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

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ABSTRACT

Background

To date, no specific risk score for predicting cardiovascular events in the oldest old in secondary prevention exists. 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 decisions curves were constructed. An external validation of the four models was performed in the Leiden 85-Plus Study.

Results

In total, 260 subjects with a mean age of 85.3 ± 3.8 years were included. Model 1 included all the traditional cardiovascular risk factors; model 2 added NT-proBNP and hs-CRP; model 3 included age, gender, cholesterol, history of major cardiovascular event, NT-proBNP and hs-CRP; model 4 included age, gender, history of major cardiovascular event, NT-proBNP and hs-CRP. Model 2 showed a Harrell's C statistics of 0.70 and had the highest NRI and relative IDI as compared to model 1 (0.38 (95%CI 0.09 – 0.070) and 0.53 (95%CI 0.23 - 0.90) respectively). Model 3 also showed a high relative IDI compared to model 1 (0.33 (95%CI 0.04 - 0.70)). Model 4 was not better than model 1. Overall model 2 showed a higher net benefit compared to model 1.

Conclusion

This study showed a reduced predictive value of traditional cardiovascular risk markers in subjects aged 80 and older in secondary prevention. Adding NT-proBNP and hs-CRP significantly improved the prediction of cardiovascular mortality and morbidity. However, a simplified model based on the history of a major cardiovascular event and biomarkers did not improve the prediction of the combined end-point.

Key words

"Secondary cardiovascular prevention", "oldest old", "aged 80 and over", "risk prediction"

ABSTRACT

Achtergrond

Tot op heden bestaat er geen specifieke risicoscore voor cardiovasculaire events bij de oudste ouderen in secundaire preventie. Deze studie werd uitgevoerd om een nieuw risicomodel te ontwikkelen voor cardiovasculaire morbiditeit en mortaliteit in de komende 3 jaar, gebaseerd op de traditionele risicofactoren en biomarkers.

Methode

Nieuwe risicomodellen werden ontwikkeld in de BELFRAIL populatie, een bevolkingsgerichte cohort studie in België. Met behulp van een Cox regressie analyse werd de hazard ratio van de verschillende risicofactoren berekend. Vier verschillende risicomodellen werden opgesteld. Voor elk model werd de Harrell's C, "net reclassification improvement" (NRI) en de "integrated discrimination index" (IDI) berekend om de voorspellende waarde van de verschillende modellen te kunnen schatten. De "net benefit" werd berekend en "decision curves" werden gemaakt. Een externe validatie van de vier modellen werd uitgevoerd in de Leiden 85-Plus Studie.

Resultaten

In totaal werden 260 patiënten, met een gemiddelde leeftijd van 85.3 ± 3.8 jaar, geïncludeerd. Model 1 omvatte alle traditionele cardiovasculaire risicofactoren; in model 2 werd er NT-proBNP en hs-CRP toegevoegd; model 3 bevatte leeftijd, geslacht, cholesterol, voorgeschiedenis van een cardiovasculaire gebeurtenis, NT-proBNP en hs-CRP; model 4 omvatte leeftijd, geslacht, geschiedenis van een cardiovasculaire gebeurtenis, NT-proBNP en hs-CRP. Model 2 had een Harrell's C index 0.70 en de hoogste NRI en relatieve IDI in vergelijking met model 1 (respectievelijk 0.38 (95%BI 0.09 – 0.070) and 0.53 (95%BI 0.23 - 0.90)). Model 3 toonde een hoge relatieve IDI in vergelijking met model 1 (0.33 (95%BI 0.04 - 0.70)). Model 4 toonde geen meerwaarden ten op zichte van model 1. Enkel model 2 toonde een hogere "net benefit" in vergelijking met model 1.

Conclusie

Deze studie toonde dat de traditionele cardiovasculaire risicofactoren een verminderde voorspellende warden hebben bij patiënten van 80 jaar en ouder in secundaire preventie. Het toevoegen van NT-proBNP en hs-CRP verbeterde de voorspelling van cardiovasculaire mortaliteit en morbiditeit significant. Echter, een vereenvoudigd model, dat enkel gebaseerd is op de voorgeschiedenis van een ernstige cardiovasculaire gebeurtenis en biomarkers, verbeterde de predictie van een fataal of niet-fataal cardiovasculair event niet.

Kernwoorden

"secundaire cardiovasculaire preventie", "oudste ouderen", "risico predictie"

Background

Cardiovascular diseases (CVD) are still the leading cause of death in Western countries[1,2]. But because of better and advanced treatment options for CVD, mortality due to cardiovascular events is decreasing. This results in an increasing amount of aged people living with chronic CVD[3]. Therefore secondary prevention in the oldest old is getting more and more important.

Guidelines provide clinicians with advice on secondary prevention for patients with a history of CVD[4], but they do not include clear recommendations for the oldest old. Moreover secondary prevention in people aged 80 and over with CVD has proven to be very difficult because traditional risk markers lose their predictive value with age[5]. Furthermore, previous research suggests that biomarkers such as albuminuria with impaired renal function (eGFR)[6], increased N-terminal pro-B-type Natriuretic Peptide (NT-proBNP)[7-11,13], troponines[12], high-sensitive-C Reactive Protein (hs-CRP) and homocysteine[13] might be better makers to estimate the risk of a recurrent cardiovascular event in the oldest old.

The SMART Risk Score (Second Manifestation of ARTerial disease) was the first risk score that included biomarkers. It is used to predict the 10-year risk of recurrent cardiovascular events - (myocardial infarction, stroke or vascular death) - in patients between 18 and 80 years old with any type of arterial disease. It is the first risk calculator to include renal function (eGFR) and hs-CRP, in addition to all traditional risk markers[14]. Poortvliet et al. compared the 'traditional cardiovascular risk factors and the SMART Risk Score and all of them with and without NT-proBNP in subjects aged 70-82 years old. They concluded that a model with age, sex and NT-proBNP was the most simple and accurate model to predict the 2,5-year risk of non-fatal or fatal cardiovascular events[15].

Currently there is no validated cardiovascular risk model for subjects aged 80 and over with a history of CVD that includes biomarkers[15]. Therefore, this study was performed to develop new risk models to predict 3-year cardiovascular mortality and morbidity in the oldest old with a history of cardiovascular events, based on traditional risk factors and biomarkers, by using data of the BELFRAIL cohort study[16]. An external validation of the new risk models was performed in the Leiden 85-plus Study[17,18].

Methods

Study population

The BELFRAIL study is a prospective, observational, population based cohort study of subjects aged 80 years and older in three well-circumscribed areas in Belgium. The study design and the characteristics of this cohort have been described in detail previously[16]. In short between November 2008 and September 2009, in 29 general practice centers, 567 individuals aged 80 years and older were recruited, excluding only those with severe dementia, in palliative care or medical emergencies. At baseline the general practitioner (GP) recorded socio-demographic data and the medical history. A clinical research assistant performed a standardized assessment at the participants' home including electrocardiogram (ECG) and blood sample collection. All patients gave their informed consent and the study protocol was approved by the Biomedical Ethics Committee of the Medical School of the Université Catholique de Louvain (UCL) of Brussels, Belgium (B40320084685)[16].

Clinical variables

The 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 minor cardiovascular event was defined as a positive response for the history of angina pectoris, transient ischemic attack (TIA), peripheral arterial disease and episode of decompensated heart failure. The history of a major cardiovascular event was defined as the history of myocardial infarction (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))), the history of stroke and important cardiovascular interventions or surgery (percutaneous transluminal coronary angioplasty (PTCA) or stenting, coronary or arterial surgery). 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 two minutes. The highest

systolic and diastolic blood pressure (left or right) after two 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 (hs-CRP) were measured using the UniCel® DxC 800 Synchron (Beckman-Coulter, Brea, USA). Glomerular filtration rate was estimated (eGFR) using the MDRD formula[19,20]. 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 GP's 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 GP's assessment and subsequent review by two 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 and stroke) three 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 GP 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[17,18].

Data analysis

Descriptive statistics for baseline characteristics and outcome variables are presented as mean and standard deviation (SD), median and inter-quartile range or counts and percentages. NT-proBNP levels and hs-CRP 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 ≤ 0.20 in the univariate analysis and age and gender were included in the multivariate analysis (model 3); fourth, only the statistically significant biomarkers from the univariate analysis and age, gender and history of major cardiovascular event 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-the-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)[21-25].

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[25-27]. Decision curve analysis[27] tries to incorporate clinical relevance and consequences instead of only giving a metrics that concern accuracy (NRI, IDI and Harrell’s C index). It is a simple way of giving an answer on the question which model would lead to a better clinical outcome.

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. Furthermore, the Harrell’s C of the different models was also calculated in the Leiden 85-plus 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, 280 subjects had a history of cardiovascular events at baseline. For 260 of these 280 subjects (93%) all variables were available. Table 1 shows the description of the study population. The mean age of the study population was 85.3 ± 3.8 years and 47% were men. All in all, 183 subjects (70%) had a history of a major cardiovascular event.

Follow-up data were available for all 260 subjects. After 3 years 24 subjects (9.2%) developed a cardiovascular event and 39 subjects (15%) died due to a cardiovascular cause. The combined end-point was present in 56 subjects (21.5%).

Multicollinearity was found between total cholesterol and LDL cholesterol ($r = 0.94$, $P < 0.001$). Univariate Cox regression analysis showed a significant correlation between total cholesterol, history of major cardiovascular event, NT-proBNP and hsCRP and the combined end-point. 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. The Harrell's C statistic of model 2 was higher compared to model 1, but this was not statistically significant (difference 0.017 (95% CI -0.025; 0.063), P > 0.05). Based on the risk reclassification improvement measures (NRI and IDI), compared to model 1, model 2 improved the risk reclassification for 19% of events and 19% of non-events. This gives a total improvement in risk reclassification of 38%. Model 3 and 4 did not show a significantly improved risk reclassification compared to model 1. Overall, compared to model 1, model 2 had the highest relative IDI for 3-year cardiovascular mortality and morbidity (0.53), increasing the difference of mean predicted probability of events and non-events with 53%. Also model 3 showed a high relative IDI.

Figure 1 shows the decision curve analysis. Overall model 2 had the highest net benefit, although model 1 showed to be the model with the highest net benefit at a threshold probability of 0.20 to 0.27.

Additionally three extra models were investigated: a model with age, gender, a history of major cardiovascular event and hsCRP (model 5); a model with age, gender, a history of major cardiovascular event and NT-proBNP (model 6); and a model with age, gender and a history of major cardiovascular event (model 7) (Appendix Table 1). The Harrell's C statistics of all three models were lower than that of model 1 (0.66, 0.63 and 0.60 respectively). Compared to model 1, model 5 and 6 did not significantly improve the risk reclassification, but model 7 significantly worsened the risk reclassification for 24.3% of events and 14.3% of non-events. Model 7 also showed a low relative IDI compared to model 1 (-0.58 (95% CI -0.67; -0.47)) (Appendix Table 2).

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 (45% versus 21.5%). The Harrell's C statistics of the different models was 0.52 (model 1), 0.63 (model 2), 0.64 (model 3) and 0.65 (model 4).

Discussion

This study showed that the predictive value of traditional cardiovascular risk markers is reduced in subjects aged 80 and older in secondary prevention. Adding biomarkers to the model, such as NT-proBNP and hs-CRP significantly improved the prediction of cardiovascular mortality and morbidity. However simplified models based on age, gender, the history of a major event and biomarkers did not improve or even worsened the prediction of the combined end-point.

Although the traditional cardiovascular risk factors showed a reduced predictive value, the history of a major cardiovascular event and the level of total cholesterol showed a significant association with the combined end-point in all models. The importance of the severity of the previous event has already been proven in younger patients[31,32], but also in the oldest old[33]. In subjects aged 85 and older van Peet et al. demonstrated that a history of a minor event only showed half the risk of having a recurrent event compared to a history of a major event. This study concluded that the history of a myocardial infarction or stroke had the highest prognostic value to determine which patients are at high risk for cardiovascular mortality and morbidity, functional decline, and all-cause mortality[33]. The correlation between cholesterol and the combined end-point in our study is in contrast with the findings of Weverling-Rijnsburger et al. who concluded that total cholesterol is not a significant risk marker for cardiovascular mortality in older subjects with a history of CVD. Only low HDL-cholesterol was a risk factor for fatal coronary artery disease and stroke, not high LDL- or high total cholesterol[34].

Previous studies also found that adding biomarkers to the traditional risk markers gave a better and more correct risk stratification[29,30]. Zengin et al. found diabetes was the strongest predictor for a recurrent cardiovascular event of all traditional cardiovascular risk markers and identified an added value of CRP. However, they did not add NT-proBNP as a biomarker and they only used subjects with a history of coronary diseases[30]. On the other hand, Scirica et al. did add NT-proBNP as a biomarker and included more than 12.000 subjects aged between 39 and 99 years old. This study was done in the SAVOR TIMI 53 trial population and all subjects had diabetes with overt CVD. They found that adding high-sensitivity troponin T or NT-proBNP or hs-CRP to the classical clinical variables improved the prediction of cardiovascular death, myocardial infarction and hospitalization for heart failure[29]. The

PROSPER data confirmed these findings, but concluded that NT-proBNP (compared to hs-CRP, eGFR and homocysteine) was the strongest biomarker to add to the traditional cardiovascular risk markers to predict cardiovascular mortality and morbidity in secondary prevention[10]. However, the results of the current study do not harmonize in all perspectives with the results from the PROSPER data. Poortvliet et al. concluded that the model based on age, sex and NT-proBNP was the most simple and accurate model to predict the 2,5-year risk of fatal and non-fatal cardiovascular event in subjects aged between 70 and 82 years old with a history of CVD[15]. The current study showed that the simple models were not better than the model based on the traditional risk factors. This difference might be explained by the difference in age as the oldest old were not included in the PROSPER data. Furthermore, the PROSPER study population was collected 10 years before the BELFRAIL study population and was a more homogeneous trial population compared to the heterogeneous population of the BELFRAIL study.

To date NT-proBNP and hs-CRP are not reimbursed for risk prediction by health insurances in numerous countries, for instance Belgium. However, as already shown in younger populations, the current study showed that adding biomarkers to traditional risk factors would improve the risk stratification in secondary prevention in the oldest old. Better identification of patients at high risk for cardiovascular events will lead to more accurate selection of patients that might benefit from specific pharmaceutical or non-pharmaceutical treatment strategies. Therefore, future research should focus on developing easy-to-use risk scores for the oldest old in daily practice, and investigating the effect of preventive treatments in better-identified patients at risk.

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 in secondary prevention, 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 of the risk models in de oldest old populations might be needed. A limitation of the current study was the rule of thumb of ten events per variable when performing survival analyses, was relaxed. Although this rule has

generated a lot of discussion and has been considered too conservative[28]. Another limitation may be the misclassification of the causes of death into cardiovascular and non-cardiovascular cause although this classification was reviewed by two independent researchers blinded to all clinical data and based on the detailed cause of death as reported by the GP.

Conclusion

Traditional cardiovascular risk markers showed a reduced predictive value for cardiovascular mortality and morbidity in subjects aged 80 and older in secondary prevention. Adding NT-proBNP and hs-CRP to the traditional risk models significantly improved the prediction of fatal and non-fatal cardiovascular events. However, simplified models based on the history of major cardiovascular event and biomarkers did not improve or even worsened the prediction of the combined end-point.

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Figures and tables

Table 1. Description of the study population (n = 260)

Age, mean ± SD (years)	85.25 ± 3.79
Male gender, n (%)	122 (46.9)
Total cholesterol, mean ± SD (mg/dL)	192.42 ± 42.86
HDL cholesterol, mean ± SD (mg/dL)	52.41 ± 13.42
Systolic blood pressure, mean ± SD (mmHg)	140.80 ± 19.94
Current or past smoking, n (%)	102 (39.2)
Presence of diabetes[a], n (%)	56 (21.5)
Presence of hypertension[b], n (%)	185 (71.2)
Antihypertensive medication[c], n (%)	224 (86.2)
Lipid lowering medication, n (%)	103 (39.6)
History of major cardiovascular event	183 (70.4)
NT-proBNP, median (IQR) (pg/mL)	253.60 (125.00 - 752.05)
eGFR, mean ± SD (mL/min)	59.73 ± 22.40
hsCRP, median (IQR) (mg/dL)	0.175 (0.082 - 0.431)

[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 secondary prevention (n = 260)

	Univariate analysis HR (95% CI)	Multivariate analysis HR (95% CI)			
		Model 1	Model 2	Model 3	Model 4
Age (per year increase)	1.04 (0.97 - 1.11)	1.04 (0.97 - 1.11)	1.03 (0.96 - 1.11)	1.03 (0.96 - 1.11)	1.03 (0.96 - 1.11)
Male gender	0.90 (0.53 - 1.52)	0.64 (0.32 - 1.26)	0.68 (0.35 - 1.31)	0.89 (0.51 - 1.56)	0.81 (0.47 - 1.39)
Total cholesterol (per 10mg/dL increase)	1.05 (0.99 - 1.11)	1.08 (1.01 - 1.15)	1.09 (1.02 - 1.17)	1.08 (1.01 - 1.15)	
HDL cholesterol (per 10mg/dL increase)	0.89 (0.72 - 1.09)	0.78 (0.62 - 0.99)	0.84 (0.66 - 1.07)		
Systolic BP (per 10mmHg increase)	0.997 (0.87 - 1.14)	0.99 (0.87 - 1.14)	0.98 (0.85 - 1.13)		
Current or past smoking	1.23 (0.73 - 2.09)	1.45 (0.76 - 2.78)	1.39 (0.73 - 2.65)		
Presence of diabetes	0.71 (0.35 - 1.44)	0.67 (0.33 - 1.40)	0.76 (0.36 - 1.58)		
History of major cardiovascular event	1.95 (1.01 - 3.77)	2.35 (1.17 - 4.68)	2.31 (1.15 - 4.64)	2.34 (1.17 - 4.67)	2.06 (1.05 - 4.04)
NT-proBNP (Log transformed)	1.80 (1.16 - 2.79)		1.66 (1.00 - 2.77)	1.61 (0.96 - 2.70)	1.46 (0.89 - 2.40)
eGFR (per mL/min increase)	0.99 (0.98 - 1.01)				
hsCRP (Log transformed)	1.92 (1.24 - 2.97)		1.41 (0.85 - 2.36)	1.66 (1.04 - 2.65)	1.63 (1.04 - 2.56)

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 secondary prevention (n = 260)

	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	0.68 (0.61-0.75)					
Model 2	0.695 (0.62-0.765)	0.38 (0.09, 0.70)	19	19	0.03 (0.02, 0.06)	0.53 (0.23, 0.90)
Model 3	0.68 (0.61-0.745)	0.09 (-0.21, 0.40)	5	3.5	0.02 (0.003, 0.04)	0.33 (0.04, 0.70)
Model 4	0.67 (0.60-0.74)	-0.03 (-0.34, 0.27)	-2.4	0.7	0.0004 (-0.02, 0.02)	0.006 (-0.26, 0.35)

Model 1: Age, gender, total cholesterol, HDL, systolic blood pressure, smoking, diabetes, major event; Model 2: Age, gender, total cholesterol, HDL, systolic blood pressure, smoking, diabetes, major event, NT-proBNP, hsCRP; Model 3: Age, gender, total cholesterol, major event, NT-proBNP, hsCRP; Model 4: Age, gender, major event, NT-proBNP, hsCRP.

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

Figure 1. DCA curves

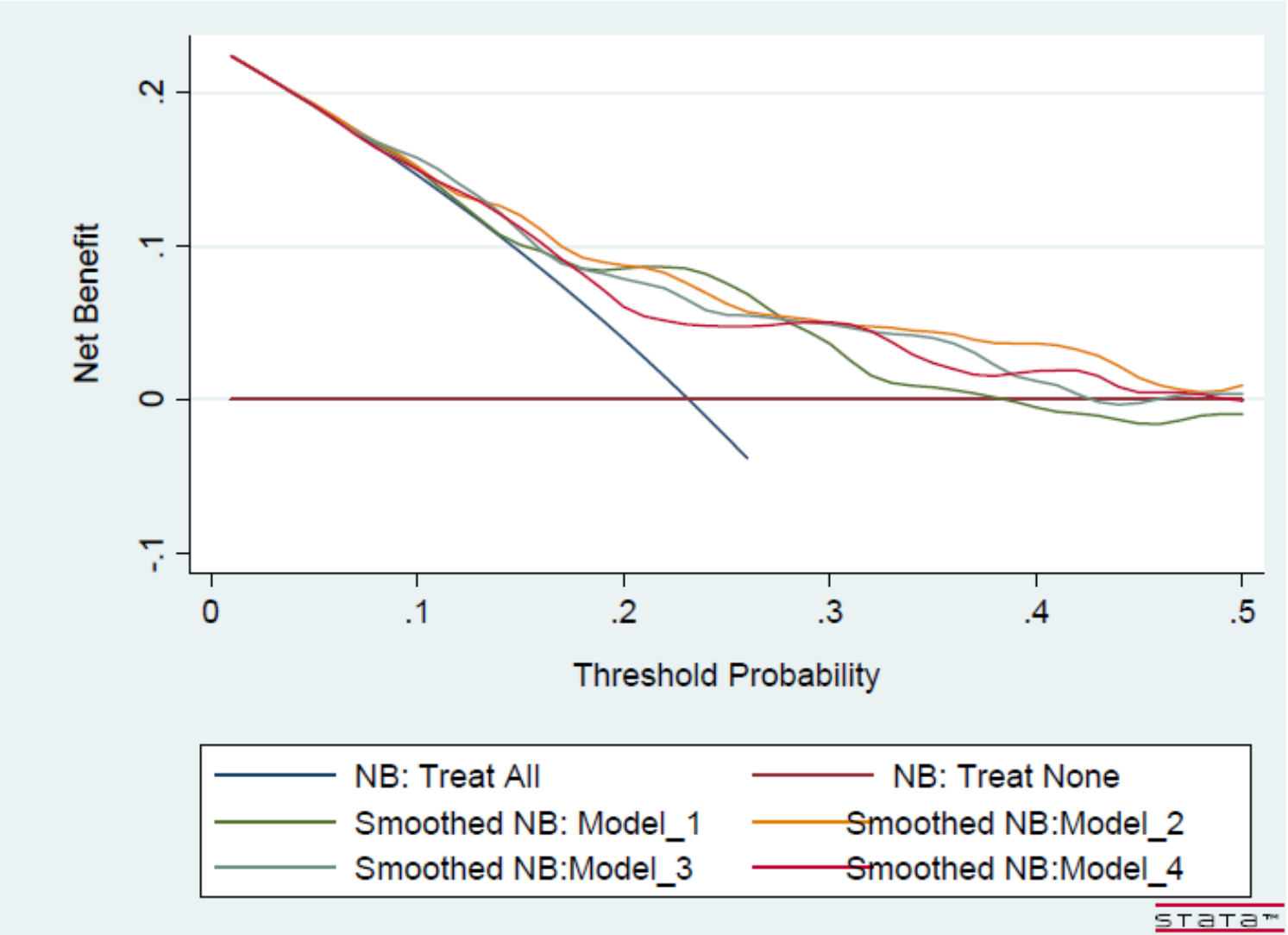
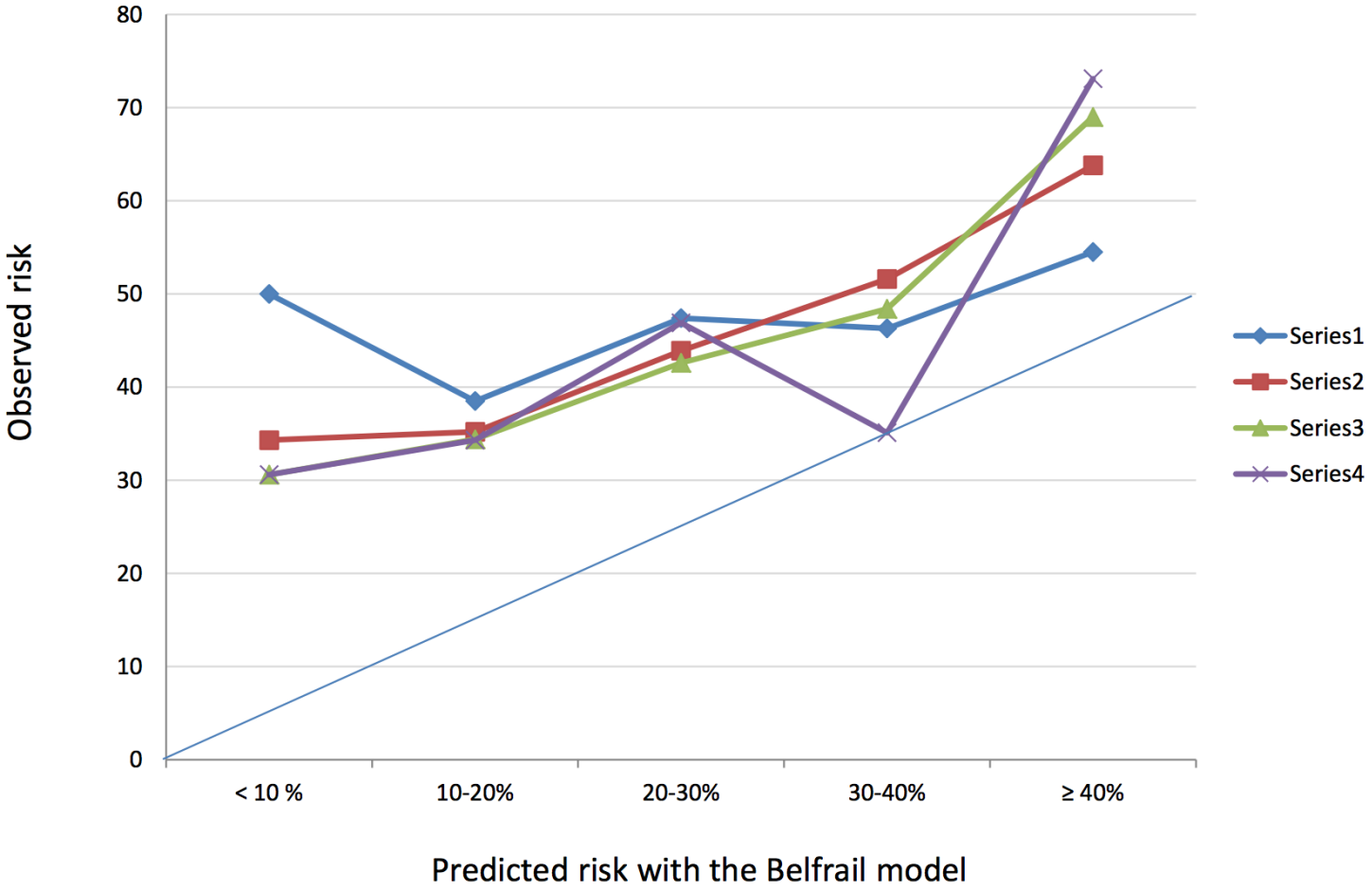


Figure 2. Predicted versus observed risk in the Leiden 85-Plus study



Appendix

Appendix Table 1. Cox regression analysis for the prediction of 3-year cardiovascular morbidity and mortality in subjects in secondary prevention (n = 260)

	Multivariate analysis HR (95% CI)		
	Model 5	Model 6	Model 7
Age (per year increase)	1.04 (0.97 - 1.12)	1.03 (0.96 - 1.10)	1.04 (0.98 - 1.12)
Male gender	0.82 (0.48 - 1.42)	0.81 (0.47 - 1.40)	0.84 (0.49 - 1.45)
History of major cardiovascular event	2.08 (1.06 - 4.07)	2.05 (1.04 - 4.02)	2.11 (1.08 - 4.13)
NT-proBNP (Log transformed)		1.72 (1.09 - 2.72)	
hsCRP (Log transformed)	1.85 (1.21 - 2.83)		

NT-proBNP: N-terminal pro B type natriuretic peptide; hsCRP: high sensitive C reactive protein.

Appendix Table 2. Discrimination statistics of the different models for 3-year cardiovascular morbidity and mortality in subjects in secondary prevention (n = 260)

	Harrell's C index	NRI_{cf} (95% CI)	NRI_{cf} Events, %	NRI_{cf} Non-events, %	IDI absolute (95% CI)	IDI relative (95% CI)
Model 5	0.66 (0.59-0.72)	-0.24 (-0.54, 0.07)	-17.1	-7.1	-0.007 (-0.03, 0.012)	-0.10 (-0.35, 0.19)
Model 6	0.63 (0.56-0.71)	-0.27 (-0.57, 0.02)	-12.9	-13.9	-0.02 (-0.03, 0.002)	-0.24 (-0.43, 0.02)
Model 7	0.60 (0.53-0.67)	-0.39 (-0.68, -0.10)	-24.3	-14.3	-0.04 (-0.05, -0.03)	-0.58 (-0.67, -0.47)

Model 5: Age, gender, major event, hsCRP; Model 6: Age, gender, major event, NT-proBNP; Model 7: Age, gender, major event.

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

Total number of events was 56 (21.5%). For the category dependent NRI we used 20%

Mandatory attachments

Goedgekeurd protocol

Gunstig advies van OBC

2016-03-25 17:28:00

Bekijk status geschiedenis

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_____
Aanvulling of nieuwe elemen..	Het onderzoek is een aanvulling of bevat 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

- 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 / vragenlij... 71879_1457774481_6638_Belfrail1__1__pdf.pdf

Gunstig advies Ethisch Comité

Email op 25/03/2016:

Betreft uw aanvraag Ethische begeleiding masterproeven met titel "Cardiovasculaire risico-inschatting bij 80-plussers" (mp11239)

Martine Goossens <martine.goossens@med.kuleuven.be>

vr 25/03/2016 17:28

Aan: Tinne Serneels <tinneke.serneels@student.kuleuven.be>; Bert Vaes <bert.vaes@kuleuven.be>;

CC: Paulien Indestege <paulien.indestege@student.kuleuven.be>;

English version below

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.)

Op Toledo vanaf 25/03/2016:

Verstuurde aanvragen (in behandeling, geweigerd en/of goedgekeurd)

Master in de huisartsgeneeskunde (Leuven e.a.)

CAT 1: Het onderzoek is onderdeel van een groter project waarvoor reeds goedkeuring van de Ethische commissie werd bekomen.

Openstaande aanvragen 0

	Reg. nr.	Titel van de studie	Status	Beheer

Aanvragen voor advies bij CTC/EC 0

Gunstig advies van OBC 1

	Reg. nr.	Titel van de studie	Status	Beheer
	mp11239	Cardiovasculaire risico-inschatting bij 80-plussers Student(en): Paulien Indestege, Tinne Serneels Promotor: Bert Vaes	Gunstig advies van OBC	

Geweigerde aanvragen 0

Master in de geneeskunde (Leuven)