT/VF

suppression therapy in ICD patients and this was evident in the baseline characteristics of the patients analyzed in studies included in this review. Almost all patients had a history of amiodarone treatment which was either unsuccessful or contraindicated at some point. However, the history of CA differed with a date of publication. In the study by Gao et al. study published in 2013, patients with recurrent VT/VF were treated with combinations of different AADs and CA was performed after a number of interactions of AAD treatment.[29] On the other hand, 2021 Mugnai et al. study enrolled exclusively patients after a failed CA or in whom CA was contraindicated.[17] Taking into account other two included studies, it seems that the current position of mexiletine in this population is a III/IV line therapy when CA or amiodarone are either contraindicated or such therapy failed. We did not find data to compare mexiletine to other therapies initiated after CA and amiodarone failure (e.g. procainamide).[34]

Despite highly relevant differences between included studies, mexiletine seemed to consistently reduce the number of ICD therapies, both shocks and ATPs, and prevent recurrence of electrical storm (Table 2.). In direct comparison to CA in an ICM population, where CA displays its highest effectiveness in VT and SHD, mexiletine was significantly inferior despite low numbers of patients in both groups. CA was superior to the escalated AAD therapy also in the main analysis of the VANISH trial.[27] On the other hand, results of two studies which enrolled patients after a failed CA or in case of contraindications to CA suggest mexiletine may be an option if CA is not. Unfortunately, detailed information of the CA technique was not provided hence it is not possible to assess the quality or number of previous CA procedures. A single-centre study describing outcomes of mexiletine treatment in 56 patients with EF <40% and unknown HF etiology and available only as an abstract reported only 11 patients free of any appropriate ICD therapy/sustained VT/VT ablation/heart transplant/ left ventricular assist device/documented arrhythmic death during the 12-month follow-up.[28]

The safety of the mexiletine treatment was controversial (Tab. 2). Overall, a minority of patients (13.5%) suffered serious adverse reactions leading to discontinuation. However, the studies by Deyell

et al. and Sobiech et al. reported almost 30% withdrawal rate. What is important, over half of withdrawals reported in the included studies occurred early after mexiletine initiation, after less than a month of treatment. As expected, two main reasons for mexiletine discontinuation were gastro-intestinal or neurological adverse events. Similar reactions to mexiletine were described before.[12-14, 28] There was also a report of severe heart failure decompensation among 4 out of 56 patients with EF<40% treated with mexiletine.[28] Temporal dose reduction or mexiletine administration during meal may alleviate gastro-intestinal issues and allow drug continuation.[8, 13, 14] In a LQT 1 or 2 syndrome out of 11 patients, five patients had gastro-intestinal discomfort but only one required dose reduction.[20] Apart of betablockers, AAD therapy differed between studies (Tab. 1.). Gao et al. reported a number of combinations of AADs including co-administration of amiodarone, mexiletine and other AADs.[29] In this case mexiletine was hardly ever used as a stand-alone drug but its dosage seemed to be lower than in other studies. All patients in Deyell et al. had mexiletine administered together with amiodarone.[7] On the other hand, majority of patients described by Mugnai et al. and Sobiech et al. had mexiletine administered in monotherapy.[8, 17] Daily dose of mexiletine was similar in those three papers typically ranging between 400 mg and 600 mg. Based on the results of our systematic review, there is no data to formulate a clear recommendation as if to administer mexiletine in monotherapy or in combination with amiodarone or other AAD except of betablocker. The available data suggest that even without amiodarone, mexiletine has clinically relevant potential to suppress VT/VF in patients with SHD and ICD (Tab. 2.).

The general quality of included studies was low (Tab. S2, Supplementary material online). While VANISH trial had clear inclusion/exclusion criteria and a contemporary comparator, other included studies are prone to a strong selection bias based on the off-guideline indication for the reported treatment. Outcomes of those studies are assessed without a control group and based on a matching time period before/after mexiletine. The longer the period the more potential cofounders potentially influencing the result of the study.

The present systematic review was focused on chronic oral administration of mexiletine in SHD patients with ICD and therefore numerous studies over mexiletine treatment in other indications were excluded (Table S1, Supplementary material online).

Limitations

This systematic review identified only four studies with a total population of 86 patients treated with mexiletine. Randomized data was derived from a *post-hoc* analysis of one moderate-quality controlled study that was not designed to investigate the efficacy of mexiletine. The majority of information is brought by three low-quality before-after studies prone to selection and other significant biases. One single-centre study comprising 56 patients was not included in the analysis due to lack of full-text publication an therefore inability to access most of the data of interest. Significant heterogeneity in terms of study population and treatment did not allow for a meta-analysis of results. ICM was by far the most common etiology of SHD in our review hence data on mexiletine effectiveness in non-ischemic cardiomyopathy should be interpreted with even more caution than in ICM.

Conclusion

Oral mexiletine seems to be an option for the long-term treatment to prevent recurrent ventricular arrhythmia in adult patients with structural heart disease, especially ischemic cardiomyopathy, and implantable cardioverter-defibrillator in whom catheter ablation was unsuccessful or not suitable. However, this conclusion is based on a low-quality data and should be interpreted with caution.

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Table 1. Summary of all included studies.

Study	Study design (number of centers)	Inclusion criteria	Population											Mexiletine dose per day (mg)	Endpoint assessment	
			Number of patients	Age (years)	Males	Etiology	Before mexiletine		On mexiletine				LVEF (%)		Matching time period before and after mexiletine	ICD interrogation
							Amio	RFA	BB	Amio	Other AAD	RFA				
Mugnai 2021*	Before-after study (1)	Failed RFA, contraindication/not qualified for RFA	34	74.0±9.5	27 (79.4)	100% ICM	28 (82.4)	8 (23.5)	34 (100)	4 (11.8)	0 (0.0)	0 (0.0)	33.7±11.7	400 to 600	Yes	Yes
Deyell 2018 (VANISH)**	RCT subanalysis (22)	Recurrent VT despite first-line AAD	11	72.8 (68.1, 74.2)	11 (100)	100% ICM	11 (100)	0 (0.0)	11 (100)	11 (100)	0 (0.0)	7 (63.6)	26.5 (21.0, 35.0)	400 (200 to 900)	No	Yes
Sobiech 2017*	Before-after study (1)	Failed RFA, contraindication/not qualified for RFA, waiting for RFA	12	59.0±15.3	7 (58.3)	58% ICM	9 (75.0)	5 (41.7)	12 (100)	3 (25.0)	0 (0.0)	4 (33.3)	30.2±13.5	400 to 600	Yes	Yes
Gao 2013	Before-after study (1)	Frequent VT/VF: electrical storm or on average >1 VT/VF per month requiring ICD therapy	29	71 (44 to 92)	26 (89.7)	76% ICM	29 (100)	0 (0.0)	29 (100)	20 (70.0)	15 (51.7)	10 (34.4)	32	300 (100 to 400)	Yes	Yes

Data are presented as number of observations (percentage) or mean ± standard deviation or median (1st quartile, 3rd quartile; or range).

* Results from the analysis of individual patients' data performed for this systematic review.

** Results presented for mexiletine subgroup only.

AAD, antiarrhythmic drugs; Amio, amiodarone; ICD, implantable cardioverter-defibrillator; ICM, ischemic cardiomyopathy; LVEF, left ventricular ejection fraction; RCT, randomized controlled trial; RFA, radiofrequency ablation; VT/VF, ventricular tachycardia/ventricular fibrillation

Table 2. Outcome and safety events before initiation of mexiletine treatment and on mexiletine.

Study	No. of patients	Follow-up (months)	Death		Electrical storm	ICD therapy (shock or ATP) per patient	Patients free from ICD therapy (shock and ATP)	VT/VF episodes per patient	SAE leading to discontinuation	Type of SAE
			n	Cause of death						
Mugnai 2021*	34	26.5 (19, 38) or (12 to 100)	5 (14.7)	Heart failure in 4 patients; cancer in 1	0 (0.0)	3.41 ± 4.74 vs. 1.53 ± 2.65 or 2 (0, 3) vs. 0 (0, 2), P=.018	10 (29.4) vs 18 (52.9), P=.049	2.18 ± 1.90 vs. 0.97± 1.64 or 1 (1, 3) vs 0 (0, 1), P=.002	6/40 patients (15.0) **	Severe dizziness in 3 patients; significant abdominal pain in 2; vomiting and tremors in 1
Deyell 2018 (VANISH)	11 on mexiletine vs 8 after ablation	9.2 (1.1 to 43.4) vs. 30.0 (6.1 to 64.5)	4 (36.4) vs 4 (50.0); HR 1.99 (0.36-10.9)	Mexiletine group: VT after RFA in 2 patients; cancer in 1; renal failure/pneumonia in 1	7 (63.6) patients on mexiletine vs. 2 (25) after ablation; HR 4.35 (95% CI: 0.88, 21.5)	N/A	3 (37.3) patients on mexiletine vs. 5 (72.5) after ablation; HR 0.11 (95% CI: 0.02, 0.61)	N/A	Mexiletine group: 3 (27.3)	Mexiletine group: ataxia in 2 patients; nausea, vomiting, fatigue, and headaches in 1
Sobiech 2017*	12	13.9 (6.5, 23.4) or (1 to 61.5)	0 (0.0.)	N/A	Patients: 8 (66.7) vs. 2 (16.7), P=.036 Episodes per patient: 1 (0, 1) vs. 0 (0, 0), P=.018	28.7±47.8 vs. 8.7±23.4 or 9 (4.5, 20) vs. 0 (0, 3.5), P=.010	0 (0.0) vs. 7 (58.3), P=.005	23.0±28.5 vs. 13.1± 27.7 or 6.5 (3.5, 45.5) vs 0 (0, 5.5) P=.045	4/16 patients (25.0) ***	Severe abdominal pain in 3 patients; severe dizziness in 1
Gao 2013	29	12 (3 to 57)	11 (37.9)	Heart failure in 4 patients; cancer in 3; cerebrovascular disease in 1; infection in 1; surgery in 1; renal failure in 1	Episodes per patient: 1 (0, 2) vs. 0 (0, 0.5), P=.002	Total shocks: 4 (1, 14) vs. 1 (0, 6), P=.084 Appropriate shocks: 4 (0.5, 12) vs. 1 (0, 5.5), P=.076 Appropriate ATP: 21 (9, 82.5) vs. 14 (4.5, 38.5), P=.026	N/A	Episodes: 17 (7.5, 50.5) vs. 9 (3, 47.5), P=.053	0 (0.0)	N/A

Data are presented as number of observations (percentage) or mean ± standard deviation or median (1st quartile, 3rd quartile; or range).

* Results from the analysis of individual patients' data performed for this systematic review.

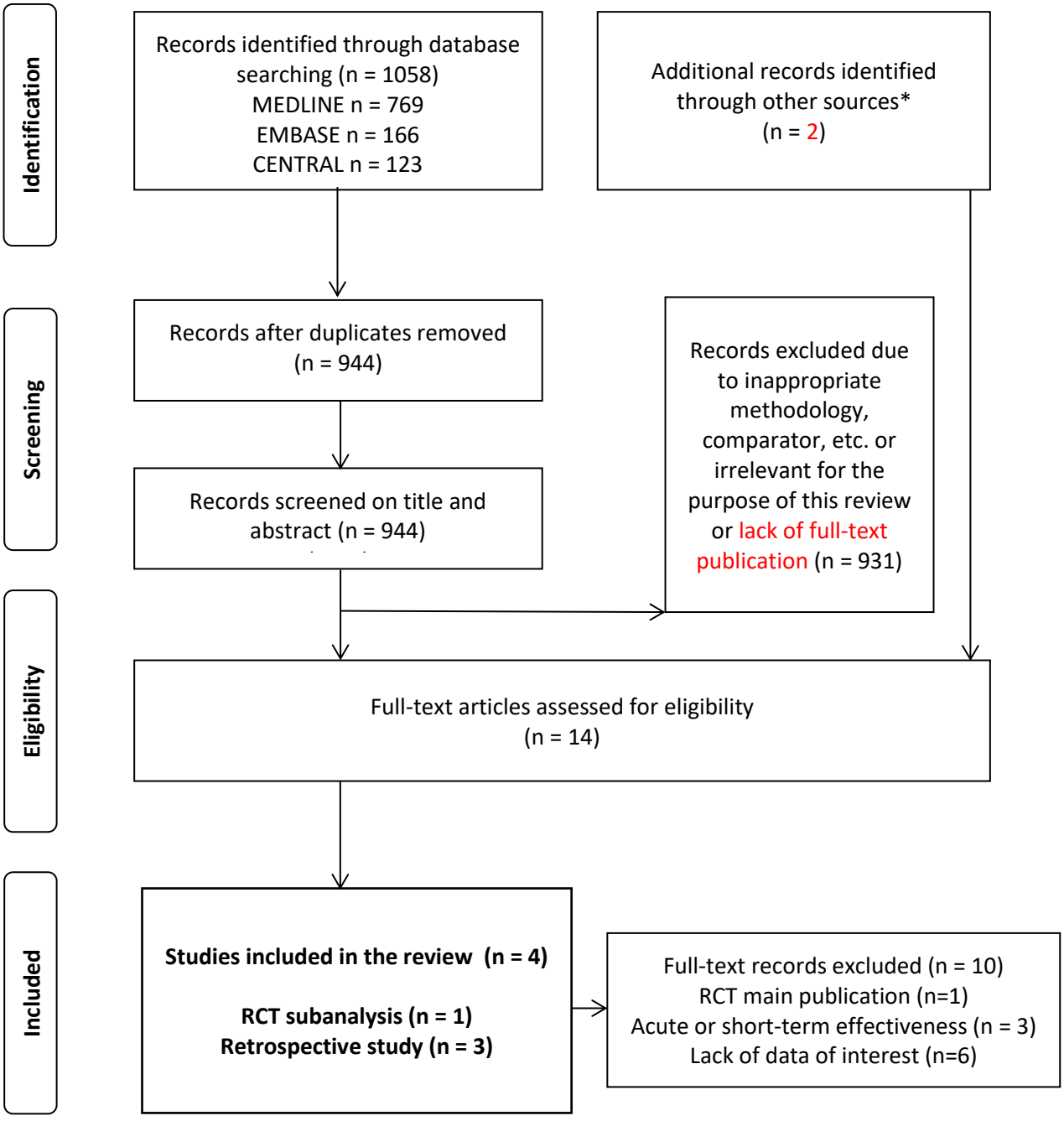
** N=40, includes six additional patients not included in the effectiveness analysis with early mexiletine discontinuation due to SAE

*** N=16, includes four additional patients not included in the effectiveness analysis of whom two had SAE leading to early mexiletine discontinuation

ATP, anti-tachycardia pacing; ICD, implantable cardioverter-defibrillator; N/A, not applicable; RFA, radiofrequency ablation; SAE, serious adverse event; VT/VF, ventricular tachycardia/ventricular fibrillation

Figure 1.

Figure 1. PRISMA flow diagram for study selection process.



*Manual search of reference lists of included studies and relevant reviews, contact with key opinion leaders, review process of the article.

RCT, randomized controlled trial.