The ACCORD Trial: Review of Design and Results

Highlights from presentations made at the ADA 68th Scientific Sessions, June 10, 2008

Action to Control Cardiovascular Risk in Diabetes

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ACCORD Glycemia Research Question and Study Design

- Glycemia Research Question:

  In middle aged or older adults with type 2 DM at high risk for a CVD event because of ***existing CVD or additional CVD risk factors***, does a ***therapeutic strategy*** that targets ***A1C <6.0%*** reduce the rate of CVD events more than a strategy that targets ***A1C 7.0% to 7.9%?***

- Design:
  - Multi-center, randomized, controlled, double 2x2 factorial trial – 3 questions: glycemia, BP, Lipids
  - Glycemia Trial: Open Label Blinded Endpoint Assessment
  - Sample size 10,251
  - Randomized to intensive vs standard glycemia management

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ACCORD Participant Eligibility

- Stable Type 2 Diabetes for 3+ months
- A1C ≥7.5% ***AND*** ≤9% (more meds) ***OR*** ≤11% (fewer meds)
- Age 40-79 + previous CVD events ***OR***
- Age 55-79 with:
  - anatomical ASCVD, albuminuria, LVH ***OR***
  - ≥ 2 additional CVD risk factors (dyslipidemia, hypertension, smoking, obesity)
- BMI ≤ 45; Cr ≤ 1.5 mg/dL (133 uM)
- No frequent/recent serious hypoglycemia
- Able/willing to take insulin, do glucose monitoring
- Also eligible for BP or Lipid Trial

ACCORD Prespecified Outcomes

- ***Primary:***
  - First occurrence of nonfatal MI ***OR*** Nonfatal Stroke ***OR*** CV Death
- ***Secondary/Other:***
  - Each component of 1^0
  - Expanded CVD: 1^0 + Revasc & HF Hosp
  - Total mortality
  - Microvascular (nephropathy, neuropathy, eye)
  - Eye photo substudy (N = 3537)
  - HRQL (N = 2053); Cost (N = 4311)
  - MIND: cognition, brain volume (MRI)
  - Falls/Fractures/BMD (ancillary study)

ACCORD Key Baseline Characteristics

Age	62 years
Women	38.6%
Median DM Duration	10 years
Previous CVD Event	35%
White	65%
Mean BMI	32 kg/cm^2
Mean A1C	8.3%
Mean SBP/DBP	136/75 mmHg
Mean LDL	105 mg/dL

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ACCORD Last Clinic Measurement

	Intensive	Standard	P
LDL-C	91 mg/dL	91 mg/dL	0.74
SBP	126 mmHg	127 mmHg	0.002
DBP	67 mmHg	68 mmHg	<0.001
BP Drug (%)	91%	92%	0.06
ACE-I (%)	70%	72%	0.02
ASA (%)	76%	76%	0.98
Beta Blocker (%)	48%	49%	0.27

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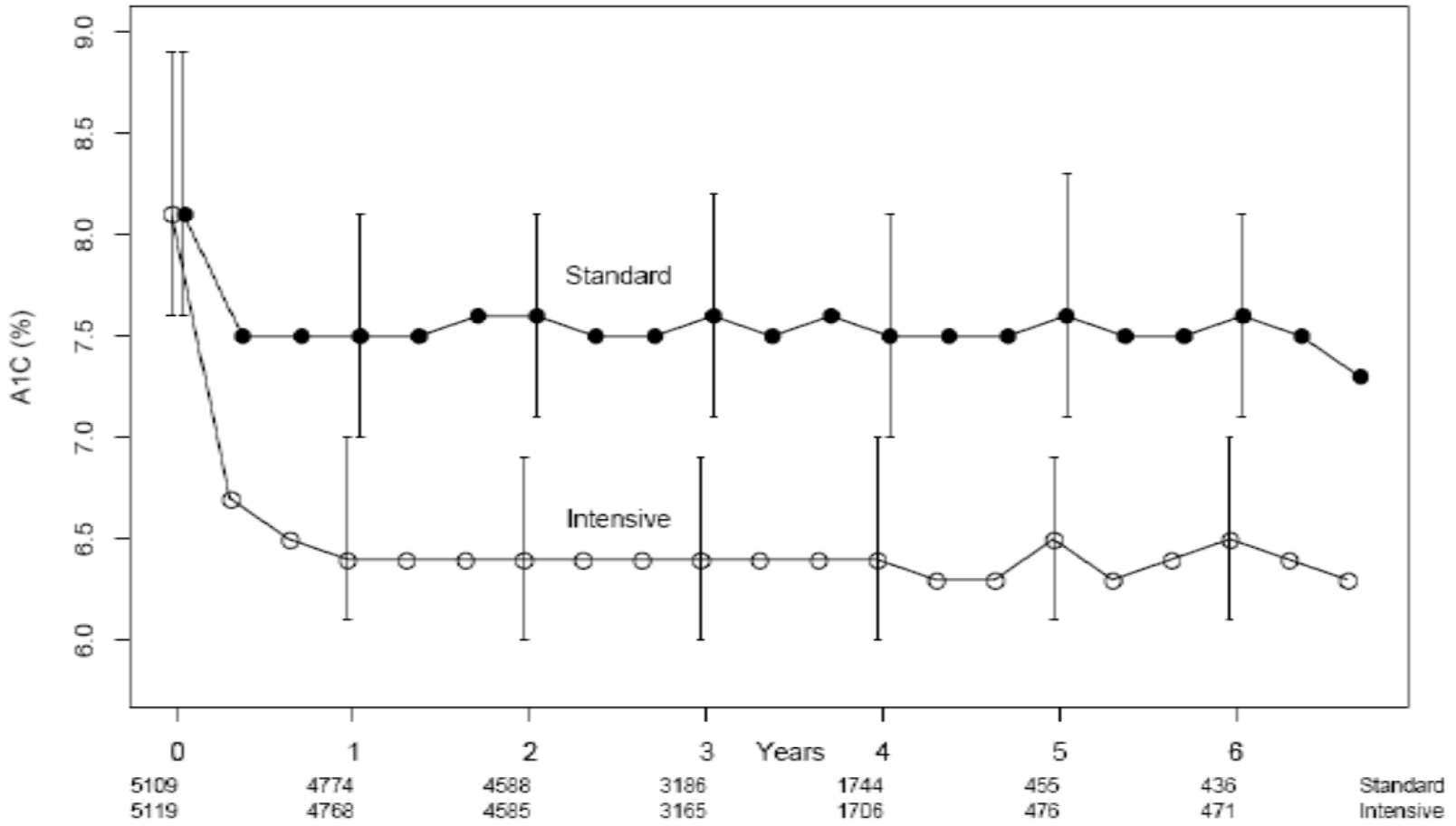
Median A1C and Interquartile Ranges



The mean difference during the trial was 1.1%

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Medications Ever Used During the Trial

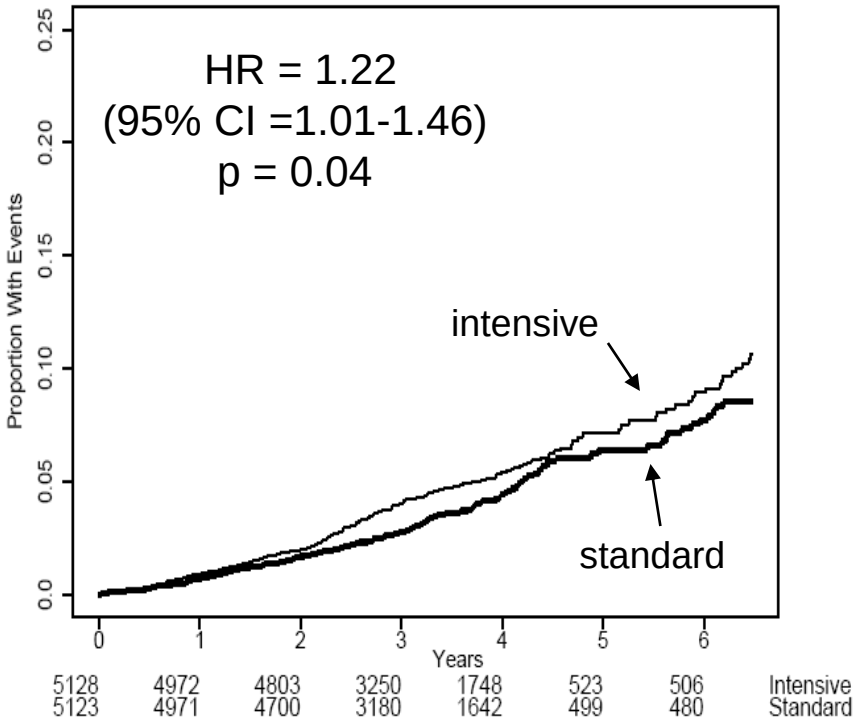
Drug Class/Drug (% of participants)	Intensive (N = 5128)	Standard (N = 5123)
Any Insulin (%)*	77	55
Bolus Insulin (%)	55	35
Metformin (%)	95	87
Secretagogue (%)	87	74
Thiazolidinedione (%)	92	58
Rosiglitazone (%)	91	58
Acarbose (%)	23	5
Exenatide/Sitagliptin (%)	18	5
Exenatide (%)	12	4

Compared with the standard strategy, the intensive strategy had:

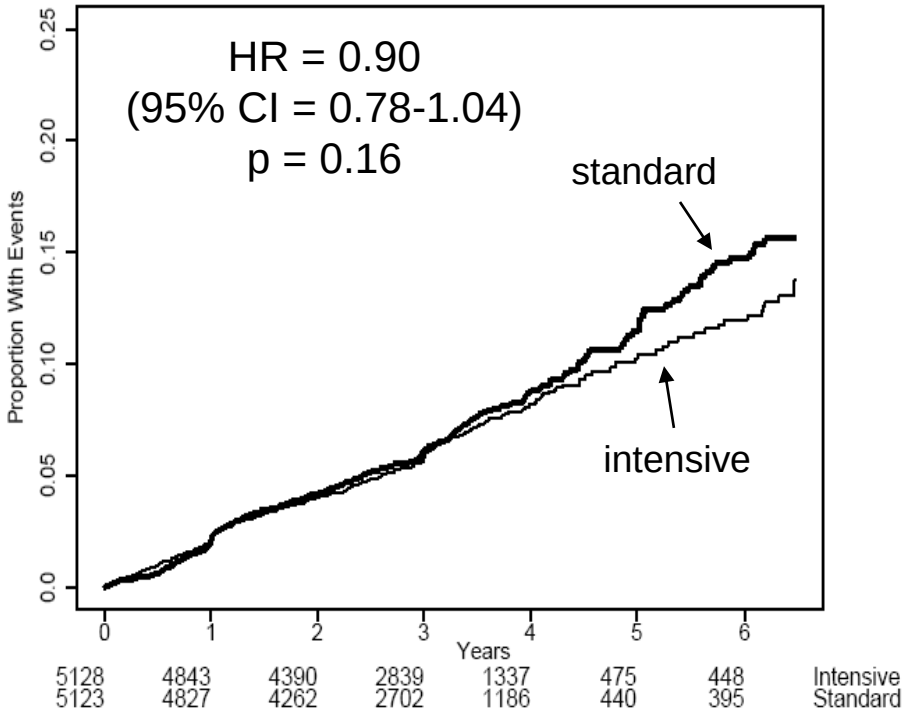
Lower A1C	
Targets (achieved median)	<6% (6.4%) vs 7-7.9% (7.5%)
Greater use of medications:	
More multiple oral meds	70% vs 45% on 3-5 oral classes
More insulin	77% vs 55% on insulin
More combination orals + insulin	62% vs 18% on 3-5 orals + insulin
More consequences of therapy:	
Severe hypoglycemia	10.5% vs 3.5% w/ hypoglycemia event requiring medical assistance
Weight gain	28% vs 14% >10 kg gain
More SAEs	2.2% vs 1.6% w non-hypo SAE

ACCORD All-Cause Mortality and Primary Outcome Event Curves

Mortality



Primary outcome (composite nonfatal MI, nonfatal stroke, CVD death)



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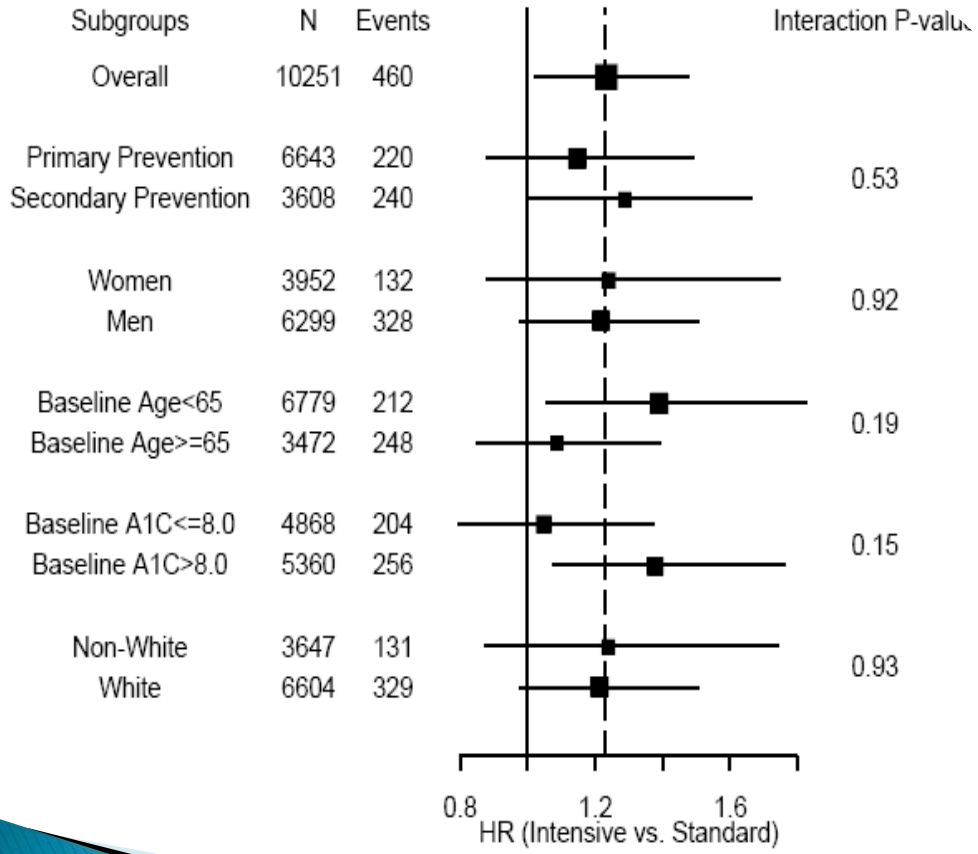
ACCORD Subgroup Analyses

Mortality



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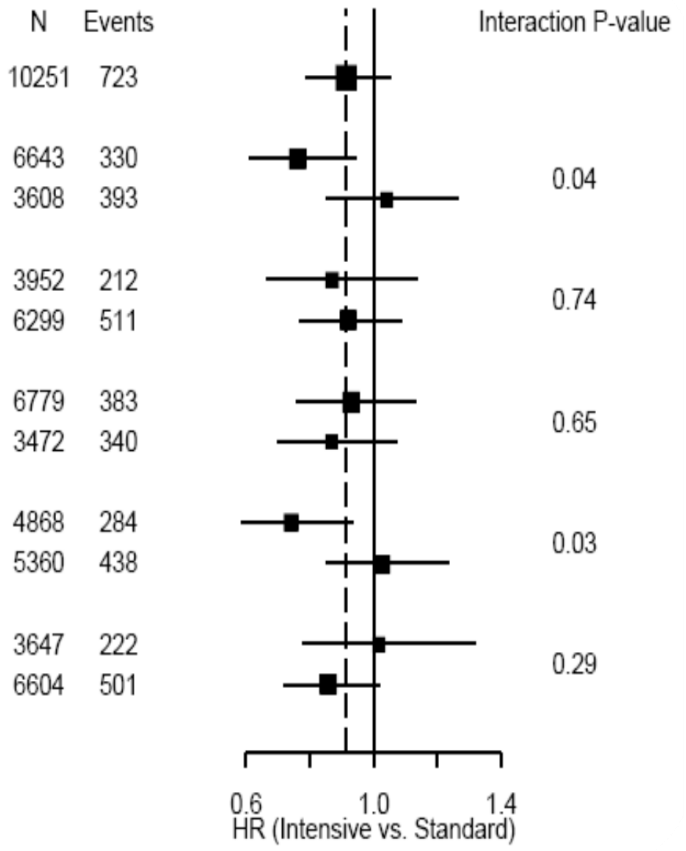

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ACCORD Conclusions

- Compared to a strategy targeting A1C levels of 7-7.9%, a therapeutic strategy using currently available therapies to target near-normal A1C levels in people with longstanding T2DM and either CVD or additional CVD risk factors – over average 3.5 years:
  - Increased mortality
  - Did not reduce a composite of major CVD events (primary outcome)
  - Mortality results consistent across several subgroups
  - Suggestion of reduced major CVD events in 2 subgroups: primary prevention and A1C <8% @ BL

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ACCORD Conclusions, cont.

- ACCORD identified a previously unknown harm of a strategy of intensive glucose lowering in high-risk individuals with T2DM
- ACCORD designed to test a ***therapeutic strategy***, not any specific component(s) of the strategy; numerous factors differed between the randomized groups
  - Potential causes are difficult, if not impossible, to separate out from other factors that differ by group
  - Example: An ACCORD participant may or may not be on a drug for various reasons, so we can't separate out effects of the drug from effects of patient characteristics (some of which were not measured)
- Exploratory analyses examined various medications and hypoglycemia – no specific cause of higher mortality found

Additional Analyses of ACCORD data: current and planned

- Glycemia trial results on microvascular outcomes
- Comparisons of intensive vs. standard glycemia groups in post-hoc subgroups defined by:
  - Baseline characteristics
  - Post-randomization changes in clinical factors
  - Post-randomization occurrence of events
- Epidemiologic analyses, including associations between:
  - A1C and hypoglycemia; A1C and morbidity/mortality outcomes
  - Various medications and: A1C, hypoglycemia, mortality
- Final glycemia trial data and BP and Lipid trial main results expected in 2010