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Development and validation of an ankle brachial index risk model for the prediction of cardiovascular events

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Conflict of interest

The authors declare that there is no conflict of interest.

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Abstract

Background—The ankle brachial index (ABI) is related to risk of cardiovascular events independent of the Framingham risk score (FRS). The aim of this study was to develop and evaluate a risk model for cardiovascular events incorporating the ABI and FRS.

Design—An analysis of participant data from 18 cohorts in which 24,375 men and 20,377 women free of coronary heart disease had ABI measured and were followed up for events.

Methods—Subjects were divided into a development and internal validation dataset and an external validation dataset. Two models, comprising FRS and FRS + ABI, were fitted for the primary outcome of major coronary events.

Results—In predicting events in the external validation dataset, C-index for the FRS was 0.672 (95% CI 0.599 to 0.737) in men and 0.578 (95% CI 0.492 to 0.661) in women. The FRS + ABI led to a small increase in C-index in men to 0.685 (95% CI 0.612 to 0.749) and large increase in women to 0.690 (95% CI 0.605 to 0.764) with net reclassification improvement (NRI) of 4.3% (95% CI 0.0 to 7.6%, $p = 0.050$) and 9.6% (95% CI 6.1 to 16.4%, $p < 0.001$), respectively. Restricting the FRS + ABI model to those with FRS intermediate 10-year risk of 10 to 19% resulted in higher NRI of 15.9% (95% CI 6.1 to 20.6%, $p < 0.001$) in men and 23.3% (95% CI 13.8 to 62.5%, $p = 0.002$) in women. However, incorporating ABI in an improved newly fitted risk factor model had a nonsignificant effect: NRI 2.0% (95% CI 2.3 to 4.2%, $p = 0.567$) in men and 1.1% (95% CI 1.9 to 4.0%, $p = 0.483$) in women.

Conclusions—An ABI risk model may improve prediction especially in individuals at intermediate risk and when performance of the base risk factor model is modest.

Keywords

Ankle brachial index; cardiovascular diseases; risk assessment

Introduction

The accurate prediction of major cardiovascular events in individuals without vascular disease is an important public health goal, allowing targeting of preventive measures to those at increased risk. The Framingham risk score (FRS), which combines classic cardiovascular risk factors such as cigarette smoking and total cholesterol, is the most well-known method of risk prediction. However, the FRS has limited accuracy¹, and attempts have been made to improve prediction by incorporating additional risk factors, novel biomarkers, and measures of subclinical atherosclerosis.²

The ankle brachial index (ABI), which is the ratio of ankle:arm systolic pressure, is a measure of atherosclerosis in symptomatic and asymptomatic individuals. Originally

developed as a diagnostic tool for leg artery disease, the ABI is also an indicator of generalized atherosclerosis and of future cardiovascular events, independent of established risk factors.³ Since the ABI can be measured using only a handheld Doppler probe and sphygmomanometer in many healthcare settings, the possibility of using the ABI to enhance risk prediction is of interest.

The ABI Collaboration was formed of investigators performing longitudinal studies of the ABI and incident cardiovascular events. In a meta-analysis comprising 48,294 subjects, a low ABI (< 0.90) compared to a normal ABI (1.11 – 1.40) was related to a 2–3-fold increase in both 10-year major coronary events and cardiovascular mortality independent of the FRS.³ Furthermore, in cardiovascular risk stratification using the FRS, subsequent inclusion of the ABI resulted in reclassification of risk (low, intermediate, high) in 1 in 5 men and 1 in 3 women. However, the impact of reclassification in improving risk prediction was not assessed.

In this present study, our aim was to develop an ABI prediction model incorporating FRS and ABI into a single equation. The ABI model was then evaluated in a different population and the effect of reclassification of 10-year risk assessed. Since risk prediction varies according to gender and ethnic group,⁴ the model was developed separately in men and women and only in whites who comprised the largest ethnic group in the ABI Collaboration studies.

Methods

Study design

The study design was an analysis of individual participant data from 18 prospective cohort studies. Risk prediction models were fitted in a development dataset and evaluated in internal and external validation datasets.

Inclusion and exclusion of studies

The study was based on 20 cohort datasets in the ABI Collaboration. The literature search and collation of data from 16 of these studies^{5–20} were described previously.³ Since then, experts informed us of four further studies,^{21–24} from which corresponding data were acquired. Two studies included only non-White ethnic groups^{7,8} and were excluded, leaving 18 studies in the final analysis. Individual participant data were extracted and analysed using version 9.2 of SAS System for Windows (2002–2008; SAS Institute, Cary, NC, USA).

Subjects, variables, and missing data

Subjects with nonvalid ABI, with prevalent coronary heart disease as defined in each study at baseline, and without follow up for vital status were excluded. Framingham covariates extracted were age, gender, systolic and diastolic blood pressures, total and high-density lipoprotein cholesterol, and smoking and diabetes indicators. ABI, study location, and ethnic group were obtained and only subjects included who were classified as ‘white’ using individual study classifications. Analyses were not performed on non-White ethnic groups because of small sample sizes. The numbers of men and women in the final analysis were

24,375 and 20,377, respectively. Only 7.4% of data in men and 2.9% in women were missing, predominantly for total and high-density lipoprotein cholesterol. Imputation was performed separately by gender using the SAS procedure PROC MI with the MCMC full-data imputation method. FRS was calculated for all individuals using the methods of Wilson et al.²⁵ In keeping with our previous investigation,³ ABI was categorized into four groups: 0.90, 0.91–1.10, 1.11–1.40, >1.40.

Development, internal validation, and external validation datasets

The studies were divided into two groups separately by gender to create, first, a model development and internal validation dataset and, secondly, an external validation dataset. Studies were allocated to these datasets based on study location (USA or not), earlier vs. later start date, larger vs. smaller study, age range of participants, and median duration of follow up in order to achieve a balance across datasets. Studies with one or more wholly imputed covariates were constrained to be in the external validation dataset. The characteristics of the studies are shown in Table 1. The first dataset was then divided in two by randomly selecting half the participants in each study. Prediction models were fitted in the first half (development dataset) and validated in the other half (internal validation dataset) and finally in the external validation dataset.

Model fitting

Two models were fitted each for the primary outcome of major coronary events (myocardial infarction or death due to coronary heart disease) and the secondary outcome of cardiovascular mortality (death due to coronary heart disease or stroke) using Cox's proportional hazards model, as follows: model 1: Framingham risk score²⁵ fitted as a continuous variable (FRS); model 2: as per model 1 with addition of ABI group (FRS + ABI).

These models were first fitted for men and women separately in the development datasets. Details of the fitted FRS + ABI for major coronary events are shown in Supplementary Table 1 and measures of model performance^{26–28} in Supplementary Table 2 (available online).

For comparison with the FRS, an additional risk factor model was fitted in the development dataset in which, instead of using the overall single FRS value, each individual Framingham risk covariate, such as smoking, was used separately. And then a further model was fitted with addition of ABI group (Supplementary Table 1). Assumptions for Cox's analyses were checked formally.

Outcome measures

To quantify the effect of inclusion of the ABI in risk prediction models, the C-index and net reclassification improvement (NRI) were derived.

The C-index is analogous to C-statistic, which is the area under the receiver operating characteristic curve and is a measure of the model's discrimination of events and non-events. The C-index is for survival data, being the fraction of occasions where the predictor

score correctly predicts the earlier event for pairs of individuals in the sample. This was achieved using the methods of Harrell et al.²⁹ and Pencina and D'Agostino³⁰ adopting the simplified method for confidence intervals.

For the calculation of the NRI, reclassification tables comparing predicted risk categories for models with and without ABI were constructed for the external validation dataset. Ten-year risk categories of <10%, 10–19%, and ≥20% were selected for major coronary events and <2%, 2–4%, and ≥5% for cardiovascular mortality. NRIs were calculated taking account of censored data.³¹ Confidence intervals and *p*-values were derived using methods for the standard NRI.

For major coronary events, analysis was repeated with a wider intermediate group of 5–19%, akin to some recent studies of risk prediction.^{32,33}

Results

Predicting events in the whole study population

Table 2 shows that C-indices in the internal validation dataset were mostly similar to those in the development dataset but in the external validation dataset were mostly lower. In the latter, C-indices for the FRS in men were 0.672 (95% CI 0.599 to 0.737) for major coronary events and 0.684 (95% CI 0.625 to 0.738) for cardiovascular mortality, and in women were particularly low: 0.578 (95% CI 0.492 to 0.661) and 0.449 (95% CI 0.377 to 0.523), respectively. Incorporation of the ABI led to a modest increase in the C-index for men to 0.685 (95% CI 0.605 to 0.764) for major coronary events and 0.710 (95% CI 0.652 to 0.762) for cardiovascular mortality. However, in women, the increase was much larger, to 0.690 (95% CI 0.605 to 0.764) for major coronary events and 0.652 (95% CI 0.579 to 0.719) for cardiovascular mortality so that the C-indices approximated more closely to those of men.

The effect of the FRS + ABI model on prediction, in comparison to the FRS, is shown in Figure 1 according to low, intermediate, and high 10-year risk for a major coronary event. Within each FRS risk category, the FRS+ABI model refined the degree of risk corresponding to trends in event rates (except for a low event rate in women classified at intermediate risk of 10–19% by both models).

The impact of reclassification of risk using the FRS + ABI model compared to the FRS is shown in Table 3. For major coronary events, the NRI was 4.3% (95% CI 0.0 to 7.6%, *p*=0.050) in men and 9.6% (95% CI 6.1 to 16.4%, *p* < 0.001) in women and included a net increase in risk category in those having an event. For cardiovascular mortality, the NRI was 5.7% (95% CI 2.7 to 7.9%, *p* < 0.001) in men and 15.7% (95% CI 11.3 to 20.2%, *p* < 0.001) in women in whom improved classification occurred in those having and not having a cardiovascular death. Detailed reclassification data for the primary outcome of major coronary events are shown in Supplementary Table 3 and Supplementary Table 4.

Predicting events in subjects at intermediate risk

Restricting use of the ABI model to only those at intermediate 10-year FRS risk had a greater effect (Table 4) than in all subjects. In those with a 10–19% risk for a major

coronary event, incorporation of the ABI resulted in a NRI of 15.9% (95% CI 6.1 to 20.6%, $p < 0.001$) in men and 23.3% (95% CI 13.8 to 32.8%, $p = 0.002$) in women. This was due to a net increase in subjects having an event reclassified as higher risk and in those not having an event reclassified as lower risk. In restricting use of the ABI to those at intermediate 10-year risk of 2–4% for cardiovascular death, NRIs were likewise higher than in the whole population but were similar in men and women: 20.2% (95% CI 11.5 to 29.1%, $p < 0.001$) and 18.0% (95% CI 13.1 to 22.9%, $p < 0.001$), respectively.

The impact of reclassification on major coronary events using the FRS + ABI model was analysed using a wider FRS intermediate 10-year risk category of 5–19% (Supplementary Tables 5 and 6). This categorization resulted in very few numbers in the <5% risk group. In the whole population, the NRI for men was modest (3.1% (95% CI 0.6 to 6.4%, $p = 0.018$)) but for women was considerable (20.4% (95% CI 11.6 to 22.5%, $p < 0.001$)), with improved net reclassification for those having and not having an event. Restricting the FRS + ABI model to the 5–19% intermediate group led to a higher NRI in men (7.9% (95% CI 3.7 to 11.5%, $p < 0.001$)) but a lower NRI in women (13.0% (95% CI 7.3 to 17.9%, $p < 0.001$)).

Predicting events using cardiovascular risk covariate model

C-indices for the newly developed risk factor model in predicting major coronary events in the external validation dataset were 0.683 (95% CI 0.611 to 0.748) in men and 0.788 (95% CI 0.709 to 0.850) in women, which were slightly higher in men and considerably higher in women than the corresponding FRS C-indices in Table 2. Incorporation of the ABI resulted in only a slight improvement, increasing C-indices to 0.690 (95% CI 0.618 to 0.754) in men and 0.791 (95% CI 0.712 to 0.852) in women, with nonsignificant NRIs of 2.0% (95% CI –2.3 to 4.2%, $p = 0.567$) and 1.1% (95% CI –1.9 to 4.0%, $p = 0.483$), respectively. In only those at intermediate 10–19% risk, NRIs were 7.7% (95% CI 0.0 to 13.0%, $p = 0.049$) in men and 2.4% (95% CI –3.0 to 10.5%, $p = 0.275$) in women.

Discussion

Main findings

In this analysis combining data from 18 population-based studies, a new ABI risk model incorporating the FRS+ABI was developed and then validated in an external population. In comparison to the FRS, as measured by C-index and NRI, the ABI model led to an improvement in performance, but mostly in women. Restricting use of the ABI model to those at intermediate 10-year risk of 10–19% for major coronary events resulted in higher NRIs than in the whole population. In a wider intermediate risk group of 5–19%, the NRIs were lower than in the 10–19% risk group.

The more impressive results in women than in men might be related to the particularly poor performance of the FRS in women in the external validation dataset in which C-indices were much lower than in the development and internal validation datasets (Table 2). This may have been due to chance or unexpected population differences. The main effect of incorporating the ABI may have been to compensate for this poor performance by bringing the C-indices up towards those of men and not that the ABI model was inherently superior

in women than in men. When a better performing model based on fitting individual risk covariates was used instead of the FRS, incorporation of the ABI in the prediction of major coronary events led to no significant improvement. These results suggest that the impact of the ABI is not a fixed phenomenon but is influenced by how well the base risk factor model performs.

Other studies

The Multi-Ethnic Study of Atherosclerosis (MESA) found that the ABI contributed to an improvement in classification of cardiovascular events and non-events compared to traditional risk factors as measured by integrated discrimination improvement.³⁴ In the Atherosclerosis Risk in Communities (ARIC) Study and Rotterdam Study, each components of the ABI Collaboration, the effect on prediction of adding the ABI to a cardiovascular risk equation was examined^{32,35} and found, in the whole study populations, to have minimal impact. In keeping with the present study, both the ARIC and Rotterdam studies found improved performance if the ABI was used only in patients at intermediate risk. In all men and women combined, the NRI was 0.8% in the ARIC Study and 0.6% in the Rotterdam Study and, in those at intermediate risk, was 8.3% and 7.3%, respectively. A similar result (NRI 7.0%) was found in the elderly aged 70–79 years at intermediate risk in the Health, Aging and Body Composition Study.³⁶ However, it has been pointed out recently that findings in intermediate groups may be overly optimistic due to possible bias in their estimation.³⁷

Comparison with coronary artery calcium

In the Rotterdam Study, coronary artery calcium (CAC) showed better prediction than the ABI when added to a locally developed risk factor model.³⁵ The NRIs for models in the whole population were 19.3% for CAC and 0.6% for ABI and, in those at intermediate risk, were 39.3% for CAC and 7.3% for ABI. Likewise in intermediate risk individuals in MESA, the NRI was much higher for CAC than for other measures of subclinical atherosclerosis including ABI.³⁶ However, measurement of CAC is technically sophisticated, expensive, and involves radiation exposure,³⁸ and so is less suited than the ABI to measurement in primary care or in population screening. The ABI can be measured easily with minimal training, using simple inexpensive equipment and in less than 15 min.³⁹ A risk prediction programme incorporating measures of subclinical disease might benefit from tiered assessment with more complex and costly tests targeted on fewer individuals. Research is required on the costs and effectiveness of such an approach.

Limitations

A principal strength of this study was that, due to large numbers of subjects, models could be tested in both internal and external validation datasets derived from 18 population studies from several countries. A limitation of using multiple studies is that measurement of variables, including ABI, and the ascertainment and definition of endpoints were not identical. However, studies were only included where consistent and valid methods were used. Furthermore, using two study outcomes with hard endpoints (major coronary events and cardiovascular mortality) and finding broadly similar results, provided some reassurance on validity. Nevertheless, very large simulated datasets have been used as an alternative

approach to overcoming some of these difficulties.⁴⁰ A further limitation of the study was that the exclusion criteria at baseline of only subjects with coronary heart disease meant that some subjects with other cardiovascular disease would be included, but were likely to make up a small proportion of the total population. Insufficient data were available to study non-White populations.

The FRS applied in this study²⁵ has been adopted in many practice settings but, more recently, the Framingham group produced a general cardiovascular disease risk factor model to be used in primary care for predicting a wider range of events.⁴¹ Due to limitations in our dataset, assessment of these outcomes was not feasible but, if predicting a wide range of events was desirable, evaluation of ABI risk models in this context would be useful, as would the contribution of the ABI to other risk models such as SCORE.⁴²

Clinical implications

The ABI has been recognized for some time as potentially useful in screening healthy individuals for cardiovascular risk.⁴³ However, guidelines have varied recommendations on use of the ABI. Recently, the US Preventive Services Task Force, while recognizing that use of the ABI would reclassify some men and women in the FRS intermediate risk category, considered the evidence insufficient to assess the benefits and harms, and concluded that clinical discretion was required.⁴⁴ On the other hand, an American College of Cardiology Foundation/American Heart Association guideline included a recommendation, based on level of evidence B (nonrandomized studies), that 'Measurement of ABI is reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk'.⁴⁵ Recent multi-Society European guidelines had a similar recommendation.⁴⁶ The results of our study provide some support for the use of an ABI risk model especially in individuals at intermediate risk and when performance of the base risk factor model is modest. Furthermore, if physicians are uncertain about how well the FRS performs in their practice, using the ABI model is likely to compensate for any deficiencies in the FRS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix 1: Studies, institutions, and investigators participating in the Ankle Brachial Index Collaboration

Co-ordinating centre	University of Edinburgh	Isabella Butcher, Gerry Fowkes, Gordon Murray
Atherosclerosis Risk in Communities Study	University of Minnesota University of North Carolina	Aaron Folsom, Alan Hirsch David Couper
Belgian Physical Fitness Study	Ghent University University Libre de Bruxelles	Guy deBacker Marcel Kornitzer
Cardiovascular Health Study	University of Pittsburgh University of Vermont	Anne Newman, Kim Sutton-Tyrell*
Edinburgh Artery Study	University of Aberdeen University of Edinburgh	Mary Cushman Amanda Lee Gerry Fowkes, Jackie Price
Framingham Offspring Study	Boston University	Ralph d'Agostino, Joanne Murabito
Health ABC Study	University of Pittsburgh	Anne Newman, Kim Sutton-Tyrell*
Health in Men Study	University of Western Australia	Paul Norman
Honolulu Heart Program	University of Hawaii	Kamal Masaki
Hoorn Study	VU University Amsterdam Maastricht University	Lex Bouter, Robert Heine Coen Stehouwer
InCHIANTI Study/Women's Health and Aging Study	Northwestern University Feinberg School of Medicine	Mary McDermott

Co-ordinating centre	University of Edinburgh	Isabella Butcher, Gerry Fowkes, Gordon Murray
Limburg PAOD Study	Maastricht University	Jelle Stoffers, Andre Knottnerus
Men born in 1914 Study	University of Uppsala	Mats Ogren
	Lund University	Bo Hedblad
MONICA Augsburg Study	University of Ulm	Wolfgang Koenig
	Helmholtz Centrum Munich	Christa Meisinger
Mr OS Study/Study of Osteoporotic Fractures	University of Pittsburgh	Jane Cauley
Rotterdam Study	Erasmus Medical Centre	Oscar Franco, Albert Hofman, Myriam Hunink, Jacqueline Witteman,
San Diego Study	University of California San Diego	Michael Criqui
	University of Nevada School of Medicine	Robert Langer
San Luis Valley Diabetes Study	University of Colorado	William Hiatt
	Colorado School of Public Health	Richard Hamman

* deceased.

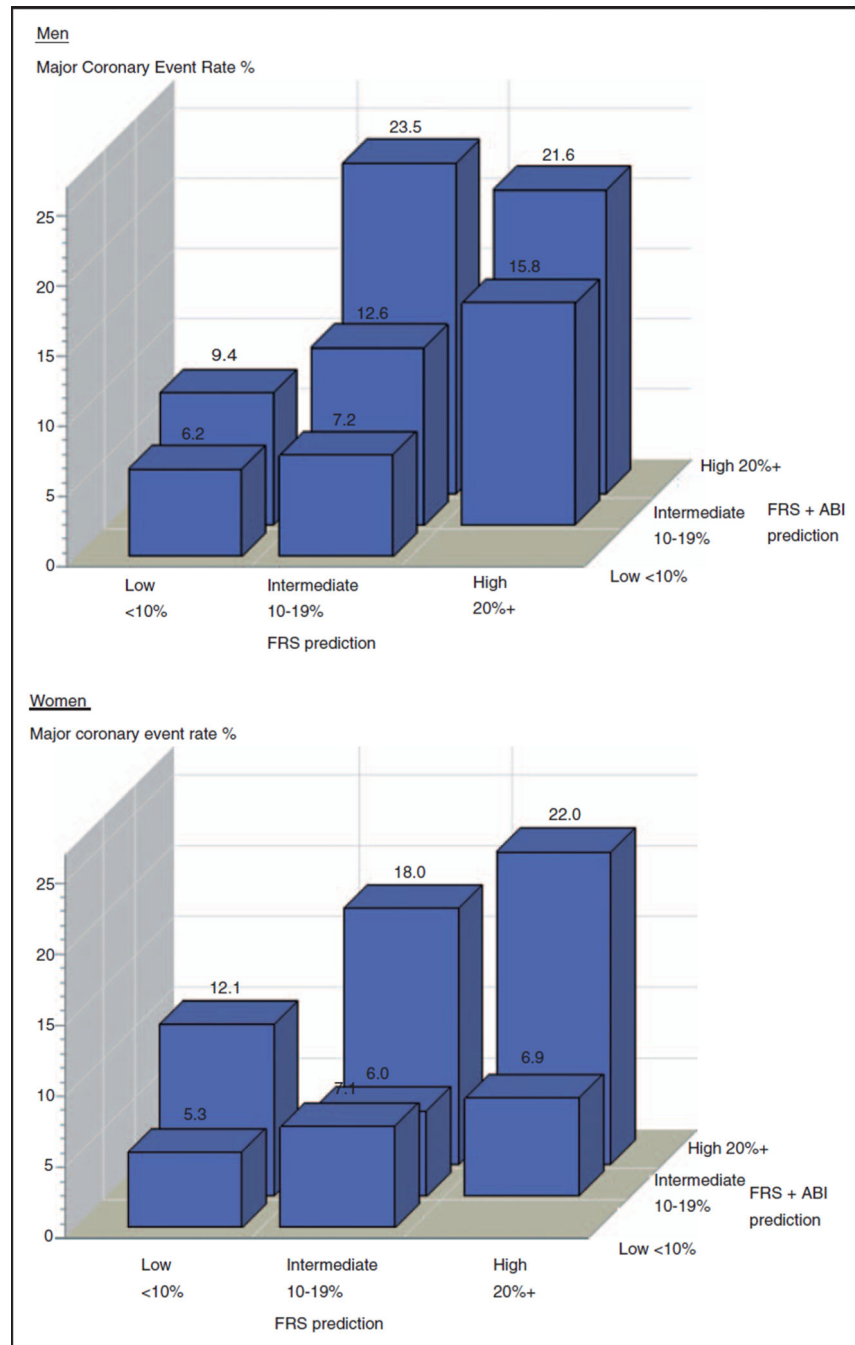


Figure 1. Kaplan–Meier 10-year rates in men and women for major coronary events in risk categories predicted by the Framingham risk score with ankle brachial index and the Framingham risk score

Major coronary events are myocardial infarction and death due to coronary heart disease. Kaplan–Meier rates, derived from external validation dataset, are sometimes estimated from small numbers of events and may be imprecise. FRS, Framingham risk score; ABI, ankle brachial index.

Table 1
Participants and characteristics of studies in the development/internal validation and external validation datasets for men and women

	Study sample	Location	Age (range years)	Follow up (median, IQR) (years)	Cardiovascular deaths	Major coronary events	Study start
Men							
Development/internal validation studies							
Belgian Physical Fitness Study ¹³	2020	EU	40–57	10.0 (10.0–10.0)	22	32	1976
Edinburgh Artery Study ⁹	690	EU	55–76	15.5 (9.0–15.9)	84	113	1987
MONICA Augsburg Survey ²¹	654	EU	25–74	12.8 (12.6–12.9)	54	51	1989
InCHIANTI Study ¹⁷	507	EU	23–94	6.0 (5.9–6.1)	34	–	1998
Hoom Study ¹⁶	271	EU	51–77	12.5 (9.8–13.1)	27	–	1989
ARIC Study ⁵	4748	USA	45–64	13.2 (12.4–13.9)	111	452	1987
Cardiovascular Health Study ⁶	1555	USA	65–96	11.2 (7.4–11.6)	223	363	1989
San Luis Valley Diabetes Study ¹⁹	675	USA	24–74	15.6 (14.4–16.9)	53	98	1984
Health ABC Study ²²	663	USA	68–80	9.1 (8.5–9.4)	43	74	1997
San Diego Study ¹⁸	243	USA	41–81	16.6 (10.3–22.3)	77	80	1978
All studies	12,026				728	1263	
External validation studies							
Limburg PAOD Study ¹⁰	1037	EU	41–78	7.1 (6.6–7.7)	35	83	1987
Men Born in 1914 Study ¹¹	392	EU	68–69	13.2 (8.1–13.9)	85	92	1982
Health in Men Study ¹⁵	3217	Australia	65–83	6.3 (6.0–6.6)	142	–	1997
Mr OS Study ²⁴	4167	USA	64–100	6.9 (6.4–7.4)	215	–	2003
Framingham Offspring Study ¹⁴	1423	USA	29–86	7.4 (6.6–8.2)	20	56	1995
Rotterdam Study ¹²	2113	EU	55–98	10.9 (8.3–11.9)	216	230	1990
All studies	12,349				713	461	
Women							
Development/internal validation studies							
Edinburgh Artery Study ⁹	702	EU	54–75	15.8 (14.2–16.1)	41	57	1987
MONICA Augsburg Survey ²¹	629	EU	25–74	12.8 (12.7–12.9)	20	13	1989
Hoom Study ¹⁶	286	EU	50–76	12.6 (10.5–13.2)	25	–	1989

	Study sample	Location	Age (range years)	Follow up (median, IQR) years	Cardiovascular deaths	Major coronary events	Study start
InCHIANTI Study ¹⁷	654	EU	21–95	6.1 (5.9–6.2)	34	–	1998
San Diego Study ¹⁸	313	USA	38–81	19.6 (13.0–22.6)	76	65	1978
San Luis Valley Diabetes Study ¹⁹	838	USA	21–71	15.8 (14.6–17.1)	56	70	1984
ARIC Study ⁵	5719	USA	45–64	13.2 (12.5–14.0)	73	235	1987
Cardiovascular Health Study ⁶	2322	USA	64–100	11.3 (10.0–11.7)	224	302	1989
Women's Health and Ageing Study ²⁰	476	USA	65–101	5.0 (3.8–5.1)	63	115	1992
Health ABC Study ²³	742	USA	68–80	9.2 (8.8–9.4)	41	52	1997
All studies	12,681				653	909	
External validation studies							
Limburg PAOD Study ¹⁰	1324	EU	40–78	7.1 (6.7–7.6)	27	54	1987
Study of Osteoporotic Fractures ²³	1233	USA	65–89	17.1 (11.5–20.4)	244	–	1986
Framingham Offspring Study ¹⁴	1703	USA	29–86	7.4 (6.6–8.3)	5	24	1995
Rotterdam Study ¹²	3436	EU	55–106	11.1 (9.6–12.2)	334	239	1990
All studies	7696				610	317	

Subjects in each of the development/internal validation studies were allocated randomly to either the development or internal validation datasets. –, not available.

Table 2

C-indices for Framingham risk score predictions of major coronary events and cardiovascular mortality in men and women with and without the ankle brachial index for the development and internal and external validation datasets

Prediction model	Development	Internal validation	External validation
Major coronary events			
Men	(n = 5632)	(n = 5638)	(n = 4962)
FRS alone	0.715 (0.655–0.768)	0.721 (0.664–0.722)	0.672 (0.599–0.737)
FRS+ABI	0.721 (0.661–0.773)	0.721 (0.664–0.722)	0.685 (0.612–0.749)
Women	(n = 5869)	(n = 5872)	(n = 6459)
FRS alone	0.661 (0.587–0.728)	0.676 (0.599–0.745)	0.578 (0.492–0.661)
FRS+ABI	0.681 (0.607–0.746)	0.710 (0.633–0.775)	0.690 (0.605–0.764)
Cardiovascular mortality			
Men	(n = 6010)	(n = 6016)	(n = 12,349)
FRS alone	0.809 (0.737–0.865)	0.794 (0.719–0.852)	0.684 (0.625–0.738)
FRS+ABI	0.817 (0.746–0.872)	0.797 (0.723–0.855)	0.710 (0.652–0.762)
Women	(n = 6339)	(n = 6342)	(n = 7696)
FRS alone	0.568 (0.484–0.647)	0.604 (0.514–0.688)	0.449 (0.377–0.523)
FRS+ABI	0.667 (0.585–0.740)	0.689 (0.600–0.765)	0.652 (0.579–0.719)

Values are C-index (95% CI); The number of subjects in major coronary events data sets are lower than in cardiovascular mortality datasets because of nonfatal events not ascertained in four studies in men (Health in Men, Mr Os, Hoorn, INCHIANTI) and three studies in women (Hoorn, InCHIANTI, Study of Osteoporotic Fractures); ABI, ankle brachial index; cardiovascular mortality, death due to coronary heart disease or stroke; FRS, Framingham risk score; major coronary event, myocardial infarction or death due to coronary heart disease.

Reclassification in predicting major coronary events and cardiovascular mortality for the Framingham risk score with ankle brachial index compared to Framingham risk score alone in men and women

Table 3

	<u>Persons having event</u>		<u>Persons not having event</u>		NRI	p-value
	Up	Down	Up	Down		
Major coronary events						
Men	9.1	6.7	6.8	8.3	4.3 (0.0–7.6)	0.050
Women	18.9	2.5	8.0	2.9	9.6 (6.1–16.4)	<0.001
Cardiovascular mortality						
Men	5.3	6.2	4.5	10.6	5.7 (2.7–7.9)	<0.001
Women	19.2	10.7	6.2	13.4	15.7 (11.3–20.2) ^a	<0.001

Values are % (95% CI). Results derived from external validation dataset. Data for primary outcome of major coronary events shown in Supplementary Tables 3 and 4. Reclassification up and down shows the percentage of persons in whom the 10-year risk category increased or decreased, respectively, between < 10%, 10–19%, and 20% for major coronary events and <2%, 2–4%, and 5% for cardiovascular mortality

^aBased on crude event rates and not survival method because lack of subjects in low risk group did not permit accurate estimation; Cardiovascular mortality, death due to coronary heart disease or stroke; major coronary event, myocardial infarction or death due to coronary heart disease; NRI, net reclassification improvement: $NRI = \{P(event|up) - P(event)\} * P(up) + \{P(event|down) - P(event)\} * P(down) / \{P(event) * (1 - P(event))\}$, with $P(event)$, $P(event|up)$, and $P(event|down)$ all estimated using the Kaplan–Meier approach.

Table 4

Reclassification in predicting major coronary events and cardiovascular mortality for the Framingham risk score with ankle brachial index compared to Framingham risk score alone in men and women at intermediate risk

	<u>Persons having event</u>		<u>Persons not having event</u>		NRI	p-value
	Up	Down	Up	Down		
Major coronary events						
Men	14.7	8.9	8.1	15.7	15.9 (6.1–20.6)	<0.001
Women	38.9	13.9	13.2	26.4	23.3 (13.8–62.5)	0.002
Cardiovascular mortality						
Men	24.7	4.1	9.1	8.8	20.2 (11.5–29.1)	<0.001
Women	26.5	0.0	8.5	0.0	18.0 (13.1–22.9) ^a	<0.001

Values are % (95% CI). Results derived from external validation dataset. Data for primary outcome of major coronary events shown in Supplementary Tables 3 and 4. Study subjects are only those in FRS 10-year intermediate risk categories of 10–19% for major coronary events and 2–4% for cardiovascular mortality. Reclassification up and down shows the percentage of persons in whom 10-year risk either increased above or decreased below intermediate risk category, respectively

^aBased on crude event rates and not survival method because probability estimates not feasible when no person reclassified down; Cardiovascular mortality, death due to coronary heart disease or stroke; major coronary event, myocardial infarction or death due to coronary heart disease; NRI, net reclassification improvement: $NRI = \{ (P(event|up) - P(event)) * P(up) + (P(event|down) - P(event)) * P(down) \} / (P(event) * (1 - P(event)))$, with $P(event)$, $P(event|up)$, and $P(event|down)$ all estimated using the Kaplan–Meier approach.