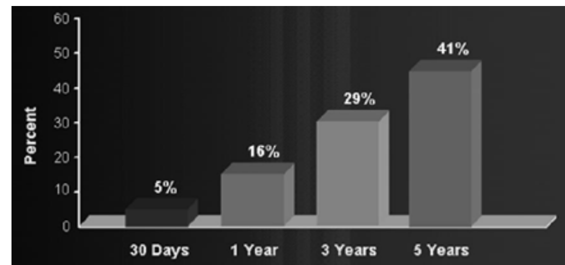
二次中風的風險

Time after Stroke	Cumulative
30 days	3% to 10%
1 year	5% to 14%
5 years	25% to 40%

Cumulative Mortality After Ischemic Stroke

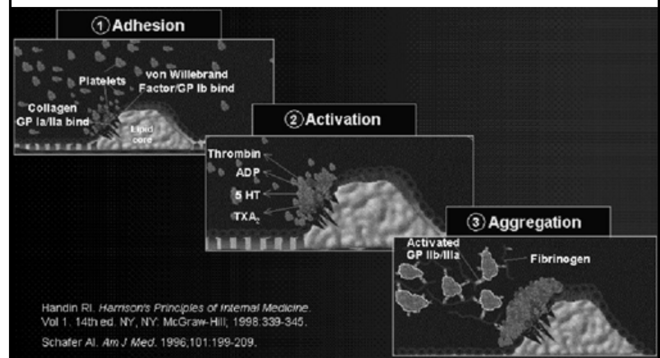


Hartmann A et al. Neurology. 2001;57:2000-2005

Thrombotic Stroke

Secondary Prevention

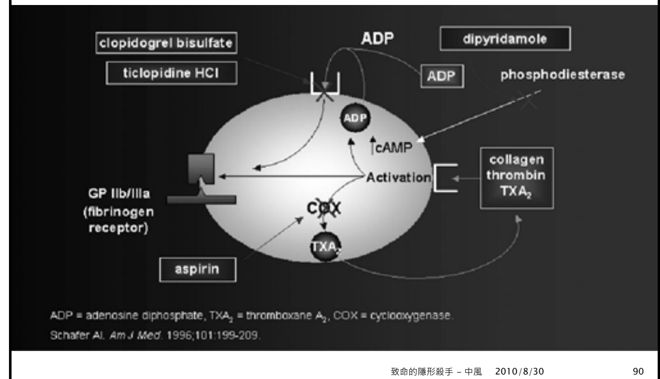
Platelet Cascade in Thrombus Formation



Antiplatelet Agents for Secondary Prevention of Noncardiogenic Stroke

- Three antiplatelet agents
  - Aspirin
  - Clopidogrel
  - Dipyridamole (in combination with aspirin)

Mechanisms of Action of Oral Antiplatelet Therapies



(Table 1)
Current Guidelines for Secondary Prevention of Stroke [14]

AHA/ASA Recommendations for Secondary Prevention of Stroke at a Glance

Class I Recommendations

For patients with noncardioembolic ischemic stroke or TIA, antiplatelet agents rather than oral anticoagulation agents are recommended to reduce the risk of recurrent stroke (*Class I, Level of Evidence A*)

Aspirin (50–325 mg/d) monotherapy, the combination of aspirin and extended-release dipyridamole, and clopidogrel are all acceptable options for initial therapy (*Class I, Level of Evidence A*)

The combination of aspirin and extended-release dipyridamole is recommended over aspirin alone (*Class I, Level of Evidence B*)

Class II Recommendations

Clopidogrel may be considered over aspirin alone on the basis of direct-comparison trials (*Class IIb, Level of Evidence B*)

For patients allergic to aspirin, clopidogrel is reasonable (*Class IIa, Level of Evidence B*)

Class III Recommendations

The addition of aspirin to clopidogrel increases the risk of hemorrhage. Combination therapy of aspirin and clopidogrel is not routinely recommended for ischemic stroke or TIA patients unless they have a specific indication for this therapy (*Class III*)

Abbreviations:

Update to the AHA/ASA recommendations for the prevention of stroke in patients with stroke and TIA. Stroke. 2008;39(5):1647-1652

Effects of Antiplatelet Therapy on Vascular Events

Category of Trial	No of Trials with Data	Vascular Events: Allocated Antiplatelet (%)	Vascular Events: Adjusted Control (%)	% Odds Reduction (SE)
Previous MI	12	13.5	17.0	25 (4)
Acute MI	15	10.4	14.2	30 (4)
Previous stroke/ transient ischemic attack	21	17.8	21.4	22 (4)
Acute stroke	7	8.2	9.1	11 (3)
Other high risk	140	8.0	10.2	26 (3)
Subtotal: all except acute stroke	188	11.7	14.8	25 (2)
All trials	**195**	**10.7**	**13.2**	**22 (2)**

Odds Ratio (CI) Antiplatelet:Control — 0, 0.5, 1.0, 1.5, 2.0; Antiplatelet better / Antiplatelet worse

Heterogeneity of odds reductions between:
5 categories of trial: $\chi^2 = 2.14$, df = 4, $P = 0.0003$
Acute stroke v other: $\chi^2 = 18.0$, df = 1; $P = 0.00002$

Treatment effect $P < 0.0001$

Antithrombotic Trialists' Collaboration. BMJ.2002;324:71-86

Aspirin

- Aspirin inhibits the cyclooxygenase enzyme, preventing the production of prostaglandin and thromboxane A2 (TXA2) from arachidonic acid.
- TXA2 activates the GP IIb/IIIa binding site on the platelet, allowing fibrinogen to bind.

Mechanisms of Action of Oral Antiplatelet Therapies

Aspirin – How Effective

- Secondary stroke risk reduction of 15% to 18% compared with placebo.
- TIA risk reduction of 22% compared with placebo.

Diener HC, et al. J Neurol Sci.1996;143(1-2):1-13
Johnson ES, et al.Arch Intern Med.1999;159(11):1248-1253

Efficacy of Aspirin Doses on Vascular Events in High Risk Patients

Aspirin Dose	# Trials	OR* (%)
500–1500 mg	34	19
160–325 mg	19	26
75–150 mg	12	32
<75 mg	3	13
Any aspirin	65	23

Odds Ratio — 0, 0.5, 1.0, 1.5, 2.0; Antiplatelet Better / Antiplatelet Worse

*Odds reduction.
Treatment effect $P < 0.0001$

Antithrombotic Trialists' Collaboration. BMJ.2002;324:71-86

CHARISMA post-hoc study, 2009

- 2009, post-hoc analysis of the Clopidogrel for High Atherothrombotic risk and Ischemic Stabilization Management, and Avoidance
- Assessed efficacy of various aspirin doses (75-162 mg daily) for primary prevention of cardiovascular disease
  - Regardless of aspirin dose, combined endpoint of death, MI, or stroke did not vary
  - Furthermore, no additional benefit with higher doses
  - Concluded: 75-81 mg likely provide best balance between efficacy and safety when used for long-term prevention

Steinhubl SR, et al. Ann Intern Med. 2009;150(6):379-386

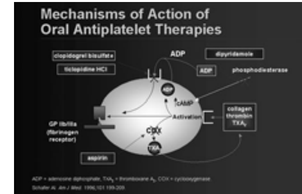
Current ASA/AHS Recommendation

- Aspirin (50–325 mg/d) monotherapy is an acceptable option for initial treatment for the prevention of stroke in patients with history of stroke or TIA (Class I, Level of Evidence A).

Update to the AHA/ASA recommendations for the prevention of stroke in patients with stroke and TIA. Stroke. 2008;39(5):1647–1652

Dipyridamole

- Directly stimulates prostacyclin synthesis
- Potentiates the platelet inhibitory actions of prostacyclin
- Inhibits phosphodiesterase to raise platelet cyclic AMP (cAMP) levels



Dipyridamole – ESPS2 Trial

Study Population	6602 patients with prior stroke or TIA in previous 3 months followed for 2 years
Primary End Points	Stroke (fatal and nonfatal) Stroke and/or death Death (all causes)
Treatments	Placebo Aspirin 25 mg bid (ASA) Dipyridamole 200 mg bid (DP) DP 200 mg bid + ASA 25 mg bid (DP/ASA)

Diener HC et al. J Neurol Sci. 1996;143:1–13

Dipyridamole – ESPS2 Trial

Pairwise Comparisons	Relative Risk Reduction (%)					
	Stroke	*P* value	Stroke or Death	*P* value	Death	*P* value
ASA vs placebo	18.1	0.013	13.2	0.016	10.9	NS
DP vs placebo	16.3	0.039	15.4	0.015	7.3	NS
DP + ASA vs placebo	37.0	<0.001	24.4	<0.001	8.5	NS
DP + ASA vs ASA	23.1	0.006	12.9	NS	-2.7	NS
DP + ASA vs DP	24.7	0.002	10.7	NS	1.3	NS

Diener HC et al. J Neurol Sci. 1996;143:1–13

Dipyridamole – Cochrane Review

- 29 Trials
- Dipyridamole alone does reduce the risk of vascular events but is no more efficacious than aspirin alone

Dipyridamole – ESPS2

- Dipyridamole alone was equally effective as aspirin alone
- High Dose Dipyridamole further reduce stroke when combined with aspirin (13.2% vs 9.9%)

De Schryver EL et al. Cochrane Database Syst Rev. 2003;(1):CD001820
Diener HC et al. J Neurol Sci. 1996;143:1–13

Dipyridamole – ESPRIT

- ESPRIT
  - 2006, European/Australasian Stroke Prevention in Reversible Ischemia Trial: RCT;2739 pts
  - Compared aspirin alone with aspirin plus extended-release dipyridamole for secondary stroke prevention
  - Additional 1% per-year absolute risk reduction when dipyridamole was added to aspirin

ESPRIT Study Group. Lancet.2006;367(9523):1665–1673

Dipyridamole – Meta-analysis

- Aspirin plus dipyridamole versus aspirin for prevention of vascular events after stroke or TIA: a meta-analysis
- 2009 meta-analysis
- Adding extended-release dipyridamole to aspirin
  - -> relative risk of 0.76 for stroke
  - -> relative risk of 0.82 for the composite endpoint of stroke, MI, or vascular death

Ro P et al. Stroke2008;39(4):1358-1363

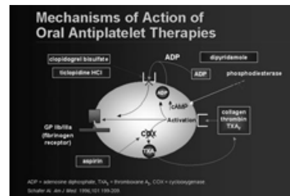
Current ASA/AHS Recommendation

- The combination of aspirin and extended-release dipyridamole is an acceptable option for initial treatment for the prevention of stroke in patients with history of stroke or TIA (Class I, Level of Evidence A).
- The combination of aspirin and extended-release dipyridamole is recommended over aspirin alone (Class I, Level of Evidence B).

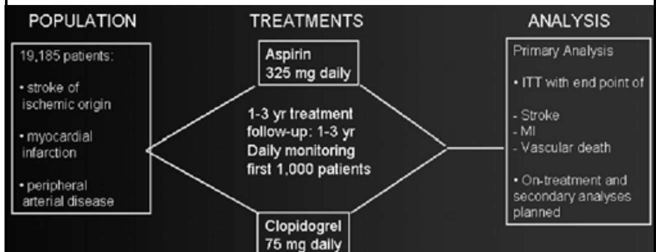
Update to the AHA/ASA recommendations for the prevention of stroke in patients with stroke and TIA. Stroke. 2008;39(5):1647-1652

Clopidogrel

- Irreversibly blocks binding of ADP to platelet receptors
- Blocking of these receptors impedes platelet aggregation and activation of the GP IIb/IIIa complex

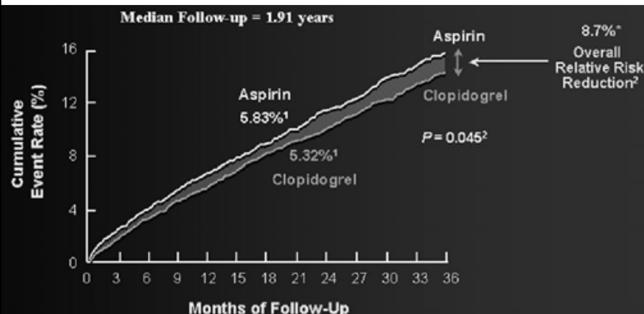


Clopidogrel – CAPRIE



CAPRIE Steering Committee. Lancet. 1996;348:1329-1339

Clopidogrel – CAPRIE



CAPRIE Steering Committee. Lancet. 1996;348:1329-1339

Clopidogrel – PRoFESS

- 2008, the Prevention Regimen for Effectively Avoiding Second Strokes trial
- Randomized, placebo-controlled trial, 20332 patients with history of ischemic stroke
- [25 mg aspirin + 200 mg extended-release dipyridamole] bid vs 75 mg Clopidogrel qd
- Primary outcome: first recurrence of any stroke

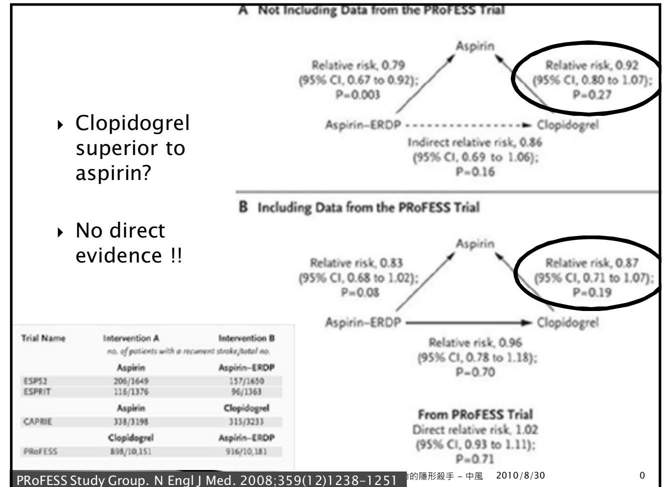
PRoFESS Study Group. N Engl J Med. 2008;359(12)1238-1251

Clopidogrel – PRoFESS

- Incidence of recurrent stroke in both groups **essentially identical**:
  - 9% in ASA-ERDP vs 8.8% in clopidogrel grp
- Overall net risk of recurrent stroke or major hemorrhagic event similar too:
  - 11.7% in ASA-ERDP vs 13.1%

PRoFESS Study Group. N Engl J Med. 2008;359(12)1238-1251

- Clopidogrel superior to aspirin?
- No direct evidence !!



Trial Name	Intervention A	Intervention B
	no. of patients with a recurrent stroke/total no.	
	Aspirin	**Aspirin–ERDP**
ESPS2	206/1649	157/1650
ESPRIT	116/1376	96/1363
	Aspirin	**Clopidogrel**
CAPRIE	338/3198	315/3233
	Clopidogrel	**Aspirin–ERDP**
PRoFESS	898/10,151	916/10,181

PRoFESS Study Group. N Engl J Med. 2008;359(12)1238-1251

Current ASA/AHS Recommendation

- Clopidogrel monotherapy is an acceptable option for initial treatment for the prevention of stroke in patients with history of stroke or TIA (Class I, Level of Evidence A).
- Clopidogrel may be considered over aspirin alone on the basis of direct-comparison trials (Class IIb, Level of Evidence B).
- For patients allergic to aspirin, clopidogrel is reasonable (Class IIa, Level of Evidence B).

Update to the AHA/ASA recommendations for the prevention of stroke in patients with stroke and TIA. Stroke. 2008;39(5):1647-1652

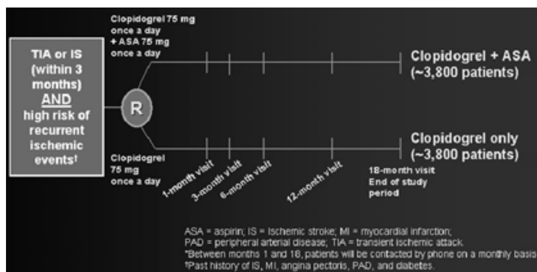
Aspirin + Clopidogrel

- CURE (2001, Clopidogrel in Unstable Angina to Prevent Recurrent Events)
  - Clopidogrel + Aspirin decreased the rates of serious vascular events in patients who have had acute coronary syndrone and percutaneous coronary intervention)

Yusuf s et al. N Engl J Med. 2001;345(7)494-502

Aspirin + Clopidogrel

- MATCH (2004, Management of Atherothrombosis with Clopidogrel in High-Risk Patients)



Hacke W. Cerebrovasc Dis.2002;13:22-26

Aspirin + Clopidogrel – MATCH

- Nonsignificant reduction in vascular events
- A significant increase in life-threatening bleeding that offset any potential benefit
- The only completed RCT investigating aspirin/clopidogrel combination for 2nd stroke prevention
- Limitation:
  - Majority of strokes microangiopathic and "might not be of pure atherothrombotic origin"

Diener HC et al. Lancet. 2004;364(9431):331-337

Current ASA/AHS Recommendation

- The addition of aspirin to clopidogrel increases the risk of hemorrhage. Combination therapy of aspirin and clopidogrel is not routinely recommended for ischemic stroke or TIA patients unless they have a specific indication for this therapy (ie, coronary stent or acute coronary syndrome) (Class III).

Update to the AHA/ASA recommendations for the prevention of stroke in patients with stroke and TIA. Stroke. 2008;39(5):1647-1652

Embolic Stroke

Secondary Prevention

Warfarin for the Prevention of Cardioembolic Stroke

- Atrial fibrillation – leading cause of cardiac embolism, accounted for 50% of cardiogenic emboli
- Oral anticoagulation is effective for primary and secondary prevention of stroke in patients with atrial fibrillation
- Warfarin (INR of 2.5) is effective for the prevention of cardioembolic stroke in high risk patients

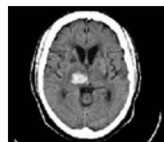
Albers GW, et al. Chest. 2001;119:300S-320S

出血性腦中風

- 臨床症狀
  - 突發的局部神經症狀
    - 常併有頭痛（40%）
    - 噁心嘔吐（35%）
    - 血壓偏高（87%）
    - 意識障礙（50%）
    - 少數會有癲癇發作現象(6.1%)
  - 約35% 的病人早期症狀會有惡化的現象，此乃發作6小時內持續出血而致血塊擴大

出血性腦中風

- 不宜外科手術的情況
  - 小出血（<10 cc）或神經症狀很輕微者
  - 但需注意觀察超急性ICH（< 3 小時）常會有擴大情況
  - 昏迷指數（GCS）< 5，表示已太嚴重，手術效果均不好
    - 但若為小腦出血壓迫腦幹時，就另當別論，需緊急開刀。
  - 視丘或腦幹出血
    - 除非產生水腦症，需做引流手術外，以不採開顱手術為原則
    - 其他的手術療法，如內視鏡或立體定位手術等可能可施用於視丘或腦幹出血，但需有更多的臨床證據來支持



出血性腦中風

- 宜外科手術者
  - 小腦出血 > 3 cc 或 > 30 cc且有症狀惡化現象，如壓迫腦幹或造成水腦症時
  - 動脈瘤（Aneurysm）
動靜脈畸形（AVM）
海綿狀血管瘤（cavernous hemangioma）
等特殊腦血管病變所造成的腦出血時，可**視情況**做外科手術

出血性腦中風

- 宜外科手術者
  - 較年青的病患（＜60歲者）
  - 中度至重度的腦葉或基底核的腦出血（lobar or basal ganglion hemorrhage）
    - 出血量超過 50 cc, GCS ≦ 14
    - 出血量 30-50 cc, GCS ＜ 12可考慮外科手術。
- 而 30 cc 以下或高齡患者則視個別情況而定

腦中風的復健

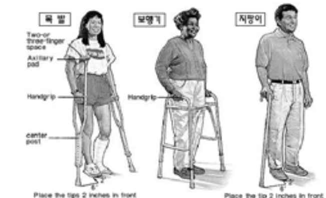
- 積極的物理治療
- 幫忙恢復部分喪失的功能
  - 如何在一腳乏力的情況下走路，或一手乏力的情況下拿東西

腦中風的復健

- 幫忙發掘新功能
  - 如運用沒中風的另一邊的手、腳
- 如何盡量恢復獨立能力及回到工作崗位
- 對病人及家屬的鼓勵精神支持
- 中風後前三至六個月進步的空間最大
- 半年後進步就會緩慢下來

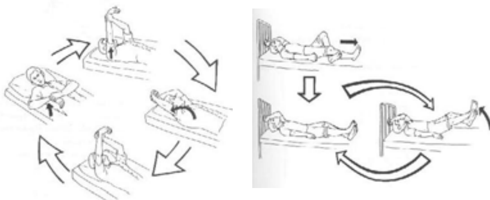
腦中風的復健

- 接下來的一到兩年還會有陸陸續續的進步
- 每個人恢復的速度會有很大的差別
  - 中風的種類
  - 影響的位置
  - 範圍的大小
  - 身體的健康
  - 動機



何時可以開始復健

- 在非危急的情況下，應該可以馬上開始
  - 病人清醒，可以配合復健醫師及復健師的指導及治療
- 開始時時間可能會比較短，但會隨著病情穩定而延長
- 意識不清或病情較重的病人，也可以做被動式的肢體復健



急性腦中風期的吞嚥功能

- 吞嚥功能障礙是引起吸入性肺炎的主因
- 在醫師評估前儘量不要讓病人進食
- 如果要的話，先試小口清水，看有沒有咳嗽等嗆到的徵兆
- 如吞嚥不好不可勉強以口進食
- 如意識不清也需要以鼻胃管灌食

如何預防腦中風

- 腦中風高危險群
  - 高血壓
  - 抽煙
  - 高血脂
  - 頸動脈狹窄
  - 糖尿病
  - 心臟病
  - 年齡
  - 缺乏運動

殆

預後

- 6-Month Survivors: ~1/3 independent
- 約15%完全康復
- 至少有一半會恢復很好的功能

謝謝