Long-term electrocardiographic safety monitoring in clinical drug development: A report from the Cardiac Safety Research Consortium

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This white paper, prepared by members of the Cardiac Safety Research Consortium (CSRC), discusses important issues regarding scientific and clinical aspects of long-term electrocardiographic safety monitoring during clinical drug development. To promote multistakeholder discussion of this topic, a Cardiac Safety Research Consortium–sponsored Think Tank was held on 2 December 2015 at the American College of Cardiology's Heart House in Washington, DC. The goal of the Think Tank was to explore how and under what circumstances new and evolving ambulatory monitoring technologies could be used to improve and streamline drug development. This paper provides a detailed summary of discussions at the Think Tank: it does not represent regulatory guidance. (Am Heart J 2017;187:156-169.)

A Think Tank sponsored by the Cardiac Safety Research Consortium (www.cardiac-safety.org) was convened at the American College of Cardiology's Heart House in Washington, DC, on December 2, 2015, to discuss long-term electrocardiographic (ECG) safety monitoring during clinical drug development. Based on the principles of the United States Food and Drug Administration's Critical Path Initiative,[1] the CSRC was created in 2006 to facilitate collaborations among academicians, industry professionals, and regulators to develop consensus approaches addressing cardiovascular safety issues that can arise in the development and therapeutic use of medical products.[2]

A key issue in drug development is the potential for drugs to have deleterious electrophysiologic effects. Although drug-induced changes in ECG intervals (eg, the PR, QRS, and QT intervals) are readily evaluated via careful ECG collection and analysis, the elucidation of actual drug-induced arrhythmias such as clinically significant bradyarrhythmias, atrial fibrillation (AF), or ventricular tachycardia (VT) is difficult to capture and assess using traditional ambulatory monitoring techniques, including Holter monitoring. These traditional techniques have limited sensitivity due to the limited temporal sampling for ECG analysis. Recently, approaches to collect longer periods of ECG data using patch, implanted, real-time telemetry, or mobile technologies have created the potential for more comprehensive safety and, in some cases, efficacy assessments during pharmacologic development programs. However, these technologies are not cost neutral, generate a tremendous amount of data, and increase the risk of detecting "ambient" or background arrhythmia of little or no clinical significance. This CSRC Think Tank convened to explore how and under what circumstances these new and evolving ambulatory monitoring technologies could be used to improve and streamline drug development. This article summarizes the Think Tank findings by a broad range of experts, now further extended by the CSRC writing group. The CSRC views expressed herein do not represent regulatory policy.

Table I. ECG parameters for consideration

- Heart rate
- Ectopic beats
- Repolarization morphology
  o T wave alternans
- Beat-to-beat variability
  o Heart rate variability
- Heart rate dependent repolarization abnormalities
  o Corrected QT interval
- Autonomic nervous system
  o Heart rate turbulence

Adapted from Farkas and Nattel.[3]

Table II. Characteristics of ambulatory ECG monitors

AECG type	Typical duration of monitoring (d)	Monitors for asymptomatic arrhythmias	Provides real-time feedback of ECG being acquired
First-generation AECG monitors			
Standard Holter	1-2	Yes	No
Patient-activated event recorder	30	No[*]	No[†]
Loop recorder	30	No	No
Second-generation AECG monitors			
Patch-based Holter	14	Yes	No
Ambulatory telemetry	30	Yes	Yes
Third-generation AECG monitors			
Patch-based telemetry	30	Yes	Yes
Smartphone-based applications	Indefinite	No[*]	Yes
Insertable cardiac monitors	Several years	Yes	No[‡]

[*] Patient can screen for asymptomatic arrhythmias by acquiring an ECG randomly.
[†] Patient can transmit acquired data via a telephone line for further review; if this happens soon after the ECG is acquired, it provides near–real-time information to the clinician.
[‡] ECG data acquired during the day are downloaded that evening and then available for review the next day.

Historic development, current state, and limitations of cardiac monitoring

ECG monitoring plays a critical role in the assessment of safety (and in some cases efficacy) of a new cardiovascular drug. Table I outlines the ECG parameters of concern in cardiovascular safety.[3] In particular, there is the need to detect (1) a change in a specific ECG parameter (eg, interval measurements such as heart rate, PR interval, QRS duration, and QT interval as well as ECG morphologic changes), (2) development of a new arrhythmia (eg, atrial or ventricular ectopy, AF, non-sustained VT, torsade de pointes [TdP]), or (3) suppression of an existing arrhythmia. There are few tools that are currently available for extended ECG monitoring in clinical practice. Each has its inherent strengths and limitations.[4,5] Moreover, the background rates for dysrhythmias are poorly known, so decisions about what arrhythmias might be related to drug treatment are poorly informed. Thus, there is no accepted criterion standard for extended ECG monitoring to assess cardiac safety (or efficacy of a cardiovascular drug) during the drug development process. To determine the optimal method for ECG monitoring in the assessment of drug safety, the following 3 critical questions must be kept in mind (Table II): (1) how long do we need to monitor (informed by pharmacokinetics and patient population), (2) do we need to monitor for asymptomatic arrhythmias, and (3) is real-time ECG feedback necessary? This section reviews the strengths and limitation of the various forms of ECG monitoring available today (Figure 1).

Twelve-lead ECG

Historically, the 10-second 12-lead ECG has served as the criterion standard for assessment of drug-induced ECG effects. Although well validated, the 12-lead ECG also has important limitations. First, from a practical standpoint, it is burdensome for a patient or investigational site to record ECGs multiple times over the course of a day or multiple times per week. Second, the standard 10-second 12-lead ECG is not well suited to picking up changes that may be occurring only intermittently, or

asymptomatically, or during physiologic conditions such as exercise or sleep. In this regard, the evolving field of novel ambulatory ECG monitoring technology provides promise for extended continuous monitoring that provides enhanced disclosure with enhanced arrhythmic characterization, that is, presence, frequency, duration, and burden.

First-generation ("legacy") ECG monitoring tools

Historically, 24-48 hours of Holter monitoring has been used when a single ECG is insufficient to make a clinical diagnosis or too brief to assess a safety or efficacy issue during drug development. Holter monitors are well suited to determine the average heart rate and heart rate range, quantify atrial and ventricular ectopy counts, determine whether more persistent forms of AF are present, and correlate rate and rhythm findings with activity and with symptoms if present (via the diary or event marker). Information regarding the shortest and longest duration of AF, burden of AF, the heart rate during AF, and pattern of initiation and termination of AF (and other arrhythmias) can be determined during the monitored period.[3] However, it is generally impractical to wear a Holter monitor for more than 24-48 hours because of the requirements to change batteries and flashcards, skin irritation from the skin electrodes, and the inconvenience of wearing a device connected to the skin electrodes by multiple cables. A 1- or 2-day monitoring period may simply be too short to detect infrequent but important atrial or ventricular arrhythmias or episodes of
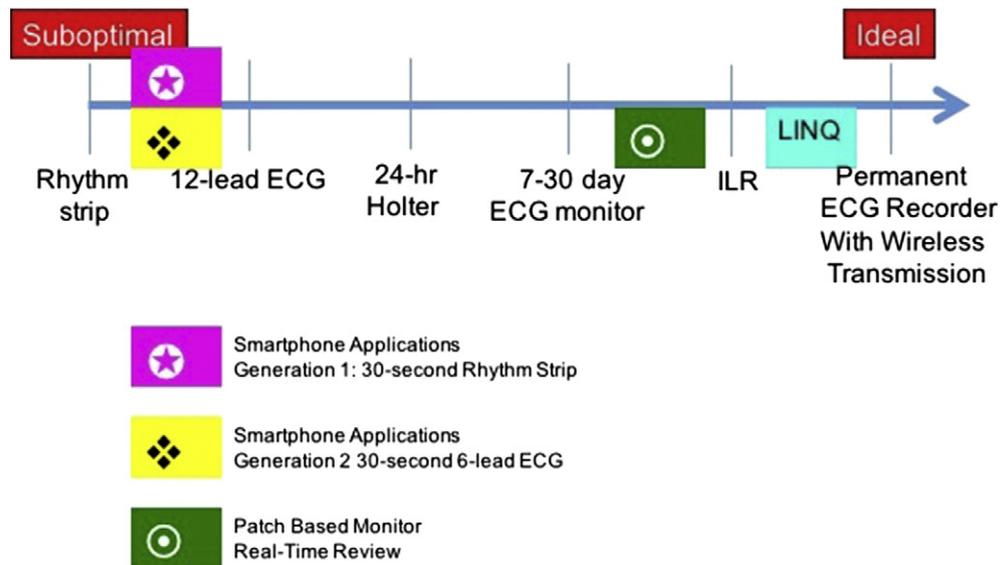
Spectrum of ambulatory external ECG monitoring modalities. As one moves from left to right, the duration of monitoring increases, which in turn increases the diagnostic yield. *ILR*, implantable loop recorder; LINQ, Medtronic LINQ ILR (Minneapolis, MN). Adapted from Mittal et al.[5]

conduction block. Longer-term monitoring is possible using patient-activated event recorders and nonmemory loop recorders; however, both require an intervention by the patients before an ECG recording is stored, and therefore, these devices are better suited for assessment of *symptomatic* arrhythmias. When assessing safety and efficacy of a drug in development, both longer-term ECG monitoring and the ability to capture information about both symptomatic as well as asymptomatic arrhythmias are required. Limitations of these first-generation tools include lack of real-time feedback on recorded ECG events, challenges to patient acceptance and adherence, and the logistical burden for operationalizing within clinical research (ie, consistent equipment availability, flash cards, data transfers, and central adjudication).

Second-generation ECG monitoring tools

Second-generation ECG monitoring technologies generally have the ability to monitor for both symptomatic and asymptomatic arrhythmias for an extended duration of time. These include patch-based extended Holter monitors, autotriggered memory loop monitors, and lead-based mobile cardiac telemetry systems.[5,6] The major difference among the 3 systems is the ability to obtain real-time feedback on the ECG. In the case of patch-based Holters, no information is available until the ECG data are acquired, the monitoring period is completed, the patch is returned to the manufacturer for analysis, and a report is created for physician review.

Lead-based mobile cardiac telemetry systems overcome this limitation, although the requirement for a 24/7 monitoring center which must be staffed at all times markedly increases the costs. Patch-based extended Holter systems with a median 11 days of monitoring have been shown to detect more events than a 24-hour Holter monitor.[7]

Third-generation ECG monitoring tools

Further refinements have led to the development of third-generation systems. These include smartphone-based systems where an electrode-embedded module is attached to a patient's smartphone. The module detects electrical impulses from the user's fingertips and transmits signals to the smartphone when contact is maintained with the electrodes. The recording can be stored as a PDF file that can then be directly e-mailed from the phone to the clinician. The advantages to this type of technology include the use of inexpensive hardware and the capture of real-time and high-fidelity ECG data that are immediately available to the patient (albeit with many implications that require careful consideration in research). In addition, ECG data can be intermittently acquired over an indefinite period of time. A limitation of this type of system is that the ECG data are only collected when the patient makes contact with the electrodes, that is, not continuous monitoring to characterize arrhythmic burden and asymptomatic events, and it is really best suited for intermittent monitoring as controlled by the user/patient.

The other type of third-generation system uses patch-based real-time telemetry. These systems combine the patient convenience of patch-based systems with the ability to acquire *all* ECG data and the capability of allowing near–real-time review. Additional benefits include the following: early notification of any arrhythmia of concern (specifically useful when the study compound has a potential arrhythmic signal), the ability to remotely monitor patient compliance with ECG monitoring, and reduction in "dead time" inherent to waiting for data to enable clinical or study decision making, that is, potential to reduce study timelines or reduce patient or site burden.Again, an important consideration is whether the cost of maintaining a 24/7 ECG monitoring center may preclude the use of such systems during drug development.

Insertable cardiac monitors

Implantable subcutaneous ECG monitors can collect ECG data over a period of several years. As an example, the most recent iteration of the device (Reveal LINQ™, Medtronic Inc) is small enough to allow simpler insertion, records cardiac information automatically in response to detected arrhythmias (or on demand based on patient activation), and uses cardiac telemetry to transmit data to the physician. These type of devices are particularly well suited to defining the occurrence (including time to first occurrence) and burden of episodes of AF or other infrequent arrhythmias.[7] Although the costs and invasive nature of this technology are limitations for clinical trial application, it is the only device available that allows continuous ECG monitoring for up to 3 years and that can detect arrhythmia burden over time (including AF) without the need for active intervention by the patient.[8]

Electrocardiographic monitoring technology is evolving and provides novel approaches for integration in drug development. There are clinical benefits and limitations to each technology. In the context of clinical research, the technology must be validated and supported with a scalable compliant global operational process. The smartphone-based and patch-based technologies hold promise (Figure 2).

Cardiac monitoring and big data

Big data have revolutionized healthcare, including cardiovascular medicine.[9] Although there is a growth of big data in general, this is particularly true in the arena of arrhythmia science and heart rhythm medicine. For example, the availability of continuous monitoring data from cardiac implanted electronic devices (CIEDs) in nationwide remote monitoring databases has allowed clinicians, industry, and other stakeholders to assess device and lead performance in a much more timely fashion with much greater power to detect significant differences in device and hardware function.[10] These advantages also extend to improved and more detailed diagnosis in individuals with suspicion for arrhythmia. For example, in one study of 120,000 patients monitored with patch-based Holter technology and median analyzable time of 9 days, up to 20% had evidence of ventricular arrhythmia (18% nonsustained and 1.4% sustained).[11] Thus, analysis of big datasets in continuous monitoring has shown that sensitivity is clearly increased. This also raises the question as to what is "ambient" background arrhythmia in different populations (eg, young, old, structural heart disease).

Big data sources have also facilitated comparative effectiveness analyses that compare emerging technologies with more established therapies.[12] Continuous monitoring in CIEDs has also allowed for more "in-depth" data, even without very "big data." For example, continuous monitoring in only 1,195 CIED patients has demonstrated that patterns of AF and temporal persistence are highly variable across physician-based clinical classifications of AF type. In this study, authors observed that fewer than 50% of patients diagnosed with paroxysmal AF truly had paroxysmal AF that terminated within 7 days as defined by continuous device monitoring.[13]

Given these contributions in the clinical and arrhythmia science realm, how can "big data" in heart rhythm diagnostics positively impact drug safety assessment? There are many possibilities, including continuous QT monitoring in larger populations and improved predictive modeling of arrhythmic risk by harnessing data across multiple populations with different drug exposures (and thus different target channel profiles). Continuous monitoring will enable even more comprehensive analyses of emerging QT analysis strategies, including dynamic beat-to-beat QT assessment and ECG restitution (the QT-TQ relationship).[14] "Big data" may also be helpful in improving the characterization of ambient arrhythmia in studied populations and thus help discern proarrhythmia (signal) from background arrhythmia (noise). The availability of these large data sets will also benefit from new data analytic methodologies, including machine learning and "deep learning."

That said, there are many limitations to the use of big data. First, big data often lack depth. Although a given data source may contain many observations, the number of characteristics at the individual level is usually less than traditional data formats (ie, administrative claims versus registry data). Loss of critical variables that influence prognosis may predispose "big data" analyses to greater levels of residual confounding. In addition, big data analyses are complex and require automation and verification to ensure validity. Finally, given the real-time nature of many big data analyses, methods to ensure frequent updating of core data are important.[15]

Figure 2
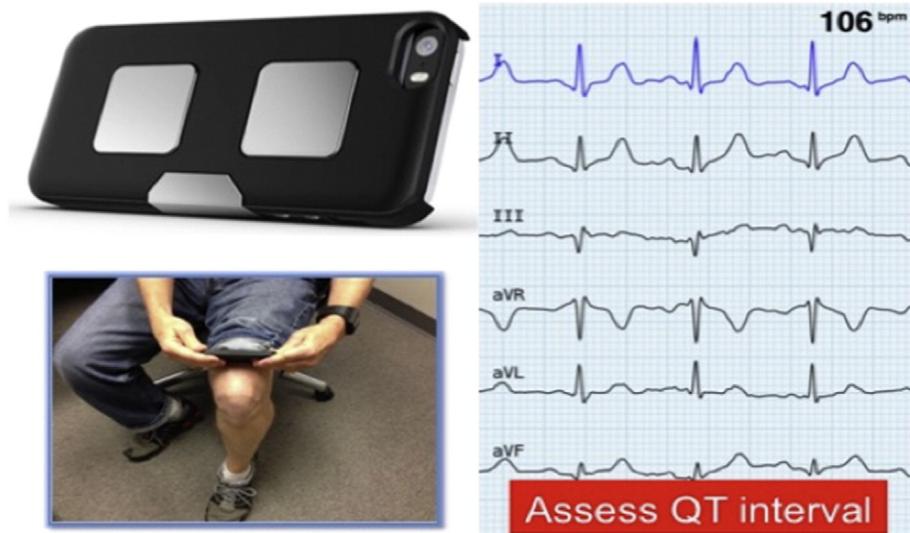
Promising ambulatory external ECG monitoring techniques to assess the QT/QTc interval. (Top) Novel smartphone-based application to assess the heart rate and produce all 6 limb leads of the ECG. In this manner, lead II (a commonly used lead to assess the QT/QTc interval) can be obtained and analyzed as many times as clinically appropriate. The acquired ECG data can be transmitted to the clinician using e-mail. (Image reproduced with permission of AliveCor) (Bottom) A patch monitor is applied in the left infraclavicular space in an orientation designed to mirror lead II of the surface 12-lead ECG. The acquired ECG data are downloaded to a receiver carried by the patient, which transmits the information using cellular signal to a central monitoring station. In this manner, real-time information about the heart rate and arrhythmias is available. (Image reproduced with permission from Medtronic.)

## When should cardiac monitoring be used in drug development?

Bradyarrhythmia

The assessment of any potential ECG and dysrhythmic effects is an important part of the development process for all new pharmaceutical agents. Of chief concern is the development of new tachyarrhythmias, including both supraventricular proarrhythmia (eg, AF) and ventricular proarrhythmia (eg, TdP). However, significant bradyarrhythmias can also occur and can pose significant risk in some patients.

The type, duration, and timing of monitoring are important variables in ECG assessment. Selecting the type and timing of monitoring must be based, in part, on the pharmacokinetics of both the parent compound and any active metabolites. Drug-induced ECG changes are typically stable by the time steady state is reached, whereas the development of arrhythmias may be dependent not only upon attainment of steady state but also upon a change of concomitant medications, change of electrolyte or metabolic status, comorbid disorders, and/or changes in autonomic tone. For example, if a drug prolongs the QT interval modestly with an increased risk for TdP, such TdP may not become manifest until the patient adds another drug that further prolongs the QT interval, such as erythromycin; the patient develops hypokalemia or hypomagnesemia, such as with gastroenteritis; or the patient becomes bradycardic, such as during a vasovagal episode.

The type and duration of monitoring are also dependent upon issues of practicality. For a drug with a short half-life (eg, 4-6 hours) (parent, active metabolite) and no drug or disease interactions, an appropriate monitoring period regarding potential bradycardia/conduction changes will most likely be the first 24-48 hours. Serial ECGs, Holter monitoring, or in-hospital telemetry would all suffice. In the case of a drug with a prolonged and uncertain half-life (eg, amiodarone), many drug interactions, or active metabolites, the timing and duration of bradyarrhythmias are different than those for short half-life drugs, as would be its monitoring requirements. Finally, drugs that can induce hypothyroidism or other secondary causes of bradyarrhythmia with long-term therapy (such as amiodarone and lithium) require prolonged recording techniques (such as mobile cardiac outpatient telemetry [MCOT], 30-day loop recorders, daily transtelephonic tracings over time, or insertable cardiac monitors) and/or repeat periods of monitoring depending upon the addition/development or removal/resolution of interacting agents or disorders.

Figure 3
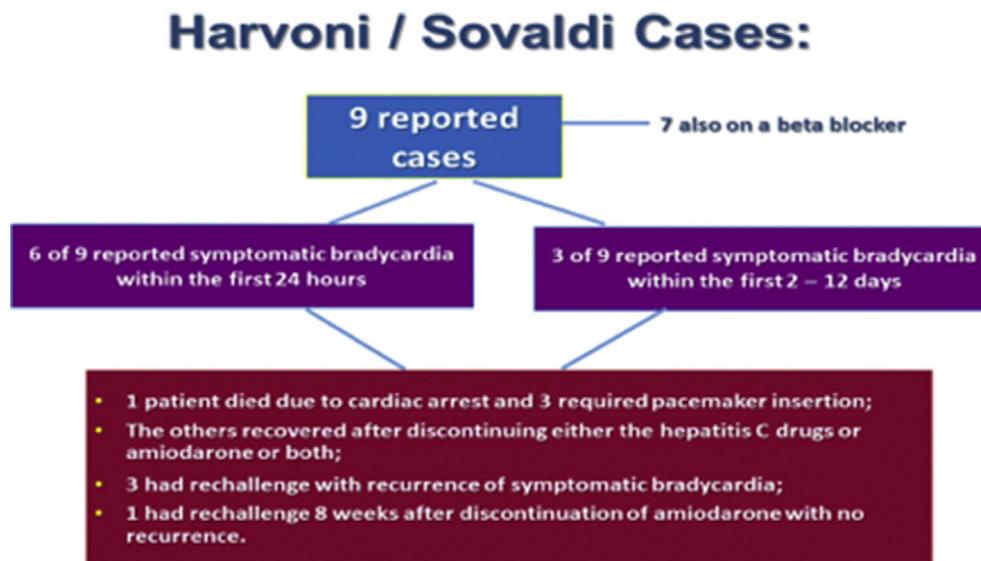
A textual diagram of the reported cases of Harvoni-associated bradyarrhythmias.

Case study in drug-induced bradyarrhythmia: Harvoni

Postmarketing cases of serious and life-threatening symptomatic bradycardia, as well as 1 fatal cardiac arrest and several cases requiring pacemaker insertion, have been reported[16-22] when either Harvoni (a fixed-dose combination of ledipasvir/sofosbuvir) or Sovaldi (sofosbuvir) was given to patients taking amiodarone (Figure 3). Bradycardia has been observed within the first few hours or days of initiation, as well as up to 2 weeks after coadministration. Accordingly, cautions have been added to the package inserts of these agents. More recently, 3 more cases of bradyarrhythmias associated with sofosbuvir-based regimens were reported—this time, only 1 in association with amiodarone.[23]

The mechanism of action for Harvoni- or Sovaldi-associated bradycardia is uncertain. All patients had underlying cardiac disease, concomitant β-blocker therapy, and/or advanced liver disease. It is possible that the new drug altered the I_f current, already prone to dysfunction due to the underlying disease or concomitant medication, and/or impaired conduction out of the sinus node (SN). Several characteristics of these cases suggest a causal association: (1) the short time to symptom onset from starting either Harvoni or Sovaldi combined with a direct-acting antiviral, (2) resolution of symptoms upon drug discontinuation, and (3) recurrence of symptoms upon rechallenge. Understanding the mechanism underlying the Harvoni-amiodarone story might help prevent a similar outcome with other agents in the future. Without this understanding, it is difficult to know how one might extrapolate this experience to future drug development or which patients might need prophylactic monitoring.

SN, atrioventricular node, His-Purkinje tissue

Sinus node function, atrioventricular node (AVN) function, and His-Purkinje (H-P) conduction can all be impaired by medications and result in bradyarrhythmia. Furthermore, SN and AVN function can also be affected by changes in autonomic balance due to drug effects. The extent to which their function becomes abnormal is in large part dependent upon any baseline dysfunction present, the dose of the drug given, its direct and indirect actions, any interacting coadministered agents, and sometimes the time at which it is examined. With respect to the latter, a drug that is parasympathomimetic might only produce substantial SN or AVN dysfunction at times when physiologic vagotonia is also high, such as during sleep or gastrointestinal distress, when the effects can be synergistic.

Importantly, ECG monitoring is the major noninvasive method to assess the effect of a drug on these specialized cardiac tissues. However, we need to recognize that the interpretation of monitor recordings requires knowledge of the normal range of function seen in these tissues across (1) the diurnal cycle, (2) activity levels during

monitoring, and (3) the patient's age. Consider the AV node as an example:

Atrioventricular Wenckebach and even periods of complete heart block at the AVN can be normal during sleep in young or physiologically trained healthy individuals. This has been demonstrated by monitoring studies in military recruits and in medical students, among others.[24] However, AV Wenckebach and complete heart block in older individuals, especially during wakeful hours, are pathologic. Hence, the interpretation of findings must be made with an understanding of what observations represent physiology within the normal range in the population being examined and which represent pathophysiology that requires further study or treatment. This challenge becomes even more important as more sensitive monitoring technologies are introduced into research and clinical practice.

Medications that are parasympathomimetic or are direct depressants of the AVN may produce high-degree AV block—but do so most commonly if there is underlying dysfunction present prior to their administration (such as noted by a prolonged PR interval) or if there is disease-mediated AVN injury concomitant with their administration (such as with an acute inferior infarction). Accordingly, if a drug with potential adverse effects on the AVN is given to a patient with either baseline dysfunction or a concomitant potentially interacting condition, the probability of developing a bradycardic response should be greater. It should also increase from drug initiation to attainment of steady state. Hence, ECG monitoring would best be used from initiation until steady state is reached. A similar precaution should be taken if a patient with manifest H-P dysfunction, such as bundle-branch block, is given a drug with sodium channel–blocking properties.

Understanding a new drug's pharmacology and pharmacokinetics should help determine what risks may be encountered and what type and duration of monitoring should be used during its development. When a scenario such as the Harvoni story is encountered, the most important consideration to address is the mechanism, which will play a major role in determining what monitoring should be used going forward.

Representative examples

There are well-known and underappreciated medications that can affect the SN and AVN. Among the well-known agents are β-blockers, nondihydropyridine calcium channel blockers, sympatholytic agents (including centrally acting ones such as clonidine), amiodarone, digitalis (infrequently at the SN), and ivabradine (at the SN). Less well-known but also important are lithium (more at the SN), cimetidine, ticagrelor, and others. Some drugs rarely affect SN or AVN function in healthy hearts but can have adverse effects if underlying dysfunction

(recognized or not) is present, including flecainide and propafenone. Examples of drugs that can affect H-P function include sodium channel blockers, including class IA and IC antiarrhythmics, tricyclic antidepressants, and intravenous amiodarone. In the Cardiac Arrhythmia Pilot Study,[25] new conduction abnormalities were seen as often with imipramine as with encainide and flecainide.

Steady state should affect monitoring duration

Steady state is generally thought to be attained after 5 half-lives. However, many drugs have a wide range of half-lives, depending upon the patient's age, hepatic and renal function, genetic factors, and concomitant therapies. Figure 4 uses flecainide as an example. In this figure, the significant variability in half-life can be seen.
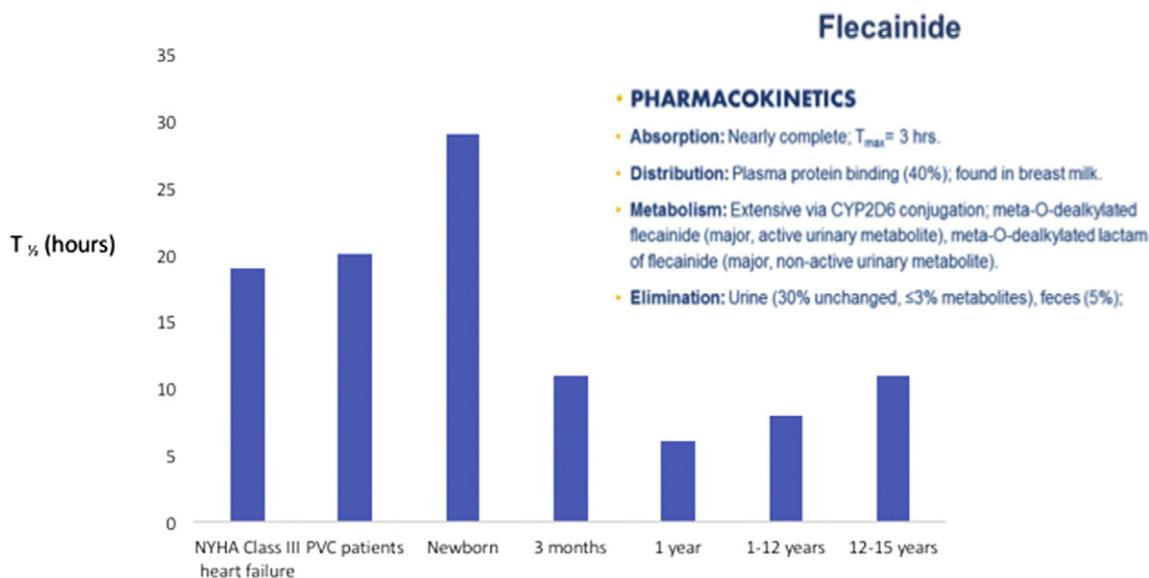
When monitoring a patient after dosing until steady state is attained (parent compound and any active metabolite), to assess ECG effects, safety, and possibly efficacy before increasing the dose or changing treatment—*especially in the outpatient setting*—it is best to use the *maximal, not the mean*, half-life when estimating the optimal duration of ECG monitoring.

For example, monitoring flecainide for 24 hours may suffice if its half-life were short (eg, 3-5 hours) but should be almost 6 days if the half-life were 29 hours. Thus, monitoring might require a Holter (24 hours) or 1 week of a patch monitor, autotriggered loop recording, MCOT, or daily ECG tracings. This same consideration would be appropriate for agents under development once their pharmacokinetic characteristics are known.

How should we monitor for bradyarrhythmias in drug development?

Considering the example of Harvoni, where the observation of significant bradyarrhythmias only became apparent long after its approval and clinical use, and only under the specific circumstance of amiodarone coadministration, can regulators be better prepared to detect such issues prior to a new drug's approval? The challenge is not simply what type of monitoring to use but to understand the mechanism of such interactions so that perhaps they may be more predictable and investigations most appropriately designed and timed during the drug development stage. Short of that, recognizing which agents are known to affect SN, AVN, and H-P tissues (channels, receptors, currents, autonomic interactions), and by what mechanism, plus extrapolation to new agents with similar mechanistic characteristics could determine what monitoring approach might best be used during phase I-III trials (Table III). The Harvoni case

Figure 4

Flecainide

- **PHARMACOKINETICS**
- **Absorption:** Nearly complete; T_{max} = 3 hrs.
- **Distribution:** Plasma protein binding (40%); found in breast milk.
- **Metabolism:** Extensive via CYP2D6 conjugation; meta-O-dealkylated flecainide (major, active urinary metabolite), meta-O-dealkylated lactam of flecainide (major, non-active urinary metabolite).
- **Elimination:** Urine (30% unchanged, ≤3% metabolites), feces (5%);

Variation in pharmacokinetics observed with flecainide.

reminds us that we do not know all we need to know during drug development. Moving forward, when a significant pharmacologicallyinduced bradyarrhythmia occurs with a mechanism that is uncertain, regulators should consider requiring that additional mechanistic studies be initiated as a requirement for continuing marketing of the drug.

Tachyarrhythmia

Long-term ECG monitoring is often considered during drug development to document tachycardias—both supraventricular arrhythmias (primarily AF) as well as VTs (primarily nonsustained VT). This is most commonly performed using Holter monitors with recording durations of 24-48 hours but may also involve use of long-term ECG monitoring with event recorders, MCOT, or even implantable monitoring devices. The decision to perform long-term ECG monitoring during a drug development program is generally related to concerns that a therapy may either promote the initiation of arrhythmias directly or increase the prevalence of arrhythmias in a particularly susceptible population with preexistent cardiac disease, where patients are already at substantial risk of arrhythmias.

Drugs that do not have effects on cardiac ion channels or autonomic tone are unlikely to initiate arrhythmias. In the absence of any mechanism that might promote arrhythmias, long-term ECG monitoring would generally not be warranted during a drug development program. When long-term ECG monitoring is performed during

drug development, any detected tachyarrhythmias are far more likely to represent the background prevalence of arrhythmia in healthy individuals than drug-related effects. It is often difficult or impossible to determine if an arrhythmia detected in an individual subject in a clinical trial is related to a drug-mediated effect or is a manifestation of underlying cardiac disease or the low prevalence of tachyarrhythmias in healthy individuals. Thus, when long-term monitoring is performed and a small number of tachyarrhythmias are detected, it may be impossible to tell if a small imbalance in the event frequency between treatment groups represents a true drug-related effect or not. In light of ambient arrhythmia detected in healthy individuals during long-term ECG monitoring, it is prudent to consider long-term ECG monitoring only when a drug has characteristics which might promote arrhythmias or when the treatment population is at particularly high risk. It can be helpful to have a relatively long period of monitoring prior to drug administration to better define an individual's background arrhythmia frequency.

Supraventricular tachyarrhythmias

Few drugs currently available are unequivocally known to produce supraventricular tachyarrhythmias in healthy individuals. Many drugs, however, do produce increases in sinus heart rate. Other than adrenergic agonists, most drugs that increase chronotropy increase the heart rate by only a few beats per minute. It may be very difficult to detect such an effect with standard vital sign assessments or with data recorded from standard ECGs, but long-term

Table III. Proposed monitoring for arrhythmias during drug development

Monitoring technology	Potential circumstances for use
ECG	• Daily monitoring from dosing until achievement of steady state • Documentation with symptoms
Holter monitor (24-48 h)	• Daily monitoring from dosing until achievement of steady state • Documentation with frequent but intermittent symptoms (<1-2 d between episodes)
14-d patch ambulatory monitor	• Drugs with longer-half lives
30-d ambulatory monitor with memory (loop monitor)	• Documentation of intermittent symptoms less frequent (>48 h between episodes)

MCOT	• High risk of severe arrhythmia
	• Detection of arrhythmias that require a rapid response
	• If remotely monitoring patient compliance with monitoring is desired
	• If reduced timeline to obtaining data provides value
	  o Reduced study timelines
	  o Reduction in site or patient burden

Implantable loop monitor	• Drugs with very long half-lives • Rare and infrequent arrhythmias • If defining time to reoccurrence or burden of arrhythmic episodes is desired

monitoring with Holter recorders is very useful for documenting small drug-induced changes in heart rate. Holter recordings allow assessment of heart rate over a full 24-hour period or during shorter periods; most Holters can report mean heart rate on an hourly basis or even in smaller increments. This may be useful for relating heart rate changes to drug dosing and to drug pharmacokinetics.

However, in patients who may have preexisting cardiac disease or pulmonary disease, some drugs are thought to induce AF (and atrial flutter). These drugs include adrenergic agonists (dobutamine), adenosine, digoxin, and anticholinergics. There has been concern that inhaled β-agonists and anticholinergics may induce AF, particularly in patients with severe chronic obstructive pulmonary disorder, many of whom may also have preexistent cardiovascular disease and very high risk of AF. Similar concerns hold for patients with severe heart failure and left ventricular dysfunction, who are at high risk for both ventricular and supraventricular arrhythmias. It is therefore common during drug development of therapies targeted at populations with underlying left ventricular dysfunction or severe chronic obstructive pulmonary disorder to include some assessment of the risk of induction of AF. This may include Holter monitoring (24-48 hours). However, Holter monitoring may be inadequate to detect a small increase in the incidence of AF. More extended monitoring for a period of up to a month is more likely to document asymptomatic episodes of self-terminating or paroxysmal AF. A major concern, however, is that long-term monitoring in

susceptible populations is more likely to detect AF unrelated to drug therapy. It is therefore critical to collect adequate-duration pretreatment ECG monitoring data and, whenever possible, to provide for a placebo or at least standard-of-care control group. Careful attention to the duration of pretreatment monitoring and to the randomization ratio is also warranted to avoid biased detection of episodes of AF.

Adrenergic agonists may also promote the development of reentrant supraventricular tachycardias (SVTs) (atrial tachycardias, AV nodal reentry, or AV reentry) in susceptible individuals. Such patients may already have had episodes of SVT in the past, but adrenergic stimulation may promote SVT in patients with dual AV node pathways or an accessory AV pathway who have never had documented SVT previously. Drugs which have indirect effects on autonomic tone may also promote AF or SVT indirectly; for instance, a potent vasodilator may lead to a large sympathetic response which might provoke supraventricular tachyarrhythmias in a susceptible patient.

Ventricular tachyarrhythmias

Drugs may also cause ventricular proarrhythmia, which may also be detected during drug development via long-term ECG monitoring. The ventricular arrhythmia that provokes the greatest concern during drug development is drug-induced TdP.[26] Fourteen drugs have been removed from the market worldwide because of unanticipated drug-induced TdP[27] generally due to drug-induced block of the hERG-encoded IKr potassium

channel. Long-term ECG monitoring is not, however, likely to be useful for detection of drug-induced TdP during clinical drug development programs because of its extreme rarity even with relatively potent torsadogenic drugs. Although class I and class III antiarrhythmics may produce TdP in 1%-3% of patients, most of the drugs withdrawn because of TdP produced documented arrhythmias far less frequently. It has been estimated that terfenadine produced TdP in approximately 1 in 50,000 prescriptions. It is therefore impractical to detect drugs which are at risk for drug-induced TdP with long-term ECG monitoring, and instead, the use of surrogate markers (as described in the ICH E14 guidance) is recommended.

Drugs that block the cardiac sodium channel NaV1.5 have also been associated with VTs (tricyclic antidepressants, flecainide in patients with heart failure and reduced systolic function). Few such drugs are in common use, and the incidence of VT in patients receiving sodium channel blockers (other than antiarrhythmic agents) is unknown. During the development of a new drug with known sodium channel blockade in which the channel kinetics (slow onset and offset kinetics are more concerning than faster kinetics) and/or effect on the QRS interval raises significant concern, it may be appropriate to perform long-term ECG monitoring to allay concerns about drug-induced VT. For drugs thought to have a significant risk of inducing VT, initial monitoring in an inpatient setting with continuous telemetry would be most appropriate. For drugs thought to have a possible low risk of inducing VT, outpatient dosing, possibly while patients wear an MCOT device, capable of detecting sustained ventricular arrhythmias and immediately notifying a full-time monitoring center who are able to notify emergency services may be appropriate. For such drugs, monitoring with a Holter recorder or standard event recorder would not be sufficient because of the lack of real-time arrhythmia detection and activation of emergency responders.

Nonpharmacologic therapies for heart failure, such as stem cell therapy, have also raised concerns about increasing ventricular proarrhythmia. Early trials of skeletal muscle–derived stem cells seemed to show an increase in ventricular tachyarrhythmias; current trials of cardiac stem cells now generally include long-term ECG monitoring to assess for the risk of promoting VT.

Dose-finding studies

First-in-human (FIH) phase I ascending-dose studies and phase I/II dose-finding studies in patients are trials in which long-term ECG monitoring may also be used. These trials generally involve administration of new drugs (or dosages of established drugs which have never been tested) to either healthy individuals or individuals with the condition of clinical concern. In such cases, the human tolerability and adverse effect profiles are not known. In these studies, inpatient telemetry may be used to detect potential arrhythmic adverse events. However, long-term ECG monitoring may also be of value. A new agent might produce bradyarrhythmias (SN slowing or AV block) or tachyarrhythmias (SVT or VT); long-term ECG monitoring during trials testing increasing drug dosages might detect a subtle, but clinically relevant, signal during dose escalation.

In reality, most ascending-dose phase I trials in healthy volunteers or phase I/II patient trials generally use very small cohort sizes, and detection of new brady- or tachyarrhythmias during such trials would be very unlikely. For drugs that have not shown any signals of concern during preclinical testing (no ion channel block in patch clamp studies; no arrhythmias or ECG interval changes during telemetered animal studies), long-term ECG monitoring during ascending-dose trials is generally not warranted. As discussed previously, it is far more likely that an arrhythmia detected in such a small trial represents underlying cardiac pathology or simply the occasional occurrence of AV block or tachyarrhythmias in healthy populations.

However, for drugs that do have a preclinical signal suggesting a potential for arrhythmogenesis, a known class effect, or for use in a very high risk population, long-term ECG monitoring may be warranted during early ascending-dose trials. Common wisdom would suggest that the incidence of arrhythmias should rise with dosage and exposure, although there are clearly drugs that have different ion channel effects at different exposures and for which the risk of arrhythmia may not be directly dose proportional. It is therefore recommended that if long–term ECG monitoring is being considered, one should perform the same extent of monitoring at all planned dosages. It is also recommended that careful consideration be given to the duration of pretreatment monitoring (to document the baseline occurrence of arrhythmias) and to the use of a placebo or standard-of-care control group. Again, the presence of an adequately sized pretreatment assessment period or control group is important to discriminate proarrhythmia versus ambient arrhythmia.

Pragmatic use

Long-term ECG monitoring has an important role in clinical drug development, but a number of considerations suggest that its indiscriminate use is likely to result in more confusion than clear benefit. Foremost among these is our relatively poor understanding of the true background occurrence of arrhythmias in healthy volunteers as well as in patient populations. If AV block and nonsustained SVT and VT never occurred in healthy individuals, it would be a simple matter to use long-term ECG monitoring in clinical trials and, if any arrhythmias were detected, to conclude that they were drug induced. However, AV block, short episodes of SVT, and even

episodes of nonsustained VT (eg, benign outflow tract VT) are often documented in healthy individuals with no structural heart disease and on no medications. Furthermore, the incidence of these arrhythmias increases with age and in the presence of cardiovascular and pulmonary disease and is more likely to be observed with longer versus shorter monitoring. Discrimination of morphology (monomorphic inferiorly directed axis versus polymorphic) also provides important information. High-quality multilead ECG monitoring can be very helpful in this regard.

It is therefore important that long-term ECG monitoring be used appropriately during drug development programs. For drugs with a clean preclinical slate, long-term ECG monitoring is far more likely to detect unrelated arrhythmias than drug-related effects. Furthermore, the longer the monitoring duration, the higher the likelihood of detecting "baseline" arrhythmias. One should therefore use long-term ECG monitoring in circumstances where it is likely to be helpful. For drugs with a known class effect, such as S1P1 modulators, which are known to produce first-dose bradycardia and AV block, long-term ECG monitoring is critical for detecting the risk of arrhythmic adverse events and for determining how clinicians should best monitor for and treat such arrhythmias. Careful attention should be paid to trial design. One should ensure an adequate duration of pretreatment monitoring to detect patients who may have preexisting arrhythmias and to document the baseline incidence of arrhythmias in the trial population. Careful consideration should be given to having an adequate-sized placebo or standard-of-care treatment group. In cases where a placebo or other control group is not feasible, one might consider a longer duration of pretreatment monitoring or potentially long-term ECG monitoring after the end of drug treatment.

Consideration should also be given to the type of long-term ECG monitoring to be used. Standard 24-hour Holter recordings may be sufficient to detect (or exclude) a large increase in arrhythmias but may be inadequate to detect a small increase in either bradycardic or tachycardic events. In such cases, either a larger sample size or use of longer-term ECG monitoring with one of the new technologies such as MCOT for 2-4 weeks, or even an insertable cardiac monitor, might be required.

Interpretation of monitoring data and limitations
Discerning pathologic versus "ambient" arrhythmia: the pitfalls of small datasets

By the time a new drug reaches the stage of large phase III trials, sponsors and investigators typically understand the channel-blocking profile of the drug being tested and hopefully have some insight into the organ-specific metabolic toxicities of a compound and/or its metabolites

that were demonstrated during nonclinical testing. Pharmacokinetic profiles of the parent molecule and its metabolites are usually well understood. In the circumstance of a known membrane-active channel-blocking agent for which the overall proarrhythmic profile is either unclear or potentially different for different subject substrates (eg, underlying coronary artery disease or not, important myocardial hypertrophy or not, poor left ventricular function or not), phase III trials can be designed and powered appropriately to delineate benefit/risk profiles in subpopulations that may be vulnerable to drug-induced proarrhythmia or drug-induced failures of impulse generation and conduction. Cardiac rhythm safety can be assessed based on placebo-adjusted occurrences of these types of events.

In contrast, FIH studies and phase I single- and multiple-dose exploration studies are typically conducted at a time when much about the human safety of the drug is unknown, and are generally performed in small subject cohorts. These small cohort sizes make individual patient assessments mandatory because of the potentially high inter-subject variability in the occurrence of arrhythmias, with each subject serving as his or her own control for assessments of the on-drug occurrence or worsening of arrhythmic events (typically ventricular but occasionally atrial as well). Accordingly, the primary source of variability that limits the interpretation of arrhythmias in early development is the intra subject variability of these events that can be affected by diurnal variation, autonomic tone, dietary factors, and environmental factors. In this circumstance, if an individual's ambient arrhythmia baseline is either poorly defined (or not defined at all), the documentation of new potentially important arrhythmias during telemetry in the phase I setting can be profoundly problematic; cause substantial program delays; and, in the worstcase scenario, cause the development of a promising, potentially life-saving therapy to be wrongly abandoned. The following example of real-life drug X illustrates this point.

Case example. Drug X is a first-in-class therapy for a serious and often fatal disease. During preclinical animal testing, elevated cardiac troponin-I (cTnI) was seen in several animals of 2 species, and 1 animal experienced a 4-beat run of nonsustained ventricular tachycardia (NSVT) following exposure to this drug. There were no cardiac histopathological changes, and there were no safety issues during FIH and phase I single ascending dose testing. However, during the human multiple ascending dose testing, 2 drug-related, treatment-emergent adverse events occurred. First, several subjects developed transient low-grade cTnI elevation. Second, an episode of NSVT occurred in an apparently healthy, middle-aged subject (Figure 5).

This 14-beat, >3 second episode of monomorphic NSVT (rate > 200 beats per minute) caused much

Figure 5
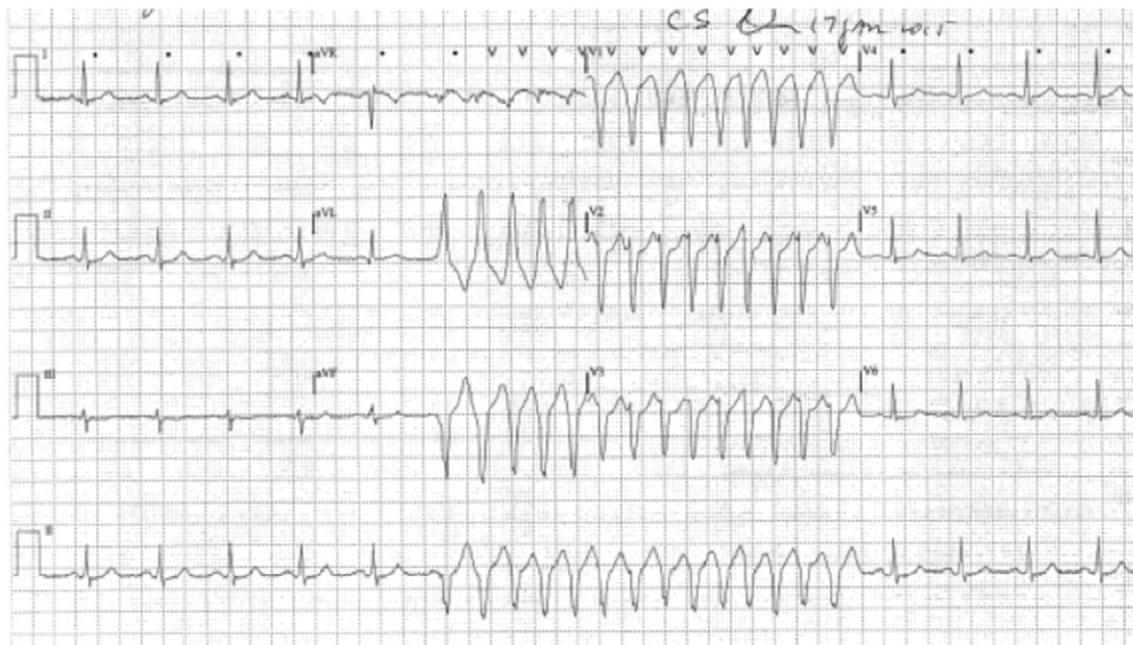
Nonsustained VT complicating monitoring in drugdevelopment with evidence of low-grade troponin elevation in an animal model.

concern because it had a left superior axis that is not typical for either outflow tract VT or fascicular VT (common "normal heart" VTs), and this subject had no history of ischemic cardiovascular disease, and his QT/QTc was not prolonged. Because of the small number of subjects that had been exposed to this drug, together with the troponin elevations and NSVT that had been seen in animal testing, and because there was no predrug baseline monitoring to document NSVT as a baseline arrhythmia for this subject, this development program was placed on full regulatory hold in the interest of trial participant safety. However, there was ongoing concern both within the drug-specific Review Division and the Division of Cardiovascular and Renal Products that the few findings in the animals may not have been drug-related and that the ECG could have represented this subject's normal ambient ventricular arrhythmia profile.

Given the potential importance of this first-in-class therapy for a fatal disease, the sponsor pushed forward with a comprehensive strategy to either confirm or exclude the possibility that drug-induced cardiotoxicity caused this arrhythmia. This strategy included the following:

- Longer-term preclinical studies were repeated with stringent handling, acclimation, and animal selection criteria, and no evidence of cardiovascular toxicity was seen.

- In vitro and human ECG data did not suggest that this drug or its metabolites affected the QTc interval.
- The individual who experienced NSVT underwent extensive post-trial cardiac evaluations to further define baseline cardiovascular status including magnetic resonance imaging, echocardiography, stress-perfusion exercise testing, and thyroid function testing. The results of all of these were normal. Thirteen-day Holter monitoring off any drugs demonstrated a run of monomorphic NSVT on monitoring day 11 as well as frequent premature ventricular contractions (PVCs) on monitoring day 13. After reviewing this information, the sponsor's external cardiovascular expert review panel determined that the probability was low that the NSVT that this subject experienced in the clinical trial was drug-related.

Based on these findings, clinical testing was allowed to resume with the incorporation of baseline and on-treatment 13-day Holter monitoring, cardiac telemetry during drug initiation, ECGs, cTnI assessments, sequential echocardiograms, and stringent exclusion criteria based on screening Holter monitoring. Importantly, this process of post-trial subject evaluation and preclinical study repetition caused an approximately 1-year delay in this program. Had the involved subject not been willing to take part in poststudy cardiac testing, a study restart may not have been possible at all.

How much monitoring is necessary? The question that frequently arises from sponsors is, "How much post-exposure monitoring is necessary?" Given what occurred in the example of drug X, we would encourage sponsors and investigators to think about this issue more broadly, to include the question, "How much pre-exposure monitoring is necessary?" These are related questions, and as is often the case, the answers depend on where a new therapy falls on the continuum of cardiotoxic risk and, separately, on the vulnerability of the patient population in which it is intended to be used.

Thinking about postexposure monitoring first, it has been shown previously that "…increasing the duration of recording from 24 to 36 hours increased the probability of detecting maximal and more complex grade PVCs by 25% and 50%, respectively."[28,29] We also note that the subject of concern in the above example of drug X did not demonstrate NSVT in posttrial follow-up testing until day 11 of long-term continuous monitoring off drug. Therefore, we see several possible lines of reasoning for the intensity of postexposure monitoring, some examples of which would include the following:

- A limited monitoring approach for a drug for which there is long experience with the class being noncardiotoxic and for which there were no concerns for cardiotoxicity raised in preclinical studies.
- A limited or, depending on the target patient population, intermediate monitoring approach for a first-in-class therapy which has no important channel-blocking activity (reported as IC_{50} values for the panel of channels assessed), no metabolic blocking properties (either for nucleic acid mediated grow-repair-reproduction or for intracellular energetics pathways), and no evidence of cardiotoxicity in preclinical testing.
- A more extensive monitoring approach for drugs that have (or belong to a class that has) known cardiotoxic effects, either in channel blocking studies or in preclinical studies, or are known to be metabolic blockers of some variety.

The issue, then, that the drug X example brings up is what to do if, from limited monitoring, a worrisome finding emerges. As in that case, monitoring had to be intensified to define whether the observed NSVT was a drug toxicity or an ambient arrhythmia. In the absence of baseline testing, a year-long program delay occurred. This argues for some degree of baseline monitoring in all subjects undergoing postexposure monitoring. In the drug X example, the NSVT did not recur until monitoring day 11 off drugs. New technologies make longer-duration monitoring feasible. The degree to which sponsors incorporate comprehensive baseline monitoring into development programs will likely be influenced by newness of the class, experience with other class members, and preclinical testing results. Some may consider 24 to 48 hours of preexposure baseline monitoring as part of phase I drug exposures, either prior to or at the time of phase I unit admission. In the end, this is a balance between the cost of obtaining baseline monitoring information versus the risk of a substantial program delay in the absence of that information. These decisions will undoubtedly be made on a case-by-case basis.

Summary of recommendations

In summary, evolving technologies for cardiac rhythm monitoring will enable improved collection of heart rhythm function during drug development. Similarly, these technologies will also present new challenges alongside their benefits. Based upon the input from multiple stakeholders in academic medicine, clinical practitioners, industry, and regulatory bodies, the following consensus recommendations have been put forward.

1. The selection of heart rhythm monitoring technologies during drug development should be principally based upon the half-life of the drug and metabolites, the proposed mechanism of action of any potential proarrhythmia, and the underlying risk of the studied population (Table III).
2. A single bipolar ECG recording represents the minimum standard for cardiac rhythm monitoring. The device should be medical grade with appropriate regulatory agency approval. Devices such as smart watches that use non-ECG electrode modalities, including but not limited to photoplethysmography and pulse rate accelerometry, should not be used until there is sufficient evidence, regulatory approval, and clinical consensus.
3. The intensity of heart rhythm monitoring should be guided by the level of anticipated risk. The highest intensity of monitoring should be reserved for drugs with cardiotoxic effects demonstrated in nonclinical investigation or other analyses (Table III).
4. Cardiac rhythm monitoring during drug development is of greatest value when pretreatment monitoring is incorporated to help discern background arrhythmia versus drug-induced proarrhythmia.
5. Signals for potential arrhythmia need to be interpreted in light of the underlying treated population (eg, incidence of AF in younger versus elderly patients).

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