

ACCORD Lipid & BP Trial Overview

Cardiovascular (CV) Risk in Type 2 Diabetes Mellitus (T2DM): Treatment Strategies

- ◆ ACCORD¹ evaluated drug intervention & aggressive pursuit of targets to ↓ CV risk in T2DM (~10yr history of T2DM) & CV disease or high CV risk.
- ◆ **3 Trials:** randomized, multicenter USA & CDN; all participants enrolled in the *glycemia* trial & also in either the *lipid* or *BP* sub-trials (double 2x2 factorial).
ACCORD Glycemia: n=10,251; terminated 17 months early due to **increased death** in the intensive A1C target (NNH=95 / 3.5yrs).²
ACCORD Lipid³: n=5,518 double-blind, placebo controlled. **4.7 years** mean follow-up. **ACCORD BP**⁴: n=4,733 unblinded, open label. **4.7 years** mean follow-up

Treatments studied:	<p>ACCORD Lipid³: open-label simvastatin ZOCOR 20-40mg/day + either masked fenofibrate LIPIDIL 160mg/day starting & adjusted to GFR (<=160mg/day) or placebo. (Both groups used a 4 week run-in with simvastatin before adding fenofibrate or placebo; simvastatin average dose: ~22.3mg).</p> <p>ACCORD BP⁴: participants randomized into intensive therapy targeting SBP < 120 mm Hg, or standard therapy, targeting SBP <140 mm Hg. Aim of study was to evaluate treatment strategy not a specific drug regimen; average 3.4 medications after 1 year in intensive therapy group and 2.1 in standard-therapy. (Open Label) {At "Last Visit" the % of pts on 4 or 5 antihypertensives was 23% vs 12% & 18% vs 4% respectively for the intensive & standard groups.}</p>
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- ◆ **Baseline Population Studied**⁵: All were **high CV risk**: presence of CVD eg. previous MI, stroke, history of coronary/carotid/peripheral revascularization, angina [Publicly funded: NIH] or evidence in last 2 yrs suggesting high likelihood of CVD eg. microalbuminuria, ankle brachial index < 0.9/ LVH by ECG or ECHO, or > 50% stenosis of a coronary, carotid, or lower extremity artery or 2+ factors that ↑CVD risk eg. on lipid lowering meds or untreated LDL-C >3.38 mmol/l, low HDL-C (<1.04 mmol/l for ♂ & <1.29 mmol for ♀), on BP lowering meds or untreated SBP >140 or DBP > 95 mm Hg, smoking, BMI > 32 kg/m2.
- ACCORD Lipid**³: Age 62±7 years, 31% ♀, 68% Caucasian, 37% previous CV event, current smoker 15%, LDL 2.6±0.8 HDL 0.99±0.2 mmol/l, Weight 95kg
- ACCORD BP**⁴: Age 62±7 years, 48% ♀, 61% Caucasian, 34% previous CV event, current smoker 13 %, SBP 139.4±16 DBP 75.7±10.5, Weight 92kg, BMI =32

Table 1: ACCORD Inclusion/Exclusion Criteria⁵:

	ACCORD Lipid	ACCORD BP
Inclusion	For both trials (as part of the ACCORD Glycemia): known type 2 DM according to 1997 ADA criteria with duration > 3 months & with stable treatment > 3 months; age 40-79 with history of CVD or age 55-79 without history of CVD; at high risk of CVD event. (A1C needed to be ≥7.5% & on average was 8.3%)	
	LDL-C 1.55-4.65 mmol/l if not on a lipid lowering agent during screening, or, if on a lipid-lowering agent, the LDL-C between the drug/dose-specific cut points (as outlined in trial) And HDL-C <1.42 mmol/l for women or African-Americans or HDL-C <1.29 mmol/l for all other gender/race groups And TG <8.47 mmol/l on no therapy or < 4.52 mmol/l on lipid lowering drugs	SBP: 130-160 mm Hg and patient is on 0-3 antihypertensive medications or SBP: 161-170 mm Hg and patient is on 0-2 antihypertensive medications, or SBP: 171-180 mm Hg and patient is on 0 or 1 antihypertensive medication And dipstick protein in a spot urine is < 2+, or protein-to-creatinine ratio in a spot urine is <700 mg/gm creatinine, or 24-hour protein excretion is <1 gm/24 hours
Exclusion	For both trials (as part of the ACCORD Glycemia): history of hypoglycemia coma/seizure within 12 months before trial; hypoglycemia needing 3 rd party assistance within 3 months before trial with glucose <3.3 mmol/l; history consistent with type 1 DM; unwilling to do self BG checks or administer insulin frequently; BMI > 45 kg/m ² ; ↑Scr >132.6 μmol/l, transaminase >2x ULN or active liver disease; ongoing medical therapy with known interaction with glyemic intervention eg. corticosteroids, protease inhibitors; CV event/procedure or hospitalization for unstable angina within 3 months of trial; symptomatic HF or history of NYHA Class III or IV HF or EF <25%; medical condition limiting survival to < 3 years or malignancy within the last 2 years except non-melanoma skin cancer; factors likely to limit adherence eg. dementia; participation in 2 nd clinical trial; living with a participant in ACCORD trial; organ transplant; recurrent requirements for phlebotomy or transfusion of RBCs; weight loss > 10% in last 6 months; pregnant or trying to become pregnant or of child-bearing potential and with no birth control.	
	hypersensitivity to statins or fibrates; requirements for use of erythromycin, clarithromycin, cyclosporine, systemic azole antifungals, or nefazodone or trazodone; refusal to stop current lipid-lowering drugs; history of pancreatitis; untreated/inadequately treated thyroid disease; breastfeeding women; previous myositis/myopathy; pre-existing gallbladder disease eg. history of gall-stones	

Table 2: ACCORD Lipid results³: [LDL 2.6 ⇒ 2.1 Feno, 2.07 P] *adjusted for interim monitoring (e.g. reflects confidence from more than just first & last endpoints)

Endpoints Recruitment Jan03-Sep05. Participants followed for an average of 4.7 years; 5 years for death.	Fenofibrate no. of events (rate/yr) n=2765	Placebo no. of events (rate/yr) n=2753	ARR/ ARI (%)	NNT/ NNH Over 4.7yrs	Hazard Ratio (95% CI)	P Value
1^o First occurrence of major CV event non fatal MI or stroke, or death from CV causes	291 (2.24) 10.5% / ~4.7yrs	310 (2.41) 11.3% / ~4.7yrs	↓0.74	NS	0.92 (0.79-1.08)	0.32*
^{2^o} 1 ^o outcome + revasc. or hospitalization for HF	641 (5.35)	667 (5.64)	↓1.05	NS	0.94 (0.85-1.05)	0.30
^{2^o} major coronary event eg. Fatal, nonfatal MI, unstable angina	332 (2.58)	353 (2.79)	↓0.82	NS	0.92 (0.79-1.07)	0.26
^{2^o} non fatal MI	173 (1.32)	186 (1.44)	↓0.5	NS	0.91 (0.74-1.12)	0.39
^{2^o} stroke	51 (0.38)	48 (0.36)	↑0.1	NS	1.05 (0.71-1.56)	0.80
- nonfatal	47 (0.35)	40 (0.3)	↑0.25	NS	1.17 (0.76-1.78)	0.48
^{2^o} death	203 (1.47)	221 (1.61)	↓0.69	NS	0.91 (0.75-1.10)	0.33*
from CV cause	99 (0.72)	114 (0.83)	↓0.56	NS	0.86 (0.66-1.12)	0.26

- ◆ **ACCORD LIPID:** fenofibrate+simvastatin did **not** significantly improve rate of 1^o outcome vs simvastatin alone.
- ◆ **Subgroups (1^o):** ↑ risk in ♀ 9.1% vs 6.6% vs ♂ 11.2% vs 13.3% p=0.01. Trend for benefit of fenofibrate+simvastatin in dyslipidemia (TG ≥ 2.3 & HDL ≤ 0.88 mmol/l) p=0.06.

Table 3: ACCORD BP results⁴:

Endpoints [BP 139.4 ⇒ 133.5 Intensive, 119.3 Standard] Recruitment Jan03-Oct05; followed for an average of 4.7 years.	Intensive Tx no. of events (%/yr) n=2363	Standard Tx no. of events (%/yr) n=2371	ARR/ ARI (%)	NNT Over 4.7yrs	Hazard Ratio (95% CI)	P Value
1^o First occurrence of major CV event non fatal MI or stroke, or death from CV causes	208 (1.87) 8.8% / ~4.7yrs	237 (2.09) 10% / ~4.7yrs	↓1.19	NS	0.88 (0.73-1.06)	0.20
^{2^o} 1 ^o outcome + revasc. or nonfatal HF	521 (5.1)	551 (5.31)	↓1.19	NS	0.95 (0.84-1.07)	0.40
^{2^o} major coronary disease event eg. Fatal coronary event, nonfatal MI, unstable angina	253 (2.31)	270 (2.41)	↓0.68	NS	0.94 (0.79-1.12)	0.50
^{2^o} non fatal MI	126 (1.13)	146 (1.28)	↓0.83	NS	0.87 (0.68-1.10)	0.25
^{2^o} stroke	36 (0.32)	62 (0.53)	↓1.09	92	0.59 (0.39-0.89)	0.01
- nonfatal	34 (0.3)	55 (0.47)	↓0.88	114	0.63 (0.41-0.96)	0.03
^{2^o} death	150 (1.28)	144 (1.19)	↑0.27	NS	1.07 (0.85-1.35)	0.55
from CV cause	60 (0.52)	58 (0.49)	↑0.09	NS	1.06 (0.74-1.52)	0.74
^{2^o} fatal or nonfatal HF	83 (0.73)	90 (0.78)	↓0.28	NS	0.94 (0.70-1.26)	0.67

- ◆ **ACCORD BP:** showed **no** significant difference in annual rate of 1^o outcome between groups treated with intensive therapy & standard therapy. The annual rate of stroke, a 2^o outcome, was significantly reduced from 0.53% in the standard group to 0.32% in the intensive group. **NNT=92** over 4.7yr. **Serious adverse events (SAE)** death, life threatening event, disability, hospitalization were more frequent in the intensive tx group: **3.3 vs 1.27%**, **NNH=50** p=<0.001 over 4.7yr.

Table 4: ACCORD Lipid Adverse Events Results⁶ (AE): Fenofibrate vs Placebo

Adverse Events # of events (%) Color denotes risk or benefit	Fenofibrate N=2765 No. of events (%)	Placebo (N=2753) No. of events (%)	ARR/ ARI (%)	NNT/ NNH Over 4.7yrs	P Value
Any occurrence of severe muscle aches/pains not associated with known activity; Regardless of CPK	1110 (40.1)	1115 (40.5)	↓0.36	NS	0.81
Myopathy/myositis/rhabdomyolysis SAE	4 (0.1)	4 (0.1)	0	NS	1.00
Any hepatitis SAE	3 (0.1)	0 (0)	↑0.11	NS	0.18
Any SAE from lipid medications	27 (1)	19 (0.7)	↑0.29	NS	0.24
SCr elevation: Women ever >114.92 mmol/l	235 (27.9)	157 (18.7)	↑2.8	36	<0.001
Men ever >132.6 mmol/l	698 (36.7)	350 (18.5)	↑12.53	8	<0.001
Post-randomization microalbuminuria (≥30 to <300 mg/g*)	1050 (38.2)	1137 (41.6)	↓3.33	30	0.01
Post-randomization macroalbuminuria (≥300 mg/g*)	289 (10.5)	337 (12.3)	↓1.79	56	0.03

*mg albumin/g creatinine

Table 5: ACCORD BP⁴ Adverse Events Results (AE): Intensive Therapy vs Standard Therapy

Adverse Events # of events (%) Color denotes risk or benefit	Intensive Therapy (N=2362)	Standard Therapy (N=2371)	ARR/ ARI (%)	NNT/ NNH Over 4.7yrs	P Value
Event due to BP medications Serious Adverse Events (SAE)	77 (3.3)	30 (1.27)	↑1.99	50	<0.001
Hypotension	17 (0.7)	1 (0.04)	↑0.68	148	<0.001
Syncope	12 (0.5)	5 (0.21)	↑0.3	NS	0.10
Bradycardia or arrhythmia	12 (0.5)	3 (0.13)	↑0.38	262	0.02
Hyperkalemia	9 (0.4)	1 (0.04)	↑0.34	295	0.01
Angioedema	6 (0.3)	4 (0.17)	↑0.09	NS	0.55
Renal failure	5 (0.2)	1 (0.04)	↑0.17	NS	0.12
End-stage renal disease or need for dialysis	59 (2.5)	58 (2.4)	↑0.05	NS	0.93
Potassium <3.2 mmol/l	49 (2.1)	27 (1.1)	↑0.94	107	0.01
Potassium >5.9 mmol/l	73 (3.1)	72 (3)	↑0.05	NS	0.93
Elevation in serum creatinine >132.6 μmol/l ♂	304 (12.9)	199 (8.4)	↑4.48	22	<0.001
>114.9 μmol/l ♀	257 (10.9)	168 (7.1)	↑3.79	26	<0.001
Estimated GFR <30ml/min/1.73 m ²	99 (4.2)	52 (2.2)	↑2	50	<0.001
Macroalbuminuria no./total no. (%)	143/2174 (6.6)	192/2205 (8.7)	↓2.13	47	0.009

Of Note: BP and lipid trials did not show “all-cause death” as a harm with intensive therapy, unlike the glycemia trial.**What we knew and what these results add to our knowledge⁷:**

- ◆ HOT⁸ study found that lowering DBP ≤80 (vs ≤90) was associated with lower rates of CV events (MI, stroke & CV death).
- JNC 7 Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, & Tx of High BP recommended a BP <130/80 for type 2 diabetics, which was not based on RCT evidence⁹.
- ACCORD BP found no primary difference between intensive^{SBP <120} & standard^{SBP <140} therapy, but had an increased risk of serious adverse events.
- ◆ Lowering LDL with a statin (HPS¹⁰ and CARDS¹¹ trials) reduces CV risk. Fenofibrate lacks convincing evidence for benefit in trials to date.
- ACCORD Lipid trial found that the addition of fenofibrate to simvastatin did not reduce CV risk compared to simvastatin alone. (Generalizability may be of some concern considering study population weight, baseline LDL level, gender, race etc.) For T2DM, statins plus lifestyle measures remain the key lipid intervention to ↓ CV risk.

Questions remaining:

- ◆ Did the open-label design of the ACCORD BP arm affect results such as the reporting of adverse events?
- ◆ Did the embedding of the 2x2 lipid and BP factorial trials within the glycemic trial cloud the results in some way?
- ◆ Would similar results be found in non-diabetic patients on intensive lipid or BP therapy?
- ◆ In the lipid trial, would results differ with a different approach to dosing?
- ◆ In the BP trial, would patients with micro- or macroalbuminuria have done better with intensive BP control?

AASK trial subgroup: more intensive BP 128/78 vs 141/85, may retard renal disease progression in some pts with baseline urinary protein-to-creatinine ratio of >0.22.

TAKE HOME: *Let the target serve the patient, not the patient the target!***ACCORD-LIPID:** *to add or not to add a fibrate?*

- ⇒ Routinely adding a fibrate to statin therapy in T2DM does not add benefit according to the overall ACCORD-Lipid trial.
- ⇒ A subgroup who may benefit include T2DM patients with high TGs & low HDL (TG ≥ 2.3 and HDL ≤ 0.88mmol/l); but women may do worse.

ACCORD-BP: *should we be even more aggressive in our SBP targets?*

- ⇒ no difference found between intensive^{SBP <120} and standard^{SBP <140} therapy, also seen in INVEST¹²; adverse events more common with intensive therapy.
- ⇒ The ACCORD trials found that more intensive (glycemia & BP control) or additional (lipid) therapy did not benefit patients with T2DM.
- ⇒ **Goals and targets should be flexible when treating hyperglycemia, BP and dyslipidemia risks in patients with T2DM.**

Specific patient characteristics and treatment choices should be considered. Individualize treatment!

BP=blood pressure CI=confidence interval CPK=creatinine phosphokinase CV=cardiovascular CVD=cardiovascular disease HDL=high density lipoprotein HF=heart failure HR=hazard ratio HS=high sensitivity LDL=low density lipoprotein MI=myocardial infarction NS=not significant DM=diabetes mellitus TG=triglycerides SBP=systolic blood pressure EF=ejection fraction NYHA=New York Heart Association ULN=upper limit of normal ARR= absolute risk reduction ARI= absolute risk increase NNT=needed to treat over 4.7 years NNH= needed to harm over 4.7 years 1^o=primary outcome 2^o=secondary outcome SAE=serious adverse event www.RxFiles.ca Original Workup by : Christina Takla, Brent Jensen, Loren Regier.

¹ ACCORD Study Group. Effects of Intensive Glucose Lowering in Type 2 Diabetes. NEJM 2008; Online June 09, 2008. www.nejm.org.

² RxFiles Trial Summary: ACCORD Intensive Glucose. May 2008; accessed online at <http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-Targets-ACCORD-A1C.pdf>

³ ACCORD Study Group. Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus. N Engl J Med. 2010 Mar 18. Supplement App. http://www.nejm.org/doi/suppl/10.1056/NEJMoa1001282/suppl_file/nejm_accord_1563sa1.pdf

⁴ ACCORD Study Group. Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus. N Engl J Med. 2010 Mar 14. DOI: 10.1056/NEJMoa1001282. Accessed on April 14, 2010 <http://content.nejm.org/cgi/data/NEJMoa1001282/DC2/1>

⁵ Supplement to: The ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 2010. DOI: 10.1056/NEJMoa1001282. Accessed on April 14, 2010 <http://content.nejm.org/cgi/data/NEJMoa1001282/DC1/1>

⁶ Supplement to: The ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 2010. DOI: 10.1056/NEJMoa1001282. Accessed on April 16, 2010 www.rxfiles.ca

⁷ All-cause mortality outcomes from major lipid trials Accessed April 16, 2010 www.rxfiles.ca

⁸ Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet. 1998 Jun 13;351(9118):1755-62.

⁹ Nilsson PM. ACCORD and Risk-Factor Control in Type 2 Diabetes. N Engl J Med. 2010 Mar 14. [Epub ahead of print].

¹⁰ Heart Protection Study (HPS) Collaborative Group. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20 536 people with cerebrovascular disease or other high-risk conditions. Lancet 2004 Mar 6;363(9411): 757-67.

¹¹ Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS). Lancet 2004;364:685-96.

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