# Incretin treatment and risk of pancreatitis in patients with type 2 diabetes mellitus: systematic review and meta-analysis of randomised and non-randomised studies

Incretin Safety Study Investigators

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## STUDY QUESTION

Do incretins—either glucagon-like peptide-1 (GLP-1) receptor agonists or dipeptidyl peptidase-4 (DPP-4) inhibitors—increase the risk of pancreatitis in patients with type 2 diabetes mellitus?

## SUMMARY ANSWER

Available evidence suggests that the incidence of pancreatitis among patients taking incretins is low and that incretins are not associated with an increased risk of pancreatitis.

## WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Concerns and debates have arisen regarding the risk of pancreatitis associated with the use of incretins, and studies of this issue have provided conflicting results. Our study suggests that the incidence of pancreatitis in patients with type 2 diabetes taking incretins is low, and that incretins are not associated with an increased pancreatitis risk.

### Selection criteria for studies

We searched Medline, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov, for randomised controlled and non-randomised trials that compared an incretins with control (placebo or active drugs) in adults with type 2 diabetes.

### Primary outcome

Pancreatitis events.

**Risk of pancreatitis among patients with type 2 diabetes receiving incretin treatment**

| Comparison | No of studies (events) | Effect estimate (95%CI) |
|---|---|---|
| **Randomised controlled trials** | | |
| Incretin *v* control | 55 (37) | OR 1.11 (0.57 to 2.17) |
| GLP-1 subgroup | 29 (16) | OR 1.05 (0.37 to 2.94) |
| DDP-4 subgroup | 28 (23) | OR 1.06 (0.46 to 2.45) |
| **Cohort studies** | | |
| Exenatide *v* control | 1 (87) | Adjusted HR 0.9 (0.6 to 1.5) |
| Exenatide *v* control | 1 (1312) | Adjusted OR 0.93 (0.63 to 1.36) |
| Sitagliptin *v* control | 1 (132) | Adjusted HR 1.0 (0.7 to 1.3) |
| Sitagliptin *v* insulin glargine | 1 (0) | Not estimable |
| **Case-control studies** | | |
| Incretin *v* control | 1 (1003) | Adjusted OR 0.98 (0.69 to 1.38) |
| Sitagliptin or exenatide in 2 years *v* no use | 1 (1269) | Adjusted OR 2.07 (1.36 to 3.13) |

OR=odds ratio; HR=hazard ratio.

### Main results and role of chance

We included 60 studies (n=353 639 patients), consisting of 55 randomised controlled trials (n=33 350) and five observational studies (three retrospective cohort studies and two case-control studies; n=320 289). Pooled estimates from the 55 randomised controlled trials (low or moderate risk of bias, 37 events, raw event rate 0.11%) did not suggest an increased risk of pancreatitis with incretins (odds ratio 1.11, 95% confidence interval 0.57 to 2.17). Estimates by type of incretin suggested similar results (1.05, 0.37 to 2.94, for GLP-1 agonists *v* control; 1.06, 0.46 to 2.45, for DPP-4 inhibitors *v* control). Three retrospective cohort studies (moderate to high risk of bias, 1466 events, raw event rate 0.47%) did not find an increased risk of pancreatitis associated with either exenatide (adjusted odds ratio 0.93, 0.63 to 1.36, in one study, adjusted hazard ratio 0.9, 0.6 to 1.5, in another) or sitagliptin (adjusted hazard ratio 1.0, 0.7 to 1.3). One case-control study at moderate risk of bias (1003 cases, 4012 controls) found no significant association between incretin use and pancreatitis (adjusted odds ratio 0.98, 0.69 to 1.38); however, another case-control study (1269 cases, 1269 controls) at moderate risk of bias suggested that the use of either exenatide or sitagliptin was associated with significantly increased odds of acute pancreatitis (use within two years *v* no use, adjusted odds ratio 2.07, 1.36 to 3.13).

### Bias, confounding, and other reasons for caution

The number of pancreatitis events was small among randomised controlled trials and the length of follow-up was relatively short. The confidence intervals around effect estimates are thus wide. Trials tend to enrol patients with fewer risk factors for pancreatitis than typical patients, which threatens generalisability. The five observational studies, involving patients in real practice, had large sample sizes but were limited by use of claims data or patient medical records (inadequate ascertainment of exposure to incretins; control drugs and exposure to other confounding factors might not have been accurately documented), leaving the possibility of an undetected increase in risk of pancreatitis.

### Study funding/potential competing interests

This study was funded by Young Investigator Award, Sichuan University (project No 2013SCU04A37).

# Incretin based drugs and risk of acute pancreatitis in patients with type 2 diabetes: cohort study

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## STUDY QUESTION

Is the use of the recently marketed incretin based drugs (glucagon-like peptide 1 analogues and dipeptidyl peptidase-4 inhibitors) associated with an increased risk of acute pancreatitis?

## SUMMARY ANSWER

The use of incretin based drugs is not associated with an increased risk of acute pancreatitis, when compared with sulfonylureas, although a modest increased risk cannot be precluded.

## WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The occurrence of acute pancreatitis associated with incretin based drugs is controversial, given conflicting data from preclinical animal studies, randomised controlled trials, adverse event databases, and observational studies. This cohort study using data from a large population based general practice database provides additional evidence of a null association.

### Participants and setting

Patients newly prescribed incretin based drugs or sulfonylureas from 1 January 2007 to 31 March 2013, identified from the United Kingdom's Clinical Practice Research Datalink.

### Design, size, and duration

This was a cohort study comparing 20 748 new users of incretin based drugs with 51 712 users of sulfonylureas. Patients were followed until a diagnosis of acute pancreatitis, death from any cause, end of registration with the general practice, or the end of the study period (31 March 2013), whichever came first. Cox proportional hazards models were used to estimate hazard ratios and 95% confidence intervals for acute pancreatitis associated with the use of incretin based drugs compared with the use sulfonylureas. Secondary analyses were conducted to determine whether the risk varied with duration of use and by sex. All models were adjusted for tenths of the high dimensional propensity score (hdPS), which is a method that considered over 500 variables along with haemoglobin A1c, body mass index (BMI), excessive alcohol use, and duration of treated diabetes.

**Adjusted hazard ratios for acute pancreatitis associated with use of incretin based drugs compared with sulfonylureas**

| | | |
|---|---|---|
| Sulfonylureas | 1.47 (1.23 to 1.76) | 1.00 (reference) |
| Incretin based drugs | 1.45 (0.99 to 2.11) | 1.00 (0.59 to 1.70) |

*Adjusted for tenths of high dimensional propensity score and year of cohort entry.

### Main results and the role of chance

There were a total of 146 cases of acute pancreatitis during up to seven years of follow-up (overall incidence rate 1.47 per 1000 patients per year). The rates were similar for patients taking incretin based drugs (crude incidence rate 1.45 per 1000 patients per year) and sulfonylureas (crude incidence rate 1.47 per 1000 patients per year). In models adjusted for tenths of hdPS, the use of incretin based drugs was not associated with an increased risk of acute pancreatitis when compared with the use of sulfonylureas (hazard ratio 1.00, 95% confidence interval 0.59 to 1.70). In secondary analyses, the risk of acute pancreatitis did not vary with duration of use or according to sex.

### Bias, confounding, and other reasons for caution

Despite the use of the high dimensional propensity scores that account for all available covariates, residual confounding from unmeasured confounders is possible given the observational nature of the study. Moreover, the rarity of the acute pancreatitis outcome does not preclude a modest increased risk of acute pancreatitis with the use of incretin based drugs, as indicated by the upper bound of the confidence interval.

### Generalisability to other populations

The results of this study can be generalised to populations in which incretin based drugs are being used as second line and third line treatments in people with type 2 diabetes.

### Study funding/potential competing interests

This study was funded by the Canadian Institutes of Health Research and the Canada Foundation for Innovation; SS has participated in advisory board meetings and/or been a speaker at conferences for AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers-Squibb, Merck and Novartis.

# Helmet therapy in infants with positional skull deformation: randomised controlled trial

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## STUDY QUESTION

What is the effectiveness of helmet therapy for positional skull deformation compared with allowing the condition to run its natural course in infants aged 5 to 6 months, measured at 24 months?

## SUMMARY ANSWER

This study found no evidence of a significant or clinically meaningful difference in improvement of skull shape at 2 years of age between infants who were treated with a helmet and those in which the natural course of skull deformation was awaited.

## WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Helmet therapy is often prescribed in infants with positional skull deformation, whereas evidence from randomised controlled trials for its effectiveness compared with the natural course is lacking. This randomised controlled trial did not find an additional effect of helmet therapy for skull deformation compared with the natural course of the condition.

### Design

This study was a pragmatic randomised single blind controlled trial using computer generated block randomisation. Infants were randomised 1:1 to the helmet therapy group or the natural course group. Parents were instructed to ensure that the helmet was worn for 23 hours a day until their infant was 12 months of age or until obtaining satisfying outcomes. In the natural course group natural skull growth was monitored.

### Participants and setting

Between July 2009 and July 2011, 29 specially trained paediatric physiotherapists in paediatric physiotherapy practices in the east of the Netherlands recruited infants to the trial. Eligible infants had moderate to severe skull deformation, were aged 5 to 6 months, born after 36 weeks of gestation, and had no muscular torticollis, craniosynostosis, or dysmorphic features. 84 were included in the study.

Analysis of covariance of primary outcome

| Change score* | Adjusted means (95% CI) Helmet therapy (n=39) | Natural course (n=40) | P value |
|---|---|---|---|
| Plagiocephaly | 3.4 (2.6 to 4.2) | 2.6 (1.8 to 3.4) | 0.13 |
| Brachycephaly | 6.4 (5.3 to 7.5) | 7.4 (6.4 to 8.5) | 0.20 |

Covariate: baseline measurement.
*Measurement at baseline (age 5 months) minus measurement at 24 months of age.

### Primary outcome

The primary outcome was change in skull shape from baseline to 24 months of age assessed using plagiocephalometry (anthropometric measurement instrument). Change scores for plagiocephaly (oblique diameter difference index) and brachycephaly (craniproportional index) were each included in an analysis of covariance using baseline values as the covariate.

### Main results and the role of chance

The change score for both plagiocephaly and brachycephaly was equal between the helmet therapy and natural course groups, with a mean difference (helmet therapy minus natural course) of −0.2 (95% confidence interval −1.6 to 1.2, P=0.80) and 0.2 (−1.7 to 2.2, P=0.81), respectively. Full recovery was achieved in 10 of 39 (26%) participants in the helmet therapy group and 9 of 40 (23%) in the natural course group (odds ratio 1.2, 95% confidence interval 0.4 to 3.3, P=0.74). The table shows the results of the analysis of covariance.

### Harms

Helmet therapy did not influence motor development or health related quality of life in infants, but all parents reported one or more side effects.

### Bias, confounding, and other reasons for caution

Despite randomisation, differences in baseline values of the primary outcome measure existed between both trial arms.

### Generalisability to other populations

Results are not generalisable to infants with very severe skull deformation, with an underlying congenital condition, with muscular torticollis, or born preterm.

### Study funding/potential competing interests

This study was funded by ZonMw, the Netherlands Organization for Health Research and Development (grant No 170.992.501). All researcher activities were independent of the funding source.

### Trial registration number

Current Controlled Trials ISRCTN18473161.

# Influence of healthy candidate bias in assessing effectiveness for implantable cardioverter-defibrillators: cohort study of older patients with heart failure

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## STUDY QUESTION

What is the contribution of unmeasured general health status to selection of patients for implantable cardioverter-defibrillator (ICD) therapy and potential bias in observational studies using registries and claims data?

## SUMMARY ANSWER

Lower risks of unrelated events (admission for non-traumatic hip fracture, admission to a skilled nursing facility, and 30 day mortality) in patients with an ICD likely reflect unmeasured differences in the baseline comorbidity and frailty between patients with and without ICDs.

## WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Healthy worker effect or healthy user bias has been shown in occupational epidemiology and pharmacoepidemiology. Our study suggests that healthy candidate bias for device therapies limits assessments of the real world effectiveness of ICDs in the general population.

### Participants and setting

The study population included older patients admitted to hospital with heart failure from the Center for Medicare & Medicaid Services ICD registry (2005-08); the National Cardiovascular Database Registry's ICD registry (2005-08); a national clinical registry of patients with heart failure aggregated from several quality improvement and accreditation programs, including the American Heart Association's Get With the Guidelines program (2005-08); and Medicare claims data (2004-09).

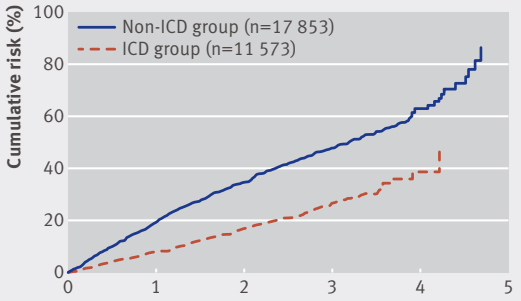
### Design, size, and duration

We conducted a retrospective cohort study of 29 426 patients admitted to hospital with heart failure who were 66 years or older and eligible for ICD therapy for primary prevention using linked data from an ICD registry, a heart failure registry, and Medicare claims for ICDs implanted in 2005 through 2009. We compared three outcomes among patients with and without ICD therapy that can reflect general health status but are unlikely to be improved by ICD therapy: admission for non-traumatic hip fracture, admission to a skilled nursing facility, and 30 day mortality.

### Main results and the role of chance

Compared with 17 853 patients without ICD therapy, 11 573 patients with ICD therapy were younger and had lower ejection fractions and more cardiac admissions to hospital but fewer non-cardiac admissions and comorbid conditions. The cumulative incidence curves for the unrelated outcomes were lower in patients with an ICD and diverged immediately after the device was implanted. Patients with ICD therapy had greater freedom from unrelated events after adjusting for age and sex: hip fracture (hazard ratio 0.77, 95% confidence interval 0.64 to 0.92), admission to a skilled nursing facility (0.53, 0.50 to 0.55), and 30 day mortality (0.12, 0.10 to 0.15).

**Survival curves of patients with and without ICD therapy for admission to hospital for non-traumatic hip fracture**




### Bias, confounding, and other reasons for caution

We had limited ability to identify those patients who did not receive ICD therapy who would have derived meaningful life extension from prevention of sudden death or those who may have declined ICD therapy despite an appropriate recommendation. There may have been early excess non-sudden death in the ICD arm in the comparison of 30 day mortality, which is likely to underestimate the contribution of healthy candidate bias.

### Generalisability to other populations

Our cohort represented older patients with heart failure who were admitted to hospital or potentially indicated for implantation of an ICD in the United States. The results are likely generalizable to modern clinical practice settings in industrialized countries.

### Study funding/potential competing interests

This project was funded under contract number HHSA290200500161, task order 3, from the Agency for Healthcare Research and Quality (AHRQ), US Department of Health and Human Services, as part of the Developing Evidence to Inform Decisions about Effectiveness program; and contract number HHSM500201000001I, task orders 2 and 6, from the Centers for Medicare & Medicaid Services, US Department of Health and Human Services. SS was supported by a midcareer development award K02HS017731 from the AHRQ.