Background: QT interval prolongation on the surface electrocardiogram (ECG) predicts cardiovascular complications in high-risk subjects, but its prognostic role in uncomplicated hypertension has been understudied.

Methods: For up to 13 years (average, 5.3 years), we followed up 2110 white patients with initially untreated essential hypertension (mean±SD age, 49±12 years; 55% men) without prevalent cardiovascular or renal disease who underwent 12-lead ECG before therapy. We excluded patients with ECG abnormalities including ischemia, necrosis, complete bundle branch block, atrial fibrillation, arrhythmias, and ventricular preexcitation.

Results: Heart rate–corrected QT interval (QTc) showed a weak but significant direct association with systolic blood pressure ($r=0.07; P<0.001$), diastolic blood pressure ($r=0.11; P<0.001$), and Cornell voltage ($r=0.06; P=0.006$). During follow-up, 84 patients developed new-onset ischemic heart disease (0.75 event per 100 patient-years). After adjustment (Cox model) for the effects of age, sex, diabetes mellitus, serum cholesterol level, serum creatinine level, smoking, left ventricular hypertrophy, and 24-hour systolic blood pressure, patients with a prolonged QTc ($\geq 450$ milliseconds in women and $\geq 440$ milliseconds in men) had a nearly 2-fold increase in risks of coronary events (hazard ratio, 1.95; 95% confidence interval, 1.12-3.42; $P=0.02$) and cardiovascular death (hazard ratio, 2.05; 95% confidence interval, 1.03-4.37; $P=0.04$). Coronary heart disease risk was independently higher by 33% (95% confidence interval, +7% to +66%; $P=0.01$) for each 32-millisecond increase in QTc.

Conclusions: Prolonged ventricular repolarization is a risk factor for ischemic heart disease and cardiovascular mortality in subjects with uncomplicated hypertension. Its prognostic significance adds to that of several traditional cardiovascular risk factors, including left ventricular hypertrophy.

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opportunity to investigate the relationship between QT interval duration and incident coronary heart disease in subjects with essential hypertension without prevalent cardiovascular disease at the baseline examination.

METHODS

The PIUMA study is a prospective follow-up study of white adults with essential hypertension. Hypertensive subjects were referred to 1 of 3 participating centers (Perugia, Città della Pieve, and Castiglione del Lago) for baseline evaluation by a group of general physicians practicing in Umbria in central Italy. A total of 2129 white subjects enrolled between 1988 and 1998, for whom good-quality 12-lead ECG recordings were available, were included in the present analysis. All study subjects fulfilled the following criteria: (1) office systolic blood pressure (BP) of 140 mm Hg or higher, diastolic BP of 90 mm Hg or higher, or both on 3 or more visits at 1-week intervals; (2) no previous treatment for hypertension (70%), or withdrawal from antihypertensive drug therapy 4 weeks or longer before the study; (3) no clinical or laboratory evidence of heart failure, coronary heart disease, previous stroke, valvular defects, secondary causes of hypertension, cancer, renal failure, or hepatic disease; (4) 1 or more valid BP measurements per hour during the 24 hours; and (5) no ECG exclusion criteria. All subjects gave informed consent to participate in the study, which was approved by each center’s institutional review board.

BASELINE MEASUREMENTS

Office BP was measured by a physician in the hospital clinic with a mercury sphygmomanometer after the subject sat for 10 minutes or longer. The average of 3 or more measurements on each of 2 or more sessions was considered for the analysis. Ambulatory BP was recorded with an oscillometric device (models 90202 and 90207; SpaceLabs, Redmond, Wash) that was set to take a reading every 15 minutes throughout the 24 hours.

Standard 12-lead ECGs were recorded for all subjects at 25-mm/s and 1-mV/cm calibration. Tracings were interpreted by 2 investigators (G.S. and T.R.) without knowledge of other patient data. Subjects with complete bundle branch block or intraventricular block, previous myocardial infarction, Wolff-Parkinson-White syndrome, ischemia, or atrial fibrillation or flutter were excluded from the analysis. None of the subjects were taking Digitalis or drugs that influence QT interval, in- cluding antiarrhythmics, B-blockers, or tricyclic and tetracyclic antidepressants. The QT interval was manually measured to the nearest 0.01 milliseconds in all leads from the onset of the QRS complex to the end of the T wave, and the longest QT interval was chosen. The average of 3 consecutive normal beats was considered for the analysis. T wave end was defined as the point of maximum change of slope as the T wave merges with the baseline. In case of visible U waves, T wave end was defined as the nadir between the T wave and the U wave. In the repeated measurements of 60 ECG samples, the interobserver coefficient of variability of the QT interval was 2.3%. Heart rate correction of QT interval (QTc) was performed using the Bazett formula: QTc = QT / R-R interval (in seconds). The LVH was defined by the Perugia criteria, which requires 1 or more of the following 3 criteria: modified sex-specific Cornell voltage criterion (sum of the amplitudes of S wave in lead V1 and R wave in lead aVL > 2.4 mV in men and > 2.0 mV in women), typical left ventricular strain, or a Romhilt-Estes score of 3 points or more. The Perugia criterion exhibits a greater attributable risk for cardiovascular morbidity and mortality than do other traditional criteria.

Follow-up data were available for 2110 (99%) of the 2129 subjects, and only 1% were lost to follow-up. At entry (Table 1), the subjects with future ischemic heart disease were older and had higher systolic BP, serum creatinine level, self-reported duration of hypertension, and QTc duration. They were also more likely to be male and to have diabetes and LVH. Table 2 reports the main clinical characteristics of the study subjects stratified by normal and prolonged QTc. Prolonged QTc occurred in 210 subjects (10%); compared with the remaining subjects, these subjects had

FOLLOW-UP PROCEDURES AND END POINT EVALUATION

All subjects were followed up by their family physicians in cooperation with the outpatient clinic of the referring hospital and treated through the use of standard lifestyle and pharmacologic measures. At the follow-up visit, 66% of the study patients were taking antihypertensive drugs and 34% were receiving lifestyle measures only. Contact with family physicians and telephone interviews were periodically undertaken to determine the incidence of coronary heart disease. For the subjects who developed a cardiovascular event during follow-up, hospital record forms and other available original source documents were reviewed in conference by the authors. Coronary events included myocardial infarction, unstable angina with documentation of ischemic ECG changes, and sudden cardiac death. We also assessed the occurrence of cerebrovascular events and cardiovascular and all-cause mortality. The international standard criteria used to diagnose cardiovascular events in the PIUMA study have been described elsewhere.

STATISTICAL ANALYSIS

Parametric data are reported as mean ± SD. The rates of cardiovascular events are presented as the number of events per 100 patient-years. For those subjects who experienced multiple events, survival analysis was restricted to the first event. Survival curves were compared with the use of the Mantel-Haenszel (log-rank) test. The effect of prognostic factors on survival was evaluated with the use of the stepwise Cox semiparametric regression model. The assumption of linearity for the Cox model was tested through visual inspection, and no violation of proportional hazards was found. We tested the variables of age, sex, 24-hour systolic BP, serum cholesterol level, serum creatinine level, diabetes, smoking habits, and LVH. The QTc interval was considered as both a continuous and binary variable. Abnormal QTc was defined as greater than 450 milliseconds in women and greater than 440 milliseconds in men, values approximating the upper 95th percentile in 361 white normotensive healthy adults (age, 45 ± 13 years; BP, 128/80 ± 8/6 mm Hg; 52% men). Because of the limited number of events, the number of predictor variables included in the multivariable Cox models was reduced to 6 for all-cause mortality (age, 24-hour systolic BP, diabetes, smoking habits, and LVH) and QTc and 4 for cardiovascular mortality (age, 24-hour systolic BP, diabetes, and QTc). We also tested the prognostic significance of the JT interval as a depolarization-independent measure of ventricular repolarization. The corrected JT interval (JTc) was calculated as QTc minus QRS. The prognostic power of QTc and JTc was compared by adding the 2 variables, one at a time, to a basic model of prognostic variables. The −2 log likelihood statistics were used to compare the different models.

RESULTS

Follow-up data were available for 2110 (99%) of the 2129 subjects, and only 1% were lost to follow-up. At entry (Table 1), the subjects with future ischemic heart disease were older and had higher systolic BP, serum creatinine level, self-reported duration of hypertension, and QTc duration. They were also more likely to be male and to have diabetes and LVH. Table 2 reports the main clinical characteristics of the study subjects stratified by normal and prolonged QTc.
higher systolic and diastolic BP values and a greater proportion of LVH. After adjustment for age and sex, QTc showed a significant, albeit weak, direct correlation with systolic BP (partial $r = 0.07$ and 0.09 for office and 24-hour values; $P < .001$ for both), diastolic BP (partial $r = 0.11$ and 0.11 for office and 24-hour values; $P < .001$ for both), and Cornell voltage (partial $r = 0.06$; $P = .006$) and a strong residual direct correlation with heart rate (partial $r = 0.31$; $P < .001$), whereas no significant associations were found with body mass index ($P = .20$) or serum cholesterol ($P = .23$), glucose ($P = .21$), or creatinine ($P = .92$) concentrations. The proportion of subjects who were receiving antihypertensive drug treatment at follow-up did not differ in the group with prolonged QTc (67%) and in those with normal left ventricular repolarization (65%).

### CORONARY EVENTS

During a mean±SD follow-up period of 5.3±3.0 years (range, 1-12 years), 84 new coronary heart disease events occurred (0.75 event per 100 patient-years). Specifically, 46 subjects had fatal or nonfatal myocardial infarction, 10 had sudden cardiac death, and 28 had unstable angina with concomitant ECG ischemic changes. Overall, 68 coronary heart disease events occurred in the group with normal QTc duration ($n = 1900$; 0.68 event per 100 patient-years), and 16 events occurred in the group with prolonged QTc ($n = 210$; 1.44 events per 100 patient-years). Event-free survival curves differed significantly among the 2 groups (log-rank test; $P = .003$; Figure).

Results of the multivariate survival analysis are reported in Table 3. QTc maintained an association with subsequent coronary heart disease after adjustment for the confounding effect of age, sex, smoking, diabetes, serum cholesterol concentration, serum creatinine level, LVH, and average 24-hour systolic BP. Ischemic heart disease risk increased by 33% (95% confidence interval, +7% to +66%; $P = .01$) for each 1-SD increase in QTc (1 SD = 32 milliseconds). Patients with prolonged QTc had an almost 2-fold age- and risk factor–adjusted excess coronary risk when compared with patients with normal QTc (hazard ratio, 1.95; 95% confidence interval, 1.12-3.42; $P = .02$).

In addition, JTc was an independent predictor of ischemic heart disease, and the goodness-of-fit of the model that included JTc duration did not differ from that of the model that included QTc duration ($\chi^2$ improvement: 0.6 vs 7.6; $P = .36$). Coronary risk increased by 30% (95% confidence interval, +6% to +60%; $P = .01$) for each 1-SD increase in JTc (1 SD = 30 milliseconds).

### CEREBROVASCULAR EVENTS

During follow-up, 71 new cerebrovascular events were reported (0.64 event per 100 patient-years), including 52 strokes and 19 transient cerebral ischemic events. The event rate in patients with normal QTc (0.63 event per 100 patient-years) did not differ from that in the group with prolonged QTc (0.72 event per 100 patient-years; log-rank test; $P = .64$). In a multivariate Cox analysis, the risk of cerebrovascular events was independently predicted by age, sex, diabetes, average 24-hour systolic BP, serum creatinine level, and LVH but not by QTc duration.

### MORTALITY

During follow-up, we registered 63 deaths from all causes (0.57 event per 100 patient-years), of which 36 were from cardiovascular causes (7 fatal myocardial infarctions, 10 sudden cardiac deaths, 6 other cardiac deaths, and 13 fatal strokes). Cardiovascular death rates were 0.27 and 0.57 per
Prolongation of the QT interval on the surface ECG was shown to be predictive of adverse cardiovascular outcomes in different clinical situations, especially among subjects with coronary heart disease, or those at high risk for cardiovascular disease. The predictive value of a prolonged QT interval is low-risk populations is more controversial. In an analysis that excluded patients with coronary heart disease, the Framingham Heart Study failed to demonstrate a relationship between QT duration and subsequent coronary artery disease–related death. In other observational studies, exclusion of subjects with prevalent coronary heart disease either decreased or abolished the prognostic impact of prolonged QT interval. In the biracial Atherosclerosis Risk in Communities study, an independent relationship between QTc duration and cardiovascular morbidity and mortality was found in black but not white subjects. In the same database, QTc interval was nonpredictive of future coronary events in men but significant in women; however, no adjustment for LVH was performed in that study.

In a recent overview of prospective studies, a consistent association between QTc interval and total and cardiovascular mortality was observed among subjects with, but not in those without, prior cardiovascular disease. In the Losartan Intervention for Endpoint Reduction in Hypertension study, QT interval was predictive of future cardiovascular outcomes in a population of patients with LVH. Taken together, the available studies do not provide an answer to the question regarding the independent clinical significance of prolonged ventricular repolarization in patients with uncomplicated essential hypertension.

In this large, prospective, observational study of white men and women with essential hypertension who had no clinically overt cardiovascular disease at the baseline examination, QTc interval duration was found to be an important risk factor for subsequent ischemic heart disease. The relationship was statistically significant and persisted after correction for the influence of several traditional risk factors, including age, sex, diabetes, cigarette smoking, serum cholesterol and creatinine levels, and BP. Interestingly, the association held after adjustment for average 24-hour BP, which is a better risk marker than office BP in hypertensive subjects. Notably, the independent association between QTc and future cardiovascular morbidity held after adjustment for LVH. The QT interval duration was also associated with a higher rate of all-cause and cardiovascular mortality. We have extended these results, which were obtained in patients with hypertensive LVH, to the hypertensive population as a whole.

Since the QT interval encompasses ventricular depolarization, independent markers of repolarization such as the JT interval might have better prognostic value, at least among subjects with increased QRS duration. We found that these observations might not apply to subjects with normal QRS duration. In our study, JTc was not superior to QTc as a predictor of coronary heart disease in a population of subjects with QRS duration of less than 120 milliseconds.

The relationship between prolonged QTc and future cardiac morbidity and mortality may be attributed to ventricular electrical instability and dispersion of repolarization, which give rise to early afterdepolarizations. Prolonged QT interval has also been hypothesized as a marker of underlying subclinical atherosclerotic disease and might be viewed as a manifestation of subclinical myocardial ischemia. Atherosclerotic disease either decreased or abolished the prognostic impact of QT interval. In a multivariate Cox regression analysis, only age, diabetes, and with QT prolongation (log-rank test; P = .03). However, in a multivariate Cox regression analysis, only age, diabetes, and with QT prolongation (log-rank test; P = .03). However, in a multivariate Cox regression analysis, only age, diabetes, and 24-hour systolic BP were independent predictors (hazard ratio, 2.05; 95% confidence interval, 1.01-4.37; P = .02). The cardiovascular death hazard ratio was 1.33 (95% confidence interval, 1.01-1.78) for each 1-SD increase in QTc duration. All-cause deaths were 0.50 and 0.96 per 100 patient-years in the groups without and with QT prolongation (log-rank test; P = .03). However, in a multivariate Cox regression analysis, only age, diabetes, and 24-hour systolic BP were independent predictors of all-cause death, and the prognostic impact of QT interval was no longer statistically significant (P = .13).

Prolongation of the QT interval in low-risk populations is more controversial. Since the QT interval encompasses ventricular depolarization, independent markers of repolarization such as the JT interval might have better prognostic value, at least among subjects with increased QRS duration. We found that these observations might not apply to subjects with normal QRS duration. In our study, JTc was not superior to QTc as a predictor of coronary heart disease in a population of subjects with QRS duration of less than 120 milliseconds.

The relationship between prolonged QTc and future cardiac morbidity and mortality may be attributed to ventricular electrical instability and dispersion of repolarization, which give rise to early afterdepolarizations. Prolonged QT interval has also been hypothesized as a marker of underlying subclinical atherosclerotic disease and might be viewed as a manifestation of subclinical myocardial ischemia.
chemia, fibrosis, autonomic dysfunction, and LVH. However, LVH does not seem to fully account for our findings because the adverse prognostic significance of QTc interval was independent of the effect of LVH. On the other hand, QT prolongation might be an indirect marker of subclinical ischemia in our study. This hypothesis is supported by the fact that in contrast with LVH, which is a powerful predictor of both coronary and cerebrovascular morbidity events, 30 QT interval was found to predict coronary but not cerebrovascular disease in the present study.

STUDY LIMITATIONS

Our findings, which were obtained in initially untreated white subjects, may not be extended to different ethnic groups or to subjects receiving antihypertensive treatment at the time of the qualifying examination. The true importance of QTc duration is likely to be underestimated in our study, in which ECG classification was based on a single examination, not taking into account the spontaneous variability of QTc over time. 31, 32 The PIUMA database does not include information about BP control during follow-up in the whole population or about occasional changes in antihypertensive regimen over time.

CLINICAL IMPLICATIONS

QTc prolongation is often encountered as an incidental finding during the routine ECG examination of a hypertensive patient without clinically apparent cardiac disorder. Our findings suggest that QTc prolongation represents an independent risk factor for future ischemic heart disease and cardiovascular mortality in these subjects. Above and beyond the prognostic information provided by age, sex, LVH, and all other established risk markers, the simple, inexpensive assessment of repolarization duration on the standard 12-lead ECG may contribute to refine cardiovascular risk stratification and deserves to be included in the clinical evaluation of all hypertensive patients. Patients with QTc prolongation are at increased risk for coronary heart disease and require a more vigorous preventive approach and possibly a more comprehensive diagnostic workup to exclude the presence of clinically silent coronary disease.

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