

Chapter 4:

Prediction of individualized lifetime benefit from cholesterol lowering, blood pressure lowering, antithrombotic therapy, and smoking cessation in apparently healthy people.

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Abstract

Aims: The benefit an individual can expect from preventive therapy varies based on risk-factor burden, competing risks, and treatment duration. We developed and validated the LIFEtime-perspective CardioVascular Disease (LIFE-CVD) model for the estimation of individual-level 10-year and lifetime treatment-effects of cholesterol-lowering, blood-pressure lowering, antithrombotic therapy, and smoking cessation in apparently healthy people.

Methods and Results: Model development was conducted in the Multi-Ethnic Study of Atherosclerosis (n=6,715) using clinical predictors. The model consists of two complementary Fine and Gray competing-risk adjusted left-truncated subdistribution hazard functions: one for hard CVD-events, and one for non-CVD mortality. Therapy-effects were estimated by combining the functions with hazard ratios from preventive therapy trials. External validation was performed in the Atherosclerosis Risk in Communities (n=9,250), Heinz Nixdorf Recall (n=4,177), and the European Prospective Investigation into Cancer and Nutrition – Netherlands (n=25,833) and Norfolk (n=23,548) studies. Calibration of the LIFE-CVD model was good and c-statistics were 0.67–0.76. The output enables the comparison of short-term vs. long-term therapy-benefit. In two people aged 45 and 70 with otherwise identical risk-factors, the older patient has a greater 10-year absolute risk reduction (15.8% versus 1.6%) but a smaller gain in life-years free of CVD (3.9 versus 4.5 years) from the same therapy. The model was developed into an interactive online calculator available via www.U-Prevent.com.

Conclusion: The model can accurately estimate individual-level prognosis and treatment-effects in terms of improved 10-year risk, lifetime risk, and life-expectancy free of CVD. The model is easily accessible and can be used to facilitate personalized-medicine and doctor-patient communication.

Introduction

Cardiovascular disease (CVD) is a significant cause of worldwide morbidity and healthcare costs. While healthy lifestyles should be universally recommended, in people without cardiovascular disease, lipid-lowering, blood-pressure lowering, and antithrombotic therapy are recommended only when the risk-factor burden is high or a certain 10-year CVD-risk threshold has been reached.^{1 2} The benefit an individual can expect from preventive therapy varies based on risk-factor burden, competing risks, and treatment duration. For example, a high pre-treatment risk and longer treatment duration confer a greater absolute risk reduction (ARR).

Estimating 10-year CVD-risk is thus an important aspect of CVD-prevention and various risk-assessment models have been endorsed by national and international guidelines.¹⁻⁵ Age is a major driver of 10-year risk, and consequentially, the use of such short-term risk may delay treatment in young individuals with a high lifetime-benefit until an age at which a 10-year risk threshold is crossed. Conversely, therapy may provide a large 10-year ARR in older individuals, but an advanced age and limited life-expectancy may restrict gain in healthy life-years from preventive therapy.^{6 7} In recent years, guidelines have begun endorsing the use of lifetime risk-assessment in conjunction with short-term estimations.^{1 2} Existing lifetime scores such as QRISK-lifetime⁸ and the Pooled Cohorts Equations⁹ provide estimations of lifetime risk and the potential benefits of risk-factor modification. However, certain obstacles for the implementation of these scores are present. Not accounting for competing-risks or older baseline data commonly leads to over-estimation. Moreover, lifetime risk is not estimated for all ages, and the international generalizability or the availability of the external algorithms is lacking.^{2 10} There is thus a need to develop an internationally validated competing-risk adjusted model with the ability to estimate both 10-year and lifetime therapy-benefit. Such a model should estimate the effects of starting, stopping, altering, or postponing specific pharmacotherapies and lifestyle strategies.

The objective of the present study was to develop and internationally validate a competing-risk adjusted LIFETIME-perspective model for individualizing CardioVascular Disease prevention strategies in apparently healthy people (LIFE-CVD). The LIFE-CVD model aims to estimate the effect of cholesterol lowering, blood pressure lowering, aspirin therapy, and smoking cessation in terms of 10-year and lifetime CVD-risk, and life-years gained free of CVD in apparently healthy people. The model will be made available via an online, interactive calculator.

Methods

Study populations

The study was conducted using data from multiple North-American and European cohorts. The Multi-Ethnic Study of Atherosclerosis (MESA) cohort commenced recruitment in 2000 and is an ethnically and geographically diverse American cohort.¹¹ The Atherosclerosis Risk in Communities Study (ARIC) commenced approximately 10-years earlier than MESA, but was otherwise similar in recruitment strategy and design. Due to the difference in commencement years, the fourth follow-up visit in ARIC (1996-1998) was used as the baseline for these analyses.¹² The Heinz Nixdorf Recall (Risk factors, Evaluation of Coronary Calcium and Lifestyle) Study (HNR, 2000-2003) is a population-based cohort study from the Ruhr area of Germany.¹³ The European Prospective Investigation into Cancer-Netherlands (EPIC-NL, 1993-1997) study is formed by the Dutch MORGEN-EPIC and the Prospect-EPIC cohorts.¹⁴ The European Prospective Investigation into Cancer-Norfolk (EPIC-Norfolk, 1993-1997) is a population-based cohort from Norfolk area of the United Kingdom.¹⁵ Participants <45 years, with a history of CVD, heart-failure, CKD-EPI eGFR <30 mL/min/1.73m² (not available in EPIC-NL), and terminal malignancy at baseline (not available in HNR) were excluded. Cohort details are described in supplemental table 1. As the model aims to estimate both therapy initiation, cessation, and alteration, no exclusion of participants was made based on medication use. As the model aims to estimate 10-year and lifetime risk for people aged 45-80 years, people >80 years at baseline were not included in validation cohorts. The upper age of 80 years was set because predictions become unstable as the size of an age-group becomes limited in the development cohort.¹² Patients aged >80 years at baseline were included in the development cohort to provide stable estimations between the 80th and 90th life-years.

Clinically applicable predictors

Predictors were pre-specified based on the literature and availability in clinical practice: gender, systolic blood-pressure (SBP, mmHg), non-high-density lipoprotein cholesterol (non-HDLc, mmol/L), body-mass index (BMI, kg/m²), smoking status (current, former, never), presence of diabetes mellitus (yes / no, according to the 2007 American Diabetes Association fasting criteria), positive history of premature (prior to age 60) MI in either parent.^{12,8} Missing data handling is described in supplemental methods 1.

Outcomes

CVD-events were defined as fatal or non-fatal myocardial infarction (MI) or stroke, resuscitated cardiac arrest, and CHD-death. The competing-risk outcome was death from any other (non-CVD) cause. Follow-

up time was defined as years until any of the first CVD-events, death, or end of follow-up. Supplemental table 2 provides an overview of the outcome definitions and adjudication processes.

Model development

The model was developed in the MESA-cohort due to the wide range of baseline ages, relatively recent commencement in the year 2000, and a high degree of racial/ethnic diversity. The statistical methods have previously been described in detail.¹⁶ In brief, the model comprises of two complementary Fine and Gray competing-risk adjusted left-truncated subdistribution hazard functions: one for CVD-events (subdistribution hazard function A) and one for non-CVD mortality (subdistribution hazard function B). Age was used as the time-scale (i.e. left truncation), meaning participants contributed from the age of cohort entry to the age at end of follow-up. Continuous predictors were winsorized at the 1st and 99th percentile and transformed if this improved model fit. An interaction between age and predictor was used if non-proportionality indicated that the strength of a predictor changes with age (i.e. Schoenfeld residual $p < 0.05$). Transformations and non-proportional hazards are described in the supplemental methods 1.

Individual estimation of prognosis

Individual estimations are based on life-tables with one-year age intervals. Each life-year has an age-specific 1-year baseline survival for both CVD-events and CVD-mortality (supplemental table 3). The baseline survival was combined with the clinical predictors to estimate the risk of having a CVD-event or non-CVD mortality for each life-year as shown in supplemental table 4. The cumulative survival for each life-year was subsequently estimated by multiplying the survival probability of that life-year (1 minus CVD risk minus non-CVD mortality risk) by the survival probability at the beginning of each life-year. The (cumulative) survival thus depends on the combination of CVD-risk and non-CVD risk. The process was repeated until age 90 years to provide estimations of 10-year risk in people with baseline age up to 80 years. A complete, reproducible, patient example of a life table is provided in supplemental table 5. Lifetime risk was defined as the risk of having a CVD-event before the 90th life-year. The CVD-free life-expectancy is defined as the median survival without a CVD-event or death, and is thus equivalent to the age at which the cumulative survival probability becomes smaller than 0.5.

Table 1: Baseline characteristics

	MESA (n=6,715)	ARIC (n=9,250)	HNR (n=4,177)	EPIC-NL (n=25,833)	EPIC- Norfolk (n=23,548)
Age (years)	62 (53-70)	62 (58-67)	59 (52-65)	55 (51-60)	59 (52–67)
Gender (male)	53%	42%	47%	17%	44%
Race					
Caucasian	39%	78%	100%	96%	100%
African American	28%	22%	0%	0%	0%
Other	34%	0%	0%	4%	0%
Parental History of Premature MI	15%	16%	22%	13%	7%
Body-mass index (kg/m ²)	28 (25-31)	28 (25-31)	27 (25-30)	26 (23-28)	26 (24-28)
Non-HDL (mmol/L)	3.7 (3.1-4.2)	3.9 (3.3-4.5)	4.4 (3.8-5.1)	4.3 (3.6-5.0)	4.7 (3.9–5.5)
Systolic blood-pressure (mmHg)	124 (111-140)	125 (114-138)	132 (118-145)	129 (117-141)	134 (123–147)
Smoking Status					
Current	14%	14%	23%	27%	12%
Former	37%	42%	33%	35%	42%
Diabetes Mellitus	14%	15%	12%	3%	2%

Legend: Data are presented as median (25th percentile – 75th percentile) or frequency (%). Abbreviations MI = myocardial infarction; non-HDL = non high-density lipoprotein cholesterol; EPIC-NL is assumed to be 96% Caucasian based on genetic analyses.¹⁷ HNR is assumed to be 100% Caucasian.

Model validation

Internal validation was performed on a set of MESA participants drawn by bootstrapping from the dataset of individuals aged 45-80 years at baseline. The lifetime model is based on one-year life table intervals, and may thus require internal intercept recalibration. Hence, the expected versus observed ratio of CVD-events and non-CVD mortality in MESA was used to recalibrate the intercepts. External validation was then performed in ARIC, HNR, EPIC-NL, and EPIC-Norfolk. Agreement between expected-and-observed 10-year risks was assessed using calibration plots for CVD-events, non-CVD mortality, and the combined risk of these two events (i.e. the LIFE-CVD model). Geographical differences in event rates were corrected for by recalibrating the intercept in the HNR-study, and using the same recalibration coefficients for the other European cohorts. No recalibration was performed in ARIC as this has the same geographic location as the MESA-cohort.

Race sensitivity analyses

Race/ethnicity was not selected as a predictor due to the heterogeneity of definitions between countries, and the complex and poorly generalizable mechanisms via which race may mediate cardiovascular risk.¹⁸ However, in order to investigate model accuracy for different race/ethnicities, a race-stratified validation of the developed LIFE-CVD model was performed for African Americans and Caucasians in MESA and ARIC. Additionally, to compare the effects of race/ethnicity in the separate cohorts, two exploratory models were developed (one derived in MESA, the other in ARIC) which included race (i.e. African American, Caucasian or other) as a predictor. The multivariable hazard ratios (HRs) for race in these two models were compared.

Individual therapy-benefit

Altering the patient-characteristics to reflect updated risk-factors provides an observational, rather than a causal assessment, of risk-factor changes.⁹ In order to estimate the causal effects of therapy, the developed subdistribution hazard functions were combined with HRs obtained from randomized clinical trials and meta-analyses for cholesterol-lowering, blood pressure lowering, antithrombotic therapy, (i.e. aspirin or equivalent therapy) and smoking.⁹ By using the HRs from meta-analyses which analyzed trials including people both receiving and not receiving preventive therapy at baseline, the effect of starting, stopping, intensifying, postponing, or reducing therapy can be estimated. Details are provided in supplemental methods 2. Cause-specific 1-year on-treatment survival was calculated by inserting the HR of treatment into either the proportional hazard function (A), (B), or both, as shown in supplemental table 4. The 10-year and lifetime ARR is the difference between on- and off-treatment predicted CVD-

risk after 10-years or until 90 years of age, respectively. The gain in life-years free of CVD is estimated as the difference between on- and off-treatment CVD-free life-expectancy. Three patient examples are provided to demonstrate use of the LIFE-CVD tool to predict therapy-effects.

Results

Study population

Baseline characteristics of the 69,523 participants are shown in table 1. The 6,715 MESA participants used for the derivation of the LIFE-CVD model were ethnically diverse, with 39% self-reporting as Caucasian, 28% as African American, 22% as Hispanic, and 12% as Chinese American. In MESA, 621 CVD-events and 795 non-CVD deaths occurred over a median follow-up duration of 13.0 years.

Development of the LIFE-CVD model

Subdistribution HRs for CVD-events (A) and non-CVD mortality (B) are shown in table 2. These HRs are prognostic in nature and should not be viewed causally. Age-specific baseline survival (supplemental table 3) and the completed algorithm for both subdistribution hazard functions (supplemental table 4) are provided to enable external use of the full model.

Table 2: Multivariable hazard ratios (HR) used in the LIFE-CVD model.

	Subdistribution hazard function A (CVD-events)	Subdistribution hazard function B (non-CVD mortality)
Gender (Male)	1.62 (1.38-1.92)	0.98 (0.83-1.17) *
Systolic blood-pressure (per 10 mmHg)	1.12 (1.08-1.17)*	1.03 (1.00-1.07)
Non-HDL Cholesterol (mmol/L)	1.13 (1.03-1.24)	0.83 (0.64-1.07) [§]
Body Mass Index (kg/m ²)	1.01 (1.00-1.03)	0.98 (0.62-1.56) [§]
Former Smoker	1.03 (0.86-1.23)	1.26 (1.07-1.47)
Current Smoker	1.59 (1.25-2.02)*	2.04 (1.65-2.52) *
Diabetes Mellitus	1.76 (1.42-2.20)*	1.30 (1.04-1.63)*
Parental History of Premature MI	1.46 (1.19-1.79)	0.93 (0.76-1.14)

* Age-dependent variables. HRs shown for the median age of 62 years. [§] Transformed variable. HRs shown for the 75% inter quartile range versus the 25% inter quartile range (non-HDL-c 4.24 mmol/L versus 3.08 mmol/L; BMI 31 kg/m² versus 25 kg/m²)

Internal Validation

Of the 6,715 participants used for derivation, the 6,526 individuals between 45-80 years at baseline were resampled with replacement. The median predicted 10-year CVD risk is depicted in supplemental table 6. In this validation-set, the predicted 10-year risk for both CVD-events, non-CVD mortality, and combined outcome of CVD-events and all-cause mortality (i.e. the LIFE-CVD model), showed good agreement with the 10-year observed risk over all quintiles (figure 1). C-statistics for discrimination of the predicted versus observed 10-year CVD-risk was 0.73 (95% CI 0.71-0.74), non-CVD mortality risk was 0.76 (95% CI 0.75-0.78), and combined risk 0.74 (95% CI 0.73-0.75).

External Validation

The expected versus observed ratio in the HNR study was 1.17 for CVD-events and 0.85 for non-CVD mortality. These recalibration coefficients were subsequently used and validated in the EPIC-NL and EPIC-Norfolk cohorts. The predicted and observed 10-year risk for the combined outcome of CVD-events and all-cause mortality showed good agreement (figure 2). C-statistics for discrimination ranged from 0.68 - 0.76 for CVD-risk, from 0.67 - 0.74 for the non-CVD mortality risk, and from 0.69- 0.76 for combined risk (supplemental table 7).

Race Sensitivity analyses

Race-stratified analyses were performed on the 1,887 African Americans and 2,600 Caucasians in the MESA validation set and the 2,029 African Americans and 7,194 Caucasians in the ARIC study. Stratified calibration plots are provided in supplemental figure 1. C-statistics ranged from 0.69 to 0.76 for African Americans and from 0.67 to 0.77 for Caucasians (supplemental table 8). In the exploratory model derived in MESA, which included race as a predictor, the multivariate HR for African-American compared versus Caucasians was non-significant. When the model was derived in ARIC, HRs were significant, but of different direction than those derived in MESA (supplemental table 9).

Individual estimation of prognosis

The developed LIFE-CVD model can be accessed via www.U-Prevent.com. Patient characteristics, current and future treatment, and age of treatment initiation can be entered into the tool. Three patient-examples are provided in figure 3, in which the effect of concurrently achieving a blood-pressure target

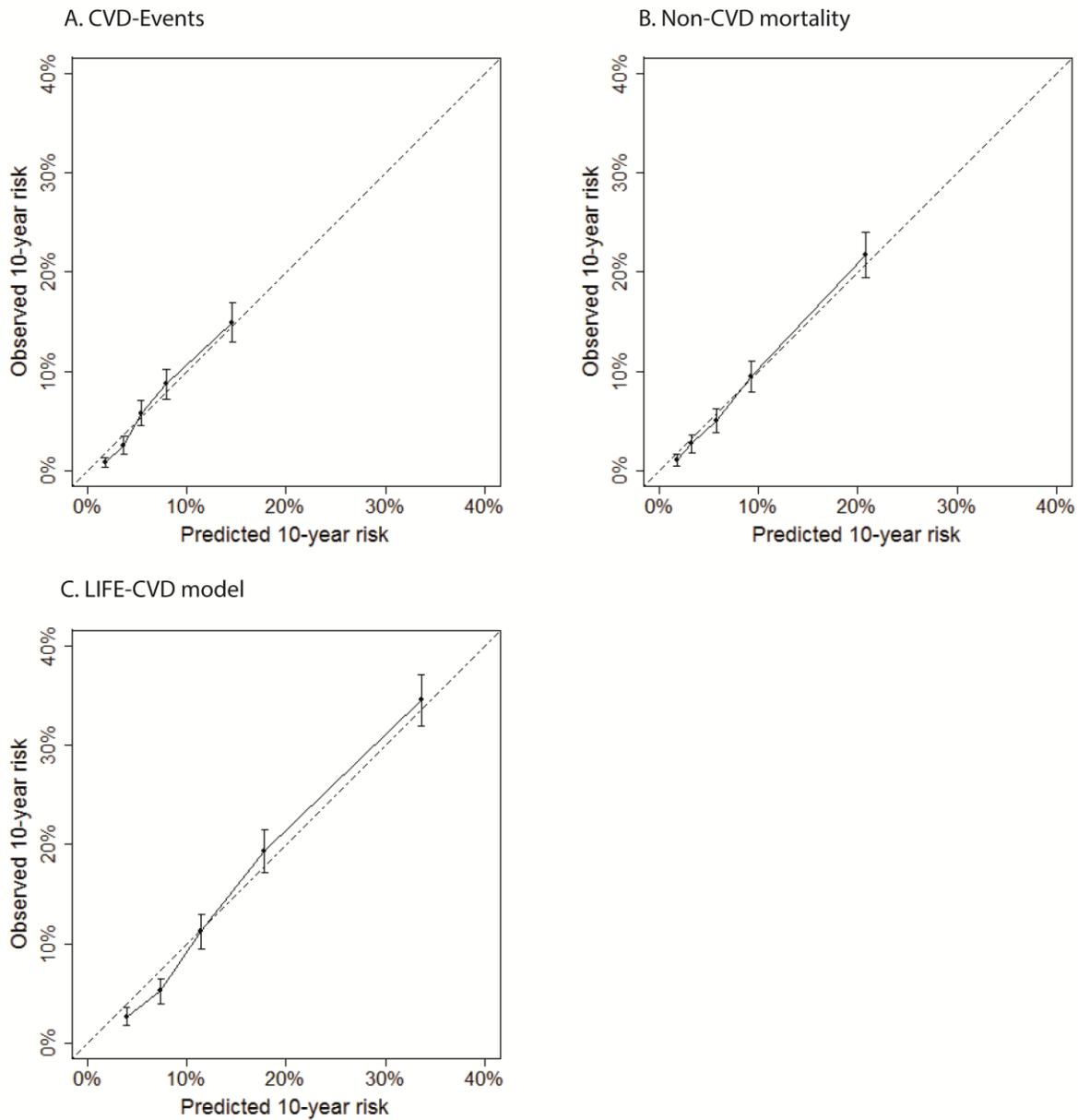


Figure 1: Internal calibration of predicted versus observed 10-year risk with 95% confidence intervals in the MESA-validation cohort for A) cause-specific CVD-event risk, B) cause-specific non-CVD mortality risk, and C) CVD-event and non-CVD mortality risk combined (i.e. the LIFE-CVD model).

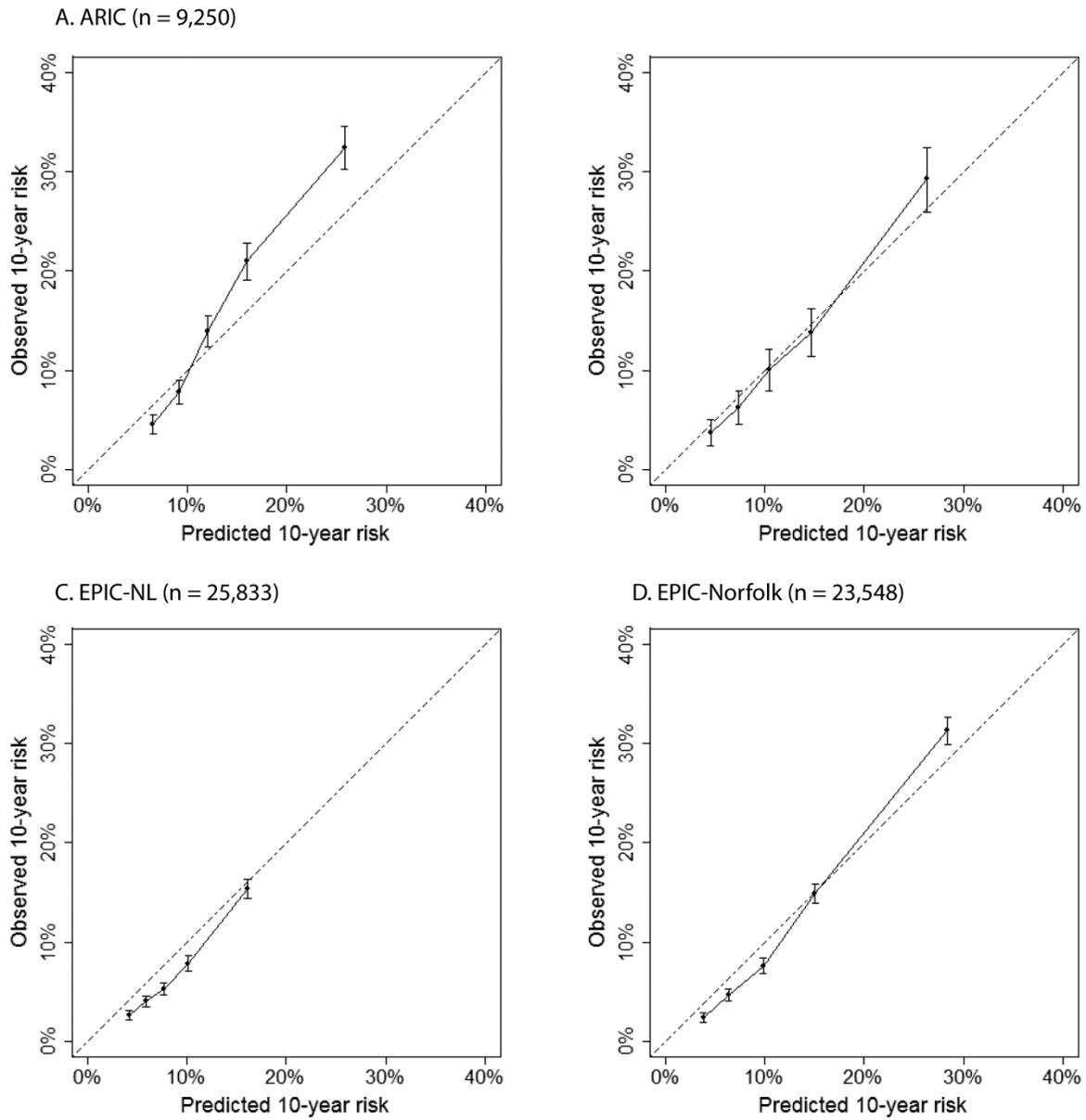


Figure 2: External calibration of predicted versus observed 10-year risk of CVD-event and non-CVD mortality risk combined (i.e. the LIFE-CVD model) with 95% confidence intervals in A) ARIC B) HNR and C) EPIC-NL and D) EPIC-Norfolk studies

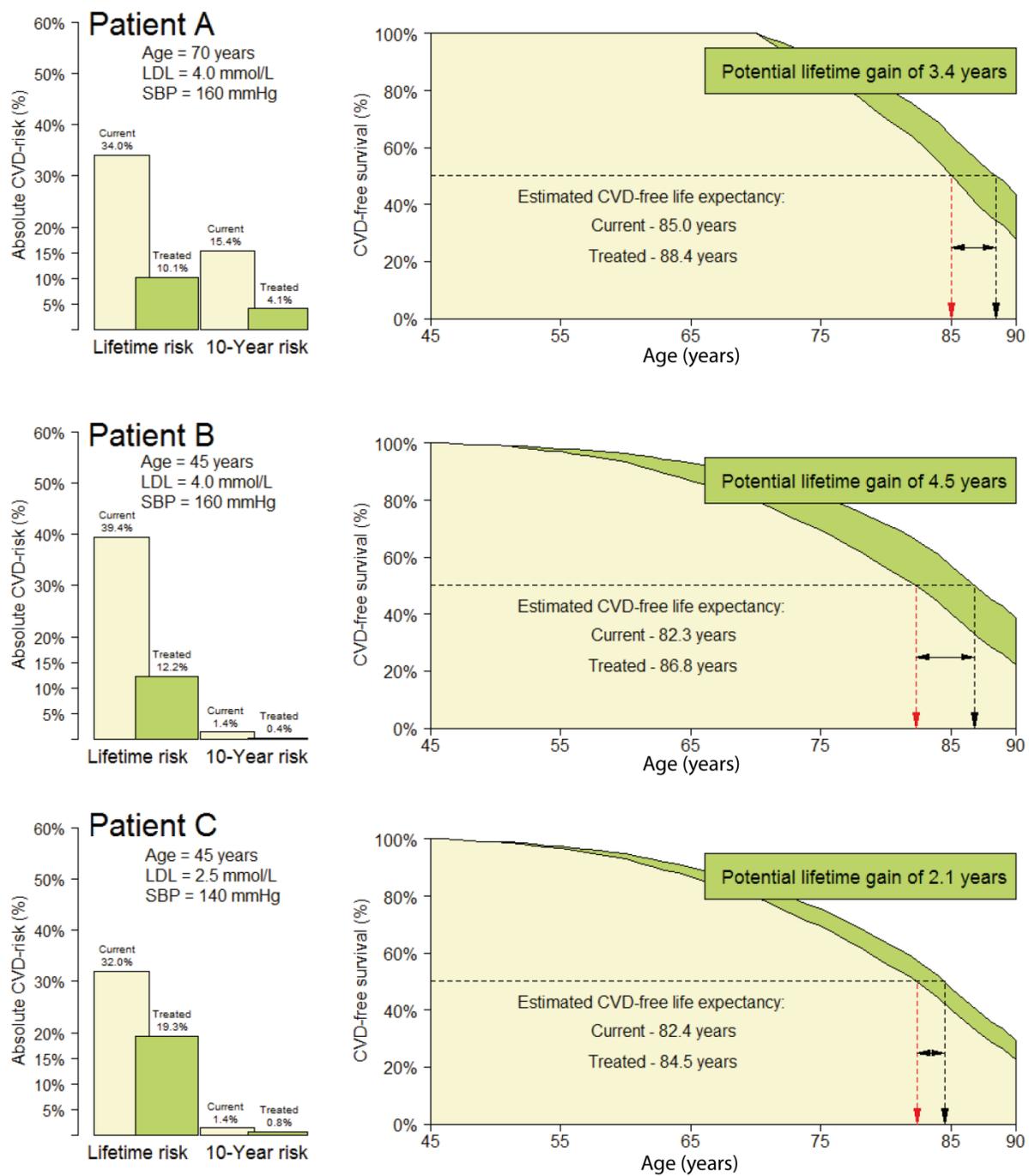


Figure 3: Individualized therapy- benefit from atorvastatin 40 mg and achieving an SBP of 130 mmHg in three non-diabetic, former-smoking, European males with a BMI of 28 kg/m². MI = Myocardial infarction

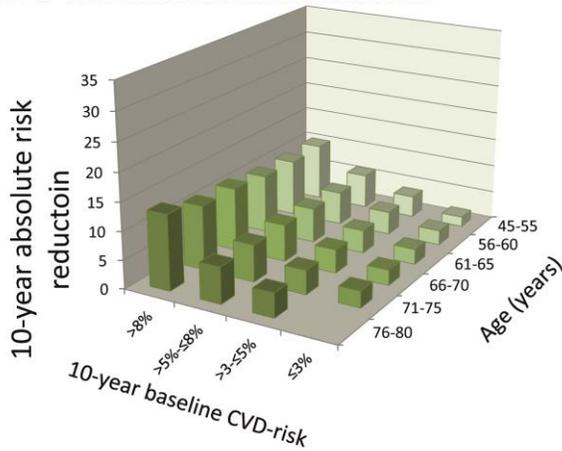
	Patient A	Patient B	Patient C
Non-HDL (mmol/L)	5.0	5.0	3.0
Parental History of MI	No	No	Yes
Current Prognosis			
10-year CVD risk (%)	15.4	1.4	1.4
Lifetime CVD risk (%)	34.0	39.4	32.0
CVD-free life-expectancy (years)	85.0	82.3	82.4
Therapy-benefit			
10-year ARR (%)	11.3	1.0	0.6
Lifetime ARR (%)	23.8	27.2	12.7
Gain in CVD-free years	3.4	4.5	2.1

of 130 mmHg and initiating daily atorvastatin 40mg are compared. The 70-year old patient A has the exact same risk-profile as the 45-year old patient B. Patient A however has a higher 10-year CVD risk (15.5% versus 1.4%), but a lower lifetime risk (34.0% versus 39.4%) and a higher life-expectancy (85.0 versus 82.3 years). Patients B and C have the same age and 10-year risk. Patient B has higher SBP and LDL-c levels and thus a greater gain in CVD-free life-expectancy from modifying these risk-factors. The same risk-modifying strategy modelled in the individual patient examples (i.e. starting atorvastatin 40 mg and achieving an SBP-target of 130 mmHg) was applied to the MESA-validation population and is shown in figure 4. Ten-year ARR increased with increasing baseline risk, and remained relatively consistent over each age stratum. Lifetime ARR and gain in CVD-free life-expectancy also increased with increasing baseline risk, but decreased with baseline age.

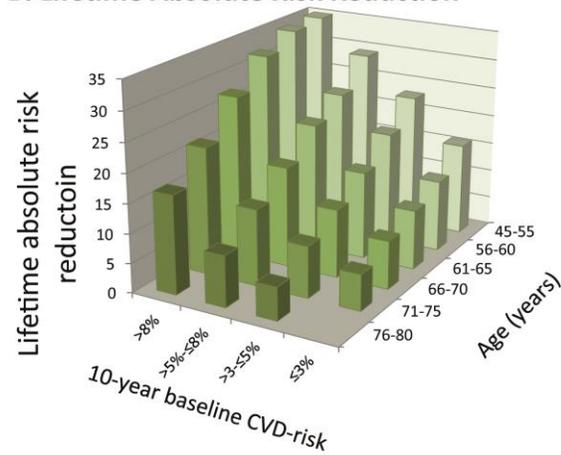
Discussion

In this study of 69,523 individuals, we developed and validated the LIFE-CVD model for apparently healthy people without cardiovascular disease between 45-80 years of age. International validation demonstrated the predictive reliability of the model. Individualized effects cholesterol lowering, blood pressure lowering, aspirin therapy, and smoking cessation can be estimated in terms of 10-year ARR, lifetime ARR, and gain in CVD-free life-years using readily available clinical characteristics. Calibration and discrimination are comparable to existing primary prevention models such as the Pooled Cohort Equations.¹ For researchers, the fully specified algorithm with completed examples are presented to enable external use. The clinical tool can be accessed freely via www.U-Prevent.com.

A. 10-Year Absolute Risk Reduction



B. Lifetime Absolute Risk Reduction



C. Gain in CVD-Free Life-Expectancy

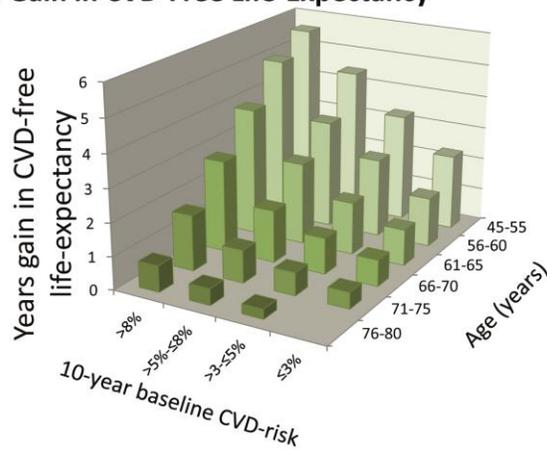


Figure 4: Distribution of individual A) 10-year ARR% B) Lifetime ARR% and C) gain in life-expectancy estimated for the 6,526 individuals in the MESA validation-cohort for immediate initiation of atorvastatin 40 mg and achieving an SBP of 130 mmHg stratified by baseline 10-year risk and age. No change in smoking status or aspirin use was modelled.

Although the atherosclerotic process can begin in early adulthood, the majority of CVD-events happen after middle-age.¹⁹ Therefore, most younger adults have a lower 10-year CVD risk, and most older adults have a higher 10-year risk, regardless of risk-factor burden. However, the lifetime benefit decreases with age and increases with increasing risk-factor burden. Early initiation of risk-modifying strategies therefore results in greater lifetime therapy-benefit.⁶ This is intuitively demonstrated by the greater lifetime gain from quitting smoking at age 30 compared to age 60.²⁰ It is therefore not surprising that a benefit-based approach to other therapies would shift eligibility away from older individuals and towards younger individuals with a high risk-factor burden. Lifetime risks in the ACC-AHA-ASCVD risk-estimator (based on the Pooled Cohort Equation) are based on cumulative risk of CVD over 30 years, and

the score does not provide estimations of CVD-free life-expectancy. Although 30-year risk provides a greater time-horizon than 10-years, the use of a fixed time-horizon makes it difficult to compare the therapy benefit between individuals of different ages. Accordingly, the risk-calculator for this score does not provide 30-year risk estimations for individuals over 59 years of age.

Lifetime estimates may be easier for the patient to understand, and integrating these estimates into decision-tools may enhance the clinician-patient risk-discussion.²¹ The use in clinical practice could help patients and clinicians gain insight into the individual effects of prevention when considering starting therapy, but also when side-effects are being experienced and therapy cessation, or daily-dose lowering, is desired. Lifetime estimates can also help identify patients who would benefit from early therapy-initiation. However, early initiation also means a longer treatment duration, and thus also greater costs. On a population-level, cost-effectiveness studies can determine what gain in CVD-free life-years will outweigh the increased costs and harms of early treatment.

The strengths of this study include combining a competing-risk adjusted model with the best available evidence on risk-reduction from therapy. Not accounting for competing risks leads to an overestimation of pretreatment CVD-risk in young individuals over the long term, or in any individual where the risk of a competing event is high. Trials and meta-analyses provide a comprehensive group-level analysis for individuals both on- and off- medications. As reliable evidence become available in the future, new prevention strategies will be added to the LIFE-CVD model. The study further used data from ethnically and geographically diverse population-based cohorts, allowing for both geographic recalibration, and the subsequent validation of the recalibration coefficients. The slight underestimation of risk was seen in the highest baseline risk quintile of the external validation (observed CVD-risk > 10%). However, this may be of reduced clinical relevance, as the estimated risk already exceeds treatment thresholds (7.5%) above which pharmacotherapy is often indicated in people without prior CVD.^{10 22} Race can be poorly defined and have different cultural definitions and gene/environment interactions in separate regions;²³ a view point reflected in the HRs for race found in the exploratory models when derived in both MESA and ARIC. For these reasons the model was derived in a multi-ethnic cohort, and the risk-factors thought to mediate the biological effects of race were included. A third strength is the use of the contemporary MESA cohort to derive the model, which commenced in 2000. Models derived using older baseline data may provide clinically significant overestimations of CVD-risk in contemporary populations.^{24 25}

Certain limitations should be acknowledged. Validation is performed for 10-year risk, as it is not feasible to perform validation over the course of an individual's lifetime. Lifetime models assume that baseline

risks for each life-year remain stable over time. Previous studies have however shown the validity of lifetime predictions for up to 17 years.¹⁶ Nevertheless, as the follow-up duration in the validation cohort increases, the LIFE-CVD model could be updated and validated over the long-term. Also, lifetime estimations assume that all risk-factors, except age, remain stable over time. In reality, a patient may have an increase in blood-pressure over the course of a few years, or may develop co-morbidities. Therefore, lifetime estimations should be performed at regular time-intervals, such as every 10-years. Another important assumption of lifetime therapy-benefit estimations is that patients will be fully adherent to the prescribed medication for their remaining lifetimes. However, therapy-adherence is a common problem, and the LIFE-CVD model could be used as communication aid to address the importance of adherence and the consequences of non-adherence.

CVD-prevention guidelines state that lifetime may be useful as a communication tool and that competing non-CVD death causes makes providing lifetime CVD estimates for some groups problematic.^{1 2} Although a few scores such as the QRISK provide lifetime estimations⁸, there are no competing-risk adjusted lifetime models which have been developed for the primary prevention populations in Europe as a whole.² Similarly, the PCE lacks competing-risk adjustment and only provides long-term estimates for younger individuals. The competing-risk adjusted LIFE-CVD model therefore fills gap. For populations not used in the development or validation (i.e. eastern European or Asian populations), the LIFE-CVD model represents the best available model to estimate treatment-effects. Further investigations may also involve specific validation and eventual recalibration of the model to these geographic locations. In the future, including characteristics such as the presence of a monogenetic dyslipidemias, might improve predictions for those with these relatively rare characteristics. However, the addition of new markers to a well-functioning prognostic model rarely provides meaningful prognostic value to the model as a whole.²⁶

In conclusion, the LIFE-CVD model can estimate therapy-benefit from CVD risk-modification in apparently healthy people. The developed individualized-treatment tool is freely available via www.U-Prevent.com and estimates the individualized benefit from cholesterol- and blood pressure- lowering, antithrombotic therapy, and smoking cessation in terms of 10-year and lifetime absolute CVD-risk reduction, and gain in CVD-free life-expectancy. Use of the tool may increase insight into therapy-benefit via the complementary use of 10-year and lifetime estimates and may facilitate individualized medicine and doctor-patient communication.

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Supplemental Methods 1

Missing data

Missing data was imputed separately in each cohort using additive regression and predictive mean matching with optimal weighted probability based on non-missing patient characteristics (aregImpute-algorithm in R, Hmisc package). The frequency of missing data in each cohort is described below.

In MESA, the percent of imputed variables was as follows: 0.03% for SBP, 0.04% for total cholesterol, 0.09% for HDL-cholesterol, 0.3% for smoking status, 0.40% for diabetes status, 3.3% for parent's age at MI where applicable and 10.8% for parental history of MI.

In ARIC the percent of imputed variables was as follows: systolic blood-pressure 0.02%, body-mass index (kg/m^2) 0.11%, diabetes status 0.47%, smoking status 0.53%, parental history of MI 8.0% and age at parental history of MI where applicable 8.2%.

In the HNR study, the percent of imputed variables was as follows: HDL cholesterol 0.02%, systolic blood-pressure 0.2%, smoking status 0.1%, body-mass index 0.4%, parental myocardial infarction 7.8%, and age at parent's MI when applicable 6.2%.

In the EPIC-NL, the percent of imputed variables was as follows: body-mass index 0.1%, systolic blood pressure 0.3%, smoking status 0.5%, diabetes 0.6%, total cholesterol 3.7%, HDL-cholesterol 5.1%, age at parent's myocardial infarction (12.4%) and parental history of myocardial infarction (yes, no, or unknown, 34.2%).

In EPIC-Norfolk, the percent of imputed variables was as follows: diabetes status 0.1%, parental history of MI 0.1%, age at parent's MI when applicable 0.1%, body-mass index (kg/m^2) 0.2%, systolic blood-pressure 0.3%, smoking status 0.9%, total cholesterol 6.9%, HDL cholesterol 9.9%.

Transformations and non-proportionality of predictors

For the CVD-sub distribution hazard model, no transformation of linear predictors was required. Non-proportionality was seen with systolic blood-pressure (chi-squared = 6.5, $p=0.01$), current smoking (chi-squared = 30.0, $p=4.9 \times 10^{-8}$), and type 2 diabetes (chi-squared = 6.5, $p=0.011$). For the competing-risk non-CVD mortality model, logarithmic transformations of non-HDL cholesterol and quadratic transformation of BMI improved model fit. Non-proportionality was seen for gender (chi-squared 4.1,

p=0.04), current smoking (chi-squared 1.3, p=2.5 x10⁻⁴), and type 2 diabetes (chi-squared 1.5, p=1.4x10⁻⁴).

Supplemental Methods 2

CVD-events were defined as fatal or non-fatal myocardial infarction (MI) or stroke, resuscitated cardiac arrest, and CHD-death and is modelled with the subdistribution hazard function A. The competing-risk outcome was death from any other (non-CVD) cause and is modelled with subdistribution hazard B. As such, the effect of medication is modelled on the respective outcome (as shown in supplemental table 4), and not the separate components of a composite outcome.

Lipid-lowering effect

The prediction of therapy-effects for lipid-lowering medications depends on the estimated change in LDL-c compared to baseline due to the medication. A 1 mmol/L reduction in LDL-c corresponds to a CVD hazard ratio of 0.78, and the expected relative risk reduction is modelled with $0.78^{(\text{LDL-c reduction from baseline})}$.²⁷ In the interactive calculator, the user can switch between prescription therapies (i.e. between atorvastatin 40 mg and atorvastatin 80mg). The expected LDL-c -reduction from baseline for each dose and type of statin is calculated based on a meta-analysis of 164 statin trials.²⁸ The expected LDL-c from ezetimibe was derived from a meta-analyses and assumed to be 23.5% .²⁹ The resulting hazard ratio for the effect of LDL-reduction is inserted into cardiovascular events subdistribution hazards function (A). Thus, although LDL-c is not used as a clinical predictor in the model, it is necessary to input the LDL-value into the interactive calculator in order to obtain the CVD hazard ratio for the effect of LDL-c reduction.

Blood-pressure lowering effect

The effect of SBP-reduction was modelled into cardiovascular events subdistribution hazards function (A). A 10 mmHg reduction in SBP corresponds to a CVD hazard ratio of 0.74 (95% CI 0.67-0.83).³⁰ Thus, an individual relative risk reduction associated with achieving a treatment target is $0.74^{((\text{baseline SBP} - \text{target SBP}) / 10)}$. In the interactive calculator, the user can estimate the effect of achieving certain systolic blood-pressure targets, as the choice of specific pharmacotherapy for blood-pressure lowering depends on the co-morbidities of the patient and significant blood-pressure lowering may be achieved with

lifestyle modification. The effect of blood-pressure lowering was truncated at 130 mmHg with any reduction under 130 assumed to give a hazard ratio of 1.0.

Antithrombotic effect

The effect of antithrombotic therapy (aspirin or equivalent) was modelled into cardiovascular events subdistribution hazards model (A). The CVD hazard ratio associated with the effect of aspirin therapy is 0.88 (95% CI 0.82 – 0.94) and derived from a meta-analysis of six primary prevention trials.³¹ We assume that aspirin cessation is estimated as the inverse (i.e. HR $1/0.88 = 1.13$). Other anti-coagulation therapy such as DOAC are generally recommended in the primary prevention setting.

Smoking effect

The effect of smoking cessation was modelled into both cardiovascular events subdistribution hazards function (A) and non-cardiovascular mortality subdistribution hazards function (B) and are derived from a large systematic reviews and meta-analyses. The hazard ratio for the CVD-event function (A) was derived using the reported hazard ratios for acute coronary events: former- versus never smokers 1.18 (1.06 – 1.32); current-versus never smoker 1.98 (95% CI 1.75 – 2.25).³² The HR for former versus current smokers was thus estimated to be $1.18 / 1.98 = 0.60$. The hazard ratio for model (B) was derived using the reported hazard ratios for all-cause mortality: former- versus never smokers 1.34 (95% CI 1.28-1.40); current- versus never smokers 1.83 (95% CI, 1.65-2.03).³³ The HR for former versus current smokers was estimated to be $1.34 / 1.83 = 0.73$.

Combined effects

The relative risk reduction for the combination of treatment are obtained by multiplying the HR's for each therapy being considered, and inserting the log of the combined HR into the linear predictor. This corresponds to the effects of combined medication independent of each other. This is done separately for CVD-events and non-CVD mortality as shown in supplemental table 4.

Median and area under the survival curve (AUC) estimations:

When the median on- or off-treatment life-expectancy is estimated to be >90 years, the median survival does not reach 0.5. In these situations, the estimated gain in CVD-free life-expectancy is defined as the difference in the sum of the CVD-free survival probabilities for each remaining life-year. Graphically, this is equal to the on-treatment area under the survival curve (AUC) minus of off-treatment AUC.

Supplemental table 1: Cohort details

MESA ¹¹	<p><i>Method of Recruitment:</i> Probability sampling from four communities (Forsyth County, NC; Northern Manhattan and the Bronx, NY; Baltimore City and Baltimore County, MD; St. Paul, MN; Chicago and the village of Maywood, IL; and Los Angeles County, CA) proceeded according to the discretion of the Field center according to the characteristics of its community, past experience, available resources, and site-specific logistics. Inclusion proceeded via pre-defined sex and race/ethnicity proportions.</p> <p><i>Enrollment period:</i> 2000-2002</p> <p><i>Cohort participation criteria:</i> Subjects must be living within geographic boundaries of a field center, between 45-84 years of age, free of known (self-reported) clinical cardiovascular disease, active cancer treatment, pregnancy, any serious medical condition which would prevent long-term participation; weight >136 kg; cognitive inability as judged by the interviewer; living in a nursing home or on the waiting list for a nursing home; plans to leave the community within five years; language barrier; chest CT scan in the past year.</p>
ARIC ¹²	<p><i>Method of Recruitment:</i> Probability sampling within four communities (Forsyth County, North Carolina; Jackson, Mississippi; Minneapolis, Minnesota; and Washington County, Maryland) was used to randomly select households. All individuals aged 45-64 years were asked to participate. Participants were re-examined every three years.</p> <p><i>Enrollment period:</i> Initial recruitment: 1987-1989. For this study, variables collected at the fourth follow-up visit were used (1996-98).</p> <p><i>Cohort participation criteria:</i> Willing and able to participate.</p>
HNR ¹³	<p><i>Method of Recruitment:</i> Random samples of men and women aged 45-74 were drawn from mandatory residency lists of three cities in the Ruhr area of Northwestern Germany (Essen, Mülheim and Bochum). Participants were invited via letter, and a maximum of two reminder letters and phone calls were made to the initial non-responders.</p> <p><i>Enrollment period:</i> December 2000 – August 2003</p> <p><i>Cohort participation criteria:</i> All subjects without cardiovascular disease willing to participate, without any conditions precluding follow-up over 5 years, pregnancy, or severe psychiatric illness.</p>
EPIC-NL ¹⁴	<p><i>Method of Recruitment:</i> The Monitoring Project on Chronic Risk Factors (MORGEN project) recruited a random sample of participants from the general Dutch population, and included those aged 20-65. Prospect-EPIC cohort is based on volunteers recruited among women participating in a regional breast cancer screening program for whom all women, aged 50-69 receive biannual invitations.</p> <p><i>Enrollment period:</i> 1993 – 1997</p> <p><i>Cohort participation criteria:</i> Willing and able to participate and allow for linkage with the national hospital registries and mortality registries.</p>
EPIC-Norfolk ¹⁵	<p><i>Method of Recruitment:</i> Recruited men and women aged 39-79 from the county of Norfolk from the population-based sampling frame of people registered with 35 participating General Practices.</p> <p><i>Enrollment period:</i> 1993 – 1997</p> <p><i>Participation criteria:</i> Willing and able to participate in baseline health.</p>

Legend: MESA = Multi-ethnic Study of Atherosclerosis; ARIC = Atherosclerosis Risk in Communities Study; HNR = Heinz Nixdorf Recall Study; EPIC-NL = European Prospective Investigation into Cancer and Nutrition-Netherlands; EPIC-Norfolk = European Prospective Investigation into Cancer and Nutrition-Netherlands.

Supplemental table 2: Outcome evaluation and definition

MESA ¹¹	<p><i>Outcome evaluation:</i> Trained personnel evaluate the outcome based on ICD-codes and hospital records</p> <p><i>Acute myocardial infarction:</i> Abnormal cardiac biomarkers (2 times upper limits of normal) regardless of pain or ECG findings; evolving Q waves regardless of pain or biomarker findings; or a combination of chest pain, and ST-T evolution or new LBBB, and biomarker levels 1-2 times upper limits of normal.</p> <p><i>Resuscitated Cardiac Arrest:</i> Successfully recovered from a resuscitated cardiac arrest through pulmonary resuscitation (including cardioversion)</p> <p><i>Stroke (not TIA):</i> Focal neurologic deficit lasting 24 hours or until death, or if < 24 hours, there was a clinically relevant lesion on brain imaging. Patients with focal neurologic deficits secondary to brain trauma, tumor, infection, or other non-vascular cause were excluded.</p> <p><i>CHD Death:</i> Documented MI within the previous 28 days, chest pain within the 72 hours before death, and required absence of a known non-atherosclerotic or non-cardiac cause of death.</p> <p><i>End of follow-up:</i> December 31st, 2014</p>
ARIC ¹²	<p><i>Outcome evaluation:</i> Events are ascertained by trained personnel by a combination of reviewing hospital records, and query of the patients, physicians, and family members, and are subsequently adjudicated by a committee of physicians.</p> <p><i>Acute myocardial infarction:</i> Definite hospitalized MI defined as either 1. evolving diagnostic ECG pattern, or 2. diagnostic ECG pattern and abnormal enzymes, or 3. cardiac pain and abnormal enzymes in combination with either evolving ST-T pattern or equivocal ECG pattern. Probable hospitalized MI is defined as absence for definite MI and 1. Cardiac pain and abnormal enzymes, or 2. Cardiac pain and equivocal enzymes and either and evolving ST-T pattern or diagnostic ECG pattern, or 3. Abnormal enzymes and evolving ST-T pattern.</p> <p><i>Resuscitated Cardiac Arrest:</i> Cardiac arrest, cause unspecified (ICD-10 427.5)</p> <p><i>Stroke:</i> Potential strokes were identified using ICD 9 discharge codes 160-167 or with mention of stroke in hospital discharge or death records and were evaluated by trained personnel. Strokes thought to be caused by vasculitis, major trauma, malignant neoplasm, infection, or hematological abnormalities were not included.</p> <p><i>CHD Death:</i> Definite or probable fatal CHD defined as lack of sufficient evidence to diagnose definite fatal MI, no known non-atherosclerotic or non-cardiac death that was probably lethal, and the presence of either a history of chest pain within 72 hours of death or a history of chronic ischemic heart disease such as coronary insufficiency or angina pectoris</p> <p><i>End of follow-up:</i> December 31st, 2014</p>
HNR ¹³	<p><i>Outcome evaluation:</i> Vital status in subjects not reached by yearly follow-up is extracted</p>

from mandatory citizen registries. For all possible primary study endpoints, hospital and nursing home records including electrocardiograms, laboratory values, and pathology reports were collected. For deceased subjects, death certificates were collected and interviews with general practitioners, relatives and eyewitnesses were undertaken if possible. Medical records were obtained in 100% of all reported endpoints. An external criteria and endpoint committee blinded for conventional risk factor status and CAC scores reviewed all available documents of possible primary endpoints and classified the endpoints thereafter.

Acute myocardial infarction: We considered a myocardial infarction event according to the WHO MONICA diagnostic categories derived from symptoms, signs of electrocardiography, and enzymes (levels of creatine kinase (CK-MB)) as well as troponin T or I, and necropsy as (1) non-fatal acute myocardial infarction and (2) coronary death, which occurred after the baseline examination.

Resuscitated Cardiac Arrest: Physician or emergency physicians documented fatal or non-fatal cardiac arrest with resuscitation.

Stroke (not TIA): Rapidly developing focal neurologic symptoms lasting at least 24 hours or until death due to no other than vascular cause.

CHD Death: Death related to coronary heart disease documented in hospital records and confirmed by the event committee unrelated to any time intervals.

End of follow-up: May 2017

EPIC-NL¹⁴ *Outcome evaluation:* Cause of death was obtained from Statistics Netherlands. Morbidity data (hospital contact) were obtained by linkage to the national hospital discharge register (HDR) using a validated probabilistic method. All outcomes were coded according to the Ninth Revision of the International Classification of Diseases (ICD-9) until 1996, after which the Tenth Revision of the International Statistical Classification of Diseases (ICD-10) was used for hospital discharge diagnoses.

Acute myocardial infarction: Hospitalization or death due to I21-I22

Cardiac arrest: Hospitalization or death due to I46

Stroke: Hospitalization or death due to I60-I66

CHD Death: Death due to ICD I21-I25, I50, I46, R96

End of follow-up: December 31st, 2010

EPIC-Norfolk¹⁵ *Outcome evaluation:* Cause of death was obtained via linkage to the UK Office of National statistics and death certificated coded by trained personnel. Morbidity data (hospital contact) were identified using linkage with the East Norfolk Health Authority (ENCORE) database, which records all hospital contacts throughout England and Wales for Norfolk residents. All outcomes were coded according to the Tenth Revision of the International Classification of Diseases (ICD-10).

Acute myocardial infarction: Hospitalization or death due to I21-I22

Resuscitated cardiac arrest: Hospitalization or death due to I46

Stroke: Hospitalization or death due to I60-I69

CHD Death: Death due to ICD I21-I25, I46, I50

End of follow-up: December 31st, 2013

Supplemental table 3: Age-specific baseline survival for CVD-events (A) and non-CVD mortality (B)

Age	1-Year events (A)	1-Year survival (B)	Age	1-Year survival (A)	1-Year survival (B)
45	1	1	68	0.999645771	0.970398098
46	1	0.979380684	69	0.999663492	0.965410198
47	0.999725398	0.985480904	70	0.999566041	0.956805621
48	1	0.978988162	71	0.999513256	0.95465345
49	1	1	72	0.999692656	0.955233741
50	0.99987841	0.98607217	73	0.999702516	0.953443559
51	0.999516952	0.988522333	74	0.999679667	0.969421315
52	0.999591619	0.985415629	75	0.999647779	0.947674229
53	0.999792279	0.979056609	76	0.999630632	0.939724478
54	0.9998799	0.985072499	77	0.999686488	0.954401682
55	0.99941209	0.98989693	78	0.999661579	0.930794801
56	0.999571482	0.990764307	79	0.999598915	0.9475237
57	0.999699809	0.985900751	80	0.999725086	0.944907534
58	0.999682114	0.986623736	81	0.999769337	0.931903316
59	0.999511434	0.98713859	82	0.999684311	0.918651265
60	0.999322636	0.97987487	83	0.999603926	0.916640537
61	0.999656409	0.973393148	84	0.999668146	0.882636308
62	0.999481427	0.966878497	85	0.999583733	0.90274824
63	0.99963019	0.985990456	86	0.999488751	0.896307118
64	0.999465298	0.977289395	87	0.999585936	0.884407038
65	0.99972681	0.964981886	88	0.999723251	0.91857471
66	0.999772552	0.976599292	89	0.999513316	0.868249158
67	0.999693501	0.967697361			

Supplemental table 4: Equation parameters for estimation of cause-specific 1-year survival

Cardiovascular events proportional hazards function (A)

1-year risk = $1 - (\text{age-specific 1-year baseline survival}^{\text{‡}})^{\exp(\text{linear predictor A})}$

Linear Predictor A =

$0.4847013518(\text{if male}) - 0.0166499486 * \text{SBP}(\text{mmHg}) + 0.0004577939 * \text{SBP}(\text{mmHg}) * \text{age} + 0.1234667275 * \text{non-HDL}(\text{mmol/L}) + 0.0115363192 * \text{BMI}(\text{kg/m}^2) + 0.0277998921(\text{if former smoker}) + 2.1116151356 * (\text{if current smoker}) - 0.0265661110 * \text{age}(\text{if current smoker}) + 1.7320361178(\text{if diabetes mellitus}) - 0.0187873243 * \text{age}(\text{if diabetes mellitus}) + 0.3787129210(\text{if positive parental history of premature MI}) - \log(1.21) - \log(1.17)(\text{if Western Europe or Other}) + \log(\text{CVD-specific hazard ratio of risk-modifying strategy})^{\text{§}}$

Non-cardiovascular mortality proportional hazards function (B)

1-year risk = $1 - (\text{age-specific 1 year baseline survival}^{\text{‡}})^{\exp(\text{linear predictor B})}$

Linear Predictor B =

$- 2.622119558(\text{if male}) + 0.041989661 * \text{age}(\text{if male}) + 0.003298955 * \text{SBP}(\text{mmHg}) - 0.596734702 * \log(\text{non-HDL}(\text{mmol/L})) - 0.112139195 \text{BMI}(\text{kg/m}^2) + 0.001953504 * \text{BMI}(\text{kg/m}^2) * \text{BMI}(\text{kg/m}^2) + 0.228458365(\text{if former smoker}) - 0.790213483(\text{if current smoker}) + 0.024262826 * \text{age}(\text{if current smoker}) + 0.687610988(\text{if diabetes mellitus}) - 0.006812761 * \text{age}(\text{if diabetes mellitus}) - 0.072315309(\text{if positive parental history of premature MI}) - \log(0.98) - \log(0.85)(\text{if Western Europe or Other}) + \log(\text{n-CVD mortality specific hazard ratio of risk-modifying strategy})^{\text{§}}$

[‡] Age-specific baseline survival functions are depicted in supplemental table 2.

[§] Hazard ratio of risk-modifying strategy is explained in supplemental methods.

SBP = systolic blood pressure; HDL = high-density lipoprotein cholesterol; BMI = Body mass index; CVD= cardiovascular disease; MI = myocardial infarctions

Supplemental table 5: Example of a life table

Age	Cumulative Survival	CVD Risk (%)	Non-CVD mortality risk (%)	Attributable CVD-risk	Sum attributable risk
70	1.000000	1.53	1.20	1.53	1.53
71	0.972664	1.85	1.31	1.80	3.33
72	0.941904	1.26	1.35	1.19	4.52
73	0.917303	1.31	1.47	1.20	5.72
74	0.891815	1.52	1.00	1.35	7.07
75	0.869370	1.79	1.80	1.56	8.63
76	0.838166	2.02	2.16	1.69	10.33
77	0.803100	1.85	1.70	1.48	11.81
78	0.774635	2.14	2.71	1.66	13.47
79	0.737078	2.72	2.13	2.01	15.48
80	0.701320	2.02	2.33	1.41	16.89
81	0.670840	1.82	3.01	1.22	18.11
82	0.638402	2.67	3.77	1.71	19.82
83	0.597302	3.59	4.02	2.14	21.96
84	0.551825	3.24	5.96	1.79	23.75
85	0.501053	4.35	5.12	2.18	25.93
86	0.453623	5.71	5.69	2.59	28.52
87	0.401910	4.99	6.63	2.01	30.53
88	0.355205	3.62	4.82	1.28	31.81
89	0.325224	6.73	8.22	2.19	34.00
90	0.276593				

Legend: Lifetable for patient example A (figure 3), 70 year old non-diabetic, formerly smoking male with a BMI of 28 kg/m², a non-HDL-c of 5.0 mmol/L, a SBP of 160mmHg, and a negative parental history of premature MI. CVD-risk(%) and non-CVD(mortality) are derived using the equations depicted in supplemental table 4. CVD-free life-expectancy is the age at which the cumulative survival drops below 0.5. For The sum of the attributable risk at the end of each life-year is the risk associated with that time-frame. this individual, the 10-year risk of CVD-events is 15.5%, the lifetime risk of CVD-events is 34.0 and the CVD-free life-expectancy is 85.0 years. Attributable risk = CVD risk / (Non-CVD mortality risk + CVD risk)*(cumulative survival at beginning of current life-year – cumulative survival at beginning of next life-year).

Supplemental table 6: Median predicted 10-year risk of CVD per age

Age	Median Predicted 10-Year	Median Predicted 10-Year
	CVD Risk Men (%)	CVD Risk Woman(%)
45	1.31	0.81
46	1.91	1.16
47	2.49	1.49
48	3.05	1.82
49	3.57	2.12
50	4.06	2.42
51	4.52	2.70
52	4.95	2.97
53	5.36	3.23
54	5.74	3.47
55	6.08	3.70
56	6.41	3.92
57	6.71	4.12
58	6.95	4.28
59	7.11	4.40
60	7.27	4.51
61	7.48	4.69
62	7.75	4.90
63	8.04	5.11
64	8.33	5.35
65	8.64	5.62
66	8.93	5.93
67	9.22	6.25
68	9.54	6.62
69	9.92	7.03
70	10.35	7.47
71	10.80	7.95
72	11.29	8.46
73	11.82	9.01
74	12.37	9.59
75	12.97	10.21
76	13.60	10.87
77	14.26	11.56

78	14.96	12.28
79	15.70	13.04
80	16.47	13.84

Legend: Predicted values for 10-year CVD risk in men (n=3,241) and women (n=3,474) based on the respective loess curves (locally weighted scatterplot smoothing) of predicted 10-year risk as a function of age in the validation cohort of the Multi - Ethnic Study of Atherosclerosis

Supplemental table 7: Discrimination of the LIFE-CVD model

	Subdistribution Hazard Function A (CVD-events)	Subdistribution Hazard Function B (Non-CVD) mortality	Combined events (LIFE-CVD model)
MESA (n = 6,526)	0.73 (0.71-0.75)	0.76 (0.75-0.78)	0.74 (0.73-0.75)
ARIC (n = 9,250)	0.68 (0.66-0.69)	0.71 (0.70-0.72)	0.70 (0.69-0.71)
HNR (n = 4,177)	0.71 (0.68-0.74)	0.72 (0.70-0.75)	0.72 (0.70-0.74)
EPIC-NL (n = 25,833)	0.71 (0.70-0.72)	0.67 (0.66-0.68)	0.69 (0.68-0.70)
EPIC-Norfolk (n=23,548)	0.76 (0.76-0.77)	0.74 (0.73-0.75)	0.76 (0.75-0.76)

Legend: Discrimination of expected versus observed risk is given as C-statistic (95% confidence interval) for both internal (MESA) and external (ARIC, HNR, EPIC-NL) validation of 10-year risk. MESA = Multi-ethnic Study of Atherosclerosis; ARIC = Atherosclerosis Risk in Communities Study; HNR = Heinz Nixdorf Recall Study; EPIC-NL = European Prospective Investigation into Cancer and Nutrition-Netherlands; EPIC-Norfolk = European Prospective Investigation into Cancer and Nutrition-Norfolk.

Supplemental table 8: Race-stratified discrimination of the LIFE-CVD model

	Subdistribution Hazard Function A (CVD-events)	Subdistribution Hazard Function B (Non-CVD) mortality	Combined events (LIFE-CVD model)
MESA			
Caucasian	0.74 (0.71-0.77)	0.77 (0.74-0.79)	0.74 (0.72-0.76)
African American	0.69 (0.66-0.73)	0.76 (0.73-0.79)	0.73 (0.71-0.75)
ARIC			
Caucasian	0.67 (0.66-0.69)	0.71 (0.70-0.73)	0.70 (0.69-0.71)
African American	0.68 (0.65-0.70)	0.70 (0.68-0.73)	0.69 (0.68-0.72)

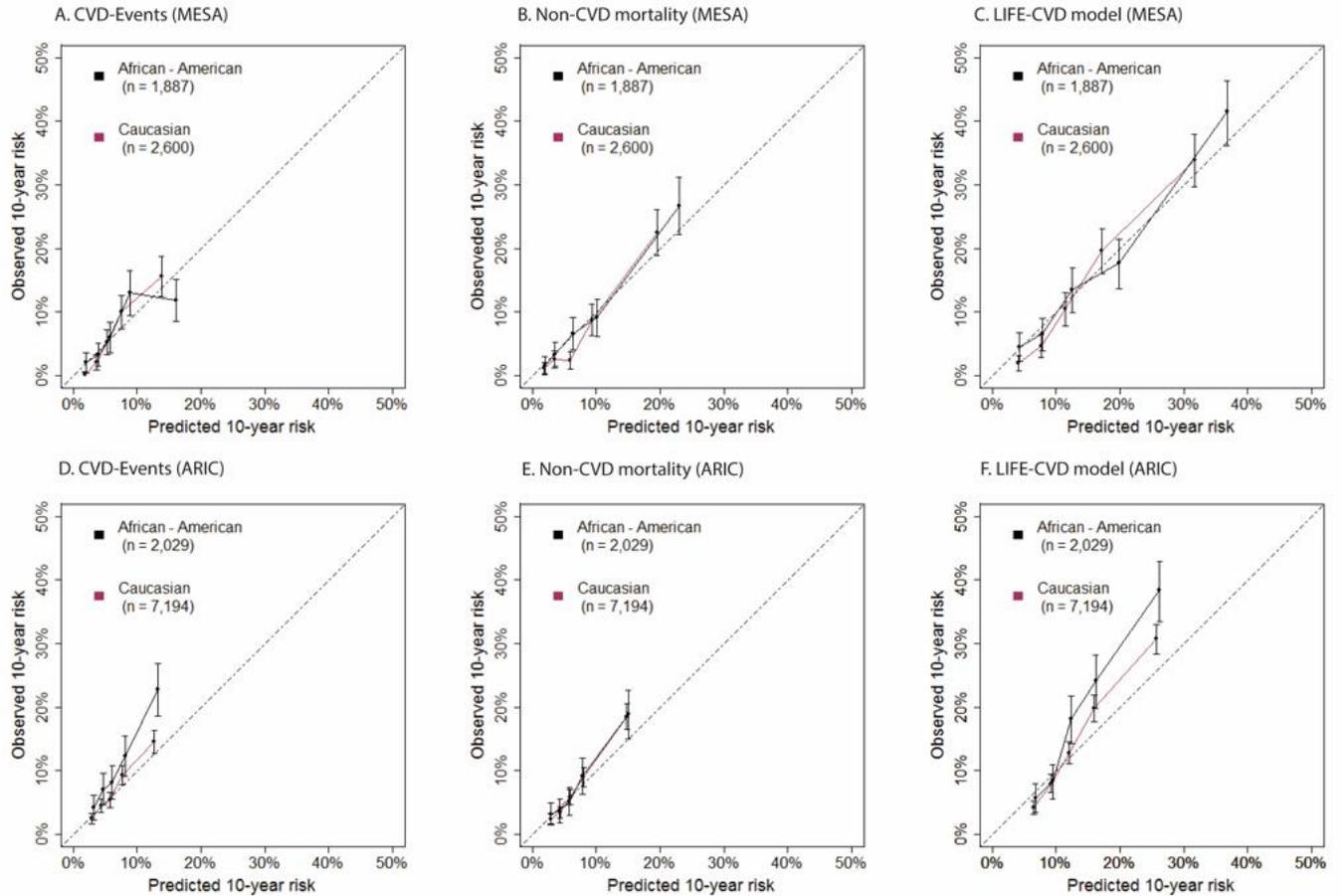
Legend: Discrimination of expected versus observed risk is given as C-statistic (95% confidence interval) for both internal (MESA) and external (ARIC) validation of 10-year risk, stratified by race. MESA = Multi-Ethnic Study of Atherosclerosis; ARIC = Atherosclerosis Risk in Communities Study; HNR = Heinz Nixdorf Recall Study;

Supplemental table 9: Multivariable hazard ratios African-American versus Caucasian

	Subdistribution hazard function A (CVD-events)	Subdistribution hazard function B (non-CVD mortality)
African-American (MESA)	0.90 (0.73-1.10)	1.03 (0.86-1.22)
African-American (ARIC)	1.34 (1.18-1.52)	0.89 (0.78 – 1.01)*

Legend: Multivariate hazard ratios for African-American compared to Caucasian (ref) for a model derived in the Multi-Ethnic Study of Atherosclerosis (MESA) and a model derived in the Atherosclerosis Risk in Communities Study (ARIC).

*Age-dependent variables. Hazard ratios shown for the median age of 62 years.



Supplemental figure 1: Internal and external validation of the predicted versus observed 10-year risk of CVD-events and non-CVD mortality combined in MESA (A-C) and ARIC (D-F) stratified by race (African-American) and Caucasian. Bars represent 95% confidence intervals of observed risk in each quintile.