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TITLE PAGE

Title: Development and external validation of risk scores for cardiovascular hospitalisation and rehospitalisation in diabetes patients

Short title: Risk score for CV (re) hospitalisation in diabetes

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ABSTRACT

Context

Cardiovascular disease (CVD) is a common and costly reason for hospitalisation and re-hospitalisation among patients with type 2 diabetes.

Objective

This study aimed to develop and externally validate two risk prediction models for cardiovascular hospitalisation and cardiovascular re-hospitalisation.

Design

Two independent prospective cohorts.

Setting

The derivation cohort includes 4,704 patients with type 2 diabetes from 18 general practices in Cambridgeshire. The validation cohort comprises 1,121 patients with type 2 diabetes from post-trial follow-up data.

Main Outcome Measure

Cardiovascular hospitalisation over 2 years and cardiovascular re-hospitalisation after 90 days of the prior CVD hospitalisation.

Results

The absolute rate of cardiovascular hospitalisation and re-hospitalisation was 12.5% and 6.7% in the derivation cohort, and 16.3% and 7.0% in the validation cohort. Discrimination of the models was similar in both cohorts, with C statistics above 0.70, and excellent calibration of observed and predicted risks.

Conclusion

Two new prediction models that quantify risks of cardiovascular hospitalisation and re-hospitalisation have been developed and externally validated. They are based on a small number of clinical measurements that are available for patients with type 2 diabetes in many developed countries in primary care settings and could serve as the tools to screen the population at high risk of cardiovascular hospitalisation and re-hospitalisation.

MAIN TEXT

INTRODUCTION

The prevalence and cost of diabetes is growing rapidly worldwide (1). People with diabetes are twice as likely to be admitted to hospital, and at least 10% of those in hospital have diabetes at any one time (2). In some age groups, it is as many as one in five (3). The associated costs of excess admissions, as well as increased costs per admission, are significant contributors to the financial burden borne by healthcare systems from diabetes and often reflect preventable morbidity suffered by patients (4).

Previously, two prediction tools have been developed, both based on secondary care data, to identify those with diabetes, at high risk of either all-cause excessive length of stay or all-cause inpatient mortality over four years (5), or all-cause re-admission within 30 days among hospitalised patients (6). However, the practical application of both prediction models was limited by lack of external validation, non-specificity for people with type 2 diabetes, the use of predictors derived from secondary care rather than primary care data, variations on predictors recorded in different datasets (e.g. comorbidity) and a relative short time-gap between baseline and outcome (30 days' readmission).

Among hospital admissions, cardiovascular events are the major cause for hospitalisation in people with type 2 diabetes (7). Although risk factors such as blood pressure and HbA1c are recognised as warranting intervention on their own (8), (9), there has been no current algorithm to estimate the absolute risk of cardiovascular hospitalisation and rehospitalisation in people with type 2 diabetes.

Using a model to make predictions for individual patients with type 2 diabetes is more comprehensive than using individual risk factors, and is preferred to the risk grouping approach (10), (11).

The aim of our study was to develop and externally validate new prediction models based on reliable clinical measurements in primary care settings for cardiovascular hospitalisation over the next 2 years and cardiovascular re-hospitalisation up to 90 days following a prior cardiovascular hospitalisation.

MATERIALS AND METHODS

Data source and study population

We utilised two cohorts from Cambridgeshire, England: one (Derivation) based on the electronic health record data from primary care settings to develop our cardiovascular hospitalisation and re-hospitalisation risk scores and another (Validation) based on post-trial cohort data for external validation.

Derivation cohort

Patient lists from 18 general practices across Cambridgeshire, England, in 2008/2009 were collated and linked with hospital admissions (Secondary Uses Service (SUS)) data as part of an evaluation of diabetes care across the county by the local health board, National Health Service (NHS) Cambridgeshire. This cohort was limited to volunteer practices using the Egton Medical Information Systems (EMIS) general practitioner (GP) software system, from which a predefined set of data could be extracted. There was no systematic selection process for these surgeries, and data extracted were for their entire diabetes population. All patients with diabetes had follow-up hospitalisation data to 2010–2011. Hospital admissions to NHS and private hospitals within and outside Cambridgeshire

were followed-up. No personal identifiers were released to researchers, and all subsequent analyses were conducted on anonymised datasets.

Validation cohort

The design and methods of the RAPSID trial have been published previously (12), as have its CONSORT (Consolidated Standards of Reporting Trials) diagram and the results of its primary outcomes (12). Briefly, RAPSID was a 2x2 factorial cluster RCT comparing 4 groups: Controls, 1:1 (individual) peer support, group peer support, and combined 1:1 and group peer support among patients with type 2 diabetes. Participants had their diabetes for at least 12 months and those with dementia or psychotic illness were excluded. Participants were recruited from communities across Cambridgeshire and neighbouring areas of Essex and Hertfordshire. Follow up data were only available for participants in Cambridgeshire and neighbouring areas of Hertfordshire that are served by the Cambridgeshire and Peterborough Clinical Commissioning Group (CCG). Clusters were defined by local government ('parish council') boundaries. The intervention was developed following a pilot (13), using a framework defined by Peers for Progress (14). Peers facilitating peer support were termed peer support facilitators and there selection, training, support and the overall programme are described elsewhere (15). The intervention lasted 8-12 months and was commenced and concluded, cluster by cluster, between 02/06/11 to 12/04/12. Ethics approval was received from the Cambridgeshire REC2 Committee (10/H0308/72), and signed consent included agreement for access to hospital data.

At baseline, demographic data, blood pressure, and HbA1c and lipid profiles information were collected. Each participant was followed up until June 2015 (0.91-4.07 years' follow-up from beginning/entry into the trial). Hospitalisation (NHS hospitals & private hospitals), Accident & Emergency (A&E) and outpatient visits within/outside

Cambridgeshire and the included areas of Hertfordshire were completely collected through Cambridgeshire and Peterborough Clinical CCG (16) and the elective/non-elective status, and International Classification of Diseases (ICD-10) codes (8).

Defining cardiovascular hospitalisation and re-hospitalisation

The primary outcome of the study was having at least one hospitalisation with cardiovascular disease (CVD) as the primary diagnosis (ICD-10: I20–I25, I60–I69 and I73 in the first ICD field) over the 2-year follow-up and having at least one CVD re-hospitalisation after 90 days of prior CVD hospitalisation.

Candidate predictors, missing data, and power calculations

To achieve the maximum extrapolation application of our risk algorithm, objective clinical measurements were used as predictors in the model, including body mass index (BMI) , blood pressure (systolic (SBP) and diastolic (DBP)) and the metabolic variables glycated haemoglobin (HbA1c) and lipid profiles. We also included demographic characteristics, (age and gender) and whether the patient was on lipid lowering treatment. Patients with diabetes were invited to have their blood pressure and metabolic variables measured at least once a year after the diagnosis of diabetes and the most recent was taken before 1 April 2009 (a minimum of 50 days before the first admission). Diabetes duration was not universally recorded, and hence was not usefully available for analysis. Diabetes therapy was not included in the dataset. Lipid-lowering treatment was recorded.

Our derivation cohort had missing information on body mass index (3.17%), systolic blood pressure (9.95%), diastolic blood pressure (9.95%), total cholesterol (12.35%), high density lipoprotein (14.56%), and low density lipoprotein (16.27%). We used multiple imputation to replace missing values by using a chained equation approach based on all candidate predictors and outcomes. We created 16 imputed datasets for missing variables that were then combined across all datasets by using Rubin's rule to obtain final model estimates.

Limited information was missing (<1%) in our external validation dataset and the complete dataset was used in our analysis. On the basis of an estimated 588 cardiovascular hospitalisations and 316 cardiovascular re-hospitalisations and 16 predictors or levels in our derivation cohort, we had an effective sample size of 37 cardiovascular hospitalisation and 21 cardiovascular re-hospitalisation per predictor or level, above the minimum requirement suggested by Peduzzi et al (17).

Ethical approval

The derivation cohort work had approval from the Cambridgeshire research ethics committee as part of a wider service evaluation. Ethics approval for validation cohort was received from the Cambridgeshire REC2 Committee (10/H0308/72), and signed consent included agreement for access to hospital data.

Statistical analysis for model derivation and external validation

We treated incidence occurrence of cardiovascular hospitalization after the first 90 days since the start of follow-up and the incident occurrence of cardiovascular re-hospitalisation as binary outcome measures. For each of the 15 candidate predictors or levels, we used a univariate logistic regression model to calculate the unadjusted odds ratios. For derivation of the risk prediction model, we initially included all candidate predictors in a multivariable logistic regression model. We used fractional polynomials to model potential non-linear relationships between continuous predictors and outcome.

Through backward elimination, we excluded lower lipid treatment from the multivariate model as it was not statistically significant (P>0.1 based on change in log likelihood). After elimination, we reinserted the excluded predictor into the final model to further check whether it became statistically significant. We also rechecked fractional polynomial terms at this stage and re-estimated them if necessary. We formed the risk equations for predicting the log odds of cardiovascular hospitalisation and cardiovascular re-

hospitalisation by using the estimated regression coefficients multiplied by the corresponding predictors included in our models together with the intercepts. This process ultimately led to equations for the predicted risk=$1/(1+e^{-riskscore})$, whether the "risk score" is the predicted log odds of cardiovascular hospitalisation or cardiovascular re-hospitalisation from the developed models.

To facilitate model utilisation in clinical practice, the logistic regression equations were transformed into prognostic score charts. The coefficients in the logistic regression equation were multiplied by 50 and rounded to the nearest integer to obtain the prognostic score per predictor. Multiplication by 50 was chosen to get the majority of the coefficients close to an integer, thereby minimizing the effects of rounding. The sum of all prognostic scores reflects patients' probability of cardiovascular hospitalisation or cardiovascular re-hospitalisation.

We assessed the performance of the models in terms of the C statistics and calibration slope (where 1.00 is ideal). The C statistics represents the probability that for any randomly selected pair of people with type 2 diabetes with and without outcomes, the patient with outcomes had a higher predicted risk (18). A value of 0.50 indicated no discrimination and 1.00 represents perfect discrimination. We then undertook internal validation to correct measures of predictive performance for optimism (over-fitting) by bootstrapping 100 samples of the derivation data. We repeated the model derivation process in each bootstrap sample to produce a model, applied the model to the same bootstrap sample to quantify apparent performance, and applied the model to the original dataset to test model performance (calibration slope and C-statistics) and optimism (difference in the test performance and apparent performance). We then estimated the overall optimism across all models.

We applied our risk prediction model to each patient with type 2 diabetes in the external validation cohort on the basis of the presence of one or more predictors. We examined the performance of this final model both in the derivation dataset and then in external validation dataset in terms of discrimination by calculating the C statistics. We examined calibration by plotting agreement between predicted and observed risks across tenth of the predicted risks.

We used Stata V14.0 for all statistical analyses. This study was conducted and reported in line with the Transparent Reporting of a multivariate prediction model for Individual Prediction Diagnosis (TRIPOD) guidelines (19).

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

RESULTS

Study participants

In our derivation cohort, we analysed information on 4,704 type 2 diabetes patients with 588 cardiovascular hospitalisations within 2 years and 316 re-hospitalisations after 90 days since a prior cardiovascular hospitalisation. Our validated cohort had information on 1,121 type 2 diabetes patients with 183 cardiovascular hospitalisations and 78 re-hospitalisations. Table-1 summarises the basic characteristics and potential predictors of the study population. Patients with type 2 diabetes in both cohorts had similar age, gender, blood pressure and total cholesterol. Patients in the derived cohort had a higher level of high density lipoprotein, low density lipoprotein, and HbA1c. Compared with the derivation cohort, those in the validation cohort were more likely to be prescribed lowering lipid medicine and had more cardiovascular hospitalisation and re-hospitalisation.

Model derivation, performance measure, and validation

In the derivation dataset, the absolute risks of cardiovascular hospitalisation within 2 years and re-hospitalisation within 90 days post cardiovascular hospitalisation were 12.5% and 6.7%, respectively. Univariable associations between cardiovascular hospitalisation and cardiovascular re-hospitalisation are listed in supplemental Table-1. Of the 10 candidate predictors (16 categories), 9 predictors (15 categories) were statistically significantly associated with cardiovascular hospitalisation and re-hospitalisation in the final multivariable model (**Table-2**). Table-2 shows apparent and internal validation performance statistics of the risk prediction model. After adjustment for optimism, the final risk prediction model was able to discriminate type 2 diabetes patients with and without cardiovascular hospitalisation with a C statistics of 0.7094 (95% confidence interval 0.7067 to 0.7205), and discriminate type 2 diabetes patients with and without cardiovascular re-hospitalisation with a C statistics 0.7118 (0.7077 to 0.7159). The agreement between the observed and predicted proportion of cardiovascular hospitalisation and re-hospitalisation showed good apparent calibration (**Figure-1**, top left for cardiovascular hospitalisation and top right for cardiovascular re-hospitalisation). The optimism adjusted calibration slope was 1.0301 (0.9856 to 1.0747) and 1.0001 (0.9711 to 1.0247) for cardiovascular hospitalisation and re-hospitalisation, respectively (**Table-3**).

External validation

In the external validation cohort, the absolute risks for cardiovascular hospitalisation and re-hospitalisation were 16.3% and 7.0%, respectively. Applying our final risk prediction model to the independent population gave a C statistic of 0.7092 (0.7033 to 0.7151) for cardiovascular hospitalisation and 0.7098 (0.7014 to 0.7182) for cardiovascular re-hospitalisation, and good calibration (Figure-1, bottom left for cardiovascular hospitalisation and bottom right for cardiovascular re-hospitalisation), with the

calibration slope 1.0001 (0.9807 to 1.0195) and 0.9981 (0.9948 to 1.0482) for cardiovascular hospitalisation and re-hospitalisation, respectively.

Performance at the threshold for 10% and 20% of patients at highest risk

Table-4 shows the sensitivity, specificity, and observed risk for the 5%, 10%, 15%, 20% and 25% of patients at the highest predicted risk of each outcome in the validation cohort shown for illustrative purposes. For example, when a risk threshold of 24.53% for cardiovascular hospitalisation and 7.93% for cardiovascular re-hospitalisation is used to identify the 20% at highest predicted risk, the sensitivity was 33.40% for cardiovascular hospitalisation and 45.20% for cardiovascular re-hospitalisation, the specificity was 84.60% for cardiovascular hospitalisation and 75.90% for cardiovascular rehospitalisation, and the observed risk was 30.09% for cardiovascular hospitalisation and 11.98% for cardiovascular re-hospitalisation, respectively.

Clinical examples

Supplemental Chart-1 gives a clinical example of the application of prognostic score charts with graphical illustrations for cardiovascular hospitalisation and re-hospitalisation risk prediction models to predict 2-year risk of cardiovascular hospitalisation and risk of re-hospitalisation within 90 days of a prior cardiovascular hospitalisation.

DISCUSSION

We have developed two new risk prediction models to estimate the absolute risk of cardiovascular hospitalisation within 2 years and cardiovascular re-hospitalisation after 90 days of prior cardiovascular hospitalisation in a cohort of patients with type 2 diabetes in England. We then externally validated this model in another English cohort. The two prediction models had excellent calibration and useful discrimination, with C statistics of

300 greater than 0.70 both in the derivation cohort and external validation cohort. The two
301 prediction models were built from clinical variables usually recorded and accessible in
302 primary care settings, implying that they can be readily applied in routine primary care.

303 **Strengths and limitations**

304 Our two risk algorithms have several advantages over those in utilisation in many
305 developed countries. Our models are based on absolute risks determined and validated in
306 two independent populations. The models are developed from routinely recorded
307 demographic and clinical measurements in primary care settings, which suggests that
308 they can be straightforwardly applied in general practice and are readily amenable for
309 further external validations in countries that have routine recorded data accessible for
310 such aims. And the two risk algorithms can be easily integrated into online calculators for
311 implementation in general practices.

312 The methods used to derive and validate the model are similar to those for other risk
313 prediction algorithms derived from the CPRD and QResearch databases (20), (21). The
314 majority of predictors in our final model are accurate and reliable clinical measurements
315 (22) routinely recorded in primary care settings and updated and reviewed for patients
316 with type 2 diabetes, and are less varied than in other datasets. Moreover, the proportion
317 of missing values was low, which would lead to little variation in external applications,
318 although multiple imputation was still applied in our study. We acknowledge that our
319 prediction models do not take into account diabetes duration, antidiabetes treatments,
320 anti-hypertensive treatments, prior history of cardiovascular diseases, other diabetes
321 complications (e.g. renal failure), lifestyle risk factors (like smoking), and other
322 comorbidities due to limitations in the original data due to limitations in the original data,
323 but we feel that the clinical measurements included in our models could be proxies for
324 missing predictors. Data limitations also prevented extending our model to all diabetes

complications rather than those relating to cardiovascular hospitalisation. The relatively low sensitivities of our models to identify individuals at high risk of cardiovascular hospitalisation and re-hospitalisation is another limitation of the study. Due to the similarity between the derivation and validation cohorts, further external validation (e.g. cohorts from other countries) are warranted.

Comparison with other studies

Nirantharakumar et al. developed a prediction model among patients with diabetes to estimate adverse events (either excessive length of stay or inpatient mortality) over 4 years using a secondary care dataset in Birmingham, England (5). The predictors applied in this model covered demographic characteristics, clinical pathological test results, and use of insulin, recorded within 72 hours of hospitalisation. That population represented the people with at least previous inpatient hospitalisation, and probably reflects a cohort with more severe conditions, and likely higher prior probabilities of an event. The ranges of clinical measurements during a hospital admission would tend to be greater than in the community, as patients would be sicker and e.g. blood glucose control could be the reason for hospitalisation, or exacerbated by acute illness, making the dataset difficult to use as a basis for a prediction tool in routine care. Most importantly, this prediction model has not been externally validated and the model performance needs to be further evaluated in external populations before its application in clinical practices.

Rubin et al developed a tool to predict the risk of all-cause re-admission within 30 days among hospitalised patients with diabetes using hospitalised data (6). The short time-gap between predictor measurements and outcome made the tool less useful for clinical practice. The reasons for hospitalisation could be quite mixed, with different pathway and potential interventions. Therefore, using the all-cause hospitalisation risk as the outcome provides different information and allows less targeted interventions. As with

Nirantharakumar et al's model (5), this model has also not been externally validated in any independent population.

Previous studies have not focussed on cardiovascular disease as both a major cause and cost for hospital admission among patients with diabetes. To understand the potential risk of cardiovascular hospitalisation in the next year, and the risk of a new episode (within 90 days) of a cardiovascular event (re-hospitalisation) could be helpful for clinicians to facilitate tailored, more intensive care to those with high risk profiles and to reduce hospitalisation inpatient cost.

Conclusion and policy implication

As far as we are aware, our study is the first study to develop prediction tools to estimate the 2-year risk of cardiovascular hospitalisation and re-hospitalisation within 90 days of a previous hospitalisation. Our two prediction models have two important implications for clinical practice. First, they can be used as tools to screen populations at high risk of cardiovascular hospitalisation and re-hospitalisation. Both algorithms are based on readily accessible clinical data routinely recorded in primary care and reviewed by diabetes management teams. They can be readily integrated into primary care computer systems or developed into an app for a handheld device for ease of use. Secondly, our risk prediction models could be used to establish new treatment thresholds in clinical practice through consensus development of national guidelines.

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FIGURE LEGENDS AND TABLES

Figure-1. Assessing calibration in the derivation cohort (left) and the validation cohort (right) for cardiovascular hospitalisation (above panel) and cardiovascular re-hospitalisation (below panel)

Table-1. Baseline Characteristics of study populations.

	Derivation cohort	External validation cohort
N	4,704	1,121
Cardiovascular hospitalisation, n (%)	588 (12.5)	183 (16.3)
Cardiovascular rehospitalisation, n (%)	316 (6.7)	78 (7.0)
Age, years	65.0±16.3	65.5±11.4
Female, n (%)	1,919 (40.8)	444 (39.6)
Systolic blood pressure, mmHg	134.5±16.0	139.7±20.2
Diastolic blood pressure, mmHg	76.3±10.0	75.5±11.5
Total cholesterol, mmol/L	4.3±1.2	4.2±1.7
High density lipoprotein, mmol/L	1.3±0.6	1.1±1.2
Low density lipoprotein, mmol/L	2.5±1.4	1.4±3.0
Body mass index, kg/m^2	30.8±6.9	32.2±6.0
HbA1c, mmol/mol	61.5±17.2	56.2±15.1
Lipid Lowering treatment, n (%)	3,342 (71.4)	731 (65.2)

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489

490 Table-2. Final multivariate analysis for cardiovascular hospitalisation and re-hospitalisation
491 risk among people with type 2 diabetes in derivation cohort

Predictors	Coefficient	95% Confidence Interval
Cardiovascular Hospitalisation		
Age ≥ 70 years	0.815914	(0.793045 to 0.838784)
Male gender	0.228943	(0.206719 to 0.251168)
HbA1c ≥ 57 mmol/mol (7.4%)	-0.03967	(-0.06088 to -0.01846)
(Body mass index/10)^-2	-1.85384	(-2.39533 to -1.31235)
(Body mass index/10)^0.5	0.690585	(0.551284 to 0.829887)
(Systolic blood pressure/100)^2	-0.40302	(-0.58492 to -0.22111)
(Systolic blood pressure/100)^2*ln(Systolic blood pressure/100)	0.966205	(0.758028 to 1.174381)
(Diastolic blood pressure/100)^-2	0.474014	(0.387498 to 0.56053)
(Diastolic blood pressure/100)^-2*ln(Diastolic blood pressure/100)	0.2724	(0.188226 to 0.356575)
ln(Total cholesterol/10)	0.514695	(0.27381 to 0.75558)
(Total cholesterol/10)^0.5	-1.05803	(-1.86382 to -0.25223)
ln(High density lipoprotein)	0.073489	(0.04377 to 0.103208)
(High density lipoprotein)^3	-0.02384	(-0.02699 to -0.02069)
(Low density lipoprotein/10)^0.5	-0.55634	(-0.67239 to -0.44028)
ln(Low density lipoprotein/10)* (Low density lipoprotein/10)^0.5	-0.83161	(-1.01001 to -0.65322)
Constant	-3.80246	(-4.67529 to -2.92963)
Cardiovascular Re-hospitalisation		
Age ≥ 70 years	0.90054	(0.86384 to 0.93724)
Male	0.22328	(0.188299 to 0.258261)
HbA1c ≥ 57 mmol/mol (7.4%)	0.004076	(-0.0294 to 0.037547)
(Body mass index/10)^-2	-4.17347	(-4.62492 to -3.72202)
(Body mass index/10)^3	0.001821	(0.001318 to 0.002324)
(Systolic blood pressure/100)^2	-1.16118	(-1.46728 to -0.85507)
(Systolic blood pressure/100)^3	0.773551	(0.637616 to 0.909486)
(Diastolic blood pressure/100)^-2	0.5875	(0.439237 to 0.735763)
(Diastolic blood pressure/100)^-2*ln(Diastolic blood pressure/100)	0.4095	(0.260667 to 0.558332)

(Total cholesterol/10)^-2	-0.00798	(-0.01031 to -0.00565)
(Total cholesterol/10)^2	-0.02734	(-0.23117 to 0.176482)
ln(High density lipoprotein/10)	0.051443	(0.004285 to 0.0986)
(High density lipoprotein/10)^3	-0.02718	(-0.03277 to -0.02159)
Low density lipoprotein/10	-1.34491	(-1.56307 to -1.12675)
ln(Low density lipoprotein/10)	-0.88347	(-1.28497 to -0.48196)
Constant	-4.55873	(-4.8866 to -4.23086)

492

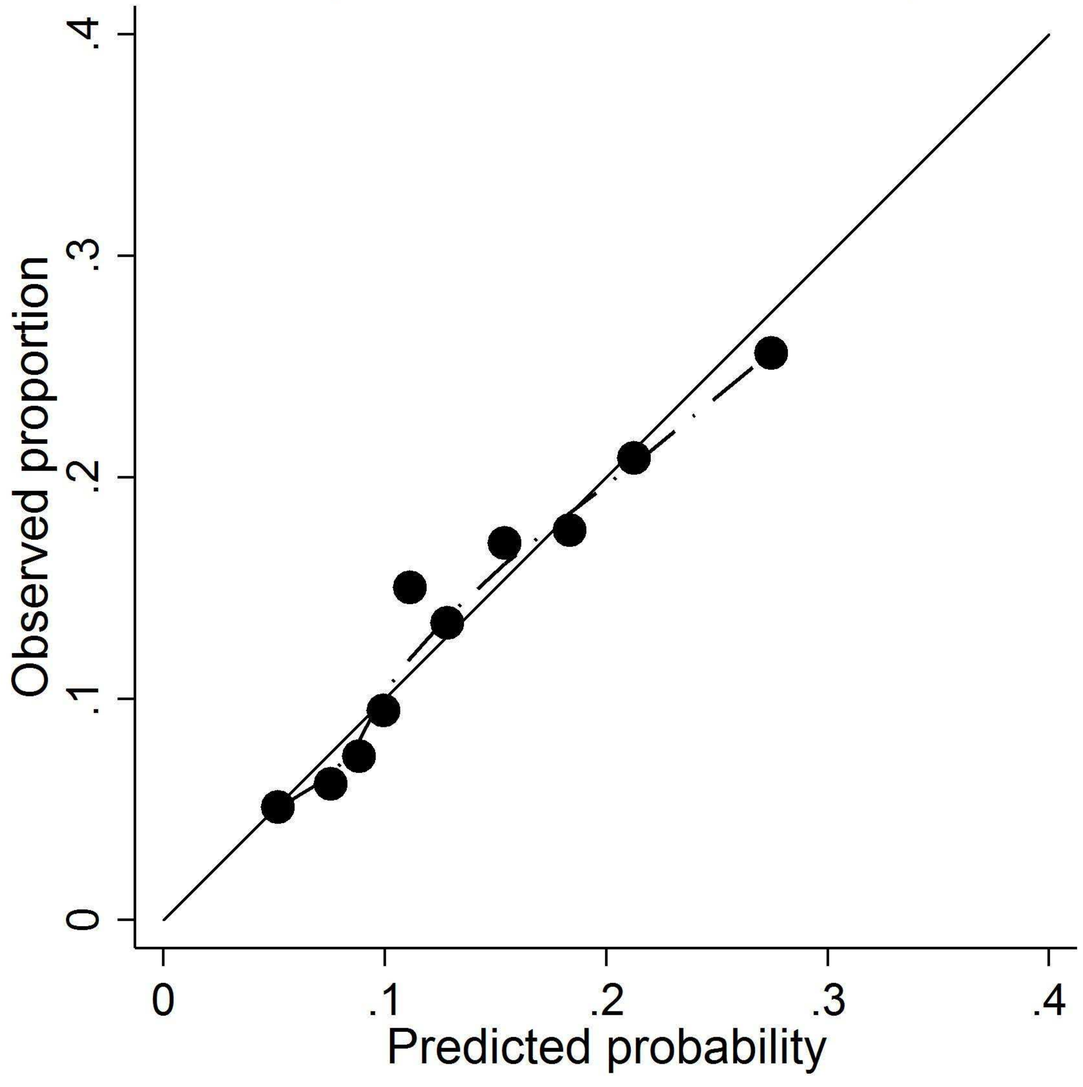
Table-3. Model diagnostics (with 95% CI)

	Derivation				Validation
Measure	Apparent performance	Test performance	Average optimism	Optimism corrected	
	Cardiovascular Hospitalisation				
C statistic	0.7163 (0.7136 to 0.7190)	0.7027 (0.6996 to 0.7058)	+0.0069	0.7094 (0.7067 to 0.7205)	0.7092 (0.7033 to 0.7151)
Calibration slope	1.0000 (0.9806 to 1.0194)	0.9933 (0.9899 to 0.9966)	+0.0067	0.9933 (0.9739 to 1.0127)	1.0001 (0.9807 to 1.0195)
	Cardiovascular Re-hospitalisation				
C statistic	0.7154 (0.7113 to 0.7195)	0.7136 (0.7105 to 0.7167)	+0.0036	0.7118 (0.7077 to 0.7159)	0.7098 (0.7014 to 0.7182)
Calibration slope	1.0000 (0.9766 to 1.0234)	0.9976 (0.9949 to 1.0003)	+0.0024	0.9976 (0.9742 to 0.9796)	0.9981 (0.9948 to 1.0482)

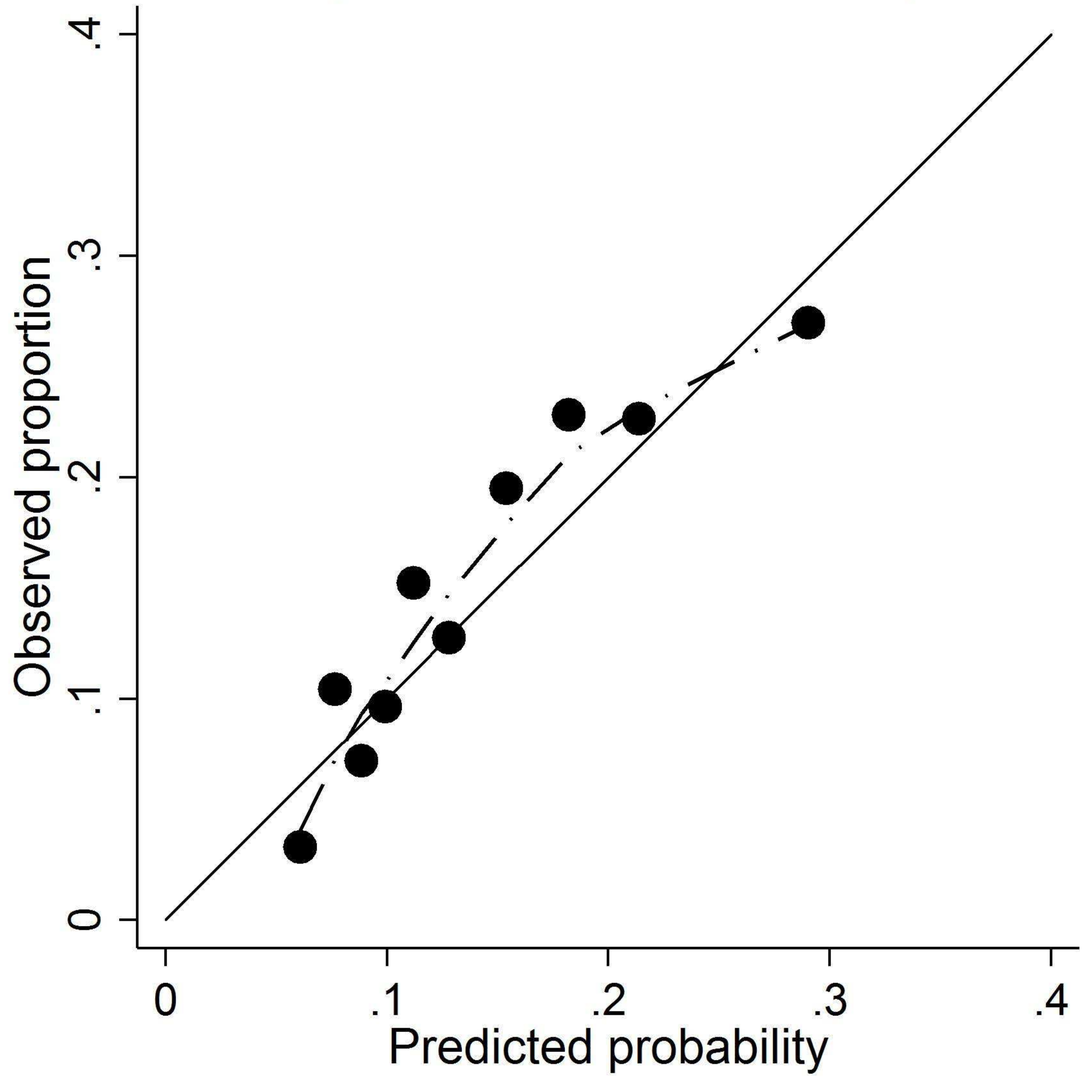
Table-4. Predicted risk of cardiovascular hospitalisation and re-hospitalisation the validation cohort based on various cut-offs.

	Cut-off (%) for risk	Mean predicted risk (%)	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Observed risk %
Cardiovascular hospitalisation						
Top 5%	38.17	51.96	10.30 (9.70 to 10.90)	97.40 (97.20 to 97.50)	43.50 (41.50 to 45.50)	43.48
Top 10%	31.73	43.35	17.50 (16.80 to 18.30)	94.60 (94.40 to 94.80)	38.60 (37.20 to 40.10)	38.62
Top 15%	27.54	37.71	24.70 (23.90 to 25.60)	90.10 (89.80 to 90.40)	32.80 (31.80 to 33.90)	32.83
Top 20%	24.53	33.77	34.00 (33.10 to 35.00)	84.60 (84.20 to 84.90)	30.10 (29.20 to 31.00)	30.09
Top 25%	22.22	31.05	42.80 (41.80 to 43.80)	78.40 (78.00 to 78.70)	27.90 (27.20 to 28.60)	27.89
Cardiovascular re-hospitalisation						
Top 5%	11.34	15.86	26.20 (24.90 to 27.50)	91.20 (91.00 to 91.50)	18.30 (17.40 to 19.30)	18.33
Top 10%	9.67	13.63	34.50 (33.10 to 36.00)	84.30 (84.00 to 84.60)	14.20 (13.50 to 14.90)	14.22
Top 15%	8.69	12.59	40.50 (39.00 to 42.00)	79.10 (78.80 to 79.50)	12.70 (12.20 to 13.30)	12.73
Top 20%	7.93	12.02	45.20 (43.70 to 46.70)	75.90 (75.50 to 76.30)	12.40 (11.90 to 12.90)	12.37
Top 25%	7.16	11.46	50.00 (48.50 to 51.50)	72.40 (72.00 to 72.70)	12.00 (11.50 to 12.50)	11.98

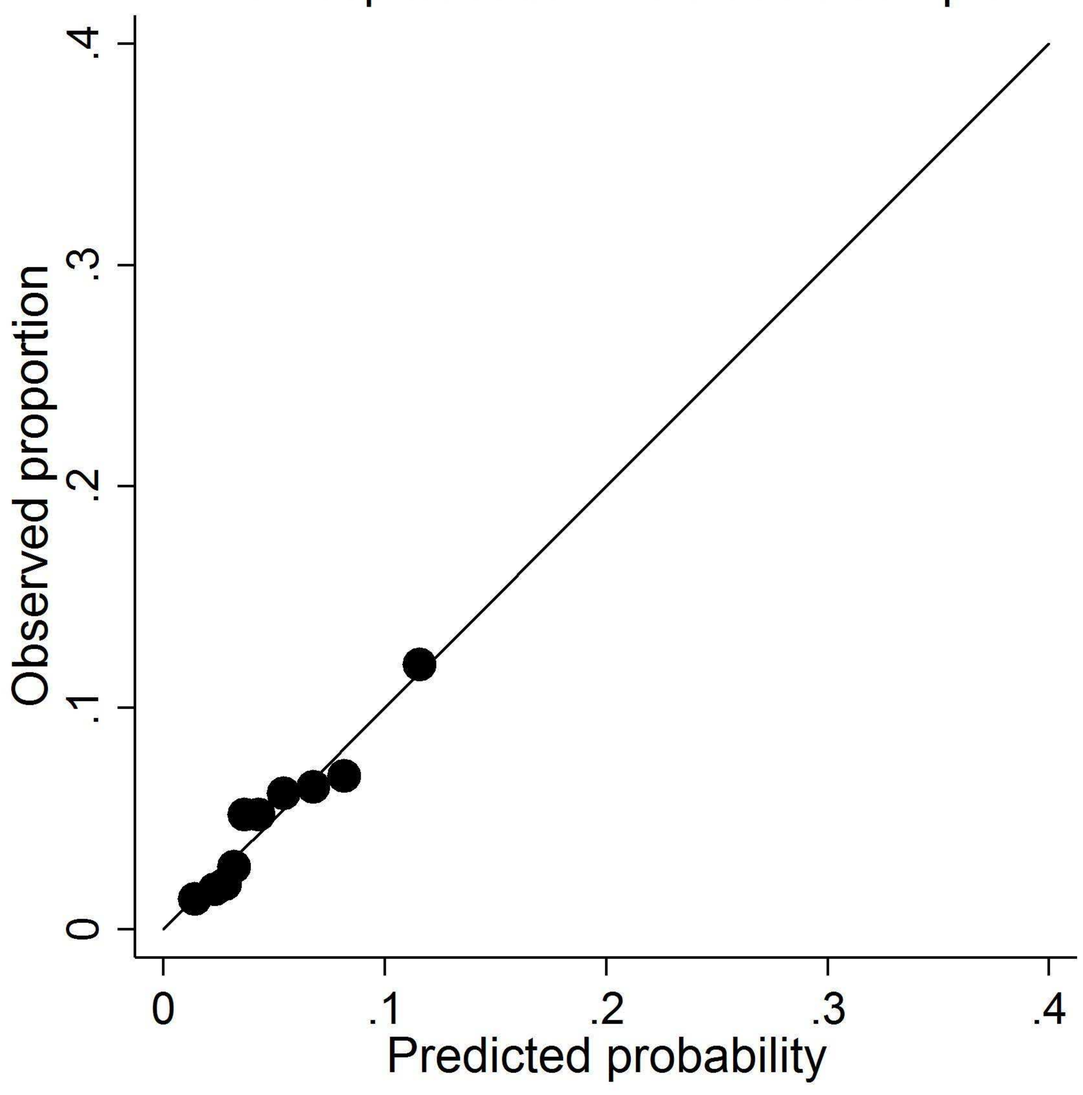
Hospitalisation:Derivation Sample



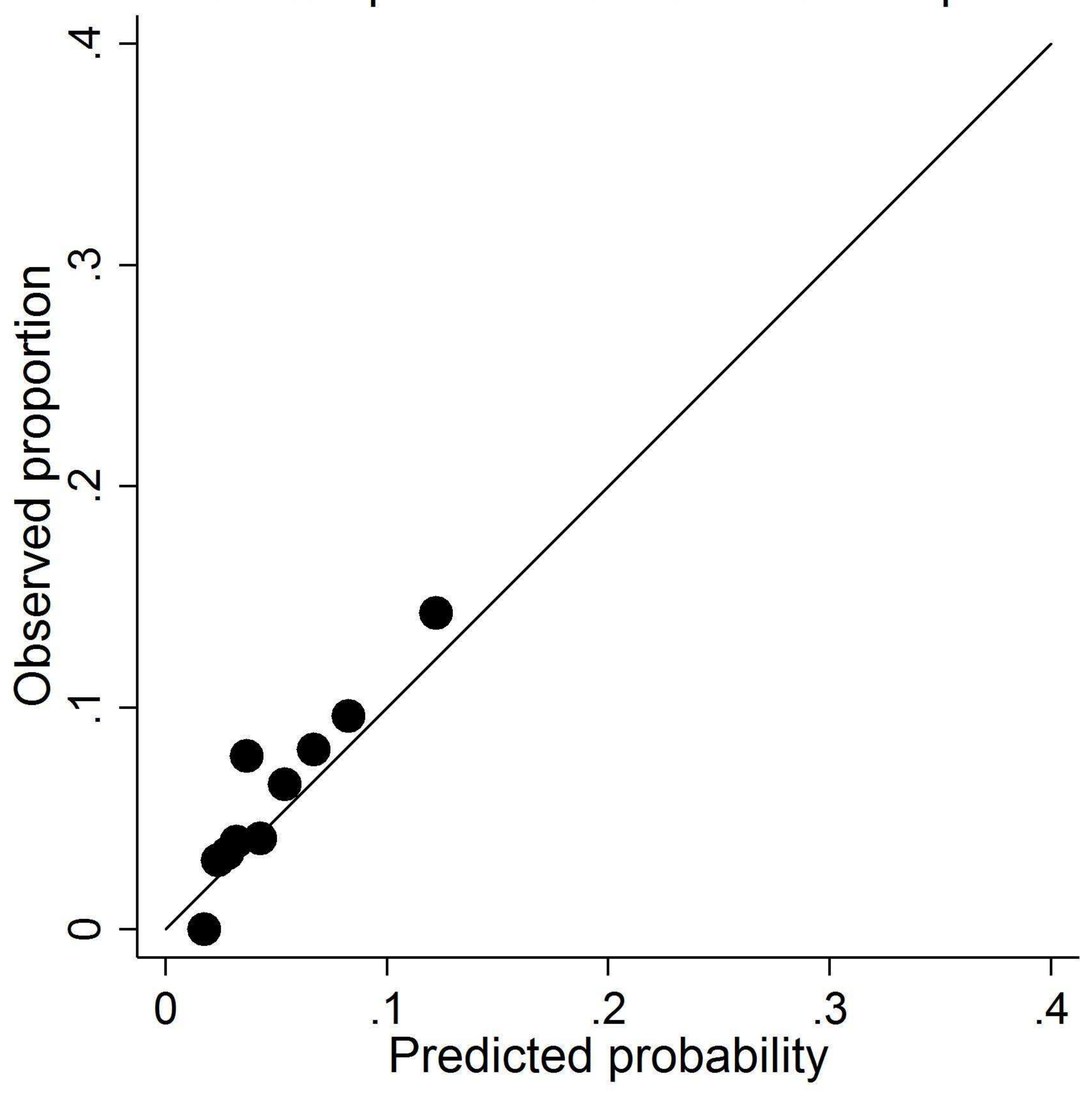
Hospitalisation:Validation Sample



Re-hospitalisation:Derivation Sample



Re-hospitalisation:Validation Sample



Supplemental Table-1. Univariate analysis for cardiovascular hospitalisation and re-hospitalisation risk among people with type 2 diabetes in derivation cohort

Predictors	Coefficient	95% Confidence Interval
Cardiovascular Hospitalisation		
Age ≥ 70 years	0.846665	(0.8262905 to 0.8670392)
Male gender	0.176845	(0.1563107 to 0.1973798)
HbA1c ≥ 57 mmol/mol	-0.133750	(-0.1537015 to -0.1137988)
(Body mass index/10)^-2	-3.814109	(-4.339377 to -3.288841)
(Body mass index/10)^0.5	-0.175857	(-0.3110282 to -0.0406859)
(Systolic blood pressure/100)^2	-0.326099	(-0.4951727 to -0.157025)
(Systolic blood pressure/100)^2*ln(Systolic blood pressure/100)	0.899080	(0.7036069 to 1.094553)
(Diastolic blood pressure/100)^-2	0.288490	(0.255288 to 0.3216911)
(Diastolic blood pressure/100)^-2*ln(Diastolic blood pressure/100)	0.123622	(0.0999253 to 0.1473193)
ln(Total cholesterol/10)	2.518678	(2.307047 to 2.73031)
(Total cholesterol/10)^0.5	-8.727267	(-9.433486 to -8.021047)
ln(High density lipoprotein)	0.088652	(0.061444 to 0.1158604)
(High density lipoprotein)^3	-0.037348	(-0.0403706 to -0.0343245)
(Low density lipoprotein/10)^0.5	-0.741638	(-0.849156 to -0.6341195)
Ln(Low density lipoprotein/10)* (Low density lipoprotein/10)^0.5	-1.234349	(-1.402307 to -1.066391)
Cardiovascular Re-hospitalisation		
Age ≥ 70 years	0.929657	(0.8966139 to 0.962701)
Male gender	0.179317	(0.1465089 to 0.2121253)
HbA1c ≥ 57 mmol/mol	-0.097652	(-0.1294095 to -0.0658946)
(Body mass index/10)^-2	-3.526998	(-3.948076 to -3.105919)
(Body mass index/10)^3	0.000793	(0.0002554 to 0.0013296)
(Systolic blood pressure/100)^2	-0.854411	(-1.140125 to -0.5686968)
(Systolic blood pressure/100)^3	0.645979	(0.5180567 to 0.7739015
(Diastolic blood pressure/100)^-2	0.224379	(0.1539288 to 0.2948295)
(Diastolic blood pressure/100)^-2*ln(Diastolic blood pressure/100)	0.101419	(0.0399049 to 0.1629332)
(Total cholesterol/10)^-2	-0.000040	(-0.0002732 to 0.0001938)
(Total cholesterol/10)^2	-0.728174	(-0.8790058 to -0.5773416)
ln(High density lipoprotein/10)	0.089334	(0.0450915 to 0.1335771)
(High density lipoprotein/10)^3	-0.046205	(-0.0516534 to -0.0407557)
Low density lipoprotein/10	-2.005945	(-2.203394 to -1.808495)
Low density lipoprotein/10*Ln(Low density lipoprotein/10)	-1.326986	(-1.711652 to -0.9423188)

Supplemental Chart-1. Practical prognostic score charts for predicting cardiovascular hospitalisation and re-hospitalisation

Clinical example: type 2 diabetes patient aged 75 years, female gender, 69.6mmol/mol (8.5%) HbA1c, 29.6kg/m² of body mass index, 102 mmHg systolic blood pressure, 60mmHg diastolic blood pressure, 6.7mmol/L triglyceride, 1.5mmol/L high density lipoprotein, 1.8mmol/L low density lipoprotein.

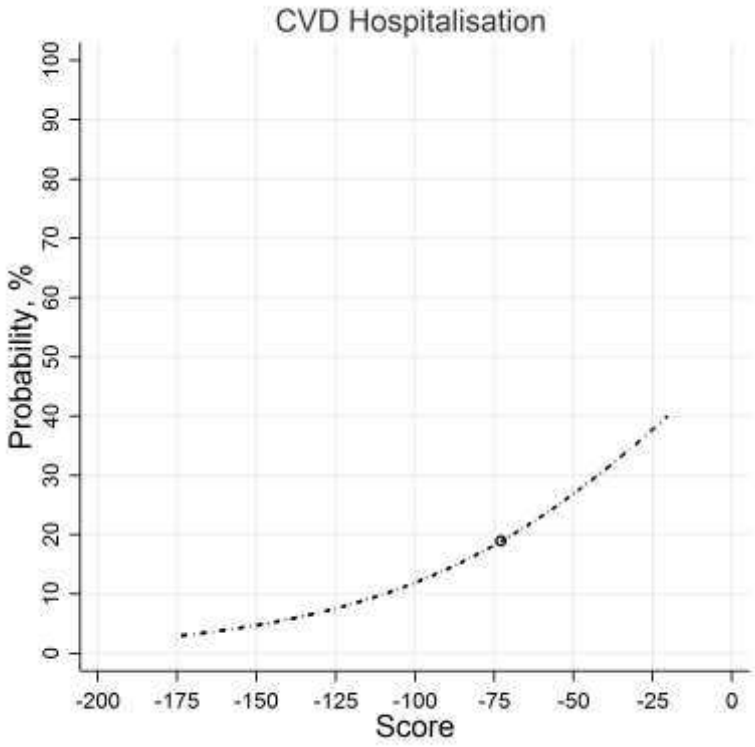
A: Prognostic score chart for predicting cardiovascular hospitalisation

Left chart of prognostic score

Predictors	***Description***	***Value***	***Score***	***Score range***
Age	Age ≥ 70 years=1	1	82	[0 to 82]
Gender	Male gender=1	0	0	[0 to 11]
HbA1c	HbA1c ≥ 57 mmol/mol (7.4%)=1	1	-2	[-2 to 0]
Body mass index-1	(Body mass index/10)^-2	0.11	-11	[-27 to -3]
Body mass index-2	(Body mass index/10)^0.5	1.72	59	[13 to 78]
Systolic blood pressure-1	(Systolic blood pressure/100)^2	1.04	-21	[-65 to -20]
Systolic blood pressure-2	(Systolic blood pressure/100)^2*ln(Systolic blood pressure/100)	0.02	1	[0 to 92]
Diastolic blood pressure-1	(Diastolic blood pressure/100)^-2	2.78	66	[12 to 87]
Diastolic blood pressure-2	(Diastolic blood pressure/100)^-2*ln(Diastolic blood pressure/100)	-1.42	-19	[-33 to -1]
Total cholesterol-1	ln(Total cholesterol/10)	-0.40	-10	[-56 to -7]
Total cholesterol-2	(Total cholesterol/10)^0.5	0.82	-43	[-46 to -18]
High density lipoprotein-1	ln(High density lipoprotein)	0.41	1	[-5 to 5]
High density lipoprotein-2	(High density lipoprotein)^3	3.38	-4	[-35 to 0]
Low density lipoprotein-1	(Low density lipoprotein/10)^0.5	0.42	-12	[-22 to -5]
Low density lipoprotein-2	ln(Low density lipoprotein/10)* (Low density lipoprotein/10)^0.5	-0.73	30	[15 to 31]
Constant	Constant=1	1	-190	[-190 to -190]
Sum Score		**-73**		
Predicted probability of cardiovascular hospitalisation		**18.9%**		

Right chart of prognostic score

Figure-2. Graphical illustration of cardiovascular hospitalisation prognostic score for the clinical example.



B: Prognostic score chart for predicting cardiovascular re-hospitalisation					
Left chart of prognostic score					*Right chart of prognostic score*
		Value	Score	Score range	**Figure-3. Graphical illustration of cardiovascular re-hospitalisation prognostic score for the clinical example.**
Age	Age ≥ 70 years=1	1	90	[0 to 90]	
Gender	Male	0	0	[0 to 11]	
HbA1c	HbA1c ≥ 57 mmol/mol (7.4%)=1	1	0.2	[-2 to 0]	
Body mass index-1	(Body mass index/10)^-2	0.11	-24	[-61 to -8]	
Body mass index-2	(Body mass index/10)^3	25.93	2	[1 to 13]	
Systolic blood pressure-1	(Systolic blood pressure/100)^2	1.04	-60	[-187 to -58]	
Systolic blood pressure-2	(Systolic blood pressure/100)^3	1.06	41	[38 to 225]	
Diastolic blood pressure-1	(Diastolic blood pressure/100)^-2	2.78	82	[29 to 109]	
Diastolic blood pressure-2	(Diastolic blood pressure/100)^-2*ln(Diastolic blood pressure/100)	-1.42	-29	[-49 to -2]	
Total cholesterol-1	(Total cholesterol/10)^-2	2.23	-1	[-33 to -1]	
Total cholesterol-2	(Total cholesterol/10)^2	0.45	-1	[-1 to 0]	
High density lipoprotein-1	ln(High density lipoprotein/10)	0.41	1	[-4 to 3]	
High density lipoprotein-2	(High density lipoprotein/10)^3	3.38	-5	[-40 to]	
Low density lipoprotein-1	Low density lipoprotein/10	0.18	-12	[-43 to -2]	
Low density lipoprotein-2	ln(Low density lipoprotein/10)	-0.31	14	[4 to 16]	
Constant	Constant=1	1	-228	[-228 to -228]	
Sum Score		**-129**			
Predicted probability of cardiovascular hospitalisation		**7.0%**