# Cerebrovascular disease and diabetes


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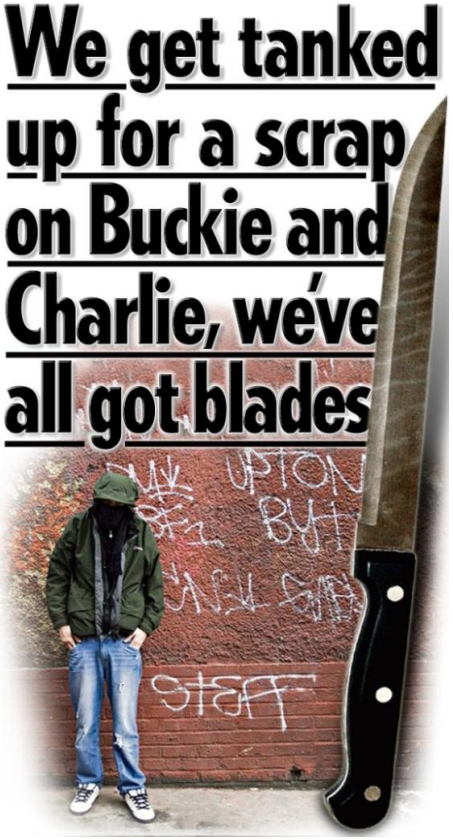
# European City of Culture 1989



# Why discuss stroke?

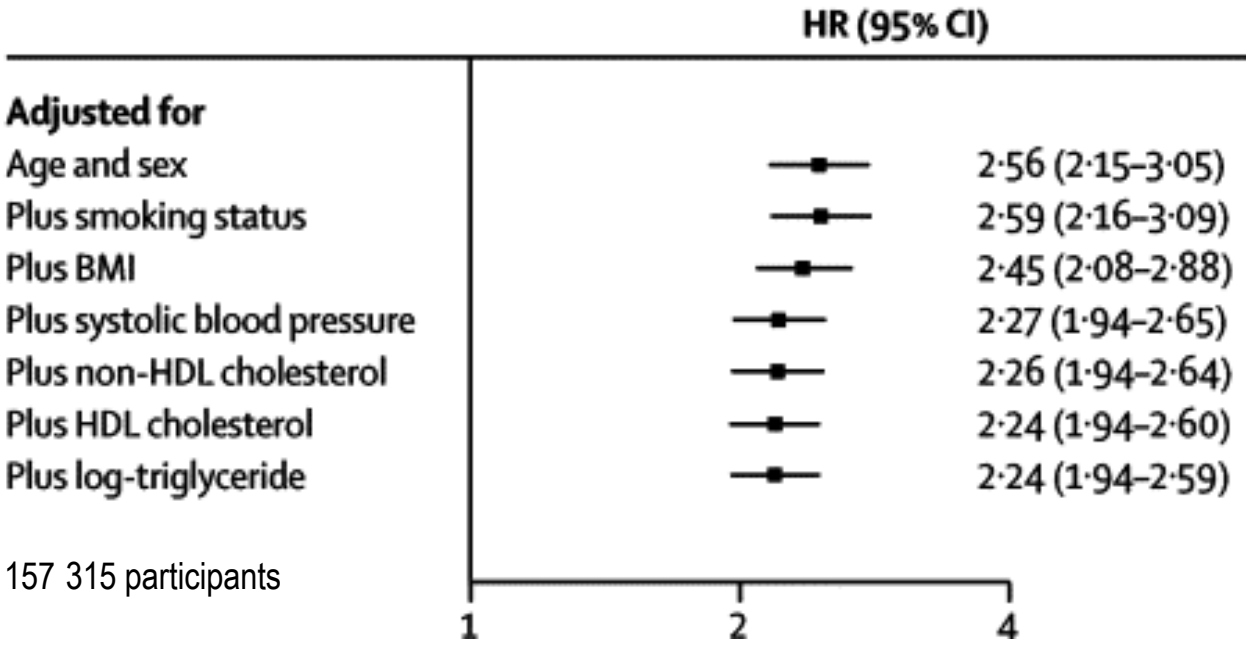
- # 1 cause of disability
- 20-30% of stroke patients die within a month
- # 3 cause of death (12%)
- 130,000 per year in UK
- Approx £3 billion direct NHS costs annually
- *Almost as much as diabetes...*
- 7% NHS beds
- Reverse the historical perception of stroke…

# Diabetes and the burden of stroke

- Effect on stroke risk
- Effect on stroke outcome
- Therapeutic considerations

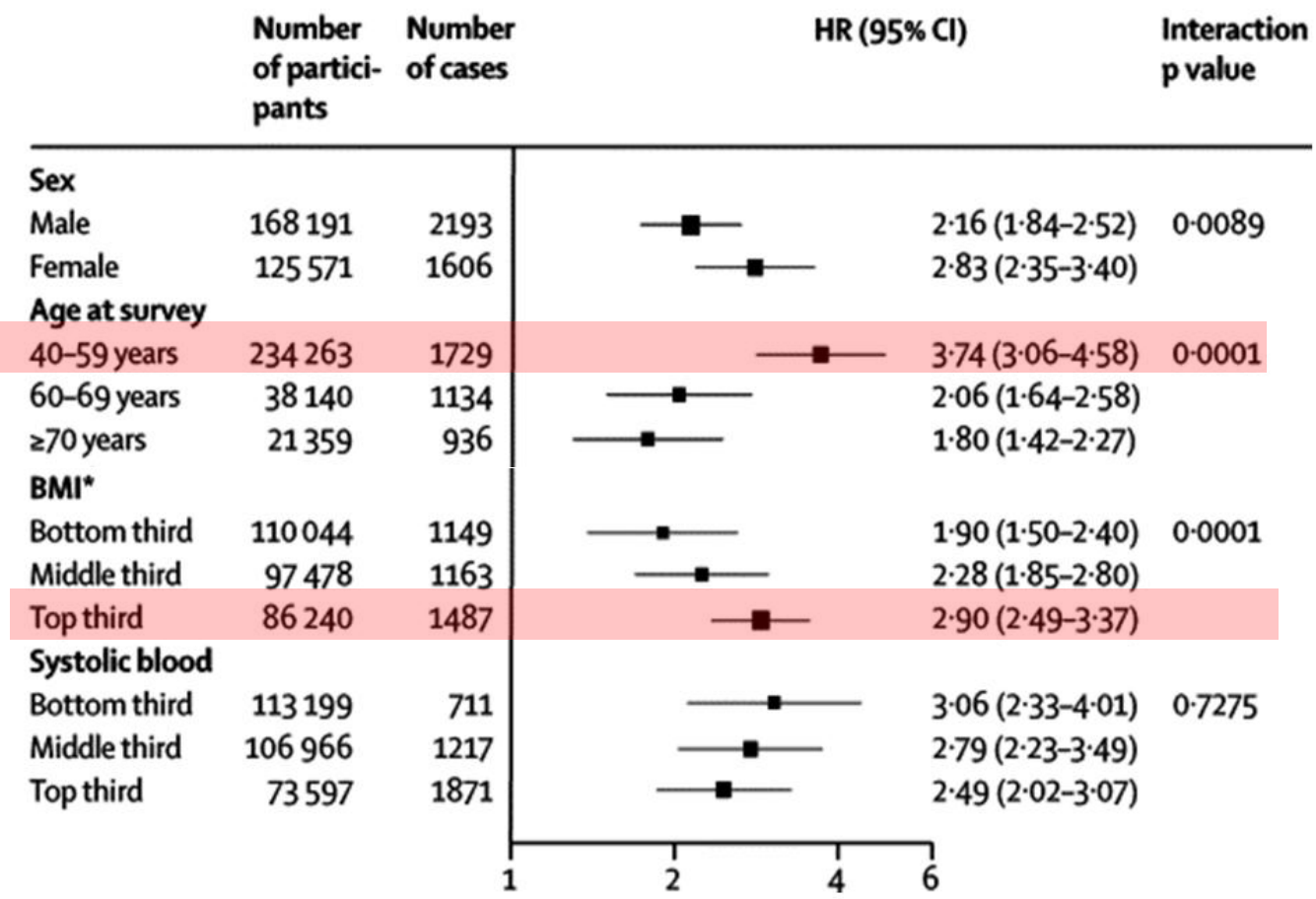
# Diabetes and stroke risk

- Diabetes accounts for **10%** of population risk of stroke, and about half of the stroke risk in an individual
- Diabetes *more than doubles* an individual's risk of ischaemic stroke correcting for other factors




Lancet 2010;375:2215–2222

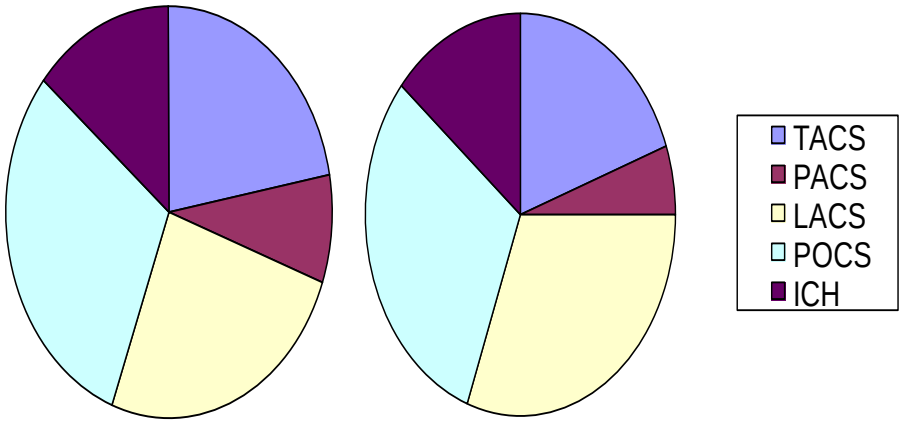
# Diabetes and stroke risk



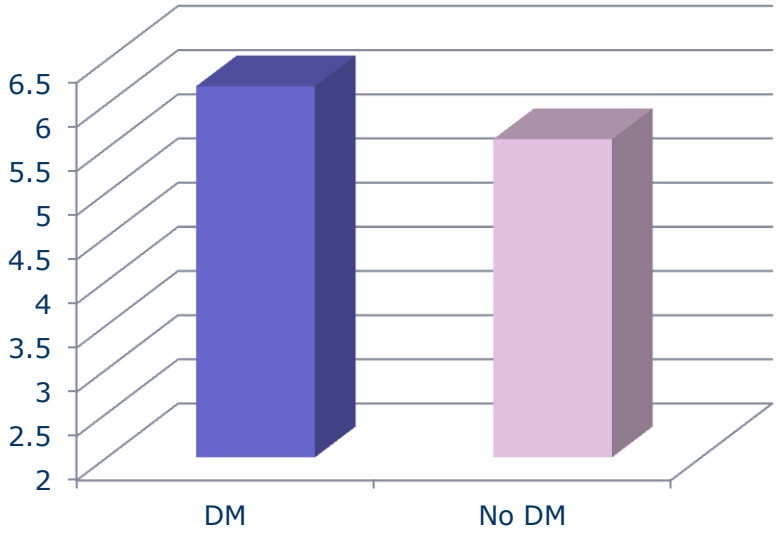
| | Number of participants | Number of cases | HR (95% CI) | Interaction p value |
|---|---|---|---|---|
| **Sex** | | | | |
| Male | 168 191 | 2193 | 2·16 (1·84–2·52) | 0·0089 |
| Female | 125 571 | 1606 | 2·83 (2·35–3·40) | |
| **Age at survey** | | | | |
| 40–59 years | 234 263 | 1729 | 3·74 (3·06–4·58) | 0·0001 |
| 60–69 years | 38 140 | 1134 | 2·06 (1·64–2·58) | |
| ≥70 years | 21 359 | 936 | 1·80 (1·42–2·27) | |
| **BMI*** | | | | |
| Bottom third | 110 044 | 1149 | 1·90 (1·50–2·40) | 0·0001 |
| Middle third | 97 478 | 1163 | 2·28 (1·85–2·80) | |
| Top third | 86 240 | 1487 | 2·90 (2·49–3·37) | |
| **Systolic blood** | | | | |
| Bottom third | 113 199 | 711 | 3·06 (2·33–4·01) | 0·7275 |
| Middle third | 106 966 | 1217 | 2·79 (2·23–3·49) | |
| Top third | 73 597 | 1871 | 2·49 (2·02–3·07) | |

# Diabetes on stroke units

- 20% prevalence in acute cerebrovascular trials
- True prevalence probably approaches 30%
- *Suggestion* that small vessel stroke over-represented
- Longer average length of stay in almost all studies



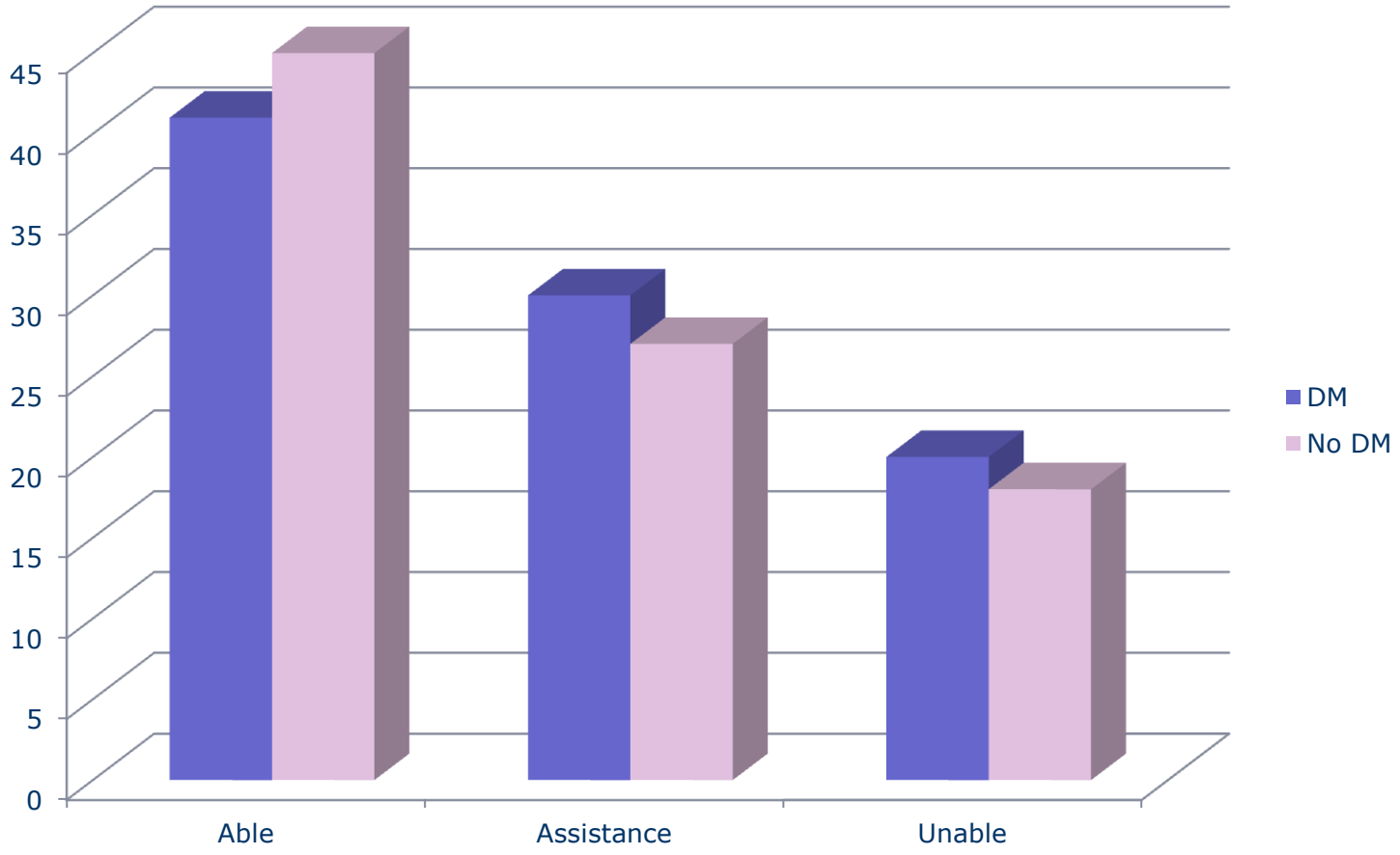

No diabetes Diabetes






*Stroke* 2010;41:e409-e417

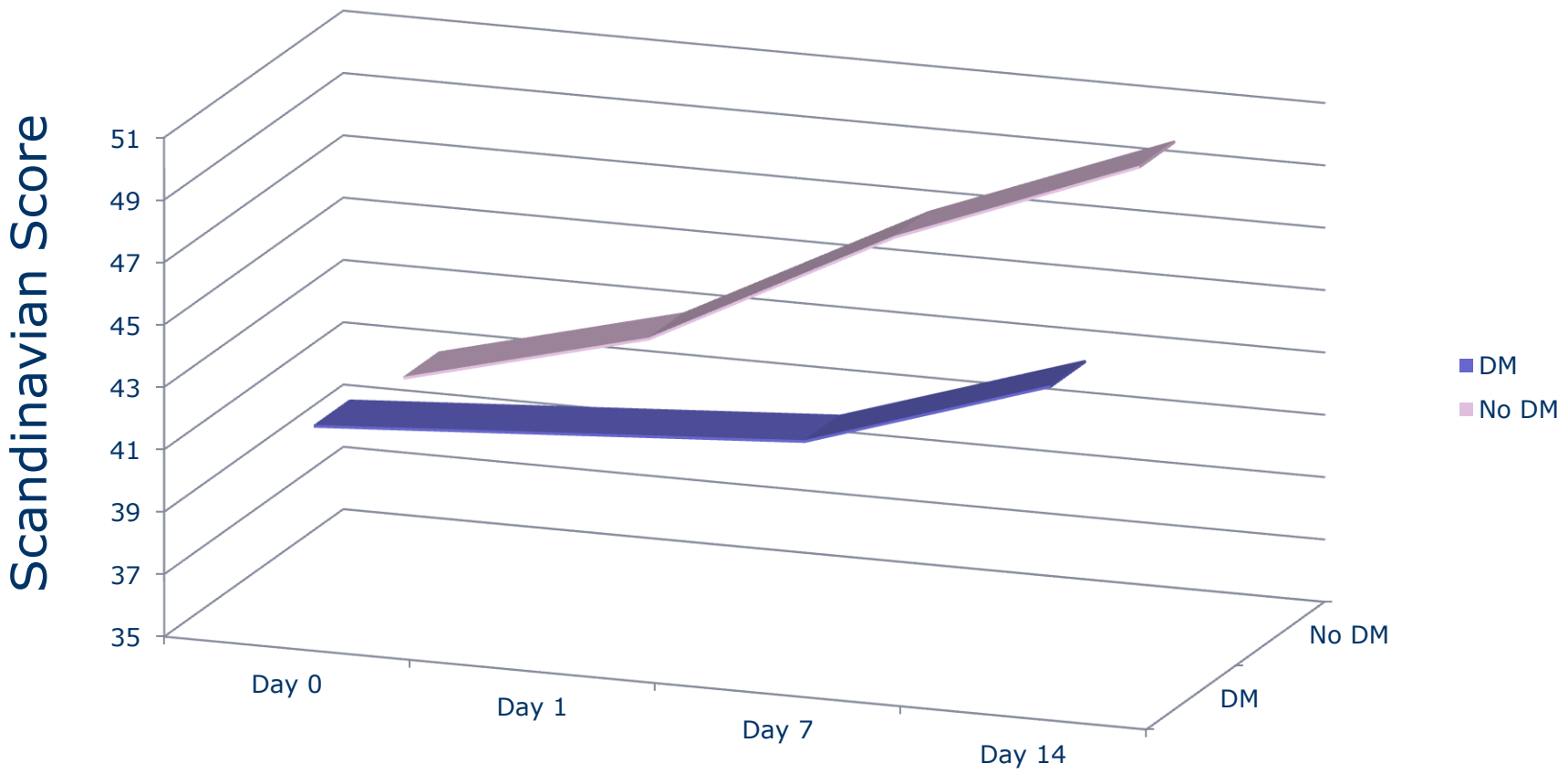
# Ambulatory status at discharge






*Stroke* 2010;41:e409-e417

# Delayed stroke recovery



# 10 year survival after stroke

| | Model with SSS score ($R^2 = 22.4\%$) | | |
|---|---|---|---|
| | Odds ratio | Lower 95% | Upper 95% |
| Hypertension | 0.75 | 0.51 | 1.09 |
| Ischemic heart disease | 0.82 | 0.53 | 1.28 |
| Previous stroke | 0.49 | 0.30 | 0.80 |
| Other disabling diseases | 0.59 | 0.37 | 0.92 |
| Daily alcohol consumption | 1.39 | 0.92 | 2.11 |
| Diabetes | 0.50 | 0.30 | 0.82 |
| Daily smoking | 0.52 | 0.35 | 0.78 |
| Atrial fibrillation | 0.46 | 0.26 | 0.81 |
| Stroke subtype | 0.34 | 0.16 | 0.72 |

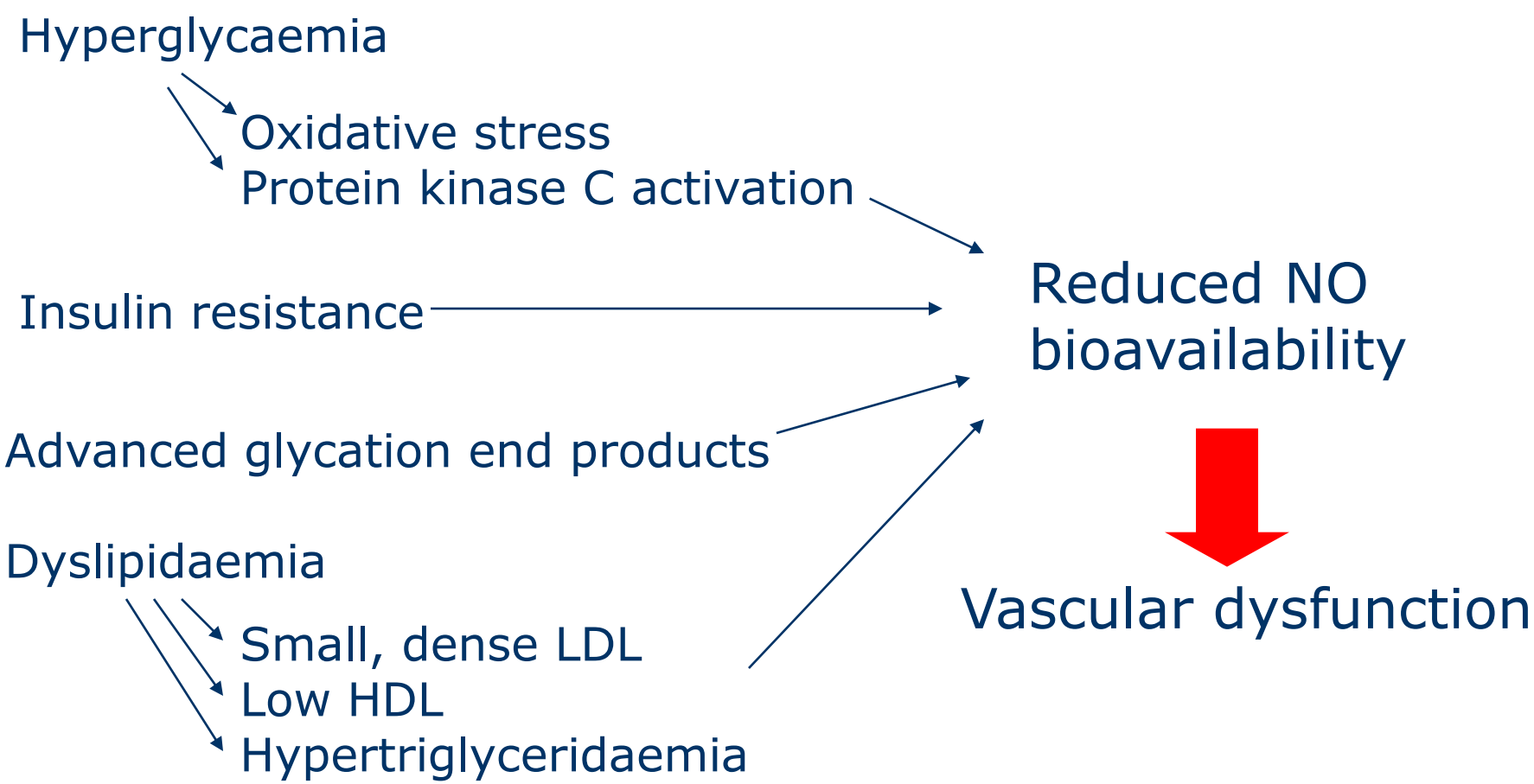
Journal of Stroke and Cerebrovascular Diseases 2011;20:117-23

# Diabetes and stroke

- Patients with diabetes are:
  - More likely to have a stroke
  - Less likely to do well afterwards

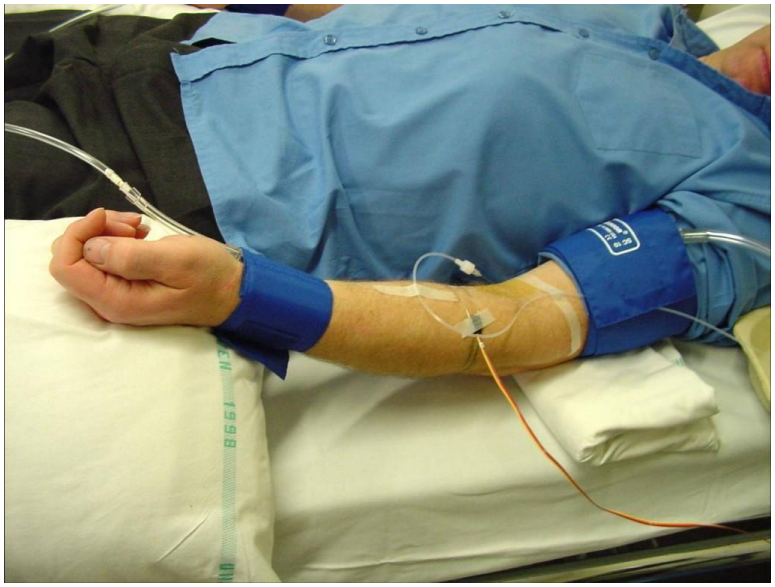
**Why?**

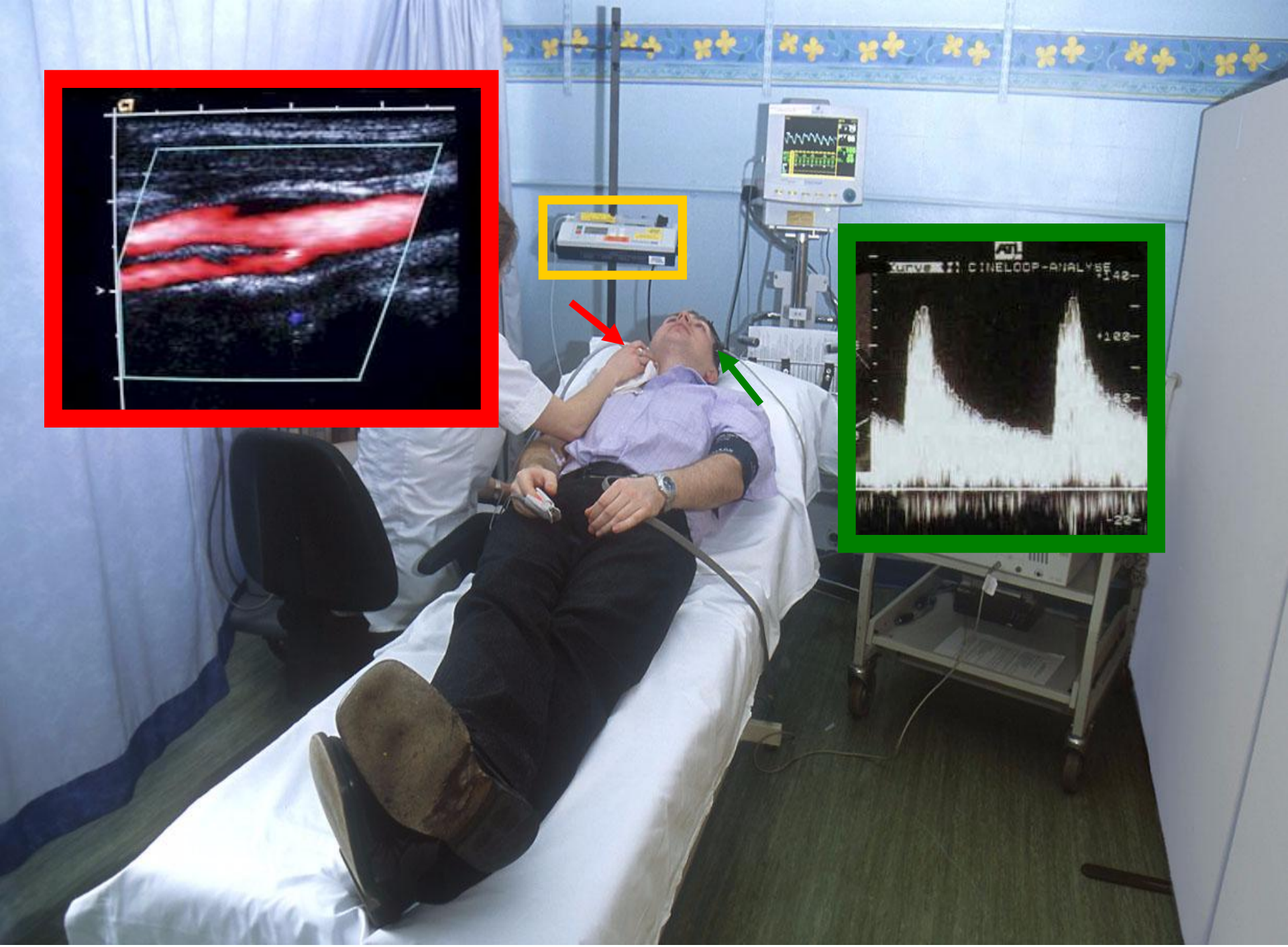
# Mediators of endothelial damage in diabetes



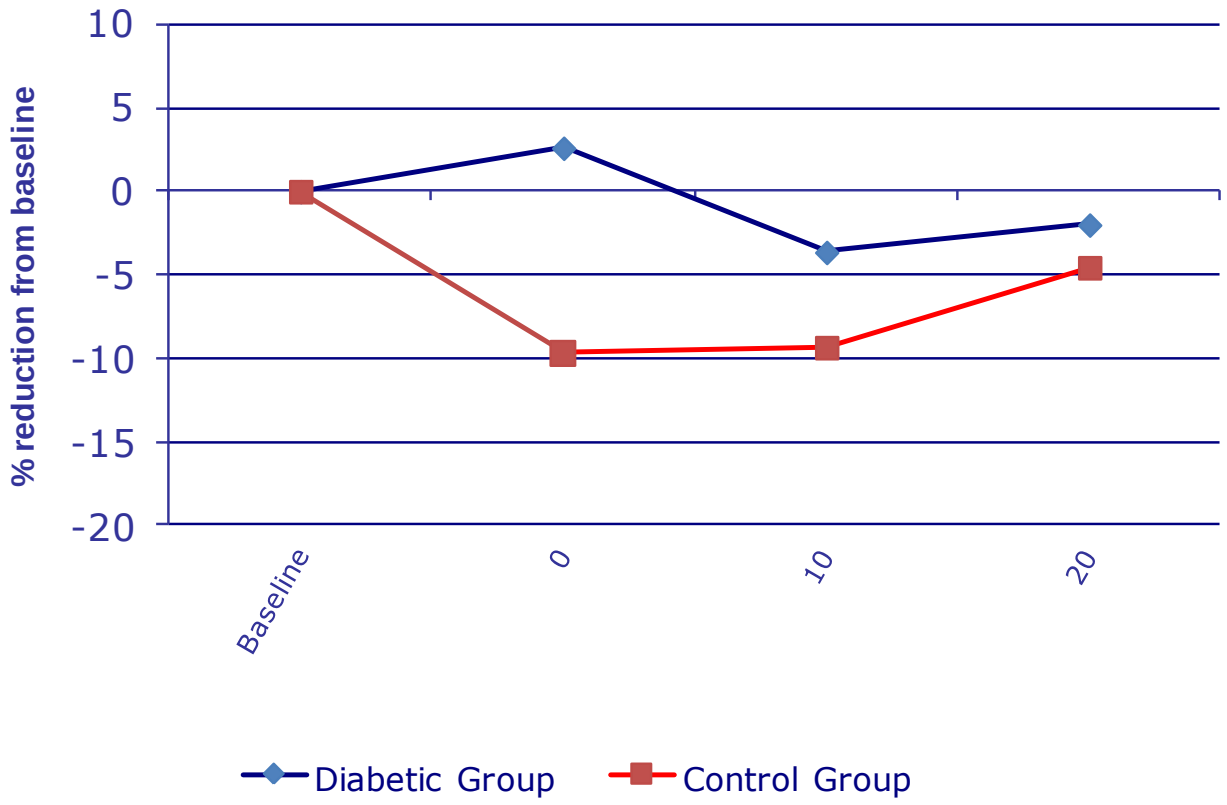
# Vascular dysfunction in diabetes

- Extensively studied in the forearm and other human vascular beds
- The cerebral vasculature behaves very differently...
- ...but it’s harder to study




CINELOOP-ANALYSE
+142
+100
+58
-22

# Carotid blood flow after NOS inhibition




**Blunted response to L-NMMA in diabetic subjects, suggesting *reduced* cerebral NO bioavailability**

Diabetes Care 32:135–137, 2009

# Diabetes and stroke

- Patients with diabetes are:
  - More likely to have a stroke
  - Less likely to do well afterwards
- Pathophysiology complex and incompletely understood: chronic vascular dysfunction is likely to be an important factor

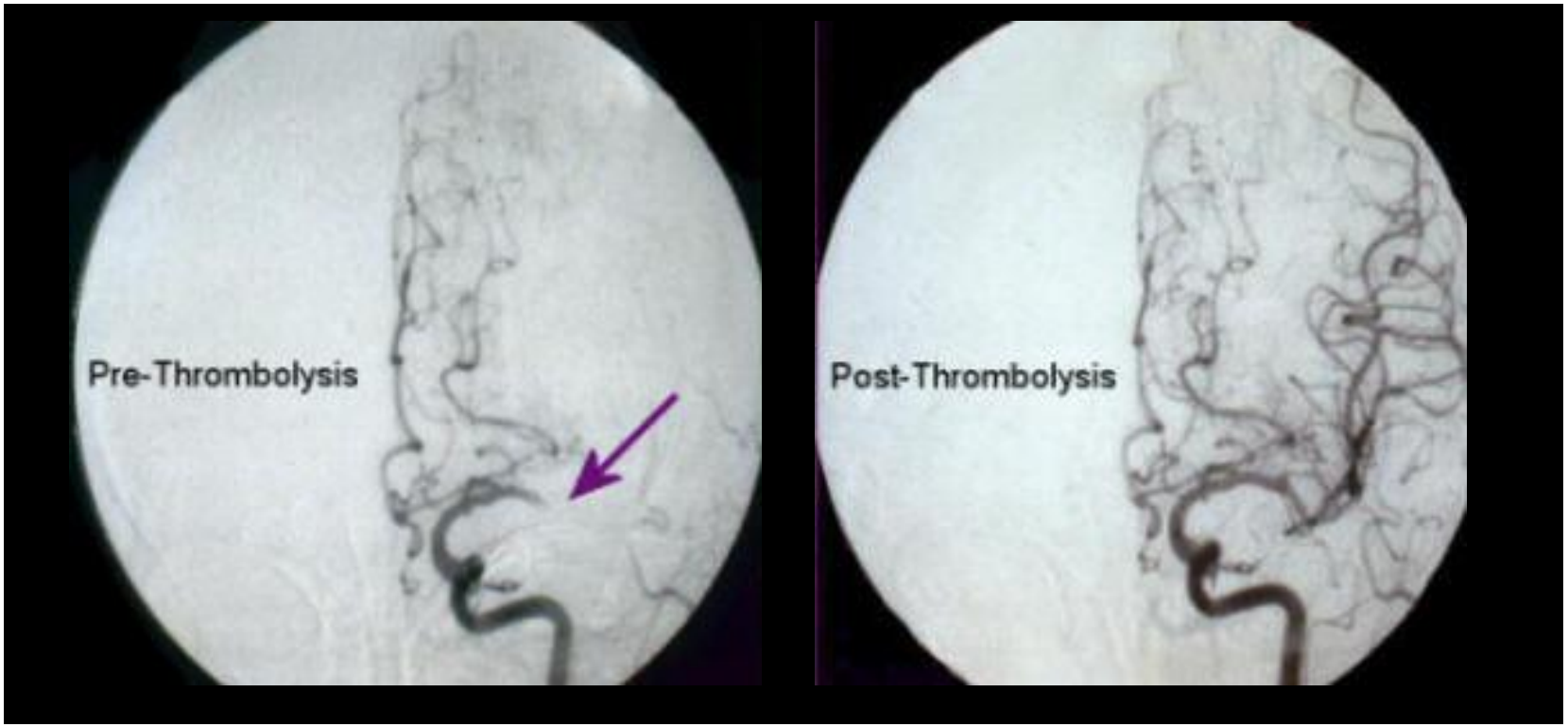
**What are the practical therapeutic implications?**

# Treatment of stroke in the diabetic population

- Thrombolytic therapy
- Glycaemic control
- Blood pressure reduction

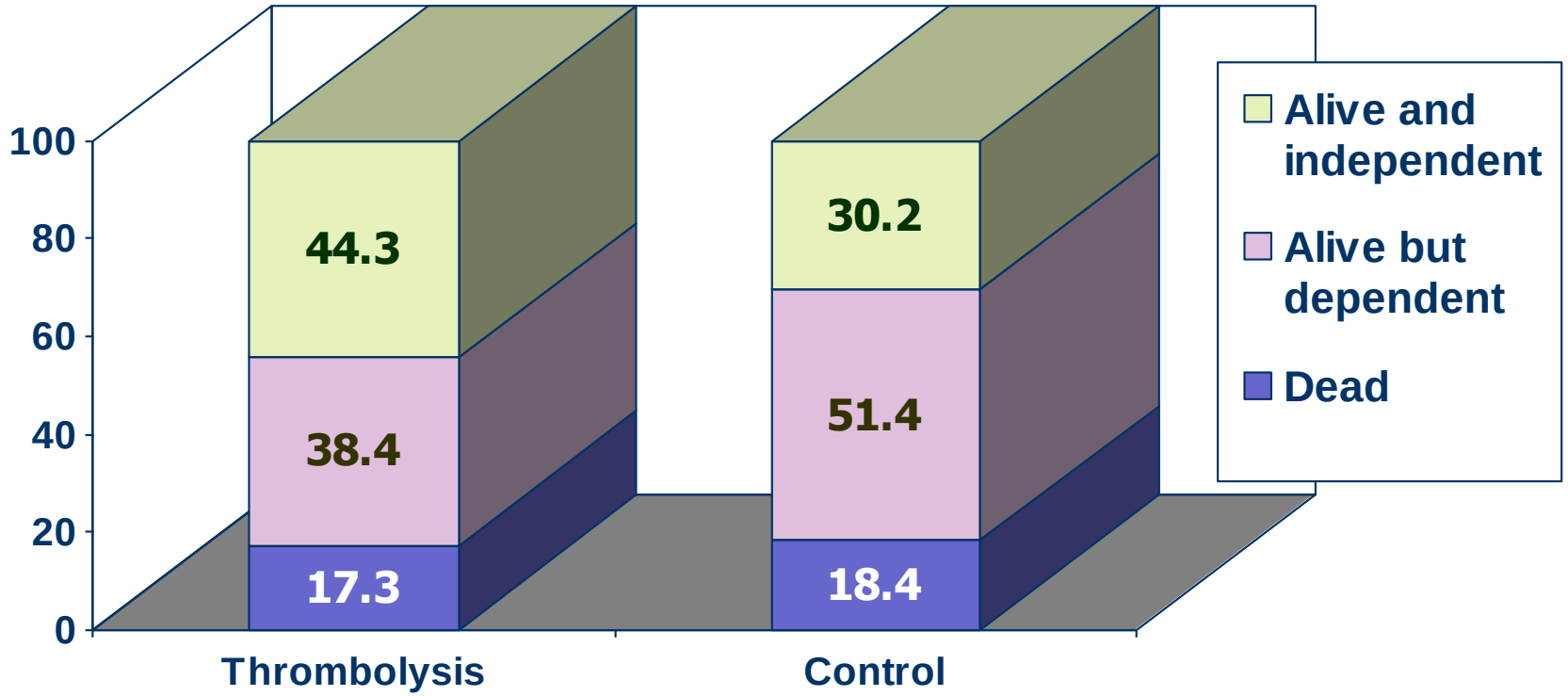
# Thrombolysis

The proven acute pharmacological strategy for ischaemic stroke




Recipients at least **30%** more likely to have little or no disability *in RCTs*

# Meta-analysis of IV rt-PA trials

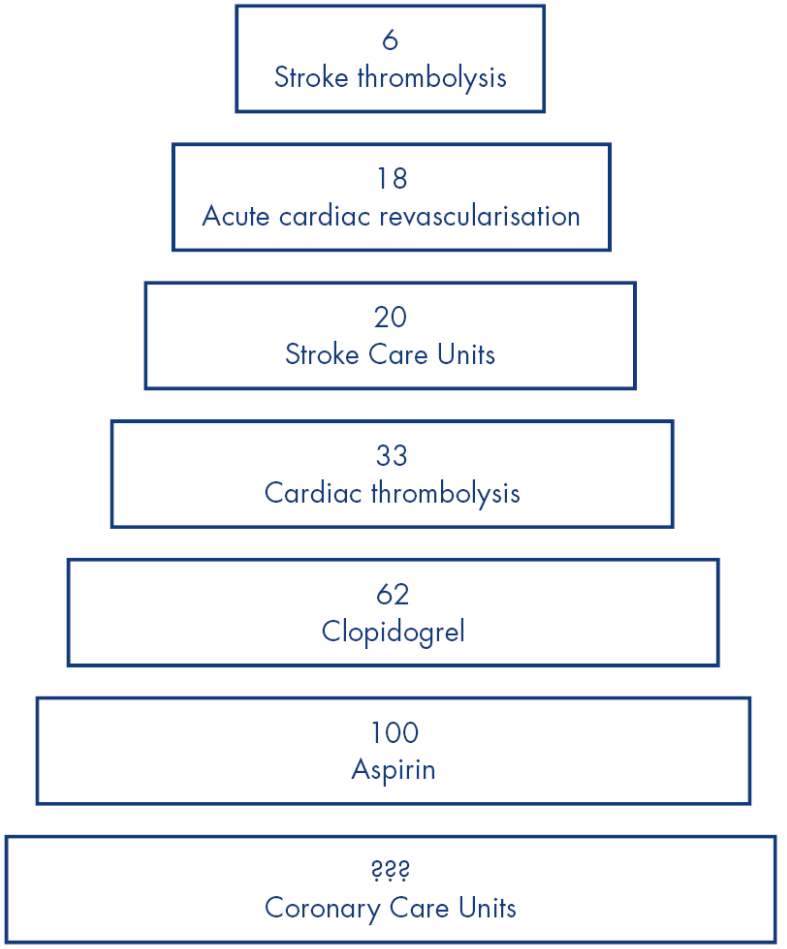



**Difference/1000:** **141 extra alive and independent** **(P<0.01)**
**130 fewer dependent survivors** **(P<0.01)**

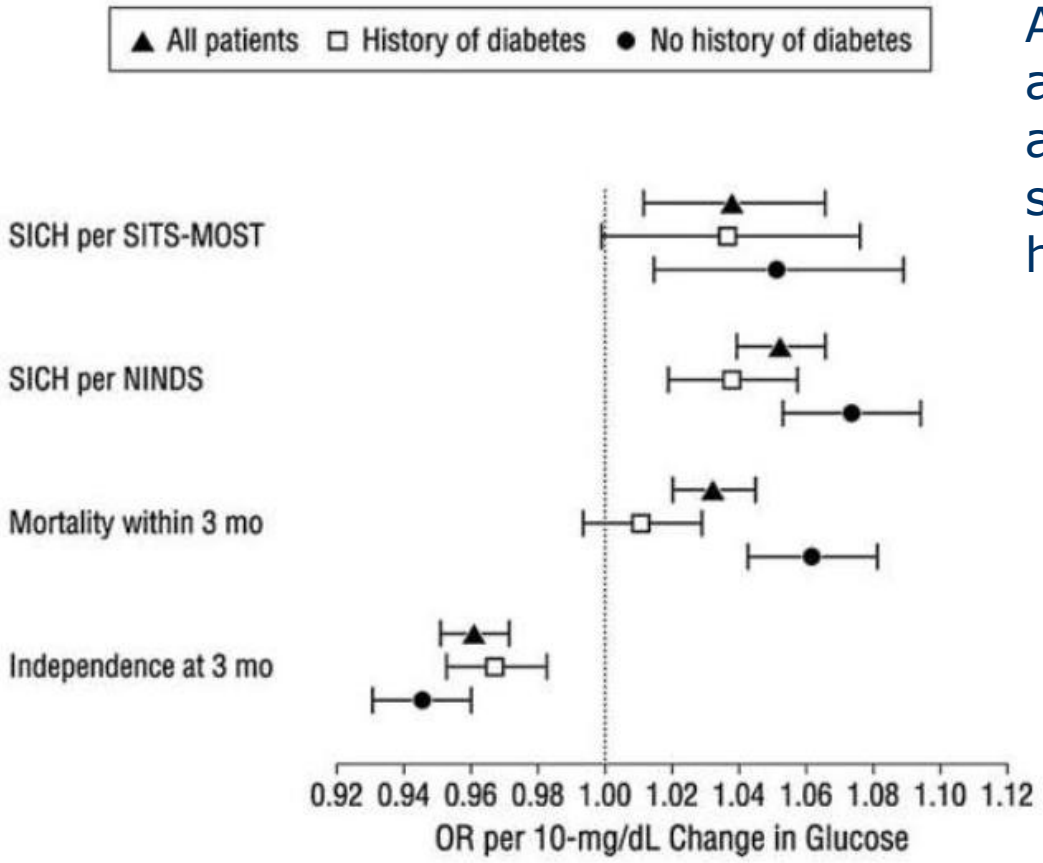
Hacke et al. Lancet 2004;363:768

# NNT in context

- RCTs: relatively large treatment effect
- Compares favourably with:
  - Other stroke therapies
  - Established coronary interventions



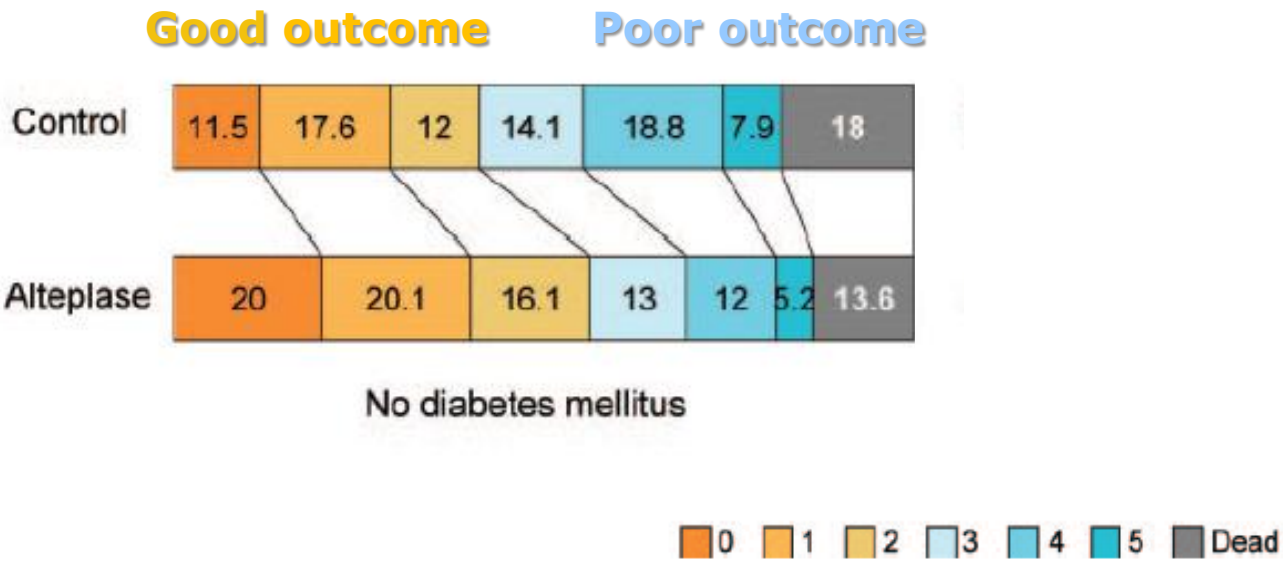
# Theoretical concern over lysis of diabetic / hyperglycaemic stroke patients




Admission hyperglycaemia is associated with poor outcome and increased risk for symptomatic intracerebral haemorrhage

Ahmed et al. 2010. Archives of Neurology 67:1123-30

# Effect of thrombolysis: SITS and VISTA




Outcomes in diabetic tpa recipients are equivalent to untreated non-diabetic patients

Neurology 2011;77:1866–1872

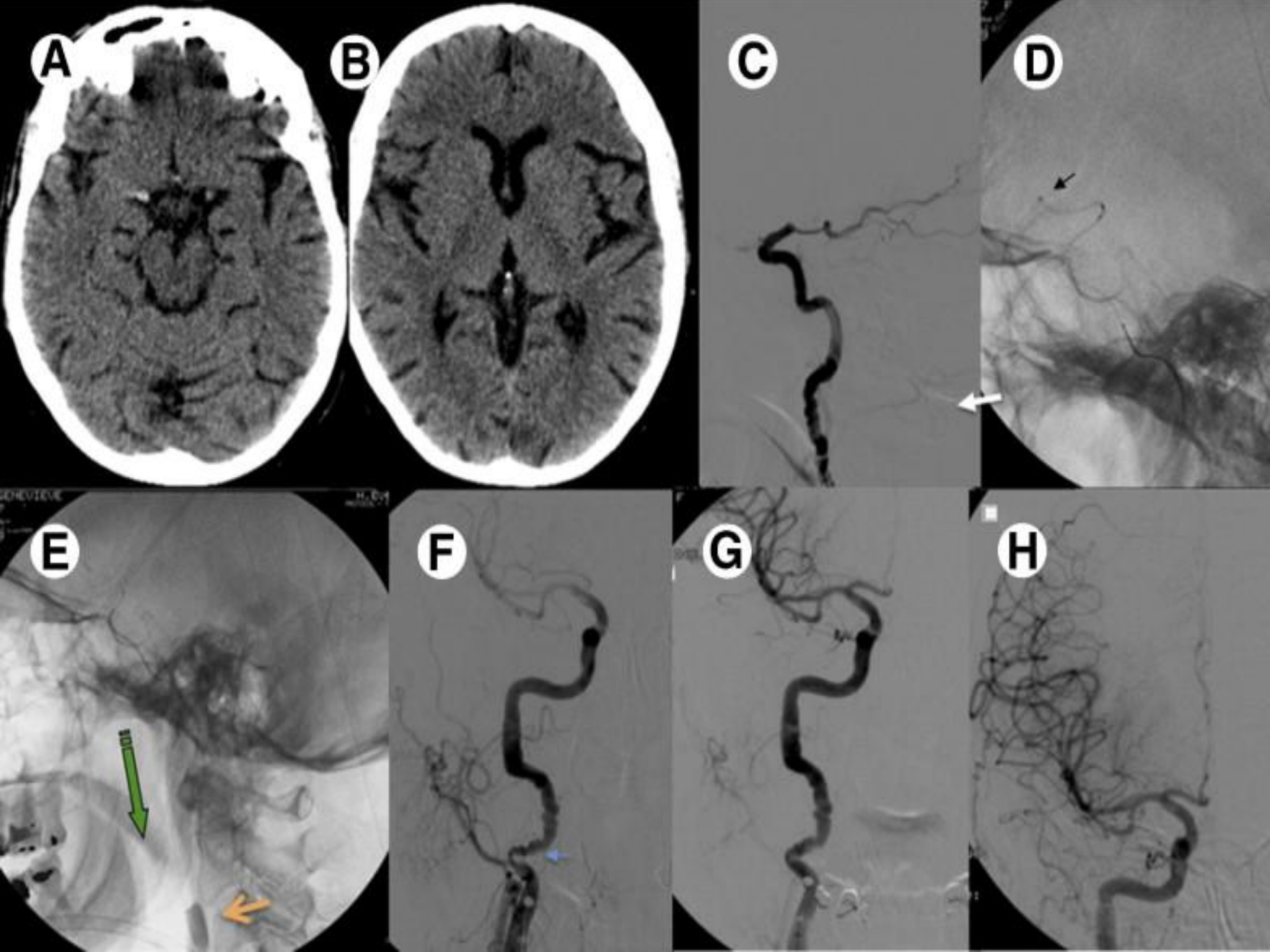
# Effect of thrombolysis: SITS and VISTA

| Patients' group | Analyses type | Forest Plot | OR (95%CI) | N |
|---|---|---|---|---|
| No diabetes | Unadjusted |  | 1.7 (1.6, 1.8), | 23453 |
| | Age and baseline severity adjusted | | 1.6 (1.5, 1.7) | 23246 |
| | Favorable outcome | | 1.9 (1.8, 2.1) | 23246 |
| | Excellent outcome | | 1.6 (1.5, 1.7) | 23246 |
| | Survival | | 1.2 (1.1, 1.3) | 23246 |
| | All adjusted | | 1.6 (1.5, 1.8) | 19621 |
| Diabetes | Unadjusted | | 1.3 (1.2, 1.4) | 5411 |
| | Age and baseline severity adjusted | | 1.4 (1.3, 1.6) | 5354 |
| | Favorable outcome | | 1.8 (1.5, 2.0) | 5354 |
| | Excellent outcome | | 1.6 (1.4, 1.8) | 5354 |
| | Survival | | 1.1 (0.9, 1.2) | 5354 |
| | All adjusted | | 1.6 (1.3, 1.8) | 4322 |

Neurology 2011;77:1866–1872

# Thrombolytic therapy

- Magnitude of benefit comparable in patients with and without diabetes
- Aggressive acute provision of lytic therapy in patients with diabetes is warranted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# A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke

Olvert A. Berkhemer, M.D., Puck S.S. Fransen, M.D., Debbie Beumer, M.D., Lucie A. van den Berg, M.D., Hester F. Lingsma, Ph.D., Albert J. Yoo, M.D., Wouter J. Schonewille, M.D., Jan Albert Vos, M.D., Ph.D., Paul J. Nederkoorn, M.D., Ph.D., Marieke J.H. Wermer, M.D., Ph.D., Marianne A.A. van Walderveen, M.D., Ph.D., Julie Staals, M.D., Ph.D., et al., for the MR CLEAN Investigators*

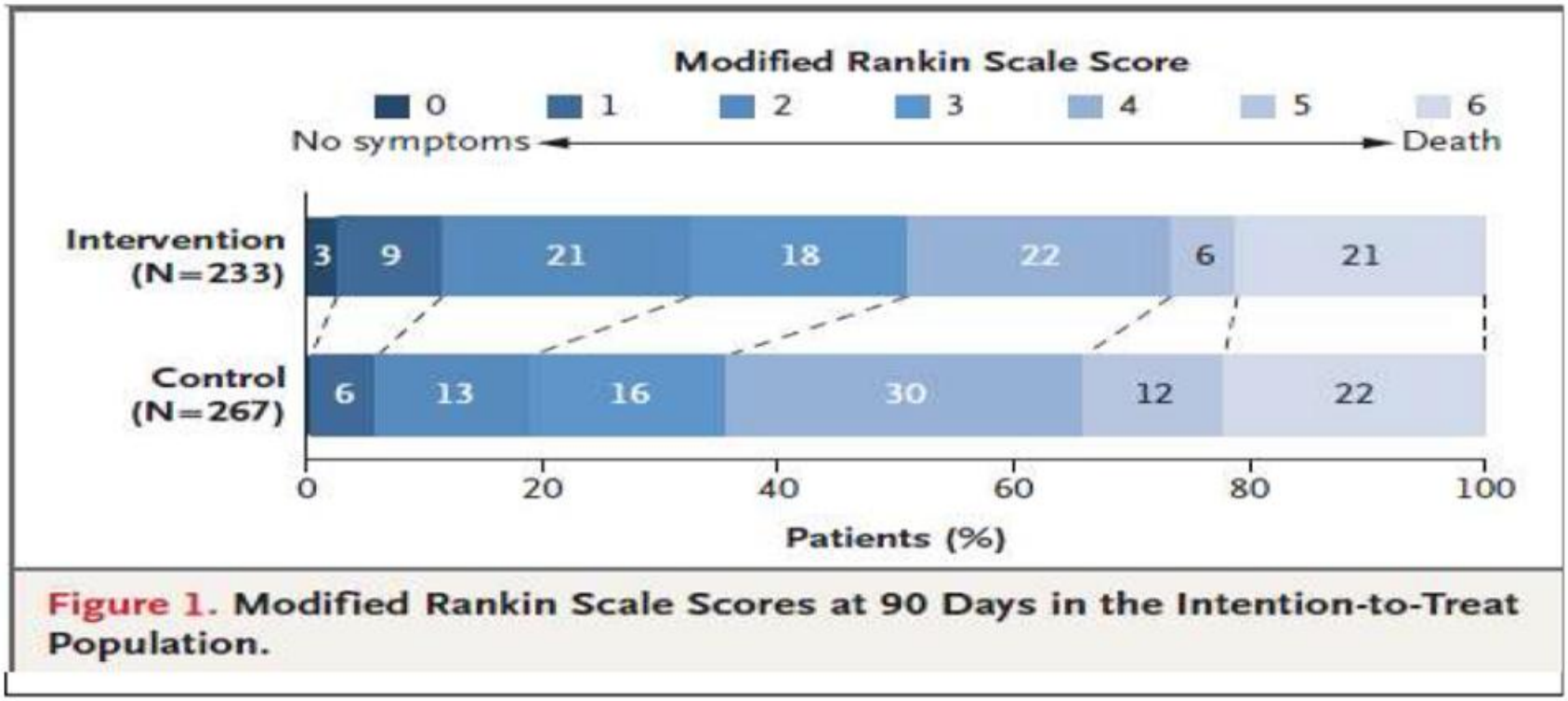
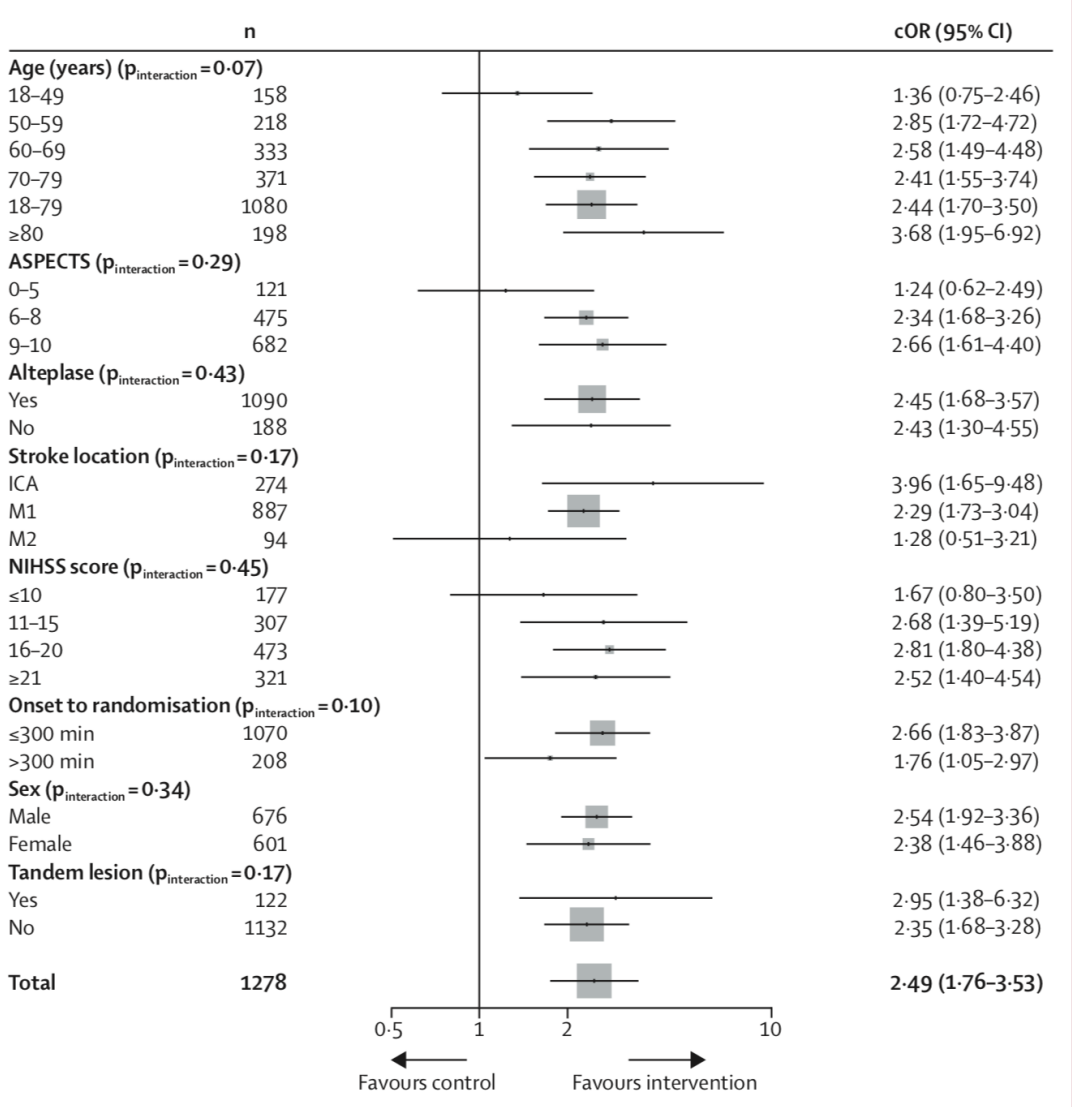



**Figure 1. Modified Rankin Scale Scores at 90 Days in the Intention-to-Treat Population.**

January 1, 2015
N Engl J Med 2015; 372:11-20
DOI: 10.1056/NEJMoa1411587

# Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials



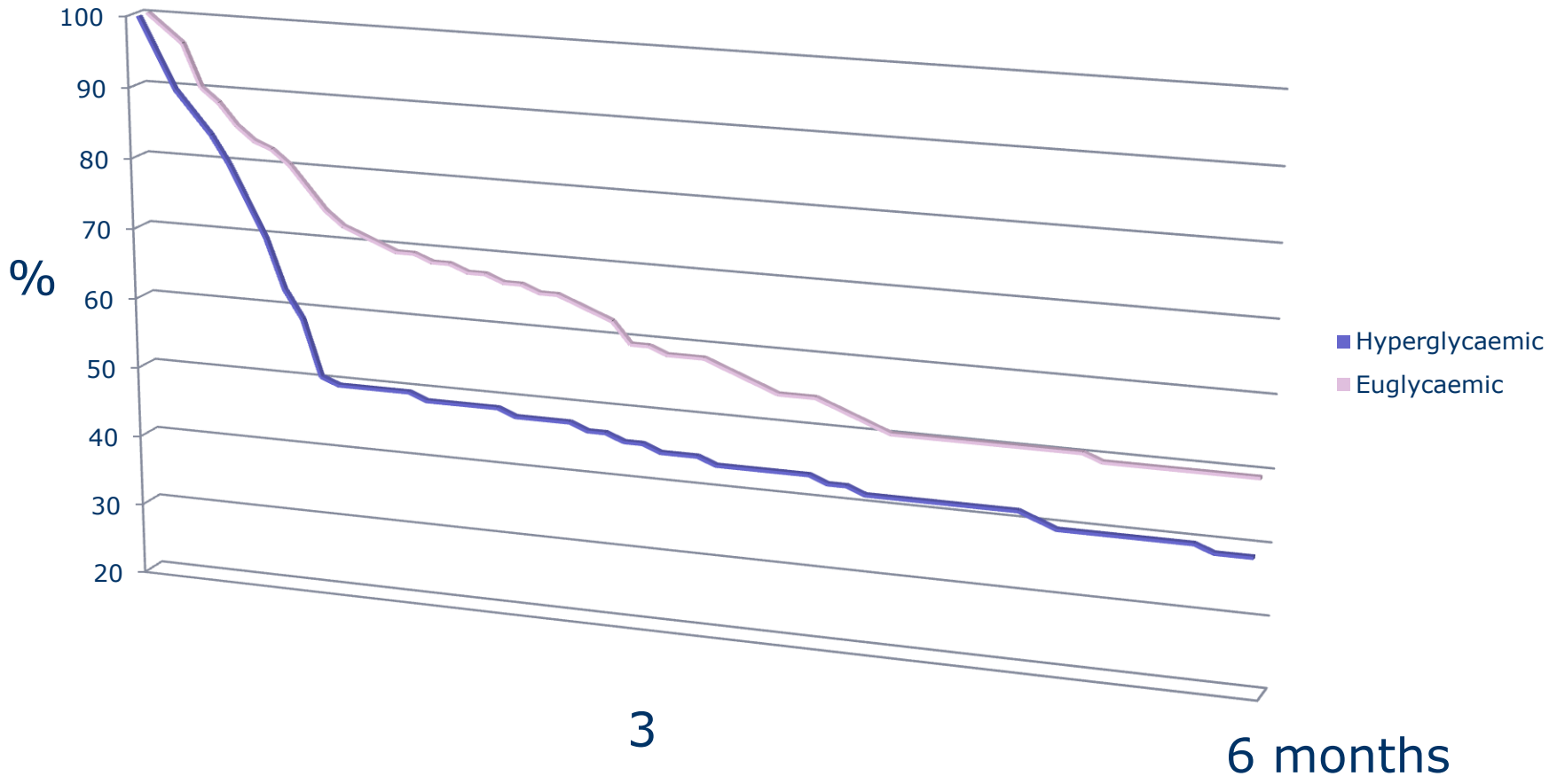

"Benefits are seen across a wide range of age and initial stroke severity, and apply to patients irrespective of eligibility of IV alteplase"

*Lancet* 2016; 387: 1723–31
Published Online
February 18, 2016
http://dx.doi.org/10.1016/S0140-6736(16)00163-X

# Treatment of 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
  - And is associated with worse outcomes

# Short term survival after stroke



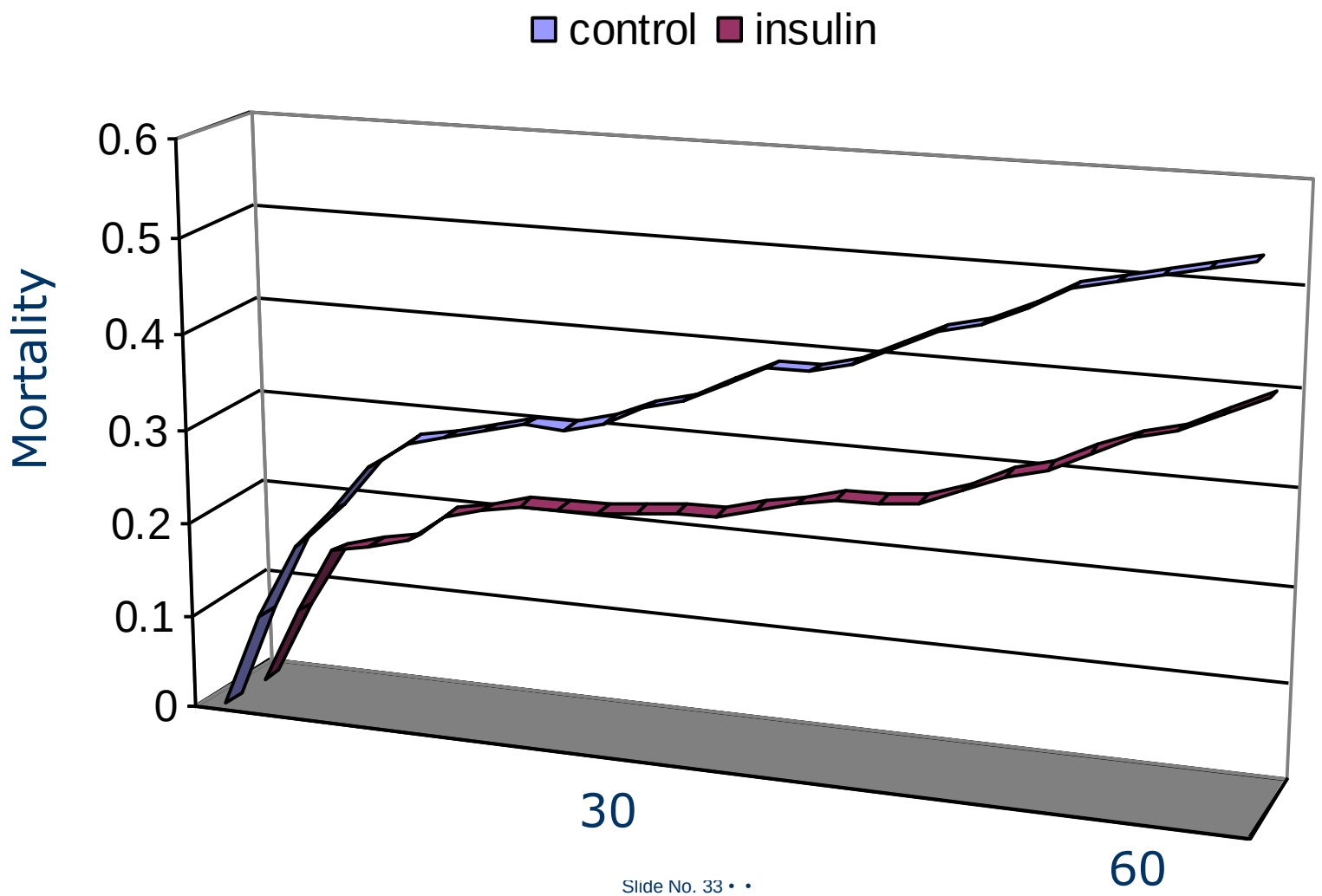



BMJ. 1997 May 3; 314(7090): 1303–1306

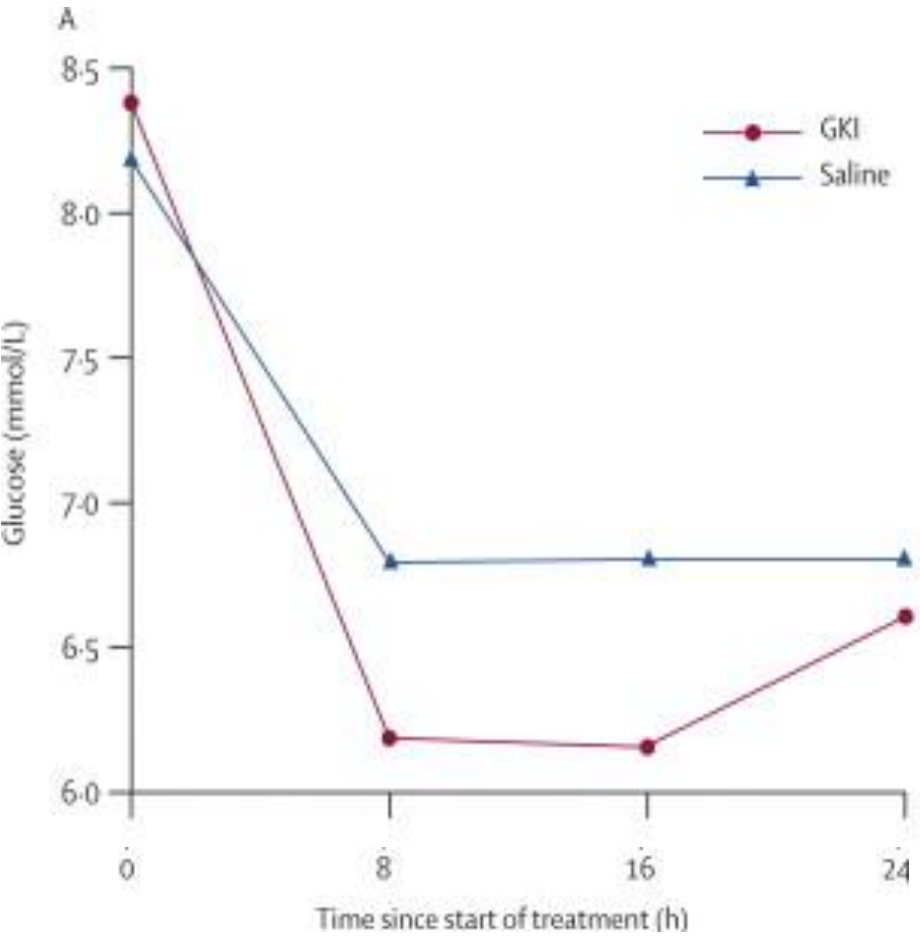
# Hyperglycaemia after stroke

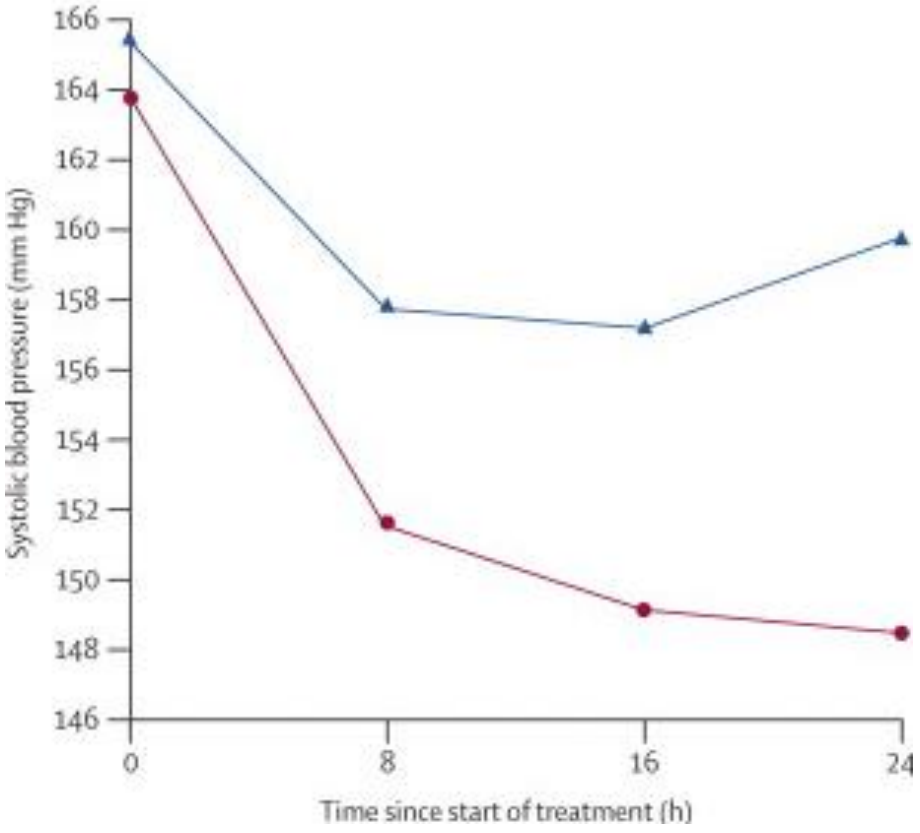
- Intervention with insulin:
  - May reverse this
  - Neuromodulatory effect independent of glycaemia?
  - Seems to work when coronary arteries get blocked…

# Glycaemic control post MI



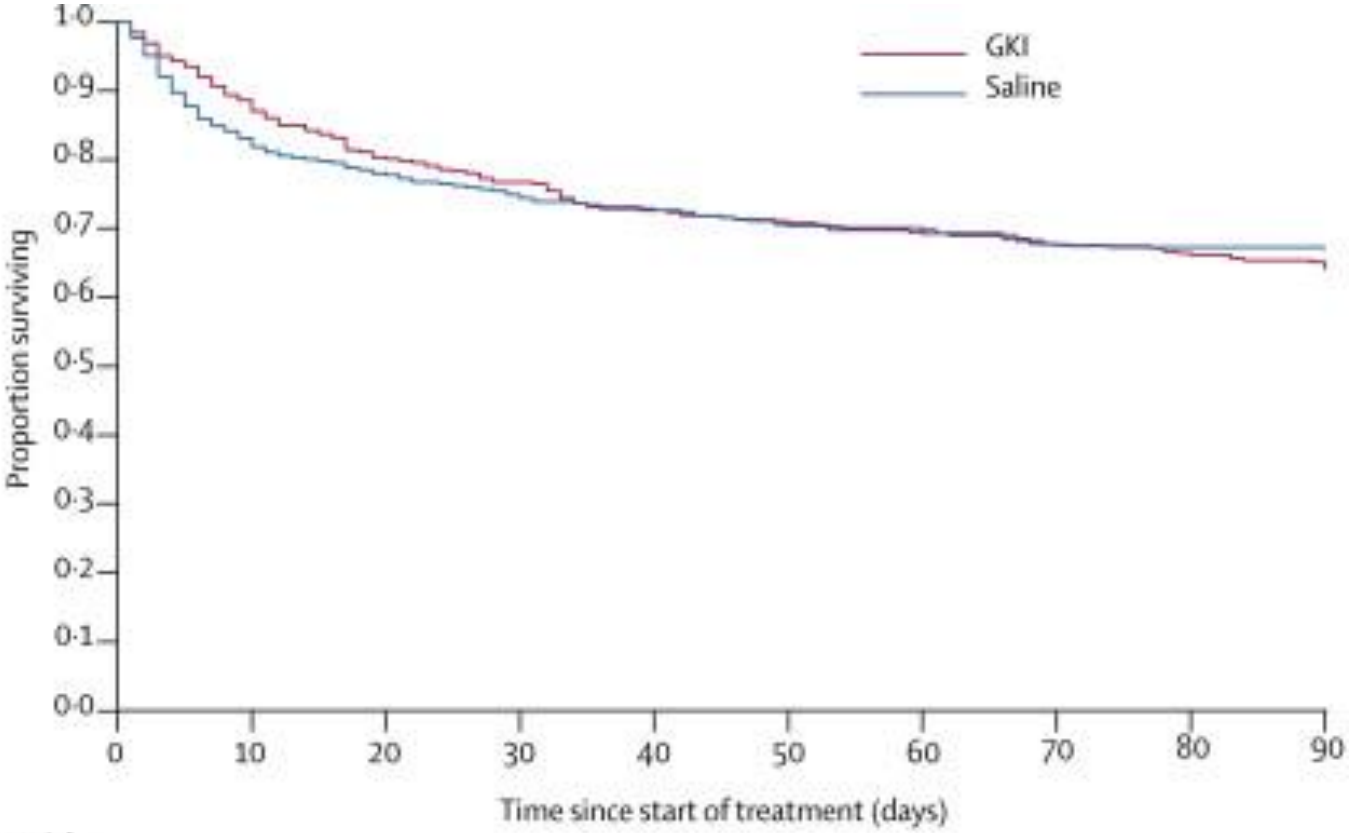
# Intervention in stroke with GKI – effect on glycaemia and BP




Lancet Neurology 2010;6:397-406

# GIST -outcome




**Numbers at risk**

| | | | | | | |
|---|---|---|---|---|---|---|
| GKI | 464 | 388 | 359 | 346 | 334 | 325 |
| Saline | 469 | 383 | 363 | 352 | 342 | 341 |

Lancet Neurology 2010;6:397-406

# GIST trial

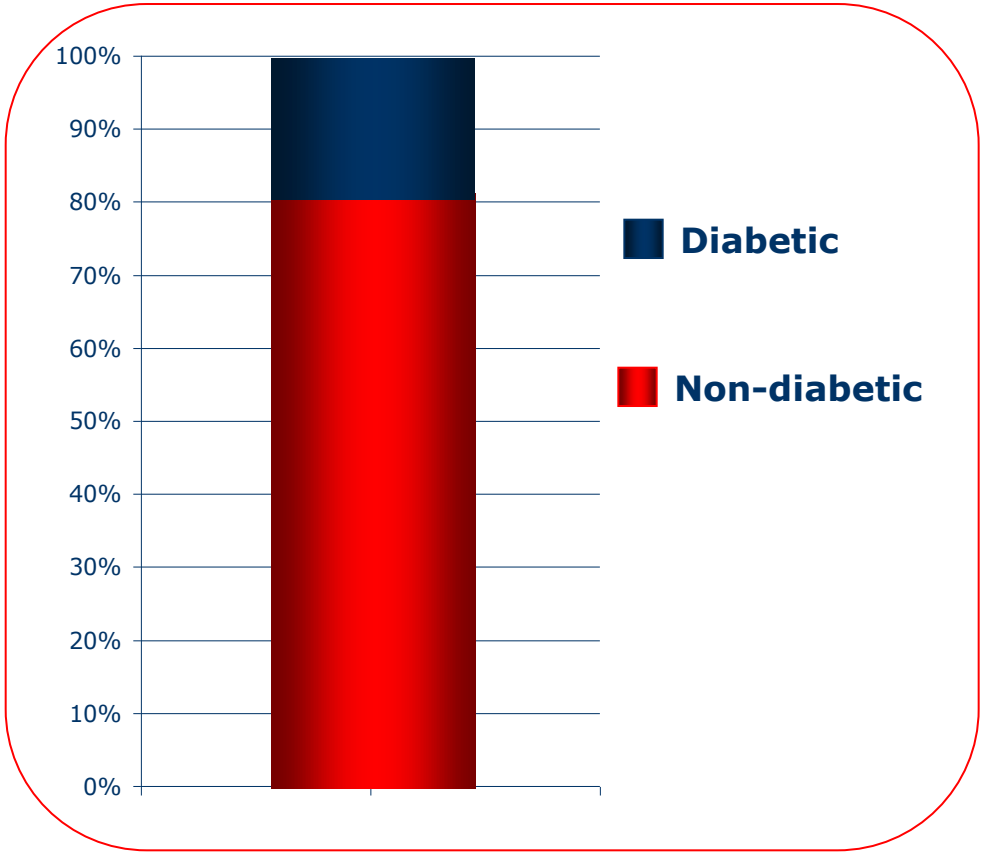
- **Underpowered**
  - **933** of a proposed **2355** patients recruited
- **Similar glycaemic profiles between groups**
  - Absolute reduction in glucose of 0.57 mmol/L induced by insulin infusion. (*cf* 2.1 mmol/L in DIGAMI)
- **Mild hyperglycaemia**
  - Small proportion with baseline blood sugar concentrations >10 mmol/L

# In the absence of evidence…

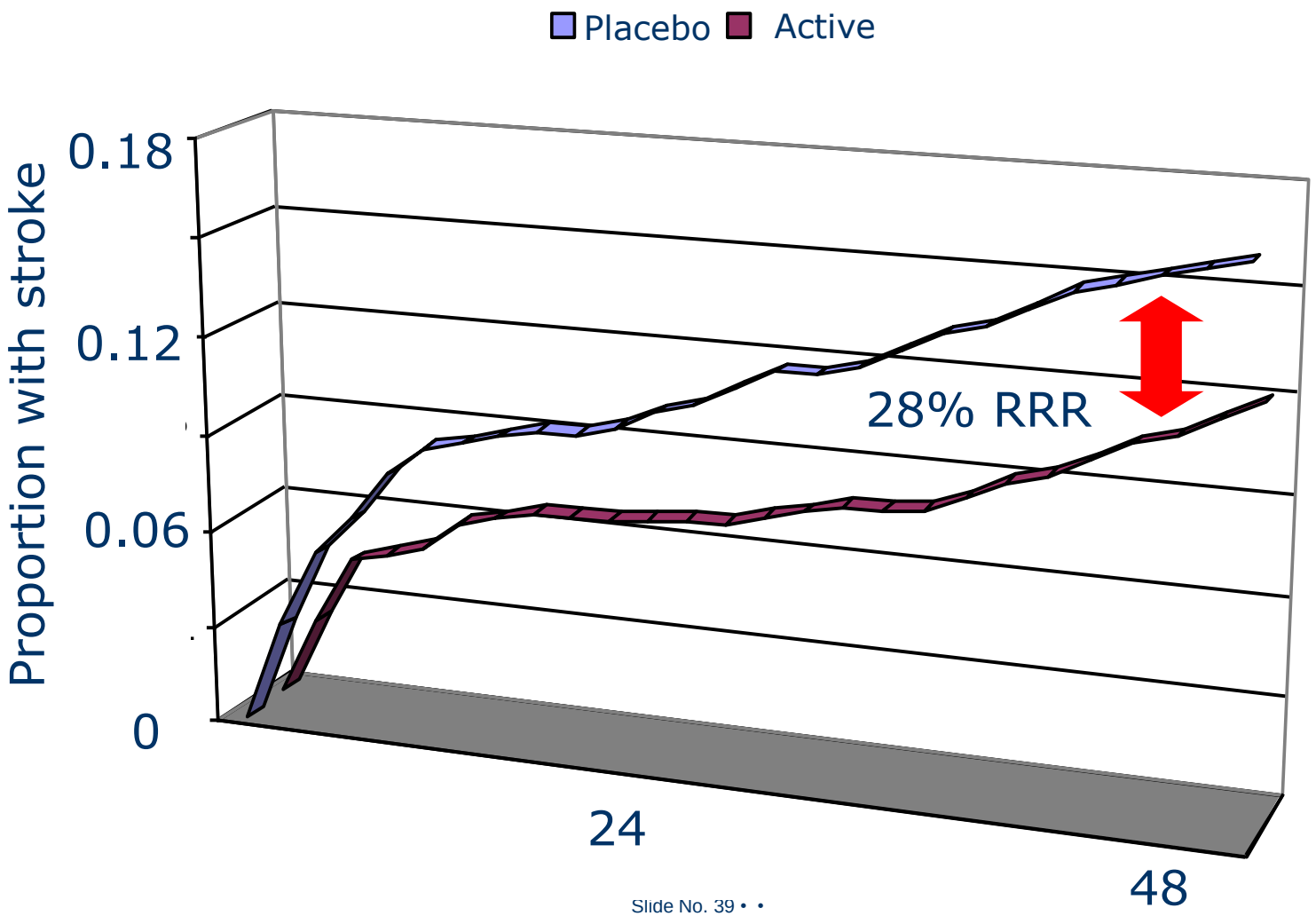
- Guidelines vary:
  - **RCP**
    - *"Maintain euglycaemia"*
  - **EUSI**
    - *"IV insulin if glucose > 10mmol/L"*
  - **AHA**
    - *"Insufficient evidence to guide management"*

# Blood pressure control: PROGRESS

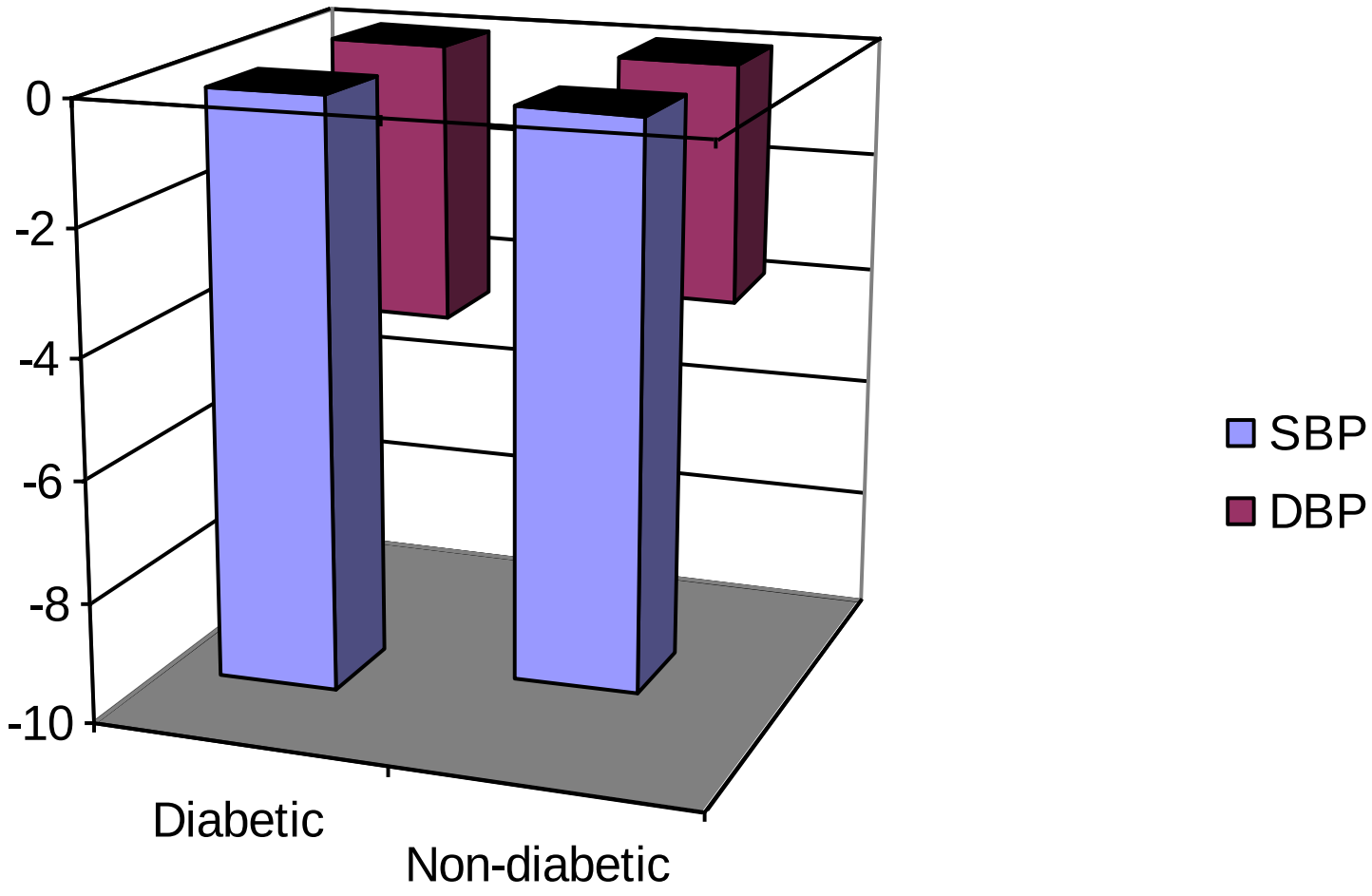
- 6105 stroke survivors
- Any type of stroke
- ACEI + Diuretic vs placebo
- 4 year follow up



# PROGRESS: overall results

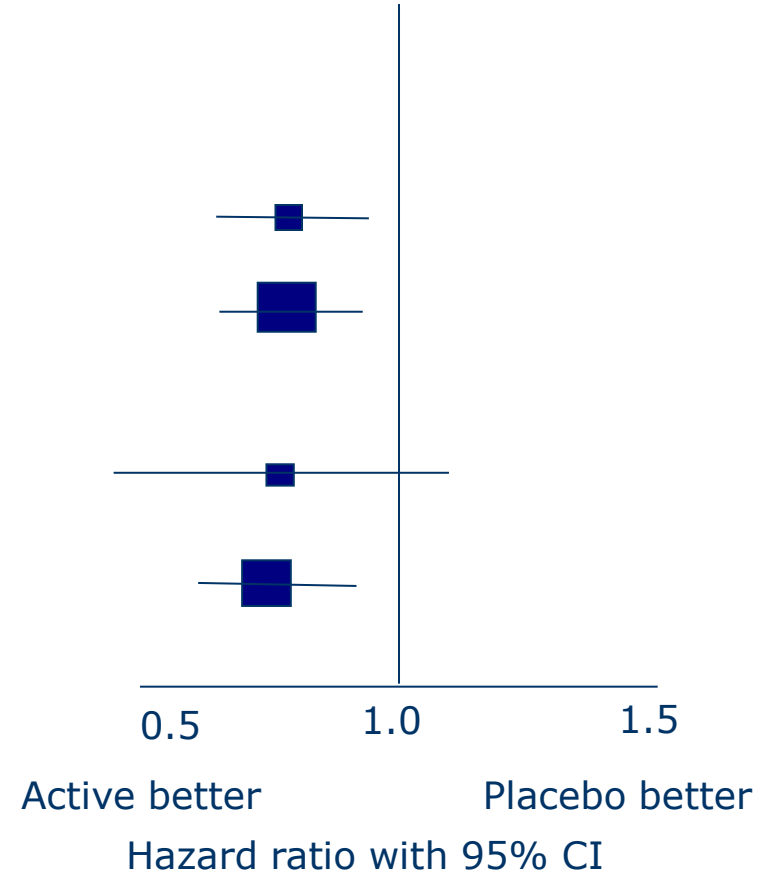


# PROGRESS: effect on BP



# BP reduction and outcomes

- Benefits at least as great in diabetic subgroup
- Subgroups:
  - Recurrent stroke
    - Diabetes
    - No diabetes
  - Any vascular event
    - Diabetes
    - No diabetes



# Blood pressure reduction

- Diuretic plus ACEI mainstay of preventative therapy post stroke for all patients
- Used even in those with “normal” blood pressure
- Benefit at least as great in diabetic population
- Consistent message from many other prevention trials

# Summary

- Diabetic patients are very prone to cerebrovascular disease
- Stroke hits diabetic patients harder
- Current acute strategies limited:
  - Thrombolysis works
  - Tight glycaemic control of uncertain benefit
- Secondary prevention strategies:
  - BP lowering particularly effective