ARIC Manuscript Proposal # 3008

PC Reviewed: 7/11/17 **Status: _____** **Priority: 2**

SC Reviewed: _____ **Status: _____** **Priority: ____**

1.

a. Full Title: Individualized estimation of cardiovascular disease-free survival in primary prevention to facilitate personalized treatment with lipid, antihypertensive, and antiplatelet therapy: A collaborative analysis of three community-based cohorts.

b. Abbreviated Title (Length 26 characters): CVD-free Survival Estimation

2. Writing Group:

Department of Vascular Medicine University Medical Center Utrecht

- N.E.M. Jaspers, F.L.J. Visseren, Y. van der Graaf , J.A.N. Dorresteijn.

ARIC

- Kunihiro Matsushita & Vijay Nambi (on behalf of ARIC investigators)

EPIC-NL (Prospect & MORGEN Cohorts)

- Y.T. van der Schouw (on behalf of EPIC-NL investigators)

MESA

- M.J. Blaha (on behalf of MESA investigators)

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. **[NEMJ].**

First author: N.E.M. Jaspers MD

Address: University Medical Center Utrecht
Department of Vascular Medicine
Internal mail no F02.126
Phone: + 31 88 75 55650
E-mail: n.e.m.jaspers@umcutrecht.nl

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

Name: Kunihiro Matsushita

Address: Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health
Welch Center for Prevention, Epidemiology, and Clinical Research
2024 E. Monument St., Suite 2-600 (Rm 2-602), Baltimore, MD 21287

Phone: (443) 287-8766
Fax: (410) 367-2384
E-mail: kmatsus5@jhmi.edu

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

4. Rationale:

Cardiovascular disease (CVD) accounts for nearly 30% of deaths world-wide[1]. Despite efforts in primary prevention, the majority of individuals will develop clinical CVD during their lifetime.[2] Lipid-lowering, antihypertensive, and antiplatelet therapy are key components of many CVD prevention guidelines.[3 4] Those guidelines usually recommend preventive therapy to individuals with high predicted cardiovascular risk[5 6] based on a risk score, such as the QRISK and the ACC/AHA risk calculator (i.e., the Pooled Cohort Equation).[3 7] However, many existing risk prediction scores estimate prognosis in terms of absolute (10-year) risk of cardiovascular disease, and not in terms of life-expectancy free of cardiovascular disease. A 10-year risk does not reflect the long-term process of atherosclerosis development.[8 9] Moreover, use of 10-year risk may not identify individuals who (most due to a younger age) have a low 10-year absolute risk, but both a relatively high risk compared to their peers and a high cumulative life-time risk.

Aside from the use of 10-year risk to estimate prognosis, existing risk prediction scores have a few other limitations, such as not considering the competing risk of non-CVD mortality or not being based on international data, and therefore have limited generalizability, or are prone to several types of bias.[7] Also, expressing prognosis in terms of life-expectancy free of cardiovascular disease, rather than an absolute risk-percent (i.e. a probability), may increase patient understanding of prognosis. Therefore, here, we propose to develop a life-expectancy prediction model and validate using established community-based cohorts in the US and Europe. Once that life-expectancy prediction model is developed and validated, we will try to develop an interactive application that can indicate the effects of preventive therapy as the gain in life-expectancy (i.e. months or years). This application may facilitate doctor-patient communication and may positively influence adherence to preventive therapies.

5. Main Hypothesis/Study Questions:

a. Aims:

1. To develop and externally validate a competing-risk model for individualized prediction of CVD-free survival in patients without clinical CVD using data from US and Western-European populations based on easy-to-measure clinical characteristics
2. To develop an interactive application which combines the prediction score from Aim 1 with average treatment effects from meta-analyses of clinical trials (i.e. relative risk reduction) in order

to estimate and effectively communicate the effects of anti-lipid, antihypertensive, and antiplatelet therapy for real-time individual patients in terms of months or years gain in CVD-free life-expectancy.

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 participants with necessary risk factor data will be included, so long as these are *without* clinical CVD, and without conditions associated with a poor prognosis at baseline (e.g. severe chronic kidney disease, eGFR <30 ml/min/1.73m^2, known (terminal) malignancy, or chronic heart failure at baseline).

b. Study Design: Life-time prediction using cohort data

Current Cohorts:

- Atherosclerosis Risk in Communities Study (ARIC)[10]
    - Data derived from the 4th visit (inclusion 1996), in order to minimize the effects of the differences in cohort commencement dates with EPIC and MESA
    - Planning to use as a validation cohort
- European Prospective Investigation Into Cancer and Nutrition (EPIC) cohort, comprised of two separate cohorts:
    - The Prospect cohort and the Monitoring Project on Risk Factors for Chronic Disease (MORGEN) cohort[11 12] (baseline inclusion 1993 – 1997)
    - Planning to use as a validation cohort
- Multi-ethnic Study of Atherosclerosis (MESA)[13]
    - Baseline visit (inclusion 2000)
    - Planning to use as the derivation cohort (justification is described below)

c. Exposures:

Potential Predictors: Potential predictors are pre-selected based on literature, availability in clinical practice, and availability in the dataset.

Score 1: age, sex, smoking status, systolic blood pressure, total cholesterol and HDL-cholesterol,[3] as well as race/ethnicity, presence of diabetes, and family history of coronary heart disease.

Score 2: Coronary Artery Calcium Score (CAC) in addition to predictors from score 1 (ARIC data will not be used in Score 2 given lack of CAC data).

d. Outcomes:

The primary outcomes across all cohorts will be:

1) Main Outcome: Major cardiovascular events, defined as fatal or non-fatal CHD or stroke, or death due to a cardiovascular event.
2) Competing-outcome: death from any non-cardiovascular cause.

e. Statistical Analysis (Brief):

Statistical analysis will be performed using R-Statistical Software.

Model Development for Aim 1:

The MESA cohort, due to a wide range of baseline ages, an ethnically/racially diverse population, and cohort commencement in 2000, is the most optimal cohort for model development. Multiple imputation will be used to handle missing data (assuming missing-at-random values) using predictive mean matching, since complete cases analysis may lead to both bias and loss of statistical power. Continuous variables will be truncated at the highest and lowest 1% to limit the effect of outliers. Continuous variables will be transformed based on the Akaike Information Criterion of the full model, where a difference of >2 points indicate necessary variable transformation (i.e. logarithmic or quadratic transformation).[14] Predictors will be pre-specified to avoid testimation bias which may lead to overfitting. Specifying predictors based on withstanding a statistical test (e.g. backward or stepwise selection) tends to select predictors with extreme effects, and may not select true predictors with small effects.[14 15]

Lifetime model analysis will be performed using competing-risk adjusted Fine and Gray models with left truncation and right censoring (i.e. using age as the time-scale).[16 17] Proportional hazards assumption will be visually checked using Schoenfelds residuals, and an interaction with the time-axis (i.e. age) will be added when appropriate. Using patient age, instead of follow-up duration as the time-axis, means that patients are enrolled between age of study entry and age of study exit. This results in overlapping observations, allowing for lifetime predictions to be made across the entire range of baseline ages.

The age-specific baseline 1-year survival free CVD and 1-year survival free of non-cardiovascular mortality will be calculated for each available age based on cause-specific cumulative incidence. To obtain cumulative survival for each individual, the estimated survival at the beginning of each life-year will be multiplies by the survival probability (1 minus cardiovascular risk minus non-cardiovascular mortality risk) of that year. Estimated CVD-free life-expectancy will be defined as median estimated survival, defined as the age where the predicted individual survival curve is 50% (median).

Given the implication on Aim 2, we will repeat the development process for individuals who were not taking key medications for preventing CVD (e.g., statin and aspirin) at baseline and evaluate the extent of differences in estimated CVD-free life-expectancy in the primary and this secondary approach.

A description of this technique written by our group can be found elsewhere.[16] A video explanation can also be found: https://www.youtube.com/watch?v=eVHaxVam3CA

Model accuracy and performance in Aim 1: Predictive performance will be assessed by determining discrimination using the concordance-statistic and calibration by plotting predicted versus observed survival in a calibration plot. Cohorts not used for development will be used for external validation (i.e., EPIC-NL & ARIC). As noted above, to minimize the impact of differences in baseline calendar year between MESA and ARIC, we will use data from visit 4 for ARIC. Incidence rates of CVD and mortality may differ between different geographical regions, requiring recalibration by accounting region-specific baseline survival and predictor distribution or by the addition of coefficients for geographical region. Overfitting will be calculated; however, applying a shrinkage factor may not be necessary as the predictors are pre-specified and thus testimation bias is avoided.

The model development will be based on cohort data in which a proportion of patients are already using statin medication at baseline. However, we will conduct a sensitivity analysis to compare the model based on the entire population described in the section "Participant Inclusion," to a model which excludes all patients using statin therapy at enrollment (or V4 for ARIC). The accuracy and performance of these two models will be compared in order to assess how inclusion of patients on statin medications at baseline effects the estimates.

Method for developing an interactive application that can indicate the effects of preventive therapy as the gain in life-expectancy (i.e. months or years) for aim 2. We aim to develop an application to estimate the gain in life-expectancy (i.e. months or years) by an additional medication (i.e. new prescription or alteration of dose), or the negative consequences of less medication (i.e. cessation of dose-lowering) for a patient in real-time. The algorithm which we use for this aim uses a combination of the (1) developed and validated model from aim 1 and (2) the effect of preventative medication (RR's) established from meta-analyses of existing clinical trials. The beneficial effect thus proceeds via risk-factor level modification (e.g. lipid-lowering). We will provide an example using statins below:

The relative risk associated with a 1 mmol/L decrease in LDL is 0.78.[18] The LDL-reduction associated with a specific statin has also been described.[19] The on-treatment CVD-survival function will be modified by the addition of the (logarithm of) 0.80^(the specific LDL-c change) to the linear predictor. The gain of life from novel therapy is the difference between the age at which the predicted individual survival curve is 50%, i.e. the difference in median survival time, expressed as months gain/loss

f. Limitations:

1. As our life-time models will predict beyond the actual follow-up duration for each individual, life-time validation is not possible. However, the life-time prediction model developed by our group using 10 years follow-up of the Woman's Health Study was validated against 17 years of follow-up data. Survival probabilities were well-calibrated, as the observed and predicted survival corresponded well.[16]

2. It is an inherent limitation of the life-time model proposed that the linear predictor of the model and the coefficients remain the same over time. However, there are a number of factors which should lessen concerns about this limitation. Firstly, the prediction model will be developed in a dataset with a considerable median follow-up time of 8.6 years (i.e. MESA). This means that some degree of intra-individual change of risk factor levels (i.e. the mean change) is already reflected by the magnitude of the models' coefficients. Secondly, as aforementioned, our past work has shown predicted and observed estimations to be well calibrated beyond range in which the model was derived (i.e., the model was derived based on 10 years follow-up data and was validated using 17-years follow-up data in the Woman's Health study) We currently have two other life-time prediction models (either in the journal submission or manuscript stage) in which similar validation results were seen; model derivation was performed with a shorter average follow-up time than model validation, and the predicted versus observed probabilities remained well-calibrated.

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

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

b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ____ Yes __X__ No

8. 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. __ X __ Yes ____ No

9. **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)?** There are several ARIC proposals aiming to develop risk prediction models as listed below, but none of them are aiming to estimate life expectancy. Also, this proposal is unique as it is for an international collaborative analysis of three community-based cohorts, ARIC, MESA, and EPIC.

- #1110 (McGeechan et al):Risk Prediction of Coronary Heart Disease and Stroke using Retinal Arteriolar and Venular Signs
- #1808 (Nambi et al): The utility high sensitivity cardiac troponin t in the prediction of heart failure risk
- #1904 (D'Agostino et al):Cardiovascular Disease Risk Prediction in Combined Cohort Studies
- #1915 (Matsushita et al): Improvement of cardiovascular risk prediction using non-traditional risk factors in the chronic kidney disease (CKD) population

10.

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

b. If yes, is the proposal

1) primarily the result of an ancillary study (list number* _____)

2) **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 http://www.cscc.unc.edu/aric/forms/

11. 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.

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. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __X__ No.

14. References:

A) Recent Publications Relating to Individualized Prediction From Our Group

1: 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). pii: e004648. doi: 10.1161/JAHA.116.004648. PubMed PMID:28214794.

2: Kaasenbrood L, Boekholdt SM, van der Graaf Y, Ray KK, Peters RJ, Kastelein JJ, Amarenco P, LaRosa JC, Cramer MJ, Westerink J, Kappelle LJ, de Borst GJ, Visseren FL. Distribution of Estimated 10-Year Risk of Recurrent Vascular Events and Residual Risk in a Secondary Prevention Population. Circulation. 2016 Nov 8;134(19):1419-1429. PubMed PMID: 27682883.

3: van der Leeuw J, Visseren FL, Woodward M, van der Graaf Y, Grobbee DE, Harrap S, Heller S, Mancia G, Marre M, Poulter N, Zoungas S, Chalmers J. Estimation of individual beneficial and adverse effects of intensive glucose control for patients with type 2 diabetes. Diabetologia. 2016 Dec;59(12):2603-2612. PubMed PMID: 27586250.

4: Stam-Slob MC, Visseren FL, Wouter Jukema J, van der Graaf Y, Poulter NR, Gupta A, Sattar N, Macfarlane PW, Kearney PM, de Craen AJ, Trompet S. Personalized absolute benefit of statin treatment for primary or secondary prevention of vascular disease in individual elderly patients. Clin Res Cardiol. 2017 Jan;106(1):58-68. doi: 10.1007/s00392-016-1023-8. PubMed PMID: 27554244; PubMed Central PMCID: PMC5226996.

5: van der Sande NG, Dorresteijn JA, Visseren FL, Dwyer JP, Blankestijn PJ, van der Graaf Y, Heerspink HL. Individualized prediction of the effect of angiotensin receptor blockade on renal and cardiovascular outcomes in patients with diabetic nephropathy. Diabetes Obes Metab. 2016 Nov;18(11):1120-1127. doi: 10.1111/dom.12708. PubMed PMID: 27337598.

6: 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. doi: 10.1161/CIRCOUTCOMES.115.001980. PubMed PMID: 27174798.

7: 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. doi: 10.1136/bmj.i1548. PubMed PMID: 27029390.

8: van Kruijsdijk RC, Visseren FL, Ridker PM, Dorresteijn JA, Buring JE, van der Graaf Y, Cook NR. Individualised prediction of alternate-day aspirin treatment effects on the combined risk of cancer, cardiovascular disease and gastrointestinal bleeding in healthy women. Heart. 2015 Mar;101(5):369-76. doi: 10.1136/heartjnl-2014-306342. PubMed PMID: 25475110; PubMed Central PMCID: PMC4536552.

9: van der Leeuw J, Visseren FL, Woodward M, Zoungas S, Kengne AP, van der Graaf Y, Glasziou P, Hamet P, MacMahon S, Poulter N, Grobbee DE, Chalmers J. Predicting the effects of blood pressure-lowering treatment on major cardiovascular events for individual patients with type 2 diabetes mellitus: results from Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation. Hypertension. 2015 Jan;65(1):115-21. doi: 10.1161/HYPERTENSIONAHA.114.04421. PubMed PMID: 25312436.

10: van der Leeuw J, van Dieren S, Beulens JW, Boeing H, Spijkerman AM, van der Graaf Y, van der A DL, Nöthlings U, Visseren FL, Rutten GE, Moons KG, van der Schouw YT, Peelen LM. The validation of cardiovascular risk scores for patients with type 2 diabetes mellitus. Heart. 2015 Feb;101(3):222-9. doi:10.1136/heartjnl-2014-306068. Review. PubMed PMID: 25256148.

11: van der Leeuw J, Ridker PM, van der Graaf Y, Visseren FL. Personalized cardiovascular disease prevention by applying individualized prediction of treatment effects. Eur Heart J. 2014 Apr;35(13):837-43. doi: 10.1093/eurheartj/ehu004. PubMed PMID: 24513790.

12: van der Leeuw J, Oemrawsingh RM, van der Graaf Y, Brugts JJ, Deckers JW, Bertrand M, Fox K, Ferrari R, Remme WJ, Simoons ML, Boersma E, Visseren FL. Prediction of absolute risk reduction of cardiovascular events with perindopril for individual patients with stable coronary artery disease - results from EUROPA. Int J Cardiol. 2015 Mar 1;182:194-9. doi: 10.1016/j.ijcard.2014.12.046. PubMed PMID: 25577762.

13: Dorresteijn JA, Boekholdt SM, van der Graaf Y, Kastelein JJ, LaRosa JC, Pedersen TR, DeMicco DA, Ridker PM, Cook NR, Visseren FL. High-dose statin therapy in patients with stable coronary artery disease: treating the right patients based on individualized prediction of treatment effect. Circulation. 2013 Jun 25;127(25):2485-93. doi: 10.1161/CIRCULATIONAHA.112.000712. PubMed PMID: 23674398.

14: Dorresteijn JA, Visseren FL, Wassink AM, Gondrie MJ, Steyerberg EW, Ridker PM, Cook NR, van der Graaf Y; SMART Study Group.. Development and validation of a prediction rule for recurrent vascular events based on a cohort study of patients with arterial disease: the SMART risk score. Heart. 2013 Jun;99(12):866-72. doi: 10.1136/heartjnl-2013-303640. PubMed PMID: 23574971.

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16: 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. doi: 10.1136/bmj.d5888. PubMed PMID: 21968126; PubMed Central PMCID: PMC3184644.

B) References in Proposal:

1. (WHO) WHO. Global status report on noncommunicable diseases 2014.
2. Berry JD, Dyer A, Cai X, et al. Lifetime risks of cardiovascular disease. N Engl J Med 2012;**366**(4):321-9.
3. Goff DC, Jr., Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;**129**(25 Suppl 2):S49-73.
4. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2016;**37**(29):2315-81.
5. Dorresteijn JAN, Visseren FLJ, Ridker PM, et al. Estimating treatment effects for individual patients based on the results of randomised clinical trials. Brit Med J 2011;**343**.
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7. Hippisley-Cox J, Coupland C, Robson J, et al. Derivation, validation, and evaluation of a new QRISK model to estimate lifetime risk of cardiovascular disease: cohort study using QResearch database. BMJ 2010;**341**:c6624.
8. Berenson GS, Srinivasan SR, Hunter SM, et al. Risk factors in early life as predictors of adult heart disease: the Bogalusa Heart Study. Am J Med Sci 1989;**298**(3):141-51.
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11. Beulens JW, Monninkhof EM, Verschuren WM, et al. Cohort profile: the EPIC-NL study. Int J Epidemiol 2010;**39**(5):1170-8.
12. van der Meer MG, van der Graaf Y, Schuit E, et al. Added Value of Female-Specific Factors Beyond Traditional Predictors for Future Cardiovascular Disease. J Am Coll Cardiol 2016;**67**(17):2084-6.
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18. Cholesterol Treatment Trialists C, Mihaylova B, Emberson J, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 2012;**380**(9841):581-90.
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