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Ankle–brachial index predicts stroke in the general population in addition to classical risk factors

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ABSTRACT

Background: Predictors of future stroke events gain importance in vascular medicine. Herein, we investigated the value of the ankle-brachial index (ABI), a simple non-invasive marker of atherosclerosis, as stroke predictor in addition to established risk factors that are part of the Framingham risk score (FRS).
Methods: 4299 subjects from the population-based Heinz Nixdorf Recall study (45–75 years; 47.3% men) without previous stroke, coronary heart disease or myocardial infarcts were followed up for ischemic and hemorrhagic stroke events over 109.0 ± 23.3 months. Cox proportional hazard regressions were used to evaluate ABI as stroke predictor in addition to established vascular risk factors (age, sex, systolic blood pressure, LDL, HDL, diabetes, smoking).
Results: 104 incident strokes (93 ischemic) occurred (incidence rate: 2.69/1000 person-years). Subjects suffering stroke had significantly lower ABI values at baseline than the remaining subjects (1.03 ± 0.22 vs. 1.13 ± 0.14, $p < 0.001$). In a multivariable Cox regression, ABI predicted stroke in addition to classical risk factors (hazard ratio = 0.77 per 0.1, 95% confidence interval = 0.69–0.86). ABI predicted stroke events in subjects above and below 65 years, both in men and women. ABI specifically influenced stroke risk in subjects belonging to the highest (>13%) and intermediate (8–13%) FRS tercile. In these subjects, stroke incidence was 28.13 and 8.13/1000 person-years, respectively, for ABI < 0.9, compared with 3.97 and 2.07/1000 person-years for 0.9 ≤ ABI ≤ 1.3.
Conclusions: ABI predicts stroke in the general population, specifically in subjects with classical risk factors, where ABI identifies subjects at particularly high stroke risk.

1. Introduction

The identification of markers of subclinical atherosclerosis enabling the identification of subjects with an increased risk for stroke has gained strong interest among clinicians. Complex technical diagnostic work-up methods have been introduced and are commonly used but require huge logistic efforts or resources. Specifically, Doppler/duplex sonography of intima-media thickness [1] or electron beam-computed tomography of vascular calcification [2] has been used. Among vascular diseases, peripheral artery disease (PAD) confers a particularly high stroke risk, indicative of advanced atherosclerosis [3–5]. In the REduction of Atherothrombosis for Continued Health (REACH) registry, subjects with

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PAD had a higher likelihood of stroke and other vascular events than coronary heart disease (CHD) patients [6].

Robust evidence exists from primary care patients that asymptomatic PAD, defined by an ankle-brachial index (ABI) < 0.9, and symptomatic PAD are associated with an elevated stroke risk [7–10]. In population-based studies, the association between ABI, a simple ratio of two systolic blood pressure values, and vascular diseases is still not well-defined. In the Multi-Ethnic Study of Atherosclerosis (MESA), ABI values < 1.0 predicted a combined endpoint including CHD, stroke and other vascular events [11], whereas in the Framingham study [12], Cardiovascular Health Study (CHS) [13], and Atherosclerosis Risk in Communities (ARIC) study [14], ABI values < 0.9 were not (Framingham study and CHS) or only weakly (ARIC) predictive of CHD or a combined endpoint including CHD and stroke. So far, few studies specifically examined the association between ABI and stroke risk. In ARIC, low ABI values did not predict stroke in multivariable analyses [15].

Primary care patients represent preselections of (co-)morbid individuals, which are influenced by referral pathways that may accumulate or not accumulate risk factors or specific clinical manifestations. Thus, primary care patients rarely allow inferences to the general population. In view of the lack of population-based studies, we evaluated how ABI influences stroke incidence in addition to established risk factors.

2. Methods

2.1. Study cohort

The Heinz Nixdorf Recall (HNR) cohort is a random sample of 4814 men and women aged 45–75 years who were prospectively enrolled via mandatory citizen registries in Essen, Bochum and Mülheim/Ruhr, three cities of the industrialized Ruhr area, between December 2000 and August 2003 in order to study the role of risk factors and signs of subclinical atherosclerosis in the development of overt vascular diseases [16]. Based on its age profile and specific focus on vascular pathologies, as well as state-of-the-art population enrollment, assessment and endpoint evaluation structures enabling exceptional follow-up rates of as much as 90% of subjects at 5 years, the HNR study is well suited for analyzing stroke predictors [1]. The HNR study was designed and powered for vascular events with incidence rates $\geq$300 per 100,000 per year, analyzing relative risks (RR) ≥ 2.5, for which statistically valid results could be expected over an only 5 year follow-up period for comparisons between the 1st and 4th quartile. [16] With these assumptions made, a statistical power of 90% was achieved with a total of 3150 subjected being re-examined after five years (type I error: $\alpha = 0.05$; type II error: $\beta = 0.10$) [16].

Exclusion criteria were inability or unwillingness to give informed consent, conditions (medical or other) precluding follow-up over 5 years, severe psychiatric disorders or illegal substance abuse, and pregnancy in women. Computer-assisted interviews and questionnaires were used to document medical histories. The study was approved by the institutional review board. All subjects gave written informed consent. Subjects were followed up over 109.0 ± 23.3 months. The data set was closed for the purpose of this study in March 2013, the last patient follow-up was on November 22, 2012. During the follow-up period, stroke events (both ischemic and hemorrhagic), defined as focal neurological deficits of presumed cerebrovascular origin that persisted over a period of $\geq$24 h, were assessed in annual questionnaires and a follow-up visit after 5 years. Stroke events were validated by an independent internal and external endpoint committee that provided consensus decisions in case of disagreements. Stroke events were allocated to the date of stroke diagnosis, non-stroke cases were censored at the date of last contact when the person was still alive or date of death. 'Trial of Org 10172 in Acute Stroke Treatment' (TOAST) classifications were performed, attributing strokes as macroangiopathic, microangiopathic, cardioembolic and unknown etiology [17].

Of 4814 subjects included into HNR, 4356 subjects had a negative history for previous stroke, CHD and myocardial infarcts, qualifying them for analyses of stroke risk in subjects without clinically overt vascular disease. Of these, ABI measurements were obtained in 4299 subjects. The baseline characteristics of these subjects did not differ from the whole cohort (not shown).

2.2. Classical risk factors

Systemic blood pressure was measured with an automated oscillometric blood pressure device (Omron 705-CP, Omron, Mannheim, Germany), taking the mean of the second and third of three measurements with a minimum of 3 min between the measurements. In some cases automated blood pressure values were missing. Then values from a random-zero blood pressure device measurement (Mark II, Hawksley Techn., Lancing, UK) were used. Hypertension was classified according to Joint National Committee (JNC)-7 thresholds [18]. Participants were considered diabetic in cases of physician-diagnosed diabetes, or when anti-diabetic medication was prescribed. For evaluating consequences of smoking, only current smoking was evaluated. Total, LDL and HDL cholesterol and triglycerides were measured with standardized enzymatic methods. Anti-hypertensive, lipid-lowering, anti-diabetic and anti-platelet medications were noted. With the data obtained, the Framingham Risk Score (FRS) was determined using the score described by Wilson et al. [19] that was introduced for predicting CHD risk (this score was chosen for reasons of consistency within the HNR cohort). Standardized height and weight measurements were used for calculating the body mass index (BMI). Medical history of PAD was assessed by a standardized interview requesting cases of known PAD as well as prior PAD treatment. Atrial fibrillation was classified in an ECG that was routinely recorded in all subjects on occasion of the baseline examination. Level of education was evaluated according to International Standard Classification of Education (ISCED) in years [20].

2.3. ABI

Blood pressure measurements were performed using an 8 MHz Doppler transducer on subjects resting on a flat couch for 15 min (Logidop, Kranzbühler, Germany) [21]. For systolic ankle pressure measurement, the Doppler transducer was placed above the posterior tibial and dorsal foot arteries. The cuff was rapidly inflated to a pressure at which pulse noise diminished. Maximal cuff pressure was 300 mmHg, deflation velocity was 2 mmHg/sec. Brachial pressures were measured by placing the Doppler transducer above the cubital segment of both brachial arteries. Measurements were always done in the order left foot, right foot, right arm, left arm. ABI was calculated per leg as ratio of the highest ankle artery pressure recorded either in the posterior tibial or dorsal foot artery and the highest systolic pressure measured in the right and left arm. For further analyses, the lower ABI of both legs was used. In 25 of 4299 subjects receiving ABI measurements, ABI could only be assessed on one side due to technical difficulties or leg amputations.

2.4. Statistical analysis

Continuous data are presented as mean $\pm$ SD (normally distributed data) or median (Q1; Q3) (non-normally distributed data), categorical data as counts (%). Cox proportional hazard models for continuous and categorical regressors were used to