Drug-Induced *Torsade de Pointes* and Implications for Drug Development[1]

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Running Title: **Drug-Induced *Torsade de Pointes***

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[1] This document is here presented approximately as it was submitted to the *Journal of Cardiovascular Electrophysiology,* where it was published in 2004 on pages 475-495 of Volume 15, Issue 4. This version omits the numerous rhetorical, grammatical, and typographic errors that were introduced in the editing process at *JCE.* In addition, it includes suggestions (by RRF, not to be interpreted as the views that the whole group would necessarily endorse) as to how it might be extended if it were to be reissued. The new suggestions appear in red, mainly as footnotes.

ABSTRACT

Torsade de pointes is a potentially lethal arrhythmia that occasionally appears as an adverse effect of pharmacotherapy. Recently-developed understanding of the underlying electrophysiology allows better estimation of the drug-induced risks, and explains the failures of older approaches through the surface electrocardiogram.

The article expresses a consensus reached by an independent academic task force on the physiologic understanding of drug-induced repolarization changes, on their preclinical and clinical evaluation, and on the risk-benefit interpretation of drug-induced *torsade de pointes.*

The consensus of the task force includes suggestions on how to evaluate the risk of *torsade* within drug development program. Individual sections of the text discuss the techniques and limitations of methods directed at drug-related ion-channel phenomena, investigations aimed at action potentials changes, preclinical studies of phenomena seen only in the whole (or nearly whole) heart, and at interpretation of human electrocardiograms obtained in clinical studies. A final section of the text discusses drug-induced *torsade* within the larger evaluation of drug-related risks and benefits.

1 Overview

1.1 Introduction[2]

Torsade de pointes (from the French for "twisting of the points") is a polymorphic ventricular tachycardia seen in the setting of QT prolongation. The electrocardiographic pattern (Figure 1) is distinctive, sometimes described as a sine wave within a sine wave. The pattern is called "twisting" because when the peaks are at their smallest in one lead, they are generally at their largest in another, as if the several leads were different views of a vibrating string whose plane of vibration was being slowly rotated about the long axis of the string.
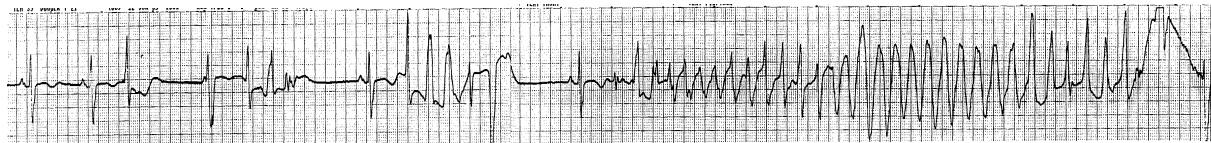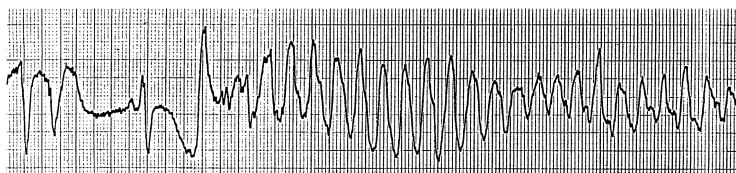
Figure 1, *torsade de pointes, in patients receiving dofetilide (top panel) and sotalol (bottom panel).*

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[2] A new organizing principle, perhaps allowing the original contents of the paper to be better understood in context, is the notion that there are several different possible tasks related to drug-induced changes in ventricular repolarization, and the several tasks present different challenges.

(1) Most of the paper is concerned with **determining the extent to which a drug is likely to induce** *torsade de pointes***;** but

(2) some of the paper is concerned with **obtaining a precise estimate of the extent to which a drug prolongs the electrocardiographic QT interval.**

(3) We touch tangentially on the task of **protecting subjects and patients in clinical trials** from *torsade de pointes* and its consequences, but

(4) we say nothing at all about the harder task of **protecting free-ranging patients**, and

(5) the paper is not directly concerned with the task of **meeting current regulatory requirements** for drugs seeking registration. This task might be expected to resemble task (1), but it is now closer to an uninformed version of (2).

Like some other ventricular tachycardias, *torsade* is often self-limited, but it can persist, deteriorate to ventricular fibrillation, and thereby lead to sudden death. It is more common in women, in patients with hypokalemia,(1) in patients with certain congenital syndromes mentioned below, and in several other settings. This article describes an approach to *torsade* as an adverse effect of pharmacotherapy.

Some antiarrhythmics (including dofetilide, quinidine, and sotalol) induce *torsade* in up to a few percent of all patients who receive them.(2) These drugs are intended to affect cardiac electrophysiology, so the frequent unintended occurrence of pro-arrhythmia should not be surprising. For the most part, we focus our discussion on *torsade* as an adverse effect of drugs other than antiarrhythmics, where electrophysiological effects might be expected to be rare.

Indeed, such effects are rare. Astemizole, cisapride, grepafloxacin, terfenadine, and terodiline were each withdrawn from marketing in all or some countries because of drug-induced *torsade,* but the total number of attributable cases of *torsade* with each of these drugs was no more than a few dozen, out of millions or tens of millions of patients exposed. Less publicly, real or perceived risks of *torsade* have caused other drug-development programs to be aborted or greatly delayed. Could these losses (of a few lives and several billion dollars) have been averted?

1.2   Monitoring for torsade

Since *torsade* is the phenomenon of concern, one might hope to screen drugs by simply being alert for the occurrence of *torsade* during the human trials in drug development. However, because *torsade* is usually so rare (with non-antiarrhythmics, less than one case per 10 000 or 100 000 exposures(2)), little reassurance is provided by the non-observation of *torsade* among the 2000–3000 subjects in a typical program, let alone the 1500 subjects recommended in guidelines of the International Conference on Harmonization.

Even after marketing, when the rate of exposure is greatly increased, the lack of controls and reduction in intensity of monitoring may make *torsade* difficult to detect. Syncope and sudden death may be observed, but it may be difficult to determine that these events are increased in frequency over the background incidence in the population receiving a drug. When an event occurs in a patient taking multiple drugs, it may be difficult to choose which of them to hold responsible.

Torsade is hardly unique in being an adverse drug effect of great concern even though its incidence is low. Chloramphenicol-induced aplastic anemia, hydrochlorothiazide-induced pancreatitis, and angiotensin-receptor-blocker-induced eosinophilic nephritis are similarly rare. A distinguishing characteristic of *torsade* is that its mechanism has been at least partially understood, so it is tempting to focus upon early manifestations of the mechanism, and to use these manifestations as predictors of *torsade*, overcoming the rarity of the clinical arrhythmia. Some predictors might be usable in earlier stages of drug development, both reducing the risk to human subjects and allowing development funds to be shifted to other candidate pharmaceuticals.

1.3   Working with the human QT interval

Inasmuch as *torsade* is (by definition) always preceded by QT prolongation, QT measurement is an obvious candidate as a predictor. The QT duration can be measured in most subjects, so such measurement might be more efficient than waiting for rare events.

As further described in Section 5 below, however, useful QT measurements are more difficult to obtain than is generally acknowledged. Even after precise measurement and careful adjustment for physiological co-factors, interpretation may be difficult. For example, some drugs can cause substantial prolongation of the QT interval but have rarely (amiodarone(3-5)) or never (pentobarbital,(6, 7) verapamil) been associated with *torsade* or other malignant tachyarrhythmias. Also, modern techniques have revealed that small drug-induced QT prolongations are ubiquitous, but we know of no example of *torsade* induction by a drug that — despite overdose or metabolic interference — causes *only* small QT changes.

1.4   Biological model

If *torsade de pointes* is too rare to be awaited, and if QT prolongation in human subjects is only a mediocre predictor, then decision-making must be based (at least in part) on other observations. These other observations can be credibly pertinent only in the light of an accepted biological model of how *torsade de pointes* arises. Parts of our current model can be called classical, but other parts reflect results that have been obtained only recently.

1.4.1   Cardiac ion channels

All the electrical activity of the heart starts in voltage-gated ion channels. Ion flux through these channels causes a cell's transmembrane voltage to vary over time, and the functions of channels can be altered by the presence of drugs. Drugs' interactions with ion channels can be studied by a variety of techniques described below in Section 2. Interference with the normal function of certain of the ion channels is necessary, but not sufficient, for the induction of *torsade*.

1.4.2   Action potentials

A voltage-gated ion channel is normally open only within a set range of transmembrane voltage, and the charges carried by ions moving through the channel cause the cell's transmembrane voltage to change. As a result, opening any channel begins a process that will inevitably lead to its closing and to the opening and/or closing of other channels as well, so the cell enters a stereotyped sequence in which the intracellular voltage rises from its resting level (the cell **de**polarizes) and then returns to the resting level (the cell **re**polarizes). Each such excursion is called an **action potential.**

The surface electrocardiogram sums the action potentials of all of the cells of the heart. Conduction delays between parts of the myocardium might in principle allow normal action potentials starting at different times to sum to an electrocardiogram in which repolarization — the QT interval — appeared to be prolonged, but this phenomenon does not occur in electrocardiograms considered to have interpretable QT intervals. In interpretable electrocardiograms, QT prolongation is a manifestation of action potentials that are themselves prolonged, in at least some region of the ventricular myocardium. Prolongation of action potentials is necessary, but not sufficient, for the induction of *torsade*. The techniques and limitations of action-potential studies are further discussed in Section 3 below.

1.4.3 Transmural dispersion of repolarization

The action potentials of uninjured adjacent cells of the same kind are likely to have the same form and duration. On the other hand, cells of different kinds express different mixtures of ion channels, and they therefore display different resulting action potentials, in the native state or as affected by drugs. In particular, every cross-section of the normal myocardium in some species (including humans) contains at least three different populations of cells, with different native electrophysiological properties and different responses to drugs. When adjacent cells' action potentials are more than slightly different in duration, the scene is set for reentrant arrhythmias, notably *torsade*.

Torsade can be reproduced in whole animals, in isolated-heart preparations, and even in preparations that use only a portion of a ventricle. These techniques are described in Section 4 below.

1.5 Structure of the article

As noted variously above, the next few sections of the article discuss the techniques and limitations of methods directed at ion-channel phenomena (Section 2), at action potentials (Section 3), at phenomena seen only in the whole (or nearly whole) heart (Section 4), and at interpretation of human electrocardiograms (Section 5). In Section 6, we discuss the place of drug-induced *torsade* within the larger evaluation of drug-related risks and benefits.

2 Ion-channel effects

Ion-channel studies are the lowest-level studies that are pertinent to the prediction of *torsade de pointes*, and they are attractive for their simplicity. Some ion-channel studies can be performed by automated, high-throughput apparatus, using only microgram quantities of drug. These relatively inexpensive studies can be performed early in the drug-development process, perhaps helping the developer choose among a portfolio of candidate compounds.

Twenty-odd different types of ion channels have been found in the human heart, but nearly all the drugs associated with human *torsade* have — whatever their effects on other currents — turned out to be blockers of I_{Kr}, the (repolarizing) rapid delayed-rectifier potassium current. Three other currents (the depolarizing currents I_{CaL} and I_{Na} and the repolarizing current I_{Ks}) are commonly studied, and have been shown to contribute to the QT-prolonging effects of many drugs and toxins. I_{Na} and I_{Ks} are also of interest because of their demonstrated role in the congenital long-QT syndromes.

2.1   Implications of findings in patients with congenital LQT syndromes

Much of our current thinking about drug-induced ion-channel effects in humans has been influenced by our knowledge of the congenital long-QT syndromes.(8) Patients with these syndromes are at risk of *torsade* and sudden death, with about half of them sustaining major arrhythmic events before the age of 40. These patients are thus at high risk by the standards of everyday life, but their event-free longevity is measured in decades. It should no longer be surprising that *torsade* is rarely seen in a clinical trial of typical duration, even when the trial exposes subjects to a drug that effectively simulates one or another of the congenital syndromes.

Although many different types of human ion channels have been identified, only four currents (the depolarizing current I_{Na} and the repolarizing currents I_{Kr}, I_{Ks}, and I_{K1}) are affected in any of the common congenital syndromes. (Mutations in a non-ion channel encoding gene, Ankyrin B, cause a long-QT syndrome through mechanisms that are not yet well understood.(9))

Each of the congenital syndromes is caused by dysfunction of the product of a specific gene, and thus a specific channel. For example, the LQT2 syndrome is caused by dysfunction of the **HERG** protein that, assembled into a homotetramer of 4 identical HERG units, forms the I_{Kr} channel. The congenital long-QT syndromes are in this way simpler than most drug-induced syndromes, inasmuch as most drugs have effects on multiple channels.

Each of the congenital syndromes is heterogeneous, however, in ways that have no direct analogs among the drug-induced syndromes. Two patients with the same congenital LQT syndrome are unlikely to have the same mutation. As of mid-2003, the seven congenital syndromes were known to arise from more than 300 different mutations.(10)

Also, the simple monogenetic inheritance of the mutations is not reflected in simple Mendelian inheritance of the phenotypic manifestations. In a family carrying a known LQT mutation, the carriers will typically have QT intervals ranging from normal (in about a third of carriers) to grossly prolonged. The

frequency of arrhythmic events is elevated in mutation carriers, even in those with normal QT intervals. It increases with increasing QT interval in some syndromes, but not in others.(11-13)[3]

The mutations associated (in at least some patients) with frank QT prolongation and spontaneous arrhythmias are not the only important genetic defects in human genes related to ion channels. Mutations (present in < 1% of the population) and polymorphisms (present in ≥ 1% of the population) of these genes are widespread, especially in certain subgroups. Some of these gene variants may be clinically silent until the patient is exposed to a drug that, in a person with a normal genotype, would have no pro-arrhythmic effect. Splawski *et al.*, for example, found a specific ion-channel polymorphism present in 57% of 23 African-American patients who had sustained arrhythmias (many drug-induced), but in only 13% of 100 race-matched controls ($P < 0.000\ 028$).(18) Similarly, among 98 unselected patients who had had drug-induced *torsade,* Sesti *et al.*(19) found that 3 had subclinical mutations of *KCNE2,* the gene that is implicated in congenital syndrome LQT1. Some of the mutations and polymorphisms that have been implicated in these and similar cases are listed in Table 1.[4]

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[3] Patients with a related syndrome associated with abnormally *short* QT intervals have a similarly elevated risk of premature sudden death, casting further doubt on the use of QT duration as a simple predictor.(14-17)

[4] Possibly we should mention the difficulty of screening for these mutations, especially in view of the possibilities of chimerism.(20)

Gene	Coding effect (reference)	Drug	Remarks
KCNE2	T8A(21)	quinidine	allele frequency 1.6%
KCNE2	T8A(19)	sulfamethoxazole/ trimethoprim	allele frequency 1.6%
KCNE2	**Q9E**(21)	clarithromycin	
KCNE2	**M54T**(19)	procainamide	
KCNE2	**I57T**(19)	oxatomide	
KCNE2	**A116V**(19)	quinidine	
KCNH2	**P486R**(22)	quinidine	
KCNH2	**R784W**(23)	amiodarone	
KCNQ1	**Y315C**(24)	cisapride	
KCNQ1	**R555C**(25)	terfenadine (1) disopyramide (1) mefloquine (1) diuretics (1)	**3 families, 5 events**
KCNQ1	**R583C**(23)	dofetilide	
SCN5A	**G615E**(23)	quinidine	
SCN5A	**L618F**(23)	quinidine	
SCN5A	S1102Y(18)	various drugs	allele frequency among African-Americans 13%
SCN5A	**F1250L**(23)	sotalol	
SCN5A	**V1667I**(26)	halofantrine	**4 carriers with QT prolongation, one symptomatic with drug**
SCN5A	**L1825P**(27)	cisapride	

Table 1, mutations (in boldface), polymorphisms, and *torsade de pointes*

2.2 Technique

Drug-channel interactions, like other drug-receptor interactions, follow the familiar rules of mass action, so a drug's effect on a channel becomes detectable, increases, and finally reaches saturation as drug concentrations increase over (typically) 2–4 orders of magnitude. For convenience, the potency of an interaction is commonly communicated by citing the **IC_{50}**, which is the drug concentration at which the current magnitude is halved.

No method of evaluating drug-channel interactions could be cheaper, or require smaller quantities of the drug, than one performed computationally. In the case of the I_{Kr} channel, some investigators have identified common 3-dimensional features of known channel-blocking drugs, and they have used these features to "train" a model that was then tested on other compounds.(28, 29) By comparing mutant and wild-type channel

proteins, other investigators have identified the binding sites of known channel blockers, and they have then modeled possible interactions between other drugs and these sensitive sites on the channel protein.(30) These *in silico* models are promising, but they cannot yet replace studies of living cells.

2.2.1 Voltage-clamp techniques

2.2.1.1 Preparations

Until recently, most ion-channel studies have been performed using isolated single cells, usually cardiac myocytes, in which the channel of interest was naturally present. The use of cardiac myocytes guarantees that any as-yet-undefined auxiliary subunits or intracellular factors that may modulate channel activity are intact. On the other hand, the use of isolated myocytes poses technical difficulties, including the need to isolate fresh myocytes on each experimental day and possible overlap of the current of interest with other ionic currents.

I_{Kr} is the current most frequently studied. I_{Kr} can be measured in isolated ventricular myocytes from a number of species, and guinea pig, rabbit, and dog are the most commonly used. Rats and mice have a very small I_{Kr} and are not appropriate species for this purpose. Recording I_{Kr} from isolated myocytes requires that other currents that are normally activated over a similar voltage range be eliminated with specific blockers or reduced by special voltage-clamp protocols. For example, Ca^{++} currents can be eliminated by dihydropyridines, and Na^+ current can be blocked by tetrodotoxin or eliminated by holding the membrane at a voltage level at which Na^+ channels are inactivated. I_{Kr} can be measured as activating current during a depolarizing pulse, or as deactivating tail currents during repolarization from a positive test potential.

Instead of using myocytes from one or another non-human species, many investigators have more recently used non-cardiac mammalian cells that have been made to express human ion channels by transfection with human DNA. The cells can be chosen for their ease of maintenance in culture and ease of high-resistance seal formation with microelectrodes; this approach also eliminates the complexities of interference from currents other than the one of interest, although ancillary proteins — whose expression may vary among cell types — have been reported to affect the potency or kinetics of I_{Kr} block.(19, 31) The most frequently used cells have been human embryonic kidney cells and Chinese-hamster ovarian cells. For study of I_{Kr}, most investigators transfect with *HERG* cDNA alone, but others co-transfect with cDNA encoding MiRP1, a putative accessory protein of the I_{Kr} channel.(21, 32)

Instead of using mammalian cells, some investigators have undertaken drug-effect studies on *Xenopus* oocytes injected with *HERG* cDNA. The drug concentrations needed to achieve channel-blocking effects in these cells are typically about an order of magnitude greater than those needed in other preparations, so it is difficult to integrate results obtained in *Xenopus* oocytes with the results of other studies.

Automated patch-clamp techniques that enable simultaneous electrical recording from multiple single cells at once are still in the development and testing stage, but some are expected to be commercially available

in early 2004. Combinations of newly-developed electrode arrays, automated perfusion systems, and novel data analyses promise to enable high-throughput screening. The availability of these methods may greatly increase the number of compounds that can be evaluated by voltage clamp, but their anticipated high cost will (at least initially) be a barrier to widespread use.

2.2.1.2 Measurement

Over the course of each experiment, the cells of the preparation lose their viability, and all of the current amplitudes gradually decline. These declines are annoying at best, but they become critical during the study of drugs that penetrate cells slowly and exert their effects — as most HERG blockers are believed to do — on the intracellular side of the affected channel(s). To decrease the rates of these declines, most investigators prefer to work with the preparation at room temperature. An IC_{50} derived at room temperature may differ from that derived at physiological temperature by almost an order of magnitude, but similar differences are sometimes seen at the same temperature in different preparations, or in the same preparation in the hands of different investigators.(33)

Many drugs block channels in a frequency-dependent manner, which may translate into a heart-rate-dependent change in QT interval. Thus, it is useful to determine if channel block varies with pulsing frequency (*e.g.,* 0.1 *vs.* 2 Hz).

The concentration-effect relationship of a drug and an ion channel is estimated by gradually increasing the drug concentration, generally escalating in half-log increments from an approximate no-effect level until at least 80% block is attained. The preparation can be calibrated by including a potent, specific blocker (*e.g.*, in the case of I_{Kr}, dofetilide or E-4031) in the same study. The relationship between drug concentration and percentage of current blocked can be fitted to a Hill equation to determine IC_{50}.

2.2.2 Other techniques

Radioligand binding assays are routinely used to quantify the interaction of new drugs with some channels (*e.g.,* with L-type Ca^{++} channels), but they are less widely used to assay for blockade of I_{Kr}. However, competitive displacement of ^{3}H-dofetilide or similar compounds from membranes of cells transfected with *HERG* cDNA appears to be a robust assay.(34) A disadvantage of radioligand displacement assays is that they may not detect a signal for drugs that bind to domains of HERG distinct from the site used by the radioligand. Also, there is concern that in some cells ^{3}H-dofetilide may bind to sites other than the HERG channel.(35)

Potassium channels are also highly permeable to rubidium, so measurements of drug effects on the flow of nonradioactive Rb^+ (using atomic absorption spectroscopy) or of radioactive [86]Rb^+ (using standard tracer techniques) have been used as assays of drug effects on these channels.(36) Suppression of Rb^+ flux is more predictive of genuine HERG channel block than fluorescent-dye-based assays,(37) but neither technique is sensitive, and probably neither should be used if quantitative results are desired.

2.3 Interpretation

Of the three most common congenital long-QT syndromes, only one (LQT2) is the result of dysfunction of I_{Kr}. In animals, LQT1 can be simulated by blockade of I_{Ks}, and LQT3 can be simulated by administering reagents that prevent normal termination of I_{Na}. Sooner or later, a drug intended for human pharmacotherapy will prove to cause *torsade* even though it has no effect on I_{Kr}.

On the other hand, the prominence of I_{Kr} blockade in the drug-induced human syndromes is probably not a chance finding. The I_{Kr} channel is distinguished from other potassium channels by a large, funnel-like vestibule, and (probably more important) by the prominence of aromatic amino acids along the center of the channel. These features may make it easier for many small molecules to enter and sometimes to block the passage of ions.(30) Whatever the underlying biochemical reason turns out to be, the current emphasis on I_{Kr} vis-à-vis other currents does not seem inappropriate.

Not many human drugs have IC_{50} for I_{Kr} blockade < 10 nM; every such drug (*e.g.*, astemizole, IC_{50} = 0.9 nM;(38) terodiline, 3.7 nM (Yang and Roden, unpublished observations); dofetilide, 3.9 nM;(39) cisapride, 6.5 nM(40)) seems to have turned out to cause *torsade*. At the other extreme, *torsade* has been reported with *d*-sotalol (100 µM (41)), although not with cetirizine, 108 µM (42) or ciprofloxacin, 966 µM (43).

In the much more densely populated middle ground, the degree of I_{Kr} blockade has proven to be an imperfect predictor, failing to distinguish verapamil (IC_{50} = 143 nM (44)) and loratadine (173 nM (45)) from terfenadine (150 nM (46)) and quinidine (0.2–1.0 µM at normal potassium levels (1, 46)). Evidently, some of the mechanisms leading to *torsade* emerge only at higher levels of organization.

Verapamil, for example, is a moderately potent I_{Kr} blocker (IC_{50} = 143 nM),(44) and thus it might be expected at ordinary concentrations to prolong repolarization, perhaps a first step toward induction of *torsade*. In fact, because verapamil blocks L-type Ca^{++} channels with similar potency,(47) the usual effect of verapamil is to *shorten* repolarization, and verapamil has never been associated with tachyarrhythmias.[5]

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[5] The congenital short-QT syndromes provide further evidence of the looseness of the link between QT duration and risk. Patients with these syndromes might naively be expected to be more electrophysiologically stable than normals, but in fact they have an elevated risk of premature sudden death.(14-17, 48)

It was said (need reference) that as of late 2004 only 30 short-QT patients had been reported, but that this is about as many LQT patients had been reported during the first 12 years after those syndromes were first described. In the same vein, pharmacologic hERG **agonists** are now beginning to be described.(49)

3   Action-potential studies

Figure 2 shows the relation between the action potential in three different (simulated) canine ventricular myocytes, with parallel displays of the calculated currents through the most important of
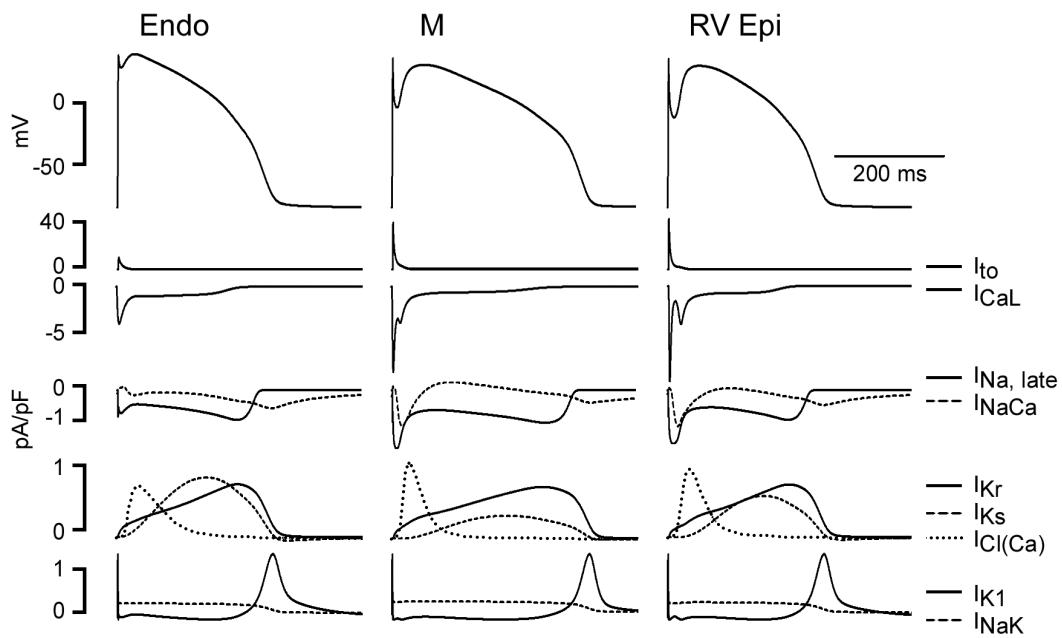

Figure 2

the contributing ion channels, where I_{to} is the transient outward K^+ current; I_{CaL} is the L-type Ca^{++} current; I_{Na} is the sodium current (the early sodium current is not seen in the figure because its initial peak is so much larger [typically 200 pA/pF] than any of the other peaks shown); I_{NaCa} is the Na^+-Ca^{++} exchange current; I_{Kr} is the rapid delayed-rectifier K^+ current; I_{Ks} is the slow delayed-rectifier K^+ current; $I_{Cl(Ca)}$ is a transient outward Cl^- current, activated by intracellular Ca^{++}; I_{K1} is the inward rectifier K^+ current; and I_{NaK} is the sodium-potassium exchange (the "sodium pump").

It may not be meaningful to ask, without specifying the tissue to be studied, what effect a drug has on "the" action potential. For example, the deep notch that immediately follows the initial peak of the **epi**cardial action potential (rightmost column) in Figure 2 is the result of the strong I_{to} shown just below. In the **endo**cardial action potential (leftmost column), only a tiny notch is seen, because I_{to} is scarcely present in these cells. A drug that blocked I_{to} might therefore be expected to affect the **epi**cardium by making its action potential resemble that of the **endo**cardium; the same drug might be expected to have little or no effect on the electrical properties of the **endo**cardium.

The most frequent drug-induced changes in action potentials are not major morphological changes of the sort just described. Sometimes, the action potential can be shortened by drugs that block depolarizing currents

or prevent the normal closure of repolarizing channels. Conversely, the action potential is more or less prolonged when a drug blocks repolarizing channels or defers closure of depolarizing Na^+ or Ca^{++} channels. When the prolongation lasts long enough, repolarization can be interrupted (perhaps because some Ca^{++} channels recover their ability to open during the long repolarization) by an afterdepolarization, as seen in Figure 3.
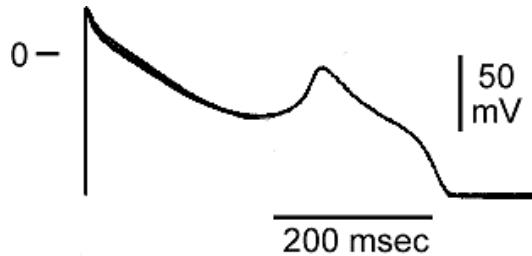
Figure 3, early afterdepolarization induced by sotalol in a guinea-pig M cell.

3.1   Technique

3.1.1 Action-potential recording techniques

3.1.1.1 Preparations

The preparation most commonly used for action-potential studies is the isolated canine Purkinje fiber, but single ventricular myocytes isolated from guinea pigs, rabbits, or dogs are also frequently used, and some investigators have used isolated papillary muscles or ventricular strips. Some findings in cardiac tissues from rats and mice have been provocative,(50) but because the dominant ion channel in these tissues is I_{to}, they are not frequently used during human drug development.

Purkinje fibers are attractive because they tend to be more sensitive to action-potential-prolonging drugs, and because stable microelectrode impalements are relatively easy to maintain in them. On the other hand, Purkinje fibers often fail to respond to blockers of I_{Ks}, so some drugs' effects may be underestimated.(51, 52)

3.1.1.2 Measurement

As noted above in Section 2.1, a drug that affects any of the ion channels is likely to affect others too. Quinidine, for example, blocks I_{to}, I_{Kr}, I_{K1}, I_{Ks}, I_{Na}, and I_{Ca-L}. As the concentration of quinidine is increased, the net effect on the action potential varies in a complex fashion, as one ion-channel effect and then another goes through its concentration-effect range. To characterize the effects of a drug on action potentials, it is thus important to use several concentrations of the drug, usually escalated in half-log increments over a range covering at least two orders of magnitude.

The rate of stimulation is also important. For example, most I_{Kr} blockers prolong action potentials more effectively at slow than at fast rates of stimulation, while many $I_{Ca\text{-}L}$ blockers are more effective at fast rates than at slow rates. These effects may reflect rate-dependent drug-channel interactions or intrinsic differences in the behavior of these and other ion channels (*e.g.*, I_{Ks}) during an action potential.

Changes in action-potential duration are usually quantified by measuring the time required for the repolarization process to reach 50% (**APD$_{50}$**) or 90% (**APD$_{90}$**) completion.

3.1.2 Other techniques

A simpler and higher-throughput approach is to determine the effect of compounds on the effective refractory period (ERP) of isolated papillary muscles, using paired-pulse electrical stimulation and using contractile activity as a signal.(53) One disadvantage with this method is that some I_{Na} blockers induce post-repolarization refractoriness (that is, they cause the ERP to last much longer than the action potential), and thus they produce a false-positive response.

3.2 Interpretation

From the timing and magnitude of the currents shown in Figure 2, many drugs' effects on action potentials can be roughly predicted. Na$^+$ channel blockers will reduce the maximum upstroke velocity of the action potential; I_{to} blockers, as noted above, will generally abolish an early notch, if one is present; Ca^{++} channel blockers will shorten APD$_{50}$; I_{Kr} and I_{Ks} blockers will prolong APD$_{50}$ and APD$_{90}$ with little change in the rate of terminal repolarization; and I_{K1} blockers will reduce the resting potential, prolong APD$_{90}$, and slow the rate of terminal repolarization.

The value of action-potential studies comes not from these single-channel phenomena, but rather from emergent phenomena that reveal the interaction of multiple channels. In particular, early afterdepolarizations seen in action-potential studies tend to be associated with proarrhythmia later on.(54) Action-potential prolongation by itself is somewhat worrisome, but several drugs (*e.g.,* pentobarbital(6)) cause action-potential prolongation and yet are anti-arrhythmic.(6, 7, 55) Plainly, the mechanism of *torsade* does not fully emerge until a level of integration that is even higher than that of the action potential.

4 Whole-heart and related studies

When electrically-excitable tissues with different repolarization characteristics are juxtaposed, the scene is set for re-entrant arrhythmias. Clinicians are familiar with this notion from infarction models and other studies. In the last several years, it has become apparent that a similar mechanism is responsible for *torsade de pointes.*

The pivotal discovery was the finding that the cells of the ventricular myocardium are heterogeneous.(56, 57) In every species tested, including dogs, rabbits, guinea pigs, pigs, and humans,(58-60) the myocardium has been found to include three different tissues, roughly(61) layered with the endocardium, a middle region (the "M cells"), and the epicardium.(62) The three layers are histologically indistinguishable, but electrophysiologically distinct, as seen in Figure 2. Among many other differences,

- the repolarizing current I_{Ks} is important in the epicardium and endocardium, but much less so in the M cells; and
- once depolarization is well under way, the depolarizing current I_{Na} tapers off rapidly in epicardium and endocardium, but it lingers, opposing the repolarization currents, in M cells.

With protracted influx of Na^+ and reduced opposing K^+ efflux via I_{Ks}, the action potentials of M cells are normally somewhat longer than those of the epicardium and endocardium, as shown on the left side of Figure 4. The voltage gradients between the M cells and the others appear, at least in the wedge model (see Section 4.1.3 below), as the T wave on the electrocardiogram.
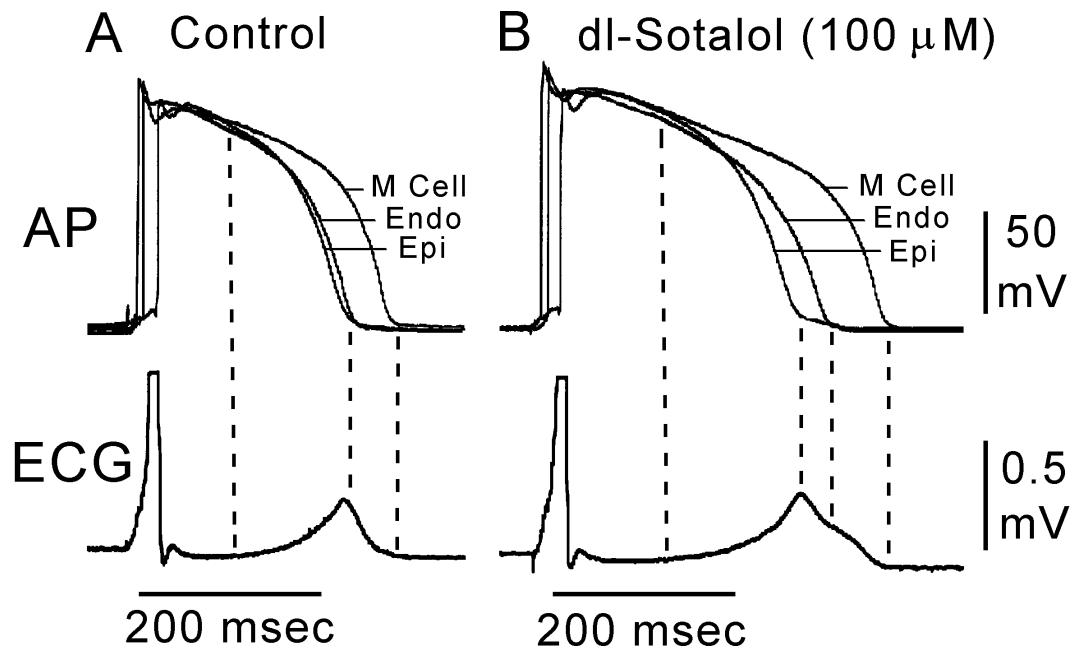
Figure 4, transmembrane potentials and a transmural ECG recorded from an arterially-perfused canine left ventricular wedge preparation. Action potentials from epicardial (Epi), M, and endocardial (Endo) sites were simultaneously recorded using floating glass microelectrodes, together with a transmural ECG. Opposing voltage gradients on either side of the M-cell region are responsible for the inscription of the T wave; the peak of the T wave coincides with the completion of epicardial repolarization, and the end of the T wave marks the completion of M-cell repolarization. Reproduced from (63), with permission.

The transmural differences in action-potential duration are normally no more than a few milliseconds, but drug effects can change the picture. With relatively low I_{Ks} activity, the repolarization of M cells is critically dependent on I_{Kr}. When I_{Kr} is blocked, repolarization is delayed everywhere, but (as shown on the right side of Figure 4, where I_{Kr}-blocking concentrations of *dl*-sotalol were used) much more in the M cells than in those of the epicardium or endocardium. As a result, not only is the QT interval prolonged, but the transmural dispersion of repolarization (**TDR**) is prolonged to an even greater degree.

Moreover, the effect upon TDR turns out to be the more important one. For example, pentobarbital is an I_{Kr} blocker, but it is a much more potent blocker of I_{Ks} and of the late portion of I_{Na}. As a result (as shown in Figure 5), administration of pentobarbital causes the QT interval to be prolonged (superscripted numbers in the last row of the Figure), but with the action potentials of the epicardium and endocardium prolonged more than that of the M cells (first three rows of the Figure), so TDR (numbers at the bottom of the Figure) actually decreases. The reduction in TDR explains the paradoxical-seeming observation that despite its effect on the QT interval, pentobarbital is **anti**arrhythmic in familiar animal models,(6) and it suppresses sotalol-induced early afterdepolarizations.(7) Similar results are obtained with amiodarone,(64) ranolazine,(65, 66)[6] and the experimental agent chromanol 293B.(67) In modeling *torsade de pointes*, there seems to be benefit in models that contain more than a few homogeneous ventricular myocytes.
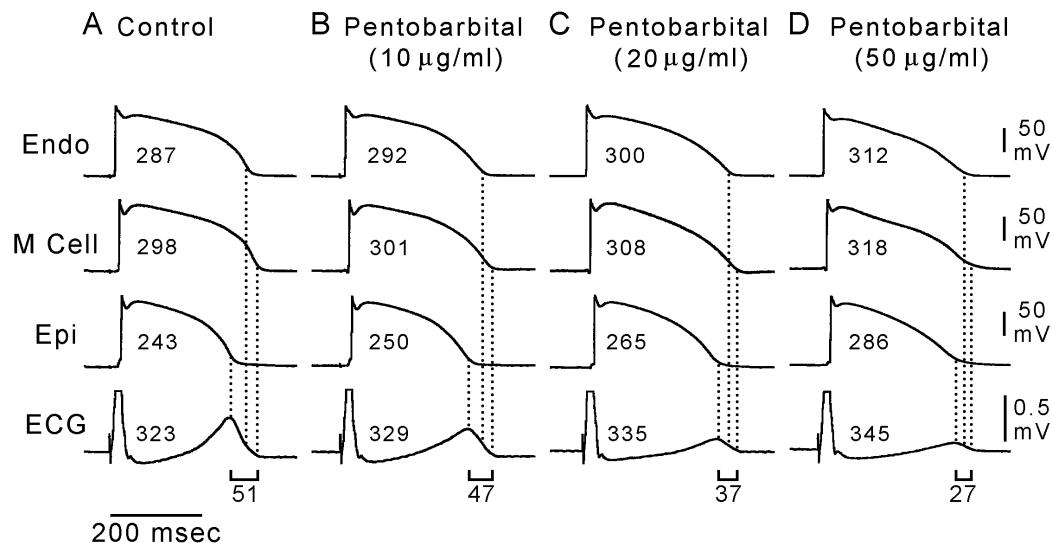
Figure 5, dose-dependent effect of sodium pentobarbital (10, 20, 50 µg/ml) on transmembrane and ECG activity in an arterially-perfused canine left ventricular wedge preparation. Numbers within the figure are all in milliseconds, showing the APD$_{90}$s (numbers within the domes of the action potentials),

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[6] The second reference here is new.

the QT intervals (numbers above the ST segments of the ECGs), and the transmyocardial dispersion of repolarization (numbers beneath the ECGs). Reproduced from (6), with permission.

4.1   Technique

4.1.1   Whole animals

One obvious way to obtain a preparation that contains all of the pertinent tissues is to use a whole animal. This sounds straightforward, but naïve implementation gives rise to the same problems that are found in human studies: *Torsade* is rare, and lesser electrocardiographic changes are of uncertain predictive value. In particular, variations of animals' QT intervals with heart rate, autonomic influences, and so on (see Section 5.1.6) are as complex as those seen in humans, with a smaller body of pertinent data to guide the investigator.

To get away from the difficulties of deriving predictions from QT changes, several groups of investigators have developed models in which animals are pre-treated so as to make them more likely to develop frank *torsade.* Then, drugs are tested by seeing whether they induce *torsade,* or whether they enhance or reduce other drugs' tendency to do so.

As with any whole-animal studies, these investigations of a drug will be credibly predictive only to the extent that the human and animal metabolism of the drug are appropriately similar. An effect seen in one species might be absent in another, if the culprit substance were a metabolite not produced in the second species.

4.1.1.1 Methoxamine-treated rabbits

In a model initially developed by Carlsson *et al.*,(68) α-chloralose-anesthetized rabbits are pretreated with methoxamine, an alpha$_1$ agonist. These animals then have greatly increased sensitivity to the repolarization-altering effects of some drugs, especially those that are relatively pure I_{Kr} blockers (dofetilide, sotalol, *etc.*). As the dose of one of these drugs is increased, the rabbits predictably exhibit marked QT prolongation, large U waves, epicardial early afterdepolarizations, and finally polymorphic ventricular tachycardia.

Most of the reported experience with the rabbit model has come from studies of the I_{Kr} blockers, characterizing their proarrhythmic properties and investigating methods for terminating drug-induced arrhythmias. Experience with drugs of other kinds has been limited. When methoxamine-treated rabbits were exposed to increasing concentrations of terfenadine and quinidine, polymorphic ventricular tachycardias were not induced.(69) The quinidine effect likely reflects the drug's alpha-blocking properties, inhibiting methoxamine actions in this model, but the general sensitivity and specificity of the rabbit model remain unsettled.

4.1.1.2 AV-blocked dogs

Dogs used in this model undergo ablation of the atrioventricular node, either by injection of formaldehyde via thoracotomy or by application of radio-frequency energy (70) via a catheter. Pacing electrodes are placed, and the dogs are then followed for 2-4 months to allow for bradycardia-induced ventricular remodeling.(71) In one version of this model, the dogs' susceptibility to *torsade de pointes* is further increased by using furosemide to induce hypokalemia.(72)

Studies using this model are generally conducted on conscious, quietly restrained animals, so all routes of drug administration are possible. Cross-over studies after appropriate washout are also possible with this model. The total reported experience is not large, but (as shown in Table 2) drugs known to produce (or not to produce) *torsade* in humans have generally produced (or not produced) *torsade* in A-V blocked dogs**.** Quinidine has been a borderline exception; sotalol induced *torsade* in five of six dogs studied by Weissenburger,(73) but quinidine, in the same animals, induced only various less distinctive ventricular tachyarrhythmias.

drug (reference)	N	incidence of torsade
almokalant (74)	14	64%
amiodarone (3)	7	0
azimilide (75)	9	56%
dofetilide (75)	9	67%
dronedarone (3)	8	38%
d-sotalol (76)	20	5%
d-sotalol (74)	14	0%
ibutilide*	12	67%
*Cantilena, unpublished observations		

Table 2, selected results from published studies of drug-induced torsade in AV-blocked dogs.

## 4.1.2 Isolated perfused hearts

Arrhythmogenesis has also been studied in the whole, isolated, perfused hearts of rabbits (77-80) and guinea pigs.(81) The sensitivity and specificity of these models are uncertain, and they provide no information

as to potential arrhythmogenic mechanisms. These models have been substantially superseded, in our view, by the wedge model described in the next section.

4.1.3 The wedge preparation

Because the principal substrate for the development of *torsade* is thought to be due to amplification of transmural dispersion of repolarization, a transmural segment of myocardium provides a minimally complete model in which to study the genesis of the arrhythmia. Antzelevitch and colleagues have demonstrated that a full-thickness slab of ventricular wall (a "**wedge**") can indeed be isolated and studied, providing insight into *torsade* and a variety of related electrophysiological phenomena.

As shown in Figure 6, the wedge preparation is a few square centimeters of full-thickness ventricular wall. The specimen is immersed in a physiological bath, and it is also perfused through its native vessels. Electrodes in the bath at some distance from the endocardial and epicardial surfaces record a pseudo-electrocardiogram, while floating glass microelectrodes record simultaneous action potentials in each layer of tissue from the transmural surface.
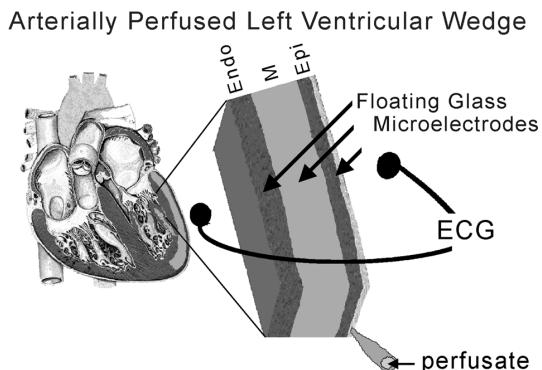
Figure 6, schematic of the arterially-perfused canine left ventricular wedge preparation. Reproduced from (82), with permission.

By providing results like those shown in Figure 4 and Figure 5, the wedge preparation has been pivotal in providing our current understanding of torsadogenesis. As shown in Table 3, human *torsade* is much better correlated with TDR than with the length of the QT interval. In particular, compounds that have been shown to increase TDR have all turned out to cause *torsade* in humans, and of all of the compounds that have been shown *not* to increase TDR, amiodarone is the only one that has ever been convincingly (albeit rarely) associated with human *torsade*.[7]

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[7] For example, the wedge model has led to a unified model covering the pro-arrhythmic mechanisms of the LQT syndromes and the short-QT syndromes.(83)

drug	canine LV tissue studied				effect in canine LV		effect in humans	
	M*	Epi*	PF*	wedge	EADs	⇑TDR	*torsade*	⇑QT
amiodarone	✓	✓			−	−	±	+
azimilide	✓	✓			+	+	+	+
cisapride	✓	✓	✓	✓	+	+	+	+
erythromycin	✓	✓		✓	+	+	+	+
⇓I_{Ks}* with βstim*	✓	✓	✓	✓	−	+	+	+
⇓I_{Ks}* with βblock*	✓	✓	✓	✓	−	−	−	+
pentobarbital	✓	✓		✓	−	−	−	+
quinidine, low conc	✓	✓	✓		+	+	+	+
quinidine, high conc	✓	✓	✓		−	−	−	+
sotalol	✓	✓	✓	✓	+	+	+	+
terfenadine	✓	✓		✓	+	+	+	+
verapamil	✓	✓	✓	✓	−	−	−	±

* Epi = epicardial cells; ⇓I_{Ks} = LQT1 (I_{Ks} defect) in humans, drug-induced I_{Ks} blockade in dogs; βblock = beta-adrenergic blockade; βstim = beta-adrenergic stimulation; M = M cells; PF = Purkinje fibers; EADs = early afterdepolarizations; TDR = transmyocardial dispersion of repolarization; LV = left ventricle

Table 3, transmural dispersion of repolarization and QT duration as predictors of human *torsade de pointes*

The wedge preparation is technically demanding, but some of Antzelevitch's former co-workers and other investigators have now begun to replicate it in other laboratories.(84-86) The level of transmural dispersion of repolarization needed to precipitate *torsade* in the wedge often requires long pauses or slow rates, hypokalemia, or epicardial activation, conditions similar to those that predispose to *torsade* in the clinic. Confirming the findings of the wedge model, the ability of a drug to significantly amplify transmural dispersion can be delineated via studies of the individual layers (that is, in tissue slices isolated from the epicardial and M regions of the ventricular wall).

4.1.4 *In silico* techniques

Computer simulations of the myocardium (87) and of the whole human heart (88) have reproduced the electrophysiological effects of drugs, ischemia, and other conditions. These simulations have required massive computational resources, but such resources are increasingly available. Simulations are not yet familiar enough to be fully trusted, but a growing number of developers are using them to suggest prioritization of more traditional investigations.

4.2 Interpretation

The physiological completeness of the models described in this section is sufficient for the appearance of *torsade de pointes*, strictly resembling the human arrhythmia. These models are — notwithstanding imperfect sensitivity and specificity — better predictors of human torsade than any other studies known, including (as suggested in Table 3) measurement of QT intervals in human electrocardiograms.

5 Electrocardiography

Adequate pre-clinical screening by the methods described above may be able to keep most drugs likely to induce *torsade* from ever being tested in clinical trials. Even so, and despite the imperfection of QT measurement as a predictor of pro-arrhythmia, early drug trials must include some evaluation of the effect of a new drug on the human QT interval.

5.1 Technique

5.1.1 QT intervals that should not be measured

Some electrocardiograms are technically defective (with muscle artifact, misplaced leads, or other problems), and one should not attempt to derive useful data from them. This is an old and well-understood problem, although it is one that investigators in pharmaceutical studies are still occasionally pressured to ignore. Even in the best laboratories, about 3% of ECGs cannot be used for meaningful measurements.

5.1.1.1 Hysteresis

The importance of hysteresis was recognized much more recently. As will be discussed in Section 5.1.6.2.1 below, the interpretation of measured QT intervals must take the concurrent heart rate into account. When the heart rate changes, the QT interval also changes, but it is now known that the QT interval takes a minute or two to reach a new steady state.(89) When the QT interval is measured during or just after a change in heart rate, the heart rate to use in the analysis of that QT interval is not defined. (Figure 7)
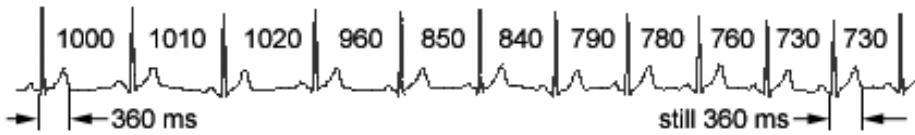
Figure 7, continuous recording during which the RR intervals were shortening (upper numbers), but the QT interval was constant

Failure to take account of hysteresis can result in a biased analysis. If acceleration is more rapidly completed than deceleration, then the QT-RR mismatch may be small during and after deceleration, but occasionally large just after acceleration, leading to the false detection of "outlier" values with abnormal prolongation. Adopting a criterion of moderate rigor (say, analyzing only those beats preceded by at least 2 minutes of heart rate stable to ± 3 beats per minute) leaves only a minority of beats in a typical Holter recording available for analysis (Malik, unpublished observations).

Recordings of complexes seen during and just after changes in heart rate should not be discarded, even though methods for their analysis and interpretation have not been developed. In some preclinical models, predictors of arrhythmia are seen only during or just after changes in cycle length.(90) Techniques to derive useful information out of the hysteresis-affected electrocardiographic complexes are not yet available, but this is an area of intense current research. Very recent investigations suggest that the pattern of QT/heart rate adaptation is subject-specific, and that protracted adaptation is a risk marker for arrhythmic complications in cardiac patients.(91, 92)

5.1.2 Electrocardiographic leads

Some investigators have defined the QT interval as the longest interval measured in any measurable lead, others have used the interval that appeared to be measurable with greatest precision (*e.g.,* the one in which the descending limb of the T wave was steepest), others have adopted a specific lead (usually Lead II) as standard, and still others have utilized a mixed strategy, perhaps using Lead II whenever it is measurable, then using Lead V_2 as a second choice, and so on. These various strategies can give radically different results, and the results from some strategies are often unstable. For example, Figure 8 shows the unpredictable differences between QT intervals in Leads II and V2, carefully measured in 10 332 digital electrocardiograms. Careful digital superimposition of all available (up to all 12) simultaneously recorded leads seems to solve the problem of lead selection, and it frequently makes the Q wave onset and T wave offset easier to detect.
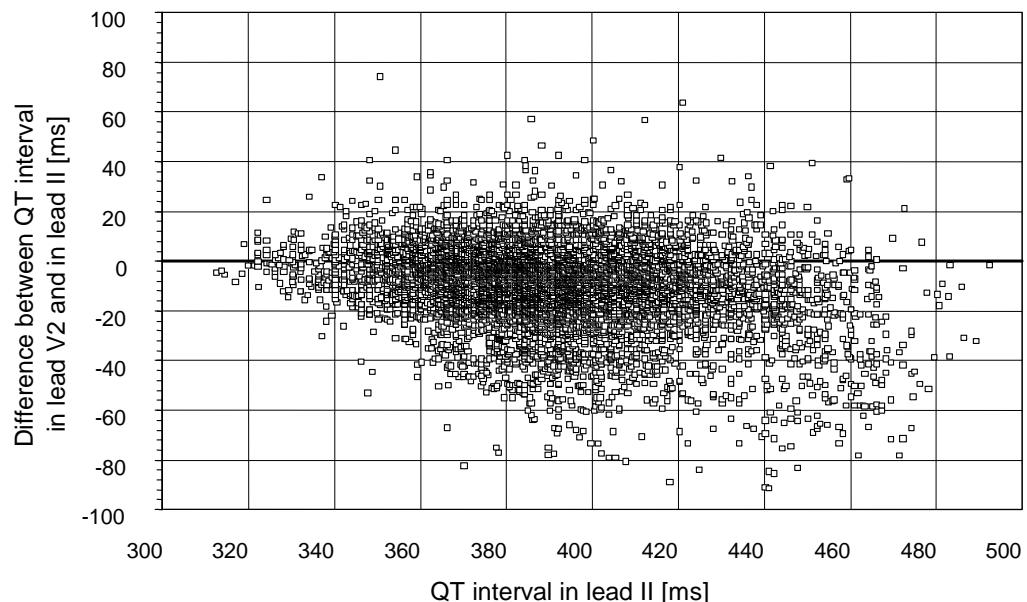
Figure 8, difference between QT intervals in lead V2 and lead II, as a function of QT interval in lead II, from manual measurements (made on the computer screen using previously published technology (93)) in 10 332 digital 10-s 12-lead electrocardiograms.

5.1.3 U waves

The origin of U waves was obscure for many years. U waves had been said to be manifestations of repolarization of the Purkinje fibers, since these fibers are slow to repolarize (consistent with normal U wave timing) and of low mass (consistent with normal U wave diminutive magnitude).(57) On the other hand, it was hard to reconcile this account with the occasional appearance of U waves that were somewhat earlier and much larger. Some authors included the U wave in their measurements of QT intervals, but others did not.

It now appears that the small U waves and large U waves have different origins. In particular, studies using the wedge preparation have demonstrated that under appropriate conditions (hypokalemia or drug infusion), a large U wave can be repeatably produced during repolarization of isolated ventricular myocardium, and that it is produced by the same mechanisms that produce the T wave.(57)

5.1.4 QT dispersion

As noted in Section 5.1.2, the measured QT interval commonly varies from lead to lead of the electrocardiogram. This circumferential or regional variation has been called *QT dispersion*; it is different from the radial phenomenon of transmyocardial dispersion discussed in Section 4. QT dispersion is increased in congenital and drug-induced long-QT syndromes and in other conditions associated with increased arrhythmic risk; an analogous measure was predictive of arrhythmia in a dog model.(94). Various measures of

human QT dispersion have been proposed as measures of risk, but their reproducibility is poor, and none has proven to have independent predictive value.(95-97) In hindsight, the insensitivity of these measures might have been expected, inasmuch as each of the proposed measures was sensitive to differences in repolarization between regions of ventricular tissue that were physically far separated from each other, and therefore unlikely to join in hosting reentrant arrhythmias.(98)

5.1.5 Measurement *per se*

In other areas of biology, the notion of the width of a curve peak is usually defined so as to avoid the difficulties that accompany gradual return to a noisy baseline. For example, the reported width of a chromatographic peak is the width of the peak at half of its maximum height. Because the electrocardiographic intervals are defined to last until the tracing has entirely returned to baseline, there is no possible gold-standard method of measurement. Strategies that improve precision in some situations (*e.g.,* increasing the paper speed or frequency of sampling, which improves precision of measuring the timing of signals that are changing rapidly) can be useless in others (*e.g.,* in measuring the timing of a signal changing very slowly).

Manual readings from paper tracings have a repeatability of about ±25 ms in good hands, but even the best readers demonstrate greater or lesser degrees of digit preference and occasional major errors.(99-101) Using electronic calipers on the computer screen allows for arbitrary rescaling, superimposition of multiple leads or complexes, and other techniques, with a resulting improvement in precision to about ±5 ms. As it happens, the beat-to-beat variation in the QT interval of normal subjects under optimal steady-state conditions is also about ±5 ms (Malik, unpublished observations).

The familiar interval measurements are the easiest measurements for humans to make from paper tracings, but other metrics are under active investigation. Some are more susceptible to precise computerized measurement (*e.g.,* the time from the QRS onset until the point at which 90% of the area under the T-wave curve is past), and others are suggestively linked to the current electrophysiological model (*e.g.,* the time from the peak of the T wave to its end (56, 102-104)).[8] None of these new metrics is yet of proven utility, but the possibility of changes in metric justifies our strong recommendation that electrocardiograms be collected digitally, so that possible future manipulation will not entail reexamination of paper tracings.

Simple automatic measurements of QT interval are provided by most electrocardiographs. However, these are frequently grossly inaccurate (Figure 9) and cannot be recommended for studies of potential drug-induced QT interval prolongation.(93) Recent developments in advanced electrocardiographic pattern recognition suggest that reliable automatic measurements may be available in the near future.

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[8] Short-term variability of repolarization(105) may turn out to deserve a mention here.

```
QT  406 ms          QT  506 ms
QTC 390 ms          QTC 491 ms

10 mm/mV            10 mm/mV
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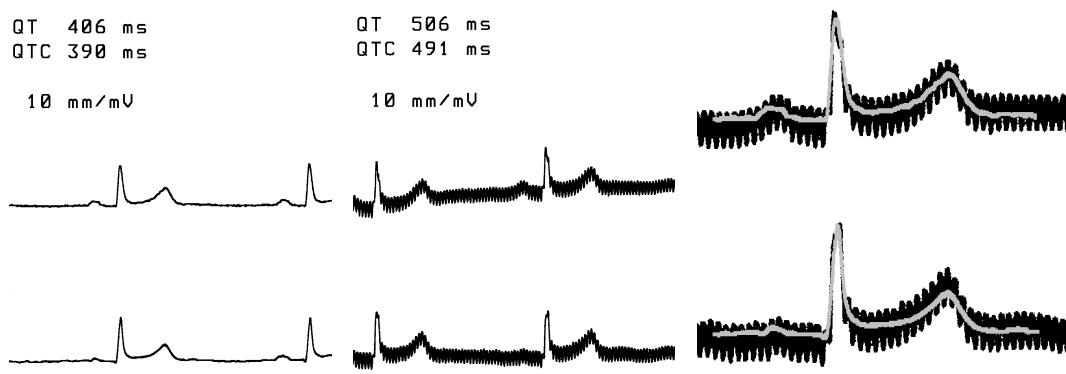
Figure 9, automatic measurements by contemporary electrocardiogram machines. The left and middle panels show scans of leads I and II of two automatically-measured electrocardiograms; the right panel shows superimposition of the electrocardiographic patterns from the two tracings. The QT interval duration is the same in both tracings, but the machine reports a difference of 100 ms. Reproduced from (106), with permission.

5.1.6 Co-factors affecting the QT interval

The purpose of QT measurement during drug development is to estimate the size of a drug effect, if any, on the duration of the QT interval. This task is made more difficult by the fact that the QT interval is affected by multiple co-factors, and any drug effect must be separated from these. Some of these factors are immutable (sex), some change little during typical trials (age), and some can be held constant or let vary unrelated to treatment (patient position or time of day (107)) so as to reduce their potential for confounding. Others are more difficult to control, because drugs typically have multiple effects, and it may not be possible or even meaningful to isolate the QT effect from the others.

5.1.6.1 Serum potassium

For example, the duration of the QT interval is prolonged during frank hypokalemia, but the effects of minor variations in serum potassium levels have not been reported. Although use of thiazide diuretics is said to be a risk factor for *torsade,* this association is presumably mediated by the occurrence of diuretic-induced hypokalemia.(108) The statement that a specific thiazide diuretic prolongs the QT interval would generally be taken to mean that it does so even when the serum potassium is somehow held constant. Whenever a drug has a nonzero effect on serum potassium, precise estimation of a QT effect may require adjustment of the raw measurements to separate a direct effect from one mediated by changes in serum potassium. Data that might be used for such adjustment have not been reported.

Because lowering serum potassium increases the risk of *torsade*,(108) concern about distinguishing thiazide effects on serum potassium from direct effects on QT duration might be dismissed as a semantic exercise: By whatever mechanism, use of thiazide diuretics increases the risk of *torsade*. Other drugs, however, might have effects that affected repolarization in different directions. For example, a potassium-sparing diuretic might have direct effects on ion channels that increased the risk of *torsade* but — because of the drug's effect on serum potassium — a net effect that made *torsade* less likely.

5.1.6.2 Heart rate

Heart rate is the best known of the co-factors affecting QT duration: A QT interval that is normal at one heart rate may be abnormal at another.

Clinicians might have come to deal with rate-related changes in QT duration by using tables, similar to common height-weight tables. It might have become customary to look up an observed age, sex, heart rate, and QT duration, and to see in which percentile the observed QT duration fell. This solution was not adopted. Instead, clinicians have used one or another QT normalization formula, just as many clinicians use the body-mass index instead of less practical height-weight tables.

More than thirty different formulas have appeared in the literature.(109) Each relies on a model of how the QT duration normally varies with heart rate. Many of the published models are of the form

$$QT \propto \beta \bullet RR^{\alpha} \tag{1}$$

for some α and β, where **RR** is the cycle length (60 / heart rate). The α parameters of several of the published formulas are shown in Table 4.

Author (reference)	year	α
Fridericia* (110)	1920	0.33
Bazett (111)	1920	0.5
Mayeda (112)	1934	0.603
Simonson (113)	1962	0.32
Boudoulas (114)	1981	0.398
Kawataki (115)	1984	0.25
Yoshinaga (116)	1993	0.31
Hodges (117)	1997	0.38
* Using curve-fitting tools, Fridericia actually estimated α to be 0.3558, but he concluded that ⅓ was a reasonable approximation.		

Table 4, parameters of some published QT/RR models in the form of Equation 1.

In each model based on Equation 1, the α exponent adjusts for the variation in heart rate. Given a measured QT duration and heart rate, for any given model from the Equation-1 family one can effectively invert the equation, computing the β coefficient needed to allow the measured values to be consistent with the given α exponent. If the RR interval is measured in seconds, then the β coefficient is equal to the expected QT interval at an RR interval of one second, and β is called the "corrected" QT interval, **QTc**. ("Corrected" is a misnomer, since the measured QT intervals may be hard to interpret, but they are not incorrect. A body weight might need to be corrected if it were measured when the subject was heavily dressed, but using the body-mass-index formula is not a correction.) Similar calculations are possible with models other than those based on Equation 1.

In the case of models from the Equation 1 family, the general form

$$QTc = f(QT, RR) \tag{2}$$

(where QT is the measured QT duration and RR is the measured cycle length) becomes

$$QTc = QT / RR^{\alpha} \tag{3}$$

The value of this calculation is that if the α parameter is numerically correct, then the computed QTc may be compared to a known normal range without further attention to the measured QT duration and the measured

heart rate. This process is akin to the one that allows clinicians who believe that weight varies with height according to

$$weight \propto \beta \bullet height^2$$

to use the computed body-mass index

$$BMI = weight\Big/ height^2 .$$

Loosely, formulas like Equations 2 and 3 are sometimes said to be telling us what the QT interval "would have been" if other things were equal and the heart rate were 60; in the same way, a patient's body-mass index might be interpreted as indicating what the patient's weight "would have been" if other things were equal and the patient's height were one meter.

Since all of the associated models from Table 4 are of the form shown in Equation 1, the different choices of α must give different results, and the differences can be substantial. There has been at least one trial (118) that separated heart-rate effects from direct effects on ventricular repolarization. Volunteers in that study received atropine, and in one phase of the trial their hearts were paced to prevent the increase in heart rate that atropine normally produces. Under these conditions, the measured QT interval was shortened from baseline by 24 ms (Figure 10). In another arm of the study, the same volunteers received atropine in the absence of pacing. The measured QT interval was decreased by 49 ms, combining the direct effect (24 ms) with an extra 25 ms induced by the rate change. An adequate "correction" formula would have adjusted for the rate and come out with a decrease close to the gold-standard 24 ms (probably somewhat larger, since Equation 1 is multiplicative, and the paced rate was probably faster than 60/min). The Bazett correction ($\alpha = 0.5$) falsely computed that these subjects had suffered a 43 ms *increase* in their true QT intervals.
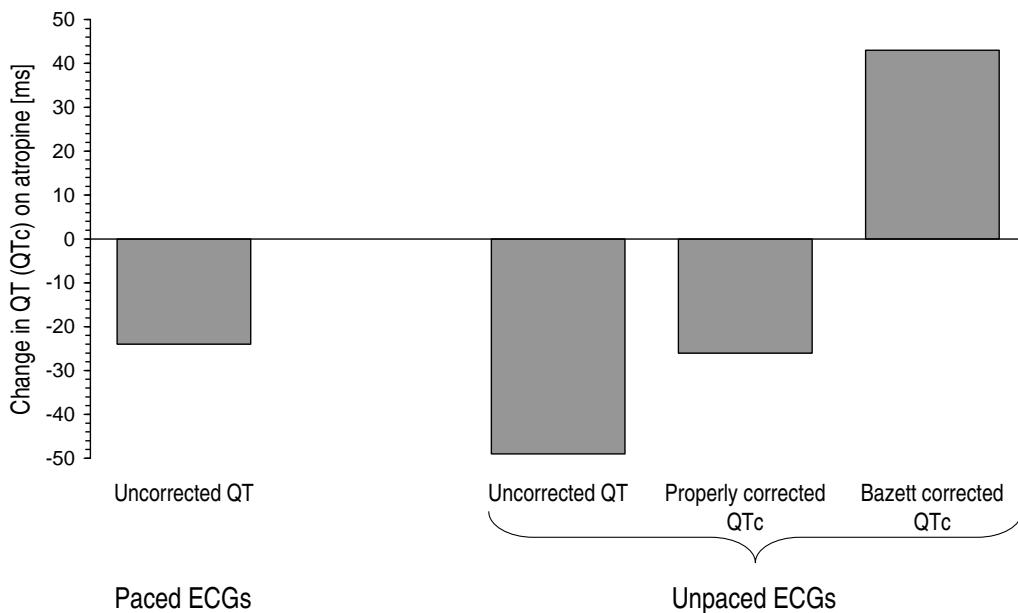
Figure 10, misleading "correction" by Bazett formula in a study of QT/QTc changes induced by atropine

Many authors have commented on the inadequacy of the Bazett formula,(113, 115, 119-132) but other proposals are equally problematic. Table 4 provides a variety of other α values to choose among, but in the decades since the reports of Bazett and Fridericia, the α values do not appear to be converging over time. Different workers have come up with different values because each value was the best fit to data from a limited population, and the α parameter is one with high intersubject variance.(133, 134)

The typical extent of intersubject variance is seen in Figure 11, which shows the QT interval and heart rate from each of about 100 electrocardiograms in each of two subjects. Points plotted with the same symbol come from electrocardiograms of the same subject. The intersubject differences may be easier to see in
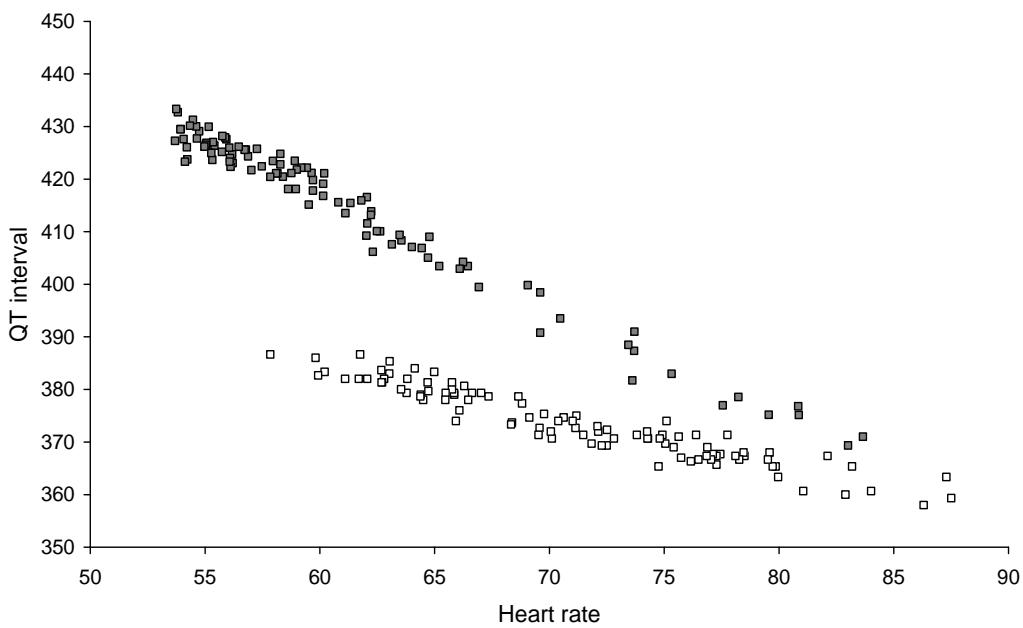
Figure 11, heart rate and QT interval measurements in 100 electrocardiograms from each of two normal middle-aged male subjects. Only stable electrocardiograms free of QT/RR hysteresis and of recording noise were selected from continuous day-time 12-lead recordings. Measurement was performed manually using previously described technology.(93)

Figure 12, where different subjects are represented by just the best-fitted line of the form of Equation 1. Each of the subjects had QT intervals that were consistently related to heart rate in a linear or curvilinear manner, but the individual curves differed in position, slope, and curvature. It is not hard to see how different investigators might, from small samples, come out with different best-fit formulas. In terms of Equation 1, each subject would be best fit by personal values of α and β.
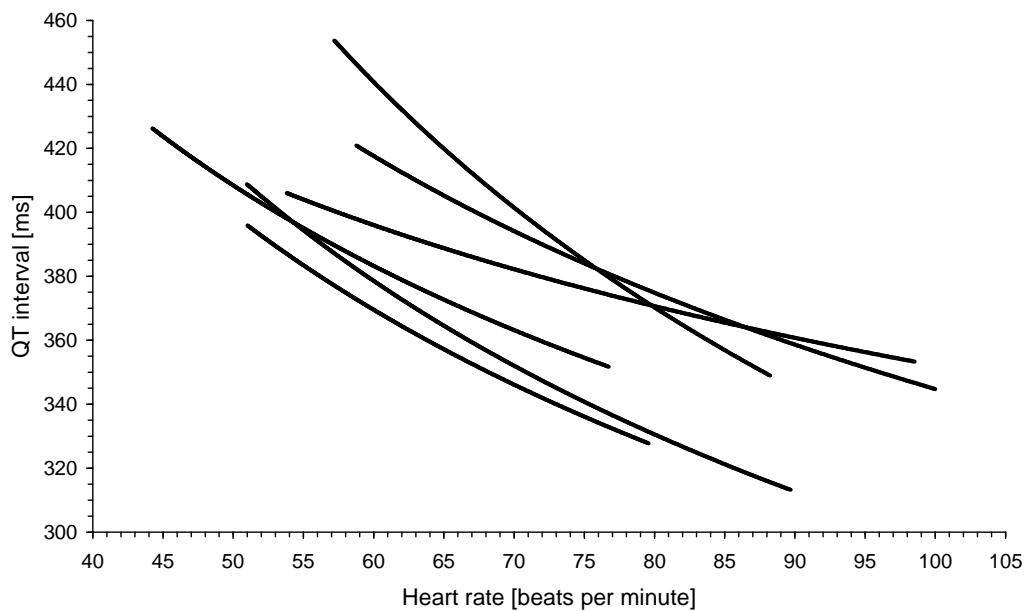
Figure 12, QT/heart rate relationships in 6 normal middle-aged subjects. The data of each subject were fitted with a regression line corresponding to the individualized form of Equation 1.

High variance might be inescapable if the RR-QT relationship varied not only between subjects, but even within the same subject from time to time. Fortunately, this turns out not to be the case. In studies of the same subjects repeated over a period of one month, Malik *et al.* found that each subject's RR-QT relationship was preserved over time.(135, 136) More recent observations confirm that the stability of these relationships persists for at least 2 years.(137)

Once an individual's RR-QT relationship has been characterized, it should be easy to check where any new (RR, QT) pair lies with respect to the usual measurements of the same subject. Specifically, the extent to which drug treatment can properly be said to have altered the QT interval of a subject is the extent to which drug-affected (RR, QT) pairs are outside the usual drug-free distribution of (RR, QT) pairs. If the subjects in a trial can be seen each to have demonstrated the same (RR, QT) pairs on and off drug, then there is no place for concern arising from a model (Bazett or other) of how the QT duration *should* vary with heart rate.

Although the evaluation of any given (RR, QT) is straightforward, there is no scalar expression for the difference (possibly a drug effect) between two different RR-QT relationships. When the effect of drug treatment is not so much to shift the QT/RR curve as to change its slope or curvature, the estimated change in QTc could be positive or negative, depending on the RR interval. When the only description of the difference is the difference in QTc (that is, the estimated difference in QT at RR = 1000 ms), information has been discarded.

5.1.6.2.1 Pacing heart-rate variation away

Cardiac pacing might — as in the study shown in Figure 10 — be an attractive means of eliminating drug-induced changes in heart rate, apparently simplifying investigation of drug-induced changes in repolarization. There are no recent reports of this methodology,[9] perhaps because of the ethical difficulties of transvenous pacing, and the discomfort induced by percutaneous pacing, of healthy volunteers. Even if these difficulties could be overcome, pacing studies would necessarily be of limited duration, data could be collected only within a relatively narrow range of (rapid) heart rates, and the stress responses likely to be associated with temporary pacing might raise questions about generalizability of the results.

5.1.6.2.2 Each patient as his or her own control

To determine the extent to which an observation made during treatment reveals a drug effect, it is necessary to compare that observation to observations made in the absence of treatment, but with other co-factors unchanged. One attraction of large trials is that co-factors unaffected by drug treatment will on average have the same distribution in each arm of any such trial.

Large trials are not necessarily helpful when one or more co-factors are affected by the drug treatment. In the specific case of heart rate as a co-factor determining QT duration, one is asking how an observed QT duration, seen during treatment when the subject had a stable heart rate, compares to the QT intervals ordinarily seen in the same patient off treatment and with the same stable heart rate.

5.1.6.2.2.1   Bin methods

Theoretically, the most straightforward approach to this question is model-free. (RR, QT) pairs are collected while the patient is not receiving the treatment to be tested, and these pairs are distributed into "bins" according to the immediately preceding RR value. With a bin width of (say) 10 ms, the bins might contain all of those pairs with $500 \leq RR < 509$ ms, $510 \leq RR < 519$ ms, . . ., $1190 \leq RR < 1199$ ms, and $1200 \leq RR < 1209$ ms, respectively. To evaluate a new (RR, QT) pair obtained during drug treatment, standard statistical techniques are used to ask how the new QT value compares to those in the bin to which the new RR value would be mapped.(139-142)[10]

In part because of the problem of excluding complexes not preceded by adequate periods of stable heart rate (see Section 5.1.1.1), collecting data sufficient for implementation of a bin method is labor-intensive, and adequate statistical power may be difficult to achieve unless the population of each relevant bin is > 50.

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[9] Pacing has actually been used in one recent QT study, albeit only briefly.(138)

[10] The best reference for the bin method(143) is new since the date of our paper.

Especially if the drug effect on the heart rate is large, the RR intervals observed during treatment may have appeared rarely or not at all before treatment started. Increasing the bin widths can alleviate this problem, but only at the cost of decreased precision and increasing bias (essentially regression bias (144)) toward false detection of outliers. Further, since similar on- and off-drug heart rates may appear at different times of the day, the precision of the bin method is decreased by circadian effects on the QT interval.(145) Similarly, if the drug changes heart rate considerably, similar on- and off-drug heart rates are bound to be associated with different levels of other co-factors, potentially leading to inappropriate comparisons.

5.1.6.2.2.2   Formula-based methods

By making minimal mathematical assumptions, the data requirements of the bin methods can be reduced, and the problems of bias can be substantially eliminated. As shown in the typical examples depicted in Figure 11 and Figure 12, individual RR-QT relationships may vary, but all are smooth and of limited curvature. If a reasonable number of off-treatment (RR, QT) pairs is collected from a given subject, spanning a reasonable range of RR values, standard curve-fitting techniques can be used to find the best-fitting member (say, QT = f(RR)) of a family of parametric curves. Thereafter, an (RR_0, QT_0) pair obtained during treatment can be tested by applying standard statistical tests to the residual $\Delta QT = QT_0 – f(RR_0)$. When individualized formulas have been computed for each of a population of subjects, the individualized ΔQT values can be pooled and similarly tested.(109) Since the objective is to fit the off-treatment (RR,QT) pairs best, different families of parametric curves might be applied to different subjects.

Use of formula-based methods reduces the data requirements of individualized adjustment for heart rate, but the requirements are still substantial. It is not possible to predict exactly how many electrocardiograms are needed for each subject, but stable estimates of the curve fitting parameters (*e.g.*, for curves of the Equation 1 family, stable estimates of α and β) are rarely obtained with fewer than 20 electrocardiograms. Even when many electrocardiograms have been obtained, stable estimates will not be able to be produced if — as is often the case with electrocardiograms obtained at rest at the same time of day — the heart rate varied only within a narrow range.

Most of our experience of formula-based heart-rate adjustment has used the family of curves defined by Equation 1 and a few others.(136) While there is no *a priori* reason to restrict attention to any family of curves, or even to require that all of the subjects in a study be fitted with curves from the same family, experience with different mathematically defined curves suggests that QTc values at moderate heart rates will rarely differ by more than 5 milliseconds when computed by individualized curves from different families. Even at very slow or very fast heart rates, we have not seen differences between individualized curves from different families greater than 15 ms.

Two large databases (Fenichel and Malik, unpublished observations) were explored with individualized curves from the family of Equation 1. The results are shown in Table 5; parameters of a new population might be as different from each of these as these were from each other.

		Study 1	Study 2
N		50	229
	data quality	excellent	less precise
α	minimum	0.23	0.06
	1st quartile	0.33	0.20
	median	0.37	0.27
	3rd quartile	0.41	0.34
	maximum	0.49	0.78
β	minimum	0.37	
	1st quartile	0.39	
	median	0.40	N/A
	3rd quartile	0.41	
	maximum	0.45	

Table 5, numerical values of parameters of Equation 1 from two unpublished studies

5.1.6.2.3 Norms derived from the study population

The data requirements can be reduced still further by fitting a single curve to pooled off-drug data from all of the subjects in a study, but this approach brings problems of its own. A curve that attempted to describe the 2-subject population of Figure 11, for example, would pass somewhere through the middle of that graph. On-treatment (RR, QT) pairs seen in these subjects might lie directly on the population-derived line and still be grossly abnormal for either subject.

Conversely, any number of on-treatment (RR, QT) pairs seen in these subjects might lie far from the central line and still each be typical of the baseline RR-QT pairs of the affected subject. A non-individualized RR-QT formula can be optimal for the population overall, but still a very poor fit to many (or even all) of its members, so specificity may be extremely poor. Because the population QT/RR slope may be different from the mean of the individual slopes, such a formula may provide biased estimates of the average change in QT interval, and it is totally inappropriate for identification of noteworthy responses in individual subjects.

In terms of Equation 1, an erroneously *high* value for α causes one to expect that with increasing heart rate, the QT interval will decrease more rapidly than it actually does. As a result, normal reductions of QT duration with heart rate will be perceived as insufficient, falsely suggesting that some concomitant process is prolonging the QT interval. With decreasing heart rate, an erroneously high value of α will lead to acceptance as normal of QT durations that are actually abnormally long. Erroneously *low* values of α have, of course, the opposite effects.

5.1.6.2.4 Assumed, population-independent norms

Instead of fitting a curve to the mean RR-QT relationship of the population to be studied, one may posit a standard relationship, choosing (for example) one of the formulas of Table 4 or another of the 30 or 40 formulas in the literature. With luck, one might be no worse off (but surely no better off) than with a population-fitted formula.

5.1.6.2.4.1 The Bazett formula

Every formula from the Equation 1 family (with $\alpha > 0$) postulates that the QT interval should shorten as the heart rate increases, and for most clinical purposes it may make little difference which is used. Even so, the lasting popularity of the Bazett formula ($\alpha = 0.5$) is difficult to understand.

The Bazett formula was derived empirically by pre-statistical methods, using data from a small population,[111] and the exponent 0.5 appears to have been chosen fairly casually, as much on the grounds of ease of computation as anything else. An α value of 0.5 would be greater than any of those seen in the 50 subjects of the better-quality study described above in Section 5.1.6.2.2.2, so at heart rates above 60, any QTc values computed by the Bazett formula would be falsely elevated in each of these subjects, and at heart rates below 60 (where the risk of *torsade* is greatest), the Bazett formula would give false reassurance in every case.

Even in evaluating patients whose heart rate is exactly 60/min, clinicians are probably carrying unwanted baggage from the years of uncritical acceptance of the Bazett formula. When the heart rate is 60/min, the accepted upper limit of normal for the QT duration is given in most texts as 440 ms. This range might have been obtained by studying a population of subjects whose heart rates happened to be 60/min, but we suspect

that it was actually obtained by pooling the QTc values, computed by the Bazett formula, of subjects at various heart rates, mostly greater than 60/min. Because the great majority of these QTc values will have been falsely elevated as described above, the actual upper limit of normal QT duration at a heart rate of 60 is probably somewhat lower than the accepted upper limit. In the light of such considerations as these, it is strange to see the Bazett formula being occasionally defended on the grounds that its errors are always conservative and prudent.

5.1.6.2.5 Mixed strategies

For operational robustness, some recent investigators have used mixed strategies. For example, at least one group (unpublished data) organized each subject's baseline data into bins, but also computed a best-fit formula to the baseline data for each subject, and finally computed a best-fit formula to the baseline data for the whole population. Then, they evaluated each on-treatment (RR, QT) pair

- by comparing its QT value to those of the subject's appropriate bin, if that bin was adequately populated;

- otherwise, by using the subject-specific formula, if the baseline data had been adequate for stable parameter estimation for this subject; and

- otherwise, by using the study-population-specific formula.

5.2 Interpretation

QT prolongation is a mediocre predictor of *torsade* or other ill effects. Some drugs (amiodarone, pentobarbital, *etc.*) can cause large QT prolongations, but — by reducing transmyocardial dispersion of repolarization — they actually *reduce* the likelihood of *torsade*. At the other extreme, some patients with congenital long-QT syndromes have normal QT duration, but they still have an increased risk of sudden death. Small studies in patients with cardiovascular disease have tended to show an association between modest QT prolongation and mortality, but in a review of 7 prospective studies of 36 031 persons, Montanez *et al.* found no such association, except possibly in the subgroup of persons with pre-existing cardiovascular disease.(146)

Notwithstanding these caveats, it is reasonable to be concerned about large QT prolongations, and to derive some comfort from QT intervals that remain unchanged during drug treatment. In fact, **every drug convincingly associated with human *torsade* has been shown — perhaps only at supratherapeutic doses and/or in the presence of co-administered metabolic inhibitors — to cause QT prolongation of at least 60 ms.** This is not to say that all human *torsade*-inducers cause large QT prolongations at conventional doses. As is well known, metabolically-intact subjects who receive normal doses of cisapride or terfenadine sustain QT prolongations of only a few milliseconds, scarcely distinguishing these drugs from placebo. But these drugs can easily be made to cause large QT changes by increased dosing and/or metabolic inhibition.

5.2.1 Early trials

These considerations suggest a strategy for early human studies of a new drug. The purpose of such studies should be to observe the QT effects of the **maximal possible exposure** to the drug and/or —if the electrophysiological effects of the drug are mediated by metabolites — to its metabolites. Including hundreds of subjects is not likely to provide additional information, if a dozen or so subjects have been studied with adequate intensity. QT responses in women and in patients with heart failure are typically greater than those in healthy young men, but the differences are not large, and the quality and stability of electrocardiograms in heart-failure patients is frequently problematic.

Two or more waves of these studies may be necessary, if the first studies are begun before all of the human metabolites are identified and characterized, or before the pertinent metabolic pathways have been identified. If an electrophysiologically-active metabolite accumulates only very slowly, studies of maximal exposure may entail direct administration of the metabolite. Multiple on-treatment measurements are necessary, to be sure that the measurements have been made near the times of peak activity of all of the relevant molecular species.

New drugs are often potential replacements for older drugs that were never properly studied. To simplify interpretation of weakly positive findings, it will sometimes be prudent to include dosing of older drugs of the same therapeutic class in parallel arms of each of these early trials. Ziprasidone, for example, was found to cause non-zero changes in the QT interval, but the same studies were able to show that older medications (phenothiazines and butyrophenones) caused similar changes.(147) Similarly, some agents used as metabolic inhibitors (*e.g.,* ketoconazole) turn out to have small non-zero QT effects of their own,(148) so it may be necessary to include arms for these as well.[11]

In most respects, aggressive maximization of exposure in early trials is appropriate regardless of the adverse effect of interest, but repolarization changes are special in two ways. First, the associated risk (death as the result of malignant tachyarrhythmias) is one from which — by intensive monitoring — Phase 1 subjects can be relatively well protected. When an appropriately monitored Phase 1 subject has had a suspicious electrocardiogram, the option to continue dosing might be more reasonable than it would be if the subject had had an equally suspicious panel of hepatocellular enzymes.

Second, a subject with an unusual repolarization response to a new drug is reasonably likely to have similar responses to others, and electrophysiological evaluation of the subject is therefore in the interest of both

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[11] Grapefruit juice, also important as a CYP3A4 inhibitor, may have a similar effect.(149) Unfortunately, the studies reported used Bazett correction of machine-measured recordings from two fixed leads. The reported findings may therefore not be reliable enough to mention, but possibly they will be repeated with more up-to-date technology.

the drug developer and the subject. No similar statements can be made when a subject's response to a studied drug suggests hematologic or hepatic toxicity.

The observation of large drug-induced QT changes in these trials is important, even if such changes are seen in only one or two subjects, and only at extreme doses. The subjects exhibiting the large changes should be studied further, possibly identifying special risk factors (such as polymorphisms in genes known to be associated with congenital long QT syndrome). Whether or not special risk factors are identified, the observation of large QT changes might make it worthwhile for the developer to return to preclinical studies, possibly demonstrating that the drug is — like amiodarone — one of the few whose QT-prolonging effects are associated with a reduced, rather than an increased, risk of *torsade*.

If exposure was limited (say, by other adverse effects) to only small multiples of that seen with therapeutic dosing, then the non-observation of large drug-induced changes is relatively uninformative. In this situation, the preclinical data are of increased importance.

If only small QT changes are observed, despite exposure exceeding that of ordinary dosing by one or two orders of magnitude, then these trials can be taken to be strongly reassuring.

5.2.2 Later trials and post-marketing surveillance

It is rarely feasible to subject the numerous subjects and patients in later trials to the extensive baseline studies and intensive monitoring that are appropriate in early studies. For these reasons, precise QT interpretation will generally not be possible in the later studies, and aggressive maximization of exposure may be open to ethical question. Some patient populations (notably patients with congestive heart failure (150)) are known to be at increased risk of *torsade,* but even in these populations, *torsade* has not been attributed to drugs that could not, in normal subjects, be made to induce large QT changes. The only interpretable events in later reports will be large QT changes and occasional occurrences of *torsade.* These should be followed up, but important repolarization-related discoveries in these later trials are unlikely if proper attention has been given to early ones.

6   Risk and benefit

The first step in any discussion of risk must be the decision as to whether risk is actually present. Unconfounded observation of human *torsade de pointes* speaks for itself, and *torsade* induced in animals or wedge preparations should also be taken as solid evidence of risk — albeit unquantified — in humans.

Once a drug has been found to carry genuine risk of inducing *torsade*, it is reasonable to expect the duration of the QT interval — properly measured — to be positively associated with the magnitude of risk. In particular, risk may be expected to be reduced when dosing is guided by QT measurement. On the other hand,

the rate of increase of risk with increasing QT interval may differ from drug to drug, just as it differs from one congenital LQT syndrome to another.(151)

More often, preclinical and early clinical studies will provide no direct evidence of risk. They may provide evidence of, *e.g.,* HERG blockade and QT prolongation, but these phenomena are easily produced by agents that do not induce *torsade de pointes* or other malignant tachyarrhythmias. HERG blockade and QT prolongation by themselves are not strong evidence of genuine risk.

On the other hand, to date there has been no example of human *torsade de pointes* induced by a drug that does not block I_{Kr} or by a drug that cannot cause substantial increases in QT duration. We say "to date" because (as noted above) *torsade* certainly occurs in congenital LQT syndromes in which I_{Kr} is unaffected, and it even occurs in LQT patients who have the culprit mutations but normal electrocardiograms. Drug-induced polymorphic ventricular tachycardia unrelated to I_{Kr} and with minimal (or no) QT prolongation will probably sooner or later be reported. Nevertheless, for the moment one can be comforted upon finding that a drug does not block I_{Kr}, or upon finding that it cannot be made to greatly prolong the QT interval.

These comforting findings of inactivity should be convincing only when they are the results of due experimental diligence. For example, normal doses of terfenadine lead to QT prolongations averaging only a few milliseconds when given to metabolically-competent subjects, but the prolongations can be more than an order of magnitude higher when drug metabolism is impaired;(152) the latter effects are the effects of interest. **Before concluding that the QT-prolonging effects of a drug are small, the investigator must have explored the full range of tolerated doses,** under all relevant conditions of metabolic interference.

The techniques of *in vitro* studies and QT interpretation described above have greatly increased the precision with which electrophysiological effects of drugs can be detected and compared. Even when genuine risk has not been demonstrated, one might be tempted to use these measurements as figures of relative merit. For example, developers might be tempted to abandon development of an antibiotic whose IC_{50} for I_{Kr} was 300 nM, preferring to develop a related compound whose IC_{50} in the same assay was 400 nM. Such temptations should be resisted. It is unlikely that differences of this magnitude have any predictive value at all, and other features of the two drugs (*e.g.,* subtle differences in antibiotic efficacy) are likely to be much more important.

When there is evidence of genuine risk (that is, as noted above, reports of *torsade* or presumptive *torsade* in humans or other intact or near-intact higher animals), this evidence must be combined with the evidence of unrelated risks and with the evidence for benefit.

Unrelated risks will in many cases be more important than *torsade,* even if they are not associated with convenient markers like the electrophysiologic and electrocardiographic markers of altered repolarization. When drugs are used in intensive-care settings, *torsade de pointes* should rarely lead to irreversible harm, while other toxicities (*e.g.,* hepatotoxicity or myelotoxicity) may be much more difficult to reverse, even if

they are detected equally promptly. When drugs are prescribed for outpatient use, where *torsade* is more likely to be lethal, *torsade* may still be so rare that it is outweighed in importance by other toxicity.

The ultimate evaluation of risks and benefits will occasionally be simple. Compared to older drugs, the new drug might provide greater benefits at the same or reduced risk, or — as with fexofenadine compared to terfenadine — equal benefits at lower risk. In such a case, the older drugs are what economists call "dominated strategies," and the new drug is uniquely attractive. Conversely, the new drug might be easily rejected if it differs from older alternatives only in providing similar or lesser benefits at greater risk.

If the new drug is not a dominated or dominating strategy, but there is evidence of benefit with respect to a mortality endpoint, the decision is again simple. Regardless of whether *torsade* was or was not seen in the clinical trials, mortality trials have by definition incorporated the ill effects of *torsade*. If there is convincing evidence of net benefit (as in trials of highly torsadogenic arsenic compounds in the treatment of acute promyelocytic leukemia (153-157)), then — unless there is doubt about the generalizability of the trials — there should be no residual concern about *torsade*.

Sometimes the expected benefit of a drug is a reduction in irreversible harm (*e.g.,* a reduction in the incidence of stroke), but the available data show only benefit with respect to a surrogate endpoint (*e.g.,* reduction in blood pressure). These cases are difficult, although it may sometimes be possible when risk has been bounded (*e.g.,* no cases of *torsade* in 10 000 patient-years of exposure) to compare the upper-bound risk of *torsade* to the benefit thought to be linked to the effect on the surrogate endpoint.

If none of the above cases apply, and the expected benefit of the drug is symptomatic, then the integration of risk and benefit may need to be deferred to the affected patients. It is sometimes said that irreversible harm is never acceptable for "mere" symptomatic treatment, but as a description of how informed people commonly behave, this statement is simply false. Some people accept the small mortal risks of taking acetaminophen for common headache, or ibuprofen for dysmenorrhea, but others do not. Some people would choose surgery over radiation therapy for laryngeal cancer because of improved survival, but others would choose radiation therapy because of improved preservation of speech.(158) In the same vein, the recent U.S. Preventive Services Task Force report on postmenopausal hormone replacement therapy (159) acknowledged that "the harmful effects of [such therapy] are likely to exceed the [irreversible-harm] prevention benefits in most women," but stated that in view of the symptomatic benefits "the balance of benefits and harms for an individual woman will be influenced by her personal preferences. . . ." FDA's recent re-approval of alosetron for irritable bowel syndrome (160) appears to have been based on (belated) similar reasoning.

When the risks are even more extreme, society intervenes; therapies carrying high risks and only remote possibilities of benefit are not offered by clinicians, and drug therapies with these characteristics are not approved for marketing. Short of that point, non-dominated pharmacologic therapy for minor symptoms need

not be risk-free to be appropriately developed, registered, and — when the patient informedly agrees — prescribed.

7   Summary and future directions

Put most simply, there is concern about drug-induced *torsade de pointes,* but *torsade* is so rare that seeking it is an impractical, insensitive study. The best predictor of human *torsade* is increased transmural dispersion of repolarization, but this is measurable only in preclinical studies of limited availability. The situation is unsatisfactory.

One might hope that ongoing rapid genetic advances will allow populations at higher risk to be identified, so that detection of risk becomes a practical means of screening, and so that patients at increased risk can be identified and, perhaps, excluded from some therapies. These hopes may be unrealistic. Genotyping for any of the hundreds of LQTS variations is now so expensive that such screening must be limited to research settings. Technological advances may substantially reduce these costs, but even if they do, widespread screening appears unlikely to be adopted rapidly. We say this because humans with known characteristics leading to adverse reactions to some pharmacotherapy (CYP2D6 poor metabolizers, for example, or persons with pseudocholinesterase deficiency) have been easily identifiable for many years, but few such patients are in practice identified prospectively. In a risk-averse regulatory environment, the prospect of therapies indicated for, or contraindicated in, only people of certain genotypes is sure to be problematic.

Unlike the overall QT interval, some T-wave-derived measurements appear — as described in Section 5.1.5 — to be more directly linked to transmural dispersion of repolarization. These measurements are promising, but their validation may be difficult in the absence of an accepted methodology in populations at high risk of drug-induced *torsade de pointes.*

Contributors

The project was organized by RRF and MM. Initial position statements were submitted by CA (implications of transmyocardial dispersion of repolarization), LC (preclinical in vivo investigations), DMR (clinical and regulatory implications), RRF (introduction, risks and benefits), MM (electrocardiography), SGP (genetic considerations), JR (clinical considerations), and MS (in vitro investigations), and these contributions were then criticized by other members. After a 2-day strategy meeting attended by CA, LC, DMR, RRF, RJL, MM, and JR, and with continuing interactions among all of the members, the manuscript was written by RRF and edited by MM.

Disclosures of potential conflicts of interest

In the past two years, CA has received consulting fees or research support from Aventis Pharmaceuticals, Chugai Pharmaceutical, CV Therapeutics, Eli Lilly Pharmaceuticals, Pfizer Pharmaceuticals, and Physiome Sciences; LC has received consulting fees from Almirall Prodesfarma, ICOS, Eli Lilly, Sanofi-Synthélabo, and ViroPharma; RRF has received consulting fees from Abbott Laboratories, Actelion Pharmaceutical, Aderis Pharmaceuticals, Almirall Prodesfarma, AstraZeneca LP, Aventis Pharmaceuticals, Berlex Laboratories, Boehringer-Ingelheim Pharmaceuticals, Bristol-Myers Squibb, Centocor, Corgentech, Corvas International, CV Therapeutics, DepoMed, Forest, GlaxoSmithKline, Hoffman-LaRoche, Lilly Research Laboratories, H. Lundbeck A/S, Meditor, Medtronic, MetaPhore Pharmaceuticals, Mylan Laboratories, Myogen, NeuroSearch, Novartis, Otsuka, Penwest Pharmaceuticals, Pfizer Pharmaceuticals, Pharmacia & Upjohn, Physiome Sciences, Procter and Gamble, Purdue, Reddy, Ross, Roxane Laboratories, Sanofi-Synthélabo, Schwarz BioSciences, Scios, Sepracor, Sigma Tau, Somerset, Synpac, Theravance, Upsher-Smith, United Therapeutics, Watson Pharma, WinPharm, Wyeth-Ayerst, Yamanouchi Pharma America, and Zengen; RJL has received consulting fees from Academic Pharmaceuticals, Abbott Laboratories, Actelion Pharmaceuticals, Alexion Pharmaceuticals, Almirall Prodesfarma, Alteon Inc., Amylin Pharmaceuticals, Angiogenix Inc, Astra Zeneca LP, Aventis Pharmaceuticals, Bayer, BioCryst, BioMarin Pharmaceuticals, Boehringer-Ingelheim Pharmaceuticals, Biovail, Bracco Diagnostics, Collegium Pharmaceutical, Combinatorix Inc., CV Therapeutics, CuraGen Corporation, Diakron Pharmaceuticals, Dr Reddy's Laboratory, eNos Pharmaceuticals, Esperion, Fujisawa, GlaxoSmithKline, Hyseq Pharmaceuticals, ICOS, Indevus, INO Therapeutics, Jansen (Johnson & Johnson), King, LaJolla, Lilly Research Laboratories, H. Lundbeck A/S, The Medicines Company, Medifacts (Med Therapeutics), Medtronic AVE, Inc., Mission Pharmaceuticals, Mylan Laboratories, Myogen, Inc., Nerosearch, Novartis, Otsuka, Pfizer, Pharmacia & Upjohn, Point Biomedical, Provensis, Reliant, Restoregen, Sanofi-Synthélabo, Scios, Sepracor, Shire, Sigma Tau, Solvay, Speedel, Synergy Research, Taro, Transform, United Therapeutics, VDDI, Vivus, Wellspring and Wyeth-Ayerst Pharmaceuticals; MM has received consulting fees from Abbott Laboratories, Almirall Prodesfarma, Alza Corporation, Antisoma Ltd, AstraZeneca, Aventis Pharma, Boehringer-Ingelheim Pharmaceuticals, Cardionetics Ltd, CV Therapeutics, Eisai Ltd, Forum Bioscience Holding, GlaxoSmithKline, Global Medical Solutions, Grünenthal GmbH, Icon Clinical Research, Janssen Research Foundation, Lilly Research Laboratories, Lundbeck A/S, Lorex Synthelabo, Medtronic, Merck Research Laboratories, Neurosearch, Novartis, Otsuka, Pfizer Pharmaceuticals, Roche Products Ltd, Sanofi-Synthelabo, Schering AG, and Takeda Pharmaceuticals; SGP has received consulting fees from Almirall Prodesfarma, H. Lundbeck A/S, and Pharmacia & Upjohn; DMR has received consulting or speaking fees from Abbott Laboratories, Alza, AstraZeneca LP, Bayer, Boehringer Ingelheim Japan , Bristol-Myers Squibb, CV Therapeutics, GlaxoSmithKline, Johnson & Johnson, Medtronic, Pfizer Pharmaceuticals, Pharmacia, Schering Plough, Solvay Pharmaceuticals, and Yamanouchi Pharma America; JR has received consulting fees and honoraria from Almirall Prodesfarma, Bristol-Myers Squibb, Cryo Cath, CV

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