



Considerations for assessing the potential effects of antidiabetes drugs on cardiac ventricular repolarization: A report from the Cardiac Safety Research Consortium

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Thorough QT studies conducted according to the International Council on Harmonisation E14 guideline are required for new nonantiarrhythmic drugs to assess the potential to prolong ventricular repolarization. Special considerations may be needed for conducting such studies with antidiabetes drugs as changes in blood glucose and other physiologic parameters affected by antidiabetes drugs may prolong the QT interval and thus confound QT/corrected QT assessments. This review discusses potential mechanisms for QT/corrected QT interval prolongation with antidiabetes drugs and offers practical considerations for assessing antidiabetes drugs in thorough QT studies. This article represents collaborative discussions among key stakeholders from academia, industry, and regulatory agencies participating in the Cardiac Safety Research Consortium. It does not represent regulatory policy. (Am Heart J 2015;170:23-35.)

During the last 30 years, serious and sometimes fatal proarrhythmic events have been reported for patients receiving noncardiac drugs. These events led to the recognition that some drugs alone, or interacting with others, may impair cardiac ventricular repolarization with serious consequences, including potentially life-threatening ventricular proarrhythmia.¹ As a result, regulatory agencies established expectations that, prior to approval, new nonantiarrhythmic drugs will undergo rigorous evaluation for potential effects to prolong ventricular repolarization as assessed by the QT and/or corrected QT (QTc) interval. In 2005, the International Conference on

Harmonisation (ICH)² released the E14 guideline *The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs*. This guideline provides uniform recommendations for designing, conducting, analyzing, and interpreting the results of “thorough QT” (TQT) assessments for QT/QTc prolongation with investigational drugs.

Antidiabetes drugs possess a unique set of issues when assessing the potential for QT prolongation. Available antidiabetes drugs reduce blood glucose via a host of mechanisms including but not limited to direct and indirect effects on endogenous insulin. Changes in blood glucose concentrations, and possibly insulin itself, have been reported to correlate with changes in the QT/QTc interval,^{3,4} but further characterization of these relationships is warranted.⁵ Coupled with other physiologic perturbations,⁶⁻⁹ the glucose-lowering actions of antidiabetes drugs could produce an increase in the QT/QTc interval that would be incorrectly attributed to a direct action of the drug on ventricular repolarization. Conversely, if there is a true drug-induced QT/QTc prolongation, the mechanisms may not be easily distinguished from a drug's glycemic actions. Understanding the mechanism of QT/QTc prolongation can aid in drug development, characterization of a drug's safety profile, and ultimately clinical management of patients receiving antidiabetes drugs.

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The Cardiac Safety Research Consortium (CSRC; see www.cardiac-safety.org) was developed based upon the US Food and Drug Administration (FDA) Critical Path Initiative, with the objective of fostering productive collaborations among academics, scientists working in the pharmaceutical industry, and regulators to ensure the cardiovascular safety of new medical products. A CSRC Working Group was established to facilitate stakeholder discussion regarding the assessment of cardiac ventricular repolarization in the clinical context of antidiabetes drug development.

This article summarizes conclusions of the CSRC Working Group and focuses on what is known, not known, and controversial in light of the ICH E14 guideline, in addition to practical aspects for TQT studies and electrocardiogram (ECG) monitoring during early and late clinical development of primarily oral and non-insulin-injectable antidiabetes treatments. To that end, this article reviews approaches for assessing cardiac ventricular repolarization and potentially confounding factors with antidiabetes drugs, such as glucose changes, while providing practical considerations for these factors in drug development. Nonclinical data such as effects on the human ether-à-go-go related gene (hERG)-encoded myocardial potassium (K^+) channel and animal studies of ECG effects are also discussed. The use of outcomes studies to evaluate the clinical impact of antidiabetes drugs on cardiovascular health and the use of nonclinical mechanistic methods (eg, the Comprehensive In Vitro Proarrhythmia Assay) to evaluate proarrhythmic risk¹⁰ are considered out of scope for this review.

This White Paper is offered as an aid to pharmaceutical companies, clinicians, and regulatory authorities involved in the development of antidiabetes drugs with potential concerns about effects on ventricular repolarization. The opinions and conclusions expressed are solely the views of the authors and do not represent new regulations and policies of the FDA or the authors' affiliated organizations.

Antidiabetes drugs and potential mechanisms for QT/QTc prolongation

Overview of antidiabetes drug classes and their potential for inducing hypoglycemia

Special considerations may be needed for conducting TQT studies with antidiabetes drugs as changes in blood glucose and other physiologic parameters affected by antidiabetes drugs may prolong the QT interval and thus confound QT/QTc assessments. All medications that treat diabetes mellitus (diabetes) are intended to reduce blood glucose to therapeutic target levels, a consequence of which could be hypoglycemia with aggressive glucose management.

Supplementing or replacing endogenous insulin with an exogenous source of insulin is the most potent glucose-lowering treatment. Hypoglycemic risk with insulin varies, in part, based on the type of preparation

and its properties. For example, insulin analogues with longer, less variable, and flatter pharmacokinetic profiles have a lower risk of (especially nocturnal) hypoglycemia compared with intermediate-acting insulins.¹¹ Independent of the type of insulin, hypoglycemia is a risk with all insulin products if dose and timing of injections are not appropriately matched with meal ingestion.

Sulfonylureas and glinides both bind to the sulfonylurea receptor (SUR1) on the β -cell membrane promoting insulin release. Because the increased release of insulin continues as long as drug stimulation is present (provided the pancreatic β cells are functional), sulfonylureas can cause excessive and long-lasting hypoglycemia even when glucose concentrations are already below the normal physiologic threshold for glucose-stimulated insulin release.¹² Glinides bind to a different site on the SUR1 and produce a rapid but short-lived stimulation of insulin secretion resulting in less frequent hypoglycemia.¹³

Hypoglycemia is rare with metformin, thiazolidinediones, α -glucosidase inhibitors, and sodium-glucose cotransporter 2 (SGLT2) inhibitors administered alone or in combination with other antidiabetes therapies because none of these drugs directly stimulate insulin secretion at normal glucose levels. Metformin acts primarily by suppressing glucose production in the liver. Thiazolidinediones decrease insulin resistance in the periphery and liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output. α -Glucosidase inhibitors delay the degradation of complex carbohydrates in the gastrointestinal tract and thereby lower postprandial blood glucose concentrations. SGLT2 inhibitors increase glucose excretion by blocking reabsorption of glucose in the kidney.

Incretin-based therapies (dipeptidyl peptidase 4 inhibitors [DPP-4is] and injectable glucagon-like peptide 1 [GLP-1] receptor agonists) operate by 2 distinctly different mechanisms. GLP-1 receptor agonists are injectable peptides that act directly on the GLP-1 receptor of pancreatic β cells leading to insulin release. DPP-4is are small molecules administered orally that inhibit the conversion of native GLP-1 into its inactive form by the DPP-4 enzyme. The risk of hypoglycemia is also low with these therapies due to the glucose-dependent action of GLP-1 on the β cells. Specifically, insulin secretion occurs when plasma glucose is abnormally elevated and is not seen with GLP-1 receptor agonists when plasma glucose is below the normoglycemic range.¹⁴

Potential mechanisms for QT/QTc prolongation with antidiabetes drugs

The hERG encodes the α subunit of a transmembrane cardiac ion channel conducting K^+ efflux (the rapid delayed-rectifier K^+ current [IKr]), which is an important component of cardiac repolarization.¹⁵ Blocking this current slows ventricular repolarization, which is one mechanism that can lead to QT prolongation. Blockade of

additional outward K^+ currents or activation of inward cation currents can also prolong the cardiac action potential; however, blockade of IKr is the predominant mechanism for drug-induced QT prolongation. Before the first tests of a new drug in humans, nonclinical studies are normally conducted to evaluate the compound's potential to prolong ventricular repolarization via blockade of the hERG channel (ICH S7B, *The Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals*).¹⁶ Studies with agents such as MK-499, an antiarrhythmia drug and potent blocker of this channel, suggest that most drugs gain access to hERG channel binding sites from within the channel pore on the intracellular side of the cell membrane.^{17,18} Thus, smaller molecules that easily traverse the cell membrane have greater potential to prolong the QT interval through blockage of hERG channels than do larger molecules like large targeted proteins or peptides, unless endocytosis, an active transport mechanism, is operative.¹⁹ Very large proteins are unlikely to interact with the channel, even with the extracellular side.

Nonclinical, in vivo evaluations suggest that reductions in blood glucose may lead to QT prolongation. The information available from nonclinical in vivo assessments, however, is limited. For at least one insulin (HMR1964, insulin glulisine), a large peptide molecule unlikely to directly inhibit the hERG channel, QT prolongation was detected in conscious dogs.²⁰ Although many mechanisms may have contributed to this effect, the relationship between hypoglycemia and hypokalemia is of particular interest.^{21,22} Hanton et al²³ noted in conscious dogs an approximate 10% increase in QT length per 1 mM fall in extracellular K^+ . This association of extracellular K^+ and QT prolongation occurs through an indirect effect on the hERG channel.²⁴ Zhang and colleagues⁸ demonstrated with in vitro techniques that hypoglycemia also has an inhibitory effect on hERG channels, thereby reducing IKr.

In conscious dogs, changes in the QT/QTc interval during experimental hyperinsulinemic-euglycemic clamp have been observed that are similar to those already observed in humans.^{21,25} These data suggest that blood glucose is not the only factor associated with antidiabetes treatment that might affect ventricular repolarization. Insulin lowers serum K^+ by direct effects on Na^+/K^+ ATPase,²⁶ which might prolong QT/QTc intervals by reducing current flow through K^+ rectifier channels. Sulfonylureas are not believed to mediate QT/QTc interval changes directly via hERG,²⁷ but may affect QT/QTc interval by stimulating endogenous insulin release.²⁸ Moreover, hypoglycemia induced by insulin (or sulfonylureas) can lead to QT/QTc prolongation by activating the sympathoadrenal nervous system.⁶ The autonomic nervous system responds to a drop in blood glucose below approximate mean 63 mg/dL (3.5 mmol/L)

with sympathetic activation and release of epinephrine into the circulation.²⁹ This action, in turn, causes both a continued lowering of serum K^+ (and further effects on K^+ rectifier channels)³⁰ and effects on calcium (Ca^{+2}) L-type channels.³¹ The latter further prolongs the QT/QTc interval and potentially stimulates early after-depolarizations which could activate reentry ventricular tachycardias and cause sudden death.³² The physiologic situation is complicated further as β -adrenergic catecholamines shorten ventricular repolarization.³³

An increase in glucose concentrations also reduces the IKr, but through different mechanisms⁸ as reflected in the clinical observation that blood glucose concentrations greater than 270 mg/dL (15 mmol/L) lead to QT/QTc prolongation.³⁴ In heterologous expression systems in vitro, hyperglycemia inhibits the K^+ current by a second-messenger pathway distinct from the pathway associated with hypoglycemia.⁸ A similar impact on the K^+ current, however, has not been shown in isolated cardiac tissue studies, nor is it clear if other ion channels might be similarly affected.

These data indicate that changes in blood glucose and other physiologic parameters like insulin might affect ventricular repolarization by direct or indirect mechanisms. Care must therefore be taken to consider not only direct effects on the hERG channel but also secondary effects linked to shifts in these other parameters.

Clinical evidence for QT/QTc prolongation with changes in blood glucose

Nocturnal hypoglycemia has been linked with the rare phenomenon “dead-in-bed” syndrome, which is sudden, nocturnal death in young adults with type 1 diabetes.³⁵ Both experimental and clinical hypoglycemia can lead to QT/QTc prolongation, which, in turn, is a risk factor for potentially fatal ventricular arrhythmias.³⁶⁻³⁹

Experimental clinical models using glucose and insulin clamps

The effects of glucose and insulin on QT/QTc interval duration have been examined clinically in both natural, physiologic settings and under more artificial conditions. The hyperinsulinemic glucose clamp is an experimental clinical model, adapted from an approach to measure insulin resistance. This model permits plasma insulin levels and blood glucose to be fixed at stable levels (hyperglycemic, euglycemic, or hypoglycemic) while ECGs and other physiologic measurements are made.⁴⁰ Insulin is infused intravenously (IV) at physiologic or pharmacologic concentrations. Glucose is also infused IV with the glucose infusion rate adjusted frequently according to “arterialized” glucose concentrations measured at the bedside, to maintain a predetermined plateau. Electrocardiograms are used to record QT intervals at discrete time points while glucose levels are

Table I. Summary of TQT studies for antidiabetes drugs in healthy volunteers

Drug class	Drug	n	Dose(s)	Supratherapeutic dose?*	Design	Result (mean max $\Delta\Delta$ QT)	Upper bound 1-sided 95% CI	Other CV findings†	Ref
GLP-1 receptor agonist	Exenatide (SC)	62	10 μ g (single dose)	No (TH only)	CO	≤ 5 ms	<10 ms	HR \uparrow ≤ 10.2 beats/min PR interval \uparrow ≤ 7.1 ms	50
	Exenatide (IV)	75	IV infusion TH conc (253 pg/mL) SPT conc (627 pg/mL)	Yes (2.5-fold)	CO	5.6 ms (TH conc) <5 ms (SPT conc)	<10 ms	HR \uparrow <16.8 beats/min PR interval \uparrow 2.5 ms	51
	Dulaglutide (SC)	147	4 or 7 mg (single dose)	Yes (2.7-fold, 4.7-fold)	CO	NR	<10 ms	NR	52
	Liraglutide (SC)	51	0.6, 1.2, 1.8 mg ($\times 7$ d each, stepwise increase)	No (TH only)	CO	<5 ms	<10 ms	HR \uparrow <9 beats/min PR interval \uparrow ≤ 10 ms	53,54
	Albiglutide (SC)	174	30 mg ($\times 2$ QW) 50 mg ($\times 4$ QW)	No (TH only)	PRL	<5 ms	<10 ms	HR \uparrow ≤ 7.8 beats/min PR interval \uparrow ≤ 4.5 ms	55
	Lixisenatide (SC)	91	20 μ g QD (28 d, stepwise increase) 30 μ g BID (28 d, stepwise increase)	Yes (3-fold)	PRL	NR	<10 ms	HR \uparrow 1.0 beats/min (20 μ g) \uparrow 4.7 beats/min (30 μ g) PR interval \uparrow (value NR)	56,57
		264	20 μ g QD (28 d, stepwise increase) 30 μ g BID (28 d, stepwise increase)	Yes (3-fold)	PRL	<5 ms	<10 ms	HR \uparrow 7.0 beats/min PR interval \uparrow (value NR)	56,57
DPP-4 inhibitor	Sitagliptin	79	100 mg, 800 mg (single dose)	Yes (8-fold)	CO	<5 ms (100 mg) 8 ms (800 mg)	<10 ms (100 mg) 10.6 ms (800 mg)	NR	58
	Vildagliptin	101	100 mg, 400 mg ($\times 5$ d)	Yes (4-fold)	PRL	5.1 ms (100 mg at 1 h postdose) <5 ms (400 mg)	<10 ms, except 100 mg at 1 h (12.3 ms) and 8 h (11.9 ms) postdose	HR \uparrow at SPT dose (value NR)	59
	Saxagliptin	40	10 mg QD ($\times 4$ d) 40 mg ($\times 4$ d)	Yes (2-fold, 8-fold)	CO	NR	<10 ms	NR	60
	Linagliptin	44	5 mg, 100 mg (single doses)	Yes (20-fold)	CO	<5 ms	<10 ms	HR \uparrow ≤ 4 beats/min (SPT dose) PR interval Δ <1.5 ms	61
PPAR agonist	Aleglitazar	52	300 μ g, 3000 μ g (single doses)	Yes (2-fold, 20-fold)	CO	<5 ms	<10 ms	HR \uparrow 3 beats/min (2-fold dose) 11 beats/min (20-fold dose)	62
SGLT2 inhibitor	Dapagliflozin	50	20 mg, 150 mg (single doses)	Yes (2-fold, 15-fold)	CO	<5 ms	<10 ms	PR interval Δ <9 ms	63
	Empagliflozin	30	25 mg, 200 mg (single doses)	Yes (8-fold)	CO	<5 ms	<10 ms	HR Δ ≤ 1.5 beats/min	64

Abbreviations: n, Number of subjects enrolled; $\Delta\Delta$ QT, placebo- and baseline-corrected QT interval; Ref, reference (citation); CV, cardiovascular; TH, therapeutic; CO, crossover; HR, heart rate; conc, concentration; SPT, supratherapeutic; NR, not reported; QW, once weekly; PRL, parallel; QD, once daily; BID, twice daily; PPAR, peroxisome proliferator-activated receptor. * Except for exenatide IV, SPT dose refers to the multiple of the proposed or approved maximal therapeutic dose. For exenatide IV, SPT refers to the multiple of the plasma concentration associated with therapeutic dose.

† Results presented are change from baseline with or without placebo correction per available data in source.

stabilized. This can be done stepwise, allowing physiologic measurements at different plasma glucose levels from euglycemia to hypoglycemia.

Studies using clamp methodology provide a framework for exploring the potential relationship between QT/QTc interval and glucose, insulin, and other physiologic parameters in both healthy volunteers and patients with type 1 or type 2 diabetes (eg, Refs. 4,6,7,25,34,36,41,42). A wide range of QT/QTc changes, frequently assessed with Bazett correction (QTcB), have been reported with this methodology. The most pervasive finding across these studies is QT/QTc prolongation with hypoglycemia (blood glucose approximately 45-54 mg/dL [2.5-3 mmol/L]). For example, Lee et al²⁵ reported a mean QTc increase of 25 ms in patients with type 1 diabetes and advanced cardiac autonomic neuropathy, whereas Marques et al³⁶ observed an increase in median QTc of approximately 150 ms in patients with type 1 diabetes and no neuropathy during hypoglycemic clamp. Such studies facilitate characterization of QT/QTc interval changes during stable euglycemia,³⁶ identification of both magnitude and direction of QT/QTc interval changes with hyperglycemia,^{34,43} assessment of insulin's contributions to QTc changes observed during euglycemia and hypoglycemia,³⁴ and examination of how parameters such as circulating K⁺ and catecholamines^{6,7} may mediate changes in QT/QTc interval as glucose levels change.

Studies using these experimental clinical models vary widely in design and controls, such as subject characteristics, use of K⁺ replacement, methods to correct for heart rate, and clamp methodologies, including insulin infusion rates. These differences complicate direct comparisons between studies and the ability to draw firm conclusions regarding causal relationships. For example, comorbidities such as neuropathy that affect autonomic nerves can affect QT/QTc intervals.^{25,44} Whether autonomic neuropathy is present in the experimental clamp populations is not always identified. Likewise, during clamp procedures, insulin infusion stimulates Na⁺/K⁺ ATPase. Robinson⁶ observed that at normal glucose levels, a small resulting decrease in K⁺ (approximately 0.4 mEq/L [0.4 mmol/L]) was associated with an increase in QT/QTc interval duration on the order of 5 to 10 ms, an effect that can be prevented with sufficient infusion of K⁺ to maintain stable concentrations. In practice, however, few investigators give K⁺ infusions during glucose clamps.

Methods for measuring QT intervals can also affect numerical results and interpretation. During hypoglycemia, T waves may widen (be "broader") and flatten, sometimes with the U wave fused. These conditions make it difficult to define the end of the T wave. Methods such as the robust tangent method should be used to determine the end of the T wave.^{1,45} These methods may not be used consistently across studies and thereby contribute to the observed inconsistencies in QT/QTc

intervals collected during clamps and other types of studies. Similar concerns exist with respect to methods used to correct for heart rate effects on the QT interval. As discussed later in this article, some of the correction methods, particularly QTcB as applied in the early clamp studies, have known limitations.

The studies conducted using clamp methodology described above identified potentially important relationships between QT/QTc interval and numerous physiologic parameters such as glucose, insulin, and K⁺ that are mediated by antidiabetes treatments. The differences in QT/QTc interval trends observed across these studies because of inconsistencies or limitations in the study designs emphasize the importance of careful control in both study conduct and data analysis when assessing QT/QTc intervals, particularly in TQT studies with antidiabetes drugs.

Clinical observations

Extending experimental clamp results to a more natural clinical setting is difficult because of the experimental conditions (eg, supraphysiologic insulin concentrations) required to achieve steady-state euglycemia, hypoglycemia, and hyperglycemia. It is believed that the relationships between physiologic parameters and QTc changes observed in clamp studies are also active within the physiologic range of blood glucose. Robinson et al⁴⁶ measured QT intervals during episodes of spontaneous nocturnal hypoglycemia in patients with type 1 diabetes. Mean QTcB increased by 27 ms from baseline during nights with hypoglycemia (glucose <45 mg/dL [2.5 mmol/L]) compared with a 9-ms increase on nights without hypoglycemia. Murphy et al⁴⁷ also observed increases in QTcB in children and adolescents with type 1 diabetes during spontaneous nocturnal hypoglycemia. Technologies allowing ambulatory assessments for real-time data collection, such as Holter and continuous glucose monitoring, can be used to correlate spontaneous changes in glucose and other parameters throughout a 24-hour period with changes in the QT/QTc interval.⁵ Relationships between QT/QTc and physiologic parameters may also be examined in environments with intermediate levels of control, such as during 2-hour oral glucose tolerance testing⁴⁸ and following subcutaneous (SC) injections of insulin with or without IV glucose infusion.⁴⁹ Physiologic changes (eg, sympathoadrenal responses) during less controlled settings are typically less pronounced than those reported in a clamp procedure.⁴⁶

Practical considerations when performing TQT/QTc studies with antidiabetes drugs

Results of studies conducted to-date with antidiabetes drugs

Many oral antidiabetes drugs were developed prior to the ICH E14 guideline (eg, sulfonylureas, metformin, and thiazolidinediones) and therefore were not evaluated in

TQT studies. Nor have TQT studies been conducted with any marketed insulin. Table 1 summarizes publicly available results of TQT studies for other, newer antidiabetes drugs conducted in healthy volunteers. Thorough QT studies for 2 of these agents, vildagliptin and sitagliptin, were considered “positive” because the baseline-adjusted, placebo-corrected QTc ($\Delta\Delta$ QTc) exceeded the 10-ms upper boundary of the 2-sided 90% CI. Food and Drug Administration–approved prescribing information for the marketed agents in the United States addresses the TQT studies, including cases where there was no regulatory concern.

One of the negative TQT studies explored the relationship of QTc with blood glucose and insulin concentrations collected at time points concurrent with ECG measurements. Linnebjerg et al⁵⁰ found a negative correlation between glucose concentrations and changes in QTc interval after a single SC 10- μ g dose of exenatide, but no relationship was observed between changes in QTc and insulin concentrations in the healthy volunteers.

Considerations for TQT studies with antidiabetes drugs

The TQT studies conducted to date with antidiabetes drugs used similar methodologies but with some notable differences. For long-acting GLP-1 receptor agonists, which are given as SC injections, it is difficult to achieve supratherapeutic plasma concentrations within a reasonable time frame, and this presents specific challenges which have been addressed using IV infusions or gradual upward titration. Some antidiabetes drugs such as GLP-1 receptor agonists and DPP-4i appear to be associated with heart rate increases and, in some cases, with other ECG changes (eg, PR interval prolongation). Moreover, antidiabetes drugs are designed to affect glucose concentrations which, as discussed above, may affect the QT/QTc interval. Because multiple concomitant medications are often used to treat diabetes and its complications, the risk for QT/QTc interval prolongation may be augmented by pharmacokinetic and pharmacodynamic interactions. Hence, antidiabetes drugs should be investigated for their proarrhythmic potential.

Study population. Thorough QT studies are generally conducted in healthy subjects. If a supratherapeutic dose cannot be evaluated in healthy subjects for reasons such as safety or tolerability, the target population may be required to reach the high range of drug exposure.² The objective of the TQT study is, however, not to determine whether a drug may cause proarrhythmias in the targeted patient population but to determine for which compounds a potential QT/QTc effect needs to be further characterized in patients during later-phase studies.

There is evidence that diabetes itself is a risk factor for QT prolongation, which could further increase cardiovascular morbidity and mortality in this patient population.⁶⁵ Diabetes populations (type 1 and type 2) often have prolonged QT/QTc compared with nondiabetes popula-

tions, putting them at further increased risk for proarrhythmia when exposed to a QT-prolonging drug.^{66,67} Contributing factors to prolonged QT/QTc include high blood pressure, increased left ventricular mass, coronary artery disease, and reduced insulin sensitivity,⁶⁸ as well as subclinical atherosclerosis.⁶⁹ In addition, short-term glycemic control and autonomic neuropathy influence baseline QT in patients with diabetes.

The concept of predicting potential QT/QTc effects in patients based on data derived from healthy volunteers exposed to supratherapeutic plasma levels has gained wide acceptance. From this perspective, the TQT study can be viewed as a pharmacologic “stress test” performed in healthy volunteers under strictly controlled experimental conditions to minimize variability of the primary endpoint ($\Delta\Delta$ QTc). Most measures undertaken to reduce the variability in studies in healthy subjects are not specific to TQT studies with antidiabetes drugs and have been discussed elsewhere.^{70,71}

Food effects. The standard practice in clinical pharmacology studies is that subjects in each treatment group are either fasted or fed. Sporadic publications over the last 7 decades noted increases in heart rate, QT interval shortening (not directly associated with RR interval), and T-wave flattening during the postmeal period.^{72,73} Much of this literature on meal and ECG effects relates to T-wave changes (flat, notched, or inversion) seen in the postmeal period (eg, Ref. 74).

Taubel et al⁷⁵ recently reported that food alters the QT-RR relationship, shortening both QT/QTc and PR intervals. Subjects were randomly assigned to a sequence of food vs overnight fasting. Placebo was administered in a fasted or a fed condition, and sensitivity of the study was confirmed with moxifloxacin. During the fed compared with the fasted condition, there was an increase in mean heart rate of 9.4 beats/min during the 2 hours after the meal and a corresponding shortening of uncorrected QT interval (27 ms). The Fridericia-QTc (QTcF) interval was shortened notably for 4 hours, with the maximum decrease of 8.2 ms and a concurrent shortening of the PR interval up to 5.6 ms. Based on results of a euglycemic clamp procedure in which no change in QTc was observed with physiologic changes in insulin, Taubel et al⁵ postulated that physiologic levels of insulin were not involved in QTc changes observed after meals. More clinical studies are necessary to elucidate these complex interrelationships.

These studies indicate that food effects on QT interval may complicate interpretation of a TQT study. The effect for some molecules would be similar to that of the clamp; that is, the glucose would be controlled postprandially while exposed to the active agent, whereas the other treatment groups would demonstrate the expected postprandial excursions. The situation becomes more complex if the effect on glucose lowering is likely to interfere with postprandial values. In most clinical

pharmacology studies, overnight fasting is followed by a midday meal, which would circumvent the issue of the meal effect. For drugs where fasting is possible, that is the preferred design. It is important that the period of fasting covers both the maximum and minimum concentrations of both drug and metabolite(s) so that the effect of meal is nullified. In the case of agents known to lower blood glucose significantly, fasting may not be possible and food should be provided during all treatment periods (active agent, positive control, and placebo) to reduce the chance of confounding by meals.

Antidiabetes drug dose. Plasma concentrations for a drug in a TQT study should cover at a minimum those observed in patients. This is in accordance with ICH E14 guideline, which states, “If not precluded by considerations of safety or tolerability due to adverse effects, the drug should be tested at substantial multiples of the anticipated maximum therapeutic exposure.”² In practice, this requirement has been translated as plasma levels that are above those anticipated in patients under the “worst-case” scenario. Renal impairment is a frequent comorbidity in the diabetes population. For a renally cleared drug, plasma levels achieved only in patients with severe renal impairment may not have to be reproduced in the TQT study if the drug is contraindicated in these patients. The suprathreshold dose in the TQT study, however, should be sufficient to cover the increase in exposure expected in patients with mild to moderate renal impairment after any intended dose adjustments. The selection of the suprathreshold dose to be tested is an important part of the dialogue between drug development sponsors and regulators that should occur before the study is initiated.

For antidiabetes agents, the therapeutic dose may produce hypoglycemia, especially in healthy subjects, which, as already discussed, may lead to perturbation of QT/QTc intervals. To counter this effect, subjects may need to be fed, and the meal-related effects on QT/QTc interval described in the previous section need to be considered.

It is common for a chemical entity to be developed into various formulations with different dosing regimens or routes of administration for different patient populations. According to the ICH E14 guideline, an additional TQT study may be required if the therapeutic exposures are anticipated to be higher than those seen from the previous product(s). For instance, a total of 2 TQT studies were conducted for 2 different formulations of marketed exenatide (Byetta and Bydureon, AstraZeneca Pharmaceuticals LP, Wilmington, DE). The first TQT study was conducted for Byetta at a single 10- μ g SC dose. The negative results were accepted by the FDA and are reflected in the prescribing information. After a therapeutic dose of Bydureon (exenatide 2 mg once weekly), the plasma exenatide concentration is at least twice that of Byetta. Therefore, the FDA could not draw any definitive conclusion regarding the QT/QTc effect of

Bydureon from the first TQT study with Byetta, and a second study was required.⁷⁶

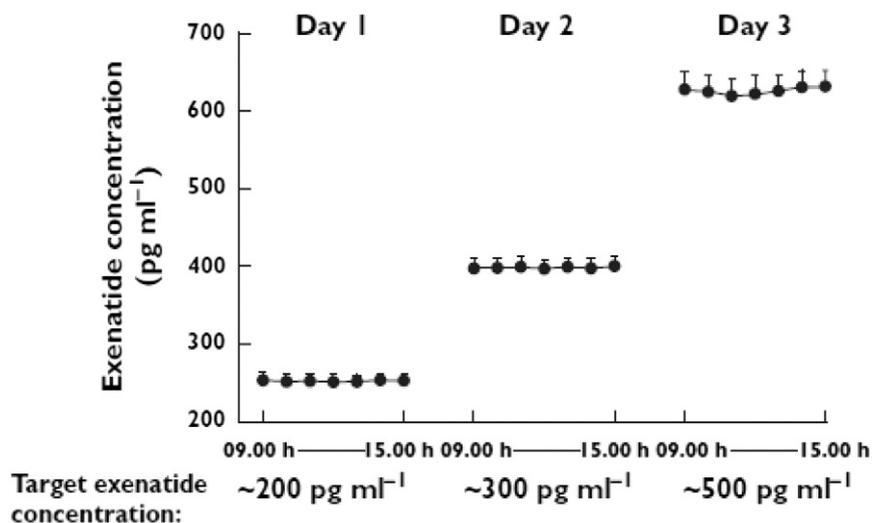
Drugs for which therapeutic or suprathreshold plasma levels are difficult to achieve in healthy volunteers pose specific challenges. As an example, GLP-1 receptor agonists are given SC. In some TQT studies with GLP-1 receptor agonists, dose escalation has been performed over a few weeks to reach suprathreshold plasma levels in healthy volunteers. The first 2 TQT studies of the GLP-1 receptor agonists, liraglutide and exenatide (Byetta), were conducted with the therapeutic dose only.^{50,55} An alternative route of administration can be used to achieve adequate plasma levels for a TQT study provided that drug-metabolite ratios are not different from those results from the intended route of administration. For example, to cover the exposure expected with Bydureon, a TQT study was conducted using an IV formulation and an infusion scheme that allowed suprathreshold plasma levels to be reached within 3 days. Stable plasma concentrations were maintained at preselected levels for the duration of the QT/QTc assessments (ie, over several hours; see Figure).⁵¹ The TQT study result for Bydureon was negative, and the results are reflected in the prescribing information.

Heart rate changes. Some antidiabetes compounds have been associated with positive chronotropic findings (see Table D). These changes may result from effects on autonomic tone⁷⁷ secondary to drug-induced hypoglycemia or to other unclear mechanisms.

QT interval correction methods are aimed at “normalizing” the measured QT interval duration to a nominal heart rate of 60 beats/min.⁷⁸ The greater the difference in the actual heart rate value from 60 beats/min, the greater the likelihood for overcorrection or undercorrection with artifactual results. When the drug-associated change in heart rate is small (eg, peak effect <5 beats/min), the QT interval can be corrected for heart rate changes using standard approaches such as QTcF. As discussed earlier, QTcB was used frequently in the past to correct for heart rate effects, but it is used less often now because it overcorrects at higher heart rates. When a drug is associated with a more pronounced change in heart rate, in either direction, standard correction methods cannot be relied upon and alternative approaches must be sought. Methods that may be considered include individualized QT corrections derived from a broad range of heart rates, or QT beat-to-beat and Holter-bin techniques that both use the uncorrected QT/RR at baseline for comparison and concentration-effect modeling using heart rate as a covariate.⁷⁷

Using an inappropriate method to correct QT interval for heart rate can lead to a biased estimate of the potential effect of drugs that change heart rate. Problems of 2 types arise with corrections based on an individual's drug-free QT-heart rate data. Multiplicity issues arise when the choice of the functional formula is not algorithmically specified. A second problem arises because models fitted to an

Figure



Geometric mean (SE) plasma exenatide concentrations achieved with continuous IV infusion. The three targeted plasma concentrations (~200, ~300, and ~500 pg/mL) were exceeded and remained stable during the ECG assessment period. Therapeutic concentrations of exenatide: ~200 and ~300 pg/mL. Figure reproduced from Darpo et al⁵¹ with permission of John Wiley & Sons, Inc.

individual's data result in an estimate for the QTc, that is, one that properly conveys a CI. The individual value's CI needs to be incorporated into, and increase the confidence limits around, the population estimates. Each approach has unique characteristics and limitations.

An optimal evaluation for QT data is important. However, meticulous data collection for a TQT study is more critical. Drug-free data allow for measuring or estimating QT interval duration at heart rates seen on treatment. The range of heart rates can be increased at baseline by collecting ambulatory ECG recordings in addition to those collected under semisupine, resting conditions, as described earlier.

In the pilot study to the Bydureon TQT study,⁵¹ the IV formulation, unlike the SC version used in treatment for patients with diabetes, was associated with an increase in heart rate. To obtain QT/RR values at higher heart rates than typically seen with subjects resting in a supine position, additional time points were added at baseline during which subjects were less restricted in terms of moving around in the unit, or with supine-to-standing maneuvers. This approach resulted in a broader range of heart rates on which QTc was derived using several different methods, such as linear, nonlinear, individual, or population-based regression methods. Methods were then evaluated in accordance with a prospective analysis plan using the approach suggested by members of the FDA QT-Interdisciplinary Review Team (QT-IRT),⁷⁹ and the primary endpoint was selected based on this evaluation.⁵¹ The same approach, or other methods to obtain a sufficiently broad range of heart rates at baseline such as using the full 24-hour baseline QT/RR graphed as a scatterplot (ie, all QT vs RR data plotted individually),

can be used for any drug with a chronotropic effect. Importantly, whether or not a new molecular entity has an effect on heart rate should be known from earlier clinical pharmacology studies, and the TQT study should be planned accordingly.

Other ECG parameters. Drug-associated changes in other ECG parameters, such as PR interval and QRS complex duration as well as heart rate changes, are not always given in publications on TQT studies. In the Health Canada Summary Basis of Decision,⁵⁴ it was reported that liraglutide at therapeutic doses of 1.2 and 1.8 mg causes a sustained increase in heart rate and prolongation of the PR interval at steady state. The incidence of subjects with heart rate values greater than 90 beats/min was 20% for 1.2 mg and 24% for 1.8 mg liraglutide, as compared with 8% and 4% on the respective day for placebo. A peak placebo- and baseline-adjusted mean PR prolongation of 9.0 to 10.0 ms was seen. The Byetta (exenatide SC) TQT study did not assess steady-state effects; however, a mean increase in placebo- and baseline-adjusted heart rate of 10.2 beats/min and a maximum increase in mean PR interval of 7.1 ms (maximum increases) were observed after a single therapeutic dose of 10 µg.⁵⁰ Increases in PR interval and heart rate have likewise been reported with other antidiabetes drugs (Table I). Although phase 3 trials provide an opportunity to assess the clinical relevance of PR interval increases, these are informative only if the scheduling and rigor of the late-phase ECG assessments are adequate.

It now seems prudent to analyze all ECG parameters in TQT studies using measures of central tendency and

categorical analyses of outliers.⁸⁰ An approach similar to that used for evaluating QTc interval, at least descriptively, that is, as placebo-corrected, change from baseline at each time point and across doses, is routinely used. In the event QT interval is difficult to measure, morphologic assessments may be useful.

Electrocardiogram monitoring for anti-diabetes drugs during clinical development

Early clinical development

Although historically less regulatory attention has been paid to early clinical development where the conventional approach of single and multiple ascending-dose studies in healthy subjects is used, it has become common practice to include more substantial ECG monitoring and evaluation, including QT interval, during those studies. In the past, if the nonclinical profile and earliest clinical observations with a drug suggested the induction of ECG effects (eg, QT prolongation or heart rate effects in the projected potential therapeutic range of drug concentrations and doses), more stringent ECG assessments would be performed to characterize these observations and inform the design and timing of the TQT study. This type of profile, however, would suggest to many sponsors that the new antidiabetes drug development should be halted. If a decision were made to perform more intensive assessments, these could include features of TQT studies such as the use of blinded centralized assessments of high-quality digital ECGs collected at key time points in the drug's pharmacokinetic profile.⁸¹ These data would be used in conjunction with pharmacokinetic/pharmacodynamic modeling to characterize QT/QTc effects and potential exposure-response relationships. In recent times, the emphasis of this modeling has increased and helps inform the evaluation of whether a compound may have effects on the QT/QTc interval.⁸²

After ECG assessments in healthy volunteers, it is likely that patients with diabetes would need to be recruited as any agent leading to overt hypoglycemia would prevent further dose escalation in healthy subjects. For this reason, the introduction of a cohort with diabetes is often an element of these early studies, with the recognition that untreated patients with type 2 diabetes are difficult to enroll. Electrocardiogram collection would be expected nonetheless during these studies.

Later clinical development

The design and rigor of QT assessments in later phase diabetes studies are largely driven by observations from the earlier nonclinical and clinical development programs, including the TQT study. The ICH E14 Questions and Answers (R2)⁸³ outlines considerations for QT/QTc assessments during late-stage drug development. Comorbidities in the patient population that could increase the

potential for proarrhythmic effects and the degree of QT/QTc prolongation observed in the TQT study are key determinants of the intensity of the late-phase ECG monitoring. If the drug has a negative TQT study result and there are no other meaningful observations related to QT/QTc in the drug development program, standard assessments may be sufficient for continued ECG safety monitoring. Identifying the risk for outlying drug effects (QT/QTc interval >500 ms or increases ≥ 60 ms) with or without central readings would be of primary interest. As with earlier phase studies, the timing of assessments would be determined by the profile of the drug with the desire to characterize effects at times closest to maximum concentrations. The results of these late-phase assessments could ultimately influence risk mitigation measures for continued development and commercialization of the drug.

Regulatory experience and perspective

Since the adoption of the ICH E14 guideline in 2005, a practice for the design and conduct of TQT studies has evolved through interactions between drug development sponsors and regulatory agencies, particularly the FDA QT-IRT that was formed in 2006.^{2,71,79,84} Almost all TQT studies are submitted to the QT-IRT, which provides comments and advice to the review division managing the application. As of July 2014, 379 studies had been reviewed. This interaction between drug development sponsors and regulatory agencies has resulted in a large degree of consistency across TQT studies in different therapeutic areas.

Table II summarizes the 24 TQT studies for antidiabetes drugs reviewed by the FDA from 2006 through April 2013. In contrast to Table I, which presents only publicly available data, the list in Table II spans data from new drug applications and investigational new drugs stratified by mechanism of antidiabetes action. The results of these studies are consistent with those presented earlier in that most studies (90%) were considered to be a "negative" TQT study result. Also shown in the table is the summary of exposure-response analysis and whether the high-exposure scenario (worse case) was covered by the suprathreshold dose tested.

For the 2 DPP-4i with positive TQT study results, the study result was positive only at suprathreshold doses (4- to 8-fold the therapeutic doses). The means (1-sided 95% upper bound) for these 2 drugs at the suprathreshold dose were 7 (13) ms and 10.7 (14.4) ms. Both studies exhibited a positive exposure-response relationship. No exposure-response relationship was identified for the 21 drugs that showed negative results for the ICH E14 analysis. It is important to note that for cases in which the suprathreshold dose did not cover the high exposure-clinical scenario for the drug, this was mainly because of the lack of knowledge of intrinsic factors or

Table II. Summary of TQT studies of antidiabetes drugs reviewed by the QT-IRT, FDA (2006 through April 2013)

Pharmacologic class (n)	ICH E14 analysis (n)	ER relationship (n)	High-exposure scenario not covered
GLP-1 analogues (7)*	Negative [†] (7)	None (7)	2
	Positive (0)	–	–
DPP-4 inhibitors (6)	Negative [†] (4)	None (4)	2
	Positive (2)	Positive (2)	1
PPAR agonists (1)	Negative [†] (1)	None (1)	–
	Positive (0)	–	–
SGLT2 inhibitors (6)	Negative [†] (6)	None (6)	3
	Positive (0)	–	–
Others (4)	Negative [†] (3)	None (3)	–
	Positive (1)	Positive (1)	1

Abbreviations: *n*, Number of drug candidates; *ER*, exposure-response; *PPAR*, peroxisome proliferator-activated receptor.

* One of the studies was inconclusive as assay sensitivity could not be demonstrated.
† Upper bound of the 95% 1-sided CI for the largest time-matched mean effect of the drug on the QTc interval excluded 10 ms.

extrinsic factors affecting the pharmacokinetics of the drug or the lack of knowledge of the ultimate therapeutic dose.

Assessment of potential QT effects of antidiabetes drugs, specifically those with rapid and potent effects on glucose and insulin concentrations, poses a unique set of challenges secondary to glucose, insulin, and other physiologic effects discussed earlier. Thorough QT studies for oral antidiabetes drugs have been predominantly glucose-dependent insulin secretagogues or agents that lower the renal threshold for glucose excretion. These drugs are not normally associated with increased risk of hypoglycemia. As shown in Table II, the QT-IRT experience is limited or negligible with drugs that cause significant hypoglycemia (eg, glucokinase activators).⁸⁵ Given this limited experience, it is not possible to comment on QT prolongation secondary to drug-induced hypoglycemia. It is possible that drug development is halted prior to the conduct of a TQT study if QT prolongation is noted in early phase I studies. In these cases, there may be concerns regarding drug approval as the benefit-risk assessment may be unfavorable.

Although drug-induced changes in glucose might alter the QT/QTc interval, it is important to acknowledge that this is not the only possibility. A drug targeted to treat diabetes could, independently of its effect to alter glucose levels, inhibit ventricular repolarization. Therefore, regulators would expect nonclinical evaluations (as described in ICH S7B) with these drugs, as with other drug classes. The FDA encourages sponsors to submit the subject-level data for glucose and K⁺ in the TQT studies for antidiabetes drugs so that the hypothesis regarding hypoglycemia-induced QT/QTc prolongation can be adequately assessed.

Summary and conclusions

Glucose-lowering medications are used to treat patients who, by the nature of having diabetes, are at relatively high cardiovascular risk. Therefore, determination of whether an individual drug increases the possibility of cardiovascular events is important. With regard to the potential for prolonging the QT/QTc interval, we now recognize that the pharmacology of some antidiabetes drugs may be associated with QT effects independent of a direct drug effect on ventricular repolarization. Specifically, changes in glucose and/or insulin along with associated K⁺ shifts into cells may prolong the QT/QTc interval.

A number of design factors should be considered when conducting QT interval assessments with an antidiabetes drug. If food must be ingested during the study, consumption needs to be carefully controlled, and ideally, QT/QTc assessments should not be performed in the near postprandial time frame, a period of serum glucose and insulin shifts and heart rate increases. Given that patients with diabetes tend to have prolonged QT/QTc intervals compared with the overall population and that neuropathic complications can conceivably cause QT/QTc and heart rate lability, it is likely best, except in extenuating situations, that the TQT evaluation is performed in healthy volunteers. Glucose levels, and possibly K⁺, should be measured to permit later pharmacokinetic/pharmacodynamic modeling if warranted. If a compound produces profound hypoglycemia, the only way to perform the study safely may be to use glucose clamping, which to date is untried in the context of a TQT study. The glucose infusion itself, however, could confound QT/QTc observations via endogenous insulin release and changes in K⁺ concentrations. Alternatively, a study conducted in patients with type 1 diabetes may be considered if the primary antihyperglycemia mechanism is β -cell stimulation. In addition, many newer glucose-lowering medications are associated with a mild increase in heart rate. These increases in heart rate can result in spurious QTc prolongation because of limitations in correction properties, independent of direct effects on repolarization. It is therefore critical to use adequate correction methods when performing studies specifically addressing QT/QTc effects of such agents, ideally using a prospectively determined methodology to choose the correction method that results in the flattest QT/RR slope.^{77,79} However, even with these QT/QTc correction methods, assessing accurate estimates of potential QT/QTc effects is challenging in the context of heart rate and autonomic effects, and superimposing metabolic alterations will need particular vigilance in analysis and interpretation of potential QT/QTc findings.

It is reassuring that most TQT study results performed on newer antidiabetes medications have been negative despite the multiplicity of mechanisms of action of antidiabetes drugs, the potential direct and indirect mechanisms by which antidiabetes drugs could affect the QT/QTc interval, the complexities of potential

confounding factors, and the many pertinent issues in drug development raised in this article. The effect on ventricular repolarization may be different with insulin itself or other agents that cause larger glucose or insulin shifts in healthy volunteers and are perhaps associated with autonomic effects. Sharing and publishing pertinent scientific and clinical data will be informative and useful in advancing the development of antidiabetes drugs with minimal risk of QT/QTc prolongation, and characterizing the risk earlier in development for drugs with a potential risk of prolonging ventricular repolarization.

Disclaimer

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References

1. Salvi V, Karnad DR, Panicker GK, et al. Update on the evaluation of a new drug for effects on cardiac repolarization in humans: issues in early drug development. *Br J Pharmacol* 2010;159:34-48.
2. International Conference on Harmonization. ICH E14 Guideline. The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. International Conference on Harmonisation step 4 guideline, EMEA, CHMP/ICH/2/04. Available at: <http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html> 2005. [Accessed 11 July 2014].
3. Suys B, Heuten S, De Wolf D, et al. Glycemia and corrected QT interval prolongation in young type 1 diabetic patients. *Diabetes Care* 2006;29:427-9.
4. Gastaldelli A, Emdin M, Conforti F, et al. Insulin prolongs the QTc interval in humans. *Am J Physiol Regul Integr Comp Physiol* 2000;279:R2022-5.
5. Taubel J, Lorch U, Ferber G, et al. Insulin at normal physiological levels does not prolong QTc interval in thorough QT studies performed in healthy volunteers. *Br J Clin Pharmacol* 2013;75:392-403.
6. Robinson RT. Mechanisms of abnormal cardiac repolarization during insulin-induced hypoglycemia. *Diabetes* 2003;52:1469-74.
7. Lee SP, Harris ND, Robinson RT, et al. Effect of atenolol on QTc interval lengthening during hypoglycaemia in type 1 diabetes. *Diabetologia* 2005;48:1269-72.
8. Zhang Y, Han H, Wang J, et al. Impairment of human ether-à-go-go-related gene (HERG) K⁺ channel function by hypoglycemia and hyperglycemia. *J Biol Chem* 2003;278:10417-26.
9. Marfella R, Rossi F, Giugliano D. Hyperglycemia and QT interval: time for re-evaluation. *Diabetes Nutr Metab* 2001;14:63-5.
10. Sager PT, Gintant GA, Turner JR, et al. Rechanneling the cardiac proarrhythmia safety paradigm: a meeting report from the Cardiac Safety Research Consortium. *Am Heart J* 2014;167:292-300.
11. American Diabetes Association. Standards of medical care in diabetes—2012. *Diabetes Care* 2012;35(Suppl 1):S11-63.
12. Salas M, Caro JJ. Are hypoglycaemia and other adverse effects similar among sulphonylureas? *Adverse Drug React Toxicol Rev* 2002;21:205-17.
13. Doyle ME, Egan JM. Pharmacological agents that directly modulate insulin secretion. *Pharmacol Rev* 2003;55:105-31.
14. Nauck MA, Heimesaat MM, Behle K, et al. Effects of glucagon-like peptide 1 on counterregulatory hormone responses, cognitive functions, and insulin secretion during hyperinsulinemic, stepped hypoglycemic clamp experiments in healthy volunteers. *J Clin Endocrinol Metab* 2002;87:1239-46.
15. Sanguinetti MC, Tristani-Firouzi M. hERG potassium channels and cardiac arrhythmia. *Nature* 2006;440:463-9.
16. International Conference on Harmonization. ICH S7B Guideline. The non-clinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals. International Conference on Harmonisation step 4 guideline, EMEA, CHMP/ICH/12/05. Available at: <http://www.ich.org/products/guidelines/safety/article/safety-guidelines.html> 2005. [Accessed 11 July 2014].
17. Mitcheson JS, Chen J, Sanguinetti M. Trapping of a methanesulfonanilide by closure of the HERG potassium channel activation gate. *J Gen Physiol* 2000;115:229-39.

18. Zou A, Curran ME, Keating MT, et al. Single HERG delayed rectifier K⁺ channels expressed in *Xenopus* oocytes. *Am J Physiol Heart Circ Physiol* 1997;272:H1309-14.
19. Rodriguez I, Erdman A, Padhi D, et al. Electrocardiographic assessment for therapeutic proteins—scientific discussion. *Am Heart J* 2010;160:627-34.
20. Food and Drug Administration. Pharmacology Review (Application Number 21-629): Insulin Glulisine (HMR1964). Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-629_Apidra.cfm 2004. [Accessed 11 July 2014].
21. Clawson CA, Moore MC, Waterhouse TH. Hypoglycemia prolongs the QT interval and decreases blood pressure in a canine glucose-clamp model. *J Pharmacol Toxicol Methods* 2010;62:e38.
22. Parrish AE, Sugar SJN, Fazekas JF. A relationship between electrocardiographic changes and hypokalemia in insulin-induced hypoglycemia. *Am Heart J* 1952;43:815-20.
23. Hanton G, Yvon A, Provost J-P. Quantitative relationship between plasma potassium levels and QT interval in beagle dogs. *Lab Anim* 2007;41:204-17.
24. Yang T, Roden DM. Extracellular potassium modulation of drug block of IKr: implications for torsade de pointes and reverse use dependence. *Circulation* 1996;93:407-11.
25. Lee SP, Yeoh L, Harris ND, et al. Influence of autonomic neuropathy on QTc interval lengthening during hypoglycemia in type 1 diabetes. *Diabetes* 2004;53:1535-42.
26. Gavryck WA, Moore RD, Thompson RC. Effect of insulin upon membrane-bound (Na⁺ + K⁺)-ATPase extracted from frog skeletal muscle. *J Physiol* 1975;252:43-58.
27. Webster R, Leishman D, Walker D. Towards a drug concentration effect relationship for QT prolongation and torsades de pointes. *Curr Opin Drug Discov Devel* 2002;5:116-26.
28. Montague W, Taylor KW. Islet-cell metabolism during insulin release. Effects of glucose, citrate, octanoate, tolbutamide, glucagon and theophylline. *Biochem J* 1969;115:257-62.
29. Laitinen T, Huopio H, Vauhkonen I, et al. Effects of euglycaemic and hypoglycaemic hyperinsulinaemia on sympathetic and parasympathetic regulation of haemodynamics in healthy subjects. *Clin Sci (Colch)* 2003;105:315-22.
30. Struthers AD, Reid JL, Whitesmith R, et al. The effects of cardioselective and non-selective beta-adrenoceptor blockade on the hypokalaemic and cardiovascular responses to adrenomedullary hormones in man. *Clin Sci (Colch)* 1983;65:143-7.
31. Ogawa S, Barnett JV, Sen L, et al. Direct contact between sympathetic neurons and rat cardiac myocytes in vitro increases expression of functional calcium channels. *J Clin Invest* 1992;89:1085-93.
32. Zeng J, Rudy Y. Early after depolarizations in cardiac myocytes: mechanism and rate dependence. *Biophys J* 1995;68:949-64.
33. Sager PT. Modulation of antiarrhythmic drug effects by beta-adrenergic sympathetic stimulation. *Am J Cardiol* 1998;82:201-301.
34. Marfella R, Nappo F, De Angelis L, et al. The effect of acute hyperglycaemia on QTc duration in healthy man. *Diabetologia* 2000;43:571-5.
35. Tattersall RB, Gill GV. Unexplained deaths of type 1 diabetic patients. *Diabet Med* 1991;8:49-58.
36. Marques JL, George E, Peacey SR, et al. Altered ventricular repolarization during hypoglycaemia in patients with diabetes. *Diabet Med* 1997;14:648-54.
37. Heller SR. Discussion of cardiac arrhythmias in hypoglycaemia. *Diabetes Nutr Metab* 2002;15:465-7.
38. Heller SR. Cardiac arrhythmias in hypoglycaemia. *Diabetes Nutr Metab* 2002;15:461-5.
39. Nordin C. The case for hypoglycaemia as a proarrhythmic event: basic and clinical evidence. *Diabetologia* 2010;53:1552-61.
40. De Fronzo R, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* 1979;273:E214-23.
41. Robinson RTCE, Harris ND, Ireland RH, et al. Comparative effect of human soluble insulin and insulin aspart upon hypoglycaemia-induced alterations in cardiac repolarization. *Br J Clin Pharmacol* 2003;55:246-51.
42. Rothenbuhler A, Petit Bibal C, Le Fur S, et al. Effects of a controlled hypoglycaemia test on QTc in adolescents with type 1 diabetes. *Diabet Med* 2008;25:1483-5.
43. Gordin D, Forsblom C, Ronnback M, et al. Acute hyperglycaemia disturbs cardiac repolarization in type 1 diabetes. *Diabet Med* 2008;25:101-5.
44. Ewing DJ, Clarke BF. Autonomic neuropathy: its diagnosis and prognosis. *Clin Endocrinol Metab* 1986;15:855-88.
45. Ireland RH, Robinson RT, Heller SR, et al. Measurement of high resolution ECG QT interval during controlled euglycaemia and hypoglycaemia. *Physiol Meas* 2000;21:295-303.
46. Robinson RTCE, Harris ND, Ireland RH, et al. Changes in cardiac repolarization during clinical episodes of nocturnal hypoglycaemia in adults with type 1 diabetes. *Diabetologia* 2004;47:312-5.
47. Murphy NP, Ford-Adams ME, Ong KK, et al. Prolonged cardiac repolarisation during spontaneous nocturnal hypoglycaemia in children and adolescents with type 1 diabetes. *Diabetologia* 2004;47:1940-7.
48. Dekker JM, Feskens EJM, Schouten EG, et al. QTc duration is associated with levels of insulin and glucose tolerance: the Zutphen elderly study. *Diabetes* 1996;45:376-80.
49. Christensen TF, Cichosz SL, Tarnow L, et al. Hypoglycaemia and QT interval prolongation in type 1 diabetes—bridging the gap between clamp studies and spontaneous episodes. *J Diabetes Complications* 2014;28:723-8.
50. Linnebjerg H, Seger M, Kothare PA, et al. A thorough QT study to evaluate the effects of single dose exenatide 10 µg on cardiac repolarization in healthy subjects. *Int J Clin Pharmacol Ther* 2011;49:594-604.
51. Darpo B, Sager P, MacConell L, et al. Exenatide at therapeutic and supratherapeutic concentrations does not prolong the QTc interval in healthy subjects. *Br J Clin Pharmacol* 2013;75:979-89.
52. Loghini C, Chien JY, Cui S, et al. LY2189265, a long-acting GLP-1 analog, does not prolong QTc interval in healthy subjects at supratherapeutic doses. *Diabetes* 2011;69(Suppl 1):A299. [Abstract 1089P].
53. Chatterjee DJ, Khutoryansky N, Zdravkovic M, et al. Absence of QTc prolongation in a thorough QT study with subcutaneous liraglutide, a once-daily human GLP-1 analog for treatment of type 2 diabetes. *J Clin Pharmacol* 2009;49:1353-62.
54. Health Canada. Summary Basis of Decision (SBD) Victoza, Liraglutide, 6 mg/mL solution. Novo Nordisk Canada Inc. Submission Control Number: 119928. Available at: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2010_victoza_119928-eng.php 2010. [Accessed 15 July 2014].
55. Darpo B, Zhou M, Matthews J, et al. Albiglutide does not prolong the QTc interval in healthy subjects: a thorough QT/QTc study. *Diabetes Ther* 2014;5:141-53.
56. European Medicines Agency. Lyxumia assessment report. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002445/human_med_001615.jsp&mid=WC0b01ac058001d124 2012. [Accessed 15 July 2014].
57. Pharmaceuticals and Medical Devices Agency Japan. Report on deliberation results, Lyxumia. Available at: <http://www.pmda.go.jp/files/000153885.pdf> 2013. [Accessed 15 July 2014].
58. Bloomfield DM, Krishna R, Hreniuk D, et al. A thorough QTc study to assess the effect of sitagliptin, a DPP4 inhibitor, on ventricular repolarization in healthy subjects. *J Clin Pharmacol* 2009;49:937-46.

59. He Y-L, Zhang Y, Serra D, et al. Thorough QT study of the effects of vildagliptin, a dipeptidyl peptidase IV inhibitor, on cardiac repolarization and conduction in healthy volunteers. *Curr Med Res Opin* 2011;27:1453-63.
60. Patel CG, Li L, Komoroski BJ, et al. No effect of saxagliptin on QTc interval in healthy subjects. *Diabetes* 2009;58(Suppl 1):A533. [Abstract 2072-PO].
61. Ring A, Port A, Graefe-Mody EU. The DPP-4 inhibitor linagliptin does not prolong the QT interval at therapeutic and supratherapeutic doses. *Br J Clin Pharmacol* 2011;72:39-50.
62. Sturm S, Bentley D, Jordan P, et al. No evidence of QT prolongation with supratherapeutic doses of aleglitazar. *J Cardiovasc Pharmacol* 2012;59:288-97.
63. Carlson GF, Tou CKP, Parikh S, et al. Evaluation of the effect of dapagliflozin on cardiac repolarization: a thorough QT/QTc study. *Diabetes Ther* 2011;2:123-32.
64. Ring A, Brand T, Macha S, et al. The sodium glucose cotransporter 2 inhibitor empagliflozin does not prolong QT interval in a thorough QT (TQT) study. *Cardiovasc Diabetol* 2013;12:70.
65. Li W, Bai Y, Sun K, et al. Patients with metabolic syndrome have prolonged corrected QT interval (QTc). *Clin Cardiol* 2009;32:E93-9.
66. Veglio M, Chinaglia A, Cavallo Perin P. The clinical utility of QT interval assessment in diabetes. *Diabetes Nutr Metab* 2000;13:356-65.
67. Chugh SS, Reinier K, Singh T, et al. Determinants of prolonged QT interval and their contribution to sudden death risk in coronary artery disease: the Oregon Sudden Unexpected Death Study. *Circulation* 2009;119:663-70.
68. Festa A, D'Agostino R, Rautaharju P, et al. Relation of systemic blood pressure, left ventricular mass, insulin sensitivity, and coronary artery disease to QT interval duration in nondiabetic and type 2 diabetic subjects. *Am J Cardiol* 2000;86:1117-22.
69. Festa A, D'Agostino R, Rautaharju P, et al. Is QT interval a marker of subclinical atherosclerosis in nondiabetic subjects? The Insulin Resistance Atherosclerosis Study (IRAS). *Stroke* 1999;30:1566-71.
70. Malik M, Garnett CE, Zhang J. Thorough QT studies: questions and quandaries. *Drug Saf* 2010;33:1-14.
71. Darpo B. The thorough QT/QTc study 4 years after the implementation of the ICH E14 guidance. *Br J Pharmacol* 2010;159:49-57.
72. Simonson E, Alexander H, Henschel A. The effect of meals on the electrocardiogram of normal subjects. *Am Heart J* 1946;32:202-14.
73. Lipsitz LA, Ryan SM, Parker JA. Hemodynamic and autonomic nervous system responses to mixed meal ingestion in healthy young and old subjects and dysautonomic patients with postprandial hypotension. *Circulation* 1993;87:391-400.
74. Widerlov E, Jostell KB, Claesson L. Influence of food intake on electrocardiograms of healthy male volunteers. *Eur J Clin Pharmacol* 1999;55:619-24.
75. Taubel J, Wong AH, Naseem A, et al. Shortening of the QT interval after food can be used to demonstrate assay sensitivity in thorough QT studies. *J Clin Pharmacol* 2012;52:1558-65.
76. Food and Drug Administration. Clinical Pharmacology and Biopharmaceutics Review(s) (Application Number 022200): Bydureon. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/022200Orig1s000TOC.cfm 2012. [Accessed 15 October 2014].
77. Garnett CE, Zhu H, Malik M, et al. Methodologies to characterize the QT/QTc interval in the presence of drug-induced heart rate changes or other autonomic effects. *Am Heart J* 2012;163:912-30.
78. Fermini B, Fossa AA. The impact of drug-induced QT interval prolongation on drug discovery and development. *Nat Rev Drug Discov* 2003;2:439-47.
79. Tornøe CW, Garnett CE, Wang Y, et al. Creation of a knowledge management system for QT analyses. *J Clin Pharmacol* 2011;51:1035-42.
80. Nada A, Gintant GA, Kleiman R, et al. The evaluation and management of drug effects on cardiac conduction (PR and QRS intervals) in clinical development. *Am Heart J* 2013;165:489-500.
81. Vik T, Pollard C, Sager P. Early clinical development: evaluation of drug-induced torsades de pointes risk. *Pharmacol Ther* 2008;119:210-4.
82. Darpo B, Garnett C, Benson CT, et al. Cardiac Safety Research Consortium: can the thorough QT/QTc study be replaced by early QT assessment in routine clinical pharmacology studies? Scientific update and a research proposal for a path forward. *Am Heart J* 2014;168(3):262-72.
83. ICH E14 Implementation Working Group. ICH E14 Guideline: the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs—questions and answers (R2). Available at: <http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html> 2014. [Accessed 15 July 2014].
84. Food and Drug Administration, Center for Drug Evaluation and Research. Policy and procedures: interdisciplinary review team for QT studies. Available at: <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm082015.pdf> 2012. [Accessed 15 July 2014].
85. Meiningner GE, Scott R, Alba M, et al. Effects of MK-0941, a novel glucokinase activator, on glycemic control in insulin-treated patients with type 2 diabetes. *Diabetes Care* 2011;34:2560-6.

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