

# Challenges and unrealised potential of clinical research

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Action Research Professor of Neurology  
University of Oxford

AJS MacFadzean Lecture, 19 Nov 2017



Medical Student 1936



Prof McFadzean and Dr Rosie Young at his retirement party, ca 1974



Group photo: farewell party for Dr and Mrs CC Wong, Kum Ling Restaurant prior to their departure for the UK, ca 1952  
Back row (from left): Drs J Pan, ST Hiew, Gerald Choa, Olaf Skinsnes, CT Huang, Profs AJS McFadzean and PC Hou, Drs Stephen Chang, KH Chau, Ramon Ruiz, SS Leung, TW Wu, ---, Mr Yung (chief technologist in pathology)  
Front row (from left): Dr HC Kwaan, Mrs CT Huang, ---, Mrs PC Hou, Mrs CC Wong, Dr CC Wong, Mrs McFadzean, Miss Glen Mitchell (Nursing Sister, UMU), Dr Irene Osmund, ---, Dr D Todd



Barnett K., et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet 2012

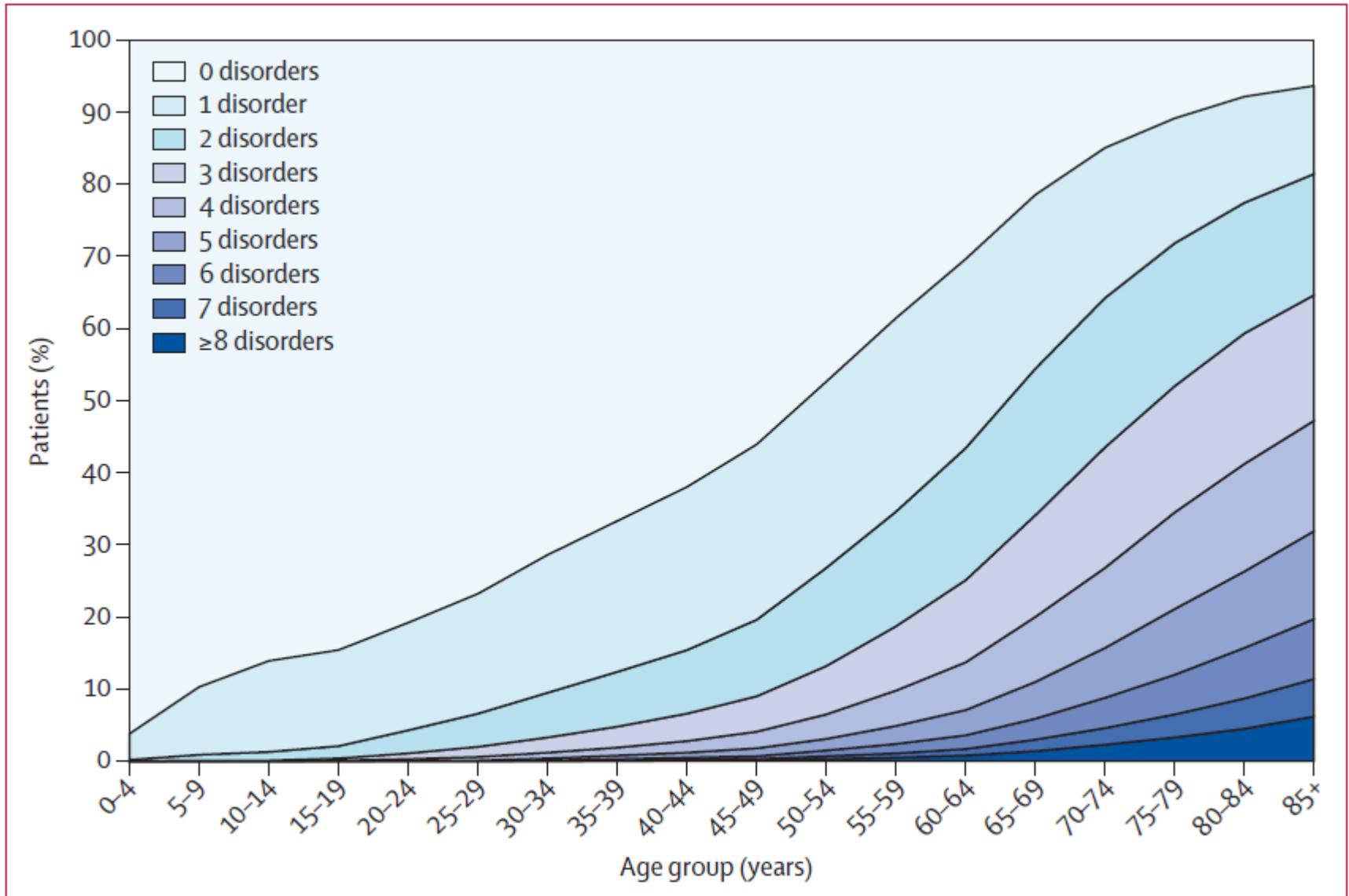


Figure 1: Number of chronic disorders by age-group

# Medical research pathway

Basic laboratory science  
Clinical laboratory science  
“Translational research”  
Cohort studies  
Randomized trials  
Population studies  
Clinical practice



## % of total research funding

### Research activity

MRC WT BHF CRUK

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Underpinning †,*	41.2	49.2	27.5	24.3
Aetiology *	38.5	40.5	48.8	35.2
Prevention	2.9	1.9	1.8	2.1
Detection & diagnosis	4.5	1.7	6.0	6.1
Treatment development *	5.6	4.3	9.3	17.3
Treatment evaluation	4.5	1.7	5.2	11.7
Disease management	1.2	0.2	0.8	2.9
Health services	1.6	0.5	0.6	0.4

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† Research aimed at understanding normal biological functioning \* Laboratory-based

Rothwell PM. **Funding for practice-oriented clinical research.** *Lancet* 2006; 368: 262-6

Rothwell PM. **Medical academia is failing patients and clinicians.** *BMJ* 2006; 332:863-4

# Spectrum of medical research

Clinical  
innovation

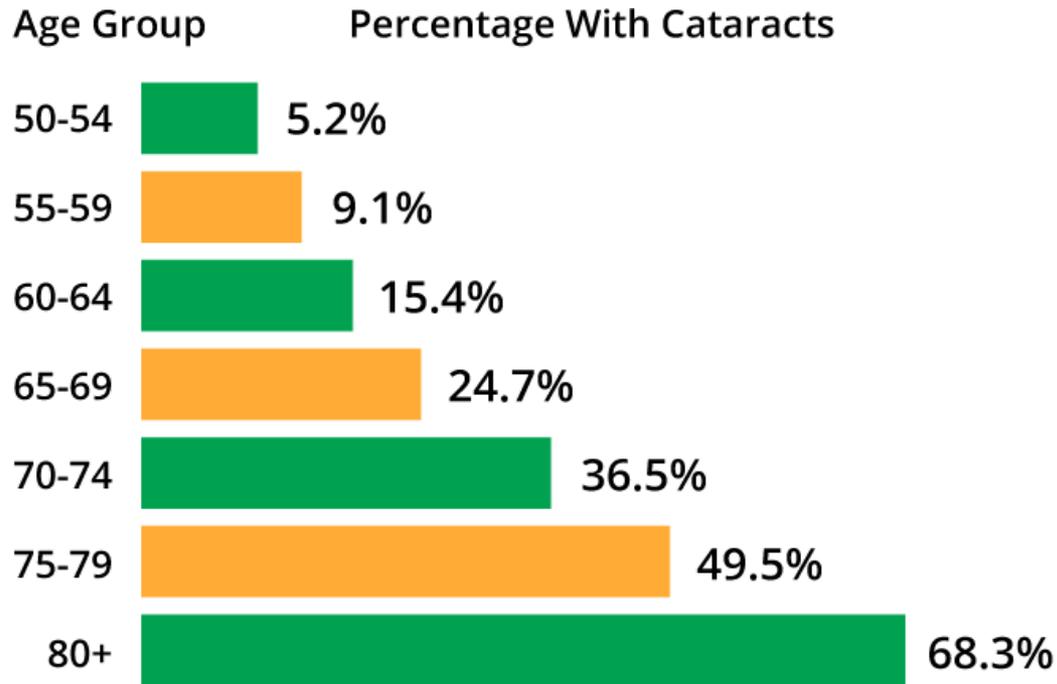
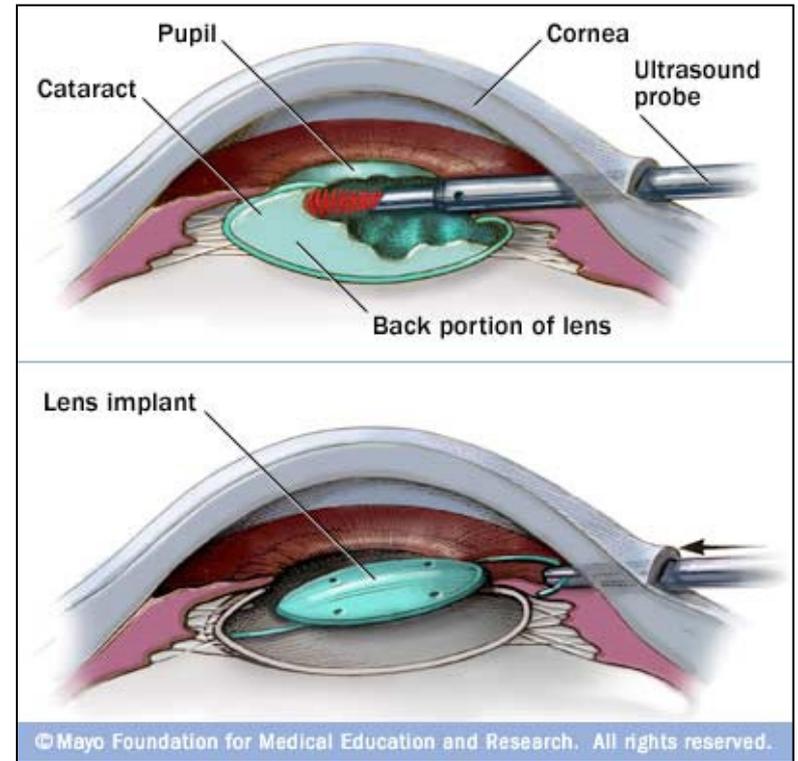
Clinical  
effectiveness

Clinical  
exploration

Basic laboratory science  
Clinical laboratory science  
“Translational research”  
Cohort studies  
Randomized trials  
Population studies  
Clinical practice



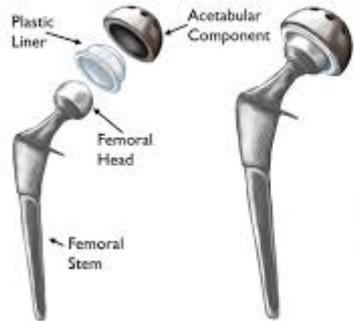
# Cataract Surgery

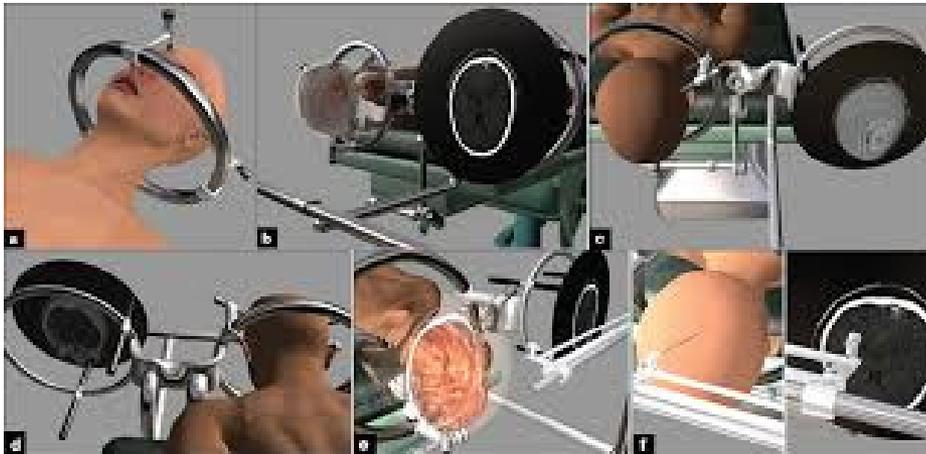
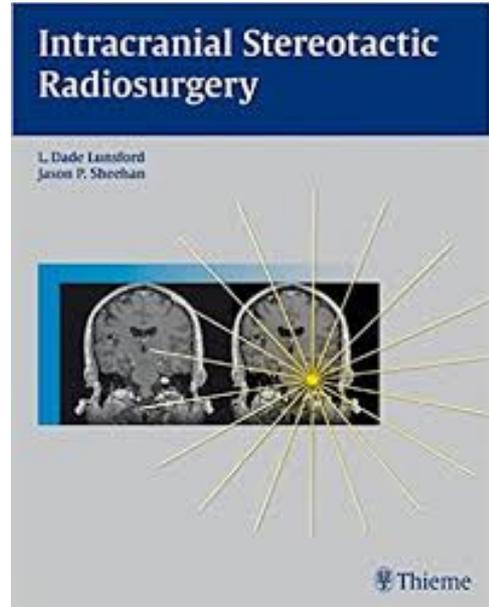
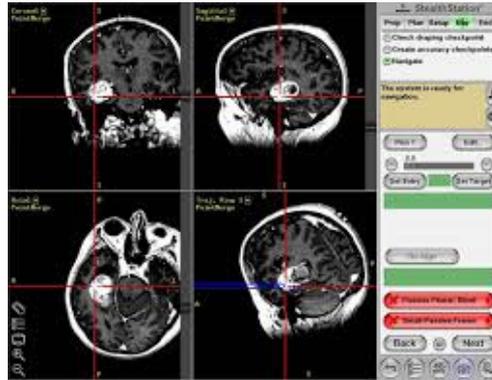


Source: National Eye Institute (NEI), U.S. National Institutes of Health



# Joint replacement surgery



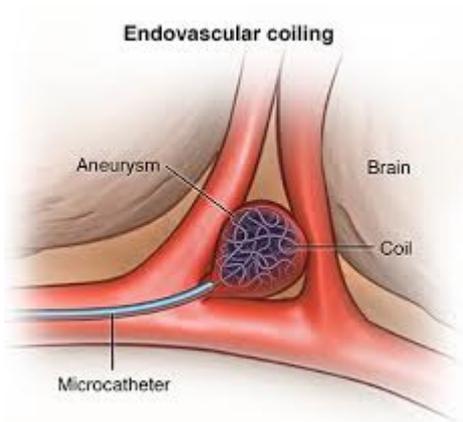




# The durability of endovascular coiling versus neurosurgical clipping of ruptured cerebral aneurysms: 18 year follow-up of the UK cohort of the International Subarachnoid Aneurysm Trial (ISAT)



Andrew J Molyneux, Jacqueline Birks, Alison Clarke, Mary Sneade, Richard S C Kerr



## Balloon assisted coiling:

In slightly wide necked aneurysms balloon assistance is taken to coil an aneurysm in order to prevent prolapse of coil mass into the artery.

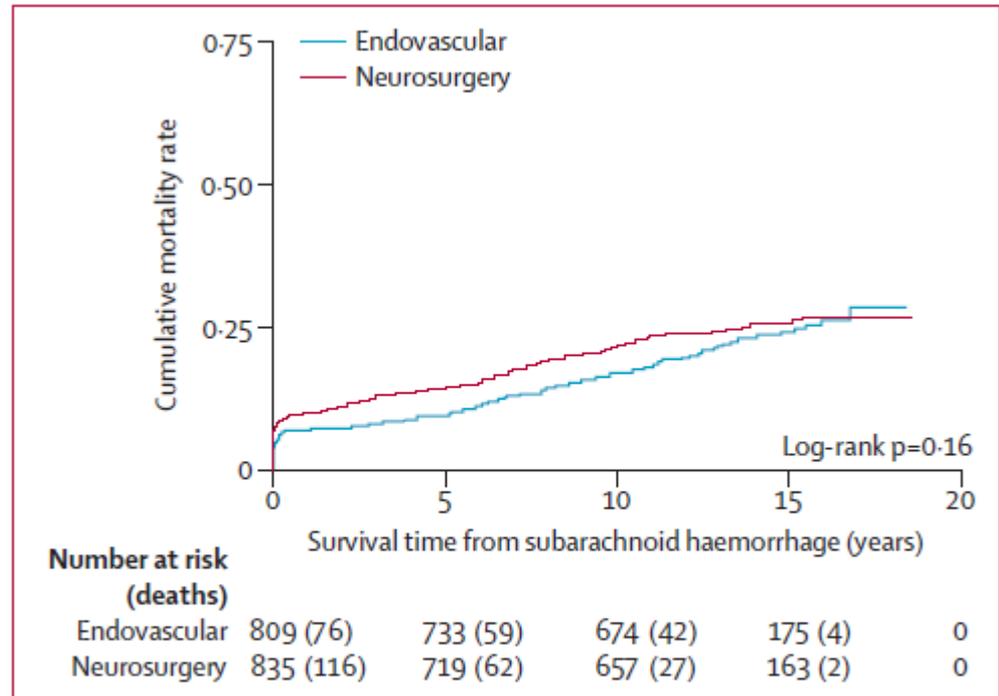
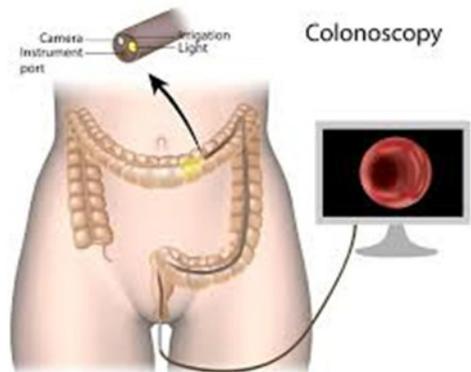
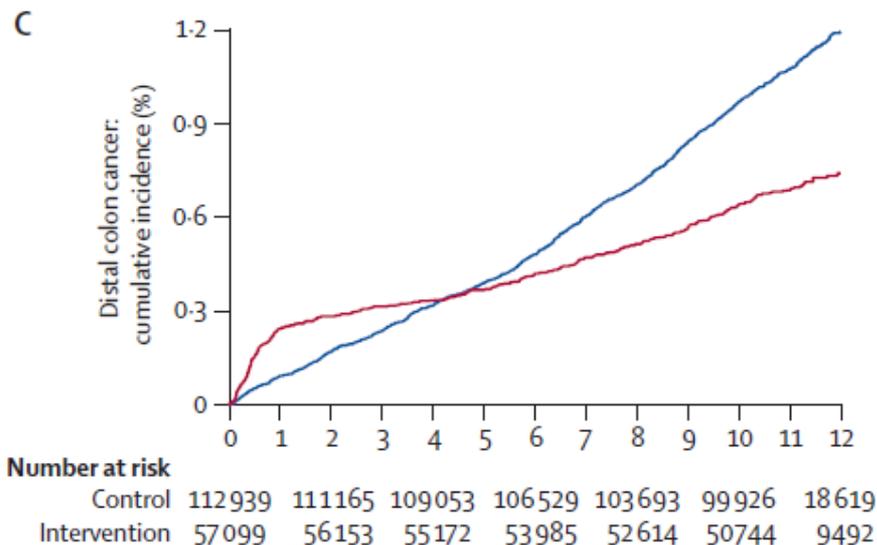


Figure 2: Kaplan-Meier plot of cumulative mortality Patients observed for 10-18.5 years in 22 UK centres.

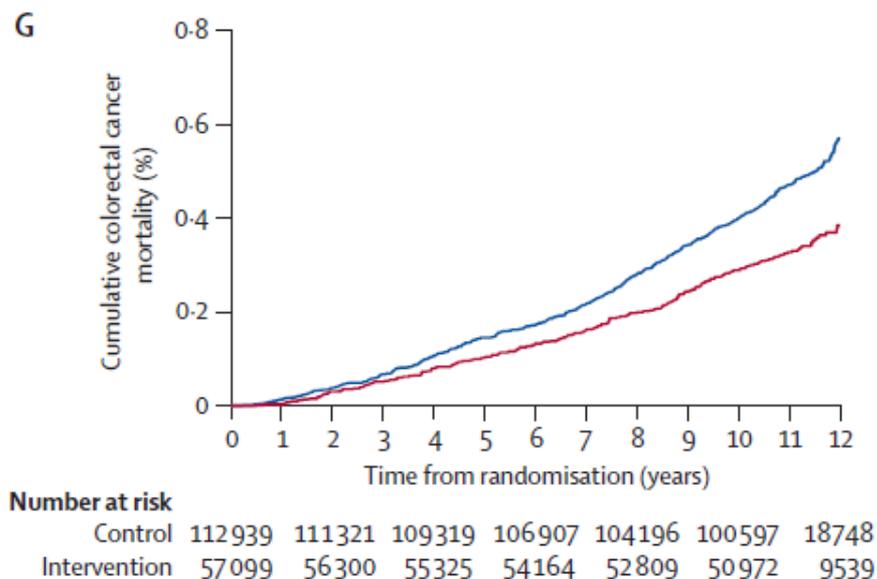


## Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial

Wendy S Atkin, Rob Edwards, Ines Kralj-Hans, Kate Wooldrage, Andrew R Hart, John M A Northover, D Max Parkin, Jane Wardle, Stephen W Duffy, Jack Cuzick, UK Flexible Sigmoidoscopy Trial Investigators

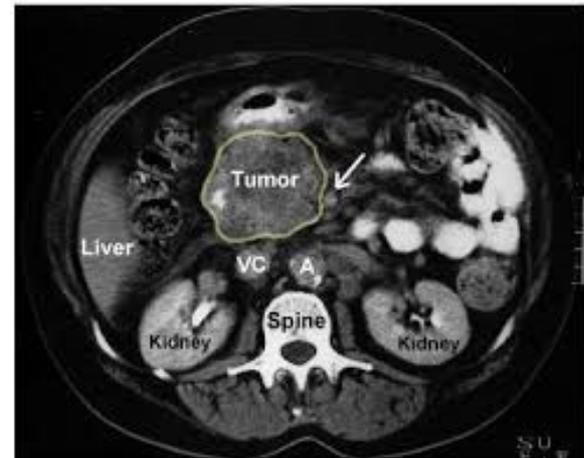
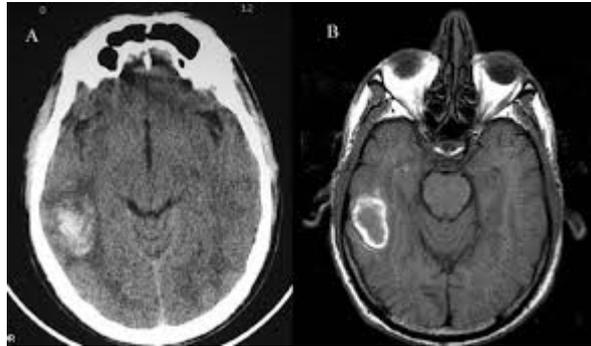


Distal colorectal cancer

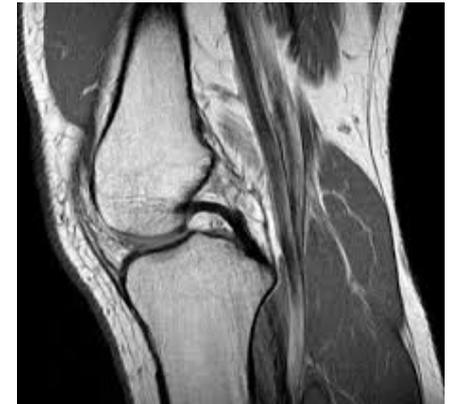
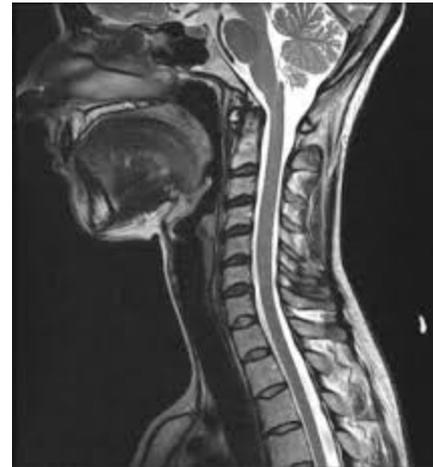
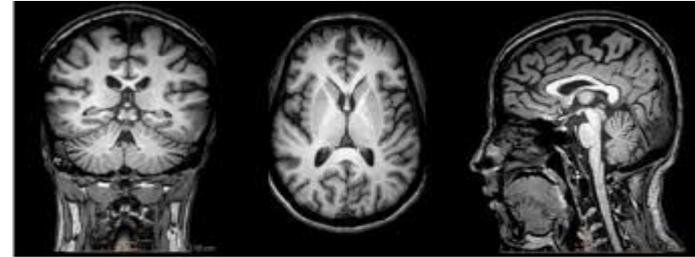


Colorectal cancer deaths

# CT scan



# MRI scan



# Spectrum of medical research

Clinical  
innovation

Clinical  
effectiveness

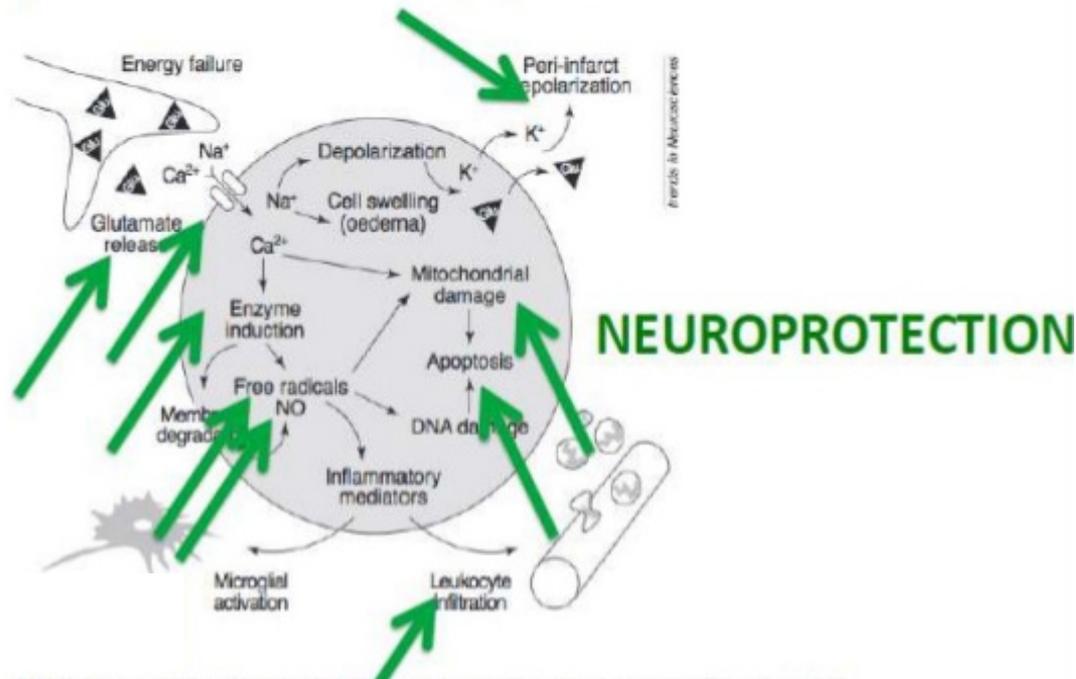
Clinical  
exploration

Basic laboratory science  
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“Translational research”  
Cohort studies  
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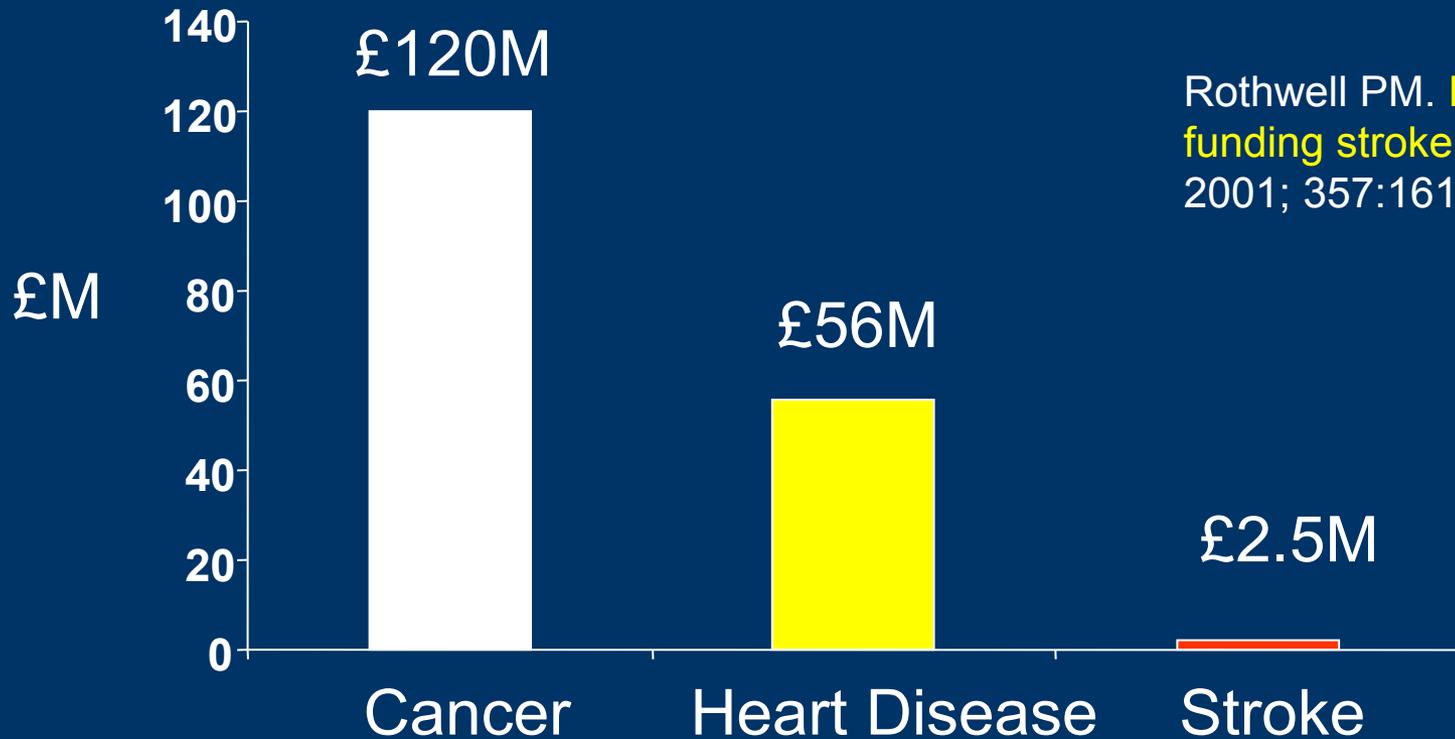
# Neuroprotection in acute ischaemic stroke

## Experimental approaches



More than 1000 compounds tested in animal studies and clinical trials

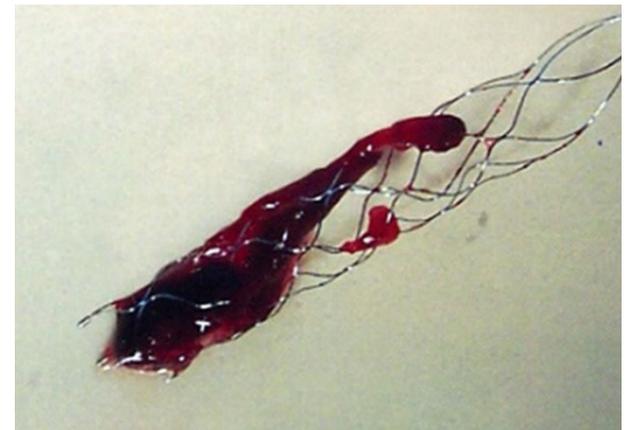
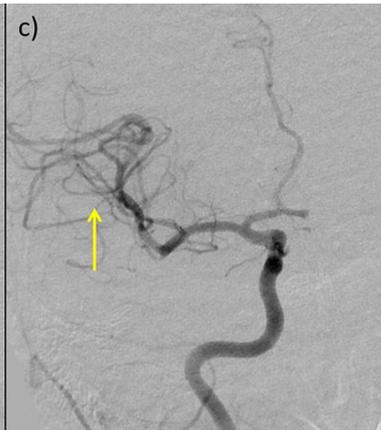
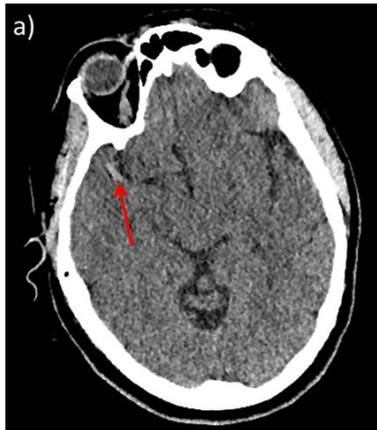
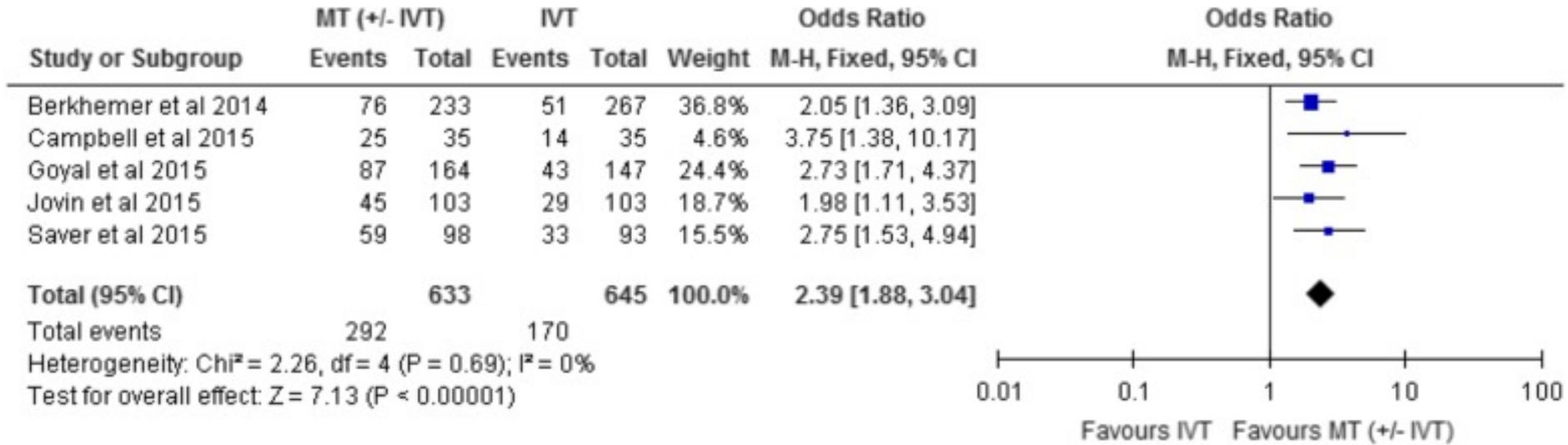
# UK stroke research funding - 1998



Rothwell PM. High cost of not funding stroke research. *Lancet* 2001; 357:1612-16.

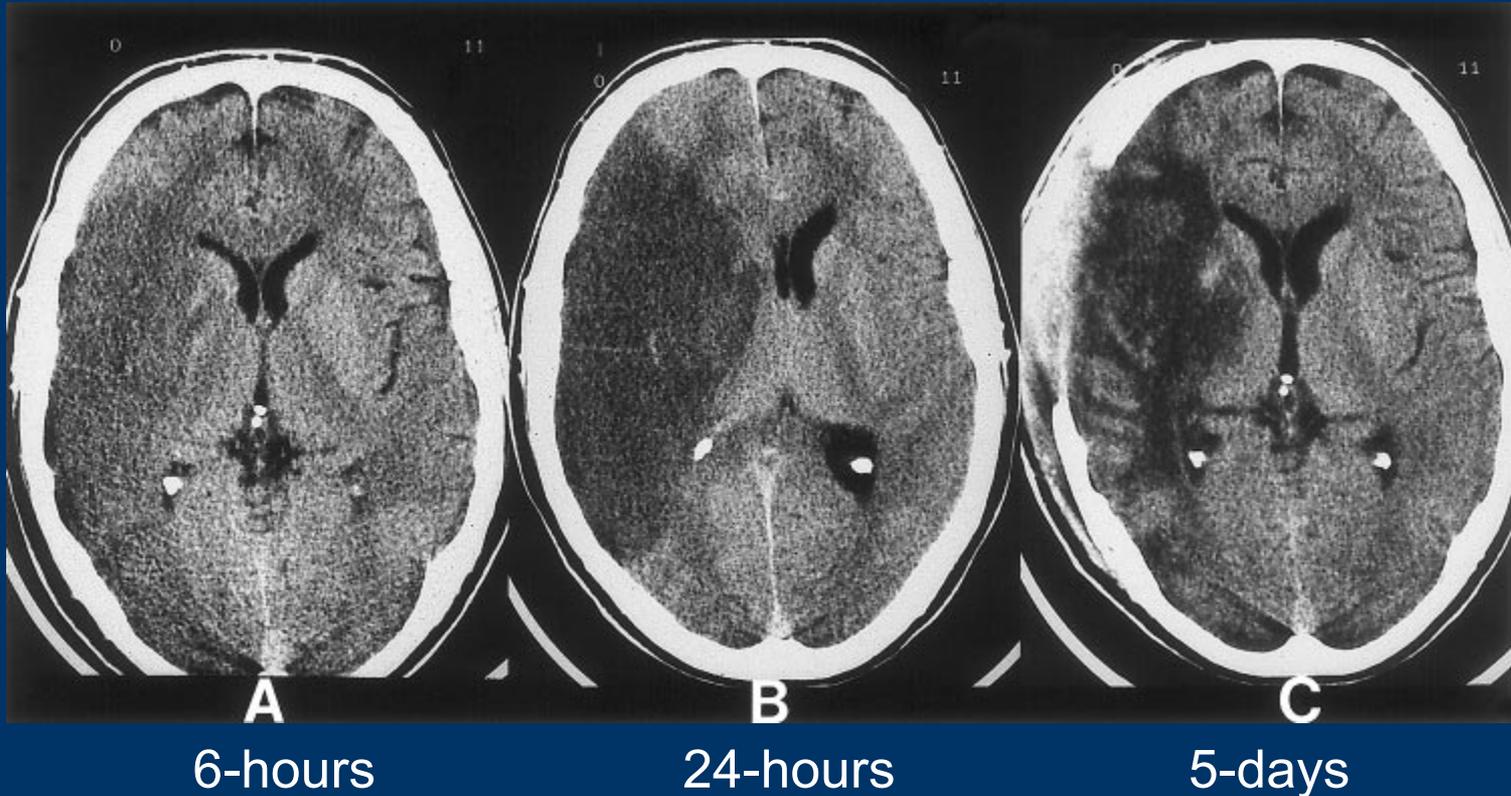
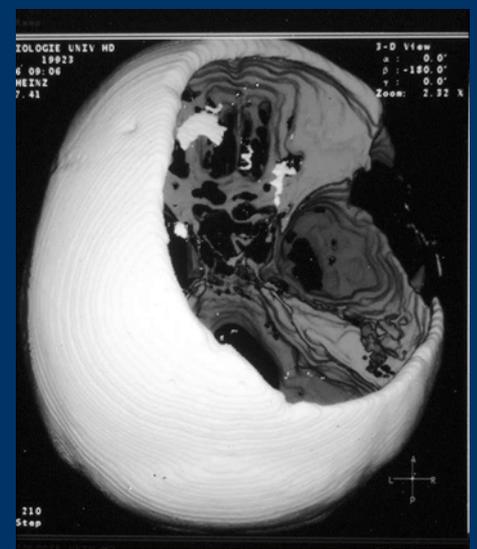
- **MRC** - only 1 of 238 new grants was for stroke
  - 3 ongoing RCTs in stroke vs 65 in cancer
- **Wellcome Trust** - £123,000 (0.03%) spent on stroke research out of a total spend of £392.6 million.

# Trials of mechanical thrombectomy in patients with acute ischaemic stroke



# Hemicraniectomy in major hemispheric stroke

41 year old man with ischaemic stroke due to a right carotid dissection

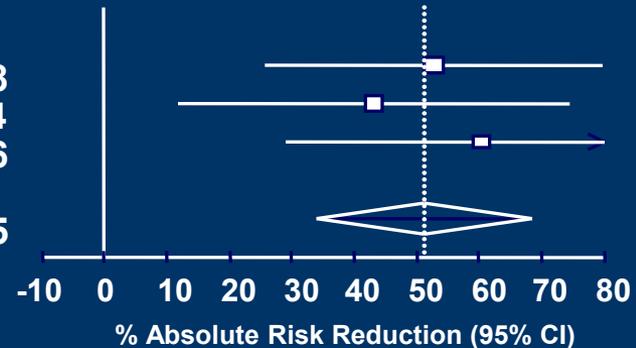


# Hemicraniectomy vs conservative Rx

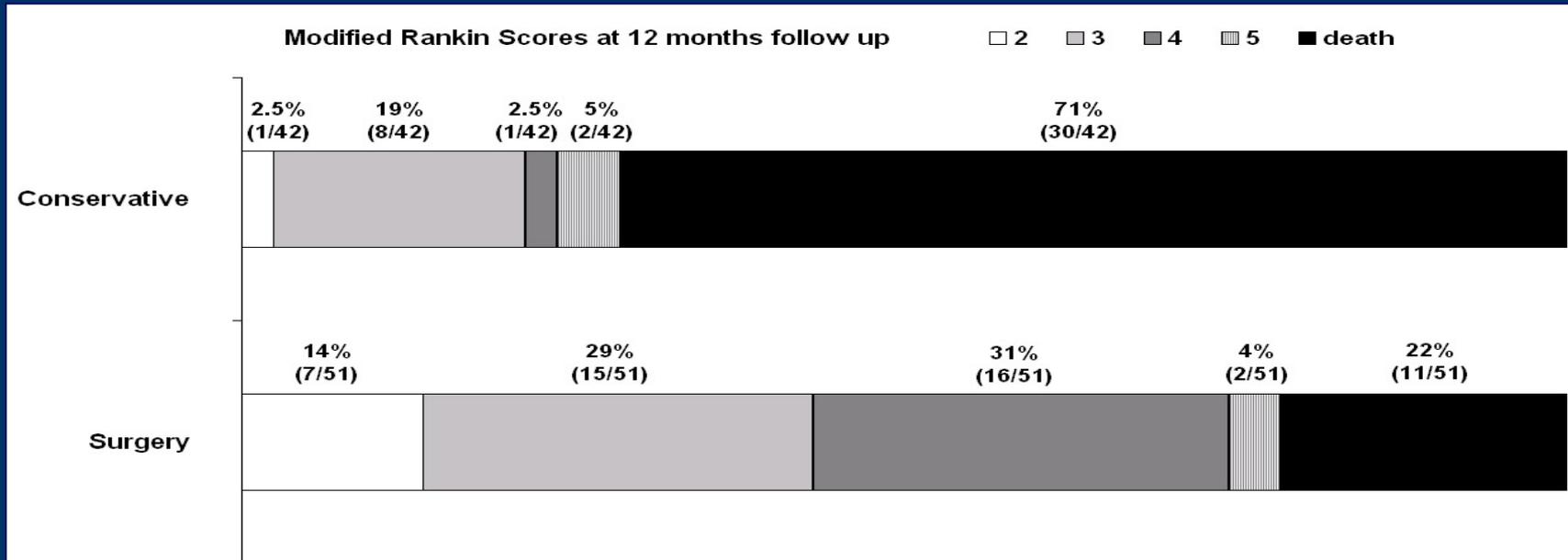
## Outcome / Patients

	Conservative	Surgery	ARR (%)	95% CI
DECIMAL	14 / 18	5 / 20	52.8	25.8-79.8
DESTINY	10 / 15	4 / 17	43.1	11.9-74.4
HAMLET	8 / 9	4 / 14	60.3	29.0-91.6
<b>TOTAL</b>	<b>32 / 42</b>	<b>13 / 51</b>	<b>51.2</b>	<b>33.9-68.5</b>

mRS >4 at 12 months

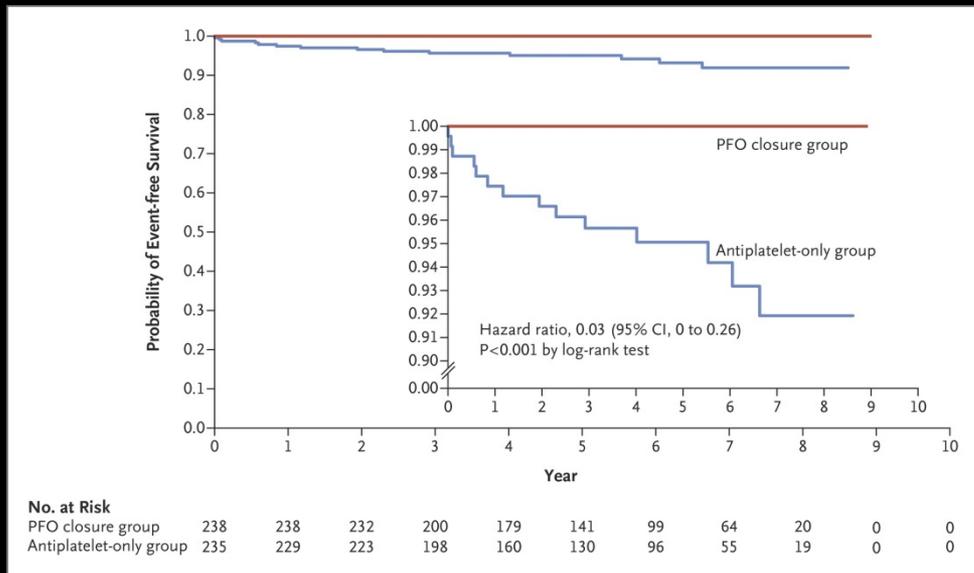


Significance  $p < 0.0001$  Heterogeneity  $p = 0.74$



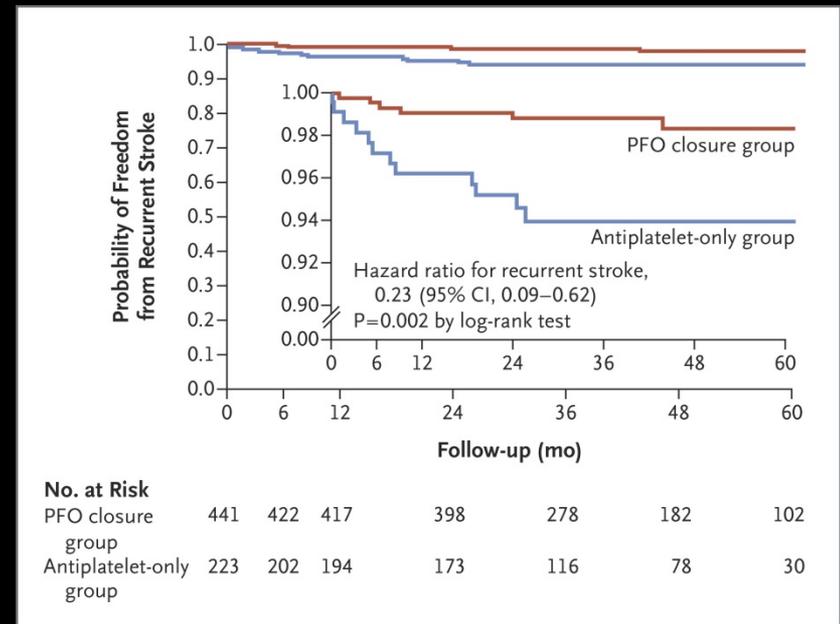
# Trials of closure of patent foramen ovale in young patients with cryptogenic stroke

Kaplan–Meier Cumulative Estimates of Probability of Stroke in the PFO Closure Group versus the Antiplatelet-Only Group.



Mas J-L et al. N Engl J Med 2017;377:1011-1021

Probability of Freedom from Clinical Evidence of Recurrent Ischemic Stroke.



Søndergaard L et al. N Engl J Med 2017;377:1033-1042

# Association of PFO and cryptogenic stroke by age (<60) in the Oxford Vascular Study

	<b>Cryptogenic</b>	<b>Known aetiology</b>	<b>OR</b>	<b>p</b>
	<b>n/total (%)</b>	<b>n/total (%)</b>	<b>(95%CI)</b>	
<b>Any right-to-left shunt</b>				
≤60	29/76 (38.2)	16/50 (32.0)	1.31 (0.62-2.79)	0.48
>60	70/194 (36.1)	42/202 (20.8)	2.15 (1.37-3.37)	0.001
Total	99/270 (36.7)	58/252 (23.0)	1.94 (1.32-2.84)	0.001
<b>Large right-to-left shunt</b>				
≤60	16/76 (21.1)	12/50 (24.0)	0.84 (0.36-1.98)	0.70
>60	25/194 (12.9)	15/202 (7.4)	1.84 (0.94-3.62)	0.07
Total	41/270 (15.2)	27/252 (10.7)	1.49 (0.89-2.51)	0.13

# Spectrum of medical research

Clinical  
innovation

Clinical  
effectiveness

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exploration

Basic laboratory science  
Clinical laboratory science  
“Translational research”  
Cohort studies  
Randomized trials  
Population studies  
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# Getting the simple things right

## NHS 2017

->1 million patient interactions / day

-£120 billion / year

## More effective use of existing preventive strategies by:

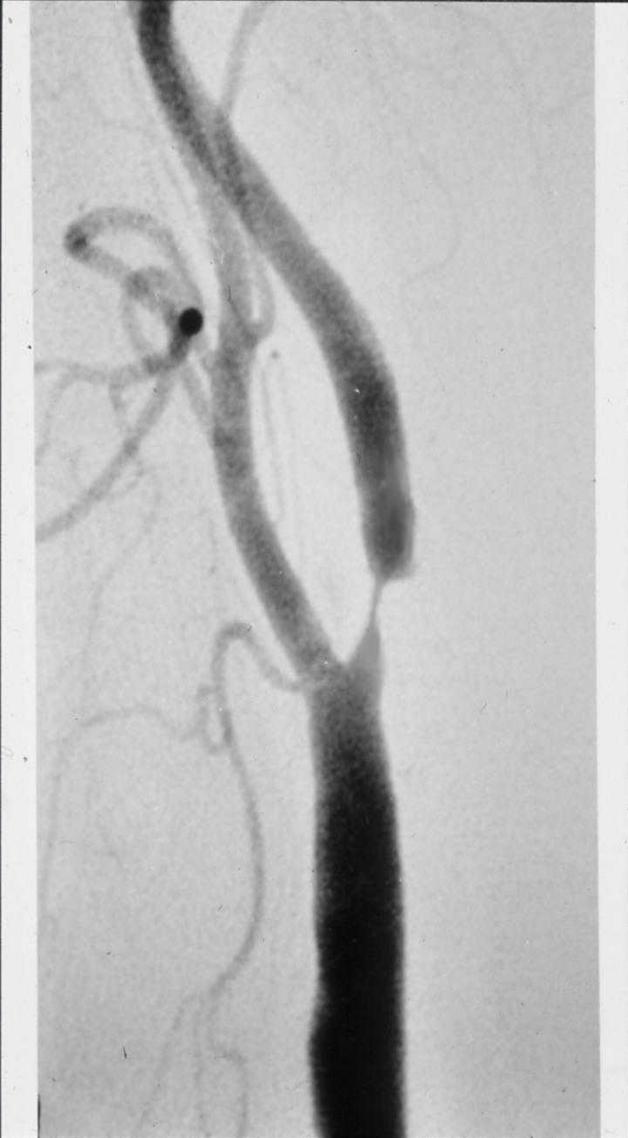
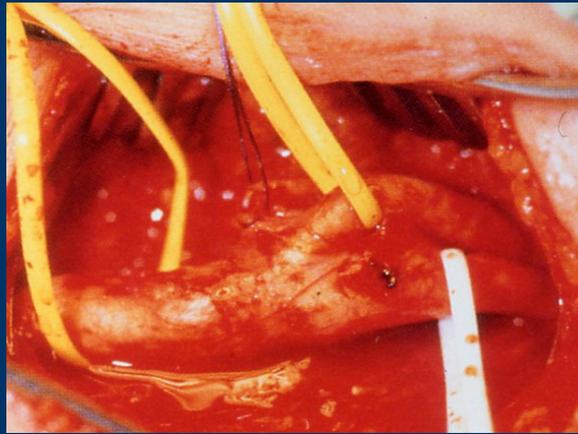
- *Better prognostication*
- *Better phenotyping*
- *Better understanding of known risk factors*
- *Better understanding of existing treatments*



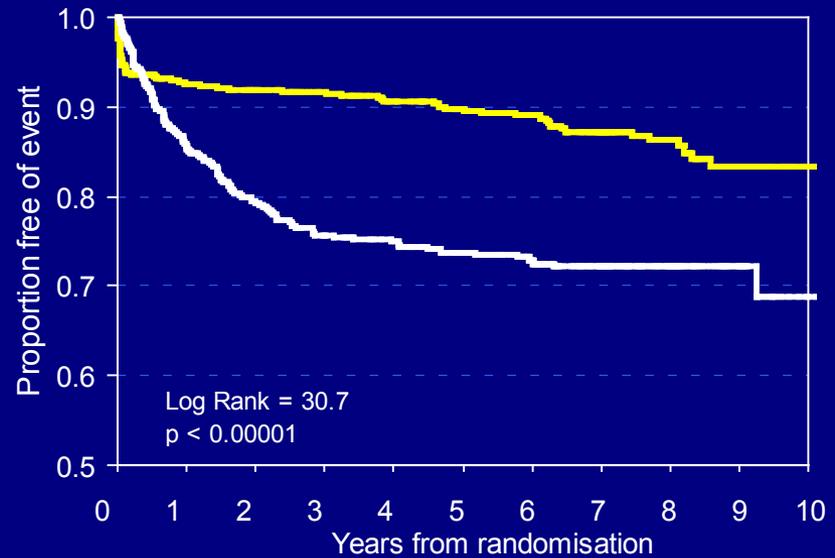
Rothwell PM. Funding for practice-oriented clinical research. Lancet 2006; 368: 262-6

Rothwell PM. Medical academia is failing patients & clinicians. BMJ 2006; 332:863-4

# Carotid endarterectomy



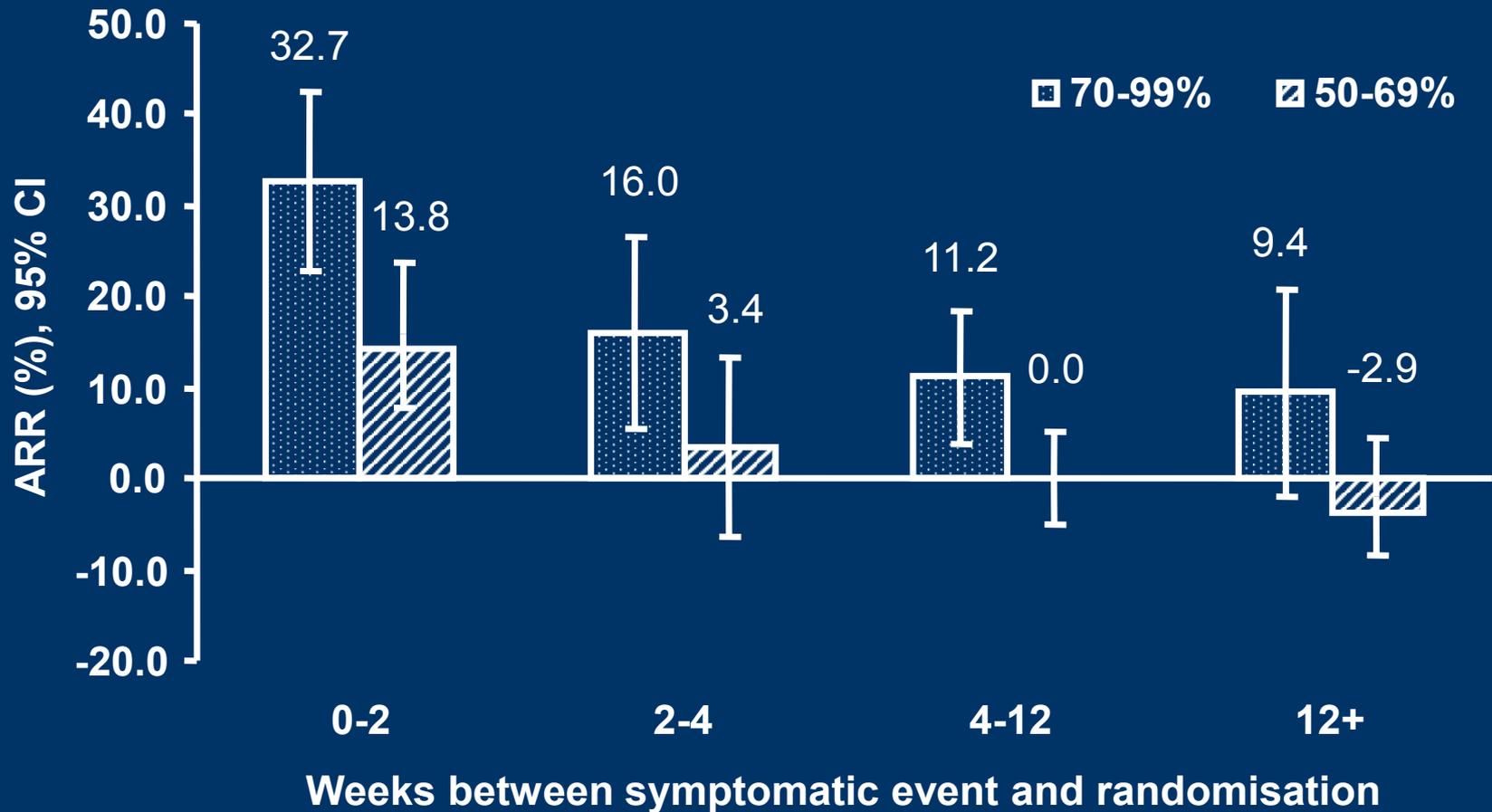
Stenosis 70-99% (excluding post-stenotic narrowing)  
 Ipsilateral Carotid Territory Ischaemic Stroke  
 Plus Any Surgical Stroke or Surgical Death



Patients											
Surgery	573	487	454	427	404	374	315	237	157	86	20
No surgery	498	393	332	299	284	254	218	166	90	36	10

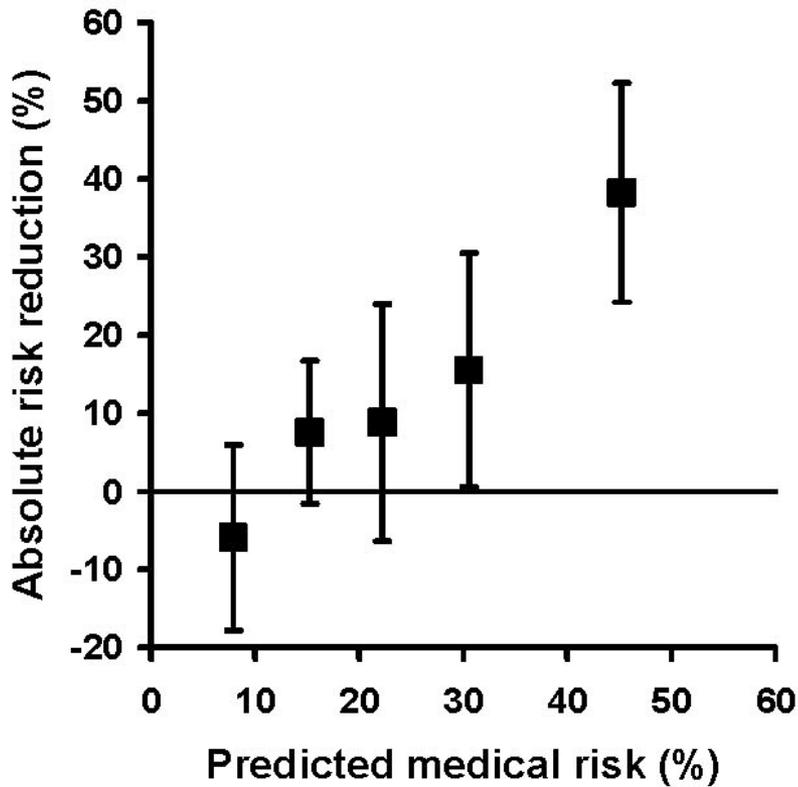
# Effect of carotid endarterectomy stratified by time from last event to randomisation

Ipsilateral ischaemic stroke and operative stroke or death

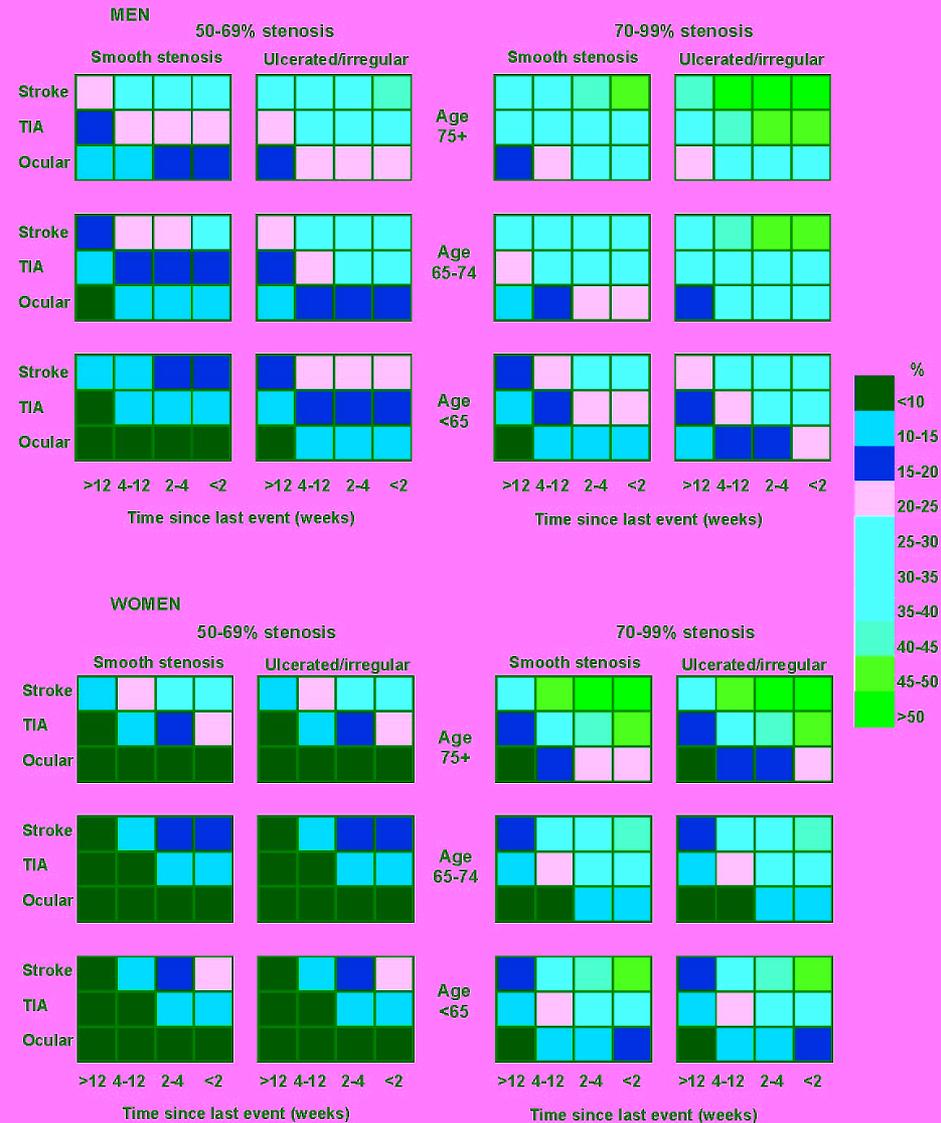


# Risk stratification for endarterectomy for symptomatic carotid stenosis

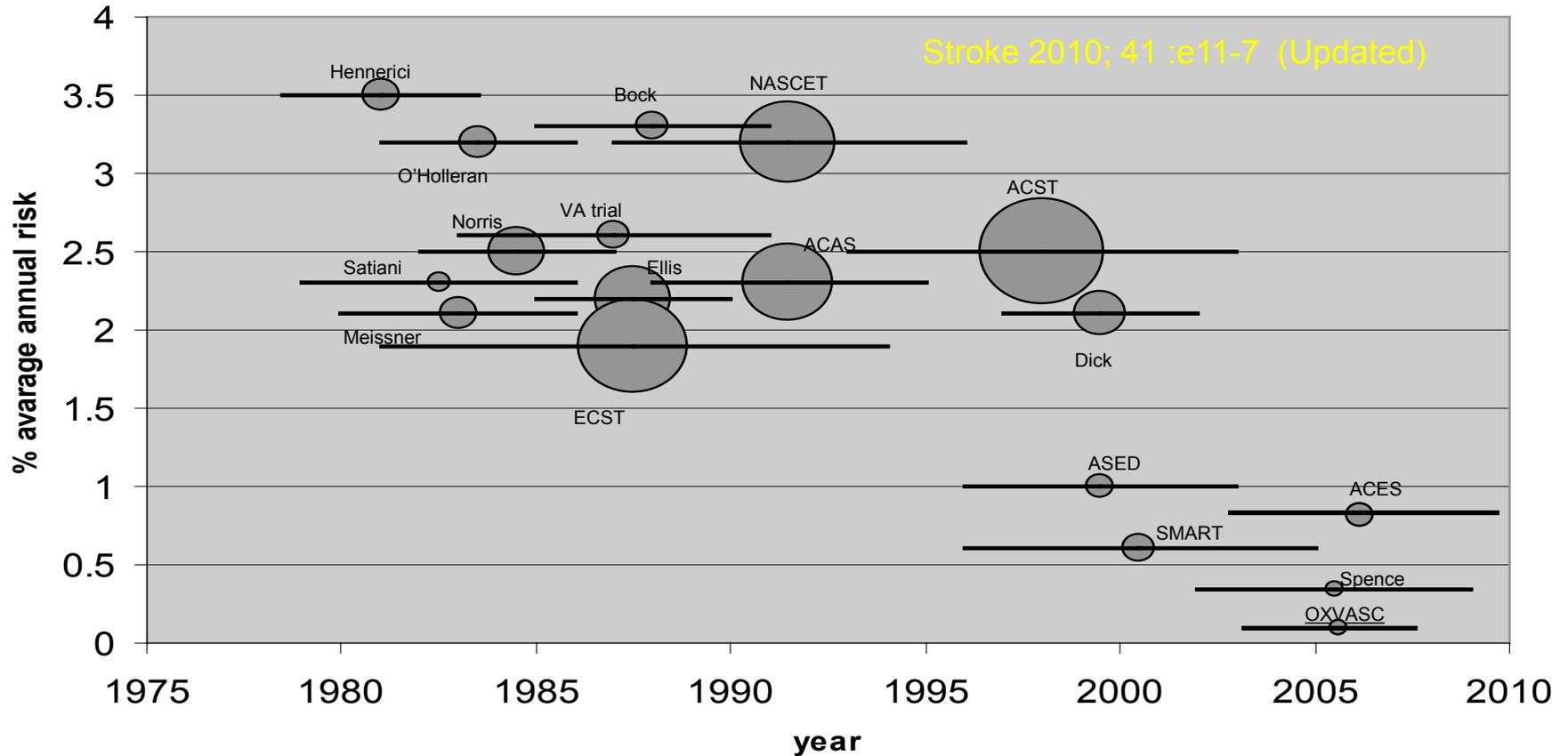
## 70-99% stenosis



Lancet 2005; 365; 256-65.



# Risk of ischaemic stroke distal to 50-99% asymptomatic carotid stenosis



Events	N	FU (person yrs)	Rate (annual risk)
Ipsilateral Stroke	3*	520	0.58 (0.22 – 1.54)
Ipsilateral TIA or Stroke	10	511	1.96 (1.05 - 3.64)
Mortality	48**	524	9.16 (6.90 - 12.15)

\* 2 strokes occurred in patients with AF; \*\* No deaths due stroke ipsilateral stroke

# Oxford Vascular Study

Population: 92,000 (cf Framingham: 5209)

- All acute TIA, stroke, ACS, AAA, PVD
  - Phase 1 (2002-2012): >8000 patients
- 9 general practices (100 GPs)
- Acute assessment
  - Detailed phenotyping; blood, DNA
- Regular face-to-face follow-up
  - Cognitive assessments at each visit
- No upper age limit (30% events >80 yrs)
- Electronic record linkage



Acute Vascular Imaging Centre



## OXVASC-Cog 1

- 2002-2007
- n=1516
- mainly CT-based

## OXVASC-Cog 2

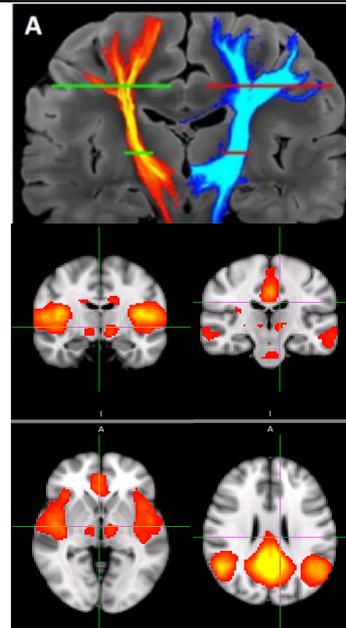
- 2007-2012
- n=1492
- partly MRI-based

## OXVASC-Cog 3

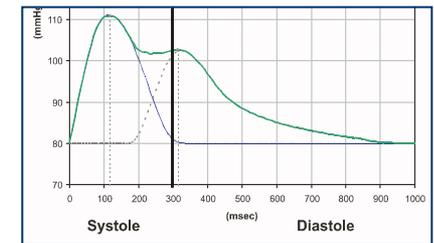
- 2012-2017
- n=1500
- MRI & fMRI (AVIC)
- Vascular physiolog.

## “Fully-phenotyped Cohort”

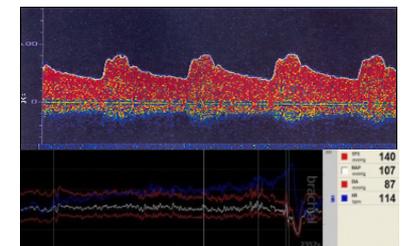
- Brain imaging (MRI; fMRI; PET)
- Vascular imaging (MRA; TCD)
- Cardiac imaging (Echo)
- Cardiac monitoring (R-test)
- Vascular physiology
- BP monitoring (COMMITT)
- Biomarkers
- Genetics



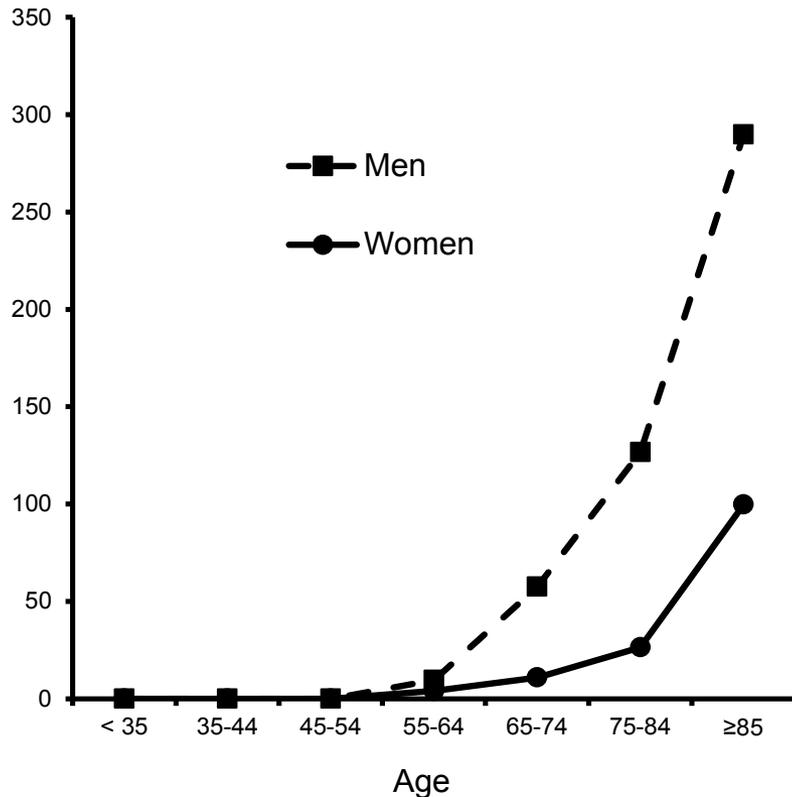
## Cardiovascular physiology



## Cerebrovascular physiology



# Age- and sex-specific rates per 100,000 population (2002-12) of incident acute abdominal aortic aneurysm (AAA)



155 people had 174 AAA (44% of events missed by routine coding)  
- only 22.2% in men aged 65-74

The **new UK screening programme** for men aged 65 will prevent only 5.6% of all aneurysm-related deaths (121 scans per year of life saved).

Screening only male smokers aged 65 and then all men at age 75 would prevent 21.1% of deaths and 33.3% of life-years lost (34 per year of life saved).

**Current screening will prevent only 2.1% of all aneurysm-related deaths by 2030**, by which time 91.0% will occur at age  $\geq 75$ , 61.6% at  $\geq 85$  and 28.6% in women.

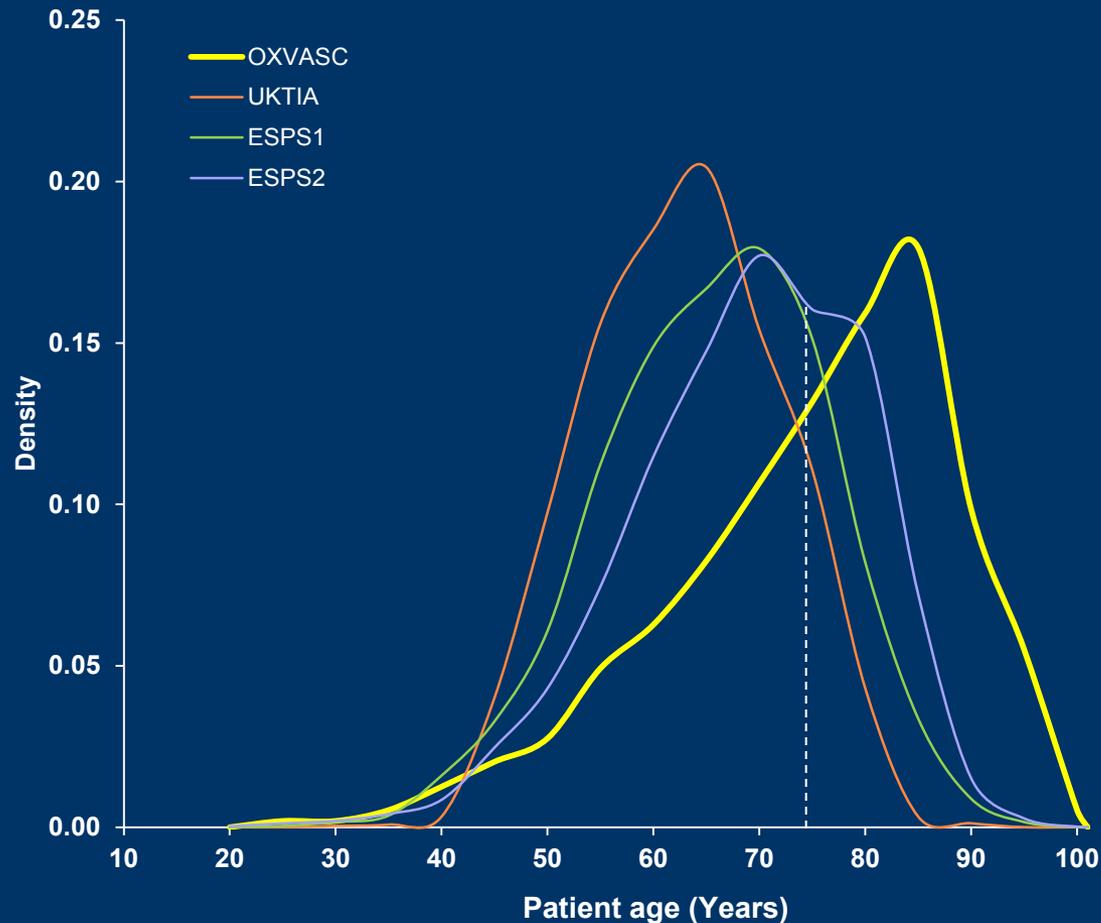
Br J Surg 2014; 102: 907-15.

J Am Heart Assoc 2015; 4. pii: e001926.

Circulation 2015 Sep 8. [Epub ahead of print]

# Antiplatelet treatment in secondary prevention of vascular events

- 50% of patients taking antiplatelet drugs are now aged  $\geq 75$ y



# Long-term risk of bleeding

## Study design and analysis

All first TIA and ischaemic stroke in OXVASC  
(01/04/2002 to 31/03/2012)

Excluded

Not treated with antiplatelet medication

New warfarin use

All patients on antiplatelet treatment (n=2072)

Censored

New warfarin use

Death

End of follow-up (31/03/2013)

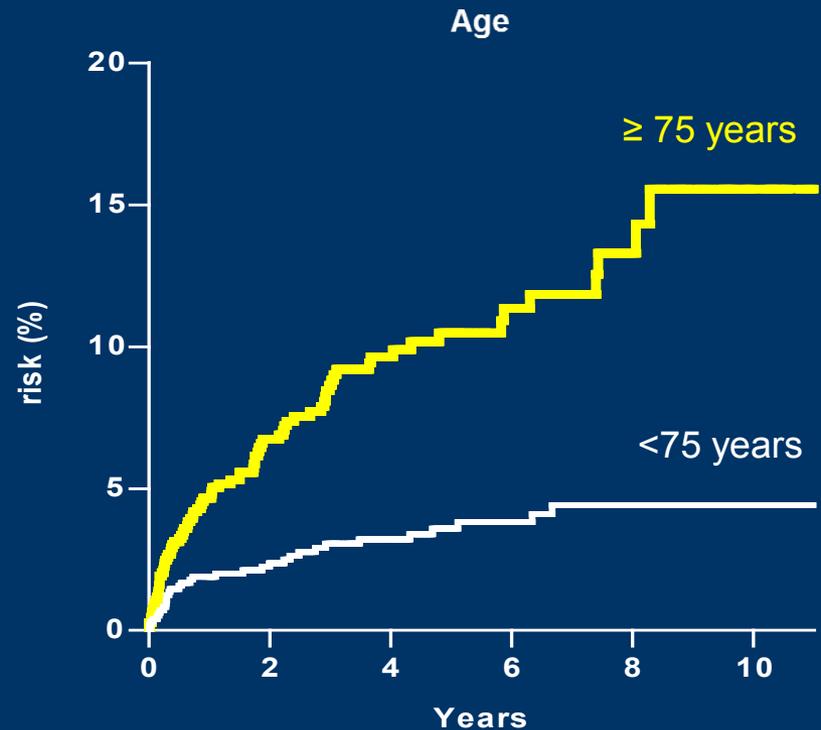
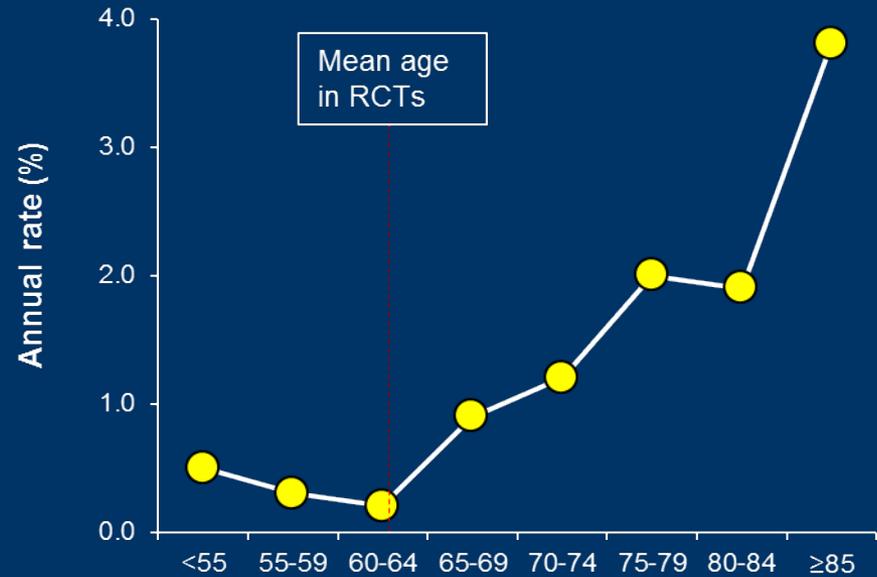
Bleeds details (n=254)

Severity (CURE criteria)

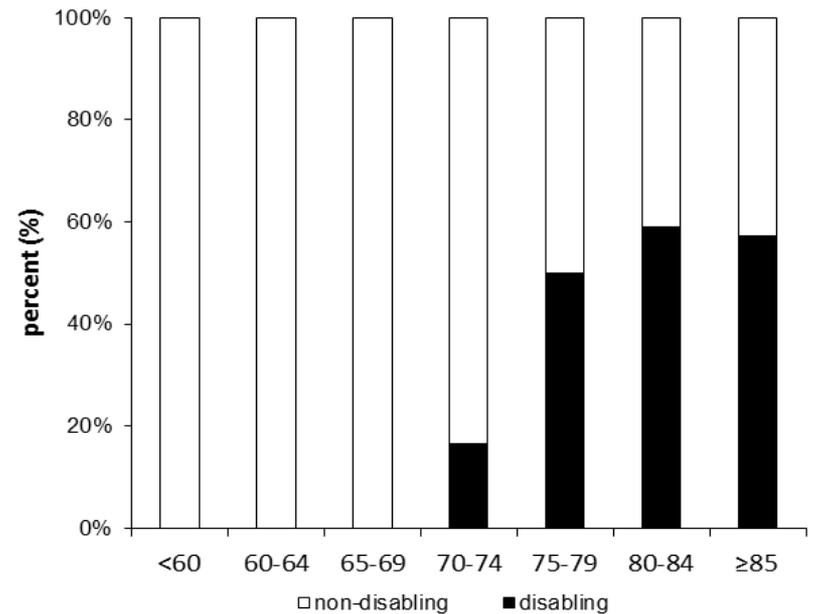
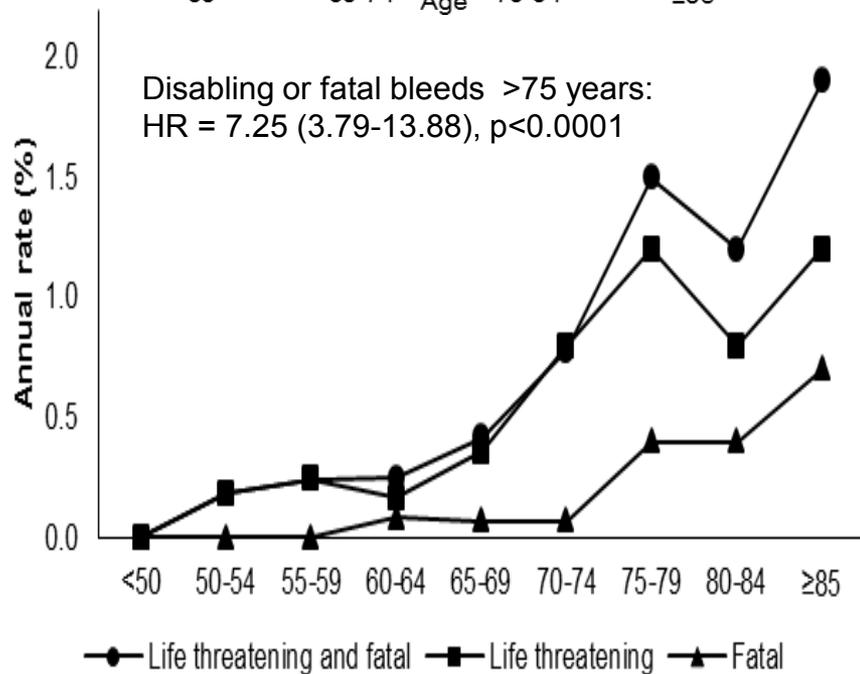
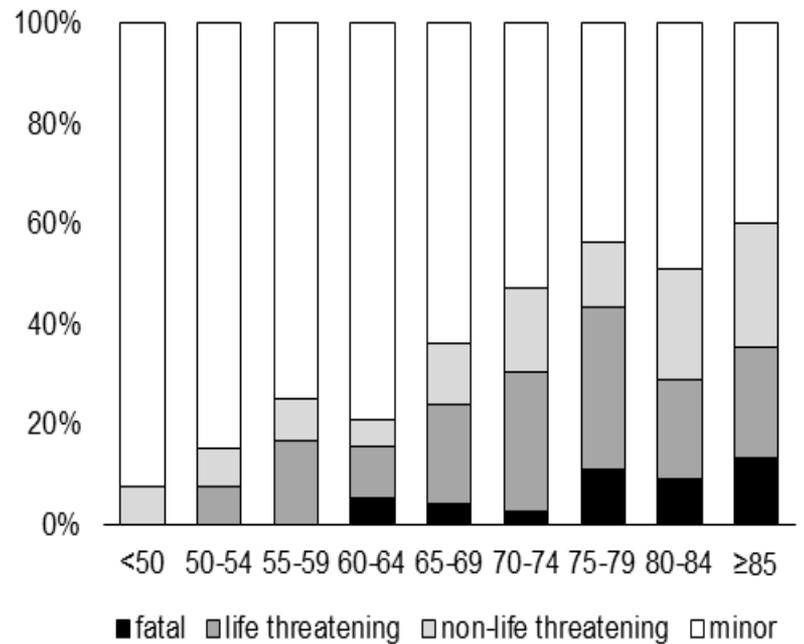
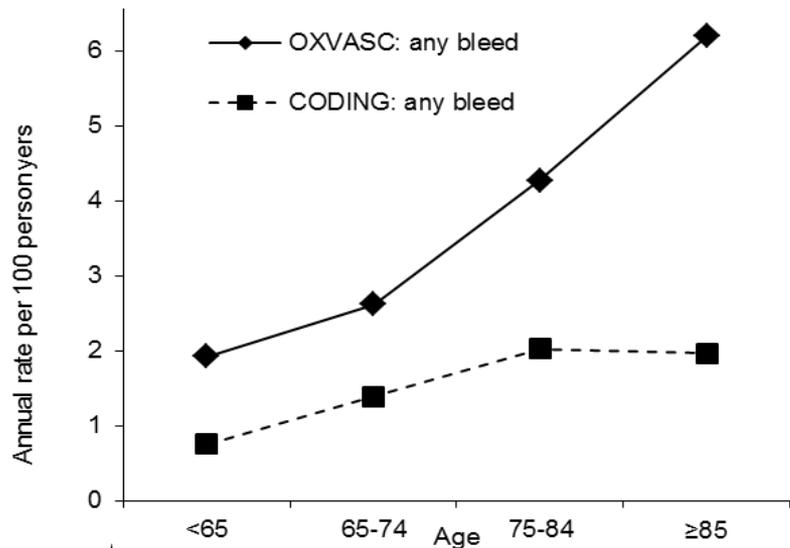
Outcome (non-disabling, disabling, fatal)



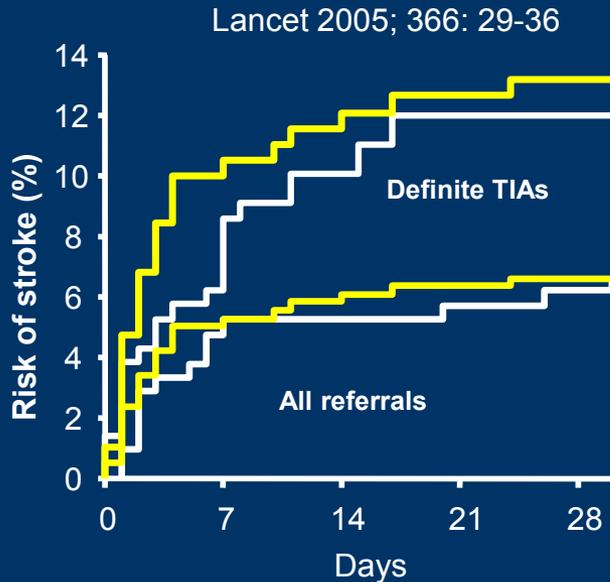
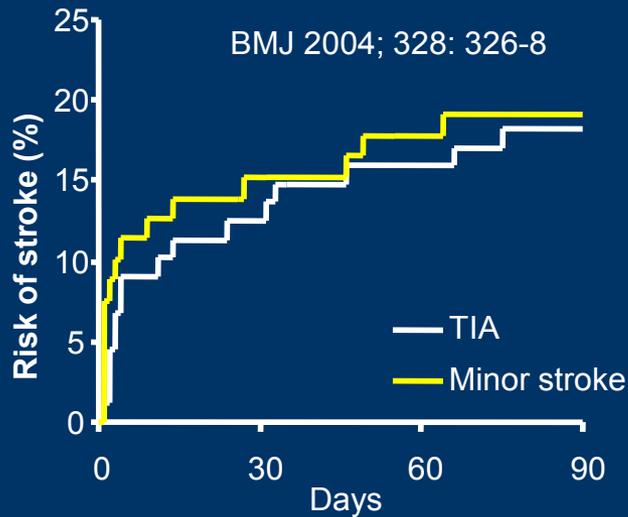
Lancet 2017; 390: 490-499



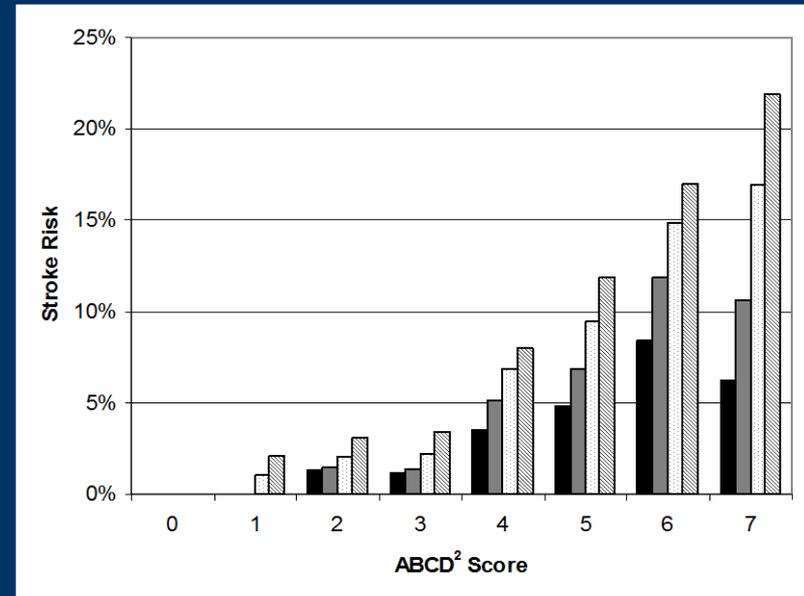
# Major bleeding events in OXVASC



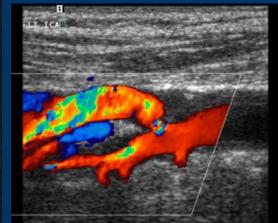
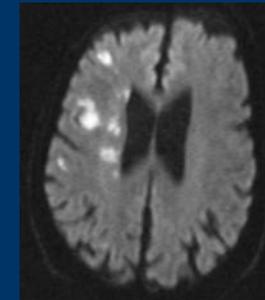
# Early risk of major stroke



# ABCD System



Lancet 2005; 366: 29-36  
Lancet 2007; 369:283-92  
Lancet Neurol 2010;9:106-9



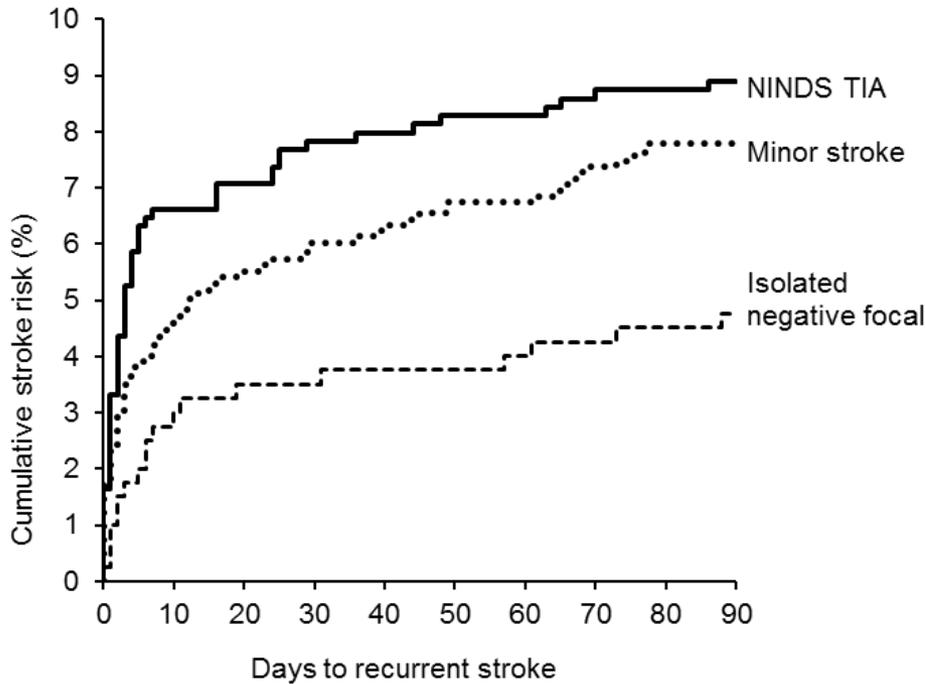
Stroke 2003; 34: e138-e40  
Stroke 2004; 35:1925-9  
Neurology 2005; 64: 817-20  
Stroke 2006; 37: 1254-60  
Lancet 2007;369:283-92  
Stroke 2010; 41: 667-73  
Lancet Neurol 2010: 9:1060-9

Brain 2003; 126:1940-54  
BMJ 2004; 328: 326-328  
Lancet 2005; 366: 29-36  
Lancet Neurol 2006; 5: 323-31  
Lancet Neurol 2007; 6:1063-72  
Stroke 2010; 41: 851-6  
Lancet 2011; 377; 1681-92

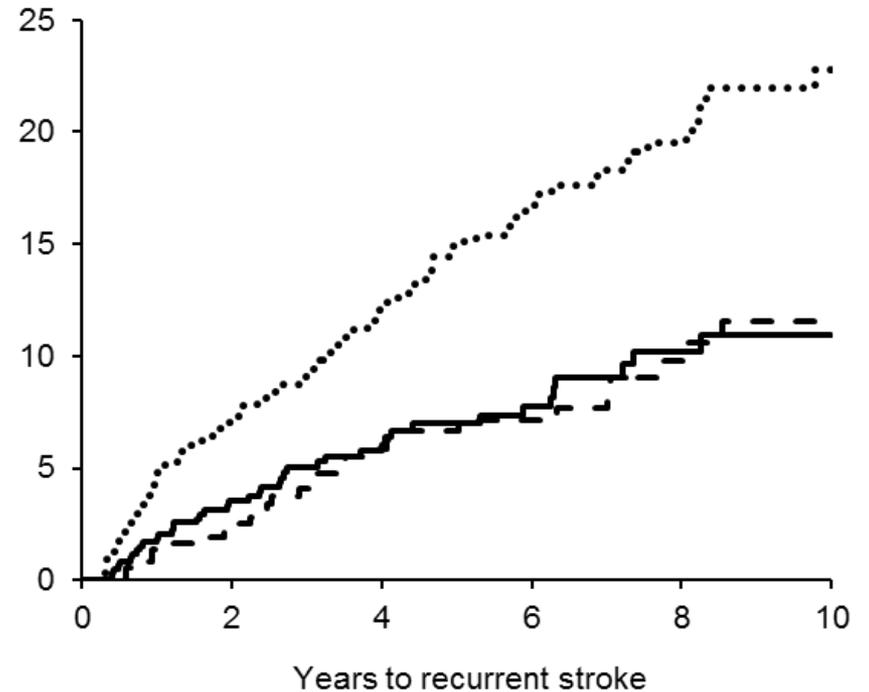
Neurology 2004; 62: 569-74  
Lancet 2004; 363: 915-24  
Stroke 2006; 37:320-2  
Cerebrovasc Dis 2007;24:231-5  
Neurology 2009; 72:1941-7  
Stroke 2010; 41:1907-13

# The short and long-term risk of stroke after minor stroke, TIA and isolated negative focal neurological symptoms in 3000 patients from the Oxford Vascular Study

## 90-day risk of stroke

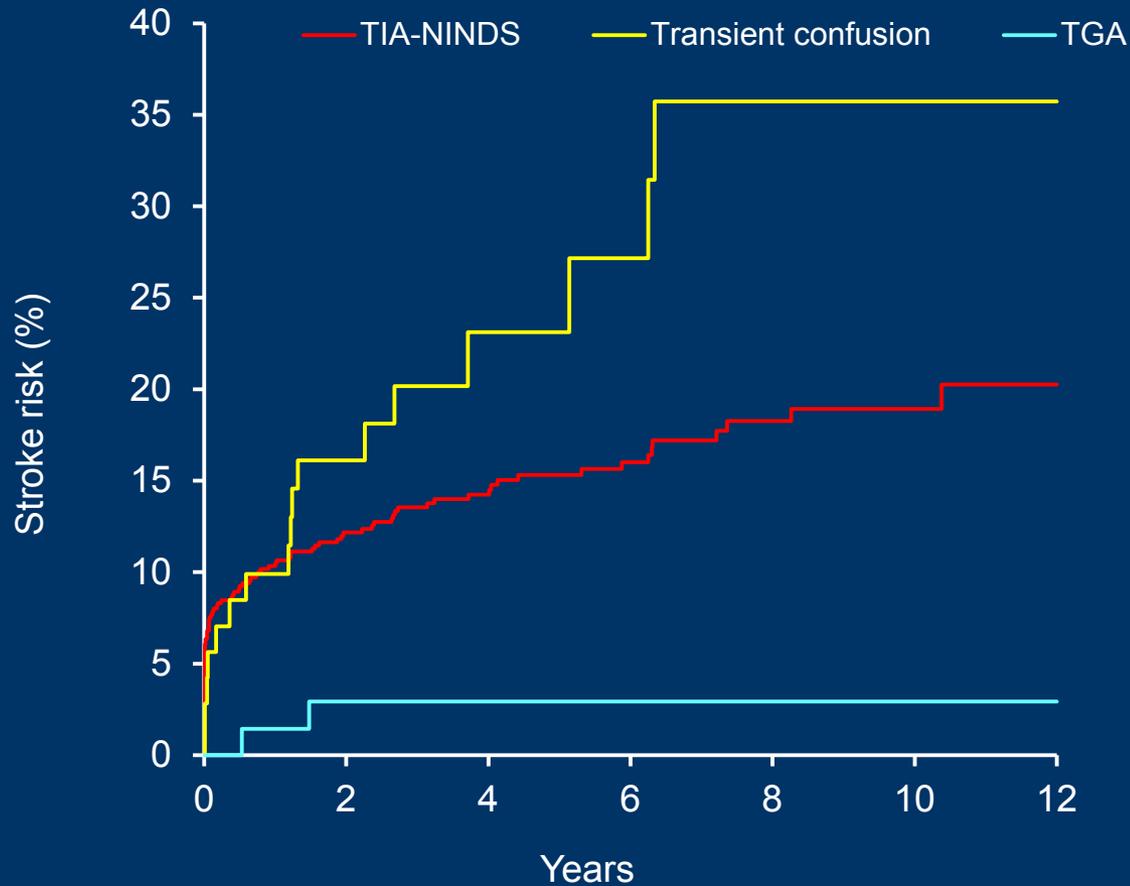


## 90-day to 10-year risk of stroke



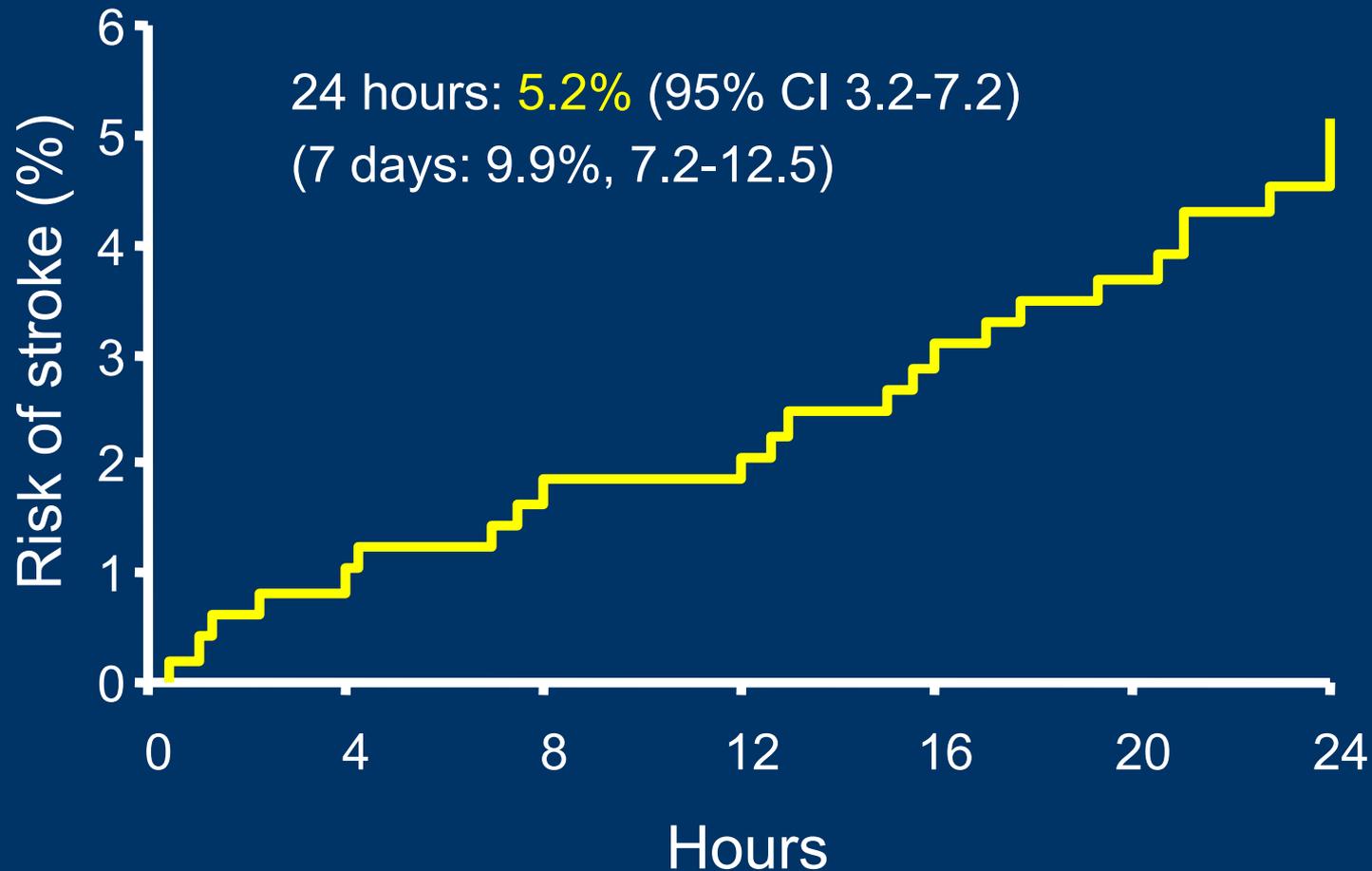
Unpublished data

# Long-term risk of stroke following an episode of transient confusion



# The 24 hour risk of recurrent stroke after TIA

## OXVASC years 1-5



# EXPRESS Study

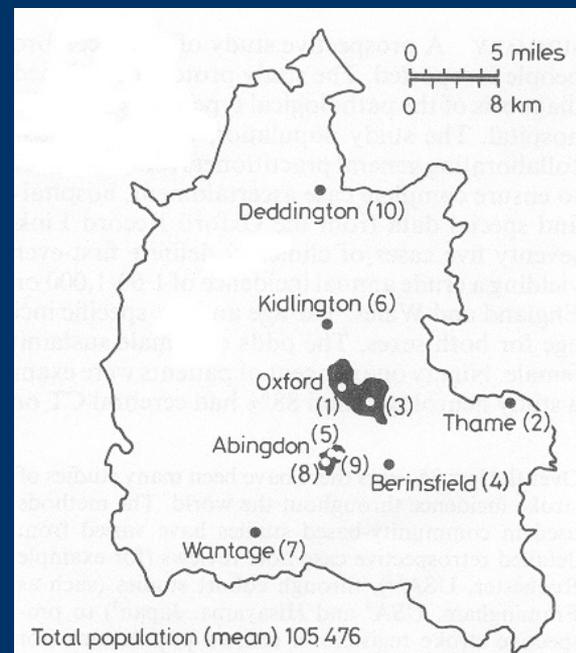
## Phase 1: months 1-30

- daily appointment clinic
- advice faxed to GP

## Phase 2 : months 30-60

- emergency clinic
- treatment given in clinic

- Antiplatelet treatment
  - Aspirin (300mg loading / 75mg daily)
  - Clopidogrel in high-risk cases
    - 300mg load + 75mg daily for 1 month
  - Dipyridamole after 1 month
- Simvastatin 40mg
- Perindopril 4mg + indapamide 1.25mg

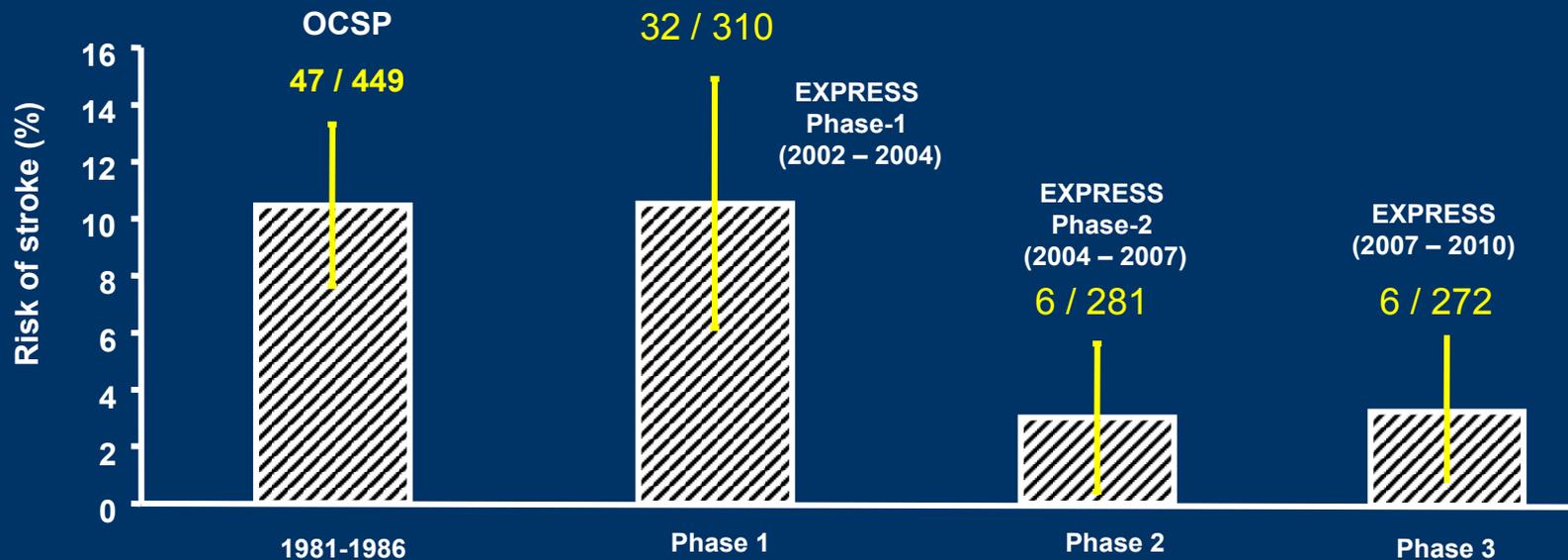
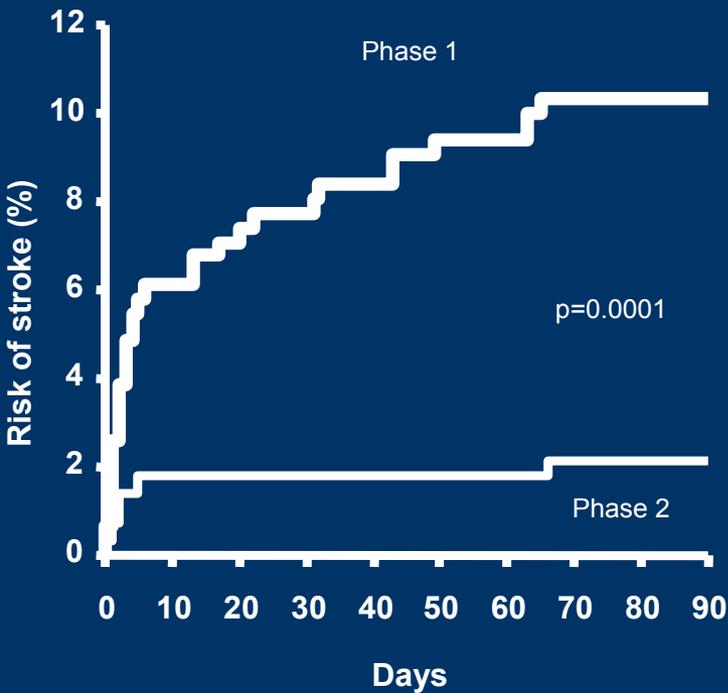


# EXPRESS Study

90-day risk of recurrent stroke after first seeking medical attention in all patients with TIA or stroke referred to the EXPRESS study clinic

Lancet 2007; 370:1432-42

Lancet Neurol 2009; 8:235-43

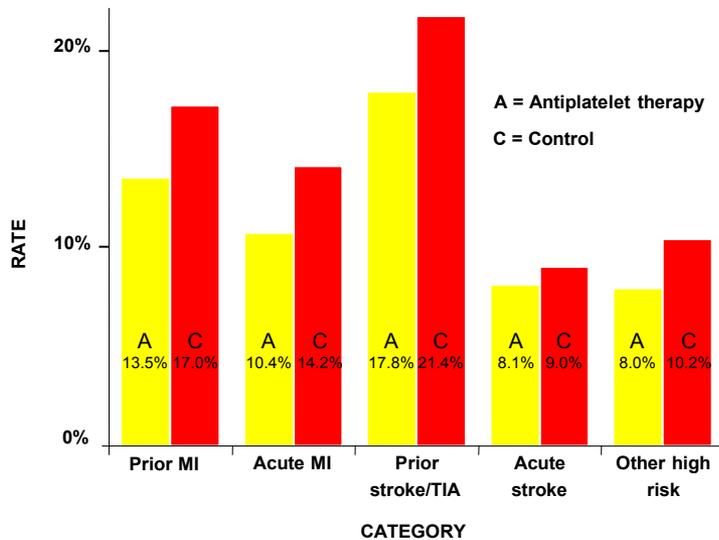


# Aspirin after TIA or ischaemic stroke

## Antithrombotic Trialists' Collaboration, 2002

Absolute effects on vascular events in various high-risk groups

Benefit per 1000(SE):	36(5)	38(5)	36(6)	9(3)	22(3)
Average duration:	27 m	1.3 m	29 m	0.7 m	22 m
P-value:	<0.00001	<0.00001	<0.00001	0.002	<0.00001



Effect of aspirin on risk of recurrent stroke after TIA or non-disabling stroke

Algra A. J van Gijn. **Aspirin at any dose above 30mg offers only modest protection after cerebral ischaemia.** JNNP 1996; 60: 197-99.

10 RCTs

Outcome: Stroke, MI, vasc.death

**Relative risk reduction = 13% (4-21)**

High-dose: 14% (2-24)

Medium-dose: 9% (-9-24) **ns**

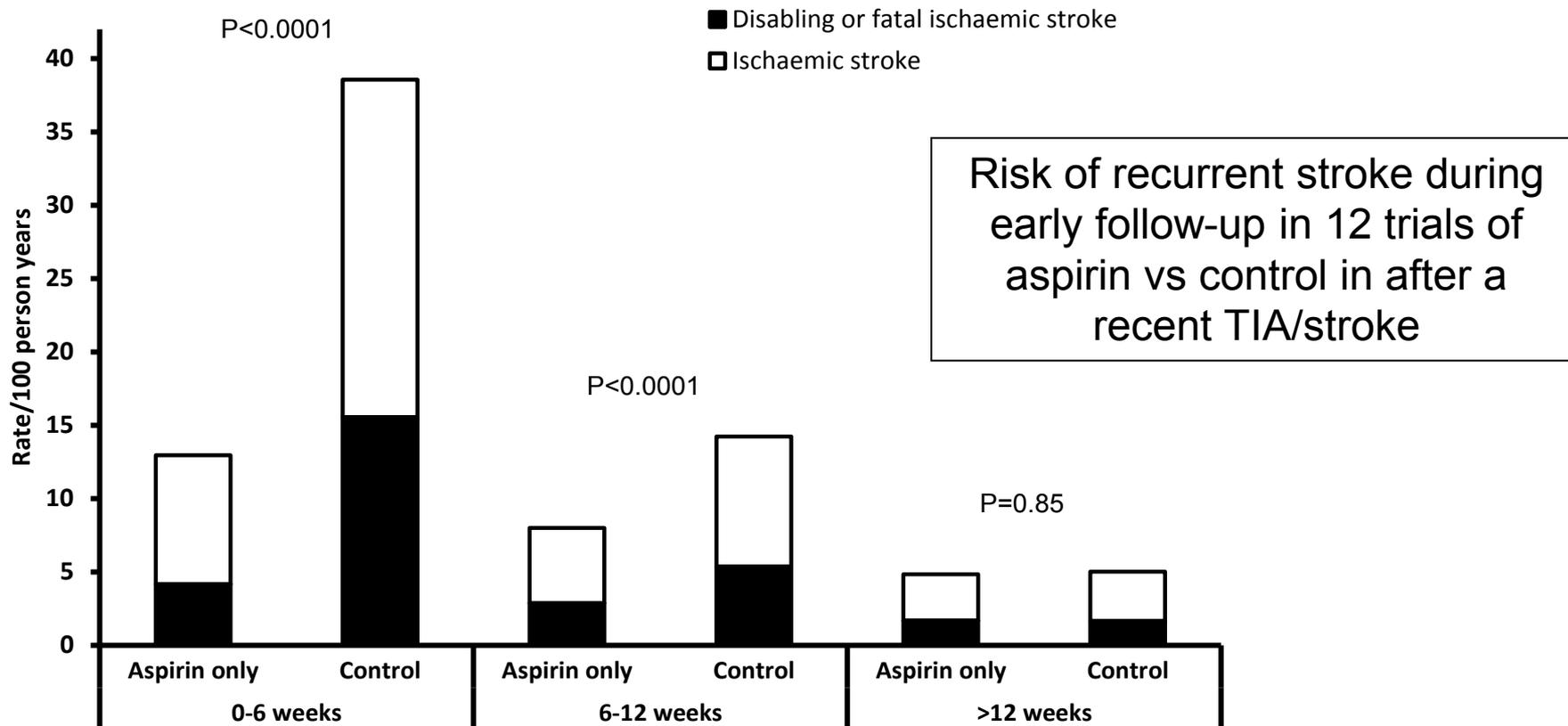
Low-dose: 13% (-3-27) **ns**

# Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials

Peter M Rothwell, Ale Algra, Zhengming Chen, Hans-Christoph Diener, Bo Norrving, Ziyah Mehta

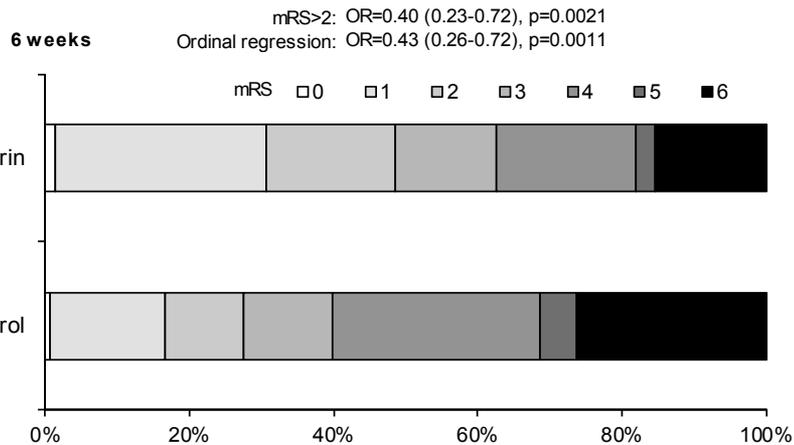


Lancet 2016 May 18<sup>th</sup> (online)

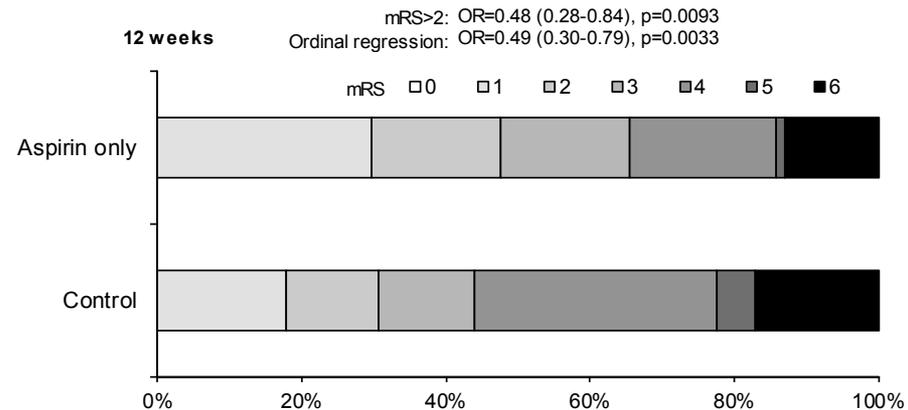
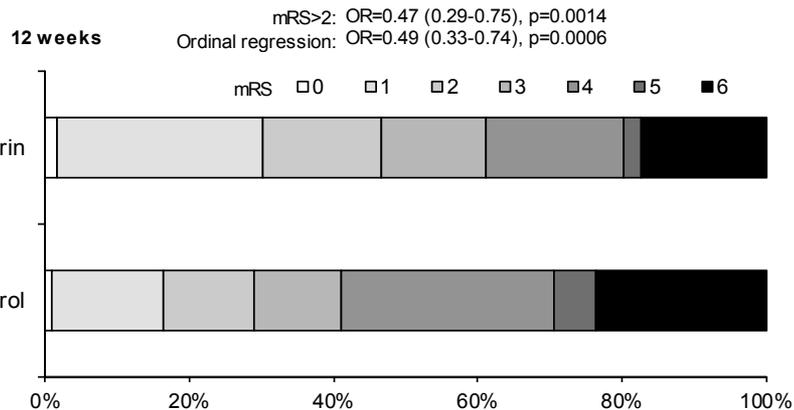
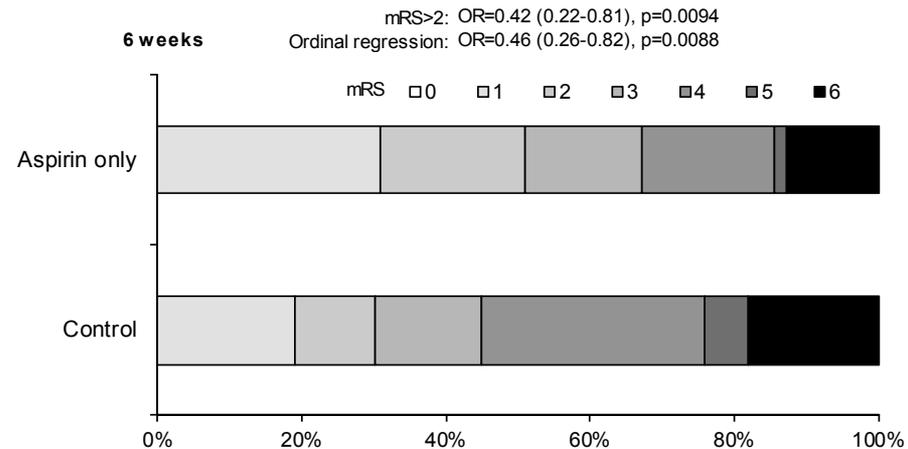


# Effect of aspirin vs control on the severity (mRS on follow-up) of recurrent ischaemic strokes in the first 6 and 12 weeks after randomisation in trials in secondary prevention after TIA and ischaemic stroke

**ANY ASPIRIN vs CONTROL**



**ASPIRIN ONLY vs CONTROL**

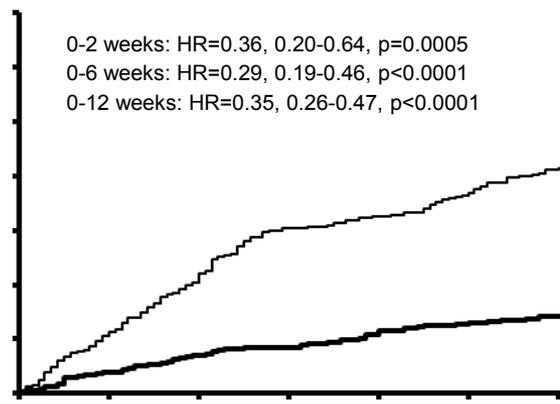
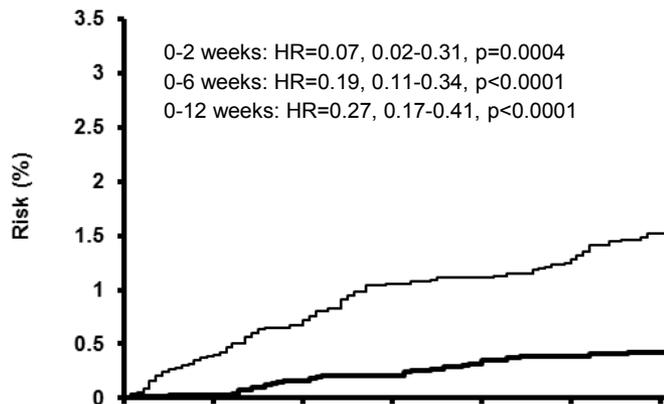


# Pooled analysis of the early risk of recurrent stroke in 12 trials of any aspirin vs control in secondary prevention after a recent TIA and ischaemic stroke

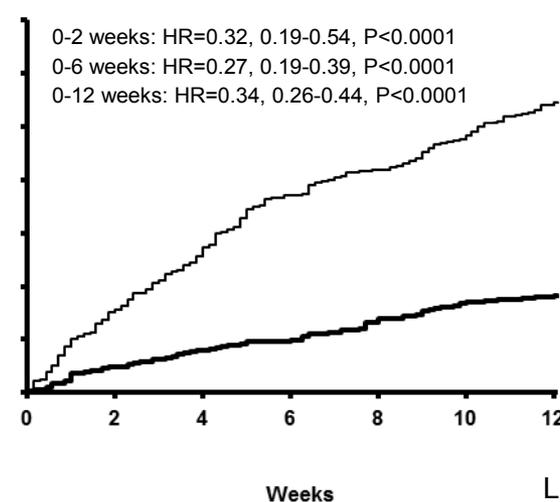
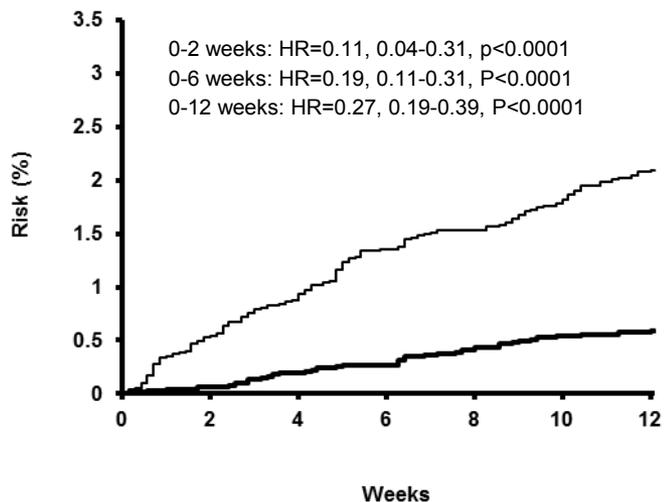
Patients with TIA and minor stroke only

All patients

## Disabling ischaemic stroke

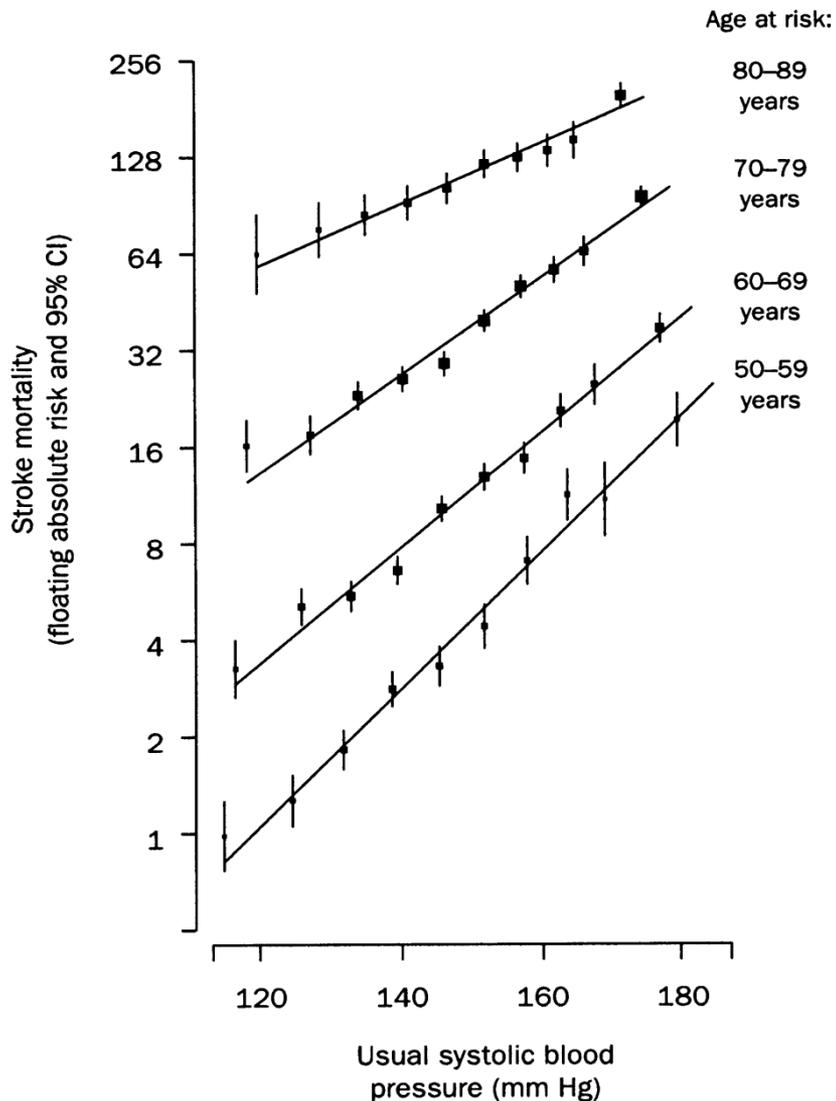


## Disabling ischaemic stroke and acute MI



# Prospective Studies Collaboration

**A: Systolic blood pressure**



Lancet 2002; 360: 1903-13

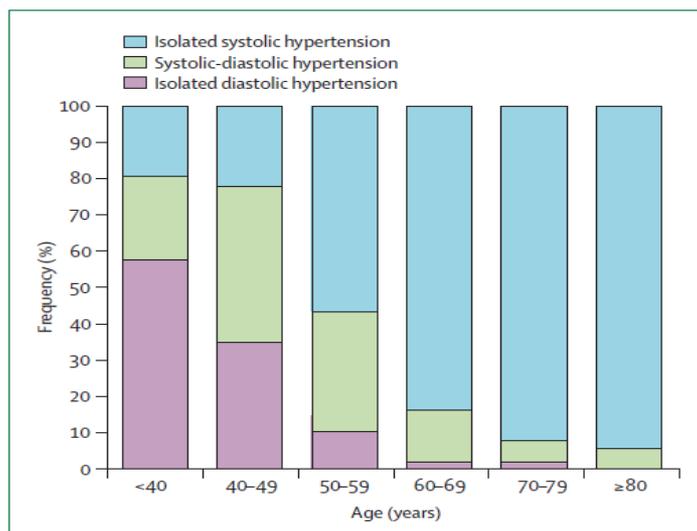
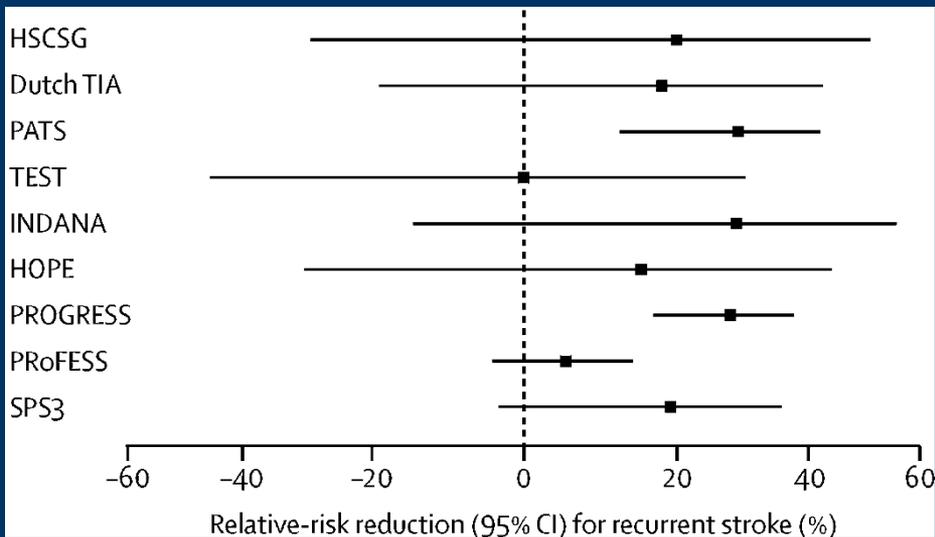
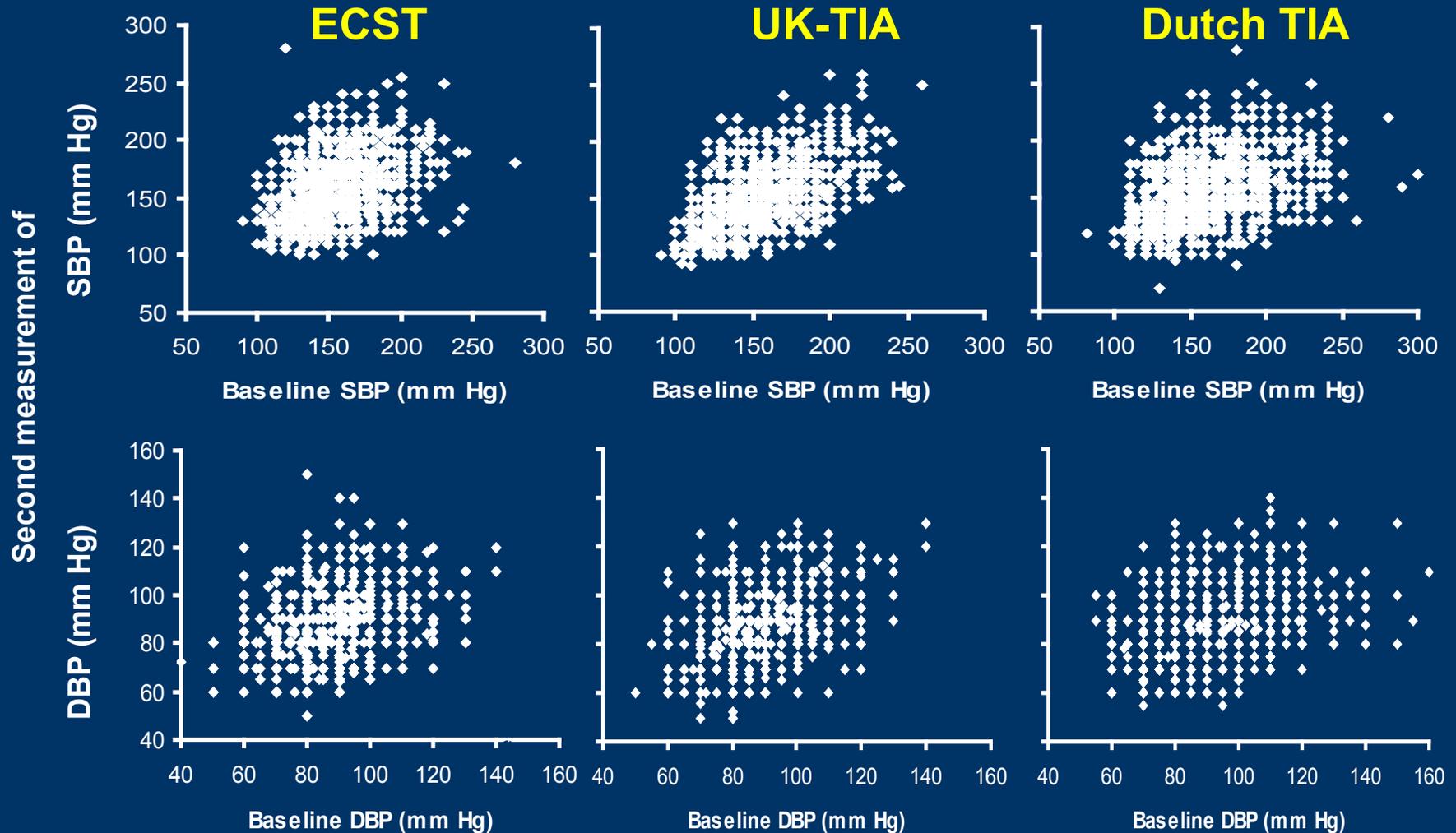


Figure: Categories of blood pressure in untreated hypertensive patients illustrating the importance of systolic blood pressure beyond age 50 years. Adapted from reference 7, with permission.

## Consistent results from trials of BP-lowering in secondary prevention after TIA/stroke



# Variation in BP – baseline vs first follow-up



## Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension

Peter M Rothwell

## Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension

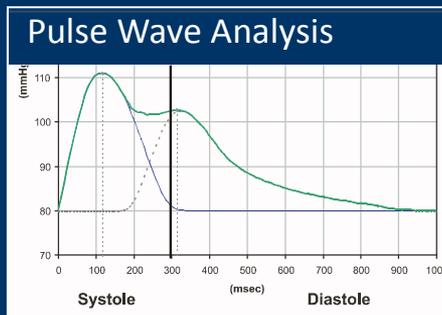
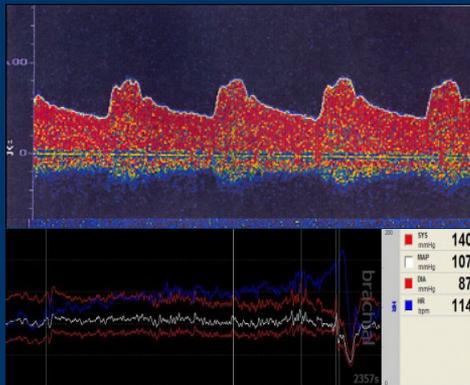
Peter M Rothwell, Sally C Howard, Eamon Dolan, Eoin O'Brien, Joanna E Dobson, Bjorn Dahlöf, Peter S Sever, Neil R Poulter

## Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis

Alastair J S Webb, Urs Fischer, Ziyah Mehta, Peter M Rothwell

## Effects of $\beta$ blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke

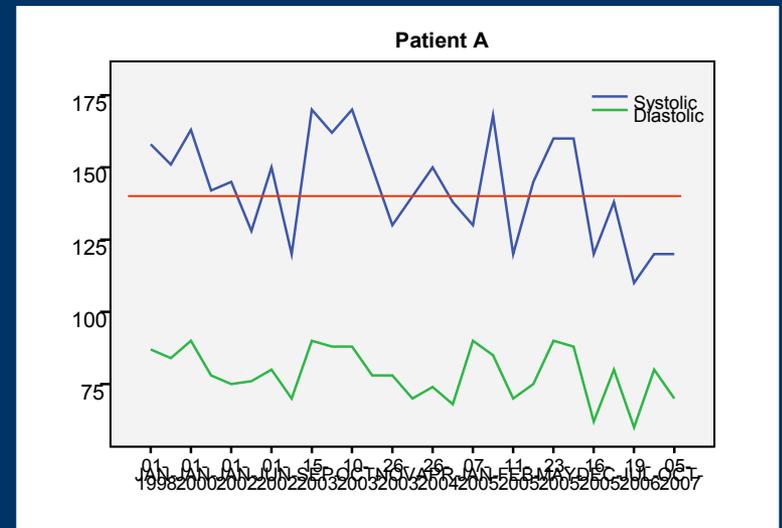
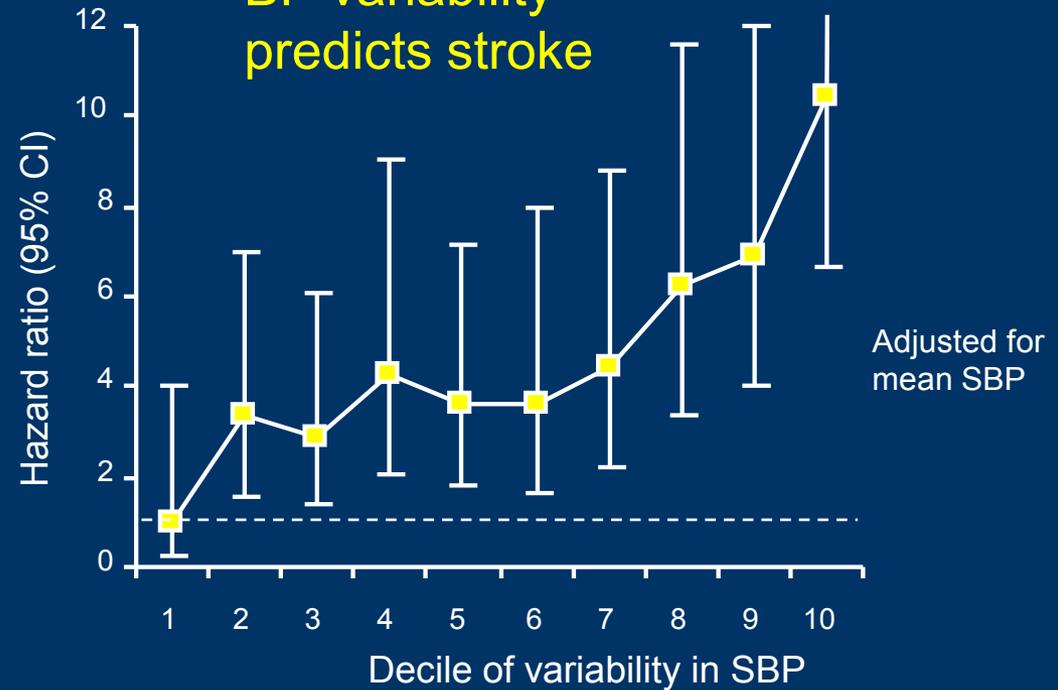
Peter M Rothwell, Sally C Howard, Eamon Dolan, Eoin O'Brien, Joanna E Dobson, Bjorn Dahlöf, Neil R Poulter, Peter S Sever, on behalf of the ASCOT-BPLA and MRC Trial Investigators



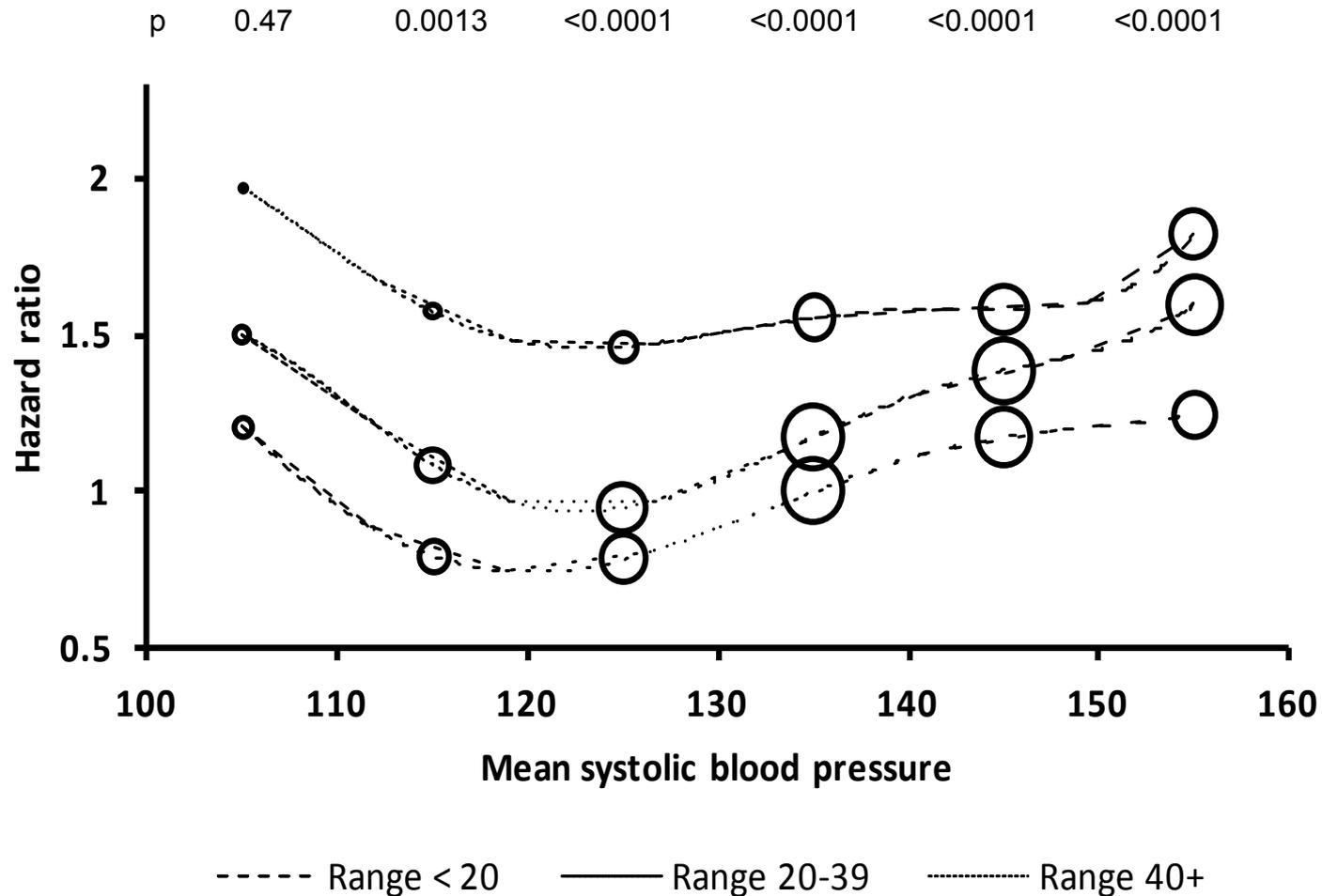
Aortic BP

Aortic stiffness

## BP variability predicts stroke

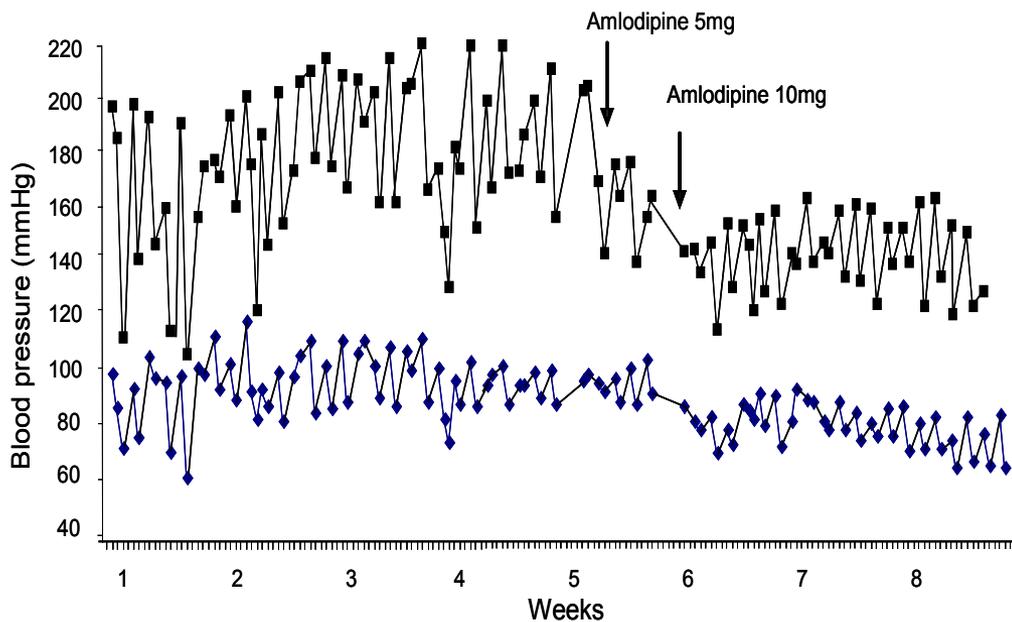
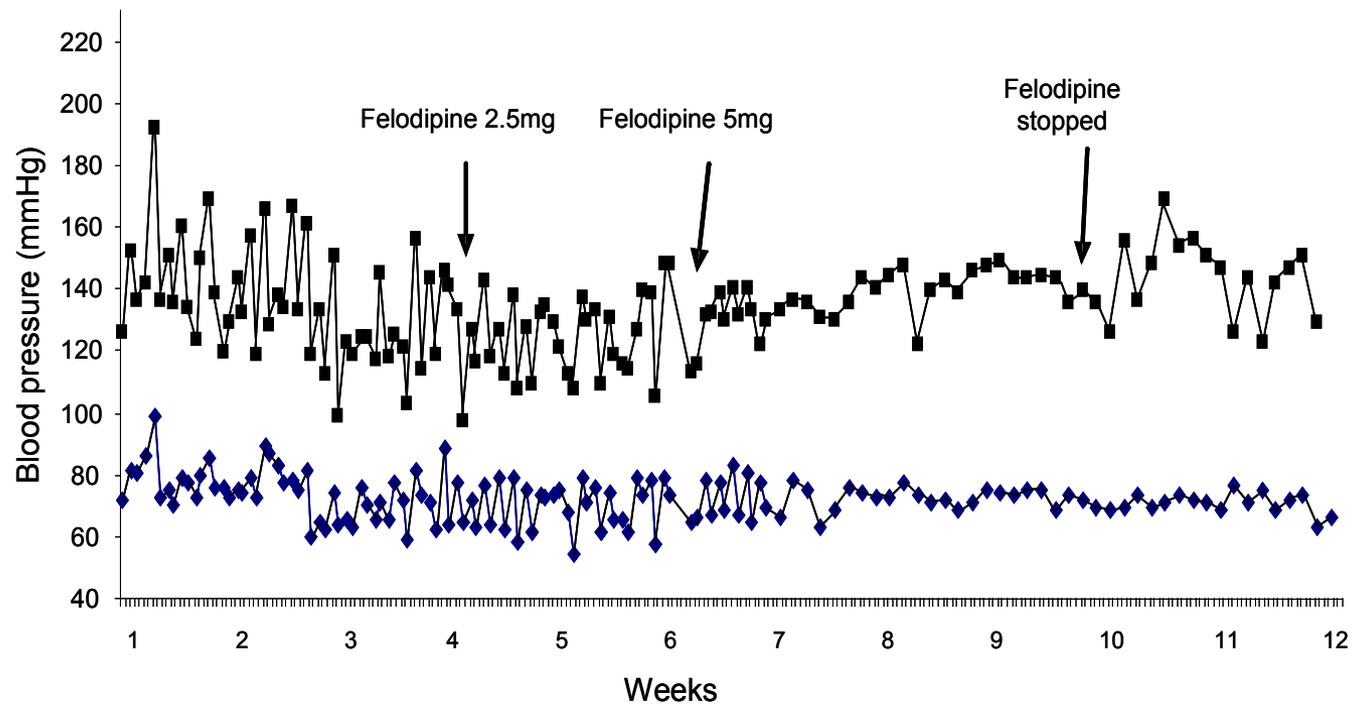


# BPLTC pooled analysis of 28 trials: Risk of stroke and CV events vs mean and range of SBP



Unpublished data

# OXVASC Bluetooth Home BP monitoring

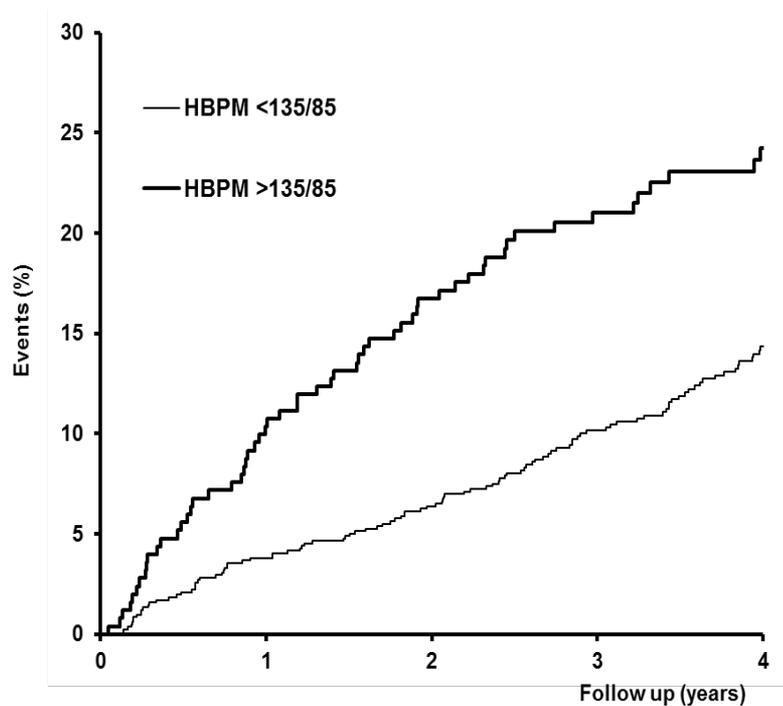


## COMMIT Study

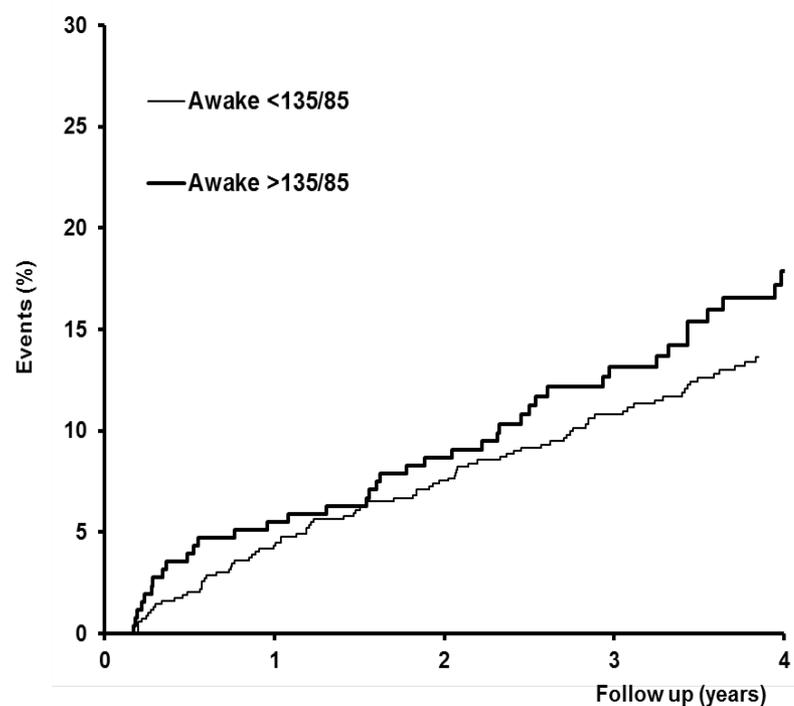
- 1200 patients
- 2886 drug changes
- 92% uptake

# Predictive value for all cardiovascular events of residual hypertension based on home telemetric BP-monitoring versus 24 hour ambulatory monitoring (COMMIT Study)

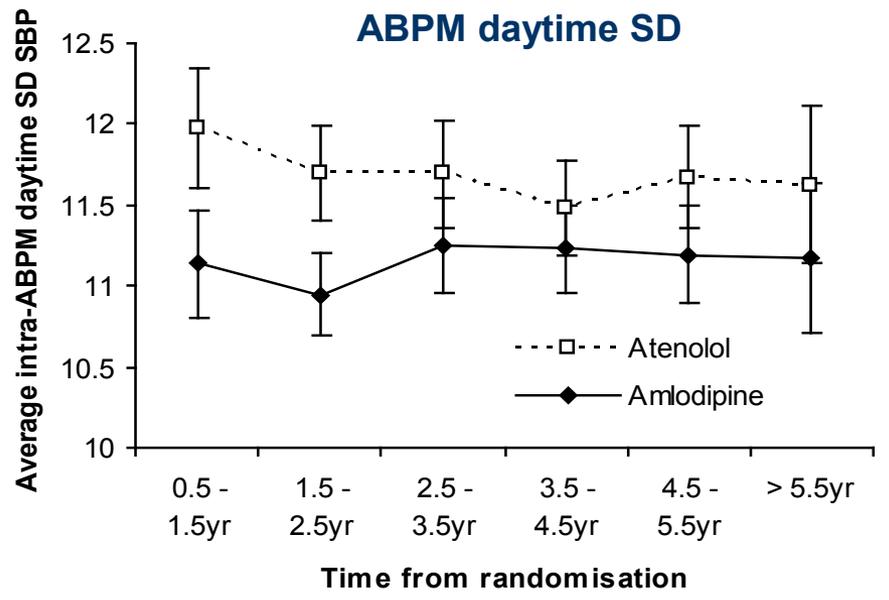
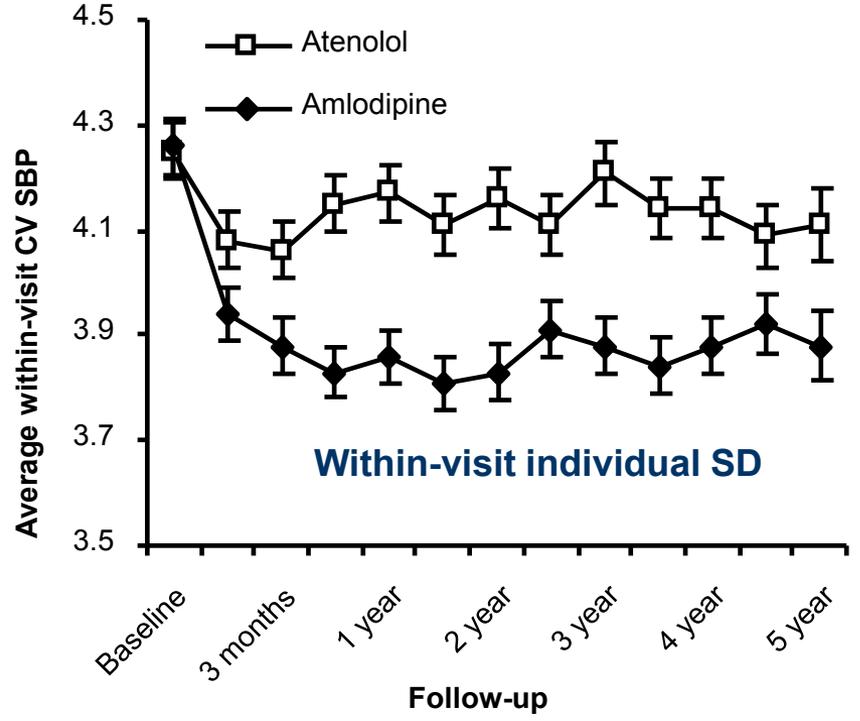
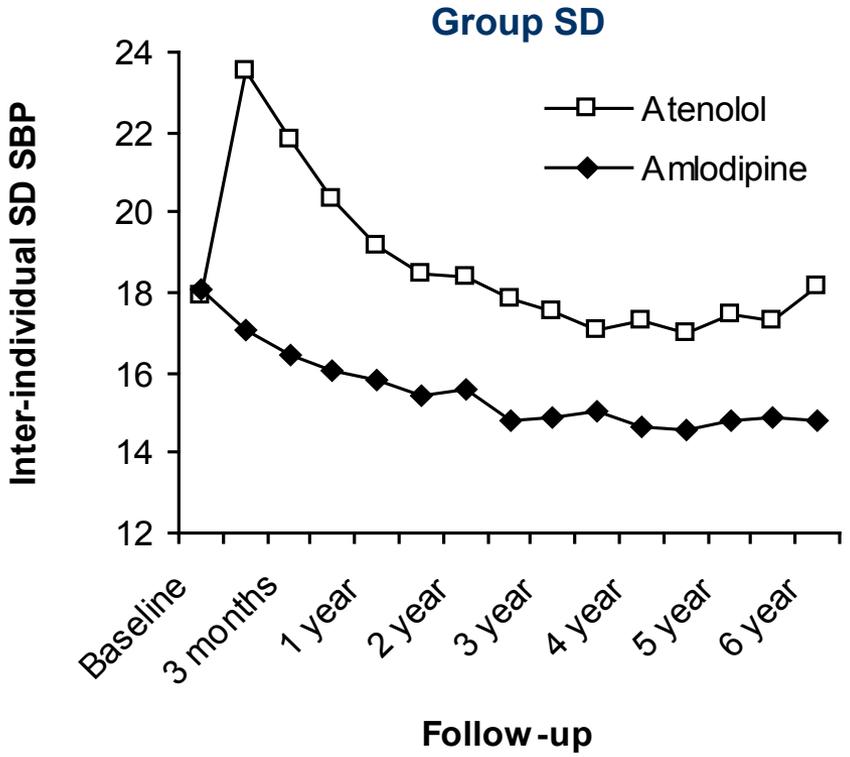
## Hypertension on home monitoring



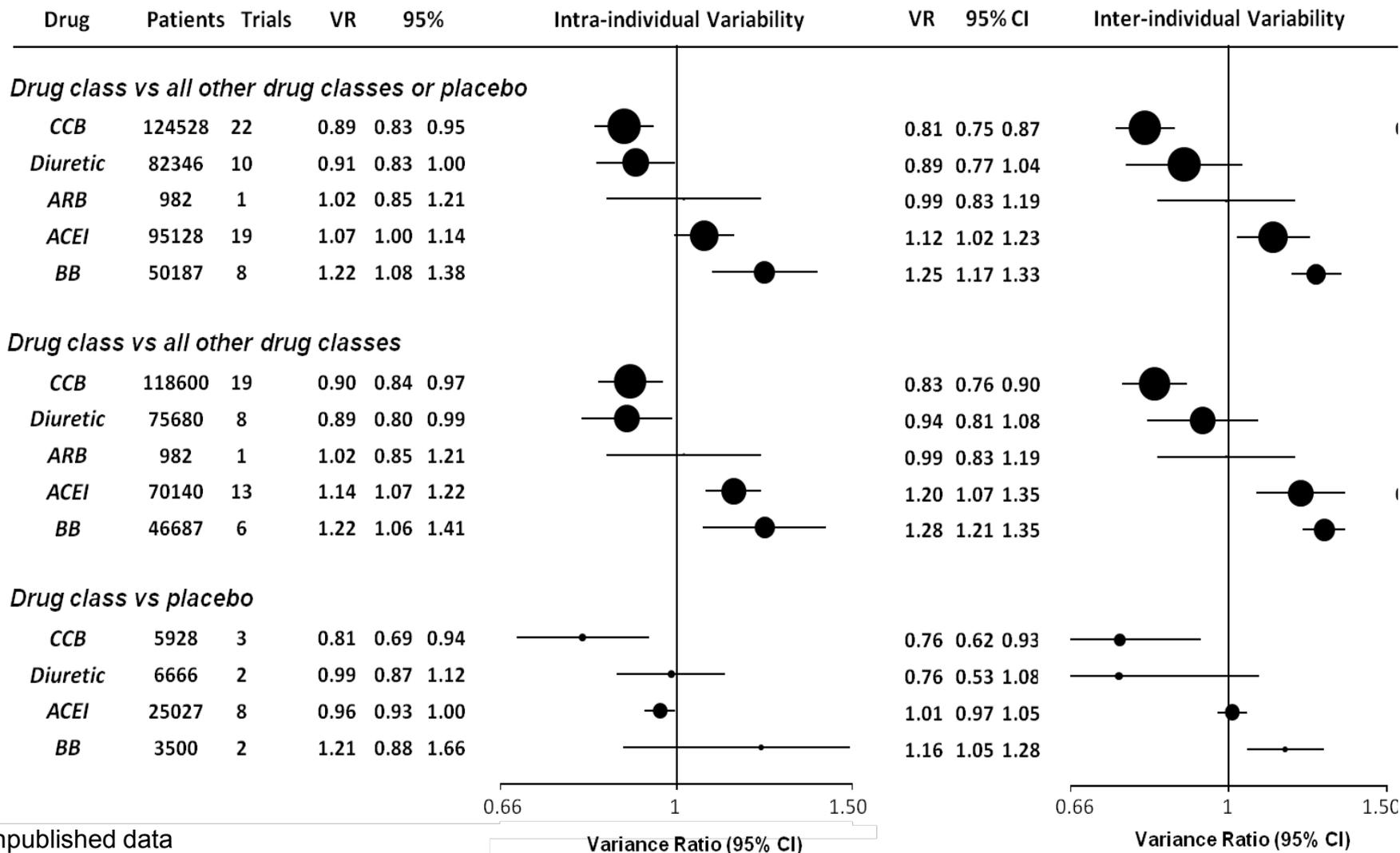
## Hypertension on 24-hour ABPM



# Effect of treatment on variability in SBP in ASCOT-BPLA



# Pooled estimates of VR in parallel group trials in BPLTC: Intra-individual versus inter-individual variability



Unpublished data

# Spectrum of medical research

Clinical  
innovation

Clinical  
effectiveness

Clinical  
exploration

Basic laboratory science  
Clinical laboratory science  
“Translational research”  
Cohort studies  
Randomized trials  
Population studies  
Clinical practice



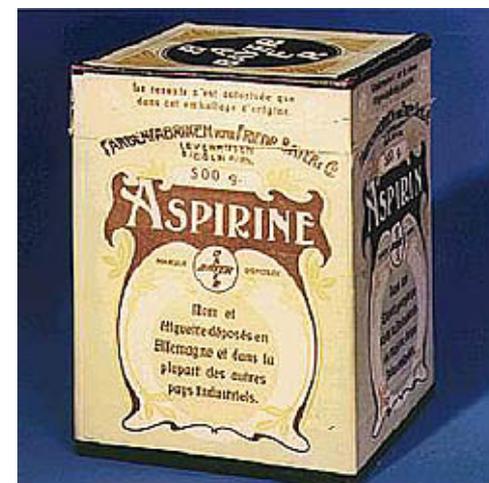
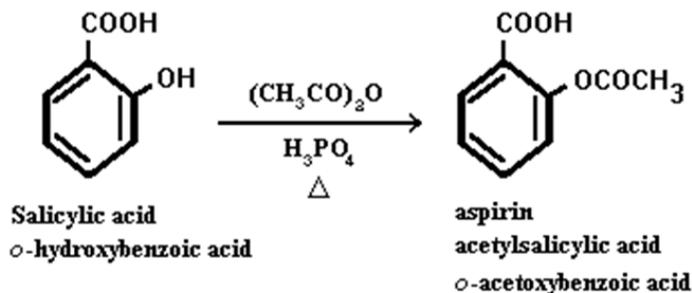
# First ever synthetic pharmaceutical

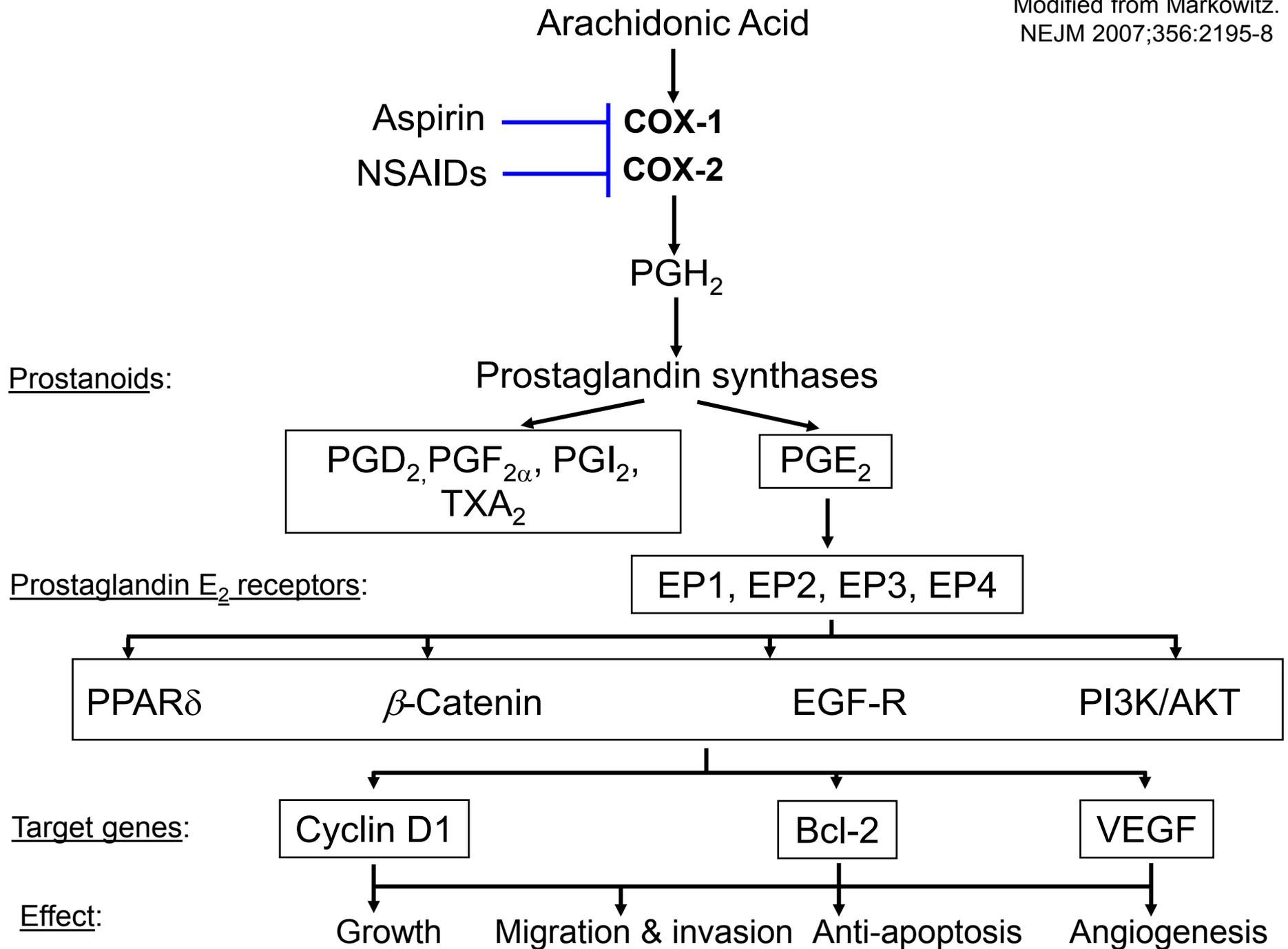
•1897 – August 10<sup>th</sup> – first sample prepared by **Felix Hoffman** - tries it out on colleagues & family – great for rheumatism

•**A-** Acetylation, **SPIR** – *Spiraea ulmaria* (meadowsweet), **IN** (ending for all drug names)

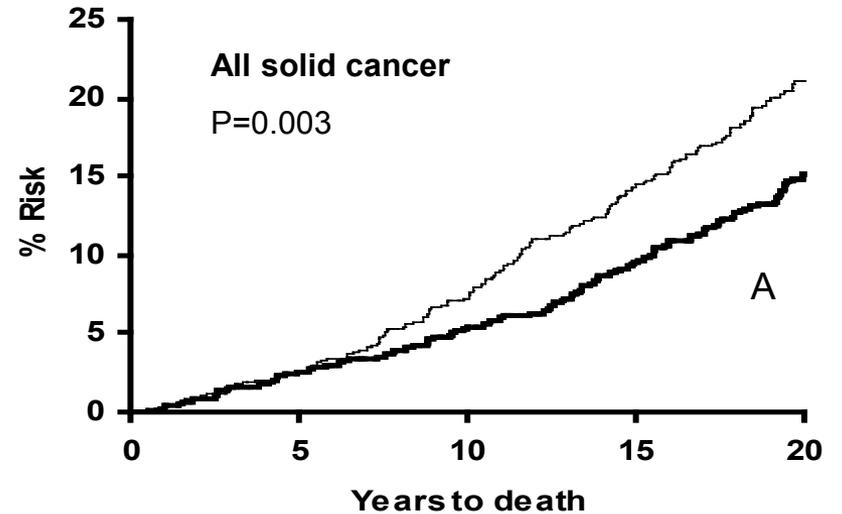
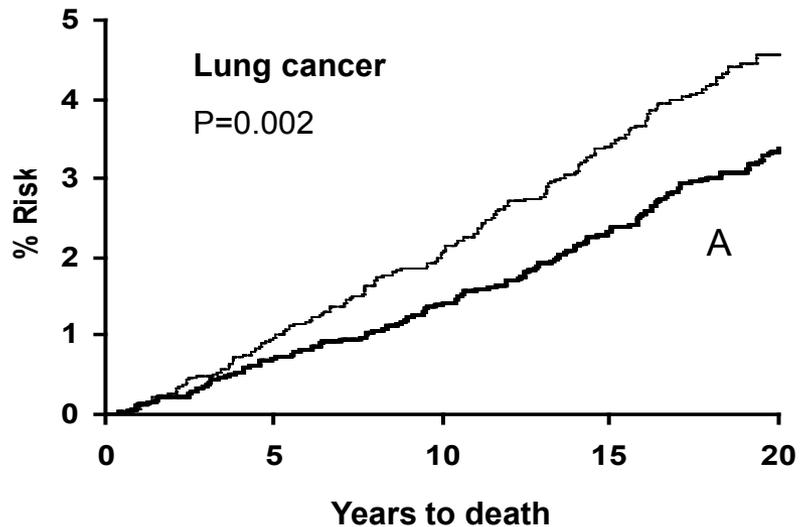
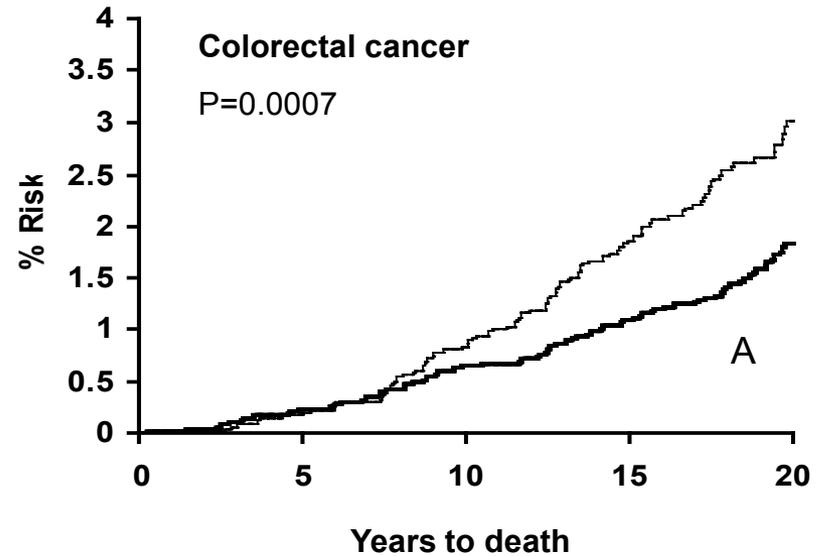
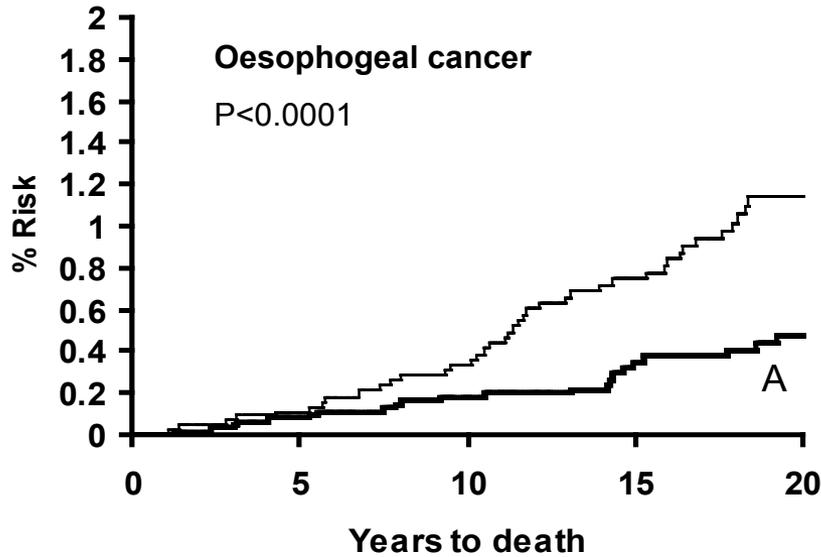
•1899 – Bayer releases acetyl-salicylic acid in a powder form for medicinal purposes, credits Hoffman with the discovery.

•1853 – French Chemist, **Charles Frederich Gerhardt** combined sodium salicylate and acetyl chloride to get acetyl-salicylic acid (ASA).

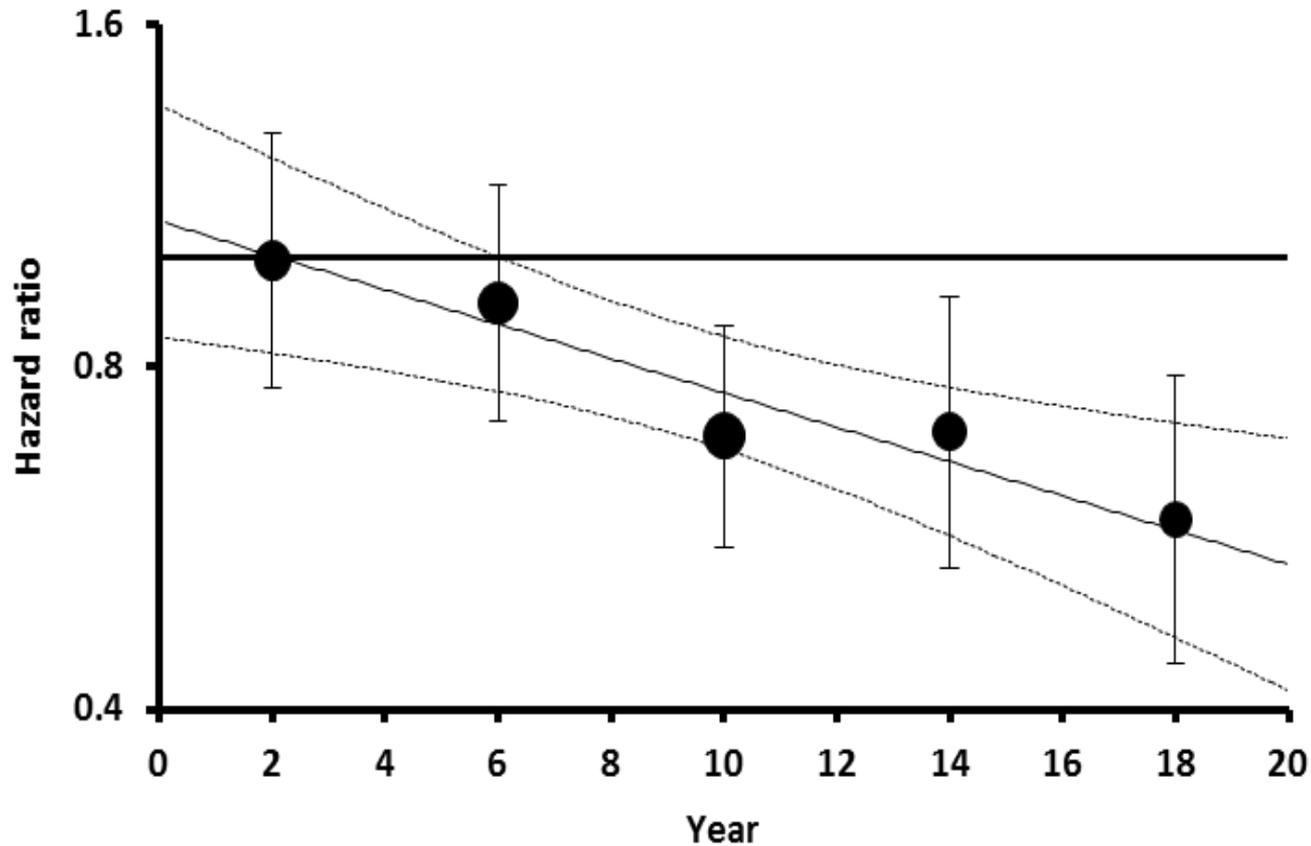




Risk of death due to cancer during **20-year follow-up** of three RCTs of aspirin versus control: 12,659 patients; 1364 cancer deaths



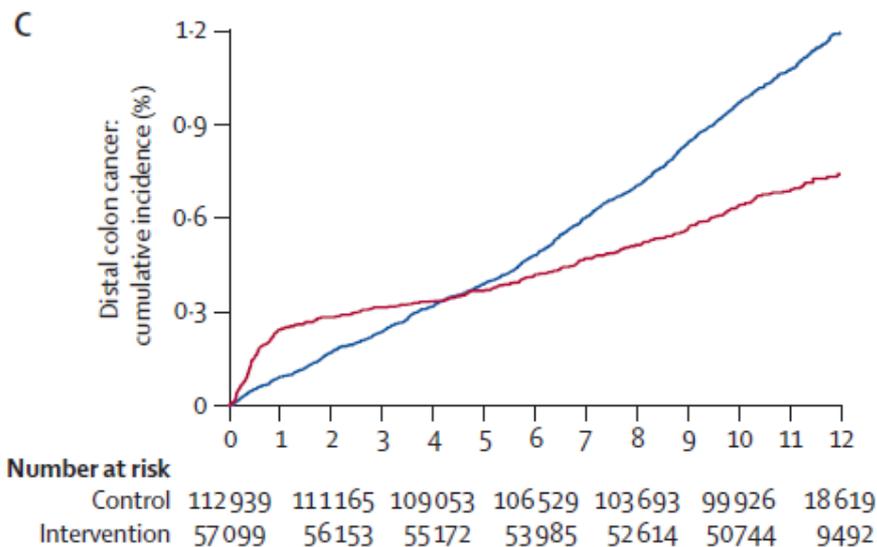
Effect of aspirin on risk of colorectal cancer in relation to dose, frequency and duration, baseline characteristics, and tumour site: long-term follow-up of 80,000 subjects from randomised trials



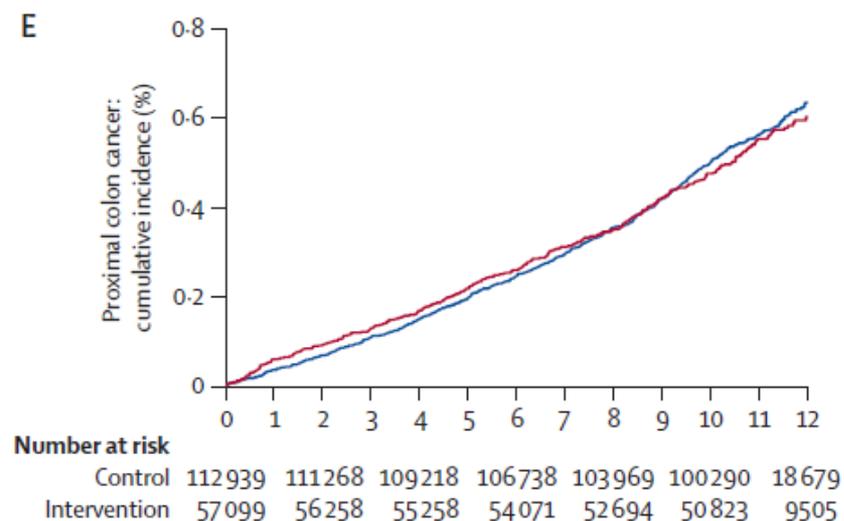


# Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial

Wendy S Atkin, Rob Edwards, Ines Kralj-Hans, Kate Wooldrage, Andrew R Hart, John M A Northover, D Max Parkin, Jane Wardle, Stephen W Duffy, Jack Cuzick, UK Flexible Sigmoidoscopy Trial Investigators

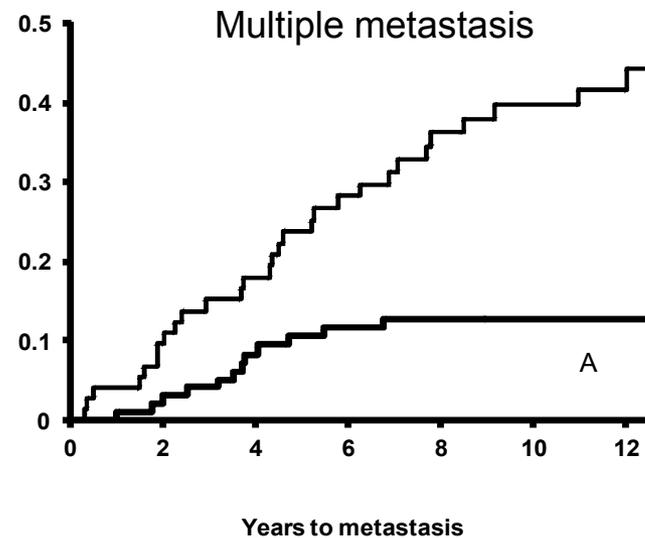
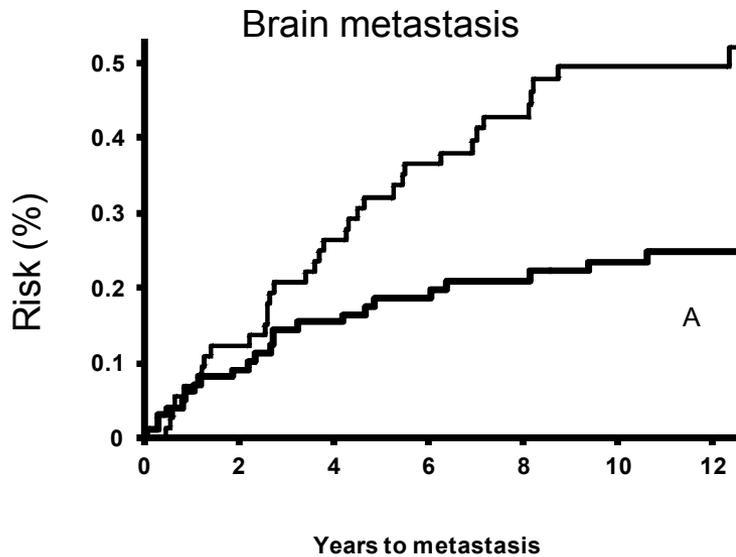
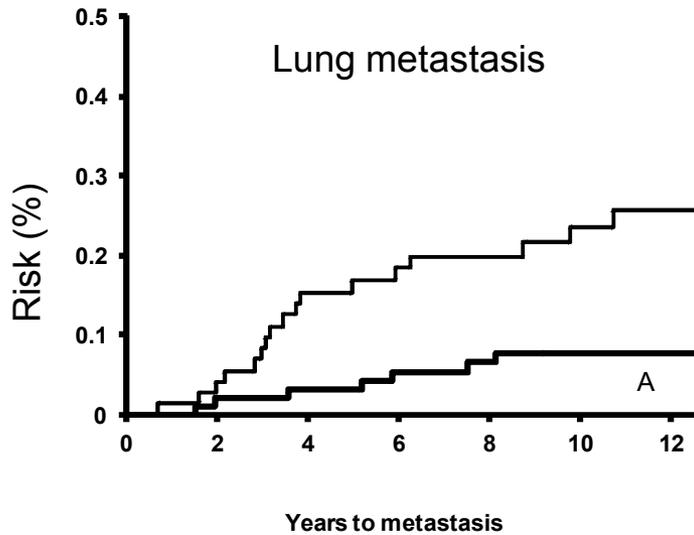


Distal colorectal cancer



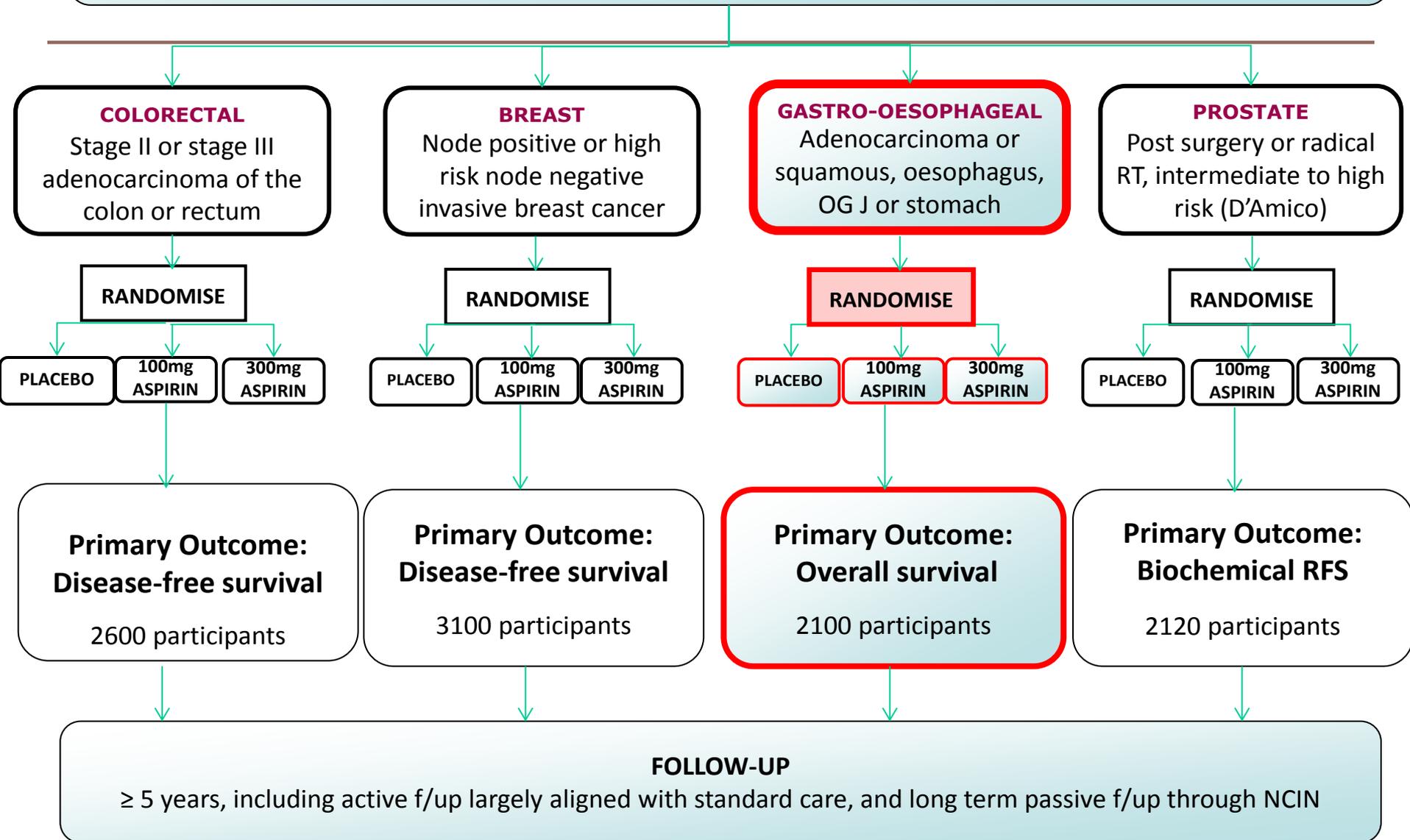
Proximal colon cancer

# Effect of aspirin on risk of distant metastasis by site of metastasis: time from randomisation to presentation of metastasis



# Add-Aspirin Trial: 4 PHASE III TRIALS - OVERARCHING PROTOCOL

Participants undergone primary treatment with curative intent for an early stage common solid tumour  
RUN IN PERIOD – 8 weeks Aspirin 100mg daily



# Spectrum of medical research

Clinical  
innovation

Clinical  
effectiveness

Clinical  
exploration

Basic laboratory science  
Clinical laboratory science  
“Translational research”  
Cohort studies  
Randomized trials  
Population studies  
Clinical practice



