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VASCULAR AGE AS A NEW RISK COMMUNICATION TOOL AND COMPARISON OF SCORE, FRAMINGHAM RISK SCORE AND PULSE-WAVE VELOCITY-BASED VASCULAR AGEING METHODS FOR ITS ASSESSMENT

PhD thesis

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List of Abbreviations

BMI	body mass index
Chr. non-ResHT	patients with chronic, non-resistant hypertension
Chr. ResHT	patients with chronic, resistant hypertension
CV	cardiovascular
cfPWV	carotid-femoral pulse wave velocity
DBP	diastolic blood pressure
ePWV	estimated pulse wave velocity
EVA	early vascular ageing
FRS	Framingham Risk Score
GFR- EPI	glomerular filtration rate assessed by the chronic kidney disease epidemiology collaboration glomerular filtration rate equation
HDL	high density lipoprotein
LDL	low density lipoprotein
MORGAM Project	MOnica Risk, Genetics, Archiving and Monograph Project
PWV	pulse wave velocity
SBP	systolic blood pressure
SCORE	Systematic COronary Risk Evaluation
SUPERNOVA	supernormal vascular ageing
White- Coat HT	patients with white coat hypertension

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1. Introduction

1.1. Importance of cardiovascular diseases

Cardiovascular (CV) diseases are the leading causes of morbidity and mortality globally; according to the Global Burden of Disease Study (1), 17.9 million people died from CV diseases in 2018. This represents an increase of approximately 21% in deaths from CV diseases between 2007 and 2017, however death rates decreased from 259.9 deaths (257.1–263.7) per 100 000 in 2007 to 233.1 (229.7–236.4) per 100 000 in 2017 (1). Ischemic heart disease and stroke were responsible for almost 50% and 35% of these deaths, respectively (1). CV diseases also remain the most common causes of death in Europe. According to a 2016 study, more than 4 million deaths were caused by CV diseases across the European region, responsible for 45% of all deaths (2).

According to the Hungarian Central Statistical Office, CV diseases, including acute myocardial infarction, ischemic heart disease and cerebrovascular diseases, accounted for 42,3% of deaths in 2021 (3). CV diseases also place a heavy burden on primary care in Hungary. In 2021, among patients registered to general practitioners, there were 4,006.6 patients with hypertension (ICD codes I10–I15), 1,419.6 patients with ischemic heart diseases (ICD codes I20–I25), and 720.1 patients with cerebrovascular diseases (ICD codes I60–I69) per 10,000 inhabitants (4). According to the database of the World Health Organization, the prevalence of hypertension among adults in Hungary was 48% and only 23% of hypertensive patients were effectively controlled in 2019 (5).

1.2. Importance of pharmacological treatment in cardiovascular diseases

There are non-modifiable risk factors (e.g. age, male sex, family history) and modifiable risk factors for CV diseases, such as smoking, obesity, unhealthy diet, and hypertension. Lowering blood pressure significantly reduces the risk of developing CV diseases and mortality in various patient groups. Overall, lowering systolic blood pressure by 10 mmHg reduces the risk of major CV disease events by 20%, coronary heart disease by 17%, stroke by 27%, heart failure by 28%, and the risk of death from any cause by 13% and different groups of antihypertensive drugs have been largely effective in preventing a variety of

outcomes, such as stroke, renal failure, and heart failure (6). Besides lowering blood pressure, lowering cholesterol levels also affects CV outcomes. A meta-analysis conducted by the Cholesterol Treatment Trialists collaboration showed that a 1 mmol/l reduction in LDL-cholesterol levels significantly reduces the risk of CV events by 22% over a 5-year period. (7)

1.3. Adherence to medication

Adherence plays a major role in reducing CV events, alongside appropriate drug selection. Although non-adherence to cardiovascular medications can lead to an increase in prevalence of CV events (8), medication adherence is not sufficient even in secondary prevention. According to the PREMIER Registry, only 66% of patients take their essential medications after an acute myocardial infarction (9). Van Wijk et al. conducted a retrospective cohort study using Dutch pharmacy and hospital records to assess long-term persistence with antihypertensive therapy. Among 2,325 patients who initiated treatment in 1992, only 39% remained continuously adherent over a 10-year period and 22% temporarily discontinued and restarted treatment. The study identified factors associated with higher persistence included older age, male sex, initiation with ACE inhibitors or combination therapy, and the type of the prescriber (e.g. general practitioner, internist, cardiologist) also had an impact to the adherence (10). There are several studies examining adherence in relation to other diseases than hypertension that influence cardiovascular risk. According to a study, performed in Italy, adherence to allopurinol therapy among gout patients was generally low, with 45,9% were adherent after one month and only 3,2% remaining adherent after one year. Factors influencing adherence included patient awareness, with those experiencing frequent gout flares or having hypertension being more likely to adhere to treatment (11). Several factors were associated with reduced adherence to glucagon-like-peptid-1 receptor agonist therapies among patients with obesity. Approximately half of the individuals using glucagon-like-peptid-1 receptor agonists for weight management remained on treatment for at least 12 weeks, indicating a high likelihood of achieving clinically meaningful weight loss. Those who had more frequent provider visits during the initial 12 weeks were more likely to maintain treatment adherence. Individuals prescribed the medication by an endocrinologist

or obesity medicine specialist were more likely to continue treatment. Patients with underlying health conditions like diabetes or liver disease were more likely to continue their treatment. Additionally, younger age and certain demographic characteristics were linked to lower adherence rates (12). In primary prevention, the non- adherence to antihypertensive medications also persists, causing public health and clinical difficulties (13). There is growing evidence that patients who are more informed and committed to decisions about their conditions are more likely to adhere to their chosen medication and might have better outcomes (14). As with informed patient decision-making, physician assessment and communication of CV risk can alert the patient to potential consequences, which may result in greater motivation for long-term medication adherence and lifestyle change.

1.4. Risk communication in cardiovascular diseases

The traditional way of expressing CV risk in absolute terms can be misleading, as classical CV risk estimation methods give a percentage for the likelihood of a CV event occurring within 10 years, and this percentage may be relatively low. On the contrary, vascular age expresses the additional risk that can be associated with the risk factors of a patient in years, and this can help motivate patients to make long-term changes to their health. The idea of vascular age was created to demonstrate whether the arteries of a patient are older than their chronological age (15). According to an online survey that provides participants with the same hypothetical CV risk in different ways, using vascular age led to improvements in several aspects of risk understanding and intentions to take actions independent of their cognitive skills. The inclusion of vascular age also positively affected motivation to visit the GP for further screening (16).

1.5. Concept of vascular ageing

Vascular ageing leads to structural and functional changes in the vascular wall, and this ageing is naturally moderate. There are both functional and structural implications of changes in the wall of the blood vessel. Functional ageing is mainly manifested in endothelial dysfunction, with a decrease in nitric-oxide production. Increased collagen production, collagen crosslinking, reduction, fracture, and calcification of elastin cause structural changes in larger elastic arteries. There is also an increase in vascular smooth muscle growth,

which contributes to thickening of arterial walls and an increase in arterial stiffness (17). These changes are exacerbated by CV risk factors in addition to CV diseases, leading to an early onset of vascular ageing compared to natural ageing. This concept is referred to as early vascular ageing (EVA) (18). On the other hand, supernormal vascular ageing (SUPERNOVA) describes a condition in which someone has exceptionally lower arterial stiffness than expected based on age and gender. Figure 1 by Bruno RM et al. shows the concept of EVA, normal vascular ageing, and SUPERNOVA (19).

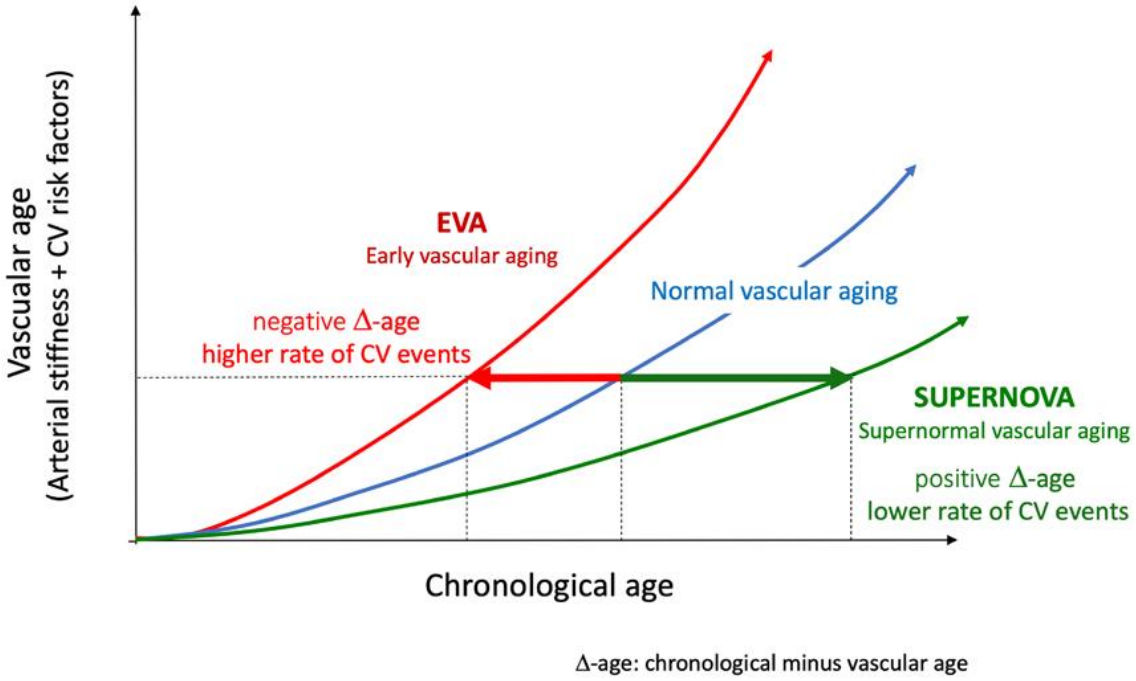

Figure 1. The theory of vascular ageing. For the same vascular age and CV risk profile, subjects with EVA are significantly younger, whereas subjects with SUPERNOVA are markedly older than subjects with normal vascular ageing. Consequently, the difference in chronological and vascular age (Δ-age) of SUPERNOVA subjects is positive, whereas the Δ-age of EVA subjects is negative. Accordingly, SUPERNOVA subjects have a lower CV event rate, whereas EVA subjects have a higher CV event rate, i.e. Δ-age is inversely proportional to the CV event rate. Figure of Bruno RM et. al. (19).

1.6. Evaluating cardiovascular risk

The most accepted measurement of arterial stiffness that can detect early vascular ageing is pulse wave velocity (PWV) (20). Carotid-femoral PWV (cfPWV) is an independent predictor of future cardiovascular events in hypertensive individuals. Estimated PWV (ePWV), which does not require measurement and is calculated from age and blood pressure, showed excellent agreement with the measured cfPWV (21). Besides cfPWV, ePWV was an independent predictor of the primary outcome and all-cause mortality in the Systolic Blood Pressure Intervention Trial (SPRINT) population (22) and was significantly associated with the risk of new-onset heart failure (23).

The Framingham Risk Score (FRS) is a widely used method for stratifying CV risk, especially in the US. The score was derived from data of the 8,491 participants of the Framingham Study, and was published in 2008 (15). Altogether, 1,174 participants had their first CV event during the 12-year follow up. FRS provides sex-specific predictions of a 10-year risk of a fatal or non-fatal CV event. The same study that introduced the FRS also introduced the concept of vascular age. This estimation is derived by first calculating the FRS of an individual and then identifying the chronological age of an individual who has the same predicted risk but only normal levels for all other established CV risk factors (15).

The Systematic Coronary Risk Evaluation (SCORE) is another established tool for estimating the 10-year risk of fatal CV events and was popular in clinical use for more than a decade, mostly in Europe, until the introduction of SCORE2 in 2021 (24). The SCORE approach is based on a combined database from 12 European cohort studies, primarily focusing on the general population. The database contains data from 205,178 subjects, representing 2.7 million person-years of follow-up. During this follow-up period, 7,934 CV deaths were registered, with coronary heart disease accounting for 5,652 of these deaths (25). In 2010, a SCORE-based vascular age calculation was also published (26). The definition of vascular age within the SCORE shares similarities with the FRS-based definition. In both methods, the vascular age expresses the chronological age of an individual with an identical CV risk profile, but has only normal levels for all other established CV risk factors.

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Essentially, this estimated vascular age reflects the predicted CV risk attributable solely to age and sex (26).

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2. Objectives

The aims of our studies were to evaluate whether there was any difference between the calculated vascular ages evaluated with different CV risk-based methods.

1. In the first study, we aimed to compare vascular age calculations based on FRS and SCORE in a population of a GP praxis who were screened for CV risk estimation. We also aimed to compare subjects with elevated vascular age identified by cfPWV, FRS or SCORE.

2. The aim of the second study was to compare SCORE and FRS-based vascular age calculation methods and their relation to early vascular ageing based on ePWV in a population-based sample in Hungary.

Our hypothesis was that various methods could yield significantly different results, potentially affecting patient management.

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3. Methods

3.1. Study 1: patients and methods

The first study was a cross-sectional study conducted between August 2012 and January 2019. The study included Caucasian subjects aged 40-65 years from three general practitioner practices in Budapest, Hungary. The patients participated in a CV screening program. The CV screening program consisted of an autoquestionaire about medical history and lifestyle, BP and cfPWV measurement, and laboratory test. Healthy subjects, patients with white-coat hypertension, patients with chronic treated/ non-resistant hypertension, and patients with resistant hypertension participated in the study. Exclusion criteria were atrial fibrillation (which does not allow measurement of carotid-femoral PWV) and dementia (potentially interfering with the completion of the auto-questionnaire). People were considered healthy patients if they had no chronic illnesses and hypertension was defined according to the actual European guidelines (27). White-coat hypertension was defined as elevated blood pressure in the office (>140/90 mmHg), but blood pressure values in normal ranges during 24-hour ambulatory blood pressure measurement. Normal values were considered as a 24-hour average <130/80 mmHg, daytime average <135/85 mmHg, nighttime average <120/70 mmHg (27). Resistant hypertension was defined as blood pressure remaining above 140/90 mmHg despite the current use of three different classes of antihypertensive agents including a diuretic, or as blood pressure controlled by the more than three medications (28). All patients gave written consent before enrollment. The study was approved by the Scientific and Research Ethics Committee of the Medical Research Council, the Hungarian Ministry of Health (ETT TUKEB 842/PI/ 2011) and was carried out according to the principles of the Declaration of Helsinki.

3.1.1. Clinical measurements

During the screening, subjects completed a questionnaire containing information on personal and family medical history. An appointment was scheduled between 7.00–8.00 a.m. when office brachial blood pressure and cfPWV were measured. Measurements were followed by blood sampling. Vascular age was calculated after the blood test results were available.

3.1.1. Measurement of office brachial blood pressure

Blood pressure was measured twice on each arm with a validated oscillometric device (Omron M3, Kyoto, Japan) in the morning of the clinical measurements after 5 minutes of rest. The average of the higher side (left or right) was used for the rest of the study. This device was also used during the measurement of cfPWV.

3.1.2. Measurement of carotid-femoral pulse wave velocity

cfPWV was evaluated using the gold-standard tonometric method (PulsePen, DiaTecne, Milan, Italy) (29) Two measurements were taken for each subject, and the mean was used for statistical analysis. The consensus was that 80% of the carotid-femoral distance was used to calculate cfPWV (30). The intra- and interobserver variability of PWV measurements obtained with the PulsePen device in our laboratory in hypertensive patients was 4.6 and 6.3%, respectively.

3.1.3. Calculaton of vascular age based on the Framingham Risk Score

FRS-based calculation of vascular age was performed using the method by D'Agostino et al. (15). It uses age, brachial systolic blood pressure, ongoing treatment for hypertension, total cholesterol, high density lipoprotein cholesterol (HDL), smoking and diabetes status to calculate and give sex-specific results. The original paper also includes vascular age estimation based first on FRS calculation and then the age of a person with the same predicted risk, but with all other risk factor levels in the normal range (15). The highest value for the FRS vascular age calculation is ’80+’, but for the mathematical calculations, we used the age of 80 years for these patients.

3.1.4. Calculation of vascular age based on SCORE

The calculation of the SCORE risk score differs between European countries with low and high CV risk, and is based on age, sex, brachial systolic blood pressure, total cholesterol, and smoking status (25). As with FRS-based methods, SCORE-derived vascular age reflects the chronological age of an individual with an equivalent CV risk profile, but all traditional risk factors are within the normal range. This essentially equates vascular age with CV risk, which is solely attributable to age and sex (26). Vascular ageing is classified as supernormal (SCORE−, FRS−) for an age difference less than −2 years, normal (SCORE normal, FRS

normal) for an age difference between −2 and 2 years, and early (SCORE+, FRS+) for an age difference more than 2 years.

3.1.5. Statistical analysis

Descriptive data are expressed as percentages, median with interquartile ranges or mean± standard deviation. The Kolmogorov-Smirnov test was used to test the normality of continuous parameters. Wilcoxon signed rank test was used to compare vascular ages calculated by FRS or SCORE in the entire cohort and in the subgroups studied as well (patients with diabetes; patients with chronic hypertension; and healthy subjects together with patients with white-coat hypertension). Cochran's Q test was used to compare the proportion of subjects with lower or higher vascular age based on cfPWV, FRS or SCORE. To compare subjects older than their chronological age by different methods (PWV+, FRS+, SCORE+), we used ANOVA with Tukey's post hoc test or Kruskal-Wallis test for normally or non-normally distributed continuous variables, respectively. Pearson's Chi-Square test was used to compare nominal variables of these groups. Study participants were divided into groups according to a pre-defined cut-off of the 2-year difference between their SCORE or FRS vascular age and their chronological age. The Mann-Whitney U test was used to compare PWVs between subgroups (age difference -2, age difference between -2 and 2, and age difference 2, in case of SCORE and FRS, respectively). A two-sided $p<0.05$ was significant. SPSS 22.0 for Windows (IBM Corp., Armonk, NY, USA) was used for all calculations.

3.2. Study 2: participants and methods

The Three Generations for Health program, a collaboration between the National Directorate General for Hospitals and the Gottsegen György National Cardiovascular Center of Hungary, aims to reduce the prevalence of CV mortality and coronary heart disease. This program is in line with the objectives of the Health Sector Strategy of Hungary (31). The Three Generations for Health program prioritizes the strengthening of primary healthcare and promotes cooperation between general practitioners, health promotion offices, and local governments. This collaborative approach aims to improve health care and disease prevention within communities (31). In addition to assessing CV risk factors within the

population, the Three Generations for Health program also aims to promote healthy lifestyle practices and primary prevention tools. After mapping the individual risks within the practice communities- where necessary, initiating or modifying pharmacological therapy- general practitioners primarily launched lifestyle change programs. To implement these programs, participants could enlist the help of additional professionals, such as physiotherapists, dieticians, psychologists, health psychologists, fitness trainers, or health visitors. These efforts facilitated personalized solutions, such as identifying the most suitable form of exercise, providing smoking cessation support, and offering dietary counseling as needed. The program encompasses 806 general practitioner practices nationwide, focusing on three age groups of participants (0–18 years, 40–65 years, and 65+ years). This study complied with the ethical principles of the Declaration of Helsinki and the General Data Protection Regulation (GDPR) 2016/679 on the protection of personal data. All participants gave their informed consent to participate in the program. No approval from an ethics committee was needed according to the Medical Research Council, as all procedures were performed in compliance with the adaptable standards and regulations, taking full account of the decision made by the government.

3.2.1. Calculation of vascular age based on Framingham Risk Score and SCORE

Calculation of the FRS and SCORE vascular age was the same as in Study 1.

3.2.2. Calculation of estimated pulse wave velocity

The equation of the ePWV was derived by the Reference Values for Arterial Stiffness' Collaboration (32) and described in the study by Greve et al. (21). The equation is used for subjects with CV risk factors, and given the fact that Hungary is a high-risk country (24), this calculation might provide a more realistic value for this population. Age and MBP were used to evaluate ePWV according to the formula:

$$ePWV = 9.587 - 0.402 \times age + 4.560 \times 10{-}3 \times age^2 - 2.621 \times 10{-}5 \times age^2 \times MBP + 3.176 \times 10{-}3 \times age \times MBP - 1.832 \times 10{-}2 \times MBP.$$

The mean BP was calculated as diastolic BP (DBP) + 0.4 (SBP − DBP).

3.2.3. Supernormal, Normal, and Early Vascular Ageing

Bruno RM et al. (19) defined supernormal, normal, and early vascular ageing as <10%, 10–90%, and >90% ePWV values for the patients.

3.2.4. Statistical Analysis

Descriptive data measured on a continuous scale are presented as frequencies, median and interquartile ranges. Data were analyzed using chi-squared tests for categorical variables. Kruskal–Wallis tests were used to analyze data on continuous scale due to the non-symmetric distribution of the data in all cases. Stata Statistical Software (version 13.0, Stata Corp, College Station, TX, USA) was used for the statistical analysis, and $p < 0.05$ was considered significant.

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4. Results

4.1. Study 1: Comparison of SCORE, Framingham Risk Score and pulse wave velocity-based methods for vascular age calculation

Altogether, 172 patients were involved in the study. Table 1 shows demographic data, laboratory measurements and hemodynamic parameters. Table 1 also shows the above parameters for the groups of subjects whose vascular age was higher than the chronological age with the three methods used, and the chronological age, FRS and SCORE vascular ages of the different groups.

Table 1. Characteristics of study participants

PWV+: subjects with elevated vascular age according to cfPWV; FRS+: subjects with elevated vascular age according to the Framingham Risk Score method; SCORE+: subjects with elevated vascular age according tothe Systematic COronary Risk Evaluation method; FRS vasc. age: vascular age according to the Framingham Risk Score method; SCORE vasc. age: vascular age according to the Systematic COronary Risk Evaluation method; Chr. non-ResHT: patients with chronic, non-resistant hypertension; Chr. ResHT: patients with chronic, resistant hypertension; CV disease: cardiovascular disease; BMI: body mass index; GFR-EPI glomerular filtration rate as assessed by the chronic kidney disease epidemiology collaboration glomerular filtration rate equation; LDL-chol: low-density lipoprotein cholesterol; HDL-chol: high-density lipoprotein cholesterol; PWV: carotid-femoral pulse wave velocity;

Data are presented as mean ± standard deviation or median (interquartile ranges). Categorical parameters are presented as n (%). Significant differences are indicated in bold and italics: *significant difference from PWV+; “X” significant difference from FRS+; #significant difference from SCORE+.

	All Subjects	**PWV+**	**FRS+**	**SCORE+**
N (% of all Subjects)	172	69 (40.1)	***135 (78.5) *,#***	55 (32)

Chronological age (years)	55.5 (48.83 - 61.18)	51.2 (47.05 - 58.85)	54.1 (48.3 - 60.7)	***58.8 (51. -61.7)*,X***
FRS vasc. age (years)	64 (54-79)	64 (51-80)	68 (59-80)	***76 (60-80)*,X***
SCORE vasc. age (years)	55 (44.2-60.7)	50 (41.5-56.5)	54 (44-62)	***62 (56-68)****
Sex (male/female)	72 (41.9%)/ 100 (58.1%)	39 (56.5%)/ 30 (43.5%)	63 (46.7%)/ 72 (53.3%)	23 (41.8%)/ 32 (58.2%)
Healthy control	26 (15.1%)	***6 (8.7%)#***	***6 (4.4%)#***	12 (21.8%)
Chr. non-ResHT	109 (63.4%)	48 (69.5%)	***97 (71.8%)#***	32 (58.2%)
Chr. ResHT	13 (7.6%)	4 (5.8%)	13 (9.6%)	6 (10.9%)
White-coat HT	24 (13.9%)	11 (15.9%)	19 (14.1%)	5 (9.1%)
Smoking	40 (23.3%)	15 (21.7%)	39 (28.9%)	***29(52.7%)*,X***
Diabetes	18 (10.5%)	9 (13%)	18 (13.3%)	7 (12.7%)
CV disease	9 (5.2%)	6 (8.7%)	8 (5.9%)	3 (5.4%)
BMI [kg/m^2]	27.28 ± 4.57	27.35 ± 4.06	27.59 ± 3.93	25.65 ± 4.07
glucose [mmol/l]	5.39 (4.94 - 6.09)	5.48 (4.92 - 6.39)	5.4 (5 - 6.26)	5.4 (5.00 - 6.01)
GFR-EPI [ml/min/1.73m^2]	87.2 ± 13.89	89.67 ± 15.29	93.27 ± 15.00	95.90 ± 11.29
Total cholesterol [mmol/l]	5.59 (4.97 - 6.47)	5.6 (5.11 - 6.43)	5.65 (5.06 - 6.48)	***6.42 (5.6 -7.02)*,X***
LDL-chol [mmol/l]	3.61 ± 0.97	3.43 ± 0.94	3.65 ± 1.17	4.07 ± 1.12

HDL-chol [mmol/l]	1.42 (1.18 - 1.66)	1.40 (1.16 - 1.51)	1.37 (1.15 - 1.59)	1.48 (1.21 - 1.82)
Triglyceride [mmol/l]	1.29 (0.94 - 1.98)	1.38 (0.940 - 2.05)	1.43 (0.98 - 2.05)	1.33 (1.03 - 2.03)
Systolic BP [mmHg]	136.16 ± 16.41	134.6 ± 10.77	132.4 ± 10.31	126.23 ± 12.00
Diastolic BP [mmHg]	82.81 ± 10.68	79.23 ± 10.44	80.42 ± 9.41	79.05 ± 6.11
Heart rate [beat/min]	74 ± 10.97	75 ± 11.38	73 ± 11.07	81 ± 10.74
PWV [m/s]	8.41 (7.6 - 9.38)	***9.34*** ***(8.41- 10.69)X,#***	8.58 (7.81 - 9.46)	8.67 (7.45 - 9.99)

The low proportion of resistant hypertension patients and patients with diabetes or CV disease suggests that it was a relatively low-risk population. Subjects with elevated vascular age according to SCORE had a higher prevalence of smoking and total cholesterol compared to those identified as PWV+ and FRS+. The chronological age was also higher in the SCORE+ group. In PWV+ subjects, pulse wave velocity was higher compared to both FRS+ and SCORE+ groups. PWV and FRS methods identified less healthy controls compared to SCORE. All diabetic patients of this population and almost all patients with CV disease had elevated vascular age with the FRS method. FRS vascular age was higher in SCORE+ patients, compared to PWV+ and FRS+ and SCORE, vascular age was higher compared to PWV+ patients.

FRS calculation showed that 35 patients (20.3%) were classified as ’80+’. Figure 2 shows that FRS vascular age (64 [54, 79] years) was higher compared to the chronological age (55.5 [48.8, 61.2] years, with a difference of 10.9 [1.5,18] years, $p<0.05$) and SCORE vascular age was lower (55 [44.2, 60.7] years) than chronological age (difference: -1.9 [-4.3, 1.1] years, $p<0.05$) and FRS vascular age (difference: -12 [-17, -5] years, $p<0.05$). The percentage of

FRS+ subjects (n=135, 78.5%) was higher compared to SCORE+ (n=55, 32%) and PWV+ (n=69, 40.1%) subjects (p<0.05).

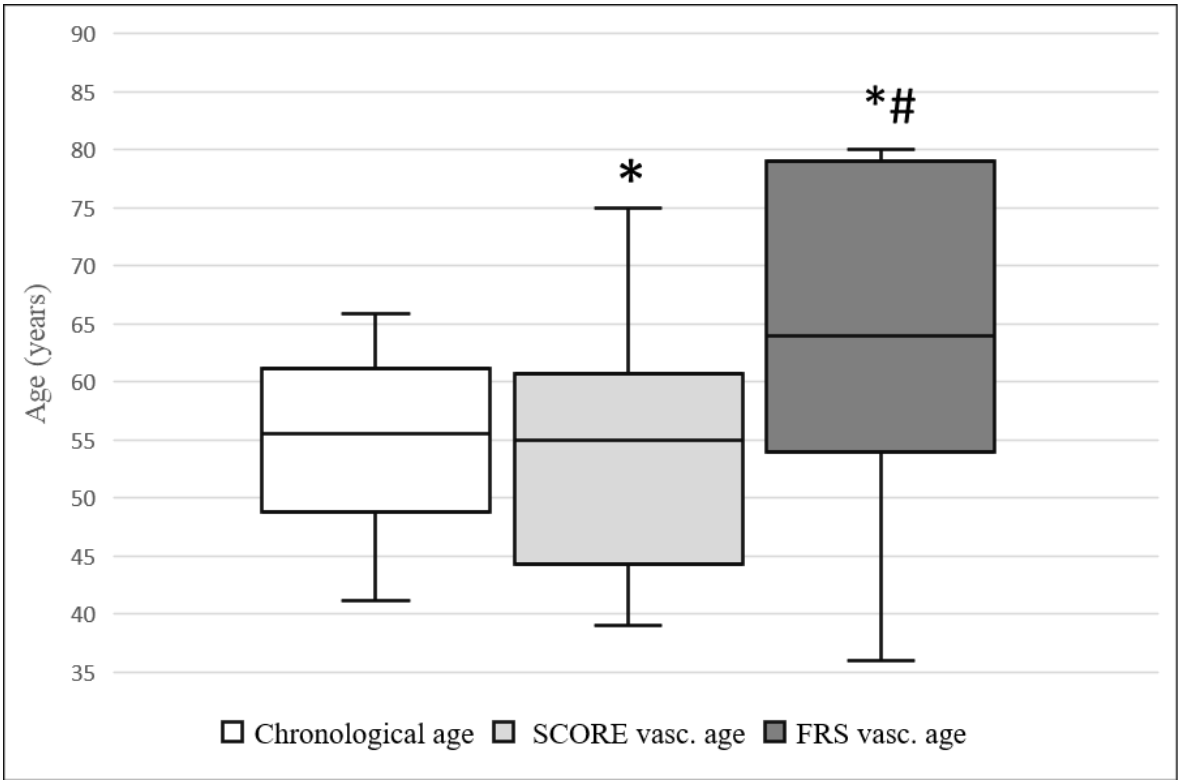

Figure 2. Chronological age, vascular age calculated based on the Systematic COronary Risk Evaluation (SCORE vasc. age) and vascular age calculated based on the Framingham Risk Score (FRS vasc. age) of the study population. Data are presented as median (minimal and maximal values in error bars). *p<0.05 compared with Chronological Age; #p<0.05 compared with SCORE vasc. age (33).

Figure 3 shows the chronological age, SCORE vascular age, and FRS vascular age for different patient subgroups. In chronic treated hypertensive patients, FRS vascular age was higher compared to chronological age and SCORE vascular age (Figure 3A, 68 (57–80), 58.3 (51.3–61.9) and 56 (49.2–62) years, respectively, p<0.05). In diabetic patients (n=18), FRS vascular age was excessively higher compared with chronological age and SCORE vascular age (Figure 3B, 80 (79–80), 59.7 (55.8–61.8) and 58 (54–65) years p<0.05). In healthy

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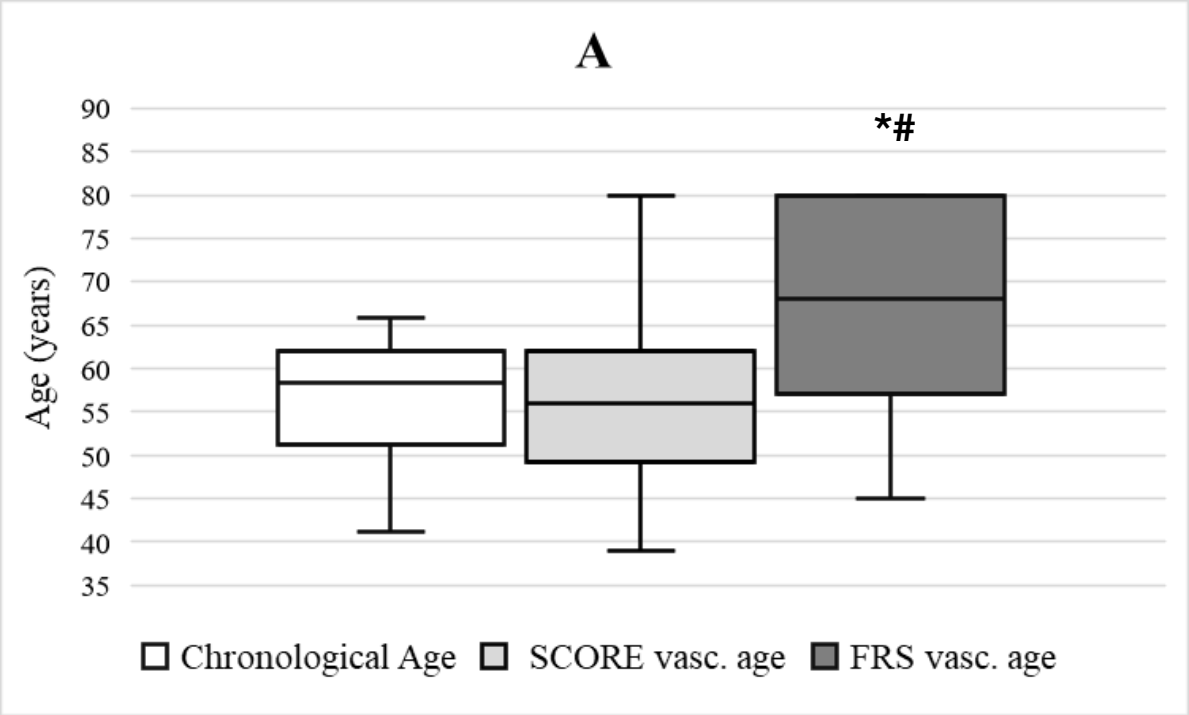
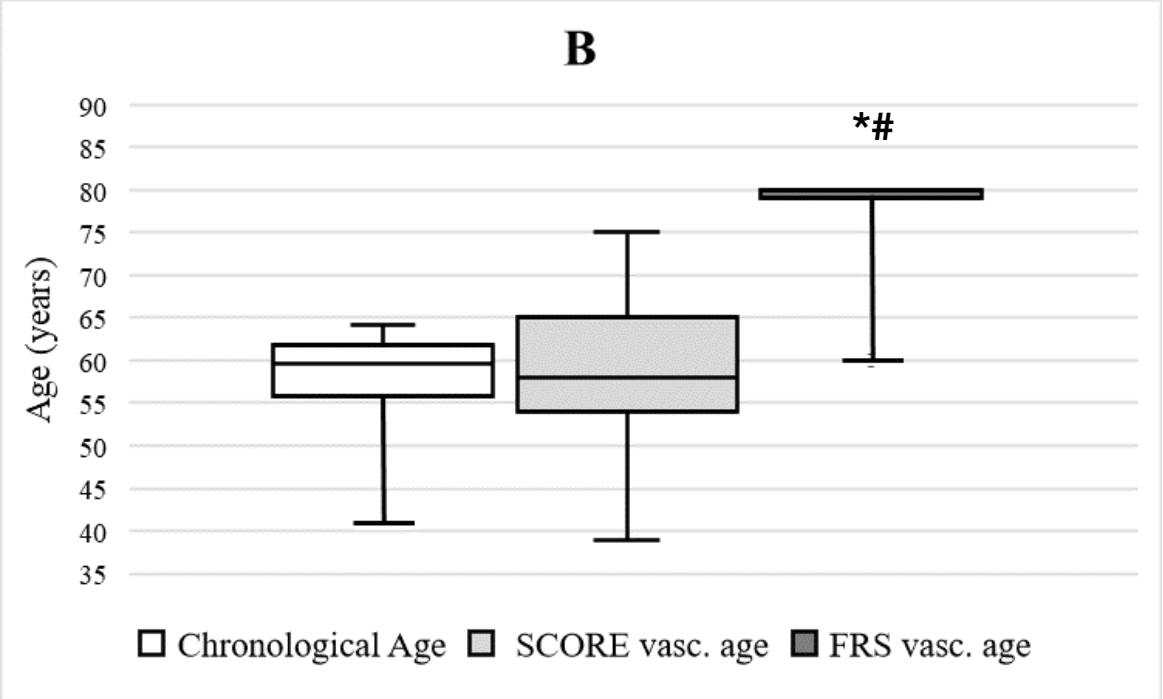
subjects and white-coat hypertensive patients, the chronological and the vascular ages were identical with the two methods (Figure 3C, chronological age: 55.5 (48.9, 60.9) years, SCORE vascular age: 55 (42, 59.7) years, FRS vascular age: 54 (48, 63) years $p<0.05$)





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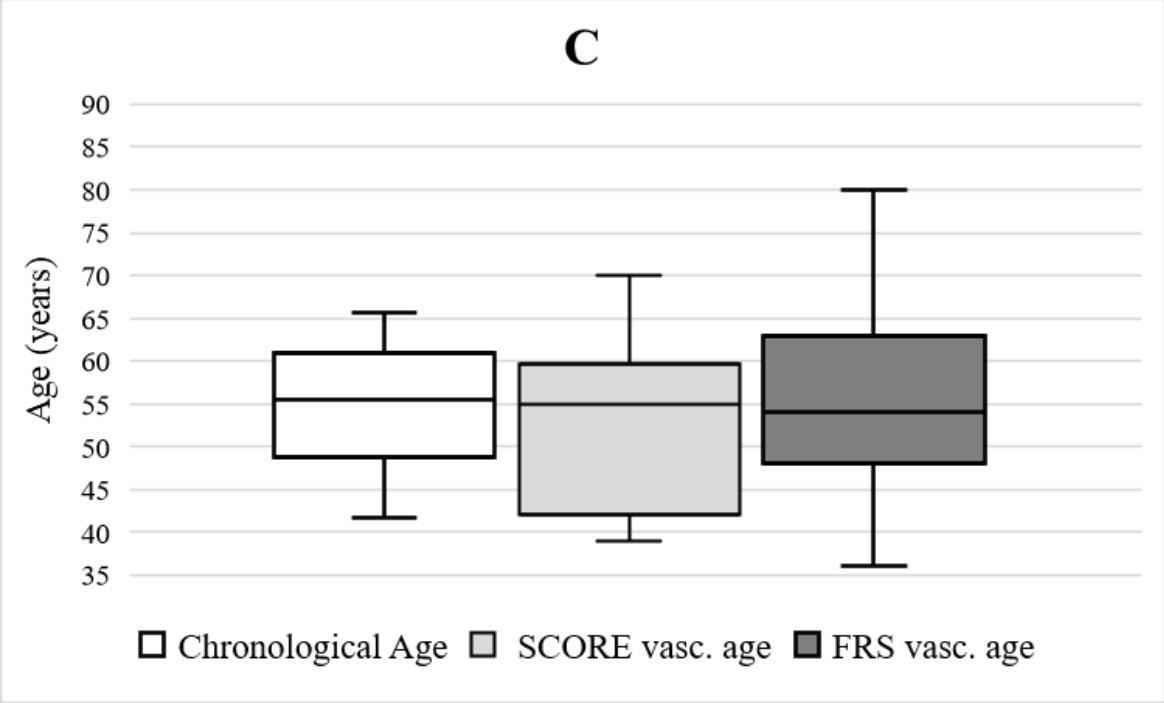

Figure 3. Chronological age, vascular age calculated based on Systematic COronary Risk Evaluation (SCORE vasc. age) and vascular age calculated based on Framingham Risk Score (FRS vasc. age) in patients with chronic hypertension (n=122, “A”), in patients with diabetes (n=18, “B”) and in healthy subjects or patients with white-coat hypertension (n=50, “C”). Data are presented as median (minimal and maximal values in error bars). *$p<0.05$ compared with Chronological Age; #$p<0.05$ compared with SCORE vasc. age (33).

The vascular age of 9.3% (n=16) of the subjects was higher than their chronological age with all three methods. On the other hand, only 11% of the subjects (n=19) had healthy vasculature with all three methods. A total of 84% (n=58) of the PWV+ subjects was also FRS+, and this rate was also high for SCORE+ patients (85.4%, n=47,). In contrast, a moderate overlap was found between PWV+ and SCORE+ patients, as only 30.9% (n=17) of SCORE+ subjects were PWV+, which was only 24.6% of the PWV+ subjects. Figure 4 shows the overlap between subjects identified with early vascular ageing using different methods.

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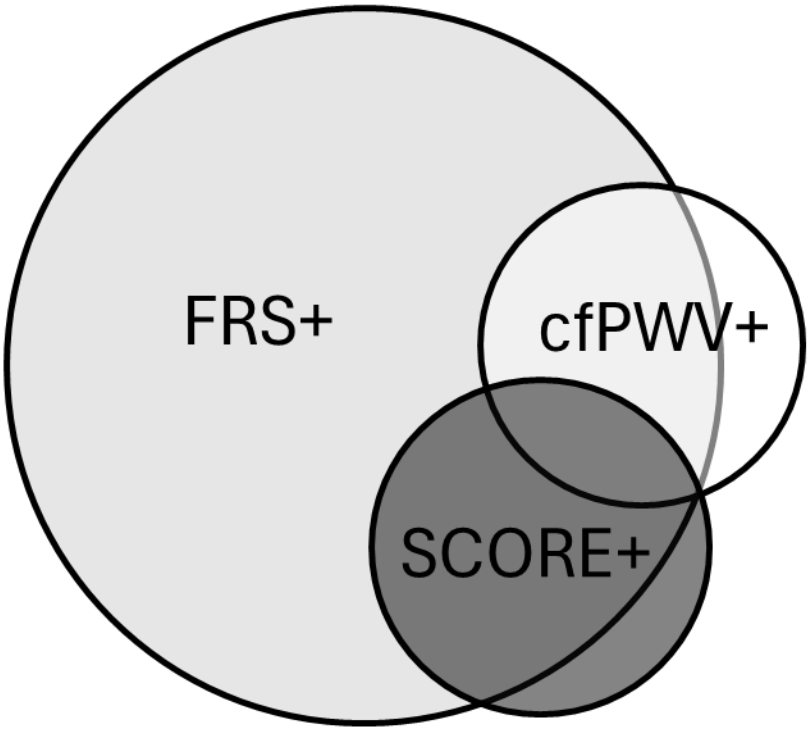

Figure 4. Overlap between subjects identified with early vascular ageing as more than 2 years of difference with chronological age with FRS-based method (FRS+), SCORE-based method (SCORE+) and early vascular age by carotid-femoral pulse wave velocity (cfPWV+) (33).

Figure 5 shows that patients with SCORE age more than 2 years lower than their chronological age had higher cfPWV than patients with FRS age more than 2 years lower than their chronological age (Figure 5A, 8.2 (7.5–9.4) m/s and 7.8 (7.5–8.3) m/s, respectively, $p<0.05$). cfPWV was also higher in patients with a SCORE age more than 2 years higher than chronological age than in patients with FRS age more than 2 years higher (Figure 5C, 9 (8.2, 11) m/s and 8.6 (7.8, 9.6) m/s, respectively, $p<0.05$). cfPWV did not differ between patients in the SCORE age and FRS age groups between -2 or +2 years (Figure 5B, 8.2 (7.6, 9) m/s in SCORE and 7.7 (7.1, 8.8) m/s in FRS vascular age). The cut-off value for PWV was 9 m/s in the SCORE vascular age and 8.6 m/s in the FRS vascular age based on the arbitrary definition of elevated vascular age of 2 years.

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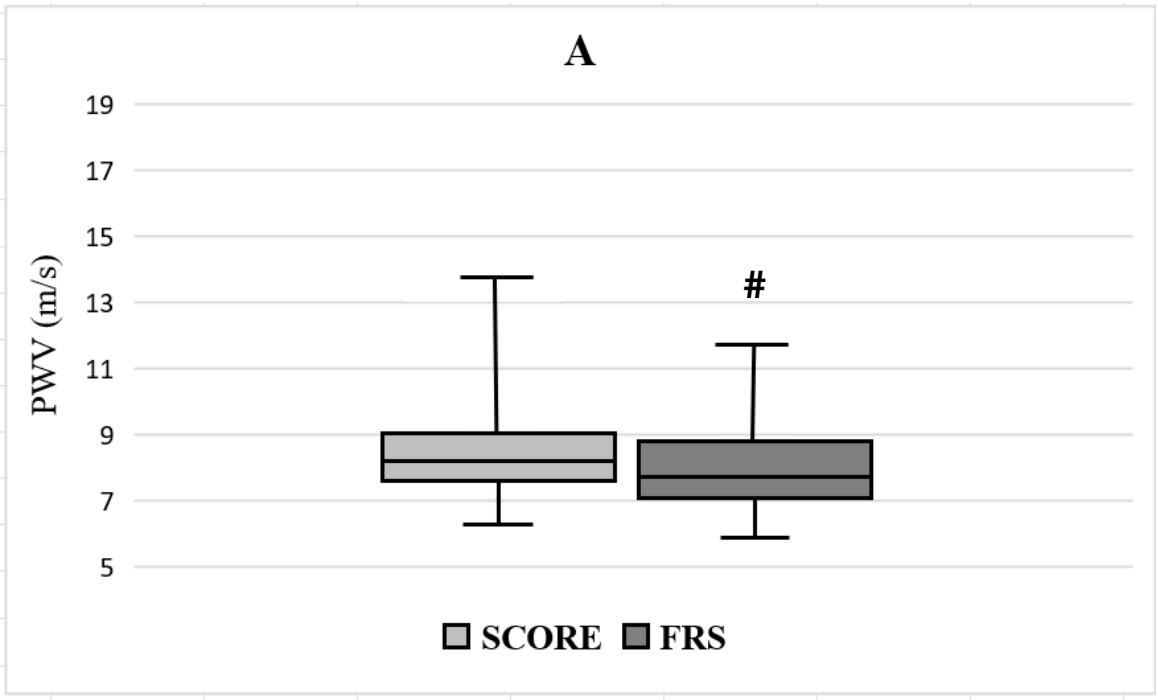

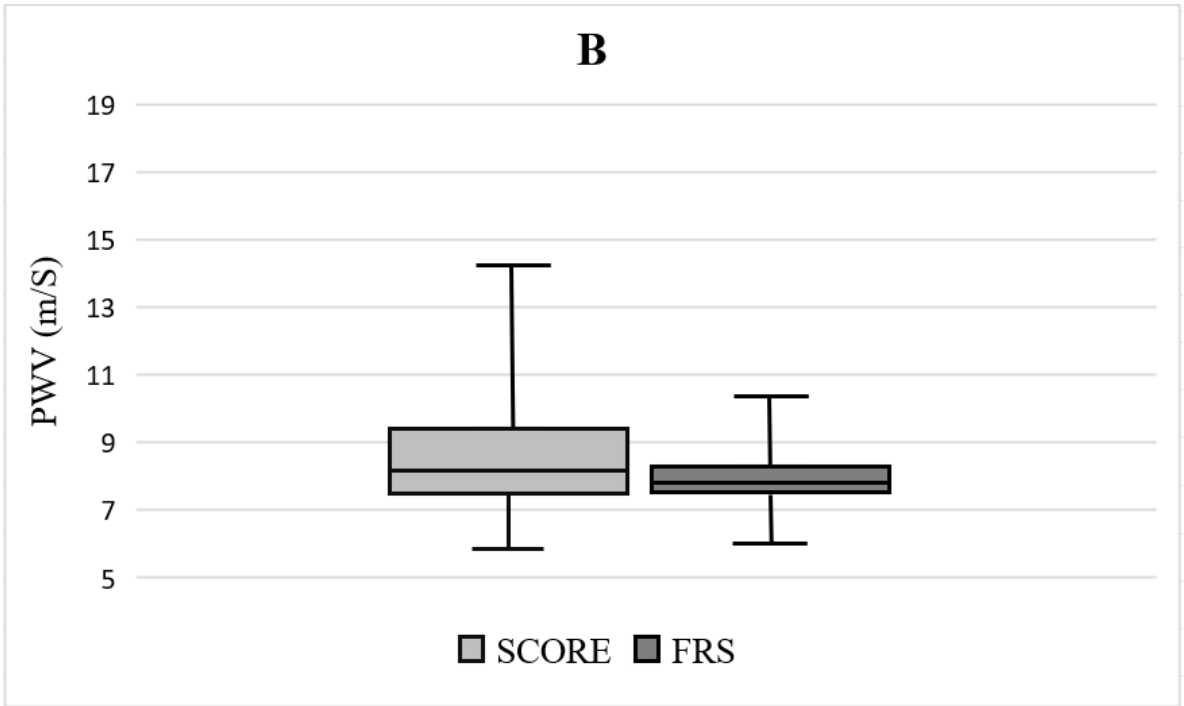

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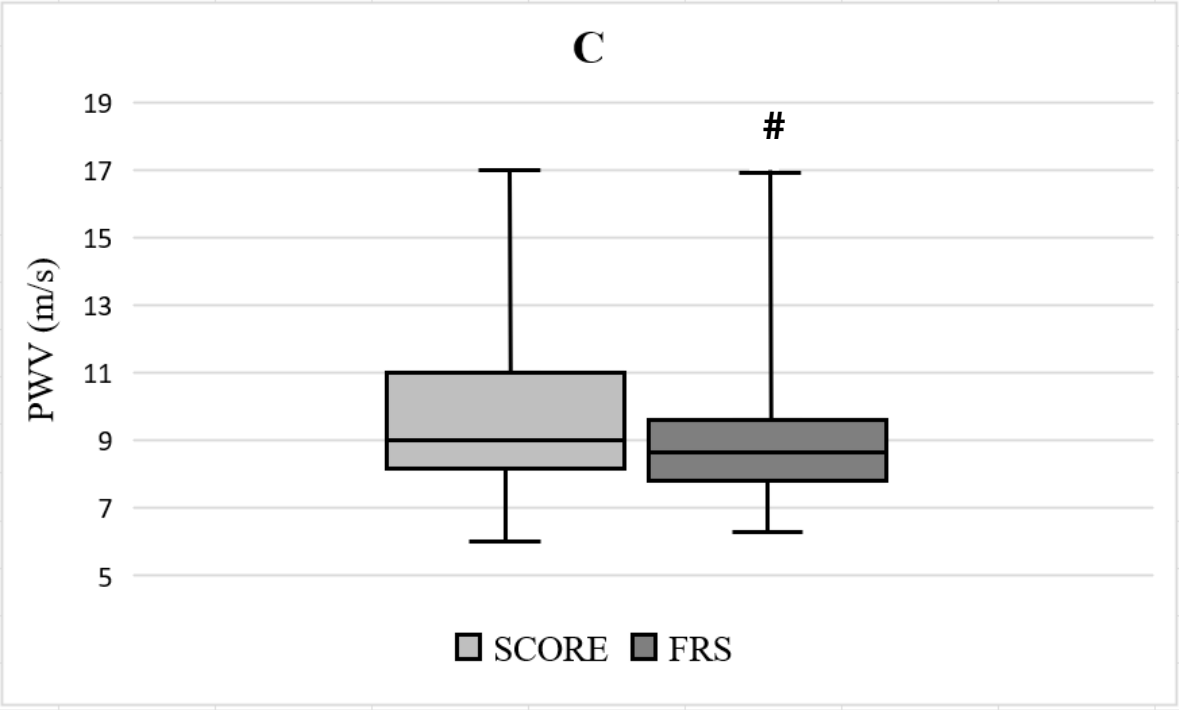

Figure 5. Carotid-femoral pulse wave velocity (PWV) in different vascular age ranges compared with chronological age. A: Systematic COronary Risk Evaluation (SCORE) and Framingham Risk Score (FRS) vascular ages are more than 2 years lower than chronological age; B: SCORE and FRS vascular ages are between minus to plus 2 years compared with chronological age; C: SCORE and FRS vascular ages are 2 years higher than chronological age. Data are presented as median (minimal and maximal values in error bars). #$p<0.05$ compared with SCORE vasc. age pulse wave velocity (PWV) (33).

4.2. Study 2: Differences between SCORE, Framingham Risk Score, and estimated pulse wave velocity-based vascular age calculation methods

The study included 99,231 patients, with 49,191 patients with hypertension and 15,921 patients with diabetes. Table 2 shows demographic data and baseline laboratory parameters.

Table 2. Demographic data and baseline laboratory parameters. Data are presented as median (interquartile ranges). ePWV, estimated pulse wave velocity, HDL-cholesterol, high density lipoprotein cholesterol

N	99,231
Age (years)	54.0 (48.0 - 60.0)
Men	40,443 (40.8 %)
Women	58,788 (59.2 %)
Hypertension	49,191 (49.6 %)
Diabetes	15,921 (16.0 %)
Smoking	28,956 (29.2 %)
Systolic BP [mmHg]	130.0 (122.0 – 130.0)
Diastolic BP [mmHg]	80.0 (76.0 – 86.0)
ePWV [m/s]	9.0 (8.1 – 10.0)
Cholesterol [mmol/l]	5.4 (4.7 – 6.2)
HDL- cholesterol [mmol/l]	1.4 (1.2 – 1.7)

The median chronological age was 54.0 (48.0–60.0) years in the entire cohort, the median vascular age calculated with SCORE and FRS were 59.0 (51.0–66.0) and 64.0 (51.0 80.0) years, respectively. In patients with hypertension, the chronological, SCORE, and FRS vascular ages were 57.0 (51.0–62.0), 63.0 (56.0–68.0), and 79.0 (64.0–80.0) years, respectively ($p<0.05$). In patients with diabetes, the chronological, SCORE, and FRS vascular ages were 58.0 (52.0–62.0), 63.0 (56.0–68.0), and 80.0 (76.0–80.0) years, respectively ($p<0.05$). Chronological, SCORE, and FRS vascular ages were not clinically significantly different in those without hypertension or diabetes (51.0 (45.0–57.0), 54.0 (47.0–62.0), and 51.0 (45.0–64.0) years, respectively). Figure 6 shows the chronological, SCORE and FRS vascular ages in the whole group, in patients with hypertension, in patients with diabetes, and in patients without hypertension or diabetes.

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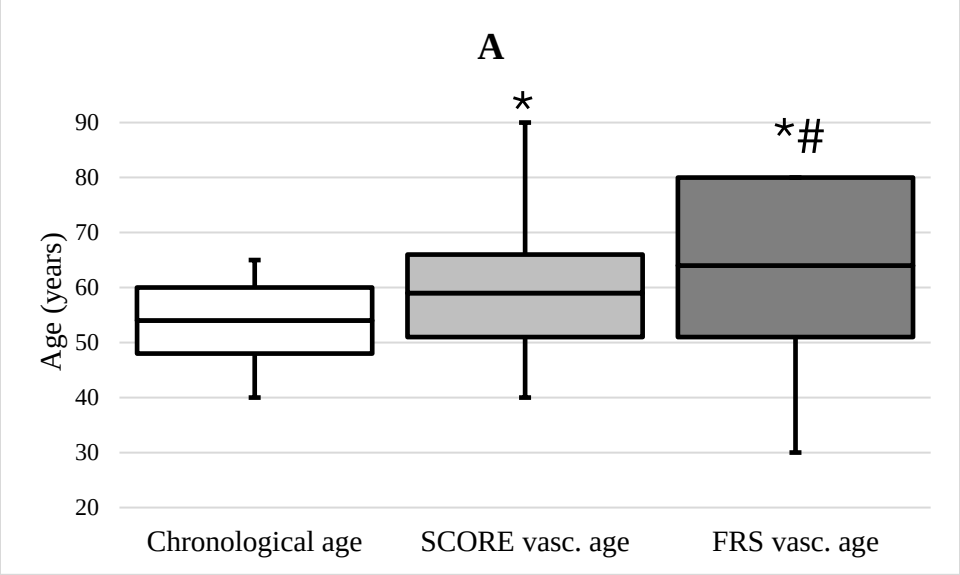

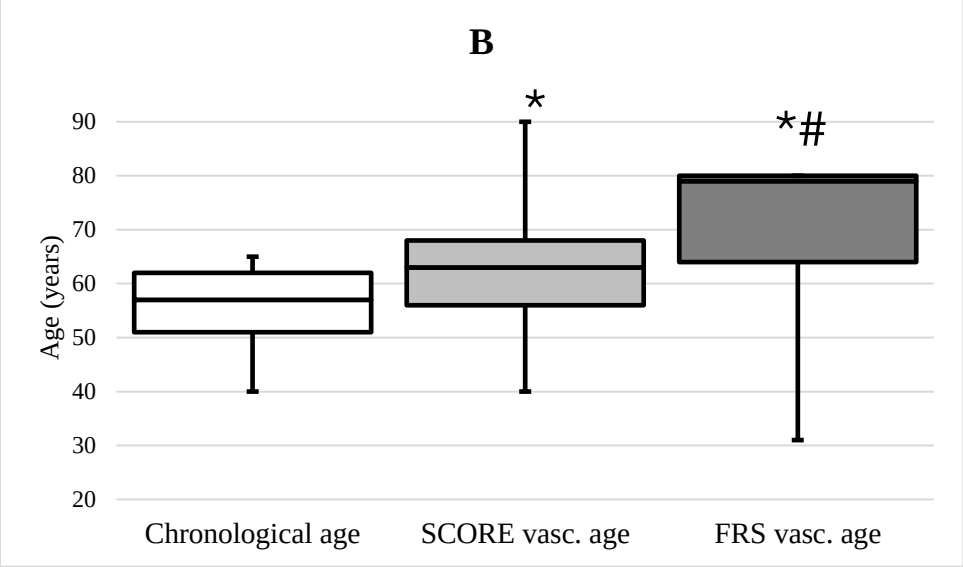

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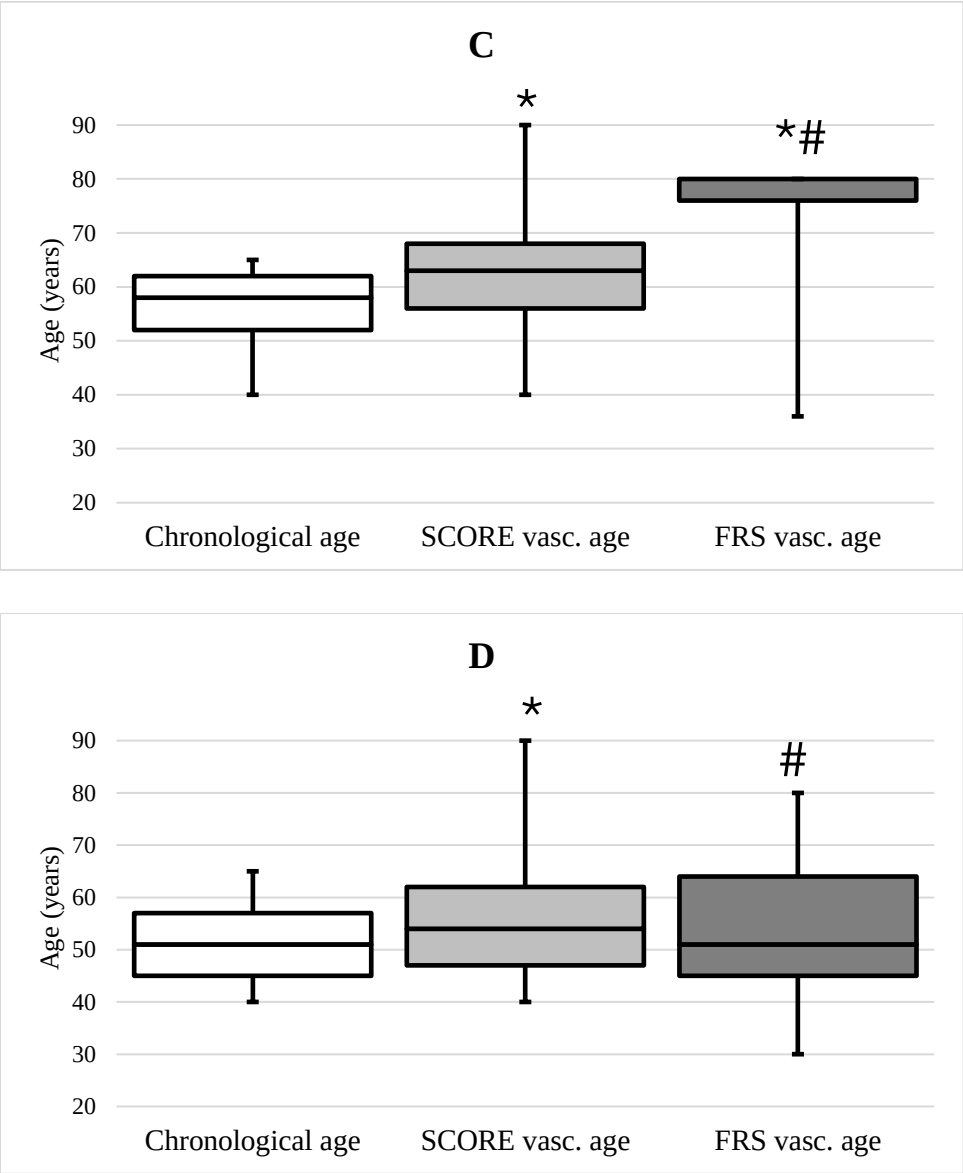

Figure 6. Chronological age, vascular age calculated based on Systematic COronary Risk Evaluation (SCORE vasc. age) and vascular age calculated based on Framingham Risk Score (FRS vasc. age) in the total population (A) in patients with hypertension (B), diabetes (C) and patients without diabetes and hypertension (D). Data are shown as median (interquartile ranges in error bars). *p<0.05 compared with chronological age; #p<0.05 compared with SCORE vasc. age (34).

On the basis of our previous study, subjects were categorized according to a 2-year difference between SCORE or FRS vascular age and chronological age, which defined the following groups:

- age difference < −2 years: SCORE−, FRS−: supernormal vascular ageing:

- age difference between −2 and 2 years: SCORE normal, FRS normal: normal vascular ageing.

- age difference > 2 years: SCORE+, FRS+: early vascular ageing.

On the basis of this categorization, 17.3% (n=17 210) and 10.7% (n=10 608) of the patients were classified as normal vascular ageing according to SCORE and FRS, respectively. Altogether, 57.9% (n=57 433) of the subjects were SCORE− and 24.5% (n=24 588) of the subjects were SCORE+. According to the FRS vascular age calculation, 18.8% (n=18 659) of the patients were FRS− and 70.5% (n=69 964) of the patients were FRS+. The ePWV was 9.0 (8.1–10.0) m/s in the total population, 9.6 (8.7–10.3) m/s in patients with hypertension, and 9.7 (8.8–10.4) m/s in patients with diabetes. The characteristics of supernormal, normal, and early vascular ageing patients based on ePWV are shown in Table 3. FRS vascular age was higher compared to SCORE vascular age ($p < 0.05$) in all ePWV-based vascular ageing categories. Among patients with early vascular ageing, 27.7% (n=2 718) of the subjects had neither hypertension nor diabetes.

Table 3. Characteristics of study participants in relation to their ePWV-based vascular ageing status. Data are presented as median (interquartile ranges) SCORE vascular age, vascular age according to the Systematic COronary Risk Evaluation method; FRS vascular age, vascular age according to the Framingham Risk Score method; ePWV, estimated pulse wave velocity; HDL-cholesterol, high density lipoprotein cholesterol. Significant differences are indicated as bold and italics

	Supernormal vascular ageing	**Normal vascular ageing**	**Early vascular ageing**
N	10,557 (10.6%)	78,855 (79.5%)	9,819 (9.9%)
Men	2,671 (25.3%)	32,703 (41.5%)	***5,069 (51.6%)***
Women	7,886 (74.7%)	***46,152 (58.5%)***	4,750 (48.4%)
Chronological age (years)	51.0 (45.0 - 60.0)	54.0 (48.0 - 61.0)	***57.0 (48.0 - 62.0)***
SCORE vascular age (years)	52.0 (46.0 - 60.0)	59.0 (51.0 - 66.0)	***67.00 (58.0 - 74.0)***
FRS vascular age (years)	59.0 (48.0 - 80.0)	64.0 (51.0 - 80.0)	***80.0 (68.0 - 80.0)***
ePWV [m/s]	7.80 (6.9 - 8.7)	9.0 (8.2- 9.9)	***10.6 (9.80 - 11.5)***
Hypertension	2,892 (27.4%)	39,436 (50.0%)	***6,863 (69.9%)***
Diabetes	935 (8.9%)	12,936 (16.4%)	***2,050 (20.9%)***
No hypertension or diabetes	***7,375 (69.8%)***	36,757 (46.6%)	2,718 (27.7%)
Smoking	2,844 (26.9%)	22,851 (29.0%)	***3,261 (33.2%)***
Systolic BP [mmHg]	115.0 (110.0 - 120.0)	130.0 (125.0 - 140.0)	***157.0 (150.0 - 167.0)***
Diastolic BP [mmHg]	70.0 (67.0 - 72.0)	80.0 (78.0 - 85.0)	***95.0 (90.0 - 100.0)***
Cholesterol [mmol/l]	5.3 (4.6 - 6.1)	5.4 (4.7 - 6.2)	***5.6 (4.81 - 6.40)***
HDL-cholesterol [mmol/l]	***1.5 (1.2 – 1.8)***	1.4 (1.2- 1.7)	1.4 (1.2 - 1.7)

Table 4 shows the overlap between supernormal, normal, and early vascular ageing groups using three different methods. On the basis of ePWV, FRS identified patients with early vascular ageing with a higher sensitivity (97.3%) compared to (13.3%); however, the proportion of the FRS+ patients was high in all vascular ageing categories.

Table 4. Overlap between participants identified as having supernormal, normal, or early vascular ageing with different methods. Data are presented as median (interquartile ranges), categorical parameters as n (%). SCORE- and FRS- were defined as 2 years younger compared with chronological age. The range between -2-+2 years was defined as normal, and >2 years older was defined as SCORE+ and FRS+.

	Supernormal vascular ageing	**Normal vascular ageing**	**Early vascular ageing**
FRS – (n %)	5,521 (52.3)	13,077 (16.6)	61 (0.1)
FRS normal (n %)	1,554 (14.7)	8,854 (11.2)	200 (0.6)
FRS+ (n %)	3,482 (33)	56,924 (72.2)	9,558 (97.3)
SCORE – (n %)	2,776 (26.3)	47,742 (60.5)	6,915 (70.4)
SCORE normal (n %)	1,868 (17.7)	13,742 (17.4)	1,600 (16.3)
SCORE+ (n %)	5,913 (56.0)	17,371 (22.1)	1,304 (13.3)

Differences between SCORE and FRS vascular ageing categories were significant in all settings ($p<0.05$). Elevated vascular age was determined by SCORE and FRS in 24.8%, and 70.5% of cases, respectively. However, only 3.9% of the FRS+ patients were also SCORE+, and in SCORE+ patients, there was an 11% overlap with FRS+. Approximately 13.7% of FRS+ patients were found to have early vascular ageing based on ePWV, and only 5.3% of SCORE+ patients were confirmed by ePWV. Approximately 97.3% of ePWV+ patients were FRS+; on the other hand, only 13.3% of ePWV+ subjects were SCORE+. With all three methods, only 1.1% of the subjects were found to be older than their chronological age. Figure 7 demonstrates the overlap between subjects identified with early vascular ageing using different methods.

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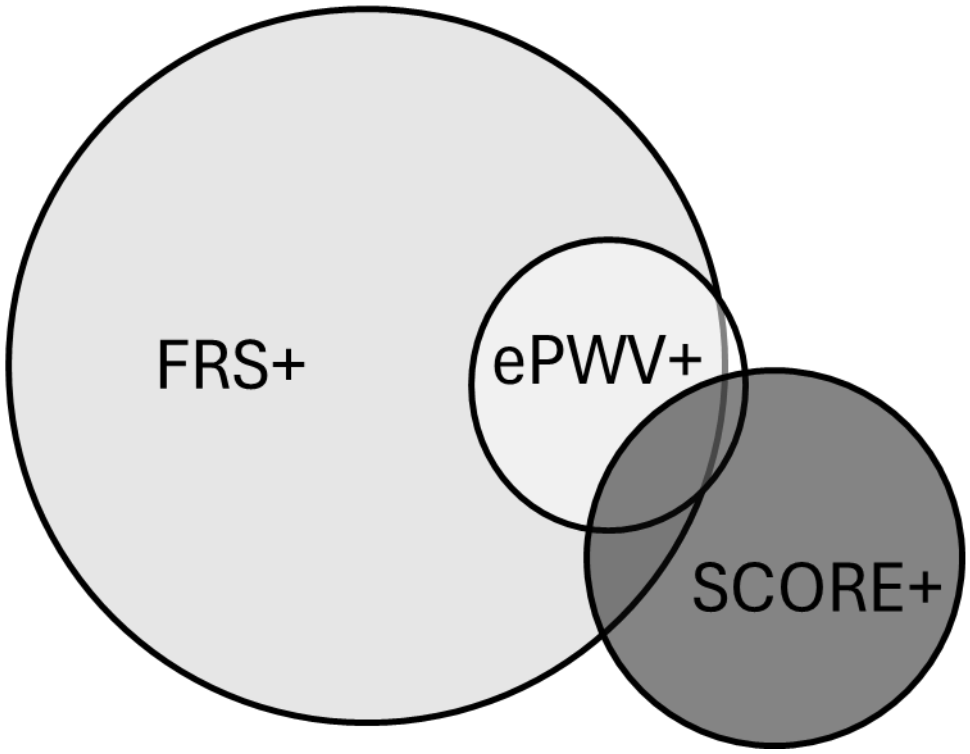

Figure 7. Overlap between subjects identified with early vascular ageing identified by FRS-based method (FRS+), SCORE-based method (SCORE+) or estimated pulse wave velocity (ePWV) as a difference of more than 90% compared to chronological age as a difference of more than two years (34).

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5. Discussion

The two studies in this thesis were the first in the literature to compare vascular ages calculated with different CV risk calculation methods and also using measured or estimated pulse wave velocity. The first study found significant differences in the proportion of subjects with impaired vascular age assessed by cfPWV, FRS or SCORE or. Defining the threshold of elevated vascular age as 2 years older than chronological age, we found higher cfPWV in patients with elevated SCORE vascular age than in patients with elevated FRS vascular age. In the second study, in line with Study I, a population based-study found differences between vascular ages calculated with FRS or SCORE in patients with diabetes and hypertension, suggesting that the FRS-based method should be more convincing for risk communication in these conditions. On the basis of ePWV, subjects with early vascular ageing were identified with high sensitivity using the FRS-based method, whereas only a small proportion of participants were identified by SCORE.

In patients with diabetes and treated hypertension, our findings were confirmed by a study by Kozakova et al. including 528 patients (35). In this study, the early vascular ageing group was defined by the common carotid artery distensibility coefficient and the study found that FRS vascular age was higher compared to SCORE vascular age in the early vascular ageing group. In addition, our research group also reported similar results in a study of 241 participants who underwent coronary computed tomography angiography and used coronary artery calcium score-based vascular age in addition to FRS and SCORE (36).

These studies suggest that in treated hypertension and diabetes, the FRS-based vascular age calculation method might be more convincing in communicating CV risk than the SCORE-based method. Identifying patients with a vascular age higher than their chronological age is crucial for implementing more intensive CV preventive strategies beyond pharmacological treatment for blood pressure reduction via. These strategies may include strictly followed lifestyle changes such as increased physical activity (37), dietary considerations (38) and reduction of salt intake (39). Intensive monitoring of drug adherence may be another option.

In contrast, patients who are not identified may be disadvantaged in the long term due to missed opportunities for lifestyle modifications.

In our two studies, we found only minor overlap between patients with early vascular ageing assessed by different methods, and these findings are also in line with the study by Vecsey-Nagy et al. where 38.2% of the patients were found to be older than their chronological age with all three methods, 83.4% and 93.8% of the population had elevated vascular age by FRS and SCORE, whereas only 42.3% had elevated vascular age by coronary artery calcium score (36). The differences between the patients identified may be due to methodological differences. The SCORE calculation only considers the 10-year risk of CV mortality and does not take into account the presence of diabetes and treated hypertension in contrast to the FRS. For FRS, the calculation considers treated hypertension and diabetes and predicts non-lethal CV events besides CV mortality. This may explain why the FRS-based method was found to have higher vascular ages in patients with diabetes and also those with treated hypertension. In subjects without hypertension or diabetes, there were significant differences between the groups; however, the clinical significance was moderate, suggesting that in generally healthy subjects, the two methods can be used interchangeably.

According to the 2021 ESC cardiovascular prevention guidelines, SCORE2 is the recommended calculation for evaluating CV risk (24). A main difference between SCORE and SCORE2 is that similarly to the FRS, SCORE2 considers the non-lethal CV events while SCORE only estimates the probability of fatal CV events. Due to this change, SCORE2 estimation may approach the FRS calculation. Vascular age calculation is available based on SCORE2 (40), but as SCORE2 was published after the publication of our Study I, we did not calculate with this method. Recently we calculated and compared the vascular ages in the population of the Study I, with FRS, SCORE and SCORE2 (unpublished data). Altogether, only 154 patients of Study I were involved as in 18 patients the SCORE2 vascular age calculation did not give result because of total cholesterol or HDL outlier values. Among the 154 patients, 107 had hypertension and 13 had diabetes. The chronological age of the total population was 54.6 (58.4 – 63.7) years, while SCORE, SCORE2 and FRS vascular ages were 55.0 (44.0 – 60.0), 57.5 (51.0 – 63.0) and 64.0 (54.0 – 76.8) years, respectively. In HT

patients chronological age, SCORE, SCORE2 and FRS vascular ages were 54.1 (48.0 – 61.0), 55.0 (45.0 – 60.0), 58.0 (52.0 – 64.0) and 68.0 (59.0 – 80.0) years, respectively. In DM patients chronological age, SCORE, SCORE2 and FRS vascular ages were 58.6 (48.3 – 62.5), 58.0 (45.0 – 62.5), 60.0 (51.0 – 66.0) and 80.0 (76.0 – 80.0) years, respectively ($p<0.05$). Based on these unpublished data it can be concluded that however, SCORE2 vascular age is higher than SCORE vascular age, but a marked difference is still present in comparison with FRS vascular age.

In contrast to vascular age risk calculations based on CV risk score, cfPWV-based vascular ageing is based on the measurement of the vascular properties of each patient, rather than a derived calculation based on a populational approach alone. A study by Yoav Ben-Shlomo et al. found that cfPWV improves prediction of CV events and re-classification of patients at risk, especially among individuals at intermediate risk (41). A meta- analysis of 19 studies by Qi Zhong et al. showed that subjects with higher cfPWV according to each classification standard had an increased pooled relative risk of CV events or mortality compared to subjects with lower cfPWV (42). ePWV is calculated as a function of mean blood pressure and age Calculated ePWV values showed acceptable accuracy with measured cfPWV (43). ePWV has been shown to be a strong predictor of CV outcome. A prospective study by Yi Shi t. al. that involved 14,396 hypertensive patients found that ePWV was associated with higher risks of all-cause and CV mortality (44). Prelevic et al. reproduced this result in 1,086 subjects from the general Croatian adult population, where ePWV was independently associated with the risk of all-cause mortality and CV mortality in high-risk patients in the general population (45). In our studies, cfPWV and ePWV identified different patients with early vascular ageing, compared to SCORE and FRS. This may be explained by the fact that PWV hypothetically reflects vascular ageing of the larger arteries compared to SCORE and FRS, both reflecting the changes in micro-and macrovasculature due to relevant parameters, such as smoking, cholesterol or diabetes.

Besides risk score-based and vascular function-based methods of calculating vascular ageing, calculations based on morphological alterations in the arteries are also available, and recent studies have also found differences between functional and morphological methods. Both

Yurdadogan T et al. and Sigl M et al. found significant differences between PWV-based (functional) and carotid artery intima-media thickness-based (morphological) methods in the assessment of early vascular ageing (46) (47).

It is also important to note that although ePWV has predictive power, but its calculated value cannot be a full substitute for direct measurement. In addition, there are various methods for calculating ePWV, each with its own limitations. The ARCSolver method, used in the Mobil-O-Graph device to estimate PWV (48), is used as a predictor of CV outcomes in patients with suspected coronary artery disease (similar to the ePWV method used in our current study) (49), but was ineffective in patients with Marfan syndrome (50). Furthermore, in the MORGAM (MOnica Risk, Genetics, Archiving and Monograph) Project, which included 107,599 subjects in 38 cohorts from 11 countries, ePWV was associated only with all-cause mortality and not with CV mortality after adjusting for traditional CV risk factors (51). These findings indicate that, as with vascular age calculation methods, further research is needed to fully understand the strengths and limitations of ePWV before it can be routinely used in clinical practice.

cfPWV is considered as the “gold standard” approach for measuring arterial stiffness with robust amount of data of clinical validity. Despite its considerable potential to prevent cardiovascular disease, cfPWV measurement is not widely used in clinical practice and the updated 2021 ESC guidelines for CV disease prevention advise against the widespread use of PWV measurements in clinics due to challenges with accuracy and precision of measurement (52). However, the recent European hypertension guidelines of the European Society of Hypertension recommend measurement of cfPWV for the assessment of hypertension-mediated organ damage (53). Moreover, over a 6-year follow-up period, cfPWV accurately predicted major adverse cardiovascular events, independently of conventional risk factors and cfPWV was recognized as an independent and complementary predictor to SCORE2 for the occurrence of such events (54).

5.2. Limitations

Study I has some limitations. First, there is no clear recommendation for a cut-off value for a positive bias in vascular age compared to chronological age that would indicate the need for lifestyle changes or more aggressive therapy, we did not make a distinction between subjects with differences of only a few months and those of many years in the initial part of our study. We arbitrarily chose the threshold of a 2-year difference, which lacks consensus. However, with these limitations, we observed significant differences in the vascular age calculated using the three methods, as well as differences in the PWVs of the FRS and SCORE-based methods. Furthermore, this study was conducted in a patient population with low CV risk, which may limit the generalizability of our results. In addition, the modest number of subjects and the cross-sectional design of the study limited the scope for further analysis.

Study II also has some limitations that should be considered. Being a cross-sectional study, it also does not allow us to draw conclusions on the outcomes of patients of different vascular ages. Prospective data and direct comparison of various preventive strategies based on different vascular age calculation methods are needed to determine the most effective method. In addition, we chose an arbitrary threshold of a 2-year difference similar to Study I, which is not based on consensus.

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6. Conclusions

Our initial study demonstrated that vascular ages calculated using different methods can vary significantly, and the identification of subjects with elevated vascular age depends on the method used. We confirmed these findings in a second population-based cohort study and showed that different vascular age calculation methods can produce different results and identify different subjects with early vascular ageing. Our studies have highlighted the methodological differences in vascular age calculation methods and urge the need of further studies and consensus papers to resolve potential confounding in the application of preventive strategies.

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7. Summary

Our studies aimed to compare the differences between methods for calculating vascular ageing.

Study I with 172 patients, calculated vascular age using FRS and SCORE, and measured carotid-femoral PWV. Study II included 99,231 patients in a national screening program, and we calculated vascular age with FRS and SCORE and early vascular ageing with ePWV.

In Study I, we found differences between the calculated vascular ages and the identified subjects with elevated vascular age. In Study II, we confirmed these findings in a population-based cohort, that different vascular age calculation methods can give different vascular age results.

Further prospective studies are needed to determine the importance of this finding for the implementation of cardiovascular preventive strategies.

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9. Bibliography of the candidate's publications

9.2. Publications related to the thesis

Gyöngyösi H*, Szőllősi GJ*, Csenteri O, Jancsó Z, Móczár C, Torzsa P, Andréka P, Vajer P, Nemcsik J. Differences between SCORE, Framingham Risk Score, and Estimated Pulse Wave Velocity-Based Vascular Age Calculation Methods Based on Data from the Three Generations Health Program in Hungary. Journal of Clinical Medicine. 2023 Dec 29;13(1):205 (2023) IF: 3.0

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9.3. Publications not directly related to the thesis

Gyöngyösi Helga, Vecsey-Nagy Milán, Nemcsik János Különböző cardiovascularis rizikóbecslő pontrendszereken, a pulzushullám-terjedési sebességen és a coronaria-kalcium pontszámon alapuló artériás életkor számítási módszereinek összehasonlítása. Hypertonia és Nephrologia 26 : 6 pp. 257-265. (2022)

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