Mentor, disciplinarian, friend for fellows

Clinical Implications of Diabetes mellitus Intensive Control
(A1c less than 8% is fine for most adults)
(The A1C Dilemma)

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Semi Annual Meeting
Dr. Manuel Paniagua Post Graduate Diabetes Course

Disclosure

I will be talking about disease and will make reference to generic name medications, so I have nothing to disclose.

Objectives

- ❑ Discuss the clinical importance of keeping Diabetes mellitus A1C less than 8% in most adults
- ❑ Discuss the risk of Diabetes mellitus complication incidence per 1% increase of A1C over 7%

Clinical Implications of Glycemic Control

There are several crucial implications for practitioners.

- Even mild sustained elevations in HbA_{1c}, as a reflection of overall blood glucose control, are associated with increased risks of complications and in particular the risk of MI.
- Every effort should be made to lower HbA_{1c}, because any reduction in HbA_{1c} will translate into a reduction in the risk of complications.
- The individuals who are most likely to benefit from risk reduction are those with the highest initial blood glucose values.
- Physicians caring for patients with type 2 diabetes should aim for the best possible glycemic control. Unless contraindications exist, a near-normal or normal level of glycemia, as manifested in a normal HbA_{1c}, should be the goal of diabetic therapy.

Factors that should be taken in consideration when setting Type 2 Diabetes mellitus glycemic goals

- Age
- Duration of the condition
- Co-morbid conditions
  - Macrovascular complications
  - Arterial Hypertension
  - Microvascular complications
  - Advance Ca
  - Patient in Hospice or Rehabilitation facilities
- Life expectancy
- Therapy complication

What is Known*

- Tight glycemic control is considered an essential strategy to prevent chronic complications in patients with type 2 diabetes mellitus.
- Practice guidelines recommendations, quality improvement program, and clinical care all promote tight glycemic control.
- Uncontrolled type 2 diabetes is associated with all sorts of very bad things.
- So of course, it made good sense that the lower the blood sugar, the lower the chances of bad things happening to our patients.

Glycemic Control for Patients With Type 2 Diabetes mellitus: Our Evolving Faith in the Face of Evidence (Rene Rodriguez-Gutierrez)

A1C General Recommendations

Nevertheless: Clinicians should personalize goals for glycemic control in patients with type 2 diabetes on the basis of a discussion of benefits and harms of pharmacotherapy, patients' preferences, patients' general health and life expectancy, treatment burden, and costs of care.

Rethinking A1C Goals for Diabetes mellitus Patient

“Treat the patient, not the number.” This is a very old and sound medical school teaching. However, when it comes to blood sugar control in diabetes, we have tended to treat the number, thinking that a lower number would equal better health.

Monique Tello, MD, MPH

What the Studies Adds

- The evidence accrued in the past 2 decades consistently demonstrates that there is no significant benefit of tight glycemic control on patient-important micro- and macrovascular outcomes, with the exception of a 15% relative-risk reduction in nonfatal myocardial infarction.
- So, the widespread consensus about the value of tight glycemic control to prevent complications in patients with type 2 diabetes mellitus needs to be recalibrated.

Hemoglobin A_{1c} Targets for Glycemic Control With Pharmacologic Therapy for Nonpregnant Adults With Type 2 Diabetes Mellitus

A Guidance Statement Update From the American College of Physicians

2018

Glycemic Target for Nonpregnant Adults

AACE

- A1C
  - Individualize on the base of age, comorbities, and duration of disease
    - ≤ 6.5% for most
    - Closer to normal for healthy
    - Less stringent for “less healthy”
- FPG: < 110 mg/dL
- 2 – hours postprandial: < 140 mg/dL

ADA

- A1C
  - < 6.5% for patients who meet the following criteria
    - Short duration of diabetes
    - Long life expectancy
    - No concurrent illness
    - Goal can be achieved w/o significant adverse effects of treatment
  - < 7.0% reasonable goal for many patients
  - < 8.0% for the following
    - History of severe hypoglycemia
    - Limited life expectancy
    - Advanced micro and macrovascular complications
    - Extensive comorbid conditions
- FPG: 80 – 130 mg/dL
- 2 – hours postprandial : < 180 mg/dL

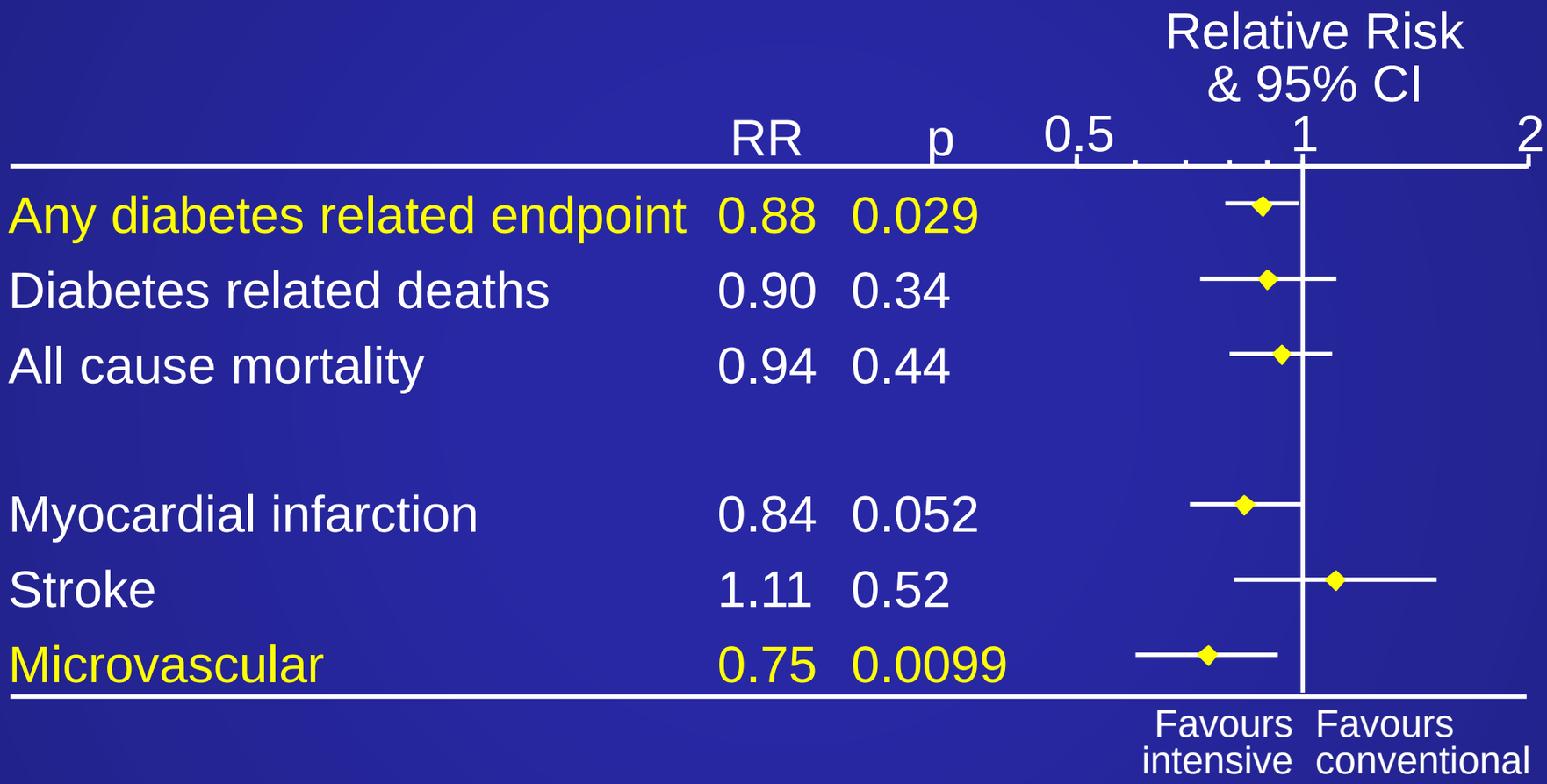
Does we have clinical evidence to support the recommendation that A1c below 8% is fine for most Type 2 non-pregnant diabetes mellitus adults?

- **Clinical Trials**
  - UKPDS 33 and 35
  - ACCORD
  - ADVANCE
  - VADT
- **Meta-Analysis Review**
  - Glycemic Control for Patients With Type 2 Diabetes mellitus: Our Evolving Faith in the Face of Evidence (Rene Rodriguez-Gutierrez)
  - Survival as a Function of HgbA1c in People with Type diabetes: A retrospective cohort study (Craig J. Currie, et al)
  - Glycosilated Hemoglobin in Relationship to Cardiovascular Outcomes and in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis (Yurong Zhang, et al)
  - Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: Meta-analysis of randomized controlled trials
  - Glycated Hemoglobin and All-cause and Cause-specific Mortality Among Adults with and Without Diabetes (Fu-Rong Li, et al)

UKPDS 33 Design

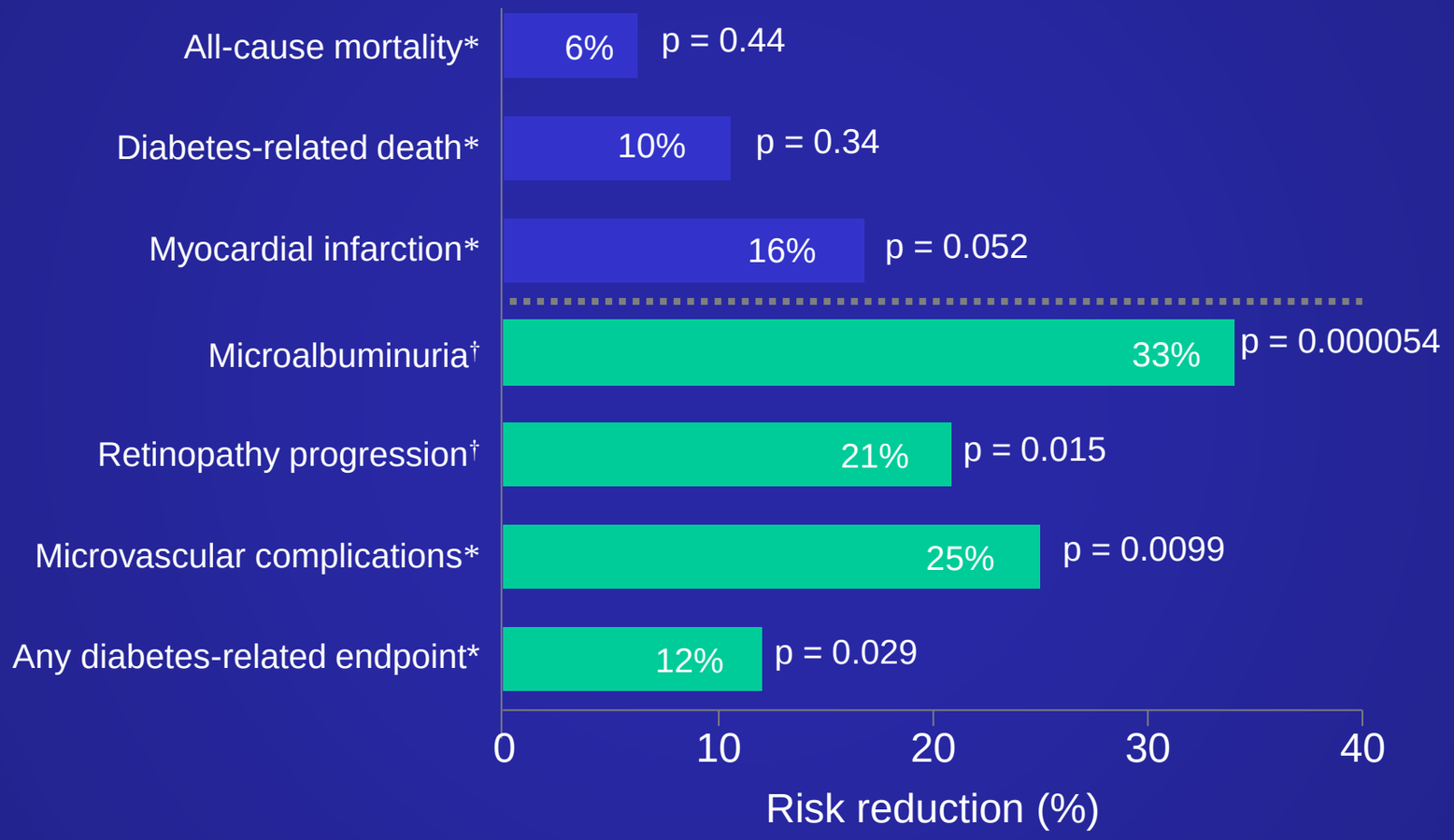
- 5102 newly diagnosed Type 2 diabetic patients (33% with retinopathy)
- Mean age: 54 years
- Glycemic Target: 108 mg/dL
- HbA1c: (Goal)
  - Intensive therapy: 7.0%
  - Standard therapy: 7.9%
- HbA1c (Median) 9.1%
- Hypertensive 39%
- Median follow up 10%

Aggregate Clinical Endpoints



UKPDS 33

UKPDS: Intensive glycaemic control reduced microvascular but not macrovascular outcomes



*Median follow-up, 10 years; †assessed as surrogate endpoints; follow-up, 12 years.

UKPDS 33. Lancet 1998;352:837–53.

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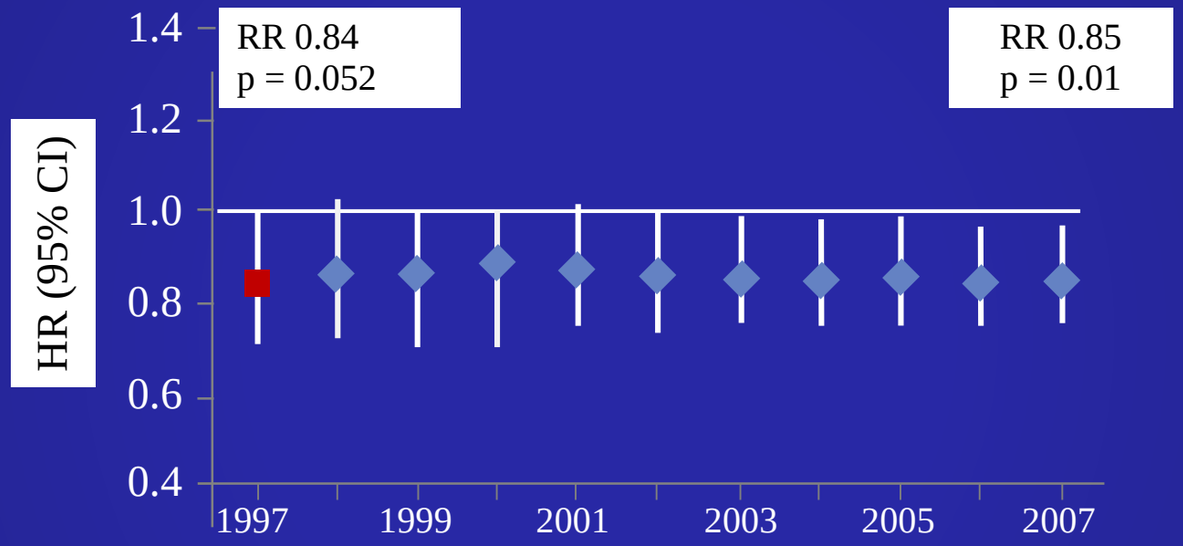
UKPDS 33: Intensive vs. Standard Control

Intensive blood-glucose control by either sulphonylureas or insulin substantially decreases the risk of microvascular complications, but not macrovascular disease, in patients with type 2 diabetes.

UKPDS: Long-term follow-up revealed significant reduction in MI associated with previous intensive glycaemic control

Fatal or non-fatal MI: Intensive treatment



No. of events						
Conventional therapy	186	212	239	271	296	319
Sulphonylurea–insulin	387	450	513	573	636	678

■ Overall values at the end of the study in 1997

◆ Annual values during the 10-year post-trial monitoring period

Holman et al. N Engl J Med 2008;359:1577–89.

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UKPS: Aggregate Outcomes for Patients during 10 years Follow-up

Outcome	Decrease per 1% Reduction	P-value
Any Diabetes Related Endpoint	21%	<0.0001
Diabetes Related Deaths	21%	<0.0001
All Cause Mortality	14%	<0.0001
Fatal and Non-Fatal Myocardial Infarction	14%	<0.0001
Fatal and Fatal-Stroke	12%	0.035%
Microvascular Endpoints	37%	<0.0001
Amputation or Death from Peripheral Vascular Disease	43%	<0.0001
Heart Failure	16%	0.016

“Psssst. Have you heard? 2008

Three large clinical trials presented this month show that lowering your blood sugar to near-normal levels produces no cardiovascular health benefits and may even be harmful.”

Differences in ACCORD/ADVANCE/VADT

Baseline	ACCORD	ADVANCE	VADT
Number of Patients	10,251	11,140	1,791
Diabetes Duration (years)	10	8	11.5
Hx. of Microvascular Disease (%)	35	32	40
Baseline A1c (%)	8.1	7.2	9.4
Intervention: Intensive vs. Standard			
Target A1c	< 6	≤ 6.5	< 6.5
Outcome (Intensive vs Standard)	6.4 vs 7.5%	6.4 vs 7.0%	6.9 vs 8.5%

ACCORD Glucose (Action to Control Cardiovascular Risk in Diabetes — Glucose-lowering arm)

National Heart, Lung, and Blood Institute
ACCORD telebriefing prepared remarks; February 6, 2008

- Goal:

  To test whether an intensive strategy that targets HbA_{1c} levels <6.0% reduces the rate of CV events more than a standard strategy that targets an HbA_{1c} of 7.0% to 7.9%

- Population and treatment:

  10 000 patients with type 2 diabetes and either heart disease or two risk factors for heart disease

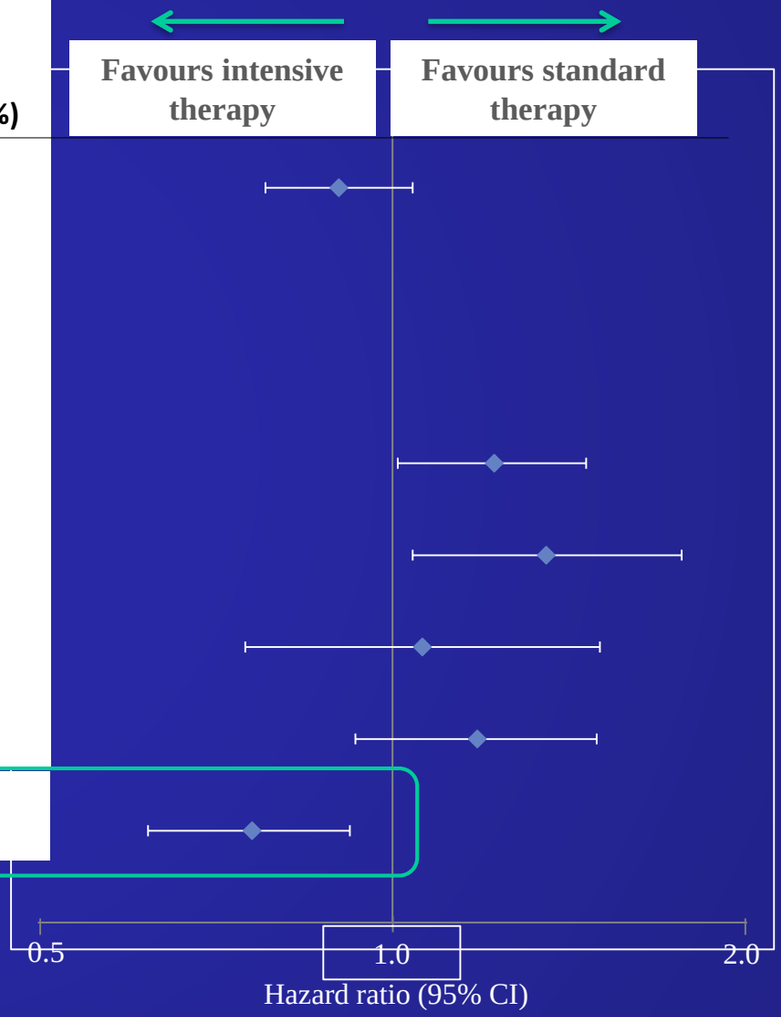
  Randomly assigned to intensive blood sugar lowering or to standard blood sugar lowering

- Primary outcome:

  A composite of fatal and nonfatal major CV events

ACCORD: Intensive glucose-lowering arm terminated early (after 3.5 years) because of higher mortality

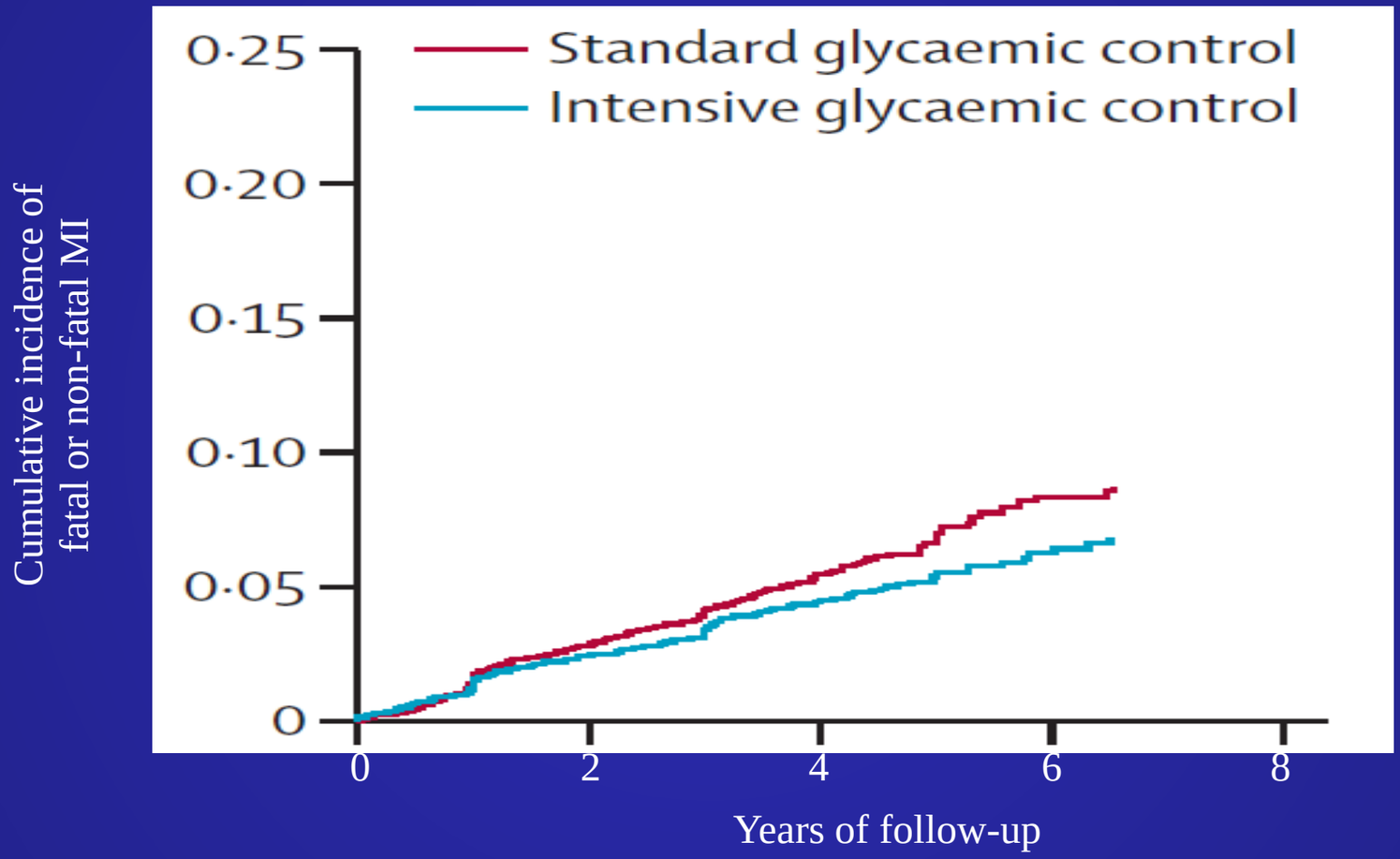
Outcome	Intensive therapy (n = 5128) No. of patients (annual event rate, %)	Standard therapy (n = 5123) No. of patients (annual event rate, %)
Primary outcome*	352 (2.11)	371 (2.29)
Secondary outcome		
Death		
Any cause	257 (1.41)	203 (1.14)
CV cause	135 (0.79)	94 (0.56)
Non-fatal stroke	67 (0.39)	61 (0.37)
Fatal or non-fatal CHF	152 (0.90)	124 (0.75)
Non-fatal MI	186 (1.11)	235 (1.45)



*First occurrence of non-fatal MI or non-fatal stroke or death from CV causes.

Gerstein et al. N Engl J Med 2008;358:2545–59.

In ACCORD, intensive glycaemic control reduces the risk of MI in patients with T2D

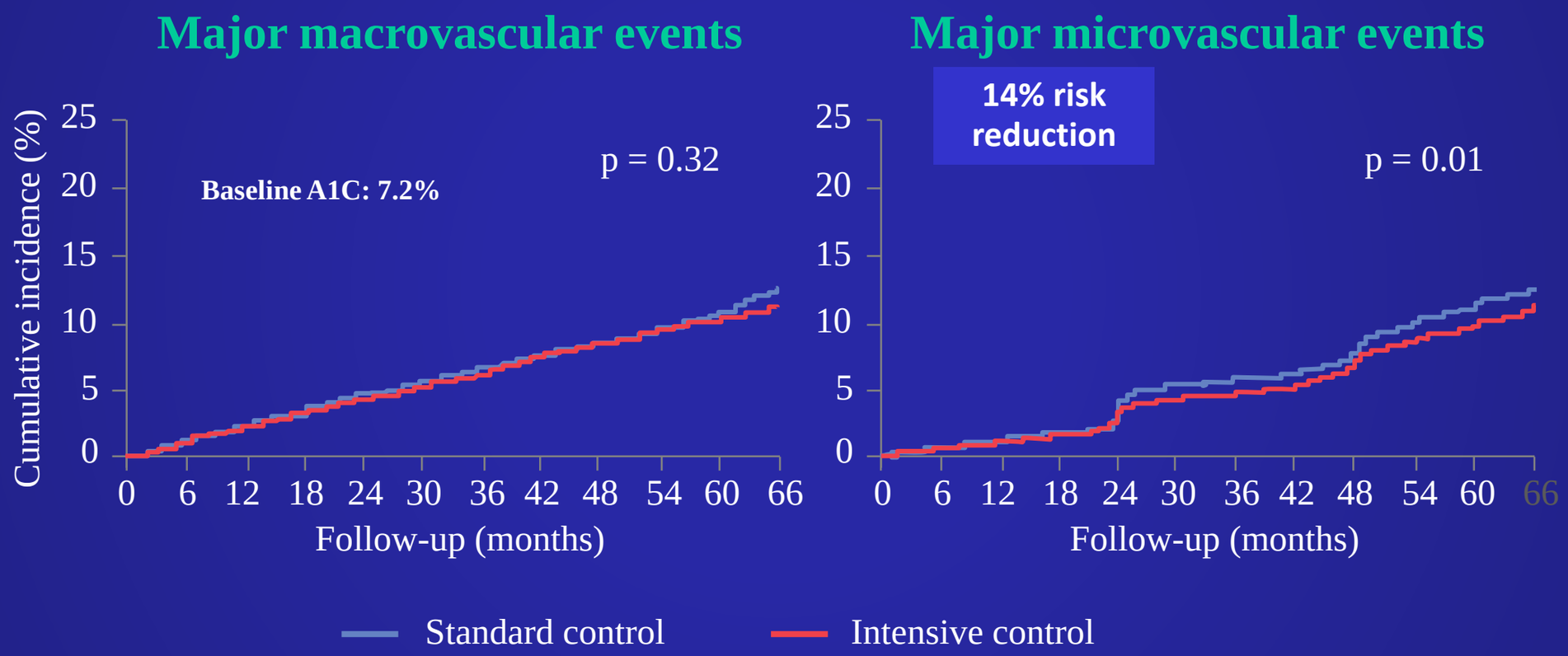


Gerstein et al. Lancet 2014;384:1936–41.

Conclusions

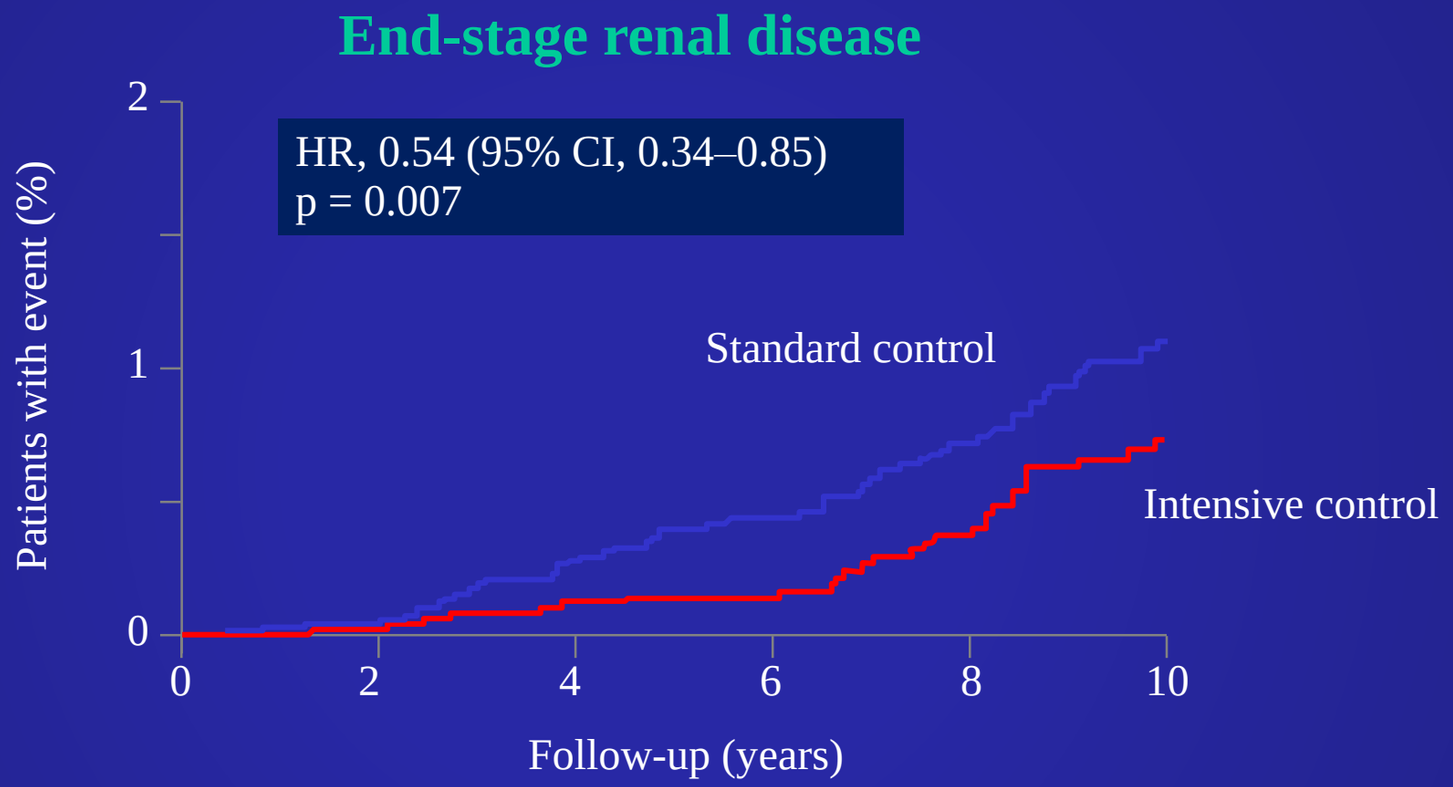
- Intensive treatment of glycaemia in the ACCORD cohort did not reduce the risk of composite measures of advanced microvascular outcomes
- Intensive therapy delayed the onset of albuminuria and some measures of eye complications and neuropathy
- Microvascular benefits of intensive therapy should be weighed against increase in total and CVD-related mortality, increased weight gain, and high risk for severe hypoglycemia

ADVANCE: intensive glycaemic control reduced microvascular but not macrovascular events



Patel et al. N Engl J Med 2008;358:2560–72.

ADVANCE-ON: intensive glycaemic control had significant benefit for end-stage renal disease



No. at risk						
Intensive	5571	5402	5186	4124	3764	2811
Standard	5569	5400	5173	4041	3681	2683

Zoungas et al. N Engl J Med 2014;371:1392-406.

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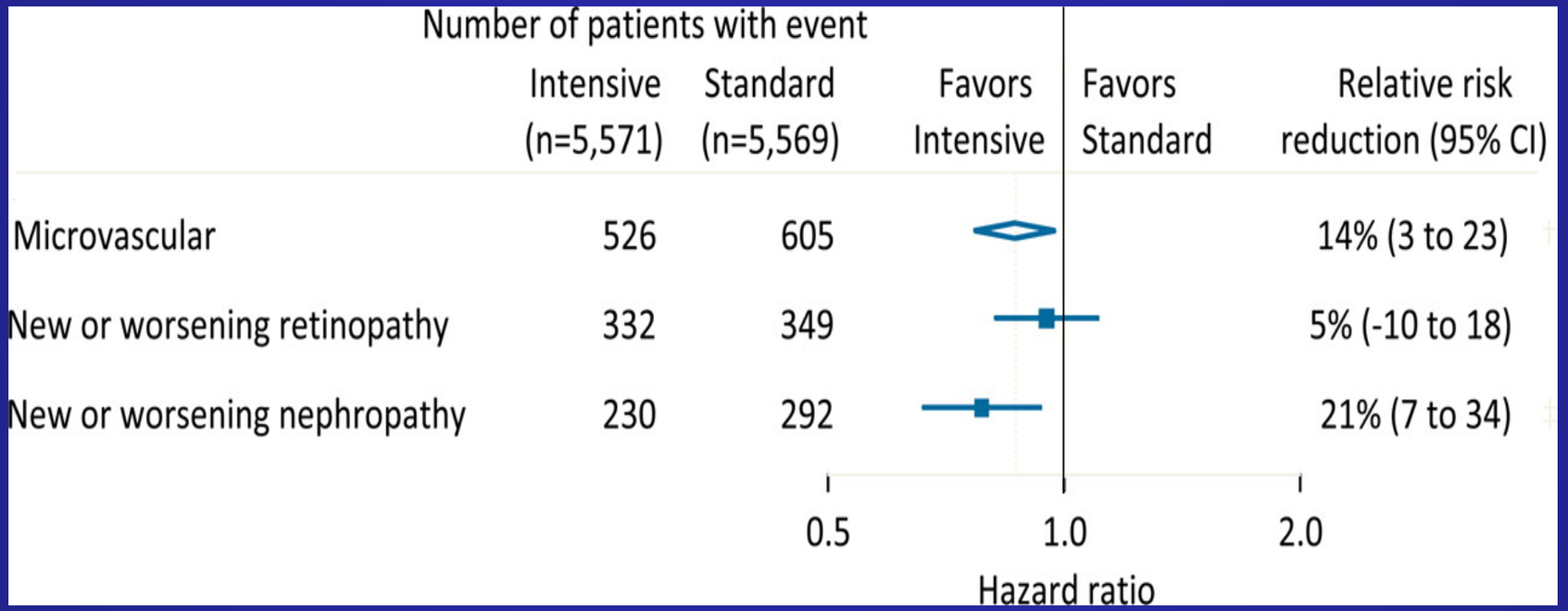
Relative effects of glucose-control strategy on microvascular disease.



Simon R. Heller, and on behalf of the ADVANCE Collaborative Group Dia Care 2009;32:S357-S361

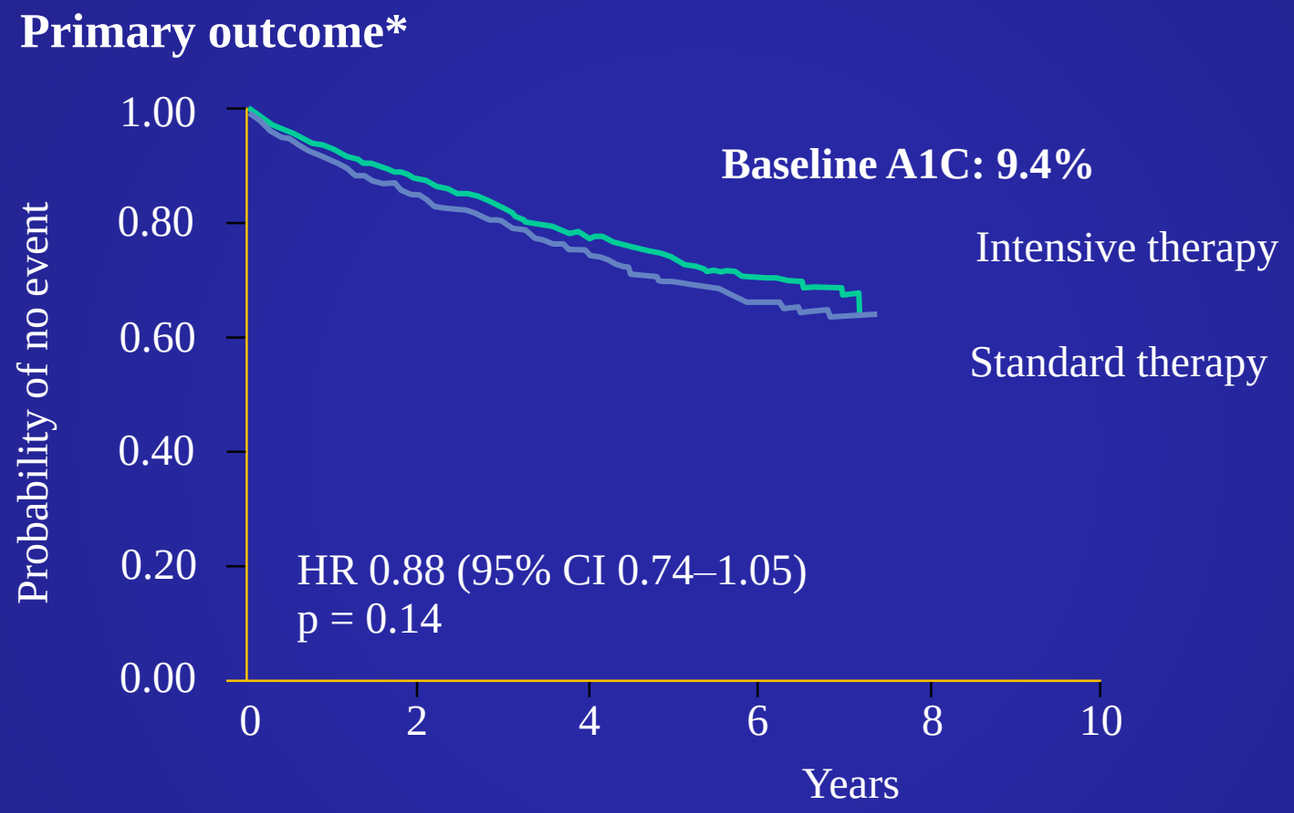
American Diabetes Association.

Veterans Affairs Diabetes Trial
VDAT (2009)

- Compare effects of intensive glucose control vs. standard control in veterans with type 2 DM
- 20 VA centers (n=1,791) started in 2000
- 7.5 years
- Intervention:
  - –intensive (A1c <6.0%) vs. improved (A1c 8-9.0%)
  - – BP and lipid treatment goals equal
- Mean A1c difference between groups was 1.5 %
- **Found no difference in deaths/CVD morbidity**

N Engl J Med 2009; 361:1024-1025

VADT: No difference in primary endpoint between intensive and standard glucose-lowering therapy after 5.6 years



*composite of MI, stroke, CV death, CHF, surgery for vascular disease, inoperable coronary disease, and amputation for ischaemic gangrene Duckworth et al. N Engl J Med 2009;360:129–39.

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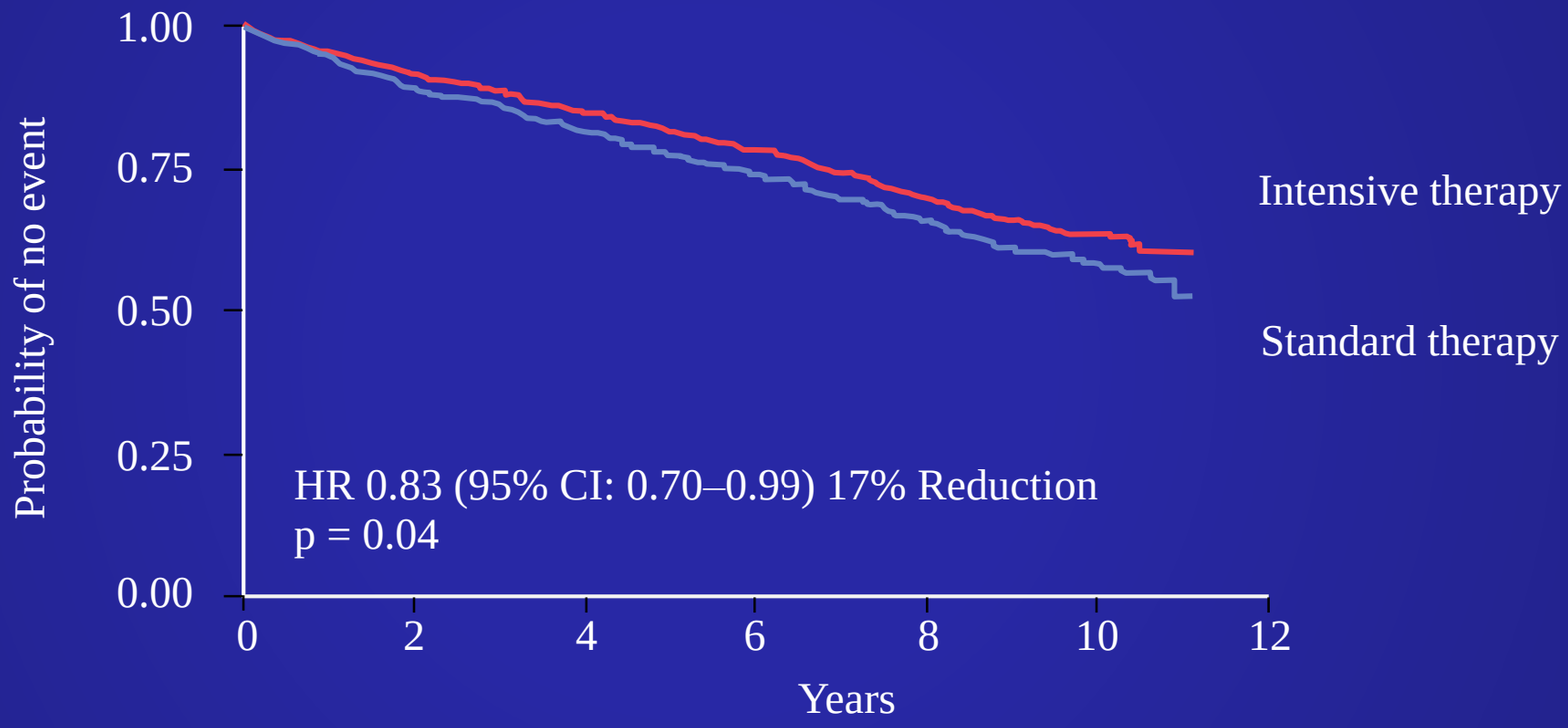
VADT: Significant benefit of intensive vs. standard glucose-lowering therapy in primary endpoint at 10-year follow up

Primary outcome*



*composite of heart attack, stroke, new or worsening congestive heart failure, amputation for ischemic gangrene, or death from cardiovascular causes
Hayward et al. N Engl J Med 2015;372:2197-206.

VADT Conclusion

Intensive glucose control in patients with poorly controlled type 2 diabetes had no significant effect on the rates of major cardiovascular events, death, or microvascular complications, with the exception of progression of albuminuria (P=0.01)..... but

There is a significant benefit of intensive vs. standard glucose-lowering therapy in primary endpoint at 10-year follow up.

Glucose-lowering studies confirmed benefit on microvascular complications but mixed results on macrovascular outcomes

Study[1]	Baseline HbA_{1c} Control vs intensive	Mean duration of diabetes at baseline (years)	Microvascular		CVD		Mortality	
UKPDS	9%→ 7.9% vs 7%	Newly diagnosed	↓	↓	↔	↓	↔	↓
ACCORD[1–3]	8.3%→ 7.5% vs 6.4%	10.0	↓*		↔		↑	
ADVANCE	7.5 %→ 7.3% vs 6.5%	8.0	↓	↔**	↔	↔	↔	↔
VADT	9.4 %→ 8.4% vs 6.9%	11.5	↓	?	↔	↓	↔	↔

Long-term follow-up[1,4,5]

*No change in primary microvascular composite but significant decreases in micro/macroalbuminuria[2,3]

**No change in major clinical microvascular events but significant reduction in ESRD (p = 0.007)[5]

1. Table adapted from Bergenstal et al. Am J Med 2010;123:374.e9–e18. 2. Genuth et al. Clin Endocrinol Metab 2012;97:41–8.
3. Ismail-Beigi et al. Lancet 2010;376:419–30. 4. Hayward et al. N Engl J Med 2015;372:2197-206 (VADT). 5. Zoungas et al. N Engl J Med 2014;371:1392-406.

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Survival as a Function of A1C in People with Type 2 DM*

Retrospective Cohort Study (N=27,965)

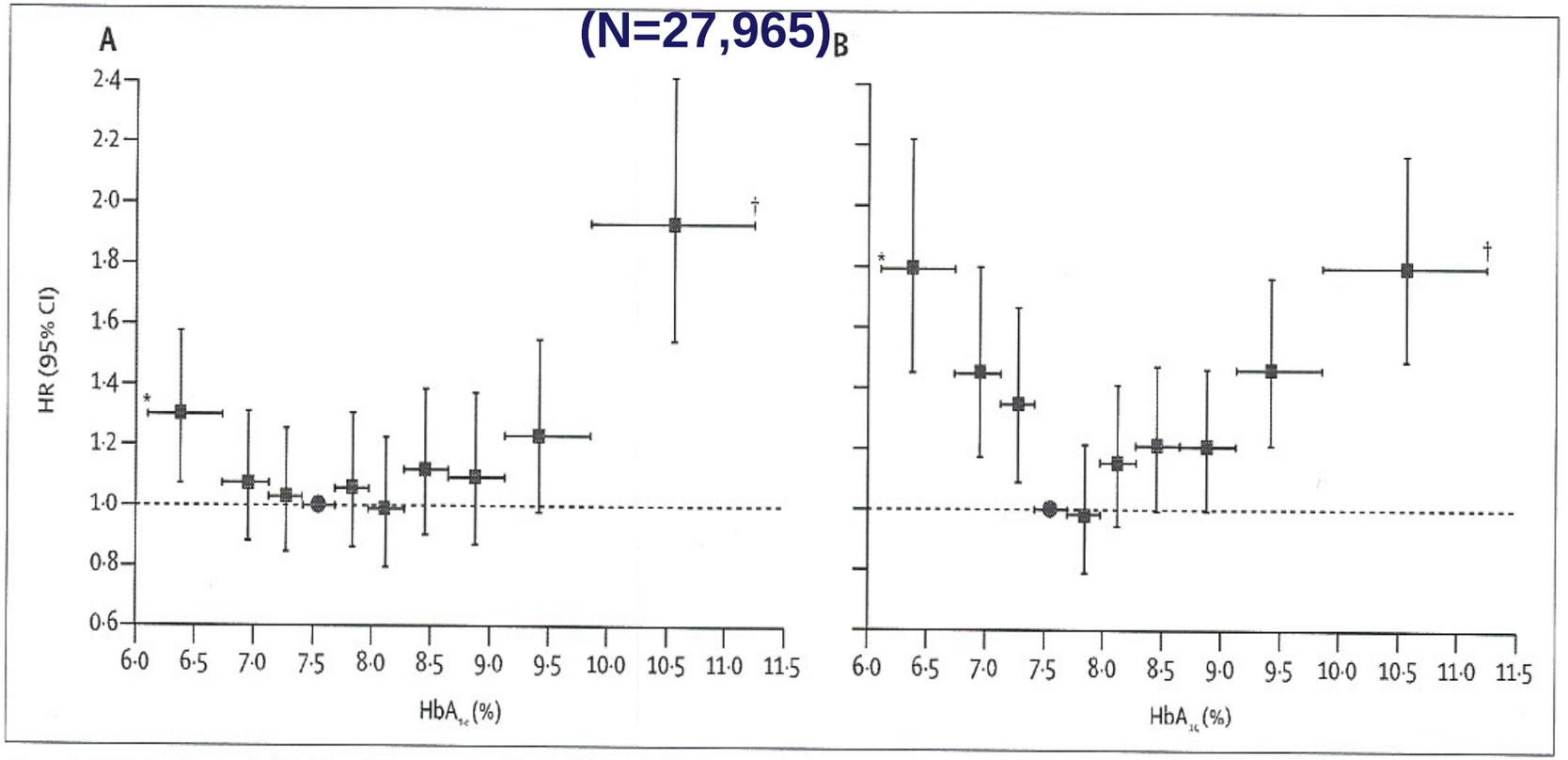
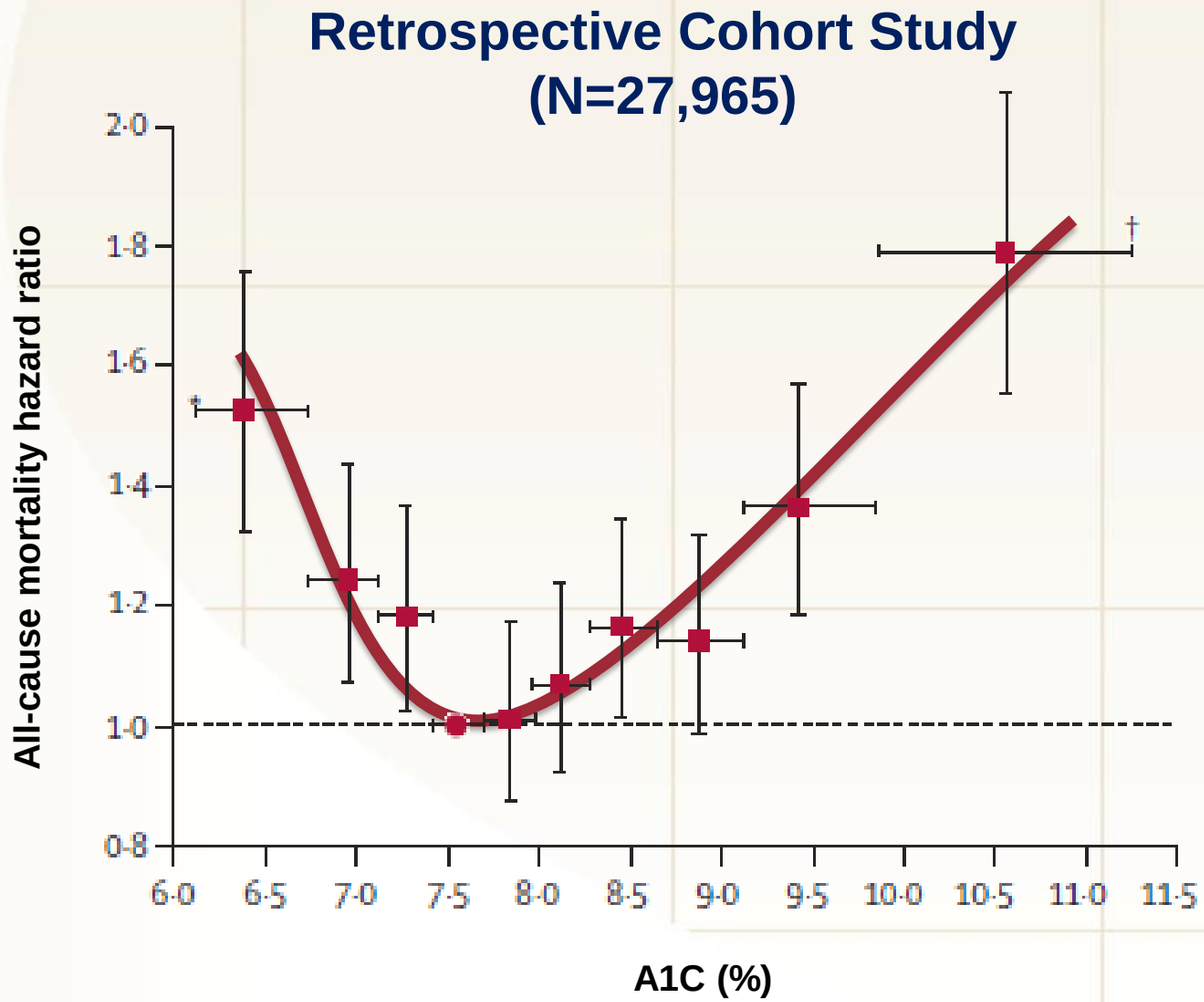


Figure 1: **Adjusted hazard ratios for all-cause mortality by HbA_{1c} deciles in people given oral combination and insulin-based therapies**

Cox proportional hazards models were used, with the HbA_{1c} base case scenario. Vertical error bars show 95% CIs, horizontal bars show HbA_{1c} range. Red circle=reference decile. *Truncated at lower quartile. †Truncated at upper quartile. Metformin plus sulphonylureas (A); and insulin-based regimens (B).

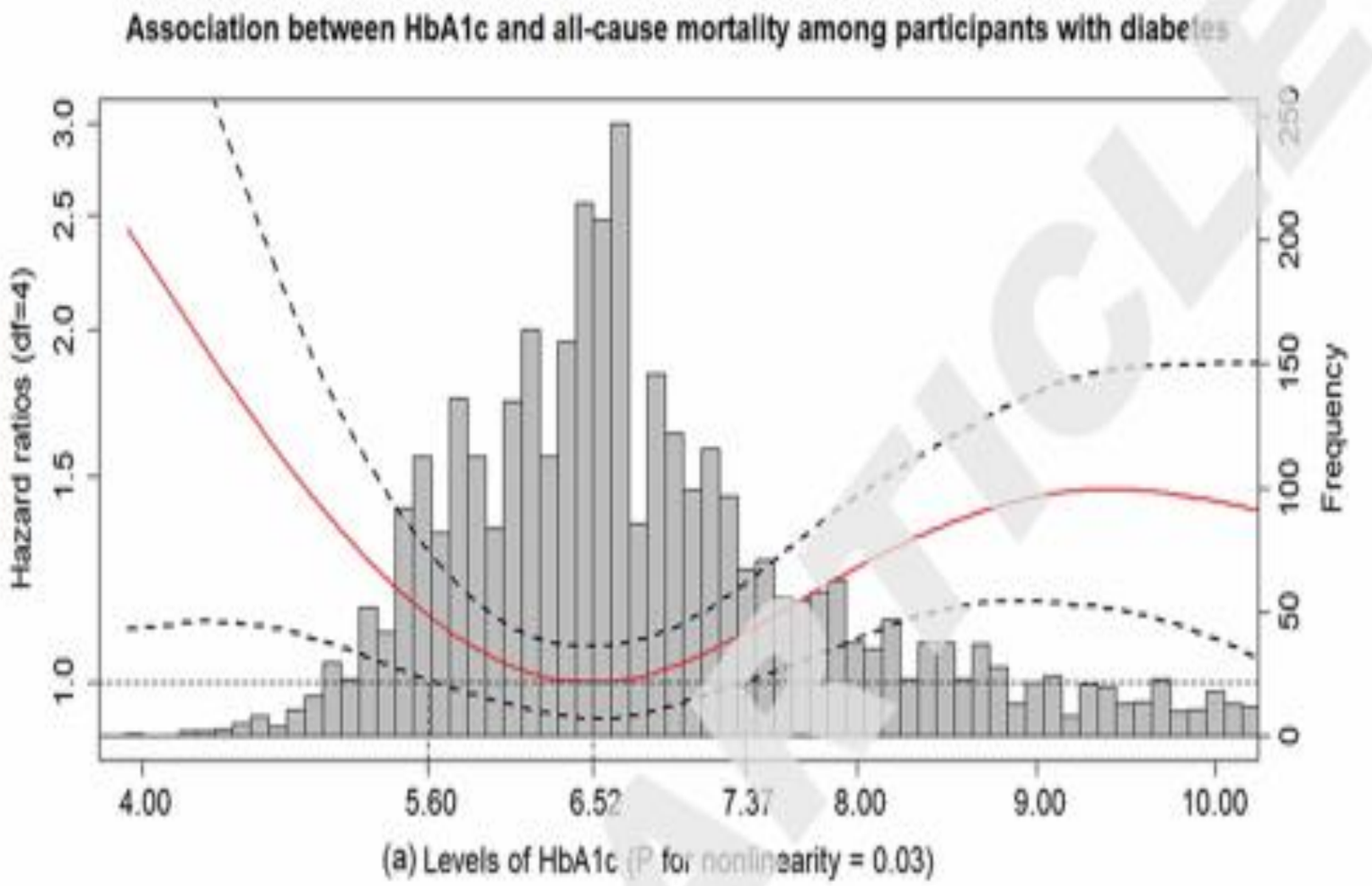
* Craig J Currie, John R Peters, et al Lancet vol 375, February 2010

A1C and Mortality in Clinical Practice



Currie CJ, et al. *Lancet.* 2010;375:481-489.

Glycated Hb A1C and All-cause and Cause-specific Mortality Among Adults with and Without Diabetes



The Journal of Clinical Endocrinology & Metabolism Online March 21, 2019

Individualized Care

Before start treatment of elderly (over 65) adopt an individualized approach to diabetes care that is tailored to the needs and circumstances of adults with type 2 diabetes, taking into account their personal preferences, comorbidities, risks from polypharmacy, and their ability to benefit from long-term interventions because of reduced life expectancy.

Such an approach is especially important in the context of multimorbidity. Reassess the person's needs and circumstances at each review and think about whether to stop any medicines that are not effective

Individualized Therapy

The available evidence, albeit limited, suggests that in younger patients with relatively recent onset of T2DM and little, if any, micro- and macrovascular complications, near-normal glycemic targets should be the standard. Here, the aim is to help prevent complications over the many years of life.

In older individuals with longstanding T2DM and evidence of CVD (or multiple CVD risk factors), somewhat higher targets should be considered.

Proposed Approximate HbA1c Targets by Clinical Characteristic (In the absence of Hypoglycemia) (2011)

Age (Years)	Duration of DM	Complications		Treatment Intensity
		Macrovascular	Microvascular	
< 45	Any Any	None and/or Established and/or	Non or Early Advanced	< 6.5% < 7.%
> 45 -65	Short Long Any	None and None and Established and	None or Early None or Early Abnormal	6.5 – 7 % 7% 7 – 8%
> 65	Short Long Any	None and None and Established and/or	None or early None or early Advanced	7% 7- 8% 8%
> 75	Any	Any and/or	Any	8%

Conclusion

- Young patient, patient recently diagnose of Type 2 DM with no diabetes-related complications and no cardiovascular complications should be targeted to an A1C less than 7% but greater than 6%.
- Elderly patients with no cardiovascular complications should be targeted to an A1C between 7 and 8%.
- Elderly patients with cardiovascular complication and a life expectancy of less than 10 years should be targeted to an A1c between 7.5 and 8.5%.
- Both, very low (A1C less than 6%) and high (A1C over 8%) increased the hazard of cardiovascular mortality.
- There is no evidence to sustain the recommendation that an A1C less than 7% reduce the incidence of microvascular or macrovascular complication.

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Thanks