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QT Myopia and Cardiac Safety: Expanding the Aperture of Arrhythmia Assessment in Early Phase Drug Development

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ABSTRACT

Regulatory agencies such as the Food and Drug Administration (FDA), European Medicines Agency (EMA), Health Canada, and the Japanese Pharmaceutical and Medical Device Agency (PMDA) provide scientific and public health guidance with cardiac safety being paramount in drug development of new investigational products (IP). Cardiac safety is not a singular undertaking but rather encompasses many elements to be considered beyond measurement of the QT interval before a candidate drug receives regulatory approval. These safety assessments may include evaluation of additional targeted and non-targeted cardiovascular effects such as whether the IP mediates cardiac or pericardial inflammation or affects blood pressure, the coronary or systemic vasculature, heart valves, or cardiac muscle. Historically, the primary cardiac safety concern of regulators was the proarrhythmic risk of new chemical entities and has been centered on the QT interval as a marker of a drug's ability to delay ventricular repolarization and its potential to precipitate lethal ventricular rhythms. Beyond this biomarker, there has only been tangential focus on the PR and QRS intervals, conduction disturbances and supraventricular arrhythmias, and formal regulatory guidance pertaining to these findings has not been published. Hence, this review is designed to expand the myopic view of cardiac safety beyond the QT interval and highlight the importance of clinical nonlethal arrhythmias and conduction abnormalities involving novel non-antiarrhythmic small molecules for which more robust monitoring and surveillance should be contemplated.

1 | QT Centric Focus: Historical Background

During the 1990s there were multiple reports of ventricular arrhythmias and sudden death related to non-cardiac drugs. Chief amongst these arrhythmias was Torsades de Pointes (TdP) which was seen in the setting of a long QT interval due to delayed ventricular repolarization [1]. This arrhythmia most commonly stemmed from blockade of IKr, a critical potassium channel current encoded by the human ether a-go-go gene (hERG). As a consequence of these reports, regulators from Europe, Japan and the United States with input from Canada came together to create the International Conference on Harmonization (ICH) guidance documents in 2005 to assess the clinical (ICH E14) [2] and nonclinical (ICH S7B) [3] proarrhythmic potential of non-antiarrhythmic small molecules with systemic exposure. The ICH E14 and S7B guidance documents that were drafted were *NOT* intended to characterize the risk of TdP which is extremely rare in the absence of confounding factors nor was it a key objective to evaluate the effect of drugs on cardiac conduction liability and the occurrence of supraventricular arrhythmias [2, 3]. In fact, the original ICH E14 [2] guidelines do not explicitly mention measurement of the PR and QRS intervals or mandate routine monitoring for nonlethal arrhythmias and conduction disorders which have been linked to prolongation of these parameters. Moreover, during the past two decades, regulatory safety communication involving PR and QRS measurements with attention to arrhythmia risks has been limited, with noteworthy examples being tricyclic antidepressants [4], protease inhibitors [5], as well as the antiepileptic and mood stabilizer lamotrigine [6], and the intravenous form of the antiemetic dolasetron [7]. It is therefore

understandable that the mission of ICH members in 2005 was to introduce guidelines designed to safeguard the public's health given the profound consequences of QT prolongation compared to the more modest safety concerns associated with less pernicious supraventricular arrhythmias and conduction disturbances. In fulfilling this mission, regulatory guidance over the past 20 years has been successful as no new torsadogenic drugs have been approved. ICH E14 and S7B Question and Answer proarrhythmic updates have been instrumental in contributing to this success and our understanding of arrhythmias bolstered by prescriptive best practice details for clinical and nonclinical studies [8, 9]. Translating this prescriptive paradigm to supraventricular arrhythmias and conduction disturbances when integrated with advancements in wearable monitoring technology, would create a framework capable of expanding the aperture and utility of arrhythmia surveillance beyond QT centric 'short sightedness'.

2 | "Silent" Arrhythmias: The Problem and Argument for Expanded Monitoring

The spectrum of potentially serious arrhythmias, conduction abnormalities, and electrocardiogram (ECG) waveform morphology changes encountered in early phase healthy volunteer studies is quite broad and has been observed with non-antiarrhythmic drugs from a variety of therapeutic classes [10]. The arrhythmias listed in Table 1 all occurred during elective ECG telemetry monitoring as part of a clinical trial and were noted during the daytime or at night, occurring in either placebo or active treatment subjects. Each arrhythmia was identified in only one individual and was not associated with any abnormal findings in their history, physical examination, laboratory data, and predose ECG tracing. Essential information regarding participant demographics, whether subjects received active drug, what type of study design was executed, pharmacologic details about the IP being evaluated, and drug exposure data corresponding to each arrhythmia was not readily available for review. It is acknowledged that these are only some of the factors and considerations that would be crucial to fully characterize an arrhythmic event per FDA guidance. Also of interest is that all of these arrhythmias were transient and would not have been discovered if the study participants had not been placed on ECG telemetry monitoring, nor were there any predicate signals that would have foretold these events prior to dosing of the IP. Thus, there is an unmet need for cost-effective real-time longitudinal monitoring to capture dysrhythmias that convey important implications for drug product liability and labeling while also

TABLE 1 | Examples of arrhythmias detected in heathy participants during a clinical trial.

Arrhythmia	Comment
Brief episode of profound PR prolongation	Related to vagal effects on fast AV node pathway (see Figure 1)
Brief episode of sinus node arrest occurring during nighttime sleep	Not uncommon due to increased parasympathetic tone during sleep or obstructive sleep apnea (see Figure 2)
Short bursts of atrial fibrillation	Also known as paroxysmal atrial fibrillation, lasting several minutes to less than 7 days
Atrioventricular node (AV) re-entrant tachycardia	Byproduct of dual AV node pathways and physiology (see Figure 3)
Non-sustained ventricular tachycardia	Lasting < 30 s in duration (see Figure 3)
Catecholaminergic polymorphic ventricular tachycardia (CPVT)	Often precipitated by a "catecholamine surge" related to physical activity or emotional stress (see Figure 4)
Bidirectional ventricular tachycardia	Rare and regarded as pathognomonic of digitalis toxicity and specific for CPVT (see Figure 4)
ST elevation with suspected coronary vasospasm	May occur spontaneously or secondary to IP (see Figure 4)
Frequent premature atrial and ventricular contractions	May represent background or ambient arrhythmias in healthy participants

Note: Arrhythmias were observed during the course of a clinical trial in either placebo or active drug cohorts. Participants did not have any abnormal ECG or laboratory findings at screening or prior to dosing.

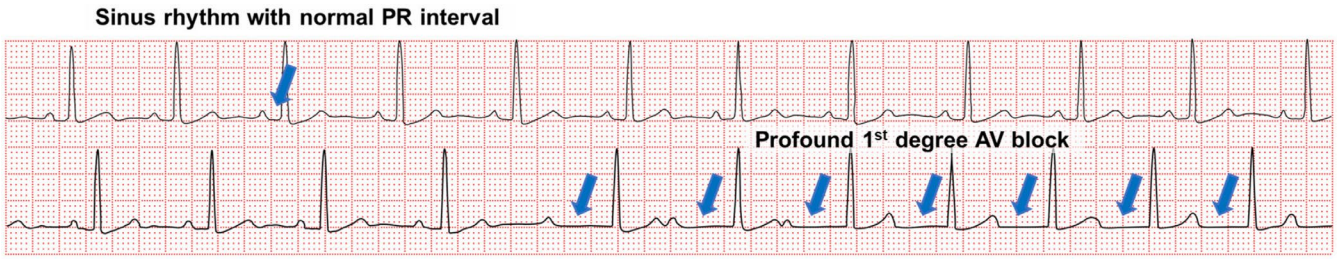

FIGURE 1 | Example of normal sinus rhythm and sudden onset profound 1st degree AV block. Blue arrows indicate (top) normal sinus rhythm and (bottom) sudden lengthening of PR interval in Lead II.

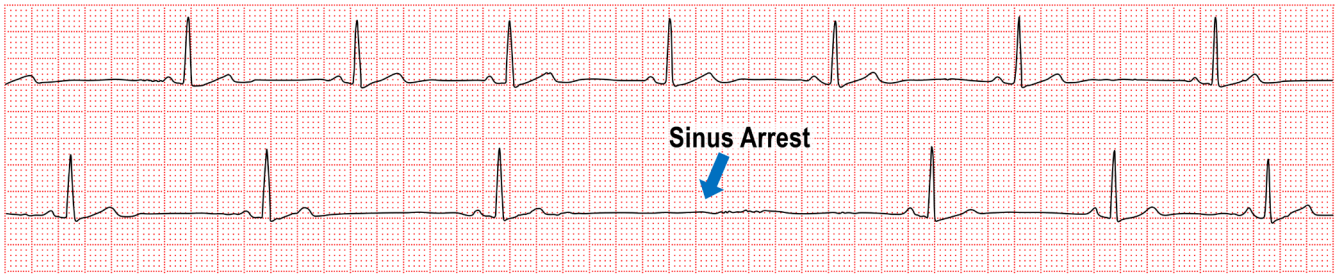

FIGURE 2 | Illustration of sinus arrest during sleep. Blue arrow indicates 3.4 s episode of sinus arrest preceded by sinus bradycardia in Lead II, likely due to increased vagal tone.

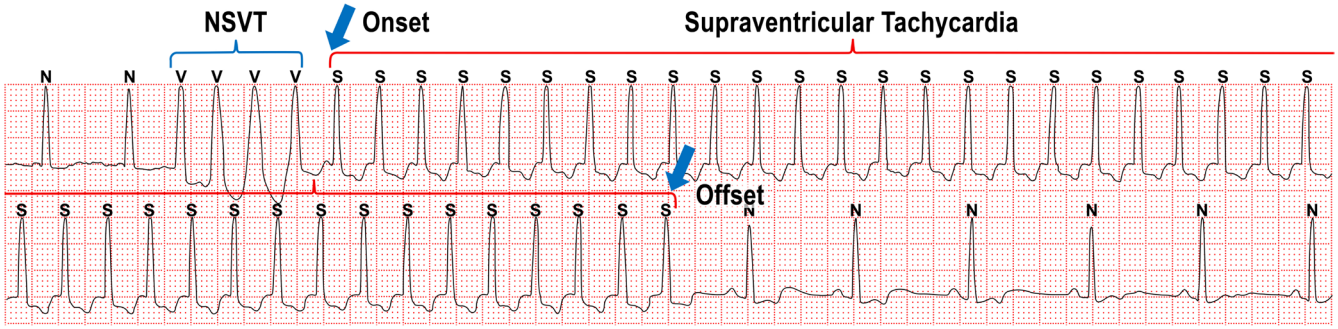

FIGURE 3 | Example of nonsustained ventricular tachycardia (NSVT) precipitating supraventricular tachycardia. Four beat run of ventricular tachycardia (V) followed by supraventricular tachycardia (S) before returning to normal sinus (N) rhythm in Lead II. Blue arrows indicate onset and offset of supraventricular tachycardia.

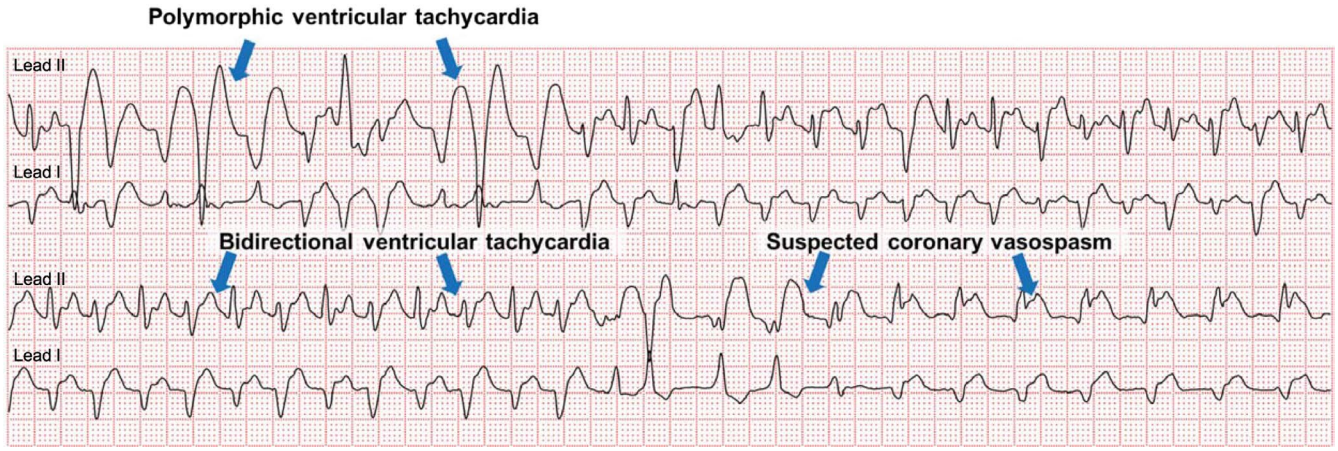

FIGURE 4 | Polymorphic and bidirectional ventricular tachycardia with suspected coronary vasospasm. Self-terminating episode of multiple ventricular tachycardia morphologies and possible coronary vasospasm following administration of a catecholaminergic agent in a healthy professional athlete.

impacting subject safety, IP dosing decisions, and overall clinical management.

3 | Shortcomings of Real-Time Arrhythmia Monitoring

Early clinical evaluation of TdP arrhythmic risk revolves around measurement of an imperfect biomarker, the QT interval, which unless markedly prolonged or significantly increased relative to baseline values, falls short in both sensitivity and specificity regarding arrhythmia prediction. This measurement is normally performed on both safety and cardiodynamic ECGs which are integral design elements in a dedicated thorough QT (TQT) study and also in first-in-human (FIH) single and multiple ascending dose protocols [11]. While a digital 12-lead recording device (i.e., Holter) is the standard technology used for ECG extractions and subsequent interval measurements, QT determinations may also be obtained from active telemetry recordings or wearable devices. The latter collection methods would be primarily for subject safety rather than formal assessment of the candidate drug's proarrhythmic potential. Also of note, is that telemetry monitoring can be performed simultaneously with Holter recordings particularly in cases where real-time

detection of cardiac arrhythmias or determination of heart rate variability is warranted.

Safety ECGs are usually obtained intermittently after drug administration, are commonly single replicate 10 s tracings, and are reviewed in *real time* by the principal investigator or their designee to identify any findings of concern. A common scenario for these safety ECGs is to acquire up to six 10 s tracings during the first 24 h following drug dosing which collectively would comprise approximately 1 min worth of diagnostic and interval data. On the other hand, cardiodynamic ECGs are intended to assess QT liability of the candidate drug *post dosing* and are extracted from a Holter recording over a 5-min window with an average of 10–12 extraction timepoints per 24 h. Typically, 3 or more replicate ECGs spanning 10–14 s are secured at each nominal timepoint coinciding with pharmacokinetic blood samples and they are reviewed retrospectively (i.e., several days following their acquisition) by a "skilled reader" occasionally after the participant has been discharged from the clinical research facility. In total cumulative time, they provide approximately 5 min worth of ECG data. Hence, combining the total safety and cardiodynamic ECG recording times during a representative 24-h Holter monitoring session, more than 23 h of information is not routinely analyzed for significant arrhythmias, conduction disturbances or morphologic abnormalities which may be transient and asymptomatic. These findings, although uncommon in a healthy volunteer trial, may be overlooked if not captured by serendipity on either safety or cardiodynamic ECGs. To address this shortcoming and, given the limited role of safety ECGs as the principal real-time tool for arrhythmia detection, there is an unfulfilled need for subjects to electively be placed on some form of extended continuous ECG monitoring to augment surveillance for arrhythmias and other abnormalities which inform clinical management. Ultimately, the use of extended monitoring is an optional undertaking and a shared decision by the sponsor and principal investigator based upon study objectives, potential safety concerns and the properties of the compound under investigation.

4 | Arrhtyhmia Detection Paradox

As noted above, review of 10 s safety ECGs acquired following drug administration is the main method of real-time detection of arrhythmias and conduction disturbances in the absence of concurrent telemetry monitoring or wearable devices. Achieving the highest drug exposures and the most intensive ECG collections are features of early phase studies yet the likelihood of detecting arrhythmias is compromised by the relatively small number of healthy participants, typically 8–12 per cohort. In contrast, despite much larger numbers of patients in later phase trials, lower drug exposures and less robust ECG collections similarly reduce the probability of arrhythmia discovery. As a result of this apparent paradox, there is a need to develop a clinical real-time monitoring scheme and methodologies applicable to early drug development that incorporate mechanistic electrophysiologic data from nonclinical assays designed to define the proarrhythmic potential of novel drug candidates [8].

In this regard, there are a number of innovative and automated nonclinical electrophysiologic investigations, some of which are detailed in the Comprehensive in vitro Proarrhythmic Assay (CiPA) initiative [12], that can be undertaken to provide an understanding of arrhythmia pathophysiology. These include evaluation of multiple non-hERG ionic currents with sodium ($Na_v1.5$) being the second most analyzed; in silico modeling of action potential morphology and proarrhythmic risk; optical imaging of well plate human induced pluripotent stem cell cardiomyocytes (hIPSC); testing of the IP in 3-dimensional heart models; and the application of deep learning convoluted neural networks integrated with computer modeling to characterize the electrophysiologic properties of the IP [13]. Each of these assays individually and collectively can be useful in predicting the occurrence of *ventricular* arrhythmias in early phase human trials, aiding clinical study design, and addressing the type, scope and intensity of cardiac monitoring that may be required. Moreover, despite species and trial design differences, in vivo telemetry studies in non-rodent animals when coupled with in silico modeling data can be highly predictive of human QT prolongation [14]. These studies, however, are not useful for predicting TdP nor are they capable of accurately ascertaining the risk of supraventricular arrhythmias and conduction abnormalities.

5 | PR and QRS Determination: The "Forgotten" ECG Intervals

While the QT interval remains the primary biomarker regarding arrhythmia monitoring and risk prediction, there are other ECG intervals that deserve important consideration as they can independently and indirectly predispose to arrhythmias, thereby affecting cardiac safety. These include the PR interval which reflects atrioventricular (AV) conduction and the QRS interval which represents electrical impulse propagation through ventricular tissue [15]. Significant PR interval prolongation has been linked to a higher risk of atrial fibrillation, pacemaker implantation and symptoms of fatigue, palpitations and decreased exercise tolerance. AV block is considered highly significant when the PR interval exceeds 300 msec [16] or there is third degree AV block. However, 1st degree AV block stemming from increased vagal tone is most often asymptomatic and transient. It is typically a benign finding with an excellent prognosis and rarely would dictate therapeutic intervention. Regarding QRS duration, drug associated QRS widening beyond 120 msec induces ventricular desynchrony which *may* confer an increased long-term risk of serious reentrant ventricular arrhythmias, major cardiac events and mortality even in healthy adults [4, 17]. QRS prolongation is usually asymptomatic when it is an isolated finding and does not necessitate any immediate treatment although dosing modification or cessation of the IP may be necessary especially if the change in width is > 25% compared to baseline or > 160 msec [15]. Measurement and monitoring the PR and QRS intervals in real time via telemetry, wearables, or safety ECGs is preferentially performed on either multiple complexes in the same single ECG lead or on a representative median beat and plays a crucial role in early evaluation of conduction liability. Moreover, 24 h Holter monitors can also be utilized for full disclosure arrhythmia analysis, interval measurements and T wave morphology changes, although the results are delayed until the recording data is cleaned, processed and formally reviewed.

In an effort to augment the recognition and contribution of the seemingly marginalized PR and QRS intervals, current guidance recommends categorical analysis and reporting of these parameters in all submitted datasets [18]. Exposure-response modeling of these measurements, while not explicitly mandated by the FDA, is also recommended as it can furnish insights into a drug's potential impact on multiple ionic currents other than hERG and provide a scientific basis for arrhythmias and conduction disturbances. Surprisingly, a consensus statement regarding threshold PR and QRS values of safety concern has not been formally drafted and universally adopted. Nonetheless, FDA regulators have proposed the following PR and QRS ranges to be detailed in the final clinical study report (RML personal communication). These values are intended to define thresholds that would incriminate the IP as conferring a higher risk of arrhythmias and major cardiac events.

- *QRS interval*: $\leq$120 msec and *abnormal* >120 msec with and without a 25% increase over baseline
- *PR interval*: $\leq$200 msec; >200 msec and <220 msec and *abnormal* >220 msec with and without a 25% increase over baseline

Compounds which block L-type calcium currents ($Ca_v1.2$) or acetylcholine G protein gated potassium channels (IKACh) can impact AV node depolarization, slow sinus node impulse conduction, and lengthen the PR interval [19]. Additionally, chemical entities which block inward sodium currents ($Na_v1.5$) and voltage gated channels can delay ventricular depolarization and generally produce QRS widening in a linear fashion based upon plasma concentration [4, 20]. In this regard, Bergenholm et al. developed mathematical computational models to predict PR and QRS prolongation effects in humans based upon nonclinical in vitro and in vivo data involving multiple compounds which were tested in dogs and guinea pigs [21]. Similarly, Garcia and colleagues applied nonclinical novel methodologies including microphysiologic systems to evaluate and successfully translate the proarrhythmic potential of vanorexine to humans [22].

However, translating nonclinical data into a clinically useful paradigm has historically proved challenging and imperfect as evidenced by the cautionary tale of the Cardiac Arrhythmia Suppression Trials (CAST I and II) [23]. Based upon the sodium channel blocking properties of class 1C antiarrhythmic agents in animal studies (i.e., flecainide, encainide and moricizine), the investigators hypothesized that suppression of premature ventricular contractions would be beneficial in patients with coronary artery disease and depressed left ventricular systolic function. Unfortunately, the presumed beneficial nonclinical antiarrhythmic properties did not translate to patients, as unanticipated proarrhythmic effects occurred resulting in excess mortality due to shock and sudden cardiac death. Therefore, with respect to nonclinical models for QRS and PR conduction abnormalities, their positive predictive power in humans may be tenuous and unreliable due to variability in the animal species chosen, the testing protocol, the heterologous assay systems employed, and the inability to replicate the pathophysiologic conditions encountered in clinical patient studies. Hence development of a conduction liability risk stratification matrix remains elusive and a topic for further exploration.

6 | Wearables Versus Ambulatory Telemetry

The use of centralized patient telemetry monitoring is common practice when real-time arrhythmia assessment of subjects in FIH clinical trials is desired. The advantage of this modality is that it is capable of monitoring multiple ECG leads with validated software and alarms, which yields immediate information about drug liability and patient safety. The major limitations of multilead telemetry are that it is relatively expensive to implement especially with continued surveillance by trained health care personnel; subjects are required to wear the electrodes and attached leads for an extended period of time which are uncomfortable, cumbersome and may cause skin irritation; and perhaps most salient, is that the incidence of significant arrhythmias in a healthy volunteer trial is extremely low raising the question as to whether this approach adds value and is cost effective. Thus, the decision to deploy telemetry in a FIH clinical study is based upon a number of factors to be weighed by the principal investigator and sponsor teams. These include (1) whether nonclinical data suggests an arrhythmic risk, (2) the demographics of the healthy volunteer population being studied, (3) whether similar compounds have been associated with arrhythmias, (4) the cost of implementing this technology and (5) does it comport with the sponsor's preference and objectives.

An alternative and increasingly favored approach to early phase arrhythmia detection has been the advent of extended telemetry monitoring using wearable devices that can yield information for either real-time evaluation or deferred analysis [24]. Real-time systems are preferred to identify potentially serious arrhythmias as well as guide clinical management and may be utilized during subject confinement or outside the clinical conduct site. There are a number of FDA 510(k)-cleared, prescription-only wearables designed to satisfy these objectives. For example, one device is a dual channel precordial patch that can be worn for up to 30 days and uses participant activated messaging when symptoms are present. This patch system continuously records the ECG in both channels where the information is sent in *real time* to a central monitoring station which alerts the healthcare provider if any significant arrhythmia is present [25, 26]. An alternative device design employs a single channel chest patch which can record continuous ECG data for up to 14 days for comprehensive *deferre*d review and analysis after the recording session is completed [25, 26]. These widely adopted and cost-effective patch systems are well tolerated by users, permit showering during use, are constructed to capture both supraventricular and ventricular arrhythmias as well as conduction abnormalities, and can obviate the need for prolonged confinement of subjects at the clinical research facility. Both technologies represent the most popular strategy for long term noninvasive arrhythmia surveillance outside of the domiciled setting. Lastly, there have been recent advances in patch technology that include artificial intelligence (AI) deep neural learning algorithms for arrhythmia detection which can furnish a deferred analysis full disclosure report to the ordering health care provider after the monitoring period is terminated [24].

In addition to the aforementioned continuous monitoring options, the FDA has cleared numerous simple, inexpensive, and less sophisticated nonprescription single channel consumer wearables such as heart ring monitors and smartwatches for identification of common arrhythmias [27]. Ring monitors are cleared only for atrial fibrillation recognition, while some smartwatch models have garnered FDA 510(k) clearance for sinus bradycardia, sinus tachycardia, and atrial fibrillation, with most published articles reporting very high device specificity (95%–97%) and sensitivity (89%–97%) for atrial fibrillation detection [28]. All of the commercially available nonprescription wearables utilize either ECG sensors integrated with machine learning and generative AI algorithms, photoplethysmography, and most recently, seismocardiography [29].

Accurate and cost-effective real-time identification of PR and QRS conduction disorders beyond values present in safety ECG tracings is technically problematic for virtually all noninvasive wearable devices. One exception to address this shortcoming is the development of a wearable multimodal sensor which recently received FDA 510(k) clearance. This sensor records cardiac electrical signals that can both detect arrhythmias as well as measure PR and QRS intervals [29]. It can also acquire physiologic data that, when paired with deep learning AI algorithms, may offer a unique noninvasive tool for assessment of hemodynamics and overall cardiac function. Nonetheless, despite their cost and practical utility, concerns have been voiced about wearable monitoring related to the confidentiality and security of patient data and the challenge regarding what measures can be implemented to mitigate frequent false positive alarms without compromising diagnostic accuracy [30]. To remedy this latter concern, a possible solution might involve a hybrid paradigm in which spontaneous or patient triggered alarms would be coupled with real-time centralized expert review resulting in immediate feedback to the user. This scheme would optimize subject safety, preserve diagnostic accuracy and confidentiality, and guide appropriate medical oversight.

7 | Arrhythmias Related to the Investigational Product or an Epiphenomenon

A major conundrum regarding post dose arrhythmias is the determination as to whether these are engendered by the candidate drug or represent the subject's ambient arrhythmias that were present prior to IP administration. There is a paucity of information regarding this issue beyond the publication by Hingorani et al. who analyzed 1237 predose Holter monitors from healthy volunteers and categorized arrhythmias and conduction disturbances seen in this population, none of which were deemed serious or life threatening [31]. Similar results were obtained by Skovgaard et al. in a smaller cohort of 207 healthy obese individuals who underwent 24 h predose Holter monitoring [32]. They identified only occasional benign arrhythmias and no advanced conduction system pathology in the recordings. These reports provide prevalence metrics which may be helpful in deciding whether an arrhythmia seen after dosing is consistent with published findings noted in healthy individuals or associated with the IP. Optimally, having routine extended predose monitoring of participants and careful scrutiny of preclinical in vitro and in vivo cardiotoxicity data would be beneficial to clarify if a post-dose arrhythmia is new or represents a pre-existing background finding. For example, if a new arrhythmia or conduction abnormality is seen post-dose or there is worsening of a predose arrhythmia which coincides with peak drug exposure, then it should be presumed to be a drug-mediated event unless proven otherwise. Furthermore, if multiple subjects in a study develop new and similar abnormal ECG findings that occur at approximately the same time post dosing, then the assumption would be that these abnormalities are associated with the IP.

8 | Conclusion and Recommendations

Regulatory guidance applicable to candidate drugs has primarily focused on their proarrhythmic potential rooted in their ability to delay ventricular repolarization as manifested by QT prolongation on the ECG. This approach during the past two decades has been successful in safeguarding the public from torsadogenic agents. It is acknowledged that the small sample size in early phase clinical trials and enrollment of healthy volunteers diminishes the likelihood of finding any important ventricular or supraventricular arrhythmia or conduction disturbance, thereby suggesting that more aggressive monitoring may not be productive. However, the true incidence of post-dose ECG rhythm disorders in early phase studies has not been clearly delineated due to limited real-time surveillance performed during these trials. Thus, until more routine and rigorous monitoring is enacted, the value of such an undertaking remains uncertain and therefore merits further investigation (Table 2).

To address this uncertainty, the spectrum of proarrhythmic monitoring either during or after participant confinement should be expanded beyond safety and cardiodynamic ECG analyses of the heart rate and the QT, PR, and QRS intervals. It is proposed that this expansion should employ continuous single or multilead digital surveillance for both supraventricular and ventricular arrhythmias, changes in interval measurements, significant alterations in T wave morphology, and the presence of pathologic U waves [33]. In light of the current void in a real time commercially available 12-lead telemetry system configured for drug trials, there is an opportunity to incorporate subject wearables enhanced by AI software into a platform designed to fulfill both sponsor and regulatory monitoring objectives. Development of this system would play a pivotal role in ensuring subject safety, documenting and reporting adverse events, informing dosing decisions, and determining whether a subject should be referred for further cardiac evaluation. Moreover, this system would help to elucidate whether any new ECG findings were related to the IP, which could influence further drug development and product labeling.

In addition to enhanced clinical monitoring, there are multiple nonclinical assays exploring the mechanisms underlying the proarrhythmic effect of new drug candidates which include changes in ionic currents and cell signaling. These preclinical studies, such as those enumerated in the CiPA initiative and the extensive review of drug induced sodium channel blockade by Chaudhary et al. [4], highlight the rationale for deploying more robust arrhythmia monitoring in FIH clinical trials. Another interesting innovation is that of open-source computational web-based models for drug-induced proarrhythmic risk assessments [34]. To this end, Iftkhar and colleagues developed

TABLE 2 | Overall insights and takeaways.

Key considerations
• The QT centric focus of TQT and cQT ascending dose drug studies needs to be expanded
• Cardiac arrhythmia and conduction system assessment restricted to safety and cardiodynamic ECGs comprises limited time windows for data collection and analysis
• The role of prescription and nonprescription consumer wearables is a cost effective and important evolving technology that should be considered for enhanced and extended arrhythmia monitoring during or after participant confinement
• Any laboratory abnormalities that may predispose to arrhythmias and conduction disturbances should be corrected prior to dosing, along with recognition of potential proarrhythmic drug–drug interactions
• Performing comprehensive supplemental in vitro and in vivo nonclinical assays following "best practices" may be helpful in profiling and predicting the proarrhythmic risk of the IP
• Categorical and exposure response analysis of the PR and QRS intervals are important elements of cardiac safety assessment
• The application of generative AI algorithms to ECG recordings may permit earlier identification of arrhythmic risk and latent conduction system disorders
• Comprehensive and detailed regulatory guidance and a risk stratification matrix regarding supraventricular arrhythmias and conduction disturbances is lacking and would be instrumental in profiling additional cardiac liability of IPs

a model [35] to predict small molecule cardiac toxicities such as cardiac arrhythmias including heart block. Finally, proliferation of wearable devices along with the bourgeoning role of artificial intelligence could facilitate the detection of potential drug–drug interactions related to the IP, as recently discussed by Bischof and colleagues [36] and Raschi et al. [37] It is hoped that many of these initiatives, if combined and leveraged, will enable earlier identification and a more comprehensive portrait of arrhythmia and conduction liability for non-antiarrhythmic small molecule moieties undergoing evaluation in early phase trials, thereby enabling cardiac safety assessment to expand beyond the current QT myopic focus.

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Conflicts of Interest

The authors declare no conflicts of interest.

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