**Supplementary Table 1.** DISCOVER inclusion and exclusion criteria.

|  |
| --- |
| Inclusion criteria |
| * Diagnosis of type 2 diabetes
* Aged ≥18 yearsa
* Initiating a second-line therapy (add-on or switching) after a first-line oral treatment with monotherapy, dual therapy, or triple therapyb
* Provision of written informed consent
 |
| Exclusion criteria |
| * Type 1 diabetes
* Pregnancy
* Initiation of dual therapy after having previously received two different lines of monotherapy (e.g. initiation of a combination of a sulphonylurea and a DPP-4 inhibitor after successive metformin monotherapy and sulphonylurea monotherapy)
* Current treatment with chemotherapy or oral or intravenous steroids
* Undergoing dialysis or has had a renal transplant
* First-line treatment was insulin or another injectable agentc
* First-line treatment was herbal remedies/natural medicines alone
* Participation in an interventional trial
* Condition or circumstance which, in the opinion of the investigator, could significantly compromise the 3-year follow-up (e.g. life-threatening comorbidities, tourist, non-native speaker or does not understand the local language when interpreter services are not reliably available, psychiatric disturbances, dementia, alcohol or drug abuse)
* Not willing to sign the informed consent form
 |

a≥20 years for Japan.
bFor Japan, only patients using an oral monotherapy as first-line treatment were included.
cPatients who received short-term initial treatment with insulin followed by oral therapy were eligible if the treatment with insulin lasted no more than 2 weeks and occurred at least 6 months before initiation of second-line therapy. In such cases, insulin was considered not as a first-line treatment, but as an acute treatment to lower glycemic levels quickly before starting regular treatment.
DDP-4, dipeptidyl peptidase-4.

**Supplementary Table 2.** Main inclusion and exclusion criteria for CANVAS, DECLARE-TIMI 58, EMPA‑REG OUTCOME, and VERTIS‑CV.

| **Criterion** | **CANVAS** | **DECLARE‑TIMI 58** | **EMPA‑REG OUTCOME** | **VERTIS‑CV** |
| --- | --- | --- | --- | --- |
| **All patients** |
| HbA1c, % | 7.0 to 10.5 | 6.5 to 12.0 | 7.0 to 10.0 | 7.0 to 10.5 |
| CKD history | Patients with eGFR <30 mL/min/1.73 m2 or a diagnosis code for CKD were excluded | Patients with eGFR <60 mL/min/1.73 m2 or a diagnosis code for CKD were excluded | Patients with eGFR <30 mL/min/1.73 m2 or a diagnosis code for CKD were excluded | No exclusion criterion |
| BMI, kg/m2 | No criterion | ≥18.0 |
| **Patients with** **CV risk factors but no established CVD** |
| Age, years | ≥50 | >55 (men), >60 (women) | NAa | NAa |
| CV risk factors | At least **two** of the following risk factors:* hypertension (SBP >140 mmHg) and/or on antihypertensive therapy
* dyslipidemia (LDL-C ≥154 mg/dL and/or HDL-C ≤39 mg/dL) and/or on lipid-lowering drug
* duration of diabetes ≥10 years
* tobacco use (≥0.5 packet per day)
 | At least **one** of the following risk factors:* dyslipidemia (LDL-C >130 mg/dL within the last 12 months and/or on lipid-lowering therapy)
* hypertension (BP >140/90 mmHg) and/or on antihypertensive therapy
* tobacco use (≥5 cigarettes per day for at least 1 year)
 | NAa | NAa |
| **Patients with established CVD** |
| Age, years | ≥30 | ≥40 | ≥18 | ≥40 |
| CV history | History of at least **one** of the following:* ACS (treated in hospital)
* angina
* CABG
* CHD
* HF
* ischemic stroke
* MI
* PCI
 | History of at least **one** of the following:* ankle/brachial index <0.90 documented within last 12 months
* CABG
* carotid stenting or endarterectomy
* current symptoms of intermittent claudication
* ischemic stroke
* lower extremity amputation because of peripheral arterial obstructive disease
* MI
* objective stenosis (>50%) in at least two coronary arteries
* PCI
* peripheral arterial stenting or surgical revascularization
 | History of at least **one** of the following:* angina
* CABG
* CAD
* ischemic or hemorrhagic stroke
* MI
* objective stenosis (>50%) in at least two coronary arteries
* occlusive PAD (limb angioplasty stenting or bypass surgery, limb or foot amputation due to circulatory insufficiency, evidence of significant peripheral artery stenosis)
* PCI
 | History of at least **one** of the following:* angina
* CABG
* CAD
* ischemic stroke
* MI
* PAD
* PCI
 |

aNo patients without established CVD in EMPA‑REG OUTCOME and VERTIS‑CV.
ACS, acute coronary syndrome; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHD, coronary heart disease; CKD, chronic kidney disease; CV, cardiovascular; CVD; cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NA, not applicable; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SBP, systolic blood pressure.

**Supplementary Table 3.** Baseline characteristics of DISCOVER patients included in the analysis, and patients participating in DECLARE‑TIMI 58, CANVAS, EMPA‑REG OUTCOME, and VERTIS‑CV trials.

|  | **DISCOVERN=11 385** | **CANVASN=10 142** | **DECLARE-TIMI 58N=17 160** | **EMPA‑REG OUTCOMEN=7034** | **VERTIS‑CVN=8237** |
| --- | --- | --- | --- | --- | --- |
| Men, % | 56.1 | 64.2 | 62.6 | 71.5 | 70.0 |
| Region, % |  |  |  |  |  |
| North America | 1.9 | 24.0 | 31.9 | 41.0a | Not reported |
| Latin America | 10.2 | 10.1 | 10.9 | 15.4 | Not reported |
| Asia-Pacific | 45.7 | 30.3 | 12.7 | 19.1 | Not reported |
| Europe | 19.1 | 35.6 | 44.5 | 20.0 | Not reported |
| Middle East and Africa | 23.0 | 0.0 | 0.0 | 4.4 | Not reported |
| Age, mean (SD), years | 57.4 (12.1) | 63.3 (8.3) | 63.8 (6.8) | 63.1 (8.6) | 64.4 (8.1) |
| HbA1c, mean (SD)  | 8.3 (1.7) | 8.2 (0.9) | 8.3 (1.2) | 8.1 (0.8) | 8.3 (0.9) |
| BMI, mean (SD), kg/m2 | 29.1 (5.9) | 32.0 (5.9) | 32.1 (6.0) | 30.6 (5.3) | 32.0 (5.4) |
| Time since T2D diagnosis, mean (SD), years | 5.6 (5.2) | 13.5 (7.8) | 11.8 (7.8) | NA | 12.9 (8.3) |
| Current smoker, % | 15.8 | 17.8 | 14.5 | 13.2 | Not reported |
| History of CVD, % | 14.4b | 64.8 | 40.6 | 99.2c | 99.0 |
| Use of antihypertensive drugs, % | 50.5 | 79.8 | 89.4 | 94.4 | Not reported |

aAlso includes patients from Australia and New Zealand.
bProportion of patients for whom macrovascular complications (coronary heart disease, cerebrovascular disease, peripheral artery disease, heart failure, or implantable cardioverter defibrillator use) were marked as present by the investigator.
cProportion of patients with a history of myocardial infarction, single-vessel coronary artery disease, multi-vessel coronary artery disease, coronary artery bypass graft, stroke, or peripheral occlusive arterial disease.
BMI, body mass index; CVD, cardiovascular disease; HbA1c, glycated hemoglobin; SD standard deviation; T2D, type 2 diabetes.

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**Supplementary Figure 1.** Estimated proportions of DISCOVER patients who would have been eligible for CANVAS, DECLARE-TIMI 58, EMPA‑REG OUTCOME, and VERTIS‑CV in countries in which some data were extracted from existing databases, compared with all other countries.
CV, cardiovascular; CVD, cardiovascular disease; eCRF, electronic case report form.