

Prognostic impact of electrocardiographic signs in patients with Type 2 diabetes and cardiovascular disease: results from the PROactive study

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Abstract

Aims Although a resting electrocardiograph is broadly applied in clinical practice for evaluating patients with Type 2 diabetes and cardiovascular disease, the independent prognostic relevance of electrocardiographic signs has not thoroughly been examined.

Methods Baseline 12-lead electrocardiographs available in 5231 of the 5238 participants of the PROactive trial were analysed for heart rate, heart rate corrected QT-interval, presence of atrial fibrillation/flutter, left axis deviation, right and left bundle branch block. The association of electrocardiographic signs with total mortality, the principal secondary composite endpoint (death, myocardial infarction and stroke) and serious adverse heart failure events was examined by Cox-regression analysis.

Results Two hundred and twenty-three (4.3%) patients showed atrial fibrillation/flutter, 213 (4.1%) patients had right bundle branch block, 111 (2.1%) patients had left bundle branch block and 706 (13.5%) patients had left axis deviation. Mean cQT-interval was 418 ms (± 25 ms) and mean heart rate was 72/min (± 14 /min). In multivariate adjusted analyses, heart rate and cQT-interval were significantly associated with mortality, the composite secondary endpoint and heart failure, whereas right and left bundle branch blocks were significantly associated with heart failure only. Left axis deviation was associated with heart failure and atrial fibrillation/flutter was associated with mortality and heart failure in univariate but not multivariate analyses.

Conclusion Easily assessable electrocardiographic signs such as heart rate, cQT-interval and bundle branch blocks were predictive for adverse outcome independently of multiple risk factor adjustment and should be considered in clinical care.

Keywords : atrial fibrillation ; bundle branch block ; diabetes ; heart rate ; QT-interval

Introduction

A resting 12-lead electrocardiograph (ECG) is a commonly applied tool to evaluate patients with cardiovascular disease for signs of myocardial ischaemia. In patients with diabetes mellitus, a variety of abnormal ECG signs have been described, not only resulting from ischaemia [1]. So far there are only few studies addressing the prognostic role of ECG signs in diabetes-specific populations and no studies focusing merely on patients with diabetes and manifest cardiovascular disease. There are, however, several reasons for examining this population separately. Diabetes itself is a strong predictor of several ECG signs such as QT-interval or atrial fibrillation, which partly explains their prognostic relevance [2,3]. On the one hand, diabetes-related risk factors such as hypertension, coronary ischaemia or proteinuria are also associated with ECG alterations [1,4]. An independent prognostic effect of these ECG signs is therefore questionable after adequate adjustment. On the other hand, diabetes-specific co-morbidity such as autonomic neuropathy can influence ECG signs such as heart rate or QT-interval, thereby modifying their prognostic impact [5,6]. Finally, patients with diabetes and manifest cardiovascular disease undergo an extensive characterization in terms of patient history and laboratory risk factors on a routine basis and it is unclear whether ECG signs add independent information.

Earlier studies on patients with diabetes (e.g. evaluating the role of QT-interval) have the limitation of small and heterogeneous samples, combining patients with and without prevalent cardiovascular disease, which does not give reliable estimates for either patient group and even leads to contradictory results [7-10]. Here, we report an

analysis of the PROactive trial that examines the prognostic relevance of the following ECG signs: resting heart rate, corrected QT-interval (cQT), atrial fibrillation/flutter, left axis deviation and right as well as left bundle branch block for the outcome of total mortality, the composite secondary endpoint (including first event of mortality, myocardial infarction and stroke) and serious heart failure.

Patients and methods

PROactive is a multi-center double-blind placebo-controlled cardiovascular outcomes trial, which has previously been described in detail [11,12]. Briefly, 5238 patients who had Type 2 diabetes (aged 35-75 years) and had documented evidence of cardiovascular disease (defined as one or more of the following: myocardial infarction, stroke, percutaneous coronary intervention, or coronary artery bypass graft ≥ 6 months before entry into the study; acute coronary syndrome ≥ 3 months before entry into the study; objective evidence of coronary artery disease; or symptomatic peripheral arterial obstructive disease) were recruited. Patients with New York Heart Association Class II-IV heart failure at screening were excluded. Patients were randomly assigned to receive pioglitazone ($n = 2605$) or matching placebo ($n = 2633$) in addition to their existing guideline-directed glucose-lowering and cardiovascular medications. All patients provided written informed consent. The study protocol was approved by local and national ethics committees and regulatory agencies and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Endpoints

This analysis is restricted to all-cause mortality, the pre-specified principal secondary composite endpoint (time to the first event of all-cause mortality, myocardial infarction and stroke) and serious heart failure. The definition of non-fatal myocardial infarction was survival for > 24 h from onset of symptoms and, in the absence of percutaneous coronary intervention or coronary artery bypass surgery, at least two of the following: (i) symptoms suggestive of myocardial infarction (ischaemic chest pain or discomfort) lasting > 30 min; (ii) ECG evidence of myocardial infarction; or (iii) elevation of cardiac serum markers, or following percutaneous coronary intervention or coronary artery bypass surgery if there was ECG evidence of myocardial infarction. All potential endpoint events were adjudicated centrally by an independent committee of clinical experts. Heart failure was a pre-specified as either a serious or non-serious adverse event. Because of missing standardized, objective criteria in the study design for distinguishing non-serious heart failure from oedema alone, this analysis is restricted to serious heart failure events. These were defined as that which requires hospitalization or prolongation of a hospitalization stay, was fatal or life-threatening, or resulted in persistent significant disability or incapacity. Details on the definition and adjudication of serious events have previously been published [12].

Procedures

Blood samples for various analyses were taken at baseline and every 6 months. Details of assays and specific methodology have previously been described [12]. Standard 12-lead ECGs were obtained at baseline, at yearly intervals and at the last visit. All available baseline ECGs were analysed by an experienced cardiologist, who was blinded to patient characteristics after the study was finished. The following variables were assessed according to recent recommendations [13,14]: heart rate (/min), pacemaker rhythm, right and left bundle branch block, left axis deviation, atrial fibrillation or flutter and QT-interval duration. QT-interval duration was measured manually in lead V2 or V3 because of a high rate of ECGs without automatic digital analysis. The QT-interval was corrected for heart rate by the Framingham formula [15]: $cQT = QT + 154 \times (1 - 60/\text{heart rate})$, as previously described and recommended. Tachycardia was defined as heart rate $> 100/\text{min}$, while bradycardia was defined as heart rate $< 50/\text{min}$. Short QT interval was defined if $cQT \leq 390$ ms, while long QT interval was defined as $cQT \geq 450$ ms and $cQT \geq 460$ ms in men and women, respectively.

Statistical analysis

Statistical methods used for the sample size calculation and endpoint analysis for PROactive have previously been reported [12]. The data presented here are from the intention-to-treat population. Continuous variables are presented as mean and standard deviation and categorical variables as number and percentage. Time-to-event analyses were performed by fitting a Cox proportional hazards survival model with pre-specified ECG signs as covariates. Multivariate Cox models were used to test the independent effect of ECG signs; variable selection was carried out using a backward stepwise selection algorithm at a significance level of 0.05, with the following variables initially included in addition to ECG signs: age, gender, diabetes duration, smoking status, presence of metabolic syndrome (defined by criteria of the Adult Treatment Panel III of the National Cholesterol Education Program), baseline measures of combined blood pressure, creatinine, HbA_{1c}, LDL cholesterol, HDL cholesterol,

triglycerides, body mass index and microalbuminuria, history of coronary artery disease, acute coronary syndrome, percutaneous coronary intervention/bypass surgery, stroke and myocardial infarction, peripheral arterial occlusive disease, baseline use of insulin, metformin and sulphonylurea, diuretics, statins, beta-blocker and ACE inhibitor and pioglitazone treatment.

Table 1 Prevalence of baseline ECG signs in patients with Type 2 diabetes and cardiovascular disease

	Pioglitazone (n = 2601)	Placebo (n = 2630)	Total (n = 5231)
Atrial fibrillation/flutter	111 (4.3%)	112 (4.3%)	223 (4.3%)
Right bundle branch block	105 (4.0%)	108 (4.1%)	213 (4.1%)
Left bundle branch block	54 (2.1%)	57 (2.2%)	111 (2.1%)
Left axis deviation	349 (13.4%)	357 (13.6%)	706 (13.5%)
Pacemaker rhythm	18 (0.7%)	17 (0.6%)	35 (0.7%)
cQT-interval (ms), mean (SD)	418 (25)	417 (26)	418 (25)
Short QT	305 (11.7%)	333 (12.7%)	638 (12.2%)
Long QT	183 (7.0%)	213 (8.1%)	396 (7.6%)
Heart rate (/min), mean (SD)	72 (14)	72 (14)	72 (14)
Bradycardia	51 (2.0%)	49 (1.9%)	100 (1.9%)
Tachycardia	73 (2.8%)	82 (3.1%)	155 (3.0%)

Results

Baseline characteristics of the study patients have been extensively described previously [11,12]. Briefly, 66.1% of the 5238 patients were male, the mean age was 62 years (\pm 8 years), the mean duration of diabetes was 9.5 years (\pm 7 years), 94.7% had known cardiovascular disease, 46.7% had previous myocardial infarction and 21.8% had known cerebrovascular disease. Baseline ECGs were available in 2601 of 2605 (99.8%) patients in the treatment group and in 2630 of 2633 (99.9%) patients in the placebo group. Findings of the baseline ECGs are shown in Table 1.

Univariate association of ECG signs with mortality, the secondary composite endpoint and heart failure is shown in Fig. 1 and Table 2. Patients with baseline pacemaker rhythm were excluded from all analyses except for isolated atrial fibrillation/flutter. Increasing heart rate, increasing QT-interval, atrial fibrillation/flutter and left bundle branch block were significantly associated with increased mortality risk. Increasing heart rate, increasing QT-interval and left bundle branch block were significantly associated with an increased risk for the secondary composite endpoint. Only heart rate was significantly associated with both individual secondary endpoints of myocardial infarction [hazard ratio (HR) 1.11 per 10/min, 95% CI 1.01-1.21, $P = 0.04$] and stroke (HR 1.11 per 10/min, 95% CI 1.01-1.22, $P = 0.04$), while atrial fibrillation/ flutter was significantly associated with stroke (HR 1.92, 95% CI 1.13-3.25, $P = 0.02$). Increasing heart rate, increasing QT-interval, atrial fibrillation/flutter, right bundle branch block, left axis deviation and left bundle branch block were significantly associated with heart failure.

Beta-blockers influence heart rate and the cQT-interval and may also affect outcome. Adjustment for beta-blocker use did not attenuate the risk associated with heart rate and cQT-interval (Table 2). There was no evidence for interaction between heart rate or cQT-interval and beta-blocker use at baseline (test for interaction: all $P > 0.18$).

The independent prognostic effect of the ECG signs was tested in multivariate Cox models with stepwise backward elimination. Table 3 shows the ECG signs significantly associated with outcome in the final models. Heart rate and cQT-interval were significantly associated with mortality and the composite secondary endpoint. Heart rate, cQT-interval, right bundle branch block and left bundle branch block were significantly associated with serious heart failure.

Table 4 shows the predictive characteristics of the ECG signs, which proved a significant association with particular outcomes independently of known risk factors, corresponding to Table 3. Consistently, all ECG signs had weak sensitivity, but very high specificity and high negative predictive value.

Discussion

We found that easily assessable ECG signs are independently predictive for adverse outcome in patients with diabetes and known cardiovascular disease after adjusting for multiple risk markers that are routinely assessed. Heart rate and cQT-interval were associated with total mortality and the composite endpoint of mortality, myocardial infarction and stroke. Heart rate, cQT-interval, right and left bundle branch blocks were associated with heart failure. These ECG signs particularly showed high specificity for adverse outcomes, but limited sensitivity. Atrial fibrillation/flutter was not a significant predictor of outcome in adjusted analyses.

In contrast to our results in a recent analysis of the ADVANCE trial, baseline atrial fibrillation was robustly related to mortality and cerebrovascular events as well as heart failure in patients with diabetes after multivariate adjustment [16]. One explanation is the more than doubled frequency of oral anticoagulants in our atrial fibrillation group compared with ADVANCE, which is expected to attenuate the rate of cardiovascular outcomes in particular. In addition, the exclusion of symptomatic heart failure in PROactive might be a major reason for the clearly lower baseline frequency of atrial fibrillation (4.3% compared with 7.6% in ADVANCE) despite a higher rate of cardiovascular co-morbidity. Heart failure is associated with an increased risk of atrial fibrillation [17] and, conversely, atrial fibrillation can be used as a surrogate marker of heart failure. It can be expected that atrial fibrillation is a more accurate marker than 'history of hospitalization for heart failure', which was the only heart-failure-indicating covariate in the multivariate analysis of ADVANCE. Hence, differences in the study population may be responsible for the contrary results on the independent prognostic role of atrial fibrillation, underscoring the necessity of clearly defined populations to derive risk markers.

We confirm previous results on the association of heart rate and cardiovascular outcome in patients with diabetes [7-9] and further extend these to an independent prediction of heart failure. So far, heart rate as a predictor of heart failure has only been described in population-based approaches [18,19]. Important to note, heart rate is discussed not only as a marker that indicates increased risk but that also might causally contribute to the development or progression of cardiovascular disease [20]. Experimental data indicate that the increased magnitude and frequency of shear and tensile stress, which is associated with high heart rate, can promote the pathogenesis of atherosclerosis [21]. This is of special interest for patients with diabetes as diabetic neuropathy is associated with tachycardia.

In our study, left and right bundle branch blocks were both predictive for heart failure, but not mortality or cardiovascular outcomes, in multivariate analysis. In the HOPE trial, which included approximately 38% high-risk patients with diabetes also excluding manifest heart failure, left bundle branch block was associated with total and cardiovascular mortality and most robustly with heart failure, while right bundle branch block was related to neither of the outcomes [22]. Thus, our findings are in concordance with HOPE in terms of left bundle branch block being mainly a marker of occult cardiac dysfunction predictive for heart failure-associated outcomes. The discrepancy regarding right bundle branch block could be attributed to a diabetes-specific association. In a population-based study, Jeong *et al.* found diabetes to be a determinant of right bundle branch block, whereas cardiac disease was a determinant of left bundle branch block [23].

To the best of our knowledge, we present the largest analysis on the impact of cQT-interval in a diabetes-specific population with manifest cardiovascular disease. We confirm findings of some reports on the association of cQT-interval with total mortality and cardiovascular outcomes. As an important novelty, we found a predictive impact of increasing cQT-interval for heart failure. The cQT-interval was shown to be strongly correlated with coronary heart disease and left-ventricular hypertrophy in patients with diabetes, which both are known predictors of heart failure [24]. cQT-interval was also inversely related to the severity of disease within heart failure patients [25]. Accordingly, cQT-interval can contribute to the prediction of heart failure both by association with known risk factors and by indicating occult cardiac dysfunction.

The strong and independent prognostic impact of ECG signs, especially in terms of future heart failure events, raises the question about clinical implications. Heart failure is currently of particular interest in patients with diabetes and thiazolidinedione therapy, as these drugs are associated with a significant increase in heart failure exacerbation [26]. Simple clinical markers indicating increased risk for heart failure are needed to identify patients who need close monitoring. Because of the low sensitivity, ECG signs are obviously not suitable as 'standalone' markers for screening of high-risk patients. However, the high specificity suggests that detection of tachycardia, long cQT-interval or bundle branch blocks might alert physicians to increased risk for adverse outcomes such as heart failure. The limited positive predictive value found in our population is in part attributable to the low rate of adverse outcomes (5-13%), and can be improved by combining ECG with other risk markers, thus increasing pre-test probability for adverse outcomes.

FIGURE 1 Univariate analysis of ECG signs for prediction of outcomes (* $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$). A. fib: atrial fibrillation; LAD: leftaxis deviation; LBBB: left bundle branch block; RBBB: right bundle branch block.

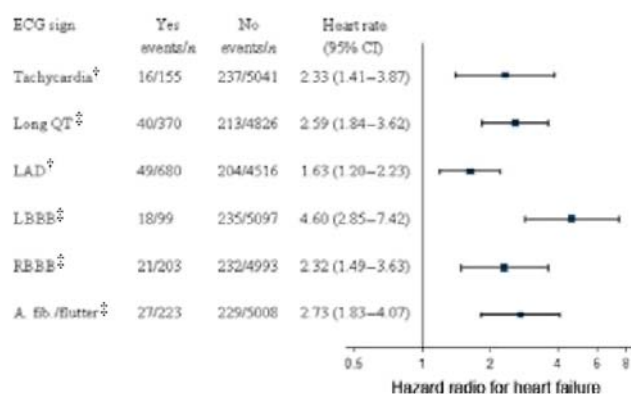
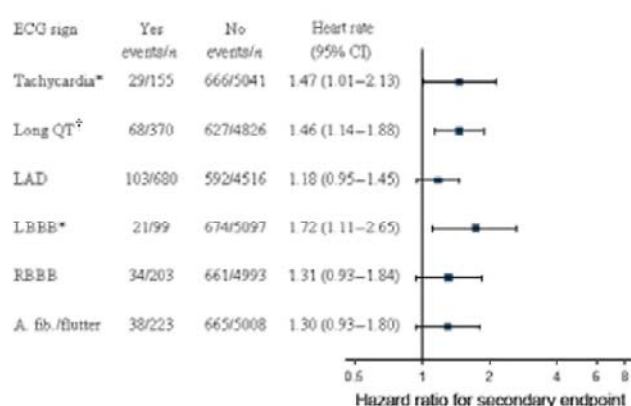
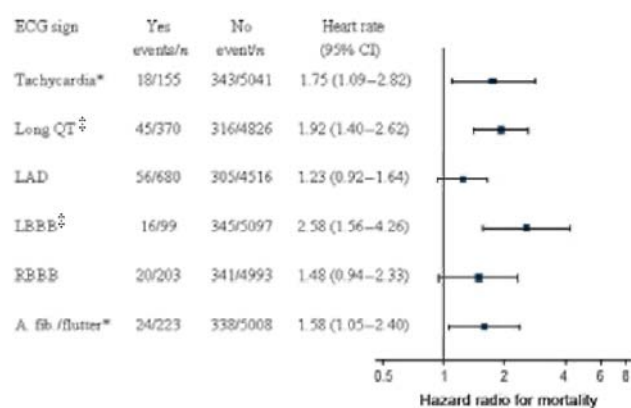


Table 2 Prediction of outcomes by heart rate and cQT-interval with and without adjustment for beta-blocker use in patients with Type 2 diabetes and cardiovascular disease

ECG sign	Outcome	Unadjusted		Adjusted for beta-blocker use	
		Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Heart rate	Mortality	1.23 (1.15-1.31)	< 0.0001	1.20 (1.12-1.29)	< 0.0001
	Secondary composite endpoint	1.16 (1.10-1.22)	< 0.0001	1.15 (1.09-1.21)	< 0.0001
	Serious heart failure	1.30 (1.20-1.40)	< 0.0001	1.31 (1.21-1.41)	< 0.0001
cQT interval	Mortality	1.11 (1.07-1.16)	< 0.0001	1.12 (1.07-1.16)	< 0.0001
	Secondary composite endpoint	1.06 (1.03-1.09)	0.0002	1.06 (1.03-1.09)	0.0002
	Serious heart failure	1.13 (1.08-1.19)	< 0.0001	1.13 (1.08-1.19)	< 0.0001

Table 3 Multivariate analysis of ECG signs for prediction of outcomes in patients with Type 2 diabetes and cardiovascular disease

	Mortality*		Secondary composite endpoint [†]		Serious heart failure [‡]	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Heart rate (per 10/min)	1.20 (1.11-1.29)	< 0.001	1.13 (1.07-1.19)	< 0.001	1.29 (1.19-1.40)	< 0.001
cQT-interval (per 10 ms)	1.11 (1.07-1.16)	< 0.001	1.06 (1.03-1.09)	< 0.001	1.06 (1.01-1.12)	0.03
RBBB	NS		NS		1.91 (1.16-3.12)	0.01
LBBB	NS		NS		2.28 (1.3-3.99)	0.004

*Final model included in addition to ECG signs: age, creatinine, duration of diabetes, HbA_{1c}, history of myocardial infarction, percutaneous coronary intervention/bypass surgery, peripheral arterial obstructive disease, stroke, use of diuretics.

[†]Final model included in addition to ECG signs: age, micralbuminuria, body mass index, creatinine, duration of diabetes, HbA_{1c}, history of myocardial infarction, percutaneous coronary intervention/bypass surgery, peripheral arterial obstructive disease, stroke, pioglitazone treatment, smoking status, statin use, triglycerides, use of diuretics.

[‡]Final model included in addition to ECG signs: age, micralbuminuria, creatinine, duration of diabetes, HbA_{1c}, LDL cholesterol, history of myocardial infarction, pioglitazone treatment, use of diuretics.

LBBB, left bundle branch block; NS, not significant; RBBB, right bundle branch block.

Table 4 Sensitivity, specificity, positive and negative predictive value for outcomes by independent ECG signs

Outcome	Incidence* (%)	ECG sign	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Mortality	7	Tachycardia	5.0	97.2	11.6	93.2
		Long-QT	12.5	93.3	12.2	93.5
Secondary composite endpoint	13	Tachycardia	4.1	97.2	18.7	86.8
		Long-QT	9.8	93.3	18.4	87.0
Serious heart failure	5	Tachycardia	6.3	97.2	10.3	95.3
		Long-QT	15.8	93.3	10.8	95.6
		RBBB	8.3	96.3	10.3	95.4
		LBBB	7.1	98.4	18.2	95.4

* Calculated per study follow-up time.

LBBB, left bundle branch block; RBBB, right bundle branch block.

There are some limitations of our study that need to be addressed. There are plenty of other ECG signs described in the literature to be associated with prognosis such as QT-dispersion, indices of myocardial hypertrophy or early repolarization, which were not assessed here [13,27,28]. We focused on easily assessable and interpretable ECG signs. This approach seems reasonable as mostly general practitioners who might be less experienced with complex ECG analysis will analyse the ECGs in clinical routine and, in addition, in many facilities there might still be no automatic digital ECG analysis, for example, for QT-dispersion. Further, our results cannot be transferred to patients with diabetes and without cardiovascular disease or with heart failure as the prevalence and the prognostic impact of ECG signs might differ by co-morbidity. Finally, observational studies cannot clarify causality in associations. Most ECG signs that are examined here must be assumed to be secondary as a result of structural changes in the heart caused by diabetes or associated risk factors [1] and it remains unclear whether they causally contribute to the adverse outcome. In addition, there might be confounders that were not assessed in this study, for example, physical activity is known to affect heart rate as well as outcome [29].

In conclusion, affordable and easily assessable electrocardiographic signs such as heart rate, cQT-interval and bundle branch block are predictive for adverse outcome in patients with Type 2 diabetes and known cardiovascular disease independently of demographic and clinical risk factors and should be considered in clinical care.

Competing interests

EE and CAS have served as consultants to and have received honoraria for speaking engagements from Takeda. RP and RC have nothing to declare.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. List of PROactive investigators.

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