Predicting Cardiac Arrhythmias and Sudden Death in Diabetic Users of Proarrhythmic Drugs

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In diabetic patients, the corrected QT (QTc) interval is relatively long (1). In accordance with the concept of "reduced repolarization reserve" (2), a subsequent increase in QTc interval by proarrhythmic drugs may lead to cardiac arrhythmias and sudden death. Recently, it was shown that patients with diabetes are at increased risk of drug-induced arrhythmias (3). We developed a decision tool to predict the risk of serious ventricular arrhythmias and sudden death among diabetic users of nonantiarrhythmic proarrhythmic drugs.

RESEARCH DESIGN AND METHODS

— A cohort study among 61,280 diabetic patients using nonantiarrhythmic proarrhythmic medication (amitriptyline, astemizole, chloroquine, chlorpromazine, cisapride, clarithromycin, clomipramine, cotrimoxazole, diphenhydramine/dimenhydrinate, domperidone, doxepine, droperidol, erythromycin, grepafloxacin, halofantrine, haloperidol, indapamide, ketanserin, lidoflazine, mianserine, pentamidine, pimozide, probucol, promethazine, protriptyline, sulfamethoxazole, sultopride, tacrolimus, terfenadine, terodiline, thioridazine, trimethoprim, and zimeldine) (4) in the General Practice Research Database (1987–2001) was performed. This database contains computerized medical records of ~650 general practices, including ~6.5% of the population of England and Wales. Diabetic patients were followed from the 1st day of prescription of any nonantiarrhythmic proarrhythmic drug. Follow-up was censored when the duration of (one of) the prescription(s) had elapsed, when the study outcome occurred, in case of death, upon exit from the study population, or at the end of the study period, whichever of these events came first. The combined study outcome included ventricular tachycardia, ventricular fibrillation and flutter, cardiac arrest, and sudden death. Candidate predictors included:

- sex, age, and diabetes duration
- morbidities, i.e., other cardiac arrhythmias (mainly atrial fibrillation), ischemic heart disease, heart failure, hypertension (5), and pulmonary disease (6)
- concomitant medication associated with potassium imbalance or ventricular arrhythmias, i.e., antiarrhythmic drugs (7), oral potassium, and blood potassium–lowering drugs (8), including non–potassium-sparing diuretics (9), laxatives, systemic corticosteroids, or β_2-agonists (10)
- prescription characteristics, i.e., dosage and prescriptions for the same drug during the previous year
- lifestyle factors, i.e., smoking (11) and BMI (12,13)

All candidate predictors were included in a multivariate logistic regression model that was reduced by deleting predictors with P values >0.15, based on the log likelihood ratio test. The model was internally validated using bootstrapping techniques. The performance of the final model (goodness of fit and discriminative ability) was tested by the Hosmer and Lemeshow test and by calculating the area under the receiver operator characteristic (ROC) curve. To obtain an easily applicable rule, regression coefficients from the final model were multiplied by 10 and rounded to the nearest integer.

RESULTS

— The 61,280 diabetic patients (mean age 65 years) received one or more nonantiarrhythmic proarrhythmic drugs during 396,853 physician visits. Mean prescription length was 26 days. During follow-up, 94 events occurred (incidence 24 of 100,000 prescriptions), including 49 sudden deaths, 34 cardiac arrests, and 11 ventricular arrhythmias.

Events were more frequent in men and in older patients. Other cardiac arrhythmias, ischemic heart disease, and heart failure as well as all concomitant medications studied were associated with the outcome (Table 1, crude association). The majority (77%) of prescribed drugs were psychotropic (174,183 prescriptions) or antimicrobic (130,778 prescriptions) medications, with amitriptyline (82,745 prescriptions), trimethoprim (58,261 prescriptions), and erythromycin (47,262 prescriptions) the most frequently used drugs. On 11,848 occasions two or more proarrhythmic drugs were prescribed at the same time. Halofantrine, ketanserine, lidoflazine, pentamidine, sulfamethoxazol (without trimethoprim), sultopride, and zimeldine were not prescribed.

The initial multivariable model with

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Abbreviations: ROC, receiver operator characteristic; QTc, corrected QT.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Incidence, crude associations, and final bootstrapped model of association between predictors and outcome*

	Incidence			Crude association		Final model	
Candidate predictor	Events	Rx	Inc*	OR† (95% CI)	*P* value	OR	Score
Sex (male)	51	153,178	33	2.49 (1.12–5.53)	0.025	2.26	8
Age (years)	63.6 ± 18			1.03 (1.00–1.06)	0.024	1.02	0.2
Diabetes duration (years)	1.9 ± 2.1			0.99 (0.83–1.18)	0.889		
Comorbidity							
Other arrhythmia	17	30,596	56	4.18 (1.77–9.85)	0.001	2.02	7
Ischemic heart disease	40	84,835	47	3.22 (1.51–6.85)	0.002	1.89	6
Heart failure	33	48,035	69	3.18 (1.40–7.21)	0.006		
Elevated blood pressure	38	155,256	24	1.26 (0.59–2.72)	0.549		
Pulmonary disease	14	63,012	22	1.11 (0.40–3.12)	0.842		
Concomitant drugs							
Antiarrhythmics	4	2,213	181	8.02 (1.33–48.4)	0.023		
Oral potassium	4	3,051	131	4.70 (0.47–47.4)	0.190		
Potassium-lowering drugs‡	51	145,130	35	2.10 (0.98–4.49)	0.056		
Study drugs							
≥2 defined daily doses/day	6	28,475	21	0.77 (0.17–3.53)	0.732		
Prescription for current drug last year	69	292,096	24	0.93 (0.42–2.08)	0.862		
Smoking	19	86,994	22	0.68 (0.24–1.95)	0.475		
BMI (kg/m^2)							
<20	5	17,426	29	1.18 (0.17–8.49)			
20–25	17	90,799	19	Reference	0.959		
25–30	37	145,965	25	1.17 (0.42–3.29)			
≥30	35	142,663	25	1.33 (0.48–3.70)			
Total	94	396,853	24				

Data are means ± SD unless otherwise indicated. *Incidence per 100,000 prescriptions; †OR per year; ‡non–potassium-sparing diuretics, laxatives, systemic corticosteroids, or systemic β_2-agonists. Rx, prescription(s).

all 15 predictors yielded an ROC area of 0.71 (95% CI 0.66–0.77). Of these 15, only 4 predictors, i.e., age, sex, ischemic heart disease, and other cardiac arrhythmia than the study outcome, independently contributed to the prediction of the outcome defined as a *P* value ≤0.15. The other univariate predictors were not independent predictors in the multivariable analysis. Apparently, their predictive information was already provided for by the four retained predictors. The reduced model including the four predictors yielded an ROC area of 0.69 (0.63–0.74), and after bootstrapping, the ROC area of the final model remained at 0.69 (0.63–0.74), which is regarded as reasonable. The goodness of fit of this final model was excellent (*P* value by Hosmer and Lemeshow test 0.91).

The risk score for predicting serious ventricular arrhythmias and sudden death among diabetic users of proarrhythmic drugs derived from the final model was age (years) × 0.2 + male sex × 7 + other arrhythmias than the study outcome × 8 + ischemic heart disease × 6 points. A male (7 points) of 60 years of age (60 × 0.2 = 12 points) with ischemic heart disease (6 points) without history of any cardiac arrhythmias (0 points), for example, receives a risk score of 8 + 12 + 6 = 25 points. Patients can be divided into five risk groups according to their risk score. A score of <15 points corresponds to a probability for the study outcome of <25 per 100,000 prescriptions. Scores between 15 and 21, 22 and 25, and 26 and 28 correspond to probabilities between 25 and 50, 50 and 75, and 75 and 100 events per 100,000 prescriptions, respectively. Patients with a score ≥29 have a probability of >100 per 100,000 prescriptions for ventricular arrhythmias and sudden death and have a more than four times increased risk for an arrhythmic event compared with the lowest category.

In clinical practice, a prescribing physician may wish to define a cutoff point above which additional security measures, e.g., pretherapy electrocardiogram measurements or prescribing therapeutic alternatives, are required. Sensitivity and specificity are important measures to evaluate the consequences of such a threshold. The sensitivity of cutoff points 15, 22, 26, and 29 were 0.85, 0.49, 0.27, and 0.15, respectively. Corresponding specificities were 0.37, 0.78, 0.91, and 0.96, respectively. When taking extra security measures for patients with a score ≥29, 15% of the 94 prescriptions during which an event actually happened would be treated correctly (sensitivity or true-positive rate), whereas in those with a score <29, in 96% extra security measures are correctly withheld (specificity or true-negative rate).

CONCLUSIONS — As for the interpretation of results and design, one should bear in mind that this study was not designed to study the use of drugs as an etiologic cause of cardiac arrhythmias. This prognostic study, without an unexposed control group, was designed to be applicable to patients exposed to proarrhythmic drugs and to identify prognostic factors to predict the outcome among those who must be exposed.

We found that the absolute risk of serious ventricular arrhythmias and sudden death among diabetic users of nonantiarrhythmic proarrhythmic drugs is low. The provided scoring rule can be used to identify patients with a considerable increased risk. Prescribing proarrhythmic drugs to these patients should be reconsidered or closely monitored.

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