Incretin based treatments and mortality in patients with type 2 diabetes: systematic review and meta-analysis

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ABSTRACT

OBJECTIVE

To assess the impact of incretin based treatment on all cause mortality in patients with type 2 diabetes.

DESIGN

Systematic review and meta-analysis of randomised trials.

DATA SOURCES

Medline, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov.

ELIGIBILITY CRITERIA

Randomised controlled trials that compared glucagon-like peptide-1 (GLP-1) receptor agonists or dipeptidyl peptidase-4 (DPP-4) inhibitors with placebo or active anti-diabetic drugs in patients with type 2 diabetes.

DATA COLLECTION AND ANALYSIS

Paired reviewers independently screened citations, assessed risk of bias of included studies, and extracted data. Peto's method was used as the primary approach to pool effect estimates from trials, sensitivity analyses were carried out with other statistical approaches, and meta-regression was applied for six prespecified hypotheses to explore heterogeneity. The GRADE approach was used to rate the quality of evidence.

RESULTS

189 randomised controlled trials (n=155 145) were included, all of which were at low to moderate risk of bias; 77 reported no events of death and 112 reported 3888 deaths among 151 614 patients. Meta-analysis of 189 trials showed no difference in all cause mortality between incretin drugs versus control (1925/84 136 *v* 1963/67 478; odds ratio 0.96, 95% confidence interval 0.90 to 1.02, I^2=0%; risk difference 3 fewer events (95% confidence interval 7 fewer to 1 more) per 1000 patients over five years; moderate quality evidence). Results suggested the possibility of a mortality benefit with GLP-1 agonists but not DPP-4 inhibitors, but the subgroup hypothesis had low credibility. Sensitivity analyses showed no important differences in the estimates of effects.

CONCLUSIONS

Current evidence does not support the suggestion that incretin based treatment increases all cause mortality in patients with type 2 diabetes. Further studies are warranted to examine if the effect differs between GLP-1 agonists versus DPP-4 inhibitors.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Concern has arisen as to whether incretin based treatments are associated with increased mortality, given a recent large randomised trial (SAVOR-TIMI 53 study) that suggested possible increased mortality with saxagliptin versus placebo

Although previously meta-analyses have explored this question, they had important methodological limitations and did not consider much of the currently available evidence

WHAT THIS STUDY ADDS

The current evidence provides no support for the hypothesis that incretin based treatment increases all cause mortality in patients with type 2 diabetes

Further studies are warranted to examine if the effect differs between GLP-1 agonists and DPP-4 inhibitors

Introduction

Incretin based treatments, including dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, represent important options for treating people with type 2 diabetes.[1] The American Diabetes Association and the European Association for the Study of Diabetes (EASD) have recommended these drug classes as second line agents for treatment of type 2 diabetes.[2] Their effects on glucose control are well established,[3-5] with additional benefits of weight loss, antihypertensive effects, and minimal risk of hypoglycemia.[4-11]

A recent large randomised trial (SAVOR-TIMI 53 study[12]) including patients with type 2 diabetes with established, or at risk for, cardiovascular disease, however, suggested possible increased mortality with saxagliptin versus placebo (5.1% *v* 4.6%). In response, the US Food and Drug Administration released the following statement in 2015: "A potential increase in all cause mortality with saxagliptin was observed—The ITT on-study analysis suggested an increase in all-cause mortality (HR=1.11, 95.1% CI [0.96 to 1.27]) based on about 800 observed deaths—Sensitivity analyses that censored subjects after treatment exposure showed more unfavorable trends in the risk of all cause mortality—Such trends were observed for both CV and non-CV related causes of death."[13]

This observation raised concern as to whether incretin based treatments could be associated with increased mortality; however, findings from other large trials were inconsistent. The TECOS[14] and the EXAMINE trial[15]—testing effects of sitagliptin and alogliptin—found no significant increase in mortality. Evidence from observational studies is also inconsistent.[16-21] We therefore carried out a systematic review and meta-analysis of randomised controlled trials to determine the effect of incretin based treatments on mortality in patients with type 2 diabetes.

Methods

We followed the reporting standards for systematic reviews and meta-analyses of randomised controlled trials according to the PRISMA statements.[22]

Eligibility criteria

We included randomised controlled trials that compared GLP-1 agonists or DPP-4 inhibitors against placebo, lifestyle modification, or active anti-hyperglycaemic drugs in patients with type 2 diabetes. Eligible studies reported ≥12 weeks' follow-up and explicitly reported data on all cause mortality.

Literature search

We searched Medline, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify relevant studies from inception to 18 February 2017, without language restrictions. We used database specific subject headings (such as MeSH terms) and free texts terms to search for potentially eligible studies (appendix 1). We searched ClinicalTrials.gov to identify additional relevant clinical trials and confirmed mortality data from all eligible published trials. This trial registry documents all phase II-IV drug trials as required by section 801 of the US Food and Drug Administration Amendments Act (FDAAA 801)[23] and typically includes extensive lists of adverse events.[24]

Study selection

Paired reviewers, trained in research methods, independently and in duplicate screened titles/abstracts and full texts for eligible articles, assessed risk of bias, and extracted data from each eligible study using standardised pilot tested forms with detailed instructions. Reviewers dealt with discrepancies through discussion or, if necessary, arbitration by a third reviewer.

Risk of bias assessment

Two reviewers independently assessed risk of bias of randomised controlled trials using a modified Cochrane risk of bias instrument that includes response options of "definitely or probably yes" (assigned a low risk of bias) or "definitely or probably no" (assigned a high risk of bias), an approach we have previously validated.[25-27] The items included random sequence generation; allocation concealment; blinding of participants, caregivers, outcome assessors and outcome adjudicators; infrequent missing outcome data; selective outcome reporting; and other sources of bias (details available at www.evidencepartners.com/resources/methodological-resources/).

Data extraction

For randomised controlled trials, we collected information regarding study characteristics (such as author name, year of publication, study design, sample size, length of follow-up), intervention characteristics (such as baseline treatment, type, dose, and duration of study treatment); patients' characteristics (such as age, sex, duration of type 2 diabetes, cardiovascular disease, body mass index (BMI), baseline HbA_{1c}, fasting plasma glucose); and mortality outcomes (that is, number of deaths and patients included for analyses in each treatment group). If a published trial did not report the number of deaths, while the corresponding registry report from ClinicalTrials.gov reported mortality, we used outcome data from the registry report. In an extension phase of a trial, if the initial treatment assignment was switched, we collected the outcome data before that point. For trials with multiple follow-up points, data, or reports, we collected outcome data at the longest follow-up.[28]

Data analysis and rating quality of evidence

We conducted a meta-analysis of all included trials using the reported deaths from treatment and control groups. Given the low event rates in many trials, we used Peto's method as the primary analysis to pool effect estimates across studies.[29] We excluded studies in which no deaths occurred in either study arm.

We conducted sensitivity analyses to examine the impact of using alternative effect measures (odds ratio versus relative risk), pooling methods (Peto versus Mantel-Hanszel (M-H)), statistical models (fixed versus random effects), continuity correction of 0.5 for trials with no events when pooling with the M-H method (versus excluding such trials),[30 31] and analysis of trials with two or more events (that is, excluding trials with no events or only one event).

We generated a funnel plot and applied Egger's test to examine publication bias. We also conducted an additional test for publication bias by excluding trials with only one event.

We used the Cochran's χ^2 test and the I^2 statistic to examine statistical heterogeneity. Following recent guidance for a credible subgroup effect,[32] we planned six hypotheses to explain variability in effect estimates of all cause mortality between studies: risk of cardiovascular disease at baseline (with low versus high versus unclear risk; larger effect in patients with low risk of cardiovascular comorbidities at baseline); type of incretin drug (DPP-4 inhibitors versus GLP-1 agonists; larger effect in trials testing GLP-1 agonists); length of follow-up (52 weeks or shorter versus over 52 weeks; larger effect in trials with longer follow-up); type of control (placebo versus active treatment; larger effect in trials with placebo control); mode of treatment (monotherapy versus add on/combination; larger effect in trials with add on/combination treatment); and individual incretin drugs (different incretins). We conducted univariable random effects meta-regression for each of the six hypotheses, when there were at least 10 trials available for analysis. We also conducted a post hoc multiple regression analysis adjusting for risk of cardiovascular disease at baseline, type of incretin drug, length of follow-up, type of control, and mode of treatment. To explore consistency of an apparent subgroup effect, we additionally conducted two univariable exploratory subgroup analyses by type of incretin drug, one on all cause mortality and another on cardiovascular events, using data from the six large cardiovascular outcome trials that compared either GLP-1 agonists or DPP-4 inhibitors versus placebo.

We used the GRADE approach to rate the quality of evidence and generate absolute estimates of effect for the outcomes.[33] To calculate the absolute increase in risk for mortality, we estimated the baseline risk for death from a large cohort study[16] that enrolled patients without previous myocardial infarction or stroke.

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Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Results

Of 19 250 unique reports, reviewers judged 1187 as potentially eligible at title and abstract screening; of these, 189 randomised controlled trials involving 155 145 participants proved eligible (fig 1).

Study characteristics

All 189 randomised controlled trials were funded by industry. Among those, 126 enrolled patients with type 2 diabetes at low risk of cardiovascular disease at baseline (specifically excluding patients with certain cardiovascular diseases), and 55 enrolled patients with unclear risk of cardiovascular disease at baseline (without mention of excluding patients with cardiovascular disease). The eight others enrolled patients at high risk of, or with established, cardiovascular disease at baseline, including six large cardiovascular outcomes trials (tables A and B in appendix 2).

The six large cardiovascular outcome trials (TECOS,[14] LEADER,[34] SUSTAIN-6,[35] ELIXA,[36] SAVOR-TIMI 53,[12] and EXAMINE[15] trial) enrolled 3297 to 16 492 patients at high risk of, or with established, cardiovascular disease at baseline, followed patients for a median of 1.5 to 3.8 years, and evaluated one of six incretin agents (sitagliptin, liraglutide, semaglutide, lixisenatide, saxagliptin, or alogliptin) versus placebo. The trials enrolled similar patients: mean age range 60.3-65.0, mean BMI 29.5-32.8, mean baseline HbA_{1c} 7.2-8.7%, mean fasting plasma glucose 8.2-8.7 mmol/L, and a mean or median duration of diabetes of 7.2-13.9 years (table A in appendix 2).

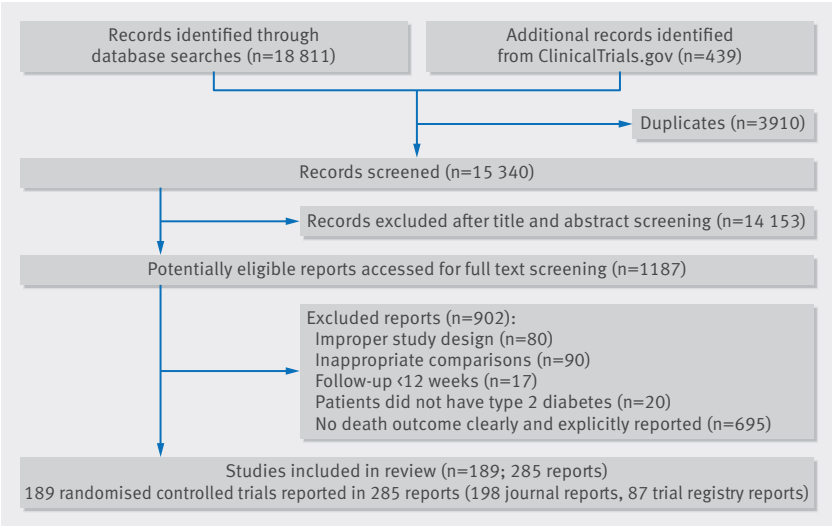


Fig 1 | Flow chart of selection of studies on incretin based treatments and mortality in patients with type 2 diabetes

Of the 183 other trials, 153 (83.6%) were clearly labelled as phase III studies. The length of follow-up was 12-234 weeks (median 24 weeks; interquartile range 24-52 weeks); the mean age of participants range was 49.7-74.9; mean or median BMI 21.7-37.1; mean baseline HbA_{1c} 6.6%-10.2%; mean fasting plasma glucose 6.2-12.2 mmol/L; and mean or median duration of diabetes 1.0-15.9 years (table A in appendix 2); 119 tested DPP-4 inhibitors, 68 GLP-1 agonists, and four tested both agents; 130 tested incretin drug versus placebo, 69 versus active comparator, 16 versus both placebo and active comparator; 71 used incretin drugs as monotherapy, 121 as add on/combination treatment, and nine administered both treatment options (table C in appendix 2).

Risk of bias assessment

Among the six large cardiovascular outcome trials, all adequately generated their randomisation sequence, concealed allocation, blinded patients and caregivers, and were free from reporting bias. Five (83.3%) trials had infrequent missing outcome data. The baseline characteristics were generally similar between treatment groups across all the trials (table D in appendix 2).

Of the 183 other randomised controlled trials, 177 (96.7%) adequately generated their randomisation sequence, 170 (92.9%) concealed allocation, and 155 (84.7%) blinded patients and caregivers. The baseline characteristics were generally similar between treatment groups in each trial. Only 47 (25.7%), however, were free from frequent missing outcome data (table D in appendix 2).

Effects on all cause mortality

Of the 189 trials, 77 (40.7%) reported that no deaths occurred during the course of study. The 112 other trials (59.3%) reported 3888 deaths among 151 614 patients, of which 3592 (92.4%) were reported from the six large cardiovascular outcome trials.

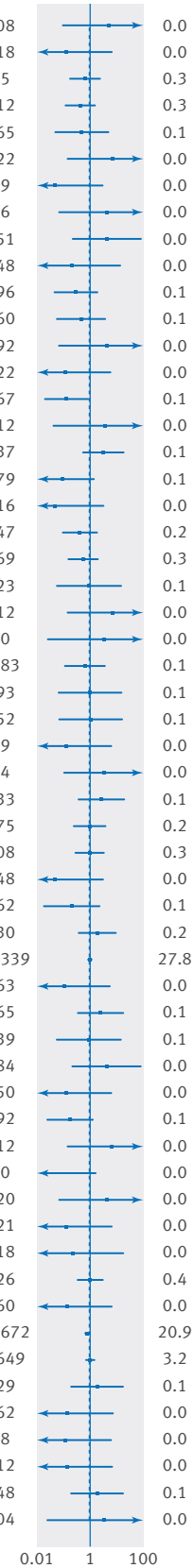
Our meta-analysis including the 112 trials that reported at least one death showed no difference in mortality between incretin drug versus control (1925/84 136 *v* 1963/67 478; odds ratio 0.96, 95% confidence interval 0.90 to 1.02, I^2=0%; risk difference 3 fewer events (95% confidence interval 7 fewer to 1 more) per 1000 patients over five years; moderate quality evidence, rated down because of inconsistency between GLP-1 agonists and DPP-4 inhibitors) (fig 2 and table 1). Trials that compared incretin treatment against placebo or no treatment contributed 97% of the weight to the analysis, and trials with an active comparator 4%.

Our funnel plot and statistical test showed no evidence of publication bias (fig 3 , Egger's test P=0.21). Our analysis excluding trials with no events or one event across arms found a similar result (fig A in appendix 3, Egger's test P=0.33). Sensitivity analyses using an alternative effect measure (M-H relative risk 0.95, 95% confidence interval 0.90 to 1.01), pooling method (M-H odds ratio 0.95, 0.89 to 1.01), statistical model (random effects M-H odds ratio 0.95, 0.89 to 1.02), continuity correction of 0.5 for trials with no events (M-H odds ratio 0.95, 0.89 to 1.01), and by excluding trials with no events

Study/subgroup	No of events/total: Incretin	Control	Peto fixed OR (95% CI)	Weight (%)	Peto fixed OR (95% CI)
Ahren 2014	1/604	0/408		0.0	5.34 (0.10 to 290.35)
Arechavaleta 2011	0/516	1/518		0.0	0.14 (0.00 to 6.85)
Arjona Ferreira 2013a	4/64	6/65		0.3	0.66 (0.18 to 2.39)
Arjona Ferreira 2013b	3/210	7/212		0.3	0.45 (0.13 to 1.56)
Aroda 2016	1/365	2/365		0.1	0.51 (0.05 to 4.94)
Aschner 2010	1/528	0/522		0.0	7.31 (0.14 to 368.20)
Bajaj 2014	0/183	1/89		0.0	0.05 (0.00 to 3.07)
Barnett 2012	1/151	0/76		0.0	4.50 (0.07 to 286.14)
Barnett 2013b	2/304	0/151		0.0	4.48 (0.24 to 85.32)
Bergenstal 2009	0/124	1/248		0.0	0.22 (0.00 to 14.26)
Blonde 2015	2/588	3/296		0.1	0.30 (0.05 to 1.95)
Bolli 2014	2/322	2/160		0.1	0.47 (0.06 to 3.76)
Bosi 2009	1/589	0/292		0.0	4.46 (0.07 to 286.98)
Buse 2011	0/137	1/122		0.0	0.12 (0.00 to 6.07)
Chacra 2011	1/501	4/267		0.1	0.13 (0.02 to 0.85)
Davies 2015	1/632	0/212		0.0	3.80 (0.04 to 348.86)
Davies 2016	4/140	1/137		0.1	3.31 (0.57 to 19.33)
DeFronzo 2009	1/564	2/179		0.1	0.10 (0.01 to 1.37)
DeFronzo 2012	0/1037	1/516		0.0	0.05 (0.00 to 3.16)
DeFronzo 2015	2/541	5/547		0.2	0.43 (0.10 to 1.89)
Del Prato 2014	6/1751	5/869		0.3	0.57 (0.16 to 2.02)
Diamant 2014a	1/233	1/223		0.1	0.96 (0.06 to 15.36)
Diamant 2014b	1/315	0/312		0.0	7.32 (0.15 to 368.87)
Dungan 2016	1/239	0/60		0.0	3.49 (0.03 to 466.30)
Ferrannini 2009	2/1389	3/1383		0.1	0.67 (0.12 to 3.86)
Filozof 2010	1/510	1/493		0.1	0.97 (0.06 to 15.48)
Fonseca 2007	1/144	1/152		0.1	1.06 (0.07 to 16.98)
Forst 2015	0/82	1/79		0.0	0.13 (0.00 to 6.57)
Frederich 2012	2/291	0/74		0.0	3.52 (0.11 to 111.02)
Frías 2016	3/231	1/233		0.1	2.76 (0.39 to 19.72)
Gallwitz 2012a	4/776	4/775		0.2	1.00 (0.25 to 4.01)
Gallwitz 2012b	5/511	5/508		0.3	0.99 (0.29 to 3.45)
Garber 2009	0/497	1/248		0.0	0.05 (0.00 to 3.17)
Giorgino 2015	1/545	2/262		0.1	0.21 (0.02 to 2.35)
Goke 2013	4/428	2/430		0.2	1.96 (0.39 to 9.78)
Green 2015 (TECOS)	547/7332	537/7339		27.8	1.02 (0.90 to 1.16)
Haak 2012	0/428	1/363		0.0	0.11 (0.00 to 5.78)
Henry 2014	3/581	1/565		0.1	2.65 (0.37 to 18.87)
Hermans 2012	1/147	1/139		0.1	0.95 (0.06 to 15.20)
Hollander 2011	2/381	0/184		0.0	4.42 (0.23 to 85.25)
Hollander 2012	0/154	1/150		0.0	0.13 (0.00 to 6.64)
Home 2015	0/271	4/392		0.1	0.18 (0.02 to 1.35)
Inagaki 2012	1/215	0/212		0.0	7.29 (0.14 to 367.26)
Kadowaki 2013c	0/244	1/80		0.0	0.02 (0.00 to 1.64)
Kaku 2016	1/240	0/120		0.0	4.48 (0.07 to 286.49)
Kothny 2013	0/227	1/221		0.0	0.13 (0.00 to 6.64)
Lavalle-Gonzalez 2013	0/366	1/918		0.0	0.25 (0.00 to 18.97)
Lukashevich 2011	8/287	6/226		0.4	1.05 (0.36 to 3.06)
Lukashevich 2014	0/157	1/160		0.0	0.14 (0.00 to 6.95)
Marso 2016 (LEADER)	381/4668	447/4672		20.9	0.84 (0.73 to 0.97)
Marso 2016 (SUSTAIN-6)	62/1648	60/1649		3.2	1.04 (0.72 to 1.49)
Mathieu 2015	2/329	1/329		0.1	1.95 (0.20 to 18.83)
Matthaei 2015	0/153	1/162		0.0	0.14 (0.00 to 7.22)
Mori 2016	0/40	1/38		0.0	0.13 (0.00 to 6.48)
Moses 2015	0/210	1/212		0.0	0.14 (0.00 to 6.89)
Nauck 2007	2/253	1/248		0.1	1.91 (0.20 to 18.49)
Nauck 2009	1/423	0/104		0.0	3.48 (0.03 to 478.41)
Nauck 2013a	2/724	0/363		0.0	4.49 (0.24 to 85.01)
Nauck 2013b	1/715	2/322		0.1	0.19 (0.02 to 2.18)
Nauck 2014	3/921	0/177		0.0	3.30 (0.15 to 71.84)
Nauck 2016	3/200	0/101		0.1	4.55 (0.41 to 50.38)
NCT00086515 2010	2/464	0/237		0.0	4.54 (0.24 to 85.17)
NCT00095056 2010	1/65	0/26		0.0	4.06 (0.05 to 310.62)
NCT00106704 2010	2/222	1/219		0.1	1.93 (0.20 to 18.62)
NCT00289848 2010	1/352	0/178		0.0	4.51 (0.07 to 285.90)
NCT00337610 2009	0/96	1/94		0.0	0.13 (0.00 to 6.68)
NCT00713830 2016	1/574	0/285		0.0	4.47 (0.07 to 286.89)
NCT00715624 2016	1/328	0/167		0.0	4.52 (0.07 to 285.56)
NCT00800683 2011	1/68	1/65		0.1	0.96 (0.06 to 15.45)
NCT00819091 2011	1/161	0/84		0.0	4.58 (0.07 to 284.55)
NCT00839527 2014	1/271	0/392		0.0	11.55 (0.21 to 622.27)
NCT00881530 2014	0/56	1/388		0.0	0.32 (0.00 to 116.67)
NCT01075282 2014	0/545	1/262		0.0	0.05 (0.00 to 3.02)
NCT01318083 2011	2/209	0/103		0.0	4.47 (0.23 to 85.58)
NCT01644500 2015	1/536	0/269		0.0	4.49 (0.07 to 286.29)
NCT01648582 2015	1/526	0/257		0.0	4.43 (0.07 to 287.89)
NCT01682759 2016	2/375	1/375		0.1	1.95 (0.20 to 18.81)
NCT01717313 2016	0/165	1/164		0.0	0.13 (0.00 to 6.78)
NCT01890122 2016	0/320	1/322		0.0	0.14 (0.00 to 6.86)
Nowicki 2011	3/85	4/85		0.2	0.74 (0.16 to 3.36)
Oyama 2016	3/222	2/220		0.1	1.48 (0.25 to 8.63)
Pan 2012	1/284	0/284		0.0	7.39 (0.15 to 372.38)
Pfeffer 2015 (ELIXA)	211/3034	223/3034		11.1	0.94 (0.78 to 1.15)
Pfutzner 2011	5/978	5/328		0.2	0.26 (0.06 to 1.11)
Pinget 2013	0/323	2/161		0.0	0.05 (0.00 to 0.93)
Pratley 2009a	1/397	0/97		0.0	3.47 (0.02 to 482.16)
Probstfield 2016	1/47	0/45		0.0	7.08 (0.14 to 357.20)
Reasner 2011	1/625	2/621		0.1	0.51 (0.05 to 4.91)
Riddle 2013	1/328	0/167		0.0	4.52 (0.07 to 285.56)
Roden 2015	1/223	1/676		0.0	3.87 (0.16 to 95.87)
Rosenstock 2009	1/260	0/129		0.0	4.46 (0.07 to 286.93)
Rosenstock 2013a	0/306	1/95		0.0	0.01 (0.00 to 1.47)
Rosenstock 2014	1/574	0/285		0.0	4.47 (0.07 to 286.89)
Rosenstock 2016b	1/233	3/467		0.1	0.69 (0.09 to 5.53)
Russell-Jones 2012	0/411	1/409		0.0	0.13 (0.00 to 6.79)
Scherbaum 2008	0156	1/150		0.0	0.13 (0.00 to 6.56)
Schernthaner 2013	0/378	2/377		0.1	0.13 (0.01 to 2.16)
Schernthaner 2015	1/359	1/359		0.1	1.00 (0.06 to 16.02)
Schweizer 2007	2/511	2/249		0.1	0.46 (0.06 to 3.69)
Schweizer 2009	1/167	0/165		0.0	7.30 (0.14 to 367.98)
Scirica 2013 (SAVOR-TIMI 53)	420/8280	378/8212		21.0	1.11 (0.96 to 1.28)
Seck 2010	1/588	8/584		0.2	0.21 (0.06 to 0.77)
Seino 2010	1/268	0/132		0.0	4.45 (0.07 to 287.37)
Seino 2012b	0/154	1/157		0.0	0.14 (0.00 to 6.95)
Sheu 2015	4/405	1/80		0.1	0.77 (0.07 to 8.29)
Strain 2013	1/139	1/139		0.1	1.00 (0.06 to 16.07)
Terauchi 2014	1/108	0/37		0.0	3.83 (0.04 to 343.21)
Weissman 2014	3/504	3/241		0.1	0.44 (0.08 to 2.47)
White 2013 (EXAMINE)	153/2701	173/2679		8.5	0.87 (0.70 to 1.09)
Williams-Herman 2010	3/551	2/540		0.1	1.46 (0.25 to 8.48)
Wysham 2014	2/835	0/141		0.0	3.22 (0.06 to 166.37)
Yki 2013	5/631	5/630		0.3	1.00 (0.29 to 3.46)
Total (95% CI)	1925/67 754	1963/56 791		100.0	0.96 (0.90 to 1.02)

Heterogeneity: x^2=107.99, df=111, P=0.56, I^2=0

Test for overall effect: z=1.38, P=0.17



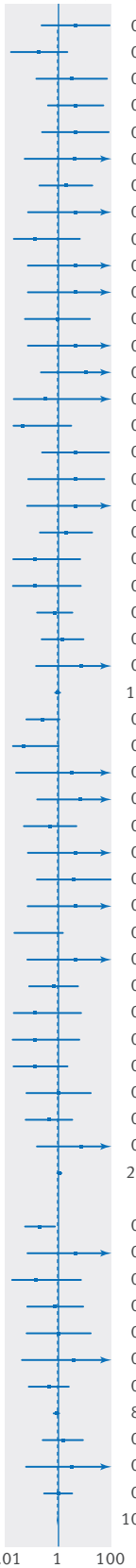


Fig 2 | All cause mortality in patients with type 2 diabetes receiving incretin based treatment versus control in randomised controlled trials

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Table 1 | GRADE evidence profile of incretin based treatment and all cause mortality in randomised controlled trials in patients with type 2 diabetes

Quality assessment							Summary of findings				
							Study event rates			Anticipated absolute effects (5 year time frame)	
No of participants (studies), follow-up time	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias		With control	With incretin	OR (95% CI)	Risk with control	Risk difference with incretin (95% CI)	Quality of evidence
151 614 (189), 12-234 weeks	No serious limitations	Serious limitations*	No serious limitations	No serious limitations	Undetected		1963/67 478 (2.9%)	1925/84 136 (2.3%)	0.96 (0.90 to 1.02)	71 per 1000†	3 fewer (7 fewer to 1 more)	⊕⊕⊕⊕ Moderate

*Effects might differ in GLP-1 agonists v DPP-4 inhibitors.
†Baseline risk estimate for death in 5 year time frame comes from control arm of one large cohort study we identified to best represent our target population,[16] with 948 events of death in 31 950 patients (29.7/1000) over median of 2.1 years' follow-up period in control arm.

or one event across arms (Peto odds ratio 0.96, 0.90 to 1.02) showed similar results (table 2).

Univariable meta-regression showed no association between all cause mortality and any of our six subgroup factors (P=0.38 for length of follow-up; P=0.20 for risk of cardiovascular disease at baseline; P=0.52 for type of incretin drug; P=0.05 for type of control; P=0.80 for mode of treatment; P=0.86 for individual incretin agents; table 3). Subgroup analyses by type of incretin drug (GLP-1 agonists or DPP-4 inhibitors), with data from six large randomised trials that compared incretin agents versus placebo, showed similar finding for all cause mortality (interaction test P=0.09; GLP-1 agonists versus placebo: 654/9350 *v* 730/9355; M-H odds ratio 0.89, 95% confidence interval 0.80 to 0.99; DPP-4 inhibitors versus placebo: 1120/18 313 *v* 1088/18 230; 1.02, 0.91 to 1.14; fig 4) and composite cardiovascular events (interaction test P=0.19; GLP-1 agonists versus placebo: 1113/9350 *v* 1229/9355; 0.88, 0.74 to 1.04; DPP-4 inhibitors versus placebo: 1527/18 313 *v* 1527/18 230; 0.99, 0.92 to 1.07; fig 5).

Multiple meta-regression, adjusted for length of follow-up, risk of cardiovascular disease at baseline, type of control, and mode of treatment, suggested that GLP-1 agonists, but not DPP-4 inhibitors, are associated with lower all cause mortality (P=0.01 for interaction).

Discussion

Findings and interpretations

Our systematic review and meta-analysis provides no support for the hypothesis that incretin based treatment is associated with increased mortality in patients with type 2 diabetes. This finding should reassure patients and clinicians and refutes the concern raised by the SAVOR-TIMI trial suggesting increased mortality.

In our univariable meta-regression, we found no differential effects among the six prespecified hypotheses; however, multiple meta-regression suggested that GLP-1 agonists, but not DPP-4 inhibitors, could be associated with lower mortality. When checked against 11 criteria[32] for assessing the credibility of an apparent subgroup effect, the following supports the hypothesis. The subgroup analysis was one of the small number of prespecified hypotheses tested; the characteristics were measured at baseline; the test for interaction, based on multiple meta-regression, was significant and the

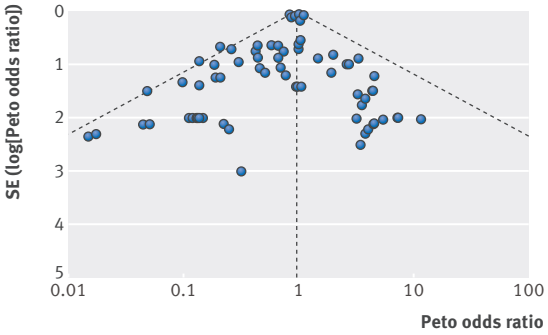

Fig 3 | Funnel plot of mortality in patients with type 2 diabetes receiving incretin based treatment versus control in randomised controlled trials

Table 2 | Sensitivity analyses of mortality associated with incretin based treatment in meta-analysis of randomised controlled trials in patients with type 2 diabetes. Figures are Mantel-Hanzel point estimates (relative risk or odds ratio) unless stated otherwise

Comparison	Point estimate (95% CI)
Primary analysis	Peto OR 0.96 (0.90 to 1.02)
Sensitivity analyses	
Alternative effect measure: RR (fixed model)	RR 0.95 (0.90 to 1.01)
GLP-1 agonists *v* control	RR 0.89 (0.81 to 0.98)
DPP-4 inhibitors *v* control	RR 0.99 (0.92 to 1.07)
Alternative pooling method: Mantel-Hanszel's method (fixed model)	OR 0.95 (0.89 to 1.01)
GLP-1 agonists *v* control	OR 0.89 (0.80 to 0.98)
DPP-4 inhibitors *v* control	OR 0.99 (0.92 to 1.08)
Statistical models: random effects	OR 0.95 (0.89 to 1.02)
GLP-1 agonists *v* control	OR 0.88 (0.80 to 0.98)
DPP-4 inhibitors *v* control	OR 1.00 (0.92 to 1.08)
A continuity correction of 0.5	OR 0.95 (0.89 to 1.01)
Excluding trials with zero or one event across arms	Peto OR 0.96 (0.90 to 1.02)

additional exploratory subgroup analysis of a subset of the six large cardiovascular outcome trials showed a similar trend; the subgroup findings seemed to be consistent across related outcomes (such as cardiovascular events, fig 5); and, in terms of biological rationale, animal studies and randomised controlled trials in humans have shown that GLP-1 agonists are associated with a larger sustainable reduction of HbA_{1c},[37] weight loss, and systolic blood pressure control than DPP-4 inhibitors.[38 39]

On the other hand, the subgroup analysis is based on a comparison between trials; it is not robust across statistical analyses (the effect did not appear in the univariable analysis but only in the meta-regression, and the meta-regression is at high risk of over-fitting—six trials account for 92.5% of the weight), and was not prespecified; the apparent reduction in mortality with GLP-1 is both small and of borderline significance. We thus conclude that the subgroup hypothesis has low credibility.

Strengths and limitations

Strengths of our review include a systematic and rigorous approach to the identification of randomised controlled trials investigating the impact of incretin based treatment on mortality. We conducted a limited number of preplanned subgroup analyses to explore for differences in risk of mortality. We used the GRADE approach to assess the quality of evidence that showed

Table 3 | Effect of incretin based treatment on mortality in patient with type 2 diabetes: subgroup analyses and meta-regressions

Comparison	Peto odds ratio (95% CI)	P value	
		Univariable meta-regression	Multiple meta-regression
Subgroup by patients cardiovascular disease risk at baseline:			
Low baseline risk	0.77 (0.58 to 1.03)	0.20	0.58
High baseline risk or established CVD	0.97 (0.91 to 1.04)		
Unclear risk	0.75 (0.49 to 1.15)		
Subgroup by type of incretin drugs*:			
GLP-1 agonists *v* control	0.89 (0.80 to 0.99)	0.52	0.01
DPP-4 inhibitors *v* control	1.00 (0.92 to 1.08)		
Subgroup by type of control:			
Incretin drugs *v* placebo	0.94 (0.89 to 1.01)	0.05	0.44
Incretin drugs *v* active drugs	0.65 (0.47 to 0.91)		
Subgroup by length of follow-up:			
≤52 weeks	0.81 (0.59 to 1.12)	0.38	0.52
>52 weeks	0.96 (0.90 to 1.03)		
Subgroup by mode of treatment:			
Monotherapy	0.88 (0.59 to 1.31)	0.80	0.80
Add-on/combination treatment	0.96 (0.89 to 1.02)		
Subgroup by individual agents:			
Alogliptin	0.86 (0.69 to 1.07)	0.86	NA†
Linagliptin	0.72 (0.36 to 1.45)		
Omarigliptin	0.90 (0.20 to 4.08)		
Saxagliptin	1.07 (0.94 to 1.23)		
Sitagliptin	1.00 (0.89 to 1.13)		
Teneligliptin	0.02 (0.00 to 1.64)		
Vildagliptin	0.72 (0.38 to 1.37)		
Albiglutide	0.86 (0.30 to 2.48)		
Dulaglutide	0.68 (0.23 to 2.00)		
Exenatide	1.32 (0.60 to 2.90)		
Liraglutide	0.85 (0.74 to 0.98)		
Lixisenatide	0.93 (0.76 to 1.12)		
Semaglutide	1.04 (0.72 to 1.49)		
Taspoglutide	0.17 (0.02 to 1.36)		

CVD=cardiovascular disease; NA=not applicable.
*M-H random effects model also used to pool trials by type of incretin drugs. Effect estimates were OR 1.00 (95% CI 0.92 to 1.08) for DPP-4 inhibitors and 0.88 (0.80 to 0.98) for GLP-1 inhibitors.
†Variable "individual agents" was not included in multiple meta-regression analysis because of colinearity with type of incretin drugs.

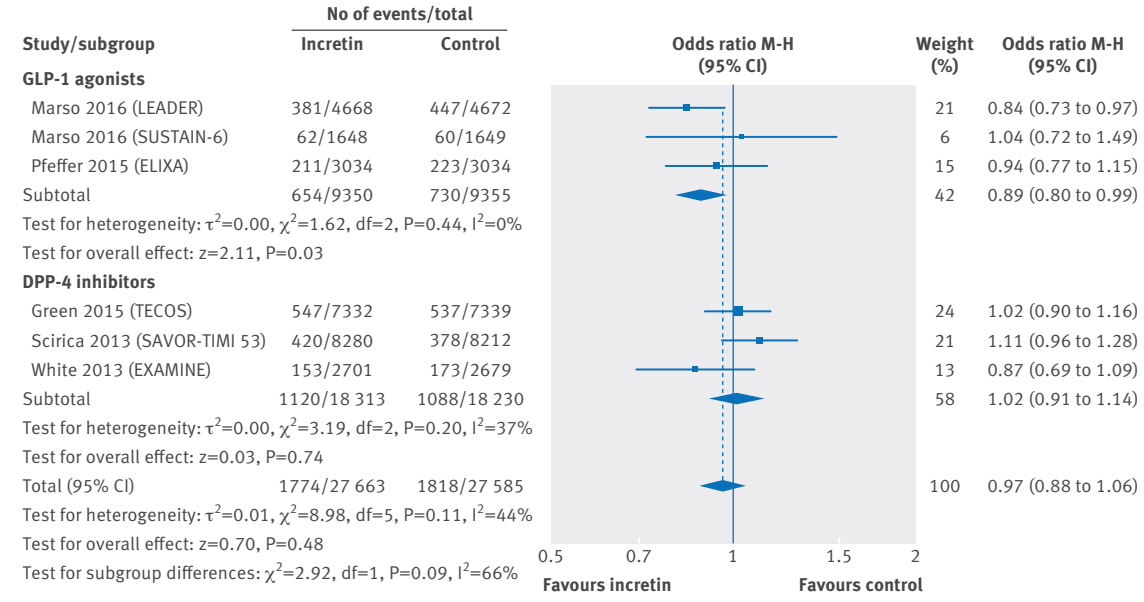

Fig 4 | All cause mortality in patients with type 2 diabetes receiving incretin based treatment versus placebo in large cardiovascular outcomes trials

convincing evidence that incretin drugs do not increase mortality (table 1).

Our study also has limitations. Firstly, studies might selectively report data regarding death in their full publications, which could lead to risk of selection bias; we attempted to mitigate this risk by reviewing records on ClinicalTrials.gov for unreported deaths and included outcome data from 23 trial registry reports. Secondly, we were unable to assess the long term effects of these drugs: among the 189 trials, only 40 had long term follow-up over 52 weeks, and the longest follow-up in the large trials was 3.8 years. Our subgroup analysis suggesting a possible reduction in mortality with GLP-1 agonists but not with DPP4 inhibitors has limited credibility. We identified 11 trials reporting head-to-head comparison,[40-50] but with limited information—15 events from 6736 participants—and thus estimates were uninformative.

Comparison with other studies

Three previous meta-analyses[51-53] have reported the effect of GLP-1 agonists, versus placebo or active treatments, on all cause mortality among patients with type 2 diabetes. One, including 33 trials with more than 12 weeks' follow-up, nine of which reported at least one death, showed that GLP-1 receptor agonists did not seem to be associated with increased mortality (odds ratio 0.67, 95% confidence interval 0.26 to 1.78)[51]; another one, including 33 trials with more than 24 weeks' follow-up, 14 of which reported at least one death, found similar results (0.89, 0.46 to 1.70).[52] The other recently published meta-analysis, including five trials with the outcome of mortality, found no effect of GLP-1 agonists on mortality (relative risk 0.90, 95% confidence interval 0.70 to 1.15).[53] In comparison, our results, primarily based on large cardiovascular

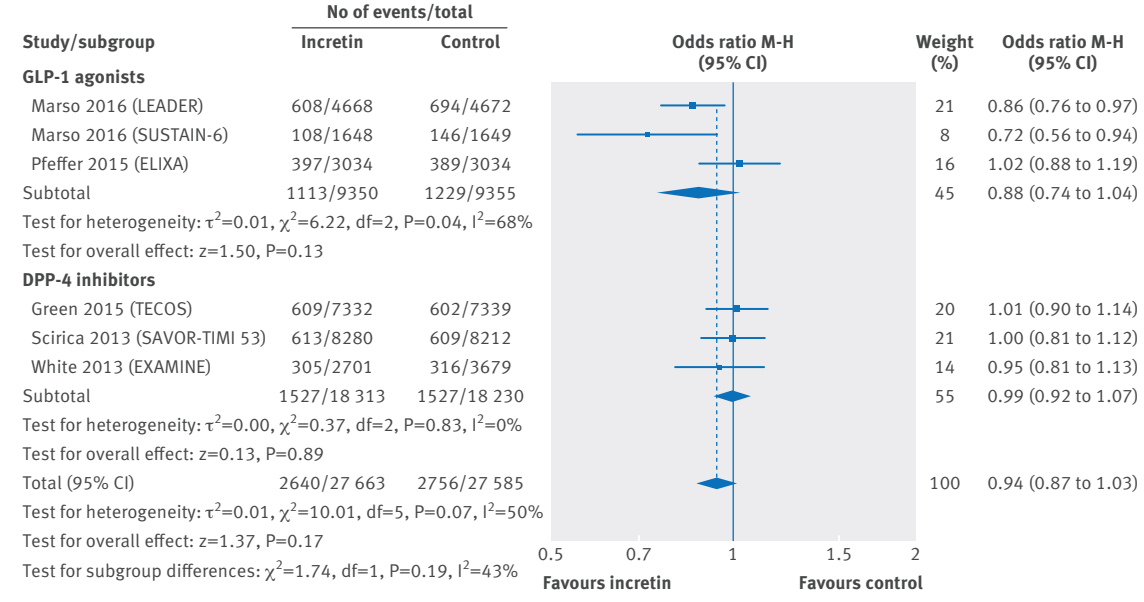

Fig 5 | Composite cardiovascular events (death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke) in patients with type 2 diabetes receiving incretin based treatment versus placebo in large cardiovascular outcomes trials

outcome trials, suggest that GLP-1 agonists could be associated with lower mortality in patients at high risk of, or with, established cardiovascular disease.

Four previous meta-analyses have reported the effect of DPP-4 inhibitors, versus placebo or active treatments, on all cause mortality among patients with type 2 diabetes.[54-57] Monami and colleagues, who included 41 trials with more than 12 weeks' follow-up, 18 of which reported at least one death, suggested that DPP-4 inhibitors did not increase mortality (odds ratio 0.78, 95% confidence interval 0.40 to 1.51).[54] Savarese and colleagues found no effect of DPP-4 inhibitors on mortality regardless of length of follow-up (relative risk 1.06, 95% confidence interval 0.56 to 2.01, for follow-up <29 weeks; 1.01, 0.91 to 1.13, for follow-up ≥29 weeks).[55] Wu and colleagues, who included 43 randomised controlled trials with 50 982 patients and 1228 deaths, found similar results (1.01, 0.91 to 1.13).[56] The final study, also by Savarese and colleagues, included 66 trials with sample size more than 200 patients and report of at least one death, and again found no effect on mortality (odds ratio 1.01, 95% confidence interval 0.93 to 1.09).[57] Our study, including 122 smaller trials and three larger trials, showed, with much narrower confidence intervals, that DPP-4 inhibitors had minimal or no impact on mortality.

Compared with these studies, we included a large number of additional studies (38 additional randomised controlled trials of GLP-1 agonists and 56 of DPP-4 inhibitors) and conducted more thorough analyses. The addition of large cardiovascular outcome trials provided more reliable estimates of effects on mortality, and subgroup analysis raised the possibility of differential effects of the two classes of incretin drugs—though the subgroup hypothesis has low credibility.[32]

Conclusions

Our results provide no support for the hypothesis that incretin based treatment are associated with increased all cause mortality in patients with type 2 diabetes. Additional large well designed randomised trials with adequate follow-up will be necessary to definitively establish or refute possible differences in the effect of GLP-1 agonists and DPP-4 inhibitors on all cause mortality.

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Ethical approval: Not required.

Data sharing: No additional data available.

Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Appendix 1: Search strategies
Appendix 2: Supplementary tables A-D
Appendix 3: Supplementary funnel plots