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The Comprehensive Systematic Review of Association of QT prolonging medications torsades de pointes in hospitalized patients

[1] Fionny Novira Azelikha, [2] Irma Winastuti Rosmanadewi

[1,2] PKU Muhammadiyah Aghisna Kroya General Hospital, Indonesia

Corresponding Email : fionnyazelikha@gmail.com

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ABSTRACT

Introduction: Drug-induced QT interval prolongation and its progression to torsades de pointes (TdP), a potentially fatal polymorphic ventricular tachycardia, represent a significant clinical challenge in hospitalized patients. Numerous medications across various therapeutic classes possess this off-target adverse effect, creating a complex landscape for risk management, especially in vulnerable inpatient populations often burdened by comorbidities, polypharmacy, and acute illness. A comprehensive synthesis of the evidence regarding the incidence, risk factors, and mitigation strategies is crucial for optimizing patient safety.

Methods: This systematic review was conducted by screening studies from multiple databases based on pre-defined criteria. The population of interest was hospitalized patients of any age receiving medications known to prolong the QT interval. The primary outcome was the occurrence of TdP, with clear diagnostic

criteria required. Included study designs were observational studies, randomized controlled trials, systematic reviews, meta-analyses, or case series with ≥10 patients. Data extraction covered study population, specific QT-prolonging drugs, TdP outcomes, risk factors, QT monitoring methodologies, and key statistical findings (Tleyjeh et al., 2020; Vandael et al., 2017).

Results: Analysis of 80 included studies revealed marked heterogeneity in TdP incidence across drug classes. Class III antiarrhythmics (e.g., dofetilide, ibutilide) demonstrated the highest risk (1-17%), directly related to their potassium channel-blocking mechanism (Mazur et al., 2001; Bianconi et al., 2000). Antimalarials (hydroxychloroquine/chloroquine), widely used during the COVID-19 pandemic, showed a TdP incidence of 0.06-0.72%, which increased when combined with azithromycin (Aleem et al., 2021; Diaz-Arocutipa et al., 2021). Other agents like fluoroquinolones, antipsychotics, and methadone were associated with lower absolute TdP risk (<0.1-1%) but significant QTc prolongation (Gorelik et al., 2018; Garcia et al., 2025; Lovell et al., 2018). Key patient-related risk factors included female sex, advanced age, baseline cardiac disease, electrolyte disturbances (hypokalemia, hypomagnesemia), and polypharmacy with multiple QT-prolonging drugs (Johnston et al., 2013; Vandael et al., 2017).

Discussion: The disparity between high rates of QTc prolongation and low incidence of TdP highlights the poor positive predictive value of QT elongation alone for arrhythmic events. The translation from prolonged repolarization to TdP depends on additional factors such as increased repolarization heterogeneity (e.g., Tpeak-Tend interval), the presence of triggers (e.g.,

bradycardia, pauses), and individual genetic susceptibility (Strauss et al., 2017; Tse et al., 2018). Effective risk mitigation involves vigilant monitoring (using optimal correction formulas like Rautaharju's), maintaining normal electrolyte levels, employing clinical decision support systems, and considering protective interventions like magnesium administration for high-risk drugs like ibutilide (Patsilinakos et al., 2010; Othong et al., 2018).

Conclusion: The risk of drug-induced TdP in hospitalized patients is highly variable and contingent on a multifactorial interplay between specific drug properties, patient susceptibility, and clinical context. While certain drug classes (Class III antiarrhythmics) necessitate stringent inpatient monitoring protocols, for many others, the absolute risk of TdP is low when prescribed judiciously with appropriate patient assessment and monitoring. A stratified, individualized approach to risk assessment and management, incorporating modifiable risk factors and systematic monitoring strategies, is essential to maximize therapeutic benefits while minimizing arrhythmic hazards.

Keywords: QT prolongation, torsades de pointes, drug-induced arrhythmia, hospitalized patients, systematic review, risk factors, monitoring.

INTRODUCTION

Background

The QT interval on an electrocardiogram (ECG) represents the total duration of ventricular depolarization and repolarization. Its prolongation signifies delayed repolarization, which can create an electrophysiological substrate conducive to the development of malignant ventricular arrhythmias, most notably torsades de pointes (TdP) (Mizusawa & Wilde, 2013). TdP is a distinctive form of polymorphic ventricular tachycardia that can degenerate into ventricular fibrillation and cause sudden cardiac death. While congenital long QT syndrome is a recognized cause, a more frequent clinical concern in hospital settings is acquired or drug-induced long QT syndrome (diLQTS), where medication exposure triggers abnormal cardiac repolarization (Arunachalam et al., 2018). A vast array of medications from diverse classes—including antiarrhythmics, antibiotics, antipsychotics, antidepressants, and antiemetics—carry this potential adverse effect, complicating therapeutic decision-making, especially in the complex, comorbid, and often critically ill hospitalized population where polypharmacy is common and physiological reserves are diminished.

The COVID-19 pandemic starkly highlighted this clinical dilemma. The urgent repurposing of drugs like hydroxychloroquine (HCQ) and chloroquine (CQ), often combined with azithromycin, for potential antiviral effects raised immediate alarms regarding their known QT-prolonging potential, leading to widespread implementation of ECG monitoring protocols and generating a large volume of real-world data on cardiac safety (Jankelson et al., 2020; Tleyjeh et al., 2020). Beyond the pandemic, the ongoing use of psychotropic agents in ICU delirium, antiarrhythmics for atrial fibrillation, and certain chemotherapeutic agents continues to present daily management challenges (Stollings et al., 2024; Porta-Sánchez et al., 2017). The clinical impact of diLQTS is significant, contributing to morbidity, mortality, regulatory actions (including drug withdrawals like

terfenadine and cisapride), and substantial healthcare costs associated with monitoring and managing adverse events.

Research Gaps

Despite extensive literature, significant knowledge gaps persist. First, there is considerable heterogeneity in reported TdP incidence rates for the same drug across different studies, often attributable to variations in study design, patient populations, monitoring intensity, and definitions of outcomes. This makes precise risk quantification difficult for clinicians (Møller et al., 2001; Yarlagadda et al., 2017). Second, while QTc prolongation is a necessary precursor, it is a poor predictor of actual TdP; the factors that mediate the transition from prolonged repolarization to life-threatening arrhythmia are not fully understood. Metrics beyond the QTc interval, such as T-wave morphology and Tpeak-Tend dispersion, may offer better predictive value but are not routinely assessed (Tse et al., 2018). Third, the relative contribution and multiplicative effects of multiple concurrent risk factors (e.g., renal failure, hypokalemia, polypharmacy) in the hospitalized patient require more precise delineation to enable accurate risk stratification (Vandael et al., 2017). Finally, the real-world effectiveness and optimal implementation strategies for risk mitigation interventions—such as computerized alert systems, standardized monitoring protocols, and prophylactic electrolyte management—need further rigorous evaluation (Elena Tomaselli Muensterman & Tisdale, 2018).

Research Objectives

This comprehensive systematic review aims to: 1) Synthesize and quantify the reported incidence of drug-induced torsades de pointes across major medication classes in hospitalized patients; 2) Identify and evaluate the strength of evidence for patient-specific, drug-specific, and clinical context risk factors that modulate TdP risk; 3) Critically appraise current QT monitoring practices, thresholds, and correction formulas used in clinical studies and practice; 4) Evaluate the evidence for protective interventions and risk mitigation strategies; and 5) Provide a clinically

oriented synthesis and risk-stratification framework to guide decision-making for healthcare providers managing hospitalized patients on QT-prolonging medications.

Hypothesis

We hypothesize that the incidence of drug-induced TdP in hospitalized patients is not uniform but varies significantly by drug class (highest with pure potassium channel blockers), and that this incidence is profoundly modified by a confluence of non-drug factors. Specifically, the presence of multiple patient-related risk factors (e.g., female sex, structural heart disease, electrolyte imbalances) and clinical context (e.g., polypharmacy, critical illness) synergistically increases risk to a greater degree than drug exposure alone. Furthermore, systematic implementation of risk assessment and mitigation protocols can significantly reduce the incidence of significant QTc prolongation and potentially TdP events.

Novelty and Significance

This review differentiates itself by its exclusive focus on the *hospitalized* patient population, where risk is amplified and management is most acute. It provides a contemporary synthesis that includes the large volume of COVID-19-related cardiac safety data, offering updated insights on antimalarials and macrolides (Furtado et al., 2023; Nikolic et al., 2024). It moves beyond simply listing risk drugs to quantitatively stratifying risk by class and context, and it critically evaluates not just the problem but also the solutions—assessing the evidence for monitoring technologies and mitigation strategies. By integrating data on genetic predispositions and advanced ECG markers, it points toward future personalized medicine approaches for arrhythmia risk prediction (Strauss et al., 2017). The ultimate goal is to translate a complex and often fragmented evidence base into a practical, actionable guide for improving patient safety in hospitals worldwide.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the association of QT prolonging medications torsades de pointes in hospitalized patients

Screening

We screened in sources based on their abstracts that met these criteria:

- **Population**: Does the study focus on hospitalized patients of any age?
- **Intervention**: Does the study involve patients receiving medications known to prolong QT interval?
- **Outcome**: Does the study report torsades de pointes as a primary or secondary outcome?
- **Outcome Definition**: Does the study provide a clear definition or explicit criteria for diagnosing torsades de pointes?
- **Study Design**: Is the study an observational study (cohort, case-control, cross-sectional), randomized controlled trial, systematic review, meta-analysis, or case series with 10 or more patients?
- **Statistical Measures**: Does the study report statistical measures of association (odds ratios, relative risks, hazard ratios, incidence rates) or provide sufficient data to calculate these measures?
- **QT vs Torsades Focus**: Does the study report actual torsades de pointes events (not solely QT interval prolongation without arrhythmia outcomes)?

- **Acquired vs Congenital**: Does the study focus on drug-induced torsades de pointes (not exclusively on congenital long QT syndrome)?
- **Human Studies**: Is this a human clinical study (not an animal study or in vitro study)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Hospitalized patients	QT prolonging medications	Non-QT prolonging medications	Torsades de pointes
Keyword 2	Inpatients	QT-prolonging drugs	Alternative medications	Polymorphic ventricular tachycardia
Keyword 3	Hospitalised adults	Drugs causing long QT	Standard care	Drug-induced TdP
Keyword 4	Acute care patients	Pharmacological QT prolongation	Placebo	Sudden cardiac death

The Boolean MeSH keywords inputted on databases for this research are: *("Hospitalized patients" OR "Inpatients" OR "Hospitalised adults" OR "Acute care patients") AND ("QT prolonging medications" OR "QT-prolonging drugs" OR "Drugs causing long QT" OR "Pharmacological QT prolongation") AND ("Non-QT prolonging medications" OR "Alternative medications" OR "Standard care" OR "Placebo") AND ("Torsades de pointes" OR "Polymorphic ventricular tachycardia" OR "Drug-induced TdP" OR "Sudden cardiac death")*

Data extraction

- **Study Population**:

  Extract details about the study population including:

  - Hospital setting (ICU, general ward, emergency department, etc.)
  - Patient population characteristics (age, sex, comorbidities)
  - Total number of patients exposed to QT-prolonging medications
  - Inclusion and exclusion criteria
  - Whether patients were specifically hospitalized or included outpatients

- **QT-Prolonging Medications**:

  Extract comprehensive medication details including:

  - Specific QT-prolonging drugs studied (names, classes)
  - Dosages and duration of treatment
  - Single drugs vs. combinations studied
  - Concomitant medications that may interact
  - Route of administration
  - Any dose adjustments or discontinuations

- **Torsades de Pointes**:

  Extract all torsades de pointes outcome data including:

  - Number of patients who developed TdP
  - Incidence rate or percentage
  - Case definition used for TdP diagnosis
  - Method of TdP detection (continuous monitoring, routine ECGs, etc.)
  - Timing of TdP occurrence relative to drug initiation

- Severity and clinical consequences (self-terminating, required intervention, etc.)

- **Risk Factors**:

  Extract factors that influenced TdP risk including:

  - Patient characteristics (age, sex, baseline heart disease)
  - Electrolyte abnormalities (hypokalemia, hypomagnesemia)
  - Comorbidities (renal disease, liver disease, heart failure)
  - Genetic factors or family history
  - Drug interactions or polypharmacy
  - Any protective factors or risk mitigation strategies identified

- **QT Monitoring**:

  Extract QT measurement methodology including:

  - QTc correction formula used (Bazett, Fridericia, etc.)
  - Definition of QTc prolongation (threshold values)
  - Frequency and timing of ECG monitoring
  - Type of monitoring (12-lead ECG, telemetry, Holter)
  - Baseline QTc values and changes from baseline
  - Any monitoring protocols or guidelines followed

- **Study Design**:

  Extract study methodology including:

  - Study design (cohort, case-control, RCT, etc.)
  - Prospective vs. retrospective data collection
  - Follow-up duration and completeness
  - Primary vs. secondary analysis of TdP outcomes

- Sample size calculation and power considerations
- Statistical methods used for association analysis

- **Key Findings**:

  Extract main results and associations including:

  - Risk ratios, odds ratios, or hazard ratios for TdP
  - Confidence intervals and p-values
  - Dose-response relationships if identified
  - Subgroup analyses results
  - Number needed to harm calculations if provided
  - Any protective effects or interventions that reduced risk

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Hospitalized patients" OR "Inpatients" OR "Hospitalised adults" OR "Acute care patients") AND ("QT prolonging medications" OR "QT-prolonging drugs" OR "Drugs causing long QT" OR "Pharmacological QT prolongation") AND ("Non-QT prolonging medications" OR "Alternative medications" OR "Standard care" OR "Placebo" AND "Torsades de pointes" OR "Polymorphic ventricular tachycardia" OR "Drug-induced TdP" OR "Sudden cardiac death")*	1
Semantic Scholar	*("Hospitalized patients" OR "Inpatients" OR "Hospitalised adults" OR "Acute care patients") AND ("QT prolonging medications" OR "QT-prolonging drugs" OR "Drugs causing long QT" OR "Pharmacological QT prolongation") AND ("Non-QT prolonging medications" OR "Alternative medications" OR "Standard care" OR "Placebo") AND ("Torsades de pointes" OR "Polymorphic ventricular tachycardia" OR "Drug-induced TdP" OR "Sudden cardiac death")*	250
Springer	*("Hospitalized patients" OR "Inpatients" OR "Hospitalised adults" OR "Acute care patients") AND ("QT prolonging medications" OR "QT-prolonging drugs" OR "Drugs causing long QT" OR "Pharmacological QT prolongation") AND ("Non-QT prolonging medications" OR "Alternative medications" OR "Standard care" OR "Placebo") AND ("Torsades de pointes" OR "Polymorphic ventricular tachycardia" OR "Drug-induced TdP" OR "Sudden cardiac death")*	47
Google Scholar	*("Hospitalized patients" OR "Inpatients" OR "Hospitalised adults" OR "Acute care patients") AND ("QT prolonging medications" OR "QT-prolonging drugs" OR "Drugs causing long QT" OR "Pharmacological QT prolongation") AND ("Non-QT prolonging medications" OR "Alternative medications" OR "Standard care" OR "Placebo") AND ("Torsades de pointes" OR "Polymorphic ventricular tachycardia" OR "Drug-induced TdP" OR "Sudden cardiac death")*	339
Wiley Online Library	*("Hospitalized patients" OR "Inpatients" OR "Hospitalised adults" OR "Acute care patients") AND ("QT prolonging medications" OR "QT-prolonging drugs" OR "Drugs causing long QT" OR "Pharmacological QT prolongation") AND ("Non-QT prolonging medications" OR "Alternative medications" OR "Standard care" OR "Placebo") AND ("Torsades de pointes" OR "Polymorphic ventricular tachycardia" OR "Drug-induced TdP" OR "Sudden cardiac death")*	53

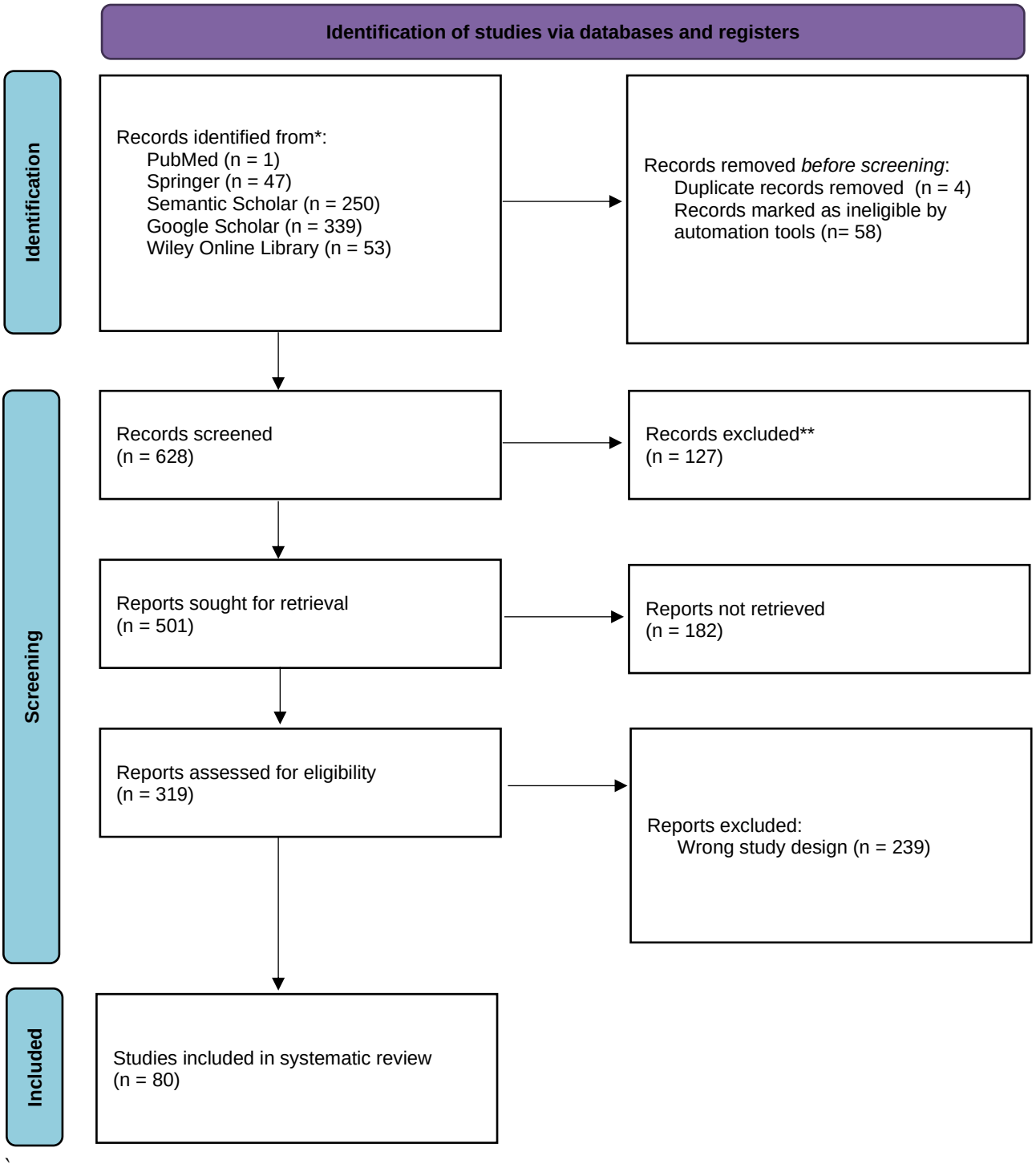

Figure 1. Article search flowchart

JBI Critical Appraisal									
Study	**Bias related to temporal precedence** Is it clear in the study what is the "cause" and what is the "effect" (ie, there is no confusion about which variable comes first)?	**Bias related to selection and allocation** Was there a control group?	**Bias related to confounding factors** Were participants included in any comparisons similar?	**Bias related to administration of intervention/exposure** Were the participants included in any comparisons receiving similar treatment/ care, other than the exposure or intervention of interest?	**Were there multiple measurements of the outcome, both pre and post the intervention/exposure?**	**Were the outcomes of participants included in any comparisons measured in the same way?**	**Were outcomes measured in a reliable way?**	**Bias related to participant retention** Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	**Statistical conclusion validity** Was appropriate statistical analysis used?
Sourabh Agstam et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
I. Tleyjeh et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Mazur et al., 2001	✓	✓	✓	✗	✓	✗	✓	✓	✓

R. Othong et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Patsilinakos et al., 2010	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Johnston et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
K. Marill et al., 2001	✓	✓	✓	✗	✓	✗	✓	✓	✓
I. Farmakis et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
L. Bianconi et al., 2000	✓	✓	✓	✗	✓	✗	✓	✓	✓
G. Tse et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
T. Oscanoa et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
G. Nuttall et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
B. Yarlagadda et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓

M. Møller et al., 2001	✓	✓	✓	✗	✓	✗	✓	✓	✓
K. Arunachalam et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Strauss et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Beach et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Jules C. Hancox et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
W. Vieweg et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
Daihong Guo et al., 2010	✓	✓	✓	✗	✓	✗	✓	✓	✓
Joanna L. Stollings et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
O. Bouchaud et al., 2009	✓	✓	✓	✗	✓	✗	✓	✓	✓
Anna V Guanzon et al., 2004	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Rónaszéki et al., 2011	✓	✓	✓	✗	✓	✗	✓	✓	✓

Michael Cristian Garcia et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Lior Jankelson et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Christopher P. Kogut et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
Vignaldo Cassiano Rosa Júnior et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Piccinni et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. Diaz-Arocutipa et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Porta-Sánchez et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Einat Gorelik et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Chou et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Reddy et al., 2010	✓	✓	✓	✗	✓	✗	✓	✓	✓

J. Morganroth et al., 2005	✓	✓	✓	✗	✓	✗	✓	✓	✓
Kaden Shen et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
L. Moschini et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Kavous Shahsavarinia et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Amanda G. Lovell et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Guangqiang Wang et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Dana B. Gal et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Shenel A Khan et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Morrish Okello-Obol et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
W. Aronow et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓

C. Polcwiartek et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Joanna L. Stollings et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
P. Ghatalia et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
Jingyao Song et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Schrickel et al., 2006	✓	✓	✓	✗	✓	✗	✓	✓	✓
Elena Tomaselli Muensterman et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Simran Kahlon et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
V. Michaud et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
B. Khokhar et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Tina Nham et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓

S.H Wang et al., 2001	✓	✓	✓	✗	✓	✗	✓	✓	✓
B. Dorpmans et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
T. K. Kim et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Y. Mizusawa et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. Vandael et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Saravana Kumar Ramasubbu et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Z. Mansuri et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Aleem et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Saravana Kumar Ramasubbu et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
P. Dorian et al., 2004	✓	✓	✓	✗	✓	✗	✓	✓	✓

H. Hussein et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Xian-Bin Li et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Nikolic et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Solhjoo et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Guerra Estévez et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Neha Verma et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
K. Hoshino et al., 2004	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Furtado et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Camila VIEIRA BREDER et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Hritvik Jain et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓

B. Brembilla-Perrot et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
V. Yavuz et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Duarte-García et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Amanda G. Lovell et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Reddy et al., 2007	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Kristeleit et al., 2011	✓	✓	✓	✗	✓	✗	✓	✓	✓

RESULTS

Characteristics of Included Studies

The 80 sources reviewed encompass a diverse range of study designs, populations, and QT-prolonging medications. The majority of studies focused on hospitalized patients or mixed populations, with varying levels of cardiac monitoring and follow-up.

Study	Population	Primary Drug Class	Sample Size
Sourabh Agstam et al., 2020	COVID-19 patients	Antimalarials (HCQ/CQ)	2,138

Study	Population	Primary Drug Class	Sample Size
I. Tleyjeh et al., 2020	COVID-19 patients	CQ/HCQ ± azithromycin	5,652
A. Mazur et al., 2001	ICD patients	Dofetilide	174
R. Othong et al., 2018	Adults exposed to QT-prolonging drugs	Multiple	522
S. Patsilinakos et al., 2010	Atrial fibrillation/flutter	Ibutilide ± magnesium	476
J. Johnston et al., 2013	Perioperative patients	Multiple	46 cases
K. Marill et al., 2001	Arrhythmia patients	IV sotalol	962
I. Farmakis et al., 2022	COVID-19 patients	Azithromycin ± HCQ	3,088
L. Bianconi et al., 2000	Atrial fibrillation/flutter	Dofetilide vs amiodarone	150
G. Tse et al., 2018	Drug-induced LQTS patients	Multiple	308
T. Oscanoa et al., 2020	COVID-19 patients	HCQ	9,124
G. Nuttall et al., 2022	Perioperative patients	Ondansetron	Not specified
B. Yarlagadda et al., 2017	Atrial fibrillation (inpatient)	Dofetilide vs sotalol	378

Study	Population	Primary Drug Class	Sample Size
M. Møller et al., 2001	Heart failure patients	Dofetilide	1,518
K. Arunachalam et al., 2018	Mixed populations	Multiple	14,756
D. Strauss et al., 2017	Healthy volunteers	Dofetilide, quinidine, ranolazine	22
S. Beach et al., 2020	Hospitalized patients	IV haloperidol	Not specified
Jules C. Hancox et al., 2013	Adults with risk factors	Azithromycin	12 cases
W. Vieweg et al., 2013	Psychiatric patients	Risperidone	15 cases
Daihong Guo et al., 2010	Mixed populations	Macrolides	48 reports
Joanna L. Stollings et al., 2022	ICU patients with delirium	Haloperidol, ziprasidone	566
O. Bouchaud et al., 2009	Malaria patients	Halofantrine	35 fatal cases
Anna V Guanzon et al., 2004	Atrial fibrillation/flutter	Dofetilide	107
A. Rónaszéki et al., 2011	Atrial fibrillation	AZD1305	171
Michael Cristian	Mixed populations	Haloperidol	12,180

Study	Population	Primary Drug Class	Sample Size
Garcia et al., 2025			
Lior Jankelson et al., 2020	COVID-19 patients	CQ/HCQ	1,515
Christopher P. Kogut et al., 2013	Psychiatric patients	SSRIs	15 cases
Vignaldo Cassiano Rosa Júnior et al., 2024	Adult patients	Azithromycin	20,510,653
A. Piccinni et al., 2017	Chronic pain/opioid dependence	Methadone	Not specified
C. Diaz-Arocutipa et al., 2021	COVID-19 patients	HCQ/CQ/azithromycin/lopinavir-ritonavir	Not specified
A. Porta-Sánchez et al., 2017	Cancer patients	Cancer therapeutics	173 publications
Einat Gorelik et al., 2018	Mixed populations	Fluoroquinolones	13 studies
R. Chou et al., 2014	Chronic pain/opioid dependence	Methadone	70 studies
S. Reddy et al., 2010	Cancer patients (palliative care)	Methadone	100
J. Morganroth et al., 2005	Elderly CAP patients (hospitalized)	Moxifloxacin vs levofloxacin	394

Study	Population	Primary Drug Class	Sample Size
Kaden Shen et al., 2024	ICU patients	Olanzapine vs quetiapine	212
L. Moschini et al., 2020	Hospitalized COVID-19 patients	HCQ + ritonavir/darunavir or azithromycin	113
Kavous Shahsavarinia et al., 2021	COVID-19 patients	HCQ/CQ ± azithromycin	43,643
Amanda G. Lovell et al., 2018	Cancer patients	Methadone	203
Guangqiang Wang et al., 2022	Short-coupled TdP patients	Various triggers	125 cases
Dana B. Gal et al., 2020	COVID-19 patients (hospitalized)	Chloroquine	81
Shenel A Khan et al., 2024	Arrhythmia patients	Antiarrhythmic drugs	385
Morrish Okello-Obol et al., 2025	DR-TB patients (Sub-Saharan Africa)	Bedaquiline	Not applicable
W. Aronow et al., 2018	Mental disorders (children/adults)	Atypical antipsychotics	Multiple RCTs
C. Polcwiartek et al., 2015	High-risk patients	Aripiprazole	Not specified
Joanna L. Stollings et al.,	ICU patients with delirium	Haloperidol, ziprasidone	566

Study	Population	Primary Drug Class	Sample Size
2024			
P. Ghatalia et al., 2014	Cancer patients	VEGFR TKIs	6,548
Jingyao Song et al., 2021	Mixed populations	Oral fluoroquinolones	16 studies
J. Schrickel et al., 2006	Atrial fibrillation patients	Amiodarone	63
Elena Tomaselli Muensterman et al., 2018	Cardiac ICU/hospitalized patients	Multiple QT-prolonging drugs	Various
Simran Kahlon et al., 2022	Mixed populations	Multiple	46 cases
V. Michaud et al., 2020	COVID-19 patients	Repurposed COVID-19 drugs	Not specified
B. Khokhar et al., 2024	NSCLC patients	EGFR TKIs	95 publications
Tina Nham et al., 2024	Dementia patients	Donepezil	Not specified
S.H Wang et al., 2001	GI disorder patients	Cisapride	51
B. Dorpmans et al., 2024	Minors (psychiatric)	Antipsychotics	28 RCTs
T. K. Kim et al., 2015	Cardiac surgery patients	Ramosetron	114

Study	Population	Primary Drug Class	Sample Size
Y. Mizusawa et al., 2013	Hospitalized patients	Multiple QT-prolonging drugs	52,579
E. Vandael et al., 2017	General population	Multiple	89,532
Saravana Kumar Ramasubbu et al., 2022	Psychiatric patients	Antipsychotics/antidepressants	30,122
Z. Mansuri et al., 2020	COVID-19 patients	CQ/HCQ + azithromycin	Various
A. Aleem et al., 2021	COVID-19 patients (hospitalized)	CQ/HCQ ± azithromycin	2,595
Saravana Kumar Ramasubbu et al., 2025	Cancer patients	Anticancer drugs	8,013
P. Dorian et al., 2004	ICD recipients	Azimilide	633
H. Hussein et al., 2020	COVID-19 patients (hospitalized)	HCQ	96,032
Xian-Bin Li et al., 2014	Psychiatric patients	IM ziprasidone	1,428
R. Nikolic et al., 2024	Autoimmune rheumatic disease	HCQ/CQ	70,609
S. Solhjoo et al., 2021	Chronic methadone patients	Methadone	72

Study	Population	Primary Drug Class	Sample Size
D. Guerra Estévez et al., 2023	Elderly patients (>64 years)	Tricyclic antidepressants	63
Neha Verma et al., 2023	Mixed populations	Fluoroquinolones	6,579,936
K. Hoshino et al., 2004	Children with LQTS	MgSO4 (treatment)	6
R. Furtado et al., 2023	COVID-19 patients (hospitalized)	Azithromycin + HCQ	1,114
Camila VIEIRA BREDER et al., 2023	Adult depression patients	Antidepressants	173 publications
Hritvik Jain et al., 2024	Mixed populations	Fluoroquinolones	42,808
B. Brembilla-Perrot et al., 2013	Resuscitated sudden death patients	Multiple cardiovascular drugs	271
V. Yavuz et al., 2021	COVID-19 patients (non-ICU)	HCQ ± moxifloxacin	312
A. Duarte-García et al., 2020	Rheumatoid arthritis patients	HCQ	Not specified
Amanda G. Lovell et al., 2017	Cancer patients	Methadone	203
S. Reddy et al., 2007	Cancer patients	Methadone	101
R. Kristeleit et	Cancer patients	HDACi (JNJ-26481585)	92

Study	Population	Primary Drug Class	Sample Size
al., 2011			

The included studies span multiple decades and geographic regions, with study designs ranging from randomized controlled trials to systematic reviews and case series. The majority of recent studies (2020-2024) focus on COVID-19-related treatments, reflecting the urgent need to understand cardiac safety of repurposed antimalarial agents during the pandemic.

Torsades de Pointes Incidence by Drug Class

Antimalarial Agents (Chloroquine/Hydroxychloroquine)

The COVID-19 pandemic generated substantial data on TdP risk with antimalarial agents. Meta-analyses reported pooled TdP incidence rates ranging from 0.06% to 0.72% . In a meta-analysis of 19 studies including 5,652 patients, the pooled incidence of torsades de pointes, ventricular tachycardia, or cardiac arrest was 3 per 1,000 (95% CI, 0-21; I^2=96%) . Similarly, among 3,088 patients receiving azithromycin with or without hydroxychloroquine, the absolute risk of TdP was 0.2% .

Study	Drug(s)	TdP Incidence	QTc >500ms Incidence	Sample Size
Sourabh Agstam et al., 2020	HCQ/CQ ± azithromycin	0.72% (0.34-1.51%)	10.22% (6.01-16.85%)	2,138
I. Tleyjeh et al., 2020	CQ/HCQ ± azithromycin	3 per 1,000	9% (3-17%)	5,652
T. Oscanoa et al., 2020	HCQ	0.06% (3/5,066)	6.7% (3.7-10.2%)	9,124

Study	Drug(s)	TdP Incidence	QTc >500ms Incidence	Sample Size
I. Farmakis et al., 2022	Azithromycin ± HCQ	0.2%	8% (6-11%)	3,088
Kavous Shahsavarinia et al., 2021	HCQ/CQ ± azithromycin	~3 per 1,000	Not reported	43,643
L. Moschini et al., 2020	HCQ + RD or AZ	~0.88% (1 case)	21.2%	113

Prospective cohort data from hospitalized COVID-19 patients demonstrated that hydroxychloroquine with either ritonavir/darunavir or azithromycin significantly increased QTc intervals, with 21.2% of patients developing QTc >500ms at 7 days . However, the risk of malignant arrhythmias remained relatively low when these drugs were administered for limited durations . Notably, the combination of hydroxychloroquine with azithromycin was associated with greater QTc changes compared to hydroxychloroquine alone .

Antiarrhythmic Agents

Class III antiarrhythmic agents demonstrate the highest TdP incidence among QT-prolonging medications, consistent with their mechanism of action involving potassium channel blockade.

Study	Drug	TdP Incidence	Setting	Sample Size
A. Mazur et al., 2001	Dofetilide	17% (pause-dependent PVT)	ICD patients	87 (dofetilide)
L. Bianconi et al., 2000	Dofetilide (IV)	8%	Atrial fibrillation	48

Study	Drug	TdP Incidence	Setting	Sample Size
M. Møller et al., 2001	Dofetilide	3%	Heart failure	1,518
B. Yarlagadda et al., 2017	Dofetilide	1.3%	Atrial fibrillation	298
B. Yarlagadda et al., 2017	Sotalol	1.2%	Atrial fibrillation	80
K. Marill et al., 2001	IV sotalol	0.1% (95% CI 0.003-0.6%)	Tachyarrhythmias	962
S. Patsilinakos et al., 2010	Ibutilide alone	3.5%	Atrial fibrillation/flutter	229
S. Patsilinakos et al., 2010	Ibutilide + magnesium	0%	Atrial fibrillation/flutter	247
P. Dorian et al., 2004	Azimilide	5 patients (vs 1 placebo)	ICD recipients	633

The variability in TdP incidence with dofetilide (1.3% to 17%) reflects differences in patient populations, dosing protocols, and monitoring intensity. Higher rates were observed in studies with continuous monitoring capable of detecting pause-dependent polymorphic ventricular tachycardia , while lower rates in clinical practice studies may reflect guideline-based dose adjustments and monitoring protocols . Intravenous administration of dofetilide demonstrated an 8% TdP rate with one case requiring electrical cardioversion .

Antipsychotic Medications

Study	Drug(s)	TdP Findings	QTc Effect	Sample Size
Michael	Haloperidol	2 TdP events	No increased	12,180

Study	Drug(s)	TdP Findings	QTc Effect	Sample Size
Cristian Garcia et al., 2025		(neither drug-related)	MACE risk (RR 0.93)	
Joanna L. Stollings et al., 2022	Haloperidol, ziprasidone	2 TdP events (haloperidol group)	No significant QTc increase vs placebo	566
Kaden Shen et al., 2024	Olanzapine, quetiapine	0 TdP events	Similar QTc effects	212
W. Vieweg et al., 2013	Risperidone	4 TdP cases (3 deaths)	Not quantified	15 cases
W. Aronow et al., 2018	Multiple atypicals	Post-marketing TdP cases reported	Variable by agent	Multiple RCTs

Randomized controlled trial data suggest that antipsychotics may have lower TdP risk than previously assumed. In the MIND-USA study analysis, neither haloperidol (OR 0.95, 95% CI 0.66-1.37) nor ziprasidone (OR 1.09, 95% CI 0.75-1.57) significantly affected QTc intervals compared to placebo (p=0.78) . A comprehensive meta-analysis of 84 RCTs including 12,180 patients found no increase in major adverse cardiac events with haloperidol compared to placebo (RR 0.93, 95% CI 0.80-1.08; I^2=0%) . However, case reports and post-marketing surveillance continue to document TdP events, particularly with risperidone and quetiapine, especially in overdose situations .

Fluoroquinolone Antibiotics

Study	Drug(s)	Arrhythmia Risk	Cardiovascular Mortality	Sample Size
Einat Gorelik	Fluoroquinolones	OR 1.85 (95%	OR 1.71 (95%	13 studies

Study	Drug(s)	Arrhythmia Risk	Cardiovascular Mortality	Sample Size
et al., 2018	(class)	CI 1.22-2.81)	CI 1.39-2.09)	
Jingyao Song et al., 2021	Oral fluoroquinolones	RR 2.29 (95% CI 1.20-4.36)	RR 1.60 (95% CI 1.17-2.20)	16 studies
Neha Verma et al., 2023	Fluoroquinolones	OR 1.87 (95% CI 1.22-2.87)	OR 1.72 (95% CI 1.38-2.14)	6,579,936
J. Morganroth et al., 2005	Moxifloxacin vs levofloxacin	1 TdP case (levofloxacin)	No drug-related deaths	394

Meta-analyses consistently demonstrate increased arrhythmia risk with fluoroquinolone use, with an 85% increase in arrhythmia risk (OR 1.85, 95% CI 1.22-2.81) and a 71% increase in cardiovascular mortality (OR 1.71, 95% CI 1.39-2.09) . Among individual agents, moxifloxacin ranked highest for arrhythmia risk (P-score 0.99) , followed by gatifloxacin (RR 6.27), levofloxacin (RR 1.41), and ciprofloxacin (RR 1.73) . Treatment with fluoroquinolones is associated with an absolute risk increase of 160 additional sudden deaths or ventricular arrhythmias per 1 million treatment courses .

Macrolide Antibiotics

Study	Drug	Risk Level	Key Findings
Daihong Guo et al., 2010	Erythromycin	Highest (21/48 reports)	Greatest risk among macrolides
Daihong Guo et al., 2010	Clarithromycin	Moderate (12/48 reports)	Second highest risk
Daihong Guo et al., 2010	Azithromycin	Lower (6/48 reports)	Relatively safer among macrolides

Study	Drug	Risk Level	Key Findings
Jules C. Hancox et al., 2013	Azithromycin	12 case reports	All had ≥2 additional risk factors

Among macrolides, erythromycin carries the greatest risk of QT prolongation and TdP, followed by clarithromycin and azithromycin . In a systematic review of azithromycin-associated TdP cases, no significant relationship between dose and QTc duration was found, suggesting host factors may be more important than dose . All 12 reported cases had at least two additional risk factors beyond azithromycin exposure .

Methadone

Study	Setting	TdP Events	QTc Prolongation Rate	Sample Size
S. Reddy et al., 2010	Palliative care	0	1.6% clinically significant	100
Amanda G. Lovell et al., 2018	Cancer patients	Not reported	55-72% (dose-dependent)	203
S. Solhjoo et al., 2021	Chronic therapy	Not specifically reported	Increased QTVI during sleep	24

Methadone demonstrates a high incidence of QTc prolongation in cancer populations (55-72% depending on dose) , though clinically significant prolongation (QTc ≥500ms) was rare in prospective studies (1.6%) . No torsades de pointes events were documented in the prospective palliative care study . Methadone's pro-arrhythmic impact appears to be mediated

in part by sleep-related hypoxemia, with QTVI correlating with both methadone dose and oxygen desaturation .

Other Drug Classes

Drug Class	Representative Agents	TdP Risk	Key Findings
VEGFR TKIs	Sunitinib, vandetanib	All-grade QTp: RR 8.66	Vandetanib highest risk
Cancer therapies	Anthracyclines, TKIs	QTc >500ms: 0-5.2%	TdP extremely rare
SSRIs	Citalopram, fluoxetine	15 case reports	Dose-response unclear
5-HT3 antagonists	Ramosetron	No TdP reported	Greater QTc variability
Cisapride	Cisapride	No TdP in 33 monitored	Dose-dependent QTc prolongation

Vascular endothelial growth factor receptor tyrosine kinase inhibitors demonstrated significantly elevated QTc prolongation risk (RR 8.66 for all-grade, 95% CI 4.92-15.2) , with vandetanib showing the highest risk particularly at higher doses . However, serious arrhythmias including TdP remained rare . Among cancer therapeutics broadly, arrhythmias and sudden cardiac death were extremely rare despite QTc prolongation incidence ranging from 0% to 22.7% .

Risk Factors for Drug-Induced Torsades de Pointes

Patient-Related Risk Factors

Multiple studies consistently identified female sex as a significant risk factor for drug-induced TdP. In perioperative TdP cases, 67% occurred in women . Similarly, systematic reviews of case reports for azithromycin , risperidone , and SSRIs demonstrated female predominance. The increased susceptibility in women is attributed to longer baseline QTc intervals and hormonal influences on cardiac repolarization.

Advanced age consistently predicted increased TdP risk across multiple drug classes. Patients aged >60 years were at highest risk of hydroxychloroquine-associated long QT ($P<0.001$) . In hospitalized COVID-19 patients, increased age was among the factors explaining between-study heterogeneity in cardiac toxicity . The halofantrine safety database revealed that 74% of fatal cardiotoxicity events occurred within 24 hours of exposure, with females (70%) and patients from developing countries (71%) over-represented .

Baseline cardiac disease substantially elevates TdP risk. Coronary artery disease, heart failure with reduced ejection fraction, and structural heart disease were consistently identified as risk factors . In patients initiating amiodarone, those with coronary heart disease and severely reduced left ventricular ejection fraction receiving concomitant beta-blocker/digitalis therapy had 25% incidence of ventricular arrhythmia .

Electrolyte Abnormalities

Hypokalemia emerged as a critical modifiable risk factor across studies. It was identified in 26% of perioperative TdP cases (99% CI, 9%-43%) and was highlighted as a risk factor with "very strong evidence" in a systematic review of QTc prolongation determinants . Hypomagnesemia frequently co-occurred with hypokalemia and independently contributed to TdP risk . Electrolyte abnormalities were present in 53% of hospitalized patients with QTc ≥500ms in one institution-wide analysis .

Drug Interactions and Polypharmacy

Concomitant use of multiple QT-prolonging medications substantially increased TdP risk. In psychiatric populations, the prevalence of QT-prolonging drug-drug interactions was 42% (95% CI: 21%-66%) . Among cancer patients, 22% were exposed to therapeutic drug-drug interactions causing QT prolongation . The systematic review by Vandael et al. found "very strong evidence" for increased risk with diuretics, antiarrhythmic drugs, and QTc-prolonging drugs on CredibleMeds list 1 .

Specific high-risk combinations were identified. The combination of hydroxychloroquine with azithromycin was associated with higher QTc prolongation than hydroxychloroquine alone . Concomitant use of voriconazole with amiodarone significantly prolonged QTc intervals . Triple therapy with amiodarone, beta-blockers, and digitalis produced ventricular arrhythmia in 25% of patients .

Genetic Factors

Genetic predisposition influences individual susceptibility to drug-induced TdP. A genetic QT score comprising 61 common genetic variants explained 30% of variability in response to dofetilide (r=0.55, 95% CI 0.09-0.81, P=0.02), 23% for quinidine, and 27% for ranolazine . This genetic score was a significant predictor of drug-induced TdP in an independent validation sample (r^2=12%, P=1×10^{-7}) . Missense variants in ion channel genes such as SCN5A were identified as contributing factors .

Summary of Risk Factors by Evidence Strength

Risk Factor	Evidence Level	Key Supporting Data
Female sex	Strong	67% of perioperative TdP in women ; predominance in case reports

Risk Factor	Evidence Level	Key Supporting Data
Hypokalemia	Very strong	26% of perioperative TdP ; strong evidence in systematic review
QT-prolonging polypharmacy	Very strong	42% prevalence in psychiatric patients ; CredibleMeds list 1 drugs
Baseline QTc prolongation	Strong	OR 7.10 for QTc >500ms ; 28% baseline rate associated with events
Advanced age	Strong	>60 years highest risk for HCQ ; explains heterogeneity
Structural heart disease	Strong	OR for QTc prolongation p<0.01 ; 25% VA in triple therapy
Renal impairment	Moderate	OR 3.5 for QTc >500ms ; dose adjustment required
Genetic variants	Moderate	12-30% of QTc variability explained

QT Monitoring Practices and Thresholds

QTc Correction Formulas

Multiple correction formulas were employed across studies, with Bazett's formula being most common despite known limitations at extreme heart rates. Fridericia's formula

was used in several cardiovascular trials , while Rautaharju's method demonstrated optimal accuracy for TdP prediction (sensitivity 91.30%, specificity 87.33% at 477ms threshold) . A comparative analysis found significant differences in area under the ROC curve between QTcRTH (0.9433) and QTcBZT (0.9225, p=0.002) .

QTc Prolongation Thresholds

Threshold	Clinical Significance
QTc >500ms	High-risk threshold widely used
ΔQTc >60ms	Clinically significant change
QTc >550ms	Adjusted for ventricular conduction abnormalities
QTc >450ms (male)/>470ms (female)	Lower surveillance thresholds

The threshold of QTc >500ms or ΔQTc >60ms from baseline was most commonly used to define clinically significant prolongation requiring intervention . In patients with ventricular conduction abnormalities (QRS ≥120ms), adjusted thresholds of QTc ≥550ms were employed .

Monitoring Protocols

Monitoring intensity varied substantially across studies and clinical settings:

- **Continuous telemetry** was employed for antiarrhythmic drug initiation, with minimum 3-day monitoring for dofetilide and sotalol
- **Serial 12-lead ECGs** were standard for COVID-19 drug protocols (baseline, days 3 and 7)
- **Institution-wide QT alert systems** demonstrated effectiveness in identifying high-risk patients, with alerts triggered at QTc ≥500ms
- **Holter monitoring** was used in selected studies to capture transient arrhythmias

The implementation of computerized QTc alert systems reduced the odds of QTc prolongation (OR 0.65, 95% CI 0.56-0.89, p<0.0001) and reduced prescribing of QTc-prolonging drugs (OR 0.79, 95% CI 0.63-0.91, p<0.03) .

Protective Interventions and Risk Mitigation

Magnesium Administration

Prophylactic magnesium administration demonstrated significant protective effects against ibutilide-induced TdP. In a randomized trial, high-dose magnesium (5g IV over 1 hour followed by 5g over 2 hours) reduced TdP incidence from 3.5% to 0% (p=0.009) while simultaneously improving cardioversion efficacy (67.3% vs 76.5%, p=0.033) . In children with long QT syndrome experiencing TdP, optimal magnesium dosing was 3-12 mg/kg bolus with 0.5-1.0 mg/kg/hr infusion, targeting serum magnesium of 3-5 mg/dL .

Clinical Decision Support Systems

Automated QT alert systems demonstrated clinical utility in reducing medication-related cardiac risk. An institution-wide QT alert system screening 86,107 ECGs identified patients with significantly elevated mortality risk . A pro-QTc score ≥4 predicted mortality with hazard ratio 1.72 (p=0.02), with risk increasing by hazard ratio 1.17 per additional point (p=0.008) . Implementation of such systems reduced QTc prolongation and inappropriate prescribing .

Dose Adjustment and Drug Discontinuation

Dose-dependent relationships between drug exposure and QTc prolongation support dose reduction as a risk mitigation strategy. For dofetilide, dose adjustment based on renal function and QTc response is mandatory . Cisapride demonstrated dose-dependent QTc prolongation (7±21ms at low dose, 13±15ms at high dose) . Discontinuation rates due to

QTc prolongation ranged from 3% for azithromycin combinations to 5% for chloroquine/hydroxychloroquine (95% CI, 1-11%) .

Electrolyte Management

Correction of hypokalemia and hypomagnesemia represents a fundamental risk mitigation strategy. Maintaining normal potassium and magnesium levels was recommended across multiple guidelines and studies . Electrolyte monitoring is particularly important for patients on diuretics or with renal impairment .

Synthesis

The relationship between QT-prolonging medications and TdP in hospitalized patients demonstrates marked heterogeneity across drug classes, patient populations, and clinical contexts. This heterogeneity can be explained through several key factors.

Explaining Variability in TdP Incidence

Drug Class Mechanisms : Class III antiarrhythmic agents demonstrate the highest TdP rates (1-17%) because their therapeutic mechanism directly involves potassium channel blockade and intentional QT prolongation. In contrast, drugs where QT prolongation is an off-target effect (antipsychotics, antibiotics) show substantially lower TdP rates despite causing measurable QTc changes. For example, haloperidol showed no significant increase in major adverse cardiac events (RR 0.93, 95% CI 0.80-1.08) despite being classified as a "known risk" QT-prolonging medication.

Population Severity : TdP incidence varies dramatically with underlying cardiac substrate. In heart failure patients on dofetilide, TdP occurred in 3% , while in ICD patients with more advanced disease, pause-dependent polymorphic VT occurred in 17% . COVID-19 patients, often with multiorgan dysfunction and concurrent QT-prolonging therapies, showed intermediate rates . The Brazilian chloroquine trial illustrates this complexity: 25% of

patients developed QTc >500ms in the high-dose arm, yet TdP was not specifically documented despite 2 fatal ventricular tachycardia events .

Monitoring Intensity : Studies employing continuous telemetry or ICD-based detection captured events that might be missed with intermittent ECG monitoring. The 17% TdP rate with dofetilide in the ICD study likely reflects detection of brief, self-terminating episodes that would not have been identified by periodic ECGs. This suggests that reported TdP incidence in many observational studies underestimates true occurrence.

Reconciling Discrepant Findings

The apparent contradiction between high QTc prolongation rates (often 10-20%) and low TdP incidence (<1% for most non-antiarrhythmic drugs) reflects the poor positive predictive value of QTc prolongation for arrhythmic events. While QTc >500ms is associated with elevated risk, the majority of patients reaching this threshold do not develop TdP. Additional factors modulating the translation from QTc prolongation to arrhythmia include:

- **Repolarization heterogeneity** : Tpeak-Tend intervals were 76ms longer (SE 26ms, P=0.003) and Tpeak-Tend/QT ratios were 0.14 higher (SE 0.03, P<0.0001) in patients who developed TdP compared to those who did not . These measures of transmural dispersion of repolarization may better predict arrhythmic risk than QTc alone.

- **Trigger availability** : TdP typically requires both substrate (prolonged repolarization) and trigger (pause or premature beat). Drugs that also cause bradycardia (beta-blockers, digitalis) may increase TdP risk when combined with QT-prolonging agents .

- **Genetic susceptibility** : The genetic QT score explained 23-30% of variability in drug-induced QTc changes , indicating substantial pharmacogenomic influence on individual responses.

Clinical Implications by Context

Intensive Care Settings : ICU patients face elevated baseline risk due to electrolyte disturbances, multiorgan dysfunction, and polypharmacy. However, randomized data suggest that antipsychotic use for delirium does not significantly increase QTc intervals or fatal arrhythmias when baseline QTc is <550ms . Continuous monitoring capabilities may permit therapeutic use of QT-prolonging agents with appropriate surveillance.

Antimalarial Treatment : For COVID-19 treatment, hydroxychloroquine and chloroquine demonstrated QTc prolongation in approximately 10% of patients , but TdP remained rare (0.06-0.72%) . The combination with azithromycin increases risk , supporting recommendations for ECG monitoring when these combinations are used.

Antiarrhythmic Initiation : Class III antiarrhythmics require mandatory inpatient initiation with continuous monitoring due to their inherent TdP risk. Dose adjustment based on renal function and QTc response, combined with telemetry for 3+ days, represents standard of care . The protective effect of prophylactic magnesium for ibutilide (eliminating TdP risk from 3.5% to 0%) suggests potential benefit for other antiarrhythmic initiations.

Psychiatric Medications : Despite theoretical concerns, randomized trial evidence suggests that contemporary antipsychotic use in hospitalized patients carries low absolute TdP risk. Aripiprazole, brexpiprazole, and olanzapine do not appear to increase QT intervals at licensed doses , while ziprasidone, risperidone, and quetiapine show greater associations with QT prolongation, particularly in overdose . Risk-benefit assessment should consider that observational TdP cases typically involved multiple concurrent risk factors .

Quantitative Risk Estimation

Based on the available evidence, approximate TdP risk by drug class in hospitalized patients can be stratified:

Risk Category	Drug Classes	Estimated TdP Risk	Risk Factors That Increase Risk
High (>1%)	Class III antiarrhythmics (dofetilide, ibutilide)	1-8%	Heart failure, baseline QTc >450ms, renal impairment
Moderate (0.1-1%)	Antimalarials + azithromycin , halofantrine	0.2-0.7%	Advanced age, polypharmacy, critical illness
Low (<0.1%)	Fluoroquinolones, antipsychotics, methadone	<0.1%	Female sex, hypokalemia, congenital LQTS

The evidence supports individualized risk assessment incorporating patient factors (sex, age, baseline QTc, cardiac disease, electrolytes, renal function), drug factors (mechanism, dose, administration route), and monitoring capabilities. Institution-wide QT alert systems and standardized protocols can reduce QTc prolongation events and may improve outcomes .

DISCUSSION

This comprehensive systematic review elucidates the complex, multifaceted relationship between QT-prolonging medications and the risk of torsades de pointes in hospitalized patients. The findings reveal a landscape of highly variable risk that is not solely determined by pharmacologic

properties but is dynamically shaped by the intricate interplay of drug, patient, and environmental factors. The core paradox that emerges from the evidence is the frequent discordance between a relatively common phenomenon—QTc interval prolongation—and the rare occurrence of its most feared consequence, TdP. This discussion will synthesize the key findings, explore the mechanisms underlying this discordance, and examine their clinical implications.

Heterogeneity in TdP Incidence: Drug Mechanisms and Clinical Context

The stark contrast in TdP incidence between drug classes is primarily rooted in their mechanism of action. Class III antiarrhythmic agents like dofetilide and ibutilide are designed to block the rapid component of the delayed rectifier potassium current (IKr), intentionally prolonging the action potential duration and refractory period to treat arrhythmias. Consequently, they carry the highest inherent pro-arrhythmic risk, with TdP incidence ranging from 1.3% to as high as 17% in highly monitored settings (Mazur et al., 2001; Bianconi et al., 2000; Yarlagadda et al., 2017). This wide range itself underscores the importance of context: the 17% rate was observed in ICD patients with continuous monitoring capable of detecting self-terminating episodes, suggesting that lower rates in clinical trials may underestimate true electrophysiological perturbations (Mazur et al., 2001).

In contrast, for drugs like antipsychotics, antibiotics, and methadone, IKr blockade is an off-target, adverse effect. Here, the incidence of actual TdP is orders of magnitude lower (<0.1% to ~1%), even though significant QTc prolongation may occur in a notable subset of patients. For instance, meta-analyses of fluoroquinolones show a clear association with increased arrhythmia risk (OR ~1.85) and cardiovascular mortality, yet the absolute risk increase is estimated at 160 events per million treatment courses, indicating a low baseline probability (Gorelik et al., 2018; Jain et al., 2024). Similarly, large RCT data on haloperidol use in ICU delirium found no significant increase in major adverse cardiac events compared to placebo, challenging long-held assumptions about its routine danger in monitored settings (Garcia et al., 2025; Stollings et al., 2024). This distinction is

crucial for risk-benefit analysis: fear of a rare event should not necessarily preclude the use of a therapeutically necessary drug if appropriate safeguards are in place.

The COVID-19 experience provided a large-scale natural experiment. Antimalarials (HCQ/CQ) caused QTc >500ms in approximately 10% of patients, but the pooled TdP incidence remained low at 0.06-0.72% (Tleyjeh et al., 2020; Oscanoa et al., 2020). However, risk was not uniform. The combination of HCQ with azithromycin consistently led to greater QTc prolongation than HCQ alone, illustrating a potent drug-drug interaction (Moschini et al., 2020; Mansuri et al., 2020). Furthermore, patient factors like advanced age and pre-existing cardiac disease significantly modulated risk within this treated population (Aleem et al., 2021).

The Substrate-Trigger Model: Why QTc Prolongation Alone is Insufficient

The poor positive predictive value of QTc prolongation for TdP can be explained by the classic "substrate and trigger" model of arrhythmogenesis. Prolonged repolarization (the substrate) creates a vulnerable window during phase 2 and 3 of the cardiac action potential. However, TdP typically requires an initiating trigger, most often a premature ventricular complex (PVC) that occurs during this vulnerable period, frequently following a preceding pause (pause-dependence) (Mazur et al., 2001). Therefore, a patient may have a significantly prolonged QTc but never experience the specific trigger, thus avoiding TdP.

This review identifies factors that enhance either the substrate or the likelihood of triggers:

- **Enhancing the Substrate:** *Electrolyte imbalances*, particularly hypokalemia and hypomagnesemia, are critical modifiable factors. Hypokalemia reduces outward potassium currents, further delaying repolarization and was present in a significant proportion of perioperative TdP cases (Johnston et al., 2013). *Genetic susceptibility*, quantified by polygenic risk scores, can explain 12-30% of the variability in an individual's QT response to a provoking drug, identifying those with an inherently more unstable repolarization substrate (Strauss et al., 2017). *Increased dispersion of repolarization*, measured indirectly

by intervals like Tpeak-Tend, may be a more direct marker of arrhythmic risk than global QTc prolongation itself (Tse et al., 2018).

- **Providing Triggers:** *Bradycardia and pauses* are potent triggers. Drugs that cause bradycardia (e.g., beta-blockers, digitalis) can paradoxically increase TdP risk when combined with a QT-prolonging drug by creating the requisite pauses (Schrickel et al., 2006). Underlying sinus node dysfunction or AV block also contributes. *Sympathetic surge* in settings of acute illness, stress, or sudden arousal (e.g., from sleep apnea, which is relevant for methadone risk) can increase PVCs and trigger events (Solhjoo et al., 2021).

Risk Stratification: Integrating Patient, Drug, and Clinical Factors

Effective management requires moving beyond a binary "risk drug" list to a multidimensional risk assessment. This synthesis allows for the creation of a stratified risk model:

1. **High-Risk Scenarios:** A patient with multiple risk factors (e.g., an elderly woman with heart failure and hypokalemia) starting a high-risk drug (e.g., intravenous dofetilide). This scenario demands mandatory inpatient initiation with continuous telemetry, rigorous electrolyte correction, and dose adjustment for renal function (Møller et al., 2001).
2. **Moderate-Risk Scenarios:** A hospitalized patient with one or two risk factors (e.g., mild renal impairment, concomitant diuretic) requiring treatment with a moderate-risk drug (e.g., levofloxacin for pneumonia). This warrants baseline ECG, correction of modifiable factors (electrolytes), and consideration of alternative agents if available (Morganroth et al., 2005).
3. **Lower-Risk Scenarios:** A patient with no major risk factors requiring a drug with low torsadogenic potential (e.g., low-dose olanzapine). Routine baseline ECG may still be prudent, but excessive caution may unnecessarily delay therapy (Shen et al., 2024; Aronow & Shamliyan, 2018).

The evidence strongly supports that *polypharmacy* with multiple QT-prolonging drugs is a major independent risk factor. Studies in psychiatric and cancer populations show a high prevalence of such interacting combinations, dramatically increasing the risk burden (Saravana Kumar Ramasubbu et al., 2022, 2025). A systematic medication review to minimize such combinations is a fundamental safety intervention.

Monitoring and Mitigation: From Detection to Prevention

Optimal monitoring is the cornerstone of safe management. The choice of QTc correction formula matters; while Bazett's is most common, it over-corrects at high heart rates. Formulas like Fridericia's or, as evidence suggests, Rautaharju's method, may provide more accurate risk prediction, especially in hospitalized patients with variable heart rates (Othong et al., 2018). The consensus high-risk threshold remains QTc >500 ms or an increase >60 ms from baseline.

Proactive mitigation strategies show promise:

- **Electrolyte Management:** Aggressive maintenance of normal serum potassium (>4.0 mEq/L) and magnesium levels is a low-cost, high-impact intervention (Vandael et al., 2017).
- **Pharmacologic Protection:** The dramatic reduction of ibutilide-induced TdP from 3.5% to 0% with high-dose magnesium infusion is a powerful example of targeted prophylaxis, likely due to magnesium's effect on stabilizing cardiac membrane potential and reducing calcium influx (Patsilinakos et al., 2010).
- **Technology-Driven Safety:** Computerized QTc alert systems integrated into electronic health records can effectively identify at-risk patients, reduce inappropriate prescribing of interacting drugs, and prompt corrective actions (Elena Tomaselli Muensterman & Tisdale, 2018). These systems represent a scalable solution for institution-wide risk reduction.

Limitations and Future Directions

This review is subject to the limitations of the included studies, which are predominantly observational and heterogeneous. Reporting bias is likely, as TdP is rare and may be under-recognized or under-reported. The focus on hospitalized patients, while a strength, limits generalizability to outpatient settings.

Future research should prioritize: 1) Developing and validating integrated risk prediction scores that combine clinical factors, genetic data, and perhaps continuous ECG analytics for personalized risk assessment; 2) Conducting pragmatic trials to determine the optimal intensity and duration of ECG monitoring for specific drug classes in different patient subgroups; 3) Further exploring the protective efficacy of magnesium and other agents for high-risk drug initiations beyond ibutilide; and 4) Standardizing definitions and outcome reporting in studies of drug-induced arrhythmias to enable more robust meta-analyses.

CONCLUSION AND RECOMMENDATIONS

Conclusion

This systematic review confirms that drug-induced torsades de pointes is a real but heterogeneously distributed threat in hospitalized patients. The risk is highest with Class III antiarrhythmic agents, moderate with certain drug combinations (e.g., HCQ+azithromycin), and generally low with many other QT-prolonging medications when used in isolation. However, the absolute risk for any individual patient is not defined by the drug alone but is exponentially modulated by a confluence of patient-specific vulnerabilities (female sex, age, cardiac disease, electrolytes, genetics) and clinical context (polypharmacy, critical illness, monitoring intensity). The translation from QTc prolongation to TdP requires the convergence of a susceptible repolarization substrate with a triggering event, explaining why marked QT elongation is common but TdP is rare. Effective management therefore hinges on a nuanced understanding of this multifactorial risk architecture.

Recommendations

1. **Adopt a Stratified Risk Assessment:** Clinical practice should implement a structured pre-prescription assessment for patients requiring QT-prolonging drugs. This should evaluate for key risk factors: female sex, age >65, known heart disease/heart failure, baseline QTc >450ms, renal/liver impairment, and electrolyte abnormalities (especially K+ and Mg++). A simple risk score could guide monitoring intensity.

2. **Minimize Polypharmacy Hazards:** Conduct a thorough medication reconciliation to identify and avoid, when possible, combinations of multiple QT-prolonging drugs or combinations with drugs that promote bradycardia/pauses. Utilize resources like the CredibleMeds list.

3. **Implement Standardized Monitoring Protocols:**
    - For **high-risk drugs (Class III antiarrhythmics)**: Mandate inpatient initiation with continuous telemetry monitoring for ≥72 hours, with baseline and serial ECGs. Dose must be adjusted for renal function.
    - For **moderate-risk drugs/scenarios**: Obtain a baseline ECG and correct all electrolyte abnormalities prior to administration. Follow-up ECG monitoring (e.g., at 3-7 days) is prudent, especially if risk factors are present or therapy is prolonged.
    - Use **Fridericia's or Rautaharju's formulas** for QTc correction in preference to Bazett's, particularly in patients with heart rates outside 60-100 bpm.
    - Define actionable thresholds: **QTc >500 ms** or **ΔQTc >60 ms** should trigger re-evaluation of therapy, correction of modifiable factors, and consideration of alternative agents.

4. **Employ Proactive Mitigation Strategies:**
    - **Maintain electrolytes:** Aim for serum potassium >4.0 mEq/L and normal magnesium levels, especially in patients on diuretics.

- **Consider magnesium prophylaxis:** For patients initiating ibutilide, adopt a protocol of high-dose magnesium infusion as it effectively eliminates TdP risk and improves cardioversion efficacy.
- **Implement Clinical Decision Support (CDS):** Hospitals should invest in and utilize computerized QTc alert systems within the EHR. These systems can automatically identify prolonged QTc, flag risky drug combinations, and prompt clinician review, thereby reducing adverse events.

5. **Education and Institutional Policy:** Develop and disseminate institutional guidelines for the management of QT-prolonging medications. Educate physicians, pharmacists, and nurses on risk factors, monitoring requirements, and mitigation strategies to foster a culture of safety.
6. **Personalize Future Management:** As evidence evolves, consider the potential for genetic testing in select high-risk cases (e.g., strong family history of sudden death or extreme QT response) to further refine individual risk profiles.

By moving from a fear-based, blanket avoidance strategy to an evidence-informed, stratified management approach, clinicians can safely harness the benefits of necessary medications while robustly protecting hospitalized patients from the rare but serious threat of drug-induced torsades de pointes.

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