Blood Pressure Lowering Effects of Sodium Glucose Transporter 2 Inhibitors Among Adult Patients with Type 2 Diabetes Mellitus: A Meta-Analysis

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Abstract

Introduction: Sodium glucose transporter 2 (SGLT2) inhibitors are a new class of anti-diabetic agents that not only lower down blood sugar but can potentially cause weight loss and decrease in blood pressure. The aim of this meta-analysis is to evaluate the magnitude of changes in blood pressure and safety parameters with the use of SGLT2 inhibitors among adult patients with type 2 diabetes mellitus (DM).

Methods: Randomized controlled trials (RCTs) were retrieved from electronic databases. We used the method recommend by the Cochrane Collaboration to perform a meta-analysis of RCTs of SGLT2 inhibitor for type 2 DM.

Results: Of 137 studies retrieved in the literature search, 28 were eligible for inclusion. A total of 23,728 patients with average age of 50-63 years old, when SGLT2 inhibitor were compared with placebo or active comparators there were statistically significant reduction in systolic (MD: -4.01, 95% CI -4.03 to -3.99) and diastolic blood pressure (MD: -1.48, 95% CI -1.49 to -1.46). There were no significant differences in the incidence of hypoglycemia (RR: 0.94, 95% CI 0.90 to 0.99, *P*<0.00001) between SGLT2 inhibitors and control groups. The incidence of urinary tract infections was similar between the SGLT2 inhibitors and the control groups (RR: 1.12, 95% CI 1.01 to 1.25, *P*=1.00). There was statistically greater incidence of orthostatic hypotension among patients given SGLT2 inhibitors than the control group (RR: 1.41, 95% CI 1.14 to 1.75, *P*=0.99).

Conclusion: Treatment with SGLT2 inhibitor provided statistically significant reductions in systolic and diastolic blood pressure in patients with type 2 DM compared with placebo or other anti-diabetic agents.

Keywords: blood pressure, sodium glucose transporter 2 inhibitor, type 2 diabetes mellitus

Introduction

In recent years, anti-diabetic drugs with new mechanisms of action have become available, expanding the treatment options for diabetes management. The sodium glucose transporter 2 (SGLT2) inhibitors are one such agents and they have already been included in the guidelines of many international associations including American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) as one of the second line agents for the treatment type 2 diabetes mellitus (DM).[1] The SGLT2 inhibitors block renal glucose reabsorption and lower the renal threshold for glucose, thereby markedly increasing urinary glucose excretion (UGE).[1-3] Because of their mechanism of Philippine Journal of Internal Medicine Meta-Analysis action by causing diuresis, these drugs also have a secondary effect of lowering the blood pressure.[1,3] This has been shown consistently across various type of agents in this drug class but the magnitude of the blood pressure lowering effect has not been well elaborated.

Most of patients with type 2 DM also have other concomitant cardiovascular problems, such as hypertension and dyslipidemia. Thus, many diabetic individuals also take anti-hypertensive medications aside from their antihyperglycemic agent. Therefore, the intake of anti diabetic drugs with secondary blood pressure lowering effects such as the SGLT2 inhibitors along with the typical anti-hypertensive medications may lead to significant drug interactions causing adverse drug reactions such as orthostatic hypotension. There are variability results on the degree of blood pressure changes in using SGLT2 inhibitor agents for adult patients with type 2 DM. Thus, the aim of this current study was to perform a meta-analysis to determine the magnitude of the blood pressure changes with the use intake of SGLT2 inhibitor agents for adult type 2 DM patients. We also would like to investigate the side effects of hypoglycemia, orthostatic hypotension and urinary tract infection.

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Methods

We conducted a systematic literature search using PubMed and ProQuest for studies of adults with type 2 DM using SGLT2 inhibitors. The search strategy combined the Medical Subject Headings (MeSH) Terms: "diabetes mellitus, non-insulin dependent or type 2 diabetes mellitus", and "sodium glucose transporter 2", and limited the studies to controlled clinical trials (Phase 3), and keywords canagliflozin, dapagliflozin, empagliflozin. We only included phase III trials because we want to see the effect of SGLT2 inhibitors compared with active comparators or placebo. All potentially relevant articles were reviewed according to inclusion criteria.

The following inclusion criteria were used: (1) types of participants: adult patients with type 2 DM according to the standard criteria, including American Diabetes Association (ADA) 1997 and World Health Organization (WHO) 1998; (2) types of interventions: patients treated with SGLT 2 inhibitor agent (dapagliflozin, empagliflozin, or canagliflozin) for at least 12 weeks, compared with placebo or active agent(s); (3) types of outcome measures: systolic and diastolic blood pressure changes from baseline; and (4) language: we only included articles published in English.

The following exclusion criteria were applied: (1) participants with type 1 diabetes, or unstable cardiac disease, (2) participants with severe chronic kidney disease, and (3) results published in reviews, letters, and abstracts. In cases in which there were two or more published reports on the same population or group of participants, we only included the most recent study.

Risk of bias in the included studies was assessed by several domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants (performance bias), outcome assessment(detection bias), incomplete outcome data (attrition bias), presence of selective reporting (reporting bias), and presence of other biases. All the included studies were of low risk for bias.

We analyzed the number of participants reporting changes in systolic and diastolic blood pressure. The mean differences (MD) and 95% confidence intervals (CIs) for change from baseline in experimental (SGLT2 inhibitors) versus control (placebo) groups were calculated for these continuous variables. Chi^2 test and the I^2 statistic were used to evaluate heterogeneity. A meta-analysis was done for the outcomes of mean differences in blood pressure, and for the other safety outcomes of incidence of hypoglycemia, urinary tract infections and orthostatic hypotension by combining different groups of studies, using the Review Manager statistical software package (version 5.3)

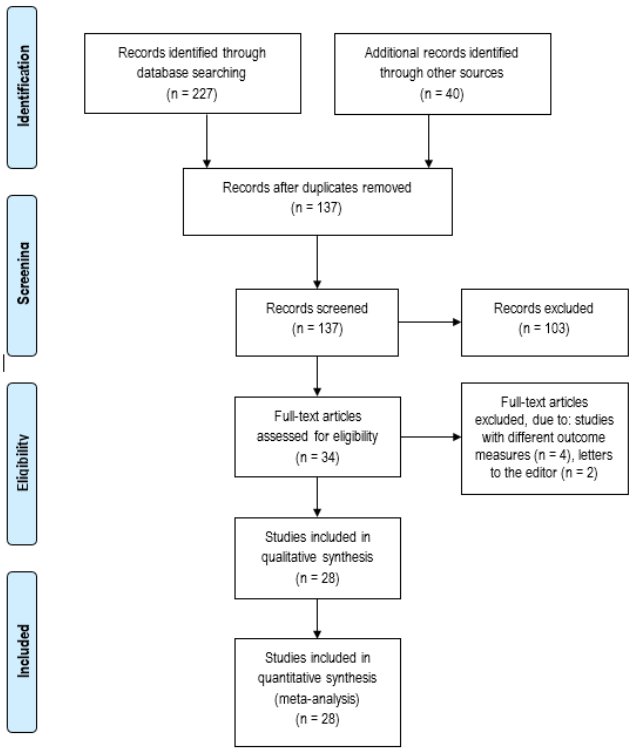

Figure 1. Flow chart of the study selection process

Results

The study selection process is summarized in Figure 1. A total of 34 phase III clinical trials were identified, and 28 articles were judged according to our inclusion criteria to be appropriate for the meta-analysis. There were ten RCTs (n=12227) evaluated canagliflozin, eleven RCTs (n=5456) evaluated dapagliflozin, seven RCTs (n=6045) evaluated empagliflozin. All twenty eight studies were assessed to be low risk for biases. These SGLT2 inhibitors were compared to either placebo or active comparators such as metformin, sulfonylurea, or multiple injections of insulin. (Appendices A and B)

Overall effects of SGLT2 inhibitors on blood pressure based on the meta-analysis, is a small decrease in the systolic blood pressure with a mean difference (MD) of-4.01mmHg, 95% CI -4.03 to -3.99, P<0.00001 (Appendix C) and diastolic blood pressure MD of -1.48mmHg, 95% CI -1.49to -1.46, P<0.00001 (Appendix D). Pooled studies had high heterogeneity for systolic blood pressure changes (I^2 of 99%, P<0.00001) and diastolic blood pressure changes (I^2 of 99%, P<0.00001).

To investigate the source of heterogeneity, a sensitivity analysis was performed. In a pre-specified subgroup analysis (Appendices E and F), we analyzed SGLT2 inhibitors based on their types, canagliflozin, dapagliflozin, empagliflozin. We found that canagliflozin gave the largest decrease in systolic blood pressure (-4.15 mmHg, 95% CI -4.18 to -4.13,

P<0.00001), followed by empagliflozin (-3.8 mmHg, 95% CI -3.84 to -3.76, *P*<0.00001), and dapagliflozin (-3.69 mmHg, 95% CI -3.78 to -3.59, *P*<0.00001). (Appendix E) On the other hand, dapagliflozin gave the largest decrease in diastolic blood pressure (-1.56 mmHg, 95% CI -1.61 to -1.51, *P*<0.00001), followed by canagliflozin (-1.52 mmHg, 95% CI -1.54 to -1.50, *P*<0.00001), then empagliflozin (-1.38 mmHg, 95% CI -1.40 to -1.36, *P*<0.00001). (Appendix F) All of these subgroup analysis results also still showed high heterogeneity.

The common adverse events that were reported in these studies were urinary tract infection, hypoglycemia and orthostatic hypotension. There were no significant differences in the incidence of hypoglycemia (RR: 0.94, 95% CI 0.90 to 0.99, *P*<0.00001) between SGLT2 inhibitors and control groups (Appendix G), with a trend towards decreased risk for hypoglycemia for SGLT2 inhibitors. The incidence of urinary tract infection was similar between the SGLT2 inhibitors and the control groups (RR: 1.12, 95% CI 1.01 to 1.25, *P*=1.00). (Appendix H) There was statistically greater incidence of orthostatic hypotension among patients given SGLT2 inhibitors than the control groups (RR: 1.41, 95% CI 1.14 to 1.75, *P*=0.99). (Appendix I)

Discussion

This meta-analysis assessed the blood pressure (BP) changes with the use of SGLT2 inhibitors among adult type 2 DM patients and demonstrated that the treatment with SGLT2 inhibitor agents provided statistically meaningful reduction in systolic and diastolic blood pressure compared with placebo. In this meta-analysis, the results showed that the use of SGLT2 inhibitors decreased systolic BP by 4.01 mmHg (-4.03 to -3.99) and diastolic blood pressure by 1.48 mmHg (-1.49 to -1.46).

The magnitude of decrease in blood pressure is not only statistically significant but also has clinical significance in terms of reducing cardiovascular disease risk. It was reported that lowering systolic blood pressure even by only 2 mmHg, could result in approximately seven percent lower mortality risk from ischemic heart disease and a 10% lower mortality risk from stroke.[31] In "The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure" (JNC 7), it has been estimated that a 5 mmHg reduction of systolic blood pressure would result in a 14% reduction in mortality due to stroke, a nine percent reduction in mortality, and a seven percent decrease in all cause of mortality.[32] It should be noted that in some of the studies especially with the use of higher doses of the SGLT2 inhibitors, the systolic blood pressure lowering did reach -5 mm Hg, and for a few studies even as high as 7 mm Hg drop in blood pressure. There is potential therefore for these drugs to significantly modify the cardiovascular outcomes of patients with type 2 DM.

However, this BP lowering effect may also potentiate the side effects related to BP changes such as orthostatic hypotension or dizziness among those whose blood pressures are either normal or controlled by anti-hypertensive agents. This latter effect is especially an important precaution among the elderly. Although, our study only included patients from 50-63 years old in average and thus, we cannot conclude BP lowering effect of SGLT2 inhibitors on elderly patients.

Previous meta-analysis study done by Liu, et al., with fourteen studies included also showed a significantly reduced systolic blood pressure (for one year result: -2.87 mmHg and two years result: -7.5 mmHg) and diastolic blood pressure (for one year result: -1.95 mmHg and two years result: -2.19 mmHg).[33]

To our knowledge, this paper is the most updated meta-analysis on this topic. This study had shown that the use of SGLT2 inhibitors led to a statistically significant reduction in systolic and diastolic blood pressure, but it was drawn from a high heterogeneity data. This has become the main limitation of our study. The other limitation is the possibility that important published articles and unpublished data were missed. Searches were limited only to some SGLT2 inhibitor agents (dapagliflozin, empagliflozin, and canagliflozin) and published in English language articles, and it is likely we missed some RCTs published in other languages. Furthermore, different time and position while BP measured were used in the included RCTs.

Conclusion

Treatment with SGLT2 inhibitor provided statistically significant reductions in systolic (-4.01mmHg) and diastolic (-1.48mmHg) blood pressure in adult patients with type 2 DM compared with placebo. These agents also had statistically greater incidence of orthostatic hypotension compared to the control groups (RR: 1.41). Further studies on more homogenous, larger population of participants and longer duration of treatment are necessary to provide a more conclusive evidence on the long-term effects of SGLT2 inhibitors on BP changes for adult patients with type 2 DM.

Conflict of interest

The primary author, Dr. Alius Cahyadi has nothing to disclose. On the other hand, Dr. Jimeno is a member of the advisory board and a speaker for Johnson and Johnson, the manufacturers of Canagliflozin. She has also conducted Phase 3 clinical trials for both dapagliflozin and empagliflozin.

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Appendices

Appendix A. Characteristics of studies included in the meta-analysis of SGLT2 inhibitors and their effects on lowering blood pressure

Study Name	Study Design	SGLT2 group	n	Follow up (weeks)	Average Age (y)	Baseline SBP	Baseline DBP
Cefalu et al (2013)	R, DB, AC	CANA 100 mg/day	483	52	56.4±9.5	130.0±12.4	78.7±8.0
		CANA 300 mg/day	485		55.8±9.2	130.0±13.8	79.2±8.4
		glim 6-8 mg/day	482		56.3±9.0	129.5±13.5	79.0±8.4
Forst et al (2014)	R, DB, PC	CANA 100 mg/day	113	26	56.7±10.4	126.4±12.3	75.6±7.8
		CANA 300 mg/day	114		57.0±10.2	126.7±12.0	76.6±8.3
		Placebo	115		58.3±9.6	128.2±12.3	77.1±8.2
Inagaki et al (2013)	R, DB, PC	CANA 50 mg/day	82	12	57.4±10.8	NR	NR
		CANA 100 mg/day	74		57.7±10.5		
		CANA 200 mg/day	76		57.0±10.7		
		CANA 300 mg/day	75		57.1±10.1		
		Placebo	75		57.7±11.0		
Ji et al (2015)	R, DB, PC	CANA 100 mg/day	223	18	56.5±8.3	130.0±13.8	77.4±8.5
		CANA 300 mg/day	227		56.4±9.2	129.5±14.4	77.1±8.7
		Placebo	226		55.8±9.4	129.0±14.0	77.5±8.7
Leiter et al (2015)	R, DB, AC	CANA 100 mg/day	483	104	56.4±9.5	130.0±12.4	78.7±8.0
		CANA 300 mg/day	485		55.8±9.2	130.0±13.8	79.2±8.4
		glim 6-8 mg/day	482		56.3±9.0	129.5±13.5	79.0±8.4
Levalle-Gonzalez et al (2013)	R, DB, AC	CANA 100 mg/day	368	26	55.5±9.4	128.0±12.7	77.7±8.4
		CANA 300 mg/day	367		55.3±9.2	128.7±13.0	77.9±8.3
		sita 100 mg/day	366		55.5±9.6	120.0±13.5	77.5±8.0
Neal et al (2014)	R, DB, PC	CANA 100 mg/day	692	52	62	136.9±16.7	76.2±9.9
		CANA 300 mg/day	690		63	137.1±16.7	76.3±9.8
		Placebo	690		63	137.8±16.2	77.2±10.3
Rosenstock et al (2012)	R, DB, PC	CANA 50 mg/day	64	12	53.3±8.5	127±11	77±8
		CANA 100 mg/day	64		51.7±8.0	127±13	78±8
		CANA 200 mg/day	65		52.9±9.6	124±11	77±9
		CANA 300 mg/day	64		52.3±6.9	126±12	80±8
		CANA 300 mg BID	64		55.2±7.1	128±13	79±8
		Placebo	65		53.3±7.8	125±10	78±8
Schernthaner et al (2013)	R, DB, AC	CANA 300 mg/day	377	52	56.6±9.6	131.2±13.2	79.2±7.8
		sita 100 mg/day	378		56.7±9.3	130.1±14.0	78.6±8.9
Stenlof et al (2013)	R, DB, PC	CANA 100 mg/day	195	26	55.1±10.8	126.7±12.5	77.7±6.8
		CANA 300 mg/day	197		55.3±10.2	128.5±12.7	79.1±8.3
		Placebo	192		55.7±10.9	127.7±13.7	77.4±8.4
Bailey et al (2010)	R, DB, PC	DAPA 2.5 mg/day	137	24	55.0±9.3	126.6±14.5	79.5±8.7
		DAPA 5 mg/day	137		54.3±9.4	126.9±14.3	80.8±8.5
		DAPA 10 mg/day	135		52.7±9.9	126.0±15.9	79.0±10.2
		placebo	137		53.7±10.3	127.7±14.6	80.9±9.0
Bolinder et al (2012)	R, DB, PC	DAPA 10 mg/day	89	24	60.6±8.2	135.9	80.6
		placebo	91		60.8±6.9	133.3	80.4
Bolinder et al (2014)	R, DB, PC	DAPA 10 mg/day	89	102	60.6±8.2	136.1±13.8	80.6±8.0
		placebo	91		60.8±6.9	133.3±13.7	80.4±8.3
Ferrannini et al (2010)	R, DB, PC	DAPA 2.5 mg/day	65	24	53.0±11.7	NR	NR
		DAPA 5 mg/day	64		52.6±10.9		
		DAPA 10 mg/day	70		50.6±10.0		
		placebo	75		52.7±10.3		
Heerspink et al (2013)	R, DB, AC-PC	DAPA 10 mg/day	24	12	53.7±9.4	133±13	76±8

Appendix A. Characteristics of studies included in the meta-analysis of SGLT2 inhibitors and their effects on lowering blood pressure

Study Name	Study Design	SGLT2 group	n	Follow up (weeks)	Average Age (y)	Baseline SBP	Baseline DBP
		hctz 25 mg/day	26		54.8±9.9	122±12	69±9
		placebo	25		58.0±9.5	131±11	74±6
List et al (2009)	R, DB, PC	DAPA 2.5 mg/day	59	12	55±11	127±14	78±8
		DAPA 5 mg/day	58		55±12	126±13	76±8
		DAPA 10 mg/day	47		54±9	127±16	77±8
		DAPA 20 mg/day	59		55±10	127±15	77±8
		DAPA 50 mg/day	56		53±10	126±16	77±9
		placebo	54		53±11	126±16	77±8
Nauck et al (2011)	R, DB, AC	DAPA 2.5-10 mg/day	406	52	58±9	132.8	80.6
		glip 5-20 mg/day	408		59±10	133.8	80.6
Rosenstock et al (2012)	R, DB, PC	DAPA 5 mg/day	141	48	53.2±10.9	NR	NR
		DAPA 10 mg/day	140		53.8±10.4		
		placebo	139		53.5±11.4		
Schumm-Draeger et al (2015)	R, DB, PC	DAPA 2.5 mg BID	100	16	58.3±9	132.4±13.3	80.5±7.4
		DAPA 5 mg BID	99		55.3±9.3	130.3±11.4	81.3±6.7
		DAPA 10 mg/day	99		58.5±9.8	132.2±12	79.4±7.7
		placebo	101		58.5±9.4	133.4±11.9	81.5±6.7
Wilding et al (2009)	R, DB, PC	DAPA 10 mg/day	24	12	55.7±9.2	130.7±14.5	78.9±8.7
		DAPA 20 mg/day	24		56.1±10.6	126.9±13.9	76.5±5.2
		placebo	23		58.4±6.5	128.9±14.0	76.9±9.3
Wilding et al (2012)	R, DB, PC	DAPA 2.5 mg/day	202	48	59.8±7.6	139.6±17.7	79.5±10.1
		DAPA 5 mg/day	211		59.3±7.9	137.8±16.2	81.1±8.9
		DAPA 10 mg/day	194		59.3±8.8	140.6±16.7	79.9±9.3
		placebo	193		58.8±8.6	136.1±17.2	80.0±9.6
Haring et al (2013)	R, DB, PC	EMPA 10 mg/day	225	24	57.0±9.2	128.7±13.9	78.4±9.6
		EMPA 25 mg/day	216		57.4±9.3	129.3±14.2	79.0±8.4
		placebo	225		56.9±9.2	128.8±14.3	78.3±8.6
Haring et al (2014)	R, DB, PC	EMPA 10 mg/day	217	24	55.5±9.9	129.6±14.1	79.6±8.0
		EMPA 25 mg/day	213		55.6±10.2	130.0±15.1	78.4±8.4
		placebo	207		56.0±9.7	128.6±14.7	78.1±7.9
Ridderstrale et al (2014)	R, DB, AC	EMPA 25 mg/day	432	104	56.2±10.3	133.4±15.9	79.5±9.6
		glim 1-4 mg/day	421		55.7±10.4	133.5±16	79.4±9.2
Roden et al (2013)	R, DB, PC	EMPA 10 mg/day	224	24	56.2±11.6	133.0±16.6	79.2±9.6
		EMPA 25 mg/day	224		53.8±11.6	129.9±17.5	78.3±9.4
		placebo	228		54.9±10.9	130.4±16.3	78.9±9.6
Rosenstock et al (2013)	R, DB, PC	EMPA 1 mg/day	71	12	57±8.8	132.7	79.2
		EMPA 5 mg/day	71		60±7.3	133.2	79.4
		EMPA 10 mg/day	71		59±9.0	132.4	79.1
		EMPA 25 mg/day	70		59±8.1	135.3	81.9
		EMPA 50 mg/day	70		56±9.4	130.9	80.1
		placebo	71		60±8.5	136	79.9
Rosenstock et al (2014)	R, DB, PC	EMPA 10 mg/day	186	52	56.7±8.7	134.2±16.4	79.5±8.5
		EMPA 25 mg/day	189		58.0±9.4	132.9±14.2	78.7±8.5
		placebo	188		55.3±10.1	132.6±15.8	78.2±8.8
Tikkanen et al (2015)	R, DB, PC	EMPA 10 mg/day	276	12	60.6±8.5	142.3±12.1	84.1±7.3
		EMPA 25 mg/day	276		59.9±9.7	141.9±12.5	83.8±6.8
		placebo	271		60.3±8.8	142.0±12.4	83.7±7.1

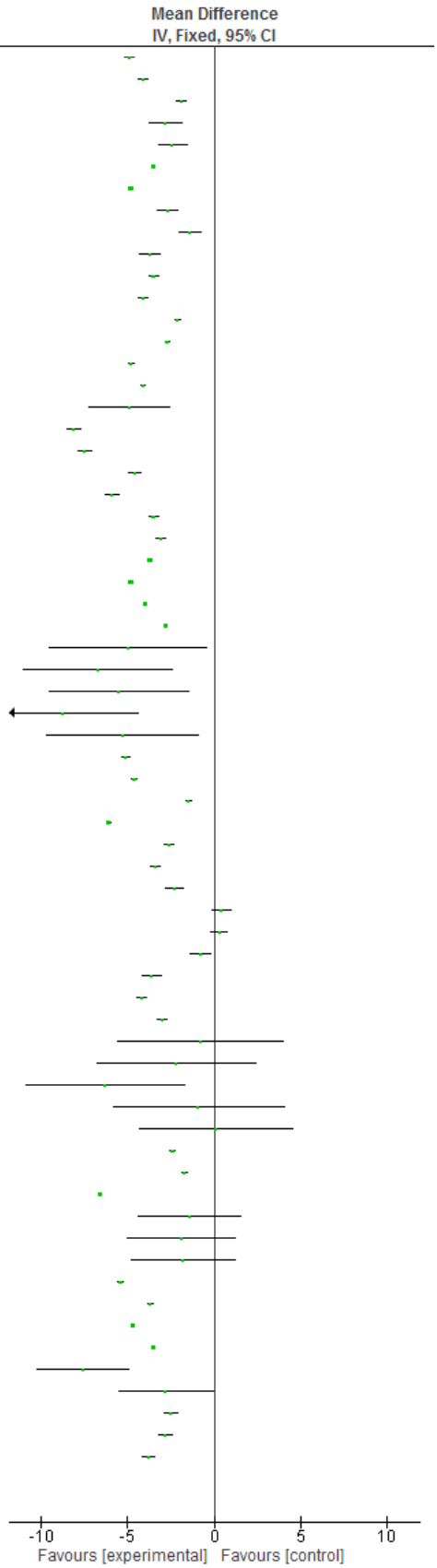
AC: active controlled, CANA: canagliflozin, DAPA: dapagliflozin, DB: double blind, DBP: diastolic blood pressure, EMPA: empagliflozin, glim: glimepiride, hctz: hydrochlorthiazide, NR: not reported, PC: placebo controlled, R: randomized, sita: sitagliptin, SBP: systolic blood pressure, SGLT2: sodium glucose transporter 2 inhibitor

Appendix B. Studies included in meta-analysis

Variables	N = 23,728
Age	50-63 years old
Duration of studies	12-104 weeks
Canagliflozin[2,4-12]	Cefalu 2013, Forst 2014, Inagaki 2013, Ji 2015, Leiter 2015, Levalle-Gonzalez 2013, Neal 2014, Rosenstock 2012, Scherthaner 2013, Stenlof 2013
Dapagliflozin[13-23]	Bailey 2010, Bolinder 2012, Bolinder 2014, Ferrrannini 2010, Heerspink 2013, List 2009, Nauck 2011, Rosenstock 2012, Schumm-Draeger 2015, Wilding 2009, Wilding 2012
Empagliflozin[24-30]	Haring 2013, Haring 2014, Ridderstrale 2014, Roden 2013, Rosenstock 2013, Rosenstock 2014, Tikkanen 2015

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bailey 2010 Dapa	-5.1	1.3	135	-0.2	1.2	137	0.5%	-4.90 [-5.20, -4.60]
Bailey 2010 Dapa	-4.3	1.3	137	-0.2	1.2	137	0.5%	-4.10 [-4.40, -3.80]
Bailey 2010 Dapa	-2.1	1.1	137	-0.2	1.2	137	0.6%	-1.90 [-2.17, -1.63]
Bolinder 2012 Dapa	-2.7	3.2	89	0.1	3.2	91	0.1%	-2.80 [-3.74, -1.86]
Bolinder 2014 Dapa	-1.3	3	89	1.1	2.6	91	0.1%	-2.40 [-3.22, -1.58]
Cefalu 2013 Cana	-3.3	0.6	485	0.2	0.6	482	8.2%	-3.50 [-3.58, -3.42]
Cefalu 2013 Cana	-4.6	0.6	483	0.2	0.6	482	8.2%	-4.80 [-4.88, -4.72]
Ferrannini 2010 Dapa	-3.6	1.9	70	-0.9	1.8	75	0.1%	-2.70 [-3.30, -2.10]
Ferrannini 2010 Dapa	-2.3	1.9	64	-0.9	1.8	75	0.1%	-1.40 [-2.02, -0.78]
Ferrannini 2010 Dapa	-4.6	1.8	65	-0.9	1.8	75	0.1%	-3.70 [-4.30, -3.10]
Forst 2014 Cana	-4.7	1	114	-1.2	1	115	0.7%	-3.50 [-3.76, -3.24]
Forst 2014 Cana	-5.3	1	113	-1.2	1	115	0.7%	-4.10 [-4.36, -3.84]
Haring 2013 Empa	-3.5	0.7	216	-1.4	0.7	225	2.8%	-2.10 [-2.23, -1.97]
Haring 2013 Empa	-4.1	0.7	225	-1.4	0.7	225	2.8%	-2.70 [-2.83, -2.57]
Haring 2014 Empa	-5.2	0.7	213	-0.4	0.7	207	2.6%	-4.80 [-4.93, -4.67]
Haring 2014 Empa	-4.5	0.7	217	-0.4	0.7	207	2.7%	-4.10 [-4.23, -3.97]
Heerspink 2013 Dapa	-5.6	4.6	24	-0.7	3.6	25	0.0%	-4.90 [-7.22, -2.58]
Inagaki 2013 Cana	-9.3	1.2	76	-1.2	1.2	75	0.3%	-8.10 [-8.48, -7.72]
Inagaki 2013 Cana	-8.7	1.2	75	-1.2	1.2	75	0.3%	-7.50 [-7.88, -7.12]
Inagaki 2013 Cana	-5.8	1.2	82	-1.2	1.2	75	0.3%	-4.60 [-4.98, -4.22]
Inagaki 2013 Cana	-7.1	1.2	74	-1.2	1.2	75	0.3%	-5.90 [-6.29, -5.51]
Ji 2015 Cana	-5.5	1.5	223	-2	1.5	224	0.6%	-3.50 [-3.78, -3.22]
Ji 2015 Cana	-5.1	1.5	222	-2	1.5	224	0.6%	-3.10 [-3.38, -2.82]
Leiter 2015 Cana	-2	0.6	483	1.7	0.6	482	8.2%	-3.70 [-3.78, -3.62]
Leiter 2015 Cana	-3.1	0.6	485	1.7	0.6	482	8.2%	-4.80 [-4.88, -4.72]
Levalle-Gonzalez 2013 Cana	-4.7	0.6	367	-0.7	0.6	366	6.2%	-4.00 [-4.09, -3.91]
Levalle-Gonzalez 2013 Cana	-3.5	0.6	368	-0.7	0.6	366	6.2%	-2.80 [-2.89, -2.71]
List 2009 Dapa	-2.6	13.1	56	2.4	11.1	54	0.0%	-5.00 [-9.53, -0.47]
List 2009 Dapa	-4.3	12.3	59	2.4	11.1	54	0.0%	-6.70 [-11.01, -2.39]
List 2009 Dapa	-3.1	10.7	59	2.4	11.1	54	0.0%	-5.50 [-9.53, -1.47]
List 2009 Dapa	-6.4	11.4	47	2.4	11.1	54	0.0%	-8.80 [-13.20, -4.40]
List 2009 Dapa	-2.9	12.7	58	2.4	11.1	54	0.0%	-5.30 [-9.71, -0.89]
Nauck 2011 Dapa	-4.3	1.8	406	0.8	1.2	408	1.1%	-5.10 [-5.31, -4.89]
Neal 2014 Cana	-6.2	1.5	690	-1.6	1.5	690	1.9%	-4.60 [-4.76, -4.44]
Neal 2014 Cana	-3.1	1.5	692	-1.6	1.5	690	1.9%	-1.50 [-1.66, -1.34]
Ridderstrale 2014 Empa	-3.1	0.9	432	3	0.9	421	3.2%	-6.10 [-6.22, -5.98]
Roden 2013 Empa	-2.9	1.6	224	-0.3	1.6	228	0.5%	-2.60 [-2.90, -2.30]
Roden 2013 Empa	-3.7	1.6	224	-0.3	1.6	228	0.5%	-3.40 [-3.70, -3.10]
Rosenstock 2012 Cana	-3.6	1.4	64	-1.3	1.5	65	0.2%	-2.30 [-2.80, -1.80]
Rosenstock 2012 Cana	-0.9	1.7	64	-1.3	1.5	65	0.2%	0.40 [-0.15, 0.95]
Rosenstock 2012 Cana	-1	1.3	64	-1.3	1.5	65	0.2%	0.30 [-0.18, 0.78]
Rosenstock 2012 Cana	-2.1	1.8	65	-1.3	1.5	65	0.1%	-0.80 [-1.37, -0.23]
Rosenstock 2012 Cana	-4.9	1.5	64	-1.3	1.5	65	0.2%	-3.60 [-4.12, -3.08]
Rosenstock 2012 Dapa	-2.2	1.2	140	2	1.2	139	0.6%	-4.20 [-4.48, -3.92]
Rosenstock 2012 Dapa	-1	1.1	141	2	1.2	139	0.6%	-3.00 [-3.27, -2.73]
Rosenstock 2013 Empa	-3	14.5	71	-2.2	14.8	71	0.0%	-0.80 [-5.62, 4.02]
Rosenstock 2013 Empa	-4.4	13.1	71	-2.2	14.8	71	0.0%	-2.20 [-6.80, 2.40]
Rosenstock 2013 Empa	-8.5	12.8	70	-2.2	14.8	71	0.0%	-6.30 [-10.87, -1.73]
Rosenstock 2013 Empa	-3.1	15.2	70	-2.2	14.8	71	0.0%	-0.90 [-5.85, 4.05]
Rosenstock 2013 Empa	-2.1	12.1	71	-2.2	14.8	71	0.0%	0.10 [-4.35, 4.55]
Rosenstock 2014 Empa	-3.6	0.8	186	-1.2	0.8	188	1.8%	-2.40 [-2.56, -2.24]
Rosenstock 2014 Empa	-2.9	0.8	189	-1.2	0.8	188	1.8%	-1.70 [-1.86, -1.54]
Schernthaner 2013 Cana	-5.7	0.7	377	0.9	0.7	378	4.7%	-6.60 [-6.70, -6.50]
Schumm-Draeger 2015 Dapa	-3	10.9	100	-1.6	10.5	101	0.0%	-1.40 [-4.36, 1.56]
Schumm-Draeger 2015 Dapa	-3.5	12.2	99	-1.6	10.5	101	0.0%	-1.90 [-5.06, 1.26]
Schumm-Draeger 2015 Dapa	-3.4	11.1	99	-1.6	10.5	101	0.0%	-1.80 [-4.80, 1.20]
Stenlof 2013 Cana	-5	0.8	197	0.4	0.8	192	1.9%	-5.40 [-5.56, -5.24]
Stenlof 2013 Cana	-3.3	0.8	195	0.4	0.8	192	1.9%	-3.70 [-3.86, -3.54]
Tikkanen 2015 Empa	-4.5	0.5	276	0.2	0.5	271	6.7%	-4.70 [-4.78, -4.62]
Tikkanen 2015 Empa	-3.3	0.5	276	0.2	0.5	271	6.7%	-3.50 [-3.58, -3.42]
Wilding 2009 Dapa	-5.5	1.7	24	2.1	6.2	23	0.0%	-7.60 [-10.22, -4.98]
Wilding 2009 Dapa	-0.7	2.6	24	2.1	6.2	23	0.0%	-2.80 [-5.54, -0.06]
Wilding 2012 Dapa	-4	2	194	-1.5	2	193	0.3%	-2.50 [-2.90, -2.10]
Wilding 2012 Dapa	-4.3	2	211	-1.5	2	193	0.3%	-2.80 [-3.19, -2.41]
Wilding 2012 Dapa	-5.3	2	202	-1.5	2	193	0.3%	-3.80 [-4.19, -3.41]
Total (95% CI)			**11882**			**11846**	**100.0%**	**-4.01 [-4.03, -3.99]**

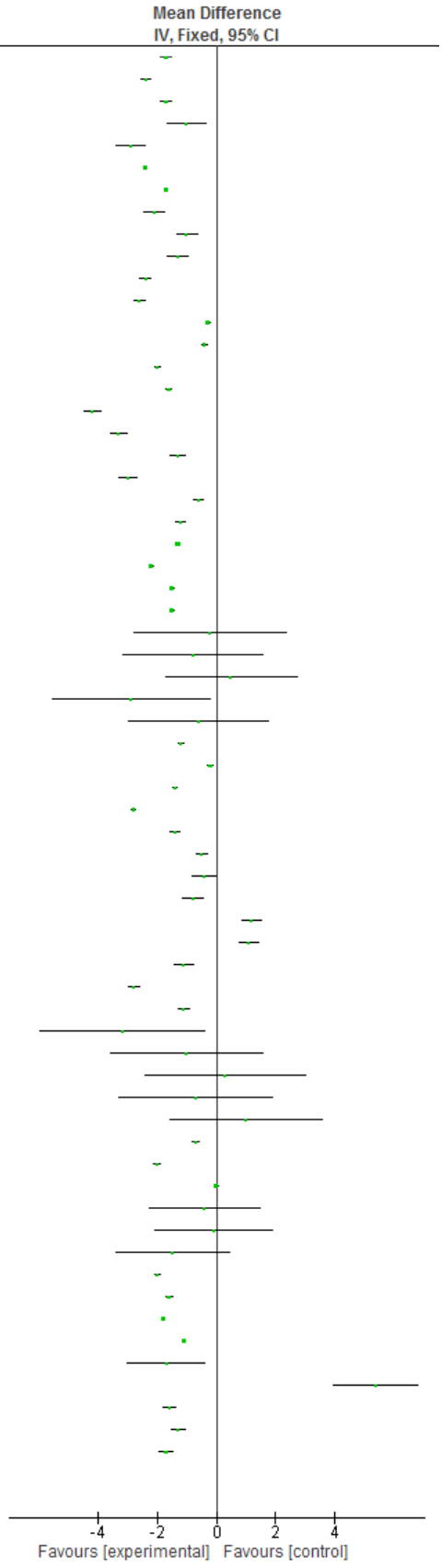
Heterogeneity: Chi² = 12206.96, df = 64 (P < 0.00001); I² = 99%
Test for overall effect: Z = 362.44 (P < 0.00001)



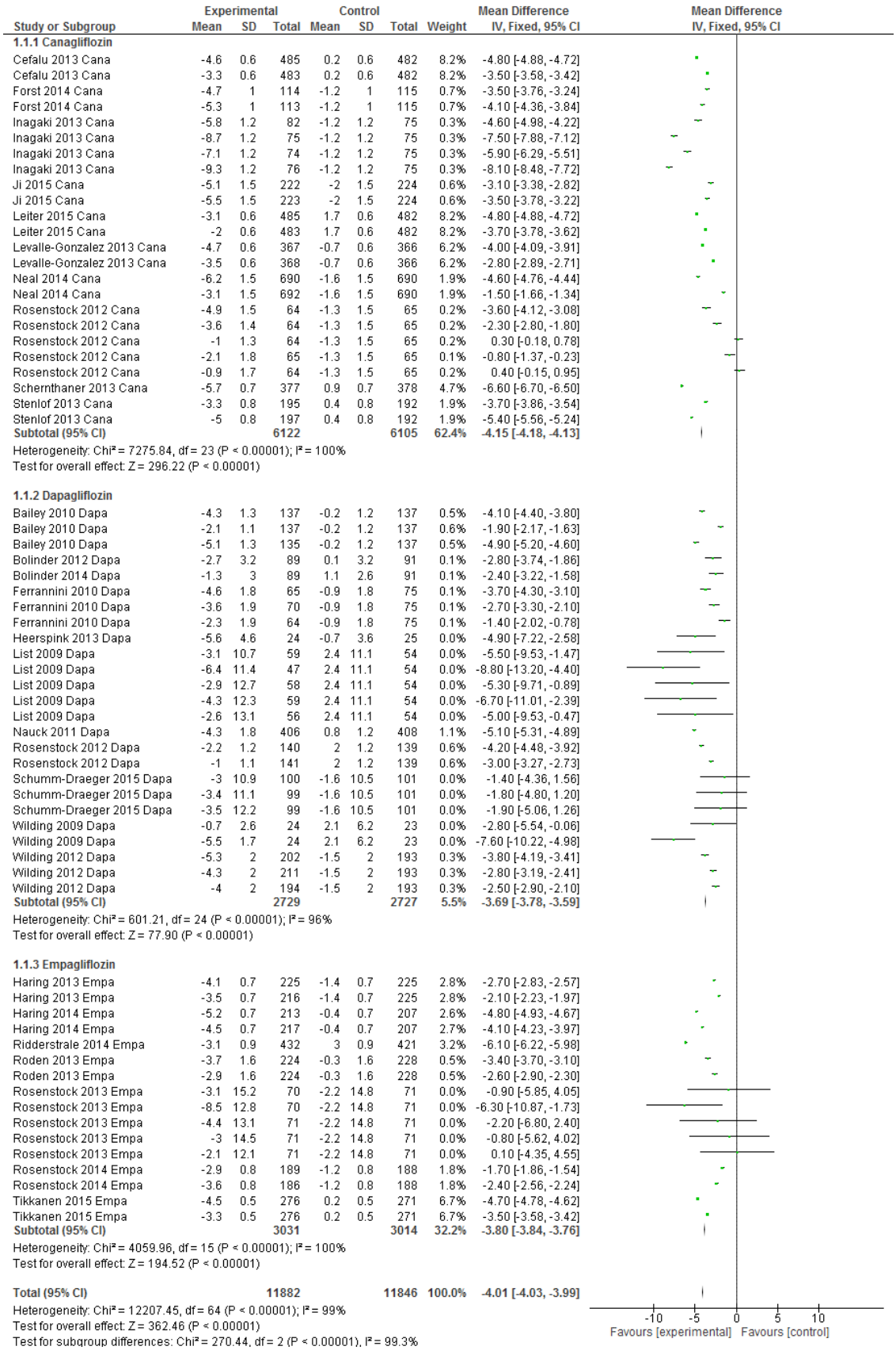
Appendix C. Mean difference in change in systolic blood pressure

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bailey 2010 Dapa	-1.8	0.9	137	-0.1	0.7	137	0.5%	-1.70 [-1.89, -1.51]
Bailey 2010 Dapa	-2.5	0.8	137	-0.1	0.7	137	0.6%	-2.40 [-2.58, -2.22]
Bailey 2010 Dapa	-1.8	0.8	135	-0.1	0.7	137	0.6%	-1.70 [-1.88, -1.52]
Bolinder 2012 Dapa	-0.7	2.2	89	0.3	2.2	91	0.0%	-1.00 [-1.64, -0.36]
Bolinder 2014 Dapa	-2.1	1.6	89	0.8	1.7	91	0.1%	-2.90 [-3.38, -2.42]
Cefalu 2013 Cana	-2.5	0.4	485	-0.1	0.4	482	7.4%	-2.40 [-2.45, -2.35]
Cefalu 2013 Cana	-1.8	0.4	483	-0.1	0.4	482	7.4%	-1.70 [-1.75, -1.65]
Ferrannini 2010 Dapa	-2.8	1.1	65	-0.7	1	75	0.2%	-2.10 [-2.45, -1.75]
Ferrannini 2010 Dapa	-1.7	1.1	64	-0.7	1	75	0.2%	-1.00 [-1.35, -0.65]
Ferrannini 2010 Dapa	-2	1.1	70	-0.7	1	75	0.2%	-1.30 [-1.64, -0.96]
Forst 2014 Cana	-3.3	0.7	113	-0.9	0.7	115	0.6%	-2.40 [-2.58, -2.22]
Forst 2014 Cana	-3.5	0.7	114	-0.9	0.7	115	0.6%	-2.60 [-2.78, -2.42]
Haring 2013 Empa	-2.1	0.4	225	-1.8	0.4	225	3.4%	-0.30 [-0.37, -0.23]
Haring 2013 Empa	-2.2	0.4	216	-1.8	0.4	225	3.4%	-0.40 [-0.47, -0.33]
Haring 2014 Empa	-2	0.5	217	0	0.5	207	2.1%	-2.00 [-2.10, -1.90]
Haring 2014 Empa	-1.6	0.5	213	0	0.5	207	2.1%	-1.60 [-1.70, -1.50]
Inagaki 2013 Cana	-5.1	0.8	76	-0.9	0.9	75	0.3%	-4.20 [-4.47, -3.93]
Inagaki 2013 Cana	-4.2	0.8	75	-0.9	0.9	75	0.3%	-3.30 [-3.57, -3.03]
Inagaki 2013 Cana	-2.2	0.8	82	-0.9	0.9	75	0.3%	-1.30 [-1.57, -1.03]
Inagaki 2013 Cana	-3.9	0.9	74	-0.9	0.9	75	0.2%	-3.00 [-3.29, -2.71]
Ji 2015 Cana	-2.4	0.9	223	-1.8	0.9	226	0.7%	-0.60 [-0.77, -0.43]
Ji 2015 Cana	-3	0.9	227	-1.8	0.9	226	0.7%	-1.20 [-1.37, -1.03]
Leiter 2015 Cana	-1.3	0.4	483	0	0.4	482	7.4%	-1.30 [-1.35, -1.25]
Leiter 2015 Cana	-2.2	0.4	485	0	0.4	482	7.4%	-2.20 [-2.25, -2.15]
Levalle-Gonzalez 2013 Cana	-1.8	0.4	367	-0.3	0.4	366	5.6%	-1.50 [-1.56, -1.44]
Levalle-Gonzalez 2013 Cana	-1.8	0.4	368	-0.3	0.4	366	5.6%	-1.50 [-1.56, -1.44]
List 2009 Dapa	0.1	8	56	0.3	5.7	54	0.0%	-0.20 [-2.79, 2.39]
List 2009 Dapa	-0.5	7.1	59	0.3	5.7	54	0.0%	-0.80 [-3.17, 1.57]
List 2009 Dapa	0.8	6.4	59	0.3	5.7	54	0.0%	0.50 [-1.73, 2.73]
List 2009 Dapa	-2.6	7.7	47	0.3	5.7	54	0.0%	-2.90 [-5.58, -0.22]
List 2009 Dapa	-0.3	7	58	0.3	5.7	54	0.0%	-0.60 [-2.96, 1.76]
Nauck 2011 Dapa	-1.6	0.6	406	-0.4	0.6	408	2.8%	-1.20 [-1.28, -1.12]
Neal 2014 Cana	-1.2	0.8	692	-1	0.8	690	2.6%	-0.20 [-0.28, -0.12]
Neal 2014 Cana	-2.4	0.8	690	-1	0.8	690	2.6%	-1.40 [-1.48, -1.32]
Ridderstrale 2014 Empa	-1.9	0.6	432	0.9	0.5	421	3.4%	-2.80 [-2.87, -2.73]
Roden 2013 Empa	-1.9	1	224	-0.5	0.9	228	0.6%	-1.40 [-1.58, -1.22]
Roden 2013 Empa	-1	1	224	-0.5	0.9	228	0.6%	-0.50 [-0.68, -0.32]
Rosenstock 2012 Cana	-1.7	1.3	65	-1.3	1	65	0.1%	-0.40 [-0.80, -0.00]
Rosenstock 2012 Cana	-2.1	1.1	64	-1.3	1	65	0.1%	-0.80 [-1.16, -0.44]
Rosenstock 2012 Cana	-0.1	1	64	-1.3	1	65	0.2%	1.20 [0.85, 1.55]
Rosenstock 2012 Cana	-0.2	1	64	-1.3	1	65	0.2%	1.10 [0.75, 1.45]
Rosenstock 2012 Cana	-2.4	1	64	-1.3	1	65	0.2%	-1.10 [-1.45, -0.75]
Rosenstock 2012 Dapa	-2.4	0.7	140	0.4	0.9	139	0.5%	-2.80 [-2.99, -2.61]
Rosenstock 2012 Dapa	-0.7	0.7	141	0.4	0.9	139	0.5%	-1.10 [-1.29, -0.91]
Rosenstock 2013 Empa	-4.2	8.7	70	-1	8.2	71	0.0%	-3.20 [-5.99, -0.41]
Rosenstock 2013 Empa	-2	7.5	70	-1	8.2	71	0.0%	-1.00 [-3.59, 1.59]
Rosenstock 2013 Empa	-0.7	8.4	71	-1	8.2	71	0.0%	0.30 [-2.43, 3.03]
Rosenstock 2013 Empa	-1.7	7.5	71	-1	8.2	71	0.0%	-0.70 [-3.28, 1.88]
Rosenstock 2013 Empa	0	7.47	71	-1	8.2	71	0.0%	1.00 [-1.58, 3.58]
Rosenstock 2014 Empa	-1.2	0.6	186	-0.5	0.6	188	1.3%	-0.70 [-0.82, -0.58]
Rosenstock 2014 Empa	-2.5	0.6	189	-0.5	0.6	188	1.3%	-2.00 [-2.12, -1.88]
Schernthaner 2013 Cana	-0.3	0.4	377	-0.3	0.4	378	5.8%	0.00 [-0.06, 0.06]
Schumm-Draeger 2015 Dapa	-1.3	7.3	100	-0.9	6.2	101	0.0%	-0.40 [-2.27, 1.47]
Schumm-Draeger 2015 Dapa	-1	8	99	-0.9	6.2	101	0.0%	-0.10 [-2.09, 1.89]
Schumm-Draeger 2015 Dapa	-2.4	7.6	99	-0.9	6.2	101	0.0%	-1.50 [-3.42, 0.42]
Stenlof 2013 Cana	-2.1	0.5	197	-0.1	0.5	192	1.9%	-2.00 [-2.10, -1.90]
Stenlof 2013 Cana	-1.7	0.5	195	-0.1	0.5	192	1.9%	-1.60 [-1.70, -1.50]
Tikkanen 2015 Empa	-1.7	0.3	276	0.1	0.3	271	7.4%	-1.80 [-1.85, -1.75]
Tikkanen 2015 Empa	-1	0.3	276	0.1	0.3	271	7.4%	-1.10 [-1.15, -1.05]
Wilding 2009 Dapa	-5.8	1.8	24	-4.1	2.7	23	0.0%	-1.70 [-3.02, -0.38]
Wilding 2009 Dapa	1.3	2.3	24	-4.1	2.7	23	0.0%	5.40 [3.96, 6.84]
Wilding 2012 Dapa	-2.9	1.1	194	-1.3	1.2	193	0.4%	-1.60 [-1.83, -1.37]
Wilding 2012 Dapa	-2.6	1.1	211	-1.3	1.2	193	0.4%	-1.30 [-1.53, -1.07]
Wilding 2012 Dapa	-3	1.1	202	-1.3	1.2	193	0.4%	-1.70 [-1.93, -1.47]
Total (95% CI)			**11863**			**11825**	**100.0%**	**-1.48 [-1.49, -1.46]**

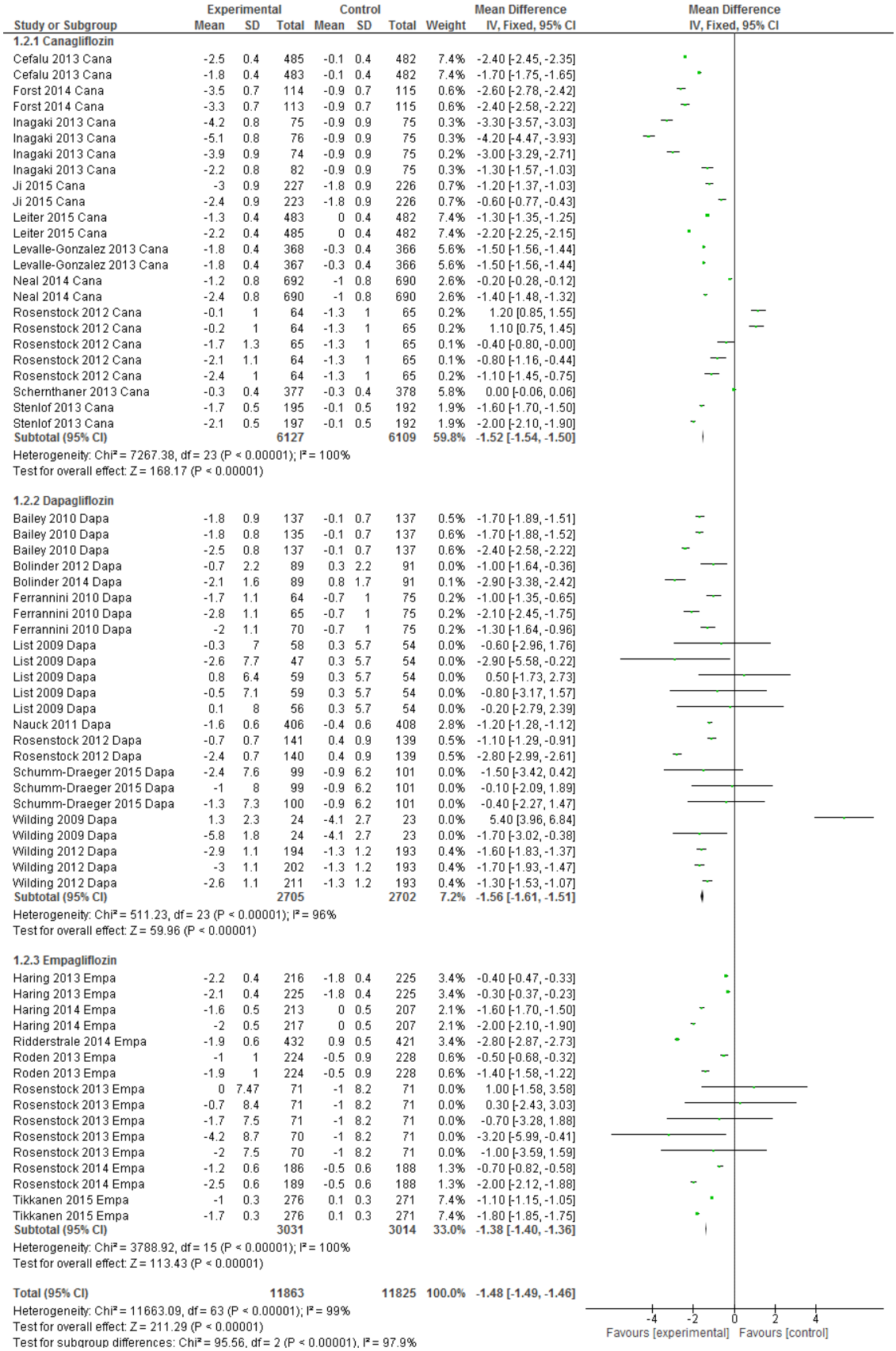
Heterogeneity: Chi² = 11663.09, df = 63 (P < 0.00001); I² = 99%
Test for overall effect: Z = 211.29 (P < 0.00001)



Appendix D. Mean difference in change in diastolic blood pressure



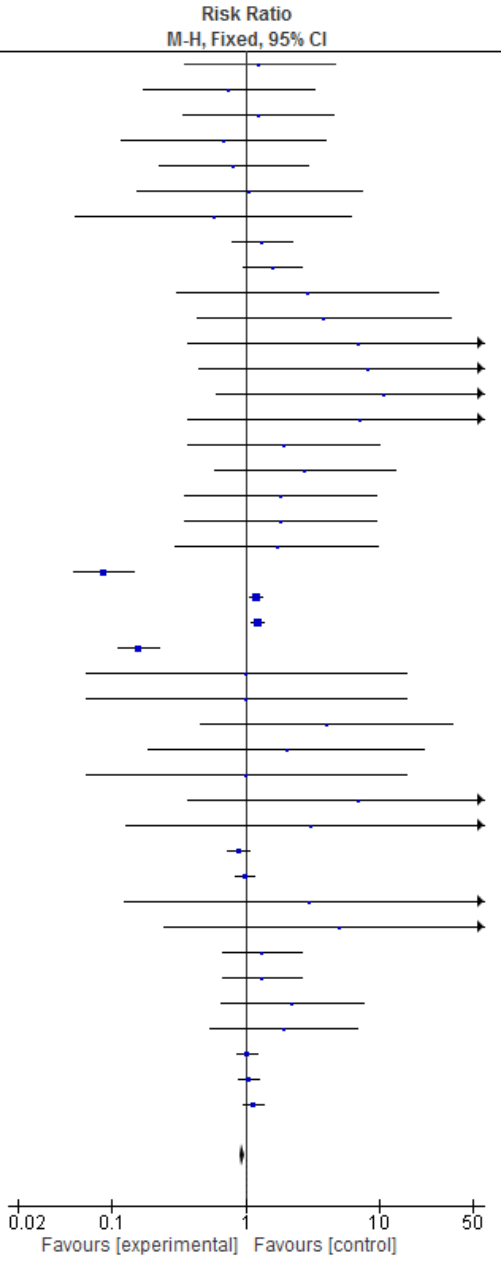
Appendix E. Mean difference in systolic blood pressure based on types of SGLT2 inhibitor agent



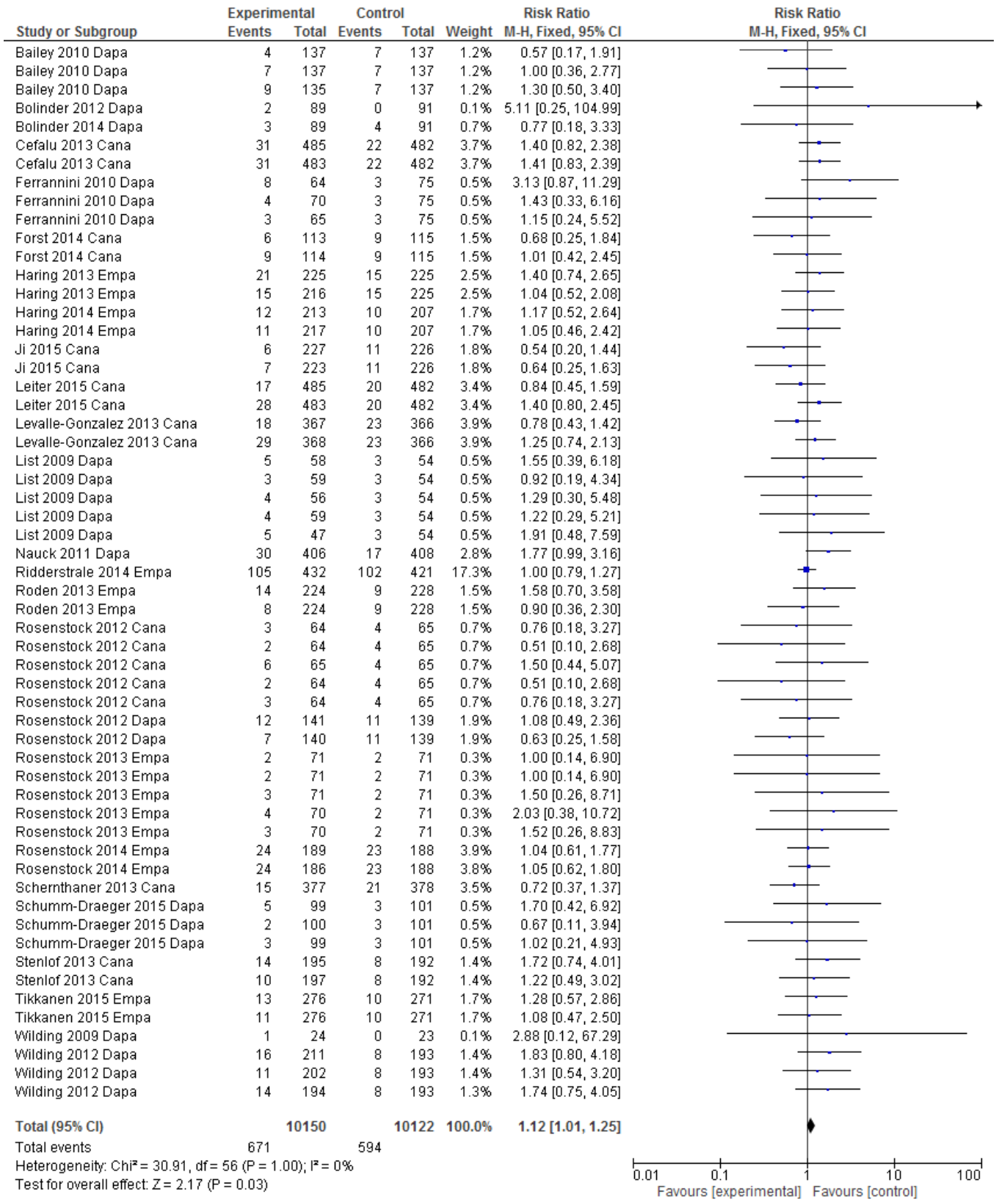
Appendix F. Mean difference in diastolic blood pressure based on types of SGLT2 inhibitor agent

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bailey 2010 Dapa	5	135	4	137	0.2%	1.27 [0.35, 4.62]
Bailey 2010 Dapa	3	137	4	137	0.2%	0.75 [0.17, 3.29]
Bailey 2010 Dapa	5	137	4	137	0.2%	1.25 [0.34, 4.56]
Bolinder 2012 Dapa	2	89	3	91	0.2%	0.68 [0.12, 3.98]
Bolinder 2014 Dapa	4	89	5	91	0.3%	0.82 [0.23, 2.95]
Ferrannini 2010 Dapa	2	70	2	75	0.1%	1.07 [0.16, 7.40]
Ferrannini 2010 Dapa	1	65	2	75	0.1%	0.58 [0.05, 6.22]
Haring 2013 Empa	28	216	22	225	1.3%	1.33 [0.78, 2.24]
Haring 2013 Empa	35	225	22	225	1.3%	1.59 [0.96, 2.62]
Haring 2014 Empa	3	213	1	207	0.1%	2.92 [0.31, 27.80]
Haring 2014 Empa	4	217	1	207	0.1%	3.82 [0.43, 33.86]
Inagaki 2013 Cana	3	75	0	75	0.0%	7.00 [0.37, 133.22]
Inagaki 2013 Cana	4	82	0	75	0.0%	8.24 [0.45, 150.54]
Inagaki 2013 Cana	5	76	0	75	0.0%	10.86 [0.61, 192.96]
Inagaki 2013 Cana	3	74	0	75	0.0%	7.09 [0.37, 134.98]
List 2009 Dapa	4	56	2	54	0.1%	1.93 [0.37, 10.10]
List 2009 Dapa	6	58	2	54	0.1%	2.79 [0.59, 13.25]
List 2009 Dapa	4	59	2	54	0.1%	1.83 [0.35, 9.60]
List 2009 Dapa	4	59	2	54	0.1%	1.83 [0.35, 9.60]
List 2009 Dapa	3	47	2	54	0.1%	1.72 [0.30, 9.88]
Nauck 2011 Dapa	14	406	162	408	9.6%	0.09 [0.05, 0.15]
Neal 2014 Cana	396	690	333	690	19.8%	1.19 [1.08, 1.31]
Neal 2014 Cana	409	692	333	690	19.8%	1.22 [1.11, 1.35]
Ridderstrale 2014 Empa	32	432	197	421	11.8%	0.16 [0.11, 0.22]
Roden 2013 Empa	1	224	1	228	0.1%	1.02 [0.06, 16.17]
Roden 2013 Empa	1	224	1	228	0.1%	1.02 [0.06, 16.17]
Rosenstock 2012 Cana	4	65	1	65	0.1%	4.00 [0.46, 34.83]
Rosenstock 2012 Cana	2	64	1	65	0.1%	2.03 [0.19, 21.85]
Rosenstock 2012 Cana	1	64	1	65	0.1%	1.02 [0.06, 15.89]
Rosenstock 2013 Empa	3	71	0	71	0.0%	7.00 [0.37, 133.09]
Rosenstock 2013 Empa	1	70	0	71	0.0%	3.04 [0.13, 73.43]
Rosenstock 2014 Empa	97	186	111	188	6.6%	0.88 [0.74, 1.06]
Rosenstock 2014 Empa	110	189	111	188	6.6%	0.99 [0.83, 1.17]
Schumm-Draeger 2015 Dapa	1	100	0	101	0.0%	3.03 [0.12, 73.50]
Schumm-Draeger 2015 Dapa	2	99	0	101	0.0%	5.10 [0.25, 104.90]
Tikkanen 2015 Empa	19	276	14	271	0.8%	1.33 [0.68, 2.60]
Tikkanen 2015 Empa	19	276	14	271	0.8%	1.33 [0.68, 2.60]
Wilding 2009 Dapa	7	24	3	23	0.2%	2.24 [0.66, 7.62]
Wilding 2009 Dapa	6	24	3	23	0.2%	1.92 [0.54, 6.77]
Wilding 2012 Dapa	105	194	102	193	6.1%	1.02 [0.85, 1.23]
Wilding 2012 Dapa	118	211	102	193	6.3%	1.06 [0.88, 1.27]
Wilding 2012 Dapa	122	202	102	193	6.2%	1.14 [0.96, 1.36]
Total (95% CI)		**6962**		**6924**	**100.0%**	**0.94 [0.90, 0.99]**
Total events	1598		1672			

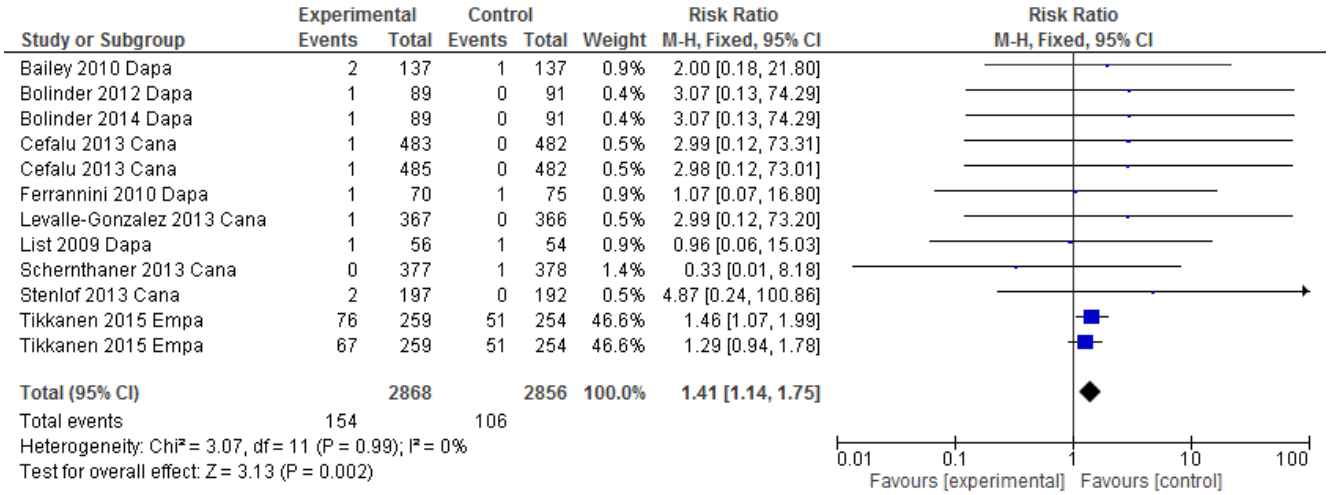
Heterogeneity: Chi² = 266.42, df = 41 (P < 0.00001); I² = 85%
Test for overall effect: Z = 2.16 (P = 0.03)



Appendix G. Rate of hypoglycemia for SGLT2 inhibitors vs control groups



Appendix H. Rates of urinary tract infections for SGLT2 inhibitors vs control groups



Appendix I. Rates of orthostatic hypotension for SGLT2 inhibitors vs control groups