Supplementary Table 1: ICD-9 codes for rheumatic heart disease, valvular heart disease, endocarditis, congenital heart diseases and other non-atherosclerotic causes of structural heart diseases

|  |  |
| --- | --- |
| Condition | ICD-9 codes |
| Rheumatic heart disease | 391.0, 391.1, 391.2, 391.8, 391.9, 392.0, 393, 394.1, 394.9, 395.0, 395.1, 395.2, 395.9, 396.9, 397.0, 397.1, 397.9, 398.0, 398.90, 398.91, 398.99,  |
| Valvular heart disease | 394.0, 394.2, 394.9, 396.0-396.9, 397.0, 424.0, 424.2, 424.3, 424.1, 440.0, 746.02, 746.09, 746.1, 746.3, 746.4, 746.5, 746.6, 746.83, 747.21, 747.31,  |
| Endocarditis | 421.0, 421.9, 424.0, 424.90, 424.99 |
| Congenital heart disease | 745.0, 745.2, 745.4, 745.5, 745.60, 745.69, 745.8, 745.9, 746.00, 746.01, 746.02, 746.09, 746.1, 746.2, 746.3, 746.4, 746.5, 746.81, 746.83, 746.89, 746.9, 747.10, 747.21, 747.22,  |
| Other non-atherosclerotic causes of structural heart diseases | 242.9, 265.0, 271.0, 277.39, 416.0, 422.90, 422.91, 422.92, 425.1, 425.4, 425.7, 429.0, 429.1, 429.71, 429.9 |

Supplementary Table 2: Baseline clinical characteristics of 1,195 Chinese with type 2 diabetes with incident heart failure with or without echocardiography

|  |  |  |  |
| --- | --- | --- | --- |
|  | Patients with echocardiography | Patients without echocardiography | p-value |
| Number | 611 | 584 |  |
| Demographics |
| Male sex, n (%) | 279 (45.7) | 244 (41.8) | 0.196 |
| Age at enrolment, years | 65.70 ± 10.41 | 69.93 ± 9.74 | <0.001 |
| Cardio-metabolic risk factors |
| Duration of diabetes, years | 9.00 [4.00, 15.00] | 10.00 [4.75, 16.00] | 0.132 |
| Smoking, n (%) |  |  | 0.558 |
| Previous | 131 (21.5) | 129 (22.2) |  |
| Current | 67 (11.0) | 53 (9.1) |  |
| BMI, kg/m2  | 26.15 ± 4.28 | 26.07 ± 4.37 | 0.760 |
| Systolic BP, mmHg | 145.42 ± 21.52 | 146.06 ± 21.93 | 0.614 |
| Diastolic BP, mmHg | 76.49 ± 11.93 | 74.62 ± 11.31 | 0.006 |
| HbA1c, %  | 8.03 ± 1.89 | 7.91 ± 1.76 | 0.259 |
| HDL cholesterol, mmol/L  | 1.28 ± 0.37 | 1.29 ± 0.37 | 0.504 |
| LDL cholesterol, mmol/L  | 3.02 ± 1.01 | 3.04 ± 1.10 | 0.756 |
| Triglyceride, mmol/L | 1.50 [1.05, 2.30] | 1.51 [1.10, 2.20] | 0.878 |
| Estimated GFR, ml/min/1.73m2  | 64.82 ± 24.46 | 58.71 ± 24.42 | <0.001 |
| Urine ACR, mg/mmol  | 13.90 [2.27, 85.94] | 14.32 [2.44, 86.39] | 0.670 |
| Diabetes-related complications, n (%) |
| Albuminuria | 417 (70.3) | 400 (72.6) | 0.432 |
| Chronic kidney disease | 257 (42.1) | 312 (53.4) | <0.001 |
| Diabetic sensory neuropathy | 183 (30.0) | 181 (31.0) | 0.743 |
| Diabetic retinopathy  | 196 (48.2) | 155 (40.9) | 0.048 |
| Coronary heart disease | 116 (19.0) | 104 (17.8) | 0.653 |
| Stroke  | 34 (5.6) | 59 (10.1) | 0.005 |
| Cancer | 24 (3.9) | 20 (3.4) | 0.758 |
| Use of medications, n (%) |
| RAAS inhibitor | 241 (39.4) | 248 (42.5) | 0.316 |
| BP lowering drugs | 444 (72.7) | 443 (75.9) | 0.233 |
| Lipid lowering drugs | 195 (31.9) | 200 (34.2) | 0.427 |
| Insulin | 185 (30.3) | 179 (30.7) | 0.939 |
| Non-insulin glucose lowering drugs | 461 (75.5) | 431 (73.8) | 0.556 |

Data are expressed as number (percentage), mean ± standard deviation, or median (inter-quartile range)

ACR, albumin-to-creatinine; BMI, body mass index; BP, blood pressure; GFR, glomerular filtration rate; HDL, high density-lipoprotein; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LDL, low density-lipoprotein; RAAS, renin-angiotensin-aldosterone system

Supplementary Table 3: Baseline clinical characteristics of 22,682 Chinese with type 2 diabetes with or without incident heart failure

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | HFrEF | HFmrEF | HFpEF | Without HF | p-value for HFrEF vs without HF\* | p-value for HFmrEF vs without HF\* | p-value for HFpEF vs without HF\* |
| Number | 147 | 93 | 371 | 22,071 |  |  |  |
| Demographics |
| Male sex (%) | 79 (53.7) | 47 (50.5) | 153 (41.2) | 11626 (52.7) | 0.861 | 0.861 | <0.001 |
| Age at enrolment, years  | 63.8 ± 11.2 | 66.8 ± 10.5 | 66.2 ± 10.0 | 58.1 ± 12.3 | <0.001 | <0.001 | <0.001 |
| Cardio-metabolic risk factors |
| Duration of diabetes, years | 8.0 [3.0, 13.0] | 10.0 [6.0, 18.0] | 9.0 [4.0, 15.0] | 5.0 [1.0, 10.0] | <0.001 | <0.001 | <0.001 |
| Smoking, n (%) |  |  |  |  | 0.184 | 0.184 | 0.184 |
| Previous | 34 (23.3) | 24 (25.8) | 73 (19.7) | 4124 (18.7) |  |  |  |
| Current | 24 (16.4) | 8 (8.6) | 35 (9.5) | 2787 (12.6) |  |  |  |
| BMI, kg/m2  | 25.4 ± 3.7 | 25.7 ± 4.7 | 26.6 ± 4.4 | 25.6 ± 4.2) | 0.757 | 0.958 | <0.001 |
| Systolic BP, mmHg | 142.1 ± 21.0 | 148.2 ± 23.3 | 146.0 ± 21.2 | 134.3 ± 19.0 | <0.001 | <0.001 | <0.001 |
| Diastolic BP, mmHg | 76.8 ± 11.5 | 77.1 ± 11.7 | 76.2 ± 12.2 | 77.1 ± 10.7 | 0.966 | 0.966 | 0.542 |
| HbA1c, % | 8.2 ± 2.1 | 7.8 ± 1.8 | 8.0 ± 1.8 | 7.5 ± 1.7 | <0.001 | 0.115 | <0.001 |
| HDL cholesterol, mmol/L | 1.25 ± 0.36 | 1.23 ± 0.39 | 1.30 ± 0.36 | 1.31 ± 0.37 | 0.0.071 | 0.071 | 0.493 |
| LDL cholesterol, mmol/L | 3.1 ± 1.0 | 3.0 ± 1.1 | 3.0 ± 1.0 | 2.8 ± 1.0 | 0.002 | 0.065 | 0.002 |
| Triglyceride, mmol/L | 1.5 [1.1, 2.2] | 1.6 [1.1, 2.6] | 1.5 [1.0, 2.3] | 1.3 [1.0, 2.0] | 0.007 | 0.002 | 0.001 |
| Estimated GFR, ml/min/1.73m2 | 68.6 ± 24.4 | 58.0 ± 26.9 | 65.1 ± 23.6 | 82.8 ± 23.0 | <0.001 | <0.001 | <0.001 |
| Urine ACR, mg/mmol  | 5.4 [1.5, 23.6] | 28.3 [8.0, 157.1] | 15.6 [2.5, 91.4] | 1.7 [0.7, 6.7] | <0.001 | <0.001 | <0.001 |
| Diabetes-related complications, n (%) |
| Albuminuria | 88 (61.5) | 73 (82.0) | 256 (70.9) | 8123 (38.0) | <0.001 | <0.001 | <0.001 |
| Chronic kidney disease  | 56 (38.1) | 51 (54.8) | 150 (40.4) | 3570 (16.2) | <0.001 | <0.001 | <0.001 |
| Diabetic sensory neuropathy | 41 (27.9) | 32 (34.4) | 110 (29.6) | 2337 (10.6) | <0.001 | <0.001 | <0.001 |
| Diabetic retinopathy | 46 (46.5) | 35 (56.5) | 115 (46.7) | 3449 (24.1) | <0.001 | <0.001 | <0.001 |
| Coronary heart disease | 29 (19.7) | 18 (19.4) | 69 (18.6) | 1962 (8.9) | <0.001 | 0.013 | <0.001 |
| Stroke | 7 (4.8) | 9 (9.7) | 18 (4.9) | 1229 (5.6) | 0.671  | 0.559  | 0.671  |
| Cancer  | 5 (3.4) | 8 (8.6) | 11 (3.0) | 982 (4.4) | 0.539  | 0.239  | 0.239  |
| Use of medications, n (%) |
| RAAS inhibitor | 52 (35.4) | 44 (47.3) | 145 (39.1) | 7288 (33.0) | 0.545  | 0.022  | 0.027  |
| BP lowering drugs  | 99 (67.3) | 73 (78.5) | 272 (73.3) | 11935 (54.1) | 0.002 | <0.001 | <0.001 |
| Lipid lowering drugs | 48 (32.7) | 31 (33.3) | 116 (31.3) | 7966 (36.1) | 0.575  | 0.575  | 0.142  |
| Insulin | 32 (21.8) | 33 (35.5) | 120 (32.3) | 3525 (16.0) | 0.056 | <0.001 | <0.001 |
| Non-insulin glucose lowering drugs | 115 (78.2) | 71 (76.3) | 275 (74.1) | 17021 (77.1) | 0.862  | 0.862  | 0.577  |

Data are expressed as number (percentage), mean ± standard deviation, or median (inter-quartile range)

ACR, albumin-to-creatinine; BMI, body mass index; BP, blood pressure; GFR, glomerular filtration rate; HDL, high density-lipoprotein; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LDL, low density-lipoprotein; RAAS, renin-angiotensin-aldosterone system

\* P-values for multiple comparisons were adjusted using the Benjamini-Hochberg method.

Supplementary Table 4: Baseline clinical characteristics of 611 Chinese men and women with type 2 diabetes with incident heart failure

|  |  |  |  |
| --- | --- | --- | --- |
|  | Women | Men | p-value |
| Number | 332 | 279 |  |
| Demographics |
| Age at enrolment, years | 66.7 ± 10.1 | 64.5 ± 10.7 | 0.012 |
| Cardio-metabolic risk factors |
| Duration of diabetes, years | 10.0 [6.0, 16.0] | 8.0 [3.0, 13.0] | <0.001 |
| Smoking, n (%) |  |  | <0.001 |
| Previous | 21 (6.3) | 110 (39.6) |  |
| Current | 11 (3.3) | 56 (20.1) |  |
| BMI, kg/m2  | 26.3 ± 4.6 | 26.0 ± 3.9 | 0.404 |
| Systolic BP, mmHg | 147.7 ± 21.6 | 142.7 ± 21.1 | 0.004 |
| Diastolic BP, mmHg | 75.7 ± 11.8 | 77.4 ± 12.0 | 0.081 |
| HbA1c, %  | 8.2 ± 1.9 | 7.8 ± 1.8 | 0.011 |
| HDL cholesterol, mmol/L  | 1.4 ± 0.4 | 1.2 ± 0.3 | <0.001 |
| LDL cholesterol, mmol/L  | 3.1 ± 1.0 | 2.9 ± 1.0 | 0.016 |
| Triglyceride, mmol/L | 1.6 [1.1, 2.4] | 1.4 [1.0, 2.2] | 0.011 |
| Estimated GFR, ml/min/1.73m2  | 63.4 ± 24.6 | 66.5 ± 24.2 | 0.125 |
| Urine ACR, mg/mmol  | 15.6 [3.0, 84.3] | 11.4 [1.6, 89.6] | 0.099 |
| Diabetes-related complications, n (%) |
| Albuminuria | 233 (72.1) | 184 (68.1) | 0.333 |
| Chronic kidney disease | 146 (44.0) | 111 (39.8) | 0.336 |
| Diabetic sensory neuropathy | 103 (31.0) | 80 (28.7) | 0.587 |
| Diabetic retinopathy  | 117 (53.4) | 79 (42.0) | 0.028 |
| Coronary heart disease | 44 (13.3) | 72 (25.8) | <0.001 |
| Stroke  | 15 (4.5) | 19 (6.8) | 0.292 |
| Cancer | 16 (4.8) | 8 (2.9) | 0.304 |
| Use of medications, n (%) |
| RAAS inhibitor | 120 (36.1) | 121 (43.4) | 0.082 |
| BP lowering drugs | 236 (71.1) | 208 (74.6) | 0.386 |
| Lipid lowering drugs | 95 (28.6) | 100 (35.8) | 0.068 |
| Insulin | 111 (33.4) | 74 (26.5) | 0.078 |
| Non-insulin glucose lowering drugs | 243 (73.2) | 218 (78.1) | 0.187 |
| HF subtypes, n (%) |  |  | 0.021 |
| HFrEF | 68 (20.5) | 79 (28.3) |  |
| HFmrEF | 46 (13.9) | 47 (16.8) |  |
| HFpEF | 218 (65.7) | 153 (54.8) |  |

Data are expressed as number (percentage), mean ± standard deviation, or median (inter-quartile range)

ACR, albumin-to-creatinine; BMI, body mass index; BP, blood pressure; GFR, glomerular filtration rate; HDL, high density-lipoprotein; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LDL, low density-lipoprotein; RAAS, renin-angiotensin-aldosterone system

Supplementary Table 5: Univariate analysis for baseline and time-varying factors associated with incident heart failure according to heart failure subtypes

|  |  |  |  |
| --- | --- | --- | --- |
|  | HFrEF *vs* without HF | HFmrEF *vs* without HF | HFpEF *vs* without HF |
|  | HR (95% CI) | p-value | HR (95% CI) | p-value | HR (95% CI) | p-value |
| Male sex | 1.21 (0.88, 1.68) | 0.248 | 1.03 (0.68, 1.54) | 0.904 | 0.73 (0.60, 0.90) | 0.004 |
| Age at enrollment | 1.06 (1.04, 1.07) | <0.001 | 1.08 (1.06, 1.10) | <0.001 | 1.08 (1.07, 1.09) | <0.001 |
| Duration of diabetes | 1.05 (1.03, 1.07) | <0.001 | 1.08 (1.06, 1.10) | <0.001 | 1.07 (1.06, 1.08) | <0.001 |
| Previous smoking | 1.70 (1.14, 2.52) | 0.009 | 1.66 (1.03, 2.66) | 0.037 | 1.22 (0.94, 1.59) | 0.127 |
| Current smoking | 1.54 (0.98, 2.41) | 0.063 | 0.73 (0.35, 1.53) | 0.405 | 0.75 (0.53, 1.07) | 0.117 |
| BMI | 1.00 (0.96, 1.04) | 0.955 | 1.01 (0.96, 1.06) | 0.671 | 1.06 (1.04, 1.08) | <0.001 |
| Systolic BP | 1.02 (1.01, 1.03) | <0.001 | 1.03 (1.02, 1.04) | <0.001 | 1.03 (1.03, 1.03) | <0.001 |
| Diastolic BP | 1.00 (0.99, 1.02) | 0.859 | 1.00 (0.98, 1.02) | 0.801 | 1.00 (0.99, 1.01) | 0.360 |
| History of diabetic retinopathy  | 3.09 (2.08, 4.60) | <0.001 | 4.50 (2.72, 7.45) | <0.001 | 3.11 (2.42, 4.00) | <0.001 |
| History of diabetic sensory neuropathy  | 2.50 (1.74, 3.60) | <0.001 | 3.60 (2.33, 5.55) | <0.001 | 2.68 (2.14, 3.35) | <0.001 |
| Use of RAAS inhibitor  | 1.71 (1.21, 2.42) | 0.002 | 2.53 (1.67, 3.85) | <0.001 | 2.03 (1.63, 2.51) | <0.001 |
| Use of BP lowering drugs  | 2.68 (1.88, 3.82) | <0.001 | 4.34 (2.62, 7.17) | <0.001 | 3.65 (2.88, 4.63) | <0.001 |
| Use of lipid lowering drugs  | 1.43 (1.00, 2.04) | 0.052 | 1.28 (0.82, 2.00) | 0.274 | 1.35 (1.07, 1.69) | 0.010 |
| HbA1C\_time varying variable | 1.05 (0.95, 1.17) | 0.325 | 1.03 (0.89, 1.18) | 0.710 | 1.02 (0.95, 1.10) | 0.531 |
| HDL cholesterol\_time varying variable | 0.51 (0.31, 0.83) | 0.007 | 0.19 (0.09, 0.38) | <0.001 | 0.77 (0.58, 1.02) | 0.072 |
| LDL cholesterol\_time varying variable | 0.81 (0.66, 0.99) | 0.039 | 0.89 (0.69, 1.13) | 0.338 | 0.78 (0.69, 0.89) | <0.001 |
| Triglyceride\_time varying variable | 1.02 (0.91, 1.14) | 0.715 | 1.04 (0.93, 1.16) | 0.475 | 1.03 (0.97, 1.10) | 0.344 |
| Estimated GFR\_time varying variable | 0.96 (0.96, 0.97) | <0.001 | 0.95 (0.95, 0.96) | <0.001 | 0.96 (0.95, 0.96) | <0.001 |
| Log urine ACR\_time varying variable | 1.48 (1.37, 1.61) | <0.001 | 1.75 (1.56, 1.96) | <0.001 | 1.69 (1.61, 1.78) | <0.001 |
| History of coronary heart disease\_time varying variable | 19.71 (14.00, 27.76) | <0.001 | 6.53 (5.29, 8.04) | <0.001 | 23.97 (15.43, 37.22) | <0.001 |
| History of stroke\_time varying variable | 3.83 (2.59, 5.67) | <0.001 | 3.58 (2.79, 4.60) | <0.001 | 3.46 (2.07, 5.80) | <0.001 |

ACR, albumin-to-creatinine; BMI, body mass index; BP, blood pressure; CI, confidence interval; GFR, glomerular filtration rate; HDL, high density-lipoprotein; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; LDL, low density-lipoprotein; RAAS, renin-angiotensin-aldosterone system

Supplementary Figure 1: Patient flow in the Hong Kong Diabetes Register

