

Female Gender as a Risk Factor for Torsades de Pointes Associated With Cardiovascular Drugs

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Objective.—To test the hypothesis that female prevalence is greater than expected among reported cases of torsades de pointes associated with cardiovascular drugs that prolong cardiac repolarization.

Data Sources.—A MEDLINE search of the English-language literature for the period of 1980 through 1992, using the terms *torsade de pointes*, *polymorphic ventricular tachycardia*, *atypical ventricular tachycardia*, *proarrhythmia*, and *drug-induced ventricular tachycardia*, supplemented by pertinent references (dating back to 1964) from the reviewed articles and by personal communications with researchers involved in this field.

Study Selection.—Ninety-three articles were identified describing at least one case of polymorphic ventricular tachycardia (with gender specified) associated with quinidine, procainamide hydrochloride, disopyramide, amiodarone, sotalol hydrochloride, bepridil hydrochloride, or prenylamine. A total of 332 patients were included in the analysis following application of prospectively defined criteria (eg, corrected QT [QT_c] interval of 0.45 second or greater while receiving drug).

Data Extraction.—Clinical and electrocardiographic descriptors were extracted for analysis. Expected female prevalence for torsades de pointes associated with quinidine, procainamide, disopyramide, and amiodarone was conservatively estimated from gender-specific data reported for antiarrhythmic drug prescriptions in 1986, as derived from the National Disease and Therapeutic Index, a large pharmaceutical database; expected female prevalence for torsades de pointes associated with sotalol, bepridil, and prenylamine was assumed to be 50% or less since these agents are prescribed for male-predominant cardiovascular conditions.

Results.—Women made up 70% (95% confidence interval, 64% to 75%) of the 332 reported cases of cardiovascular-drug-related torsades de pointes, and a female prevalence exceeding 50% was observed in 20 (83%) of 24 studies having at least four included cases. When analyzed according to various descriptors, women still constituted the majority (range, 51% to 94% of torsades de pointes cases), irrespective of the presence or absence of underlying coronary artery or rheumatic heart disease, left ventricular dysfunction, type of underlying arrhythmia, hypokalemia, hypomagnesemia, bradycardia, concomitant digoxin treatment, or level of QT_c at baseline or while receiving drug. When cases of torsades de pointes were analyzed by individual drug, observed female prevalence was always greater than expected, representing a statistically significant difference ($P < .05$) for all agents except procainamide.

Conclusions.—These findings strongly suggest that women are more prone than men to develop torsades de pointes during administration of cardiovascular drugs that prolong cardiac repolarization. The pathophysiological basis for, and therapeutic implications of, this gender disparity should be further investigated.

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TORSADES de pointes is defined as polymorphic ventricular tachycardia occurring in the setting of a lengthened QT interval, reflecting prolonged cardiac repolarization.¹⁻⁶ This arrhythmia may cause syncope or even precipitate ventricular fibrillation and cardiac arrest.^{2,3,7} Although some individuals may be prone to torsades de pointes on the basis of a congenital abnormality of cardiac repolarization,^{8,9} the arrhythmia is more commonly seen as an acquired disorder in the setting of electrolyte abnormalities (particularly hypokalemia) or following administration of drugs that can prolong the QT interval.^{2-6,10}

While many agents have been implicated, certain cardiovascular medications—class IA and class III antiarrhythmic agents and some antianginal drugs—constitute the most extensively documented group of offenders. For quinidine alone it has been estimated that torsades de pointes may occur in 1.5% of patients treated with this class IA agent over a 1-year period¹¹; in earlier reports of patients receiving quinidine for atrial fibrillation, 2.9% to 8.5% developed known or presumed torsades de pointes¹²⁻¹⁵ and 0.5% to 5.9% died suddenly.^{14,16,17}

Torsades de pointes appears to be mechanistically distinct from other types of ventricular proarrhythmia.¹⁸ Whereas non-torsades de pointes proarrhythmia is more likely to occur in patients with prior myocardial scarring and depressed left ventricular function,^{19,20} clinical factors other than coexistent electrolyte disturbances that may promote the occurrence of torsades de pointes during drug administration are not well defined.

Some clinical reports²¹⁻²⁴ and anecdotal observations²⁵ have suggested that women may be more prone to develop drug-related torsades de pointes, but this impression has never been critically assessed. In the present investigation, female prevalence among patients who developed torsades de pointes during treatment with cardiovascular drugs

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that prolong repolarization was evaluated in 332 cases systematically identified from the literature.

METHODS

Literature Search

We conducted a comprehensive search of the medical literature (in English) for the period from 1980 (the year of a comprehensive review by Smith and Gallagher²) through 1992, using MEDLINE, searching titles and abstracts for the following terms: *torsade de pointes*, *polymorphic ventricular tachycardia*, *atypical ventricular tachycardia*, *proarrhythmia*, and *drug-induced ventricular tachycardia*. An additional search was made combining known offending drugs used in the treatment of cardiovascular diseases, ie, quinidine, procainamide hydrochloride, disopyramide, sotalol hydrochloride, amiodarone, prenylamine, and bepridil hydrochloride, with the term *toxicity*. Bibliographies from these articles were studied to uncover further reports dating back to 1964, the year of the classic article by Selzer and Wray²⁶ on the mechanism of "quinidine syncope." Personal communication with investigators in the field yielded additional information on three published articles,^{22,27,28} and another submitted for publication (L. Brent Mitchell, MD, written communication, October 1992) that came to our attention from a recent preliminary report.²⁹

Patient Selection and Data Extraction

The articles identified by literature search were reviewed using prospectively defined inclusion and exclusion criteria. An article was included if it (1) was published (or referred to and described in detail) in the English-language literature; or (2) described at least one case of polymorphic ventricular tachycardia, with specification of patient gender, occurring in association with therapeutic administration of one of the following drugs: quinidine, procainamide, disopyramide, amiodarone, sotalol, bepridil, or prenylamine. Within a given article, individual patients were excluded if one or more of the following criteria applied: (1) they had not been taking one of the aforementioned drugs; (2) their gender was not specified; (3) they did not have polymorphic ventricular tachycardia; (4) they had polymorphic ventricular tachycardia without manifest QT prolongation (as defined below); (5) they were reported to have congenital long-QT syndrome; or (6) they represented duplicate reports of patients already included in other series.

When available, the following data were extracted for each patient: age,

gender, drug(s) administered, type of underlying arrhythmia, absolute QT and rate-corrected QT (QT_c) intervals at baseline and while receiving drug(s), and presence or absence of hypokalemia, hypomagnesemia, or bradycardia prior to the onset of torsades de pointes, concomitant digoxin therapy, rheumatic heart disease, hypertension, coronary artery disease, or left ventricular failure. In studies in which individual patient data were unavailable,^{11,21,30-32} aggregate data (eg, mean age, total number of men and women, and type of drug[s] administered) were used and decisions regarding patient exclusions were always made in favor of the null hypothesis (ie, deliberately biased to reduce female prevalence of torsades de pointes.)

Definitions

The following prospectively developed definitions were used:

Torsades de Pointes.—Polymorphic ventricular tachycardia in the setting of a prolonged QT interval^{1-6,23}; this definition is in accord with the generally accepted impression that polymorphic ventricular tachycardia without QT prolongation is a mechanistically and electropharmacologically distinct entity.^{4,31,33}

QT Prolongation.—A QT_c interval (measured by Bazett's formula, QT/\sqrt{RR}) of 0.45 second or greater; this conventional definition³⁴ is a liberal one in that it permits the inclusion of individuals with borderline QT_c prolongation.⁹ All QT_c and QT values were specified in increments of 0.01 second. In the minority of cases in which QT_c was either not provided or not calculable based on specified QT and heart rate, we arbitrarily required the absolute QT interval while receiving drug to be 0.50 second or greater for a patient to be included. Although some authors have used an absolute QT criterion as high as 0.60 second,¹¹ such a value could exclude many cases of drug-related torsades de pointes.³ Our working cutoff value of 0.50 second or greater for absolute QT was intended to minimize the number of such exclusions while also minimizing the inclusion of cases of polymorphic ventricular tachycardia without QT prolongation,^{4,34,35} which may have been mistaken for drug-induced torsades de pointes. When neither QT_c nor absolute QT while receiving drug was specified in the article, the QT interval measured from the published electrocardiographic tracing was used, if available.

Baseline QT_c.—The QT_c value (specified or calculated) prior to institution of drug or, if not available, the lowest value specified after discontinuation of the drug.

QT_c While Receiving Drug.—The QT_c value (specified or calculated) immediately prior to the onset or after the termination of torsades de pointes.

Bradycardia.—Heart rate less than 60 beats per minute.

Hypokalemia.—Serum potassium level less than 3.5 mmol/L.

Hypomagnesemia.—Serum magnesium level less than 0.82 mmol/L (2 mg/dL).

Left Ventricular Dysfunction.—Ejection fraction of 45% or less, or specification in the article of congestive heart failure.

Statistical Analysis

To evaluate female prevalence among published cases of drug-related torsades de pointes, we compared the proportion of women with torsades de pointes observed with that which was expected. We estimated this expected proportion, in part, from a Food and Drug Administration report by Hine et al³⁶ concerning outpatient antiarrhythmic drug use over the last two decades, as derived from the pharmaceutical databases produced by IMS America, Plymouth Meeting, Pa. Hine et al³⁶ reported that of the approximately 6.0 million, 8.8 million, and 11.5 million antiarrhythmic-agent prescriptions dispensed in the United States in the years 1977, 1981, and 1986, respectively, the corresponding proportion of women among drug recipients was 38%, 42%, and 44%, respectively. Hence, we conservatively estimated that the expected overall prevalence of women among cases of antiarrhythmic-drug-related torsades de pointes was 44%. Whereas total drug prescription data reported by Hine et al³⁶ were derived from the National Prescription Audit, demographic information, including gender distribution, could be obtained only through the National Disease and Therapeutic Index.³⁶ Accordingly, for four individual drugs—quinidine, procainamide, disopyramide, and amiodarone—expected female prevalence was derived from summary data on 4.7 million drug appearances (entries) for antiarrhythmic agents in the National Disease and Therapeutic Index for 1986, provided by IMS America (Richard A. Fehring, written communication, January 1992). For the three drugs bepridil, prenylamine, and sotalol, no data were available for estimating expected female prevalence. In these cases we arbitrarily used an expected female prevalence of 50%. This is clearly a conservative estimate favoring the null hypothesis, as these drugs are used to treat coronary artery disease (bepridil and prenylamine), hypertension (sotalol), or sustained ventricular tachyarrhythmias (sotalol), all male-predominant conditions.³⁷⁻⁴¹

The observed proportion of torsades de pointes cases involving women for each drug and for various clinical subcategories was calculated together with exact two-tailed 95% confidence limits.⁴² Regarding specific drugs, if the expected proportion of women fell below the lower 95% confidence limit, we concluded that women were significantly overrepresented.

Comparisons between two groups were made using the unpaired Student's *t* test or the Wilcoxon two-sample test, as appropriate. The effects of gender and QT_c at baseline on QT_c while receiving drug and ΔQT_c (change in QT_c while receiving drug) were assessed using two-way analysis of variance (ANOVA), followed by appropriate post hoc contrasts. All hypothesis tests were two-tailed and considered statistically significant if *P* values were less than .05.

RESULTS

Article Selection

Ninety-three articles* met the inclusion criteria. One relevant French article,⁵⁰ cited in detail by an English-language publication,¹²² was included. Another study,¹²³ also in French, was used to provide data to supplement a more extended English article by the same authors.⁷ Patients described in these articles were then subjected to the exclusion criteria. Ten articles were totally excluded from the analysis because all patients in these articles met exclusion criteria.^{3,113-121} Of the remaining 83 articles, 24 each yielded four or more patients who met the inclusion criteria and were analyzed as distinct studies.† The other 59 articles^{2,7,26,32,58-112} each contained one to three cases that met the inclusion criteria, which yielded a total of 77 patients; for simplicity of presentation, these patients were grouped together as one "study" and labeled "Case reports" (Table 1).

Description of Excluded Patients

Of the 644 patients reported among the 93 articles, 312 were omitted after application of the prospectively defined exclusion criteria: 56 were not receiving the appropriate drugs; information about gender was unavailable for 53 patients; 46 were not known to have polymorphic ventricular tachycardia; 121 did not have QT prolongation or information on QT interval was lacking; five had congenital long-QT syndrome; and 31 represented

duplicate reports of patients already included in other series. Thus, we present an analysis of 25 studies reporting a total of 332 cases of cardiovascular-drug-related torsades de pointes.

Characteristics of the Included Studies

The number of patients in the 25 studies included in our analysis ranged from four to 77 (Table 1). Four studies^{11,21,30,31} yielded aggregate data only (45 patients); the remaining 21 studies provided individual data on 287 patients. Eight of the 25 studies consisted of patients exposed to a single agent.^{11,21,22,28,44,45,48,53} Information on both gender and drug was available for 314 (95%) individual patients, and of these, 19 (6%) were receiving two of the implicated drugs. Information on both gender and age was available for 282 (85%) individual patients; median age was 66 years for men and 65 years for women (range for all patients, 16 to 90 years).

Overall Female Prevalence

Women made up 70% (95% confidence interval, 64% to 75%) of all cases of cardiovascular-drug-related torsades de pointes included in our analysis. A high prevalence of women (63%; 95% confidence interval, 58% to 67%) was also found among all 453 cases with known gender and polymorphic ventricular tachycardia associated with cardiovascular drugs, prior to the application of the prospectively determined QT exclusion criteria. Moreover, of the cases of torsades de pointes that met the inclusion criteria, a female prevalence exceeding 50% was observed in 21 (84%) of the studies (Table 1).

Female Prevalence in Various Clinical Subcategories

To assess whether any clinical parameters might account for the greater-than-expected female prevalence, we analyzed the proportion of women in various clinical subcategories (Table 2). A high female prevalence (range, 58% to 94%) was observed irrespective of the presence or absence of hypokalemia, hypomagnesemia, concomitant digoxin treatment, hypertension, bradycardia, left ventricular dysfunction, underlying coronary artery or rheumatic heart disease, or type of underlying arrhythmia.

Female Prevalence for Different Drugs

When female prevalence among cases of torsades de pointes for each cardiovascular drug was compared with each expected prevalence, every agent was associated with more female cases of torsades de pointes than expected (Table

3). These differences were statistically significant for all drugs except procainamide.

In the 173 patients (52%) for whom dosage data were available, doses of administered drugs fell within common clinical ranges. There were no statistically significant differences in doses between women and men, although in most cases women were taking lower doses of drug. Only limited data on drug blood levels were available. The most information available for a single drug was derived from 47 patients taking quinidine; no statistically significant differences in blood levels of quinidine were found between 24 women vs 23 men receiving the drug (4.1 ± 2.2 μg/mL vs 5.4 ± 4.3 μg/mL, respectively).

Relation to QT Interval

The QT_c at baseline ranged from 0.30 second to 0.65 second (*n*=164); the QT_c while receiving drug, from 0.45 second to 0.88 second (*n*=283); and the absolute QT while receiving drug, from 0.34 second to 0.84 second (*n*=237). There was no significant difference between women and men with respect to the attained mean QT_c while receiving drug (Table 4), yet a greater prevalence of women among torsades de pointes cases was observed for each level of QT_c or absolute QT prolongation while receiving drug: mild (0.50 second or less); moderate (0.51 to 0.60 second); and severe (greater than 0.60 second) (Table 2). There were no statistically significant gender differences in mean baseline QT_c ($.43 \pm .05$ second in women vs $.45 \pm .05$ second in men). However, for each of three ranges of baseline QT_c—normal (0.41 second or less), equivocal (0.42 to 0.46 second) and prolonged (0.47 second or greater), as established by Keating et al¹²⁴—female predominance among torsades de pointes cases was evident (Tables 2 and 4).

Table 4 contains information on the 154 patients for whom QT_c data were available both at baseline and while receiving drug. For each of the three ranges of baseline QT_c, there was no difference in QT_c attained while receiving drug between men and women, nor was there a difference in mean change in QT_c (ΔQT_c). Regardless of gender, however, the mean change in QT_c was significantly greater for individuals with baseline QT_c of 0.41 second or less or 0.42 to 0.46 second vs those with a baseline QT_c of 0.47 second or greater (*P*<.005).

COMMENT

Although some investigators have commented on an apparent increased female prevalence among patients with

*References 2, 3, 7, 11, 21, 22, 26-30-32, 35, 43-121, and an unpublished study (L. Brent Mitchell, MD, written communication, October 1992).

†References 11, 21, 22, 27, 28, 30, 31, 35, 43-57, and an unpublished study (L. Brent Mitchell, MD, written communication, October 1992).

Table 1.—Articles Reporting Cases of Cardiovascular Drug-Related Torsades de Pointes

Author	Year	Form of Data Specification*	No. of Patients Included in Final Analysis	Median Age, y (Range)	Drug(s) Implicated and No. of Patients†	Female Prevalence, %
DiSegni et al ⁴³	1980	Individual	8	42 (30-82)	Q=5, Pr=1, Q+Pr=1, PA+Pr=1	87
Grenadier et al ⁴⁴	1980	Individual	8	73 (62-84)	Pr=8	75
Strasberg et al ⁴⁵	1981	Individual	4	64 (54-67)	PA=4	25
Khan et al ⁴⁶	1981	Individual	6	66 (46-75)	A=1, Pr=3, Q=2	83
Keren et al ³⁰	1981	Aggregate	9	NA‡	D=3, Q=4, A+D=2	89
Denes et al ⁴⁷	1981	Individual	5	61 (51-65)	Q=4, Q+PA=1	60
Sclarovsky et al ⁴⁸	1983	Individual	5	69 (33-72)	A=5	60
Abinader et al ²¹	1983	Aggregate	7	71§	Pr=7	71
Kay et al ⁴⁹	1983	Individual	29	61 (28-79)	A=1, D=2, PA=4, Q=19, A+PA=1, PA+D=1, PA+Q=1	48
Leclercq et al ⁵⁰	1983	Individual	15	77 (61-90)	B=14, B+Q=1	87
Lewis et al ⁵¹	1983	Individual	4	56 (56-75)	PA=1, Q=3	100
McKibbin et al ⁵²	1984	Individual	12	65 (31-75)	S=10, S+D=2	92
Manouvrier et al ⁵³	1986	Individual	9	72 (65-82)	B=9	89
Roden et al ¹¹	1986	Aggregate	20	NA	Q=20	55
Brown et al ⁵⁴	1986	Individual	5	69 (33-72)	A=3, A+D=2	100
Nguyen et al ⁵⁵	1986	Individual	19	67 (50-82)	A=3, D=1, PA=5, Q=9, S=1	58
Tzivoni et al ³¹	1988	Aggregate	9	NA	A=1, PA=3, Q=3, Q+A=1, PA+A=1	78
Mattioni et al ⁵⁵	1989	Individual	10	66 (38-75)	D=1, PA=4, Q=3, S=2	60
Jorens et al ⁵⁶	1989	Individual	12	56 (49-85)	A=10, A+Pr=1, A+PA=1	67
Kadish et al ⁵⁷	1990	Individual	8	60 (21-84)	D=1, PA=3, Q=4	50
Ohe et al ²⁷ ¶	1990	Individual	15	55 (16-83)	D=6, PA=4, Q=3, D+PA=1, PA+Q=1	80
Mitchell¶	1990	Individual	11	71 (43-78)	D=2, PA=2, Q=7	55
Kasanuki et al ²² #	1992	Individual	21	67 (39-83)	D=21	86
Singh ^{28**}	1992	Individual	4	55 (55-70)	B=4	25
Case reports††	1964-1992	Individual	77	65 (21-84)	A=5, D=15, Q=29, Pr=4, PA=12, S=8, Q+D=3, Q+A=1	70

*The term *Individual* pertains to studies in which information is provided for each patient, whereas the term *Aggregate* is used for summary-type presentations of patient data. †A indicates amiodarone; B, bepridil hydrochloride; D, disopyramide; PA, procainamide hydrochloride; Pr, prenylamine; Q, quinidine; and S, sotalol hydrochloride. ‡NA indicates not available.

§Mean value; age range not available.

¶Additional data obtained by written communication with Tohru Ohe, MD, December 1992.

¶¶Written communication with L. Brent Mitchell, MD, October 1992.

#Additional data obtained by written communication with Hiroshi Kasanuki, MD, December 1992.

**Additional data obtained by written communication from the drug manufacturer (Laura M. Litzemberger, PharmD, McNeil Pharmaceutical, Spring House, Pa, November 1992).

††This category consists of articles^{2,7,26,32,58-112} which, after application of patient exclusion criteria (see text), yielded fewer than four patients per article.

drug-induced torsades de pointes,²¹⁻²⁵ this potential association has never been systematically evaluated. The absence of such an analysis heretofore may explain why the possible contributory role of female gender was not mentioned in recent reviews of drug-induced arrhythmias and torsades de pointes.^{3,6,19}

Consistency of Female Gender Predominance

The most striking aspect of our quantitative study of the literature is the consistency of female preponderance evident throughout various phases of our analysis and among multiple different clinical subgroupings of the reported cases of torsades de pointes. Thus, a greater female prevalence was observed among all cases of cardiovascular-drug-related polymorphic ventricular tachycardia both before and after application of the QT exclusion criteria. The fact that female gender predominance was also noted in 84% of the studies analyzed (Table 1) attests to the consistency of the observation over time. Furthermore, a preponderance of female

over male cases of drug-related torsades de pointes was maintained independent of the presence or absence of various clinical descriptors (Table 2), including those that might promote torsades de pointes (eg, hypokalemia).

Within each of three ranges of progressively prolonged QT_c or absolute QT intervals (less than 0.50 second, 0.51 to 0.60 second, and greater than .60 second) recorded while the study patients were receiving the offending drugs, female gender predominance was evident. Thus, female overrepresentation would have been maintained even if we had required for inclusion a QT_c or absolute QT interval while receiving drugs that was greater than the cutoff values of 0.45 second and 0.50 second, respectively.

When reported cases of torsades de pointes were grouped by associated cardiovascular drug (Table 3), observed female prevalence was greater than expected for all seven agents included in the analysis, and the differences were statistically significant for each drug except procainamide.

Methodological Issues

Retrospective reviews are subject to several methodological problems, most notably incompleteness of sampling, selection bias, inconsistencies in data reporting among articles in the literature, and selection of an appropriate control group.¹²⁵ We attempted to counter these obvious limitations in several ways.

First, articles for analysis were obtained not only through a MEDLINE search but also through examination of references cited in the bibliographies of all articles obtained by computer, supplemented by personal communication. One might argue that even if our search were 100% inclusive, there may have been unreported cases of torsades de pointes associated with cardiovascular drugs in which males predominated to a degree that would cancel out the increased female prevalence we observed among reported cases. In view of the scant attention devoted to this subject in the proarrhythmia literature, however, it is difficult to imagine why, or on what basis, authors would preferentially report

cases of drug-related torsades de pointes in women. Yet, we must also consider the possibility that indirect gender biases may have been operative. For example, some male cases may never have reached an investigator's attention because those patients died prior to diagnosis, perhaps owing to a lower probability of their being successfully resuscitated from ventricular fibrillation (the most extreme manifestation of torsades de pointes). The large Seattle, Wash, experience with community treatment of cardiac arrest patients,¹²⁶ however, has not revealed any difference in sex ratio for victims vs survivors of out-of-hospital ventricular fibrillation. Moreover, we calculate that we would have had to miss 143 cases of torsades de pointes occurring exclusively in men to render statistically nonsignificant the comparison of overall observed (70%)

and expected (44%) proportions of women with torsades de pointes.

Second, given the variations and degree of clinical detail and type of data reported in the literature, we sought to enhance the interpretability of our analysis by applying uniform, prospectively developed working clinical definitions and exclusionary criteria.

Third, we estimated the expected value of female prevalence among cases of torsades de pointes in a conservative manner (ie, favoring the null hypothesis). For the antiarrhythmic agents quinidine, procainamide, disopyramide, and amiodarone, estimates of expected female prevalence were derived from a large national pharmaceutical database from 1986, the year corresponding to the peak proportional use of these drugs by women (44%) from 1977 through 1986.³⁶ This figure is strikingly concordant with those recently reported among 143 patients taking quinidine (45% women) and 210 patients taking procainamide (42% women) for various arrhythmic indications.¹²⁷ The high estimate for the expected prevalence of women among patients developing torsades de pointes while receiving disopyramide likely reflects a lower utilization rate of the drug in men owing to urinary

tract side effects. With regard to bepridil, prenylamine, and sotalol, we believe that an expected female prevalence of 50% clearly represents an upper-limit estimate (see "Methods").

Gender Differences in Susceptibility to Quinidine Syncope

It is now appreciated that when investigators reported the occurrence of syncope or aborted cardiac arrest during quinidine administration for atrial fibrillation or flutter prior to the 1980s,^{12-14,113} they were most likely describing manifestations of quinidine-related torsades de pointes.^{3,15,26,58-62} Based on the present findings, therefore, one would expect an increased female prevalence also among these cases of quinidine syncope. Relevant data are available from a 1968 report by Cramer¹³ that describes in great detail the clinical course of 237 patients treated with quinidine for conversion of atrial fibrillation. Of the 16 patients in that study who developed syncope (associated with cyanosis or apnea in six and documented ventricular tachycardia or fibrillation in another two) during quinidine administration, 15 (94%) were women, a much greater prevalence than expected (47%; $P < .001$).

Table 2.—Female Prevalence Among Cases of Torsades de Pointes, by Clinical Descriptors

	No.	Female Prevalence, % (95% CI)*
All cases	332	70 (64-75)
No rheumatic disease	122	62 (53-71)
Rheumatic disease	47	94 (82-99)
No coronary artery disease	103	80 (70-87)
Coronary artery disease	103	62 (52-72)
No hypertension	101	74 (64-83)
Hypertension	60	63 (49-76)
No left ventricular dysfunction	50	86 (73-95)
Left ventricular dysfunction	88	58 (47-69)
Atrial arrhythmia	92	78 (68-87)
Ventricular arrhythmia	111	59 (48-68)
No hypokalemia	158	69 (61-76)
Hypokalemia	66	73 (60-83)
No hypomagnesemia	64	73 (60-84)
Hypomagnesemia	9	67 (29-93)
No digoxin	98	74 (64-83)
Digoxin	103	70 (60-79)
No bradycardia	73	67 (55-78)
Bradycardia	52	71 (56-83)
QT _c while receiving drug, s		
≤0.50	27	63 (42-81)
0.51-0.60	114	70 (60-79)
>0.60	117	70 (61-79)
QT (absolute) while receiving drug, s		
≤0.50	42	64 (48-79)
0.51-0.60	91	65 (54-75)
>0.60	79	77 (66-86)
QT _c at baseline, s†		
≤0.41	51	75 (60-86)
0.42-0.46	65	65 (51-76)
≥0.47	39	51 (34-68)

*CI indicates confidence interval.
†These three corrected QT (QT_c) interval ranges are based on the stratification of Keating.¹²⁴

Table 3.—Comparison of Observed vs Expected Female Prevalence Among Cases of Torsades de Pointes, by Drug

Drug	No.*	Median Age, y	Observed Female Prevalence		Expected Female Prevalence	
			%	95% CI†	%	P
Quinidine	108	64	60	50-70	43‡	<.002
Procainamide hydrochloride	39	66	49	32-66	38‡	.21
Disopyramide	49	66	86	72-94	63‡	<.002
Amiodarone	28	64	68	47-85	32‡	<.001
Sotalol hydrochloride	21	65	76	52-92	50§	<.04
Bepridil hydrochloride	27	73	74	53-89	50§	<.02
Prenylamine	23	71	78	56-93	50§	<.02
Two drugs	19	66	89	63-99	NA	NA

*Total number of patients adds up to 314 (rather than 332) because two aggregate studies,^{30,31} totaling 18 patients, included cases of exposure to more than one drug, making it impossible to calculate female prevalence for specific drugs.

†CI indicates confidence interval.
‡Based on data provided through a large national pharmaceutical marketing research database produced by IMS America, Plymouth Meeting, Pa, with specific reference to outpatient use of antiarrhythmic drugs in 1986, originally reported by Hine et al³⁶ and supplemented by written communication (Richard A. Fehring, IMS America, January 1992).

§For sotalol, bepridil, and prenylamine, where extensive data were not available to estimate expected female prevalence, a conservative estimate of 50% was used. (An even lower prevalence is actually expected, since these drugs are mainly used to treat male predominant conditions.)

||NA indicates not applicable.

Table 4.—QT_c While Receiving Drug, as a Function of QT_c at Baseline, for Women and Men With Torsades de Pointes*

QT _c at Baseline, s	Women			Men			Women and Men		
	No.	QT _c While Receiving Drug, s	ΔQT _c , s†	No.	QT _c While Receiving Drug, s	ΔQT _c , s†	No.	QT _c While Receiving Drug, s	ΔQT _c , s†
≤0.41	38	0.58±0.06	0.20±0.05	13	0.58±0.04	0.19±0.06	51	0.58±0.06	0.20±0.05
0.42-0.46	42	0.61±0.08	0.17±0.08	23	0.58±0.06	0.14±0.06	65	0.60±0.07	0.16±0.08
≥0.47	20	0.58±0.08	0.07±0.08‡	18	0.57±0.07	0.08±0.07‡	38	0.58±0.07	0.07±0.08‡
Total, All Values	100	0.59±0.07	0.16±0.08	54	0.58±0.06	0.13±0.08	154	0.59±0.07	0.15±0.08

*Corrected QT (QT_c) interval while receiving drug and ΔQT_c values are expressed as mean±SD.

†ΔQT_c is the difference between QT_c while receiving drug and QT_c at baseline.

‡Significantly different ($P < .005$) from ΔQT_c corresponding to shorter values of QT_c at baseline (ie, .42 to .46, or ≤.41).

Possible Explanations for Female Gender Predominance

Both extracardiac and intrinsic cardiac factors must be considered in trying to explain our findings. Although drug dosages were comparable in male and female cases of torsades de pointes included in our series, it might be argued that the smaller body mass of women, on average, predisposed them to higher serum drug levels, which might have facilitated the occurrence of torsades de pointes. Although such an explanation cannot be absolutely excluded, it is unlikely, because the occurrence of torsades de pointes does not appear to be related to any critical serum drug level.^{3,129} Moreover, among patients in whom quinidine was the implicated agent in our study, there was no significant difference in serum levels of this drug among men and women for whom such data were available. These findings are consistent with previous observations in patients with quinidine syncope.¹³

Another theoretical contributory factor to consider is hypothyroidism, which is more common in women,¹²⁹ and which can certainly cause QT prolongation and precipitate torsades de pointes.¹³⁰ The possibility of a preponderance of female cases with unrecognized clinical hypothyroidism in our study is mitigated, however, by the finding of a normal baseline QT_c (less than 0.41 second) in a greater proportion of women than men with torsades de pointes (38 of 100 vs 13 of 54, respectively; Table 4). Subclinical hypothyroidism may also have been more prevalent in the female study patients,¹³¹ but there is no evidence to date that this entity facilitates the occurrence of torsades de pointes.

Our results also indicate that other potential extracardiac factors such as hypokalemia, hypomagnesemia, or digoxin administration are not likely to account for the increased female prevalence in cardiovascular-drug-related torsades de pointes, since women predominated even among cases in which these factors were absent. Thus, we must consider the possibility that intrinsic cardiac electrophysiological differences between women and men may explain our observations.

Female Gender and Susceptibility to Repolarization Abnormalities

The present findings are compatible with a number of other observations in the literature pointing to a female predisposition to prolonged cardiac repolarization and torsades de pointes. Even in the normal population, women have been shown to possess a longer average QT_c interval than men.^{35,132,133} Using com-

puter analyses of digitized electrocardiographic tracings drawn from a database of 423 normal individuals, Merri and coworkers¹³³ documented in women a relative prolongation not only of QT_c but also of a newly derived independent index of early repolarization duration ("S-offset T-max").

In a recent report of the large international registry of congenital long-QT syndrome, 69% of the probands were women, as were 60% of all affected family members.¹³⁴ Considering that this inherited disorder of cardiac repolarization most commonly displays autosomal dominant hereditary transmission,^{124,135} one would expect a female prevalence of only 50%.

The theme of female-gender predominance with respect to prolonged repolarization also extends to torsades de pointes with syncope (Stokes-Adams attacks) in patients with marked bradycardia due to complete heart block.^{136,137} Moreover, an analysis of electrocardiograms from 100 hospitalized patients exhibiting global T-wave inversion, another acquired prolonged repolarization syndrome that can predispose to torsades de pointes, revealed an overwhelming preponderance of cases involving women (female to male ratio of 4:1).¹³⁸

Implications

The present study supports the notion that women are more likely than men to develop torsades de pointes in response to commonly implicated cardiovascular drugs. This association should be further assessed through prospective multicenter studies. Additional clinical studies are also needed to determine whether women are more likely to develop torsades de pointes as a result of exposure to other QT-prolonging medications, such as various antipsychotic drugs and tricyclic antidepressants,^{3,10,139} and certain antibiotics^{5,10,106,140} and antihistamines.¹⁴¹ Complementary basic research would be of interest for elucidating electrophysiological mechanisms underlying gender differences in susceptibility to torsades de pointes.

Close monitoring of the QT interval and serum electrolytes can reduce the incidence of torsades de pointes associated with cardiovascular (and other) drugs that prolong cardiac repolarization. The evidence assembled in the present report suggests that it would be prudent for physicians prescribing these medications to exercise even greater caution when administering them to women.

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References

1. Dessertenne F. La tachycardie ventriculaire a deux foyers opposes variables. *Arch Mal Coeur Vaiss.* 1966;59:263-272.
2. Smith WM, Gallagher JJ. 'Les torsades de pointes': an unusual ventricular arrhythmia. *Ann Intern Med.* 1980;93:578-584.
3. Jackman WM, Friday KJ, Anderson JL, Aliot EM, Clark M, Lazzara R. The long QT syndromes: a critical review, new clinical observations and a unifying hypothesis. *Prog Cardiovasc Dis.* 1988;31:115-172.
4. Akhtar M. Clinical spectrum of ventricular tachycardia. *Circulation.* 1990;82:1561-1573.
5. Cleland JG, Krikler DM. Torsade de pointes: chaos, sixteen years on? *Br Heart J.* 1992;67:1-3.
6. Leenhardt A, Coumel P, Slama R. Torsades de pointes. *J Cardiovasc Electrophysiol.* 1992;3:281-292.
7. Bayes deLuna A, Coumel P, Leclercq JF. Ambulatory sudden cardiac death: mechanisms of production of fatal arrhythmia on the basis of data from 157 cases. *Am Heart J.* 1989;117:151-159.
8. Schwartz PJ, Periti M, Malliani A. The long QT syndrome. *Am Heart J.* 1975;89:378-390.
9. Moss AJ, Robinson J. Clinical features of the idiopathic long QT syndrome. *Circulation.* 1992;85 (suppl 1):I-140-I-144.
10. Stratmann HG, Kennedy HL. Torsades de pointes associated with drugs and toxins: recognition and management. *Am Heart J.* 1987;113:1470-1482.
11. Roden DM, Woosley RL, Primm RK. Incidence and clinical features of the quinidine-associated long QT syndrome: implications for patient care. *Am Heart J.* 1986;111:1088-1093.
12. Rokseth R, Storstein O. Quinidine therapy of chronic auricular fibrillation. *Arch Intern Med.* 1963;111:184-189.
13. Cramer G. Early and late results of conversion of atrial fibrillation with quinidine: a clinical and hemodynamic study. *Acta Med Scand.* 1968;184 (suppl 490).
14. Radford MD, Evans DW. Long-term results of DC reversion of atrial fibrillation. *Br Heart J.* 1968;30:91-96.
15. Ejvinsson G, Orinius E. Prodromal ventricular premature beats preceded by a diastolic wave. *Acta Med Scand.* 1980;208:445-450.
16. Lown B, Wolf M. Approaches to sudden death from coronary heart disease. *Circulation.* 1971;44:130-142.
17. Sodermark T, Jonsson B, Olsson A, et al. Effect of quinidine on maintaining sinus rhythm after conversion of atrial fibrillation or flutter: a multicenter study from Stockholm. *Br Heart J.* 1975;37:486-492.
18. Levine JH, Morganroth J, Kadish AH. Mechanisms and risk factors for proarrhythmia with type Ia compared with Ic antiarrhythmic drug therapy. *Circulation.* 1989;80:1063-1069.
19. Benditt DG, Bailin S, Remole S, Milstein S. Proarrhythmia: recognition of patients at risk. *J Cardiovasc Electrophysiol.* 1991;2(suppl):S221-S232.
20. Minardo JD, Heger JJ, Miles WM, Zipes DP, Prystowsky EN. Clinical characteristics of patients with ventricular fibrillation during antiarrhythmic drug therapy. *N Engl J Med.* 1988;319:257-262.
21. Abinader EG, Shahar J. Possible female preponderance in prenylamine-induced 'torsade de pointes' tachycardia. *Cardiology.* 1983;70:37-40.
22. Kasanuki H, Ohnishi S, Tamura K, Nirei T, Shoda M, Hosoda S. Acquired long QT syndrome due to antiarrhythmic drugs and bradyarrhythmias. QT prolongation and ventricular arrhythmias. *Ann N Y Acad Sci.* 1992;644:57-73.
23. Fontaine G. A new look at torsades de pointes, QT prolongation and ventricular arrhythmias. *Ann N Y Acad Sci.* 1992;644:157-176.
24. Coumel P. Safety of bepridil: from review of the European data. *Am J Cardiol.* 1992;69(suppl):75D-78D.
25. Zipes DP. Proarrhythmic effects of antiarrhythmic drugs. *Am J Cardiol.* 1987;59(suppl):26E-31E.

26. Selzer A, Wray HW. Quinidine syncope: paroxysmal ventricular fibrillation occurring during treatment of chronic atrial arrhythmias. *Circulation*. 1964;30:17-26.
27. Ohe T, Kurita T, Aihara N, Kamakura S, Matsuhisa M, Shimomura K. Electrocardiographic and electrophysiologic studies in patients with torsades de pointes: role of monophasic action potentials. *Jpn Circ J*. 1990;54:1323-1330.
28. Singh BN. Safety profile of bepridil determined from clinical trials in chronic stable angina in the United States. *Am J Cardiol*. 1992;69(suppl):68D-74D.
29. Hii JTY, Gillis AM, Wyse G, Ramadan D, Mitchell LB. Torsade de pointes induced by class Ia drugs: incidence and predictive value of exercise testing in 175 consecutive patients. *Circulation*. 1990;82(suppl III):III-55. Abstract.
30. Keren A, Tzivoni D, Gavish D, et al. Etiology, warning signs and therapy of torsade de pointes: a study of 10 patients. *Circulation*. 1981;64:1167-1174.
31. Tzivoni D, Banai S, Schuger C, et al. Treatment of torsade de pointes with magnesium sulfate. *Circulation*. 1988;77:392-397.
32. Sclarovsky S, Strasberg B, Lewin RF, Agmon J. Polymorphous ventricular tachycardia: clinical features and treatment. *Am J Cardiol*. 1979;44:339-344.
33. Tzivoni D, Keren A, Stern S. Torsades de pointes versus polymorphous ventricular tachycardia. *Am J Cardiol*. 1983;52:639-640.
34. Algra A, Tijssen J, Roelandt J, Pool J, Lubsen J. QTc prolongation measured by standard 12-lead electrocardiography is an independent risk factor for sudden death due to cardiac arrest. *Circulation*. 1991;83:1888-1894.
35. Nguyen PT, Scheinman MM, Seger J. Polymorphous ventricular tachycardia: clinical features and treatment. *Am J Cardiol*. 1979;44:339-344.
36. Hine LK, Gross TP, Kennedy DL. Outpatient antiarrhythmic drug use from 1970 through 1986. *Arch Intern Med*. 1989;149:1524-1527.
37. Lerner DJ, Kannel WB. Patterns of coronary heart disease morbidity and mortality in the sexes: a 26-year follow-up of the Framingham population. *Am Heart J*. 1986;111:388-390.
38. Centers for Disease Control and Prevention. Coronary heart disease incidence, by sex. *MMWR Morb Mortal Wkly Rep*. 1992;41:526-529.
39. National Center for Health Statistics. *Blood Pressure Levels and Hypertension in Persons Ages 6-74 Years: United States, 1976-80*. Hyattsville, Md: Public Health Service; October 8, 1982. US Dept of Health and Human Services publication PHS 82-1250. Advance Data From Vital and Health Statistics, No. 84.
40. Wilber DJ, Garan H, Finkelstein D, et al. Out-of-hospital cardiac arrest: use of electrophysiologic testing in the prediction of long-term outcome. *N Engl J Med*. 1988;318:19-24.
41. Steinbeck G, Andresen D, Bach P, et al. A comparison of electrophysiologically guided antiarrhythmic drug therapy with beta-blocker therapy in patients with symptomatic, sustained ventricular tachyarrhythmias. *N Engl J Med*. 1992;327:987-992.
42. Zar JH, Jerrold H. *Biostatistical Analysis*. 2nd ed. Englewood Cliffs, NJ: Prentice-Hall International Inc; 1984.
43. DiSegni E, Klein HO, David D, Libhaber C, Kaplinsky E. Overdrive pacing in quinidine syncope and other long QT-interval syndromes. *Arch Intern Med*. 1980;140:1036-1040.
44. Grenadier E, Keidar S, Alpan G, Marmor A, Palant A. Prenylamine-induced ventricular tachycardia and syncope controlled by ventricular pacing. *Br Heart J*. 1980;44:330-334.
45. Strasberg B, Sclarovsky S, Erdberg A, et al. Procainamide-induced polymorphous ventricular tachycardia. *Am J Cardiol*. 1981;47:1309-1314.
46. Khan MM, Logan KR, McComb JM, Adgey AAJ. Management of recurrent ventricular tachyarrhythmias associated with Q-T prolongation. *Am J Cardiol*. 1981;47:1301-1308.
47. Denes P, Gabster A, Huang SK. Clinical, electrocardiographic and follow-up observations in patients having ventricular fibrillation during Holter monitoring. *Am J Cardiol*. 1981;48:9-16.
48. Sclarovsky S, Lewin RF, Kracoff O, Strasberg B, Arditti A, Agmon J. Amiodarone-induced polymorphous ventricular tachycardia. *Am Heart J*. 1983;105:6-12.
49. Kay GN, Plumb VJ, Arciniegas JG, Henthorn RW, Waldo AL. Torsades de pointes: the long-short initiating sequence and other clinical features: observations in 32 patients. *J Am Coll Cardiol*. 1983;2:806-817.
50. Leclercq JF, Kural S, Valere PE. Bepridil et torsade de pointes. *Arch Mal Coeur Vaiss*. 1983;76:341-347.
51. Lewis BH, Antman EM, Graboyes TB. Detailed analysis of 24 hour ambulatory electrocardiographic recordings during ventricular fibrillation or torsade de pointes. *J Am Coll Cardiol*. 1983;2:426-436.
52. McKibbin JK, Pocock WA, Barlow JB, Millar RNS, Obel IWP. Sotalol, hypokalaemia, syncope, and torsade de pointes. *Br Heart J*. 1984;51:157-162.
53. Manouvrier J, Sagot M, Caron C, et al. Nine cases of torsade de pointes with bepridil administration. *Am Heart J*. 1986;111:1005-1007.
54. Brown MA, Smith WM, Lubbe WF, Norris RM. Amiodarone-induced torsades de pointes. *Eur Heart J*. 1986;7:234-239.
55. Mattioni TA, Zheutlin TA, Sarmiento JJ, Parker M, Lesch M, Kehoe RF. Amiodarone in patients with previous drug-mediated torsade de pointes: long-term safety and efficacy. *Ann Intern Med*. 1989;111:574-580.
56. Jorens PG, Van Den Heuvel PA, Ranquin REF, Van Den Branden FA, Parizel GA. Amiodarone induced torsades de pointes: report of three cases and review of literature. *Acta Cardiol*. 1989;44:411-421.
57. Kadish AH, Weisman HF, Veltri EP, Epstein AE, Slepian MJ, Levine JH. Paradoxical effects of exercise on the QT interval in patients with polymorphic ventricular tachycardia receiving type Ia antiarrhythmic agents. *Circulation*. 1990;81:14-19.
58. Oravetz J, Slodki SJ. Recurrent ventricular fibrillation precipitated by quinidine: report of a patient with recovery after 28 paroxysms. *Arch Intern Med*. 1968;122:63-65.
59. Miller DS, Blount AW Jr. Quinidine-induced recurrent ventricular fibrillation: quinidine syncope treated with transvenous pacemaker. *South Med J*. 1971;64:597-601.
60. Jenzer HR, Hagemeyer F. Quinidine syncope: torsade de pointes with low quinidine plasma concentrations. *Eur J Cardiol*. 1976;4:447-451.
61. Reynolds EW, Vander Ark CR. Quinidine syncope and the delayed repolarization syndromes. *Mod Concepts Cardiovasc Disease*. 1976;45:117-122.
62. Koster RW, Wellens HJJ. Quinidine-induced ventricular flutter and fibrillation without digitalis therapy. *Am J Cardiol*. 1976;38:519-523.
63. Dhurandhar RW, Nadermanee K, Goldman AM. Ventricular tachycardia-flutter associated with disopyramide therapy: a report of three cases. *Heart Lung*. 1978;7:783-787.
64. Nicholson WJ, Martin CE, Gracey JG, Knoch HR. Disopyramide-induced ventricular fibrillation. *Am J Cardiol*. 1979;43:1053-1055.
65. Tri B. Disopyramide-induced syncope. *Am J Cardiol*. 1979;44:391-392.
66. Commerford PJ, Beck W. Ventricular tachycardia with torsade de pointes morphology induced by oral disopyramide. *S Afr Med J*. 1980;58:447-448.
67. Riccioni N, Bartolomei C, Soldani S. Prenylamine-induced ventricular arrhythmias and syncope attacks with Q-T prolongation. *Cardiology*. 1980;66:199-203.
68. Rothman MT. Prolonged QT interval, atrioventricular block, and torsade de pointes after antiarrhythmic therapy. *BMJ*. 1980;280:922-923.
69. Kontopoulos A, Filindris A, Manoudis F, Metaxas P. Sotalol-induced torsade de pointes. *Postgrad Med J*. 1981;57:321-323.
70. Meanock CI, Noble MIM. A case of prenylamine toxicity showing the torsade de pointes phenomenon in sinus rhythm? *Postgrad Med J*. 1981;57:381-384.
71. Wald RW, Waxman MB, Colman JM. Torsade de pointes ventricular tachycardia: implication of disopyramide shared with quinidine. *J Electrocardiol*. 1981;14:301-306.
72. Ko PT, Gulamhusein S, Kostuk WJ, Klein GJ. Torsade de pointes, a common arrhythmia induced by medication. *Can Med Assoc J*. 1982;127:368-372.
73. Nikolic G, Bishop RL, Singh JB. Sudden death recorded during Holter monitoring. *Circulation*. 1982;66:218-225.
74. Olshansky B, Martins J, Hunt S. N-acetyl procainamide causing torsades de pointes. *Am J Cardiol*. 1982;50:1439-1441.
75. Schweitzer P, Mark H. Torsade de pointes caused by disopyramide and hypokalemia. *Mt Sinai J Med*. 1982;49:110-114.
76. Soffer J, Dreifus LS, Michelson EL. Polymorphous ventricular tachycardia associated with normal and long Q-T intervals. *Am J Cardiol*. 1982;49:2021-2029.
77. Koenig W, Schinz AM. Spontaneous ventricular flutter and fibrillation during quinidine medication. *Am Heart J*. 1983;105:863-865.
78. Panidis IP, Morganroth J. Sudden death in hospitalized patients: cardiac rhythm disturbances detected by ambulatory electrocardiographic monitoring. *J Am Coll Cardiol*. 1983;2:798-805.
79. Riccioni N, Castiglioni M, Bartolomei C. Disopyramide-induced QT prolongation and ventricular tachyarrhythmias. *Am Heart J*. 1983;105:870-871.
80. Swiryn S, Kim SS. Quinidine-induced syncope. *Arch Intern Med*. 1983;143:314-316.
81. Campbell WB. EKG of the month: torsades de pointes. *J Tenn Med Assoc*. 1984;77:401-403.
82. Feiler HE. Atypical ventricular tachycardia (torsades de pointes): report of two cases. *J Am Osteopath Assoc*. 1984;84:276-281.
83. Kuck KH, Kunze KP, Roewer N, Bleifeld W. Sotalol-induced torsade de pointes. *Am Heart J*. 1984;107:179-180.
84. Rakovec P, Cercek B, Rode P, Brucan A, Horvat M. Sotalol-induced torsade de pointes. *Cathet Cardiovasc Diagn*. 1984;10:167-170.
85. Santinelli V, Chiariello M, Santinelli C, Condorelli M. Ventricular tachyarrhythmias complicating amiodarone therapy in the presence of hypokalemia. *Am J Cardiol*. 1984;53:1462-1463.
86. Herre JM, Thompson JA. Polymorphic ventricular tachycardia and ventricular fibrillation due to N-acetylprocainamide. *Am J Cardiol*. 1985;55:227-228.
87. Krapf R, Gertsch M. Torsade de pointes induced by sotalol despite therapeutic plasma sotalol concentrations. *BMJ*. 1985;290:1784-1785.
88. Sarmiento JJ, Shea PM, Goldberger AL. Unusual ventricular depolarizations associated with torsade de pointes. *Am Heart J*. 1985;109:377-379.
89. Stevenson WG, Weiss J. Torsades de pointes due to N-acetylprocainamide. *PACE Pacing Clin Electrophysiol*. 1985;8:528-531.
90. Stratmann HG, Walter KE, Kennedy HL. Torsade de pointes associated with elevated N-acetylprocainamide levels. *Am Heart J*. 1985;109:375-377.
91. Lew WYW, Goldberger AL. Torsades de pointes and sudden death in a patient with a permanent pacemaker. *Can J Cardiol*. 1986;2:86-87.
92. Moro C, Romero J, Corres Peiretti MA. Amiodarone and hypokalemia: a dangerous combination. *Int J Cardiol*. 1986;13:365-368.
93. Nguyen KPV, Thomsen G, Liem B, Swerdlow CD, Franz MR. N-acetylprocainamide, torsades de pointes, and hemodialysis. *Ann Intern Med*. 1986;104:283-284.
94. Perticone F, Adinolfi L, Bonaduce D. Efficacy of magnesium sulfate in the treatment of torsade de pointes. *Am Heart J*. 1986;112:847-849.
95. Wang T, Bergstrand RH, Thompson KA, et al. Concentration-dependent pharmacologic properties of sotalol. *Am J Cardiol*. 1986;57:1160-1165.
96. Leroy G, Haiat R, Barthelemy M, Lionnet F. Torsade de pointes during loading with amiodarone. *Eur Heart J*. 1987;8:541-543.

97. Smith MS, Lindsay WC, Flowers NC. Treatment of torsades de pointes with esophageal atrial pacing. *Am J Med.* 1987;83:971-972.
98. Martinez-Lopez JI. EKG of the month. *J La State Med Soc.* 1988;140:11-13.
99. El-Sherif N, Bekheit SS, Henkin R. Quinidine-induced long QTU interval and torsade de pointes: role of bradycardia-dependent early afterdepolarizations. *J Am Coll Cardiol.* 1989;14:252-257.
100. Schattner A, Gindin J, Geltner D. Fatal torsade de pointes following jaundice in a patient treated with disopyramide. *Postgrad Med J.* 1989;65:333-334.
101. Warden T, Sacchetti A, Klodnicki WE. Magnesium sulfate termination of torsades de pointes following failure of cardioversion. *Am J Emerg Med.* 1989;7:126-127.
102. Andrivet P, Beasley V, Canh VD. Torsade de pointes with flecainide-amiodarone therapy. *Intensive Care Med.* 1990;16:342-343.
103. Della Bella P, Tondo C, Marenzi G, Grazi S. Polymorphous ventricular tachycardia as undesirable effect of the association of quinidine treatment with hysteresis ventricular inhibited pacing. *Eur Heart J.* 1990;11:1124-1126.
104. Habbab MA, El-Sherif N. Drug-induced torsade de pointes: role of early afterdepolarizations and dispersion of repolarization. *Am J Med.* 1990;89:241-244.
105. Kadiwar RM, MacMahon B. Prenylamine induced torsade de pointes. *Irish Med J.* 1990;83:163.
106. Nattel S, Ranger S, Talajic M, Lemery R, Roy D. Erythromycin-induced long QT syndrome: concordance with quinidine and underlying cellular electrophysiologic mechanism. *Am J Med.* 1990;89:235-238.
107. Rankin AC, Pringle SD, Cobbe SM. Acute treatment of torsade de pointes with amiodarone: proarrhythmic and antiarrhythmic association of QT prolongation. *Am Heart J.* 1990;119:185-186.
108. Bajaj BP, Baig MW, Perrins EJ. Amiodarone-induced torsades de pointes: the possible facilitatory role of digoxin. *Int J Cardiol.* 1991;33:335-338.
109. Singh SN, Lazin A, Cohen A, Johnson M, Fletcher RD. Sotalol-induced torsade de pointes successfully treated with hemodialysis after failure of conventional therapy. *Am Heart J.* 1991;121:601-602.
110. Arstall MA, Hii JTY, Lehman RG, Horowitz JD. Sotalol-induced torsade de pointes: management with magnesium infusion. *Postgrad Med J.* 1992;68:289-290.
111. Habbab MA, El-Sherif N. TU alternans, long QTU and torsade de pointes: clinical and experimental observations. *PACE Pacing Clin Electrophysiol.* 1992;15:916-931.
112. Hii JTY, Wyse DG, Gillis AM, Duff HJ, Solylo MA, Mitchell LB. Precedial QT interval dispersion as a marker of torsade de pointes: disparate effects of class Ia antiarrhythmic drugs and amiodarone. *Circulation.* 1992;86:1376-1382.
113. Davies P, Leak D, Oram S. Quinidine-induced syncope. *BMJ.* 1965;2:517-520.
114. Surawicz B. Electrophysiologic substrate of torsade de pointes: dispersion of repolarization or early afterdepolarizations? *J Am Coll Cardiol.* 1989;14:172-184.
115. Schieman G, Blacky AR, Nicod PH, Ditttrich HC. Prolonged asymptomatic torsade de pointes. *J Electrophysiol.* 1988;2:46-48.
116. Meltzer RS, Robert EW, McMorro M, Martin RP. Atypical ventricular tachycardia as a manifestation of disopyramide toxicity. *Am J Cardiol.* 1978;42:1049-1052.
117. Boccardo D, Pitchon R, Wiener I. Adverse reactions and efficacy of high-dose procainamide therapy in resistant tachyarrhythmias. *Am Heart J.* 1981;102:797-798.
118. Tartini R, Kappenberger L, Steinbrunn W, Meyer UA. Dangerous interaction between amiodarone and quinidine. *Lancet.* 1982;1:1327-1329.
119. Kempf FC, Josephson ME. Cardiac arrest recorded on ambulatory electrocardiograms. *Am J Cardiol.* 1984;53:1577-1582.
120. Fields CD, Ezri MD, Denes P. 'Quinidine syncope' without lengthening of Q-Tc interval in the presence of left bundle branch block: role of programmed ventricular stimulation studies. *Chest.* 1988;94:111-113.
121. Bauman JL, Bauernfeind RA, Hoff JV, Strasberg B, Swiryn S, Rosen KM. Torsade de pointes due to quinidine: observations in 31 patients. *Am Heart J.* 1984;107:425-430.
122. Prystowsky EN. Electrophysiologic and antiarrhythmic properties of bepridil. *Am J Cardiol.* 1985;55(suppl):59C-62C.
123. Leclercq JF, Coumel P, Maison-Blanche P, et al. Mise en évidence des mécanismes déterminants de la mort subite. *Arch Mal Coer Vaiss.* 1986;79:1024-1033.
124. Keating M. Linkage analysis and long QT syndrome: using genetics to study cardiovascular disease. *Circulation.* 1992;85:1973-1986.
125. Gehlbach SH. *Interpreting the Medical Literature.* Lexington, Mass: DC Heath & Company; 1982:17-74.
126. Cobb LA, Weaver WD, Fahrenbruch CE, Hallstrom AP, Copass MK. Community-based interventions for sudden cardiac death: impact, limitations, and changes. *Circulation.* 1992;85(suppl I):I-98-I-102.
127. Hilleman DE, Mohiuddin SM, Gannon JM. Adverse reactions during acute and chronic class I antiarrhythmic therapy. *Curr Ther Res.* 1992;51:730-738.
128. Thompson KA, Murray JJ, Blair IA, Woosley RL, Roden DM. Plasma concentrations of quinidine, its major metabolites, and dihydroquinidine in patients with torsades de pointes. *Clin Pharmacol Ther.* 1988;43:636-642.
129. Larsen PR. The thyroid. In: Wyngaarden JB, Smith LH Jr, Bennett JC, eds. *Cecil Textbook of Medicine.* 19th ed. Philadelphia, Pa: WB Saunders Co; 1992:1248-1271.
130. Kumar A, Bhandari AK, Rahimtoola SH. Torsade de pointes and marked QT prolongation in association with hypothyroidism. *Ann Intern Med.* 1987;106:712-713.
131. Bagchi N, Brown TR, Parish RF. Thyroid dysfunction in adults over age 55 years. *Arch Intern Med.* 1990;150:785-787.
132. Macfarlane PW, Lawrie TDV. The normal electrocardiogram and vectorcardiogram. In: MacFarlane PW, Lawrie TDV, eds. *Comprehensive Electrocardiology: Theory and Practice in Health and Disease.* Elmsford, NY: Pergamon Press Inc; 1989;1:407-463.
133. Merri M, Benhorin J, Alberti M, Locati E, Moss AJ. Electrocardiographic quantitation of ventricular repolarization. *Circulation.* 1989;80:1301-1308.
134. Moss AJ, Schwartz PJ, Crampton RS, et al. The long QT syndrome: prospective longitudinal study of 328 families. *Circulation.* 1991;84:1136-1144.
135. Hashiba K. Hereditary QT prolongation syndrome in Japan: genetic analysis and pathological findings of the conducting system. *Jpn Circ J.* 1978;42:1133-1150.
136. Jensen G, Sigurd B, Sandoe E. Adams-Stokes seizures due to ventricular tachydysrhythmias in patients with heart block: prevalence and problems of management. *Chest.* 1975;67:43-48.
137. Kurita T, Ohe T, Marui N, et al. Bradycardia-induced abnormal QT prolongation in patients with complete atrioventricular block with torsades de pointes. *Am J Cardiol.* 1992;69:628-633.
138. Walder LA, Spodick DH. Global T wave inversion. *J Am Coll Cardiol.* 1991;17:1479-1485.
139. Wilt JL, Minnema AM, Johnson RF, Rosenblum AM. Torsade de pointes associated with the use of intravenous haloperidol. *Ann Intern Med.* 1993;119:391-394.
140. Lopez JA, Harold JG, Rosenthal MC, Oseran DS, Schapira JN, Peter T. QT prolongation and torsades de pointes after administration of trimethoprim-sulfamethoxazole. *Am J Cardiol.* 1987;59:376-377.
141. Woosley RL, Chen Y, Freiman JP, Gillis RA. Mechanism of the cardiotoxic actions of terfenadine. *JAMA.* 1993;269:1532-1536.