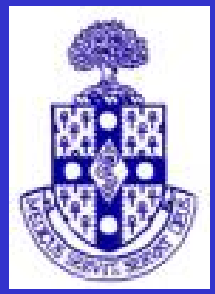
Cardiovascular Complications and Current Treatments

Alice Y.Y. Cheng, MD, FRCPC

April 19, 2005



Outline

- Epidemiology of CV disease & DM
- Vascular protection
  - ACE-I
  - Aspirin
  - Blood pressure control
  - Glycemic control
  - Lipid control
  - Lifestyle, smoking cessation
- Erectile dysfunction

Diabetes: complications

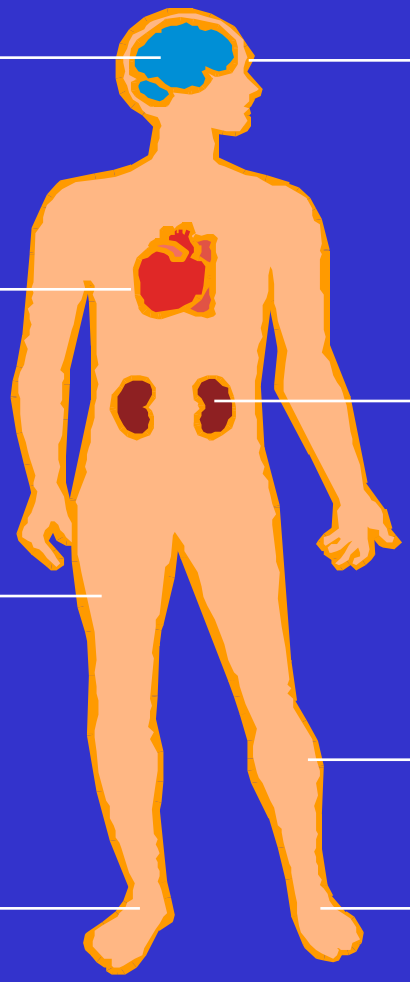
Macrovascular

Stroke

Heart disease and hypertension

Peripheral vascular disease

Foot problems



Microvascular

Diabetic eye disease (retinopathy and cataracts)

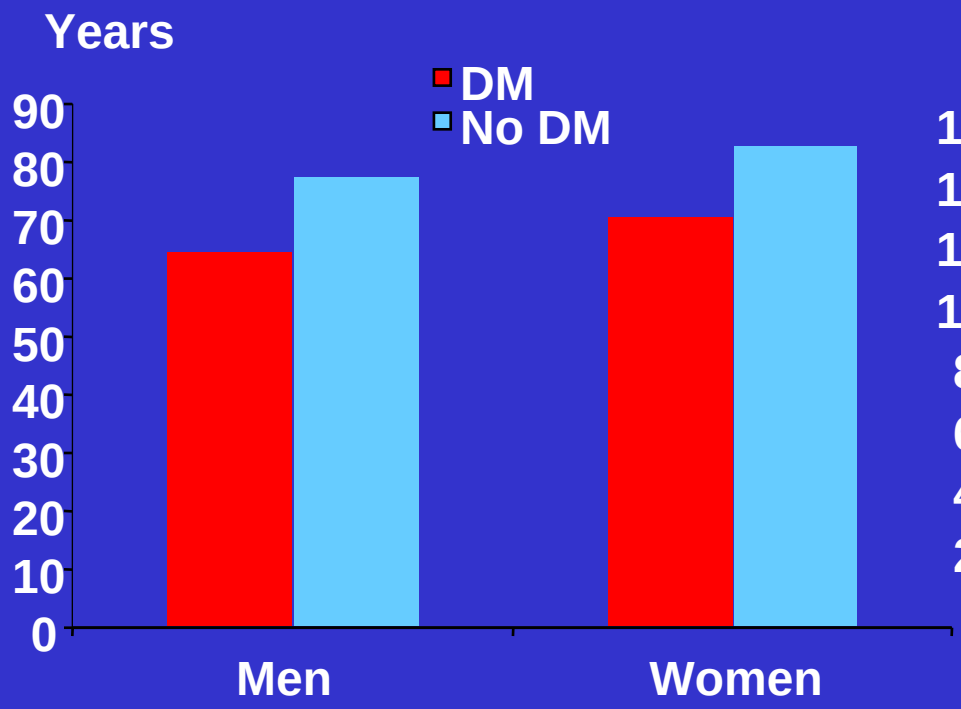
Renal disease

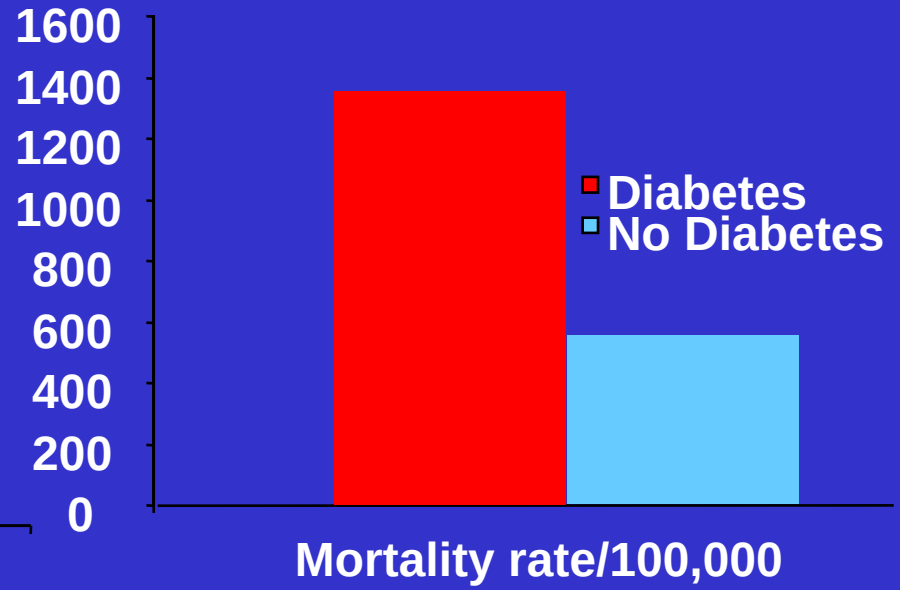
Neuropathy

Foot problems

Epidemiologic Trends: Cardiovascular Disease and Diabetes

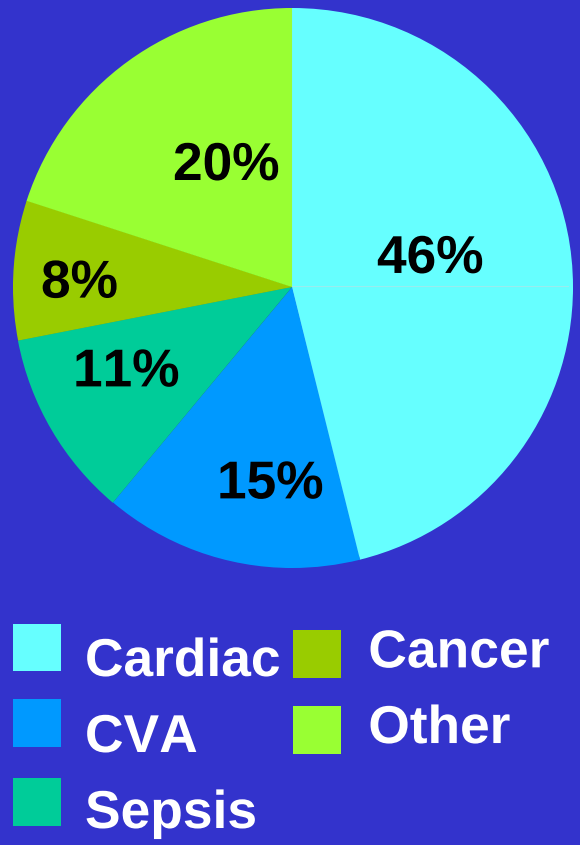
Life Expectancy with Diabetes





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

Causes of death in diabetes



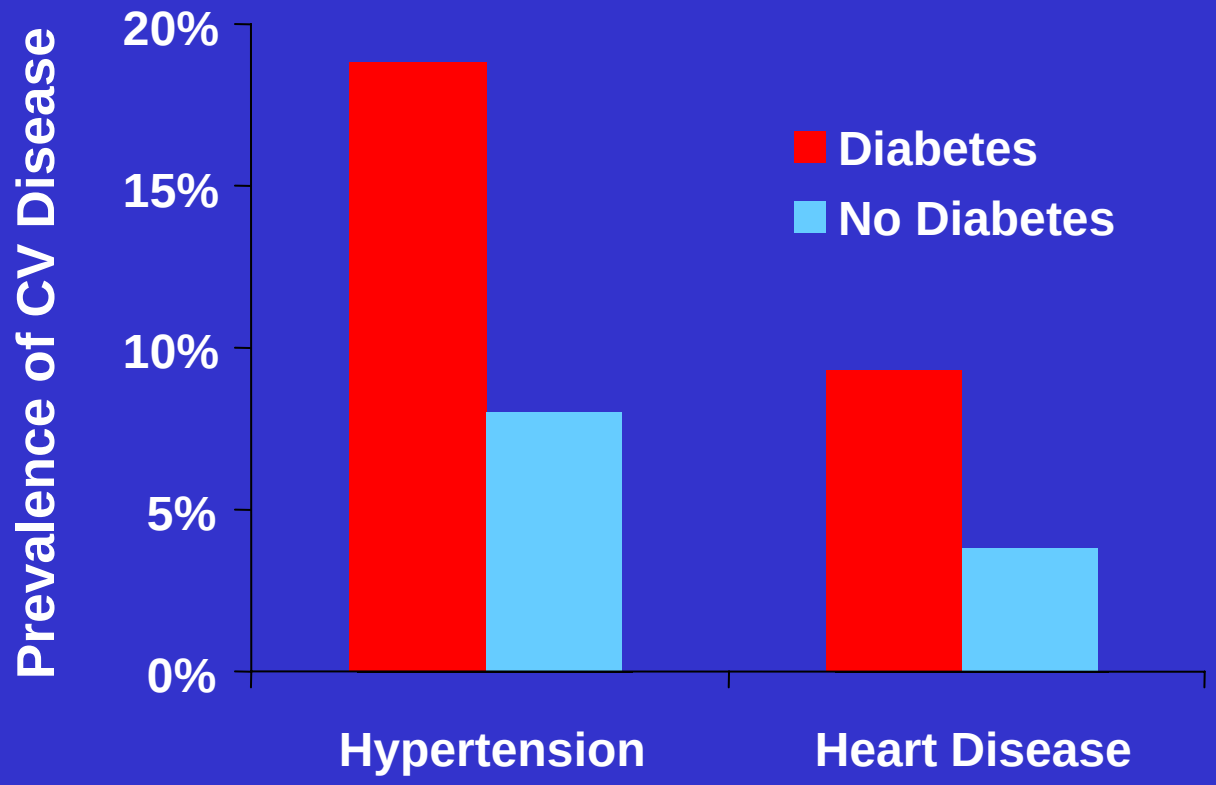
Cardiac disease and stroke accounts for

60%

of death in diabetes

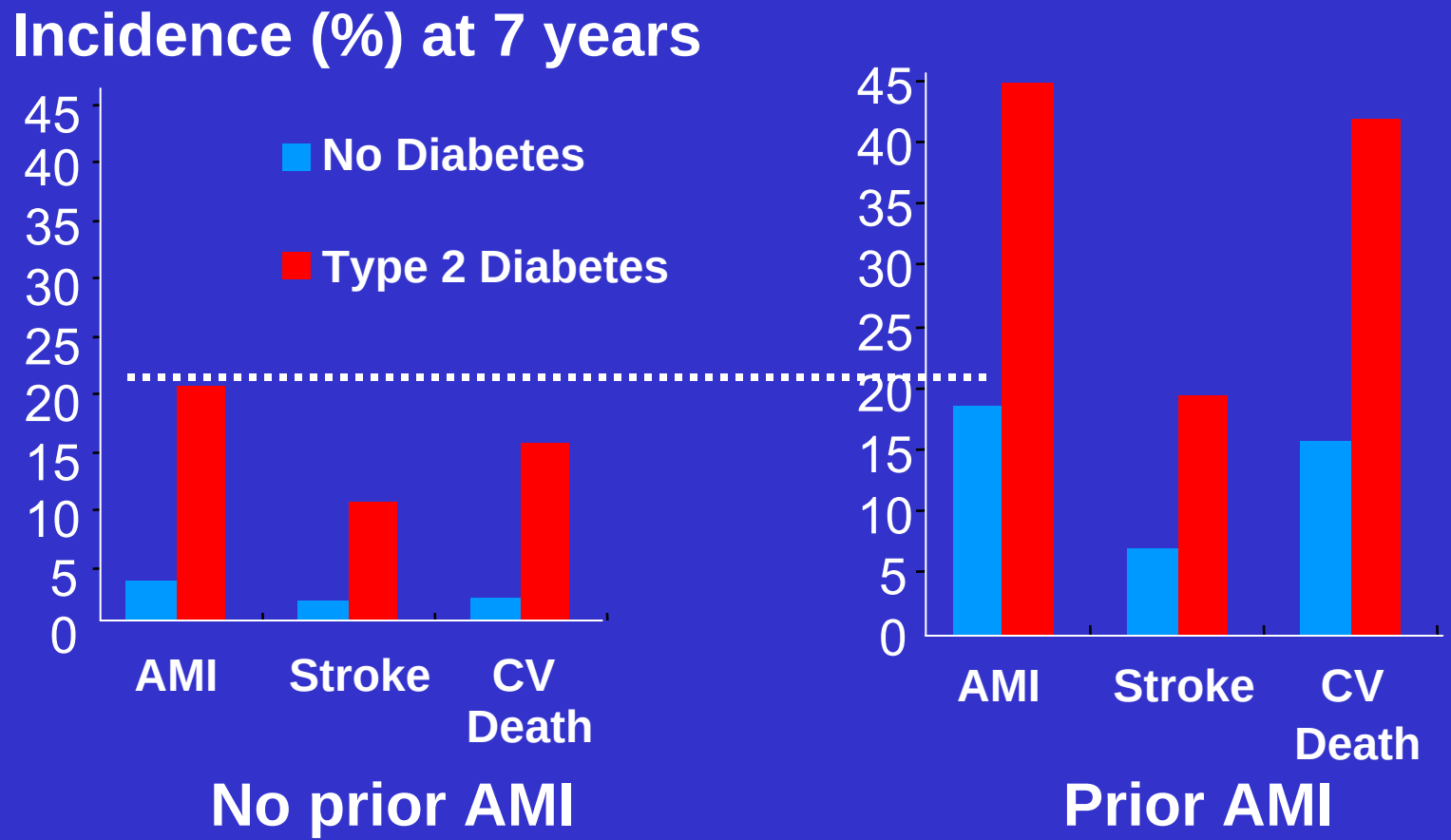
Hux JE, et al. Diabetes in Ontario, an ICES Practice Atlas 2003.

Prevalence of CVD in Ontario Men



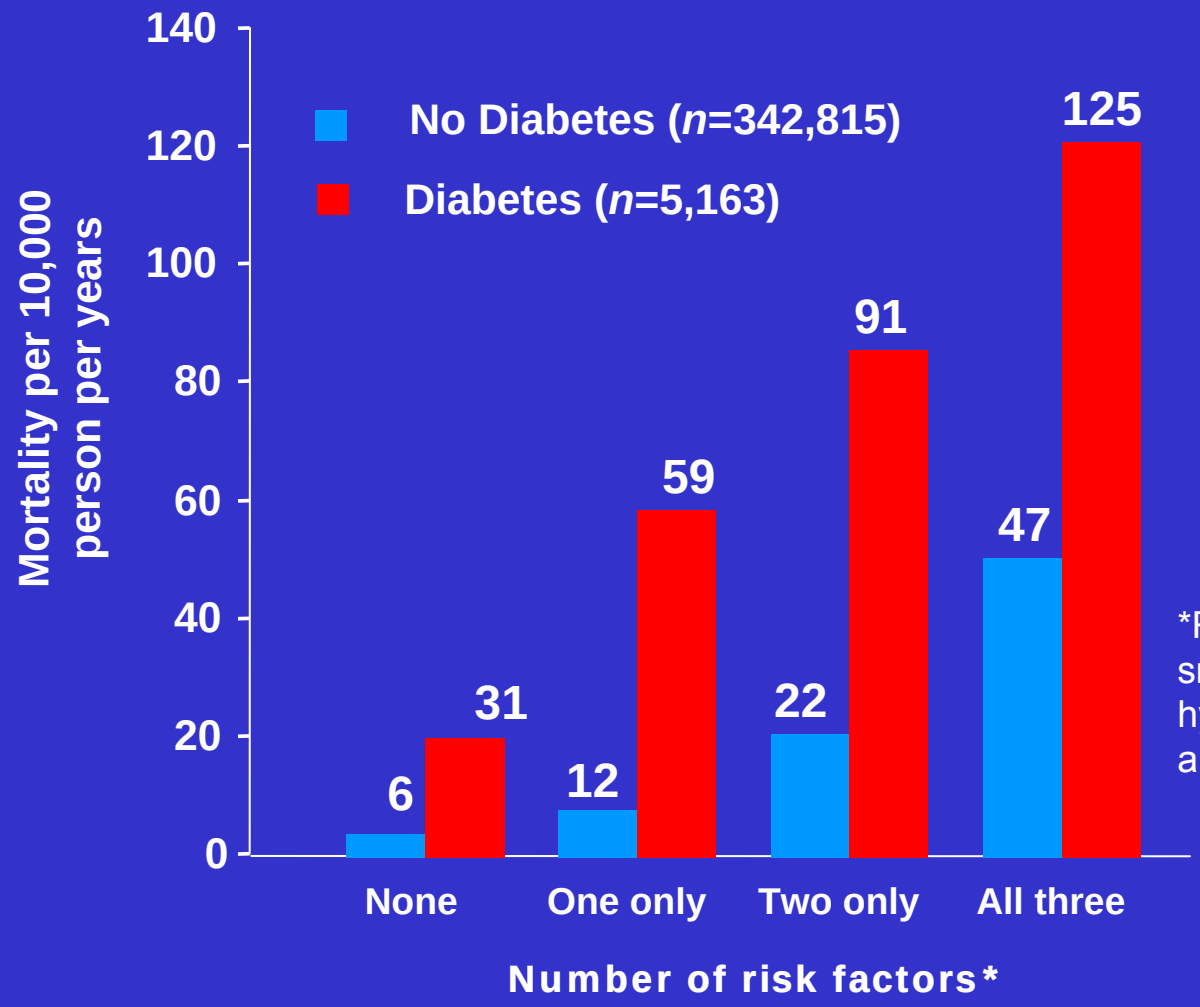
Hux JE, et al. Diabetes in Ontario, an ICES Practice Atlas 2003.

Cardiovascular Events in Type 2 DM



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

Impact of DM on CV Mortality (MRFIT)



*Risk factors analyzed: smoking, hypercholesterolemia, and hypertension.

Stamler J, et al. Diabetes Care 1993;16:434-444.

Glucose Intolerance in Chronic CAD

Fasting glucose in 1612 pts undergoing PCI

- **61%** had Glucose Intolerance
  - Known DM 24%
  - **Undiagnosed DM 18%**
  - **IFG (Glucose 6.1 – 6.9 mmol/L) 18%**

Mortality by Fasting Glucose (Average 2.8 yrs)

Normal (≤ 6.0 mmol/L)	1.9%	
IFG	6.6%	p=0.002
Undiagnosed DM	9.5%	p<0.001
DM	11.2%	p<0.001

Muhlestein, et al. Am Ht J 2003;146:351.

Cardiovascular Disease & DM

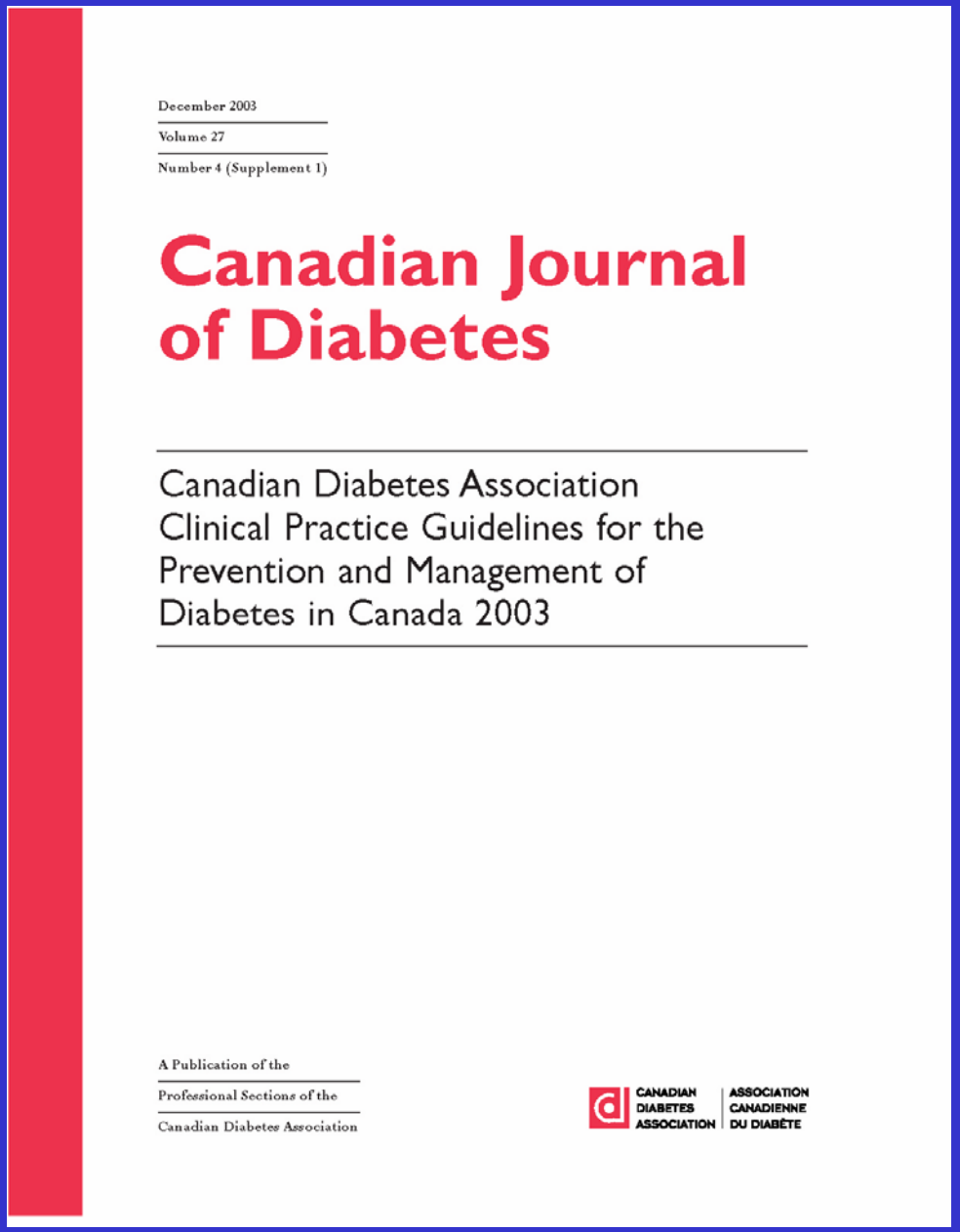
- CVD is 2-4 x more prevalent in DM
- CVD prevalence increases with age
  - Age 18-44 yrs 4%, >65 yrs 20%
- DM erases the protection of female sex
- Dysglycemia (IGT and IFG) is a risk factor for cardiovascular mortality

What should be done about this?

PREVENTION IS THE KEY!!

2003 Canadian Diabetes Association Clinical Practice Guidelines

http://www.diabetes.ca



Cardiovascular Prevention:

Vascular Protection

CDA Guidelines

Cardiorenal Prioritization

1. Vascular Protection

2. Hypertension Control

3. Control of Nephropathy

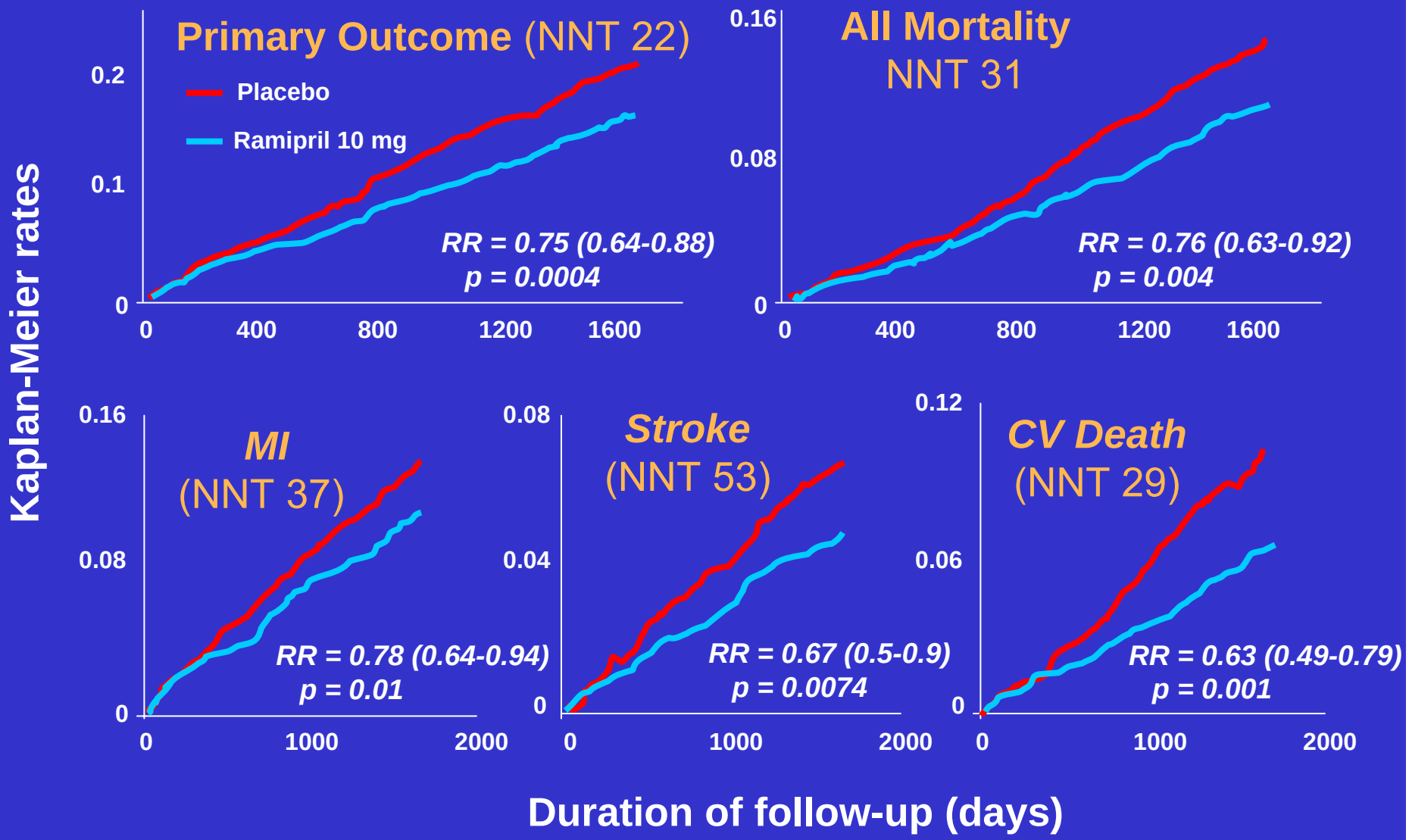
Components

- ACE-inhibitors
- Aspirin therapy
- Blood pressure control
- Lipid-lowering therapy
- Glycemic control
- Smoking cessation
- Lifestyle modifications

Vascular and metabolic effects of ACE-inhibition

- *Lowering Angiotensin-2 ….*
  - ↓ blood pressure
  - ↓ smooth muscle proliferation, LVH
  - ↓ vasoconstriction
  - ↓ endothelin, PAI-1
  - ↓ platelet aggregation, coagulation
  - ↓ vasoconstriction
  - ↓ pancreatic ischemia
  - ↓ potassium loss
  - ↓ noradrenaline
  - ↓ lipolysis & FFA
  - ↓ (?) hepatic glucose flux
  - ↑ (?) preadipocyte → adipocyte
- *Raising bradykinin ….*
  - ↑ NO, PGI-2
  - ↑ vasodilatation
  - ↓ platelet adhesion
  - ↓ smooth muscle proliferation
  - ↑ skeletal blood flow
  - ↑ insulin induced vasodilatation
  - ↑ peripheral glucose uptake
  - ↓ (?) inflammation

Micro-HOPE: CV benefits



EUROPA

Population: **12,218 people w/CAD (1502 had diabetes)**

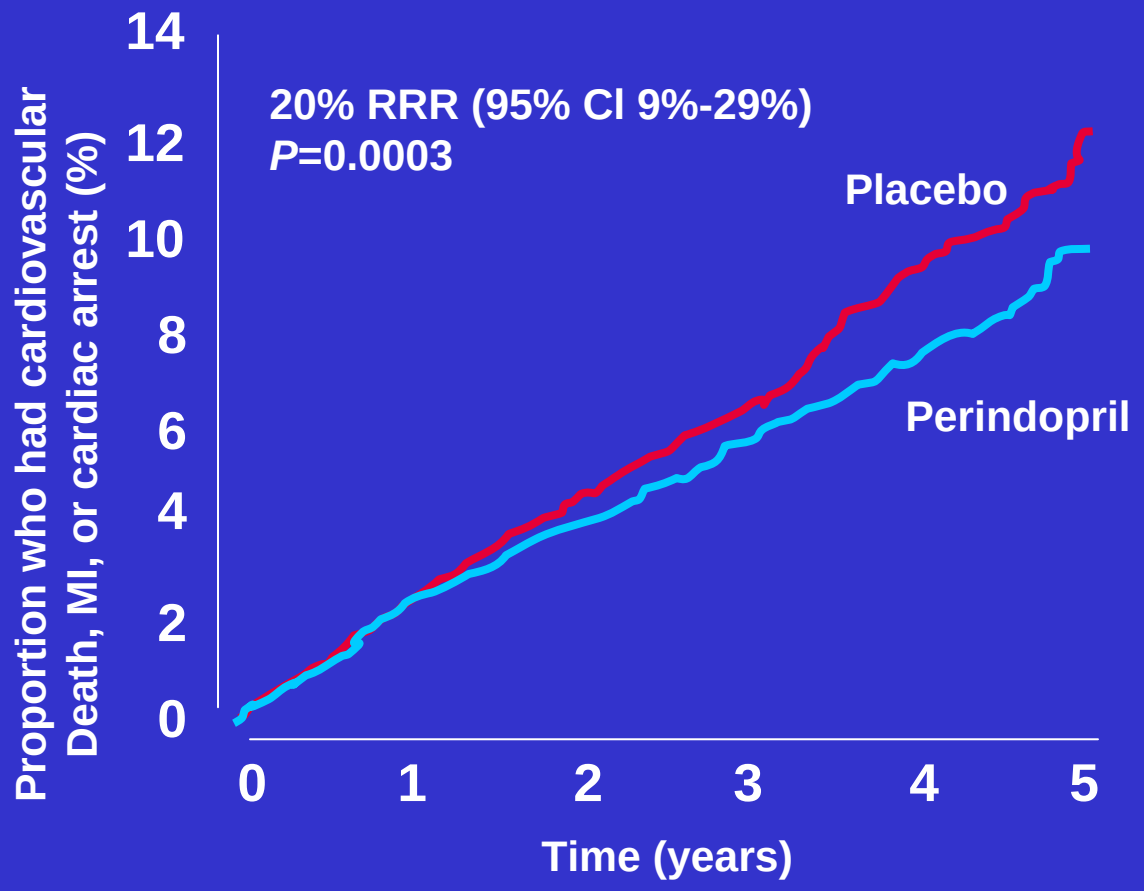
Intervention: **perindopril 8 mg vs placebo**

Mean follow-up: **4.2 years**

Primary outcome: **MI or cardiac arrest or CV death (stroke NOT included)**

Secondary outcomes: **all-cause death**

Results: **RRR 20% (RR 0.80; 95% CI 0.71-0.91) for primary outcome Diabetes (RR 0.87; 95% CI 0.68-1.04)**



Patients at risk

Placebo	6108	5943	5781	5598	4450	71
Perindopril	6110	5957	5812	5653	4515	64

EUROPA Investigators, Lancet 2003;362(9386):782-788.

PROGRESS

- N=6105, previous CVA or TIA
- Perindopril-based vs placebo
- 761 had DM, FU 3.9 yrs
- Outcome: recurrent stroke

	Diabetes	No diabetes
RRR	38%	28%
CI	(8-58%)	(16-39%)

Berthet K. *Blood Pressure* 2004;13:7-13.

PEACE

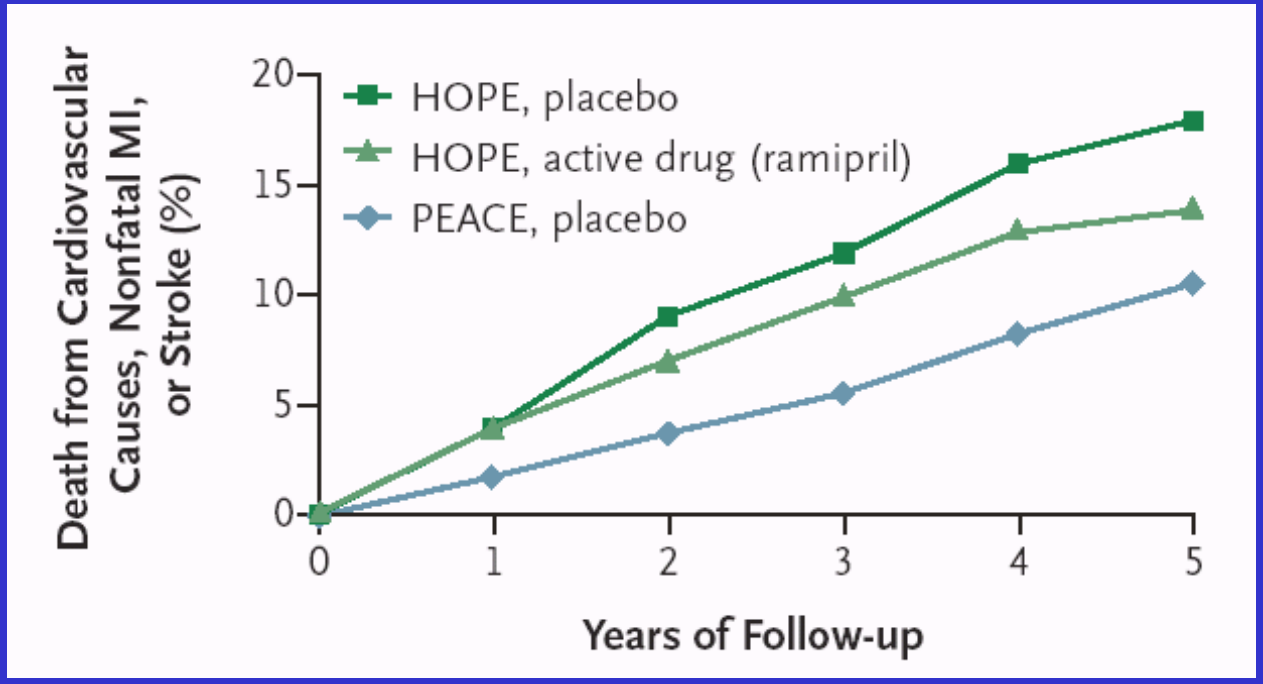
- N = 8290, >50y, stable CAD, norm LVF
- Trandolapril 4 mg OD vs. placebo
- Primary end-point:
  - CV death, nonfatal MI, coronary revasc
- Median follow-up 4.8 years

	Trandolapril	Placebo	
Incidence	21.9%	22.5%	NS

Peace Trial Investigators. *N Engl J Med* 2004;351:2058-68.

PEACE

- More patients “intensively” treated
- More lipid-lowering therapy
- More revascularization



PEACE Trial Investigators. *NEJM* 2004;351:2058-2068.

Summary: ACE-I (vascular protection)

- Antihypertensive, vascular protective, antithrombotic, & anti-inflammatory
- Reduce vascular events (e.g. ramipril, perindopril)
- Reduce atherosclerosis
- Reduce renal disease (& renal disease is a strong CV risk factor)

Components

- ACE-inhibitors
- Aspirin therapy
- Blood pressure control
- Lipid-lowering therapy
- Glycemic control
- Smoking cessation
- Lifestyle modifications

Aspirin therapy: Primary prevention

- First MI: RRR 32%
- All vascular event: RRR 15%
- Nonfatal stroke: NS reduction
- Vascular death: NS reduction

- Safe in patients with diabetes

Eidelman RS. *Arch Intern Med* 2003;163:2006

Aspirin therapy: Secondary prevention

- Meta-analysis
- All-cause mortality: RRR 18%
- Stroke: RRR 20%
- MI: RRR 30%
- Other vascular events: RRR 30%
- NNT prevent one death = 67

Weisman SM. *Arch Intern Med* 2002;162:2197.

Aspirin therapy: Secondary prevention

- 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)

Harpaz, et al. Am J Med 1998;105:494.

Summary: ASA therapy

ASA (80-325 mg daily) if:

- > 30 years
- Atherosclerotic risk factors

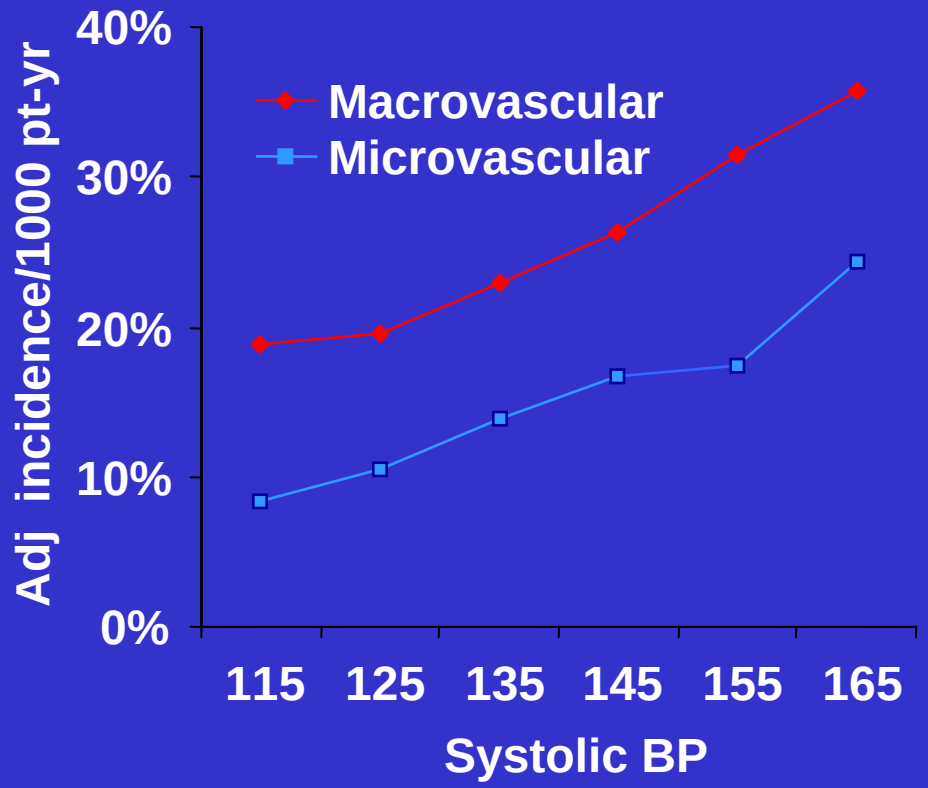
or

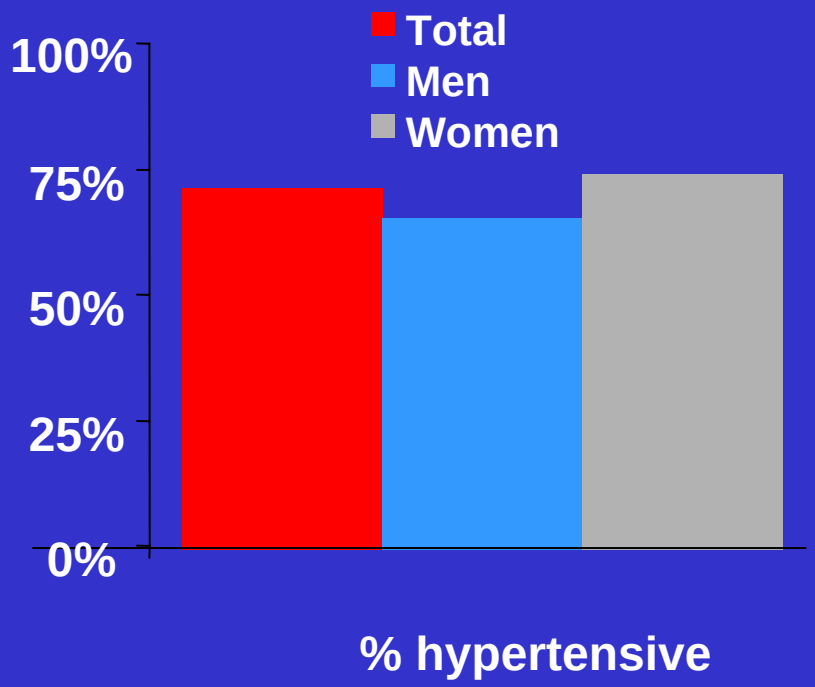
- Vascular disease

Components

- ACE-inhibitors
- Aspirin therapy
- Blood pressure control
- Lipid-lowering therapy
- Glycemic control
- Smoking cessation
- Lifestyle modifications

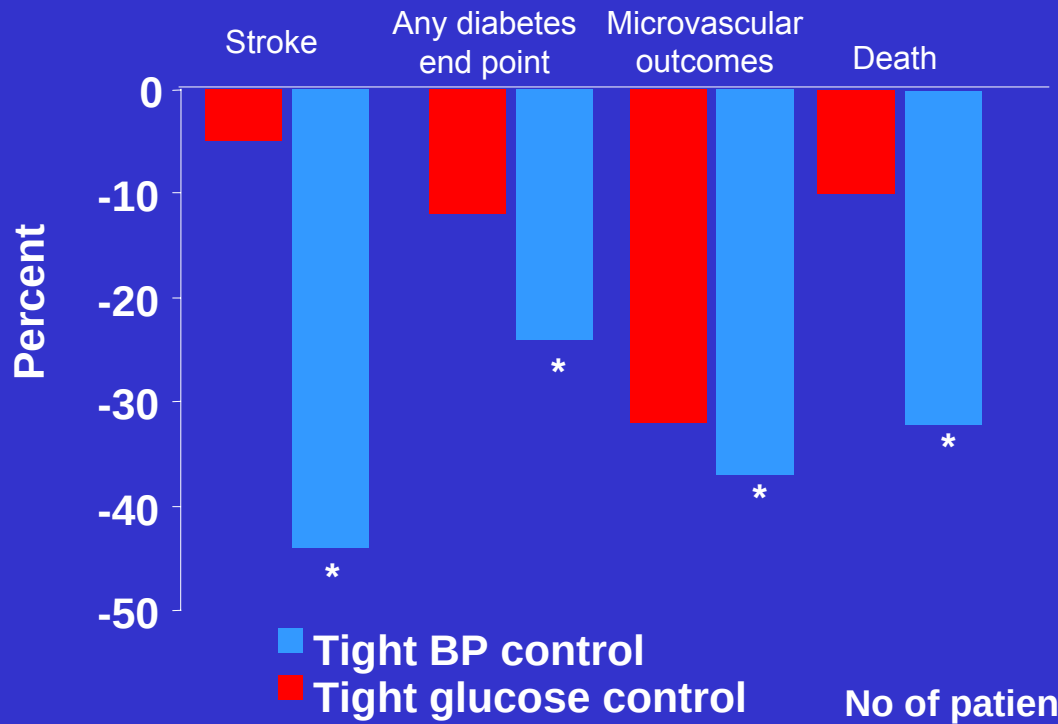
Diabetes & HTN

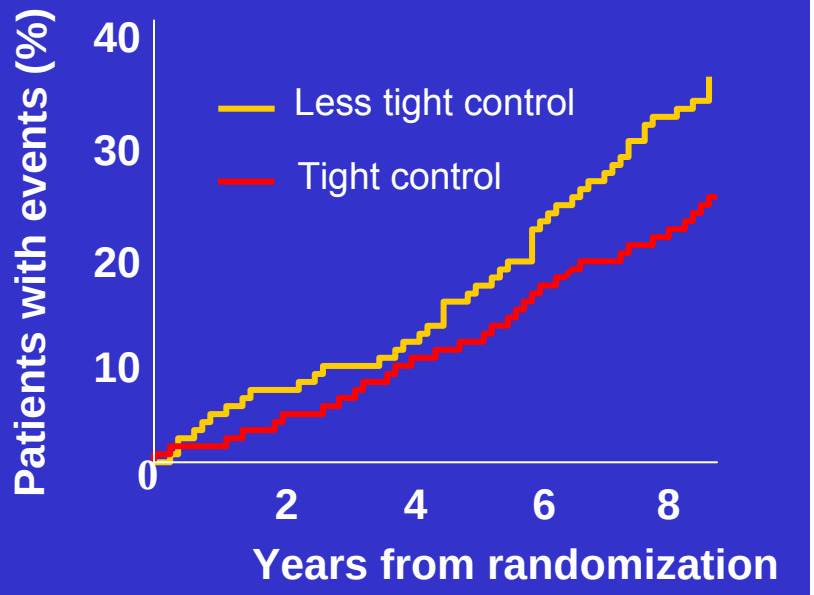




Adler AI, et al. BMJ 2000;321(7258):412-419.

UKPDS





*P<0.05.
Tight BP control = 144/82 mm Hg. Tight glucose control = HbA_{1c} = 7.0%.

No of patients at risk:

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)

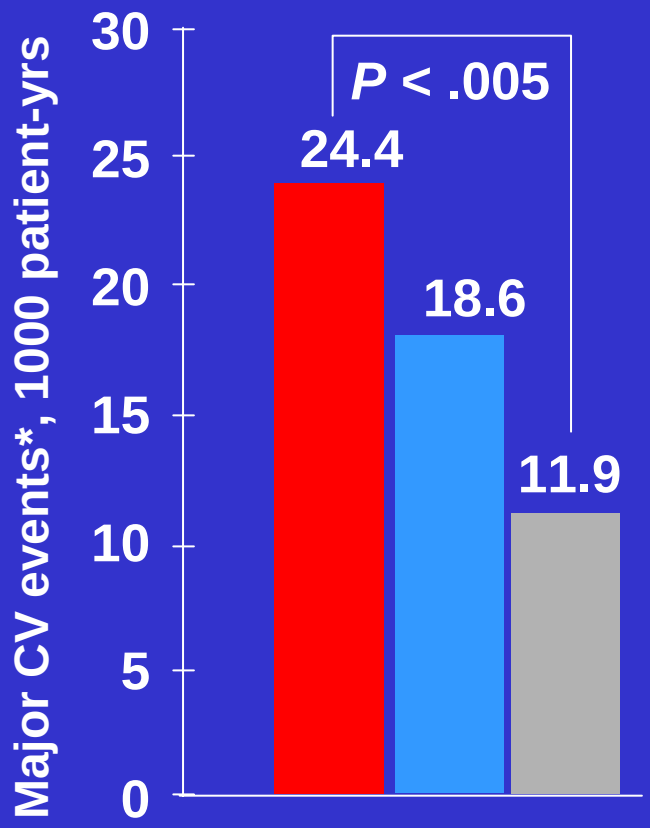
UKPDS Group. BMJ 1998;317:703. UKPDS Group. BMJ. 1998;317:713.

HOT Trial

Diabetes Subgroup

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

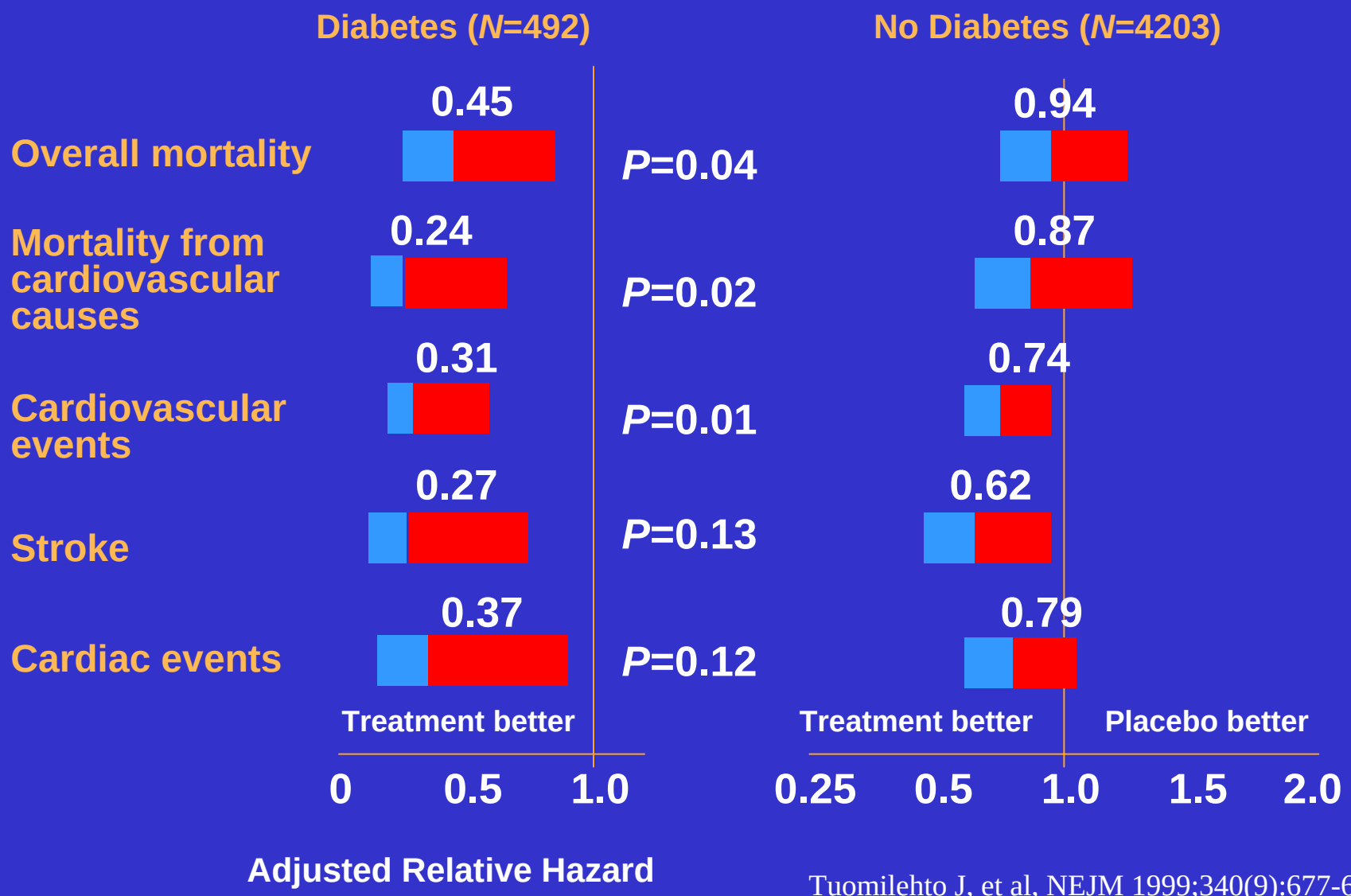
† Achieved = Mean of all BPs from 6 months of follow-up to end of study



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

Hansson L, et al. Lancet. 1998;351:1755–1762.

Reduces the risk …



Tuomilehto J, et al, NEJM 1999;340(9):677-684.

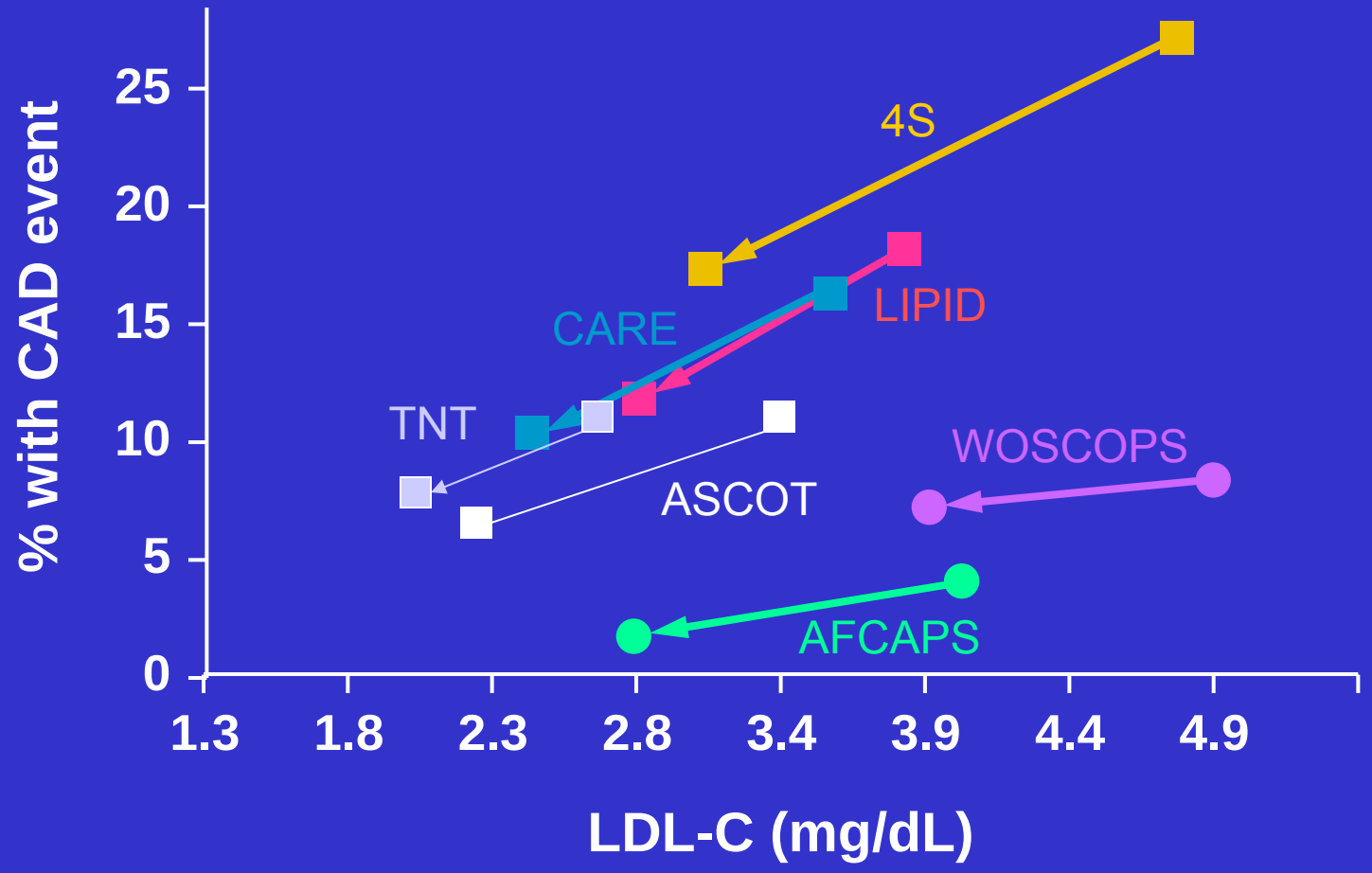
Summary: BP control

- Target ≤ 130/80 mmHg

Components

- ACE-inhibitors
- Aspirin therapy
- Blood pressure control
- Lipid-lowering therapy
- Glycemic control
- Smoking cessation
- Lifestyle modifications

Lipid-lowering reduces CVD risk



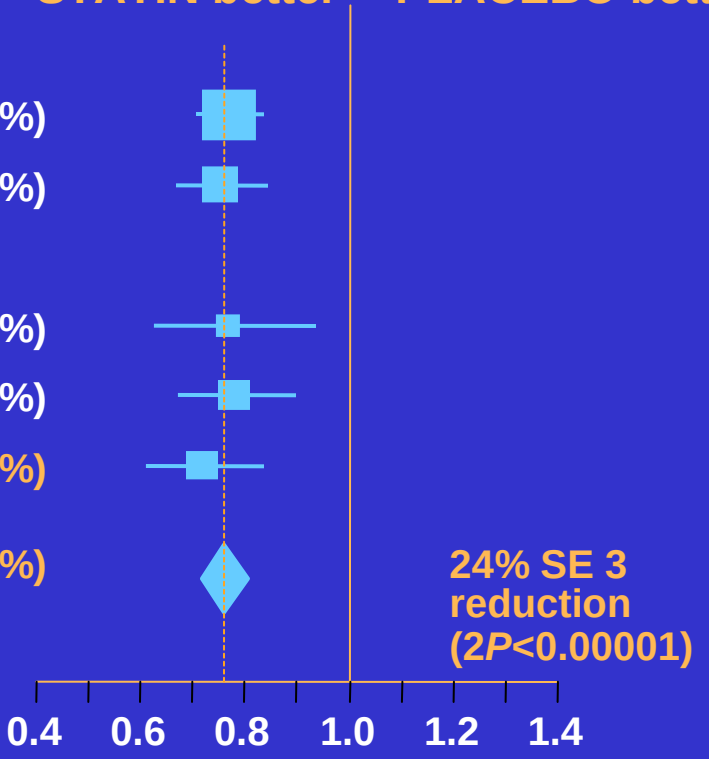
Statins in DM: subgroup analyses

Study	Drug	N	CHD Risk Reduction (overall)	CHD Risk Reduction (diabetes)
Primary Prevention				
AFCAPS/TexCAPS	Lovastatin	239	37%	43%
Secondary Prevention				
CARE	Pravastatin	586	23%	25% (*p*=0.05)
4S	Simvastatin	202	32%	55% (*p*=0.002)
LIPID	Pravastatin	782	25%	19%
4S-Extended	Simvastatin	483	32%	42% (*p*=0.001)

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.

HPS

	SIMVASTATIN (10269)	PLACEBO (10267)
Previous MI	999 (23.5%)	1250 (29.4%)
Other CHD (not MI)	460 (18.9%)	591 (24.2%)
No prior CHD		
CVD	172 (18.7%)	212 (23.6%)
PVD	327 (24.7%)	420 (30.5%)
Diabetes	276 (13.8%)	367 (18.6%)
ALL PATIENTS	2033 (19.8%)	2585 (25.2%)



HPS *Lancet* 2002;360:7-22

VA-HIT:
Nonfatal MI, stroke and CVD death

	*Placebo**	*Gemfibrozil**	*Risk Reduction*	*P Value*
Diabetes	**116/318 (36)**	**88/309 (28)**	**24%**	**0.05**
No diabetes	**214/949 (23)**	**170/955 (18)**	**24%**	**0.009**

*Values are numbers with events/total numbers (%).

Adapted from Rubins HB, et al. N Engl J Med 1999;341:410-418.

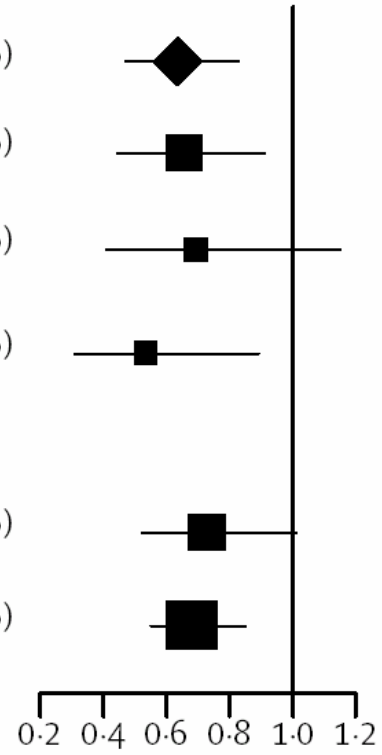
CARDS

- n = 2838
- Age 40-75, no history of CVD
- T2DM plus one or more:
  - Retinopathy
  - Albuminuria
  - Hypertension
  - Smoking
- Intervention: atorvastatin 10 mg vs placebo
- Outcome: ACS, revascularization, stroke

Colhoun HM, et al. *Lancet* 2004;364:685.

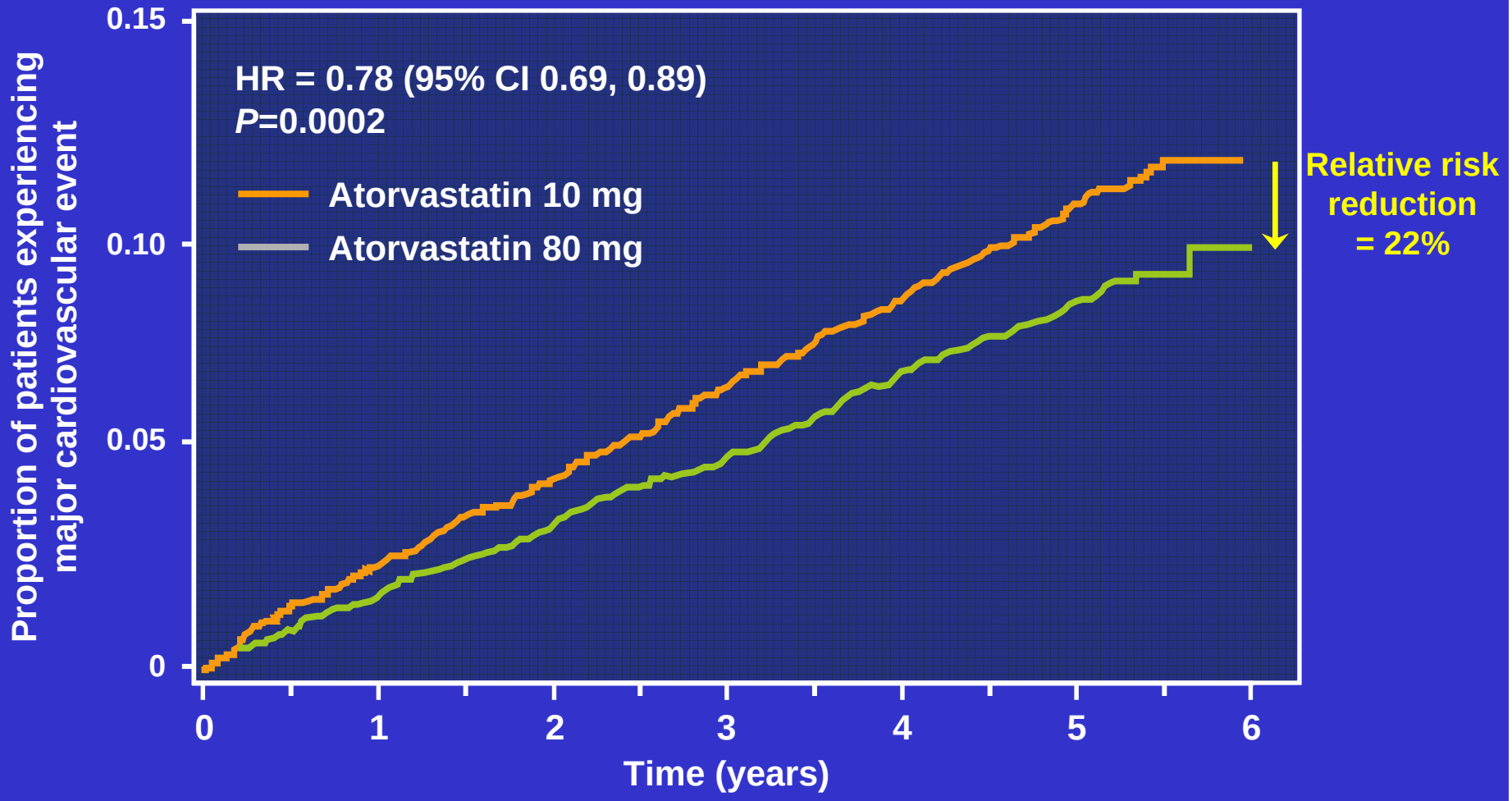
CARDS

	Number of patients with an event (%)		Hazard ratio (95% CI)	p
	Placebo	Atorvastatin 10 mg		
Primary endpoint	127 (9·0%)	83 (5·8%)	0·63 (0·48–0·83)	0·001
Acute coronary events	77 (5·5%)	51 (3·6%)	0·64 (0·45–0·91)	
Coronary revascularisation	34 (2·4%)	24 (1·7%)	0·69 (0·41–1·16)	
Stroke	39 (2·8%)	21 (1·5%)	0·52 (0·31–0·89)	
Secondary endpoint				
Death from any cause	82 (5·8%)	61 (4·3%)	0·73 (0·52–1·01)	0·059
Any acute cardiovascular disease event	189 (13·4%)	134 (9·4%)	0·68 (0·55–0·85)	0·001



Colhoun HM, et al. *Lancet* 2004;364:685.

TNT



*CHD death, nonfatal non–procedure-related MI, resuscitated cardiac arrest, fatal or nonfatal stroke

LaRosa JC, *et al. N Eng J Med.* 2005;352

Summary: lipid therapy

- Treat to target for all patients w/DM
- Consider treatment if at target but has other CV risk factors (CARDS, HPS)
- Maybe lower?

	LDL-c (mmol/L)	TC / HDL
High	< 2.5	< 4

Components

- ACE-inhibitors
- Aspirin therapy
- Blood pressure control
- Lipid-lowering therapy
- Glycemic control
- Smoking cessation
- Lifestyle modifications

A1c correlates with CVD risk: DM or non-DM

- Continuous relationship
  - A1c and CVD risk (cardiac or stroke)
  - A1c and all-cause mortality
- Similar for DM or non-DM
- A1c < 5% had lowest risk

Selvin E, et al. *Ann Intern Med* 2004;141:421.

Khaw KT, et al *Ann Intern Med* 2004;141:413..

Glycemic control reduces CVD risk

- Every 1.0% change in A1c:
  - 14% reduction in myocardial infarction
  - 16% reduction in heart failure
  - 12% reduction in stroke
  - 43% reduction in amputation or death from PVD

Stratton IM, *et al. BMJ* 2000;321:405-412.

Summary: glycemic control

	A1c (%)	Preprandial PG (mmol/L)	2-h postprandial PG (mmol/L)
For most patients	≤ 7.0*	4.0-7.0¶	5.0-10.0¶
Normal	≤ 6.0†	4.0-6.0†	5.0-8.0†

* Micro [Grade A, Level 1A], macro [Grade C, Level 3]

¶ Grade B, Level 2 † Grade D, consensus

Components

- ACE-inhibitors
- Aspirin therapy
- Blood pressure control
- Lipid-lowering therapy
- Glycemic control
- Smoking cessation
- Lifestyle modifications

CDA Guidelines 2003 and Smoking

- Smoking cessation is a priority for achieving vascular protection.
- Smoking cessation reduces the risk of foot ulceration/amputation (Grade B, Level 2)
- Smoking is a risk factor for erectile dysfunction

Lifestyle related strategies

- Achieve and maintain healthy body weight
  - Improve BP, increase insulin sensitivity
- Decrease saturated and trans fatty acids
- Use of lower glycemic index carbs
- Increase physical activity
- Limit sodium, alcohol, and caffeine

STENO-2 :

Proven benefit of Vascular Protection Approach to diabetes

- N = 160 patients T2DM + MAU randomized
- 8 years of follow-up
- **Intervention Group**
  - Behavioral & drug therapies
  - Targets in glycemia, lipids, BP & microalbuminuria
  - Multidisciplinary care q3months
  - ASA & ACE inhibitors for vascular protection
- **Control Group**
  - Conventional DM by family MD +/- specialist
  - aimed at achieving clinical practice guideline targets

Gaede P, et al. NEJM, 2003;348(5):383-393.

Treatment targets

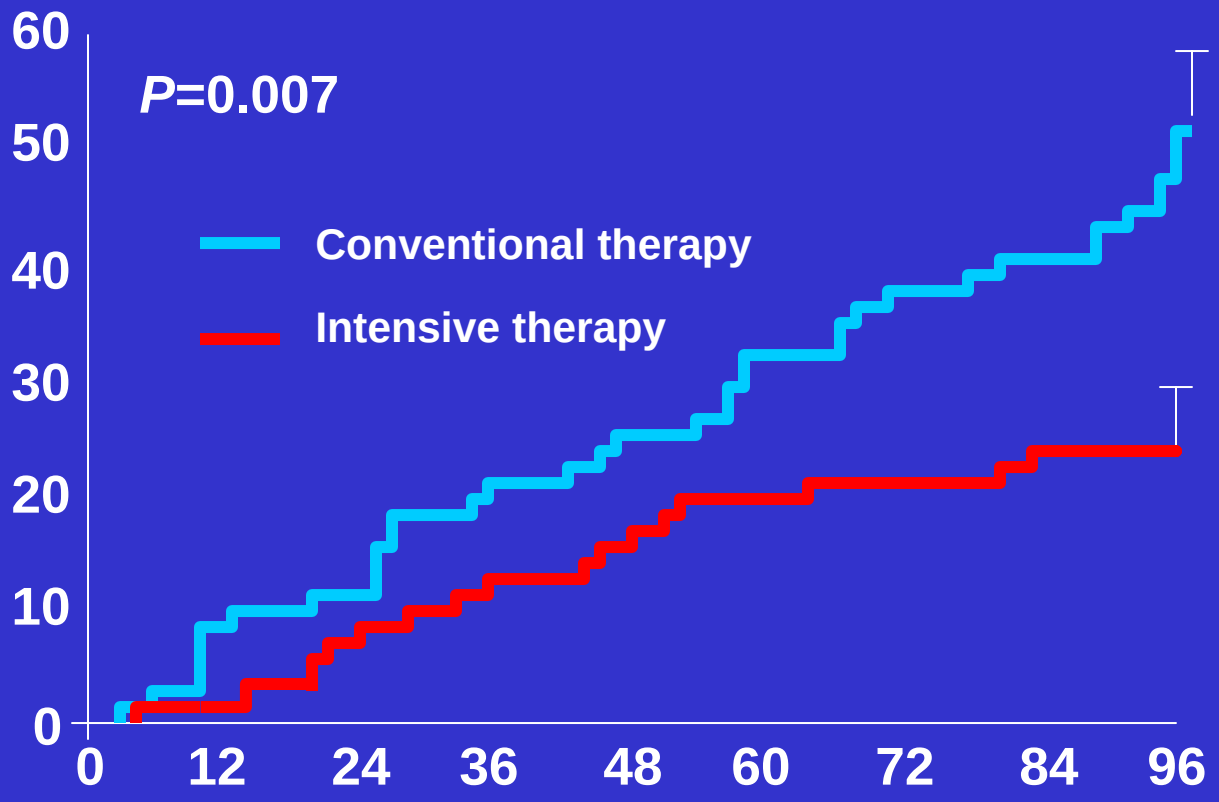
	Conventional		Intensive	
	1993-1999	2000-2001	1993-1999	2000-2001
ACE-I	No	Yes	No	Yes
A1c	<7.5%	<6.5%	<6.5%	<6.5%
TC (mmol/L)	<6.5	<4.9	<4.9	<4.5
TG (mmol/L)	<2.2	<2.0	<1.7	<1.7
BP	<160/95	<135/85	<140/85	<130/80

Gæde P *et al. New Engl J Med* 2003;348:383-393

Combined CV Outcomes

RR 0.53

NNT 5



No. at Risk									
Conventional Therapy	80	72	70	63	59	50	44	41	13
Intensive therapy	80	78	74	71	66	63	61	59	19

Gaede P, et al, NEJM 2003;348(5):383-393

Therefore …

- Aggressive multifactorial care can reduce cardiovascular risk
- CDA 2003 guidelines: vascular protection as the first priority of DM care
  - ACE inhibition, ASA, lipid, BP, smoking cessation, glycemic control, lifestyle

Erectile Dysfunction (ED)

ED Prevalence

- Persistent (at least 6 months) inability to attain and maintain erection sufficient to permit satisfactory sexual performance

- 40-70% of men with diabetes
- 65% untreated

Giuliano FA et al. Urology 2005;64:1196.
2003 CDA Practice Guidelines

Risk Factors for ED

- Age
- Duration of DM
- Poor glycemic control
- Cigarette smoking
- Hypertension
- Dyslipidemia
- Cardiovascular disease

Etiology in DM

- Microvascular disease
- Macrovascular disease
- Neuropathy
- Medications (antihypertensives)

Screening

- All adult men should be screened periodically for ED
- Screening should begin at diagnosis

Grade D consensus

Treatment

- Non-pharmacologic

- Pharmacologic
  - PDE5-inhibitors
    - Enhance NO action = relax corpus cavernosal
  - Intracorporal injection
  - Intraurethral injection
  - Vacuum, penile prosthesis

PDE5 Inhibitors
sildenafil, vardenafil, tadalafil

- First line treatment (Grade A, Level 1)

- Contraindications
  - Nitrate use, unstable CAD
- Adverse effects
  - Headache, flushing, nasal congestion, dyspepsia

PDE5 Inhibitors

- Still requires sexual stimulation
- May need to try many times
- Food delays action (except tadalafil)

- Sildenafil (Viagra) – up to 12 hours
- Vardenafil (Levitra) – up to 12 hours
- Tadalafil (Cialis) – up to 25-36 hours

Referral if …

- No response to PDE5-inhibitor
- Contraindication to PDE5-inhibitor

Grade D consensus

Summary

Summary

- Cardiovascular disease is COMMON
- CVD is #1 cause of death among DM
- Prevention is the key:
  - ACE-I, ASA
  - BP (<130/80)
  - glucose (A1c < 7% or < 6%)
  - Lipids (LDL < 2.5 and ratio <4)
  - lifestyle, smoking cessation

Summary

- Erectile dysfunction is COMMON
- Must screen effectively
- PDE5-inhibitors are FIRST-LINE
- Referral if above not successful or contrainidicated

Thank you for your attention

Questions??