PC Reviewed: 12/11/18   **Status: _____**   **Priority: 2**
SC Reviewed: _____   **Status: _____**   **Priority: ____**

1.a. Full Title: Estimating absolute treatment effect of blood pressure lowering therapy for individual elderly patients

   b. Abbreviated Title (Length 26 characters): Predicting BP Tx effect

2.   Writing Group:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. **[TIdV]**

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3. **Timeline**: We aim to have a full manuscript approximately 6-9 months after acquiring necessary data.

4. **Rationale**:

Age is the one of the strongest risk factors for cardiovascular events, and as such the risk of cardiovascular disease (CVD) is high in elderly patients (1). Furthermore, hypertension is one of the most important preventable risk factors for CVD (2) and the prevalence of hypertension increases with age (3). However, because remaining life-expectancy is shorter in older adults, high cardiovascular risk does not automatically converge to high preventive treatment benefit in this population. Furthermore, there is a potential risk of overtreatment, polypharmacy, and the impact of side effects particularly in frail elderly patients. Therefore, the benefit of cardiovascular risk management in elderly patients is debated extensively (4,5).

In 2008, the Hypertension in the Very Elderly Trial (HYVET) showed conclusively that antihypertensive treatment is still beneficial in hypertensive elderly patients (≥80 years) in reducing stroke and all-cause mortality. Lowering systolic blood pressure from above 160 mmHg to below 150 mmHg reduced the risk of both stroke and all-cause mortality by 30% and 21%, respectively (6). In 2015, the Systolic Blood Pressure Intervention Trial (SPRINT) confirmed that blood pressure reduction in elderly patients (≥75 years) results in the reduction of major cardiovascular events (7).

In elderly patients especially, polypharmacy is common, and many elderly patients take drugs more than medically needed. This can lead to negative consequences such as adverse effects, drug-drug interactions, and medication non-adherence (8). Therefore, in clinical practice, it is necessary to identify those with highest cardiovascular risk and highest gain from antihypertensive treatment.

Unfortunately, subgroup analyses from the HYVET and SPRINT studies have not displayed any significant patient characteristics that modify the relative effect of treatment (7,9). However, such subgroup analyses have disadvantages that should be acknowledged, including a lack of statistical power. Moreover, only one characteristic is studied at the time, whilst the effect of treatment is likely to be determined by a combination of patient characteristics (10,11).

A multivariable model to predict cardiovascular risk and absolute treatment effects provides more information on the expected benefit of therapy for the individual elderly patient. Cardiovascular risk calculators expressing estimated absolute treatment effect for an individual elderly patient may greatly aid in the patient-centered clinical decision making.

Unfortunately, classic risk prediction models have a moderate or poor performance in elderly patients, especially in the very old (over 85 years old) (12–14). This may partially be due to the fact that these traditional prediction scores do not consider the competing risk of non-CVD mortality, which is especially high in elderly patients, leading to overestimation of the risk of cardiovascular disease in

elderly populations (15–17). Furthermore, it is recognized that the relationship between classical risk factors and cardiovascular disease attenuates with age (18).

Therefore, the competing-risk (i.e. non-vascular death) adjusted "Elderly risk model" was previously developed in the "PROspective Study of Pravastatin in Elderly at Risk" (PROSPER) trial population (19) in patients with and without vascular disease aged ≥ 70 years (based on the following predictors: age, sex, current smoking, diabetes mellitus, number of medications, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, eGFR, statin treatment, polyvascular disease) (20) and externally validated in the "Secondary Manifestations of ARTerial disease" (SMART) study cohort for patients with vascular disease (21), and in the "Anglo-Scandinavian Cardiac Outcomes Trial – Lipid-Lowering Arm" (ASCOT-LLA) trial for patients without vascular disease (22). With this model, treatment effects of statin treatment in elderly patients can be predicted. However, this model has not previously been used to estimate absolute risk reductions from antihypertensive treatment in elderly patients. Therefore, we propose to update and validate this existing "Elderly risk model" to include the prediction of treatment effects of antihypertensive treatment in elderly patients.

Finally, the "Elderly risk model" does not take into account heart failure as an outcome, while this is an emerging and very important source of morbidity and loss in quality of life in elderly patients (23). Therefore, we further propose to update the "Elderly risk model" to be able to predict not only myocardial infarction, stroke, and cardiovascular mortality, but also incident heart failure.

5. Main Hypothesis/Study Questions:

Overall aim:

To estimate the absolute 5- and 10-year treatment effect of blood pressure lowering for the individual elderly patient (>70 years) with hypertension on the risk of major cardiovascular events (MACE; stroke, myocardial infarction, heart failure and cardiovascular mortality) using the previously derived, externally validated "Elderly risk model";

Sub-objectives:

1. To perform geographical validation of the "Elderly risk model" in several populations

2. To update the "Elderly risk model" to include incident heart failure in the composite cardiovascular endpoint;

3. To improve the predictive value of the "Elderly risk model" by adding optional extra patient characteristics to the model;

4. To validate the updated and improved risk score for the prediction of blood pressure lowering treatment effect in elderly patients >70 years.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

a. **Participant inclusion/exclusion criteria**

All patients aged 70 years or older will be included, both with and without clinical cardiovascular disease at baseline, but without conditions associated with poor prognosis at baseline (e.g. severe chronic kidney disease, eGFR <30 ml/min/1.73m^2, or known (terminal) malignancy at baseline).

b. **Study Design:** Risk and treatment effect prediction using cohort and trial data

Cohorts and trials:

- Hypertension in the Very Elderly Trial (HYVET)
  - 3,845 patients aged 80 years and older eligible for analysis
  - Inclusion 2001-2007
- Atherosclerosis Risk in Communities Study (ARIC)
  - Patients aged 70 years and older eligible for analysis
  - Data derived from the 5th visit (inclusion 2011-2013), in order to minimize the effects of the differences in cohort commencement dates with the other cohorts and trials.
- Multi-ethnic Study of Atherosclerosis (MESA)
  - Patients aged 70 years and older eligible for analysis
  - Baseline visit (inclusion 2000)
- Systolic Blood Pressure Intervention Trial (SPRINT) trial
  - Patients aged 70 years and older eligible for analysis
  - Inclusion 2010-2013
  - Obtained through NHLBI data request

c. **Exposures:**

Potential Predictors: Potential predictors are pre-selected according to literature, availability in clinical practice, and availability in the datasets:

Age, sex, current smoking, diabetes mellitus, number of medications, systolic and diastolic blood pressure, LDL-cholesterol, HDL-cholesterol, eGFR, statin treatment, polyvascular disease (defined as ≥2 locations of CVD out of coronary artery disease, cerebrovascular disease, or peripheral artery disease), history of coronary artery disease, history of peripheral artery disease, history of cerebrovascular disease, frailty (as defined in [10.1093/gerona/glw199]), ankle-brachial index, orthostatic hypotension, measures of vascular stiffness (Pulse wave velocity), hsCRP, NT-proBNP,

high-sensitivity cardiac troponin T (hs-cTnT), history of heart failure, baseline medication use, micro-albuminuria, left ventricular hypertrophy (LVH) on ECG, hematocrit, urinary albumin.

d. Outcomes:

The primary outcomes across all cohorts will be:

1. (Time to) major cardiovascular events, defined as fatal or non-fatal CHD or stroke, or death due to a cardiovascular event.
2. (Time to) major cardiovascular events plus hospitalization for heart failure
3. (Time to) competing mortality from non-cardiovascular cause

e. Statistical Analysis:

All analyses will be performed in R-Statistic Programming (R Foundation for Statistical Computing, Vienna, Austria). Single imputation will be used to handle missing data, since complete case analysis may lead to both bias and loss of statistical power.

The "Elderly risk model": geographic validation

The predictive performance of the "Elderly risk model" will be assessed by determining discrimination using the concordance-statistic (C-statistic) and calibration by plotting predicted versus observed survival in a calibration plot for all trials and cohorts. As incidence rates of CVD and mortality may differ between different geographical regions, recalibration may be required by recalibration of baseline risk and mean linear predictor.

Including incident heart failure in the composite endpoint

As incident heart failure is a major cause of morbidity in elderly patients, we will update the composite cardiovascular endpoint of the model to include hospitalization from heart failure using the ARIC and MESA study data. As the incidence rates of the updated composite endpoint will be higher than of the original composite endpoint, recalibration of baseline risk and mean linear predictor will likely be required. Using this methodology, it is assumed that the coefficients for heart failure are similar to those for the original definition of MACE. We will first investigate whether this assumption is true by comparing the predictive value of the model with and without heart failure in the endpoint. The predictive value of the model for the updated endpoint will be assessed using the C-statistic for discrimination and observed-versus-predicted survival plots for calibration. If this assumption is not the case, we will consider deriving a new prediction model for heart failure.

Extending the model with new variables

With the aim to improve the predictive value of the existing "Elderly risk model", we will investigate the added value of adding optional information from additional risk factors. These additional risk factors will include frailty, presence of orthostatic hypotension, micro- or macro-albuminuria, hsCRP, hs-cTnT, NT-proBNP, pulse wave velocity, haematocrit, urinary albumin and the presence of LVH on ECG, but other available characteristics in the datasets may also be considered.

These determinants will be added to the model using a so-called naïve approach (14). This method gives predictions based on the population baseline survival and does not use regression modelling to predict individual risks. The advantage of this method is that in clinical practice, physicians do not need to have knowledge of all available added determinants and can still use the information they do have.

Instead of using the population baseline survival, in this study the 'baseline' individual predicted risk from the original model is calculated. Then, the population prevalence of a categorical value or the mean population value of a continuous predictor is used. When possible, hazard ratios for the additional determinants will be used from existing meta-analysis, or otherwise will be derived in the study populations. These together enable the updated calculation of the individual risk based on the following formula: *baseline individual predicted risk^(hazard ratio/population relative risk)*, where the population relative risk is the *(prevalence of a factor)*HR of the factor + (1-prevalence) * 1.0.* This can be performed for every additional risk factor to improve individual model predictions.

Model performance of the updated model will be assessed with the c-statistic (95% CI) for discrimination and with calibration plots of predicted versus observed risk.

Estimating treatment effect of antihypertensive treatment

To estimate the effect of antihypertensive treatment on MACE, average relative treatment effects will be added to the model in HYVET and SPRINT. The relative treatment effect will be derived from a meta-analysis with 613 815 participants from randomized controlled trials of blood pressure lowering treatment, including trials with elderly patients (>70 years): hazard ratio per 10 mmHg systolic blood pressure: 0.77 (95% confidence interval 0.71-0.81) for people with and 0.74 (95% confidence interval 0.67-0.81) for patients without cardiovascular disease at baseline (24). Model performance of the model updated with antihypertensive treatment effect will be assessed with the c-statistic (95% CI) for discrimination and with calibration plots of predicted versus observed risk.

Treatment benefit for individual patients, absolute benefit of using antihypertensive medication, is defined as the patient's predicted absolute 5- and 10-year risk of MACE according to the "Elderly risk model" minus the patient's absolute risk of MACE when using antihypertensive medication, and was expressed as an absolute risk reduction (ARR). This ARR will be translated into an individual

number needed to treat (iNNT), the number of patients with the exact same risk profile needed to treat to prevent 1 event in 5 or 10 years, respectively.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes __X__ No

8.a. Will the DNA data be used in this manuscript? ____ Yes __X__ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at:
http://www.cscc.unc.edu/aric/mantrack/maintain/search/dtSearch.html

___**X**___ Yes   _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

Study proposal #3008, Nicole Jaspers
This study is performed by the same research group; both studies involve risk prediction and prediction of treatment effect of preventive therapies including antihypertensive therapy.
However, the current study proposal includes elderly patients (>70 years old) with and without a history of cardiovascular disease, whereas study #3008 includes patients over a wide age range without a history of cardiovascular disease only. Furthermore, the current study uses a risk prediction model for 10 year predictions of CVD risk, and estimates treatment effects in terms of absolute risk reductions. Study #3008, on the other hand, predicts disease-free life expectancy, and estimates treatment effects in terms of disease-free life years gained. Finally, the current study proposal aims to predict the risk of heart failure as well as myocardial infarction, stroke, and cardiovascular mortality, whereas the prediction model in proposal #3008 does not predict the risk of heart failure.

DOI: 10.1016/j.jacc.2018.02.050, *Anum Saeed*
This study also looks at disease risk prediction in older adults, and also included heart failure hospitalization in the outcome. The main goal of this study was not to provide a clinically ready-to-use risk model, but rather to determine whether adding biomarkers to an existing risk score improves the risk prediction in elderly over a shorter time period. They also added NT-proBNP, hs-cTnT, and hsCRP, which will also be used in the current study.
Important differences with the current study are that in the current proposal, we aim to provide a ready-to-use model for risk prediction in clinical practice. Furthermore, in the current study, these models will be used to predict the therapy effect from statin treatment and antihypertensive use in elderly patients.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __X__ No

11.b. If yes, is the proposal

    ___   A. primarily the result of an ancillary study (list number* _____)

    ___   B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number at https://www2.cscc.unc.edu/aric/approved-ancillary-studies

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

13. References:

A)   References in Proposal:

1.   North BJ, Sinclair DA. The intersection between aging and cardiovascular disease. Circ Res [Internet]. 2012 Apr 13;110(8):1097–108. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22499900

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4.   Nilsson PM. Blood pressure strategies and goals in elderly patients with hypertension. Exp Gerontol. 2017 Jan;87(Pt B):151–2.

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B) Recent Publications Relating to Individualized Prediction From Our Group

1. Kaasenbrood L, Bhatt DL, Dorresteijn JA, Wilson PW, D'Agostino RB, Massaro JM, van der Graaf Y, Cramer MJ, Kappelle LJ, de Borst GJ, Steg PhG, Visseren FL. Estimated life-expectancy without recurrent cardiovascular events in patients with vascular disease: the REACH-SMART model. J Am Heart Assoc. 2018;7:e009217.

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3. Stam-Slob MC, van der Graaf Y, Greving JP, Dorresteijn JA, Visseren FL. Cost-Effectiveness of Intensifying Lipid-Lowering Therapy With Statins Based on Individual Absolute Benefit in Coronary Artery Disease Patients. J Am Heart Assoc. 2017 Feb 18;6(2).

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9. Kaasenbrood L, Poulter NR, Sever PS, Colhoun HM, Livingstone SJ, Boekholdt SM, Pressel SL, Davis BR, van der Graaf Y, Visseren FL; CARDS, ALLHAT, and ASCOT Investigators. Development and Validation of a Model to Predict Absolute Vascular Risk Reduction by Moderate-Intensity Statin Therapy in Individual Patients With Type 2 Diabetes Mellitus: The

Anglo Scandinavian Cardiac Outcomes Trial, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, and Collaborative Atorvastatin Diabetes Study. Circ Cardiovasc Qual Outcomes. 2016 May;9(3):213-21.

10.   Dorresteijn JA, Kaasenbrood L, Cook NR, van Kruijsdijk RC, van der Graaf Y, Visseren FL, Ridker PM. How to translate clinical trial results into gain in healthy life expectancy for individual patients. BMJ. 2016 Mar 30;352:i1548.

11.   Krikke M, Hoogeveen RC, Hoepelman AI, Visseren FL, Arends JE. Cardiovascular risk prediction in HIV-infected patients: comparing the Framingham, atherosclerotic cardiovascular disease risk score (ASCVD), Systematic Coronary Risk Evaluation for the Netherlands (SCORE-NL) and Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) risk prediction models. HIV Med. 2016 Apr;17(4):289-97.

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21. Dorresteijn JA, Visseren FL, Ridker PM, Wassink AM, Paynter NP, Steyerberg EW, van der Graaf Y, Cook NR. Estimating treatment effects for individual patients based on the results of randomised clinical trials. BMJ. 2011 Oct 3;343:d5888.