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Risk Score for Lower-Limb Amputation and its Ability to Predict Major Kidney and Cardiovascular Events in People with Type 1 Diabetes

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ABSTRACT

Background:

To develop a 10-year risk score to predict lower-limb amputation (LLA) in individuals with type 1 diabetes, and to assess whether this score also predicts kidney failure, and cardiovascular disease (CVD).

Methods

The LLA risk score was derived from GENEDIAB and GENESIS, two prospective French and Belgian cohorts of 828 individuals with type 1 diabetes. External validation was assessed in SURGENE, an independent cohort of 247 individuals with type 1 diabetes. LLA was defined as a non-traumatic amputation above the metatarsophalangeal joint, kidney failure as the need for renal replacement therapy, transplantation, or an estimated glomerular filtration rate (eGFR) <15 ml/min/1.73m², CVD as the occurrence of myocardial infarction, heart failure, or stroke, and major adverse cardiac event (MACE) as a composite of myocardial infarction, stroke, heart failure, or all-cause death.

Results

During 12 years of follow-up, LLA, kidney failure, CVD and MACE occurred in 71 (9%), 84 (11%), 138 (17%) and 265 (32.0%) of participants, respectively. Sex, diabetes duration, prior LLA, eGFR, and albuminuria were identified as independent determinants of incident LLA and were used to construct the risk score. Compared to participants in the lowest score, those in the highest score had a significantly increased risks of LLA (multivariable-adjusted HR 6.02 [95% CI, 1.92 – 18.89]), kidney failure (8.97 [3.95 – 20.37]), CVD (2.50 [1.34 – 4.64]) and MACE (1.91 [1.24 – 2.96]). The score demonstrated good discriminative performance for LLA (C-index 0.82 [0.77 – 0.87]), kidney failure (0.86 [0.82 – 0.91]), CVD (0.73 [0.68 – 0.78]), and MACE (0.71 [0.68 – 0.75]). Similar predictive performance was observed in the validation cohort.

Conclusion

This newly developed 10-year LLA risk score achieved excellent ability to identify individuals with type 1 diabetes at high risk for LLA, kidney failure, CVD, and MACE.

Keywords. Lower-limb amputation, Cardiovascular disease, End-stage kidney disease, Kidney Failure, Prediction, Prognosis, Risk score, Type 1 diabetes, Albuminuria.

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Research Insights**What is currently known about this topic?**

Risk scores have been developed for specific outcomes in individuals with type 1 diabetes. However, it is unclear whether a score of a single outcome can predict other events.

What is the key research question?

Could a lower-limb amputation score also predict kidney and cardiovascular events?

What is new?

A new lower-limb amputation score was developed based on routine data from individuals with type 1 diabetes. It demonstrates a high level of accuracy in predicting amputation. It also predicts kidney failure, cardiovascular disease, and major adverse cardiac events.

How might this study influence clinical practice?

This risk score could help identify individuals with type 1 diabetes at high risk of major outcomes.

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BACKGROUND

Individuals living with type 1 diabetes have a dramatically higher risk of non-traumatic lower-limb amputation (LLA) than the general population (1). LLA is a destructive complication that leads to an impaired quality of life, a significant increase in healthcare costs and a shorter life expectancy (2–5). The risk of LLA depends on a variety of factors, particularly chronic hyperglycaemia, diabetic neuropathy, peripheral arterial disease (PAD), and diabetic foot ulcers and infections (2,6,7). Despite improvements in the management of diabetes and the control of the most prominent risk factors, LLA remains a pressing issue associated with a worse prognosis (8,9) requiring efficient risk stratification. Unlike several risk scores developed for assessing cardiovascular disease (CVD) (10) and chronic kidney disease (CKD) (11), few studies have examined LLA risk stratification in individuals with type 1 diabetes (12).

Major diabetes complications, including LLA, CVD and CKD are tightly interconnected, driven by overlapping risk factors and jointly lead to high morbidity, mortality, and poor quality of life in individuals with type 1 diabetes (12,5,13). We hypothesised that a risk score based on independent predictors of non-traumatic LLA could also predict other major diabetes-related outcomes. We then developed a pragmatic clinical risk score to predict the 10-year risk of non-traumatic LLA using data from two prospective cohorts of individuals with type 1 diabetes. We tested the ability of the LLA risk score to predict CVD and kidney failure and validated its predictive performance in an independent cohort of individuals with type 1 diabetes.

METHODS

Participants

All three of the cohort studies that were used for the present work complied with the Declaration of Helsinki. The study protocol for each cohort was approved by the Ethics

Committee of the University Hospital of Angers in France. All participants provided written informed consent prior to the start of the study. The designs and methods have been published previously (14–16), and the key characteristics of each cohort's participants at baseline are shown in Additional File Table S1.

Investigation cohort

We used two bi-national, multicentre, prospective cohorts of individuals with type 1 diabetes for the construction and assessment of the LLA risk score (14,15). The *Génétique de la Néphropathie Diabétique* (GENEDIAB cohort) was a multi-center cohort conducted in 17 centers of diabetes in France and Belgium. Participants were recruited between May 1994 and April 1995 based on a diagnosis of type 1 diabetes before the age of 35, a diabetes duration of at least 5 years, and a past or present history of pre-proliferative or proliferative diabetic retinopathy requiring laser photocoagulation therapy (14). The *Genesis France-Belgique* study (GENESIS cohort) was a family-based cohort study including individuals with type 1 diabetes for at least 5 years. Participants were recruited between November 1998 and December 2000 based on the following criteria: a diagnosis of type 1 diabetes before the age of 35, initial ketosis, and the need for permanent insulin treatment within one year of diagnosis, past or present diagnosis of diabetic retinopathy (15). Participants in the GENEDIAB and GENESIS studies were followed from enrolment in their respective cohorts until death or their latest clinical visit, up to 31 May 2019. Data from the two cohorts were pooled for the current analysis. Of the 1,100 participants in the pooled cohorts, 272 were excluded due to a lack of LLA information during follow-up (including 94 deaths and 178 cases of loss to follow-up). The final analysis included 828 participants with complete data on LLA outcomes.

Validation Cohort

For the purposes of external validation only, we used the Survival Genetic Nephropathy (SURGENE) cohort. This was a single-centre, prospective study of volunteers with type 1 diabetes who attended the diabetes clinic at the University Hospital of Angers in France (16). Participants were selected between 1989 and 1996 based on a diagnosis of type 1 diabetes before the age of 40 and a duration of diabetes of more than 3 years. The SURGENE participants were followed until their death or their last clinical visit, whichever occurred first, up to 31 May 2019. Of the 340 participants in the SURGENE cohort, 93 were excluded because they had also participated in either the GENEDIAB or GENESIS studies. Therefore, a total of 247 participants were included in the validation analyses.

Definition of key clinical conditions at baseline

A history of LLA at baseline was defined as amputation of the lower limb above the metatarsophalangeal joint due to non-traumatic causes. Peripheral diabetic neuropathy was diagnosed by the absence of the Achilles reflex and either loss of 10-g monofilament sensation or impaired vibration perception. Lower-limb PAD was defined as the absence of foot pulses and/or intermittent claudication. CVD was defined at baseline a documented history of non-fatal myocardial infarction and/or stroke. Myocardial infarction was diagnosed based on clinical symptoms, electrocardiographic abnormalities and elevated cardiac enzyme levels. Stroke was diagnosed based on an abnormal neurological examination and/or cerebral computed tomography scan result.

The biological parameters were measured at baseline using standardized methods: HbA1c by high-performance liquid chromatography, and serum creatinine by a derivation of the Jaffé method with adjustment to the enzymatic method when it was introduced in routine practice. The creatinine-based estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (17). The urinary albumin concentration was measured by nephelometry. The types of urine collection varied

from one center to another. They were either random samples collected at the clinic (expressed as mg/L), overnight urine collections (expressed as $\mu\text{g}/\text{min}$), or over 24 hours (expressed as mg/24 hours). All collections were repeated two to three times over three consecutive visits. In this study, we used albuminuria collected at the clinic, as it was a common and comprehensive measure across centers and cohorts.

Definition of outcomes during follow-up

Incident LLA was defined as the occurrence of a non-traumatic amputation above the metatarsophalangeal joint during follow-up. Kidney failure was defined as the need for permanent renal replacement therapy (dialysis or renal transplantation) or consistent eGFR <15 mL/min/1.73m² recorded at more than one follow-up visit among individuals without a history of kidney failure at baseline. Incident CVD was defined as the occurrence during follow-up of myocardial infarction, heart failure (HF), or stroke whichever came first. Myocardial infarction and stroke outcome criteria were consistent with the definitions at baseline. HF was defined as the presence of specific clinical symptoms with at least one of the following criteria: elevated cardiac biomarker, radiological or hemodynamic evidence of cardiac dysfunction, and treatment intensification for HF, or hospitalization or emergency department visit for HF. A 4-point major adverse cardiac event (MACE) was defined as a composite of myocardial infarction, stroke, HF, or all-cause death. Outcomes were collected from hospital case records or by contacting participants' family physicians. Vital status was cross-checked by contacting the civil registry in the participants' place of birth. An independent adjudication committee validated diagnoses of LLA, kidney failure and cardiovascular outcomes, during follow-up.

Statistical Methods

All investigation analyses were performed on the GENEDIAB and GENESIS pooled cohorts. Categorical variables were presented as the number of participants with the corresponding

percentage. Continuous variables were expressed as mean \pm standard deviation (SD) or median (interquartile range, IQR) for variables with skewed distribution. Missing data were rare and participants with missing values for a given covariate were excluded from all analyses that included the covariate.

Cox proportional hazards models were used to assess the relationship between independent variables and outcomes. The proportional hazards assumption was checked using the Schoenfeld residuals method. All continuous variables were standardized to a mean of 0 and SD of 1 before being included in the Cox models. Nonlinearity was tested by comparing the spline models (10th, 25th, 75th and 90th as knots and median as reference) versus the linear models, using likelihood ratio tests. The Fine and Gray method was used to account for competing risks of mortality (18). Statistical analyses were performed using JMP software version 17 (SAS Institute, Cary NC; www.sas.com), and Stata software, version 15 (StataCorp, College Station, TX; www.stata.com). A p value less than 0.05 was considered as significant.

Computation of LLA Score Engine

To identify independent risk factors for incident LLA, Cox models with forward selection were performed, starting with all candidate predictors as shown in Table 1. Total cholesterol was excluded due to missing data in a substantial proportion of participants; use of lipid-lowering drugs was included in the model as a proxy for dyslipidemia. A 10-year LLA risk score was then calculated for each participant using the beta coefficients and survival function from the final Cox model (see the formula in the additional material). As linearity had not been established for all outcomes (the p-values for non-linearity were 0.61, 0.01, 0.09 and 0.004 for LLA, kidney failure, CVD, and MACE respectively), we examined the association between the outcomes and the categories of the LLA risk score using tertiles corresponding to low (first tertile), intermediate (second tertile) and high (third tertile) risk.

Association between LLA Score and Outcomes

Kaplan–Meier curves were used to estimate event-free survival according to LLA tertiles. Incidence curves were compared using the log-rank test. We computed multivariate adjusted hazard ratio (HR) and associated 95% confidence interval (95% CI) for each outcome according to the intermediate and highest LLA risk score with the lowest score as reference. All models were adjusted for cohort membership, age, body mass index, smoking status, history of diabetic retinopathy, systolic and diastolic blood pressure, glycated hemoglobin (HbA1c), and use of antihypertensive and lipid-lowering medications. Competing risk models additionally estimated subdistribution hazard ratio (SHR), considering all-cause mortality as a competing risk, while adjusting for the same covariates as reported above.

Discrimination performance of LLA Score

Harrell C-statistics were used to evaluate the ability of the LLA risk score to predict outcomes during follow-up (19). We also plotted the receiver operating characteristic (ROC) curve and calculated the area under the curve (AUC) for outcomes that occurred within the follow-up period of 10 years. The prognostic performance was first assessed in the investigation cohorts (GENDIAB and GENESIS) and subsequently replicated in the validation cohort (SURGENE). We performed two sensitivity analyses in the GENEDIAB and GENESIS pooled cohorts. First, we assessed the C-index of the 10-year risk of LLA in individuals without a baseline history of LLA, as well as the C-index of the 10-year risk of CVD and MACE in individuals without a baseline history of CVD. Second, we compared the ability of our LLA risk score versus the 5-year kidney failure Steno Type 1 Risk Engine (ST1RE for kidney failure) (11) to predict the 5-year risk of LLA, kidney failure, CVD, and MACE. Finally, the calibration was assessed by categorising the GENEDIAB and GENESIS pooled cohorts into ten groups according to their predicted risk. The Hosmer and Lemeshow test was then used to compare the observed and predicted risks (20).

RESULTS

Characteristics of Participants at Baseline

Of the 828 participants in the pooled cohort included in the present analysis, 326 (39%) were from the GENEDIAB and 502 (61%) were from the GENESIS. The mean age of the participants was 42 ± 12 years, 46% were female, the mean duration of diabetes was 26 ± 9 years, and the mean HbA1c was 70 ± 17 mmol/mol. Prior LLA and CVD were reported at baseline in 53 (6%) and 52 (6%) participants, respectively (Table 1). The baseline characteristics of GENEDIAB/GENESIS participants who were excluded and those who remained in the analyses are shown in Additional File Table S2.

Incidence of Outcomes during Follow-up

During a median follow-up period of 12 years (IQR 6; 18), incident LLA, kidney failure, CVD, and MACE occurred in 71 (8.6%), 84 (11.3%), 138 (16.8%) and 265 (32.0%) of the participants, respectively. The corresponding incidence rates were 6.9 (95% CI, 5.5 – 8.7), 16.1 (95% CI, 13.0 – 19.9), 14.0 (95% CI, 11.8 – 16.4), and 27.0 (95% CI, 23.9 – 30.4) per 1,000 person-years. Compared to participants without LLA, those who experienced LLA during the follow-up period were older and had had a longer duration of diabetes. They also had higher systolic blood pressure and albuminuria and a lower eGFR (Table 1 and Additional File Table S3). They were also less likely to be female and more likely to have a history of proliferative diabetic retinopathy, CVD, LLA, PAD and peripheral neuropathy at baseline. They were also more likely to take antihypertensive medication, particularly angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs).

Independent Determinants of Incident LLA

Five variables emerged as independent determinants of incident LLA (Additional Table S4): sex; history of LLA, duration of diabetes, albuminuria and eGFR. The risk of LLA was lower

in females (HR 0.55 [95% CI, 0.32 – 0.96]) and higher in participants with a history of LLA (HR 7.57 [95% CI, 4.37 – 13.11]). The risk was also higher for each SD increase in diabetes duration (HR 1.61 [95% CI, 1.23 – 2.11]) and albuminuria (HR 1.30 [95% CI, 1.03 – 1.64]), and lower for each SD increase in eGFR (HR 0.58 [95% CI, 0.43–0.80]). The computed LLA risk score, based on these independent determinants (see the formula in the additional material), ranged from 0 to 0.99, with a median of 0.31 (IQR, 0.18; 0.57).

LLA Score and Incidence of Outcomes

Kaplan–Meier survival curves stratified by tertiles of LLA risk score are presented in Figure 1. Progressive relationships were observed between the LLA risk score and the incidence of outcomes during follow-up. The proportion of individuals who experienced incident LLA was 1.5%, 5.3% and 17.3% across the 3 progressive LLA score tertiles. The progressive relationships were also observed between the tertiles of LLA risk score and the incidence of kidney failure (4.7%, 5.4%, and 24.8%), CVD (7.6%, 12.9%, and 27.8%), and MACE (15.8%, 25.2%, and 52.3%). The incidence of outcomes was significantly higher in individuals in the highest LLA score, compared with those who were in the lowest score. These associations remained significant after adjusting for confounders (Figure 2) and when considering all-cause mortality as a competing risk (Additional file Fig. S1). The strongest associations were observed between the LLA risk score and incident LLA and kidney failure. Thus, compared to individuals whose LLA risk score were in the lowest tertile, multivariable adjusted HR (95% CI) for each higher tertile were 1.83 (95% CI, 0.56 – 5.94), and HR 6.02 (95% CI, 1.92 – 18.89) for incident LLA; and HR 1.68 (95% CI, 0.68 – 4.15), and HR 8.97 (95% CI, 3.95 – 20.37) for incident kidney failure; HR 1.16 (95% CI, 0.63 – 2.13) and HR 2.50 (95% CI, 1.34 – 4.64) for incident CVD; and HR 1.01 (95% CI, 0.65 – 1.53) and HR 1.91 (95% CI, 1.24 – 2.96) for MACE, respectively (Figure 2).

Prognostic performance of LLA score to predict outcomes

The LLA risk score yielded high C-statistic indexes for incident outcomes during the follow-up period in GENEDIAB and GENESIS pooled cohorts: LLA 0.82 (95% CI, 0.77 – 0.87), kidney failure 0.86 (95% CI, 0.82 – 0.91), CVD 0.73 (95% CI, 0.68 – 0.78), and MACE 0.71 (95% CI, 0.68 – 0.75). The C-index for LLA was comparable when individuals with a history of LLA at baseline were excluded from the analysis (0.77, 95% CI, 0.70 – 0.84). The C-indexes for CVD (0.71, 95% CI, 0.64 – 0.77) and MACE (0.70, 95% CI, 0.65 – 0.74) were also comparable when individuals with a baseline history of CVD were excluded.

The prognostic performance of the LLA risk score in predicting outcomes remained consistent when the GENEDIAB and GENESIS cohorts were considered individually (Additional file Table S5). The C-statistic indexes were also high in the independent SURGENE validation cohort: 0.88 (95% CI, 0.77 – 0.98) for LLA, 0.93 (95% CI, 0.86 – 0.99) for kidney failure, 0.89 (95% CI, 0.77 – 0.99) for CVD, and 0.81 (95% CI, 0.72 – 0.90) for MACE. ROC analyses show similar prognostic performance for the 10-year risk of outcomes (Figure 3 and Additional file Fig. S2). The LLA risk score was well calibrated, as there was no significant difference between the observed and predicted risks of the outcomes (all Hosmer and Lemeshow tests $p > 0.05$, Additional file Fig. S3). Finally, our LLA risk score yielded a significantly higher AUC than the STIRE for kidney failure in predicting the 5-year risk of LLA, CVD, and MACE, but a lower AUC for the 5-year risk of kidney failure (Additional file Fig. S4).

DISCUSSION

In this study, we developed a simple and clinically accessible risk score to estimate the 10-year risk of LLA in individuals with long-standing type 1 diabetes. The model incorporates five routinely collected clinical and biological variables: sex, prior history of LLA, diabetes duration, eGFR, and albuminuria. Compared with individuals in the lowest tertile of LLA risk score, those in the highest tertile had a 10-year risk of LLA, kidney failure, CVD, and MACE

that was 6-fold, 9-fold, 2.5-fold, and 2-fold higher, respectively. These relationships remained robust after adjustment for the main confounding factors and when accounting for all-cause mortality as a competing risk.

In addition to its ability to predict LLA, the score demonstrated strong prognostic performance in identifying individuals with type 1 diabetes who were at high risk of kidney failure, CVD, and MACE. These prognostic performances were reliable in individuals without a baseline history of LLA or CVD. These findings were also consistent across two well-characterized multicentre prospective cohorts (GENEDIAB and GENESIS), as well as an independent cohort (SURGENE). This supports the reproducibility and potential clinical utility of this score in individuals with type 1 diabetes.

The 5 independent determinants selected to compose the LLA risk score are key risk factors for the occurrence of LLA, diabetic kidney disease (DKD) and CVD (12). It is not surprising that kidney biomarkers (eGFR and albuminuria) constitute core part of the risk evaluation as DKD is a major amplifier of cardiovascular risk, and decreased eGFR and increased albuminuria are both associated with atherosclerosis, HF and cardiovascular death, as well as LLA (12,21,22). Our risk score equation is comparable to kidney failure risk equations (KFREs), especially the four-variable equation that uses age, sex, eGFR and albuminuria (23). The KFREs have been suggested as useful tools for predicting progression from CKD to kidney failure in Canadian patient cohorts with and without diabetes, and validated in other large, multinational cohorts (23). We may be puzzled that neither HbA1c, systolic blood pressure, history of PAD, nor smoking status were retained in the final Cox model, especially as these factors are known to be significant predictors of diabetes outcomes. The variables incorporated in our score may already encompass the prognostic information provided by other risk factors, limiting their incremental predictive value.

As far as we know, this is the first LLA risk score engine that predict a range of chronic diabetes complications including LLA, kidney failure, myocardial infarction, stroke and HF. While several models have been developed for CVD, few addressed the specific risk of LLA, especially in individuals with type 1 diabetes (10,24). Previous LLA risk scores were developed mainly to determine the prognosis of diabetic foot ulcerations. In this context, Lipsky et al. computed a risk score to predict LLA in individuals with diabetes (regardless of the type of diabetes) hospitalised for a foot infection (25). The Steno Type 1 Risk Engine for CVD (ST1RE for CVD) was developed to predict non-fatal cardiovascular events, including ischaemic heart disease, ischaemic stroke, HF, and PAD (10). This was subsequently followed by the creation of the ST1RE predicting the 5-year risk of kidney failure (11). Interestingly, our score shares several predictors with both ST1RE models, including male sex, longer duration of diabetes, higher albuminuria and lower eGFR (10). Our LLA risk score outperformed the ST1RE for kidney failure in predicting the 5-year risks of LLA, CVD, and MACE. However, it was less effective in predicting the 5-year risk of kidney failure. A prior risk model from EURODIAB Prospective Complications Study (PCS) included LLA as part of a broad composite outcome (composite of coronary heart disease, stroke, kidney failure, LLA, blindness and mortality) in individuals with type 1 diabetes (26). The predictive performance of this score for individual diabetes complications was not reported, likely because the incidence of each outcome was very low in the EURODIAB PCS. Compared with EURODIAB PCS, participants in our cohorts were older (42 versus 30 years), had longer duration of diabetes (26 versus 11 years), and follow-up (12 versus 7 years), thereby increasing the statistical power to assess the incidence of long-term complications.

The comparable predictive performance of the LLA risk score to identify individuals with type 1 at high risk of LLA, kidney failure, CVD, and MACE may be explained by mutual risk factors, and underlying pathophysiological mechanisms (28-33). Previous studies have

demonstrated that diabetes outcomes share common underlying pathways, including endothelial dysfunction, low-grade inflammation, a pro-thrombotic state, and oxidative stress (28–32). Taken together, these findings confirm that microvascular and macrovascular complications are closely related, particularly in individuals with diabetes (13,33) as highlighted by the recent concept of cardio-reno-metabolic health. This concept models the multidirectional relationships between CKD, CVD and metabolic condition (34).

The main strength of our study is the use of well-described prospective, binational multicentric cohorts of individuals living with long-standing type 1 diabetes followed for a median duration of 12 years. The predictive ability of the LLA risk score was validated in an independent cohort of individuals with type 1 diabetes. Our study also has some limitations that need to be highlighted. Firstly, we did not have access to accurate information regarding the underlying conditions that led to LLA. Data on diabetic foot ulcers and its gradation, as well as infections, were unavailable in our cohorts. PAD and peripheral neuropathy were not defined according to the current international consensus and recommendations. Although the diagnoses were based only on simple clinical criteria, they seem accurate, as individuals with a baseline history of peripheral neuropathy and PAD were 11 and 8 times more likely, respectively, to develop incident LLA during follow-up than those without these conditions. Our cohorts also lacked data on some key clinical information, such as baseline history of HF or physical activity. Finally, our findings may not be applied to people of other ethnic backgrounds or other geographical regions, as we studied mainly individuals of European descent from France and Belgium.

CONCLUSIONS

In summary, this pragmatic 10-year LLA risk score, derived from simple measures available in routine clinical practice, achieved excellent ability to identify individuals with type 1

diabetes who are at high risk of amputation, kidney failure, CVD and MACE. The 10-year LLA risk score is a practical tool that helps clinicians identify individuals at high risk of long-term diabetes-related complications, inform targeted surveillance, and guide the implementation of preventive strategies.

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LIST OF ABBREVIATIONS

ACE: Angiotensin-converting enzyme inhibitors

AUC: Area under the curve

ARBs: Angiotensin receptor blockers

CI: Confidence interval

CKD: Chronic kidney disease

CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration equation

CVD: Cardiovascular disease

DKD: Diabetic kidney disease

eGFR: estimated glomerular filtration rate

EURODIAB PCS: EURODIAB Prospective Complications Study

GENEDIAB: *Génétique de la Néphropathie Diabétique* cohort

GENESIS: *Genesis France-Belgique* study cohort

HbA1C: glycated hemoglobin

HF: Heart failure

HR: Hazard ratio

IQR: Interquartile range

KFREs: Kidney Failure Risk Equations

LLA: Lower-limb amputation

MACE: Major Adverse Cardiac Events

PAD: Peripheral arterial disease

ROC: Receiver operating characteristic

SD: Standard deviation

SHR: Subdistribution hazard ratio

ST1RE: Steno Type 1 Risk Engine

SURGENE: Survival Genetic Nephropathy cohort

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DECLARATIONS

Ethics approval and consent to participate

GENEDIAB, GENESIS and SURGENE cohort complied with the Declaration of Helsinki. The study protocol for each cohort was approved by the Ethics Committee of the University Hospital of Angers in France. All participants provided written informed consent prior to the start of the study.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and analysed during the current study are not publicly available due to many ongoing active collaborations, and to continuing analyses by the study investigators, but may be available from the last author on reasonable request.

Competing interests

M.C. reports personal fees from Boehringer-Ingelheim, Eli Lilly, Sanofi, and Pierre Fabre. LP reports grants, personal fees and non-financial support from Bayer, Novo Nordisk, Sanofi, Eli Lilly, Boehringer Ingelheim and AstraZeneca. S.H. reports personal fees and non-financial support from AstraZeneca, Sanofi, MSD, and Servier, grants and personal fees from Bayer, personal fees from Boehringer Ingelheim, Eli Lilly, Valbiotis, and Novartis, grants from Dinno Santé and Pierre Fabre Santé, non-financial support from LVL. A.S. reports personal fees and non-financial supports from AstraZeneca, Boehringer Ingelheim, Eli Lilly, MSD, Novo Nordisk, and Sanofi. MM reports personal fees for lectures from Novo-Nordisk, Sevier, and Ajanta. PJS reports personal fees and non-financial support from Novo Nordisk, Abbott, Sanofi, and AstraZeneca. K.M. reports consulting fees from Novo Nordisk; honoraria for lectures, presentations, or speaker bureaus from Novo Nordisk, AstraZeneca, Boehringer-

Ingelheim, Eli Lilly, Sanofi, Lifescan, Abbott, and Bayer; and participation to Advisory Board from Novo Nordisk, Sanofi, and Amarin. There are no further conflicts of interest to declare.

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Author's Contributions and Guarantor Statement

MC and KM designed the study, researched data and drafted the manuscript. VR, SH, AS, GV, and MM researched data, contributed to discussion and reviewed/edited the manuscript. LP, AL and PJS contributed to discussion and reviewed and edited the manuscript. All authors read and approved the final version of the manuscript. KM is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1. Characteristics of Participants at Baseline by the Incidence of Major Outcomes during Follow-up in the Investigation Cohort

	All	Incident LLA		Kidney Failure		Incident CVD		MACE	
		No	Yes	No	Yes	No	Yes	No	Yes
n (%)	828	757 (91.4)	71 (8.6)	657 (88.7)	84 (11.3)	686 (83.2)	138 (16.8)	562 (68.0)	265 (32.0)
GENEDIAB cohort, n (%)	326 (39)	276 (36)	50 (70)	232 (35)	48 (57)	246 (36)	80 (58)	170 (30.3)	156 (58.9)
GENESIS cohort, n (%)	502 (61)	481 (64)	21 (30)	425 (65)	36 (43)	440 (64)	58 (42)	392 (69.7)	109 (41.1)
Female sex, n (%)	377 (46)	353 (47)	24 (34)	296 (45)	38 (45)	327 (48)	48 (35)	278 (49.5)	98 (37.0)
Age (years)	42 ± 12	42 ± 12	47 ± 11	43 ± 12	38 ± 10	41 ± 12	48 ± 11	39.6 ± 10.7	48.2 ± 11.9
Diabetes duration (years)	26 ± 9	26 ± 9	31 ± 10	27 ± 9	25 ± 9	26 ± 9	31 ± 10	24.7 ± 8.2	30.2 ± 10.5
Body mass index (kg/m ²)	24 ± 4	24 ± 4	24 ± 4	24 ± 3	24 ± 4	24 ± 3	25 ± 4	24.2 ± 3.4	24.1 ± 3.5
Tobacco smoking status, n (%)									
Former	101 (12)	90 (12)	11 (16)	80 (12)	11 (13)	67 (10)	34 (25)	50 (8.9)	51 (19.3)
Current	212 (26)	197 (26)	15 (21)	167 (25)	22 (26)	179 (26)	32 (23)	138 (24.6)	74 (27.9)
Systolic blood pressure (mmHg)	134 ± 20	134 ± 20	144 ± 18	132 ± 18	149 ± 22	133 ± 19	142 ± 20	131 ± 19	141 ± 19
Diastolic blood pressure (mmHg)	77 ± 11	77 ± 11	81 ± 12	76 ± 10	86 ± 12	77 ± 11	80 ± 10	77 ± 11	80 ± 10
HbA1c (%)	8.6 ± 1.6	8.6 ± 1.5	9.0 ± 2.2	8.5 ± 1.5	9.3 ± 2.1	8.6 ± 1.5	8.7 ± 1.7	8.5 ± 1.4	8.7 ± 1.8
HbA1c (mmol/mol)	70 ± 17	70 ± 16	74 ± 24	69 ± 16	78 ± 23	70 ± 17	72 ± 18	70 ± 16	72 ± 20
Total cholesterol (mmol/l) [§]	5.77 ± 1.39	5.77 ± 1.37	5.81 ± 1.51	5.62 ± 1.30	6.48 ± 1.56	5.72 ± 1.39	5.99 ± 1.36	5.65 ± 1.26	5.96 ± 1.53
eGFR (mL/min/1.73m ²)	83 ± 31	85 ± 30	64 ± 31	91 ± 24	55 ± 31	85 ± 31	75 ± 28	89 ± 30	72 ± 30
Urinary albumin concentration (mg/l)	19 (6; 181)	17 (6; 158)	105 (16; 923)	13 (6; 53)	1155 (277; 2273)	16 (6; 128)	52 (8; 494)	15 (6; 94)	41 (8; 381)
Medical history at baseline, n (%)									
Proliferative diabetic retinopathy	413 (50)	362 (48)	51 (72)	282 (43)	61 (73)	325 (47)	84 (61)	245 (43.6)	167 (63.0)
Prior CVD	52 (6.3)	40 (5)	12 (17)	36 (6)	7 (8)	26 (4)	23 (17)	17 (3.0)	34 (12.8)
Prior LLA	53 (6)	28 (4)	25 (35)	31 (5)	8 (10)	31 (5)	22 (16)	15 (2.7)	38 (14.3)
Peripheral diabetic neuropathy	356 (43)	302 (40)	54 (76)	252 (38)	54 (64)	278 (41)	77 (56)	206 (36.6)	150 (56.6)
Peripheral artery disease	83 (10)	57 (8)	26 (37)	53 (8)	12 (14)	52 (8)	30 (22)	32 (6.0)	51 (19.3)
Drug use, n (%)									
Antihypertensive drugs	410 (50)	358 (47)	52 (75)	287 (44)	72 (86)	319 (47)	88 (65)	241 (43.0)	168 (63.9)
ACE inhibitors or ARBs	320 (39)	286 (38)	34 (49)	225 (34)	60 (71)	254 (37)	63 (46)	198 (35.3)	121 (46.0)
Lipid-lowering drugs	68 (8)	57 (8)	11 (16)	49 (8)	10 (12)	47 (7)	20 (14)	33 (5.9)	34 (12.8)

Quantitative variables are presented as mean \pm SD or as median (IQR) for those with skewed distribution. §Data available for 473 participants. LLA, lower-limb amputation; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ACE, angiotensin-converting enzyme inhibitors; ARBs, angiotensin-receptor blockers. MACE, major adverse cardiac event.

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FIGURE LEGENDS

Fig. 1- Survival without Major Outcomes by LLA Risk Score

Kaplan–Meier survival curves showing the probability of remaining free from lower-limb amputation (LLA, Panel A), kidney failure (Panel B), cardiovascular disease (CVD, Panel C), and major adverse cardiac event (MACE, Panel D) during follow-up stratified by tertiles of LLA risk score: red line, highest score; blue line, intermediate score; green line, lowest score. Participants with missing data for any component of the risk score were excluded. Analyses were performed on participants with complete data (n = 798 for LLA, n = 738 for kidney failure, n = 809 for CVD, and n=797 for MACE).

Fig. 2- Incidence of Outcomes by Tertiles of LLA Risk Score

Data expressed as number of outcome/total participants (%) in each group of score.

Hazard ratios (HR), with associated 95% CI of outcomes for the second (intermediate score) and the third (highest score) versus the first tertile (lowest score).

HR (95% CI) adjusted for cohort membership, age, BMI, former and current smoking, history of diabetic retinopathy, systolic and diastolic blood pressure, HbA1c, and use of antihypertensive drugs, and lipid-lowering drugs. Participants with at least one missing value regarding any variable that composed the risk score or was included in the multivariable-adjusted Cox model were excluded. The analyses were performed on participants with complete data (n = 798 for LLA, n = 718 for kidney failure, n = 795 for CVD, and n=798 for MACE). LLA, lower-limb amputation; CVD, cardiovascular disease; MACE, major adverse cardiac event.

Fig. 3- ROC curves for the 10-year risk of outcomes by the LLA risk score

Receiver operating characteristic (ROC) curves and area under the curve (AUC) for the 10-year risk of lower-limb amputation (LLA, Panel A), kidney failure (Panel B), cardiovascular

disease (CVD, Panel C), and major adverse cardiac event (MACE, Panel D) according to the LLA risk score.

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12-year Follow-up

828 People with Long-Standing Type
1 Diabetes

HR 6.02 (1.92 – 18.89)

HR 8.97 (3.95 – 20.37)

Baseline data

Modeling a 10-year
LLA Risk Score

HR 2.50 (1.34 – 4.64)

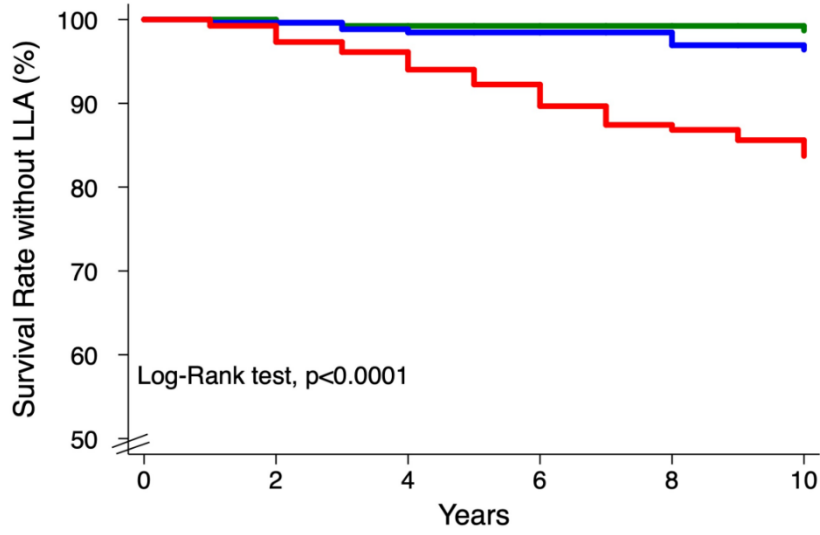
HR 1.91 (1.24 – 2.96)

Sex
Prior LLA
Duration of diabetes
eGFR
Albuminuria

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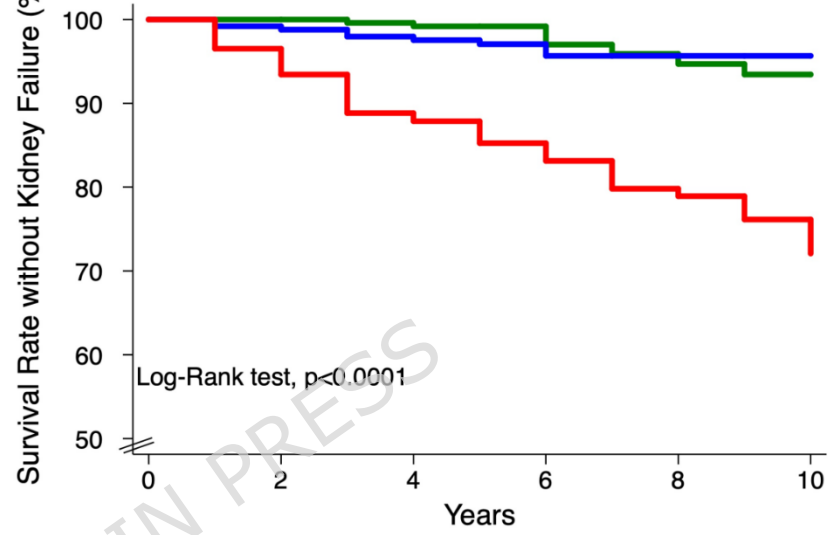


A- LLA Risk by LLA score



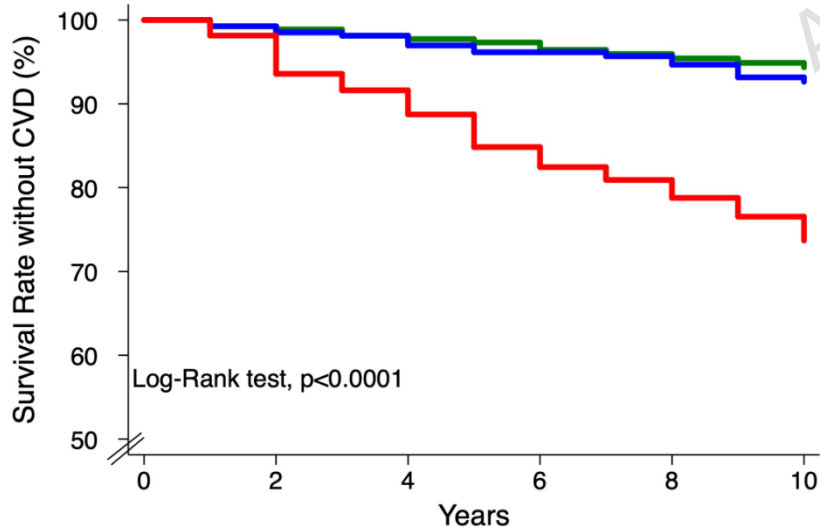
Number at risk	0	2	4	6	8	10
Lowest LLA Score	266	264	249	220	185	180
Intermediate LLA Score	266	264	248	219	194	186
Highest LLA Score	266	257	229	179	148	136

B- Kidney Failure Risk by LLA score

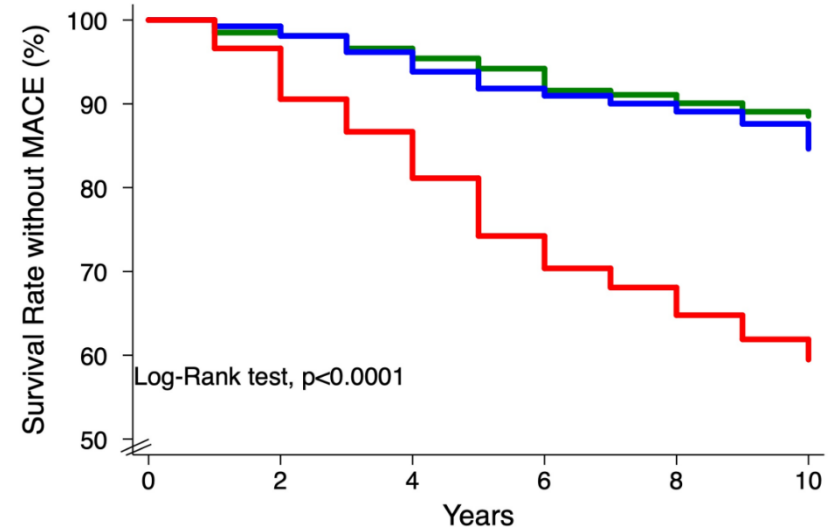


Number at risk	0	2	4	6	8	10
Lowest LLA Score	259	258	238	137	80	65
Intermediate LLA Score	249	245	229	139	92	86
Highest LLA Score	230	219	183	121	90	75

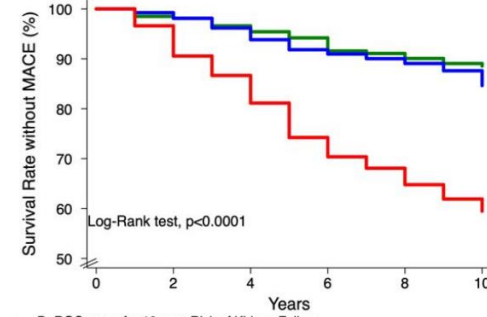
C- CVD Risk by LLA score



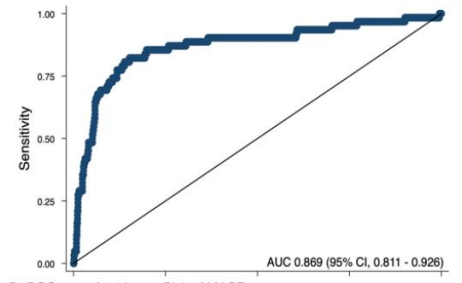
D- MACE Risk by LLA score



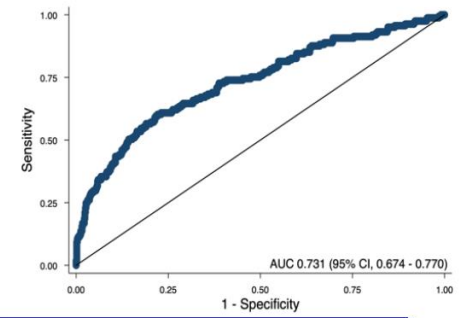
D- MACE Risk by LLA score

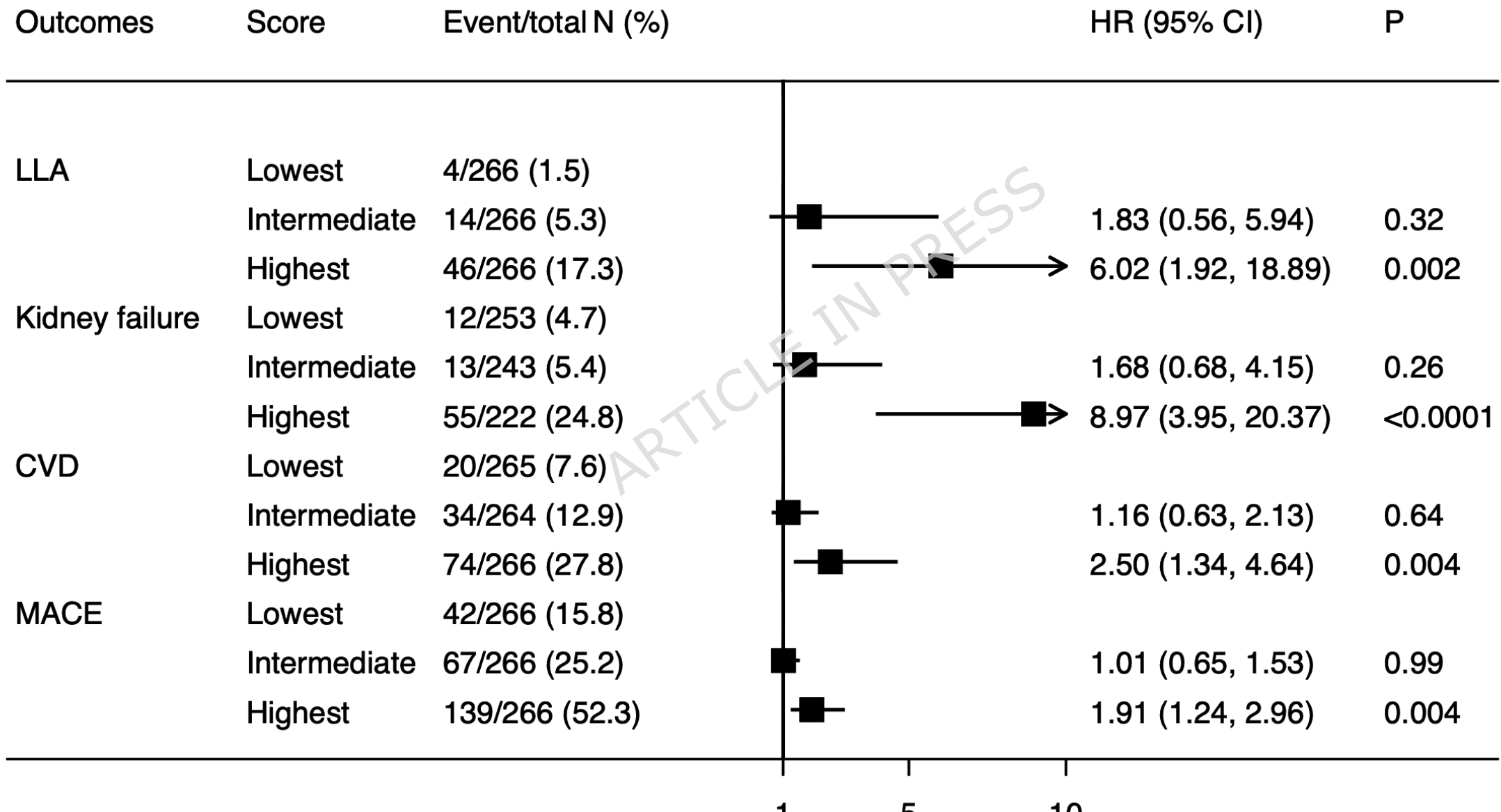


B- ROC curve for 10-year Risk of Kidney Failure

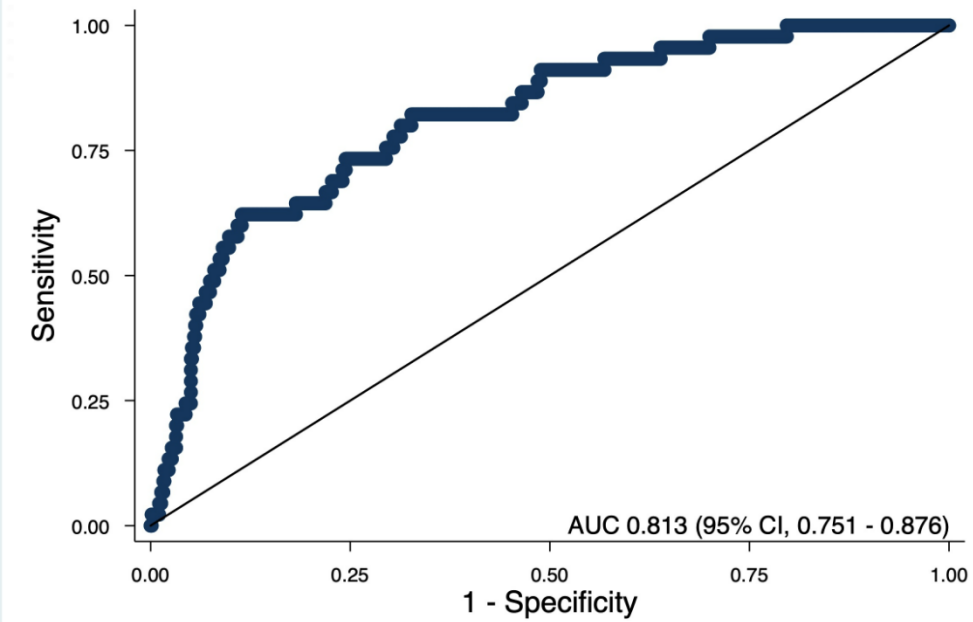


D- ROC curve for 10-year Risk of MACE

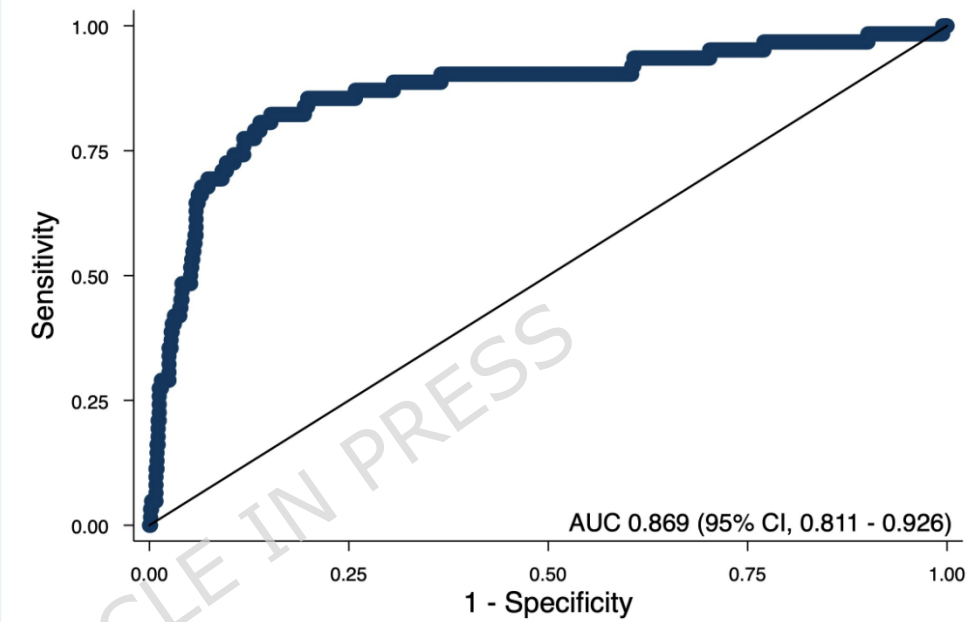




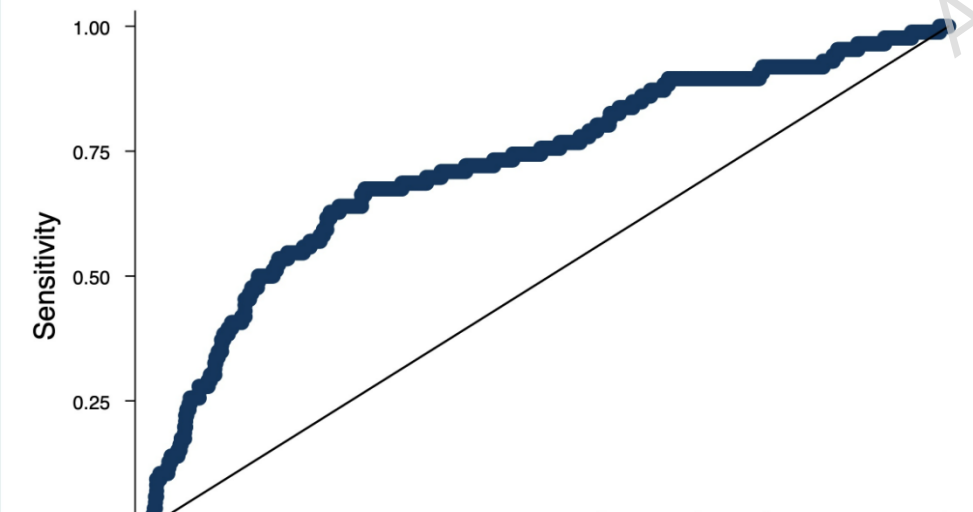
A- ROC curve for 10-year Risk of LLA



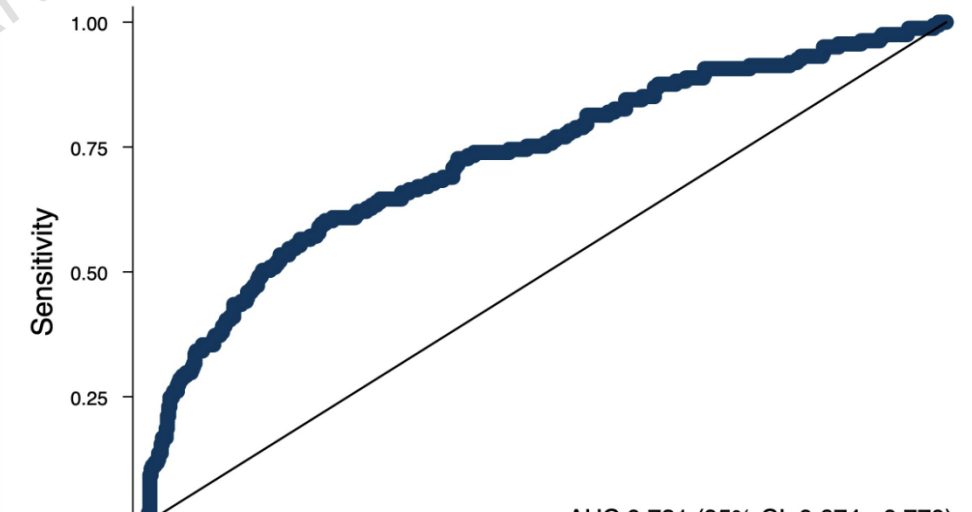
B- ROC curve for 10-year Risk of Kidney Failure



C- ROC curve for 10-year Risk of CVD



D- ROC curve for 10-year Risk of MACE



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