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The added value of ECG abnormalities in predicting incident cardiovascular disease risk for people with type 2 diabetes: The Hoorn Diabetes Care System cohort

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Introduction: Cardiovascular disease (CVD) prediction models that help clinicians make personalized treatment decisions for people with type 2 diabetes perform only moderately, with c-statistics for discrimination typically around 0.7 (theoretical range: 0.5-1.0). ECG abnormalities are good candidates for improving prediction because they are associated with incident CVD, are common in people with type 2 diabetes without pre-existent CVD, and might be part of the pathophysiology. We aimed to investigate if adding ECG abnormalities as a predictor improves the performance of incident CVD-risk prediction models currently recommended for people with type 2 diabetes.

Methods: We evaluated the ASCVD, AD-ON, and ADVANCE Cox-prediction models that are recommended by guidelines (American College of Cardiology/American Heart Association (ACC/AHA), the European Society of Cardiology (ESC), and Dutch Society of General Practitioners (NHG)) in 11,277 people with type 2 diabetes without CVD (heart disease/failure, stroke, thrombosis) from the dynamic Hoorn Diabetes Care System cohort (1998-2018). Baseline measurements, taken at entry into the cohort, included CVD risk factors and ECG abnormalities coded according to the Minnesota Classification as minor or major. Annual follow-up for CVD continued until 2018. After calibration to ensure good model fit, the performance of the prediction models was assessed with and without the addition of ECG abnormalities and compared using c-statistics, net reclassification indices (NRIs), and the integrated discrimination index (IDI).

Results: For ASCVD, AD-ON and ADVANCE, respectively, including ECG abnormalities as an additional predictor changed c-statistics (+0.02, +0.01 and +0.03), categorical NRI (0.04, 0.04 and 0.07), continuous NRI (95% CI) (0.166 (0.018-0.192), 0.117 (0.005-0.153) and 0.076 (0.12-0.129)), and IDI (95% CI) (0.004 (0.000-0.007), 0.003 (0.001-0.007) and 0.001 (0.000-0.004)).

Conclusion: Adding ECG abnormalities to incident CVD risk prediction models consistently but moderately improves model performance and the ability of models to correctly classify people with type 2 diabetes in the appropriate CVD risk category.

Conflicts of interest to disclose: We declare no competing interests

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A global perspective on cardiovascular risk factor management in patients with CHD and different educational level: SURF CHD II

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Background: Clinical guidelines recommend that patients with established coronary heart disease (CHD) change health behaviors and use medication to control risk factors (RF), yet RF control in secondary prevention remains suboptimal. Patients with low educational level tend to have higher cardiovascular risk, though this association varies by context. We aim to investigate RF management by educational level in CHD patients from four world regions.

Methods: The Survey of Risk Factors in Coronary Heart Disease (SURF CHD) II is a clinical audit on RF management, undertaken in CHD patients during routine outpatient visits. The cross-sectional survey is easy to perform, allowing participation of low-resource centers. We assessed differences in guideline-defined RF target attainment and treatment by educational level using logistic regression adjusted by age and sex, and stratified by region. RF included smoking, physical activity, waist circumference, blood pressure, LDL, non-HDL cholesterol, triglycerides, and Hba1c (among diabetics).

Results: 13884 patients were enrolled in Europe, South-East Asia (SEA), Americas, and North Africa Eastern Mediterranean (NAEM) regions. 47.0% of participants had tertiary, 34.5% secondary, and 18.6% primary education. Target attainment ranged from 15.9% (waist circumference) to 76.9% (smoking). 50.5% participated in cardiac rehabilitation.

Highly educated patients were more likely to meet RF targets for smoking (odds ratio and 95% confidence interval in the Americas 1.79, 1.17-2.77; Europe 1.7, 1.46-1.97; SEA 2.97, 3.14-2.43), physical activity (Americas 3.04, 2.01-4.66; Europe 1.75, 1.5-2.05), LDL (SEA 1.79, 1.45-2.22), non-HDL cholesterol (Americas 3.96, 2.1-7.64; SEA 1.6, 1.29-1.99) and Hba1c (Americas 1.74, 1.04-2.92; SEA 2.29, 1.6-3.27). Patients with higher education participated more often in cardiac rehabilitation (Europe 1.49, 1.3-1.69; Americas 3.2, 1.42-8.22; NAEM 4.23, 1.01-29.44).

Conclusion: Health inequalities persist in secondary prevention of CHD: highly educated patients are generally more likely to meet RF targets and attend cardiac rehabilitation. However, these associations present specific patters by RF and region.

Conflicts of interest to disclose: We declare no competing interests

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Prognostic value of temporal patterns of left atrial reservoir strain in patients with heart failure with reduced ejection fraction

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Background: We investigated whether repeatedly measured left atrial reservoir strain (LASr) in heart failure with reduced ejection fraction (HFrEF) patients provides incremental prognostic value over a single baseline LASr value, and whether temporal patterns of LASr provide incremental prognostic value over temporal patterns of other echocardiographic markers and NT-proBNP.

Methods: In this prospective observational study, 153 patients underwent 6-monthly echocardiography. During a median follow-up of 2.5 years, a median of 3 (25th-75th percentile: 2-4) echocardiograms were obtained per patient. Hazard ratios (HRs) were calculated for LASr from Cox models (baseline) and joint models (repeated measurements). The primary endpoint (PEP) comprised HF hospitalization, left ventricular assist device, heart transplantation, and cardiovascular death.

Results: Mean age was 58 ± 11 years, 76% were men, 82% were in NYHA class I/II and mean LVEF was 29% ± 10%. The PEP was reached by 50 patients. Baseline and repeated measurements of LASr (HR per SD change [95% CI]: 0.20 [0.10-0.41] and (0.13 [0.10-0.29]) were both significantly associated with the PEP, independent of both baseline and repeated measurements of other echo-parameters and NT-proBNP (Table 1). Although LASr was persistently lower over time in patients with PEP, temporal trajectories did not diverge in patients with versus without the PEP as the PEP approached (Figure 1).

Conclusion: LASr was associated with adverse events in HFrEF patients, independent of baseline and repeated other echo-parameters and NT-proBNP. Temporal trajectories of LASr showed decreased but stable values in patients with the PEP, and do not provide incremental prognostic value for clinical practice compared to single measurements of LASr, over a follow-up time of 2.5 years. A single measurement of LASr showed stronger prognostic value than conventional echocardiographic parameters. Therefore, LASr should be considered for routine use in clinical practice in patients with HFrEF, for prognostication and potentially for guiding treatment.

Conflicts of interest to disclose: We declare no competing interests

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VAC4EU study to identify risk factors for the development of myocarditis and pericarditis after mRNA-1273 vaccination in four European countries: methodological considerations

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Introduction: Myocarditis and pericarditis are among the identified risks following COVID-19 mRNA vaccination, including the mRNA-1273 vaccine. Most cases occur within 14 days following the second dose, and incidence is highest among young males. Additional data are needed to characterize risk factors and the clinical course of these events. The study objectives include: (1) Identifying possible risk factors for myocarditis and pericarditis following mRNA-1273 vaccination; and, (2) examining the clinical course of myocarditis and pericarditis of varying origin and its prognostic factors.

Methods: The study will draw on electronic healthcare records (EHRs) from five data sources in Denmark (Danish health registers), Norway (Norwegian health registers), Spain (SIDIAP, VID) and the UK (CPRD). The ConcePTION common data model (CDM) is used across data sources, with analyses run locally. All cases will be validated using criteria from the Brighton Collaboration Case Definition. A case-cohort design will address Objective (1) and will include all cases of myocarditis and pericarditis following mRNA-1273 vaccination, as well as a sub-cohort of vaccinated controls. A Cox Proportional Hazards model including demographic variables, medical history and vaccination records will be used to investigate risk factors. Objective (2) will be addressed through a cohort design including all cases of myocarditis and pericarditis in the data, where the clinical course of myocarditis and pericarditis will be compared between mRNA-1273 vaccinated and other cases via a Cox Proportional Hazards model.

Results: The source population includes over 6 million vaccinated individuals, with 150-1500 myocarditis and pericarditis cases expected in each study design. The time period for study analysis will continue through 2023 and 2024 to most accurately describe current risk factor profiles of interest.

Conclusion: By drawing on EHRs and using the ConcePTION CDM, this study allows for identification of risk factors for the development and clinical course of myocarditis and pericarditis.

Conflicts of interest to disclose: Brianna M Goodale discloses interests in Ava FemTech, Delfina, Julius Clinical Research, and LiveCircle. Daina Esposito, Samantha St Laurent, David Martin, Veronica Urdaneta, Magalie Emilebacker disclose interest in Moderna. Daniel Weibel discloses intere

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Biomarkers of microvascular dysfunction and cerebral white matter connectivity: The Maastricht Study

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Introduction: Microvascular dysfunction may contribute to the development of various cerebral disorders, including cognitive dysfunction, dementia, and certain forms of depression. The suggested mechanism through which microvascular dysfunction contributes to these disorders is by disrupting white matter tracts and altering brain connectivity, but evidence is scarce. We investigated the association between multiple biomarkers of microvascular function and cerebral white matter connectivity.

Methods: We used cross-sectional data from The Maastricht Study, a Dutch population-based cohort (n=4,326, mean±SD age 59.4±8.6, 49.7% women). Measures of microvascular function included urinary albumin excretion, central retinal arteriolar and venular calibers (CRAE and CRVE), a composite score of flicker light induced retinal arteriolar and venular dilation response, and a composite score of plasma biomarkers of endothelial dysfunction (soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular cell adhesion molecule-1 (sVCAM-1), soluble E-selectin (sE-selectin) and von Willebrand factor (vWF)). White matter connectivity was calculated from 3T diffusion MRI to quantify the number (average node degree) and organization (characteristic path length, global efficiency, clustering coefficient and local efficiency) of white matter connections.

Results: A higher endothelial dysfunction composite score was associated with a longer characteristic path length (beta per SD: 0.066 [95% CI: 0.017-0.114]) after adjustment for sociodemographic, lifestyle and cardiovascular factors, but not with any of the other connectivity measures. All other measures of microvascular dysfunction were not associated with any of the connectivity measures after adjustments.

Conclusion: The present study suggests that microvascular dysfunction, as quantified by a set of various measures, is not consistently associated with cerebral white matter connectivity. Only a composite score of plasma biomarkers of endothelial dysfunction was associated with a longer characteristic path length, being indicative for a topographically less integrated and less efficient cerebral network. Future studies are needed to further understand the role of microvascular dysfunction in the development of cerebral disorders.

Conflicts of interest to disclose: We declare no competing interests

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Prognostic factors and models for patients with peripheral artery disease to predict mortality: a systematic review

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Introduction: Patients with peripheral artery disease (PAD) have high mortality risk. Prognostic models help to estimate individual risk. However, it remains unclear which models are specifically developed for patients with PAD. We aim to systematically evaluate the recent evidence on prognostic factors and models for all-cause mortality in PAD.

Methods: We searched PubMed, EMBASE, and the Cochrane library to identify studies examining individual prognostic factors and those aimed to develop, internally or externally, validate a model predicting all-cause mortality risk at any time in patients with PAD. We extracted information on study design, population and model characteristics. We used the Quality In Prognosis Studies tool and the Prediction model Risk Of Bias ASsessment Tool to assess the risk of bias in the identified studies.

Results: Forty-nine studies investigated prognostic factors, and six developed or validated prognostic models. The sample size ranged from 129 to 16,888, with a median of 647 [378-951 participants]. The population was predominantly males (median: 66% [62%-73%]), and follow-up ranged from one to 94 months (median: 48 [22-62.5 months]). We identified 94 prognostic factors, for which age was the only factor included in all the studies, as a factor of interest or adjustment in the multivariable model. Other common factors were sex (67.3%), diabetes (69.3%), and smoking status (61.2%). The six studies on prognostic models have similar discrimination abilities, and none excelled over the others. All prognostic models showed a high risk of bias and low concern regarding applicability.

Conclusion: A large number of studies investigate prognostic factors within patients with PAD. Nevertheless, unlike prognostic models, a single factor is doubtful to be the sole determinant of patient outcomes. Rather than study single prognostic factors, existing models should be validated more often, and if necessary, authors might consider updating by adding new predictors not contained in existing models.

Conflicts of interest to disclose: We declare no competing interests

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Systematic review protocol registration: the perspectives of researchers, peer-reviewers and journal editors through an online survey

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Introduction: As systematic reviews (SRs) inform healthcare decisions, it is key that they address relevant questions and use rigorous methodology. The exponential increase in published SRs, introduced redundancy in available SRs in certain health topics. Registration of SR protocols is proposed to help researchers identify relevant topics to review and avoid duplication of effort. Currently, most SR protocols are not registered. Gaining understanding in the perspectives of the research community would help guide future recommendations on prospective registration of SRs. Therefore, this study aims to examine the experiences with for prospective SR registration amongst researchers, peer reviewers and journal editors and identify potential barriers and facilitators.

Methods: Survey study among SR authors and journal editors informed by Consolidated Framework for Implementation Research (CFIR). Data was analysed through qualitative and quantitative methods.

Results: In total, 22 journal editors and 65 researchers (of whom 37 were peer reviewers) took part in the survey. Almost all respondents (95%) were familiar with SR protocol registration and most researchers (81%) registered a protocol for at least one SR. Four journal editors indicated that protocol registration was currently mandatory for SR publication within their journal. Moreover, 8 journal editors believed that SR protocol registration should be mandatory. Overall, researchers and journal editors had a positive attitude towards SR protocol registration. Shared barriers were a lack of time and resources, increased bureaucracy, and the potential to steal research ideas. Both researchers and journal editors suggested a variety of ideas on how flexible SR protocol registration should be positioned.

Conclusion: Researchers and journal editors were familiar with SR protocol registration and had a positive attitude towards it. This study gives direction to several barriers that prevent SR protocol registration to be addressed in the future.

Conflicts of interest to disclose: We declare no competing interests