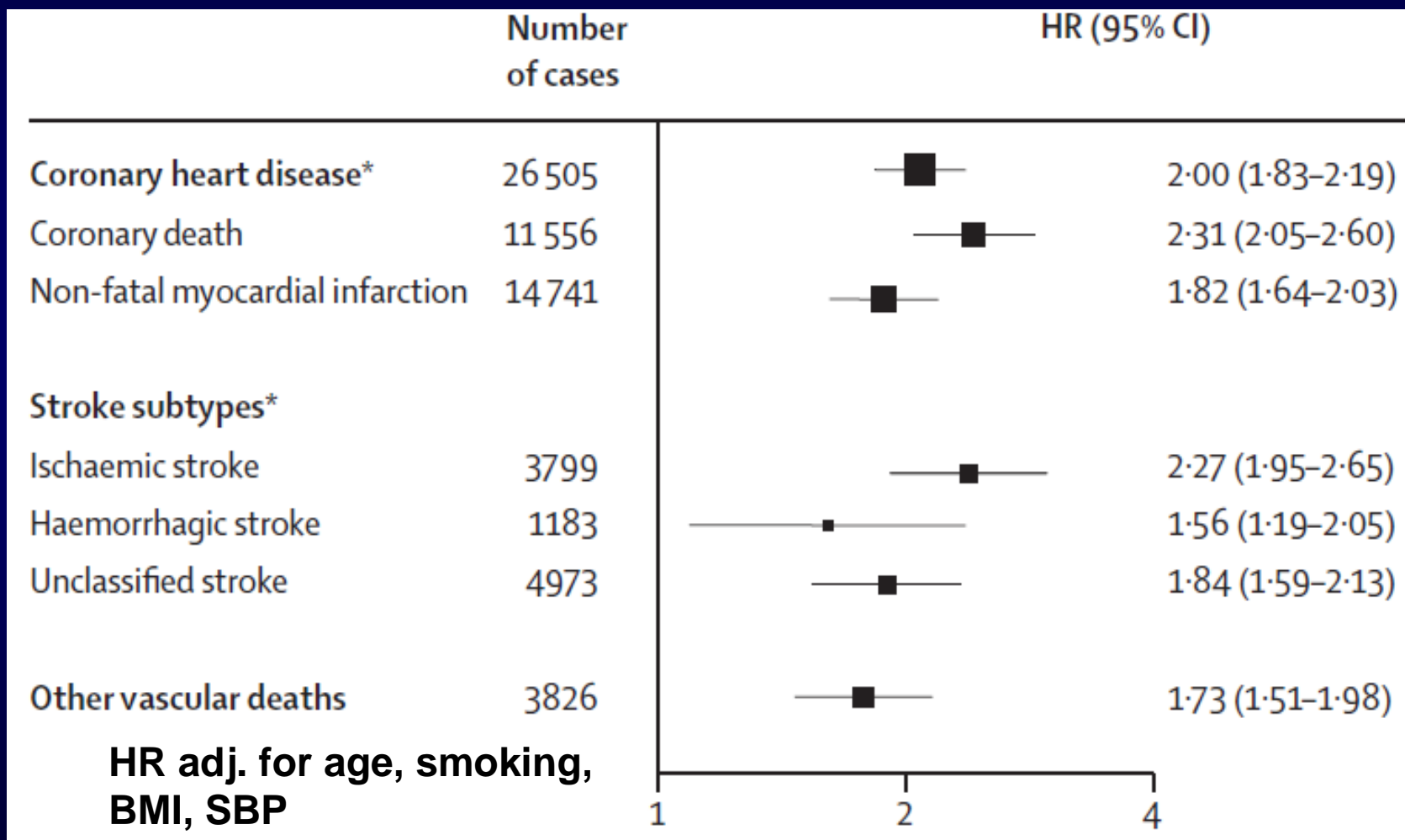


Cardioprotective Therapies in Diabetes

The Evidence

Hertzel C. Gerstein MD MSc FRCPC
McMaster University & Population Health Research Institute

DM & the Risk of CV Outcomes

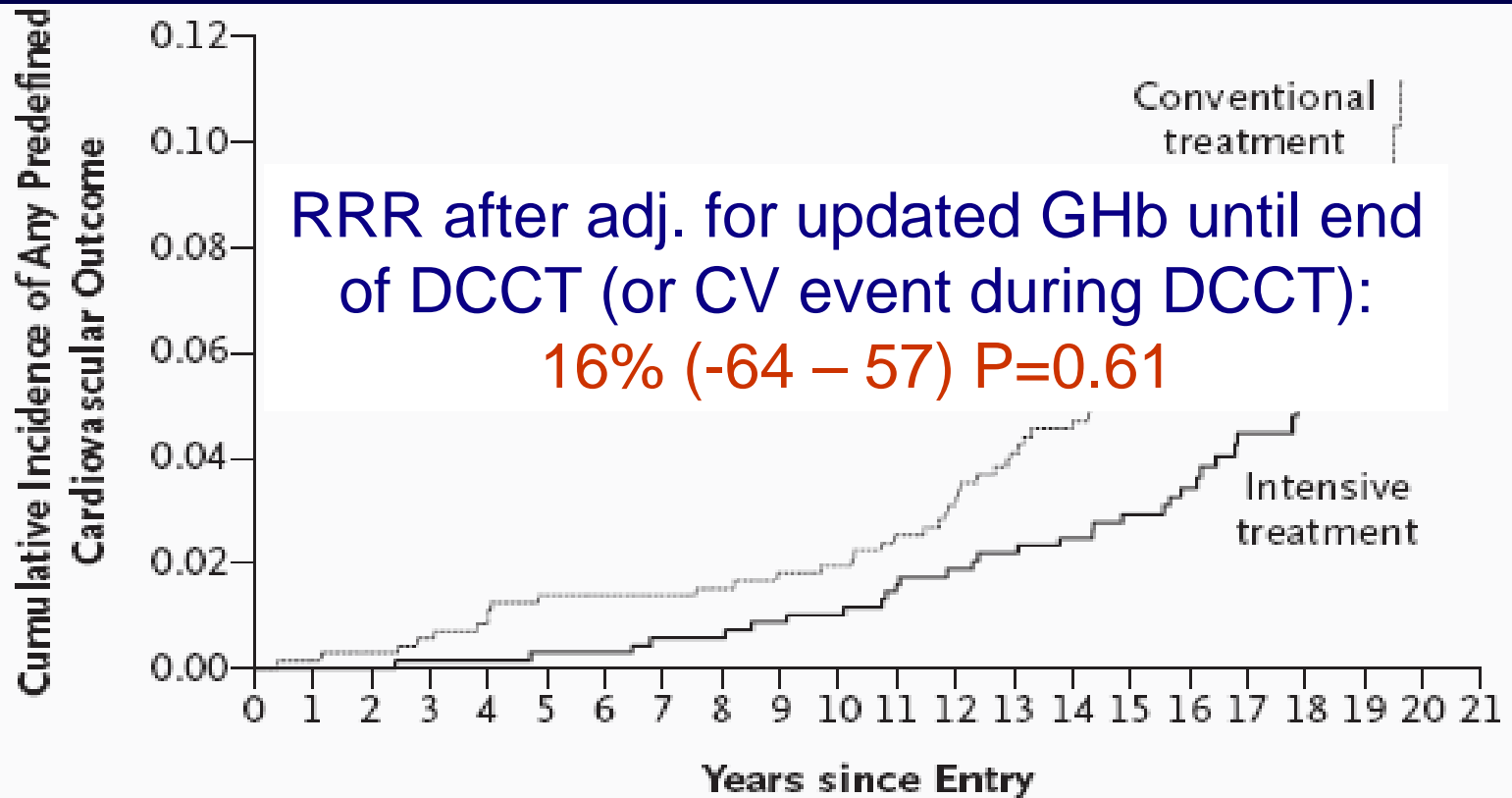


Cardioprotective Therapies

- Trials of Glucose Lowering Intensity
- Trials of Glucose Lowering Approaches
- Surgical Trials
- BP/Lipid Lowering Trials
- Trials of RAS blockade
- Trials of ASA

Intensive Insulin & CVD: Type 1 DM

DCCT/EDIC NEJM 2005;353:2643



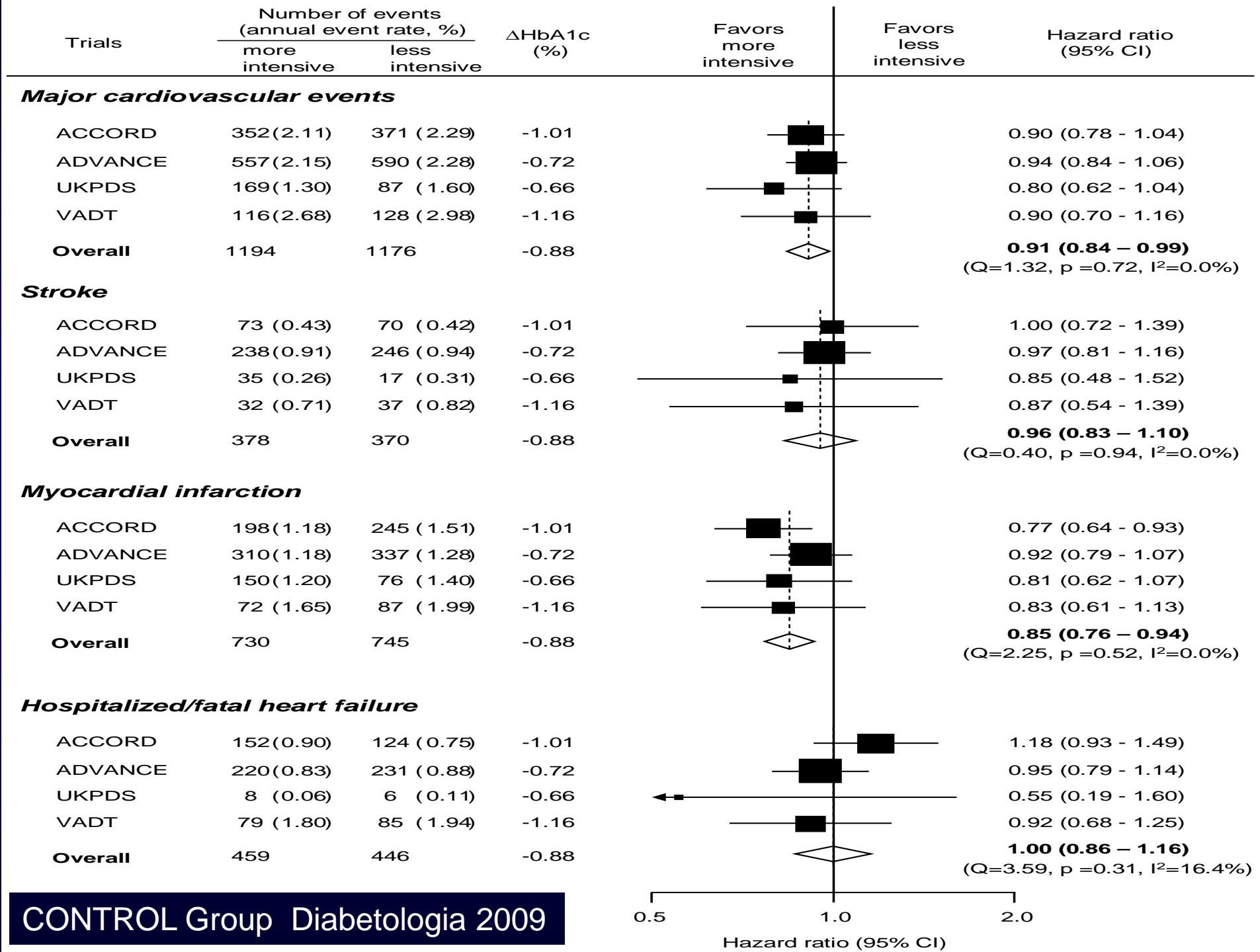
No. at Risk

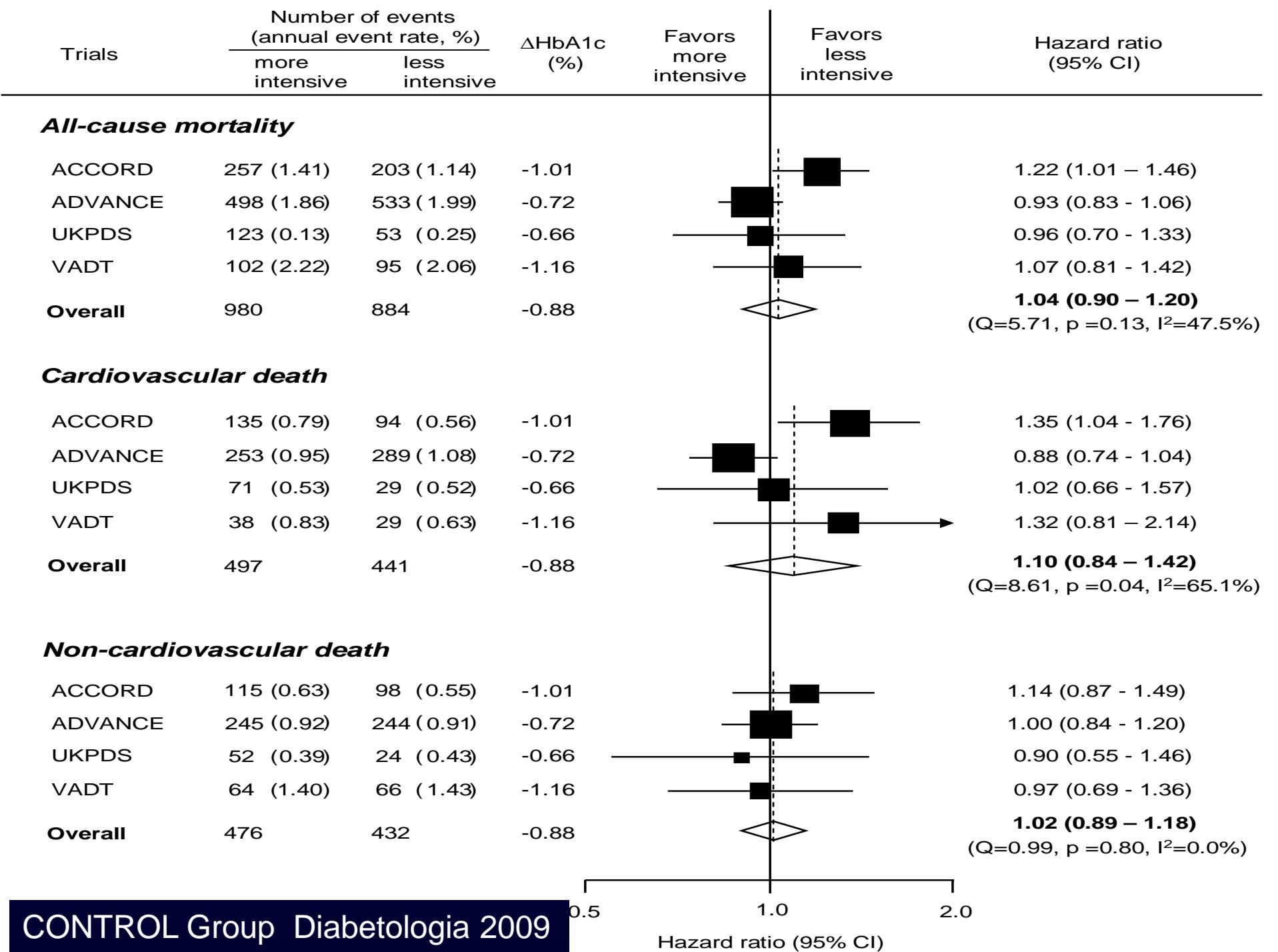
| | | | | |
|------------------------|-----|-----|-----|-----|
| Intensive treatment | 705 | 683 | 629 | 113 |
| Conventional treatment | 714 | 688 | 618 | 92 |

Trials of More vs. Less G Lowering

Type 2 Diabetes

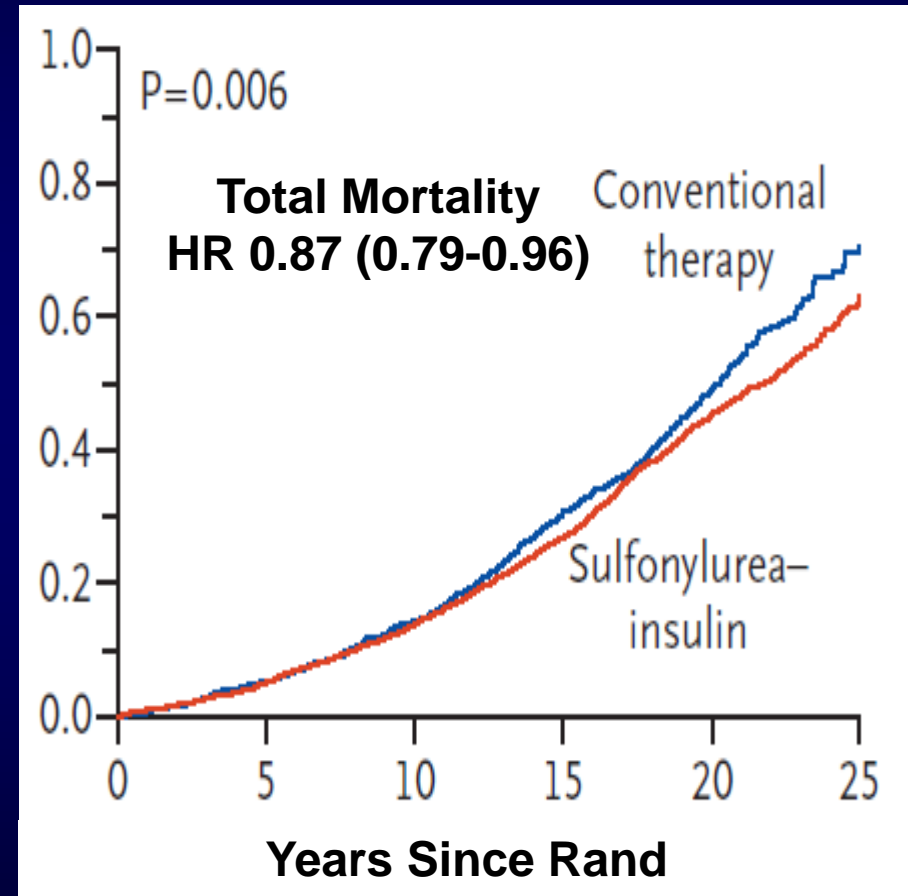
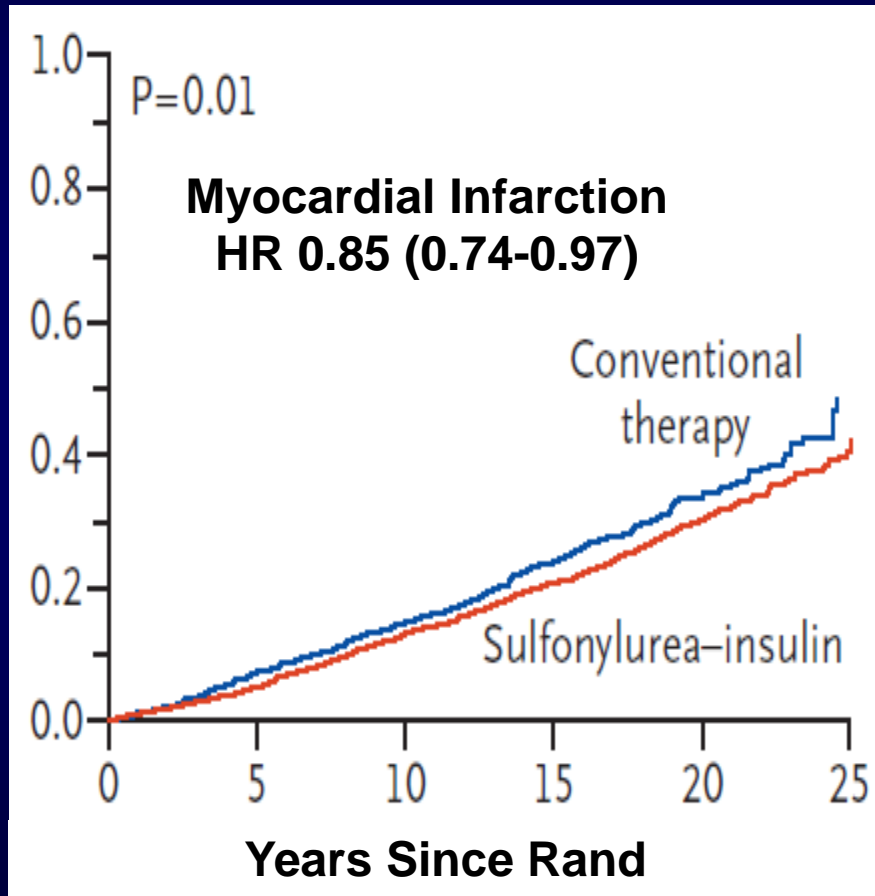
| Study Name | Duration (yrs) | N | Glycemia | |
|------------|----------------|-------|---------------|------------------------|
| | | | Target | Achieved |
| UKPDS | 10 | 3867 | FPG < 6 (110) | A1C = 7.0% vs. 7.9% |
| ACCORD | 3.5 | 10251 | A1C < 6.0% | A1C = 6.4% vs. 7.5% |
| ADVANCE | 5 | 11140 | A1C < 6.5% | A1C = 6.5% vs. 7.3% |
| VADT | 6.3 | 1791 | A1C < 6.0% | A1C = 6.9% vs. 8.4% |





Intensive Rx & Outcomes: New T2DM

UKPDS F/U NEJM 2008;359:1-13



Cardioprotective Therapies

- Trials of Glucose Lowering Intensity
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- Trials of ASA

BARI 2D Trial

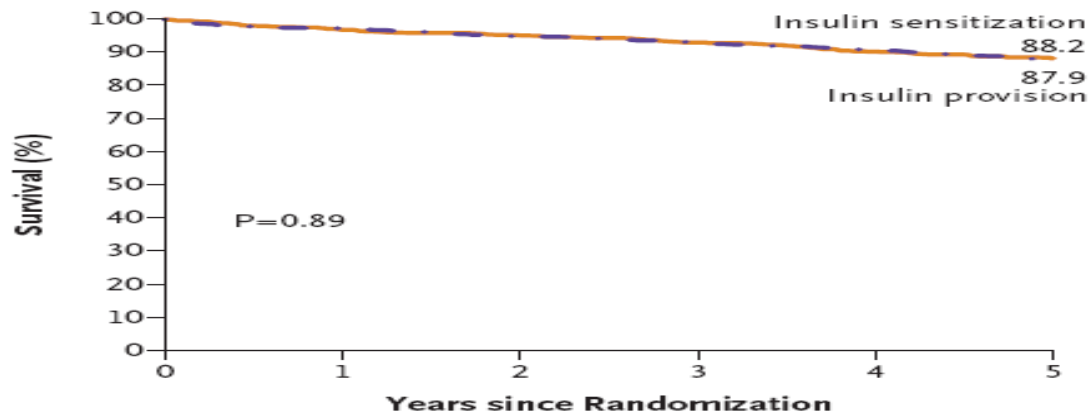
- **Participants:** N=2368 with type 2 DM (30% female; mean age = 63; median A1C = 7.7%, mean DM duration 10.4 years)

Angiographically proven CAD with symptoms

- **Stratification:** best treated with PCI (1605) or CABG (763)
- **Allocation:** a) insulin sensitization vs. provision
b) medical Rx vs. revascularization
- **Mean F/U:** 5.3 years

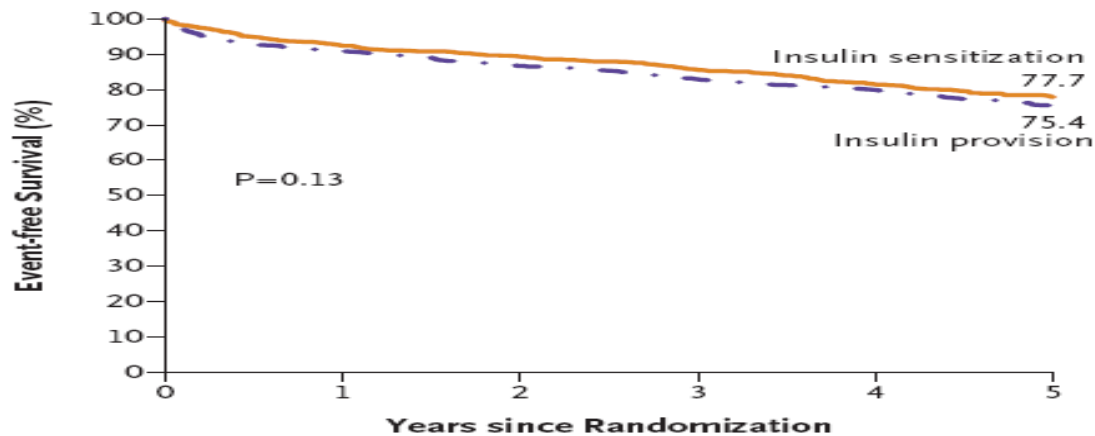
Insulin Sensitization vs. Provision

B Survival, Insulin Sensitization vs. Insulin Provision



No. at Risk 2368 2296 2247 2197 1892 1196

D Freedom from Major Cardiovascular Events, Insulin Sensitization vs. Insulin Provision



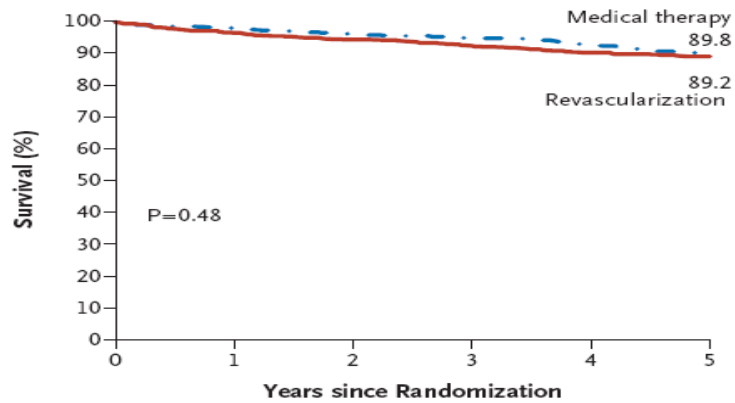
risk 2368 2094 1984 1807 1459 823

Cardioprotective Therapies

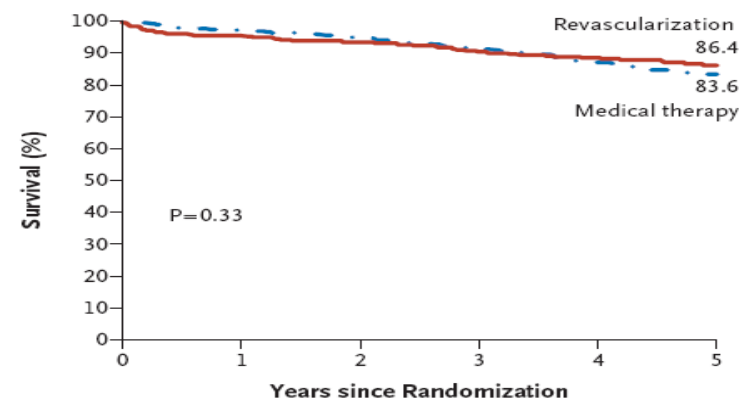
- Trials of Glucose Lowering Intensity
- Trials of Glucose Lowering Approaches
- Surgical Trials
- BP/Lipid Lowering Trials
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- Trials of ASA

Revascularization vs. Medical Rx

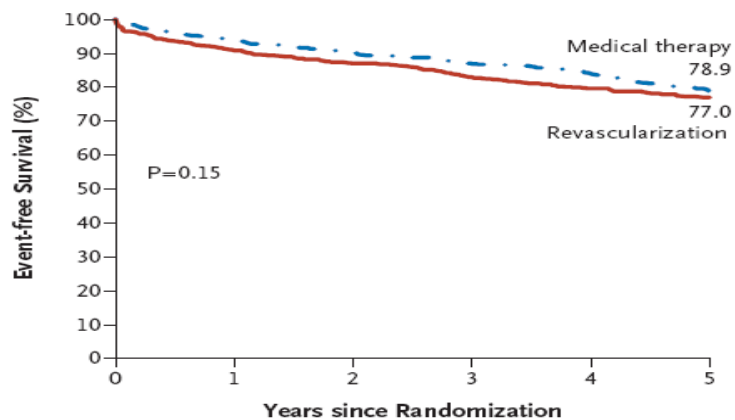
A Survival in PCI Stratum



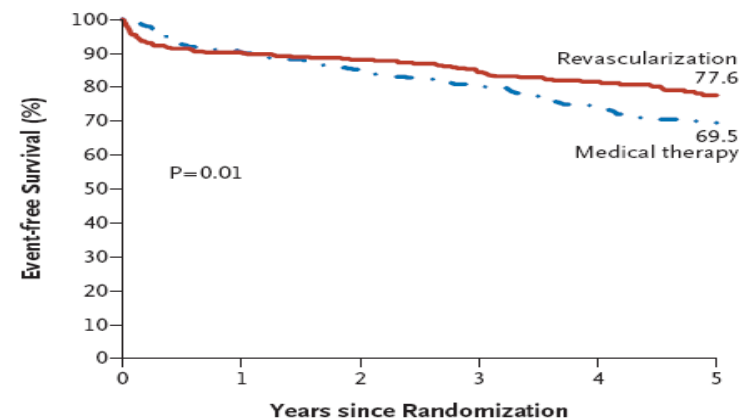
B Survival in CABG Stratum



C Freedom from Major Cardiovascular Events in PCI Stratum



D Freedom from Major Cardiovascular Events in CABG Stratum



Cardioprotective Therapies

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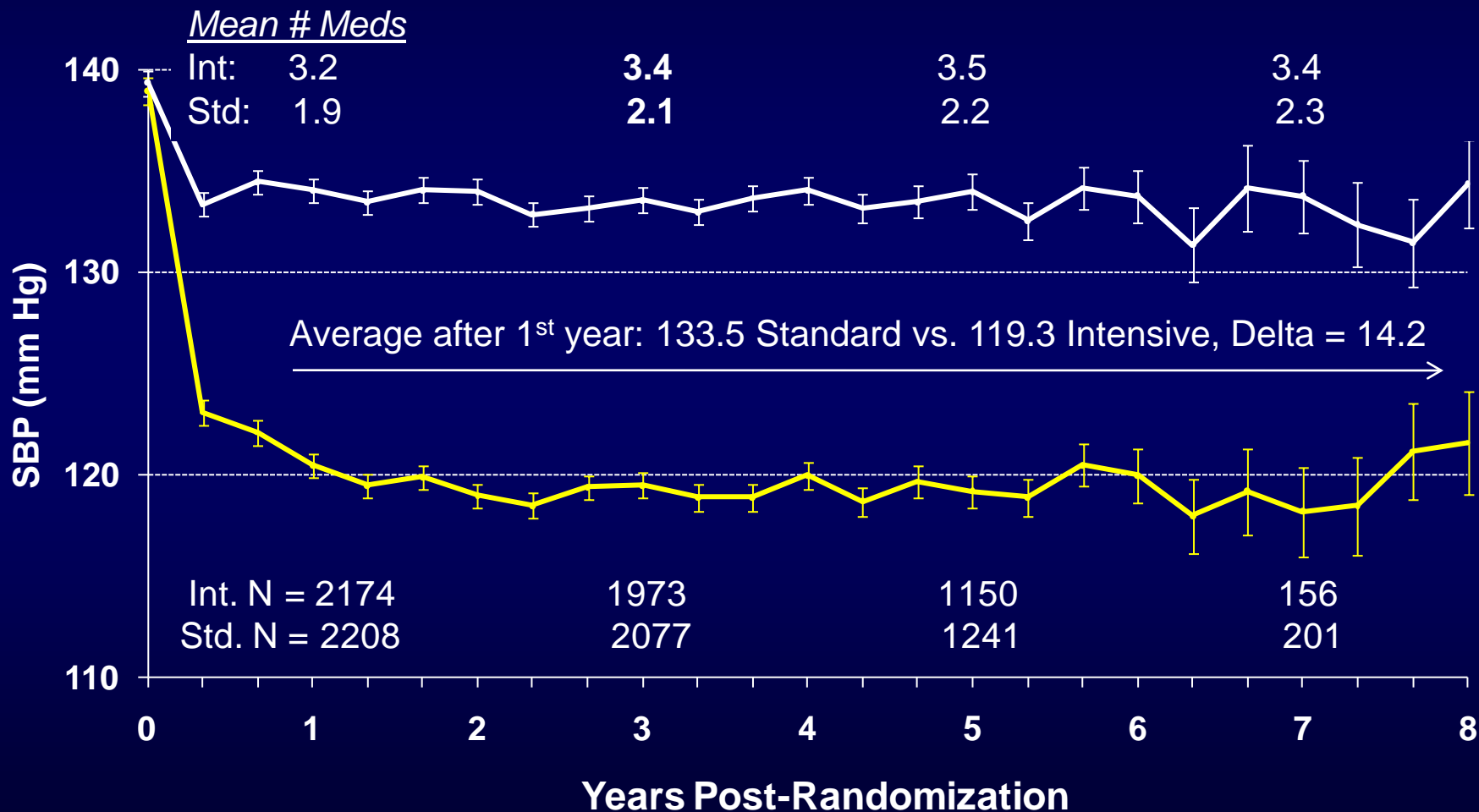
Clinical Trials of BP Lowering in Patients with Diabetes: SBP Goals, Mean Achieved SBP, Outcomes

| Trial | N | Mean SBP less intense | SBP Goal | Mean SBP more intense | CVD Risk Reduction |
|----------|--------|--------------------------|-----------|--------------------------|-----------------------|
| SHEP | 583 | 155 | <148 | 146 | 22-56% |
| Syst-Eur | 492 | 162 | <150 | 153 | 62-69% |
| HOT | 1,501 | 148 | DBP Goals | 144 | 30-67% |
| UKPDS | 1,148 | 154 | <150 | 144 | 32-44% |
| ABCD | 470 | 138 | DBP Goals | 132 | No CVD reduc |
| ADVANCE | 11,140 | 140 | none | 135 | 14% mortality reduc |

Cushman, et al. *Am J Cardiol* 2007;99[suppl]:44i-55i; Patel, et al. *Lancet* 2007;370:829-840;
ACCORD Study Group. *NEJM* 2010;362:1575-85.

ACCORD BP Trial (N=4733)

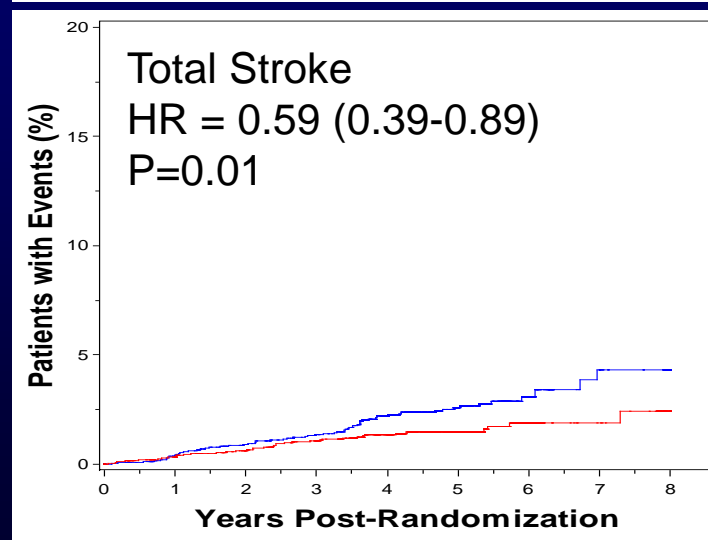
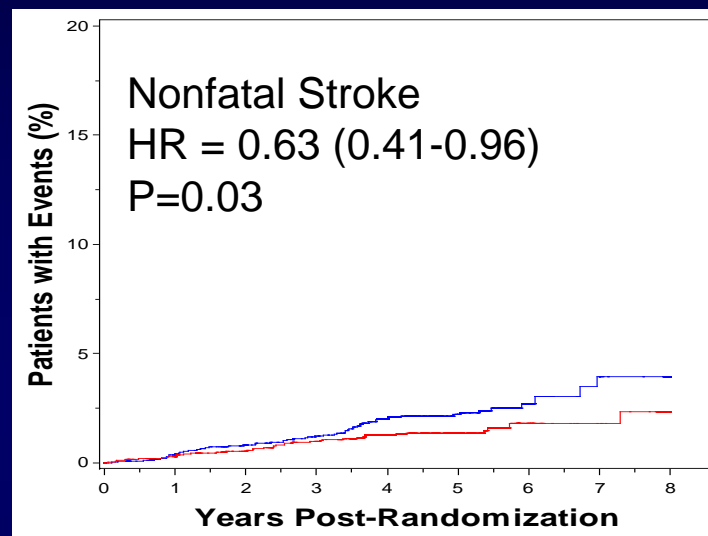
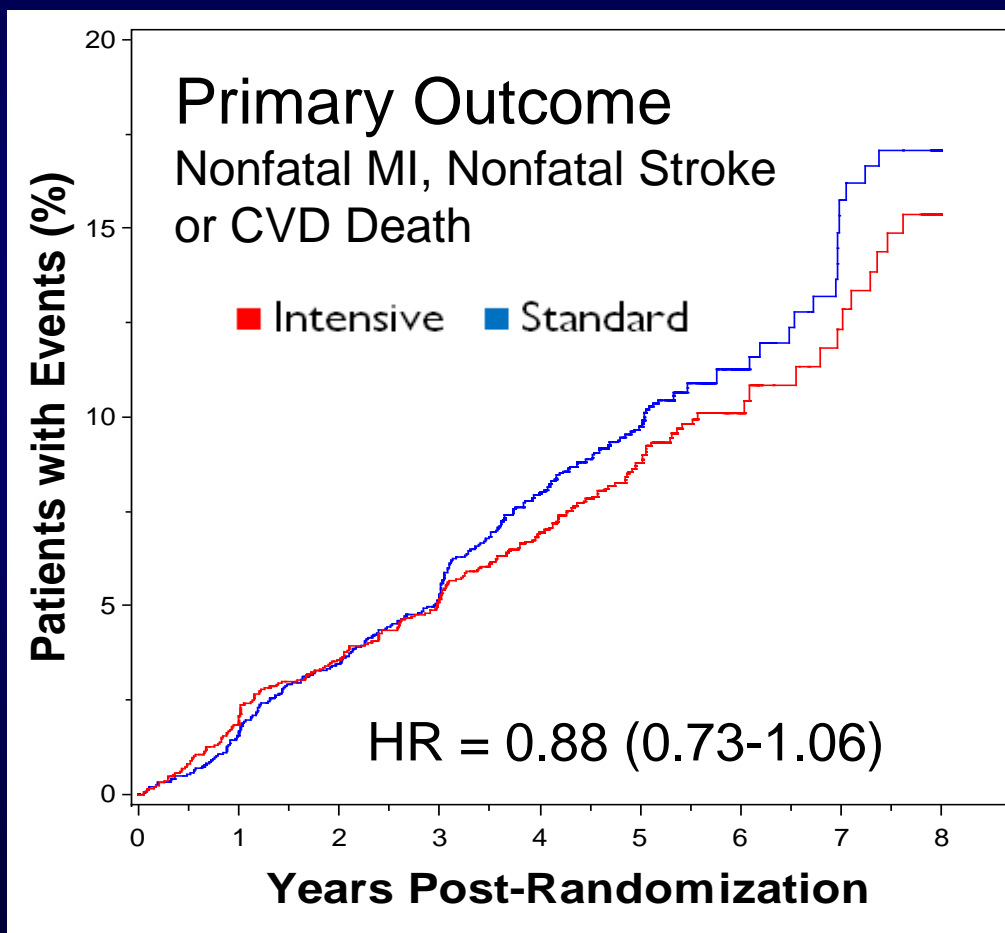
Systolic BP < 120 vs. < 140



— Intensive — Standard

ACCORD BP Trial (N=4733; F/U 4.7y)

Systolic BP < 120 vs. < 140



Clinical Trials of BP Lowering in Patients with Diabetes: SBP Goals, Mean Achieved SBP, Outcomes

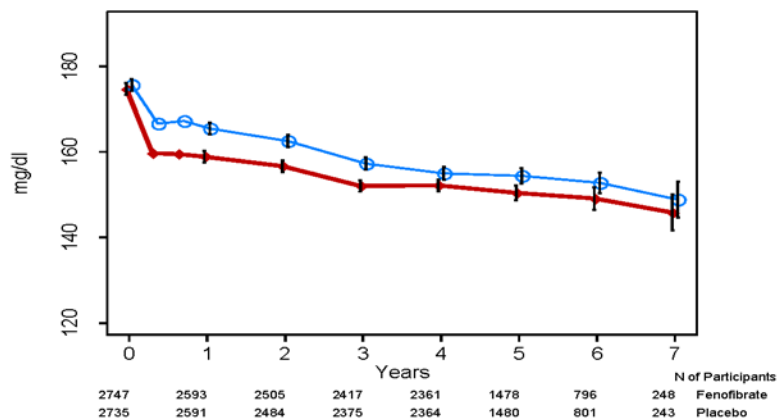
| Trial | N | Mean SBP less intense | SBP Goal | Mean SBP more intense | CVD Risk Reduction |
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| ADVANCE | 11,140 | 140 | none | 135 | 14% mortality reduc |
| ACCORD-BP | 4,733 | 134 | <120 | 119 | NSD in CVD 41% stroke reduc |

Cushman, et al. *Am J Cardiol* 2007;99[suppl]:44i-55i; Patel, et al. *Lancet* 2007;370:829-840;
ACCORD Study Group. *NEJM* 2010;362:1575-85.

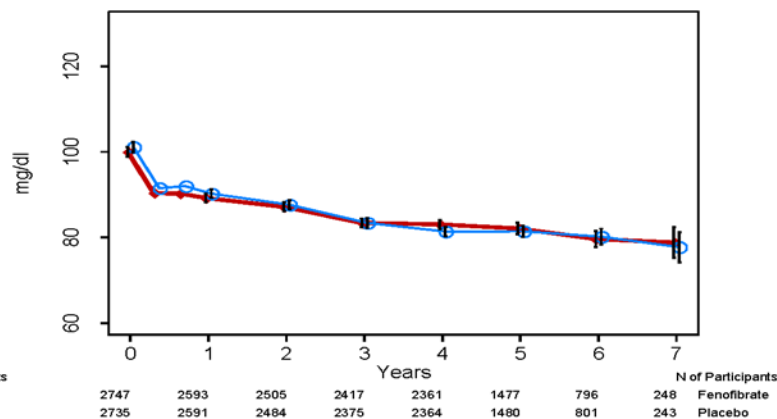
ACCORD Lipid Trial (N=5518)

Statin + (Fenofibrate vs. Placebo)

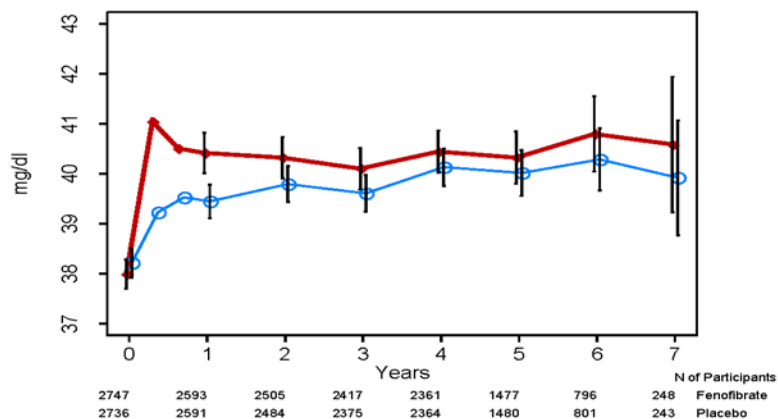
(A) Mean Total Cholesterol



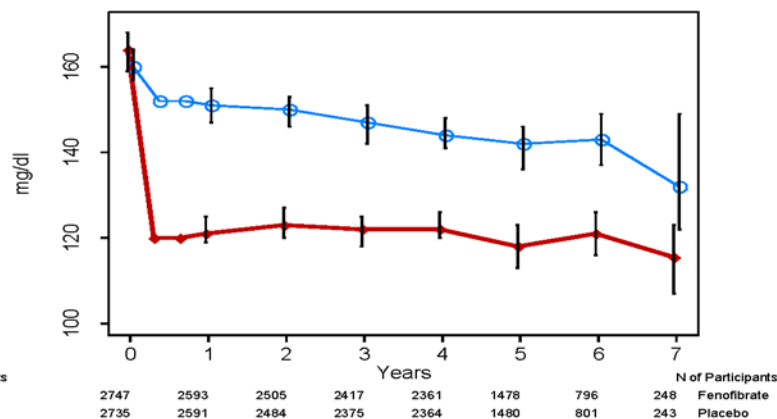
(B) Mean LDL-C



(C) Mean HDL-C



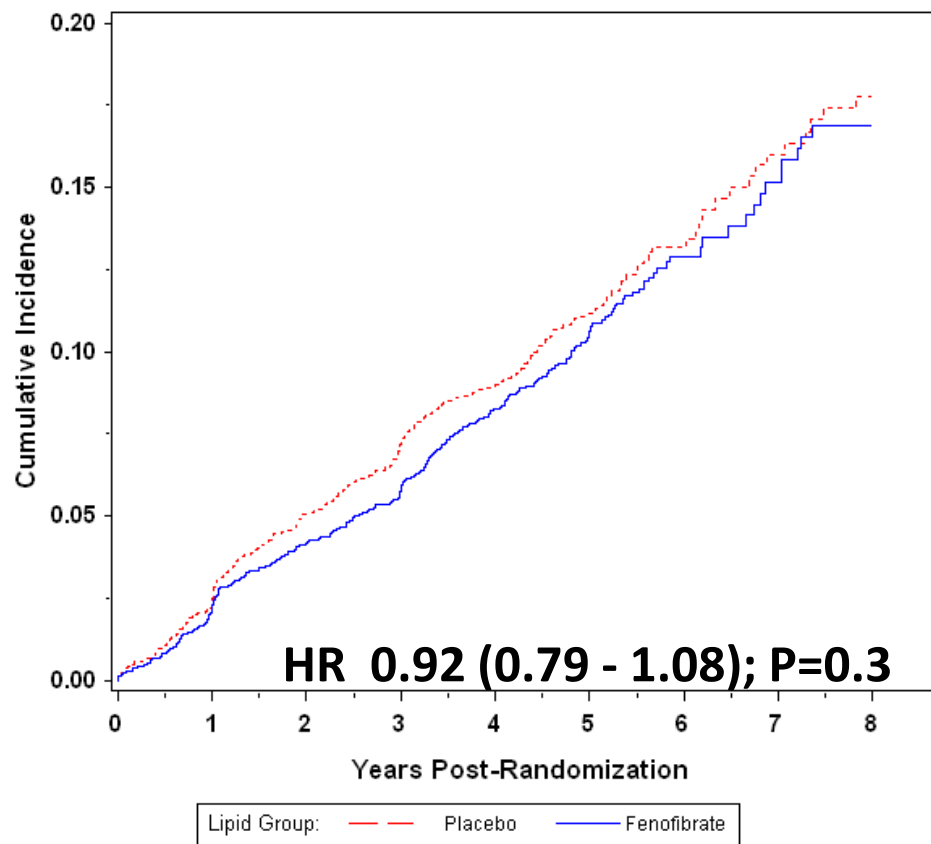
(D) Median Triglycerides



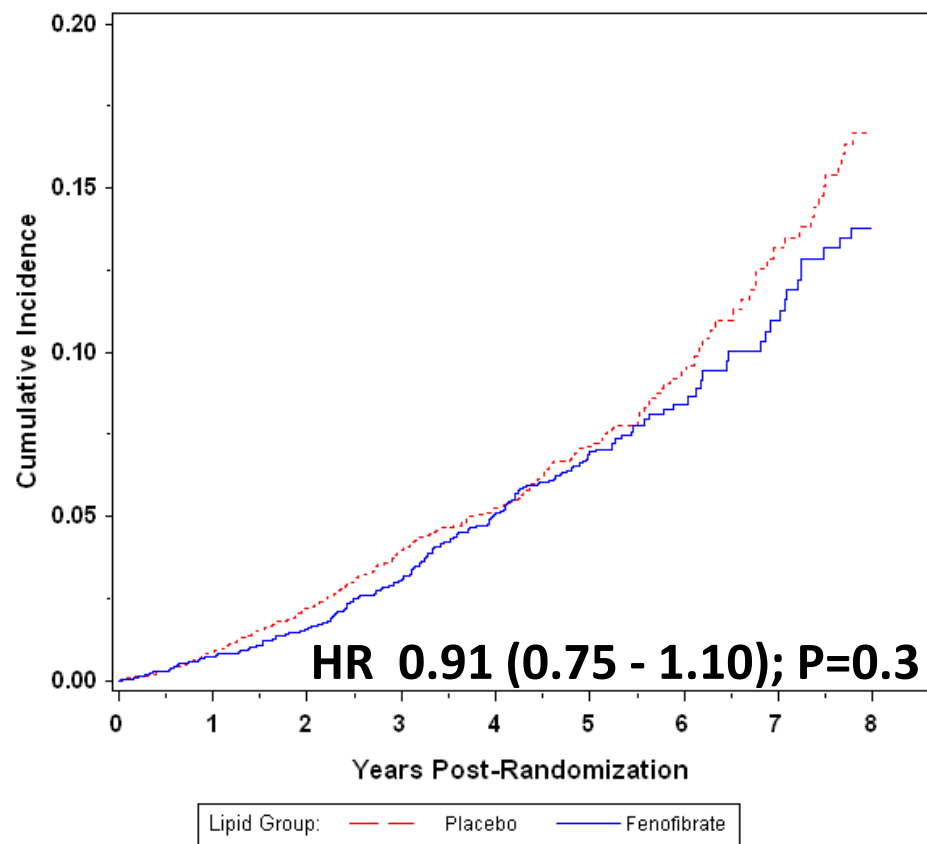
ACCORD Lipid Trial (N=5518)

Statin + (Fenofibrate vs. Placebo)

Kaplan-Meier Estimates of Cumulative Incidence
Lipid Trial - Primary Outcome



Kaplan-Meier Estimates of Cumulative Incidence
Lipid Trial - Total Mortality



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Evidence from Outcomes RCTs

- *Intensive glucose lowering..*
 - **in type 1 DM & new type 2 DM** reduces CVD & death (long-term)
 - **in advanced type 2 DM** may reduce MI but there remains an unexplained mortality signal in ACCORD
- *CABG reduces CVD but not mortality*
- *SBP lowering to ~ 135 reduces CVD; lower may reduce stroke*
- *Statins but not fibrates reduce CVD & mortality*
- *RAS blockade reduces CVD*
- *Metformin may have a mortality benefit*
- *Several ongoing studies are testing novel strategies*
- *A combination statin, ACE-I, diuretic & perhaps metformin → worthwhile*