

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

Diabetic Vasculopathy:

Impact of Gender

By

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Introduction

- **CVD is the commonest cause of mortality all over the world in both male and female especially the later (55% Vs 43%)**
- **There is a common myth among young females that breast cancer is most important danger to them**
- **Diabetes mellitus is a powerful predictor & risk factor of CHD and carries a worse prognosis in women than in men.**

Introduction

- **Diabetic women more commonly have coexisting risk factors. For example, the metabolic syndrome**
- **When diabetics who survived an initial MI were studied, women were at twice the risk of men for recurrence of infarction.**
- **Diabetic women are also at high risk for cardiac failure than non-diabetic (4 fold)**

The Interaction Of Gender & Diabetes **In Cardiovascular Disease**

Women with Type 2 Diabetes have a greater relative risk of CHD morbidity and mortality than men. Is it due to...

- Failure to diagnose CHD
- Misdiagnoses and under treatment in women occur despite classic symptom description, possibly reflecting a preconceived notion that women are somehow "protected" from CV disease.
- Treatment gap for MI, CHF, Prevention
- More atherogenic CV risk factor profile
- Female gender-risk factor synergy

The Interaction Of Gender & Diabetes *In Cardiovascular Disease*

Women with Type 2 Diabetes have a greater relative risk of CHD morbidity and mortality than men. Is it due to...

- Risk factor and end-organ interaction
- Inherent difference in CV pathobiology
- Estrogen-Androgen “Switch”
- Gender-Insulin sensitivity/resistance issue
- "women with diabetes seem to lose most of their inherent protection against developing CVD"

And what are the implications for treatment ?

Cardiovascular Risk Factors in Women

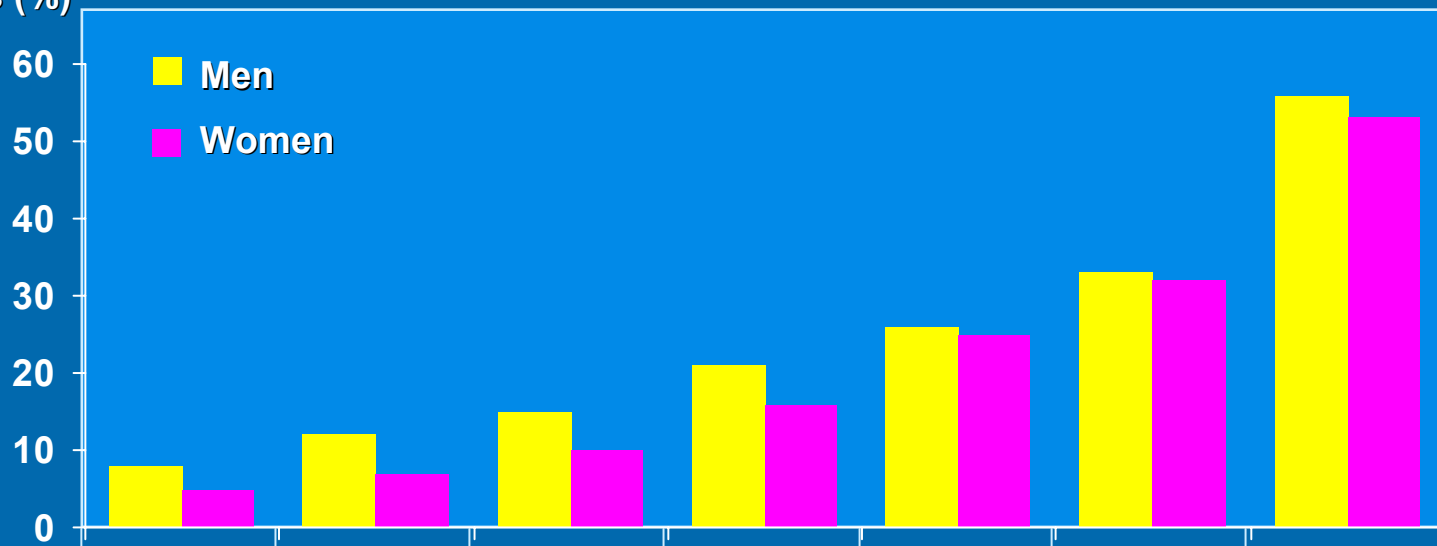
TABLE 1. Spectrum of CVD Risk in Women

Risk Group	Framingham Global Risk (10-y Absolute CHD Risk)	Clinical Examples
High risk	>20%	<ul style="list-style-type: none">• Established CHD• Cerebrovascular disease*• Peripheral arterial disease• Abdominal aortic aneurysm• Diabetes mellitus• Chronic kidney disease†
Intermediate risk	10% to 20%	<ul style="list-style-type: none">• Subclinical CVD‡ (eg, coronary calcification)• Metabolic syndrome• Multiple risk factors§• Markedly elevated levels of a single risk factor • First-degree relative(s) with early-onset (age: <55 y in men and <65 y in women) atherosclerotic CVD
Lower risk	<10%	<ul style="list-style-type: none">• May include women with multiple risk factors, metabolic syndrome, or 1 or no risk factors
Optimal risk	<10%	<ul style="list-style-type: none">• Optimal levels of risk factors and heart-healthy lifestyle

Framingham Heart Study: Loss of Gender Protection Against CHD Events

Patients (%)

Estimated
10 year CAD
Event rate



Systolic BP mm Hg

120

180

160

160

150

180

180

Cholesterol, mg/dL

220

220

269

259

259

259

259

HDL-C, mg/dL

50

50

50

35

35

35

35

Diabetes Mellitus

-

-

-

-

+

+

+

Cigarette Smoking

-

-

-

-

-

+

+

LVH

-

-

-

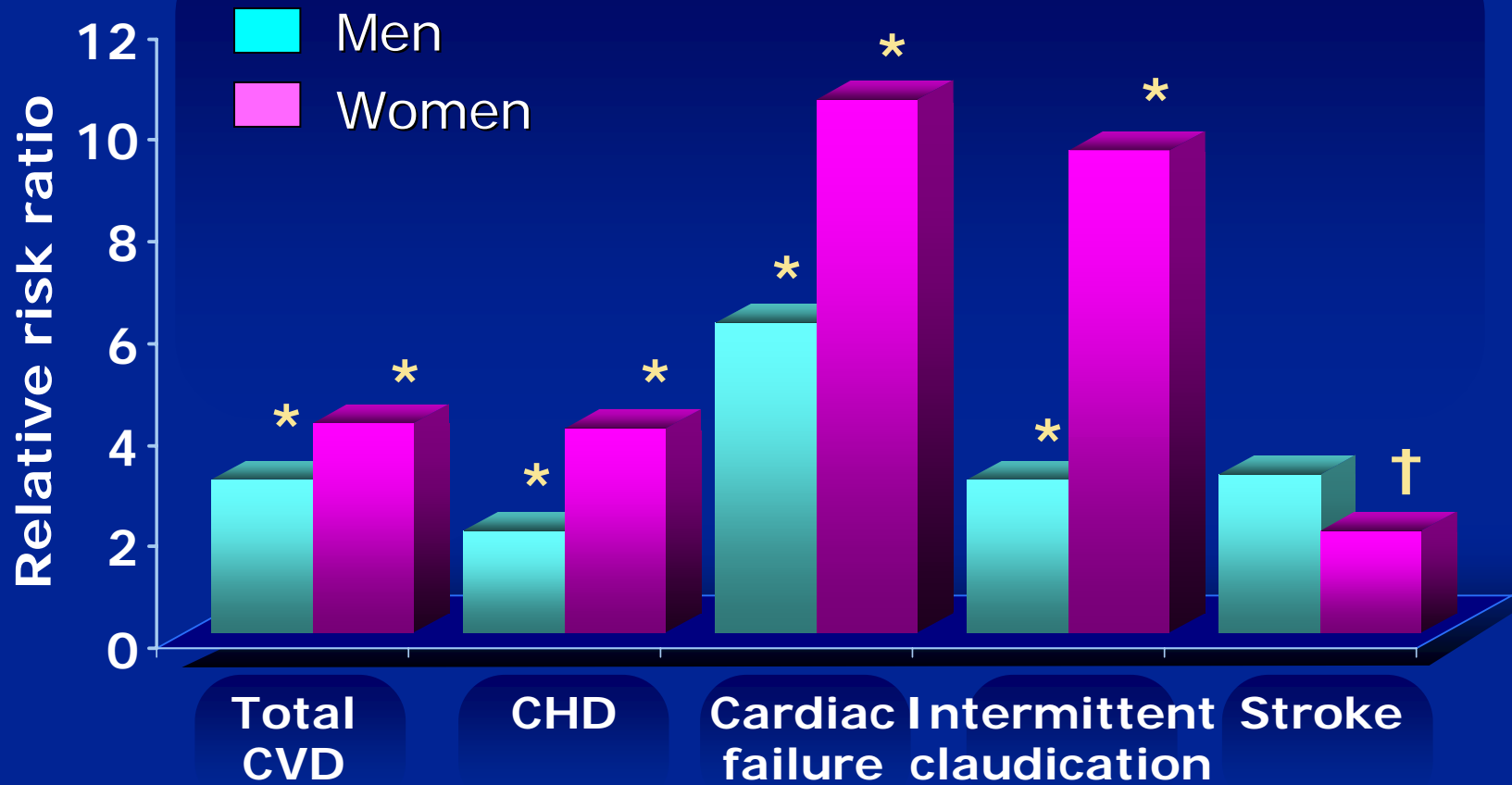
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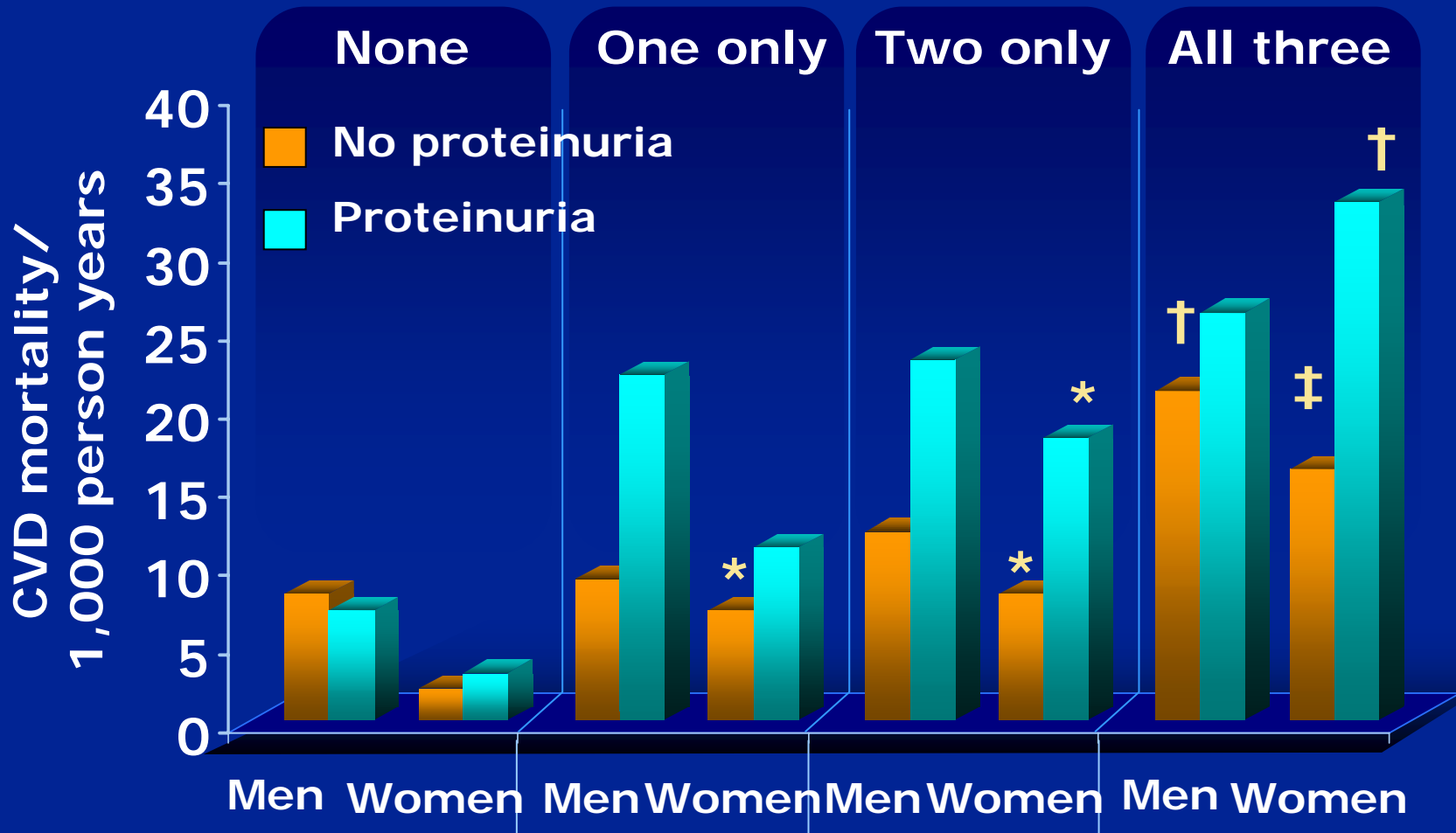
+

Framingham Heart Study CVD Events in Diabetics



CVD=cardiovascular disease CHD=coronary heart disease *P<0.01 †P<0.05

Age-Adjusted CVD Mortality by Number of Risk Factors in Type 2 Diabetics

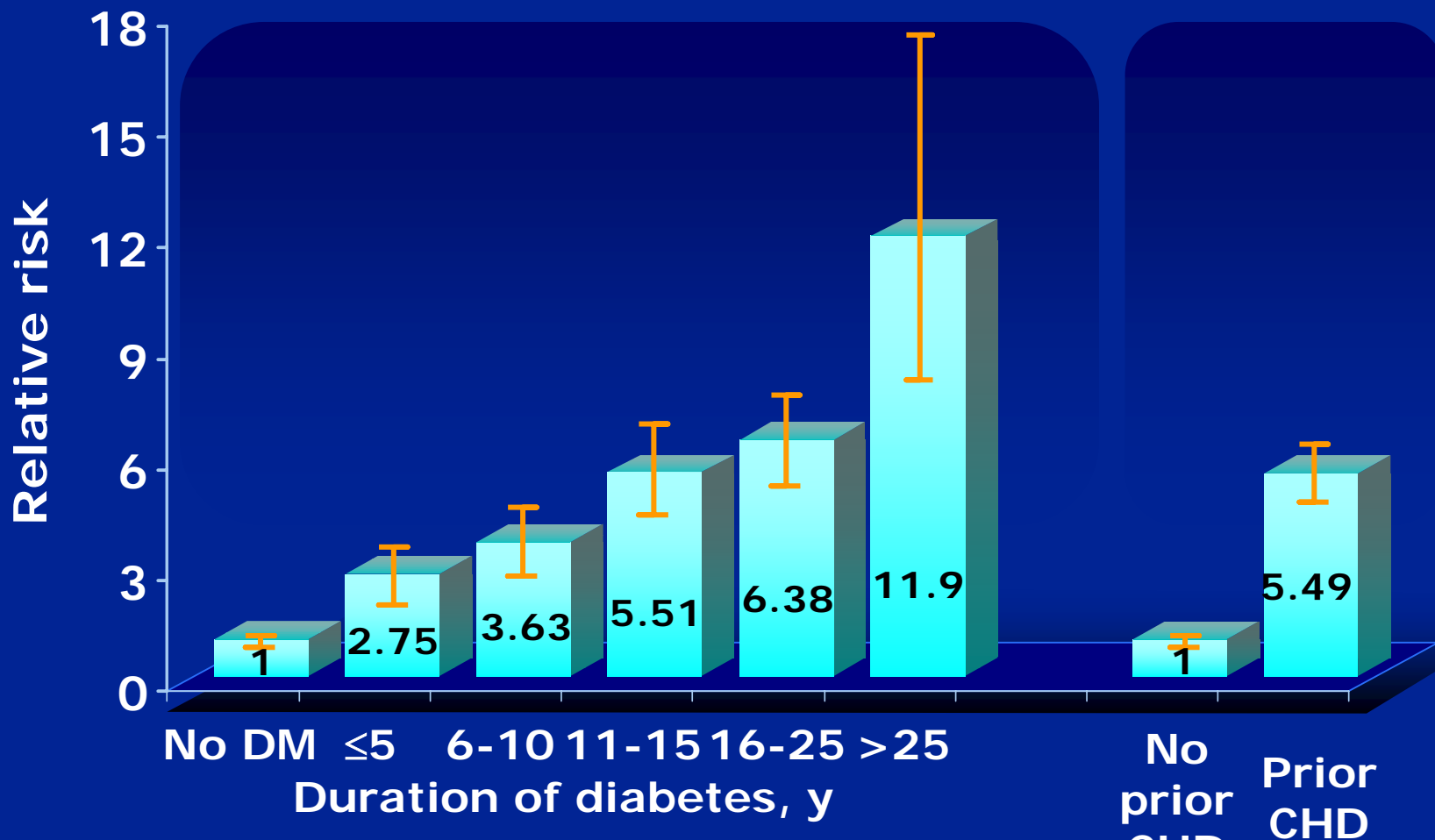


CVD=cardiovascular disease

For comparison of risk factors to "none" *P<0.05 †P<0.01 ‡P<0.001

Fuller JH, et al. Diabetologia. 2001;44[suppl2]:S54-S64.

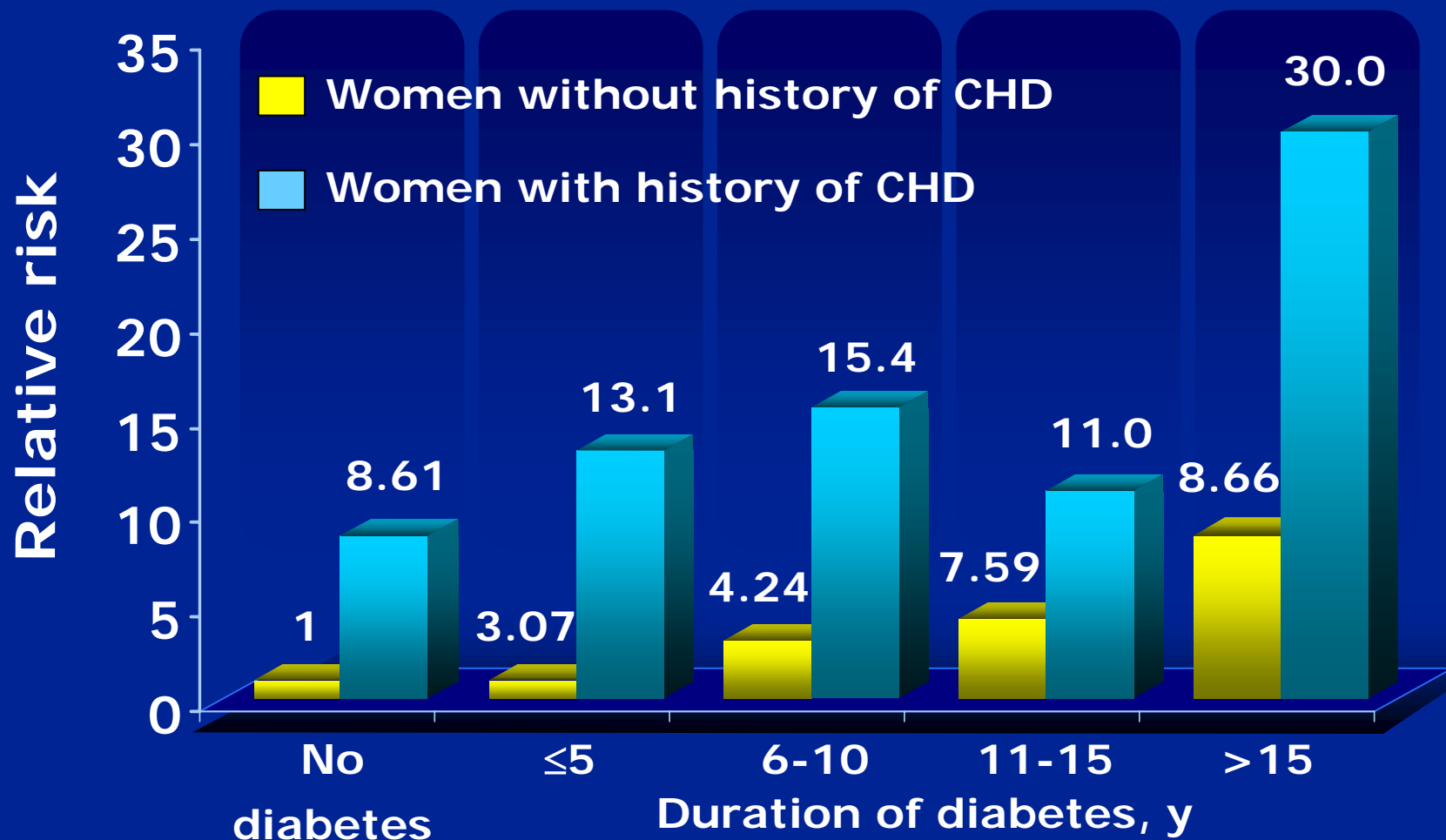
Multivariate Relative Risk of Fatal CHD in Women*



CHD=coronary heart disease DM=diabetes mellitus

*P<0.001 for trend across categories of duration

Multivariate Relative Risk* of Fatal CHD in Women With and Without History of CHD

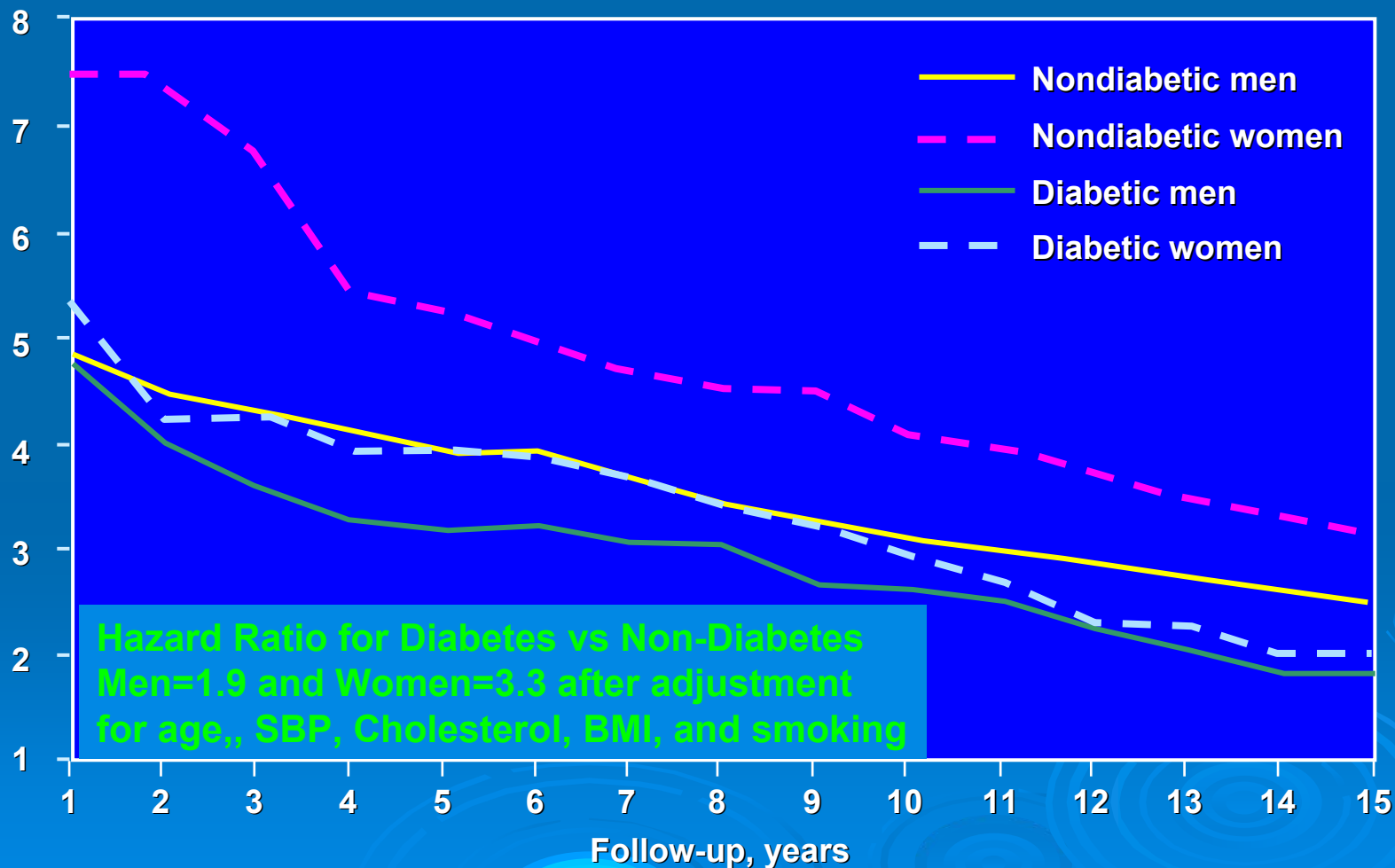


*P<0.001 for trend across categories of duration

Why is Diabetes a Stronger Risk Factor for Fatal CHD in Women than Men?

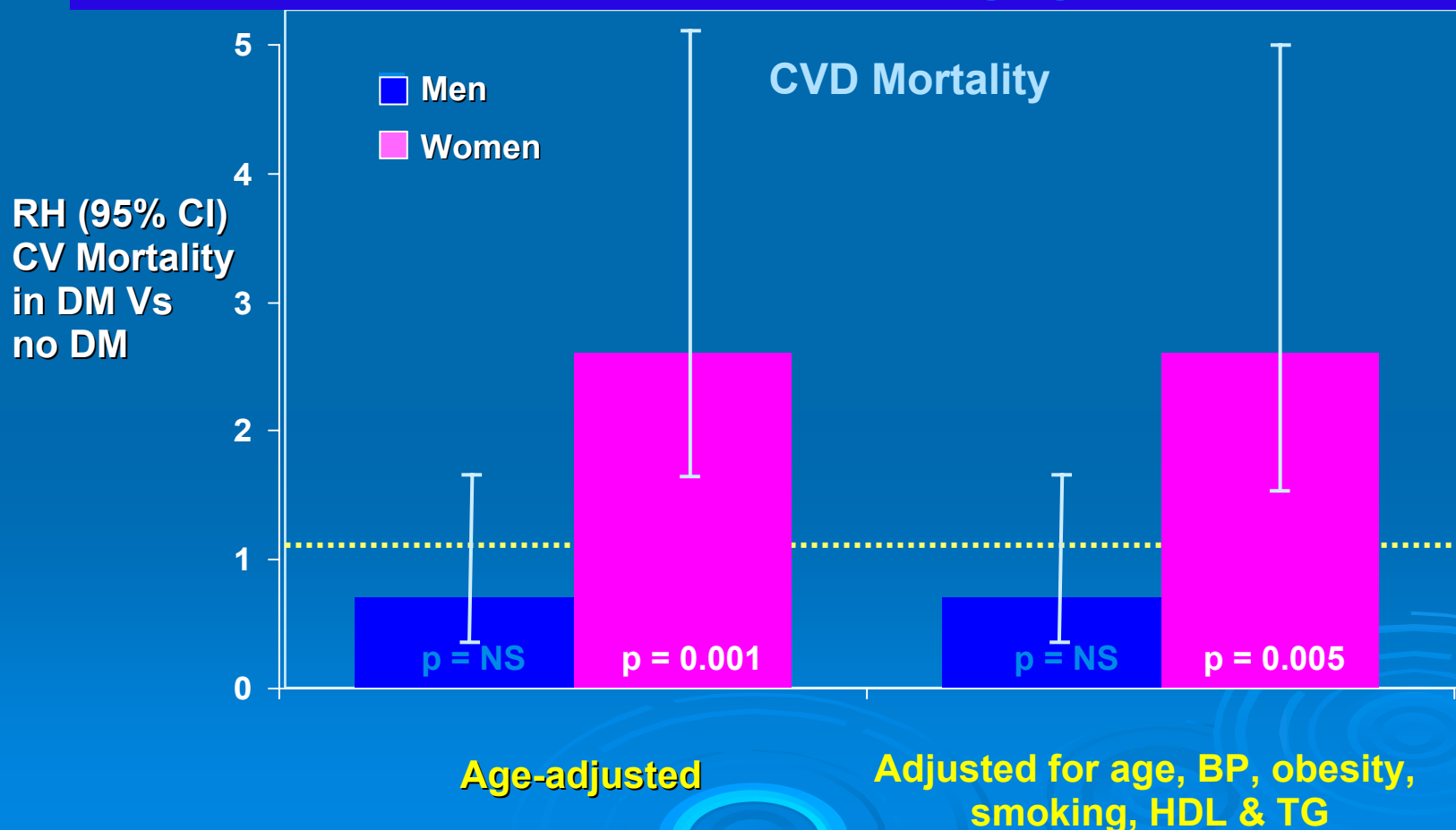
Rancho Bernardo Study

-Log (-Log Survival)



Isolated Post Challenge Hyperglycemia and CVD Mortality in Men and Women: Rancho Bernardo Study

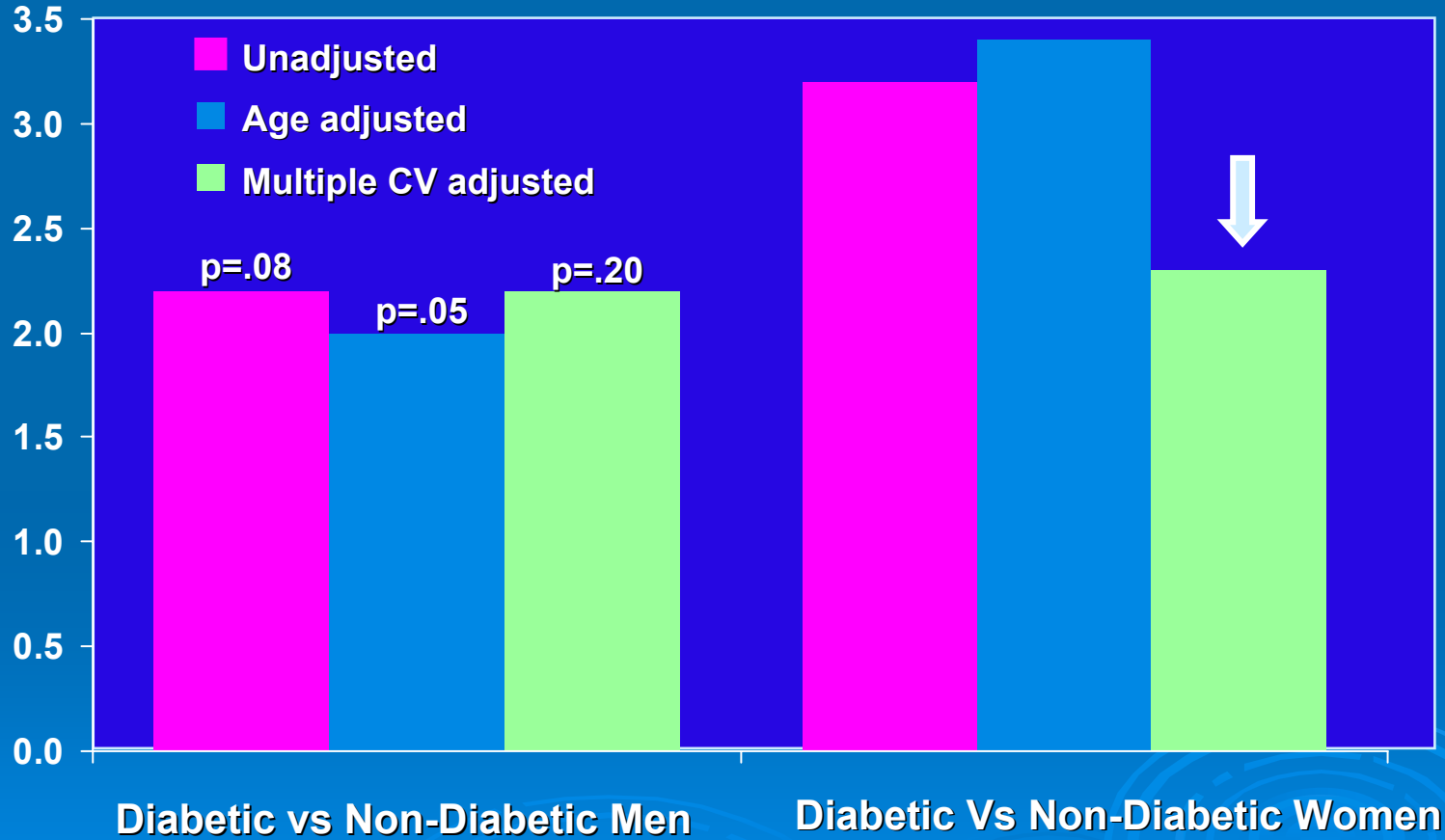
Prospective 7 year F/U of 769 older men and 1089 older women with FPG < 7.0 mmol/L and post-challenge glucose > 11.1 mmol/L



CHD Risk Factors Account for Excess Relative Risk of CHD Mortality in Women vs. Men with Diabetes

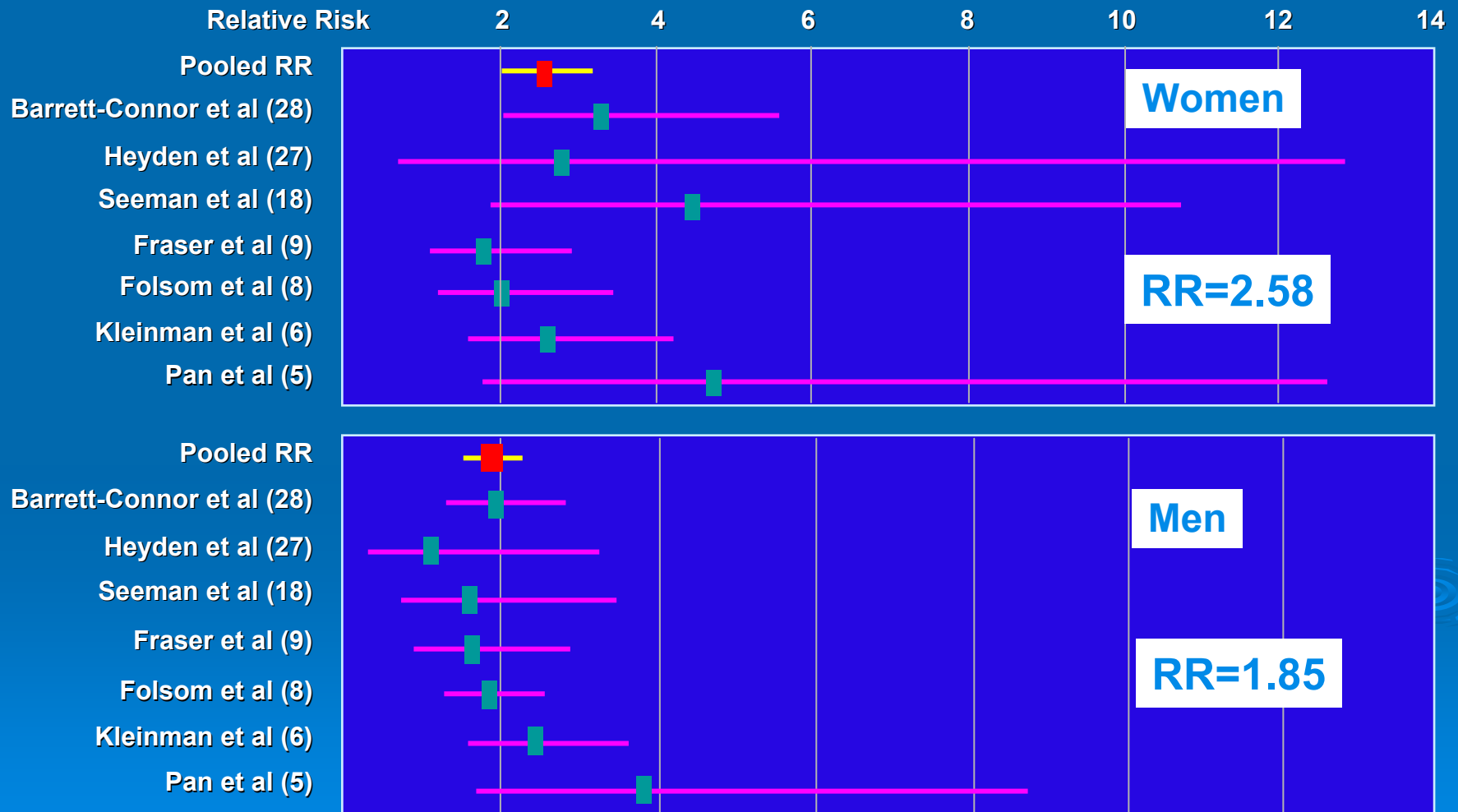
Odds ratio

Meta-analysis of 16 studies with Multivariate RF Analyses



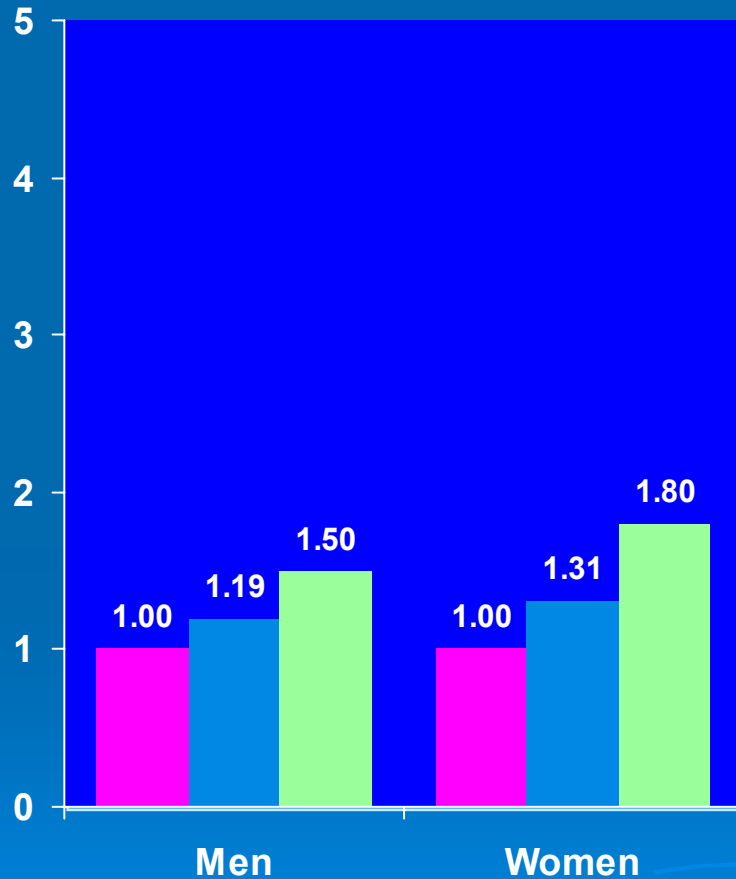
Impact of Diabetes on CHD Death in Women and Men; Meta-analysis of Prospective Studies

CV Risk Factor Adjusted Relative Risk for CHD Death--Diabetes versus No Diabetes

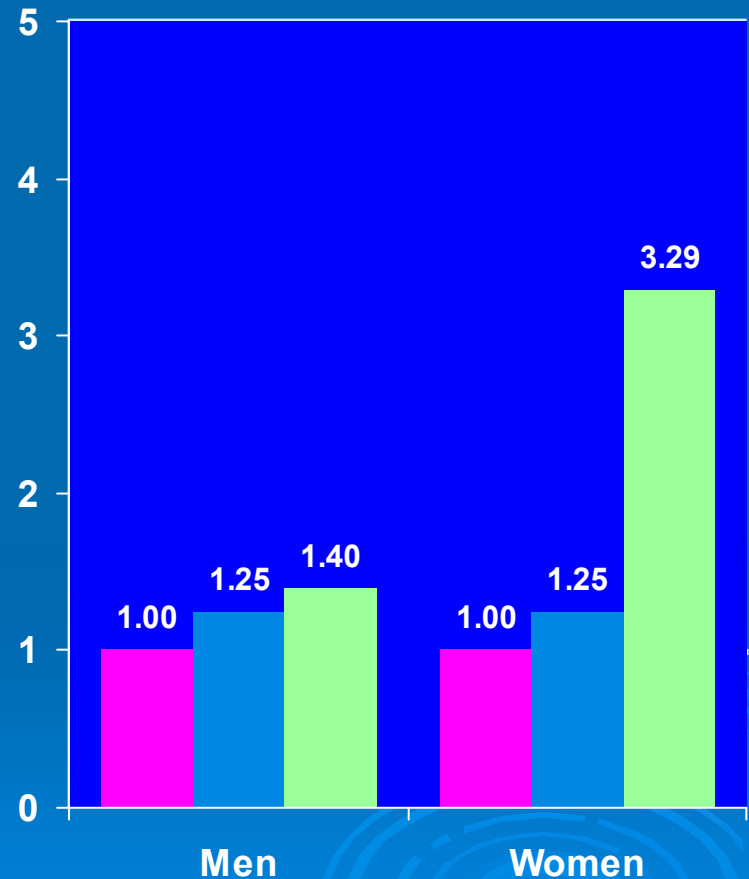


Gender Difference in All-Cause and CV Mortality Related to Hyperglycemia and Newly-diagnosed DM: DECODE

Hazards ratio of all-cause mortality*



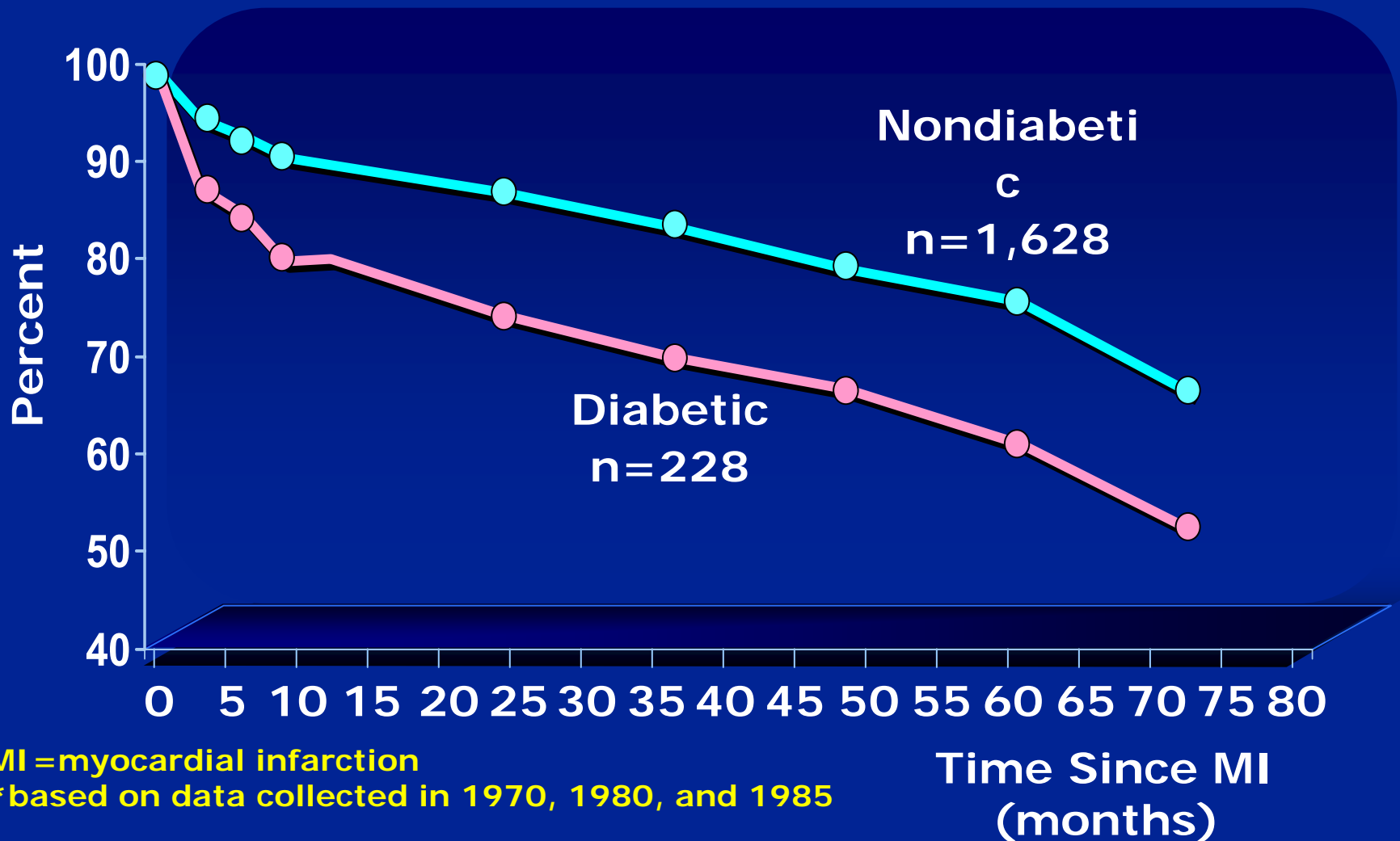
Hazards ratio of cardiovascular disease mortality*



* Adjusted for age, BMI, BP, cholesterol, smoking

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Minnesota Heart Survey Post-MI Survival in Men*

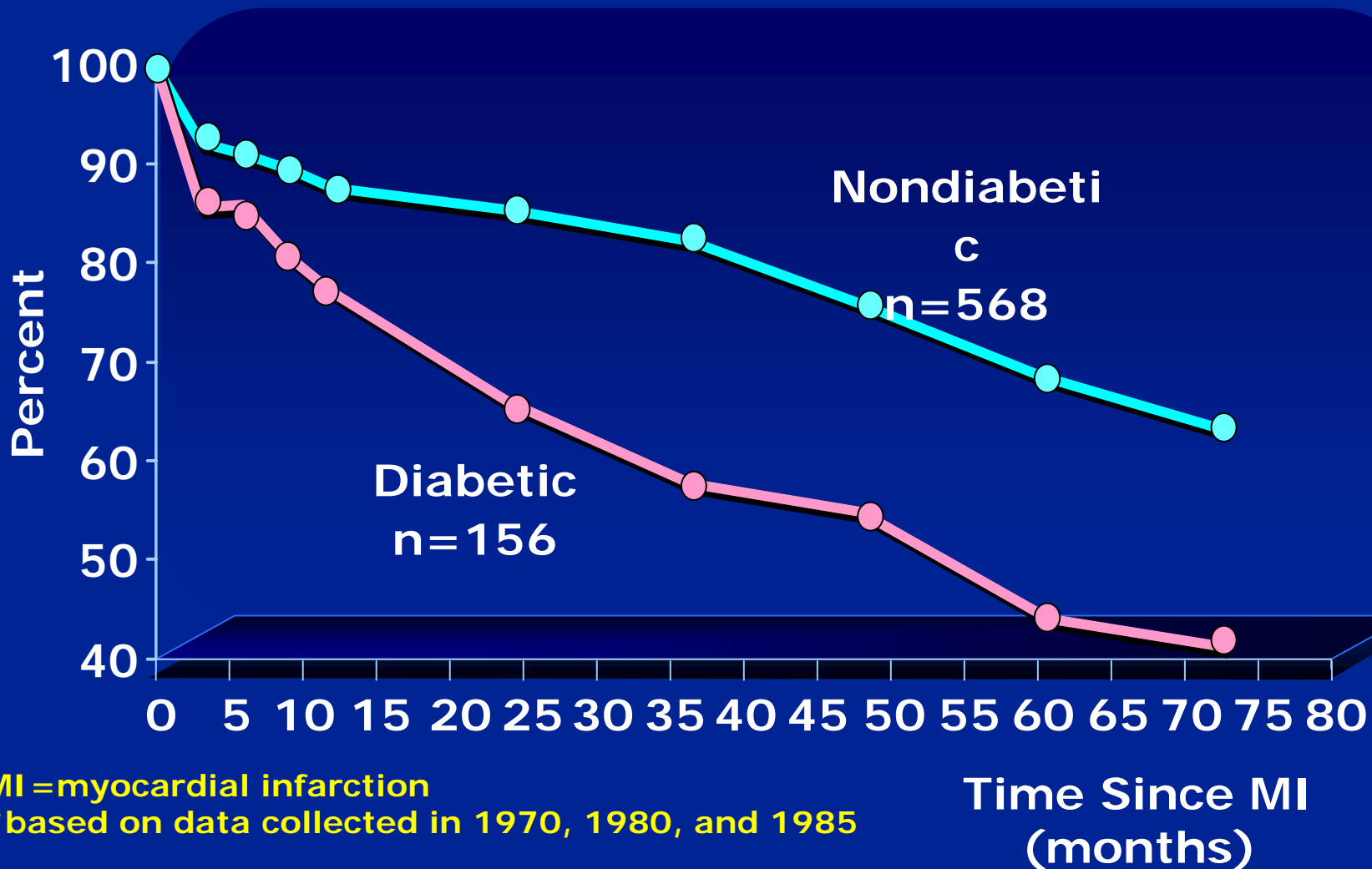


MI = myocardial infarction

*based on data collected in 1970, 1980, and 1985

Sprafka JM, et al. *Diabetes Care*. 1991;14:537-543.

Minnesota Heart Survey Post-MI Survival in Women*

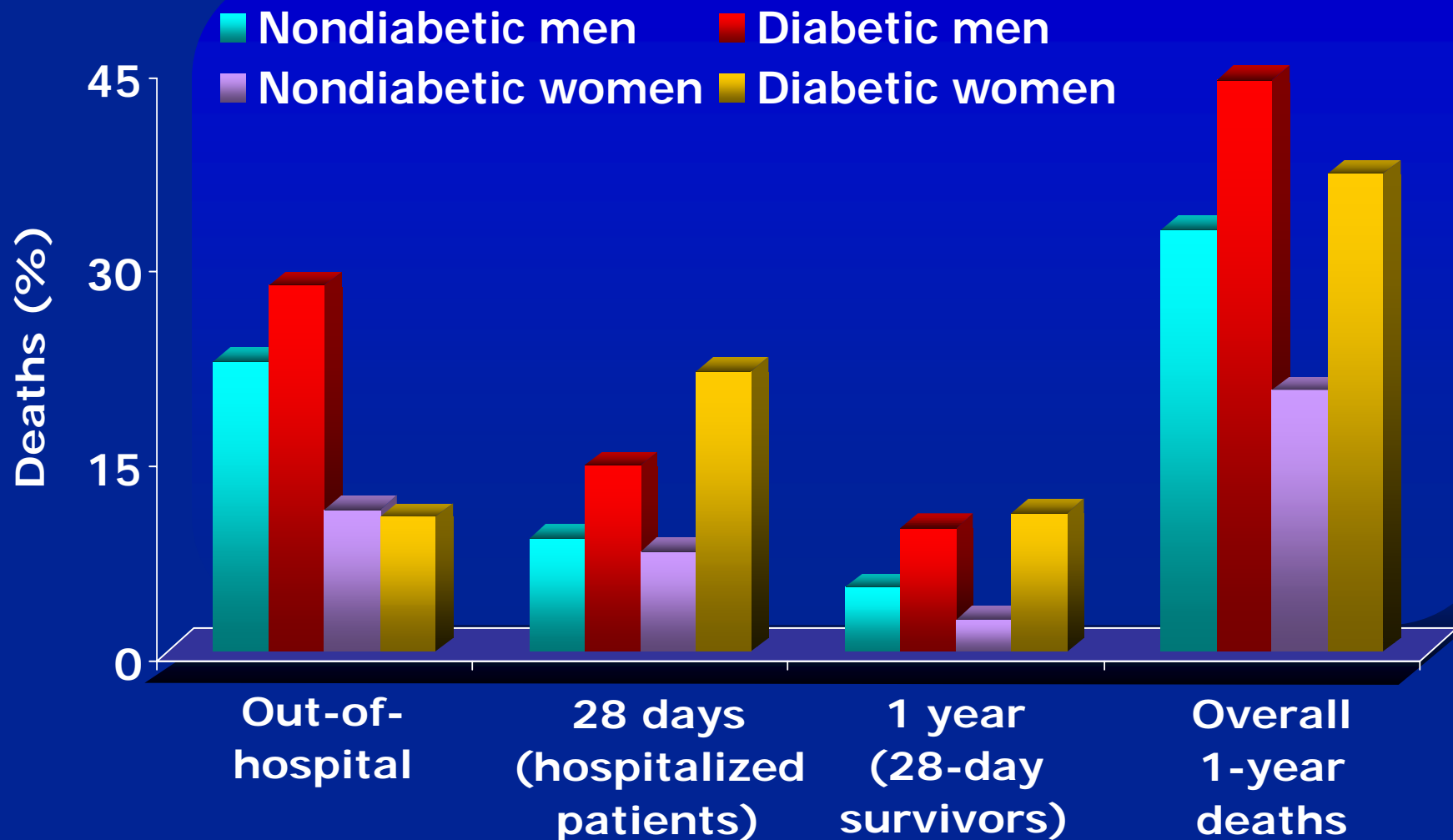


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Sprafka JM, et al. Diabetes Care. 1991;14:537-543.

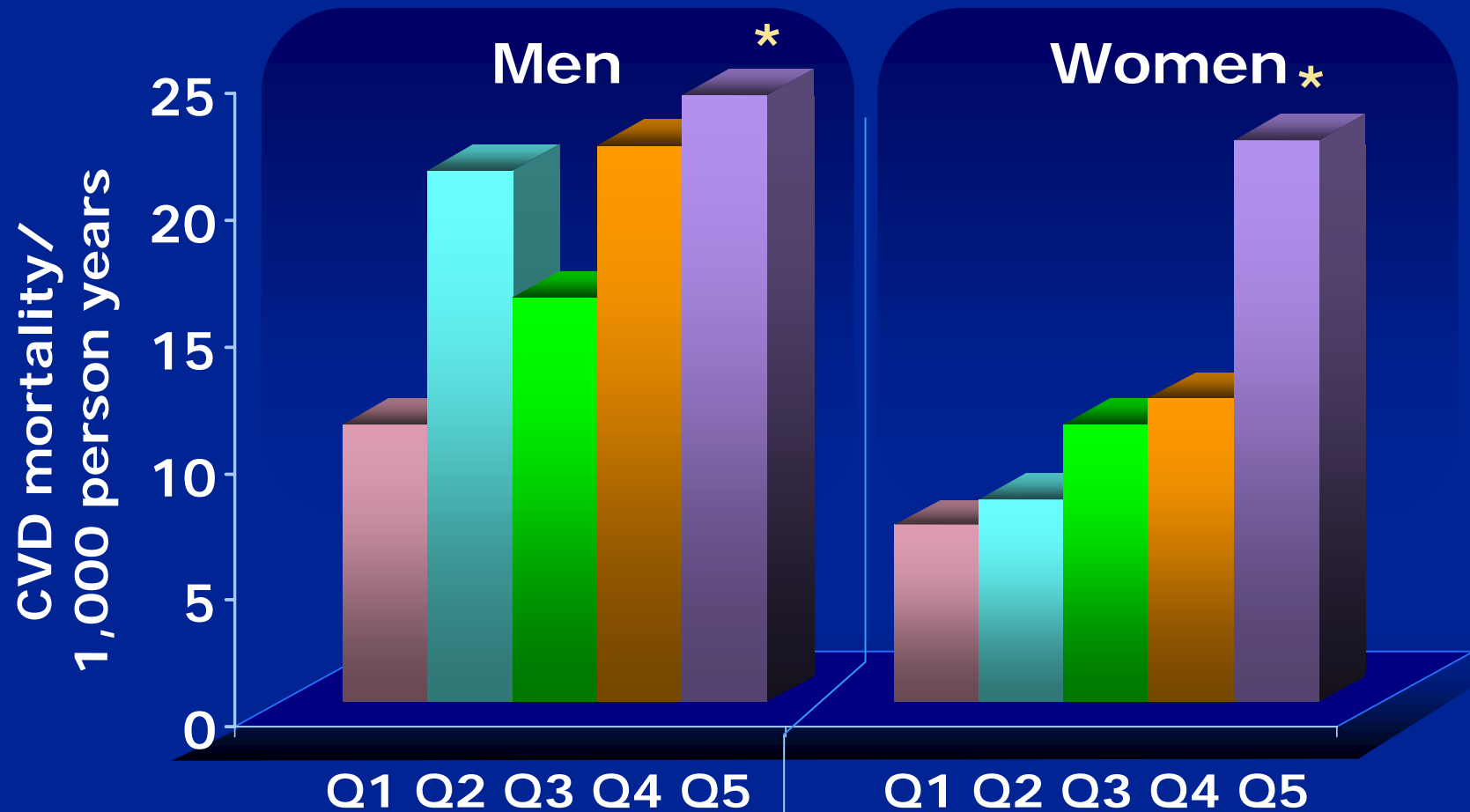
1-Year Mortality After First MI



MI = myocardial infarction

Miettinen H, et al. Diabetes Care. 1998;21:69-75.

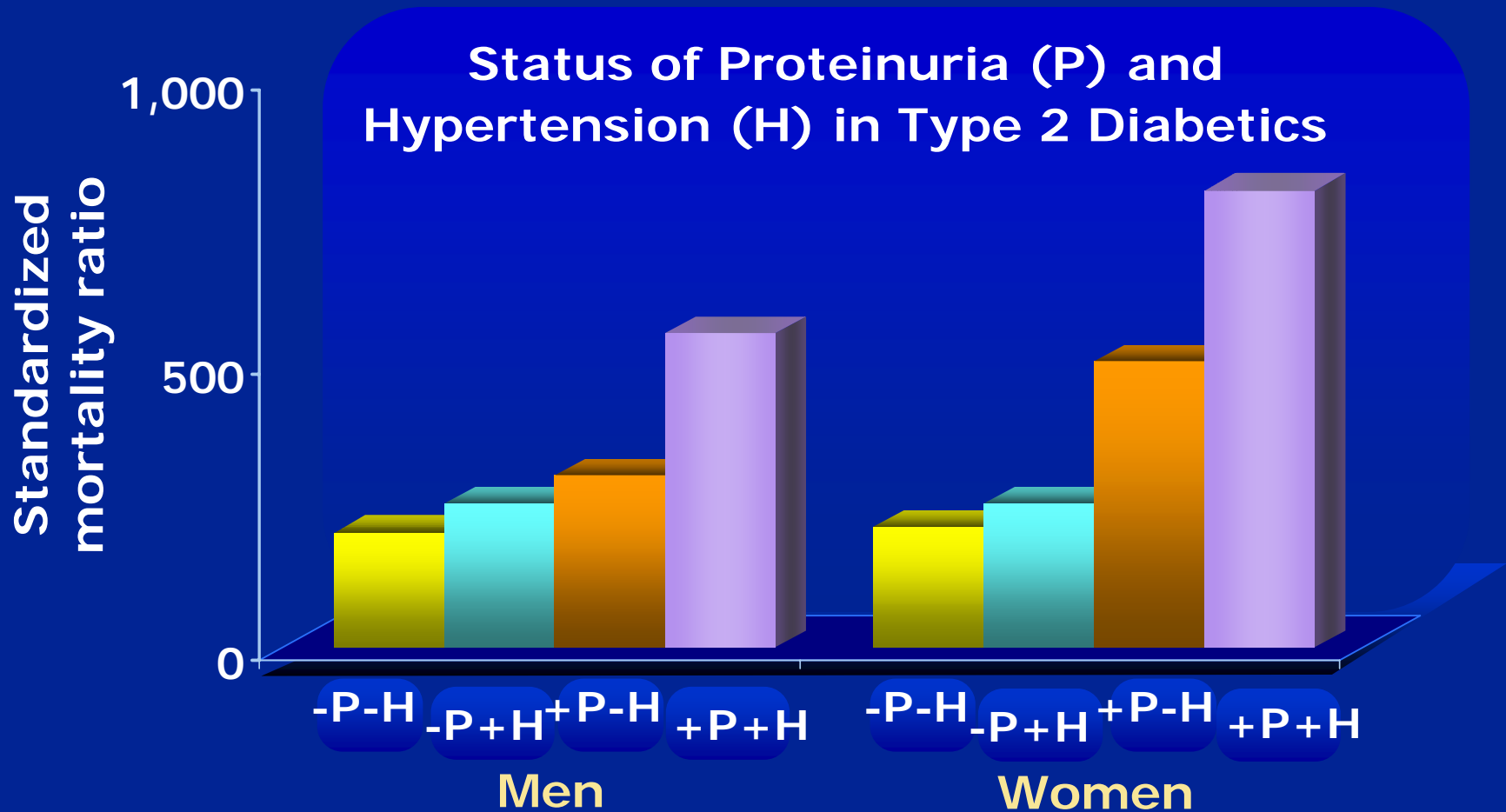
Age-Adjusted CVD Mortality by Quintile* of Fasting Serum Triglyceride (mmol/l)



CVD=cardiovascular disease *P<0.01 compared to Q1
Q1<1.10; Q2=1.11-1.50; Q3=1.51-2.02; Q4=2.03-2.93; Q5>2.94.

Fuller JH, et al. Diabetologia. 2001;44[suppl2]:S54-S64

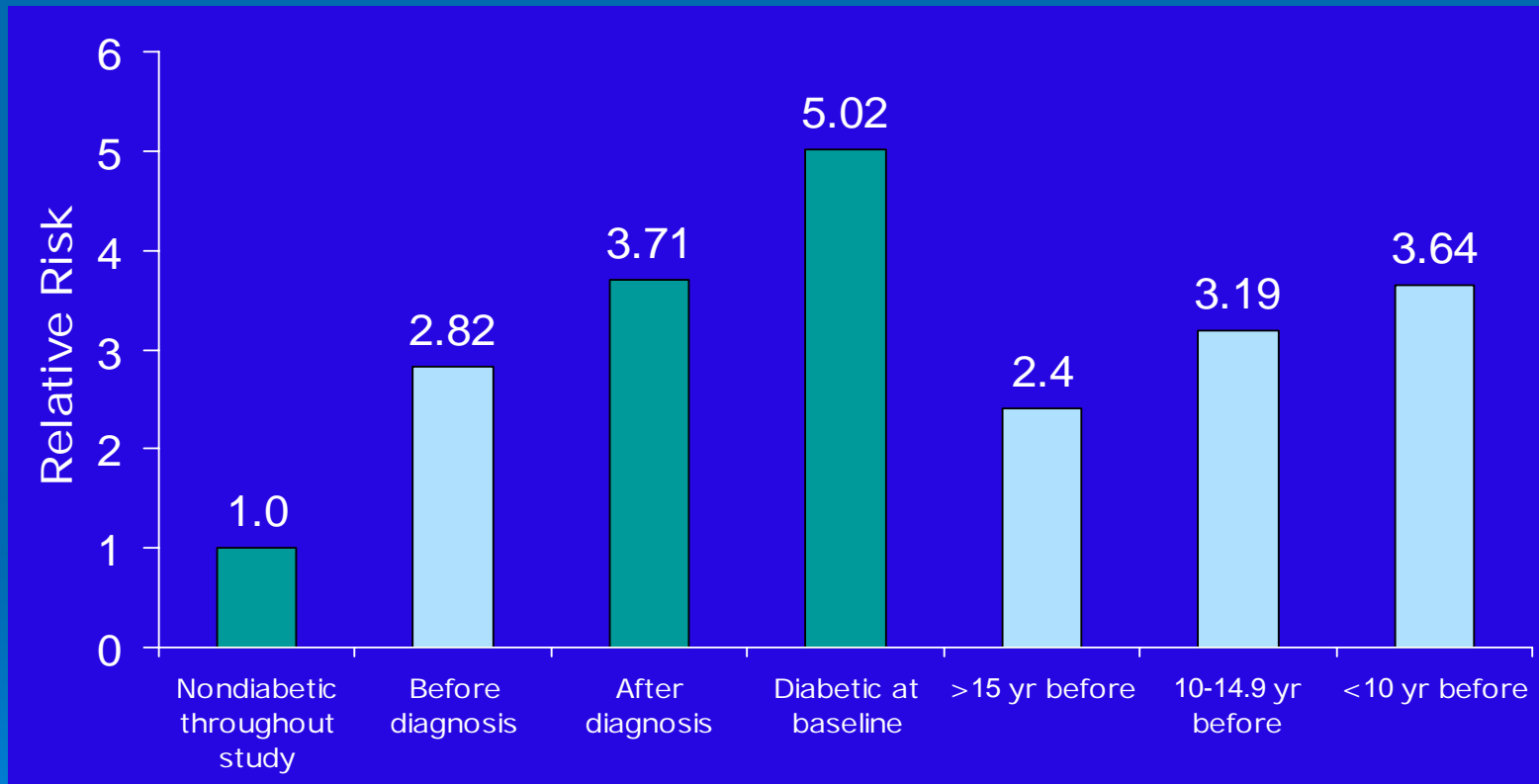
Proteinuria and Hypertension in Type 2 Diabetes



Nurses' Health Study: Increased Risk of CVD Prior to Diagnosis of Type 2 Diabetes

- 117,629 female nurses, aged 30-55 yr
- 20-yr follow-up: 5,894 developed type 2 diabetes
- Cardiovascular outcomes:
 - 1,556 new cases of MI
 - 1,405 strokes
 - 815 fatal CHD
 - 300 fatal strokes

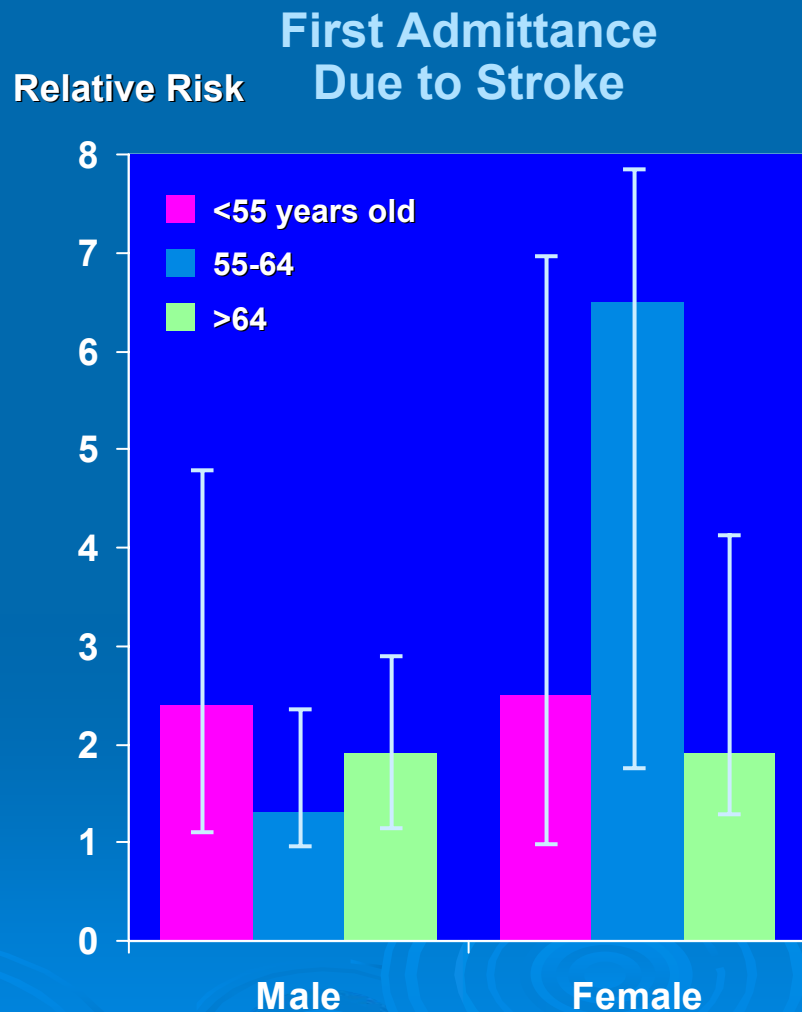
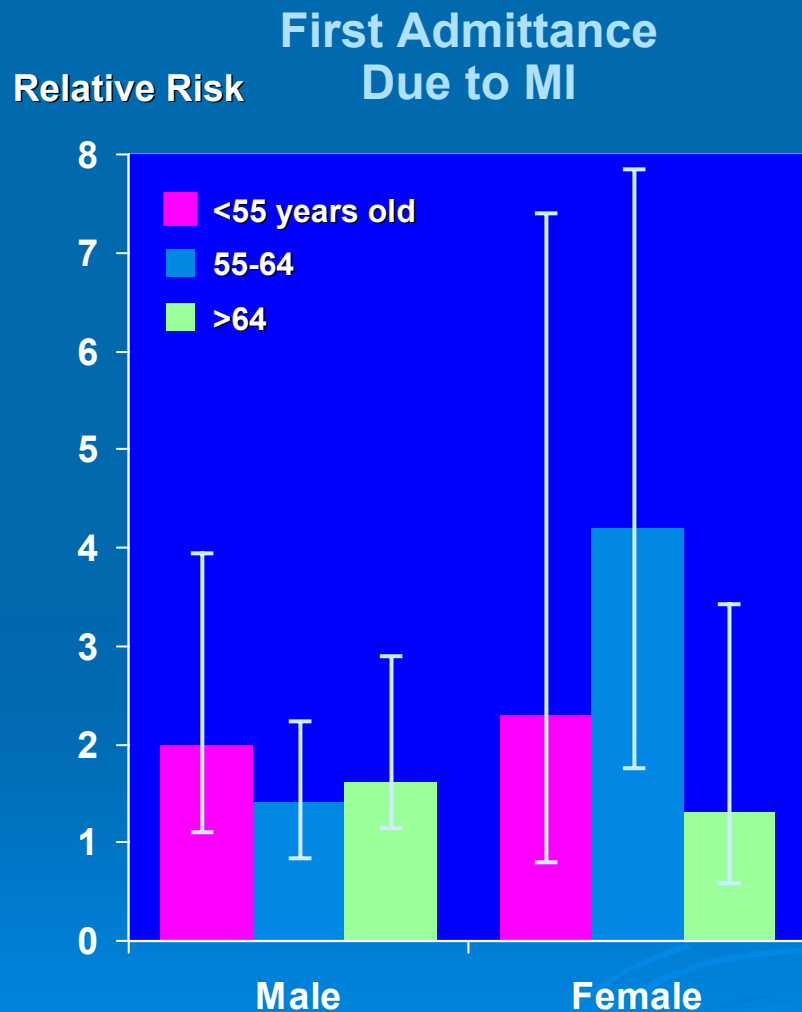
Nurses' Health Study: Increased Risk of CVD Prior to Diagnosis of Type 2 Diabetes



**Risk of MI or Stroke
by Diabetes Status**

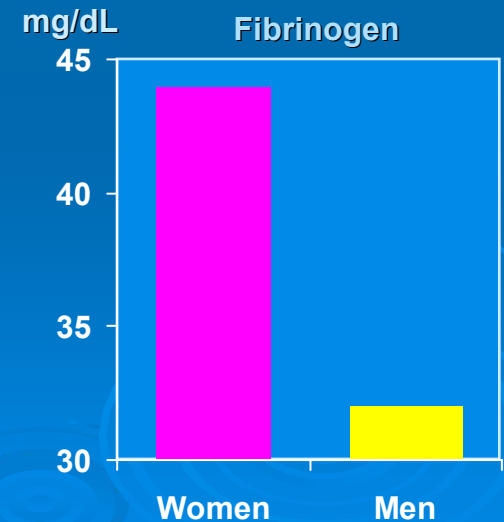
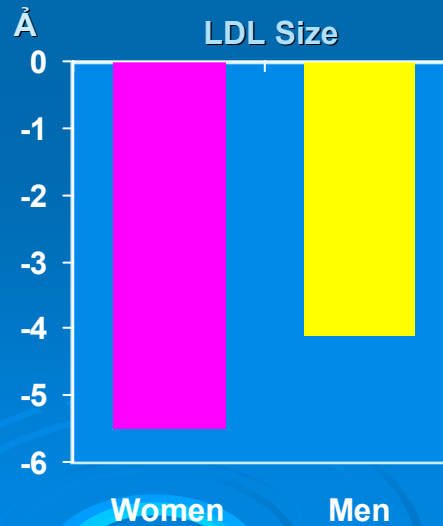
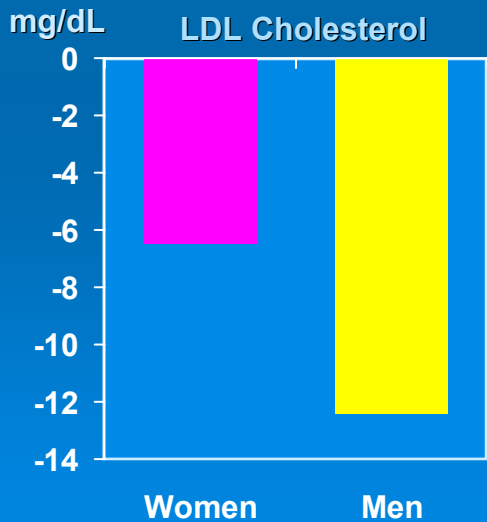
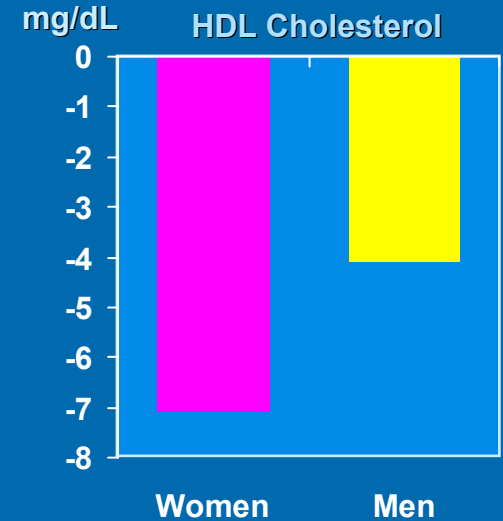
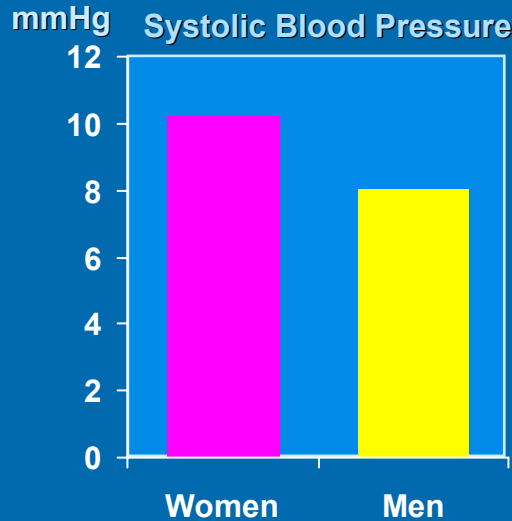
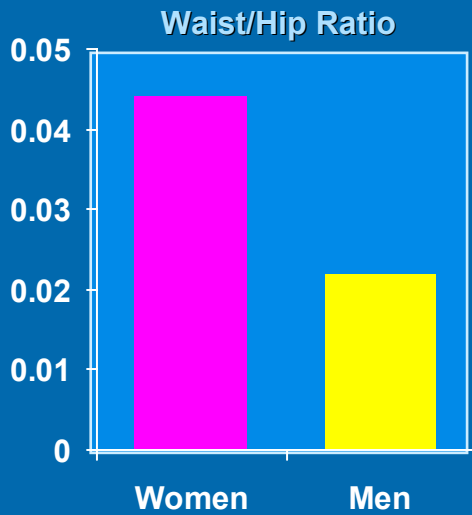
**Risk of MI or Stroke by Time
Before Dx of Diabetes**

Interaction of Gender and Age on Risk for First MI & Stroke in Type II Diabetes : Copenhagen Heart Study



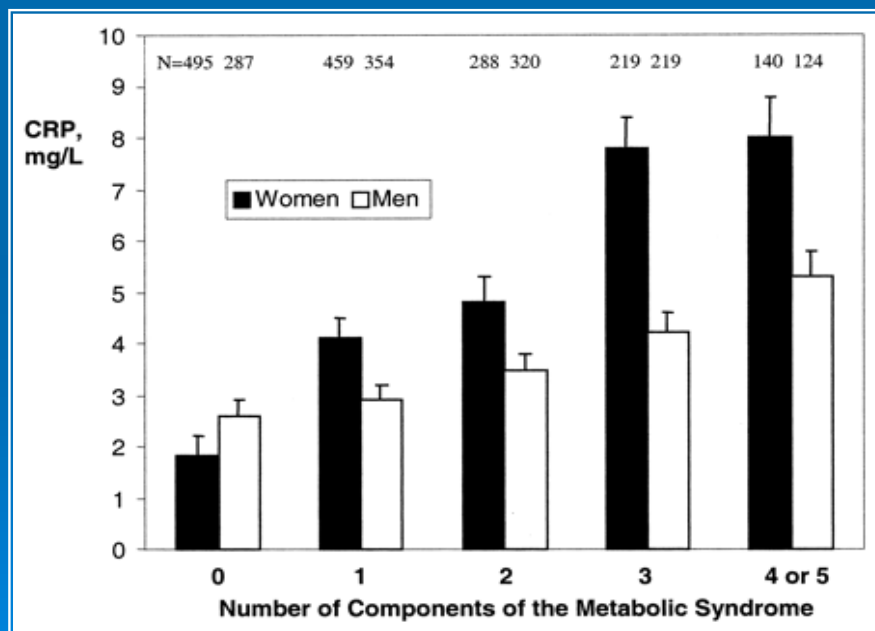
RR is fully adjusted for CV Risk Factors

Adverse Effects of Diabetes on CV Risk Factors in Women: Strong Heart Study



C-Reactive Protein, the Metabolic Syndrome, and Prediction of Cardiovascular Events in the Framingham Offspring Study

- 3037 subjects (mean age =54 yrs.)
- Self-reported and newly diagnosed DM excluded

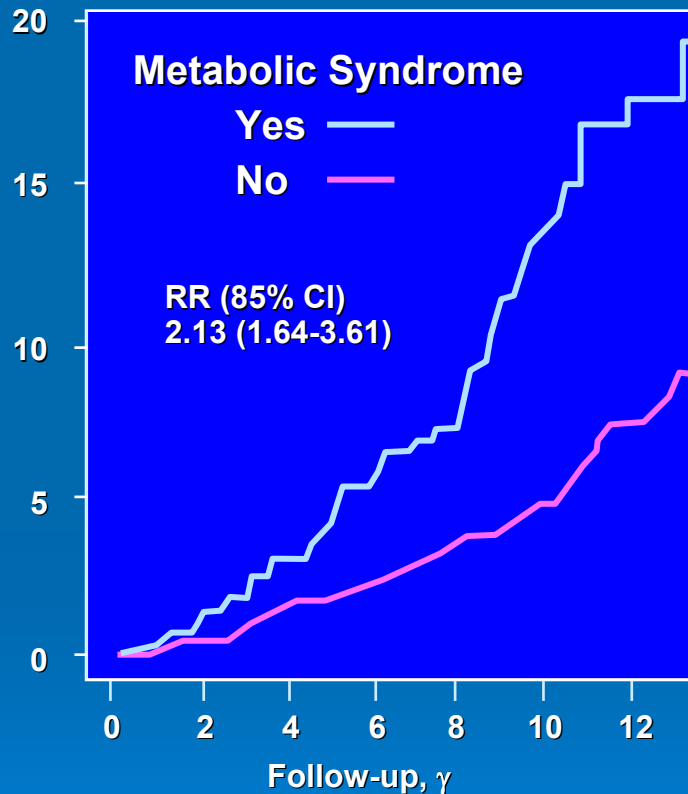


- MS present in 24%
- MS and CRP predicted incident CV events
 - HR for MS = 2.1
 - HR for high v. low CRP $q = 2.2$
- Combining MS and CRP did not improve prediction of incident CV events over either alone.
- Women had higher CRP levels for any number of MS criteria

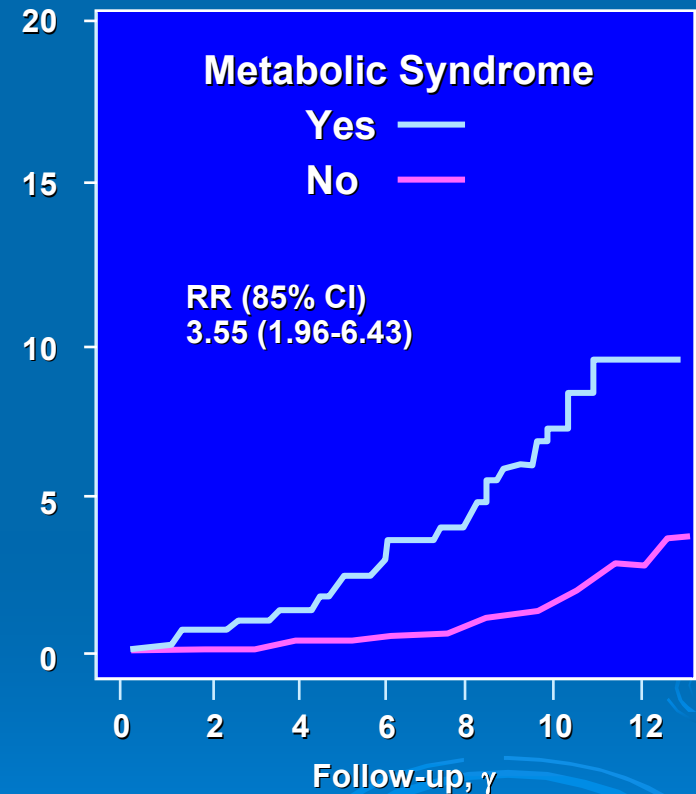
Metabolic Syndrome: Total and CV Mortality in Middle-Aged Men in Kuopio Heart Study

Cumulative Hazard (%)

All-Cause Mortality



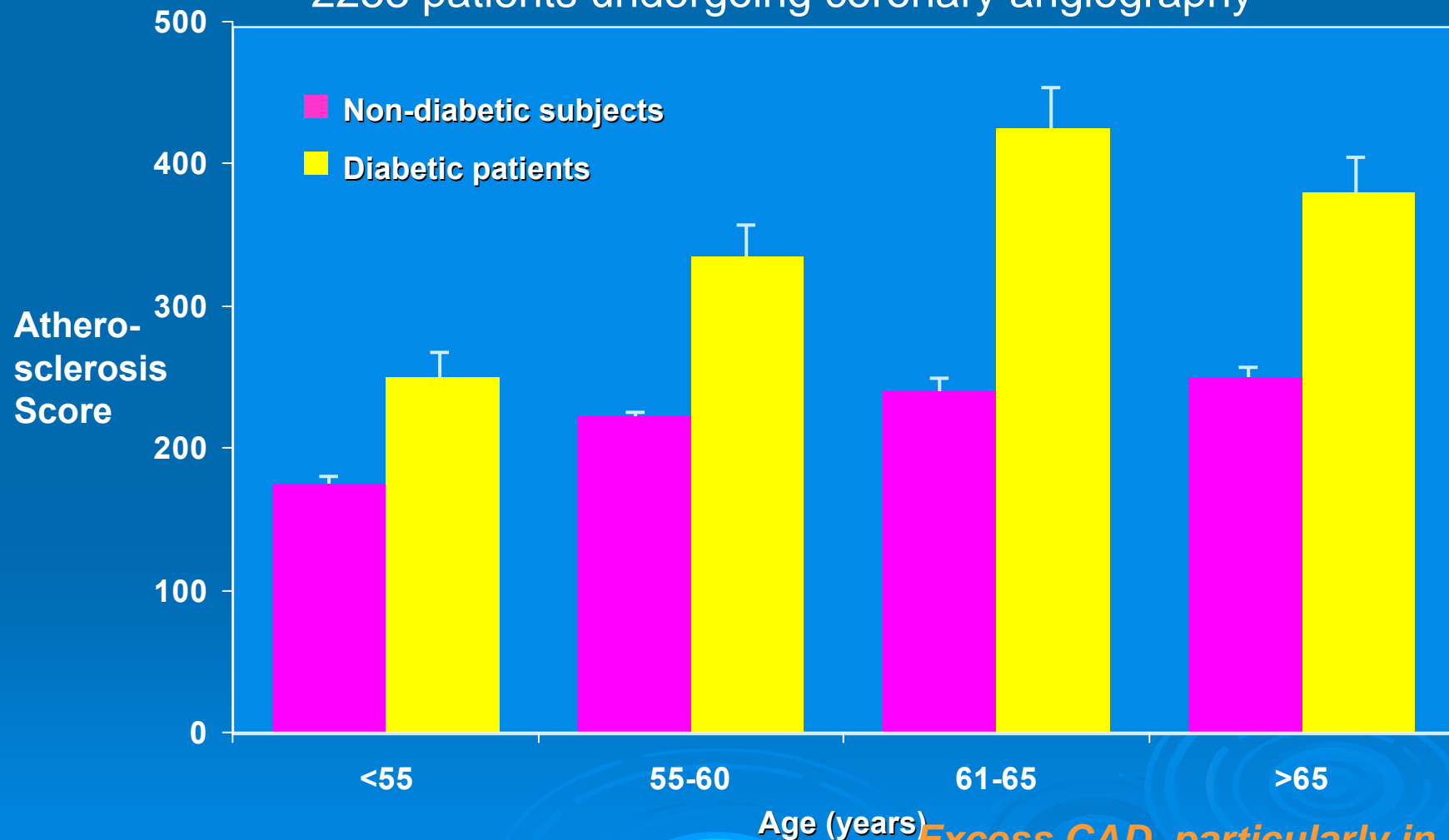
Cardiovascular Disease Mortality



RR indicates relative risk; CI, confidence interval. Median follow-up (range) for survivors was 11.6 (9.1-19.7) years

CAD is More Extensive in the Presence of Type 2 Diabetes

2253 patients undergoing coronary angiography



Natali A et al. Diabetologia 2000;43:632-641

Excess CAD, particularly in women, not explained by CV RF

ASYMPTOMATIC people with Metabolic Syndrome, PCOS, and Type 2 DM have twice the prevalence and twice the extent of CAD when screened with Electron Beam Computed Tomography (EBCT)



Median CAC score in men 50-59 yrs:
No diabetes= 43
Type 2 DM= 111

J Am Coll Cardiol 2003; 41: 1008-1014

Coron Artery Disease 2003; 14: 317-322

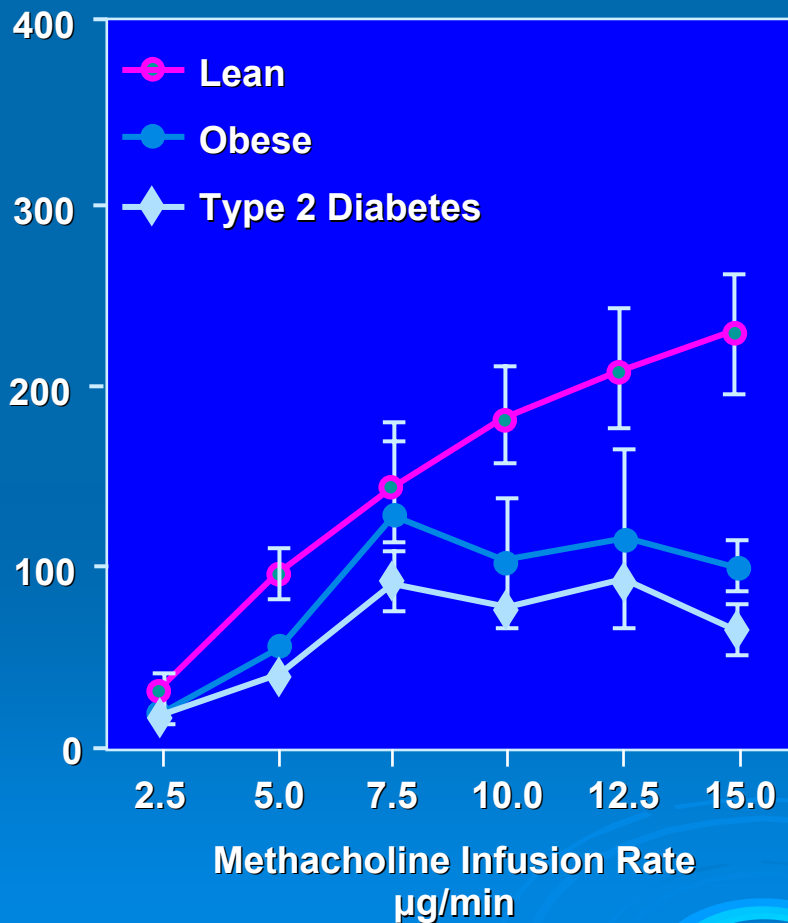
J Cardiovasc Risk 2002; 9: 369-376

J Clin Endocrinol Metab 2003; 88: 2562-2568

Type II Diabetes Abrogates Sex Difference in Endothelial Function in Pre-menopausal Women

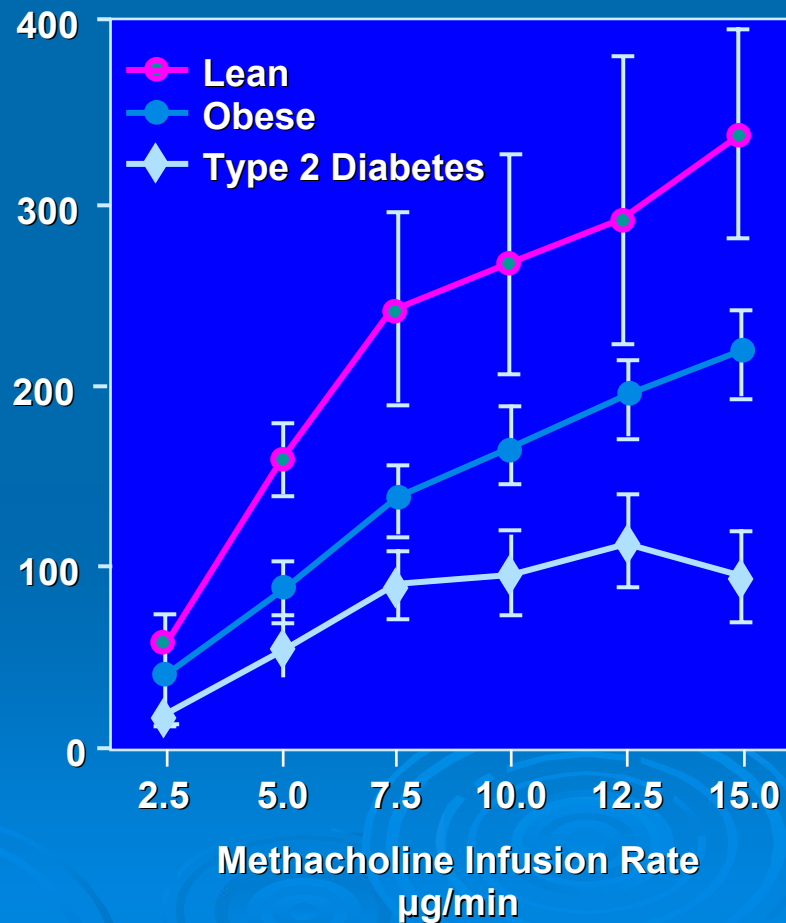
Males

Δ % Leg Blood Flow



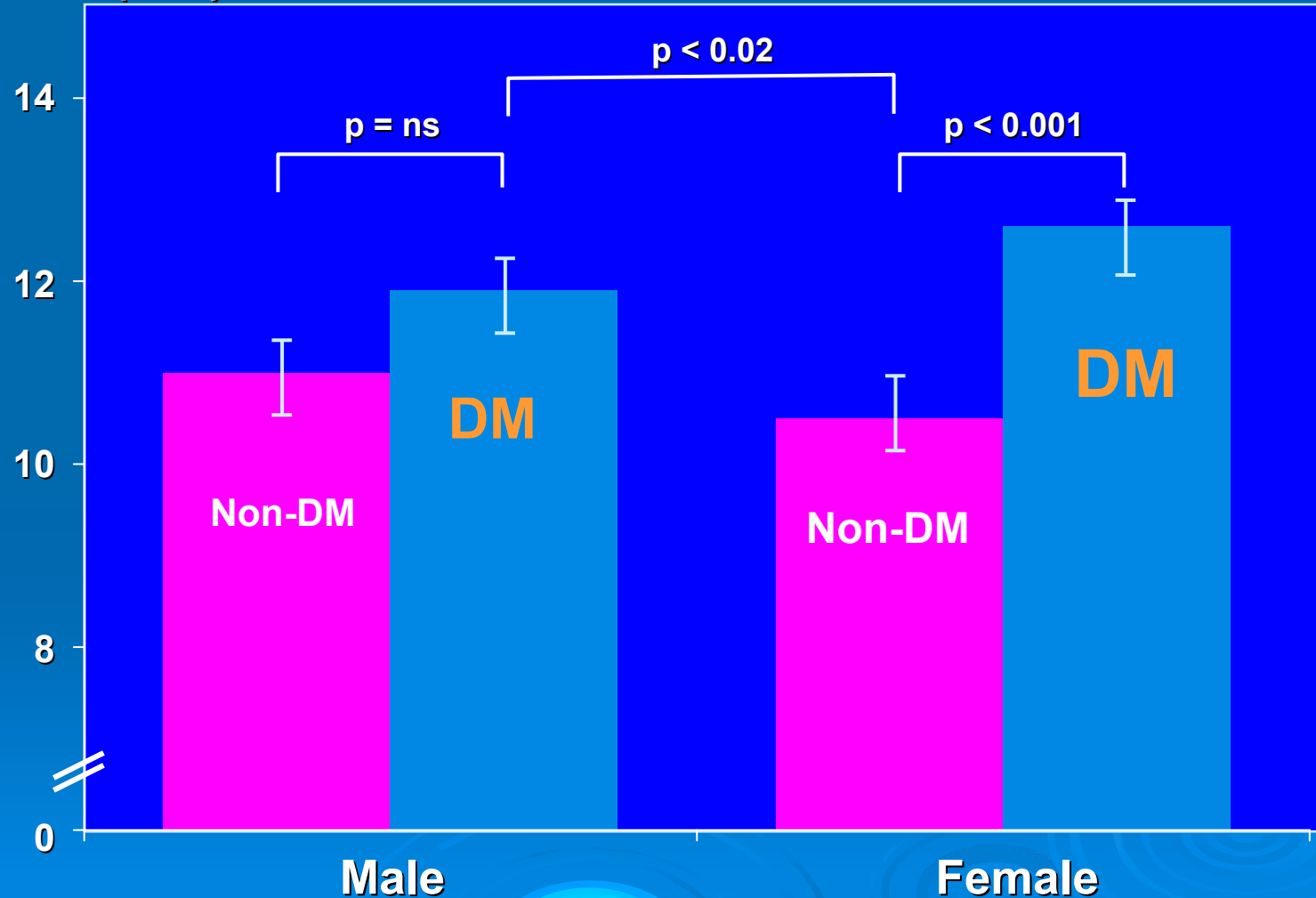
Females

Δ % Leg Blood Flow

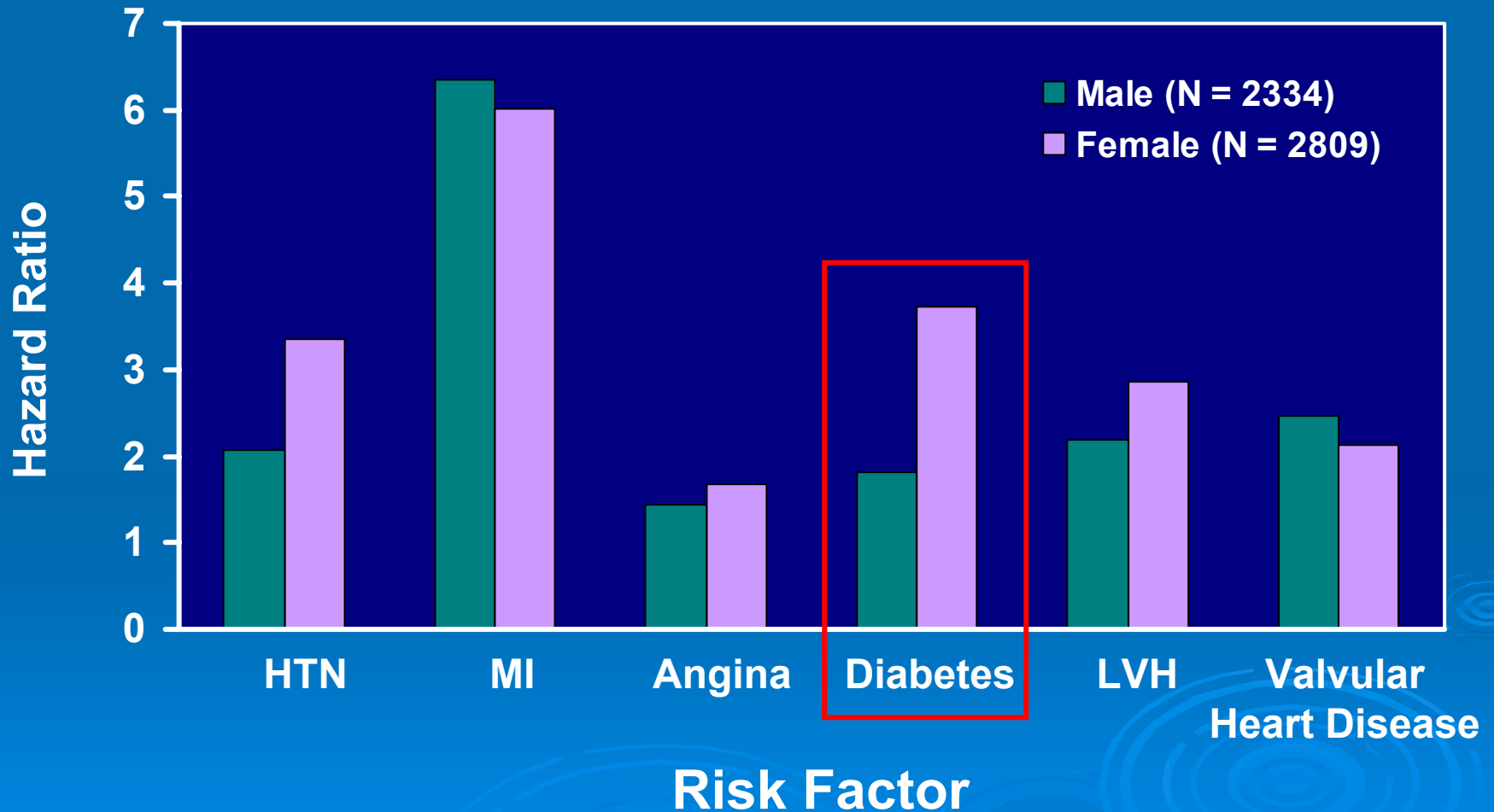


Gender Differences in Age-Related Stiffness of Aorta in Type 2 DM

PWV (m/s)



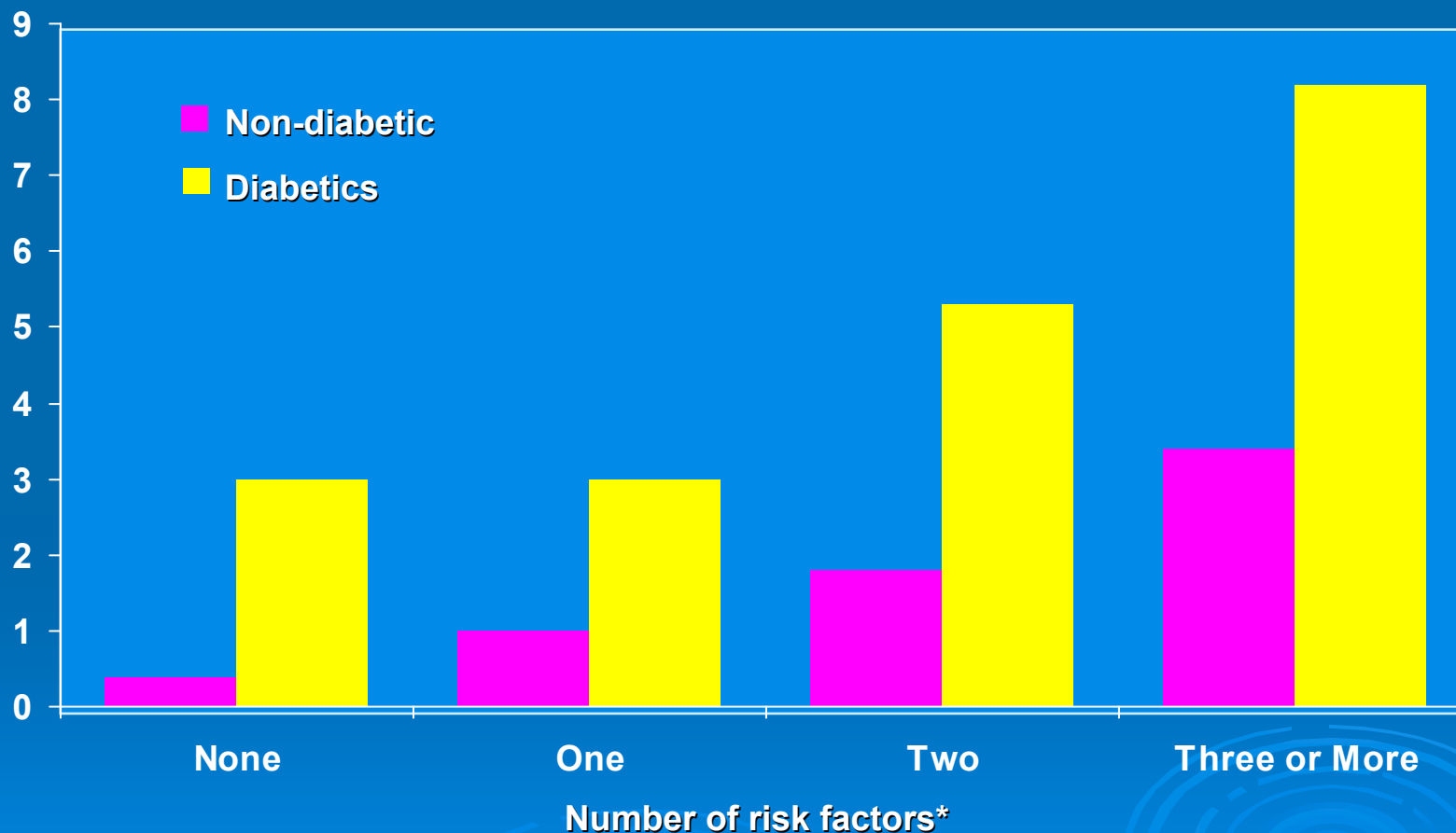
Risk for the Development of CHF –Framingham Study



Levy, D, et al. JAMA. 1996; 275: 1557-62.

HERS: Diabetes is a Powerful Predictor of CHF in Women with CAD

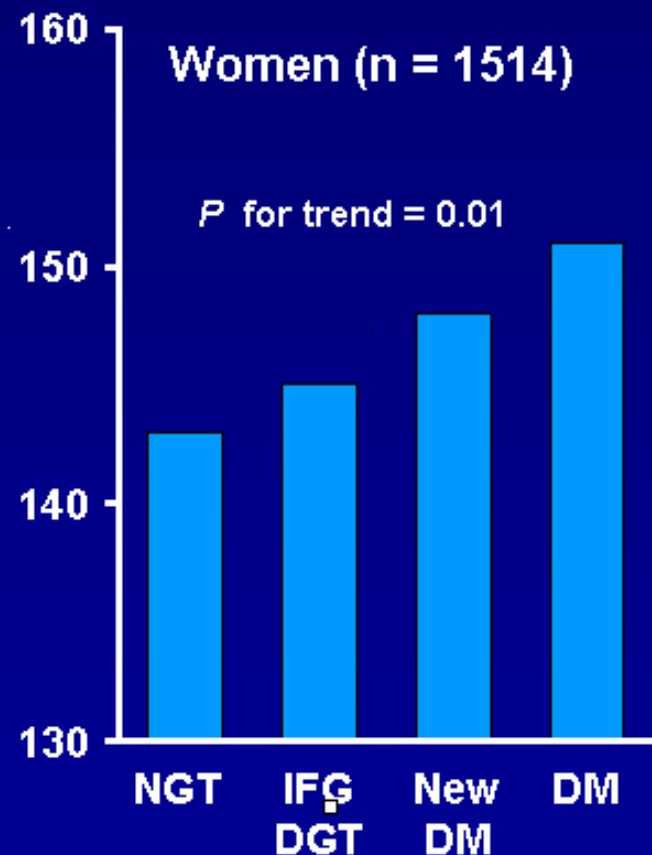
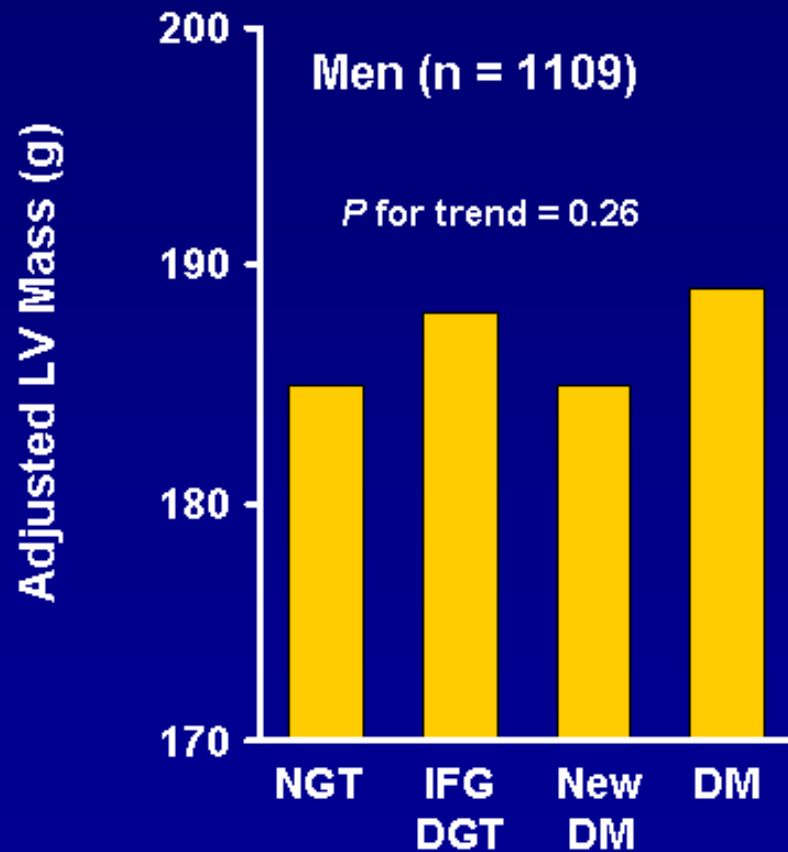
Annual incidence ratio (%)



* Risk factors = AF, MI, CrCl <40, SBP >120mmHg, current smoker, BMI >35kg/m², LBBB, LVH

Across the Range of Glucose Tolerance, Women Have Greater LV Mass Than Men

Framingham Offspring Study

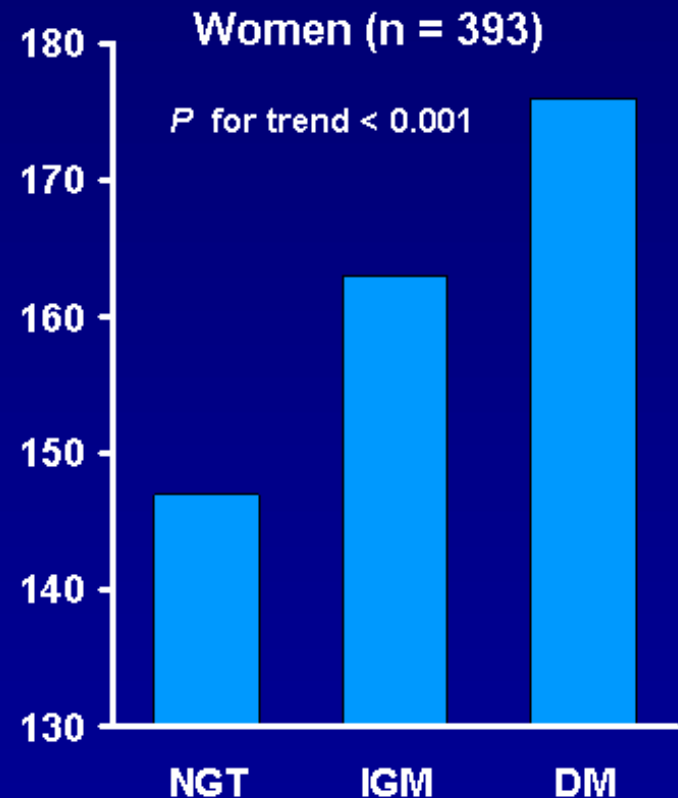
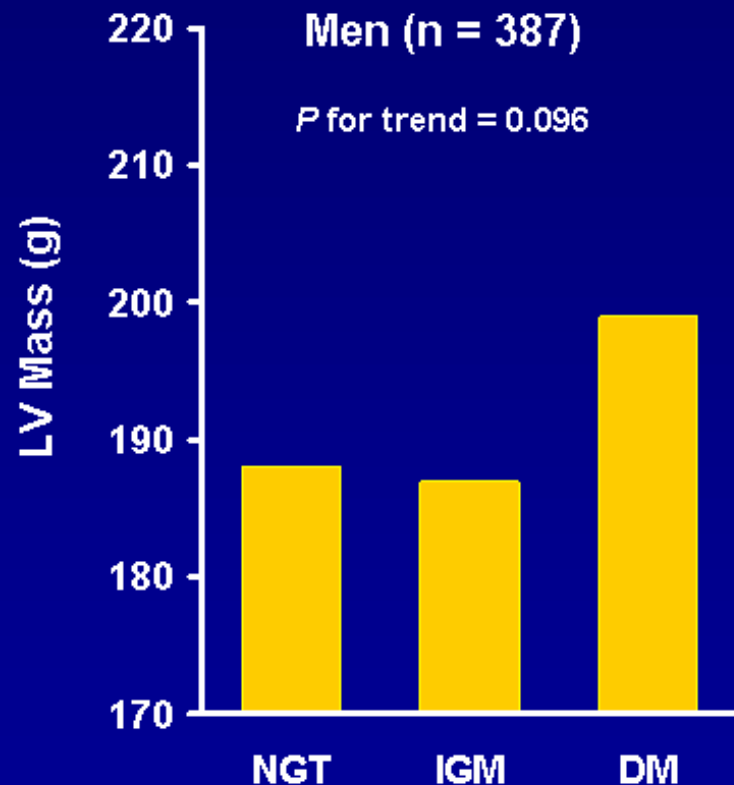


LV mass adjusted for age, height, heart rate, systolic blood pressure, BMI.

Rutter MK, et al. *Circulation*. 2003;107:448-54.

Across the Range of Glucose Tolerance, Women Have Greater LV Mass Than Men

Hoorn Study



Hospitalization for Heart Failure in the Presence of a Normal Left Ventricular Ejection Fraction

J Am Coll Cardiol 2004; 43: 1432-1438

Prospective identification of patients admitted with “pure” CHF and EF>50% in NY Heart Failure Registry

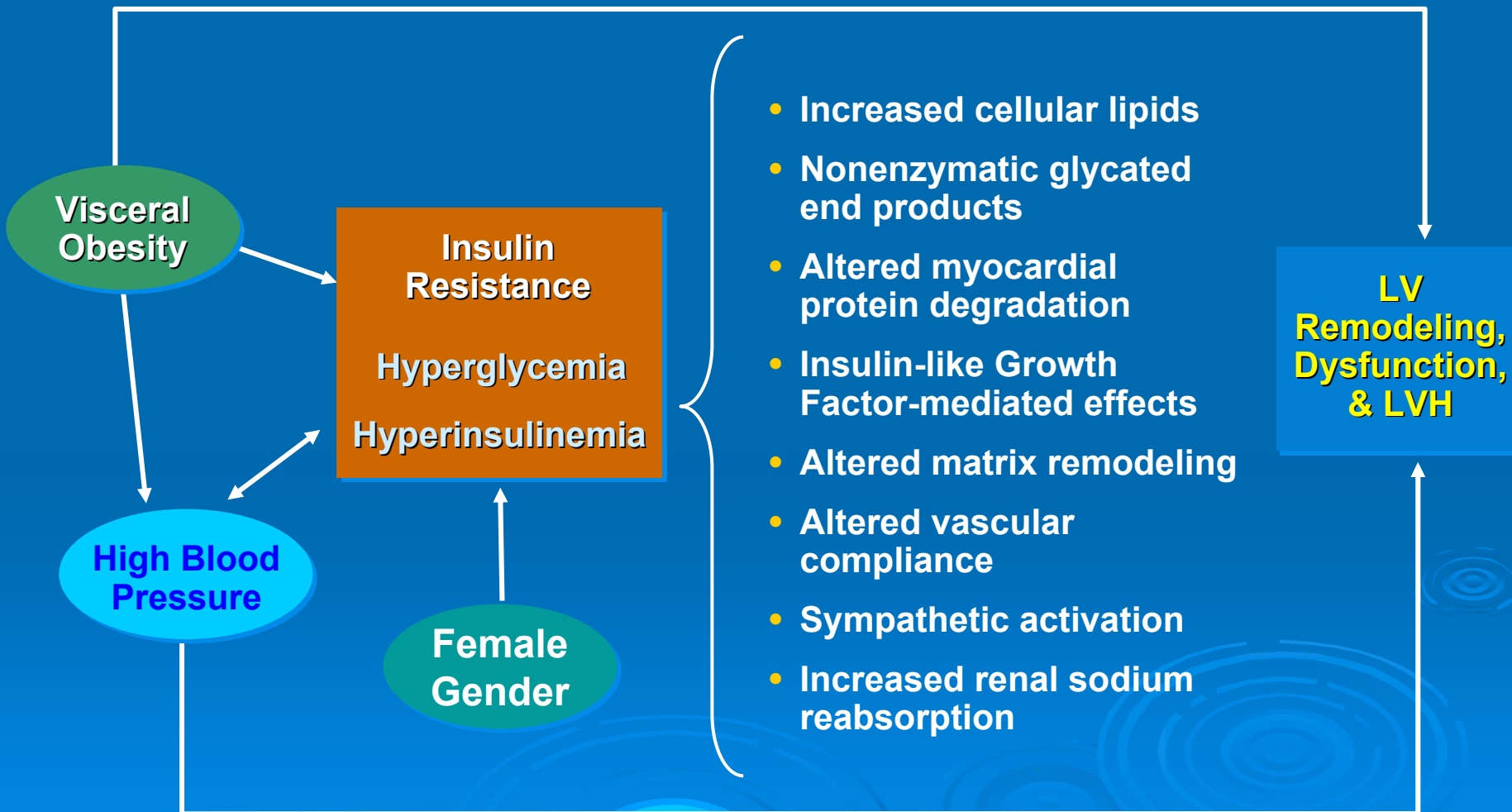
- 619 patients 73% women
- Women 8 years younger than men
- Co-morbid conditions
 - Hypertension 78%
 - Diabetes 46%
 - Obesity 46%
 - CAD 40%
 - Increased LV Mass

Diabetes and/or insulin resistance syndromes underlie most cases of non-systolic CHF, particularly in women

Mechanisms Promoting LV Remodeling and Dysfunction in Insulin Resistance

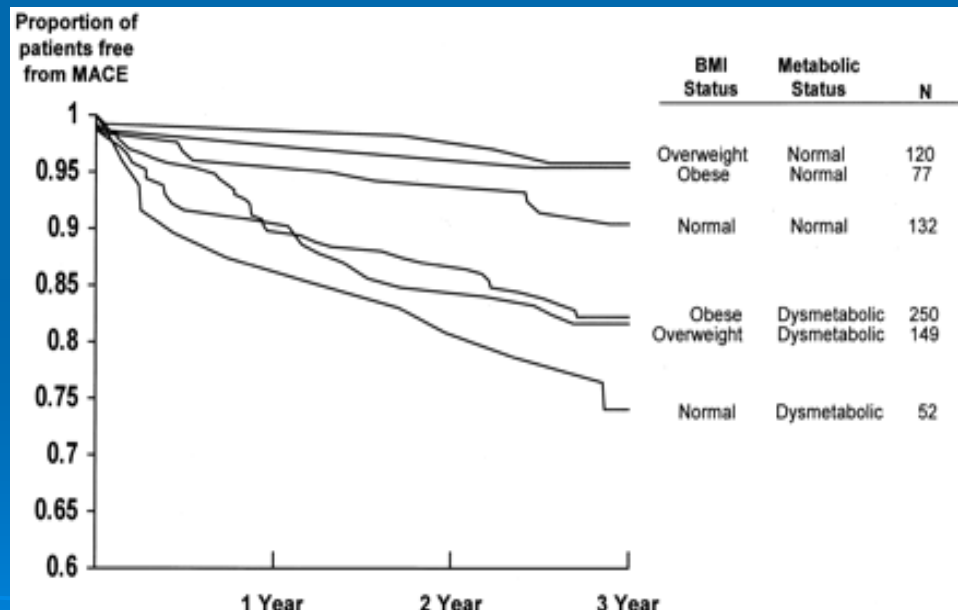
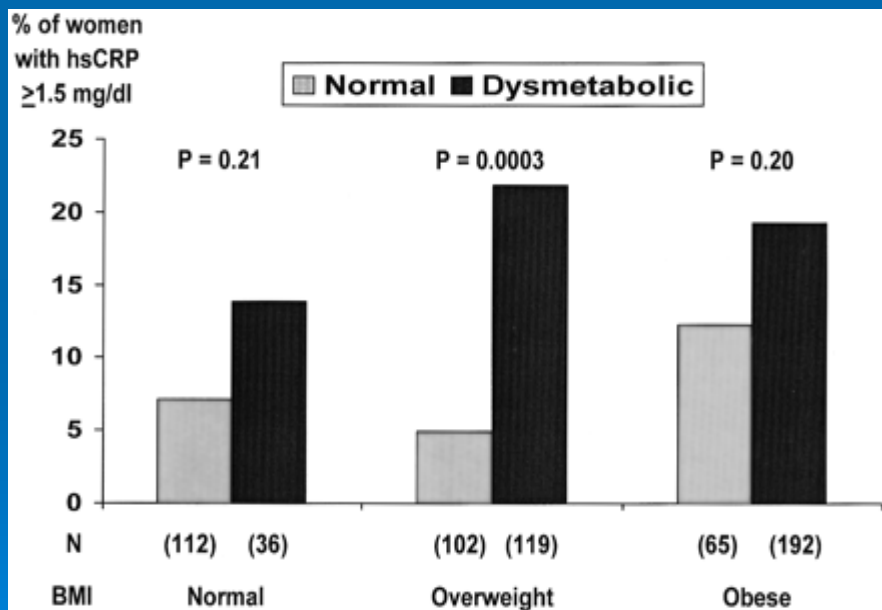
Metabolic
Dysregulation

Potential
Mechanisms



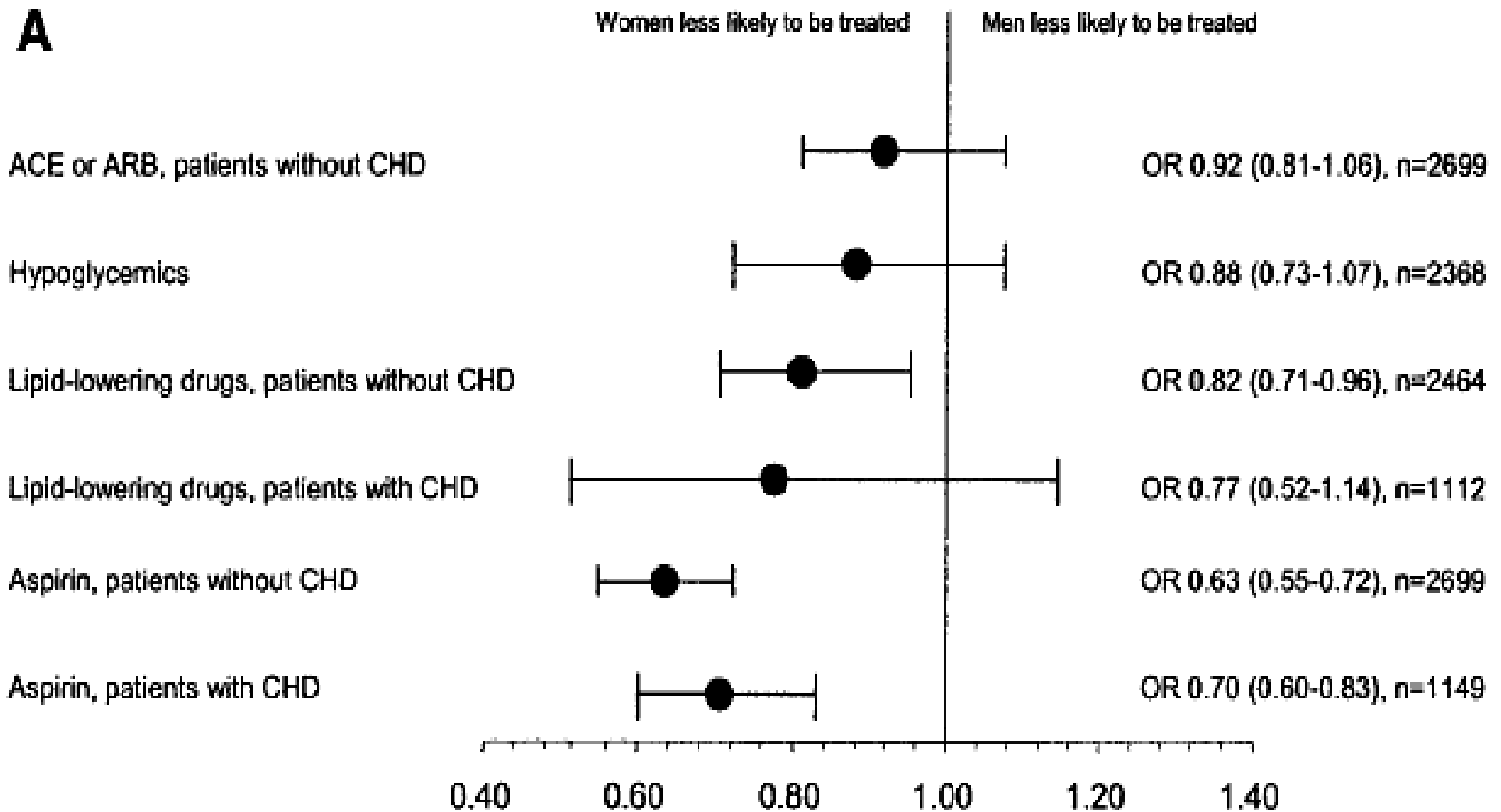
Importance of Obesity Versus the Metabolic Syndrome in CV Risk in Women: Women's Ischemia Syndrome Evaluation Study (WISE)

- 780 women referred for coronary angio on basis of suspected CAD
- Classified into BMI <24.9, >25.0, >30, +/- CAD, +/- MS.
- 3 year MACE (death, nonfatal MI, CVA, CHF) based on above criteria



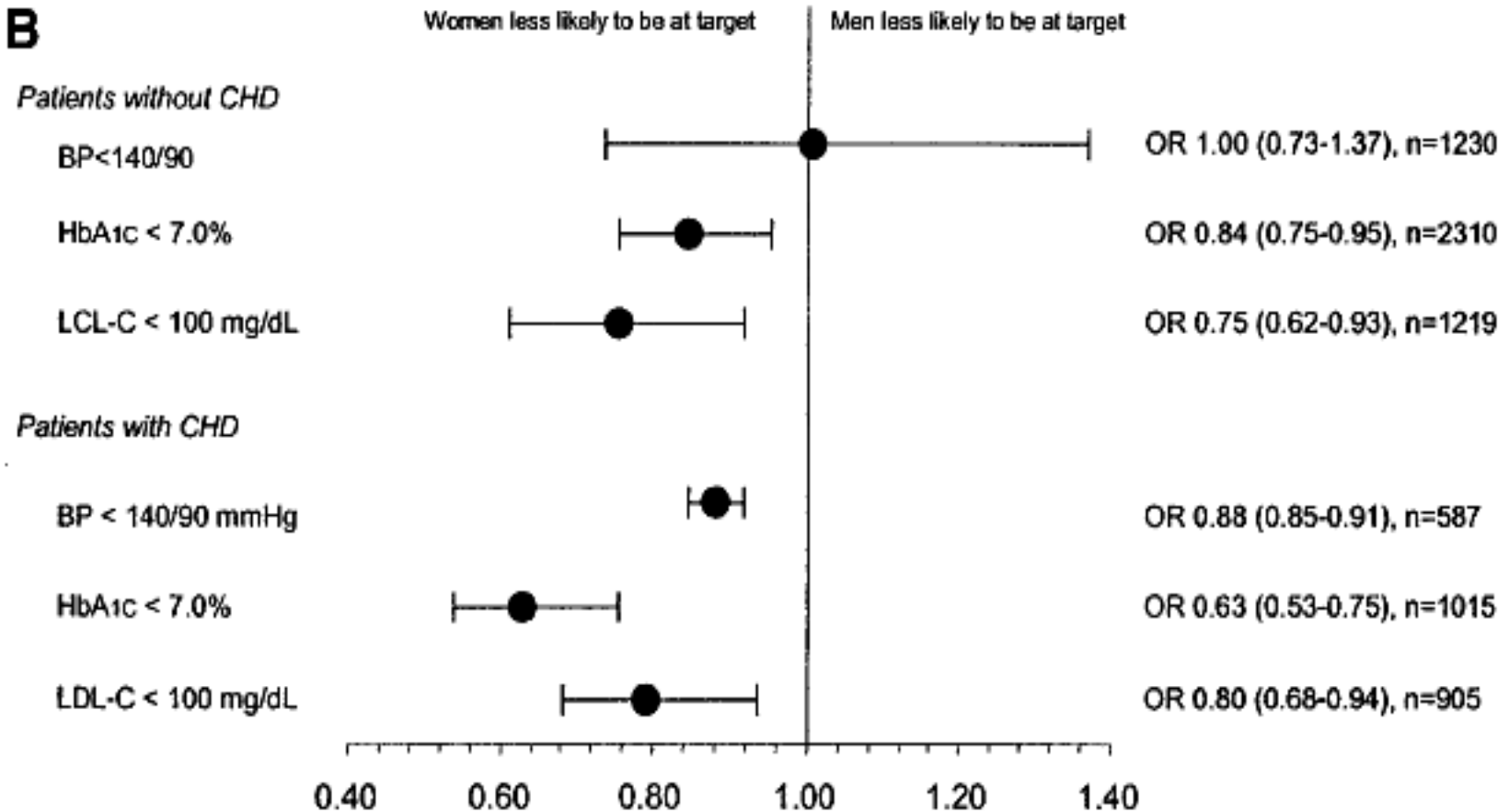
Best predictor of MACE was metabolic status and CAD extent

Sex disparities in CV risk treatment in diabetics



Sex disparities in CV risk treatment in diabetics

B



Conclusions

- **DM is an important risk factor of CHD in both sexes but have more prognostic impact on CV morbidity and mortality in diabetic females**
- **This fact had been confirmed in many epidemiological and clinical trials**
- **The pathogenic mechanisms underling this effects is not definitely known and is explained by multiple speculations**

Conclusions

- **Aggressive preventive and therapeutic interventions are needed to avoid the prognostic implication of female gender on diabetic macroangiopathy**
- **The metabolic syndrome is a common problem in diabetic female with clustering of many CAD risk factors that need more aggressive intervention**

Conclusions

- The role of HRT in 1ry or 2ry prevention of CAD is doubtful in diabetic and non-diabetic females after the results of HERS II and WHI trials
- The angiographic pattern of CAD in diabetic females (small arteries with extensive disease and poor microcirculation) put many nightmares in front of awakened intervention cardiologist

مستشفى الباطنة التخصصي

Specialized Medical Hospital



Thank you

17/05/2004 09:50:31

