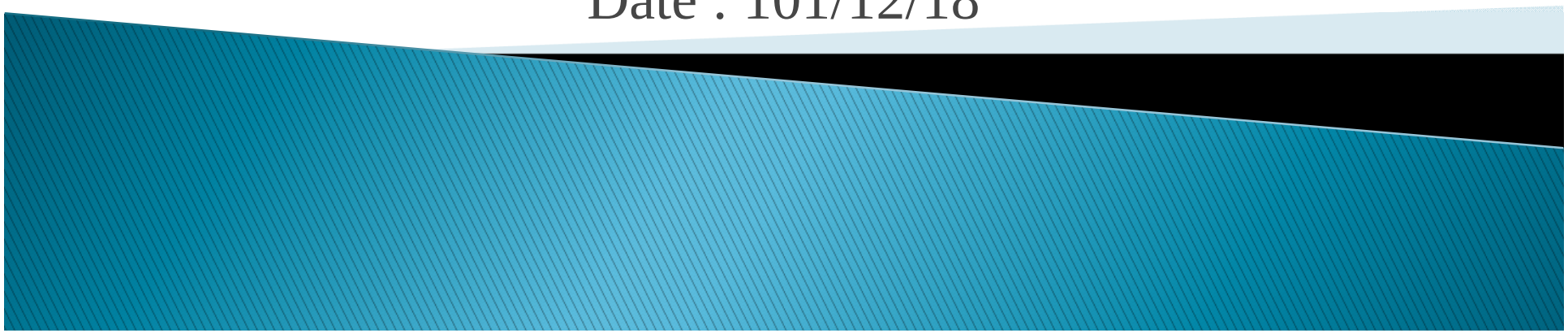
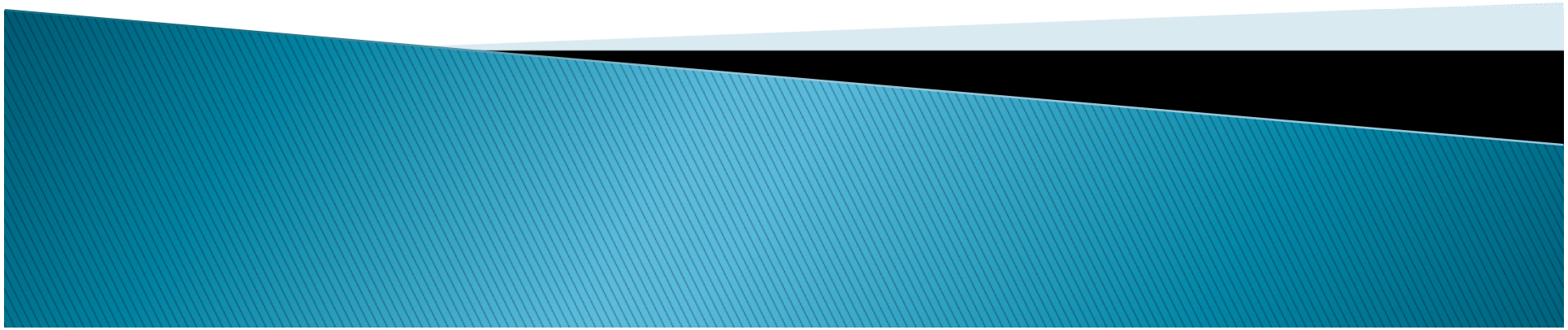
實證醫學 病例討論報告
Evidance-Based Medicine

Presenter: PGY 余珮華
科別：一般內科
Supervisor: 王程遠醫師
Date : 101/12/18



Clinical scenario



Patient's profiles

- Name: 林◯敏
- Age: 75 y/o
- Sex: female
- Chart number: 20757697
- Date of admission: 101/11/27

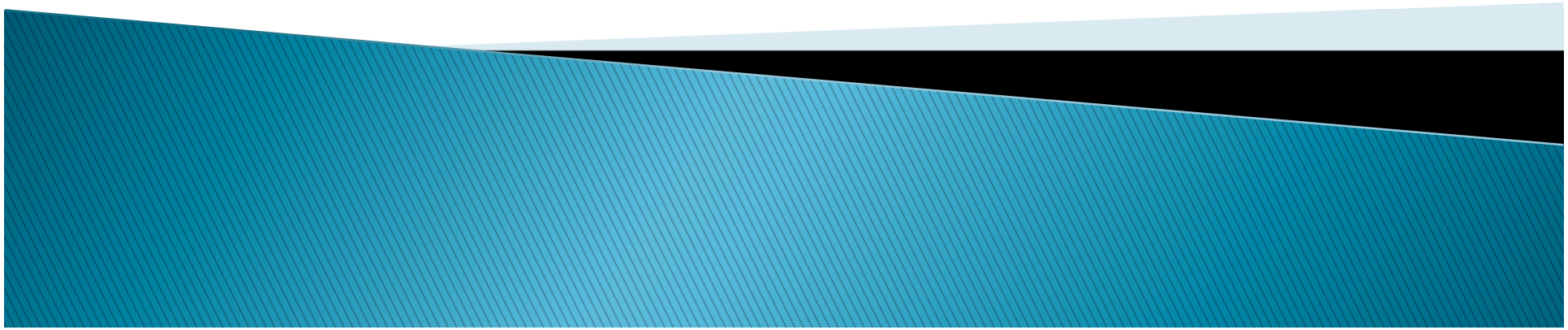
Brief history of case

- A 75-year-old female has the history of
  - Hypertension without medicine control
  - Type 2 diabetes mellitus without medicine control

  who was admitted due to bilateral lower lung pneumonia and urinary tract infection.

- She has just suffered from cerebrovascular accident in this August, with sequela of right hemiplegia.
- To avoid of secondary stroke, **anti-coagulant agent** was necessary.

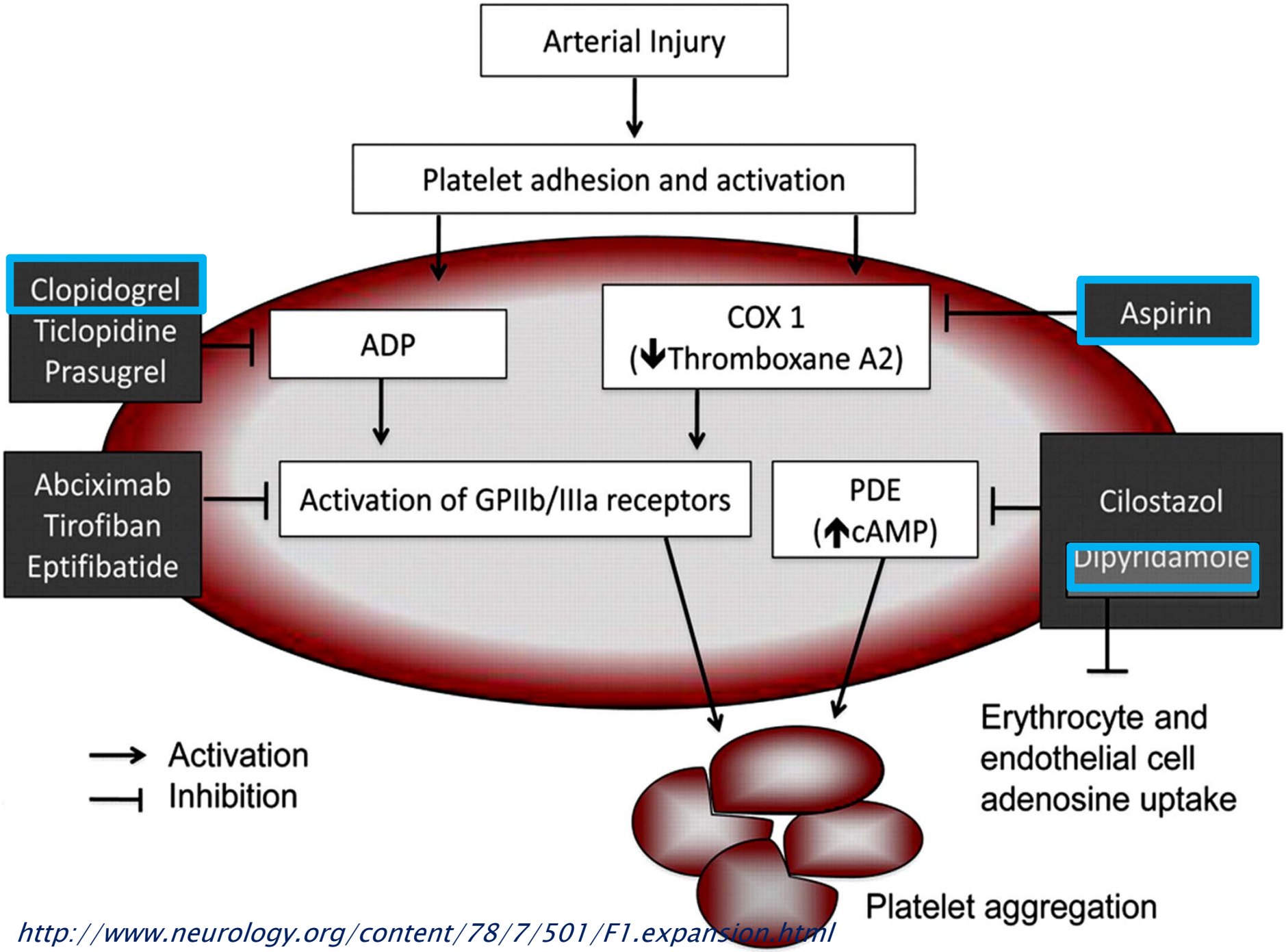
Background questions



What kind of anti-coagulant agents is used to prevent secondary stroke?

- ***Aspirin***
  - Inhibiting the enzyme cyclooxygenase
- ***Clopidogrel***
  - Inhibiting ADP-dependent platelet aggregation
- ***Dipyridamole***
  - Adenosine reuptake inhibitor

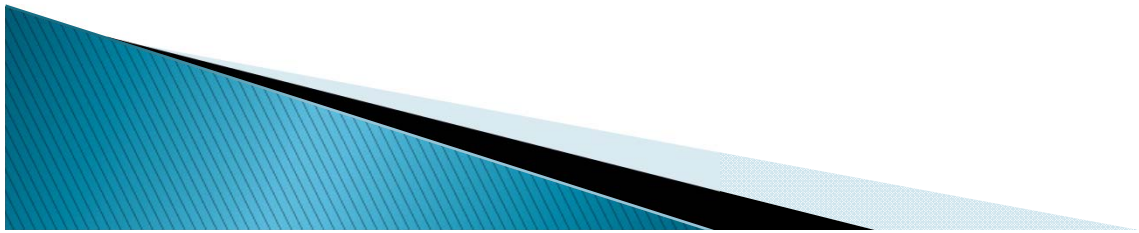
- **Other agent:**
  - Ticlopidine
  - Cilostazol
  - Triflusal



http://www.neurology.org/content/78/7/501/F1.expansion.html

What is the common side effect of anti-coagulant agent?

- ***Aspirin***
  - Gastrointestinal upset, gastrointestinal bleeding
- ***Clopidogral***
  - Rash and diarrhea
  - Lower frequent of gastric upset or gastrointestinal bleeding
- ***Dipyridamole***
  - Headache



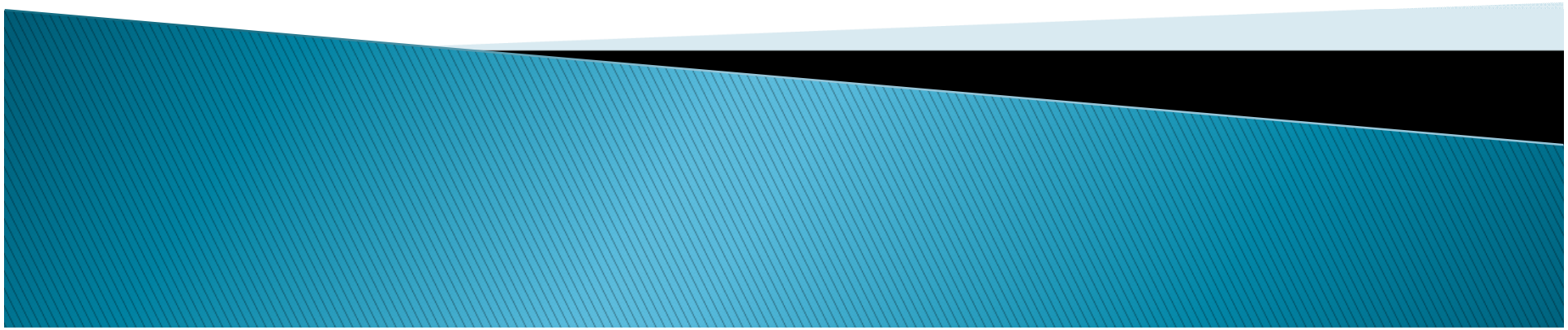
UpToDate.

What is the common anti-coagulant regimen to prevent secondary stroke?

- **Aspirin monotherapy**
- **Clopidogral monotherapy**
- **Combined therapy**
  - Aspirin + dipyridamole

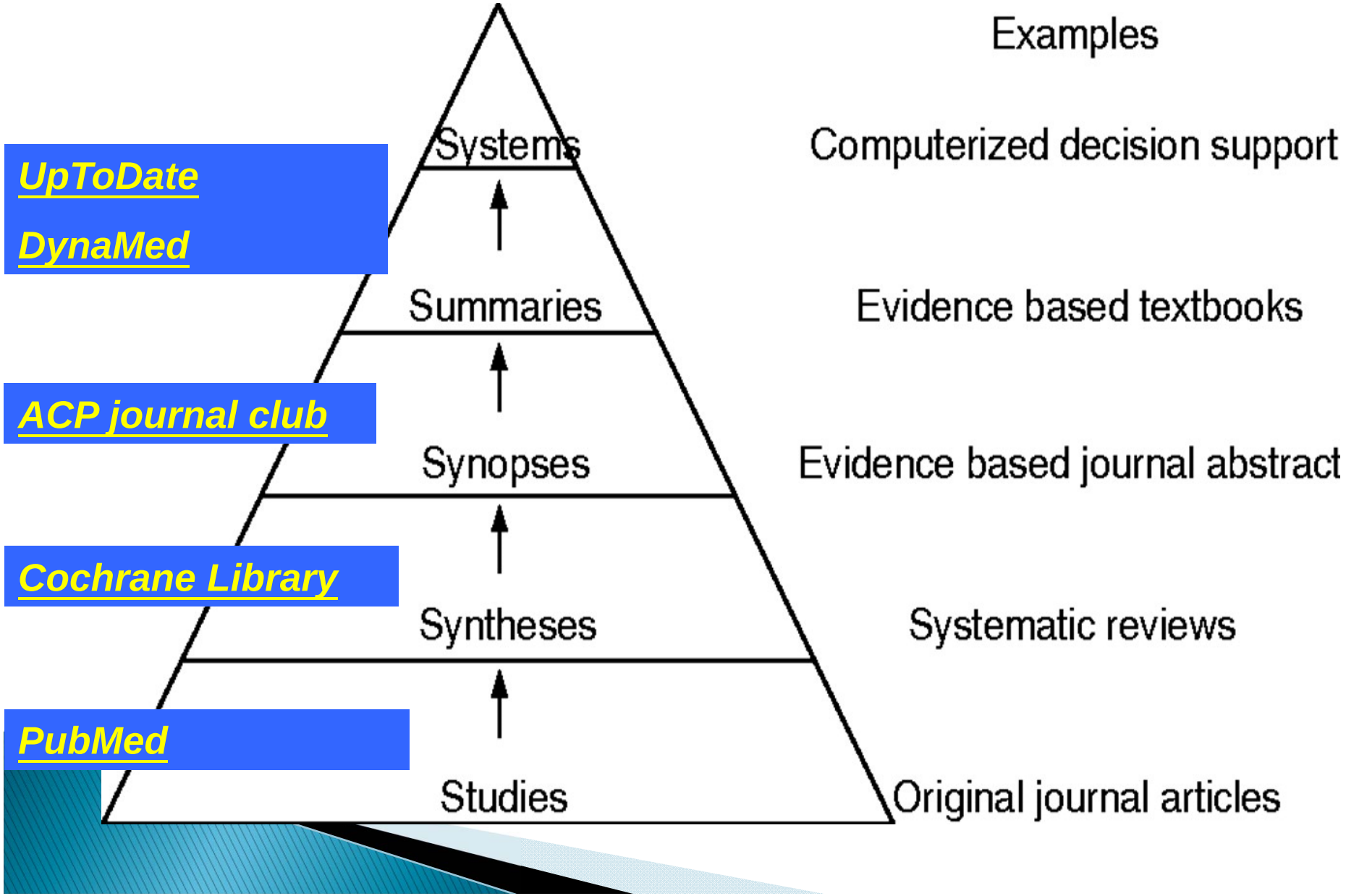
UpToDate.

Foreground question



PICO

Patient	Patient suffering from cerebrovascular accident
Intervention	Aspirin + dipyridamole
Comparison	Aspirin
Outcome	Rate of recurrent stroke


Examples
Systems
Computerized decision support
UpToDate
DynaMed
Summaries
Evidence based textbooks
ACP journal club
Synopses
Evidence based journal abstract
Cochrane Library
Syntheses
Systematic reviews
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Original journal articles


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Antiplatelet therapy for secondary preven…
anticoagulation secondary stroke
Secondary prevention of stroke: Risk fact…
www.uptodate.com/contents/search?search=anticoagulation+secondary+stroke&sp=0&searchType=PLAIN_TEXT&source=USER_INPUT&searchControl=TOP_PULLDOWN&searchOf
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Antiplatelet therapy for secondary prevention of stroke
Ischemic stroke in children: Secondary prevention
Spontaneous cerebral and cervical artery dissection: Treatment and prognosis
Surgical and endovascular repair of popliteal artery aneurysm
Antithrombotic treatment of acute ischemic stroke and transient ischemic attack
Secondary prevention of cardiovascular disease
Secondary prevention of stroke: Risk factor reduction
Secondary prevention for specific causes of ischemic stroke and transient ischemic attack
Stroke in patients with atrial fibrillation
Cryptogenic stroke
Treatment of atrial septal abnormalities (PFO, ASD, and ASA) for prevention of stroke in adults
Antithrombotic therapy to prevent embolization in nonvalvular atrial fibrillation
Topic Outline
INTRODUCTION
ASPIRIN
Dose of aspirin
- Toxicity and risk of bleeding
CLOPIDOGREL
Side effects of clopidogrel
Aspirin plus clopidogrel
- Stroke subtypes
DIPYRIDAMOLE
Side effects of dipyridamole
- Cardiac effects
Aspirin plus dipyridamole
Aspirin plus extended-release dipyridamole versus clopidogrel
OTHER AGENTS
Ticlopidine
- Side effects of ticlopidine
Cilostazol
開始
anticoagulation s...
Stroke-2008-Ver...
未命名 - 小畫家
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Evidance Based ...
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case 1
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Uptodate

- The beneficial effects of aspirin and dipyridamole for secondary stroke prevention appear to be **additive** such that the combination of aspirin-extended-release dipyridamole is significantly **more effective** than aspirin alone for stroke prevention.

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secondary stroke dipyridamole Search

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2005 - Review: **Dipyridamole** given with or without aspirin **...**

2006 - Aspirin plus **dipyridamole** was more effective than **...**

2003 - Low-intensity warfarin therapy prevented recurrent **...**

2006 - No cardiac testing for intermediate-risk patients on beta **...**

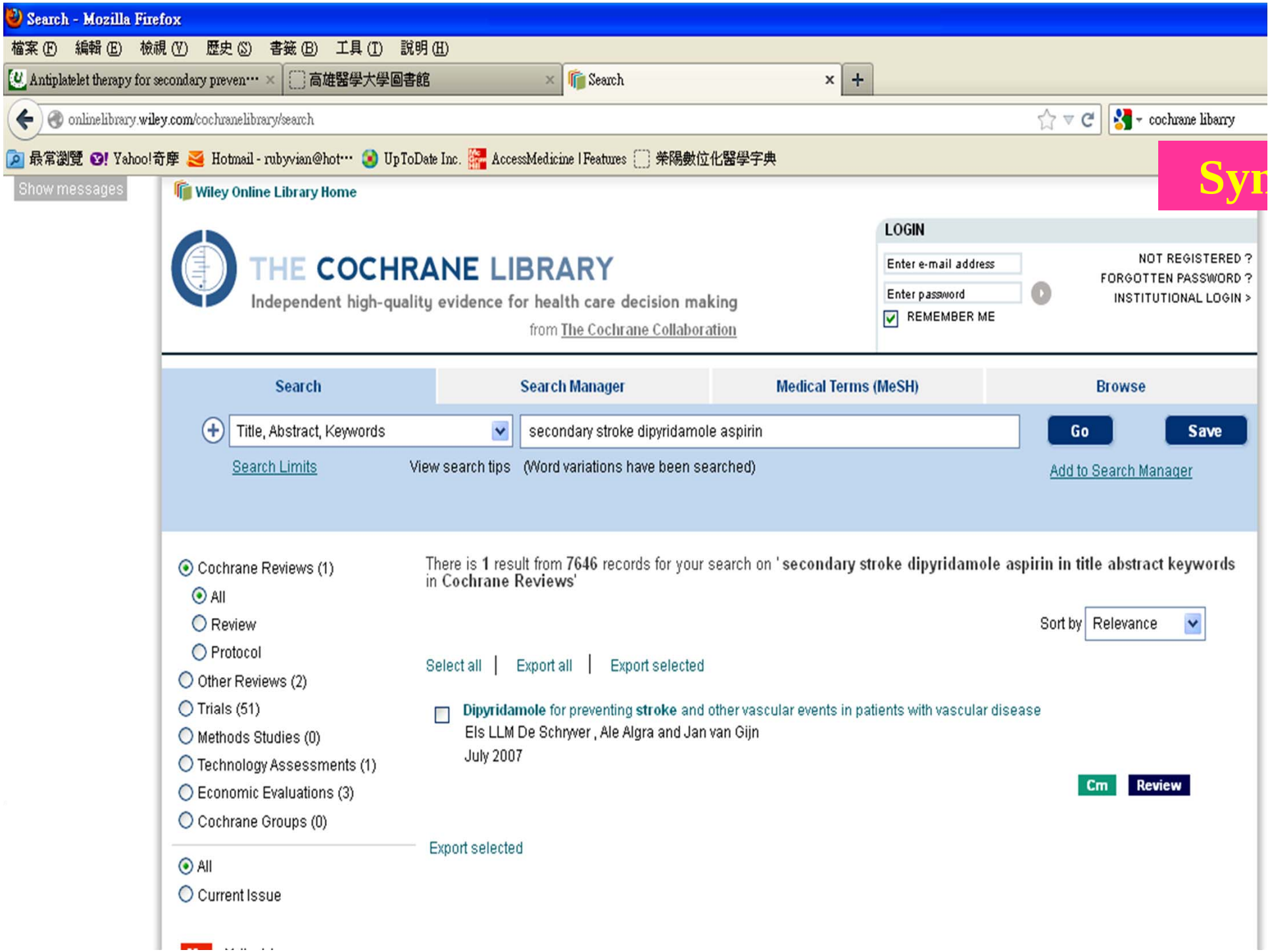
Therapeutics

Aspirin plus dipyridamole was more effective than aspirin alone for preventing vascular events after minor cerebral ischemia

Cardiology ★★★★★★ Neurology ★★★★★★★

Aspirin plus dipyridamole vs aspirin alone to prevent vascular events after minor cerebral ischemia at mean 3.5 years†

Outcomes	Aspirin + dipyridamole	Aspirin alone	RRR (95% CI)	NNT (CI)
Composite endpoint‡	13%	16%	19% (2 to 32)	35 (20 to 347)
Death from all causes	6.8%	7.8%	12% (−16 to 32)	Not significant
Death from all vascular causes	3.2%	4.4%	25% (−10 to 48)	Not significant
Death from all vascular causes or stroke	10%	12%	21% (3 to 36)	39 (23 to 287)
All major ischemic events	10%	13%	18% (−1 to 33)	Not significant
All vascular events	11%	14%	21% (3 to 35)	35 (21 to 257)
First cardiac event	3.2%	4.4%	27% (−8 to 50)	Not significant
Major bleeding event	2.6%	3.9%	33% (−3 to 56)	Not significant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Dipyridamole for preventing stroke and other vascular events in patients with vascular disease
Els LLM De Schryver , Ale Algra and Jan van Gijn
July 2007
Cm
Review
Export selected

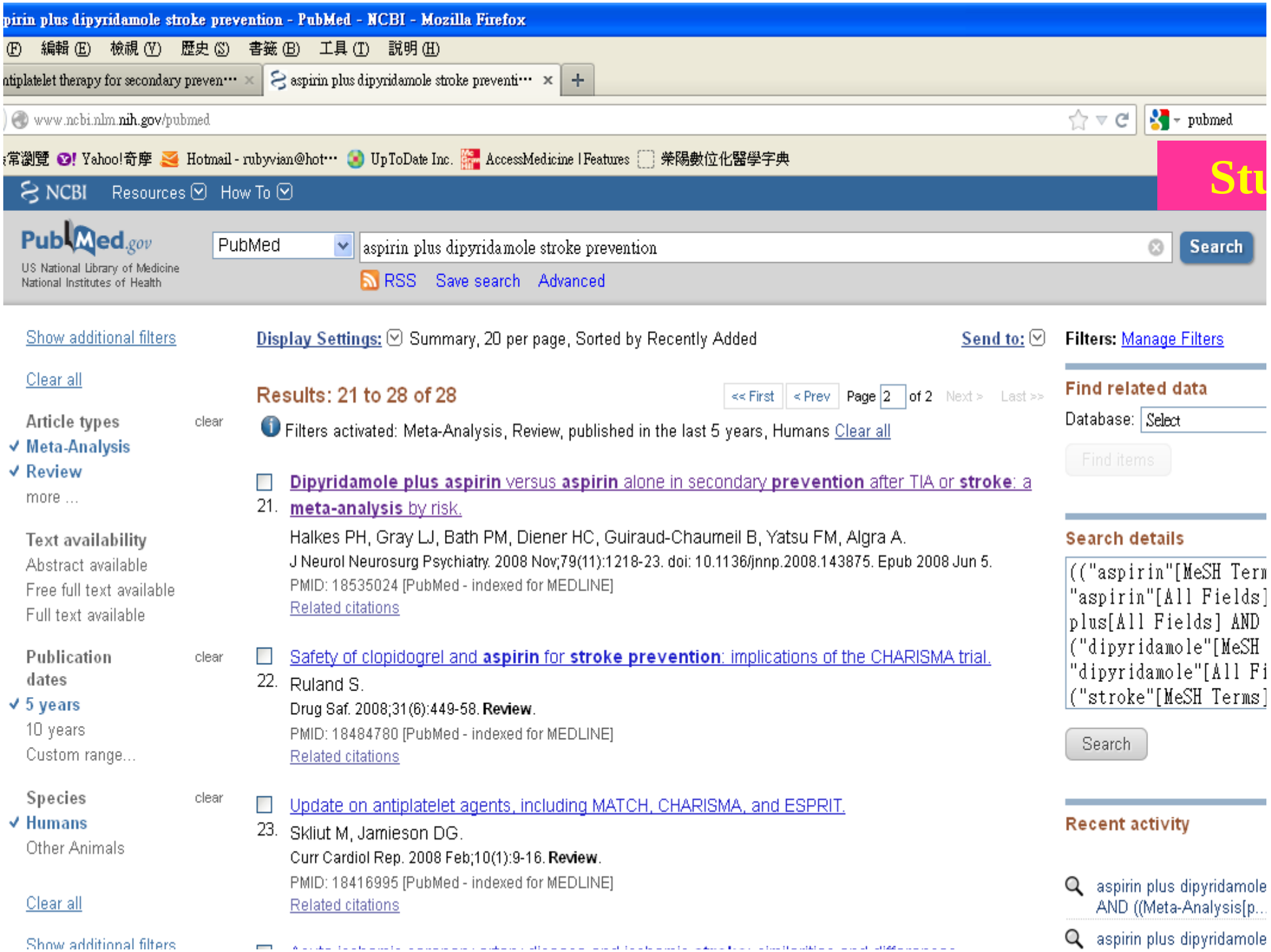
Dipyridamole for preventing stroke and other vascular events in patients with vascular disease

Els LLM De Schryver[2], Ale Algra[1,*], Jan van Gijn[3]

Database Title

The Cochrane Library

- For patients who presented with arterial vascular disease, there was no evidence that dipyridamole, in the presence or absence of another antiplatelet drug reduced the risk of vascular death, though it reduces the risk of further vascular events. This benefit was found only in patients presenting after cerebral ischaemia. There was no evidence that dipyridamole alone was more efficacious than aspirin.


pirin plus dipyridamole stroke prevention - PubMed - NCBI - Mozilla Firefox
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<< First < Prev Page 2 of 2 Next > Last >>
Filters activated: Meta-Analysis, Review, published in the last 5 years, Humans Clear all
21. Dipyridamole plus aspirin versus aspirin alone in secondary prevention after TIA or stroke: a meta-analysis by risk.
Halkes PH, Gray LJ, Bath PM, Diener HC, Guiraud-Chaumeil B, Yatsu FM, Algra A.
J Neurol Neurosurg Psychiatry. 2008 Nov;79(11):1218-23. doi: 10.1136/jnnp.2008.143875. Epub 2008 Jun 5.
PMID: 18535024 [PubMed - indexed for MEDLINE]
Related citations
22. Safety of clopidogrel and aspirin for stroke prevention: implications of the CHARISMA trial.
Ruland S.
Drug Saf. 2008;31(6):449-58. Review.
PMID: 18484780 [PubMed - indexed for MEDLINE]
Related citations
23. Update on antiplatelet agents, including MATCH, CHARISMA, and ESPRIT.
Skliut M, Jamieson DG.
Curr Cardiol Rep. 2008 Feb;10(1):9-16. Review.
PMID: 18416995 [PubMed - indexed for MEDLINE]
Related citations
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Search details
(("aspirin"[MeSH Term
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aspirin plus dipyridamole

Aspirin Plus Dipyridamole Versus Aspirin for Prevention of Vascular Events After Stroke or TIA

A Meta-Analysis

Piero Verro, MD, MS; Phillip B. Gorelick, MD, MPH; Danh Nguyen, PhD

Stroke. 2008;39:1358-1363; originally published online March 6, 2008;
doi: 10.1161/STROKEAHA.107.496281
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

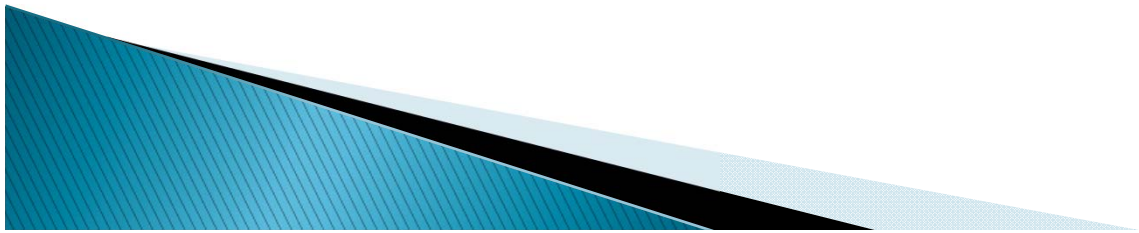
Print ISSN: 0039-2499. Online ISSN: 1524-4628

Objectives

- to systematically review randomized controlled trials comparing **aspirin plus dipyridamole** with **aspirin alone** in patients with minor stroke and TIA to determine the efficacy of these agents in preventing serious vascular events, including recurrent stroke

Criteria

- Randomized control trials
- Patients: with a history of stroke or TIA
- Outcome:
  - Endpoint 1: prevention of stroke
  - Endpoint 2: prevention of myocardial infarction and vascular death or the composite end point



Results

Table 1. Aspirin and Dipyridamole: Total Daily Dose and Formulation

	ASA	ASA+DP
Caneschi et al[20]	300 mg	ASA 150 mg+IR-DP 225 mg
Guiraud-Chaumeil et al[17]	990 mg	ASA 990 mg+IR-DP 150 mg
AICLA[18]	990 mg	ASA 990 mg+IR-DP 225 mg
ACCSG[19]	1300 mg	ASA 1300 mg+IR-DP 300 mg
ESPS-2[9]	50 mg	ASA 50 mg+ER-DP 400 mg
ESPRIT[10]	75 mg†	ASA 75 mg†+DP‡ 400 mg

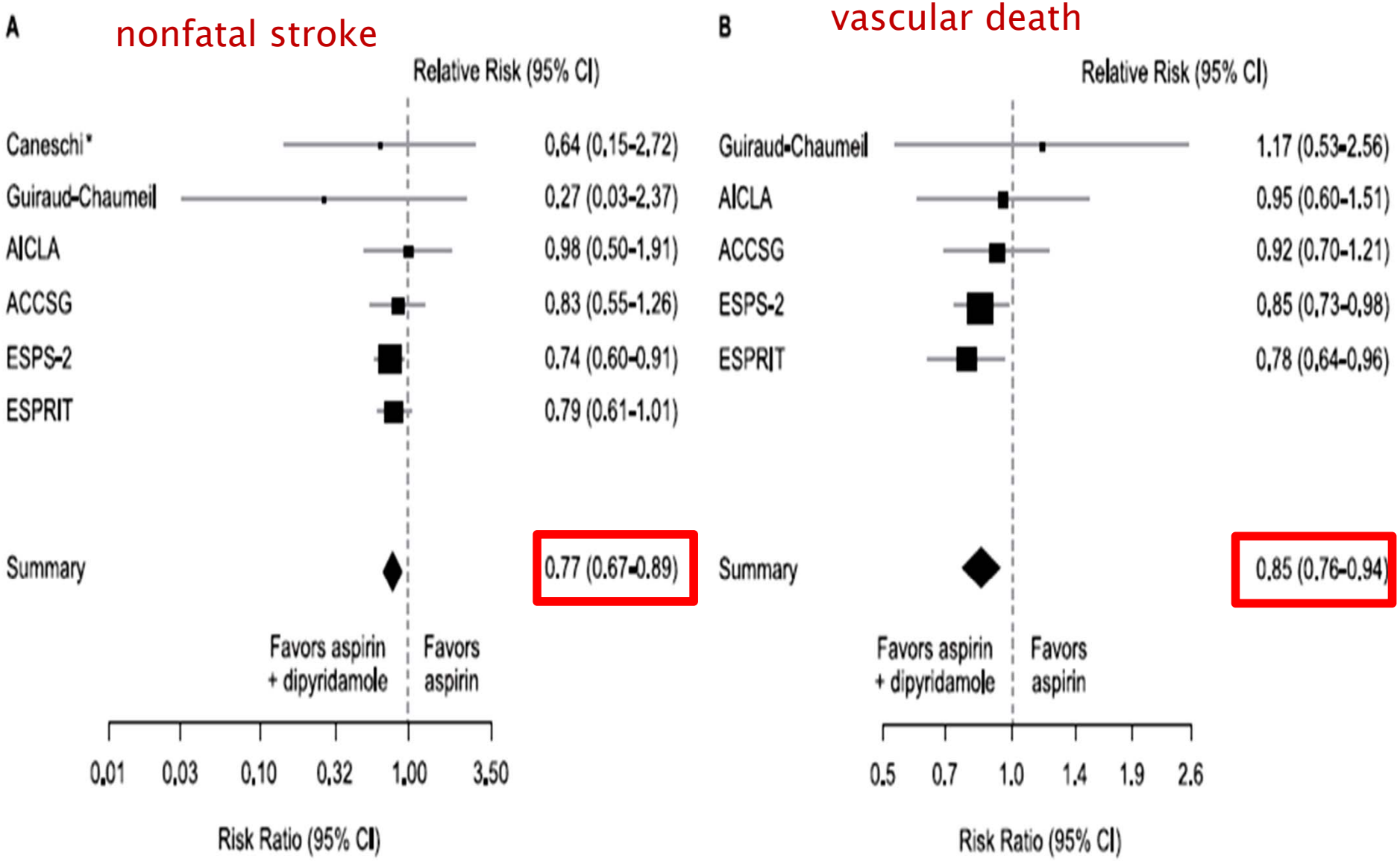
ASA indicates aspirin; IR-DP, immediate-release dipyridamole; ER-DP, extended-release dipyridamole.

†Median dose. Allowable dose of ASA 30–325 mg.

‡83% ER-DP, 17% IR DP.

Results

composite outcome of nonfatal stroke, nonfatal myocardial infarction, and vascular death



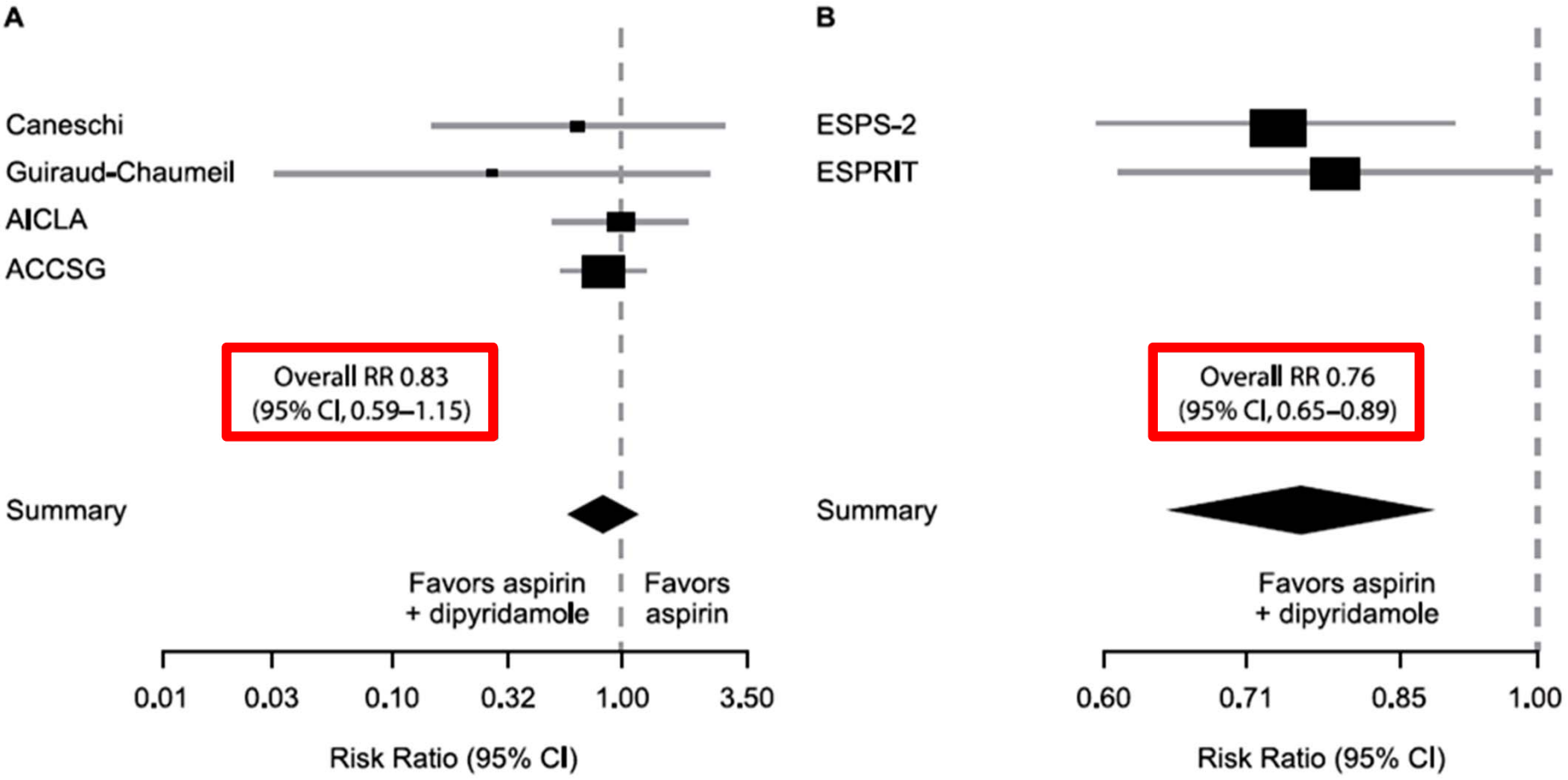
Results

Table 2. Results for Stroke-Alone End Point and the Composite End Point

Study	Aspirin+DP	Aspirin	Stroke			Stroke/MI/Vascular Death		
	Patients (n)	Patients (n)	Aspirin+DP Events (n)	Aspirin Events (n)	RR (95% CI)	Aspirin+DP Events (n)	Aspirin Events (n)	RR (95% CI)
Caneschi et al[20]	22	14	3	3	0.64 (0.15–2.72)	...	...	...
Guiraud-Chaumeil et al[17]	138	147	1	4	0.27 (0.03–2.37)	12	11	1.17 (0.53–2.56)
AICLA[18]	202	198	16	16	0.98 (0.50–1.91)	30	31	0.95 (0.60–1.51)
ACCSG[19]	448	442	38	45	0.83 (0.55–1.26)	79	85	0.92 (0.70–1.21)
ESPS-2[9]	1650	1649	137	186	0.74 (0.60–0.91)	272	321	0.85 (0.73–0.98)
ESPRIT[10]	1363	1376	99	127	0.79 (0.61–1.01)	149	192	0.78 (0.64–0.96)
Total Population	3823	3826	294	381	0.77 (0.67.–0.89)	542	640	0.85 (0.76.–0.94)

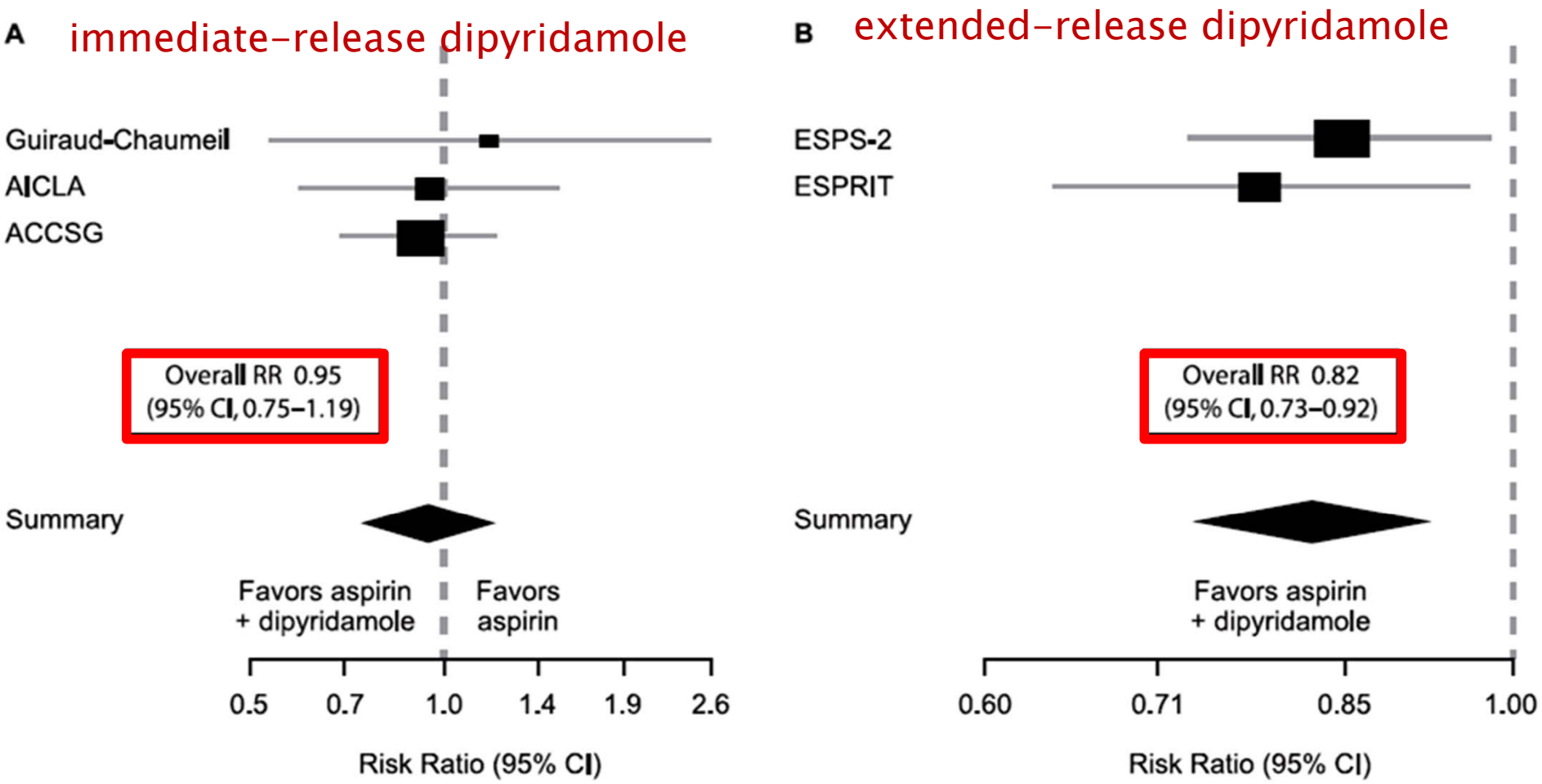
n indicates the No. of patients or events in each subgroup; DP, dipyridamole; MI, myocardial infarction; RR, relative risk.

Results nonfatal stroke



Results

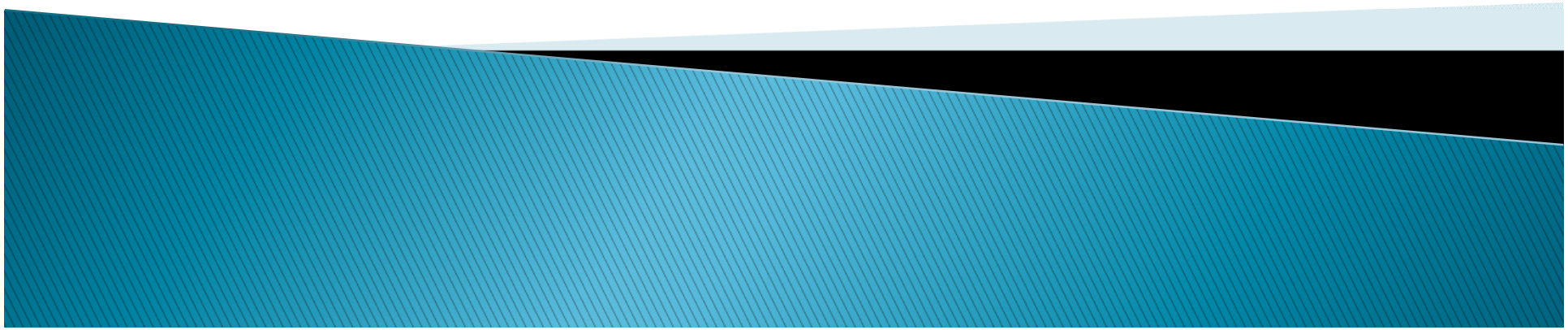
Meta-analysis of composite outcome of nonfatal stroke, nonfatal myocardial infarction, and vascular death



Conclusion

- The combination of aspirin plus dipyridamole is more effective than aspirin alone in preventing stroke and other serious vascular events in patients with minor stroke and TIAs.
- Aspirin-extended-release dipyridamole is more effecetive than aspirin monotherapy.

Appraisal



證據等級

Level	與[治療/預防/病因/危害]有關的文獻
1a	**用多篇RCT所做成的綜合性分析(SR of RCTs)**
1b	單篇RCT(有較窄的信賴區間)
1c	All or none
2a	用多篇世代研究所做成的綜合性分析
2b	單篇cohort及低品質的RCT
2c	Outcome research / ecological studies
3a	SR of case-control studies
3b	Individual case-control studies
4	Case-series(poor quality :cohort / case-control studies)
5	沒有經過完整評讀醫學文獻的專家意見

Q1: What question did the systematic review addressed? (此系統性的回顧要探討的問題為何？)

評判標準：內容應清楚闡明文章想要回答的問題，暴露因子(包括治療、檢驗等)與結果的因果關係應求簡單明瞭。

- P: Patients with a history of stroke or TIA
- I : Aspirin plus dipyridamole
- C: Aspirin monotherapy
- O (end point):
  - Endpoint 1: prevention of stroke
  - Endpoint 2: prevention of myocardial infarction and vascular death or the composite end point

評判結果：yes

Q2: Is it unlikely that important, relevant studies were missed? (有沒有遺漏重要的文獻?)

評判標準：資料搜尋是否完整，包含
-重要的資料庫如Medline, Cochrane, EMBASE等
-不只限於英文資料
-搜尋策略包括MESH term及text words
-相關研究的參考文獻
-向專家請教，特別是尚未刊載的研究

- Search from MEDLINE: Randomized, controlled trials
- Cochrane Database: Systematic of reviews
- Other: the reference lists of all relevant publications

評判結果：Unclear

Q3:Were the criteria used to select articles for inclusion appropriate? (選擇文獻的準則適當?)

評判標準：事先清楚界定「收入」及「排除」文章的準則(準則的描述應包括病人群的特性、介入治療的方法或暴露因子、有興趣的研究結果、研究的類型及研究設計)

Item	Inclusion criteria
Patient's characteristics	patients with previous noncardioembolic stroke or TIA
Intervention:	immediate-release, extended-release dipyridamole, or both formulations
Outcome	Primary end point: prevention of stroke Additional end points: myocardial infarction (MI) and vascular death or the composite
Type of studies	randomized controlled trials

評判結果：yes

Q4: Were the included studies sufficiently valid for the type of question asked? (選擇的文獻有效回答所問的問題?)

評判標準：應描述所回顧的每篇文章研究的品質 (研究品質的判定準則依不同臨床問題而事先擬定的，如隨機分配、雙盲、追蹤的完整度等)。

- Definition of high quality:
  - Double blinded concealment of treatment allocation,
  - provided assessment of compliance and completeness of follow-up
  - blinded outcome adjudication
- *But lack of objective scale to evaluate quality…*

評估結果：unclear

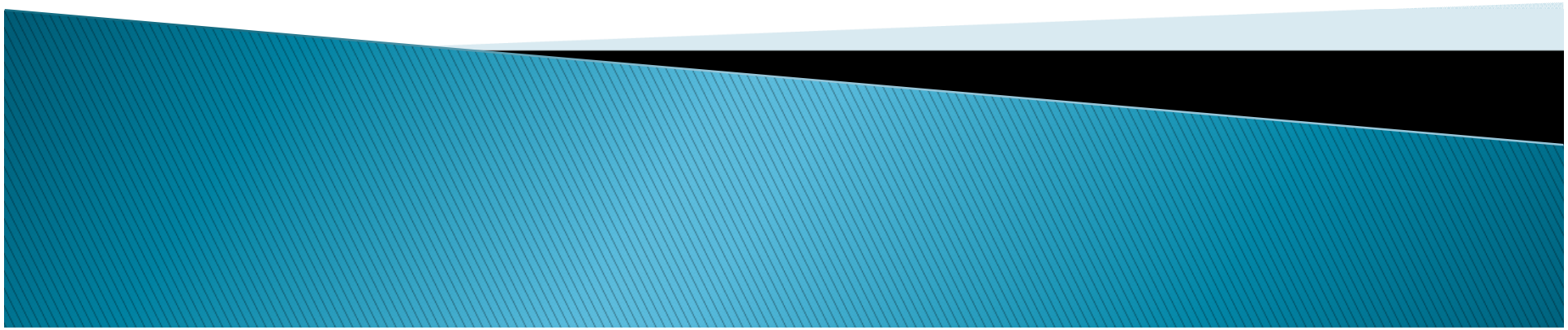
Q5: Were the results similar from study to study? 各研究的結果相似?

評判標準：最理想的狀況是各研究的結論一致或差異不大
- 如果各研究的結果有差異，作者以統計的方法檢驗是否達到有統計意義的差別
- 同時，也要加以探討各研究結論差異的原因

- 每項meta-analysis皆有探討異質性。
- 但文中並未針對造成異質性的原因加以探討。

評判結果：unclear

Apply

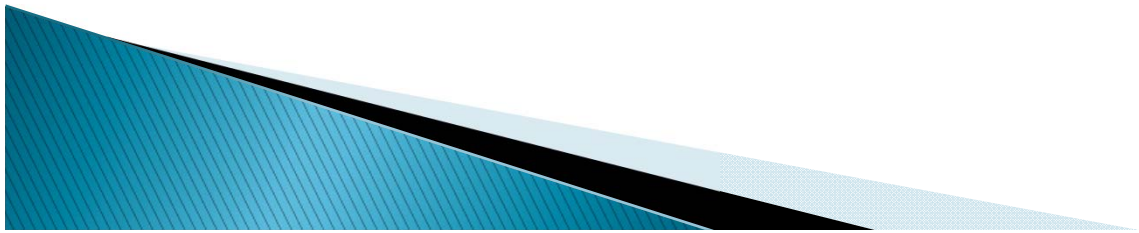


Apply to this case

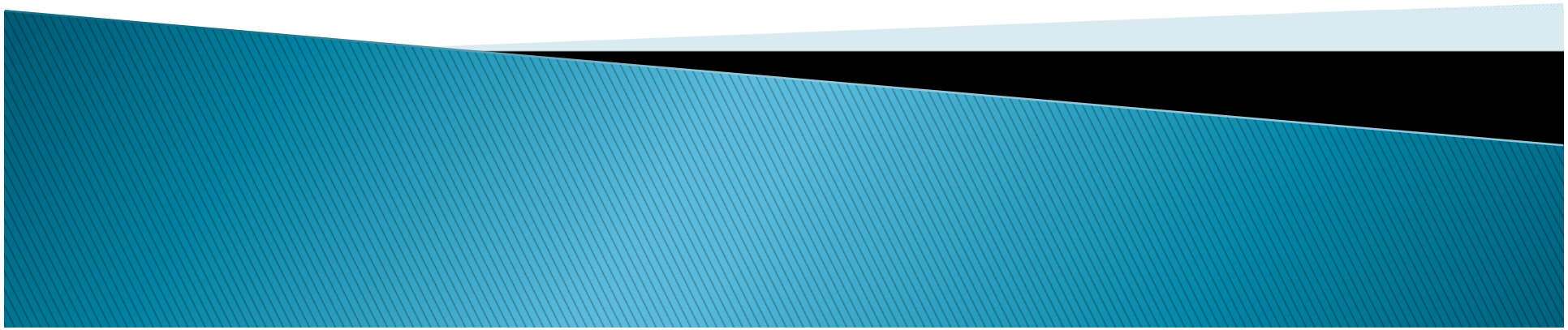
醫療現況	病人意願
由此次的實證醫學可知，使用aspirin + dipyridamole(特別是長效性的)之combination therapy效果會較單一使用aspirin之效果好。	只要是任何能預防stroke之復發的方式，病人和其家屬都願意接受相關治療。
生活品質	**社會經濟脈絡**
二次中風，很有可能會導致腦部急劇退化，因此若能使用combination therapy來預防中風的復發，對於病人的日常生活功能及品質都有一定的影響。	由於病人為腦中風之病患，使用solantin 或 agrrenox皆可採用健保給付，沒有自費的問題。

Other need to know~

- Dosage of Aspirin and Dipyridamole
- Side effect of Dipyridamole



Audit



在「提出臨床問題」方面的自我評估

- 我提出的問題是否具有臨床重要性？有，因為腦中風盛行率頗高，預防再次復發與神經退化情況也有一定的關係，是相當重要的主題。
- 我是否明確的陳述了我的問題？
  - 我的foreground question 是否可以清楚的寫成PICO？可以
  - 我的background question是否包括what, when, how, who等字根？無
- 我是否清楚的知道自己問題的定位？（亦即可以定位自己的問題是屬於診斷上的、治療上的、預後上的或流行病學上的），並據以提出問題？知道
- 對於無法立刻回答的問題，我是否有任何方式將問題紀錄起來以備將來有空時再找答案？還沒有，只記在腦裡

在「搜尋最佳證據」方面的自我評估

- 我是否已盡全力搜尋？是
- 我是否知道我的問題的最佳證據來源？知道
- 我是否從大量的資料庫來搜尋答案？是
- 我工作環境的軟硬體設備是否能支援我在遇到問題時進行立即的搜尋？可以
- 我是否在搜尋上愈來愈熟練了？是
- 我會使用「斷字」、布林邏輯、同義詞、MeSH term，限制（limiters)等方法來搜尋？尚不熟練
- 我的搜尋比起圖書館人員或其他對於提供病人最新最好醫療有熱情的同事如何？尚可

關於「嚴格評讀文獻」方面的自我評估

- 我是否盡全力做評讀了？已盡力評讀
- 我是否了解worksheet每一項的意義？是
- 評讀後，我是否做出了結論？是

關於「應用到病人身上」的自我評估

- 我是否將搜尋到的最佳證據應用到我的臨床工作中？是
- 我是否能將搜尋到的結論如NNT, LR用病人聽得懂的方式解釋給病人聽？尚需練習
- 當搜尋到的最佳證據與實際臨床作為不同時，我如何解釋？此部份經驗較少

改變「醫療行為」的自我評估

- 當最佳證據顯示目前臨床策略需改變時，我是否遭遇任何阻止改變的阻力？沒有，老師會指導我查資料
- 我是否因此搜尋結果而改變了原來的治療策略？做了那些改變？沒有什麼改變

效率評估

- 這篇報告，我總共花了多少時間？大約8個小時~
- 我是否覺得這個進行實證醫學的過程是值得的？值得，但很累。
- 我還有那些問題或建議？PICO很重要

THE END

~ Thank you for your attention ~