Lee, M. M.Y., Ghouri, N., McGuire, D. K., Rutter, M. K. and Sattar, N. (2021) Meta-analyses of results from randomized outcome trials comparing cardiovascular effects of SGLT2i and GLP-1RA in Asian vs. White patients with and without type 2 diabetes. *Diabetes Care*, (doi: 10.2337/dc20-3007).

This is the author's final accepted version.

There may be differences between this version and the published version. You are advised to consult the publisher's version if you wish to cite from it.

http://eprints.gla.ac.uk/233271/

Deposited on: 04 February 2021

Enlighten – Research publications by members of the University of Glasgow
http://eprints.gla.ac.uk

Full Title: Meta-analyses of results from randomized outcome trials comparing cardiovascular effects of SGLT2i and GLP-1RA in Asian vs. White patients with and without type 2 diabetes

Short Title: SGLT2i and GLP-1RA effects in Asians vs. Whites

Authors:
Matthew M. Y. Lee MBChB[1], Nazim Ghouri MD[1,2], Darren K. McGuire MD[3], Martin K. Rutter MD[4,5], Naveed Sattar MD[1]

Affiliations:
[1]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK
[2]Department of Diabetes and Endocrinology, Queen Elizabeth University Hospital, Glasgow, UK
[3]University of Texas Southwestern Medical Center, and Parkland Health and Hospital System, Dallas, TX, USA
[4]Division of Diabetes, Endocrinology and Gastroenterology, School of Medical Sciences, University of Manchester, Manchester, UK and Centre for Pharmacoepidemiology
[5]Diabetes, Endocrinology and Metabolism Centre, Manchester University NHS Foundation Trust, Manchester Academic Health Sciences Centre, Manchester, UK

Correspondence:
Professor Naveed Sattar
Professor of Metabolic Medicine
Institute of Cardiovascular and Medical Sciences
BHF Glasgow Cardiovascular Research Centre
University of Glasgow
126 University Place
Glasgow, G12 8TA
United Kingdom
Tel: +44 141 330 3419
Email: Naveed.Sattar@glasgow.ac.uk

Word Count: 1803 (main text)

Tables:	1
Figures:	3
Supplementary Figures:	2

ABSTRACT

BACKGROUND:
Results of cardiovascular outcome trials (CVOTs) suggest Asians may derive greater benefit than Whites with newer classes of antihyperglycemic medications.

PURPOSE:
To provide summary hazard ratio (HR) estimates for cardiovascular efficacy of sodium-glucose co-transporter 2 inhibitors (SGLT2i) and glucagon-like peptide receptor agonists (GLP-1RA) stratified by race (Asian vs. White).

DATA SOURCES:
A systematic review performed in PubMed from January 01, 2015 to December 08, 2020.

STUDY SELECTION:
Randomized placebo-controlled CVOTs of SGLT2is and GLP-1RAs that reported HR (95% CI) for (i) MACE, and (ii) cardiovascular (CV) death/ and hospitalization for heart failure (HHF).

DATA EXTRACTION AND SYNTHESIS:
The HR (95% CI) for selected outcomes in Asians and Whites was extracted from each trial, adhering to PRISMA guidelines. Random-effects meta-analyses were performed to examine differences between the selected outcomes in Asians vs. Whites.

RESULTS:
In 5 SGLT2i trials, the MACE outcome HR (95% CI) in 3,980 Asians vs. 29,007 Whites was 0.81 (0.60, 1.01) vs. 0.86 (0.76, 0.97), respectively ($p_{interaction}$=0.64). In 2 SGLT2i trials, the CV death/HHF outcome in 1,788 Asians vs. 5,962 Whites was 0.60 (0.47, 0.74) vs. 0.82 (0.73, 0.92), respectively ($p_{interaction}$=0.01). In 6 GLP-1RA trials, the MACE outcome in 4,195 Asians vs. 37,530 Whites was 0.68 (0.53, 0.84) vs. 0.87 (0.81, 0.94), respectively ($p_{interaction}$=0.03).

LIMITATIONS:
Lack of individual patient-level data, relatively short duration of trial observation, and lack of granular categorization of race with the broadly-defined Asian subgroups.

CONCLUSIONS:
Compared with Whites, Asians may derive greater HHF/CV death benefit from SGLT2is and MACE benefit from GLP-1RA.

PROSPERO registration number: CRD42020224993

Key Words: SGLT2 inhibitors, GLP-1 receptor agonists, type 2 diabetes, meta-analysis, race, ethnicity, Asian

INTRODUCTION

Randomized trial results and their meta-analyses have demonstrated the cardiovascular (CV) benefits of novel antihyperglycemic medications for type 2 diabetes such as sodium-glucose co-transporter 2 inhibitors (SGLT2i) and glucagon-like peptide receptor agonists (GLP-1RA) (1,2). Further, certain populations such as Asians, which form nearly 60% of the world's population, including South Asians and East/Southeast Asians (collectively here categorized as 'Asian' due to the way most trials categorize race), experience a greater burden of type 2 diabetes compared with Whites, though they vary markedly in their risk for atherosclerotic cardiovascular disease (ASCVD) (3,4). Results from a recent meta-analysis pooling data for Asians with type 2 diabetes also indicated a significant reduction in major adverse cardiovascular events (MACE) with GLP-1RAs but not with SGLT2is compared with placebo in Asians. However, this study did not directly compare Asians vs. Whites, and did not consider all relevant SGLT2i trials (5).

In the present paper, we meta-analyzed summary hazard ratio (HR) estimates from cardiovascular outcome trials (CVOTs) of SGLT2is and GLP-1RAs for effect modification of the efficacy of study drugs by race (Asian vs. White) with regard to selected CV outcomes. Of the antihyperglycemic drug classes, SGLT2is and GLP-1RAs are the only ones to show consistent benefits on cardiovascular outcomes, and therefore we set out to examine only these two drug classes.

METHODS

Data Sources and Searches

A systematic review (PROSPERO registration number CRD42020224993) was performed in PubMed from January 01, 2015 to December 08, 2020 to identify published large, randomized placebo-controlled trials of SGLT2is and GLP-1RAs (6). Our search strategy is detailed in our Supplementary Fig. 1 PRISMA diagram.

Study Selection

Inclusion criteria included CVOTs of SGLT2is and GLP-1RAs providing effect size estimates (HR (95% confidence interval (CI)) for the outcomes of (i) MACE, and (ii) CV death/hospitalization for heart failure (HHF), in the subgroups of interest, e.g., Asians and Whites. Patients with and without type 2 diabetes were included.

Data Extraction and Quality Assessment

The HR (95% CI) for the outcomes of interest in Asians and Whites was extracted from each study by at least two researchers independently, adhering to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (7). Risk of bias was assessed using version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) (Supplementary Fig. S2) (8).

Data Synthesis and Analysis

We used the statistical software Stata/SE 16.0, using the Stata command ‘meta’ to perform a random effects model (DerSimonian and Laird method) meta-analysis (9). Our primary analyses compared CV outcomes reported by race of Asian and White, in addition to tests for group differences ($p_{interaction}$).

RESULTS

We identified 11 SGLT2i trials and 7 GLP-1RA trials (Supplementary Fig. S1 PRISMA diagram).
(10–17).

Two SGLT2i trials (DECLARE-TIMI 58, SOLOIST-WHF) were excluded because the HR (95% CI) was not available for the subgroups of Asian and White patients (18,19). In SOLOIST-WHF, in the Asian subgroup, the HR could not be estimated due to 0 events in one of the treatment groups (19). Two further SGLT2i trials in patients with chronic kidney disease (CREDENCE, DAPA-CKD) were excluded because the reported outcomes available for Asian vs. White patients were neither MACE or CV death/HHF (13,14).

Seven trials of SGLT2is were analyzed (Table 1): 5 diabetes trials (EMPA-REG OUTCOME, CANVAS Program (CANVAS and CANVAS-R), VERTIS CV, SCORED) reported MACE, and 2 heart failure trials (Dapa-HF, EMPEROR-Reduced) reported CV death/HHF (10–12,15–17).

In 5 SGLT2i outcome trials including 3,980 Asian and 29,007 White patients with type 2 diabetes, the HR (95% CI) for the MACE outcome in Asian vs. White patients was 0.81 (0.60, 1.01) vs. 0.86 (0.76, 0.97) respectively ($p_{interaction}$=0.64) (Fig. 1).

In 2 SGLT2i outcome trials including 1,788 Asian and 5,962 White patients with heart failure and reduced ejection fraction (HFrEF), the HR (95% CI) for CV death/HHF in Asian vs. White patients was 0.60 (0.47, 0.74) vs. 0.82 (0.73, 0.92) respectively ($p_{interaction}$=0.01) (Fig. 2).

One GLP-1RA trial (ELIXA) was excluded because the HR (95% CI) was not extractable for the subgroups of Asian and White patients (20).

Six trials of GLP-1RAs were analyzed (Table 1): LEADER, SUSTAIN-6, EXSCEL, HARMONY OUTCOMES, REWIND, PIONEER 6 (21–26) reported MACE.

In 6 GLP-1RA trials with 4,195 Asian and 37,530 White patients, the HR (95% CI) for the MACE outcome in Asian vs. White patients was 0.68 (0.53, 0.84) vs. 0.87 (0.81, 0.94) respectively ($p_{interaction}$=0.03) (Fig. 3).

DISCUSSION

Results of clinical outcomes trials of SGLT2is and GLP-1RAs, comparing CV outcomes in Asians vs. Whites suggest differential treatment effects of SGLT2i (in those with HFrEF) and GLP-1RA by race, with greater benefits of both classes in Asians. Since the interaction between Asian race and outcomes seems consistent across different groups of studies, particular for the GLP-1RA class, it seems unlikely that random variation in baseline characteristics between trial arms explains the results.

The recent meta-analysis by Singh and Singh of 3 SGLT2i trials found no significant reduction in MACE, HHF or CV death in Asians and postulated whether these results were due to low statistical power, underrepresentation of Asians, or a true ethnic difference (5). However, there appears benefit in terms of reduction in risk for CV death/HHF when the two HFrEF trials are meta-analyzed. This suggests that

SGLT2is lessen risk in Asians at least as well as in white Europeans and potentially better in patients with heart failure. Perhaps more significantly, we show GLP-1RA-derived MACE benefits are significantly ($p_{interaction}$=0.03) better in Asians (mean 32% [16 to 47%] risk reduction) than in Whites (13% [6 to 19%]) with, remarkably, lower HRs in Asians vs. Whites in all of the 6 trials. In other words, GLP-1RAs have a ~2.5-fold larger relative risk reduction for the MACE endpoint in Asians compared to Whites.

These findings are all hypothesis generating and several limitations should be considered before concluding that such therapies, in particular GLP-1RA, lessen MACE risks more in Asians. Firstly, the Asian sub-population is often derived from several countries that collectively have a heterogeneous racial make-up, including East, South East and South Asians subgroups. While all Asian sub-groups are at elevated type 2 diabetes risk compared with Whites, their atherosclerotic cardiovascular disease risk can vary markedly, being higher in South Asians vs. Whites, but lower in other Asian subgroups (4). The findings are complex, however, as we noted lower CV mortality in South Asians compared to Whites in a recent observational study of people with type 2 diabetes (27). Furthermore, due to lack of breakdown of baseline characteristics by race in trials, it is not known to what extent Asian populations were (pre)treated with standard preventative therapies in each of the trials examined. It is possible that some Asian subgroups were less likely to be on comparative preventative therapy compared with Whites, leading to an apparent accentuated benefit seen with SGLT2i and/or GLP-1RA therapy in this treatment-naïve group, though even if this were true, such an observation would be clinically important.

Alternatively, there may be other genuine biological explanations for these differences which merit future investigation. For example, as diabetes onset is earlier in Asian subgroups, and at lower body mass index (BMI), it may be that MACE or other cardiac risk driven by glycaemia affected pathways are more pronounced in Asian groups and that such pathways are better targeted by novel diabetes therapies (28,29). This is speculative, however, and more work is needed to determine if differences are genuine and if so, to determine potential mechanisms including effects on multiple risk pathways.

There may have been differences in the proportion of Asian vs. White patients with type 2 diabetes and chronic kidney disease within the HF trials, although this information was not routinely available. A recent meta-analysis by Zannad et al of the two SGLT2i trials in patients with HFrEF showed no clear difference in outcomes by either diabetes status or eGFR levels above or below 60 ml/min/1.73m^2 (30). Therefore, it seems unlikely that at least these characteristics explain any potential differences in HHF/CV death outcomes by ethnicity.

Our meta-analysis has several limitations. Detailed analyses of specific sub-populations of Asians are not possible from these trials due to limitations of relevant data collection. There was heterogeneity between the studies, in particular in the SGLT2i outcome trials, with I^2 ranging from 0% to over 60%. That noted, there was far less heterogeneity within Asian and White groups in the analyses for which we report differences, namely for SGLT2i and heart failure, and in the GLP-1RA analysis (I^2 up to maximum of 28.6%). Whilst not definitive, these findings lend some

confidence to the findings we report. The primary outcomes varied amongst the 5 diabetes CVOTs vs. the 2 heart failure trials. Although trials reported data on Asians, as mentioned, data was lacking on more specific subgroups e.g., South Asians, East Asians or Southeast Asians. Definitions of race or ethnicity varied i.e., reported by patients in VERTIS CV, EMPEROR-Reduced, EXSCEL and HARMONY Outcomes, reported by investigators in SCORED and Dapa-HF, and not clearly specified in EMPA-REG OUTCOME, CANVAS Program, LEADER, SUSTAIN-6, REWIND or PIONEER 6. Our main goal, as pre-defined in PROSPERO, was to examine Asians vs. Whites, and therefore other races and ethnic groups were not analyzed. However, we feel that examining differences in other races and ethnic groups should form the basis of a separate report. Finally, individual patient-level data was not used for analyses, and therefore, we could not adjust for potential important differences such as duration of diabetes, baseline treatment, or baseline characteristics such as BMI or smoking histories, which vary between groups, which could have impacted the MACE and CV death/HHF outcomes.

Going forwards, we suggest an individual participant meta-analysis would be informative when all trial data are made available, including looking at the risk of adverse effects by ethnic group. It might also be of interest to look at adherence to therapy and the proportion of people who completed the trial or dropped out by ethnic group. For example, it might be that Asians recruited into CVOTs are more “compliant” with therapy than whites are. Such possibilities could also be assessed through secondary analyses.

In conclusion, there is an apparent greater benefit of GLP-1RA therapy in Asians compared to whites across all classes of GLP-1RA so far tested. In addition, Asians have at least as good an effect of SGLT2is on MACE and potentially better for HHF/CV death outcomes than do whites. For future trials to be more informative, Asian race needs to be recorded with greater granularity, rather than grouping by geographic region. In particular, Asian race (a grouping that now covers nearly 60% the world's population) should be broken down into more specific groups. We also suggest a need for more outcome-specific trials in Asian countries to further explore and validate the findings for GLP-1RAs. The findings of these analyses are relevant to the design, data capture and reporting of future CVOTs.

ACKNOWLEDGMENTS

Funding: This work was supported by the British Heart Foundation Centre of Research Excellence Grant RE/18/6/34217 to N.S. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Duality of Interest: M.M.Y.L reports employer, the University of Glasgow, has received grant support from Boehringer Ingelheim. N.G reports receiving honoraria from Astra Zeneca and consultancy fees from Sanofi, both unrelated to submitted work. D.K.M. reports receiving honoraria for clinical trial leadership from AstraZeneca, Boehringer Ingelheim, Eisai, Esperion, GlaxoSmithKline, Janssen, Lexicon, Merck, Novo Nordisk, CSL Behring, and Sanofi, and consultancy fees from Afimmune, Applied Therapeutics, AstraZeneca, Boehringer Ingelheim, Lilly, Merck, Pfizer, Novo Nordisk, Metavant, and Sanofi outside the submitted work, and personal fees and nonfinancial support from Merck and nonfinancial support from Pfizer outside the submitted work. MKR reports receiving research funding from Novo Nordisk, consultancy fees from Novo Nordisk and Roche Diabetes Care, and modest owning of shares in GlaxoSmithKline all outside the submitted work. N.S. reports grant and personal fees from Boehringer Ingelheim, and personal fees from Afimmune, Amgen, AstraZeneca, Eli Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer and Sanofi, outside the submitted work.

Author Contributions: M.M.Y.L., N.G. and N.S. extracted the data, performed the statistical analysis, interpreted the data and drafted the manuscript. N.G. and N.S. conceptualized and designed the study. D.K.M. and M.K.R. critically edited the manuscript. N.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility of the integrity of the data and the accuracy of the data analysis.

Acknowledgements: The authors thank Liz Coyle, University of Glasgow, for assistance with the preparation of this article.

REFERENCES

1. McGuire DK, Shih WJ, Cosentino F, et al. Association of SGLT2 Inhibitors With Cardiovascular and Kidney Outcomes in Patients With Type 2 Diabetes: A Meta-analysis. JAMA Cardiol. 7 October 2020 [Epub ahead of print]. DOI: 10.1001/jamacardio.2020.4511
2. Kristensen SL, Rørth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet Diabetes Endocrinol 2019;7:776–785
3. Sattar N, Gill JMR. Type 2 diabetes in migrant south Asians: mechanisms, mitigation, and management. Lancet Diabetes Endocrinol 2015;3:1004–1016
4. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ 2017;357:j2099
5. Singh AK, Singh R. Cardiovascular outcomes with SGLT-2 inhibitors and GLP-1 receptor agonist in Asians with type 2 diabetes: A systematic review and meta-analysis of cardiovascular outcome trials. Diabetes Metab Syndr 2020;14:715—722
6. National Institute for Health Research (NIHR) Centre for Reviews and Dissemination University of York. International Prospective Register of Systematic Reviews (PROSPERO) [Internet]. 2020 [cited 2020 Dec 8]. Available from: https://www.crd.york.ac.uk/prospero/
7. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1
8. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898
9. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–188
10. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med 2015;373:2117–2128
11. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med 2017;377:644–657
12. Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. N Engl J Med 2020;383:1425–1435
13. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med 2019;380:2295–2306
14. Heerspink HJL, Stefánsson B V, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med 2020;383:1436–1446
15. Bhatt DL, Szarek M, Pitt B, et al. Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease. N Engl J Med. 16 November 2020 [Epub ahead of print]. DOI: 10.1056/NEJMoa2030186
16. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med 2019;381:1995–2008
17. Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med 2020;383:1413–1424
18. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular

outcomes in type 2 diabetes. N Engl J Med 2019;380:347–357
19. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. N Engl J Med. 16 November 2020 [Epub ahead of print]. DOI: 10.1056/NEJMoa2030183
20. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. N Engl J Med 2015;373:2247–2257
21. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2016;375:311–322
22. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med 2016;375:1834–1844
23. Holman RR, Bethel MA, Mentz RJ, et al. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2017;377:1228–1239
24. Hernandez AF, Green JB, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. Lancet 2018;392:1519–1529
25. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet 2019;394:121–130
26. Husain M, Birkenfeld AL, Donsmark M, et al. Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med 2019;381:841–851
27. Wright AK, Kontopantelis E, Emsley R, et al. Life Expectancy and Cause-Specific Mortality in Type 2 Diabetes: A Population-Based Cohort Study Quantifying Relationships in Ethnic Subgroups. Diabetes Care 2017;40:338–345
28. Ntuk UE, Gill JMR, Mackay DF, Sattar N, Pell JP. Ethnic-Specific Obesity Cutoffs for Diabetes Risk: Cross-sectional Study of 490,288 UK Biobank Participants. Diabetes Care 2014;37:2500–2507
29. Wright AK, Welsh P, Gill JMR, et al. Age-, sex- and ethnicity-related differences in body weight, blood pressure, HbA_{1c} and lipid levels at the diagnosis of type 2 diabetes relative to people without diabetes. Diabetologia 2020;63:1542–1553
30. Zannad F, Ferreira JP, Pocock SJ, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. Lancet 2020;396:819–829

Table 1 - SGLT2i and GLP-1RA trials

Trial	Year	Population	Primary Outcome	Events/Patients, n/N		Events/Patients, n/N		Total Patients, N	
				Asian		White		Asian	White
				Treatment	Placebo	Treatment	Placebo		
SGLT2i primary MACE outcome trials (3,980 Asian + 29,007 White)									
EMPA-REG OUTCOME (10)	2015	Type 2 diabetes and high CV risk	Composite of CV death / nonfatal MI / nonfatal stroke	79 / 1,006	58 / 511	366 / 3,403	205 / 1,678	1,517	5,081
CANVAS Program* (11)	2017	Type 2 diabetes and high CV risk	Composite of CV death / nonfatal MI / nonfatal stroke	NR	NR	NR	NR	1,284	7,944
VERTIS CV (12)	2020	Type 2 diabetes and ASCVD	MACE (Composite of CV death / nonfatal MI / nonfatal stroke)	36 / 336	19 / 161	573 / 4,820	278 / 2,413	497	7,233
SCORED† (15)	2020	Type 2 diabetes, chronic kidney disease and risks for CV disease	Composite of total number of CV death / HFH / urgent visits for HF (original coprimary endpoints: first occurrence of CV death / nonfatal MI / nonfatal stroke and first occurrence of CV death / HFH)	NR	NR	NR	NR	682	8,749
SGLT2i primary CV death / HFH outcome trials (1,788 Asian + 5,962 White)									
Dapa-HF (16)	2019	HF with reduced ejection fraction, with and without type 2 diabetes	Composite of worsening HF (hospitalization or urgent visit resulting in IV therapy for HF) / CV death	78 / 552	118 / 564	275 / 1,662	348 / 1,671	1,116	3,333
EMPEROR-Reduced (17)	2020	HF with reduced ejection fraction, with and without type 2 diabetes	Composite of CV death / hospitalization for worsening HF	62 / 337	99 / 335	264 / 1,325	289 / 1,304	672	2,629
GLP-1RA primary MACE outcome trials (4,195 Asian + 37,530 White)									
LEADER (21)	2016	Type 2 diabetes and high CV risk	First occurrence of CV death / nonfatal MI / nonfatal stroke	40 / 471	56 / 465	494 / 3,616	543 / 3,622	936	7,238
SUSTAIN-6 (22)	2016	Type 2 diabetes and high CV risk	First occurrence of CV death / nonfatal MI / nonfatal stroke	8 / 121	17 / 152	93 / 1,384	118 / 1,352	273	2,736
EXSCEL (23)	2017	Type 2 diabetes with or without previous CV	First occurrence of CV death / nonfatal MI / nonfatal stroke	60 / 725	74 / 727	683 / 5,554	712 / 5,621	1,452	11,175

		disease							
HARMONY OUTCOMES (24)	2018	Type 2 diabetes and CV disease	First occurrence of CV death / MI / stroke	13 / 228	19 / 242	248 / 3,295	323 / 3,288	470	6,583
REWIND (25)	2019	Type 2 diabetes with previous CV disease or CV risk factors	First occurrence of nonfatal MI / nonfatal stroke / CV death	21 / 216	30 / 218	462 / 3,754	505 / 3,744	434	7,498
PIONEER 6 (26)	2019	Type 2 diabetes and high CV risk	First occurrence of MACE (CV death / nonfatal MI / nonfatal stroke)	9 / 324	19 / 306	46 / 1,148	55 / 1,152	630	2,300

*CANVAS Program comprises of two trials, CANVAS and CANVAS-R. † Sotagliflozin is a dual inhibitor of SGLT2 and SGLT1. ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; HFH, heart failure hospitalization; IV, intravenous; MACE, major adverse cardiovascular event; MI, myocardial infarction; NR, not reported; SGLT2i, sodium-glucose co-transporter 2 inhibitor.

Figure Legends

Figure 1 - SGLT2i cardiovascular outcome trials reporting MACE outcome by race

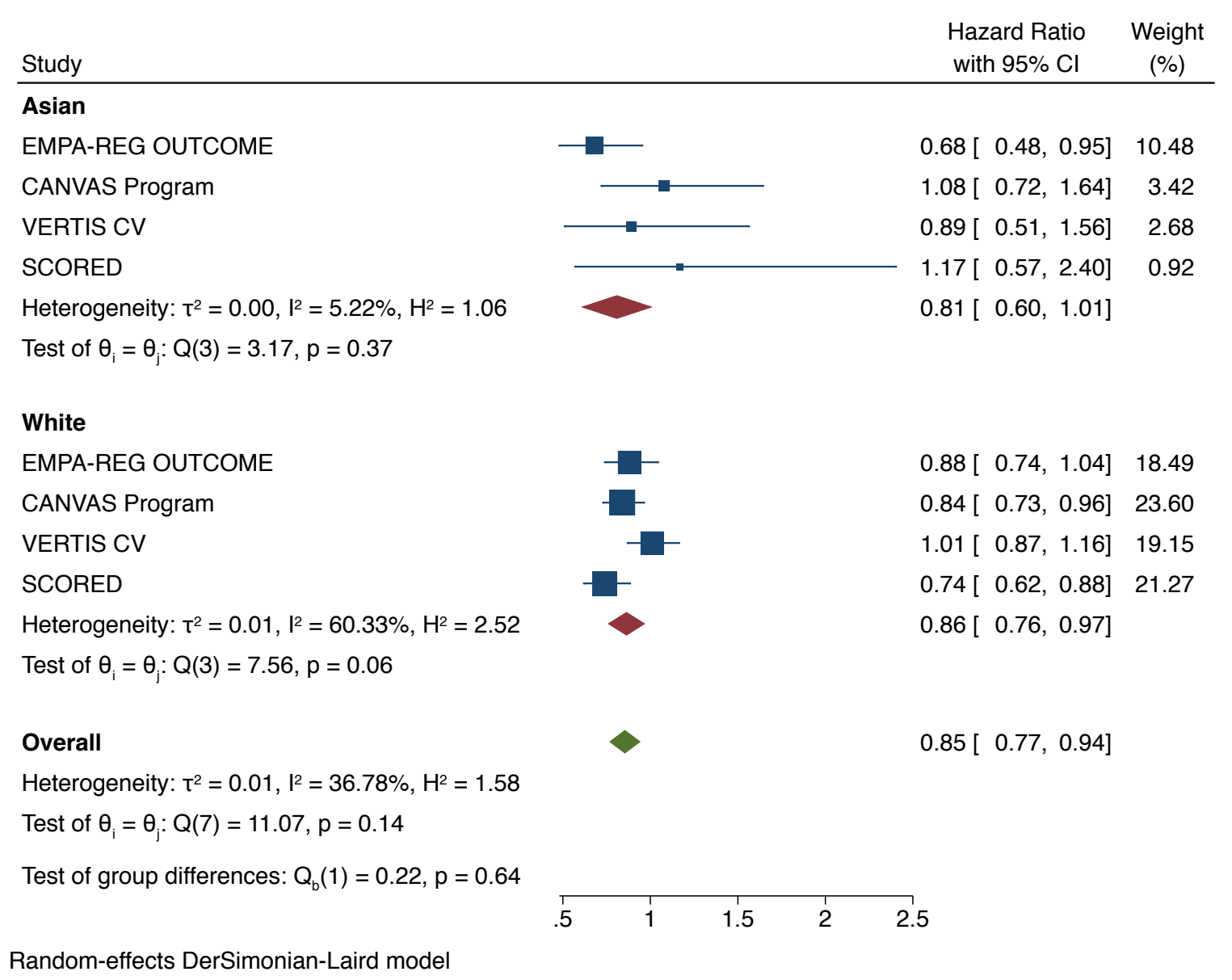
MACE, major adverse cardiovascular event; SGLT2i, sodium-glucose co-transporter 2 inhibitor.

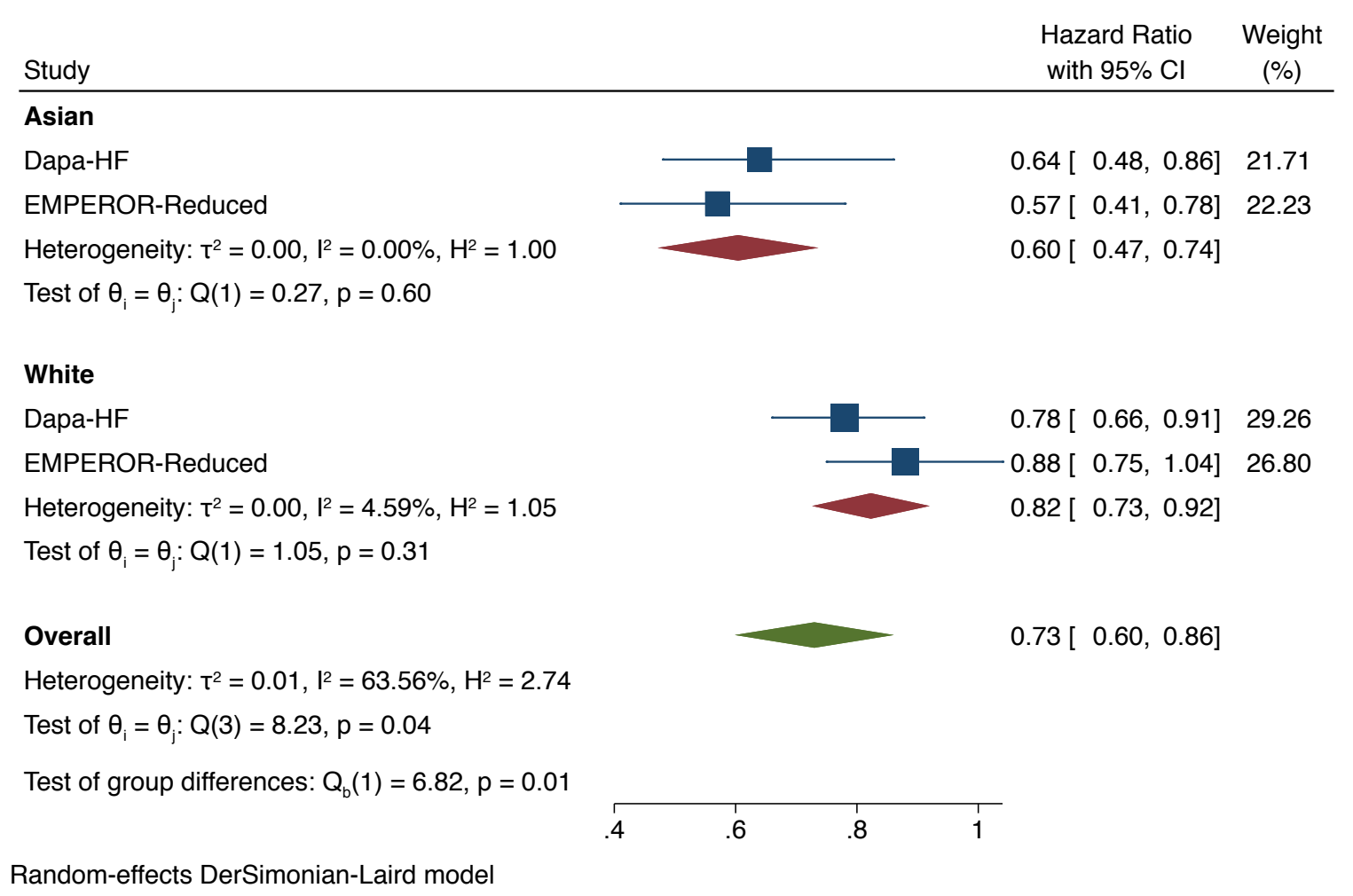
Figure 2 - SGLT2i cardiovascular outcome trials reporting CV death/HHF outcome by race

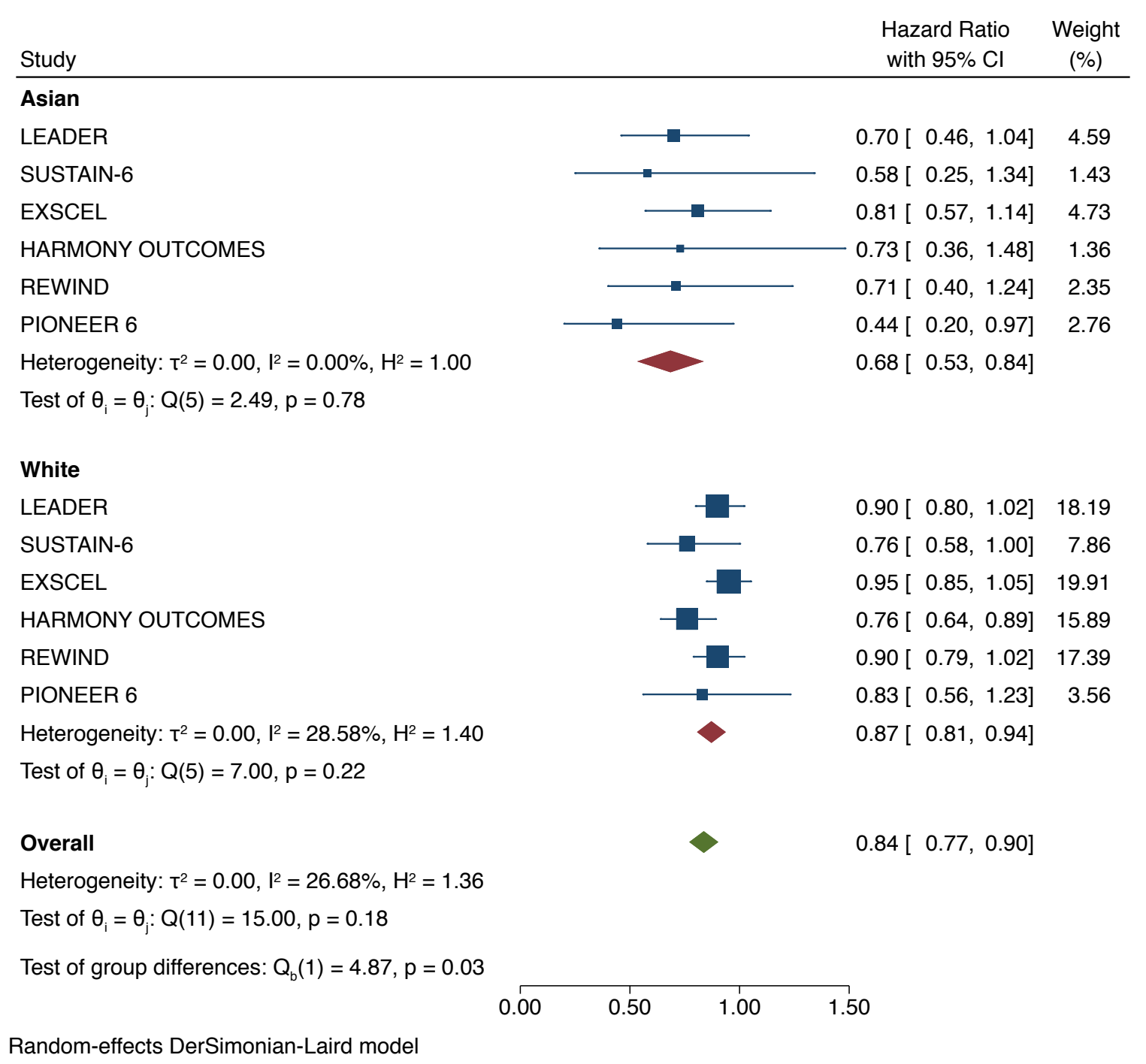
CV, cardiovascular; HHF, hospitalization for heart failure; SGLT2i, sodium-glucose co-transporter 2 inhibitor.

Figure 3 - GLP-1RA cardiovascular outcome trials reporting MACE outcome by race

GLP-1RA, glucagon-like peptide-1 receptor agonist; MACE, major adverse cardiovascular event.


Study
Hazard Ratio with 95% CI
Weight (%)
Asian
EMPA-REG OUTCOME 0.68 [0.48, 0.95] 10.48
CANVAS Program 1.08 [0.72, 1.64] 3.42
VERTIS CV 0.89 [0.51, 1.56] 2.68
SCORED 1.17 [0.57, 2.40] 0.92
Heterogeneity: τ² = 0.00, I² = 5.22%, H² = 1.06 0.81 [0.60, 1.01]
Test of θi = θj: Q(3) = 3.17, p = 0.37
White
EMPA-REG OUTCOME 0.88 [0.74, 1.04] 18.49
CANVAS Program 0.84 [0.73, 0.96] 23.60
VERTIS CV 1.01 [0.87, 1.16] 19.15
SCORED 0.74 [0.62, 0.88] 21.27
Heterogeneity: τ² = 0.01, I² = 60.33%, H² = 2.52 0.86 [0.76, 0.97]
Test of θi = θj: Q(3) = 7.56, p = 0.06
Overall 0.85 [0.77, 0.94]
Heterogeneity: τ² = 0.01, I² = 36.78%, H² = 1.58
Test of θi = θj: Q(7) = 11.07, p = 0.14
Test of group differences: Qb(1) = 0.22, p = 0.64
.5
1
1.5
2
2.5
Random-effects DerSimonian-Laird model


Study
Hazard Ratio with 95% CI
Weight (%)
Asian
Dapa-HF
0.64 [0.48, 0.86] 21.71
EMPEROR-Reduced
0.57 [0.41, 0.78] 22.23
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00
0.60 [0.47, 0.74]
Test of θi = θj: Q(1) = 0.27, p = 0.60
White
Dapa-HF
0.78 [0.66, 0.91] 29.26
EMPEROR-Reduced
0.88 [0.75, 1.04] 26.80
Heterogeneity: τ² = 0.00, I² = 4.59%, H² = 1.05
0.82 [0.73, 0.92]
Test of θi = θj: Q(1) = 1.05, p = 0.31
Overall
0.73 [0.60, 0.86]
Heterogeneity: τ² = 0.01, I² = 63.56%, H² = 2.74
Test of θi = θj: Q(3) = 8.23, p = 0.04
Test of group differences: Qb(1) = 6.82, p = 0.01
.4
.6
.8
1
Random-effects DerSimonian-Laird model


Study
Hazard Ratio with 95% CI
Weight (%)
Asian
LEADER 0.70 [0.46, 1.04] 4.59
SUSTAIN-6 0.58 [0.25, 1.34] 1.43
EXSCEL 0.81 [0.57, 1.14] 4.73
HARMONY OUTCOMES 0.73 [0.36, 1.48] 1.36
REWIND 0.71 [0.40, 1.24] 2.35
PIONEER 6 0.44 [0.20, 0.97] 2.76
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00 0.68 [0.53, 0.84]
Test of θi = θj: Q(5) = 2.49, p = 0.78
White
LEADER 0.90 [0.80, 1.02] 18.19
SUSTAIN-6 0.76 [0.58, 1.00] 7.86
EXSCEL 0.95 [0.85, 1.05] 19.91
HARMONY OUTCOMES 0.76 [0.64, 0.89] 15.89
REWIND 0.90 [0.79, 1.02] 17.39
PIONEER 6 0.83 [0.56, 1.23] 3.56
Heterogeneity: τ² = 0.00, I² = 28.58%, H² = 1.40 0.87 [0.81, 0.94]
Test of θi = θj: Q(5) = 7.00, p = 0.22
Overall 0.84 [0.77, 0.90]
Heterogeneity: τ² = 0.00, I² = 26.68%, H² = 1.36
Test of θi = θj: Q(11) = 15.00, p = 0.18
Test of group differences: Qb(1) = 4.87, p = 0.03
0.00
0.50
1.00
1.50
Random-effects DerSimonian-Laird model