Original Article Safety assessment of canagliflozin for type 2 diabetes mellitus

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Abstract: Importance: Type 2 diabetesmellitus (T2DM) is chronic, progressive, heavy-burden disease. The efficacy of canagliflozinfor T2DM has been well validated, but its safety profile still remains controversial. Objective: This systematic review and meta-analysis of randomized control trials was performed to assess the safety of canagliflozin. the first approved sodium glucose co-transporter 2 receptor inhibitors (SGLT2), inT2DM patients. Data sources: PubMed, EMBASE, clinicaltrials.gov, and the Cochrane Library. Study selection: Randomized controlled trials (RCTs) of canagliflozin in T2DM patients by February 2015 utilizing the key words "canagliflozin", "JNJ-28431754", "TA-7284" and "invokana" with no language, origin or other limits were screened and selected. Data extraction and synthesis: Review Manager 5.0.24 was used to conduct the meta-analysis. Main outcomes and measures: Genital infection. Results: A total of 14 RCTs were included for meta-analysis. Canagliflozin significantly increase the risk of genital infection [RR=4.80; 95% CI (3.80-6.07); P< 0.00001; I²=0%], vulvovaginal mycotic infection [RR=7.66, 95% CI (3.04, 19.29), P<0.001; I²=0%], osmotic duresis related AEs [RR=2.95; 95% CI (2.26-3.85); P< 0.00001; I²=0%] and nausea [RR=2.36; 95% Cl (1.24-4.50); P=0.009; I²=0%]. Canagliflozin slightly increase the risk of volume depletion related AEs [RR=1.36; 95% CI (0.99-1.88); P=0.06; I²=0%], upper respiratory inflammation [RR=1.29; 95% CI (0.73-2.27); P=0.39; l²=0%] and hypoglycaemia [RR=1.40; 95% CI (0.70-2.79); P=0.34; l²=0%].Canagliflozin did not increase the risk of urinary tract infection [risk ratio (RR)=1.11; 95% CI (0.94-1.29); P=0.21; I²=0%], severe hypoglycaemia [RR=1.01; 95% CI (0.67-1.52); P =0.96; I²=0%], GI related AEs [RR=1.11; 95% CI (0.78-1.59); P=0.55; l²=0%], headache [RR=1.18; 95% CI (0.76-1.82); P=0.46; l²=0%] or dizziness [RR=1.01; 95% CI (0.45-2.28); P=0.98; I²=0%]. Canagliflozin was associated with a lightly lower risk of diarrhoea [RR=0.66; 95% Cl (0.36-1.18); P=0.16; I²=0%], death [RR 0.84; 95% CI (0.40-1.76); P=0.64; I²=0%] and nasopharyngitis [RR 0.81; 95% CI (0.58-1.13); P=0.21; I²=0%]. Conclusions and relevance: Canagliflorin is relatively safe for treatment of T2DM patients eitherin monotherapy or add-on treatment, but the increased risk of genital infection, osmotic duresis related AEs and nausea should not be neglected. More long-term clinical trials are required to refine this evidence.

Keywords: Canagliflozin, type 2 diabetes mellitus, sodium-glucose transporter-2 inhibitor, safety

Introduction

Diabetes has become the seventh cause of death in America, and 8.3% Americans were reported to have diabetes [1]. Type 2 diabetesmellitus (T2DM) accounts for 90% diabetes, and the incidence trendwill have a significant increase in the next two decades [2]. Patients with T2DM are resistant to insulin and have a great decrease in glucose-stimulated insulin secretion [3]. These features are associated with the insensitivity of the insulin receptor and the impairment of insulin signaling [4]. Management of T2DM includes diet and exercise, followed by monotherapy with anti-hyperglycemic agents (AHAs) when lifestyle intervention is inadequate [2, 5]. However, many patients didn't achieve expectedgoals with firstline therapy like metformin, thus a combination therapy with a second glycaemia-control agent like sulphonylureas, thiazolidinediones or even insulin is often required [6, 7]. Despite achieving a long-term glucose level control, many of these combination therapy lead to severe insulin resistance anda large amount of complications [8], which make the tolerability and safety

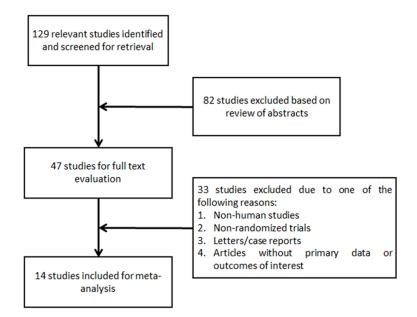


Figure 1. The flow and the results of study selection

of these medications highly concerned. In this regard, a new class of AHAs which can both control the blood glucose level while combined with less complications is strongly expected [9].

Sodium-linked glucose transporter 2 (SGLT2), with an insulin-independent mechanism, is newly developed and may be provedas an attractive alternation [10-12]. SGLT2 is mainly expressed in the early proximal renal tubule, and induces glucose excretion via urine by reducing ingested calories, at the same time achieve good blood glucose control [9]. In April 2013, the U.S. Foodand Drug Administration (FDA) approved canagliflozin as the first SGLT2 class agent for the treatment of T2DM [13]. Canagliflozin is proved to decrease the renal threshold for glucose, thus reduce plasma glucose level and body weight without causing hypoglycemia [1, 10].

Previously, three meta-analysis [14] analyzing the efficacy and safety of the SGLT2 inhibitors (including canagliflozin) for the treatment of T2DM were conducted. However, in Clar and Musso's study [15, 16], only onerandomized controlled trial (RCT) on canagliflozin is included. The efficacy of canagliflozin has been well validated for the treatment of T2DM, but some safety concerns still remain and no pooled analysis of large robust studies with long duration outcomeswas available to clarify this issue [9, 17-19]. The purpose of this metaanalysis is to fully illustrate the clinical safety of canagliflozin as either monotherapy or with other background treatment in T2DM patients.

Methods

Data sources and searches

An exhaustive online search was conducted on mainstream computerized databases of interest, they are: PubMed, MEDLINE, Embase, ClinicalTrials.gov and Cochrane Collaborative database by February 2015. The search terms were "canagliflozin", "JNJ-28431754", "TA-72-

84" and "invokana" with no language, origin or other limits. All the retrieved articles were scanned and all additional studies of potential interest were imported into Endnote for further identification and analysis.

Study selection

Inclusion criteria were following the Population Intervention Comparison Outcome (PICO) strategy [20], which were conducted as follows. P: participants were adults of any sex or ethnic origin, who had T2DM and were not adequatelycontrolled with diet, exercise, or other antihyperglycemia drugs like metformin and (or) sulphonylurea and (or) pioglitazone and (or) insulin; I: treatment with canagliflozin; C: comparison with placebo or active comparators such as metformin, glimepiride and sitagliptin; O: rate of the adverse events (AEs) was analyzed to evaluate the safety outcomes. Exclusion criteria were: non-human studies, non-randomized trials, letters/case reports, articles without primary data or outcomes of interest.

Two authors (Yifan Liu and Yuxin Zhang) independently reviewed the titles and abstracts of references extracted from the searches and identified potentially relevant studies. Two reviewers (Ruoshuang Han and Yuxin Zhang) independently analyzed the list of references

Author (year) (citation)	Phase n study, NCT	n patients, age (y), BMI (kg/m²)	Mean ini- tial HbA1c (%)	Duration of T2DM (y)	Canagliflozin dose vs. drug	Background treatment	Treatment du- ration (weeks)
Rosenstock (2013)	3, NCT00642278	451, 52.9, 31.5	7.8	6	50 mg, 100 mg, 200 mg, 300 mg vs. placebo	Metformin	12 w
Schernthaner (2013)	3, NCT01137812	756, 56.7, 31.6	8.1	9.6	300 mg vs. sitagliptin	Metformin Plus Sulfonylurea	52 w
Lavalle-González (2013)	3, NCT01106677	1284, 55.4, 31.8	7.9	6.9	100 mg, 300 mg vs sitagliptin	Metformin monotherapy	52 w
Forst (2014)	3, NCT01106690	342, 57.4, 32.5	7.9	10.5	100 mg, 300 mg vs placebo/sitagliptin	Metformin and pioglitazone	52 w
Inagaki (2013)	NCT01022112	382, 57.4, 25.7	8.1	-	50 mg, 100 mg, 200 mg, 300 mg vs. placebo	Antidiabetic drugs	12 w
Li (2014)	NCT01381900	676, 56.2, 25.7	8.0	6.7	100 mg, 300 mg vs. placebo	Metformin aloene or Metformin Plus Sulfonylurea	18 w
Wilding (2013)	3, NCT01106625	469, 56.8, 33.1	8.1	9.6	100 mg, 300 mg vs. placebo	Metformin plus sulphonylurea	52 w
Leiter (2014)	3, NCT00968812	1450, 56.2, 31.0	7.8	6.6	100 mg, 300 mg vs. glimepiride	Metformin	104 w
Bays (2014)	2b, NCT00650806	376, 44.8, 37	-	-	50 mg, 100 mg, 300 mg vs. placebo	Nutritional counseling, limitation of calories and routine physical activity	12 w
Bode (2014)	3, NCT01106651	716, 63.6, 31.6	7.7	11.7	100 mg, 300 mg vs. placebo	-	104 w
Nyiryjesy (2012)	2, NCT00642278	215, 52.9, 32.1	7.8	-	50 mg, 100 mg, 200 mg, 300 mg vs. placebo&sitagliptin	Metformin	12 w
Yale (2013)	3	272, 68.5, 33.0	8	16.3	100 mg, 300 mg vs. placebo	AHA therapies at baseline	52 w
Devineni (2012)	1b	29, 48.5, 33.5	8.4	-	100 mg, 300 mg vs. placebo	Insulin and Metformin	4 w
Stenlöf (2014)	3, NCT01081834	587, 55.4, 31.6	8	4.3	Placebo/sitagliptin	Diet and exercise	52 w

 Table 1. Characteristics of randomized controlled trials included in the meta-analysis

	No of	Quality of the	Relative		Anticipated absolute effects
Outcomes	Participants (studies) Follow up	evidence (GRADE)	effect (95% CI)	Risk with Control	Risk difference with Safety assessment of Canagliflozin (95% CI)
Genital infections	8930	$\oplus \oplus \oplus \Theta$	OR 5.25		Study population
	(11 studies)	MODERATE ¹ due to impreci-	(4.12 to 6.69)	19 per 1000	73 more per 1000 (from 55 more to 96 more)
		sion			Moderate
				18 per 1000	70 more per 1000 (from 52 more to 91 more)
Osmotic duresis related AEs	8930	••••	OR 3.05		Study population
	(11 studies)	HIGH	(2.32 to 4.01)	17 per 1000	32 more per 1000 (from 21 more to 47 more) Moderate
				15 per 1000	29 more per 1000 (from 19 more to 43 more)
Volume depletion related AEs	8968	$\oplus \oplus \oplus \oplus$	OR 1.37		Study population
	(12 studies)	HIGH	(0.99 to 1.91)	14 per 1000	5 more per 1000 (from 0 fewer to 12 more) Moderate
				15 per 1000	5 more per 1000 (from 0 fewer to 13 more)
Death	7402	$\oplus \oplus \oplus \oplus$	OR 0.84		Study population
	(8 studies)	HIGH	(0.39 to 1.78)	3 per 1000	1 fewer per 1000 (from 2 fewer to 3 more) Moderate
				4 per 1000	1 fewer per 1000 (from 2 fewer to 3 more)
Severe hypoglycaemia	6836	$\oplus \oplus \oplus \oplus$	OR 1.01		Study population
	(9 studies)	HIGH	(0.67 to 1.53)	12 per 1000	0 more per 1000 (from 4 fewer to 6 more) Moderate
				6 per 1000	0 more per 1000 (from 2 fewer to 3 more)
Urinary tract infection	8930	⊕ ⊕ ⊕ ⊖	OR 1.11		Study population
•	(11 studies)	MODERATE ¹	(0.94 to	63 per 1000	6 more per 1000 (from 4 fewer to 18 more)
		due to impreci-	1.32)		Moderate
		sion		63 per 1000	6 more per 1000 (from 4 fewer to 19 more)
Headache	1109	⊕ ⊕ ⊕ ⊖	OR 1.2		Study population
	(3 studies)	MODERATE ¹	(0.74 to 1.94)	61 per 1000	11 more per 1000 (from 15 fewer to 51 more)
		due to impreci-			Moderate
		sion		79 per 1000	14 more per 1000 (from 19 fewer to 64 more)
GI related AES	1642	⊕ ⊕ ⊕ ⊖	OR 1.13		Study population
	(4 studies)	MODERATE ¹ due to impreci-	(0.76 to 1.68)	65 per 1000	8 more per 1000 (from 15 fewer to 40 more) Moderate
		sion		40 per 1000	5 more per 1000 (from 9 fewer to 25 more)
Nasopharyngitis	2014	⊕⊕⊖⊖	OR 0.79		Study population
	(3 studies)	LOW ^{1,2}	(0.55 to 1.14)	71 per 1000	14 fewer per 1000 (from 31 fewer to 9 more)
		due to impreci- sion, publica-			Moderate
		tion bias		34 per 1000	7 fewer per 1000 (from 15 fewer to 5 more)
Upper respiratory inflammation	1162	⊕ ⊕ ⊕ ⊖	OR 1.3		Study population
	(2 studies)	MODERATE ^{1,2}	(0.72 to 2.37)	34 per 1000	10 more per 1000 (from 9 fewer to 42 more)
		due to impreci- sion			Moderate
		0.011		13 per 1000	4 more per 1000 (from 4 fewer to 17 more)
Nausea	1109	$\oplus \oplus \oplus \oplus$	OR 2.51		Study population
	(3 studies)	HIGH	(1.26 to 5.03)	18 per 1000	26 more per 1000 (from 5 more to 68 more) Moderate
				23 per 1000	33 more per 1000 (from 6 more to 83 more)
Diarrhoea	1109	$\oplus \oplus \oplus \Theta$	OR 0.64		Study population
	(3 studies)	MODERATE ¹ due to impreci-	(0.35 to 1.19)	46 per 1000	16 fewer per 1000 (from 29 fewer to 8 more) Moderate
		sion		56 per 1000	19 fewer per 1000 (from 36 fewer to 10 more)
Dizziness	592	⊕⊕⊖	OR 1.01	00 pci 1000	Study population
2.2211000	(2 studies)	LOW ^{1,2}	(0.43 to	35 per 1000	0 more per 1000 (from 20 fewer to 45 more)
	-	den de transment	0.00)	-0 pc. 1000	
		due to impreci- sion, publica-	2.38)		Moderate

Table 2. Quality of evidence for clinically relevant outcomes

Hypoglycaemia	1679 (3 studies)	⊕ ⊕ ⊕ ⊖ MODERATE ^{1,2,3} due to impreci- sion	OR 1.41 (0.7 to 2.83)	12 per 1000	Study population 5 more per 1000 (from 4 fewer to 21 more) Moderate 6 more per 1000 (from 4 fewer to 26 more)
based on the assumed risk in the	comparison group an uality: Further researcl	d the relative effect of h is very unlikely to ch	the intervention (ange our confiden	in footnotes. The co and its 95% Cl). Cl: ce in the estimate	nrresponding risk (and its 95% confidence interval) is Confidence interval; OR: Odds ratio; GRADE Working of effect. Moderate quality: Further research is likely

to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. ¹Unconformity. ²Publication bias. ³No explanation was provided.

and identified the RCTs of interests. The fulltext articles were assessed by two authors (Xiaofei Guan and Yanjie Zhu). Any discrepancies of selection would be resolved by discussion until consensus was reached. If an agreement failed to reach by discussion, a third author (GuoxinFan) was consulted. Data was retrieved from included studies and entered into RevMan 5.0.24 for analysis.

Data extraction and quality assessment

Two reviewers (Ruoshuang Han and Guoxin Fan) independently extracted or check data in duplicate with a predefined protocol following the Cochrane Handbook for Systematic Reviews of Intervention; discrepancies were resolved by discussion. Study characteristics were extracted with Excel; the quality of RCTs was assessed by the Cochrane Risk-of-Bias Tool, attributing 1 point to each item (total score range: 0-8) [21]; the strength of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Data synthesis and analysis

This systematic review with meta-analysis was reported according to PRISMA guidelines [22]. We performed all the analyses using RevMan 5.0.24 (The Nordic Cochrane Centre, Copenhagen, Denmark) from Cochrane Collaboration, 2008). Dichotomous data (AEs) would be presented as relative risk (RR) with 95% confidence interval (CI), while continuous variables asweighed mean differences (MMD) with 95% CI. Treatments were evaluated on an intentionto-treat principle. Statistical heterogeneity was evaluated using I² statistic: if no heterogeneity $(I^{2} < 50\%)$ was detected, we would use a fixeffect model; if significant heterogeneity was present ($I^2 \ge 50\%$), we would use a randomeffect model along with the sensitive analysis to investigate for possible explanations. Two authors (Ruoshuang Han and Yuxin Zhang) independently assessed the risk of bias as described in the Cochrane Handbook for Systematic Reviews of Interventions [23]. If more than 10 studies were included, a funnel plot analysis would be employed to assess the reporting biases [24].

Results

The agreement between two reviewers for study selection was 0.85 and for quality assessment of trials was 0.86.

Search results

The flow and the results of study selection are reported in **Figure 1**. After exclusions, made according to the study protocol, 14 RCTs included for further analysis and discussion.

Study characteristics

The characteristics and results of the included studiesare shown in Table 1. All included trials were double-blind RCTs, trial durations rangedfrom 2 to 104 weeks (median 33 weeks). Most trials hadlonger-term extension periods (not completed/reportedin all cases). At the end of selection, 14 RCTs assessing canagliflozin (8015 participants, trial duration ranging 2-104 weeks, daily dose ranging 50-300 mg) were included [2, 5, 6, 25-35]. The mean initial HbA1c across the study population of 11 RCTs ranges from 4.3% to 16.3%, and background anti-diabetic treatments consist of metformin monotherapy in four RCTs [25, 29, 32, 33], metformin plus another agent in five RCTs [6, 28, 30, 31, 36] (including metformin alone or metformin plus sulfonylurea in one RCT), diet and exercise [5, 26] in two RCTs, AHA therapies at baseline [34] in one RCT, unclear anti-diabetic drugs [2] in one RCT and unknown treatment [27] in one RCT.

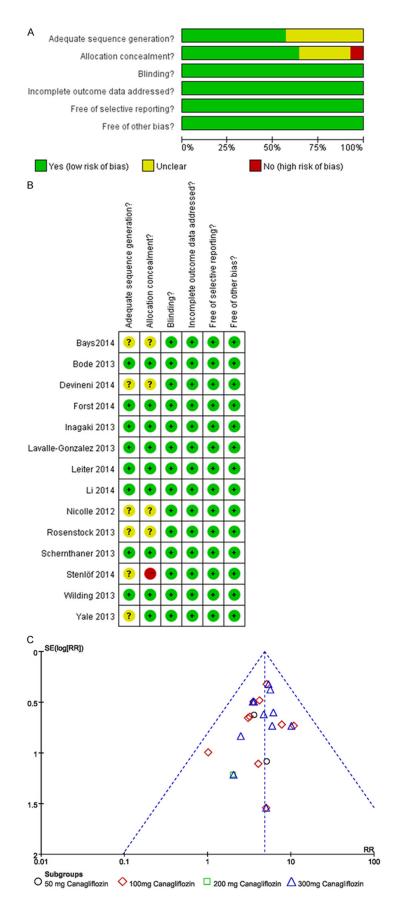


Figure 2. Cochrane risk of bias of included studies. A: Graph; B: Summary; C: Funnel plot.

Quality of included studies and grading of evidence

Overall quality grading is demonstrated in **Table 2**. Quality of evidence was downgraded due to unconformity and publication bias. Generally speaking, the evidence of 5 outcomes was graded to be high, 7 outcomes were graded to be moderate and 2 outcomes were graded to be low.

Cochrane risk of bias

Risk of bias are demonstrated in Figure 2A, 2B. The reporting quality was rated as 'high' in 8 ofthe studies, 'medium' in 5 studies and 'low' in 1 study. The funnel plot did not detect a significant publication bias (Figure 2C).

Genital infections and urinary tract infection

Generally, canagliflozin treatment was associated with an extremely increased risk of genital infections (RR 4.80; 95% CI (3.80-6.07); $P < 0.00001; I^2 = 0\%$) (Figure 3A). In particular, canagliflozin treatment was strongly correlated with a higher risk of vulvovaginal mycotic infection (RR=7.66, 95% CI (3.04, 19.29), $P<0.001; l^2=0\%)$ (Figure 3B). However, canagliflozin did not increase rate of urinary tract infections (UTIs) (RR 1.11; 95% CI (0.94-1.29); P=0.21; I²=0%) (Figure 3C).

Hypoglycaemia

Incidences of hypoglycaemia and severe hypoglycaemia were both low in allclinical trials. Canagliflozin slighty increase the risk of hypoglycaemia (RR 1.40; 95% CI (0.70-2.79); P=0.34; $I^2=0\%$)

Study or Subgroup	Events	Total	Ever	nts T	otal We	ight	M-H, F	ixed, 9	5% CI	M-H, Fi	xed, 95% Cl
2.2.1 50 mg Canagliflozi Bays2014	n 12	98		3	89 3	3.8%	3.63	[1.06, 1	2.46]		
Rosenstock 2013	5	64		1	65 1	.2%	5.08	0.61, 4	2.27]	-	
Subtotal (95% CI)		162			154 4	4.9%	3.98 [1.37, 1	1.52]		
Total events Heterogeneity: Chi² = 0.03	17 7 df = 1 (P = 0.79	$1^2 = 0$	4							
Test for overall effect: Z =			,								
2.2.2 100mg Canaglifloz	in										
Bays2014	10	93		3		3.7%		0.91, 1			
Bode 2013	22	241				2.4%		2.57, 4			
Forst 2014 Lavalle-Gonzalez 2013	9 31	113 368				3.5% 3.2%		[0.85, 1 [1.87, 3			· · · · · · · · · · · · · · · · · · ·
Leiter 2014	56	483				3.1%		[2.70,			
Li 2014	2	223			226 2	2.4%		[0.14,			+
Rosenstock 2013	4	64		1		1.2%		0.47, 3		_	
Stenlöf 2014 Wilding 2013	18 21	195 157				3.0% 3.0%		[1.34,			
Yale 2013	21	90		0).6%		[1.61, 1 0.24, 10			- · · ·
Subtotal (95% CI)		2027		1	835 42	2.1%		[3.24,			◆
Total events	175			34							
Heterogeneity: Chi ² = 5.3 Test for overall effect: Z =				0%							
2.2.2 100mg Canagliflozin			-							1	I
Bays2014	10	93	3	89	3.7%	3	19 [0.91	, 11.21]	I		
3ode 2013	22	241	2	237	2.4%	10	82 [2.57	45.49]	Í		
Forst 2014 avalle-Gonzalez 2013	9 31	113 368	3	115 183			.05 [0.85 .71 [1.87			Ť -	
eiter 2014	56	368 483	11	482			5.08 [2.7				
Li 2014	2	223	2	226	3 2.4%		1.01 [0.1	4, 7.13]	. —		
Rosenstock 2013	4	64 105	1	65			06 [0.47				
Stenlöf 2014 Vilding 2013	18 21	195 157	5 5	192 156			3.54 [1.3 .17 [1.61			_	
rale 2013	2	90	ō	90	0.6%	5.0	0 [0.24,	102.71]	· ·		
Subtotal (95% CI)		2027		1835	42.1%		.66 [3.2				◄
Fotal events Heterogeneity: Chi ² = 5.37, Fest for overall effect: Z = 8			34 = 0%								
2.2.3 200 mg Canagliflozir	n										
Rosenstock 2013	2	65	1	65			.00 [0.19				
Subtotal (95% CI)	•	65		65	5 1.2%	5 2.	00 [0.19	21.52]	_		
Fotal events Heterogeneity: Not applicat	2 ole		1								
Test for overall effect: Z = 0		.57)									
2.2.4 300mg Canagliflozin											
Bays2014	20	96	3	89			18 [1.90			-	
Bode 2013 Forst 2014	20 14	236 114	2	237 115			.04 [2.37 .71 [1.39			_	
avalle-Gonzalez 2013	24	367	2	183			.98 [1.43			-	
eiter 2014	60	485	11	482			42 [2.89				
.i 2014 Rosenstock 2013	5 2	227 64	2	226 65			.49 [0.49 .03 [0.19				·
Schernthaner 2013	45	378	8	378			.63 [2.69				
Stenlöf 2014	18	197	5	192			3.51 [1.3	3, 9.26]	l l		
Vilding 2013 Yale 2013	18 2	156 89	5 0	156			3.60 [1.3 6 [0.25,				
Subtotal (95% CI)		2409	•	2213			5.06 [3.6				•
Fotal events Heterogeneity: Chi ² = 3.49,			42 ² = 09	6							
Test for overall effect: Z = 9	.84 (P < 0	.00001)									
Γotal (95% CI) Γotal events	422	4663	81	4267	100.0%	6 4	.80 [3.8	0, 6.07]			•
Heterogeneity: Chi ² = 9.69,	df = 23 (P			6					0.01 0.1		10 100
Fest for overall effect: Z = 1 Fest for subgroup difference			3 (P =	= 0.86), j² = 0%				Favours experi	mental Fav	
	nagiifiozi		acebo			RI	sk Ratio			Risk Ratio	
Study or Subgroup Ev		otal Eve			Weight		Fixed, 9		M-	H, Fixed, 95	% CI
2.3.1 50mg canagliflozin Bays2014	8	98	1	89	20.6%	7.2	7 [0.93, 5	6.94]			
Rosenstock 2013	4	64	0	65	9.7%	9.14	[0.50, 16	6.35]		+	\rightarrow
Subtotal (95% Cl) Fotal events	12	62	1	154	30.3%	7.87	[1.47, 4	∠.09]			
leterogeneity: Chi ² = 0.02,		= 0.90); l²	•								
Test for overall effect: Z = 2											
2.3.2 100mg canaglifiozin											
Bays2014	5	93 64	1	89 65	20.1%		8 [0.57, 4		_		,
Rosenstock 2013 Subtotal (95% Cl)	2	64 157	0	65 154	9.7% 29.8%		[0.25, 10 [0.86, 2				
Fotal events	7		1				,-				
Heterogeneity: Chi ² = 0.00, Fest for overall effect: Z = 1			= 0%								
		65 65	0	65	9.8%		0.49, 16				· · · · · · · · · · · · · · · · · · ·
2.3.3 200mg canagilfiozin Rosenstock 2013	4	65	0	65	9.8%	9.00	0.49, 16	J.85]			
2.3.3 200mg canaglifiozin Rosenstock 2013 Subtotal (95% CI)	4		-								
2.3.3 200mg canaglifiozin Rosenstock 2013 Subtotal (95% CI) Fotal events Heterogeneity: Not applicat	4 ble	14)									
2.3.3 200mg canaglifiozin Rosenstock 2013 Subtotal (95% CI) Fotal events Heterogeneity: Not applicat Fest for overall effect: Z = 1	4 ble .48 (P = 0	.14)									
2.3.3 200mg canaglifiozin Rosenstock 2013 Subtotal (95% CI) Fotal events Heterogeneity: Not applicat Fest for overall effect: Z = 1 2.3.4 300mg canaglifiozin	4 ole .48 (P = 0			90	20.44	12.0	2 [4 74 4	6 601			
2.3.3 200mg canaglifiozin Rosenstock 2013 Subtotal (95% CI) Total events Heterogeneity: Not applicat Fest for overall effect: Z = 1 2.3.4 300mg canaglifiozin Bays2014	4 ble .48 (P = 0	96	1	89 65	20.4% 9.7%		8 [1.74, 9 5 [0.13, 7				<u> </u>
2.3.3 200mg canaglifiozin Rosenstock 2013 Subtotal (95% CI) Fotal events fest for overall effect: Z = 1 2.3.4 300mg canaglifiozin Bays2014 Rosenstock 2013 Subtotal (95% CI)	4 ble .48 (P = 0 14 1		0	89 65 154	20.4% 9.7% 30.1%	3.0	8 [1.74, 9 5 [0.13, 7 6 [1.84, 5	3.41]		-	
2.3.3 200mg canaglifiozin Rosenstock 2013 Subtotal (95% CI) Total events Heterogeneity: Not applicat fest for overall effect: Z = 1 2.3.4 300mg canaglifiozin Jays2014 Rosenstock 2013 Subtotal (95% CI) Fotal events Heterogeneity: Chi ² = 0.59,	4 ble .48 (P = 0 14 1 15 df = 1 (P	96 64 160 = 0.44); l ²	0	65 154	9.7%	3.0	5 [0.13, 7	3.41]		-	
2.3.3 200mg canaglifiozin Rosenstock 2013 Subtotal (95% CI) Total events Heterogeneity: Not applicat fest for overall effect: Z = 1 2.3.4 300mg canaglifiozin 3ays2014 Rosenstock 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 0.59, fest for overall effect: Z = 2	4 ble .48 (P = 0 14 1 15 df = 1 (P = 0 .68 (P = 0	96 64 160 = 0.44); l ² 0.007)	0 1 = 0%	65 154	9.7% 30.1%	3.05 9.77	5 [0.13, 7 [1.84, 5	'3.41] 1.80]		-	
2.3.3 200mg canaglifiozin Rosenstock 2013 Subtotal (95% CI) Total events fest for overall effect: Z = 1 2.3.4.300mg canaglifiozin Bays2014 Rosenstock 2013 Subtotal (95% CI) Total events fest for overall effect: Z = 2 Total (95% CI)	4 ble .48 (P = 0 14 1 15 df = 1 (P .68 (P = 0	96 64 160 = 0.44); l ²	0 1 = 0%	65 154	9.7%	3.05 9.77	5 [0.13, 7	'3.41] 1.80]	_	-	•
2.3.3 200mg canaglifiozin Rosenstock 2013 Subtotal (95% CI) Total events teterogeneity: Not applicat fest for overall effect: Z = 1 2.3.4 300mg canaglifiozin 3ays2014 Sosenstock 2013 Subtotal (95% CI) Total events teterogeneity: Chi ² = 0.59, fest for overall effect: Z = 2	4 ble .48 (P = 0 14 1 15 df = 1 (P .68 (P = 0 .68 (P = 0	96 64 160 = 0.44); l ²).007) 544	0 1 = 0% 3	65 154 527	9.7% 30.1%	3.05 9.77	5 [0.13, 7 [1.84, 5	(3.41] 1.80] 9.29]	0.01 0.1	-	

	Canaglif Events		Place Events		Weight	Risk Ratio M-H, Fixed, 95% Cl	Risk Ratio M-H. Fixed, 95% Cl
2.4.1 50mg Canagliflozin							
Bays2014	10	98	6	89	2.3%	1.51 [0.57, 4.00]	
Rosenstock 2013 Subtotal (95% CI)	3	64 162	4	65 154	1.4% 3.7%	0.76 [0.18, 3.27]	
	13	102	10	134	3.170	1.22 [0.55, 2.71]	
Total events Heterogeneity: Chi ² = 0.59,		- 0 44					
Test for overall effect: Z = 0			; = 0%				
2.4.2 100mg Canagliflozir							
Bays2014	7	93	6	89	2.2%	1.12 [0.39, 3.19]	
Bode 2013	14	241	12	237	4.4%	1.15 [0.54, 2.43]	
Forst 2014	6	113	9	115	3.2%	0.68 [0.25, 1.84]	
Lavalle-Gonzalez 2013	29	368	12	183	5.8%	1.20 [0.63, 2.30]	
Leiter 2014	51	483	33	482	12.0%	1.54 [1.01, 2.35]	
Li 2014	7	223	11	226	4.0%	0.64 [0.25, 1.63]	
Rosenstock 2013	2	64	4	65	1.4%	0.51 [0.10, 2.68]	
Stenlöf 2014	16	195	12	192	4.4%	1.31 [0.64, 2.70]	
Wilding 2013 Yale 2013	13 5	157 90	12 5	156 90	4.4% 1.8%	1.08 [0.51, 2.28]	
Subtotal (95% CI)	5	2027	5	1835	43.6%	1.00 [0.30, 3.34] 1.16 [0.92, 1.47]	•
Total events	150	LULI	116	1000	40.070	110 [0.02, 1.47]	·
Heterogeneity: Chi ² = 5.58, Test for overall effect: Z = 1	, df = 9 (F						
2 4 2 200 mg Conselilleri	-						
2.4.3 200 mg Canagliflozi Rosenstock 2013	n 6	65	4	65	1.4%	1.50 [0.44, 5.07]	
Subtotal (95% CI)	0	65	4	65	1.4%	1.50 [0.44, 5.07]	
Total events	6	•••	4				
Heterogeneity: Not applical Test for overall effect: Z = 0	ble	0.51)					
2.4.4 300mg Canaglifiozir	n						
Bays2014	8	96	6	89	2.3%	1.24 [0.45, 3.42]	_
Bode 2013	8 19	236	12	237	2.3% 4.3%	1.59 [0.79, 3.20]	+
Forst 2014	9	114	9	115	3.2%	1.01 [0.42, 2.45]	
Lavalle-Gonzalez 2013	18	367	12	183	5.8%	0.75 [0.37, 1.52]	-+-
Leiter 2014	42	485	33	482	12.0%	1.26 [0.82, 1.96]	
Li 2014	6	227	11	226	4.0%	0.54 [0.20, 1.44]	
Rosenstock 2013	2	64	4	65	1.4%	0.51 [0.10, 2.68]	
Schernthaner 2013	15	378	21	378	7.6%	0.71 [0.37, 1.36]	
Stenlöf 2014	14	197	12	192	4.4%	1.14 [0.54, 2.40]	
Wilding 2013	13	156	12	156	4.3%	1.08 [0.51, 2.30]	
Yale 2013	7	89	5	90	1.8%	1.42 [0.47, 4.29]	
				2213	51.3%	1.04 [0.83, 1.29]	T
Subtotal (95% CI)	153	2409	137		•		
Subtotal (95% CI) Total events Heterogeneity: Chi ² = 7.20, Test for overall effect: Z = ((P = 0.71	137 I); I² = 09				
Total events Heterogeneity: Chi ² = 7.20, Test for overall effect: Z = 0 Total (95% Cl)	, df = 10 (0.31 (P =	(P = 0.71	l); l² = 09	6	100.0%	1.11 [0.94, 1.29]	•
Total events Heterogeneity: Chi ² = 7.20, Test for overall effect: Z = 0	, df = 10 (0.31 (P = 322	(P = 0.71 0.76) 4663	1); l ² = 09 267	4267			
Total events Heterogeneity: Chi ² = 7.20, Test for overall effect: Z = 0 Total (95% Cl) Total events	, df = 10 (0.31 (P = 322 7, df = 23 1.25 (P =	(P = 0.71 0.76) 4663 4663 4(P = 0.9 0.21)	267 267); I ² = 09	% 4267)%	100.0%		0.01 0.1 1 10 100 Favours experimental Favours control
Total events Heterogeneity: $Ch^2 = 7.20$, Test for overall effect: Z = (Total (95% Cl) Total events Heterogeneity: $Ch^2 = 14.11$ Test for overall effect: Z = 1 Test for subgroup difference	, df = 10 (0.31 (P = 322 7, df = 23 1.25 (P = xes: Chi ² ;	(P = 0.71 0.76) 4663 6 (P = 0.9 0.21) = 0.81. d	267 227 292); I ² = 0 If = 3 (P =	4267)% = 0.85).	100.0%	1.11 [0.94, 1.29]	Favours experimental Favours control
Total events Heterogeneity: $Ch^2 = 7.20$, Test for overall effect: Z = 0 Total (95% Cl) Total events Heterogeneity: $Ch^2 = 14.1$ Test for overall effect: Z = 1 Test for subgroup difference	, df = 10 (0.31 (P = 322 7, df = 23 1.25 (P = ces: Chi ² : anaglifio	(P = 0.71 0.76) 4663 6 (P = 0.9 0.21) = 0.81. d	267 2267 22); I ² = 0 If = 3 (P = Placebo	4267)% = 0.85).	100.0% ² = 0%	1.11 [0.94, 1.29] Risk Ratio	Favours experimental Favours control Risk Ratio
Total events Heterogeneity: Chi ² = 7.20, Tostal effect: Z = (Total events Heterogeneity: Chi ² = 14.1 Test for subgroup difference Study or Subgroup Ca	, df = 10 (0.31 (P = 322 7, df = 23 1.25 (P = ces: Chi ² : anaglifio	(P = 0.71 0.76) 4663 6 (P = 0.9 0.21) = 0.81. d	267 2267 22); I ² = 0 If = 3 (P = Placebo	4267)% = 0.85).	100.0% ² = 0%	1.11 [0.94, 1.29] Risk Ratio	Favours experimental Favours control
Total events Heterogeneity: $Ch^2 = 7.20$, Test for overall effect: Z = (Total (95% Cl) Total events Heterogeneity: $Ch^2 = 14.11$ Test for overall effect: Z = 1 Test for subgroup difference Study or Subgroup 2.5.1 50mg canagliflozin	, df = 10 (0.31 (P = 322 7, df = 23 1.25 (P = 2es: Chi ² : anaglifio <u>rents</u>	(P = 0.71 0.76) 4663 8 (P = 0.9 0.21) = 0.81. d zin Total E	267 267 92); I ² = 0 91f = 3 (P Placebo Svents	4267)% = 0.85). o [otal)	100.0% ² = 0% <u>Veight</u>	1.11 [0.94, 1.29] Risk Ratio M-H, Fixed, 95% Cl	Favours experimental Favours control Risk Ratio
Total events Heterogeneity: $Ch^2 = 7.20$, Test for overall effect: Z = (Total (95% Cl) Total events Heterogeneity: $Ch^2 = 14.1$ Test for overall effect: Z = 1 Test for subgroup difference Cartes of subgroup Events Study or Subgroup Events 2.5.1 50mg canagliflozin Bays2014	, df = 10 (0.31 (P = 322 7, df = 23 1.25 (P = 225: Chi ² : anaglifio vents	(P = 0.71 0.76) 4663 8 (P = 0.9 0.21) = 0.81. d zIn Total E 98	267 227 22); I ² = 0 22); I ² = 0 If = 3 (P Placebo <u>vents</u>	4267)% = 0.85). Cotal_1 89	100.0% ² = 0% <u>Veight</u> 15.3%	1.11 [0.94, 1.29] Risk Ratio M-H. Fixed, 95% Cl 0.45 [0.04, 4.92]	Favours experimental Favours control Risk Ratio
Total events Heterogeneity: Chi ² = 7.20, Test for overall effect: Z = (Total (95% Cl) Total events Heterogeneity: Chi ² = 14.1; Test for overall effect: Z = 1 Test for subgroup difference C. Study or Subgroup Ev 2.5.1 50mg canagliflozin Bays2014 Inagaki 2013	, df = 10 (0.31 (P = 322 7, df = 23 1.25 (P = 2005: Chi ² : anaglifio cents 1 3	(P = 0.71 0.76) 4663 6 (P = 0.9 0.21) = 0.81. d zIn Total E 98 82	267 227 22); I ² = 0 22); I ² = 0 If = 3 (P Placebo <u>vents</u> 2 0	4267)% = 0.85). 5 <u>[otal_1</u> 89 75	100.0% ² = 0% <u>Veight</u> 15.3% 3.8%	1.11 [0.94, 1.29] Risk Ratio M-H. Fixed, 95% Cl 0.45 [0.04, 4.92] 6.41 [0.34, 122.07]	Favours experimental Favours control Risk Ratio
Total events Heterogeneity: $Ch^2 = 7.20$, Test for overall effect: Z = (Total (95% Cl) Total events Heterogeneity: $Ch^2 = 14.1$ Test for overall effect: Z = 1 Test for subgroup difference Cartes of subgroup Events Study or Subgroup Events 2.5.1 50mg canagliflozin Bays2014	, df = 10 (0.31 (P = 322 7, df = 23 1.25 (P = 225: Chi ² : anaglifio vents	(P = 0.71 0.76) 4663 8 (P = 0.9 0.21) = 0.81. d zIn Total E 98	267 227 22); I ² = 0 22); I ² = 0 If = 3 (P Placebo <u>vents</u>	4267)% = 0.85). Cotal_1 89	100.0% ² = 0% <u>Veight</u> 15.3%	1.11 [0.94, 1.29] Risk Ratio M-H. Fixed, 95% Cl 0.45 [0.04, 4.92]	Favours experimental Favours control Risk Ratio
Total events Heterogeneily: $Ch^2 = 7.20$, Test for overall effect: Z = (Total (95% Cl) Total events Heterogeneily: $Ch^2 = 14.11$ Test for overall effect: Z = 1 Test for subgroup difference Study or Subgroup C: 2.5.1 50mg canagliflozin Bays2014 Inagaki 2013 Rosenstock 2013	, df = 10 (0.31 (P = 322 7, df = 23 1.25 (P = 2005 Chi ² : anaglifio cents 1 3 0 4	(P = 0.76) 4663 4663 (P = 0.5 0.21) = 0.81. d zin Total E 98 82 64 244	267 22; P = 09 22; P = 0 Flacebo vents 1 2 0 1 3	4267)% = 0.85). 5 [otal_1] 89 75 65 229	100.0% ² = 0% <u>Veight</u> 15.3% 3.8% 10.8%	1.11 [0.94, 1.29] Risk Ratio M-H, Fixed, 95% Cl 0.45 [0.04, 4.92] 6.41 [0.34, 122.07] 0.34 (0.01, 8.16]	Favours experimental Favours control Risk Ratio
Total events Heterogeneity: Chi ² = 7.20, Test for overall effect: Z = (Total (95% Cl) Total events Heterogeneity: Chi ² = 14, 1; Test for overall effect: Z = 1 Test for subgroup Study or Subgroup 2.5.1 50mg canagliflozin Bays2014 Inagaki 2013 Rosenstock 2013 Subtotal (95% Cl) Total events	, df = 10 (0.31 (P = 322 7, df = 23 1.25 (P = 285: Chi ² : anaglifio cents 1 3 0 4 , df = 2 (f	(P = 0.76) 4663 4(P = 0.9 0.21) = 0.81. d zin Total E 98 82 64 244 P = 0.29	267 22; P = 09 22; P = 0 Flacebo vents 1 2 0 1 3	4267)% = 0.85). 5 [otal_1] 89 75 65 229	100.0% ² = 0% <u>Veight</u> 15.3% 3.8% 10.8%	1.11 [0.94, 1.29] Risk Ratio M-H, Fixed, 95% Cl 0.45 [0.04, 4.92] 6.41 [0.34, 122.07] 0.34 (0.01, 8.16]	Favours experimental Favours control Risk Ratio
Total events Heterogeneily: $Ch^2 = 7.20$, Test for overall effect: $Z = ($ Total (95% Cl) Total events Heterogeneily: $Ch^2 = 14.17$ Test for overall effect: $Z = 1$ Test for subgroup difference Study or Subgroup Cr 2.5.1 50mg canagliflozin Bays2014 Inagaki 2013 Rosenstock 2013 Subtotal (95% Cl) Total events Heterogeneily: $Ch^2 = 2.47$, df = 10 (0.31 (P = 322 7, df = 23 1.25 (P = 2005: Chi ² anaglifio yents 1 3 0 4 4 , df = 2 (f 0.23 (P =	(P = 0.76) 4663 4(P = 0.9 0.21) = 0.81. d zin Total E 98 82 64 244 P = 0.29	267 22; P = 09 22; P = 0 Flacebo vents 1 2 0 1 3	4267)% = 0.85). 5 [otal_1] 89 75 65 229	100.0% ² = 0% <u>Veight</u> 15.3% 3.8% 10.8%	1.11 [0.94, 1.29] Risk Ratio M-H, Fixed, 95% Cl 0.45 [0.04, 4.92] 6.41 [0.34, 122.07] 0.34 (0.01, 8.16]	Favours experimental Favours control Risk Ratio
Total events Heterogeneity: $Ch^{2} = 7.20$, Test for overall effect: Z = (Total (95% Cl) Total events Heterogeneity: $Ch^{2} = 14.11$ Test for overall effect: Z = 1 Test for subgroup Ev 2.5.1 50mg canagliflozin Bays2014 Inagaki 2013 Rosenstock 2013 Subtotal (95% Cl) Total events Heterogeneity: $Ch^{2} = 2.47$ Test for overall effect: Z = 1 2.5.2 100mg canagliflozin Bays2014	, df = 10 (0.31 (P = 322 7, df = 23 1.25 (P = xes: Chi ² anagliflo cents 1 3 0 4 , df = 2 (f 0.23 (P = 1 0	(P = 0.76) 4663 4663 4663 (P = 0.6 0.21) = 0.81. d zin Total E 98 82 64 244 P = 0.29 : 0.82) 93	267 32); I ² = 09 32); I ² = 0 if = 3 (P = Placebo vents 1 2 0 1 3); I ² = 19 2	4267 % = 0.85). (otal 1) 89 75 65 229 % 89	100.0% ² = 0% <u>Veight</u> 15.3% 3.8% 10.8% 29.9%	1.11 [0.94, 1.29] Risk Ratio M-H. Fixed, 95% Cl 0.45 [0.04, 4.92] 0.45 [0.34, 122.07] 0.34 [0.21, 8.16] 1.17 [0.31, 4.35]	Favours experimental Favours control Risk Ratio
Total events Heterogeneily: Chi ² = 7.20, Test for overall effect: Z = (Total (95% Cl) Total events Heterogeneity: Chi ² = 14.11 Test for overall effect: Z = 1 Test for subgroup Study or Subgroup 2.5.1 50mg canagliflozin Bays2014 Inagaki 2013 Rosenstock 2013 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = 2.47 Test for overall effect: Z = 1 2.5.2 100mg canagliflozin Bays2014 Inagaki 2013	, df = 10 (0.31 (P = 322 7, df = 23 1.25 (P = 2008: Chi ² : anaglifio cents 1 3 0 4 , df = 2 (f 0.23 (P = 1 0 2	(P = 0.76) 4663 4663 (P = 0.5 0.21) = 0.81. d zIn Total E 98 82 64 244 P = 0.29 0.82) 93 74	267 92); I ² = 09 92); I ² = 0 92; I ² = 0 92; I ² = 0 1 1 3 3); I ² = 19 ⁴ 2 0	4267 % = 0.85). 5 5 5 5 5 5 5 5 5 229 % 89 75	100.0% ² = 0% <u>Veight</u> 15.3% 3.8% 10.8% 29.9% 18.6% 3.6%	1.11 [0.94, 1.29] Risk Ratio M-H, Fixed, 95% Cl 0.45 [0.04, 4.92] 6.41 [0.34, 122.07] 0.34 [0.01, 8.16] 1.17 [0.31, 4.35] 0.19 [0.01, 3.83]	Favours experimental Favours control Risk Ratio
Total events Heterogeneily: $Ch^2 = 7.20$, Test for overall effect: $Z = ($ Total (95% Cl) Total events Heterogeneily: $Ch^2 = 14.17$, Test for overall effect: $Z = 1$ Test for subgroup difference Study or Subgroup Cr 2.5.1 50mg canagliflozin Bays2014 Inagaki 2013 Rosenstock 2013 Subtotal (95% Cl) Total events Heterogeneily: $Ch^2 = 2.47$ Test for overall effect: $Z = 4$ 2.5.2 100mg canagliflozin Bays2014 Inagaki 2013 Rosenstock 2013	, df = 10 (0.31 (P = 322 7, df = 23 1.25 (P = xes: Chi ² anagliflo cents 1 3 0 4 , df = 2 (f 0.23 (P = 1 0	(P = 0.74) 4663 4663 (P = 0.62) = 0.81. d 21 70 64 244 P = 0.29 93 74 64	267 32); I ² = 09 32); I ² = 0 if = 3 (P = Placebo vents 1 2 0 1 3); I ² = 19 2	% 4267 % = 0.85). 5 5 5 5 5 229 % 89 75 65	100.0% I ² = 0% <u>Weight</u> 15.3% 3.8% 10.8% 29.9% 18.6% 3.6% 7.2%	1.11 [0.94, 1.29] Risk Ratio M-H, Fixed, 95% CI 0.45 [0.04, 4.92] 6.41 [0.34, 122.07] 0.34 [0.01, 8.16] 1.17 [0.31, 4.35] 0.19 [0.01, 3.93] 0.19 [0.01, 3.93]	Favours experimental Favours control Risk Ratio
Total events Heterogeneity: $Ch^{2} = 7.20$, Tost for overall effect: Z = (Total (95% Cl) Total events Heterogeneity: $Ch^{2} = 14.12$ Test for overall effect: Z = 1 Test for subgroup difference Study or Subgroup Ev 2.5.1 50mg canagliflozin Bays2014 Inagaki 2013 Rosenstock 2013 Subtotal (95% Cl) Total events Heterogeneity: $Ch^{2} = 2.47$ Test for overall effect: Z = 1 2.5.2 100mg canagliflozin Bays2014 Inagaki 2013 Rosenstock 2013 Rosenstock 2013 Rosenstock 2013 Subtotal (95% Cl)	, df = 10 (0.31 (P = 322 7, df = 23 1.25 (P = 2008: Chi ² : anaglifio cents 1 3 0 4 , df = 2 (f 0.23 (P = 1 0 2	(P = 0.76) 4663 4663 (P = 0.5 0.21) = 0.81. d zIn Total E 98 82 64 244 P = 0.29 0.82) 93 74	267 92); I ² = 09 92); I ² = 0 97 97 97 97 97 97 97 97 97 97 97 97 97	4267 % = 0.85). 5 5 5 5 5 5 5 5 5 229 % 89 75	100.0% ² = 0% <u>Veight</u> 15.3% 3.8% 10.8% 29.9% 18.6% 3.6%	1.11 [0.94, 1.29] Risk Ratio M-H, Fixed, 95% Cl 0.45 [0.04, 4.92] 6.41 [0.34, 122.07] 0.34 [0.01, 8.16] 1.17 [0.31, 4.35] 0.19 [0.01, 3.83]	Favours experimental Favours control Risk Ratio
Total events Heterogeneily: Chi ² = 7.20, Tost for overall effect: Z = (Total (95% Cl) Total events Heterogeneily: Chi ² = 14.1; Test for subgroup difference Study or Subgroup 2.5.1 50mg canagliflozin Bays2014 Inagaki 2013 Rosenstock 2013 Subtotal (95% Cl) Total events Heterogeneily: Chi ² = 2.47 Test for overall effect: Z = 4 2.5.2 100mg canagliflozin Bays2014 Inagaki 2013 Rosenstock 2013 Subtotal (95% Cl) Total events Heterogeneily: Chi ² = 2.47 Test for overall effect: Z = 4 2.5.2 100mg canagliflozin Bays2014 Inagaki 2013 Rosenstock 2013 Subtotal (95% Cl) Total events	, df = 10 (0.31 (P = 3222 7, df = 231 1.25 (P = xes: Chi ² ; anaglifio rents 1 3 0 4 , df = 2 (f 0.23 (P = 1 0 2 1 3	(P = 0.7') 4663 (P = 0.1') 0.21) = 0.81 d 221 Total E 98 82 64 64 64 2244 P = 0.29 0.82) 93 74 64 231); ² = 09 2677 (2677) 22); ² = (1 2 0 1 3 ;); ² = 19 2 0 1 3 3 3 3 3	 4267 3% = 0.85). 5 65 229 % 89 75 65 229 	100.0% I ² = 0% <u>Weight</u> 15.3% 3.8% 10.8% 29.9% 18.6% 3.6% 7.2%	1.11 [0.94, 1.29] Risk Ratio M-H, Fixed, 95% CI 0.45 [0.04, 4.92] 6.41 [0.34, 122.07] 0.34 [0.01, 8.16] 1.17 [0.31, 4.35] 0.19 [0.01, 3.93] 0.19 [0.01, 3.93]	Favours experimental Favours control Risk Ratio
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		lozin	Place		Walacha	Risk Ratio	Risk Ratio
Study or Subgroup 2.6.1 50 mg Canagliflozin	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	CI M-H, Fixed, 95% Cl
Bays2014	1	98	2	89	4.7%	0.45 [0.04, 4.92]	· · · · · · · · · · · · · · · · · · ·
Inagaki 2013	3	82	ō	75	1.2%	6.41 [0.34, 122.07]	
Rosenstock 2013	0	64	1	65	3.3%	0.34 [0.01, 8.16]	
Subtotal (95% CI)		244		229	9.2%	1.17 [0.31, 4.35]	
Total events	4		3				
Heterogeneity: Chi ² = 2.47, Test for overall effect: Z = 0			; I² = 19%	6			
2.6.2 100mg Canagliflozir	n						
Bays2014	0	93	2	89	5.7%	0.19 [0.01, 3.93]	
Bode 2013	3	241	7	237	15.8%	0.42 [0.11, 1.61]	
Forst 2014	0	113	0	115		Not estimable	
Inagaki 2013	2	74	0	75	1.1%	5.07 [0.25, 103.78]	
Lavalle-Gonzalez 2013	1	368	1	366	2.2%	0.99 [0.06, 15.84]	
Li 2014	2	223	0	226	1.1%	5.07 [0.24, 104.95]	
Rosenstock 2013	1	64	1	65 156	2.2% 2.2%	1.02 [0.06, 15.89]	
Wilding 2013 Subtotal (95% CI)	1	157 1333	1	1329	2.2% 30.4%	0.99 [0.06, 15.75] 0.85 [0.39, 1.84]	
Total events	10	1000	12	1020	00.470	0.00 [0.00] 1.04]	
Heterogeneity: Chi ² = 4.70,		P = 0.58					
Test for overall effect: Z = 0	•		,				
2.6.3 200mg Canagliflozir							
Inagaki 2013	n 2	77	0	75	1.1%	4.87 [0.24, 99.82]	
Rosenstock 2013	2	64	1	75 65	2.2%	4.06 [0.47, 35.37]	
Subtotal (95% CI)	-	141		140	3.3%	4.34 [0.75, 25.17]	
Total events	6	- / •	1				
Heterogeneity: Chi ² = 0.01,	•	= 0.92)	; l² = 0%				
Test for overall effect: Z =			,				
2.6.4 300mg Canagliflozir	n ad						
Bays2014	2	96	2	89	4.6%	0.93 [0.13, 6.44]	
Bode 2013	1	236	7	237	15.6%	0.14 [0.02, 1.16]	
Forst 2014	o o	114	0	115		Not estimable	
Inagaki 2013	1	75	ō	75	1.1%	3.00 [0.12, 72.49]	
Lavalle-Gonzalez 2013	0	367	0	366		Not estimable	
Li 2014	1	227	0	226	1.1%	2.99 [0.12, 72.93]	
Rosenstock 2013	0	65	1	65	3.4%	0.33 [0.01, 8.03]	
Schernthaner 2013	15	377	13	378	29.0%	1.16 [0.56, 2.40]	· · · · · · · · · · · · · · · · · · ·
Wilding 2013	1	156	1	156	2.2%	1.00 [0.06, 15.85]	
Subtotal (95% CI)		1713		1707	57.1%	0.88 [0.50, 1.54]	•
Total events	21		24				
Heterogeneity: Chi ² = 4.94, Test for overall effect: Z = 0							
Test for overall effect: Z = 0		0.65)		2405	100.0%	4 04 10 67 4 521	
Test for overall effect: Z = (Total (95% CI)	0.45 (P =		; I ² = 0%	3405	100.0%	1.01 [0.67, 1.52]	•
Test for overall effect: Z = (Total (95% CI) Total events	0.45 (P = 41	0.65) 3431	; I² = 0% 40		100.0%	1.01 [0.67, 1.52]	_, _, _, _, _, _, _, _, _, _, _, _, _, _
Test for overall effect: Z = 0 Total (95% CI) Total events Heterogeneity: Chi ² = 14.8 Test for overall effect: Z = 0	0.45 (P = 41 6, df = 18 0.05 (P =	0.65) 3431 (P = 0.6 0.96)	; i² = 0% 40 57); i² = 0	%			0.01 0.1 1 10 10
Test for overall effect: Z = 0 Total (95% CI) Total events Heterogeneity: Chi ² = 14.80	0.45 (P = 41 6, df = 18 0.05 (P =	0.65) 3431 (P = 0.6 0.96)	; i² = 0% 40 57); i² = 0	%			
Test for overall effect: $Z = 0$ Total (95% Cl) Total events Heterogeneity: Chi ² = 14.8 Test for overall effect: $Z = 0$ Test for subgroup difference	0.45 (P = 41 6, df = 18 0.05 (P = xes: Chi ² : Canaglifi	0.65) 3431 (P = 0.6 0.96) = 3.10. d	40 57); I ² = 0% f = 3 (P = Placeb	% = 0.38). 10	l² = 3.2%	Risk Ratio	0.01 0.1 1 10 10 Favours experimental Favours control Risk Ratio
Test for overall effect: $Z = 0$ Total (95% CI) Total events Heterogeneity: Chi ² = 14.8 Test for overall effect: $Z = 0$ Test for subgroup difference Study or Subgroup	0.45 (P = 41 6, df = 18 0.05 (P = æs: Chi ² : Canaglifi <u>Events</u>	0.65) 3431 (P = 0.6 0.96) = 3.10. d	40 57); I ² = 0% f = 3 (P = Placeb	% = 0.38). 10	l² = 3.2%		0.01 0.1 1 10 10 Favours experimental Favours control Risk Ratio
Test for overall effect: $Z = 0$ Total (95% Cl) Total events Heterogeneity: Chi ² = 14.8 Test for overall effect: $Z = 0$ Test for subgroup difference	0.45 (P = 41 6, df = 18 0.05 (P = æs: Chi ² : Canaglifi <u>Events</u>	0.65) 3431 (P = 0.6 0.96) = 3.10. d	40 67); I ² = 0% f = 3 (P = Placeb	% = 0.38). 10	l² = 3.2%	Risk Ratio	0.01 0.1 1 10 10 Favours experimental Favours control Risk Ratio
Test for overall effect: Z = (Total (95% CI) Total events Heterogeneity: Chi ² = 14.8 Test for overall effect: Z = (Test for subgroup difference Study or Subgroup 2.7.1 100mg canaglifiozin	0.45 (P = 41 6, df = 18 0.05 (P = 2es: Chi ² = Canaglifi <u>Events</u>	0.65) 3431 (P = 0.6 0.96) = 3.10. d ozin Total	40 (7); I ² = 0% (7); I ² = 0 (7) = 3 (7) (7) = 0 (7) = 0 (7	% = 0.38). o Total	l² = 3.2%	Risk Ratio M-H. Flxed, 95% Cl	0.01 0.1 1 10 10 Favours experimental Favours control Risk Ratio
Test for overall effect: Z = (Total (95% CI) Total events Heterogeneity: Chi ² = 14.8 Test for overall effect: Z = 1 Test for subgroup difference Study or Subgroup 2.7.1 100mg canagliflozin Bode 2013	0.45 (P = 41 6, df = 18 0.05 (P = ces: Chi ² = Canaglifi <u>Events</u> 0	0.65) 3431 (P = 0.6 0.96) = 3.10. d ozin Total 241	40 37); I ² = 0% f = 3 (P = Placeb Events 0	% = 0.38). o <u>Total</u> 237	l² = 3.2% Weight	Risk Ratio <u>M-H. Fixed, 95% CI</u> Not estimable 0.17 [0.01, 4.06] 1.50 [0.25, 8.92]	0.01 0.1 1 10 10 Favours experimental Favours control Risk Ratio
Test for overall effect: Z = (Total (95% Cl) Total events Heterogeneity: Chi ² = 14.8 Test for overall effect: Z = (Test for subgroup difference Study or Subgroup 2.7.1 100mg canagliflozin Bode 2013 Lavalle-Gonzalez 2013	41 6, df = 18 0.05 (P = ces: Chi ^a = Canaglifi <u>Events</u> 0 0	0.65) 3431 (P = 0.6 0.96) = 3.10. d ozin Total 241 368 483 223	; ² = 0% 40 57); ² = 0 f = 3 (P = Placel: Events 0 1 2 0	% = 0.38). 00 <u>Total</u> 183 482 226	I² = 3.2% <u>Weight</u> 13.4%	Risk Ratio <u>M-H. Fixed, 95% CI</u> Not estimable 0.17 [0.01, 4.06]	0.01 0.1 1 10 10 Favours experimental Favours control Risk Ratio
Test for overall effect: Z = (Total (95% CI) Total events Heterogeneity: Chi ² = 14.8 Test for overall effect: Z = (Test for subgroup 2.7.1 100mg canaglificzin Bode 2013 Lavalle-Gonzalez 2013 Leiter 2014 Stenlöf 2014	41 6, df = 18 0.05 (P = 2005 Chi ² : Canaglifi <u>Events</u> 0 0 3 0 1	0.65) 3431 (P = 0.6 0.96) = 3.10. d ozin Total 241 368 483 223 195	; ² = 0% 40 57); ² = 0 f = 3 (P = Placeb Events 0 1 2 0 2	% = 0.38). 00 <u>Total</u> 237 183 482 226 192	I² = 3.2% <u>Weight</u> 13.4%	Risk Ratio M-H, Fixed, 95% CI Not estimable 0.17 (0.01, 4.06] 1.50 (0.25, 8.92] Not estimable 0.49 (0.05, 5.38]	0.01 0.1 1 10 10 Favours experimental Favours control Risk Ratio
Test for overall effect: Z = (Total (95% CI) Total events Heterogeneity: Chi ² = 14.8 Test for overall effect: Z = (Test for subgroup difference Study or Subgroup 2.7.1 100mg canagliflozin Bode 2013 Lavalle-Gonzalez 2013 Leiter 2014 Li 2014 Stenköf 2014 Wilding 2013	0.45 (P = 41 6, df = 18 0.05 (P = 2005 (P = 20	0.65) 3431 (P = 0.6 0.96) = 3.10. d lozin Total 241 368 483 223 195 157	; ² = 0% 40 57); ² = 0 f = 3 (P = Placeb Events 0 1 2 0 2 0	% = 0.38). Total 237 183 482 226 192 156	² = 3.2% Weight 13.4% 13.5% 13.5%	Risk Ratio M-H. Fixed, 95% CI Not estimable 0.17 [0.01, 4.06] 1.50 [0.25, 8.92] Not estimable 0.49 [0.05, 5.38] Not estimable	0.01 0.1 1 10 10 Favours experimental Favours control Risk Ratio
Test for overall effect: Z = 0 Total (95% CI) Total events Heterogeneity: Chi ² = 14.8 Test for overall effect: Z = 0 Test for subgroup difference Study or Subgroup 2.7.1 100mg canagliftozin Bode 2013 Lavalle-Gonzalez 2013 Leiter 2014 Li 2014 Stenlőf 2014 Widing 2013 Yale 2013	41 6, df = 18 0.05 (P = 2005 Chi ² : Canaglifi <u>Events</u> 0 0 3 0 1	0.65) 3431 (P = 0.6 0.96) = 3.10. d ozin Total 241 368 483 223 195 157 90	; ² = 0% 40 57); ² = 0 f = 3 (P = Placeb Events 0 1 2 0 2	% = 0.38). Total 237 183 482 226 192 156 90	l ² = 3.2% <u>Weight</u> 13.4% 13.5% 13.5% 6.7%	Risk Ratio M-H, Fixed, 95% CI Not estimable 0.17 [0.01, 4.06] 1.50 [0.25, 8.92] Not estimable 0.49 [0.05, 5.38] Not estimable 1.00 [0.06, 15.74]	0.01 0.1 1 10 10 Favours experimental Favours control Risk Ratio
Test for overall effect: Z = (Total (95% Cl) Total events Heterogeneity: Chi ² = 14.80 Test for overall effect: Z = 1 Test for subgroup 2.7.1 100mg canagliflozin Bode 2013 Lavale-Gonzalez 2013 Leiter 2014 Li 2014 Stenlöf 2014 Wilding 2013 Subtotal (95% Cl)	0.45 (P = 41 6, df = 18 0.05 (P = xes: Chi ² : Canagliff Events 0 0 3 0 1 0 1	0.65) 3431 (P = 0.6 0.96) = 3.10. d lozin Total 241 368 483 223 195 157	40 67); I ² = 0% if = 3 (P = Placeb Events 0 1 2 0 2 0 1	% = 0.38). Total 237 183 482 226 192 156	² = 3.2% Weight 13.4% 13.5% 13.5%	Risk Ratio M-H. Fixed, 95% CI Not estimable 0.17 [0.01, 4.06] 1.50 [0.25, 8.92] Not estimable 0.49 [0.05, 5.38] Not estimable	0.01 0.1 1 10 10 Favours experimental Favours control Risk Ratio
Test for overall effect: Z = (Total (95% Cl) Total events Heterogeneity: Chi ² = 14.8 Test for overall effect: Z = (Test for subgroup 2.7.1 100mg canaglificzin Bode 2013 Lavalle-Gonzalez 2013 Leiter 2014 Li 2014 Stenlőf 2014 Wilding 2013 Yale 2013 Subtotal (95% Cl) Total events	0.45 (P = 41 6, df = 18 0.05 (P = xes: Chi ² : Canagliff <u>Events</u> 0 0 3 0 1 0 1 5	0.65) 3431 (P = 0.6 0.96) = 3.10. d ozin Total 241 368 483 223 195 155 157	; ² = 0% 40 57); ² = 0 f = 3 (P = Placeb Events 0 1 2 0 2 0 1 1 6	% = 0.38). Total 237 183 482 226 192 156 90	l ² = 3.2% <u>Weight</u> 13.4% 13.5% 13.5% 6.7%	Risk Ratio M-H, Fixed, 95% CI Not estimable 0.17 [0.01, 4.06] 1.50 [0.25, 8.92] Not estimable 0.49 [0.05, 5.38] Not estimable 1.00 [0.06, 15.74]	0.01 0.1 1 10 10 Favours experimental Favours control Risk Ratio
Test for overall effect: Z = (Total (95% Cl) Total events Heterogeneity: Chi ² = 14.8 Test for overall effect: Z = 1 Test for subgroup 2.7.1 100mg canagliflozin Bode 2013 Lavalle-Gonzalez 2013 Leiter 2014 Li 2014 Stenlöf 2014 Wilding 2013 Subtotal (95% Cl)	0.45 (P = 41 6, df = 18 0.05 (P = 2005: Chi ² = Canaglifi Events 0 0 3 0 1 0 1 5 4f = 3 (P	0.65) 3431 (P = 0.6 0.96) = 3.10. d ozin Total 241 368 483 223 195 157 90 1757 = 0.66);	; ² = 0% 40 57); ² = 0 f = 3 (P = Placeb Events 0 1 2 0 2 0 1 1 6	% = 0.38). Total 237 183 482 226 192 156 90	l ² = 3.2% <u>Weight</u> 13.4% 13.5% 13.5% 6.7%	Risk Ratio M-H, Fixed, 95% CI Not estimable 0.17 [0.01, 4.06] 1.50 [0.25, 8.92] Not estimable 0.49 [0.05, 5.38] Not estimable 1.00 [0.06, 15.74]	0.01 0.1 1 10 10 Favours experimental Favours control Risk Ratio
Test for overall effect: Z = (Total (95% Cl) Total events Heterogeneity: Chi ² = 14.8 Test for overall effect: Z = 1 Test for subgroup 2.7.1 100mg canagliflozin Bode 2013 Lavalle-Gonzalez 2013 Leiter 2014 Li 2014 Stenlöf 2014 Wilding 2013 Yale 2013 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = 1.59, Test for overall effect: Z = 0	0.45 (P = 41 6, df = 18 0.05 (P = 2005: Chi ² : Canaglift Events 0 0 3 0 1 0 1 5 5 df = 3 (P 0.49 (P = 1)	0.65) 3431 (P = 0.6 0.96) = 3.10. d ozin Total 241 368 483 223 195 157 90 1757 = 0.66);	; ² = 0% 40 57); ² = 0 f = 3 (P = Placeb Events 0 1 2 0 2 0 1 1 6	% = 0.38). Total 237 183 482 226 192 156 90	l ² = 3.2% <u>Weight</u> 13.4% 13.5% 13.5% 6.7%	Risk Ratio M-H, Fixed, 95% CI Not estimable 0.17 [0.01, 4.06] 1.50 [0.25, 8.92] Not estimable 0.49 [0.05, 5.38] Not estimable 1.00 [0.06, 15.74]	0.01 0.1 1 10 10 Favours experimental Favours control Risk Ratio
Test for overall effect: Z = 0 Total (95% CI) Total events Heterogeneity: Chi ² = 14.8 Test for overall effect: Z = 1 Test for subgroup 27.1 100mg canagliffozin Bode 2013 Lavalle-Gonzalez 2013 Leiter 2014 Li 2014 Stenlöf 2014 Wilding 2013 Yale 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 1.59, Test for overall effect: Z = 0 2.7.2 300mg canagliffozin	0.45 (P = 41 6, df = 18 0.05 (P = 2005: Chi ² = Canaglift Events 0 0 3 0 1 0 1 5 5 df = 3 (P 0.49 (P = 1)	0.65) 3431 (P = 0.6 0.96) = 3.10. d lozin Total 241 368 483 223 195 157 90 1757 = 0.66); 0.62)	40 57); I ² = 0% f = 3 (P = Placeb Events 0 1 2 0 1 2 0 1 1 6 I ² = 0%	% = 0.38). Total 237 183 482 226 192 156 90 1566	l ² = 3.2% <u>Weight</u> 13.4% 13.5% 13.5% 6.7%	Risk Ratio M-H, Fixed, 95% CI Not estimable 0.17 (0.01, 4.06] 1.50 (0.25, 8.92] Not estimable 0.49 (0.05, 5.38] Not estimable 1.00 [0.06, 15.74] 0.76 [0.25, 2.27]	0.01 0.1 1 10 10 Favours experimental Favours control Risk Ratio
Test for overall effect: $Z = 0$ Total (95% CI) Total events Heterogeneity: $Chi^2 = 14.8i$ Test for subgroup difference Study or Subgroup 2.7.1 100mg canagliflozin Bode 2013 Lavalle-Gonzalez 2013 Leiter 2014 Li 2014 Steniöf 2014 Wilding 2013 Yale 2013 Subtotal (95% CI) Total events Heterogeneity: $Chi^2 = 1.59$, Test for overall effect: $Z = 0$ 2.7.2 300mg canagliflozin Bode 2013	0.45 (P = 41 6, df = 18 0.05 (P = 2005; Chi [≥] : Canaglifi Events 0 0 3 0 1 0 1 5 , df = 3 (P 0.49 (P = 1	0.65) 3431 (P = 0.6 0.96) = 3.10. d iozin Total 241 368 483 223 155 157 90 1757 = 0.68); 0.62)	; ² = 0% 40 67); ² = 0 f = 3 (P = Placeb Events 0 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 6 ² = 0%	% = 0.38). to Total 237 183 482 226 192 1566 90 1566 237	I ² = 3.2% Weight 13.4% 13.5% 13.5% 6.7% 47.2%	Risk Ratio M-H, Fixed, 95% CI Not estimable 0.17 [0.01, 4.06] 1.50 [0.25, 8.92] Not estimable 0.49 [0.05, 5.38] Not estimable 1.00 [0.06, 15.74] 0.76 [0.25, 2.27]	0.01 0.1 1 10 10 Favours experimental Favours control Risk Ratio
Test for overall effect: Z = (Total (95% CI) Total events Heterogeneity: Chi ² = 14.80 Test for overall effect: Z = (Study or Subgroup 2.7.1 100mg canagliftozin Bode 2013 Lavalle-Gonzalez 2013 Leiter 2014 Vilcing 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 1.59, Test for overall effect: Z = 0 2.7.2 300mg canagliftozin Bode 2013 Lavalle-Gonzalez 2013	0.45 (P = 41 6, df = 18 0.05 (P = 2005 2005 2005 2005 2005 2005 2005 2005	0.65) 3431 (P = 0.6 0.96) = 3.10. d iozin Total 241 368 483 195 157 90 1757 = 0.66); 0.62) 236 367	; ² = 0% 40 57); ² = 0 f = 3 (P = Placeb Events 0 1 2 0 1 6 ² = 0% 0 1 6 1 6 1 7 1 0 1 1 0 1 1 0 1 1 0 1 1 1 1 1 1 1 1 1 1 1 1 1	% Total 237 183 482 226 192 1566 90 1566 237 183	I ² = 3.2% Weight 13.4% 13.5% 13.5% 6.7% 47.2%	Risk Ratio M-H, Fixed, 95% Cl Not estimable 0.17 [0.01, 4.06] 1.50 [0.25, 8.92] Not estimable 0.49 [0.05, 5.38] Not estimable 1.00 [0.06, 15.74] 0.76 [0.25, 2.27]	0.01 0.1 1 10 10 Favours experimental Favours control Risk Ratio
Test for overall effect: Z = (Total (95% CI) Total events Heterogeneity: Chi ² = 14.8 Test for overall effect: Z = 1 Test for subgroup 2.7.1 100mg canagliflozin Bode 2013 Lavalle-Gonzalez 2013 Leiter 2014 Steniöf 2014 Wilding 2013 Yale 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 1.59, Test for overall effect: Z = 0 2.7.2 300mg canagliflozin Bode 2013 Lavalle-Gonzalez 2013 Leiter 2014	0.45 (P = 41 6, df = 18 0.05 (P = 2005; Chi [≥] : Canaglifi Events 0 0 3 0 1 0 1 5 , df = 3 (P 0.49 (P = 1	0.65) 3431 (P = 0.6 0.96) = 3.10. d ozin Total 241 366 483 195 157 195 157 90 1757 = 0.66); 0.62) 236 367 485	40 57); I ² = 0% f = 3 (P = Placeb Events 0 1 2 0 1 1 1 1 1 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1 1 2 1 2 1 1 1 2 1 1 1 2 1 1 1 1 1 1 1 1 1 1 1 1 1	% = 0.38). Total 237 183 482 228 192 1566 90 1566 237 183 482	I ² = 3.2% Weight 13.4% 13.5% 13.5% 6.7% 47.2%	Risk Ratio M-H, Fixed, 95% CI Not estimable 0.17 [0.01, 4.06] 1.50 [0.25, 8.92] Not estimable 0.49 [0.05, 5.38] Not estimable 1.00 [0.06, 15.74] 0.76 [0.25, 2.27]	0.01 0.1 1 10 10 Favours experimental Favours control Risk Ratio
Test for overall effect: Z = 0 Total (95% CI) Total events Heterogeneity: Chi ² = 14.80 Test for overall effect: Z = 1 Test for subgroup 2.7.1 100mg canagliftozin Bode 2013 Lavalle-Gonzalez 2013 Leiter 2014 Wilding 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 1.59, Test for overall effect: Z = 0 2.7.2 300mg canagliftozin Bode 2013 Lavalle-Gonzalez 2013	0.45 (P = 41 6, df = 18 0.05 (P = 2005: Chi ² : Canaglift Events 0 0 3 0 0 1 0 1 5 5 (df = 3 (P 0.49 (P = 1) 0 1 3	0.65) 3431 (P = 0.6 0.96) = 3.10. d iozin Total 241 368 483 195 157 90 1757 = 0.66); 0.62) 236 367	; ² = 0% 40 57); ² = 0 f = 3 (P = Placeb Events 0 1 2 0 1 6 ² = 0% 0 1 6 1 6 1 7 1 0 1 1 0 1 1 0 1 1 0 1 1 1 1 1 1 1 1 1 1 1 1 1	% Total 237 183 482 226 192 1566 90 1566 237 183	I ² = 3.2% Weight 13.4% 13.5% 13.5% 6.7% 47.2%	Risk Ratio M-H. Fixed. 95% CI Not estimable 0.17 (0.01, 4.06] 1.50 (0.25, 8.92] Not estimable 0.49 (0.05, 5.38] Not estimable 1.00 [0.06, 15.74] 0.76 [0.25, 2.27] Not estimable 0.50 (0.03, 7.93] 1.49 (0.25, 8.88]	0.01 0.1 1 10 10 Favours experimental Favours control Risk Ratio
Test for overall effect: Z = 0 Total (95% CI) Total events Heterogeneity: Chi ² = 14.8 Test for overall effect: Z = 1 Test for subgroup 21.1 100mg canagliffozin Bode 2013 Lavalle-Gonzalez 2013 Leiter 2014 Widing 2013 Yale 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 1.59, Test for overall effect: Z = 0 2.7.2 300mg canagliffozin Bode 2013 Lavalle-Gonzalez 2013 Leiter 2014 Lavalle-Gonzalez 2013 Leiter 2014 Lavalle-Gonzalez 2013 Leiter 2014	0.45 (P = 41 6, df = 18 0.05 (P = 2es: Chi ^a = Canaglifi Events 0 0 3 0 1 0 1 5 .49 (P = 1 0 0 1 0 1 0 1 0 1 0 1 0 1 3 0 0	0.65) 3431 (P = 0.6 0.96) = 3.10. d ozin Total 241 368 483 223 195 157 90 1757 = 0.66); 0.62) 236 367 485 227	; ² = 0% 40 57); ² = 0 f = 3 (P = Placeb Events 0 1 2 0 1 1 1 6 ² = 0% 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 0 1 2 0 0 2 0 0 1 1 2 0 0 2 0 0 1 1 0 2 0 0 1 2 0 0 1 1 0 2 0 0 1 1 0 2 0 0 1 0 1 0 0 2 0 0 1 2 0 0 1 0 0 0 0 1 2 0 0 0 0 0 0 0 0 0 0 0 0 0	% = 0.38). Total 237 183 482 226 192 1566 90 1566 237 183 482 226	² = 3.2% <u>Weight</u> 13.4% 13.5% 13.5% 6.7% 47.2% 9.0% 13.5%	Risk Ratio M-H, Fixed, 95% CI Not estimable 0.17 [0.01, 4.06] 1.50 [0.25, 8.92] Not estimable 0.49 [0.05, 5.38] Not estimable 1.00 [0.06, 15.74] 0.76 [0.25, 2.27] Not estimable 0.50 [0.03, 7.93] 1.49 [0.25, 8.88] Not estimable	0.01 0.1 1 10 10 Favours experimental Favours control Risk Ratio
Test for overall effect: Z = 0 Total (95% CI) Total events Heterogeneity: Chi ² = 14.8 Test for overall effect: Z = 1 Test for subgroup difference Study or Subgroup 2.7.1 100mg canagliftozin Bode 2013 Lavalle-Gonzalez 2013 Leiter 2014 Li 2014 Widing 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 1.59, Test for overall effect: Z = 0 2.7.2 300mg canagliftozin Bode 2013 Lavalle-Gonzalez 2013 Leiter 2014 Li 2014 Schernthaner 2013	0.45 (P = 41 6, df = 18 0.05 (P = xes: Chi ² : Canaglifi Events 0 0 3 0 1 0 3 0 1 0 3 0 1 0 1 5 5 4f = 3 (P 2 9 0 1 3 0 1 2	0.65) 3431 (P = 0.6 0.96) = 3.10. d iozin Total 241 368 483 223 195 157 157 = 0.66); 0.62) 236 367 485 227 378	; ² = 0% 40 67); ² = 0 f = 3 (P = Placeb Events 0 1 2 0 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 2 0 1 2 0 0 1 2 0 0 1 2 0 0 1 2 0 0 1 2 0 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 0 1 2 0 0 1 2 0 0 1 2 0 0 1 2 0 0 1 2 0 0 1 2 0 0 0 0 0 0 1 2 0 0 0 0 0 0 0 0 0 0 0 0 0	% Total 237 183 482 226 192 1566 237 183 482 226 378	I ² = 3.2% Weight 13.4% 13.5% 13.5% 6.7% 47.2% 9.0% 13.5% 3.4%	Risk Ratio M-H, Fixed, 95% CI Not estimable 0.17 [0.01, 4.06] 1.50 [0.25, 8.92] Not estimable 0.49 [0.05, 5.38] Not estimable 1.00 [0.06, 15.74] 0.76 [0.25, 2.27] Not estimable 0.50 [0.03, 7.93] 1.49 [0.25, 8.88] Not estimable 5.00 [0.24, 103.80]	0.01 0.1 1 10 10 Favours experimental Favours control Risk Ratio
Test for overall effect: Z = 0 Total (95% CI) Total events Heterogeneity: Chi ² = 14.8 Test for overall effect: Z = 0 Study or Subgroup 2.7.1 100mg canagliftozin Bode 2013 Lavalle-Gonzalez 2013 Leiter 2014 Li 2014 Steniof 2014 Wilding 2013 Yale 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 1.59, Test for overall effect: Z = 0 2.7.2 300mg canagliftozin Bode 2013 Leiter 2014 Li 2014 Schernthaner 2013 Steniof 2014 Wilding 2013 Steniof 2014 Schernthaner 2013 Steniof 2014 Wilding 2013 Yale 2013	0.45 (P = 41 6, df = 18 0.05 (P = 2005 Chi ² : Canaglift Events 0 0 3 0 1 0 1 5 5 4f = 3 (P 0.49 (P = 1) 1 3 0 1 3 0 2 0	0.65) 3431 (P = 0.6 0.96) = 3.10.4 (p = 0.6 0.96) = 3.10.4 (p = 0.6 y = 0.68) (p	; ² = 0% 40 57); ² = 0 f = 3 (P = Placeb Events 0 1 2 0 1 1 6 ² = 0% 0 1 2 0 0 1 2 0 0 1 2 0 0 1 2 0 0 2 0 1 2 0 2 0 1 2 0 2 0 1 2 0 2 0 1 2 0 2 0 1 2 0 2 0 1 2 0 2 0 1 2 0 2 0 1 2 0 2 0 1 2 0 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 0 2 0 0 1 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 0 0 2 0 0 0 2 0 0 0 0 0 0 0 0 0 0 0 0 0	% = 0.38). or Total 237 183 482 226 90 1566 1566 2377 183 482 226 378 192 256 378 192 156 90	I ² = 3.2% Weight 13.4% 13.5% 13.5% 6.7% 47.2% 9.0% 13.5% 3.4% 17.0% 10.0%	Risk Ratio M-H, Fixed, 95% CI Not estimable 0.17 [0.01, 4.06] 1.50 [0.25, 8.92] Not estimable 0.49 [0.05, 5.38] Not estimable 1.00 [0.06, 15.74] 0.76 [0.25, 2.27] Not estimable 0.50 [0.03, 7.93] 1.49 [0.25, 8.88] Not estimable 5.00 [0.24, 103.80] 0.19 [0.01, 4.03] Not estimable 0.34 (0.01, 8.16]	0.01 0.1 1 10 10 Favours experimental Favours control Risk Ratio
Test for overall effect: $Z = 0$ Total (95% CI) Total events Heterogeneity: Chi ² = 14.80 Test for overall effect: $Z = 1$ Test for subgroup difference Study or Subgroup 2.7.1 100mg canagliftozin Bode 2013 Lavalle-Gonzalez 2013 Leiter 2014 Li 2014 Steniof 2014 Wilding 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 1.59, Test for overall effect: $Z = 0$ 2.7.2 300mg canagliftozin Bode 2013 Lavalle-Gonzalez 2013 Leiter 2014 Li 2014 Schernthaner 2013 Steniof 2014 Wilding 2013 Steniof 2014 Wilding 2013 Steniof 2014 Wilding 2013 Steniof 2014 Wilding 2013 Steniof 2014 Steniof 2014 Steniof 2014 Steniof 2014 Steniof 2013 Steniof 2014 Steniof 2015 Steniof 2014 Steniof 2015 Steniof 2015 Steniof 2015 St	0.45 (P = 41 6, df = 18 0.05 (P = 2005 Chi ² : Canagliff Events 0 0 3 0 1 0 3 0 1 0 1 0 1 0 1 0 1 0 1 0	0.65) 3431 (P = 0.6 0.96) = 3.10. d ozin Total 241 366 483 195 157 195 157 90.62) 226 367 485 227 378 197 156	; ² = 0% 40 67); ² = 0 f = 3 (P = Placeb Events 0 1 2 0 1 2 0 1 1 6 ² = 0% 1 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 1 2 0 0 1 2 0 0 1 2 0 0 1 2 0 0 1 2 0 0 1 2 0 0 1 2 0 0 1 2 0 0 1 2 0 0 1 2 0 0 1 2 0 0 1 2 0 0 1 2 0 0 1 2 0 0 1 2 0 0 1 2 0 0 1 2 0 0 1 2 0 0 1 2 0 0 1 2 0 0 1 2 0 0 1 2 0 0 1 2 0 1 1 1 1 1 1 1 1 1 1 1 1 1	% = 0.38). po Total 237 183 482 226 90 1566 237 183 482 226 378 482 226 378 482 226 378 192	I ² = 3.2% Weight 13.4% 13.5% 13.5% 6.7% 47.2% 9.0% 13.5% 3.4% 17.0%	Risk Ratio M-H. Fixed. 95% Cl Not estimable 0.17 (0.01, 4.06] 1.50 (0.25, 8.92] Not estimable 0.49 (0.05, 5.38] Not estimable 1.00 [0.06, 15.74] 0.76 [0.25, 2.27] Not estimable 0.50 (0.03, 7.93] 1.49 (0.25, 8.88] Not estimable 5.00 (0.24, 103.80] 0.19 (0.01, 4.03] Not estimable	0.01 0.1 1 10 10 Favours experimental Favours control Risk Ratio
Test for overall effect: Z = 0 Total (95% CI) Total events Heterogeneity: Chi ² = 14.8 Test for overall effect: Z = 0 Study or Subgroup 2.7.1 100mg canagliftozin Bode 2013 Lavalle-Gonzalez 2013 Leiter 2014 Li 2014 Steniof 2014 Wilding 2013 Yale 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 1.59, Test for overall effect: Z = 0 2.7.2 300mg canagliftozin Bode 2013 Leiter 2014 Li 2014 Schernthaner 2013 Steniof 2014 Wilding 2013 Steniof 2014 Schernthaner 2013 Steniof 2014 Wilding 2013 Yale 2013	0.45 (P = 41 6, df = 18 0.05 (P = 2005 Chi ² : Canaglift Events 0 0 3 0 1 0 1 5 5 6 1 3 0 1 0 1 3 0 1 5 5 6 1 3 0 0 1 3 0 0 1 3 0 0 1 3 0 0 1 3 0 0 1 3 0 0 5 6 1 8 1 8 1 8 1 8 1 8 1 8 1 8 1 8 1 8 1	0.65) 3431 (P = 0.6 0.96) = 3.10. d ozin Total 241 368 483 195 157 195 1757 = 0.66); 0.62) 236 367 485 227 378 367 197 156 89 2135	; ² = 0% 40 57); ² = 0 f = 3 (P = Placeb Events 0 1 2 0 1 1 2 0 1 1 6 ² = 0% 0 1 2 0 1 2 0 1 2 0 1 1 6 1 ² = 0%	% = 0.38). or Total 237 183 482 226 90 1566 1566 2377 183 482 226 378 192 256 378 192 156 90	I ² = 3.2% Weight 13.4% 13.5% 13.5% 6.7% 47.2% 9.0% 13.5% 3.4% 17.0% 10.0%	Risk Ratio M-H, Fixed, 95% CI Not estimable 0.17 [0.01, 4.06] 1.50 [0.25, 8.92] Not estimable 0.49 [0.05, 5.38] Not estimable 1.00 [0.06, 15.74] 0.76 [0.25, 2.27] Not estimable 0.50 [0.03, 7.93] 1.49 [0.25, 8.88] Not estimable 5.00 [0.24, 103.80] 0.19 [0.01, 4.03] Not estimable 0.34 (0.01, 8.16]	0.01 0.1 1 10 10 Favours experimental Favours control Risk Ratio
Test for overall effect: Z = (Total (95% Cl) Total events Heterogeneity: Chi ² = 14.8 Test for overall effect: Z = 1 Test for subgroup 2.7.1 100mg canagliflozin Bode 2013 Lavalle-Gonzalez 2013 Leiter 2014 Stenlöf 2014 Wilding 2013 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = 1.59, Test for overall effect: Z = 0 2.7.2 300mg canagliflozin Bode 2013 Lavalle-Gonzalez 2013 Leiter 2014 Stenlöf 2014 Wilding 2013 Subtotal (95% Cl) Total events Leiter 2014 Li 2014 Schernithaner 2013 Stenlöf 2014 Wilding 2013 Yale 2013 Subtotal (95% Cl) Total events	0.45 (P = 41 6, df = 18 0.05 (P = 2x9s: Chi ^a : Canaglift Events 0 0 3 0 1 0 1 5 5 (F = 3 (P 0 1 5 0.49 (P = 1) 0 1 3 0 2 0 0 1 3 0 0 4 f = 3 (P 2 0 0 1 0 5 5 6 1 8 0 0 5 9 1 9 1 9 1 9 1 9 1 9 1 9 1 9 1 9 1 9	0.65) 3431 (P = 0.6 0.96) = 3.10. d ozin Total 241 368 483 223 195 157 90 90 90 90 90 90 90 90 90 90	; ² = 0% 40 57); ² = 0 f = 3 (P = Placeb Events 0 1 2 0 1 1 2 0 1 1 6 ² = 0% 0 1 2 0 1 2 0 1 2 0 1 1 6 1 ² = 0%	% = 0.38). or Total 237 183 482 226 90 1566 1566 2377 183 482 226 378 192 256 378 192 156 90	I ² = 3.2% Weight 13.4% 13.5% 13.5% 6.7% 47.2% 9.0% 13.5% 3.4% 17.0% 10.0%	Risk Ratio M-H, Fixed, 95% CI Not estimable 0.17 [0.01, 4.06] 1.50 [0.25, 8.92] Not estimable 0.49 [0.05, 5.38] Not estimable 1.00 [0.06, 15.74] 0.76 [0.25, 2.27] Not estimable 0.50 [0.03, 7.93] 1.49 [0.25, 8.88] Not estimable 5.00 [0.24, 103.80] 0.19 [0.01, 4.03] Not estimable 0.34 (0.01, 8.16]	0.01 0.1 1 10 10 Favours experimental Favours control Risk Ratio
Test for overall effect: Z = 0 Total (95% CI) Total events Heterogeneity: Chi ² = 14.80 Test for overall effect: Z = 1 Test for subgroup difference Study or Subgroup 2.7.1 100mg canagliflozin Bode 2013 Lavalle-Gonzalez 2013 Leiter 2014 Stenlöf 2014 Wilding 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 1.59, Test for overall effect: Z = 0 2.7.2 300mg canagliflozin Bode 2013 Leiter 2014 Lavalle-Gonzalez 2013 Leiter 2014 Stenlöf 2014 Events Heterogeneity: Chi ² = 1.59, Test for overall effect: Z = 0 Schernthaner 2013 Stenlöf 2014 Wilding 2013 Stenlöf 2014 Wilding 2013 Stenlöf 2014 Wilding 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 3.05, Test for overall effect: Z = 0	0.45 (P = 41 6, df = 18 0.05 (P = 2x9s: Chi ^a : Canaglift Events 0 0 3 0 1 0 1 5 5 (F = 3 (P 0 1 5 0.49 (P = 1) 0 1 3 0 2 0 0 1 3 0 0 4 f = 3 (P 2 0 0 1 0 5 5 6 1 8 0 0 5 9 1 9 1 9 1 9 1 9 1 9 1 9 1 9 1 9 1 9	0.65) 3431 (P = 0.6 0.96) = 3.10. d iozin Total 241 368 483 195 157 = 0.66); 0.62) 236 367 485 227 378 197 156 99 2135 = 0.55); 0.85)	; ² = 0% 40 57); ² = 0 f = 3 (P = Placeb Events 0 1 2 0 1 1 2 0 1 1 6 ² = 0% 0 1 2 0 1 2 0 1 2 0 1 1 6 1 ² = 0%	% = 0.38). no Total 237 183 482 226 192 1566 90 1566 237 183 482 226 192 1566 378 192 1569 1944	I ² = 3.2% Weight 13.4% 13.5% 13.5% 6.7% 47.2% 9.0% 13.5% 3.4% 17.0% 10.0% 52.8%	Risk Ratio M-H, Fixed, 95% Cl Not estimable 0.17 [0.01, 4.06] 1.50 [0.25, 8.92] Not estimable 0.49 [0.05, 5.38] Not estimable 1.00 [0.06, 15.74] 0.76 [0.25, 2.27] Not estimable 0.50 [0.03, 7.93] 1.49 [0.25, 8.88] Not estimable 5.00 [0.24, 103.80] 0.19 [0.01, 4.03] Not estimable 0.34 [0.01, 8.16] 0.91 [0.33, 2.48]	0.01 0.1 1 10 10 Favours experimental Favours control Risk Ratio
Test for overall effect: Z = (Total (95% Cl) Total events Heterogeneity: Chi ² = 14.8 Test for overall effect: Z = 1 Test for subgroup 2.7.1 100mg canagliflozin Bode 2013 Lavalle-Gonzalez 2013 Leiter 2014 Stenlöf 2014 Wilding 2013 Yale 2013 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = 1.59, Test for overall effect: Z = 0 2.7.2 300mg canagliflozin Bode 2013 Leiter 2014 Lavalle-Gonzalez 2013 Leiter 2014 Schernthaner 2013 Stenlöf 2014 Wilding 2013 Yale 2013 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = 3.05, Test for overall effect: Z = 0 Total (95% Cl)	0.45 (P = 41 6, df = 18 0.05 (P = 2x9s: Chi ^a : Canaglift Events 0 0 3 0 1 0 1 5 5 (F = 3 (P 0 1 5 0.49 (P = 1) 0 1 3 0 2 0 0 1 3 0 0 4 f = 3 (P 2 0 0 1 0 5 5 6 1 8 0 0 5 9 1 9 1 9 1 9 1 9 1 9 1 9 1 9 1 9 1 9	0.65) 3431 (P = 0.6 0.96) = 3.10. d ozin Total 241 368 483 223 195 157 90 90 90 90 90 90 90 90 90 90	; ² = 0% 40 57); ² = 0 f = 3 (P = Placeb Events 0 1 2 0 1 1 2 0 1 1 6 ² = 0% 0 1 2 0 1 2 0 1 2 0 1 1 6 1 ² = 0%	% = 0.38). no Total 237 183 482 226 192 1566 90 1566 237 183 482 226 192 1566 378 192 1569 1944	I ² = 3.2% Weight 13.4% 13.5% 13.5% 6.7% 47.2% 9.0% 13.5% 3.4% 17.0% 10.0%	Risk Ratio M-H, Fixed, 95% CI Not estimable 0.17 [0.01, 4.06] 1.50 [0.25, 8.92] Not estimable 0.49 [0.05, 5.38] Not estimable 1.00 [0.06, 15.74] 0.76 [0.25, 2.27] Not estimable 0.50 [0.03, 7.93] 1.49 [0.25, 8.88] Not estimable 5.00 [0.24, 103.80] 0.19 [0.01, 4.03] Not estimable 0.34 (0.01, 8.16]	0.01 0.1 1 10 10 Favours experimental Favours control Risk Ratio
Test for overall effect: Z = 0 Total (95% CI) Total events Heterogeneity: Chi ² = 14.80 Test for overall effect: Z = 1 Test for subgroup difference Study or Subgroup 2.7.1 100mg canagliflozin Bode 2013 Lavalle-Gonzalez 2013 Leiter 2014 Stenlöf 2014 Wilding 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 1.59, Test for overall effect: Z = 0 2.7.2 300mg canagliflozin Bode 2013 Leiter 2014 Lavalle-Gonzalez 2013 Leiter 2014 Stenlöf 2014 Events Heterogeneity: Chi ² = 1.59, Test for overall effect: Z = 0 Schernthaner 2013 Stenlöf 2014 Wilding 2013 Stenlöf 2014 Wilding 2013 Stenlöf 2014 Wilding 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 3.05, Test for overall effect: Z = 0	0.45 (P = 41 6, df = 18 0.05 (P = 2005; Chi [≥] : Canaglifi Events 0 0 3 0 1 0 3 0 1 5 5 4f = 3 (P 0 0 1 5 0 1 0 1 5 0 1 0 1 2 0 0 0 0 1 1 3 0 0 1 1 5 0 1 1 5 0 6 (f = 18 8 0.05 (P = 2005) 1 1 0 0 0 0 1 1 1 0 0 0 0 0 0 0 0 0 0	0.65) 3431 (P = 0.6 0.96) = 3.10.4 (ozin Total 241 368 483 223 157 90 1757 = 0.68); 0.62) 236 367 485 367 485 367 197 195 195 195 195 195 195 195 195	; $P = 0\%$ 40 57); $P = 0$ f = 3 (P = Placeb Events 0 1 2 0 2 0 1 P 6 P = 0\% 0 1 2 0 1 P 6 P 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 2 0 1 1 1 2 0 1 1 1 2 0 1 1 1 1 1 1 1 1 1 1 1 1 1	% = 0.38). no Total 237 183 482 226 192 1566 90 1566 237 183 482 226 192 1566 378 192 1569 1944	I ² = 3.2% Weight 13.4% 13.5% 13.5% 6.7% 47.2% 9.0% 13.5% 3.4% 17.0% 10.0% 52.8%	Risk Ratio M-H, Fixed, 95% Cl Not estimable 0.17 [0.01, 4.06] 1.50 [0.25, 8.92] Not estimable 0.49 [0.05, 5.38] Not estimable 1.00 [0.06, 15.74] 0.76 [0.25, 2.27] Not estimable 0.50 [0.03, 7.93] 1.49 [0.25, 8.88] Not estimable 5.00 [0.24, 103.80] 0.19 [0.01, 4.03] Not estimable 0.34 [0.01, 8.16] 0.91 [0.33, 2.48]	0.01 0.1 1 10 10 Favours experimental Favours control Risk Ratio

G	Canagli	Rozin	Placeb			Risk Ratio	Risk I	Catio	
Study or Subgroup	-				Weight	M-H, Fixed, 95% CI			
2.8.1 50 mg Canaglif	lozin								
Bays2014	6	98	3	89	4.4%	1.82 [0.47, 7.05]			
Inagaki 2013	8	82	10	75	14.5%	0.73 [0.30, 1.76]			
Rosenstock 2013	5	64	2	65	2.8%	2.54 [0.51, 12.61]			
Subtotal (95% CI)	10	244	45	229	21.7%	1.18 [0.62, 2.26]			
Total events Heterogeneity: Chi ² =	19 2 41 df - 2	/P - 0	15 20): 12 - 1	70/					
Test for overall effect:				/ /0					
2.8.2 100mg Canagli									
Bays2014	1	93	3	89	4.3%	0.32 [0.03, 3.01]			
Inagaki 2013	10 0	74 64	10 2	75 65	13.8% 3.5%	1.01 [0.45, 2.29]	• · · · · · · · · · · · · · · · · · · ·		
Rosenstock 2013 Subtotal (95% CI)	0	231	2	229	21.5%	0.20 [0.01, 4.15] 0.75 [0.36, 1.53]		•	
Total events	11	201	15	220	21.070	0.70 [0.00, 1.00]			
Heterogeneity: Chi ² =		2 (P = 0.4		%					
Test for overall effect:	Z = 0.80 (F	P = 0.43)							
2.8.3 150mg Canagli	flozin								
Inagaki 2013	8	75	10	75	13.9%	0.80 [0.33, 1.92]		_	
Subtotal (95% CI)	-	75		75	13.9%	0.80 [0.33, 1.92]	-		
Total events	8		10						
Heterogeneity: Not ap									
Test for overall effect:	Z = 0.50 (F	P = 0.62)							
2.8.4 200mg Canagli	flozin								
Bays2014	1	96	3	89	4.3%	0.31 [0.03, 2.92]			
Inagaki 2013	8	77	10	75	14.1%	0.78 [0.33, 1.87]			
Rosenstock 2013	0	65	2	65	3.5%	0.20 [0.01, 4.09]	· · · ·		
Subtotal (95% CI)	-	238	-	229	21.9%	0.59 [0.27, 1.28]		•	
Total events	9		15						
Heterogeneity: Chi ² =				%					
Test for overall effect:	Z = 1.32 (F	e = 0.19)							
2.8.5 300mg canagili	lozin								
Bays2014	1	96	3	89	4.3%	0.31 [0.03, 2.92]			
Inagaki 2013	9	75	10	75	13.9%	0.90 [0.39, 2.09]			
Rosenstock 2013	1	64	2	65	2.8%	0.51 [0.05, 5.46]			
Subtotal (95% CI)		235		229	21.0%	0.73 [0.35, 1.52]	-		
Total events	11		15						
Heterogeneity: Chi ² =				%					
Test for overall effect:	Z = 0.85 (F	^o = 0.40)							
		1023			100 09/	0.81 [0.58, 1.13]			
Total (95% CI)		1023		991	100.0%				
Total (95% CI) Total events	58	1025	70	991	100.0%	0.01 [0.30, 1.13]			
Total events Heterogeneity: Chi ² =	7.58, df = 1	12 (P = 0	.82); ² = (100.0%	0.01 [0.30, 1.13]		10	100
Total events Heterogeneity: Chi ² = Test for overall effect:	7.58, df = 1 Z = 1.25 (F	I2 (P = 0 P = 0.21)	.82); l² =	0%			0.01 0.1 1 Favours experimental	10 Favours control	100
Total events Heterogeneity: Chi ² =	7.58, df = 1 Z = 1.25 (F	I2 (P = 0 P = 0.21)	.82); l² =	0%			0.01 0.1 1 Favours experimental		100
Total events Heterogeneity: Chi ² = Test for overall effect:	7.58, df = 1 Z = 1.25 (F	l2 (P = 0 P = 0.21) hi ² = 2.06	.82); l² =	0% P = 0.7				Favours control	100
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff H Study or Subgroup	7.58, df = 1 Z = 1.25 (F erences: Ch Canaglif Events	l2 (P = 0 P = 0.21) hi ² = 2.06 flozin	0.82); ² = (6. df = 4 (F Placeb	0% P = 0.7	2). I² = 0%		Favours experimental	Favours control	100
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diffi H <u>Study or Subgroup</u> 2.9.1 50 mg Canaglif	7.58, df = 1 Z = 1.25 (F erences: Ch Canaglif Events lozin	l2 (P = 0 P = 0.21) hi ² = 2.06 flozin Total	0.82); ² = (6. df = 4 (F Placet Events	0% P = 0.7 Do <u>Total</u>	2). I² = 0% Weight	Risk Ratio M-H. Fixed. 95% Cl	Favours experimental	Favours control	100
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diffi H <u>Study or Subgroup</u> 2.9.1 50 mg Canaglif Bays2014	7.58, df = 1 Z = 1.25 (F erences: Ch Canaglit Events lozin 6	l2 (P = 0 P = 0.21) hi ² = 2.06 flozin <u>Total</u> 98	0.82); ² = 0 3. df = 4 (F Placek Events 5	0% P = 0.7 00 <u>Total</u> 89	2). I ² = 0% <u>Weight</u> 26.1%	Risk Ratio <u>M-H. Fixed, 95% Cl</u> 1.09 (0.34, 3.45)	Favours experimental	Favours control	100
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diffi H 2.9.1 50 mg Canaglif Bays2014 Inagaki 2013	7.58, df = 1 Z = 1.25 (F erences: Ch Canaglif Events lozin	12 (P = 0 P = 0.21) hi ² = 2.06 flozin Total 98 82	0.82); ² = (6. df = 4 (F Placet Events	0% P = 0.7 xo <u>Total</u> 89 75	2). I ² = 0% <u>Weight</u> 26.1% 7.8%	Risk Ratio <u>M-H. Fixed, 95% Cl</u> 1.09 [0.34, 3.45] 0.31 [0.01, 7.38]	Favours experimental	Favours control	100
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff H <u>Study or Subgroup</u> 2.9.1 50 mg Canaglif Bays2014 Inagaki 2013 Subtotal (95% CI)	7.58, df = 1 Z = 1.25 (F erences: Ch Canaglit Events lozin 6	l2 (P = 0 P = 0.21) hi ² = 2.06 flozin <u>Total</u> 98	0.82); ² = (6. df = 4 (F Placek Events 5 1	0% P = 0.7 00 <u>Total</u> 89	2). I ² = 0% <u>Weight</u> 26.1%	Risk Ratio <u>M-H. Fixed, 95% Cl</u> 1.09 (0.34, 3.45)	Favours experimental	Favours control	100
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff H <u>Study or Subgroup</u> 2.9.1 50 mg Canaglif Bays2014 Inagaki 2013 Subtotal (95% CI) Total events	7.58, df = 1 Z = 1.25 (F erences: Ch Canaglit Events lozin 6 0	l2 (P = 0 P = 0.21) hi ² = 2.06 flozin Total 98 82 180	0.82); ² = (3. df = 4 (F Placek Events 5 1 6	0% P = 0.7 00 <u>Total</u> 89 75 164	2). I ² = 0% <u>Weight</u> 26.1% 7.8%	Risk Ratio <u>M-H. Fixed, 95% Cl</u> 1.09 [0.34, 3.45] 0.31 [0.01, 7.38]	Favours experimental	Favours control	100
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff H 2.9.1 50 mg Canaglif Bays2014 Inagaki 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² =	7.58, df = 1 Z = 1.25 (F erences: Ch <u>Events</u> lozin 6 0 55, df = 1	l2 (P = 0 P = 0.21) hi ² = 2.06 flozin Total 98 82 180 I (P = 0.4	0.82); ² = 0 3. df = 4 (F Placet: Events 5 1 6 46); ² = 0	0% P = 0.7 00 <u>Total</u> 89 75 164	2). I ² = 0% <u>Weight</u> 26.1% 7.8%	Risk Ratio <u>M-H. Fixed, 95% Cl</u> 1.09 [0.34, 3.45] 0.31 [0.01, 7.38]	Favours experimental	Favours control	100
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff H 	7.58, df = 1 Z = 1.25 (F erences: Ch Canaglit Events lozin 6 0.55, df = 1 Z = 0.18 (F	l2 (P = 0 P = 0.21) hi ² = 2.06 flozin Total 98 82 180 I (P = 0.4	0.82); ² = 0 3. df = 4 (F Placet: Events 5 1 6 46); ² = 0	0% P = 0.7 00 <u>Total</u> 89 75 164	2). I ² = 0% <u>Weight</u> 26.1% 7.8%	Risk Ratio <u>M-H. Fixed, 95% Cl</u> 1.09 [0.34, 3.45] 0.31 [0.01, 7.38]	Favours experimental	Favours control	100
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff H 2.9.1 50 mg Canaglif Bays2014 Inagaki 2013 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = Test for overall effect: 2.9.2 100mg Canagli	7.58, df = 1 Z = 1.25 (F erences: CP Canagliti <u>Events</u> lozin 6 0.55, df = 1 Z = 0.18 (F flozIn	2 (P = 0 P = 0.21) hi ² = 2.06 flozin Total 98 82 180 I (P = 0.46)	9.82); ² = (9. df = 4 (f Placet Events 5 1 6 46); ² = 0 ¹	0% P = 0.7 70 70 89 75 164	2). I ² = 0% <u>Weight</u> 26.1% 7.8% 33.8%	Risk Ratio <u>M-H, Fixed, 95% Cl</u> 1.09 [0.34, 3.45] 0.31 [0.01, 7.38] 0.91 [0.32, 2.62]	Favours experimental	Favours control	100
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff H 2.9.1 50 mg Canaglif Bays2014 Inagaki 2013 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = Test for overall effect: 2.9.2 100mg Canaglif Bays2014	7.58, df = 1 Z = 1.25 (F erences: Cr Canagliti <u>Events</u> lozin 6 0.55, df = 1 Z = 0.18 (F flozIn 6	2 (P = 0 P = 0.21) hi ² = 2.06 flozin Total 98 82 180 ((P = 0.4 P = 0.86) 93	9.82); ² = () 3. df = 4 (f Placet <u>Events</u> 5 1 6 46); ² = 0'	0% P = 0.7 50 <u>Total</u> 89 75 164 %	2). ² = 0% <u>Weight</u> 26.1% 7.8% 33.8% 25.4%	Risk Ratio M-H. Fixed, 95% Cl 1.09 [0.34, 3.45] 0.31 [0.01, 7.38] 0.91 [0.32, 2.62] 1.15 [0.36, 3.63]	Favours experimental	Favours control	100
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff H 	7.58, df = 1 Z = 1.25 (F erences: CP Canagliti <u>Events</u> lozin 6 0.55, df = 1 Z = 0.18 (F flozIn	2 (P = 0 P = 0.21) hi ² = 2.06 flozin 98 82 180 I (P = 0.4 P = 0.86) 93 74	9.82); ² = (9. df = 4 (f Placet Events 5 1 6 46); ² = 0 ¹	0% P = 0.7 00 <u>Total</u> 89 75 164 %	2). I ² = 0% <u>Weight</u> 26.1% 7.8% 33.8% 25.4% 4.9%	Risk Ratio M-H. Fixed, 95% CI 1.09 (0.34, 3.45) 0.31 [0.01, 7.38] 0.91 [0.32, 2.62] 1.15 [0.36, 3.63] 5.07 [0.61, 42.34]	Favours experimental	Favours control	100
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff H 2.9.1 50 mg Canaglif Bays2014 Inagaki 2013 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = Test for overall effect: 2.9.2 100mg Canaglif Bays2014	7.58, df = 1 Z = 1.25 (F erences: Cr Canagliti <u>Events</u> lozin 6 0.55, df = 1 Z = 0.18 (F flozIn 6	2 (P = 0 P = 0.21) hi ² = 2.06 flozin Total 98 82 180 ((P = 0.4 P = 0.86) 93	9.82); ² = () 3. df = 4 (f Placet <u>Events</u> 5 1 6 46); ² = 0'	0% P = 0.7 50 <u>Total</u> 89 75 164 %	2). ² = 0% <u>Weight</u> 26.1% 7.8% 33.8% 25.4%	Risk Ratio M-H. Fixed, 95% Cl 1.09 [0.34, 3.45] 0.31 [0.01, 7.38] 0.91 [0.32, 2.62] 1.15 [0.36, 3.63]	Favours experimental	Favours control	100
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff H 2.9.1 50 mg Canaglif Bays2014 Inagaki 2013 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = Test for overall effect: 2.9.2 100mg Canaglif Bays2014 Inagaki 2013 Subtotal (95% Cl)	7.58, df = 1 Z = 1.25 (F erences: Cr Canaglin Events lozin 6 0.55, df = 1 Z = 0.18 (F flozin 6 5 11	12 (P = 0 > = 0.21) hi ² = 2.06 flozin Total 98 82 180 1 (P = 0.4 > = 0.86) 93 74 167	9.82); ² = (9. df = 4 (F Placeb Events 5 1 6 46); ² = 0' 5 1 6 46); ² = 0' 5 1 6	0% P = 0.7 50 Total 89 75 164 % 89 75 164	2). I ² = 0% <u>Weight</u> 26.1% 7.8% 33.8% 25.4% 4.9%	Risk Ratio M-H. Fixed, 95% CI 1.09 (0.34, 3.45) 0.31 [0.01, 7.38] 0.91 [0.32, 2.62] 1.15 [0.36, 3.63] 5.07 [0.61, 42.34]	Favours experimental	Favours control	100
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff H 2.9.1 50 mg Canaglif Bays2014 Inagaki 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 2.9.2 100mg Canaglif Bays2014 Inagaki 2013 Subtotal (95% CI) Total events	7.58, df = 1 Z = 1.25 (F erences: Cr Canaglii <u>Events</u> lozin 6 0.55, df = 1 Z = 0.18 (F flozin 6 5 11 1.49, df = 1	2 (P = 0 > = 0.21) hi ² = 2.06 flozin Total 98 82 180 I (P = 0.4 > = 0.86) 93 74 167 I (P = 0.1	9.82); ² = 4 3. df = 4 (F Placet: Events 5 1 6 46); ² = 0' 5 1 6 22); ² = 3:	0% P = 0.7 50 Total 89 75 164 % 89 75 164	2). I ² = 0% <u>Weight</u> 26.1% 7.8% 33.8% 25.4% 4.9%	Risk Ratio M-H. Fixed, 95% CI 1.09 (0.34, 3.45) 0.31 [0.01, 7.38] 0.91 [0.32, 2.62] 1.15 [0.36, 3.63] 5.07 [0.61, 42.34]	Favours experimental	Favours control	100
Total events Heterogeneity: Ch ² = Test for overall effect: Test for subgroup diff H 2.9.1 50 mg Canaglif Bays2014 Inagaki 2013 Subtotal (95% Cl) Total events Heterogeneity: Ch ² = Test for overall effect: 2.9.2 100mg Canagli Bays2014 Inagaki 2013 Subtotal (95% Cl) Total events Heterogeneity: Ch ² = Test for overall effect:	7.58, df = 1 Z = 1.25 (F erences: CF <u>Events</u> lozin 6 0.55, df = 1 Z = 0.18 (F flozIn 6 5 11 1.49, df = 1 Z = 1.18 (F	2 (P = 0 > = 0.21) hi ² = 2.06 flozin Total 98 82 180 I (P = 0.4 > = 0.86) 93 74 167 I (P = 0.1	9.82); ² = 4 3. df = 4 (F Placet: Events 5 1 6 46); ² = 0' 5 1 6 22); ² = 3:	0% P = 0.7 50 Total 89 75 164 % 89 75 164	2). I ² = 0% <u>Weight</u> 26.1% 7.8% 33.8% 25.4% 4.9%	Risk Ratio M-H. Fixed, 95% CI 1.09 (0.34, 3.45) 0.31 [0.01, 7.38] 0.91 [0.32, 2.62] 1.15 [0.36, 3.63] 5.07 [0.61, 42.34]	Favours experimental	Favours control	100
Total events Heterogeneity: Ch ² = Test for overall effect: Test for subgroup diff H 2.9.1 50 mg Canaglif Bays2014 Inagaki 2013 Subtotal (95% CI) Total events Heterogeneity: Ch ² = Test for overall effect: 2.9.2 100mg Canaglif Bays2014 Inagaki 2013 Subtotal (95% CI) Total events Heterogeneity: Ch ² = Test for overall effect: 2.9.3 300mg canaglif	7.58, df = 1 Z = 1.25 (F erences: Cr Canaglii <u>Events</u> lozin 6 0.55, df = 1 Z = 0.18 (F flozin 1.49, df = 1 Z = 1.18 (F flozin	$12 (P = 0)$ $2 = 0.21)$ $11^{12} = 2.06$ flozin 98 82 180 $1 (P = 0.4)$ 93 74 167 $1 (P = 0.24)$	9.82); ² = 4 9. df = 4 (F Placet Events 5 1 6 46); ² = 0 5 1 6 22); ² = 3:	0% P = 0.7 00 Total 89 75 164 % 89 75 164 3%	2). P = 0% <u>Weight</u> 26.1% 7.8% 33.8% 25.4% 4.9% 30.3%	Risk Ratio M-H, Fixed, 95% Cl 1.09 [0.34, 3.45] 0.31 [0.01, 7.38] 0.91 [0.32, 2.62] 1.15 [0.36, 3.63] 5.07 [0.61, 42.34] 1.79 [0.68, 4.70]	Favours experimental	Favours control	100
Total events Heterogeneity: Ch ² = Test for overall effect: Test for overall effect: 2.9.1 50 mg Canaglif Bays2014 Inagaki 2013 Subtotal (95% Cl) Total events Heterogeneity: Ch ² = Test for overall effect: 2.9.2 100mg Canaglif Bays2014 Inagaki 2013 Subtotal (95% Cl) Total events Heterogeneity: Ch ² = Test for overall effect: 2.9.3 300mg canaglif Bays2014	7.58, df = 1 Z = 1.25 (F erences: Cf Canaglii <u>Events</u> lozin 6 0.55, df = 1 Z = 0.18 (F flozin 1.49, df = 1 Z = 1.18 (F flozin 5	$\begin{array}{l} 2 \ (P=0) \\ = \ 0.21) \\ 2 \ = \ 0.21) \\ 2 \ = \ 0.20 \\ \hline \ 2 \ = \ 0.20 \\ \$	9.82); ² = 4 3. df = 4 (F Placet Events 5 1 6 46); ² = 0' 5 1 6 22); ² = 3: 5	0% P = 0.7 Total 89 75 164 % 89 75 164 3% 89 89	2). I ² = 0% <u>Weight</u> 26.1% 7.8% 33.8% 25.4% 4.9% 30.3% 25.8%	Risk Ratio M-H. Fixed, 95% CI 1.09 [0.34, 3.45] 0.31 [0.01, 7.38] 0.91 [0.32, 2.62] 1.15 [0.36, 3.63] 5.07 [0.61, 42.34] 1.79 [0.68, 4.70] 0.93 [0.28, 3.10]	Favours experimental	Favours control	100
Total events Heterogeneity: Ch ² = Test for overall effect: Test for overall effect: 2.9.1 50 mg Canaglif Bays2014 Inagaki 2013 Subtotal (95% CI) Total events Heterogeneity: Ch ² = Test for overall effect: 2.9.2 100mg Canaglif Bays2014 Inagaki 2013 Subtotal (95% CI) Total events Heterogeneity: Ch ² = Test for overall effect: 2.9.3 300mg canaglif Bays2014 Inagaki 2013	7.58, df = 1 Z = 1.25 (F erences: Cr Canaglii <u>Events</u> lozin 6 0.55, df = 1 Z = 0.18 (F flozin 1.49, df = 1 Z = 1.18 (F flozin	2 (P = 0	9.82); ² = 4 9. df = 4 (F Placet Events 5 1 6 46); ² = 0 5 1 6 22); ² = 3:	0% P = 0.7 50 Total 89 75 164 % 89 75 164 3% 89 75 164	2). I ² = 0% Weight 26.1% 7.8% 33.8% 25.4% 4.9% 30.3% 25.8% 5.0%	Risk Ratio <u>M-H, Fixed, 95% CI</u> 1.09 [0.34, 3.45] 0.31 [0.01, 7.38] 0.91 [0.32, 2.62] 1.15 [0.36, 3.63] 5.07 [0.61, 42.34] 1.79 [0.68, 4.70] 0.93 [0.28, 3.10] 1.00 [0.06, 15.69]	Favours experimental	Favours control	100
Total events Heterogeneity: Ch ² = Test for overall effect: Test for subgroup diff H 2.9.1 50 mg Canaglif Bays2014 Inagaki 2013 Subtotal (95% Cl) Total events Heterogeneity: Ch ² = Test for overall effect: 2.9.2 100mg Canaglif Bays2014 Inagaki 2013 Subtotal (95% Cl) Total events Heterogeneity: Ch ² = Test for overall effect: 2.9.3 300mg canaglif Bays2014 Inagaki 2013 Subtotal (95% Cl)	7.58, df = 1 Z = 1.25 (F erences: Ch Canaglii <u>Events</u> lozin 6 0.55, df = 1 Z = 0.18 (F flozin 1.49, df = 1 Z = 1.18 (F flozin 5	$\begin{array}{l} 2 \ (P=0) \\ = \ 0.21) \\ 2 \ = \ 0.21) \\ 2 \ = \ 0.20 \\ \hline \ 2 \ = \ 0.20 \\ \$	9.82); ² = 4 3. df = 4 (F Placet Events 5 1 6 46); ² = 0' 5 1 6 22); ² = 3: 5	0% P = 0.7 Total 89 75 164 % 89 75 164 3% 89 89	2). I ² = 0% <u>Weight</u> 26.1% 7.8% 33.8% 25.4% 4.9% 30.3% 25.8%	Risk Ratio M-H. Fixed, 95% CI 1.09 [0.34, 3.45] 0.31 [0.01, 7.38] 0.91 [0.32, 2.62] 1.15 [0.36, 3.63] 5.07 [0.61, 42.34] 1.79 [0.68, 4.70] 0.93 [0.28, 3.10]	Favours experimental	Favours control	100
Total events Heterogeneity: Chi ² = Test for overall effect: Test for overall effect: Test for subgroup diff Bays2014 Inagaki 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 2.9.2 100mg Canaglif Bays2014 Inagaki 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 2.9.3 300mg canaglif Bays2014 Inagaki 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² =	7.58, df = 1 Z = 1.25 (F erences: CF Canagliti <u>Events</u> 10zin 6 0.55, df = 1 Z = 0.18 (F flozIn 6 5 11 1.49, df = 1 Z = 1.18 (F flozin 5 1 0.00, df = 1	$\begin{array}{l} 2 \ (P=0) \\ 2 \ (P=0,0.21) \\ 1^{2} ^{2}=2.06 \\ 1^{2} ^{2} ^{2}=2.06 \\ 1^{2} ^{2} ^{2} ^{2} ^{2} ^{2} ^{2} ^{2} $	0.82); ² = 4 3. df = 4 (F Placeb Events 5 1 6 46); ² = 0' 5 1 6 22); ² = 3: 5 1 6 6 96); ² = 0'	0% P = 0.7 po <u>Total</u> 89 75 164 % 89 75 164 3%	2). I ² = 0% Weight 26.1% 7.8% 33.8% 25.4% 4.9% 30.3% 25.8% 5.0%	Risk Ratio <u>M-H, Fixed, 95% CI</u> 1.09 [0.34, 3.45] 0.31 [0.01, 7.38] 0.91 [0.32, 2.62] 1.15 [0.36, 3.63] 5.07 [0.61, 42.34] 1.79 [0.68, 4.70] 0.93 [0.28, 3.10] 1.00 [0.06, 15.69]	Favours experimental	Favours control	100
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff H <u>Study or Subgroup</u> 2.9.1 50 mg Canaglif Bays2014 Inagaki 2013 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = Test for overall effect: 2.9.2 100mg Canaglif Bays2014 Inagaki 2013 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = Test for overall effect: 2.9.3 300mg canaglif Bays2014 Inagaki 2013 Subtotal (95% Cl) Total events	7.58, df = 1 Z = 1.25 (F erences: CF Canagliti <u>Events</u> 10zin 6 0.55, df = 1 Z = 0.18 (F flozIn 6 5 11 1.49, df = 1 Z = 1.18 (F flozin 5 1 0.00, df = 1	$\begin{array}{l} 2 \ (P=0) \\ 2 \ (P=0,0.21) \\ 1^{2} ^{2}=2.06 \\ 1^{2} ^{2} ^{2}=2.06 \\ 1^{2} ^{2} ^{2} ^{2} ^{2} ^{2} ^{2} ^{2} $	0.82); ² = 4 3. df = 4 (F Placeb Events 5 1 6 46); ² = 0' 5 1 6 22); ² = 3: 5 1 6 6 96); ² = 0'	0% P = 0.7 po <u>Total</u> 89 75 164 % 89 75 164 3%	2). I ² = 0% Weight 26.1% 7.8% 33.8% 25.4% 4.9% 30.3% 25.8% 5.0%	Risk Ratio <u>M-H, Fixed, 95% CI</u> 1.09 [0.34, 3.45] 0.31 [0.01, 7.38] 0.91 [0.32, 2.62] 1.15 [0.36, 3.63] 5.07 [0.61, 42.34] 1.79 [0.68, 4.70] 0.93 [0.28, 3.10] 1.00 [0.06, 15.69]	Favours experimental	Favours control	100
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff Bays2014 Inagaki 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 2.9.2 100mg Canagli Bays2014 Inagaki 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 2.9.3 300mg canaglil Bays2014 Inagaki 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect:	7.58, df = 1 Z = 1.25 (F erences: Cr Canaglii Events lozin 6 0.55, df = 1 Z = 0.18 (F flozin 6 5 11 1.49, df = 1 Z = 1.18 (F flozin 5 1 6 0.00, df = 1 Z = 0.11 (F	$\begin{array}{l} 2 \ (P=0) \\ 2 \ (P=0,0.21) \\ 1^{2} ^{2}=2.06 \\ 1^{2} ^{2} ^{2}=2.06 \\ 1^{2} ^{2} ^{2} ^{2} ^{2} ^{2} ^{2} ^{2} $	0.82); ² = 4 3. df = 4 (F Placeb Events 5 1 6 46); ² = 0' 5 1 6 22); ² = 3: 5 1 6 6 96); ² = 0'	0% P = 0.7 po <u>Total</u> 89 75 164 % 89 75 164 3%	2). I ² = 0% Weight 26.1% 7.8% 33.8% 25.4% 4.9% 30.3% 25.8% 5.0%	Risk Ratio <u>M-H, Fixed, 95% CI</u> 1.09 [0.34, 3.45] 0.31 [0.01, 7.38] 0.91 [0.32, 2.62] 1.15 [0.36, 3.63] 5.07 [0.61, 42.34] 1.79 [0.68, 4.70] 0.93 [0.28, 3.10] 1.00 [0.06, 15.69]	Favours experimental	Favours control	100
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff H 	7.58, df = 1 Z = 1.25 (F erences: Cr Canaglin Events lozin 6 0.55, df = 1 Z = 0.18 (F flozin 1.49, df = 1 Z = 1.18 (F flozin 6 0.00, df = 1 Z = 0.11 (F flozin	$\begin{array}{l} 2 \ (P=0) \\ = 0.21 \)\\ 1 ^2 = 2.0 \ \\ \hline \\$	9.82); ² = 4 9. df = 4 (F Placet Events 5 1 46); ² = 0 5 1 6 22); ² = 3: 5 1 6 96); ² = 0'	0% = = 0.7 500 Total 89 75 164 % 89 75 164 3% 89 75 164 %	2). I ² = 0% Weight 26.1% 7.8% 33.8% 25.4% 4.9% 30.3% 25.8% 5.0% 30.8%	Risk Ratio M-H, Fixed, 95% CI 1.09 [0.34, 3.45] 0.31 [0.01, 7.38] 0.91 [0.32, 2.62] 1.15 [0.36, 3.63] 5.07 [0.61, 42.34] 1.79 [0.68, 4.70] 0.93 [0.28, 3.10] 1.00 [0.06, 15.69] 0.94 [0.31, 2.83]	Favours experimental	Favours control	100
Total events Heterogeneity: Ch ² = Test for overall effect: Test for subgroup diff H 2.9.1 50 mg Canaglif Bays2014 Inagaki 2013 Subtotal (95% CI) Total events Heterogeneity: Ch ² = Test for overall effect: 2.9.2 100mg Canaglif Bays2014 Inagaki 2013 Subtotal (95% CI) Total events Heterogeneity: Ch ² = Test for overall effect: 2.9.3 300mg canaglif Bays2014 Inagaki 2013 Subtotal (95% CI) Total events Heterogeneity: Ch ² = Test for overall effect: 2.9.3 300mg canaglif Bays2014 Inagaki 2013 Subtotal (95% CI) Total events Heterogeneity: Ch ² = Test for overall effect: 2.9.4 200mg Canaglif Inagaki 2013	7.58, df = 1 Z = 1.25 (F erences: Cr Canaglii Events lozin 6 0.55, df = 1 Z = 0.18 (F flozin 6 5 11 1.49, df = 1 Z = 1.18 (F flozin 5 1 6 0.00, df = 1 Z = 0.11 (F	$\begin{array}{c} 2 \ (P=0) \\ = 0.21 \\ 1^{2} ^{2} = 2.06 \\ \hline \\ $	0.82); ² = 4 3. df = 4 (F Placeb Events 5 1 6 46); ² = 0' 5 1 6 22); ² = 3: 5 1 6 6 96); ² = 0'	0% P = 0.7 Total 89 75 164 % 89 75 164 33% 89 75 164 % 75	2). I ² = 0% Weight 26.1% 7.8% 33.8% 25.4% 4.9% 30.3% 25.8% 5.0% 5.0%	Risk Ratio <u>M-H. Fixed, 95% CI</u> 1.09 [0.34, 3.45] 0.31 [0.01, 7.38] 0.91 [0.32, 2.62] 1.15 [0.36, 3.63] 5.07 [0.61, 42.34] 1.79 [0.68, 4.70] 0.93 [0.28, 3.10] 1.00 [0.06, 15.69] 0.94 [0.31, 2.83] 2.92 [0.31, 27.47]	Favours experimental	Favours control	100
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Total events Heterogeneity: Chi ² = Test for overall effect: Test for overall effect: Test for subgroup diff H 	7.58, df = 1 Z = 1.25 (F erences: CF Canagliti Events fozin 6 0.55, df = 1 Z = 0.18 (F flozin 6 5 11 1.49, df = 1 Z = 1.18 (F flozin 5 0.00, df = 1 Z = 0.11 (F flozin 3 yplicable	$\begin{array}{c} 2 \ (P=0) \\ 2 \ (P=0.21) \\ 2 \ (P=0.24) \\ 2 \ (P=0.$	9.82); ² = 4 3. df = 4 (F Placeb Events 5 1 6 46); ² = 0' 5 1 6 22); ² = 3: 5 1 6 96); ² = 0' 1 1 1 1	0% P = 0.7 Total 89 75 164 % 89 75 164 33% 89 75 164 % 75	2). I ² = 0% Weight 26.1% 7.8% 33.8% 25.4% 4.9% 30.3% 25.8% 5.0% 5.0%	Risk Ratio <u>M-H. Fixed, 95% CI</u> 1.09 [0.34, 3.45] 0.31 [0.01, 7.38] 0.91 [0.32, 2.62] 1.15 [0.36, 3.63] 5.07 [0.61, 42.34] 1.79 [0.68, 4.70] 0.93 [0.28, 3.10] 1.00 [0.06, 15.69] 0.94 [0.31, 2.83] 2.92 [0.31, 27.47]	Favours experimental	Favours control	100
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Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff Bays2014 Inagaki 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 2.9.2 100mg Canaglif Bays2014 Inagaki 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 2.9.3 300mg canaglif Bays2014 Inagaki 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 2.9.4 200mg Canaglif Inagaki 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 2.9.4 200mg Canaglif Inagaki 2013 Subtotal (95% CI) Total events Heterogeneity: Not ap Test for overall effect: Total (95% CI)	7.58, df = 1 Z = 1.25 (F erences: CP Events Events flozin 6 0.55, df = 1 Z = 0.18 (F flozin 1.49, df = 1 Z = 1.18 (F flozin 5 1 2 = 0.11 (F flozin 3 yplicable Z = 0.94 (F	$\begin{array}{c} 2 \ (P=0) \\ 2 \ (P=0.21) \\ 2 \ (P=0.24) \\ 2 \ (P=0.$.82); ² = 4 3. df = 4 (F Placeb Events 5 1 6 46); ² = 0' 5 1 6 22); ² = 3: 5 1 6 96); ² = 0' 1 1 1 1	0% P = 0.7 500 Total 89 75 164 3% 89 75 164 3% 89 75 164 3% 75 164 3%	2). I ² = 0% Weight 26.1% 7.8% 33.8% 25.4% 4.9% 30.3% 25.8% 5.0% 5.0%	Risk Ratio <u>M-H. Fixed, 95% CI</u> 1.09 [0.34, 3.45] 0.31 [0.01, 7.38] 0.91 [0.32, 2.62] 1.15 [0.36, 3.63] 5.07 [0.61, 42.34] 1.79 [0.68, 4.70] 0.93 [0.28, 3.10] 1.00 [0.06, 15.69] 0.94 [0.31, 2.83] 2.92 [0.31, 27.47]	Favours experimental	Favours control	
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Total events Heterogeneity: Ch ² = Test for overall effect: Test for overall effect: 2.9.1 50 mg Canaglif Bays2014 Inagaki 2013 Subtotal (95% CI) Total events Heterogeneity: Ch ² = Test for overall effect: 2.9.2 100mg Canaglif Bays2014 Inagaki 2013 Subtotal (95% CI) Total events Heterogeneity: Ch ² = Test for overall effect: 2.9.3 300mg canaglif Bays2014 Inagaki 2013 Subtotal (95% CI) Total events Heterogeneity: Ch ² = Test for overall effect: 2.9.4 200mg Canaglif Inagaki 2013 Subtotal (95% CI) Total events Heterogeneity: Ch ² = Test for overall effect: 2.9.4 200mg Canaglif Inagaki 2013 Subtotal (95% CI) Total events Heterogeneity: Ch ² = Total (95% CI)	7.58, df = 1 Z = 1.25 (F erences: CF Canaglit <u>Events</u> lozin 6 0.55, df = 1 Z = 0.18 (F flozIn 6 5 11 1.49, df = 1 Z = 0.11 (F flozin 3 0.00, df = 1 Z = 0.11 (F flozin 3 yplicable Z = 0.94 (F 26 3.33, df = 6	$\begin{array}{c} 2 \ (P=0) \\ = 0.21 \\ 1^{2} = 2.06 \\ \hline \\ $	$(.82); ^2 = 4$ $(.82); ^2 = 4$ $(.82); ^2 = 4$ $(.82); ^2 = 0$ $(.82); ^2 = 0$ $(.82); ^2 = 0$ $(.82); ^2 = 0$ $(.82); ^2 = 3$ $(.82); ^2 = 3$ $(.82); ^2 = 0$ $(.82); ^2$	0% P = 0.7 Total 89 75 164 % 89 75 164 3% 89 75 164 % 75 164 % 75 567	2). P = 0% Weight 26.1% 7.8% 33.8% 25.4% 4.9% 30.3% 25.8% 5.0% 5.0% 5.0%	Risk Ratio M-H, Fixed, 95% CI 1.09 [0.34, 3.45] 0.31 [0.01, 7.38] 0.91 [0.32, 2.62] 1.15 [0.36, 3.63] 5.07 [0.61, 42.34] 1.79 [0.68, 4.70] 0.93 [0.28, 3.10] 1.00 [0.06, 15.69] 0.94 [0.31, 2.83] 2.92 [0.31, 27.47] 2.92 [0.31, 27.47]	Favours experimental Risk I M-H. Fixe	Favours control	100
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff H 2.9.1 50 mg Canaglif Bays2014 Inagaki 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 2.9.2 100mg Canaglif Bays2014 Inagaki 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 2.9.3 300mg canaglif Bays2014 Inagaki 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 2.9.4 200mg Canaglif Inagaki 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 2.9.4 200mg Canaglif Inagaki 2013 Subtotal (95% CI) Total events Heterogeneity: Not ap Test for overall effect: Total (95% CI) Total events	7.58, df = 1 Z = 1.25 (F erences: Cr Canagliti Events lozin 6 0.55, df = 1 Z = 0.18 (F flozin 6 5 11 1.49, df = 1 Z = 0.18 (F flozin 5 1 0.00, df = 1 Z = 0.11 (F flozin 3 yplicable Z = 0.94 (F 26 3.33, df = 6 Z = 0.87 (F 2 = 0.87 (F 5 = 0.94 (F))	$\begin{array}{l} 2 (P = 0 \\ 2 (P = 0.21) \\ 1^{12} = 2.06 \\ \hline \text{flozin} \\ \hline \text{Total} \\ 180 \\ 1 (P = 0.21) \\ 180 \\ 1 (P = 0.21) \\ 180 \\ 1 (P = 0.68) \\ 110 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\ 100 \\$	1,82); ² = 4 3. df = 4 (F Placeb Events 5 1 6 46); ² = 0' 5 1 6 6 22); ² = 3: 5 1 6 6 96); ² = 0' 1 1 1 1 19 77); ² = 0'	0% = = 0.7 Total 89 75 164 % 89 75 164 % 75 75 567 %	2). ² = 0% Weight 26.1% 7.8% 33.8% 25.4% 4.9% 30.3% 25.8% 5.0% 5.0% 5.0% 100.0%	Risk Ratio M-H, Fixed, 95% CI 1.09 [0.34, 3.45] 0.31 [0.01, 7.38] 0.91 [0.32, 2.62] 1.15 [0.36, 3.63] 5.07 [0.61, 42.34] 1.79 [0.68, 4.70] 0.93 [0.28, 3.10] 1.00 [0.06, 15.69] 0.94 [0.31, 2.83] 2.92 [0.31, 27.47] 2.92 [0.31, 27.47] 1.29 [0.73, 2.27]	Favours experimental Risk I M-H, Fixe	Favours control	

Study or Subgroup	Events	lozin Total	Placeb Events		Weight	Risk Ratio M-H, Fixed, 95% C	Risk Ratio I M-H. Fixed, 95% Cl
2.11.1 50 mg Canagli Bays2014	flozin 6	98	7	89	21.6%	0.78 [0.27, 2.23]	
Bays2014 Rosenstock 2013	1	98 64	2	89 65		0.78 [0.27, 2.23]	
Subtotal (95% CI)		162	-	154	27.5%	0.72 [0.28, 1.88]	
Total events	7		9				
Heterogeneity: Chi ² = Test for overall effect:				%			
		0.00,					
2.11.2 100 mg Canag		93	-		~ ~ ~		
Bays2014 Devineni 2014	11 3	10	7	89 9		1.50 [0.61, 3.71] 1.35 [0.29, 6.34]	
Rosenstock 2013	5	64	2	65		2.54 [0.51, 12.61]	
Subtotal (95% CI)		167		163	33.1%	1.66 [0.82, 3.34]	-
Total events Heterogeneity: Chi ² =	19 0 28 df = 2	/B = 0.9	11 11 = 0	2/			
Test for overall effect:				70			
2.11.3 200 mg Canag Rosenstock 2013	lifiozin 2	65	2	65	5.9%	1.00 [0.15, 6.89]	
Subtotal (95% CI)	-	65	-	65	5.9%	1.00 [0.15, 6.89]	
Total events	2		2				
leterogeneity: Not ap		- 1 001					
Test for overall effect:	Z = 0.00 (P	= 1.00)					
2.11.4 300 mg Canag	liflozin						
Bays2014	4	96	7	89		0.53 [0.16, 1.75]	
Devineni 2014	6	10	2	9		2.70 [0.72, 10.14]	
Rosenstock 2013 Subtotal (95% CI)	3	64 170	2	65 163	5.9% 33.5%	1.52 [0.26, 8.82] 1.11 [0.52, 2.33]	
Fotal events	13		11				Γ
leterogeneity: Chi ² =	3.34, df = 2		19); l² = 4	0%			
Test for overall effect:	Z = 0.26 (P	= 0.79)					
Total (95% CI)		564		545	100.0%	1.18 [0.76, 1.82]	
Total events	41		33				[
Heterogeneity: Chi ² =				%			0.01 0.1 1 10 100
Test for overall effect: Test for subgroup diffe) = 0 *	(8) 12 - 0°	4	Favours experimental Favours control
. cor tor aubyroup diffe							
Study or Subsecur	Canaglifi Evente		Placeb		Weight	Risk Ratio	Risk Ratio M-H, Fixed, 95% Cl
<u>Study or Subgroup</u> 2.12.1 100mg canagli		1 Juli	syents		maight		m-TI, FIX84, 33% GI
Bays2014	2	93	2	89	18.7%	0.96 [0.14, 6.65]	
Devineni 2014	1	10	2	9	19.2%	0.45 [0.05, 4.16]	
Subtotal (95% CI) Total events	3	103		98	37.9%	0.70 [0.17, 2.95]	
Heterogeneity: Chi ² = ((P = 0.6		, D			
Test for overall effect:							
2 4 2 2 200	florin						
2.12.2 300mg canagli							
Bavs2014	4	96	2	89	19.0%	1.85 (0.35 9.89)	
Bays2014 Devineni 2014	4 0	96 10	2 2	89 9	19.0% 23.9%	1.85 [0.35, 9.88] 0.18 [0.01, 3.35]	
Devineni 2014 Subtotal (95% CI)			2				
Devineni 2014 Subtotal (95% CI) Total events	0	10 106	2 4	9 98	23.9%	0.18 [0.01, 3.35]	
Devineni 2014 Subtotal (95% CI) Total events Heterogeneity: Chi ² =	0 4 1.86, df = 1	10 106 (P = 0.1	2 4	9 98	23.9%	0.18 [0.01, 3.35]	
Devineni 2014 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect:	0 4 1.86, df = 1 Z = 0.13 (P	10 106 (P = 0.1	2 4	9 98	23.9%	0.18 [0.01, 3.35]	
Devineni 2014 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 2.12.3 50mg canaglifi	0 4 1.86, df = 1 Z = 0.13 (P	10 106 (P = 0.1 = 0.90)	2 4 7); I ² = 46	9 98 %	23.9% 42.9%	0.18 [0.01, 3.35] 0.92 [0.26, 3.29]	
Devineni 2014 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect:	0 4 1.86, df = 1 Z = 0.13 (P	10 106 (P = 0.1	2 4	9 98	23.9%	0.18 [0.01, 3.35]	
Devineni 2014 Subtotal (95% CI) Total events Heterogeneity: Chi ² = - Test for overall effect: 2.12.3 50mg canaglift Bays2014 Subtotal (95% CI) Total events	0 4 1.86, df = 1 Z = 0.13 (P lozin 4	10 106 (P = 0.1 = 0.90) 98	2 4 7); I ² = 46	9 98 % 89	23.9% 42.9% 19.2%	0.18 [0.01, 3.35] 0.92 [0.26, 3.29] 1.82 [0.34, 9.68]	
Devineni 2014 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = : Test for overall effect: : 2.12.3 50mg canaglifi Bays2014 Subtotal (95% Cl) Total events Heterogeneity: Not app	0 4 1.86, df = 1 Z = 0.13 (P lozin 4 blicable	10 106 (P = 0.1 = 0.90) 98 98	2 4 7); I ² = 46 2	9 98 % 89	23.9% 42.9% 19.2%	0.18 [0.01, 3.35] 0.92 [0.26, 3.29] 1.82 [0.34, 9.68]	
Devineni 2014 Subtotal (95% CI) Total events Heterogeneity: Chi ² = - Test for overall effect: 2.12.3 50mg canaglift Bays2014 Subtotal (95% CI) Total events	0 4 1.86, df = 1 Z = 0.13 (P lozin 4 blicable	10 106 (P = 0.1 = 0.90) 98 98	2 4 7); I ² = 46 2	9 98 % 89	23.9% 42.9% 19.2%	0.18 [0.01, 3.35] 0.92 [0.26, 3.29] 1.82 [0.34, 9.68]	
Devineni 2014 Subtotal (95% CI) Total events Heterogeneity: ChP = Test for overall effect: 2.12.3 50mg canagliff Bays2014 Subtotal (95% CI) Total events Heterogeneity: Not app Test for overall effect: Total (95% CI)	0 4 1.86, df = 1 Z = 0.13 (P fozin 4 blicable Z = 0.70 (P	10 106 (P = 0.1 = 0.90) 98 98	2 4 7); I ² = 46 2 2	9 98 % 89 89	23.9% 42.9% 19.2%	0.18 [0.01, 3.35] 0.92 [0.26, 3.29] 1.82 [0.34, 9.68]	
Devineni 2014 Subtotai (95% CI) Total events Heterogeneity: Chi ² = : Test for overall effect: 2.12.3 50mg canagliff Baya2014 Subtotai (95% CI) Total events Heterogeneity: Not app Test for overall effect: Total (95% CI) Total events	0 4 1.86, df = 1 Z = 0.13 (P ozin 4 bilcable Z = 0.70 (P 11	10 106 (P = 0.1 = 0.90) 98 98 98 = 0.48) 307	2 4 7); I ² = 46 2 2 10	9 98 % 89 89 89	23.9% 42.9% 19.2% 19.2%	0.18 (0.01, 3.35) 0.92 (0.26, 3.29) 1.82 (0.34, 9.68) 1.82 (0.34, 9.68) 1.82 (0.34, 9.68)	
Devineni 2014 Subtotal (95% CI) Total events Heterogeneity: ChP = Test for overall effect: 2.12.3 50mg canagliff Bays2014 Subtotal (95% CI) Total events Heterogeneity: Not app Test for overall effect: Total (95% CI)	0 4 1.86, df = 1 Z = 0.13 (P ozin 4 5 5 5 5 5 7 7 7 7 7 7 7 7 7 7 7 7 7 7	10 106 (P = 0.1 = 0.90) 98 98 98 = 0.48) 307 (P = 0.5	2 4 7); I ² = 46 2 2 10	9 98 % 89 89 89	23.9% 42.9% 19.2% 19.2%	0.18 (0.01, 3.35) 0.92 (0.26, 3.29) 1.82 (0.34, 9.68) 1.82 (0.34, 9.68) 1.82 (0.34, 9.68)	
Devineni 2014 Subtotai (95% CI) Total events Heterogeneity: Chi ² = : Test for overall effect: 2.12.3 50mg canagliff Bays2014 Subtotai (95% CI) Total events Heterogeneity: Not app Test for overall effect: Total events Heterogeneity: Chi ² = : Test for overall effect:	0 4 1.86, df = 1 Z = 0.13 (P iozin 4 2 = 0.70 (P 11 2.82, df = 4 Z = 0.02 (P	10 106 (P = 0.1 = 0.90) 98 98 98 = 0.48) 307 (P = 0.5 = 0.98)	2 4 7); ² = 46 2 2 2 10 ;9); ² = 09	9 98 % 89 89 89 285	23.9% 42.9% 19.2% 19.2%	0.18 (0.01, 3.35) 0.92 (0.26, 3.29) 1.82 (0.34, 9.68) 1.82 (0.34, 9.68) 1.82 (0.34, 9.68)	0.01 0.1 1 10 100 Favours [experimental] Favours [control]
Devineni 2014 Subtotai (95% CI) Total events Heterogeneity: Chi ² = : Test for overall effect: 2.12.3 50mg canagliff Bays2014 Subtotai (95% CI) Total events Heterogeneity: Not app Test for overall effect: Total events Heterogeneity: Chi ² = : Test for overall effect:	0 4 1.86, df = 1 Z = 0.13 (P iozin 4 2 = 0.70 (P 11 2.82, df = 4 Z = 0.02 (P	10 106 (P = 0.1 = 0.90) 98 98 = 0.48) 307 (P = 0.5 = 0.98) ² = 0.74	2 4 7); ² = 46 2 2 2 10 ;9); ² = 09	9 98 % 89 89 89 285 % = 0.6	23.9% 42.9% 19.2% 19.2%	0.18 (0.01, 3.35) 0.92 (0.26, 3.29) 1.82 (0.34, 9.68) 1.82 (0.34, 9.68) 1.82 (0.34, 9.68)	
Devineni 2014 Subtotai (95% CI) Total events Heterogeneity: Chi ² = : Test for overail effect: 2.12.3 50mg canagliff Bays2014 Subtotai (95% CI) Total events Heterogeneity: Chi ² = : Totai (95% CI) Total events Heterogeneity: Chi ² = : Test for overail effect: Test for overail effect: Test for subgroup diffe	0 4 1.86, df = 1 Z = 0.13 (P ozin 4 5 5 5 5 5 7 7 7 7 7 7 7 7 7 7 7 7 7 7	10 106 (P = 0.1 = 0.90) 98 98 = 0.48) 307 (P = 0.5 = 0.98) ² = 0.74 ozin	2 4 7); I ² = 46 2 2 3 9); I ² = 09 . df = 2 (P Placeb	9 98 % 89 89 89 285 5 = 0.61	23.9% 42.9% 19.2% 19.2%	0.18 [0.01, 3.35] 0.92 [0.26, 3.29] 1.82 [0.34, 9.68] 1.82 [0.34, 9.68] 1.82 [0.34, 9.68]	Favours [experimental] Favours [control]
Devineni 2014 Subtotal (95% CI) Total events Heterogeneity: Ch ² = : Test for overall effect: 2.12.3 50mg canagliff Bays2014 Subtotal (95% CI) Total events Heterogeneity: Not app Test for overall effect: Total (95% CI) Total events Heterogeneity: Ch ² = : Test for subgroup diffe Study or Subgroup 2.13.1 100mg canagli	0 4 1.86, df = 1 Z = 0.13 (P iozin 4 4 2 2 = 0.70 (P 2.82, df = 4 Z = 0.02 (P rences: Chi Canagliff Events flozin	10 106 (P = 0.1 = 0.90) 98 98 98 = 0.48) 307 (P = 0.5 = 0.98) ² = 0.74 ozin Total	2 4 7); 1 ² = 46 2 2 2 10 (9); 1 ² = 09 . df = 2 (P Placeb-	9 98 % 89 89 89 285 5 5 5 5 7 7 7 7	23.9% 42.9% 19.2% 19.2% 100.0% 9). P = 0% Weight	0.18 (0.01, 3.35) 0.92 (0.26, 3.29) 1.82 (0.34, 9.68) 1.62 (0.34, 9.68) 1.62 (0.34, 9.68) 1.01 (0.45, 2.28) Risk Ratio M-H, Fixed, 95% Cl	Favours [experimental] Favours [control] Risk Ratio
Devineni 2014 Subtotal (95% CI) Total events Heterogeneity: Ch ² = : Test for overail effect: 2.12.3 50mg canagliff Bays2014 Subtotal (95% CI) Total events Heterogeneity: Not app Test for overail effect: Total (95% CI) Total events Heterogeneity: Ch ² = : Test for overail effect: Test for subgroup diffe Study or Subgroup 2.13.1 100mg canagli Bays2014	0 4 1.86, df = 1 Z = 0.13 (P iozin 4 5 5 5 5 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	10 106 (P = 0.1 98 98 = 0.48) 307 (P = 0.5 = 0.98) ² = 0.74 ozin Total 93	2 4 7); ² = 46 2 2 2 10 (9); ² = 09 . df = 2 (P Placeb: Events	9 98 % 89 89 89 285 5 5 70 70 70 89	23.9% 42.9% 19.2% 19.2% 100.0% 9). P = 0% Weight 16.5%	0.18 [0.01, 3.35] 0.92 [0.26, 3.29] 1.82 [0.34, 9.68] 1.82 [0.34, 9.68] 1.01 [0.45, 2.28] Risk Ratio <u>M-H. Fixed, 95% C1</u> 2.87 [0.60, 13.85]	Favours [experimental] Favours [control] Risk Ratio
Devineni 2014 Subtotal (95% CI) Total events Heterogeneity: Ch ² = : Test for overall effect: 2.12.3 50mg canagliff Bays2014 Subtotal (95% CI) Total events Heterogeneity: Not app Test for overall effect: Total (95% CI) Total events Heterogeneity: Ch ² = : Test for subgroup diffe Study or Subgroup 2.13.1 100mg canagli	0 4 1.86, df = 1 Z = 0.13 (P iozin 4 4 2 2 = 0.70 (P 2.82, df = 4 Z = 0.02 (P rences: Chi Canagliff Events flozin	10 106 (P = 0.1 98 98 98 = 0.48) 307 (P = 0.5 = 0.98) 2 = 0.74 ozin Total 93 10	2 4 7); ² = 46 2 2 2 9); ² = 09 . df = 2 (P Placeb Events	9 98 % 89 89 89 285 5 5 70tal 89 9	23.9% 42.9% 19.2% 100.0% 9). P = 0% Weight 16.5% 17.0%	0.18 (0.01, 3.35) 0.92 (0.26, 3.29) 1.82 (0.34, 9.68) 1.82 (0.34, 9.68) 1.82 (0.34, 9.68) 1.01 (0.45, 2.28) Risk Ratio <u>M-H, Fixed, 95% C1</u> 2.87 (0.60, 13.85) 0.90 (0.16, 5.13)	Favours [experimental] Favours [control] Risk Ratio
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Devineni 2014 Subtotai (95% CI) Total events Heterogeneity: Ch ² = : Test for overall effect: 2.12.3 50mg canagliff Bays2014 Subtotai (95% CI) Total events Heterogeneity: Not ap Test for overall effect: Total (95% CI) Total events Heterogeneity: Ch ² = : Test for overall effect: Test for subgroup Lats.1 100mg canagli Bays2014 Devineni 2014 Rosenstock 2013 Subtotai (95% CI) Total events	0 4 1.86, df = 1 2 = 0.13 (P iozin 4 5 5 5 5 5 6 7 1 1 2.82, df = 4 2 = 0.70 (P 1 1 2.82, df = 4 2 = 0.70 (P 1 1 2.82, df = 4 2 = 0.70 (P 1 2.82, df = 1 2.83, df = 1 4 5 5 5 6 1 1 1 1 2.83, df = 1 2.83, df = 1 4 5 5 5 6 7 1 1 2.83, df = 1 2.83, df = 1 2.93, df = 1	10 106 (P = 0.1 98 98 98 = 0.48) 307 (P = 0.5 = 0.98) 307 (P = 0.5 = 0.98) 310 64 167 (P = 0.5 (P = 0.5 (P = 0.5) (P = 0.5)	2 4 7); ² = 46 2 2 2 9); ² = 09 . df = 2 (P Placeb: Events 2 2 0 4	9 98 % 89 89 89 285 5 5 5 5 7 5 7 5 7 5 7 5 7 5 89 9 9 5 5 163	23.9% 42.9% 19.2% 19.2% 100.0% 0). P = 0% Weight 16.5% 17.0% 4.0%	0.18 [0.01, 3.35] 0.92 [0.26, 3.29] 1.82 [0.34, 9.68] 1.82 [0.34, 9.68] 1.82 [0.34, 9.68] 1.01 [0.45, 2.28] Risk Ratio <u>M-H. Fixed, 95% C1</u> 2.87 [0.60, 13.85] 0.90 [0.16, 5.13] 3.05 [0.13, 7.4.1]	Favours [experimental] Favours [control] Risk Ratio
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Devineni 2014 Subtotai (95% CI) Total events Heterogeneity: Chi ² = : Test for overall effect: 2.12.3 50mg canagliff Bays2014 Subtotai (95% CI) Total events Heterogeneity: Not app Test for overall effect: Test for overall effect: Test for subgroup diffe Study or Subgroup Attained and State State State Subtotai (95% CI) Total events Heterogeneity: Chi ² = : Test for overall effect: 2.13.100mg canagli Bays2014 Devineni 2014 Rosenstock 2013 Subtotai (95% CI) Total events Heterogeneity: Chi ² = : Test for overall effect: 2.13.2 300mg canagli Bays2014 Devineni 2014 Rosenstock 2013 Subtotai (95% CI) Total events Heterogeneity: Chi ² = : East for overall effect: 2.13.3 50mg canagliff Bays2014 Rosenstock 2013 Subtotai (95% CI) Total events Heterogeneity: Chi ² = :	0 4 1.86, df = 1 Z = 0.13 (P iozin 4 4 5 5 5 5 5 5 5 5 5 5 5 5 5	$\begin{array}{c} 100\\ 106\\ (P=0.1\\ 98\\ 98\\ 98\\ = 0.48\\ 307\\ (P=0.5\\ = 0.98\\ 307\\ (P=0.5\\ = 0.98\\ 307\\ (P=0.5\\ 10\\ 64\\ 167\\ (P=0.4\\ 170\\ 0\\ 64\\ 170\\ 98\\ 64\\ 162\\ (P=0.6\\ 162\\ (P=0.6\\ 162\\ (P=0.6\\ 162\\ 162\\ 162\\ (P=0.6\\ 162\\ 162\\ 162\\ 162\\ 162\\ 162\\ 162\\ 16$	2 4 2 2 2 2 10 0 9); I ² = 09 9; I ² = 09 8); I ² = 09 2 2 0 4 7); I ² = 09 2 0 2 0 2 0 2	9 98 89 89 89 285 5 5 5 5 5 5 5 5 5 5 5 6 5 6 5 163 5 89 95 65 163 5 89 89 85 154	23.9% 42.9% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2%	0.18 [0.01, 3.35] 0.92 [0.26, 3.29] 1.82 [0.34, 9.68] 1.82 [0.34, 9.68] 1.82 [0.34, 9.68] 1.01 [0.45, 2.28] 2.87 [0.60, 13.85] 0.90 [0.16, 5.13] 3.05 [0.13, 73.41] 2.00 [0.66, 5.82] 1.39 [0.24, 8.13] 0.90 [0.16, 5.13] 7.11 [0.37, 134.90] 1.78 [0.66, 14.90] 7.11 [0.37, 134.90]	Favours [experimental] Favours [control] Risk Ratio
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Devineni 2014 Subtotai (95% CI) Total events Heterogeneity: Ch ² = : Test for overall effect: 2.12.3 50mg canagliff Bays2014 Subtotai (95% CI) Total events Heterogeneity: Not app Test for overall effect: Total (95% CI) Total events Heterogeneity: Ch ² = : Test for subgroup diffe Study or Subgroup Attained and State State Subtotai (95% CI) Total events Heterogeneity: Ch ² = : Test for overall effect: 2.13.100mg canagli Bays2014 Devineni 2014 Rosenstock 2013 Subtotai (95% CI) Total events Heterogeneity: Ch ² = : Test for overall effect: 2.13.2 300mg canagli Bays2014 Devineni 2014 Rosenstock 2013 Subtotai (95% CI) Total events Heterogeneity: Ch ² = : Test for overall effect: 2.13.3 50mg canagliff Rosenstock 2013 Subtotai (95% CI) Total events Heterogeneity: Ch ² = : Test for overall effect: 2.13.3 200mg canagliff Rosenstock 2013 Subtotai (95% CI) Total events Heterogeneity: Ch ² = : Test for overall effect: 2.13.4 200mg canagliff Rosenstock 2013 Subtotai (95% CI) Total events Heterogeneity: Ch ² = :	0 4 1.86, df = 1 Z = 0.13 (P iozin 4 4 5 5 4 4 5 5 5 5 5 5 5 5 5 5 5 5 5	$\begin{array}{c} 100\\ 106\\ (P=0.1\\ 98\\ 98\\ 98\\ = 0.48\\ 307\\ (P=0.5\\ = 0.98\\ 307\\ (P=0.5\\ = 0.98\\ 307\\ (P=0.5\\ 10\\ 64\\ 167\\ 170\\ 98\\ 64\\ 162\\ (P=0.4\\ 162\\ (P=0.4\\ 162\\ 162\\ (P=0.5\\ 65\\ 65\\ 85\\ \end{array}$	2 4 4 2 2 2 2 9); * = 46 2 2 2 9); * = 09 Placebb Eventa 2 2 0 4 9; * = 09 Placebb Eventa 2 2 0 7; * = 47 8 9; * = 09 9; * = 09 Placebb 2 2 0 7; * = 09 9; * = 09 9; * = 09 9; * = 09 9; * = 09 Placebb Eventa 2 2 0 0 7; * = 09 9; * = 09 2 0 0 0 0; * = 09 2 0 0 0 0 0; * = 09 2 0 0 0 0 0; * = 09 2 0 0 0 0 0 0; * = 09 2 0 0 0 0 0 0 0 0 0 0; * = 0 0 0 0 0 0 0; * = 0 0 0 0 0 0 0 0; * = 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	9 98 98 % 285 5 285 5 5 5 5 5 5 6 5 163 5 89 65 154 5 65	23.9% 42.9% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2%	0.18 [0.01, 3.35] 0.92 [0.26, 3.29] 1.82 [0.34, 9.68] 1.82 [0.34, 9.68] 1.82 [0.34, 9.68] 1.01 [0.45, 2.28] 2.87 [0.60, 13.85] 0.90 [0.16, 5.13] 3.05 [0.13, 73.41] 2.00 [0.66, 5.82] 1.39 [0.24, 8.13] 0.90 [0.16, 5.13] 7.11 [0.37, 134.80] 1.78 [0.60, 5.27] 3.18 [0.68, 14.90] 7.11 [0.37, 134.80] 3.93 [1.01, 15.24] 3.00 [0.12, 72.31]	Favours [experimental] Favours [control] Risk Ratio
Devineni 2014 Subtotai (95% CI) Total events Heterogeneity: Chi ² = : Test for overall effect: 2.12.3 50mg canagliff Bays2014 Subtotai (95% CI) Total events Heterogeneity: Not app Test for overall effect: Total (95% CI) Total events Heterogeneity: Chi ² = : Test for overall effect: Test for overall effect: Test for overall effect: 2.13.100mg canaglif Bays2014 Devineni 2014 Rosenstock 2013 Subtotai (95% CI) Total events Heterogeneity: Chi ² = : Test for overall effect: 2.13.2 300mg canaglif Bays2014 Devineni 2014 Rosenstock 2013 Subtotai (95% CI) Total events Heterogeneity: Chi ² = : Test for overall effect: 2.13.3 50mg canaglif Bays2014 Devineni 2014 Rosenstock 2013 Subtotai (95% CI) Total events Heterogeneity: Chi ² = : Test for overall effect: 2.13.3 50mg canaglif Bays2014 Rosenstock 2013 Subtotai (95% CI) Total events Heterogeneity: Chi ² = : Test for overall effect: 2.13.4 200mg canaglif Bays2014 (95% CI) Total events Heterogeneity: Chi ² = : Test for overall effect: 2.13.4 200mg canaglif Subtotai (95% CI) Total events Heterogeneity: Chi ² = : Test for overall effect: 2.13.4 200mg canaglif Subtotai (95% CI) Total events Heterogeneity: Not app Test for overall effect:	0 4 1.86, df = 1 Z = 0.13 (P iozin 4 4 5 5 4 4 5 5 5 5 5 5 5 5 5 5 5 5 5	$\begin{array}{c} 100\\ 106\\ (P=0.1\\ 98\\ 98\\ 98\\ = 0.48\\ 307\\ (P=0.5\\ = 0.98\\ 307\\ (P=0.5\\ = 0.98\\ 307\\ (P=0.5\\ 10\\ 64\\ 167\\ 170\\ 98\\ 64\\ 162\\ (P=0.4\\ 162\\ (P=0.4\\ 162\\ 162\\ (P=0.5\\ 65\\ 65\\ 85\\ \end{array}$	2 4 4 2 2 2 2 9); * = 46 2 2 2 9); * = 09 Placebb Eventa 2 2 0 4 9; * = 09 Placebb Eventa 2 2 0 7; * = 47 8 9; * = 09 9; * = 09 Placebb 2 2 0 7; * = 09 9; * = 09 9; * = 09 9; * = 09 9; * = 09 Placebb Eventa 2 2 0 0 7; * = 09 9; * = 09 2 0 0 0 0; * = 09 2 0 0 0 0 0; * = 09 2 0 0 0 0 0; * = 09 2 0 0 0 0 0 0; * = 09 2 0 0 0 0 0 0 0 0 0 0; * = 0 0 0 0 0 0 0; * = 0 0 0 0 0 0 0 0; * = 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	9 98 98 % 285 5 285 5 5 5 5 5 5 6 5 163 5 89 65 154 5 65	23.9% 42.9% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2%	0.18 [0.01, 3.35] 0.92 [0.26, 3.29] 1.82 [0.34, 9.68] 1.82 [0.34, 9.68] 1.82 [0.34, 9.68] 1.01 [0.45, 2.28] 2.87 [0.60, 13.85] 0.90 [0.16, 5.13] 3.05 [0.13, 73.41] 2.00 [0.66, 5.82] 1.39 [0.24, 8.13] 0.90 [0.16, 5.13] 7.11 [0.37, 134.80] 1.78 [0.60, 5.27] 3.18 [0.68, 14.90] 7.11 [0.37, 134.80] 3.93 [1.01, 15.24] 3.00 [0.12, 72.31]	Favours [experimental] Favours [control] Risk Ratio
Devineni 2014 Subtotai (95% CI) Total events Heterogeneity: $Ch^2 = :$ Test for overall effect: 2.12.3 50mg canagliff Bays2014 Subtotai (95% CI) Total events Heterogeneity: Not app Test for overall effect: Total (95% CI) Total events Heterogeneity: $Ch^2 = :$ Test for overall effect: Test for subgroup 2.13.1 100mg canaglif Bays2014 Devineni 2014 Rosenstock 2013 Subtotai (95% CI) Total events Heterogeneity: $Ch^2 = :$ Test for overall effect: 2.13.2 300mg canaglif Bays2014 Devineni 2014 Rosenstock 2013 Subtotai (95% CI) Total events Heterogeneity: $Ch^2 = :$ Test for overall effect: 2.13.2 300mg canaglif Bays2014 Devineni 2014 Rosenstock 2013 Subtotai (95% CI) Total events Heterogeneity: $Ch^2 = :$ Test for overall effect: 2.13.4 200mg canagliff Bays2014 Rosenstock 2013 Subtotai (95% CI) Total events Heterogeneity: $Ch^2 = :$ Test for overall effect: 2.13.4 200mg canagliff Bays2014 Rosenstock 2013 Subtotai (95% CI) Total events Heterogeneity: NP = : Test for overall effect: 2.13.4 200mg canagliff Rosenstock 2013 Subtotai (95% CI) Total events Heterogeneity: NP = : Test for overall effect: 2.13.4 200mg canagliff Rosenstock 2013 Subtotai (95% CI) Total events Heterogeneity: NP = : Test for overall effect: 2.13.4 200mg canagliff Rosenstock 2013 Subtotai (95% CI)	0 4 1.86, df = 1 Z = 0.13 (P iozin 4 4 5 102 licable Z = 0.70 (P rences: Chi Canaglifi Canaglifi Canaglifi Canaglifi Canaglifi 102 licable 2 = 1.27 (P flozin 1.51, df = 2 Z = 1.04 (P iozin 7 3 10 0.23, df = 1 Z = 1.98 (P flozin 1 Jicable Z = 0.68 (P	$\begin{array}{c} 100\\ 106\\ (P=0.1\\ 98\\ 98\\ 98\\ = 0.48\\ 307\\ (P=0.5\\ = 0.98\\ 307\\ (P=0.5\\ = 0.98\\ 307\\ (P=0.5\\ 10\\ 64\\ 167\\ 170\\ 98\\ 64\\ 162\\ (P=0.4\\ 162\\ (P=0.4\\ 162\\ 162\\ (P=0.5\\ 65\\ 65\\ 85\\ \end{array}$	2 4 4 2 2 2 10 9); * = 09 Placebe Eventa 2 2 0 4 5 7; * = 09 2 0 4 7; * = 09 2 0 2 0 10 9); * = 09 2 0 2 0 10 9); * = 09 2 0 10 9); * = 09 2 0 10 10 10 10 10 10 10 10 10	9 98 98 % 89 89 89 2255 6 5 7 0 7 0 7 0 7 0 89 9 65 163 6 5 163 6 5 154 6 5 6 5 6 5 6 5	23.9% 42.9% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2%	0.18 [0.01, 3.35] 0.92 [0.26, 3.29] 1.82 [0.34, 9.68] 1.82 [0.34, 9.68] 1.82 [0.34, 9.68] 1.01 [0.45, 2.28] 2.87 [0.60, 13.85] 0.90 [0.16, 5.13] 3.05 [0.13, 73.41] 2.00 [0.66, 5.82] 1.39 [0.24, 8.13] 0.90 [0.16, 5.13] 7.11 [0.37, 134.80] 1.78 [0.60, 5.27] 3.18 [0.68, 14.90] 7.11 [0.37, 134.80] 3.93 [1.01, 15.24] 3.00 [0.12, 72.31]	Favours [experimental] Favours [control] Risk Ratio
Jevineni 2014 Subtotal (95% CI) Fotal events feterogeneity: Chi ² = i fest for overall effect: 2.12.3 50mg canagliff Jays2014 Subtotal (95% CI) Fotal events fest for overall effect: fest for overall effect: 2.13.100mg canaglif Jays2014 Jevineni 2014 Rosenstock 2013 Subtotal (95% CI) Fotal events feterogeneity: Ch ² = f fest for overall effect: 2.13.2 300mg canaglif Jays2014 Subtotal (95% CI) Fotal events feterogeneity: Ch ² = f fest for overall effect: 2.13.3 50mg canagliff Jays2014 Subtotal (95% CI) Fotal events feterogeneity: Ch ² = f fest for overall effect: 2.13.3 50mg canagliff Jays2014 Subtotal (95% CI) Fotal events feterogeneity: Ch ² = f fest for overall effect: 2.13.3 50mg canagliff Jays2014 Subtotal (95% CI) Fotal events feterogeneity: Ch ² = f fest for overall effect: 2.13.4 200mg canagliff Jubtotal (95% CI) Fotal events feterogeneity: Ch ² = f fest for overall effect: 2.13.4 200mg canagliff Jubtotal (95% CI) Fotal events feterogeneity: Ch ² = f feterogeneity: Ch ² = f fest for overall effect: 2.13.4 200mg canagliff Jubtotal (95% CI) Fotal events feterogeneity: Not app fest for overall effect:	$\begin{array}{c} 0 \\ 4 \\ 1.86, df = 1 \\ 2 = 0.13 (P \\ iozin \\ 4 \\ 4 \\ 2 = 0.70 (P \\ 11 \\ 2 = 0.70 (P \\ 11 \\ 2 = 0.02 (P \\ rences: Chi \\ 2 \\ 2 = 0.02 (P \\ rences: Chi \\ 2 \\ 2 \\ 3 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10 $	$\begin{array}{c} 10\\ 106\\ (P=0.1\\ 98\\ 98\\ 98\\ = 0.48\\ 307\\ (P=0.5\\ = 0.98)\\ = 0.74\\ 307\\ (P=0.5\\ = 0.98)\\ = 0.74\\ 107\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10$	2 4 4 2 2 2 2 10 0 4 9); ² = 09 9 10 0 4 8); ² = 09 2 2 0 4 8); ² = 09 2 2 0 4 3 0; ² = 09 2 0 0 4 9 0 1 0 0 0 1 1 0 0 0 1 1 0 0 0 1 1 0 0 0 1 1 0 0 0 1 1 0 0 0 1 1 0 0 0 1 1 0 0 0 1 1 0 0 0 1 1 0 0 0 1 1 0 0 0 0 1 1 0 0 0 0 1 1 0 0 0 0 1 1 0 0 0 0 1 1 0 0 0 0 0 1 1 0 0 0 0 0 0 0 1 1 0 0 0 0 0 0 0 1 1 0 0 0 0 0 0 0 0 0 0 0 0 0	9 98 98 % 89 89 89 285 5 5 7 7 0 163 5 89 9 65 163 5 89 9 65 163 5 65 5 45 5 45	23.9% 42.9% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2%	0.18 [0.01, 3.35] 0.92 [0.26, 3.29] 1.82 [0.34, 9.68] 1.82 [0.34, 9.68] 1.82 [0.34, 9.68] 1.01 [0.45, 2.28] 2.87 [0.60, 13.85] 0.90 [0.16, 5.13] 3.05 [0.13, 73.41] 2.00 [0.68, 5.82] 1.39 [0.24, 8.13] 0.90 [0.16, 5.13] 7.11 [0.37, 134.90] 1.78 [0.60, 5.27] 3.18 [0.68, 14.90] 7.11 [0.37, 134.90] 3.93 [1.01, 15.24] 3.00 [0.12, 72.31] 3.00 [0.12, 72.31]	Favours [experimental] Favours [control] Risk Ratio

Study or Subgroup	Canaglifi Events		Placebo Events		Weight	M-H, Fixed, 95% Cl	Risk Ratio <u>M-H, Fixed, 95% Cl</u>
2.14.1 100mg canaglifi		IVIAI	-+01118	out	weigint		
Bays2014	3	93	5	89	19.2%	0.57 [0.14, 2.33]	
Devineni 2014	0	10	1	9	5.9%	0.30 [0.01, 6.62]	
Rosenstock 2013	1	64	2	65	7.5%	0.51 [0.05, 5.46]	
Subtotal (95% CI)		167		163	32.6%	0.51 [0.17, 1.56]	
Total events	4	(n - 0 03	8				
Heterogeneity: Chi ² = 0 Test for overall effect: Z			5); 1- = 0%	•			
2.14.2 300mg canaglif	lozin						
Bays2014	2	96	5	89	19.5%	0.37 [0.07, 1.86]	
Devineni 2014	3	10	1	9	4.0%	2.70 [0.34, 21.53]	
Rosenstock 2013	2	64	2	65	7.5%	1.02 [0.15, 6.99]	
Subtotal (95% CI)	_	170		163	30.9%	0.82 [0.31, 2.20]	
Total events Heterogeneity: Chi ² = 2	7 .24. df = 2	(P = 0.33	8 3): l² = 11	%			
Test for overall effect: Z	2 = 0.39 (P	= 0.70)					
2.14.3 50mg canaglific							
Bays2014	5	98	5	89	19.7%	0.91 [0.27, 3.03]	
Rosenstock 2013	1	64	2	65	7.5%	0.51 [0.05, 5.46]	
Subtotal (95% CI)	•	162	7	154	27.1%	0.80 [0.27, 2.32]	
Total events	6 19 df - 1	(n - 0 ez					
Heterogeneity: Chi ² = 0 Test for overall effect: Z); 1~ = 0%	•			
2.14.4 200mg canaglifi	lozin						
Rosenstock 2013	0	65	2	65	9.4%	0.20 [0.01, 4.09]	• • • • • • • • • • • • • • • • • • • •
Subtotal (95% CI)		65		65	9.4%	0.20 [0.01, 4.09]	
Total events	0		2				
Heterogeneity: Not app							
Test for overall effect: Z	. = 1.05 (P	= 0.30)					
Total (95% CI)		564		545	100.0%	0.66 [0.36, 1.18]	-
Total events	17		25				
Heterogeneity: Chi ² = 3			s); l² = 0%	•			0.01 0.1 1 10 100
Test for overall effect: Z Test for subgroup differ			df = 3 (P	= 0 77) I ² = 0%		Favours [experimental] Favours [control]
Test for subgroup differ	ences. Chi	- 1.12.	ui – 3 (F	- 0.77			
Study or Subgroup	Canag Events		Place		Weight	Risk Ratio M-H, Fixed, 95% C	Risk Ratio CI M-H, Fixed, 95% CI
Study or Subgroup		Total	Evenus	TOTAL	weight	M-H, FIXED, 93% C	
2.16.1 50 mg Canaglifl	ozin						
2.16.1 50 mg Canaglifi Bavs2014		98	2	89	2.9%	1.36 [0.23, 7.97]	·
2.16.1 50 mg Canaglifl Bays2014 Rosenstock 2013	ozin 3 2	98 64	2 1	89 65	2.9% 1.4%	1.36 [0.23, 7.97] 2.03 [0.19, 21.85]	
Bays2014 Rosenstock 2013 Subtotal (95% CI)	3 2		1				
Bays2014 Rosenstock 2013	3 2 5 .07, df = 1	64 162 P = 0.79	1 3	65	1.4%	2.03 [0.19, 21.85]	
Bays2014 Rosenstock 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 0. Test for overall effect: Z 2.16.2 100mg Canaglif	3 2 5 .07, df = 1 2 = 0.63 (P 10zin	64 162 P = 0.79 = 0.53)	1 3); I² = 0%	65 154	1.4% 4.3%	2.03 [0.19, 21.85] 1.58 [0.38, 6.47]	
Bays2014 Rosenstock 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 0. Test for overall effect: Z 2.16.2 100mg Canaglif Bays2014	3 2 5 .07, df = 1 2 = 0.63 (P 10zin 3	64 162 (P = 0.79 = 0.53) 93	1 3); I ² = 0% 2	65 154 89	1.4% 4.3% 2.8%	2.03 [0.19, 21.85] 1.58 [0.38, 6.47] 1.44 [0.25, 8.39]	
Bays2014 Rosenstock 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 0. Test for overall effect: Z 2.16.2 100mg Canaglif Bays2014 Bode 2013	3 2 5 07, df = 1 = 0.63 (P flozin 3 10	64 162 (P = 0.79 = 0.53) 93 241	1); I ² = 0% 2 5	65 154 89 237	1.4% 4.3% 2.8% 7.0%	2.03 [0.19, 21.85] 1.58 [0.38, 6.47] 1.44 [0.25, 8.39] 1.97 [0.68, 5.67]	
Bays2014 Rosenstock 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 0. Test for overall effect: Z 2.16.2 100mg Canaglif Bays2014 Bode 2013 Forst 2014	3 2 5 07, df = 1 2 = 0.63 (P 3 10 10 11	64 162 (P = 0.79 = 0.53) 93 241 113	1 3); I ² = 0% 2 5 1	65 154 89 237 115	1.4% 4.3% 2.8% 7.0% 1.4%	2.03 [0.19, 21.85] 1.58 [0.38, 6.47] 1.44 [0.25, 8.39] 1.97 [0.68, 5.67] 11.19 [1.47, 85.29]	
Bays2014 Rosenstock 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 0, Test for overall effect: Z 2.16.2 100mg Canaglif Bays2014 Bode 2013 Forst 2014 Lavalle-Gonzalez 2013	3 2 5 07, df = 1 2 = 0.63 (P 3 10 11 23	64 162 (P = 0.79 = 0.53) 93 241 113 368	1 3); I ² = 0% 2 5 1 1	65 154 89 237 115 183	1.4% 4.3% 2.8% 7.0% 1.4% 1.9%	2.03 [0.19, 21.85] 1.58 [0.38, 6.47] 1.58 [0.25, 8.39] 1.97 [0.68, 5.67] 11.19 [1.47, 56.29] 11.44 [1.56, 84.03]	
Bays2014 Rosenstock 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 0. Test for overall effect: Z 2.16.2 100mg Canaglif Bays2014 Bode 2013 Forst 2014 Lavalle-Gonzalez 2013 Leiter 2014	3 2 07, df = 1 = 0.63 (P 10zin 3 10 11 23 28	64 162 (P = 0.79 = 0.53) 93 241 113 368 483	1 3); I ² = 0% 2 5 1 1 10	65 154 89 237 115 183 482	1.4% 4.3% 2.8% 7.0% 1.4% 1.9% 13.9%	2.03 [0.19, 21.85] 1.58 [0.38, 6.47] 1.58 [0.38, 6.47] 1.97 [0.68, 5.67] 11.19 [1.47, 85.29] 11.44 [1.56, 84.03] 2.79 [1.37, 5.69]	
Bays2014 Rosenstock 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 0, Test for overall effect: Z 2.16.2 100mg Canaglif Bays2014 Bode 2013 Forst 2014 Lavalle-Gonzalez 2013	3 2 5 07, df = 1 (= 0.63 (P lozin 3 10 11 23 28 2 8 2	64 162 (P = 0.79 = 0.53) 93 241 113 368	1 3); I ² = 0% 2 5 1 1	65 154 89 237 115 183	1.4% 4.3% 7.0% 1.4% 1.9% 13.9% 4.1%	2.03 [0.19, 21.85] 1.58 [0.38, 6.47] 1.58 [0.25, 8.39] 1.97 [0.68, 5.67] 11.19 [1.47, 85.29] 11.44 [1.56, 84.03] 2.79 [1.37, 5.69] 0.68 [0.11, 4.00]	
Bays2014 Rosenstock 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 0. Test for overall effect: Z 2.16.2 100mg Canaglif Bays2014 Bode 2013 Forst 2014 Lavalle-Gonzalez 2013 Leiter 2014 Li 2014	3 2 07, df = 1 = 0.63 (P 10zin 3 10 11 23 28	64 162 (P = 0.79 = 0.53) 93 241 113 368 483 223	1 3); ² = 0% 2 5 1 1 10 3	65 154 89 237 115 183 482 226	1.4% 4.3% 7.0% 1.4% 13.9% 4.1% 1.4%	2.03 [0.19, 21.85] 1.58 [0.38, 6.47] 1.58 [0.38, 6.47] 1.97 [0.68, 5.67] 11.19 [1.47, 85.29] 11.44 [1.56, 84.03] 2.79 [1.37, 5.69]	
Bays2014 Rosenstock 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 0. Test for overall effect: Z 2.16.2 100mg Canaglif Bays2014 Bode 2013 Forst 2014 Lavalle-Gonzalez 2013 Leiter 2014 I 2014 Rosenstock 2013	3 2 5 .07, df = 1 = 0.63 (P lozin 3 10 11 23 28 28 2 3	64 162 (P = 0.79 = 0.53) 93 241 113 368 483 223 64	1 3); ² = 0% 2 5 1 1 10 3 1	65 154 89 237 115 183 482 226 65	1.4% 4.3% 7.0% 1.4% 13.9% 4.1% 1.4%	2.03 [0.19, 21.85] 1.55 [0.38, 6.47] 1.57 [0.38, 6.47] 1.97 [0.68, 5.67] 11.9 [1.47, 85.29] 11.44 [1.56, 84.03] 2.79 [1.37, 5.69] 0.68 [0.11, 4.00] 3.05 [0.33, 28.53]	
Bays2014 Rosenstock 2013 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = 0. Test for overall effect: Z 2.16.2 100mg Canaglif Bays2014 Bode 2013 Forst 2014 Lavalle-Gonzalez 2013 Leiter 2014 Li 2014 Rosenstock 2013 Steniőf 2014 Wilding 2013	3 2 5 .07, df = 1 = 0.63 (P 3 10 11 23 28 2 3 9 9	64 162 (P = 0.79 = 0.53) 93 241 113 368 483 223 64 195 157 90	1 3); ² = 0% 2 5 1 1 10 3 1 4	65 154 89 237 115 183 482 226 65 192 156 90	1.4% 4.3% 7.0% 1.4% 13.9% 4.1% 1.4% 5.6% 4.2%	2.03 [0.19, 21.85] 1.55 [0.38, 6.47] 1.55 [0.38, 6.47] 1.97 [0.68, 5.67] 11.9 [1.47, 85.29] 11.44 [1.56, 84.03] 2.79 [1.37, 5.69] 0.68 [0.11, 4.00] 3.05 [0.33, 28.53] 2.22 [0.89, 7.07] 2.98 [0.82, 10.80] 2.00 [0.18, 21.67]	
Bays2014 Rosenstock 2013 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = 0. Test for overall effect: Z 2.16.2 100mg Canaglif Bays2014 Bode 2013 Forst 2014 Lavalle-Gonzalez 2013 Leiter 2014 Li 2014 Rosenstock 2013 Stenlöf 2014 Wilding 2013 Yale 2013 Subtotal (95% Cl)	3 2 5 007, df = 1 1 = 0.63 (P 10 10 11 23 28 2 2 3 3 9 9 9 2	64 162 (P = 0.79 = 0.53) 93 241 113 368 483 223 64 195 157	1); l² = 0% 2 5 1 1 10 3 1 4 3 1	65 154 89 237 115 183 482 226 65 192 156	1.4% 4.3% 2.8% 7.0% 1.4% 13.9% 4.1% 1.4% 5.6% 4.2%	2.03 [0.19, 21.85] 1.58 [0.38, 6.47] 1.58 [0.38, 6.47] 1.97 [0.68, 5.67] 11.19 [1.47, 85.29] 11.44 [1.56, 84.03] 2.79 [1.37, 5.69] 0.68 [0.11, 4.00] 3.05 [0.33, 28.53] 2.22 [0.68, 7.07] 2.98 [0.82, 10.80]	
Bays2014 Rosenstock 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 0. Test for overall effect: Z 2.16.2 100mg Canaglif Bays2014 Bode 2013 Forst 2014 Lavalle-Gonzalez 2013 Leiter 2014 Li 2014 Rosenstock 2013 Steniöf 2014 Wilding 2013 Yale 2013 Subtotal (95% CI) Total events	3 2 5 007, df = 1 = 0.63 (P 10 10 11 23 28 2 2 3 9 9 9 2 2 100	64 162 (P = 0.79 = 0.53) 93 241 113 368 483 223 64 195 157 900 2027	1); ² = 0% 2 5 1 1 10 3 1 4 3 1 31	65 154 89 237 115 183 482 226 65 192 156 90	1.4% 4.3% 7.0% 1.4% 13.9% 4.1% 1.4% 5.6% 4.2%	2.03 [0.19, 21.85] 1.55 [0.38, 6.47] 1.55 [0.38, 6.47] 1.97 [0.68, 5.67] 11.9 [1.47, 85.29] 11.44 [1.56, 84.03] 2.79 [1.37, 5.69] 0.68 [0.11, 4.00] 3.05 [0.33, 28.53] 2.22 [0.89, 7.07] 2.98 [0.82, 10.80] 2.00 [0.18, 21.67]	
Bays2014 Rosensbock 2013 Subtotal (95% C1) Total events Heterogeneity: Chi ² = 0. Test for overall effect: Z 2.16.2 100mg Canaglif Bays2014 Bode 2013 Forst 2014 Lavalle-Gonzalez 2013 Leiter 2014 Li 2014 Rosensbock 2013 Steniöf 2014 Wilding 2013 Subtotal (95% C1) Total events Heterogeneity: Chi ² = 7.	3 5 07, df = 1 = 0.63 (P 10zin 3 10 11 23 28 28 3 9 9 2 2 3 3 9 9 9 2 2 100 0 59, df = 9	64 162 (P = 0.79 = 0.53) 93 241 113 368 483 223 64 195 157 90 2027 (P = 0.58	1 3); l ² = 0% 2 5 1 1 1 10 3 1 4 3 1 1 4 3 1); l ² = 0%	65 154 89 237 115 183 482 226 65 192 156 90	1.4% 4.3% 7.0% 1.4% 13.9% 4.1% 1.4% 5.6% 4.2%	2.03 [0.19, 21.85] 1.55 [0.38, 6.47] 1.55 [0.38, 6.47] 1.97 [0.68, 5.67] 11.9 [1.47, 85.29] 11.44 [1.56, 84.03] 2.79 [1.37, 5.69] 0.68 [0.11, 4.00] 3.05 [0.33, 28.53] 2.22 [0.89, 7.07] 2.98 [0.82, 10.80] 2.00 [0.18, 21.67]	
Bays2014 Rosenstock 2013 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = 0. Test for overall effect: Z 2.16.2 100mg Canaglif Bays2014 Bode 2013 Forst 2014 Lavalle-Gonzalez 2013 Leiter 2014 Li 2014 Rosenstock 2013 Steniőf 2014 Wilding 2013	3 5 607, df = 1 = 0.63 (P 102in 3 10 11 23 28 2 3 9 9 2 100 .59, df = 9 = 5.17 (P	64 162 (P = 0.79 = 0.53) 93 241 113 368 483 223 64 195 157 90 2027 (P = 0.58	1 3); l ² = 0% 2 5 1 1 1 10 3 1 4 3 1 1 4 3 1); l ² = 0%	65 154 89 237 115 183 482 226 65 192 156 90	1.4% 4.3% 7.0% 1.4% 13.9% 4.1% 1.4% 5.6% 4.2%	2.03 [0.19, 21.85] 1.55 [0.38, 6.47] 1.55 [0.38, 6.47] 1.97 [0.68, 5.67] 11.9 [1.47, 85.29] 11.44 [1.56, 84.03] 2.79 [1.37, 5.69] 0.68 [0.11, 4.00] 3.05 [0.33, 28.53] 2.22 [0.89, 7.07] 2.98 [0.82, 10.80] 2.00 [0.18, 21.67]	
Bays2014 Rosenstock 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 0. Test for overall effect: Z 2.16.2 100mg Canaglif Bays2014 Bode 2013 Forst 2014 Lavalle-Gonzalez 2013 Leiter 2014 Li 2014 Rosenstock 2013 Steniöf 2014 Wilding 2013 Yale 2013 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 7. Test for overall effect: Z	3 5 607, df = 1 = 0.63 (P 102in 3 10 11 23 28 2 3 9 9 2 100 .59, df = 9 = 5.17 (P	64 162 (P = 0.79 = 0.53) 93 241 113 368 483 223 64 195 157 90 2027 (P = 0.58	1 3); l ² = 0% 2 5 1 1 1 10 3 1 4 3 1 1 4 3 1); l ² = 0%	65 154 89 237 115 183 482 226 65 192 156 90	1.4% 4.3% 7.0% 1.4% 1.9% 13.9% 4.1% 5.6% 4.2% 4.2% 4.2% 4.3.7%	2.03 [0.19, 21.85] 1.55 [0.38, 6.47] 1.55 [0.38, 6.47] 1.97 [0.68, 5.67] 11.9 [1.47, 85.29] 11.44 [1.56, 84.03] 2.79 [1.37, 5.69] 0.68 [0.11, 4.00] 3.05 [0.33, 28.53] 2.22 [0.89, 7.07] 2.98 [0.82, 10.80] 2.00 [0.18, 21.67]	
Bays2014 Rosenstock 2013 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = 0. Test for overall effect: Z 2.16.2 100mg Canaglif Bays2014 Bode 2013 Forst 2014 Lavalle-Gonzalez 2013 Leiter 2014 Li 2014 Rosenstock 2013 Steniöf 2014 Wilding 2013 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = 7. Test for overall effect: Z 2.16.3 200 mg Canagli	3 2 5 0.07, df = 1 10, 3 10 11 23 28 2 3 9 9 9 2 100 5.59, df = 9 100 5.59, df = 9 100 5.59, df = 9 100 100	64 162 (P = 0.79 = 0.53) 93 241 113 368 483 243 64 195 157 90 2027 (P = 0.58 < 0.0000	1 3 2 5 1 1 10 3 1 4 3 1 2 5 7 10 3 1 1 3 1 1 3 1 3 1 1 3 1 1 3 1 3 1	65 154 89 237 115 183 482 226 65 192 156 90 1835	1.4% 4.3% 2.8% 7.0% 1.4% 1.9% 13.9% 4.1% 5.6% 4.2% 1.4%	2.03 [0.19, 21.85] 1.58 [0.38, 6.47] 1.58 [0.38, 6.47] 1.97 [0.68, 5.67] 11.19 [1.47, 85.29] 11.44 [1.56, 84.03] 2.79 [1.37, 5.69] 0.68 [0.11, 4.00] 3.05 [0.33, 28.53] 2.22 [0.69, 7.03] 2.98 [0.82, 10.80] 2.90 [0.82, 10.80] 2.93 [1.95, 4.41]	
Bays2014 Rosenstock 2013 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = 0. Test for overall effect: Z 2.16.2 100mg Canaglif Bays2014 Bode 2013 Forst 2014 Lavalle-Gonzalez 2013 Leiter 2014 Rosenstock 2013 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = 7. Test for overall effect: Z 2.16.3 200 mg Canagli Rosenstock 2013	3 2 5 0.07, df = 1 10, 3 10 11 23 28 2 3 9 9 9 2 100 5.59, df = 9 100 5.59, df = 9 100 5.59, df = 9 100 100	64 162 (P = 0.79 = 0.53) 93 241 113 368 483 223 64 195 157 90 2027 (P = 0.58 < 0.0000 65	1 3 2 5 1 1 10 3 1 4 3 1 2 5 7 10 3 1 1 3 1 1 3 1 3 1 1 3 1 1 3 1 3 1	65 154 89 237 115 183 482 226 65 192 156 65 90 1835	1.4% 4.3% 2.8% 7.0% 1.4% 1.9% 13.9% 4.1% 5.6% 4.2% 1.4%	2.03 [0.19, 21.85] 1.58 [0.38, 6.47] 1.58 [0.38, 6.47] 1.97 [0.68, 5.67] 11.19 [1.47, 85.29] 11.44 [1.56, 84.03] 2.79 [1.37, 5.69] 0.68 [0.11, 4.00] 3.05 [0.33, 28.53] 2.22 [0.69, 7.07] 2.98 [0.82, 10.80] 2.00 [0.18, 21.67] 2.93 [1.95, 4.41] 1.00 [0.06, 15.65]	
Bays2014 Rosenstock 2013 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = 0. Test for overall effect: Z 2.16.2 100mg Canaglif Bays2014 Bode 2013 Forst 2014 Lavalle-Gonzalez 2013 Leiter 2014 Li 2014 Rosenstock 2013 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = 7. Test for overall effect: Z 2.16.3 200 mg Canagli Rosenstock 2013 Subtotal (95% Cl)	3 2 5 07, df = 1 i = 0.63 (P 10zin 11 23 28 2 3 3 9 9 2 1000 59, df = 9 5.17 (P flozin 1 1 10zin 1 11 23 28 2 3 3 9 12 10 10 10 11 23 28 11 11 23 28 12 11 12 28 12 12 12 12 12 12 12 12 12 12 12 12 12	64 162 (P = 0.79 = 0.53) 93 2411 13368 4433 2433 64 455 157 90 2027 (P = 0.58 65 65	1 3 2 5 1 1 10 3 1 4 3 1 2 5 5 1 1 10 3 1 1 3 1 1 3 1 3 1 1 3 1 3 1 1 3 1 1 3 1 1 3 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	65 154 89 237 115 183 482 226 65 192 156 65 90 1835	1.4% 4.3% 2.8% 7.0% 1.4% 1.9% 13.9% 4.1% 5.6% 4.2% 1.4%	2.03 [0.19, 21.85] 1.58 [0.38, 6.47] 1.58 [0.38, 6.47] 1.97 [0.68, 5.67] 11.19 [1.47, 85.29] 11.44 [1.56, 84.03] 2.79 [1.37, 5.69] 0.68 [0.11, 4.00] 3.05 [0.33, 28.53] 2.22 [0.69, 7.07] 2.98 [0.82, 10.80] 2.00 [0.18, 21.67] 2.93 [1.95, 4.41] 1.00 [0.06, 15.65]	
Bays2014 Rosenstock 2013 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = 0. Test for overall effect: Z 2.16.2 100mg Canaglif Bays2014 Bode 2013 Forst 2014 Lavalle-Gonzalez 2013 Leiter 2014 Li 2014 Rosenstock 2013 Steniöf 2014 Wilding 2013 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = 7. Test for overall effect: Z 2.16.3 200 mg Canagli Rosenstock 2013 Subtotal (95% Cl) Total events Heterogeneity: Not appl Test for overall effect: Z	3 2 3 3 3 3 4 5 5 6 1 1 2 3 10 11 2 3 2 3 9 9 2 3 9 9 2 3 10 5 9, df = 1 1 2 3 10 11 23 28 2 3 9 9 2 3 10 10 23 28 2 3 10 10 23 28 2 3 10 10 23 28 2 3 10 10 23 28 2 3 10 10 23 28 2 3 10 10 23 28 2 3 9 9 2 10 10 23 28 2 3 10 10 23 28 2 3 10 10 23 28 2 3 9 9 2 10 10 23 28 2 3 10 10 23 28 2 3 10 10 23 28 2 3 10 10 23 28 2 3 10 10 23 28 2 3 10 10 25 9 10 10 10 25 10 10 10 10 10 10 10 10 10 10	64 162 (P = 0.79 = 0.53) 93 2411 13368 4433 2433 64 455 157 90 2027 (P = 0.58 65 65	1 3 2 5 1 1 10 3 1 4 3 1 2 5 5 1 1 10 3 1 1 3 1 1 3 1 3 1 1 3 1 3 1 1 3 1 1 3 1 1 3 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	65 154 89 237 115 183 482 226 65 192 156 65 90 1835	1.4% 4.3% 2.8% 7.0% 1.4% 1.9% 13.9% 4.1% 5.6% 4.2% 1.4%	2.03 [0.19, 21.85] 1.58 [0.38, 6.47] 1.58 [0.38, 6.47] 1.97 [0.68, 5.67] 11.19 [1.47, 85.29] 11.44 [1.56, 84.03] 2.79 [1.37, 5.69] 0.68 [0.11, 4.00] 3.05 [0.33, 28.53] 2.22 [0.69, 7.07] 2.98 [0.82, 10.80] 2.00 [0.18, 21.67] 2.93 [1.95, 4.41] 1.00 [0.06, 15.65]	
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Bays2014 Rosenstock 2013 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = 0. Test for overall effect: Z 2.16.2 100mg Canaglif Bays2014 Bode 2013 Forst 2014 Lavalle-Gonzalez 2013 Leiter 2014 Li 2014 Rosenstock 2013 Steniöf 2014 Wilding 2013 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = 7. Test for overall effect: Z 2.16.3 200 mg Canaglif Rosenstock 2013 Subtotal (95% Cl) Total events Heterogeneity: Not appl Test for overall effect: Z 2.16.3 300mg Canaglif Bays2014 Bode 2013 Forst 2014 Lavalle-Gonzalez 2013 Leiter 2014 Lavalle-Gonzalez 2013 Leiter 2014 Lavalle-Gonzalez 2013 Schemthaner 2013 Steniöf 2014 Wilding 2013	3 2 5 0,07, df = 1 0,63 (P 102in 3 10 11 23 28 2 3 3 9 9 2 2 3 9 9 9 2 2 3 9 9 9 2 2 3 100 5,59, df = 9 5,17 (P flozin 1 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 1 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102in 102i 102in 1002in 102i 102in 1000 1000 1000 1000 10000000000000000	64 162 (P = 0.79) = 0.53) 33 241 113 368 44 33 86 4 43 195 2027 (P = 0.58) 5157 90 2027 2027 = 0.58 55 55 = = 1.00) 96 65 55 = = 1.00) 96 65 216 45 197 455 227 64 378 197 455 227 64 378 197 196 65 216 216 216 216 216 216 216 216 216 216	1 3 3 2 5 5 1 1 1 1 0 0 3 1 1 4 3 3 1 1 1 1 2 5 5 1 1 1 1 0 0 3 1 1 1 1 3 1 1 3 1 3 1 1 3 1 1 3 1 1 1 1 1 1 0 3 3 1 1 1 1	65 154 89 237 115 183 226 65 90 1835 65 65 65 89 237 115 183 482 226 65 5 5 5 5 5 5 5 5 221 378 183 482 226 5 5 5 5 5 5 5 5 221 7 221 5 6 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	1.4% 4.3% 7.0% 1.4% 1.9% 1.4% 5.6% 4.2% 4.3,% 4.3,% 4.3,% 4.3,% 4.3,% 1.4% 6.8% 1.4% 1.4% 5.6% 4.2% 1.4%	2.03 [0.19, 21.85] 1.58 [0.38, 6.47] 1.58 [0.38, 6.47] 1.77 [0.68, 5.67] 11.19 [1.47, 85.29] 11.44 [1.56, 84.03] 2.79 [1.37, 5.69] 0.68 [0.11, 4.00] 2.00 [0.18, 21.67] 2.93 [1.95, 4.41] 1.00 [0.06, 15.65] 1.00 [0.06, 15.65] 1.00 [0.06, 15.65] 1.10 [1.46, 84.55] 1.85 [0.35, 9.88] 3.21 [1.20, 8.63] 11.10 [1.46, 84.55] 1.80 [0.61, 5.32] 3.65 [1.24, 10.81] 3.67 [1.04, 12.89] 4.04 [0.46, 35.48]	
Bays2014 Rosenstock 2013 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = 0. Test for overall effect: Z 2.16.2 100mg Canaglif Bays2014 Bode 2013 Forst 2014 Lavalle-Gonzalez 2013 Leiter 2014 Li 2014 Rosenstock 2013 Steniöf 2014 Wilding 2013 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = 7. Test for overall effect: Z 2.16.3 200 mg Canaglif Rosenstock 2013 Subtotal (95% Cl) Total events Heterogeneity: Not appl Test for overall effect: Z 2.16.3 200 mg Canaglif Bays2014 Bode 2013 Forst 2014 Lavalle-Gonzalez 2013 Leiter 2014 Lavalle-Gonzalez 2013 Schemthaner 2013 Steniöf 2014 Wilding 2013 Yale 2013 Subtotal (95% Cl) Total events	3 2 5 0,07, df = 1 1 0,051 10 10 10 10 10 10 10 10 10 10 10 10 10	64 162 (P = 0.79) 93 241 113 368 483 223 2027 (P = 0.58 65 65 65 65 65 65 65 65 65 65 65 65 65	1 3 3 2 5 5 1 1 1 1 1 3 1 3 1 3 1 3 1 3 1 1 1 1	65 154 89 237 115 183 226 65 90 1835 65 65 65 89 237 115 183 482 226 65 5 5 5 5 5 5 5 5 221 378 183 482 226 5 5 5 5 5 5 5 5 221 7 221 5 6 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	1.4% 4.3% 7.0% 1.4% 1.9% 1.4% 5.6% 4.2% 4.3,% 4.3,% 4.3,% 4.3,% 4.3,% 1.4% 6.8% 1.4% 1.4% 5.6% 4.2% 1.4%	2.03 [0.19, 21.85] 1.58 [0.38, 6.47] 1.58 [0.38, 6.47] 1.77 [0.68, 5.67] 11.19 [1.47, 85.29] 11.44 [1.56, 84.03] 2.79 [1.37, 5.69] 0.68 [0.11, 4.00] 2.00 [0.18, 21.67] 2.93 [1.95, 4.41] 1.00 [0.06, 15.65] 1.00 [0.06, 15.65] 1.00 [0.06, 15.65] 1.10 [1.46, 84.55] 1.85 [0.35, 9.88] 3.21 [1.20, 8.63] 11.10 [1.46, 84.55] 1.80 [0.61, 5.32] 3.65 [1.24, 10.81] 3.67 [1.04, 12.89] 4.04 [0.46, 35.48]	
Bays2014 Rosenstock 2013 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = 0. Test for overall effect: Z 2.16.2 100mg Canaglif Bays2014 Bode 2013 Forst 2014 Lavalle-Gonzalez 2013 Leiter 2014 Li 2014 Rosenstock 2013 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = 7. Test for overall effect: Z 2.16.3 200 mg Canaglif Bays2014 Bode 2013 Subtotal (95% Cl) Total events Heterogeneity: Not appl Test for overall effect: Z 2.16.4 300mg Canaglif Bays2014 Bode 2013 Forst 2014 Lavalle-Gonzalez 2013 Eiter 2014 Lavalle-Gonzalez 2013 Schembhaner 2013 Steniof 2014 Wilding 2013 Steniof 2014 Wilding 2013 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = 6. Heterogeneity: Chi ² = 6.	3 2 5 0,07, df = 1 1 0,051 10 10 10 10 10 10 10 10 10 10 10 10 10	64 162 (P = 0.79) 93 241 113 368 483 223 2027 (P = 0.58 65 65 65 65 65 65 65 65 65 65 65 65 65	1 3 3 2 5 5 1 1 1 1 1 3 1 3 1 3 1 3 1 3 1 1 1 1	65 154 89 237 115 183 482 226 65 90 1835 156 90 1835 65 65 89 237 115 183 482 226 65 5 5 5 5 89 237 115 154 90 227 378 183 482 226 65 5 65 65 65 65 65 65 65 65 65 65 65	1.4% 4.3% 7.0% 1.4% 1.9% 1.4% 5.6% 4.2% 4.3,% 4.3,% 4.3,% 4.3,% 4.3,% 1.4% 6.8% 1.4% 1.4% 5.6% 4.2% 1.4%	2.03 [0, 19, 21, 85] 1.58 [0.38, 6.47] 1.58 [0.38, 6.47] 1.77 [0.68, 5.67] 11.19 [1.47, 85.29] 11.44 [1.56, 84.03] 2.79 [1.37, 5.69] 0.68 [0.11, 4.00] 3.05 [0.33, 28.53] 2.22 [0.89, 7.07] 2.98 [0.82, 10.80] 2.00 [0.18, 21, 67] 2.93 [1.95, 4.41] 1.00 [0.06, 15, 65] 1.00 [0.06, 15, 65] 1.00 [0.06, 15, 65] 1.00 [0.06, 15, 65] 1.10 [1.68, 6.40] 0.66 [0.11, 3.93] 2.03 [0.19, 21, 85] 1.80 [0.61, 5, 32] 3.65 [1.24, 10.81] 3.67 [1.04, 12, 89] 4.04 [0.46, 35, 48] 3.13 [2.16, 4.54]	
Bays2014 Rosenstock 2013 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = 0. Test for overall effect: Z 2.16.2 100mg Canaglif Bays2014 Bode 2013 Forst 2014 Lavalle-Gonzalez 2013 Leiter 2014 Rosenstock 2013 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = 7. Test for overall effect: Z 2.16.3 200 mg Canaglif Rosenstock 2013 Subtotal (95% Cl) Total events Heterogeneity: Not appl Test for overall effect: Z 2.16.4 300mg Canaglif Bays2014 Bode 2013 Forst 2014 Rosenstock 2013 Subtotal (95% Cl) Total events Heterogeneity: Not appl Test for overall effect: Z 2.16.4 300mg Canaglif Bays2014 Bode 2013 Forst 2014 Lavalle-Gonzalez 2013 Schemthaner 2013 Schemthaner 2013 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = 6. Test for overall effect: Z Total (95% Cl) Total events	3 5 5 607, df = 1 1 102in 10 11 23 28 2 3 9 9 2 100 59, df = 9 2 100 59, df = 9 10 11 123 28 9 9 2 10 10 5.9, df = 9 10 10 11 23 28 9 9 2 10 10 5.9, df = 9 10 10 11 23 28 9 9 2 10 10 10 11 23 28 9 9 2 10 10 11 23 28 9 9 2 10 10 11 23 28 9 9 2 10 10 11 23 28 2 3 9 9 2 10 10 11 23 28 9 9 2 10 10 11 12 11 10 11 10 11 11 13 23 2 10 10 11 11 13 32 2 2 10 10 11 11 13 32 2 2 2 10 10 11 11 13 32 2 2 2 10 10 11 11 13 32 2 2 2 10 11 11 13 32 2 2 2 11 11 13 32 2 2 11 11 13 32 2 2 11 11 13 32 2 2 9 9 15 11 11 13 32 2 2 9 9 15 11 11 13 32 2 2 9 15 11 11 11 13 32 2 2 2 11 11 11 15 16 16 16 16 17 17 18 19 19 10 11 11 13 2 2 2 9 15 11 11 15 16 10 15 15 17 11 15 15 15 15 15 15 15 15 15	64 162 (P = 0.79 = 0.53) 933 241 113 368 483 423 157 157 90 2027 (P = 0.58 65 65 65 65 65 65 65 65 65 65 65 65 65	1 3 3 2 5 5 1 1 1 1 0 3 3 1 1 4 4 3 1 1 1 1 1 1 1 1 1 1 1 1 1	65 154 89 237 115 183 482 226 65 90 1835 65 65 65 65 65 65 89 237 115 183 482 226 65 378 85 227 156 90 2213 482 226 65 65 65 65 65 65 65 65 65 65 65 65 65	1.4% 4.3% 7.0% 1.4% 1.9% 1.4% 4.1% 4.2% 1.4% 4.2% 1.4% 5.6% 1.4% 5.6% 1.9% 5.6% 1.4% 5.0%	2.03 [0.19, 21.85] 1.58 [0.38, 6.47] 1.58 [0.38, 6.47] 1.77 [0.68, 5.67] 11.19 [1.47, 85.29] 11.44 [1.56, 84.03] 2.79 [1.37, 5.69] 0.68 [0.11, 4.00] 2.00 [0.18, 21.67] 2.93 [1.95, 4.41] 1.00 [0.06, 15.65] 1.00 [0.06, 15.65] 1.00 [0.06, 15.65] 1.10 [1.46, 84.55] 1.85 [0.35, 9.88] 3.21 [1.20, 8.63] 11.10 [1.46, 84.55] 1.80 [0.61, 5.32] 3.65 [1.24, 10.81] 3.67 [1.04, 12.89] 4.04 [0.46, 35.48]	
Bays2014 Rosenstock 2013 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = 0. Test for overall effect: Z 2.16.2 100mg Canaglif Bays2014 Bode 2013 Forst 2014 Lavalle-Gonzalez 2013 Leiter 2014 Li 2014 Rosenstock 2013 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = 7. Test for overall effect: Z 2.16.3 200 mg Canaglif Bays2014 Bode 2013 Subtotal (95% Cl) Total events Heterogeneity: Not appl Test for overall effect: Z 2.16.4 300mg Canaglif Bays2014 Bode 2013 Forst 2014 Lavalle-Gonzalez 2013 Eiter 2014 Lavalle-Gonzalez 2013 Schembhaner 2013 Steniof 2014 Wilding 2013 Steniof 2014 Wilding 2013 Subtotal (95% Cl) Total events Heterogeneity: Chi ² = 6. Test for overall effect: Z Total events	3 2 5 107, df = 1 102 102 102 102 102 102 102 10	64 162 (P = 0.79) = 0.53) 933 2411 113 3688 443 368 445 155 155 2027 (P = 0.58 65 55 = 1.00) 96 65 65 55 = 1.00) 96 65 65 52 27 64 378 197 196 64 378 197 196 64 378 197 196 64 378 197 196 64 196 24 65 55 227 196 24 197 2027 197 2027 197 2027 2027 2027 2027 2027 2027 2027 20	1 3 3 2 5 5 1 1 1 1 0 3 3 1 1 4 3 1 1 1 1 1 1 1 1 1 1 2 5 5 1 1 1 1 1 1 1	65 154 89 237 115 183 482 226 65 90 1835 65 65 65 65 65 65 89 237 115 183 482 226 65 378 85 227 156 90 2213 482 226 65 65 65 65 65 65 65 65 65 65 65 65 65	1.4% 4.3% 7.0% 1.4% 1.9% 1.4% 4.1% 4.2% 1.4% 4.2% 1.4% 5.6% 1.4% 5.6% 1.9% 5.6% 1.4% 5.0%	2.03 [0, 19, 21, 85] 1.58 [0.38, 6.47] 1.58 [0.38, 6.47] 1.77 [0.68, 5.67] 11.19 [1.47, 85.29] 11.44 [1.56, 84.03] 2.79 [1.37, 5.69] 0.68 [0.11, 4.00] 3.05 [0.33, 28.53] 2.22 [0.89, 7.07] 2.98 [0.82, 10.80] 2.00 [0.18, 21, 67] 2.93 [1.95, 4.41] 1.00 [0.06, 15, 65] 1.00 [0.06, 15, 65] 1.00 [0.06, 15, 65] 1.00 [0.06, 15, 65] 1.10 [1.68, 6.40] 0.66 [0.11, 3.93] 2.03 [0.19, 21, 85] 1.80 [0.61, 5, 32] 3.65 [1.24, 10.81] 3.67 [1.04, 12, 89] 4.04 [0.46, 35, 48] 3.13 [2.16, 4.54]	

Study or Subgroup E	Canaglifi Events		Events	Total	Welght	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
2.20.1 50 mg canagliflozin Bays2014	4	98	2	89	3.3%	1.82 [0.34, 9.68]	
Rosenstock 2013	o	64	1	65	2.4%	0.34 [0.01, 8.16]	
Subtotal (95% CI)		162	_	154	5.7%	1.20 [0.30, 4.84]	
Total events Heterogeneity: Chi² = 0.84, c	4 	- 0 26)	3 - 0%				
Test for overall effect: $Z = 0.2$, I [_] = 0%				
2.20.2 100mg canagliflozin	1						
Bays2014	2	93	2	89	3.2%	0.96 [0.14, 6.65]	
Bode 2013 Devineni 2014	4	241 10	1	237 9	1.6% 3.3%	3.93 [0.44, 34.94]	
Forst 2014	9	113	4	9 115	5.3% 6.3%	0.45 [0.05, 4.16] 2.29 [0.73, 7.22]	
avalle-Gonzalez 2013	2	368	1	183	2.1%	0.99 [0.09, 10.90]	
Leiter 2014	8	483	11	482	17.4%	0.73 [0.29, 1.79]	
Li 2014	1	223	0	226	0.8%	3.04 [0.12, 74.23]	
Rosenstock 2013 Stenlöf 2014	4 3	64 195	1	65 192	1.6% 1.6%	4.06 [0.47, 35.37] 2.95 [0.31, 28.15]	
Wilding 2013	1	157	3	152	4.8%	0.33 [0.03, 3.15]	
Yale 2013	1	90	ō	90	0.8%	3.00 [0.12, 72.68]	
Subtotal (95% CI)		2037		1844	43.5%	1.32 [0.81, 2.15]	-
Fotal events Heterogeneity: Chi ² = 8.08, c Fest for overall effect: Z = 1.			26 ?); I² = 0%				
2.20.3 200mg canaglifiozin							
Rosenstock 2013	3	65	1	65	1.6%	3.00 [0.32, 28.09]	
Subtotal (95% CI)	~	65		65	1.6%	3.00 [0.32, 28.09]	
Total events Heterogeneity: Not applicabl	3 le		1				
Test for overall effect: Z = 0.		0.34)					
2.20.4 300mg canagliflozin			~		3 90/	1 95 10 25 0 00	
Bays2014 Bode 2013	4	96 236	2	89 237	3.3% 1.6%	1.85 [0.35, 9.88] 4.02 [0.45, 35.67]	
Devineni 2014	ō	10	2	- 9	4.2%	0.18 [0.01, 3.35]	<
Forst 2014	5	114	4	115	6.3%	1.26 [0.35, 4.58]	
Lavalle-Gonzalez 2013 Leiter 2014	3	367	1	183	2.1%	1.50 [0.16, 14.28]	
Leiter 2014 Li 2014	12 0	485 227	11 0	482 226	17.5%	1.08 [0.48, 2.43] Not estimable	[
Rosenstock 2013	1	64	1	65	1.6%	1.02 [0.06, 15.89]	
Schernthaner 2013	0	378	3	378	5.5%	0.14 [0.01, 2.76]	·
Stenlöf 2014 Milding 2013	4 6	197	1 3	192	1.6%	3.90 [0.44, 34.57]	
Wilding 2013 Yale 2013	6 3	156 89	3	156 90	4.8% 0.8%	2.00 [0.51, 7.86] 7.08 [0.37, 135.07]	
Subtotal (95% CI)	v	2419	5	2222	49.2%	1.36 [0.86, 2.15]	►
Total events	42		29				
Test for overall effect: Z = 1. Total (95% CI) Total events	32 (P =	4683	59	4285	100.0%	1.36 [0.99, 1.88]	<u> </u>
Total (95% CI) Total events Heterogeneity: Chi ² = 17.36, Fest for overall effect: Z = 1.	85 df = 24 88 (P =	0.19) 4683 (P = 0.8 0.06)	59 3); I² = 0	4285 %		1.36 [0.99, 1.88]	0.01 0.1 1 10 100 Favours [control]
Total (95% CI) Total events Heterogeneity: Chi ² = 17.36, Fest for overall effect: Z = 1. Test for subgroup difference	85 df = 24 88 (P = s: Chi ² =	0.19) 4683 (P = 0.8 0.06) = 0.52. d	59 33); I² = 0 f = 3 (P =	4285 % : 0.91).			Favours [experimental] Favours [control]
Total (95% CI) Total events Heterogeneity: Chi ² = 17.36, Fest for overall effect: Z = 1. Test for subgroup difference Ca	85 , df = 24 88 (P = 1 s: Chi ² =	0.19) 4683 (P = 0.8 0.06) = 0.52. d ozin	59 33); I ² = 0 f = 3 (P = Placel	4285 % = 0.91).	l² = 0%	1.36 [0.99, 1.88] Risk Ratio <u>M-H, Fixed, 95% C</u>	Favours [experimental] Favours [control] Risk Ratio
Total (95% CI) Total events Heterogeneity: Chi ² = 17.36, Fest for overall effect: Z = 1. Test for subgroup difference Ca Study or Subgroup Event 2.21.1 50 mg CanagliffozI	85 , df = 24 88 (P = 1 88 (P = 1 88 (P = 1 9 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	0.19) 4683 (P = 0.8 0.06) = 0.52. d ozin Total	59 33); I ² = 0 f = 3 (P = Placet Events	4285 % : 0.91). : : : : : : : : : : : : : : : : : : :	l² = 0% Weight	Risk Ratio M-H, Fixed, 95% C	Favours [experimental] Favours [control] Risk Ratio
Total (95% CI) Total events Heterogeneity: Chi ² = 17.36, Test for overall effect: Z = 1. Test for subgroup difference Ca Study or Subgroup Ev 2.21.1 50 mg Canaglifiozi Bays2014	82 (P = 85 , df = 24 88 (P = s: Chi ² = anagliffe rents n 17	0.19) 4683 (P = 0.8 0.06) = 0.52. d ozin Total 98	59 33); ² = 0 f = 3 (P = Placet Events 9	4285 % : 0.91). : : : : : : : : : : : : : : : : : : :	² = 0% <u>Weight</u> 18.3%	Risk Ratio M-H, Fixed, 95% C 1.72 [0.81, 3.65]	Favours [experimental] Favours [control] Risk Ratio M-H, Fixed, 95% Cl
Total (95% CI) Total events Heterogeneity: Chi ² = 17.36, Fest for overall effect: Z = 1. Test for subgroup difference Cz Study or SubgroupEv 2.21.1 50 mg Canaglifiozi Bays2014 Bays2013	82 (P = 85 df = 24 88 (P = s: Chi ² = anagliffe rents 17 3	0.19) 4683 (P = 0.8 0.06) = 0.52. d ozin Total 98 82	59 3); ² = 0 f = 3 (P = Placel Events 9 3	4285 % : 0.91). : : : : : : : : : : : : : : : : : : :	² = 0% <u>Weight</u> 18.3% 6.1%	Risk Ratio M-H. Fixed, 95% C 1.72 [0.81, 3.65] 0.91 [0.19, 4.39]	Favours [experimental] Favours [control] Risk Ratio M-H, Fixed, 95% Cl
Total (95% CI) Total events Heterogeneity: Chi ² = 17.36, Test for overall effect: Z = 1. Test for subgroup difference Ca Study or Subgroup Ev 2.21.1 50 mg Canaglifiozi Bays2014	82 (P = 85 , df = 24 88 (P = s: Chi ² = anagliffe rents n 17	0.19) 4683 (P = 0.8 0.06) = 0.52. d ozin Total 98	59 13); ² = 0 f = 3 (P = Placet Events 9	4285 % : 0.91). : : : : : : : : : : : : : : : : : : :	² = 0% <u>Weight</u> 18.3%	Risk Ratio <u>M-H, Fixed, 95% C</u> 1.72 [0.81, 3.65] 0.91 [0.19, 4.39] 2.03 [0.39, 10.70]	Favours [experimental] Favours [control] Risk Ratio M-H. Fixed, 95% Cl
Total (95% CI) Total events Heterogeneity: Chi ² = 17.36, Test for overall effect: Z = 1. Test for subgroup difference Ca Study or Subgroup Effect Rays2014 Inagaki 2013 Rosenstock 2013	82 (P = 85 df = 24 88 (P = s: Chi ² = anagliffe rents 17 3	0.19) 4683 (P = 0.8 0.06) = 0.52. d ozin Total 98 82 64	59 3); ² = 0 f = 3 (P = Placel Events 9 3	4285 % : 0.91). : : : : : : : : : : : : : : : : : : :	I ² = 0% Welght 18.3% 6.1% 3.9%	Risk Ratio M-H. Fixed, 95% C 1.72 (0.81, 3.65) 0.91 (0.19, 4.39)	Favours [experimental] Favours [control] Risk Ratio M-H. Fixed, 95% Cl
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Figure 3. Safety profile of canagliflozin compared with active agents or placebo in forest plot. A: Genital infection; B: Vulvovaginal mycotic infection; C: Urinary tract infection; D: Hypoglycaemia; E: Severe hypoglycaemia; F: Dealth; G: Nasopharyngitis; H: Upper respiratory inflammation; I: Headache; J: Dizziness; K: Nausea; L: Diarrhea; M: Osmotic diuresis related AEs; N: Volume depletion related AEs; O: GI related AEs.

(Figure 3D), but it did not increase the risk ofsevere hypoglycaemia (RR=1.01; 95% CI (0.67-1.52); P=0.96; l^2 =0%) (Figure 3E).

Death

A total of 8 RCTs (n=7402) reported 23 deaths. Canagliflozin was associated with a lower death rate (RR 0.84; 95% CI (0.40-1.76); P=0.64; l^2 =0%) (**Figure 3F**).

Nasopharyngitis and upper respiratory inflammation

Canagliflozin was revealed to have a relatively lower risk of nasopharyngitis (RR 0.81; 95% Cl (0.58-1.13); P=0.21; $l^2=0\%$) (Figure 3G). However, canagliflozin was associated with a slightly higher risk of upper respiratory inflammation (RR 1.29; 95% Cl (0.73-2.27); P=0.39; $l^2=0\%$) (Figure 3H).

Headache and dizziness

Canagliflozin did not increase the risk of headache (RR 1.18; 95% Cl (0.76-1.82); P=0.46; $l^2=0\%$) (**Figure 3I**), or the incidence of dizziness (RR 1.01; 95% Cl (0.45-2.28); P=0.98; $l^2=0\%$) (**Figure 3J**).

Nausea and diarrhea

A total of 38 patients were identified with nausea among 3 RCTs (n=1109). Canagliflozin was associated with a higher risk of nausea(RR 2.36; 95% CI (1.24-4.50); P=0.009; l^2 =0%) (**Figure 3K**). However, canagliflozin was associated with a slightly lower incidence of diarrhea (RR 0.66; 95% CI (0.36-1.18); P=0.16; l^2 =0%) (**Figure 3L**).

Other adverse events

Canagliflozinwas revealed to have a strongly higher risk of osmotic diuresis related AEs (RR 2.95; 95% CI (2.26-3.85); P< 0.00001; I^2 =0%) (**Figure 3M**), and it slightly increase the risk of volume depletion related AEs(RR 1.36; 95% CI (0.99-1.88); P=0.06; I^2 =0%) (**Figure 3N**). However, canagliflozin did not increase the risks of GI related AEs (RR 1.11; 95% CI (0.78-1.59); P=0.55; $I^2=0\%$) (Figure 30). In addition, Bays et al. [26] also reported 9 cases of sinusitis in canagliflozin group, 10 cases of constipation in canagliflozin group and 6 cases in control group. Rosenstock et al. [25] reported 8 cases of pollakiuria in canagliflozin group and 4 in control group.

Discussion

This systematic review provided themost up-todate summary considering thesafety of canagliflozin as of February 2015.In this meta-analysis, we compared canagliflozinwith placebo or other AHAs from safety aspect. The results demonstrated that canagliflozin significantly increase the risk of genital infections, osmotic duresis related AEs, vulvovaginal mycotic infection and nausea. Canagliflozin was also associated with a slightly increased risk of volume depletion related AEs, upper respiratory inflammation, and hypoglycaemia, but it didn't increase the risk of severe hypoglycemia, UTI, GI related AEs or dizziness.

The meta-analysis showed that canagliflorin act well as an add-on drug to previous conventional AHAs in terms of safety. Previous RCTs demonstrated that a more severe situation of insulin resistance and other complications was made by many AHAsin T2DM patients [8]. For instance, sulphonulureas, glitazonesand insulin lead to weight gain, sulphonylureas and insulin lead to hypoglycaemia and pioglitazone can lead to edema, heart failure and fractures [16]. In our study, canagliflozin showed well tolerance among T2DM patients and most of the AEs mentioned above were hardly significant during the treatment.

The optimum dose of canagliflozin for T2DM treatment remains controversial. In most of included RCTs, 100 and 300 mg canagliflozin were adopted. Previous evidences suggested the preferred dose of canagliflozin was 100 mg per day since AEs appeared to be moderate, and higher dosage would not lead to improvement in efficiency [15]. From economy aspect, canagliflozin appears to be less competitive compared with sulphonylureas [16].

However, canagliflozin could be the first choice for those T2DM patients who are insufficiently controlled or having problems tolerating conventional drugs like metformin and sulphonylureas.

AEs were evaluated in all RCTs included in this meta-analysis. Overall, canagliflozin was well tolerated in most of the trials. Most of the AEs were mild and transient. Some AEs like genital infection and osmotic duresis were significantly enhanced in canagliflozin groups compared with control. The incidences of some serious AEs like death were slightly lower across placebo andcontrol agents.

UTIs

It is obvious that glucosuria caused by treatment of canagliflozin is likely to induce UTI since glucose is the culture medium of bacteria. Some trails did show the increase risk of UTI, while in our study the incidence of UTI didn't increase with canagliflozin treatment compared with control. UTIs were very common in canagliflozin but usually moderate and responded well to normal therapy. The mechanisms remain controversial. It may be attributed to the increased glycosuria which may predispose to bacteria [15]. Since the results showed that canagliflozin was related to a higher risk of UTIs, T2DM patients treating with canagliflozin should be noted to report clinical signs and symptoms of UTIs to their physicians in time. A monitor for UTIs is appropriate to prevent furtherrenal infections. Future RCTs are expected to evaluate the safety of canagliflozin among patients with renal disfunction

Genetic mycotic infection

Genetic mycotic infectionshowed strong correlations with canagliflozin in our study. Fortunately, the infections are usually not serious and are easy to treat. Nevertheless, both patients and doctors should pay close attention to it.The increased genetic mycotic infection could be related to the increase in urinary glucose excretion by canagliflozin. Infection recurrent frequently and patients with history of genital mycotic infections are more prone to develop this type of infection [37]. Canagliflozin was revealed to increase the incidence of renalrelated AEs in subjectswith moderate renal impairment more easily compared with control. In that case, patients with mild tomoderate renal insufficiency should monitor kidney functionand adjust the dosage more carefully.

Osmotic diuresis

Osmotic diuresis is another AE that strongly correlated with canagliflozin treatment. Indeed, the osmotic diuresis we discussed is distinct from classical osmotic diuresis for the loss of sodium, which may attributed to the co-transport with glucose by SGLT2 [9]. Osmotic diuresis along with volume depletion may contribute to the decrease in blood pressure, hypotension, postural dizziness, which may attribute to improvement of T2DM.

Hypoglycemia

Given the mechanism of SGLT2 receptor inhibitors, the risk and severity of hypoglycaemia would be expected to be low. The majority of glucose reabsorption is managed by the early proximal renal tubule in kidney, where SGLT2 is mainly expressed [38, 39]. The threshold for hypoglycemia (RTG) is 72 mg/dL, and the RTG is among 80 to 90 mg/dL with canagliflozin treatment [36], which is not low enough to cause severe hypoglycemia. The background treatment like metformin is presented as the high risk factors to hypoglycemia incidence [40]. Similarly, one previous study carried out by Nauck et al. [41] found that the incident of hypoglycaemia is notably higher in the sulphonyurea group than that in canagliflozin group.The presented meta-analysis also concluded that canaglflozin did not increase the incidence of severe hypoglycemia.Moreover, the ADA guidelines emphasized the necessity to add SGLT2 inhibitor in the treatment of T2DM in order to prevent hypoglycemiawhile reduce the dose of other AHAs (including insulin) at the same time [2].

Other AEs

Other sideeffects include:dizziness, headache, upper respiratory inflammation, nausea, Gl related AEs, death, nasopharyngitis and diarrhea. Interestingly, canagliflozinwas associated with a lower risk of diarrhea, death or nasopharyngitis.Several rare AEs that were reported in a single research like increased blood ketone bodies, hypoglycaemia unawareness, gastrointestinal disorders, malaise and pollakiuriawere not included in meta-analysis.

Totally3 systemic reviews [14-16] had assessed the efficacy and safety of the SGLT2 inhibitors (including canagliflorin)in the treatment of T2DM. To compare, our review had several differences and stimulating points. First, only one RCT of canagliflozin was enrolled in Clar [16] and Musso's [15] research, while we included 13 RCTs that solely focus on canagliflozin; Second, they accessed both efficiency and safety while our meta-analysis was dedicated to safety assessment, which would be more specific.In our study, 14 RCTs were included and were divided into 4 subgroups based on the dosage of canagliflozin. 100 mg and 300 mg dosage groups were adopted in most RCTs, whereas the 50 mg and 200 mg groups were only included in 3 RCTs [2, 25, 26], and 1209 patients were enrolled to that arm. Actually, no significant differences were detected between subgroups with different doses. In order to keep the constancy of the meta-analysis, we adopted the overalleffects of each particular AE, regardless of its subgroups. Plus, statics in this meta-analysis showed that the SGLT2 receptor inhibitors might be especially useful in patients with longer duration. The capacity of β cell was diminishedunder long-termtreatment of other agents like sulphonylureas.

There were no strict limitations of the application of canagloflozin. These findings may help physicians make advisable decision for the treatment of T2DM. However, some limitations should be noted in this meta-analysis: 1) The limited number of existing RCTs may increase the risk of overestimating the R² in metaregression, 2) For each AE, we used the whole effects of ranged dose of canagliflozin to keep consistency of the study. However, if significant differences appeared between subgroups, they were discussed separately. 3) Fiveof the included RCTs were sponsored by institutions or corporations, which might introduce some potential bias, due to a concern that industry funding was strongly associated with favorable outcomes. We will update out meta-analysis with further RCTs that have proper registration and less potential biases. 4) There were some additional issues that should be noted in post-marketing surveillance including relationships with cardiovascular events and weight loss, decrease in blood pressure and safety of the appliance in children and pregnancy with T2DM.

Generally, our meta-analysis focused on the overall safety of canagliflozin, disregarded the duration and sample capacity. However, before clinical practicing, evaluation for long-term safety of canagliflozin is needed, which requiresRCTs with adequate power and duration. In conclusion, canagliflorin was a relatively safe T2DM drugs both for monotherapy and add-on treatment assessed from existing researches, but the increased risk of genital infection, osmotic duresis related AEs and nausea should not be neglected.

Disclosure of conflict of interest

None.

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