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Effects of sodium-glucose cotransporter-2 inhibitors use in asia towards cardiorenal outcomes: Updating systematic review and meta-analysis

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SUPPLEMENTARY MATERIAL

Supplementary Appendix to the "***EFFECTS OF SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS USE IN ASIA TOWARDS CARDIORENAL OUTCOMES: UPDATING SYSTEMATIC REVIEW AND META-ANALYSIS***"

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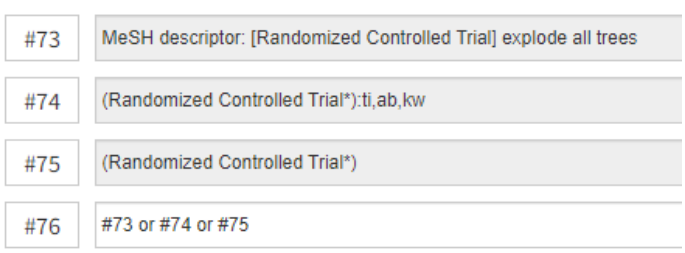
Appendix 1. Keywords in Search Strategy

PUBMED	
Patient/ Problem	• ((((((((((((((((((((((((Diabetes Mellitus, Type 2[MeSH Terms]) OR (Diabetes Mellitus, Type 2[Title/Abstract])) OR (Diabetes Mellitus, Noninsulin-Dependent[MeSH Terms])) OR (Diabetes Mellitus, Noninsulin-Dependent[Title/Abstract])) OR (Diabetes Mellitus, Non Insulin Dependent[MeSH Terms])) OR (Diabetes Mellitus, Non Insulin Dependent[Title/Abstract])) OR (Diabetes Mellitus, Non-Insulin-Dependent[MeSH Terms])) OR (Diabetes Mellitus, Non-Insulin-Dependent[Title/Abstract])) OR (Non-Insulin-Dependent Diabetes Mellitus[MeSH Terms])) OR (Non-Insulin-Dependent Diabetes Mellitus[Title/Abstract])) OR (Diabetes Mellitus, Type II[MeSH Terms])) OR (Diabetes Mellitus, Type II[Title/Abstract])) OR (NIDDM[MeSH Terms])) OR (NIDDM[Title/Abstract])) OR (Diabetes Mellitus, Noninsulin Dependent[MeSH Terms])) OR (Diabetes Mellitus, Noninsulin Dependent[Title/Abstract])) OR (Type 2 Diabetes Mellitus[MeSH Terms])) OR (Type 2 Diabetes Mellitus[Title/Abstract])) OR (Noninsulin-Dependent Diabetes Mellitus[MeSH Terms])) OR (Noninsulin-Dependent Diabetes Mellitus[Title/Abstract])) OR (Noninsulin Dependent Diabetes Mellitus[MeSH Terms])) OR (Noninsulin Dependent Diabetes Mellitus[Title/Abstract])) OR (Type 2 Diabetes[MeSH Terms])) OR (Type 2 Diabetes[Title/Abstract])) OR (Diabetes, Type 2[MeSH Terms])) OR (Diabetes, Type 2[Title/Abstract]) • ((Asian People[Text Word]) OR (Asia[Text Word])) OR (Asia*[Text Word])
Intervention	((Sodium Glucose Transporter 2 Inhibitors[MeSH Terms]) OR (Sodium Glucose Transporter 2 Inhibitors[Title/Abstract])) OR (SGLT-2 Inhibitors[MeSH Terms])) OR (SGLT-2 Inhibitors[Title/Abstract])) OR (SGLT 2 Inhibitors[MeSH Terms])) OR (SGLT 2 Inhibitors[Title/Abstract])) OR (SGLT 2 Inhibitors[MeSH Terms])) OR (SGLT 2 Inhibitors[Title/Abstract])) OR (Sodium-Glucose Transporter 2 Inhibitor[MeSH Terms])) OR (Sodium-Glucose Transporter 2 Inhibitor[Title/Abstract])) OR (Sodium Glucose Transporter 2 Inhibitor[MeSH Terms])) OR (Sodium Glucose Transporter 2 Inhibitor[Title/Abstract])) OR (SGLT2 Inhibitor[MeSH Terms])) OR (SGLT2 Inhibitor[Title/Abstract])) OR (Inhibitor, SGLT2[MeSH Terms])) OR (Inhibitor, SGLT2[Title/Abstract])) OR (Gliflozins[MeSH Terms])) OR (Gliflozins[Title/Abstract])) OR (Gliflozin[MeSH Terms])) OR (Gliflozin[Title/Abstract])) OR (SGLT-2 Inhibitor[MeSH Terms])) OR (SGLT-2 Inhibitor[Title/Abstract])) OR (Inhibitor, SGLT-2[MeSH Terms])) OR (Inhibitor, SGLT-2[Title/Abstract])) OR (SGLT 2 Inhibitor[MeSH Terms])) OR (SGLT 2 Inhibitor[Title/Abstract])) OR (dapagliflozin[Title/Abstract])) OR (empagliflozin[Title/Abstract])) OR (ertugliflozin[Title/Abstract])) OR (Canagliflozin[MeSH Terms])) OR (Canagliflozin[Title/Abstract])) OR (Sodium-Glucose Transporter 2 Inhibitors[MeSH Terms])) OR (Sodium-Glucose Transporter 2 Inhibitors[Title/Abstract])) OR (atigliflozin[Title/Abstract])) OR (bexagliflozin[Title/Abstract])) OR (enavogliflozin[Title/Abstract])) OR (ipragliflozin[Title/Abstract])) OR (licogliflozin[Title/Abstract])) OR

	(luseogliflozin[Title/Abstract])) OR (mizagliflozin[Title/Abstract])) OR (remogliflozin etabonate[Title/Abstract])) OR (sergliflozin etabonate[Title/Abstract])) OR (sotagliflozin[Title/Abstract])) OR (tofogliflozin[Title/Abstract])
Study Design	Following Cochrane Highly Sensitive Search Strategy for identifying randomized trials in Pubmed: #9 ••• > Search: **#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8** #8 ••• > Search: **groups [tiab]** #7 ••• > Search: **trial [tiab]** #6 ••• > Search: **randomly [tiab]** #5 ••• > Search: **drug therapy [sh]** #4 ••• > Search: **placebo [tiab]** #3 ••• > Search: **randomized [tiab]** #2 ••• > Search: **controlled clinical trial [pt]** #1 ••• > Search: **randomized controlled trial [pt]** #9 ••• > Search: **#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8** #8 ••• > Search: **groups [tiab]** #7 ••• > Search: **trial [tiab]** #6 ••• > Search: **randomly [tiab]** #5 ••• > Search: **drug therapy [sh]** #4 ••• > Search: **placebo [tiab]** #3 ••• > Search: **randomized [tiab]** #2 ••• > Search: **controlled clinical trial [pt]** #1 ••• > Search: **randomized controlled trial [pt]**
EMBASE	
Patient/ Problem	'non insulin dependent diabetes mellitus'/exp OR 'non insulin dependent diabetes mellitus' OR 'adult onset diabetes':ti,ab OR 'adult onset diabetes mellitus':ti,ab OR 'diabetes mellitus type 2':ti,ab OR 'diabetes mellitus type ii':ti,ab OR 'diabetes mellitus, maturity onset':ti,ab OR 'diabetes mellitus, non insulin dependent':ti,ab OR 'diabetes mellitus, non-insulin-dependent':ti,ab OR 'diabetes mellitus, type 2':ti,ab OR 'diabetes mellitus, type ii':ti,ab OR 'diabetes type 2':ti,ab OR 'diabetes type ii':ti,ab OR 'diabetes, adult onset':ti,ab OR 'dm 2':ti,ab OR 'insulin independent diabetes':ti,ab OR 'insulin independent diabetes mellitus':ti,ab OR 'ketosis resistant diabetes mellitus':ti,ab OR 'maturity onset diabetes':ti,ab OR 'maturity onset diabetes mellitus':ti,ab OR 'maturity onset diabetes of the young':ti,ab OR 'niddm':ti,ab OR 'niddm (non insulin dependent diabetes mellitus)':ab,ti OR 'non insulin dependent diabetes':ti,ab OR 'non-insulin-dependent diabetes mellitus':ti,ab OR 'noninsulin dependent diabetes':ti,ab OR 'noninsulin dependent diabetes mellitus':ti,ab OR 't2dm':ab,ti OR 'type 2 diabetes':ti,ab OR 'type 2 diabetes mellitus':ti,ab OR 'type ii diabetes':ti,ab OR 'type ii diabetes mellitus':ti,ab OR 'non insulin dependent diabetes mellitus':ti,ab

	'heart failure'/exp OR 'backward failure, heart':ti,ab OR 'cardiac backward failure':ti,ab OR 'cardiac decompensation':ti,ab OR 'cardiac failure':ti,ab OR 'cardiac incompetence':ti,ab OR 'cardiac insufficiency':ti,ab OR 'cardiac stand still':ti,ab OR 'cardial decompensation':ti,ab OR 'cardial insufficiency':ti,ab OR 'chronic heart failure':ti,ab OR 'chronic heart insufficiency':ab,ti OR 'decompensatio cordis':ti,ab OR 'decompensation, heart':ti,ab OR 'heart backward failure':ti,ab OR 'heart decompensation':ti,ab OR 'heart incompetence':ti,ab OR 'heart insufficiency':ti,ab OR 'insufficientia cardis':ti,ab OR 'myocardial failure':ab OR 'myocardial insufficiency':ab,ti OR 'heart failure':ti,ab 'chronic kidney failure'/exp OR 'chronic kidney disease':ti,ab OR 'chronic kidney disorder':ti,ab OR 'chronic kidney insufficiency':ti,ab OR 'chronic nephropathy':ti,ab OR 'chronic renal disease':ti,ab OR 'chronic renal failure':ti,ab OR 'chronic renal insufficiency':ti,ab OR 'kidney chronic failure':ti,ab OR 'kidney disease, chronic':ti,ab OR 'kidney failure, chronic':ti,ab OR 'kidney function, chronic disease':ab,ti OR 'renal insufficiency, chronic':ti,ab OR 'chronic kidney failure':ti,ab 'asia'/exp OR 'arabia':ti,ab OR 'orient':ab,ti OR 'asia':ti,ab OR 'far east':ti,ab OR 'middle east':ab OR 'asian'/exp OR 'asian people':ti,ab OR 'asians':ti,ab OR 'asian':ti,ab
Intervention	'sodium glucose cotransporter 2 inhibitor'/exp OR 'gliflozin':ab,ti OR 'gliflozin derivative':ti,ab OR 'gliflozins':ti,ab OR 'sglt2 inhibitor':ti,ab OR 'sglt2 inhibitors':ti,ab OR 'sodium dependent glucose cotransporter 2 inhibitor':ti,ab OR 'sodium glucose co-transporter 2 inhibitor':ti,ab OR 'sodium-glucose transporter 2 inhibitors':ti,ab OR 'sodium glucose cotransporter 2 inhibitor':ti,ab OR 'atigliflozin':ti,ab OR 'bexagliflozin':ab,ti OR 'canagliflozin':ti,ab OR 'dapagliflozin':ti,ab OR 'empagliflozin':ti,ab OR 'enavogliflozin':ti,ab OR 'ertugliflozin':ti,ab OR 'ipragliflozin':ti,ab OR 'licogliflozin':ti,ab OR 'luseogliflozin':ti,ab OR 'mizagliflozin':ti,ab OR 'remogliflozin etabonate':ti,ab OR 'sergliflozin etabonate':ti,ab OR 'sotagliflozin':ti,ab OR 'tofogliflozin':ti,ab
CENTRAL	
Study Design	
	
Patient/Problem	

- Type 2 diabetes mellitus:

#1	MeSH descriptor: [Diabetes Mellitus, Type 2] explode all trees
#2	(Diabetes Mellitus, Maturity-Onset):ti,ab,kw
#3	(Diabetes Mellitus, Noninsulin Dependent):ti,ab,kw
#4	(Maturity-Onset Diabetes Mellitus):ti,ab,kw
#5	(Diabetes Mellitus, Non-Insulin-Dependent):ti,ab,kw
#6	(Diabetes Mellitus, Noninsulin-Dependent):ti,ab,kw
#7	(Noninsulin Dependent Diabetes Mellitus):ti,ab,kw
#8	(NIDDM):ti,ab,kw
#9	(Diabetes Mellitus, Slow Onset):ti,ab,kw
#10	(Maturity-Onset Diabetes):ti,ab,kw
#11	(Diabetes, Maturity-Onset):ti,ab,kw
#12	(Adult-Onset Diabetes Mellitus):ti,ab,kw
#12	(Adult-Onset Diabetes Mellitus):ti,ab,kw
#13	(Diabetes Mellitus, Ketosis-Resistant):ti,ab,kw
#14	(Ketosis-Resistant Diabetes Mellitus):ti,ab,kw
#15	(Diabetes Mellitus, Maturity Onset):ti,ab,kw
#16	(Type 2 Diabetes Mellitus):ti,ab,kw
#17	(Diabetes, Type 2):ti,ab,kw
#18	(Diabetes Mellitus, Non Insulin Dependent):ti,ab,kw
#19	(Diabetes Mellitus, Slow-Onset):ti,ab,kw
#20	(Diabetes Mellitus, Type II):ti,ab,kw
#21	(Diabetes Mellitus, Stable):ti,ab,kw
#22	(Stable Diabetes Mellitus):ti,ab,kw
#23	(Diabetes Mellitus, Adult Onset):ti,ab,kw
#24	(Diabetes Mellitus, Adult-Onset):ti,ab,kw
#25	(MODY):ti,ab,kw
#26	(Type 2 Diabetes):ti,ab,kw
#27	(Slow-Onset Diabetes Mellitus):ti,ab,kw
#28	(Maturity Onset Diabetes Mellitus):ti,ab,kw
#29	(Diabetes Mellitus, Ketosis Resistant):ti,ab,kw
#30	(Maturity Onset Diabetes):ti,ab,kw
#31	(Noninsulin-Dependent Diabetes Mellitus):ti,ab,kw
#32	(Non-Insulin-Dependent Diabetes Mellitus):ti,ab,kw
#33	(Diabetes Mellitus, Type 2):ti,ab,kw
#34	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33

- Asia:

MeSH descriptor: [Asia] explode all trees
MeSH descriptor: [Asian] explode all trees
(Asia):ti,ab,kw
(Asian):ti,ab,kw
(Asia*):ti,ab,kw
(Asia*)
#35 or #36 or #37 or #38 or #39 or #40

- Heart Failure:

#79	MeSH descriptor: [Heart Failure] explode all trees
#80	(Myocardial Failure):ti,ab,kw
#81	(Heart Failure, Right Sided):ti,ab,kw
#82	(Right Sided Heart Failure):ti,ab,kw
#83	(Heart Failure, Right-Sided):ti,ab,kw
#84	(Right-Sided Heart Failure):ti,ab,kw
#85	(Cardiac Failure):ti,ab,kw
#86	(Heart Failure, Left Sided):ti,ab,kw
#87	(Heart Failure, Left-Sided):ti,ab,kw
#88	(Left Sided Heart Failure):ti,ab,kw
#89	(Left-Sided Heart Failure):ti,ab,kw
#90	(Decompensation, Heart):ti,ab,kw
#91	(Heart Decompensation):ti,ab,kw
#92	(Heart Failure, Congestive):ti,ab,kw
#93	(Congestive Heart Failure):ti,ab,kw
#94	(Heart Failure):ti,ab,kw
#95	#79 or #80 # 81 or #82 or #83 or #84 or #85 or #86 or #87 or #88 or #89 or #90 or #91 or #92 or #93 or #94

- Chronic Kidney Disease:

#96	MeSH descriptor: [Renal Insufficiency, Chronic] explode all trees	
#97	(Renal Insufficiency, Chronic):ti,ab,kw	S
#98	(Diseases, Chronic Kidney):ti,ab,kw	S
#99	(Disease, Chronic Renal):ti,ab,kw	S
#100	(Disease, Chronic Kidney):ti,ab,kw	S
#101	(Chronic Renal Disease):ti,ab,kw	S
#102	(Kidney Disease, Chronic):ti,ab,kw	S
#103	(Diseases, Chronic Renal):ti,ab,kw	S
#104	(Chronic Renal Diseases):ti,ab,kw	S
#105	(Chronic Kidney Disease):ti,ab,kw	S
#106	(Kidney Diseases, Chronic):ti,ab,kw	S
#107	(Renal Disease, Chronic):ti,ab,kw	S
#108	(Renal Diseases, Chronic):ti,ab,kw	S
#109	(Chronic Kidney Diseases):ti,ab,kw	S
#110	(Chronic Renal Insufficiency):ti,ab,kw	S
#111	(Chronic Kidney Insufficiencies):ti,ab,kw	S
#112	(Kidney Insufficiency, Chronic):ti,ab,kw	S
#113	(Renal Insufficiencies, Chronic):ti,ab,kw	S
#114	(Chronic Renal Insufficiencies):ti,ab,kw	S
#115	(Kidney Insufficiencies, Chronic):ti,ab,kw	S
#116	(Chronic Kidney Insufficiency):ti,ab,kw	S
#117	#96 or #97 or #98 or #99 or #100 or #101 or #102 or #103 or #104 or #105 or #106 or #107 or #108 or #109 or #110 or #111 or #112 or #113 or #114 or #115 or #116	

Intervention

#42	MeSH descriptor: [Sodium-Glucose Transporter 2 Inhibitors] explode all trees	#52	(Inhibitor, SGLT-2):ti,ab,kw	#63	(bexagliflozin):ti,ab,kw
#43	(Gliflozins):ti,ab,kw	#53	(SGLT 2 Inhibitor):ti,ab,kw	#64	(ipragliflozin):ti,ab,kw
#44	(Gliflozin):ti,ab,kw	#54	(Sodium Glucose Transporter 2 Inhibitors):ti,ab,kw	#65	(licogliflozin):ti,ab,kw
#45	(Inhibitor, SGLT2):ti,ab,kw	#55	(Sodium Glucose Transporter 2 Inhibitor):ti,ab,kw	#66	(lueseogliflozin):ti,ab,kw
#46	(Sodium-Glucose Transporter 2 Inhibitor):ti,ab,kw	#56	(sodium-glucose co-transporter 2 receptor*):ti,ab,kw	#67	(mizagliflozin):ti,ab,kw
#47	(SGLT-2 Inhibitors):ti,ab,kw	#57	(dapagliflozin):ti,ab,kw	#68	(remogliflozin):ti,ab,kw
#48	(SGLT2 Inhibitor):ti,ab,kw	#58	(empagliflozin):ti,ab,kw	#69	(sergliflozin):ti,ab,kw
#49	(SGLT 2 Inhibitors):ti,ab,kw	#59	(canagliflozin):ti,ab,kw	#70	(tofogliflozin):ti,ab,kw
#50	(SGLT2 Inhibitors):ti,ab,kw	#60	(ertugliflozin):ti,ab,kw	#71	(sodium-glucose transporter 2 inhibitors):ti,ab,kw
#51	(SGLT-2 Inhibitor):ti,ab,kw	#61	(sotagliflozin):ti,ab,kw		

#72	#42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71

Appendix 2. Eligibility Criteria from Each Study

Name of Trial	Eligibility Criteria*
DELIVER	At least 40 years of age; had stabilized heart failure, with or without type 2 diabetes mellitus; had a left ventricular ejection fraction of more than 40%; had evidence of structural heart disease; and had an elevated natriuretic peptide level. Patients who had had a previous left ventricular ejection fraction of 40% or less were eligible provided that they had an ejection fraction of more than 40% at the time of enrollment. Patients could have been enrolled either as outpatients or during hospitalization for heart failure (1).
EMPA-KIDNEY	Adults with a race-adjusted eGFR (calculated with the use of the Chronic Kidney Disease Epidemiology Collaboration formula16) of at least 20 but less than 45 ml per minute per 1.73 m2, regardless of the level of albuminuria, or with an eGFR of at least 45 but less than 90 ml per minute per 1.73 m2 with a urinary albumin to creatinine ratio of at least 200 at the screening visit (2).
EMPA-REG OUTCOME	Adults (≥18 years of age) with a body-mass index (the weight in kilograms divided by the square of the height in meters) of 45 or less and an estimated glomerular filtration rate (eGFR) of at least 30 ml per minute per 1.73 m2 of body-surface area, according to the Modification of Diet in Renal Disease criteria. All the patients had established cardiovascular disease (as defined in Section C in the Supplementary Appendix) and had received no glucose-lowering agents for at least 12 weeks before randomization and had a glycated hemoglobin level of at least 7.0% and no more than 9.0% or had received stable glucose-lowering therapy for at least 12 weeks before randomization and had a glycated hemoglobin level of at least 7.0% and no more than 10.0% (3).
CANVAS Program	Participants were men and women with type 2 diabetes (glycated hemoglobin level, ≥7.0% and 10.5%) and were either 30 years of age or older with a history of symptomatic atherosclerotic cardiovascular disease or 50 years of age or older with two or more of the following risk factors for cardiovascular disease: duration of diabetes of at least 10 years, systolic blood pressure higher than 140 mm Hg while they were receiving one or more antihypertensive agents, current smoking, microalbuminuria or macroalbuminuria, or high-density lipoprotein (HDL) cholesterol level of less than 1 mmol per liter (38.7 mg per deciliter). Participants were required to have an estimated glomerular filtration rate (eGFR) at entry of more than 30 ml per minute per 1.73 m2 of body-surface area and to meet a range of other criteria (4).
EMPEROR-REDUCED	Adults (≥18 years of age) who had chronic heart failure (functional class II, III, or IV) with a left ventricular ejection fraction of 40% or less (5).
DAPA-CKD	Adults with or without type 2 diabetes who had an estimated glomerular filtration rate (GFR) of 25 to 75 ml per minute per 1.73 m2 of body-surface area and a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of 200 to 5000 were eligible for participation (6).
EMPEROR-PRESERVED	Participants were men or women, 18 years of age or older, who had New York Heart Association functional class II–IV chronic heart failure and a left ventricular ejection fraction of more than 40%. The protocol required patients to have an N-terminal pro–B-type natriuretic peptide (NT-proBNP) level of more than 300 pg per milliliter or, for patients with atrial fibrillation at baseline, an NT-proBNP level of more than 900 pg per milliliter (7).

	required to have a plasma level of N-terminal pro–B-type natriuretic peptide (NT-proBNP) of at least 600 pg per milliliter (or ≥400 pg per milliliter if they had been hospitalized for heart failure within the previous 12 months). Patients with atrial fibrillation or atrial flutter on baseline electrocardiography were required to have an NT-proBNP level of at least 900 pg per milliliter, regardless of their history of hospitalization for heart failure (8).
SCORED	Persons 18 years of age or older with type 2 diabetes mellitus with a glycated hemoglobin level of 7% or higher, chronic kidney disease (eGFR, 25 to 60 ml per minute per 1.73 m2 of body-surface area), and additional cardiovascular risk factors were enrolled. The risk factors consisted of at least one major cardiovascular risk factor in those 18 years of age or older or at least two minor cardiovascular risk factors in those 55 years of age or older (9).
SOLOIST-WHF	18 to 85 years of age and had been hospitalized because of the presence of signs and symptoms of heart failure and received treatment with intravenous diuretic therapy. Patients were also required to have received a previous diagnosis of type 2 diabetes before the index admission or to have laboratory evidence to support a diagnosis of type 2 diabetes during the index admission (10).
CREDENCE	At least 30 years of age and had type 2 diabetes, with a glycated hemoglobin level of 6.5 to 12.0% (6.5 to 10.5% in Germany, according to a country amendment). They were also required to have chronic kidney disease, defined as an estimated glomerular filtration rate (GFR, as calculated by the Chronic Kidney Disease Epidemiology Collaboration formula) of 30 to <90 ml per minute per 1.73 m2 of body-surface area and albuminuria (urinary albumin- to-creatinine ratio, >300 to 5000, with albumin measured in milligrams and creatinine in grams), as measured in a central laboratory. There was a prespecified plan to include approximately 60% of patients with an estimated GFR of 30 to <60 ml per minute per 1.73 m2 (11).
DECLARE-TIMI 58	40 years of age or older and had type 2 diabetes, a glycated hemoglobin level of at least 6.5% but less than 12.0%, and a creatinine clearance of 60 ml or more per minute. Eligible patients also had multiple risk factors for atherosclerotic cardiovascular disease or had established atherosclerotic cardiovascular disease (defined as clinically evident ischemic heart disease, ischemic cerebrovascular disease, or peripheral artery disease). Participants with multiple risk factors were men 55 years of age or older or women 60 years of age or older who had one or more traditional risk factors, including hypertension, dyslipidemia (defined as a low-density lipoprotein cholesterol level >130 mg per deciliter [3.36 mmol per liter] or the use of lipid lowering therapies), or use of tobacco (12).
VERTIS-CV	At least 40 years of age and had type 2 diabetes (with a glycated hemoglobin level of 7.0 to 10.5%) and established atherosclerotic cardiovascular disease involving the coronary, cerebrovascular, or peripheral arterial systems (13).

*) Based on the real definition stated in the published paper

Appendix 3. Sites Included in Each Trial

Name of Trial	Sites Included
CANVAS Program	Argentina, Australia, Belgium, Brazil, Canada, China, Colombia, Czech Republic, Estonia, France, Germany, Great Britain, Hungary, India, Israel, Italy, Korea, Luxembourg, Malaysia, Mexico, The Netherlands, New Zealand, Norway, Poland, Puerto Rico, Russia, Spain, Sweden, Taiwan, Ukraine, United States
CREDENCE	Argentina, Australia, Brazil, Bulgaria, Canada, Chile, China, Colombia, Czech Republic, France, Germany, Guatemala, Hungary, India, Italy, Japan, Lithuania, Malaysia, Mexico, New Zealand, Philippines, Romania, Russia, Serbia, Slovakia, South Africa, South Korea, Spain, Taiwan, Ukraine, United Arab Emirates, United Kingdom, United States,
DAPA-CKD	Argentina, Brazil, Canada, China, Denmark, Germany, Hungary, India, Japan, Korea, Mexico, Peru, Philippines, Poland, Russia, Spain, Sweden, Ukraine, United Kingdom, United States, Vietnam
DAPA-HF	Argentina, Brazil, Bulgaria, Canada, China, Czech Republic, Denmark, Germany, Hungary, India, Japan, The Netherlands, Poland, Russian Federation, Slovakia, Sweden, Taiwan, United Kingdom, United States, Vietnam
DECLARE-TIMI 58	Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, China, Czech Republic, France, Germany, Hong Kong, Hungary, India, Israel, Italy, Japan, Mexico, The Netherlands, Philippines, Poland, Republic of Korea, Romania, Russian Federation, Slovakia, South Africa, Spain, Sweden, Taiwan, Thailand, Turkey, Ukraine, United Kingdom, United States, Vietnam
DELIVER	Argentina, Belgium, Brazil, Bulgaria, Canada, China, Czech Republic, Hungary, Japan, Mexico, Netherlands, Peru, Poland, Romania, Russia, Saudi Arabia, Spain, Taiwan, United States, Vietnam
EMPA-KIDNEY	Germany, United States, United Kingdom, China, Malaysia, Japan, Canada, Italy
EMPA-REG OUTCOME	Argentina, Australia, Austria, Belgium, Brazil, Canada, Colombia, Croatia, Czech Republic, Denmark, Estonia, France, United Kingdom, Greece, Hong Kong, Hungary, India, Indonesia, Italy, Japan, Republic of Korea, Malaysia, Mexico, Netherlands, New Zealand, Norway, Peru, Poland, Romania, Russia, Singapore, South Africa, Spain, Taiwan, Ukraine, United States
EMPEROR-PRESERVED	Argentina, Australia, Belgium, Brazil, Canada, China, Colombia, Czech Republic, Germany, Hungary, India, Italy, Japan, Korea, Mexico, Netherlands, Poland, Romania, Singapore, Spain, United Kingdom, United States
EMPEROR-REDUCED	Argentina, Australia, Belgium, Brazil, Canada, China, Czech Republic, France, Germany, Hungary, India, Italy, Republic of Korea, Mexico, Republic of Korea, Netherlands, Poland, Spain, United Kingdom, United States
SCORED	Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, China, Chile, Czech Republic, Denmark, Estonia, France, Georgia, Germany, Greece, Guatemala, Hungary, India, Israel, Italy, Republic of Korea, Latvia, Lithuania, Macedonia, Mexico, Netherlands, New Zealand, Norway, Peru, Poland, Portugal, Romania, Russia, Serbia, Slovakia, South Africa, Spain, Sweden, Switzerland, Taiwan, Turkey, Ukraine, United Kingdom, United States,
SOLOIST-WHF	United States, Argentina, Russian Federation, Spain, Brazil, Hungary, Germany, Czech Republic, Israel, Italy, Chile, Poland, Turkey, Greece, Romania, United Kingdom, Finland, France, Netherlands, Portugal, Belgium, Lithuania, Republic of Korea, Denmark, Austria, Latvia, New Zealand, Slovakia, Sweden, Canada, Australia, Switzerland
VERTIS-CV	Argentina, Australia, Bosnia and Herzegovina, Bulgaria, Canada, Colombia, Czech Republic, Croatia, Georgia, Greece, Hong Kong, Hungary, Israel, Italy, Republic of Korea, Latvia, Lithuania, Mexico, Netherlands, New Zealand, Philippines, Poland, Romania, Russian Federation, Serbia, Slovakia, South Africa, Sweden, Taiwan, Thailand, Turkey, Ukraine, United Kingdom, United States

Appendix 4. Detailed Characteristics of Each Study

Name of Trial	First Author	Publication Year	Size of Asian Race (n)	Size of Asia Region (n)	Clinical Trial Registry	Median Follow-up (years)	Outcomes Included in Analysis*	Events/Patients (n/N) for Primary Outcome		Events/Patients (n/N) for Primary Outcome	
								Asian Race		Asia Region	
								Treatment	Placebo	Treatment	Placebo
DELIVER	Solomon	2022	1274	1226	NCT03619213	2.3	**Cardiovascular death / worsening of heart failure in Asian race and Asia region**	97/630	106/644	92/607	103/619
EMPA-KIDNEY	The EMPA-KIDNEY Collaborative Group	2022	-	2244	NCT03594110	2.0	**Progression of Renal Disease in Asia region**	N/A	N/A	157/1116	235/1128
EMPA-REG OUTCOME	Zinman	2015	1517	1347	NCT01131676	3.1	**3-Point MACE in Asia region**	79/1006	58/511	71/897	50/450
	Kadowaki	2018					**3-Point MACE in Asian race**				
	Kaku	2017					Cardiovascular death in Asian, safety profile in Asian, cardiovascular death / HHF in Asian				
CANVAS Program	Neal	2017	1284	Unknown	NCT01032629; NCT01989754	2.4	**3-Point MACE in Asian race and Asia region**	18,8/1000 patient-years	18,4/1000 patient years	26/1000 patient years	28,2 / 1000 patient years
	Perkovic	2018					Progression of Renal Disease in Asian race and Asia region				

	Packer	2020					**Composite of cardiovascular death / HHF** (in sensitivity analysis)				
EMPEROR-REDUCED	Lam	2021	672	493	NCT03057977	1.3	Cardiovascular death in Asian race and Asia region, composite of cardiovascular death / worsening of heart failure in Asian race and Asia region	62/337	99/335	49/248	80/245
	Heerspink	2020					**Progression of Renal Disease in Asian race and Asia region**				
	Vart	2022					All-cause mortaility in Asia, safety profile in Asia; composite of cardiovascular death / HHF				
DAPA-CKD	Correa-Rotter	2021	1467	1346	NCT03036150	2.4	Safety profile in Asia (serious adverse events and discontinuation due to adverse events)	53/749	77/718	50/692	69/654
EMPEROR-	Anker	2021	824	686	NCT03057951	2.2	**Composite of**	54/413	77/411	45/343	69/343

PRESERVED							**cardiovascular death / HHF in Asian race and Asia region**				
	Chopra	2022					Composite of cardiovascular death / HHF in Asia region				
	McMurray	2019					**Composite of cardiovascular death / worsening of heart failure in Asian race and Asia region**				
DAPA-HF	Docherty	2022	1116	1096	NCT03036124	1.5	Cardiovascular death in Asia, all-cause mortality in Asia, safety profile in Asia	78/552	118/564	77/543	114/553
SCORED	Bhatt	2020	N/A	1273	NCT03315143	1.3	**Composite of cardiovascular death / worsening of heart failure in Asia**	N/A	N/A	6,7/100 Patient years	9,8/100 patient years
SOLOIST-WHF	Bhatt	2020	N/A	75	NCT03521934	**0.8**	**Composite of cardiovascular death / worsening of heart failure in Asia**	N/A	N/A	48,4/100 Patient years	78,3/100 patient years
CREDENCE	Perkovic	2019	877	1414	NCT02065791	2.6	**Progression of Renal Disease in Asian race**	49/425	76/452	70/698	119/716

							and Asia region				
	Mahaffey	2019					3-Point MACE in Asian race and Asia region				
	Wada	2021					Cardiovascular death in Asia, all-cause mortaility in Asia, safety profile in Asia; composite of cardiovascular death / worsening of heart failure in Asia				
DECLARE-TIMI 58	Wiviott	2018	-	2186	NCT01730534	4.2	**3-Point MACE**	N/A	N/A	76/1093	79/1093
							Composite of cardiovascular death / HHF in Asia	N/A	N/A	36/1093	37/1093
							Progression of Renal Disease in Asia Region	N/A	N/A		
VERTIS-CV	Cannon	2020	497	522	NCT01986881	3.0	**3-Point MACE in Asian race and Asia region**	36/336	19/161	54/350	21/172
	Ji	2019					Safety profile in Asian				

*) Bold characters meaning primary outcomes

Appendix 5. Baseline Characteristics of Each Study

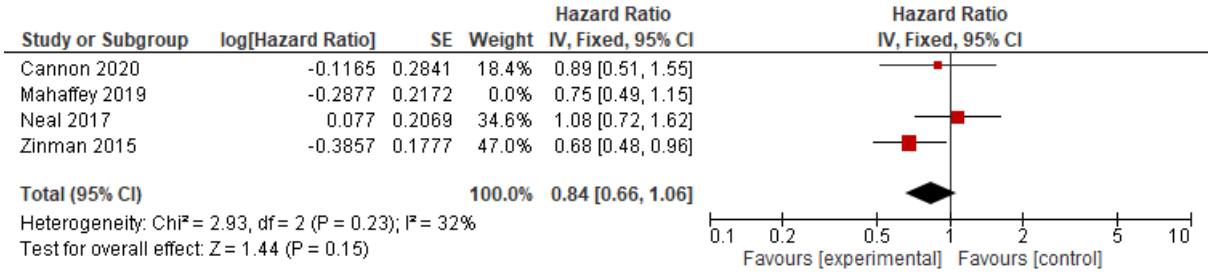
Trial Name	Age (yr)*		Female (n (%))		Asian Race (n (%))		Asia Region (n (%))		BMI (kg/m^2)*		HbA1c (%)*		eGFR (ml/min/1.73^2)*		History of HF (n (%))		History of any ASCVD (n (%))	
	SGLT2I	Placebo	SGLT2I	Placebo	SGLT2I	Placebo	SGLT2	Placebo	SGLT2	Placebo	SGLT2	Placebo	SGLT2	Placebo	SGLT2	Placebo	SGLT2	Placebo
CANVAS (4)	63.2 ± 8.3	63.4 ± 8.2	2036 (35.1)	1597 (36.7)	777 (13.4)	507 (11.7)	N/A	N/A	31.9 ± 5.9	32.0 ± 6.0	8.2 ± 0.9	8.2 ± 0.9	76.7 ± 20.3	76.2 ± 20.8	5188 (89.5)	3937 (90.6)	4127 (71.2)	3197 (73.5)
CREDENCE (11)	62.9 ± 9.2	63.2 ± 9.2	762 (34.6)	732 (33.3)	425 (19.3)	452 (20.6)	698 (31.7) ##	716 (32.6) ##	31.4 ± 6.2	31.3 ± 6.2	8.3 ± 1.3	8.3 ± 1.3	56.3 ± 18.2	56.0 ± 18.3	329 (14.9)	323 (14.7)	N/A	N/A
DAPA-CKD (6)	61.8 ± 12.1	61.9 ± 12.1	709 (32.9)	716 (33.3)	749 (34.8)	718 (33.4)	692 (32.16)	654 (30.39)	29.4 ± 6.0	29.6 ± 6.3	N/A	N/A	43.2 ± 12.3	43.0 ± 12.4	235 (10.9)	233 (10.8)	N/A	N/A
DAPA-HF (8)	66.2 ± 11.0	66.5 ± 10.8	564 (23.8)	545 (23.0)	552 (23.3)	564 (23.8)	543 (22.9) **	553 (23.3) **	28.2 ± 6.0	28.1 ± 5.9	N/A	N/A	66.0 ± 19.6	65.5 ± 19.3	2373 (100)	2371 (100)	N/A	N/A
DECLARE-TIMI 58 (12)	63.9 ± 6.8	64.0 ± 6.8	3171 (36.9)	3251 (37.9)	1148 (13.4)	1155 (13.5)	1093 (12.7) **	1093 (12.7) **	32.1 ± 6.0	32.0 ± 6.1	8.3 ± 1.2	8.3 ± 1.2	85.4 ± 15.8	85.1 ± 16.0	852 (9.9)	872 (10.2)	3474 (40.5)	3500 (40.8)
DELIVER (1)	71.8 ± 9.6	71.5 ± 9.5	1364 (43.6)	1383 (44.2)	630 (20.1)	644 (20.6)	607 (19.4)	619 (19.8)	29.8 ± 6.2	29.9 ± 6.1	N/A	N/A	61 ± 19	61 ± 19	3131 (100)	3132 (100)	N/A	N/A
EMPA-KIDNEY (2)	63.9 ± 13.9	63.8 ± 13.9	1097 (33.2)	1095 (33.1)	1194 (36.1)	1199 (36.3)	1116 (34)	1128 (34)	29.7 ± 6.7	29.8 ± 6.8	N/A	N/A	37.4 ± 14.5	37.3 ± 14.4	324 (10)	334 (10)	N/A	N/A
EMPA-REG OUTCOME (3) ***	63.1 ± 8.6	63.2 ± 8.8	1351 (28.8)	653 (28)	1006 (21.5)	511 (21.9)	897 (19.1)	450 (19.3)	30.6 ± 5.3	30.7 ± 5.2	8.07 ± 0.85	8.08 ± 0.84	74.2 ± 21.6	73.8 ± 21.1	N/A	N/A	N/A	N/A
EMPEROR-Preserved (7)	71.8 ± 9.3	71.9 ± 9.6	1338 (44.6)	1338 (44.7)	413 (13.8)	411 (13.7)	343 (11.4)	343 (11.5)	29.77 ± 5.8	29.90 ± 5.9	N/A	N/A	60.6 ± 19.8	60.6 ± 19.9	2997 (100)	2991 (100)	N/A	N/A
EMPEROR-Reduced (5)	67.2 ± 10.8	66.5 ± 11.2	437 (23.5)	456 (24.4)	337 (18.1)	335 (17.9)	248 (13.3)	245 (13.1)	28.0 ± 5.5	27.8 ± 5.3	N/A	N/A	61.8 ± 21.7	62.2 ± 21.5	1863 (100)	1867)	N/A	N/A
SCORED (9)	69 (63–74) #	69 (63–74) #	2347 (44.3)	2407 (45.5)	317 (6.0)	365 (6.9)	636 (12.0) ##	637 (12.0) ##	31.9 (28.1–36.2)#	31.7 (28.0–36.1) #	8.3 (7.6–9.3) #	8.3 (7.6–9.4) #	44.4 (37.0–51.3)#	44.7 (37.0–51.5) #	1640 (31.0)	1643 (31.0)	N/A	N/A
SOLOIST-WHF (10)	69 (63–76) #	70 (64–76) #	198 (32.6)	214 (34.9)	8 (1.3)	7 (1.1)	38 (6.2) ##	38 (6.2) ##	30.4 (26.3–34.3)#	31.1 (27.3–34.5) #	7.1 (6.4–8.3) #	7.2 (6.4–8.2) #	49.2 (39.5–61.2)#	50.5 (40.5–64.6) #	608 (100)	614 (100)	N/A	N/A
VERTIS-CV (13)	64.4 ± 8.1	64.4 ± 8.0	1633 (29.7)	844 (30.7)	336 (6.1)	162 (5.9)	350 (6.4)	173 (6.3)	31.9 ± 5.4	32.0 ± 5.5	8.2 ± 1.0	8.2 ± 0.9	76.1 ± 20.9	75.7 ± 20.8	1286 (23.4)	672 (24.5)	N/A	N/A

*) Mean ± SD
**) Asia-Pacific
***) The SGLT2I group consists of empagliflozin 10 mg and empagliflozin 25 mg groups
#) Median (IQR)
##) Rest of the world

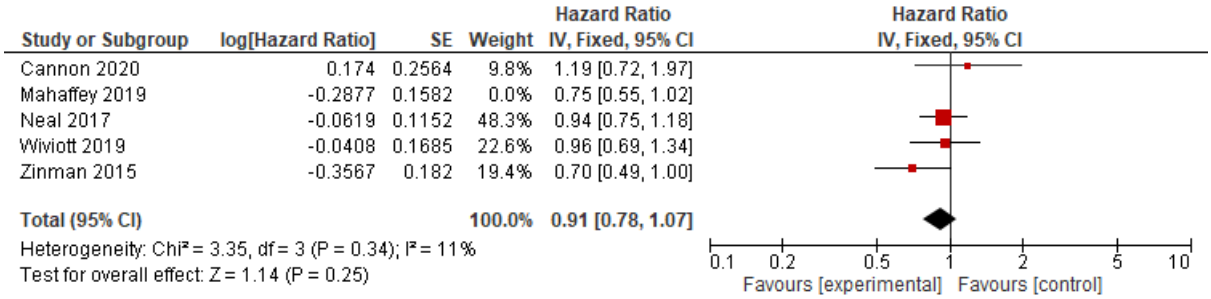
Appendix 6. Subgroup Analysis Forest Plots

3-Point MACE

Type 2 diabetes and ASCVD risk (Asian Race)

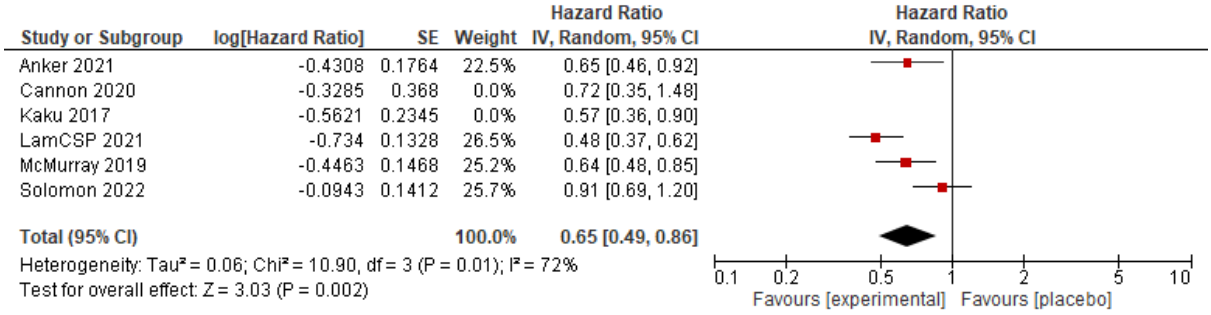


Type 2 diabetes and ASCVD risk (Asia Region)

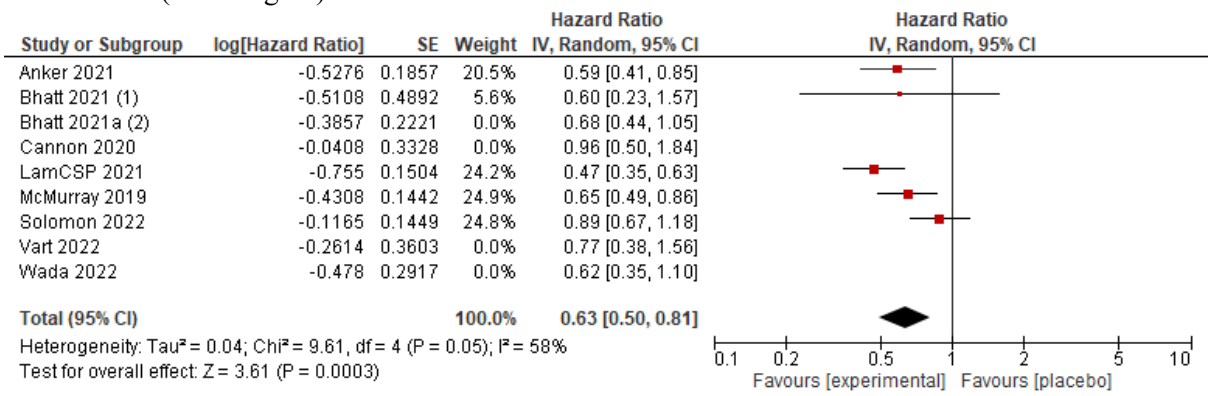


Composite of cardiovascular death / worsening of heart failure

Heart failure (Asian Race)

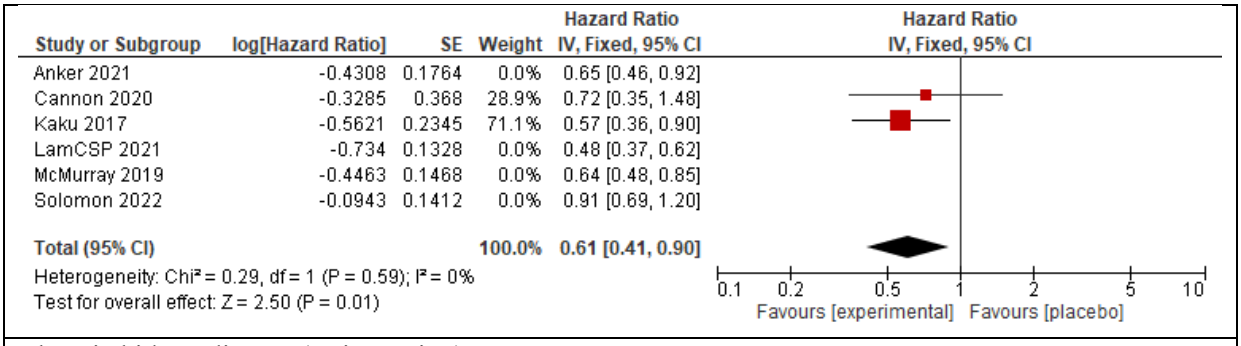


Heart failure (Asia Region)

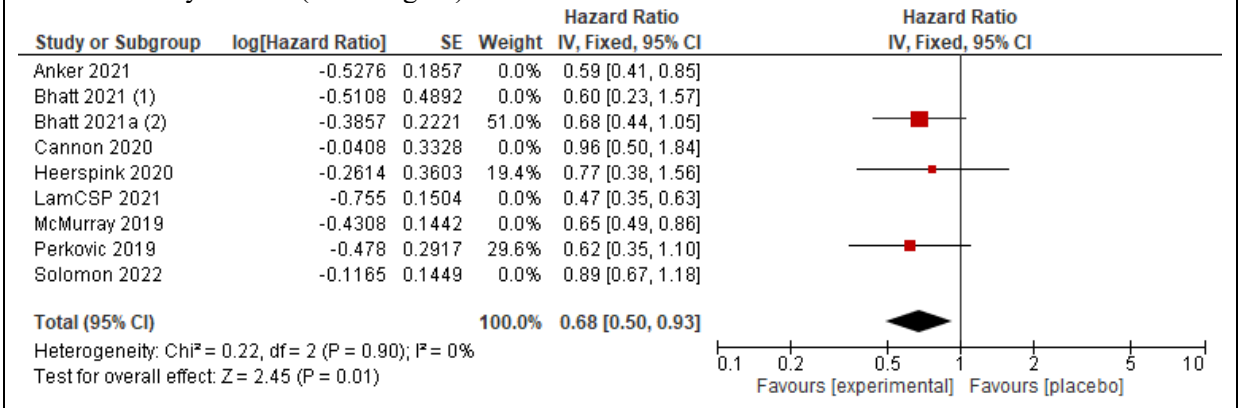


Footnotes
(1) SOLOIST-WHF
(2) SCORED

Type 2 diabetes and ASCVD risk (Asian Race)



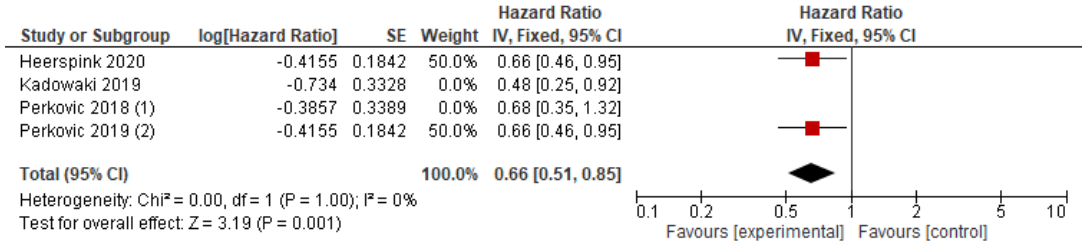
Chronic kidney disease (Asia Region)



Footnotes
(1) SOLOIST-WHF
(2) SCORED

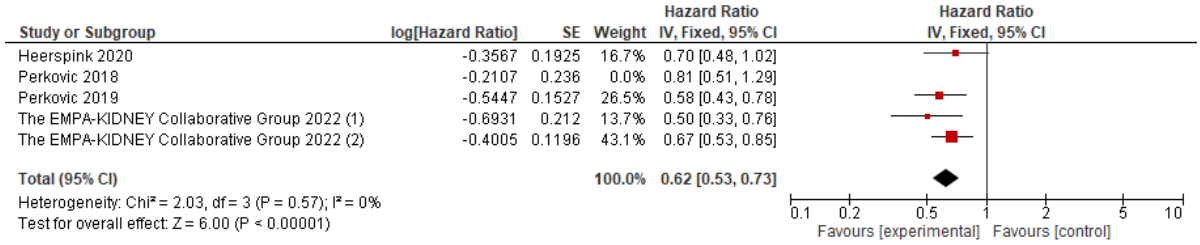
Progression of renal disease

Chronic kidney disease (Asian Race)



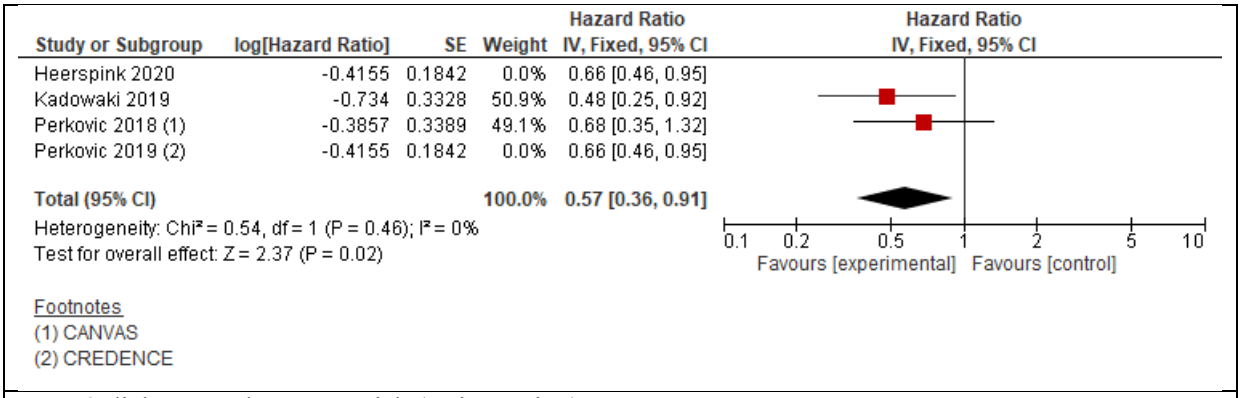
Footnotes
(1) CANVAS
(2) CREDENCE

Chronic kidney disease (Asia Region)

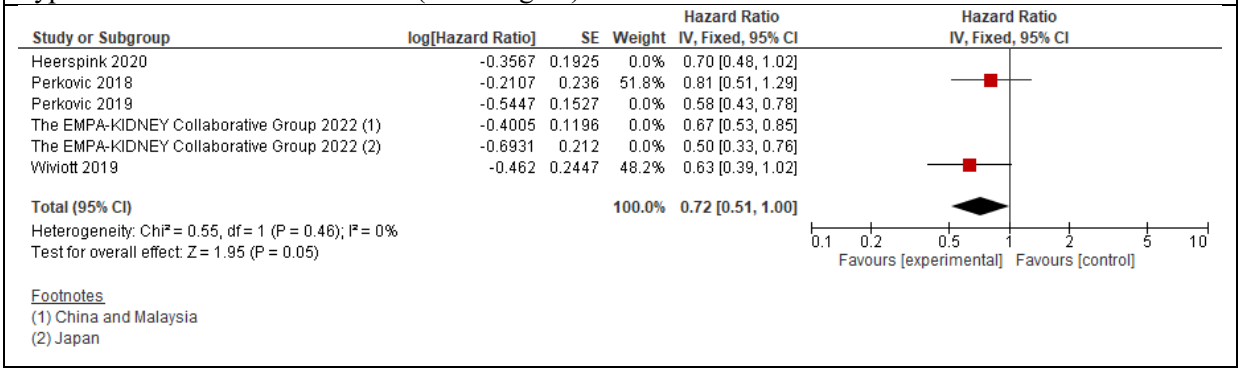


Footnotes
(1) Japan
(2) China and Malaysia

Type 2 diabetes and ASCVD risk (Asian Race)



Type 2 diabetes and ASCVD risk (Asia Region)

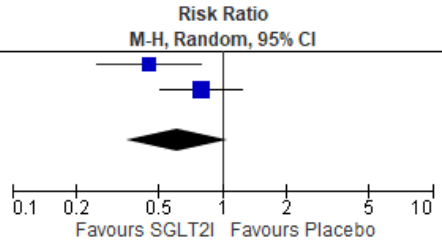


Appendix 7. Forest Plots of Secondary Outcomes

Cardiovascular Death (Asian Race)

Study or Subgroup	SGLT2I Events	SGLT2I Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Kaku 2017	22	1006	25	511	45.3%	0.45 [0.25, 0.78]
LamCSP 2021	31	337	39	335	54.7%	0.79 [0.51, 1.24]
Total (95% CI)		**1343**		**846**	**100.0%**	**0.61 [0.35, 1.06]**
Total events	53		64			

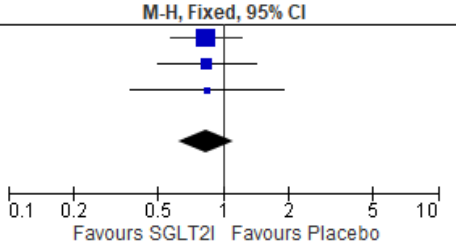
Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 2.41$, df = 1 (P = 0.12); $I^2 = 59\%$
Test for overall effect: Z = 1.74 (P = 0.08)



Cardiovascular Death (Asia Region)

Study or Subgroup	SGLT2I Events	SGLT2I Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Docherty 2022	44	543	54	553	57.8%	0.83 [0.57, 1.21]
LamCSP 2021	23	248	27	245	29.3%	0.84 [0.50, 1.43]
Wada 2022	10	301	12	303	12.9%	0.84 [0.37, 1.91]
Total (95% CI)		**1092**		**1101**	**100.0%**	**0.83 [0.63, 1.11]**
Total events	77		93			

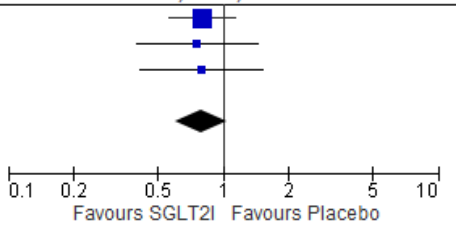
Heterogeneity: $Chi^2 = 0.00$, df = 2 (P = 1.00); $I^2 = 0\%$
Test for overall effect: Z = 1.23 (P = 0.22)



All-Cause Mortality (Asia Region)

Study or Subgroup	SGLT2I Events	SGLT2I Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Docherty 2022	49	543	62	553	60.9%	0.80 [0.56, 1.15]
Vart 2022	16	692	20	654	20.4%	0.76 [0.40, 1.45]
Wada 2022	15	301	19	303	18.8%	0.79 [0.41, 1.53]
Total (95% CI)		**1536**		**1510**	**100.0%**	**0.79 [0.60, 1.05]**
Total events	80		101			

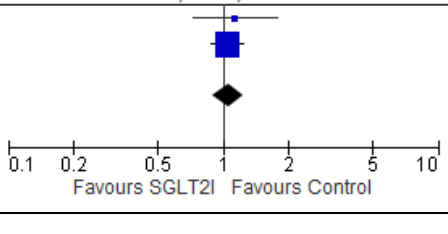
Heterogeneity: $Chi^2 = 0.03$, df = 2 (P = 0.99); $I^2 = 0\%$
Test for overall effect: Z = 1.61 (P = 0.11)



Drug-Related Adverse Events (Asian Race)

Study or Subgroup	SGLT2I Events	SGLT2I Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ji 2019	53	339	23	167	14.6%	1.14 [0.72, 1.79]
Kaku 2017	280	1006	136	511	85.4%	1.05 [0.88, 1.25]
Total (95% CI)		**1345**		**678**	**100.0%**	**1.06 [0.90, 1.25]**
Total events	333		159			

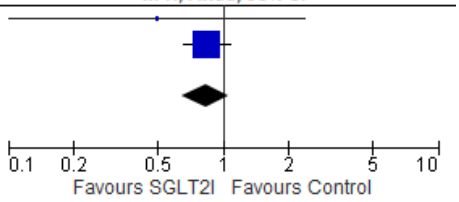
Heterogeneity: $Chi^2 = 0.11$, df = 1 (P = 0.74); $I^2 = 0\%$
Test for overall effect: Z = 0.69 (P = 0.49)



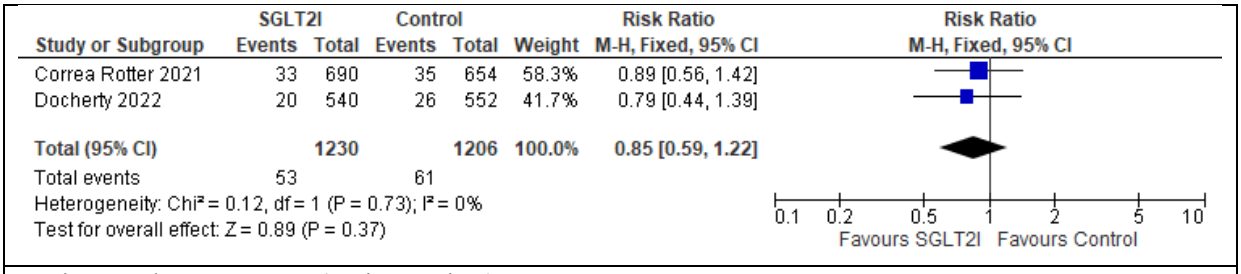
Adverse Event Leading to Discontinuation (Asian Race)

Study or Subgroup	SGLT2I Events	SGLT2I Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ji 2019	3	339	3	167	3.6%	0.49 [0.10, 2.41]
Kaku 2017	134	1006	81	511	96.4%	0.84 [0.65, 1.08]
Total (95% CI)		**1345**		**678**	**100.0%**	**0.83 [0.64, 1.06]**
Total events	137		84			

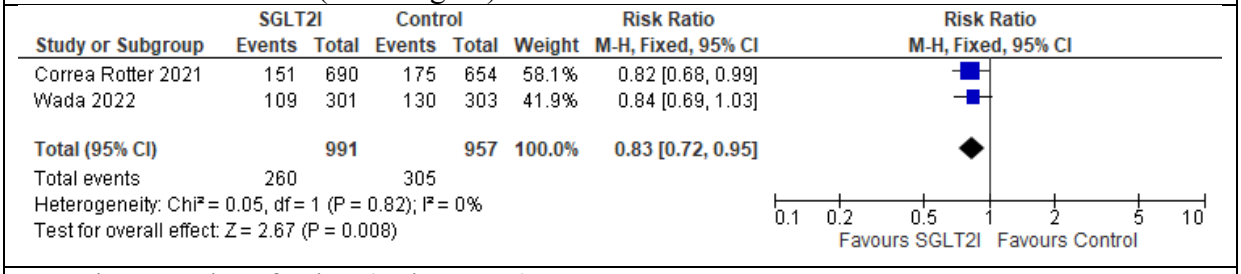
Heterogeneity: $Chi^2 = 0.42$, df = 1 (P = 0.52); $I^2 = 0\%$
Test for overall effect: Z = 1.48 (P = 0.14)



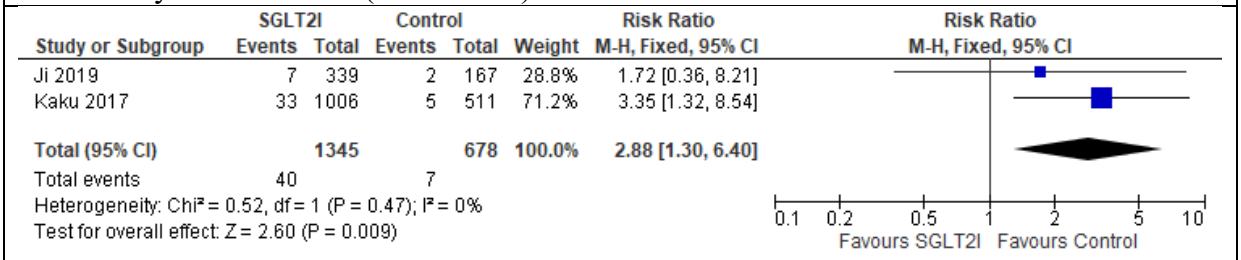
Adverse Event Leading to Discontinuation (Asia Region)



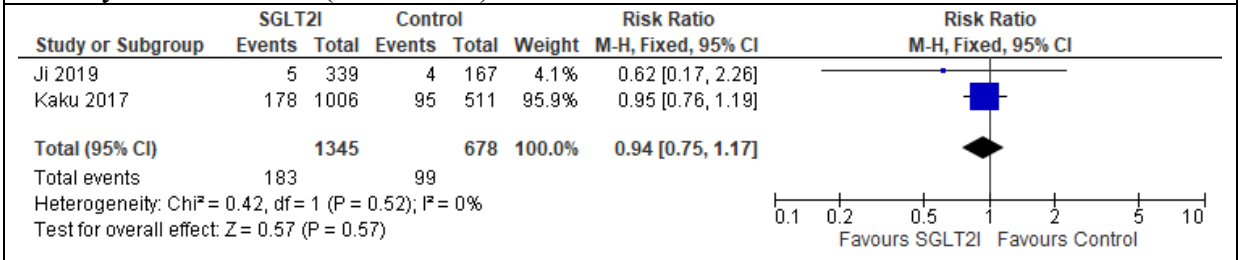
Serious Adverse Event (Asia Region)



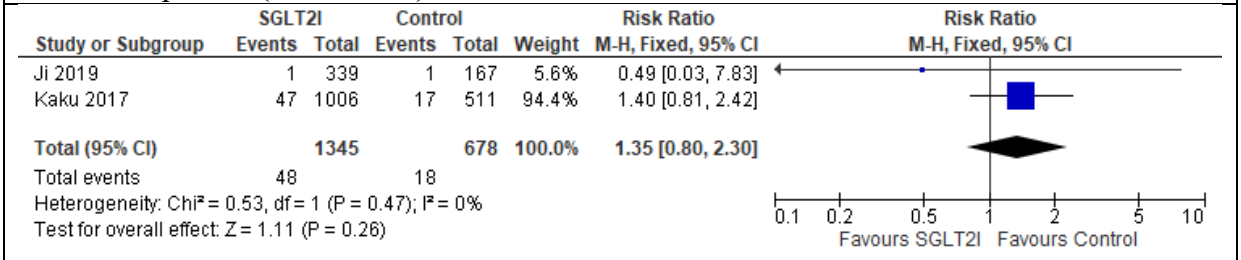
Genetic Mycotic Infection (Asian Race)



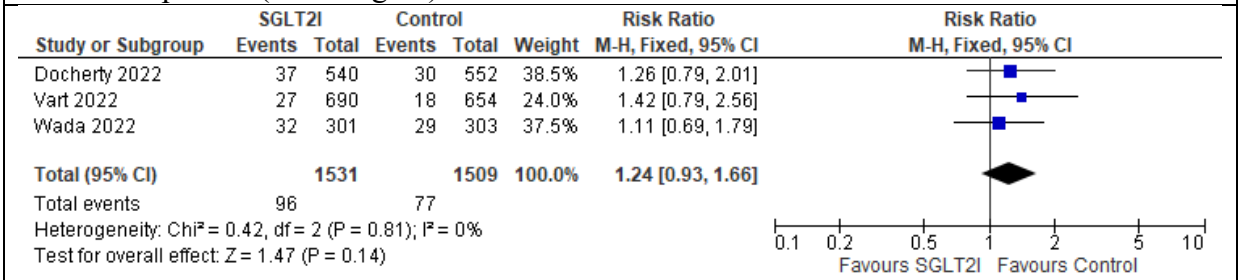
Urinary Tract Infection (Asian Race)



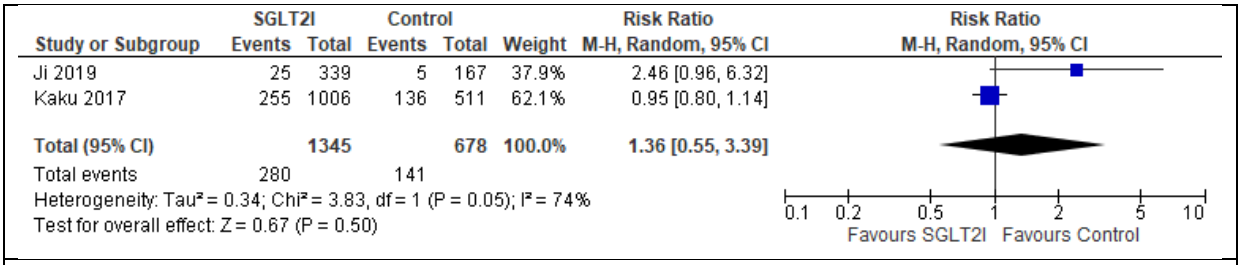
Volume Depletion (Asian Race)



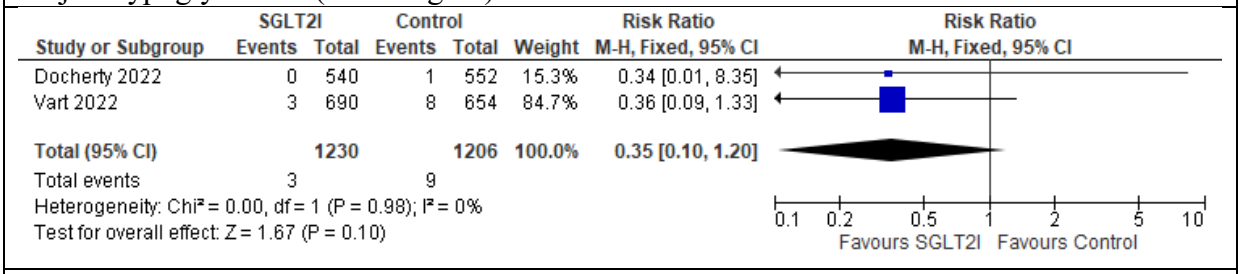
Volume Depletion (Asia Region)



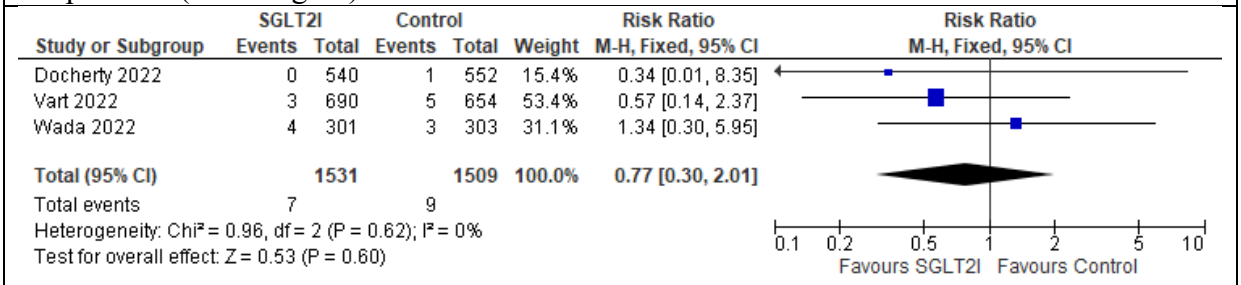
Documented Hypoglycaemia (Asian Race)



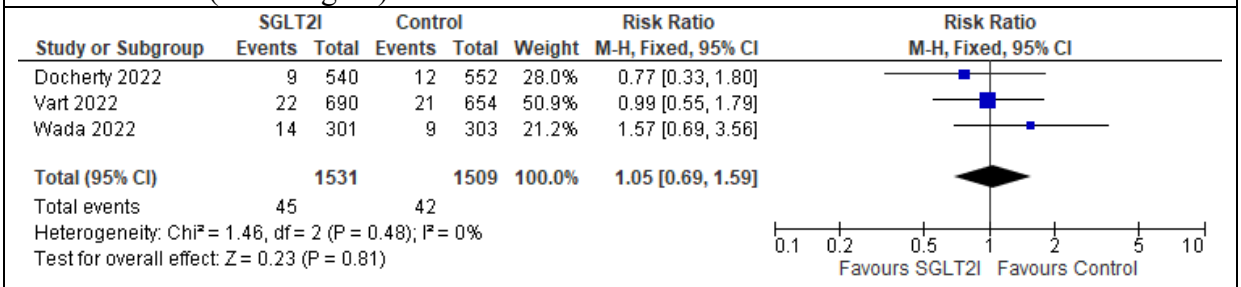
Major Hypoglycaemia (Asia Region)



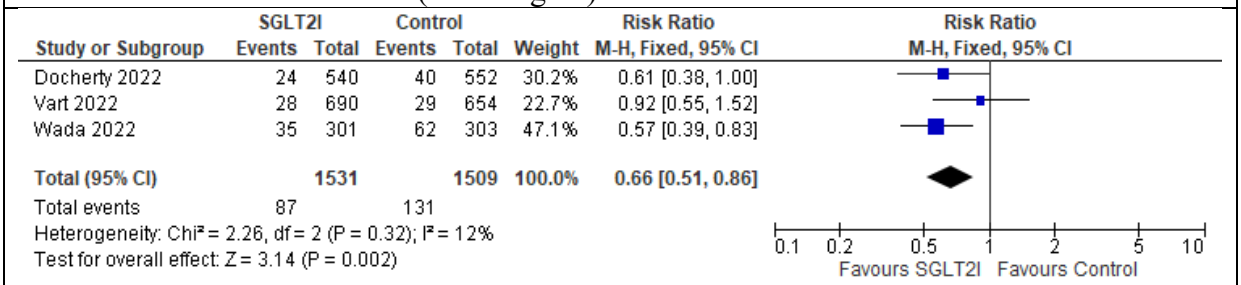
Amputation (Asia Region)



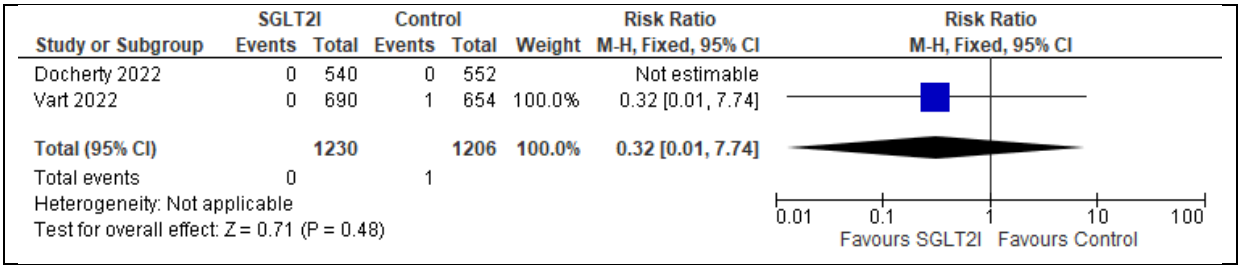
Bone Fracture (Asia Region)



Renal-Related Adverse Events (Asia Region)



Diabetic Ketoacidosis (Asia Region)



Appendix 8. Detailed GRADE Analysis

- OUTCOME: 3-Point MACE (Asian Race)

GRADE domains	Rating (circle one)	Footnotes (reasons for downgrading)	Certainty
Risk of Bias	No serious (-1) very serious (-2)	All components of the RoB2 assessment show a low risk of bias.	⊕⊕⊕⊕ High ⊕⊕⊕◯ Moderate ⊕⊕◯◯ Low ⊕◯◯◯ Very Low
Inconsistency	No serious (-1) very serious (-2)	I2 = 4%. The 95% CIs overlap.	
Indirectness	No serious (-1) very serious (-2)	Appropriate inclusion criteria, appropriate comparisons, using end-point outcomes.	
Imprecision	No serious (-1) very serious (-2)	CI range with the same conclusion (the lowest and highest points produce the same conclusion).	
Publication Bias	Undetected Strongly suspected (-1)	The author made an effort to include all research results by carrying out conversions and contacting the author if complete information is needed. The author also carried out hand searching. The results of the funnel plot indicate minimal risk of publication bias.	

- OUTCOME: 3-Point MACE (Asia Region)

GRADE domains	Rating (circle one)	Footnotes (reasons for downgrading)	Certainty
Risk of Bias	No serious (-1) very serious (-2)	All components of the RoB2 assessment show a low risk of bias.	⊕⊕⊕⊕ High ⊕⊕⊕◯ Moderate ⊕⊕◯◯ Low ⊕◯◯◯ Very Low
Inconsistency	No serious (-1) very serious (-2)	I^2 = 13%. It is said to have a high risk of heterogeneity if I^2>50%. The 95% CIs overlap.	
Indirectness	No Moderately serious (-0.5) serious (-1) very serious (-2)	Inclusion criteria are appropriate, and comparisons are appropriate, using end-point outcomes. Still, the CREDENCE and Canvas Study includes Asian populations in the rest of the world, while DECLARE-TIMI 58 refers to the Asia region as Asia-Pacific. Thus, there might be other populations besides Asia.	
Imprecision	No Moderately serious (-0.5) serious (-1) very serious (-2)	CI with different conclusions (lowest and highest points produce different conclusions). However, if we look at the power with a rule-of-thumb of at least 400 events for dichotomous data, this data synthesis fulfills the rule-of-thumb, with a total of more than 400 events.	
Publication Bias	Undetected Strongly suspected (-1)	The author made an effort to include all research results by carrying out conversions and contacting the author if complete information is needed. The author also carried out hand searching. The results of the funnel plot indicate minimal risk of publication bias.	

- OUTCOME: Kidney Disease Progression (Asian Race)

GRADE domains	Rating (circle one)	Footnotes (reasons for downgrading)	Certainty
Risk of Bias	No serious (-1) very serious (-2)	All components of the RoB2 assessment show a low risk of bias.	⊕⊕⊕⊕ High ⊕⊕⊕◯ Moderate ⊕⊕◯◯ Low ⊕◯◯◯ Very Low
Inconsistency	No serious (-1) very serious (-2)	I2 = 0%. The 95% CIs overlap.	
Indirectness	No serious (-1) very serious (-2)	The DAPA-CKD study not only included type 2 diabetes mellitus patients but also non-diabetic patients. However, if sensitivity analysis is carried out, the results are similar (the direction and range of results are similar). HR = 0.84 (CI95% = 0.51 – 0.80) with DAPA-CKD vs. HR = 0.62 (CI95% = 0.47 – 0.83) without DAPA-CKD study.	
Imprecision	No serious (-1) very serious (-2)	CI range with the same conclusion (the lowest and highest points produce the same conclusion).	
Publication Bias	Undetected Strongly suspected (-1)	The author made an effort to include all research results by carrying out conversions and contacting the author if complete information is needed. The author also carried out hand searching. The results of the funnel plot indicate minimal risk of publication bias.	

- OUTCOME: Kidney Disease Progression (Asia Region)

GRADE domains	Rating (circle one)	Footnotes (reasons for downgrading)	Certainty
Risk of Bias	No serious (-1) very serious (-2)	All components of the RoB2 assessment show a low risk of bias.	⊕⊕⊕⊕ High ⊕⊕⊕◯ Moderate ⊕⊕◯◯ Low ⊕◯◯◯ Very Low
Inconsistency	No serious (-1) very serious (-2)	I^2 = 0%. The 95% CIs overlap.	
Indirectness	No Moderately serious (-0.5) serious (-1) very serious (-2)	The DAPA-CKD study not only included type 2 diabetes mellitus patients but also non-diabetic patients. However, if sensitivity analysis is carried out, the results are similar (the direction and range of results are similar). HR = 0.64 (CI95% = 0.55 – 0.74) with DAPA-CKD vs. HR = 0.63 (CI95% = 0.54 – 0.74) without DAPA-CKD study. In addition, the CREDENCE and CANVAS studies include Asian populations in the rest of the world, while DECLARE-TIMI 58 refers to the Asia region as Asia-Pacific, thus there may be populations in other areas included in this section.	
Imprecision	No serious (-1) very serious (-2)	CI range with the same conclusion (the lowest and highest points produce the same conclusion).	
Publication Bias	Undetected Strongly suspected (-1)	The author made an effort to include all research results by carrying out conversions and contacting the author if complete information is needed. The author also carried out hand searching. The results of the funnel plot indicate minimal risk of publication bias.	

- OUTCOME: Cardiovascular Death / Worsening of Heart Failure (Asian Race)

GRADE domains	Rating (circle one)	Footnotes (reasons for downgrading)	Certainty
Risk of Bias	No serious (-1) very serious (-2)	All components of the RoB2 assessment show a low risk of bias.	⊕⊕⊕⊕ High ⊕⊕⊕◯ Moderate ⊕⊕◯◯ Low ⊕◯◯◯ Very Low
Inconsistency	No serious (-1) very serious (-2)	I2 = 56%. The 95% CIs do not overlap.	
Indirectness	No Moderately serious (-0.5) serious (-1) very serious (-2)	The EMPEROR-PRESERVED, EMPEROR-REDUCED, DAPA-HF, and DELIVER studies not only included type 2 diabetes mellitus patients, but also non-diabetic patients. However, if sensitivity analysis is carried out, the results are similar (the direction of the results is similar). HR = 0.64 (CI95% = 0.52 – 0.80) with all four studies vs. HR = 0.61 (CI95% = 0.41 – 0.90) without all four studies.	
Imprecision	No serious (-1) very serious (-2)	CI range with the same conclusion (the lowest and highest points produce the same conclusion).	
Publication Bias	Undetected Strongly suspected (-1)	The author made an effort to include all research results by carrying out conversions and contacting the author if complete information is needed. The author also carried out hand searching.	

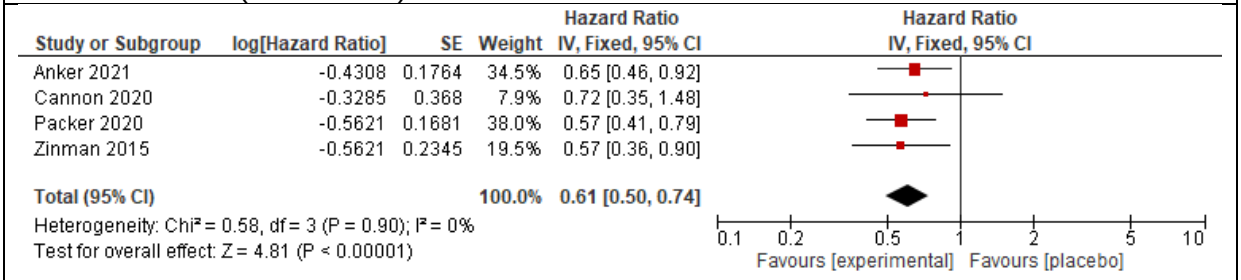
- OUTCOME: Cardiovascular Death / Worsening of Heart Failure (Asia Region)

GRADE domains	Rating (circle one)	Footnotes (reasons for downgrading)	Certainty
Risk of Bias	No Moderately serious (-0.5) serious (-1) very serious (-2)	All RoB2 assessment components show a low risk of bias, except in SOLOIST-WHF, where there is a “some concern” assessment for the "Selection of the reported results" component.	⊕⊕⊕⊕ High ⊕⊕⊕◯ Moderate ⊕⊕◯◯ Low ⊕◯◯◯ Very Low
Inconsistency	No serious (-1) very serious (-2)	I2 = 29%. It is said to have a high risk of heterogeneity if I^2>50%. The 95% CIs overlap.	
Indirectness	No Moderately serious (-0.5) serious (-1) very serious (-2)	The EMPEROR-PRESERVED, EMPEROR-REDUCED, DAPA-HF, DAPA-CKD, and DELIVER studies included not only type 2 diabetes mellitus patients but also non-diabetic patients. However, if sensitivity analysis is carried out, it shows similar results: HR = 0.66 (CI95% = 0.58 – 0.75) with all five studies vs. HR = 0.70 (CI95% = 0.53 – 0.94) without all five studies. In addition, the SCORED and SOLOIST-WHF studies include Asian populations in the rest of the world, so there may be other populations besides Asia. The CREDENCE and EMPEROR-REDUCED studies do not include India in the Asian region.	
Imprecision	No serious (-1) very serious (-2)	CI range with the same conclusion (the lowest and highest points produce the same conclusion).	

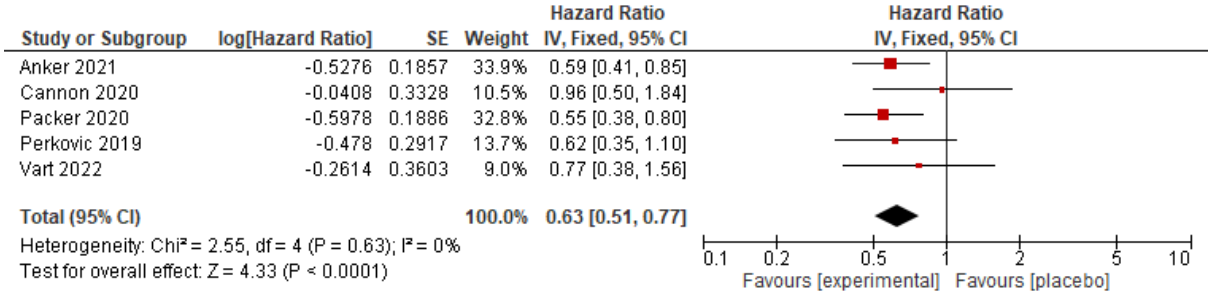
Publication Bias	Undetected Moderately suspected (-0.5) Strongly suspected (-1)	The author made an effort to include all research results by carrying out conversions and contacting the author if complete information is needed. The author also carried out hand searching. The results of the funnel plot show only one trial outside the funnel.

Appendix 9. Sensitivity Analysis Forest Plots

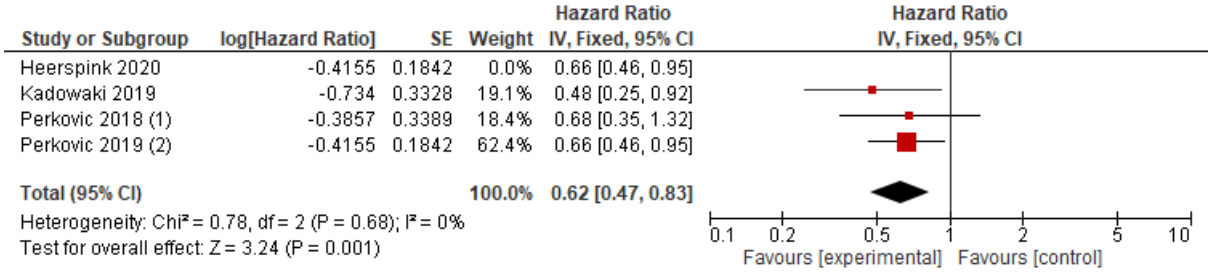
Composite of Cardiovascular Death / Hospitalization for Heart Failure, Without Urgent Visit for Heart Failure (Asian Race)



Composite of Cardiovascular Death / Hospitalization for Heart Failure, Without Urgent Visit for Heart Failure (Asia Region)

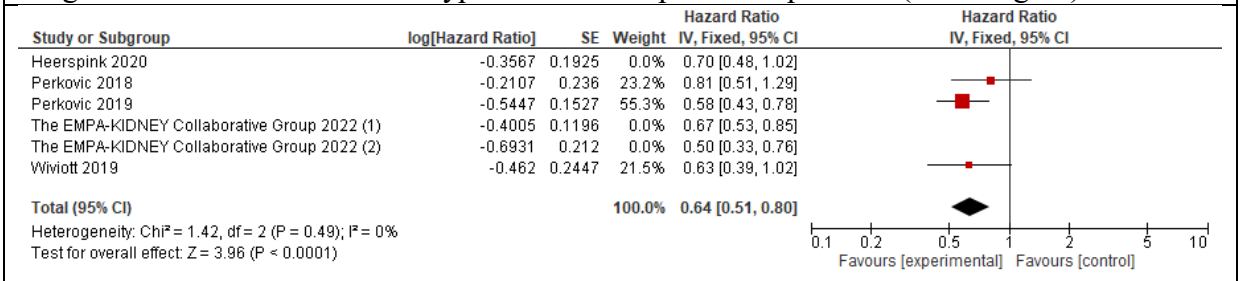


Progression of Renal Disease – Type 2 Diabetes Specific Population (Asian Race)



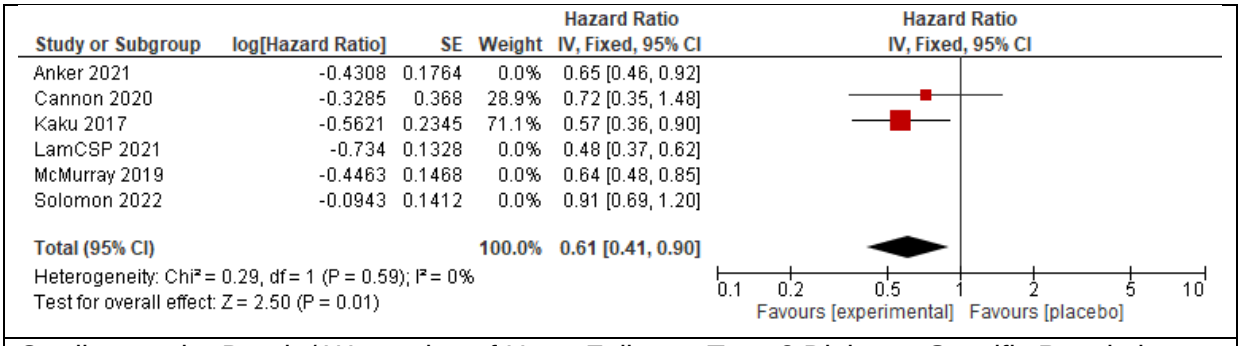
Footnotes
(1) CANVAS
(2) CREDENCE

Progression of Renal Disease – Type 2 Diabetes Specific Population (Asia Region)

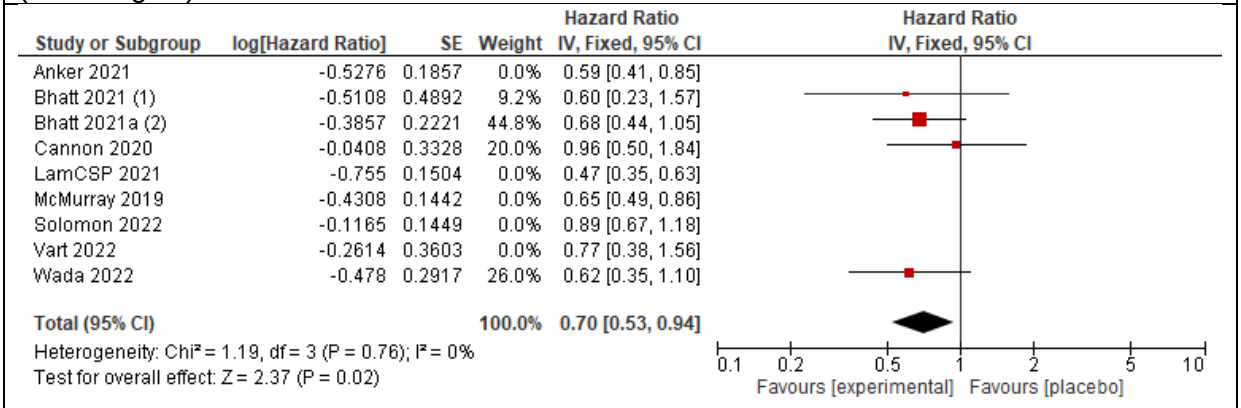


Footnotes
(1) China and Malaysia
(2) Japan

Cardiovascular Death / Worsening of Heart Failure – Type 2 Diabetes Specific Population (Asian Race)



Cardiovascular Death / Worsening of Heart Failure – Type 2 Diabetes Specific Population (Asia Region)



Footnotes
(1) SOLOIST-WHF
(2) SCORED

Appendix 10. Definitions of Renal Primary Outcomes from Each Study

Name of Study	Progression of Renal Disease Definition

DAPA-CKD	A composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes (6).
CREDENCE	A composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 ml per minute per 1.73 m2), a doubling of the serum creatinine level, or death from renal or cardiovascular causes (11).
EMPA-REG OUTCOME	Doubling of serum creatinine (accompanied by eGFR ≤45 mL/min/1.73 m2), initiation of renal-replacement therapy or death due to renal disease (14).
CANVAS Program	A composite of 40% reduction in eGFR, end-stage kidney disease, or death from renal causes (15).
EMPA-KIDNEY	A composite of progression of kidney disease (defined as end-stage kidney disease, a sustained decrease in eGFR to <10 ml per minute per 1.73 m2, a sustained decrease in eGFR of ≥40% from baseline, or death from renal causes) or death from cardiovascular causes (2)
DECLARE-TIMI 58	Death from cardiovascular or renal causes, end-stage kidney disease, or GFR decrease 40% ≥ to <60% (16)

Appendix 11. PRISMA 2020 Abstract Checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes (through certainty assessment)
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	(in main document)
Registration	12	Provide the register name and registration number.	Yes

Appendix 12. PRISMA 2020 CHECKLIST

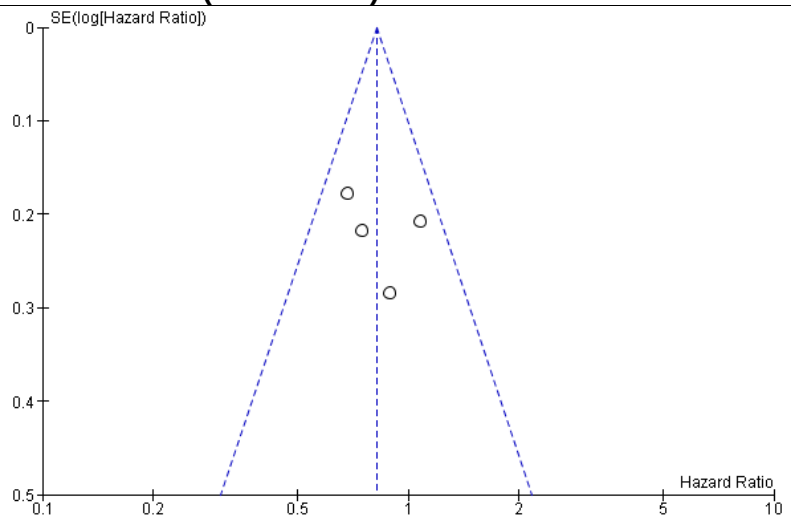
Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3-5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5-6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	5-6
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6-7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	7-8
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	7-8
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	8

Section and Topic	Item #	Checklist item	Location where item is reported
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	8
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	9
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	8-9
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	9
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	11
Study characteristics	17	Cite each included study and present its characteristics.	10
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	9
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	10-14
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	9-14
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	10-14
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	11-13
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	11
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	14
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	14
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	14-17
	23b	Discuss any limitations of the evidence included in the review.	17-18
	23c	Discuss any limitations of the review processes used.	17-18

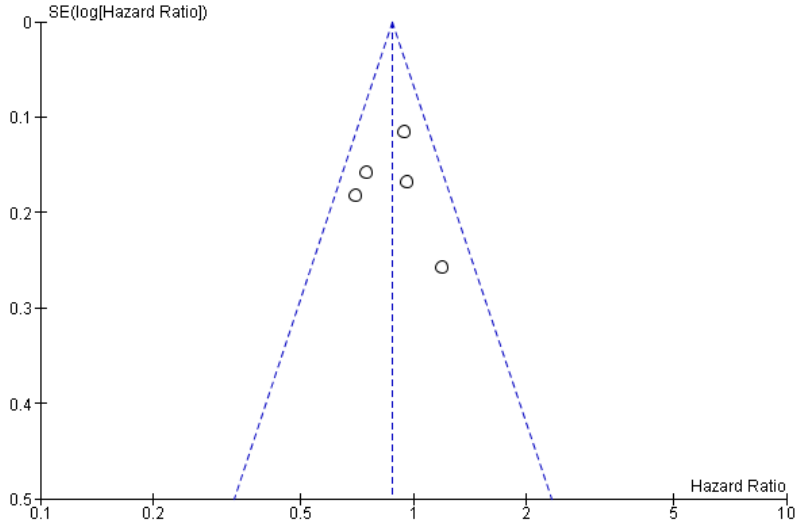
Section and Topic	Item #	Checklist item	Location where item is reported
	23d	Discuss implications of the results for practice, policy, and future research.	16, 19
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	5
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	This meta-analysis received no funding
Competing interests	26	Declare any competing interests of review authors.	No competing interests of review authors
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	27

Appendix 13. Funnel Plot of Primary Outcomes

3-Point MACE (Asian Race):

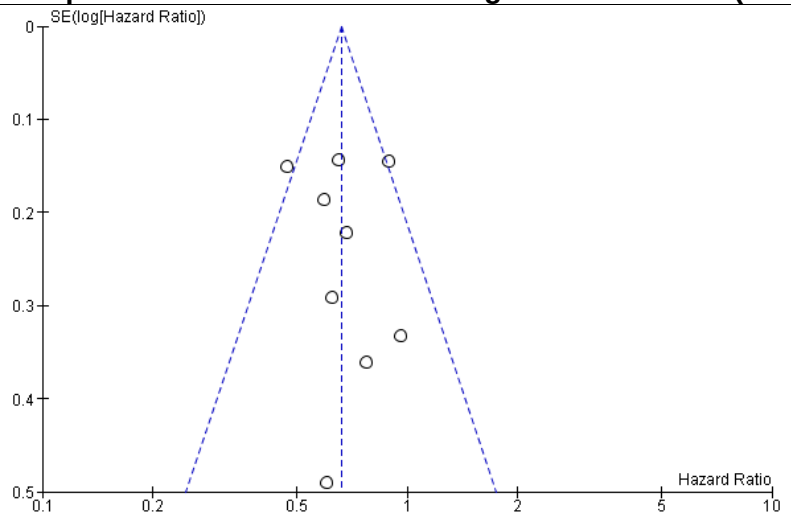


3-Point Mace (Asia Region):

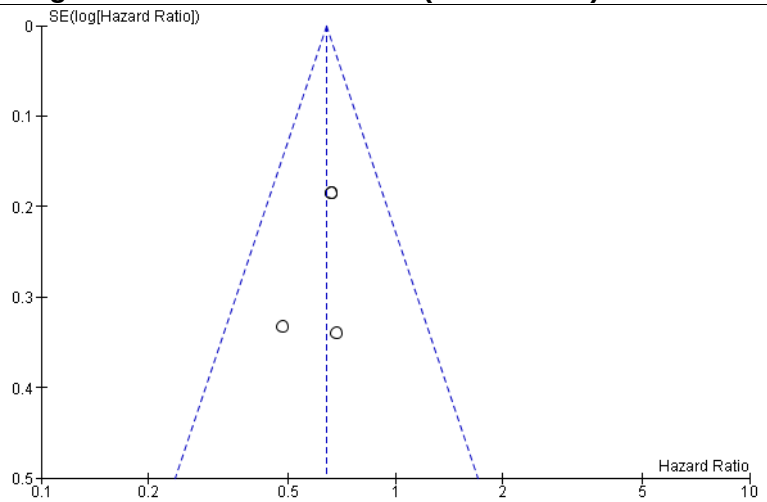


Composite of CV Death / Worsening of Heart Failure (Asian Race): Random effect model (funnel plot not generated)

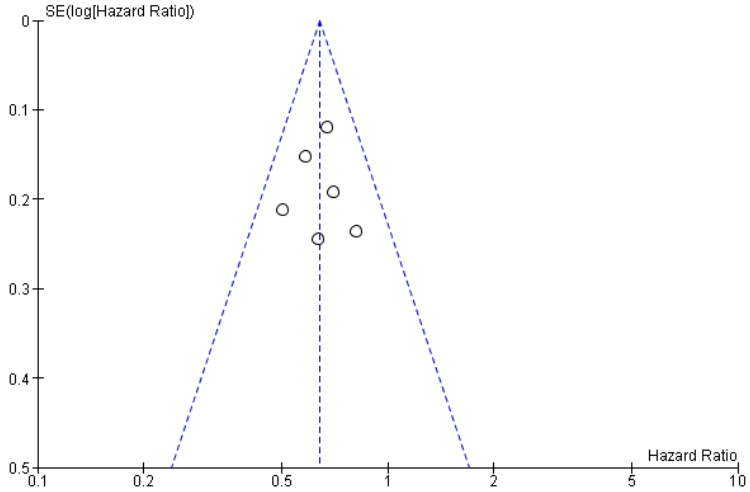
Composite of CV Death / Worsening of Heart Failure (Asia Region):



Progression of Renal Disease (Asian Race):



Progression of Renal Disease (Asia Region):



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