Albuminuria-lowering effect of dapagliflozin alone and in combination with saxagliptin and effect of dapagliflozin and saxagliptin on glycaemic control in patients with type 2 diabetes and chronic kidney disease (DELIGHT): a randomised, double-blind, placebo-controlled trial

Prof Carol Pollock, MD

Bergur Stefánsson, MD

Daniel Reyner, DrPH

Prof Peter Rossing, MD

C David Sjöström, MD

Prof David C Wheeler, MD

et al.

Show all authors

Published: April 13, 2019

DOI: https://doi.org/10.1016/S2213-8587(19)30086-5

Summary

Background

In patients with type 2 diabetes, intensive glucose control can be renoprotective and albuminuria-lowering treatments can slow the deterioration of kidney function. We assessed the albuminuria-lowering effect of the sodium-glucose co-transporter-2 inhibitor dapagliflozin with and without the dipeptidyl peptidase-4 inhibitor saxagliptin, and the effect of dapagliflozin–saxagliptin on glycaemic control in patients with type 2 diabetes and moderate-to-severe chronic kidney disease.

Methods

In this double-blind, placebo-controlled trial (DELIGHT), we enrolled patients at 116 research centres in Australia, Canada, Japan, South Korea, Mexico, South Africa, Spain, Taiwan, and the USA. We included patients with a known history of type 2 diabetes, increased albuminuria (urine albumin-to-creatinine ratio [UACR] 30–3500 mg/g), an estimated glomerular filtration rate of 25–75 mL/min per 1·73 m^2, and an HbA_{1c} of 7·0–11·0% (53–97 mmol/mol), who had been receiving stable doses of angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker therapy and glucose-lowering treatment for at least 12 weeks. After a 4-week, single-blind placebo run-in period, participants were randomly assigned (1:1:1; via an interactive voice–web response system) to receive dapagliflozin (10 mg) only, dapagliflozin (10 mg) and saxagliptin (2·5 mg), or placebo once-daily for 24 weeks. Primary endpoints were change from baseline in UACR (dapagliflozin and dapagliflozin–saxagliptin

groups) and HbA $_{1c}$ (dapagliflozin–saxagliptin group) at week 24 in all randomly allocated patients with available data (full analysis set). This study is registered with ClinicalTrials.gov, number NCT02547935 and is completed.

Findings

The study took place between July 14, 2015, and May 18, 2018. 1187 patients were screened, of whom 461 were randomly assigned: 145 to the dapagliflozin group, 155 to the dapagliflozin–saxagliptin group, and 148 to the placebo group (13 patients were excluded because of data integrity issues). Dapagliflozin and dapagliflozin–saxagliptin reduced UACR versus placebo throughout the study period. At week 24, the difference (*vs* placebo; n=134 patients with available data) in mean UACR change from baseline was −21·0% (95% CI −34·1 to −5·2; p=0·011) for dapagliflozin (n=132) and −38·0% (−48·2 to −25·8; p<0·0001) for dapagliflozin–saxagliptin (n=139). HbA $_{1c}$ was reduced in the dapagliflozin–saxagliptin group (n=137) compared with the placebo group (n=118) at week 24 (−0·58% [−0·80 to −0·37; p<0·0001]). The numbers of patients with adverse events (79 [54%] in the dapagliflozin group, 104 [68%] in the dapagliflozin–saxagliptin group, and 81 [55%] in the placebo group) or serious adverse events (12 [8%], 12 [8%], and 16 [11%], respectively) were similar across groups. There were no new drug-related safety signals.

Interpretation

Dapagliflozin with or without saxagliptin, given in addition to angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker treatment, is a potentially attractive option to slow the progression of kidney disease in patients with type 2 diabetes and moderate-to-severe chronic kidney disease.

Funding

AstraZeneca.

• View related content for this article

References

1.Coutinho M Gerstein HC Wang Y Yusuf S

The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95 783 individuals followed for 12·4 years.

Diabetes Care. 1999; **22**: 233-240

View in Article

Scopus (0)

PubMed

Crossref

Google Scholar

2.Fox CS Matsushita K Woodward M et al.

Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis.

Lancet. 2013; **380**: 1662-1673

View in Article

Scopus (393)

Summary

Full Text

Full Text PDF

Google Scholar

3.Perkovic V Heerspink HL Chalmers J et al.

Intensive glucose control improves kidney outcomes in patients with type 2 diabetes.
Kidney Int. 2013; **83**: 517-523

View in Article
Scopus (165)
PubMed
Summary
Full Text
Full Text PDF
Google Scholar

4.Zoungas S Arima H Gerstein HC et al.
Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials.
Lancet Diabetes Endocrinol. 2017; **5**: 431-437

View in Article
Scopus (81)
PubMed
Summary
Full Text
Full Text PDF
Google Scholar

5.Heerspink HJ Greene T Tighiouart H et al.
Change in albuminuria as a surrogate endpoint for progression of kidney disease: a meta-analysis of treatment effects in randomised clinical trials.
Lancet Diabetes Endocrinol. 2019; **7**: 128-139

View in Article
Scopus (3)
PubMed
Summary
Full Text
Full Text PDF
Google Scholar

6.Heerspink HJ Perkins BA Fitchett DH Husain M Cherney DZ

Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes: cardiovascular and kidney effects, potential mechanisms and clinical applications.
Circulation. 2016; **134**: 752-772

View in Article
PubMed
Crossref
Google Scholar

7.Muskiet MHA Tonneijck L Smits MM et al.
GLP-1 and the kidney: from physiology to pharmacology and outcomes in diabetes.
Nat Rev Nephrol. 2017; **13**: 605-628

View in Article
Scopus (43)
PubMed
Crossref
Google Scholar

8.Petrykiv S Sjostrom CD Greasley PJ Xu J Persson F Heerspink HJL
Differential effects of dapagliflozin on cardiovascular risk factors at varying degrees of renal function.
Clin J Am Soc Nephrol. 2017; **12**: 751-759

View in Article
PubMed
Crossref
Google Scholar

9.Dekkers CCJ Wheeler DC Sjöström CD Stefansson BV Cain V Heerspink HJL
Effects of the sodium-glucose co-transporter 2 inhibitor dapagliflozin in patients with type 2 diabetes and stages 3b–4 chronic kidney disease.
Nephrol Dial Transplant. 2018; **33**: 2005-2011

View in Article
Scopus (15)
PubMed
Crossref
Google Scholar

10. Perkovic V de Zeeuw D Mahaffey KW et al.

Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS Program randomised clinical trials.

Lancet Diabetes Endocrinol. 2018; **6**: 691-704

View in Article
Scopus (5)
PubMed
Summary
Full Text
Full Text PDF
Google Scholar

11. Fioretto P Stefansson BV Johnsson E Cain VA Sjostrom CD

Dapagliflozin reduces albuminuria over 2 years in patients with type 2 diabetes mellitus and renal impairment.

Diabetologia. 2016; **59**: 2036-2039

View in Article
Scopus (36)
PubMed
Crossref
Google Scholar

12. Cherney DZI Zinman B Inzucchi SE et al.

Effects of empagliflozin on the urinary albumin-to-creatinine ratio in patients with type 2 diabetes and established cardiovascular disease: an exploratory analysis from the EMPA-REG OUTCOME randomised, placebo-controlled trial.

Lancet Diabetes Endocrinol. 2017; **5**: 610-621

View in Article
Scopus (78)
PubMed
Summary
Full Text
Full Text PDF
Google Scholar

13. Wiviott SD Raz I Bonaca MP et al.

Dapagliflozin and cardiovascular outcomes in type 2 diabetes.

N Engl J Med. 2019; **380**: 347-357

View in Article

Scopus (117)

PubMed

Crossref

Google Scholar

14. Heerspink HJ Desai M Jardine M Balis D Meininger G Perkovic V

Canagliflozin slows progression of renal function decline independently of glycemic effects.

J Am Soc Nephrol. 2017; **28**: 368-375

View in Article

Scopus (105)

PubMed

Crossref

Google Scholar

15. Heerspink HJ Johnsson E Gause-Nilsson I Cain VA Sjöström CD

Dapagliflozin reduces albuminuria in patients with diabetes and hypertension receiving renin-angiotensin blockers.

Diabetes Obes Metab. 2016; **18**: 590-597

View in Article

Scopus (72)

PubMed

Crossref

Google Scholar

16. Mosenzon O Leibowitz G Bhatt DL et al.

Effect of saxagliptin on renal outcomes in the SAVOR-TIMI 53 trial.

Diabetes Care. 2017; **40**: 69-76

View in Article

Scopus (65)

PubMed

Crossref
Google Scholar

17. Rosenstock J Perkovic V Johansen OE et al.
Effect of linagliptin *vs* placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial.
JAMA. 2019; **321**: 69-79

View in Article
Scopus (22)
PubMed
Crossref
Google Scholar

18. Groop P-H Cooper ME Perkovic V et al.
Linagliptin and its effects on hyperglycaemia and albuminuria in patients with type 2 diabetes and renal dysfunction: the randomized MARLINA-T2D trial.
Diabetes Obes Metab. 2017; **19**: 1610-1619

View in Article
Scopus (36)
PubMed
Crossref
Google Scholar

19. Levey AS Coresh J Greene T et al.
Expressing the modification of diet in renal disease study equation for estimating glomerular filtration rate with standardized serum creatinine values.
Clin Chem. 2007; **53**: 766-772

View in Article
Scopus (1112)
PubMed
Crossref
Google Scholar

20. Matsuo S Imai E Horio M et al.
Revised equations for estimated GFR from serum creatinine in Japan.

Am J Kidney Dis. 2009; **53**: 982-992

View in Article
Scopus (2848)
PubMed
Summary
Full Text
Full Text PDF
Google Scholar

21. Chen LI Guh JY Wu KD et al.

Modification of diet in renal disease (MDRD) study and CKD epidemiology collaboration (CKD-EPI) equations for Taiwanese adults.

PLoS One. 2014; **9**: e99645

View in Article
Scopus (0)
PubMed
Crossref
Google Scholar

22. Men P Li XT Tang HL Zhai SD

Efficacy and safety of saxagliptin in patients with type 2 diabetes: a systematic review and meta-analysis.

PLoS One. 2018; **13**: e0197321

View in Article
Scopus (1)
PubMed
Crossref
Google Scholar

23. Ptaszynska A Johnsson KM Parikh SJ de Bruin TW Apanovitch AM List JF

Safety profile of dapagliflozin for type 2 diabetes: pooled analysis of clinical studies for overall safety and rare events.

Drug Saf. 2014; **37**: 815-829

View in Article
PubMed

Crossref
Google Scholar

24. Rosenstock J Hansen L Zee P et al.
Dual add-on therapy in type 2 diabetes poorly controlled with metformin monotherapy: a randomized double-blind trial of saxagliptin plus dapagliflozin addition versus single addition of saxagliptin or dapagliflozin to metformin.
Diabetes Care. 2015; **38**: 376-383

View in Article
Scopus (151)
PubMed
Crossref
Google Scholar

25. Mathieu C Ranetti AE Li D et al.
Randomized, double-blind, phase 3 trial of triple therapy with dapagliflozin add-on to saxagliptin plus metformin in type 2 diabetes.
Diabetes Care. 2015; **38**: 2009-2017

View in Article
Scopus (56)
PubMed
Crossref
Google Scholar

26. Heerspink HJ Ninomiya T Persson F et al.
Is a reduction in albuminuria associated with renal and cardiovascular protection? A post hoc analysis of the ALTITUDE trial.
Diabetes Obes Metab. 2016; **18**: 169-177

View in Article
PubMed
Crossref
Google Scholar

27. de Zeeuw D Remuzzi G Parving HH et al.
Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: lessons

from RENAAL.

Kidney Int. 2004; **65**: 2309-2320

View in Article

Scopus (685)

PubMed

Summary

Full Text

Full Text PDF

Google Scholar

28. Panchapakesan U Pegg K Gross S et al.

Effects of SGLT2 inhibition in human kidney proximal tubular cells—renoprotection in diabetic nephropathy?.

PLoS One. 2013; **8**: e54442

View in Article

Scopus (0)

PubMed

Crossref

Google Scholar

29. Esterline RL Vaag A Oscarsson J Vora J

Mechanisms in endocrinology: SGLT2 inhibitors: clinical benefits by restoration of normal diurnal metabolism?.

Eur J Endocrinol. 2018; **178**: R113-R125

View in Article

Scopus (5)

PubMed

Crossref

Google Scholar

30. Gilbert RE

SGLT2 inhibitors: β blockers for the kidney?.

Lancet Diabetes Endocrinol. 2016; **4**: 814

View in Article

PubMed

Summary
Full Text
Full Text PDF
Google Scholar

31. Kohan DE Fioretto P Tang W List JF
Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control.
Kidney Int. 2014; **85**: 962-971

View in Article
Scopus (311)
PubMed
Summary
Full Text
Full Text PDF
Google Scholar

32. Fioretto P Del Prato S Buse JB et al.
Efficacy and safety of dapagliflozin in patients with type 2 diabetes and moderate renal impairment (chronic kidney disease stage 3A): the DERIVE study.
Diabetes Obes Metab. 2018; **20**: 2532-2540

View in Article
Scopus (9)
PubMed
Crossref
Google Scholar

33. Neal B Perkovic V Mahaffey KW et al.
Canagliflozin and cardiovascular and renal events in type 2 diabetes.
N Engl J Med. 2017; **377**: 644-657

View in Article
Scopus (612)
PubMed
Crossref
Google Scholar

34. Jabbour S Seufert J Scheen A Bailey CJ Karup C Langkilde AM
Dapagliflozin in patients with type 2 diabetes mellitus: a pooled analysis of safety data from phase IIb/III clinical trials.
Diabetes Obes Metab. 2018; **20**: 620-628

View in Article
Scopus (1)
PubMed
Crossref
Google Scholar

Article Info

Publication History

Published: April 13, 2019

Identification

DOI: https://doi.org/10.1016/S2213-8587(19)30086-5

Copyright

ScienceDirect

Access this article on ScienceDirect

Linked Articles

SGLT2 inhibitor and incretin mimetic therapy for type 2 diabetes and chronic kidney disease

Full-Text • PDF

Related Clinics

Diabetes, type 2

The Lancet Clinic

Commissions

Series

Picture Quiz

GLOBAL HEALTH

Hub

Commissions

Series

Global Burden of Disease

CONNECT

About

Contact Us

Customer Service

ACCESS

Information for Readers

Register

Subscription Options

My Account

Existing Print Subscribers

The Lancet *Updates*

Recommend Lancet journals to your librarian

The Lancet App

The Lancet Choice