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SYSTEMATIC REVIEW

Use of Electrocardiogram Monitoring in Adult Patients Taking High-Risk QT Interval Prolonging Medicines in Clinical Practice: Systematic Review and Meta-analysis

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Abstract

Introduction Electrocardiogram (ECG) monitoring is an important tool to detect and mitigate the risk of potentially fatal drug-induced QT prolongation and remains fundamental in supporting the quality use of high-risk QT interval prolonging medicines.

Objective The aim of this systematic review was to determine the prevalence of baseline and/or follow-up ECG use in adult patients taking high-risk QT interval prolonging medicines in clinical practice.

Methods CINAHL, Cochrane Library, Embase, PubMed, EThOS, OpenGrey and Proquest were searched for studies in adults that reported ECG use at baseline and/or at follow-up in relation to the initiation of a high-risk QT interval prolonging medicine in any clinical setting; either hospital or non-hospital. Two reviewers independently assessed the methodological quality of included studies. Proportional meta-analysis was conducted with all studies reporting baseline ECG use, before medicine initiation, and follow-up ECG use, within 30 days of medicine initiation.

Results There was variability in baseline ECG use according to the practice setting. The prevalence of baseline ECG use for high-risk QT interval prolonging medicines was moderate to high in the hospital setting at 75.1% (95% CI 64.3–84.5); however, the prevalence of baseline ECG use was low in the non-hospital setting at 33.7% (95% CI 25.8–42.2). The prevalence of follow-up ECG use was low to moderate in the hospital setting at 39.2% (95% CI 28.2–50.8) and could not be determined for the non-hospital setting.

Conclusions The use of ECG monitoring for high-risk QT interval prolonging medicines is strongly influenced by the clinical practice setting. Baseline ECG use occurs more in the hospital setting in comparison to the non-hospital setting. There is lower use of follow-up ECG in comparison to baseline ECG.

Key Points

High-risk QT interval prolonging medicines have compelling evidence for risk of torsades de pointes (TdP) and ECG monitoring remains unequivocally recommended for their use.

The use of ECG for drug safety monitoring of high-risk QT interval prolonging medicines in clinical practice is variable and limited.

There is a clear lack of policy and research for ECG monitoring of high-risk QT interval prolonging medicines in the non-hospital setting.

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1 Introduction

Medicines with the potential to cause QT prolongation belong to a wide spectrum of therapeutic classes and their use is expected in all types of healthcare settings. It has previously been estimated that the use of QT interval prolonging medicines could result in > 15,000 deaths annually in the US and Europe [1]. Therefore, prevention of this adverse drug reaction remains a fundamental consideration of therapeutic decision making in all areas of clinical practice.

QT prolongation remains the best measure, although an imperfect predictor [2, 3], for the more serious risk of torsades de pointes (TdP) and sudden cardiac death (SCD). Electrocardiographic (ECG) monitoring remains the best available tool to assess and mitigate the risk of TdP [4, 5], and hence support the safe use of high-risk QT interval prolonging medicine therapy.

Since 2004, guidelines published by the American Heart Association (AHA) have recommended the use of ECG monitoring before and after the commencement of high-risk QT interval prolonging medicines [6–8]. These guidelines have generally focussed on medicines used in the hospital setting. In contrast to the hospital setting, there is very limited guidance for ECG monitoring specifically relating to prevention of drug-induced QT prolongation in non-hospital settings. Trinkley et al. (2013) [5] recommended that risk mitigation strategies and QT interval monitoring are needed in every care setting. Despite this notion, very few recommendations have been published specifically relating to the non-hospital setting [9, 10].

There has been a strong emphasis on ECG monitoring of hospitalised patients as they are considered at greater risk of QT prolongation and TdP due to the increased prevalence of risk factors. However, complex patients with multiple risk factors for QT prolongation and TdP are increasingly being managed in non-hospital settings such as outpatient clinics, primary care and in residential care facilities. Although differing healthcare systems, personnel and equipment influence the feasibility of risk management strategies, medicines safety and patient management principles in relation to high-risk QT interval prolonging medicines remain the same.

Initiation of high-risk QT interval prolonging medicines, and indeed non–high-risk QT interval prolonging medicines, in contrast to their continuing use, has compelling cause for ECG monitoring and provides a clear platform on which to summarise the prevalence of ECG use, in all areas of clinical practice, at key points of therapeutic decision making. The objective of this review was to determine the prevalence of ECG monitoring conducted at baseline and the prevalence of ECG monitoring conducted at follow-up, for patients taking high-risk QT interval prolonging medicines, in any clinical setting.

2 Methods

The JBI (formerly Joanna Briggs Institute) methodological approach to systematic reviews of prevalence and incidence was followed [11, 12]. Reporting of this review is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [13]. The study protocol was previously published [14] and registered with the International Prospective Register of Systematic Reviews (PROSPERO, CRD42021240762).

2.1 Inclusion and Exclusion Criteria

Inclusion was restricted to adults (aged ≥ 18 years) initiated on a high-risk QT interval prolonging medicine, rather than on stable or ongoing medicine therapy. Medicines listed in the 'known risk of TdP' category, as defined by the University of Arizona Center for Education and Research on Therapeutics (AZCERT) [15], were considered high-risk medicines for this systematic review. Medicines that were not classified as 'known risk of TdP' at the time of original study were excluded from the review.

Baseline ECG was included if conducted at any time prior to the initiation of a high-risk QT interval prolonging medicine. Follow-up ECG had to occur within 30 days from medicine initiation. Follow-up ECG that occurred due to a raised QT threshold at baseline ECG were excluded.

ECG use was excluded if described in any way other than a discrete non-continuous ECG test. Studies intentionally conducting ECGs were excluded.

Any study types, except for case studies and case series, were considered, from any country and conducted in any clinical setting including any hospital and non-hospital settings.

2.2 Search Strategy and Study Selection

A comprehensive search was conducted on 15 February 2021. Published studies were searched using CINAHL (EBSCO), Cochrane Library, Embase (Ovid) and MEDLINE (PubMed). Conference abstracts were excluded. Unpublished studies were searched using EThOS, OpenGrey and ProQuest Dissertations and Theses Global. No language restrictions were applied. See Electronic Supplementary Material (ESM) 1 for the full search strategy.

The search start date was 2004, relating to the first prominent practice standards discussing ECG monitoring of high-risk QT interval prolonging medicines [6].

All titles and abstracts identified by the searches were screened for inclusion using Endnote X9 (Clarivate Analytics, PA, USA), and potentially relevant articles were retrieved in full. Duplicates were initially identified automatically in

Endnote X9 and then manually following automation. To assist study selection, authors of papers were contacted to request additional data for clarification.

Any uncertainties were resolved through discussion with a second reviewer (MW). The reference lists of all studies selected for quality assessment were screened for additional studies.

2.3 Quality Assessment

Quality assessment of eligible studies was undertaken independently by two reviewers (MP, CB) using a standardised critical appraisal instrument from JBI for studies reporting prevalence data [11, 12, 16].

Any discrepancies were resolved through discussion between the two reviewers (MP, CB) or with a third reviewer (MW). Authors of papers were contacted to request missing or additional data for clarification.

The assessment criteria of the critical appraisal instrument were adapted to suit the needs of this review. Specifically, domain four of the instrument involved whether the clinical setting was sufficiently described to be able to identify its place in the healthcare system. Domain seven involved whether the time frames for baseline and/or follow-up ECG were described clearly.

To be eligible to be deemed of high-quality, studies had to perform well on domains four and seven and had to achieve a total score of at least seven out of nine on the critical appraisal instrument.

2.4 Data Extraction

Data was extracted using a modified version of the JBI standardised data extraction instrument [11], including population characteristics, high-risk medicines studied, information about baseline and/or follow-up ECG use, reasons for ECG, and details of the clinical setting. Any ambiguities associated with data extraction were resolved following discussion with a second reviewer (MW).

Sample size related to the total cohort of patients on newly initiated high-risk QT prolonging medicine(s) only. Studies with pre-intervention and post-intervention cohorts were extracted as two separate samples, which are identified in this review as data group (a) and data group (b), respectively.

ECG use data that were reported separately for different cohorts based on various descriptors such as specific clinical locations were combined into a single sample.

2.5 Data Synthesis

Studies were pooled with proportional meta-analysis using the JBI System for Unified Management, Assessment and Review of Information (JBI SUMARI) [17].

Results of each individual study included numerator and denominator for ECG use at baseline and for ECG use at follow-up, proportion (expressed as a percentage) and 95% confidence intervals (CIs). The Freeman-Tukey transformation was used for the meta-analysis. Proportions were pooled using the random effects model due to the heterogeneity between studies [18] and reported as a percentage with a 95% CI. Forest plots were used to display the results. Heterogeneity was reported using the I^2 statistic. Publication bias was not assessed, as there is no evidence that proportional data adequately adjusts for these tests [18].

Separate analyses were conducted for each category of baseline ECG use and follow-up ECG use and additionally within these groups, according to clinical setting (hospital setting and non-hospital setting). Furthermore, sensitivity analyses were conducted to determine the impact of exclusion of poor-quality studies; 'leave one (or more) out' analyses were conducted where there were sufficient study level reasons to explore the impact of exclusion of individual studies with biases not otherwise accounted for by quality assessment. All analyses were conducted with at least two studies in each category.

3 Results

Searches of databases returned 9871 records. Following the removal of duplicates, the titles and abstracts of 6548 unique records were screened. Following the exclusion of 6460 records, 88 were eligible for full-text review. Three non-English records (all French) were identified, two of which could not be located and one of which had an English abstract which was used to determine eligibility. Multiple reports of the same study were not identified. Seventy-four studies were excluded. See ESM 2 for reasons for exclusion of full-text studies. Fourteen studies (14 reports) were included, all of which were retrospective cohort studies (Fig. 1).

Thirteen studies included data relating to baseline ECG use, involving 18,581 participants. Only seven studies included data relating to follow-up ECG use, involving 43,321 participants.

3.1 Study Characteristics

Characteristics of the included studies are reported in Table 1. Most studies were conducted in the hospital setting. Hospital settings were heterogenous, including an emergency department, various clinical units including general medicine, cardiology and psychiatry and there was one inpatient headache centre. Many studies did not describe the specific location of hospital care, rather describing patients in other ways such as "total hospital population"

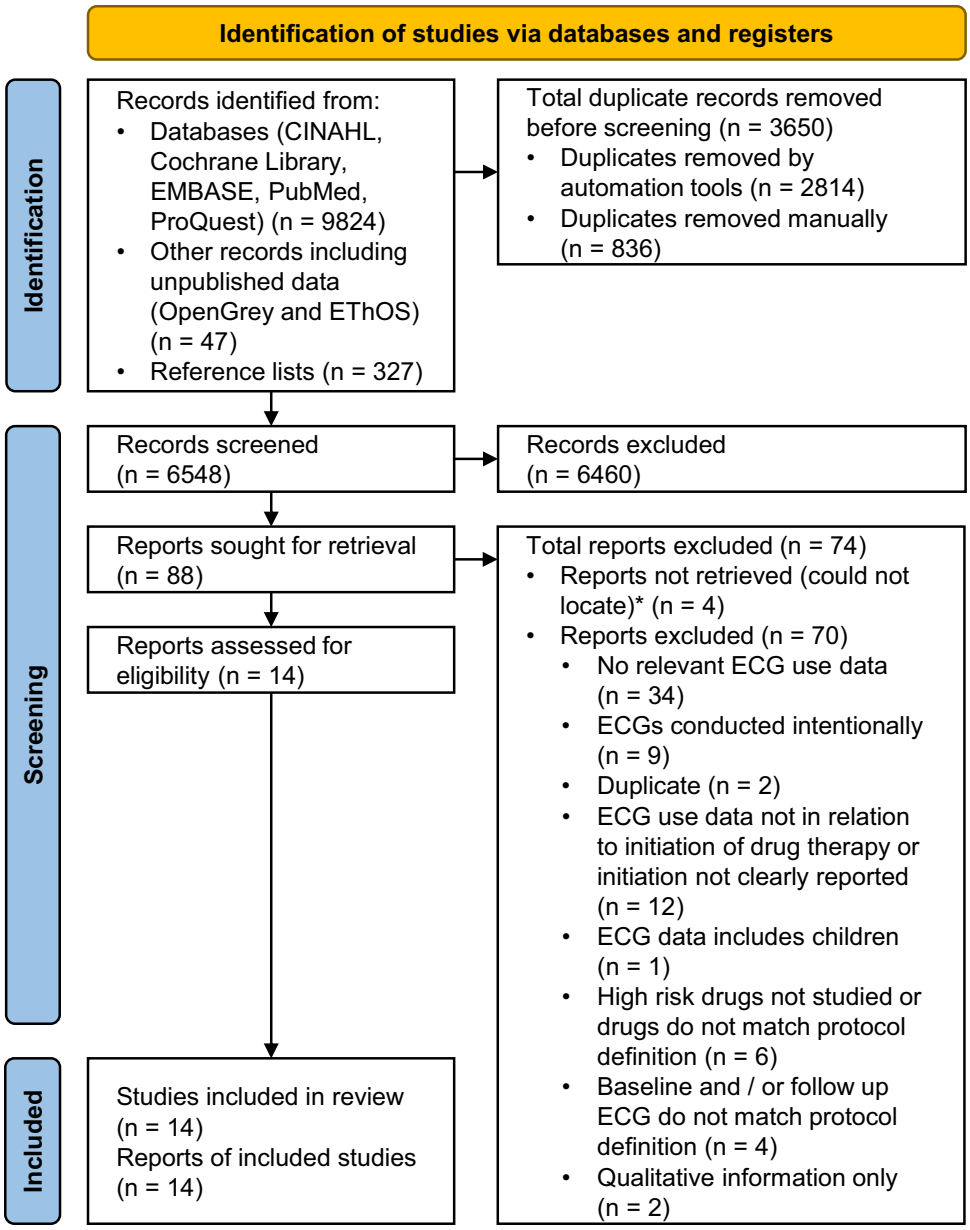

Fig. 1 Flow diagram of search results and review process (PRISMA 2020) [13]

[19], "medically ill and/or hospitalised inpatients" [20, 21], "inpatients" [22, 23] and "admitted patients" [24].

Three studies involved pre-intervention and post-intervention cohorts, which are identified in this review as data group (a) and data group (b), respectively. The intervention in two studies, Forbes et al. [23] and Dunker et al. [24], was passive in nature, in which ECG use was determined relative to the publication of a national public health warning relating to drug-induced QT prolongation. The intervention in the study by Muzyk et al. [20] was active in nature, in which ECG use was determined relative to the implementation of a computerised physician order entry set which involved generation of automated baseline and daily ECG orders in all patients prescribed the medicine of interest. The pre-intervention and post-intervention cohorts in each study involved two separate data sets (Table 1).

3.2 Methodological Quality

Methodological quality was deemed to be high for five out of 14 studies. See ESM 3 for assessment of methodological quality.

Table 1 Characteristics of included studies

Study, year	Study design	Setting description	No. of patients	ECG test(s) analysed	High-risk medicine(s) studied
Hospital setting					
Cole et al. [25], 2020	Retrospective observational	Emergency department, USA	16,546	Baseline ECG Follow-up ECG	Droperidol
Atayee et al. [21], 2017	Retrospective observational	Two-hospital academic health system, USA	100	Baseline ECG	Methadone
Vandael et al. [19], 2016	Retrospective observational	University hospital, Belgium	222	Baseline ECG Follow-up ECG	Haloperidol
Robbins et al. [26], 2016	Retrospective observational	Headache centre, USA	74	Baseline ECG	Domperidone
Girgis et al. [27], 2016	Retrospective observational	Community hospital, USA	38	Baseline ECG Follow-up ECG	Citalopram, escitalopram, haloperidol and methadone
Forbes et al. [23], 2016 (a)	Retrospective observational Pre-intervention cohort	Three-centre tertiary care network, Canada	207	Baseline ECG	Domperidone
Forbes et al. [23], 2016 (b)	Retrospective observational Post-intervention cohort		113		
Dunker et al. [24], 2016 (a)	Retrospective observational Pre-intervention cohort	Academic medical centre, USA	55	Baseline ECG	Azithromycin
Dunker et al. [24], 2016 (b)	Retrospective observational Post-intervention cohort		50		
Choo et al. [28], 2014	Retrospective observational	Teaching hospital, UK	60	Baseline ECG Follow-up ECG	Amiodarone, citalopram, clarithromycin, domperidone, erythromycin, flecainide, methadone and sotalol
Macey et al. [29], 2013	Retrospective observational	Veterans affairs medical centre, USA	92	Baseline ECG	Methadone
Cheung et al. [22], 2013	Retrospective observational	Urban tertiary care centre, USA	556	Baseline ECG	Haloperidol
Muzyk et al. [20], 2012 (a)	Retrospective observational Pre-intervention cohort	University hospital, USA	84	Baseline ECG Follow-up ECG	Haloperidol
Muzyk et al. [20], 2012 (b)	Retrospective observational Post-intervention cohort		67	Baseline ECG Follow-up ECG	
Non-hospital setting					
Manchia et al. [30], 2017	Retrospective observational	Community mental health centre, Italy	162	Baseline ECG	Unspecified antipsychotics
Ehrenpreis et al. [31], 2017	Retrospective observational	Community multi-specialty practice, USA	155	Baseline ECG	Domperidone
Unspecified clinical setting					
Pezo et al. [32], 2019	Retrospective observational	Residents of Ontario, Canada	26,230	Follow-up ECG	Unspecified

Two studies involved very large cohorts in the thousands and all other studies involved small to very small cohorts of < 100 or in the low hundreds.

Three studies involved additional biases that were not recognised in the formal assessment of methodological quality. Cole et al. [25] involved a medicine which was only deemed high-risk for 1 out of 5 years of their study period (R. Woosley, personal communication, 19 October 2021). Robbins et al. [26] specified that baseline ECG was obtained in all patients, and it is not clear within the study whether baseline ECG was conducted intentionally. Muzyk et al. [20] (b) involved active intervention of

ECG monitoring behaviour through automated baseline and daily ECG orders following prescription of high-risk medicine.

3.3 Prevalence of Baseline ECG Monitoring

The prevalence of baseline ECG monitoring for high-risk QT interval prolonging medicines was strongly influenced by the practice setting.

The prevalence of baseline ECG monitoring in the hospital setting (11 studies, $n = 18{,}264$) was generally moderate to high with a pooled proportion estimate of 73.0% (95% CI 57.0–86.5). Removing studies identified with additional biases from the analysis due to their previously described limitations, the prevalence estimate in the consequent analysis (9 studies, $n = 1577$) was only marginally increased to 75.1% (95% CI 64.3–84.5) (Fig. 2).

By removing the poor-quality studies from the analysis of the hospital setting, the final pooled proportion in the consequent analysis (4 studies, $n = 17{,}188$) was moderately reduced to 58.6% (95% CI 21.9–90.5).

However, by removing poor-quality studies and studies identified with additional biases from the analysis, the final pooled proportion in the consequent analysis (3 studies, $n = 642$) was corrected upward to 74.3% (95% CI 48.9–93.2).

Heterogeneity for all these baseline ECG pooled proportion estimates was considerable and demonstrated by $I^2 > 90\%$.

In contrast with studies conducted in the hospital setting, the prevalence of baseline ECG monitoring in the non-hospital settings were much lower. The pooled proportion estimate for the non-hospital setting (2 studies, $n = 317$), was calculated to be 33.7% (95% CI 25.8–42.2) (Fig. 3). Heterogeneity was only moderate in this analysis, described by an I^2 value of 60, however this was not statistically significant ($p = 0.1138$).

3.4 Prevalence of Follow-up ECG Monitoring

In comparison with baseline ECG monitoring, uptake of follow-up ECG monitoring was generally poorer. The prevalence of follow-up ECG monitoring in the non-hospital setting could not be determined due to lack of studies.

The prevalence of follow-up ECG monitoring in the hospital setting was low to moderate. The pooled proportion

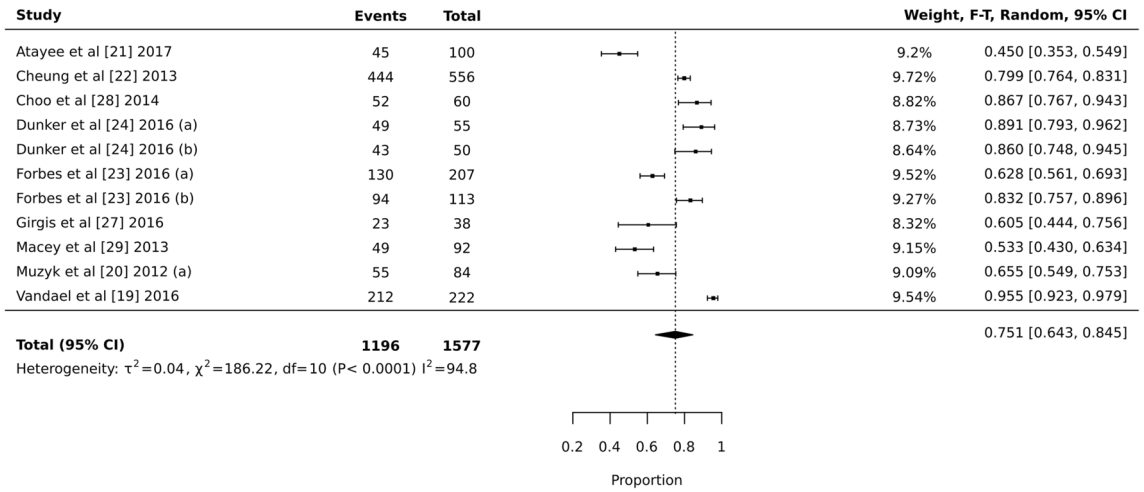

Fig. 2 Proportional meta-analysis of baseline ECG use—hospital setting only and leave three out (studies with additional biases)

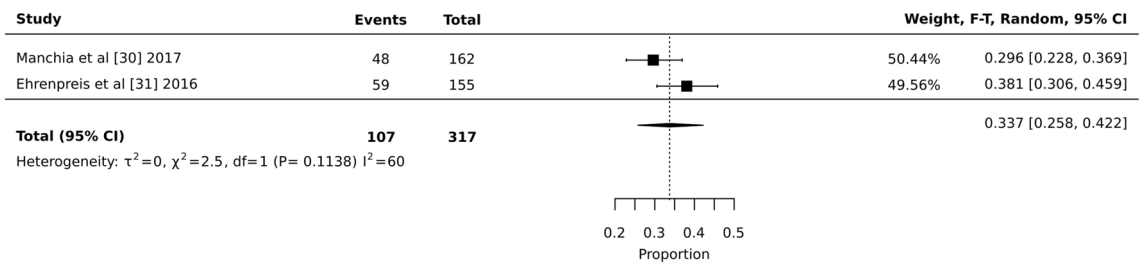

Fig. 3 Proportional meta-analysis of baseline ECG use—non-hospital setting only

estimate in the hospital setting (6 studies, $n = 17{,}091$) was 34.2% (95% CI 22.7–46.7). By removing studies with additional biases from the analysis of the hospital setting, due to their previously described limitations, the pooled proportion in the consequent analysis (5 studies, $n = 461$) was marginally increased to 39.2% (95% CI 28.2–50.8) (Fig. 4). The heterogeneity of these pooled proportion estimates was considerable, described by I^2 values of 94.9% and 81.6%, respectively.

Removing poor-quality studies from the analysis of the hospital setting considerably reduced the prevalence estimate, and the pooled proportion in the consequent analysis (2 studies, $n = 16{,}768$) was 21.9% (95% CI 4.7–46.9) (Fig. 5). However, one the two remaining studies in this analysis involved additional bias not recognised in the formal assessment of methodological quality. Heterogeneity was considerable in this analysis, described by $I^2 = 98.5\%$.

The prevalence of follow-up ECG monitoring in any clinical practice setting (7 studies, $n = 43{,}321$) included only one additional study, in comparison to the prevalence of follow-up ECG monitoring in the hospital setting. The additional study did not specify the healthcare setting in which medicine prescription or ECG use occurred and included the largest cohort out of all the studies in the review, involving more than 20,000 patients. The prevalence of follow-up ECG monitoring in any clinical setting was lower in comparison to the prevalence of follow-up ECG monitoring in the hospital setting, and the pooled proportion estimate was calculated to be 33.6% (95% CI 23.7–44.3). Heterogeneity was considerable, described by $I^2 = 99.6\%$. By removing studies with additional biases from the analysis of any clinical practice setting, the pooled proportion of the consequent analysis (6 studies, $n = 26{,}708$) was only slightly reduced to 32.7% (95% CI 29.1–36.5) (Fig. 6). Heterogeneity was only moderate, described by an I^2 of 38.3, although was not statistically significant ($p = 0.1675$).

Removing the poor-quality studies from the analysis of any clinical practice setting, the pooled proportion of the consequent analysis (2 studies, $n = 16{,}768$) was 21.9% (95% CI 4.7–46.9) (Fig. 5) and in fact provided the same result as for the prevalence of follow-up ECG monitoring in the hospital setting with poor-quality studies removed.

The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach, based on the

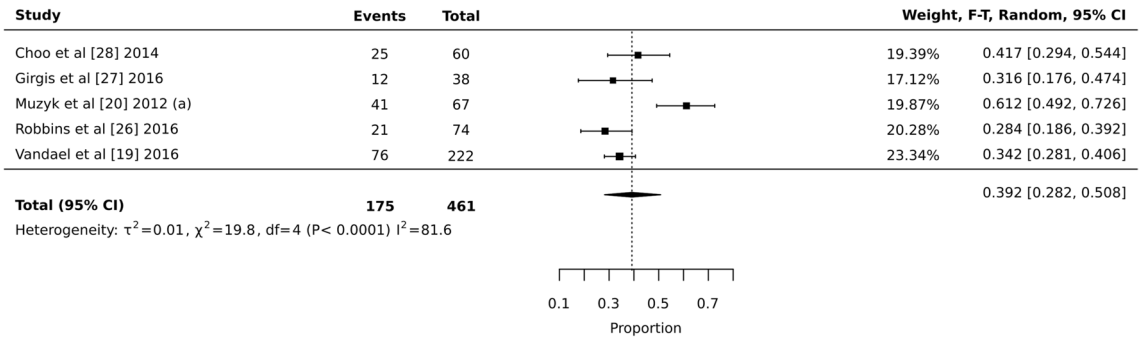

Fig. 4 Proportional meta-analysis of follow-up ECG use—hospital setting only and leave two out (studies with additional biases)

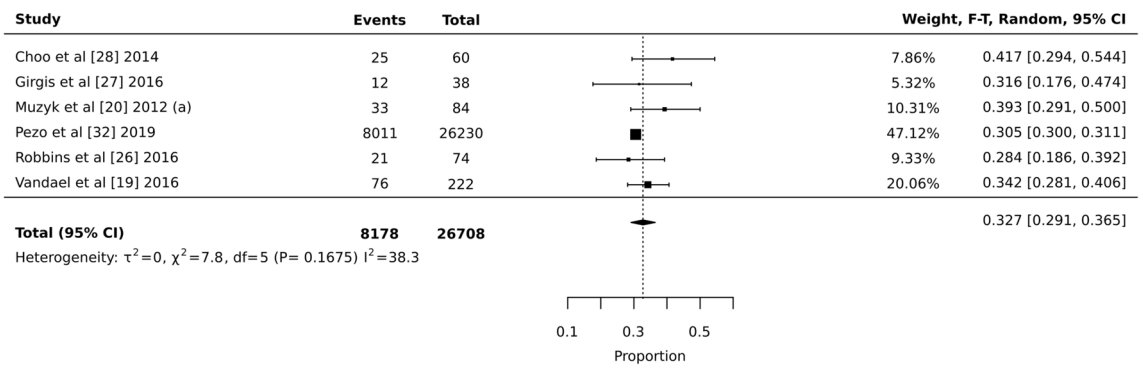

Fig. 5 Proportional meta-analysis of follow-up ECG use—hospital setting only and high-quality studies only; any clinical setting and high-quality studies only

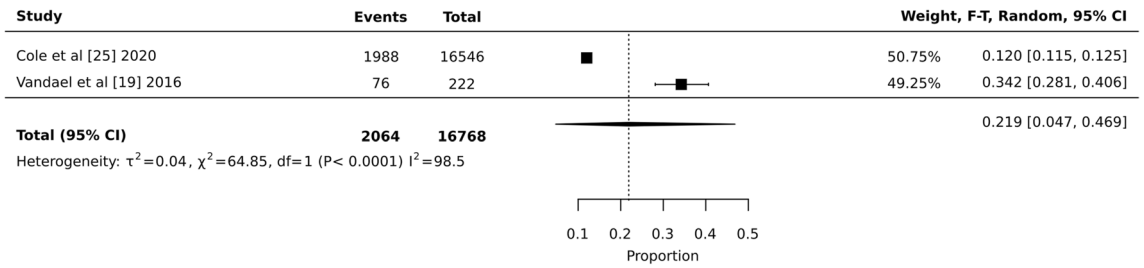

Fig. 6 Proportional meta-analysis of follow-up ECG use—any clinical setting and leave two out (studies with additional biases)

Table 2 Summary of findings (GRADE)—quality assessment

No. of studies	No. of subjects	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	Publication bias	Proportion (95% CI)	Certainty of evidence (GRADE)
Proportion of adult patients who get an ECG at baseline of initiation of high-risk QT prolonging medicine therapy—hospital setting									
9	1577	Observational studies	Not serious[a]	Very serious[b]	Serious[c]	Not serious	Not serious	75.1% (64.3–84.5)	Very low ⊕◯◯◯
Proportion of adult patients who get an ECG at baseline of initiation of high-risk QT prolonging medicine therapy—non-hospital setting									
2	317	Observational studies	Very serious[d]	Serious[e]	Serious[f]	Serious[g]	Not serious	33.7% (25.8–42.2)	Very low ⊕◯◯◯
Proportion of adult patients who get an ECG at follow-up of initiation of high-risk QT prolonging medicine therapy—any clinical setting									
6	26,708	Observational studies	Not serious[h]	Serious[e]	Not serious	Not serious[i]	Not serious	32.7% (29.1–36.5)	Moderate ⊕⊕⊕◯
Proportion of adult patients who get an ECG at follow-up of initiation of high-risk QT prolonging medicine therapy—hospital setting									
5	461	Observational studies	Very serious[j]	Very serious[b]	Serious[c]	Not serious	Not serious	39.2% (28.2–50.8)	Very low ⊕◯◯◯

GRADE Working Group grades of evidence: High certainty: We are very confident that the true effect lies close to that of the estimate of the effect; Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect; Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]Pooled proportions similar following separate analysis excluding poor-quality studies and studies with additional biases

[b]Extremely large differences between confidence interval points between studies (large point estimate inter-variation). Heterogeneity is considerable

[c]Wide confidence interval range within pooled estimate. Imprecision largely driven by significant inconsistency

[d]Small sample size. A poor-quality study [30] provides higher weight to pooled proportion

[e]Moderate differences between confidence interval points between studies (moderate point estimate inter-variation). Moderate heterogeneity, however, not statistically significant

[f]Moderately wide confidence interval range within pooled estimate

[g]Non-hospital setting represented by a single community mental health centre and a single specialist community practice only

[h]Pooled proportions are similar following separate analysis excluding studies with additional biases. The pooled proportion following separate analysis for high-quality studies only is limited by a remaining study with additional bias [25]. Although there is one high-quality study, its point estimate is consistent with the pooled proportion of all studies

[i]Although most studies are conducted in the inpatient hospital setting, Pezo et al. [32] contributes a very large sample size and provides data for medicine therapy and ECG use not biased toward any specific healthcare setting, and therefore would likely include medicine therapy and ECG use from all clinical settings

[j]Pooled proportions moderately differ following sensitivity analysis excluding poor quality studies. Small sample size. A study with additional bias included in sensitivity analysis [25] provides higher weight to pooled proportion

assessment of evidence about prognosis [33], was utilised to generate a Summary of Findings (Table 2).

4 Discussion

The focus of this review was to determine the prevalence of ECG monitoring in relation to high-risk QT interval prolonging medicines, to aid in the understanding of the likely utilisation of this risk management strategy in real-world clinical practice settings.

Low or inadequate use of ECG monitoring in relation to the prevention of drug-induced QT prolongation has been widely acknowledged and reported [4, 10, 32, 34–38]. This is the first systematic review to summarise the prevalence of ECG use for high-risk QT interval prolonging medicines in clinical practice.

This review indicates that the prevalence of ECG monitoring seems to be influenced by the clinical practice setting, in which baseline ECG monitoring occurs with reasonable frequency in the hospital setting, and much less commonly in the non-hospital setting. Follow-up ECG monitoring, specifically in the hospital setting, occurs far less frequently than baseline ECG monitoring. Overall, there is sparse evidence that any type of ECG monitoring occurs in the non-hospital setting. On the basis of the studies identified in this review there is a need to improve the strength of evidence of the reported prevalence estimates relating to both baseline and follow-up ECG monitoring. There is a need for larger studies, in a greater variety of clinical settings, across a wider variety of countries. Furthermore, well conducted studies are needed, including with clear reporting and distinction of included medicines, clearly articulated timeframes for ECG monitoring in relation to medicine therapy, and clear reporting of reasons for ECG use.

There was very limited reporting on the reason for ECG monitoring, and it is unknown if the use of ECG monitoring was related in any way to specifically monitoring the QT interval. Only one study in the entire review reported the reasons for use of ECG, and only 4.7% of ECG use was determined to relate to QT monitoring [26]. Hence, it is possible that the use of ECG monitoring for high-risk QT interval prolonging drugs is overestimated, and therefore the prevalence estimates for both baseline and follow-up ECG monitoring are lower than reported. Certainly, ECG use is undertaken more readily in hospitalised patients in the context of investigation of acute illness. The moderate to high prevalence estimates of baseline ECG monitoring of high-risk QT interval prolonging medicines could possibly be an artefact of hospitalisation rather than QT monitoring for the purposes of drug safety management per se. Hospitalisation itself may provide a high probability of safeguard for ECG monitoring for those commenced on a high-risk QT interval prolonging medicine; however, this is probably less likely for those that are not hospitalised.

Other reasons can contribute to the limited use of ECG monitoring for high-risk QT interval prolonging medicines. It has been recognised that clinicians are often unable to identify the medicines and risk factors that can prolong the QT interval [39]. Furthermore, it has been recognised that clinicians have difficulty in accurately measuring a QT interval, and clinicians frequently ignore QT prolongation even if it is recognised [40].

Mortality and morbidity outcomes and economic impact associated with use of ECG in relation to drug-induced QT prolongation still remain unknown [10, 41, 42], largely due to the low absolute risk of TdP and SCD [34]. Despite lack of evidence for these important endpoints, ordering an ECG before and during therapy with high-risk QT interval prolonging medicines remains a practical and reliable risk management strategy to support the safe use of QT interval prolonging medicine therapy.

This review gives prominence to the lack of policy and research for use of ECG monitoring in non-hospital settings. The prescribing of QT interval prolonging medicines is reported to have at least doubled in recent times [37]. Several studies report that prescription of QT prolonging medicines is common in outpatient settings [43, 44]. It is well recognised that the use of QT prolonging medicines in other non-hospital settings such as community-based primary care practice and residential care facilities is also common [45].

Policies and guidelines alone are likely not enough to ensure use of ECG monitoring in practice, as highlighted by this review. Practical approaches are needed to improve use of ECG monitoring and risk mitigation of drug-induced QT prolongation.

There is still great potential for digital technologies to be leveraged to improve the management of drug-induced QT prolongation. Simpler and more accessible methods to monitor QT, such as wearable digital devices, may offer a solution for the non-hospital settings. However, these remain immature and unvalidated in the context of drug-induced QT prolongation and further research is needed to confirm the feasibility of these [39, 46, 47]. Further development of remote monitoring for drug safety management is likely to be supported by improving awareness of drug safety benefits of both clinicians and consumers.

Although clinical decision support tools relating to QT interval prolonging medicines have been developed, these have been associated with limitations [46, 48–50]. Alternative information management systems such as data-driven drug-induced QT prolongation surveillance using adverse reaction signals derived from electrocardiogram data [51] are only just emerging and may hold important solutions to improve drug safety management at the point of care.

Access to, and clinicians' awareness of, reliable online information sources of QT interval prolonging medicines are not well reported yet may be a simple and effective strategy to improve identification and risk management of the highest risk QT interval prolonging medicines.

4.1 Limitations

Most studies in this review involved small samples, and studies often occurred in very specialised practice settings, mostly represented by hospital settings where there is likely reliable access to ECG monitoring. There was very limited representation of non-hospital, in particular, non-inpatient settings; there was no representation of community-based primary care practice.

This review focussed on comparison of ECG use in the hospital and non-hospital settings and did not investigate ECG use according to specific clinical areas or units. Furthermore, the review did not include use of continuous ECG monitoring. Both types of information would be important in strengthening understanding of ECG use trends.

There are numerous facets of complexity in the use of ECG monitoring in relation to drug safety and management of QT interval prolonging medicines. These include the feasibility of ECG use, clinicians' skill and expertise in relation to ECG use and more specifically, QT interval monitoring, clinicians' awareness of QT interval prolonging potential of medicines and understanding clinicians' actual therapeutic decision-making process. Prevalence estimates by themselves do not provide insights into any of these elements. Qualitative research would be beneficial to fully explore the complex clinical decision-making process of high-risk QT interval prolonging medicine use, and also the use of risk management strategies including ECG monitoring. Improved quantitative evidence complemented by qualitative data provides the ultimate basis on which to determine the most effective improvement strategies in relation to drug safety and management of QT interval prolonging medicines.

5 Conclusions

Use of ECG monitoring is a key strategy to reduce risk of the potentially fatal adverse reaction that is drug-induced QT prolongation. This review highlights the limited and variable use of both baseline and follow-up ECG monitoring of high-risk QT interval prolonging medicines in adult patients in clinical practice. There is a clear lack of information on the use of ECG monitoring in non-inpatient and non-hospital settings. This review also highlights the need for research in these under-recognised healthcare settings to aid safe use of high-risk QT interval prolonging medicines.

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Declarations

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