Development of a new cardiovascular risk model for primary prevention in subjects aged 80 and older

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Table of contents

Abstract (ENG) 3

Abstract (NL) 4

Background 5

Methods 6

- Study population 6
- Clinical variables 6
- Outcome 7
- External validation 7
- Data analysis 8

Results 9

Discussion 10

Conclusion 12

References 13

Tables and figures 16

Mandatory attachments 21

Abstract

Background

To date, no specific risk scores for estimating primary cardiovascular risk in the oldest old exist. This study was performed to develop a new risk model to predict 3-year cardiovascular morbidity and mortality based on traditional cardiovascular risk factors and biomarkers.

Methods

New risk models were developed in the BELFRAIL study, a population-based cohort study in Belgium. Cox regression analysis was used to estimate the hazard ratio of individual risk factors for the combined end-point. Four different risk models were built. Harrell's C statistics, net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were used to compare the predictive value of the different models. The net benefit was calculated and decision curves were constructed. An external validation of the four models was performed in the Leiden 85-Plus Study.

Results

In total, 266 subjects with a mean age of 84.3±3.6 years were included. Model 1 included all the traditional cardiovascular risk factors; model 2 included all traditional risk factors and NT-proBNP; model 3 included age, gender, cholesterol and NT-proBNP; model 4 included age, gender and NT-proBNP. Model 2 showed a Harrell's C statistic of 0.72 and had the highest NRI and relative IDI as compared to model 1 (0.56 (95%CI 0.16-0.99) and 4.01 (95%CI 2.19-6.28), respectively). Model 3 and 4 also showed very high relative IDIs compared to model 1 (3.69 (95%CI 1.72-6.38) and 3.44 (95%CI 1.56-6.09), respectively). All models showed a higher net benefit at each threshold probability compared to model 1, and approached each other.

Conclusion

Traditional cardiovascular risk factors poorly predicted 3-year cardiovascular morbidity and mortality in the oldest old with no history of cardiovascular events. However, NT-proBNP showed a strong added predictive value. Even a prediction model only based on NT-proBNP, age and gender performed extremely well as opposed to the traditional risk factors.

Key words

Aged 80 and over; primary cardiovascular prevention; NT-proBNP; risk prediction

Ontwikkeling van een nieuw cardiovasculair risicomodel voor primaire preventie in de oudste ouderen

Abstract

Achtergrond

Tot op heden bestaan er geen specifieke risico scores om een inschatting te maken van het cardiovasculair risico voor de oudste ouderen in primaire preventie. Deze studie werd uitgevoerd met als doel een nieuw risicomodel voor de voorspelling van 3-jaars cardiovasculaire morbiditeit en mortaliteit te ontwikkelen gebaseerd op traditionele cardiovasculaire risicofactoren en biomarkers.

Methode

Nieuwe risicomodellen werden ontwikkeld in de BELFRAIL-studie, een bevolkingsgerichte cohortstudie in België. Een Cox regressie analyse werd uitgevoerd om de hazard ratio's van de individuele risicofactoren te bepalen voor het gecombineerde eindpunt. Vier verschillende risicomodellen werden opgesteld. Harrell's C statistics, 'net reclassification improvement' (NRI) en 'integrated discrimination improvement' (IDI) werden berekend om de voorspellende waarde van de verschillende modellen te vergelijken. De 'net benefit' werd bepaald en 'decision curves' werden opgesteld. Een externe validatie van de vier modellen werd uitgevoerd in de Leiden 85-Plus Studie.

Resultaten

In totaal werden er 266 personen met een gemiddelde leeftijd van 84.3 ± 3.6 jaar geïncludeerd. Model 1 omvatte alle traditionele cardiovasculaire risicofactoren; model 2 omvatte alle traditionele risicofactoren en NT-proBNP; model 3 omvatte leeftijd, geslacht, cholesterol en NT-proBNP; model 4 omvatte leeftijd, geslacht en NT-proBNP. Model 2 toonde een Harrell's C statistic van 0,72 en had de hoogste NRI en relatieve IDI vergeleken met model 1 (0.56 (95%CI 0.16-0.99) en 4.01 (95%CI 2.19-6.28), respectievelijk). Model 3 en 4 toonden ook zeer hoge relatieve IDIs vergeleken met model 1 (3.69 (95%CI 1.72-6.38) en 3.44 (95%CI 1.56-6.09), respectievelijk). Alle modellen toonden een hogere net benefit voor elke treshold probability in vergelijking met model 1 en benaderden elkaar.

Conclusie

Traditionele cardiovasculaire risicofactoren voorspelden zeer slecht 3-jaars cardiovasculaire morbiditeit en mortaliteit bij de oudste ouderen in primaire preventie. Echter, NT-proBNP toonde een sterke toegevoegde voorspellende waarde. Zelfs een predictiemodel alleen gebaseerd op NT-proBNP, leeftijd en geslacht deed het extreem goed in tegenstelling tot de traditionele risicofactoren.

Kernwoorden: 80 jaar en ouder; oudste ouderen; primaire cardiovasculaire preventie; NT-proBNP; risico predictie

Background

Subjects aged 80 years and older are the fastest growing age segment in the developed world. By 2050, about 1 in 10 individuals living in Belgium will be aged 80 years or older [1]. Delaying or preventing new-onset cardiovascular disease is very important in this elderly population. Cardiovascular disease is a considerable cause of disability, morbidity and mortality [2] and cardiovascular disease status is of important prognostic value in old age [3]. Therefore, early detection and treatment of cardiovascular disease in very old people with no history of cardiovascular events might help in preserving cognitive function, independency, functional status and quality of life [2].

To estimate the cardiovascular risk of a patient with no history of cardiovascular events, clinicians can use pre-existing risk scores and risk charts. The SCORE [4] and the Framingham Risk Score [5 - 6] are the most commonly used and best known risk scores. Other examples are the QRISK [7 - 8] and the ACC-AHA risk calculator [9]. However, these risk scores were derived from data of middle-aged people and have not been validated in the oldest old.

Little is known about primary cardiovascular prevention in the oldest old. To date, there are no specific risk scores developed for subjects aged 80 years and older. Moreover, observational studies have shown that traditional cardiovascular risk factors lose their predictive value in the oldest old or even act in the reverse direction [2, 10 - 18]. Furthermore, there is evidence that biomarkers, such as NT-proBNP [2, 19 - 20], C reactive protein [11], interleukin 6 [11, 16] and homocysteine [11] can be used as a predictor of cardiovascular morbidity and mortality and improve the accuracy of risk estimation in the oldest old when added to traditional risk factors, but also in isolation [11]. There is an increasing need to generate a simple, easily applicable risk model for primary cardiovascular risk prediction in the oldest old [10, 21 - 22].

Therefore, this study was performed to develop a new risk model to predict 3-year cardiovascular morbidity and mortality in the oldest old with no history of cardiovascular events, based on traditional risk factors and biomarkers by using data of the BELFRAIL cohort study [23]. An external validation of the new risk models was performed in the Leiden 85-plus Study [24].

Methods

Study population

The BELFRAIL cohort study is an observational population-based prospective cohort study of oldest old in three well-circumscribed areas in Belgium. The study protocol and sampling methods have been described previously [23]. Briefly, between November 2008 and September 2009, 567 individuals aged 80 years and older were recruited in 29 general practice centers, excluding only those with severe dementia, in palliative care or medical emergencies. At baseline, the general practitioners recorded socio-demographic data and medical history. A clinical research assistant performed a standardized assessment at the participants' home including electrocardiogram (ECG) and blood sample collection. The Biomedical Ethics Committee of the Medical School of the Université catholique de Louvain (UCL) of Brussels, Belgium, approved the study protocol (B40320084685). All participants gave informed consent [23].

Clinical variables

The general practitioner (GP) was asked to record the medical history of the study subjects at baseline. The presence of hypertension and diabetes was registered. The history of a cardiovascular event was defined as a positive response for the history of angina pectoris, transient ischemic attack (TIA) or stroke, peripheral arterial disease, episode of decompensated heart failure and important cardiovascular interventions or surgery (percutaneous transluminal coronary angioplasty (PTCA) or stenting, coronary or arterial surgery). A history of myocardial infarction was reported by the GP or present on the ECG (Minnesota Code 1-1 or 1-2, excluding 1-2-8) (QRS Universal ECG device (QRS Diagnostic, Plymouth, USA)). Smoking status was registered.

The Anatomical Therapeutic Chemistry classification system was applied to register medication use. Data on relevant cardiovascular medication, including diuretics, β-blockers, calcium antagonists, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and lipid lowering agents, were used.

Blood pressure was measured in the sitting position on both arms with the GP's own blood pressure meter and was repeated after 2 minutes. The highest systolic and diastolic blood pressure (left or right) after 2 minutes was used in the analyses.

A blood sample was collected in the morning after fasting, and plasma (EDTA) and serum samples were stored at -80°C. Total cholesterol, low density lipoprotein (LDL) and high density lipoprotein cholesterol (HDL), creatinine and high-sensitive C-Reactive Protein (hsCRP) were measured using the UniCel® DxC 800 Synchron (Beckman-Coulter, Brea, USA). Glomerular filtration rate was estimated (eGFR) using the MDRD formula. Serum levels of N-terminal pro-B-type Natriuretic Peptide (NT-proBNP) were measured using the Dade-Dimension® Xpand (Siemens, Deerfield, USA). The coefficient of variation ranged from 3.9 to 4.3%.

Outcome

Three detailed follow-up questionnaires were filled in by the participating GPs after 1.4 ± 0.3 years (mean ± standard deviation (SD)), after 3.0 ± 0.3 years and after 5.1 ± 0.3 years. These questionnaires included questions on mortality and cause of death. The causes of death were divided into cardiovascular and non-cardiovascular causes according to the GPs' assessment and subsequent review by 2 independent researchers blinded to all clinical data. The two first questionnaires also included questions of the incidence of major cardiovascular events such as myocardial infarction and stroke. The outcome for the present study was the combination of cardiovascular mortality and morbidity (myocardial infarction or stroke) 3 years after baseline whatever came first.

External validation

The Leiden 85-plus Study is an observational population-based prospective follow-up study of inhabitants of the city of Leiden, the Netherlands. Subjects were aged 85 years at baseline. Between September 1997 and September 1999, all inhabitants of Leiden, born between 1912 and 1914, were asked to participate from their 85th birthday onwards. There were no exclusion criteria. At baseline and yearly up to the age of 90, the participants were visited at their place of residence to take questionnaires, functional tests, blood samples and to record an ECG. Medical history was obtained from the participant's general practitioner or nursing home physician, and between age 85 and 90 incident events were obtained yearly. The Medical Ethics Committee of the Leiden University Medical Centre approved the study, and all participants provided informed consent [24].

Data analysis

Descriptive statistics for baseline characteristics and outcome variables are presented as mean and standard deviation, median and inter-quartile range or counts and percentages. NT-proBNP levels and hsCRP levels were log transformed because of the strongly skewed nature of the data. Cox proportional hazards regression models were used to estimate the hazard ratio (HR) of individual risk factors for the combined end-point of cardiovascular mortality and morbidity. To build the different risk models the following strategy was used: first, a multivariate model with all the traditional risk factors was composed (model 1); second, a multivariate model that included all traditional risk factors and statistically significant biomarkers from the univariate analysis was built (model 2); third, all risk factors with a *P*-value ≤0.25 in the univariate analysis and age and gender were included in the multivariate analyses (model 3); fourth, only the statistically significant biomarkers from the univariate analysis and age and gender were included in the multivariate model (model 4). Models were checked for the proportional hazard assumption. In the case of multicollinearity (r-value >0.80), only one of the two covariables was considered in the multivariable model. A goodness-of-fit test was performed with the Hosmer-Lemeshow test and was reported when the model did not fit the observed data (*P* <0.05).

Harrell's C, continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were used to compare the predictive value of the different models using the model with the traditional cardiovascular risk factors as the reference model. The continuous NRI is the sum of the proportion of correctly reclassified events (NRI events) and non-events (NRI non-events) considering all changes in predicted risk between two models for events and non-events, without a defined risk categorization. The IDI is the difference in discrimination slopes between two models (absolute IDI) or difference in discrimination slopes over the slope of the reference model (relative IDI) [25 - 28]. To evaluate and to compare the different prediction models, the net benefit was calculated. Decision curves were constructed by plotting net benefit against the threshold probability (range 0.05 – 0.50). The curves show the expected net benefit per patient when treated according to different prediction models relative to no treatment at all. The net benefit for a given threshold probability can be interpreted as the equivalent of the increase in the proportion of true positives for a given prediction model relative to ‘‘treat none,’’ without an increase in false positives [27, 29 - 30].

Finally, an external validation of the four models was performed in the Leiden 85-Plus Study population. The 3-year predicted risk for cardiovascular mortality and morbidity was calculated and plotted against the observed results and the Harrell's C and decision curves of the different models were calculated in the Leiden population.

Statistical analysis was performed with SPSS 23.0 (SPSS Inc., Chicago, IL, USA), Stata 13.0 (StataCorp., College Station, TX, USA) and SAS University Edition (SAS Institute Inc., Cary, NC, USA).

Results

The initial BELFRAIL cohort consisted of 567 participants. In total, 286 subjects did not have a history of cardiovascular events at baseline. For 266/286 subjects (93%) all variables were available. Table 1 shows the description of the study population. The mean age of the study population was 84.3 ± 3.6 years and 26% were men.

Follow-up data were available for all subjects. After 3 years 13 subjects (4.9%) developed a cardiovascular event and 17 subjects (6.4%) died due to a cardiovascular cause. The combined end-point was present in 26 subjects (9.8%).

Multicollinearity was found between total cholesterol and LDL cholesterol (r = 0.94, *P* <0.001). All further analyses were done with total cholesterol and not LDL cholesterol. The univariate Cox regression analysis showed a strong correlation between log transformed NT-proBNP levels and the combined end-point (HR 3.7, 95% CI 1.9 - 6.9). Also total cholesterol was associated with the combined end-point (HR 1.06, 95% CI 0.97 - 1.15, *P* = 0.22). Four different multivariate models were built as described in the Methods section (Table 2). The Hosmer-Lemeshow test was not significant (P >0.05) for all models, showing an acceptable goodness-of-fit of each model.

Table 3 represents discrimination statistics of the different models for 3-year cardiovascular mortality and morbidity with model 1 as the reference model. Although the Harrell's C statistic of model 2, 3 and 4 were higher compared to model 1, this was not statistically significant (*P* <0.05). Based on the risk reclassification improvement measures (NRI and IDI), compared to model 1, model 2 improved the risk reclassification for 16.7% of events and 39.6% of non-events. This can be interpreted as: 56% of the subjects were better classified with respect to the baseline model. Model 3 improved risk reclassification for 9.8% of events and 32.1% of non-events, while model 4 improved risk reclassification for 7.5% of

events and 24.3% of non-events. Overall, compared to model 1, model 2 had the highest relative IDI for 3-year cardiovascular mortality and morbidity (4.01), increasing the difference of mean predicted probability of events and non-events with 401%. Model 3 and model 4 also showed very high relative IDIs.

Figure 1 shows the decision curve analyses. Model 1 showed to be the model with the lowest net benefit. The other models showed a higher net benefit at each threshold probability compared to model 1 and approached each other. Depending on the threshold probability, model 2 or model 3 or 4 showed the highest net benefit. In general model 2, 3 and 4 can be considered as models of higher clinical value and have higher rates of avoiding unnecessary treatment of elderly people in comparison with the traditional cardiovascular risk model.

Figure 2 shows the predicted versus the observed risk of the four models in the Leiden 85-plus Study population. Although, the curves of models 2, 3 and 4 were roughly parallel with the ideal curve (predicted = observed risk) there was a strong miscalibration (Hosmer-Lemeshow test, $p<0.05$ for all models), since the baseline risk in the Leiden population was much higher compared to the BELFRAIL population (25% vs 10%). The Harrell's C statistic of the different models was 0.42 (model 1), 0.63 (model 2), 0.64 (model 3) and 0.66 (model 4).

Discussion

This study developed and validated cardiovascular risk models for the oldest old with no history of cardiovascular events. It was shown that traditional cardiovascular risk factors poorly predicted 3-year cardiovascular mortality and morbidity. However, NT-proBNP showed a strong added predictive value with highly significant NRIs and relative IDIs for the models that included NT-proBNP as compared to the model based on the traditional risk factors alone. Furthermore, even NT-proBNP in isolation performed extremely well. This study emphasized the high clinical value of NT-proBNP in predicting 3-year cardiovascular mortality and morbidity in old subjects in primary prevention.

These results are in line with other observational studies showing that the traditional cardiovascular risk factors lose their predictive value in the oldest old [2, 10 - 11, 13 - 16, 18]. Moreover, other studies have shown that adding biomarkers to a model consisting of traditional risk markers improved the risk prediction in the old [16, 31]. Although the study of Zethelius et al. focused on an older population (mean age 71 years), the current study included the oldest old and men as well as women. Cooney et al. also estimated the cardiovascular risk

in older persons and generated the SCORE O.P. This model has been derived from data from an elderly population, but they incorporated only the conventional risk factors and developed this model to estimate the risk up to the age of 80 [21].

The current study illustrates the risk factor paradox in the oldest old, showing that traditional cardiovascular risk factors lose their predictive value and their association with cardiovascular mortality and morbidity might even be reversed. High cholesterol [18] and high blood pressure [14 - 15, 17] have been shown to be associated with better survival in old age compared to low cholesterol and low blood pressure, respectively. Possibly the traditional cardiovascular risk factors become more important for other causes of morbidity and mortality, like cancer and infection [32]. Another reason for the poor predictive value of traditional risk factors might be the fact that metabolism and homeostatic mechanisms are different in middle-aged people compared to very old persons. Furthermore, the status of traditional cardiovascular risk markers in the oldest old possibly does not reflect the lifetime status and evolution of these markers and thus are not able to effectively stratify cardiovascular risk in old age.

On the other hand, other risk markers, such as NT-proBNP, become more important in old age for diverse reasons. First, NT-proBNP remains a disease-specific marker of cardiac illness, even in the oldest old. Low levels of NT-proBNP can be used to exclude echocardiographic abnormalities in very old age [33]. Second, NT-proBNP has been shown to predict mortality and first cardiovascular events [33 - 34], in elderly with and without specific cardiac diagnoses [20]. Moreover, the prognostic information from NT-proBNP is independent of traditional cardiovascular risk factors, prevalent cardiovascular disease, as well as left ventricular dysfunction and renal function [19, 34]. Elevated plasma concentrations of NT-proBNP in elderly patients (≥80 years of age) without previous hospitalizations for cardiac disease or evidence of heart failure may be caused by occult conditions, such as asymptomatic heart failure, myocardial hypertrophy and left ventricular diastolic dysfunction, all of which are common in the elderly [35].

This study confirmed the high relevance of NT-proBNP as a predictor of cardiovascular mortality and morbidity. The current study showed that even in isolation this biomarker predicts very well cardiovascular mortality and morbidity. This generates new opportunities for cardiovascular risk prediction in general practice. As the traditional cardiovascular risk factors perform poorly, the determination of NT-proBNP represents a simple and easily applicable strategy for primary cardiovascular risk prediction in the oldest

old. However, a thorny issue at this moment is the cost price of this biomarker. In many countries health care insurers do not reimburse the determination of NT-proBNP for this indication.

This study has several strengths. This is the first study that developed a new risk model to predict 3-year cardiovascular mortality and morbidity in the oldest old with no history of cardiovascular events, based on traditional risk factors and biomarkers. Both an internal and external validation was performed. Although started 10 years before, the Leiden 85-plus Study population is quite similar to that of the BELFRAIL study. The similarities between these two populations may be seen as a disadvantage, and further external validation in oldest old populations might be needed. A limitation of the current study was that the rule of thumb when performing survival analyses of ten events per variable was relaxed. Although this rule has generated a lot of discussion and has been considered too conservative [36]. Another limitation may be the misclassification of the causes of death into cardiovascular and non-cardiovascular causes although this classification was reviewed by 2 independent researchers blinded to all clinical data and based on the detailed cause of death as reported by the GP.

Conclusion

We cannot rely on pre-existing risk scores and risk charts to predict cardiovascular mortality and morbidity in subjects aged 80 and over in primary prevention. Therefore, this study developed a new risk model to predict 3-year cardiovascular morbidity and mortality in the oldest old with no history of cardiovascular events, based on traditional risk factors and biomarkers. Traditional cardiovascular risk factors poorly predicted 3-year cardiovascular mortality and morbidity. However, NT-proBNP showed a strong added predictive value. Even a prediction model only based on NT-proBNP, age and gender performed extremely well as opposed to the traditional risk factors. This opens new perspectives for general practitioners, who are in need of a simple, easily applicable strategy for primary cardiovascular risk prediction in the oldest old.

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Table 1. Description of the study population (n = 266)

Age, mean ± SD (years)	84.29 ± 3.57
Male gender, n (%)	70 (26.3)
Total cholesterol, mean ± SD (mg/dL)	210.52 ± 42.83
HDL cholesterol, mean ± SD (mg/dL)	58.38 ± 15.87
Systolic blood pressure, mean ± SD (mmHg)	142.25 ± 20.55
Current or past smoking, n (%)	61 (22.9)
Presence of diabetes[a], n (%)	44 (16.5)
Presence of hypertension[b], n (%)	184 (69.2)
Antihypertensive medication[c], n (%)	201 (75.6)
Lipid lowering medication, n (%)	69 (25.9)
NT-proBNP, median (IQR) (pg/mL)	140.40 (77.33 - 270.45)
eGFR, mean ± SD (mL/min)	67.92 ± 21.48
hsCRP, median (IQR) (mg/dL)	0.188 (0.078 - 0.401)

[a], according to the general practitioner or the prescription of blood glucose lowering medication; [b], according to the general practitioner; [c], β-blocker, diuretic, calcium antagonist, ACE inhibitor or AT II receptor antagonist.

SD: standard deviation; HDL: high-density lipoprotein; NT-proBNP: N-terminal pro B type natriuretic peptide; IQR: interquartile range; eGFR: estimated glomerular filtration rate; hsCRP: high sensitive C reactive protein.

Table 2. Cox regression analysis for the prediction of 3-year cardiovascular morbidity and mortality in subjects in primary prevention (n = 266)

	Univariate analysis	Multivariate analysis			
	HR (95% CI)	HR (95% CI)			
		Model 1	Model 2	Model 3	Model 4
Age (per year increase)	0.99 (0.88 - 1.11)	0.98 (0.87 - 1.10)	0.91 (0.80 - 1.04)	0.92 (0.81 - 1.05)	0.94 (0.82 - 1.06)
Male gender	1.53 (0.68 - 3.43)	2.85 (1.03 - 7.90)	3.29 (1.21 - 8.99)	2.21 (0.96 - 5.10)	1.96 (0.86 - 4.46)
Total cholesterol (per 10mg/dL increase)	1.06 (0.97 - 1.15)	1.08 (0.98 - 1.19)	1.09 (0.98 - 1.21)	1.09 (0.99 - 1.20)	
HDL cholesterol (per 10mg/dL increase)	1.06 (0.84 - 1.35)	1.04 (0.79 - 1.37)	1.09 (0.82 - 1.45)		
Systolic BP (per 10mmHg increase)	1.01 (0.83 - 1.21)	1.05 (0.86 - 1.28)	1.00 (0.82 - 1.23)		
Current or past smoking	0.79 (0.30 - 2.10)	0.42 (0.13 - 1.33)	0.52 (0.17 - 1.61)		
Presence of diabetes	0.95 (0.33 - 2.76)	0.97 (0.32 - 2.93)	1.12 (0.37 - 3.43)		
NT-proBNP (Log transformed)	3.65 (1.92 - 6.93)		4.65 (2.30 - 9.42)	4.68 (2.37 - 9.24)	4.31 (2.20 - 8.44)
eGFR (per mL/min increase)	0.99 (0.97 - 1.01)				
hsCRP (Log transformed)	1.21 (0.61 - 2.42)				

HDL: high-density lipoprotein; NT-proBNP: N-terminal pro B type natriuretic peptide; eGFR: estimated glomerular filtration rate; hsCRP: high sensitive C reactive protein.

Table 3. Discrimination statistics of the different models for 3-year cardiovascular morbidity and mortality in subjects in primary prevention (n = 266).

	Harrell's C index	NRI_{cf} (95% CI)	NRI_{cf} Events, %	NRI_{cf} Non-events, %	IDI absolute (95% CI)	IDI relative (95% CI)
Model 1	0.61 (0.49-0.73)					
Model 2	0.72 (0.61-0.83)	0.56 (0.16, 0.99)	16.7	39.6	0.10 (0.06, 0.16)	4.01 (2.19, 6.28)
Model 3	0.70 (0.59-0.81)	0.42 (-0.03, 0.86)	9.8	32.1	0.09 (0.05, 0.16)	3.69 (1.72, 6.38)
Model 4	0.67 (0.53-0.79)	0.32 (-0.12, 0.74)	7.5	24.3	0.09 (0.04, 0.14)	3.44 (1.56, 6.09)

Model 1: age, gender, systolic BP, total cholesterol, HDL, smoking, diabetes; Model 2: age, gender, systolic BP, total cholesterol, HDL, smoking, diabetes, NT-proBNP; Model 3: age, gender, total cholesterol, NT-proBNP; Model 4: age, gender, NT-proBNP.

NRI_{cf}: category free net reclassification improvement; CI: confidence interval; IDI: integrative discrimination index.

Figure 1**.** DCA curves

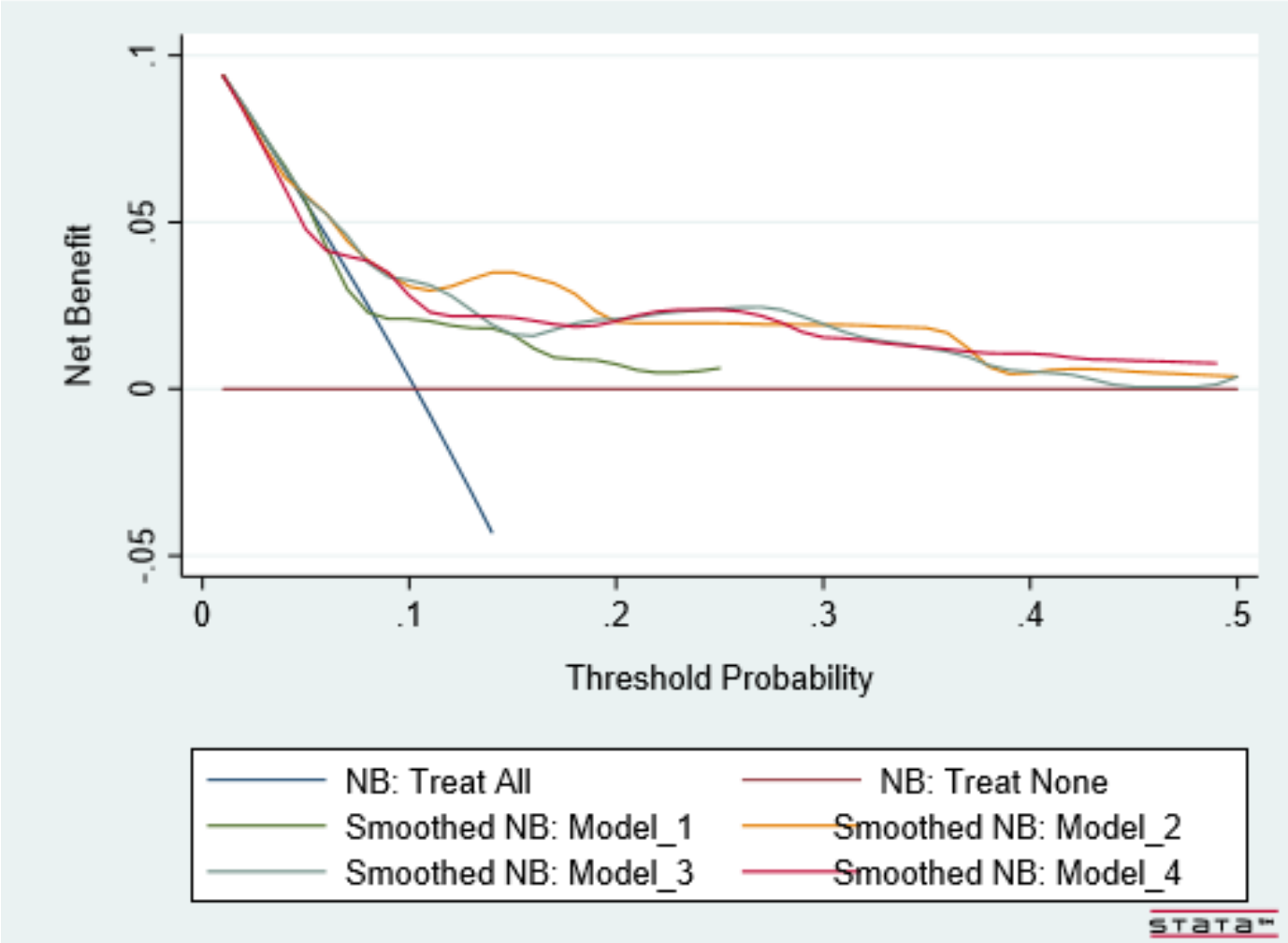
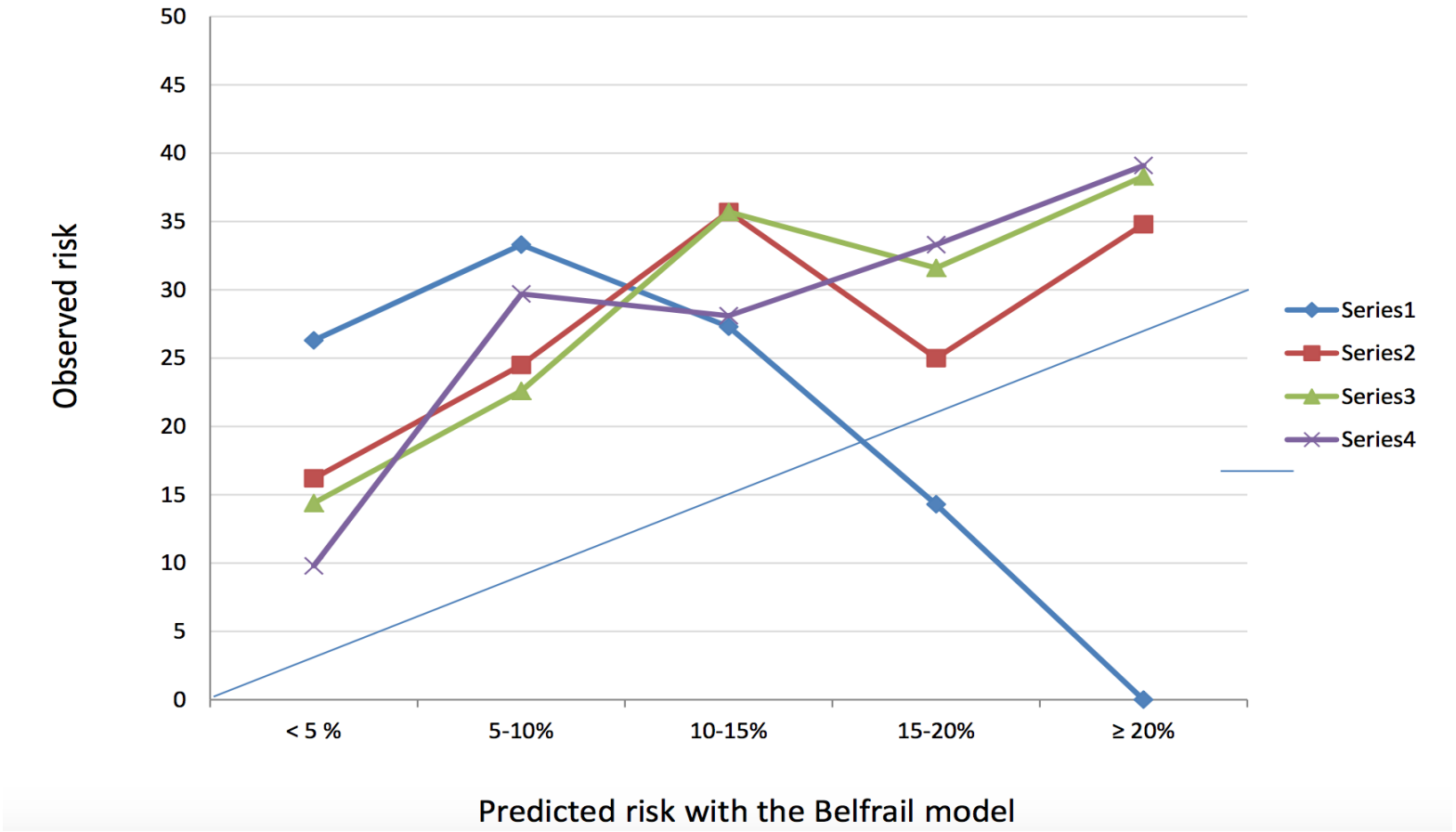


Figure 2. Predicted versus observed risk in the Leiden 85-Plus study



Verplichte bijlagen

Gunstig advies van OBC

2016-03-25 17:28:00

Goedkeuringsnummer EC werd inderdaad toegevoegd, dus oké

Student(en):

Paulien Indestege
Tinne Serneels

Promotor:

Bert Vaes (bert.vaes@med.kuleuven.be - u0087897 - Acad. Centr. voor Huisartsgeneeskunde)

Hoofdonderzoeker:

/

Faculteit:

Geneeskunde

Opleiding:

Master in de huisartsgeneeskunde (Leuven e.a.)

Het onderzoek is:

multicentrisch

De opdrachtgever is:

academisch (universiteit,...)

Het onderzoek is:

Het onderzoek is onderdeel van een groter project waarvoor reeds goedkeuring van de Ethische commissie werd bekomen.

CTC s-nummer:

S_____

Het onderzoek is een aanvulling of bevat nieuwe elementen.

Aanvulling of nieuwe elementen

Om artsen te begeleiden bij het inschatten van de morbiditeit en mortaliteit van 80-plussers, zullen wij een “Risk Chart” opstellen aan de hand van patiëntengegevens uit de BELFRAIL Studie. Deze studie is lopende sinds 2008 en goedgekeurd door de ethische commissie van het “Biomedical Ethics Committee” aan de UCL te Brussel (B40320084685). We willen onderzoeken welke predictoren voorspellend zijn bij 80-plussers wat betreft cardiovasculaire morbiditeit (MI, stroke etc.) en mortaliteit (zowel primaire preventie als secundaire

preventie). Vervolgens zullen we deze “Risk Chart” extern valideren in de Leiden 85-plus populatie. De Leiden 85-plus studie is een longitudinale bevolkingsstudie waarbij 85-plussers die in Leiden (Nederland) wonen gevolgd worden sinds 1987. In 1997 werd er aan deze cohorte een tweede cohorte toegevoegd. Deze studie werd goedgekeurd door de Commissie Medische Ethiek van het Leids Universitair Medisch Centrum. Uit deze studie verschenen reeds vele internationale artikels in het verleden.

Bijkomende gegevens:

Achtergrond:

Om een inschatting te maken van het cardiovasculair risicoprofiel van een patiënt kunnen artsen zich baseren op de “SCORE – European High Risk Chart” (1) of de “US Framingham Risk Score” (2). Beide scores geven ons een idee over de cardiovasculaire mortaliteit en morbiditeit aan de hand van een aantal risicofactoren. De SCORE Risk Chart richt zich op patiënten zonder cardiovasculaire voorgeschiedenis en geeft een inschatting van het risico op een eerste fataal atherosclerotisch event (coronair + niet-coronair) in de komende tien jaar. De Framingham Risk Score richt zich zowel op patiënten met als zonder cardiovasculaire voorgeschiedenis en kan dus zowel in primaire als in secundaire preventie worden toegepast. In tegenstelling tot de SCORE Risk Chart die een inschatting geeft van het risico op een fataal atherosclerotisch event, geeft de initiële Framingham Risk Score ons een idee over het risico op een fataal of niet-fataal coronair event (3). In 2008 verscheen er een nieuwe versie van de Framingham Risk Score (= Framingham General Cardiovascular Risk Score) die een idee geeft over het tienjaars risico op om het even welk cardiovasculair event (4).

De cardiovasculaire risicofactoren waar beide risicoanalyses zich op baseren zijn: leeftijd, geslacht, rookgewoonten, systolische bloeddruk en totaal cholesterol. De Framingham Risk Score gebruikt bijkomend nog HDL-cholesterol en diabetes om het risicoprofiel te schetsen (3). In de Framingham General Cardiovascular Risk Score excludeert men patiënten met diabetes omdat men deze eerder vanuit secundaire preventie wil benaderen (4).

Beide scores zijn gevalideerd bij patiënten van middelbare leeftijd. Men ging er initieel vanuit dat deze risicoanalyses ook van toepassing zouden zijn op 80-plussers. Echter, uit recent literatuuronderzoek is gebleken dat de klassieke cardiovasculaire risicofactoren, zoals hierboven beschreven, hun waarde verliezen bij de oudste ouderen (5,6). Zo blijkt een systolische bloeddruk van minder dan 140mmHg bij de fraile oudste ouderen geassocieerd te zijn met een hogere totale mortaliteit (7-9). Bij 90-plussers zal een systolische bloeddruk van minder dan 150mmHg zelfs leiden tot een verhoogde cardiovasculaire alsook niet-cardiovasculaire mortaliteit (10,11). In tegenstelling tot de verwachtingen, is een hogere bloeddruk bij de fraile oudste ouderen niet geassocieerd met een verhoogd risico op stroke. Bij diegenen met fysieke en cognitieve beperkingen blijkt een hogere bloeddruk zelfs een kleiner risico op stroke met zich mee te brengen (12). Ook stelt men vast dat verlaagde LDL-cholesterolwaarden bij de oudste ouderen met matig tot ernstig hartfalen gecorreleerd zijn met een hoger risico op overlijden (13). Uit onderzoek uitgevoerd op de Leiden 85-plus populatie, besluit men dat traditionele cardiovasculaire risicofactoren geen

correcte inschatting geven van het risico op cardiovasculaire mortaliteit en morbiditeit bij de oudste ouderen (6). Het gaat in deze studie(s) wel om fraile oudste ouderen; voor de oudste ouderen die niet als frail worden bestempeld en geen cognitieve beperking hebben, vindt men andere resultaten terug in de literatuur (HYVET) (14).

Buiten de studies die onderzoek hebben verricht naar de predictieve waarde van klassieke cardiovasculaire risicofactoren bij de oudste ouderen, vindt men in de literatuur tevens studies terug waarin men de klassieke risk charts/risk scores heeft toegepast om een inschatting te maken van het cardiovasculair risicoprofiel van de oudste ouderen. Hieruit is gebleken dat de klassieke risk charts/risk scores bij deze populatie slechts een zwakke voorspellende waarde hebben. Dit valt te verklaren door het feit dat de bestaande modellen ontwikkeld zijn op basis van gegevens van personen van middelbare leeftijd en door het feit dat klassieke risicofactoren hun waarde verliezen bij de oudste ouderen (15).

Toch bestaan er ook factoren welke predictief blijken te zijn bij de oudste ouderen wat betreft cardiovasculaire en niet-cardiovasculaire mortaliteit: NT-proBNP (16-20), wandelsnelheid (21,22), nierfunctie (23), handknijpkracht (24), IL-6 en/of CRP (25,26), anemie (27) en cardiovasculaire voorgeschiedenis (28). Uit de literatuur is dan ook gebleken dat het toevoegen van biomarkers aan een Risk Chart de predictieve waarde van risk calculatoren kan verhogen (15,29, 30).

Vraagstelling:

Om artsen te begeleiden bij het inschatten van de morbiditeit en mortaliteit van 80-plussers, zullen wij een “Risk Chart” opstellen aan de hand van patiëntengegevens uit de BELFRAIL Studie. Deze studie is lopende sinds 2008 en goedgekeurd door de ethische commissie van het “Biomedical Ethics Committee” aan de UCL te Brussel (B40320084685). We willen onderzoeken welke predictoren voorspellend zijn bij 80-plussers wat betreft cardiovasculaire morbiditeit (MI, stroke etc.) en mortaliteit (zowel primaire preventie als secundaire preventie). Vervolgens zullen we deze “Risk Chart” extern valideren in de Leiden 85-plus populatie. De Leiden 85-plus studie is een longitudinale bevolkingsstudie waarbij 85-plussers die in Leiden (Nederland) wonen, gevolgd worden sinds 1987. In 1997 werd er aan deze cohorte een tweede cohorte toegevoegd. Deze studie werd goedgekeurd door de Commissie Medische Ethiek van het Leids Universitair Medisch Centrum. In het verleden verschenen reeds vele internationale artikels welke gebaseerd zijn op deze studie.

Aangezien we met twee werken zullen we een duidelijke taakverdeling hanteren in ons werk.

Vraagstelling Paulien:

1. Welke zijn de cardiovasculaire risicofactoren bij 80-plussers?
2. Valideren van een CV risk calculator voor ouderen.

Vraagstelling Tinne:

1. Welke zijn de cardiovasculaire risicofactoren bij 80-plussers?
2. Ontwikkeling van een CV risk calculator voor ouderen.

Methodologie:
Variabelen in de Risk Chart
a) Primaire preventie
- Age
- Sex
- SBP
- TC
- HDL
- LDL
- Currrent smoking
- (history of) DM
- History of HT
- NT-proBNP
- IL-6 en/of CRP
- MDRD/eGFR
- Rx for HT (Betablocker, ACE inhibitors, ARB blockers, diuretics, calcium channel blockers)
- Gait speed
- Handgrip stength
- Anemie
b) Secundaire preventie
- Age
- Sex
- SBP
- TC
- HDL
- LDL
- Currrent smoking
- (history of) DM
- History of HT
- NT-proBNP
- IL-6 en/of CRP
- MDRD/eGFR
- Rx for HT (Betablocker, ACE inhibitors, ARB blockers, diuretics, calcium channel blockers)
- Gait speed
- Handgrip strength
- Anemie
- History of MI
- History of Stroke
- History of Heart failure
- History of PAD
- History of angina
- History of TIA

Met behulp van patiëntengegevens uit de BELFRAIL Studie zullen we op basis van variabelen die significant blijken te zijn bij 80-plussers een Risk Chart opstellen.

Eens deze Risk Chart is opgesteld, zullen we deze extern valideren in de Leiden 85-plus populatie.

Statistische mogelijkheden:

1. **Cox regressie univariate en multivariate:**

Uitkomstvariabele is time to event:

-> aparte analyses (cox regressie): telkens een andere verklarende variabele gebruiken (univariate analyses)

-> een analyse (cox regressie): alle verklarende variabelen tezamen in 1 model (multivariate analyses)

Omdat we waarschijnlijk te veel variabelen hebben om mee te starten (zie lijst boven), kunnen we bv. beginnen met enkel de variabelen die in onze univariate analyses significant zijn op 15% significantieniveau. Vanuit dit "full model" zullen we beurtelings niet-significante variabelen weglaten (achterwaartse modelselectie), zodat we enkel variabelen overhouden die significant zijn.

Op deze manier zullen we dus de effecten van de verklarende variabelen nagaan op de uitkomst, zijnde de time-to-event variabele (hoelang duurt het (tijd) vooraleer iemand een event ondergaat, bv. sterfte, stroke, MI etc.)

2. Uitkomstvariabele is binair (1/0) (sterfte of niet, MI of niet, hier gaat het niet om de tijd die verstreken is vooraleer er een event plaat vindt, maar over het al dan niet plaatsvinden van een event)

-> aparte analyses zoals hierboven, maar dan via een **logistische regressie**

-> achterwaartse modelselectie via een logistische regressie (zie boven). Ook kunnen we weeral beginnen met een selectie van variabelen, weer bepaald uit de univariate analyses op bv. 15% significantieniveau.

-> NIEUW: zodra we ons finaal model hebben uit de vorige stap, kunnen we dat model onze score-formule noemen. We krijgen schatters voor de beta's en dat is dus een goede manier om een score samen te stellen. A.d.h.v. deze score, de zogenaamde lineaire predictor (= de formule rechts van het gelijkheidsteken, dus het deel waarin de beta's staan), kunnen we dan ook een **ROC curve** samen stellen. Die ROC curve geeft dan aan welke cut-off values zorgen voor een goede voorspelling. We doen hier aan C- statistic van het model, waarbij de AUC een maat is voor de accuraatheid.

-> a.d.h.v. datzelfde model kunnen we een risk chart maken. Daarbij is het belangrijk dat we de continue verklarende variabelen categorisch maken, bv. age wordt agegroup (vb. 80-83 jaar).

3. **Risk Chart** maken voor berekening absoluut 3-jaars risico op cardiovasculaire morbiditeit en mortaliteit, zowel primair als secundair (op basis van de bekomen statistische gegevens).

4. Risk Chart **extern valideren** in de Leiden 85-plus populatie.

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Informed consent / vragenlijsten / interviewprotocols:

71879_1457774481_6638_Belfrail1__1__pdf.pdf

Geachte Heer/Mevrouw

De Opleidingspecifieke Ethische Begeleidingscommissie van de opleiding "Master in de huisartsgeneeskunde (Leuven e.a.)" heeft uw voorstel tot Masterproef "Cardiovasculaire risico-inschatting bij 80-plussers" onderzocht en gunstig geadviseerd. Dit betekent dat de commissie van oordeel is dat de studie, zoals beschreven in het protocol, wetenschappelijk relevant en ethisch verantwoord is. Dit gunstig advies van de commissie houdt niet in dat zij de verantwoordelijkheid voor de geplande studie op zich neemt. U blijft hiervoor zelf verantwoordelijk. Indien u van plan bent uw masterproef te publiceren kan deze e-mail dienen als bewijs van goedkeuring.

Dear Mr/Ms

The Supervisory Committee on Medical ethics of the "Master in de huisartsgeneeskunde (Leuven e.a.)" programme has reviewed your master's thesis project proposal "Cardiovasculaire risico-inschatting bij 80-plussers" and advises in its favour. This means that the committee has acknowledged that your project, as described in the protocol, is scientifically relevant and in line with prevailing ethical standards. This favourable advice does not entail the committee's responsibility for the planned project, however. You remain solely responsible. If you intend to publish your master's thesis, this e-mail may be used as proof of the committee's consent.

Goedkeuringsnummer EC werd inderdaad toegevoegd, dus oké

Met vriendelijke groeten

Opleidingsspecifieke begeleidingscommissie van de opleiding Master in de huisartsgeneeskunde (Leuven e.a.)

Université Catholique de Louvain
Faculté de Médecine

**Commission d'Éthique Biomédicale
Hospitalo-Facultaire**

Bruxelles, ce vendredi 2 avril 2010

Professor Jean-Marie DEGRYSE
CAMG - UCL 5360

To Whom It May Concern:

Concern : **2008/02OCT/281** (à rappeler dans toute correspondance concernant ce projet)
N° d'enregistrement belge : B403200846S5

Title : **Le diagnostic de l'insuffisance et de la dysfonction cardiaque chez la personne âgée : une étude de cohorte prospective**

The CEBHF certify that the design of the above mentioned study has been approved by our Commission on 27th OCT 2008.

Sincerely yours.
Best Regards.

Professor J.M. MALOTEAUX
Chairman

Avenue Hippocrate 55.14
Tour Harvey , niveau 0
1200 Bruxelles

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