Norfolk and Norwich University Hospitals NHS
NHS Foundation Trust

Update on Diabetes

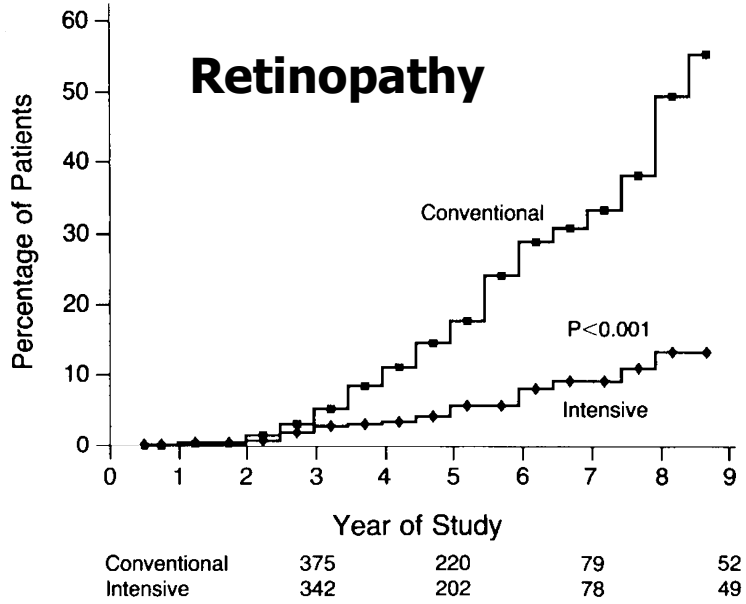
Why it's Not Just About Glucose Lowering Any More

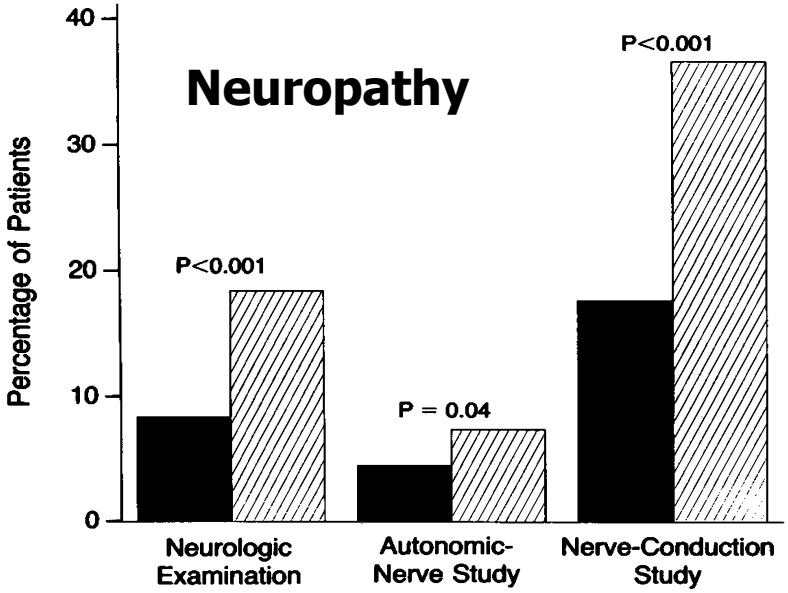
Ketan Dhatariya

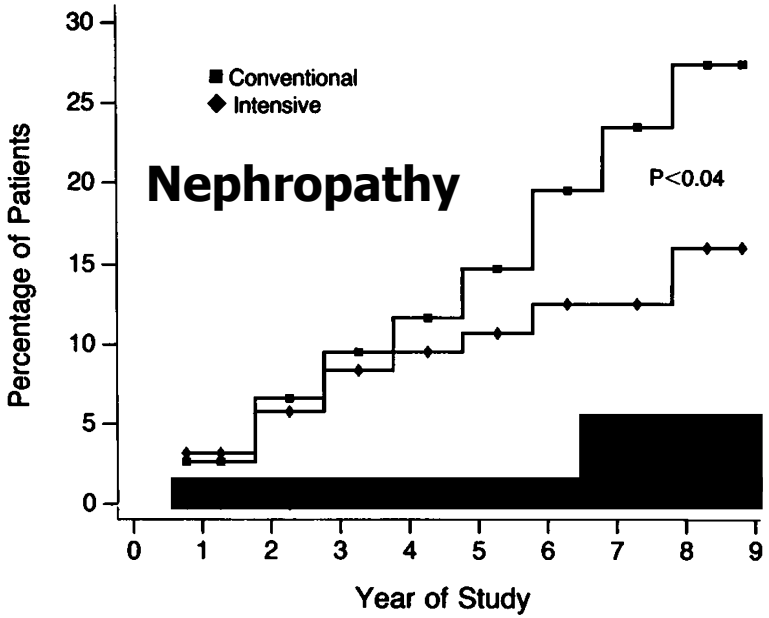
Consultant in Diabetes NNUH

The Story So Far…..

DCCT



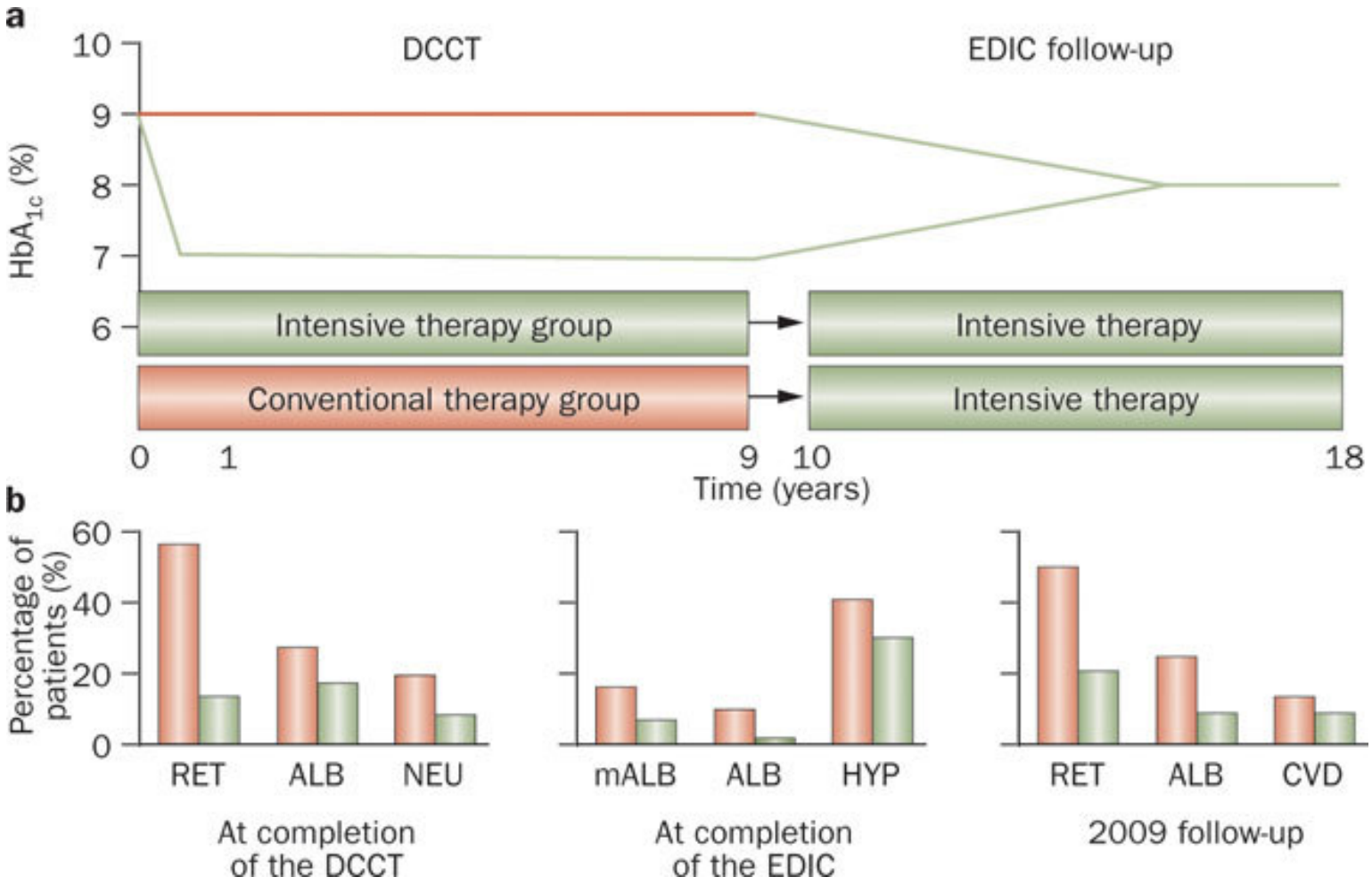




Intensive glucose control in people with newly diagnosed people type 1 diabetes significantly lowered the risk of long term microvascular events

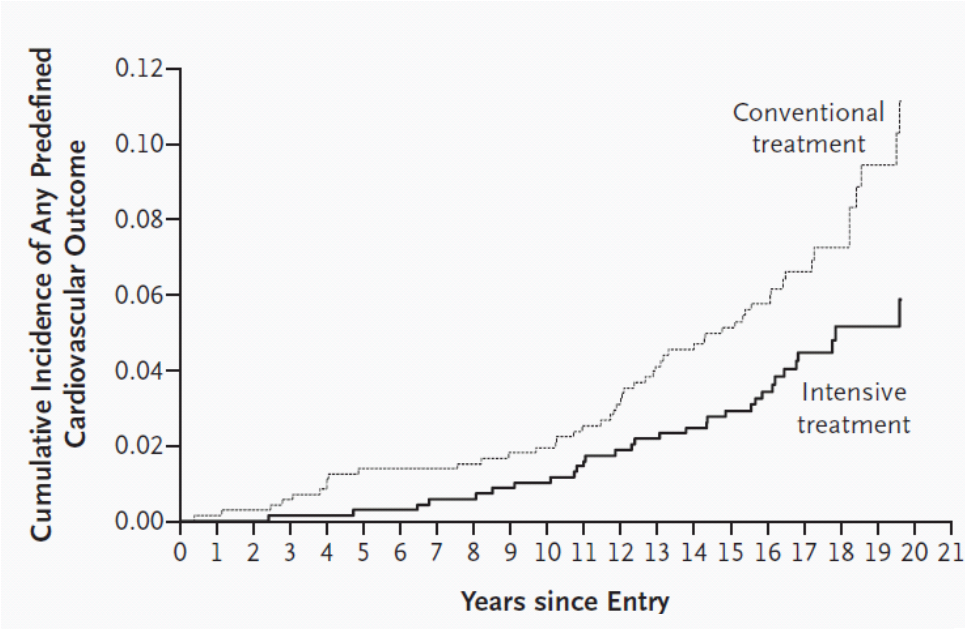
DCCT Study Group NEJM 1993;329(14):977-986

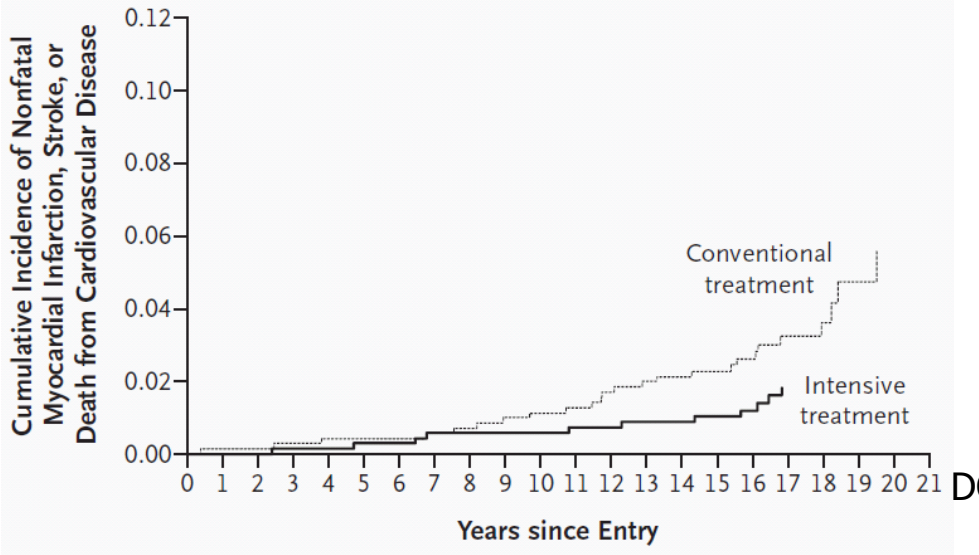
After the DCCT Finished



Pirola L et al. Nat Rev Endocrinol 2010:6(12):665-675

DCCT / EDIC





Long term follow up of the original 1441 patients showed significant benefit in cardiovascular outcomes as well

DCCT/EDIC Study Group NEJM 2005;353(25):2643-2653

UKPDS

- A 10 year sustained reduction in HbA1c of 0.9% (8 mmol/mol) led to significant improvements
  - 12% for any diabetes related endpoint p=0.029
  - 25% for microvascular endpoints p=0.0099
  - 16% for myocardial infarction p=0.052
  - 24% for cataract extraction p=0.046
  - 21% for retinopathy at twelve years p=0.015
  - 33% for albuminuria at twelve years p=0.000054

UKPDS 33 Lancet 1998;352(9131):837-853

How it is - UKPDS Follow-Up

The NEW ENGLAND JOURNAL of MEDICINE

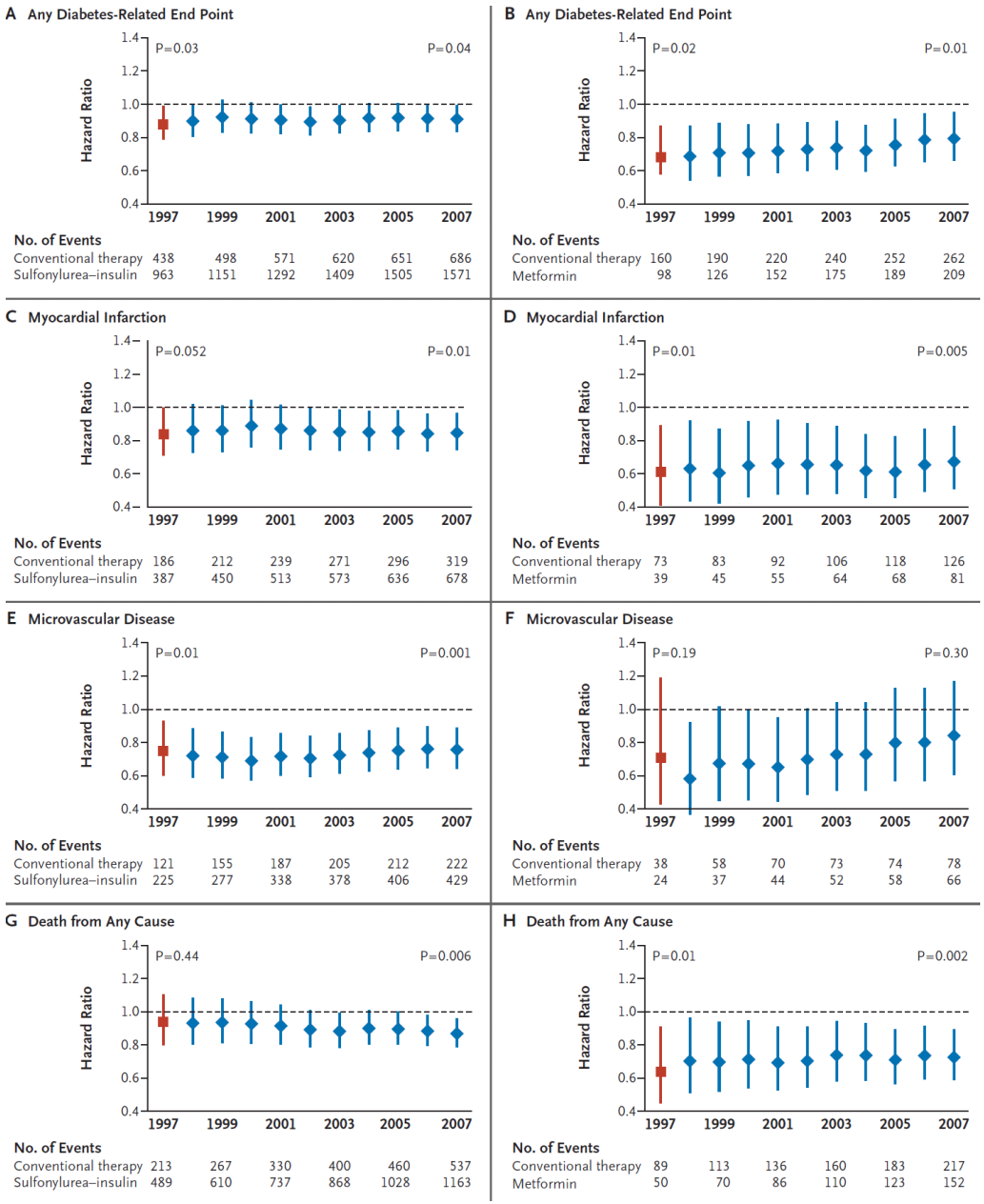
ORIGINAL ARTICLE

10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes

Rury R. Holman, F.R.C.P., Sanjoy K. Paul, Ph.D., M. Angelyn Bethel, M.D.,
David R. Matthews, F.R.C.P., and H. Andrew W. Neil, F.R.C.P.

N ENGL J MED 359;15 WWW.NEJM.ORG OCTOBER 9, 2008

UKPDS 10 Year Follow-Up Data



Holman RR et al NEJM 2008;359(15):1577-1589

DCCT and UKPDS

- Together, these 2 studies have dictated what diabetologists have done for their patients over the last 15 years or so

- However, the premise that ‘lower is better’ has recently been challenged

3 Recent (VERY large) Trials

- ACCORD: Action to Control Cardiovascular Risk in Diabetes

ACCORD Study Group NEJM 2008;358:2545-59

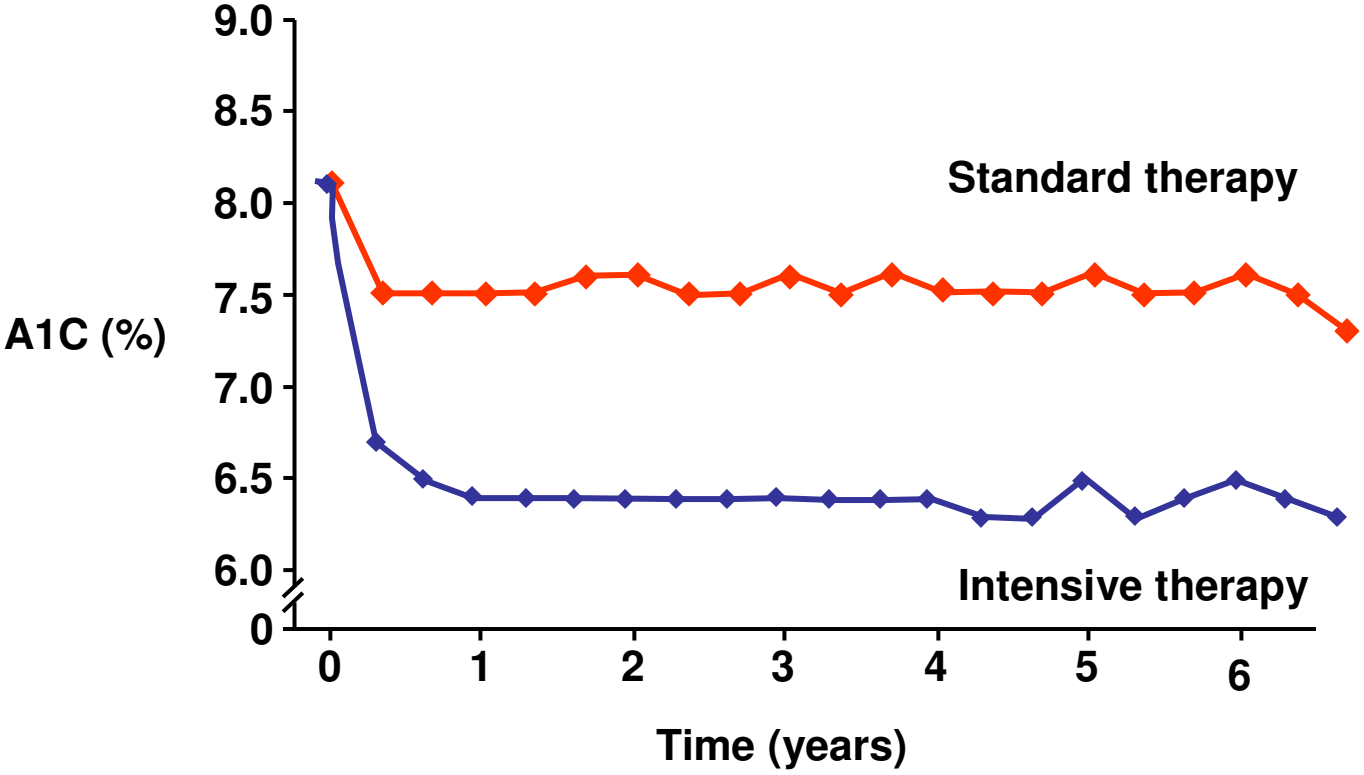
- ADVANCE: Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation

ADVANCE Collaborative Group NEJM 2008;358:2560-72

- VADT – Veterans Affairs Diabetes Trial

Duckworth et al NEJM 2009;360(2):129-39

ACCORD

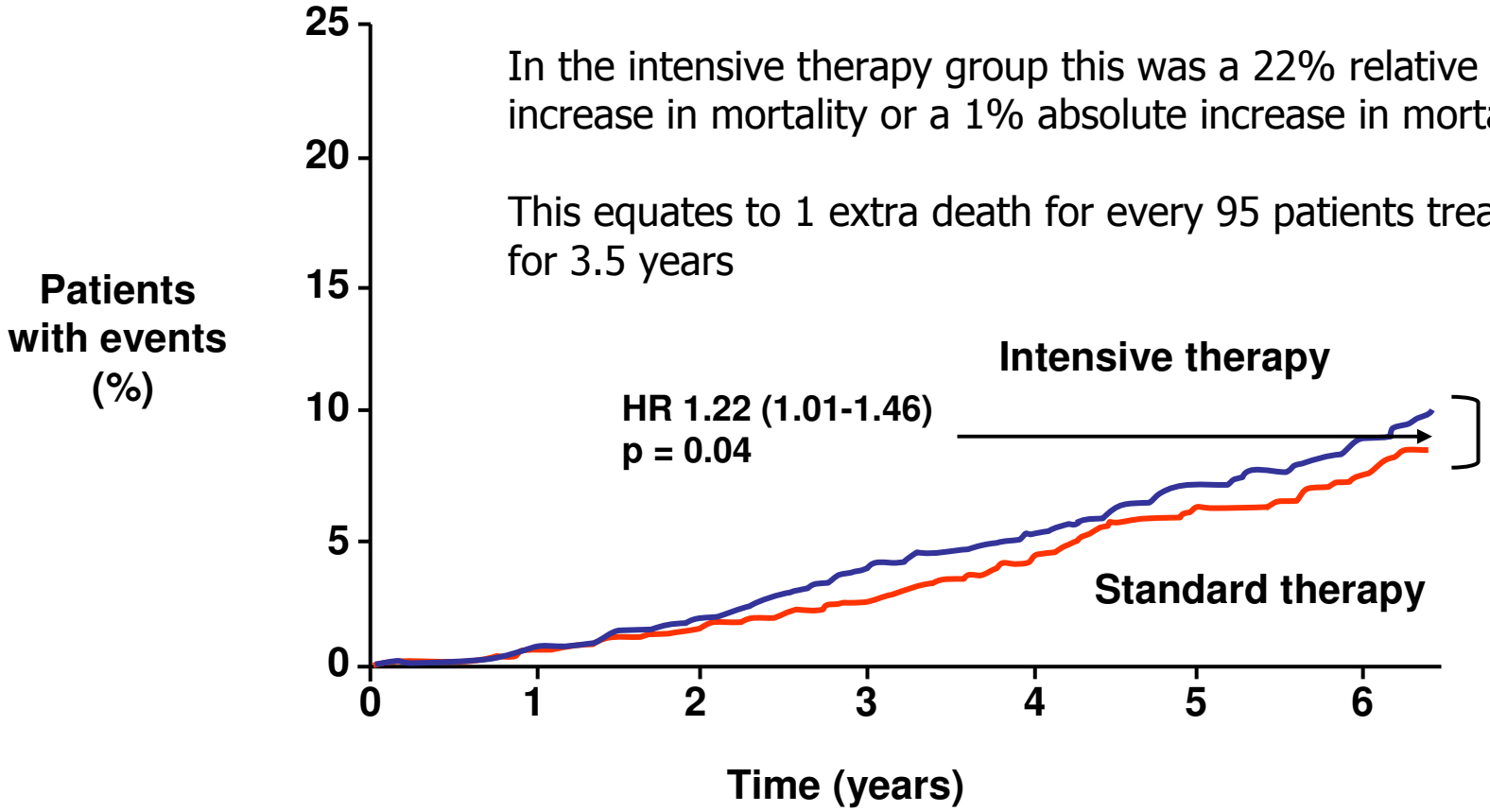


ACCORD Study Group NEJM 2008;358:2545-59

ACCORD: Treatment effect on all-cause mortality

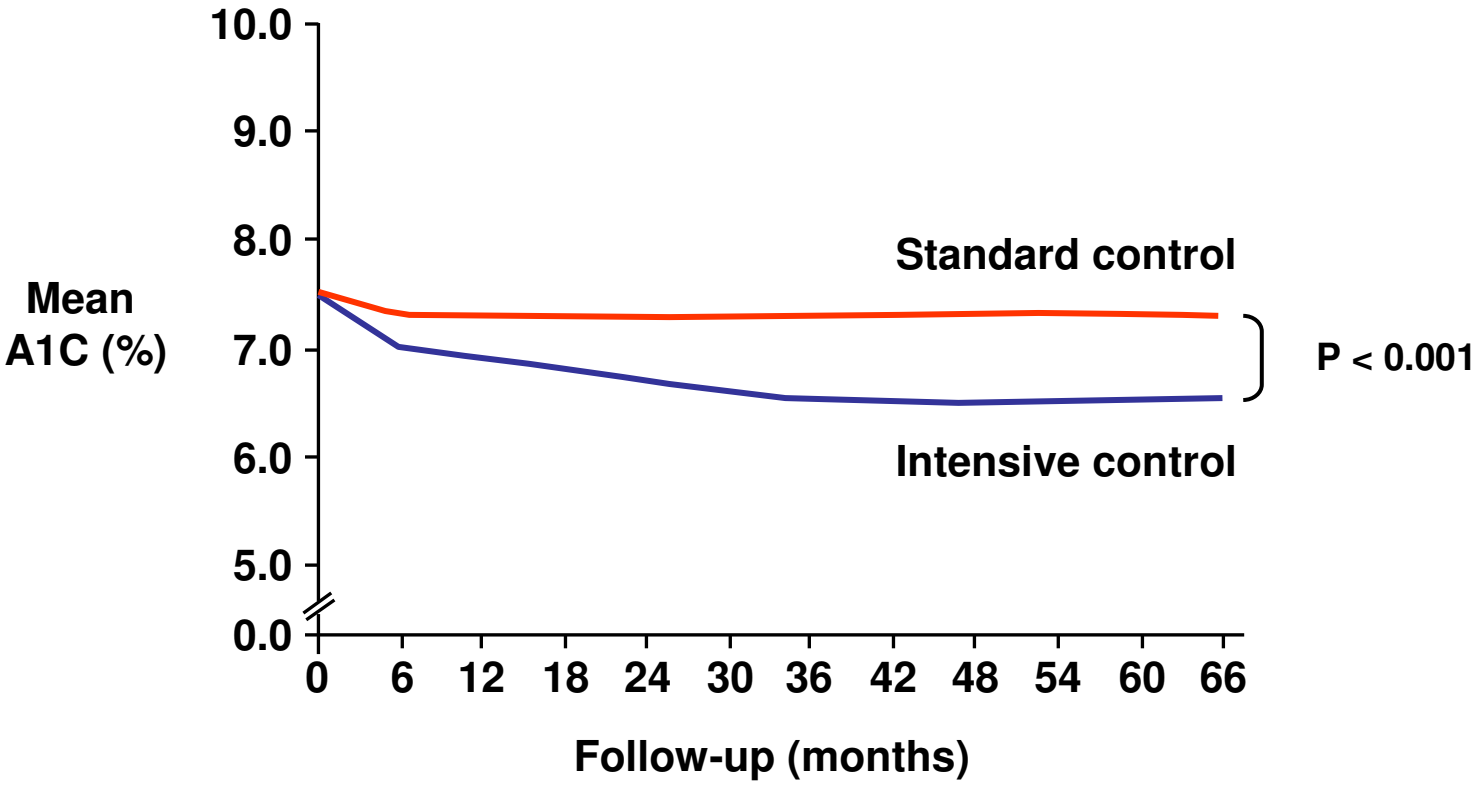
In the intensive therapy group this was a 22% relative increase in mortality or a 1% absolute increase in mortality

This equates to 1 extra death for every 95 patients treated for 3.5 years



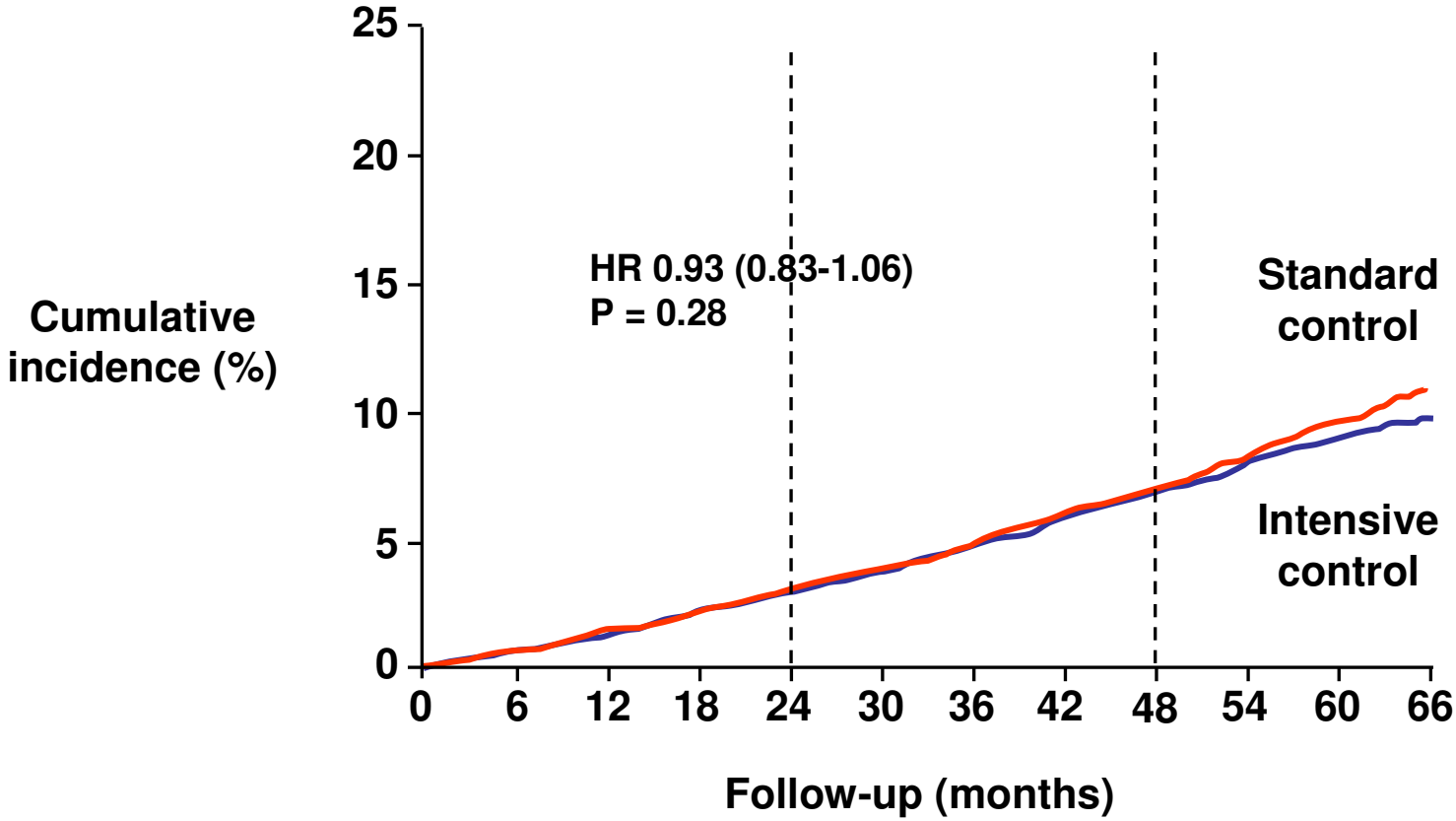
ACCORD Study Group NEJM 2008;358:2545-59

ADVANCE



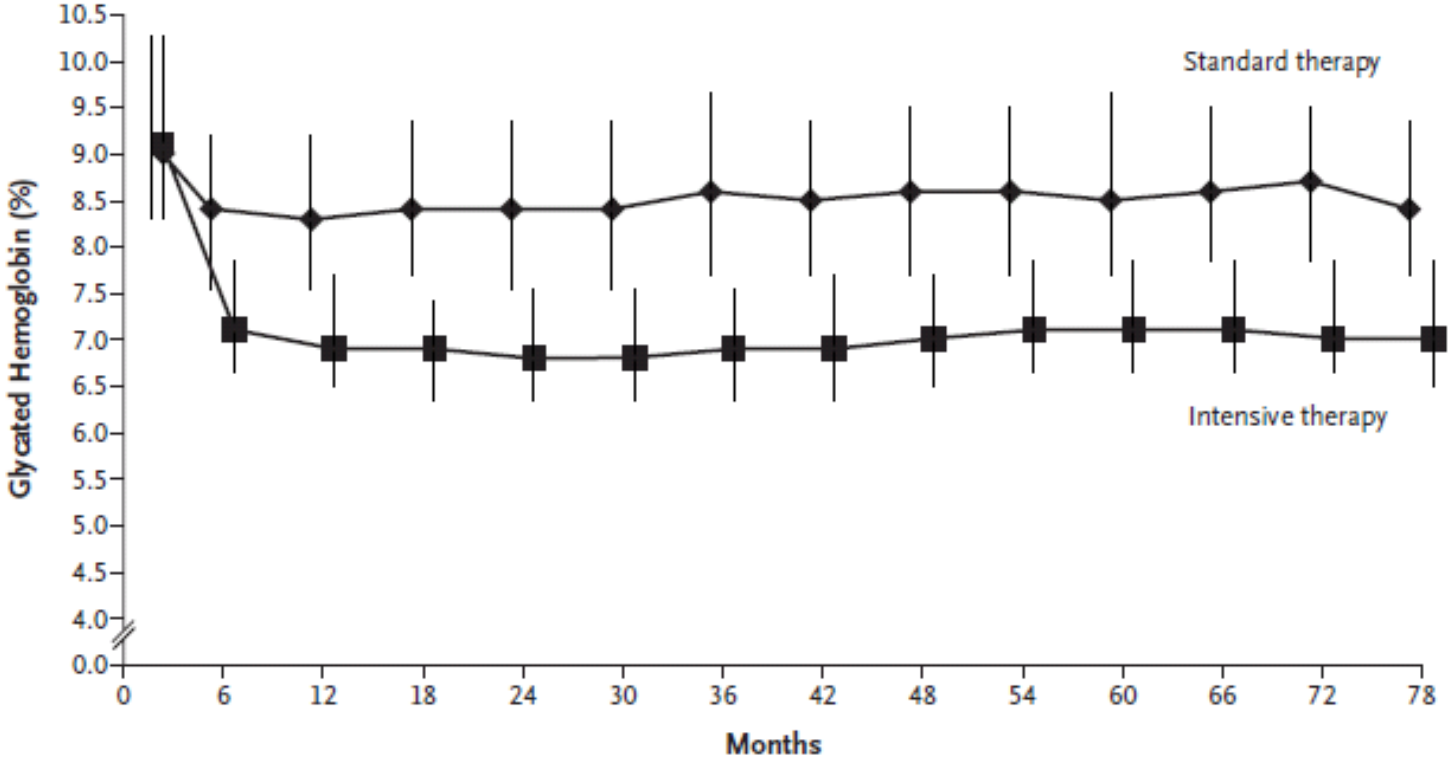
ADVANCE Collaborative Group NEJM 2008;358:2560-72

ADVANCE: Treatment effect on all-cause mortality



ADVANCE Collaborative Group NEJM 2008;358:2560-72

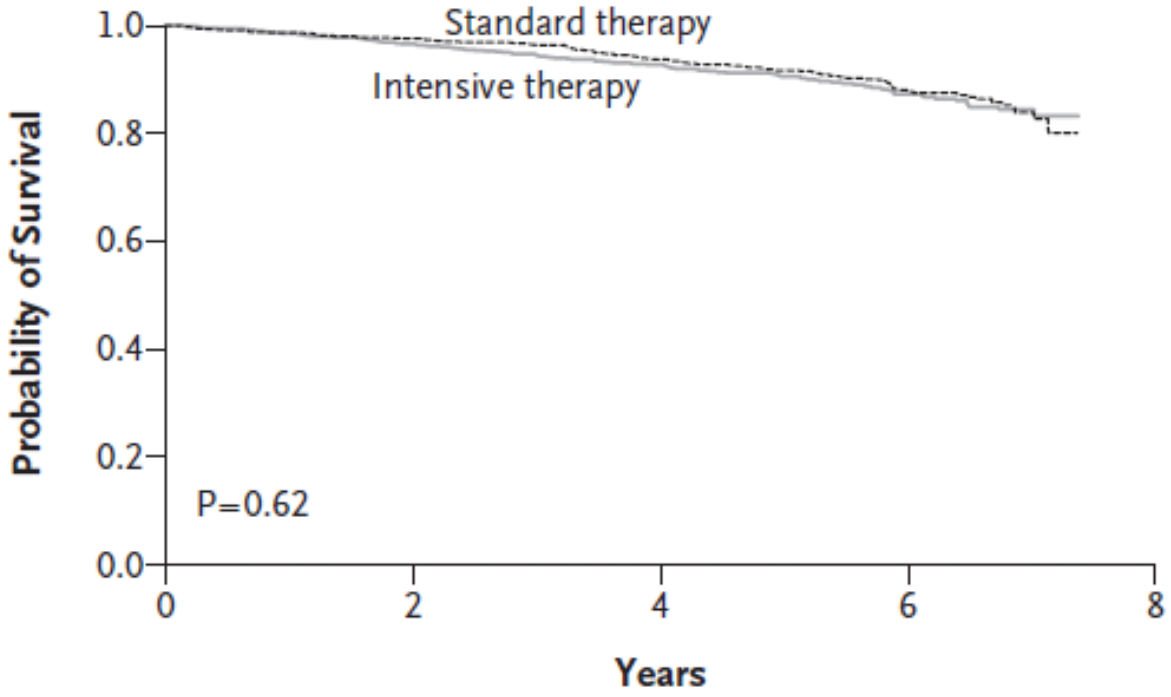
VADT



No. at Risk													
Standard therapy	899	811	812	759	760	727	727	707	688	667	644	472	329	225
Intensive therapy	892	801	805	763	754	729	706	692	668	661	639	489	340	223

Duckworth et al NEJM 2009;360(2):129-39

VADT Treatment effect on all-cause mortality



No. at Risk

Standard therapy	899	836	801	772	727	637	322	76	0
Intensive therapy	892	832	791	752	720	650	341	86	0

Duckworth et al NEJM 2009;360(2):129-39

So Now Diabetes Doctors Are Confused

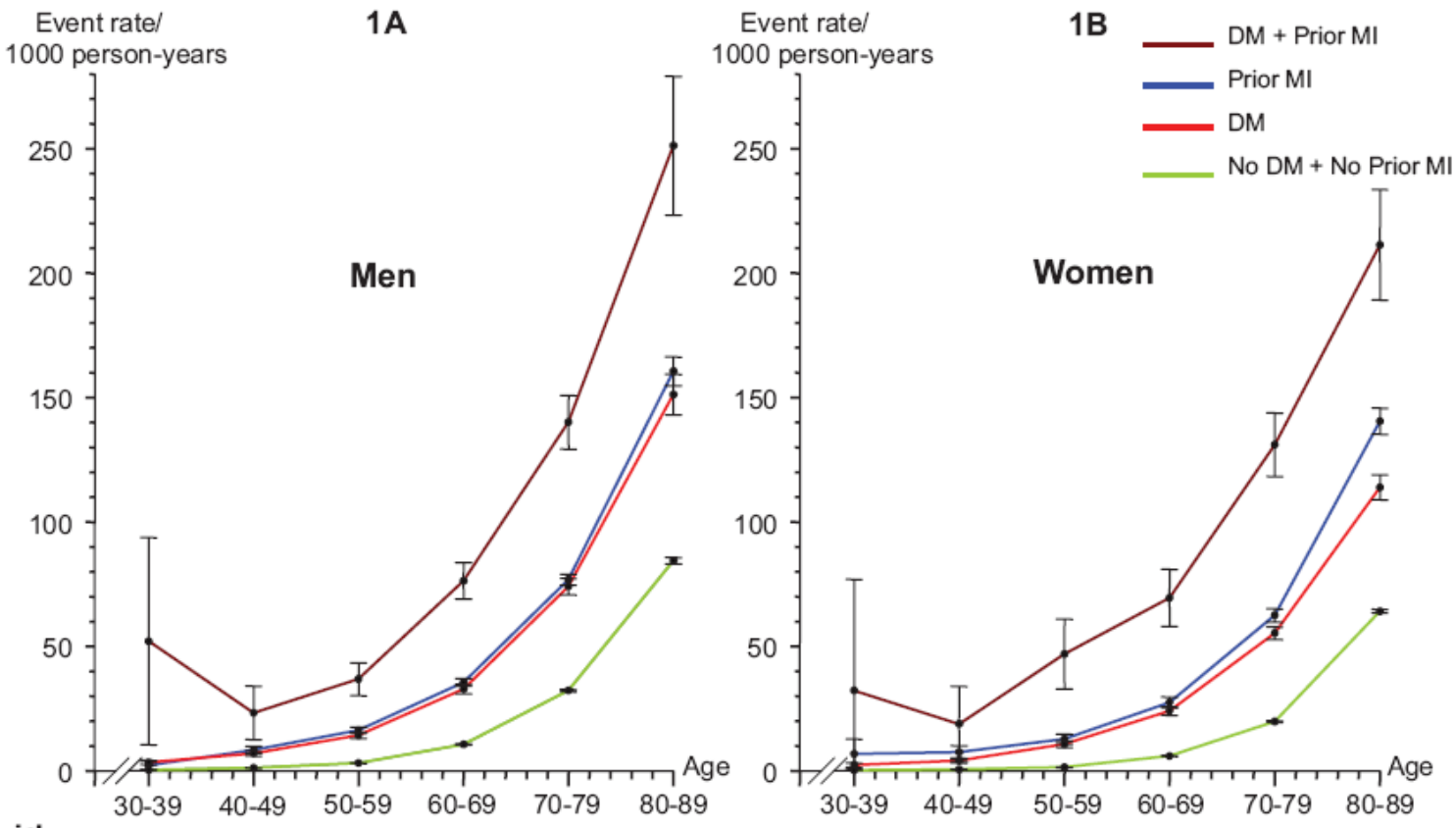
- Previous studies have shown that good glycaemic control has improved long term outcomes

- Newer, larger, studies have not shown this, and at least 1 study has shown that aggressive blood glucose lowering is associated with an increased mortality

The Probable Interpretation of This?

- Early tight glycaemic control is good
- Later introduction of tight glycaemia is bad

Data From 3.3M Danes

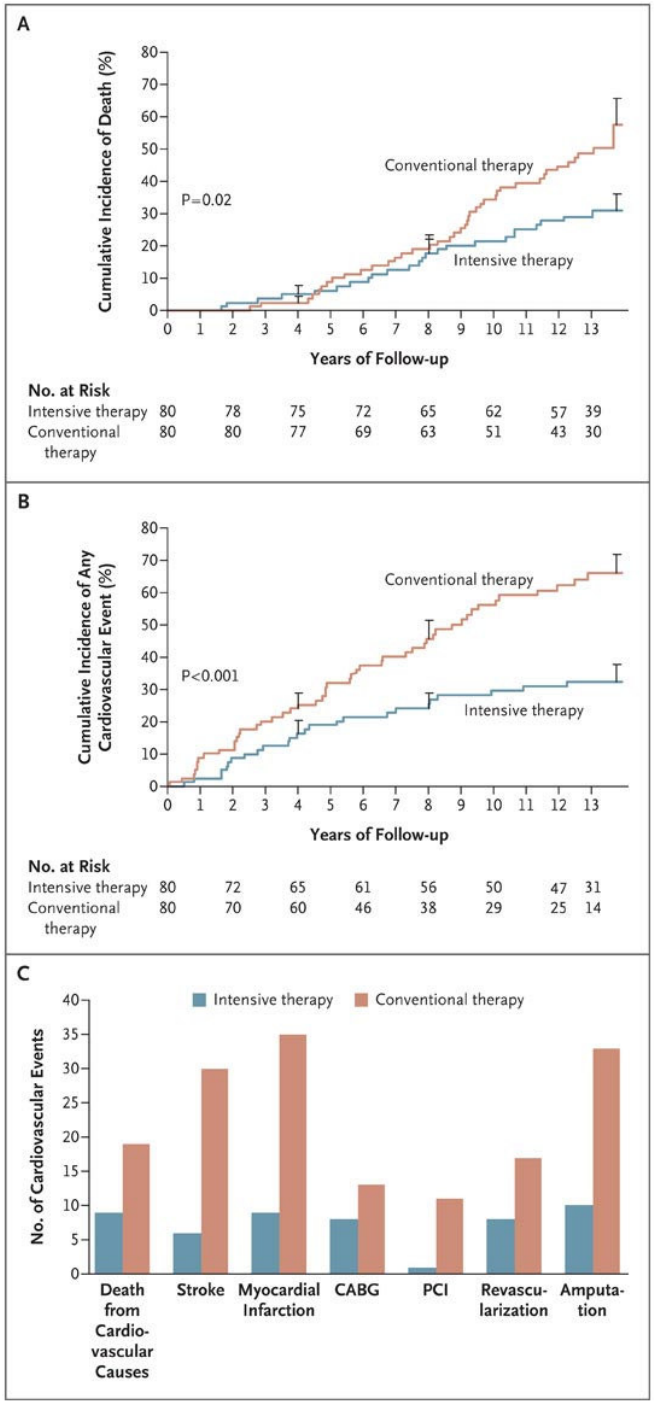


Numbers at risk:

No DM + No Prior MI	407 796	374 738	323 089	197 672	134 052	57 626	389 797	368 588	328 918	229 144	193 244	124 858
Prior MI	561	3 299	9 733	14 580	14 769	6 416	149	801	2 585	5 404	7 954	6 905
DM	2 989	4 895	7 985	8 032	6 738	3 102	2 271	3 355	5 101	6 901	8 328	5 685
DM + Prior MI	28	168	735	1 363	1 348	508	13	67	207	502	874	606

Schramm TK et al Circulation 2008;117:1945-1954

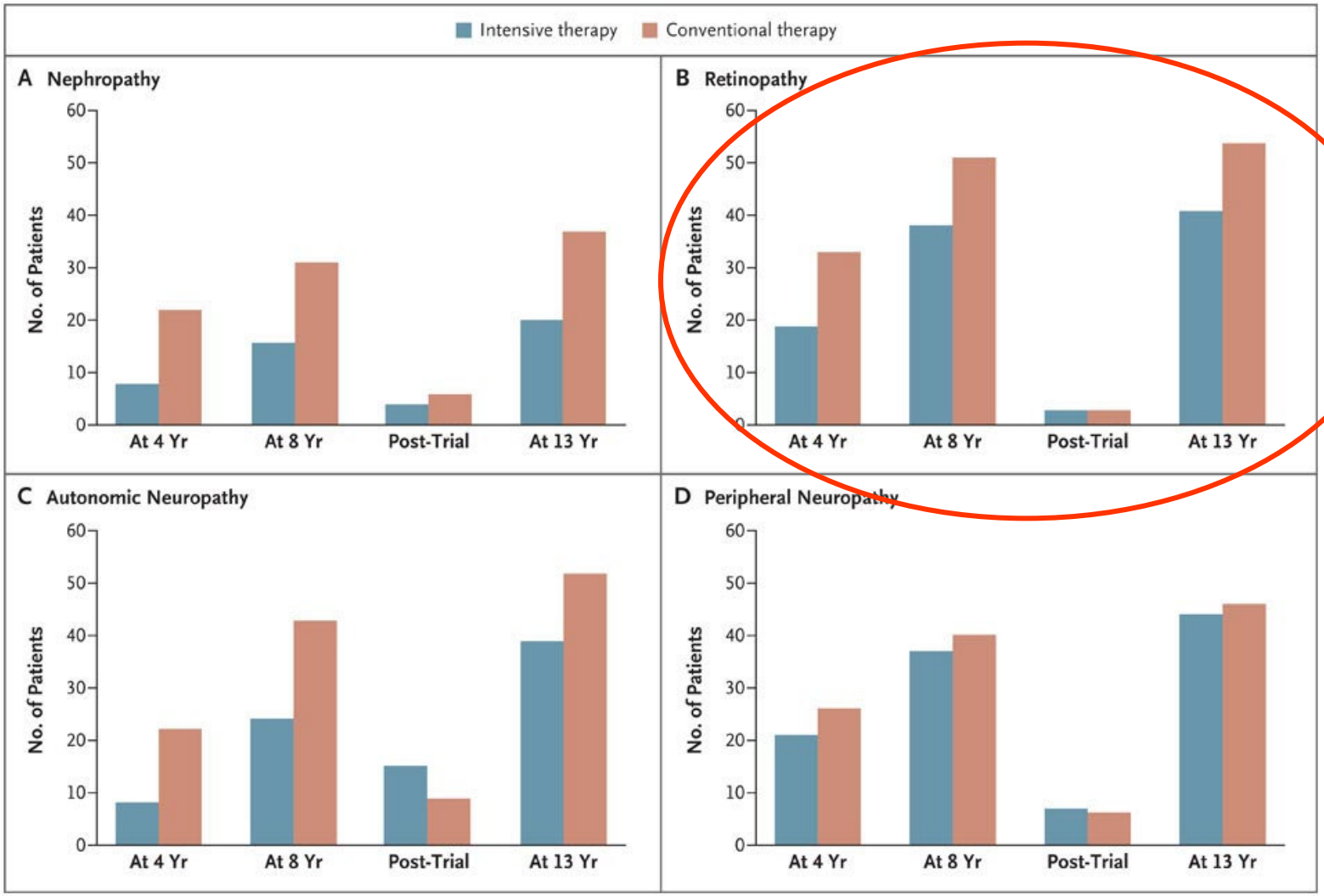
Steno-2



Use of tight glycaemic control, renin-angiotensin system blockers, aspirin and lipid lowering agents

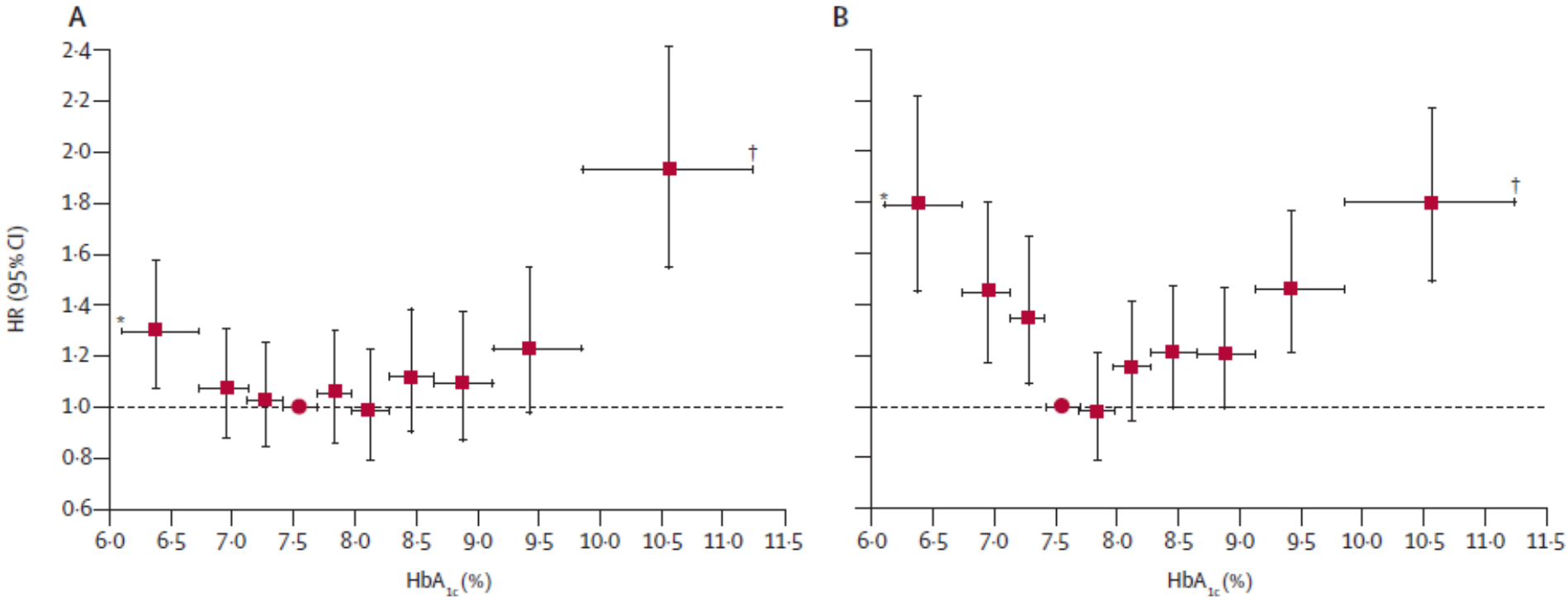
Gaede P et al NEJM 2008;358:580-591

Steno-2



Gaede P et al NEJM 2008;358:580-591

So Where Does That Leave Us?



All cause mortality according to HbA1c

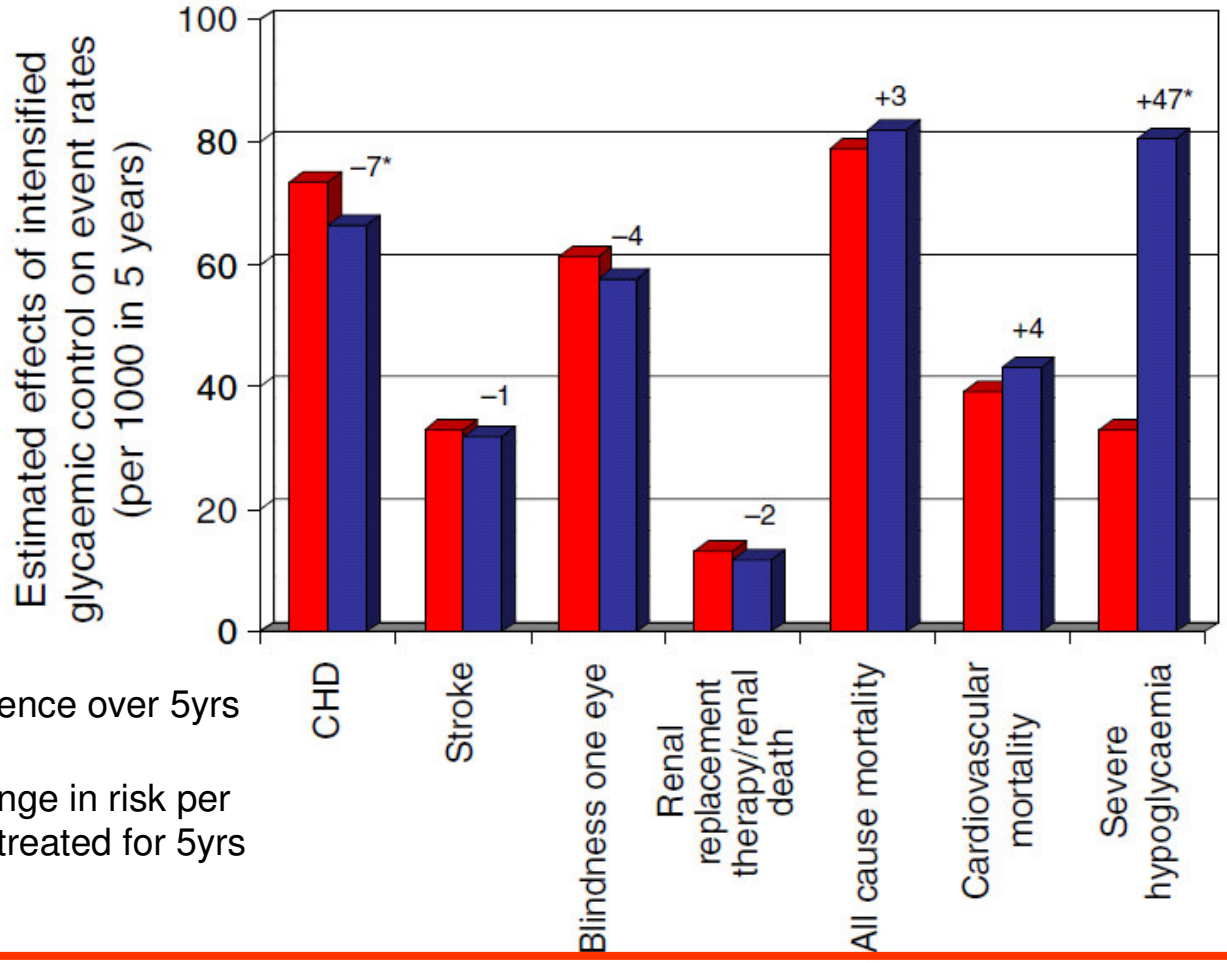
MTF + Su's **Insulin based regimens**

Currie et al Lancet 2010; 275(9713):481-489

How Many People Need to be Treated?

- For insulin in type 1 diabetes – NNT = 1
- For antibiotics in sepsis – NNT = 1
- For statins NNT = 20 people for 10 years to prevent 1 death
  - Treating 200 people for 1 year would save 1 life, the other 199 would have the same outcome

What about NNT with Glycaemic Control?



Number NTT for 5 years (95% CI) for benefit/harm	140.3 (77.7–1,407.1)	767.7 (180.5–∞ –307.7)	271.6 (81.5–∞ –162.9)	627.0 (250.8–∞ –684.0)	328.9 (66.2–∞ –130.9)	259.0 (62.0–∞ –161.1)	21.1 (14.3–34.1)

Yudkin et al Diabetologia 2010;53(10):2079-2085

Yes, But What about Eyes and Diabetes?

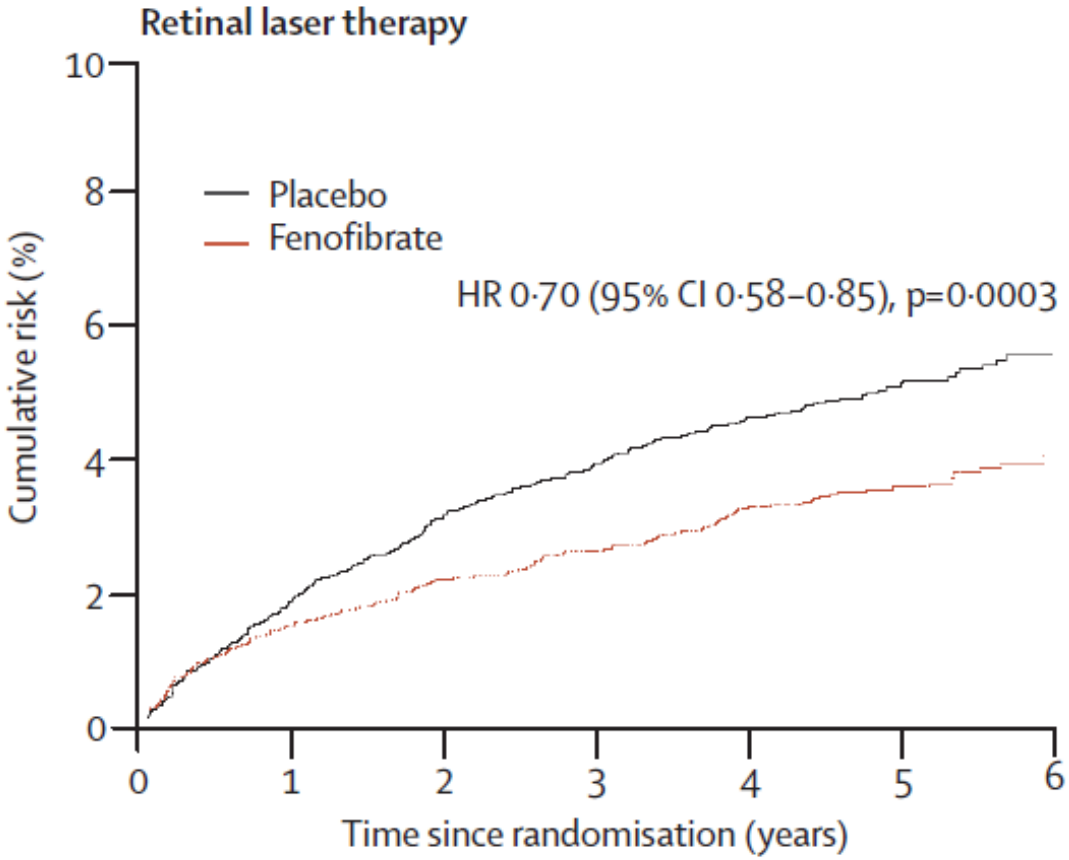
Table 3. Effects of Enalapril and Losartan on Retinopathy, as Measured by the Odds Ratio of Progression, during the Five-Year Follow-up Period.

Progression	No. of Events *no./total no. (%)*	Adjusted Odds Ratio (95% CI)*	P Value
By two steps or more			
Placebo	28/74 (38)	Reference	Reference
Enalapril	19/77 (25)	0.35 (0.14–0.85)	0.02
Losartan	15/72 (21)	0.30 (0.12–0.73)	0.008
By three steps or more			
Placebo	21/74 (28)	Reference	Reference
Enalapril	15/77 (19)	0.41 (0.16–1.05)	0.06
Losartan	9/72 (12)	0.21 (0.07–0.62)	0.005

* The odds ratio was adjusted for baseline characteristics, center, and baseline grade on the 15-point diabetic retinopathy severity scale.

Mauer et al NEJM 2009;361:40-51

What About Fibrates?



Numbers at risk

Placebo	4900	4775	4664	4573	4472	2518	835
Fenofibrate	4895	4792	4701	4618	4502	2529	841

FIELD Lancet 2005;366(9500):1869-1861

ACCORD Eye Results

Table 2. Effects of Intensive Glycemic Control, Fenofibrate, and Intensive Blood-Pressure Control on Progression of Diabetic Retinopathy and Moderate Vision Loss.*

Treatment	Progression of Diabetic Retinopathy	Adjusted Odds Ratio (95% CI)	P Value	Moderate Vision Loss	Adjusted Hazard Ratio (95% CI)	P Value
	no./total no. (%)			*no./total no. (%)*		
Glycemia therapy		0.67 (0.51–0.87)	0.003		0.95 (0.80–1.13)	0.56
Intensive	104/1429 (7.3)			266/1629 (16.3)		
Standard	149/1427 (10.4)			273/1634 (16.7)		
Dyslipidemia therapy†		0.60 (0.42–0.87)	0.006		1.04 (0.83–1.32)	0.73
With fenofibrate	52/806 (6.5)			145/908 (16.0)		
With placebo	80/787 (10.2)			136/893 (15.2)		
Antihypertensive therapy		1.23 (0.84–1.79)	0.29		1.27 (0.99–1.62)	0.06
Intensive	67/647 (10.4)			145/749 (19.4)		
Standard	54/616 (8.8)			113/713 (15.8)		

NB: low event rate

Conclusions

- Glycaemic control remains paramount
- A target HbA1c of ~7.5% (58 mmol/mol) seems reasonable
- Tighter control has yet to be shown to be beneficial after 10 years of diabetes
- Fibrates may have a role
- Optimise all other risk factors

Thank you for your attention