

# The evaluation and management of drug effects on cardiac conduction (PR and QRS Intervals) in clinical development

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Recent advances in electrocardiographic monitoring and waveform analysis have significantly improved the ability to detect drug-induced changes in cardiac repolarization manifested as changes in the QT/corrected QT interval. These advances have also improved the ability to detect drug-induced changes in cardiac conduction. This White Paper summarizes current opinion, reached by consensus among experts at the Cardiac Safety Research Consortium, on the assessment of electrocardiogram-based safety measurements of the PR and QRS intervals, representing atrioventricular and ventricular conduction, respectively, during drug development. (*Am Heart J* 2013;165:489-500.)

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The assessment of drug-induced changes in cardiac electrical activity remains a key component in the development of safe pharmacotherapeutic agents. Prior efforts to evaluate cardiac safety have focused on changes in cardiac repolarization (and, specifically, the QT interval on the electrocardiogram [ECG]), partly because of the ICH E14 Guideline (Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs), the maturation of systems for ECG monitoring and analysis, and the evolution of the thorough QT/corrected QT interval (QTc) study. As a result of these advances, further resolution of drug effects on cardiac conduction (manifesting as changes in the PR and QRS intervals) has been realized. To aid in the interpretation of these new data, a Cardiac Safety Research Consortium subgroup was established to foster stakeholder discussion about PR and QRS interval assessments in drug development. Evolving data sets are

providing information regarding appropriate techniques, expected variability, and overall use of evaluating drug-induced changes in the PR and QRS intervals during early-phase clinical drug development. However, limited clinical experience related to sustained changes of these intervals in different patient populations serves to constrain defining specific recommendations regarding acceptable limits for such drug-induced changes. This White Paper summarizes discussions within the Cardiac Safety Research Consortium and focuses on what is known, not known, and controversies regarding the use of PR and QRS intervals in drug development. In addition, we believe that this study will be useful to those engaged in or regulating drug development activities. We suggest that the relative lack of knowledge about these ECG-based safety measurements as end points will be considered when applying the concepts discussed, and we hope that this White Paper will spur much-needed research in this area. The opinions and conclusions expressed in this article are solely the views of the authors and do not represent the new regulatory policy.

## Technical considerations in the assessment of PR and QRS intervals

Technical details related to the methods used for the measurement of the PR interval and the QRS duration may significantly affect the validity of the measurements. Historically, manual measurements of the PR interval and the QRS duration were made using calipers applied to single or multiple leads of paper 12-lead ECGs, often

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Submitted January 17, 2013; accepted January 17, 2013.

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0002-8703/\$ - see front matter

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<http://dx.doi.org/10.1016/j.ahj.2013.01.011>

recorded at 25 mm/s (and less commonly at 50 mm/s), with a limit of resolution of approximately 4 to 6 ms or greater. More recently, measurements may be performed on unfiltered digital 12-lead ECG (dECG) files either by machine algorithm, automated algorithms used by central ECG laboratories, or by an expert using on-screen calipers, with a limit of resolution of approximately 2 ms or less being feasible. On-screen measurements may be performed using a global median beat methodology, or may be performed on dECG complexes from a single lead. Electrocardiogram machine measurements can now be performed on unfiltered digital files by machine algorithm. Electrocardiogram machine algorithms generally use a global median beat method, whereby a single summed or ideal beat is generated from superimposition of waveforms from each lead.

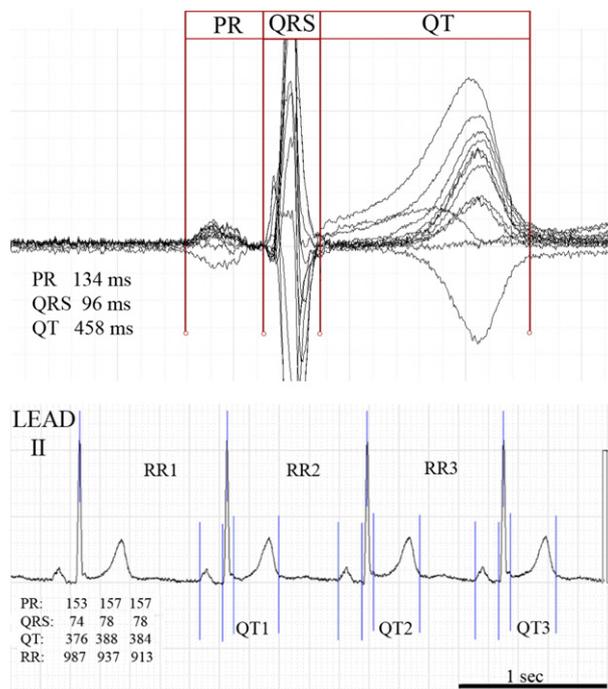
### The PR interval

The PR interval is measured from the earliest P-wave onset to the earliest onset of the QRS complex (Q- or R-wave) onset, and the QRS duration is measured from the earliest Q (or R)-wave onset to the latest QRS (S wave or R or r' wave) offset. Both PR and QRS may be measured in a single lead or across all 12 leads. The P wave on the ECG is the body surface representation of atrial myocardial activation, usually traversing from upper right to left and caudally from the sinus node. The PR interval includes both atrial activation (P wave) and the time for conduction through the atrioventricular (AV) node in the AV junction, and then through the specialized His-Purkinje conduction system to the ventricles simultaneously via the bundle branches. Delay in atrial activation, conduction through the AV node, or conduction through the His-Purkinje system may contribute to PR prolongation. Consequently, drugs affecting atrial electrical activity may change P-wave morphology or prolong the PR interval.

### The QRS interval

The QRS complex represents activation of ventricular myocardium, and QRS prolongation may result from a wide range of processes involving the conduction system primarily, the myocardium, or both. QRS prolongation may involve either diffuse processes such as hypertrophic or infiltrative diseases, or drugs, or focal damage from infarction or infiltration. The time course of effects in relation to drug administration and exposure-response relationship are usually useful in characterizing drug effects in both healthy subjects and patients, regardless of whether ECGs are normal or abnormal at baseline. However, high-quality dECG data should be collected, analyzed, and interpreted in the context of Pharmacokinetics (PK)/Pharmacodynamics (PD) modeling and clinical conditions. Prolongation of the QRS (ventricular depolarization) will result in a direct increase in the QT/QTc interval, related to the actual QRS increase, and may also

**Figure**



Technical approaches to ECG intervals measurements. Upper panel: ECG interval measurements using a global median beat method. Lower panel: measurements made in a single lead. Artifact or baseline wander may make precise assignment of the P onset, Q (or R) onset, or S (or R) wave offset difficult. Changes in lead positioning between ECGs may provide different PR and QRS interval measures, complicating the assessment of drug-induced changes with time.

result in an additional QT/QTc prolongation, related to a direct or secondary effect on ventricular repolarization.

A global median beat method, as illustrated in [Figure](#), will usually yield a greater PR interval or QRS duration than measurement in a single lead, but determination of the best point to measure P onset or S offset may be difficult in the presence of 12 overlapping complexes. As also shown in [Figure](#), measurement in a single lead is usually less difficult, but because the initial or terminal portions of the P wave or QRS may be isoelectric in a specific lead, the PR or QRS duration may be underestimated. This is particularly noticeable in the presence of complete right bundle-branch block (RBBB), where the broad S wave characteristic of RBBB may not be evident in lead II; this may lead to underestimation of the QRS duration if lead II is used. Similarly, when the P wave is multiphasic or has very low amplitude, the P-wave onset may be better seen in some leads than others. In light of the differences between these methodologies, it may be inappropriate to compare measurements of PR intervals and QRS durations, which have been performed with different methods. Rather, it may be preferable to

use a consistent approach to minimize unwanted increases in variability.

## Part I. PR interval prolongation: AV block

### Clinical relevance of AV block

Ascribing clinical meaningfulness to lower degrees of AV block (AVB; first degree and type I second degree) is less clear compared with higher-grade AVB (type II second degree and third degree), which indicates advanced conduction system dysfunction. *First-degree AVB* is a term used to characterize AV conduction delay or slowing (rather than actual AV conduction block) and is manifest as PR (or PQ) interval prolongation, relative to normative values, typically beyond 200 to 220 ms, during sinus rhythm, at heart rates in the range of 60 to 100 beats/min in adults. Intermittent first-degree AVB and type I second-degree AVB (progressive PR prolongation preceding a nonconducted P wave), on the other hand, do not necessarily indicate an underlying pathologic condition and may be related to normal physiologic variations. Although lower degrees of AVB are often not clinically concerning, if they are drug induced, they may presage more significant AV conduction problems. Hence, drug-induced PR prolongation and AVB are often viewed as potentially deleterious. Many drugs resulting in slowing of AV conduction, such as  $\beta$ -blockers and calcium antagonists, are used routinely in high-risk patients with overt cardiovascular (CV) disease and in clinically appropriate patients who have net beneficial effect on CV outcomes. Nevertheless, in early-phase clinical studies, subjects with more than mild first-degree AVB (200-220 ms) or type I second-degree block at rest on screening ECGs might not be ideal for assessing potential drug effects, in particular for compounds with a possible preclinical signal on AV conduction. Subjects with more advanced AVB are typically excluded from early-phase clinical studies. A selected list of drugs associated with PR interval prolongation based on product labels (US full-prescribing information) is found in Table.

PR interval shortening has been reported with some drugs (eg, prucalopride and plerixafor), and variably short PR intervals may also be associated with increases in sympathetic tone, sympathomimetics, vagolytics, or sinus tachycardia. Cardiac conditions may also be associated with variable AV conduction, most notably the Wolf-Parkinson-White syndrome in which accelerated AV conduction via accessory AV pathways may result in short PR intervals and wider QRS complexes with appearance of initial  $\delta$  waves, which correspond to ventricular preexcitation. Drugs may also affect conduction in these patients, making them less suitable for inclusion in early-phase studies.

A selected but not all inclusive list of drugs associated with PR interval prolongation is found in Table.

**Table** Electrophysiologic effects of select drugs on PR and QRS intervals based on product labeling

Drug	Action	Indications
Affecting AV nodal conduction (PR interval)		
Adenosine	Adenosine receptor	PSVT
Amiodarone	Cardiac ion channels	Antiarrhythmics
Disopyramide		
Encainide		
Flecainide		
Moricizine		
Propafenone		
Verapamil		
Arsenic trioxide	Multiple actions	Acute promyelocytic Leukemia
Atazanavir	HIV-1 protease inhibitors	Antiretroviral inhibitor
Lopinavir/Ritonavir		
Saquinavir		
Digoxin	Multiple actions	Congestive heart failure
Dolasetron	5HT <sub>3</sub> receptor antagonist	Antiemetic
Fingolimod	S1P receptor modulator	Multiple sclerosis
Lacosamide	Not fully characterized	Partial-onset seizures
Pregabalin	Not fully characterized	Neuropathic pain
Mefloquine	Plasmodicidal effects	Antimalarial
Affecting ventricular conduction (QRS interval)		
Disopyramide (1A)	Cardiac sodium current block	Antiarrhythmic
Procainamide (1A)	1A Moderate effect	
Moricizine (1C)	1C Strong effect	
Propafenone (1C)		
Dolasetron	5HT <sub>3</sub> receptor antagonist Multiple cardiac channel blocks	Antiemetic

Drugs were initially screened using the PDR3D database for PR interval prolongation using terms "PR interval prolongation," "AV block," "AV conduction delay," or "heart block." For drugs affecting QRS duration, the terms "prolonged and QRS," "prolongation and QRS," "slowed ventricular," or "prolonged ventricular" were used. Drugs were subsequently selected for inclusion on the basis of descriptions of PR prolongation/AVB or QRS prolongation contained within Warnings or Precautions sections of drug labels. Effects manifest at supratherapeutic concentrations (eg, QRS prolongation with TCA overdose or pharmacokinetic drug-drug interactions) are not included.

PSVT, Paroxysmal supraventricular tachycardia.

Drug-induced AV conduction delay frequently resolves shortly after discontinuation (eg, with  $\beta$ -blockers and calcium channel blockers). However, these changes often relapse in these patients, suggesting that drug-induced AV conduction disturbances may serve to uncover underlying conduction system disease. Such patients should be monitored carefully for signs of recurrent AVB.<sup>1</sup> Clinical conditions associated with PR interval prolongation and AVB include hypothyroidism, infective endocarditis, ischemic heart disease, congenital conditions, iatrogenic causes (ie, postsurgery or interventional manipulation or ablation), and inflammatory or infiltrative disease (myocarditis, collagen diseases).

**Prognosis of PR interval prolongation.** First-degree AVB was long thought to have a benign prognosis based primarily on observations from 2 large studies that evaluated about 5,000 healthy subjects.<sup>2,3</sup> Subsequent

investigations of 1,832 middle-aged men without known heart disease suggested that PR prolongation at baseline was often normalized at follow-up several years later and that progression to high-grade AVB over that time frame was rare.<sup>4</sup> However, a recent analysis of 7,575 participants in the Framingham Heart Study, including older individuals and those with medical comorbidities, reported that prolongation of the PR interval was associated with increased risks of pacemaker implantation, development of atrial fibrillation, and all-cause mortality.<sup>5</sup> Some limitations are inherent to the interpretation of this data set, including the potential of confounding association with PR interval prolongation with causality for adverse CV outcomes in different populations. However, these recent findings may suggest that the earlier data on the natural history of PR prolongation in young healthy men may not be representative of the prognosis of PR prolongation in older populations of patients, particularly those with concomitant illnesses such as coronary artery disease (CAD). Recently, it has been shown that PR interval prolongation was associated with higher risk for congestive heart failure and death in patients with stable CAD.<sup>6</sup> Furthermore, these population studies suggest that elderly patients may be at higher risk for complications from drugs that affect AV conduction. First-degree AVB in healthy subjects in early-phase clinical studies cannot be considered to have the same clinical or prognostic importance as the same ECG finding in either middle-aged patients with underlying CV disease or CV risk factors, or in elderly patients with impaired cardiac conduction or overt or advanced CV disease.

**Variability of the PR interval.** Several factors can complicate the interpretation of PR interval changes as a surrogate marker for proarrhythmic risk in drug development. First, differences in ECG measurement and analysis techniques can increase the variability between serial measurements.<sup>7</sup> Second, changes in physiologic conditions may contribute to intrasubject and intersubject interval variability in clinical trials, rendering causality assessments difficult. Variability related to circadian rhythms may be partly accounted for by heart rate and autonomic tone.<sup>8-12</sup> The AV node is sensitive to changes in autonomic tone, and vagal stimulation slows AV conduction.

Finally, data from about 12,000 dECGs taken from healthy volunteers in phase I clinical trials of drugs not known to prolong the PR interval are concordant with PR interval values obtained from approximately 80,000 individuals included in pharmaceutical-sponsored clinical trials, as reported by Mason et al,<sup>13</sup> and show that baseline-adjusted prolongation of more than 20% to 25% is rare, as is the shift from normal to high at a cutoff of 200 or 220 ms.<sup>13,14</sup>

**Second- and third-degree AVB.** In type I second-degree AVB with narrow QRS complexes, conduction

block is usually within the AV node and is observed in up to 1% of healthy young subjects, especially during sleep.<sup>15-17</sup> Higher-degree/advanced AVB usually involves infranodal block and structural cardiac abnormalities<sup>15</sup> and carries an increased risk for progression to complete AVB. The presence of relevant symptoms, advanced AVB, bradycardia with escape rhythm <40 beats/min, abnormally wide QRS complexes, ventricular pauses longer than 3 seconds, or a verified intra- or infra-His-located block are all risk factors for worse prognosis.<sup>18</sup>

Type II second-degree AVB is very rare in healthy individuals. Normalization of AV conduction in subjects with type I second-degree AVB after awakening, during physical exercise or emotional stress, or after administration of atropine reflects the normal physiologic variability of AV conduction, whereas the lack of variability of high-grade AVB during an increase in heart rate is a pathologic and clinically relevant response that could be associated with a more serious clinical prognosis.

#### Nonclinical assessment of PR interval prolongation and AVB

The nonclinical assessment of PR prolongation liabilities can be considered based on (a) cellular and subcellular experimental approaches and (b) interval recordings derived from tissues and in vitro or in vivo intact hearts. Subcellular methodologies used include measures of primary ionic currents involved in AV nodal excitability and conduction (including L-type calcium current, Cav1.2). It is possible to describe/predict the dromotropic effects of drugs based on the consideration of key individual ionic currents, but this approach has been used mainly to guide compound selection. Recordings from the regions of slowest or decremental conduction from the node may also be particularly relevant in delineating mechanisms of AVB (eg, extracellular electrograms or intracellular action potential studies). Such studies likely represent a more complete, integrated drug response that involves active and passive electrophysiologic components, changes in excitability, decremental conduction, simultaneous effects on multiple ion channels, and autonomic tone (eg, with  $\beta$ -blockers and cardiac glycosides). The first suggestion of dromotropic effects with evolving compounds is often discovered in the evaluation of PR intervals recorded in vitro or in vivo. Further details of dromotropic effects may be provided using His bundle electrograms to delineate the level of slowing or block in the AV node.

The preclinical evaluation of the effects of verapamil on the PR interval provides a useful example of translational studies. In vitro, verapamil prolongs the effective refractory period of the rabbit AV node and elicits rate-dependent slowing of conduction by reducing the amplitude of action potentials recorded from upper and middle nodal regions,<sup>19</sup> consistent with its block of cardiac L-type calcium current (Cav1.2). In vivo,

verapamil prolongs the PR interval in anesthetized<sup>20</sup> and conscious<sup>21</sup> dogs.

These preclinical findings are in agreement with clinical findings of concentration-dependent slowing of AV conduction and block at comparable concentrations.<sup>22,23</sup> Differences in dromotropic effects across species may also be related to differences in ionic current densities within the AV node, receptor coupling to ion channels, autonomic tone, or differences in drug metabolism.<sup>24</sup>

Clinical trial design to mitigate risks related to PR interval prolongation and AVB

#### **Selection criteria and clinical monitoring during clinical trials.**

**Healthy volunteers.** If safety pharmacology studies are negative with respect to PR interval prolongation or AVB and there are no other relevant concerns based on structural/pharmacologic drug class considerations, it is probably safe to enroll healthy volunteers with first-degree AVB and second-degree AVB type I (when sleep associated). PR prolongation and AVB are then monitored according to standard cardiac monitoring for a clinical pharmacology study. It should be recognized that by causing R-R irregularity, AVB can compromise QT/QTc assessments if not properly recognized during study reviews. First-in-human studies are often expected to provide robust ECG evaluation, including PR interval.

On the other hand, if safety pharmacology studies are equivocal or suggestive of drug-induced PR interval prolongation or AVB or there is relevant concern based on structural pharmacologic drug class considerations, enrolling subjects with PR intervals  $\leq 200$  to 220 ms, without any evidence of second-degree AVB, might be advisable. There is increasing interest in making more effective use of high-quality early-phase ECG data to make earlier and more definitive assessments of drug exposure-response (and PK/PD modeling) and time course of effect characterizations of ECG effects, including PR, QRS, and QT/QTc intervals. Consequently, in early-phase clinical studies, subjects with more than mild first-degree AVB (200-220 ms) or type I second-degree block at rest on screening ECGs might not be best suited for fully assessing potential drug effects. For drugs with potential clinical effects, additional intensive CV monitoring, such as with real-time cardiac telemetry and Holter monitoring, can be added as warranted, to ensure volunteers' safety, profile relevant drug effects, and clear exposures intended for less monitored settings.

**Patients.** Exposure margins in ambulatory patients are usually maintained below those found to be safe in healthy volunteers. The intensity of the clinical and ECG monitoring schedules should be guided by PK characteristics, administered comedications, associated morbidity, clinical feasibility, and possible CV conditions.

Exploring differences in relevant responses between healthy subjects and patient populations early in devel-

opment can be very informative. However, individuals with relatively high probability of having underlying relevant CV conditions, with AVB, or taking concomitant medications that can cause PR interval prolongation are probably at higher risk for adverse events. Such patients could be excluded from clinical trials with investigational drugs that may adversely affect AV conduction until relevant exposure risk has been better profiled in healthy subjects, or in definitive CV studies. If definitive CV studies are not feasible, careful screening may be necessary to exclude subjects with moderate PR interval prolongation (eg, >220-240 ms), higher-grade AVB, or documented history of relevant symptoms (eg, syncope). It is important in patient trials, as well as in healthy volunteer studies, to exclude subjects who manifest accessory pathways, for example, ventricular preexcitation ( $\delta$  waves).

**Definitive ECG studies.** With the possible exception of small-molecule oncology drugs and monoclonal antibodies, definitive ECG studies, or thorough QT/QTc (ECG) studies, are almost always required before expanded patient exposure in phase III clinical trials and provide robust ECG-based intervals analyses. Generally, the analyses from definitive ECG studies include the following:

- Central tendency analysis: for example, absolute mean PR interval measurements with 95% confidence interval (CI), baseline-adjusted PR interval with 90% CI, and placebo- and baseline-adjusted PR interval with 90% CI
- Exposure-response assessment: when analysis of central tendency or categorical analysis of outliers raises cause for concern
- Categorical outlier analysis: the number and proportion of subjects with PR interval values >200, 220, and 240 ms. Categorical values for analysis should take into consideration inclusion and exclusion criteria, such as inclusion of subjects/patients with baseline values as high as 220 ms. If outliers are detected, a follow-up categorical analysis of the number and proportion of outlier ECG values will often be needed as well as the number and proportion of outliers by time point in addition to the total number and proportion outliers over the observation period.
- Narratives provided for any subjects with AVB, especially higher-grade AVB
- Relevant ECG morphologic assessment to inform assessment of subjects with AVB
- If these definitive CV studies identify clinically significant AV conduction risks, additional expanded clinical monitoring will likely need to be implemented in at-risk patients during subsequent phase III studies. In this case, it may be helpful to also include informative PK sparse sampling that

enables exposure-response evaluation of AVB-related adverse outcomes.

**Discontinuation of subjects dosing during study conduct.** Discontinuation decisions are modulated by the overall risk/benefit assessment and will often reflect the incomplete understanding of the risk posed by drug-induced AVB at the individual subject level. The following points can be considered when selecting criteria to define discontinuation relevant to AVB issues:

A. At the individual subject level

- Absolute PR interval prolongation beyond a pre-defined threshold (eg, >240 or >260 ms)
- Relative PR interval change from baseline (eg, >25%)
- Second-degree AVB type 2 or higher
- Symptoms and signs of decreased cardiac output

B. At the study cohort level

- Serious or severe AVB relevant adverse events in 1 or more subjects
- Mean marked PR interval prolongation or change from baseline
- Clinically significant increase in incidence of AVB or adverse events suggestive of decreased cardiac output

It is important to note that many subjects with AVB in early-phase studies will not have symptoms from the AVB, and if risk/benefit is appropriate, higher values for drug discontinuation may be warranted with ECG and subject monitoring and risk mitigation. For example, in many cases, subjects become relatively hypovolemic and, after prolonged recumbency and repeated blood draws and procedures, are more prone to vagal-mediated episodes that may include orthostatic hypotension, bradyarrhythmias, and various degrees of AVB, which can be minimized by keeping subjects hydrated and recumbent.

**Event management during clinical trial conduct.**

Clinically significant PR interval prolongation and AVB observed during clinical events should be managed adequately to ensure subjects' safety. Individuals affected should be evaluated by an experienced physician. Blood sampling closest to the time of the event provides drug exposures, and clinical safety laboratory tests may rule out relevant undiagnosed conditions, for example, hypothyroidism. Additional history could uncover any unknown illnesses and medications intake that can affect the autonomic rhythm control, such as sympatholytic or vagomimetic drugs (eg, ophthalmic treatments are occasionally overlooked). This extensive evaluation will be useful for clinical study reports narratives requested by sponsor safety analysts and regulatory agencies.

**Premarketing or postmarketing analysis of adverse experience**

The following adverse events probably represent outcomes potentially related to AVB and hence are informative

to analyze when performing premarketing analyses of clinical trial data or postmarketing surveillance:

- Heart block
- Pacemaker implantation
- Atrial flutter/fibrillation
- Progression of CAD
- Clinically significant bradycardia
- Sudden death
- Symptoms of decreased cardiac output or decreased exercise tolerance
- Presyncope or syncope

**Program wide profiling and analysis of PR interval prolongation**

Evaluating treatment-emergent PR prolongation or AVB is guided by the expected variability of these end points and prognosis of findings in excess of that variability. The use of 24-hour Holter monitoring for arrhythmic screening on selected study days can be a useful strategy used to identify AVB during initial dosing and steady-state treatment with investigational drugs that may affect AV conduction. The pregabalin (Lyrica™, Pfizer, New York, NY) FDA New Drug Application review experience exemplifies an approach to evaluate results of a clinical development program, as profiled below<sup>25</sup>:

- Mean PR interval increase (placebo adjusted) supported by exposure-response analysis
- Incidence of advanced AVB on active drug compared with placebo, investigating dose dependency and high-risk subgroup analysis (see below)
- Outlier analysis comparing incidence on active drug and on placebo, and exposure dependency if any for the following subjects:
  - Absolute PR interval >200 to 220 ms
  - PR interval increase from baseline >25%
- High-risk subgroup analysis evaluating placebo-adjusted PR prolongation as well as incidence of second- and third-degree AVB for the following subgroups:
  - Subjects with baseline PR interval >200 to 220 ms
  - Subjects on concomitant medications known to prolong PR interval, or cause AVB (mitigating any attribution bias)
- Additional analyses can include relevant adverse event and serious adverse event analysis.

**Part II: QRS interval prolongation**

**Clinical relevance of QRS interval prolongation**

Slowed conduction of electrical impulses through the cardiac ventricles is marked by QRS interval widening, which can be caused by conduction system disease or by slowed propagation of electrical conduction through the ventricular myocardium. Delayed propagation of intraventricular conduction, when not directly involving the

conduction system, may prolong the QRS interval in a “non-specific intraventricular conduction delay” (IVCD) pattern. This pattern can be the result of ventricular remodeling in cardiomyopathy, ventricular fibrosis secondary to infarction or other myocardial injury, or reduced intramyocardial conduction velocity (as a result of blockade of sodium current).

When conduction system dysfunction influences the QRS duration, the QRS complex typically assumes a distinctive morphology, such as left bundle-branch block or RBBB, and/or left anterior or left posterior hemiblock.<sup>26</sup> Bundle-branch block may be functional, which usually carries a benign prognosis, or may be a sign of underlying heart disease with a poor prognosis. Functional QRS widening is frequently evident as rate-dependent aberrancy or rate-dependent bundle-branch block. Rate-dependent aberrancy may occur at a critical cycle length.<sup>27,28</sup> In the absence of underlying heart disease, the presence of rate-dependent bundle-branch block does not necessarily indicate an impaired prognosis.<sup>29</sup> However, a recent prospective study has suggested that QRS duration independently predicts risk of sudden cardiac death, with a 2.5-fold elevated risk in subjects with a QRS >110 ms compared with those with a QRS <96 ms.<sup>30</sup> Additionally, QRS prolongation in CV patients may portend a worsened outcome.<sup>31,32</sup> Pathologic causes of bundle-branch block include ischemic heart disease, hypertrophy, endocarditis, myocarditis, cardiomyopathy, congenital defects, massive pulmonary embolus, age-dependent degenerative changes, or drug effect (eg, sodium channel blockers). When associated with conduction system disease, QRS interval prolongation widening may portend an increased risk of progression to clinically significant AVB.

In the presence of CV disease, QRS interval prolongation may reflect underlying path physiologic changes that may be proarrhythmic, and the resultant mechanical dyssynchrony may worsen ventricular function. In patients with heart failure, an inverse correlation exists between QRS interval duration and left ventricular ejection fraction,<sup>33</sup> and an increase in QRS interval duration over time in these patients is a predictor of poor outcome.<sup>34</sup> In the setting of heart failure and other CV disease, QRS interval prolongation in the form of IVCD or left bundle-branch block (to a greater extent than RBBB) carries an increased risk of worsening heart failure and death.<sup>35,36</sup> Furthermore, an increased QRS interval duration in patients with left ventricular dysfunction is associated with a progressively escalating propensity to develop atrial fibrillation.<sup>37</sup> Patients who present with acute coronary syndrome and QRS prolongation have a higher subsequent risk of mortality than do patients with acute coronary syndrome without a widened QRS.<sup>38</sup> Hypertensive patients who experience or who have persistent QRS interval prolongation ( $\geq 0.11$  seconds) while on medication have a higher incidence of subsequent heart failure than do patients with a normal

QRS interval duration.<sup>39</sup> It is well documented that treatment for patients with previous myocardial infarctions and low left ventricular ejection fraction with the class 1C sodium channel blockers encainide and flecainide occasionally resulted in an incessant monomorphic ventricular tachycardia that was highly resistant to termination, including with direct current cardioversion.<sup>40</sup> These findings clearly show the increased risk for adverse outcomes in patients with CV disease associated with QRS widening and the increased risk for adverse drug effects superimposed in this milieu, particularly for drugs with the potential to further prolong depolarization and widen the QRS. What is not well established is the risk associated with drug-induced QRS widening in other conditions or underlying substrates.

### Significance of drug-induced QRS interval prolongation

Treatment with sodium channel blockers including some class IA (eg, quinidine, procainamide) or 1C (flecainide, propafenone) antiarrhythmics is commonly associated with QRS interval prolongation.<sup>41</sup> By blocking inward sodium current, the class I antiarrhythmics slow depolarization, reduce conduction velocity, and prolong the QRS interval. Although these agents can be effective under certain conditions, they can also have proarrhythmic effects, particularly in patients with structural heart disease. In fact, use of the class IC antiarrhythmics flecainide, encainide, and moricizine to suppress ventricular ectopy resulted in an increased mortality as a result of arrhythmic sudden death.<sup>41-43</sup> Of note, particularly with sodium channel blockers, is that the QT interval encompasses both depolarization and repolarization, and hence, the interval is lengthened by QRS widening, independent of ventricular repolarization. Thus, in the presence of QRS interval prolongation, assessment of the JT interval rather than the QT may be a more accurate surrogate for ventricular repolarization.<sup>44</sup> Other agents such as chloroquine can prolong the QRS interval by blocking the inward rectifier potassium current,  $I_{K1}$ , which leads to a more positive resting membrane potential, partial inactivation of sodium channels,<sup>45</sup> and conduction slowing. As such, QRS interval prolongation is considered a marker of decreased myocardial conduction velocity and potential conduction block. Because slowed conduction is a factor linked to reentrant proarrhythmia, drug-induced QRS widening may be viewed as a potential marker for increased arrhythmogenicity, especially in the setting of heart disease. In addition, some drugs that more markedly depress depolarization and widen the QRS may also have the potential to depress cardiac mechanical function, and in some cases, these drugs may increase the energy requirements for pacemaker capture or defibrillation with implanted devices.<sup>39,46</sup> However, there is evidence suggesting that changes in QRS duration observed in healthy subjects in early-phase clinical studies do not

have the same clinical or prognostic importance as the same ECG findings in either middle-aged patients with underlying CV disease or CV risk factors, or in elderly patients with overt or advanced CV disease (as appears to be in case of flecainide and propafenone). A selected list of drugs associated with QRS interval prolongation is found in [Table I](#).

### Variability of the QRS duration

At rest, the QRS interval duration varies between healthy subjects (69-109 ms, 2nd and 98th percentiles, respectively)<sup>13</sup> and is age and sex dependent, with men demonstrating a longer QRS duration.<sup>47</sup> In contrast, the intraindividual variability of the QRS duration is usually lower than that of the PR and QT intervals.<sup>48</sup> The standard deviation (SD) of the within-subject change difference between measurements for QRS interval duration in healthy subjects, measured up to 24 hours apart, was between 6.9 and 8.5 ms, which is lower than SD values for the longer PR and QT interval durations.<sup>49</sup>

A repeated measurement in an individual subject may differ compared with baseline owing to differences in the ECG recording environment, physiologic status of the subject, equipment, and analysis.<sup>7,50,51</sup> The lead positions should be marked on the chest wall or leads kept attached between the recordings to reduce variability. If the time interval between the recordings reaches more than weeks, it may make consistent lead positions more difficult to obtain, and over time, the physical fitness and body configuration of the subject may change. De Bruyne et al.<sup>52</sup> found in a study of subjects older than 55 years that the SD of the difference between 2 measurements of QRS duration in ECGs recorded with minutes interval, days interval, and 1- to 2-year interval was 6.5, 6.4, and 9.5 ms, respectively. A change in body position and body composition, for example, with more adipose tissue, may cause a change in the distance between the heart and chest wall leads, which impacts the QRS amplitudes and, to a lesser degree, the QRS duration.<sup>53</sup>

The condition and the activity of the subject (eg, fasting or fed<sup>54</sup>; deep, shallow respiration or breath-holding<sup>55</sup>; and sleeping or awake) are factors that influence the autonomic tone and heart rate. It seems that a change in heart rate may cause a small change of the QRS duration and that the type of response differs between subjects.<sup>9</sup> It is important to note that findings regarding QRS variability discussed in this section come from healthy subjects and may not be extrapolated to patients without validation.

### Nonclinical assessment of QRS prolongation risk

The nonclinical assessment of drug-induced QRS interval prolongation can use various complementary *in vivo* approaches (ECG recordings from animals) as well as *in vitro* approaches (assessment of direct interactions with the cardiac sodium channel [Nav1.5] and functional

current). *In vitro* approaches assessing interactions with sodium channels include nonfunctional binding studies that measure displacement of ligands from cardiac sodium channels. Functional studies directly measuring block of sodium current (using voltage clamp techniques) recorded from heterologous expression systems, isolated ventricular myocytes, or (more recently) cardiac stem cells are also valuable in detecting drugs that affect cardiac sodium current. *In vitro* functional studies measuring effects resulting from reduced sodium current (decreased action potential upstroke velocity or amplitude, or decreased conduction velocity in cardiac tissues) are also useful in detecting potential risks. Finally, changes in QRS interval duration measured in isolated Langendorff hearts or surface ECG recordings from smaller (mouse) as well as larger species (canine, nonhuman primate) to directly assess QRS duration changes and depressed conduction (which may promote proarrhythmia resulting from unidirectional block and reentry) are also routinely used, often later in drug discovery.

Block of cardiac sodium current is modulated by voltage, rate, and rhythm owing to different affinities and accessibility of the sodium channel receptor as the channel cycles through the resting, open, and inactivated states. These characteristics, typically evaluated *in vitro*, are described using either the modulated receptor or the guarded receptor hypothesis.<sup>56</sup> For example, the potency of block of lidocaine on cardiac sodium current is significantly greater when measured from partially depolarized vs fully polarized membrane potentials (IC<sub>50</sub> values of approximately 2.26 and 83.2 μg/mL, respectively<sup>57</sup>). This effect may contribute to proarrhythmia with sodium channel blocking drugs in the setting of ischemia and structural heart disease. Use-dependent block (greater block of sodium current at faster vs slower stimulation rates) is also readily apparent in voltage clamp, action potential, or conduction velocity studies. Use-dependent block of cardiac sodium current may be manifest as changes in ventricular conduction in animals<sup>58</sup> and humans.<sup>59-61</sup> The extent of modulation of block by rate or voltage is dependent on the different affinities for block of the resting, open, and inactivated states of the channel as well as the kinetics of recovery from block during diastole. Recovery from block will also affect refractoriness, with drugs rapidly dissociating from channels acting to transiently prolong refractoriness (thereby preventing premature responses) without affecting conduction of regular beats. Sodium channel block is associated with changes in QRS interval duration, with increasing block associated with progressive QRS prolongation (eg, excessive doses of amitriptyline); sodium channel block is not usually associated with reduced QRS amplitude (the latter typically ascribed to peripheral edema affecting the volume conductor characteristics of the torso).

Drug-induced QRS interval prolongation may be expected with some cardiac drugs (ie, class 1A or 1C antiarrhythmic agents). Some noncardiac drugs also demonstrate QRS prolongation, although this often occurs at supratherapeutic exposures (Table I). In general, there is good qualitative agreement between drugs that prolong QRS duration clinically and preclinical evidence of sodium channel block. For example, dolasetron elicits dose-dependent prolongation of the QRS interval clinically,<sup>62</sup> and concentration-dependent block of cardiac sodium current.<sup>63</sup> In general, there is good concordance between preclinical signals of QRS prolongation risk and clinical findings, although in vitro sensitivity may be greater than clinical QRS prolongation (reviewed in Gintant et al<sup>64</sup>).

### Clinical experience with drug-induced QRS prolongation

The clinical proarrhythmic effects of sodium channel blockade are modulated by use dependence, the kinetics of block (slow or rapid recovery from block), inactivated or activated sodium channels, channel binding site, channel type affected, and the degree of underlying heart disease.<sup>65</sup> For example, although encainide was removed by the sponsor from the market, flecainide and propafenone (all class 1C sodium channel blockers) were further studied for the prevention of paroxysmal atrial fibrillation and flutter and appear to be reasonably safe in appropriate patients without significant cardiac dysfunction, structural, or ischemic heart disease. Potential mechanisms whereby underlying significant structural heart disease increases the ventricular proarrhythmic risk of drug-induced QRS prolongation are multifactorial and include the following:

- Slowing of conduction and subsequent reentry in diseased ventricular tissue
- Increased susceptibility of diseased or partially ischemic areas to sodium channel blockade and conduction slowing because of disease-associated reduced resting membrane potentials
- Superimposition of acute ischemia in the setting of potent sodium channel blockade, which can increase the propensity for ventricular fibrillation, possibly because of the breakup of spiral waves<sup>66</sup>

Tricyclic antidepressants (TCAs) represent a common clinical example of an off-target effect on prolonging the QRS interval. The toxic plasma concentration of TCAs is approximately 1.0 µg/mL, 4× to 10× the therapeutic level and consistent with a relatively narrow therapeutic index.<sup>67</sup> That these drugs provoke arrhythmias, especially in the overdose setting, led physicians to believe that their quinidine-like (class 1A) antiarrhythmic properties were proarrhythmic. One particularly illustrative example of TCA-induced QRS prolongation is amitriptyline. Despite evidence of multifaceted CV toxicity, there is a

positive correlation of the width of the QRS interval with plasma drug concentration, with a width of 100 ms or greater correlating with a plasma exposure of 1.0 µg/mL or more.<sup>67,68</sup>

### Management of QRS interval prolongation during clinical development

The proposed strategies discussed in this section will be relatively limited given the significant knowledge gaps existing relevant to this issue and the lack of drugs being developed with strong sodium channel blocking activity. During early clinical development (and especially in the presence of preclinical signals of sodium channel blockade), it is probably prudent to enroll subjects who do not have an excessive underlying risk for arrhythmia or heart failure. The QRS interval can function as an appropriate marker for any underlying conduction disease; therefore, excluding subjects with QRS duration exceeding 110 to 120 ms might be considered.

At the individual subject risk level, the magnitude of QRS prolongation that is clinically relevant is not well understood, and hence, defining a threshold for drug administration discontinuation because of this effect is probably not feasible. However, there is evidence that QRS interval minimally changes from baseline values in placebo administered healthy volunteers, as discussed in the technical section. The anticipation or demonstration of meaningful drug-induced QRS prolongation in early clinical development warrants the consideration of additional safety monitoring procedures and analyses for current or subsequently enrolled subjects, such as frequent safety ECGs, evaluation of cohort mean QRS interval changes before dose escalation, and closer evaluation of adverse drug reaction that could be mechanistically linked to drug-induced QRS prolongation. Robust extraction and analysis of early development dECGs could be especially helpful to execute an informative exposure-response analysis related to QRS interval. In some cases, if associated negative inotropic effects are also anticipated, assessments of cardiac function with a method such as echocardiography may be considered.

The definitive ECG (thorough QT/QTc) study will usually provide the best opportunity to characterize the effect of a drug on the QRS duration.

The demonstration of potentially clinically meaningful drug-induced-QRS prolongation at projected therapeutic exposures intended for late clinical development will often result in reassessment of the benefit-risk ratio of the investigational drug, and if development continues, expanded ECG and CV safety monitoring related to ventricular arrhythmias could be considered. Given the same concerns identified with PR interval prolongation evaluation, formal hypothesis testing is probably not feasible to address QRS interval prolongation, as well.

Finally, for integrated review purposes, the clinical trial database will also need to address the following:

1. Central tendency analyses include examining changes from baseline over time, especially at predefined time points after drug administration, with an emphasis on early therapy (eg, first dose and shortly after steady-state has been attained).
2. Categorical analyses: a categorical analysis of outliers using a predefined threshold (eg, >110 ms) for the QRS duration might be informative, taking into consideration baseline inclusion/exclusion criteria (eg, QRS >110 or >115 or >120 ms excluded). Examining outliers of QRS prolongation at a threshold of >25% compared with baseline could be a follow-up analysis in some cases.<sup>69</sup>
3. Subgroup analyses to profile high-risk populations susceptible to QRS interval prolongation could be helpful, especially as related to preexisting decreased ejection fraction, CAD, or myocardial conduction syndromes, provided that the size of the subgroup is sufficient for meaningful analysis. The analysis could be also extended to subjects administered concomitant medications that are known to prolong QRS duration or depress myocardial contractility.
4. If these definitive CV studies identify clinically significant QRS prolongation risks, additional expanded clinical monitoring may need to be implemented related to potentially serious or life-threatening ventricular arrhythmias during subsequent phase III studies, particularly in at-risk patients with CV disease and especially heart failure. In this case, it may be helpful to also include informative PK sparse sampling that enables exposure-response evaluation of QRS prolongation-related adverse outcomes.
5. Examples of ECG-relevant morphologic evaluation include bundle-branch block, IVCD, and frequent ventricular ectopic rhythms.
6. Relevant adverse events are as follows: presyncope and syncope, ventricular arrhythmia, manifestations of heart failure, pacemaker implantation, unexplained sudden death, and others such as seizures.

## Summary and conclusion

This White Paper highlights the rapidly growing interest in evidence-based evaluation of ECG intervals other than QT/QTc. Robust assessment and analysis of PR and QRS intervals optimize the safety profiling of novel therapeutics and are needed for accurate benefit-risk projections. This is clearly justified given the ICH E14 Guidelines and is aligned with the regulatory agencies consistent demand that the PR and QRS measurements be analyzed as part of thorough QT/QTc studies required for the registration of new drugs.

In addition to providing recommendations that are intended to reflect state-of-art relevant knowledge today, this consensus effort also identified many gaps that need

to be addressed by more focused research in the field. Hence, it is clear that many of the statements and conclusions above should be viewed in this context and will continue to be updated as new science emerges.

## Disclaimer

The opinions and conclusions expressed in this article are solely the views of the authors and do not necessarily represent regulations and policies or views of the US Food and Drug Administration, Health Canada, or the authors' affiliated organizations.

## Acknowledgements

The following individuals are acknowledged for their contributions to the discussions and critical review that led to the development of this White Paper: J. Rick Turner, PhD (Clinical Communications, Quintiles, who made significant editorial contributions); Corina-Dana Dota, MD; Ahmad Ebrahimi, MD; Torbjörn Vik, MD; Judith Zander, MD; and Jean-Pierre Valentin, PhD (all AstraZeneca Cardiac Safety Knowledge Group).

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