**Table S1.** Overview of outcome classification for CAEs, according to the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms

|  |  |  |  |
| --- | --- | --- | --- |
| High Level Group Term | Preferred Term | MedDRA Code | Study Classification |
| Heart failures | Cardiac failure | 10007554 | Heart failure |
| Heart failures | Cardiac failure acute | 10007556 | Heart failure |
| Heart failures | Cardiac failure chronic | 10007558 | Heart failure |
| Heart failures | Cardiac failure congestive | 10007559 | Heart failure |
| Heart failures | Cardiogenic shock | 10007625 | Heart failure |
| Heart failures | Pulmonary oedema | 10037423 | Heart failure |
| Coronary artery disorders | Myocardial infarction | 10028596 | Myocardial Infarction |
| Coronary artery disorders | Myocardial ischaemia | 10028600 | Myocardial Infarction |
| Coronary artery disorders | Acute myocardial infarction | 10000891 | Myocardial Infarction |
| Coronary artery disorders | Acute coronary syndrome | 10051592 | Myocardial Infarction |
| Coronary artery disorders | Coronary artery occlusion | 10011086 | Myocardial Infarction |
| Coronary artery disorders | Coronary artery thrombosis | 10011091 | Myocardial Infarction |
| Coronary artery disorders | Coronary artery disease | 10011078 | Myocardial Infarction |
| Myocardial disorders | Myocardial fibrosis | 10028593 | Myocardial Infarction |
| Myocardial disorders | Ischaemic cardiomyopathy | 10048858 | Myocardial Infarction |
| Myocardial disorders | Stress cardiomyopathy | 10066286 | Myocardial Infarction |
| Myocardial disorders | Cardiomyopathy | 10007636 | Myocardial Infarction |
| Myocardial disorders | Myocarditis | 10028606 | Myocardial Infarction |
| Cardiac arrhythmias | Cardiac death | 10049993 | Cardiac arrhythmias |
| Cardiac arrhythmias | Sudden death | 10042434 | Cardiac arrhythmias |
| Cardiac arrhythmias | Sudden cardiac Death | 10049418 | Cardiac arrhythmias |
| Cardiac arrhythmias | Cardio-respiratory Arrest | 10007617 | Cardiac arrhythmias |
| Cardiac arrhythmias | Cardiac arrest | 10007515 | Cardiac arrhythmias |
| Cardiac arrhythmias | Tachycardia | 10043071 | Cardiac arrhythmias |
| Cardiac arrhythmias | Cardiac flutter | 10052840 | Cardiac arrhythmias |
| Cardiac arrhythmias | Cardiac fibrillation | 10061592 | Cardiac arrhythmias |
| Cardiac arrhythmias | Arrhythmia supraventricular | 10003130 | Cardiac arrhythmias |
| Cardiac arrhythmias | Supraventricular tachycardia | 10042604 | Cardiac arrhythmias |
| Cardiac arrhythmias | Supraventricular extrasystoles | 10042602 | Cardiac arrhythmias |
| Cardiac arrhythmias | Atrial fibrillation | 10003658 | Cardiac arrhythmias |
| Cardiac arrhythmias | Atrial flutter | 10003662 | Cardiac arrhythmias |
| Cardiac arrhythmias | Atrial tachycardia | 10003668 | Cardiac arrhythmias |
| Cardiac arrhythmias | Ventricular fibrillation | 10047290 | Cardiac arrhythmias |
| Cardiac arrhythmias | Ventricular tachycardia | 10047302 | Cardiac arrhythmias |
| Cardiac arrhythmias | Sinus tachycardia | 10040752 | Cardiac arrhythmias |
| Cardiac arrhythmias | Sinus node dysfunction | 10075889 | Cardiac arrhythmias |
| Cardiac arrhythmias | Atrioventricular block | 10003671 | Cardiac arrhythmias |
| Cardiac arrhythmias | Atrioventricular block complete | 10003673 | Cardiac arrhythmias |
| Cardiac arrhythmias | Bradycardia | 10006093 | Cardiac arrhythmias |
| Cardiac disorders, signs and symptoms NEC | Cardiac disorder | 10061024 | General |
| Cardiac disorders, signs and symptoms NEC | Cardiovascular disorder | 10007649 | General |
| Cardiac disorders, signs and symptoms NEC | Intracardiac thrombus | 10048620 | General |
| Cardiac disorders, signs and symptoms NEC | Dyspnoea | 10013968 | General |
| Cardiac disorders, signs and symptoms NEC | Dyspnoea exertional | 10013971 | General |
| Cardiac disorders, signs and symptoms NEC | Haemoptysis | 10018964 | General |
| Pericardial disorders | Pericardial effusion | 10034474 | General |
| Pericardial disorders | Pericarditis | 10034484 | General |
| Pericardial disorders | Pleuropericarditis | 10059361 | General |
| Cardiac valve disorders | Cardiac valve disease | 10061406 | General |

**Table S2.** Summary of Major Algorithms in Signal Detection

|  |  |  |
| --- | --- | --- |
| Algorithms | Equation\* | Criteria |
| ROR | ROR=(a/b)/(c/d) | 95% CI>1,  N≥2 |
| 95%CI=eln(ROR)±1.96(1/a+1/b+1/c+1/d)^0.5 |
| PRR | PRR=(a/(a+c))/(b/(b+d)) | 95% CI>1,  N≥2 |
| 95%CI=eln(PRR)±1.96(1/a-1/(a+b)+1/c-1/(c+d))^0.5 |
| BCPNN | IC=log2a(a+b+c+d)/((a+c)(a+b)) | IC025>0 |
| IC025=eln(IC)-1.96(1/a+1/b+1/c+1/d)^0.5 |
| MGPS | EBGM=a(a+b+c+d)/((a+c)(a+b)) | EBGM05>2, N>0 |
| EBGM05=eln(EBGM)-1.64(1/a+1/b+1/c+1/d)^0.5 |

\* a, number of reports containing both the suspect drug and the suspect adverse drug reaction. b, number of reports containing the suspect adverse drug reaction with other medications (except the drug of interest). c, number of reports containing the suspect drug with other adverse drug reactions (except the event of interest). d, number of reports containing other medications and other adverse drug reactions.

Abbreviations: ROR, reporting odds ratio; CI, confidence interval; N, the number of co-occurrences; PRR, proportional reporting ratio; BCPNN, Bayesian confidence propagation neural network; IC, information component; IC025, the lower limit of the 95% two-sided CI of the IC; MGPS, multi-item gamma Poisson shrinker; EBGM, empirical Bayesian geometric mean; EBGM05, the lower 90% one-sided CI of EBGM.

**Table S3.** Detected signals of SGLT2i-related CAEs by four algorithms.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Drug | N | ROR (95% CI) | PRR (95% CI) | IC (IC025) | EBGM (EBGM05) |
| SGLT2i | 2330 | 0.97, (0.93, 1.01) | 0.97, (0.94, 1.01) | -0.04, (N.A) | 0.97, (0.94) |
| Canagliflozin | 878 | 0.80, (0.74, 0.85) | 0.80, (0.75, 0.86) | -0.32, (N.A) | 0.80, (0.76) |
| Dapagliflozin | 558 | 1.05, (0.96, 1.14) | 1.05, (0.97, 1.14) | 0.07, (0.06) | 1.05, (0.98) |
| Empagliflozin | 887 | 1.20, (1.12, 1.29) | 1.19, (1.12, 1.27) | 0.25, (0.23) | 1.19, (1.12) |
| Ertugliflozin | 7 | 0.30, (0.14, 0.64) | 0.31, (0.15, 0.65) | -1.68, (N.A) | 0.31, (0.17) |

ROR, reporting odds ratio; CI, confidence interval; PRR, proportional reporting ratio; IC, information component; IC025, the lower limit of the 95% two-sided CI of the IC; EBGM, empirical Bayesian geometric mean; EBGM05, the lower 90% one-sided CI of EBGM; N.A., not available.

**Table S4.** Six most common SGLT2i-related cardiotoxicity.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| CAEs | Reports, no. (%) | ROR (95% CI) | PRR (95% CI) | IC (IC025) | EBGM (EBGM05) | |
| Myocardial infarction | 736, (31.59) | 2.82, (2.62, 3.03) | 2.79, (2.60, 3.00) | 1.47, (1.37) | 2.78, (2.61) | |
| Dyspnoea | 649, (27.85) | 0.69 (0.64, 0.74) | 0.69, (0.64, 0.75) | -0.53, (N.A.) | 0.69, (0.65) | |
| Cardiac failure | 260, (11.16) | 2.08, (1.84, 2.35) | 2.07, (1.84, 2.34) | 1.05, (0.93) | 2.07, (1.86) | |
| Tachycardia | 198, (8.50) | 1.48, (1.29, 1.71) | 1.48, (1.29, 1.70) | 0.57, (0.49) | 1.48, (1.32) | |
| Atrial fibrillation | 184, (7.90) | 1.22, (1.05, 1.41) | 1.22, (1.05, 1.40) | 0.28, (0.24) | 1.21, (1.08) | |
| Acute myocardial infarction | 121, (5.19) | 2.48, (2.07, 2.96) | 2.47, (2.07, 2.96) | 1.30, (1.09) | 2.46, (2.12) | |
| All | 2148, (92.19) |  |  |  | |  |

ROR, reporting odds ratio; CI, confidence interval; PRR, proportional reporting ratio; IC, information component; IC025, the lower limit of the 95% two-sided CI of the IC; EBGM, empirical Bayesian geometric mean; EBGM05, the lower 90% one-sided CI of EBGM; N.A., not available.