

Cerebrovascular disease and diabetes



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Proud to be a clinical pharmacologist

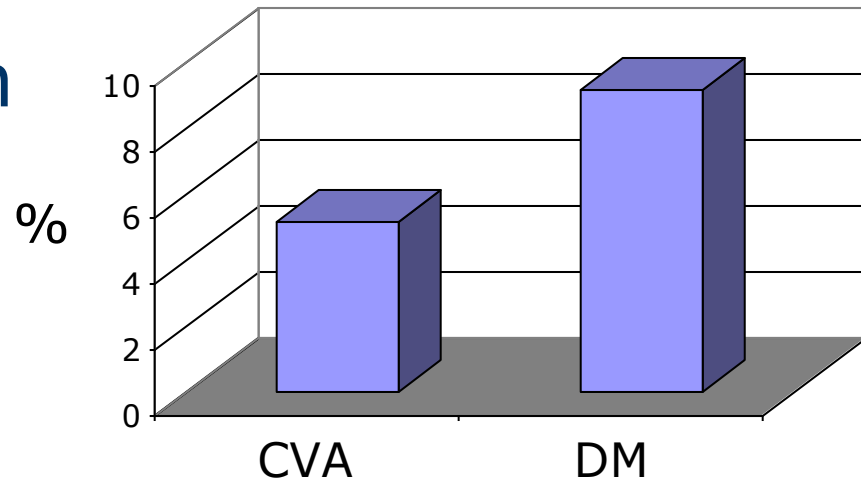


Relationship between stroke and diabetes

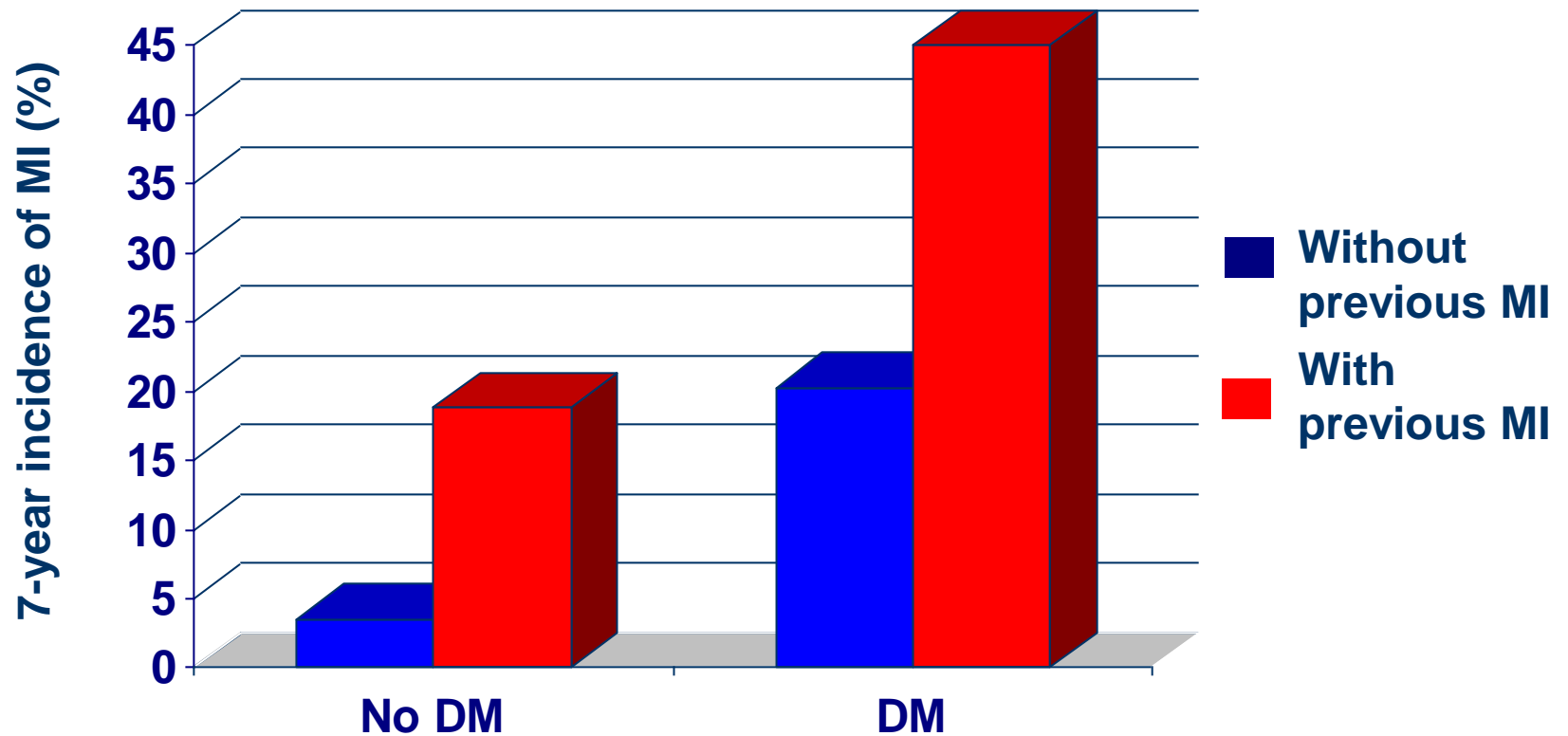
- Epidemiology
- Pathophysiology
- Therapeutics

Does stroke matter?

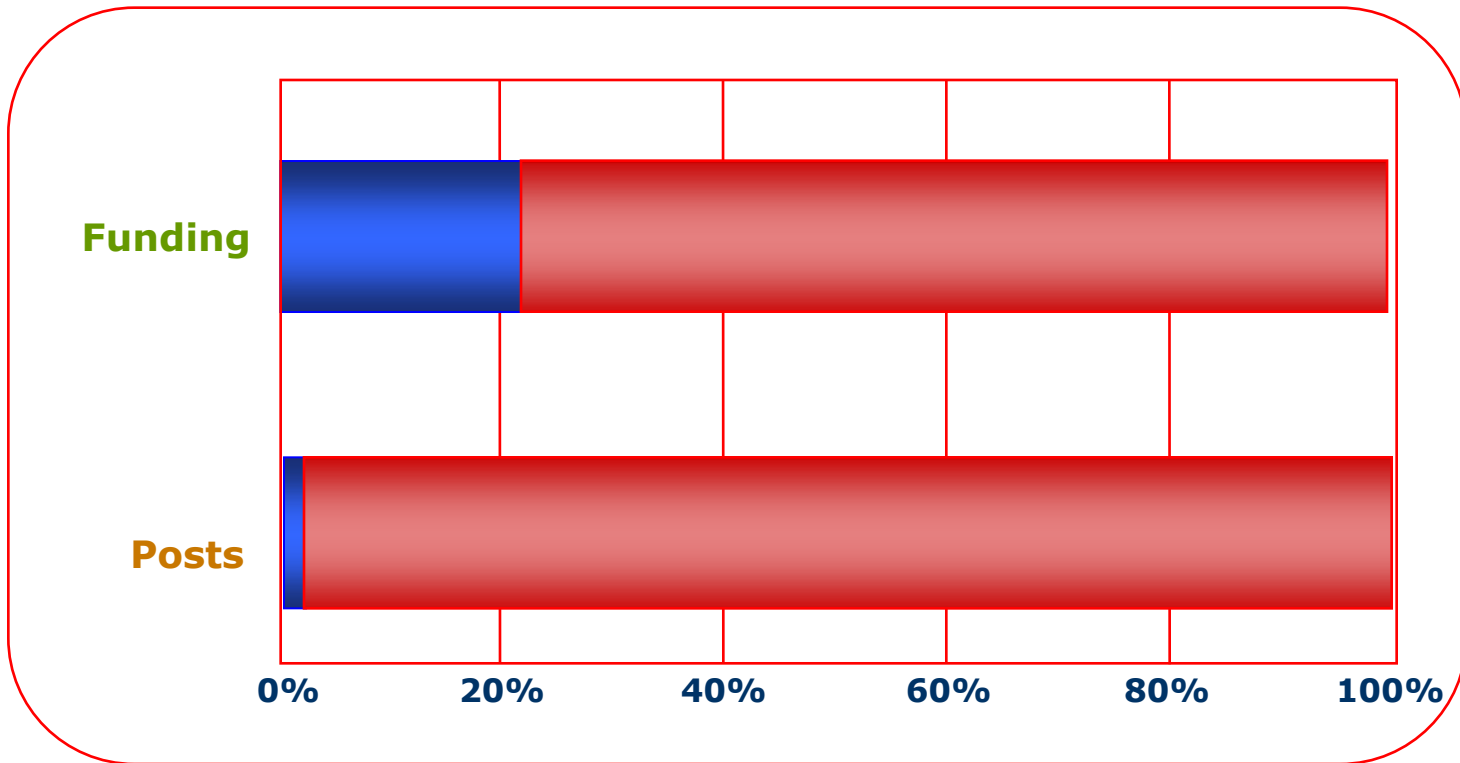
- # 1 cause of disability
- # 3 cause of death
- 7% NHS beds
- Approx £3 billion



Epidemiology: type 2 diabetes *and* MI



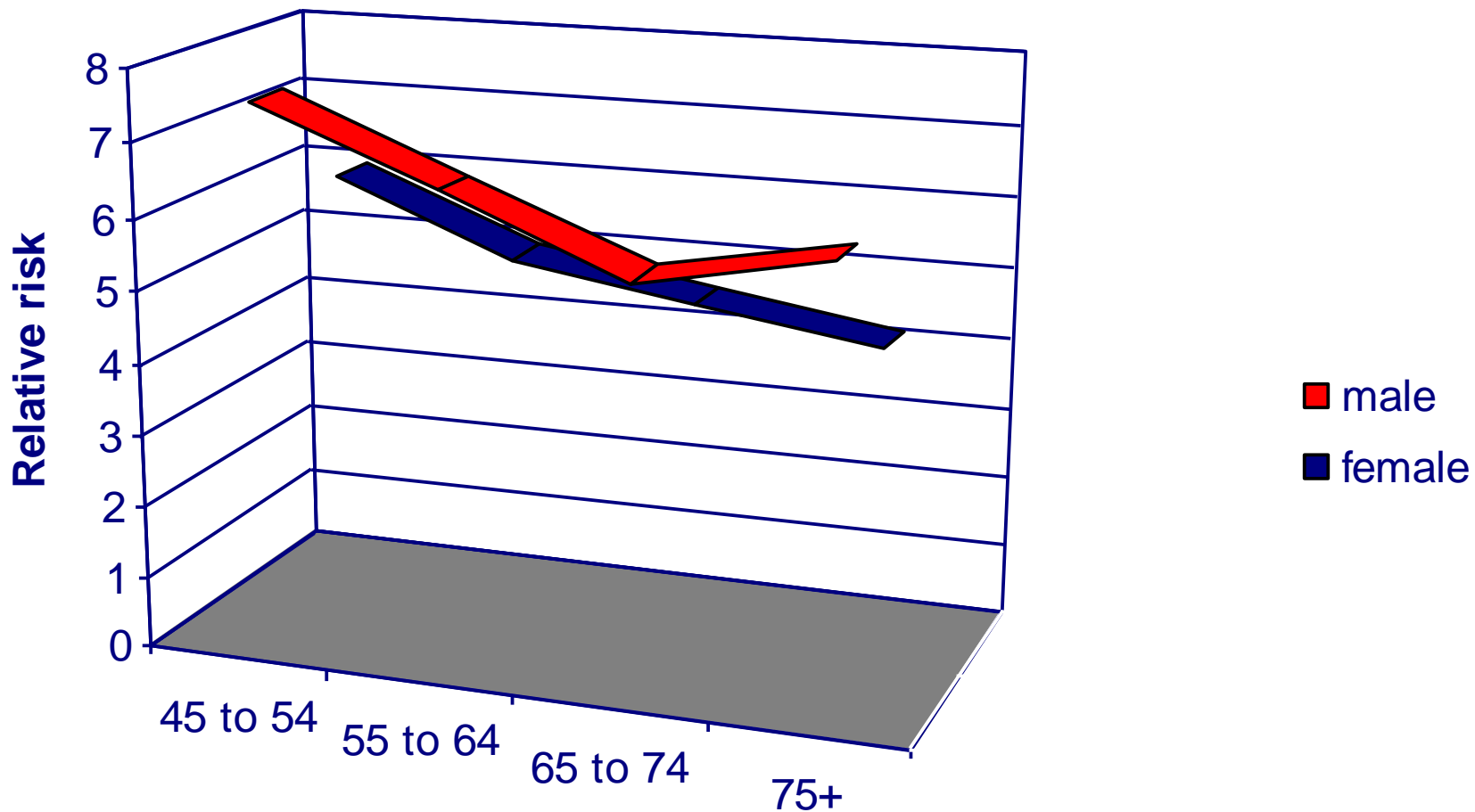
Funding of cardiovascular research in the UK



 **stroke doctors**

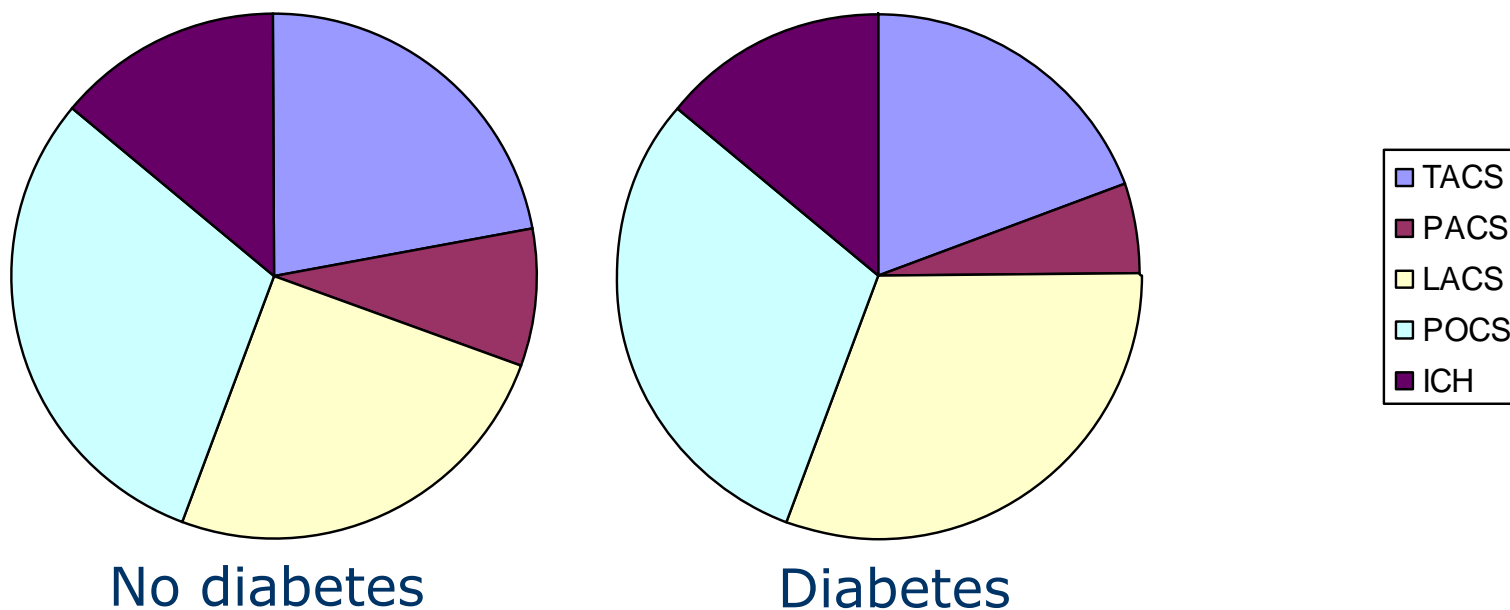
 **bloody cardiologists**

Epidemiology: type 2 diabetes *and stroke*

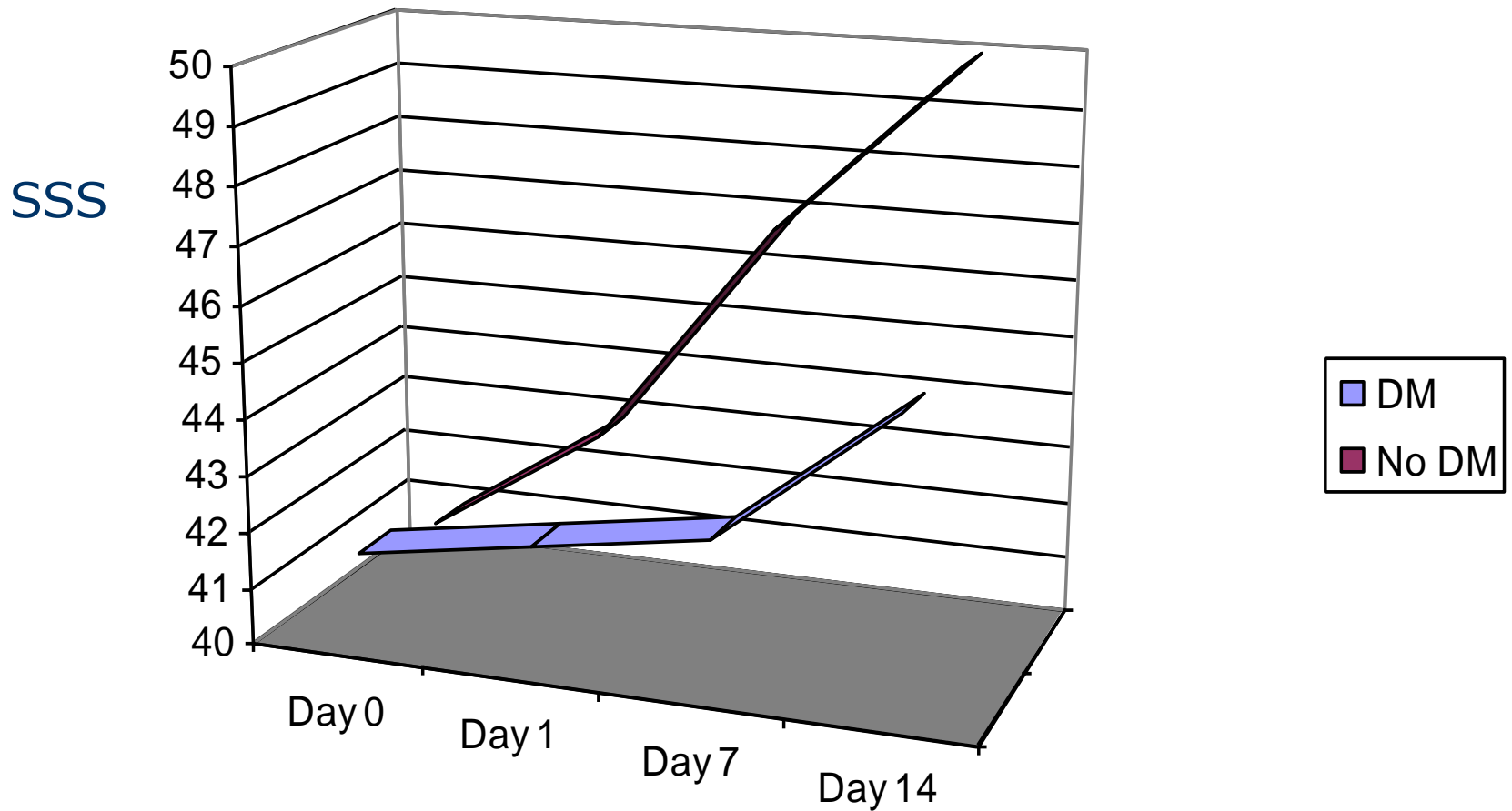


Diabetes on stroke units

- 20% prevalence in acute cerebrovascular trials
- Probably an underestimate of true prevalence
- *Suggestion* that small vessel stroke over-represented

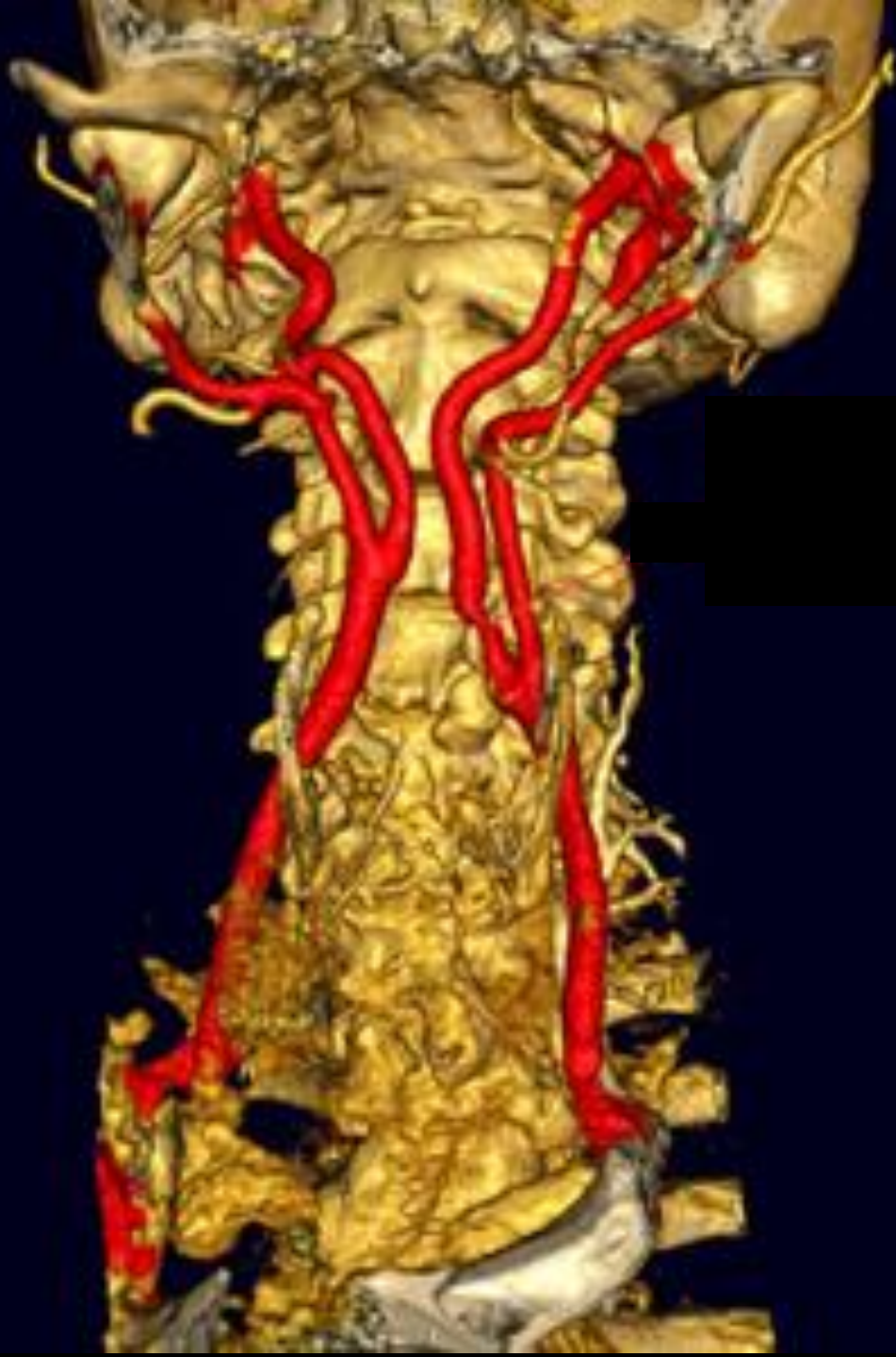


Delayed stroke recovery



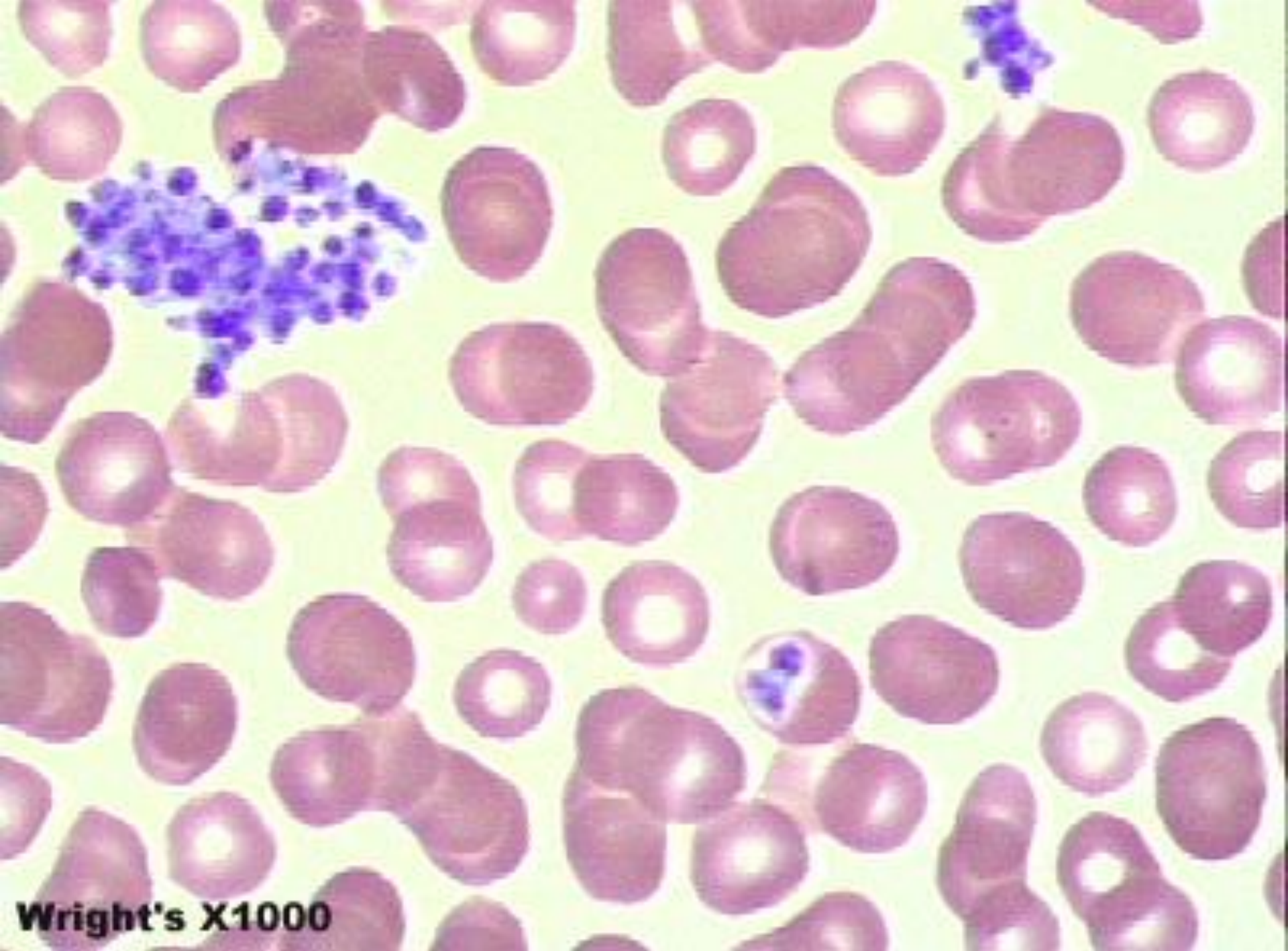
Type 2 diabetes and stroke

- Outcome worse for same initial severity
- Why?
 - Carotid disease
 - Sticky blood
 - Hyperglycaemia
 - Failure of cerebrovascular vasodilatation in response to hypoxic or ischaemic insult
 - Haemorrhagic transformation



Type 2 diabetes and stroke

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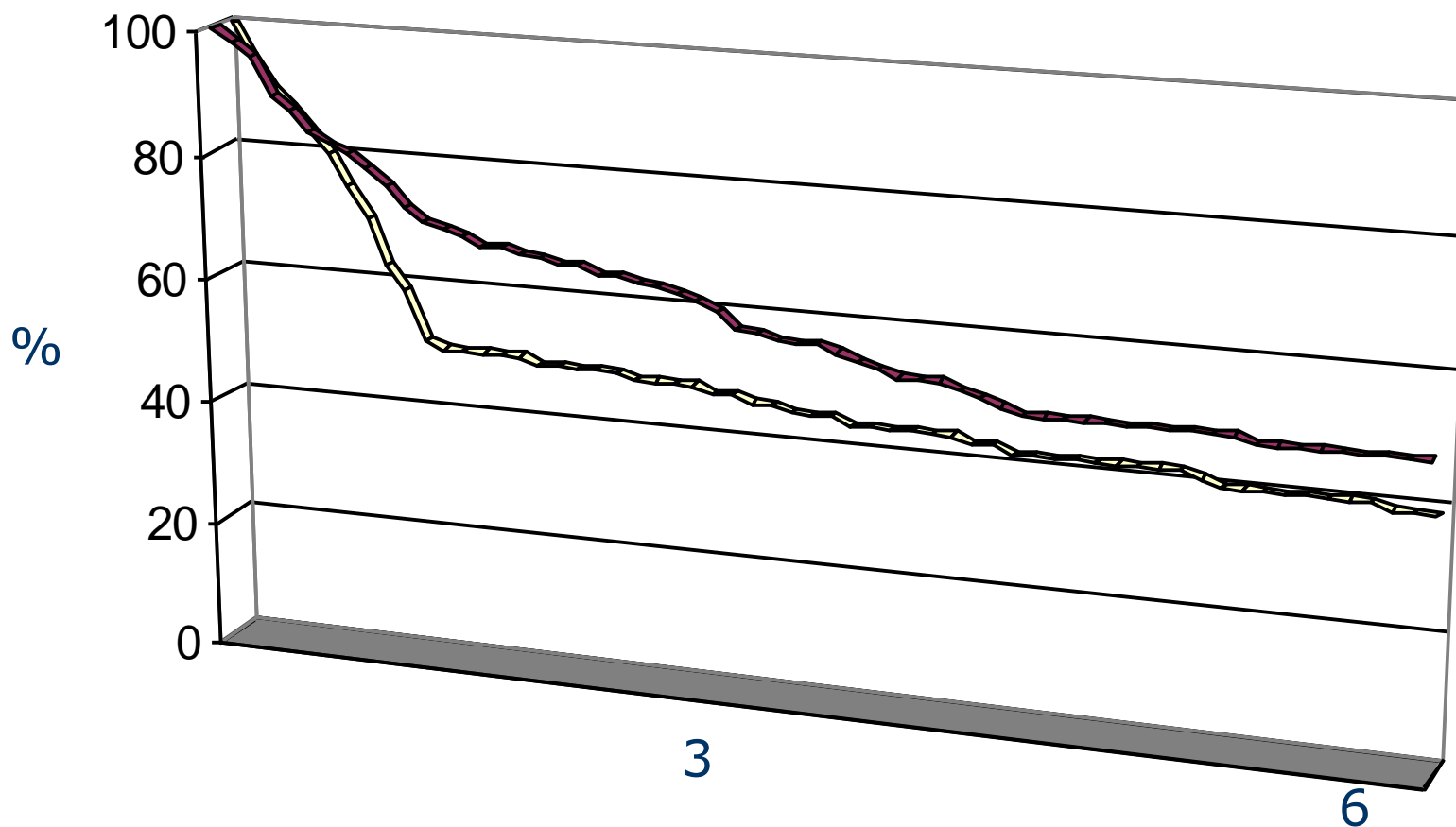
Wright's X1000

Type 2 diabetes and stroke

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Outcome after stroke

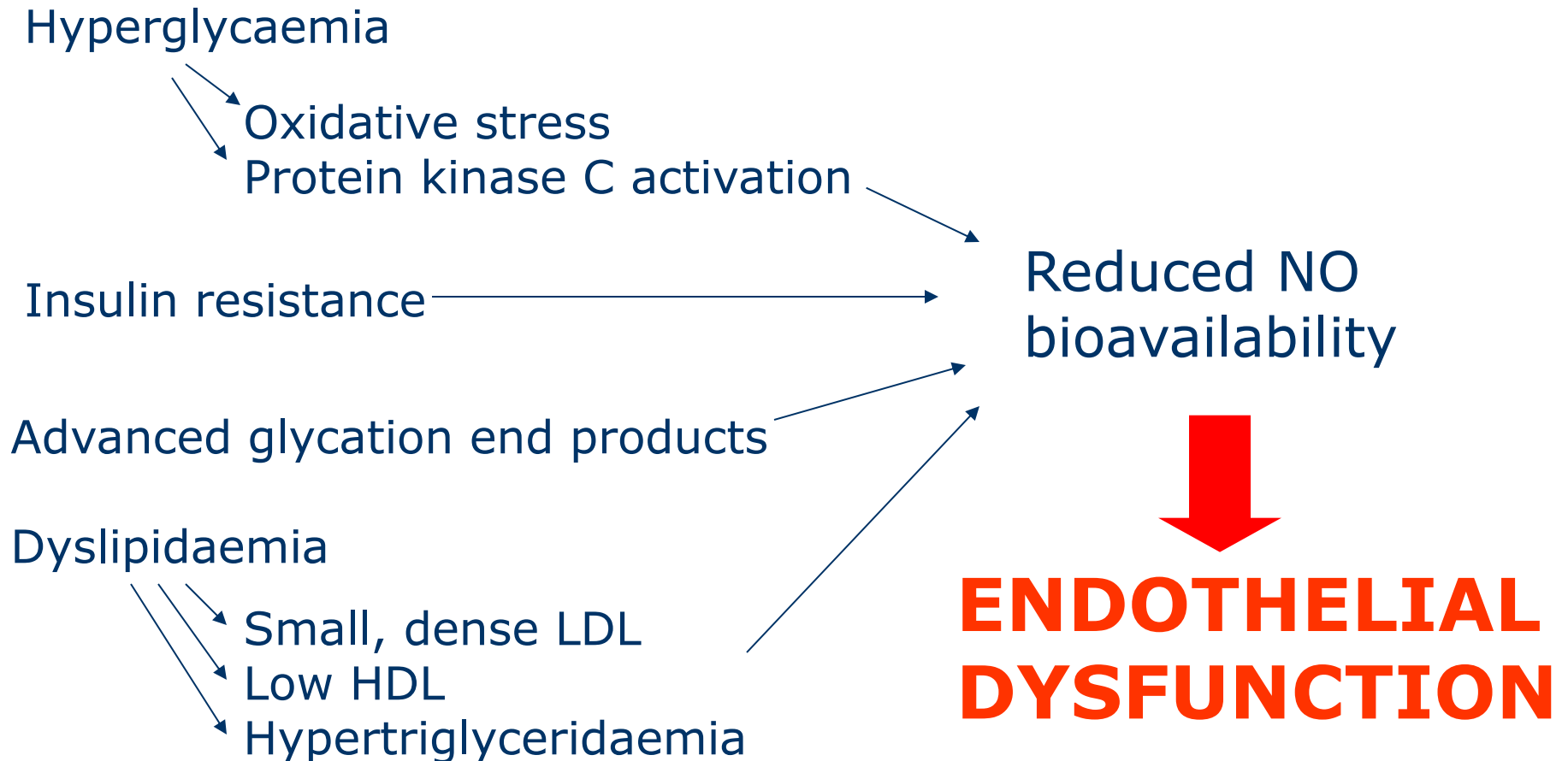
■ Euglycaemic □ Hyperglycaemic

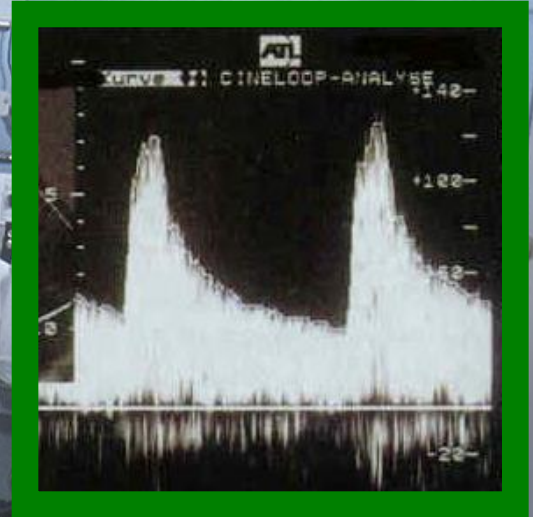
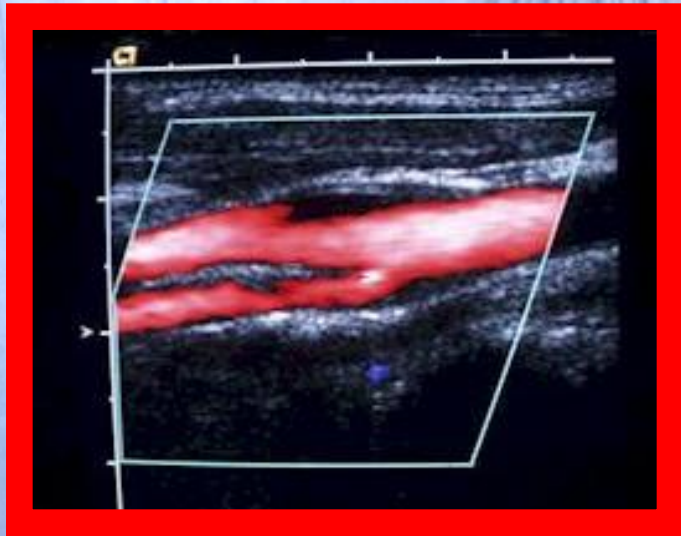


Type 2 diabetes and stroke

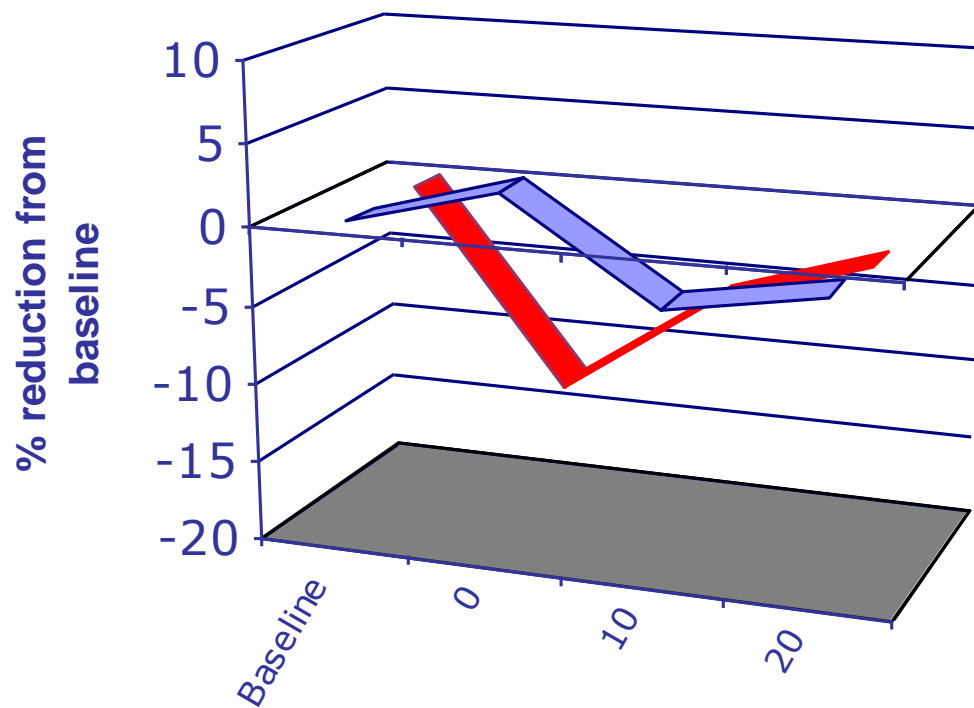
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Mediators of endothelial damage in diabetes





Carotid blood flow

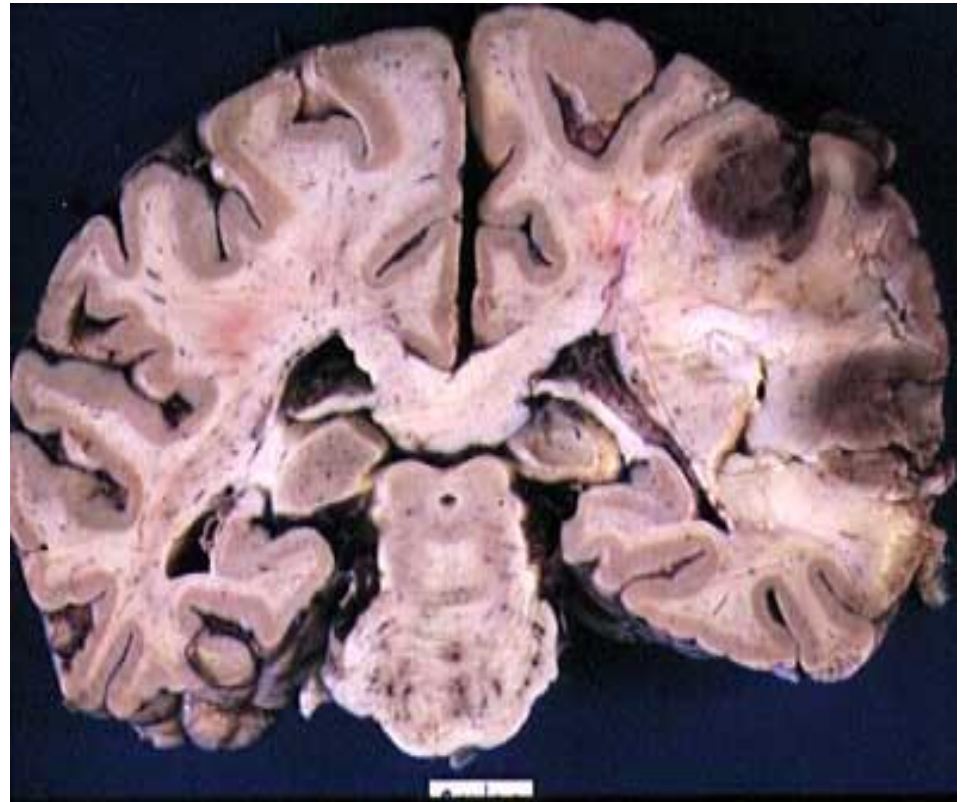
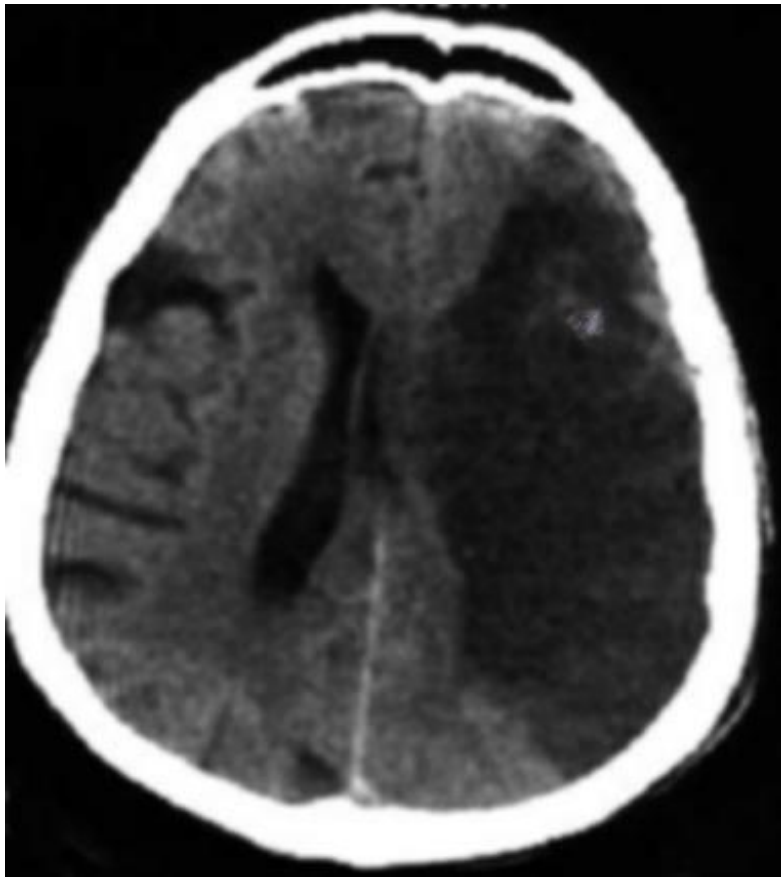


■ Diabetic Group ■ Control Group

Type 2 diabetes and stroke

- Outcome worse for same initial severity
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Haemorrhagic transformation



Diabetes and stroke

- Patients with diabetes are:
 - More likely to have a stroke
 - Less likely to do well afterwards
 - Wide variety of potential mechanisms

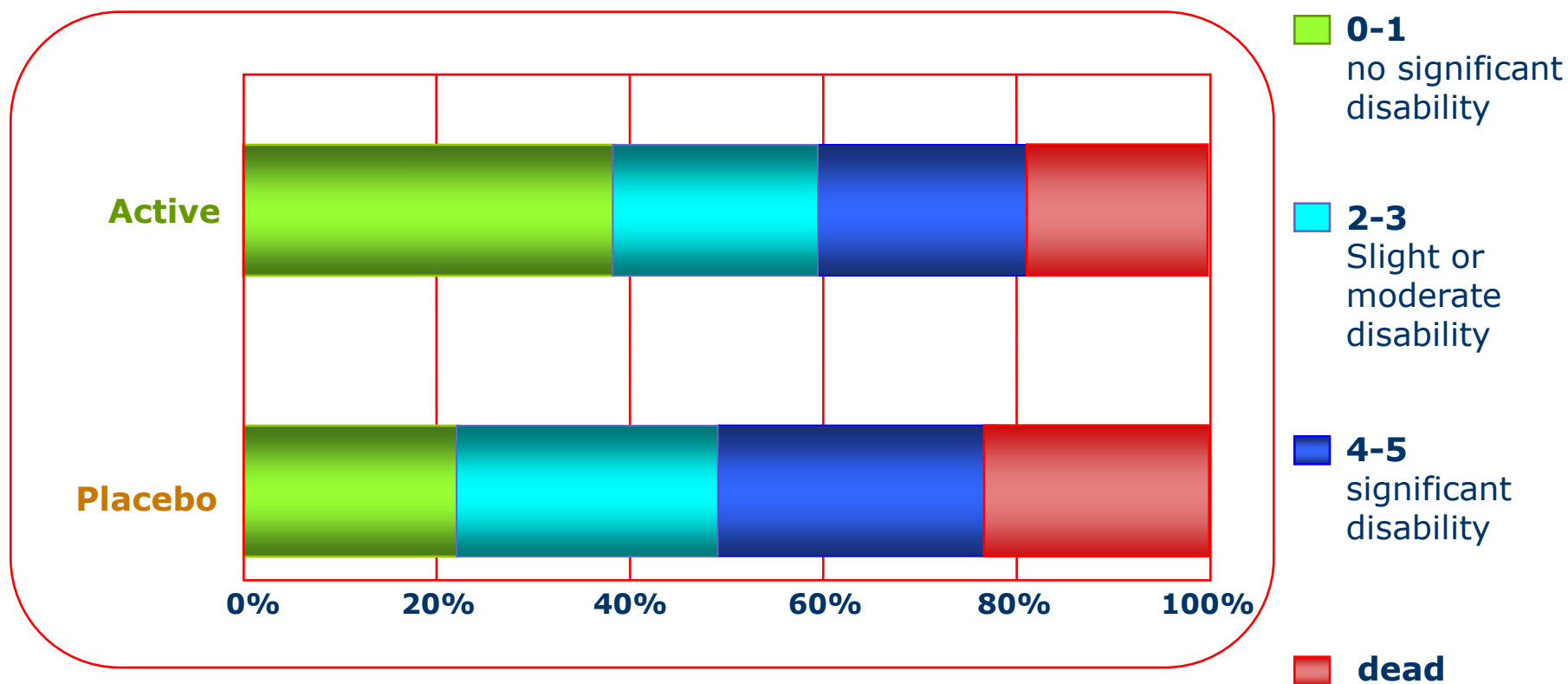
Are there any implications for treatment?



Treatment of stroke in the diabetic population

- Thrombolytic therapy
- Glycaemic control
- Blood pressure reduction
- Antiplatelet strategies

Effect of rt-PA



NNT approximately 8

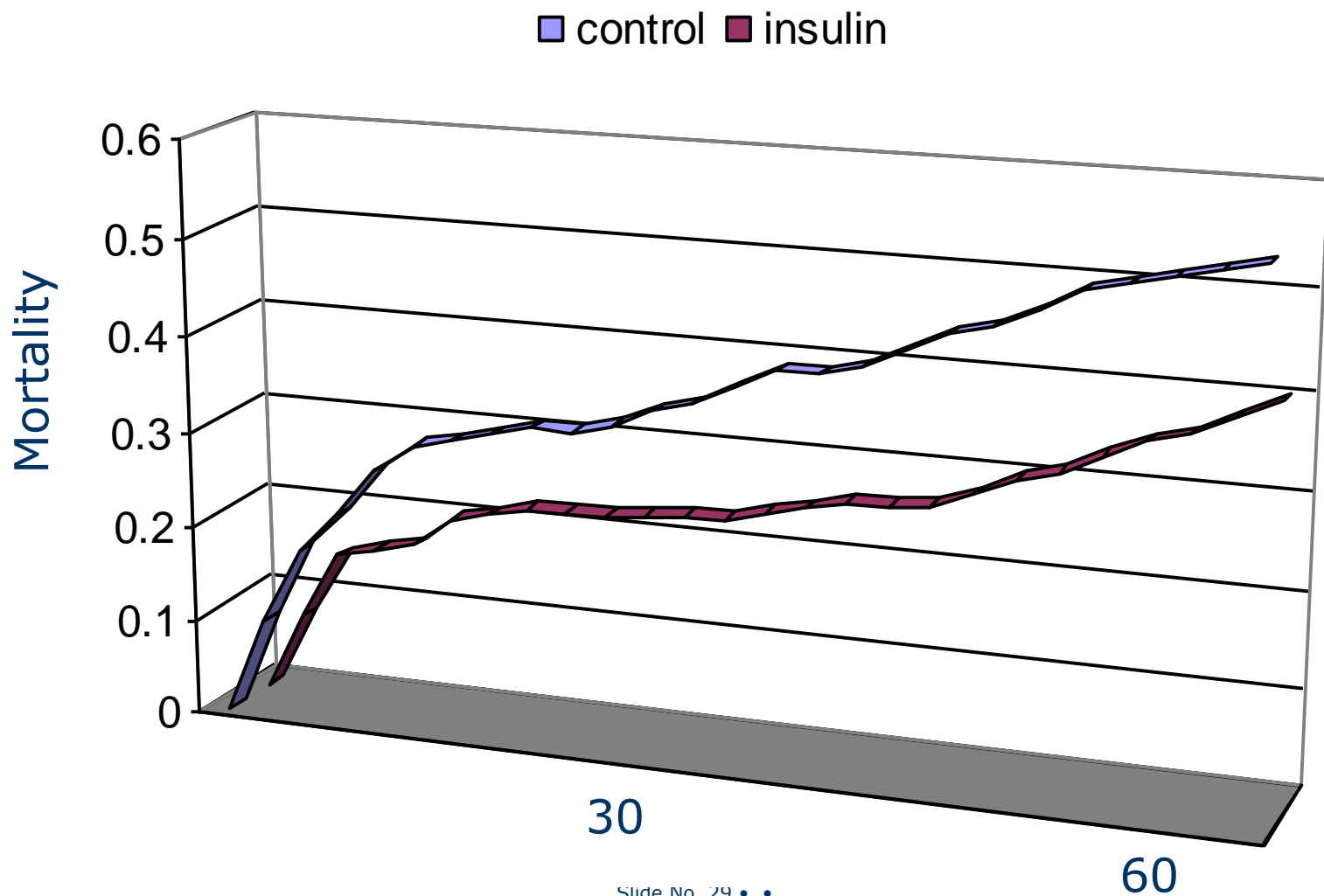
Thrombolytic therapy

- 12% ARR of poor outcome
- Magnitude of benefit comparable in patients with and without diabetes
- **No interaction** between diabetes and thrombolysis with regard to cerebral haemorrhage / haemorrhagic transformation
- Caution in context of *diabetes plus previous stroke*
 - Risk of bleeding (meta analysis of pooled patient data)
 - Unlicensed in this population

Hyperglycaemia

- Present in about 45% of acute stroke patients
- Arguably the most common and treatable abnormality
- Hyperglycaemia causes:
 - Increased substrate for anaerobic glycolysis
 - Increased cortical lactate concentration
- Intervention with insulin:
 - May reverse this
 - Neuromodulatory effect independent of glycaemia?
 - Seems to work when coronary arteries get blocked...

Glycaemic control post MI



Glycaemic control post CVA

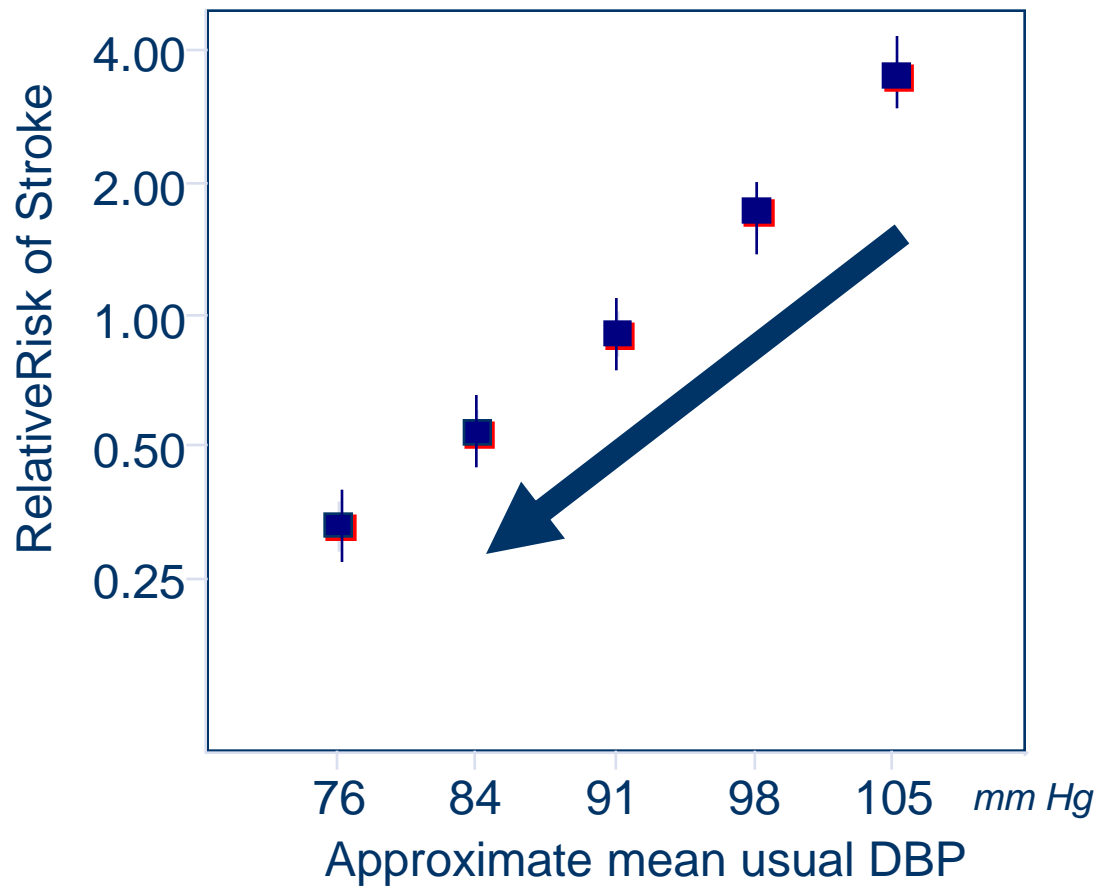
- GIST trial ongoing
- Recruitment poor: about 900 recruited, 2400 required
- Scheduled to run 1999-2002
- Wide range of glycaemia (up to 17mmol/L)
- May not provide the answer
- Further study needed

In the meantime...

- Guidelines vary:
 - **RCP**
 - *"Maintain euglycaemia"*
 - **EUSI**
 - *"IV insulin if glucose > 10mmol/L"*
 - **AHA**
 - *"Insufficient evidence to guide management"*

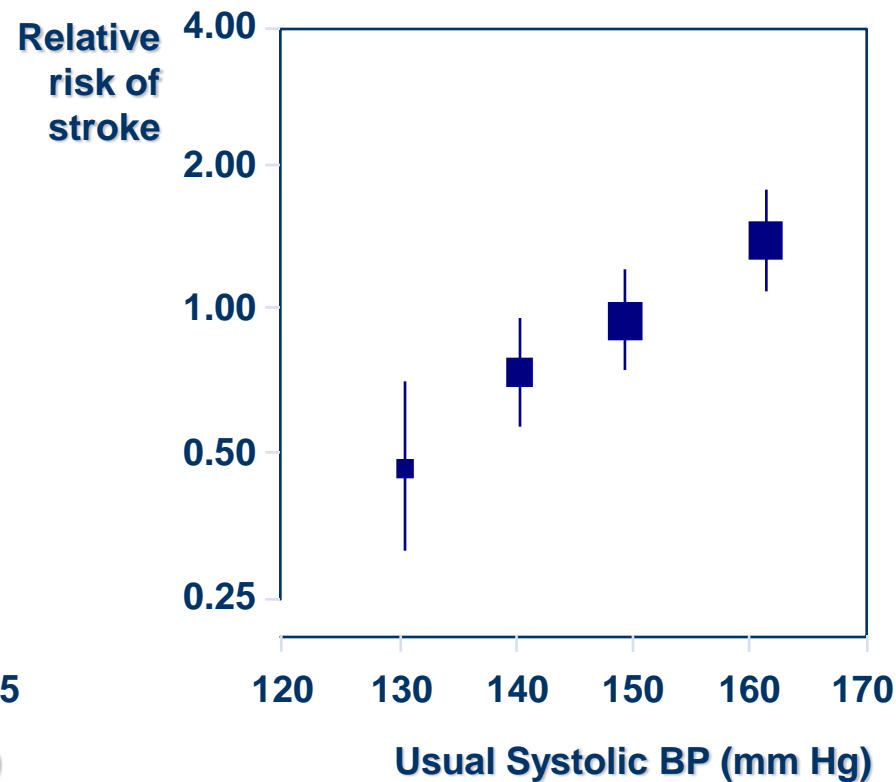
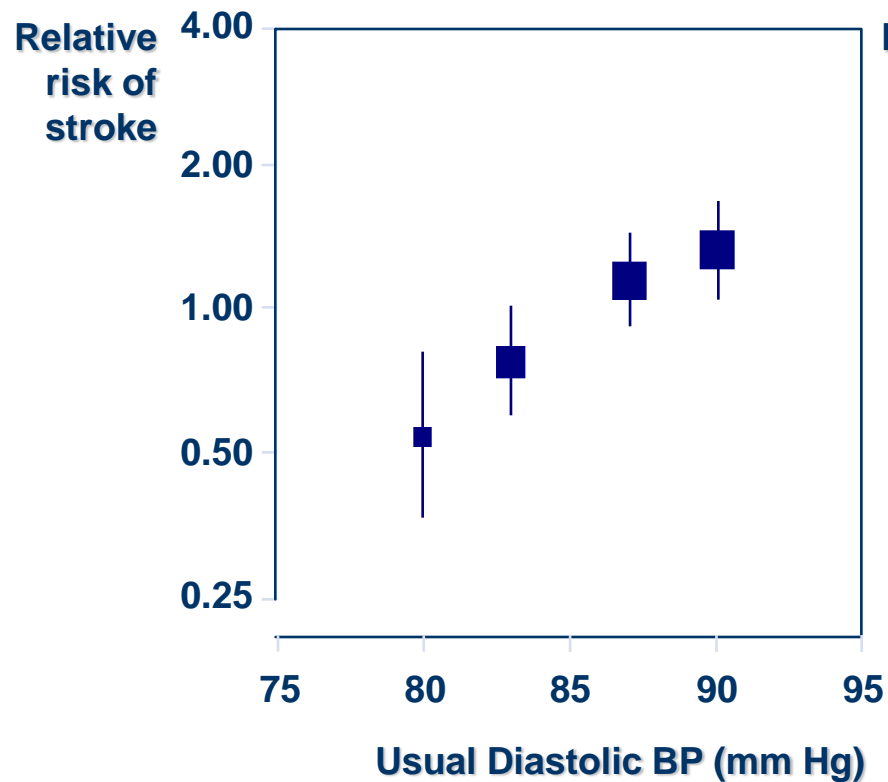
BP and risk of first stroke

7 prospective observational studies: 843 events, 405,500 individuals



BP and Risk of Recurrent Stroke

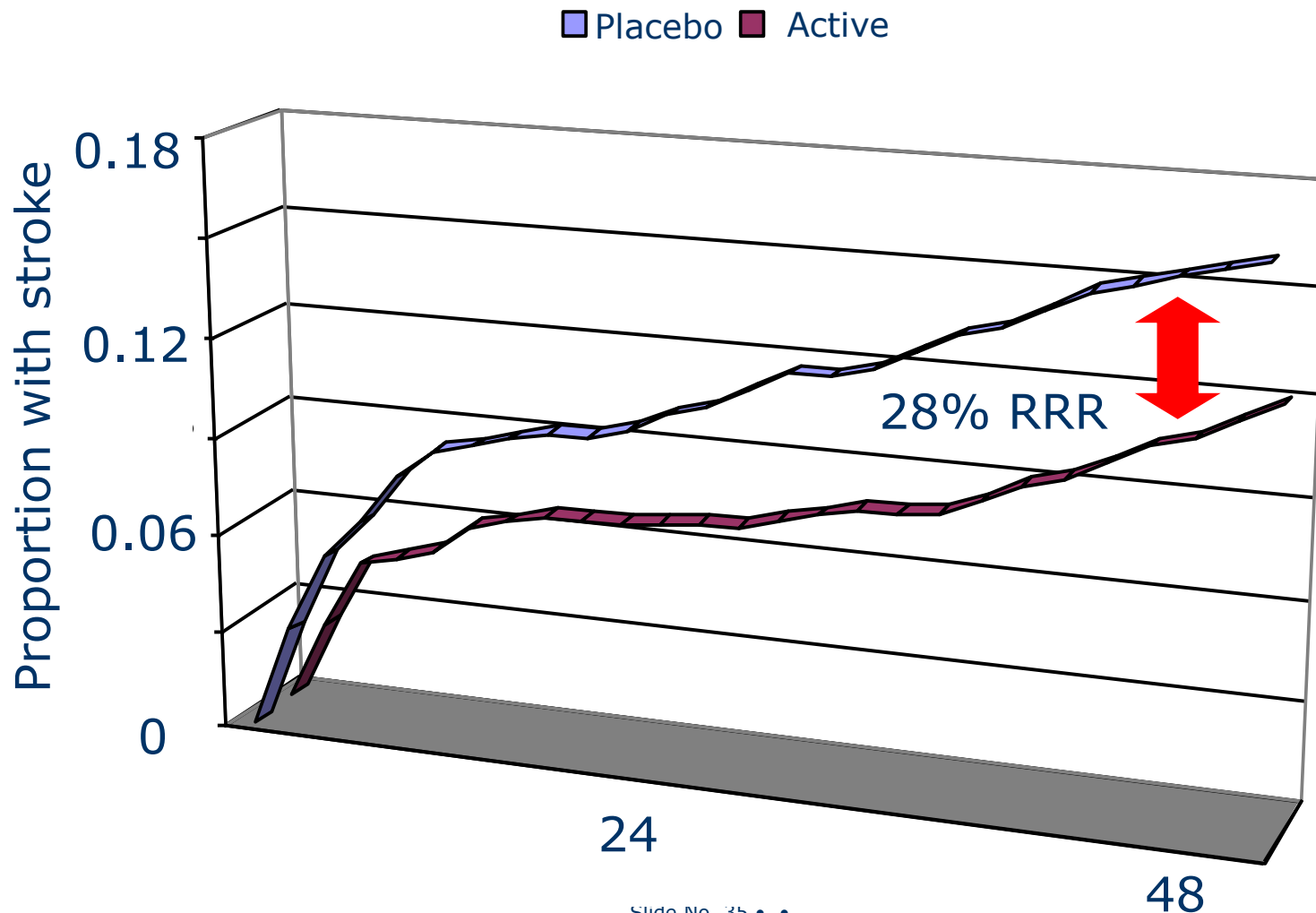
Stroke and usual BP among 2435 individuals with a history of TIA or minor stroke



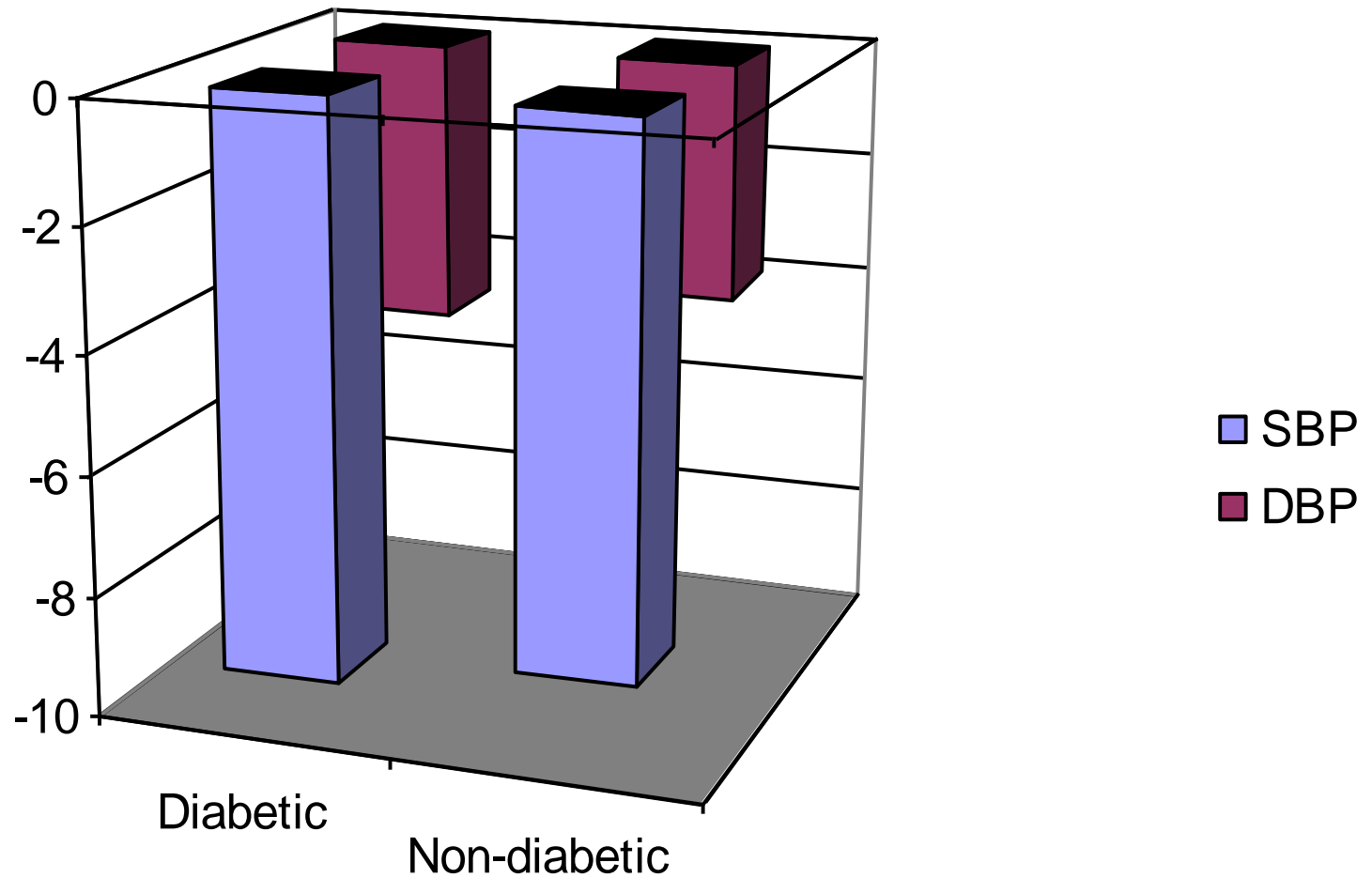
BP reduction after stroke: PROGRESS

- 6,100 stroke patients
- Any type of stroke in last 5 years
- No major disability
- ACEI + Diuretic vs placebo
- No entry blood pressure criteria
- Followed up for 4 years
- 16% had diabetes at entry

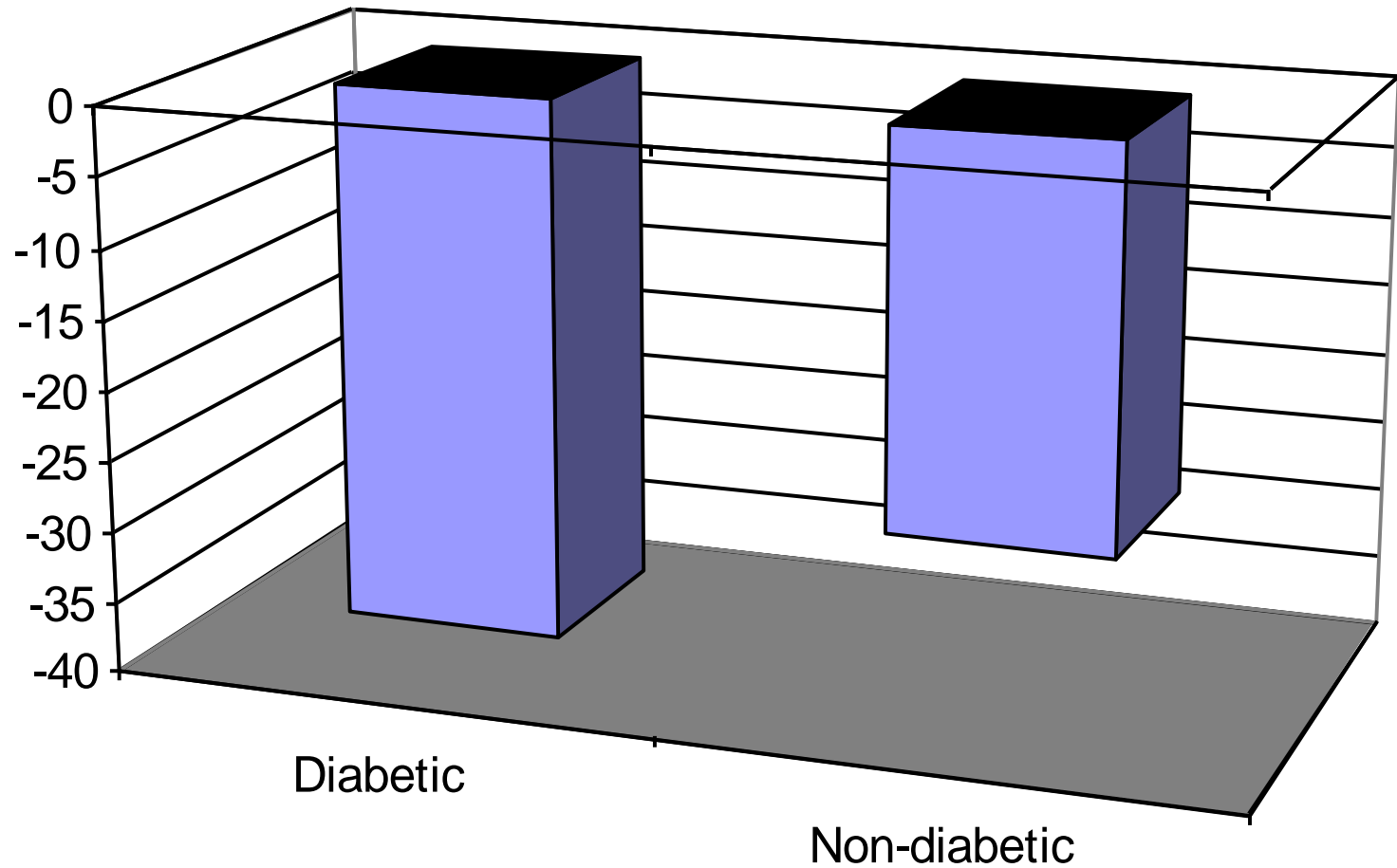
PROGRESS: overall results



PROGRESS: effect on BP



PROGRESS: Stroke RRR



Blood pressure reduction

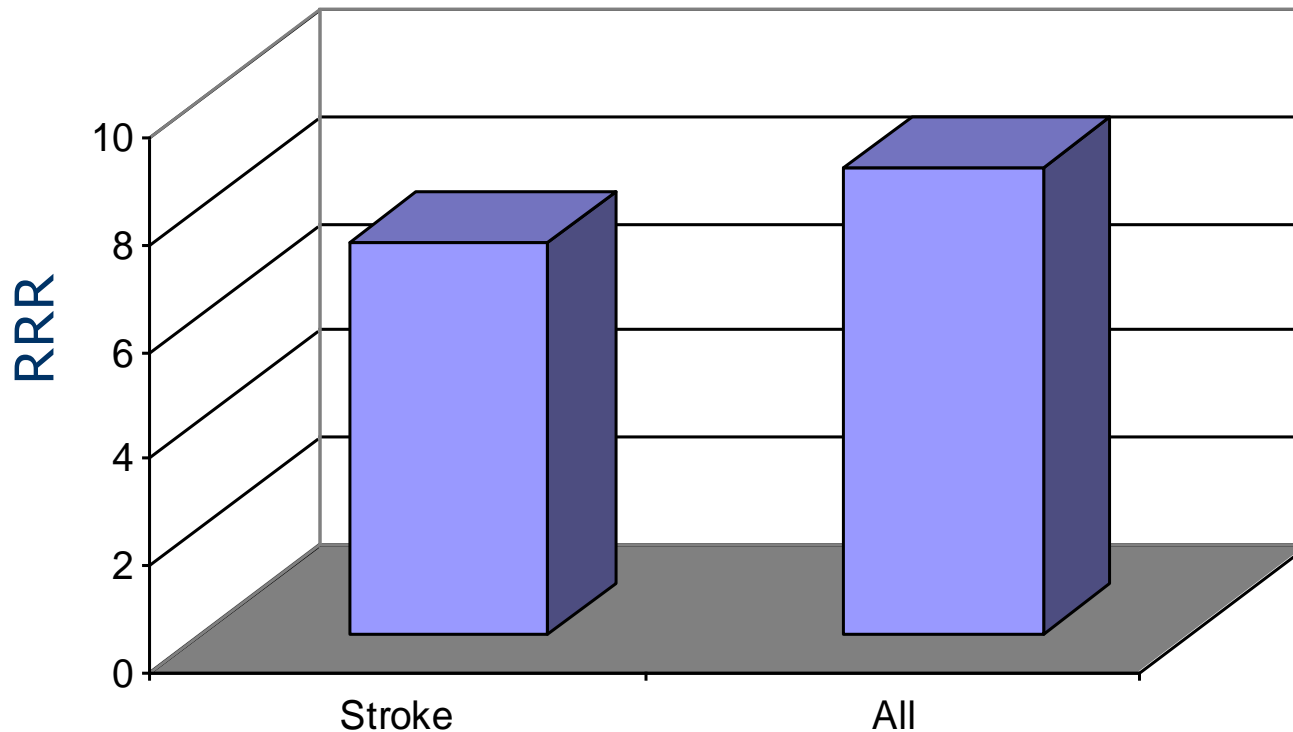
- Diuretic plus ACEI mainstay of therapy post stroke
- Used even in those with “normal” blood pressure
- Suggestion of relatively greater benefit in diabetic population
- HOPE trial also suggested greater benefit of ACEI with regard to stroke reduction in diabetic population

Antiplatelet treatment post CVA: aspirin alone

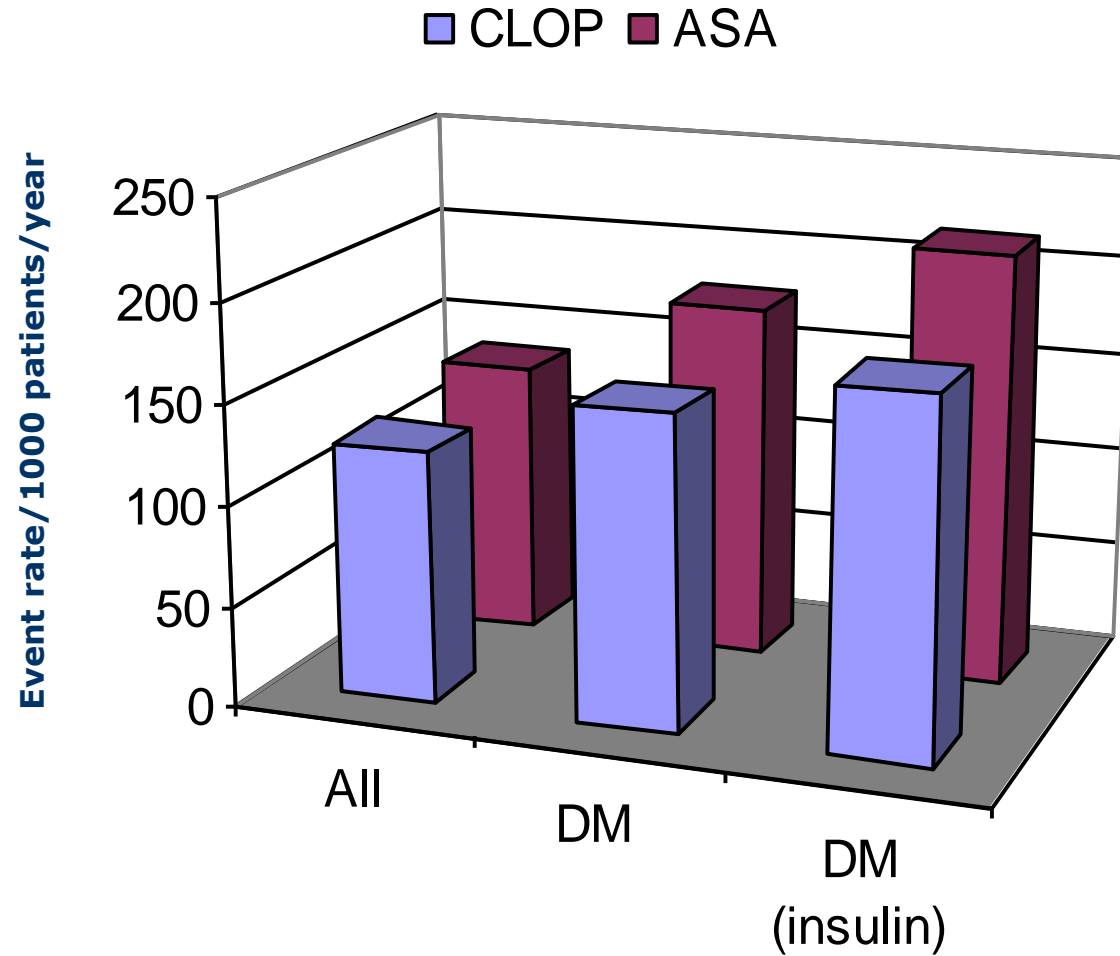
- Pooled analysis of RCTs:
 - ASA within 48 hours reduces risk of recurrent stroke or in hospital death (OR 0.89, CI 0.83 – 0.96)
 - For every 1000 ischaemic stroke patients treated for 3 years, aspirin prevents
 - 25 non-fatal strokes
 - 6 non-fatal MI's
 - 15 deaths
 - *No difference between diabetic and non-diabetic stroke patients*

If aspirin's no better, what about clopidogrel?

- No significant benefit of clopidogrel over aspirin in stroke subgroup of CAPRIE



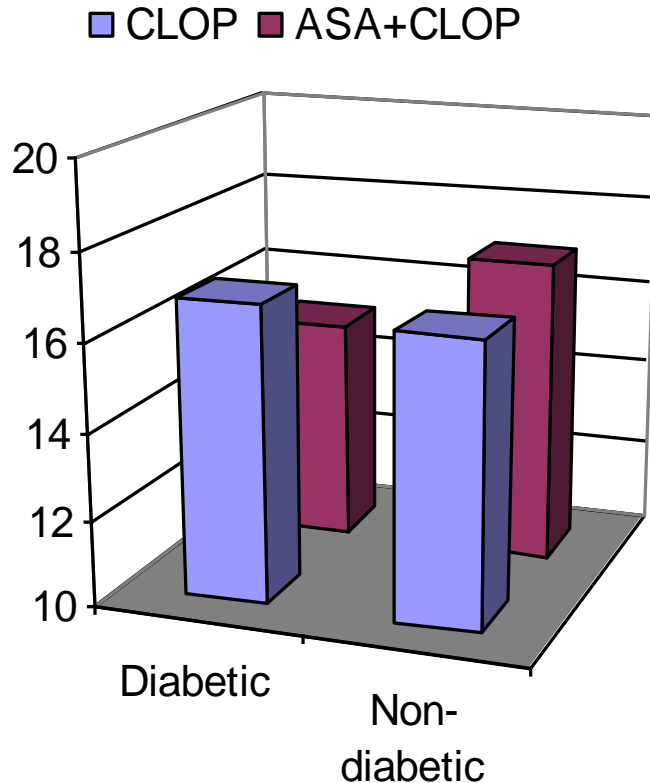
CAPRIE: diabetic subgroup



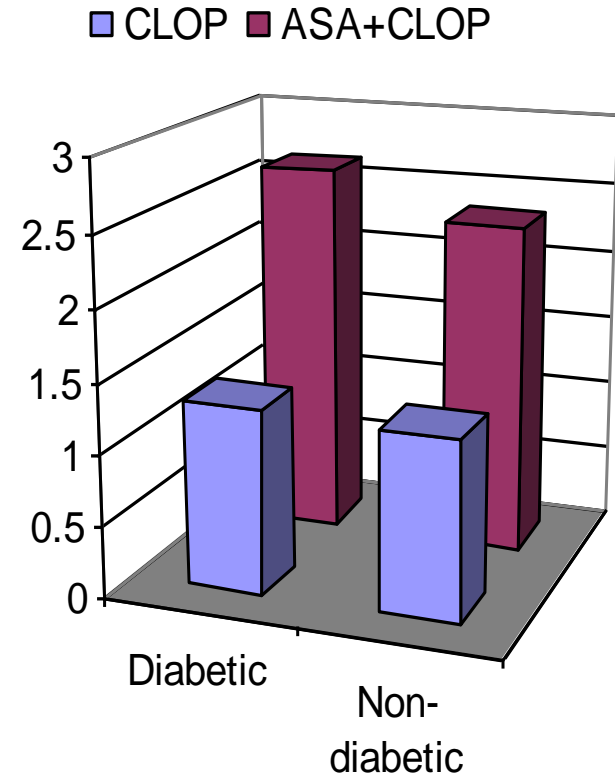
Aspirin vs clopidogrel

- Suggestion of greater reduction in ischaemic events within diabetic subgroup of CAPRIE
- Too few diabetic stroke patients for meaningful analysis
- Beneficial treatment effect of clopidogrel very small (NNT \approx 50)
- Not currently recommended in diabetic stroke patients

Combination antiplatelets: MATCH



Ischaemic events



Major bleeding

7,599 stroke patients, 68% with diabetes

MATCH conclusions

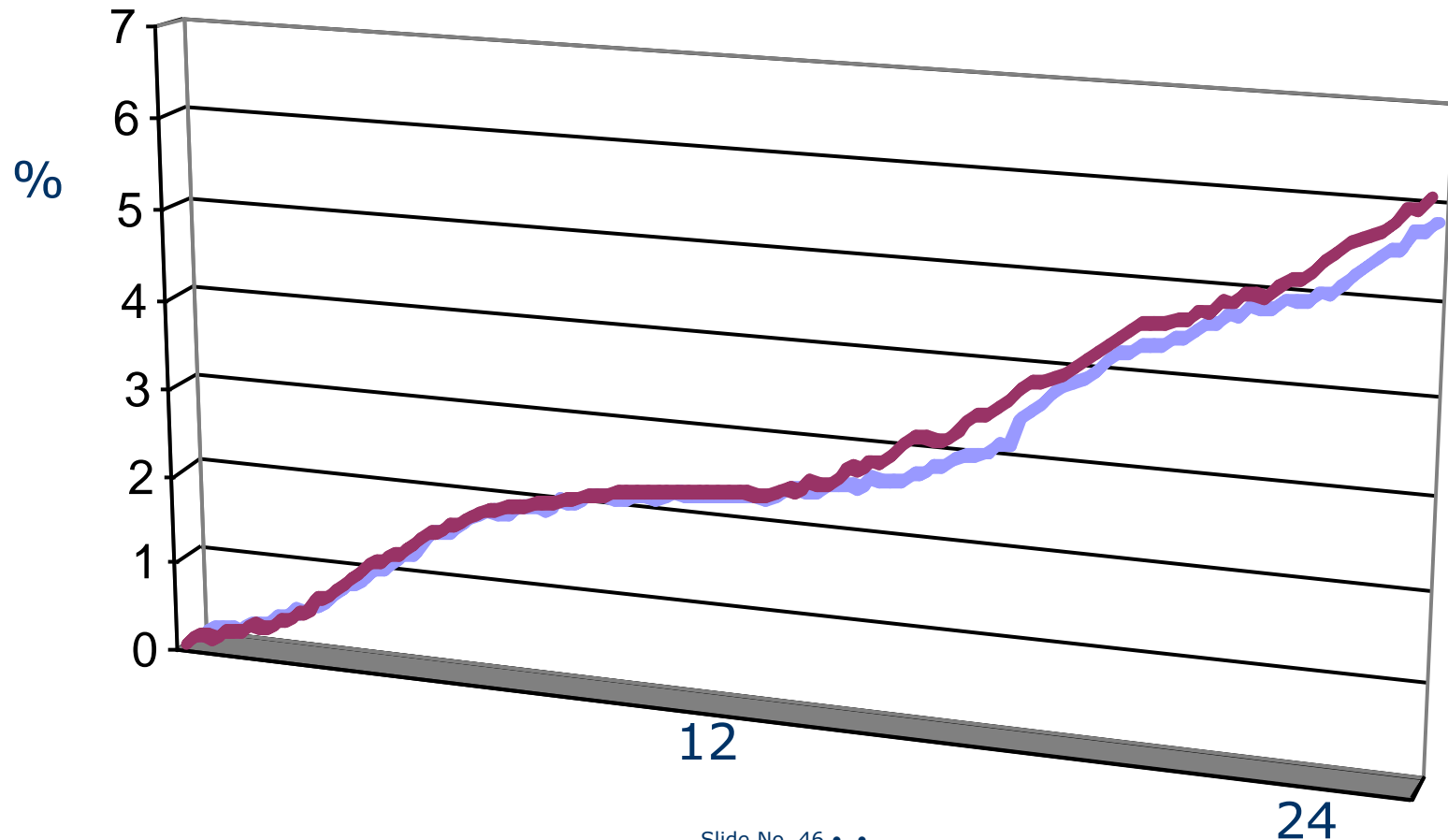
- Very modest reduction in risk of future ischaemic events
- More than offset by bleeding risk
- No significant difference between diabetic and non-diabetic subgroups
- The clinical question wasn't really what needed to be answered
- Standard comparator more meaningful (ASA not CLOP)
- "Potential benefit of adding clopidogrel to aspirin"

Combination antiplatelets: CHARISMA (NEJM 20th April)

- 15,000 patients with or at high risk of vascular disease
- 42% with diabetes
- 25% with stroke
- Aspirin or aspirin plus clopidogrel

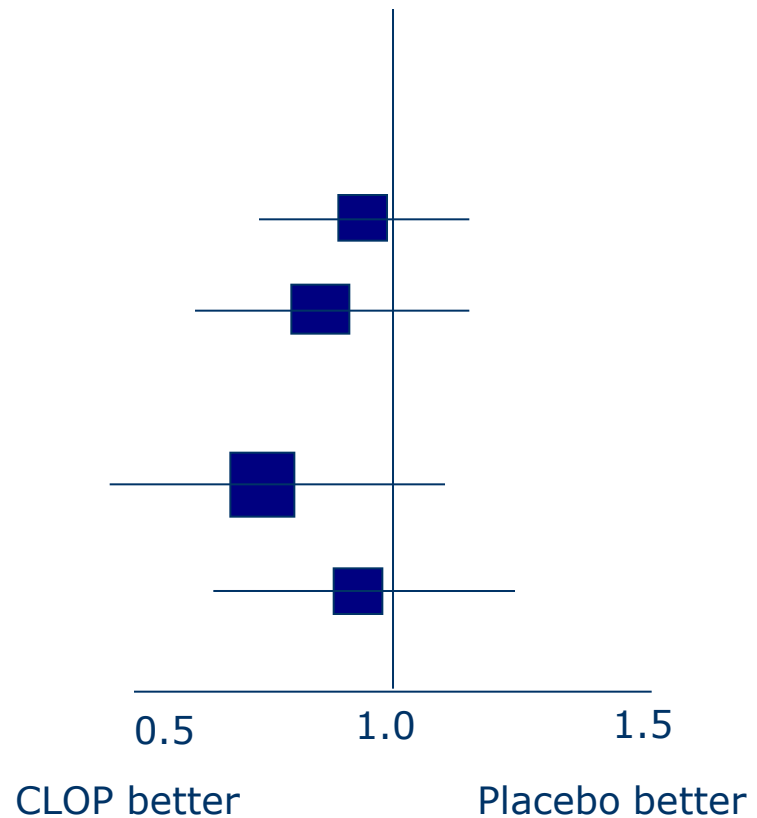
Combination antiplatelets: CHARISMA

ASA ASA+CLOP



Combination antiplatelets: CHARISMA

- No benefit of combination therapy in broad group
- Subgroups:
 - Diabetes
 - Yes
 - No
 - Stroke as index event
 - Yes
 - No



Combination antiplatelets

- No proven role in management of general stroke patients
- No evidence of benefit in diabetic individuals
- Other groups may benefit:
 - Unstable carotid disease
 - Hyperacute stroke
- Work ongoing in these areas

Summary

- Diabetic patients are prone to cerebrovascular disease
- Stroke hits diabetic patients harder
- Current acute strategies limited:
 - Thrombolysis works
 - Tight glycaemic control being evaluated
- Secondary prevention strategies:
 - BP lowering particularly effective
 - No firm evidence to support a different antiplatelet approach

