Use of electrocardiogram monitoring in adult patients taking high-risk QT interval prolonging drugs in clinical practice: A systematic review

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I, Marijana Putnikovic certify that this work contains no material that has been accepted for the award of any other degree or diploma in any university or any other tertiary institution, and, to the best of my knowledge and belief, contains no material previously published or written by any other person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint award of this degree.

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Marijana Putnikovic
June 2022

Summary

Drugs with the potential to cause QT prolongation belong to a wide spectrum of therapeutic classes and their use is expected in all types of clinical practice settings. QT prolongation can lead to serious arrythmias including torsades de pointes (TdP) which can be fatal. Detection and mitigation of QT prolongation involves use of electrocardiographic (ECG) monitoring, which remains a fundamental strategy to support quality use of high-risk QT interval prolonging drugs and to reduce patient harm, in all areas of clinical practice. The objective of this review was to summarise the best available evidence for the utilisation, and hence prevalence, of ECG monitoring at baseline and / or follow up of initiation of high-risk QT interval prolonging drugs in any clinical setting. The influence of risk factors on the prevalence of baseline and / or follow up ECG monitoring in patients taking high-risk QT interval prolonging drugs was also sought to be determined. The JBI (formerly Joanna Briggs Institute) approach to systematic reviews of prevalence and incidence was followed to determine the prevalence of ECG use in adult patients taking high-risk QT interval prolonging drugs in clinical practice.

A comprehensive literature search was conducted for studies that included adults aged 18 years or older, who had been initiated on any high-risk QT interval prolonging drug, in any clinical setting and that reported on the use of baseline and / or follow up ECG use. Any study design was considered for inclusion except for case studies and case series. Published and unpublished studies were searched in CINAHL, Cochrane Library, Embase, PubMed, EThOS, OpenGrey and Proquest Dissertations and Theses spanning from 2004, relating to the first prominent practice guidelines published on the topic of ECG monitoring and drug-induced QT prolongation.

A total of 88 studies were retrieved for review, 74 of which were excluded; 14 studies were included in the systematic review following full text-review. All 14 studies underwent critical appraisal which was conducted independently by two reviewers. All included studies were retrospective observational cohort studies. Most studies were conducted in hospital or inpatient settings, only two studies were conducted in non-hospital settings and one study did not specify the specific healthcare setting in which drug therapy or ECG use occurred. Thirteen studies included data relating to baseline ECG use, involving 18,581 participants. And 7 studies included data relating to follow up ECG use, involving 43,321 participants.

Proportional meta-analysis was conducted with all studies reporting baseline ECG use, and also with all studies reporting follow up ECG use. Separate proportional meta-analyses were conducted for ECG use across various categories or subgroups, including the hospital setting and non-hospital setting, nature of drug use (acute use or chronic use), country and specific drug. Separate analysis was also conducted to determine the influence of high-quality studies only and / or exclusion of studies deemed problematic due to various study level reasons. The influence of risk factors on the prevalence of ECG monitoring in patients taking high-risk QT interval prolonging drugs could not be determined. However, a descriptive analysis of risk factors was able to be conducted for patients taking high-risk QT interval prolonging drugs but was not possible for patients taking high-risk QT interval prolonging drugs that received a baseline and / or follow up ECG.

There was variability in baseline ECG use according to the practice setting. The prevalence of baseline ECG use for high-risk QT interval prolonging drugs was moderate to high in the hospital setting, 75.1% (95% CI 64.3% to 84.5%). However, the prevalence of baseline ECG use was low in the non-hospital setting, in which the pooled proportion was calculated to be 33.7% (CI 95% 25.8% to 42.2%).

In contrast, the prevalence of follow up ECG use was low to moderate for high-risk QT interval prolonging drugs in the hospital setting, 39.2% (95% CI 28.2% to 50.8%). The prevalence of follow up ECG use was determined to be similar in any clinical setting 32.7% (95% CI 4.7% to 46.9%) but could not be determined for the non-hospital setting.

The use of ECG monitoring for high-risk QT interval prolonging drugs is variable and limited and is strongly influenced by the clinical practice setting. Only weak conclusions can be drawn from most results about the true prevalence of ECG monitoring in patients taking high-risk QT interval prolonging drugs. Although the low prevalence of follow up ECG use relating to any clinical setting may be moderately reliable**.** Larger studies are needed, and especially involving a greater number of studies in

the non-hospital setting but also studies in the outpatient hospital setting, to improve the evidence and to strengthen the reliability of end prevalence estimates.

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Chapter One: Introduction

Preface

The discovery of drug-induced QT prolongation probably dates back almost 100 years.[1] And whilst the most significant advances in the understanding and management of this adverse drug reaction developed in the late 20th Century,[1] safe management of QT interval prolonging drugs still continues to pose a challenge to clinicians today. Over 200 drugs[2] in clinical use today have been identified with the potential to cause QT prolongation. Limited awareness of these drugs by clinicians is well recognised. Al-Khatib et al[3] 2005 determined from a survey that an appreciable number of practitioners, including physicians, nurses and pharmacists in the hospital setting, were unable to correctly identify medications that cause QT prolongation. Buss et al[4] 2018 reported low awareness of this drug related problem amongst a cohort of medication review pharmacists based in the community.

My own lived experience as a pharmacist in a large tertiary adult hospital and a state-wide Medicines Information service has resonated with these reports, commonly encountering a wide variety of healthcare practitioners, from both community and hospital settings, with limited ability to identify drugs with the potential for QT prolongation, limited knowledge of reliable drug information resources and furthermore limited knowledge of risk management strategies. Difficulty in being able to identify drugs possessing this serious adverse drug reaction potential can lead to missed opportunities in appropriate risk management, placing patients at risk of fatal arrythmias that are associated with QT prolongation.

Initially, I sought to investigate and summarise the available evidence for clinicians' *correct* and / or *incorrect* identification of patients on QT interval prolonging drugs, and the impact of this on drug safety management and related outcomes. A review of the literature failed to consistently identify *correct* or *incorrect* clinician identification of patients on QT interval prolonging drugs as a well described descriptor. Furthermore, any drug management or safety outcomes from clinicians' awareness of QT interval prolonging drug therapy was heterogeneously reported.

To assist in better framing the investigation, the literature was reviewed for more reliably described endpoints in relation to use of QT interval prolonging drug therapy, in which electrocardiogram (ECG) monitoring was determined to be reasonably measured and reported. Electrocardiogram monitoring is a well-recognised risk mitigation strategy in the use of QT interval prolonging drugs and a review of its utilisation in real-world clinical practice was lacking from the literature. Use of ECG monitoring could be conceived as a surrogate marker of clinicians' awareness of QT interval prolonging drugs. Moreover, understanding the use of ECG monitoring in relation to QT interval prolonging therapy itself holds significant merit, to determine clinicians' knowledge and practice of appropriate drug safety management. Hence the systematic review for the use of ECG monitoring in adult patients taking high-risk interval prolonging drugs in clinical practice was born. Finally, the nature of clinical practice settings can vary widely and furthermore the clinical setting can have immense impact on healthcare delivery. An important objective of this systematic review was to determine the impact of different clinical practice settings on ECG monitoring.

Background

The QT interval, QT prolongation and the electrocardiogram

The QT interval represents a measurement of cardiac electrical activity, determined from a non-invasive medical test - the electrocardiogram (ECG).[5, 2] Prolongation of the QT interval (QT prolongation) from standard reference values is an abnormality which is associated with serious cardiac arrhythmias, described by long QT syndrome (LQTS), and includes torsades de pointes (TdP) which can lead to sudden cardiac death (SCD).[6, 7] LQTS can be genetically inherited, but is more commonly acquired.

An ECG test is a pre-requisite in the diagnosis of long QT syndromes and related cardiac arrhythmias. The absence of this test means QT prolongation goes undetected.

QT prolongation is the surrogate measure for the more serious risk of TdP whereby the longer the QT interval, the greater the risk of TdP and SCD. However, QT prolongation is an imperfect predictor of TdP as this arrhythmia can be transient, variable and unpredictable[1, 8, 9]. The absence of better predictive methods to detect TdP, however, means that ECG remains the standard monitoring tool to assess and mitigate the risk of TdP.[6, 9]

Drug-induced QT prolongation

Drugs are a leading cause of QT prolongation and they have been described as the most common environmental stressor resulting in the acquired form of LQTS[10]. Drugs that have the potential to cause QT prolongation belong to many therapeutic classes[1] and are used across the clinical spectrum.

It has been estimated that the use of QT interval prolonging drugs could result in greater than 15,000 deaths annually in the US and Europe.[11] Therefore, prevention of this adverse drug reaction has the potential to save many lives.

The strength of association of a drug to cause QT prolongation and / or TdP is a key determinant of its risk. The University of Arizona Center for Education and Research on Therapeutics (AZCERT) has developed an evidence-based classification system for drugs associated with QT prolongation and TdP.[12] AZCERT was established in 2012, continuing work that was originally commenced in 1999[1] and manages a regularly updated database of QT interval prolonging drugs, called CredibleMeds. CredibleMeds has become a standard global reference for drugs that can prolong the QT interval and / or cause TdP,[1] described as the most comprehensive and easily accessible reference source[12] on the topic. Drugs classified in the CredibleMeds 'known risk of TdP' category are defined as drugs that prolong the QT interval and are clearly associated with causing TdP, even when administered as recommended.[2, 1] In this review, drugs listed in the 'known risk of TdP' category as defined by AZCERT and CredibleMeds were considered high-risk QT interval prolonging drugs.

ECG monitoring recommendations for drug-induced QT prolongation

In 2004, the American Heart Association (AHA) released practice standards for all areas of ECG monitoring in hospital settings in which recommendations for drugs with the greatest known risk of TdP, were specifically highlighted.[13] In 2010, the AHA together with the American College of Cardiology Foundation released a scientific statement focussing on the prevention of TdP in hospital settings. For drugs with a known risk of TdP, both papers recommend ECG monitoring before and (every 8 to 12 hours) after the commencement of the drug.[13, 14] These recommendations remain largely unchanged in the most recently published AHA scientific statement published in 2020,[15] reinforcing their relevance.

The recommendations around timing and duration of QT interval monitoring have evolved since the 2004 practice standards. The original standard recommends ECG monitoring for 48 to 72 hours for a limited number of high-risk drugs and recognises the importance of ECG monitoring before and after increases in drug dosage.[13] The 2010 paper recognizes important pharmacokinetic parameters including drug half-life[14], for individualised timing of ECG monitoring. The most recent guidelines specify daily ECG monitoring for a wider variety of high-risk drugs and scenarios and provide guidance on ECG monitoring for long-term drug therapy, recommending 3-6 monthly ECG monitoring.[15]

A non-systematic textual synthesis review conducted in 2013 re-iterates that optimal prevention of drug induced QT prolongation involves ECG monitoring.[9] The authors provide a prescriptive summary of timing and duration of ECG monitoring, including at baseline prior to drug initiation, then once the drug serum concentrations are stabilised (specified by 'steady state' or 5 half lives), then monthly for 6 months then every 6 to 12 months thereafter.[9]

The clinical context or the way in which a high-risk drug is used, and whether it is being used acutely or chronically affects the importance and the need for ECG monitoring in clinical practice. Baseline ECG monitoring maintains its importance in both acute and chronic drug use. Follow up ECG monitoring, however, may not be necessary or less clinically relevant for acute drug use, which is generally characterised by single doses or short courses, and in which 'steady state' may not be reached, in contrast to chronic continuous dosing. Understanding the clinical indication of a high-risk drug can provide clarity relating to the acute or chronic nature of drug use and can assist in determining the importance of ECG monitoring.

Risk factors for drug-induced QT prolongation

Besides the risk of a drug itself, many other risk factors predispose to the prolongation of the QT interval.[10]

A quantitative systematic review published in 2017[16] attempted to determine the strength of evidence of different risk factors known to cause QT prolongation. Very strong evidence was found for each of the following factors: low serum potassium (hypokalaemia), use of diuretics and the use of high-risk QT interval prolonging drugs. Strong evidence was found for each of the following risk factors: age 65 years or above, female gender, smoking, (ischaemic) cardiomyopathy, hypertension, arrhythmia, thyroid disturbances, low serum calcium (hypocalcaemia) and the use of more than one QT interval prolonging drug.

In this review, risk factors for QT prolongation will be defined as those associated with very strong and strong evidence according to the systematic review by Vandael et al[16] 2017, excluding the specified high-risk QT interval prolonging drugs.

Risk mitigation strategies for drug-induced QT prolongation

Prevention of drug induced QT prolongation requires knowledge of which drugs have the potential risk and the strength of risk associated with the drug. Risk factors for QT prolongation also need to be understood and considered, and where possible modified, prior to drug use. The fully informed clinician is best equipped for clinical decision making and is able to consciously consider the risk-benefit of QT interval prolonging drug therapy. Where risk is deemed unacceptable, drug therapy may be able to be avoided and replaced by a safer alternative. However, where drug therapy is considered essential, ECG monitoring becomes a key strategy to support the safe use of QT interval prolonging drug therapy and mitigate the risk of this potentially fatal adverse event.

The sheer number and complexity of risk factors provides challenges to health providers in recognising them and integrating their meaning at the point of prescribing. In fact, studies have demonstrated that clinicians are often unable to identify TdP risk factors or medications that can prolong the QT interval.[12] And although specific clinical decision support tools relating to drug induced QT prolongation have been devised, they are not widely in use or integrated into electronic medical records.[17] Furthermore, computer based clinical decision support systems alone even if implemented are unlikely to be enough to fully cover the complex management of this condition.[18]

Given comprehensive risk assessment is complex, and likely difficult for clinicians to complete, ordering an ECG before and during therapy with high-risk QT interval prolonging drugs may prove to be a practical and reliable risk management strategy. Use of ECG monitoring has the potential to enhance clinician's understanding of appropriateness of therapy in the absence of complete risk assessment.

Influence of healthcare location on ECG monitoring

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.[12, 14] Hence prevention guidelines have focussed on this cohort. 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. There is very limited guidance for ECG monitoring relating to drug induced QT prolongation in non-hospital settings. Trinkley et al[9] 2013 seems to have been the first to assert that risk mitigation strategies and QT interval monitoring are needed in every care setting, including outpatient services. De Lemos et al[19] 2019 published ECG monitoring recommendations for oncology drugs in the ambulatory setting. The Association of Medicine and Psychiatry published an expert consensus on ECG (QTc) monitoring,[20] acknowledging community mental health and outpatient settings. And although differing healthcare systems, personnel and equipment influence the feasibility of risk management strategies, drug safety and patient management principles in relation to high-risk QT interval prolonging therapy remain the same.

Review objective

The objective of this review was to determine the prevalence of ECG use for patients taking high-risk QT interval prolonging drugs, in any clinical setting. The review focusses on the use of ECG

monitoring following initiation of drug therapy, specifically at baseline and follow up time periods. Knowledge of the prevalence of ECG monitoring informs the state of utilisation of this risk management tool at key points of therapeutic decision making and drug use. Appropriate ECG monitoring for patients who may benefit from the use of QT interval prolonging drugs is the cornerstone of the safe use of these high-risk drugs. Best available evidence of prevalence of ECG use is vital to be able to inform practice, research and policy and improve the quality use of these drugs and reduce patient harm.

The results of the review will be able to identify how well the ECG monitoring tool is being used in various clinical settings and specifically whether there are any differences in use of baseline ECG in comparison to follow up ECG. Determining gaps in practice will assist to focus strategies, healthcare policies and guidelines in the areas of need the most. The review should highlight gaps in research and may offer impetus for not only further quantitative and qualitative research.

Review questions

What is the prevalence of ECG monitoring conducted at baseline of high-risk QT interval prolonging drugs following their initiation in adults in clinical practice?

What is the prevalence of ECG monitoring conducted at follow up of high-risk QT interval prolonging drugs following their initiation in adults in clinical practice?

Are there risk factors that can be determined to influence the prevalence of baseline and / or follow up ECG monitoring?

Context of the review

A preliminary search of PROSPERO, PubMed, Embase, the Cochrane Database of Systematic Reviews and the JBI Database of Systematic Reviews and Implementation Reports was conducted prior to commencing this review, in February 2020. No systematic reviews that investigate ECG use relating to drug induced QT prolongation were identified. During the search, several studies that report performance of ECG before and during use of high-risk QT interval prolonging drugs were identified.[21-24] The systematic review protocol[25] was published in May 2021. The search of the same databases was conducted again, at the time of writing the thesis, in January 2022, and again, no systematic reviews on this topic were located.

Low or inadequate use of ECG monitoring in relation to the prevention of drug induced QT prolongation has been widely acknowledged and reported.[6, 20-22, 26-30] This systematic review is the first to attempt to summarise the best available evidence of the utilisation of ECG monitoring relating to QT prolonging drugs in clinical practice.

Initiation of high-risk QT interval prolonging drug therapy, in contrast to their continuing use, and furthermore in contrast to non-high risk QT interval prolonging therapy, has the most compelling recommendations for ECG monitoring and provides a clear platform on which to summarise evidence for ECG use at well-defined time points.

Prevalence of ECG monitoring of the highest risk QT-interval prolonging drugs will provide a benchmark understanding for the ECG monitoring occurring for the broader group of QT-interval prolonging drugs, regardless of their risk.

Evidence synthesis, review methodology and justification of review approach

Evidence-based medicine has become an integral part of clinical decision making in healthcare, and involves the use of the best scientific research evidence in conjunction with clinical expertise and patient preferences,[31] to improve health outcomes both for individual patients and healthcare more globally. Development of evidence-based medicine (or evidence-based healthcare) is considered among the most important milestones that has shaped modern medicine.[32] Healthcare practitioners from all disciplines, and from different contexts of healthcare are expected to make evidence-based decisions.[33]

The practice of evidence-based healthcare involves determining a clinical question, the identification of the best available evidence to answer the question, critical appraisal of the evidence, applying the results to clinical practice and continually evaluating performance of evidence and its outcomes.[31, 34]

A systematic review uses explicit and robust methods to synthesise and summarises data and results from multiple studies to address a specific question. A systematic review does not seek to create new knowledge but aims to synthesize and summarise existing knowledge[33] from multiple studies, in a way that improves reliability and strengthens meaning of information in contrast to the results of a single study. A systematic review is conducted in a structured and transparent manner to limit bias and is used to comprehensively identify, select, assess, and synthesise data from eligible studies. Due to the rigor involved in the systematic review process, it is considered to be evidence of the highest level within the evidence hierarchy,[35] and therefore a cornerstone of clinical decision making.

The meaning of evidence-based practice has continued to evolve to represent the broad range of health practitioner information needs. The nature of evidence has been expanded over time to include sources of both research and non-research based evidence[31] and furthermore to include the idea that evidence-based healthcare should incorporate the "best available evidence." Best available evidence translates to evidence or information from a wide variety of sources, both published and unpublished, and from a wide variety of study designs, in contrast to evidence exclusively from higher order research, such as randomized controlled trials. Additionally, the systematic review has evolved to accommodate the wide variety of clinical questions that are generated by clinical practice and furthermore the diverse information needs of healthcare professionals.[36] There is a large variety of types of systematic reviews that exist and stem from such practice and research diversity, exemplified by guidance supported by JBI on a wide variety of systematic review methodologies. By using a broad approach to evidence, a systematic review can better inform clinical practice, healthcare policy and needs of future research.

Use of ECG monitoring in adult patients on high-risk QT prolonging drugs in clinical practice is a question of prevalence, which seeks to determine the trends in ECG use or proportion of patients that have the medical test performed over time.[36] Hence this clinical question was best suited to a systematic review of prevalence and incidence, to determine the existing state of use of this key risk management strategy in real-world clinical practice. Proportions are the typical format in which data occurs in systematic reviews of prevalence.[37] Proportional meta-analysis is the statistical platform by which to synthesise results from multiple studies of prevalence data into a single pooled estimate. And although systematic reviews of prevalence more commonly investigate a disease or a condition in a population,[37] they can be applied more broadly[38] to investigate events such as the use of ECG monitoring. Review questions for systematic reviews of prevalence are defined using the CoCoPop framework, which requires clear definition of the condition of interest, context or setting and population. The review framework should be determined a priori and creates a clear platform on which to develop the inclusion and exclusion criteria and to assist in clear definition of the expected outcomes. Use of multiple bibliographic databases ensures comprehensive capture of eligible studies. Use of more than one reviewer to independently complete key processes, including study selection and critical appraisal, aids to ensure high methodological quality. A well-conducted systematic review, regardless of the type, observes the guidelines for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

The results or recommendations of any systematic review can be better contextualised for use in practice and clinical guidelines using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach. The GRADE approach determines the confidence or trustworthiness of the systematic review results by rating the quality of evidence for each key outcome.[39, 40] The body of evidence used for the basis of an outcome is rated based on the key domains of risk of bias, imprecision, inconsistency, indirectness and publication bias.[39] An overall rating for magnitude of effect or certainty of evidence can then be determined for each result or outcome, from high to very low,[39] which assists in clarifying the strength of their meaning for end users.

This systematic review was conducted in accordance with the JBI methodology for systematic reviews of prevalence and incidence.[38, 41] Specifically, JBI provides some of the only guidance available for conduct for and reporting of systematic reviews of prevalence and incidence,[42] for which there seems to be limited published discourse.[42] Hence, JBI can be considered a fundamental source of guidance in providing clear methods in the synthesis in this important type of health information. Of interest, this is the first review of its kind to determine the prevalence of a common monitoring strategy despite the

sheer literature on the topic of drug induced QT prolongation. Possible explanations for this could include limited prominence of the methodology for conduct of systematic reviews of prevalence, in contrast to systematic reviews of effectiveness, and furthermore preferential use of prevalence reviews for the investigation of diseases or conditions, rather than events.

The objectives, inclusion criteria and methods of analysis for this review were specified in advance and documented in a protocol[25] and furthermore registered with the International Prospective Register of Systematic Reviews (PROSPERO, CRD42021240762). Reporting was conducted in accordance with the Preferred Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[43] The GRADE approach, based on the assessment of evidence about prognosis,[40] was utilised to generate a Summary of Findings.

Limitations

Prevalence data is normally generated through observational cohort studies, which traditionally have been thought to provide lower levels of evidence. The quality of the outcomes from the systematic review are limited by the methodological quality of the included studies. Despite the lower validity of cohort studies, these currently provide the best available evidence for information relating to use of ECG monitoring for high-risk QT prolonging drugs.

The appropriateness of conducting meta-analysis of prevalence data has been argued to be contentious, as the individual studies contributing to such meta-analysis has often been conducted in different contexts, and therefore an average estimate may be of limited clinical use.[37]

Chapter Two: Methods

Inclusion and exclusion criteria

Population

Inclusion was restricted to adults (aged ≥18 years) initiated on a high-risk QT interval prolonging drug.

Drugs that were not classified as 'known risk of TdP' at the time of original study were excluded from the review. Where studies did not specify or confirm the AZCERT category of the drug at the time of study, reference was made to when the drug was first listed in the 'known risk of TdP' category by AZCERT to determine inclusion.

Only studies published from 2004 were included, which relates to the first published practice standards discussing ECG monitoring of high-risk QT interval prolonging drugs.[13]

Condition

Studies were included if they reported ECG use at baseline and / or at follow up in relation to high-risk QT interval prolonging drug.

Studies were included where high-risk QT interval prolonging drugs were initiated for the first time, rather than stable or ongoing drug therapy.

Baseline ECG was included if conducted at any time prior to the initiation of a high-risk QT interval prolonging drug. Follow-up ECG was included if the first follow up ECG occurred within 30 days from drug initiation. If the time frame of the follow-up period was unclear or could not be confirmed with the author, then follow up ECGs were excluded. Follow up ECG that occurred in consequence of a raised QT threshold at baseline ECG were excluded.

To ensure fair comparison, use of ECG monitoring was included when sufficiently described as a discrete, non-continuous ECG test. ECG use was excluded if described in any other way other than a discrete ECG test before or after the first dose of a new drug. ECGs conducted with any number of leads were included.

Studies intentionally conducting ECGs at baseline and / or at follow up in relation to high-risk QT interval prolonging drugs were excluded.

Context

Studies from any country and conducted in any clinical setting including hospital and non-hospital settings, were included into this review.

Types of studies

Observational studies were considered, including prospective and retrospective cohort studies, longitudinal cohort studies, case-control and cross-sectional studies. Observational studies involving pre-intervention and post-intervention periods were also included. Studies that use an experimental design (randomized controlled or quasi-experimental design), which report on prevalence were also considered.

Case studies and case series were excluded due to incomplete and inconsistent reporting of ECG use.

Search strategy

A comprehensive search was conducted on the 15th 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. The full search strategy is available in Appendix I. No language restrictions were applied.

The search strategy spanned from 2004, relating to the to the first published practice standards discussing ECG monitoring of high-risk QT interval prolonging drugs.[13]

The reference list of all studies selected for critical appraisal were screened for additional studies.

Study selection

Following the search, all identified citations were collated and uploaded into Endnote X9 (Clarivate Analytics, PA, USA) and duplicates removed. Titles and abstracts were then be screened for assessment against the inclusion criteria to determine eligibility. Any uncertainties were resolved through discussion with a second or third reviewer (MW, ZJ).

Authors of papers were contacted to request additional data for clarification to assist determination of study selection where required.

Potentially relevant studies were retrieved in full. The full text of selected citations were assessed in detail against the inclusion criteria and uncertainties were resolved through discussion with a second reviewer (MW).

Reasons for exclusion of full text studies that do not meet the inclusion criteria were recorded (Appendix II).

Assessment of methodological quality

Citations of eligible studies were imported into the JBI System for Unified Management, Assessment and Review of Information (JBI SUMARI).[44] Eligible studies were critically appraised independently by two reviewers (MP, CB) at the study level for methodological quality in the review using a standardized critical appraisal instrument from JBI for studies reporting prevalence data.[38, 41, 45]

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, where required.

The assessment criteria of the standardised critical appraisal instrument for studies reporting prevalence were adapted to suit the needs of this systematic review. Specifically domain four involved whether the clinical setting was sufficiently described to be able to identify its place in the healthcare system, including hospital or non-hospital settings. Domain seven involved whether the time frames for baseline and / or follow up ECG were described clearly. Understanding the clinical setting provides important context for assessment and comparison of ECG use in the health system. Clear definition of baseline and follow up ECG is essential in framing rates of ECG monitoring relative to optimal time points for risk mitigation.

All studies, regardless of the results of their methodological quality underwent data extraction and data synthesis.

For the purposes of sensitivity analysis, high quality studies were deemed those in which study subjects and setting were clearly described and those in which the use of ECG, specifically baseline and / or follow up ECG were described clearly, relating to domains four and seven. If studies performed well on domains four and seven and also on other domains of the critical appraisal tool, achieving at least a score of seven or more out of nine, then they maintained their high quality status. If studies that performed well on domains four and seven but did not perform well on other domains, and achieved a score of six or less out of nine, then they were downgraded to a poor quality study.

The results of the search and study inclusion process are presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram.[43]

Data extraction

Data was extracted from studies using a modified version of the JBI standardized data extraction instrument[38] (see Appendix II). Any ambiguities associated with data extraction were resolved following discussion with a second reviewer (MW).

The data extracted included specific details about the population (including age and the names of high-risk drugs studied), condition (use of ECG at baseline and / or follow up) and context (including details of the clinical care setting, year(s) and time frame and country of study).

Sample size of each study related to the total cohort of patients on high-risk QT prolonging drug(s) only and furthermore specifically for patients initiated on high-risk drug therapy. Studies with pre-intervention and post-intervention cohorts were extracted as two separate sample sizes.

Information about ECG use from each study was sought for either baseline ECG and / or follow up ECG. Time frames for ECG tests as set within the review definitions, were closely examined. Specifically, information about time (day) of ECG, relative to day 0, where day 0 = drug initiation was recorded. If time frames were unclear, the authors were contacted for clarification. The numerator, the denominator and proportions of patients taking high-risk drug(s) with ECG conducted at baseline and the numerator, denominator and proportions of patients taking high-risk drug(s) with ECG conducted at follow up, were sought for extraction. If a numerator or denominator were missing and only a proportion was available, then the proportion was used to calculate the missing value.

ECG use data that was reported in a study in the *opposite* way to the review outcome data, for example ECG not performed, then data was converted to describe ECG use in the affirmative.

ECG use data that was reported separately for different cohorts within a study according to various descriptors, such as specific time periods or specific clinical locations or clinical units, was combined into a single sample size. For data relating to time periods to be combined into a single sample size, the time periods had to occur within the review definitions for baseline and follow up ECG. Refer to Appendix IV Characteristics of included studies and 'Notes' column for information on studies where data has been combined into a single sample.

Reasons for ECG testing were extracted from each study, wherever reported, along with any additional information reported about ECG testing, such as the number of ECG leads.

In an attempt to differentiate high-risk drugs in the context of acute or chronic use for sub-group analysis, information about clinical indication(s) for drug use and their corresponding proportions in each study were extracted. Based on this information, each study was determined to relate to either acute or chronic drug use. If studies involved mixed use of drugs, that is for both acute and chronic conditions, then categorisation was determined by the predominant nature of drug use, defined by > 50% of clinical indications of that nature. If based on this information there was inability to categorise the acute or chronic nature of drug use, other factors were considered to determine the acute or chronic nature of drug use, including the healthcare location and duration of therapy. If there was insufficient information available to determine either category, then the acute or chronic nature of drug use was not determined.

Risk factors for QT prolongation, specifically those associated with very strong and strong evidence as described by the systematic review by Vandael et al[16] 2017 were extracted, wherever possible. A narrative description of how these were reported or defined in each study relative to those risk factors reported in the systematic review by Vandael et al[16] 2017 was sought. To truly determine any potential influence of risk factors on ECG use trends, the profile of risk factors as they relate to two distinct groups was distinguished; the "first group" being the total cohort of patients on high-risk QT prolonging drugs only (and furthermore involving patients initiated on high-risk drug therapy only), and the "second group" being the cohort of patients on high-risk QT prolonging drugs only and only those initiated on high-risk drug therapy *and* who had an ECG performed (either baseline and / or follow up). Firstly, reporting of risk factors within these two distinct groups was determined. Where risk factors were reported within each distinct group, the numerator, denominator, and proportion of patients with each risk factor of interest was sought.

Data synthesis

Studies, where possible, were pooled with proportional meta-analysis using JBI SUMARI.

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 (CI). The Freeman-Tukey transformation was used for the meta-analysis. Proportions were pooled using the random effects model due to the heterogeneity between studies[37] 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.[37]

Separate analyses for each category of baseline ECG use and follow up ECG use was conducted with at least two studies in each category. The following separate analyses were conducted: ECG use by setting (hospital setting and non-hospital setting); ECG use by country where at least two studies originated from the same country (USA); ECG use by acuity of drug use (acute or chronic use); ECG use by specific drug where at least two studies exclusively reported on the specific drug (domperidone, haloperidol, methadone).

Separate analyses were also conducted to determine the impact of individual studies on the overall calculated prevalence estimates by way of exclusion of poor-quality studies. Where there were sufficient study level reasons to explore the impact of exclusion of individual “problematic” studies on the overall calculated prevalence estimates, “leave one (or more) out” analyses were also conducted.

Statistical pooling was not possible to describe which risk factors can be determined to influence the rate of baseline and / or follow up ECG monitoring. The findings were summarised in narrative form including a table.

Deviations from the published protocol

Deviations from the published protocol involved exclusion of case studies and case series from study inclusion due to their incomplete and inconsistent reporting of ECG use. The data extraction tool was amended to capture greater information about clinical indications of drugs studied and reasons for ECG monitoring. Separate analyses were amended to reflect results based on available data. Specifically separate analysis of pharmacological drug class or by risk factors was not possible due to lack of data. Conducting separate analyses based on primary, secondary, and tertiary care was not possible. Determination of what constitutes primary, secondary, or tertiary care is difficult to locate in literature, and furthermore reasonable comparison could not be assured between studies and different health systems. Hence, separate analyses were only possible for the clinical practice settings of the hospital setting and the non-hospital setting.

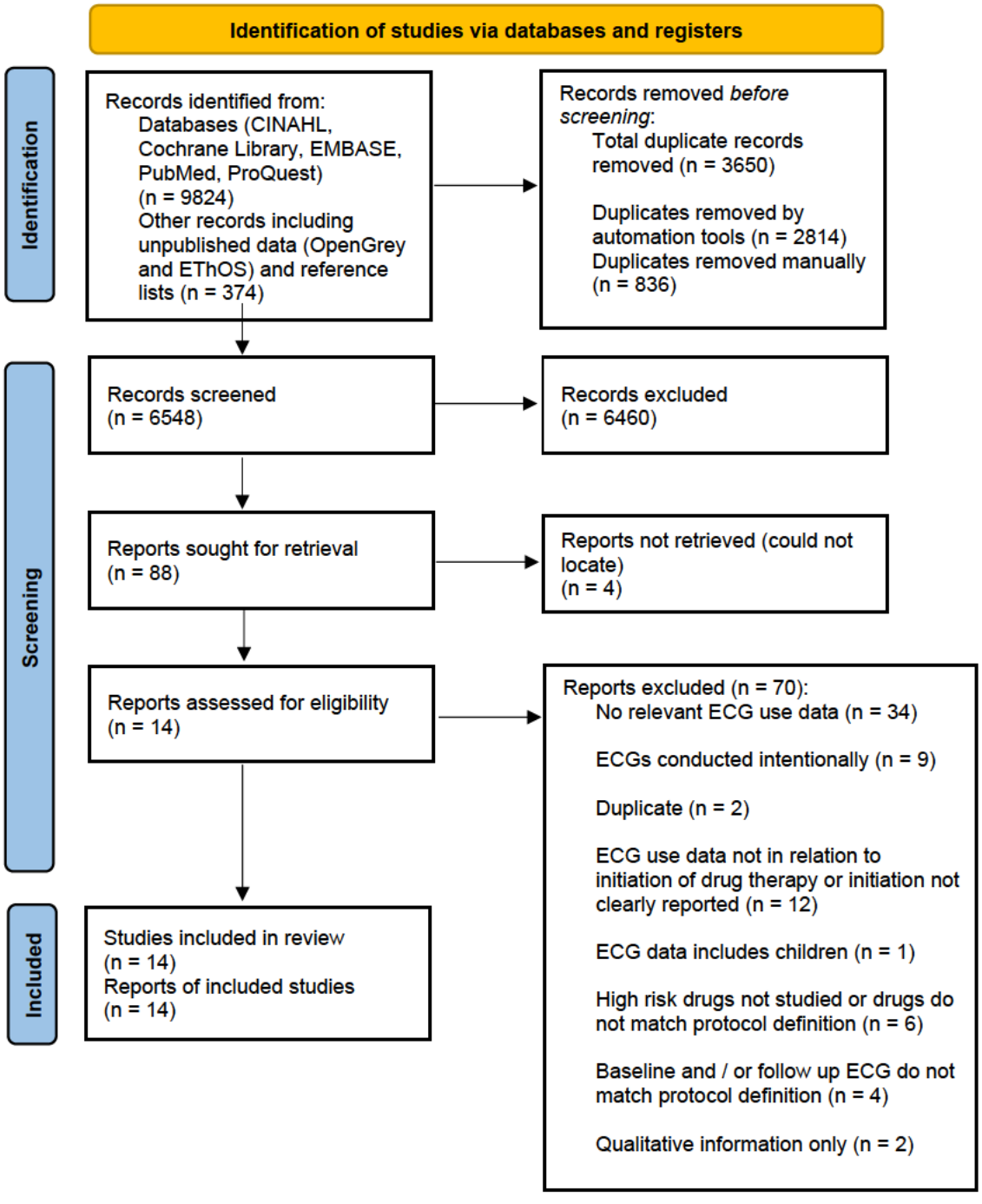
Chapter Three: Results

Search results

Searches of databases returned 9,871 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 retrieval and full-text review. Seventy-four studies were excluded, many of which did not contain any relevant ECG use data (34 studies) or ECG use data either was not in relation to initiation of drug therapy or initiation of drug therapy was not clearly reported (12 studies). Nine studies were excluded as ECGs were conducted intentionally. Overall, 14 studies (14 reports) were included, all of which were retrospective cohort studies. The reference lists of all 14 included studies were reviewed, involving 327 records and no additional records were deemed eligible for inclusion. Refer to the figure containing the PRISMA flow chart (Figure I). See Appendix III for studies excluded, and the reasons for exclusion, following full-text review.

Thirteen studies included data relating to baseline ECG use, involving 18,581 participants. Only 7 studies included data relating to follow up ECG use, involving 43,321 participants.

Figure I) – Flow diagram of search results and review process (PRISMA 2020)[43]



Description of included studies

Characteristics of the included studies are reported in Appendix V. Ten studies involved a single high risk QT prolonging drug, including droperidol (one study), methadone (two studies), domperidone (three studies), haloperidol (three studies), azithromycin (one study), whilst four studies involved high risk QT prolonging drugs described generally as a class. Of the four studies that involved high risk QT prolonging drugs generally described, one study involved antipsychotics only and another study related to psychotropic agents only. Two studies, including one, relating to generally described high risk QT prolonging medications, did not specify which drugs were involved by drug name.

The study by Cole et al[46] 2020 involved the use of high-risk QT prolonging drug therapy for only one of the five years of the entire study period, which lasted from 1st January 1997 to 30 h November, 2001. The drug of interest in this study, droperidol, was first listed as a high-risk QT prolonging drug from 17th October, 2000 (R Woosley 2021, personal communication, 19 October). All other studies involved the use of high-risk QT prolonging drugs for the entire study periods, confirmed within the study details and / or based on when the drug was first listed as a high-risk QT prolonging drug (R Woosley 2021, personal communication, 19 October).

Three studies identified 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 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[47] 2012 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 drug of interest.

One study by Robbins et al[48] 2016 specified that baseline ECG was obtained in all patients, and it is not clear within the study whether baseline ECG was conducted intentionally.

Nine studies were conducted in the USA, two were conducted in Canada, and a single study was conducted each in Italy, Belgium and the UK.

Eleven studies were conducted in hospital or inpatient settings. Hospital settings were heterogenous, including an emergency department, various clinical units including general medicine, cardiology and psychiatry and there was one inpatient headache centre. Some studies did not describe the specific locations of hospital care, rather described patients in other ways such as total hospital population,[49] medically ill and / or hospitalised inpatients,[47, 50] inpatients,[51] admitted patients,[52] and hospital inpatients.[53] One study described inclusion of all patients from a single hospital.[54] There were only two studies conducted in non-hospital settings, one of which was a community mental health centre[24] and the other which was described as a community-based multi-specialty practice.[55] One study was conducted in residents of a major province in Canada, without relation to the healthcare setting in which drug therapy or ECG use occurred.[30]

Six studies involved drug use in the context of acute medical conditions including acute agitation, delirium, nausea related specifically to dihydroergotamine, pneumonia or COPD exacerbation, and were therefore categorised as relating to acute drug use. Three studies involved drug use in the context of chronic conditions, including one study relating to antipsychotics in patients with severe mental illness in a community mental health centre and two studies relating to methadone for pain. Two studies involved drug use for a variety of medical conditions including acute and chronic conditions, however both studies involved drug use for predominantly chronic conditions, therefore these studies were categorised as chronic drug use. The acute or chronic nature of drug use could not be clearly determined in three studies, mostly due to no information about clinical indications. Categorisation of studies in relation to acute or chronic drug use is represented in Table 1.

The reason for ECG monitoring was not specified in most studies, and hence it is mostly unknown if the ECG monitoring was taken specifically for reasons of monitoring QT prolongation. Robbins et al[48] 2016 was the only study that managed to specify the indications for ECG monitoring, however this was determined for a small sub-group of the total cohort. Out of the 21 patients in this subgroup, only one patient was identified as having had an ECG for reasons of QTc monitoring and nine patients for the reason of *exit QTc screening.* Cole et al[46] 2020 and Pezo et al[30] 2019 were the only studies to specify that exposure to ECG involved any ECG obtained[30, 46] and regardless of the reason.[30] Pezo et

al[30] 2019 and Forbes et al[53] 2016 were the only two studies that acknowledged that they were not able to identify reason for ECG performance[30] and there was an inability to assess whether the ECGs performed were directly related to initiation of drug therapy.[53] Other studies described possible reasons for ECG monitoring. Girgis et al[56] 2016 asserted that general medicine patients likely received EKGs for medical reasons related to the cause of their admission and not purely for monitoring QTc intervals. Dunker et al[52] 2016 suggested prescribers may have obtained ECG for a variety of reasons. Choo et al[23] 2014 also suggested some ECGs could have been performed as a routine during admission.

Table 1 Studies categorised as relating to acute or chronic drug use

Study	**Acute or chronic drug use**
Cole et al[46] 2020	Acute
Pezo et al[30] 2019	Not determined
Manchia et al[24] 2017	Chronic
Atayee et al[50] 2017	Chronic
Ehrenpreis et al[55] 2016	Chronic*
Vandael et al[49] 2016	Acute
Robbins et al[48] 2016	Acute
Girgis et al[56] 2016	Chronic*
Forbes et al[53] 2016	Not determined
Dunker et al[52] 2016	Acute
Choo et al[23] 2014	Not determined
Macey et al[54] 2013	Chronic
Cheung et al[51] 2013	Acute
Muzyk et al[47] 2012	Acute

**Drugs in these studies were used to treat a mix of both acute and chronic medical conditions, however > 50% of study subjects were described to use drugs for chronic conditions, therefore the studies were categorised as predominantly chronic drug use.*

Methodological quality

Methodological quality was deemed to be poor in most studies, and only five out of 14 studies were assessed as high quality. Eleven out of 14 studies were eligible for high quality status, as three studies did not fulfil both domains four and seven. Assessment of methodological quality is represented in Table 2.

The study subjects, as described by age; and setting, as described by healthcare location; were described clearly in most studies. One study did not specify the setting in which patients received their drug treatment and / or ECG monitoring. Baseline ECG use was deemed to be clearly defined or sufficiently acceptable in all studies that described baseline ECG. One study described baseline ECG to include ECG that was performed within 24 hours after starting the high-risk drug, which was deemed acceptable for inclusion due to reasonable clinical intent. Clarification of study definitions for follow up ECG time frames was sought from authors of four studies. The follow up ECG data from one study was excluded from the review as the follow up period spanned eight weeks. The follow up ECG data from another study was able to be included as the follow up period was confirmed as being within 30 days of drug use. The follow up ECG data from two studies were unable to be included as the authors did not provide sufficient clarity around the way they had been defined in the studies, and therefore could not be included for use in the review.

Table 2: Assessment of methodological quality using JBI critical appraisal tools[38]

Included studies	Q1	Q2	Q3	Q4*	Q5	Q6	Q7*	Q8	Q9	Score	Quality assessment
Cole et al[46] 2020	Y	Y	Y	Y	U	Y	Y	Y	N	7	**High quality**
Pezo et al[30] 2019	N	Y	Y	N	Y	Y	Y	Y	N	6	Poor quality
Manchia et al[24] 2017	Y	Y	N	Y	Y	Y	U	N	U	5	Poor quality
Ehrenpreis et al[55] 2016	Y	Y	N	Y	Y	Y	Y	Y	U	7	**High quality**
Atayee et al[50] 2017	Y	Y	N	Y	U	Y	Y	Y	Y	7	**High quality**
Vandael et al[49] 2016	Y	Y	N	Y	Y	Y	Y	Y	Y	8	**High quality**
Robbins et al[48] 2016	Y	Y	N	Y	U	U	Y	Y	Y	6	Poor quality
Girgis et al[56] 2016	Y	Y	N	Y	U	U	Y	Y	Y	6	Poor quality
Forbes et al[53] 2016	Y	Y	N	Y	Y	Y	Y	Y	U	7	**High quality**
Dunker et al[52] 2016	Y	Y	N	Y	Y	Y	U	Y	Y	7	Poor quality
Choo et al[23] 2014	Y	Y	N	Y	U	Y	Y	Y	U	6	Poor quality
Macey et al[54] 2013	Y	Y	N	Y	N	Y	Y	Y	U	6	Poor quality
Cheung et al[51] 2013	N	Y	N	Y	U	U	Y	Y	U	4	Poor quality
Muzyk et al[47] 2012	Y	Y	N	Y	U	U	Y	N	Y	5	Poor quality

**Domains that needed both to be Y to be eligible for high quality status*
Studies were rated as Yes (Y), No (N), or Unclear (U) for each question.
An unclear rating indicates that the details either could not be located in the article or could not be clarified with the author.

Appraisal criteria for prevalence studies:
***Q1** Was the sample frame appropriate to address the target population? **Q2** Were the study participants sampled in an appropriate way? **Q3** Was the sample size adequate? **Q4** Were the study subjects and the setting described in detail? **Q5** Was the data analysis conducted with sufficient coverage of the identified sample? **Q6** Were valid methods used for the identification of the condition? **Q7** Was the condition measured in a standard, reliable way for all participants? **Q8** Was there appropriate statistical analysis **Q9** Was the response rate adequate, and if not, was the low response rate managed appropriately?*

Many studies did not provide information to determine sufficient coverage of study participants, in particular, relating to the coverage of differing adult age ranges. Most studies involved inclusion of all patients who had been treated with the high-risk drug(s) of interest within specified study periods, rather than a random selection of patients within those study periods. One study randomised the sampling process by only including patients treated with the high-risk drug of interest on one specified day of each week during the study period. Regardless of randomisation or non-randomisation, all studies were deemed to sample study participants appropriately.

Only two studies involved adequately large sample sizes, all other studies involved small to very sample sizes below 100 or low hundreds.

Most studies specified that study subjects, drug prescription and ECG use were identified through administrative databases, often electronic. Four studies either did not mention or provided very limited information about the methods of patient, drug and / or ECG identification.

In relation to statistical analysis, one study did not provide the raw denominator value relating to baseline and / or follow up ECG proportions and one study did not provide the raw numerator value relating to baseline ECG proportions; however in both cases the percentage values were provided and these were used to derive the raw values. In Manchia et al[24] 2017 following calculation of the raw denominator value of interest using the percentage provided, it was determined the calculated raw values were possibly erroneous as the total sum of data points did not equate to the final overall value provided in the study, but rather a greater value. Calculation was confirmed with a second reviewer (MW). Furthermore, these values could not be clarified with the author. If raw values for the numerator or denominator were not provided, then statistical analysis was deemed inappropriate.

Response rate was deemed adequate if studies provided information relating to confirmed drug administration in included study subjects. Assessment of response rate could also relate to information relating to confirmed ECG use. Some studies specified exclusion of patients due to reasons such as missed drug doses, or prior inclusion. One study reported that ECGs that involved bundle branch block or paced rhythm were not included in ECG use data. Another study reported that they were unable to capture use of intravenous supportive medications such as antiemetics. In both cases, response rate was not deemed adequate. Most studies provided no information relating to response rate, and it was deemed unclear whether response rate was adequate.

Findings of the review

Findings in the review are presented according to 1) the prevalence of baseline ECG use of high-risk QT interval prolonging drugs and 2) the prevalence of follow up ECG use of high-risk QT interval prolonging drugs and 3) risk factors and their influence on the use of baseline and / or follow up ECG monitoring.

"Leave one (or more) out" analyses

Three specific studies involved biases that were not recognised in the critical appraisal tool and for these reasons separate "leave one (or more) out" analyses were conducted to determine the extent of their impact on the final pooled proportion. In the discussion of results, these studies are termed studies with *additional* biases. Cole et al[46] 2020 involved a drug which was only deemed high-risk for one out of five years of their study period, therefore ECG monitoring is likely to have occurred less than naturally expected. Muzyk et al[47] 2012 (b) involved active intervention of ECG monitoring behaviour which involved generation of automated baseline and daily ECG orders for providers following prescription of the high-risk drug of interest. Therefore, ECG monitoring is likely to have occurred more than naturally expected. And finally, Robbins et al[48] 2016, specified that baseline ECG was obtained in all patients, and it is not clear within the study whether baseline ECG was conducted intentionally. ECGs conducted intentionally were grounds on which to otherwise exclude studies from this systematic review, as ECG monitoring would have occurred more than expected.

A separate "leave one out" analysis was conducted for each of these three studies in relation to baseline ECG use – all studies and follow up ECG use – all studies, to determine the impact of excluding each study on the final pooled proportion. Furthermore, a separate "leave three out" analysis was conducted in relation to baseline ECG use – all studies and follow up ECG use – all studies to determine the impact of excluding all three studies on the final pooled proportion.

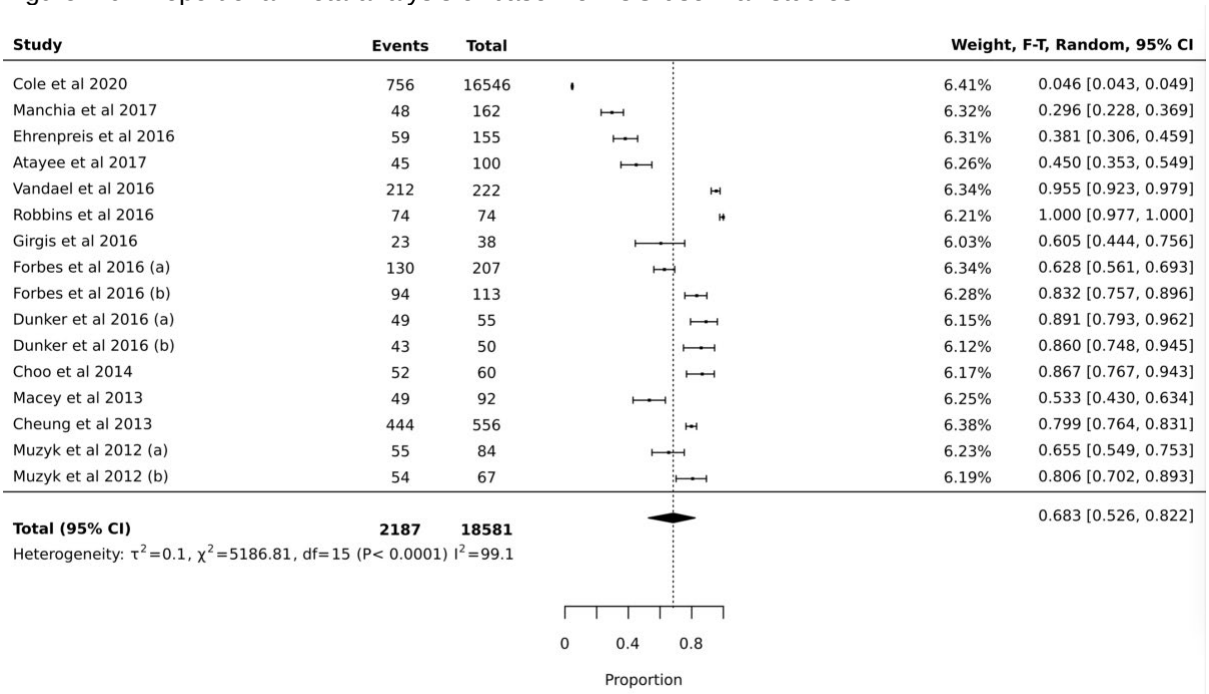
All other separate analyses which included any of these three specific studies had a "leave one (or more) out" analysis applied once only, in which the number of studies left out related to the greatest number of these three studies present.

1) Prevalence of baseline ECG use of high-risk QT interval prolonging drugs

Analysis 1.0 Baseline ECG use – all studies

Data on baseline ECG use was available from 13 studies for inclusion in a meta-analysis, including 18,581 patients. The forest plot for this meta-analysis is shown in figure 1.0. The meta-analysis shows that the final pooled proportion of baseline ECG use across all studies was 68.3% (95% CI 52.6% to 82.2%). There was statistically significant heterogeneity (p<0.0001) with an I^2 value of 99%.

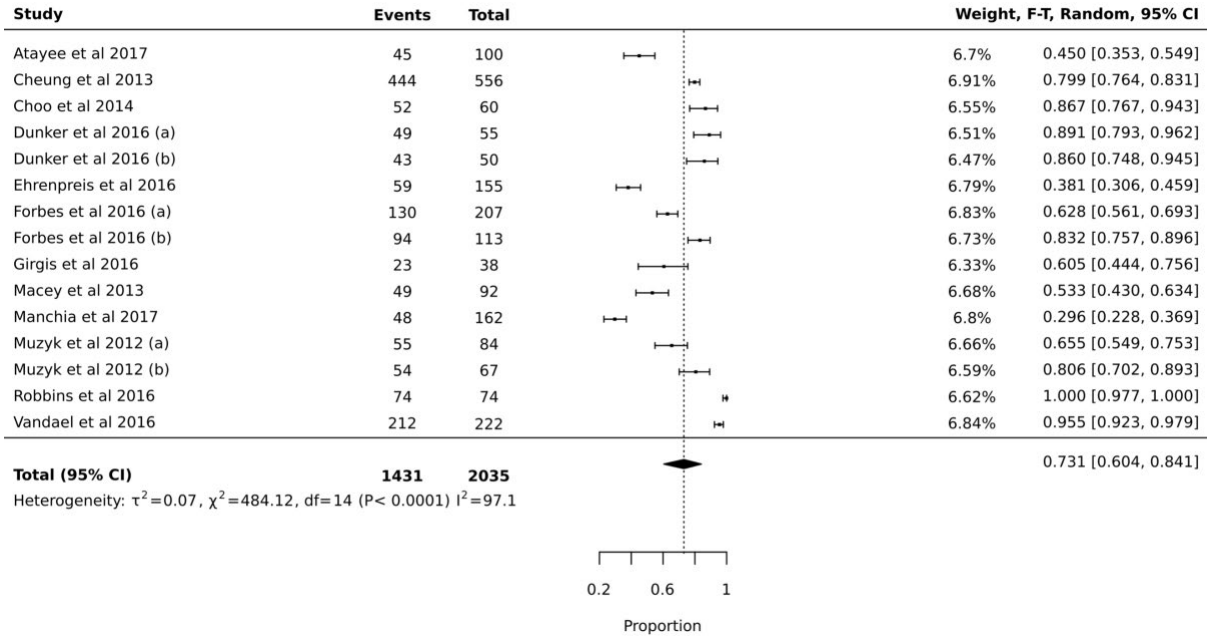
Figure 1.0: Proportional meta-analysis of baseline ECG use – all studies



Analysis 1.01 Baseline ECG use - all studies and leave one out (Cole et al 2020)

A separate analysis of baseline ECG use (all studies) whilst leaving one out (Cole et al 2020) involved 12 studies for inclusion in a meta-analysis, including 2035 patients. The forest plot for this meta-analysis is shown in figure 1.01. The meta-analysis shows that the final pooled proportion of baseline ECG use across this group without Cole et al 2020 was 73.1% (95% CI 60.4% to 84.1%). There was statistically significant heterogeneity (p<0.0001) with an I^2 value of 97.1%.

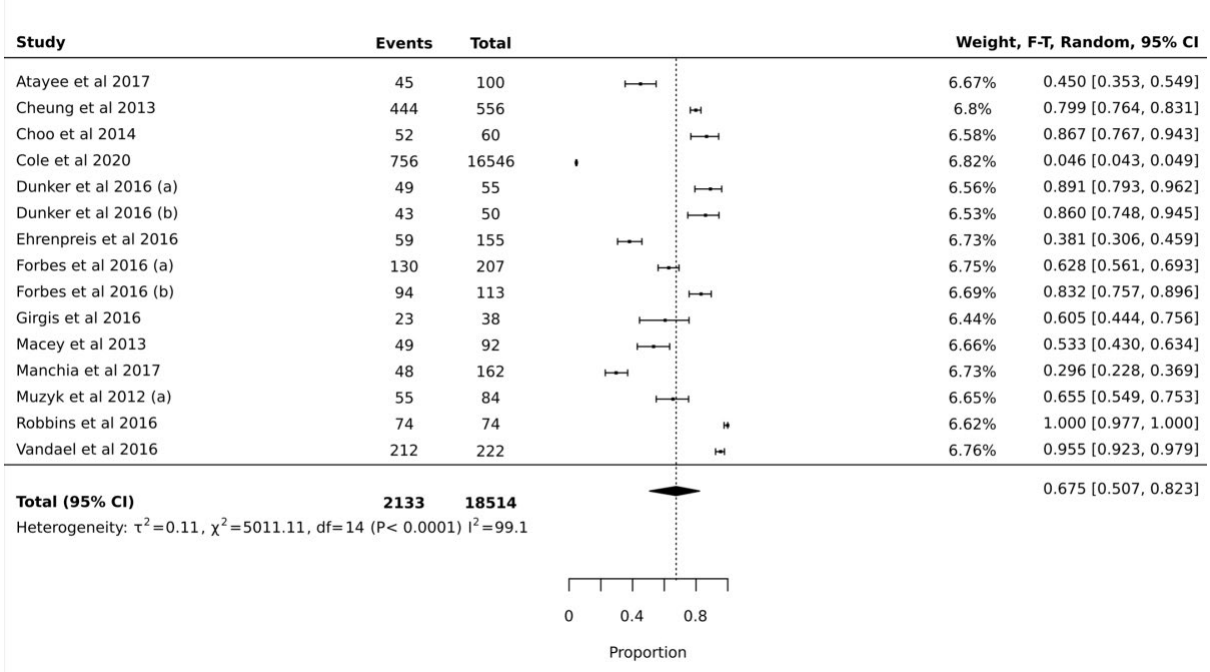
Figure 1.01: Proportional meta-analysis of baseline ECG use - all studies and leave one out (Cole et al 2020)



Analysis 1.02 Baseline ECG use - all studies and leave one out (Muzyk et al 2012 (b))

A separate analysis of baseline ECG use (all studies) whilst leaving one out (Muzyk et al 2012 (b)) involved 13 studies for inclusion in a meta-analysis, including 18,514 patients. The forest plot for this meta-analysis is shown in figure 1.02. The meta-analysis shows that the final pooled proportion of baseline ECG use across this group without Muzyk et al 2012 (b) was 67.5% (95% CI 50.7% to 82.3%). There was statistically significant heterogeneity (p<0.0001) with an I^2 value of 99.1%.

Figure 1.02: Proportional meta-analysis of baseline ECG use - all studies and leave one out (Muzyk et al 2012 (b))

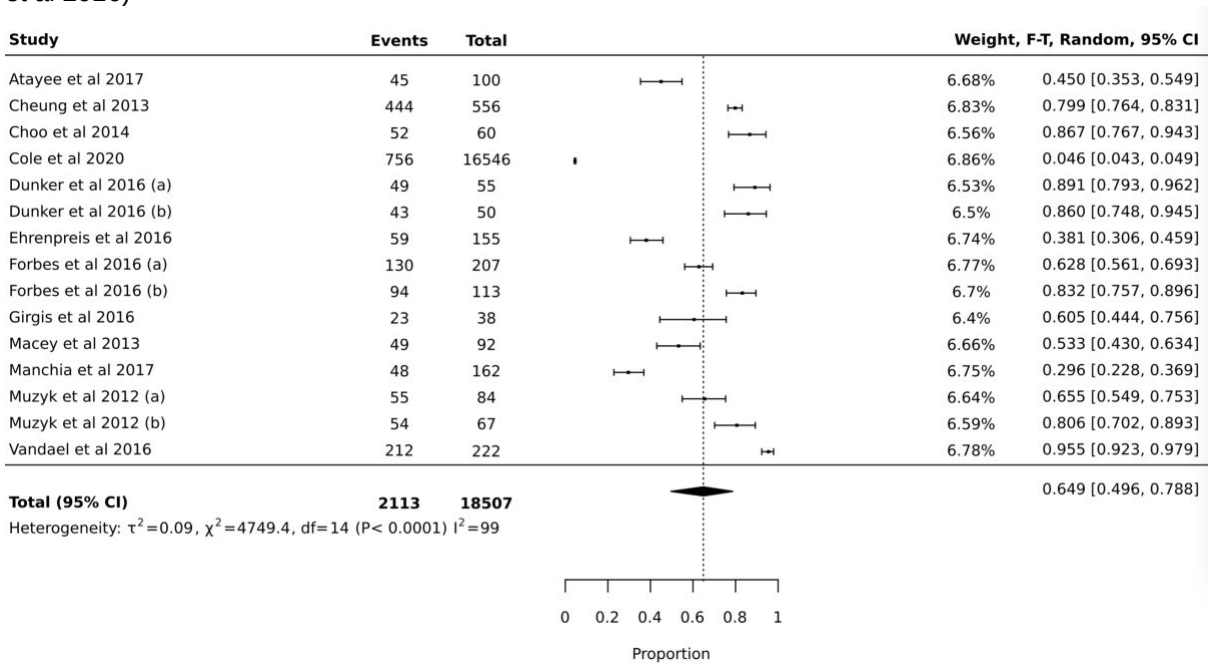


Analysis 1.03 Baseline ECG use - all studies and leave one out (Robbins et al 2016)

A separate analysis of baseline ECG use (all studies) whilst leaving one out (Robbins et al 2016) involved 12 studies for inclusion in a meta-analysis, including 18,507 patients. The forest plot for this meta-analysis is shown in figure 1.03. The meta-analysis shows that the final pooled proportion of

baseline ECG use across this group without Robbins et al 2016 was 64.9% (95% CI 49.6% to 78.8%). There was statistically significant heterogeneity (p<0.0001) with an I^2 value of 99%.

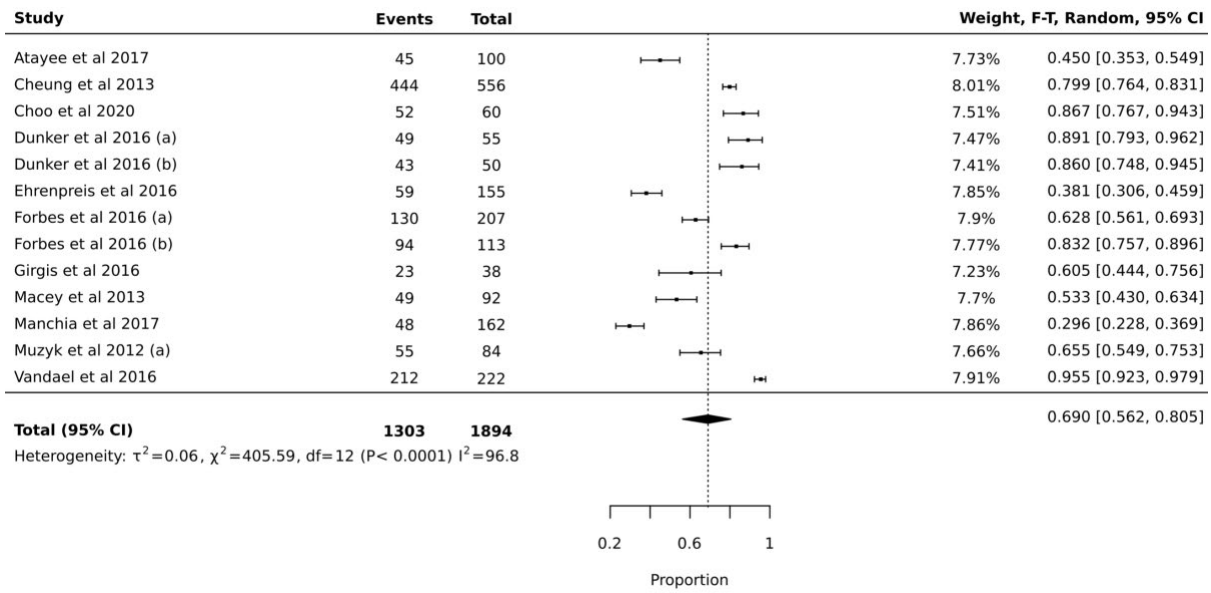
Figure 1.03: Proportional meta-analysis of baseline ECG use - all studies and leave one out (Robbins et al 2016)



Analysis 1.04 Baseline ECG use - all studies and leave three out (Cole et al 2020, Muzyk et al 2012 (b) and Robbins et al 2016)

A separate analysis of baseline ECG use (all studies) whilst leaving three out (Cole et al 2020, Muzyk et al 2012 (b) and Robbins et al 2016) involved 11 studies for inclusion in a meta-analysis, including 1894 patients. The forest plot for this meta-analysis is shown in figure 1.04. The meta-analysis shows that the final pooled proportion of baseline ECG use across this group without Cole et al 2020, Muzyk et al 2012 (b) and Robbins et al 2016 was 69.0% (95% CI 56.2% to 80.5%). There was statistically significant heterogeneity (p<0.0001) with an I^2 value of 96.8%.

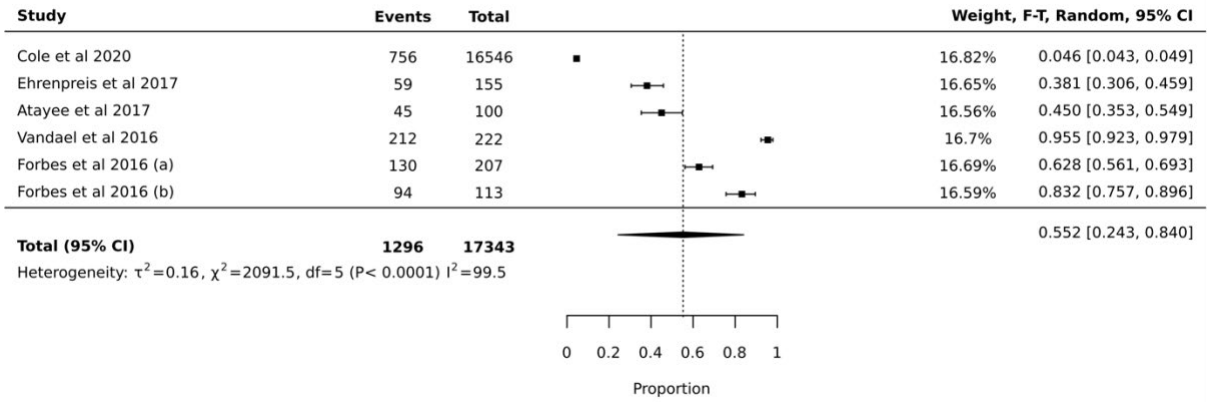
Figure 1.04: Proportional meta-analysis of baseline ECG use - all studies and leave three out (Cole et al 2020, Muzyk et al 2012 (b) and Robbins et al 2016)



Analysis 1.05 Baseline ECG use - high quality studies only

A separate analysis of baseline ECG use involving high quality studies only, in which all poor quality studies were excluded, involved 5 studies for inclusion in a meta-analysis, including 17,343 patients. The forest plot for this meta-analysis is shown in figure 1.05. The meta-analysis shows that the final pooled proportion of baseline ECG use across high quality studies only was 55.2% (95% CI 24.3% to 84.0%). There was statistically significant heterogeneity (p<0.0001) with an I^2 value of 99.5%.

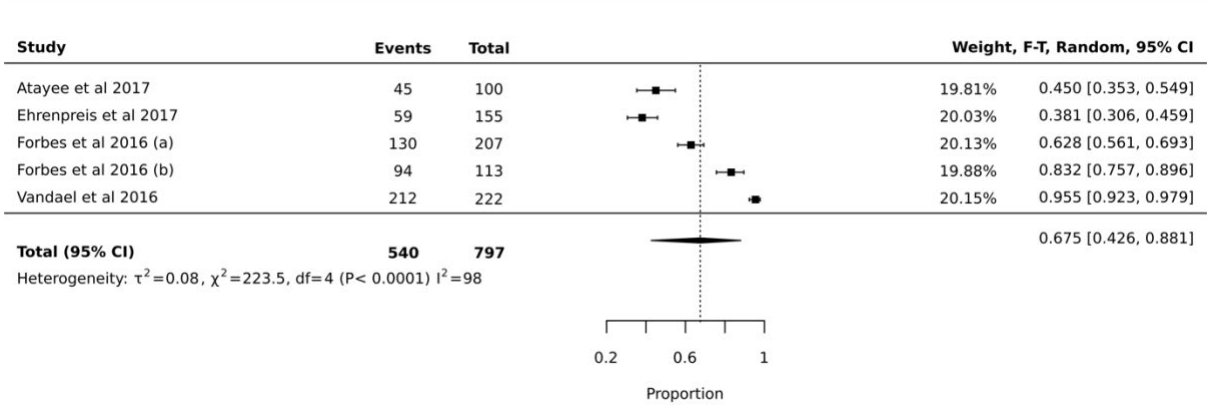
Figure 1.05: Proportional meta-analysis of baseline ECG use - high quality studies only



Analysis 1.06 Baseline ECG use - high quality studies only and leave one out (Cole et al 2020)

A separate analysis of baseline ECG involving high quality studies only and whilst leaving one out (Cole et al 2020) involved 4 studies for inclusion in a meta-analysis, including 797 patients. The forest plot for this meta-analysis is shown in figure 1.06. The meta-analysis shows that the final pooled proportion of baseline ECG use across high quality studies only without Cole et al 2020 was 67.5% (95% CI 42.6% to 88.1%). There was statistically significant heterogeneity (p<0.0001) with an I^2 value of 98%.

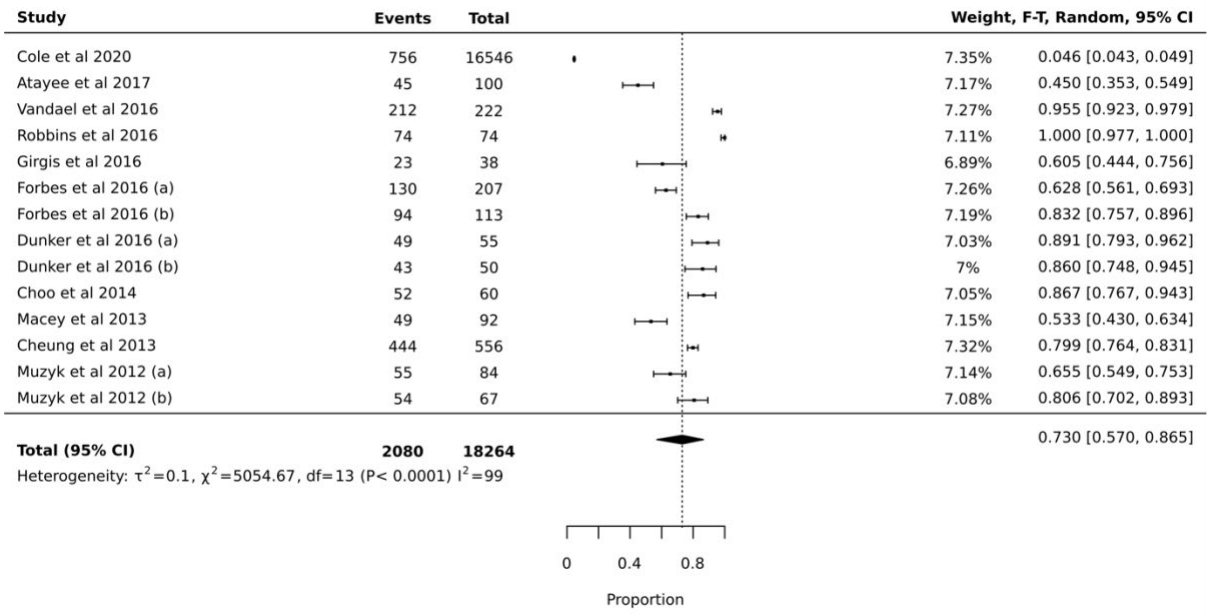
Figure 1.06: Proportional meta-analysis of baseline ECG use - high quality studies only and leave one out (Cole et al 2020)



Analysis 1.07 Baseline ECG use - hospital setting only

A separate analysis of baseline ECG use involving studies of hospital setting only, involved 11 studies for inclusion in a meta-analysis, including 18,264 patients. The forest plot for this meta-analysis is shown in figure 1.07. The meta-analysis shows that the final pooled proportion of baseline ECG use relating to the hospital setting only was 73.0% (95% CI 57.0% to 86.5%). There was statistically significant heterogeneity (p<0.0001) with an I^2 value of 99%.

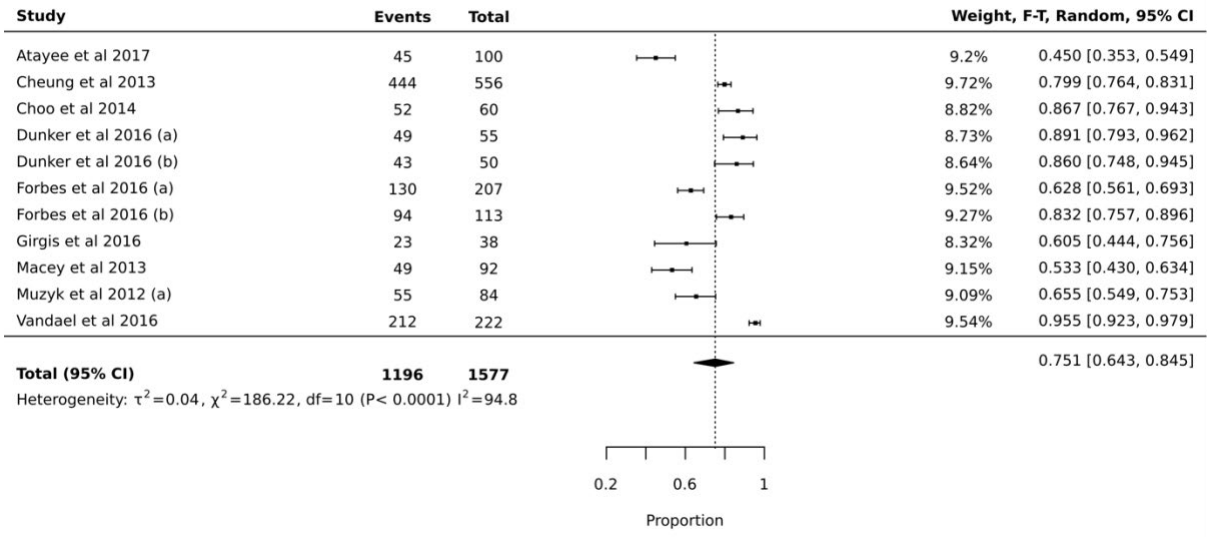
Figure 1.07: Proportional meta-analysis of baseline ECG use - hospital setting only



Analysis 1.08 Baseline ECG use - hospital setting only and leave three out (Cole et al 2020, Muzyk et al 2012 (b) and Robbins et al 2016)

A separate analysis of baseline ECG use involving studies of hospital setting only and also leaving three out (Cole et al 2020, Muzyk et al 2012 (b) and Robbins et al 2016), involved 9 studies for inclusion in a meta-analysis, including 1577 patients. The forest plot for this meta-analysis is shown in figure 1.08. The meta-analysis shows that the final pooled proportion of baseline ECG use relating to the hospital setting only and whilst also leaving three out was 75.1% (95% CI 64.3% to 84.5%). There was statistically significant heterogeneity (p<0.0001) with an I^2 value of 94.8%.

Figure 1.08: Proportional meta-analysis of baseline ECG use - hospital setting only and leave three out (Cole et al 2020, Muzyk et al 2012 (b) and Robbins et al 2016)

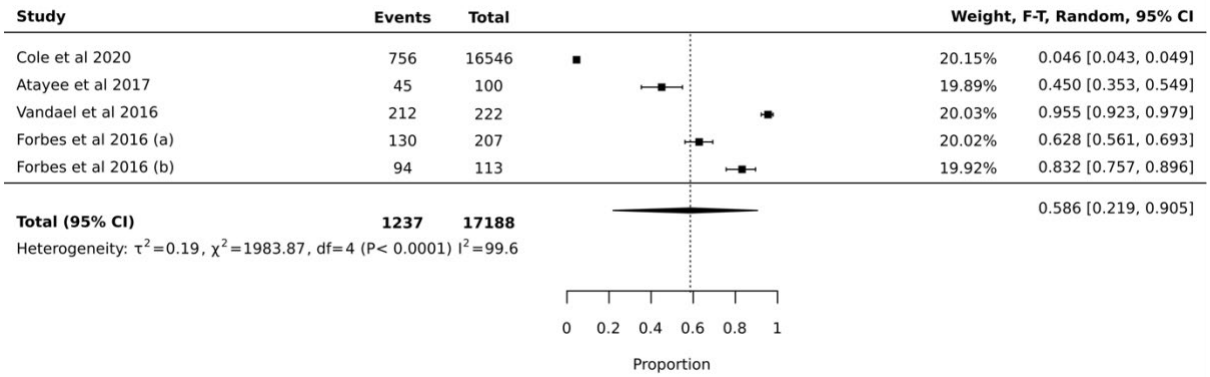


Analysis 1.08a Baseline ECG use - hospital setting only and high quality studies only

A separate analysis of baseline ECG use involving studies of hospital setting only in which only the high quality studies were included, involved 4 studies for inclusion in a meta-analysis, including 17,188 patients. The forest plot for this meta-analysis is shown in figure 1.08a. The meta-analysis

shows that the final pooled proportion of baseline ECG use relating to the hospital setting only in which only the high quality studies were included was 58.6% (95% CI 21.9% to 90.5%). There was statistically significant heterogeneity (p<0.0001) with an I^2 value of 99.6%.

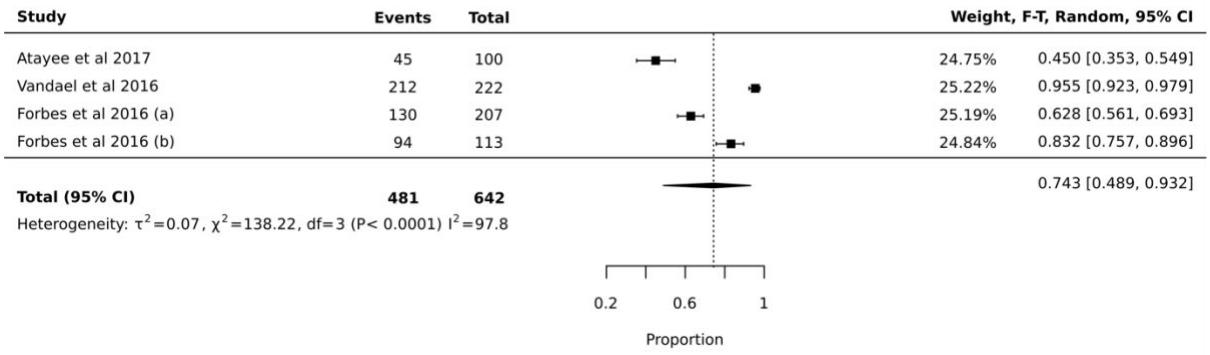
Figure 1.08a: Proportional meta-analysis of baseline ECG use - hospital setting only and high quality studies only



Analysis 1.08b Baseline ECG use - hospital setting only and high quality studies only and leave one out (Cole et al 2020)

A separate analysis of baseline ECG use involving studies of hospital setting only in which only the high quality studies were included and furthermore “leave one out” relating to Cole et al 2020 was applied, involved 3 studies for inclusion in a meta-analysis, including 642 patients. The forest plot for this meta-analysis is shown in figure 1.08b. The meta-analysis shows that the final pooled proportion of baseline ECG use relating to the hospital setting only in which only the high quality studies were included and the study by Cole et al 2020 was left out was 74.3% (95% CI 48.9% to 93.2%). There was statistically significant heterogeneity (p<0.0001) with an I^2 value of 97.8%.

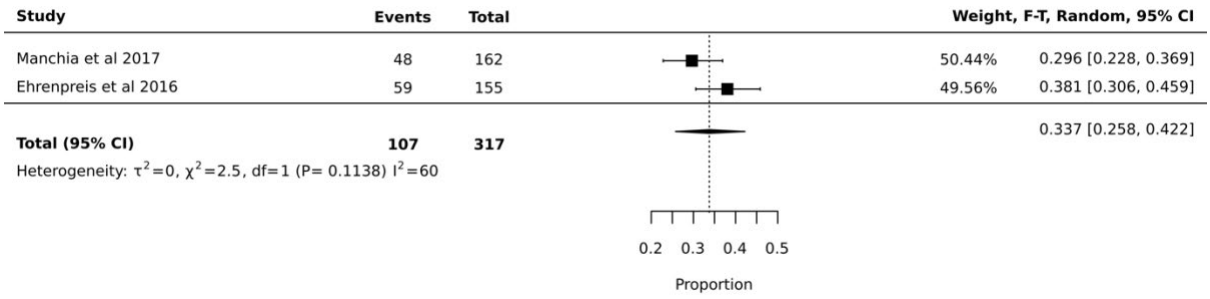
Figure 1.08b: Proportional meta-analysis of baseline ECG use - hospital setting only and high quality studies only and leave one out (Cole et al 2020)



Analysis 1.09 Baseline ECG use - non-hospital setting only

A separate analysis of baseline ECG use involving studies of non-hospital setting only, involved 2 studies for inclusion in a meta-analysis, including 317 patients. The forest plot for this meta-analysis is shown in figure 1.09. The meta-analysis shows that the final pooled proportion of baseline ECG use relating to non-hospital setting only was 33.7% (95% CI 25.8% to 42.2%). Heterogeneity was not statistically significant (p=0.1138) with an I^2 value of 60%.

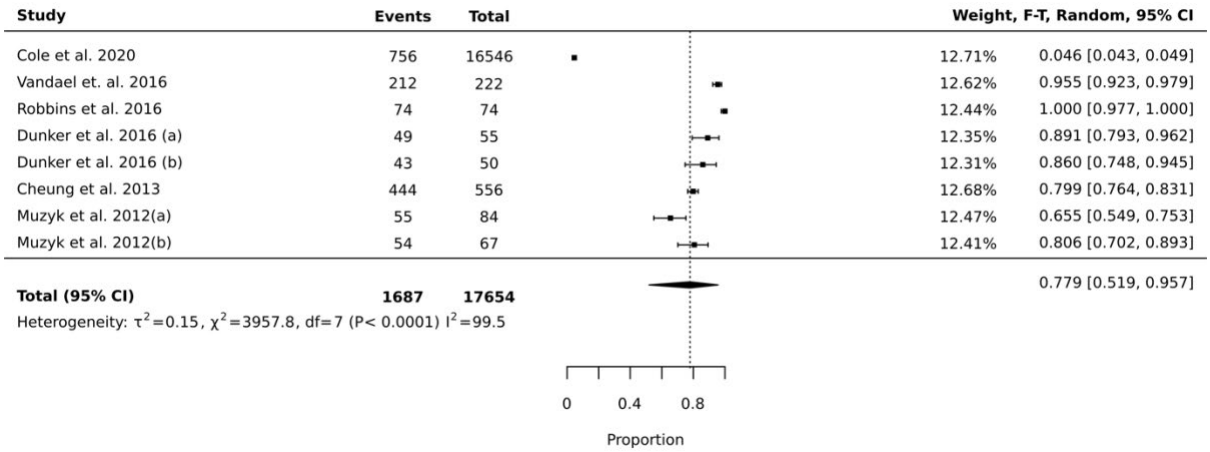
Figure 1.09: Proportional meta-analysis of baseline ECG use - non-hospital setting only



Analysis 1.10 Baseline ECG use - acute use drugs only

A separate analysis of baseline ECG use involving studies of acute use drugs only, involved 6 studies for inclusion in a meta-analysis, including 17,654 patients. The forest plot for this meta-analysis is shown in figure 1.10. The meta-analysis shows that the final pooled proportion of baseline ECG use relating to acute use drugs only was 77.9% (95% CI 51.9% to 95.7%). There was statistically significant heterogeneity (p<0.0001) with an I^2 value of 99.5%.

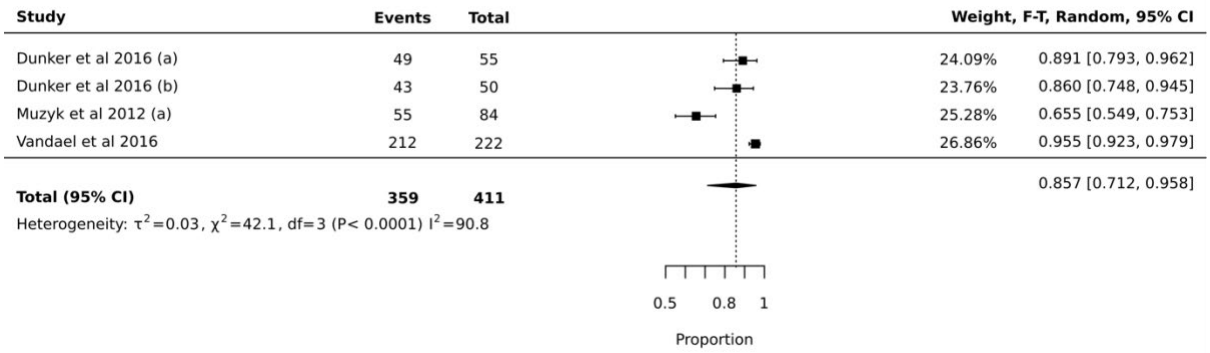
Figure 1.10: Proportional meta-analysis of baseline ECG use - acute use drugs only



Analysis 1.11 Baseline ECG use - acute use drugs only and leave three out (Cole et al 2020, Muzyk et al 2012 (b) and Robbins et al 2016)

A separate analysis of baseline ECG use involving studies of acute use drugs only and also leaving three out (Cole et al 2020, Muzyk et al 2012 (b) and Robbins et al 2016), involved 3 studies for inclusion in a meta-analysis, including 411 patients. The forest plot for this meta-analysis is shown in figure 1.11. The meta-analysis shows that the final pooled proportion of baseline ECG use relating to acute use drugs only and whilst also leaving three out was 85.7% (95% CI 71.2% to 95.8%). There was statistically significant heterogeneity (p<0.0001) with an I^2 value of 90.8%.

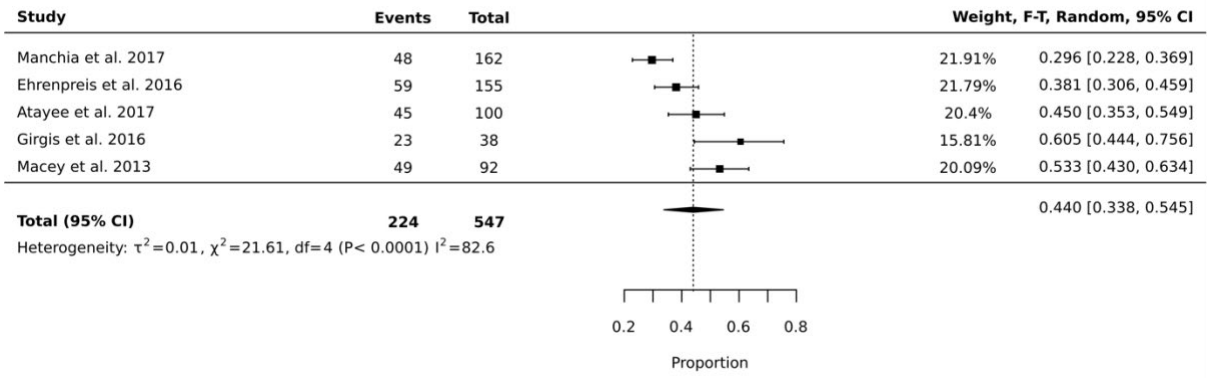
Figure 1.11: Proportional meta-analysis of baseline ECG use - acute use drugs only and leave three out (Cole et al 2020, Muzyk et al 2012 (b) and Robbins et al 2016)



Analysis 1.12 Baseline ECG use - chronic use drugs only

A separate analysis of baseline ECG use involving studies of chronic use drugs only, involved 5 studies for inclusion in a meta-analysis, including 547 patients. The forest plot for this meta-analysis is shown in figure 1.12. The meta-analysis shows that the final pooled proportion of baseline ECG use relating to chronic use drugs only was 44.0% (95% CI 33.8% to 54.5%). There was statistically significant heterogeneity (p<0.0001) with an I^2 value of 82.6%.

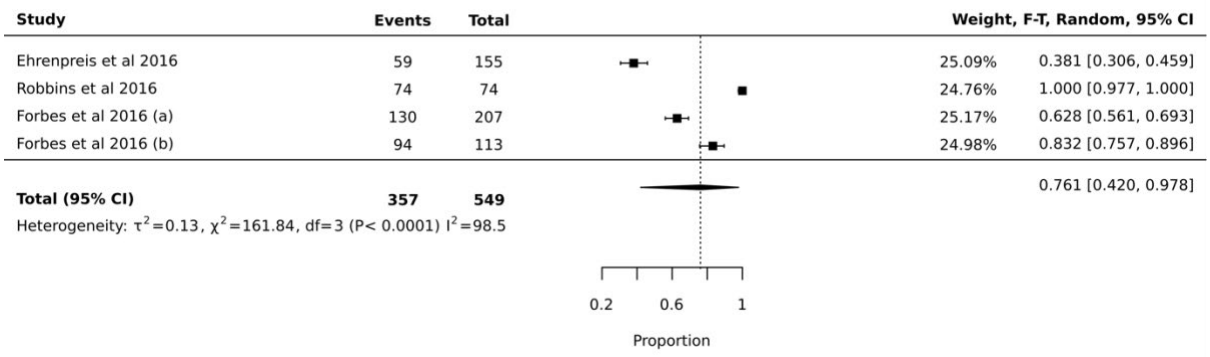
Figure 1.12: Proportional meta-analysis of baseline ECG use - chronic use drugs only



Analysis 1.13 Baseline ECG use – domperidone studies only

A separate analysis of baseline ECG use involving studies of domperidone only, involved 3 studies for inclusion in a meta-analysis, including 549 patients. The forest plot for this meta-analysis is shown in figure 1.13. The meta-analysis shows that the final pooled proportion of baseline ECG use relating to domperidone only was 76.1% (95% CI 42.0% to 97.8%). There was statistically significant heterogeneity (p<0.0001) with an I^2 value of 98.5%.

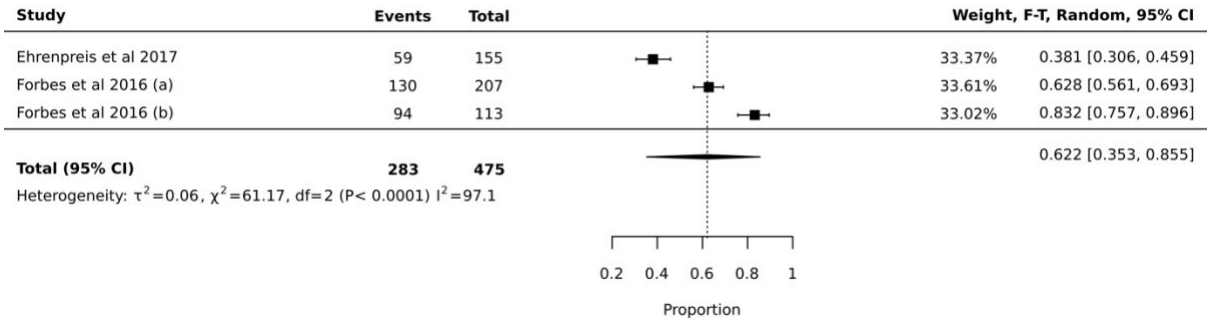
Figure 1.13: Proportional meta-analysis of baseline ECG use – domperidone studies only



Analysis 1.14 Baseline ECG use – domperidone studies only and leave one out (Robbins et al 2016)

A separate analysis of baseline ECG use involving studies of domperidone only and whilst leaving one out (Robbins et al 2016), involved 2 studies for inclusion in a meta-analysis, including 475 patients. The forest plot for this meta-analysis is shown in figure 1.14. The meta-analysis shows that the final pooled proportion of baseline ECG use relating to domperidone only and whilst leaving one out was 62.2% (95% CI 35.3% to 85.5%). There was statistically significant heterogeneity (p<0.0001) with an I^2 value of 97.1%.

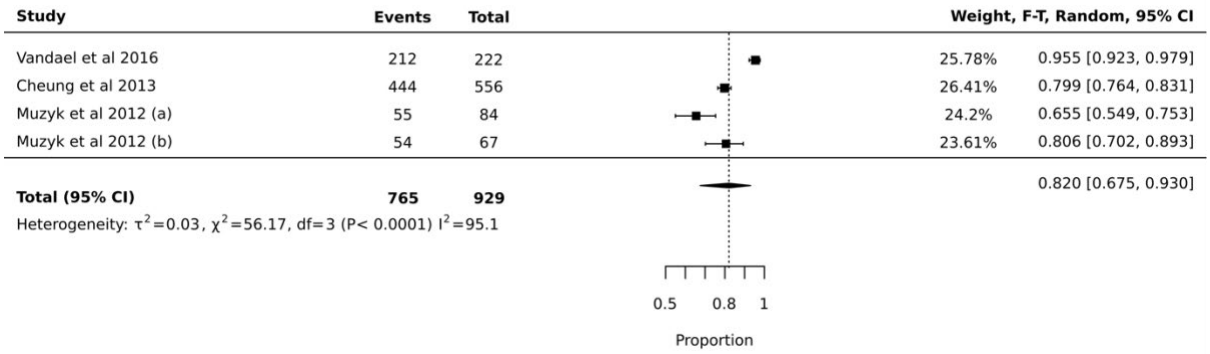
Figure 1.14: Proportional meta-analysis of baseline ECG use – domperidone studies only and leave one out (Robbins et al 2016)



Analysis 1.15 Baseline ECG use – haloperidol studies only

A separate analysis of baseline ECG use involving studies of haloperidol only, involved 3 studies for inclusion in a meta-analysis, including 929 patients. The forest plot for this meta-analysis is shown in figure 1.15. The meta-analysis shows that the final pooled proportion of baseline ECG use relating to haloperidol only was 82% (95% CI 67.5% to 93.0%). There was statistically significant heterogeneity (p<0.0001) with an I^2 value of 95.1%.

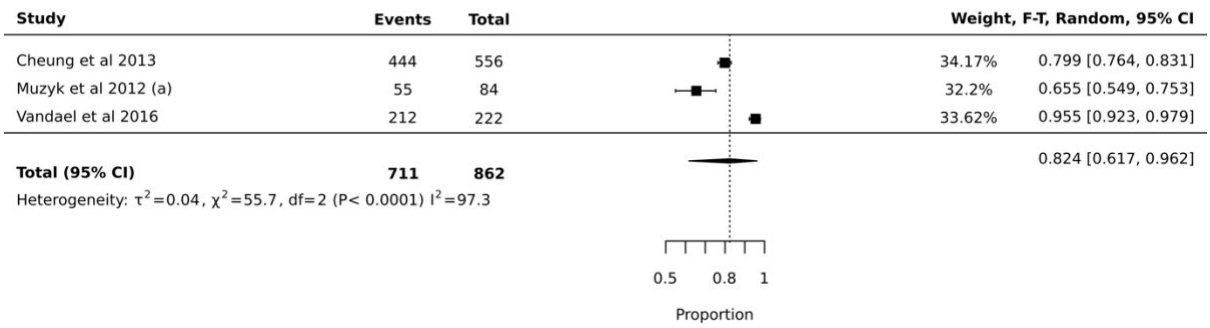
Figure 1.15: Proportional meta-analysis of baseline ECG use – haloperidol studies only



Analysis 1.16 Baseline ECG use – haloperidol studies only and leave one out (Muzyk et al 2012 (b))

A separate analysis of baseline ECG use involving studies of haloperidol only and whilst leaving one out (Muzyk et al 2012 (b)), involved 3 studies for inclusion in a meta-analysis, including 862 patients. The forest plot for this meta-analysis is shown in figure 1.16. The meta-analysis shows that the final pooled proportion of baseline ECG use relating to haloperidol only and whilst leaving one out was 82.4% (95% CI 61.7% to 96.2%). There was statistically significant heterogeneity (p<0.0001) with an I^2 value of 97.3%.

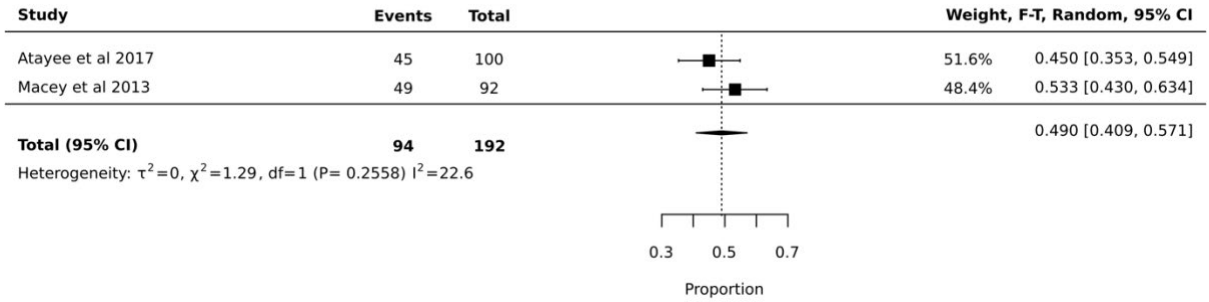
Figure 1.16: Proportional meta-analysis of baseline ECG use – haloperidol studies only and leave one out (Muzyk et al 2012 (b))



Analysis 1.17 Baseline ECG use – methadone studies only

A separate analysis of baseline ECG use involving studies of methadone only, involved 2 studies for inclusion in a meta-analysis, including 192 patients. The forest plot for this meta-analysis is shown in figure 1.17. The meta-analysis shows that the final pooled proportion of baseline ECG use relating to methadone only was 49.0% (95% CI 40.9% to 57.1%). Heterogeneity was not statistically significant (p=0.2558) with an I^2 value of 22.6%.

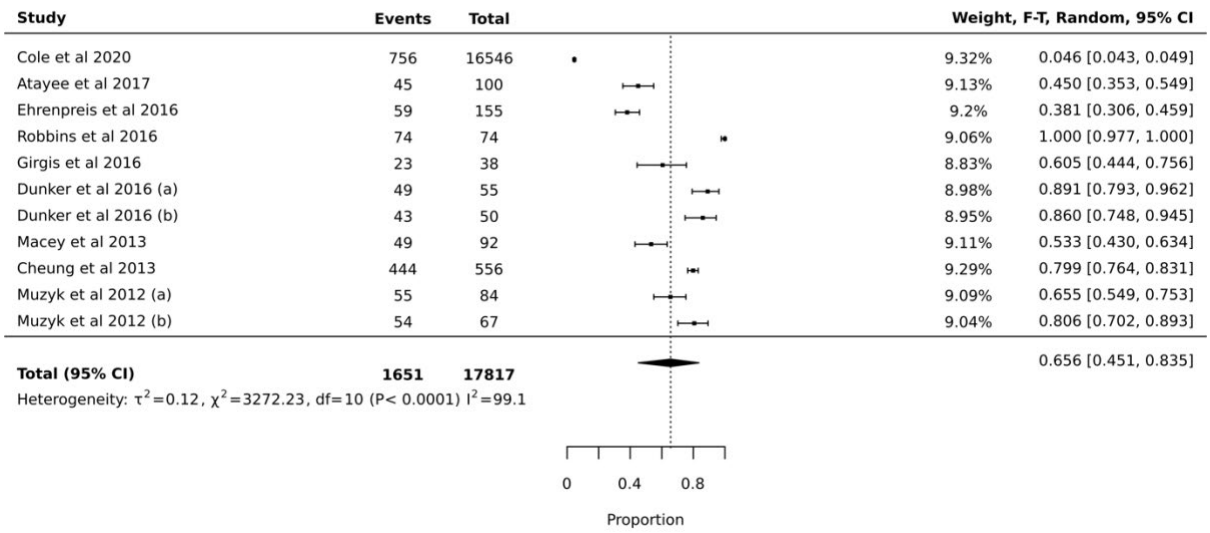
Figure 1.17: Proportional meta-analysis of baseline ECG use – methadone studies only



Analysis 1.18 Baseline ECG use – USA studies only

A separate analysis of baseline ECG use involving studies conducted in USA only, involved 9 studies for inclusion in a meta-analysis, including 17,817 patients. The forest plot for this meta-analysis is shown in figure 1.18. The meta-analysis shows that the final pooled proportion of baseline ECG use relating to USA only was 65.6% (95% CI 45.1% to 83.5%). There was statistically significant heterogeneity (p<0.0001) with an I^2 value of 99.1%.

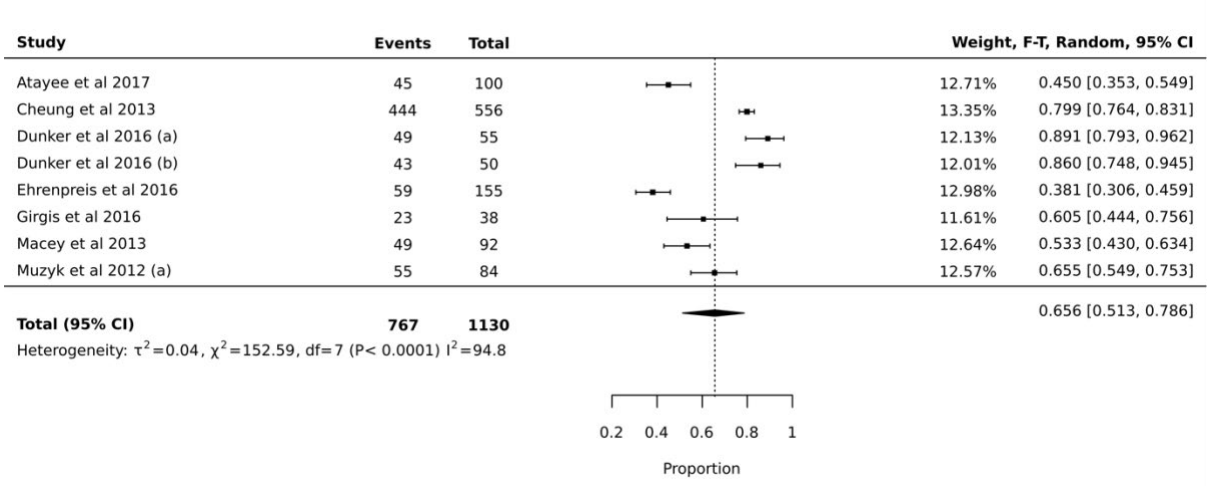
Figure 1.18: Proportional meta-analysis of baseline ECG use – USA studies only



Analysis 1.19 Baseline ECG use – USA studies only and leave three out (Cole et al 2020, Muzyk et al 2012 (b) and Robbins et al 2016)

A separate analysis of baseline ECG use involving studies conducted in USA only whilst leaving three studies out (Cole et al 2020, Muzyk et al 2012 (b) and Robbins et al 2016), involved 7 studies for inclusion in a meta-analysis, including 1130 patients. The forest plot for this meta-analysis is shown in figure 1.19. The meta-analysis shows that the final pooled proportion of baseline ECG use relating to USA only and whilst leaving three out was 65.6% (95% CI 51.3% to 78.6%). There was statistically significant heterogeneity (p<0.0001) with an I^2 value of 94.8%.

Figure 1.19: Proportional meta-analysis of baseline ECG use – USA studies only and leave three out (Cole et al 2020, Muzyk et al 2012 (b) and Robbins et al 2016)

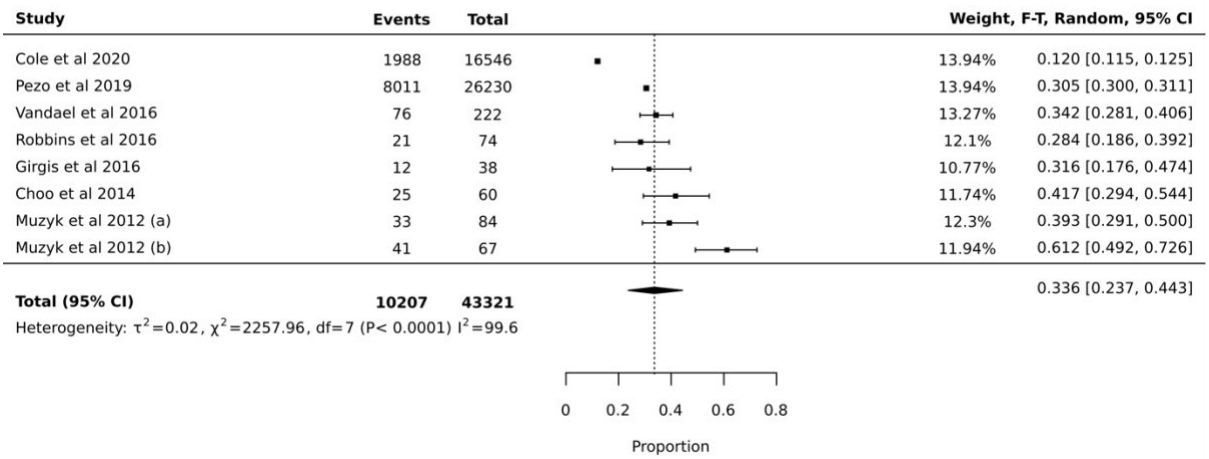


2) Prevalence of follow up ECG use of high-risk QT interval prolonging drugs

Analysis 2.0 Follow up ECG use – all studies

Data on follow up ECG use was available from 7 studies for inclusion in a meta-analysis, including 43,321 patients. The forest plot for this meta-analysis is shown in figure 2.0. The meta-analysis shows that the final pooled proportion of follow up ECG use across all studies was 33.6% (95% CI 23.7% to 44.3%). There was statistically significant heterogeneity (p<0.0001) with an I^2 value of 99.6%.

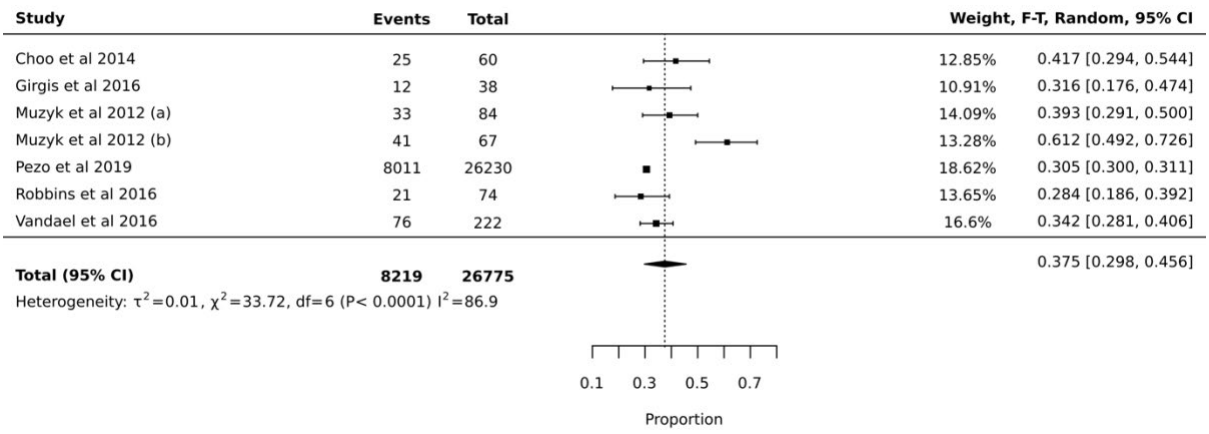
Figure 2.0: Proportional meta-analysis of follow up ECG use – all studies



Analysis 2.01 Follow up ECG use – all studies and leave one out (Cole et al 2020)

A separate analysis of follow up ECG use (all studies) whilst leaving one out (Cole et al 2020) involved 6 studies for inclusion in a meta-analysis, including 26,775 patients. The forest plot for this meta-analysis is shown in figure 2.01. The meta-analysis shows that the final pooled proportion of follow up ECG use across all studies without Cole et al 2020 was 37.5% (95% CI 29.8% to 45.6%). There was statistically significant heterogeneity (p<0.0001) with an I^2 value of 86.9%.

Figure 2.01: Proportional meta-analysis of follow up ECG use – all studies and leave one out (Cole et al 2020)

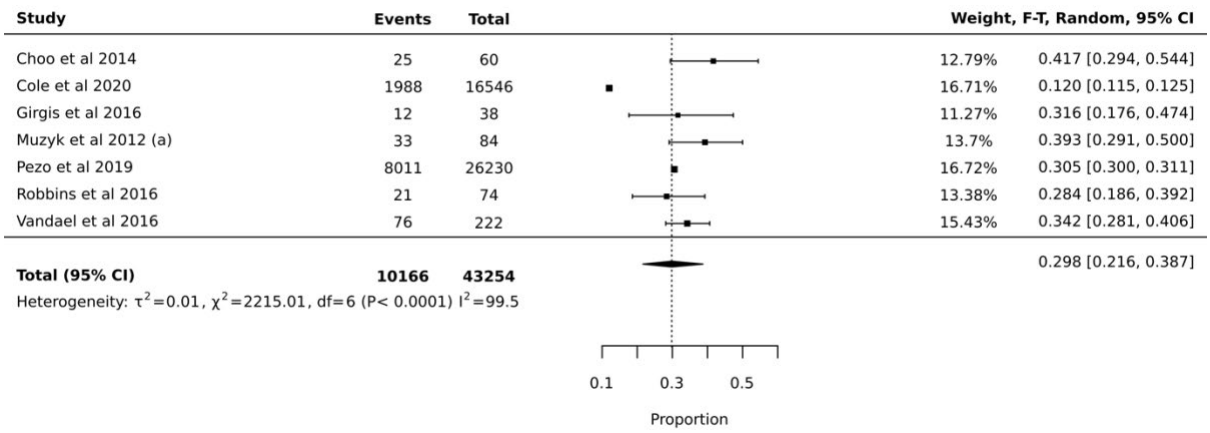


Analysis 2.02 Follow up ECG use – all studies and leave one out (Muzyk et al 2012 (b))

A separate analysis of follow up ECG use (all studies) whilst leaving one out (Muzyk et al 2012 (b)) involved 7 studies for inclusion in a meta-analysis, including 43,254 patients. The forest plot for this meta-analysis is shown in figure 2.02. The meta-analysis shows that the final pooled proportion of

follow up ECG use across all studies without Muzyk et al 2012 (b) was 29.8% (95% CI 21.6% to 38.7%). There was statistically significant heterogeneity (p<0.0001) with an I^2 value of 99.5%.

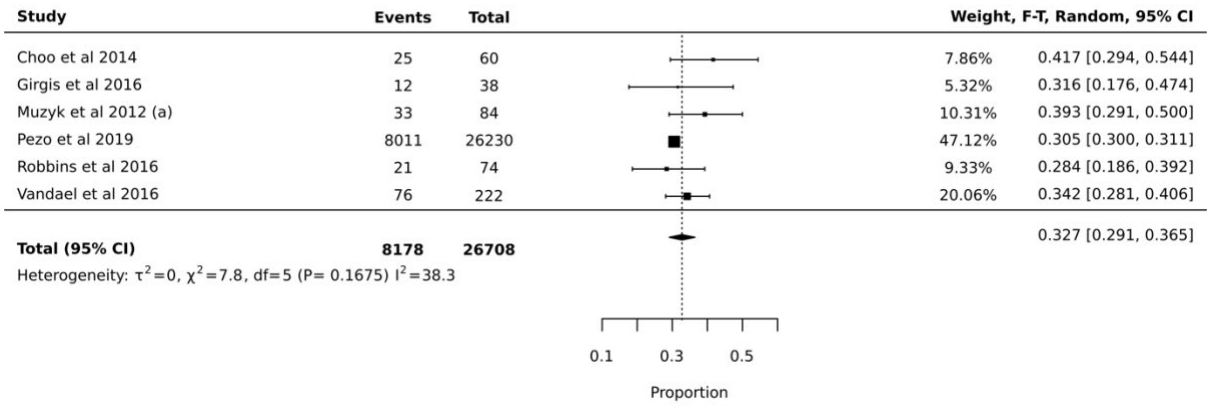
Figure 2.02: Proportional meta-analysis of follow up ECG use – all studies and leave one out (Muzyk et al 2012 (b))



Analysis 2.03 Follow up ECG use – all studies and leave two out (Cole et al 2020 and Muzyk et al 2012 (b))

A separate analysis of follow up ECG use (all studies) whilst leaving two out (Cole et al 2020 and Muzyk et al 2012 (b)) involved 6 studies for inclusion in a meta-analysis, including 26,708 patients. The forest plot for this meta-analysis is shown in figure 2.03. The meta-analysis shows that the final pooled proportion of follow up ECG use across all studies without Cole et al 2020 and Muzyk et al 2012 (b) was 32.7% (95% CI 29.1% to 36.5%). Heterogeneity was not statistically significant (p=0.1675) with an I^2 value of 38.3%.

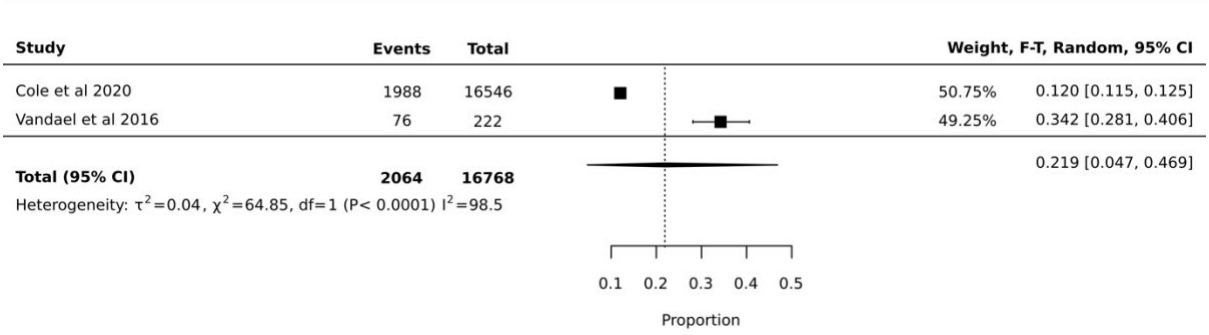
Figure 2.03: Proportional meta-analysis of follow up ECG use – all studies and leave two out (Cole et al 2020 and Muzyk et al 2012 (b))



Analysis 2.04 Follow up ECG use – high quality studies only

A separate analysis of follow up ECG use involving high quality studies only was available from 2 studies for inclusion in a meta-analysis, including 16,768 patients. The forest plot for this meta-analysis is shown in figure 2.04. The meta-analysis shows that the final pooled proportion of follow up ECG use across high quality studies only was 21.9% (95% CI 4.7% to 46.9%). There was statistically significant heterogeneity (p<0.0001) with an I^2 value of 98.5%.

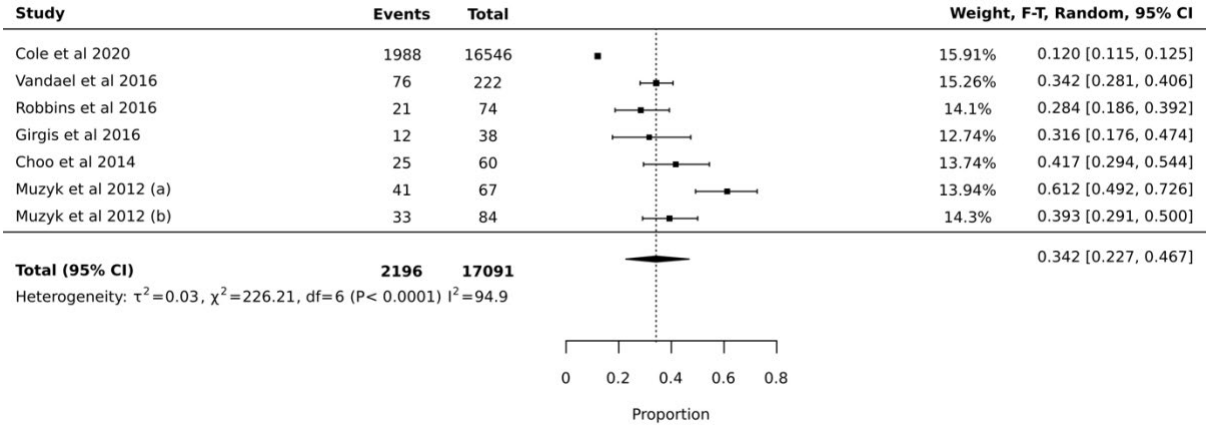
Figure 2.04: Proportional meta-analysis of follow up ECG use – high quality studies only



Analysis 2.05 Follow up ECG use – hospital setting only

A separate analysis of follow up ECG use involving studies of only the hospital setting was available from 6 studies for inclusion in a meta-analysis, including 17,091 patients. The forest plot for this meta-analysis is shown in figure 2.05. The meta-analysis shows that the final pooled proportion of follow up ECG use relating to the hospital setting only was 34.2% (95% CI 22.7% to 46.7%). There was statistically significant heterogeneity (p<0.0001) with an I^2 value of 94.9%.

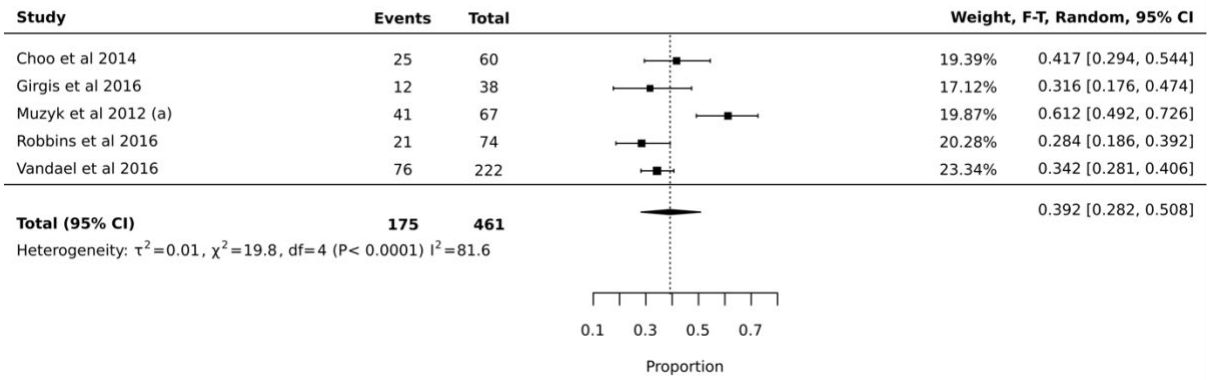
Figure 2.05: Proportional meta-analysis of follow up ECG use – hospital setting only



Analysis 2.06 Follow up ECG use – hospital setting only and leave two out (Cole et al 2020 and Muzyk et al 2012 (b))

A separate analysis of follow up ECG use involving studies of only the hospital setting and whilst leaving two out (Cole et al 2020 and Muzyk et al 2012 (b)) involved 5 studies for inclusion in a meta-analysis, including 461 patients. The forest plot for this meta-analysis is shown in figure 2.06. The meta-analysis shows that the final pooled proportion of follow up ECG use relating to the hospital setting only and whilst leaving two studies out was 39.2% (95% CI 28.2% to 50.8%). There was statistically significant heterogeneity (p<0.0001) with an I^2 value of 81.6%.

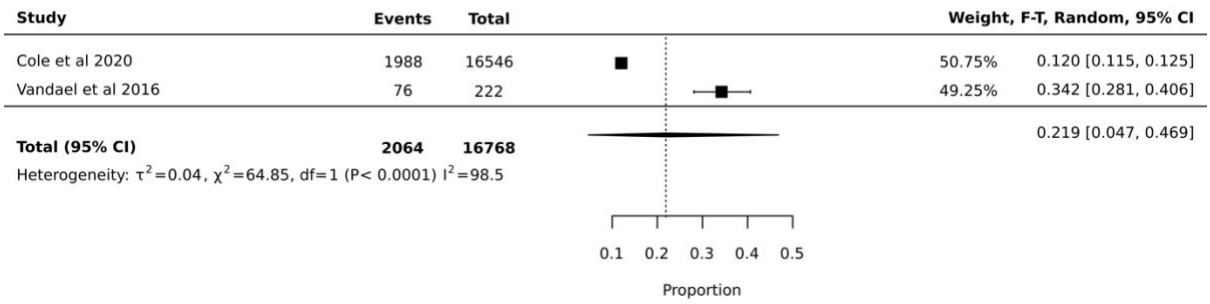
Figure 2.06: Proportional meta-analysis of follow up ECG use – hospital setting only and leave two out (Cole et al 2020 and Muzyk et al 2012 (b))



Analysis 2.06a Follow up ECG use – hospital setting only and high quality studies only

A separate analysis of follow up ECG use involving studies of only the hospital setting and furthermore only the high quality studies was available from 2 studies for inclusion in a meta-analysis, including 16,768 patients. The forest plot for this meta-analysis is shown in figure 2.06a. The meta-analysis shows that the final pooled proportion of follow up ECG use across studies of the hospital setting and also high quality studies only was 21.9% (95% CI 4.7% to 46.9%). There was statistically significant heterogeneity (p<0.0001) with an I^2 value of 98.5%. **This is the same analysis as 2.04.**

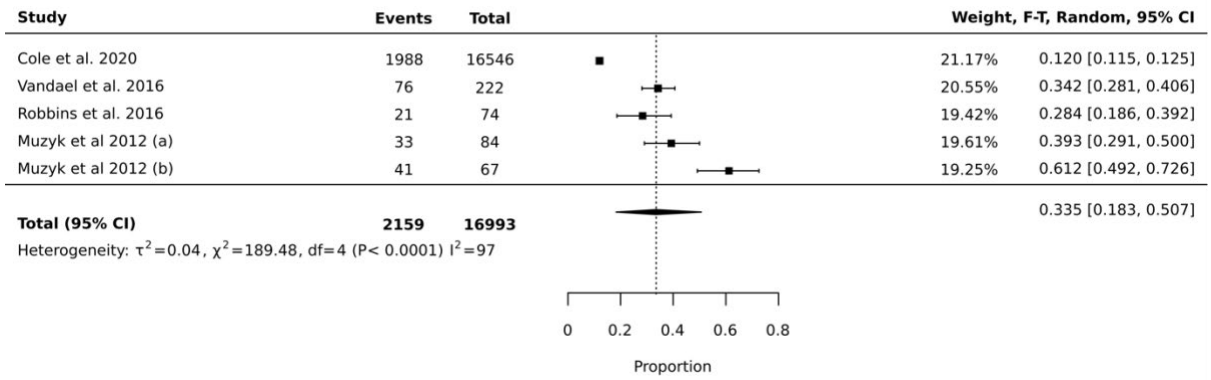
Figure 2.06a: Proportional meta-analysis of follow up ECG use – hospital setting only and high quality studies only



Analysis 2.07 Follow up ECG use - acute use drugs only

A separate analysis of follow up ECG use involving studies of acute use drugs only, involved 4 studies for inclusion in a meta-analysis, including 16,993 patients. The forest plot for this meta-analysis is shown in figure 2.07. The meta-analysis shows that the final pooled proportion of follow up ECG use relating to acute use drugs only was 33.5% (95% CI 18.3% to 50.7%). There was statistically significant heterogeneity (p<0.0001) with an I^2 value of 97%.

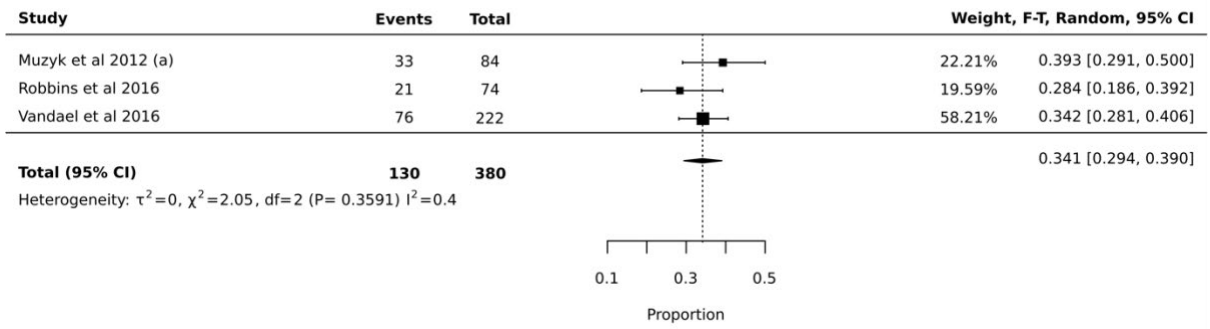
Figure 2.07: Proportional meta-analysis of follow up ECG use - acute use drugs only



Analysis 2.08 Follow up ECG use - acute use drugs only and leave two out (Cole et al 2020 and Muzyk et al 2012 (b))

A separate analysis of follow up ECG use involving studies of acute use drugs only and whilst leaving two out (Cole et al 2020 and Muzyk et al 2012 (b)), involved 3 studies for inclusion in a meta-analysis, including 380 patients. The forest plot for this meta-analysis is shown in figure 2.08. The meta-analysis shows that the final pooled proportion of follow up ECG use relating to acute use drugs only and whilst leaving two studies out was 34.1% (95% CI 29.4% to 39.0%). Heterogeneity was not statistically significant (p=0.3591) with an I^2 value of 0.4%.

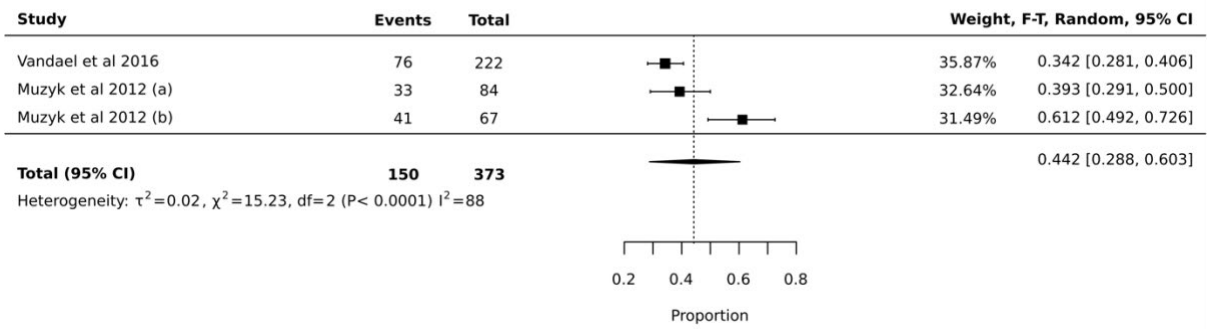
Figure 2.08: Proportional meta-analysis of follow up ECG use - acute use drugs only and leave two out (Cole et al 2020 and Muzyk et al 2012 (b))



Analysis 2.09 Follow up ECG use – haloperidol studies only

A separate analysis of follow up ECG use involving studies of haloperidol only, involved 2 studies for inclusion in a meta-analysis, including 373 patients. The forest plot for this meta-analysis is shown in figure 2.09. The meta-analysis shows that the final pooled proportion of follow up ECG use relating to haloperidol only was 44.2% (95% CI 28.8% to 60.3%). There was statistically significant heterogeneity (p<0.0001) with an I^2 value of 88%.

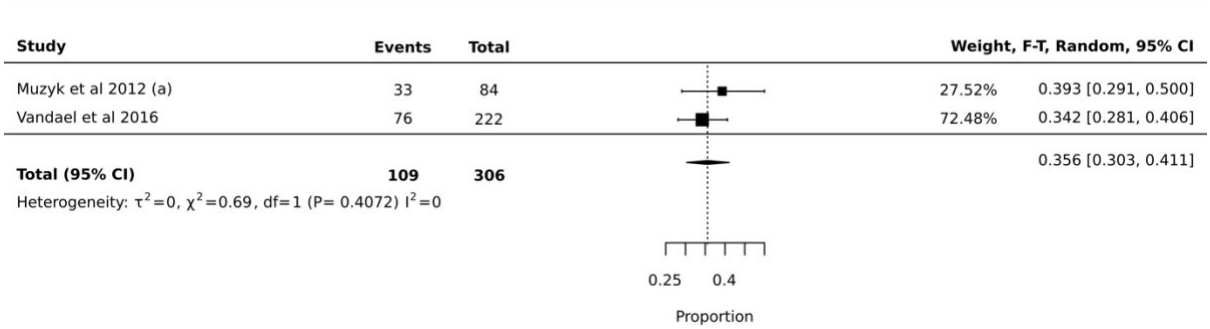
Figure 2.09: Proportional meta-analysis of follow up ECG use – haloperidol studies only



Analysis 2.10 Follow up ECG use – haloperidol studies only and leave one out (Muzyk et al 2012 (b))

A separate analysis of follow up ECG use involving studies of haloperidol only and whilst leaving one study out (Muzyk et al 2012 (b)), involved 2 studies for inclusion in a meta-analysis, including 306 patients. The forest plot for this meta-analysis is shown in figure 2.10. The meta-analysis shows that the final pooled proportion of follow up ECG use relating to haloperidol only and whilst leaving out one study was 35.6% (95% CI 30.3% to 41.1%). Heterogeneity was not statistically significant (p=0.4072) with an I^2 value of 0%.

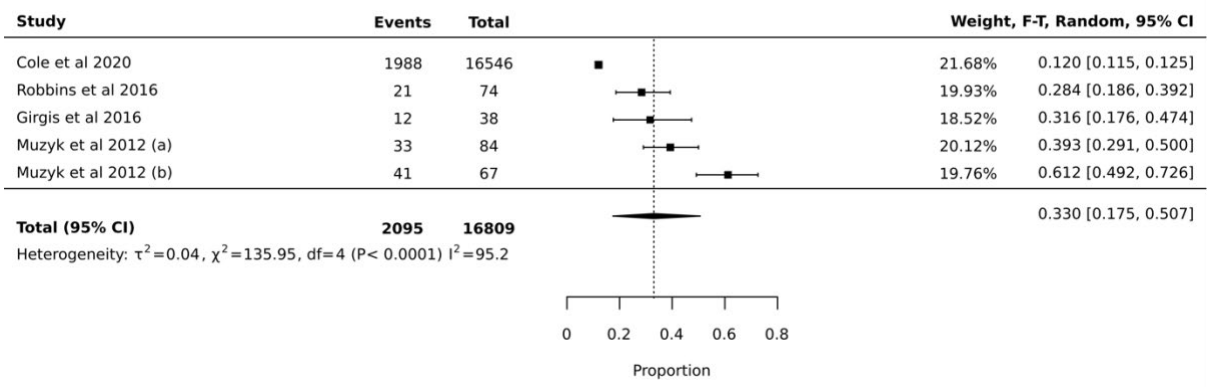
Figure 2.10: Proportional meta-analysis of follow up ECG use – haloperidol studies only and leave one out (Muzyk et al 2012 (b))



Analysis 2.11 Follow up ECG use – USA studies only

A separate analysis of follow up ECG use involving studies conducted in USA only, involved 4 studies for inclusion in a meta-analysis, including 16,809 patients. The forest plot for this meta-analysis is shown in figure 2.11. The meta-analysis shows that the final pooled proportion of follow up ECG use relating to USA only was 33.0% (95% CI 17.5% to 50.7%). There was statistically significant heterogeneity (p<0.0001) with an I^2 value of 95.2%.

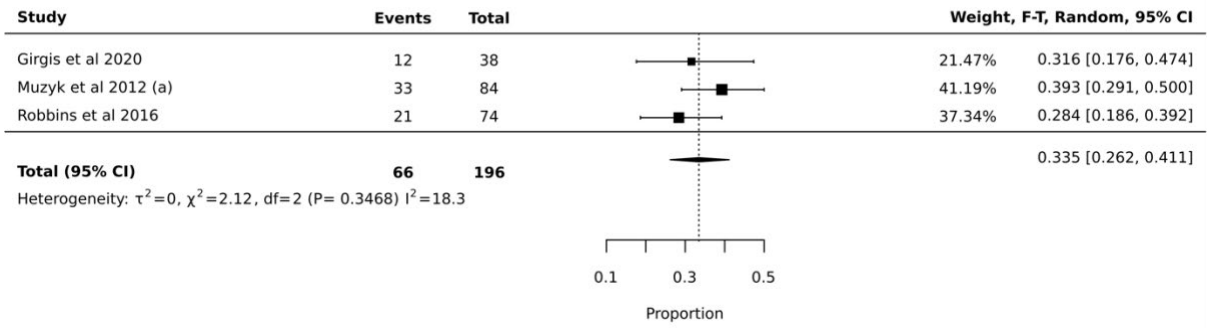
Figure 2.11: Proportional meta-analysis of follow up ECG use – USA studies only



Analysis 2.12 Follow up ECG use – USA studies only and leave two out (Cole et al 2020 and Muzyk et al 2012 (b))

A separate analysis of follow up ECG use involving studies conducted in USA only and whilst leaving two studies out (Cole et al 2020 and Muzyk et al 2012 (b)), involved 3 studies for inclusion in a meta-analysis, including 196 patients. The forest plot for this meta-analysis is shown in figure 2.12. The meta-analysis shows that the final pooled proportion of follow up ECG use relating to USA only and whilst leaving out two studies was 33.5% (95% CI 26.2% to 41.1%). Heterogeneity was not statistically significant (p=0.3468) with an I^2 value of 18.3%.

Figure 2.12: Proportional meta-analysis of follow up ECG use – USA studies only and leave two out (Cole et al 2020 and Muzyk et al 2012 (b))



3) Risk factors and their influence on the use of baseline and / or follow up ECG monitoring

Nine studies in total reported some risk factors in relation to the “first group” - the total cohort of patients on high-risk QT prolonging drugs only and involving patients initiated on high-risk drug therapy only. No study reported on all risk factors, as described by Vandael et al[16] 2017.

No study reported risk factors in relation to the “second group” - the cohort of patients on high-risk QT prolonging drugs only and involving patients initiated on high-risk drug therapy only *and* who had an ECG performed (either baseline and / or follow up).

Pezo et al[30] 2019 did report risk factors for two distinct groups (those on QT prolonging drugs and those on QT prolonging drugs and with ECG performed) however, the reporting of risk factors within the cohort taking QT prolonging drugs in this study included drugs from all risk categories – both high risk and non-high-risk drug therapy, deeming use of their data, relating to risk factors for inclusion into the review, unusable.

The influence of risk factors on the use of ECG monitoring therefore could not be determined in this review, since a comparison of risk factors between these two distinct groups would be required to determine such influence. Due to the complete absence of risk factor data for the “second group” of interest, statistical pooling of prevalence of the risk factors within the “first group,” for which some risk factor prevalence data was available, was not conducted.

For those studies that reported some risk factor data in relation to the “first group,” an overview of the number of risk factors described and the way they were described is presented in Table 3.
The risk factors described most frequently included gender, which was detailed by eight out of nine studies, followed by use of more than one QT interval prolonging drug, which was detailed by six out of nine studies. Serum potassium was detailed by four out of nine studies; however the definition of this risk factor was heterogeneously described including potassium levels unmeasured or unavailable or whether potassium was “abnormal,” “normal” or below 3.5 mmol/L. No studies reported specifically on the use of diuretics. And only three studies out of nine specified patients aged 65 years or above.

Table 3: Overview of risk factors for QT prolongation as described by each study compared to the systematic review by Vandael et al[16] 2017

Risk factors described by Vandael et al 2017[16]	Atayee et al 2017[50]	Ehrenpreis et al 2016[55]	Vandael et al 2016[49]	Robbins et al 2016[48]	Forbes et al 2016[53]	Dunker et al 2016[52]	Macey et al 2013[54]	Cheung et al 2013[51]	Muzyk et al 2012[47]
Hypokalaemia	K values not checked 24 hours prior to methadone start; K (normal value); K (abnormal value)	X	K < 3.5 mmol/L; No potassium value available	X	K level unmeasured or abnormal	X	X	X	Potassium value < 3.5 mmol/L; Subjects lacking a potassium value
Use of diuretics	X	X	X	X	X	X	X	X	X
Age 65 years or above	X	X	X	X	X	Age > 65 years	X	Patients 65 years and older	Age ≥ 65 years
Female gender	Female	Female	Female	Female	X	Male	Male	Female	Female
Tobacco smoking	X	X	Smoking	X	X	X	Nicotine use disorder	X	X
Cardiomyopathy (ischaemic)	X	X	Heart failure; Hypertropic cardiomyopathy	X	LV function depressed (EF <40%)	Heart failure	X	Cardiac disease	X
Hypertension	X	X	Hypertension	X	X	X	X	Cardiac disease	X
Arrhythmia	X	X	Atrial rhythm disturbances; Ventricular rhythm disturbances; Other rhythm disturbances	X	X	Arrythmia	X	Cardiac disease	X
Thyroid disturbances	X	X	Thyroid disturbances	X	X	X	X	X	X
Hypocalcaemia	X	X	X	X	Ca level unmeasured or abnormal	X	X	X	X
Use of more than one QT interval prolonging drug	Major drug interactions (including due to concomitant medications that prolong the QTc)	Co-prescr bed at least one QTP drug	Patients with other drugs with risk of QTc prolongation	X	Concurrent use of other QTP drug(s)	X	X	Taking one or more QTP drugs	Rates of concomitant QTP medications

X= not described

GRADE summary of findings

Table 4: 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 drug therapy Setting – any clinical setting									
11	**1894**	**Observational studies**	**Not serious[a]**	**Very Serious[b]**	**Serious[c]**	**Serious[d]**	**Not serious**	**69%** (56.2% to 80.5%)	VERY LOW ⊕◯◯◯
Proportion of adult patients who get an ECG at baseline of initiation of high-risk QT prolonging drug therapy Setting – hospital setting									
9	**1577**	**Observational studies**	**Not serious[a]**	**Very Serious[b]**	**Serious[c]**	**Not serious**	**Not serious**	**75.1%** (64.3% to 84.5%)	VERY LOW ⊕◯◯◯
Proportion of adult patients who get an ECG at baseline of initiation of high-risk QT prolonging drug therapy Setting – non-hospital setting									
2	**317**	**Observational studies**	**Very serious[e]**	**Serious[f]**	**Serious[g]**	**Serious[h]**	**Not serious**	**33.7%** (25.8% to 42.2%)	VERY LOW ⊕◯◯◯
Proportion of adult patients who get an ECG at follow up of initiation of high-risk QT prolonging drug therapy Setting – any clinical setting									
6	**26,708**	**Observational studies**	**Not serious[i]**	**Serious[f]**	**Not serious**	**Not serious[j]**	**Not serious**	**32.7%** (29.1% to 36.5%)	MODERATE ⊕⊕⊕◯
Proportion of adult patients who get an ECG at follow up of initiation of high-risk QT prolonging drug therapy Setting – hospital setting									
5	**461**	**Observational studies**	**Very Serious[k]**	**Very serious[b]**	**Serious[c]**	**Not serious**	**Not serious**	**39.2%** (28.2% to 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

Explanations

a. Pooled proportions similar following separate analysis excluding poor quality and studies with additional biases Cole et al[46] 2020 / Robbins et al[48] 2016 / Muzyk et al[47] 2012 (b)
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. Mostly includes inpatient hospital settings and only few community settings which are specialised.
e. Small sample size. A poor quality study provides higher weight to pooled proportion.
f. Moderate differences between confidence interval points between studies (moderate point estimate inter-variation). Moderate heterogeneity, however, not statistically significant.
g. Moderately wide confidence interval range within pooled estimate.
h. Non-hospital setting represented by a single community mental health centre and a single specialist community practice only.
i. Pooled proportions similar following separate analysis excluding studies with additional biases Cole et al[46] 2020 and Muzyk et al[47] 2012 (b). The pooled proportion following separate analysis for high quality studies only is limited by the included study with additional bias by Cole et al[46] 2020. Although there is one high quality study, it's point estimate is consistent with the pooled proportion of all studies.
j. Although most studies are conducted in the inpatient hospital setting, Pezo et al[30] 2019 contributes a very large sample size and provides data for drug therapy and ECG use not biased toward any specific healthcare setting, and therefore would likely include drug therapy and ECG use from all clinical settings.
k. Pooled proportions moderately differ following sensitivity analysis excluding poor quality studies. Small sample size. Study with additional bias included in sensitivity analysis provides higher weight to pooled proportion.

Chapter Four: Discussion and conclusions

Summary of findings

Prevalence of baseline ECG monitoring

The prevalence of baseline ECG monitoring for high-risk QT interval prolonging drugs was variable and limited and influenced by factors such as the clinical practice setting and the acute or chronic nature of drug use. Baseline ECG use occurred more frequently in the hospital setting in comparison to the non-hospital setting and occurred more frequently for acute use drugs in comparison to chronic use drugs.

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% to 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% to 84.5%).

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% to 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% to 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, and hence there is poorer utilisation of ECG in this setting. The pooled proportion estimate for the non-hospital setting (2 studies, n =317), was calculated to be 33.7% (CI 95% 25.8% to 42.2%). Heterogeneity was only moderate in this analysis, demonstrated by an I^2 value of 60, however this was not statistically significant (P=0.1138).

The prevalence of baseline ECG use for acute use high-risk QT interval prolonging drugs was high, in comparison to drugs used for chronic indications where prevalence of baseline ECG use was only moderate, demonstrating that baseline ECG monitoring is well utilised for drugs with acute indications.

The overall highest prevalence of baseline ECG monitoring was demonstrated for acute use drugs where three studies with additional biases were excluded (3 studies, n=411), in which the pooled proportion was 85.7% (95% CI 71.2% to 95.8%). This was similar for the prevalence of baseline ECG monitoring for studies specifically only including the acute use drug, haloperidol (3 studies, n=929), in which the pooled proportion was calculated to be 82% (95% CI 67.5% to 93.0%). Heterogeneity of both analyses was considerable and demonstrated by I^2> 90%.

In contrast to acute use drugs, the pooled proportion for high-risk QT interval prolonging drugs where the use was chronic in nature (5 studies, n=547) was calculated to be 44% (CI 95% 33.8% to 54.5%), however the heterogeneity was considerable, demonstrated by an I^2 value of 82.6%. This was similar for the prevalence of baseline ECG monitoring for studies specifically only including the chronic use drug, methadone, (2 studies, n=192), in which the pooled proportion was calculated to be 49.0% (95% CI 40.9% to 57.1%). The heterogeneity was the low for this analysis, demonstrated by an I^2 value of 22.6, however not statistically significant (P=0.2558).

Removing studies with additional biases and / or poor quality studies from analyses of baseline ECG use had small impacts on overall prevalence estimates as demonstrated in the prevalence estimates already described above. This can be further exemplified by the impact of leaving these studies out of the analysis of use of baseline ECG monitoring where all studies where included. The pooled

proportion estimate for the prevalence of baseline ECG monitoring where all 13 studies were included (any clinical setting) (n=18,581) was 68.3% (CI 95% 52.6% to 82.2%).

Removing Cole et al[46] 2020 from this analysis led to a final pooled proportion of 73.1% (95% CI 60.4% to 84.1%), which corrects the prevalence estimate upwards, consistent with baseline ECG monitoring being conducted less than naturally expected in that study as previously outlined. Likewise, by removing Robbins et al[48] 2016 from the analysis led to a final pooled proportion of 64.9% (95% CI 49.6% to 78.8%), which corrects the prevalence estimate downwards, consistent with baseline ECG monitoring being possibly conducted intentionally in that study. By removing Muzyk et al[47] 2012 (b) from the analysis led to a final pooled proportion of 67.5% (95% CI 50.7% to 82.3%), which also corrects the prevalence estimate downwards ever so slightly, to account for a higher prevalence of ECG monitoring on account of active alerts affecting prescriber behaviour in that study.

By removing all three studies with additional biases, the pooled prevalence estimate of baseline ECG monitoring including all other remaining studies (11 studies, n=1894) was 69.0% (95% CI 56.2% to 80.5%), which was largely unaffected from the original analysis including all 13 studies.

Removing poor quality studies from the prevalence of baseline ECG monitoring (where all studies were included) (5 studies, n=17,343), the pooled prevalence estimate was determined to be 55.2% (95% CI 24.3% to 84.0%), only slightly lower compared to the prevalence estimate involving all 13 studies. However, this estimate included the study by Cole et al[46] 2020 which involved additional biases. By further removing Cole et al[46] 2020 from the high quality analysis (4 studies, n=797), the final pooled proportion was determined to be 67.5% (95% CI 42.6% to 88.1%), again similar to the prevalence estimate involving all 13 studies.

The heterogeneity of all the above pooled proportion estimates was considerable, frequently demonstrated by I^2> 95%, and accompanied by very large variation between single point estimates. Confidence intervals of final pooled proportions were wide, likely driven by the large variation in single point estimates.

The prevalence of baseline ECG monitoring in the USA (9 studies, n=17,817) was moderate to high with a pooled proportion estimate of 65.6% (95% CI 45.1% to 83.5%), and hence baseline ECG monitoring seems to be well utilised in the USA. The heterogeneity was considerable, demonstrated by an I^2 value of 99.1%.

Prevalence of follow up ECG monitoring

In comparison to baseline ECG monitoring, utilisation of follow up ECG monitoring was generally poorer. Prevalence of follow up ECG monitoring was consistently low to moderate across a range of factors such as the hospital setting, any clinical setting, acute use drugs and ECG use in the USA. The prevalence of follow up ECG monitoring in the non-hospital setting and for chronic use drugs 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 estimate in the hospital setting (6 studies, n=17,091) was 34.2% (95% CI 22.7% to 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% to 50.8%). The heterogeneity of these pooled proportion estimates was considerable, described by I^2 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% to 46.9%), which was the overall lowest prevalence estimate for use of follow up ECG monitoring. Heterogeneity was considerable in this analysis, demonstrated by I^2= 98.5%. One of the two remaining studies in this analysis involved additional bias not formally recognised in the formal assessment of methodological quality and could not be removed, which would only leave a single study in the analysis, making the analysis infeasible.

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 drug

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% to 44.3%). Heterogeneity was considerable, demonstrated by I^2 99.6%. By removing (two) 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% to 36.5%). 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% to 46.9%) 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.

Removing studies with additional biases and / or poor quality studies from analyses of follow up ECG use had small to medium impacts on overall prevalence estimates, as so far described, and generally consistent with the impacts seen on prevalence estimates for baseline ECG monitoring. This is further exemplified by the impact of the removal of individual studies with additional biases on the pooled proportion estimates of follow up ECG monitoring where all studies (7 studies, n=43,321) where included.

Removing Cole et al[46] 2020 (6 studies, n=26,775) from the analysis (all studies; analysis of any clinical practice setting) led to a final pooled proportion of 37.5% (95% CI 29.8% to 45.6%), which corrected the prevalence estimate slightly upwards. This is consistent with follow up ECG monitoring being conducted less than naturally expected in that study, based on the fact that the drug of interest was not deemed high-risk for most of the study period. Removing Muzyk et al[47] 2012 (b) (7 studies, n=43,254) demonstrated a final pooled proportion of 29.8% (95% CI 21.6% to 38.7%), which corrected the prevalence estimate slightly downwards, relating to higher prevalence of ECG monitoring likely on account of active ECG monitoring alerts affecting prescriber behaviour.

The prevalence of follow up ECG monitoring for acute use drugs (4 studies, n=16,993) was low to moderate, in which the pooled proportion estimate was 33.5% (95% CI 18.3% to 50.7%). The highest overall prevalence of follow up ECG monitoring was demonstrated for studies specifically only including the acute use drug, haloperidol (2 studies, n=373), where the pooled proportion was 44.2% (95% CI 28.8% to 60.3%). Heterogeneity was considerable, demontrated by I^2= 88%. Although after removing a study with additional bias from the analysis of (2 studies, n=306), the prevalence of follow up ECG monitoring was reduced to 35.6% (95% CI 30.3% to 41.4%) and consistent with the pooled proportion estimates from other analyses of follow up ECG monitoring. In this analysis, no heterogeneity was demonstrated by I^2 = 0, although not statistically significant (P=0.4072).

The prevalence of follow up ECG monitoring for studies conducted in the USA (4 studies, n=16,809), was also low to moderate, in which the final pooled proportion was 33.0% (95% CI 17.5% to 50.7%). The heterogeneity of all these above pooled proportion estimates was considerable, frequently demonstrated by I^2> 95%.

Where considerable heterogeneity was demonstrated, very large variation between single point estimates was present, similar to that seen in analyses for the use of baseline ECG monitoring. Confidence intervals of final pooled proportions were wide, likely driven by the large variation in single point estimates.

The influence of risk factors on ECG monitoring

The influence of risk factors on the use of ECG monitoring could not be determined in this review due to a lack of data. Risk factors for QT prolongation in general were sparsely and heterogeneously reported across studies. And although a narrative summary of some risk factors for the cohort of patients taking high-risk QT interval prolonging drugs was determined, very little meaning can be inferred from this information. Any meaningful comparison of risk factors, either quantitative and / or qualitative, would require a comprehensive review of QT prolonging drugs and not only of those initiated for the first time, as in this systematic review.

Limitations

This review has some limitations. A risk of selection bias exists from the screening process conducted by a single reviewer. There is a chance eligible studies may have been missed, especially given the sheer number of records screened. However, reassuringly, screening the reference lists of studies included in the review confirmed many of the same studies that had previously been sought for retrieval but deemed ineligible following review of the full text.

Most studies involved small samples, and furthermore studies often occurred in very specialised practice settings with unique populations, most frequently in hospital settings where there is reliable access to ECG monitoring. There was very limited representation of non-hospital settings; there was no specific representation from community based primary care practices involving general practitioners. The hospital setting was almost exclusively represented by inpatient care, and no specific representation of hospital outpatient clinics.

The large inter-individual diversity in terms of clinical settings, varied study populations, and a wide variety of high-risk drugs studied are possible explanations for the significant heterogeneity seen across most meta-analyses. Heterogeneity is often high in proportional meta-analysis due to differences in the time and place where included studies are conducted and does not always mean that the data is inconsistent.[37] However, in this review high heterogeneity did translate into significant inconsistency and furthermore imprecision of pooled proportion estimates, which impacts on the reliability of results, as reflected in the GRADE assessment. Consequently, average estimates may be of limited clinical use.[37]

Only two studies involved very large samples involving the studies by Cole et al[46] 2020 and Pezo et al[30] 2019. Although Cole et a [46] 2020 was rated as a high-quality study, critical appraisal alone was not sufficient to exclude other important biases, which in this particular study involved the fact that the drug of interest, droperidol, was only recognised as a high-risk drug for a small period of the study, and therefore may have influenced behaviour relating to use of ECG monitoring. According to the review criteria, one of the reasons that the study by Pezo et al [30]2019 was ineligible for high quality status, because it did not specify the exact healthcare location in which drug therapy and / or ECG use occurred. However, the study by Pezo et al[30] 2019 is the predominant reason that risk of bias in the GRADE assessment for the proportion of patients who get an ECG at follow up of initiation of high-risk QT prolonging drug therapy (any clinical setting), was deemed not serious. The study included a very large cohort of patients identified only on their location of residence, which would significantly reduce bias of prescribing of drugs and ECG use based on location of clinical setting, and hence significantly contributed to a moderate confidence rating.

There was very limited reporting on the reason for ECG monitoring, and it can be fair to say that it is unknown if the use of ECG monitoring was related in any way to specifically monitoring the QT interval. Only one study included in the review reported the reasons for use of ECG, and out of the very small cohort, only 4.7% was determined to relate to QT monitoring.[48] Hence, it is quite possible that the use of ECG monitoring for high-risk QT interval prolonging drugs is overestimated. This same sentiment is asserted in the large study by Pezo et al[30] 2019 who suggests the actual number of patients with an ECG performed for drug safety monitoring is likely even lower than reported in their study. Although as Pezo et al[30] 2019 suggests, if an ECG was not performed, then at least it can be concluded that the QT interval was not adequately monitored. And hence if an ECG has been performed, then at least there is the opportunity to review the QT interval. However, this is not a straightforward conclusion, as it has been recognised that clinicians have difficulty in accurately measuring a QT interval, and also clinicians frequently ignore QT prolongation even if it is recognised.[57] The study by Gibbs et al[57] 2017 reported that QT prolongation was only acknowledged in patient medical records in a very low proportion (12%) of cases in which 1541 patients treated in a general community hospital were retrospectively identified with a significantly prolonged QT interval. Whether or not an ECG is conducted in relation to drug safety monitoring of QT interval prolonging drug therapy and furthermore, whether or not the important drug safety parameters of the ECG are accurately measured, recognised or understood require dedicated research and investigation to fully elucidate the likely rich qualitative complexities and barriers and enablers of ECG use for drug safety management.

In this review, the highest prevalence of ECG monitoring, both baseline and follow up seemed to occur with acute use drugs. And there was moderate to high use of baseline ECG monitoring in the

hospital setting, in comparison to baseline ECG monitoring in the non-hospital setting. However, this might be more likely to be related to the higher use of ECG monitoring likely to occur in the investigation of hospitalised patients and those with acute illness requiring acute use drugs, rather than specifically to the drug safety monitoring of high-risk of QT prolonging drugs per se. Hospitalisation itself may provide a high probability of safeguard for ECG monitoring for those commenced on high-risk QT interval prolonging drugs, however this is probably less likely for those that are not hospitalised.

This review focussed on the comparison of ECG use in only the context of two broad clinical settings, hospital and non-hospital setting, rather than specific clinical areas or units. Furthermore, the review did not include use of continuous ECG monitoring. Continuous ECG monitoring and is frequently employed in specialised hospital areas such as the intensive care unit (ICU), cardiac units and emergency departments. Some included studies intentionally excluded areas such as ICU to remove this potentially confounding factor. Whilst none of the studies specifically mentioned use of continuous ECG monitoring, exclusion of this type of ECG monitoring from the review and from observational studies would likely underestimate the use of ECG and QT monitoring. Moreover, both types of information would be important in further strengthening understanding of ECG use trends.

Not all high-risk drugs are equal in their risk of TdP, and in fact incidence of TdP varies greatly from extremely low for most drugs within this classification and is highest for anti-arrhythmic drugs[1, 7] And hence within the class of high-risk drugs, ECG monitoring may be argued to be more or less compelling depending on the specific agents. Although many studies in this review involved specific high-risk drugs, others included any drugs, often unspecified, defined as high-risk. It was not possible to determine the specific representation of high-risk drugs. The prevalence estimates may not be inclusive of all high-risk drugs or at least high-risk drugs are not equally represented, and furthermore may not be generalisable to each specific high-risk drug.

The nature of drug use, either acute or chronic has implications for the importance and need for ECG monitoring. And whilst understanding the duration of therapy would provide the ultimate clarity around the need for ECG testing, this was reported poorly throughout studies, hence the need to devise a method in the review by which to determine acute or chronic drug use by clinical indication. And whilst not the most robust system of definition, the separate analyses of acute or chronic drug use therefore might only offer crude differentiation of the importance of ECG monitoring.

Although separate analysis according to specific drugs was possible for a limited number of drugs (domperidone, methadone, and haloperidol), these analyses are limited both by a small number of studies in each separate analysis and large inter-individual diversity of clinical settings and contexts of use of these drugs. In particular, the prevalence of baseline ECG monitoring for studies specifically only including domperidone involved studies with both chronic use and acute use indications, which may impact on the validity and usefulness of this analysis.

Most studies were conducted in the United States of America (USA), the country from which the prominent ECG monitoring guidelines originated, and furthermore the country which hosts the work of CredibleMeds. This could be a reason why the prevalence of baseline ECG monitoring was moderate to high in the analysis of studies from the USA only. It has been recognised that there are significant international differences in the labelling of QT risks.[28] Furthermore, some drugs with evidence for QT-risk which are in use outside of the USA are not included in CredibleMeds.[28] Without comparative data from other countries, the usefulness of separate analyses based on the country of the study is limited.

Risk factors for drug-induced QT prolongation have been well described and understood since the recognition of long QT syndrome, however the strength of evidence for them has not been well defined until recently. Heterogeneity and sparse reporting of risk factors, as found between studies, from this review are relative to the systematic review published in 2017,[16] which was published after most of the studies included in the review. Lack of data relating to risk factors in relation to patients taking high-risk QT interval prolonging drugs and with an ECG might relate to studies included in the review frequently involving objectives other than seeking to determine the use of ECG monitoring.

There is ongoing debate about whether ECG monitoring is even necessary or the right tool[19] by which to mitigate risk of drug induced QT prolongation. There is concern about the lack of or unknown cost

effectiveness of ECG monitoring,[58, 59] feasibility and practicality of ECG use[8, 12, 17, 19, 21, 60] especially in non-hospital settings, to reduce risk of drug-induced QT prolongation. Furthermore, it is well recognised that there is lack of evidence that ECG screening reduces TdP and associated morbidity and mortality,[20, 59] mostly because the absolute risk of TdP and sudden cardiac death is low[21] and hence studies would need to be exceptionally large to determine this endpoint,[61] and would be difficult to conduct. These issues are highly relevant in understanding the true utility and importance of ECG monitoring in the management of drug-induced QT prolongation. However, consideration of these concepts either in favour or against use of ECG monitoring are beyond the scope of this review.

Strengths

There are several strengths to this review. A comprehensive search of multiple bibliographic databases, involving published and unpublished resources in any language ensured wide capture of the best available evidence on the topic. The use of the GRADE provided clarity on the trustworthiness of the evidence in relation to key outcomes, which enhances the meaning of the results for all end users, including key stakeholders and policy makers for use in evidence transfer. The use of the JBI methodology for systematic reviews of prevalence and incidence was able to transform information about a key risk management strategy in relation to a well-established adverse drug reaction into clinically relevant and operational evidence. This first-of-its kind systematic review provides an important exemplar of the synthesis of evidence that is possible for clinical questions that remain unanswered and under-investigated yet highly pertinent to daily practice decisions and broader healthcare policy. Utilisation of emerging methodological guidance[37] on a relatively modern meta-analytical technique that is proportional meta-analysis ensures reliability and validity of the results.

Alignment of the definition of high-risk drugs with that of the globally recognised, standard resource, CredibleMeds, allowed inclusion of multiple studies that also utilised this common drug classification.

The strict inclusion criteria involving clear time periods and definitions for baseline ECG and / or follow up ECG aimed to target ECG performed for the purposes of drug safety management. These time periods are clear and explicit for drugs when initiated, which can be more easily identified in practice and in the design and methods of studies, in contrast to ECG monitoring for continuing or long-term drug therapy. Many studies reporting ECG use in relation to drug therapy were excluded because they did not specify the relationship of an ECG relative to baseline or follow up, but rather only reported if any ECG was performed.

High-risk drugs have compelling evidence for risk of TdP and ECG monitoring remains unequivocally recommended for their use. Therefore, a review involving high-risk QT interval prolonging drugs provides a clear-cut, strong rationale for determining ECG use prevalence estimates. The prevalence of ECG use for high-risk QT interval prolonging drugs may be a fair benchmark for the prevalence of ECG use for other non-high-risk QT interval prolonging drugs, in which case ECG monitoring is less compelling, but still useful.

Future directions

The focus of this review was to determine the prevalence of ECG monitoring in relation to high-risk QT interval prolonging drugs, to aid in the understanding of the likely true utilisation of this risk management strategy in real-world clinical practice. Although the reliability of the evidence seems to be low for most results relating to the prevalence of baseline and follow up ECG monitoring, it seems that the evidence for low prevalence of use of follow up ECG monitoring, in any clinical setting, is moderately reliable and may accurately reflect the state of practice. To improve the reliability and improve the strength of evidence of most of the reported prevalence estimates relating to both baseline and follow up ECG monitoring, larger and well conducted studies, in a greater variety of clinical settings, across a wider variety of countries, are necessary. Furthermore, studies are needed to be conducted with clear reporting and distinction of included drugs, clearly articulated timeframes for ECGs in relation to drug therapy, and clear reporting of reasons for ECG use.

This review gives prominence to the lack of policy, research, and evidence for use of ECG monitoring in non-hospital settings. The prescribing of QT interval prolonging drugs is reported to have doubled, if not more, in recent times,[28] and it is highly likely that the use of these drugs is not limited to use in the hospital, and hence their management will occur in all care settings. Several studies report that

prescription of QT prolonging drugs is common in outpatient settings.[62, 63] A study reported that 60% of patients who developed long QT syndrome were treated on an outpatient basis.[64] It is well recognised that the use of QT prolonging drugs in other non-hospital settings such as community based primary care practice and residential care facilities is common[65] and certainly there is an absence of informed evidence on the topic of risk assessment and mitigation strategies in this population.[17]

Use of follow up ECG monitoring may be relatively more important for chronic use drugs in comparison to acute use drugs, however data was lacking for follow up ECG monitoring for chronic use drugs, for which further research is needed.

Low use of ECG monitoring has the potential to expose patients to possible risk of QT prolongation, which if unchecked, may place patients at unnecessary risk of fatal outcomes. And although prominent guidelines already exist to include the need for such monitoring, it appears these are not being translated into practice. It is critical to understand both local and broader reasons for lack of implementation of practice standards, including health-system resourcing, access to and ease of ECG monitoring and clinician skill and expertise on the topic of drug-induced QT prolongation and ECG interpretation. And whilst additional quantitative research is required to improve reliability of prevalence data, qualitative data is critical to fully explore and understand all the complexities that exist in relation to ECG use of QT interval prolonging drugs in clinical practice. ECG use could be considered a crude surrogate marker of clinician awareness of drug therapy with the potential to prolong the QT interval, however specific qualitative studies would add beneficial perspective on this matter. 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 drugs.

Multiple approaches to improving implementation of risk management strategies are likely needed to improve use of ECG monitoring and risk mitigation of drug-induced QT prolongation in clinical practice.

Improving clinicians' awareness of the vast number of drugs with the potential to cause QT prolongation, the vast number of associated risk factors and the complex risk assessment and risk management strategies involved, continues to be a challenging prospect. There seems to be lack of reporting of awareness or use of reliable drug information resources on the topic of drug-induced QT prolongation in the literature. Simply improving awareness of and access to drug information resources in everyday practice could possibly be a key strategy in improving clinicians' awareness and warrants research.

There is great potential for digital technologies to be leveraged to improve the management of drug-induced QT prolongation. These include improved access to, or even integration of, reliable online information resources into electronic medical records, through to use of more sophisticated clinical decision support tools and related alert systems. Although it is well recognised that most existing digital technologies, such as alert systems and clinical decision support tools, have various limitations[17, 18, 61, 66] and require ongoing development and refinement to optimise their impact on patient health outcomes. Alternative clinical information management systems such as data driven drug-induced QT prolongation surveillance using adverse reaction signals derived from electrocardiogram data[67] are only just emerging and may hold important solutions to improve drug safety management at the point of care. Certainly, with the increased use of electronic medical records, increased availability of electronic health data and the increasing appreciation of clinical informatics within the healthcare system likely means targeted and effective solutions for improved drug safety management are more likely to be developed. The use of clinical information management systems have the potential to significantly streamline clinical decision making relating to complex risk assessment and risk management processes, such as those involved in the use of QT interval prolonging drugs, to assist delivery of patient care.

Simpler and more accessible methods to monitor QT, rather than utilising ECG, have been suggested as a solution for improved use of risk management tools, particularly in non-hospital settings. Potential use of remote wearable monitoring devices have been explored[12, 17, 68] but remain immature and unvalidated in the context of drug-induced QT prolongation. Further development of remote monitoring for drug safety management is needed to determine their usefulness and feasibility in practice, which is likely to be supported by determining evidence for mortality, morbidity and cost

effectiveness endpoints in relation to standard ECG monitoring in the first instance and further reinforced by improved consumer and clinician awareness of drug safety benefits.

Concluding statement

Drug-induced QT prolongation is a potentially fatal adverse drug reaction. ECG monitoring is a key tool in reducing the risk of patient harm associated with this serious adverse drug reaction.

This quantitative systematic review summarises the proportion or prevalence of adult patients taking high-risk QT interval prolonging drugs in real-world clinical practice that have an ECG performed at baseline and follow up. The results show that the use of ECG monitoring in these circumstances is variable and limited, and is influenced by factors such as the type of clinical practice setting and acute or chronic nature of drug use. Furthermore, there seems to be limited use of follow up ECG monitoring in comparison to baseline ECG monitoring. Most prevalence estimates are based on weak evidence, and much more quantitative research on this topic is needed to strengthen the reliability of results, especially in the non-hospital setting.

There are multiple facets of complexity in the use of ECG monitoring in relation to drug safety and management, including the feasibility of ECG use and clinician awareness of QT interval prolonging potential of drugs, which prevalence estimates by themselves do not definitively describe. Qualitative research would be beneficial to fully explore the role of each of the elements involved in the complex clinical decision-making process of high-risk QT interval prolonging drug use, and furthermore on the use of risk management strategies including ECG monitoring.

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Chapter Six: Appendices

Appendix I – Search strategy

CINAHL (EBSCO)
Search date: January 28, 2021

Search #	Search terms	Results
1	(MH "Long QT Syndrome") OR (MH "Torsades de Pointes") OR QT OR torsade*	7,097
2	(MH "Drugs+") OR (MH "Adverse Drug Event+") OR medication* OR drug* OR adverse OR side effect* OR prescri*	1,416,569
3	(MH "Electrocardiography") OR electrocardiog* OR ECG OR ECGs OR EKG OR EKGs OR cardiac monitor*	64,243
4	1 AND 2 AND 3	1,984
5	4 Limit from 2004 to current	**1,589**

Cochrane Library
Search date: February 4, 2021

Search #	Search terms	Results
1	MeSH descriptor: [Long QT Syndrome] this term only OR MeSH descriptor: [Torsades de Pointes] this term only OR QT OR torsade*	3,970
2	MeSH descriptor: [Drug-Related Side Effects and Adverse Reactions] this term only OR medication* OR drug* OR adverse OR “side effect*” OR prescri*	768,826
3	Electrocardiog* OR ECG* OR EKG* OR “cardiac monitor*” OR “cardiac function monitor*”	30,810
4	1 AND 2 AND 3	1,862
5	Limits 4 with Cochrane Library publication date Jan 2004 – Feb 2021	**1,481**

EMBASE (Ovid)
Search date: February 4, 2021

Search #	Search terms	Results
1	Long QT syndrome/ OR QT prolongation/ OR QT.ti OR QT.ab OR torsade des pointes/ OR torsade$.ti OR torsade$.ab	49,732
2	Drug therapy/ OR prescription/ OR prescription drug/ OR medication$.ti OR medication$.ab OR drug$.ti OR drug$.ab OR adverse drug reaction/ OR adverse.ti OR adverse.ab OR side effect$.ti OR side effect$.ab OR prescri$.ti OR prescri$.ab	4,174,638
3	Exp electrocardiography/ OR electrocardiogram/ OR ECG.ti OR ECGs.ti OR ECG.ab OR ECGs.ab OR EKG.ti OR EKGs.ti OR EKG.ab OR EKGs.ab OR cardiac monitor$.ti OR cardiac monitor$.ab OR cardiac function monitor$.ti OR cardiac function monitor$.ab	306,672
4	1 AND 2 AND 3	7004
5	Limit 4 to yr=“2004-Current”	5590
6	Limit 5 to Records From Embase or MEDLINE **[Records From Conference Abstracts not included]**	**3498**

MEDLINE (PubMed)
Search date: 28 January 2021

Search #	Search terms	Results
1	QT[tiab] OR torsade*[tiab] OR "torsades de pointes"[mh] OR "long QT syndrome"[mh]	25,755
2	medication*[tiab] OR drug*[tiab] OR "drug-related side effects and adverse reactions"[mh] OR adverse[tiab] OR side effect*[tiab] OR "prescriptions"[mh] OR prescri*[tiab]	2,671,259
3	"electrocardiography"[mh] OR electrocardiog*[tiab] OR ECGs[tiab] OR ECG[tiab] OR EKG[tiab] OR EKGs[tiab] OR cardiac monitor*[tiab] OR cardiac function monitor*[tiab]	260,125
4	1 AND 2 AND 3	4,627
5	4 Filters: from 2004 – current	**3,100**

ProQuest Dissertations and Theses Global
Search date: February 4, 2021

Search #	Search terms	Results
1	Exact("Long-qt syndrome" OR "Drug-induced QT-prolongation" OR "Long QT Syndrome" OR "Long QT" OR "Long qt" OR "QT interval prolongation" OR "Long-QT syndrome" OR "Torsades" OR "Qt-prolongation" OR "Long QT Sydrome" OR "Torsades de Pointe" OR "Torsades de Pointes" OR "Acquired long QT syndrome" OR "QT prolongation" OR "Long QT interval" OR "Torsades de pointes" OR "Long QT syndrome" OR "Qt prolongation" OR "Long qt syndrome" OR "long QT syndromes") **OR** (AB,TI,SU (QT OR torsade? OR “QT prolongation” OR “long QT”))	19,307
2	(AB,TI,SU (medication? OR drug? OR prescription? OR prescri* OR adverse OR “side effect?”)) **OR** Exact("Drug-Related Side Effects and Adverse Reactions") **OR** Exact("Drug therapy management" OR "drug therapy" OR "Drug Therapy" OR "Drug therapy")	61,001
3	(AB,TI,SU (“ECG monitoring” OR ECG? OR EKG? OR electrocardiog* OR "cardiac monitor?" OR "cardiac function monitor?")) **OR** Exact("cardiac monitoring" OR "Cardiac monitoring") **OR** Exact("12-lead electrocardiography" OR "Electrocardiography [ECG]" OR "Electrocardiography (ecg)" OR "Electrocardiography" OR "Twelve-lead electrocardiography" OR "electrocardiography") **OR** Exact("electrocardiograms" OR "12-lead electrocardiogram" OR "electrocardiogram" OR "Electrocardiogram ecg" OR "Portable electrocardiogram" OR "Electrocardiograms" OR "Electrocardiogram" OR "Electrocardiogram(ECG)" OR "Prehospital electrocardiogram" OR "Electrocardiogram (ECG)" OR "Electrocardiogram (ecg)")	3,079
4	1 AND 2 AND 3	453
5	4 Limit to Publication date from 01-01-2004 to current	**200**

EThOS
Search date: February 4, 2021

Advanced search

Search	Search terms	Results
	Long QT (any word) OR QT prolongation (any word) OR torsade (any word)	38

OpenGrey
Search date: February 4, 2021

Search	Search terms	Results
	(“long QT” OR “QT prolongation” OR torsade*) AND (drug* OR medication* OR adverse OR "side effect*" OR prescri*) AND (ECG* OR EKG* OR electrocardiog* OR “cardiac monitor*” OR “cardiac function monitor*”)	9

Appendix II – Data extraction instrument

Study details

Reviewer ID:

Study ID:

Date of data extraction:

Authors:

Study title:

Journal:

Publication year:

Country of study:

Study method

Aim of study:

Setting/context:

Study design:

Time frame of study:

Sample size:

Drug(s) studied:

AZCERT classification of drug(s) studied at the time of study:

Clinical context of drug use and / or clinical indications for drug use in the study and corresponding proportions:

Baseline ECG Y/N:

Time (day) of baseline ECG, relative to day 0 (initiation of drug):

Follow up ECG Y/N:

Time (day) of follow up ECG, relative to day 0 (initiation of drug):

Any additional ECG details (eg. number of ECG leads, etc):

Reason(s) for baseline and / or follow up ECG:

Characteristics (age and risk factors: hypokalaemia, diuretics, age ≥ 65 years, female gender, tobacco smoking, (ischaemic) cardiomyopathy, hypertension, cardiac arrhythmia, thyroid disturbances, hypocalcaemia, use of more than one QT interval prolonging drug (including both high risk and non-high risk QT prolonging drugs)) of study populations of interest as relating to:

- the total cohort of patients on high-risk QT prolonging drugs only
- the cohort of patients on high-risk QT prolonging drugs only *and* who had an ECG performed (either baseline and / or follow up)
- narrative description of how age and risk factors were reported in each study

Results

Numerator (n), denominator (N) and proportion / prevalence (%) of patients taking high-risk drug with ECG at baseline

Numerator (n), denominator (N) and proportion / prevalence (%) of patients taking high-risk drug with ECG at follow up

Numerator (n), denominator (N) and proportions (%) of each characteristic (age and risk factors) relating to the total cohort of patients on high-risk QT prolonging drugs only

Numerator (n), denominator (N) and proportions (%) of each characteristic (age and risk factors) relating to the cohort of patients on high-risk QT prolonging drugs only and who had an ECG performed (either baseline and / or follow up)

Authors comments:

Reviewer comments:

Appendix III – Studies excluded on full text

Reasons for exclusion are provided for 74 studies (including 4 studies which could not be located). Studies are presented in order of year published, from most recent.

Berger, F.A., et al., *Comparison of two algorithms to support medication surveillance for drug-drug interactions between QTc-prolonging drugs.* International Journal of Medical Informatics, 2021. **145**: p. 104329.

Reason for exclusion: No relevant ECG use data - ECG use not in relation to (single) high risk drug at follow up.

Dela Cruz, M., M. Ershad, and A. Mostafa, *QTc interval prolongation associated with inpatient azithromycin therapy for pneumonia.* J Am Osteopath Assoc, 2021. **121**(1): p. 5-9.

Reason for exclusion: Could not locate.

Soghomonyan, S., et al., *PONV management in patients with QTc prolongation on the EKG.* Frontiers in Pharmacology, 2020. **11**: p. 565704.

Reason for exclusion: No relevant ECG use data.

Monzani, A., et al., *QTc evaluation in COVID-19 patients treated with chloroquine/hydroxychloroquine.* Eur J Clin Invest, 2020. **50**(6): p. e13258.

Reason for exclusion: No relevant ECG use data

Jain, S., et al., *ENHANCED ECG MONITORING OF COVID-19 PATIENTS.* Heart rhythm, 2020.

Reason for exclusion: No relevant ECG use data - ECG use data not in relation to high-risk drugs at baseline / follow-up.

Cruz, M.D., M. Ershad, and A. Mostafa, *QTc Interval Prolongation Associated With Inpatient Azithromycin Therapy for Pneumonia.* The Journal of the American Osteopathic Association, 2020.

Reason for exclusion: Duplicate and previously excluded.

Castro, E., et al., *Should we still monitor QTc duration in frail older patients on low-dose haloperidol? A prospective observational cohort study.* Age & Ageing, 2020. **49**(5): p. 829-836.

Reason for exclusion: ECGs conducted intentionally.

Field, J., et al., *Effect of Chronic Domperidone Use on QT Interval: A Large Single Center Study.* Journal of Clinical Gastroenterology, 2019. **53**(9): p. 648-652.

Reason for exclusion: Baseline and / or follow up ECG do not match protocol definition - Patients included only if baseline ECG and at least one follow up ECG available.

Shao, W., et al., *QTc Prolongation Associated with Psychiatric Medications: A Retrospective Cross-Sectional Study of Adult Inpatients.* Journal of Clinical Psychopharmacology, 2019. **39**(1): p. 72-77.

Reason for exclusion: ECG use data not in relation to initiation of drug therapy or initiation not clearly reported - drugs initiated versus stable treatment not reported; and follow up ECGs not clearly reported; and baseline ECGs conducted intentionally.

Petry, N., et al., *CYP2C19 genotype, physician prescribing pattern, and risk for long QT on serotonin selective reuptake inhibitors.* Pharmacogenomics, 2019. **20**(5): p. 343-351.

Reason for exclusion: No relevant ECG use data - ECG data not in relation to baseline and / or follow up.

Ansermot, N., et al., *Prevalence of ECG abnormalities and risk factors for QTc interval prolongation in hospitalized psychiatric patients.* Therapeutic Advances in Psychopharmacology, 2019. **9**.

Reason for exclusion: High risk drugs not studied or drugs do not match protocol definition - ECG data not in relation to high risk drugs and / or baseline and / or follow up.

Daniel, N.M., et al., *Implementation of a QTc-interval monitoring protocol by pharmacists to decrease cardiac risk in at-risk patients in an acute care inpatient psychiatric facility.* Ment Health Clin, 2019. **9**(2): p. 82-87.

Reason for exclusion: ECG use data not in relation to initiation of drug therapy or initiation not clearly reported - ECG data not in relation to initiation of drug; and drugs studied do not match protocol criteria.

Rhew, K., N. Han, and J.M. Oh, *Impact of Safety Warning on Domperidone Prescribing for Geriatric Patients in South Korea: Analysis of National Insurance Claim Data.* Int J Environ Res Public Health, 2019. **16**(16).

Reason for exclusion: ECG use data not in relation to initiation of drug therapy or initiation not clearly reported - drugs initiated versus stable treatment not reported with regard to ECG data; and ECG data combined in one single measure to include both baseline and follow up.

Heemskerk, C.P.M., et al., *Risk factors for QTc interval prolongation.* European Journal of Clinical Pharmacology, 2018. **74**(2): p. 183-191.

Reason for exclusion: High risk drugs not studied or drugs do not match protocol definition - ECG data not in relation to high risk drugs and baseline and / or follow up.

Gerlach, L.B., et al., *Electrocardiogram Monitoring After the Food and Drug Administration Warnings for Citalopram: Unheeded Alerts?* Journal of the American Geriatrics Society, 2018. **66**(8): p. 1562-1566.

Reason for exclusion: No relevant ECG use data - ECG data not in relation to baseline and / or follow up.

Choi, Y., et al., *Risk evaluation of azithromycin-induced QT prolongation in real-world practice.* BioMed Research International, 2018. **2018**: p. 1574806.

Reason for exclusion: No relevant ECG use data - ECG data not in relation to baseline and / or follow up.

Chaudhary, Z. and B. Ramaiah, *Assessment of drug induced QT interval prolongation at a tertiary care, Baptist Hospital, Bangalore.* Pakistan Journal of Medical and Health Sciences, 2018. **12**(4): p. 1871-1874.

Reason for exclusion: High risk drugs not studied or drugs do not match protocol definition - ECG data not in relation to high risk drugs and / or baseline and / or follow up.

Berling, I., et al., *A review of ECG and QT interval measurement use in a public psychiatric inpatient setting.* Australasian Psychiatry, 2018. **26**(1): p. 50-55.

Reason for exclusion: No relevant ECG use data - ECG data not in relation to baseline and / or follow up.

Berger, F., et al., *Media attention regarding sudden cardiac death associated with domperidone use does not affect in hospital ECG recording.* Pharmacoepidemiol Drug Saf, 2017. **26**(11): p. 1418-1424.

Reason for exclusion: ECG data relates not only to adults (includes children).

Vandael, E., et al., *Incidence of Torsade de Pointes in a tertiary hospital population.* International Journal of Cardiology, 2017. **243**: p. 511-515.

Reason for exclusion: No relevant ECG use data - ECG data not in relation to baseline and / or follow up.

Gerlach, L.B., et al., *Unintended Consequences of Adjusting Citalopram Prescriptions Following the 2011 FDA Warning.* American Journal of Geriatric Psychiatry, 2017. **25**(4): p. 407-414.

Reason for exclusion: No relevant ECG use data - ECG data not in relation to baseline and / or follow up.

Bart, G., et al., *Methadone and the QTc Interval: Paucity of Clinically Significant Factors in a Retrospective Cohort.* Journal of Addiction Medicine, 2017. **11**(6): p. 489-493.

Reason for exclusion: No relevant ECG use data - ECG data not in relation to baseline and / or follow up.

Sharma, S., et al., *Providers' Response to Clinical Decision Support for QT Prolonging Drugs.* Journal of Medical Systems, 2017. **41**(10): p. 1-8.

Reason for exclusion: High risk drugs not studied or drugs do not match protocol definition - drugs studied do not match protocol criteria; and ECG data not in relation to baseline and / or follow up

Westermeyer, J., et al., *Long QTc During Methadone Maintenance: Contributors and Interventions Over 4 Years.* J Nerv Ment Dis, 2017. **205**(12): p. 925-930.

Reason for exclusion: No relevant ECG use data - ECG data not in relation to baseline and / or follow up.

Lee, R.A., et al., *Evaluation of baseline corrected QT interval and azithromycin prescriptions in an academic medical center.* Journal of Hospital Medicine, 2016. **11**(1): p. 15-20.

Reason for exclusion: ECG use data not in relation to initiation of drug therapy or initiation not clearly reported - Initiated versus stable treatment not differentiated.

Nicholson, T.T., et al., *Assessing potential risks of treatment with long-term azithromycin in COPD patients: long-term oxygen users beware?* Irish Journal of Medical Science, 2016. **185**(4): p. 993-997.

Reason for exclusion: ECG use data not in relation to initiation of drug therapy or initiation not clearly reported - ECG data not in relation to initiation of high-risk drug and / or baseline and / or follow up.

Niedrig, D., et al., *Drug safety of macrolide and quinolone antibiotics in a tertiary care hospital: administration of interacting co-medication and QT prolongation.* European Journal of Clinical Pharmacology, 2016. **72**(7): p. 859-867.

Reason for exclusion: No relevant ECG use data - ECG use not in relation to (single) high risk drug at baseline.

Dixon, D.L., et al., *Effectiveness of Pharmacist-Led Amiodarone Monitoring Services on Improving Adherence to Amiodarone Monitoring Recommendations: A Systematic Review.* Pharmacotherapy, 2016. **36**(2): p. 230-236.

Reason for exclusion: Qualitative information only; and no relevant ECG use data.

Tricco, A.C., et al., *Interventions to decrease the risk of adverse cardiac events for patients receiving chemotherapy and serotonin (5-HT3) receptor antagonists: A systematic review.* BMC Pharmacology and Toxicology, 2015. **16**(1): p. 1.

Reason for exclusion: ECG conducted intentionally - ECG performed intentionally in all patients included.

Maljuric, N.M., et al., *Use of selective serotonin re-uptake inhibitors and the heart rate corrected QT interval in a real-life setting: The population-based Rotterdam Study.* British Journal of Clinical Pharmacology, 2015. **80**(4): p. 698-705.

Reason for exclusion: No relevant ECG use data - ECG data not in relation to baseline and / or follow up.

Kram, B.L., S.J. Kram, and K.R. Brooks, *Implications of atypical antipsychotic prescribing in the intensive care unit.* Journal of Critical Care, 2015. **30**(4): p. 814-818.

Reason for exclusion: High risk drugs not studied or drugs do not match protocol definition - high risk drugs not studied.

Calver, L., et al., *The Safety and Effectiveness of Droperidol for Sedation of Acute Behavioral Disturbance in the Emergency Department.* Annals of Emergency Medicine, 2015. **66**(3): p. 230-238.

Reason for exclusion: ECG conducted intentionally - follow up ECG conducted intentionally; and baseline ECG not studied.

Warnier, M.J., et al., *Are ECG monitoring recommendations before prescription of QT-prolonging drugs applied in daily practice? The example of haloperidol.* Pharmacoepidemiology and Drug Safety, 2015. **24**(7): p. 701-708.

Reason for exclusion: Baseline and / or follow up ECG do not match protocol definition - ECG data combined into a single measure for both baseline and follow up and does not match protocol definition.

Vandael, E., et al., *Frequency of use of QT-interval prolonging drugs in psychiatry in Belgium.* International Journal of Clinical Pharmacy, 2014. **36**(4): p. 757-765.

Reason for exclusion: Qualitative information only - qualitative summary of ECG monitoring for QT interval prolonging drugs provided only.

Jardin, C.G., D. Putney, and S. Michaud, *Assessment of drug-induced torsade de pointes risk for hospitalized high-risk patients receiving QT-prolonging agents.* Ann Pharmacother, 2014. **48**(2): p. 196-202.

Reason for exclusion: ECG use data not in relation to initiation of drug therapy or initiation not clearly reported - ECG data not in relation to initiation of high-risk drug.

Tisdale, J.E., et al., *Effectiveness of a clinical decision support system for reducing the risk of qt interval prolongation in hospitalized patients.* Circulation: Cardiovascular Quality and Outcomes, 2014. **7**(3): p. 381-390.

Reason for exclusion: ECG conducted intentionally - all patients underwent baseline ECG (intervention phase) and continuous cardiac telemetry.

Tay, K.Y., M.B. Ewald, and F.T. Bourgeois, *Use of QT-prolonging medications in US emergency departments, 1995-2009.* Pharmacoepidemiology and Drug Safety, 2014. **23**(1): p. 9-17.

Reason for exclusion: No relevant ECG use data - ECG data not in relation to baseline and / or follow up.

Sendelbach, S., et al., *A Computer-Assisted Electrocardiography Measurement Intervention Improves QTc Documentation in Hospital Patients Receiving QT-Prolonging Drugs.* American Journal of Critical Care, 2014. **23**(3): p. e27-8.

Reason for exclusion: Baseline and / or follow up ECG do not match protocol definition - patients excluded from study if ECG not performed.

Price, L.C., et al., *Methadone for pain and the risk of adverse cardiac outcomes.* Journal of Pain and Symptom Management, 2014. **48**(3): p. 333.

Reason for exclusion: Baseline and / or follow up ECG do not match protocol definition - ECG data do not match protocol criteria for baseline / follow up.

Katz, D.F., et al., *QTc interval screening in an opioid treatment program.* American Journal of Cardiology, 2013. **112**(7): p. 1013-1018.

Reason for exclusion: ECGs conducted intentionally.

van den Beuken-van Everdingen, M.H.J., J.W. Geurts, and J. Patijn, *Prolonged QT interval by methadone: relevance for daily practice? A prospective study in patients with cancer and noncancer pain.* Journal of Opioid Management, 2013. **9**(4): p. 263-267.

Reason for exclusion: No relevant ECG use data - ECG data not in relation to baseline and / or follow up.

Tricco, A.C., et al., *Interventions to decrease the risk of adverse cardiac events for post-surgery or chemotherapy patients taking serotonin (5-HT3) receptor antagonists: protocol for a systematic review and network meta-analysis.* Syst Rev, 2013. **2**: p. 45.

Reason for exclusion: No relevant ECG use data - protocol only of a systematic review.

Thase, M.E., et al., *The cardiovascular safety profile of escitalopram.* European Neuropsychopharmacology, 2013. **23**(11): p. 1391-1400.

Reason for exclusion: ECGs conducted intentionally - baseline and follow up ECG performed intentionally in all patients included.

Patel, N., et al., *Frequency of electrocardiogram testing among HIV-infected patients at risk for medication-induced QTc prolongation.* HIV Med, 2013. **14**(8): p. 463-71.

Reason for exclusion: No relevant ECG use data - ECG data not in relation to baseline and / or follow up.

Pani, P.P., et al., *QTc interval screening for cardiac risk in methadone treatment of opioid dependence.* Cochrane Database of Systematic Reviews, 2013. **2013**(6): p. CD008939.

Reason for exclusion: No relevant ECG use data - no ECG use data.

Linzer, M., et al., *Electrocardiographic abnormalities as potential contributors to premature mortality in patients with mental illness in a psychiatric day treatment program.* Primary Care Companion to the Journal of Clinical Psychiatry, 2013. **15**(3).

Reason for exclusion: No relevant ECG use data - ECG data not in relation to QT-interval prolonging drugs.

Haugaa, K.H., et al., *Institution-wide QT alert system identifies patients with a high risk of mortality.* Mayo Clinic Proceedings, 2013. **88**(4): p. 315-325.

Reason for exclusion: No relevant ECG use data - ECG data not in relation to QT-interval prolonging drugs and / or baseline and / or follow up.

Cunnington, A.L., K. Hood, and L. White, *Outcomes of screening Parkinson's patients for QTc prolongation.* Parkinsonism and Related Disorders, 2013. **19**(11): p. 1000-1003.

Reason for exclusion: No relevant ECG use data - ECG data not in relation to baseline and / or follow up.

Beysens, M., *Quel suivi cardiométabolique des patients traités par antipsychotiques ? (enquête auprès des généralistes et des psychiatres du Poitou-Charentes)*. Thesis in French. 2012, University of Poitiers, France. 1 vol., p. 155

Reason for exclusion: Could not locate.

Tisdale, J.E., et al., *Prevalence of QT interval prolongation in patients admitted to cardiac care units and frequency of subsequent administration of QT interval-prolonging drugs: a prospective, observational study in a large urban academic medical center in the US.* Drug Safety, 2012. **35**(6): p. 459-470.

Reason for exclusion: ECGs conducted intentionally - all patients underwent continuous cardiac telemetry and / or baseline ECG.

Miranda, D.G., C.L. McMain, and A.J. Smith, *Medication-induced QT-interval prolongation and torsades de pointes.* U.S. Pharmacist, 2011. **36**(2): p. HS2-HS8.

Reason for exclusion: Could not locate.

Mayet, S., et al., *Methadone maintenance, QTc and torsade de pointes: Who needs an electrocardiogram and what is the prevalence of QTc prolongation?* Drug and Alcohol Review, 2011. **30**(4): p. 388-396.

Reason for exclusion: No relevant ECG use data - ECG data not in relation to baseline and / or follow up.

Mabasa, V.H., et al., *Analysis of orders for QTc-prolonging medication for intensive and cardiac care unit patients with pre-existing QTc prolongation (QTIPPP study).* Canadian Journal of Hospital Pharmacy, 2011. **64**(6): p. 412-418.

Reason for exclusion: No relevant ECG use data - ECG data not in relation to baseline and / or follow up.

McNamara, J.K., et al., *Methadone-associated prolongation of the QTc interval at doses used for chronic pain.* P and T, 2011. **36**(2): p. 78-107.

Reason for exclusion: ECG use data not in relation to initiation of drug therapy or initiation not clearly reported - drug initiated versus stable treatment not reported; and insufficient information; and post-initiation ECGs not clearly defined.

Methadone-Associated Prolongation of the QTc Interval at Doses Used for Chronic Pain. 2011, MediMedia Managed Markets, an ICON Company. p. 78-107.

Reason for exclusion: Duplicate and previously excluded.

Lallemand, B.M.H., *Contribution of ECG and interest of the analysis of repolarisation (QT interval) by the general practitioner during the prescription of psychoactive drug (From a case control study of 50 patients)*. Thesis in French. 2010, Aix Marseille University, France. 1 vol., p. 96

Reason for exclusion: Could not locate.

Pickham, D.M., *Prevalence of and predictors for QT interval prolongation and adverse outcomes in an acutely ill cohort: the QTIP Study*. 2010, University of California, San Francisco. p. 184 p-184 p.

Reason for exclusion: No relevant ECG use data - ECG data not in relation to QT-interval prolonging drugs and / or baseline and / or follow up.

Pickham, D., et al., *How many patients need QT interval monitoring in critical care units? Preliminary report of the QT in Practice study.* J Electrocardiol, 2010. **43**(6): p. 572-6.

Reason for exclusion: No relevant ECG use data - ECG data not in relation to QT-interval prolonging drugs and / or baseline and / or follow up.

Ghosh, S., et al., *Monitoring electrocardiograms of service users on high-dose methadone substitution therapy: An audit.* Psychiatrist, 2010. **34**(11): p. 489-491.

Reason for exclusion: ECG use data not in relation to initiation of drug therapy or initiation not clearly reported - ECG data not in relation to initiation of high-risk drug.

Fareed, A., et al., *Onsite QTc interval screening for patients in methadone maintenance treatment.* J Addict Dis, 2010. **29**(1): p. 15-22.

Reason for exclusion: ECG use data not in relation to initiation of drug therapy or initiation not clearly reported - ECG data not in relation to initiation of high-risk drug.

Reddy, S., et al., *The effect of oral methadone on the QTc interval in advanced cancer patients: a prospective pilot study.* J Palliat Med, 2010. **13**(1): p. 33-8.

Reason for exclusion: ECGs conducted intentionally - ECG conducted with intention at baseline and follow up.

Weidman-Evans, E., et al., *Impact of a pharmacist developed protocol on the cardiac monitoring of methadone in chronic noncancer pain management.* J Am Pharm Assoc (2003), 2009: p. e102-e109.

Reason for exclusion: No relevant ECG use data - ECG use not in relation to baseline and / or follow up.

Darwiche, F.Z., S.T. Ugradar, and T. Turner, *Junior doctors' knowledge and practice of electrocardiographic monitoring for high-risk patients receiving antipsychotic medications.* Psychiatric Bulletin, 2009. **33**(10): p. 377-380.

Reason for exclusion: High risk drugs not studied or drugs do not match protocol definition - drugs studied do not match protocol criteria.

Snider, M., S. Kalbfleisch, and C.A. Carnes, *Initial experience with antiarrhythmic medication monitoring by clinical pharmacists in an outpatient setting: a retrospective review.* Clinical Therapeutics, 2009. **31**(6): p. 1209-1218.

Reason for exclusion: ECG use data not in relation to initiation of drug therapy or initiation not clearly reported - drugs initiated versus stable treatment not reported.

Van Der Sijs, H., et al., *Clinically relevant QTc prolongation due to overridden drug-drug interaction alerts: A retrospective cohort study.* British Journal of Clinical Pharmacology, 2009. **67**(3): p. 347-354.

Reason for exclusion: No relevant ECG use data - ECG use not in relation to (single) high risk drug at baseline and / or follow up.

Van Der Sijs, H., et al., *Unintended consequences of reducing QT-alert overload in a computerized physician order entry system.* European Journal of Clinical Pharmacology, 2009. **65**(9): p. 919-925.

Reason for exclusion: No relevant ECG use data – study subjects excluded if no ECG before and within 1 month (of alert override).

Frimas, V., et al., *[Cardiological monitoring of antipsychotic-treated patients: evaluation and evolution of a hospital protocol].* [Article in French]. Encephale, 2008. **34**(5): p. 467-76.

Reason for exclusion: ECG use data not in relation to initiation of drug therapy or initiation not clearly reported - ECG data not in relation to initiation of high-risk drug.

Ng, T.M.H., et al., *Pharmacist monitoring of QTc interval-prolonging medications in critically ill medical patients: A pilot study.* Annals of Pharmacotherapy, 2008. **42**(4): p. 475-482.

Reason for exclusion: ECGs conducted intentionally - ECGs routinely ordered on ICU admission; and patients without follow up ECGs excluded.

Nuttall, G.A., et al., *Does low-dose droperidol administration increase the risk of drug-induced QT prolongation and torsade de pointes in the general surgical population?* Anesthesiology, 2007. **107**(4): p. 531-6.

Reason for exclusion: No relevant ECG use data - ECG data not in relation to baseline and / or follow up.

Golzari, H., et al., *Prolonged QTc intervals on admission electrocardiograms: Prevalence and correspondence with admission electrolyte abnormalities.* Connecticut Medicine, 2007. **71**(7): p. 389-397.

Reason for exclusion: No relevant ECG use data - ECG data not in relation to QT-interval prolonging drugs and / or baseline and / or follow up.

Moosa, M.Y.H., F.Y. Jeenah, and C. Mouton, *ECG changes in patients on chronic psychotropic medication.* South African Journal of Psychiatry, 2006. **12**(3): p. 42-46.

Reason for exclusion: ECG use data not in relation to initiation of drug therapy or initiation not clearly reported - ECG data not in relation to initiation of high-risk drug

Benoit, S.R., et al., *Risk factors for prolonged QTc among US adults: Third National Health and Nutrition Examination Survey.* European Journal of Cardiovascular Prevention and Rehabilitation, 2005. **12**(4): p. 363-368.

Reason for exclusion: No relevant ECG use data - ECG data not in relation to baseline and / or follow up.

Lin, C.H., et al., *Predictive factors for QTc prolongation in schizophrenic patients taking antipsychotics.* Journal of the Formosan Medical Association, 2004. **103**(6): p. 437-441.

Reason for exclusion: No relevant ECG use data - ECG data not in relation to baseline and / or follow up.

Unnikrishnan, D., et al., *Cardiac monitoring of patients receiving arsenic trioxide therapy.* British Journal of Haematology, 2004. **124**(5): p. 610-617.

Reason for exclusion: No relevant ECG use data - No ECG use data (in the observational cohort).

Appendix IV – Characteristics of included studies

Study	**Type of study**	**Population** (Participant characteristics, drugs studied)	**Condition** (Baseline ECG and / or follow up ECG)	**Context** (Country and setting)	**Notes**
Cole et al 2020	Retrospective observational cohort study	Parenteral **droperidol**, for any indication (eg. agitation, pain, vomiting, headaches), in non-critically ill and critically ill patients. Adults 18 years and older confirmed with author. January 1997 – November 2001.	ECG before, ECG after (confirmed as within 30 days of droperidol use by author).	Hospital setting - Emergency Department of a Level I trauma center hospital, Minneapolis, USA.	ECG data for critically ill cohort and non-critically ill cohort combined into single data set. Data in *ECG both before and after groups* re-distr buted into *ECG only before* and *ECG only after* groups.
Pezo et al 2019	Retrospective observational cohort study	Patients aged ≥ 66 years residents of Ontario, Canada identified as having first diagnosis of cancer between April 2005 to March 2011 and treated with first-line anticancer systemic therapy and received a prescription for a QT-prolonging (QTP) drug. **Drugs with "known risk of TdP" specified.** The use of a QTP drug was included if it was commenced either *before* or *after* the start of the first-line anticancer systemic therapy.	ECGs performed within 30 days of the index date. The index date is defined as the date of anticancer therapy initiation for QTP drug commenced *before* the anticancer therapy; and the date of initiation of QTP drug if commenced *on* or *after* the date of initiation of anticancer therapy.	No healthcare setting specified - Residents of Ontario, Canada with universal access to healthcare services.	
Manchia et al 2017	Retrospective observational cohort study, followed up longitudinally.	Severe mental illness patients (mean age 49.1±14.7 years) treated with an **antipsychotic** (AP) that was started during the reference period (January 2010 to April 2015). **Drugs with "known risk of TdP" specified.**	Presence / absence of baseline ECG testing (before AP treatment)	Non-hospital setting - Community Mental Health Centre, Caligari, Italy.	Data for ECG testing during AP treatment (known risk of TdP drugs) excluded from analysis as time frame not clearly defined.
Atayee et al 2017	Single centre, retrospective observational cohort study.	Adult (45.4 ±16.4 years) hospitalised patients initiated on new oral **methadone** for pain management. January 2013 to January 2015.	ECG (seven days) before methadone start.	Hospital setting - Two-hospital, single academic health system, San Diego, USA.	ECG data for various departments (Medicine, Burn, Trauma, Other) combined into single data set.
Ehrenpreis et al 2016	Retrospective observational cohort study	Adult patients (age range 20-94) prescr bed **domperidone** (various indications including gastroparesis, gastro-oesophageal reflux disease, lactation, nausea). Patients selected if domperidone listed as a "New Drug" in the electronic medical record).	Baseline EKG before domperidone prescription.	Non-hospital setting - NorthShore University HealthSystem, a community-based multispecialty practice, Chicago, USA.	Data for follow up EKG excluded from analysis as not conducted within 30 days (confirmed as 8 weeks by author).

		January 2008 – December 2013.			
Vandael et al 2016	Retrospective observational cohort study.	Patients 18 years or older administered **haloperidol**, any route, in a total hospital population (but non-ICU). Haloperidol prescribed for various indications (delirium, nausea, hiccups). Patients who had already used haloperidol prior to admission excluded. 22 July 2013 to 28 October 2013.	ECG before the start of haloperidol (maximum 1 year old). ECG during therapy of haloperidol (≤ 7 days OR > 7 days - ≤ 14 days).	Hospital setting - University Hospital Leuvan, Belgium.	Data relating to ECGs before haloperidol combined into single data set descr bing data for up to 1 year before the start of haloperidol. Data relating to ECGs during therapy of haloperidol combined into single data set descr bing data within 14 days of haloperidol.
Robbins et al 2016	Retrospective observational cohort study	Adults admitted for IV dihydroergotamine (DHE) to a Headache Centre, treated with at least one dose of **domperidone** for DHE-related nausea, at the discretion of a Neurologist. July 2012 to May 2015.	Baseline ECG. Patients with repeat ECG or no repeat ECG.	Hospital setting - University of California, San Francisco, Headache Centre (tertiary hospital), USA.	
Girgis et al 2016	Retrospective observational cohort study	Adult inpatients (18 years or older) on general medicine wards and psychiatric units, taking **psychotropic agents** that have a "known risk of TdP," including citalopram, escitalopram, haloperidol and methadone. New medication during admission identified. December 2014 to January 2015.	Baseline EKG (new medication) and repeat EKG (new medication).	Hospital setting - Monmouth Medical Centre (community hospital), New Jersey, USA.	Baseline ECG performed prior to or within 24 hours after starting the studied medication, accepted for data analysis even though not exact match to protocol definition for baseline, however deemed clinically acceptable. ECG data for Psychiatry and General Medicine groups combined into single data set.
Forbes et al 2016	Retrospective observational cohort study	Adult hospital inpatients (18 years and over) that were initially prescr bed **domperidone**. Domperidone prescribed for various indications (gastro-oesophageal reflux disease, gastroparesis, anti-emesis). **Two time periods studied:** April to July 2005 **(a)** and April to July 2012 **(b),** relative to the release of a national drug safety warning about domperidone in 2012.	ECG not performed prior to initiation.	Hospital setting - Hamilton Health Sciences (tertiary care hospital network involving three centres within the network), Canada.	ECG data described as *ECG not performed prior to initiation* converted to descr be *ECG performed prior to initiation.*
Dunker et al 2016	Retrospective observational cohort study	Admitted patients aged 18 years or older treated with at least 48 hours of **azithromycin**. Patients excluded if they received one-time doses, prophylactic and anti-inflammatory dosing. **Two time periods studied:** July 2012 to February 2013 **(a)** and April 2013 to November 2013 **(b),** relative to the release of a national drug safety warning about azithromycin in March 2013.	Baseline ECG.	Hospital setting - Academic medical centre, Chicago, USA.	Data for follow up ECG excluded from analysis as does not fit protocol criteria (depends on QT threshold) or at least unclear and unable to be clarified with author.
Choo et al 2014	Retrospective observational cohort study	Patients admitted to cardiology wards and general medicine wards who were commenced on a	ECG performed prior to and 48 hours after	Hospital setting - Aberdeen Royal Infirmary, Aberdeen, UK.	ECG data described for Cardiology and General Medicine

		medication with "known risk of TdP" whilst in hospital. Average age (years) 67±12 (cardiology), 58±21 (general medicine). August 2011 – February 2012.	initiating the medication.		combined into single data set.
Macey et al 2013	Retrospective observational cohort study	Initiation of **methadone** for chronic pain in veterans (average age 54.8 years). 2008.	Baseline ECG (up to one year prior to initiation).	Hospital setting - A Veterans Affairs Medical Centre (hospital), Pacific Northwest USA.	Data for follow up ECG excluded from analysis as it does not meet protocol definition (collected up to one year post initiation).
Cheung et al 2013	Retrospective observational cohort study.	Inpatients aged 65 years or older who received at least one dose of IV **haloperidol** between January 2008 to December 2010.	ECG performed within 7 days before first dose.	Hospital setting - Academic Medical Centre (urban tertiary care centre), Denver, Colorado, USA.	Data for follow up ECG excluded from analysis as it does not meet protocol definition (depends on baseline QT threshold).
Muzyk et al 2012	Retrospective observational cohort study Two cohorts reviewed relative to an intervention (implementation of a computerised physician order entry (CPOE) set which involved automated orders for baseline and follow up ECGs following prescription of IV haloperidol).	Medically ill hospitalised patients (≥ 18 years of age) prescribed IV **haloperidol**. **Two time periods studied:** pre-CPOE June 2007 to June 2008 **(a)** and post CPOE January 2009 to January 2010 **(b).**	Baseline ECG (pre and post CPOE). Follow up ECG within 24 hours of IV haloperidol administration (pre and post CPOE).	Hospital setting - General medical unit, Duke University Hospital, Durham, North Carolina, USA.	ECG data relating to potential ECG monitoring opportunities excluded from analysis.