Turk J Pharm Sci 2026;23(2):105-112
DOI: 10.4274/tjps.galenos.2026.43334

ORIGINAL ARTICLE

Exploring the Role of Metabolites in Torsadogenic Risk Assessment: A Text-Mining Approach

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ABSTRACT

Objectives: Torsades de pointes (TdP) is a life-threatening ventricular arrhythmia often caused by the inadvertent inhibition of the human ether-à-go-go-related gene (hERG). Conventional pre-market evaluations, which emphasize parent molecules, often yield inaccurate predictions due to the multifaceted nature of TdP. This study aimed to investigate the role of metabolites and their interplay with parent molecules in the manifestation of TdP.

Materials and Methods: A literature-based text-mining approach was employed, using the adverse outcome pathway-helpFinder tool. The analysis scrutinized 64 selected active ingredients, categorized by their torsadogenic risks, to evaluate the distinct proarrhythmic contributions of their metabolites.

Results: This text-mining exploration revealed qualitative evidence that metabolites variably modulate TdP vulnerability. Specifically, certain metabolites can independently exacerbate proarrhythmic profiles, whereas others do not inhibit hERG and therefore represent safer therapeutic alternatives than their parent molecules.

Conclusion: Metabolites play a paramount role in altering the torsadogenic risk profile of pharmaceutical products. Incorporating comprehensive metabolite data into cardiac safety evaluations is essential for a more accurate risk assessment and should be considered in future pharmaceutical development.

Keywords: Adverse outcome pathway (AOP), cardiotoxicity, human ether-à-go-go-related gene (hERG), metabolites, torsades de pointes (TdP)

INTRODUCTION

Various medications, encompassing anti-histamines, anti-microbials, anti-psychotics, and gastrointestinal stimulants, have been withdrawn from the market in the past decades due to their association with the life-threatening ventricular arrhythmia, torsades de pointes (TdP).[1,2] Compounds that induce TdP tend to prolong the QT interval on the electrocardiogram (ECG).[1]

Regulatory directives, including non-clinical [International Council for Harmonization (ICH) S7A and S7B http://www.ich.org] and clinical evaluations (ICH E14), have been implemented to delineate the requisite studies for assessing whether a new drug has the potential to prolong the QT interval, despite the QT interval prolongation being an insufficient predictor of TdP.[1] Sanguinetti et al.[3] underscored the significance of the association between QT prolongation and the blockade of voltage-dependent K+ channels, predominantly the rapid delayed rectifier current (I_{Kr}) pivotal in ventricular repolarization. Moreover, the molecular interaction involving this channel is correlated with the human ether-à-go-go-related gene (hERG), which encodes the channel's primary subunit.[3] Figure 1 schematically illustrates the mechanism of TdP initiation, beginning with the blockade of hERG.[4]

Recent advancements indicate that the cardiac safety assessments of drugs largely rely on *in vitro* hERG blockade,

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Received: 01.09.2025 **Accepted:** 18.08.2026 **Publication Date:** 01.09.2026

Cite this article as: Bilgin E, Tuğcu G, Aydın A. Exploring the role of metabolites in torsadogenic risk assessment: a text-mining approach. Turk J Pharm Sci. 2026;23(2):105-112

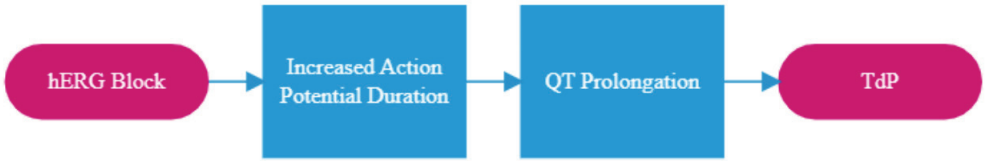

Figure 1. Mechanism of TdP caused by hERG block.
hERG, human ether-à-go-go-related gene; TdP, torsades de pointes.

the I_{Kr} current induced by the compounds, as well as *in vivo* QT interval prolongation.[5] In the case of *in vitro* hERG blockade, the hERG IC50 value is usually the initial metric employed to assess the torsadogenic risk during the drug development process; the 50% inhibitory concentration value, or the amount of drug needed to lower an ion channel's current (hERG I_{Kr} current) by 50%, is used to measure a compound's affinity for a particular channel.[6] Indeed, various studies have revealed that the obstruction of I_{Kr} amplifies the probability of proarrhythmic occurrences by fostering drug-induced long QT syndrome. Clinically, the emergence of TdP has historically been correlated with the extension of the QT interval. Nonetheless, certain hERG blockers, such as verapamil, do not induce TdP.[5]

Current methodologies for evaluating *in vitro* hERG potassium channel activity, *in vivo* pre-clinical assessments, and clinical evaluations of effects on the corrected QT (QTc) interval of the ECG are recognized as sensitive approaches for identifying torsadogenic risk. The QT interval on an ECG represents the total duration of ventricular depolarization and repolarization.[7] Since this interval is influenced by heart rate, it is adjusted using established correction formulas to calculate the QTc interval. Consequently, QTc prolongation signifies an abnormal delay in ventricular repolarization, serving as a primary biomarker for increased susceptibility to TdP and other potentially fatal arrhythmias.[8] However, these techniques may require greater precision. Moreover, the efficacy of these screening methods has been criticized because *in silico* methods predominantly focus on predicting the drug binding affinities for the hERG potassium channel, thereby providing limited information regarding the drug's impact on ventricular repolarization.[9] Furthermore, current guidelines have inherent limitations that can inadvertently halt the development of otherwise valuable therapeutics.[10]

Age, gender, electrolyte imbalances, variations in heart rate (especially bradycardia), and structural heart disease are well-recognized concurrent risk factors that significantly influence the incidence of TdP. However, the occurrence of TdP is also attributed to multi-channel interactions, hERG-independent proarrhythmic mechanisms, and the influence of drug metabolites or of the drug's anti-arrhythmic effects. These factors highlight the limitations of relying solely on surrogate markers for estimating actual TdP risks. Consequently, safety assessments should include a comprehensive evaluation that considers the combined effects of all active substances (such as parent drugs and their metabolites), rather than assessing only the parent molecule. The route-dependent pharmacokinetics of pharmaceuticals should be meticulously considered during drug safety studies.[11]

In our analysis, we used core components of the adverse outcome pathway (AOP) approach. This involves a sequence of events commencing with the interaction of a stressor with an organism that causes a disruption at the molecular level, referred to as the molecular initiating event (MIE). This sequence can then evolve through a series of interconnected "key events (KEs)", culminating in an adverse outcome (AO). The AO is considered pertinent to evaluating risk and informing decision-making.[12]

The ultimate goal of our analysis was to shed light on the role of metabolites that may affect TdP risk indicators, such as hERG inhibition and QT prolongation. The information obtained from data mining can benefit future drug design, since relying solely on the parent molecule and its hERG inhibition and/or QT prolongation may lead to false-positive risk assessments.

MATERIALS AND METHODS

We used AOP-helpFinder (https://aop-helpfinder.u-paris-sciences.fr/index.php), a web-based tool, to retrieve relevant literature from the PubMed database.[13] The operation of this system requires two primary inputs: the stressors of interest and biological events, encompassing MIE, KEs, and/or AO. Prior to execution, the tool offers two optional parameters to customize the output: a "reduced search" option and a "refinement filter". In addition, users may choose the output format.[14] Applying a 20% "reduced search" threshold is recommended because the initial portion of an abstract typically outlines a hypothesis and can therefore lead to false-positive associations.[13,15] The refinement filter provides a lemmatization procedure and reduces words to their basic, meaningful forms.[13,14]

Llopis-Lorente et al.[16] previously developed an *in silico* tool for the pre-clinical assessment of TdP risk. For their study, they compiled a comprehensive dataset of active ingredients from the CredibleMeds database and supplemented it with relevant literature for compounds not listed therein.[16] We specifically selected this robust dataset as our foundation because it is highly validated for predictive toxicology applications. Using a well-established, curated list of structurally diverse compounds allowed our text-mining study to move beyond anecdotal case reports and to systematically explore the original hypothesis that metabolites consistently modulate the TdP risk profile across a broad, representative pharmacological spectrum. This reference dataset divided the compounds into four categories: known risk, possible risk, conditional risk, and lack of evidence

for TdP risk. In our AOP-helpFinder analysis, the strict inclusion criterion was to include active ingredients with a documented risk of TdP. Therefore, from the initial list of 109 compounds, we excluded the 45 drugs categorized as having no evident TdP risk. This filtering process resulted in our final dataset of 64 active ingredients, which were then used as the stressors of interest in our study. The list of active ingredients and their respective torsadogenic risk levels is shown in Table 1.

For the biological events input required by AOP-helpFinder, we selected three specific keywords: "metabolism", "metabolite", and "torsades de pointes". To specifically investigate the contribution of metabolites to TdP risk, we restricted our search to abstracts containing at least one of these keywords, thereby refining the output. We applied the "reduced search" recommendation to our results to avoid hypothesis sections of abstracts that might produce false-positive results. The refinement filter (lemmatization) was not used because our selected keywords were already in their base forms.

The literature search encompassed all available publications in the PubMed database up to November 2022. The AOP-helpFinder tool was executed on 19 Nov 2022, capturing a comprehensive snapshot of the literature up to that point. Following execution of the search, the retrieved abstracts were exported to an Excel spreadsheet and subsequently manually reviewed and categorized. Articles deemed pertinent were then subjected to a comprehensive full-text review for in-depth analysis. Ethics committe approval and informed consent were not required for our study.

RESULTS

The AOP-helpFinder tool yielded results consistent with our pre-defined search parameters. The generated output included the publication dates, titles, PubMed IDs, and abstracts of articles co-mentioning at least one of the three keywords. Table 2 shows the number of abstracts, grouped by keywords, for each TdP risk classification.

A total of 23,042 abstracts containing the keywords were retrieved. To prevent selection bias, strict criteria were established for the manual categorization of these abstracts. Abstracts were included for full-text review only if they met the following criteria: (1) explicit discussion of the pharmacokinetic profile of the parent drug, highlighting at least one specific active metabolite; and (2) presentation of comparative empirical data (*in vitro, in vivo*, or clinical) regarding cardiotoxic parameters (such as hERG blockade, QT prolongation, or TdP incidence) between the parent molecule and its metabolite. Studies focusing solely on non-cardiac adverse events, generic pharmacokinetic studies without cardiotoxicity data,

Table 1. Torsadogenic risk levels of 64 active ingredients used in our analysis.

Known TdP risk (n = 37)		Possible TdP risk (n = 14)	Conditional TdP risk (n = 13)
Ajmaline	Halofantrine	Clozapine	Amitriptyline
Amiodarone	Haloperidol	Desipramine	Diphenhydramine
Astemizole	Ibutilide	Dolasetron	Famatidine
Azalimide	Levofloxacin	Lapatinib	Fluvoxamine
Azithromycin	Methadone	Lopinavir	Metronidazole
Bepridil	Moxifloxacin	Nilotinib	Nelfinavir
Chloroquine	Ondansetron	Paliperidone	Paroxetine
Chlorpromazine	Pimozide Procainamide	Risperidone	Propafenone
Cilostazol	Quinidine	Ritonavir	Quetiapine
Cisapride	Sotalol	Saquinavir	Quinine
Clarithromycin	Sparfloxacin	Sertindole	Ranolazine
Disopyramide	Tedisamil	Sunitinib	Solifenacin
Dofetilide	Terfenadine	Tolterodine	Voriconazole
Domperidone	Terodiline	Tamoxifen	
Donepezil	Thioridazine		
Dronedarone	Vandetanib		
Droperidol			
Erythromycin			
Flecainide			
Gatifloxacin			

TdP, torsades de pointes.

Table 2. The number of abstracts reviewed divided by the keywords according to torsadogenic risk levels.

Known TdP risk (n = 37)	Possible TdP risk (n = 14)	Conditional TdP risk (n = 13)
Metabolism = 6,305	Metabolism = 4,867	Metabolism = 2,627
Metabolite = 3,964	Metabolite = 2,397	Metabolite = 1,354
TdP = 1,346	TdP = 82	TdP = 100
Total number = 11,615	**Total number** = 7,346	**Total number** = 4,081

TdP, torsades de pointes.

or reviews lacking primary comparative data were strictly excluded. Following this rigorous manual review, 21 highly relevant articles were selected for the core qualitative analysis. Specifically, this included 12 articles from the known risk group, 4 from the possible risk group, and 5 from the conditional risk group. Among these comprehensively analyzed texts, the most illustrative examples of distinct parent-metabolite dynamics were detailed in the subsequent sections.

Active ingredients with known TdP risk

Regarding the active ingredients in the known TdP risk category, we identified relevant comparative data for thioridazine, halofantrine, methadone, procainamide, quinidine, terfenadine, and astemizole.

Salih et al.[17] discovered that both thioridazine and its metabolite, mesoridazine, similarly affect the QTc interval. Their research thus demonstrates that identical QTc prolongation is associated with both thioridazine and mesoridazine following oral administration.

It has been established that the anti-malarial drug halofantrine is linked not only to QT prolongation but also to fatal and non-fatal arrhythmias in individuals without pre-existing cardiac issues. Mbai et al.[18] concluded that both the primary drug halofantrine and its metabolite N-desbutylhalofantrine result in significant blockade of the hERG (K+) channel. Despite previous assertions that N-desbutylhalofantrine is safer than halofantrine as an antimalarial, their study suggests only a slight increase in the safety margin with respect to cardiotoxicity associated with QT interval prolongation.[18]

A pilot study found a substantial association among oral dosage, enhanced methadone metabolism (evidenced by an elevated plasma concentration of the primary methadone metabolite), and significant changes in the QTc interval. The study suggested that the oral dose and plasma concentration of 1,5-dimethyl-3,3-diphenylpyrrolidene, a methadone metabolite, could serve as valuable indicators for identifying patients susceptible to methadone-related arrhythmias.[19]

Another study reported a case of QT interval prolongation in a hemodialysis patient caused by a procainamide metabolite. The patient had been prescribed procainamide for a specific clinical indication, and one-month following procainamide administration, an ECG revealed QT interval prolongation, and procainamide dosage was reduced. However, the patient was transported to the hospital the next day following cardiopulmonary arrest. In a blood analysis, levels of N-acetyl procainamide (NAPA), a metabolite of procainamide, were significantly elevated above the recommended threshold. The administration of procainamide was stopped when NAPA was identified as the cause of the QTc prolongation. By the seventh day, the NAPA levels fell below the recommended threshold, and the QT intervals normalized. This case report documents the first reported case of long QT syndrome induced by NAPA in a hemodialysis patient. It was proposed that concentrations of both procainamide and NAPA should be monitored.[20] Procainamide, along with its metabolite NAPA, is strongly associated with the induction of TdP.[21]

Past studies have proposed that TdP induced by quinidine could be attributed to external factors such as hypokalemia or unidentified active metabolites. It was discovered that, similar to quinidine at prolonged cycle durations, its metabolites—dihydroquinidine and 3-hydroxyquinidine—prolonged the action potential and led to early afterdepolarizations.[22]

The second-generation antihistamine, terfenadine, has an active metabolite, fexofenadine, which does not cause QT prolongation. Medicinal chemists have suggested using fexofenadine/terfenadine as examples for designing zwitterionic compounds to prevent cardiotoxicity.[23] However, fexofenadine, the active metabolite of terfenadine, does not inhibit either hERG or Kv1.5, even though terfenadine efficiently blocks hERG K+ channels.[24] Due to the characteristics of terfenadine's active metabolite, fexofenadine received approval in July 1996. Because a safer version of an identical medication had been developed, the Food and Drug Administration (FDA) requested removal of terfenadine in 1997.[25]

Recent findings have indicated that the desmethyl metabolite of astemizole, which has similar potency at hERG but is present at significantly higher levels than its parent compound, likely plays a substantial role in cardiac repolarization.[26] Corroborating this, another study has posited that the proarrhythmic activity of desmethylastemizole, a metabolite of astemizole, might primarily account for the clinically observed QT prolongation and TdP associated with astemizole use.[27] Zhou et al.[28] suggested that desmethylastemizole is the principal contributor to the long QT syndrome observed in patients following astemizole administration because it becomes the predominant component in the bloodstream.

Active ingredients with possible TdP risk

Among active ingredients classified in the possible TdP risk category, the literature most prominently addresses risperidone and paliperidone.

Leishman articulated that compounds with an intermediate risk of TdP are typically susceptible to metabolic inhibition, or tend to have therapeutically active primary metabolites, or both. Some of these metabolites are recognized for their ability to block the hERG channel. Risperidone is one of the best-known of these molecules. Calculating the therapeutic window of risperidone based solely on the parent molecule and thereby revealing the relationship between hERG inhibition potential and clinical exposure actually led to risperidone being characterized as having an almost low or no TdP risk. However, hERG blockers include risperidone and its primary metabolite, paliperidone.[26] Reports suggest that the metabolite paliperidone is primarily responsible for the QTc prolongation observed after risperidone administration.[29] This circumstance illustrates why, in past years, some authors characterized risperidone as not associated with TdP. However, risperidone has recently been categorized as having an intermediate or possible risk of inducing TdP.[26] Ito et al.[30] reported on two patients experiencing severe arrhythmia due to risperidone. In these two instances, serum concentrations were examined, revealing that only the levels of the parent-molecule metabolite, paliperidone

[9-hydroxyrisperidone (9-OH-RIS)], were elevated. These findings led them to suggest that 9-OH-RIS is an essential indicator of risperidone toxicity and may cause life-threatening arrhythmia.[30]

According to clinical information, paliperidone is thought to be more strongly associated with QT prolongation than risperidone.[29] Additionally, paliperidone, an active metabolite of risperidone, has been reported to modestly prolong the QT interval, possibly by inhibiting hERG K+ channels. Since drug-induced QT interval prolongation often precedes the emergence of TdP—a ventricular arrhythmia that can be lethal—further research is recommended to explore this potential effect of paliperidone.[31]

Active ingredients with conditional TdP risk

Regarding the conditional TdP risk category, the most illustrative literature focuses on ranolazine, propafenone, and quetiapine. Moreno et al.[32] revealed that the interaction of ranolazine's active metabolites with late INa (I_{NaL}) and I_{Kr} significantly influence the therapeutic efficacy of the parent molecule and the likelihood of side effects. Although ranolazine mainly targets and inhibits the I_{NaL}, a component of the Na+ current that causes depolarization, it also interacts with and restrains the repolarizing hERG current I_{Kr} at therapeutic dosages. Overall, the result is a mild, concentration-dependent QTc prolongation. Ranolazine, like other medications, is extensively metabolized, predominantly by cytochrome P450 enzymes. Similar to the parent compound, Ranolazine, all 11 active metabolites potently inhibit I_{NaL} by 12% to 57% at 10 µmol/L. However, the inhibition of I_{Kr} produced by the four primary metabolites, which make up 30% to 40% of the original drug, is significantly less (40–50% inhibition at 50 µmol/L). According to the findings of the study, ranolazine's therapeutic potential is mainly derived from its active metabolites, which exhibit strong selectivity between repolarizing current blockade, I_{Kr}, and pathological current blockade, I_{NaL}. In order to limit the length of the ventricular action potential, I_{Kr} and I_{NaL} must be in equilibrium under the ventricular action potential. For ranolazine and its metabolites, the balance is in the direction of I_{NaL}, which causes the torsadogenic potential of ranolazine to be less.[32]

Arias et al.[33] demonstrated that propafenone and its primary active metabolite, 5-hydroxy-propafenone, block the hERG channel comparably by mainly attaching to the channel's open state. Compared with an intravenous dose yielding equivalent propafenone concentrations, the elevated 5-hydroxy-propafenone levels following oral treatment were associated with considerably greater prolongations of PQ (atrioventricular conduction time) and QRS (ventricular depolarization duration).[34] On a standard ECG, the PQ interval represents the time required for an electrical impulse to propagate from the atria to the ventricles. The QRS duration represents the time taken for the depolarization (and subsequent contraction) of the ventricles. Therefore, QRS prolongation indicates a dangerous delay in ventricular electrical activation and can independently exacerbate a drug's proarrhythmic risk profile.[35] Finally, a study was conducted to investigate the effects of propafenone and its primary metabolite, 5-hydroxy-propafenone, on ECG intervals in eight healthy individuals. A statistically significant additional effect on the QRS duration was observed in seven out of eight participants when both propafenone and 5-hydroxy-propafenone were present.[36]

Prior research has shown that quetiapine and its major metabolite, norquetiapine, have contrasting effects on cardiac currents. While quetiapine blocks the hERG potassium current, norquetiapine blocks the current through the human voltage-gated sodium channel Nav1.5 (hNav1.5). This suggests that norquetiapine's ability to block the sodium current could reduce the duration of cardiac action potentials, thereby mitigating the risks of QT prolongation that arise due to the inhibition of hERG potassium currents.[37]

The results, based on the three sections above, show that metabolites can increase or decrease the TdP risk of parent molecules due to various factors.

- While the parent molecule carries a known risk of TdP, its primary metabolite may not show QT prolongation and may therefore be used instead (e.g. terfenadine - fexofenadine).

- The metabolite formed may be even more arrhythmogenic than the parent molecule in terms of TdP risk (e.g., astemizole-desmethylastemizole).

- Metabolites may cause prolongation of the QT interval to the same extent as the parent molecule and increase the risk of TdP (e.g., thioridazine-mesoridazine).

- Even if the parent molecule inhibits the hERG channel, the metabolite formed can inhibit different currents and reverse the associated risk, so that it is not directed toward TdP (e.g., quetiapine–norquetiapine).

DISCUSSION

Mirams et al.[6] emphasized that, while accounting for the hERG blockade is essential when assessing the risk of torsadogenesis, it is insufficient on its own for accurate prediction. This is due to exceptions to the initial approach, indicating that a more comprehensive evaluation is necessary to accurately predict torsadogenic risk.[6] Apart from hERG inhibition, many factors may affect a patient's TdP risk, including multi-channel interactions, active metabolites, and anti-arrhythmic effects of a drug. Furthermore, patient-specific factors such as age, gender, electrolyte imbalances, and underlying cardiac conditions play crucial roles in TdP risk.[11] Consequently, relying on a single parameter for TdP risk evaluation can lead to erroneous conclusions and hinder the development of otherwise safe therapeutics.

In this study, we demonstrate that incorporating comprehensive metabolite data—rather than relying solely on the parent molecule's properties—yields a significantly more accurate risk assessment.

In this context, the AOP framework utilized in our study presents a distinct advantage over traditional observational reviews. Rather than evaluating risk factors in isolation, researchers using the AOP approach provide a structured, mechanistic

linkage from a MIE (such as parent- or metabolite-driven hERG blockade) to the final AO (TdP). This systematic synthesis of fragmented literature into a cohesive weight-of-evidence model allows for a more dynamic, predictive, and multi-layered risk assessment than conventional single-endpoint methodologies.

Leishman proposed a method that considers not only the parent compound but also its metabolic products when assessing torsadogenic risk. It was noted that evaluating the therapeutic window based solely on the exposure to the parent compound could create a substantial margin between clinical exposure and hERG potency. This factor may explain why, in previous years, some authors did not associate risperidone with TdP. However, when intrinsic and extrinsic factors are considered, risperidone is now classified as a possible TdP risk, and one of the most significant contributors to this reclassification is its metabolite paliperidone.[26]

A notable instance of this is Dolasetron. Thirteen years after its introduction to the market, the FDA withdrew the injectable form of Dolasetron in 2010 due to its associated risk of TdP. The core issue that surfaced was Dolasetron's function as a prodrug: its active metabolites contributed significantly to the risk of TdP.[11]

A previous *in silico* study demonstrated that the false-negative risk assessment of dronedarone likely occurred because its active metabolite was excluded from the model. This finding is critical because the metabolite accounts for one-third of the pharmacological activity and exhibits channel-blocking properties similar to those of the parent molecule. Therefore, when the metabolite was not taken into account, the *in silico* study showed that the molecule had a low TdP risk.[5]

As illustrated by the terfenadine-fexofenadine example, an active metabolite can replace the parent molecule, thereby providing a safer therapeutic alternative.[25]

Our text-mining results, alongside well-documented historical examples such as astemizole and terfenadine, illustrate how metabolites can fundamentally alter the torsadogenic risk profile relative to that of the parent molecule. To provide a more reliable and systematic framework for the TdP risk assessment of novel therapeutics, we propose the evaluation flowchart presented in Figure 2.

Study limitations

As presented in our results, we observed a significant quantitative disparity in the number of retrieved abstracts concerning TdP across the risk categories (1,346 abstracts for the known risk group versus 82 and 100 for the Possible and Conditional groups, respectively). This discrepancy is not indicative of a lack of sensitivity in our search strategy, which was uniformly applied across all groups. Rather, it reflects the well-documented publication bias in the toxicological literature: drugs classified as "known risk" have historically been the focus of far more extensive and targeted research on cardiotoxicity. Conversely, "possible" and "conditional" risk drugs generally have fewer publications explicitly linking them to TdP, either because they are newer compounds or because their proarrhythmic events manifest only under highly specific, less frequently documented clinical scenarios.

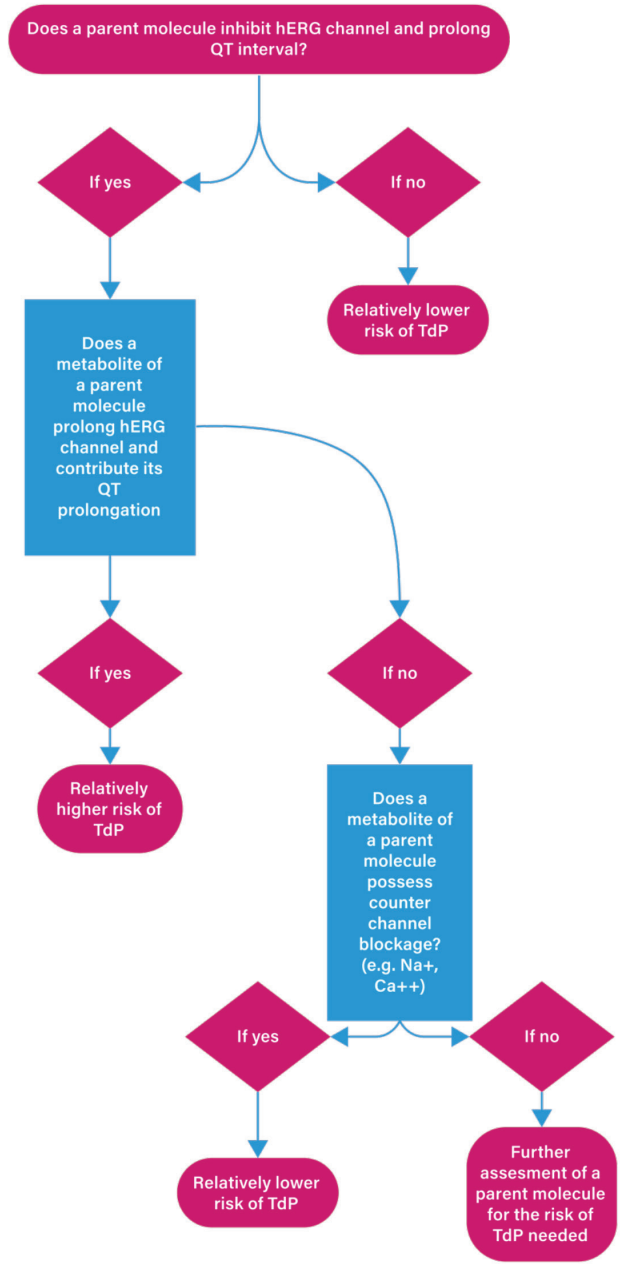

Figure 2. Proposed flowchart for better decision-making of novel products' torsadogenic risk assessment.

hERG, human ether-à-go-go-related gene; TdP, torsades de pointes.

Although assessing the 2D structural similarity of the evaluated compounds using chemoinformatic metrics like the Tanimoto coefficient provides valuable insights, it is well recognized that drug-induced hERG blockade and subsequent TdP can be triggered by structurally diverse chemical scaffolds. Given that the primary methodology of this study is rooted in literature-based text-mining for constructing an AOP framework rather than in ligand-based structure-activity relationship

modeling, detailed computational structural-alert analysis was considered to be beyond the scope of the current study. Nonetheless, integrating such molecular structural parameters with metabolite data remains a promising multimodal approach for future predictive toxicology models.

CONCLUSION

The inhibition of the hERG channel by a drug plays a pivotal role in QT prolongation and the consequential risk of TdP. Our analysis underscores that, for a more nuanced and accurate prediction of TdP risk in new pharmaceutical products, substantial emphasis should be placed on both the parent molecules and their metabolites. These metabolites, through their effects on the hERG channel and broader multi-channel interactions, play a paramount role in modulating QT prolongation. By comprehensively assessing both the parent molecules and their metabolites, the predictability and precision of TdP risk evaluation for novel products are significantly improved, fostering a more robust understanding of and facilitating mitigation of unforeseen TdP risks.

Ethics

Ethics Committee Approval: As the study did not involve human participants or animals, ethical approval from the relevant ethics committees was not required.

Informed Consent: As the study did not involve human participants or animals, patient informed consent was not required.

Footnotes

Authorship Contributions

Concept: E.B., G.T., A.A., Design: E.B., G.T., A.A., Data Collection or Processing: E.B., G.T., A.A., Analysis or Interpretation: E.B., G.T., Literature Search: E.B., Writing: E.B.

Conflict of Interest: The authors declare no conflicts of interest.

Financial Disclosure: The authors declared that this study received no financial support.

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