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Policy Conference

The potential for QT prolongation and proarrhythmia by non-antiarrhythmic drugs: clinical and regulatory implications

Report on a Policy Conference of the European Society of Cardiology

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Preamble[1]

The Policy Conference on 'The Potential for QT Prolongation and Proarrhythmia by Non-antiarrhythmic Drugs. Clinical and Regulatory Implications' was held at the European Heart House in Sophia Antipolis, France, on the initiative of Günter Breithardt, FESC, FACC, on 24 and 25 June 1999 after formal approval by the Board of the European Society of Cardiology (ESC).

The conference was organized under the auspices of the ESC Committee for Scientific and Clinical Initiatives by Günter Breithardt and Wilhelm Haverkamp, Münster, Germany, with participation of representatives of the Working Group on Arrhythmias of the ESC, the American College of Cardiology, the American Heart Association, the World Heart Federation, the European Agency for the Evaluation of Medicinal Products, the Medicines Control Agency (UK), the Food and Drug Administration (USA), the National Heart, Lung and Blood Institute (USA), the Federal Institute for Drugs and Medical Devices (Germany), and the Medical Products Agency (Sweden).

The scientific and clinical basis of drug-induced QT prolongation and proarrhythmia was summarized by formal presentations. The speakers were chosen for their particular competence in the relevant field. Furthermore, selected topics were discussed in detail in separate workshops. This document represents the executive summary of the Conference. It is based on written reports composed by the speakers and the chairs of the workshops. Before preparation of the final version of the document, a draft was circulated to all participants of the Conference for suggestions and comments. The opinions expressed in this document are those of the participants and do not necessarily reflect the official position of their organisations or agencies. The meeting was made possible by unrestricted educational grants to the Committee for Scientific and Clinical Initiatives of the ESC from several companies listed in the Appendix.

The problem

QT interval prolongation, and possibly increased QT dispersion, are risk factors in a number of cardiovascular as well as non-cardiovascular diseases. A variety of drugs prolong the QT interval, although the major example are the so-called class III antiarrhythmics. These drugs generally exert their therapeutic effect by affecting potassium ion channels, thereby reducing outward, repolarizing current, and prolonging action potential duration and the QT interval. Many of these drugs have been developed for conversion of atrial fibrillation and/or maintenance of sinus rhythm in patients with recurrent atrial fibrillation. Such patients are at low risk of potentially fatal arrhythmias, at least in the absence of antiarrhythmic drug therapy.

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[1]*This document has been reviewed by the members of the Committee for Scientific and Clinical Initiatives and by members of the Board of the European Society of Cardiology (J.-P. Bassand, C. Blomström-Lundqvist, J. L. Lopez Sendon, M. Santini, L. Rydén). The Board of the European Society of Cardiology approved the document on 14 April 2000. The full text version of this document is available on the website of the European Society of Cardiology in the section 'Scientific Information', Guidelines (http://www.escardio.org).*

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Table 1 Drugs that can prolong the QT interval (TdP=torsade de pointes)*

Class	Drug	TdP reported	Class	Drug	TdP reported
Antiarrhythmic drugs	Ajmaline	+	Psychiatric drugs *continued*	Mesoridazine	
	Almokalant	+		Nortryptiline	
	Amiodarone	+		Pericycline	+
	Aprindine	+		Pimozide	
	Azimilide	+		Prochlorperazine	+
	Bretylium	+		Sertindole	+
	Clofilium	+		Sultopride	+
	Dofetilide	+		Thioridazine	+
	Disopyramide	+		Timiperone	
	Ibutilide	+		Trifluoperazine	+
	N-acetyl-procainamide	+		Zimeldine	
	Procainamide	+			
	Propafenone	+	Antimicrobial and antimalarial drugs	Amantadine	+
	Quinidine	+		Clarythromycin	+
	Sematilide	+		Chloroquine	+
	d,l-sotalol, d-sotalol			Cotrimoxazole	+
				Erythromycin	+
Vasodilators/anti-ischaemic agents	Bepridil	+		Grepafloxacin	+
	Lipoflazine	+		Halofantrine	+
	Prenylamine	+		Ketoconazole	+
	Papaverine (intracoronary)	+		Pentamidine	+
				Quinine	+
				Spiramycine	+
Psychiatric drugs	Amitryptiline	+		Sparfloxacine	
	Clomipramine				
	Cloral hydrate	+	Antihistaminics	Astemizole	+
	Chlorpromazine	+		Diphenhydramine	+
	Citalopram	+		Ebastine	
	Desipramine	+		Hydroxyzine	
	Doxepin	+		Terfenadine	+
	Droperidol	+			
	Fluphenazine		Miscellaneous drugs	Budipine	+
	Haloperidol	+		Cisapride	+
	Imipramine	+		Probucol	+
	Lithium	+		Terodiline	+
	Maprotiline			Vasopressine	+

*Note: These data derive from what is effectively a non-controlled review of the literature. Hence, some of the drugs listed have profound effects on QT prolongation and on induction of torsades de pointes, and others have minor effects whose documentation is in some instances questionable and not clearly related to the drug given as opposed to an inter-current condition. The list is presented, then, to indicate the diversity of drugs and effects cited. However, the reader is urged to review the literature on any of these drugs before making decisions that relate to their administration.

However, antiarrhythmic drugs which prolong cardiac repolarization are not harmless, as they may induce a potentially fatal arrhythmia, known as torsade de pointes (TdP). The incidence of TdP in patients treated with quinidine whose spectrum of effects includes K channel blockade, has been estimated to range between 2·0% and 8·8%[1–4]. For d,l-sotalol, an incidence ranging between 1·8% and 4·8% has been described[5–7]. A similar incidence has been seen for newer 'class III' agents, e.g. dofetilide[8] and ibutilide[9].

Recently, it has become apparent that not only antiarrhythmic drugs but a variety of non-antiarrhythmic agents may aggravate and/or provoke TdP[10–12]. The number of non-antiarrhythmic drugs reported to induce QT interval prolongation with or without TdP continues to increase (Table 1). As many as 50 clinically available or still investigational non-cardiovascular drugs and cardiovascular non-antiarrhythmic drugs have been implicated. A number of drugs, both old and new, have either been withdrawn from the market (e.g. prenylamine, terodiline, sertindole, astemizole and in some countries terfenadine and cisapride) or have had their sale restricted (e.g. cisapride, some fluoroquinilones, pimozide and some other neuroleptics, terfenadine and halofantrine). Of concern is the interval, usually measured in years, from the marketing of these drugs to initial recognition of their association with QT interval prolongation and/or TdP.

Mechanisms of QT prolongation and TdP

Prolongation of the QT interval on the electrocardiogram is caused by prolongation of the action potentials

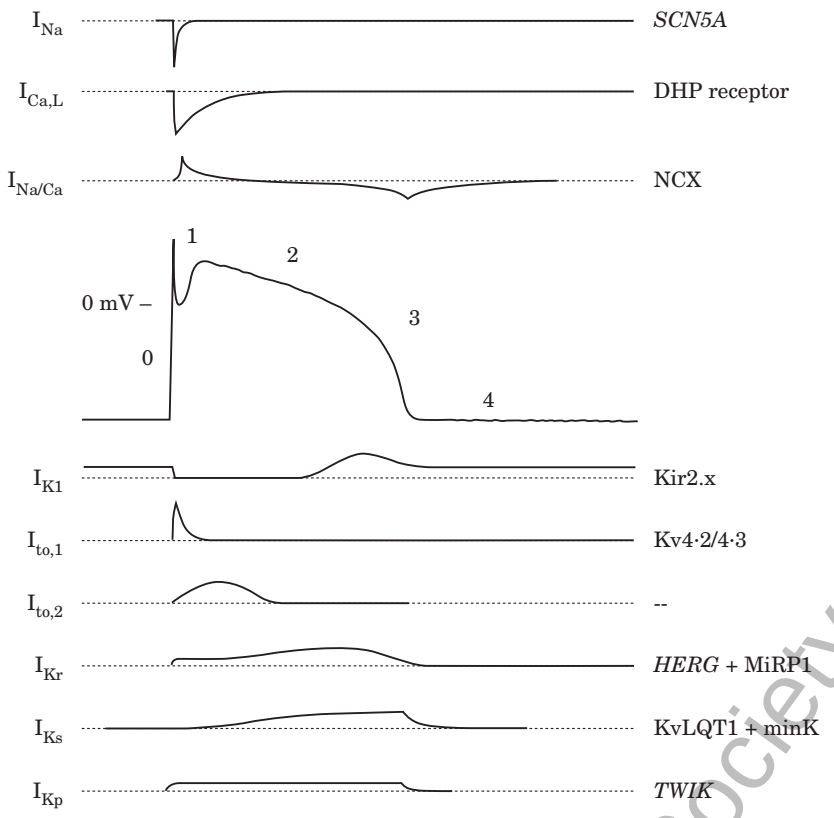

Figure 1 **Ionic and molecular basis of the cardiac action potential. The waveform results from multiple, successively activating depolarizing inward currents (*downward*) and repolarizing outward currents (*upward*). The established or most probable clones are indicated. Numbers denote phase of the action potential.**

of ventricular myocytes, brought about by a reduction of outward currents and/or enhancement of inward currents during phase 2 and 3 of the action potential. Figure 1 shows the ionic basis of the cardiac action potential. There is an intrinsic transmural heterogeneity in the density of the various ion channels that determine ventricular repolarization. Block or activation of these channels have different effects on action potential duration of the four cell types: Purkinje cells, subendocardial myocytes, mid-myocardial M cells and subepicardial myocytes, as depicted in Fig. 2. It is important to note that there are also important species and tissue differences in these currents. Thus, in isolated guinea pig, sheep and dog myocardium, both I_{Kr} and I_{Ks} are present, whilst in cat, rabbit and man, I_{Kr} is the predominant current[13]. Moreover there remains controversy over the relative roles of I_{Kr} and I_{Ks} in ventricular repolarization in individual species, such as the dog (compare references[14] and[15]). It should be pointed out that many technical issues including cell isolation methods, storage conditions, pipette solutions and 'investigator bias' in cell selection may have influenced detection of I_{ks} in cat, rabbit and man[15–17]. The transient outward current I_{to} contributes to the phase 2 notch of the action potential and is present in man and dog, but is poorly expressed in guinea pig. Block of I_{to} in myocardium from large mammals has varying effects on action potential duration and may prolong or shorten it[18]. Changes in the expression patterns of ion channels may also occur in disease and there are different patterns, as well, in normal males and females (Table 2).

A reduction in net outward current and/or an increase in inward current can potentially facilitate the development of early afterdepolarizations. Early afterdepolarizations occur preferentially in M cells and Purkinje cells due to reactivation of the L-type calcium current and/or activation of the sodium-calcium exchange current during the action potential plateau[19–22]. When accompanied by a marked increase in dispersion of repolarization there is increased likelihood that early afterdepolarization-induced extrasystoles will trigger reentry and TdP (Figures 3, 4 and 5)[23–26]. Most of our present understanding of TdP is based on the study of drugs which block I_{Kr}. Virtually all drugs that have been shown to increase the QT interval, incorporate I_{Kr} blockade in their spectrum of effects. However, any drug which reduces net repolarizing currents may pose a risk for inducing this arrhythmia.

Electrotonic cell-to-cell coupling influences the dispersion of repolarization. If myocardial cells with intrinsically different action potential duration are well coupled, electrotonic current flow attenuates the differences in

Effect on action potential duration

	Purkinje	Endo	M	Epi
I_{Kr} block	↑↑↑	↔↑	↑↑↑	↔↑
I_{Ks} block	↔	↑↑	↑↑	↑↑
I_{to} block	↓	↔	↔↓	↔↓
Activation of late I_{Na}	↑↑↑↑	↑↑	↑↑↑↑	↑↑
Activation of I_{Ca}	↑↑↑	↔↑	↑↑↑	↔↑

Figure 2 **Effect of different pharmacological agents on the action potential of the four predominant cell types found within the ventricles of larger mammals. ↔↑=little to no action potential prolongation; ↑↑↑↑=maximum action potential prolongation.**

action potential duration. Thus, in the intact left ventricular wall, differences in action potential duration are smaller than in myocytes or tissues isolated from epicardial, endocardial and M cell layers. In transmural sections of the ventricular wall (wedge preparation), the dispersion in action potential duration averaged 51 ms at a cycle length of 1000 ms[27]. In the intact left ventricular wall of open-chest dogs, the transmural differences in refractory periods or activation–recovery intervals were even smaller, in the order of 20 to 30 ms[28–30]. Selection of anaesthetic agents and extracellular recording techniques also influence the measurement of dispersion of repolarization in in vivo studies under baseline, and even more so under long QT conditions[26]. It is likely that macroscopic tissue resistance, caused by changes in fibre direction across the ventricular wall, contributes to dispersion in repolarization. Partial uncoupling due to fibrosis (as in ageing or hypertrophy) may further unmask intrinsic differences in action potential duration.

The development of early afterdepolarizations and TdP usually occurs with drugs that block I_{Kr}. For obvious reasons, the frequency with which a given drug produces QT interval prolongation and/or TdP during its uncontrolled clinical use remains largely unknown. The overall clinical incidence of TdP is probably low and not all drugs that block I_{Kr}, have the same proarrhythmic potential. For example, the estimated incidence of TdP for cisapride which blocks *HERG*[31], is 1 out of 120 000 patients treated[32] while for d,l-sotalol, a markedly higher incidence has been reported (see above). This probably reflects the fact that cisapride is more often given to patients with normal hearts than sotalol whose use is confined to patients with cardiac arrhythmias. In the congenital long QT syndrome, mutations in *HERG* have been found at many sites, and, thus far, no correlation has been established between phenotype and the extent of I_{Kr} dysfunction[33]. The precise reasons for the different effects of I_{Kr} blockers are unknown but many factors modulate the effects of drugs that block I_{Kr} (Table 2).

One factor of particular importance for the genesis of TdP is a particular predisposition of individual patients. Recently, it has been demonstrated that in patients who developed TdP secondary to class III agents, drug-induced QTc prolongation was more marked than in patients without TdP and, furthermore, it was not related to the dose of the drug[34]. Thus, patients with TdP showed an abnormal response following exposure to the drug. The reason for such a behaviour is not clear.

The presence of a forme fruste of a long QT syndrome could play a key role although genetic study of patients with drug-induced TdP revealed that only a minority of the patients had a mutation in one of the genes known to cause congenital long QT syndrome[35]. However, it cannot be excluded that yet unknown subtle genetic defects may set the stage for abnormal QT prolongation and TdP. Such subtle genetic defects have been shown to result in a low penetrance in phenotypic expression which might imply a lowered threshold for the development of abnormal QT prolongation and TdP upon challenge with a specific drug[36]

A reduced repolarization reserve[37] may underlie acquired abnormal QT prolongation and TdP. This concept emphasizes that the occurrence of TdP secondary to a repolarization prolonging drug is a patient-specific response. This hypothesis is supported by reports of patients who developed additional episodes of TdP during subsequent exposure to a repolarization prolonging drug different from the one that initially caused their arrhythmia[38–41]. 'Patient-specific response' does not necessarily mean that the individual patient will always show abnormal QT prolongation and TdP during exposure to repolarization prolonging stimuli. This becomes obvious when considering the highly variable

Table 2 Factors modulating repolarization (not comprehensive)

Hypokalaemia	Low extracellular [K] reduces I_{Kr}[73]. At low extracellular K concentrations, I_{Kr} blockade by e.g. quinidine and dofetilide is enhanced[73].
Bradycardia	Bradycardia increases action potential duration. The repolarization prolonging effect of I_{Kr} blockers is most marked at low heart rates and decreases at higher heart rates (reverse use-dependence)[74].
Gender	QT interval is longer in women than in men[63]. TdP occurs more frequently women[6,75]. Female rabbits have less I_{Kr} than male rabbits[76].
Hypertrophy and heart failure	The action potential is prolonged and both the transient outward current and the delayed rectifier current are reduced[18]. Further reduction of I_{Kr} may result in excessive action potential prolongation[77].
Metabolic factors	Certain drugs, e.g. terfenadine, are metabolized by the P450 isoenzyme CYP3A4, and the terfenadine metabolite terfenadine carboxylate, does not block I_{Kr}[78]. When drugs that inhibit CYP3A4 are co-administered (erythromycin and other macrolide antibiotics, ketoconazole and other azole antifungals, mibefradil), plasma levels of the parent drug may rise considerably, thus leading to further lengthening of the QT interval[67] and increasing the risk of TdP. The same may occur in liver disease. Renal insufficiency may result in an increased plasma concentration of drugs excreted by the kidney.
Sympathetic activity and calcium loading	In patients with congenital long QT syndrome (LQT1 and LQT2 with mutations in the genes encoding for I_{Ks} and I_{Kr} respectively), beta-adrenergic stimulation increases the dispersion in monophasic action potential duration and QT dispersion[79–80]. I_{Kr} block combined with beta-adrenergic stimulation increases transmural dispersion of repolarization because of an augmentation of residual I_{Ks} in epicardial and endocardial cells but not in M cells where I_{Ks} is intrinsically weak[81]. In rabbits, alpha-adrenergic stimulation potentiates the effect of I_{Kr} blockers[57].
Reduced repolarization reserve, 'formes frustes' of the congenital long QT syndrome	Patient-specific increased propensity to development of abnormal QT prolongation and TdP[37]. Non-symptomatic carriers of mutated genes for Na or K channels may be more susceptible to drugs that prolong repolarization[35,36].

TdP=torsade de pointes, LQT=long QT syndrome.

intervals between the initiation of drug therapy and occurrence of TdP reported in the literature.

Detecting drug-induced effects on repolarization

The risk of drug-induced TdP arrhythmias raises a dilemma of early detection of the effects of any new chemical entity on cardiac ventricular repolarization. The impressive list of drugs, already on the market or still under development that have been reported to adversely prolong repolarization, makes it imperative to investigate any new chemical entity for this potential side effect before its first use in man. Pre-clinical screening should be conducted in vitro and in vivo using the parent compound, its enantiomers when the new chemical entity is chirally active, and the major metabolites, once these have been identified. In any research project, the models used should facilitate the testing of the hypotheses put forward. A number of models having variable advantages and limitations are available

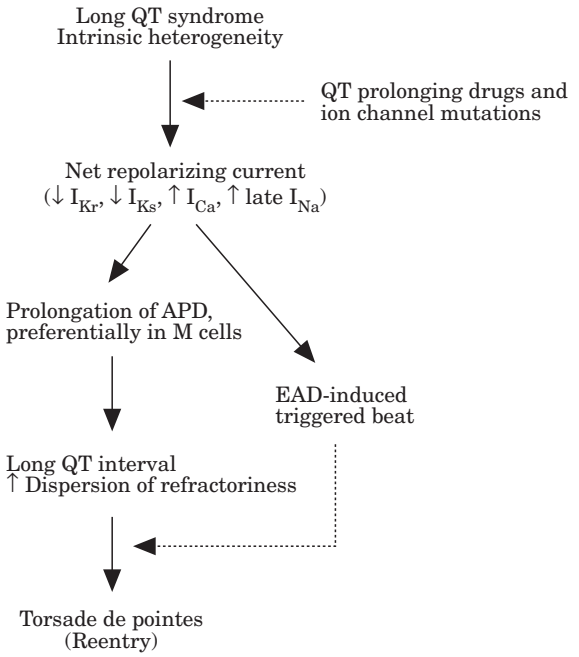

Figure 3 **Proposed cellular mechanism for the development of torsade de pointes in the long QT syndrome. Most agents that prolong QT, amplify the electrical heterogeneity that exists across the ventricular wall. This effect is secondary to a reduction of net outward current which causes a preferential prolongation of the M cell action potential duration and creation of a vulnerable window secondary to the development of a transmural dispersion of repolarization. The reduced net outward current also predisposes to the development of an early afterdepolarizations-induced extrasystoles which can capture the vulnerable window and induce a meandering spiral wave which manifest as an atypical polymorphic ventricular tachycardia VT known as torsade de pointes. I_{Ks} blockers only produce these arrhythmogenic effects in the presence of β adrenergic agents. APD=action potential duration; EAD=early afterdepolarization.**

(Table 3). Figure 6 shows a proposed flow-chart of studies designed to assess the potential of drugs to prolong repolarization.

In vitro models

There are four broad categories of in vitro models: heterologous expression systems, disaggregated cells (studied acutely or in culture), isolated tissues, and the isolated intact (Langendorff-perfused) heart.

Since the vast majority of the drugs known to inadvertently (or intentionally in case of some antiarrhythmic drugs) prolong ventricular repolarization do so by blocking I_{Kr}, heterologous expression of the channel is a useful tool for studying drug effects. Various expression systems are available. Microinjection of ion channel RNA into *Xenopus laevis* oocytes is a well-established method for heterologous expression[42–43]. Ionic currents appear 1 to 3 days after injection and are measured with conventional two-electrode voltage clamp recordings. However, owing to their large size and membrane capacitance, *Xenopus* oocytes present limitations in measuring rapidly activating voltage-gated channels[44]. Furthermore, the IC50 for drug effects may be falsely over-estimated due to the relatively large volume of lipophilic material in the oocyte[44]. Mammalian recombinant expression systems are increasingly used, as they do not share these limitations of oocytes and can be evaluated at physiological temperature. Most studies have used human embryonic kidney cells (HEK293), mouse fibroblasts (C cells) and Chinese hamster ovary (CHO) cells, all of which have relatively little endogenous voltage-gated channel activity. When such models are used for drug studies, the effects of at least four different concentrations encompassing a 100–1000-fold range should be evaluated and the IC50 of both, the parent compound and its metabolites, should be precisely determined. Overall, the results from such studies should not be considered in isolation as an absolute criterion for deciding whether or not to continue further development. This is stated because drugs that prolong repolarization for reasons other than I_{Kr} block (i.e. increasing the plateau I_{Na}[45] or I_{Ca}[46] and/or decreasing I_{Ks}[47]) would not be identified as potentially proarrhythmic unless the latter currents are included as well.

Whereas the disaggregated cell is an ideal model for studying ion currents, its action potential duration variability even when paced at a constant cycle length, reduces its utility for studying action potentials[48]. It is here that isolated tissue studies serve an important purpose. In studying isolated tissues with microelectrodes, the species selected should be one for which adequate data exist that demonstrate similarity with human material. The species most frequently used are dog, rabbit, and guinea pig. For isolated tissue studies, canine mid-myocardium and Purkinje fibres appear most susceptible to the effects of I_{Kr} block. Endo- and epicardial muscle should be studied as well to ensure that the potential for dispersion is explored[26]. Any one of several 'pure' Ikr blockers can be used for comparison, and comparators may be chosen for which clinical studies have already demonstrated significant effects in human subjects (e.g. astemizole or cisapride). In addition, a range of cycle lengths should be studied. For both, these studies and the more complex models, below, attention should be paid to gender, given the demonstration both, in human subjects[6] and animal models such as the rabbit[49], of the greater QT-prolonging and arrhythmogenic effects of I_{kr} blocking agents in females.

For screening large numbers of compounds, the Langendorff-perfused guinea pig or rabbit heart studied with electrogram or monophasic action potential recording techniques also gives consistent information on I_{Kr} blocking drugs when compared to standard compounds[50,51]. Excess prolongation of repolarization in this model indicates potential problems caused by the drug. Failure to see excess action potential prolongation does not, however, provide complete security in excluding the risk of TdP. For example, in this setting one is

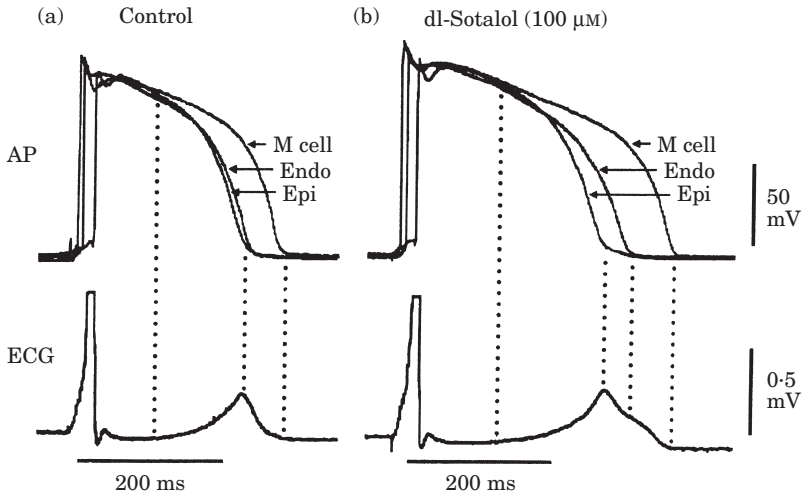

Figure 4 **Sotalol-induced long QT and torsade de pointes. Each panel shows action potentials recorded from epicardial (Epi), M region (M) and endocardial (Endo) sites (top), and a transmural electrogram simulating an ECG. The traces were simultaneously recorded from an isolated arterially perfused canine left ventricular wedge under control conditions (A) and in the presence of dl-sotalol (100 μM, 30 min; B). Sotalol produced a preferential prolongation of the M cell action potential leading to the appearance of a long QT interval in the ECG and the development of a large transmural dispersion of repolarization. Modified from Yan and Antzelevitch, *Circulation* 1998; 98: 1928–1936, with permission.**

unaware of the potential effects of metabolites. Effects of the new chemical entities on sinus rhythm should be carefully screened as K channel blockers frequently produce slight bradycardia. TdP-like polymorphic ventricular tachyarrhythmias can be induced in the isolated rabbit heart by reproducing conditions and circumstances that are clinically known to be associated with an increased propensity to develop TdP (i.e. hypokalaemia and bradycardia)[51–53].

In-vivo animal models

In vivo models can be studied using multi-lead ECG recordings in conscious or anaesthetized guinea-pigs, rabbits, dogs or pigs[54–56]. As in humans, QT duration should be measured from at least three successive beats. In dogs, T-wave morphology is highly variable which limits the possibility to study serial drug-induced changes in repolarization, unless rigorous attention is paid to maintaining the animal in the same position each time it is studied. Equations to correct QT duration for heart rate can be used, although the accuracy of the correction algorithms varies in different animal models[56]. More information can be obtained using QT-RR plots in the absence and presence of various drug dosages, or by pacing the heart at a constant rate. Telemetric recordings can provide a useful adjunct in intact animal studies.

Carlsson and co-workers[21,55,57] have shown that clofilium, almokalant, dofetilide and sematilide may induce marked QT prolongation and TdP-like polymorphic ventricular tachycardia in alpha-chloralose anaesthetized rabbits concomitantly treated with an infusion of the alpha-1-agonist methoxamine. A conscious dog model with TdP like polymorphic ventricular tachycardia has been described by Weissenburger and co-workers in which bradycardia and hypokalaemia were combined[58,59]. Bradycardia was achieved by chemically or electrically induced complete AV block, whereas hypokalaemia was induced over a period of weeks using high doses of diuretics. Vos *et al*.[60] recently described a canine model with chronic AV block exposed to d-sotalol where different pacing modes were used to mimic sequences of short/long/short intervals. Such sequences are typically observed in patients with acquired LQTS but have recently been shown to play a role in the genesis of TdP in patients with the congenital LQTS as well. Of interest is the demonstration by Vos *et al*.[60] that antiarrhythmic drugs having known proarrhythmic effects induce significant QT prolongation and torsade de pointes in this model, and the demonstration by Sosunov *et al*.[54] in the same model that an antipsychotic drug with I_{kr} blocking properties has a much lower QT prolonging or proarrhythmic effect. Hence, the model shows promise in discriminating the proarrhythmic effects of various Ikr blocking drugs.

Important to the understanding of the strengths and limitations of these models is the demonstration by Vos and associates[61] that AV block induces ventricular hypertrophy. Hence, arrhythmias induced by drugs in these animals impact on our expectations for the normal heart largely by inference, while directly impacting on the relationship between hypertrophic hearts and drugs.

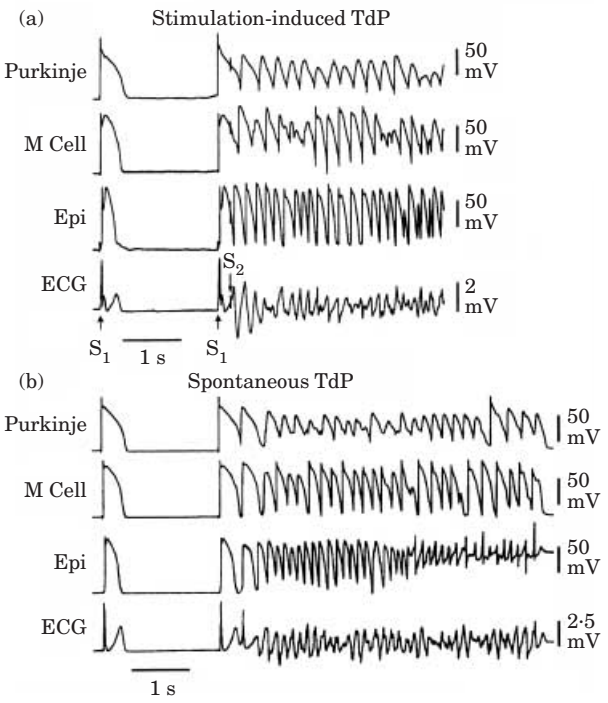

Figure 5 **Stimulation-induced and spontaneous torsade de pointes. Each panel shows a polymorphic ventricular tachycardia with features of torsade de pointes occurring following exposure of an arterially-perfused canine left ventricular wedge preparation to dl-sotalol (100 mol/L). Action potentials from the subendocardial Purkinje region, epicardial (Epi), and M region (M) were simultaneously recorded along the same of axis as the transmural electrogram. The preparation was paced from the endocardial site at a basic cycle length of 2000 ms. A: In the absence of spontaneous torsade de pointes, the arrhythmia could be readily induced by a premature extrastimulus applied to the epicardium, the site of briefest refractoriness. B: A spontaneous premature beat, originating from the deep subendocardium, initiated an episode of torsade de pointes. Modified from Yan and Antzelevitch, *Circulation* 1998; 98: 1928–1936, with permission.**

Moreover, it should be noted that while these models provide information that tends to increase or decrease one's understanding of the spectrum of drug effect, none will provide complete security with regard to drug effects in human subjects.

In light of the above, we stress the importance of not defining a single, standardized and uniform method for pre-clinical screening of the effects of drug effects on cardiac repolarization. Among the various methods available, none has demonstrated a predictive value that makes it clearly superior to others. In vivo methods introduce an intrinsic degree of variability and need for QT correction in relation to the heart rate. This may introduce an error of over-correction or under-correction depending on the equation used and the species. On the other hand, in vivo methods explore the potential effects of not only the parent compound but also of active metabolites (the exception being metabolites unique to man which must be studied in their own right in vivo and in vitro).

Finally, the potential risk / benefit ratio of any new chemical entity must be taken into account when a decision is made based on pre-clinical data. These pre-clinical data should be correlated with any clinical data available. Among the factors to be considered regarding the future development of a new chemical entity with demonstrated effects on ventricular repolarization, perhaps most important is the indication for the compound and the benefit it provides versus the risk it confers. Other factors may include the availability of alternative therapies with less risk and the margin of safety suggested by the pre-clinical data.

Clinical assessment of drug effects on repolarization

Phase I/II studies

In early Phase I/II studies, safety considerations should be directed primarily at the early identification of a change in repolarization, usually QT or QTc prolongation, which might herald the risk of proarrhythmia when the drug is administered more widely to a larger population of patients during Phase III studies[62,63]. Important questions during the early clinical phases of drug development include: (1) What electrocardiographic repolarization signal should be measured? (2) What threshold QTc signal is of concern, and what are the clinical implications of a small yet statistically significant QTc prolongation? (3) Since QTc quantifies a complex relationship between the duration of ventricular repolarization and heart rate, what are the heart rate correction issues for drugs that slow or accelerate heart rate? and (4) Which heart rate correction is preferred when evaluating the effects of a drug on ventricular repolarization?

Phase I clinical studies should be placebo-controlled trials that involve healthy volunteers who, however, may not be representative of the general population that will be exposed to the drug should it be approved and marketed (unless the drug is an antihistaminic or similar compound). Due to the increased risk of TdP in females, these studies should include sufficient numbers of females (with appropriate contraceptive precautions for women at risk of pregnancy). If there is any likelihood that the new compound will be used in children, they should also be studied at the appropriate time during the clinical development of the drug. The selection of children and decisions regarding the ages of those studied will depend on a number of ethical and personal issues, among them the potential for comprehension and co-operation, as well as parent/guardian involvement and approval.

The drug dosing should incorporate a reasonable dose-response range, with a short-term upper dosing

Table 3. Models for the assessment of drug effects on repolarization (see text for discussion)

Model	Advantages	Disadvantages
Heterologous expression systems	Ideal model for studying ion currents	Drug interaction with channel subunits has to be considered/assessed Model-related differences in IC50 Block of different or multiple channels difficult to assess Results should not be used as an absolute criterion for a 'go–no go' decisions
Disaggregated cells (studied singly or in culture)	Ideal model for studying ion currents	High APD variability when paced at a constant cycle length Methodological problems, i.e. altered action potential characteristics due to dedifferentiation Failure to see APD prolongation does not provide security
Isolated tissue	Ideal for screening large numbers of compounds Easty to change electrolyte concentrations and stimulation rates (hypokalemia and bradycardia facilitate I_{Kr} block) Easy identification of afterdepolarizations	M-cells and Purkinje fibres are most susceptible to I_{Kr} block, although endo- and epicardium should be studied as well to ensure that the extent of dispersion is explored. Failure to see APD prolongation does not provide complete security.
Isolated intact (Langendorff-perfused) heart	Ideal for screening large numbers of compounds Drug effects during sinus rhythm can be studied (Multiple) ECG and MAP recordings feasible TdP models available	Failure to see APD prolongation does not provide complete security
Intact animal (e.g. dog, pig, rabbit, guinea pig)	Studies in awake animals possible (dog) TdP models available	Expensive Not appropriate for screening

APD=action potential duration, TdP=torsade de pointes, MAP=monophasic action potential.

level as high as possible during careful safety monitoring. Plasma serum concentrations of the parent drug and relevant active metabolites should be monitored to obtain peak and trough values based on the known pharmacokinetics and the half-life of the drug and its metabolites. The duration of drug administration should continue until steady-state plasma concentrations (especially of active metabolites) are reached. Several serial 12-lead ECGs should be obtained at baseline and during follow-up after drug administration. In addition to recordings at regular intervals, the timing of these recordings should consider carefully the pharmacokinetic parameters and the concentrations of the parent drug as well as those of active metabolites.

Studies involving QT interval measurement should always be conducted under placebo control and the measurement should be processed by a laboratory experienced in good clinical practice standards and electrocardiography. Twelve-lead ECGs are preferable, as are digital recordings and storage. The measurement of the QT interval should always include the assessment of T wave morphology changes and appearance and/or disappearance of abnormal TU patterns. Since such patterns may occur in only some of the

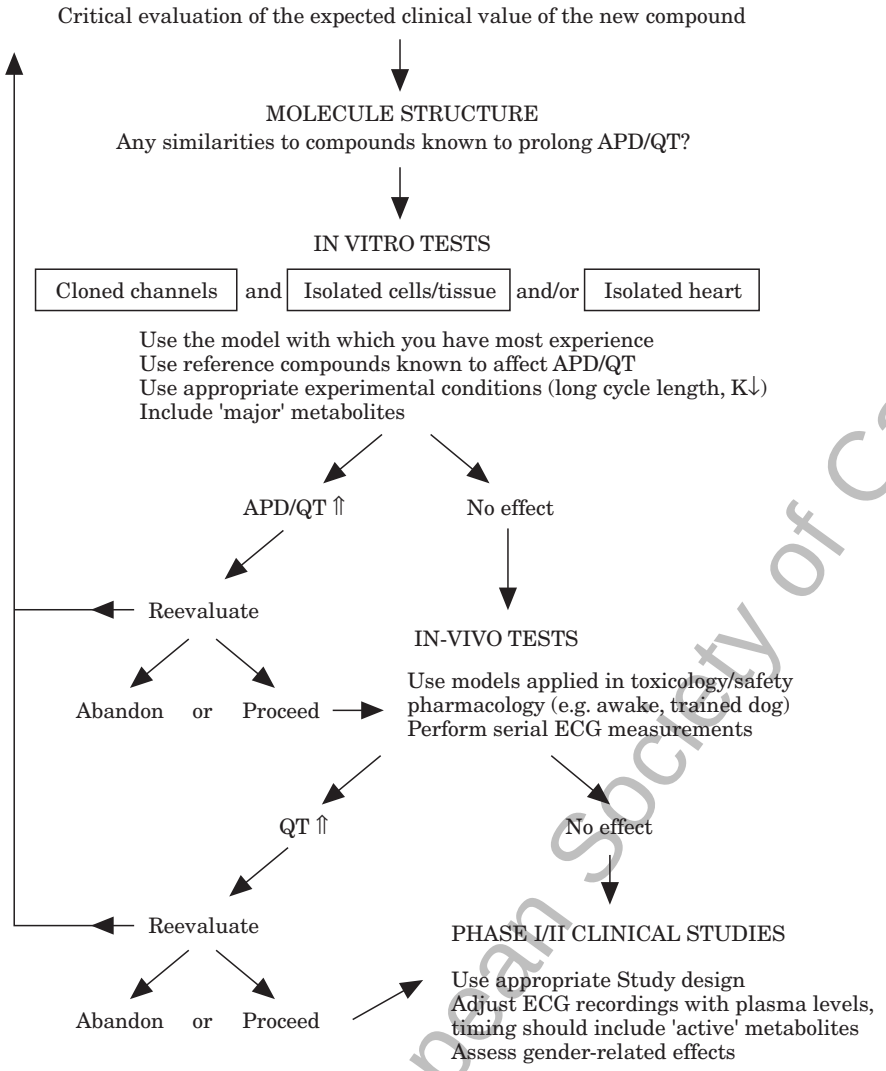

Figure 6 **Proposed flow-chart of studies necessary to assess the potential of drugs to prolong repolarization. *Note: This Figure is not meant to be used as a roadmap for testing but is an example of just one type of strategy. Depending on the individual compound(s) one is considering, other models and other sequences of testing may be more appropriate.**

electrocardiographic leads, the analysis of all 12 leads is preferable.

There is no clear consensus on methods for the measurement of the QT interval but in each study, the same method should be used. Multiple measurements in each ECG (e.g. 3 to 5 beats of each lead) are necessary to improve precision. The distribution of the maxima and minima of the QT interval among all 12 ECG leads is not stable and the selection of only one lead for measurement may create a selection bias. Measurement on computer screen seems to provide the highest precision.

Because of the lack of experience with algorithms for automatic QT interval measurement, evaluation by a qualified electrocardiographer should be mandatory. With manual measurement, a substantial proportion of the electrocardiograms (if not all) should be measured by two independent observers.

Since the duration of the QT interval is heart rate dependent, the evaluation of QT interval changes must always incorporate the consideration of the underlying changes in heart rate. Various heart rate correction formulae have been proposed (e.g. Bazett, Fridericia, Framingham, etc.)[64,65]. While these formulae are appropriate in standard clinical practice, e.g. for the diagnosis of long QT syndrome, their use in the evaluation of drug related QT changes may lead to either false positive or false negative findings. Non-linear regression analysis of the QT/RR interval data points is preferable (including the assessment of confidence intervals) as this documents QT interval changes independent of the underlying heart rate[66].

QT dispersion as determined from the maximum minus minimum QT intervals on the 12-lead ECG has not yet been adequately validated as a risk indicator of proarrhythmia. Increased QT dispersion, therefore is currently not recommended as a parameter to assess drug-induced alteration in ventricular repolarization. Only very substantial values of QT dispersion (e.g. >100 ms) seem to be a reliable indicator of repolarisation abnormalities.

The presence of pathological U waves complicates the determination of the precise QT interval duration. Often, the U wave overlaps with the T wave to such a degree that determination of the end of the T wave is not only impossible but raises the question OF whether the U wave should be included in the QT interval measurement. Although this will result in a reading of excessive QT interval duration, such an interpretation may be appropriate with regard to certain drugs.

From a safety point of view, there is no easy answer to the question as to how many subjects should be studied during Phase I/II trials. The sample size for Phase I/II studies is usually based on the need to characterise the clinical pharmacology of the drug with preliminary considerations of efficacy but with an anticipation that safety issues related to a major increase in QTc will most likely be identified. However, many issues arise here. For example, (1) there may be a small, yet significant increase in mean QTc. Whether this is meaningful, suggesting a potentially serious safety problem if the drug is subsequently approved for administration to a very large population, is controversial. (2) The number of subjects to be studied during Phase I/II trials for the purpose of safety is difficult to predict. It is suggested that if no adverse repolarization abnormalities are observed during preclinical testing, then a minimum of 100 subjects should be rigorously studied in early Phase I/II testing; if some minor yet consistent repolarization abnormalities are uncovered during preclinical or clinical testing, then 200 or more subjects should be studied[62]. (3) In Phase I/II trials, any individual who develops a prolonged QTc interval after drug administration that is generally considered to be a so-called outlier, takes on special significance. Such an outlier may reflect a true drug-related effect, i.e. an important signal; or the long QTc value may simply represent a random variation unrelated to drug administration. This issue requires careful attention, such that the subject should be rechallenged with the same drug to elucidate whether the effect on QTc is reproducible. If so, then further dose-response testing is indicated.

If early Phase I/II studies demonstrate no QTc safety concerns, then expanded Phase I/II testing is appropriate. If the age range of the initial study population was restricted, a broader age spectrum should be included in further studies. It is essential to include subjects with common clinical cardiac disorders, such as patients with coronary heart disease, hypertension, and congestive heart failure in these late Phase I/II studies if such patients are likely to receive the drug when it is marketed. Repeated doses may need to be administered to further substantiate the QTc safety of the drug if any questions had been raised during earlier testing. If the drug is metabolised by the hepatic P450 enzyme system, drug-interaction studies with appropriate inhibitors(s) of the isoform involved (for example ketoconazole and/or erythromycin in case of the cytochrome 3A4 isoform) are indicated, with particular attention to circulating drug levels and QTc effects[67,68]. During this phase of testing, high doses of the drug (as high as 10 to 50 times those recommend) may be cautiously administered.

A meaningful QT/QTc prolongation during Phase I/II studies is difficult to define in general terms. Due to the small number of subjects tested in these early studies, even a small change may be important. It has not been settled, whether a small but reproducible QTc prolongation in Phase I/II studies is indicative of a possible serious QTc-related proarrhythmia when the drug is utilized by thousands or millions of people after market approval. A single outlier with drug-induced QTc prolongation >500 ms or an increase by 60 ms or more from baseline after rechallenge during Phase I/II studies may be taken more seriously than a significant increase in the mean value. Similarly, a statistically significant increase in mean QTc as small as 6 ms between baseline and maximal drug effect at the planned (recommended) drug dose may be important[69]. Estimation of the importance depends on risk–benefit considerations for the intended use of the drug and the availability of alternative therapies with lesser risk. For example, if a drug is effective in treating oncological disorders, then some degree of QTc prolongation may be acceptable. On the other hand, if a drug will be marketed to treat allergic rhinitis in otherwise healthy people, then even minor QTc prolongation may not be acceptable, especially if alternative drugs without QTc-prolonging effects are available.

If small but significant drug-related repolarization effects are observed during Phase I/II studies, additional preclinical studies are needed to clarify the effect and to evaluate a possible underlying mechanism. For example, if a small degree of QTc prolongation is identified in early clinical studies, specific in-vitro expression studies if not previously performed, can help to determine if the drug has any influence on the I_{Kr} ion channel, an ion channel which has frequently been implicated in drug-induced repolarization abnormalities. Dose-response studies can be quickly carried out in the in-vitro setting.

It is likely that in the future a spectrum of non-invasive electrocardiographic repolarization parameters will be utilized in drug evaluation since digital ECGs are now available. Quantitative computerised processing and analysis of digital ECGs include QT/U intervals, QT/RR relationships, T-wave morphology on ECG and/or VCG, spatial heterogeneity of repolarization, and dynamic beat-to-beat T-wave changes (T-wave lability and microvolt T-wave alternans). These measurements are likely to supplement and possibly replace the manual QTc measurements of today. Such analytic techniques may identify drug-related repolarization effects more accurately and reliably than current

methods, thus improving the safety screening of drugs in Phase I/II clinical studies.

Phase III studies

If findings from Phase I/II studies are indicative of a risk, recording ECGs in all the patients in Phase III studies should be seriously considered in order to better characterize the QT safety of the drug during its post-marketing clinical use. However, these Phase III studies are highly efficacy-orientated and their results may be strongly influenced by inclusion and exclusion criteria. Therefore, it is important to consider how representative the clinical trial population of the ultimate target population is. It is helpful to include in late Phase II and Phase III studies subjects with common clinical cardiac disorders, such as patients with coronary heart disease, hypertension, and congestive heart failure if such patients are likely to receive the drug when it is marketed. For the same reasons, the inclusion of patients with other co-morbidities and co-medications should also be considered.

Post-marketing surveillance

Demonstration of both short- and long-term safety and efficacy is increasingly necessary to obtain approval of new drugs. Any conclusion that a drug is 'safe' should be reserved until post-marketing surveillance data are reviewed. Only when large numbers of patients are treated, many of whom will be taking multiple medications, who have different co-morbidities, and who are subject to other conditions that were not represented in the original clinical trial population, will adverse effects become manifest that were otherwise not recognized, appreciated or expected.

Regulatory perspectives

There has been an increasing regulatory concern about drug-induced QT prolongation and TdP. Recommendations and guidelines for the pre-clinical and clinical screening and assessment of any new drug with regard to its potential electrophysiological effects are urgently needed. In December 1997, the Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products issued a document entitled '*Points to Consider: The assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products*'[62]. This CPMP document was a strong signal to drug developers that the problem of QT interval prolongation and/or TdP by non-cardiovascular drugs is now a very significant one and, thus, requires careful scrutiny and research efforts for any compound undergoing development.

Based on experience with previously approved compounds, questions arose as to whether there had been any signals during the development of these drugs that may have pointed to the possibility of their proarrhythmic effects, and why such effects had not been detected during pre-clinical and clinical development programmes. Another question was whether one can rely on clinical trials alone to identify the risk of proarrhythmia or whether additional or alternative strategies should be used to facilitate prediction of this risk.

In the present environment, it is perhaps unlikely that any non-cardiovascular or non-antiarrhythmic drug associated with clinically documented TdP during its clinical evaluation will reach a regulatory submission stage unless it offers unique and otherwise unavailable clinical benefits. Rather than the frequency of TdP, the regulatory authorities are most often left with evaluation of the clinical significance of the degree and frequency of QT prolongation observed in the clinical trials without having observed any cases of TdP. Another problem is the evaluation of cases of sudden death in patients taking any of several non-cardiac drugs known to prolong repolarization. In these cases, it is frequently difficult if not impossible to create a link between QT prolongation and the mechanism of subsequent death if no intervening TdP has been observed.

Apart from an ever-increasing number of 'proarrhythmic non-cardiovascular' drugs, regulatory concerns have been intensified because of the increasing size of the population that may be at risk. This applies to the elderly who frequently receive multiple drugs with the potential for interaction, and to patients with cardiac, renal, hepatic or other predisposing diseases which may increase the risk of abnormal drug elimination and metabolism and create the potential for increased susceptibility to proarrhythmia. Patients with myocardial hypertrophy or heart failure with or without abnormalities in repolarization represent other high risk groups, and in all such groups, the independent risk conferred by female gender must be considered.

From the regulatory perspective, it is vitally important that the distinction between drug-induced and spontaneous QT interval prolongation is carefully made. If this is not done, a harmless drug may be inappropriately labelled and denied to needy patients. On the other hand, when repolarization abnormalities go unrecognized, the public may be placed at unnecessary risk. The overall risk/benefit assessment of a new drug that prolongs the QT interval depends on consideration of (1) the frequency and magnitude of the QT changes observed and related adverse events detected in the clinical programme, (2) the safety risks presented by the drug relative to its therapeutic potential, and (3) the availability of clinically effective alternatives with a more favourable safety profile.

The labelling implications for a drug that prolongs the QT interval are considerable. Detailed consideration of the above factors should enable a final decision to be made regarding the approvability of a new medicinal product, and where appropriate, the conditions for

clinical use to be included in its Summary of Product Characteristics (prescribing information). These conditions could have an impact on dosage schedules (maximum unit and daily doses), dose titration schedules, contraindications in terms of concurrent drugs and concurrent diseases, special warnings and precautions for use (special populations and monitoring and/or follow-up requirements), detailed descriptions of pharmacokinetic and pharmacodynamic interactions, listings of undesirable effects consequent to prolongation of QT interval, and means for monitoring and managing patients who experience an overdose of the drug.

This regulatory management of drugs which prolong the QT interval is only one aspect of an overall strategy aimed at containing or minimizing risk. In the final analysis, whether or not a patient will benefit from detailed prescribing information depends on the patient and his/her prescribing physician. Experience regarding physician compliance with prescribing restrictions and monitoring requirements to date is not encouraging. In a number of surveys relating to terfenadine[70,71] and cisapride[72], there was significant, inappropriate prescription of these drugs to patients at increased risk. In addition, monitoring requirements such as baseline and/or periodic ECGs had been ignored in many cases. Regulatory authorities have been sensitized to issues such as how and to what extent there is likely to be compliance with complex prescribing information and monitoring requirements. These considerations are attaining increased importance in the approvability of new drugs and in reviewing the safety profiles of older drugs.

Conclusions

There is increasing awareness that drugs used for non-antiarrhythmic and non-cardiovascular indications may have significant effects on repolarization and may cause serious ventricular tachyarrhythmias under specific circumstances. For new drugs, the effects on the QT interval should be identified and, if possible, quantified during pre-clinical and clinical development. Post-marketing surveillance data of approved and marketed drugs provide additional important information about drug safety. In addition, clinicians and patients should be aware of this risk of prolongation of repolarization and take precautions to further minimize it. Academic centres should be encouraged to develop new technologies for objective assessment of the repolarisation patterns including the diagnosis of the presence of pathological U waves.

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Appendix

Other speakers in the sessions and chairs of the workshops who contributed significantly and have to be considered as co-authors (in alphabetical order): Jean Thierry Barbey, MD; Jacques Barhanin, MD, PhD; Jerry L. Bauman, PhD; Ulla Björkroth, MD; Arthur M. Brown, MD, PhD; Leif Carlsson, PhD; Thomas J. Colatsky, PhD; Börje Darpö, MD, PhD; Milou-Daniel Drici, MD, PhD; Robert Fenichel, MD, PhD; Stefan Kääb, MD; André Kléber, MD; Samuel Lévy, MD; Thomas Meinertz, MD; Silvia G. Priori, MD, PhD; Michael Rubart, MD; Michael C. Sanguinetti, PhD; Peter J. Schwartz, MD; Eric Schulze-Bahr, MD; Jan Tijssen, MD; Jeffrey A. Towbin, MD.

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