Ankle brachial index combined with Framingham risk score to predict cardiovascular events and mortality - A meta-analysis

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Ankle Brachial Index Combined With Framingham Risk Score to Predict Cardiovascular Events and Mortality

A Meta-analysis

Ankle Brachial Index Collaboration

Context Prediction models to identify healthy individuals at high risk of cardiovascular disease have limited accuracy. A low ankle brachial index (ABI) is an indicator of atherosclerosis and has the potential to improve prediction.

Objective To determine if the ABI provides information on the risk of cardiovascular events and mortality independently of the Framingham risk score (FRS) and can improve risk prediction.

Data Sources Relevant studies were identified. A search of MEDLINE (1950 to February 2008) and EMBASE (1980 to February 2008) was conducted using common text words for the term *ankle brachial index* combined with text words and Medical Subject Headings to capture prospective cohort designs. Review of reference lists and conference proceedings, and correspondence with experts was conducted to identify additional published and unpublished studies.

Study Selection Studies were included if participants were derived from a general population, ABI was measured at baseline, and individuals were followed up to detect total and cardiovascular mortality.

Data Extraction Prespecified data on individuals in each selected study were extracted into a combined data set and an individual participant data meta-analysis was conducted on individuals who had no previous history of coronary heart disease.

Results Sixteen population cohort studies fulfilling the inclusion criteria were included. During 480 325 person-years of follow-up of 24 955 men and 23 339 women, the risk of death by ABI had a reverse J-shaped distribution with a normal (low risk) ABI of 1.11 to 1.40. The 10-year cardiovascular mortality in men with a low ABI (≤0.90) was 18.7% (95% confidence interval [CI], 13.3%-24.1%) and with normal ABI (1.11-1.40) was 4.4% (95% CI, 3.2%-5.7%) (hazard ratio [HR], 4.2; 95% CI, 3.3-5.4). Corresponding mortalities in women were 12.6% (95% CI, 6.2%-19.0%) and 4.1% (95% CI, 2.2%-6.1%) (HR, 3.5; 95% CI, 2.4-5.1). The HRs remained elevated after adjusting for FRS (2.9 [95% CI, 2.3-3.7] for men vs 3.0 [95% CI, 2.0-4.4] for women). A low ABI (≤0.90) was associated with approximately twice the 10-year total mortality, cardiovascular mortality, and major coronary event rate compared with the overall rate in each FRS category. Inclusion of the ABI in cardiovascular risk stratification using the FRS would result in reclassification of the risk category and modification of treatment recommendations in approximately 19% of men and 36% of women.

Conclusion Measurement of the ABI may improve the accuracy of cardiovascular risk prediction beyond the FRS.

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MAJOR CARDIOVASCULAR and cerebrovascular events including myocardial infarction and stroke often occur in individuals without known preexisting cardiovascular disease. The prevention of such events, including the accurate identification of those at risk,[1] remains a serious public health challenge. Scoring equations to predict those at increased risk have been developed using cardiovascular risk factors, including cigarette smoking, blood pressure, total and high-density lipoprotein cholesterol, and diabetes mellitus. The Framingham risk score (FRS)[2,3] is often considered the reference standard but has limited accuracy, tending to overestimate risk in low-risk populations and underestimate risk in high-risk populations.[4] The incorporation of other risk markers, such as the metabolic syndrome[5] and plasma C-reactive protein,[6,7] has had partial success in improving prediction, and attention also is being given to indicators of asymptomatic atherosclerosis, such as coronary artery calcium, carotid intima media thickness, and the ankle brachial index (ABI).[1]

The ABI, which is the ratio of systolic pressure at the ankle to that in the arm, is quick and easy to measure and

CME available online at www.jamaarchivescme.com and questions on p 225.

A complete list of the investigators participating in the Ankle Brachial Index Collaboration appears at the end of this article.
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has been used for many years in vascular practice to confirm the diagnosis and assess the severity of peripheral artery disease in the legs. Most commonly the ABI is calculated by measuring the systolic blood pressure in the posterior tibial and/or the dorsalis pedis arteries either in both legs or 1 leg chosen at random (using a Doppler probe or alternative pulse sensor), with the lowest ankle pressure then divided by the brachial systolic blood pressure. In addition to peripheral artery disease, the ABI also is an indicator of generalized atherosclerosis because lower levels have been associated with higher rates of concomitant coronary and cerebrovascular disease, and with the presence of cardiovascular risk factors.[8] In population cohort studies in the United States[9-12] and Europe,[13-17] a low ABI has been related to an increased incidence of mortality (total and cardiovascular), myocardial infarction, and stroke. These increased relative risks have been shown to be independent of baseline cardiovascular disease and risk factors, suggesting that the ABI might have an independent role in predicting cardiovascular events.

The objective of our study was to determine if the ABI provides information on the risk of cardiovascular events and mortality independently of the FRS and can improve risk prediction. To enhance the representativeness of our study and to maximize participant numbers, we formed the Ankle Brachial Index Collaboration with the intent of including all major observational studies that had investigated longitudinally the ABI and incidence of cardiovascular events and mortality in general populations. At the same time we wished to identify a normal (low risk) level of the ABI that could be used in future studies and in clinical practice.

METHODS

The study design was an individual participant data meta-analysis of population-based cohort studies. The criteria for study inclusion were that the study contained participants of any age and sex derived from a general population (ie, not a specific disease group), ABI was measured at baseline using a technique standardized in each study, and individuals were followed up systematically to detect total and cardiovascular mortality.

At initial meetings of epidemiologists interested in the ABI, studies fulfilling the inclusion criteria were identified. A search was conducted of MEDLINE from 1950 to February 2008 and EMBASE from 1980 to February 2008. Reference lists and conference proceedings also were searched to identify possible additional studies. The following search terms were used: *ABPI.tw, ABI.tw, AAI.tw, ankle brachial pressure index $.tw, ankle brachial pressure$.tw, ankle brachial index$.tw. (or ankle brachial index/), ankle arm index$.tw, ankle arm blood pressure$.tw, ankle arm blood pressure index$.tw, ankle blood pressure$.tw, follow up stud$.tw, follow up studies/ or follow up/, epidemiological stud$.tw, epidemiological studies/ or epidemiology/, cohort$.tw, cohort analysis/ or cohort studies/.*

Further studies and unpublished data were sought by discussion between collaborators, cardiovascular epidemiologists, and vascular physicians and by correspondence with the Asia Pacific Cohort Studies Collaboration. Possible studies for inclusion were independently assessed for suitability by 2 collaborators (G.F. and J.P.) and any lack of clarity or disagreement was resolved by discussion.

The principal authors or lead investigators of studies were invited to join the ABI Collaboration and, following acceptance, were sent a questionnaire enquiring about the availability of specific study data. On reviewing responses to these questionnaires, a set of data that were commonly available was agreed on, and each study transferred their relevant data to the coordinating center.

Requested data included individual demographic characteristics (eg, sex, age, height, and weight), baseline clinical cofactors (eg, systolic and diastolic blood pressure, cholesterol, diabetes, and cigarette smoking), details of baseline ABI measurements, and information on nonfatal and fatal events during follow-up. For these analyses, the participants included had no previous history of coronary heart disease (CHD) as defined in each study, a value for ABI recorded at baseline, and follow-up dates or times to events. Data from collaborators were extracted and analyzed using SPSS version 14 (SPSS Inc, Chicago, Illinois) and SAS version 9.1 (SAS Institute Inc, Cary, North Carolina).

A FRS was derived for each individual using the sex-specific prediction formulas proposed by Wilson et al[3] based on conventional cardiovascular risk factors (age, total and high-density lipoprotein cholesterol categories, blood pressure categories, diabetes, and smoking status). When data on some of the variables necessary to calculate the FRS were incomplete, missing values, amounting to 3.9% of total values, were imputed using the expectation-maximization procedure for multivariate normal data, which is implemented in SPSS.

Overall (all studies combined) hazard ratios (HRs) for ABI, subdivided into 10 categories compared with a reference range of 1.11 to 1.20, were obtained for men and women for each of 3 outcomes of total mortality, cardiovascular mortality, and major coronary events (ie, coronary death, nonfatal myocardial infarction), and patterns of risk examined. Coronary revascularization and angina were not included as end points. The HRs for low vs normal ABI, which was categorized into 4 groups for the 3 outcomes of total mortality, cardiovascular mortality, and major coronary events were obtained from a proportional hazards model stratified by sex and study, both unadjusted and adjusted for FRS (categorized into 5 strata for men and 4 for women). These HRs were then pooled using a random-effects model and summarized using forest plots (Review Manager version 4.2.9, Cochrane Collaboration, Oxford, England).

Kaplan-Meier estimates and standard errors for outcome rates (total mortality, cardiovascular mortality, and major coronary events) at 10 years were obtained for each study stratified by sex and categories for FRS and ABI. Out-

come rates for studies within strata were combined to provide overall summaries using random-effects pooling.[18] Area under receiver operating characteristic curves were calculated for the prediction of events using the FRS alone and with the addition of the ABI.

RESULTS

The literature search and information from experts identified 1075 citations from which 20 studies that fulfilled the inclusion criteria were identified (FIGURE 1). Selected investigators from 16 of these studies[9-17,19-25] agreed to participate in the ABI Collaboration and provided data prior to the analysis. The participating studies and investigators are listed at the end of this article. The studies were based in Australia, Belgium, Italy, Netherlands, Sweden, the United Kingdom, and the United States and comprised predominantly white populations except for the Honolulu Heart Program (Japanese Americans)[11] and the Strong Heart Study (American Indians).[12] The populations in the Cardiovascular Health Study[10] and the Atherosclerosis Risk in Communities Study[9] comprised 15% and 26% blacks, respectively. In the San Luis Valley Diabetes Study,[24] the included healthy population without diabetes was 42% Hispanic. Eleven studies included both sexes, 4 included only men, and 1 included only women.

The characteristics of the participants in the studies at baseline when the ABI was measured are shown in TABLE 1. A total of 24 955 men and 23 339 women without a history of CHD were included. They were late middle aged to elderly with a mean age in the studies ranging from 47 to 78 years. The 10-year mean (SD) incidence of CHD predicted by the FRS at baseline varied across studies from 11.0% (6.1%) to 31.6% (14.1%) in men and from 7.1% (6.1%) to 14.5% (10.1%) in women. The mean (SD) ABI was greater than 1.00 in all studies and ranged from 1.02 (0.13) to 1.21 (0.13) in men and 1.01 (0.16) to 1.15 (0.17) in women; most of the studies comprising both sexes had higher mean values in men than in women, as previously reported.[24]

TABLE 2 and TABLE 3 show the total mortality, cardiovascular mortality, and major coronary events occurring during follow-up in each of the studies for men and women, respectively. Median duration of follow-up ranged from 3 to

Figure 1. Flow Diagram of Selection of Studies for Inclusion in Meta-analysis

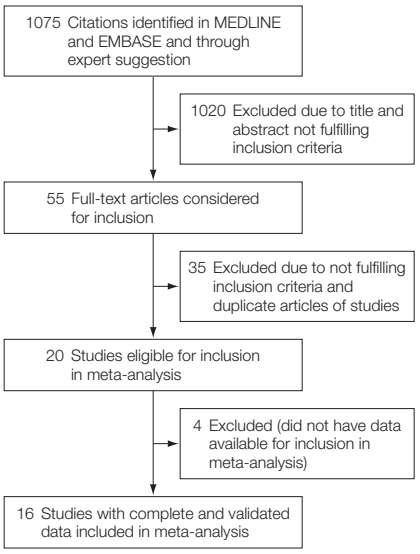


Table 1. Baseline Characteristics of Individuals in Studies in the Ankle Brachial Index (ABI) Collaboration

Source	Study	No. of Individuals[a]		Mean (SD)				
					FRS, %[b]		ABI	
		Men (n = 24 955)	Women (n = 23 339)	Age, y	Men	Women	Men	Women
Weatherley et al,[9] 2007	ARIC	6105	8004	54 (5.7)	12.8 (7.6)	7.3 (6.0)	1.17 (0.13)	1.12 (0.13)
Kornitzer et al,[17] 1995	Belgian Physical Fitness	2068	0	47 (4.4)	11.0 (6.1)	NA	1.21 (0.13)	NA
Newman et al,[10] 1999	Cardiovascular Health	1846	2779	73 (5.5)	25.4 (12.5)	8.0 (5.3)	1.10 (0.19)	1.06 (0.15)
Leng et al,[13] 1996	Edinburgh Artery	690	702	64 (5.7)	26.2 (13.0)	11.5 (6.2)	1.07 (0.19)	1.01 (0.16)
Murabito et al,[19] 2002	Framingham Offspring	1423	1703	58 (9.6)	15.3 (10.3)	7.5 (5.9)	1.16 (0.12)	1.10 (0.10)
Fowler et al,[20] 2002	Health in Men	2771	0	72 (4.4)	29.4 (9.6)	NA	1.07 (0.17)	NA
Abbott et al,[11] 2000	Honolulu Heart Program	3123	0	78 (4.6)	31.6 (14.1)	NA	1.05 (0.17)	NA
Jager et al,[21] 1999	Hoorn	270	284	63 (7.2)	26.8 (13.9)	14.5 (10.1)	1.03 (0.14)	1.02 (0.12)
McDermott et al,[22] 2004	InCHIANTI	481	569	67 (15.5)	24.8 (15.4)	8.0 (5.8)	1.04 (0.16)	1.05 (0.14)
Hooi et al,[14] 2004	Limburg PAOD	1031	1320	57 (9.4)	20.2 (10.6)	11.7 (5.8)	1.08 (0.16)	1.07 (0.13)
Ogren et al,[15] 1993	Men Born in 1914	391	0	69 (0.5)	31.5 (10.5)	NA	1.02 (0.13)	NA
Van der Meer et al,[16] 2004	Rotterdam	2134	3515	69 (9.2)	29.6 (15.6)	10.2 (7.2)	1.10 (0.21)	1.05 (0.21)
Criqui et al,[23] 1992	San Diego	244	314	66 (10.4)	21.6 (12.9)	7.8 (5.1)	1.08 (0.19)	1.02 (0.12)
Hiatt et al,[24] 1995	San Luis Valley Diabetes	674	838	53 (12.1)	15.6 (12.0)	9.1 (9.4)	1.16 (0.15)	1.10 (0.14)
Resnick et al,[12] 2004	Strong Heart	1704	2622	56 (8.0)	15.5 (9.6)	10.8 (7.3)	1.15 (0.14)	1.15 (0.17)
McDermott et al,[25] 2000	Women's Health and Aging	0	689	78 (8.1)	NA	7.1 (6.1)	NA	1.05 (0.21)

Abbreviations: ARIC, Atherosclerosis Risk in Communities; FRS, Framingham risk score; InCHIANTI, Invecchiare in Chianti; NA, not applicable; PAOD, peripheral arterial occlusive disease.
[a] No history of coronary heart disease (including myocardial infarction, angina, and revascularization as defined in each study), ABI available at baseline, and follow-up data available.
[b] Predicted percentage at 10 years for incidence of coronary heart disease, including coronary death, myocardial infarction, and angina.

16.7 years, with 9 of the 16 studies having more than 10 years of follow-up. Overall, 9924 deaths occurred during 480 325 person-years of follow-up with around one-quarter of deaths due to CHD or stroke in both men and women. The annual rates of deaths and events varied considerably between the studies. For example, men in the Belgian Physical Fitness Study had a mean (SD) age of 47 (4.4) years and the annual mortality was 0.37% (95% confidence interval [CI], 0.29%-0.45%), whereas men in the Honolulu Heart Program had a mean (SD) age of 78 (4.6) years and the annual mortality was 4.91% (95% CI, 4.59%-5.22%) (Table 2). Likewise, for women annual mortality varied between 0.55% (95% CI, 0.42%-0.68%) in the Framingham Offspring Study and 7.34% (95% CI, 6.39%-8.29%) in the Women's Health and Aging Study (Table 3).

The HRs for death for different levels of ABI compared with a reference ABI of 1.11 to 1.20 in all studies combined formed a reverse J-shaped curve for both men and women (FIGURE 2). For levels of ABI below 1.11, the HRs increased consistently with decreasing ABI. For an ABI of greater than 1.40, the HRs also were increased in men (1.38; 95% CI, 1.17-1.62) and in women (1.23; 95% CI, 1.00-1.52). For levels of ABI from 1.11 to 1.40, only small and mostly nonsignificant differences in HRs were found. TABLE 4 and TABLE 5 show the HRs for total and cardiovascular mortality and major coronary events by ABI in men and women, respectively. The patterns of risk for cardiovascular mortality and major coronary events were similar to that for total mortality; for levels of ABI below 1.11, the HRs for cardiovascular mortality were consistently higher than for total mortality.

Values of the ABI less than 0.90 have been taken traditionally as a measure of increased risk. In nearly all the studies in men (FIGURE 3), the HRs for total mortality were statistically significantly higher in individuals with an ABI of 0.90 or less compared with individuals with normal ABI values of 1.11 to 1.40 (HR, 3.33; 95% CI, 2.74-4.06). In women, the results were more heterogeneous (FIGURE 4), but the HR of 2.71 (95% CI, 2.03-3.62) was comparable

Table 2. Total Mortality, Cardiovascular Mortality, and Major Coronary Events for Men in Studies in the Ankle Brachial Index Collaboration

		Total Mortality			Cardiovascular Mortality[a]			Major Coronary Events[b]		
Study	Follow-up, Median (IQR), y	Person-Years of Follow-up (n = 233 457)	No. of Deaths (n = 5582)	Annual Mortality, % (95% CI)	Person-Years of Follow-up (n = 233 457)	No. of Deaths (n = 1507)	Annual Mortality, % (95% CI)	Person-Years of Follow-up (n = 205 628)	No. of Events (n = 2255)	Annual Events, % (95% CI)
ARIC[9]	13.1 (12.4-13.9)	76 497	903	1.18 (1.10-1.26)	76 497	170	0.22 (0.19-0.26)	73 991	571	0.77 (0.71-0.83)
Belgian Physical Fitness[17]	10.9 (10.5-11.4)	22 292	83	0.37 (0.29-0.45)	22 292	13	0.06 (0.03-0.09)	22 136	98	0.44 (0.36-0.53)
Cardiovascular Health[10]	11.0 (7.2-11.6)	16 583	839	5.06 (4.73-5.39)	16 583	263	1.59 (1.40-1.78)	15 542	432	2.78 (2.52-3.04)
Edinburgh Artery[13]	15.5 (9.0-15.9)	8667	295	3.40 (3.02-3.79)	8667	84	0.97 (0.76-1.18)	8090	113	1.40 (1.14-1.65)
Framingham Offspring[19]	7.4 (6.6-8.2)	10 182	113	1.11 (0.91-1.31)	10 182	20	0.20 (0.11-0.28)	10 052	56	0.56 (0.41-0.70)
Health in Men[20]	6.3 (5.9-6.5)	16 446	402	2.44 (2.21-2.68)	16 446	114	0.69 (0.57-0.82)	NA	NA	NA
Honolulu Heart Program[11]	6.2 (5.5-6.9)	17 976	882	4.91 (4.59-5.22)	17 976	231	1.29 (1.12-1.45)	17 703	205	1.16 (1.00-1.32)
Hoorn[21]	12.5 (9.8-13.1)	2969	88	2.96 (2.35-3.57)	2969	26	0.88 (0.54-1.21)	NA	NA	NA
InCHIANTI[22]	3.0 (2.9-3.1)	1427	30	2.10 (1.36-2.85)	1427	11	0.77 (0.32-1.22)	NA	NA	NA
Limburg PAOD[14]	7.1 (6.6-7.7)	7088	148	2.09 (1.76-2.42)	7088	34	0.48 (0.32-0.64)	6864	82	1.19 (0.94-1.45)
Men Born in 1914[15]	13.3 (8.1-13.9)	4248	182	4.28 (3.68-4.89)	4248	70	1.65 (1.26-2.03)	4028	92	2.28 (1.82-2.75)
Rotterdam[16]	10.9 (8.2-11.8)	20 538	813	3.96 (3.70-4.23)	20 538	221	1.08 (0.94-1.23)	19 805	260	1.31 (1.15-1.47)
San Diego[23]	16.7 (10.4-22.3)	3843	156	4.06 (3.44-4.68)	3843	77	2.00 (1.56-2.45)	3581	80	2.23 (1.75-2.72)
San Luis Valley Diabetes[24]	15.6 (14.4-16.9)	9765	167	1.71 (1.45-1.97)	9765	51	0.52 (0.38-0.67)	9265	82	0.89 (0.69-1.08)
Strong Heart[12]	9.7 (8.9-10.4)	14 935	481	3.22 (2.94-3.50)	14 935	122	0.82 (0.67-0.96)	14 573	184	1.27 (1.09-1.46)

Abbreviations: ARIC, Atherosclerosis Risk in Communities; CI, confidence interval; InCHIANTI, Invecchiare in Chianti; IQR, interquartile range; NA, data not available; PAOD, peripheral arterial occlusive disease.
[a] Defined as death due to coronary heart disease or stroke.
[b] Defined as myocardial infarction or deaths from coronary heart disease.

Table 3. Total Mortality, Cardiovascular Mortality, and Major Coronary Events for Women in Studies in the Ankle Brachial Index Collaboration

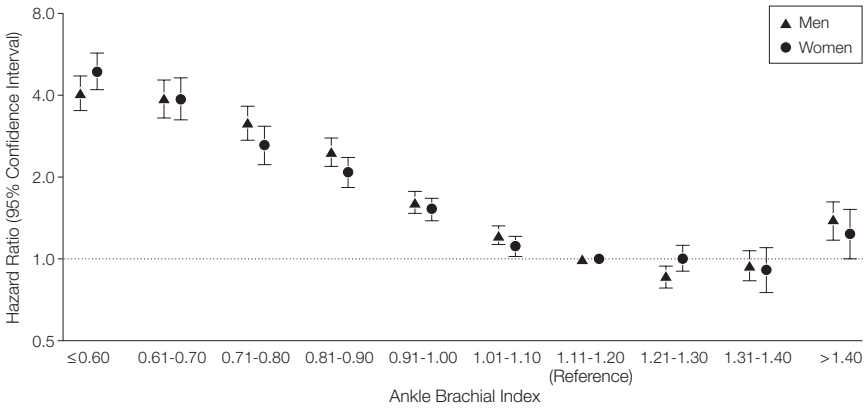
		Total Mortality			Cardiovascular Mortality[a]			Major Coronary Events[b]		
Study	Follow-up, Median (IQR), y	Person-Years of Follow-up (n = 246 868)	No. of Deaths (n = 4342)	Annual Mortality, % (95% CI)	Person-Years of Follow-up (n = 246 868)	No. of Deaths (n = 1211)	Annual Mortality, % (95% CI)	Person-Years of Follow-up (n = 238 066)	No. of Events (n = 1629)	Annual Events, % (95% CI)
ARIC[9]	13.2 (12.4-13.9)	102 458	773	0.75 (0.70-0.81)	102 458	133	0.13 (0.11-0.15)	101 121	362	0.36 (0.32-0.39)
Cardiovascular Health[10]	11.2 (8.3-11.6)	27 447	851	3.10 (2.90-3.31)	27 447	262	0.95 (0.84-1.07)	26 652	374	1.40 (1.26-1.54)
Edinburgh Artery[13]	15.8 (14.2-16.1)	9836	200	2.03 (1.75-2.31)	9836	41	0.42 (0.29-0.54)	9602	57	0.59 (0.44-0.75)
Framingham Offspring[19]	7.4 (6.6-8.3)	12 344	68	0.55 (0.42-0.68)	12 344	5	0.04 (0.01-0.08)	12 272	24	0.20 (0.12-0.27)
Hoorn[21]	12.6 (10.6-13.2)	3212	76	2.37 (1.84-2.89)	3212	23	0.72 (0.42-1.01)	NA	NA	NA
InCHIANTI[22]	3.0 (2.9-3.2)	1711	26	1.52 (0.94-2.10)	1711	12	0.70 (0.31-1.10)	NA	NA	NA
Limburg PAOD[14]	7.1 (6.7-7.6)	9273	114	1.23 (1.01-1.45)	9273	26	0.28 (0.17-0.39)	9168	53	0.58 (0.42-0.73)
Rotterdam[16]	11.1 (9.3-12.1)	35 407	1131	3.19 (3.01-3.38)	35 407	352	0.99 (0.89-1.10)	34 968	283	0.81 (0.72-0.90)
San Diego[23]	19.6 (13.0-22.6)	5443	177	3.25 (2.78-3.72)	5443	76	1.40 (1.08-1.71)	5361	65	1.21 (0.92-1.51)
San Luis Valley Diabetes[24]	15.8 (14.6-17.1)	12 542	163	1.30 (1.10-1.50)	12 542	53	0.42 (0.31-0.54)	12 293	58	0.47 (0.35-0.59)
Strong Heart[12]	9.9 (9.1-10.7)	24 305	551	2.27 (2.08-2.45)	24 305	137	0.56 (0.47-0.66)	24 010	183	0.76 (0.65-0.87)
Women's Health and Aging[25]	5.0 (3.8-5.1)	2890	212	7.34 (6.39-8.29)	2890	91	3.15 (2.51-3.79)	2620	170	6.49 (5.55-7.43)

Abbreviations: ARIC, Atherosclerosis Risk in Communities; CI, confidence interval; InCHIANTI, Invecchiare in Chianti; IQR, interquartile range; NA, data not available; PAOD, peripheral arterial occlusive disease.
[a] Defined as death due to coronary heart disease or stroke.
[b] Defined as myocardial infarction or deaths from coronary heart disease.

with that in men. Likewise, significantly increased HRs were found in men and in women both for cardiovascular mortality (men: 4.21 [95% CI, 3.29-5.39]; women: 3.46 [95% CI, 2.36-5.08]), and for major coronary events (men: 2.97 [95% CI, 2.33-3.78]; women: 3.05 [95% CI, 2.25-4.15]). Adjustment of the HRs for individuals with an ABI of 0.90 or less relative to an ABI of 1.11 to 1.40 for FRS reduced the HRs but they were still elevated substantially and significantly. The adjusted HRs for total mortality were 2.34 (95% CI, 1.97-2.78) in men vs 2.35 (95% CI, 1.76-3.13) in women; cardiovascular mortality, 2.92 (95% CI, 2.31-3.70) in men vs 2.97 (95% CI, 2.02-4.35) in women; and major coronary events, 2.16 (95% CI, 1.76-2.66) in men vs 2.49 (95% CI, 1.84-3.36) in women.

TABLE 6 and TABLE 7 show the effect of inclusion of an ABI measurement on the apparent risk of 10-year total mortality, cardiovascular mortality, and major coronary events over the range of FRS categories in men and women, respectively. Compared with the overall rates without ABI included, an ABI of 0.90 or less was associated with a greatly increased risk of mortality (total and cardiovascular) and major coronary events across all FRS categories in both men and women, but more so in the

Figure 2. Hazard Ratios for Total Mortality in Men and Women by Ankle Brachial Index at Baseline for All Studies Combined in the ABI Collaboration



Hazard ratios are not adjusted for age or cardiovascular risk factors.

lower than in the higher FRS categories. Women had especially high mortality and event rates in the lowest FRS category. Men and women with an ABI from 0.91 to 1.10 also had higher mortality and event rates compared with those with a normal ABI (1.11-1.40) but the magnitudes of the increase were much less than for those with an ABI of 0.90 or less. Those with an ABI greater than 1.40 also had higher rates across most FRS categories.

Inclusion of the ABI had an overall effect on the prediction of events, especially in women. When predicting major coronary events using only the FRS, the area under the receiver operating characteristic curve was 0.646 (95% CI, 0.643-0.657) and with the addition of the ABI was 0.655 (95% CI, 0.643-0.666) in men vs 0.605 (95% CI,

Table 4. Hazard Ratios (HRs) for Total Mortality, Cardiovascular Mortality, and Major Coronary Events by Ankle Brachial Index (ABI) at Baseline for Men in All Studies Combined in the ABI Collaboration

	ABI									
	≤0.60	0.61-0.70	0.71-0.80	0.81-0.90	0.91-1.00	1.01-1.10	1.11-1.20	1.21-1.30	1.31-1.40	>1.40
Sample size (n = 24 955)	360	279	428	774	2438	5775	7576	4936	1681	708
Total Mortality										
No. of deaths (n = 5582)	215	170	217	355	741	1338	1364	745	270	167
HR (95% CI)[a]	4.06 (3.51-4.70)	3.88 (3.30-4.55)	3.15 (2.73-3.64)	2.47 (2.19-2.78)	1.61 (1.47-1.77)	1.22 (1.13-1.32)	1 [Reference]	0.86 (0.78-0.94)	0.94 (0.83-1.07)	1.38 (1.17-1.62)
Cardiovascular Mortality[b]										
No. of deaths (n = 1507)	80	54	81	116	208	352	341	179	62	34
HR (95% CI)[a]	5.58 (4.36-7.15)	4.60 (3.44-6.14)	4.49 (3.51-5.74)	3.03 (2.45-3.75)	1.68 (1.40-2.00)	1.24 (1.07-1.44)	1 [Reference]	0.85 (0.71-1.02)	0.93 (0.71-1.22)	1.14 (0.80-1.63)
Major Coronary Events (n = 21 433)[c]										
No. of events (n = 2255)	70	48	74	119	252	516	642	353	125	56
HR (95% CI)[a]	3.45 (2.68-4.43)	2.71 (2.01-3.64)	2.76 (2.16-3.52)	2.15 (1.76-2.63)	1.43 (1.23-1.66)	1.12 (1.00-1.26)	1 [Reference]	0.78 (0.68-0.88)	0.78 (0.64-0.95)	0.90 (0.68-1.18)

Abbreviation: CI, confidence interval.
[a]The HRs are not adjusted for age or cardiovascular risk factors.
[b]Defined as death due to coronary heart disease or stroke.
[c]Defined as myocardial infarction or deaths from coronary heart disease.

Table 5. Hazard Ratios (HRs) for Total Mortality, Cardiovascular Mortality, and Major Coronary Events by Ankle Brachial Index (ABI) at Baseline for Women in All Studies Combined in the ABI Collaboration

	ABI									
	≤0.60	0.61-0.70	0.71-0.80	0.81-0.90	0.91-1.00	1.01-1.10	1.11-1.20	1.21-1.30	1.31-1.40	>1.40
Sample size (n = 23 339)	314	251	403	933	3186	6586	6862	3363	932	509
Total Mortality										
No. of deaths (n = 4342)	199	145	174	326	707	1078	999	489	125	100
HR (95% CI)[a]	4.89 (4.19-5.71)	3.88 (3.25-4.63)	2.61 (2.22-3.08)	2.08 (1.83-2.36)	1.52 (1.38-1.67)	1.11 (1.02-1.21)	1 [Reference]	1.00 (0.90-1.12)	0.91 (0.75-1.10)	1.23 (1.00-1.52)
Cardiovascular Mortality[b]										
No. of deaths (n = 1211)	79	51	66	114	218	271	241	119	24	28
HR (95% CI)[a]	7.04 (5.43-9.12)	5.06 (3.72-6.87)	3.65 (2.77-4.81)	2.77 (2.21-3.47)	1.84 (1.53-2.22)	1.14 (0.95-1.36)	1 [Reference]	1.04 (0.83-1.29)	0.74 (0.49-1.13)	1.48 (1.00-2.21)
Major Coronary Events (n = 22 486)[c]										
No. of events (n = 1629)	79	54	64	119	260	412	387	174	47	33
HR (95% CI)[a]	5.43 (4.24-6.94)	3.82 (2.86-5.11)	2.58 (1.97-3.37)	2.06 (1.67-2.53)	1.53 (1.30-1.79)	1.11 (0.97-1.28)	1 [Reference]	0.91 (0.76-1.09)	0.86 (0.64-1.17)	1.11 (0.77-1.58)

Abbreviation: CI, confidence interval.
[a]The HRs are not adjusted for age or cardiovascular risk factors.
[b]Defined as death due to coronary heart disease or stroke.
[c]Defined as myocardial infarction or deaths from coronary heart disease.

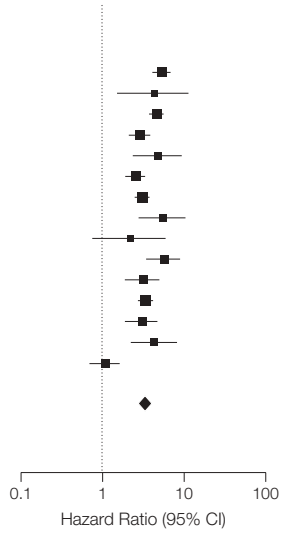
0.590-0.619) and 0.658 (95% CI, 0.644-0.672), respectively, in women.

The FRS is mostly used to predict risk of total CHD (including coronary death, myocardial infarction, and angina) and TABLE 8 shows the effect of including the ABI on this prediction. The calibration of the FRS categories was reasonable because the overall CHD rate in each FRS category was within the range predicted, except for low-risk women in which the overall CHD rate of 11% was higher than predicted. Likewise, the ability of the FRS to discriminate between risk categories was good, except that the overall CHD rate in women in the low-risk group was only slightly lower than those in the intermediate-risk group (11% vs 13%). In each category of FRS in both men and women, a low ABI (≤0.90) was associated with an increased risk of future CHD. Normal levels of the ABI (1.11-1.40) were associated with a slightly reduced risk from the overall rates but levels greater than 1.40 did not differ consistently from the overall rates, al-

Figure 3. Random Hazard Ratios for Total Mortality for Low (≤0.90) Compared With Normal (1.11-1.40) Ankle Brachial Index (ABI) in Men in Studies in the ABI Collaboration

Study	No. of Men		No. of Deaths		Hazard Ratio (95% CI)
	ABI ≤0.90	ABI, 1.11-1.40	ABI ≤0.90	ABI, 1.11-1.40	
ARIC,[9] 2007	129	4446	64	568	5.23 (4.04-6.77)
Belgian Physical Fitness,[17] 1995	25	1544	4	64	4.15 (1.52-11.37)
Cardiovascular Health,[10] 1999	220	1005	177	330	4.48 (3.72-5.39)
Edinburgh Artery,[13] 1996	94	316	69	111	2.84 (2.10-3.84)
Framingham Offspring,[19] 2002	38	1120	9	72	4.67 (2.33-9.34)
Health in Men,[20] 2002	288	1221	76	143	2.50 (1.89-3.30)
Honolulu Heart Program,[11] 2000	391	1048	204	226	3.00 (2.48-3.63)
Hoorn,[21] 1999	30	83	20	16	5.34 (2.74-10.39)
InCHIANTI,[22] 2004	53	151	7	8	2.11 (0.75-5.93)
Limburg PAOD,[14] 2004	89	459	31	36	5.50 (3.40-8.90)
Men Born in 1914,[15] 1993	46	79	35	32	3.06 (1.89-4.96)
Rotterdam,[16] 2004	318	1133	200	317	3.25 (2.72-3.88)
San Diego,[23] 1992	30	103	28	62	2.97 (1.88-4.69)
San Luis Valley Diabetes,[24] 1995	15	479	10	106	4.25 (2.22-8.13)
Strong Heart,[12] 2004	75	1006	23	288	1.06 (0.69-1.62)
Overall	1841	14 193	957	2379	3.33 (2.74-4.06)

Test for heterogeneity: $\chi^2_{14} = 64.32$; $P<.001$; $I^2 = 78.2\%$
Test for overall effect: $z = 11.98$; $P<.001$

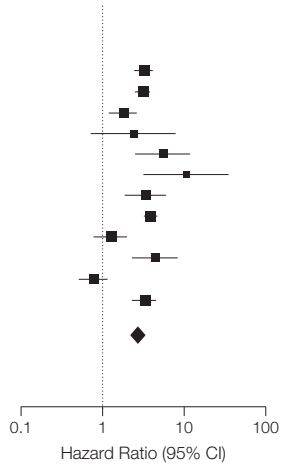


Hazard ratios are not adjusted for age or cardiovascular risk factors. Area of each square is proportional to weight of the study in the meta-analysis. ARIC indicates Atherosclerosis Risk in Communities; CI, confidence interval; InCHIANTI, Invecchiare in Chianti; PAOD, peripheral arterial occlusive disease.

Figure 4. Random Hazard Ratios for Total Mortality for Low (≤0.90) Compared With Normal (1.11-1.40) Ankle Brachial Index (ABI) in Women in Studies in the ABI Collaboration

Study	No. of Women		No. of Deaths		Hazard Ratio (95% CI)
	ABI ≤0.90	ABI, 1.11-1.40	ABI ≤0.90	ABI, 1.11-1.40	
ARIC,[9] 2007	268	4441	66	393	3.17 (2.44-4.11)
Cardiovascular Health,[10] 1999	297	1134	159	280	3.05 (2.51-3.71)
Edinburgh Artery,[13] 1996	133	192	50	46	1.77 (1.19-2.64)
Framingham Offspring,[19] 2002	46	887	3	27	2.38 (0.72-7.86)
Hoorn,[21] 1999	23	62	15	11	5.42 (2.48-11.84)
InCHIANTI,[22] 2004	37	176	8	4	10.50 (3.16-34.88)
Limburg PAOD,[14] 2004	84	486	18	33	3.34 (1.88-5.94)
Rotterdam,[16] 2004	657	1498	383	324	3.75 (3.23-4.36)
San Diego,[23] 1992	47	81	29	45	1.25 (0.78-2.00)
San Luis Valley Diabetes,[24] 1995	19	364	11	63	4.37 (2.30-8.30)
Strong Heart,[12] 2004	143	1540	24	325	0.77 (0.51-1.16)
Women's Health and Aging,[25] 2000	147	296	78	62	3.22 (2.30-4.50)
Overall	1901	11 157	844	1613	2.71 (2.03-3.62)

Test for heterogeneity: $\chi^2_{11} = 78.97$; $P<.001$; $I^2 = 86.1\%$
Test for overall effect: $z = 6.73$; $P<.001$



Hazard ratios are not adjusted for age or cardiovascular risk factors. Area of each square is proportional to weight of the study in the meta-analysis. ARIC indicates Atherosclerosis Risk in Communities; CI, confidence interval; InCHIANTI, Invecchiare in Chianti; PAOD, peripheral arterial occlusive disease.

though this may have been influenced by the relatively low numbers of participants.

The results in Table 8 also indicate in which categories of FRS the ABI is likely to change individuals' clinical risk levels (ie, between <10%, 10%-19%, and ≥20%). In men, the greatest effect would be in high-risk individuals (≥20%) with a normal ABI (1.11-1.40) in whom the risk level would be reduced to intermediate (10%-19%). All men with a low ABI (≤0.90) had a relatively high risk but their clinical risk level would not change from that predicted overall by the FRS. In women, the main effect of the ABI would be to change all women in the low FRS category (<10%) with an abnormal ABI (≤0.90 or 0.91 to 1.10 or >1.40) to a higher risk level. Also women in the intermediate FRS category (10%-19%) with a low ABI (≤0.90) would become high risk (≥20%). Table 8 also shows that the number of men changing risk category (shaded numbers) would be 4106 of 21 433 (19%) and in women would be 8154 of 22 486 women (36%).

COMMENT

Predicting future CHD and mortality accurately in individuals in the community who have no prior history of cardiovascular disease has proven difficult when based solely on traditional risk factors and scoring systems. In a recent systematic review of 27 studies using the Framingham risk equation, the predicted-to-observed ratios ranged from an underprediction of 0.43 in a high-risk population to an overprediction of 2.87 in a low-risk population.[4] We found that the ABI provided independent risk information compared with the FRS and, when combined with the FRS, a low ABI (≤0.90) approximately doubled the risk of total mortality, cardiovascular mortality, and major coronary events across all Framingham risk categories.

In predicting the 10-year risk of total CHD, our results (Table 8) indicate that approximately 1 of 5 men would have their broad category of risk (<10, 10-19, ≥20%) changed from that predicted by FRS alone to that found on inclusion of the ABI. These changes from higher to lower categories of risk would likely have an effect on decisions to commence preventive treatment, such as lipid-lowering therapy, as recommended in the Adult Treatment Panel III guidelines.[27] In contrast, the main effect in women of inclusion of the ABI would be that many at low risk with the FRS (<10%) would change to a higher risk level. In total, around 1 in 3 women would be affected. It should be recognized, however, that the proportion of men and women affected by inclusion of the ABI

Table 6. 10-Year Total Mortality, Cardiovascular Mortality, and Major Coronary Event Rates in Men by Framingham Risk Category and Ankle Brachial Index (ABI) at Baseline for All Studies Combined in the ABI Collaboration[a]

Framingham Risk Category[b]	ABI				Overall
	≤0.90	0.91-1.10	1.11-1.40	>1.40	
			Total Mortality, % (95% CI)		
1 (Lowest; n = 5746)	27.1 (16.0-38.2)	11.4 (5.9-16.8)	8.3 (5.4-11.2)	14.1 (4.2-24.0)	10.4 (6.9-13.9)
2 (n = 4319)	37.3 (17.8-56.9)	15.8 (10.6-21.0)	11.3 (8.2-14.5)	19.9 (7.5-32.4)	13.8 (9.9-17.7)
3 (n = 3544)	37.6 (26.1-49.1)	19.7 (13.6-25.9)	14.2 (9.9-18.5)	23.5 (9.5-37.6)	17.6 (13.1-22.2)
4 (n = 5814)	38.1 (28.5-47.8)	23.6 (16.9-30.4)	19.2 (14.8-23.5)	38.4 (12.3-64.6)	23.1 (17.6-28.6)
5 (Highest; n = 5532)	57.1 (45.4-68.9)	36.4 (29.1-43.7)	31.0 (25.2-36.7)	43.6 (28.1-59.1)	38.0 (30.9-45.0)
Overall (n = 24 955)	46.3 (36.1-56.6)	23.0 (15.8-30.2)	16.7 (12.4-21.0)	29.2 (18.9-39.5)	
			Cardiovascular Mortality, % (95% CI)		
1 (Lowest; n = 5746)	4.6 (0.0-10.8)	3.1 (0.0-6.5)	1.3 (0.5-2.0)	2.7 (0.0-6.8)	1.6 (0.8-2.4)
2 (n = 4319)	17.5 (6.6-28.3)	3.5 (1.5-5.5)	1.5 (0.7-2.3)	8.2 (0.0-18.8)	2.3 (1.3-3.4)
3 (n = 3544)	11.5 (2.4-20.6)	5.1 (3.1-7.2)	3.6 (1.9-5.2)	8.3 (0.3-16.2)	4.4 (2.8-6.0)
4 (n = 5814)	14.2 (10.2-18.2)	8.0 (5.2-10.8)	4.8 (3.3-6.4)	5.6 (0.0-12.2)	7.3 (5.2-9.3)
5 (Highest; n = 5532)	27.9 (20.7-35.1)	12.5 (8.9-16.1)	9.9 (6.8-13.1)	10.7 (2.0-19.4)	14.0 (10.6-17.4)
Overall (n = 24 955)	18.7 (13.3-24.1)	7.3 (5.0-9.6)	4.4 (3.2-5.7)	6.9 (2.8-11.0)	
			Major Coronary Events, % (95% CI)[c]		
1 (Lowest; n = 5643)	5.8 (0.0-12.7)	3.7 (1.4-6.0)	3.4 (2.5-4.3)	4.0 (1.1-6.8)	3.5 (2.4-4.6)
2 (n = 4151)	20.0 (9.6-30.4)	5.9 (3.6-8.1)	6.8 (5.7-8.0)	5.0 (0.7-9.3)	7.1 (5.5-8.8)
3 (n = 3241)	20.2 (8.0-32.3)	10.0 (6.2-13.8)	8.7 (6.4-11.0)	12.9 (0.0-27.8)	10.1 (7.5-12.6)
4 (n = 4179)	27.5 (18.5-36.6)	14.8 (9.9-19.7)	12.6 (9.6-15.7)	9.7 (0.0-19.7)	15.3 (11.5-19.1)
5 (Highest; n = 4219)	31.4 (21.9-40.8)	20.0 (14.4-25.5)	17.6 (12.2-23.0)	12.0 (3.6-20.3)	21.5 (16.7-26.3)
Overall (n = 21 433)	26.8 (19.5-34.1)	12.9 (9.2-16.7)	9.4 (7.4-11.4)	7.2 (4.3-10.1)	

Abbreviation: CI, confidence interval.
[a] Analysis based on random-effects pooling of Kaplan-Meier estimates from the individual studies.
[b] Categories of predicted 10-year percentage incidence of coronary heart disease, including coronary death, myocardial infarction, and angina are based on whole number cut points for scores (category 1, <10%; 2, 10%-14%; 3, 15%-19%; 4, 20%-29%; 5, ≥30%).
[c] Excludes Health in Men,[20] Hoorn,[21] and InCHIANTI[22] studies.

is approximate due to the method of estimating total CHD end points and possible residual confounding within the FRS categories.

Our results also confirm the recent findings of the Strong Heart Study,[12] Cardiovascular Health Study,[28] and Multi-ethnic Study of Atherosclerosis[29] that the relationship between ABI and cardiovascular disease is nonlinear and varies across the range of ABI. High values (>1.40) could be related to poor arterial compressibility resulting from stiffness and calcification, which may occur more commonly in those with diabetes,[29,30] and may be 1 explanation why those with an ABI greater than 1.40 are at increased risk. The differences in risk between ABI values from 1.11 to 1.40 in both men and women were so small that, for practi-

Table 7. 10-Year Total Mortality, Cardiovascular Mortality, and Major Coronary Event Rates in Women by Framingham Risk Category and Ankle Brachial Index (ABI) at Baseline for All Studies Combined in the ABI Collaboration[a]

Framingham Risk Category[b]	ABI				Overall
	≤0.90	0.91-1.10	1.11-1.40	>1.40	
			Total Mortality, % (95% CI)		
1 (Lowest; n = 5507)	44.2 (7.5-80.9)	21.3 (12.5-30.1)	14.1 (9.1-19.1)	27.4 (14.6-40.2)	18.2 (10.6-25.8)
2 (n = 6016)	28.2 (9.2-47.2)	13.3 (7.7-18.9)	10.3 (6.3-14.3)	8.1 (1.9-14.3)	12.2 (7.0-17.4)
3 (n = 5581)	27.1 (16.0-38.1)	15.2 (11.0-19.4)	10.9 (7.5-14.2)	20.6 (11.7-29.5)	15.7 (11.2-20.2)
4 (Highest; n = 6235)	31.4 (23.2-39.7)	17.6 (13.3-21.9)	16.2 (12.2-20.3)	20.9 (0.0-48.2)	19.8 (16.6-23.0)
Overall (n = 23 339)	30.1 (18.0-42.1)	16.6 (10.9-22.3)	13.1 (8.5-17.6)	26.6 (9.7-43.4)	
			Cardiovascular Mortality, % (95% CI)		
1 (Lowest; n = 5507)	45.5 (29.7-61.4)	4.5 (1.9-7.0)	4.0 (1.6-6.4)	14.1 (0.0-32.3)	4.8 (3.2-6.4)
2 (n = 6016)	15.1 (1.5-28.7)	4.1 (1.6-6.6)	2.9 (0.9-4.9)	4.3 (0.0-12.7)	3.5 (1.6-5.4)
3 (n = 5581)	9.7 (5.1-14.3)	4.4 (2.5-6.3)	3.2 (1.5-4.8)	14.7 (0.0-45.6)	4.8 (3.0-6.6)
4 (Highest; n = 6235)	15.7 (9.5-22.0)	5.1 (3.4-6.9)	5.5 (3.5-7.6)	15.5 (8.4-22.5)	6.8 (4.5-9.2)
Overall (n = 23 339)	12.6 (6.2-19.0)	4.7 (3.0-6.3)	4.1 (2.2-6.1)	6.9 (4.0-9.7)	
			Major Coronary Events, % (95% CI)[c]		
1 (Lowest; n = 5355)	29.9 (9.0-50.8)	3.9 (1.7-6.1)	5.3 (2.4-8.2)	10.7 (0.0-24.3)	5.8 (3.9-7.7)
2 (n = 5842)	16.9 (6.8-27.1)	5.1 (2.4-7.7)	3.7 (2.0-5.5)	2.1 (0.0-6.3)	4.7 (2.6-6.7)
3 (n = 5334)	15.3 (8.0-22.6)	7.5 (4.5-10.4)	5.2 (3.5-6.9)	14.1 (0.0-47.9)	6.7 (4.3-9.1)
4 (Highest; n = 5955)	23.3 (14.5-32.0)	9.8 (7.4-12.2)	9.4 (6.7-12.0)	14.9 (8.8-21.1)	11.9 (9.3-14.5)
Overall (n = 22 486)	18.9 (11.6-26.2)	7.3 (5.0-9.6)	6.1 (4.1-8.1)	5.5 (0.7-10.3)	

Abbreviation: CI, confidence interval.
[a] Analysis based on random-effects pooling of Kaplan-Meier estimates from the individual studies.
[b] Categories of predicted 10-year percentage incidence of coronary heart disease, including coronary death, myocardial infarction, and angina are based on whole number cut points for scores (category 1, ≤4%; 2, 5%-7%; 3, 8%-11%; 4, ≥12%).
[c] Excludes Hoorn[21] and InCHIANTI[22] studies.

Table 8. 10-Year Total Coronary Heart Disease (CHD) Rates in Men and Women by Framingham Risk Score (FRS) Category and Ankle Brachial Index (ABI) at Baseline for All Studies Combined in the ABI Collaboration[a]

FRS Category[b]	Total		ABI							
			≤0.90		0.91-1.10		1.11-1.40		>1.40	
	No. in FRS Category	CHD, %[c]	No. in FRS Category	CHD, %[c]	No. in FRS Category	CHD, %[c]	No. in FRS Category	CHD, %[c]	No. in FRS Category	CHD, %[c]
Men										
Low (<10%)	5643	5	76	8	1076	5	4255	4	236	5
Intermediate (10%-19%)	7392	13	245	16	2069	12	4815	12	263	8
High (≥20%)	8398	23	1149	40	3406	21	3668	18	175	14
Women										
Low (<10%)	15 505	11	1083	21	6192	10	7909	9	321	11
Intermediate (10%-19%)	5563	13	558	25	2429	12	2433	11	143	13
High (≥20%)	1418	27	200	44	598	21	577	22	43	34

[a] Excludes Health in Men,[20] Hoorn,[21] and InCHIANTI[22] studies, in which nonfatal events were not available. Shaded numbers indicate individuals who would change between low (<10%), intermediate (10%-19%), and high (≥20%) risk categories from that predicted by the FRS when ABI was included. Analysis based on random-effects pooling of Kaplan-Meier estimates from the individual studies.
[b] Categories of predicted 10-year percentage incidence of coronary heart disease, including coronary death, myocardial infarction, and angina.
[c] Includes coronary death, myocardial infarction, and angina. Rates are approximate based on observed major coronary events (coronary death or myocardial infarction) adjusted by established conversion factors.[26] The number of individuals indicates those with the specified Framingham risk category and ABI level, irrespective of whether they have coronary heart disease.

cal purposes, an ABI within this range could be considered normal. Individuals with an ABI from 0.91 to 1.10 were at slightly increased risk. These results would suggest that the widely accepted high-risk cut point of 0.90 is reasonable. However, for ABI values from 0.91 to 1.10 and greater than 1.40, individuals might be advised that their risk may be slightly higher than normal levels.

The ABI Collaboration includes 16 international cohort studies. The consistency of results, especially in men (Figure 3), across a diverse spectrum of populations strengthens the validity of our findings. This consistency also was apparent despite some differences in methods of measuring the ABI and in ascertaining outcome events. We did not recalibrate the FRS, as has been suggested in populations very different from that in Framingham,[31] because in our collaboration there was no evidence that particular studies had substantially worse calibration than others and also the FRS when used in routine clinical practice is not usually calibrated to the local population. Although the area under receiver operating characteristic curves examining the added effect of the ABI are presented, from a clinical perspective, the added value of the ABI is the extent to which its inclusion reclassifies patient risk at an individual level.[32]

Other indicators of asymptomatic atherosclerosis, notably coronary artery calcium score and carotid intima media thickness have been evaluated as incremental risk predictors to the FRS. Population studies of apparently healthy individuals have suggested that coronary artery calcium score may provide added value,[33,34] particularly in discriminating high- and low-risk individuals with an intermediate FRS (predicted 10-year coronary event risk between 10% and 20%).[35] In the Atherosclerosis Risk in Communities study,[36] inclusion of carotid intima media thickness had a modest effect on the area under the receiver operating characteristic curve for the prediction of CHD using traditional risk factors. Likewise, in patients with dyslipidaemia[37] and diabetes,[38] a combination of carotid intima media thickness and FRS improved prediction compared with FRS alone. We are not aware, however, of reports of any direct comparisons in the same study of the additional values in which different measures of asymptomatic atherosclerosis (eg, coronary artery calcium vs carotid intima media thickness) make to FRS prediction in the general population.

The ABI is potentially a useful tool for prediction of cardiovascular risk. In contrast to measurement of coronary artery calcium and carotid intima media thickness, it has the advantage of ease of use in the primary care physician's office and in community settings. The equipment is inexpensive—a handheld Doppler costs less than $600. The procedure is simple, taking less than 10 to 15 minutes,[39,40] and can be performed by a suitably trained nurse or other health care professional. Technological advances to make the test quicker and easier to apply are being investigated, including automatic pressure measurement at the ankle.[41] Given the noninvasiveness of the test and minimal discomfort, patient acceptability is high. Variability is comparable with that of routine blood pressure[42,43] and individuals with borderline results may benefit from a repeated measure at a different visit.[43]

Although widely used in specialist vascular clinics, the ABI is rarely applied in routine clinical practice. Barriers to its use include: (1) most clinicians are not aware that a low ABI is a marker of cardiovascular risk; (2) it is perceived as a specialist test for use only by vascular surgeons and physicians; and (3) most clinicians would not know how to perform the test. Physician education would be essential in promoting use of the ABI in practice. Furthermore, in a survey of physicians primed to use the ABI in 1 program in the United States, time constraints, lack of reimbursement, and staff availability were barriers to use of the ABI, each reported by around half the physicians.[40]

The yield of a screening test also is important. Our results indicate that a proportion of men and women having an ABI test would be placed in a different risk category. However, this proportion may vary considerably by age because the prevalence of a low ABI is known to increase substantially with age. For example, in the United States in 2000, the prevalence of an ABI lower than 0.90 in non–Hispanic white men aged 40 to 49 years was 1.4% but was 22.6% in those aged 80 years or older.[44] Significantly higher prevalences were found in blacks. In 12 300 men free of cardiovascular disease in the general population in Scotland, the prevalence of an ABI of 0.90 or less in those aged 50 to 54 years was 3.7% but was 12.7% in those aged 75 years or older.[45] While recognizing that most risk factors also increase with age, it is likely that the added yield of a low ABI is age-related.

Recently published guidelines by the American Heart Association and the American College of Cardiology,[46] the Transatlantic Inter-Society Consensus Working Group,[47] and the Fourth Joint European Task Force[48] have suggested that the ABI should be considered for the purposes of cardiovascular risk assessment. The results of our study indicate that, when using the FRS, this may indeed be justified to improve prediction of cardiovascular risk and provision of advice on ways to reduce that risk. A new risk equation incorporating the ABI and relevant Framingham risk variables could more accurately predict risk and our intention is to develop and validate such a model in our combined data set. Cost-effectiveness modeling of the effect of using the ABI on long-term clinical outcomes also would be of interest, as has been recommended recently by an American Heart Association expert working group on screening for atherosclerotic peripheral vascular disease (Michael H. Criqui, MD, University of California San Diego, written communication, January 2008). A cost-effectiveness analysis also would be useful because successful implemen-

tation of the ABI in programs for assessment of cardiovascular risk would require a change in reimbursement regulations in some countries.

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