# Supplementary text

## Online Search strategies

**Medline and Cochrane Central Register of Controlled Trials (Central):**

1. randomized controlled trial.pt
2. controlled clinical trial.pt
3. randomized.tw
4. clinical trial/
5. randomly.ab
6. trial.ti
7. placebo.tw
8. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7
9. sodium-glucose transporter 1/2/
10. sodium-glucose transporter 1/2.tw
11. SGLT1/2.tw
12. SGLT-1/2.tw
13. dual SGLT.tw
14. Sotagliflozin.tw OR LX4211.tw OR LP802034.tw OR SAR439954.tw OR Zynquista.tw
15. LX4211.tw
16. Sotagliflozin.tw
17. LP802034.tw
18. SAR439954.tw
19. Zynquista.tw
20. 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19
21. 8 and 20

**EMBASE**

1. 'randomized controlled trial'/exp OR 'randomized controlled trial'

2. 'sodium glucose cotransporter 1/2'/exp OR 'sodium glucose cotransporter 1/2'

3. 'sodium glucose cotransporter 1/2 inhibitor'/exp OR 'sodium glucose cotransporter 1/2 inhibitor'

4.'sotagliflozin'/exp OR 'sotagliflozin' OR 'LX4211' OR 'LP802034' OR 'SAR439954' OR 'Zynquista'

5. 2 OR 3 OR 4

22. 1 AND 5

**CLINICALTRIALS.GOV**

1. Sodium-GlucoseTransporter 1/2

2. SGLT-1/2

3. Sotagliflozin

4. LX4211

5 LP802034

6. SAR439954

7. Zynquista

**US FDA, EMA, databases**

1. Sodium-Glucose Transporter 1/2

2. SGLT-1/2

3. Sotagliflozin

4. LX4211

5. LP802034,

6. SAR439954

7. Zynquista

# International and National Trial registries search results

-**World Health Organization-International Clinical Trials Registry Platform** (http://apps.who.int /trialsearch/): 82 records

-**ClinicalTrials.gov**(https://www.clinicaltrials.gov/ct2/home): 37 records

- **Cochrane CENTRAL Register of Controlled Trials** (https://www.cochranelibrary.com/central/about-central): 47 records

- **European Union(EU) Clinical Trials Register** (https://www.clinicaltrialsregister.eu/): 13 records

-**ISRCTN** (http://www.isrctn.com/ ): 0 results

-**Epistemonikos** *(*https://www.epistemonikos.org/*): 0 records*

-**Health Canada Clinical Trial Database** (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php): 11 records

-**German Clinical Trials Register** (https://drks-neu.uniklinik-freiburg.de/drks_web/): 0 results

-**Netherlands Trial Register (Dutch**) (http://www.trialregister.nl/trialreg/index.asp): 0 results

-**Swiss National Clinical Trials Portal** (http://www.kofam.ch/en/swiss -clinical-trials-portal.html) 6 results

-**Australian New Zealand Clinical Trials Registry** (http://www.anzctr.org.au/ ): 4 records

-**ChineseClinical Trial Register** (http://www.chictr.org.cn/enIndex.aspx): 0 records

-**Clinical Trials Registry–India**(http://ctri.nic.in/): 1 record

-**Iranian Registry of Clinical Trials** (http://www.irct.ir/): 0 records

-**Japan Primary Registries Network** (http://rctportal.niph.go.jp/): 0 records

-**ClinicalResearch Information Service, Republic of Korea** (https://cris.nih.go.kr/cris/en/use_guide/cris_introduce.jsp): 0 records

-**Philippine Health Research Registry** (http://registry. healthresearch.ph/): 0 results

-**Sri Lanka Clinical Trials Registry** (http://www.slctr.lk/): 0 records

-**Thai Clinical Trials Registry** (http://www.clinicaltrials.in.th/): 0 records

-**Brazilian Clinical Trials Registry** (http://www.ensaiosclinicos.gov.br/): 0 records

-**Public Cuban Registry of Clinical Trials** (http://registroclinico.sld.cu/en/home): 0 records

-**Peruvian Registry of Clinical Trials** (http://www.ins.gob.pe/ ensayosclinicos/): 0 records

-**Pan AfricanClinical Trials Registry** (http://www.pactr.org/): 0 records

-**South African National Clinical Trials Register**: (http://www.sanctr.gov.za/): 0 records

-**Tanzania Clinical Trial Registry** (http://www.tzctr.or.tz/): 0 records

# Regulatory Agencies sites search results

### US Food and Drug Administration (FDA)

https://search.usa.gov/search?utf8=%E2%9C%93&affiliate=fda&query=sotagliflozin&commit=Search:

6 results

### European Medicines Agency (EMA)

https://www.ema.europa.eu/en/search/search?search_api_views_fulltext=sotagliflozin): 49 results

### Japanese Pharmaceutical and Medical Devices Agency(PMDA)

https://ss.pmda.go.jp/en_all/search.x?q=sotagliflozin&ie=UTF-8&page=1&x=30&y=11:

0 results

## Definitions

**Hypoglycemia:** blood glucose levels ≤ 70 mg/dL documented on self-monitoring blood glucose, regardless of symptoms. We evaluated hypoglycaemia asnumber of hypoglycemic events per patient-year[1]

**Severe hypoglycemia:** an event consistent with hypoglycemia (regardless of whether biochemical documentation of a low glucose value was obtained) when any of the following three conditions occurred:

• the patient have an episode of suspected hypoglycemia treated with any form of carbohydrate or with glucagon that required the assistance of others to treat, because the neurologic impairment was severe enough to prevent self-treatment in the opinion of those providing assistance to treat.

• the patient lost consciousness during the episode

• the patient had a seizure during the episode

**Diabetic ketoacidosis (DKA):** DKA was diagnosed based on evidence of anion-gap metabolic acidosis related to excessive ketone production without a satisfactory alternative cause for anion-gap acidosis, as outlined in Kitabchi et al 2009[2].

**Renal event:** defined according to the following Medical Dictionary for Regulatory Activities preferred terms:

Acute prerenal failure; Anuria; Azotemia; Blood creatine abnormal; Blood creatine decreased; Blood creatine increased; Blood creatinine abnormal; Blood creatinine decreased; Blood creatinine increased Blood urea abnormal; Blood urea increased; Blood urea nitrogen/creatinine ratioincreased

Coma uremic; Computerized tomogram kidney abnormal; Creatine urine abnormal; Creatine urine decreased; Creatine urine increased; Creatinine renal clearance abnormal

Creatinine renal clearance decreased; Creatinine urine abnormal; Creatinine urine decreased

Creatinine urine increased; Cystatin C abnormal; Cystatin C increased, Diabetic end stage renal disease; Glomerular filtration rate abnormal; Glomerular filtration rate decreased;

Glomerular filtration rate increased; Hypercreatinemia; Hyperparathyroidism secondary

Inulin renal clearance abnormal; Inulin renal clearance decreased; Kidney fibrosis; Nephrogenic anemia; Nitrogen balance negative; Edema due to renaldisease; OliguriaPericarditis uremicPhenolsulfonphthalein test abnormal; Postoperative renal failure Prerenal failure; Renal cortical necrosis; Renal disorder; Renal failure; Renal failure acute;Renal failure chronic; Renal function test abnormal;Renal impairment; Renal injury;Renalnecrosis;Renal papillary necrosis;Renal scan abnormal;Renal tubular acidosis;Renal tubular atrophy;Renal tubular disorder;Renal tubular necrosis;Ultrasound kidney abnormal;Uremicacidosis;Uremicencephalopathy;UremicgastropathyUremic neuropathy; Uremic pruritus;Urea renal clearance;Urea renal clearance decreased;Urea renal clearance increased;Uridosis;Urine albumin/creatinine ratio abnormal;Urine albumin/creatinine ratio decreased; Urine albumin/creatinine ratio increased;Urineoutput;Urine output decreased;Urine output increased; Urine protein/creatinine ration abnormal;Urine protein/creatinine ratio decreased; Urine protein/creatinine ratio increased.

**Volume depletion event:** defined according to the following Medical Dictionary for Regulatory Activities preferred terms:

Acute prerenal failure;Blood pressure abnormal;Blood pressure ambulatory abnormal;Blood pressure decreased;Blood pressure diastolic abnormal;Blood pressure diastolic decreased;Blood pressure fluctuation;Blood pressure immeasurable;Blood pressure inadequately controlled;Blood pressure orthostasisabnormal;Blood pressure orthostatic decreased;Blood pressure systolic abnormal;Blood pressure systolic decreased;Blood pressure systolic inspiratorydecreased;Brachial pulse abnormal; Brachial pulse decreased;BUN/creatinine ratio increased;Capillary nail refill test abnormal;Cardiac index abnormal;Cardiac index decreased;Cardiac output decreased;Cardiovascularinsufficient;Carotid pulse abnormal;Carotid pulse decreased;Central venous pressure abnormal;Central venous pressure decreased;Circulatorycollapse;Decreasedventricularpreload;Dehydration;Diastolichypotension;Femoral

pulse abnormal;Femoral pulse decreased;Hemodynamic test abnormal;Heart rate abnormal;Heart rate decreased;

Heart rate increased;Hypoperfusion;Hypotension;Hypovolemia;Hypovolemic shock;

Labile blood pressure;Left ventricular end-diastolic pressuredecreased;Maximum heart rate decreased;

Mean arterial pressure decreased;Orthostatic heart rate response increased;Orthostatic hypotension;

Orthostatic intolerance;Pedal pulse abnormal;Pedal pulse decreased;Peripheral circulatory failure;Peripheral coldness;Peripheral pulse decreased;Popliteal pulse abnormal;Popliteal pulse decreased;

Prerenal failure;Presyncope;Pulseabnormal;Pulseabsent;Pulse pressure abnormal;Pulse pressure decreased;Pulse volume decreased;Pulse waveform abnormal;Radial pulse abnormal;Radial pulse decreased;Renalischemia;Schellingtest;Shock;Syncope;Thirst;Tilt table test positive;Urine albumin/creatinine ratio increased;Urine flow decreased;Urine output decreased;

Urine protein/creatinine ratio increased;Vascular test abnormal;Venous pressure abnormal;

Venous pressure decreased;Venous pressure jugular abnormal;Venous pressure jugular decreased;

Volume blood decreased.

**Acidosis-related adverse event**

Adverse events that satisfy the trigger terms for metabolic acidosis, which are the following Medical Dictionary for Regulatory Activities preferred terms: acetonemia, acidosis, acidosis hyperchloremic, blood ketone body, blood ketone body increased, blood ketone body present, DKA, diabetic hyperglycemia, coma, diabetic ketoacidotichyperglycemic diabetic metabolic decompensation, diabetic coma, hyperglycemic coma, hyperglycemic seizure, hyperglycemic unconsciousness, ketoacidosis, ketosis, lactic acidosis,metabolic acidosis, renaltubularacidosis,uremic acidosis, urine ketone body, and urine ketone body present.

**Serious AEs**

Serious adverse events were defined as serious if they resulted in death, a life-threaten, patient hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or if they required medical intervention to prevent one of the outcomes listed above. For this meta-analysis, serious AEs were defined as the number of participants experiencing death, cancer (all cancers, bladder cancer, breast cancer), MACE, severe hypoglycaemia, serious acidosis-related adverse events..

**Management of missing data.**

Missing data were managed by contacting via e-mail the corresponding authors of the RCTs. Where this was unsuccessful, we planned to calculate missing data from the raw numbers given in tables and/or estimated from bar charts. For missing standard deviations of mean change in parameters, and where the p value was provided for a comparison between treated and control groups, we planned to calculate the standard deviation by converting the p value into a t value with appropriate degrees of freedom, and then calculating standard error and standard deviation. If neither the standard deviations nor the p values were supplied, we planned to impute a standard deviation from studies with similar measurement methods, duration and measurement error was used if available1 and tested in a sensitivity analysis and reported if the estimate differed meaningfully from previous estimates. If no similar studies were available, a narrative approach would have been used to summarize the data

[1]Workgroup on Hypoglycemia, American Diabetes Association.Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care. 2005;28:1245-9

[2]Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemiccrises in adultpatients with diabetes.Diabetes Care. 2009;32:1335-43