An Overview of IDEAL – A Comparison of Intensive Statin vs Low-Moderate Statin Therapy in stable CAD patients with a Previous MI (e.g. High-Risk Patients)

IDEAL Trial Overview [1]

- a multi-center prospective randomized **open-label**, blinded end-point trial to determine lipid lowering effects of high dose atorvastatin vs low-moderate dose simvastatin on **major coronary events** defined as 'coronary death/ non fatal acute MI/or cardiac arrest with resuscitation' in previous MI patients (intention to treat analysis; all patients enrolled were included in final analysis)
- two treatment arms:
  - **atorvastatin 80mg daily** (↓ 40mg if side effects) (n=4439) 89% adherence to therapy
  - **simvastatin 20-40mg daily** (↑ to 40mg if total cholesterol >5 mmol/l at 24wks) (n=4449) **95**% adherence to therapy
- 8,888 patients were followed for 4.8 years (4-5.9yrs) with the following characteristics:
  - males ~81% & females with previous MI (MIs: were ~21months before, with only 11% of MIs in the last 2 months)
  - **age**: mean ~62 years (<80yr) **Baseline LDL** levels: **3.14** mmol/l **BMI**: 27.3 kg/m^2 **BP**: 137/80 mm Hg
  - smokers~20%, former smokers~58%, hypertension~33% & history of diabetes~12%

Table 1: IDEAL Results (atorvastatin 80mg 13% **40mg** final dose daily vs simvastatin 20mg 23% **40mg** final dose daily)

Endpoints	Atorvastatin% (n=4439)	Simvastatin% (n=4449)	ARR %	RRR %	NNT/ 4.8 yrs	p value
1° coronary death/non fatal acute MI*/or cardiac arrest with resuscitation	9.3	10.4	1.1	11	**NS**	0.07
2° Nonfatal MI	6	7.2	1.2	17	84	0.02
2° Major cardiovascular events (1^0 + stroke)	12	13.7	1.7	13	59	0.02
2° Any CHD event **	20.2	23.8	3.6	16	28	<0.001
2° Any cardiovascular event ***	26.5	30.8	4.3	16	23	<0.001
2° Fatal or nonfatal stroke	3.4	3.9	0.5	13	NS	0.2
2° All-cause mortality	8.2	8.4	0.2	2	NS	0.81
2° Cardiovascular mortality	5	**4.9**	0.1	3	NS	0.78
2° Noncardiovascular mortality	3.2	3.5	0.3	8	NS	0.47

***** =requiring hospitalization **=coronary revascularization or hospitalization for unstable angina *** = ** plus peripheral vascular disease & hospitalizations for nonfatal HF
1°=primary outcome **2°**=secondary outcome **ARR**=absolute risk reduction **CHD**=coronary heart disease **CV**=cardiovascular **GI**=gastrointestinal
HF=heart failure **MI**=myocardial infarction **NNT**=number needed to treat to benefit 1 patient **NS**= not statistically significant **RRR**=relative risk reduction **SE**=side effects

Of Note:

- concomitant meds: ASA(79%), β-blocker(~75%), ACE-I(30%), CCB(19%), warfarin(13%), ARB(6%)
- **LDL** mean levels during treatment: atorvastatin arm: **2.1 mmol/l**; simvastatin arm: **2.7 mmol/l** (~**75%** of pts had previously been on statins ~51% on simvastatin (pts were already simv tolerant) : LDL ↓33**%** in the simvastatin naïve arm & ↓49% in the atorvastatin naïve arm at 12 wks)
- ↓ both total cholesterol by 0.74mmol/l & ↓triglycerides by 0.67mmol/l more in the atorvastatin than the simvastatin group at year 1
- ↑HDL by 0.03mmol/l more in the simvastatin group at year 1 (thus small HDL differences not likely clinically important)
- **SAFETY:**
  - **Myopathy:** Rate: 1 in 500; 11 simv pts & 6 atorv pts. **Rhabdomyolysis:** Rate: 1 in 1800; **5 cases** by investigators only 2 for atorv
  - **ALT/AST** elevations >3 x ULN occurred in 1% of patients in the **atorvastatin** arm and 0.1% in the simvastatin arm; **NNH=112** {**atorvastatin 80mg** vs 10mg in the **TNT** trial n=10,001 4.9yr: 1.2% vs 0.2% of pts had liver ALT levels >3 x ULN; **NNH=100**}
  - **permanently discontinued study med**: **atorvastatin** 14% & simvastatin 7% (most switched to a different statin)
  - **adverse events** worse with **atorvastatin**: D/C med 9.6 vs 4.2%; eg. myalgia 2.2 vs 1.1%, diarrhea 0.9 vs 0.2%, abdominal pain 0.8 vs 0.2% & nausea 0.5 vs 0.1%
  - noncardiovascular deaths higher in TNT trial 3.2% atorv 80 vs 2.5% atorv 10, but **NOT** the case in IDEAL 3.2 % atorv 80 vs 3.5% simv 20

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

- Many large RCTs, including IDEAL have shown statins reduce the risk of death or CV events in **high-risk** patients. [13] Current guidelines recommend reducing LDL to <2.5mmol/l in patients with CAD or diabetes ➔ previous studies using moderate statin doses have shown this is beneficial. TNT & IDEAL showed a ↓ in CV events but some ↑ in SE with high dose statins and resulting LDLs of ~2 mmol/l
- **IDEAL**: more aggressive lipid therapy (atorvastatin 80mg/d vs simvastatin 20-40mg/d) appears to provide greater benefit against 'major CV events & stroke' in previous MI patients. Some adverse event rates causing discontinuation are increased with the atorvastatin 80mg which may warrant **caution** and/or monitoring. **Magnitude of benefit** was "**one less** major CV event & stroke for every **59 previous MI** pts treated over **4.8 years**"; specifically less nonfatal acute **MI** 6 vs 7.2% NNT=84, but **NO** reduction in CV mortality, all-cause mortality or the 1° outcome (major coronary events)
- *Heads-Up*: 1) previous statin exposure (75%) may pre-select for patients likely to tolerate either arm
  2) most simvastatin patients at 20mg/d dose whereas most simvastatin evidence lies with a 40mg dose
  3) benefit relies on select secondary endpoints of trial since primary was not significant.
  4) may not be able to extrapolate benefit of routine high-dose atorvastatin to lower risk patients

Questions Remaining:

- What about lower risk patients requiring high dosages to reach targets? What is the benefit mechanism (ie: is it due to ↓ LDL **only**, CRP levels, anti-inflammation)? What is the long-term benefit/risk profile of higher aggressive dose statin therapy? Was it the dose of statin or the statin they dosed?

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Upcoming Trials:

SEARCH (The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine tests)[8]: comparing **simvastatin 20mg** and **80mg** in CHD patients

SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels)[9,10]: evaluating the effects of **atorvastatin 80mg/day** in 4,732 patients with previous stroke or TIA, but no hx of CHD

ASPEN (Atorvastatin Study for the Prevention of CHD Endpoints in NIDDM)[11]

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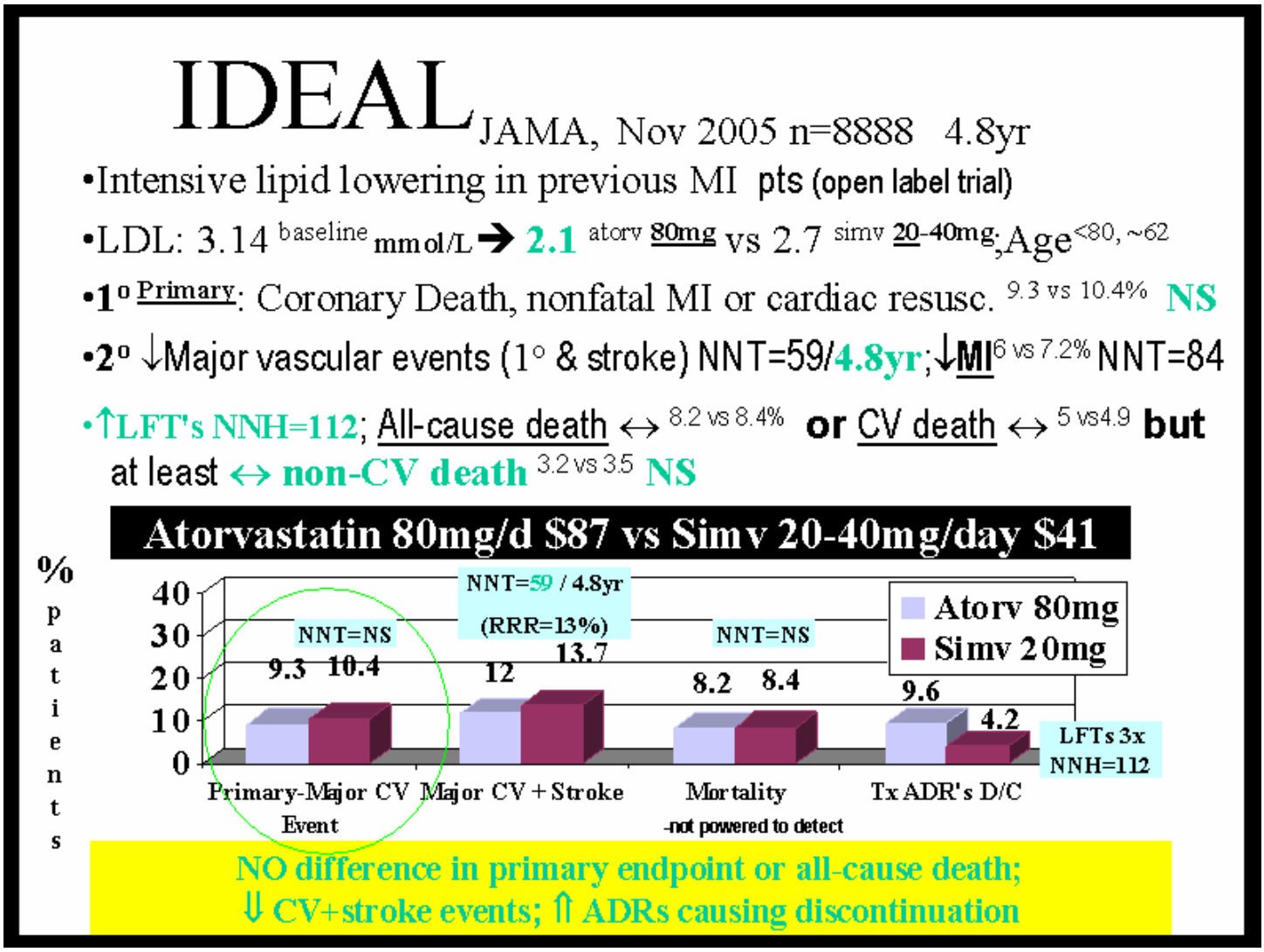

NNT= number needed to treat **NNH**= number needed to harm **NS**= not significant (statistically) **RRR**= relative risk reduction
ULN= upper limit of normal **Tx ADR's D/C**= treatment related adverse drug reactions resulting in discontinuation of therapy