

三軍總醫院

EBM-實證醫學競賽

內科部

R2 廖昶虹

R1 林宏翰、張簡芝穎



臨床情境

50歲林先生，身高175公分、體重92公斤。病史糖尿病，平時內分泌科用藥為Metformin、Glimepiride。即使罹患糖尿病，仍舊喜歡吃油炸食物，沒有運動習慣。最近內分泌科門診，醫師審視林先生抽血報告HbA1c(糖化血色素)=10.2%，因此，幫林先生加開立sitagliptin(Januvia®；佳糖維®)幫助血糖控制。

臨床情境

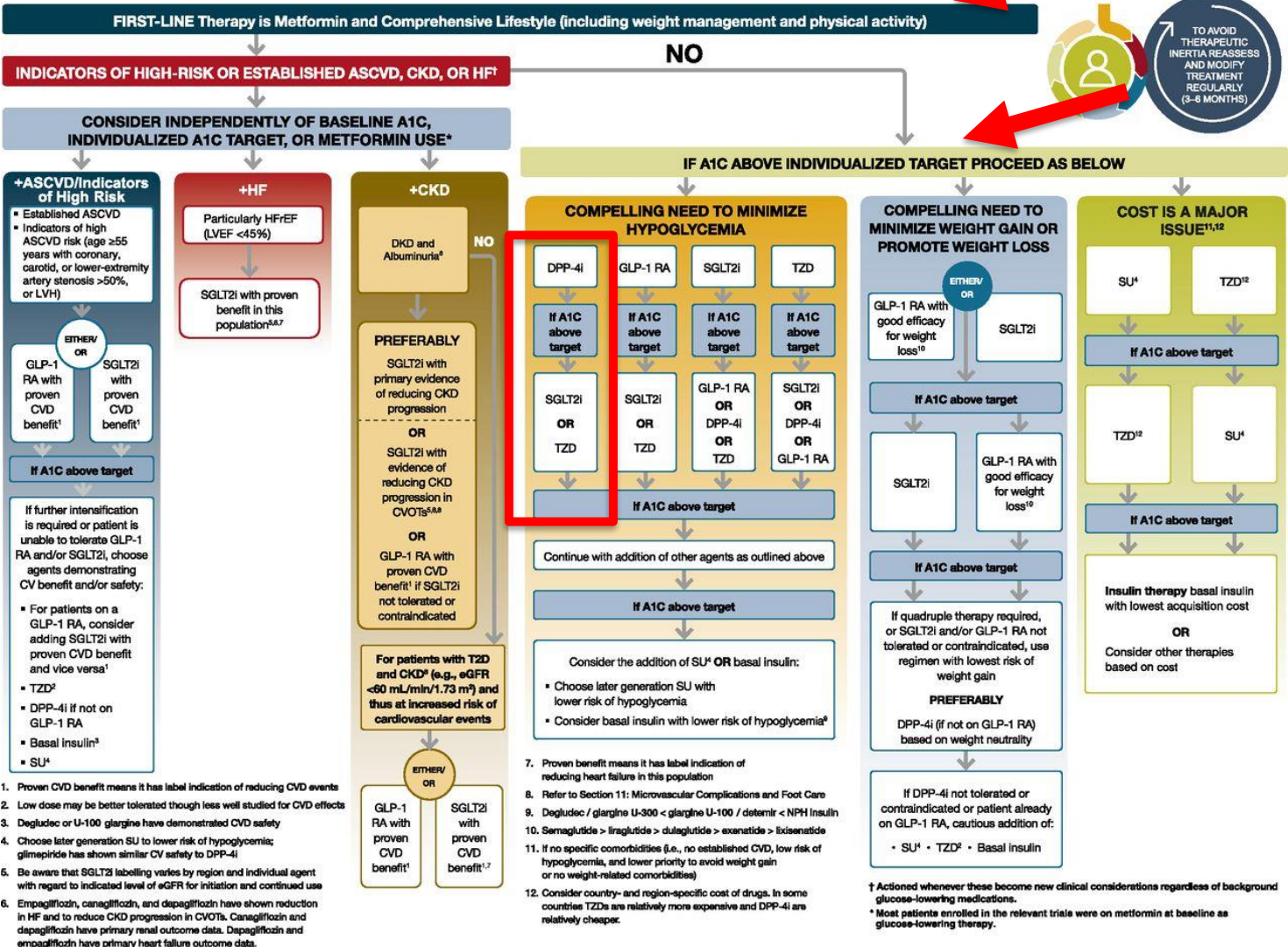
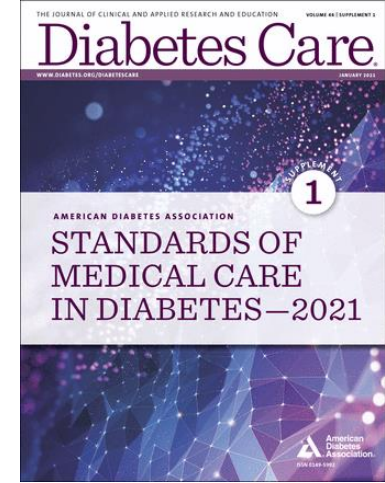
林先生上網查詢這個藥的相關資料，提到 sitagliptin (Januvia®；佳糖維®)可能會造成胰臟炎，甚至胰臟癌，看到這個消息後就不敢吃這個藥。因擔憂網路消息可能是假消息，來到藥局詢問藥師：「sitagliptin (Januvia®；佳糖維®)」真的會造成胰臟炎，甚至胰臟癌？聽到這個消息，非常害怕。」「昨天我看到電視節目說吃肉桂(Cinnamon)可以降低糖化血色素，是真的嗎？」「我可以不吃醫師開的新藥(佳糖維®)嗎？還有其他控制血糖的方法或藥物嗎？」

問題

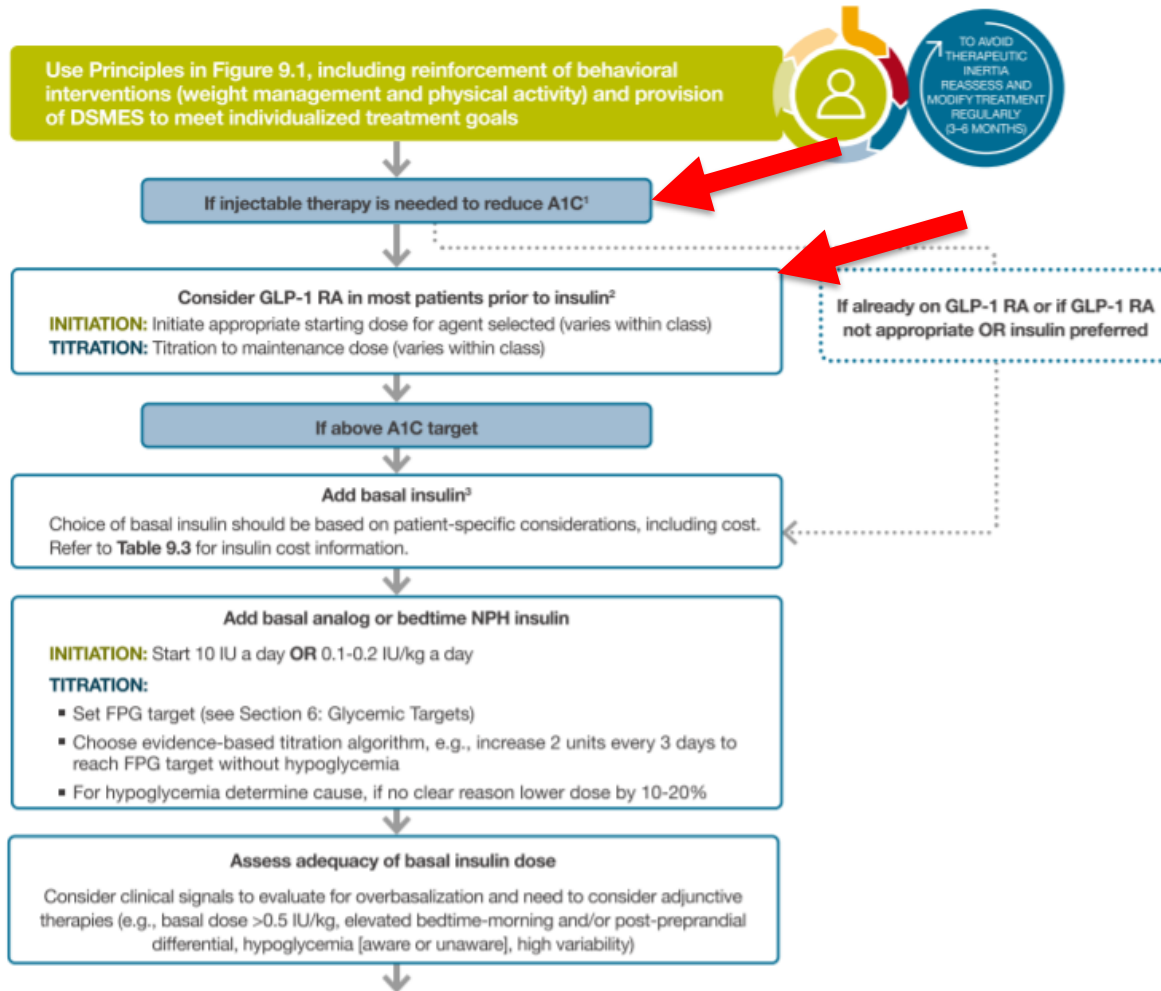
林先生 BMI:30 HbA1c(糖化血色素)=10.2%

1. Sitagliptin 是否會導致胰臟炎或者胰臟癌?
2. 吃肉桂(Cinnamon) 是否能降低糖化血色素
3. 我可以不吃醫師開的新藥(佳糖維®)嗎? 還有其他控制血糖的方法或藥物嗎?

Background knowledge



Background knowledge



Background knowledge

- Routine supplementation with antioxidants, such as vitamins E and C and carotene, is not advised due to lack of evidence of efficacy and concern related to long-term safety.
- In addition, there is insufficient evidence to support the routine use of herbals and micronutrients, such as cinnamon , curcumin, vitamin D ,or chromium, to improve glycemia



Background knowledge

- Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) enzyme inhibitor
 - Protects glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide (GLP-1) from inactivation
 - 1. Increases insulin release
 - 2. Decreases glucagon levels in the circulation in a glucose-dependent manner



檢索策略-提升檢索效率

首先以『P』、『I』做搜尋，再依據結果適當加入關鍵字及同義詞

P	AND	I	AND	C	AND	O
Adults with type 2 diabetes mellitus (18 years or older)		Sitagliptin (Januvia) Dipeptidyl Peptidase-4 inhibitors		Placebo or active drugs		Pancreatitis, Pancreatic cancer

限定搜尋範圍	Full text、Within 5 years
限定研究類型	Systematic review、Meta-analysis、Randomized controlled trial
限定語言地區	English

檢索策略-我們的主要目標



Clinical Queries

Systematic Review (**Meta-Analysis**)

Randomized Controlled Trial/Cohort study

Within **5** Years

Meet our 『**PICO**』

搜尋Cochrane Library-提升檢索效率

The screenshot shows the Cochrane Library search interface. At the top left is the Cochrane Library logo with the tagline "Trusted evidence. Informed decisions. Better health." and a "Log in / Register" link. Below the logo is a navigation bar with tabs for "Search", "Search Manager", "Medical Terms (MeSH)", and "Browse". The "Search" tab is active, showing a search box with a dropdown menu set to "Title, Abstract, Keywords". The search query is "type 2 diabetes mellitus". Below the search box are three rows of search criteria, each with a minus sign, a dropdown menu set to "AND", and a dropdown menu set to "Title Abstract Keyword". The search terms are "Sitagliptin" and "Pancreatitis, Pancreatic cancer".

with Cochrane Library publication date from May 2016 to May 2021, (Word variations have been searched)

使用Limit功能

限定『**Review**』、
『**Meta-analysis**』之文章
限定『**2016-2021**』文章

輸入關鍵字、適當使用**Truncation***
適當使用布林運算『**AND**』

Cochrane Reviews

1

Cochrane Protocols

0

Trials

10

Editorials

0

Special Collections

0

Clinical Answers

0

More



1 Cochrane Review matching type 2 diabetes mellitus in Title Abstract Keyword AND Sitagliptin in Title Abstract Keyword AND Pancreatitis, Pancreatic cancer in Title Abstract Keyword - with Cochrane Library publication date Between May 2016 and May 2021 (Word variations have been searched)

Cochrane Database of Systematic Reviews

Issue 5 of 12, May 2021

[Select all \(1\)](#) [Export selected citation\(s\)](#) [Show all previews](#)

Order by

Results per page

1

Insulin and glucose-lowering agents for treating people with diabetes and chronic kidney disease

Clement Lo, Tadashi Toyama, Ying Wang, Jin Lin, Yoichiro Hirakawa, Min Jun, Alan Cass, Carmel M Hawley, Helen Pilmore, Sunil V Badve, Vlado Perkovic, Sophia Zoungas

Intervention Review 24 September 2018 Free access

[Show PICOs](#) ^{BETA} [Show preview](#)

搜尋EMBASE-提升檢索效率

Adult AND type 2 diabetes mellitus AND Sitagliptin
AND pancreatitis AND pancreatic cancer

Search >

Mapping v

輸入關鍵字、適當使用**Truncation**
適當使用布林運算『**AND**』

Evidence Based Medicine

- Cochrane Review
- Systematic Review
- Meta Analysis

- Controlled Clinical Trial
- Randomized Controlled Trial

使用EBM Limit功能




限定『**Systematic Review**』、『**Meta-analysis**』之文章

限定『**2016-2021**』文章

14 results for search #1  Set email alert  Set RSS feed  Search details  Index miner Results View | Print | Export | Email | Add to Clipboard

1 — 14

Select number of items Selected: 0 [\(clear\)](#) [Show all abstracts](#) | Sort by: Relevance Author Publication Year Entry Date

- 1 Efficacy and safety of once-weekly semaglutide versus once-daily **sitagliptin** as add-on to metformin in patients with **type 2 diabetes** in SUSTAIN China: A 30-week, double-blind, phase 3a, randomized trial
Ji L., Dong X., Li Y., Li Y., Lim S., Liu M., Ning Z., Rasmussen S., Skjøth T.V., Yuan G., Eliaschewitz F.G.
Diabetes, Obesity and Metaboism 2021 23:2 (404-414) Cited by: 0
Embase MEDLINE [Abstract](#) [Index Terms](#) [View Full Text](#)  [Similar records >](#)
- 2 Sustained **52**-week efficacy and safety of triple therapy with dapagliflozin plus saxagliptin versus dual therapy with **sitagliptin** added to metformin in patients with uncontrolled **type 2 diabetes**
Handelsman Y., Mathieu C., Del Prato S., Johnsson E., Kurlyandskaya R., Iqbal N., Garcia-Sanchez R., Rosenstock J.
Diabetes, Obesity and Metaboism 2019 21:4 (883-892) Cited by: 9
Embase MEDLINE [Abstract](#) [Index Terms](#) [View Full Text](#)  [Similar records >](#)
- 3 Canagliflozin and **sitagliptin** induced acute **pancreatitis**
Dafalla M., Ganta V., Hagahmed N., Odonkor W., Nunlee-Bland G.
Endocrine Practice 2018 24 *Supplement 1* (30-)
Embase [Abstract](#) [Index Terms](#) [View Full Text](#)  [Similar records >](#)

- 4 Safety and efficacy of semaglutide once weekly vs **sitagliptin** once daily, both as monotherapy in Japanese people with **type 2 diabetes**
Seino Y., Terauchi Y., Osonoi T., Yabe D., Abe N., Nishida T., Zacho J., Kaneko S.
Diabetes, Obesity and Metabolism 2018 20:2 (378-388) Cited by: 37
Embase MEDLINE [Abstract](#) [Index Terms](#) [View Full Text](#) [Similar records >](#)
- 5 Efficacy and tolerability of novel triple combination therapy in drug-naïve patients with **type 2 diabetes** from the TRIPLE-AXEL trial: Protocol for an open-label randomised controlled trial
Kim N.H., Lim S., Kwak S.H., Moon M.K., Moon J.S., Lee Y.-H., Cho H.C., Lee J., Kim S.G.
BMJ Open 2018 8:9 Article Number e022448 Cited by: 1
Embase MEDLINE [Abstract](#) [Index Terms](#) [View Full Text](#) [Similar records >](#)
- 6 A randomized clinical trial of the safety and efficacy of **sitagliptin** in patients with **type 2 diabetes mellitus** inadequately controlled by acarbose alone
Wang W., Ning G., Ma J., Liu X., Zheng S., Wu F., Xu L., O'Neill E.A., Fujita K.P., Engel S.S., Kaufman K.D., Shankar R.R.
Current Medical Research and Opinion 2017 33:4 (693-699) Cited by: 6
Embase [Abstract](#) [Index Terms](#) [View Full Text](#) [Similar records >](#)
- 7 Assessing the safety of **sitagliptin** in older participants in the trial evaluating cardiovascular outcomes with **sitagliptin** (TECOS)
Bethel M.A., Engel S.S., Green J.B., Huang Z., Josse R.G., Kaufman K.D., Standl E., Suryawanshi S., Van De Werf F., McGuire D.K., Peterson E.D., Holman R.R.
Diabetes Care 2017 40:4 (494-501) Cited by: 36
Embase MEDLINE [Abstract](#) [Index Terms](#) [View Full Text](#) [Similar records >](#)

- 8 Pancreatic effects of liraglutide or **sitagliptin** in overweight patients with **type 2 diabetes**: A 12-week randomized, placebo-controlled trial
Smits M.M., Tonneijck L, Muskiet M.H.A., Kramer M.H.H., Pieters-Van Den Bos I.C., Vendrik K.E.W., Hoekstra T., Bruno M.J., Diamant M., Van Raalte D.H., Cahen D.L.
Diabetes Care 2017 40:3 (301-308) Cited by: 6
Embase MEDLINE [v Abstract](#) [v Index Terms](#) [> View Full Text](#) [Similar records >](#)
- 9 Efficacy of **sitagliptin** for the hospital management of general medicine and surgery patients with **type 2 diabetes** (Sita-Hospital): a multicentre, prospective, open-label, non-inferiority randomised trial
Pasquel F.J., Gianchandani R., Rubin D.J., Dungan K.M., Anzola I., Gomez P.C., Peng L., Hodish I., Bodnar T., Wesorick D., Balakrishnan V., Osei K., Umpierrez G.E.
The Lancet Diabetes and Endocrinology 2017 5:2 (125-133) Cited by: 76
Embase MEDLINE [v Abstract](#) [v Index Terms](#) [> View Full Text](#) [Similar records >](#)
- 10 Pancreatic safety of **sitagliptin** in the TECOS study
Buse J.B., Bethel M.A., Green J.B., Stevens S.R., Lohknygina Y., Aschner P., Grado C.R., Tankova T., Wainstein J., Josse R., Lachin J.M., Engel S.S., Patel K., Peterson E.D., Holman R.R.
Diabetes Care 2017 40:2 (164-170) Cited by: 32
Embase MEDLINE [v Abstract](#) [v Index Terms](#) [> View Full Text](#) [Similar records >](#)
- 11 **Sitagliptin** use and risk of acute **pancreatitis** in **type 2 diabetes mellitus**: A population-based case-control study in Taiwan
Liao K.-F., Lin C.-L., Lai S.-W., Chen W.-C.
European Journal of Internal Medicine 2016 27 (76-79) Cited by: 24
Embase MEDLINE [v Abstract](#) [v Index Terms](#) [> View Full Text](#) [Similar records >](#)

- 12 Efficacy and safety of switching from **sitagliptin** to liraglutide in subjects with **type 2 diabetes**: A randomized, double-blind, double-dummy, active-controlled 26-week trial
Bailey T.S., Takács R., Madueño F.T., Thomsen A.B., Kaltoft M.S., Maislos M.
Endocrine Reviews 2016 37:2 Supplement 1
Embase [▼ Abstract](#) [▼ Index Terms](#) [> View Full Text](#) [🔍 Similar records >](#)

- 13 Efficacy and safety of switching from **sitagliptin** to liraglutide in subjects with **type 2 diabetes**: A randomized, double-blind, double-dummy, active-controlled 26-week trial
Bailey T.S., Takács R., Madueño F.T., Thomsen A.B., Kaltoft M.S., Maislos M.
Endocrine Reviews 2016 37:2 Supplement 1
Embase [▼ Abstract](#) [▼ Index Terms](#) [> View Full Text](#) [🔍 Similar records >](#)

- 14 Assessing the safety of **sitagliptin** in patients with **type 2 diabetes** and chronic kidney disease in the trial evaluating cardiovascular outcomes with **sitagliptin** (TECOS)
Engel S.S., Suryawanshi S., Josse R.G., Peterson E., Holman R.R.
Diabetes 2016 65 Supplement 1 (A310-)
Embase [▼ Abstract](#) [▼ Index Terms](#) [> View Full Text](#) [🔍 Similar records >](#)

搜尋Pubmed-利用限定縮小檢索範圍

Builder

(adult) AND [(sitagliptin) OR (Dipeptidyl Peptidase-4 inhibitor)] (pancreatitis) AND (pancreatic cancer) st

AND All Fields

[Show index list](#)

or [Add to history](#)

ARTICLE TYPE

- Books and Documents
- Clinical Trial
- Meta-Analysis
- Randomized Controlled Trial
- Review
- Systematic Review

PUBLICATION DATE

- 1 year
- 5 years
- 10 years
- Custom Range

輸入關鍵字、適當使用**Truncation**
適當使用布林運算『**AND**』或『**OR**』

限定適當文章類型

『**Meta-Analysis**』、『**Systematic Reviews**』、
『**Randomized Controlled Trial**』

限定適當搜尋範圍

限定『**5年**』內之文章

限定『**Full text**』有全文可供評讀

1 **Pancreatitis and pancreatic cancer in patients treated with Dipeptidyl Peptidase-4 inhibitors: An extensive and updated meta-analysis of randomized controlled trials.**

Cite Dicembrini I, Monteregegi C, Nreu B, Mannucci E, Monami M.
Share Diabetes Res Clin Pract. 2020 Jan;159:107981. doi: 10.1016/j.diabres.2019.107981. Epub 2019 Dec 20. PMID: 31870827
AIM: Observational studies and metanalyses of randomized trials on **Dipeptidyl Peptidase-4 inhibitors** (DPP4i) reported discordant results on the risk of **pancreatitis** and **pancreatic cancer** with this class of drugs. ...Mantel-Haenszel ...

2 **Dipeptidyl peptidase-4 inhibitors, pancreatic cancer and acute pancreatitis: A meta-analysis with trial sequential analysis.**

Cite Pinto LC, Rados DV, Barkan SS, Leitão CB, Gross JL.
Share Sci Rep. 2018 Jan 15;8(1):782. doi: 10.1038/s41598-017-19055-6. PMID: 29335646 **Free PMC article.**
The use of **dipeptidyl peptidase-4** (DPP-4) **inhibitors** may be associated with **pancreatic cancer** and acute **pancreatitis**. ...In conclusion, there is no association between DPP-4 **inhibitors** and **pancreatic** ...

3 **Insulin and glucose-lowering agents for treating people with diabetes and chronic kidney disease.**

Cite Lo C, Toyama T, Wang Y, Lin J, Hirakawa Y, Jun M, Cass A, Hawley CM, Pilmore H, Badve SV, Perkovic V, Zoungas S.
Share Cochrane Database Syst Rev. 2018 Sep 24;9(9):CD011798. doi: 10.1002/14651858.CD011798.pub2. PMID: 30246878 **Free PMC article.** Review.
Nine studies compared sodium glucose co-transporter-2 (SGLT2) **inhibitors** to placebo; 13 studies compared **dipeptidyl peptidase-4** (DPP-4) **inhibitors** to placebo; 2 studies compared glucagon-like peptide-1 (GLP-1) agonists to placebo; 8 studi ...

- 4 **Risk of dipeptidyl peptidase-4 (DPP-4) inhibitors on site-specific cancer: A systematic review and meta-analysis.**
Cite Overbeek JA, Bakker M, van der Heijden AAWA, van Herk-Sukel MPP, Herings RMC, Nijpels G.
Diabetes Metab Res Rev. 2018 Jul;34(5):e3004. doi: 10.1002/dmrr.3004. Epub 2018 Apr 26.
Share PMID: 29573125 Review.
The long-term impact of **dipeptidyl peptidase-4 (DPP-4)** inhibition is unknown, and there are concerns about the influence of DPP-4 inhibition on carcinogenesis of the **pancreas** and thyroid. ...Based on the current literature, it is not poss ...
- 5 **Incretin-based therapies and risk of pancreatic cancer in patients with type 2 diabetes: A meta-analysis of randomized controlled trials.**
Cite Wang H, Liu Y, Tian Q, Yang J, Lu R, Zhan S, Haukka J, Hong T.
Diabetes Obes Metab. 2018 Apr;20(4):910-920. doi: 10.1111/dom.13177. Epub 2018 Jan 3.
Share PMID: 29193572
RESULTS: A total of 33 studies (n = 79 971), including the 6 CVOTs, with 87 **pancreatic cancer** events were identified. Overall, the **pancreatic cancer** risk was not increased in patients administered incretin drugs compared with controls (Peto odds ratio ...
- 6 **Incretin-based agents in type 2 diabetic patients at cardiovascular risk: compare the effect of GLP-1 agonists and DPP-4 inhibitors on cardiovascular and pancreatic outcomes.**
Cite Zhang Z, Chen X, Lu P, Zhang J, Xu Y, He W, Li M, Zhang S, Jia J, Shao S, Xie J, Yang Y, Yu X.
Share Cardiovasc Diabetol. 2017 Mar 1;16(1):31. doi: 10.1186/s12933-017-0512-z.
PMID: 28249585 **Free PMC article.**
BACKGROUND: Incretin-based agents, including **dipeptidyl peptidase-4 inhibitors (DPP-4Is)** and glucagon-like peptide-1 agonists (GLP-1As), work via GLP-1 receptor for hyperglycemic control directly or indirectly, but have different effect on cardiovascul ...
- 7 **Incretin-based glucose-lowering medications and the risk of acute pancreatitis and/or pancreatic cancer: Reassuring data from cardio-vascular outcome trials.**
Cite Nauck MA, Meier JJ, Schmidt WE.
Diabetes Obes Metab. 2017 Sep;19(9):1327-1328. doi: 10.1111/dom.12981. Epub 2017 May 22.
Share PMID: 28432752 No abstract available.

Primary database

Secondary database



Embase®



輸入『P』、『I』及適當同義詞，並搭配各資料庫限定或filter之功能

選擇『Systematic Review、Meta-analysis、RCT』之文章

選擇『5年內』之文章

1 results

14 results

7 results

根據Title/ Abstract選擇『符合臨床問題』之文章

0 results

0 results

1 results

各資料庫收納結果

來源	標題	年份
	Pancreatitis and pancreatic cancer in patientes treated with Dipeptidyl Peptidase-4 inhibitors: An extensive and updated meta-analysis of randomized controlled trials	2020

比較收納文獻-選出最佳文獻，並提出我們的理由



Pancreatitis and pancreatic cancer in patients treated with Dipeptidyl Peptidase-4 inhibitors: An extensive and updated meta-analysis of randomized controlled trials

M

meta-analysis



P

Adults with type 2 diabetes mellitus (> 18 years old)



I

Sitagliptin (Januvia)
Dipeptidyl Peptidase-4 inhibitors



C

Placebo or active drugs



O

Incidence of Pancreatitis, Pancreatic cancer



嚴格評讀之文章及評讀工具

- ✓ 最符合臨床情境
- ✓ 最佳的研究設計

Impact factor: 4.234



ELSEVIER

Contents available at [ScienceDirect](#)

Diabetes Research
and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres



International
Diabetes
Federation



Pancreatitis and pancreatic cancer in patients treated with Dipeptidyl Peptidase-4 inhibitors: An extensive and updated meta-analysis of randomized controlled trials



Ilaria Dicembrini¹, Chiara Montereigi, Besmir Nreu, Edoardo Mannucci, Matteo Monami*

Diabetology, Careggi Hospital and University of Florence, Italy

CASP [31.05.13]

Systematic Review Checklist





Validity

1. Did the review address a clearly focused question?
此回顧是否問了一個清楚、明確的臨床問題？

評讀結果

A MEDLINE, Cochrane database, EMBASE, and clinicaltrials.gov search was performed to identify all clinical trials (English only), up to September 30th, 2019, with duration of follow-up of at least 24 weeks, in which DPP-4i (sitagliptin or vildagliptin or omarigliptin or saxagliptin or alogliptin or trelagliptin or anagliptin or linagliptin or gemigliptin or evogliptin or teneligliptin) were compared with either placebo or active com-

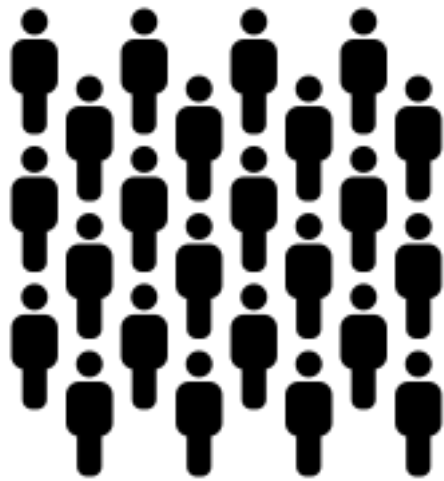
The following parameters/information were extracted: first author, year of publication, name and dose of investigational drug, comparator, add-on therapy, duration of follow-up, number of patients and pancreatitis and pancreatic cancer in each arm, mean age, duration of diabetes, HbA1c, body mass index (BMI), and proportion of women and Caucasians.

P	Adults with type 2 diabetes mellitus (> 18 years old)
I	Sitagliptin (Januvia) Dipeptidyl Peptidase-4 inhibitors
C	Placebo or active drugs
O	Incidence of Pancreatitis, Pancreatic cancer
作者清楚地說明了PICO，因此評讀結果為Yes。	

Yes

No

Unclear



RCT



Validity

2. Did the authors look for the right type of papers?
作者是否收納適當的研究類型？

評讀結果

3.1. Trial characteristics

Fig. 1 reports the trial flow summary. A total of 190 trials fulfilling inclusion criteria was identified. Of them, 28 did not report any information on the endpoints considered in the present meta-analysis (Table 4S) and were therefore excluded from the analysis.

The principal characteristics of the 162 trials included in the analysis are reported in Table 5S and Table 6S. The overall quality was satisfactory in the majority of trials for all items of the Cochrane tool, with the exception of “blinding of participants and personnel” which cannot be completely ruled out for several trials (open-label design or methods not satisfactorily described) and of “selective reporting” due to lack of adjudication of cases of pancreatitis (Fig. 1S).

Aim: Observational studies and meta-analyses of randomized trials on Dipeptidyl Peptidase-4 inhibitors (DPP4i) reported discordant results on the risk of pancreatitis and pancreatic cancer with this class of drugs. Aim of the present meta-analysis is the assessment of the effect of DPP4i treatment on the incidence of pancreatitis and pancreatic cancer, collecting all available evidence from randomized controlled trials. Methods Data Sources:

優點

1. 收錄符合治療型問題的RCT文章
2. 清楚定義了納入條件
3. 清楚定義了排除條件
4. 納入的RCT，皆使用中央電腦隨機分配
5. 有做次族群分析

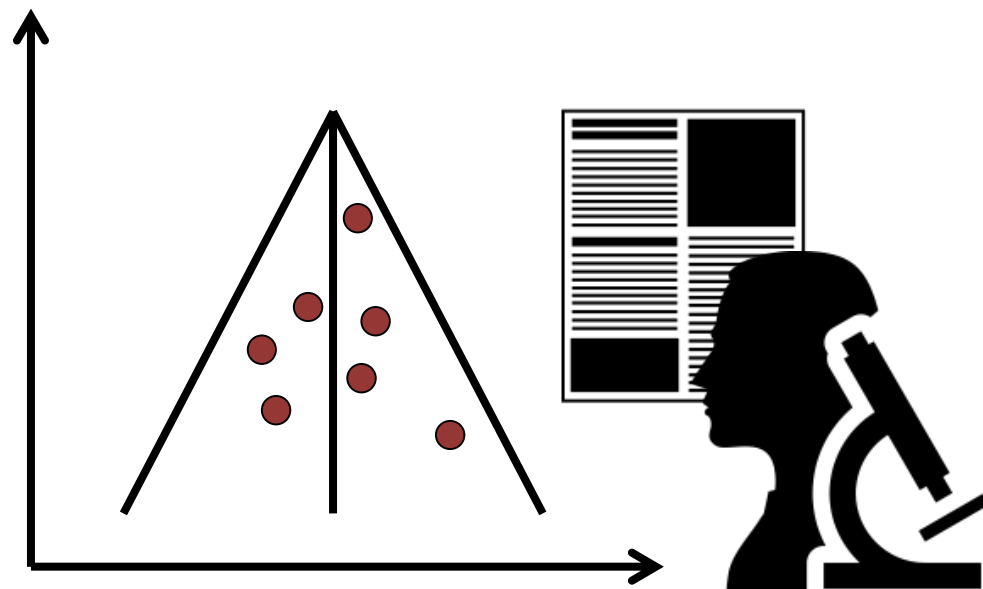
缺點

1. 納入的RCT，部分未使用雙盲
2. 納入的RCT，部分未使用Placebo

Yes

No

Unclear



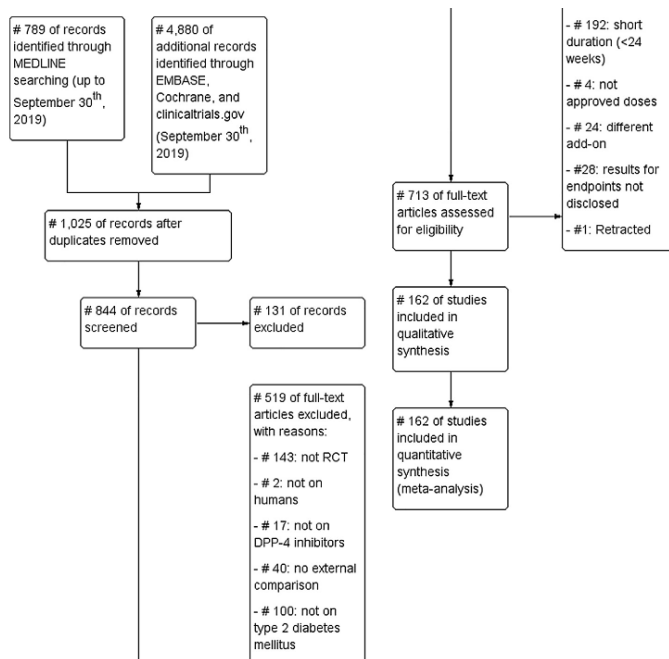
Validity

3. Do you think the important, relevant studies were included?

重要、相關的研究是否皆被納入？

評讀結果

A MEDLINE, Cochrane database, EMBASE, and clinicaltrials.gov search was performed to identify all clinical trials (English only), up to September 30th, 2019, with duration of follow-up of at least 24 weeks, in which DPP-4i (sitagliptin or vildagliptin or omarigliptin or saxagliptin or alogliptin or trelagliptin or anagliptin or linagliptin or gemigliptin or evogliptin or teneligliptin) were compared with either placebo or active com-



優點

1. 搜尋了重要一級和二級資料庫
 - MEDLINE
 - EMBASE
 - Cochrane

2. 列出flow chart

清楚說明納入、排除理由

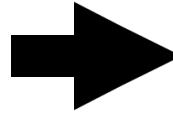
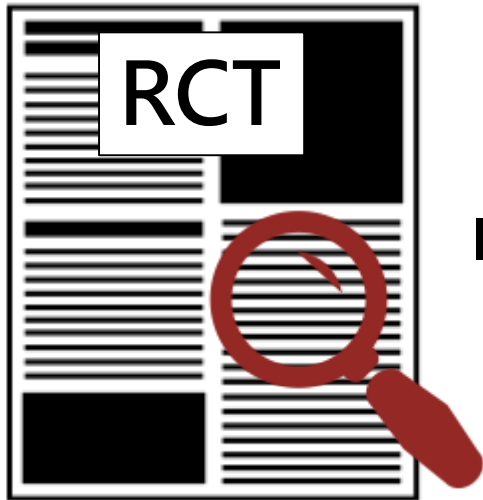
缺點

1. 限制語言英文

Yes

No

Unclear



-	-	-	?	?
-	?	-	-	?
+	+	+	+	+
?	?	+	?	?
?	?	?	?	?
?	?	-	?	?
-	?	+	?	?

Validity

4. Did the review's authors do enough to assess the quality of the included studies?

作者是否有評估收納研究的品質？

評讀結果

The identification of relevant abstracts, the selection of studies, and extraction were performed independently by two of the authors (I.D. and B.N.), and conflicts resolved by a third investigator (M.M.).

3.2. Pancreatitis

Information on pancreatitis were reported in 164 trials. Out of 164 studies (67,931 patients in DPP-4 inhibitors and 62,324 patients in control group), 46 reported at least one event of pancreatitis (143 and 133 with DPP-4 inhibitors and comparators, respectively). No publication bias was detected at visual analysis of the Funnel plot (Fig. 2S).

3.3. Pancreatic cancer

Information on pancreatic cancer was reported in 157 trials. Of those (66,897 patients in DPP-4 inhibitors and 61,597 patients in control group), 21 reported at least one case of pancreatic cancer (58 and 63 with DPP-4 inhibitors and comparators, respectively). No publication bias was detected at visual analysis of the Funnel plot (Figure 7S). DPP-4

優點

1. 由兩位作者獨立評讀並由第三位讀者解決分歧。

2. 使用Cochrane Handbook for Systematic Review of Interventions分析各RCT之Bias

(選擇.盲目性.結果.損耗.其他)。

評級依研究設計、限制、一致性判斷貢獻度

Yes

No

Unclear

Risk of Bias

Figure 1S – Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

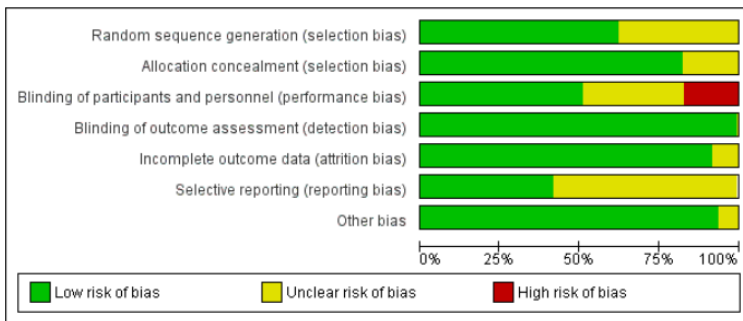


Figure 2S - Funnel plot for pancreatitis.

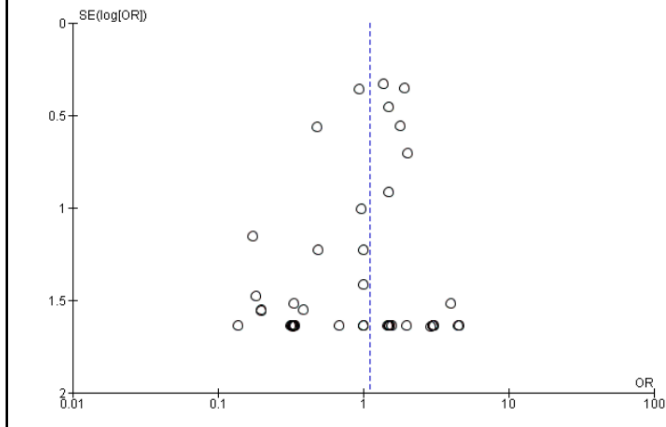
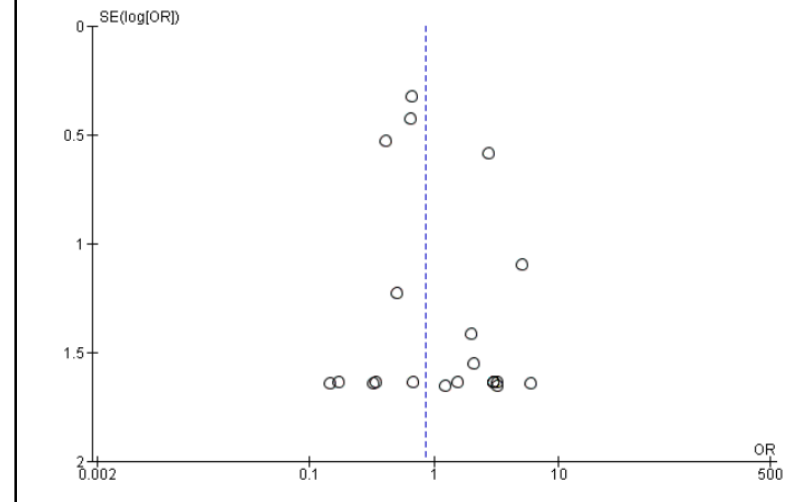
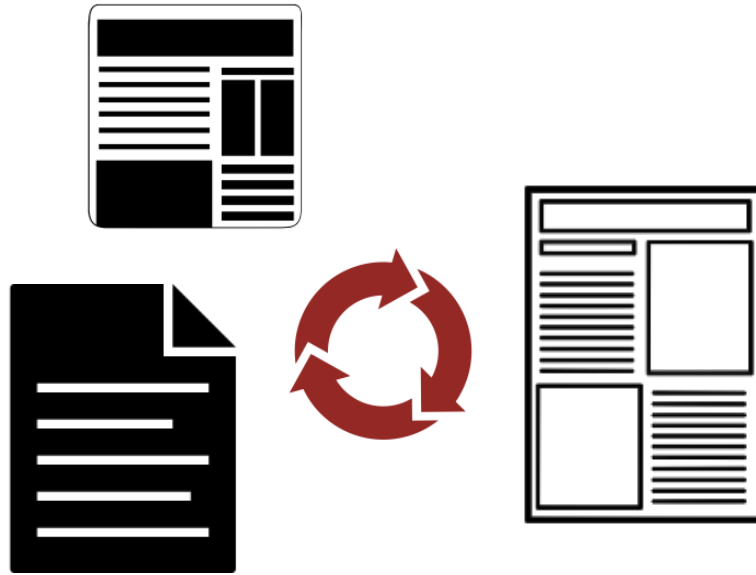


Figure 7S - Funnel plot for pancreatic cancer.





Validity

5. If the results of the review have been combined, was it reasonable to do so?

作者是否有把各個研究的結果合併起來？
這樣的合併是合理的嗎？

Yes

No

Unclear

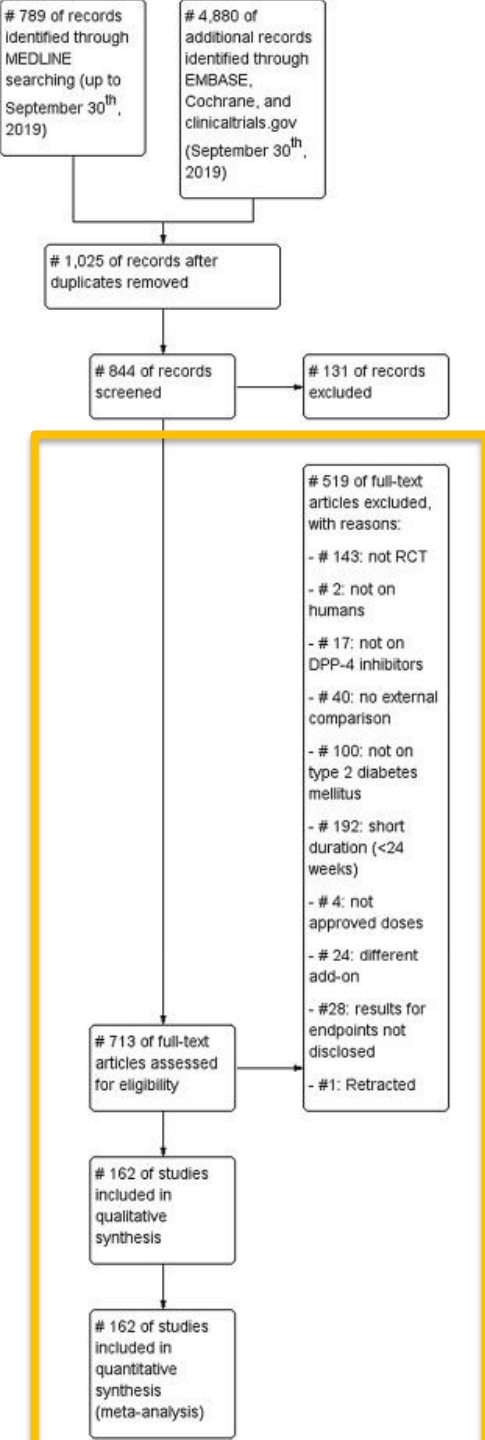


Table 5S – Principal characteristics of published trials included in the metanalysis.

Study Name (Reference)	Comparator	Trial duration (weeks)	Patients (n)	Age (years)	Female (%)	BMI (Kg/m ²)	HbA1c (%)	DM duration (years)	Pancreatitis Adjud./Excl.
Cardiovascular Outcome Trials									
Alogliptin									
Mita 2016 (26)	None	104	341	64.6	38.0	24.8	7.3	8.6	NO/NO
White 2013 (27)	Placebo	94	5,380	61.0	32.0	28.7	8.0	7.0	YES/NO
Linagliptin									
de Boer 2017 (28)	Placebo	26	44	63.0	39.0	30.4	6.3	1.0	NO/YES
Rosenstock 2019 (29)	Placebo	114	6,979	66.0	37.0	31.3	7.9	14.7	YES/NO
Rosenstock 2019 (30)	Glimepiride	307	6,033	64.0	40.0	30.1	7.2	6.2	YES/NO
Omarigliptin									
Gantz 2017 (31)	Placebo	142	4,202	63.6	30.0	31.3	8.0	12.0	YES/NO
Saxagliptin									
Scirica 2013 (32)	Placebo	109	16,492	65.0	33.0	31.1	8.0	12.0	YES/NO
Sitagliptin									
Green 2015 (33)	Placebo	156	14,671	65.5	29.3	30.2	7.2	11.6	YES/NO
Mita 2016 (34)	None	104	165	63.7	39.5	25.0	8.1	17.3	NO/NO
Oyama 2016 (35)	None	96	442	69.4	32.8	25.1	7.0	NR	NO/NO
Oe 2015 (36)	Voglibose	24	100	67.3	42.5	26.7	NR	3.6	NO/NO
Arturi 2017 (37)	Liraglutide	52	20	60.0	33.0	32.5	8.1	NR	NO/YES
Rosenstock 2019 (38)	Semaglutide	78	1,398	58.0	47.0	32.4	8.3	8.5	YES/YES
Vildagliptin									
McMurray 2018 (39)	Placebo	52	254	63.0	23.0	29.4	7.8	9.3	NO/NO
Berndt-Zipfel 2013 (40)	Glimepiride	24	44	58.5	36.4	34.0	7.4	7.3	NO/NO
Non Cardiovascular Outcomes Trials									

Table 5S – Principal characteristics of published trials included in the metanalysis.

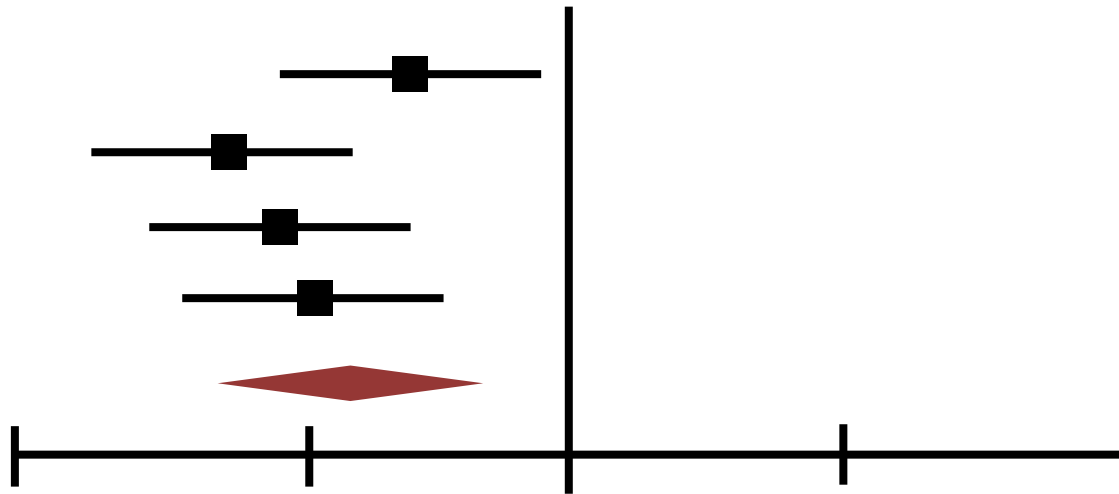
Table 6S – Principal characteristics of unpublished trials included in the metanalysis.

Study Name*	Completion date	Comparator	Trial duration (weeks)	Patients (n)	Age (years)	Female (%)	BMI (Kg/m ²)	HbA1c (%)	DM duration (years)	Pancreatitis Adjud./Excl.
Unpublished										
Alogliptin										
NCT01890122	28/11/2016	Placebo	26.0	322	54.0	43.4	26.3	NR	NR	NO/YES
NCT01890122 (a)	28/11/2016	Metformin	26.0	325	54.0	43.4	26.3	NR	NR	NO/YES
Linagliptin										
NCT01214239	01/05/2012	Placebo	24.0	299	54.4	41.5	25.4	8.0	NR	NO/NO
NCT02240680	03/07/2018	Placebo	24.0	302	72.4	39.4	NR	8.2	NR	NO/NO
NCT02061969	22/08/2018	Glargine	24.0	140	70.0	59.3	NR	NR	NR	NO/YES
NCT01183013	21/04/2014	Pioglitazone	30.0	544	57.0	45.9	NR	8.1	NR	NO/YES
Saxagliptin										
NCT00374907	21/01/2011	Metformin	104.0	36	NR	61.0	33.0	NR	NR	NO/NO
Sitagliptin										
NCT00875394	20/04/2011	None	24.0		54.7	73.5	28.8	8.5	8.4	NO/NO
NCT01186562	28/12/2016	Placebo	52.0	83	41.0	80.7	NR	NR	NR	NO/NO
NCT01549964	02/06/2016	Placebo	24.0	392	56.0	46.1	32.0	8.3	NR	NO/NO
NCT02577016	07/03/2018	Placebo	24.0	141	55.5	29.8	NR	8.0	NR	NO/NO
NCT00976937	11/10/2016	Lixisenatide	24.0	319	43.1	59.9	36.8	8.1	4.4	NO/YES
Vildagliptin										
NCT00396357	04/06/2008	Metformin	24.0	798	57.0	52.3	31.1	7.3	5.0	NO/NO
NCT00494884	07/07/2008	Placebo	24.0	402	61.0	47.0	NR	7.2	NR	NO/NO
NCT00821977	18/10/2010	Placebo	24.0	451	53.0	46.0	31.3	8.0	NR	NO/YES
NCT00860288	31/03/2011	Placebo	24.0	2,443	57.0	48.5	31.2	7.8	6.0	NO/NO

Table 6S – Unpublished trial

DPP-4 inhibitors were not associated with a significant increase in risk of pancreatitis (MH-OR 1.13 [0.86, 1.47]; Fig. 2) with no significant differences across individual molecules of the class. No heterogeneity (I^2 : 0%) was detected for this endpoint. Similar results were obtained using a fixed-effect model (MH-OR 1.07 [0.84, 1.37]), as well as in a sensitivity analysis with continuity correction (MH-OR 0.94 [0.78, 1.13]; Figure 3S).

results in subgroup analyses. Notably, when pancreatitis and pancreatic cancer were not listed as adverse events of special interest, we collected only cases reported as serious adverse events, possibly underestimating their actual incidence. In addition, although heterogeneity was low the reliability of its determination when there are many trials with few events is questionable.



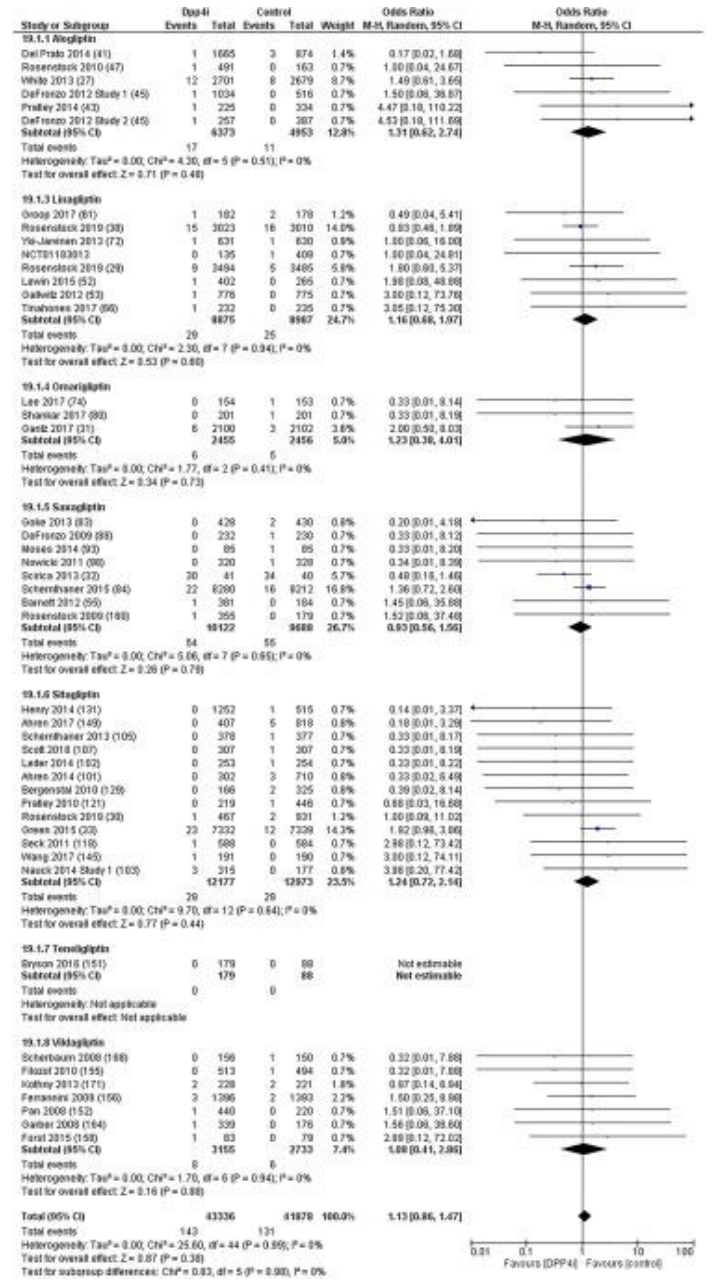
Importance

6. What are the overall results of the review?
這篇回顧呈現了什麼結果？

主要結果-pancreatitis

評讀結果

Intervention	sitagliptin
Comparison	Placebo/ Usual care
研究結果	MH-OR 1.13 [0.86, 1.47]
結論	服用Januvia不 會增加 胰臟炎之發生



Yes

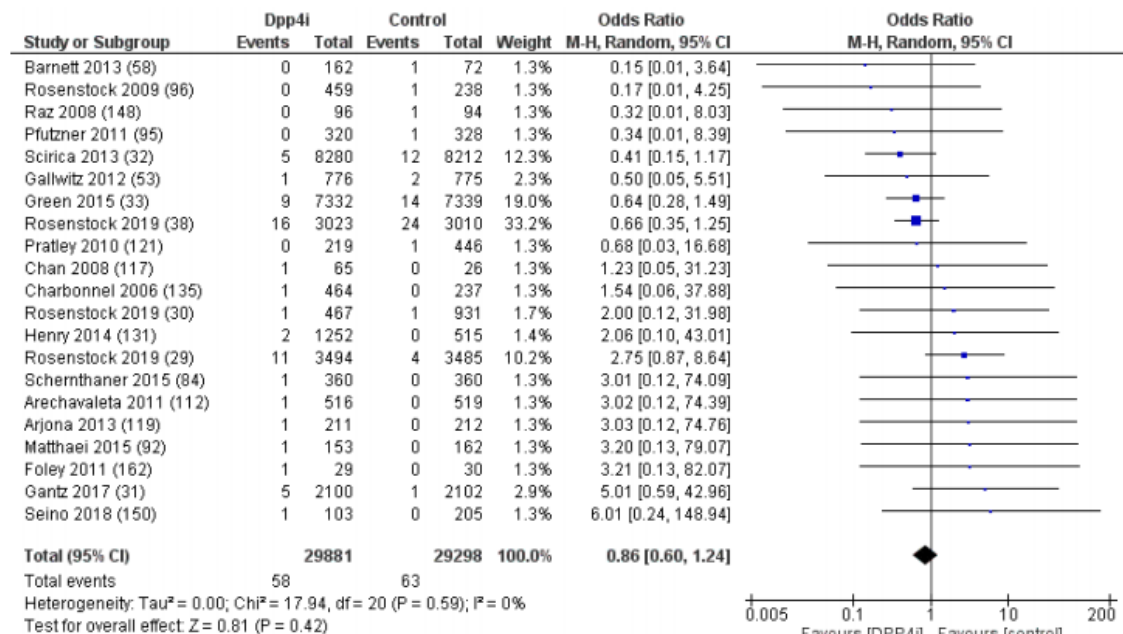
No

Unclear

主要結果- pancreatic cancer

評讀結果

Figure 8S – Risk of pancreatic cancer with DPP-4 inhibitors versus other comparators.

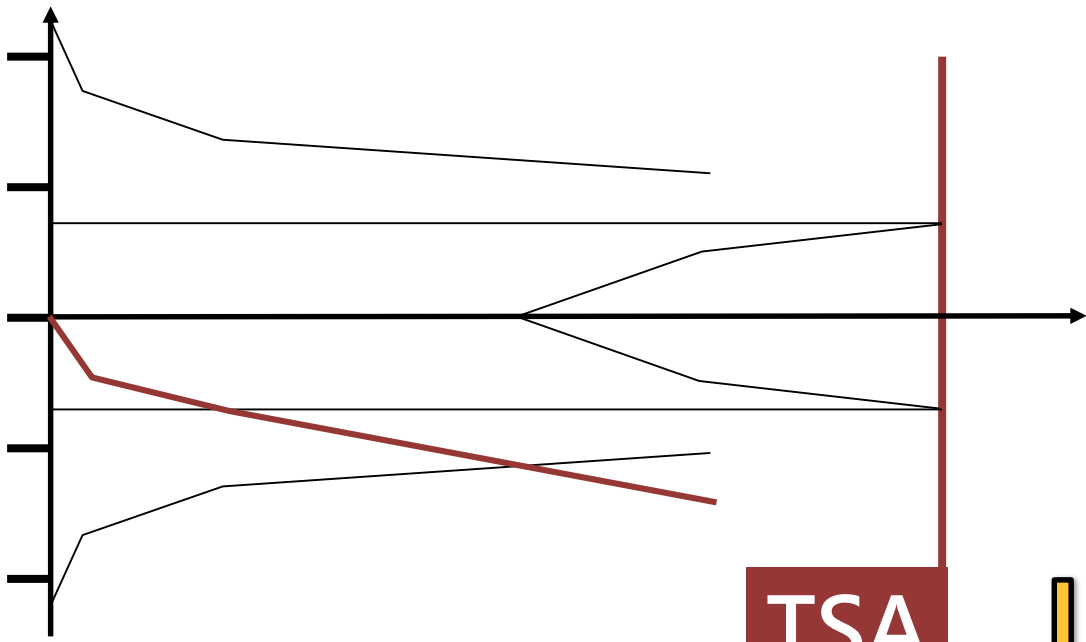


Intervention	sitagliptin
Comparison	Placebo/ Usual care
研究結果	MH-OR 0.86 [0.60, 1.24]
結論	服用Januvia 不會增加 胰臟炎之發生

Yes

No

Unclear



TSA

Importance

7. How precise are the results?
結果精準嗎？

主要結果-pancreatitis, pancreatic cancer

September 30th, 2019. All trials performed on type 2 diabetes, with duration ≥ 24 weeks, and comparing of DPP4i with placebo or active drugs were collected. The study has been registered on PROSPERO (#153344). Mantel-Haenszel odds ratio (MH-OR) with 95% Confidence Interval (95% CI) was calculated for all outcomes defined above. Results
A total of 165 eligible trials were identified. DPP-4 inhibitors were not associated with an increased risk of pancreatitis (MH-OR 1.13 [0.86, 1.47]) or pancreatic cancer (MH-OR 0.86 [0.60, 1.24]) with no significant differences across individual molecules of the class. Conclusions:

評讀結果

1. 收錄之RCT有相似之研究結果
2. 結果之95%信賴區間窄
3. 樣本數夠大 (162 trials)

Yes

No

Unclear



Practice

8. Can the results be applied to the local population?
此研究是否可應用到你的病患？

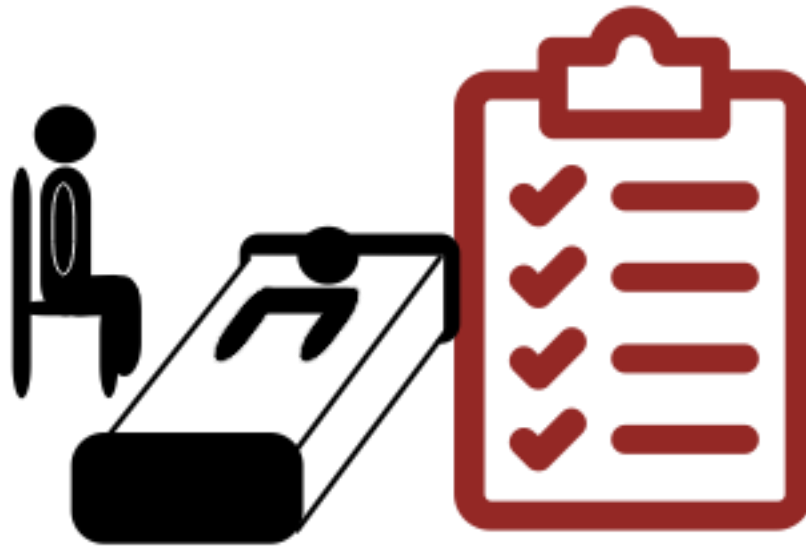
Table 5S – Principal characteristics of published trials included in the metanalysis.

Study Name <i>(Reference)</i>	Comparator	Trial duration <i>(weeks)</i>	Patients <i>(n)</i>	Age <i>(years)</i>	Female <i>(%)</i>	BMI <i>(Kg/m²)</i>	HbA1_c <i>(%)</i>	DM duration <i>(years)</i>	Pancreatitis <i>Adjud./Excl.</i>
Cardiovascular Outcome Trials									
Alogliptin									
Mita 2016 (26)	None	104	341	64.6	38.0	24.8	7.3	8.6	NO/NO
White 2013 (27)	Placebo	94	5,380	61.0	32.0	28.7	8.0	7.0	YES/NO
Linagliptin									
de Boer 2017 (28)	Placebo	26	44	63.0	39.0	30.4	6.3	1.0	NO/YES
Rosenstock 2019 (29)	Placebo	114	6,979	66.0	37.0	31.3	7.9	14.7	YES/NO
Rosenstock 2019 (30)	Glimepiride	307	6,033	64.0	40.0	30.1	7.2	6.2	YES/NO
Omarigliptin									
Gantz 2017 (31)	Placebo	142	4,202	63.6	30.0	31.3	8.0	12.0	YES/NO
Saxagliptin									
Scirica 2013 (32)	Placebo	109	16,492	65.0	33.0	31.1	8.0	12.0	YES/NO
Sitagliptin									
Green 2015 (33)	Placebo	156	14,671	65.5	29.3	30.2	7.2	11.6	YES/NO
Mita 2016 (34)	None	104	165	63.7	39.5	25.0	8.1	17.3	NO/NO
Oyama 2016 (35)	None	96	442	69.4	32.8	25.1	7.0	NR	NO/NO
Oe 2015 (36)	Voglibose	24	100	67.3	42.5	26.7	NR	3.6	NO/NO
Arturi 2017 (37)	Liraglutide	52	20	60.0	33.0	32.5	8.1	NR	NO/YES
Rosenstock 2019 (38)	Semaglutide	78	1,398	58.0	47.0	32.4	8.3	8.5	YES/YES
Vildagliptin									
McMurray 2018 (39)	Placebo	52	254	63.0	23.0	29.4	7.8	9.3	NO/NO
Berndt-Zipfel 2013 (40)	Glimepiride	24	44	58.5	36.4	34.0	7.4	7.3	NO/NO
Non Cardiovascular Outcomes Trials									

評估適用性-比較評讀文獻及臨床情境

P	AND	I	AND	C	AND	O
Adults with type 2 diabetes mellitus (18 years or older)		Sitagliptin (Januvia) Dipeptidyl Peptidase-4 inhibitors		Placebo or active drugs		Pancreatitis, Pancreatic cancer

<p>1. 我們的病患與文獻研究是否相似？</p> <p> <input checked="" type="checkbox"/>年齡 <input checked="" type="checkbox"/>性別 <input type="checkbox"/>種族 <input type="checkbox"/>共病 <input type="checkbox"/>同時服用其他治療藥物 <input type="checkbox"/>疾病嚴重度 </p>	是
<p>2. 這項治療在台灣是否可行？</p> <p> <input checked="" type="checkbox"/>Yes <input type="checkbox"/>No <input type="checkbox"/>Unclear </p>	可



Practice

9. Were all important outcomes considered?
是否所有重要的臨床結果都被考量到？

	重要臨床結果	評讀之文獻
Risk	Pancreatitis	✓
Risk	Pancreatic cancer	✓

Yes

No

Unclear



Practice

10. Are the benefits worth the harms and costs?
這些好處隨之而來的傷害和花費是否值得？

考量利益(NNT)與風險(NNH)

A治療 versus B治療

治療之利益—血糖控制

Reduced further co-morbidity of MI, stroke and ESRD

治療之風險—副作用

1. The present metanalysis of randomized trials does not confirm the association of DPP4i with the risk of pancreatitis.
2. Endocrine metabolic: Hypoglycemia (0.6% to 12.2%)
3. Neurologic: Headache (1.1% to 5.9%)
4. Respiratory: Nasopharyngitis (5.2% to 6.3%), Upper respiratory infection (4.5% to 6.3%)

這些好處隨之而來的傷害和花費是否值得？

Yes

No

Unclear

臨床問題: Sitagliptin 是否會導致胰臟炎或者胰臟癌

		結果	結果
		Pancreatitis	Pancreatic cancer
		RR: 1.13 (95%CI) [0.86, 1.47]	RR: 0.86 (95%CI) [0.60, 1.24]
研究設計		Meta-analysis	
降階	1. 存在誤差風險	●	●
	2. 結果不一致	●	●
	3. 證據不具直接性	●	●
	4. 結果不精準	●	●
	5. 存在發表誤差	●	●
升階	1. 效果顯著		
	2. 降低干擾因素		
	3. 具劑量-反應效果		
證據等級		⊕⊕⊕⊕ HIGH	⊕⊕⊕⊕ HIGH

評定證據等級-OCEBM Level of Evidence, 2011

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or <i>n</i> -of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, <i>n</i> -of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided	Case-series, case-control, or historically controlled	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or <i>n</i> -of-1 trial	Randomized trial or (exceptionally) observational study			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial			

【治療型問題】
 RCT之系統性回顧文章
 證據等級為 **Level 1**
 ※經嚴格評讀，無其他需要考慮降階理由

考慮降階之理由

- 研究品質差
- 絕對效果小
- PICO和臨床情境不相符
- 證據間沒有一致性
- 研究不精確(95%CI過大)

共享決策-Share Decision Making

醫療現況 (實證醫學)

證據等級:GRADE (High)
OCEBM (Level 1)

建議:Sitagliptin並不會增加獲得
胰臟炎以及胰臟癌的機率



病人治療偏好

希望可以藉由藥物治療改善血糖控制。



利弊平衡

穩定使用血糖藥，可獲得穩定的血糖控制，除此之外也沒有太明顯致命的副作用產生。



費用資源

健保給付藥價，並且減少因併發症(中風、心肌梗塞以及末期腎病變)住院以及死亡的機率。



臨床應用-回覆病人問題

您好，經過我們專業團隊的實證查證結果，目前有2020年的系統性回顧文獻支持。證實**Sitagliptin**並不會增加您獲得胰臟炎以及胰臟癌的機率，可以安心服用。

除此之外，根據2020年ADA出版的2021糖尿病治療指引，**平日需注意飲食**以及**適當減重**也能有效控制血糖，其他替代藥物的部分可以考慮GLP 1-agonist作為使用；治療指引同時指出不建議以補充肉桂來作為改善血糖的治療方法。

。



謝謝評審老師