hERG potassium channel inhibition by ivabradine may contribute to QT prolongation and risk of torsades de pointes

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Ivabradine is the first and only specific bradycardic agent in current clinical use. It reduces heart rate through slowing diastolic depolarization in the sinoatrial node by inhibition of the ionic current carried by the hyperpolarization-activated cyclic nucleotide-gated (HCN) ion channel family [Rushworth *et al.* 2011]. Results from the BEAUTIFUL study showed that ivabradine may reduce coronary artery disease (CAD) outcomes in a subset of patients with baseline heart rates of 70 beats/min or greater [Fox *et al.* 2008], and may also improve left ventricular ejection fraction and reverse deleterious ventricular remodelling [Ceconi *et al.* 2011]. The drug has been approved for use in Europe for some time and in April of 2015 the US Food and Drug Administration (FDA) granted approval for the use of ivabradine to decrease hospitalization from heart failure [FDA, 2015]. Under this approval, ivabradine is indicated for individuals with stable heart failure and a heart rate of 70 beats/min or more, who are already in receipt of beta-blocker therapy [FDA, 2015].

Although ivabradine has been considered to have a good cardiac safety profile [Camm and Lau, 2003; Savelieva and Camm, 2006], recent evidence has highlighted that some qualification is necessary in this regard. Thus, a meta-analysis of clinical trial data has reported an increased relative risk of atrial fibrillation in patients receiving ivabradine [Martin *et al.* 2014]. Also, in the SIGNIFY trial, which focused on patients with stable CAD without clinical heart failure and with a heart rate of 70 beats/min or more, ivabradine did not improve patient outcomes [Fox *et al.* 2014]. Indeed, in a subset of patients with activity-limiting angina, ivabradine

was associated with an increase in the primary endpoint of the trial: the composite of death from nonfatal myocardial infarction or cardiovascular causes [Fox *et al.* 2014].

A year ago, ivabradine was added to the 'CredibleMeds' database of clinically used drugs that are associated with prolongation of the QT interval of the electrocardiograph and with torsades de pointes (TdP) arrhythmia [CredibleMeds, 2014]. Ivabradine was classed as a drug with a 'conditional risk' of TdP, with the CredibleMeds update saying that: "There is substantial evidence that ivabradine is associated with TdP when taken with other medicines that prolong the QT interval, diuretics or drugs that block the metabolic breakdown of ivabradine, or electrolyte abnormalities (low potassium or low magnesium), which may be induced by co-administration of diuretics" [CredibleMeds, 2014]. Publicly accessible information on the European database of suspected drug reaction reports shows that 24 individual cases of TdP associated with ivabradine have been reported by healthcare professionals, up to March 2015 [European Medicines Agency, 2015]. Two recently published case reports also highlight an association between ivabradine use and TdP in a setting of concomitant drug use. One of these cases involved a 68-year-old man treated with ivabradine for paroxysmal sinus tachycardia, who developed TdP when additionally given azithromycin for acute sinusitis [Cocco and Jerie, 2015]. The second case involved an elderly (80 years old) woman who was given ivabradine together with ranolazine and diltiazem for the treatment of unstable angina [Mittal, 2014]. She developed a slow junctional rate, prolongation of

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the rate-corrected QT (QT_c) interval and transient TdP. The authors of the latter study highlighted that the patient had no electrolyte abnormalities, but that ivabradine and ranolazine share the same metabolic pathway (cytochrome P450 3A4) with diltiazem [Mittal, 2014].

When ivabradine was administered intravenously (0.2 mg/kg) to 14 patients (12 men, 2 women) with normal baseline electrophysiology, it was reported to lead to a heart rate reduction of 13–14 beats/min (at 0.5 h and 1 h following administration), and to prolong the QT interval, without changes in PR or QRS intervals [Camm and Lau, 2003]. However, when QT interval values were corrected for heart rate in that study, no change in QT_c interval was seen with ivabradine. These findings may be interpreted as suggestive that the role of ivabradine in TdP arising with drug co-administration is indirect rather than direct, either/both through inducing bradycardia or through impairment of metabolism of other drugs with a QT interval-prolonging propensity. However, on the basis of recent data from our laboratories [Melgari *et al.* 2015], we suggest that ivabradine itself has the potential for direct effects on ventricular repolarization. Virtually all drugs associated with TdP act as pharmacological inhibitors of human ether-à-go-go-related gene (hERG) potassium channels, which mediate the cardiac rapid delayed-rectifier potassium current [Sanguinetti and Tristani-Firouzi, 2006]. We have recently demonstrated that ivabradine inhibits hERG channels with a potency that is similar to that reported for HCN4, the predominant HCN channel isoform in the sinoatrial node [Melgari *et al.* 2015]. Moreover, we found that concentrations of ivabradine between 100 nM and 500 nM prolonged the duration of monophasic action potentials recorded from both the left ventricular apex and the base of perfused, paced guinea-pig hearts, whilst the effective refractory period was prolonged and the maximal restitution slope for basal action potentials was steepened [Melgari *et al.* 2015]. On the basis of the concentration dependence of these effects, we suggest that at low therapeutic concentrations, ivabradine normally has a small propensity to impair ventricular repolarization directly, but at higher concentrations or with tissue accumulation, it may contribute to delayed repolarization [Melgari *et al.* 2015]. A similar argument can be made for co-administration of ivabradine with drugs that impair its metabolism (thus resulting

in increased plasma ivabradine levels), or that they themselves act on the hERG, in which event synergistic effects of the combination of drugs on hERG and repolarization might occur. The ability of ivabradine to inhibit hERG has subsequently been verified independently [Lees-Miller *et al.* 2015]. Furthermore, another distinct study has provided evidence that the effects of ivabradine on repolarization may be augmented when other potassium currents are also reduced and so the 'repolarization reserve' is impaired [Koncz *et al.* 2011]. Thus, whilst it is already recognized that, due to its bradycardic action, ivabradine should not be co-administered with QT-prolonging agents [Savelieva and Camm, 2006], we suggest that an additional important reason for such caution is the drug's potential to interact with the hERG and thereby directly influence ventricular repolarization.

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Conflict of interest statement

The author declares no conflicts of interest in preparing this article.

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