Controversial Issues in DM

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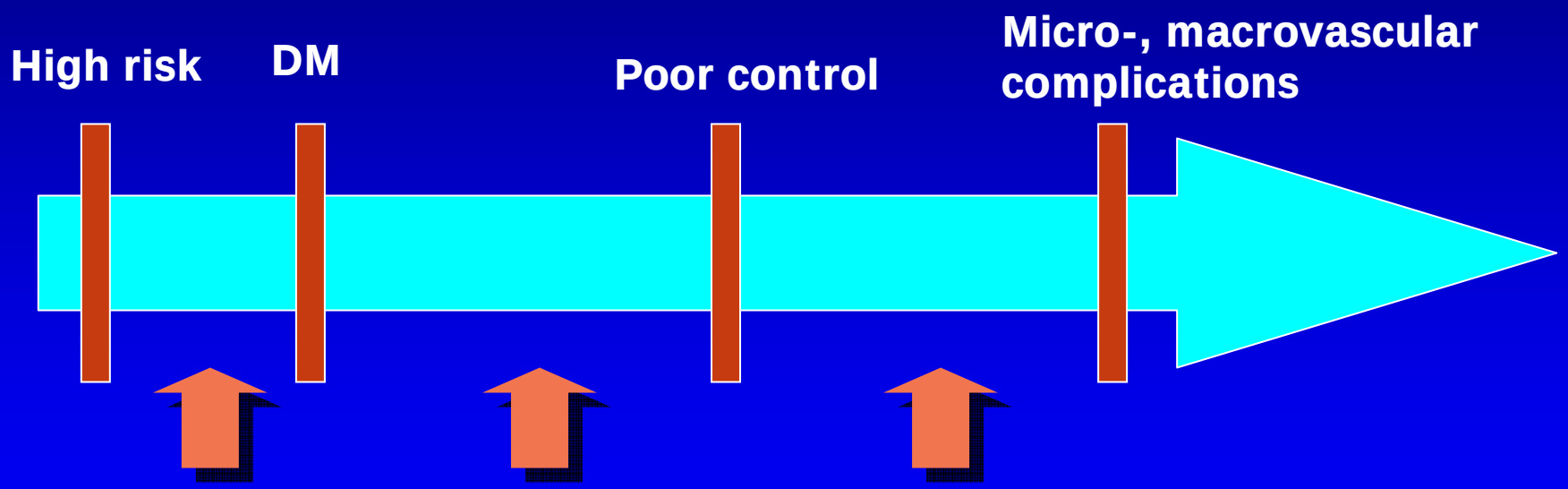
Glycemic control: intensive vs. less intensive

Stages of Intervention in DM



Glycemic Control and Microvascular Complications

- 1% decrease in HbA1c reduces microvascular complications by 25-35%
  - DCCT
  - UKPDS
  - Kumamoto

ACCORD, ADVANCE, VADT: Key Questions

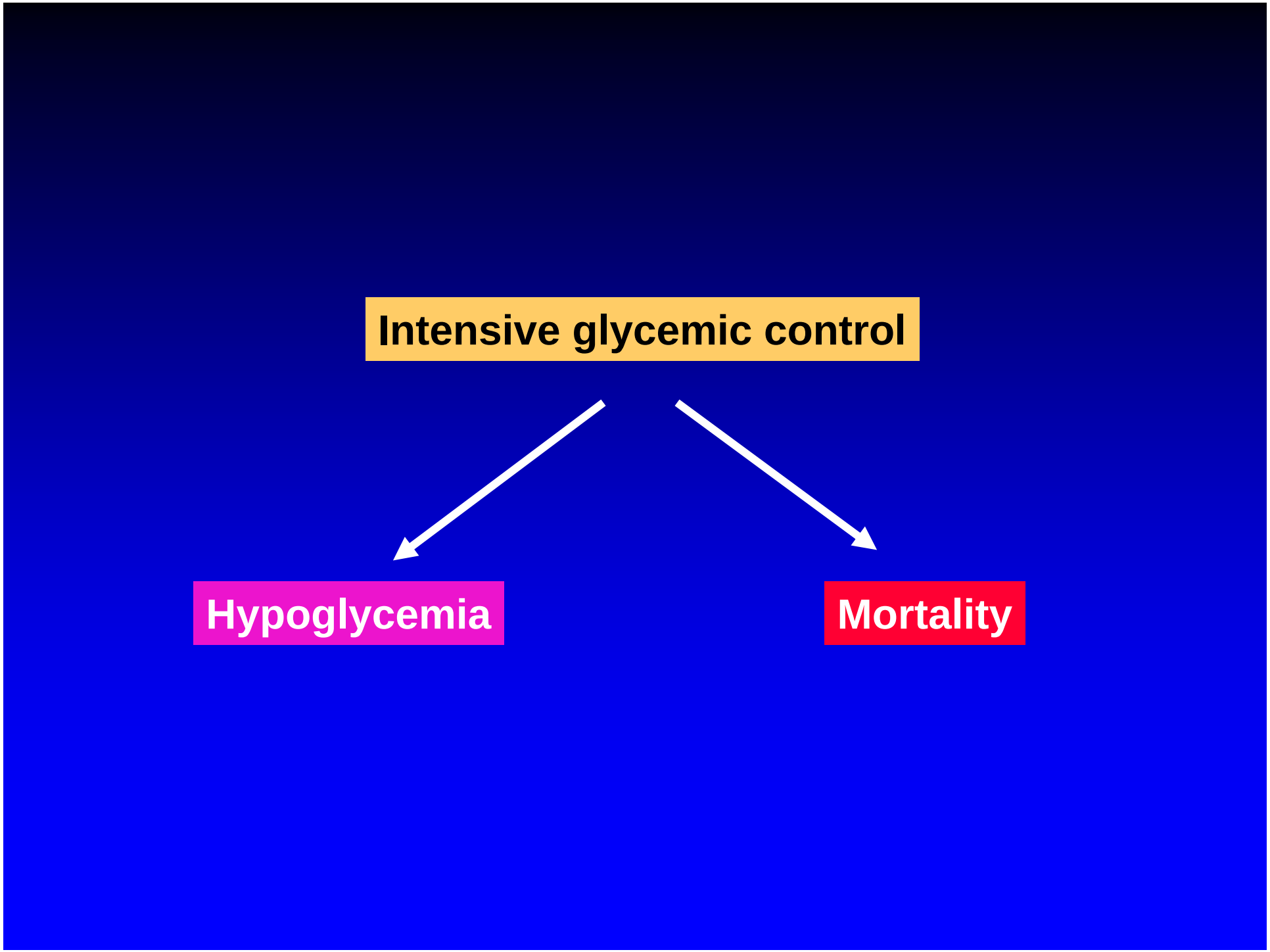
In high risk type 2 DM, are CVD reduced by

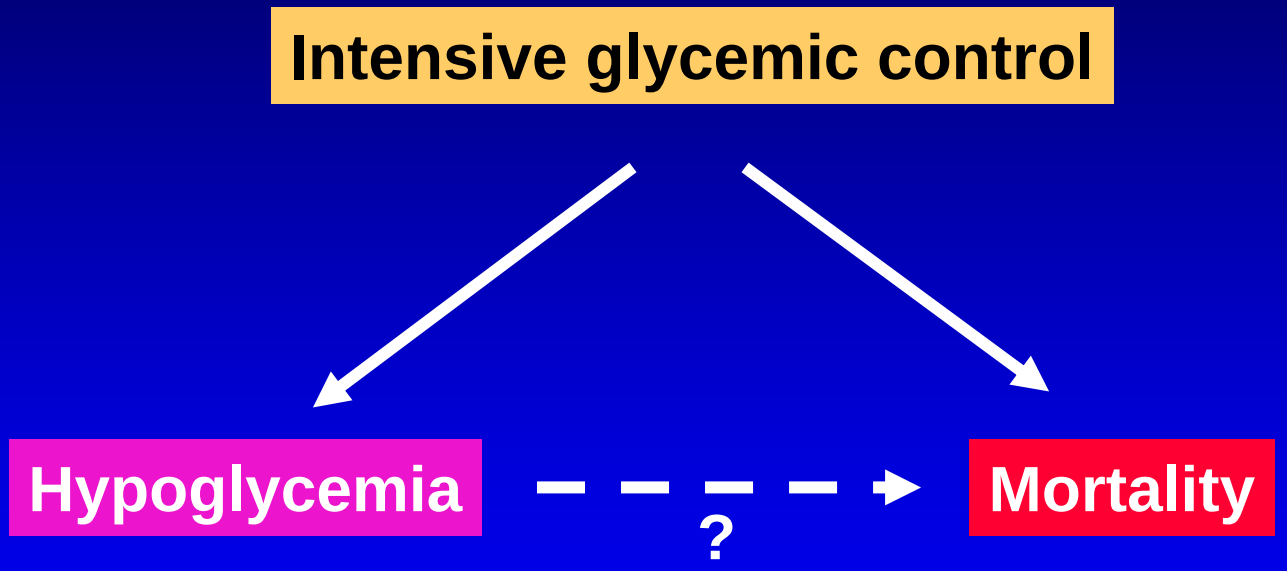
	ACCORD	ADVANCE	VADT
• Intensive glycemic control	+	+	+
• Intensive BP control	+		
• LDL-C, Trig, HDL-C control	+		

Macrovascular Disease and Tight Glycemic Control

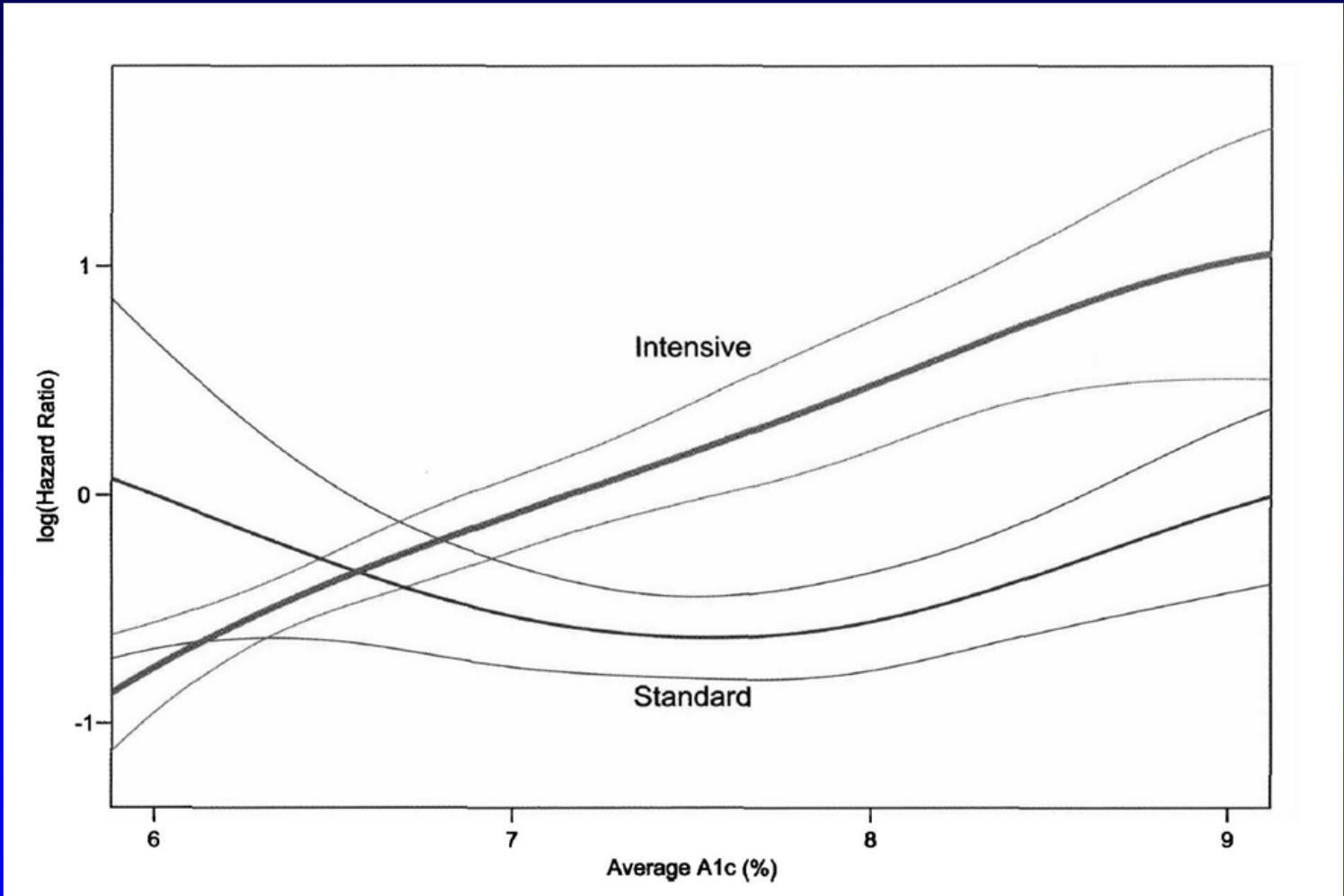
- ACCORD N Engl J Med 2008
- ADVANCE N Engl J Med 2008
- VADT N Engl J Med 2009

25,000 patients, no additional benefit to cardiovascular disease


Intensive glycemic control
Hypoglycemia
Mortality

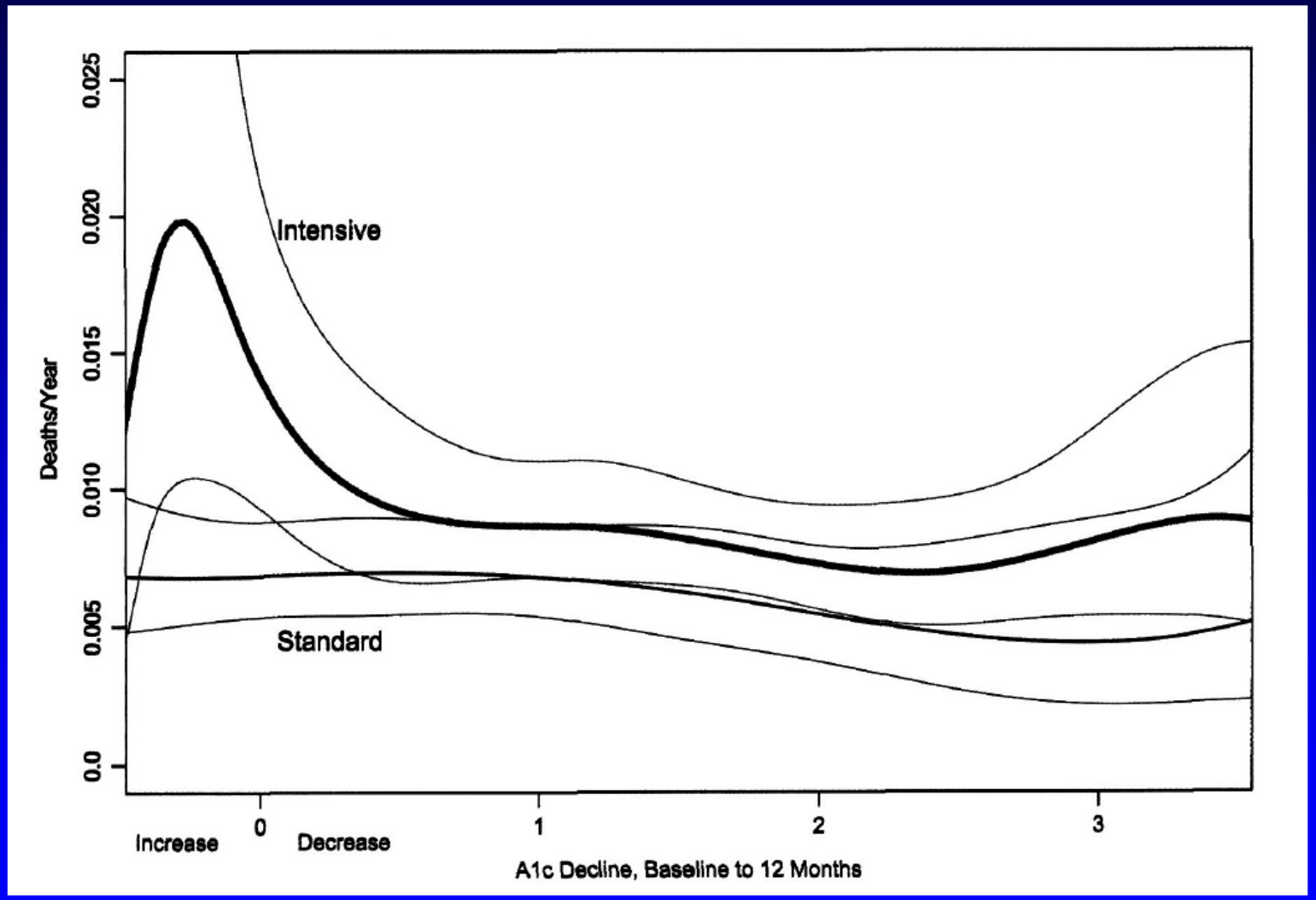

Intensive glycemic control
Hypoglycemia
?
Mortality

ACCORD: Mortality by Treatment Strategy and A1c



Riddle MC, et al. Diabetes Care May 2010

ACCORD: Mortality by Treatment Strategy and Change in A1c



Riddle MC, et al. Diabetes Care May 2010

DM and Cancer?

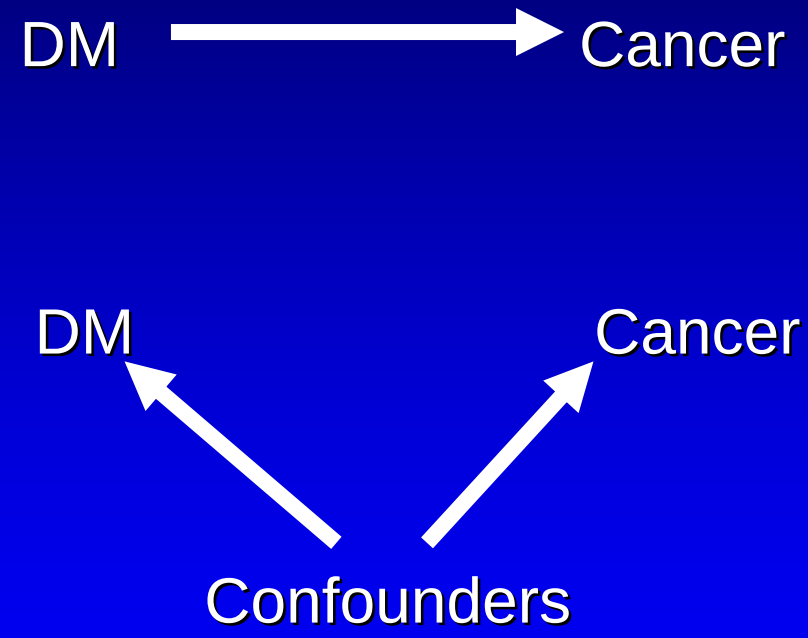
Association between Diabetes and Cancer Risk

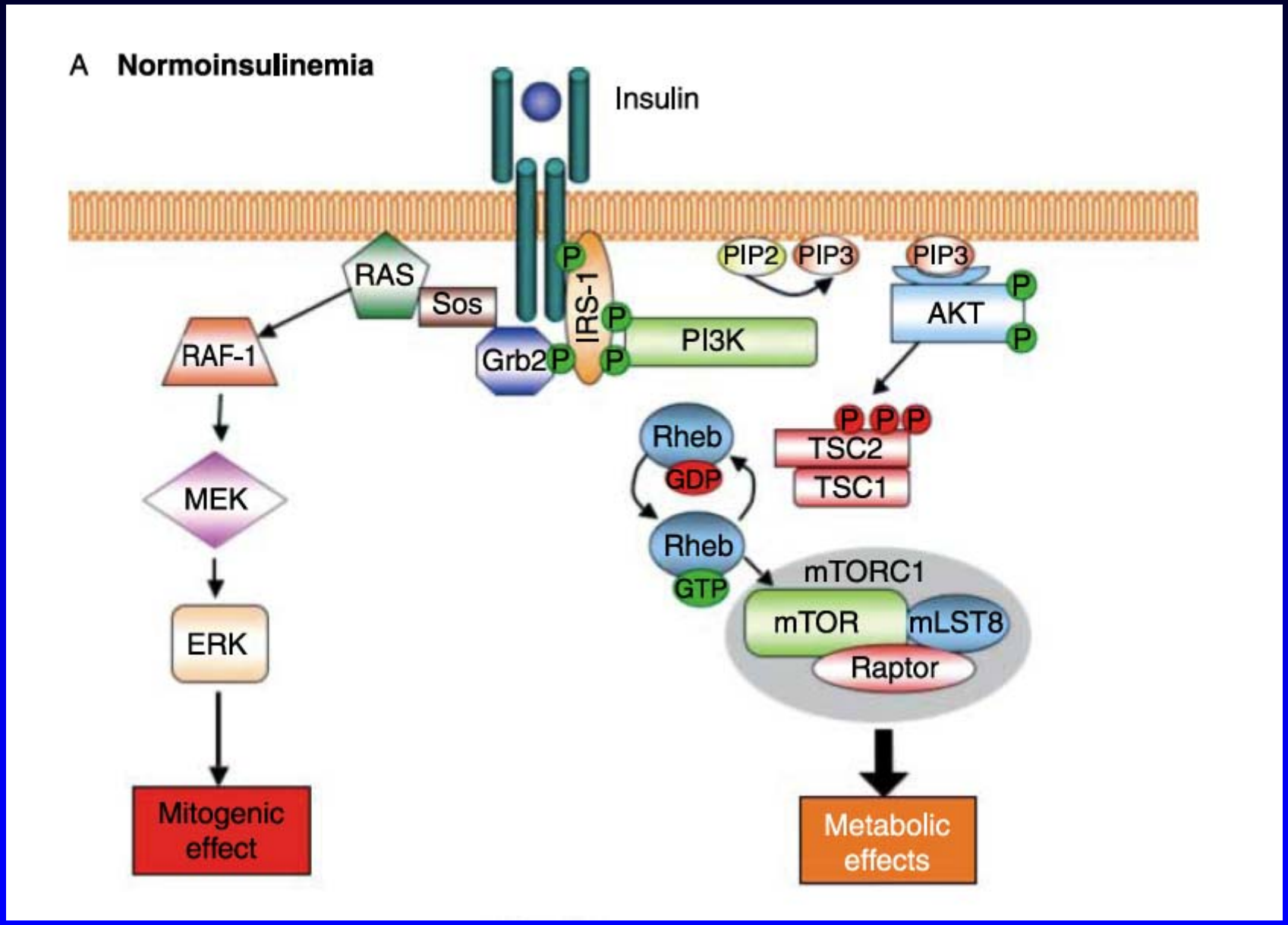
Cancer		RR (95% CI)
Liver (El-Serag *et al.* 2006)	13 case–control studies	2.50 (1.8–3.5)
	7 cohort studies	2.51 (1.9–3.2)
Pancreas (Huxley *et al.* 2005)	17 case–control studies	1.94 (1.53–2.46)
	19 cohort studies	1.73 (1.59–1.88)
Kidney[a] (Lindblad *et al.* 1999, Washio *et al.* 2007)	1 cohort study	1.50 (1.30–1.70)
	1 cohort study	2.22 (1.04–4.70)
Endometrium (Friberg *et al.* 2007)	13 case–control studies	2.22 (1.80–2.74)
	3 cohort studies	1.62 (1.21–2.16)
Colon–rectum (Larsson *et al.* 2005)	6 case–control studies	1.36 (1.23–1.50)
	9 cohort studies	1.29 (1.16–1.43)
Bladder (Larsson *et al.* 2006)	7 case–control studies	1.37 (1.04–1.80)
	3 cohort studies	1.43 (1.18–1.74)
Non-Hodgkin's lymphoma (Mitri *et al.* 2008)	5 cohort studies	1.41 (1.07–1.88)
	11 case–control studies	1.12 (0.95–1.31)
Breast (Larsson *et al.* 2007)	5 case–control studies	1.18 (1.05–1.32)
	15 cohort studies	1.20 (1.11–1.30)
Prostate (Kasper & Giovannucci 2006)	9 case–control studies	0.89 (0.72–1.11)
	10 cohort studies	0.81 (0.71–0.92)

[a]Data on kidney cancer were not obtained from meta-analysis.

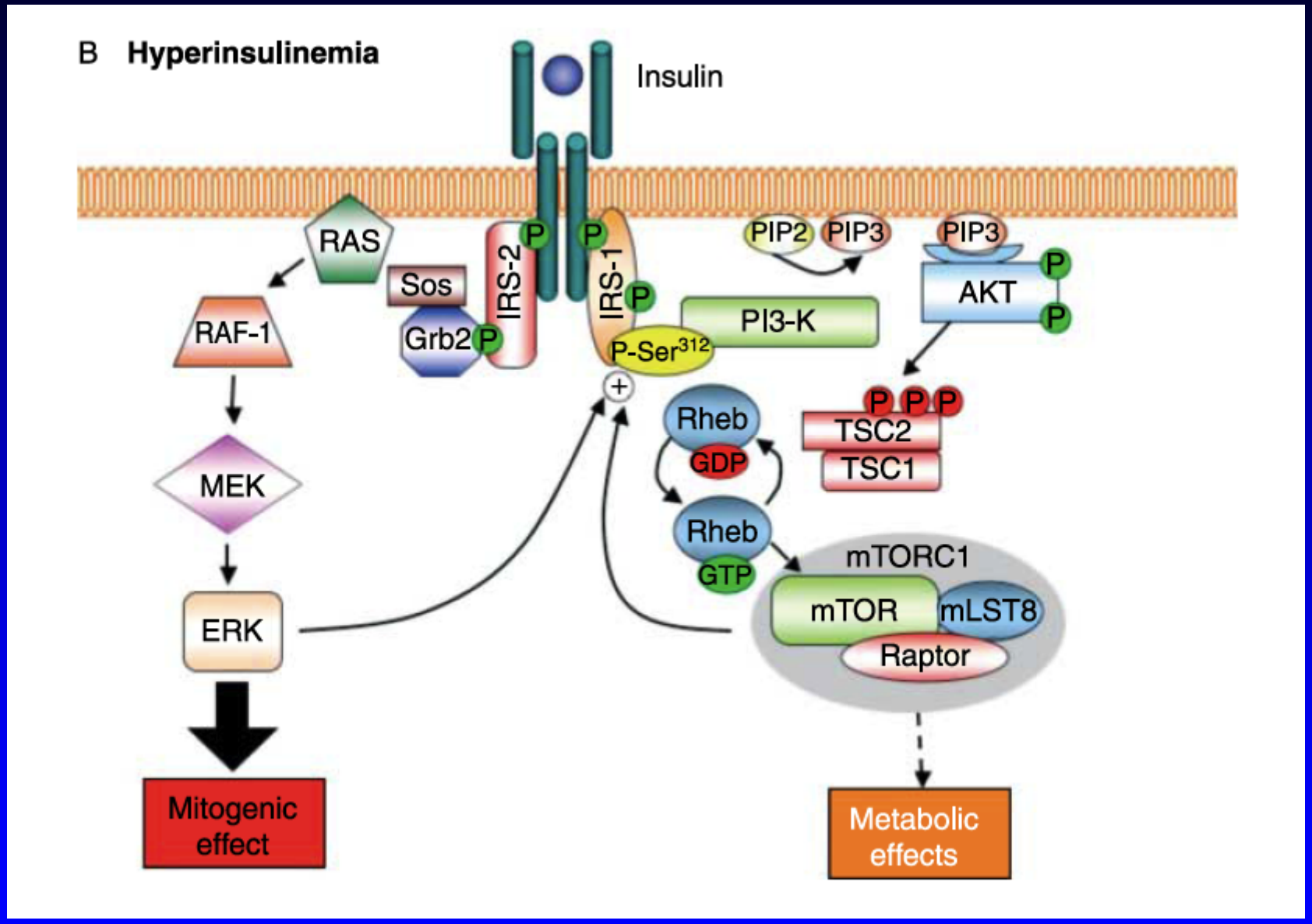
Vigneri P, et al. Endocr Relat Cancer 2009;16:1103-23

Diabetes and Cancer: Causative or Associative





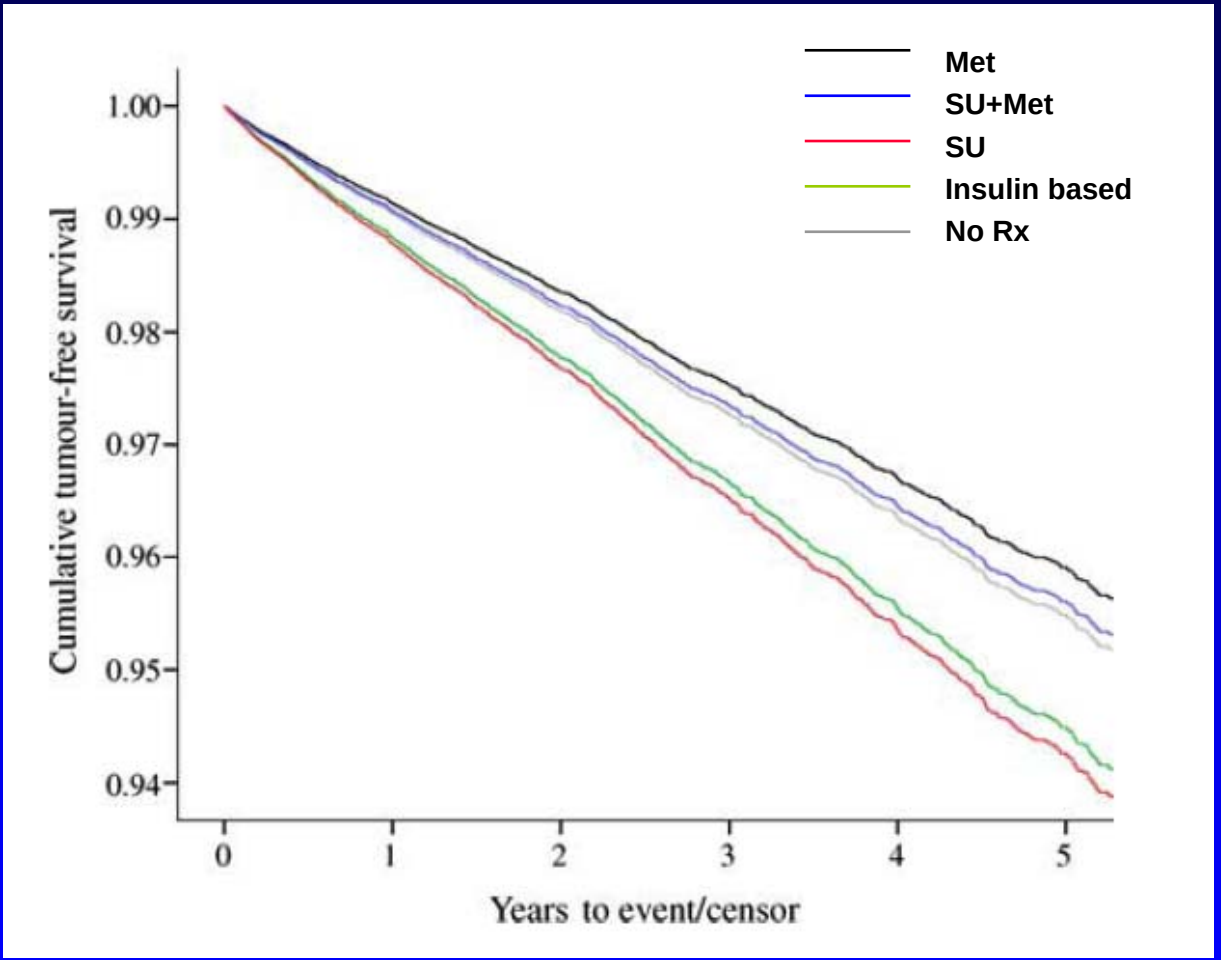
Vigneri P, et al. Endocr Relat Cancer 2009;16:1103-23



Vigneri P, et al. Endocr Relat Cancer 2009;16:1103-23

Antidiabetic Agents and Cancer?

Solid Cancers vs. Glucose-Lowering Rx



Currie CJ, et al. Diabetologia 2009;52:1766-77

Cancer Mortality vs. Glucose-Lowering Rx

Variable	Time at risk (person-days)	Cancer deaths, *n* (%)	Cancer mortality (/1000 person-years)	Adjusted HR (95% CI)[a]
Oral glucose-lowering agents				
Sulfonylurea monotherapy	16,737	162 (4.9)	9.7	1.0[b]
Metformin	38,973	245 (3.5)	6.3	0.80 (0.65–0.98)*
Insulin use (dispensations/year)[c]				
No insulin ever	52,131	323 (3.6)	–	1.0[b]
<3	400	6 (3.8)	–	2.22 (0.99–5.00)*
3 to 11	1,543	29 (5.0)	–	3.33 (2.26–4.89)**
≥12	1,636	49 (7.0)	–	6.40 (4.69–8.73)**

[a] Adjusted for age, sex and CDS

[b] Reference category for HR

[c] Specific mortality rates cannot be estimated for insulin exposure categories because of the time-varying nature of exposure. Cancer deaths were calculated on the basis of insulin category at the time of cancer death

*$p \leq 0.05$; **$p < 0.0001$

Bowker SL, et al. Diabetologia 2010;53:1631-7

Reviews/Commentaries/ADA Statements
ADA CONSENSUS REPORT

Diabetes and Cancer

A consensus report

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Epidemiologic evidence suggests that cancer incidence is associated with diabetes as well as certain diabetes risk factors and diabetes treatments. This consensus statement of experts assembled jointly by the American Diabetes Association and the American Cancer Society reviews the state of science concerning *1*) the association between diabetes and cancer incidence or prognosis, *2*) risk factors common to both diabetes and cancer, *3*) possible biologic links between diabetes and cancer risk, and *4*) whether diabetes treatments influence risk of cancer or cancer prognosis. In addition, key unanswered questions for future research are posed.

Diabetes Care 33:1674–1685, 2010

cancer has been difficult to establish because many areas do not have cancer registries, but in 2008 there were an estimated 12.4 million new cancer cases diagnosed. The most commonly diagnosed cancers are lung/bronchus, breast, and colorectal, whereas the most common causes of cancer deaths are lung, stomach, and liver cancer (1). In the U.S., the most commonly diagnosed cancers are prostate, lung/bronchus, and colon/rectum in men and breast, lung/bronchus, and colon/rectum in women. Of the world population between the ages of 20 and 79 years, an estimated 285 million people, or 6.6%, have diabetes (2). In

ADA Consensus: DM and Cancer Risk

- **Type 2 DM is associated with increased risk of some cancers**
- **May partly be due to shared risk factors**
- **Possible mechanisms include hyperinsulinemia, hyperglycemia and inflammation**
- **Heathful diets, physical activity, and weight management should be promoted**
- **Appropriate cancer screenings strongly encouraged**

Diabetes Care 2010;33:1674-85

ADA Consensus: DM and Cancer Risk

- **Evidence or specific drugs affecting cancer risk is limited**
- **Early evidence suggests that metformin is associated with a lower risk of cancer and that exogenous insulin is associated with an increased cancer risk**
- **Whether insulin glargine is more strongly associated with cancer risk needs further research**
- **Cancer risk should not be a major factor in choosing diabetes Rx for the average patient**
- **Selected patients with very high risk (occurrence or recurrence), these issues may require more careful consideration**

Diabetes Care 2010;33:1674-85

Plastics and DM?


TIME
SPECIAL REPORT
The Perils of Plastic
Chemicals in plastics and other products seem harmless, but mounting evidence links them to health problems—and Washington lacks the power to protect us
BY BRYAN WALSH
Photographs by James Day for TIME
April 2010

Association of Urinary Bisphenol A Concentration With Medical Disorders and Laboratory Abnormalities in Adults

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Tamara S. Galloway, PhD
Alan Scarlett, PhD
William E. Henley, PhD
Michael Depledge, PhD, DSc
Robert B. Wallace, MD
David Melzer, MB, PhD

Context Bisphenol A (BPA) is widely used in epoxy resins lining food and beverage containers. Evidence of effects in animals has generated concern over low-level chronic exposures in humans.

Objective To examine associations between urinary BPA concentrations and adult health status.

Design, Setting, and Participants Cross-sectional analysis of BPA concentrations and health status in the general adult population of the United States, using data from the National Health and Nutrition Examination Survey 2003-2004. Participants were 1455 adults aged 18 through 74 years with measured urinary BPA and urine creatinine concentrations. Regression models were adjusted for age, sex, race/ethnicity, education, income, smoking, body mass index, waist circumference, and urinary creatinine concentration. The sample provided 80% power to detect unadjusted odds ratios (ORs) of 1.4 for diagnoses of 5% prevalence per 1-SD change in BPA concentration, or standardized regression coefficients of 0.075 for liver enzyme concentrations, at a significance level of $P < .05$.

Main Outcome Measures Chronic disease diagnoses plus blood markers of liver function, glucose homeostasis, inflammation, and lipid changes.

Results Higher urinary BPA concentrations were associated with cardiovascular diagnoses in age-, sex-, and fully adjusted models (OR per 1-SD increase in BPA concentration, 1.39; 95% confidence interval [CI], 1.18-1.63; $P = .001$ with full adjustment). Higher BPA concentrations were also associated with diabetes (OR per 1-SD increase in BPA concentration, 1.39; 95% confidence interval [CI], 1.21-1.60; $P < .001$) but not with other studied common diseases. In addition, higher BPA concentrations were associated with clinically abnormal concentrations of the liver enzymes γ-glutamyltransferase (OR per 1-SD increase in BPA concentration, 1.29; 95% CI, 1.14-1.46; $P < .001$) and alkaline phosphatase (OR per 1-SD increase in BPA concentration, 1.48; 95% CI, 1.18-1.85; $P = .002$).

Conclusion Higher BPA exposure, reflected in higher urinary concentrations of BPA, may be associated with avoidable morbidity in the community-dwelling adult population.

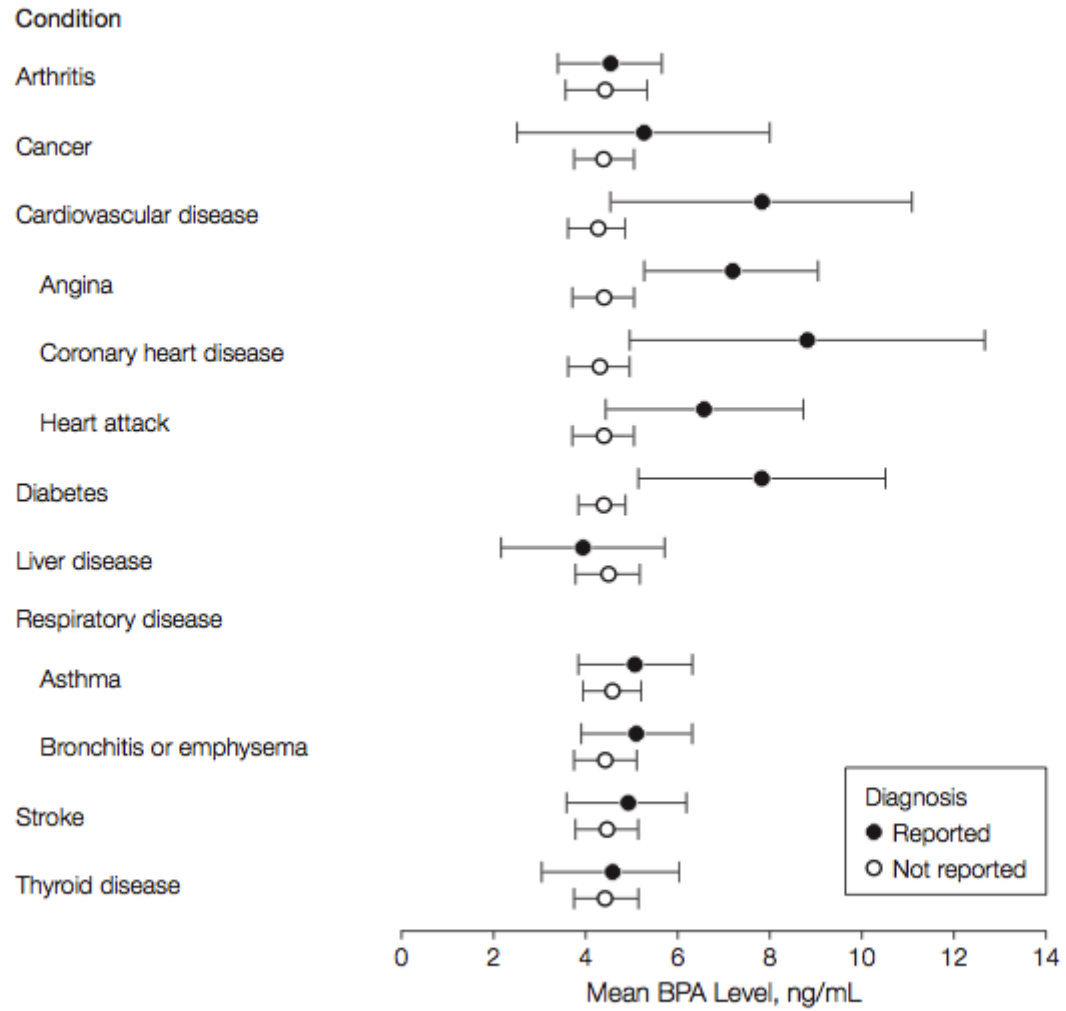
JAMA. 2008;300(11):1303-1310 www.jama.com

BISPHENOL A (BPA) IS ONE OF the world's highest production–volume chemicals, with more than 2 million metric tons produced worldwide in 2003 and annual increase in demand of 6% to 10% annually.[1] Bisphenol A is used extensively in epoxy resins lining food and beverage containers and as a monomer in polycarbonate plastics in many consumer products. Widespread and continuous exposure to BPA, primarily through food but also through drinking water, dental sealants, dermal exposure, and inhalation of household dusts, is evident from the presence of detectable levels of BPA in more than 90% of the US population.[2-4]

Most studies of the health effects of BPA have focused on well-documented

NHANES 2003/4 n = 1455

Figure. Estimated Mean Bisphenol A (BPA) Concentrations in Relation to Reported Diseases and Conditions



Estimates adjusted for age and sex. Error bars indicate 95% confidence intervals.

OPEN ACCESS Freely available online

PLoS one

Association of Urinary Bisphenol A Concentration with Heart Disease: Evidence from NHANES 2003/06

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Abstract

Background: Bisphenol A (BPA) is a high production volume chemical widely used in food and drinks packaging. Associations have previously been reported between urinary BPA concentrations and heart disease, diabetes and liver enzymes in adult participants of the National Health and Nutrition Examination Survey (NHANES) 2003/04. We aimed to estimate associations between urinary BPA concentrations and health measures in NHANES 2005/06 and in data pooled across collection years.

Methodology and Findings: A cross-sectional analysis of NHANES: subjects were n = 1455 (2003/04) and n = 1493 (2005/06) adults aged 18–74 years, representative of the general adult population of the United States. Regression models were adjusted for age, sex, race/ethnicity, education, income, smoking, BMI, waist circumference, and urinary creatinine concentration. Main outcomes were reported diagnoses of heart attack, coronary heart disease, angina and diabetes and serum liver enzyme levels. Urinary BPA concentrations in 2005/06 (geometric mean 1.79 ng/ml, 95% CI: 1.64 to 1.96) were lower than in 2003/04 (2.49 ng/ml, CI: 2.20 to 2.83, difference p-value = 0.00002). Higher BPA concentrations were associated with coronary heart disease in 2005/06 (OR per z-score increase in BPA = 1.33, 95%CI: 1.01 to 1.75, p = 0.043) and in pooled data (OR = 1.42, CI: 1.17 to 1.72, p = 0.001). Associations with diabetes did not reach significance in 2005/06, but pooled estimates remained significant (OR = 1.24, CI: 1.10 to 1.40, p = 0.001). There was no overall association with gamma glutamyl transferase concentrations, but pooled associations with alkaline phosphatase and lactate dehydrogenase remained significant.

Conclusions: Higher BPA exposure, reflected in higher urinary concentrations of BPA, is consistently associated with reported heart disease in the general adult population of the USA. Studies to clarify the mechanisms of these associations are urgently needed.

Table 3. Fully adjusted* survey weighted model estimates (odds ratios with 95% confidence intervals) of disease associations per standard deviation increase of Bisphenol A concentration: adults aged 18 to 74.

	NHANES 2003/04	NHANES 2005/06	Pooled data
Condition	**OR (95% CI), p-value**	**OR (95% CI), p-value**	**OR (95% CI), p-value**
Myocardial Infarction	**1.40 (1.07 to 1.84), p = 0.017**	1.39 (1.00 to 1.94), p = 0.051	**1.32 (1.15 to 1.52), p = 0.0003**
Angina	**1.27 (1.06 to 1.54), p = 0.015**	1.16 (0.88 to 1.53), p = 0.262	**1.24 (1.07 to 1.43), p = 0.005**
Coronary Heart Disease	**1.60 (1.11 to 2.32), p = 0.016**	**1.33 (1.01 to 1.75), p = 0.043**	**1.42 (1.17 to 1.72), p = 0.001**
CVD (any diagnoses of MI, angina or CHD)	**1.34 (1.10 to 1.66), p = 0.008**	1.18 (0.88 to 1.59), p = 0.243	**1.26 (1.10 to 1.44), p = 0.001**
Diabetes	**1.40 (1.25 to 1.56), p = 0.00001**	1.02 (0.76 to 1.38), p = 0.872	**1.24 (1.10 to 1.40), p = 0.001**

*models adjusted for age, gender, ethnicity, education, income, BMI, waist circumference, smoking status and urinary creatinine.

doi:10.1371/journal.pone.0008673.t003

PLoS ONE 2010;5:e8673

BPA Detectability and Glucose Tolerance

	Normal (80)	IGT (80)	DM (normal FPG) (44)	DM (abnormal FPG) (36)
BPA-	43(53.8%)	28(35.0%)	17(38.6%)	20(55.6%)
BPA+	37(46.3%)	52(65.0%)	27(61.4%)	16(44.4%)

$P < 0.05$

Chailurkit L, et al. 2010