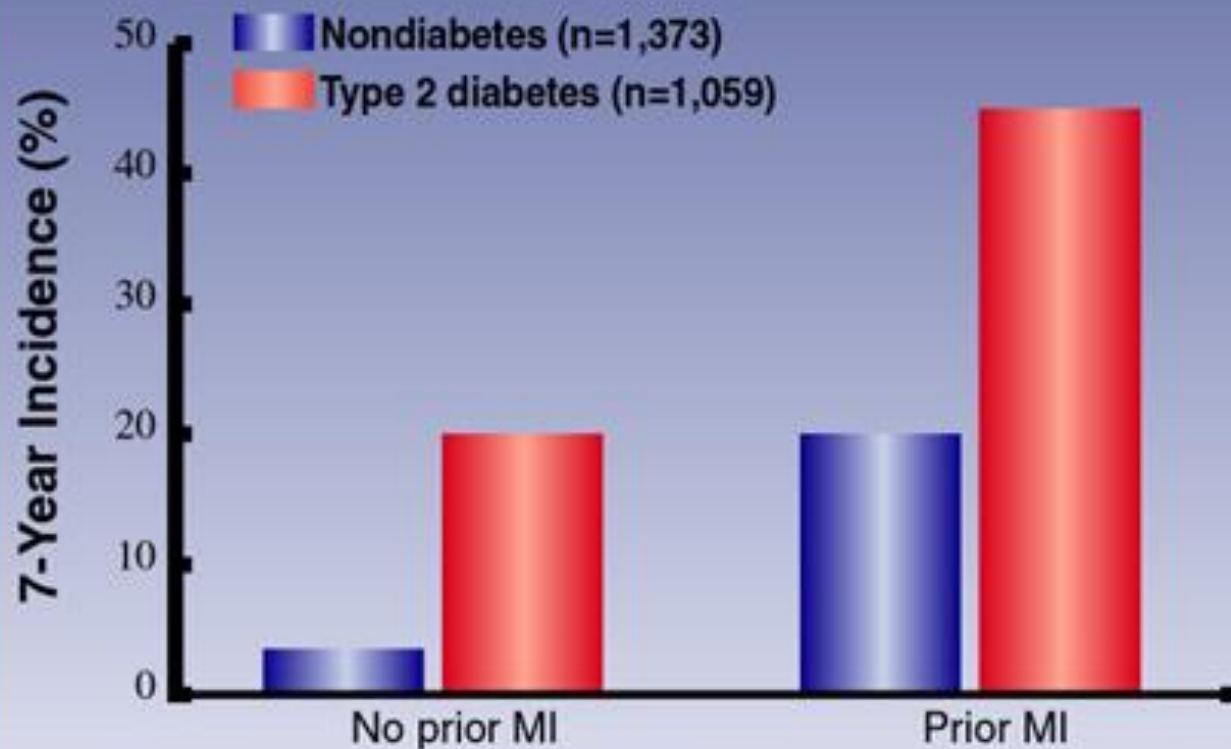# Aspirin treatment failure in diabetes

Ramzi Ajjan

The Division of Cardiovascular and Diabetes Research
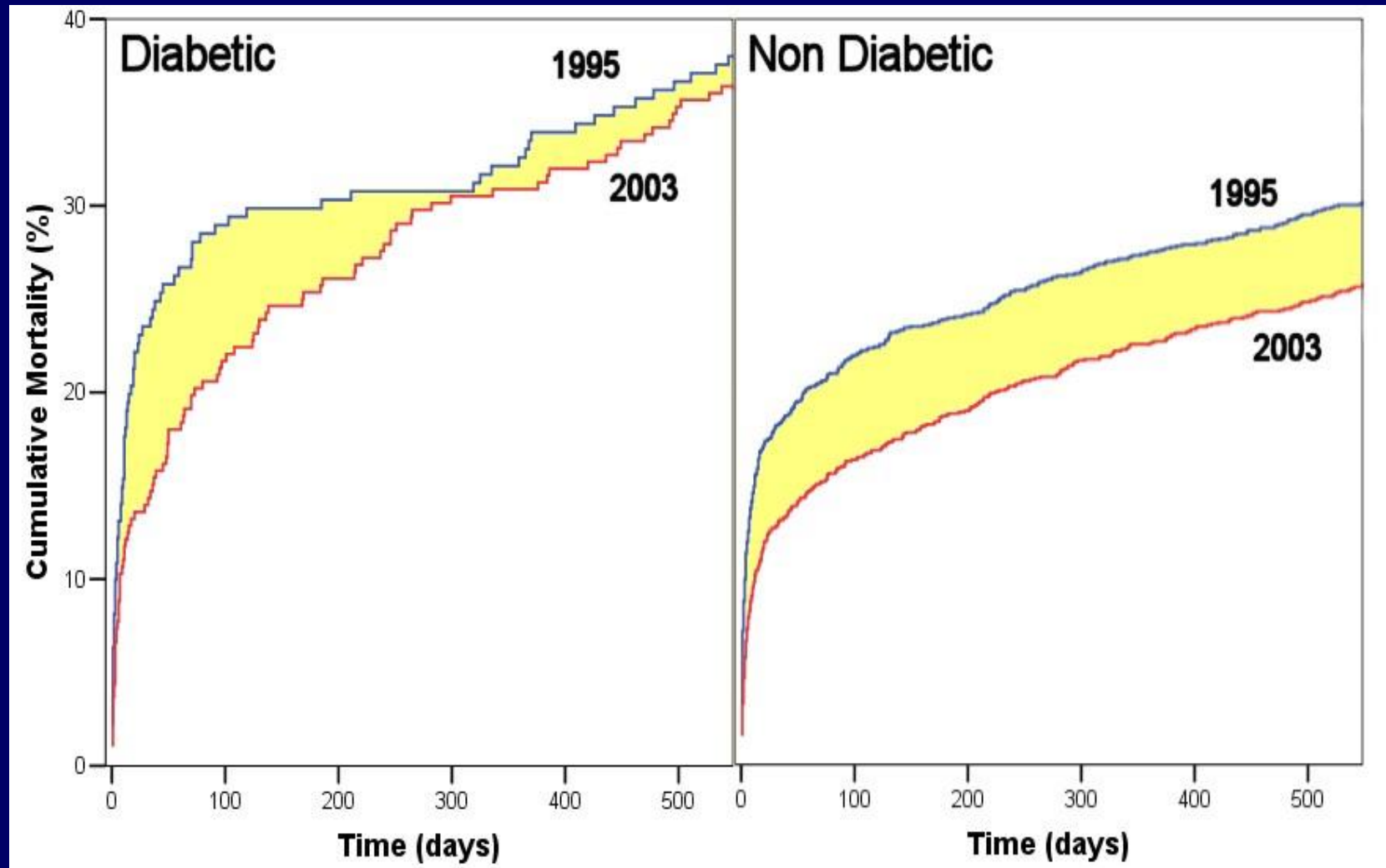
University of Leeds

Diabetes and CV risk

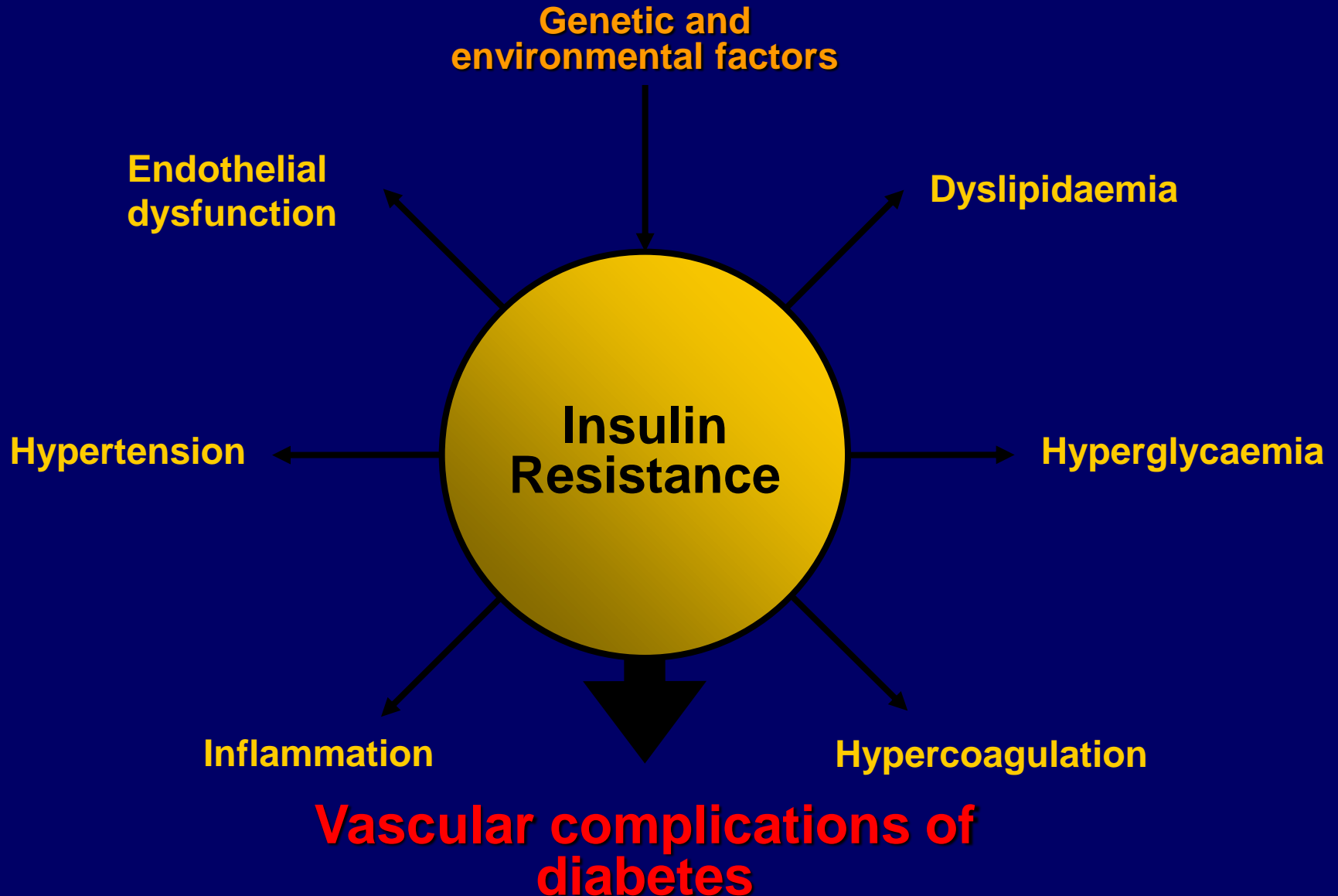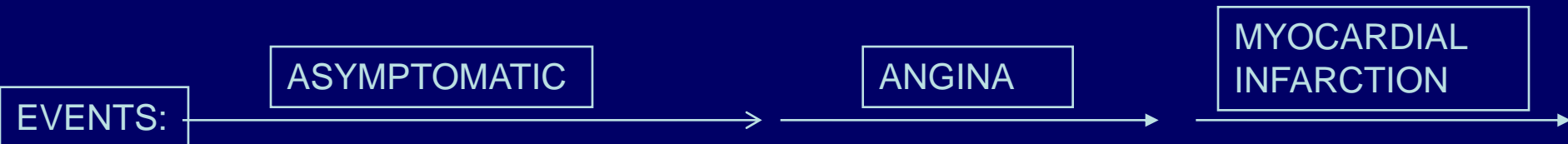Figure 2: Incidence of Myocardial Infarction in People with Type 2 Diabetes[9]

Haffner SM et al. *N Engl J Med.* 1998;339:229-234.

Comparing Mortality in patients with and without diabetes after acute myocardial infarction 1995 versus 2003

EVENTS: → ASYMPTOMATIC → ANGINA → MYOCARDIAL INFARCTION →

Platelet/fibrin clot

atheroma

ATHEROGENESIS → THROMBOSIS →
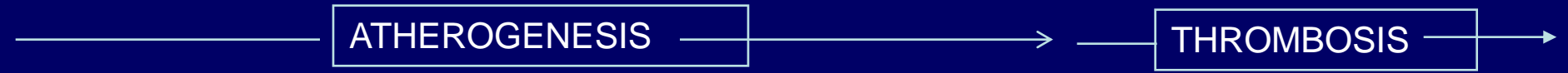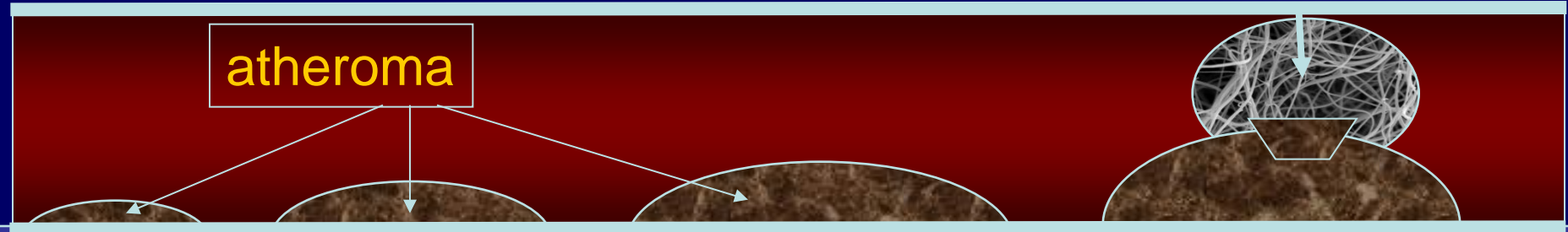
How to prevent thrombus formation in diabetes?

- NICE 2008
  - Give aspirin

Anti-thrombotic therapy

Age 50+ years and BP < 145/90 mmHg

Age < 50 years and significant other CV risk factors

Offer low-dose (75 mg) daily aspirin or, if clear aspirin intolerance, clopidogrel[1]
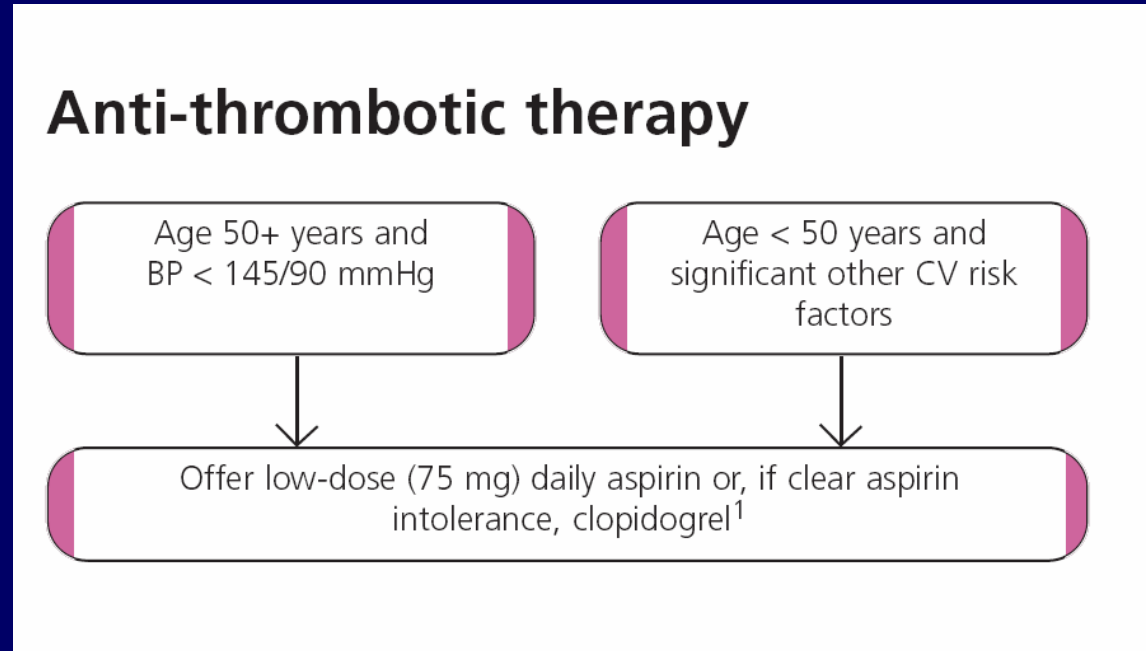
- **Conclusion**
  - **There is clear evidence that aspirin is beneficial in diabetes**

Evidence for cardiovascular protection by aspirin in diabetes

A protective role for aspirin in diabetes Where is the evidence?

- The US Physicians' Health Study:
  - aspirin at 325 mg every other day, FU 5 yrs
  - N=~22000 but only 2.3% with diabetes!
  - MI RRR 61% in men

- Early Treatment Diabetic Retinopathy Study (ETDRS)
  - aspirin 650 mg, n=3700, ~50% with CVD, FU 5 yrs
  - MI RRR 17%.

Antiplatelet treatment and CV risk

Meta-analysis of 287 studies (135000 subjects):

➢ Antiplatelet use results in 22% reduction of CV events.

➢ In a subgroup of 5000 diabetic patients risk reduction was 7% (not significant)

PPP trial
(used in NICE guidelines to support the use of aspirin in diabetes)

A

Legend:
- Aspirin No Diabetes
- No Aspirin No Diabetes
- Aspirin Diabetes
- No Aspirin Diabetes

Log-Rank Test No Diabetes $\chi^2 = 4.98$ p-value = 0.03
Log-Rank Test Diabetes $\chi^2 = 0.13$ p-value = 0.71

Y-axis: Probability
X-axis: Time

Primary Prevention Project (PPP)

	Diabetes yes		Diabetes no		RR (95%CI)
	ASA	Ctr.	ASA	Ctr.	
Main combined end-point	20 (3.9%)	22 (4.3%)	30 (1.6%)	51 (2.7%)	0.59 (0.37-0.94) 0.90 (0.50-1.62)
Total CV events	53 (10.2%)	59 (11.5%)	98 (5.3%)	142 (7.5%)	0.69 (0.53-0.90) 0.89 (0.62-1.26)
All deaths	25 (4.8%)	20 (3.9%)	42 (2.3%)	61 (3.2%)	0.70 (0.47-1.04) 1.23 (0.69-2.19)
Cardiovascular	10 (1.9%)	8 (1.6%)	8 (0.4%)	25 (1.3%)	0.32 (0.14-0.72) 1.23 (0.49-3.10)
Non-cardiovascular	15 (2.9%)	12 (2.3%)	34 (1.9%)	36 (1.9%)	0.97 (0.60-1.56) 1.23 (0.58-2.61)
All myocardial infarction	5 (1.0%)	10 (2.0%)	15 (0.8%)	22 (1.2%)	0.69 (0.36-1.35) 0.49 (0.17-1.40)

0.10   1.00   10.00

Aspirin better   Aspirin worse

Sacco et al, Diabetes Care 2003, 26:3264

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POPADAD
(n=1276 T2DM with PVD)
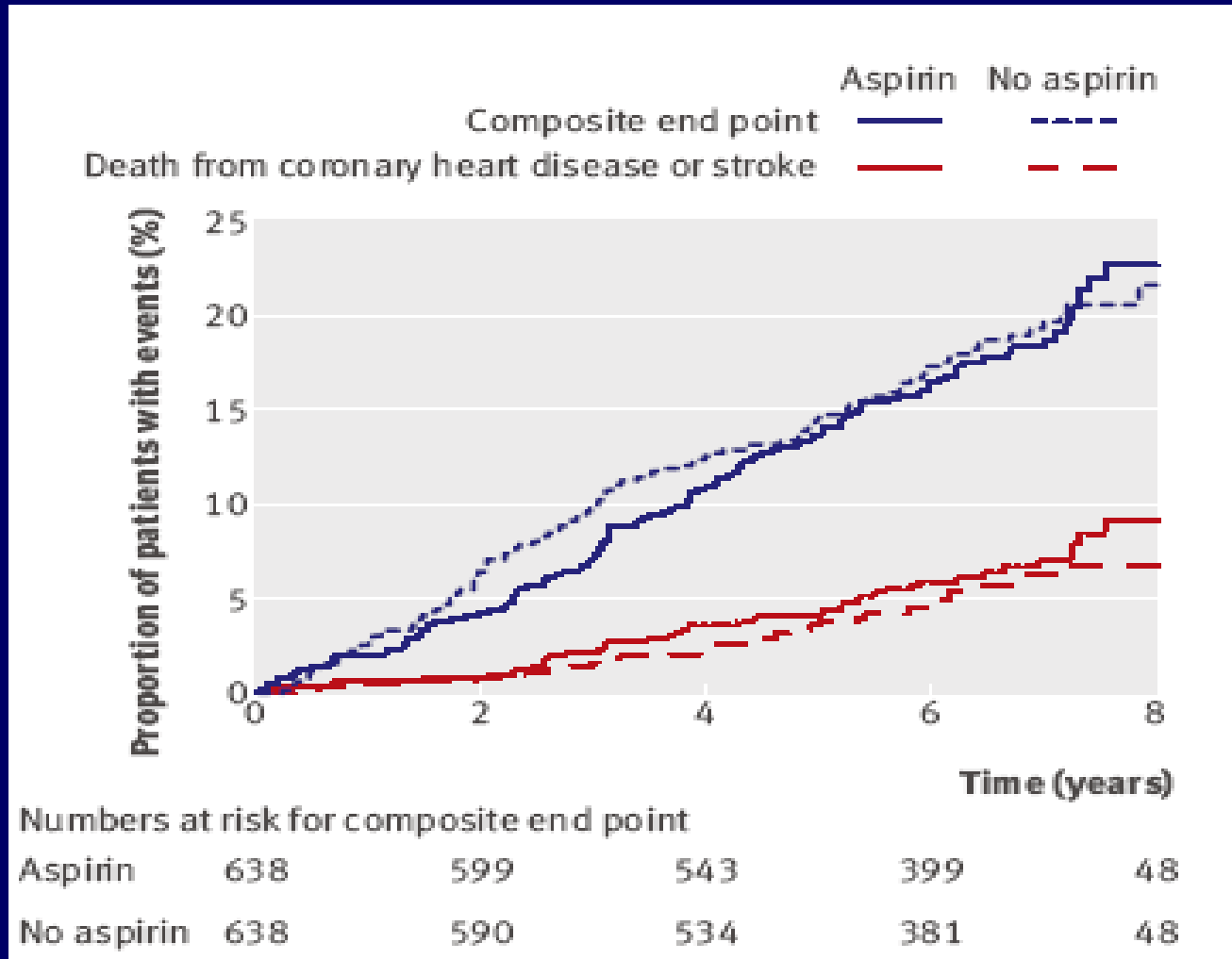
PEP1: Death from CVD, CV event or amputation
PEP2: Death from CVD

JPAD

- Randomised 2540 patients with diabetes and no known CVD (<85 yrs) to aspirin or no aspirin (81-100 mf/d; open label)

- Median F/U: 4.4 years

- PEP: fatal or nonfatal CAD/stroke or PVD

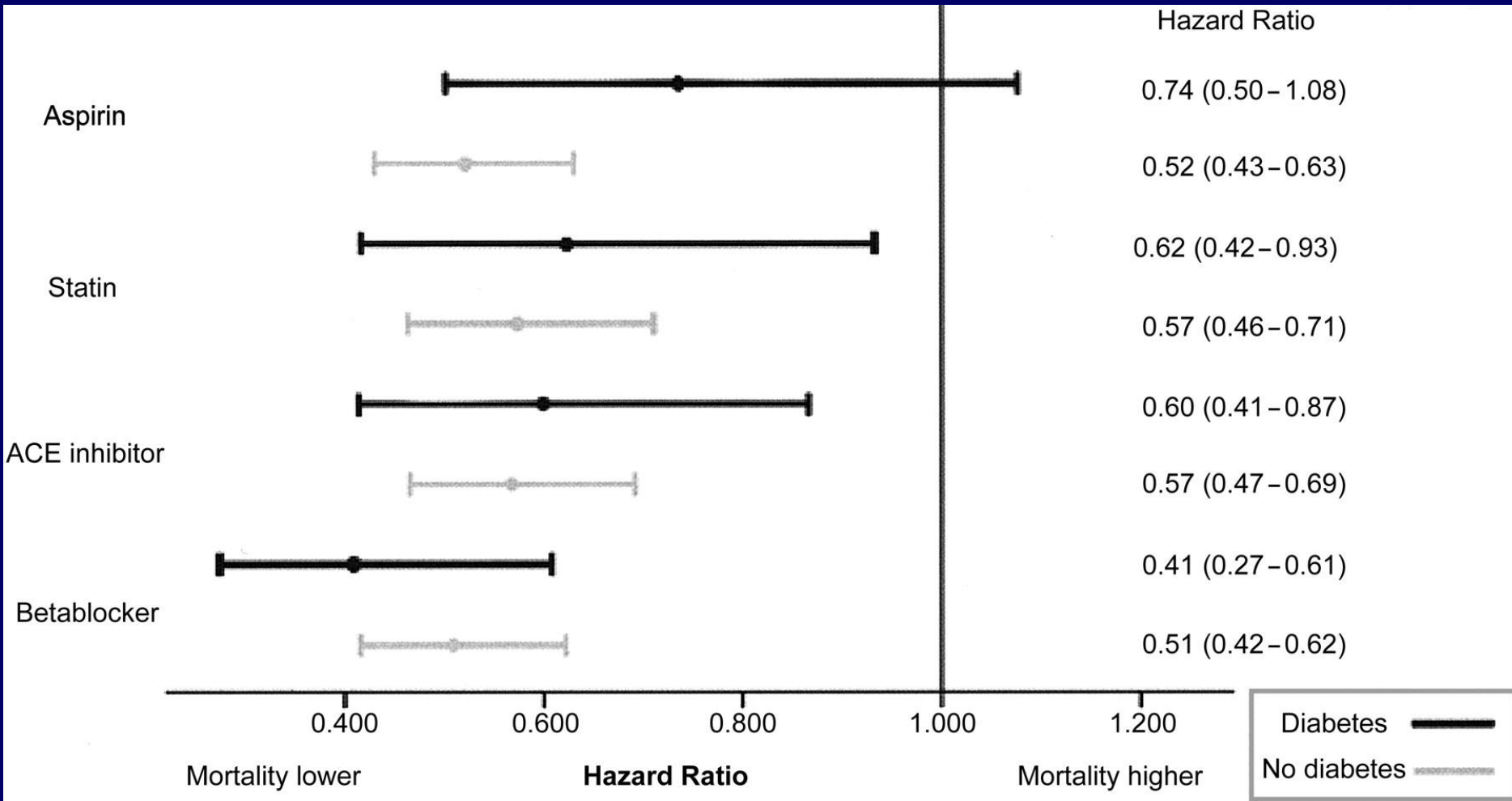- SEP: each PEP and combination of PEP and death from any cause

JPAD

Outcome	HR	p
*PEP	0.80 (0.58-1.10)	0.16
Fatal CV event	0.10 (0.01-0.79)	0.003
All cause mortality	0.90 (0.57-1.14)	0.70

*composite of sudden death; death from coronary, cerebrovascular, or aortic causes; nonfatal IHD, CVD, PVD or aortic disease
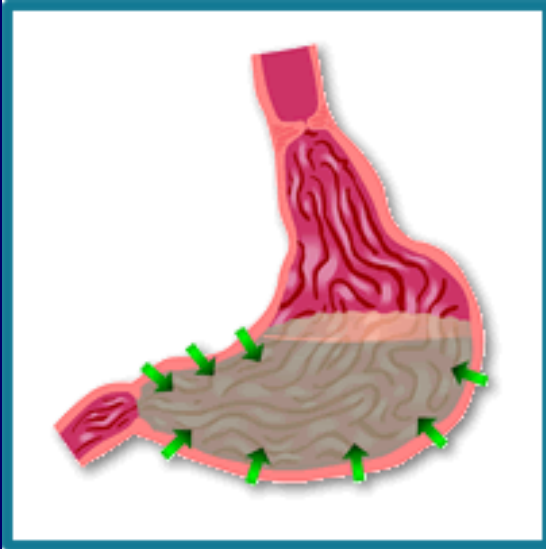
JPAD

| | Events, No./Total No. | | Hazard Ratio (95% CI) | | |
	Aspirin Group	Nonaspirin Group		Favors Aspirin	Favors No Aspirin
Age, y					
≥65	45/719	59/644	0.68 (0.46-0.99)		
<65	23/543	27/633	1.0 (0.57-1.70)		
Sex					
Male	40/706	51/681	0.74 (0.49-1.12)		
Female	28/556	35/596	0.88 (0.53-1.44)		
Hypertensive status					
Hypertensive	49/742	55/731	0.88 (0.60-1.30)		
Normotensive	19/520	31/546	0.64 (0.36-1.13)		
Lipid status					
Dyslipidemia	38/680	43/665	0.88 (0.57-1.37)		
Normolipidemia	30/582	43/612	0.71 (0.45-1.14)		
Smoking					
Current or past	36/565	42/494	0.73 (0.47-1.14)		
Nonsmoker	32/697	44/783	0.83 (0.53-1.31)		

Hazard Ratio (95% CI)

Aspirin and secondary prevention

Aspirin post ACS (mortality 2 years)

Forest plot of Hazard Ratio by treatment, comparing Diabetes (solid line) versus No diabetes (dotted line).

Treatment	Hazard Ratio
Aspirin (Diabetes)	0.74 (0.50 – 1.08)
Aspirin (No diabetes)	0.52 (0.43 – 0.63)
Statin (Diabetes)	0.62 (0.42 – 0.93)
Statin (No diabetes)	0.57 (0.46 – 0.71)
ACE inhibitor (Diabetes)	0.60 (0.41 – 0.87)
ACE inhibitor (No diabetes)	0.57 (0.47 – 0.69)
Betablocker (Diabetes)	0.41 (0.27 – 0.61)
Betablocker (No diabetes)	0.51 (0.42 – 0.62)

X-axis: Hazard Ratio — 0.400, 0.600, 0.800, 1.000, 1.200. Mortality lower (left) — Mortality higher (right).

Legend: Diabetes ———, No diabetes ········

Aspirin is not without side effects!

Aspirin and GI bleed

Aspirin causing a GI Bleed
Up to   **2.4%**

Aspirin causing a fatal GI Bleed
Up to   **0.1%**
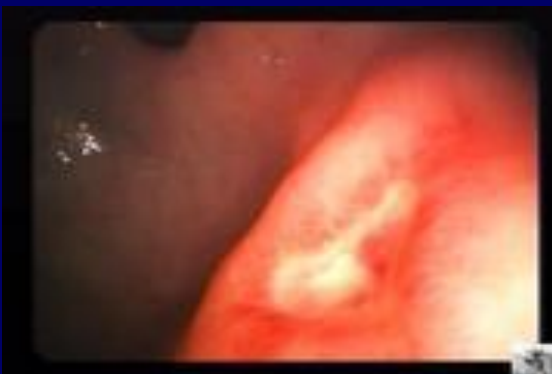
NNH=248 (conservative estimate)

Conclusions so far…

For the realist

- Aspirin does not protect against CV events in diabetes (primary prevention).
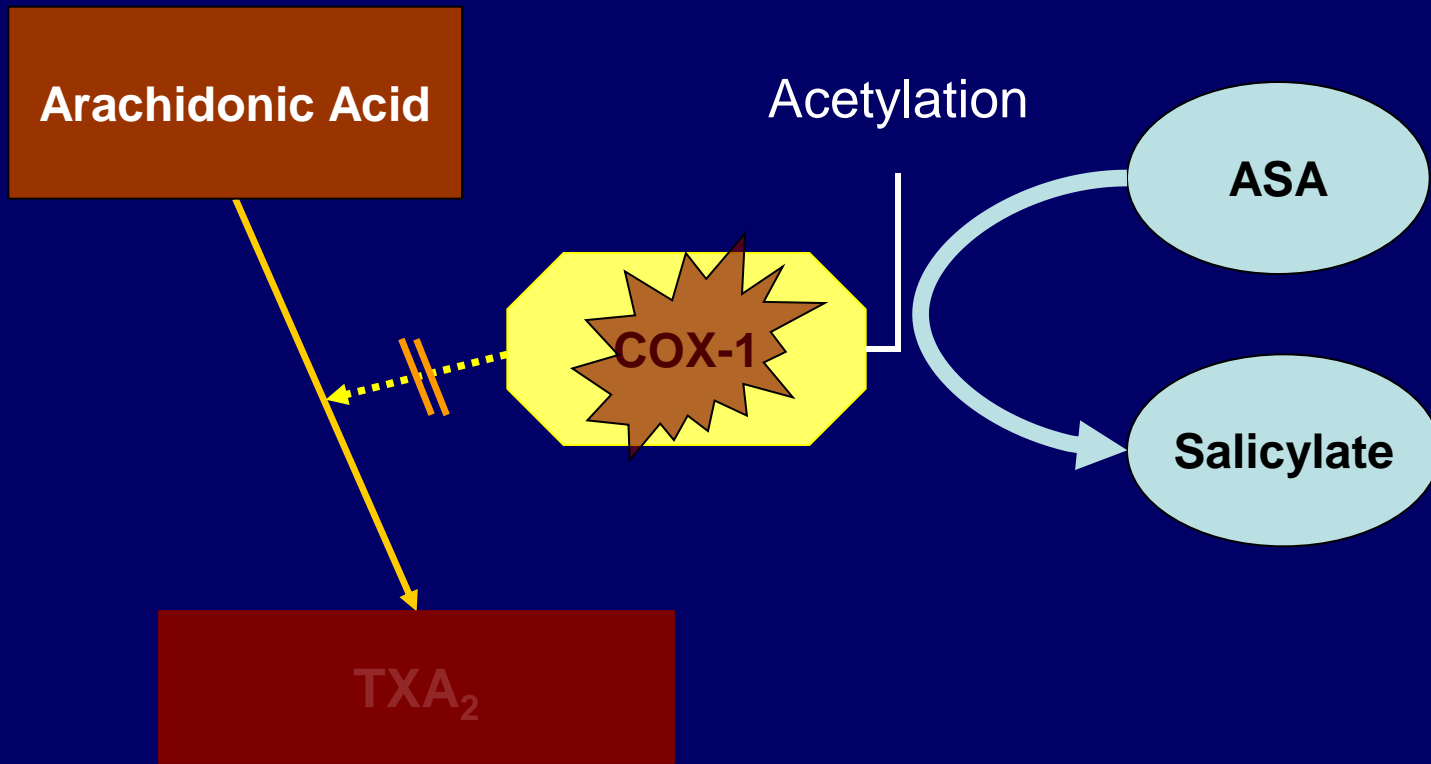
For the optimist

- The efficacy of aspirin is significantly reduced in diabetes.

Safety

Efficacy
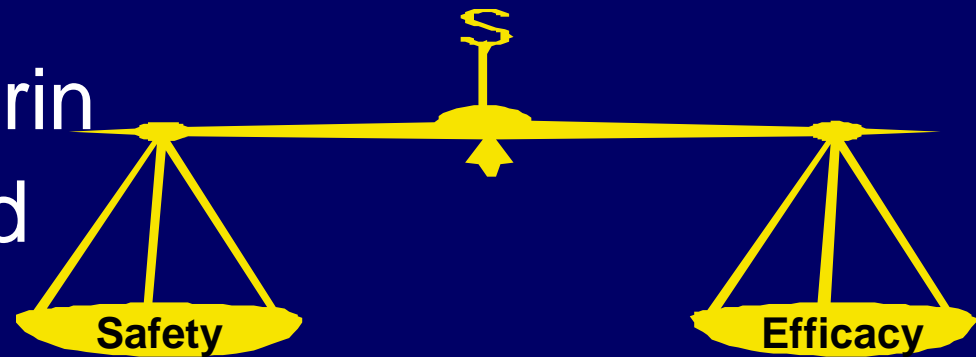
What are the mechanisms for aspirin treatment failure in diabetes?

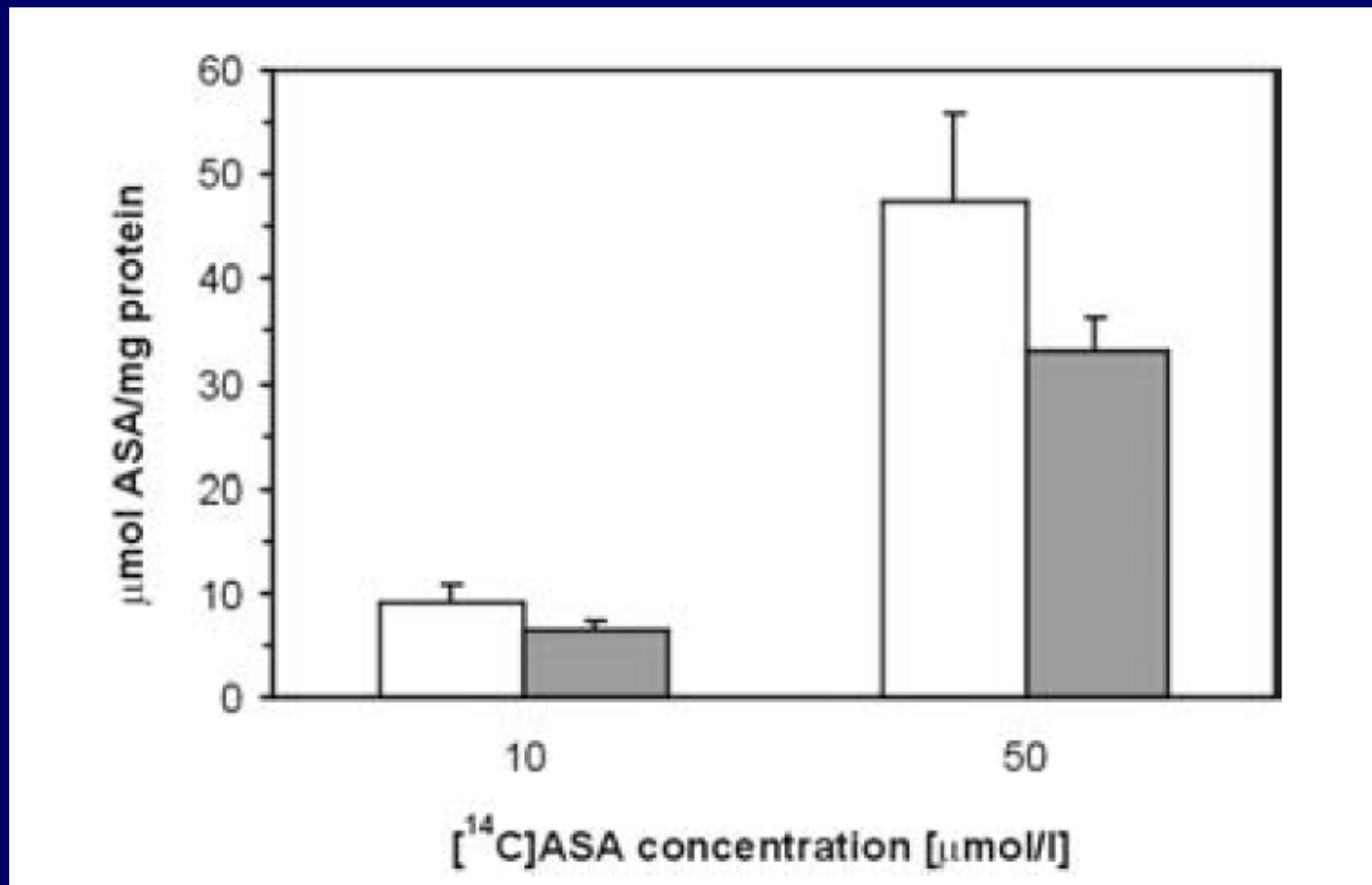# Aspirin
(mechanism of action)

Mechanisms of aspirin resistance

- External factors
  - Compliance!
  - Smoking (platelets get activated)
  - Drug-drug interaction (NSAIDs)

- Internal factors
  - Variable COX-1 structure inhibiting acetylation
  - TXA production by non-platelet cells
  - Increased platelet turnover
  - Low grade platelet activation

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  - Variable COX-1 structure inhibiting acetylation
  - TXA production by non-platelet cells
  - Increased platelet turnover
  - Low grade platelet activation
  - Glycaemia?

Potential mechanisms for the reduced efficacy of aspirin in diabetes

Time to clot lysis
(n=18 T1DM, in the absence and presence of aspirin)

Ajjan and Grant, unpublished
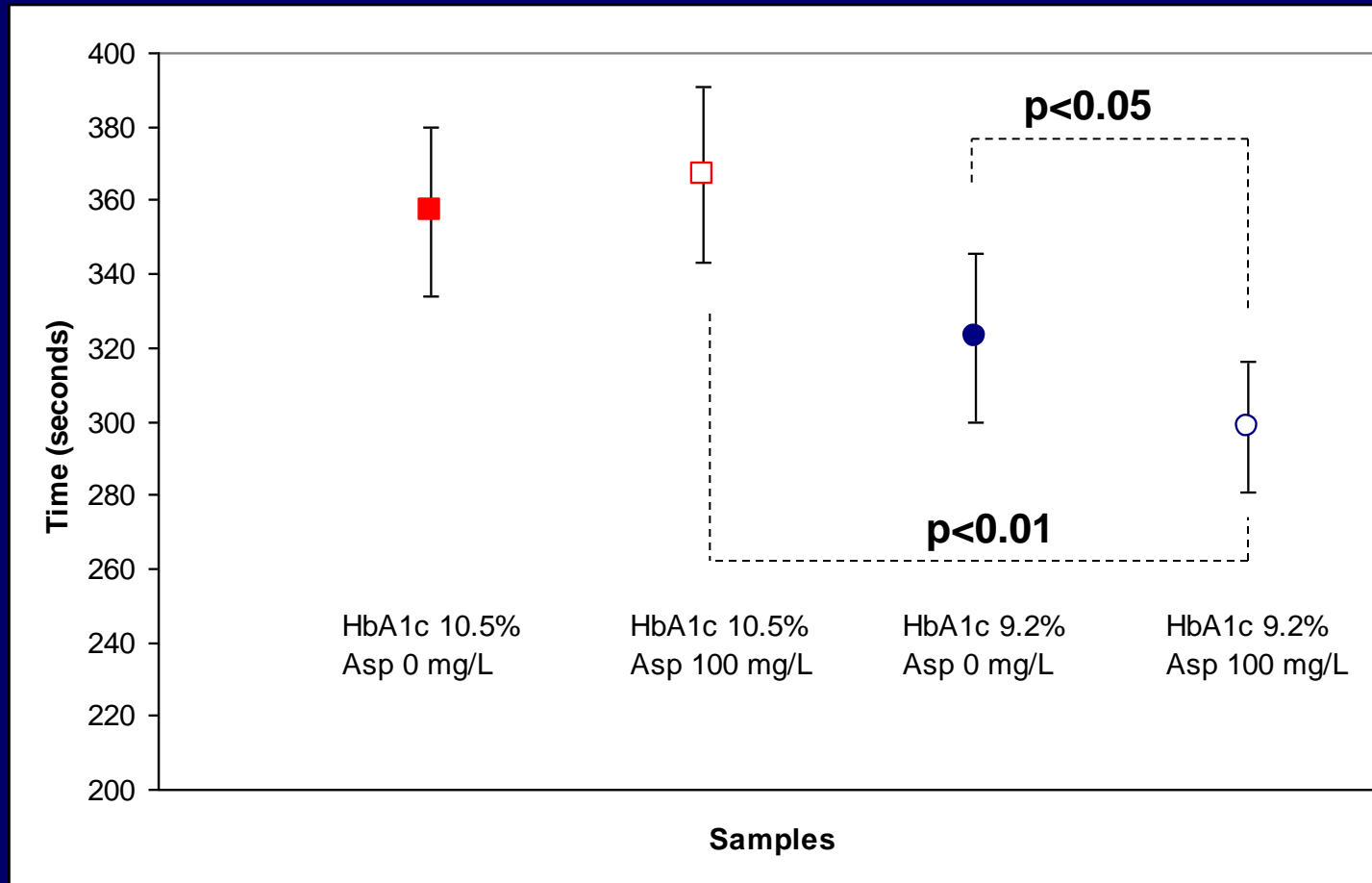
The problem

- In diabetes, we treat a cluster of risk factors and can assess response to treatment:
  - HbA1c
  - Lipids
  - Blood pressure
  - Microalbuminuria

- However:
  - We are currently unable to assess response to antiplatelet treatment

General conclusions

- Current evidence indicate that aspirin is ineffective in primary CVD protection in individuals with diabetes

- We should avoid "carpet treatment" with aspirin in individuals with diabetes

- Further work is required to clarify the mechanisms for aspirin treatment failure in diabetes

- Alternative anti-platelet agents should be considered in selected patients

Thank you…