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A cardiovascular risk prediction model for older people: Development and validation in a primary care population

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Abstract

Cardiovascular risk prediction is mainly based on traditional risk factors that have been validated in middle-aged populations. However, associations between these risk factors and cardiovascular disease (CVD) attenuate with increasing age. Therefore, for older people the authors developed and internally validated risk prediction models for fatal and non-fatal CVD, (re)evaluated the predictive value of traditional and new factors, and assessed the impact of competing risks of non-cardiovascular death. Post hoc analyses of 1811 persons aged 70-78 year and free from CVD at baseline from the preDIVA study (Prevention of Dementia by Intensive Vascular care, 2006-2015), a primary care-based trial that included persons free from dementia and conditions likely to hinder successful long-term follow-up, were performed. In 2017-2018, Cox-regression analyses were performed for a model including seven traditional risk factors only, and a model to assess incremental predictive ability of the traditional and eleven new factors. Analyses were repeated accounting for competing risk of death, using Fine-Gray models. During an average of 6.2 years of follow-up, 277 CVD events occurred. Age, sex, smoking, and type 2 diabetes mellitus were traditional predictors for CVD, whereas total cholesterol, HDL-cholesterol, and systolic blood pressure (SBP) were not. Of the eleven new factors, polypharmacy and apathy symptoms were predictors. Discrimination was moderate (concordance statistic 0.65). Accounting for competing risks resulted in slightly smaller predicted absolute risks. In conclusion, we found, SBP, HDL, and total cholesterol no longer predict CVD in older adults, whereas polypharmacy and apathy symptoms are two new relevant predictors. Building on the selected risk factors in this study may improve CVD prediction in older adults and facilitate targeting preventive interventions to those at high risk.

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1 | INTRODUCTION

Current guidelines provide insufficient support for cardiovascular disease (CVD) management in older persons.[1] Whereas a large number of CVD prediction models are available for middle-aged adults (45-65 years), for older persons (≥70 years) few CVD prediction models exist.[2-4] Hence, in daily practice, general practitioners (GPs) generally extrapolate risk calculations from models derived from middle-aged populations to older persons, but recent findings indicate that such models predict poorly for this group.[5] This is partly explained by the diminished or even reversed associations between traditional risk factors and CVD in older persons.[6] Moreover, potential other predictors of CVD in older people have been suggested, including an increased C-reactive protein (CRP) as a marker for inflammation,[3] symptoms of apathy,[7] polypharmacy,[8] cholesterol-associated circulating apolipoproteins A1 and B, and gene variants of apolipoprotein E (APOE).[9,10]

While traditionally models predict a ten-year risk of CVD mortality,[4,11,12] older persons and their GPs favor models assessing risk of developing any major atherosclerotic event within a shorter time span.[13] Hence, GPs pragmatically and intuitively weigh additional factors including frailty, multimorbidity, quality of life, and life expectancy in their decision whether or not to start preventive treatment.[14] Furthermore, while risk of death from non-cardiovascular causes competes with CVD events, most existing models in older persons do not account for this,[2,4] and so fueling overestimation of CVD risks.[5,15]

The aim of this paper was therefore to develop and internally validate a risk prediction model for fatal and non-fatal CVD, for people aged 70 years and over, by (re)evaluating the predictive value of traditional factors, exploring additional factors and taking competing risks of non-cardiovascular death into account.

2 | METHODS

This study is reported following the "STrengthening the Reporting of OBservational studies in Epidemiology" checklist.[16]

2.1 | Study population

Patients partook in Prevention of Dementia by Intensive Vascular care (preDIVA), a cluster-randomized controlled trial carried out in primary care in the Netherlands. The methodology of preDIVA has been described in detail.[17] In short, participants aged 70-78 years and free from dementia and conditions likely to hinder successful long-term follow-up according to their GP (eg, terminal illness, alcoholism) were eligible. There was no sex bias in the selection of participants. Of 6762 eligible older adults from 116 GP practices within 26 health care centers (HCC) in the Netherlands, 3526 (52.1%) signed written informed consent. Recruitment was from June 2006 through March 2009. The primary outcome was dementia, and main secondary outcomes were incident CVD and cardiovascular and all-cause mortality. The final assessment was carried out between January 2014 and March 2015. For the present post hoc analyses, all preDIVA participants without a history of CVD at baseline were included. Since no effect of the intervention was found on CVD, neither in the total study population nor in the participants without a history of CVD, the population was considered a cohort.[17,18] The preDIVA study was approved by the Medical Ethics Committee of the Academic Medical Center, Amsterdam (MEC 05/093 06.17.0640).

2.2 | Cardiovascular risk factors

At baseline, a practice nurse at the GP practice assessed data on socio-demographic characteristics, cardiovascular risk factors (blood pressure, type 2 diabetes mellitus [T2DM], cholesterol, BMI, and smoking habits), CRP, apolipoproteins, current medication, symptoms of apathy, family history of CVD, and the APOE genotype.

The traditional risk factors were those used in the SCORE-OP (SCORE for older people) model: age, sex, systolic blood pressure, smoking status, total cholesterol (TC), high-density lipoprotein cholesterol (HDL), and T2DM.[4] Eleven potential additional CVD predictors were selected based on the literature and availability in our dataset: family history of CVD, polypharmacy, antihypertensive medication (AHM) use, physical activity, BMI, apathy symptoms, CRP, low-density lipoprotein cholesterol (LDL), apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), and APOE genotype. Family history of CVD was defined as a CVD event in first-degree relatives before the age of 60. Polypharmacy was defined as the chronic use of drugs from ≥5 ATC (Anatomical Therapeutic Chemical Classification) groups (ATC3 level).[19] Physical activity was measured with the LASA physical activity questionnaire (LAPAQ) and defined as physically active according to the World Health Organization.[17,20] Symptoms of apathy were measured with the three apathy items of the 15-item Geriatric Depression Scare (GDS-3A; range 0-3 points, higher scores indicating more apathy).[7] CRP, LDL, ApoA1, ApoB, and APOE were measured in serum. APOE genotype was included as a nominal variable.

2.3 | Outcome

The outcome was a first cardiovascular event (CVD mortality, myocardial infarction, stroke, transient ischemic attack, angina pectoris, and peripheral arterial disease). In concordance with well-known cardiovascular prediction models in adults, a pragmatic outcome measure was chosen, which meets GP and older patients' preferences and is directly applicable in clinical practice.[2,12,13] During two-year assessments, self-reported history of cardiovascular morbidity was collected and cross-checked with the electronic medical record (EMR). In 73% of deaths, the cause could be retrieved from the EMR and hospital discharge letters. Subsequently, this information was evaluated by an independent outcome adjudication committee.[17]

2.4 | Statistical analyses

Analyses were performed between June 2017 and December 2018. Missing values for traditional and additional predictors were imputed using multivariate imputation by chained equations, using the R library "mice."[21] This way, twenty imputed datasets with no missing data on traditional and additional risk factors were generated. All analyses presented here were performed on all twenty datasets; subsequently, these estimates were pooled into the final result according to Rubin's rules, taking into account variance between and within datasets.

Since the preDIVA study was originally designed as a trial, we tested whether there was a difference between the survival curves for CVD based on "study group." Since this was not significantly associated with CVD risk (P-value for chi-square test for the survival curves in the two treatment groups was 0.84), the study population was further treated as a cohort.

Cox-proportional hazard models were used to derive the functions for estimating CVD morbidity and mortality, using the R library "survival."[22] Time to event was defined as time from baseline assessment to first cardiovascular event, or if no event occurred cases were censored at the last two-yearly study assessment that the participant attended. In model 1, the seven traditional risk factors were included. In model 2, from the 7 traditional and 11 additional factors, relevant predictors were selected using backward selection, with the AIC stopping rule.[23] This is an extensively used selection method in clinical prediction[23,24] that seems to achieve better parsimony in smaller datasets compared to modern tree-based methods.[23] Variables that were selected in >33% of the 20 imputed datasets were kept in the model. Age was forced in the model, since previous studies agreed on age as a risk factor, and the age range in this population was limited. The proportional hazard assumption of the Cox model was assessed by examining the Schoenfeld residuals, and splines were used to verify whether linearity of continuous variables would hold.

Subsequently, we tested for interaction among traditional risk factors, because the association between potential risk factors on the outcome might depend on other risk factors.[4,6] Models were not stratified for sex as none of the associations significantly differed between men and women. Furthermore, we checked whether multicollinearity between risk factors existed among cholesterol-related variables (TC, HDL, LDL, ApoA1, ApoB), among the use of antihypertensive and cholesterol-lowering medication and polypharmacy, and between polypharmacy, SBP, and cholesterol-related variables. The method as proposed by Fine and Gray was used to account for competing risks of non-cardiovascular death, using the R library "riskRegression."[25,26] The event was defined as first CVD event, the competing event as non-cardiovascular mortality.

2.5 | Model performance and discriminative ability

Discriminative ability was calculated and compared between models using the inverse probability of censoring weighted (IPCW) C-index. Models were internally validated using bootstrapping. Calibration slopes were generated for 100 bootstrap samples per imputed dataset. The resulting shrinkage factors after bootstrapping for the respective models were used to adjust for overestimation of the regression coefficients and overfitting of the models.

2.6 | Sensitivity analyses

To evaluate the effect of missing values, that is, the imputation process, we performed a complete case analysis for model 1. Furthermore, to explore the impact of cardiovascular medication, analyses were repeated in subgroups of participants (a) without baseline cardiovascular medication use, (b) without cardiovascular medication at baseline nor during the first 4 years of follow-up, and (c) in the control and intervention condition of preDIVA. Next, we explored the impact on predictive value and predictor selection of using cardiovascular medication (antihypertensive and cholesterol-lowering drugs) in patients with the highest cardiovascular risk. For this, backward selection was performed on a model including all 18 variables, in which, for polypharmacy, all but cardiovascular medications were counted. Lastly, baseline cholesterol-lowering medication use was added as a variable to the full model to explore its impact on cholesterol-related variables.

3 | RESULTS

Of 2254 preDIVA participants without prior CVD at baseline, 1811 (80%) had information on CVD and mortality during follow-up. The 443 participants excluded from the analyses had less often T2DM (11.7% vs 16.7%), were more often smokers (15.8% vs 11.8%) and not physically active (82.4% vs 89.7%), received more often <7 years of education (21.8% vs 30.0%), and had more often the APOE Ɛ3 - Ɛ4 variant (20.2% vs 22.6%) compared to those included in the analyses (Table S1). Of the 1811 included participants, 429 (24%) had missing information on one or more risk factors; for each risk factor, the number of missings is summed in the legend of Table 1. After multivariate imputation, twenty imputed datasets containing the 1811 cases with no missing data were available for analyses. Baseline characteristics are shown in Table 1. During a median follow-up of 6.2 years (interquartile range 3.9-7.1 years), 277 first CVD events occurred, of which 131 coronary heart disease (CHD) events. This corresponds with a 5-year cumulative incidence of 11.5% of CVD events.

For all traditional and additional predictors, linear relations between predictors and the outcome variable were appropriate. Proportional hazard assumptions were met, and interaction terms among traditional predictors were not significant and therefore disregarded in the final models. There was only relevant multicollinearity among cholesterol-related variables (ApoB*TC [Pearson's r 0.79], ApoB*LDL [Pearson's r 0.84], and TC*LDL [Pearson's r 0.92]).

Table 2 shows the results of the Cox-regression analyses after shrinkage, when including all traditional risk factors (model 1) and when including variables that remained relevant after backward selection (model 2). Within model 1, the strongest predictors were active smoking (HR 1.85 [95% CI 1.41-2.43]), T2DM (1.63 [95% CI 1.24-2.13]), and male sex (1.32 [95% CI 1.05-1.65]). Of the additional

TABLE 1 Baseline characteristics of participants[a]

Baseline characteristics	Overall (n = 1811)	Without incident CVD (n = 1534)	With incident CVD (n = 277)	P-value
Demographics				
Age in y, mean (SD)	74.1 (2.4)	74.1 (2.4)	74.2(2.5)	0.36
Sex, male (%)	717 (39.6)	588 (38.3)	129 (46.6)	0.01
Educational level, no. (%)				
<7 y	392 (21.8)	330 (21.5)	62 (22.4)	0.39
7-12 y	1169 (65.1)	1000 (65.2)	169 (61.0)	
>12 y	235 (13.1)	193 (12.6)	42 (15.2)	
Caucasian, no. (%)	1741 (97.8)	1474 (96.1)	267 (96.4)	0.11
Traditional cardiovascular risk factors				
SBP in mm Hg, mean (SD)	155.6 (20.6)	154.9 (20.2)	158.9 (22.2)	0.01
Total cholesterol in mmol/L, mean (SD)	5.51 (1.04)	5.52 (1.03)	5.42 (1.12)	0.16
HDL-cholesterol in mmol/L, mean (SD)	1.56 (0.42)	1.57 (0.42)	1.50 (0.40)	0.01
Type 2 diabetes, no. (%)	302 (16.7)	236 (15.4)	66 (23.8)	<0.001
Current smoking, no. (%)	214 (11.8)	161 (10.5)	53 (19.1)	<0.001
Additional cardiovascular risk factors				
LDL cholesterol in mmol/L, mean (SD)	3.35 (2.74-3.95)	3.36 (2.75-3.95)	3.23 (2.63-3.93)	0.23
C-reactive protein (CRP), mg/L, median (IQR)	2.00 (1.00-4.00)	2.00 (1.00-3.50)	2.00 (1.00-4.00)	0.03
Circulating apolipoproteins A1 (g/L), mean (SD)	1.51 (0.29)	1.52 (0.29)	1.46 (0.28)	<0.001
Circulating apolipoproteins B (g/L), mean (SD)	1.00 (0.25)	1.00 (0.25)	1.00 (0.26)	0.96
Apolipoprotein E gene variants, no. (%)				
Ɛ2 - Ɛ2	7 (0.4)	5 (0.3)	2 (0.7)	0.89
Ɛ2 - Ɛ3	237 (13.1)	202 (13.2)	35 (12.6)	
Ɛ3 - Ɛ3	890 (49.1)	759 (49.5)	131 (47.3)	
Ɛ3 - Ɛ4	365 (20.2)	311 (20.3)	54 (19.5)	
Ɛ4 - Ɛ4	35 (1.9)	31 (2.0)	4 (1.4)	
BMI (kg/m^2), mean (SD)	27.3 (4.3)	27.34 (4.3)	27.36 (4.2)	0.93
Polypharmacy (≥5 medicine), no. (%)	378 (20.9)	299 (19.5)	79 (28.5)	<0.001
Use of antihypertensive(s), no (%)	760 (42.0)	625 (40.7)	135 (48.7)	0.01
Family history of CVD[b], no. (%)	262 (14.5)	217 (14.1)	45 (16.2)	0.40
Physically active (WHO), no. (%)	1587 (89.7)	1347 (87.8)	240 (86.6)	0.33
Symptoms of apathy (GDS3A), no. (%)				
0	1042 (57.7)	906 (59.1)	136 (49.1)	0.01
1	484 (26.8)	402 (26.2)	82 (29.6)	
2	199 (11.0)	160 (10.4)	39 (14.1)	
3	80 (4.4)	61 (4.0)	19 (6.9)	

Note: Population without a history of CVD. Percentages reflect the proportion within participants with available information. The following variables had missing data (n): educational level (15), caucasian (30), SBP (2), total cholesterol (34), HDL (32), current smoking (2), LDL (34), CRP (60), apolipoprotein A1 (117), apolipoprotein B (117), APO E gene variants (277), BMI (1), use of antihypertensive(s) (6), physically active (41), symptoms of apathy (6).
Abbreviations: BMI, body mass index; CVD, cardiovascular disease; GDS3A, three apathy items on the 15-item geriatric depression scale; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; SBP, systolic blood pressure; SD, standard deviation; WHO, World Health Organization.
[a]Based on non-imputed data.
[b]Family history of CVD in first-degree relatives before the age of 60.

potential predictors, polypharmacy (1.41 [95% CI 1.08-1.83]) and apathy symptoms (1.19 per point increase on the GDS-3A [95% CI 1.05-1.34]) remained in model 2.

To facilitate the estimation of the predicted 5-year risk of combined cardiovascular morbidity and mortality for older persons, Table S2 shows beta-coefficients for each risk factor of models 1

TABLE 2 Hazard ratios for traditional and additional risk factors for CVD morbidity and mortality

| | | Cox-PH models | | Fine-Gray models | |
| | | Model 1: traditional risk factors | Model 2: variables selected through backward selection[a] | Model 3: traditional risk factors | Model 4: variables of model 2 |
Predictor category	Predictors	HR (95% CI)	HR (95% CI)	HR (95% CI)[b]	HR (95% CI)[b]
Traditional risk factors	Age	1.03 (0.99-1.08)	1.03 (0.98-1.08)	1.03 (0.99-1.08)	1.03 (0.98-1.08)
	Male	1.32 (1.05-1.65)	1.45 (1.16-1.81)	1.31 (1.04-1.64)	1.42 (1.14-1.78)
	Smoking status	1.85 (1.41-2.43)	1.83 (1.38-2.43)	1.76 (1.34-2.30)	1.73 (1.31-2.28)
	SBP per mm Hg	1.01 (1.00-1.01)		1.01 (1.00-1.01)	
	Total cholesterol per mmol/L	1.05 (0.94-1.18)		1.05 (0.93-1.18)	
	HDL per mmol/L	0.81 (0.61-1.09)		0.83 (0.63-1.10)	
	T2DM	1.63 (1.24-2.13)	1.44 (1.09-1.89)	1.60 (1.23-2.08)	1.40 (1.07-1.83)
Additional risk factors	Polypharmacy		1.41 (1.08-1.83)		1.40 (1.08-1.82)
	Symptoms of apathy		1.19 (1.05-1.34)		1.18 (1.05-1.33)
Performance	IPCW C-index	0.651	0.643	0.641	0.632

Note: Larger numbers indicate better performance.
All HRs shown after shrinkage. Model 3 and 4 account for competing risks of death.
Abbreviations: 95% CI, 95% confidence interval; BMI, body mass index; Cox-PH, Cox-proportional hazard; CRP C-reactive protein; CVD, cardiovascular disease; HDL, high-density lipoprotein; IPCW C-index, inverse probability of censoring weighted concordance-index; LDL, low-density lipoprotein; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus.
[a]Variables tested in the backward procedure: age, sex, smoking status, SBP, total cholesterol, HDL, T2DM, family history of CVD, polypharmacy, antihypertensive medication use, physical activity, BMI, symptoms of apathy, CRP, LDL, apolipoprotein A1, apolipoprotein B, and apolipoprotein E genotype. Age was forced into the model.
[b]Hazard ratios for the subdistribution hazards of the Fine and Gray model.[25]

and 2, and the baseline hazard for a 5-year period, for a hypothetical person with all variables set at zero. To get an impression of absolute risks when expanding CVD risk prediction in the Dutch guideline to age 70 and 75, a chart based on traditional risk factors (model 1, Equation S1) was developed, presenting five-year absolute risks of CVD morbidity or mortality (Figure S1).[27]

3.1 | Competing risks of non-cardiovascular death

During the 6.2 years of follow-up, 94 non-cardiovascular deaths occurred. Compared to models 1 and 2, not accounting for competing risk of death, the beta-coefficients and HRs for the subdistribution in the competing risk models (models 3 and 4) are slightly smaller, representing a more meaningful prediction of absolute risks.(Table 2, Table S2) Based on Equation S1, and the baseline hazard and beta-coefficients of model 3, charts presenting 5-year absolute risks of CVD morbidity or mortality accounting for competing risk of non-cardiovascular death for persons aged 70 and 75 years were developed (Figure S2).

3.2 | Model performance

The discriminative performance of the models was moderate (IPCW C-statistic 0.663 in model 1 to 0.642 in model 4) (Table 2), and differences were small. Using the six factors of model 2 and 4 resulted

in similar predictive ability to using the seven factors of models 1 and 3. Performance of a model containing all 18 variables was similar to the other models (IPCW C-statistic 0.643).

For models 1 and 2, the shrinkage factors were 0.9028 and 0.9326, and for models 3 and 4, the shrinkage factors were 0.9013 and 0.9213, respectively. Calibration risk was plotted for all models in Figure S3.

3.3 | Sensitivity analyses

Analyses in the subgroup with complete cases (n = 1382), the subgroup without cardiovascular medication at baseline (n = 920), the subgroup without cardiovascular medication at baseline nor the first 4 years of follow-up (n = 726), and subgroups for the control and intervention condition of preDIVA did not alter the results for model 1 (Table S3).

In a sensitivity analysis defining polypharmacy as ≥5 medicines, excluding cardiovascular medication, polypharmacy was no longer significantly associated with the outcome. After backward selection, smoking status, T2DM, and apathy symptoms remained relevant predictors (Table S4, Model 5). In a sensitivity analysis adding cholesterol-lowering drugs as a variable to the complete model with 18 variables, the HR for cholesterol-lowering drugs was 1.02 (95% CI 0.72-1.43) and HRs of the other 18 variables in the model did not change.

4 | DISCUSSION

In our study among 1811 community dwelling older persons with no history of CVD, age, sex, smoking status, T2DM, polypharmacy, and symptoms of apathy were predictors for CVD, whereas total cholesterol, HDL-cholesterol, SBP, and other additional factors were not.

All models had moderate ability to predict CVD. The model taking into account competing risk of non-cardiovascular death offers more meaningful estimates for the risk of cardiovascular events in this older population.

Few models of varying quality predicting 5-year risk of combined CVD morbidity and mortality in persons aged 70 and over have been published, and results regarding the predictive ability of traditional risk factors are conflicting. In some studies selecting predictors for CVD mortality in older people, all traditional risk factors contributed to risk prediction, whereas in others, none of the traditional risk factors did.[4,28-30]

In two studies, SBP, HDL-cholesterol, and total cholesterol remained among the best predictors for combined CVD morbidity and mortality,[31,32] and in one study, SBP had no predictive value and TC and HDL only when no new variables (CRP, homocysteine, waist-to-hip ratio, and self-reported health) were added to the model.[3] In another study, T2DM, smoking, and HDL, but not SBP and TC, were predictors for coronary heart disease.[31] In our study, SBP, total cholesterol, and HDL-cholesterol had no relevant predictive value beyond the six selected predictors, which is in line with the theory of reverse epidemiology in older persons.[6,28] Differences among studies can be explained by the differences in study populations (eg, age range, exclusion criteria), outcome measures (eg fatal versus combined fatal and non-fatal disease and coronary heart disease versus CVD), the set of traditional, and new, predictors added in the model, and definitions and handling of variables in the models. More high-quality studies are needed before the traditional risk factors that were disregarded in our study, can be finally disregarded as predictors for CVD in older people.

The incremental predictive ability of polypharmacy and apathy symptoms for CVD in older people has not been studied before. In our study, these two variables were predictors for fatal and non-fatal CVD in older persons. Polypharmacy as a predictor is consistent with a previous study with 1196 older people (aged ≥ 65 years) where "number of medications" was identified as an additional predictor for fatal CVD.[29] Polypharmacy is a complex product of patient characteristics, physician management, and patient preferences.[14] However, it is easy to ascertain and can therefore easily be implemented in risk prediction. When cardiovascular medication was excluded from the medication counted to assess polypharmacy, polypharmacy no longer added any relevant predictive ability. This indicates that cardiovascular medication adds to the predictive value of polypharmacy, although the use of antihypertensive or cholesterol-lowering medication were no predictors on their own. Besides, this does not disqualify polypharmacy as a predictor, since in daily

practice persons with and without cardiovascular medication receive risk assessments. Apathy symptoms have recently been independently associated with CVD in older people (mean age 74 years) in a large meta-analysis of individual participant data (n = 74 625).[7] Polypharmacy and apathy symptoms are promising new predictors for CVD in old age that are easy to ascertain without extra costs or invasive tests. Since there are no other studies testing their predictive value, our results need to be confirmed in other cohorts of older people.

In previous studies, circulating concentrations of apolipoproteins (ApoA1 [protective factor] and ApoB [risk factor]) as well as apolipoprotein E gene variants have been associated with incident CVD in populations including older persons.[9,10] In our study, they did not have incremental predictive value. ApoA1 and ApoB are correlated with serum cholesterol (TC, HDL, and LDL), which did not relevantly improve predictive value either. The incremental predictive value of BMI,[6] CRP,[3,28] and family history of CVD has previously been studied in older people, yielding conflicting results.[32] Our study suggests that BMI, CRP, physical activity, and family history of CVD are not useful in predicting CVD in older persons.

We provided models with and without accounting for competing risk. Norway is the first country to include CVD prediction models that account for competing risk of death in their clinical guidelines.[15] Absolute risks are generally slightly lower compared to risks calculated in models ignoring or censoring competing events. Implementing competing risks into prediction models is preferable, since it gives real life, and therefore, more meaningful estimates of the older persons' absolute CVD risk.

Discriminatory performance in most CVD prediction models for older people is modest. The models presented here, with IPCW c-indexes of 0.63 and 0.64 for selected risk factors with and without accounting for competing events, are no exception. C-statistics of other models developed in populations of older people ranged from 0.63[5] to 0.74.[4]

4.1 | Limitations

A strength of this study is the external validity. The population is comparable to a population from national cohort data in terms of risk factor occurrence,[33] and incidence of CVD morbidity and mortality (5-year cumulative incidence was 13.0% and 10.4% in two previously published population-based cohorts of older people, and 11.5% in our study).[3,32] Additionally, there were few exclusion criteria, and excluded participants are generally not considered for CVD risk calculation. The 24% of participants with missing predictors at the baseline were retained in the analyses by using multiple imputation. Besides, results of complete case analyses did not differ from the main analyses. The models, therefore, appear valid for use in non-acute primary care consultations.

Additional value is added by this study as it presented various models to facilitate comparison to existing models. While CHD and non-CHD events may have different predictors, with the pragmatic combined outcome measure of CVD morbidity and mortality, within

a 5-year prediction horizon, we concede to GP and older patient preferences.[13]

Treatment of baseline risk factors could have reduced overall predictive ability in our population of older people.[34] However, in analyses including cholesterol-lowering and antihypertensive medication as variables, and an analysis excluding participants that started cardiovascular medication ("treatment drop-ins"), results did not differ from the main analyses. This indicates that medication use did not influence the predictive value of our predictors, and that the models can be used in individuals with and without cardiovascular medication.

Multiple testing on a relatively small number of events (n = 277) may result in false-positive or false-negative results, but our results are robust using different methods, and in sensitivity analyses. Finally, evaluation of additional factors was limited to factors available in our dataset. There might be other factors with strong predictive ability not available in our data.[28,35]

Our results provide insight into absolute risk of CVD for older persons. However, treatment implications are patient to continued discussion. Especially in older people, the optimal cutoff value for starting treatment is unknown.[1] In middle-aged adults weighing risks and benefits from treatment, a cutoff of 20% of CVD morbidity and mortality in the next 10 years is generally agreed on.[1] With increasing age, shorter life expectancy, and multimorbidity, the balance between potential harms and benefits of long-term medication may shift, requiring doctors to reconsider whether (continued) cardiovascular medication is still justified.[36]

In conclusion, of the traditional risk factors, only age, sex, smoking status, and T2DM showed predictive ability in people aged 70-78 years, whereas total cholesterol, HDL-cholesterol, and SBP did not. From a set of eleven additional factors, polypharmacy and apathy symptoms were identified as new predictors for CVD in this age group. Accounting for competing risk of death resulted in more meaningful prediction. Building on the selected risk factors in this study combined with other potential risk factors may improve prediction of CVD in older adults and facilitate targeting preventive interventions to those at high risk.

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CONFLICT OF INTEREST

AUTHOR CONTRIBUTIONS

EFvB, MPHB, ER, WAvG, EWS, and EPMvC contributed to the conception or design of the work. EFvB, MPHB, WBB, ER, WAvG, EWS, and EPMvC contributed to the acquisition, analysis, or interpretation of data for the work. EFvB drafted the manuscript. All authors critically revised the manuscript and gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

ETHICAL APPROVAL

The study was approved by the Medical Ethics Committee of the Academic Medical Center, Amsterdam (MEC 05/093 #06.17.0640).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.