Prognostic Value of Resting Heart Rate on Cardiovascular and Renal Outcomes in Type 2 Diabetic Patients

A competing risk analysis in a prospective cohort

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OBJECTIVE—Epidemiological studies and randomized clinical trials have demonstrated in various populations that resting heart rate (RHR) was an independent predictor of cardiovascular (CV) risk and all-cause mortality. However, few data specifically evaluated the relationship between RHR and long-term CV and renal complications in a large population of type 2 diabetic (T2D) patients.

RESEARCH DESIGN AND METHODS—We performed a single-center, prospective analysis in 1,088 T2D patients. RHR was determined at baseline by electrocardiogram. The primary outcome was a composite criterion of CV and renal morbi-mortality (CV death, nonfatal myocardial infarction and/or stroke, hospitalization for heart failure, renal replacement therapy), which was adjusted for death from non-CV cause as a competing event. The secondary outcome was a renal composite criterion (renal replacement therapy or doubling of baseline serum creatinine) adjusted for all-cause death as a competing event.

RESULTS—During median follow-up of 4.2 years, 253 patients (23%) and 62 patients (6%) experienced the primary and secondary outcomes, respectively. In the subgroup of patients with CV disease history at baseline (n = 336), RHR was found to be associated with the incidence of primary outcome (P = 0.0002) but also with renal risk alone, adjusted for all-cause death as a competing event (secondary outcome; $P < 0.0001$). In patients without history of CV disease, no relation was found between RHR and the incidence of CV and/or renal events.

CONCLUSIONS—In the real-life setting, RHR constitutes an easy and less time-consuming factor that would permit identification of CV disease diabetic patients with an increased risk for long-term CV and renal complications.

Diabetes Care 35:2069–2075, 2012

Evidence has been accumulated from epidemiological studies over several decades that elevated resting heart rate (RHR) is associated with increased risk of mortality and cardiovascular events (1,2,3). The association has been reported in apparently healthy individuals (4,5) and in those with various forms of cardiovascular disease (CVD), including hypertension (6), coronary artery disease (7), and heart failure (8). The relationship between RHR and endothelial dysfunction makes it a potential risk factor not only for CVD but also for renal disease (9).

Individuals with diabetes mellitus represent a large and growing population at increased risk of cardiovascular events and mortality. Recent studies have confirmed that diabetes approximately doubles the risk of mortality and a range of vascular diseases compared with individuals without diabetes (10). As type 2 diabetes (T2D) incidence continues to increase, individuals with diabetes are likely to become an increasingly important component of the overall burden of CVD. In addition to its cardiovascular impact, T2D is also related to the incidence of renal disease. Thus, diabetic nephropathy is now the leading cause of end-stage renal disease (ESRD) in many countries (http://www.usrds.org).

The prognostic influence of elevated RHR on cardiovascular end points in individuals with T2D has received relatively little attention, and no definite data are available on renal end points. The purpose of this prospective epidemiological study was to evaluate RHR as a prognostic factor in cardiovascular and renal morbidity and mortality in the SURDIAGENE cohort (11) of patients with T2D.

RESEARCH DESIGN AND METHODS

This study is part of the ongoing prospective monocentric SURDIAGENE study, which aims to identify the genetic and environmental determinants of microvascular and macrovascular complications in type 2 diabetes (11).

Patients with T2D were recruited and followed regularly at the University Hospital of Poitiers, France, since 2002. The main exclusion criteria were residence outside the Poitiers region and evidence of nondiabetic renal disease. The Poitiers ethics committee (Comité de Protection des Personnes Ouest 3) approved the study protocol, and written informed consent was obtained from each patient.

Living status and cardiovascular and renal end points were determined from patients' hospital records and interviews with their general practitioners, every

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Received 19 December 2011 and accepted 17 April 2012.
DOI: 10.2337/dc11-2468
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc11-2468/-/DC1.
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second year since 2007. The present analysis takes data obtained in 2009 into account.

Baseline characteristics

At baseline, all patients were examined to collect clinical data including personal medical history (especially CVD), diabetes duration, smoking status, blood pressure, height, weight, and medication prescriptions. Biological determinations were routinely performed for HbA_{1c}, serum total cholesterol, urinary albumin-to-creatinine ratio, and serum creatinine, allowing the calculation of estimated glomerular filtration rate using the MDRD-4 equation (12) (methods detailed in Supplementary Material 1).

Electrocardiogram (ECG) traces were also taken, from which RHR was calculated. All ECG traces were read by two physicians; if RHR obtained on different readings differed by <5 bpm, the mean of the two values was used. If readings differed by ≥5 bpm, a third reading performed by an expert cardiologist (PS) was used for analysis.

A history of CVD at baseline was defined as a history of coronary artery disease (myocardial infarction, coronary revascularization by angioplasty, or bypass graft surgery), cerebral arterial disease (stroke, transient ischemic attack, carotid artery revascularization), or lower limb arterial disease (peripheral artery revascularization or limb/thigh amputation). A history of renal disease was defined at baseline as an estimated glomerular filtration rate <60 mL/min and/or albuminuria defined as urinary albumin-to-creatinine ratio >30 mg/mmol.

Outcome criteria

The primary outcome variable was time to incidence of the composite end point: cardiovascular mortality or nonfatal myocardial infarction, or nonfatal stroke or hospitalization for heart failure or onset of ESRD, defined as renal replacement therapy (dialysis or kidney transplantation). Cardiovascular death was defined as death as a result of causes listed in the WHO International Classification of Diseases (ICD 10 chapter IX; http://apps.who.int/classifications/apps/icd/icd10online/).

The secondary outcome was time to incidence of a composite renal outcome: development of ESRD requiring renal replacement therapy or doubling of baseline serum creatinine.

Statistical analysis

All statistical analyses were carried out using the SAS 9.2 software package (SAS, Cary, NC) and the R 2.13.1 software package (http://www.r-project.org).

The analysis was stratified according to the presence of a history of CVD at baseline (CVD BL^+ subgroup) or the absence of a history of CVD at baseline (CVD BL^- subgroup).

The cumulative incidence function (CIF) of the primary outcome was computed according to RHR classes (<70 bpm, ≥70 bpm), adjusting for death from non-CV cause as a competing risk. A similar analysis was conducted on the secondary renal outcome treating all-cause death as a competing event. The CIF was estimated using the *cmprsk* package developed by Gray.

To estimate the influence of RHR and baseline covariates on outcomes, we used the Fine and Gray model (13), which extends the Cox model to competing risk data by considering the subdistribution hazard. The strength of the association between each variable and the outcome was assessed using the subhazard ratio (SHR), which is the ratio of hazards associated with the CIF in the presence/absence of a given prognostic factor. Prognostic factors were evaluated in uni- and multivariate analyses. Variables associated with the outcome at $P < 0.15$ on the basis of the univariate models were introduced in the multivariate models. Because β-blockers are strongly influencing RHR, β-blocker use was forced into the model and the maximal model is presented. Models were fitted using the *crr* routine in the R software package.

RESULTS

Baseline cohort characteristics

Of the 1,099 patients included until 1 January 2009, 11 patients were excluded from the analysis because of baseline ESRD, leaving 1,088 patients for the current study.

Main baseline demographic and clinical characteristics of the study population are given in Table 1. A history of CVD and of renal disease was noted in 336 (31%) and 367 (34%) patients, respectively (details in Supplementary Material 2).

Incidence of outcomes

An interaction was found between RHR and history of CVD at baseline for the relation between RHR and both the primary ($P_{interaction} = 0.0001$) and secondary ($P_{interaction} = 0.03$) study outcomes (see Supplementary Fig. 1). Because of this interaction, all results were stratified according to history of CVD at baseline. No such interaction was found with history of renal disease at baseline (data not shown).

During a median of 4.2 years of follow-up, 253 patients (23%) experienced the primary composite outcome, corresponding to an incidence rate of 59.5 per 1,000 person-years, 95% CI [52.2; 66.8], in the whole cohort. Incidence rates were 104.3 [85.8; 122.8] and 42.5 [35.2; 49.8] in the CVD BL^+ and CVD BL^- subgroups, respectively.

The composite renal outcome occurred in 62 patients (6%), with incidence rates of 14.0 per 1,000 person-years, 95% CI [10.5; 17.5] in the whole cohort and 15.7 [8.8; 22.6] and 13.3 [9.3; 17.4] in the CVD BL^+ and CVD BL^- subgroups, respectively.

Fifty-one patients (5%) died of non-CV causes without first developing any other primary or secondary composite outcome events. Numbers of first and total events contributing to the outcomes are detailed in Supplementary Table 1.

RHR as a predictor of the cumulative incidence of CV end points

In the subgroup of CVD BL^+ patients, those who met the primary outcome had a higher RHR than those without any event (72 ± 16 vs. 65 ± 12 bpm, $P = 0.0002$), while RHR did not differ among CVD BL^- patients (72 ± 13 bpm in both groups) (Supplementary Table 2).

The top of Fig. 1 illustrates further the relationship between RHR (categorized as ≥70 bpm or <70 bpm) and the primary outcome, taking the competing risk of non-CV death into account. RHR ≥70 bpm was significantly associated with the incidence of the primary outcome in CVD BL^+ patients only ($P = 0.03$; top left panel). Excluding the renal component from the primary outcome did not modify this result (data not shown). When separating myocardial infarctions and strokes on one hand, and heart failure leading to hospitalization in an exploratory analysis, we were not able to see any heterogeneity of the relationship between RHR and clinical outcome (data not shown).

In multivariate analysis, RHR, expressed as a continuous variable, still remained a predictor of the primary outcome in CVD BL^+ (SHR = 1.01; $P = 0.03$), but not in CVD BL^- (Table 2).

Table 1—*Baseline characteristics of the whole cohort of patients and in the subgroups with and without a history of CVD at baseline*

Variables	All	CVD BL$^+$	CVD BL$^-$
n (%)	1,088	336 (31)	752 (69)
Sex, men/women, *n* (%)	629 (58)/459 (42)	230 (68)/106 (32)	399 (53)/353 (47)
Age (years)	65.14 ± 10.61	68.96 ± 9.18	63.44 ± 10.76
BMI (kg/m^2)	30.93 ± 6.03	29.81 ± 5.32	31.43 ± 6.26
Active smoker, *n* (%)	116 (11)	33 (10)	83 (11)
Diabetes duration (years)	14.93 ± 10.07	18.00 ± 10.57	13.56 ± 9.54
HbA_{1c} (%)	7.87 ± 1.53	7.76 ± 1.32	7.91 ± 1.62
Creatinine level (μmol/L)	101.61 ± 74.24	120.23 ± 94.08	93.31 ± 61.72
Estimated glomerular filtration rate (mL/min per 1.73 m^2)	75.53 ± 27.71	66.55 ± 26.24	79.54 ± 27.42
History of renal disease, *n* (%)	367 (34)	150 (45)	217 (29)
Blood pressure (mmHg)			
Systolic	133.64 ± 17.71	134.72 ± 19.13	133.16 ± 17.02
Diastolic	72.90 ± 10.88	71.01 ± 10.90	73.74 ± 10.78
Total cholesterol (mmol/L)	4.94 ± 1.16	4.74 ± 1.22	5.03 ± 1.12
RHR (bpm)	70.98 ± 13.58	67.74 ± 13.78	72.42 ± 13.25
β-Blocker use, *n* (%)	349 (32)	167 (50)	182 (24)

Quantitative variables are described by means ± SD.

RHR as a predictor of the cumulative incidence of renal outcome

In the subgroup of CVD BL$^+$ patients, those developing a renal outcome had a higher RHR than nonaffected patients: 77 ± 13 vs. 66 ± 12 bpm ($P < 0.0001$), while no such effect was noticed in CVD BL$^-$ patients (Supplementary Table 3).

When the competing risk of death was taken into account, CVD BL$^+$ patients with a RHR ≥70 bpm were more likely to develop the renal outcome than patients with a RHR <70 bpm ($P = 0.02$; Fig. 1, bottom left panel). When there was adjustment for risk factors identified in the univariate analysis, predictors of the secondary renal outcome in CVD BL$^+$ patients were RHR (SHR = 1.04; $P = 0.001$) and renal disease at baseline (Table 3), whereas RHR did not contribute at all to renal outcomes in CVD BL$^-$ patients.

CONCLUSIONS—The main finding of this study was that elevated RHR significantly interacted with history of CVD and that RHR was a significant predictor of CV and renal events, even after adjustment for multiple traditional risk factors and treating non-CV death as a competing event. It is interesting that RHR was a strong predictor for renal events when combined with CV events and also when considered separately.

An important feature is that diabetes is known to be associated with increased risk of death from noncardiovascular causes (14), which defines a competing risks setting. The methods used in the current study enabled us to take into account causes of failure other than the cause of interest, allowing us to identify the role of RHR on major CV events and also on renal events.

Our results are broadly consistent with previous longitudinal studies of RHR in T2D patients, suggesting a deleterious effect of increased RHR on mortality risk (all-cause or cardiovascular) and cardiovascular outcomes. In a Swiss cohort of 523 diabetic patients, followed up for more than 20 years, RHR was significantly associated with increased risk of all-cause and cardiovascular mortality, as well as cardiac disease and ischemic heart disease (15). In the Bremen Diabetes Study (16), 475 T2D patients were followed for 5 years, and elevated RHR was a strong predictor of cardiovascular death. In 990 diabetic (and 1,488 nondiabetic) Pima Indians followed for a median of 7.3 years, RHR was a significant predictor of all-cause mortality, with a hazard ratio of 1.41 for each increase of 10 bpm in diabetic subjects, very similar to our findings (17). Finally, in the Euro Heart Survey on Diabetes and the Heart (18), in the 780 patients with diabetes out of 2,507 patients with coronary artery disease followed for 1 year, RHR was significantly associated with mortality and cardiovascular events (the composite of all-cause mortality, nonfatal myocardial infarction, and stroke). A 10-bpm increment in RHR was independently associated with mortality (hazard ratio 1.34), but not cardiovascular events (hazard ratio 0.99). In a post hoc analysis of the ADVANCE study (a randomized clinical trial studying ~12,500 T2D patients), RHR was associated with cardiovascular events and all-cause mortality (19).

Our analysis identified that RHR was a significant predictor of ESRD and/or doubling of creatinine level; this extends the findings of a deleterious effect of RHR on chronic kidney disease in Japanese patients (20), although the identification of diabetic patients was not possible in that publication. So, to the best of our knowledge, our data are the first reporting a relationship between RHR and hard renal outcomes in diabetic patients, taking into account the competing risks setting. The ADVANCE study, unfortunately, did not report the effect of RHR on renal outcomes (19).

Thus, our cohort specifically dedicated to T2D is in agreement with previous reports and because of its adequate size allowed us to identify the interaction between CVD history and the prognostic role of RHR.

The mechanisms by which elevated RHR can exert adverse CV effects are becoming better understood, unlike renal effects, and include myocardial ischemia, accelerated atherosclerosis, endothelial dysfunction, and atherosclerotic plaque disruption (2,9,21,22). Other confounding factors such as glycemic control were considered in the multivariate analysis performed on this cohort. In the Diabetes Control and Complications Trial, patients with type 1 diabetes who underwent intensive diabetes treatment had significantly lower RHR than those treated with conventional therapy (23). During follow-up, the difference in heart rate between the treatment groups persisted for at least 10 years, possibly explaining, in part, the reduction in CVD observed with intensive therapy.

We clearly demonstrated that in patients with CVD at baseline, RHR was a significant predictor of the primary outcome and major renal events. By contrast, RHR did not have any prognostic value in patients without CVD. The dual effect of RHR is not likely to be because of statistical power issue; it was clearly different between those patients in primary and secondary prevention, as evidenced by a statistical interaction (see additional figure). To further support this point, according

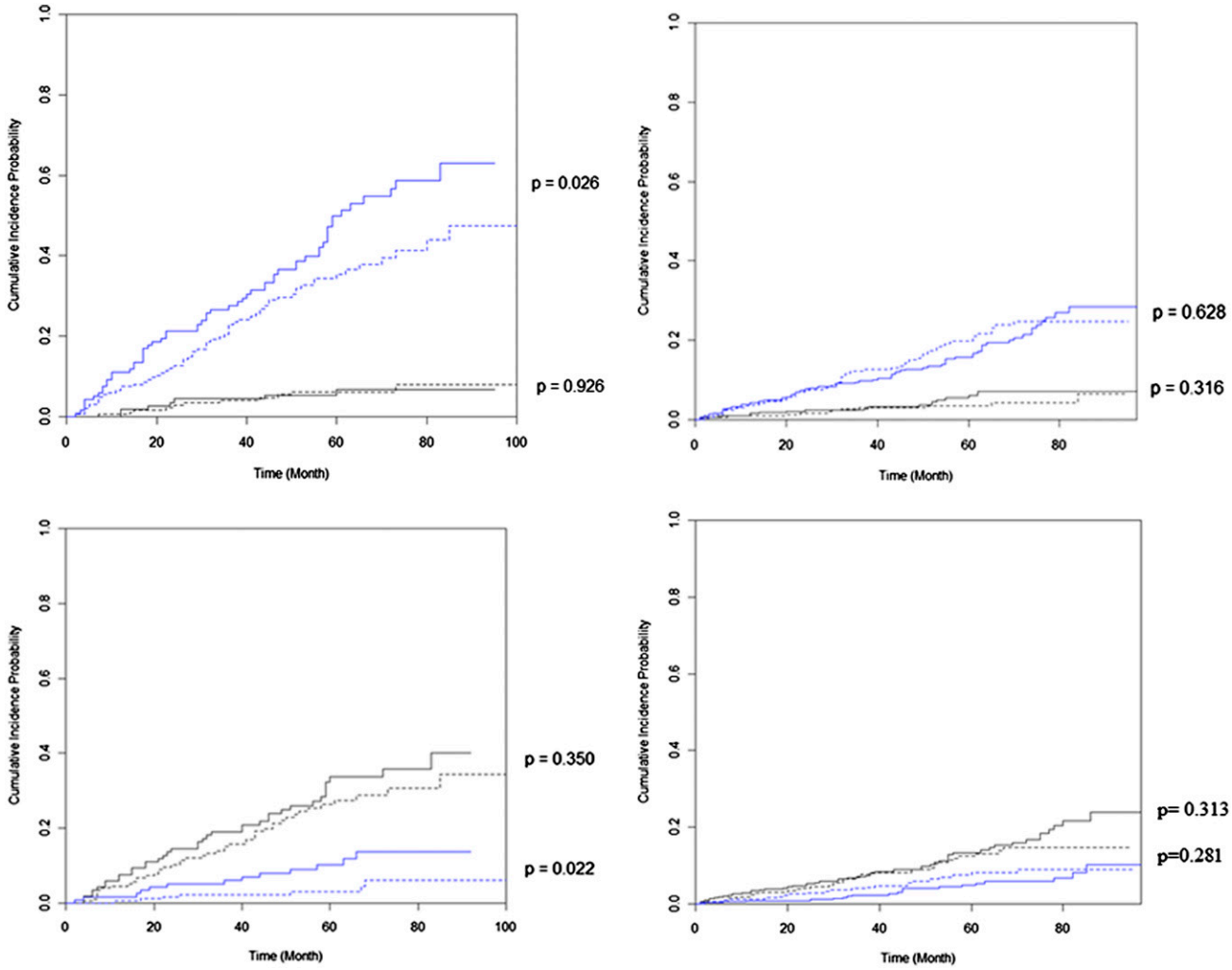

Figure 1—Top: *Cumulative incidence of cardiovascular and renal events (primary outcome) and of noncardiovascular death according to RHR (≥70 bpm vs. <70 bpm), stratified for history of CVD at baseline (CVD BL$^+$: left panel, CVD BL$^-$: right panel). Estimates of cumulative incidence curves of risk are represented in blue for the primary outcome and in black for noncardiovascular death. The continuous line is for patients with RHR ≥70, and the dotted line is for patients with RHR <70 bpm.* Bottom: *Cumulative incidence of ESRD or doubling of baseline serum creatinine level (secondary outcome) and of all-cause death according to RHR (≥70 bpm vs. <70 bpm), stratified for history of CVD at baseline (CVD BL$^+$: left panel, CVD BL$^-$: right panel). Estimates of cumulative incidence risk curves are represented in blue for the secondary outcome and in black for all-cause death. The continuous line is for patients with RHR ≥70, and the dotted line is for patients with RHR <70 bpm.*

to data from CVD BL$^+$, the statistical power was of 97% to find a similar difference in CVD BL$^-$ patients, suggesting an adequate number of outcomes in the CVD BL$^-$ subgroup. It is interesting that in the recently published ADVANCE study, the effect of RHR was nonsignificant on incident major cardiovascular events in those patients without prior macrovascular disease (19).

We hypothesize that the interaction between RHR and CVD is related to some pathophysiological link. Mechanical stress can be proposed to explain this result. Arterial stiffness seems to have a greater impact in high-risk patients, such as our patients with CVD at baseline, than in the general population (24). As RHR increases, target organs will be impacted more frequently by the mechanical stresses associated with pulsatile blood pressure and flow. Arterial stiffness will reduce the buffering action of elastic arterial walls and accentuate the damaging effect. This mechanism could explain why the impact on renal outcomes was limited to the patients in secondary prevention. To validate this speculation would require a direct assessment of arterial stiffness, which was not performed here.

In vitro techniques have been developed to assess the impact of cyclic mechanical stretch on signal transduction pathways in renal cells (25) and could become relevant tools to study the impact of changes in RHR on renal structure and function. An alternate hypothesis not excluding the previous mechanistic explanation is that autonomic neuropathy (AN), which is associated with increased RHR, can be speculated as the link between RHR and clinical outcomes. This point cannot be clearly answered with our data, since we did not study AN adequately.

Some limitations must be acknowledged in the current study. Caution must be taken to generalize our results since this cohort is not population-based, even if most of the patients were recruited on an outpatient visit. The way RHR was determined is of great importance: all

Table 2—*Competing-risk multivariate maximal models of variables associated with the cumulative incidence of the primary outcome in patients with (Part 1) or without (Part 2) a history of CVD at baseline*

	Primary outcome		Noncardiovascular death	
Variables	SHR	*P* value	SHR	*P* value
Part 1: Patients with a CVD history (CVD BL$^+$)				
RHR (bpm)	1.01	0.02	0.99	0.58
Sex	1.07	0.75	0.81	0.66
Age (years)	1.03	0.001	1.04	0.13
Diabetes duration (years)*	1.90	0.02	—	—
History of renal disease	2.35	<0.0001	—	—
Active smoking	0.76	0.47	—	—
Blood pressure (mmHg)				
Systolic	1.00	0.71	—	—
Diastolic	1.02	0.02	—	—
Total cholesterol (mmol/L)	1.21	0.02	—	—
β-Blocker use	1.12	0.55	0.59	0.34
Part 2: Patients without a CVD history (CVD BL$^-$)				
RHR (bpm)	1.00	0.76	1.03	0.02
Sex	1.52	0.02	3.28	0.005
Age (years)	1.05	<0.0001	1.08	<0.0001
Diabetes duration (years)*	1.38	0.25	—	—
History of renal disease	2.02	0.0005	2.4	0.02
Active smoking	—	—	3.23	0.01
BMI (kg/m^2)	—	—	1.001	0.97
Systolic blood pressure (mmHg)	1.01	0.25	1.01	0.14
HbA_{1c} (%)	—	—	0.81	0.07
β-Blocker use	1.17	0.46	1.53	0.29

*Log-transformed data.

ECG recordings were performed in the morning, after breakfast. However, time was 1 to 3 h after breakfast leading to some potential variability. However, this lack of standardization of ECG recording is unlikely to lead to spurious results but could blunt the relationship between RHR and cardiovascular and renal outcomes. In addition, it clearly corresponds to a real-life situation. We used ECG data, as performed by others (16) (17), rather than 1-min radial pulse measurement. Some reports suggest that ECG-derived RHR is of similar clinical value to 24-h ambulatory measurement regarding myocardial infarction risk (26), validating such an ECG-based strategy. In addition, it is easier to monitor ECG-derived data than pulse measurements, and this method thus seems to be valid and less operator dependent.

The choice of a threshold at 70 bpm is questionable. However, data considering RHR as a continuous trait showed roughly similar results, and 70 bpm also corresponds to the median of the RHR values in our study population. In addition, the threshold at 70 bpm was highly used in the literature studying RHR and clinical end points (7,27,28).

Unfortunately we cannot address the question of AN since QTc is not readily available and no Ewing test or Valsalva maneuver were performed, limiting our speculations on the role of AN.

Finally, even if renal outcomes constitute our secondary outcomes, they are of great originality; the doubling of serum creatinine is not as hard an end point compared with renal replacement therapy but this outcome is largely considered as a valuable proxy for severe renal damage in clinical trials (29,30). In addition, doubling of serum creatinine can be the first occurring event in our combined renal outcome, leading to valid conclusion on renal risk.

Interest in pharmacological heart rate lowering in patients with CVD has received fresh impetus with the introduction into clinical use of the specific heart rate lowering agent ivabradine. It acts by selectively inhibiting I_f, an ionic current that is important in pacemaking activity in the sino-atrial node of the heart. The effect of ivabradine on outcome has been evaluated in two large randomized trials (27,28). The BEAUTIFUL study did not evidence a statistically significant impact of ivabradine on the primary outcome but showed that this drug reduced the incidences of myocardial infarction by 36% and coronary revascularization by 30% in patients with a RHR of ≥70 bpm at baseline (27). The results in diabetic patients were concordant with the whole study population. In the SHIFT study in patients with systolic heart failure and heart rate ≥70 bpm, ivabradine reduced the primary end point (the composite of cardiovascular death and hospitalization for heart failure) by 18% and death as a result of heart failure by 26% (28). Again, the results were not different between the whole study population and the subgroup of diabetic patients.

Of note there are few results available to our knowledge on renal markers in the literature to support our important finding on the relationship between RHR and renal outcome.

In type 1 diabetic patients, seminal studies used β-blockers in proteinuric patients and showed a significant reduction in proteinuria, but it is accepted that the beneficial effect was mostly related to blood pressure rather than RHR reduction (31). In a cross-sectional study, when placebo was compared with β-blocker, metoprolol reduced RHR by 10 bpm but did not significantly impact urinary albumin in microalbuminuric patients (32). In the LIFE trial (33) studying diabetic patients with cardiac hypertrophy, β-blockers (atenolol) showed a weaker impact on urinary excretion compared with losartan, but the trial was not designed for hard renal end points such as what we report here. However, no long-term trials reported renal outcomes in type 2 diabetic patients, and the results on such end points are lacking in those trials with ivrabradine. Such post hoc analysis would be helpful in this context.

Whether a RHR-lowering strategy results in a benefit in renal and/or cardiovascular outcomes cannot be ascertained using a cohort follow-up and requires a clinical trial to translate from epidemiology to clinical care. However, our results support that RHR is a cheap, "easy-to-determine," and robust risk factor for CVD and renal outcomes in T2D patients that must become a key clinical variable for care and research.

Table 3—*Competing-risk multivariate maximal models of variables associated with the cumulative incidence of the secondary outcome in patients with (Part 1) or without (Part 2) a history of CVD at baseline*

	Secondary outcome		Death all causes	
Variables	SHR	*P* value	SHR	*P* value
Part 1: Patients with a CVD history (CVD BL$^+$)				
RHR (bpm)	1.03	0.04	1.01	0.36
Sex (male)	1.95	0.19	0.94	0.82
Age (years)	0.95	0.04	1.06	<0.0001
Diabetes duration (years)*	—	—	1.72	0.12
History of renal disease	5.70	0.002	1.39	0.14
Blood pressure (mmHg)				
Systolic	1.01	0.69	—	—
Diastolic	—	—	1.01	0.14
Total cholesterol (mmol/L)	—	—	1.19	0.13
β-Blocker use	0.56	0.26	0.97	0.91
Part 2: Patients without a CVD history (CVD BL$^-$)				
RHR (bpm)	0.99	0.51	1.01	0.13
Sex (male)	2.98	0.003	1.85	0.004
Age (years)	—	—	1.07	<0.0001
Diabetes duration (years)	2.97	0.02	0.86	0.62
History of renal disease	9.09	<0.0001	2.19	0.0006
Blood pressure (mmHg)				
Systolic	1.02	0.04	1.00	0.95
Diastolic	1.00	0.84	—	—
Total cholesterol	1.03	0.78	—	—
β-Blocker use	0.85	0.65	0.99	0.97

*Log-transformed data.

Acknowledgments—The SURDIAGENE study was supported by grants from PHRC-Poitiers 2004, Association Francaise des Diabétiques (AFD) (Research Grant 2003), Groupement pour l'Etude des Maladies Métaboliques et Systémiques (GEMMS Poitiers, France). The Servier pharmaceutical company (Suresnes, France) supported Alan Larkman with editing the text written in English. No other potential conflicts of interest relevant to this article were reported.

A.M. and S.H. researched data and wrote the manuscript. S.R. researched data, wrote the manuscript, and contributed to the discussion. W.H., X.P., F.T., and R.M. researched data. P.-J.S. researched data and reviewed the manuscript. P.S. researched data and contributed to the discussion. S.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The authors thank all of the patients taking part in this study and their physicians for kindly informing investigators of patients' outcome. The authors thank C. Demer (Poitiers) for secretarial assistance and Alan Larkman (Larkman Consulting Limited) for help with writing and editing the manuscript. E. Rogeon (INSERM CIC802) and the staff of the Diabetes Department are acknowledged for their help with data collection and monitoring, and S. Brishoual and G. Mauco (INSERM U927 and Biochemistry Department–Poitiers) are acknowledged for biological determinations.

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