實證醫學討論報告

Presenter：Intern曾稚富
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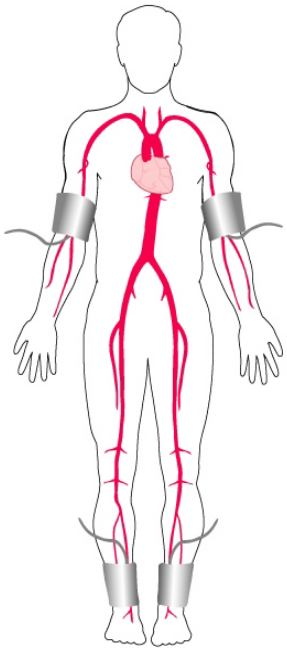
臨床場景(Clinical scenario)

Clinical scenario

- 吳先生現年71歲，最近去做健檢，發現有糖尿病的問題，診所醫師轉介他到醫院做進一步檢查，醫師替他安排眼底鏡和上下肢血壓比(Ankle brachial index, ABI)檢查



Right ABI = ratio of

Higher of the right ankle systolic pressures (posterior tibial or dorsalis pedis) mmHg

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Higher arm systolic pressure (left or right arm) mmHg

Left ABI = ratio of

Higher of the left ankle systolic pressures (posterior tibial or dorsalis pedis) mmHg

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Higher arm systolic pressure (left or right arm) mmHg

測試項目	建議頻率
眼睛：視力	1年
眼底檢查 (註1)	1年
足：脈搏	
腳踝與上臂的動脈收縮壓 (註2)	1年
神經病變：單股纖維10g壓覺	1年
頻率128Hz音叉震動感	1年
跟腱反射	1年
糖尿病人自我管理：體重	經常測體重
血壓	經常自我監測血壓
血糖	經常自我監測血糖
糖化血色素及靜脈血漿糖	3個月
膽固醇/高密度脂蛋白膽固醇/低密度脂蛋白膽固醇/三酸甘油酯 (註3)	1年
白蛋白尿(註4)	1年
肌酸酐/尿素氮/eGFR(註5)	1年
尿液篩檢	1年
糖尿病衛教	3個月
口腔檢查	1年

Clinical scenario

表3：周邊動脈阻塞程度評估：上下肢血壓比 (Ankle brachial index, ABI)

ABI	阻塞程度
> 1.30	無法壓縮的血管 (Noncompressible)
0.91–1.30	正常 (Normal)
0.41–0.90	輕度-中度阻塞 (Mild-to-moderate disease)
0.00–0.40	嚴重阻塞 (Severe disease)

資料來源: Hiatt WR: Medical treatment of peripheral arterial disease and claudication. N Engl J Med 2001; 344: 1608-21.

- R-ABI: 0.71 L-ABI: 0.83

- Interpretation:

  Mild to moderate peripheral arterial disease

Clinical Question

- 對於 Ankle brachial index 檢查小於正常值的病人，臨床上建議，開始使用aspirin來降低心血管疾病併發症。
- 有鑑於aspirin可能會造成的副作用，是否有其他抗血小板藥物可以取代？

EBM的步驟

- Asking
  - 將病人的問題寫成PICO
- Acquire
  - 找資料來回答問題
- Appraisal
  - 嚴格評讀文獻
- Apply
  - 是否可以應用到病人身上

EBM的步驟

- Asking
  - 將病人的問題寫成PICO
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-
  -

寫成PICO

P	DM was diagnosed with ABI < 0.9
I	Aspirin
C	Other antiplatelet drugs
O	Reduced macrovascular complication

EBM的步驟

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  -
- Acquire
  - 找資料來回答問題
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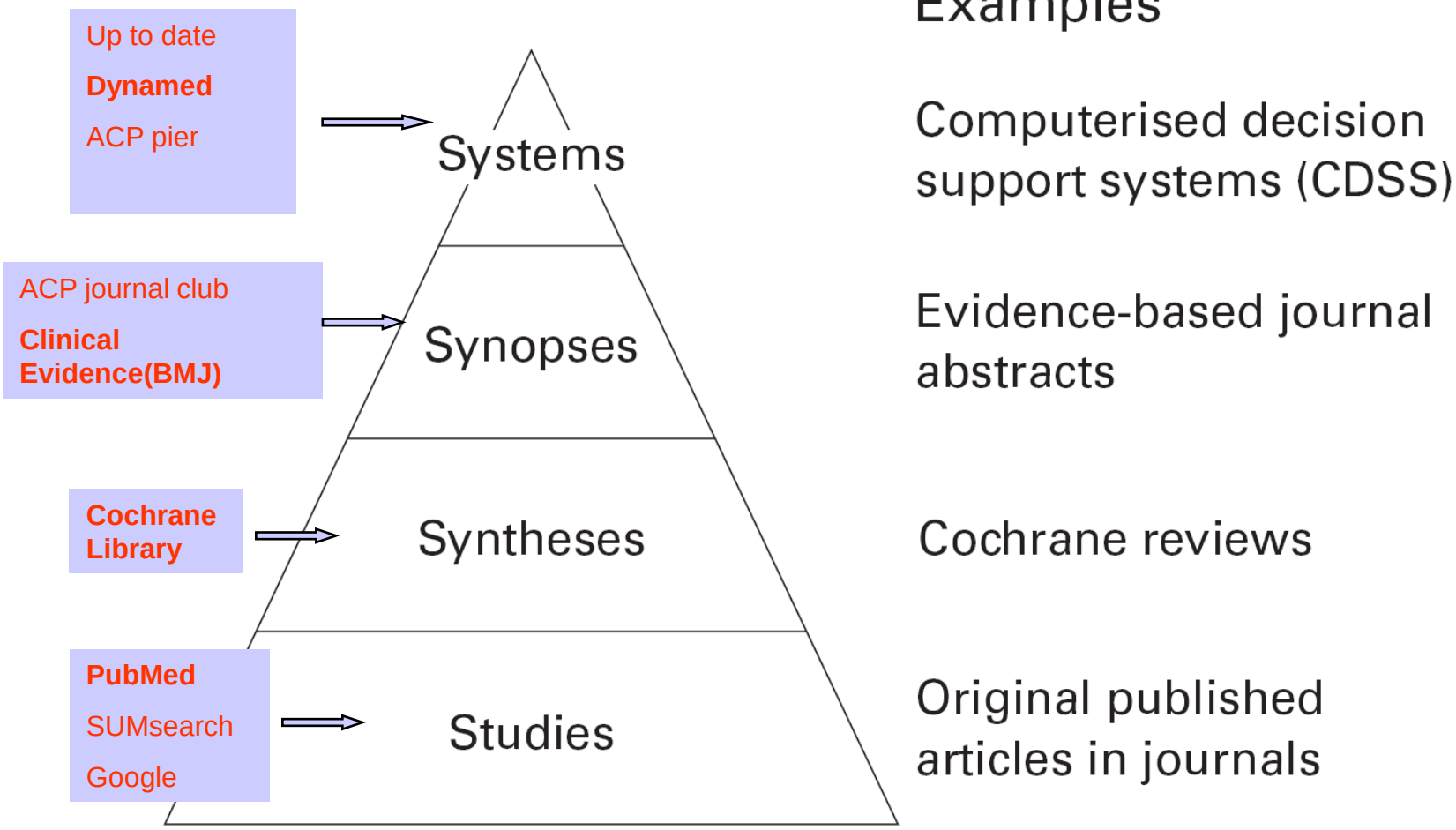


Figure "4S" levels of organisation of evidence from research.

搜尋Systems

- 出處：DynaMed
- Key word: Peripheral artery disease and diabetes mellitus

Results from searching: Summaries

Database	**DynaMed**
Title of article	**Peripheral arterial disease (PAD) of lower extremities**
Contents	◆ All patients with atherosclerotic lower extremity peripheral arterial disease (PAD), including asymptomatic patients 1. Antiplatelet therapy to reduce risk of myocardial infarction, stroke, or vascular death. 2. Suggested drugs are aspirin 75-325 mg/day • aspirin 75-100 mg once daily 3. clopidogrel (Plavix) 75 mg once daily. ◆ For intermittent claudication(not response to exercise therapy) 1. Cilostazol (Pletal) 100 mg orally twice daily 2. Trial of cilostazol recommended by ACC/AHA as initial therapy for PAD in patients without heart failure

搜尋Synopses

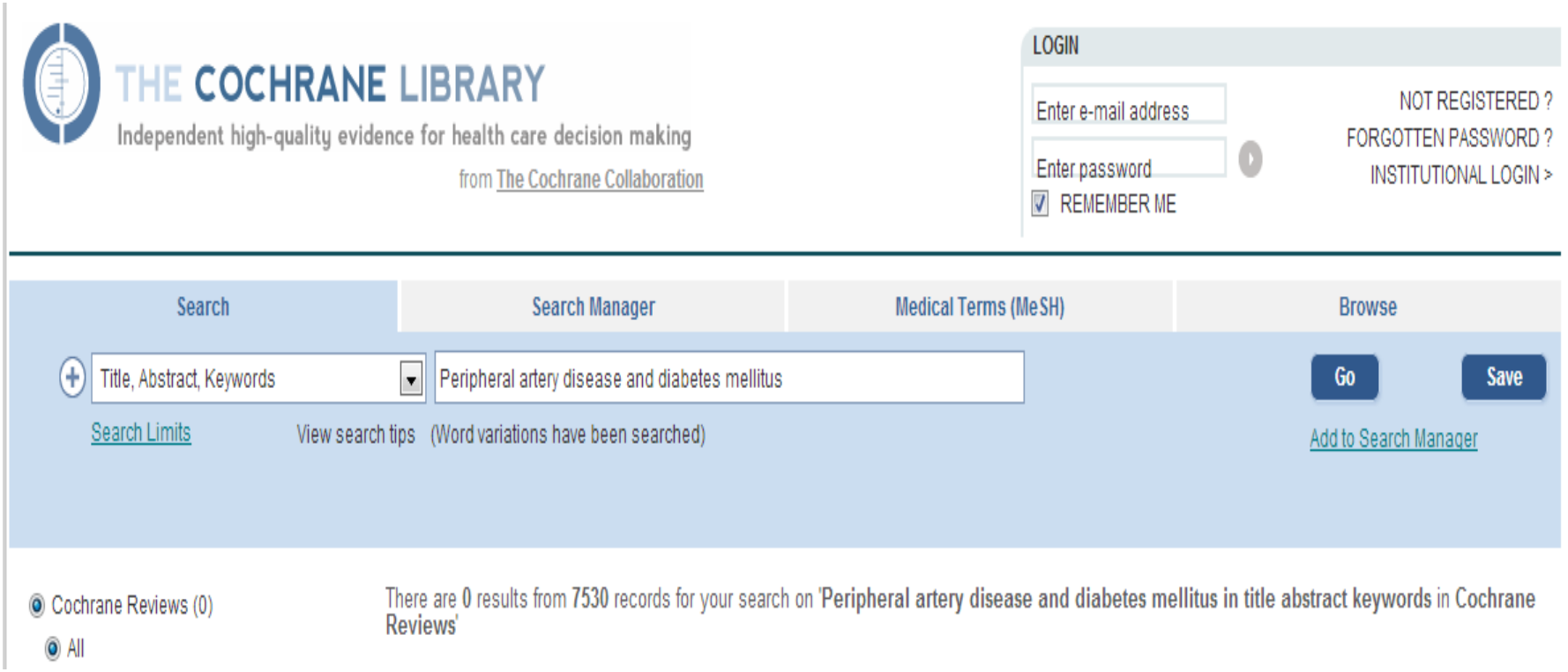
ClinicalEvidence

- 出處：ClinicalEvidence (BMJ)
- Key word: Peripheral artery disease and diabetes mellitus

Results from searching: Summaries

Database	**ClinicalEvidence (BMJ)**
Title of article	**Peripheral arterial disease**
Contents	◆ Antiplatelet agents reduce major cardiovascular events, arterial occlusion, and revascularisation compared with placebo, with the overall balance of benefits and harms supporting treatment of people with peripheral arterial disease. ◆ Cilostazol may improve walking distance compared with placebo. ◆ Cilostazol may reduce the incidence of cerebrovascular events compared with placebo but may be no more effective at reducing cardiac events. ◆ Cilostazol may be more effective than pentoxifylline at improving claudication distance.

搜尋 syntheses, Cochrane Library



搜尋Studies, Pubmed

- Key word: Peripheral artery disease and diabetes mellitus

Results from searching: Summaries

Database	**Pubmed**
Title of article	**Peripheral arterial disease and diabetes-Review article**
Ref	*Sec. Biol. Med. Sci*., MASA, XXXIII, 1, p.65–78 (2012)
Contents	◆ There are no confident results for a positive effect of anticlaudication drugs, Cilostazol and pentoxyphillin derivates in patients with stable claudication, and in revascularized patients with non-stable claudication and in critical limb ischemia in diabetic and non diabetic populations. ◆ There is an evidence for the use of *Clopidrogel and Aspirin in diabetic patients with PAD to improve* functional status and to lower cardiovascular risk. ➢ From the CAPRIE (Clopidogrel versus aspirin in patients at risk of ischemic events) ➢From the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events)

Results from searching: Summaries

Database	**Pubmed**
Title of article	**Diagnosis and management of peripheral arterial disease**
Ref	*BMJ* 2012;345:e5208
Contents	◆ Two drugs are currently available in the UK for the treatment of intermittent claudication: cilostazol and naftidrofuryl oxalate. ◆ A meta-analysis of 26 studies assessing the efficacy of these drugs found that both offer modest improvement in walking distance with minimal adverse effects. However, there is little follow-up data beyond six months and cost effectiveness remains questionable ◆The new NICE guidelines recommend only naftidrofuryl for use in patients with PAD and suggest that it be reserved for those who have failed to improve with structured exercise programmes and do not wish to be referred for angioplasty or surgery.

Results from searching: Summaries

Database	**Pubmed**
Title of article	**Diagnosis and management of peripheral arterial disease**
Ref	*BMJ* 2012;345:e5208
Contents	◆Although antiplatelet agents and vasodilators (such as nifedipine) may be useful for reducing overall cardiovascular risk, there is little evidence that these drugs offer any benefit in treating the symptoms of claudication

Results from searching: Summaries

Database	**Pubmed**
Title of article	**Long-term effects of cilostazol on the prevention of macrovascular disease in patients with type 2 diabetes mellitus**
Ref	*Diabetes Research and Clinical Practice* Volume 91, Issue 1, January 2011, e11–e14

Long-term effects of cilostazol on the prevention of macrovascular disease in patients with type 2 diabetes mellitus

- Method
  - The medical records of all patients with T2DM were retrospectively reviewed from January 1995 to February 2007.

Long-term effects of cilostazol on the prevention of macrovascular disease in patients with type 2 diabetes mellitus

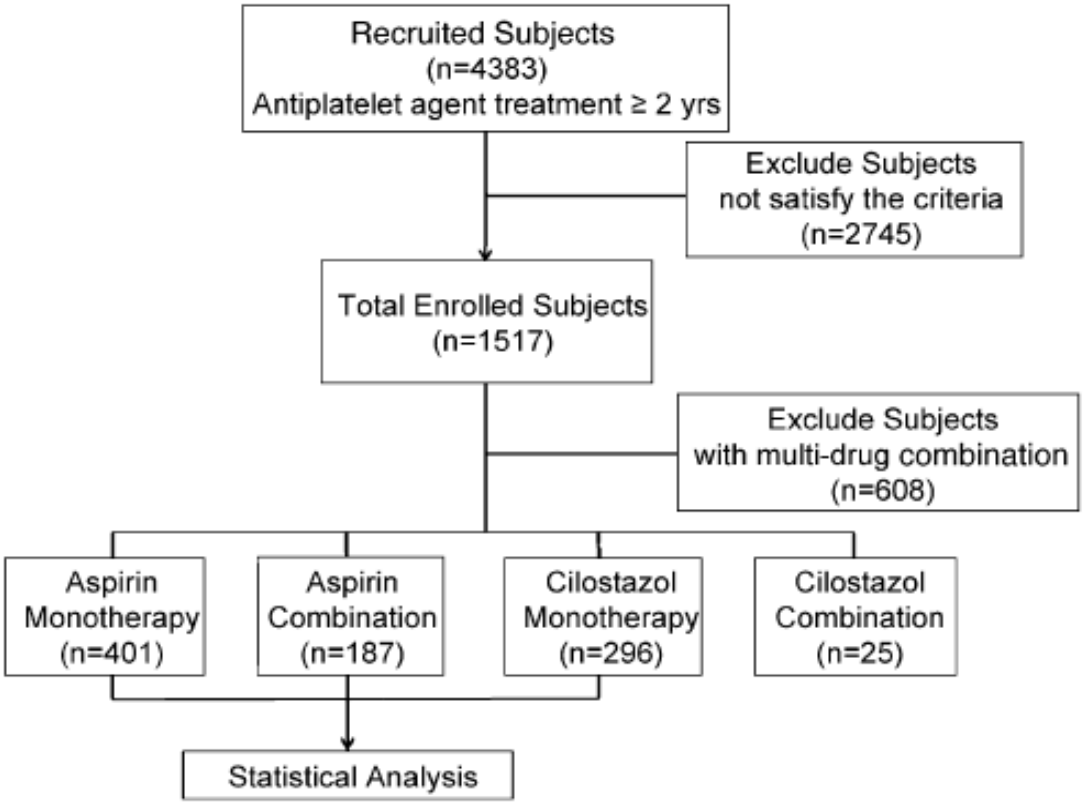


Fig. 1 – Patient disposition of the current study.

Long-term effects of cilostazol on the prevention of macrovascular disease in patients with type 2 diabetes mellitus

Table 1 – Baseline characteristics of study subjects.

Variables	Aspirin monotherapy ($n = 401$)	Aspirin combination ($n = 187$)	Cilostazol monotherapy ($n = 296$)	p
Gender (M/F)	138/263	75/112	131/165	0.029
Age (years)	55.7 ± 10.0	57.7 ± 8.4	58.2 ± 10.4	0.003
Weight (kg)	63.8 ± 11.1	62.7 ± 9.9	63.3 ± 8.9	0.046
Height (cm)	162.7 ± 8.3	161.5 ± 7.4	160.9 ± 9.0	0.558
Medication				
OHA mono	88	47	64	<0.001
OHA combi	90	26	70	
Insulin mono	30	41	66	
Insulin + OHA	29	12	22	
No medication	164	61	74	
HbA1c (%)	7.2 ± 1.6	7.7 ± 1.9	7.5 ± 1.6	0.048
PP2 (mg/dL)	171.7 ± 77.5	177.5 ± 79.1	192.7 ± 78.7	0.032
SBP (mmHg)	136.6 ± 19.3	134.5 ± 18.9	133.5 ± 15.2	0.150
DBP (mmHg)	86.6 ± 11.1	82.0 ± 11.0	84.9 ± 11.2	<0.001
T-chol (mg/dL)	199.8 ± 41.9	198.4 ± 39.1	198.5 ± 39.9	0.918
TG (mg/dL)	187.5 ± 127.5	182.5 ± 153.0	161.1 ± 100.0	0.077
BUN (mg/dL)	15.3 ± 5.2	16.3 ± 5.0	15.4 ± 5.7	0.223
Creatinine (mg/dL)	0.8 ± 0.2	0.9 ± 0.3	1.0 ± 1.2	0.109
AST (U/L)	26.7 ± 28.2	28.4 ± 18.0	24.8 ± 18.0	0.418
ALT (U/L)	31.9 ± 44.3	31.7 ± 31.6	24.8 ± 18.0	0.149

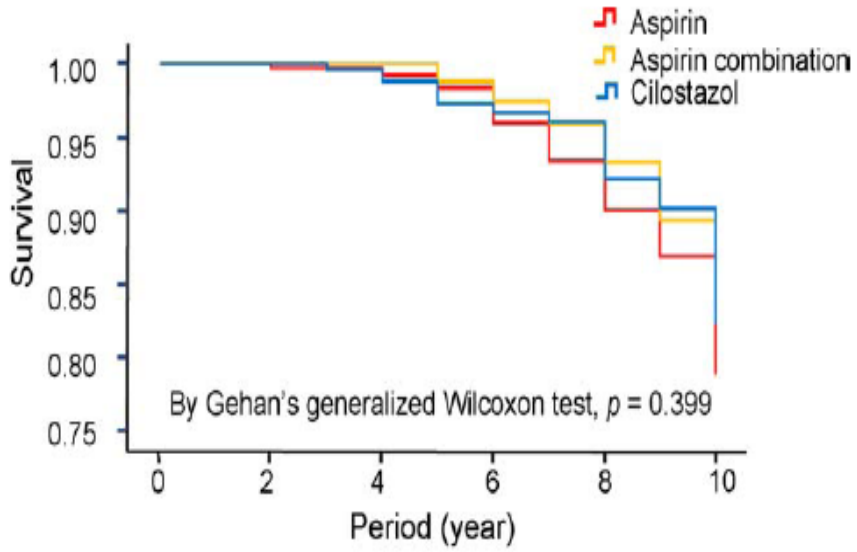
Mean ± S.D.; ANOVA, Chi-square; F/U indicates follow up; OHA, oral hypoglycemic agents; mono, monotherapy; combi, combination therapy; PP2, post-prandial 2 h glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; T-chol, total cholesterol; TG, triglyceride.

Long-term effects of cilostazol on the prevention of macrovascular disease in patients with type 2 diabetes mellitus

Table 2 - Total macrovascular disease events of the study subjects.

	Aspirin monotherapy ($n = 401$)	Aspirin combination ($n = 187$)	Cilostazol monotherapy ($n = 296$)	p
Average follow-up period (years)	6.6 ± 2.3	7.5 ± 6.1	6.1 ± 2.9	<0.001
Total affected subjects (n, %)	44 (11.0)	24 (12.8)	31 (10.5)	0.711
Cardiovascular disease (n, %)	21 (5.2)	10 (5.3)	12 (4.1)	0.743
Cerebrovascular disease (n, %)	24 (6.0)	17 (9.1)	20 (6.8)	0.382
Peripheral arterial disease (n, %)	2 (0.5)	1 (0.5)	2 (0.7)	0.952

Long-term effects of cilostazol on the prevention of macrovascular disease in patients with type 2 diabetes mellitus



	Initial	2 yrs	4 yrs	6 yrs	8 yrs	10 yrs
Aspirin alone	401	390	376	247	141	59
Aspirin combination	187	181	177	140	103	78
Cilostazol alone	296	288	224	155	109	57

Fig. 2 – Survival analyses of the study subjects. By Gehan's generalized Wilcoxon test, there were no significant differences of macrovascular disease free survival between each study subgroup.

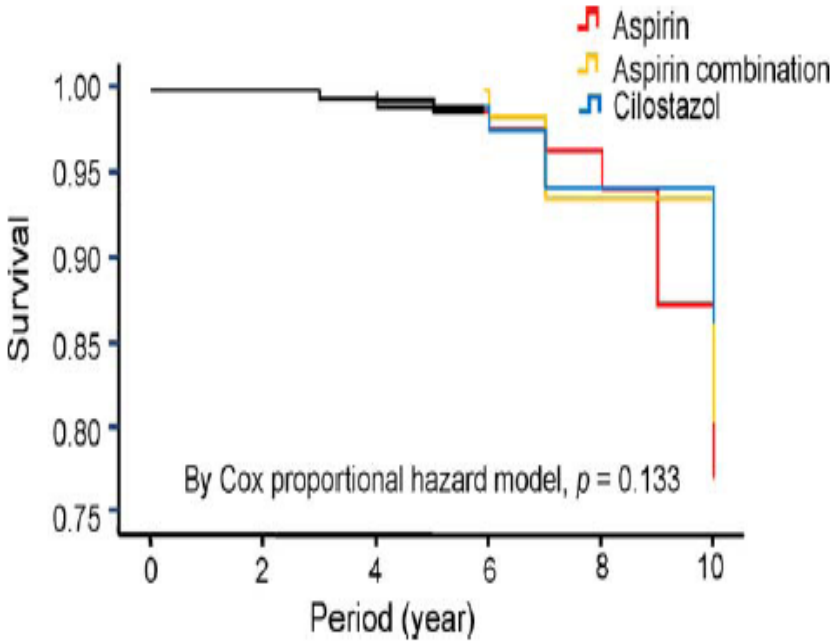


Fig. 3 – By Cox proportional hazard model, there were also no significant differences of macrovascular disease free survival between each study subgroup.

Long-term effects of cilostazol on the prevention of macrovascular disease in patients with type 2 diabetes mellitus

- The results of this study showed that the development of macrovascular disease in the cilostazol monotherapy subgroup was not significantly different from aspirin monotherapy and the aspirin combination groups

EBM的步驟

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- Appraisal
  - 嚴格評讀文獻
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證據等級

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 *n*-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, *n*-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 *n*-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

使用work sheet嚴格評讀

Was the assignment of patients to treatment randomised
是隨機分配嗎？

☐ 是	■ 否	☐ 不清楚
Ans: Random selection was not used for the determination of the treatment groups.		

Were the groups similar at the start of the trial

試驗開始時三組條件是否相似？

☐ 是	■ 否	☐ 不清楚

Ans:

1. There were significant differences in many different variables.
    a. For the aspirin monotherapy group, the patients were younger and the ratio of women was higher, and the DM related variables such as the HbA1c and post-prandial glucose were better than the other subgroups.

Long-term effects of cilostazol on the prevention of macrovascular disease in patients with type 2 diabetes mellitus

Table 1 – Baseline characteristics of study subjects.

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Mean ± S.D.; ANOVA, Chi-square; F/U indicates follow up; OHA, oral hypoglycemic agents; mono, monotherapy; combi, combination therapy; PP2, post-prandial 2 h glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; T-chol, total cholesterol; TG, triglyceride.

Aside from the allocated treatment, were groups treated equally
兩組其他治療條件一樣？

☐ 是	■ 否	■ 不清楚
Ans: Not mention about		

Were all patients who entered the trial accounted for and were they analysed in the groups to which they were randomised

所有進入試驗者皆列入統計，並依所分配的組別計算？

☐ 是	■ 否	☐ 不清楚
Ans: Because the number of subjects was significantly smaller than the other groups, the cilostazol combination subgroup was excluded and a total 884 subjects were included in the final analysis		

Were measures objective or were the patients and clinicians were blinded

結果的測量客觀，受試者及醫師都不知道所接受的治療爲何？

☐ 是	■ 否	■ 不清楚
Ans: Not mention about		

測量結果的時間點是否合乎邏輯?追蹤是否夠久?

■ 是	□ 否	□ 不清楚

Ans:

	Aspirin monotherapy ($n = 401$)	Aspirin combination ($n = 187$)	Cilostazol monotherapy ($n = 296$)	p
Average follow-up period (years)	6.6 ± 2.3	7.5 ± 6.1	6.1 ± 2.9	<0.001

EBM的步驟

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- Apply
  - 是否可以應用到病人身上

結合實證醫學的結果給予病人建議

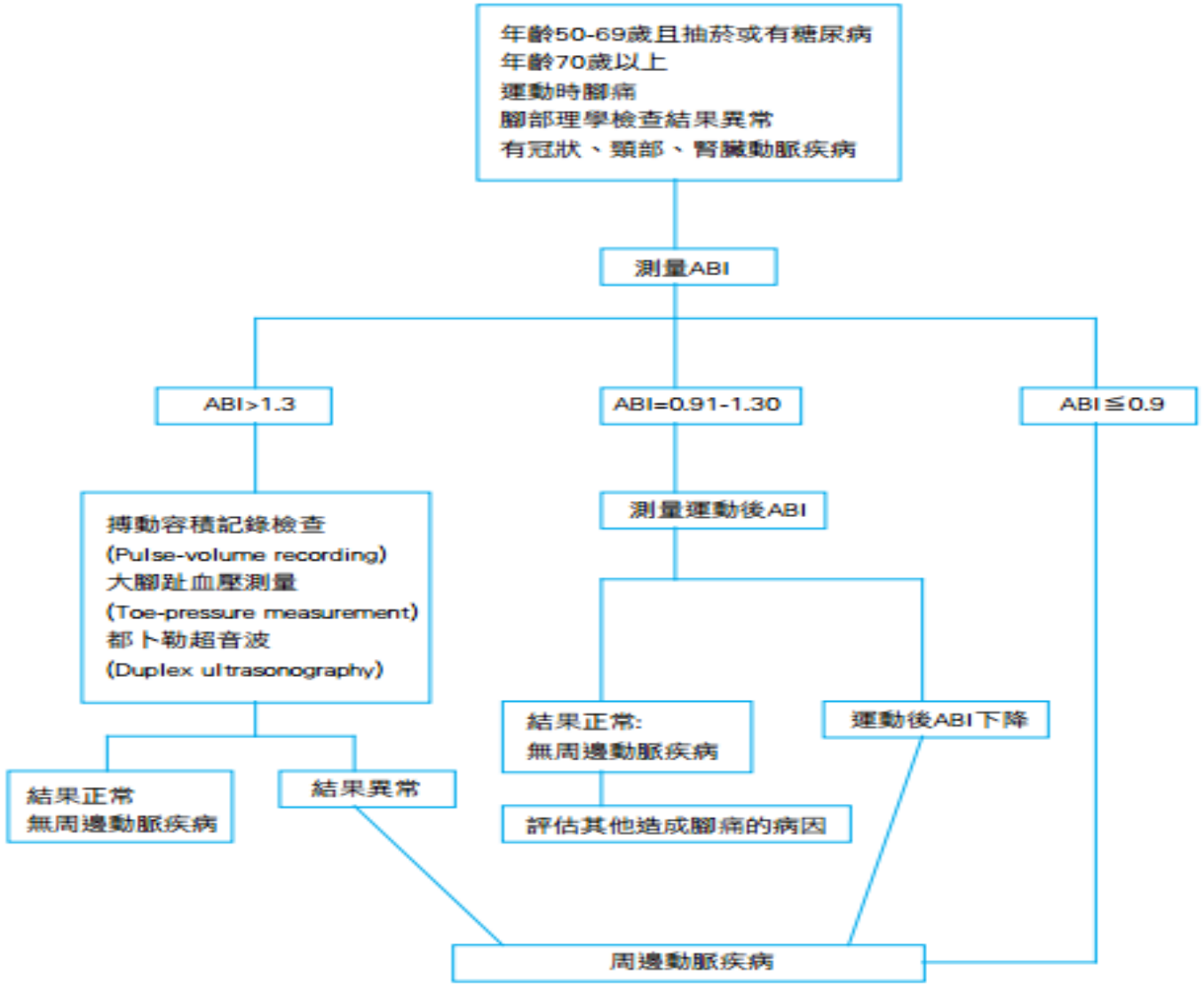
- Lifestyle modifications(smoking, diet control and weight loss) and Risk factors modification(glycemic control, HTN and dyslipidemia) are the most imporant
- Antiplatelet agents are of benefit in patients with PAD, and can reduce the risk of cardiovascular diseases.
- If intermittent claudication was noted, trial of cilostazol recommended by ACC/AHA as initial therapy for PAD in patients without heart failure

總結與討論

- An ABI < 0.9 is not only diagnostic of PAD even in the asymptomatic patient, but is also an independent marker of increased morbidity and mortality from cardiovascular diseases.
- Antiplatelet therapy can retard the onset and progression of PAD and reduce cardiovascular events in diabetic patients.
- Early, aggressive management of the risk factors and medical treatment might improve outcome in patients with PAD.

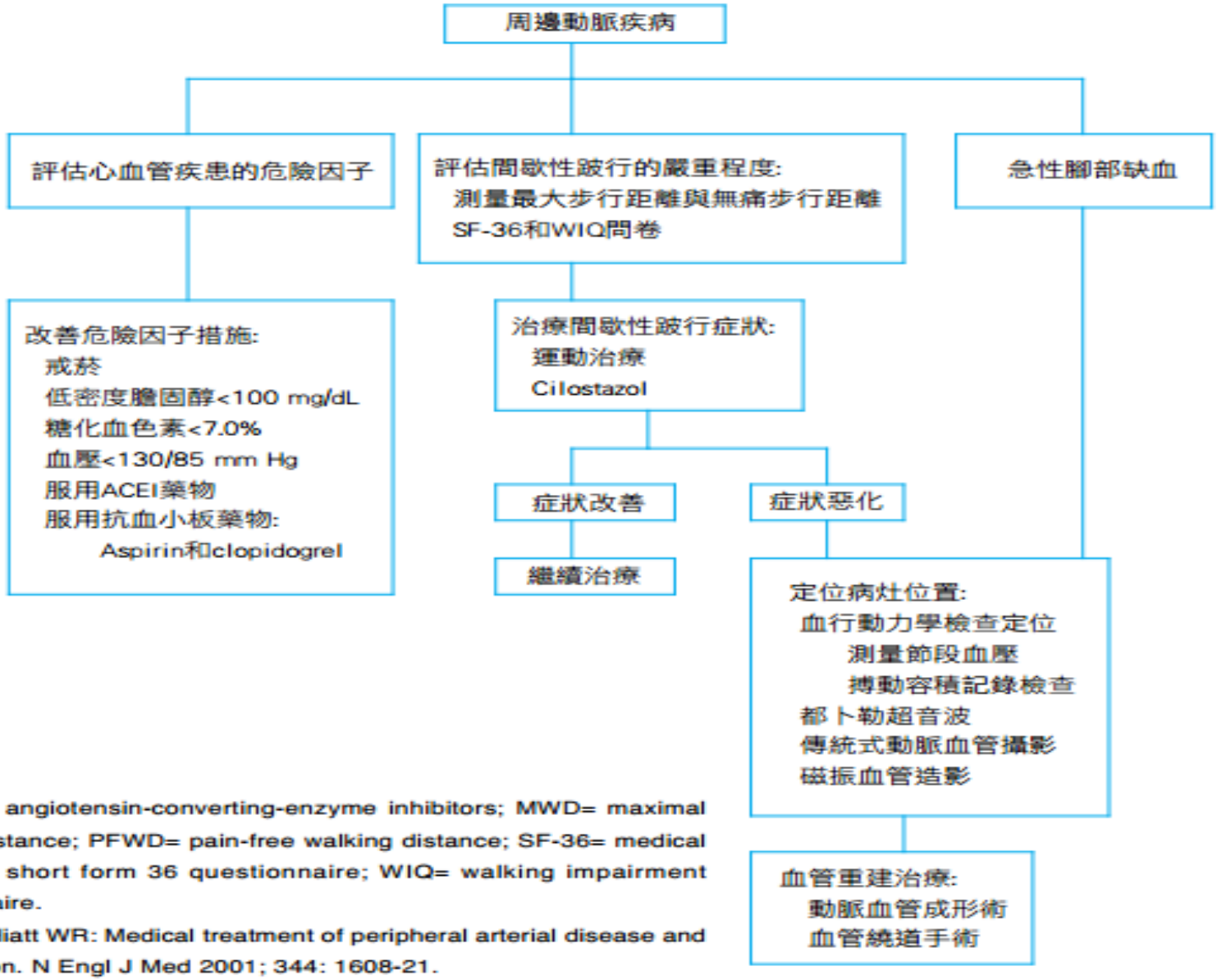
THANKS FOR YOUR LISTENING !

圖1：周邊動脈阻塞疾病的診斷流程



(資料來源:Hiatt WR: Medical treatment of peripheral arterial disease and claudication. N Engl J Med 2001; 344: 1608-21.)

圖2：周邊動脈阻塞疾病的治療模式



註: ACEI= angiotensin-converting-enzyme inhibitors; MWD= maximal walking distance; PFWD= pain-free walking distance; SF-36= medical outcomes short form 36 questionnaire; WIQ= walking impairment questionnaire.

資料來源:Hiatt WR: Medical treatment of peripheral arterial disease and claudication. N Engl J Med 2001; 344: 1608-21.