藥師核心能力 - 如何利用資料庫回答問題

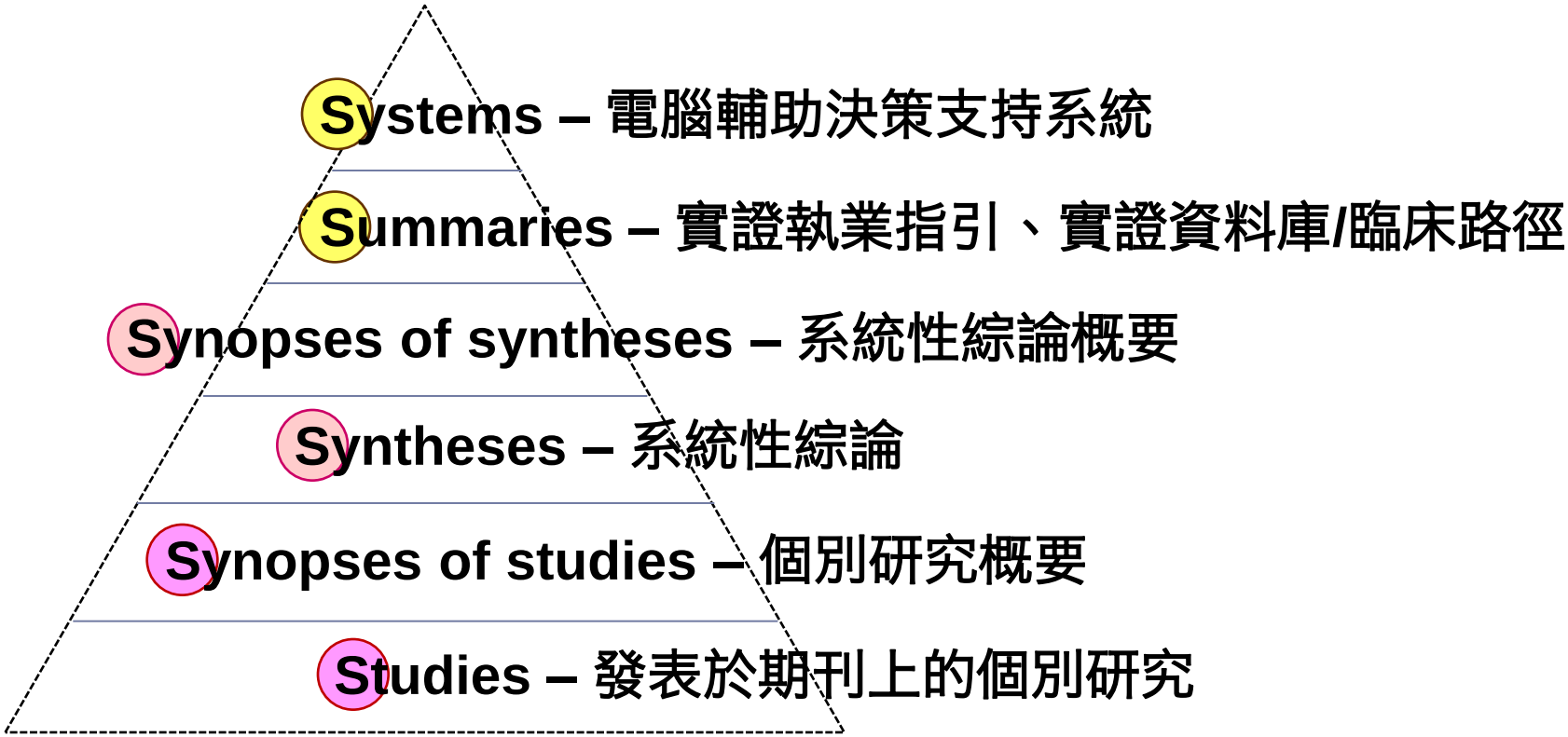
Core Clinical Skills: Systematic Approaches to Answer Question

2012/7/13 (五) 15:10~16:00 @台北榮民總醫院

新光吳火獅紀念醫院 劉人瑋藥師

談談「6S」吧!!

- 加拿大曼徹斯特大學**Brian Haynes**博士於**2009**年提出了「**6S**」概念，描述實證資源的「分類」



參考文獻 ***Ann Intern Med. 2009; 151: JC3-2.*** **[PMID 19755349]**

談談「6S」吧!!

- **電腦輔助決策支持系統 (computerized decision support systems; CDSS)**
  - 結合 實證資訊 與 病人資訊 (通常是電子病歷系統)
  - 產出 個人專一性評估 並 提供臨床醫師建議

- 摘要 **(summaries)**
  - 結合特定問題實證資訊的臨床路徑 或 教科書式摘要
    - 例如: 各式「實證為基礎且定期更新」的資料庫、以實證為基礎的執業指引 **(practice guidelines)**

參考文獻 ***Ann Intern Med. 2009; 151: JC3-2.*** **[PMID 19755349]**

這就是CDSS

- 如果「**Siri®**」在就好了…

談談「6S」吧!!

- **系統性綜論概要 (synopsis of systematic review)**
  - 針對特定問題的系統性綜論，整理結果並提供評論

有特定臨床問題

Therapeutics

Review: Statins do not increase risk for intracerebral hemorrhage

針對特定系統性綜論

Hackam DG, Woodward M, Newby LK, et al. Statins and intracerebral hemorrhage: collaborative systematic review and meta-analysis. Circulation. 2011;124:2233-42.

Clinical impact ratings: C ★★★★★★☆ En ★★★★★☆☆ H ★★★★★★☆ N ★★★★★☆☆

Question

Do statins increase risk for intracerebral hemorrhage (ICH)?

Review scope

Included studies reported data on statin use and incidence of ICH.

提供評論

Commentary

The systematic review and meta-analysis by Hackam and colleagues addresses an aspect of management ambiguity raised by the results of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial, which examined atorvastatin for secondary

整理結果

Results from randomized controlled trials of statins vs control*

Outcomes	Number of trials (*n*)	Weighted event rates†		RRI (95% CI)	NNH (CI)
		Statins	Control		
Intracerebral hemorrhage	23 (130 443)	0.40%	0.36%	10% (–14 to 41)	Not significant

Minneapolis, Minnesota, USA

References

1. **Amarenco P, Bogousslavsky J, Callahan A 3rd, et al; Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators.** High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med. 2006;355:549-59.
2. **Westover MB, Bianchi MT, Eckman MH, Greenberg SM.** Statin use

談談「6S」吧!!

- **系統性綜論 (Syntheses: systematic review)**

  - 針對特定問題的系統性綜論

Cochrane Database Syst Rev. 2011 Aug 10;(8):CD007551.

Statins for acute ischemic stroke. ← 有特定臨床問題

Squizzato A, Romualdi E, Dentali F, Ageno W.

Research Center on Thromboembolic Disorders and Antithrombotic Therapies, Department of Clinical Medicine, University of Insubria, Medicina 1, viale Borri, 57, Varese, Italy, 21100.

Abstract

BACKGROUND: Statins have been claimed to be effective in the acute phase of ischemic stroke. The potential positive actions of statins during an acute cerebrovascular ischemic event are two-fold: a neuroprotective effect, limiting damage and improving recovery; and a preventative effect on early recurrence.

OBJECTIVES: To quantify the potential benefits and harms of statins in the acute treatment of cerebrovascular ischemic events (both transient ischemic attacks (TIAs) and ischemic stroke).

SEARCH STRATEGY: We searched the Cochrane Stroke Group's Trials Register (November 2010); the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2010, Issue 4); MEDLINE (1950 to November 2010); and EMBASE (1980 to November 2010). In an effort to identify further published, unpublished and ongoing trials we searched ongoing trials and research registers

系統性搜尋並評讀 ↓

談談「6S」吧!!

- **個別研究概要 (synopsis of studies)**
  - 針對特定問題的個別研究，整理結果並提供評論

有特定臨床問題

針對單一研究

Therapeutics

Influenza vaccination reduced cardiovascular events in patients hospitalized with an acute coronary syndrome

Phrommintikul A, Kuanprasert S, Wongcharoen W, et al. Influenza vaccination reduces cardiovascular events in patients with acute coronary syndrome. Eur Heart J. 2011;32:1730-5.

Clinical impact ratings: HO ★★★★★★☆ C ★★★★★★☆ ID ★★★★★★☆

Question

Does influenza vaccination reduce cardiovascular events in patients hospitalized with an acute coronary syndrome (ACS)?

Methods

Design: Randomized controlled trial (PROBE study).

整理結果

Influenza vaccination vs no vaccination (control) for patients hospitalized with an acute coronary syndrome (ACS)‡

Outcomes	Influenza vaccination	Control	At 12 mo	
			RRR (95% CI)	NNT (CI)
Major adverse cardiovascular events§	9.5%	19%	31% (13 to 46)	17 (12 to 41)
Mortality	2.7%	5.5%	37% (–12 to 65)	Not significant
Hospitalization for ACS	4.5%	11%	31% (2 to 52)	31 (19 to 501)

Main results

Influenza vaccination reduced major adverse cardiovascular events and hospitalization for ACS but not mortality, hospitalization for heart failure, or cardiovascular mortality (Table). 1 patient in the vaccine group was hospitalized for stroke compared with no patients in the control group.

提供評論

In the meantime, there is no reason to withhold influenza vaccine from patients with ACS unless they have a specific contraindication, such as severe allergic reaction to a prior dose of influenza vaccine or known severe allergy to a vaccine component (e.g., egg protein). Much misinformation about vaccines exists among the general population; providers may want to use this study to help convince otherwise reluctant patients to be vaccinated.

Henry S. Sacks, PhD, MD
Mount Sinai School of Medicine
New York, New York, USA

談談「6S」吧!!

- 「**6S**」的意義在於**:**

  - 提供臨床工作者一個解決問題 **(problem solving)** 與做出決策 **(decision making)** 的「方法」

“當應用「**6S**」模式於臨床決策時，我們建議從頂端資源找起**…”**

  -「**6S**」與證據等級 **(level of evidence)** 沒有直接關係，利用「**6S**」模式僅在減少決策者的負擔

參考文獻 ***Ann Intern Med. 2009; 151: JC3-2.*** **[PMID 19755349]**

遇到一個臨床問題，您會怎麼做?

- 速率決定步驟: 對的搜尋策略 (對的資源、對的方法)

我們到底需要什麼?

- 我們的需求非常簡單，那就是「能夠解決問題的資源」，這些問題對藥師來說，叫做「藥物相關問題 **(drug-related problem)**」

未治療之適應症
應監測 (治療前)

無適應症治療
劑量、療程、用法不當
應監測 (治療後)
藥物、疾病交互作用
效果不佳、重複處方
有衛教需求

← 給藥前 → ← 給藥後 →

我們發現的藥物相關問題

- 分析將近**4,000**個藥物相關問題中，最常被發現的是「劑量/頻次不當」其次是「應治療而未治療之適應症」與「無適應症或療程不當」

問題	件數 (%)	介入	件數 (%)
劑量/頻次不當	**890 (23.4%)**	調整劑量/頻次	**970 (25.5%)**
應治療而未治療	**671 (17.7%)**	增加用藥	**847 (22.3%)**
無適應症/療程不當	**640 (16.8%)**	停止用藥	**826 (21.7%)**
需進行檢查/檢驗	**602 (15.8%)**	增加檢驗/檢查	**679 (17.9%)**
禁忌症/效果不佳	**356 (9.4%)**	改用其他藥物	**287 (7.6%)**
藥物交互作用	**124 (3.3%)**	改變劑型/途徑	**95 (2.5%)**

解決問題的關鍵

- 能夠解決問題的資訊，才是必要資訊，什麼樣的資訊在醫療決策中是「關鍵」？

關鍵	範例	資訊
好處/壞處	長期使用抗凝血藥物預防中風的好處 (療效)/壞處 (風險)	使用抗凝血藥物降低/增加多少風險等
費用/資源	接受藥物預防所衍生出的費用 (固定/非固定費用) 以及所耗費的資源	藥品價格、檢驗費用，成本效益比較等
病人偏好/價值	病人對於接受長期抗凝血藥物預防的意願	無 (需個人化)
研究證據	支持/反對使用該藥物的研究證據 (包括結果與品質)	研究結果/證據品質，治療指引

系統性回答問題

- 第一步 請簡化問題 **(simplify you question)**

“這位**65**歲有心房顫動 **(atrial fibrillation)** 病人，應該接受抗凝血藥物預防中風嗎**?”**

“他同時有高血壓，但沒有其他慢性疾病，之前曾經使用過 **aspirin**，但覺得吃了胃不舒服，所以不太喜歡，前幾天曾經因為心跳太快到了急診，心電圖顯示心房顫動合併心跳速率過快**…”**

簡化為 **“**合併心房顫動與高血壓病人，使用抗凝血藥物是否可以降低中風風險**?”** [療效]

系統性回答問題

- 第一步 請簡化問題 **(simplify you question)** [續]

“病人的家屬上網看了一些網友使用抗凝血藥物的心得，大都表示使用這個藥物非常麻煩，不但要常常抽血檢查，生活上又必須注意很多事情，更可能造成出血…這個藥物真的安全嗎?”

簡化為 “使用抗凝血藥物預防中風是否會增加出血風險?” [風險]

衍生問題 “是否有什麼可行的方法可以降低出血風險?” “有其他選擇嗎?”

我們常常只回答問題，但沒有對策

系統性回答問題

- 第二步 請尋求支持您論點的證據 **(find the evidence)**

「療效」問題的考量點

考量點	範例	資訊 **(MDX)**
有無效果	使用抗凝血藥物「是否」可顯著降低中風風險**?**	**CLINICAL APPLICATIONS – therapeutic uses**
效果大小	使用抗凝血藥物可以降低「多少」中風風險**?**	**CLINICAL APPLICATIONS – therapeutic uses** **CAUTIONS – adverse reactions**
其他考量	是否有更好的選擇 **(**或藥物**)?**	**CLINICAL APPLICATIONS – comparative efficacy**

系統性回答問題

- 第二步 請尋求支持您論點的證據 **(find the evidence)** [續]

  - Warfarin → CLINICAL APPLICATIONS → Therapeutic uses

Atrial fibrillation - Thromboembolic disorder

FDA Labeled Indication
a) Overview

是否為核准的適應症

FDA Approval: Adult, yes; Pediatric, no

Efficacy: Adult, Effective

Recommendation: Adult, Class I

附有證據等級與建議強度

Strength of Evidence: Adult, Category A

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

Note

請務必檢視證據等級 **(strength of evidence)** 與建議強度 **(strength of recommendation)** 的定義

系統性回答問題

- 第二步 請尋求支持您論點的證據 **(find the evidence)** [續]

- Warfarin → CLINICAL APPLICATIONS → Therapeutic uses

根據…什麼建議（治療指引）

b) Summary:

According to guidelines from the American College of Chest Physicians, patients with atrial fibrillation and intermediate or high risk of stroke, oral anticoagulation is recommended; dabigatran is suggested rather than adjusted-dose vitamin K antagonist such as warfarin [9]

Effective for the prevention of thromboembolic events in patients with atrial fibrillation [8]

High-risk patients should receive adjusted-dose warfarin for an INR between 2 and 3 [10]

The use of adjusted-dose warfarin was effective in reducing the incidence of composite outcome of fatal and nonfatal disabling stroke (ischemic or hemorrhagic), intracranial hemorrhage, and other clinically significant arterial embolism among patients aged 75 years or over with chronic atrial fibrillation or atrial flutter, with no significant difference on major extracranial hemorrhage [11]

療效與出血風險的的描述

Note

請務必檢視引用資訊來源，例如 **[9]**

系統性回答問題

- 第二步 請尋求支持您論點的證據 **(find the evidence)** [續]

- Warfarin → CLINICAL APPLICATIONS → Comparative efficacy

Dabigatran Etexilate Mesylate

Atrial fibrillation - Thromboembolic disorder; Prophylaxis

Venous thromboembolism

Atrial fibrillation - Thromboembolic disorder; Prophylaxis

與dabigatran比較的研究結果 →

a) In a 2-year randomized, prospective, noninferiority trial (n=18,113; Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY)) in patients with atrial fibrillation, a 110 mg dose of dabigatran twice daily was as effective as warfarin in preventing stroke and systemic embolism with lower occurrence of major hemorrhage, while a 150 mg dose of dabigatran twice daily was more effective than warfarin at preventing stroke and systemic embolism with similar occurrence of major hemorrhage. Patients (mean age, 71 years; 63.6% males) diagnosed with atrial fibrillation and at risk of stroke were randomized to receive either 110 mg or 150 mg dabigatran twice daily (blinded) or 1 mg, 3 mg, or 5 mg warfarin (unblinded). Warfarin was adjusted to a target INR of 2 to 3. Exclusion criteria included creatinine clearance less than 30 mL/minute and active liver disease. The primary outcome of stroke or systemic embolism occurred at a rate of 1.53% per year in the 110 mg dabigatran group, 1.11% per year in the 150 mg dabigatran group, and 1.69% per year in the warfarin group. Compared to warfarin, the 110 mg dose of dabigatran was associated with a relative risk (RR) of 0.91 (95% CI, 0.74 to 1.11; p less than 0.001 for noninferiority; p=0.34 for superiority), and the 150 mg dose of dabigatran was

系統性回答問題

- 第三步 擬定可行的計畫 **(set up a plan)**

「可行的」計畫考量點

考量點	範例	資訊 **(MDX)**
傷害	使用抗凝血藥物可能的副作用**?**	**CAUTIONS – adverse reactions, precautions**
費用**/**資源	使用抗凝血藥物需監測的項目**/**頻率**?**	**CLINICAL APPLICATIONS – monitoring parameters**
用藥指導	如何進行用藥指導**?** 內容**?**	**CLINICAL APPLICATIONS – patients instructions**

系統性回答問題

- 第三步 擬定可行的計畫 **(set up a plan)** [續]

- Warfarin → CLINICAL APPLICATIONS → Adverse reactions

Hemorrhage

有出血的危險因子

a) Summary

1) Risk factors for major or fatal bleeding in patients taking warfarin sodium include a higher starting international normalized ratio (INR), age 65 years and older, variable INRs, history of gastrointestinal bleeding, hypertension, cerebrovascular disease, serious heart disease, anemia, malignancy, trauma, renal insufficiency, concomitant drugs, and long duration of warfarin therapy [101]. Other risk factors for a major bleed occurring during warfarin anticoagulation are: comorbid conditions, atrial fibrillation and the first 90 days of warfarin therapy [124][125][126]. Regular monitoring of INR should be performed on all patients. More frequent monitoring, careful dose adjustment, and a shorter duration of therapy may be warranted in patients at high risk for bleeding. [101].

不良反應的處理建議

j) Treatment of Adverse Effects

1) The following are evidence-based guidelines from the American College of Chest Physicians for managing elevated International Normalized Ratio (INRs) or bleeding in patients on vitamin K antagonist (ie, warfarin) [139].

a) INR above therapeutic range but less than 5 with no significant bleeding:

系統性回答問題

- 第三步 擬定可行的計畫 **(set up a plan)** [續]

  - Warfarin → CLINICAL APPLICATIONS → Monitoring parameters

A) Warfarin Sodium

1) Therapeutic

a) Laboratory Parameters

1) INR

監測項目與監測頻率

a) Monitor INR daily following the initial warfarin dose until the INR stabilized to the therapeutic range; then periodically based on clinical need, generally every 1 to 4 weeks. Perform additional INR testing when other warfarin products are interchanged with Coumadin(R) or when other drugs (including botanicals) are initiated, discontinued, have dosages changed, or taken irregularly. patients with a high risk of bleeding may require more frequent INR monitoring (manufacturer) [2].

達穩定狀態後的建議監測頻率

b) Monitor INR up to every 12 weeks in patients with consistently stable INRs, defined as at least 3 months of consistent results with no need to adjust warfarin dosing. Evaluate the INR within 1 to 2 weeks if the patient experiences a single out of range value, below or above the therapeutic INR by 0.5 or less (American College of Chest Physicians guidelines) [1]

Note

監測的項目與頻率一樣重要，因為這將影響病人的順從性

系統性回答問題

- 第三步 擬定可行的計畫 **(set up a plan)** [續]

- Warfarin → CLINICAL APPLICATIONS → Patient instruction

A) Warfarin (By mouth)
Warfarin

制式的用藥指導內容

Helps to prevent new blood clots from forming, and helps to keep existing blood clots from getting worse. This medicine is a blood thinner (anticoagulant).

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to warfarin, or if you are pregnant or planning to become pregnant. Ask your doctor about using this medicine if you are having or have recently had surgery. Usually, you should not use this medicine if you are having surgery on your eyes, brain, or spine, or major surgery that will leave you with large, open wounds. This medicine should not be used if you have certain heart problems, severe or uncontrolled high blood pressure, or any condition that may cause uncontrolled bleeding (such as a stomach ulcer or hemophilia).

Note

用藥指導務必「個人化」誤流於型式，照本宣科

系統性回答問題

- 最終步 整合各項資料並做出建議 **(make a suggestion)**

考量點	範例
療效	使用抗凝血藥物預防心房顫動病人中風是有效的，也是國際上所建議的，以中風險病人 **(**每年中風機率約 **4%)** 每**1000**人預防，可減少**25**人發生中風*
副作用	會增加出血風險，但得到的好處多於壞處，透過監測「**INR**」配合劑量調整可以降低風險
其他考量	約每三個月需要抽血監測一次「**INR**」，生活上需注意飲食與其他藥物的交互作用，但仍有其他藥物選擇
最終建議	建議使用抗凝血藥物預防中風，配合定期監測與用藥衛教，減少可能的副作用

*數據引用自***Cochrane Database Syst Rev. 2005; (3): CD001927**

[PMID 16034869]

戰場是很殘酷的

- 臨床藥師的戰場在「病房」，身為一位稱職的臨床藥師，該怎麼在戰場上作戰?

戰場是很殘酷的

- 現場 (徒手) 解決問題的方法:

資源	優點	缺點
大腦 (本人的或他人的)	免費、快速	常記錯，有時候不靈光
教科書	具權威性	更新慢、篇幅有限、不易攜帶
線上資料庫	內容廣泛、快速	需連線、付費資料庫價格昂貴

現場解決問題的要件為: 簡單、快速、正確

Note

線上資料庫受限於可獲得性 (網路、設備、卡位能力)，可能不是現場解決問題的優先選擇

快問快答

- 統計將近**1,000**個諮詢問題內容，最常被問到的是「劑量調整」，其次是「副作用」與「藥物動力學」
- 快問快答的結果，經常就是「記錯了」，錯誤的資訊可能會導致錯誤的醫療決策，甚至危害到病人的用藥安全
- 您可以「現場」回答這些快問快答嗎**?**

藥物動力學

“Warfarin的口服吸收好嗎**?** 生體可用率大約多少**?”**

藥物交互作用

“不能與**warfarin**併用的藥物有哪些**?”**

禁忌症

“這位病人末期肝硬化，還可以使用**warfarin**嗎**?”**

快問快答

- 要應付快問快答，您需要「工具」

- Tmax, Oral: 4 hr
- Bioavailability, Oral: completely absorbed
- Effect of food: no effect

吸收程度

- Renal: 92%
- Bile: lesser extent
- Total body clearance: CYP2C9*1/*1 al≤ genotype, 0.065 mL/min/kg
- Total body clearance: CYP2C9*1/*2 or CYP2C9*1/*3 al≤ genotypes, 0.041 mL/min/kg
- Total body clearance: CYP2C9*2/*2 or CYP2C9*2/*3 or CYP2C9*3/*3 al≤ genotypes, 0.02 mL/min/kg

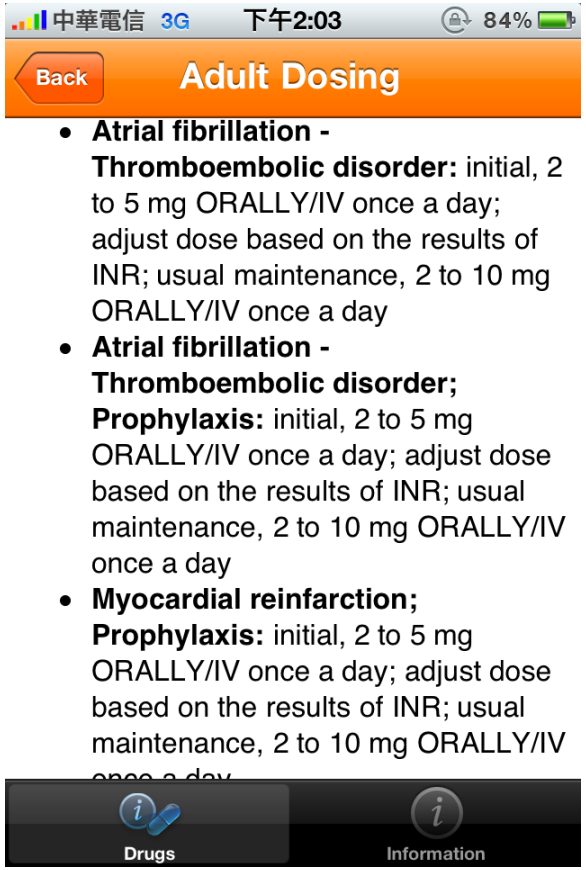
排除途徑

- Hepatic: extensive via CYP2C9 (primary isoenzyme), CYP2C19, CYP2C8, CYP2C18, CYP1A2, and CYP3A4
- Hydroxylated warfarin metabolites: inactive
- warfarin alcohols, minimally active

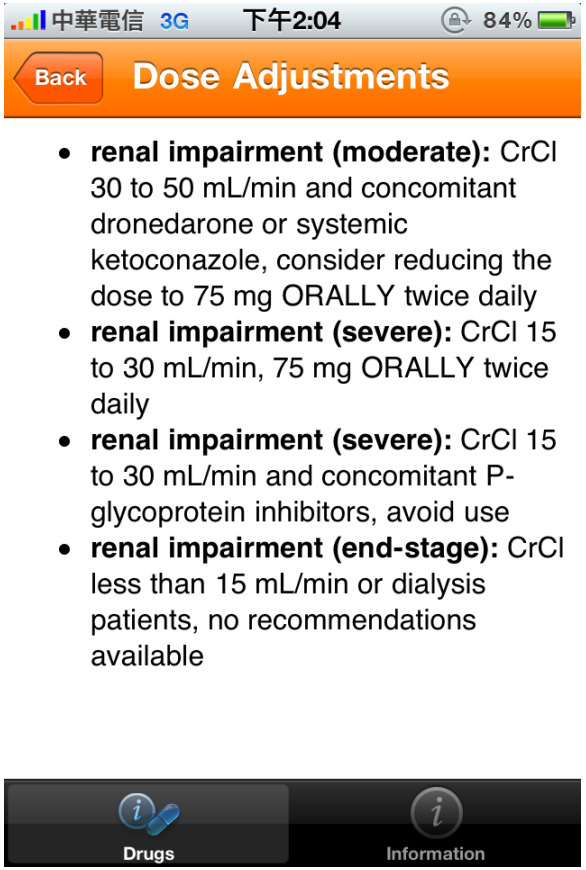
代謝途徑

快問快答

- 要應付快問快答，您需要「工具」



常用劑量



劑量調整

交互作用

快問快答

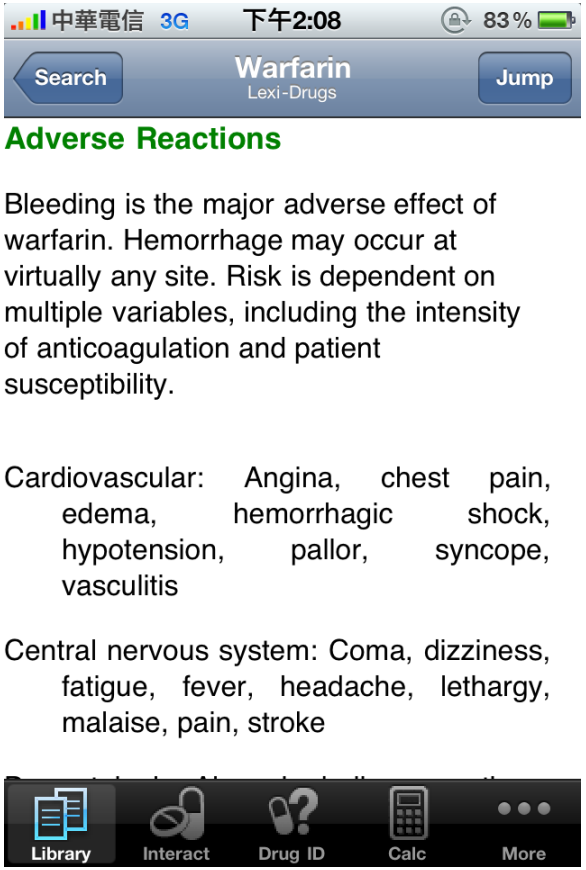
- 常用藥物相關「**App**」比較

App	MDX	Medscape	Lexicomp
價格	免費	免費	藥物資料庫 + 交互作用軟體 **115** 美金/年
更新	資料庫每**14**天更新一次	資料庫即時更新	資料庫即時更新
檢核交互作用	有，但要額外付費	有，免費	有，但要額外付費
資料量	中上，足以應付基本需求	偏少，但足以應付基本需求	最多
評比	★★★★★ **(24/28)**	★★★★☆ **(38/70)**	★★★★☆ **(3/6)**

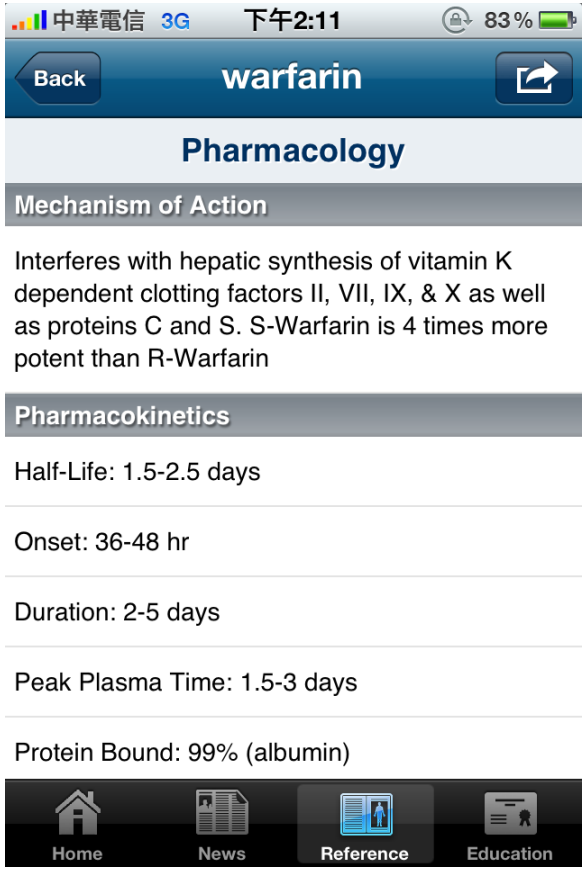
快問快答

- 要應付快問快答，您需要「工具」

交互作用



不良反應



藥物動力學


有了這些工具，我想我應該是「無敵」了

別變成走動的藥物查詢機

- 資料庫 **(**們**)** 提供藥師非常豐富且方便的資訊來源，有著無遠弗屆的影響力
- 如何「有效率」、「系統性」的回答問題是臨床藥師的核心能力之一
- 但「應用」與「整合」資訊，進行臨床決策才是臨床藥師的核心價值
- 資料庫的核心價值在於「便利性」、「可用性」與「可靠性」，過於複雜的資訊會降低醫療人員使用的意願

查詢 與 學習

- 「ㄟ...這個我查一下...嗯...我等下回覆你...」過於頻繁地查詢並不能達到學習的目的，且影響其他醫療人員對您的「信任」

- 查詢 與 學習是不同的，提醒您除了查詢之外 **(**片段知識**)**，也要熱衷於學習 **(**整體架構**)**

- 「我知道這個藥物...要...，但我不確定這麼做是不是比較好**?**」 「這個查不到，所以...」是否能夠整合資訊，進行臨床決策，並非取決於片段知識，而是整體架構 與 臨床經驗