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Aortic pulse wave velocity predicts incident cardiovascular events in patients with type 2 diabetes treated in primary care

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ABSTRACT

Aims: The aim was to evaluate the predictive value of aortic pulse wave velocity (aPWV) on incident cardiovascular events in patients with type 2 diabetes without previous cardiovascular disease who were treated in primary care, after adjustment for traditional risk factors.

Methods: We measured aPWV in 627 patients who participated in the epidemiological study CARDIPP (Cardiovascular Risk Factors in Patients with Diabetes—a Prospective Study in Primary Care; ClinicalTrials.gov identifier NCT01049737) and who did not have previously known myocardial infarction or stroke. The outcome variable was a composite endpoint consisting of cardiovascular mortality, hospitalization for myocardial infarction and hospitalization for stroke.

Results: During a median follow-up time of almost eight years, the unadjusted HR per each increment of aPWV by 1 m/s was 1.239 (95% CI 1.114–1.379, $P < 0.001$) for the primary endpoint. Following adjustments for age, sex, diabetes duration, office systolic blood pressure, resting heart rate, total cholesterol, HbA1c, estimated glomerular filtration rate and smoking status, the adjusted hazard ratio was 1.142 (95% CI 1.003–1.301, $P = 0.044$).

Conclusions: In primary preventive patients with type 2 diabetes treated in primary care, aPWV predicted a composite outcome of incident cardiovascular events independently of diabetes-specific and traditional risk factors.

1. Introduction

Non-invasive measurements of arterial stiffness are robust markers for increased cardiovascular risk (Ben-Shlomo et al., 2014), and patients with diabetes mellitus have stiffer arteries than patients without diabetes (Agnoletti et al., 2013). It has been proposed that prolonged hyperglycemia causes accelerated arterial stiffening, which contributes to the elevated risk for cardiovascular disease in diabetes mellitus (Stehouwer, Henry, & Ferreira, 2008). Observational data have shown that measures of long-term glycemic control are associated with both arterial stiffness (Chen et al., 2009) and with the development of cardiovascular disease (Eeg-Olofsson et al., 2010), and increased arterial stiffness has been associated with an increased prevalence of cardiovascular disease in patients with diabetes mellitus (Mansour et al., 2013). The prognostic performance of arterial stiffness has been described in two diabetes-specific cohort studies (Cardoso, Ferreira, Leite, & Salles, 2013; Cruickshank et al., 2002). However, in one of these studies no adjustments were made for possible confounders related to hyperglycemia (Cruickshank et al., 2002), and the other study concerned only patients with established diabetes complications or with multiple cardiovascular risk factors treated at a tertiary care university hospital (Cardoso et al., 2013). Therefore, the aim of this study was to evaluate the impact of aortic pulse wave velocity (aPWV) on incident cardiovascular events in a cohort of patients with type 2 diabetes recruited from primary care, without a previous history of myocardial infarction or stroke, using statistical models that adjust for diabetes-specific as well as classical cardiovascular risk factors.

2. Patients and methods

2.1. Patients

As described previously (Wijkman et al., 2009), CARDIPP (Cardiovascular Risk Factors in Patients with Diabetes—a Prospective Study in Primary Care) is an observational prospective cohort study with the general aim of exploring the impact of cardiovascular risk factors in patients with type 2 diabetes (Clinical Trials.gov number NCT 01049737). Between the years 2005 and 2008, 761 patients with type 2 diabetes were recruited by nurses specially trained in diabetes care at 22 different primary health care centers in the counties of Östergötland and Jönköping in Sweden. Inclusion criteria were: type 2

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diabetes treated in primary care, age 55–65 years, and willingness to participate in the study. The only exclusion criterion was known severe physical or mental disease with short life expectancy. From the total CARDIPP cohort of 761 patients, we excluded for the purpose of this analysis 134 patients in which either baseline data for aPWV measurements had not been successfully obtained ($n = 59$) or who had previously experienced either a myocardial infarction or a stroke ($n = 84$), or who had missing baseline data concerning previous cardiovascular disease status ($n = 4$). This yielded a study sample of 627 participants, since there was overlap between these exclusion criteria in 13 patients.

2.2. Arterial stiffness measurements

The gold standard for arterial stiffness measurements is considered to be aPWV (Laurent et al., 2006). To measure aPWV, ECG-gated pulse wave analyses of the carotid and femoral arteries were performed with a Millar pressure tonometer and the SphygmoCor system (Model MM3, AtCor Medical, Sydney, Australia). The pulse wave transit time was calculated by subtracting the time between the ECG R-wave and the arrival of the pulse wave to the carotid measurement site from the time between the ECG R-wave and the arrival of the pulse wave to the femoral measurement site. The surface distance was defined as the distance between the suprasternal notch and the femoral measurement site, subtracted by the distance between the suprasternal notch and the carotid measurement site. The aPWV was calculated by dividing the surface distance with the pulse wave transit time. Applanation tonometry measurements were performed by experienced personnel at the Hospitals in Linköping and Jönköping. Measurements were made in duplicate, and reported as means of the two measurements.

2.3. Blood pressure measurements

Office blood pressures were measured as described in detail previously (Jennersjo et al., 2011; Wijkman et al., 2012). In brief, office blood pressures were measured three times with the patients in the sitting position, at intervals of one minute, by specially trained nurses. Appropriately sized cuffs were used according to each patient's arm circumference. At each measurement, the blood pressure values were rounded to the nearest 2 mm Hg interval. The office blood pressure levels reported represent means of the three measurements.

2.4. Laboratory analyses

Blood samples were drawn in the morning following a 10 h overnight fast. Routine tests such as glycosylated haemoglobin A1 (HbA1c) and serum lipids were analyzed according to routines at the primary health care centers. The Swedish Mono-S HPLC standard (Hoelzel et al., 2004) was used for HbA1c analyses, but the values were subsequently converted to the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) units (mmol/mol). Lipid levels were measured by identical methods and low density lipoprotein (LDL) cholesterol was calculated according to the Friedewald formula. Serum creatinine levels were measured at the local clinical chemistry laboratory (SWEDAC accredited Lab Med in Östergötland, Sweden) using an IDMS calibrated modified Jaffe method on an Advia 1800 analyzer (Siemens Healthcare Diagnostics). Coefficients of variation (CV) for the creatinine method was 4.3% at 90 μmol/L and 3.1% at 380 μmol/L. Creatinine-based values of estimated glomerular filtration rate (eGFR) were calculated according to the Modification of Diet in Renal Disease (MDRD) study equation (Levey et al., 1999).

2.5. Outcomes

The outcome variable was a composite endpoint consisting of cardiovascular mortality, hospitalization for myocardial infarction or hospitalization for stroke. Patients were followed until an event occurred, or until December 31st, 2014. Data on outcomes were retrieved by linkage of the study database with the Swedish Cause of Death Registry (The National Board of Health and Welfare, Stockholm, Sweden) and the Inpatient Register (Ludvigsson et al., 2011), using the Swedish national Personal Identification Number (Ludvigsson, Otterblad-Olausson, Pettersson, & Ekbom, 2009) of each individual patient.

2.6. Statistics

For the statistical analyses, SPSS software (IBM SPSS Statistics 23, Chicago, IL, USA) was used. P values < 0.05 were considered as statistically significant. Unless stated otherwise, values are presented as means (inter-quartile range), or number of cases (percent). Strengths of correlations between numerical variables were tested with bivariate correlation analyses and presented as Pearson's correlation coefficients (r). Between-group differences were tested for statistical significance with two-sided independent t-tests for numerical variables or with the Chi square test for categorical variables. The associations between the time to a first endpoint event and the values of aPWV were calculated as the hazard ratio (HR) for an increase of aPWV by 1 m/s, with a corresponding 95% confidence interval (CI). Crude hazard ratios were first calculated using univariate Cox regression analyses, and adjusted hazard ratios were then calculated with multivariate Cox regression analyses. Co-variates were chosen *a priori* on the basis of biological plausibility and included: age, sex, diabetes duration, office systolic blood pressure, resting heart rate, total cholesterol, HbA1c, eGFR and smoking status. Kaplan-Meier curves were constructed, categorizing the patients at 10.80 m/s, which represented the lower cut-off for the highest tertile of aPWV. Differences in survival distribution for patients with aPWV above or below this cut-off value were then tested for statistical significance with the log-rank test. Univariate and multivariate Cox regression analyses were also performed with the same cut-off for aPWV. Two receiver operating characteristic (ROC) curves were constructed: one which included the classical cardiovascular risk factors (age, sex, diabetes duration, office systolic blood pressure, resting heart rate, total cholesterol, HbA1c, eGFR and smoking status) and one which included the classical cardiovascular risk factors with the addition of aPWV. The areas under the ROC curves were calculated, and differences between the areas of the two models were tested for statistical significance by comparison of their 95% confidence intervals.

2.7. Ethics

All participants gave written informed consent. The merging of study data with other registries was approved by the National Board of Health and Welfare and by the Swedish Data Inspection Board. The study was approved by the Regional Ethical Review Board in Linköping, Sweden. The study protocol followed the principles expressed in the Declaration of Helsinki.

3. Results

3.1. Baseline characteristics

The baseline characteristics of the 627 patients representing the study sample are presented in Table 1. There were 242 patients (38.6%) who had an HbA1c value below 48 mmol/mol, i.e., in the non-diabetic range, with or without using glucose lowering medications. No patient had end-stage renal disease. On average, men did not differ from women in terms of aPWV (10.4 m/s (9.0–11.7) vs. 10.3 m/s (8.8–11.4), $P = 0.606$) and there was no statistically significant difference between current smokers and current non-smokers (10.1 m/s (8.6–11.2) vs. 10.4 m/s (9.0–11.6), $P = 0.222$). In univariate correlation analyses, aPWV correlated significantly with age ($r = 0.198$, $P < 0.001$), diabetes duration ($r = 0.184$, $P < 0.001$), systolic blood pressure ($r = 0.211$,