Secondary stroke Prevention

what you (don't) need to know

David Spriggs

Physician Auckland Hospital

TIA Management

Recurrence rate (early)

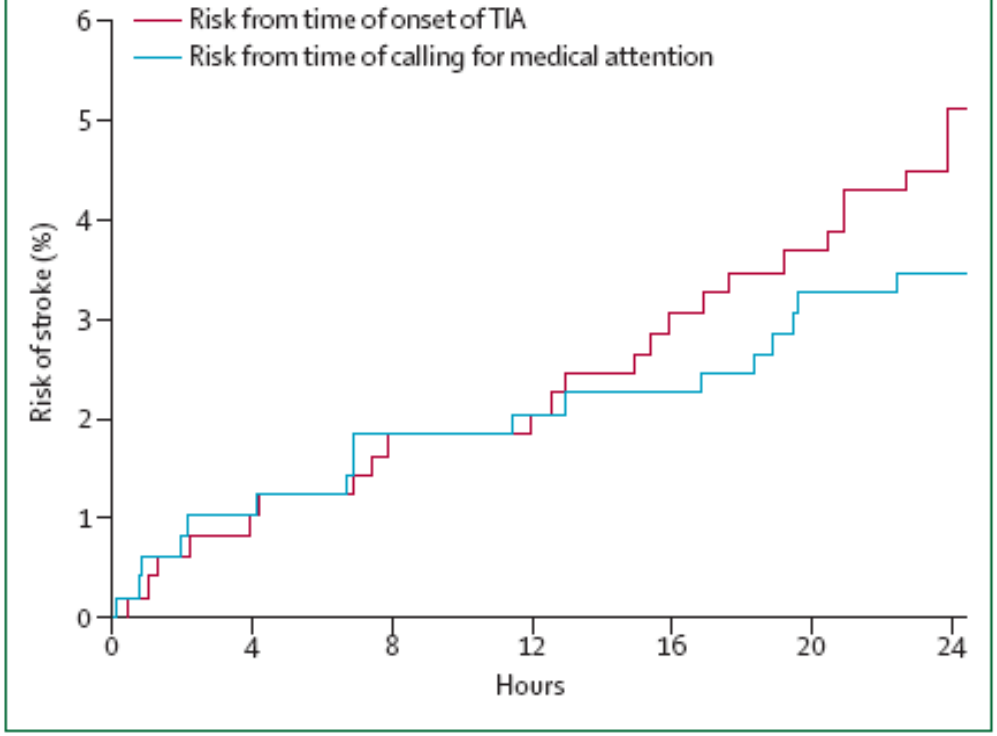


Figure 2: **The risk of stroke during the first 24 h after a TIA in a population-based study of 488 patients with first-ever TIAs[16]**
TIA=transient ischaemic attack.

Rothwell Lancet 2011;377:1681

Recurrence rate (Late)

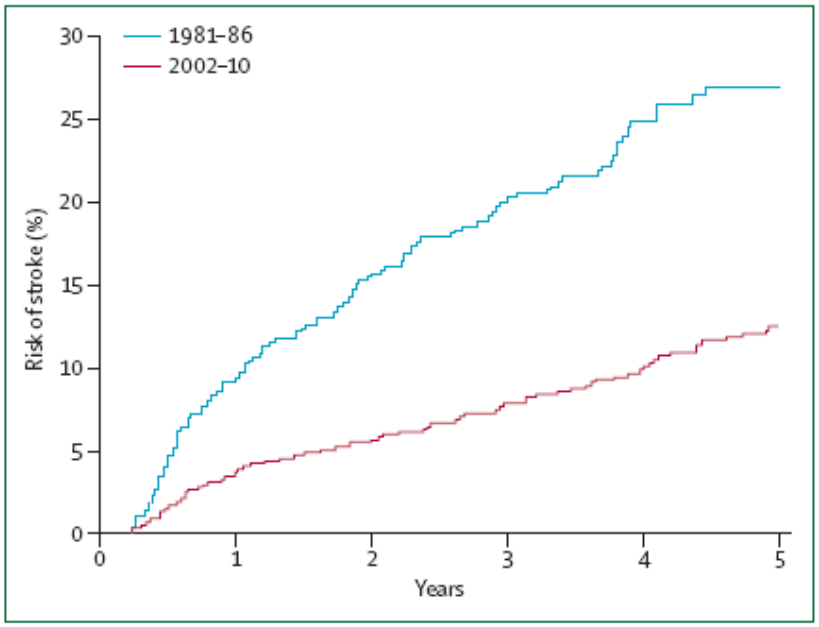


Figure 1: **The post-90 day 5-year risk of recurrent stroke after a first-ever TIA or non-disabling ischaemic stroke in the same population in 1981–86 and during 2002–10[8]**

Data for 1981–86 are from the Oxfordshire Community Stroke Project, and for 2002–10 are from the Oxford Vascular Study. TIA=transient ischaemic attack.

Rothwell Lancet 2011;377:1681

ABCD^2 Score for TIAs

	Risk factor	Category	Score
A	**A**ge	Age≥60	**1**
		Age<60	**0**
B	**B**lood pressure at assessment	SBP>140 or DBP≥90	**1**
		Other	**0**
C	**C**linical Features	Unilateral weakness	**2**
		Speech disturbance (no weakness)	**1**
		Other	**0**
D	**D**uration	≥60 minutes	**2**
		10-59 minutes	**1**
		<10 minutes	**0**
	Diabetes		**1**
	TOTAL		**7**

Predictive Value ABCD^2

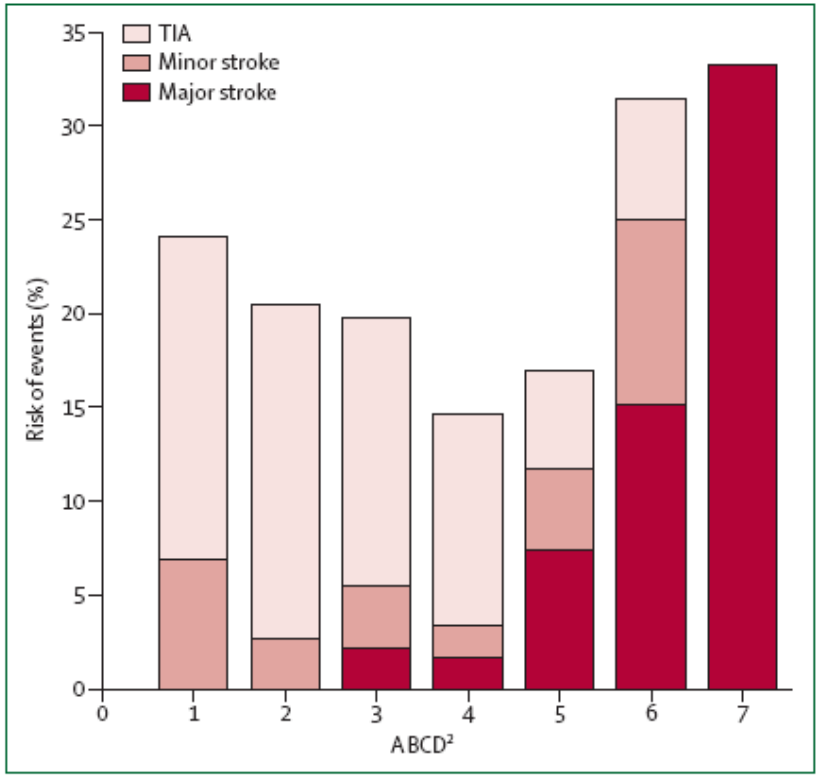


Figure 3: Population-based study of the predictive value of the ABCD^2 score for 7-day risk of recurrent stroke (n=50) and recurrent TIA (n=55) in 500 consecutive patients presenting with TIA[21]

Rothwell Lancet 2011;377:1681


THIS IS FINE, I CAN SEE ALL THE EVIDENCE I NEED FROM HERE
COST-EFFECTIVENESS
EFFECTIVENESS
EFFICACY
COCHRANE LADDER of EVIDENCE

Validation of ABCD2 Score

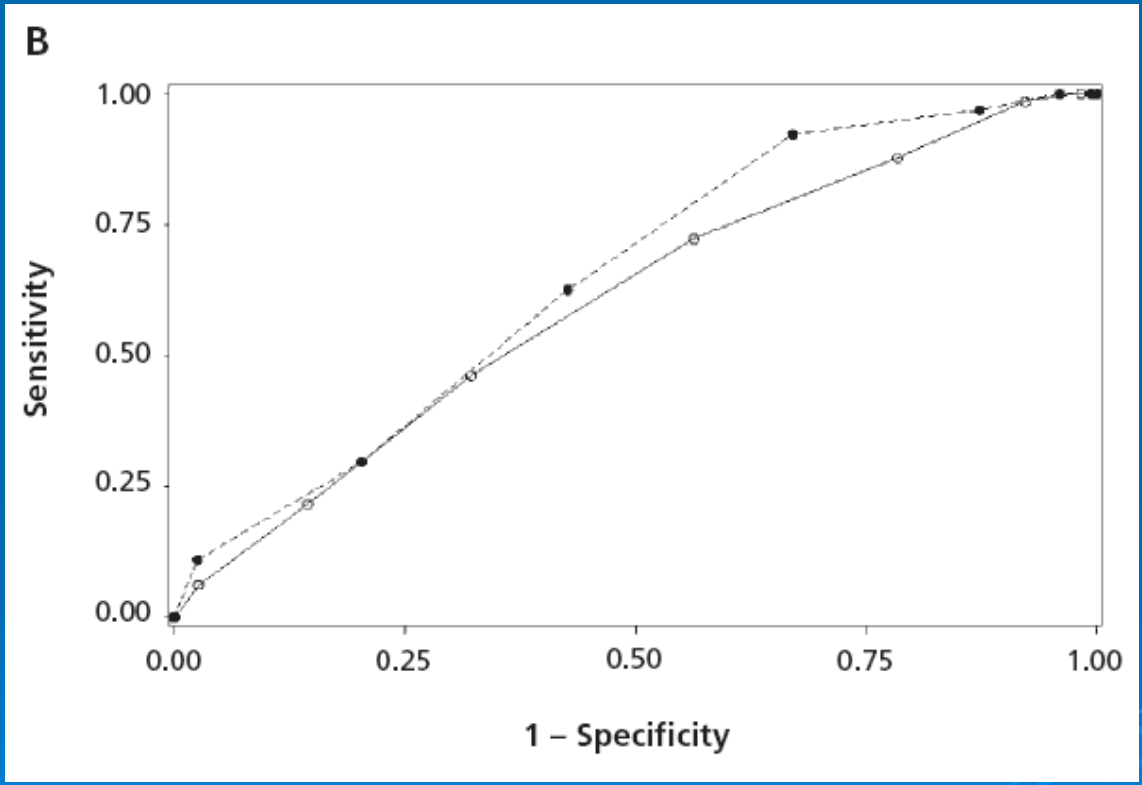
Table 4: Performance of stratified, standardized, ABCD2 scores as a predictor of stroke at 7 and 90 days among 2032 patients with transient ischemic attack

ABCD2 threshold for high risk	Stroke at 7 d *n = 38*		Stroke at 90 d *n = 65*	
	Sensitivity, % (95%CI)	Specificity, % (95%CI)	Sensitivity, % (95%CI)	Specificity, % (95%CI)
> 0	100.0 (90.8–100)	0.7 (0.4–1.1)	100.0 (94.4–100)	0.7 (0.4–1.1)
> 1	100.0 (90.8–100)	4.0 (3.2–4.9)	100.0 (94.4–100)	4.0 (3.1–5.0)
> 2*	94.7 (82.7–98.5)	12.5 (11.2–14.1)	96.9 (89.3–99.1)	12.7 (11.3–14.3)
> 3	92.1 (79.2–97.3)	32.7 (30.6–34.7)	92.3 (83.2–96.8)	33.0 (30.9–35.1)
> 4	65.8 (49.9–78.8)	57.2 (55.0–59.3)	63.1 (50.9–73.8)	57.4 (55.2–59.6)
> 5†	31.6 (19.1–47.5)	86.9 (85.3–88.3)	29.2 (19.6–41.2)	79.7 (77.9–81.4)
> 6	10.5 (4.2–24.1)	97.3 (96.5–97.9)	10.8 (53.2–20.6)	97.4 (96.6–98.0)

Note: CI = confidence interval.
*Threshold for defining high risk as recommended by the American Heart Association.
†Threshold for defining high risk as recommended in the original publication of the ABCD2 score.

CMAJ 2011. DOI:10.1503

ROC for ABCD2 for Stroke at 90 days



CMAJ 2011. DOI:10.1503

7 day risk of stroke

ADHB TIA guideline

Score	Risk
<=3	1.2%
4-5	6%
6-7	12%

Express Study

Rothwell et al Lancet 2007;370:1432

- Stroke and TIA patients
- Out-patient and in-patient care
- Before (n=634) vs after (n=644)
- Rapid assessment (median 3 vs <1 day)
- Early initiation of treatment (median 20 vs 1 day)

EXPRESS Results

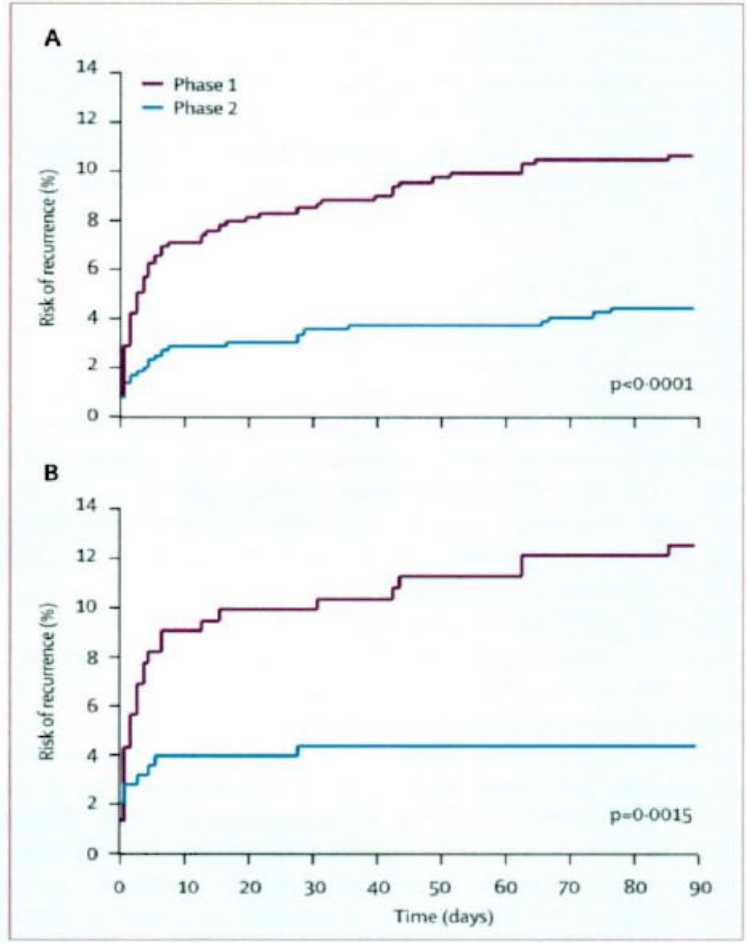


Figure 1: **Risk of recurrent stroke after first seeking medical attention in all patients with TIA or stroke in the whole study population (A) and in all patients with TIA (B)**

Rothwell et al Lancet 2007;370:1432

Secondary Prevention

Anti-platelets

Aspirin

Vs

Dipyridamole + Aspirin

Vs

Clopidogrel

PRoFESS

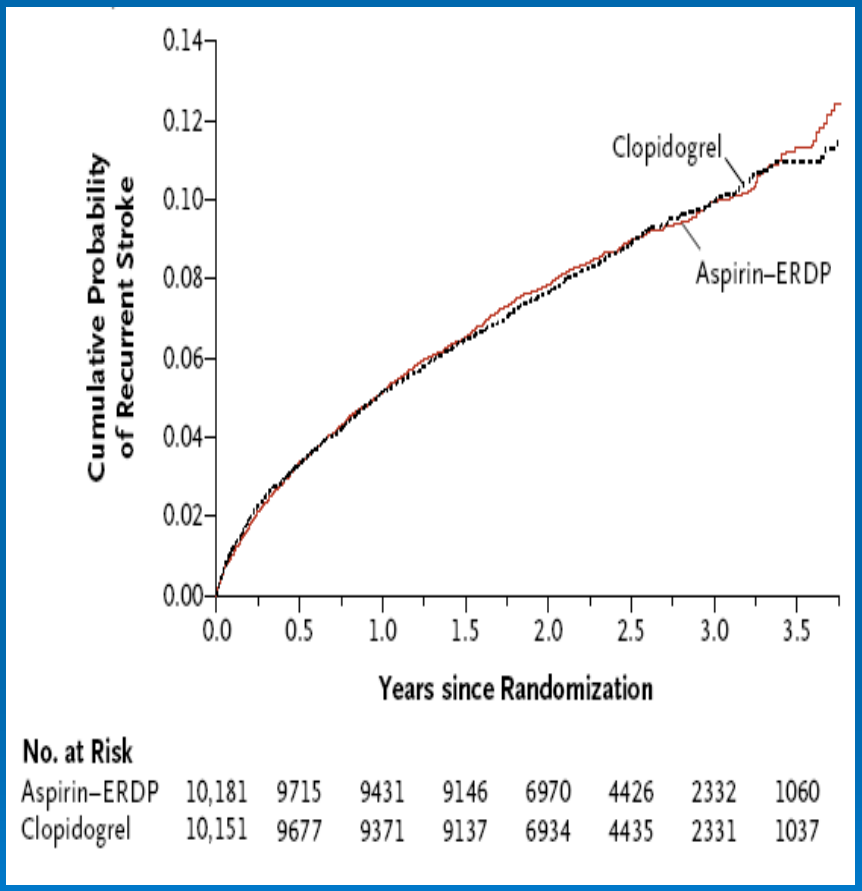
Sacco et al NEJM 2008;359:1238

- Very large (n=20,332) post Stroke/TIA
- FU 2.5 years
- Mean age 66
- Aspirin 25mg/day and Dipyridamole 200mg bd vs Clopidogrel 75mg/day
- End Point Recurrent Stroke

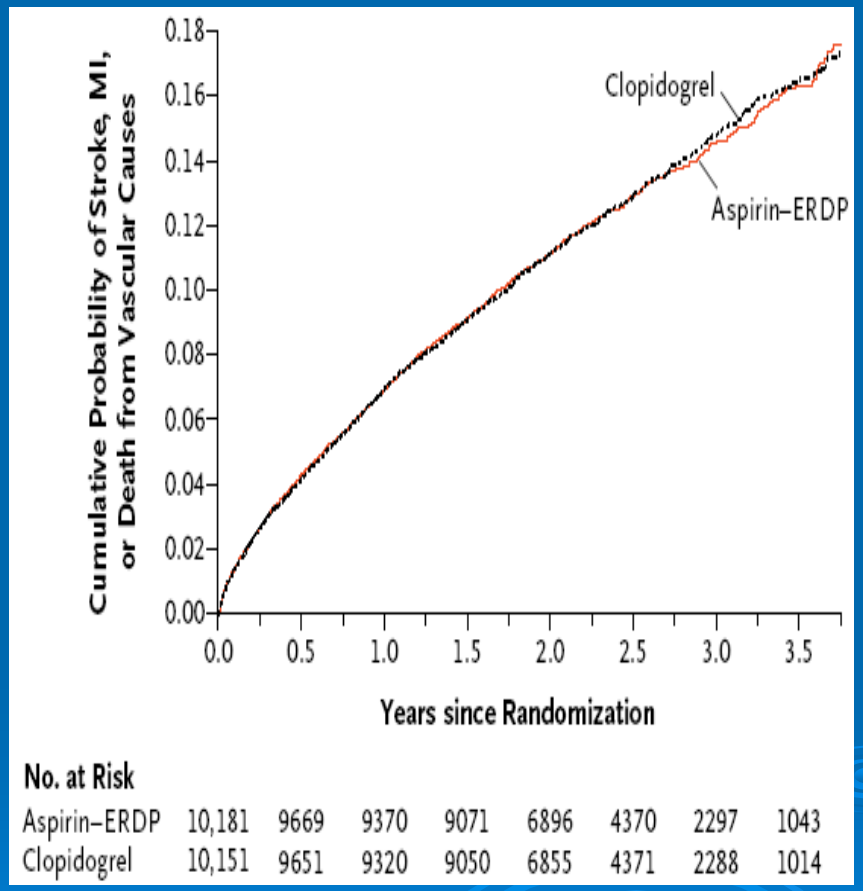
NB Low dose aspirin and young patients

PRoFESS Results

Primary



Secondary



NEJM 2008;359:1238

Adverse Events PRoFESS

Table 3. Incidence of Selected Adverse Events Leading to Permanent Discontinuation of Study Medications.*

Variable	Aspirin–ERDP	Clopidogrel
	number (percent)	
Patients receiving antiplatelet medication	10,055 (100.0)	10,040 (100.0)
Patients with adverse events leading to treatment discontinuation	1,650 (16.4)	1,069 (10.6)
Headache	593 (5.9)	87 (0.9)
Vomiting	158 (1.6)	37 (0.4)
Nausea	155 (1.5)	58 (0.6)
Dizziness	134 (1.3)	52 (0.5)
Atrial fibrillation	122 (1.2)	143 (1.4)
Diarrhea	102 (1.0)	42 (0.4)
Hypotension	54 (0.5)	35 (0.3)

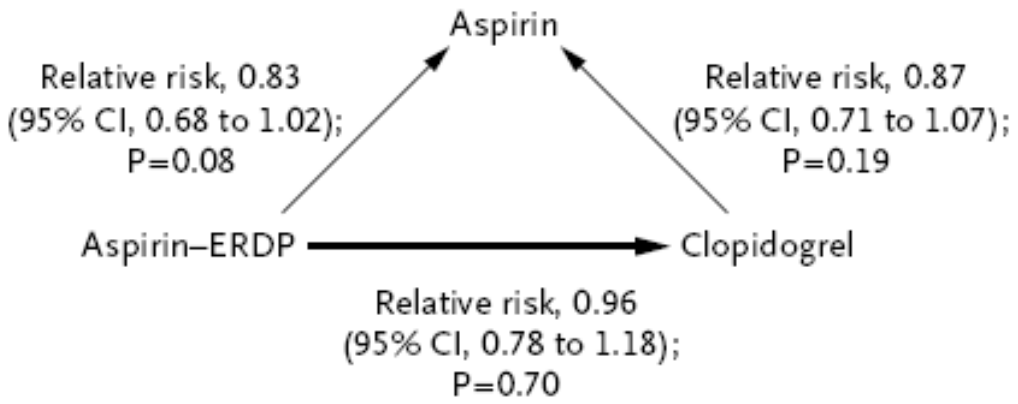
NEJM 2008;359:1238

Major Secondary prevention trials

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

NEJM 2008;359:1287

Comparative effects



NEJM 2008;359:1287

MATCH

- 7499 patients with Stroke or TIA
- Clopidogrel 75mgs vs ASA 75mgs and clopidogrel 75 mgs
- FU 18 months
- End points IS,MI,Vascular Death, Hospitalisation for acute ischeamia
- Absolute risk reduction 1% (NS)
- Absulute risk increase of ICH 1.3% (NS)

Current recommendation

- On diagnosis of TIA/Ischaemic Stroke:

- Stop Aspirin etc
- Give Clopidogrel 300mg stat and then 75mg daily
- Unless contemplating acute intervention or anticoagulants

AF and Anticoagulation

Atrial Fibrillation

- Primary prevention CHADS2 Score
  - Heart Failure =1
  - Hypertension =1
  - Age >75 =1
  - Diabetes =1
  - Stroke =2
  - **Total** **6**

  Scores >=2 suggest risk/benefit in favour of Anticoagulation

- Secondary prevention, All require consideration of Warfarin

Warfarin

- Indications

  Definite AF (INR range 2.0-3.0)

  Only possible in about 50% patients

  MS +/- AF (INR 2.0-3.0)

  Prosthetic heart valves (INR 2.5-3.5)

  Probable Mural Thrombus

  Arterial dissection

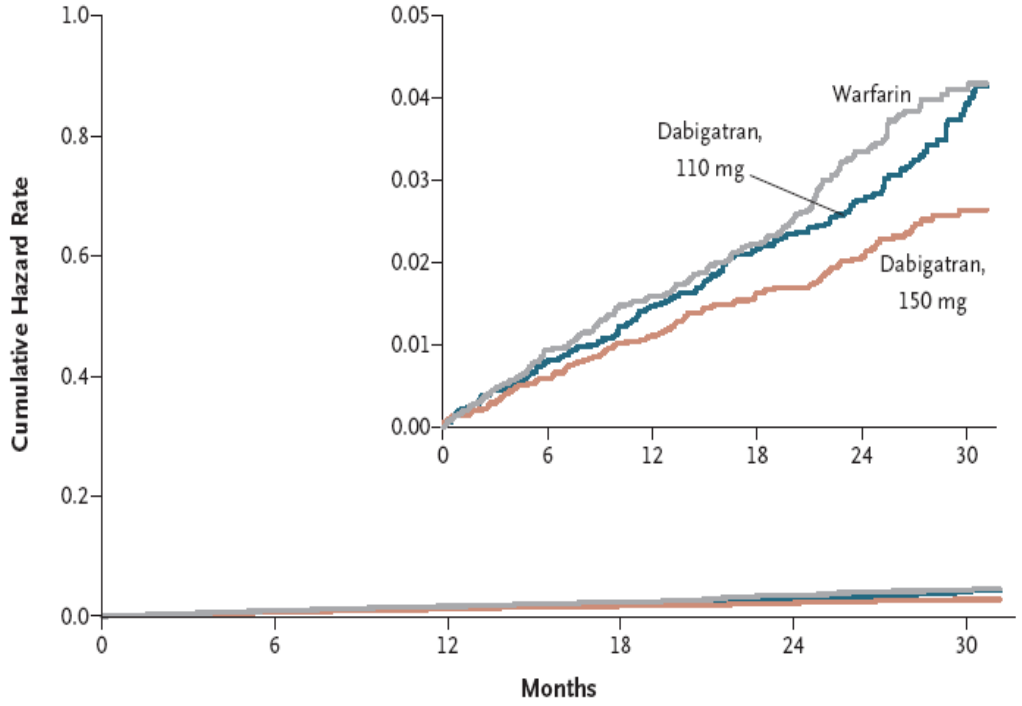
  Usually for 3-6 months, INR 2.0-3.0 but not evidence based.

RE-LY study

Connolly NEJM 2009;361:1139

- Warfarin vs Dabigatran 110mgs bd vs 150 mgs bd
  - Pro-drug of direct thrombin inhibitor
- Mean age 71.5 years
- AF “at risk of stroke”
  - 20% had already had Stroke or TIA
- GFR >30 mls/min
- FU 2 years

Result – Emboli and stroke



No. at Risk						
Warfarin	6022	5862	5718	4593	2890	1322
Dabigatran, 110 mg	6015	5862	5710	4593	2945	1385
Dabigatran, 150 mg	6076	5939	5779	4682	3044	1429

Figure 1. Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group.

Safety

Table 3. Safety Outcomes, According to Treatment Group.*

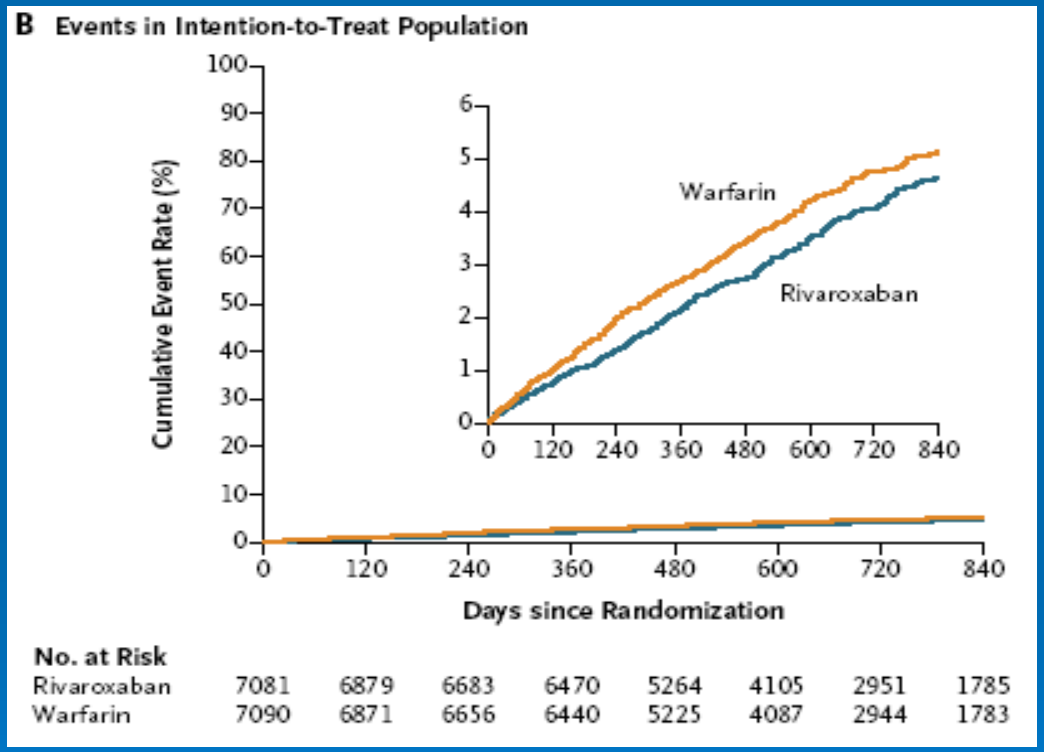
Event	Dabigatran, 110 mg		Dabigatran, 150 mg		Warfarin		Dabigatran, 110 mg, vs. Warfarin		Dabigatran, 150 mg, vs. Warfarin		Dabigatran, 150 mg vs. 110 mg	
							Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
	no. of patients	%/yr	*no. of patients*	%/yr	*no. of patients*	%/yr						
Major bleeding	322	2.71	375	3.11	397	3.36	0.80 (0.69–0.93)	0.003	0.93 (0.81–1.07)	0.31	1.16 (1.00–1.34)	0.052
Life threatening	145	1.22	175	1.45	212	1.80	0.68 (0.55–0.83)	<0.001	0.81 (0.66–0.99)	0.04	1.19 (0.96–1.49)	0.11
Non–life threatening	198	1.66	226	1.88	208	1.76	0.94 (0.78–1.15)	0.56	1.07 (0.89–1.29)	0.47	1.14 (0.95–1.39)	0.17
Gastrointestinal†	133	1.12	182	1.51	120	1.02	1.10 (0.86–1.41)	0.43	1.50 (1.19–1.89)	<0.001	1.36 (1.09–1.70)	0.007
Minor bleeding	1566	13.16	1787	14.84	1931	16.37	0.79 (0.74–0.84)	<0.001	0.91 (0.85–0.97)	0.005	1.16 (1.08–1.24)	<0.001
Major or minor bleeding	1740	14.62	1977	16.42	2142	18.15	0.78 (0.74–0.83)	<0.001	0.91 (0.86–0.97)	0.002	1.16 (1.09–1.23)	<0.001
Intracranial bleeding	27	0.23	36	0.30	87	0.74	0.31 (0.20–0.47)	<0.001	0.40 (0.27–0.60)	<0.001	1.32 (0.80–2.17)	0.28
Extracranial bleeding	299	2.51	342	2.84	315	2.67	0.94 (0.80–1.10)	0.45	1.07 (0.92–1.25)	0.38	1.14 (0.97–1.33)	0.11
Net clinical benefit outcome‡	844	7.09	832	6.91	901	7.64	0.92 (0.84–1.02)	0.10	0.91 (0.82–1.00)	0.04	0.98 (0.89–1.08)	0.66

ROCKET AF

Patel NEJM 10th Aug 2011

- Warfarin vs Rivaroxaban (Xa inhibitor)
- AF (54% previous stroke)
- Mean age 73
- N=14,265
- Follow up 700 days

Outcome – Stroke and embolism



Safety

Table 3. Rates of Bleeding Events.*

Variable	Rivaroxaban (N=7111)		Warfarin (N=7125)		Hazard Ratio (95% CI)†	P Value‡
	Events	Event Rate	Events	Event Rate		
	no. (%)	*no./100 patient-yr*	*no. (%)*	*no./100 patient-yr*		
Principal safety end point: major and nonmajor clinically relevant bleeding§	1475 (20.7)	14.9	1449 (20.3)	14.5	1.03 (0.96–1.11)	0.44
Major bleeding						
Any	395 (5.6)	3.6	386 (5.4)	3.4	1.04 (0.90–1.20)	0.58
Decrease in hemoglobin ≥2 g/dl	305 (4.3)	2.8	254 (3.6)	2.3	1.22 (1.03–1.44)	0.02
Transfusion	183 (2.6)	1.6	149 (2.1)	1.3	1.25 (1.01–1.55)	0.04
Critical bleeding¶	91 (1.3)	0.8	133 (1.9)	1.2	0.69 (0.53–0.91)	0.007
Fatal bleeding	27 (0.4)	0.2	55 (0.8)	0.5	0.50 (0.31–0.79)	0.003
Intracranial hemorrhage	55 (0.8)	0.5	84 (1.2)	0.7	0.67 (0.47–0.93)	0.02
Nonmajor clinically relevant bleeding	1185 (16.7)	11.8	1151 (16.2)	11.4	1.04 (0.96–1.13)	0.35

Current Data

- Dabigatran introduced 1st July
- ADHB 11 admission with bleed
- 4 have died during that admission

- I Thrombosis on Dabigatran
- 2 Thromboses on recent Dabi withdrawal

Anticoagulants - summary

- Warfarin is drug of choice
- Two new oral antithrombotics may become useful
  - NO monitoring
  - Fewer interactions
  - Possibly few Intra-cerebral bleeds.
  - BEWARE

BP, Diabetes and Cholesterol

Guideline Epidemic I

- 2002-2010
- 117 guidelines on prevention and treatment of cardiovascular disease

Proportion of guidelines dealing with management of risk factors for cardiovascular disease, and completeness of monitoring recommendation

Risk factor	No (%) with section on risk factor	No (%) including monitoring	No (%) with section on management	Completeness of monitoring recommendation: What to monitor: Not reported	What to monitor: Non-specific*	What to monitor: Specific	When to monitor: Not reported	When to monitor: Non-specific*	When to monitor: Specific	What to do if target is out of range: Not reported	What to do if target is out of range: Non-specific*	What to do if target is out of range: Specific
Lipids	84 (72)	53 (63)	34 (40)	31†	13	40	31†	12	41	31	23	30
Hypertension	79 (68)	40 (51)	26 (32)	39	11	29	39	12	28	39	16	24
Smoking	65 (55)	37 (57)	19 (29)	35	–	30	28	17	20	28	14	23

*Not useful in practice.
†44 guidelines provided no information or non-specific information.

BMJ 2011;342:d1289

Guideline Epidemic II

WHAT THIS STUDY ADDS

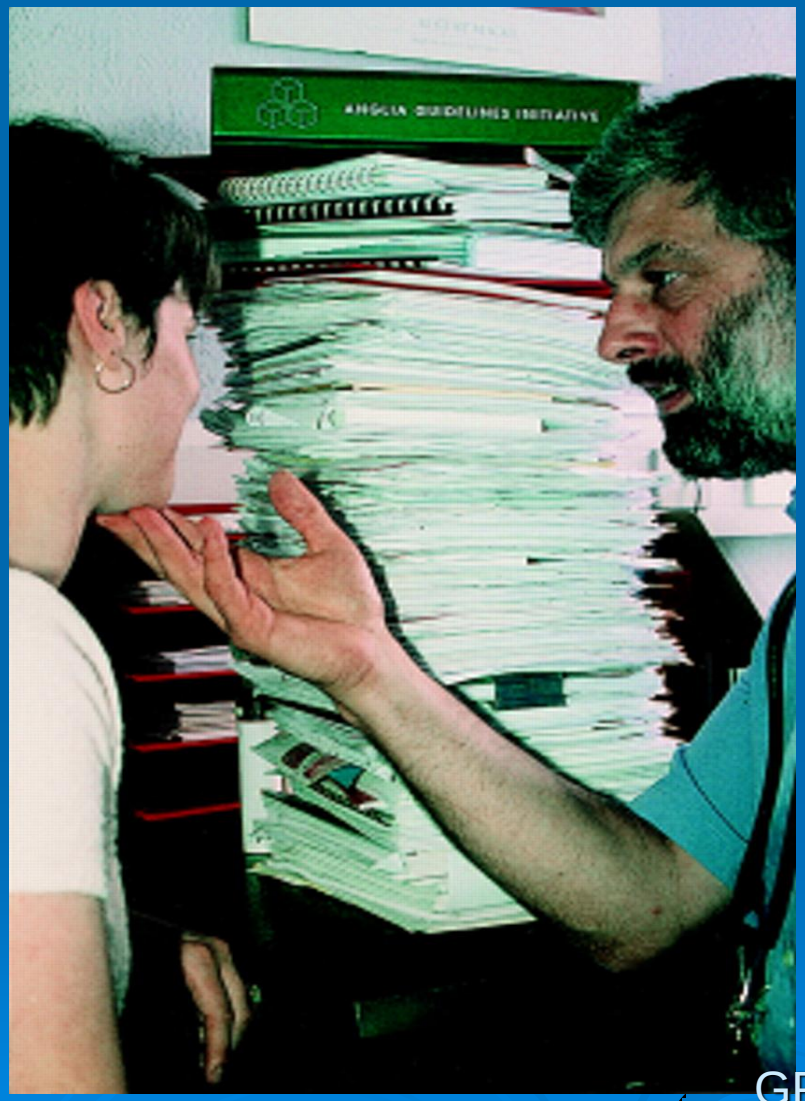
Only a fifth (23/117) of English language guidelines published or updated between 2002 and February 2009 dealt with monitoring of all three risk factors, and one or more risk factors was missing from more than half the guidelines

The monitoring recommendations in different guidelines were often confusing and contradictory

It was rare to find a clear description of the monitoring phase in any guideline that would help clinicians to apply the recommendations directly in clinical practice

BMJ 2011;342:d1289

21st Century Tower of Babel



GPs with 855 Guidelines

Hibble, A. et al. BMJ 317:862-863

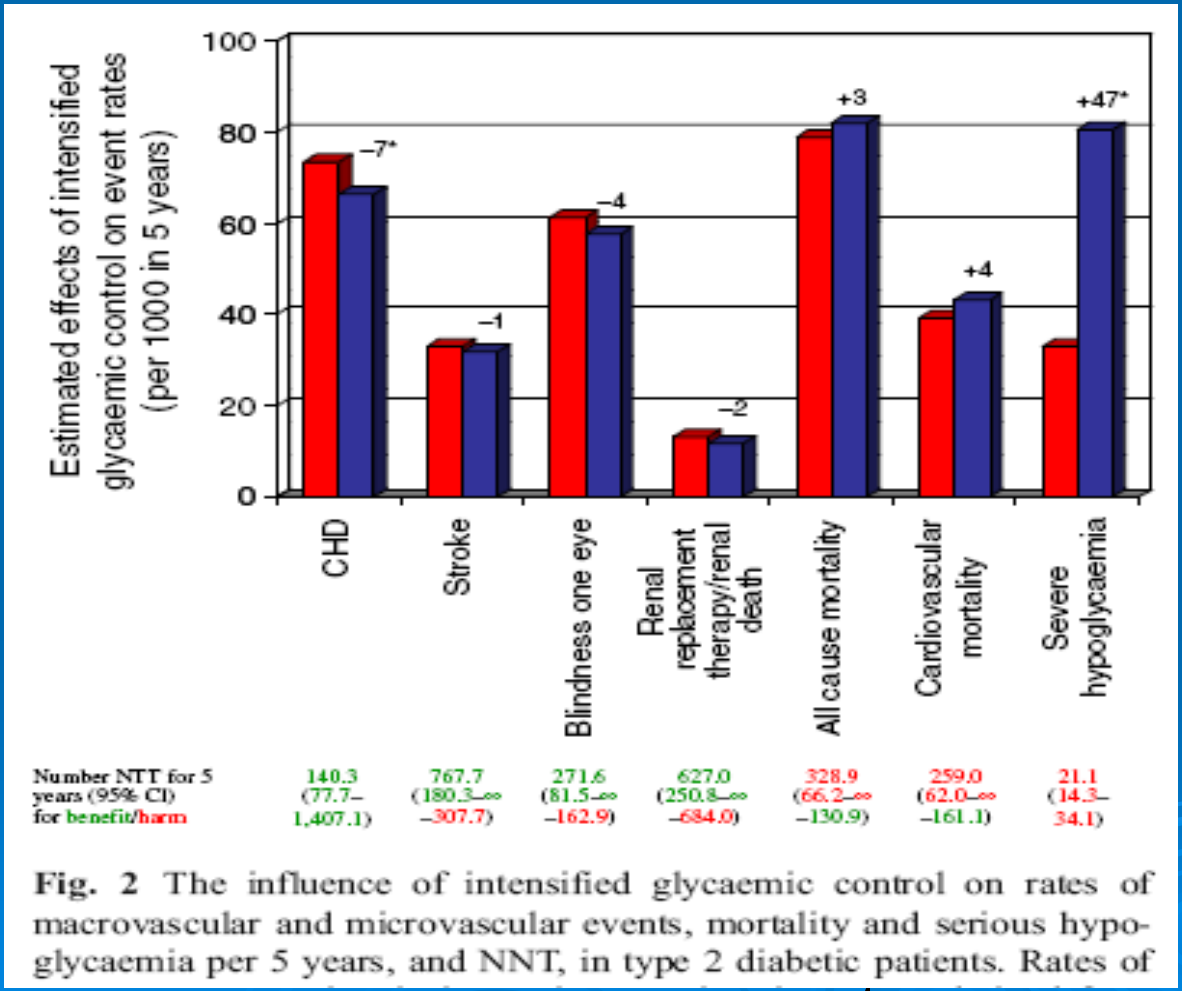
GP CME Conf 2012

Diabetes

- No evidence about early management

- Secondary prevention
  - No trials
  - Tight control might reduce recurrent macrovascular events
  - Tight control does reduce microvascular events

Harms and benefits of intensive glucose control



Standard
Intensive

Fig. 2 The influence of intensified glycaemic control on rates of macrovascular and microvascular events, mortality and serious hypoglycaemia per 5 years, and NNT, in type 2 diabetic patients. Rates of

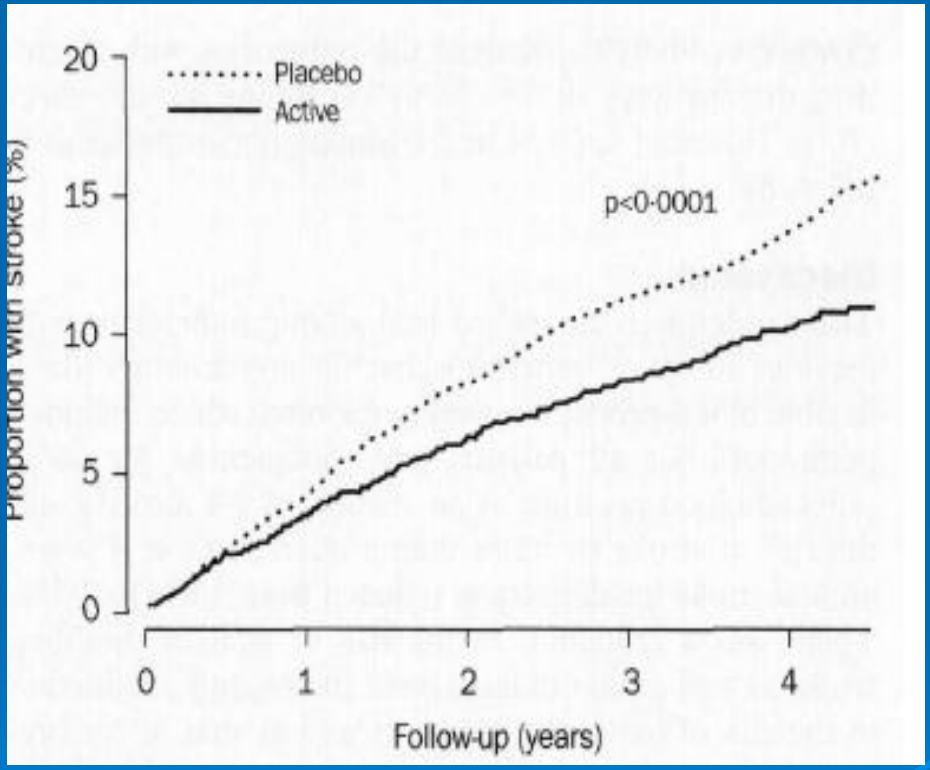
Diabetalogia 2010:53;2079

Blood Pressure

- PROGRESS
  - 6105 patients FU for 4 years
  - Treatment with Perindolpril and Indapamide
  - 28% relative risk reduction
  - 3.7% absolute reduction

NNT=27 (in those with the lowest STARTING BP NNT=23)

Secondary Prevention PROGRESS Study



Secondary Prevention Hypertension

- Effect of treatment is Independent of starting BP
- Usually need 2 agents
- ? Perindopril (and possibly all ACEs) not effective on its own
- The lower the better
- Why measure?

Variability of BP

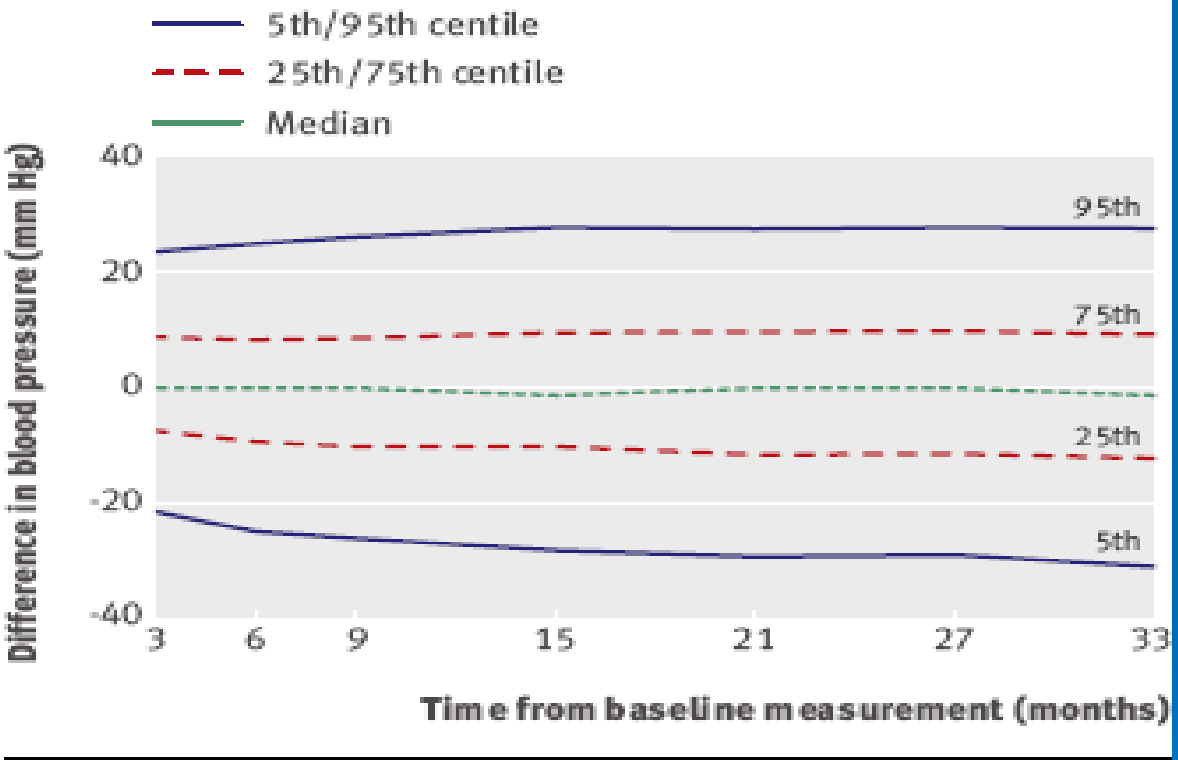


Fig 1 | Difference in systolic blood pressure (mm Hg) from baseline measurement to subsequent measurements over time to 33 months in those receiving dual treatment

BMJ 2009;338:b1492

Cholesterol

- Heart Protection Study
  3280 patients with CVD
  Treated with 40mg Simvastatin for 5 years

  Absolute risk reduction 5.1%
  NNT 20

  Irrespective of starting Cholesterol level
  The lower the better
  ?Why measure

NNT and NNH for Statins

Variables	Adjusted hazard ratio† for statin use (95% CI)	High risk patients (QRISK2 score ≥20%)		
		5 year risk of outcome in patients unexposed to statins	NNH or NNT (95% CI)	Estimated No of extra (or prevented) cases per 10 000 patients treated (95% CI)
Women				
Potential benefits:				
Cardiovascular disease*	0.76 (0.67 to 0.86)	0.1184	−37 (−64 to −27)	−271 (−374 to −157)
Oesophageal cancer	0.68 (0.52 to 0.88)	0.0025	−1266 (−3460 to −850)	−8 (−12 to −3)
Potential harms:				
Acute renal failure	1.56 (1.31 to 1.86)	0.0041	434 (284 to 783)	23 (13 to 35)
Cataract	1.3 (1.26 to 1.35)	0.1089	33 (28 to 38)	307 (260 to 355)
Liver dysfunction	1.53 (1.41 to 1.66)	0.0140	136 (109 to 175)	74 (57 to 91)
Myopathy	2.97 (2.36 to 3.74)	0.0020	259 (186 to 375)	39 (27 to 54)
Men				
Potential benefits:				
Cardiovascular disease*	0.76 (0.67 to 0.86)	0.1326	−33 (−57 to −24)	−301 (−417 to −174)
Oesophageal cancer	0.78 (0.66 to 0.91)	0.0042	−1082 (−2807 to −711)	−9 (−14 to −4)
Potential harms:				
Acute renal failure	1.61 (1.39 to 1.87)	0.0047	346 (245 to 539)	29 (19 to 41)
Cataract	1.32 (1.26 to 1.37)	0.0630	52 (44 to 63)	191 (158 to 225)
Liver dysfunction	1.53 (1.42 to 1.66)	0.0133	142 (115 to 180)	71 (56 to 87)
Myopathy	6.15 (5.19 to 7.3)	0.0021	91 (74 to 112)	110 (90 to 134)

BMJ 2010;340;c2197

Proposal

- DON’T measure BP
- DON’T measure Cholesterol

- AIM FIRE FORGET


Worth1000.com

Lifestyle changes
Chocolate

- Has Anti-hypertensive, anti-inflamatory, anti-atherogenic and anti-thrombotic effects

- Meta-analysis of observational studies high vs low chocolate intake

  37% reduction cardiovascular disease

  29% reduction stroke

  31% reduction diabetes

BMJ 2011;343:d4488

Secondary Prevention Lifestyle changes

- Stop Smoking (no good evidence)
- Limit Drinking (no good evidence)
- If obese – loose weight (no good evidence)
- Reduce added salt (no good evidence)
- Take exercise (Some evidence)
  - 30-60 minutes 3 times a week “brisk” exercise

Evidence for Lifestyle Changes

Reduced or Modified Dietary Fat for preventing Cardiovascular disease

There were no clear effects of dietary fat **changes on total mortality (RR 0.98, 95% CI 0.93 to 1.04, 71,790 participants) or** cardiovascular **mortality (RR 0.94, 95% CI 0.85 to 1.04, 65,978 participants). This did not alter with sub-grouping or sensitivity analysis.**

Multiple risk factor interventions for primary prevention of Coronary Heart Disease

"Interventions using counselling and education aimed at behaviour change do not reduce total or CHD mortality or clinical events in general populations but may be effective in reducing mortality in high-risk hypertensive and diabetic populations."

Cochrane database of Systematic Review 2011

Intracerebral Bleeding

- Little or no data
- Always Lower Blood pressure
- AVM/Aneurysms Surgery/coils etc
- Recurrence rate for Amyloid angiopathy very high – Avoid Aspirin/clopidogrel
  - What about those with IHD as well?

The Future

- Better risk stratification
- Better Anti-thrombotics
- New anti-platelets
- New endovascular techniques
- POLYPILL

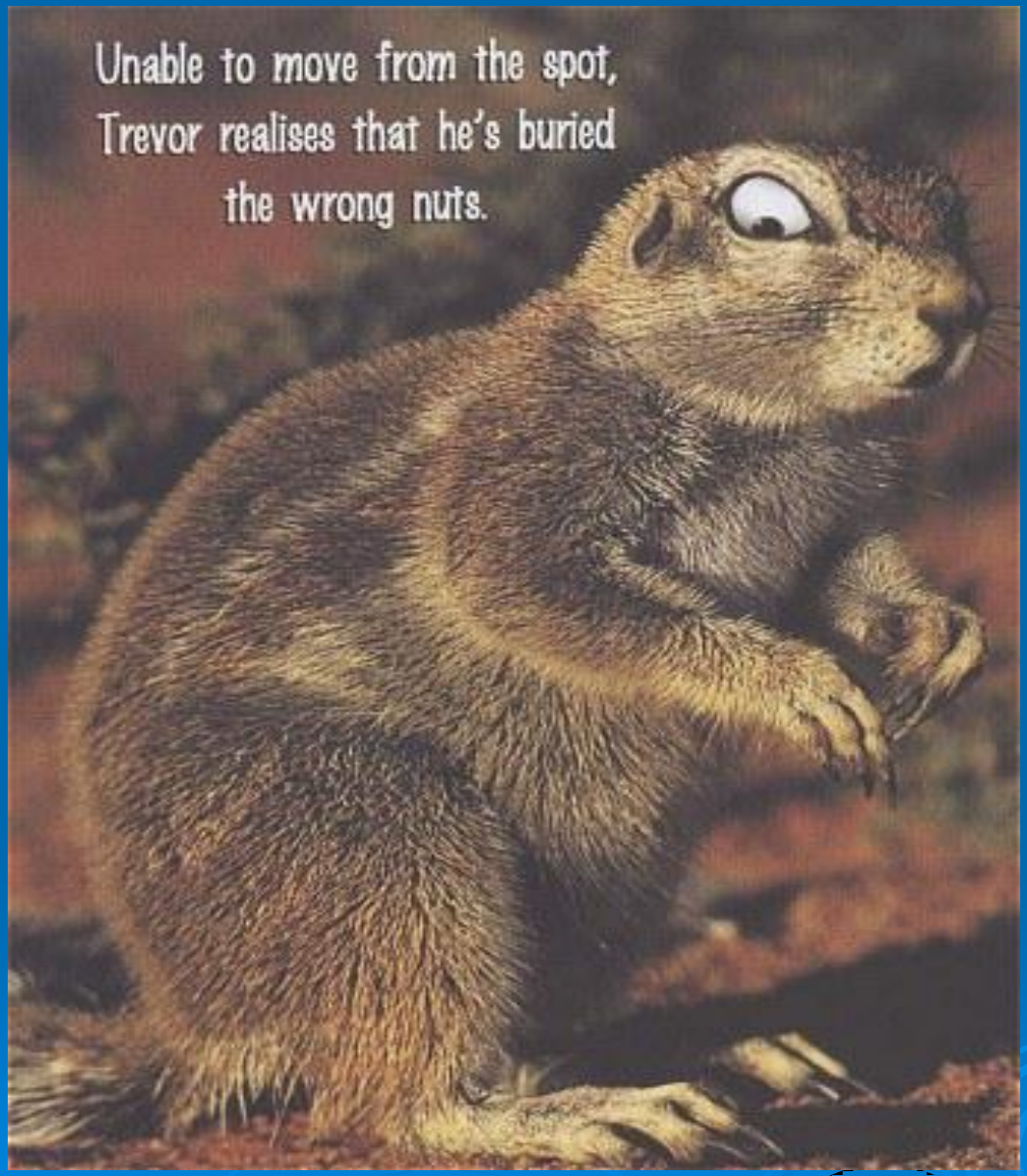
- From What will we Die?

Learning Points

- Beware EvidenceBiased Medicine/Nursing
  Please treat your patients not the disease
- Early intervention is essential
- Clopidogrel is preferred Anti-platelet agent
- New Warfarin substitutes are on their may and may help
- AIM FIRE FORGET for BP and Cholesterol
- The Future is EXCITING

Feel Positive about Us

- Interest and enthusiasm
- Healthy variability
- Whatever we are doing, we are doing well
- Real, important research
  - ARCOS, AF, MRI, Physio etc
  - Lots of opportunity


Unable to move from the spot,
Trevor realises that he's buried
the wrong nuts.