

# Comparative safety of the sodium glucose co-transporter 2 (SGLT2) inhibitors: A systematic review and meta-analysis.

## Online Appendix

### Section 1: Search Strategies

Table 1A. Pubmed Search Strategy

		Search String	Results
1	<b>Population</b>	"Diabetes Mellitus, Type 2"[Mesh] OR NIDDM[tw] OR t2dm[tw] OR (("type 2"[tw] OR "type ii"[tw] OR "adult onset"[tw] OR "mature onset"[tw] OR "late onset"[tw] OR "noninsulin-dependent"[tw] OR "non insulin dependent"[tw]) AND diabetes[tw])	167100
2	<b>Intervention: SGLT2s</b>	"Sodium-Glucose Transport Proteins/antagonists and inhibitors"[Mesh] OR "Sodium-Glucose Transporter 2"[Mesh] OR "sodium-glucose co-transporter 2"[tw] OR SGL2[tw] OR SGLT2[tw] OR gliflozin*[tw] OR "Canagliflozin"[Mesh] OR canagliflozin*[tw] OR invokana[tw] OR sulisent[tw] OR "TA 7284"[tw] OR TA7284[tw] OR "JNJ 28431754"[tw] OR JNJ28431754[tw] OR "2-(3-(4-ethoxybenzyl)-4-chlorophenyl)-6-hydroxymethyltetrahydro-2H-pyran-3,4,5-triol"[Supplementary Concept] OR dapagliflozin*[tw] OR farxiga[tw] OR forxiga[tw] OR "BMS 512148"[tw] OR BMS512148[tw] OR "empagliflozin"[Supplementary Concept] OR empagliflozin*[tw] OR jardiance[tw] OR "BI 10773"[tw] OR BI10773[tw] OR ipragliflozin[Supplementary Concept] OR ipragliflozin*[tw] OR suglat[tw] OR "ASP 1941"[tw] OR ASP1941[tw] OR "1,5-anhydro-1-(5-(4-ethoxybenzyl)-2-methoxy-4-methylphenyl)-1-thioglutitol"[Supplementary Concept] OR luseogliflozin*[tw] OR lusefi[tw] OR "TS 071"[tw] OR TS071[tw] OR "remogliflozin etabonate"[Supplementary Concept] OR remogliflozin*[tw] OR "KGT 1681"[tw] OR KGT1681[tw] OR "(2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triol" [Supplementary Concept] OR sotagliflozin*[tw] OR "LX 4221"[tw] OR LX4221[tw] OR "6-((4-ethylphenyl)methyl)-3',4',5',6'-tetrahydro-6'-(hydroxymethyl)spiro(isobenzofuran-1(3H),2'-(2H)pyran)-3',4',5'-triole"[Supplementary Concept] OR tofogliflozin*[tw] OR apleway[tw] OR deberza[tw] OR "CSG 452"[tw] OR CSG452[tw] OR "5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-1-hydroxymethyl-6,8-dioxabicyclo(3.2.1)octane-2,3,4-triole"[Supplementary Concept] OR ertugliflozin*[tw] OR "PF 04971729"[tw] OR PF04971729[tw]	2936
3	<b>#1 AND #2</b>		2080
4	<b>Study Type Filter: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and</b>	("randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR randomized[tiab] OR placebo[tiab] OR "clinical trials as topic"[Mesh:NoExp] OR randomly[tiab] OR trial[tij] NOT (animals[mh] NOT humans[mh]))	1065055

	precision-maximizing version (2008 revision). Available at <a href="http://handbook.cochrane.org/chapter_6/box_6.4_box_cochrane_hss_2008_sensprec_publications_bmed.htm">http://handbook.cochrane.org/chapter_6/box_6.4_box_cochrane_hss_2008_sensprec_publications_bmed.htm</a>		
5	#3 AND #4		743

Table 2A: Cochrane Library Search Strategy

#1	([mh "Diabetes Mellitus, Type 2"] or NIDDM or t2dm or ("type 2" or "type ii" or "adult onset" or "mature onset" or "late onset" or "noninsulin-dependent" or "non insulin dependent") and (diabetes))	25,454
#2	([mh "Sodium-Glucose Transport Proteins"/ai] or [mh "Sodium-Glucose Transporter 2"] or "sodium-glucose co-transporter 2" or SGL2 or SGLT2 or gliflozin* or [mh canagliflozin] or canagliflozin* or invokana or sulisent or "TA 7284" or TA7284 or "JNJ 28431754" or JNJ28431754 or dapagliflozin* or farxiga or forxiga or "BMS 512148" or BMS512148 or empagliflozin* or jardiance or "BI 10773" or BI10773 or ipragliflozin or suglat or "ASP 1941" or ASP1941 or luseogliflozin* or lusefi or "TS 071" or TS071 or remogliflozin* or "KGT 1681" or KGT1681 or sotagliflozin* or "LX 4221" or LX4221 or tofogliflozin* or apleway or deberza or "CSG 452" or CSG452 or ertugliflozin* or "PF 04971729" or PF04971729)	1,082
#3	#1 AND #2	959

Table 3A: Embase Search Strategy

No.	Query	Results
#5	#3 AND #4	2,016
#4 - EMBASE RCT filter from Wong 2006, best balance of sensitivity and specificity	random*:ab,ti OR placebo*:de,ab,ti OR (double NEXT/1 blind*):ab,ti	1,533,336
#3	#1 AND #2	4,869
#2	'sodium glucose cotransporter 2'/de OR 'sodium glucose cotransporter 2 inhibitor'/exp OR 'sodium-glucose co-transporter 2':ab,ti OR sgl2:ab,ti OR sglT2:ab,ti OR gliflozin*:ab,ti OR canagliflozin*:ab,ti OR invokana:ab,ti OR sulisent:ab,ti OR 'ta 7284':ab,ti OR ta7284:ab,ti OR 'jnj 28431754':ab,ti OR jnj28431754:ab,ti OR dapagliflozin*:ab,ti OR farxiga:ab,ti OR forxiga:ab,ti OR 'bms 512148':ab,ti OR bms512148:ab,ti OR empagliflozin*:ab,ti OR jardiance:ab,ti OR 'bi 10773':ab,ti OR bi10773:ab,ti OR ipragliflozin*:ab,ti OR suglat:ab,ti OR 'asp 1941':ab,ti OR asp1941:ab,ti OR luseogliflozin*:ab,ti OR lusefi:ab,ti OR 'ts 071':ab,ti OR ts071:ab,ti OR remogliflozin*:ab,ti OR 'kgt 1681':ab,ti OR kgt1681:ab,ti OR sotagliflozin*:ab,ti or 'LX 4221':ab,ti or LX4221:ab,ti or tofogliflozin*:ab,ti or apleway:ab,ti or deberza:ab,ti or 'CSG 452':ab,ti or CSG452:ab,ti or ertugliflozin*:ab,ti or 'PF 04971729':ab,ti or PF04971729:ab,ti	6,675
#1	'non insulin dependent diabetes mellitus'/de OR niddm:ab,ti OR t2dm:ab,ti OR ('type 2':ab,ti OR 'type ii':ab,ti OR 'adult onset':ab,ti OR 'mature onset':ab,ti OR 'late onset':ab,ti OR 'noninsulin dependent':ab,ti OR 'non insulin dependent':ab,ti AND diabetes:ab,ti)	258,521

Table 4A: IPA Search Strategy

#	Query	Limiters/Expanders	Results
S1	TX NIDDM OR t2dm OR (("type 2" OR "type ii" OR "adult onset" OR "mature onset" OR "late onset" OR "noninsulin dependent" OR "non insulin dependent") AND (diabetes))	Search modes - Boolean/Phrase	6,110
S2	TX "sodium-glucose co-transporter 2" OR sgl2 OR sgl2 OR gliflozin OR canagliflozin OR invokana OR sulisent OR "ta 7284" OR ta7284 OR "jnj 28431754" OR jnj28431754 OR dapagliflozin* OR farxiga OR forxiga OR "bms 512148" OR bms512148 OR empagliflozin* OR jardiance OR "bi 10773" OR bi10773 OR ipragliflozin* OR suglat OR "asp 1941" OR asp1941 OR luseogliflozin* OR lusefi OR "ts 071" OR ts071 OR remogliflozin* OR "kgt 1681" OR kgt1681 OR sotagliflozin* OR "LX 4221" OR LX4221 OR tofogliflozin* OR apleway OR deberza OR "CSG452" OR CSG452 OR ertugliflozin* OR "PF 04971729" OR PF04971729	Search modes - Boolean/Phrase	337
S3	S1 AND S2	Search modes - Boolean/Phrase	267
S4	TI randomized OR AB randomized OR TI randomised OR AB randomised OR TI placebo OR AB placebo OR TI randomly OR AB randomly OR TI trial	Search modes - Boolean/Phrase	59,232
S5	S3 AND S4	Search modes - Boolean/Phrase	130

Table 5A: ProQuest Search Strategy

all(NIDDM OR t2dm OR (("type 2" OR "type ii" OR "adult onset" OR "mature onset" OR "late onset" OR "noninsulin-dependent" OR "non insulin dependent") AND (diabetes))) AND all("sodium-glucose co-transporter 2" OR SGL2 OR SGLT2 OR gliflozin* OR canagliflozin* OR invokana OR sulisent OR "TA 7284" OR TA7284 OR "JNJ 28431754" OR JNJ28431754 OR dapagliflozin* OR farxiga OR forxiga OR "BMS 512148" OR BMS512148 OR empagliflozin* OR jardiance OR "BI 10773" OR BI10773 OR ipragliflozin OR suglat OR "ASP 1941" OR ASP1941 OR luseogliflozin* OR lusefi OR "TS 071" OR TS071 OR remogliflozin* OR "KGT 1681" OR KGT1681 OR sotagliflozin* OR "LX 4221" OR LX4221 OR tofogliflozin* OR apleway OR deberza OR "CSG 452" OR CSG452 OR ertugliflozin* OR "PF	3
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04971729" OR PF04971729)

## Section 2: List of Extracted Variables

Table 6A. List of Extracted Variables

Variable Extraction	Notes
NCT Number, Author and Year	
Country in which the study was conducted	International if applicable
Start and End years	
Observation Period (# of weeks)	
Total number of participants randomized	
Number of Males	
Number of Females	
Background diabetes therapy	
Intervention 1: SGLT2 Agent	This was captured for as many interventions that were used.
Intervention 1: Dose	
Intervention 1: Number of Persons	
Intervention 1: Mean Age	
Intervention 1: Age SD	
Intervention 1: Mean baseline HbA1C	
Intervention 1: A1C SD	
Comparison 1: SGLT2 Agent	This was captured for as many comparison groups that were used.
Comparison 1: Dose	
Comparison 1: Number of Persons	
Comparison 1: Mean Age	
Comparison 1: Age SD	
Comparison 1: Mean baseline HbA1C	
Comparison 1: A1C SD	
Acute Kidney Injury Reported (yes/no)	
Urinary Tract Infection Reported (yes/no)	
Definition of UTI	
Ketoacidosis Reported (yes/no)	
Bone Fracture Reported (yes/no)	
Amputation Reported (yes/no)	
AKI: Outcomes in Intervention 1(n/N)	This was captured for each individual intervention and control group
AKI: Outcomes in Comparison 1 (n/N)	
UTI: Outcomes in Intervention 1(n/N)	
UTI: Outcomes in Comparison 1 (n/N)	

DKA: Outcomes in Intervention 1(n/N)	
DKA: Outcomes in Comparison 1 (n/N)	
BF: Outcomes in Intervention 1(n/N)	
BF: Outcomes in Comparison 1 (n/N)	
Amp: Outcomes in Intervention 1(n/N)	
Amp: Outcomes in Comparison 1 (n/N)	

### Section 3: Study Characteristics

Table 7A: Included Study Characteristics

NCT# Author and Year	Country	Study Duration (weeks)	Total Randomized	Background Therapies	Intervention(s)	Comparator(s)	Outcomes Reported
NCT01059825 Amin, 2015	International	12	328	Prior therapy stabilized to metformin	Ertugliflozin 1mg, 5 mg, 10mg , 25mg	Placebo, Sitagliptin 100mg	UTI
NCT01059825 Amin, 2015	International	4	194	Uncontrolled on 2 agents	Ertugliflozin 1mg, 5mg, 25mg	Placebo	UTI
NCT02157298 Araki, 2016	Japan	16	182	Prior insulin therapy DPP4 allowed	Dapagliflozin 5 mg	Placebo	UTI, BF
NCT01368081 Araki	Japan	52	1160	Prior SU	Empagliflozin 10mg, 25mg	Metformin 50- 2250mg/day	UTI, BF
NCT00528879 Bailey, 2013	International	102	546	Prior metformin	Dapagliflozin 2.5mg, 5mg, 10mg	Placebo	UTI, AKI, BF
None Bailey, 2012	International	24	282	Treatment Naive	Dapagliflozin 1mg, 2.5mg, 5mg	Placebo	UTI, AKI, BF
NCT01164501 Barnett, 2014	International	52	741	Any prior therapies	Empagliflozin 10mg, 25mg	Placebo	UTI, DKA, BF
NCT01106651 Bode, 2015	International	104	716	Prior Naive mono or combo therapy	Canagliflozin 100mg, 300mg	Placebo	UTI, DKA, BF
NCT00855166 Bolinder, 2014	European	102	182	Prior metformin	Dapagliflozin 10mg	Placebo	UTI, BF
NCT01031680 Cefalu, 2015	International	52	922	Any prior therapies	Dapagliflozin 10mg	Placebo	UTI, AKI, BF
NCT01505426 Lu, 2016	Korea and Taiwan	24	171	Prior metformin	Ipragliflozin 50mg	Placebo	UTI, BF
NCT01422876 DeFronzo, 2015	International	52	686	Prior metformin	Empagliflozin 10mg, 25mg	Linagliptin 5mg	UTI
NCT00660907 Prato, 2015	International	208	816	Prior metformin	Dapagliflozin (mixed dose)	Glipizide (mixed doses)	UTI, BF

NCT00881530 Ferrannini, 2013	International	78	271	Treatment Naive	Empagliflozin 10mg, 25mg	Metformin 2000mg max	UTI, BF
NCT00881530 Ferrannini, 2013	International	78	388	Prior metformin	Empagliflozin 10mg, 25mg	Sitagliptin 100mg	UTI, BF
NCT00528372 Ferrannini, 2010	International	24	485	Treatment Naive	Dapagliflozin 2.5mg, 5mg, 10mg	Placebo	UTI
NCT01071850 Fonseca, 2013	India, Philippines, Columbia, Mexico, USA	12-	412	Treatment Naive	Ipragliflozin 12.5mg, 50mg, 150mg, 300mg	Placebo, Metormin 1500mg	UTI
NCT02229396 Frias, 2016	International	28	695	Prior metformin	Dapagliflozin 10mg	Exenatide 2mg	UTI, AKI, DKA
NCT01719003 Hadjadj, 2016	International	24	1364	Treatment Naive	Empagliflozin 10mg, 25mg	Metformin 1000mg, 2000mg	UTI, DKA, BF
NCT01289990 Haering, 2015	International	76	666	Prior Metformin and SU	Empagliflozin 10mg, 25mg	Placebo	UTI
None Heise, 2013	Germany	4	78	Not described	Empagliflozin 10mg, 25mg, 100mg	Placebo	UTI
None Heise, 2013	Germany	9 days	48	Prior Naive mono or combo therapy	Empagliflozin 2.5mg, 10mg, 25mg, 100mg	Placebo	UTI
NCT00643851 Henry, 2012	International	24	603	Treatment Naive	Dapagliflozin 5mg	Placebo	UTI, BF
NCT00643851 Henry, 2012	International	24	603	Treatment Naive	Dapagliflozin 5mg	Metformin (mixed doses)	UTI, BF
NCT00859898 Henry, 2012	International	24	641	Treatment Naive	Dapagliflozin 10mg	Placebo	UTI, BF
NCT00859898 Henry, 2012	International	24	641	Treatment Naive	Dapagliflozin 10mg	Metformin (mixed doses)	UTI, BF
NCT00800176 Ikeda; 2015	International	12	398	Naive or metformin	Tofogliflozin 2.5mg, 5mg, 10mg, 20mg, 40mg	Placebo	UTI, DKA
NCT02220920 Inagaki, 2016	Japan	16	146	Prior insulin therapy	Canagliflozin 100mg	Placebo	UTI, DKA, BF
NCT01387737 Inagaki, 2015	Japan	52	1299	Any prior therapies washed-out	Canagliflozin 100mg, 200mg	No comparator	UTI, DKA, BF



NCT01022112 Inagaki, 2013	Japan	12	383	Any prior therapies washed-out	Canagliflozin 50mg, 100mg, 200mg, 300mg	Placebo	UTI, BF
NCT01413204 Inagaki, 2014	Japan	24	272	Any prior therapies washed-out	Canagliflozin 100mg, 200mg	Placebo	UTI, BF
NCT02175784 Ishihara, 2016	Japan	16	262	Prior insulin others allowed	Ipragliflozin 50mg	Placebo	UTI
NCT00984867 Jabbour, 2013	International	48	451	Prior DPP4 maybe metformin no others	Dapagliflozin 10mg	Placebo	UTI, BF
NCT01381900 Ji, 2015	International	18	678	Prior Metformin and maybe SU	Canagliflozin 100mg, 300mg	Placebo	UTI, BF
NCT01095653 Ji, 2014	Asia	24	393	Treatment Naive	Dapagliflozin 5mg, 10mg	Placebo	UTI, BF
NCT01023945 Kadokura, 2014	Japan	2	30	Treatment Naive or monotherapy	Ipragliflozin 50mg, 100mg	Placebo	UTI
NCT01193218 Kadowaki, 2015	Japan	52	547	Treatment Naive or monotherapy	Empagliflozin 10mg, 25mg	No comparator	UTI, BF
NCT00972244 Kaku, 2013	Japan	12	279	Treatment Naive or 1 or 2 agents at low dose	Dapagliflozin 1mg, 2.5mg, 5mg, 10mg	Placebo	UTI, BF
None Kaku, 2014	Japan	24	261	Treatment Naive or monotherapy	Dapagliflozin 5mg, 10mg	Placebo	UTI, BF
None Kaku, 2014	Japan	24	235	Treatment Naive or washout	Tofogliflozin 10mg, 20mg, 40mg	Placebo	UTI, BF
NCT01242215 Kashiwagi, 2015	Japan	52	245	Prior SU	Ipragliflozin 50mg	Placebo	UTI
NCT01057628 Kashiwagi, 2015	Japan	26	131	Treatment Naive or 1 or 2 agents at low dose	Ipragliflozin 50mg	Placebo	UTI
NCT00621868 Kashiwagi, 2014	Japan	12	361	Treatment Naive or washout	Ipragliflozin 12.5mg, 25mg, 50mg, 100mg	Placebo	UTI
NCT01316094 Kashiwagi, 2015	Japan	52	165	Treatment Naive or 1 or 2 agents at low dose	Ipragliflozin 50mg	Placebo	UTI

NCT00663260 Kohan, 2014	International	104	252	Not described	Dapagliflozin 5mg, 10mg	Placebo	UTI, AKI, BF
NCT01210001 Kovacs, 2015	International	76	499	Prior pioglitazone and maybe metformin	Empagliflozin 10mg, 25mg	Placebo	UTI, BF
NCT00976495 Heerspink, 2013	International	12	75	Prior Metformin and maybe SU	Dapagliflozin 10mg	Placebo	UTI
NCT01106677 Lavalle-Gonzalez, 2013	International	52	1284	Prior Metformin and maybe SU but washed-out	Canagliflozin 100mg, 300mg	Sitagliptin 100mg	UTI, DKA, BF
NCT01042977 Leiter, 2014	International	52	964	Any prior therapies	Dapagliflozin 10mg	Placebo	UTI, AKI, BF
NCT00968812 Leiter, 2015	International	104	1450	Prior metformin	Canagliflozin 100mg, 300mg	Glimepiride 8mg	UTI, BF
NCT01422876 Lewin, 2015	International	52	677	Treatment Naive	Empagliflozin 10mg, 25mg	Linagliptin 5mg	UTI
NCT00263276 List, 2008	International	12	389	Treatment Naive	Dapagliflozin 2.5mg, 5mg, 10mg, 20mg, 50mg	Placebo, Metformin 1500mg max	UTI
NCT01646320 Mathieu, 2015	International	52	320	Prior metformin and DPP4	Dapagliflozin 10mg	Placebo	UTI, BF
NCT01392677 Matthaei, 2015	International	52	219	Prior Metformin and SU	Dapagliflozin 10mg	Placebo	UTI
None Mudaliar, 2013	International	12	44	Prior Metformin and maybe SU	Dapagliflozin 5mg	Placebo	UTI
NCT01947855 Nishimura, 2015	Japan	4	60	Treatment or monotherapy	Empagliflozin 10mg, 25mg	Placebo	UTI, DKA
NCT01340664 Qiu, 2014	International	18	279	Prior metformin	Canagliflozin 100mg, 300mg	Placebo	UTI
NCT01989754 Rodbard, 2016	International	26	218	Prior metformin and DPP4	Canagliflozin 300mg	Placebo	UTI, DKA, BF
NCT01289990 Roden, 2015	International	76	899	Treatment Naive	Empagliflozin 10mg, 25mg	Placebo, Sitagliptin 100mg	UTI, DKA
NCT00642278 Rosenstock, 2012	International	12	451	Prior metformin	Canagliflozin 50mg, 100mg, 200mg, 300mg, 600mg	Placebo, Sitagliptin 100mg	UTI
NCT01376557	United States	12	299	Prior metformin	Sotagliflozin	placebo	UTI, BF

Rosenstock, 2015					75 mg, 200mg, 400mg		
NCT01809327 Rosenstock, 2016	International	26	1186	Treatment Naive	Canagliflozin 100mg, 300mg	Metformin 500mg	UTI, DKA
NCT01606007 Rosenstock, 2015	International	24	534	Prior metformin	Dapagliflozin 10mg	Placebo	UTI, BF
NCT01306214 Rosenstock, 2014	International	52	563	Prior insulin therapy	Empagliflozin 10mg, 25mg	Placebo	UTI, DKA, BF
NCT01011868 Rosenstock, 2015	International	78	494	Prior insulin maybe metformin and SU	Empagliflozin 10mg, 25mg	Placebo	UTI, DKA
NCT00683878 Rosenstock, 2012	International	48	420	Treatment Naive or stabilized on pioglitazine	Dapagliflozin 5mg, 10mg	Placebo	UTI, BF
None Ross, 2015	International	16	983	Prior metformin	Empagliflozin 10mg, 25mg	Placebo	UTI
None Sasaki, 2015	Japan	7 days	40	Treatment Naive	Luseogliflozin 0.5mg, 1mg, 2.5mg, 5mg	Placebo	UTI
NCT01137812 Schernthaler, 2013	International	52	756	Prior Metformin and SU	Canagliflozin 300mg	Sitagliptin 100mg	UTI, BF
NCT01217892 Schumm-Draeger, 2014	International	16	400	Prior metformin	Dapagliflozin 5mg, 10mg, 20mg	Placebo	UTI, BF
None Seino, 2014	Japan	12	239	Treatment Naive	Luseogliflozin 0.5mg, 2.5mg, 5mg	Placebo	UTI
None Seino, 2014	Japan	12	282	Treatment Naive	Luseogliflozin 1mg, 2.5mg, 5mg, 10mg	Placebo	UTI, DKA
None Seino, 2014	Japan	24	158	Treatment Naive	Luseogliflozin 2.5mg	Placebo	UTI
NCT01081834 Stenlof, 2013	International	26	587	Treatment Naive or washout	Canagliflozin 100mg, 300mg	Placebo	UTI, BF
NCT00680745 Strojek, 2014	International	48	597	Prior SU	Dapagliflozin 2.5mg, 5mg, 10mg	Placebo	UTI, BF
NCT00500331 Sykes, 2015	international	12	336	Treatment Naive	Remogliflozin 100mg, 200mg, 500mg, 1000mg, 2000mg	Placebo, Pioglitazone 30mg	UTI
NCT01370005 Tikkanen, 2015	International	12	825	Treatment Naive	Empagliflozin 10mg, 25mg	Placebo	UTI, DKA, BF

None Townsend, 2016	United States	6	171	Uncontrolled on 1-3 agents	Canagliflozin 100mg, 300mg	Placebo	UTI
None Semán, 2016	Malaysia	12	110	Prior Metformin and SU	Dapagliflozin 10mg	Sulphonylureas (various agents)	UTI
NCT01137474 Weber, 2016	International	12	944	Any prior therapies	Dapagliflozin 10mg	Placebo	UTI, BF
NCT01195662 Weber, 2016	International	12	449	Any prior therapies	Dapagliflozin 10mg	Placebo	UTI, BF
NCT01106625 Wilding; 2013	International	52	469	Prior Metformin and SU	Canagliflozin 100mg, 300mg	Placebo	UTI, DKA, BF
NCT01117584 Wilding, 2013	International	12	343	Prior metformin	Ipragliflozin 12.5mg, 50mg, 150mg, 300mg	Placebo	UTI
NCT00357370 Wilding, 2009	International	12	71	Any prior therapies	Dapagliflozin 10mg, 20mg	Placebo	UTI
NCT00673231 Wilding, 2014	international	104	808	Prior insulin others allowed	Dapagliflozin 2.5mg, 5/10mg, 10mg	Placebo	UTI, BF
NCT01064414 Yale, 2014	International	52	269	Treatment Naive or 1 or 2	Canagliflozin 100mg, 300mg	Placebo	UTI, BF
NCT01316341 Zhao, 2015	China	9 days	24	Treatment Naive or 1 or 2	Empagliflozin 10mg, 25mg	Placebo	UTI
NCT01131676 Zinman, 2015	International	206	7028	Treatment Naive	Empagliflozin 10mg, 25mg	Placebo	UTI, AKI, DKA, BF
None Goto, 2012		24	168	Prior metformin	Ipragliflozin 50mg	Placebo	UTI
NCT02036515 Dagogo-Jack, 2017	International	26	463	Prior metformin and DPP4	Ertugliflozin 5mg, 15mg	Placebo	UTI, DKA, BF
NCT01734785 Maldonado- Lutomirsky, 2016	International	24	606	Prior metformin and DPP4	Empagliflozin 10mg, 25mg	Placebo	UTI, AKI, BF
NCT01289990 Merker, 2015	International	52	637	Prior metformin	Empagliflozin 10mg, 25mg	Placebo	UTI
NCT01032629 Neal, 2015	International	52	2074	Prior insulin therapy	Canagliflozin 100mg, 300mg	Placebo	UTI, BF
NCT01167881 Ridderstrale, 2014	International	104	1549	Prior metformin	Empagliflozin 25mg	Glimepiride 1-4mg	UTI, AKI, BF
NCT00495469	UK	12	252	Treatment Naive	Remogliflozin	Placebo, Pioglitazone	UTI, BF

Sykes, 2014					100mg, 250mg, 500mg, 1000mg	30mg	
None Tanizawa, 2014	Japan	52	194	Treatment Naive	Tofogliflozin 20mg, 40mg	No comparator	UTI
None Tanizawa, 2014	Japan	52	602	Any prior therapies	Tofogliflozin 20mg, 40mg	No comparator	UTI
NCT01095666 Yang, 2014		24	444	Prior metformin	Dapagliflozin 5mg, 10mg	Placebo	UTI, BF
None Gupta, 2017		76	108	Treatment Naive	Empagliflozin 10mg, 25mg	Placebo, Sitagliptin 100mg	UTI
NCT02354235 Kadowaki, 2017	Japan	24	138	Prior Teneligliptin	Canagliflozin 100mg	Placebo	UTI, DKA, BF
NCT01734785 Softeland, 2017	International	24	333	Prior metformin	Empagliflozin 10mg, 25mg	Placebo	UTI, AKI, DKA, BF
NCT01958671 Terra, 2017	International	26	461	Treatment Naive	Ertugliflozin 5mg, 15mg	Placebo	UTI
NCT 01022112 Not Published		12	383	Treatment Naive	Canagliflozin 50mg, 100mg, 200mg, 300mg	Placebo	BF
NCT02201004 Terauchi, 2017		16	211	Prior insulin therapy DPP4 allowed	Tofogliflozin 20mg, 40mg	Placebo	UTI
NCT01986855, Grunberger, 2018	International	52	468	Prior therapies (NOT metformin, pioglitazone)	Ertugliflozin 5mg, 15mg	Placebo	UTI, BF
NCT01999218, Hollander, 2018	International	52	1326	Prior metformin	Ertugliflozin 5mg, 15mg	Glimepiride	AKI, UTI, KA, BF
Ito, 2017	Japan	24	66	Treatment Naive or prior therapy (NOT glitazone or insulin)	Ipragliflozin 50mg	Pioglitazone 15-30mg	UTI, KA
NCT02099110, Pratley, 2017	International	52	1233	Prior metformin	Ertugliflozin 5mg, 15mg	Sitagliptin 100 mg	UTI, KA, BF
NCT02033889, Rosenstock, 2017	International	26	621	Prior metformin	Ertugliflozin 5mg, 15mg	Placebo	UTI, KA, F
Seino, 2018	Japan	16	233	Prior insulin	Luseogliflozin 2.5mg	Placebo	UTI

NCT02096705, Yang, 2018	Asia	24	272	Any prior antidiabetic	Dapagliflozin 10mg	Placebo	UTI, KA
NCT02429258, Henry, 2017	Unclear	4	100	Background metformin	Dapagliflozin 10mg	Placebo	UTI
NCT01606007, Ekholm, 2017	Unclear	24	534	Background metformin and saxagliptin	Dapagliflozin 10mg	Placebo	BF
Neal, 2017	International	188	10,142	Any background therapy	Canagliflozin 100-300mg	Placebo	UTI, AKI, DKA, BF, AMP

## Section 4: Additional Forest Plots

Figure 1A. Risk of Urinary Tract Infection with SGLT2 Inhibitors Compared to Placebo, break down by agent

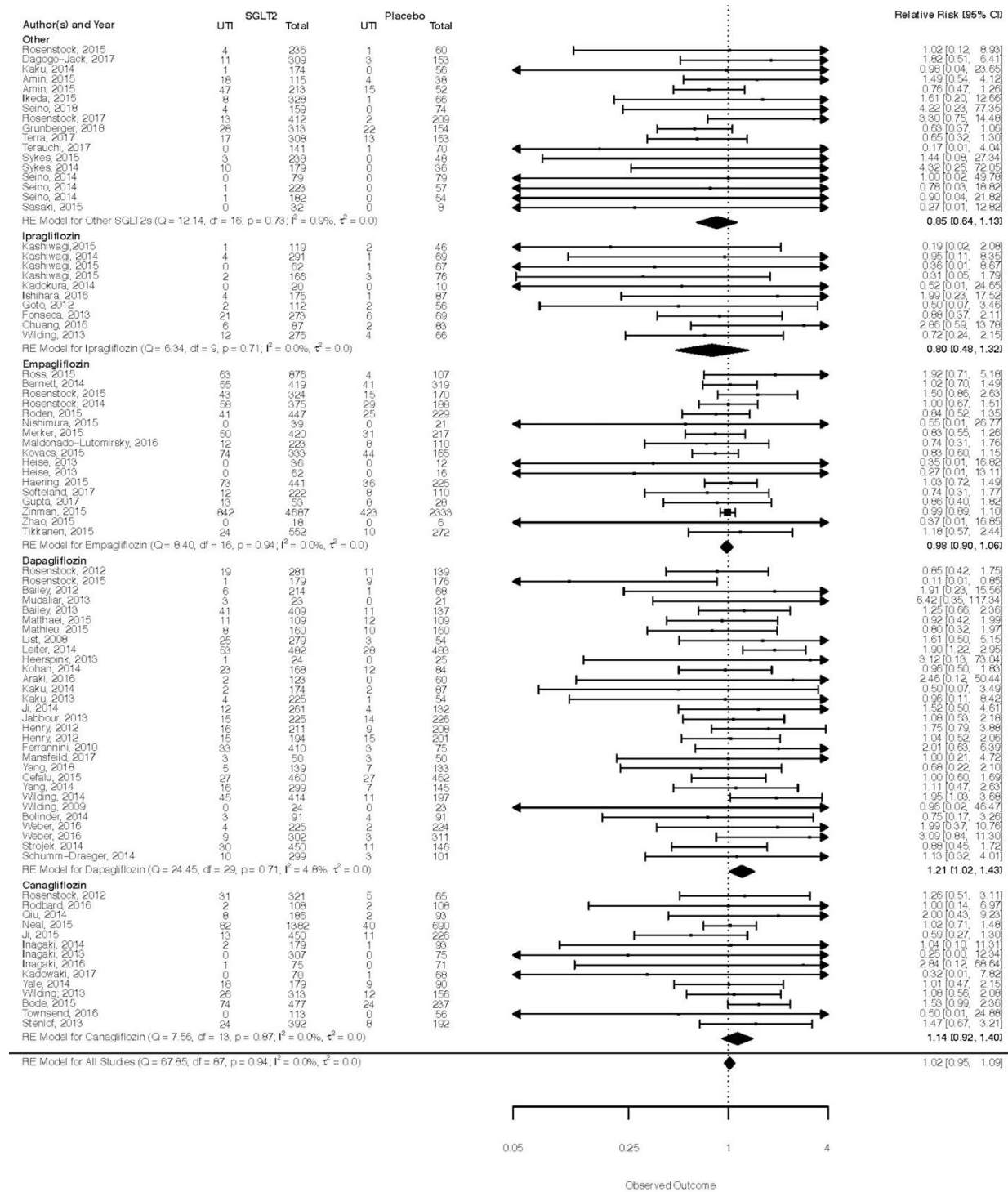


Figure 2A. Figure 1. Risk of Urinary Tract Infection with SGLT2 Inhibitors Compared to Active Comparators, Breakdown by Agent

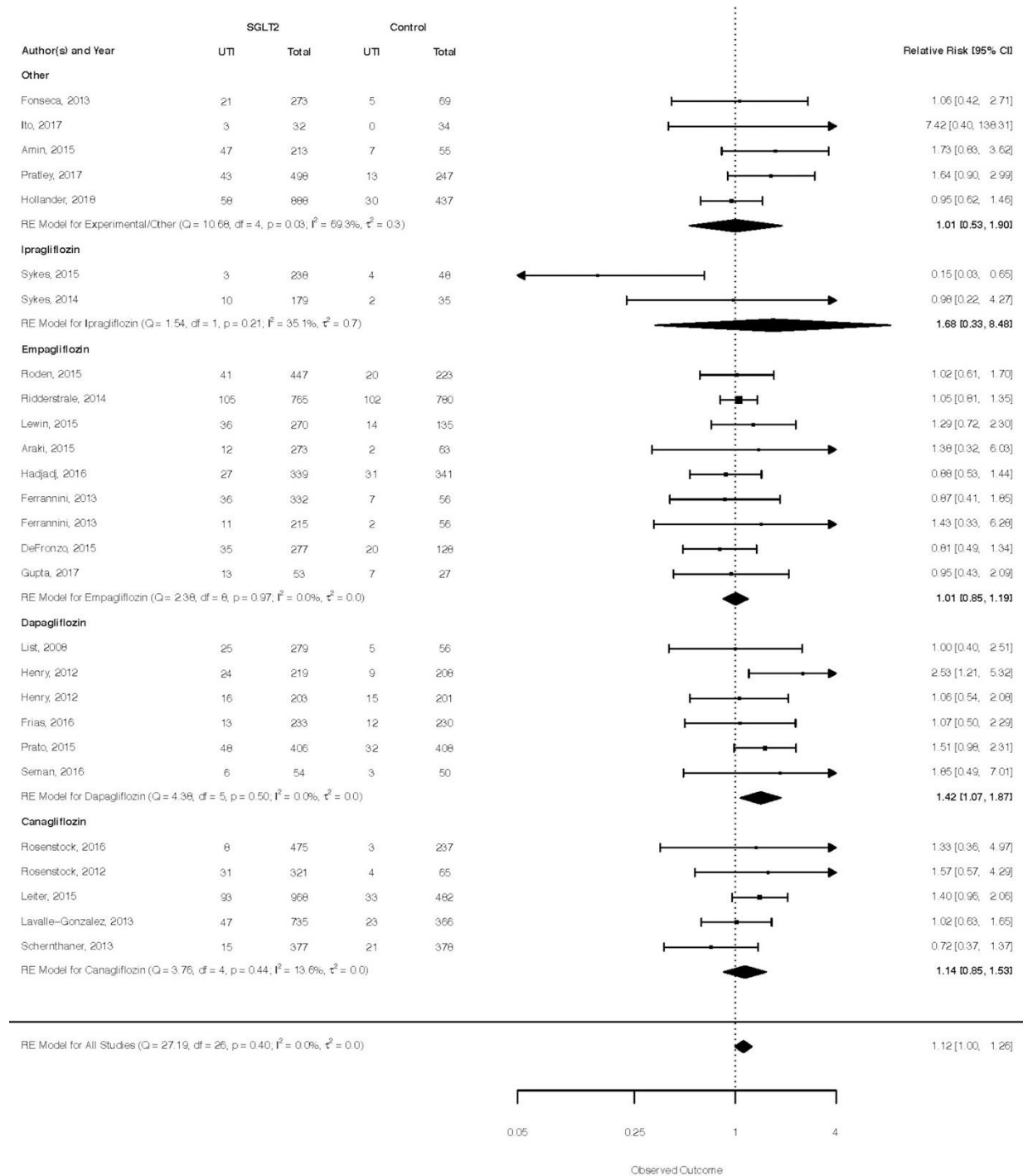




Figure 3A: Risk of Acute Kidney Injury with SGLT2 Inhibitors compared to Active Comparators

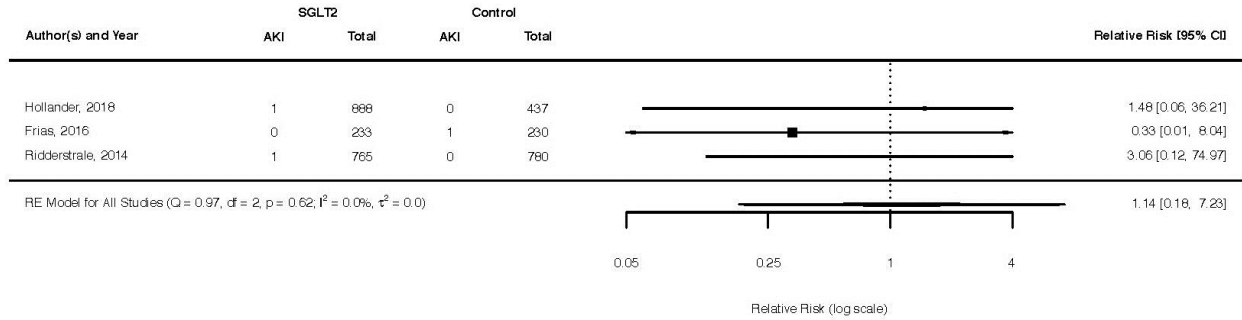


Figure 4A: Risk of Acute Kidney Injury with SGLT2 Inhibitors Compared to Placebo; excluding EMPA-REG.

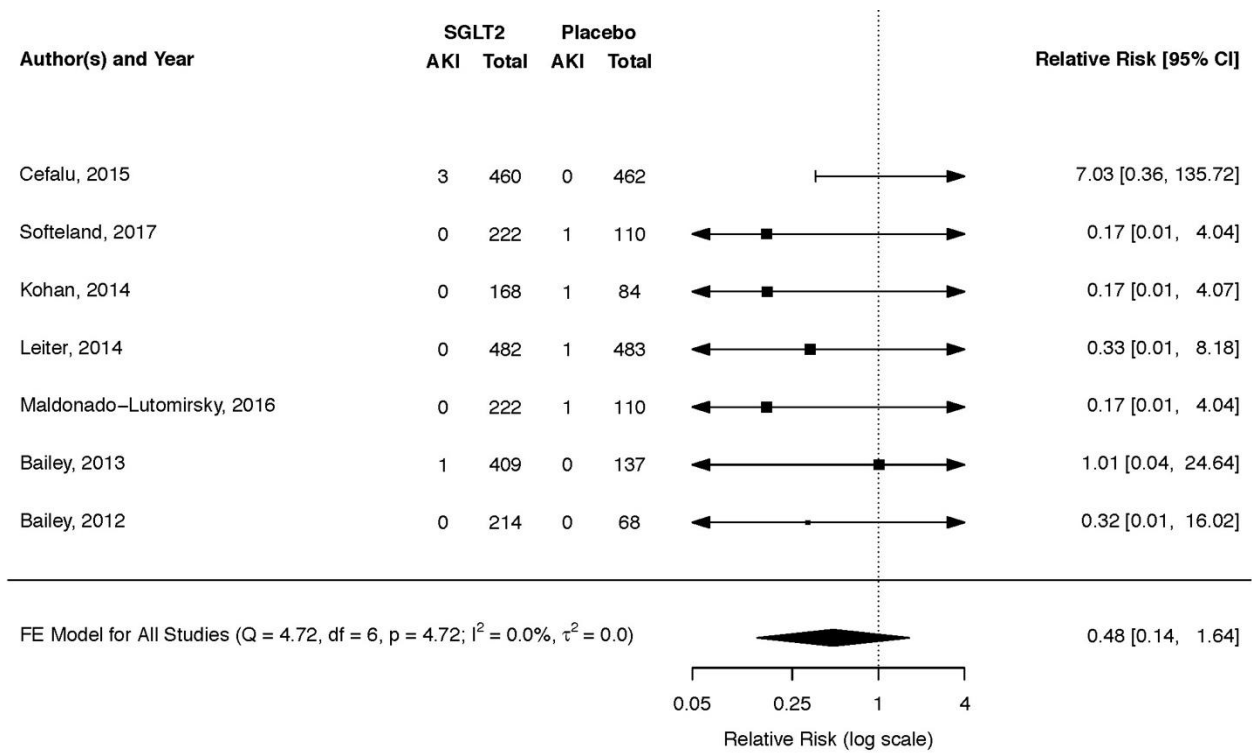


Figure 5A. Risk of Ketoacidosis among users of an SGLT2 Inhibitor compared to an Incretin

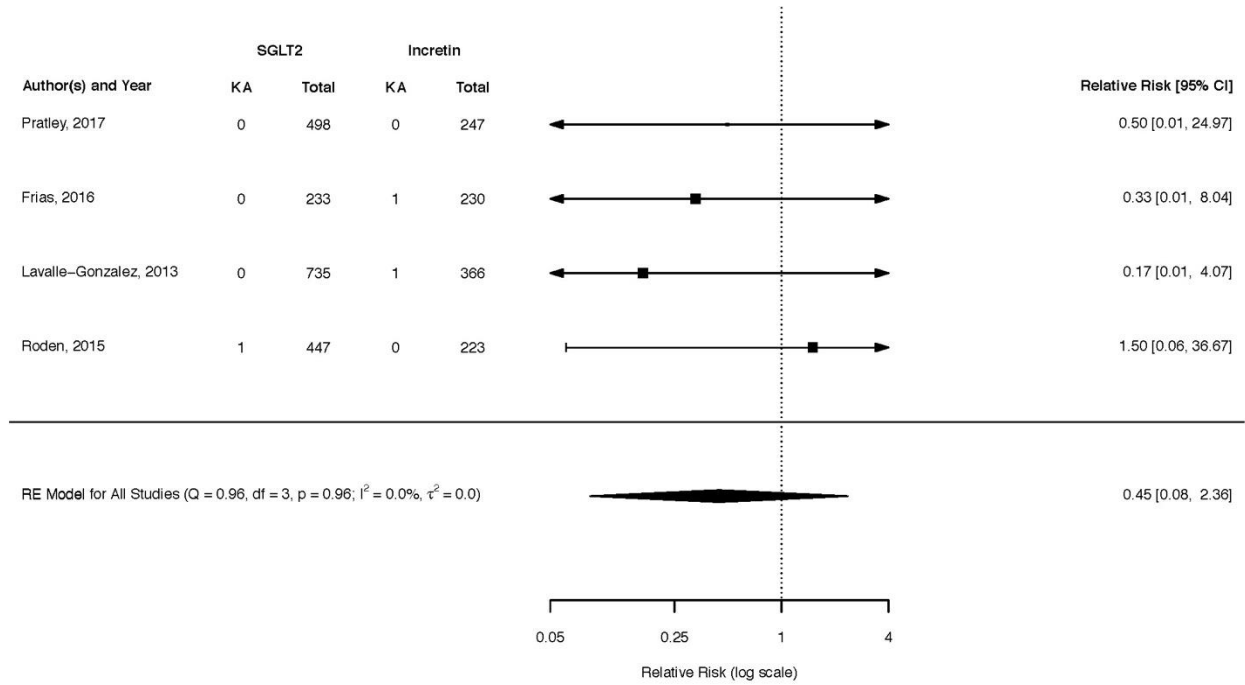


Figure 6A. Risk of Ketoacidosis among users of an SGLT2 Inhibitor Compared to Placebo in Studies with at least one Outcome

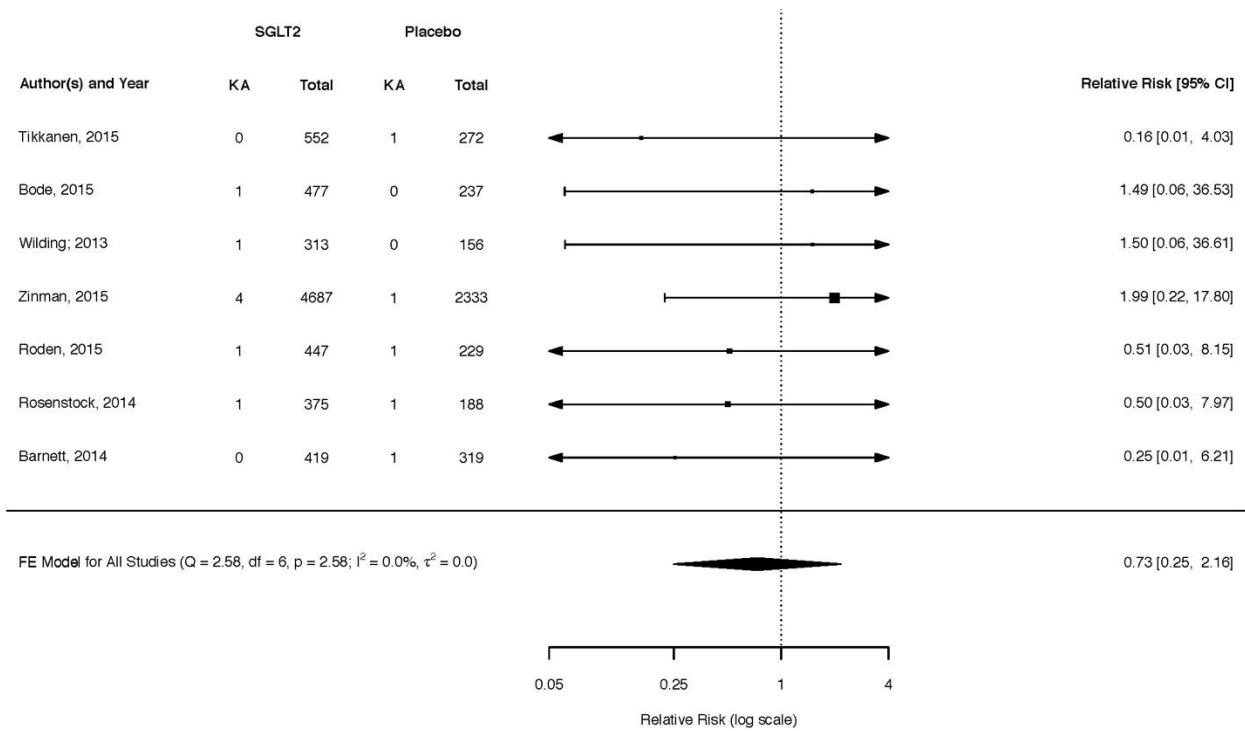


Figure 7A. Risk of Urinary Tract Infections among users of SGLT2 Inhibitors Compared to Active Controls

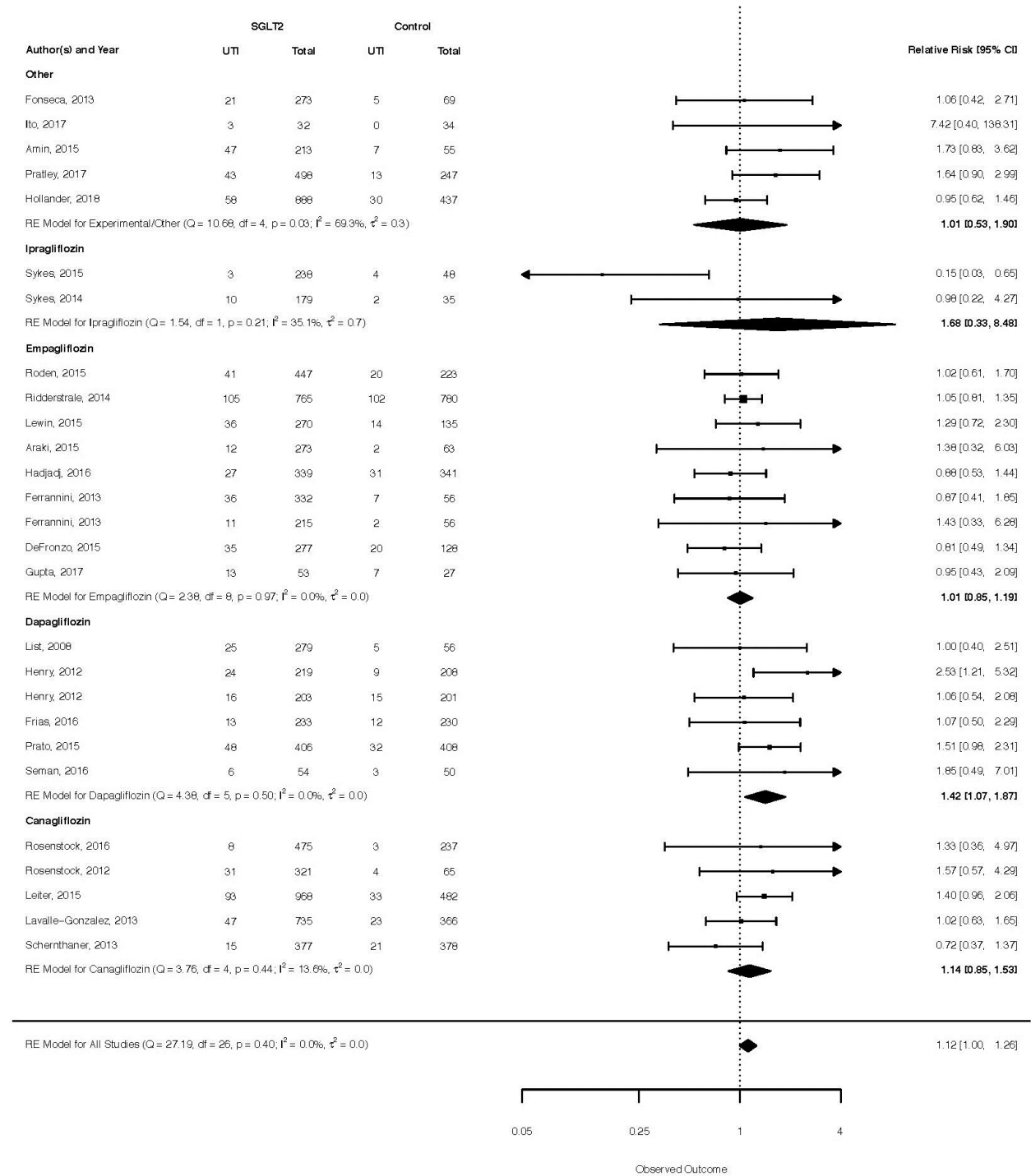


Figure 8A: Risk of Fracture with SGLT2 Inhibitors compared to Metformin

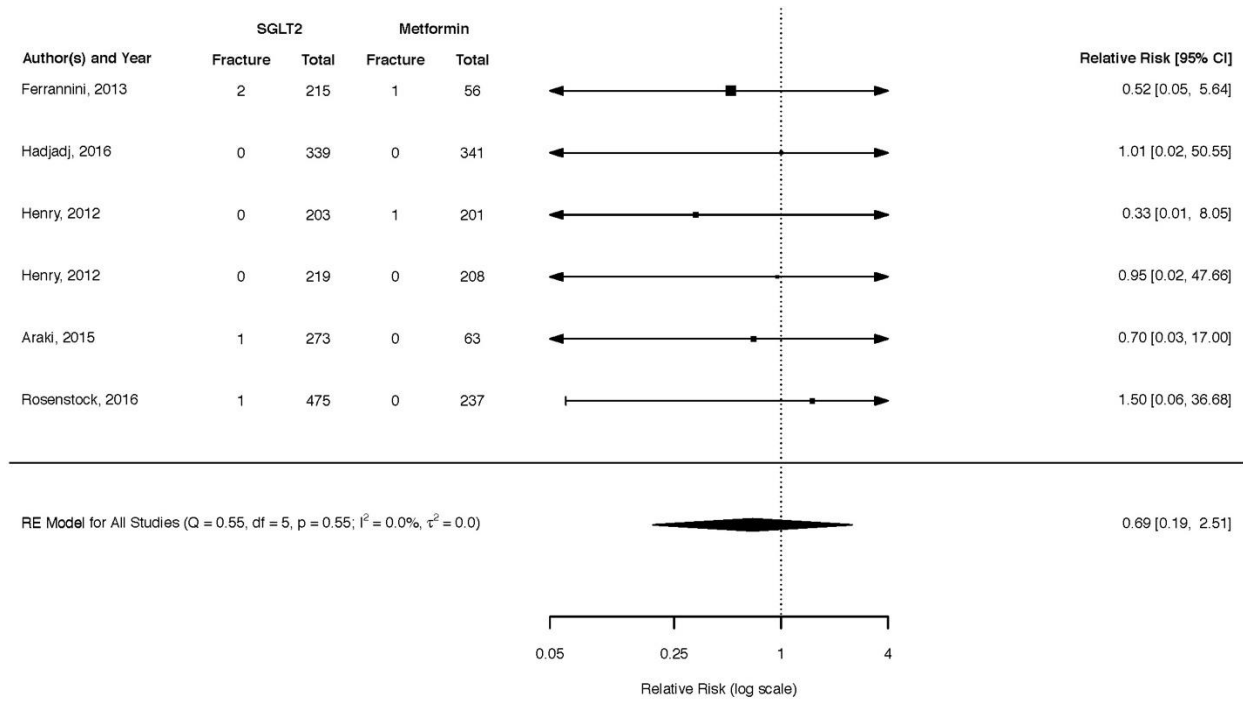


Figure 9A: Risk of Fracture with SGLT2 Inhibitors compared to Sulfonylureas

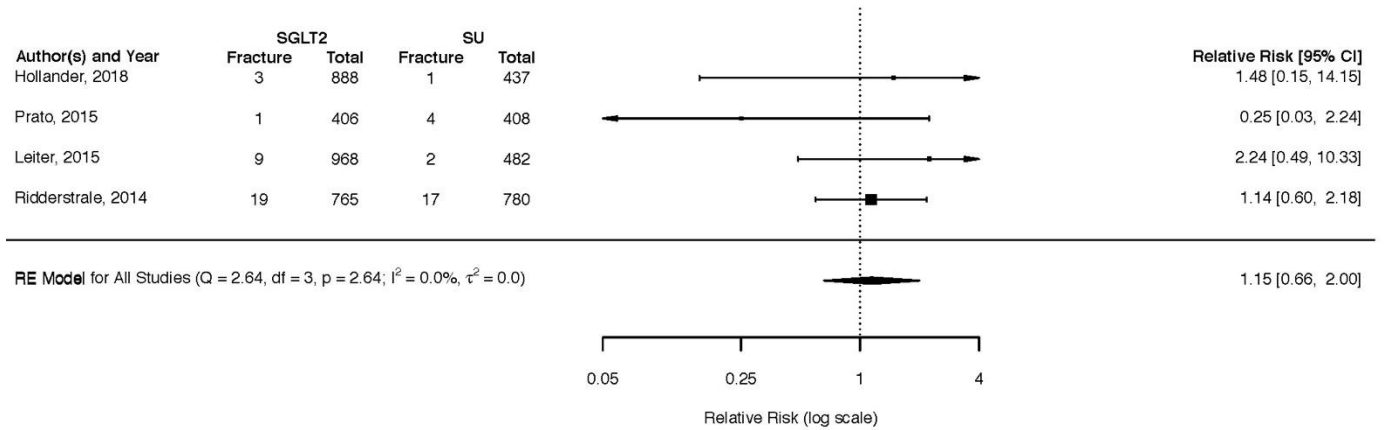


Figure 10A: Risk of Fracture with SGLT2 Inhibitors compared to Incretins

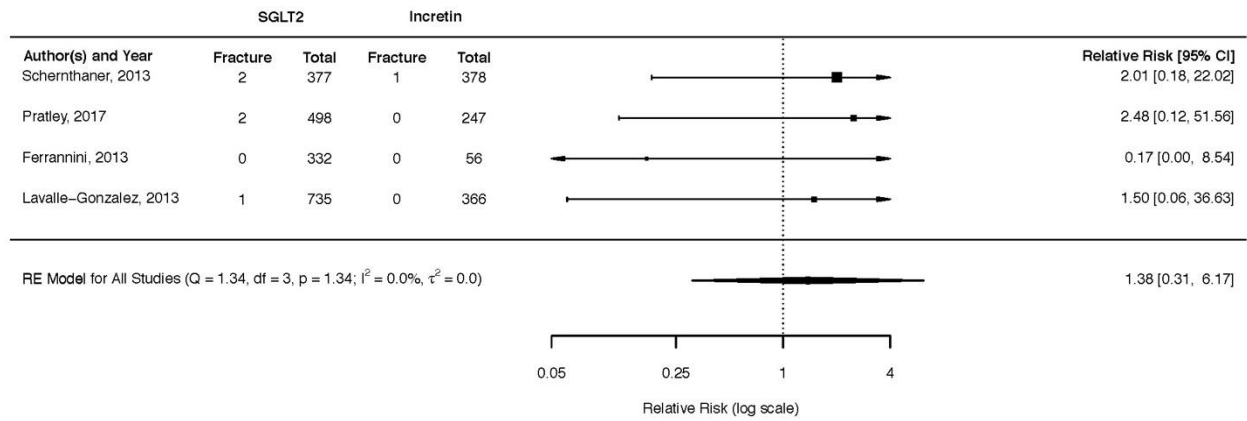
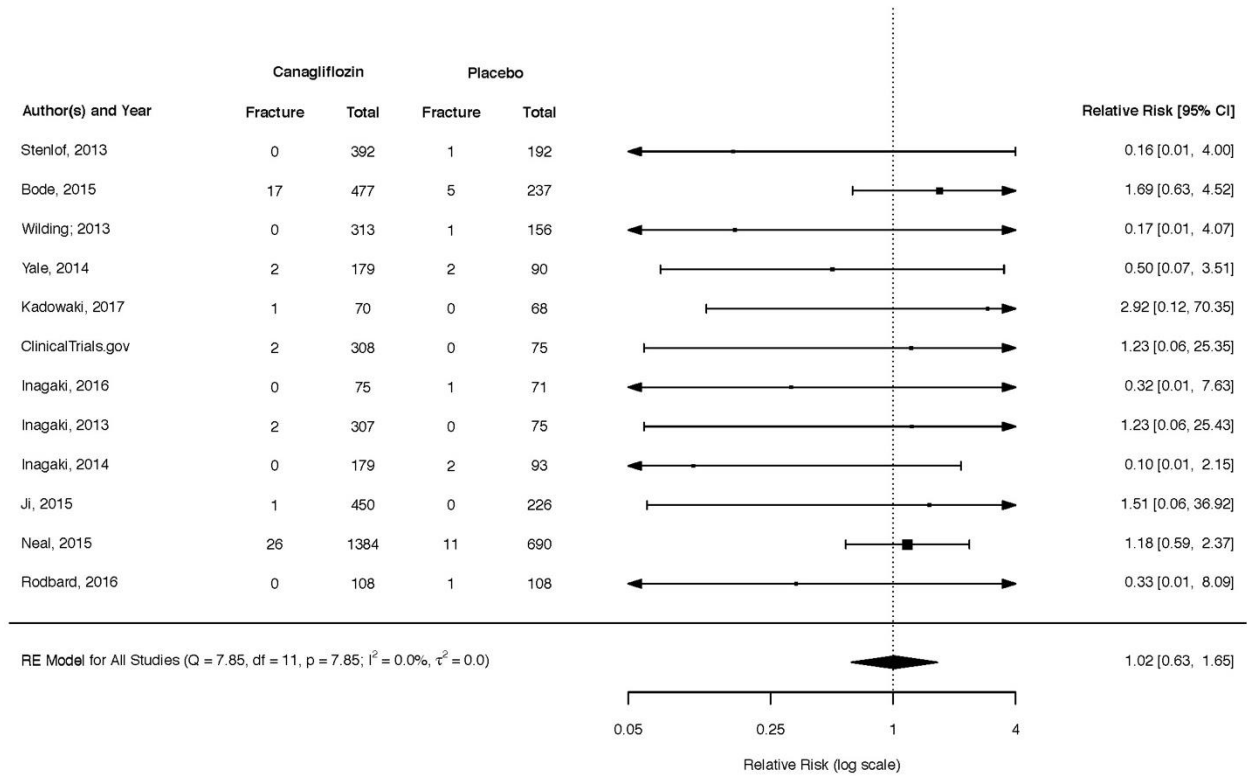


Figure 11A: Risk of Fracture with Canagliflozin compared to Placebo



## Section 5: Forest Plots for Fixed Effects Analysis

Figure 12A. Risk of Acute Kidney Injury with SGLT2 Inhibitors compared to Placebo - Fixed Effect Model

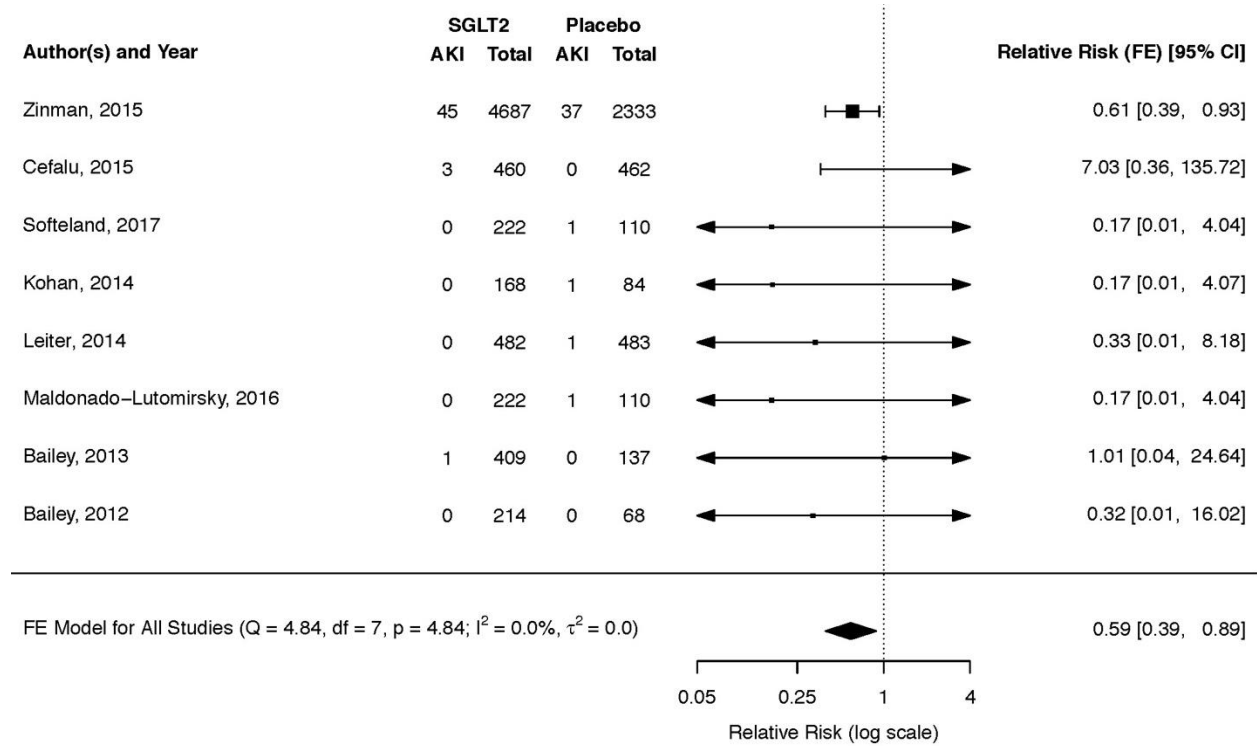


Figure 13A. Risk of Diabetic Ketoacidosis with SGLT2 Inhibitors compared to Placebo - Fixed Effect Model

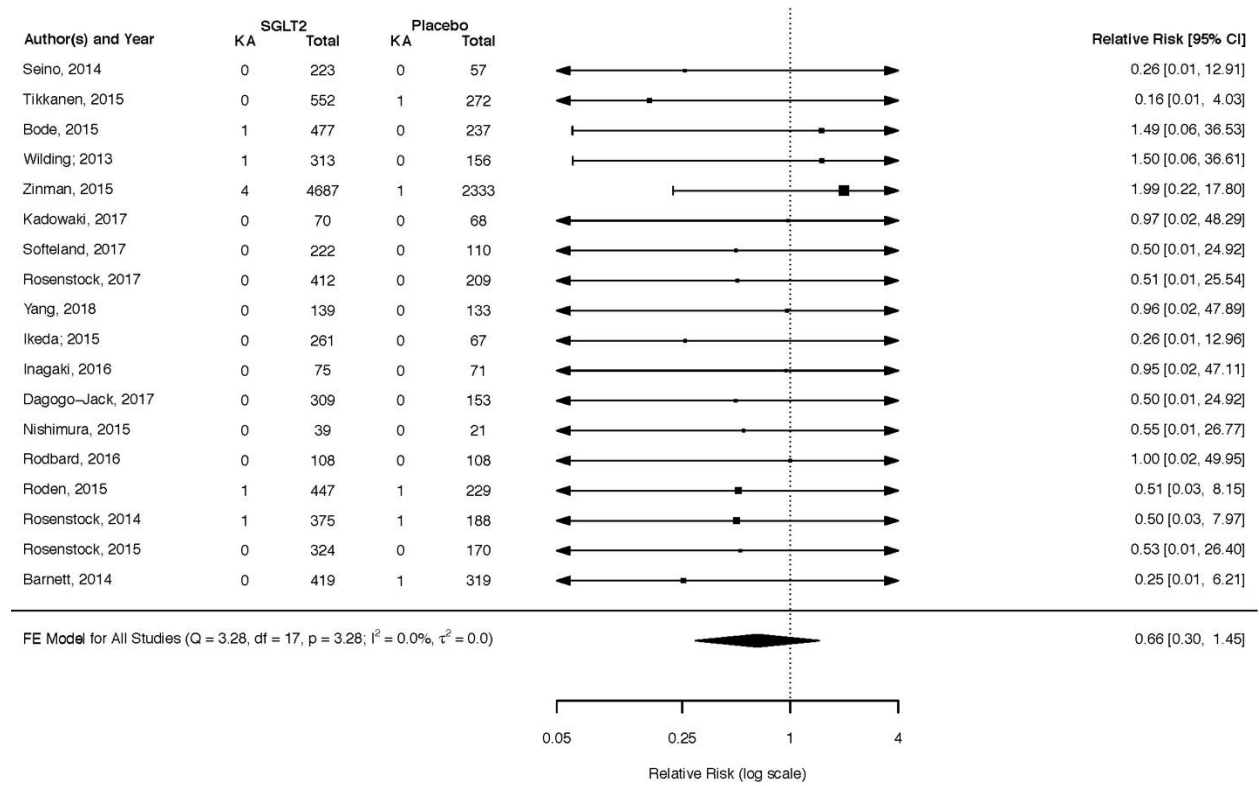


Figure 14A. Risk of Urinary Tract Infection with SGLT2 Inhibitors compared to Placebo - Fixed Effect Model

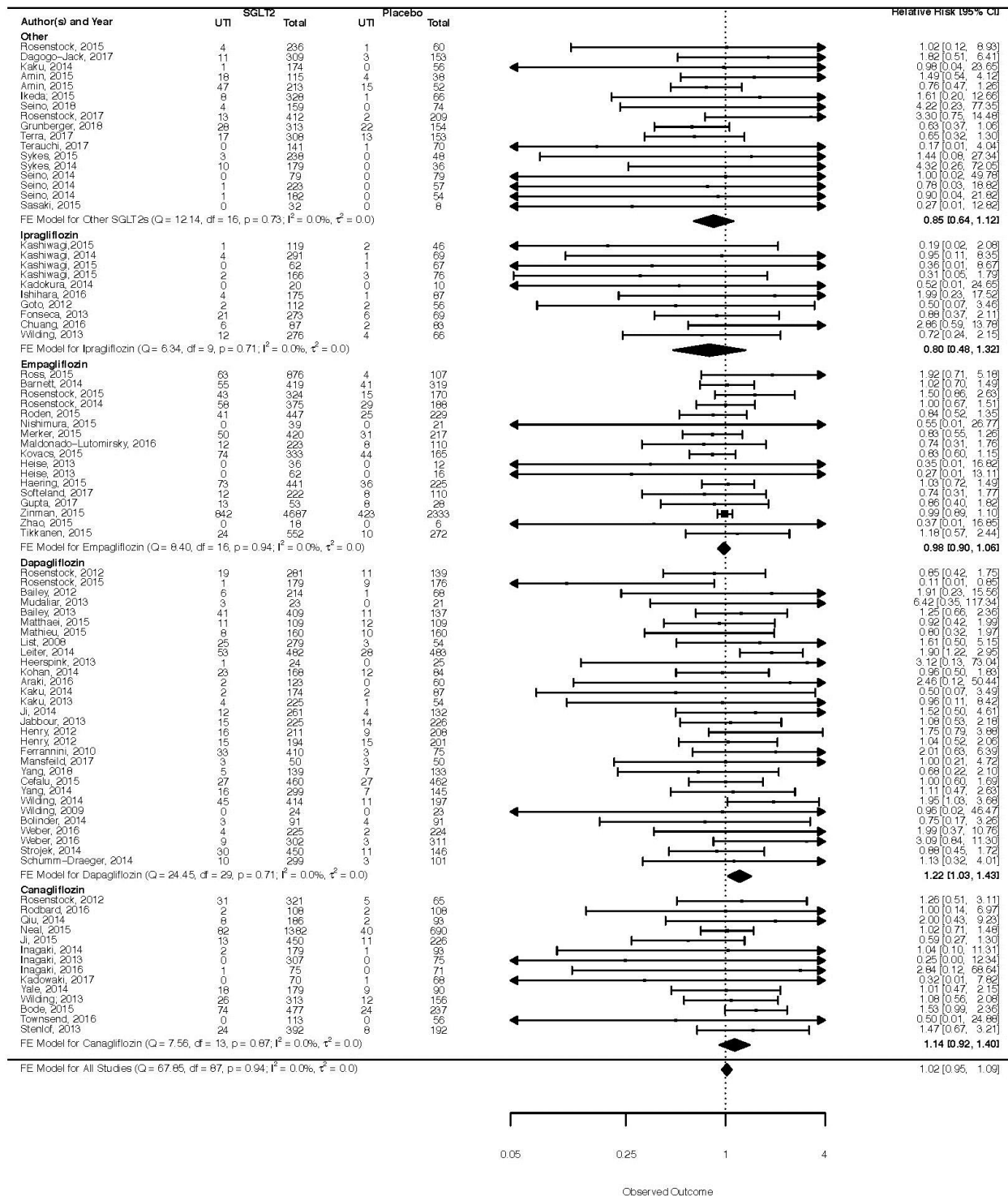
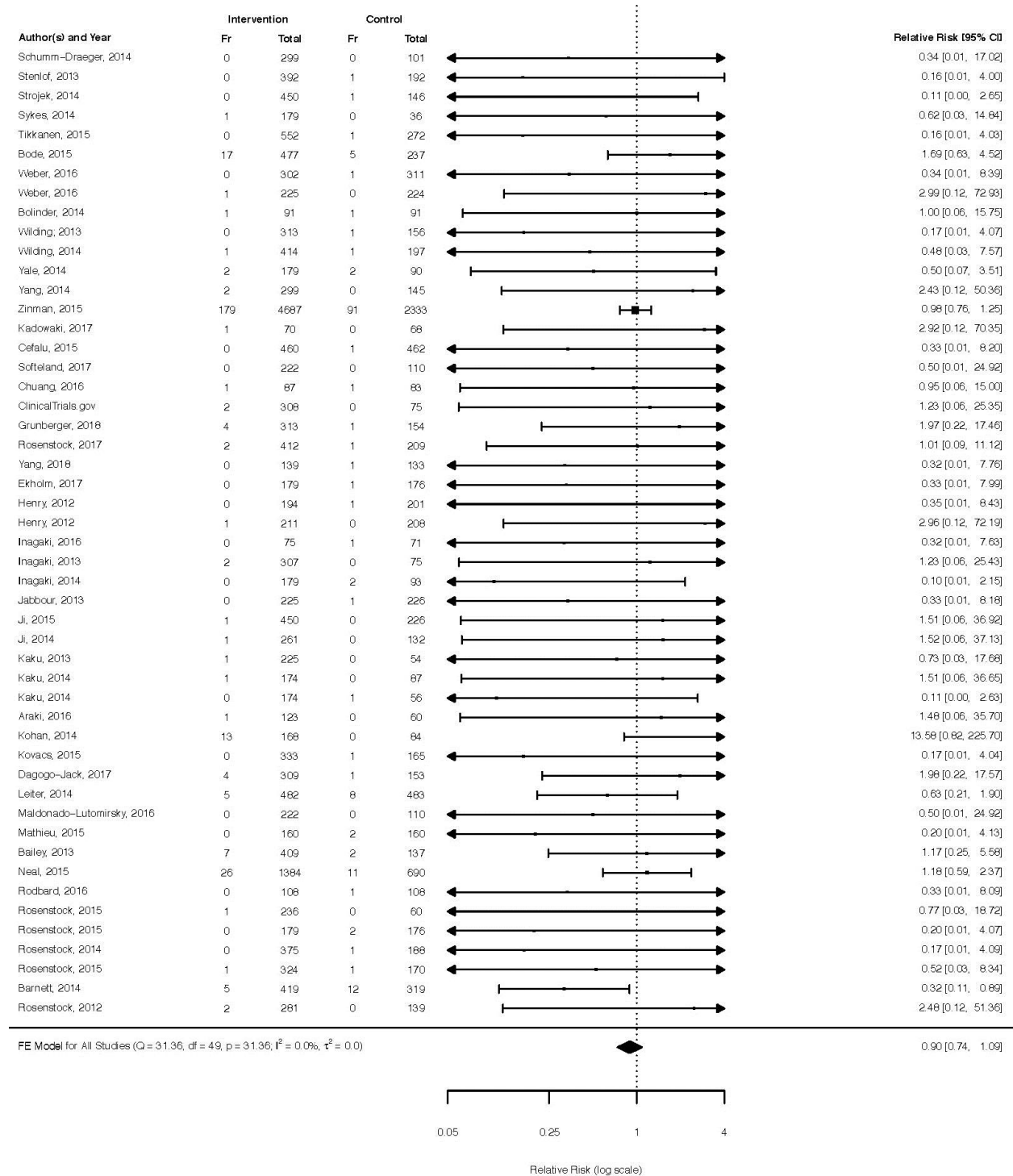




Figure 15A. Risk of Fracture with SGLT2 Inhibitors compared to Placebo - Fixed Effect Model



## Section 6: Risk of Bias Assessment

Table 7A. Risk of Bias Assessment for Included Studies

Author and Year	NCT#	Randomization Sequence	Allocation concealment	Double Blinding	Blinded Outcome Assessment	Incomplete Outcome	Selective Reporting	Other	Overall Assessment
Amin, 2015	NCT01059825	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	low
Amin, 2015	NCT01059825	Unclear Risk	Unclear Risk	Low Risk	Unclear Risk	Low Risk	Unclear Risk	Unclear risk	high
Araki, 2016	NCT02157298	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Araki	NCT01368081	Low Risk	Low Risk	Medium Risk	Unclear Risk	Low Risk	High Risk	Unclear risk	high
Bailey, 2013	NCT00528879	Low Risk	Low Risk	Low Risk	Low Risk	Medium Risk	Unclear Risk	Unclear risk	high
Bailey, 2012	None	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	low
Barnett, 2014	NCT01164501	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Bode, 2015	NCT01106651	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Bolinder, 2014	NCT00855166	Low Risk	Low Risk	Low Risk	Low Risk	low Risk	Low Risk	Unclear risk	low
Cefalu, 2015	NCT01031680	Low Risk	Low Risk	Medium Risk	Low Risk	Low Risk	High Risk	Low Risk	high
Chuang, 2016	NCT01505426	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
DeFronzo, 2015	NCT01422876	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear risk	low
Prato, 2015	NCT00660907	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Ferrannini, 2013	NCT00881530	High Risk	High Risk	High Risk	High Risk	Low Risk	High Risk	Unclear risk	high
Ferrannini, 2010	NCT00528372	Unclear Risk	Unclear Risk	Low Risk	Unclear Risk	Unclear Risk	Unclear Risk	Unclear risk	high
Fonseca, 2013	NCT01071850	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Frias, 2016	NCT02229396	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Hadjadj, 2016	NCT01719003	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Haering, 2015	NCT01289990	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear risk	low
Heise, 2013	None	Low Risk	Low Risk	Unclear Risk	Unclear Risk	Low Risk	Unclear Risk	Unclear risk	high
Heise, 2013	None	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Henry, 2012	NCT00643851	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high

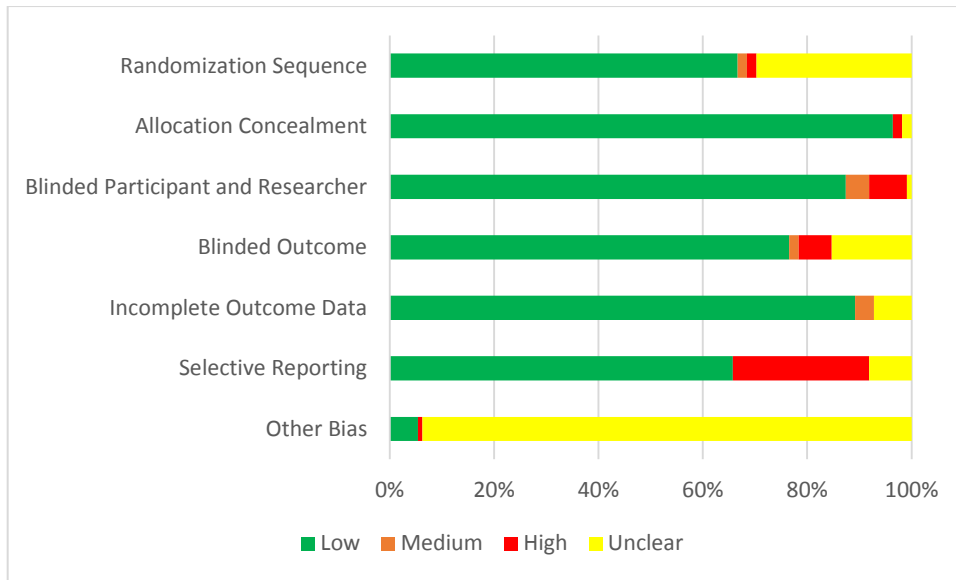
Henry, 2012	NCT00859898	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Ikeda, 2015	NCT00800176	Unclear Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear risk	high
Inagaki, 2016	NCT02220920	Low Risk	Low Risk	Low Risk	low Risk	Low Risk	Low Risk	Unclear risk	low
Inagaki, 2015	NCT01387737	Unclear Risk	Low Risk	High Risk	High Risk	Medium Risk	Unclear Risk	Unclear risk	high
Inagaki, 2013	NCT01022112	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Inagaki, 2014	NCT01413204	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Ishihara, 2016	NCT02175784	Unclear Risk	Low Risk	Medium Risk	Low Risk	Low Risk	Low Risk	Low Risk	high
Jabbour, 2013	NCT00984867	Unclear Risk	Low Risk	Medium Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Ji, 2015	NCT01381900	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Ji, 2014	NCT01095653	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Kadokura, 2014	NCT01023945	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Kadowaki, 2015	NCT01193218	Low Risk	Low Risk	Low Risk	Medium Risk	Low Risk	High Risk	Unclear risk	high
Kaku, 2013	NCT00972244	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	High Risk	Unclear risk	high
Kaku, 2014	none	Unclear Risk	low Risk	Low Risk	Unclear Risk	Medium Risk	Unclear Risk	Unclear risk	high
Kaku, 2014	None	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Kashiwagi, 2015	NCT01242215	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear risk	low
Kashiwagi, 2015	NCT01057628.	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Kashiwagi, 2014	NCT00621868	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Kashiwagi, 2015	NCT01316094	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Kohan, 2014	NCT00663260	Unclear Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear risk	high
Kovacs, 2015	NCT01210001	Low Risk	Low Risk	Low Risk	Medium Risk	Low Risk	High Risk	Unclear risk	high
Heerspink, 2013	NCT00976495	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Lavalle-Gonzalez, 2013	NCT01106677	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Leiter, 2014	NCT01042977	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Unclear risk	low
Leiter, 2015	NCT00968812	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Lewin, 2015	NCT01422876	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	low
List, 2008	NCT00263276	Unclear Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Unclear risk	high

Mathieu, 2015	NCT01646320	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Matthaei, 2015	NCT01392677	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Mudaliar, 2013	None	Unclear Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Unclear risk	high
Nishimura, 2015	NCT01947855	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Qiu, 2014	NCT01340664	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Rodbard, 2016	NCT01989754	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Roden, 2015	NCT01289990	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Rosenstock, 2012	NCT00642278	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Rosenstock, 2015	NCT01376557	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Rosenstock, 2016	NCT01809327	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Rosenstock, 2015	NCT01606007	Low Risk	Low Risk	Low Risk	Low risk	Low Risk	Low Risk	Unclear risk	low
Rosenstock, 2014	NCT01306214	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Rosenstock, 2015	NCT01011868	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear risk	high
Rosenstock, 2012	NCT00683878	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Ross, 2015	None	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Sasaki, 2015	None	Low Risk	Low Risk	Medium Risk	High Risk	Unclear Risk	Unclear Risk	High Risk	high
Schernthaner, 2013	NCT01137812	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Schumm-Draeger, 2014	NCT01217892	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Seino, 2014	None	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Seino, 2014	None	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Seino, 2014	None	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Stenlof, 2013	NCT01081834	Unclear Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear Risk	high
Strojek, 2014	NCT00680745	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear Risk	high
Sykes, 2015	NCT00500331	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Tikkanen, 2015	NCT01370005	Medium Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	high
Townsend, 2016	None	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Seman, 2016	None	Unclear Risk	Low Risk	High Risk	High Risk	Unclear Risk	Unclear Risk	Unclear Risk	high

Weber, 2016	NCT01137474	Low Risk	Low Risk	Low Risk	Low Risk	Medium Risk	High Risk	Unclear Risk	high
Weber, 2016	NCT01195662	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear Risk	high
Wilding; 2013	NCT01106625	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear Risk	high
Wilding, 2013	NCT01117584	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Wilding, 2009	NCT00357370	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Wilding, 2014	NCT00673231	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear Risk	high
Yale, 2014	NCT01064414	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Zhao, 2015	NCT01316341	Medium Risk	Low Risk	Low Risk	Low risk	Low Risk	Low Risk	Unclear Risk	high
Zinman, 2015	NCT01131676	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	low
Goto, 2012	None	Unclear Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear risk	high
Dagogo-Jack, 2017	NCT02036515	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear risk	low
Maldonado-Lutomirsky, 2016	NCT01734785	Unclear Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Unclear risk	high
Merker, 2015	NCT01289990	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Neal, 2015	NCT01032629	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	low
Ridderstrale, 2014	NCT01167881	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Sykes, 2014	NCT00495469	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Tanizawa, 2014	None	Low Risk	Low Risk	High Risk	High Risk	Low Risk	Low Risk	Unclear Risk	high
Yang, 2014	NCT01095666	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Gupta, 2017	None	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Kadowaki, 2017	NCT02354235	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Softeland, 2017	NCT01734785	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Terra, 2017	NCT01958671	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
ClinicalTrials.gov		Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Terauchi, 2017	NCT02201004	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	low
Grunberger, 2018	NCT01986855	Low Risk	Low Risk	High Risk	High Risk	High Risk	Low Risk	Unclear Risk	high
Hollander, 2018	NCT01999218	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	Low
Ito, 2017		Low Risk	Low Risk	High Risk	High Risk	Low Risk	Low Risk	Unclear risk	High

Pratley, 2017	NCT02099110	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	Low
Rosenstock, 2017	NCT02033889	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	Low
Seino, 2018		Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	Low
Yang, 2018	NCT02096705	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear risk	Low
Mansfeild, 2017	NCT02429258	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk	Low
Ekholm, 2017	NCT01606007	Unclear Risk	Low Risk	Low Risk	Low Risk	High Risk	High Risk	Unclear Risk	High

Figure 16A. Risk of Bias Assessment



## Section 7: Assessment of Publication Bias

Figure 17A. Funnel Plot for Placebo Controlled Trials: Acute Kidney Injury

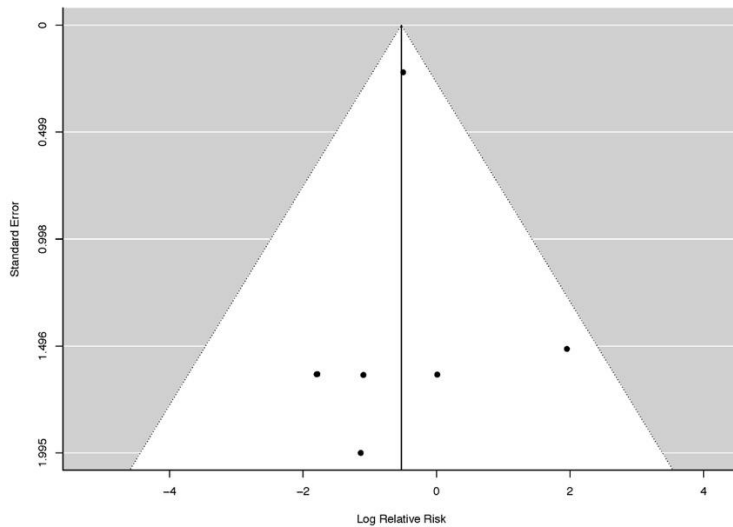


Figure 18A. Funnel Plot for Placebo Controlled Trials: Urinary Tract Infection

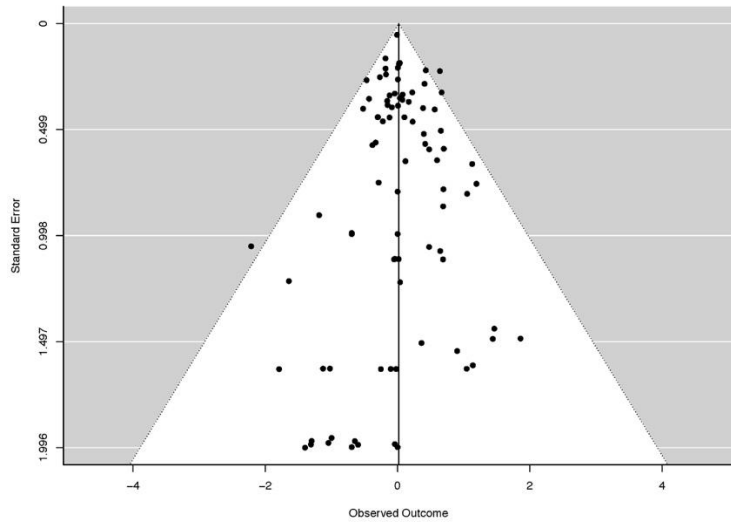


Figure 19A. Funnel Plot for Metformin Controlled Trials: Urinary Tract Infection

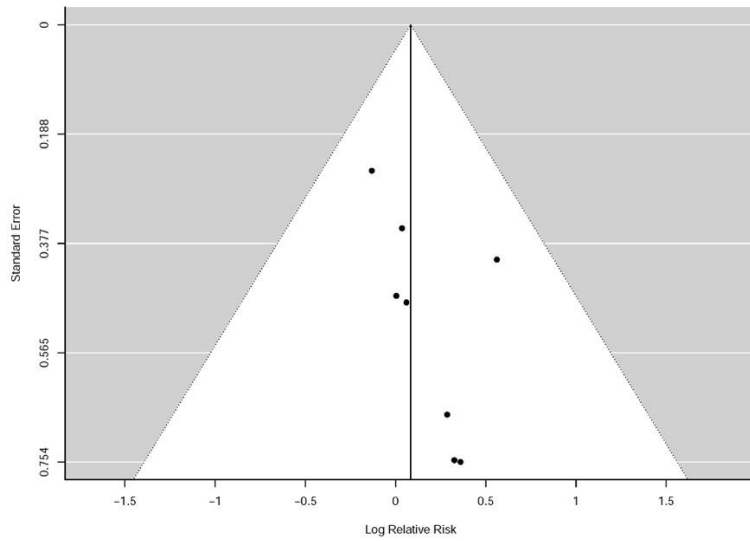




Figure 20A. Funnel Plot for Sulfonylurea Controlled Trials: Urinary Tract Infection

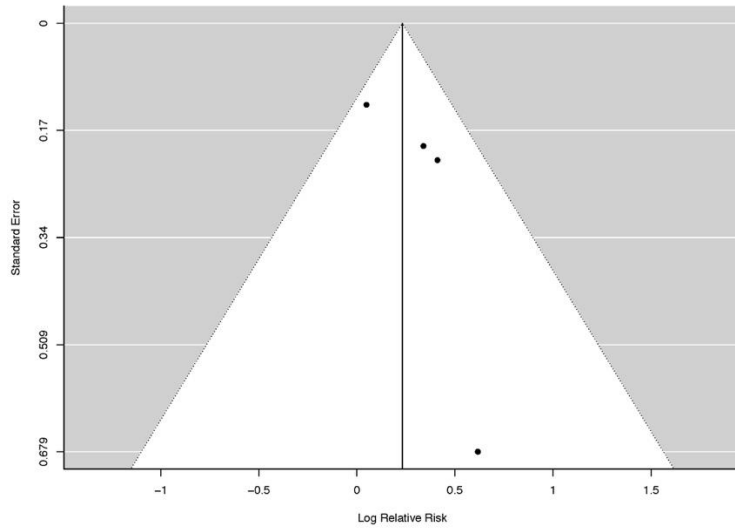


Figure 21A. Funnel Plot for Incretin Controlled Trials: Urinary Tract Infection

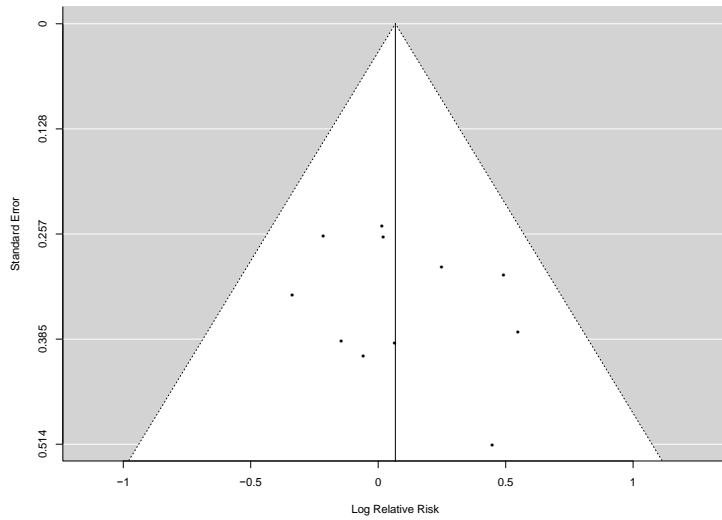


Figure 22A. Funnel Plot for Placebo Controlled Trials: Fracture

