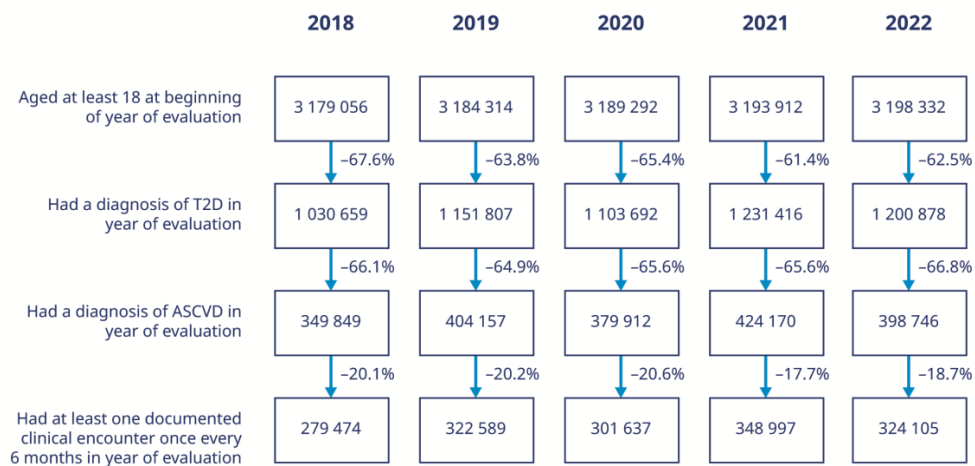


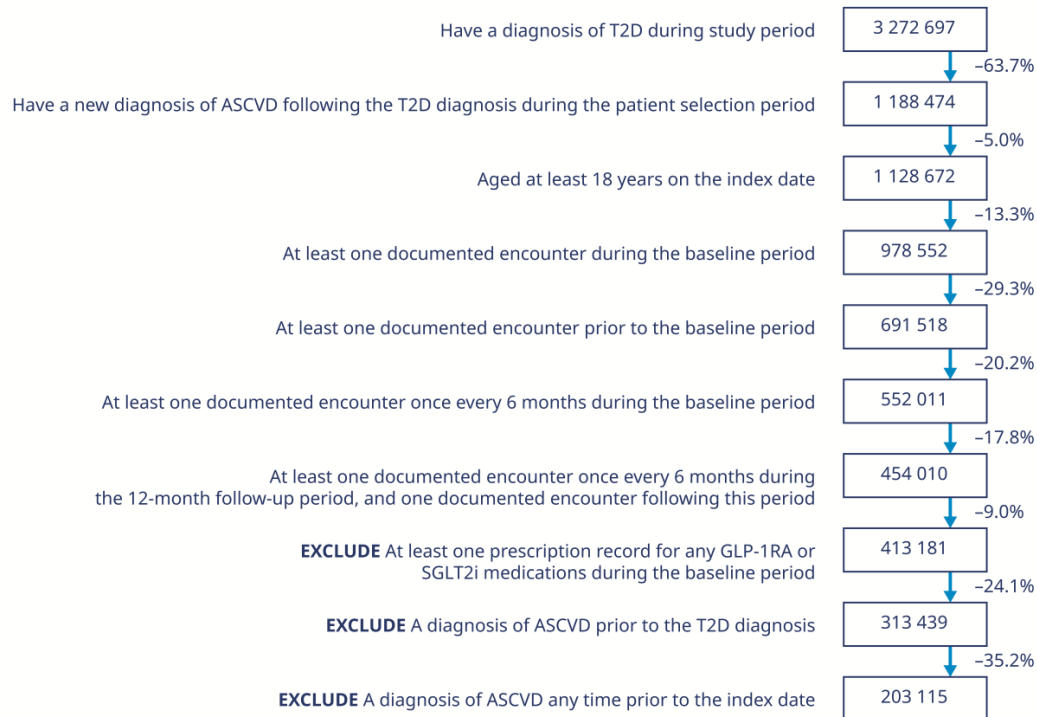
SUPPLEMENTAL MATERIAL for:**Recent trends in GLP-1 RA and SGLT-2i use among people with type 2 diabetes and atherosclerotic cardiovascular disease in the USA**

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Supplementary figure S1. Cross-sectional attrition, showing patient numbers by year meeting each inclusion criterion

ASCVD, atherosclerotic cardiovascular disease; T2D, type 2 diabetes

Supplementary figure S2. Nested cohort attrition (patient number and % reduction after applying each inclusion criterion)



%, percentage; ASCVD, atherosclerotic cardiovascular disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose co-transporter 2 inhibitor; T2D, type 2 diabetes

Supplementary table S1. Baseline demographics and clinical characteristics of nested cohort study

| | Study cohort (n=203 115) | Patients with a GLP-1 RA and/or SGLT2i prescription (n=16 635) | | Patients with GLP-1 RA prescriptions only (n=8388) | | Patients with SGLT2i prescriptions only (n=6481) | | Patients with both GLP-1 RA and SGLT2i prescriptions (n=1766) | | Patients without a GLP-1 RA and/or SGLT2i prescription (n=186 480) |
|---------------------------------------|-----------------------------|--|--------------|--|--------------|--|--------------|--|--------------|--|
| | n (%) | n (%) | ASD (%)† | n (%) | ASD (%)† | n (%) | ASD (%)† | n (%) | ASD (%)† | n (%) |
| Demographic variables at index | | | | | | | | | | |
| Mean age, years (SD) | 64.7 (13.0) | 62.2 (11.3) | 22.5* | 61.0 (11.5) | 32.0* | 64.3 (10.9) | 5.6 | 60.3 (11.0) | 38.7* | 65.0 (13.2) |
| <i>Age</i> | | | | | | | | | | |
| 18–24 | 1965 (1.0) | 47 (0.3) | 9.3 | 35 (0.4) | 7.2 | 8 (0.1) | 12.0* | 4 (0.2) | 10.2* | 1918 (1.0) |
| 25–34 | 4564 (2.2) | 230 (1.4) | 6.9 | 157 (1.9) | 3.2 | 49 (0.8) | 12.5* | 24 (1.4) | 7.2 | 4334 (2.3) |
| 35–44 | 9111 (4.5) | 911 (5.5) | 5.0 | 527 (6.3) | 8.4 | 252 (3.9) | 2.6 | 132 (7.5) | 13.0* | 8200 (4.4) |
| 45–54 | 22 826 (11.2) | 2674 (16.1) | 15.4* | 1507 (18.0) | 20.4* | 839 (12.9) | 6.6 | 328 (18.6) | 22.1* | 20 152 (10.8) |
| 55–64 | 49 183 (24.2) | 5249 (31.6) | 17.9* | 2736 (32.6) | 20.2* | 1906 (29.4) | 13.3* | 607 (34.4) | 24.1* | 43 934 (23.6) |
| 65+ | 115 466 (56.8) | 7524 (45.2) | 25.5* | 3426 (40.8) | 34.6* | 3427 (52.9) | 10.1* | 671 (38.0) | 40.6* | 107 942 (57.9) |
| <i>Sex</i> | | | | | | | | | | |
| Missing | 10 (0.0) | 2 (0.0) | - | 1 (0.0) | - | - | - | 1 (0.1) | - | 8 (0.0) |
| Female | 108 479 (53.4) | 8357 (50.2) | 6.9 | 4751 (56.6) | 5.9 | 2745 (42.4) | 22.8* | 861 (48.8) | 9.9 | 100 122 |
| Male | 94 626 (46.6) | 8276 (49.8) | 6.9 | 3636 (43.3) | 5.9 | 3736 (57.6) | 22.8* | 904 (51.2) | 9.8 | 86 350 (46.3) |
| <i>Race</i> | | | | | | | | | | |
| Black | 37 946 (18.7) | 3134 (18.8) | 0.4 | 1641 (19.6) | 2.3 | 1187 (18.3) | 0.9 | 306 (17.3) | 3.5 | 34 812 (18.7) |
| Other | 6128 (3.0) | 489 (2.9) | 0.5 | 211 (2.5) | 3.1 | 222 (3.4) | 2.3 | 56 (3.2) | 0.8 | 5639 (3.0) |
| Unknown | 21 229 (10.5) | 1810 (10.9) | 1.5 | 863 (10.3) | 0.4 | 738 (11.4) | 3.1 | 209 (11.8) | 4.5 | 19 419 (10.4) |
| White | 137 812 (67.8) | 11 202 (67.3) | 1.2 | 5673 (67.6) | 0.6 | 4334 (66.9) | 2.2 | 1195 (67.7) | 0.5 | 126 610 (67.9) |
| <i>Ethnicity</i> | | | | | | | | | | |
| Hispanic | 17 182 (8.5) | 1495 (9.0) | 2.0 | 735 (8.8) | 1.3 | 599 (9.2) | 2.9 | 161 (9.1) | 2.5 | 15 687 (8.4) |
| Not Hispanic | 149 592 (73.6) | 12 085 (72.6) | 2.5 | 6164 (73.5) | 0.6 | 4684 (72.3) | 3.3 | 1237 (70.0) | 8.2 | 137 507 (73.7) |
| Unknown | 36 341 (17.9) | 3055 (18.4) | 1.3 | 1489 (17.8) | 0.3 | 1198 (18.5) | 1.6 | 368 (20.8) | 7.6 | 33 286 (17.8) |

| | | | | | | | | | | |
|--|---------------|-------------|--------------|-------------|--------------|-------------|--------------|------------|--------------|---------------|
| <i>US region</i> | | | | | | | | | | |
| Midwest | 31 784 (15.6) | 2048 (12.3) | 10.4* | 1148 (13.7) | 6.4 | 736 (11.4) | 13.4* | 164 (9.3) | 20.2* | 29 736 (15.9) |
| Northeast | 59 273 (29.2) | 5764 (34.6) | 12.8* | 2906 (34.6) | 12.8* | 2215 (34.2) | 11.8* | 643 (36.4) | 16.5* | 53 509 (28.7) |
| South | 90 171 (44.4) | 6916 (41.6) | 6.2 | 3476 (41.4) | 6.5 | 2696 (41.6) | 6.2 | 744 (42.1) | 5.1 | 83 255 (44.6) |
| West | 19 622 (9.7) | 1857 (11.2) | 5.4 | 833 (9.9) | 1.4 | 814 (12.6) | 9.7 | 210 (11.9) | 7.7 | 17 765 (9.5) |
| Unknown | 2265 (1.1) | 50 (0.3) | 10.3* | 25 (0.3) | 10.4* | 20 (0.3) | 10.2* | 5 (0.3) | 10.6* | 2215 (1.2) |
| <i>Year of index</i> | | | | | | | | | | |
| 2018 | 53 214 (26.2) | 3148 (18.9) | 18.9* | 1923 (22.9) | 9.1 | 963 (14.9) | 29.8* | 262 (14.8) | 29.9* | 50 066 (26.8) |
| 2019 | 60 838 (30.0) | 4006 (24.1) | 14.4* | 2134 (25.4) | 11.2* | 1456 (22.5) | 18.2* | 416 (23.6) | 15.6* | 56 832 (30.5) |
| 2020 | 44 204 (21.8) | 3965 (23.8) | 5.4 | 1890 (22.5) | 2.3 | 1631 (25.2) | 8.5 | 444 (25.1) | 8.4 | 40 239 (21.6) |
| 2021 | 43 727 (21.5) | 5323 (32.0) | 26.1* | 2353 (28.1) | 17.4* | 2352 (36.3) | 35.3* | 618 (35.0) | 32.6* | 38 404 (20.6) |
| 2022 | 1132 (0.6) | 193 (1.2) | 7.2 | 88 (1.0) | 6.2 | 79 (1.2) | 7.7 | 26 (1.5) | 9.8 | 939 (0.5) |
| Comorbid and clinical measures | | | | | | | | | | |
| <i>DCSI</i> | | | | | | | | | | |
| 0 | 94 067 (46.3) | 7712 (46.4) | 0.1 | 3705 (44.2) | 4.3 | 3119 (48.1) | 3.6 | 888 (50.3) | 8.0 | 86 355 (46.3) |
| 1 | 23 548 (11.6) | 2447 (14.7) | 10.1* | 1303 (15.5) | 12.4* | 854 (13.2) | 5.7 | 290 (16.4) | 14.8* | 21 101 (11.3) |
| 2 | 44 313 (21.8) | 3106 (18.7) | 8.5 | 1504 (17.9) | 10.4* | 1308 (20.2) | 4.7 | 294 (16.6) | 13.8* | 41 207 (22.1) |
| 3 | 14 786 (7.3) | 1359 (8.2) | 3.6 | 757 (9.0) | 6.7 | 474 (7.3) | 0.4 | 128 (7.2) | 0.2 | 13 427 (7.2) |
| 4 | 14 651 (7.2) | 1053 (6.3) | 3.8 | 558 (6.7) | 2.5 | 406 (6.3) | 4.1 | 89 (5.0) | 9.4 | 13 598 (7.3) |
| ≥5 | 11 750 (5.8) | 958 (5.8) | 0.1 | 561 (6.7) | 3.7 | 320 (4.9) | 3.8 | 77 (4.4) | 6.5 | 10 792 (5.8) |
| Mean Charlson Comorbidity Index, n (SD) | 1.9 (1.6) | 1.8 (1.4) | 6.6 | 1.9 (1.5) | 0.4 | 1.7 (1.3) | 14.1* | 1.7 (1.4) | 13.6* | 1.9 (1.6) |
| Mean number of antidiabetic medications, n (SD) | 0.9 (1.1) | 1.5 (1.3) | 48.5* | 1.5 (1.3) | 53.7* | 1.4 (1.3) | 42.8* | 1.4 (1.3) | 44.7* | 0.9 (1.1) |
| Mean number of antidiabetic drug classes, n (SD) | 0.9 (1.1) | 1.4 (1.3) | 48.6* | 1.5 (1.3) | 54.0* | 1.4 (1.2) | 42.8* | 1.4 (1.3) | 44.5* | 0.9 (1.1) |
| <i>Number of antidiabetic drug classes</i> | | | | | | | | | | |
| 0 | 98 529 (48.5) | 5051 (30.4) | 41.1* | 2405 (28.7) | 45.0* | 2034 (31.4) | 38.9* | 612 (34.7) | 31.7* | 93 478 (50.1) |
| 1 | 47 931 (23.6) | 3888 (23.4) | 0.6 | 1896 (22.6) | 2.4 | 1643 (25.4) | 4.0 | 349 (19.8) | 9.4 | 44 043 (23.6) |
| 2 | 36 505 (18.0) | 4109 (24.7) | 18.1* | 2102 (25.1) | 18.9* | 1588 (24.5) | 17.6* | 419 (23.7) | 15.8* | 32 396 (17.4) |
| ≥3 | 20 150 (9.9) | 3587 (21.6) | 35.9* | 1985 (23.7) | 40.9* | 1216 (18.8) | 28.9* | 386 (21.9) | 36.6* | 16 563 (8.9) |
| <i>Antidiabetic drug classes</i> | | | | | | | | | | |
| AGIs | 221 (0.1) | 23 (0.1) | 0.9 | 14 (0.2) | 1.6 | 7 (0.1) | 0.1 | 2 (0.1) | 0.2 | 198 (0.1) |
| Basal insulin | 33 238 (16.4) | 4638 (27.9) | 30.8* | 2738 (32.6) | 41.4* | 1403 (21.6) | 16.3* | 497 (28.1) | 31.4* | 28 600 (15.3) |
| Other insulin | 50 890 (25.1) | 5310 (31.9) | 16.7* | 3003 (35.8) | 25.0* | 1747 (27.0) | 5.8 | 560 (31.7) | 16.2* | 45 580 (24.4) |
| Biguanides | 60 653 (29.9) | 7532 (45.3) | 35.3* | 3739 (44.6) | 33.9* | 3035 (46.8) | 38.6* | 758 (42.9) | 30.5* | 53 121 (28.5) |
| Meglitinides | 953 (0.5) | 117 (0.7) | 3.4 | 51 (0.6) | 2.2 | 51 (0.8) | 4.3 | 15 (0.8) | 5.0 | 836 (0.4) |
| SGLT2i | 0 (0.0) | 0 (0.0) | - | 0 (0.0) | - | 0 (0.0) | - | 0 (0.0) | - | 0 (0.0) |
| Sulfonylureas | 24 317 (12.0) | 3555 (21.4) | 28.0* | 1721 (20.5) | 25.9* | 1478 (22.8) | 31.5* | 356 (20.2) | 25.0* | 20 762 (11.1) |
| Thiazolidinediones | 3889 (1.9) | 606 (3.6) | 11.6* | 293 (3.5) | 10.8* | 254 (3.9) | 13.0* | 59 (3.3) | 10.0 | 3283 (1.8) |
| DPP4i | 13 095 (6.4) | 2236 (13.4) | 26.0* | 1102 (13.1) | 25.2* | 893 (13.8) | 27.0* | 241 (13.6) | 26.6* | 10 859 (5.8) |

| | | | | | | | | | | |
|--|----------------|---------------|--------------|-------------|--------------|-------------|--------------|-------------|--------------|----------------|
| Mean number of ASCVD-related medications, n (SD) | 1.5 (1.2) | 1.7 (1.2) | 10.2* | 1.7 (1.2) | 11.1* | 1.7 (1.2) | 13.2* | 1.5 (1.2) | 5.1 | 1.5 (1.2) |
| <i>Number of ASCVD-related medications</i> | | | | | | | | | | |
| 0 | 55 690 (27.4) | 3747 (22.5) | 12.3* | 1818 (21.7) | 14.4* | 1424 (22.0) | 13.6* | 505 (28.6) | 1.6 | 51 943 (27.9) |
| 1 | 42 842 (21.1) | 3542 (21.3) | 0.5 | 1834 (21.9) | 1.9 | 1316 (20.3) | 1.9 | 392 (22.2) | 2.7 | 39 300 (21.1) |
| 2 | 55 809 (27.5) | 5101 (30.7) | 7.7 | 2610 (31.1) | 8.6 | 2001 (30.9) | 8.1 | 490 (27.7) | 1.2 | 50 708 (27.2) |
| ≥3 | 48 774 (24.0) | 4245 (25.5) | 3.8 | 2126 (25.3) | 3.4 | 1740 (26.8) | 6.8 | 379 (21.5) | 5.8 | 44 529 (23.9) |
| <i>Type of ASCVD-related medications, n (%)</i> | | | | | | | | | | |
| Antihypertensive agents | 127 421 (62.7) | 11 313 (68.0) | 12.1* | 5737 (68.4) | 12.9* | 4484 (69.2) | 14.6* | 1092 (61.8) | 0.9 | 116 108 (62.3) |
| Antiplatelets | | 3997 (24.0) | 0.8 | 2033 (24.2) | 1.3 | 1607 (24.8) | 2.6 | 357 (20.2) | 8.4 | |
| Antihyperlipidemic agents | 48 180 (23.7) | 9050 (54.4) | 18.5* | 4569 (54.5) | 18.6* | 3626 (55.9) | 21.6* | 855 (48.4) | 6.4 | 44 183 (23.7) |
| Anticoagulants | 93 348 (46.0) | 3242 (19.5) | 6.9 | 1669 (19.9) | 5.9 | 1277 (19.7) | 6.4 | 296 (16.8) | 14.0* | 84 298 (45.2) |
| | 44 840 (22.1) | | | | | | | | | 41 598 (22.3) |
| <i>Type of ASCVD at index date</i> | | | | | | | | | | |
| Ischemic stroke | 31 412 (15.5) | 2342 (14.1) | 4.2 | 1310 (15.6) | 0.1 | 743 (11.5) | 12.1* | 289 (16.4) | 2.1 | 29 070 (15.6) |
| Transient ischemic attack | 13 419 (6.6) | 1191 (7.2) | 2.4 | 676 (8.1) | 5.8 | 377 (5.8) | 3.1 | 138 (7.8) | 4.9 | 12 228 (6.6) |
| Other atherosclerotic CBVD | 21 444 (10.6) | 1405 (8.4) | 7.8 | 686 (8.2) | 8.8 | 571 (8.8) | 6.5 | 148 (8.4) | 8.0 | 20 039 (10.7) |
| Myocardial infarction | 17 297 (8.5) | 1673 (10.1) | 5.8 | 696 (8.3) | 0.3 | 756 (11.7) | 11.0* | 221 (12.5) | 13.6* | 15 624 (8.4) |
| Other coronary heart disease | 93 012 (45.8) | 8713 (52.4) | 14.4* | 4063 (48.4) | 6.5 | 3699 (57.1) | 23.9* | 951 (53.9) | 17.4* | 84 299 (45.2) |
| Peripheral artery disease | 60 266 (29.7) | 4493 (27.0) | 6.4 | 2556 (30.5) | 1.2 | 1447 (22.3) | 22.3* | 490 (27.7) | 4.8 | 55 773 (29.9) |
| ASCVD related procedures | 3785 (1.9) | 423 (2.5) | 5.1 | 145 (1.7) | 0.6 | 227 (3.5) | 3.5 | 51 (2.9) | 7.2 | 3362 (1.8) |
| <i>Comorbidities associated with T2D</i> | | | | | | | | | | |
| Cardiovascular disease‡ | 48 259 (23.8) | 3491 (21.0) | 7.2 | 1641 (19.6) | 10.8* | 1540 (23.8) | 0.6 | 310 (17.6) | 16.0* | 44 768 (24.0) |
| Cerebrovascular disease§ | 948 (0.5) | 50 (0.3) | 2.9 | 20 (0.2) | 4.1 | 20 (0.3) | 2.8 | 10 (0.6) | 1.2 | 898 (0.5) |
| Metabolic disease¶ | 35 146 (17.3) | 3787 (22.8) | 15.0* | 2047 (24.4) | 18.8* | 1343 (20.7) | 10.0 | 397 (22.5) | 14.3* | 31 359 (16.8) |
| Nephropathy | 51 215 (25.2) | 3848 (23.1) | 5.3 | 2130 (25.4) | 0.0 | 1361 (21.0) | 10.4* | 357 (20.2) | 12.4* | 47 367 (25.4) |
| Neuropathy | 43 258 (21.3) | 4223 (25.4) | 10.6* | 2376 (28.3) | 17.2* | 1408 (21.7) | 1.9 | 439 (24.9) | 9.4 | 39 035 (20.9) |
| Peripheral vascular disease¶¶ | 18 083 (8.9) | 1720 (10.3) | 5.3 | 984 (11.7) | 9.8 | 574 (8.9) | 0.3 | 162 (9.2) | 1.4 | 16 363 (8.8) |
| Retinopathy | 22 974 (11.3) | 2051 (12.3) | 3.4 | 1112 (13.3) | 6.2 | 727 (11.2) | 0.0 | 212 (12.0) | 2.4 | 20 923 (11.2) |
| Anxiety | 41 781 (20.6) | 2932 (17.6) | 8.1 | 1704 (20.3) | 1.3 | 939 (14.5) | 16.7* | 289 (16.4) | 11.5* | 38 849 (20.8) |
| Cancer | 32 578 (16.0) | 2034 (12.2) | 11.9* | 997 (11.9) | 12.9* | 861 (13.3) | 8.7 | 176 (10.0) | 19.0* | 30 544 (16.4) |
| Depression | 40 373 (19.9) | 3091 (18.6) | 3.6 | 1807 (21.5) | 3.8 | 974 (15.0) | 13.1* | 310 (17.6) | 6.2 | 37 282 (20.0) |
| Dyslipidemia | 115 530 (56.9) | 10 136 (60.9) | 9.0 | 5109 (60.9) | 8.9 | 3976 (61.3) | 9.8 | 1051 (59.5) | 6.1 | 105 394 (56.5) |
| Heart failure | 20 107 (9.9) | 11 890 (71.5) | 2.0 | 6092 (72.6) | 4.6 | 4574 (70.6) | 0.1 | 1224 (69.3) | 2.7 | 18 321 (9.8) |
| Hypertension | 143 449 (70.6) | 1051 (6.3) | 8.4 | 554 (6.6) | 9.5 | 380 (5.9) | 6.5 | 117 (6.6) | 9.6 | 131 559 (70.5) |
| NASH/NAFLD | 9318 (4.6) | | | | | | | | | 8267 (4.4) |

Data are presented as n (%) unless otherwise stated. The baseline period was defined as the 12 months preceding (but not including) the index date (the date of the first code used to fulfill the ASCVD diagnosis criteria). Patients were defined as having a comorbidity if they have at least one record of the diagnosis code of the comorbidity of interest in any clinical setting during the baseline period.

*ASD $\geq 10\%$ was considered a meaningful difference. †Standardized difference is the difference between the 'Patients with a GLP-1 RA and/or SGLT2i prescription' and 'Patients without a GLP-1 RA and/or SGLT2i prescription'. ‡Cardiovascular disease includes certain diagnoses that are not included in the ASCVD definition: cardiac arrest, paroxysmal tachycardia, atrial fibrillation and flutter, other cardiac arrhythmias, heart failure, aneurysm of heart, coronary artery aneurysm and dissection, aortic aneurysm and dissection. Cardiovascular disease excludes old myocardial infarction, which is included in the ASCVD definition. §Cerebrovascular disease includes certain diagnoses that are not included in the ASCVD definition: nontraumatic intracerebral hemorrhage, cerebral infarction due to embolism of precerebral artery, cerebral infarction due to embolism of cerebral arteries, cerebral infarction due to cerebral venous thrombosis. ¶Metabolic disease includes metabolic complications of diabetes: hyperosmolarity, ketoacidosis, and hypoglycemia with/without coma. ¶¶ Peripheral vascular disease includes certain diagnoses that are not included in the ASCVD definition: diabetes (type 1/type 2/drug or chemical-induced/underlying condition/other) with circulatory complications, diabetes (type 1/type 2/drug or chemical-induced/underlying condition/other) with foot ulcer, aneurysm of artery of lower extremity, gangrene, non-pressure chronic ulcer of lower limb, open wound of foot.

AGI, alpha-glucosidase inhibitor; ASCVD, atherosclerotic cardiovascular disease; ASD, absolute standardized difference; CBVD, cerebrovascular disease; DCSI, Diabetes Complications Severity Index; DPP4i, dipeptidyl peptidase 4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; SD, standard deviation; SGLT2i, sodium-glucose co-transporter 2 inhibitor; T2D, type 2 diabetes