Online Table 1: Characteristics of included reviews and meta-analysis in section 1

Author (date) & research design	Aim	n of primary studies (n participants)	In-/exclusion criteria	Intervention (s) or mechanisms	Key outcome	Quality assess-ment score (OQAQ)
Abd El Aziz MS 2016 [1] Systematic review and meta-analysis	To study differences in clinical outcomes between initiating glucagon-like peptide-1 receptor agonist vs insulin treatment in T2DM patients treated with oral glucose-lowering medications.	19 RCTs (8,854)	Inclusion criteria: Studies were randomized, prospective clinical trials with a head-to-head comparison of (1) a GLP-1 RA vs long-acting or pre-mixed insulin in type 2 diabetic patients on a background treatment of oral glucose- lowering medications or (2) a GLP-1 RA vs rapid-acting insulin on a background treatment of basal insulin with or without concomitant oral glucose-lowering medications. Further inclusion criteria were a minimum duration of 12 weeks, 25 or more patients per treatment arm and report of adverse events.	GLP-1 RA	GLP-1 RA reduced weight, systolic BP, TG, and LDL-c better than insulin.	15
Baker WL (2017) [2]Systematic review and meta-analysis	To determine the magnitude of the effect SGLT2i exert on 24-hour ambulatory BP.	6 RCTs (2,098)	Inclusion criteria: (1) RCT in humans; (2) evaluated a SGLT2 inhibitor compared with either placebo or an active control; and (3) reported data on changes in 24-hour ambulatory BP from	SGLT2i	SGLT2i significantly reduce 24-hour ambulatory systolic and diastolic blood pressure.	17

			baseline in a form suitable for pooling.			
Brunstrom M (2016) [3] Systematic review and meta-analysis	To assess the effect of antihypertensive treatment on mortality and cardiovascular morbidity in people with diabetes mellitus, at different BP levels.	49 RCTs (73,738)	Inclusion criteria: randomized controlled trials with a minimum of 100 adult diabetic patients, and a mean follow-up of at least 12 months.	antihypertensive treatment	Antihypertensive treatment in T2DM patients reduced the risk of all-cause mortality, myocardial infarction, and heart failure if baseline systolic BP was 140-150 mm Hg, but increased the risk of cardiovascular mortality if baseline systolic BP was less than 140 mm Hg.	18
Bundhun PK (2017) [4] Systematic review and meta-analysis	To compare the long-term mortality following coronary artery bypass surgery in patients with and without T2DM.	11 RCTs (12,965)	Inclusion criteria: (1) Were RCTs or observational studies comparing the adverse clinical outcomes following CABG in patients with and without T2DM. (2) Reported mortality among their clinical endpoints. (3) Had a follow-up period of 1 or more years. Exclusion criteria: (1) were meta-analyses, case studies, or letters to editors. (2) Had a shorter follow-up period (<1 year). (3) Did not report mortality among their clinical endpoints. (4) Involved patients who were revascularized by CABG without the inclusion of a control group.(5) Were duplicate studies.	coronary artery bypass surgery	Long-term mortality significantly higher in T2DM patients following coronary artery bypass surgery.	15
Chou CY (2017) [5] Systematic review and	To evaluate the effects of long-term incretin-based therapies on ischemic diseases.	40 RCTs (70,162)	Inclusion criteria: (1) randomized control trials (RCTs), (2) intervention compared DPP-4 inhibitors or GLP-1 agonist	DPP-4i and GLP-1 RA	Long-term incretin-based therapies associated with a lower risk of myocardial infarction in comparison to sulfonylurea-based	18

meta-analysis			against placebo or other antidiabetic agents, (3) adults participants with type 2 diabetes, (4) at least 52 weeks follow-up, (5) Reported the events of coronary artery disease, myocardial infarction or angina in the original articles or on the ClinicalTrials.gov. Exclusion criteria: (1) duplicate reports; (2) Studies have not yet been terminated; (3) observational studies; (4) background treatment was the same as the one arm of studies.		therapy.	
Fang HJ (2016) [6] Systematic review and meta-analysis	To evaluate the benefits and harms of intensive glucose lowering therapy in treatment of T2DM patients on major cardiovascular outcomes.	13 RCTs (58,160)	Inclusion criteria: (1) RCT design; (2) compared the effect of intensive glucose lowering therapy with conventional glucose control; (3) patients with T2DM; and (4) reported at least one of the following outcomes: MACEs, total mortality, cardiac death, MI, stroke, and congestive heart failure.	Intensive glucose lowering therapy	Intensive glucose lowering therapy significantly reduced risk of CV events and myocardial infarction compared with conventional glucose control therapy without influencing the incidence of all-cause mortality.	17
Gargiulo P (2017) [7] Systematic review and meta-analysis	To assess, in a meta-analysis, the effects of Glucagon-like peptide-1 agonists on mortality, major nonfatal cardiovascular (CV) events, renal and retinal events.	77 RCTs (60,434)	Inclusion criteria: randomized allocation to GLP-1 agonists vs. placebo or other glucose-lowering drugs; enrolment of more than 200 patients; assess at least one of following major outcomes: all-cause death, CV death, MI, stroke, HF.	GLP-1 RA	Compared to control, treatment with GLP-1 RA significantly reduced the risk of all-cause and CV mortality but had no effect on the risk of myocardial infarction, stroke, heart failure, retinopathy and nephropathy.	17

Johnston R (2017) [8] Systematic review and network meta-analysis	To review the clinical effectiveness and cost-effectiveness of dapagliflozin, canagliflozin and empagliflozin, in monotherapy in people who cannot take metformin.	7 RCTs (2,674)	Inclusion criteria: RCTs with a minimum duration of 24 weeks and Observational studies, people with type 2 diabetes on diet and exercise therapy only or in people on monotherapy with a glucose-lowering agent after a washout period. trials had to investigate canagliflozin (100 mg or 300 mg), dapagliflozin (10 mg) or Empagliflozin (10 mg or 25 mg). Eligible comparators were repaglinide, gliclazide as representative of the sulfonylureas, pioglitazone, DPP-4 inhibitors (the gliptins) or placebo. Studies were eligible if they investigated at least one of the following outcomes: mortality, complications of diabetes, including cardiovascular, renal and eye, HbA1c/glycaemic control, body mass index, frequency and severity of hypoglycaemia, changes in cardiovascular risk factors, AEs of treatment, including UTIs, genital infections and malignancies, health-related QoL.	SGLT2i (Canagliflo-zin, dapa-gliflozin, and empagliflozin) mono-therapy	All three SGLT2i were shown to be effective in improving glycemic control, promoting weight loss and lowering blood pressure.	18
Li J (2016) [9] Meta-analysis	To evaluate the effects of insulin versus oral hypoglycemic agents on	3 RCTs (15,971)	Inclusion criteria: RCTs that assessed all-cause mortality and cardiovascular outcomes of	Insulin	Insulin reduced the risk of heart failure compared to oral hypoglycemic agents, but did not	17

	all-cause mortality and cardiovascular outcomes in patients with type 2 diabetes.		insulin versus OHA treatment, participants with T2D, and follow-up duration 4-3 years. Exclusion criteria: cross-over trials, studies without data on all-cause mortality or cardiovascular outcomes, and studies in which OHAs were discontinued because of severe adverse effects or OHAs are no longer used clinically.		differ in all-cause and CV mortality, myocardial infarction, angina, sudden death, or stroke.	
Mazidi M (2017) [10] systematic review and meta-analysis	To determine the effect of SGLT2 inhibitors on BP among individuals with type 2 diabetes mellitus.	43 RCTs (22,528)	Inclusion criteria: (1) controlled trials with either parallel or crossover design; (2) presentation of sufficient information on primary outcome at baseline and at the end of follow-up in each group or providing the net change values. Exclusion criteria: (1) nonclinical studies; (2) observational studies with case-control, cross-sectional, or cohort design; (3) studies that did not provide data on the levels of the outcomes of interest at baseline and/or at the end of trial; (4) Narrative reviews, comments, opinion pieces, methodological publications, editorials, letters, or any other publications lacking primary data and/or explicit method descriptions.	SGLT2i	A significant reduction in BP following treatment with SGLT2 inhibitors.	18
Monami M (2017) [11]	The effect of SGLT2i on all-cause and	71 RCTs (47,287)	Inclusion criteria: randomized clinical trials with a duration of	SGLT2i	SGLT2i was associated with a significant reduction in risk of all-	17

systematic review and meta-analysis	cardiovascular mortality.		treatment of at least 12 weeks, enrolling patients with type 2 diabetes, comparing a SGLT2 inhibitor with placebo or any other non-SGLT2 inhibitor drug, provided that concurrent treatment was the same for all treatment arms.		cause and CV mortality, and myocardial infarction, but not in stroke.	
Savarese G (2016) [12] Systematic review and meta-analysis	To evaluate the effects of DPP-4i and SGLT2-Is on CV events and mortality by meta-analysis	157 RCTs (140,470)	Inclusion criteria: randomized allocation to DPP-4-Is or SGLT2-Is vs. placebo or other antidiabetic drugs; enrollment of more than 200 patients; report of at least one clinical event among all-cause death, CV death, MI, stroke and new onset of HF.	DPP-4i and SGLT2i	Treatment with DPP-4i did not affect all-cause and CV mortality as well as risk of MI, stroke and heart failure. Treatment with SGLT2-I significantly reduced the risk of all-cause and CV mortality, MI and heart failure without effect on stroke.	17
Seidu S (2016) [13] Systematic review and meta-analysis	To quantify the effect of intensive treatment (i.e. intensive glucose lowering either alone or as part of a multifactorial intervention) on non-fatal MI, non-fatal stroke, CV mortality and all-cause mortality in T2DM patients.	19 RCTs (84,419)	Inclusion criteria: RCTs in adults (≥ 18 years old) with Type 2 diabetes of any duration (mean duration had to be specified), comparing intensive glucose lowering alone (including the pleotropic effects of the drugs being tested) or as part of a multifactorial intervention, to control groups (standard care, placebo or glycaemic control of reduced intensity). Studies had to have outcome data on at least one of four outcomes.	Intensive glucose control or multifactorial interventions (glycemic control together with blood pressure control and lipid lowering)	Intensive treatment reduced the risk of non-fatal MI, stroke, and all-cause and CV mortality while multifactorial intervention reduced the risk of non-fatal stroke, and all-cause and CV mortality.	17
Thomopoulos C (2017) [14] Systematic	Meta-analyzing all available randomized controlled trials to	41 RCTs (61,772)	Inclusion criteria: RCTs recruiting hypertensive patients or cohorts with at least 40% hypertensive	Antihypertensive drugs	In T2DM 1) there is little or no further benefit in lowering systolic BP below 130 mmHg. 2) All	17

review and meta-analysis	compare the effects on cardiovascular and renal outcomes of BP lowering to different systolic BP and diastolic BP levels or by different drug classes in patients with and without diabetes mellitus.		patients, RCTs recruiting patients with non-optimal BP (high-normal BP or prehypertension) with the specific intention of investigating the effects of BP lowering. Exclusion criteria: RCTs in patients with acute myocardial infarction and chronic heart failure, in whom drugs with BP-lowering potential are administered not to lower BP, but in view of other therapeutic properties.		antihypertensive drug classes reduced cardiovascular risk vs. placebo and 3) renin–angiotensin system blockers were most effective.	
Wang T (2016) [15] meta-analysis	To perform an updated meta-analysis of all available incretin therapies on the incidence of MACE plus arrhythmia and heart failure.	100 RCTs (102,933)	Inclusion criteria: (1) Phase III and Phase IV RCTs in type 2 diabetes, (2) RCTs with follow-up duration ≥ 24 weeks and at least 100 patients per arm; in the case of trials with several arms, we included only arms with at least 100 patients, (3) reported data on one or more primary MACE endpoints per FDA guidance plus terms for arrhythmia and heart failure, (4) comparison of IBTs relative to placebo, and/or active comparator antihyperglycemic therapies, (5) reported safety population (preferred denominator for data analysis) (i.e. patients who received at least one dose of study medication and who had at least	Exenatide (GLP1) saxagliptin (DPP-4i) sitagliptin (DPP-4i)	Exenatide increases the risk of arrhythmia and saxagliptin increases the risk of heart failure but sitagliptin reduces the risk of all-cause mortality in T2DM patients.	18

			one post baseline safety assessment); or if unavailable we used a modified intent-to-treat (mITT) (i.e. patients who received at least 1 dose of randomized study medication) or intent-to-treat (ITT) population, and (6) restricted to full-text publications and unpublished trials with complete results in the English language. Exclusion criteria: RCT studies failing to report at least one of the prespecified CV events, Head-to-head comparisons of one IBT to another IBT and trials enrolling non-diabetic or type 1 diabetic subjects.			
Zhang Z (2017) [16] Systematic review and meta-analysis	To evaluate and compare effects of incretin-based agents on CV and pancreatic outcomes in patients with T2DM and high CV risk.	6 RCTs	Inclusion criteria: [1] phase 3 and phase 4 trials; [2] compare incretin-based agents with placebo in patients with T2DM and increased risk for CV diseases; [3] follow-up for a median time of at least 52 weeks; [4] enroll at least 1000 participants; [5] report CV and other safety data for each treatment group separately. Exclusion criteria: trials enrolling fewer than 1000 patients, or those failed to randomize properly, or not double blinded,	GLP-1 RAs DPP-4i	GLP-1 RAs reduced the risk of all-cause and CV mortality and risk of severe hypoglycemia while DPP-4i showed no CV risk reduction and increased the risk of severe hypoglycemia.	16

			Head-to-head studies, early reports of the same Studies, and studies conducted in low CV risk patients.			
Zoungas S (2017) [17] meta-analysis	To estimate the effects of more intensive glucose control, compared with less intensive glucose control, on the risk of microvascular events.	4 RCTs (27,049)	Inclusion criteria: randomised controlled trials ; separately assessed the effects of assigning adult patients with type 2 diabetes to low versus high HbA1c, fasting glucose, or post-load glucose targets; if they had at least 1000 patient-years of follow-up in each treatment group and a minimum of 2 years average follow-up on randomised treatment; if they were double blind or open label and used prospectively defined (ie, prespecified) outcomes; if they were analysed by intention to treat; and if they followed up at least 90% of randomised patients for vital status. Exclusion criteria: randomised patients to multifactorial interventions (except where factorial randomisation allowed the separate assessment of the effects of glycaemic control); studied patients in high-dependency or critical care settings; or studied patients with acute myocardial infarction or	Intensive glucose control	Intensive glucose control reduced the risk of diabetic nephropathy and retinopathy but not neuropathy.	16

with acute coronary syndromes receiving invasive management strategies such as coronary revascularisation, patients with type 1 diabetes, or children aged 16 years or younger.