ACCORD Lipid & BP Trial Overview

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

- ACCORD [1] 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 Lipid [3]: 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:

ACCORD Lipid[3]: 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).

ACCORD BP [4]: 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.}

- **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 Criteria [5]:

	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 3rd 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/m²;↑Scr >132.6umol/l, transaminase >2x ULN or active liver disease; ongoing medical therapy with known interaction with glycemic 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 2nd 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 results[3]:

[LDL 2.6 ⇨2.1 Feno, 2.07 Pl] *=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 n=2765 no. of events (rate/yr)	Placebo n=2753 no. of events (rate/yr)	ARR/ ARI (%)	NNT/ NNH Over 4.7yrs	Hazard Ratio (95% CI)	P Value
1° 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° 1° outcome + revasc. or hospitalization for HF	641 (5.35)	667 (5.64)	↓1.05	NS	0.94 (0.85-1.05)	0.30
2° 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° non fatal MI	173 (1.32)	186 (1.44)	↓0.5	NS	0.91 (0.74-1.12)	0.39
2° stroke -any	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° death -from any cause	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° outcome vs simvastatin alone.
- **Subgroups** (1°): ↑ 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 results[4]:

Endpoints [BP 139.4 ⇨119.3 Intensive, 133.5 Standard] Recruitment Jan03-Oct05; followed for an average of 4.7 years.	Intensive Tx n=2363 no. of events (%/yr)	Standard Tx n=2371 no. of events (%/yr)	ARR/ ARI (%)	NNT Over 4.7yrs	Hazard Ratio (95% CI)	P Value
1° 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° 1° outcome + revasc. or nonfatal HF	521 (5.1)	551 (5.31)	↓1.19	NS	0.95 (0.84-1.07)	0.40
2° 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° non fatal MI	126 (1.13)	146 (1.28)	↓0.83	NS	0.87 (0.68-1.10)	0.25
2° stroke -any	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° death -from any cause	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° 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° outcome between groups treated with intensive therapy & standard therapy.
  The annual rate of stroke, a 2° 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 Results [6] (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 BP [4] 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 knowledge[7]:

- HOT [8] 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 evidence [9]. 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 (HPS [10] and CARDS [11] trials) reduces CV risk. Fenofibrate lacks convincing evidence for CV 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 macroalbumnuria 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? (Continue using statins & lifestyle modifications in high CV risk patients).***

⇨ 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 INVEST; 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**=creatine 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 **1º** =primary outcome **2º** =secondary outcome **SAE**=serious adverse event **www.RxFiles.ca**

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