Derivation and External Validation of a Clinical Model to Predict Heart Failure Onset in Patients with Incident Diabetes

Short Title: Predicting heARt FAilure in dIabeTes (PARFAIT)

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# ABSTRACT

Objective: Heart failure (HF) often develops in patients with diabetes and is recognized for its role in increased cardiovascular morbidity and mortality in this population. Most existing models predict risk in patients with prevalent rather than incident diabetes and fail to account for sex differences in HF risk factors. We derived sex-specific models in Ontario, Canada to predict HF at diabetes onset and externally validated these models in the UK.

Research Design and Methods: Retrospective cohort study using international population-based data. Our derivation cohort comprised all Ontario residents aged ≥18 years, who were diagnosed with diabetes between 2009-2018. Our validation cohort comprised UK patients aged ≥35 years, who were diagnosed with diabetes between 2007-2017. Primary outcome was incident HF. Sex-stratified multivariable Fine and Gray subdistribution hazard models were constructed, with death as a competing event.

Results: A total of 348,027 Ontarians (45% women) and 54,483 UK residents (45% women) were included. At 1, 5, and 9 years, respectively in the external validation cohort, the C-statistics were 0.81 (95%CI: 0.79-0.84), 0.79 (0.77-0.80), and 0.78 (0.76-0.79) for the female-specific model; 0.78 (0.75-0.80), 0.77 (0.76-0.79), and 0.77 (0.75-0.79) for the male-specific model. The models were well-calibrated. Age, rurality, hypertension duration, hemoglobin, HbA1C, and cardiovascular diseases were common predictors in both sexes. Additionally, mood disorder and alcoholism were female-specific predictors, while income and liver disease were male-specific predictors.

Conclusions: Our findings highlight the importance of developing sex-specific models and represent an important step towards personalized lifestyle and pharmacologic prevention of future HF development.

# INTRODUCTION

Over the last four decades, the number of adults with diabetes almost quadrupled worldwide.(1) Having diabetes more than doubles an individual’s risk of developing cardiovascular disease (CVD),(2) which is a leading cause of mortality(3) accounting for half of all deaths in patients with diabetes.(4) Heart failure (HF) is an important sequela of diabetes through accelerated atherosclerosis and other direct cellular mechanisms(5) and is increasingly being recognized for its role in the cardiovascular morbidity and mortality seen in this population.(6) Data from clinical trials suggest that sodium–glucose cotransporter-2 inhibitors (SGLT-2i) may reduce the likelihood of incident HF in patients with diabetes.(7) The ability to accurately identify individuals at risk of developing HF provides an opportunity for personalized preventative therapy, potentially reducing the CV disease burden in patients with diabetes.

Although several risk models have been developed to predict the onset of HF in patients with diabetes, the majority are based on patients with prevalent instead of new onset diabetes,(8) potentially missing the maximal window of opportunity for personalized prevention. Additionally, existing risk scores are based on clinical trial or aggregated cohort study data that lack real-world representation. They also fail to address the fundamental differences in HF risk, risk factors and outcomes in women and men. Women with type 2 diabetes have been found to be at higher risk of developing HF than men. A meta-analysis of 14 studies encompassing > 12 million individuals found that diabetes conferred 38% excess risk of HF, as well as a greater excess risk of all-cause and cardiovascular death in women.(9) These data emphasize the need for sex-specific approaches to risk stratification and management of patients with diabetes.(10)

Given this need, we used population-based administrative data in Ontario, Canada to derive clinical risk models to predict the onset of HF in adult women and men at the time of diabetes diagnosis and externally validated these models on a concurrent cohort of patients in the United Kingdom (UK).

# METHODS

Design and Selection Criteria

Included in this retrospective cohort study were adult patients ≥ 18 years of age, who were newly diagnosed with diabetes. Those who were ≥ 105 years of age, who were long-term care residents or were dialysis-dependent at the time of diabetes diagnosis were excluded. Patients with no HbA1c within 60 days before and 30 days after diabetes diagnosis, and those already diagnosed with HF at the time of diabetes diagnosis, were also excluded.

Data Sources and Patient Population

*Ontario Cohort*

 The Ontario cohort consisted of all patients with incident diabetes diagnosed between April 1, 2009 and March 31, 2018. Ontario is the most populous province in Canada with 13 million residents and one of the most ethnically diverse jurisdictions in the world. We used population level administrative healthcare databases that are held securely in coded form and analysed at ICES. ICES is an independent, non-profit research institute whose legal status under Ontario’s health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement.

Incident cases of diabetes were identified using a validated algorithm, based on one inpatient or two outpatient physician service claims for diabetes within two years. This algorithm was shown to have 86% sensitivity and 97% specificity for identifying diabetes onset when validated in primary care patient records.(11) We linked these records with the Registered Persons Database (demographic and vital statistics), the Canadian Institute for Health Information Discharge Abstract Database (DAD; hospitalizations and co-morbidities), and the Same Day Surgery (SDS; co-morbidities). Physician service claims data was obtained from the Ontario Health Insurance Plan (OHIP) database, and laboratory values from the Ontario Laboratory Information System. These databases have been validated for many outcomes, exposures, and co-morbidities.(11; 12)

 We estimated socioeconomic status based on patients’ neighborhood median income in the Canadian census, and determined rural versus urban residence using Statistics Canada definitions.(13) We identified hypertension,(12) asthma and chronic obstructive pulmonary disease (COPD)(14) using validated algorithms, and other co-morbidities using DAD, SDS and OHIP databases based on International Classification of Diseases 10th Revision Canada (ICD-10CA) codes on patient encounters within five years of diabetes diagnosis, using previously described methods.(15; 16)

*UK Cohort*

The external validation cohort consisted of all patients aged ≥35 years with a diagnostic code for incident type 2 diabetes, who met the selection criteria between March 1, 2007 and March 31, 2017, and registered with general practices in England eligible for linkage to external datasets. The cohort was derived from the UK Clinical Practice Research Datalink (CPRD) GOLD database, which is one of the world's largest electronic medical records (EMR) providing anonymized patient-level data and deemed as representative of the UK population.(17)

The CPRD GOLD primary care records contains sociodemographic, clinical, therapy, laboratory, and referral information from 1987 onwards. We linked the CPRD records of the eligible type 2 diabetes cohort to Hospital Episode Statistics (HES) which contains data on all hospital admissions, the Office for National Statistics mortality data, and the index of multiple deprivation (IMD) quintiles 2015 as a measure for socioeconomic status. IMD is recorded at the patient’s residential postcode level and represents a score calculated as the weighted sum of seven deprivation domains, of which income and employment are the highest contributing domains.

Outcomes

The primary outcome was incident HF. In the Ontario cohort, this was identified by a validated algorithm with 85% sensitivity and 97% specificity based on one inpatient or two outpatient billing claims for HF within one year.(18) HF was identified in from primary care and linked secondary care HES records in the UK cohort using Read and ICD-10 codes, respectively. The validity of cardiovascular diagnoses in CPRD is recognized.(19)

Statistical Analysis

Continuous variables were compared with a 2-sample *t*-test or Wilcoxon rank sum test where appropriate. Categorical variables were compared with a chi-square test. Outcomes were assessed through March 31, 2019. In Ontario, patients were censored when they died or were no longer eligible for Ontario health insurance. In the UK, patients were censored when they died or left the CPRD-contributing practice.

*Model Development*

Model development was based on Ontario data and stratified by sex. We split the female and male cohorts by random selection such that 70% of each cohort was used for derivation and 30% for internal validation.(20) The prediction of HF was accomplished using Fine and Gray subdistribution hazard models within a *competing risk framework.*(21)Candidate variables from Table 1 were selected based on Bayesian Information Criteria, using a backward stepwise elimination model with death as the competing event.(22)

Rurality and socioeconomic status were missing in <0.1% of patients, glomerular filtration rate (GFR) in 21,078 (6.1%) and hemoglobin in 28,744 (8.3%). We imputed missing values once within the SAS “proc MI” framework, where they were predicted drawing on all candidate covariates using predictive mean matching for continuous variables and logistic regression for categorical variables.(23) We examined the association between each continuous variable with the outcome using cubic spline analyses with three knots at percentiles 10, 50 and 90. As the linearity assumption held for all variables, they were entered into the model as continuous values. We validated the model on the remaining 30% of the cohort. We reported subhazard ratios, 95% confidence intervals (CI) and P-values for final covariates in each model.

*Model Evaluation*

We evaluated model discrimination using the C-statistic and estimated 95% CIs using 200 bootstraps. We assessed calibration using Brier scores(24) and time-dependent plots of observed versus predicted HF incidence rates within deciles of predicted risk in the validation cohort.

*Sensitivity Analysis*

 We conducted two sensitivity analyses to assess the robustness of our models in clinically relevant settings. First, as SGLT-2i is the recommended first-line therapy for patients with diabetes and CVD, we evaluated the performance of our models in patients without CVD. Specifically, per European and American Diabetes Association guidelines,(25; 26) we excluded those with a history of CVD including ischemic heart disease (IHD), cerebrovascular disease, and peripheral arterial disease (PAD). Second, we evaluated the performance of our models in predicting incident HF hospitalization.

Analyses were performed using SAS 9.4 (SAS Institute, Cary, NC) and R studio version 3.5.1 in the Ontario cohort and Stata 16.1 (College Station, Texas, USA) in the UK cohort, with statistical significance defined by a two-sided P-value <0.05.

# RESULTS

Derivation and Validation Cohorts

 The Ontario cohort was used for derivation and internal validation. Median follow-up for the 348,027 Ontarians with incident diabetes (45.0% women) was 5 (IQR, 3-7) years, and maximum follow-up was 9 years. In the derivation cohorts, 4,027 (3.7%) among 109,600 women and 5,803 (4.3%) among 134,018 men developed HF during the follow-up period. In the internal validation cohorts, 1,742 (3.7%) among 46,972 women and 2,469 (4.3%) among 57,437 men developed HF.

 The external validation cohort comprised of 54,483 UK residents with incident type 2 diabetes (45.3% women). Median follow-up duration was 5 (IQR, 3-7) years. Among 24,664 women, 1,107 (4.5%) developed HF. Among 29,819 men, 1,494 (5.0%) developed HF (eTable 1).

 The baseline characteristics of the Ontario and UK cohorts were similar within each sex, with the exception that the Ontario patients were younger, less likely to have atrial fibrillation (AF), IHD, cerebrovascular disease, PAD, hypothyroidism, alcoholism, chronic renal disease and primary malignancy. Ontarians were however more likely to have longstanding hypertension, valvular heart disease, COPD or to undergo cardiac testing (Table 1).

Female-Specific Model

 The multivariable risk factors of HF in women were age, rurality, duration of hypertension, valvular heart disease, IHD, AF, history of cardiac testing, COPD, alcoholism, baseline hemoglobin, HbA1C, GFR, and mood disorder (Table 2).

 The performance of the models on derivation, internal and external validation is summarized in Table 3. In the internal validation dataset, the C-statistics at 1, 5 and 9 years were 0.79 (95%CI, 0.77-0.82), 0.79 (0.78-0.81) and 0.77 (0.76-0.79); and Brier scores were 0.007 (95%CI, 0.006-0.008), 0.034 (0.032-0.035), and 0.066 (0.062-0.069), respectively. In the external validation dataset, the C-statistics at 1, 5 and 9 years were 0.81 (0.79-0.84), 0.79 (0.77-0.80), and 0.78 (0.76-0.79); and Brier scores were 0.010 (0.009-0.011), 0.038 (0.035-0.041) and 0.067 (0.062-0.071), respectively, indicating excellent calibration. eFigures 1-3 show the area under the receiver-operating characteristic (ROC) curves and Figure 1 shows the calibration plots of observed vs. expected rates of HF at 1, 5 and 9 years after diabetes diagnosis in women according to each decile of risk. The model calibrated well in all but the highest risk decile in the external validation cohort, where the model tended to overpredict.

Male-Specific Model

 The multivariable risk factors of HF in men were age, rurality, income quintile, duration of hypertension, valvular heart disease, IHD, history of coronary artery bypass grafting, AF, history of cardiac testing, COPD, liver disease, hemoglobin, HbA1C, and GFR (Table 2).

 In the internal validation dataset, the C-statistics at 1, 5 and 9 years were 0.75 (0.73-0.78), 0.78 (0.77-0.79), and 0.76 (0.75-0.77); and Brier scores were 0.008 (0.007-0.009), 0.039 (0.037-0.041), and 0.073 (0.070-0.076), respectively. In the external validation dataset, the C-statistics at 1, 5 and 9 years were 0.78 (0.75 to 0.80), 0.77 (0.76 to 0.79) and 0.77 (0.75 to 0.79); and Brier scores were 0.011 (0.010-0.012), 0.044 (0.042-0.047), and 0.072 (0.068-0.076),respectively, indicating excellent calibration (Table 3). eFigures 1-3 show the area under the ROC curves and Figure 1 shows the calibration plot of observed vs. expected rates of HF at 1, 5 and 9 years after diabetes diagnosis in men according to each decile of risk. The model calibrated well in all except the highest risk decile in the external validation cohort tended, where the model tended to overpredict.

Sensitivity Analysis

*Model Performance in Patients without CVD*

 For the female-specific model, the C-statistics at 1, 5 and 9 years were 0.82, 0.81, and 0.80, and Brier scores were 0.0010, 0.0082 and 0.022, respectively in the Ontario cohort. The C-statistics were 0.81, 0.78 and 0.77, and Brier scores were 0.0065, 0.028, and 0.049, respectively in the UK cohort.

 For the male-specific model, the C-statistics were 0.78, 0.78, and 0.77, and Brier scores were 0.0011, 0.0086, and 0.022, respectively in the Ontario cohort. The C-statistics were 0.74, 0.76, and 0.75, and Brier scores were 0.0067, 0.029, and 0.051, respectively in the UK cohort.

*Predicting Incident HF Hospitalization*

 For the female-specific model, the C-statistics at 1, 5 and 9 years were 0.83, 0.82, and 0.81, and Brier scores were 0.0013, 0.0099, and 0.025, respectively in the Ontario cohort. The C-statistics were 0.81, 0.79, and 0.77, and Brier scores were 0.0098, 0.038, and 0.067, respectively in the UK cohort.

 For the male-specific model, the C-statistics were 0.80, 0.80 and 0.78, the Brier scores were 0.0014, 0.011 and 0.027, respectively in the Ontario cohort. The C-statistics were 0.78, 0.77 and 0.76, and Brier scores were 0.011, 0.044 and 0.072, respectively in the UK cohort.

*The Sex-Specific PARFAIT Risk Calculators*

 Our sex-specific models are together termed the Predicting heARt FAilure in dIabeTes (PARFAIT) models. These models have been adapted into risk calculators and provided in the Supplements.

# DISCUSSION

Main findings

We derived and validated sex-specific models to predict incident HF in adults with new onset diabetes. We observed that 3.7-4.5% of women and 4.3-5% of men with diabetes developed HF over the study period, and that age, duration of hypertension, GFR, hemoglobin, HbA1C and prevalent CVD are risk factors of HF common to both sexes. Specific to women, mood disorder and alcoholism are additional HF risk factors, while income and liver disease are male-specific risk factors. The performance of our models was robust over 9-year follow-up. We have enclosed automated risk calculators to make these models readily applicable in clinical settings.

Alleviating the Burden of Heart Failure in Patients with Diabetes

The prevalence of diabetes is growing globally at a rapid pace. A previous UK population-based study reported that patients with type 2 diabetes are more than twice as likely to have HF as their age-sex-practice matched comparators without diabetes (men OR 2.12 (95%CI 1.76-2.54), women OR 2.27 (1.81-2.85)).(27) Given HF’s role in the development of disability(28) and other adverse long-term outcomes,(16; 29) the ability to predict HF risk will inform timely and personalised preventative therapy. Lifestyle modification and other interventions such as SGLT-2i have cardioprotective benefits and the latter is associated with nearly 25% reduction in HF hospitalisations and cardiovascular death.(7; 30) Our work describes new high-risk features in the development of HF and highlights the importance of sex-specific models in predicting future risk, particularly when risk factors may vary by sex. Additionally, our models exhibited excellent performance in predicting severe HF requiring hospitalization, particularly amongst patients for whom prophylactic SGLT-2i is not routinely recommended by guidelines. These features may play an important role in further reducing population-level risk of HF.

Findings in comparison to other studies

 Many existing risk scores were derived and validated in smaller cohorts and lack robust external validation, which effectively limits their applicability in the real world.(31-35) A number of these models were based on older clinical trial data and predicted a variety of HF-related outcomes instead of HF onset: the WATCH-DM Risk Score was derived using machine learning methods and predicted HF in patients with *prevalent* type 2 diabetes (C-statistic 0.77 on internal validation);(35) the TIMI Risk Score for HF in Diabetes (TRS-HFDM) predicted HF hospitalization (C-statistic 0.78;(31) Pfister calculated the risk for HF in people with advanced type 2 diabetes complicated by macrovascular disease (C-statistic 0.75);(34)and the UK Prospective Diabetes Study Outcomes Model (UKPDS-OM) estimated the absolute probability of first occurrence of seven major diabetes-related complications, HF being one of them.(32) Pandey (2021) used data from three cohort studies to predict HF amongst patients with prediabetes or prevalent diabetes using biomarker-based risk score (C-statistic 0.74).(33) A recent HF hospitalisation risk model was based on EMR data of 54,452 predominately-Caucasian patients with incident or prevalent type 2 diabetes from a US-based single payer system (C-statistic 0.782).(36) In contrast, our models were derived from an ethnically diverse, contemporary population of >250,000 patients within a universal healthcare system. Our models were validated externally across continents demonstrating excellent performance at all time points. In addition to their demonstrated applicability around the world, these models uniquely apply at the onset of diabetes thus affords a larger window of opportunity for HF prevention.(8; 34)

Notably, most published HF risk models in patients with diabetes are non-sex specific, in spite of known sex differences in cardiovascular risk attributable to diabetes,(9; 10) and the differences in HF risk factors and outcomes in women and men.(16; 29; 37) The only exception to this are models derived by Hippsley-Cox and Coupland, which were not specific to patients with incident diabetes, incorporated the exact same predictors in both sexes, and lacked external validation.(38) These models had similar performance to ours (C-statistics 0.769 in men, 0.783 in women).

The availability of long-term follow-up data is essential to the clinical applicability of models that predict the onset of chronic disease. Our follow-up duration exceeds most similar studies. Pfister’s derivation cohort had a mean follow-up of 34.5 months.(34) A study on the post-trial monitoring data for the UKPDS-OM risk score, found that the HF prediction model performed well in the first 3 years but overpredicted at 10 years.(39)Our models demonstrated consistent performance throughout 9-year follow-up and are based on routinely-collected data which demonstrates generalizability to jurisdictions with and without established EMR systems.

A number of risk factors have been reported in association with the future risk of HF in patients with diabetes including glycemic control, CVD or cardiovascular risk factors,(36) renal function,(34) and sociodemographic factors such as age and income.(38; 40) Our models included these variables and also highlighted other high-risk features such as hemoglobin, COPD, and alcoholism. Our report of sex-specific risk factors is important and is to our knowledge a first step towards personalized preventative medicine.

Limitations

 Our study has several limitations. *First*, our derivation cohort contained a mixed population of type 1 and 2 diabetes. However, these models performed well in an external validation cohort of exclusively type 2 diabetes patients. *Second*, our data sources do not routinely capture measures of physical activity and other lifestyle factors that may have important roles in the development of incident HF.

# CONCLUSION

We developed and externally validated sex-specific risk models to predict long-term HF risk in patients with new onset diabetes, to maximize the window of opportunity for preventative therapy. Our models demonstrated robust performance over 9-year follow-up. Our identification of sex-specific risk factors, the ability of our models to additionally predict severe HF requiring hospitalization, as well as amongst patients for whom prophylactic SGLT-2i is not routinely prescribed by current guidelines, represent an important step towards personalized lifestyle and pharmacologic prevention to potentially allow millions of patients with diabetes to live longer and better.

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Declaration of Interests: none

Data Sharing Statement:

Ontario: The dataset from this study is held securely in coded form at ICES. While legal data sharing agreements between ICES and data providers (e.g., healthcare organizations and government) prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at [www.ices.on.ca/DAS](http://www.ices.on.ca/DAS) (email: das@ices.on.ca). The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

UK: access to data can be requested via application to the Clinical Practice Research Datalink (CPRD).

# CONTRIBUTORSHIP

Conception and Design: LYS

Data acquisition and analysis: LYS, SSZ, ABE

Interpretation of data: LYS, SSZ, ABE, PPL, DSL, KT, SWT, EK, MAM

Drafting of the manuscript: LYS, SSZ

Critical revision and final approval: LYS, SSZ, ABE, PPL, DSL, KT, SWT, EK, MAM

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: LYS

# ETHICAL APPROVAL

Ontario: The use of data was authorized under section 45 of Ontario’s *Personal Health Information Protection Act*, which does not require review by a Research Ethics Board.

UK: the study was approved by the Independent Scientific Advisory Committee (ISAC) for the MHRA Database Research (protocol number 17\_168). Generic ethnical approval for observational research using CPRD with approval from ISAC has been granted by Health Research Authority (HRA) Research Ethics Committee (Ease Midlands – Derby, REC reference number 05/MRE04/87).

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# TABLES

Table 1. Baseline characteristics by sex in the Ontario and UK cohorts

|  |  |  |
| --- | --- | --- |
| Variable   | Women | Men |
| Ontario(n=156,572) | UK(n=24,664) | Ontario(n=191,455) | UK(n=29,819) |
| Demographics |   |   |   |   |
| Age, Mean ± SD, y | 57.9 ± 13.6 | 63.9 ± 13.2 | 57.2 ± 12.7 | 61.5 ± 12.2 |
| Age, Median (IQR), y | 58 (49-67) | 64 (54-74) | 57 (49-66) | 61 (52-70) |
| Rural residence, No. (%) | 14,451 (9.2) | NA | 19,810 (10.3) | NA |
| Income quintile, No. (%)\* |  |  |  |  |
|  1 (Lowest) | 36,711 (23.4) | 4,938 (20.0) | 39,398 (20.6) | 5,387 (18.1) |
|  2 | 35,265 (22.5) | 5,142 (20.9) | 40,332 (21.1) | 5,871 (19.7) |
|  3 | 32,419 (20.7) | 5,168 (21.0) | 40,118 (21.0) | 6,306 (21.2) |
|  4 | 28,860 (18.4) | 4,856 (19.7) | 38,211 (20.0) | 6,281 (21.1) |
|  5 (Highest) | 23,317 (14.9) | 4,560 (18.5) | 33,396 (17.4) | 5,974 (20.0) |
| Formally rostered to FP, No. (%) | 135,489 (86.5) | NA | 160,315 (83.7) | NA |
| Comorbidities |  |  |  |  |
| Hypertension, No. (%) | 89,272 (57.0) | 13,750 (55.8) | 103,906 (54.3) | 14,729 (49.4) |
| Hypertension duration, Mean ± SD, y | 10.8 ± 6.7 | 10.4 ± 8.4 | 10.1 ± 6.7 | 9.0 ± 7.7 |
| Hypertension duration, Median (IQR), y | 10 (5-16) | 9 (4-15) | 9 (4-15) | 7 (3-13) |
| Hypertension duration, No. (%) |  |  |  |  |
| No hypertension | 67,300 (43.0) | 10,914 (44.3) | 87,549 (45.7) | 15,090 (50.6) |
|  < 10 years | 43,620 (27.9) | 7,740 (31.4) | 55,566 (29.0) | 9,368 (31.4) |
|  10-20 years | 35,878 (22.9) | 4,349 (17.6) | 38,296 (20.0) | 3,996 (13.4) |
|  ≥ 20 years | 9,774 (6.2) | 1,661 (6.7) | 10,044 (5.2) | 1,365 (4.6) |
| Ischemic heart disease, No. (%) | 4,393 (2.8) | 4,379 (17.8) | 12,004 (6.3) | 6,755 (22.7) |
| Recent MI, No. (%) | 1,808 (1.2) | 31 (0.1) | 5,616 (2.9) | 55 (0.2) |
| Valvular heart disease, No. (%) | 440 (0.3) | 16 (0.1) | 811 (0.4) | 17 (0.1) |
| Atrial fibrillation, No. (%) | 1,520 (1.0) | 1,264 (5.1) | 2,745 (1.4) | 1,682 (5.6) |
| Previous CABG, No. (%) | 445 (0.3) | 223 (0.9) | 2,236 (1.2) | 897 (3.0) |
| Previous PCI, No. (%) | 1,698 (1.1) | 342 (1.4) | 5,536 (2.9) | 1,015 (3.4) |
| History of cardiac testing, No. (%) | 35,576 (22.7) | 2,211 (9.0) | 51,875 (27.1) | 3,692 (12.4) |
| Cerebrovascular disease, No. (%) | 1,681 (1.1) | 1,404 (5.7) | 2,602 (1.4) | 1,845 (6.2) |
| Peripheral arterial disease, No. (%) | 700 (0.4) | 483 (2.0) | 1,479 (0.8) | 926 (3.1) |
| COPD/asthma, No. (%) | 40,207 (25.7) | 5,215 (21.1) | 39,654 (20.7) | 4,635 (15.5) |
| Pulmonary circulation disorder, No. (%) | 537 (0.3) | 459 (1.9) | 605 (0.3) | 399 (1.3) |
| GFR, Mean ± SD, mL/min/1.73m2 | 88.9 ± 20.2 | 73.8 ± 19.9 | 89.4 ± 18.9 | 79.6 ± 19.4 |
| GFR, Median (IQR), mL/min/1.73m2 | 91 (76-103) | 73 (60-86) | 92 (78-102) | 78 (67-92) |
| HbA1C, Mean ± SD, % (mmol/mol) | 7.5 ± 1.9(58 ± 20.8) | 7.7 ± 1.9(61 ± 20.8) | 8.0 ± 2.2(64 ± 24.0) | 8.0 ± 2.1(64 ± 23.0) |
| HbA1C, Median (IQR), % (mmol/mol) | 7 (6-8) | 7 (7-8) | 7 (7-9) | 7 (7-9) |
| Hemoglobin, Mean ± SD, g/dL | 135.2 ± 12.1 | 136.3 ± 13.0 | 147.1 ± 12.7 | 149.2 ± 13.4 |
| Hemoglobin, Median (IQR), g/dL | 136 (128-143) | 137 (129-145) | 148 (140-155) | 150 (142-158) |
| Venous thromboembolism, No. (%) | 311 (0.2) | 1,179 (4.8) | 440 (0.2) | 1,013 (3.4) |
| Hypothyroidism, No. (%) | 1,192 (0.8) | 3,356 (13.6) | 416 (0.2) | 997 (3.3) |
| Liver disease, No. (%) | 730 (0.5) | 289 (1.2) | 1,387 (0.7) | 421 (1.4) |
| Alcohol abuse, No. (%) | 365 (0.2) | 1,051 (4.3) | 1,485 (0.8) | 3,491 (11.7) |
| Dementia, No. (%) | 1,619 (1.0) | 292 (1.2) | 1,550 (0.8) | 198 (0.7) |
| Depression, No. (%) | 1,203 (0.8) | 8,264 (33.5) | 838 (0.4) | 5,593 (18.8) |
| Psychosis, No. (%) | 280 (0.2) | 447 (1.8) | 276 (0.1) | 451 (1.5) |
| Primary cancer, No. (%) | 5,516 (3.5) | 3,107 (12.6) | 5,924 (3.1) | 3,198 (10.7) |
| Metastatic cancer, No. (%) | 1,110 (0.7) | 70 (0.3) | 778 (0.4) | 81 (0.3) |
| Paraplegia/hemiplegia, No. (%) | 256 (0.2) | 63 (0.3) | 409 (0.2) | 83 (0.3) |

\* IMD quintiles are recorded for the UK cohort.

Abbreviations: SD = standard deviation; IQR = interquartile range; NA: not applicable; FP = family physician; MI = myocardial infarction; CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; COPD = chronic obstructive pulmonary disease; GFR = glomerular filtration rate; HbA1C: glycated hemoglobin

Table 2. Multivariable predictors of heart failure in women and men with diabetes.

|  |  |  |  |
| --- | --- | --- | --- |
| Variable | Coefficient | Adjusted SHR (95% CI) | P-value |
| Women |
| Age, per y | 0.05672 | 1.06 (1.05-1.06) | <0.001 |
| Rural residence | 0.18698 | 1.21 (1.10-1.33) | <0.001 |
| Hypertension duration |  |  |  |
| No hypertension | Reference | Reference | Reference |
| < 10 years | 0.23651 | 1.27 (1.15-1.39) | <0.001 |
| 10-20 years | 0.38748 | 1.47 (1.34-1.62) | <0.001 |
| ≥ 20 years | 0.45119 | 1.57 (1.38-1.78) | <0.001 |
| Ischemic heart disease | 0.55744 | 1.75 (1.55-1.96) | <0.001 |
| Valvular heart disease | 0.6776 | 1.97 (1.50-2.58) | <0.001 |
| Atrial fibrillation | 0.89362 | 2.44 (2.11-2.83) | <0.001 |
| History of cardiac testing | 0.10943 | 1.12 (1.04-1.20) | 0.003 |
| COPD or asthma | 0.46512 | 1.59 (1.49-1.70) | <0.001 |
| HbA1C, per 1% | 0.09776 | 1.10 (1.09-1.12) | <0.001 |
| Hemoglobin, per 1 g/dL | -0.00867 | 0.991 (0.989-0.994) | <0.001 |
| GFR, per 1 mL/min/1.73 m² | -0.01025 | 0.990 (0.988-0.992) | <0.001 |
| Alcoholism | 0.84142 | 2.32 (1.44-3.75) | <0.001 |
| Mood disorder | 0.5566 | 1.75 (1.31-2.32) | <0.001 |
| Men |
| Age, per y | 0.06 | 1.06 (1.05-1.06) | <0.001 |
| Rural residence | 0.14 | 1.15 (1.06-1.24) | <0.001 |
| Income quintile |  |  |  |
| 1 (Lowest) | Reference | Reference | Reference |
| 2 | -0.11 | 0.89 (0.83-0.97) | <0.001 |
| 3 | -0.15 | 0.86 (0.80-0.93) | <0.001 |
| 4 | -0.23 | 0.79 (0.73-0.86) | <0.001 |
| 5 (Highest) | -0.25 | 0.77 (0.71-0.84) | <0.001 |
| Hypertension duration |  |  |  |
| No hypertension | Reference | Reference | Reference |
| < 10 years | 0.22 | 1.24 (1.16-1.34) | <0.001 |
| 10-20 years | 0.44 | 1.55 (1.44-1.67) | <0.001 |
| ≥ 20 years | 0.48 | 1.62 (1.45-1.81) | <0.001 |
| Ischemic heart disease | 0.48 | 1.62 (1.49-1.77) | <0.001 |
| Valvular heart disease | 0.69 | 1.99 (1.63-2.44) | <0.001 |
| Atrial fibrillation | 0.64 | 1.90 (1.68-2.14) | <0.001 |
| Previous CABG | -0.31 | 0.73 (0.62-0.87) | <0.001 |
| History of cardiac testing | 0.12 | 1.13 (1.06-1.20) | <0.001 |
| COPD or asthma | 0.37 | 1.45 (1.37-1.54) | <0.001 |
| HbA1C, per 1% | 0.08 | 1.09 (1.07-1.10) | <0.001 |
| Hemoglobin, per 1 g/dL | -0.01 | 0.992 (0.990-0.994) | <0.001 |
| GFR, per 1 mL/min/1.73 m² | -0.01 | 0.994 (0.992-0.996) | <0.001 |
| Liver disease | 0.50 | 1.65 (1.31-2.09) | <0.001 |

Abbreviations: SHR: sub-hazard ratio; COPD = chronic obstructive pulmonary disease; GFR = glomerular filtration rate; CI = confidence interval; CABG = coronary artery bypass grafting

Table 3. Model performance in the derivation and validation datasets.

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | Women | Men |
| Time, y | Population | C-statistic (95% CI) | Brier score (95% CI) | C-statistic (95% CI) | Brier score (95% CI) |
| 1 | Derivation | 0.79 (0.77-0.80) | 0.007 (0.006-0.007) | 0.75 (0.74-0.77) | 0.009 (0.008-0.009) |
| Internal validation | 0.79 (0.77-0.82) | 0.007 (0.006-0.008) | 0.75 (0.73-0.78) | 0.008 (0.007-0.009) |
| External validation | 0.81 (0.79-0.84) | 0.010 (0.009-0.011) | 0.78 (0.75-0.80) | 0.011 (0.010-0.012) |
| 2  | Derivation | 0.80 (0.79-0.81) | 0.012 (0.012-0.013) | 0.77 (0.76-0.78) | 0.016 (0.015-0.016) |
| Internal validation | 0.80 (0.78-0.82) | 0.013 (0.012-0.014) | 0.77 (0.76-0.79) | 0.015 (0.014-0.016) |
| External validation | 0.82 (0.80-0.84) | 0.016 (0.015-0.018) | 0.78 (0.77-0.80) | 0.019 (0.017-0.020) |
| 3 | Derivation | 0.79 (0.78-0.80) | 0.019 (0.018-0.020) | 0.77 (0.76-0.78) | 0.023 (0.022-0.024) |
| Internal validation | 0.80 (0.78-0.82) | 0.019 (0.018-0.021) | 0.78 (0.76-0.79) | 0.023 (0.021-0.024) |
| External validation | 0.81 (0.79-0.82) | 0.023 (0.021-0.025) | 0.78 (0.76-0.79) | 0.027 (0.025-0.029) |
| 4  | Derivation | 0.79 (0.78-0.80) | 0.026 (0.025-0.027) | 0.77 (0.76-0.78) | 0.031 (0.030-0.032) |
| Internal validation | 0.80 (0.78-0.81) | 0.026 (0.025-0.028) | 0.77 (0.76-0.79) | 0.030 (0.029-0.032) |
| External validation | 0.80 (0.78-0.82) | 0.030 (0.028-0.032) | 0.78 (0.76-0.79) | 0.036 (0.033-0.038) |
| 5 | Derivation | 0.79 (0.78-0.80) | 0.033 (0.032-0.034) | 0.77 (0.76-0.78) | 0.039 (0.038-0.040) |
| Internal validation | 0.79 (0.78-0.81) | 0.034 (0.032-0.035) | 0.78 (0.77-0.79) | 0.039 (0.037-0.041) |
| External validation | 0.79 (0.77-0.80) | 0.038 (0.035-0.041) | 0.77 (0.76-0.79) | 0.044 (0.042-0.047) |
| 6  | Derivation | 0.79 (0.78-0.80) | 0.041 (0.039-0.042) | 0.77 (0.76-0.77) | 0.047 (0.046-0.049) |
| Internal validation | 0.79 (0.78-0.80) | 0.040 (0.039-0.042) | 0.78 (0.76-0.78) | 0.048 (0.046-0.050) |
| External validation | 0.78 (0.77-0.80) | 0.045 (0.042-0.048) | 0.77 (0.76-0.78) | 0.050 (0.047-0.053) |
| 7 | Derivation | 0.78 (0.77-0.79) | 0.048 (0.046-0.050) | 0.76 (0.76-0.77) | 0.056 (0.055-0.058) |
| Internal validation | 0.79 (0.78-0.80) | 0.048 (0.046-0.050) | 0.77 (0.76-0.79) | 0.056 (0.054-0.059) |
| External validation | 0.78 (0.76-0.79) | 0.052 (0.048-0.055) | 0.77 (0.76-0.78) | 0.057 (0.053-0.059) |
| 8  | Derivation | 0.78 (0.77-0.79) | 0.056 (0.054-0.058) | 0.76 (0.76-0.77) | 0.066 (0.064-0.067) |
| Internal validation | 0.78 (0.77-0.80) | 0.057 (0.054-0.060) | 0.76 (0.75-0.78) | 0.065 (0.062-0.067) |
| External validation | 0.78 (0.76-0.79) | 0.060 (0.056-0.064) | 0.77 (0.75-0.78) | 0.065 (0.061-0.068) |
| 9  | Derivation | 0.77 (0.76-0.78) | 0.065 (0.063-0.068) | 0.76 (0.75-0.77) | 0.075 (0.073-0.078) |
| Internal validation | 0.77 (0.76-0.79) | 0.066 (0.062-0.069) | 0.76 (0.75-0.77) | 0.073 (0.070-0.076) |
| External validation | 0.78 (0.76-0.79) | 0.067 (0.062-0.071) | 0.77 (0.75-0.79) | 0.072 (0.068-0.076) |

y = year; CI = confidence interval

# FIGURE LEGENDS

Figure 1. Calibration plots of observed vs. expected rates of incident heart failure at 1, 5 and 9 years of follow-up, according to deciles of expected rates in women and men in the a) Ontario internal validation cohort and b) UK external validation cohort.