

Evidence-Based Medicine

實證醫學

陳鈺仁、賴毅軒、林冠伶

實證是守護病患健康最好的工具



臨床場景 *Clinical Scenario*

2

- 45歲黃先生，平常除了抽菸外，無其他嗜好。三年前公司體檢意外發現的第二型糖尿病(type 2 DM)，也在飲食控制及口服降血糖藥物使用下，控制得不錯。黃先生一直有健走的習慣，最近一個月來他發現自己健走的時候越來越容易累，走的距離也沒有之前長。他擔心自己是不是腳有問題，就去看了骨科。骨科醫師幫他安排X光排除腰椎問題後，就將他轉診到心臟科去。詳細問診後，心臟科醫師幫他安排了周邊動脈血管檢查，包括上下肢血壓比值(ankle-brachial index, ABI)，結果是0.6，醫師告訴他是周邊動脈阻塞疾病(peripheral arterial disease, PAD)，由於是下肢動脈狹窄引起的，需要吃cilostazol治療，也建議吃aspirin預防血栓。也可以考慮做心導管手術，將狹窄的動脈撐開，改善下肢血流循環情況。



- 黃先生對於自己的病情有疑問，他想知道，光靠測量血壓來診斷PAD準確嗎？有沒有更確定的診斷方法呢？超音波可以嗎？還是要做到血管攝影呢？另外，他也想知道，是不是一定要吃cilostazol，效果如何？如果不吃藥有其他替代的方法？光吃aspirin預防血栓夠嗎？運動可以嗎？醫師建議的心導管血管擴張手術，效果怎麼樣呢？會不會有風險？

背景知識-周邊動脈阻塞疾病

➤ 流行病學：

美國盛行率為4.6%，年齡 < 60歲 3%， >75歲 20%

➤ 病理機轉：

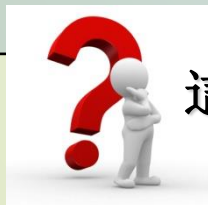
系統性的動脈粥狀硬化改變動脈的結構及功能，進而影響腦部、內臟及肢體的血流供應

➤ 症狀：

最常見是間歇性跛行，其他有夜間腿部疼痛、慢性傷口癒合不良、皮膚顏色改變等

關鍵字搜尋策略

	中文關鍵字	英文關鍵字	同義字/MeSH
P	45歲男性/周邊動脈阻塞疾病	Adult peripheral arterial disease	Adult Peripheral Artery Disease Arterial Occlusive Diseases Peripheral Vascular Diseases
I	上下肢血壓比值、超音波	ankle-brachial index, ultrasonography	Toe Brachial Index Ultrasonic Diagnosis Ultrasonic Imaging
C	血管攝影	Angiography	Arteriography Angiogram
O	診斷準確率	Accuracy	precision



這是一個

治療型



診斷型

預後型

傷害型問題

關鍵字搜尋策略

	中文關鍵字	英文關鍵字	同義字/MeSH
P	45歲男性/周邊動脈阻塞疾病	Adult peripheral arterial disease	Adult Peripheral Artery Disease Arterial Occlusive Diseases Peripheral Vascular Diseases
I	抗血小板藥物〈普達錠〉	cilostazol	Platelet Aggregation Inhibitors Phosphodiesterase 3 Inhibitors
C	其他藥物	Placebo	-/-
O	治療效果	Life quality, claudication severity	Walking distance



這是一個



治療型

診斷型

預後型

傷害型問題

搜尋資料庫

8

➤ Secondary Database



➤ Primary Database

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➤ 中文文獻



搜尋 Cochrane Library

9

Cochrane Reviews 4 | Cochrane Protocols 0 | Trials 127 | Editorials 0 | Special collections 0 | Clinical Answers 0 | Other Reviews 0

4 Cochrane Reviews matching **peripheral artery disease in Title Abstract Keyword AND cilostazol in Title Abstract Keyword - (Word variations have been searched)**

Cochrane Database of Systematic Reviews
Issue 5 of 12, May 2020

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Order by: Relevancy

- Cilostazol for intermittent claudication**
Rachel Bedenis, Marlene Stewart, Marcus Cleanthis, Peter Robless, Dimitri P Mikhailidis, Gerard Stansby
Intervention Review 31 October 2014 New search Free access
[Show preview](#)
- Antiplatelet and anticoagulant drugs for prevention of restenosis/reocclusion following peripheral endovascular treatment**
Lindsay Robertson, Maaz A Ghouri, Flora Kovacs
Intervention Review 15 August 2012 New search Free access
[Show preview](#)
- Endovascular revascularisation versus conservative management for intermittent claudication**
Farzin Fakhry, Hugo JP Fokkenrood, Sandra Spronk, Joep AW Tejjink, Ellen V Rouwet, M G Myriam Hunink
Intervention Review 8 March 2018 Free access
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- Exercise for intermittent claudication**
Risha Lane, Amy Harwood, Lorna Watson, Gillian C Leng
Intervention Review 26 December 2017 New search Free access
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Result

Title Abstract Keyword peripheral artery disease

AND Title Abstract Keyword cilostazo|

搜尋結果四篇，有三篇符合PICO

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1 A randomized, placebo-controlled trial of canakinu
Russell K.S., Yates D.P., Kramer C.M., Feller A., Mahling P., Colin L.,
Nikol S., Smith W.B., Müller O.J., Ratchford E.V., Basson C.T.
Vascular Medicine (United Kingdom) 2019 24:5 (414-421) Cited by: 0
Embase MEDLINE Abstract Index Terms [View Full Text](#) [Similar records >](#)

2 Cilostazol reduces dry eye symptoms and improve walking distance in patients with peripheral artery disease
Chisari L.M., Malaguarnera S., Grasso A., Malaguarnera M., Chisari G., Borzi A.M., Chisari C.G.
La Clinica terapeutica 2019 170:5 (e357-e363) Cited by: 0
MEDLINE Abstract Index Terms [View Full Text](#) [Similar records >](#)

3 Peripheral Revascularization in Patients With Peripheral Artery Disease With Vorapaxar: Insights From the TRA
2°P-TIMI 50 Trial
Bonaca M.P., Creager M.A., Olin J., Scirica B.M., Gilchrist I.C., Murphy S.A., Goodrich E.L., Braunwald E., Morrow D.A.
JACC: Cardiovascular Interventions 2016 9:20 (2157-2164) Cited by: 20
Embase MEDLINE Abstract Index Terms [View Full Text](#) [Similar records >](#)

4 Cilostazol attenuates the severity of peripheral arterial occlusive disease in patients with type 2 diabetes: the
role of plasma soluble receptor for advanced glycation end-products
Liu J.-S., Chuang T.-J., Chen J.-H., Lee C.-H., Hsieh C.-H., Lin T.-K., Hsiao F.-C., Hung Y.-J.
Endocrine 2015 49:3 (703-710) Cited by: 9
Embase MEDLINE Abstract Index Terms [View Full Text](#) [Similar records >](#)

5 Potential vascular mechanisms of ramipril induced increases in walking ability in patients with intermittent
claudication
Ahimastos A.A., Latouche C., Natoli A.K., Reddy-Luthmoodoo M., Golledge J., Kingwell B.A.
Circulation Research 2014 114:7 (1144-1155) Cited by: 6
Embase MEDLINE Abstract Index Terms [View Full Text](#) [Similar records >](#)

6 Cilostazol enhances mobilization and proliferation of endothelial progenitor cells and collateral formation by
modifying vasculo-angiogenic biomarkers in peripheral arterial disease
Chao T.-H., Tseng S.-Y., Chen I.-C., Tsai Y.-S., Huang Y.-Y., Liu P.-Y., Ou H.-Y., Li Y.-H., Wu H.-L., Cho C.-L., Tsai L.-M., Chen J.-H.
International Journal of Cardiology 2014 172:2(e371-e374) Cited by: 19

cilostazol

placebo

claudication

搜尋結果為249篇，其中27篇為SR，
有12篇符合PICO

搜尋 PubMed

(peripheral artery disease) AND cilostazol AND claudication

搜尋結果為12篇，有5篇符合PICO

Systematic Reviews

Results: 5 of 12

Endovascular revascularisation versus conservative management for intermittent claudication.

Fakhry F, Fokkenrood HJ, Spronk S, Tejjink JA, Rouwet EV, Hunink MGM.

Cochrane Database Syst Rev. 2018 Mar 8; 3:CD010512. Epub 2018 Mar 8.

Cilostazol for intermittent claudication.

Bedenis R, Stewart M, Cleanthis M, Robless P, Mikhailidis DP, Stansby G.

Cochrane Database Syst Rev. 2014 Oct 31; (10):CD003748. Epub 2014 Oct 31.

A systematic review to evaluate the effectiveness of carnitine supplementation in improving walking performance among individuals with intermittent claudication.

Delaney CL, Spark JI, Thomas J, Wong YT, Chan LT, Miller MD.

Atherosclerosis. 2013 Jul; 229(1):1-9. Epub 2013 Mar 15.

Systematic review of the efficacy of cilostazol, naftidrofuryl oxalate and pentoxifylline for the treatment of intermittent claudication.

Stevens JW, Simpson E, Harnan S, Squires H, Meng Y, Thomas S, Michaels J, Stansby G.

Br J Surg. 2012 Dec; 99(12):1630-8. Epub 2012 Oct 3.

Antiplatelet and anticoagulant drugs for prevention of restenosis/reocclusion following peripheral endovascular treatment.

Robertson L, Ghouri MA, Kovacs F.

Cochrane Database Syst Rev. 2012 Aug 15; (8):CD002071. Epub 2012 Aug 15.

搜尋結果

資料庫	搜尋篇數	符合PICO篇數
 THE COCHRANE LIBRARY Independent high-quality evidence for health care decision making	4	3
 Embase®	27	12
 PubMed	12	5
 airiti Library 華藝線上圖書館	0	0

嚴格評讀 *Critical Appraisal*



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Cochrane Database of Systematic Reviews

Cilostazol for intermittent claudication (Review)

Bedenis R, Stewart M, Cleanthis M, Robless P, Mikhailidis DP, Stansby G

這篇文獻「納入理由」

- ✓ 最符合臨床問題
- ✓ 最佳的研究設計

- 發表年份較新
- ✓ 有全文可供評讀

CNSP

Critical Appraisal
Skills Programme



www.casp-uk.net



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Summertown Pavilion, Middle
Way Oxford OX2 7LG

CASP Checklist: 10 questions to help you make sense of a **Systematic Review**

1. Did the review address a clearly focused question?

Main results

We included fifteen double-blind, RCTs comparing cilostazol with placebo, or medications currently known to increase walking distance e.g. pentoxifylline. There were a total of 3718 randomised participants with treatment durations ranging from six to 26 weeks. All participants had intermittent claudication secondary to PAD. Comparisons included cilostazol twice daily, with dosages of 50 mg, 100 mg and 150 mg compared with placebo, and cilostazol 100 mg, twice daily, compared with pentoxifylline 400 mg, three times daily. The

methodological quality of the trials was generally low, with the majority being at an unclear risk for selection bias, performance bias, detection bias and other bias. Attrition bias was generally low, but reporting bias was high or unclear in the majority of the studies. For eight studies data were compatible for comparison by meta-analysis, but data for seven studies were too heterogenous to be pooled. For the studies included in the meta-analysis, for initial claudication distance (ICD - the distance walked on a treadmill before the onset of calf pain) there was an improvement in the cilostazol group for the 100 mg and 50 mg twice daily, compared with placebo (WMD 31.41 metres, 95% CI 22.38 to 40.45 metres; $P < 0.00001$) and WMD 19.89 metres, 95% CI 9.44 to 30.34 metres; $P = 0.0002$), respectively. ICD was improved in the cilostazol group for the comparison of cilostazol 150 mg versus placebo and cilostazol 100 mg versus pentoxifylline, but only single studies were used for these analyses. Absolute claudication distance (ACD - the maximum distance walked on a treadmill) was significantly increased in participants taking cilostazol 100 mg and 50 mg twice daily, compared with placebo (WMD 43.12 metres, 95% CI 18.28 to 67.96 metres; $P = 0.0007$) and WMD 32.00 metres, 95% CI 14.17 to 49.83 metres; $P = 0.0004$), respectively. As with ICD, ACD was increased in participants taking cilostazol 150 mg versus placebo, but with only one study an association cannot be clearly determined. Two studies comparing cilostazol to pentoxifylline had opposing findings, resulting in an imprecise CI (WMD 13.42 metres (95% CI -43.51 to 70.35 metres; $P = 0.64$)). Ankle brachial index (ABI) was lowered in the cilostazol 100 mg group compared with placebo (WMD 0.06, 95% CI 0.04 to 0.08; $P < 0.00001$). The single study evaluating ABI for the comparison of cilostazol versus pentoxifylline found no change in ABI.

There was no association between treatment type and all-cause mortality for any of the treatment comparisons, but there were very few events, and therefore larger, adequately powered studies will be needed to assess if there is a relationship. Only one study evaluated individual cardiovascular events, and from this study there is no clear evidence of a difference between any of the treatment groups and risk of myocardial infarction or stroke. We evaluated adverse side effects, and in general cilostazol was associated with a higher odds of headache, diarrhoea, abnormal stool, dizziness and palpitations. We only reported quality of life measures descriptively as there was insufficient statistical detail within the studies to combine the results, although there was a possible indication in improvement of quality of life in the cilostazol treatment groups.

YES

NO

UNCLEAR

2. Did the authors look for the right type of papers?

16

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YES



NO



UNCLEAR

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

 YES

 NO

 UNCLEAR

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Analysis 1.1. Comparison 1 Initial claudication distance (ICD), Outcome 1 ICD cilostazol 100 mg twice daily versus placebo.	38
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Analysis 6.11. Comparison 6 Adverse effects, Outcome 11 Dizziness cilostazol 50 mg twice daily versus placebo.	48
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4. Did the review's authors do enough to assess quality of the included studies?

YES

NO

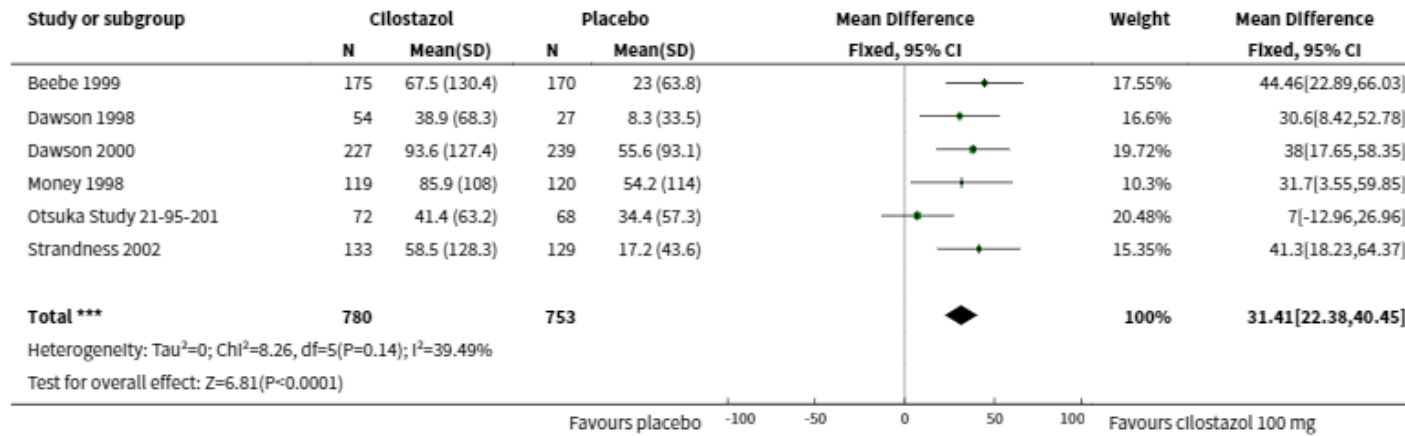
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Analysis 1.3. Comparison 1 Initial claudication distance (ICD), Outcome 3 ICD cilostazol 150 mg twice daily versus placebo.	38
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Analysis 6.10. Comparison 6 Adverse effects, Outcome 10 Dizziness cilostazol 100 mg twice daily versus placebo.	48

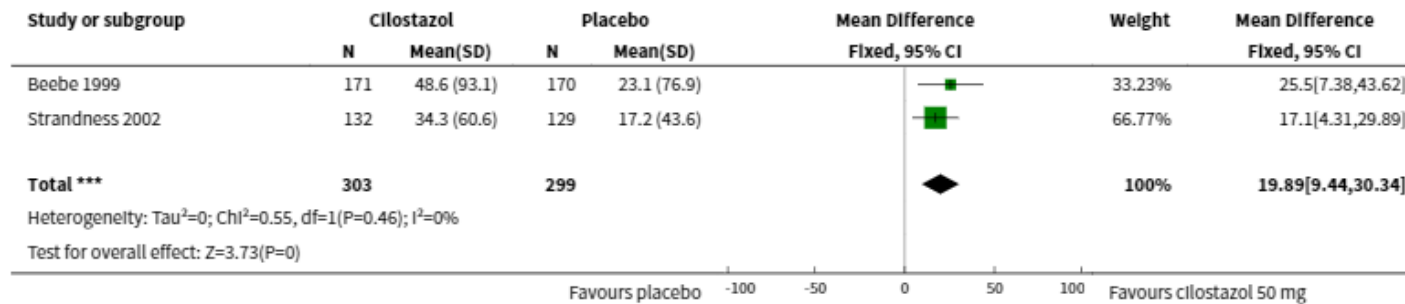
Analysis 6.11. Comparison 6 Adverse effects, Outcome 11 Dizziness cilostazol 50 mg twice daily versus placebo.	48
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Analysis 6.17. Comparison 6 Adverse effects, Outcome 17 Palpitations cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily.	50

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

Analysis 1.1. Comparison 1 Initial claudication distance (ICD), Outcome 1 ICD cilostazol 100 mg twice daily versus placebo.



Analysis 1.2. Comparison 1 Initial claudication distance (ICD), Outcome 2 ICD cilostazol 50 mg twice daily versus placebo.

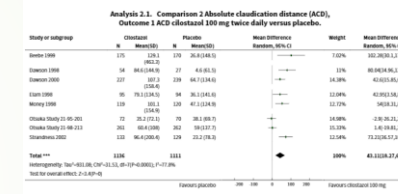


Analysis 1.4. Comparison 1 Initial claudication distance (ICD), Outcome 4 ICD cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily.

Study or subgroup	Outcome	Events/No.	Events/No.	Mean Difference	Mean Difference
				Fixed, 95% CI	Fixed, 95% CI
Dawson 2000		227/614 (37.1)	232/534 (43.4)		66.1[41.9,90.3]

Comparison 2. Absolute claudication distance (ACD)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACD cilostazol 100 mg twice daily versus placebo	6	2247	Mean Difference (IV, Random, 95% CI)	43.11 [28.27, 57.95]
2 ACD cilostazol 50 mg twice daily versus placebo	2	602	Mean Difference (IV, Fixed, 95% CI)	32.00 [24.17, 40.83]
3 ACD cilostazol 150 mg twice daily versus placebo	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 ACD Cilostazol 100 mg twice daily versus pentoxifylline 400 mg three times daily	2	982	Mean Difference (IV, Random, 95% CI)	13.41 [-4.53, 30.74]

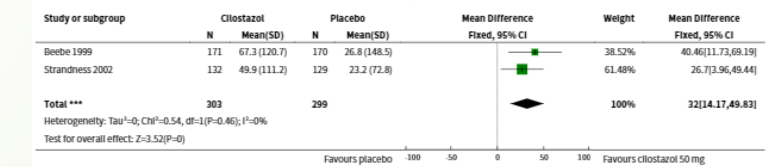


YES

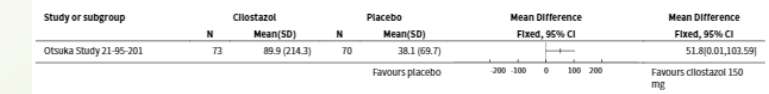
NO

UNCLEAR

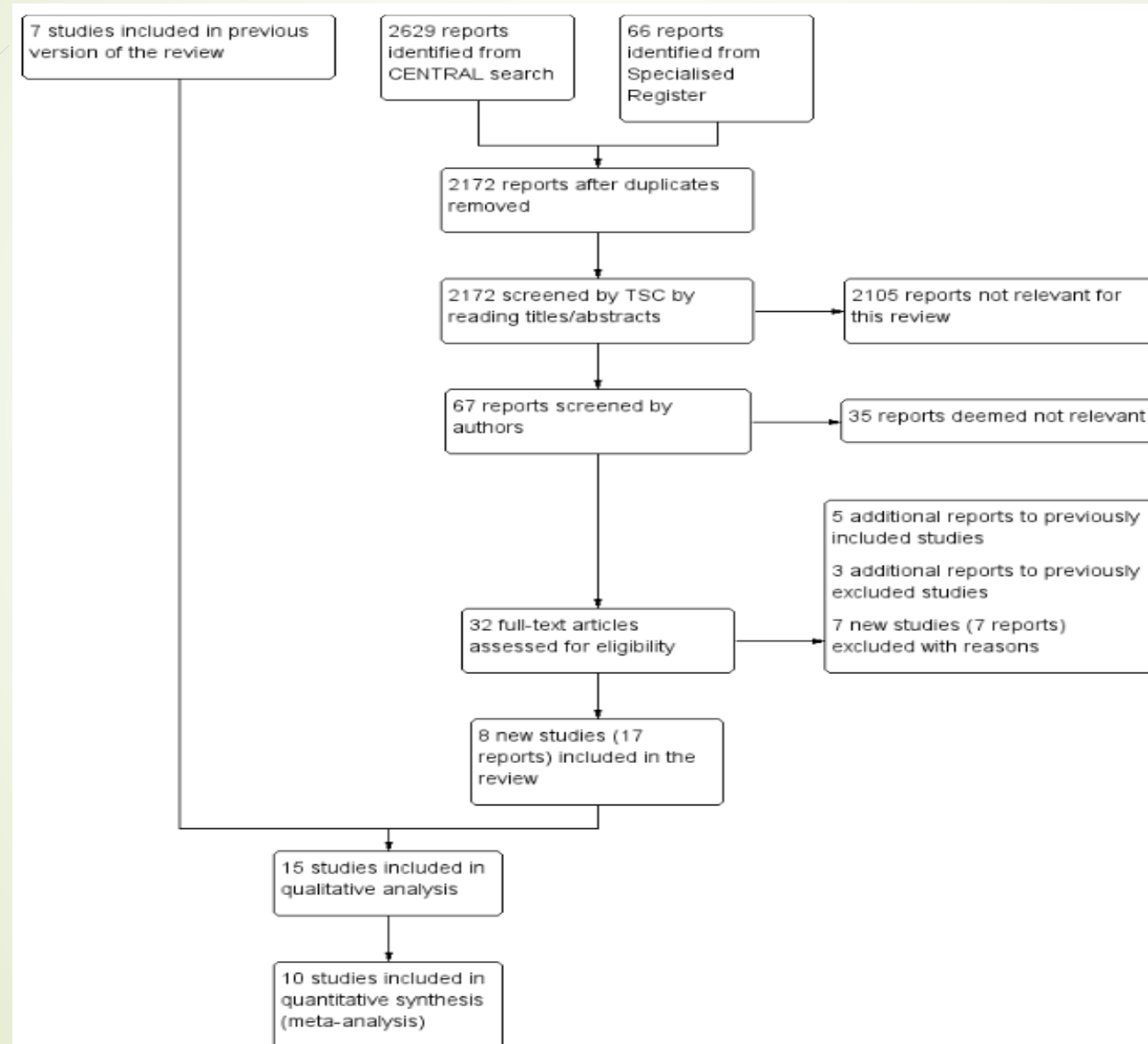
Analysis 2.2. Comparison 2 Absolute claudication distance (ACD), Outcome 2 ACD cilostazol 50 mg twice daily versus placebo.



Analysis 2.3. Comparison 2 Absolute claudication distance (ACD), Outcome 3 ACD cilostazol 150 mg twice daily versus placebo.

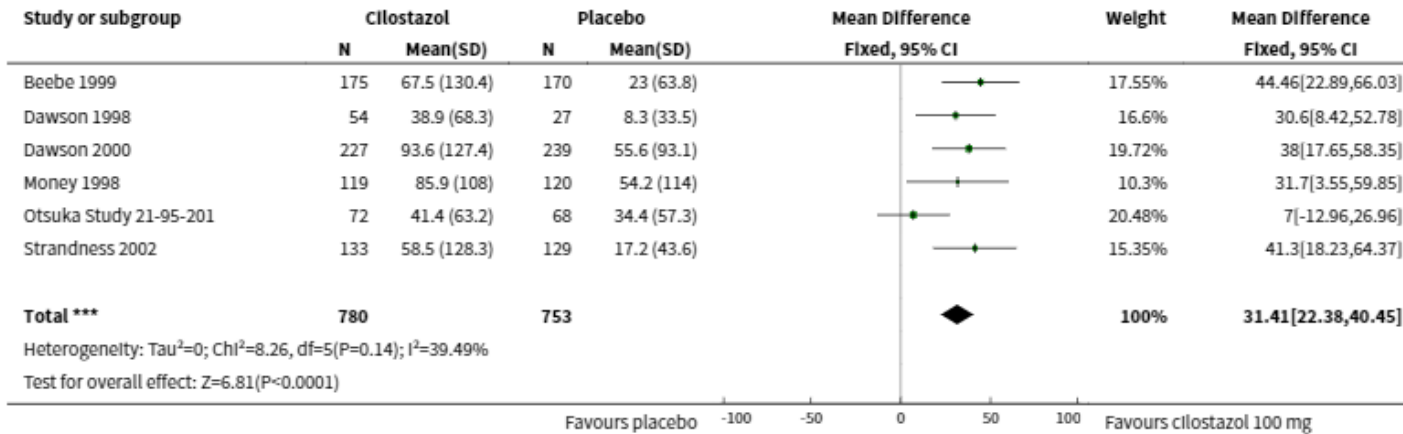


6. What are the overall results of the review?

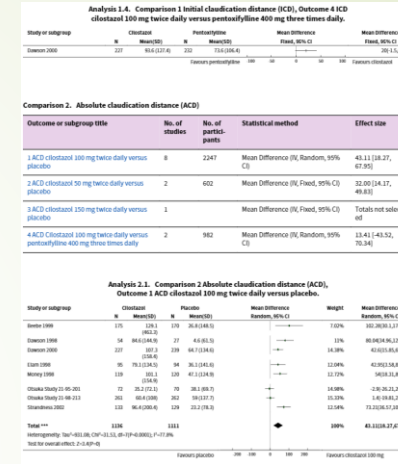
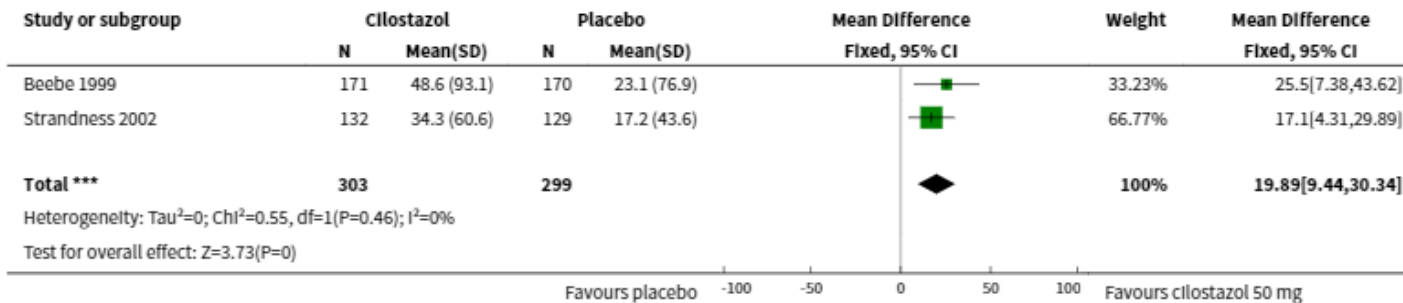


7. How precise are the results?

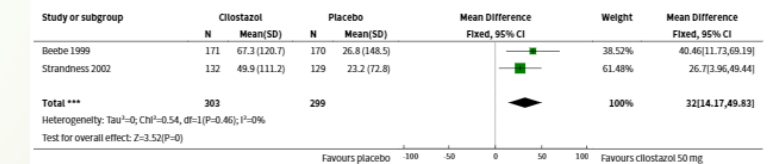
Analysis 1.1. Comparison 1 Initial claudication distance (ICD), Outcome 1 ICD cilostazol 100 mg twice daily versus placebo.



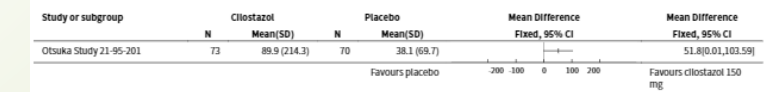
Analysis 1.2. Comparison 1 Initial claudication distance (ICD), Outcome 2 ICD cilostazol 50 mg twice daily versus placebo.



Analysis 2.2. Comparison 2 Absolute claudication distance (ACD), Outcome 2 ACD cilostazol 50 mg twice daily versus placebo.



Analysis 2.3. Comparison 2 Absolute claudication distance (ACD), Outcome 3 ACD cilostazol 150 mg twice daily versus placebo.



Levels of Evidence

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

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 with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	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 with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non-randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning



最終回覆

- ➔ 黃先生您好，經過我們專業團隊的實證查證，目前最新研究文章為2014年跨國之隨機分派試驗，研究結果顯示對於周邊動脈阻塞疾病，cilostazol 50-100mg每日兩次，可改善病患25%的最大行走距離，常見的副作用有腹瀉、心悸和頭暈，請注意有無上述情況發生。



感謝聆聽，請討論指正

