Effectiveness and safety of mexiletine in patients at risk for (recurrent) ventricular arrhythmias: a systematic review

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Aims
While mexiletine has been used for over 40 years for prevention of (recurrent) ventricular arrhythmias and for myotonia, patient access has recently been critically endangered. Here we aim to demonstrate the effectiveness and safety of mexiletine in the treatment of patients with (recurrent) ventricular arrhythmias, emphasizing the absolute necessity of its accessibility.

Methods and results
Studies were included in this systematic review (PROSPERO, CRD42020213434) if the efficacy or safety of mexiletine in any dose was evaluated in patients at risk for (recurrent) ventricular arrhythmias with or without comparison with alternative treatments (e.g. placebo). A systematic search was performed in Ovid MEDLINE, Embase, and in the clinical trial registry databases ClinicalTrials.gov and ICRP. Risk of bias were assessed and tailored to the different study designs. Large heterogeneity in study designs and outcome measures prompted a narrative synthesis approach. In total, 221 studies were included reporting on 8970 patients treated with mexiletine. Age ranged from 0 to 88 years. A decrease in ventricular arrhythmias of >50% was observed in 72% of the studies for pre-mature ventricular complexes, 64% for ventricular tachycardia, and 33% for ventricular fibrillation. Electrocardiographic effects of mexiletine were small; only in a subset of patients with primary arrhythmia syndromes, a relative (desired) QTc decrease was reproducibly observed. As for adverse events, gastrointestinal complaints were most frequently observed (33% of the patients).

Conclusions
In this systematic review, we present all the currently available knowledge of mexiletine in patients at risk for (recurrent) ventricular arrhythmias and show that mexiletine is both effective and safe.

Keywords
Mexiletine • Systematic review • Ventricular arrhythmias

Introduction
Patients at risk for recurrent ventricular arrhythmias can be treated with anti-arrhythmic drugs or ablations. For example, the anti-arrhythmic agents currently known as quinidine and digoxin have already been used for the treatment of palpitations since the 18th century. Over time, more drugs were developed and became available for the treatment of arrhythmias. However, the tide has turned after the pivotal anti-arrhythmic drug developments in the 1960s to 1980s. Since the late 1990s and early 2000s, anti-arrhythmic drugs may no longer be sufficiently profitable for the pharmaceutical industry and anti-arrhythmic drug availability has actually decreased in many countries around the globe. As a consequence, the pharmaceutical
treatment of numerous patients with (life-threatening) ventricular arrhythmias has become increasingly difficult.\textsuperscript{5-8}

Mexiletine, a sodium channel blocker and the oral lidocaine equivalent, is such an example. Mexiletine is predominantly prescribed in both cardiology and neurology. Mexiletine was initially developed as an anti-arrhythmic drug by Boehringer Ingelheim and the first results were presented in 1973.\textsuperscript{9} Although other anti-arrhythmic drugs, such as sotalol and amiodarone, surpassed mexiletine over time with regards to efficacy and safety (e.g. mortality),\textsuperscript{10} it still can be very effective drug in specific subgroups of patients. In cardiology, mexiletine is most often prescribed to adult patients with recurrent ventricular tachycardia or ventricular fibrillation (VT/VF) when other therapies have failed, and to paediatric and adult patients with severe forms of the long QT syndrome (LQTS). This use of mexiletine has also been mirrored in successive international guidelines on the prevention of VT/VF.\textsuperscript{1,11} In neurology, mexiletine has proved effective in paediatric and adult patients with the disabling neuromuscular disorder non-dystrophic myotonia.\textsuperscript{12,13} In addition, mexiletine is sometimes successfully used for pain syndromes.\textsuperscript{14}

Despite the use of mexiletine for over 40 years as an anti-arrhythmic drug, the accessibility of mexiletine in Europe is now critically endangered. After Boehringer Ingelheim withdrew Mexitil from the European market, patients had to rely on named patient import from other countries, including Canada and Japan. In 2018, the European Medicines Agency (EMA) authorized mexiletine (Namuscla, Lupin Europe GmbH, Germany) for the treatment of the neurological indication non-dystrophic myotonia as an orphan drug. The rationale behind the European (and e.g. USA) orphan drug legislation is to promote commercial interest for the development of new products for rare diseases assuming that such products will otherwise not be developed.\textsuperscript{6} This legislation was developed without exclusion of existing drugs from orphan designation, among others (Postema, 2020 #1603). This authorization of Namuscla as orphan drug for the neurological indication granted a 10-year market exclusivity. Not unexpectedly, the price of Namuscla was raised up to >30-fold for both neurology and cardiology in comparison with imported generic products, resulting in reimbursement issues.\textsuperscript{6,13,16} Remarkably, the contra-indications of Namuscla now include ventricular tachyarrhythmias and previous myocardial infarction while the guidelines on the treatment and prevention of VT/VF mexiletine can actually be an effective and safe drug of choice.\textsuperscript{1,11} This may constrain the off-label use of Namuscla for VT/VF. Herewith, the accessibility of mexiletine to prevent ventricular arrhythmias (and for the treatment of myotonia) is further compromised. This in turn may have life-threatening consequences.\textsuperscript{5}

If the effectiveness and safety of mexiletine in patients at risk for (recurrent) ventricular arrhythmias would be demonstrated, this would prove the clear needs of its accessibility. Therefore, a systematic review to summarize all available efficacy and safety data was conducted.

Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) Guidelines and registered in the International Prospective Register for Systematic Reviews (CRD42020213434).\textsuperscript{17}

Selection criteria

Studies were included in this systematic review if the efficacy and/or safety of mexiletine in any dose or route of administration were evaluated in patients at risk for (recurrent) ventricular arrhythmias with or without comparison with alternative treatments (e.g. placebo, other anti-arrhythmic drugs). Only studies with original data published in peer-reviewed journals were included and no restrictions in study design applied.

Search strategy

A comprehensive search using controlled terms and free text terms for the concepts (i) mexiletine (or brand names including, but not limited to, Mexitil and Ritalmex) and (ii) ventricular arrhythmias was performed in the Ovid MEDLINE, Embase, and in the clinical trial registry databases [ClinicalTrials.gov, International Clinical Trials Registry Platform (ICTRP) registry]. The search was restricted to studies in human subjects, no other date or language restrictions applied. The search was performed on 22 October 2020. In the Supplemental material, the complete search strategy is presented. The identified records were imported into reference management tool Endnote (X9.2; Clarivate Analytics, Philadelphia, PA, USA) and duplicates were removed.

Study selection and critical appraisal

Titles, abstracts, and subsequently the acquired relevant full-text articles were independently assessed by two reviewers (M.H.R., L.D.) for eligibility using Rayyan (Qatar Computing Research Institute, Doha, Qatar).\textsuperscript{18} The assessment of methodological quality and risk of bias was performed independently by the review team (M.H.R., L.D., N.R., N.S., S.B., and V.W.) and tailored to the different study designs, discrepancies were resolved by discussion. For case reports and case series, the tool developed by Murad and colleagues\textsuperscript{19} was used, for non-randomized intervention studies, the ROBINS-1 tool was used,\textsuperscript{20} and for randomized studies, the ROB2 tool was used.\textsuperscript{21} In case no efficacy but only safety data about mexiletine was reported, risk of bias was not assessed. As the different tools have different (overall) scores, a 3-point scale [low, moderate (some concerns), and high (critical and serious)] was constructed to enhance comparability.

Data collection and analysis

Baseline characteristics, mexiletine details (e.g. daily dose), follow-up, and outcomes were independently extracted by two members of the review team per study (M.H.R., L.D., N.R., N.S., S.B., and V.W.) using a standardized extraction form in Castor EDC,\textsuperscript{22} discrepancies were resolved by discussion during weekly meetings or by consultation of a third reviewer. Data were processed and aggregated using R version 4.0.3. Outcome data included both efficacy as well as safety and survival data. Efficacy outcome data were further stratified in effects of mexiletine on the ventricular arrhythmia burden [consisting of the burden of pre-mature ventricular complexes (PVCs), sustained VT or VF], changes in electrophysiological parameters [VT inducibility, VF inducibility, effects on cycle length, and effective refractory period (ERP)], and changes in electrocardiographic parameters [heart rate, QRS-duration, corrected QT interval (QTc)]. For the electrocardiographic changes, the results are subdivided into patients with and patients without primary arrhythmia syndrome. In case multiple subtypes of LQTS were reported in one study, by virtue of pathology, LQTS type 3 was the preferred outcome for extraction.\textsuperscript{23} If available, pre-post mexiletine outcome data were used so that patients served...
as their own controls. Safety data included adverse events, left and right ventricular ejection fraction, drug–drug interaction, and the occurrence of worsening of arrhythmias. Adverse events were scored according to the definitions of the Common Terminology Criteria for Adverse Events (CTCAE) v5.0, no grading was applied. If the adverse events were not reported in enough detail, only the organ system was scored. For the presentation of the adverse events, the organ systems with $\geq 3\%$ adverse event incidences were reported. The incidence of the adverse events is reported relative to the evaluable patients from studies reporting that specific adverse event and presented for events with $\geq 3\%$ incidence. Efficacy and safety data were summarized per stratified outcome measure in the manuscript. Efficacy data from studies considered to have a high risk of bias were excluded from the main efficacy results. Safety data from these high risk of bias studies were, however, included in the main safety results to present a complete overview of all reported adverse events available. Mexiletine was considered pro-arrhythmic if the arrhythmia worsened after the start of mexiletine [e.g. an increase in the number of PVCs or development of more malignant arrhythmias (e.g. from VT at baseline to VF during mexiletine treatment)]. The study data are available from the corresponding author upon reasonable request.

**Results**

**Search results and risk of bias**

Of the 1436 unique records identified, of which after screening based on title and abstract 432 (30%) records were assessed for eligibility, 221 (15%) studies were included in this systematic review. In Figure 1, a flow chart of the study selection is presented. Efficacy was reported in 174 (79%) of the studies (efficacy and safety: $n = 126$; only efficacy: $n = 48$), 33 (19%) were considered low risk, 80 (46%) moderate risk, and 61 (35%) high risk of bias. In 173 (78%) studies, safety was reported (efficacy and safety: $n = 126$; only safety: $n = 47$).

*Figure 1* Flow chart of study inclusion.
Table 1 The effect of mexiletine on ventricular arrhythmia burden

| Arrhythmias | Publications, n (%) | Study design | Follow-up range | Studies with therapy-resistant patients | Patients on mexiletine (years) | Type of Mexiletine dose range | Evaluable patients | Studies that show >50% reduction | Number of patients meeting the cut-off |
|-------------|---------------------|-------------|----------------|----------------------------------------|-----------------------------|--------------------------------|-------------------|----------------------------------|-------------------------------------|
| Pre-mature ventricular contractions | 611|24–83 | Non-randomized 61 | 7 days–84 months | 13 | 2369 | 0.42–88 | Ischaemic | 814 | 200–1500 mg/day | 1834 patients in pre-post design 137 patients on mexiletine vs. 152 control patients | 627/882 (72%) | 23 studies work with a cut-off 0.42–88 mg/day 61 mg/kg/day |
| Randomized 0 | Non-ischaemic 321 | | | | | | | | | | 50–95% (7) | 95/175 (54%) |
| Ventricular tachycardia | 341|25,27,31,35,36,38,39–41,43,44–47,67,71,72,79,80,82,84–99 | Non-randomized 34 | 0–70 months | 15 | 1803 | 16–87 | Ischaemic | 616 | 50–1500 mg/day | 943 patients in pre-post design 167 patients on mexiletine vs. 172 control patients | 673/822 (82%) | 23 studies work with a cut-off 0.42–88 mg/kg 4–21 mg/kg/day/kg |
| Randomized 0 | Non-ischaemic 124 | | | | | | | | | | 75% (2) | 63/85 (74%) |
| Ventricular fibrillation | 121|5,6,7,10,12,13,15,19,36,39,91,93,95,97,98,99–103 | Non-randomized 12 | 1–84 months | 4 | 870 | 1–79 | Ischaemic | 246 | 400–1200 mg/day | 358 patients in pre-post design 137 patients on mexiletine vs. 147 control patients | 100/123 (80%) | 9 studies work with a cut-off 0.42–88 mg/kg 6–8 mg/kg/day/kg |
| Randomized 0 | Non-ischaemic 34 | | | | | | | | | | 100% (9) | 290/324 (90%) |

Studies that report a percentage change or enabled us to calculate a percentage change.
Baseline characteristics
In total, 8970 patients have reportedly been treated with mexiletine. Sex was reported in 4647 (52%) patients, and of these, the majority were males (n = 3322, 72%). The patient age in the studies ranged from 0 to 88 years. Of the studies reporting mean age, the weighted average was 56.5 years. Of 5131 patients, a diagnosis category was extractable. The most frequent diagnosis was ischaemic heart disease (n = 3671, 72%), followed by non-ischaemic heart disease (n = 720, 14%) and primary arrhythmia syndromes n = 144, 3%. Of patients with a primary arrhythmia syndrome, 132 (91%) were diagnosed with LQTS. The remaining group of patients received other diagnoses (e.g. idiopathic PVC). From the 174 studies reporting on efficacy, 60 (35%) studies included therapy-resistant patients in whom previous conventional therapy was ineffective. In 157 (71%) studies, the route of administration was oral. In 24 (11%) studies, mexiletine was administered intravenously. In 13 (6%) studies, both routes of administration were used. Intramuscular administration of mexiletine was used in 1 (0.5%) study, while in 26 (12%) studies, the route of administration was not reported. Doses ranged from 50–2400 mg/day to 1–42 mg/kg/day.

Outcome
In this section, an overview of the results is presented. In the supplementary excel file, we present the extracted data for the individual studies per outcome measure. In this supplement, it is possible to filter on (multiple) variables, for example in order to select studies with a specific follow-up duration, mexiletine dose, or certain arrhythmia burden cut-offs.

Data on effectiveness of mexiletine
Results of individual studies are presented in the supplements.

Ventricular arrhythmia burden
Efficacy of mexiletine with regards to the ventricular arrhythmias is further stratified in the burden of PVC (n = 61 studies), VT (n = 34 studies), and VF (n = 12 studies). Table 1 shows the study details and outcomes. For the PVC burden, in the 38 studies (n = 1143 evaluable patients) in which a percentage change was reported or calculable, 27 (72%) studies comprising 877 evaluable patients showed a reduction of >50% in PVC burden. In 8 studies (21%, n = 197 patients), this reduction percentage was >80%.24–31 For the studies that applied a cut-off value for efficacy, the results are presented in Table 1. For the VT burden, in the 11 studies (n = 412 evaluable patients) in which a percentage change was reported or calculable, 7 (64%) studies, comprising 237 evaluable patients, showed a reduction of >50% in VT burden. Two studies applied a cut-off of >75% for efficacy, 74% of the patients met this criterion. Twenty-one studies applied a cut-off of 100%, in those studies 90% of the patients met this criterion (Table 1). For VF burden, in the 3 studies (n = 171 evaluable patients) in which a percentage change was reported or calculable, 1 (33%) study comprising of 34 evaluable patients showed a reduction of >50% in VF occurrence.

Nine studies applied a cut-off of 100%, 90% of the patients met this criterion (Table 1). In only two studies (n = 2 patients), ICDs were implanted.100,101 In the studies with recurrences, details on the episodes (sustained vs. unsustained) were sparsely reported. Worsening of arrhythmias is discussed in the ‘Safety and survival data’ section. For patients with LQTS, efficacy of mexiletine in VF reduction is reported in three studies (n = 40 patients, LQTS type 3: 100%).100–102 A reduction of >90% was achieved in 39 (98%) of these patients.100,102

Electrophysiological study parameters
Table 2 shows the study details and outcome for the studies evaluating the effect of mexiletine on VT/VF inducibility and electrophysiological parameters. Inducibility of ventricular arrhythmias was reported in 19 studies for VT, and 2 studies for VF. In 11/2379 (30%) patients, non-inducibility was achieved for VT and in 11/17 (65%) for VF (Table 2). The range in relative change percentage after mexiletine for the VT cycle length was −17% to +27%. Ten (55%) studies comprising 119 patients showed a change in cycle length of >15% after mexiletine, and most of those studies, 9/10 (90%), comprising 89 patients, showed that this change was an increase in cycle length (Table 2). With regards to the ERP, 0 (0%) of the 10 studies (n = 151 patients) showed a change of >15%. The effect ranged from −11% to +8% (Table 2).

Electrocardiographic parameters
Table 3 shows the electrocardiographic effects of mexiletine in patients without a primary arrhythmia syndrome and in Table 4, the results are presented for the patients with a primary arrhythmia syndrome. The electrocardiographic effects of mexiletine in patients without primary arrhythmia syndrome showed that the effects of mexiletine on electrocardiographic parameters were small. Only 1 study out of 16 (6%, 5 of 329 patients) showed a change of >15% on heart rate (increase). For the QRS-duration (n = 21 studies, 536 patients) and the QTc (n = 16 studies, 439 patients), no effects >15% were observed. The range in relative change for the heart rate, QRS-duration, and the QTc were between −14% and +16% (Table 3).

Patients with primary arrhythmia syndromes
In patients with a primary arrhythmia syndrome, mostly patients with LQTS (Table 4), the results for heart rate (n = 5 studies, n = 34 patients) and QRS-duration (n = 1 study, n = 12 patients) were similar (range of relative change −7% to +6%). In contrast, all studies reporting on QTc showed QTc shortening (n = 90 evaluable patients). Indeed, 3 (27.3%) of the 11 studies (22 of 90 evaluable patients) in LQTS patients report a relative decrease of >15% after mexiletine.129–131 Most of the evaluable LQTS patients were patients with type 3 (n = 64, 82%), followed by type 2 (n = 11, 14%), a combination LQT1/2 or LQT2/3 (n = 2, 3%) and type 8 (n = 1, 1%).

Safety and survival data
In 173 (78%) studies, safety is reported in total evaluating 7379 (82%) patients.9,10,24,26,27,29–77,84–97,100,103–110,118,124–126,127,128–130,132,133,136–222 Survival is reported in 151 studies (68%).9,10,25–32,35,40,43,46–50,52–63,66–71,73–80,84–87,89,91–98,100–113,119–126,128,130–139,142–145,148–159,161,162,164,165,169,171–173,175–177,181–184,188,190–194,196,199–201,204,207,208,211,212,214–217,220–229

Adverse events
In total, adverse events are reported in 128 (58%) of the studies. For the 589 adverse events reported, in 512 (86%), the number of
Table 2  The effects of mexiletine on electrophysiological study parameters

| Electrophysiology studies | Inducibility studies | Electrophysiology study parameters |
|---------------------------|----------------------|------------------------------------|
|                           | Publications, n (%)  | Study design                        |
|                           | Reports              | Studies with therapy-resistant patients |
|                           |                      | Patients on mexiletine | Age range | Type of patients (if reported) | Mexiletine dose range | Evaluable patients | Number of patients with non-inducibility |
| VT inducibility           |                      | Non-randomized | 19 | 12 | 432 | 16–79 | Ischaemic | 229 | 125–2400 mg/day | 379 patients in pre-post design | 112 (30%) |
|                           |                      | Randomized     | 0 |  |  | | | Non-ischaemic | 53 | mg/day/kg | |
|                           |                      | Non-randomized | 2 | 1 | 35 | 60 | Ischaemic | 15 | 800–1200 mg/day | 17 patients in pre-post design | 11 (65%) |
| VF inducibility           |                      | Randomized     | 0 |  |  | | | Non-ischaemic | 20 | mg/day/kg | |
|                           |                      |                |              | Arrhythmia syndrome | Other | 8 | | | |
|                           |                      | Non-randomized | 0 |  |  | | | Arrhythmia syndrome | Other | 0 | | |
|                           |                      | Randomized     | 0 |  |  | | | Other | 0 | | |
|                           |                      | Non-randomized |  |  |  | | | | | | |
|                           |                      | Randomized     | 0 |  |  | | | | | | |
|                           |                      |                |              | | | | | | | | |
| Cycle length              |                      | Non-randomized | 18 | 18 | 409 | 16–79 | Ischaemic | 179 | 125–2400 mg/day | 376 patients in pre-post design | 10/18 |
|                           |                      | Randomized     | 0 |  |  | | | Non-ischaemic | 50 | mg/day/kg | |
|                           |                      | Non-randomized | 10 | 6 | 178 | 5–79 | Ischaemic | 95 | 125–1200 mg/day | 151 patients in pre-post design | 0/10 |
|                           |                      | Randomized     | 0 |  |  | | | Non-ischaemic | 25 | mg/day/kg | |
|                           |                      | Non-randomized |  |  |  | | | Arrhythmia syndrome | Other | 0 | | |
|                           |                      | Randomized     | 0 |  |  | | | Other | 3 | | |
| Effective refractory period |                      | Non-randomized | 10 | 6 | 178 | 5–79 | Ischaemic | 95 | 125–1200 mg/day | 151 patients in pre-post design | 0/10 |
|                           |                      | Randomized     | 0 |  |  | | | Non-ischaemic | 25 | mg/day/kg | |
|                           |                      | Non-randomized |  |  |  | | | Arrhythmia syndrome | Other | 0 | | |
|                           |                      | Randomized     | 0 |  |  | | | Other | 3 | | |

NA, not applicable; VF, ventricular fibrillation; VT, ventricular tachycardia.

*aMean age based on one study, and the age is not reported in the other study.
### Table 3 Electrocardiographic effects of mexiletine in patients without primary arrhythmia syndromes

| Electrocardiographic effects | Publications, n (%) | Study design | Follow-up range | Studies with therapy-resistant patients | Patients on mexiletine | Age range (years) | Type of patients (if reported) | Mexiletine dose range | Evaluable patients | Studies that show >15% change |
|-----------------------------|---------------------|-------------|-----------------|----------------------------------------|------------------------|-----------------|-----------------------------|----------------------|---------------------|-----------------------------|
| Heart rate                  |                     | Non-randomized | 16 2 days–12 months | 7                                      | 449                    | 5–83            | Ischaemic                   | 181                  | 300–1200 mg/day         | 360 patients in pre-post design |
|                            |                     | Randomized    | 0 months         |                                        |                        |                 | Non-ischaemic               | 82                   | 4–24 mg/day/kg           | 9 patients on mexiletine vs. 26 control patients |
|                            |                     |              |                 |                                        |                        |                 | Other                        | 117                  |                     |                             |
|                            |                     | Non-randomized | 21 2 days–36 months | 9                                      | 647                    | 21–87           | Ischaemic                   | 316                  | 125–1500 mg/day         | 536 patients in pre-post design |
|                            |                     | Randomized    | 0 months         |                                        |                        |                 | Non-ischaemic               | 90                   | 7 mg/day/kg              | 0/21 Range of the change: --4% to +7% |
|                            |                     |              |                 |                                        |                        |                 | Other                        | 98                   |                     |                             |
| QTc                         |                     | Non-randomized | 16 0.1–36 months | 7                                      | 557                    | 18–87           | Ischaemic                   | 235                  | 200–1200 mg/day         | 439 patients in pre-post design |
|                            |                     | Randomized    | 0 months         |                                        |                        |                 | Non-ischaemic               | 92                   | NA mg/day/kg             | 0/16 Range of the change: --5% to +2% |
|                            |                     |              |                 |                                        |                        |                 | Other                        | 112                  |                     |                             |

NA, not applicable.
Table 4  Electrocardiographic effects of mexiletine in patients with primary arrhythmia syndromes

| Electrocardiographic studies | Publications, n (%) | Study design | Follow-up range | Patients on mexiletine | Age range (years) | Type of patients | Mexiletine dose range | Evaluable patients | Studies that show >15% change |
|-----------------------------|---------------------|-------------|-----------------|------------------------|------------------|-----------------|---------------------|-------------------|-----------------------------|
| Heart rate                  |                     |             |                 |                        |                  |                 |                     |                   |                             |
| Non-randomized              | 5                   | 12–84 months | 0               | 50                     | 1–63             | LQTS            | NA mg/day          | 34 patients in pre-post design | 0/5 Range of the change: −7% to +6% |
| Randomized                  |                     | 0           |                 |                        |                  | CPVT            | 0                   |                   |                             |
| Brugada                     |                     | 12          | 2–42 mg/day/kg  |                        |                   | CPVT            | 0                   |                   |                             |
| Brugada                     |                     | 12          | 2–42 mg/day/kg  |                        |                   | CPVT            | 0                   |                   |                             |
| Brugada                     |                     | 12          | 2–42 mg/day/kg  |                        |                   | CPVT            | 0                   |                   |                             |
| Non-randomized              | 11                  | 0.69–84 months | 0               | 115                    | 0–64             | LQTS            | 103 150–600 mg/day | 90 patients in pre-post design | 3 11–13/11% Range of the change: −19% to −1.3% |
| Randomized                  |                     | 0           |                 |                        |                  | CPVT            | 0                   |                   |                             |
| Brugada                     |                     | 12          | 2–42 mg/day/kg  |                        |                   | CPVT            | 0                   |                   |                             |
| CPVT, catholaminergic polymorphic ventricular tachycardia; LQTS, long QT syndrome; NA, not applicable. |
patients with adverse events was specified resulting in a total of 4037 evaluable patients. Table 5 shows the incidences of adverse events. The most frequently reported organ system with adverse events was the gastrointestinal tract (33%). Gastrointestinal pain was reported in 27% of the patients, gastrointestinal discomfort/distress was reported in 19%, as was nausea (19%). Adverse events concerning the nervous system were also frequently reported (31%), and in 17% of the patients, a tremor occurred. Psychiatric adverse events were reported in 12% of the patients with insomnia most frequently.

Table 5 Overview of the adverse events

| Adverse events                                      | # patients with event/number of patients in the studies reporting the event |
|-----------------------------------------------------|--------------------------------------------------------------------------------|
| Gastrointestinal                                    |                                                                             |
| 1348 patients with this type of event (33%)         |                                                                             |
| Nausea                                              | 462/2475 (19%)                                                              |
| Other (e.g. discomfort/distress or not further specified) | 341/1833 (19%)                                                              |
| Gastrointestinal pain                               | 88/329 (27%)                                                                 |
| Constipation                                         | 150/1043 (14%)                                                               |
| Diarrhoea                                           | 100/1259 (8%)                                                                |
| Nervous system disorders                            |                                                                             |
| 1267 patients with this type of event (31%)         |                                                                             |
| Tremor                                              | 414/2485 (17%)                                                               |
| Other (e.g. coordination difficulties or not further specified) | 131/1002 (13%)                                                              |
| Dizziness                                           | 293/2368 (12%)                                                               |
| Headache                                            | 165/1644 (10%)                                                               |
| Parasthesia                                         | 111/1373 (8%)                                                                |
| Psychiatric disorders                               |                                                                             |
| 475 patients with this type of event (12%)          |                                                                             |
| Insomnia                                            | 291/1457 (20%)                                                               |
| Depression                                          | 67/689 (10%)                                                                 |
| Other (e.g. anxiety, nervousness, mood changes, nightmares) | 80/1225 (7%)                                                                |
| Confusion                                           | 26/470 (6%)                                                                  |
| Musculoskeletal and connective tissue disorders     |                                                                             |
| 175 patients with this type of event (4%)           |                                                                             |
| Generalized muscle weakness                         | 171/912 (19%)                                                                |
| Joint effusion                                       | 1/32 (3%)                                                                    |
| Cardiac disorders                                   |                                                                             |
| 144 patients with this type of event (4%)           |                                                                             |
| Sinus bradycardia                                   | 36/388 (9%)                                                                  |
| Heart failure                                       | 29/533 (5%)                                                                  |
| Chest pain—cardiac                                  | 10/246 (4%)                                                                  |

The organ systems and adverse events with ≥3% incidences are presented.

Left and right ventricular ejection fraction
Only 15 (7%) of the studies (n = 476 patients) report on effects of mexiletine on cardiac function.49,55,57,58,62,65,66,97,125,126,139,155,180,181,189 In all of the studies reporting on left ventricular ejection fraction, 14 (9.3%) of the studies (475 of 476 patients) showed no negative effects of mexiletine on left ventricular ejection fraction.49,54,57,58,62,65,66,97,125,126,155,180,181,189 Three (20%) studies comprising 36 patients reported on right ventricular ejection fraction, and none of these studies demonstrated a decrease in right ventricular ejection fraction.66,125,126

Drug–drug interactions
Nine studies (n = 23 patients) report on mexiletine interacting with other drugs.95,150,158,182,183,186,216,221,222 The majority [n = 5 (56%) studies, 7 (30%) patients] of those studies report an interaction with theophylline.95,158,182,183,216 Clearance of theophylline is reduced as a consequence of CYP1A2 inhibition by mexiletine, which results in increased (possibly toxic) theophylline blood levels.

Worsening of arrhythmias
In 40 (18%) studies, worsening or not worsening of arrhythmias is actively mentioned.27,31,34,38,39,41,50,54,55,57,58,60,62,64,68,75,76,85,87,90,106,118,128,129,138,141,151,154,161,164,166,174,175,183,201,207–209,213,218 In total, in this subset of 40 studies, in 137 of 2173 (6.3%) patients, the arrhythmia worsened after start of mexiletine.

Survival
Survival is reported in 151 (68%) studies evaluating 4801 patients on mexiletine. During varying follow-up durations ranging from 0.5 h to 167 months, 213 (4%) patients reportedly died during the study follow-up. In 13 studies reporting on both survival in patients with mexiletine and control patients, the proportions of survival are similar (90% in mexiletine vs. 92% in control patients).10,35,40,56,84,93,127,137,144,152,173,176,193

Discussion
In this systematic review, we present all the currently reported knowledge from 1973 onwards on the effectiveness and safety of mexiletine in patients at risk for (recurrent) ventricular arrhythmias. The data presented confirm that mexiletine is both effective and safe in patients at risk for (recurrent) ventricular arrhythmias. The evaluation of effectiveness is extensive and comprises of several aspects, including appreciable effects on PVC, VT and VF burden and on electrocardiography. Also with regards to our safety evaluation, to the best of our knowledge, such a detailed overview of adverse event incidences of mexiletine has not been previously reported.

For example, we present incidences of several adverse events (e.g. diarrhoea and confusion) of which the incidences are currently marked as unknown.210 The presented safety data should be implemented into the product information of mexiletine to inform patients and prescribers adequately. Unfortunately, because of our broad study aim and the subsequent inclusion of studies with extremely heterogeneous designs and outcomes, it is not possible to
compare the efficacy results of mexiletine with other anti-arrhythmic drugs such as sotalol or amiodarone.\textsuperscript{2,3,11,22}

The findings of this systematic review indicate that treatment of mexiletine should be part of the therapeutic cardiology arsenal, both in paediatric (LQTS) and adult cardiology. Accessibility should thus be guaranteed. However, accessibility has been jeopardized by the market authorization as an orphan drug of Namuscla. Remarkably, the contra-indications of Namuscla actually include ventricular tachyarrhythmias and previous myocardial infarction. However, as can be appreciated from its previous anti-arrhythmic drug labelling, from the international guidelines on the treatment and prevention of VT/VF,\textsuperscript{1,11} and from our results section, mexiletine can be an effective and safe choice for the treatment and prevention of VT and VF. Furthermore, these results are mostly driven by patients with (post-)ischaemic heart disease as mexiletine was most frequently prescribed in this patient category (72%). Possibly, the indication for non-dystrophic myotonia would have been complicated by potential pro-arrhythmic effects, which is, of course, intrinsically a part of every anti-arrhythmic drug. The lack of new data may have led to declaring a contra-indication for cardiology patients whose lives are threatened by VT/VF. Importantly, labelling a contra-indication for a previous indication that is still recommended in the guidelines could have important medico-legal consequences for off-label prescription. This could further limit mexiletine use in patients who could benefit. In addition, as per European regulation, the authorization of Namuscla as an orphan drug for the neurological indication non-dystrophic myotonia granted a 10-year market exclusivity and prohibits import of mexiletine for VT/VF. Upon introduction of Namuscla, the price was raised up to >30-fold in comparison with imports which in turn led to reimbursement issues for both the cardiac and neurological indication.\textsuperscript{6,15,16}

Practical suggestion
The current use of mexiletine is constrained to (high risk and/or therapy refractory) VT/VF, which is also supported by the results of our systematic review. However, as shown, mexiletine also appears to be very successful in suppressing PVCs. Hence, mexiletine may have a position in patients without complex ventricular arrhythmias who do not respond well to conventional therapy (be it side effects or inefficacy). Mexiletine also appears to be very effective in (paediatric) patients with LQTS. Therefore, we suggest the use of mexiletine in:

- Patients at high risk for VT/VF who do not respond to conventional therapy
- Patients without complex ventricular arrhythmias who do not respond to conventional therapy
- Patients with LQTS (mainly Types 3 and 2) with ventricular arrhythmias or a high risk of ventricular arrhythmias (e.g. very long QTc)

Limitations
From 1973 onwards, 221 publications with original data regarding the efficacy and safety of mexiletine in patients with (recurrent) ventricular arrhythmias were identified. Over time, inevitably, the quality of conducting and reporting scientific research improved.\textsuperscript{23} For the efficacy data, studies with a high risk of bias were therefore excluded. Furthermore, in this review, we aimed to evaluate both the effectiveness and safety of all types of patients at risk for (recurrent) arrhythmias. As efficacy of mexiletine comprises of multiple relevant outcome measures (e.g. PVC reduction, or QTc reduction in patients with LQTS), included studies were different in methodology, follow-up duration, outcome measures, and also in the reporting of efficacy (e.g. cut-off % for efficacy) and of safety data. Therefore, a single estimate effect of mexiletine could not be calculated. Due to this heterogeneity, extracting data for standardized evaluation required modulation or interpretation of study data for some studies. Data were independently extracted by at least two members of the study team to prevent subjectivity. Also due to the large amount of data, in the body of the manuscript only a general overview of the results is presented. For more detailed results of individual studies, we refer to the supplementary excel file. This supplementary excel also allows the reader to select on specific study characteristics (e.g. follow-up duration). It is important to acknowledge that drug–drug studies not involving mexiletine treatment effectiveness or safety (i.e. healthy volunteer studies) are beyond the scope of this review. Consequently, evaluation of relevant drug–drug interactions, mainly involving the cytochrome P450 enzymes CYP1A2 and CYP2D6, is incomplete. Lastly, efforts were made to prevent double reporting of patients and outcome data in this systematic review; however, we cannot exclude that double reported data entered our results.

Conclusion
In this systematic review, we present all the currently available knowledge on the effectiveness and safety of the long-known anti-arrhythmic drug mexiletine in patients at risk for (recurrent) ventricular arrhythmias and based on the results, we conclude that mexiletine is both effective and safe. As the European accessibility of mexiletine has recently been critically endangered by its acceptance as an anti-myotonic drug, efforts should be undertaken to unchain mexiletine and assure its fair accessibility for both cardiology and neurology patients.

Supplementary material
Supplementary material is available at Europea online.

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Conflict of interest: P.G.P. is a member of the Scientific Advisory Group on Cardiovascular Issues (SAG-CVS) of the EMA since 2021. C.E.M.H. is involved in pre-marketing research with Sanofi, Protalix, and Idorsia, outside the submitted work. N.R., N.S., S.B., V.W., B.J., and C.E.M.H. are members of the platform ‘Medicijn voor de Maatschappij’. This is an academic initiative that aims to support sustainable access to medicines for rare diseases, including mexiletine. V.W. reports personal fees from Fair Medicine Foundation, personal fees from Patient One, outside the submitted work.
Data availability

As stated in the method section: The study data is available from the corresponding author upon reasonable request.

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