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Title of paper

Development and validation of a predictive risk model for all-cause mortality in Type 2 Diabetes

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Structured abstract

Aims

Type 2 diabetes is common and is associated with an approximate 80% increase in the rate of mortality. Management decisions may be assisted by an estimate of the patient's absolute risk of adverse outcomes, including death. This study aimed to derive a predictive risk model for all-cause mortality in type 2 diabetes.

Methods

We used primary care data from a large national multi-ethnic cohort of patients with type 2 diabetes in New Zealand and linked mortality records to develop a predictive risk model for 5-year risk of mortality. We then validated this model using information from a separate cohort of patients with type 2 diabetes.

Results

26,864 people were included in the development cohort with a median follow up time of 9.1 years. We developed three models initially using demographic information and then progressively more clinical detail. The final model, which also included markers of renal disease, proved to give best prediction of all-cause mortality with a C-statistic of 0.80 in the development cohort and 0.79 in the validation cohort (7,610 people) and was well calibrated. Ethnicity was a major factor with hazard ratios of 1.37 for indigenous Maori, 0.41 for East Asian and 0.55 for Indo Asian compared with European ($p<0.001$).

Conclusions

We have developed a model using information usually available in primary care that provides good assessment of patient's risk of death. Results are similar to models previously

published from smaller cohorts in other countries and apply to a wider range of patient ethnic groups.

Keywords

Diabetes mellitus, type 2

Mortality

Risk factors

Risk assessment

Survival analysis

New Zealand

Introduction

In 2010 about 285 million people worldwide had diabetes and this could rise to 439 million by 2030. [1] People with diabetes have been found to have a 70-80% increase in overall mortality rates and, if aged 50, will on average die 6 years earlier than those without diabetes.[2, 3] About 60% of this excess mortality is due to cardiovascular disease (CVD) including stroke, with the remainder being attributable to cancers and other conditions. Many causes of these excess deaths are potentially preventable by self-care and medical management.[4] It is therefore important to identify people with diabetes who are at particularly high risk of death so as to allow focussed and intensive intervention. Several predictive risk models have been developed to predict mortality in patients with diabetes.[5-8] De Cosmo's study, published in 2013, was the first to be validated with an external cohort. However this involved comparatively small cohorts with only 133 and 169 deaths in the development and validation cohorts respectively.

The aim of the current study was to develop a predictive risk model for all-cause mortality in a large cohort of ethnically diverse people with type 2 diabetes in New Zealand (NZ) using information usually available in a general practice context, and to validate it in a separate cohort.

Subjects and methods

Settings and subjects

This study uses a prospective cohort design. It uses information from two NZ general practice-based cohorts of patients with type 2 diabetes. In New Zealand almost all patients with type 2 diabetes receive care in general practice.

Development cohort

Between 2000 and 2012, general practitioners were funded to provide a free annual review for their patients with diabetes ('Get Checked' programme). Data from these reviews were recorded using a standardised template and collected regionally to provide aggregated statistics about diabetes management in primary health care. The NZ Diabetes Cohort Study (NZDCS) invited 26 of the largest organisations collecting 'Get Checked' data to participate in a cohort study. Of these, 24 organisations (92%) agreed and contributed data on primary care patients collected between 2000 and 2006.[9]

Validation cohort

The Diabetes Care Support Service (DCSS) is an independent provider that carries out a manual systematic clinical audit of diabetes care in primary care practices in south and west Auckland, New Zealand's largest city.[10] The audit data provide a summary of diabetes care over the preceding year. Patients whose care had been audited between 1994 and 2003 were included.

In both cohorts all people with Type 2 Diabetes, as determined by their primary health care physician, were included if they had complete data on the independent variables we wished to examine. The NZDCS study received ethical approval in 2004 and has on-going multi-centre approval in New Zealand (WGT/04/09/077).

Outcomes

All patients in New Zealand have a unique National Health Index (NHI) number, which is consistent across all health datasets. Patients in both cohorts were linked to New Zealand's

mortality database by an encrypted NHI number to identify all deaths that occurred over the follow-up period. To develop the models, time to death was used as the outcome. To validate the models, death during the five years following baseline audit was the outcome. In both cases we assume complete attainment of outcomes was achieved, although in rare instances patients may have emigrated during the follow up period.

Risk variables

All risk variables except prior cardiovascular disease were obtained from the primary care cohort datasets. Demographic variables were age of onset and duration of diabetes, gender, ethnicity, smoking and socioeconomic status. We used primary care ethnicity records and categorised as European, Māori (the indigenous people of NZ), Pacific, Indo-Asian, East Asian, and 'Other'. Body mass index (BMI) was calculated from weight and height recordings. Other clinical variables included blood pressure, glycosylated haemoglobin (HBA1c), total cholesterol/HDL ratio and renal function. Estimated glomerular filtration rate (eGFR) was calculated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration formula.[11] Clinically relevant categories were used for urine albumin creatinine ratio (UACR) because the variable was highly skewed and simple transformations did not create a useful variable. The predictive performance of the models was better using these categories than when using log-transformation. Categories were 'no albuminuria' (<2.5 mg/mmol in men or <3.5 mg/mmol in women), 'microalbuminuria' (≥2.5 - < 30 mg/mmol in men or ≥3.5 - <30 mg/mmol in women), 'macroalbuminuria' (≥30 and <100 mg/mmol), and 'advanced albuminuria' (≥100 mg/mmol). We also tested models that included as variables whether patients were on insulin, oral hypoglycaemics, statins,

antihypertensives, and angiotensin converting enzyme inhibitors (ACE inhibitors) or angiotensin receptor blockers (ARBs).

Prior cardiovascular disease was identified by the presence of any hospitalisation or death from myocardial infarction, angina, other ischemic heart disease, coronary artery bypass or angioplasty, cerebrovascular accident or transient ischaemic attack, or any significant peripheral arterial disease that occurred before the baseline review date and after 1 January 1988. Details are available from previous publications.[12]

Analysis

Descriptive statistics including means, medians, and proportions were used to describe the characteristics of the derivation and validation cohorts. We also examined the differences between patients with complete and missing data in both cohorts.

We developed Cox proportional hazards models for time to death to develop our predictive risk models. We first developed a model using just demographic variables and information on the onset and duration of diabetes (the ‘demographic’ model). We then sequentially added and tested clinical variables (smoking status, history of CVD, systolic blood pressure, BMI, HbA1c, and total cholesterol /HDL ratio) to develop a 'clinical’ model. We then developed a 'renal’ model by further adding eGFR and UACR. Finally, we examined the impact of adding information on whether patients were on particular drugs or combinations of drugs. For all continuous variables, we tested quadratic as well as linear relationships. We also tested a number of clinically plausible interactions such as the relationship between gender or ethnicity and age of onset or CVD history, although we did not include these in our final models.

Performance of alternative models to inform the inclusion of variables was assessed using Wald tests, likelihood ratios, and Akaike and Bayesian information criterion statistics. In all of these models, the assumptions of proportional hazards were checked using log-log plots of survival and examining Schoenfield residuals. We calculated the baseline hazard at five years for each of the three models.

Five year risk was calculated for each individual in the validation dataset using the three models developed. Discrimination was assessed using receiver operating curves and C-statistics. Net reclassification improvement was also calculated to compare the three models using 10, 15, and 20% cut-offs for 5 year risk of mortality.[13] Bar charts of observed versus predicted event rates and Hosmer-Lemeshow χ^2 tests are reported to show calibration of the models.

All analyses used the Stata 13.1 statistical package (StataCorp, College Station, TX, USA).

Results

Development cohort

The development cohort included 26,864 people with type 2 diabetes who had a record with complete data. This was 37% of all patients who had any record. In the original dataset 56% of patients had missing information on serum creatinine as this was not routinely reported to the "Get Checked" programme by all primary care organisations. All other variables were missing in less than 10% of people. Table 1 shows the baseline characteristics of people who were included and excluded from the development cohort. The characteristics of the two groups are generally very similar although the excluded group were less likely to have a history of CVD, smoking, or microalbuminuria, and had slightly

better glycaemic control on average. Fifty-seven per cent of the cohort was of European ethnicity but there were significant numbers of Māori and Pacific people, and smaller numbers of Asians.

Patients in the development cohort had a mean age of 62 years and were followed for a median of 9.1 years (interquartile range: 7.4-10.4 years) with a total follow up time of 228,904 years. During follow-up, 6,333 (23.6%) people died.

Validation cohort

7,610 people with type 2 diabetes had a record with complete data and were included in the validation cohort, which was 53% of all patients who had a record. Variables that had more than 10% missing data included serum creatinine, urine albumin creatinine ratio, BMI, HbA1c, and Total/HDL cholesterol ratio. Again the excluded patients were generally similar to the included patients although they were on average older, had slightly poorer eGFR and were more likely to have albuminuria (Table 1). Patients in the validation cohort were also similar to the patients in the development cohort although they were twice as likely to be of Pacific ethnicity (Auckland has a large Pacific population). During the 5 years of follow up 759 people died, 10.0% of the total cohort.

Models

Three final models were developed and tested (Table 2 and online appendix). In all models being Māori significantly increased risk of death, whilst being Indo-Asian or East Asian was strongly protective (all $P<0.001$). Longer duration of diabetes, being a smoker, and having any degree of albuminuria was also associated with higher mortality (all $P<0.001$).

For most continuous variables, quadratic forms were preferred indicating that relationships with mortality were not linear. An example of the difference between a linear and a quadratic model (for how mortality varies with eGFR) is provided in the on line appendix. Interactions terms were often statistically significant but were never strong and did not lead to improvements in Akaike statistics so were excluded from the final models.

We also tested models that included medications that patients were on at the time of baseline assessment. Whilst these drugs, either individually, or together, had statistically significant effects, the additional discrimination was very small and therefore they were not included in the final models presented. The model including Insulin was potentially the most useful and the discrimination and calibration are depicted for both the development and validation cohorts in Table 3.

Model performance

Table 3 shows the models' performances in predicting mortality in both the development and validation cohorts. The discrimination of the models were good with the C-statistic in the validation cohort ranging from 0.77 (95% CI 0.76-0.78) in the 'demographic' model to 0.80 (95% CI 0.79-0.81) in the 'renal' model. In each case the performance in the validation cohort was slightly less good. Calibration of the models was good in both development and validation cohorts with all Hosmer-Lemeshow χ^2 tests being non-significant (and on line appendix). Discrimination and calibration in the validation cohort was also checked for males and females separately, and for different ethnic groups and remained constant except for Pacific people where discrimination was generally slightly lower; for example the renal model had a C-statistic of 0.76 (95% CI, 0.72-0.80) in Pacific.

We also compared the models using net reclassification indices (NRI) summing over three different cut-offs (10, 15, and 20% five year risk of mortality). Moving from the 'demographic' model to the 'clinical' model resulted in an improvement of the NRI of 8.8% (95% CI, 4.9-12.8%), and from the 'clinical' to the 'renal' model' a further improvement of 6.8% (95% CI, 3.2-10.3%). There was no change in the NRI when Insulin status was added to the 'renal model' (0.8%, 95% CI, -1.1-2.7%). Table 4 provides information on the diagnostic test characteristics of the three final models at three different risk cut-offs.

Figure 1 shows how predicted risk of death increases for increasing HbA1c and for a number of other risk factors for an example of a 60 year old man.

Discussion

In this analysis we have developed predictive risk models for all-cause mortality that show good discrimination and are well calibrated. They use information that is typically available to primary care clinicians. The model including only demographic information and history of diabetes onset and duration performs well, while those that add other clinical and then renal information provide modest but useful improvements in discrimination. There was minimal loss of discrimination ability in the validation cohort in comparison to the development cohort suggesting that our model has external validity, at least to the NZ community.

A number of other models for predicting mortality in patients with diabetes have being published. [5, 6, 8, 14] These have included a wide range of variables, often including those not widely available in primary care. Like our models, all have included demographic variables and BMI. Smoking status, clinical cardiovascular risk factors such as blood

pressure, HbA1c, lipids, renal disease measures, and history of macrovascular disease were also often included. Unlike our model, all others include treatment with at least insulin and sometimes other drugs, and some included history of microvascular complications and other diseases. We did not find including drug treatment significantly improved our model and unfortunately we did not have information on microvascular disease other than renal. Figure 2 demonstrates how important risk factors, other than clinical variables such as HbA1c, are to predicting all-cause mortality. Ethnicity, the presence of a past history of CVD, or evidence of renal disease substantially changes a patient's risk profile.

Our study has a number of strengths. We are able to include a large number of participants with a long duration of follow-up in our development cohort and validate our model in a separate cohort. Only one other previous model has been validated using a separate cohort; in that instance both cohorts were far smaller than ours and were of purely European ethnicity. Secondly, our cohorts were based on primary care collected data and the models therefore reflect the information typically available, and are likely to have strong validity in the setting where risk prediction will most often be used.

Our study was also able to include a diverse range of ethnic groups. The size of the effect of ethnicity in our model is important, with hazard ratios of 1.37 for Maori, compared with Europeans, in the renal model. Failure to include this information could lead to under treatment of Maori. The hazard ratios of 0.41 and 0.55 for East Asian and Indo-Asian people respectively, is more problematic. Many Asian people are recent immigrants to NZ (over 50% have moved to NZ within 10 years [15]) so low mortality risk may reflect a health migrant effect which may not persist into the future. However, a lower mortality risk for Indo-Asian people is not inconsistent with a recent UKPDS study that showed that, while Asian Indian

with type 2 diabetes had an increased risk of complications, they had a reduced risk of all-cause mortality compared with Europeans.[16]

A weakness of the study is that, in both the development and the validation cohorts, we needed to drop a significant proportion of potential participants because of missing data. It is possible that the model would have lower predictive ability in these patients, and therefore lower in the overall population. The baseline comparison of those included and excluded in the cohorts however suggests that these groups were similar. Differences between patients with complete and incomplete data are likely to reflect both patient and practitioner factors which have not been measured and we cannot be sure whether these would also be associated with mortality.

Our group has previously developed predictive risk models for both first cardiovascular events and end-stage renal failure [12, 17] as have a number of other investigators [18-22]. The main reason for developing predictive risk models for adverse outcomes is to develop treatment strategies based upon absolute risk assessment. Is it more useful to base this upon risk of CVD or other disease specific end-points or mortality? A major opportunity for clinical management of people with diabetes is reducing the risk of the development of CVD and renal complications, and models for these end-points might seem an obvious choice where risk of the outcome is most closely related to the opportunity for intervention. However, other considerations may favour mortality as the outcome of choice. It is certainly of great significance to patients. It also assumes that the clinician will consider every opportunity to reduce risk for the patient, rather than focussing on, an admittedly important, subset of interventions. It is also important to recognise that predictive risk models are validated for measured degree of risk, and are not validated for measuring

amenability to treatment. A further technical reason for preferring all-cause mortality as an outcome is that it is very well defined with very low risk of misclassification. The same is not necessarily the case for other outcomes. This may be the reason for mortality predictive risk models usually having better discrimination than those for CVD. For example the model our group developed for CVD prediction had a C-statistic of 0.68, compared to 0.80 for the model for mortality in this model.[12]

It is likely that clinicians will be interested in different risks depending upon the clinical situation they face; thus perhaps the most useful approach is to make all the information available. With the ability to build risk models into computer systems that are often integrated into patient management systems this is easily done in an informative way. Alternatively, online risk calculators can be made available, as for our previously published equations for predicting first cardiovascular events in people with type 2 diabetes.[23][23]

In summary, we have developed three 5-year all-cause mortality risk models that performed well in two large cohorts with type 2 diabetes, and use information usually available in primary care. Routine, systematic or opportunistic risk estimation can provide a useful tool for prioritising and optimising management for individual patients.

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Tables

Table 1. Baseline characteristics of the development and validation cohorts, comparing patients included with those excluded due to missing data on some variables.

	Development			Validation		
Category	**Study cohort**	**Excluded**	**P value**	**Study cohort**	**Excluded**	**P value**
n	26,864	44,266		7,610	6,758	
Demographics						
Age (years) - mean(SD)	62 (13)	62 (13)	0.379	59 (12)	61 (14)	<0.001
Female - %(n)	51 (13,620)	48 (22,057)	<0.001	51 (3,851)	51 (3,872)	0.287
Ethnicity						
European - %(n)	57 (15,221)	54 (22,122)	<0.001	40 (3,166)	42 (3,166)	<0.001
Maori - %(n)	15 (3,943)	15 (6,122)		16 (1,244)	15 (1,098)	
Pacific - %(n)	15 (4,036)	15 (5,984)		30 (2,279)	23 (1,759)	
Indo-Asian - %(n)	3 (840)	5 (2,163)		6 (442)	6 (438)	
East Asian - %(n)	3 (746)	4 (1,829)		3 (259)	4 (281)	
Other - %(n)	8 (2,078)	7 (3,001)		4 (320)	10 (781)	
History of diabetes						
Age at onset (years) - mean(SD)	55 (14)	56 (14)	<0.001	51 (13)	54 (14)	<0.001
Duration of diabetes (years) - median(p25-p75)	4 (1-9)	3 (1-8)	<0.001	5 (2-10)	4 (2-9)	<0.001
Clinical						
BMI (kg/m^2) - median(p25-p75)	31 (27-35)	30 (26-35)		31 (27-36)	31 (27-36)	0.080
Systolic BP (mmHg) - mean(SD)	138 (19)	138 (19)	<0.001	137 (18)	138 (19)	<0.001
Smoking						
Smoker - %(n)	15 (4,086)	14 (6,070)	<0.001	16 (1,255)	13 (933)	<0.001
Ex-smoker - %(n)	28 (7,609)	24 (10,707)		16 (1,217)	11 (808)	
Non-smoker - %(n)	56 (15,169)	63 (10,707)		67 (5,111)	76 (5,407)	
Metabolic						
HbA1c (%) - median(p25-p75)	7.2 (6.4-8.6)	7.0 (6.3-8.2)	<0.001	7.6 (6.7-8.9)	7.3 (6.4-8.7)	<0.001

HbA1c (mmol/mol) - median(p25-p75)	55 (46-71)	53 (45-66)	<0.001	60 (50-74)	56 (46-72)	<0.001
Total/HDL cholesterol ratio - mean(SD)	4.4 (1.5)	4.3 (1.5)	<0.001	4.7 (3.8-5.7)	4.8 (3.9-5.8)	<0.001
Renal						
Serum creatinine (µmol/L) - median(p25-p75)	81 (70-100)	82 (70-100)	0.073	84 (72-99)	89 (75-105)	<0.001
eGFR (CKD) (mL/mim/1.73m^2) - median(p25-p75)	76 (59-91)	76 (59-91)	0.359	77 (61-92)	71 (55-87)	<0.001
Microalbuminura - %(n)	27 (7,361)	21 (9,613)	<0.001	29 (2,246)	35 (1,128)	<0.001
Macroalbuminuria - %(n)	5.6 (1,492)	4.5 (2,041)		7 (535)	7 (215)	
Advanced macroalbuminuria - %(n)	3.6 (963)	3 (1,372)		5 (411)	5 (170)	
History of CVD						
Past hospitalisation for CVD - %(n)	24 (6,516)	22 (9,882)	<0.001	19 (7,610)	21 (1,608)	0.001

Table 2: Hazard Ratios and P-values for the three different models presented

	Demographic		Clinical		Renal	
	Haz. Ratio	P - value	Haz. Ratio	P - value	Haz. Ratio	P - value
Demographic						
Age of onset (10 years)	1.402	<0.001	1.654	<0.001	1.737	<0.001
Age of onset squared	1.038	<0.001	1.027		1.019	
Duration (10 years)	3.243	<0.001	3.171	<0.001	2.731	<0.001
Duration squared	0.923	<0.001	0.932		0.951	
Female	0.739	<0.001	0.792	<0.001	0.817	<0.001
Maori	1.717	<0.001	1.552	<0.001	1.372	<0.001
Pacific	0.946	0.255	0.924	0.118	0.793	<0.001
East Asian	0.406	<0.001	0.439	<0.001	0.408	<0.001
Indo Asian	0.544	<0.001	0.573	<0.001	0.553	<0.001
Other	0.698	<0.001	0.775	<0.001	0.773	<0.001
Clinical						
Smoker			1.643	<0.001	1.622	<0.001
Ex-smoker			1.185	<0.001	1.180	<0.001
History of CVD			1.547	<0.001	1.440	<0.001
Systolic BP (per 10 mmHg)			0.674	<0.001	0.682	<0.001
Systolic BP squared			1.013		1.012	
HbA1c (per 10 mmol/mol)			0.952	<0.001	0.955	<0.001
HbA1c squared			1.006		1.005	
Total/HDL cholesterol ratio			1.056	<0.001	1.045	<0.001
BMI (per 10 kg/m^2)			0.617	<0.001	0.590	<0.001
BMI squared			1.074		1.008	
Renal						
eGFR (per 10 mL/mim/1.73m^2)					0.859	<0.001
eGFR squared					1.007	
Microalbuminuria					1.388	<0.001
Macroalbuminuria					1.653	<0.001
Advanced albuminuria					2.367	<0.001

Table 3 Discrimination and calibration for the three models and with one including in the development and validation cohorts

Model	Development cohort				Validation cohort			
	n	AUC	95% CI	HL Test	n	AUC	95% CI	HL Test
Demographic	26,864	0.770	0.762-0.779	0.342	7,610	0.751	0.733-0.769	0.745
Clinical	26,864	0.790	0.782-0.798	0.139	7,610	0.774	0.757-0.791	0.483
Renal	26,864	0.802	0.794-0.810	0.700	7,610	0.793	0.776-0.810	0.272
Insulin	20,816	0.808	0.799-0.817	0.645	7,610	0.794	0.777-0.811	0.177

(AUC – area under the receiver operator curve; HLTest - Hosmer-Lemeshow χ^2 tests)

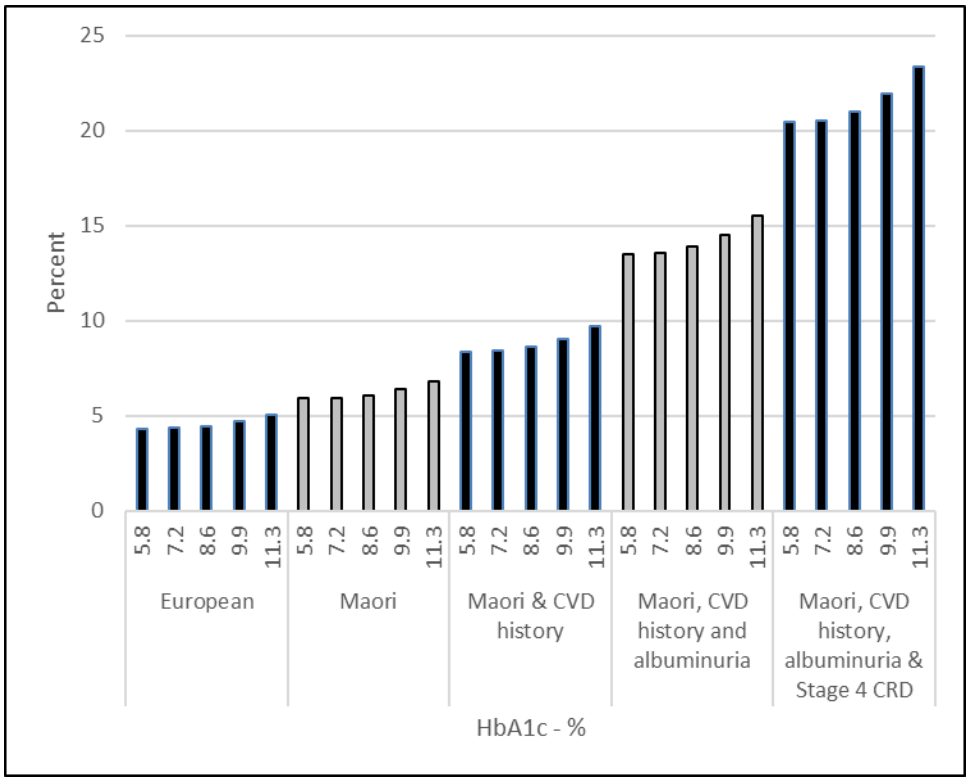
Table 4 Diagnostic test characteristics for the three different models at three different cut-offs

Model	Cut-off	Sensitivity	Specificity	PPV	NPV
Demographic	10	66.0	70.0	19.6	94.9
	15	51.6	82.6	24.7	93.9
	20	38.2	90.0	29.6	92.9
Clinical	10	69.4	71.7	21.4	95.5
	15	52.2	84.1	26.6	94.1
	20	41.2	90.9	33.3	93.3
Renal	10	71.5	73.3	22.9	95.9
	15	56.0	84.5	28.6	94.6
	20	43.2	90.7	34.1	93.5

(All figures are percentages, PPV – positive predictive value, NPV – negative predictive value)

Figures

Figure 1 Calculated 5 year mortality risk for a man depending upon his HbA1c result and various other important risk factors



Notes: Macroalbuminuria (≥30 and <100 mg/mmol) & Stage 4 CRD (Chronic Renal Disease) calculated as eGFR of 20 ml/min/1.73m^2

(Baseline: 60 years old man with diabetes for 5 years, systolic blood pressure 140mmHg, Total/HDl ratio 4.0, no albuminuria, and eGFR 75 ml/min/1.73m^2)