



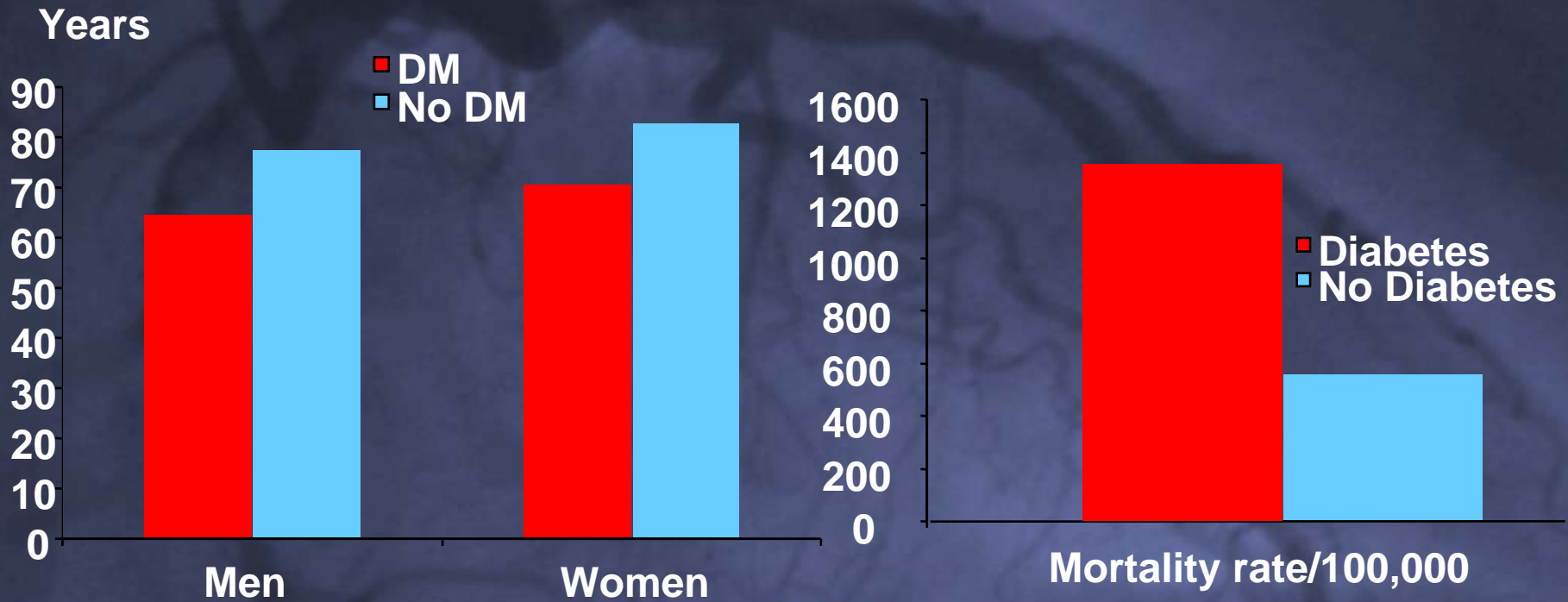
**York Central Hospital  
Stroke Prevention Symposium:  
Diabetes Management**

**Dr. Robert Schlosser  
June 24, 2008**

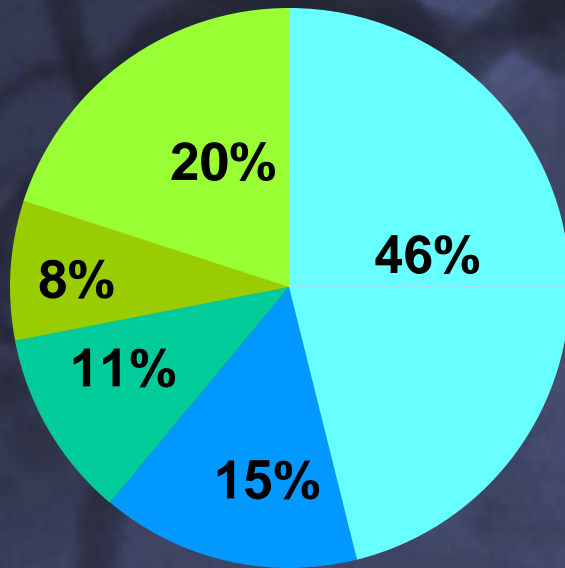


**“Be honest with me, Doc. How much longer can I go ignoring your advice to keep checking my blood glucose.”**

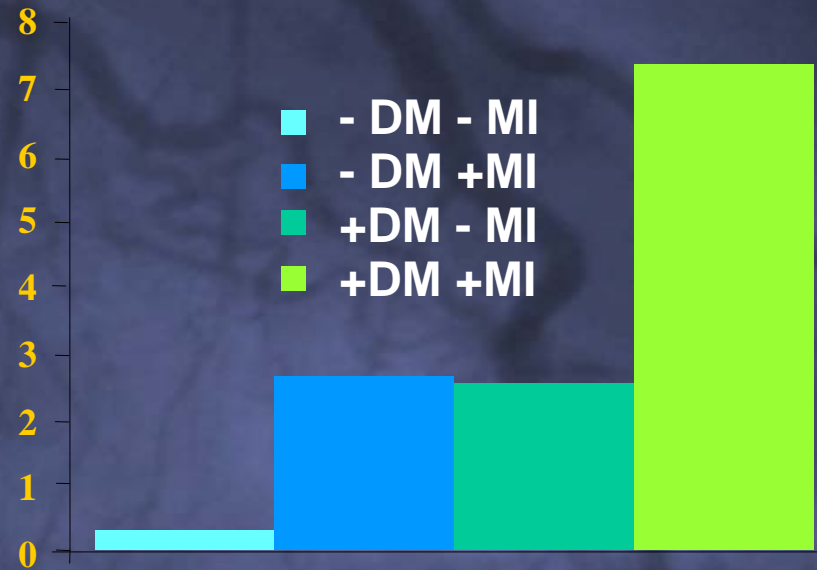
# Life Expectancy with Diabetes



# Causes of death in Diabetes



## CV Death Risk/100 pt-yr

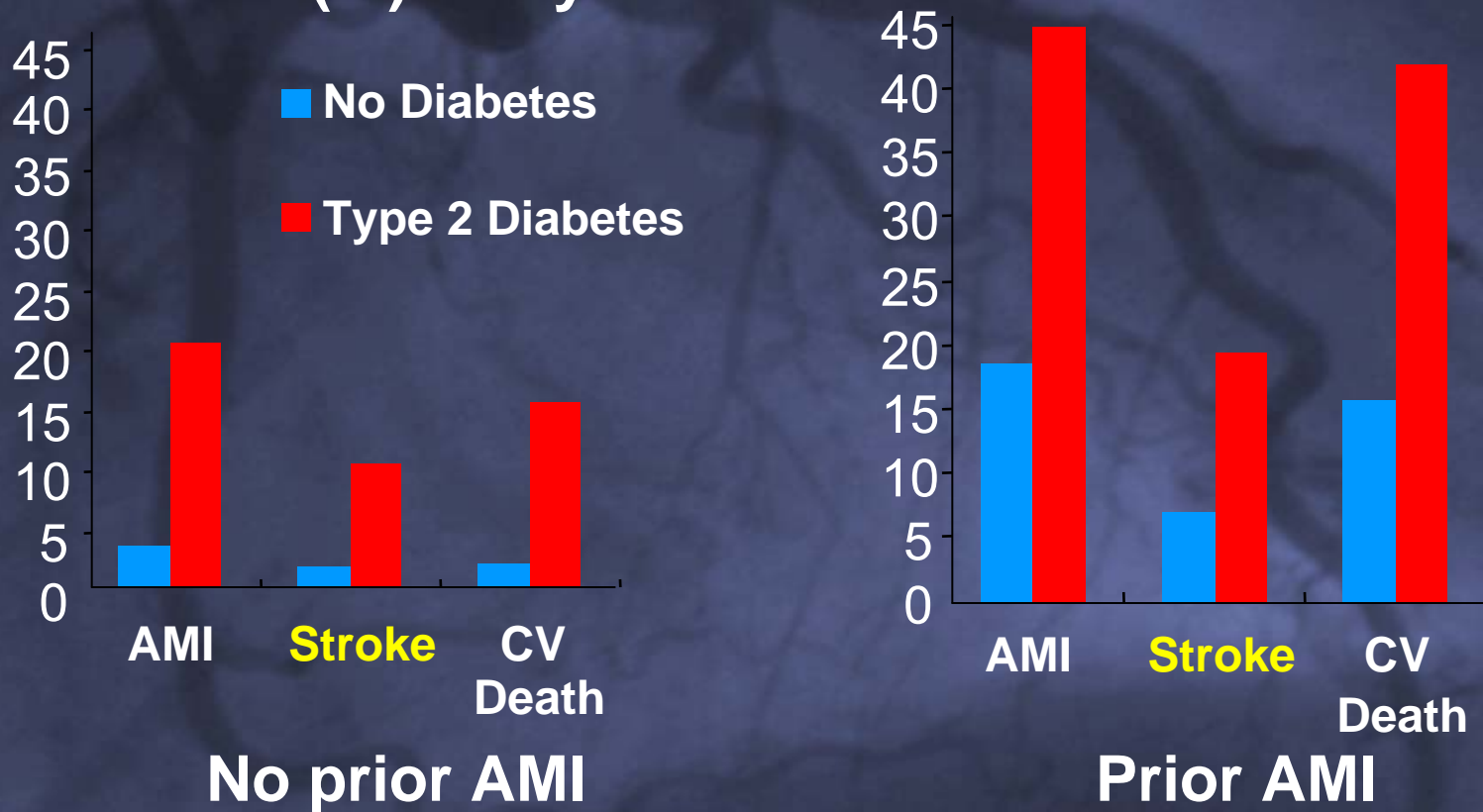


Hux JE, *et al.* Diabetes in Ontario, an ICES Practice Atlas 2003.

Haffner, *et al.* *NEJM* 1998;339:229.

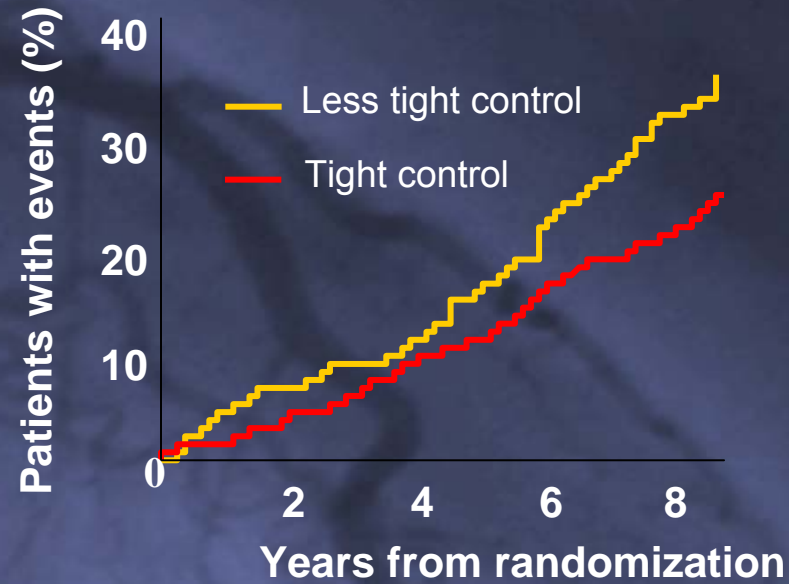
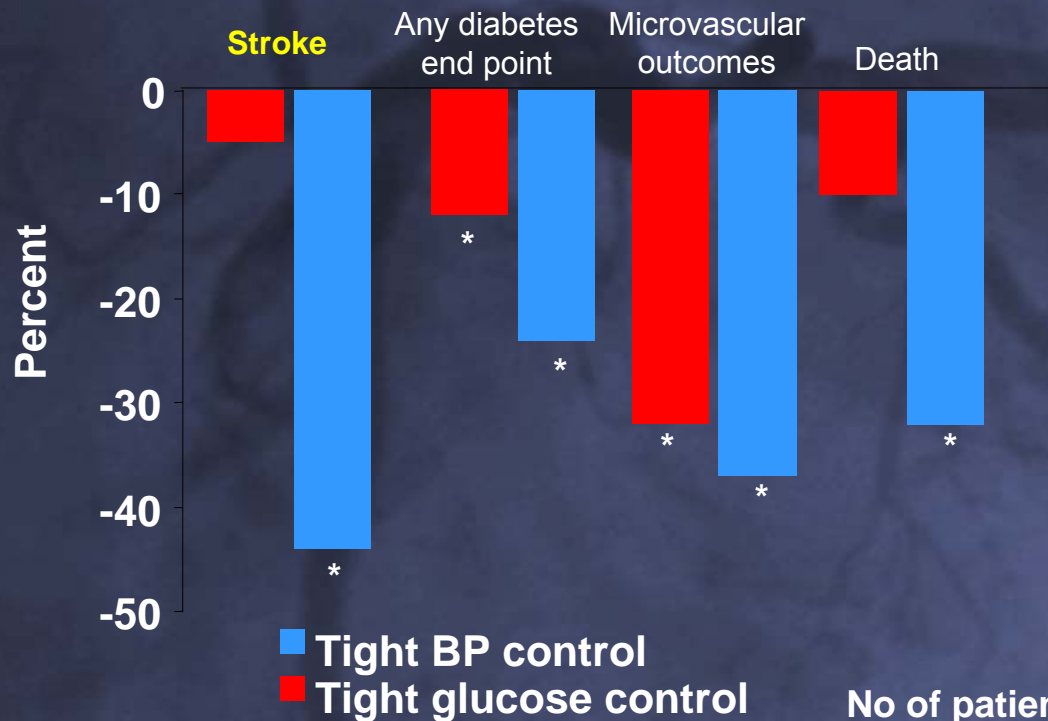
# Cardiovascular Events in Type 2 Diabetes

Incidence (%) at 7 years





# UKPDS Both Tight Glucose and Blood Pressure Control Reduce Cardiovascular Outcomes



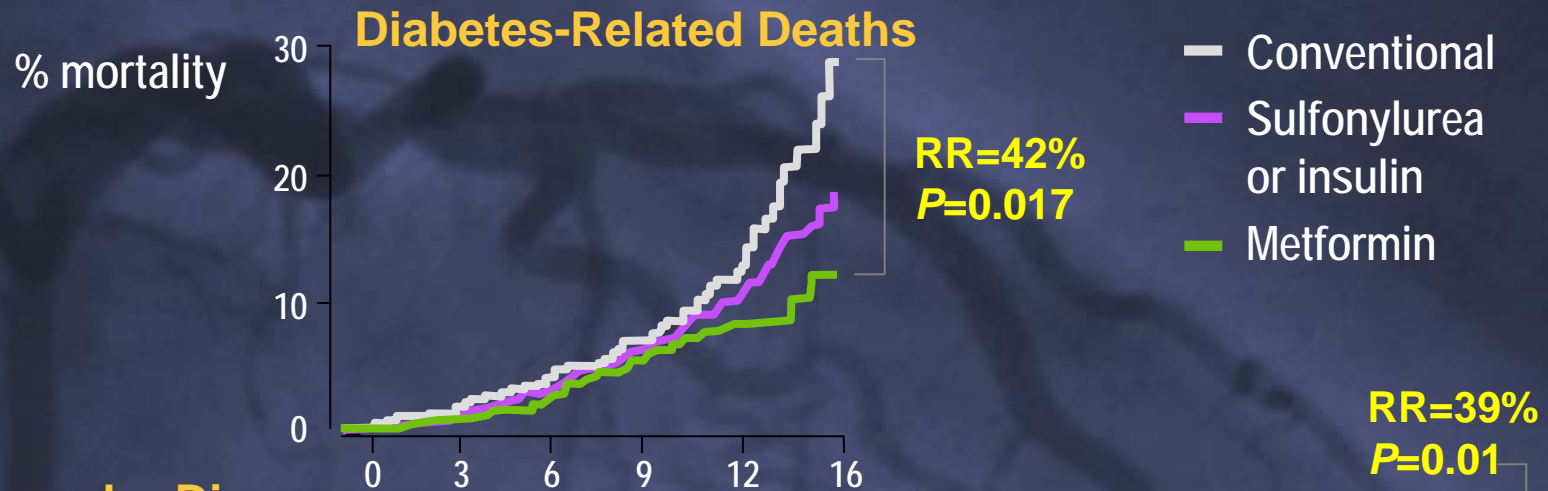
No of patients at risk:

	0	2	4	6	8
Less tight control	390	370	323	161	
Tight control	758	728	630	325	

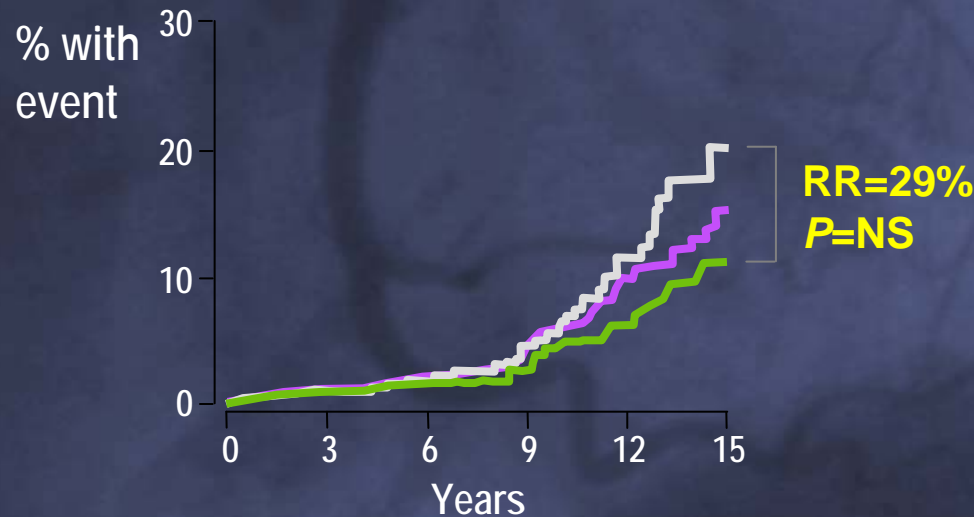
Reduction in risk with tight control 32%  
 (95% CI 6% to 51%)(P=0.019)

\*P<0.05.  
 Tight BP control = 144/82 mm Hg. Tight glucose control = HbA1c = 7.0%.

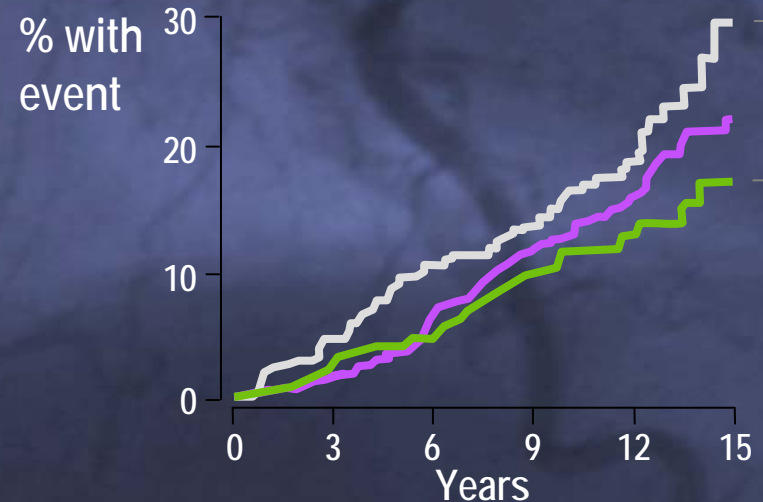
# Medical Endpoints in UKPDS Obese Substudy Comparison of Initial Therapies



### Microvascular Disease



### Myocardial Infarction





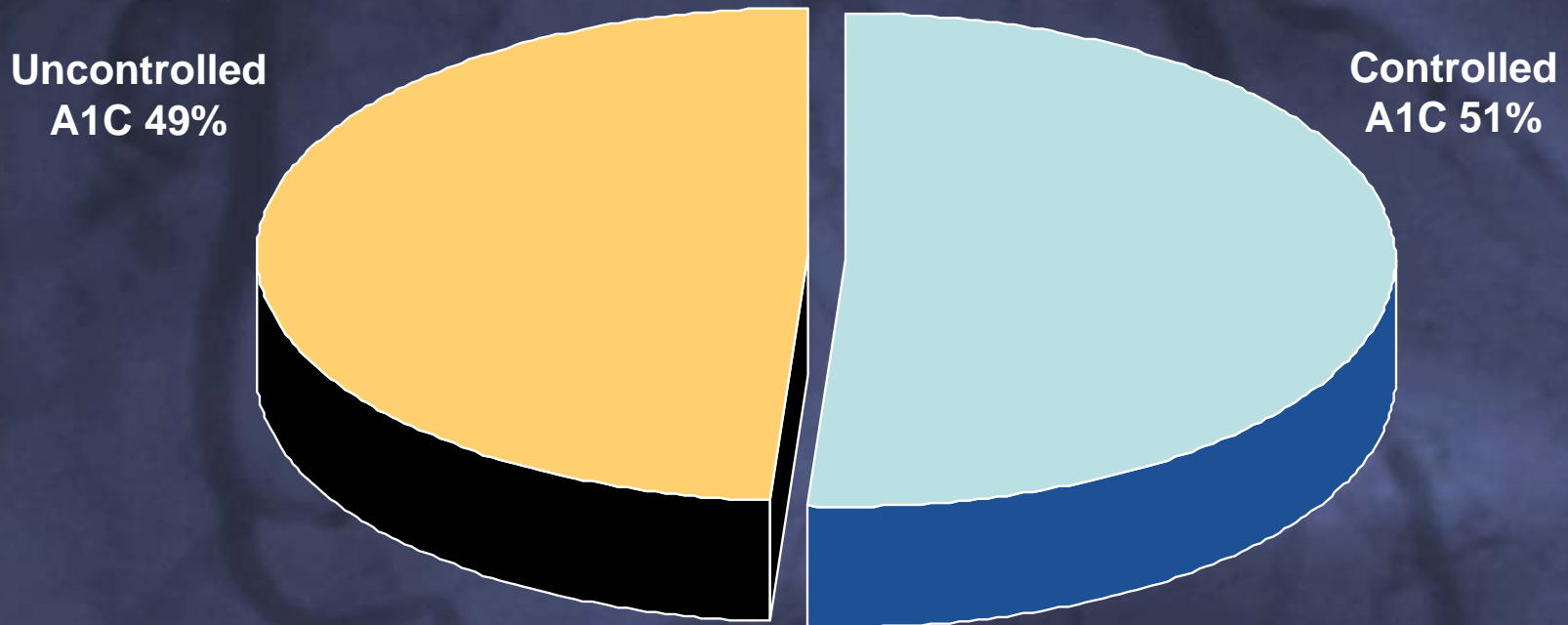
# Targets for Diabetes Management

- CDA & ADA target  $A1C < 7.0\%$
- AACE / IDF targets  $A1C \leq 6.5\%$
- Normal  $A1C < 6.0\%$

# DICE: Glycemic Control in Canada

One in two type 2 diabetes patients in Canada is not at target (< 7%)

Most recent A1C test results (n = 2,337)





# Oral Antihyperglycemic Agents for Type 2 Diabetes

## Class

Biguanide

Secretagogues

Glitazone (TZD)

DPP4-Inhbitors

$\alpha$ -Glucosidase inhibitor

## Agents

Metformin

Sulfonylureas (3) , Repaglinide

Pioglitazone, Rosiglitazone

Sitagliptin

Acarbose



# Insulin Preparations

## Class

Human insulins

Insulin analogues

Premixed insulins

## Agents

Regular (Toronto), NPH

Aspart, Lispro, Glargine, Detemir

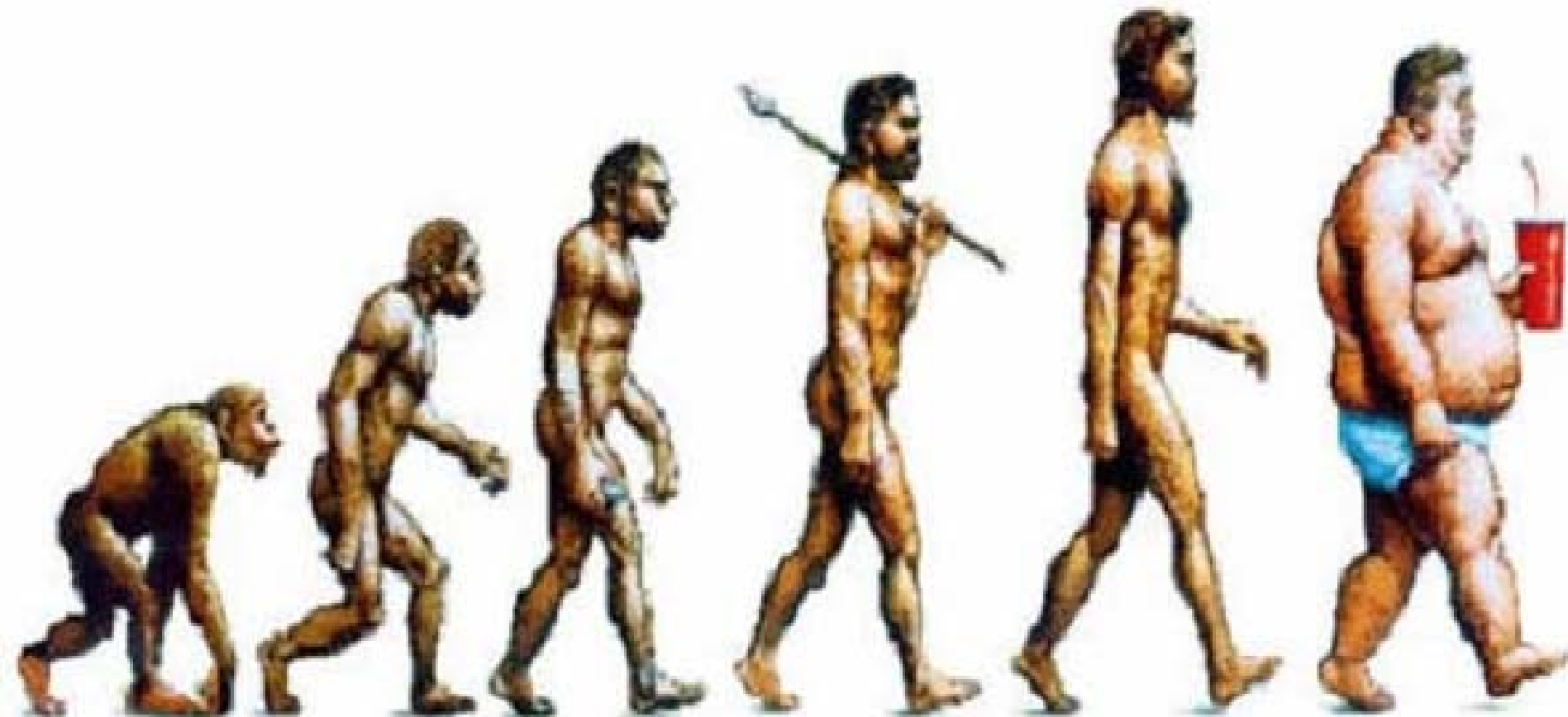
Human 30/70, 50/50

Humalog mix25, mix50

Novomix30



# Evolution of Diabetes

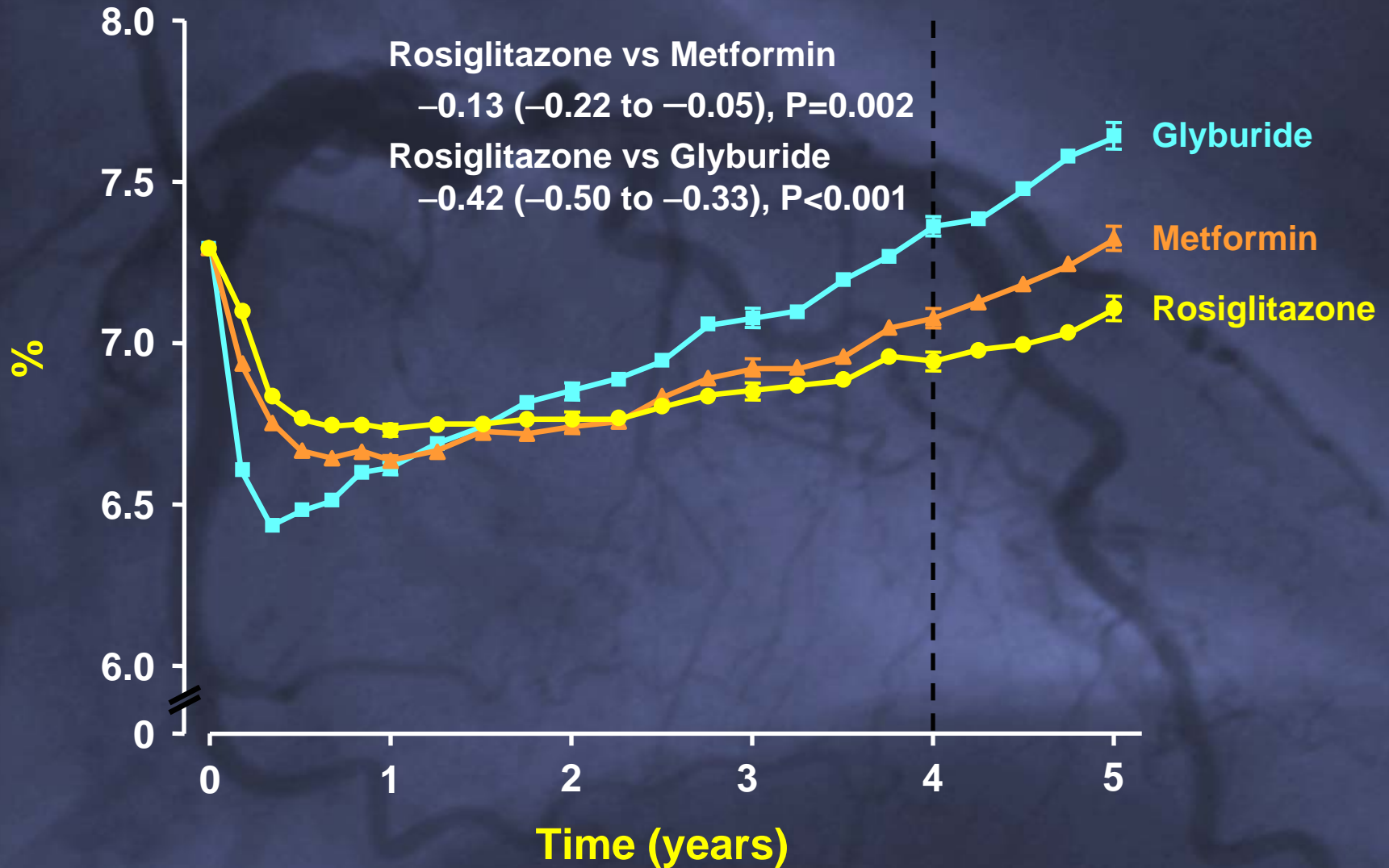




## Efficacy of Oral Antihyperglycemics Declines With Time

- A1C rises at ~0.2% to 0.3% yearly on stable therapy due to declining  $\beta$ -Cell function
- This rate is the same as for diet alone and sulfonylureas, less with Metformin & TZDs (?DPP4s)
- $\beta$ -Cell preservation is an important consideration especially in younger patients with T2DM
- Combination treatments are routinely needed to maintain adequate control

# ADOPT Study: HbA1c Over Time





# FDA – Adjudicated MACE Events: RECORD + ADOPT + DREAM

	Treatment	# of Events	Rate / 100 PY	HR (95% CI)
<b>MI/SD</b>	RSG (n=6311)	78	0.36	
	Comp (n=7756)	80	0.31	1.13 (0.82, 1.54)
<b>Stroke</b>	RSG (n=6311)	49	0.22	
	Comp (n=7756)	72	0.28	0.84 (0.58, 1.21)
<b>CV Mortality</b>	RSG (n=6311)	47	0.22	
	Comp (n=7756)	65	0.25	0.84 (0.57, 1.22)
<b>MACE</b>	RSG (n=6311)	153	0.70	
	Comp (n=7756)	174	0.67	1.03 (0.83, 1.28)



## PROactive: Fatal and nonfatal stroke with pioglitazone treatment vs placebo in patients with prior history of stroke

End point	Pioglitazone, n=486	Placebo, n=498	Hazard ratio (95% CI)	p
Recurrent stroke	27	51	0.53 (0.34– 0.94)	0.008



# CHD Prevention Trials with Statins in Diabetes: Subgroup Analyses

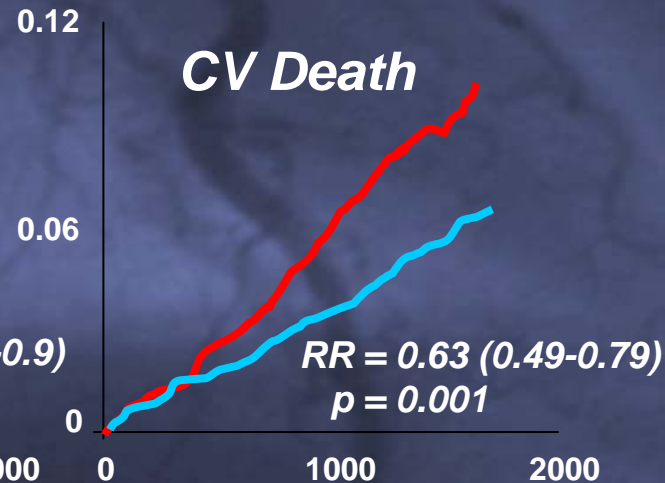
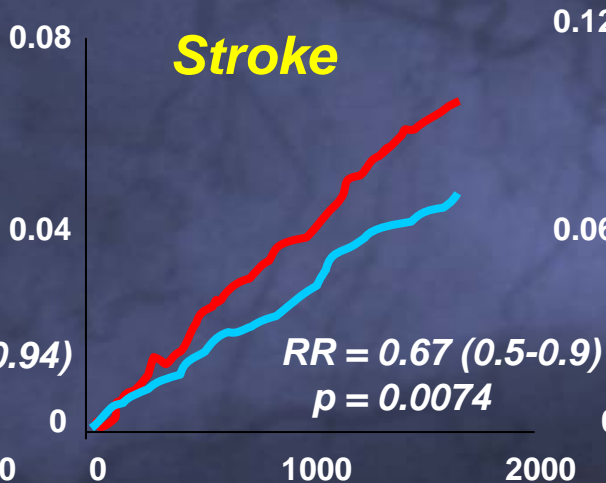
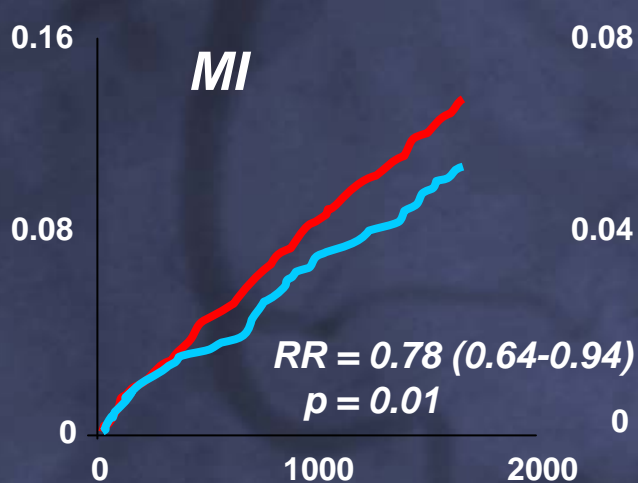
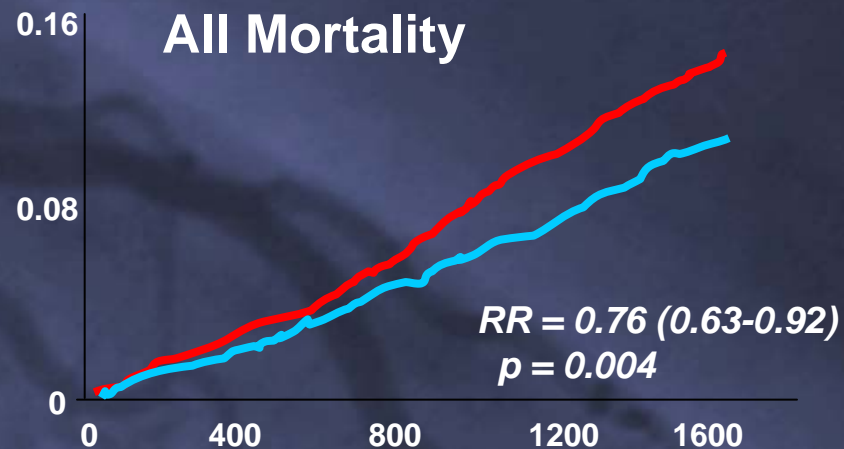
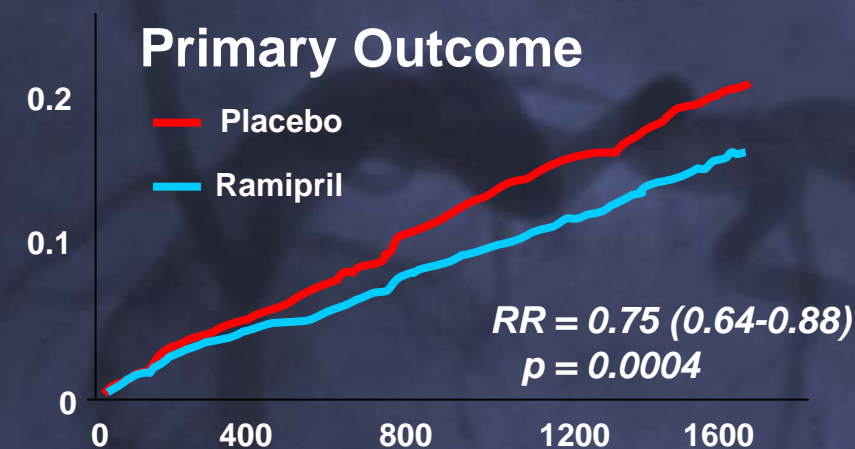
<b>Study</b>	<b>Drug</b>	<b>No.</b>	<b>CHD Risk Reduction (overall)</b>	<b>CHD Risk Reduction (diabetes)</b>
<b>Primary Prevention</b>				
AFCAPS/TexCAPS	Lovastatin	239	37%	43%
<b>Secondary Prevention</b>				
CARE	Pravastatin	586	23%	25%
4S	Simvastatin	202	32%	55%
LIPID	Pravastatin	782	25%	19%
HPS	Simvastatin	20K	24%	29%

Adapted from Downs JR, et al. *JAMA* 1998;279:1615-1622. Goldberg RB, et al. *Circulation* 1998;98:2513-2519. Pyörälä K, et al. *Diabetes Care* 1997;20:614-620. The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group. *N Engl J Med* 1998;339:1349-1357. Haffner SM, et al. *Arch Intern Med* 1999;159:2661-2667.



# Cardiovascular Benefits of Ramipril in People with Diabetes: HOPE

Kaplan-Meier rates



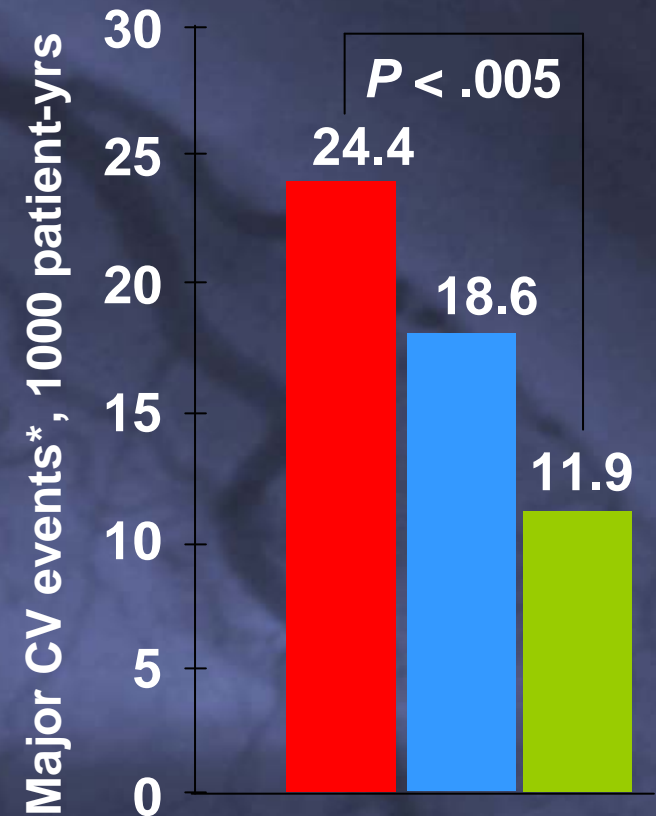
Duration of follow-up (days)

# HOT Trial: BP Control Reduces Cardiovascular Events in Diabetes

## Diabetes Subgroup

Target Diastolic BP (mmHg)	Number of Patients	Achieved <sup>†</sup> Systolic BP (mmHg)	Achieved <sup>†</sup> Diastolic BP (mmHg)
≤ 90	501	143.7	85.2
≤ 85	501	141.4	83.2
≤ 80	499	139.7	81.1

<sup>†</sup> Achieved = Mean of all BPs from 6 months of follow-up to end of study



\*includes all myocardial infarction, all strokes, and all other CV deaths



# Aspirin in the Prevention of Cardiovascular Events in Diabetes

- **Reduction of cardiovascular mortality**

Diabetes	RR 0.7 (95% CI 0.5-0.8)
No diabetes	RR 0.7 (95% CI 0.6-0.8)
- **CDA recommend ASA (80-325 mg daily) for all diabetic patients (>30 years) with atherosclerotic risk factors or with CVD**



# Summary of Intervention Studies

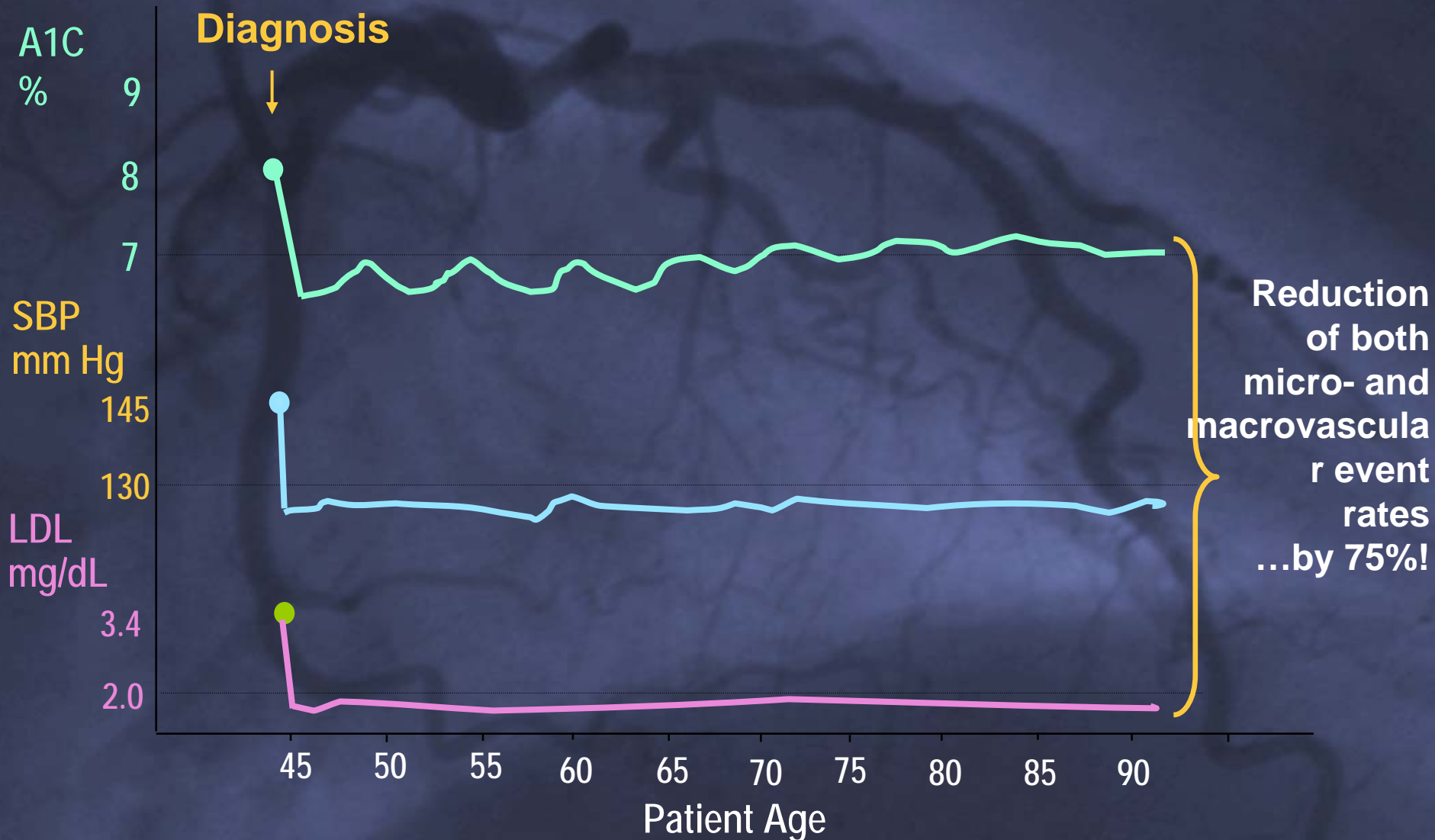
## Risk Reduction With Treatment

	Microvascular events	Macrovascular events
Blood pressure treatment	20%–40%	20%–50%
Lipid treatment	—	25%–55%
Glucose treatment	12%–35%*	0%–20%*

\*Per 1% A1C reduction



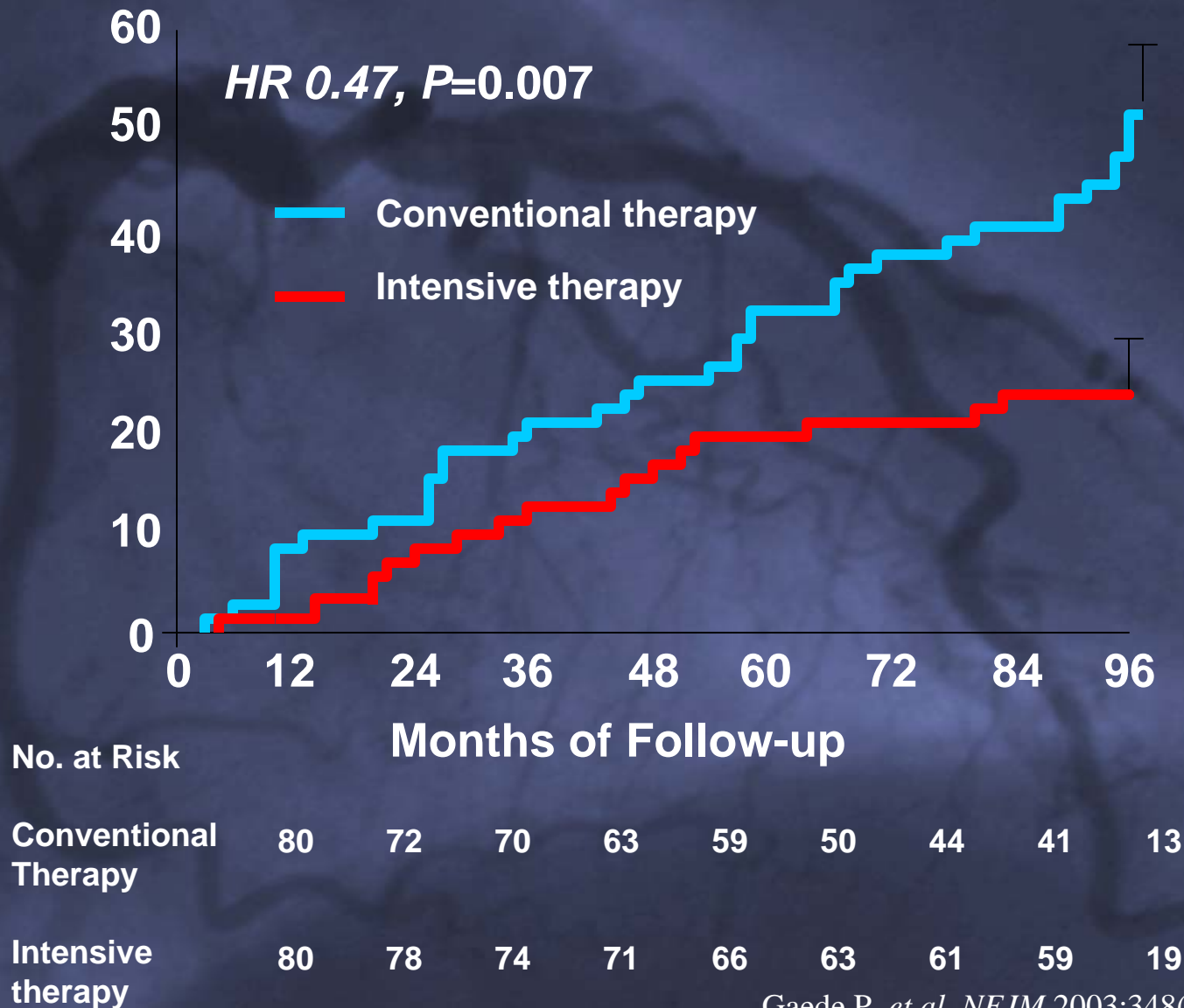
# Primary Objectives of Effective Management





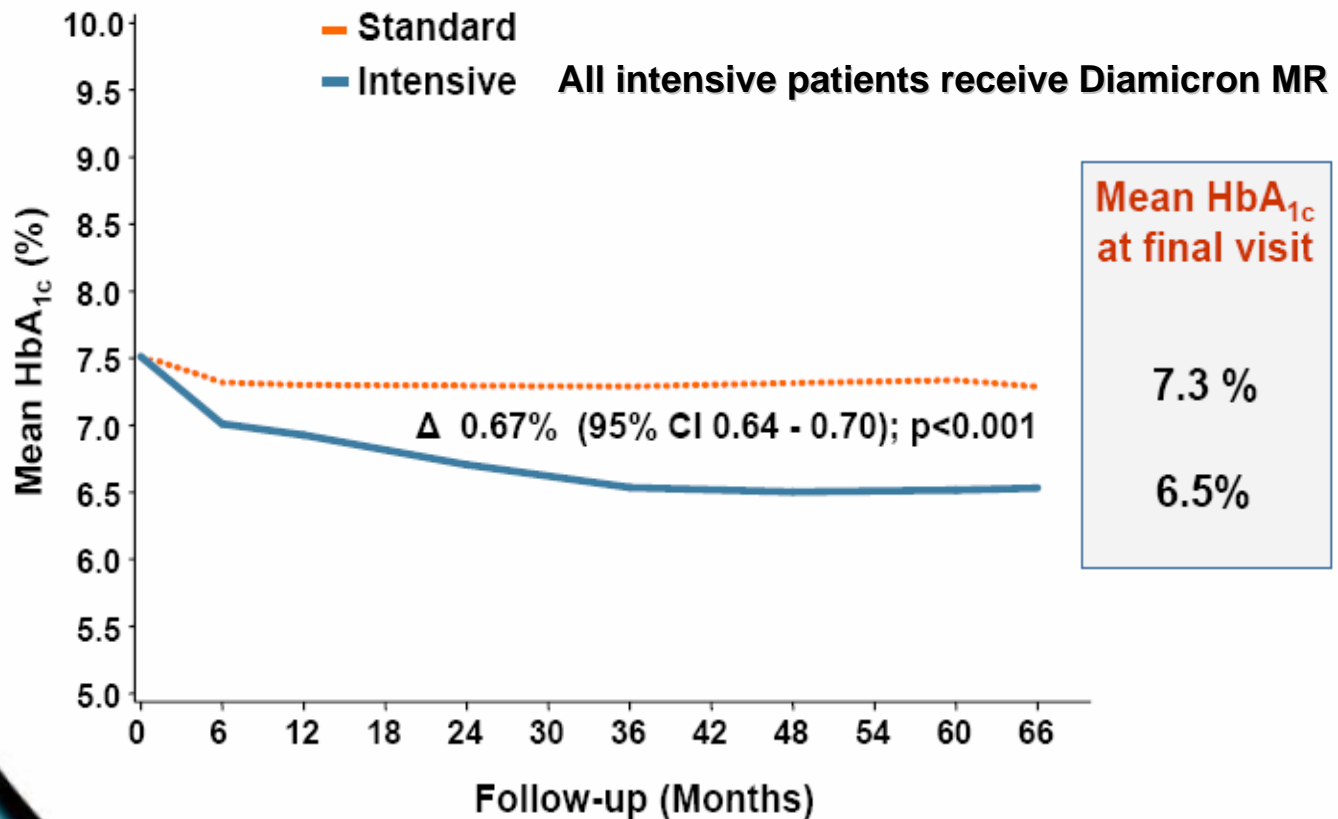
# Steno 2

## Effects on Combined CV Outcomes



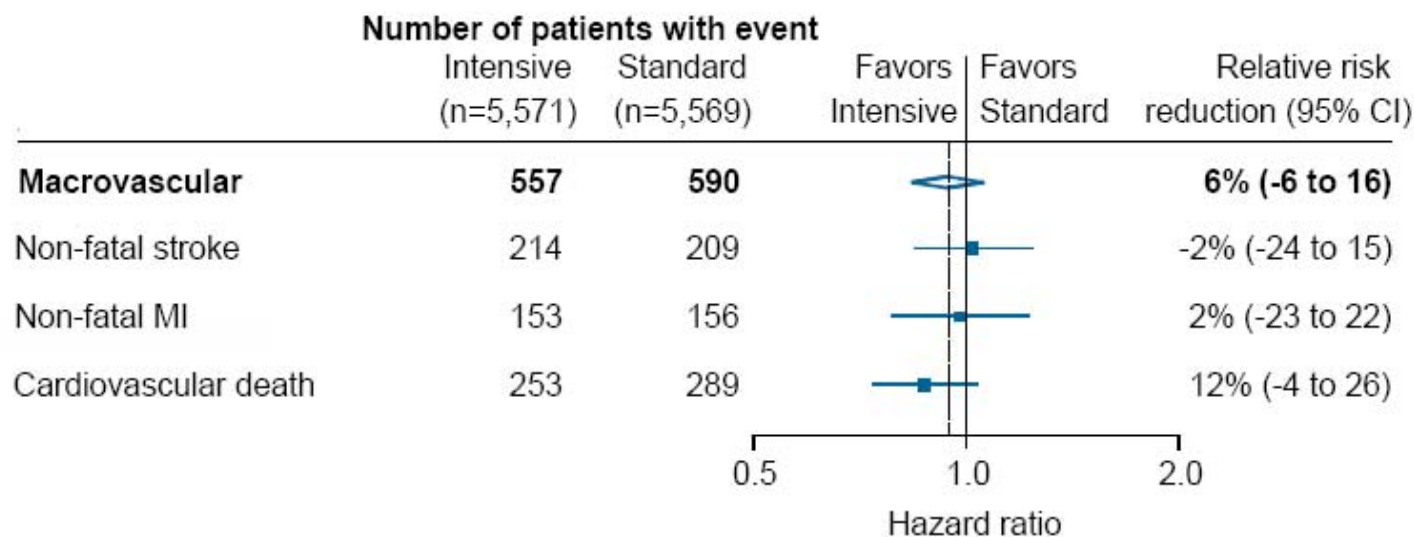
# Lower A1c Targets: ADVANCE Trial

## Hemoglobin A<sub>1c</sub>



# ADVANCE: Macrovascular results

## Major macrovascular events



**Mortality rate 17/1000PY – no difference between groups**



# ACCORD: Three Medical Strategy Questions

- **Glycemia**

- Intensive control (HbA1c < 6.0%) vs
- Standard control (HbA1c 7.0%-7.9%)

- **BP**

- Intensive control (SBP < 120 mmHg) vs
- Standard control (SBP < 140 mmHg)

- **Lipids**

- Fibrates to increase HDL-C and lower TG + statins to lower LDL-C vs
- Statins to lower LDL-C alone



# ACCORD Study

- **Study Population**

- T2DM subjects at especially high risk for heart attack or stroke
  - Existing CVD or at least 2 CV risk factors
- 10,251 patients at 77 centers in US and Canada

- **Patient Characteristics**

- Mean A1C: 8.3% at baseline
- Median duration of diabetes: 10 yrs
- Achieved A1c: 6.4% vs. 7.5%



# ACCORD: Deaths in intensive vs standard glycemic control groups

<b>Glycemic Control</b>	<b>Standard (Average HbA1C achieved = 7.5%)</b>	<b>Intensive (Average HbA1C achieved = 6.4%)</b>
<b>Deaths (n)</b>	203 (11 /1000 /y)	257 (14 /1000 /y)

## INTENSIVE ARM:

- 50% deaths CVD, 50% cancer / other. Both types of death increased.
- # severe hypoglycemic events higher, but doesn't appear to account for the mortality difference
- 10% reduction in non-fatal MI, but higher incidence of fatal MIs

# ACCORD: Outcomes

**Table 4. Primary and Secondary Outcomes.\***

Outcome	Intensive Therapy (N = 5128)		Standard Therapy (N = 5123)		Hazard Ratio (95% CI)	P Value
	no. of patients (%)	% per yr	no. of patients (%)	% per yr		
Primary outcome	352 (6.9)	2.11	371 (7.2)	2.29	0.90 (0.78–1.04)	0.16
Secondary outcome						
Death						
Any cause	257 (5.0)	1.41	203 (4.0)	1.14	1.22 (1.01–1.46)	0.04
Cardiovascular causes	135 (2.6)	0.79	94 (1.8)	0.56	1.35 (1.04–1.76)	0.02
Nonfatal myocardial infarction	186 (3.6)	1.11	235 (4.6)	1.45	0.76 (0.62–0.92)	0.004
Nonfatal stroke	67 (1.3)	0.39	61 (1.2)	0.37	1.06 (0.75–1.50)	0.74
Fatal or nonfatal congestive heart failure	152 (3.0)	0.90	124 (2.4)	0.75	1.18 (0.93–1.49)	0.17
Causes of death						
Any	257 (5.0)	1.41	203 (4.0)	1.14	1.22 (1.01–1.46)	0.04
Unexpected or presumed cardiovascular disease†	86 (1.7)		67 (1.3)			
Fatal myocardial infarction†	19 (0.4)		13 (0.3)			
Fatal congestive heart failure†	23 (0.4)		16 (0.3)			
Fatal procedure†						
For cardiovascular disease	10 (0.2)		3 (0.1)			
For noncardiovascular disease	1 (<0.1)		3 (0.1)			
Fatal arrhythmia†	4 (0.1)		10 (0.2)			
Fatal stroke†	9 (0.2)		11 (0.2)			
Other cardiovascular disease†	8 (0.2)		10 (0.2)			
Cancer	65 (1.3)		63 (1.2)			
Condition other than cancer or cardiovascular disease†	50 (1.0)		35 (0.7)			
Undetermined	7 (0.1)		11 (0.2)			



# Summary

- **Aggressive multifactorial diabetes care can reduce cardiovascular risk**
- **The CDA 2003 and 2008 guidelines advocate vascular protection as the first priority of diabetes care**
  - **Achieve vascular protection through ACE-inhibition or ARB, ASA, lipid control, lifestyle modifications, smoking cessation and control of hypertension**
  - **Aggressive glycemic goals may be employed in younger patients with diabetes for prevention of micro-vascular complications**
  - **Moderate glycemic targets are appropriate for older patients with high CV risk or those with increased risk of significant morbidity due to hypoglycemia**