Cardiovascular prognosis in patients with type 2 diabetes: Contribution of heart and kidney subclinical damage

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Background Left ventricular hypertrophy (LVH) and kidney damage (abnormal urinary albumin-to-creatinine ratio [uACR] or estimated glomerular filtration rate [eGFR]) are predictive of major cardiovascular events (MACE) in patients with type 2 diabetes (T2D) but are rarely used in cardiovascular score calculators. Our study aimed to assess their respective prognostic values for MACE and the additive information they provide to score calculators.

Methods A total of 1298 T2D (43% women) aged 65 (SD 11) years were followed up for a median of 65 months, with MACE as a primary composite end point: cardiovascular death, nonfatal myocardial infarction, or stroke. Electrocardiogram (ECG)-derived LVH was defined using Sokolow, Gubner, and Cornell product indexes; uACR was considered as abnormal if >2.5 mg/mmol in men or >3.5 mg/mmol in women and eGFR if <60 mL/min per 1.73 m^2.

Results Urinary albumin-to-creatinine ratio was higher in subjects with electrocardiographic LVH (ECG-LVH) than in subjects without (median [interquartile range] 7.61 [43.48] and 2.56 [10.53], respectively; $P < .0001$). After adjustment for age, history of myocardial infarction, and peripheral artery disease, ECG-LVH and kidney damage were strong predictors for MACE (adjusted hazard ratio [1.64; 95% CI 1.23-2.20], [1.90; 95% CI 1.43-2.53], and [1.85; 95% CI 1.42-2.41] for ECG-LVH, uACR, and eGFR, respectively). Net reclassification improvement was higher with the model including both ECG-LVH and uACR than models with ECG-LVH alone ($P < .0001$) or uACR alone ($P < .0001$). In addition, using cardiovascular risk calculators (Framingham score and others), we observed an additional prognostic value of ECG-LVH for each one of them.

Conclusions Electrocardiographic LVH is complementary to kidney damage for MACE prediction in T2D. (Am Heart J 2015;169:108-114.e7.)

Diabetes mellitus is a major public health problem. Worldwide prevalence is likely to increase from 366 million in 2011 to an estimated 552 million in 2030. In 2011, diabetes was responsible for 4.6 million deaths, 465 billion US dollars in health care expenditures, and 11% of total health care expenditures in adults.[1] The main complications are cardiovascular and renal diseases. But the absence of international consensual standards allowing for measurement of these complications deprives the worldwide medical community of reliable estimations of these major causes of disability.[1]

Left ventricular hypertrophy (LVH) and kidney subclinical damage (abnormal urinary albumin-to-creatinine ratio [uACR] and/or abnormal estimated glomerular filtration rate [eGFR]) are known to be correlated, and both are predictive of cardiovascular events in patients with type 2 diabetes mellitus (T2D). LVH is pathophysiologically related to myocardial ischemia with alteration of coronary circulation,[2] ventricular arrhythmias, sudden death, atrial fibrillation, heart failure, and stroke.[3] On the one hand, LVH is generally considered as a marker of target organ damage,[4] which is detected with high cost/benefit on a resting electrocardiogram (ECG) and helps stratify cardiovascular prognosis[5] with an adjusted risk of cardiovascular morbidity of 2.3 and an adjusted risk of all-cause mortality of 2.5.[6] On the other hand, early recognition of renal dysfunction based on the uACR[7] is a surrogate marker of diabetic microvascular disease,[8] and both uACR and low eGFR are associated independently with higher rates of mortality and cardiovascular events in T2D.[9]

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Submitted February 2, 2014; accepted September 12, 2014.

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0002-8703

http://dx.doi.org/10.1016/j.ahj.2014.09.012

Subclinical cardiac and renal damage are interrelated and carry independent prognostic values in T2D, but few studies have confronted them in a large real-life cohort, and no data are available on the predictive value of their combination. The 2 most frequently used cardiovascular risk calculators are the Framingham risk score (FRS)[10] and the European Systematic COronary Risk Evaluation (SCORE).[11] Both of them take into account age, sex, smoking status, systolic blood pressure, cholesterol, and presence of diabetes mellitus. Interestingly, none of them takes LVH or uACR or eGFR criteria into account. Most recent cardiovascular risk scores focusing on T2D have been built from the "UKPDS"[12] and the "ADVANCE" trial.[13] The UKPDS risk engine indicates the 10-year risk of a coronary heart disease[14] or stroke[15] and considers several variables other than LVH or kidney damage. The ADVANCE risk engine quantifies the risk of having a cardiovascular event over 4 years; it includes uACR but not LVH.[16] In practice, none of these currently used cardiovascular risk calculators included LVH in their initial versions, and only 1 included uACR.

Our study aimed to assess in a cohort of 1298 T2D the respective cardiovascular prognostic values of LVH and kidney damage for major adverse cardiovascular events and the added value of their combination in addition to the estimation of risk score by highly used calculators.

Methods

Patients were included in a prospective single-center follow-up study, the "SURDIAGENE" study, and regularly followed up from 2002 to 2011. This work is aimed at assessing the environmental and genetic determinants of microvascular and macrovascular complications in T2D.[17] The study design was approved by the local ethics committee ("Comité de Protection des Personnes Ouest 3"), and written informed consent was obtained from every participant.

Inclusion and exclusion criteria

The inclusion criteria were patients aged ≥18 years, with a confirmed diagnosis of T2D for ≥2 years. Exclusion criteria were presence at study admission of an *end-stage renal disease* defined as a requirement for dialysis or history of kidney transplant, a missing or noninterpretable ECG, a permanent ventricular pacemaker rhythm, and follow-up duration <1 month.

Clinical and biological data

The clinical data were obtained at inclusion from the patient records, when morphometric measurements, blood pressure, and ECG recordings were carried out. Significant histories of myocardial infarction (MI) and of peripheral artery disease (symptomatic artery stenosis) were noted.

Electrocardiograms were recorded at 25 mm/s and 0.1 mV/mm with validated equipment and centrally analyzed under blinded conditions of clinical or biological parameters. Electrocardiographic LVH was defined by the presence of one of the following criteria: Sokolow-Lyon (sum of voltage in S-V1 + [R-V5 or R-V6] >35 mm),[18] Gubner-Ungerleider (R-DI + S-DIII >25 mm),[19] gender-adjusted Cornell product (R-VL + S-V3[+8 in women]) × QRS duration >2440 mm.ms).[20]

The biological data were collected at inclusion: hemoglobin A1c and serum creatinine concentrations were determined centrally in the fasting state using a chromatography method (Adams A1c HA-8160 analyzer; Menarini, Florence, Italy) and a colorimetric method running on an automated analyzer (Kone Optima; Thermo Clinical Labsystems, Vantaa, Finland), respectively. The eGFR was calculated using the 4-variable modification of diet in renal disease formula.[21] The uACR was assessed on sterile urine collections. Urinary creatinine was measured on a Hitachi 911 automatic analyzer (Roche Diagnostics, Meylan, France) and urinary albumin by nephelometry on a Modular System P (Roche Diagnostics GmbH). Abnormal albuminuria was defined by uACR above 2.5 mg/mmol creatinine in men or 3.5 mg/mmol in women.[22]

End points

Living status and cardiovascular end points were determined from patients' hospital records and interviews with their general practitioners. The present analysis takes into account the most recent available data (2011). The primary end point was the first outcome occurring among the following "major adverse cardiovascular events (MACE)": cardiovascular death, nonfatal acute MI, or nonfatal stroke. These outcomes were also analyzed separately as secondary end points. Each event was reviewed by an adjudication committee according to international definitions of clinical outcomes.

Statistical analysis

Qualitative variables were reported as absolute values and percentages; quantitative variables were described by means and SD or median and interquartile range (IQR) when appropriate. Associations between qualitative variables were evaluated using the χ^2 square; behaviors of quantitative variables were analyzed for each of the independent variables using the Student t test or Mann-Whitney U test when appropriate. Correlation between continuous variables was estimated using the Spearman test.

We considered occurrence time of the first event as the primary end point. Survival curves were built using the Kaplan-Meier method and compared using the log-rank test. Risk prediction models established by logistic regression and Cox proportional hazard models were used to analyze the effect on study outcomes of electrocardiographic LVH (ECG-LVH), uACR, and eGFR