



Alternative Uses of the SGLT_i Class

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Norfolk and Norwich University Hospitals

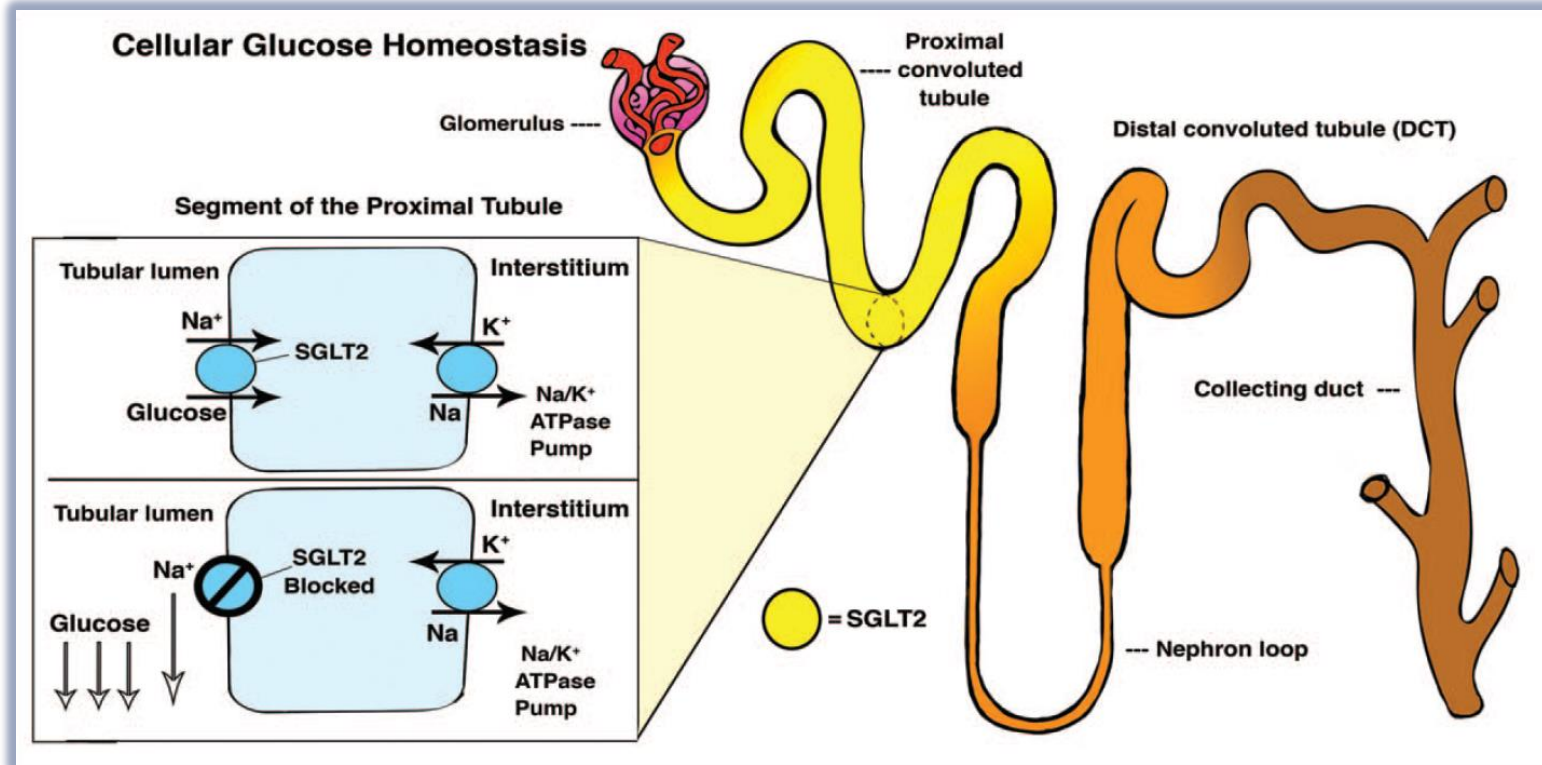


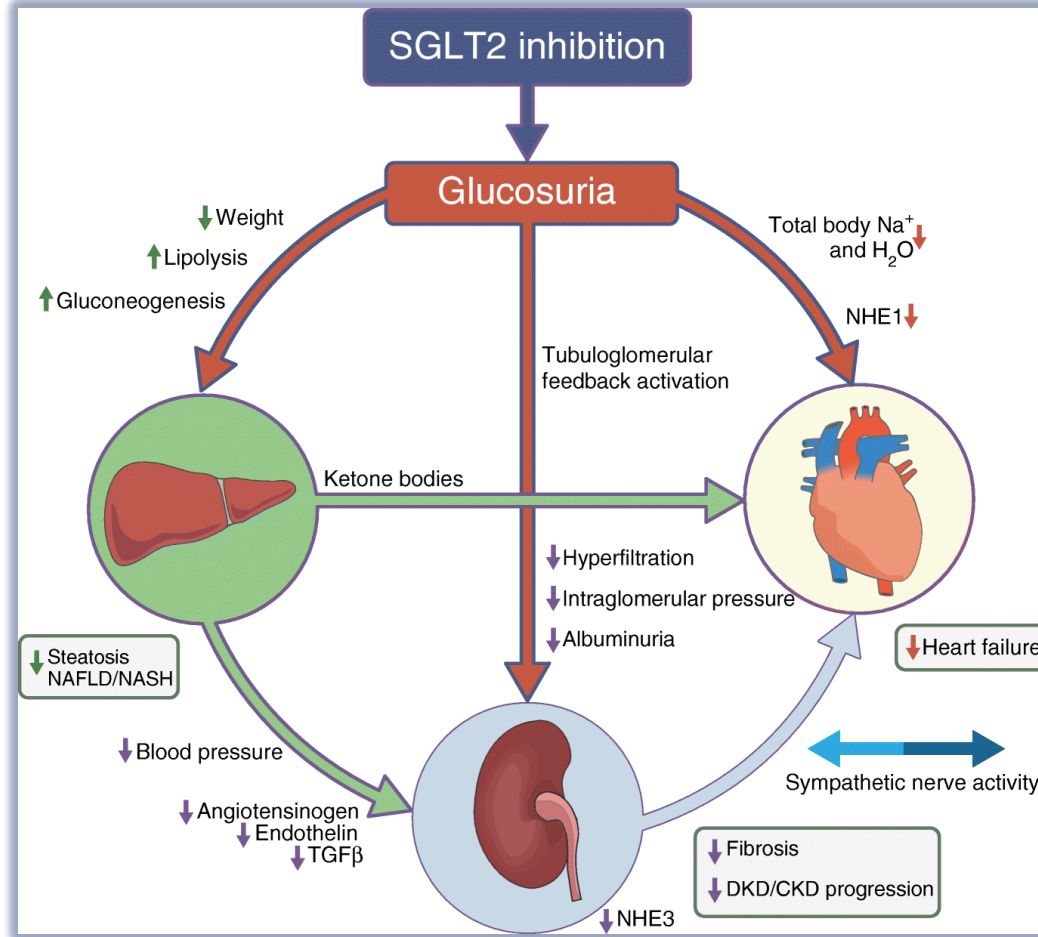
Who is This Strange Man?

- I qualified in 1991
- I trained in D&E and G(I)M in London – but started here on the IoW
- I did general practice for 2 years
- I did ITU / anaesthetics for a year
- I did research at Mayo Clinic for 2 years
- I have been in Norwich since 2004
- Currently my other roles include
 - Chair of the Specialist Clinical Exam in D&E and the European Board Exam in Endocrinology, Diabetes and Metabolism
 - President-Elect of the Endocrine Section of the Royal Society of Medicine
 - On the Steering group for the Joint British Diabetes Societies for Inpatient Care



How Do SGLT-2 Inhibitors Work?





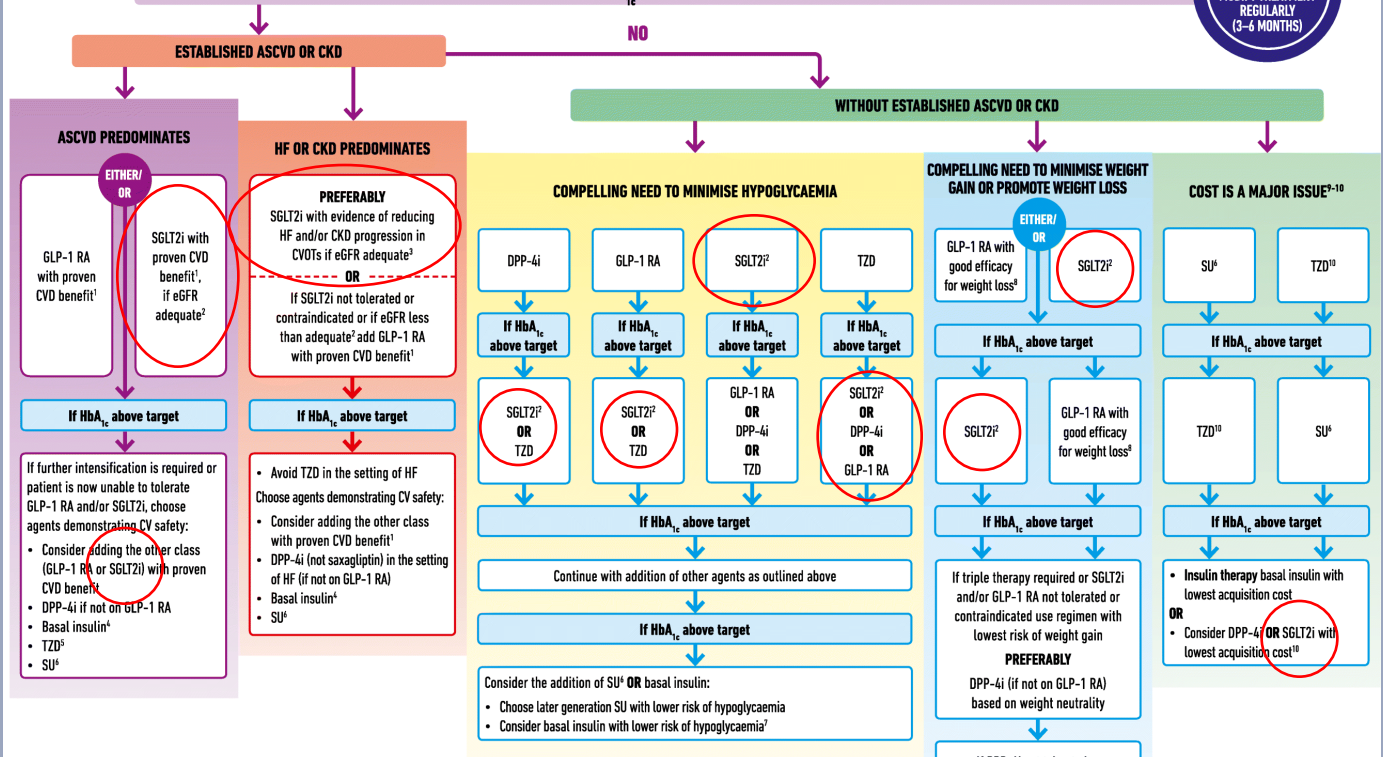
Do They Work?

- Cardiovascular mortality
- Heart failure
- Chronic kidney disease
- Weight loss
- Blood pressure

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH

**FIRST-LINE THERAPY IS METFORMIN AND COMPREHENSIVE LIFESTYLE (INCLUDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY)
IF HbA_{1c} ABOVE TARGET PROCEED AS BELOW**

TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3-6 MONTHS)

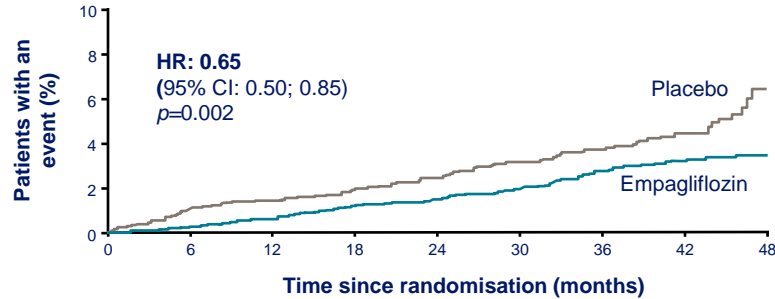


1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
 2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
 3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVDs
 4. Degludec or U100 glargine have demonstrated CVD safety

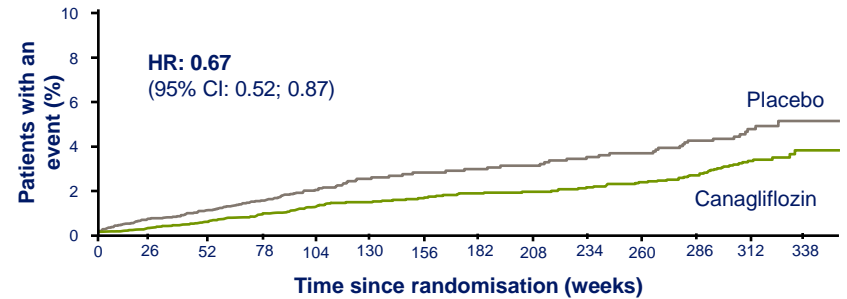
5. Low dose may be better tolerated though less well studied for CVD effects
 6. Choose later generation SU with lower risk of hypoglycaemia
 7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
 8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
 9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight-related comorbidities)
 10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

Second-Line Therapy for T2D in Patients with Established CVD or CCF

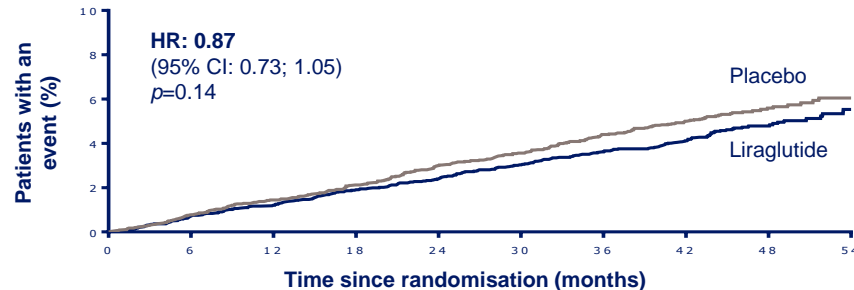
EMPA-REG OUTCOME¹



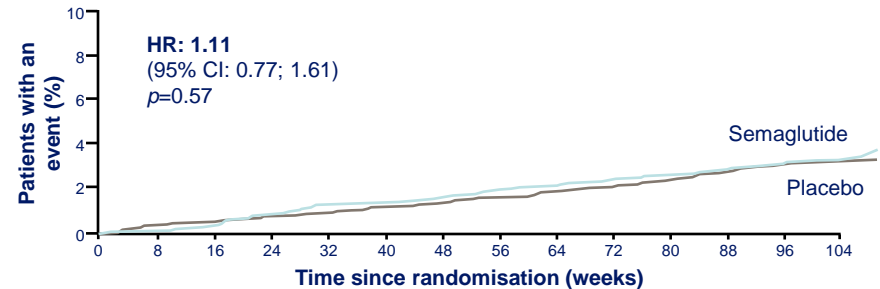
CANVAS Program²



LEADER³

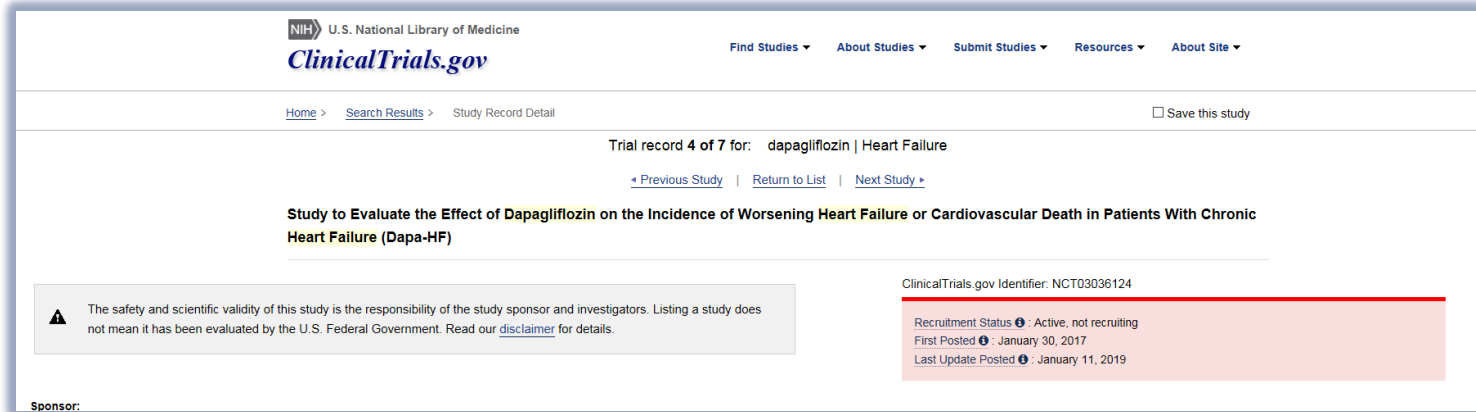


SUSTAIN 6⁴



So

- Trials are underway to use these agents in people without diabetes who have CCF or CVD



The screenshot shows the ClinicalTrials.gov website interface. At the top, it identifies the site as being from the NIH U.S. National Library of Medicine. The main header includes the 'ClinicalTrials.gov' logo and navigation links for 'Find Studies', 'About Studies', 'Submit Studies', 'Resources', and 'About Site'. Below the header, there are breadcrumb links: 'Home > Search Results > Study Record Detail' and a 'Save this study' checkbox. The central content area displays 'Trial record 4 of 7 for: dapagliflozin | Heart Failure' with navigation links for 'Previous Study', 'Return to List', and 'Next Study'. The study title is 'Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure (Dapa-HF)'. A disclaimer box on the left states that the safety and scientific validity of the study is the responsibility of the sponsor and investigators. On the right, a red-bordered box provides the ClinicalTrials.gov Identifier (NCT03036124) and recruitment details: 'Recruitment Status: Active, not recruiting', 'First Posted: January 30, 2017', and 'Last Update Posted: January 11, 2019'. The 'Sponsor:' label is partially visible at the bottom left.

NIH U.S. National Library of Medicine
ClinicalTrials.gov
Find Studies About Studies Submit Studies Resources About Site

Home > Search Results > Study Record Detail Save this study

Trial record 4 of 7 for: dapagliflozin | Heart Failure
◀ Previous Study | Return to List | Next Study ▶

Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure (Dapa-HF)

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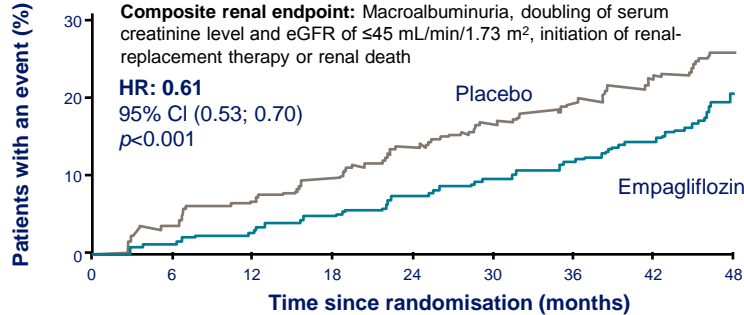
ClinicalTrials.gov Identifier: NCT03036124

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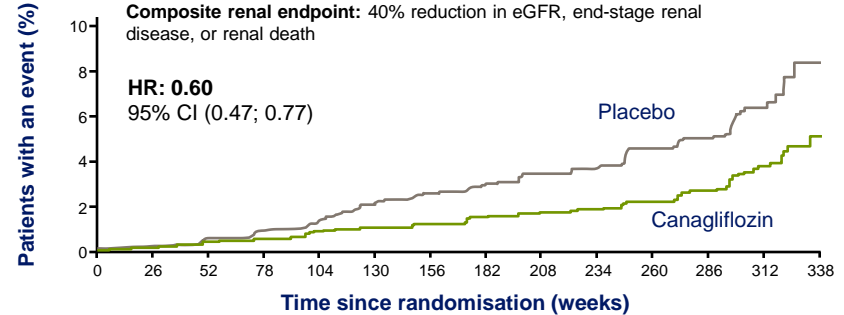
Sponsor:

Considerations Related to Chronic Kidney Disease

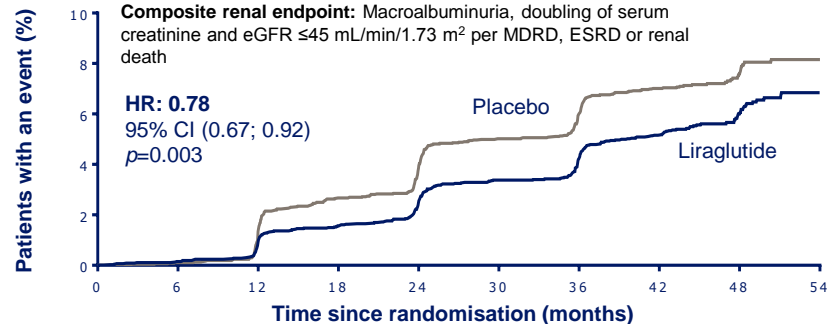
EMPA-REG OUTCOME¹



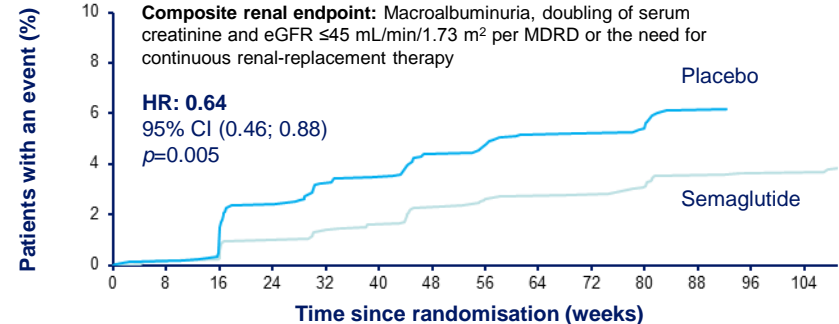
CANVAS Program²



LEADER³

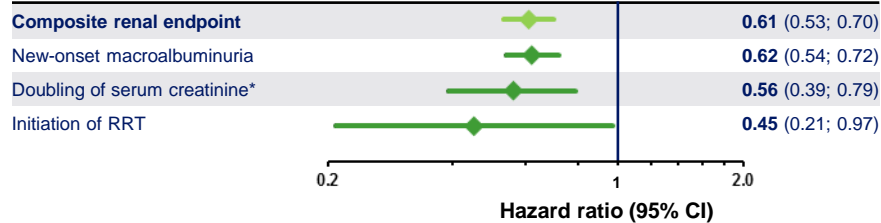


SUSTAIN 6⁴

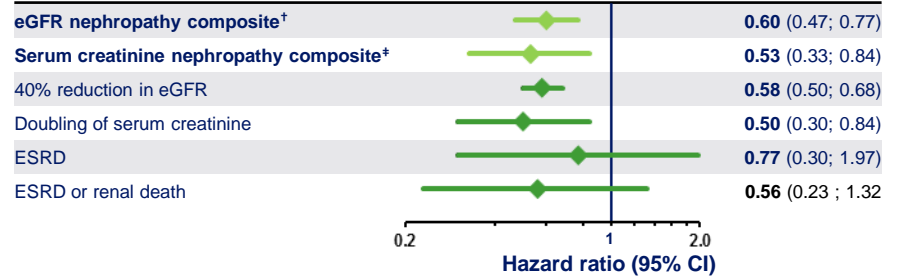


Considerations Related to Chronic Kidney Disease

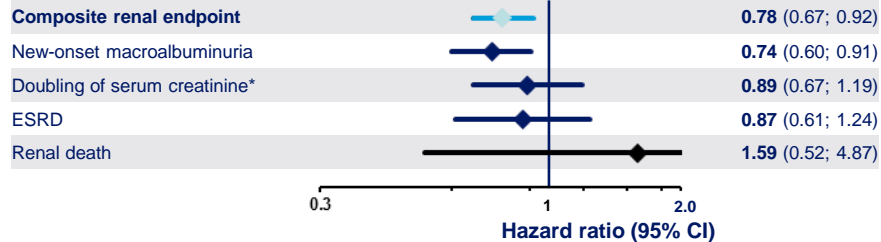
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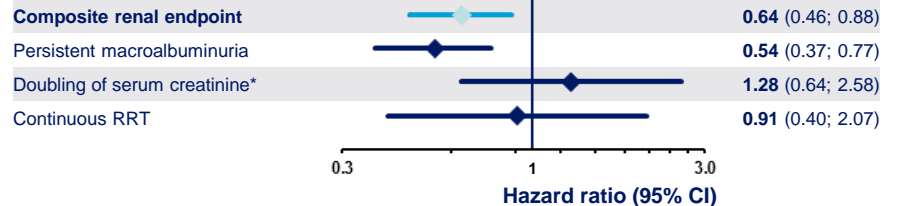
CANVAS Program²



LEADER³

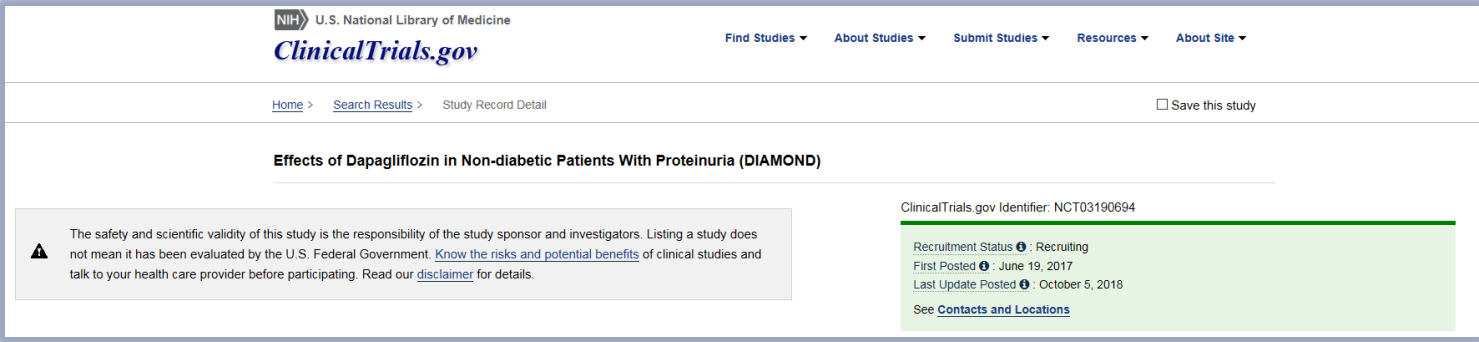


SUSTAIN 6⁴



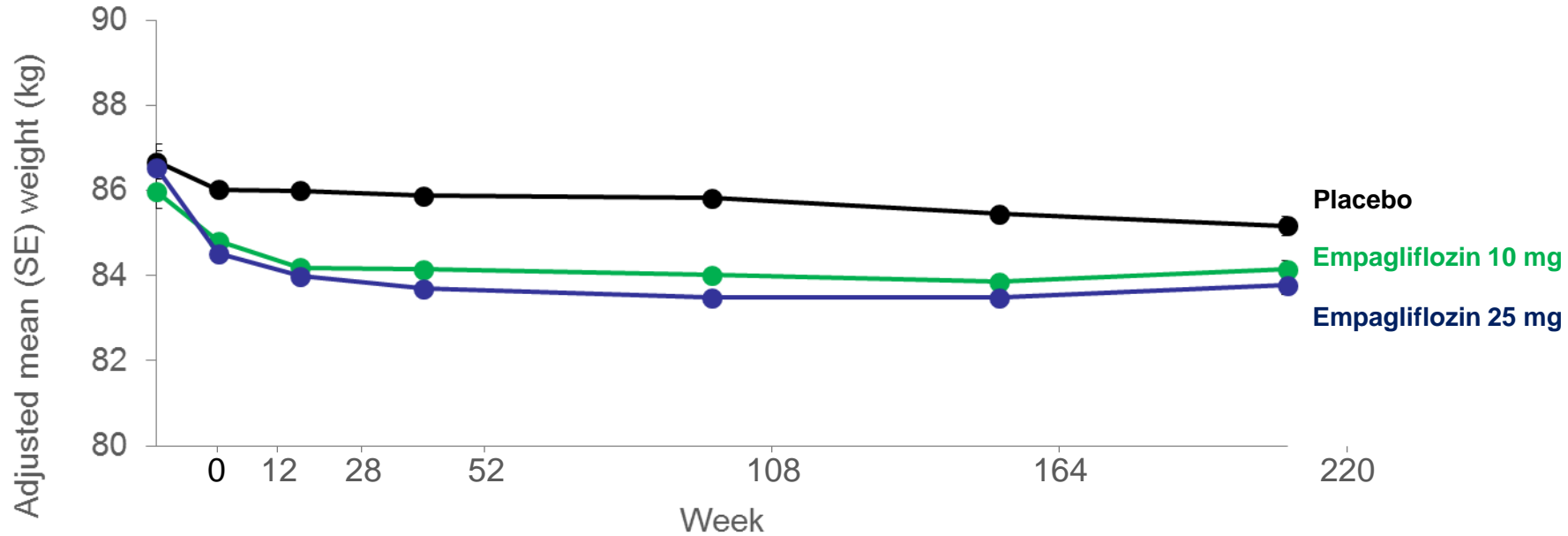
So

- Trials are underway to use these agents in people without diabetes who have impaired renal function



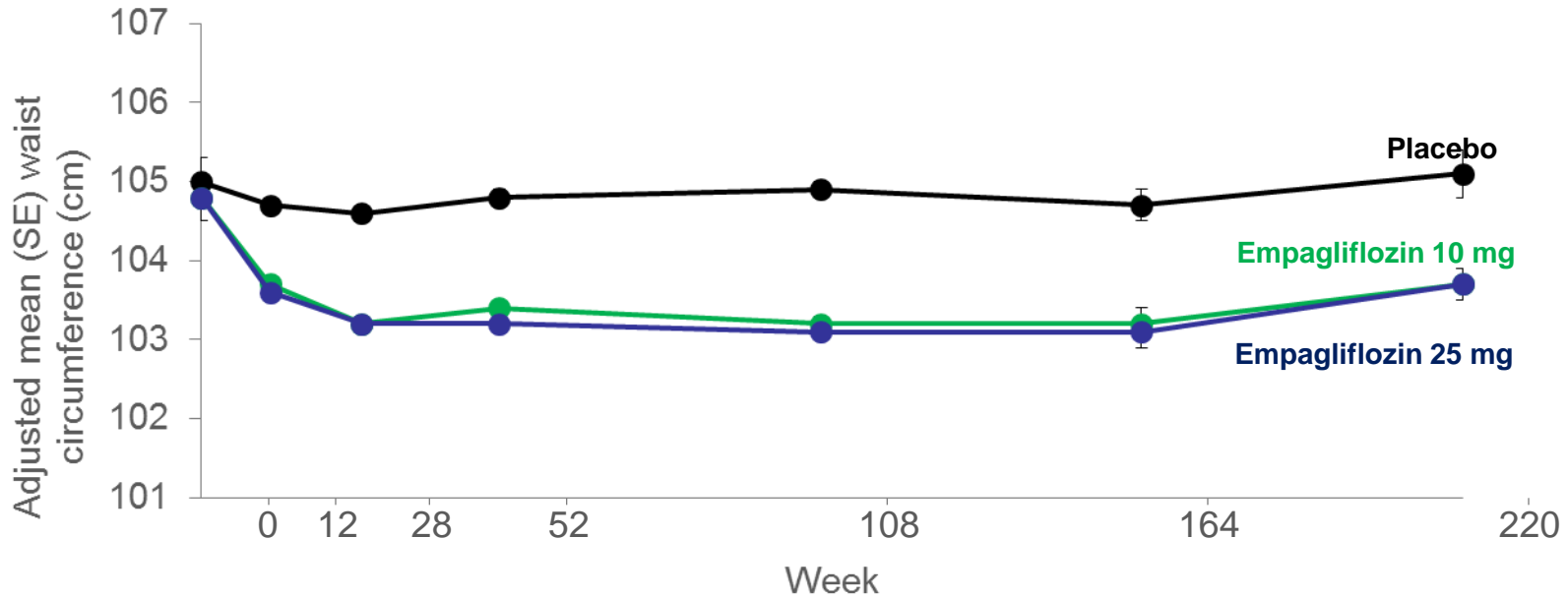
The screenshot shows the ClinicalTrials.gov website interface. At the top, it displays the NIH logo and the text 'U.S. National Library of Medicine' and 'ClinicalTrials.gov'. Navigation links include 'Find Studies', 'About Studies', 'Submit Studies', 'Resources', and 'About Site'. Below the navigation, there are breadcrumb links: 'Home > Search Results > Study Record Detail' and a 'Save this study' checkbox. The main heading of the study is 'Effects of Dapagliflozin in Non-diabetic Patients With Proteinuria (DIAMOND)'. A warning box on the left states: 'The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.' On the right, the ClinicalTrials.gov Identifier is NCT03190694. A green box contains the following information: 'Recruitment Status: Recruiting', 'First Posted: June 19, 2017', 'Last Update Posted: October 5, 2018', and a link to 'See Contacts and Locations'.

Weight



Placebo	2285	1915	2215	2138	1598	1239	425
Empagliflozin 10 mg	2290	1893	2238	2174	1673	1298	483
Empagliflozin 25 mg	2283	1891	2226	2178	1678	1335	489

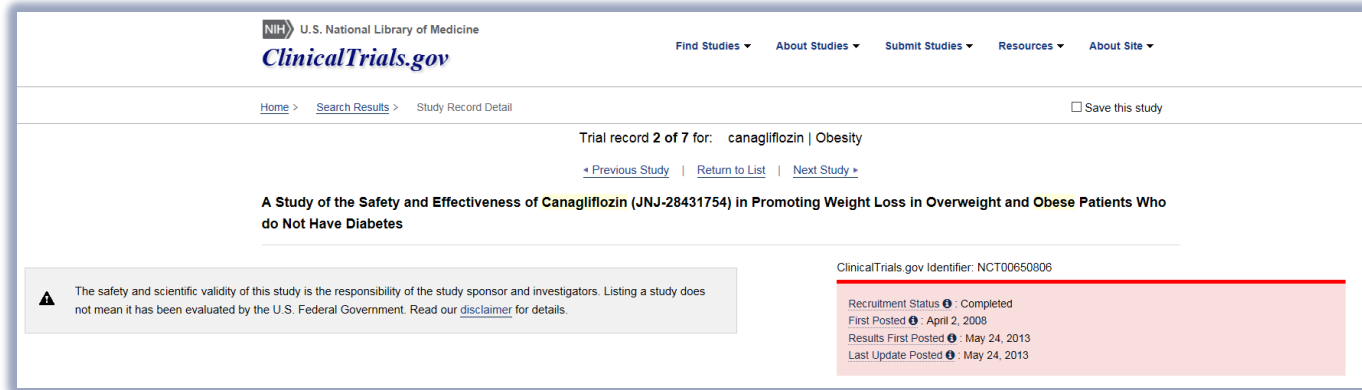
Waist Circumference



Placebo	2259	1869	2183	2110	1562	1220	418
Empagliflozin 10 mg	2272	1836	2219	2155	1644	1285	475
Empagliflozin 25 mg	2273	1857	2209	2157	1648	1329	486

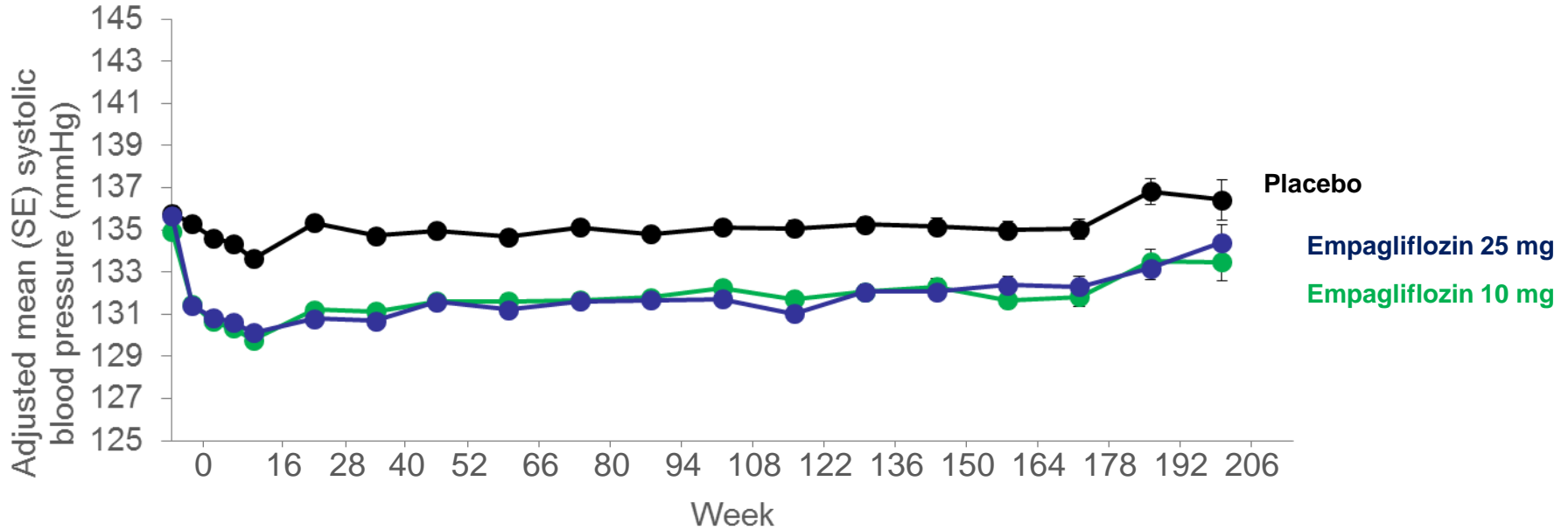
So

- Trials have been done and are underway to use these agents in people without diabetes who are overweight



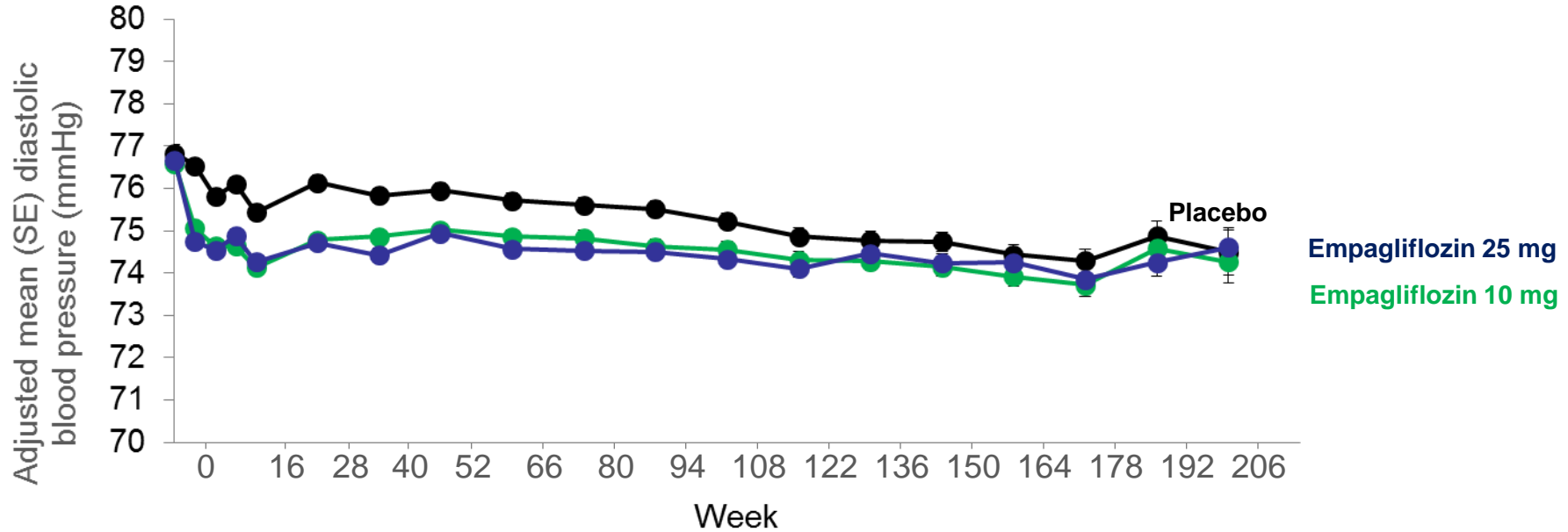
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Systolic Blood Pressure



Placebo	2322	2235	2203	2161	2133	2073	2024	1974	1771	1492	1274	1126	981	735	450	171
Empagliflozin 10 mg	2322	2250	2235	2193	2174	2125	2095	2072	1853	1556	1327	1189	1034	790	518	199
Empagliflozin 25 mg	2323	2247	2221	2197	2169	2129	2102	2066	1878	1571	1351	1212	1070	842	528	216

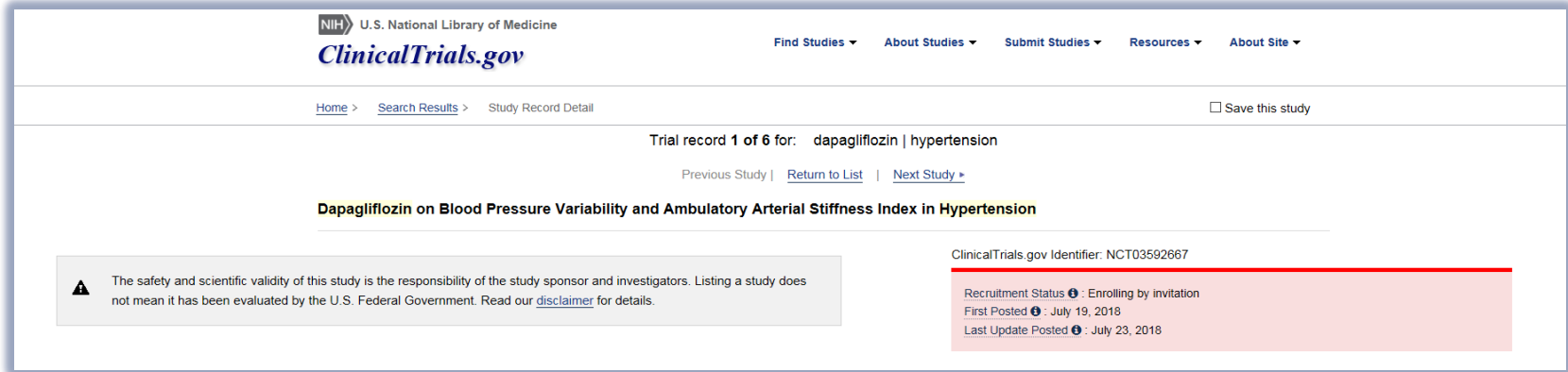
Diastolic Blood Pressure



Placebo	2322	2235	2203	2161	2133	2073	2024	1974	1771	1492	1274	1126	981	735	450	171
Empagliflozin 10 mg	2322	2250	2235	2193	2174	2125	2095	2072	1853	1556	1327	1189	1034	790	518	199
Empagliflozin 25 mg	2323	2247	2221	2197	2169	2129	2102	2066	1878	1571	1351	1212	1070	842	528	216

So

- Trials are underway to use these agents in people without diabetes who have hypertension



The screenshot shows the ClinicalTrials.gov website interface. At the top, it displays the NIH logo and 'U.S. National Library of Medicine' with the 'ClinicalTrials.gov' logo. Navigation links include 'Find Studies', 'About Studies', 'Submit Studies', 'Resources', and 'About Site'. Below the header, there are links for 'Home', 'Search Results', and 'Study Record Detail', along with a 'Save this study' checkbox. The main content area shows 'Trial record 1 of 6 for: dapagliflozin | hypertension' with navigation links for 'Previous Study', 'Return to List', and 'Next Study'. The study title is 'Dapagliflozin on Blood Pressure Variability and Ambulatory Arterial Stiffness Index in Hypertension'. A disclaimer box on the left states: 'The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.' On the right, the ClinicalTrials.gov Identifier is NCT03592667, and a red box contains the following details: 'Recruitment Status: Enrolling by invitation', 'First Posted: July 19, 2018', and 'Last Update Posted: July 23, 2018'.

Other Ongoing Areas of Study

- PCOS (vs metformin)
- Diabetes related eye disease
- Alzheimer's disease
- Gout
- NASH
- Bone metabolism

Finally – Type 1 Diabetes

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Sotagliflozin Added to Insulin in Patients with Type 1 Diabetes

Satish K. Garg, M.D., Robert R. Henry, M.D., Phillip Banks, M.S., John B. Buse, M.D., Ph.D., Melanie J. Davies, M.D., Gregory R. Fulcher, M.D., Paolo Pozzilli, M.D., Diane Gesty-Palmer, M.D., Ph.D., Pablo Lapuerta, M.D., Rafael Simó, M.D., Ph.D., Thomas Danne, M.D., Darren K. McGuire, M.D., M.H.Sc., Jake A. Kushner, M.D., Anne Peters, M.D., and Paul Strumph, M.D.

Efficacy and Safety of Dapagliflozin in Patients With Inadequately Controlled Type 1 Diabetes (the DEPICT-2 Study): 24-Week Results From a Randomized Controlled Trial

Diabetes Care 2018;41:1938–1946 | <https://doi.org/10.2337/dc18-0623>

Chantal Mathieu,¹ Paresh Dandona,² Pieter Gillard,¹ Peter Senior,³ Christoph Hasslacher,⁴ Eiichi Araki,⁵ Marcus Lind,^{6,7} Stephen C. Bain,⁸ Serge Jabbour,⁹ Niki Arya,¹⁰ Lars Hansen,¹¹ Fredrik Thorén,¹² and Anna Maria Langkilde,¹² on behalf of the DEPICT-2 Investigators*

Empagliflozin as Adjunctive to Insulin Therapy in Type 1 Diabetes: The EASE Trials

<https://doi.org/10.2337/dc18-1749>

Julio Rosenstock,¹ Jan Marquard,² Lori M. Laffel,³ Dietmar Neubacher,⁴ Stefan Kaspers,² David Z. Cherney,⁵ Bernard Zinman,⁶ Jay S. Skyler,⁷ Jyothis George,² Nima Soleymannlou,⁸ and Bruce A. Perkins⁵



Alternative Uses of the SGLT-2i Class

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 [@ketandhatariya](https://twitter.com/ketandhatariya)

