An Overview of CARDS (Collaborative Atorvastatin Diabetes Study): Primary Prevention of Cardiovascular Disease with Atorvastatin in Type 2 Diabetes

CARDS Overview [1]

- a multi-center randomized placebo controlled trial to determine hard outcomes of atorvastatin 10mg vs. placebo in patients with Type 2 **diabetes**, & at least 1 additional cardiovascular risk factor (RF) ✝ (63% had 1 RF, 30% had 2 RF, 6% had 3 RF & 1% had 4 RF), LDL ≤ $4.14_{mmol/L}$, TG ≤ $6.78_{mmol/L}$, and **without** a history of cardiovascular, cerebrovasular or peripheral vascular disease.
  ✝ (Additional CV risk factors for inclusion were: hypertension [84%], retinopathy [30%], current smoking [23%] or albuminuria [17%]; in addition, the majority of patients were male, Caucasian and over 60 years of age)
- 2,838 high risk patients were followed for **4 years** with the following baseline demographic characteristics:
  - age: **40-75** (Ave=**62 yrs**); sex: **68% male**; white ethnic origin: 94%; LDL: $3.0_{mmol/L}$; HDL: $1.4_{mmol/L}$; TG: $1.7_{mmol/L}$
- two treatment arms: **atorvastatin LIPITOR 10mg daily** (n=1428) versus **placebo** (n=1410)

Table 1: CARDS results - Atorvastatin 10mg daily vs placebo daily

Endpoints - (4 years)	Atorvastatin % (n=1428)	Placebo % (n=1410)	ARR %	RRR %	NNT	p value
1° time to 1st occurrence of: CHD death, non-fatal MI (including silent), hospitalized for unstable angina, resuscitated cardiac arrest, coronary revascularization or stroke	5.8 (83 events)	9.0 (127 events)	3.2	36	32	0.001
Acute Coronary Events	3.6	5.5	1.9	35	53	0.02
Revascularization	1.7	2.4	NS	NS	NS	0.2
Stroke	1.5	2.8	1.3	47	77	0.02
2° **All-cause mortality**	4.3	5.8	NS	NS	NS	0.06

1°=primary outcome **2°**=secondary outcome **ARR**=absolute risk reduction **CV**=cardiovascular **CHD**=coronary heart disease **MI**=myocardial infarction **NNT**=number needed to treat to benefit 1 patient **RF**=risk factor **RRR**=relative risk reduction

Of Note:

- analysis by intention to treat (an average of 9% of placebo group were taking a statin compared to 85% in treatment group)
- **LDL: initial 3.0mmol/L**(25% <2.5mmol/L); at follow up (4yrs): placebo arm: 3.12 mmol/l; **atorvastatin arm: 2.11 mmol/l**
- SAFETY : frequency of serious adverse events did not differ between groups (uncommon muscle and liver events reported in both groups)
- Exclusion criteria to ensure only carefully selected patients enrolled eg. serum creatinine ≥150umol/l, creatine phosphokinase ≥3x normal, no concomitant drugs associated with rhabdomyolysis, fibrates or other interacting medications.
- All-cause mortality: trend for benefit in atorvastatin group however, it did not reach statistical significance; trial **halted early**.

What we knew and what these results add to that knowledge:

- Patients with Type 2 diabetes are at higher risk of stroke and cardiovascular events.
- Subgroup analysis of previous secondary prevention trials have shown reductions in major CV event rates with statins.

HPS[2] - diabetes subgroup [CHD or CVD (2°) n=3051]:	Simvastatin 40m/d	NNT= 18 over 4.8 yrs
4S[3] – diabetes & FBG ≥ $7_{mmol/L}$ [n=483]:	Simvastatin 20-40mg/d	NNT = 7 over 5.4 yrs
4S[4] – diabetes & IFG (FBG ≥$6.0_{mmol/L}$) [n=678]:	Simvastatin 20-40mg/d	NNT = 9 over 5.4 yrs
CARE[5] –diabetes subgroup [n=586]:	Pravastatin 40mg/d	NNT = 13 over 5 yrs

- Diabetes subgroup analysis of previous primary prevention trials support possible benefit of statins.

HPS[6] – diabetes subgroup [no CVD (1°) n=2912]:	Simvastatin 40mg/d	NNT = 24 over 4.8 yrs
ASCOT[7] – diabetes subgroup [n=2532]:	Atorvastatin 10mg/d	Non-significant (Trend for benefit)

- CARDS is the first trial designed and powered to evaluate hard outcomes specifically in Type 2 diabetes patients with one or more cardiovascular risk factors. CARDS does not provide information on patients who are younger or without risk factors.
- **Magnitude of benefit (e.g. Number Needed to Treat) in CARDS patients (Type 2 Diabetes & risk factors): 1 less patient progressed towards a major CV event over 4 years for every 32 patients treated with atorvastatin 10mg/day.**
- CARDS supports the findings of the HPS trial that it is cardiovascular risk and not necessarily elevated LDL that predicts beneficial outcomes in patients on statins. Similar beneficial outcomes were seen regardless of initial LDL and HDL levels.

Questions Remaining:

- Would benefits be seen in younger/lower risk Type 2 diabetes patients and if so, would the numbers needed to treat justify their use?
- Is there an optimal LDL target for patients with Type 2 diabetes and if so, what is it?
- What effect would lipid lowering combinations (eg. statins + fibrates or ezetimibe) have on risks vs benefits?
- Are there any differences in risks and benefits of various statins in this population group?
- How do other lipid lowering drug classes compare to statins in patients with diabetes?

TAKE HOME: Statin treatment (atorvastatin 10mg/d) in high risk Type 2 diabetes patients with at least 1 additional risk factor significantly reduces their risk of CV & stroke events even when initial LDL is already ≤ 3mmol/L.

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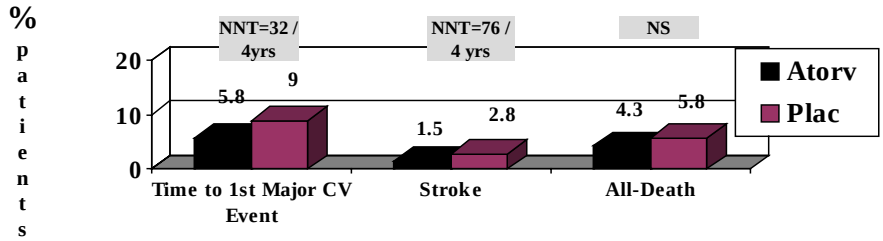
Atorvastatin benefits patients with type-2 diabetes at high risk for CVD. Benefits regardless of higher or lower initial LDL. Average atrovastatin patients achieved LDL ~ 2mmol/L

Atorvastatin 10mg/day vs Placebo in Type 2 Diabetes with 1 or more CVD risk factors, no hx of CV disease, $LDL_{mmol/L} \leq 4.14$ (Ave 3.0), TG ≤ 6.78 (Ave 1.7)



NNT= number needed to treat **NNH**= number needed to harm **NS**= not significant (statistically)
RRR= relative risk reduction

References:

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[3] Haffner SM, Alexander CM, Cook TJ, Boccuzzi SJ, Musliner TA, Pedersen TR, Kjekshus J, Pyorala K. Reduced coronary events in simvastatin-treated patients with coronary heart disease and diabetes or impaired fasting glucose levels: subgroup analyses in the Scandinavian Simvastatin Survival Study (**4S**). Arch Intern Med. 1999 Dec 13-27;159(22):2661-7.

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[5] Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels (**CARE**). N Engl J Med 1996;335:1001-9.

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