Risk of Incident Diabetes With Intensive-Dose Compared With Moderate-Dose Statin Therapy: A Meta-analysis

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By

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Cardiovascular disease (CVD) is the number one cause of mortality and morbidity world wide

- Reducing high blood cholesterol which is a risk factor for CV events is an important goal of medical treatment
- Statins are considered the first-line agents for the treatment of hyperlipidemia
- Several reviews of the effects of statins have been published highlighting their benefits particularly in people with or without a past history of CVD

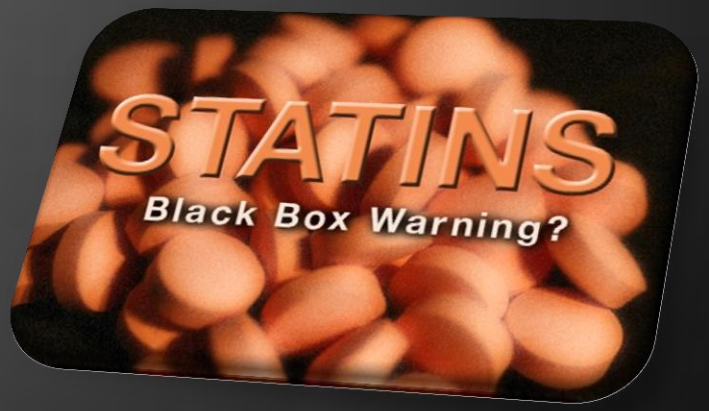
The Cochrane Library 2011, Issue 8

- **FDA**-approved indications for using statin drugs have been greatly expanded, being recommended for all cardiac patients with or without elevated cholesterol levels

- A well-conducted, RCTs proved the statin effect in causing significant reduction in heart attacks, strokes, and the need for coronary artery revascularization procedures (i.e., stents or bypass surgery).

- **Recently,** One potentially disturbing **"signal"** showed a higher risk of developing type II diabetes among patient with statins

- In particular, this finding was noted in the well-known *JUPITER* trial, the landmark trial that led the FDA to approve the statin drug Crestor® for patients with elevated CRP levels



- Many press reports claimed about the risk of new- onset type-II DM with statins use ..!!

Do statin drugs really make diabetes more likely?

And if though, to what extent ?

Studies Looking Specifically At Statins and Diabetes Risk

1) Meta analysis Study published in JAMA, in June 2011, of 33,000 patients enrolled in 5 major clinical trials using statins

2) Observational study published in the *Arch Intern Med,* in January 2012, analyzed data from 153,840 postmenopausal women between 50 and 80 years of age who were enrolled in the Women Health Initiative study.

Arch Intern Med. 2012;172(2):144-152
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Risk of Incident Diabetes With Intensive-Dose Compared With Moderate-Dose Statin Therapy

A Meta-analysis

David Preiss, MRCP; Sreenivasa Rao Kondapally Seshasai, MD; Paul Welsh,

Introduction

- Statin therapy significantly reduces CV events among individuals with and without a history of DM compared with placebo
- Intensive-dose statin therapy has also been shown to further reduce CV events compared with moderate- dose statin therapy
- A recent meta-analysis of 13 placebo and standard care RCTs involving 91,140 individuals, reported a **9% higher** risk of developing diabetes over a 4-year period among patients on statin compared to placebo or standard care group

Objective

- To examine the association of intensive-dose statin therapy Vs. moderate-dose therapy with the development of diabetes and the occurrence of major CV events, respectively

PICO

Population: Non diabetic patients using statins

Intervention: Intensive dose statin therapy

Comparison: Moderate dose statin therapy

Outcome: Incident Diabetes and CV events

Methodology

- **Study design:**

  Meta analysis study

- **Study Selection:**

  Data gathered from large randomized end-point statin trials primarily designed to assess the effect of intensive dose statin treatment compared with moderate-dose therapy on CV outcomes

- **Inclusion criteria**
  - Trials of 1000 or more participants exposed to statin therapy
  - Minimum mean follow-up of 1 year

  – Length of follow-up in both treatment groups was required to be identical to avoid bias in ascertainment of new-onset diabetes

Search Strategy

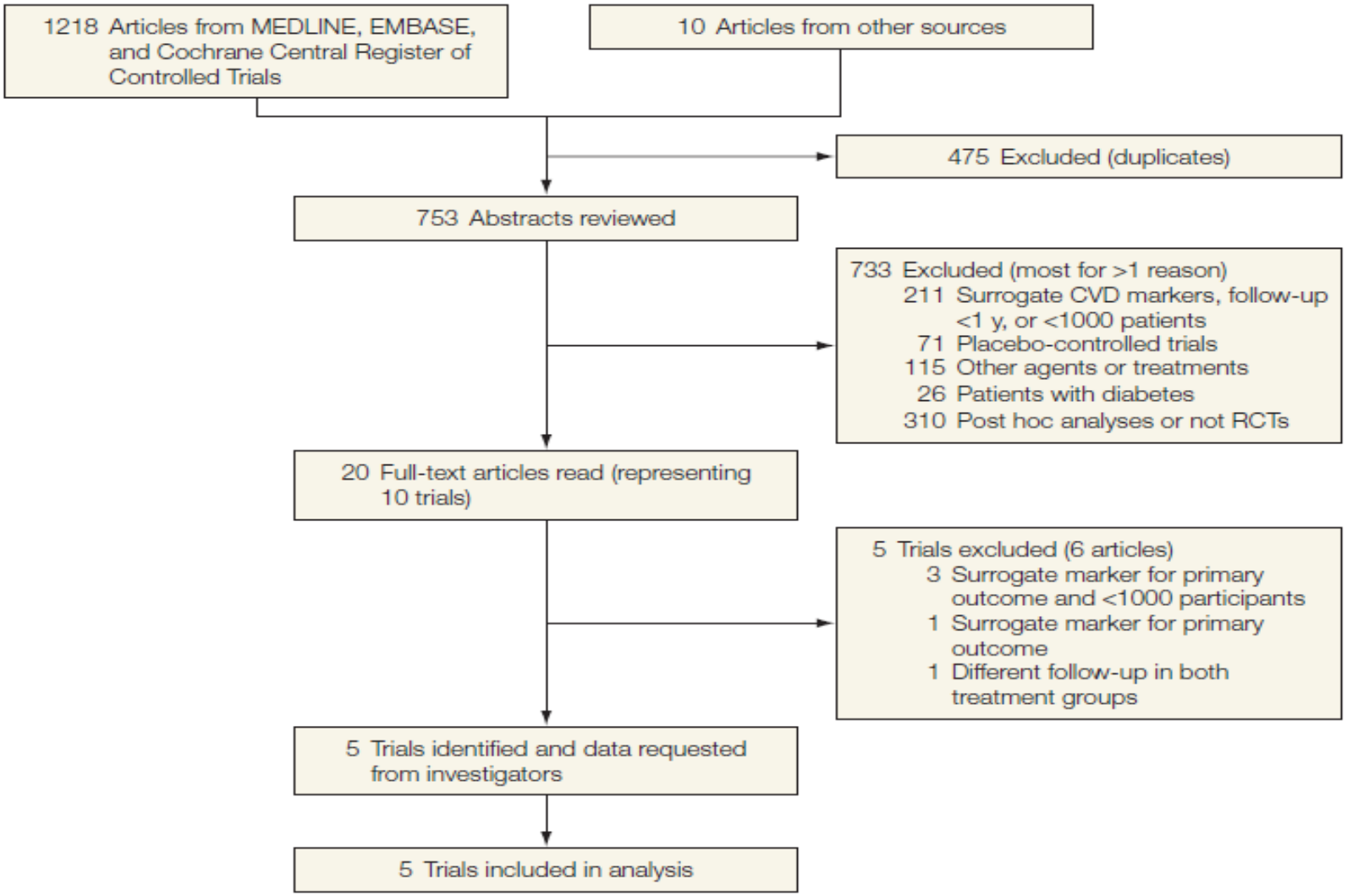
- **Search engines:**
  - MEDLINE,EMBASE, and the Cochrane Central Register of Controlled Trials
  - For studies published in English from January 1, 1996, until March 31, 2011

- **Key words:**

  Statin, HMG CoA reductase inhibitor and intensive *or* ***aggressive*** to identify trials performed in adult patients

- Initial search done in January 8, 2010 and updated April 4, 2011

Figure 1. Flow Diagram of the Literature Search



CVD indicates cardiovascular disease; RCTs, randomized controlled trials.

Search Strategy

After the full articles revision, 5 trials were included in the analysis:

1. The Treating to New Targets (TNT) trial
2. The Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) trial
3. The Aggrastat to Zocor (A to Z) trial
4. The Pravastatin or Atorvastatin Evaluation and Infection Therapy– Thrombolysis in Myocardial Infarction (PROVE IT–TIMI 22) trial
5. The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH)

Data sources

- Investigators from all 5 trials provided data for incident diabetes and major CV events according to a standard data query sheet

eFigure 1. Standard data query sheet used for collection of data from trials

Request for data from _____ trial:
Meta-analysis of incident diabetes in intensive vs. moderate dose statin trials

1. Total number of non-DM subjects at baseline ____
   a. Intensive statin ____
   b. Low dose statin ____

2. Baseline characteristics of all non-DM participants at baseline, where available
   a. Mean age (SD) yrs ____ (__)
   b. Mean BMI (SD) kg/m^2 ____ (__)
   c. Mean fasting glucose (SD) mmol/L ____ (__)
   d. Mean fasting or random HDL-c (SD) mmol/L ____ (__)
   e. Mean fasting or random Natural log [trigs] (SD), log mmol/L ____ (__)
   f. Number of male _____ and female _____ non-DM at baseline
   g. Number of current smokers _____ and not current smokers at baseline _____

3. Mean LDL-cholesterol (SD) at:
   a. Baseline:
      i. Intensive statin ___ (__)
      ii. Low dose statin ___ (__)
   b. End of study or fixed time during study
      i. Intensive statin ___ (__)
      ii. Low dose statin ___ (__)

4. Methods of diagnosis of diabetes – which of the following were used?
   a. Physician reported (i.e. Adverse Event) **YES / NO**
   b. Commencement of oral medication or insulin **YES / NO**
   c. Biochemistry (2 fasting glucose ≥7.0mmol/L) **YES / NO**

5. Number developing diabetes in each group:
   a. Intensive statin ___
   b. Low dose statin ___
   c. Hazard ratio for developing diabetes [high vs. low dose] (95%CI) ___ (__)

6. Number developing **CVD events** in each arm (*where CVD events includes the following: CVD death, non-fatal MI, non-fatal stroke, coronary revascularisation [CABG, PCI]*)
   a. Intensive statin ___
   b. Standard/low dose statin ___
   c. Hazard ratio for CVD endpoints (high vs. low dose) [HR (95%CI)] ___ (__)

7. Interactions for incident diabetes endpoint:
   a. Dichotomous: Nr developing DM / n
      i. Baseline BMI
         1. > median high dose ___ / ___ low dose ___ / ___
         2. < median high dose ___ / ___ low dose ___ / ___
      ii. baseline fasting glucose (if available)
         1. > median high dose ___ / ___ low dose ___ / ___
         2. < median high dose ___ / ___ low dose ___ / ___
      iii. baseline HDL-c (fasting or random as available)
         1. > median high dose ___ / ___ low dose ___ / ___
         2. < median high dose ___ / ___ low dose ___ / ___
      iv. Baseline Triglycerides
         1. > median high dose ___ / ___ low dose ___ / ___
         2. < median high dose ___ / ___ low dose ___ / ___
      v. baseline age
         1. > median high dose ___ / ___ low dose ___ / ___
         2. < median high dose ___ / ___ low dose ___ / ___
   b. Hazard ratios (95%CI) for developing DM: high vs. low dose
      i. Baseline BMI
         1. > median ___ (__)
         2. < median ___ (__)
      ii. baseline fasting glucose (if available)
         1. > median ___ (__)
         2. < median ___ (__)
      iii. baseline HDL-c (fasting or random as available)
         1. > median ___ (__)
         2. < median ___ (__)
      iv. Baseline Triglycerides
         1. > median ___ (__)
         2. < median ___ (__)
      v. baseline age
         1. > median ___ (__)
         2. < median ___ (__)

8. Interactions for composite CVD endpoint (see point 6):
   a. Dichotomous: Nr developing composite CVD endpoint / n
      i. Baseline BMI
         1. > median high dose ___ / ___ low dose ___ / ___
         2. < median high dose ___ / ___ low dose ___ / ___
      ii. baseline fasting glucose (if available)
         1. > median high dose ___ / ___ low dose ___ / ___
         2. < median high dose ___ / ___ low dose ___ / ___
      iii. baseline HDL-c (fasting or random as available)
         1. > median high dose ___ / ___ low dose ___ / ___
         2. < median high dose ___ / ___ low dose ___ / ___
      iv. baseline Triglycerides
         1. > median high dose ___ / ___ low dose ___ / ___
         2. < median high dose ___ / ___ low dose ___ / ___
      v. baseline age
         1. > median high dose ___ / ___ low dose ___ / ___
         2. < median high dose ___ / ___ low dose ___ / ___
   b. Hazard ratios (95%CI) for developing CVD endpoint: high vs. low dose
      i. Baseline BMI
         1. > median ___ (__)
         2. < median ___ (__)
      ii. baseline fasting glucose (if available)
         1. > median ___ (__)
         2. < median ___ (__)
      iii. baseline HDL-c (fasting or random as available)
         1. > median ___ (__)
         2. < median ___ (__)
      iv. baseline Triglycerides
         1. > median ___ (__)
         2. < median ___ (__)
      v. baseline age
         1. > median ___ (__)
         2. < median ___ (__)

End points

New- onset Diabetes end points:

A patient was considered to have developed diabetes if

(1) Adverse event report of newly diagnosed diabetes during the trial

(2) Patient commenced glucose-lowering medication during the trial

(3) Patient had 2 FPG values of ≥ 126 mg/dL (≥ 6.9 mmol/L)during the trial

Composite CV end points:

(1) CV death

(2) Nonfatal MI

(3) Nonfatal stroke

(4) PCI and CABG

(5) all-cause mortality.

Statistical Analysis

- Trial-Specific **O**dd **R**atios **(ORs)** were calculated for new-onset diabetes and major CV events To evaluate the effect of statins across clinically relevant subgroups

- **ORs** were pooled using a random-effects model meta-analysis to account for between study Heterogeneity

Statistical Analysis

- In exploratory analyses, results were compared in patients with
  - Recent ACS **Vs.** stable coronary heart disease
  - Simvastatin 80 mg **Vs.** Atorvastatin 80 mg being the respective intensive regimens

- All *P* values were 2-sided and ***P <.05*** was considered statistically significant

- Analyses were conducted using Stata version 10.1

Results

Table 1. Descriptions of the 5 Included Trials Comparing Intensive-Dose to Moderate-Dose Statin Therapy

Source	No Diabetes/ All Patients, No. (%)[a]	Trial Population	Intensive/ Moderate Regimen	Received Intensive/ Received Moderate, No.	Follow-up, y[b]	Methods of Diagnosing Diabetes
Cannon et al (PROVE IT–TIMI 22),[18] 2004	3395/4162 (82)	Recent ACS	Atorvastatin 80 mg/ pravastatin 40 mg	1707/1688	2.0 (0.6)	(1) AE report, (2) DM medication, (3) FPG ≥126 mg/dL twice
de Lemos et al (A to Z),[17] 2004	3504/4497 (78)	Recent ACS	Simvastatin 40 mg, simvastatin 80 mg/ placebo, simvastatin 20 mg	1768/1736	2.0 (1.5-2.0)	(1) AE report, (2) DM medication
LaRosa et al (TNT),[15] 2005[c]	7595/10 001 (76)	Stable CHD	Atorvastatin 80 mg/ atorvastatin 10 mg	3798/3797	5.0 (0.5)	(1) AE report, (2) DM medication, (3) FPG ≥126 mg/dL twice
Pedersen et al (IDEAL),[16] 2005[c]	7461/8888 (84)	Previous MI	Atorvastatin 80 mg/ simvastatin 20 mg or 40 mg	3737/3724	4.8 (4.4-5.0)	(1) AE report, (2) DM medication, (3) FPG ≥126 mg/dL twice
Armitage et al (SEARCH),[5] 2010	10 797/12 064 (89)	Previous MI	Simvastatin 80 mg/ simvastatin 20 mg	5398/5399	6.7 (1.4)	(1) AE report
Total	**32 752/39 612 (83)**			**16 408/16 344**	**4.9 (1.9)[d]**	

Abbreviations: ACS, acute coronary syndrome; AE, adverse event; A to Z, Aggrastat to Zocor trial; DM, diabetes mellitus; CHD, coronary heart disease; FPG, fasting plasma glucose; IDEAL, Incremental Decrease in End Points Through Aggressive Lipid Lowering study; MI, myocardial infarction; PROVE IT–TIMI 22, Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction study; SEARCH, Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; TNT, Treating to New Targets study.

SI conversion factor: To convert glucose to mmol/L, multiply by 0.0555.

[a] "No diabetes" indicates patients who did not have known diabetes mellitus at baseline.

[b] Follow-up values are mean (SD) for the TNT, SEARCH, and PROVE IT–TIMI 22 studies and median (interquartile range) for the A to Z and IDEAL studies.

[c] Excluded patients with known diabetes, FPG level of 126 mg/dL or greater, or both at baseline.

[d] Total follow-up values are pooled mean (pooled SD).

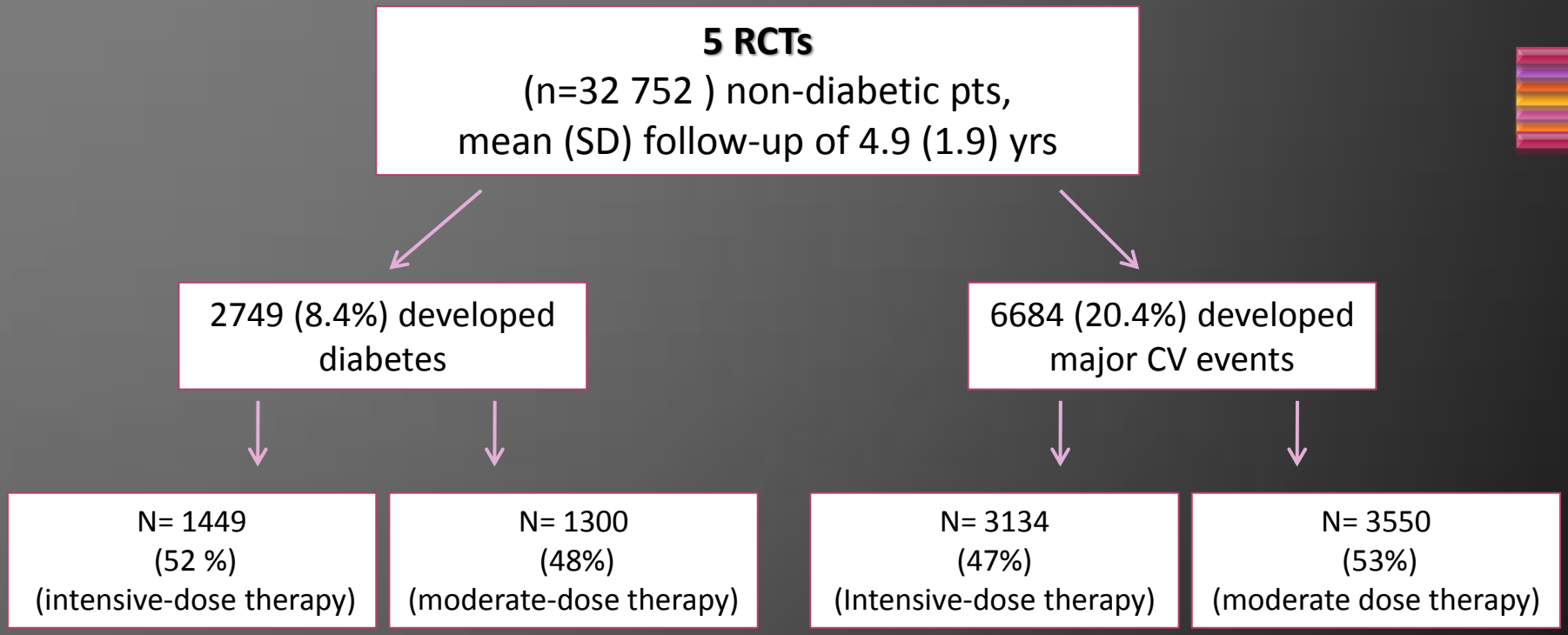
Results

Table 2. Baseline Data From Trials Comparing Intensive-Dose to Moderate-Dose Statin Therapy

Source	BMI, Mean (SD)[a]	Age, Mean (SD), y	HDL, Mean (SD), mg/dL	LDL, Mean (SD), mg/dL	LDL Reduction, Relative %[b]	ln Triglycerides, Mean (SD), mg/dL	FPG, Mean (SD), mg/dL	FPG Measured After Baseline
Cannon et al (PROVE IT–TIMI 22),[18] 2004	29 (5)	58 (11)	39 (12)	109 (31)	22	5.05 (0.44)	104 (11)[c]	Not specified[c]
de Lemos et al (A to Z),[17] 2004	NA	60 (11)	39 (12)	113 (27)	15	5.00 (0.39)	NA	NA
LaRosa et al (TNT),[15] 2005[d]	28 (4)	61 (9)	47 (12)	98 (20)	22	4.89 (0.42)	97 (11)	Annually
Pedersen et al (IDEAL),[16] 2005[d]	27 (4)	62 (10)	47 (12)	125 (35)	16	4.87 (0.44)	99 (11)	Final visit
Armitage et al (SEARCH),[5] 2010	28 (4)	64 (9)	43 (16)[e]	98 (23)[e]	12	4.97 (0.54)[e]	NA	NA

Abbreviations: A to Z, Aggrastat to Zocor trial; FPG, fasting plasma glucose; HDL, high-density lipoprotein cholesterol; IDEAL, Incremental Decrease in End Points Through Aggressive Lipid Lowering study; LDL, low-density lipoprotein cholesterol; NA, not available; PROVE IT–TIMI 22, Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction study; SEARCH, Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; TNT, Treating to New Targets study.
SI conversion factors: To convert HDL and LDL cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113; glucose to mmol/L, multiply by 0.0555.
[a] Calculated as weight in kilograms divided by height in meters squared.
[b] Calculated as [LDL(intensive-dose group)−LDL(moderate-dose group)]/LDL(baseline).
[c] For baseline FPG level, there were 315 results from the PROVE IT–TIMI 22 participants, which were similarly distributed between treatment groups.
[d] Excluded patients with known diabetes, FPG level of 126 mg/dL or greater, or both at baseline.
[e] Nonfasting.

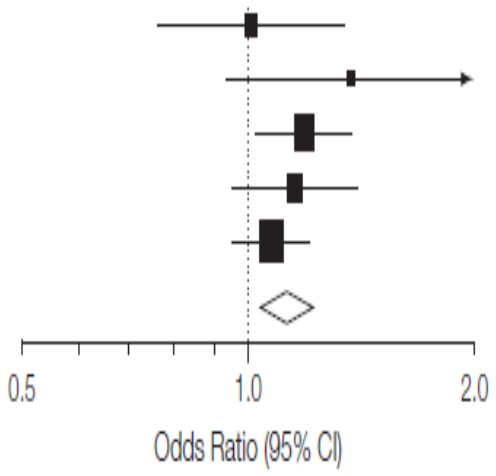
Results


5 RCTs
(n=32 752) non-diabetic pts,
mean (SD) follow-up of 4.9 (1.9) yrs
2749 (8.4%) developed diabetes
6684 (20.4%) developed major CV events
N= 1449
(52 %)
(intensive-dose therapy)
N= 1300
(48%)
(moderate-dose therapy)
N= 3134
(47%)
(Intensive-dose therapy)
N= 3550
(53%)
(moderate dose therapy)

New-Onset Diabetes

Figure 2. Meta-analysis of New-Onset Diabetes and First Major Cardiovascular Events in 5 Large Trials Comparing Intensive-Dose to Moderate-Dose Statin Therapy

Incident Diabetes	Cases/Total, No. (%) Intensive Dose	Moderate Dose	OR (95% CI)
PROVE IT–TIMI 22,[18] 2004	101/1707 (5.9)	99/1688 (5.9)	1.01 (0.76-1.34)
A to Z,[17] 2004	65/1768 (3.7)	47/1736 (2.7)	1.37 (0.94-2.01)
TNT,[15] 2005	418/3798 (11.0)	358/3797 (9.4)	1.19 (1.02-1.38)
IDEAL,[16] 2005	240/3737 (6.4)	209/3724 (5.6)	1.15 (0.95-1.40)
SEARCH,[5] 2010	625/5398 (11.6)	587/5399 (10.9)	1.07 (0.95-1.21)
Pooled odds ratio	1449/16 408 (8.8)	1300/16 344 (8.0)	1.12 (1.04-1.22)
Heterogeneity: $I^2=0\%$; $P=.60$			



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New-Onset Diabetes

- **In absolute terms**, there were 2.0 additional cases of diabetes per 1000 patient/years among those receiving intensive-dose therapy (mean [SD] 18.9 [5.2] cases per 1000 patient-years) **Vs.** (16.9 [5.5] cases per 1000 patient-years with moderate-dose therapy)

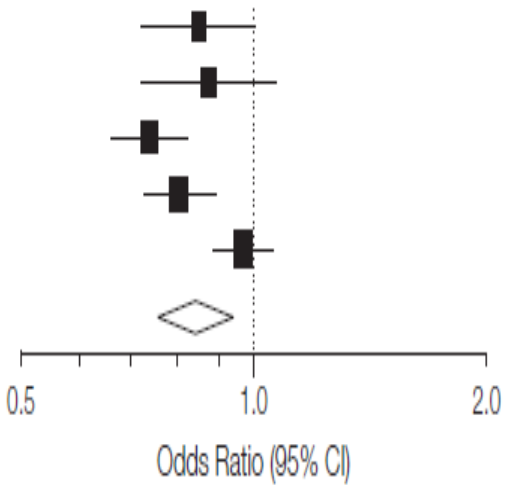
- Number needed to harm (NNH) = 498 /year.

- No significant heterogeneity between trials for new-onset diabetes , Likewise, no evidence of publication bias (*P=.54)*

CVD Benefit

Figure 2. Meta-analysis of New-Onset Diabetes and First Major Cardiovascular Events in 5 Large Trials Comparing Intensive-Dose to Moderate-Dose Statin Therapy

	Cases/Total, No. (%)		
	Intensive Dose	Moderate Dose	OR (95% CI)
Incident CVD			
PROVE IT–TIMI 22,[18] 2004	315/1707 (18.4)	355/1688 (21.0)	0.85 (0.72-1.01)
A to Z,[17] 2004	212/1768 (12.0)	234/1736 (13.5)	0.87 (0.72-1.07)
TNT,[15] 2005	647/3798 (17.0)	830/3797 (21.9)	0.73 (0.65-0.82)
IDEAL,[16] 2005	776/3737 (20.8)	917/3724 (24.6)	0.80 (0.72-0.89)
SEARCH,[5] 2010	1184/5398 (21.9)	1214/5399 (22.5)	0.97 (0.88-1.06)
Pooled odds ratio	3134/16408 (19.1)	3550/16344 (21.7)	0.84 (0.75-0.94
Heterogeneity: I^2=74%; P=.004			



Data marker size indicates relative weight of the studies; OR, odds ratio; and CI, confidence interval.

CVD Benefit

- **In absolute terms**, there were 6.5 fewer first major CV events per 1000 patient/years among those receiving intensive statin therapy (mean [SD] 44.5 [20.4] cases per 1000 patient-years Vs. 51.0 [23.6] cases per 1000 patient-years with moderate dose therapy)

- Number needed to treat (NNT) = 155 to prevent 1 CV event/year.

- There was significant heterogeneity between trials for major CV events. However, no evidence of publication bias (*P=.70)*

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Composite CV end point

Table 3. Pooled Event Rates and Odds Ratios for Individual Components of the Composite Cardiovascular End Point

End Point	Event Rate (SD) [Events/Patients, No.][a] Intensive-Dose Regimen	Moderate-Dose Regimen	OR (95% CI)	I^2 (95% CI), %	Annual NNT
Cardiovascular death	9.12 (4.78) [759/16 408]	10.04 (5.85) [789/16 342]	0.94 (0.83-1.07)	15 (0-82)	1087
Nonfatal myocardial infarction	13.74 (8.45) [912/16 408]	15.47 (8.54) [1041/16 342]	0.87 (0.79-0.95)	0 (0-79)	578
Nonfatal stroke[b]	4.74 (1.43) [394/16 407]	5.39 (1.36) [436/16 342]	0.90 (0.78-1.03)	0 (0-79)	1538
Coronary revascularization	27.92 (18.86) [1906/16 407]	33.78 (21.45) [2326/16 343]	0.80 (0.71-0.90)	63 (3-86)	171

Abbrevi
[a] Event
[b] Includ

Similar association between intensive statin therapy and each CV end point component

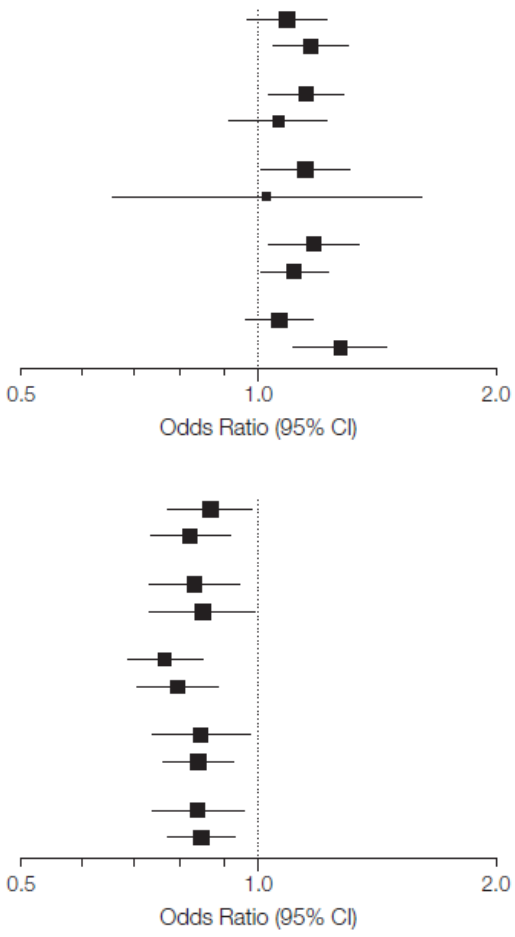
Composite CV end point

End point	Intensive doses Cases/total, No.	Moderate doses Cases/total, No.	OR (95% CI)	I^2 (95% CI), %
All cause mortality	1318 /16 408	1360 /16 342	**0.93 (0.81-1.05)**	43% (0%-79%)
Non-CV death	559 /16 408	571 /16 342	**0.98 (0.87-1.10)**	0% (0%-79%)

- Intensive-dose therapy was ***NOT*** associated with lower all-cause mortality and rates of non-CV death compared with moderate-dose statin therapy
- **No** significant heterogeneity between trials for all-cause mortality or non-CV death

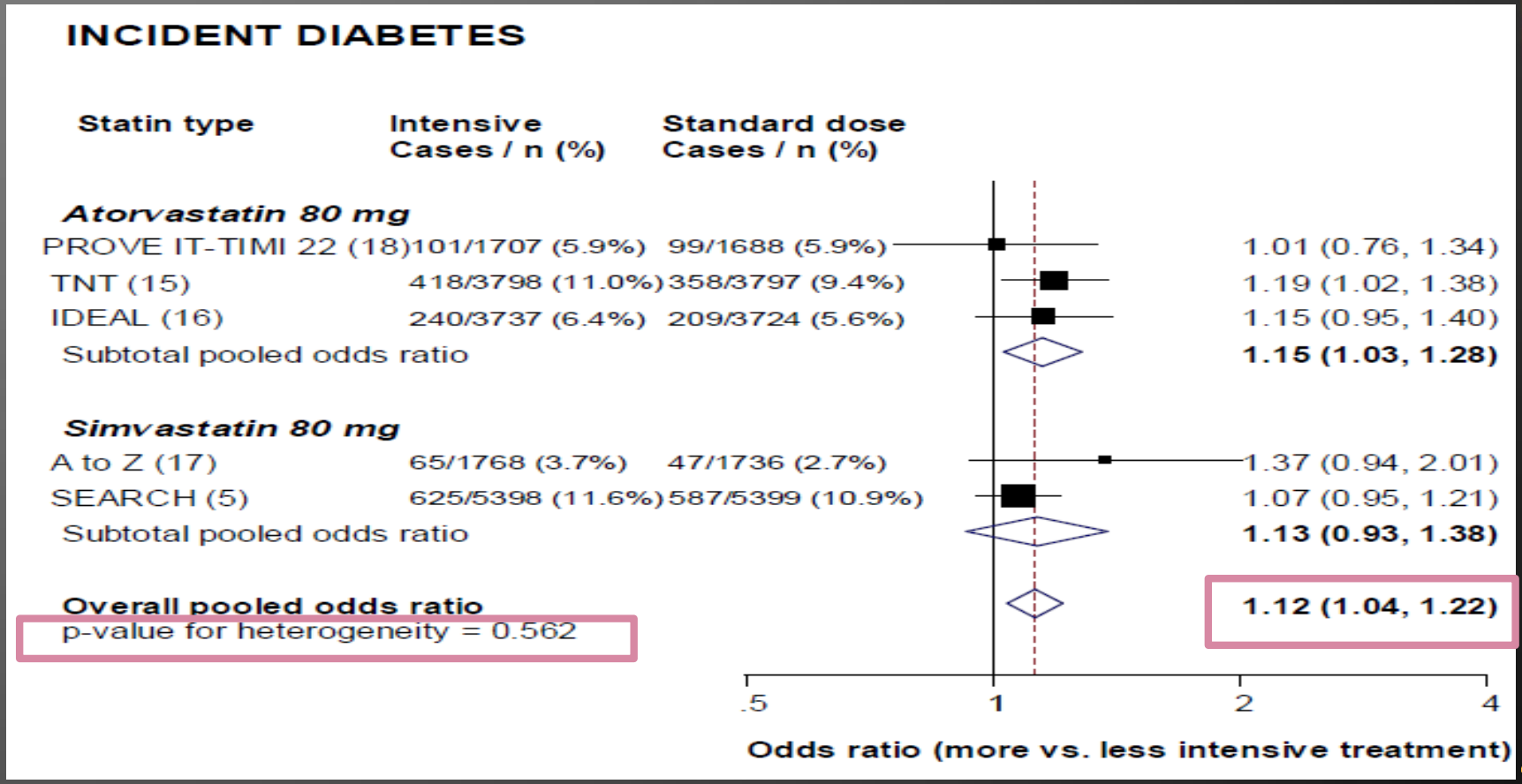
Subgroup analysis

		Developed Diabetes/No Diabetes at Baseline, Pooled No.			
		Intensive Dose	Moderate Dose	OR (95% CI)	*P* Value
Incident Diabetes					
Age	Above median	657/8103	604/8030	1.09 (0.97-1.22)	.39
	Below median	792/8305	696/8313	1.16 (1.04-1.30)	
BMI	Above median	980/7176	865/7102	1.15 (1.03-1.28)	.37
	Below median	400/7363	381/7395	1.06 (0.92-1.22)	
Fasting glucose	Above median	574/3874	505/3817	1.15 (1.01-1.31)	.55
	Below median	117/4314	106/4347	1.02 (0.65-1.61)	
HDL cholesterol	Above median	504/7698	430/7648	1.17 (1.03-1.34)	.51
	Below median	943/8516	863/8491	1.11 (1.01-1.23)	
Triglycerides	Above median	944/8049	892/7914	1.06 (0.96-1.17)	.04
	Below median	503/8165	402/8228	1.27 (1.11-1.45)	
Incident CVD					
Age	Above median	1688/8103	1853/8030	0.87 (0.77-0.98)	.49
	Below median	1446/8305	1697/8313	0.82 (0.73-0.92)	
BMI	Above median	1399/7176	1599/7102	0.83 (0.73-0.95)	.83
	Below median	1504/7363	1690/7395	0.85 (0.73-0.99)	
Fasting glucose	Above median	753/3874	918/3817	0.76 (0.68-0.85)	.65
	Below median	796/4314	969/4347	0.79 (0.70-0.89)	
HDL cholesterol	Above median	1392/7698	1561/7648	0.85 (0.73-0.98)	.93
	Below median	1709/8516	1953/8491	0.84 (0.76-0.93)	
Triglycerides	Above median	1572/8049	1763/7914	0.84 (0.73-0.96)	.91
	Below median	1529/8165	1751/8228	0.85 (0.77-0.93)	

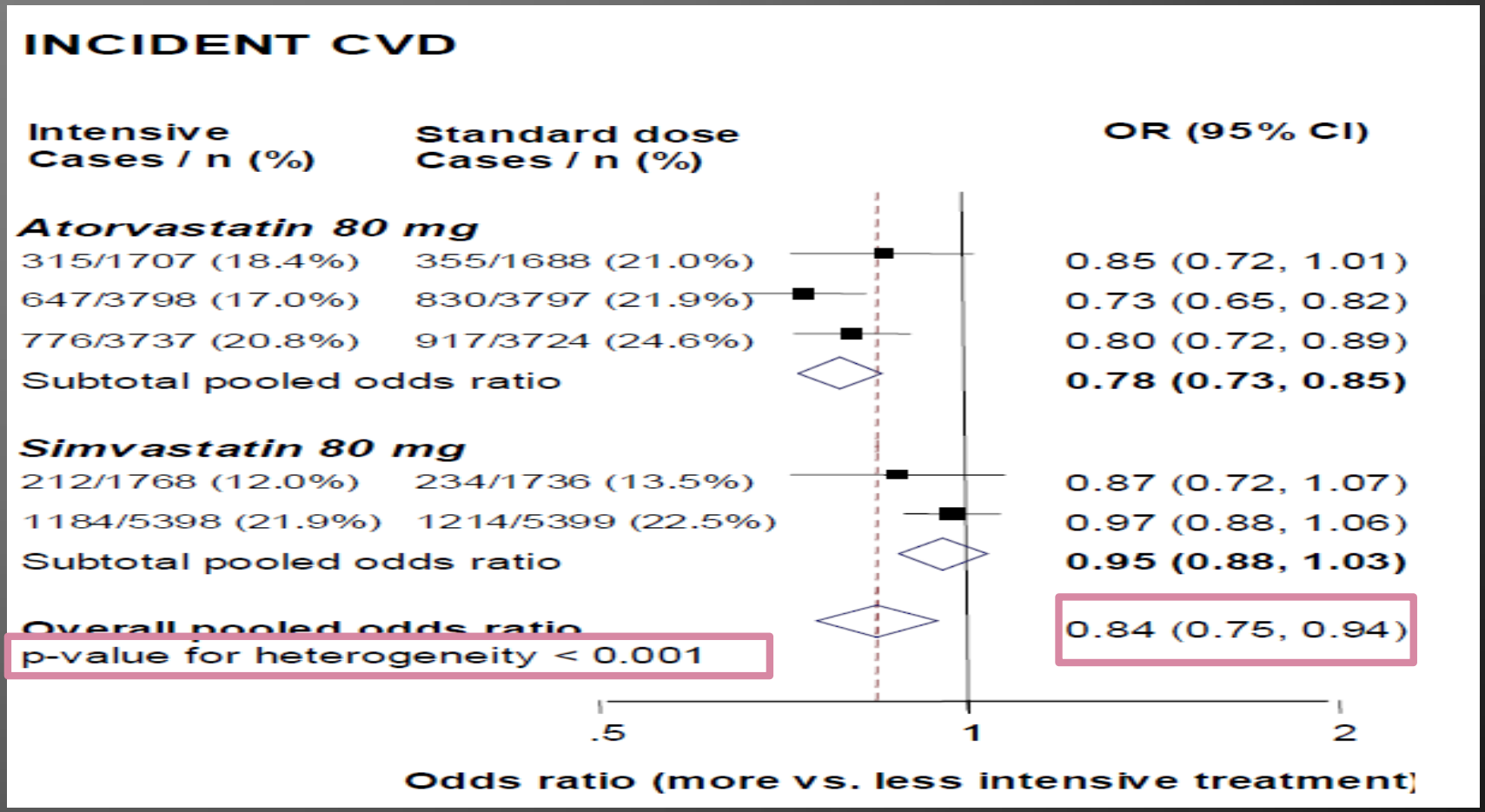


Statin Type and Trial Population (Exploratory analysis)

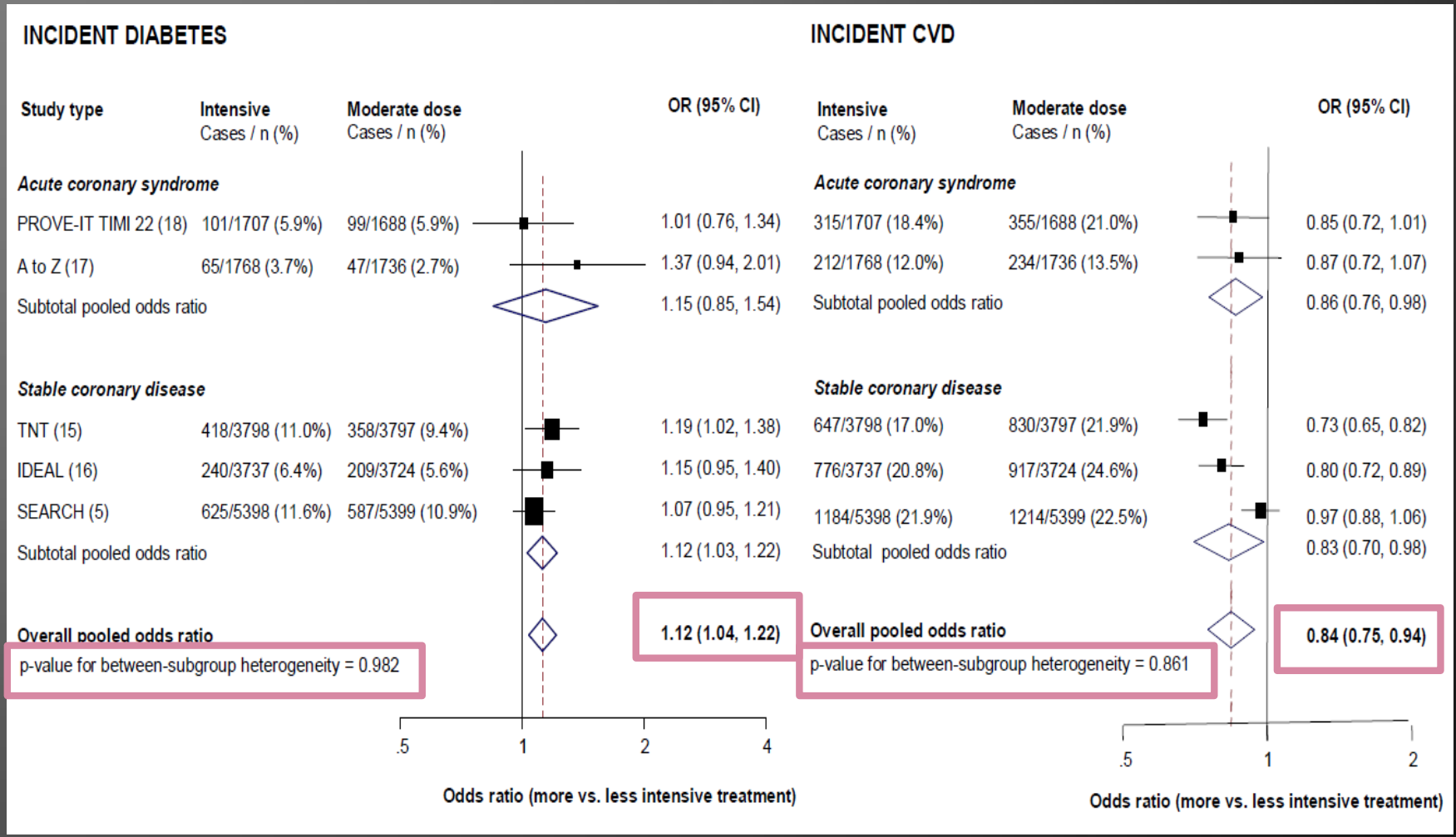
A comparison of new-onset diabetes and first major CV events:



A comparison of new-onset diabetes and first major CV event :



A comparison of new-onset diabetes and first major CV events in trials of patients following a recent ACS and patients with stable coronary heart disease:



Discussion

Discussion

- This study demonstrates that use of intensive-dose statin therapy compared with moderate-dose statin therapy was associated with a **higher incidence** of new-onset diabetes (OR, 1.12) while **fewer** major CV events (OR, 0.84)

- In relative terms, the risk of new-onset diabetes and the benefit of CV event reduction for patients receiving intensive therapy were **Similar**

- However, in absolute terms there was 1 additional case of diabetes for every 498 patients treated for 1 year (NNH) , compared with 1 fewer patient experiencing a CV event for every 155 patients treated for 1 year (NNT).

Discussion

- The benefits of statin therapy were consistent across all subgroups and for each component of the primary efficacy end point, including CV death

- Analyses of all-cause mortality were consistent with observations for CV death, although the generalizability of these findings to other populations is less clear, because these depend on the relative contributions of CV death (modified by statins) and non CV death (non modifiable by statins) in those populations

Discussion

- Higher odds of new-onset diabetes with intensive dose statin among individuals with TG concentrations (below the median level) may be a chance finding, due to absence of a biologically plausible mechanism

- The higher incidence of new-onset diabetes and lower incidence of CV events were **similar** in patients following recent ACS and those with stable coronary disease.

Discussion

- Among patients used Atorvastatin 80 mg, LDL-cholesterol reduction was **greater** than Simvastatin 80 mg, Whereas the odds of developing diabetes was **similar** on both

- There was a significantly **lower odds** of CV events in the trials with high-dose Atorvastatin but not with high-dose Simvastatin.

Queries

1. A potential mechanism of higher incident diabetes includes a direct and off target effect still unclear. Statin-induced myopathy which is associated with muscle insulin resistance, provides a potential mechanism

2. Generalized tendency for an increase in diabetes risk in many who take statins or whether there is a specific group of individuals at particular risk remains unclear . Analysis of data from subgroups did not provide conclusive data

3. The important associated long-term risks of developing micro vascular disease with statins is unknown

Queries

4. It would be of interest to investigate the impact of intensive statin therapy on glycemic control and treatment requirements in patients with established diabetes

5. Registry to examine these issues of long-term risk is a consideration to help quantify potential concerns

6. Study findings suggest that clinicians should be vigilant for the development of diabetes in patients receiving intensive statin therapy

- **To date, no large clinical studies have examined the associations of statin therapy with micro vascular disease**

Strength

1. Meta analysis study

2. Data from all the relevant clinical trials were included and thereby provide adequate power to detect potentially modest effects

3. Access to trial data allowed relevant subgroup analyses

4. Comparison of the potential risk of new-onset diabetes with CV benefit was provided, thereby providing clinically useful information

Weakness

1. Different methods for diagnosing diabetes were available for the 5 trials, and the trials were not designed to assess new-onset diabetes
   - However, the low heterogeneity in new-onset diabetes as well as the very similar sensitivity analysis using the nonstandard criteria in 2 trials provides confidence in the results obtained

2. Analyses of incident diabetes were not prespecified in the trial designs and the risk is underestimated among the trial participants

Weakness

3- All 5 trials specifically included participants with established coronary disease at high risk of future CV events rather than diabetes, so the findings may not necessarily be generalizable to populations at higher risk of incident diabetes

4- Analyses were conducted without access to individual participant data

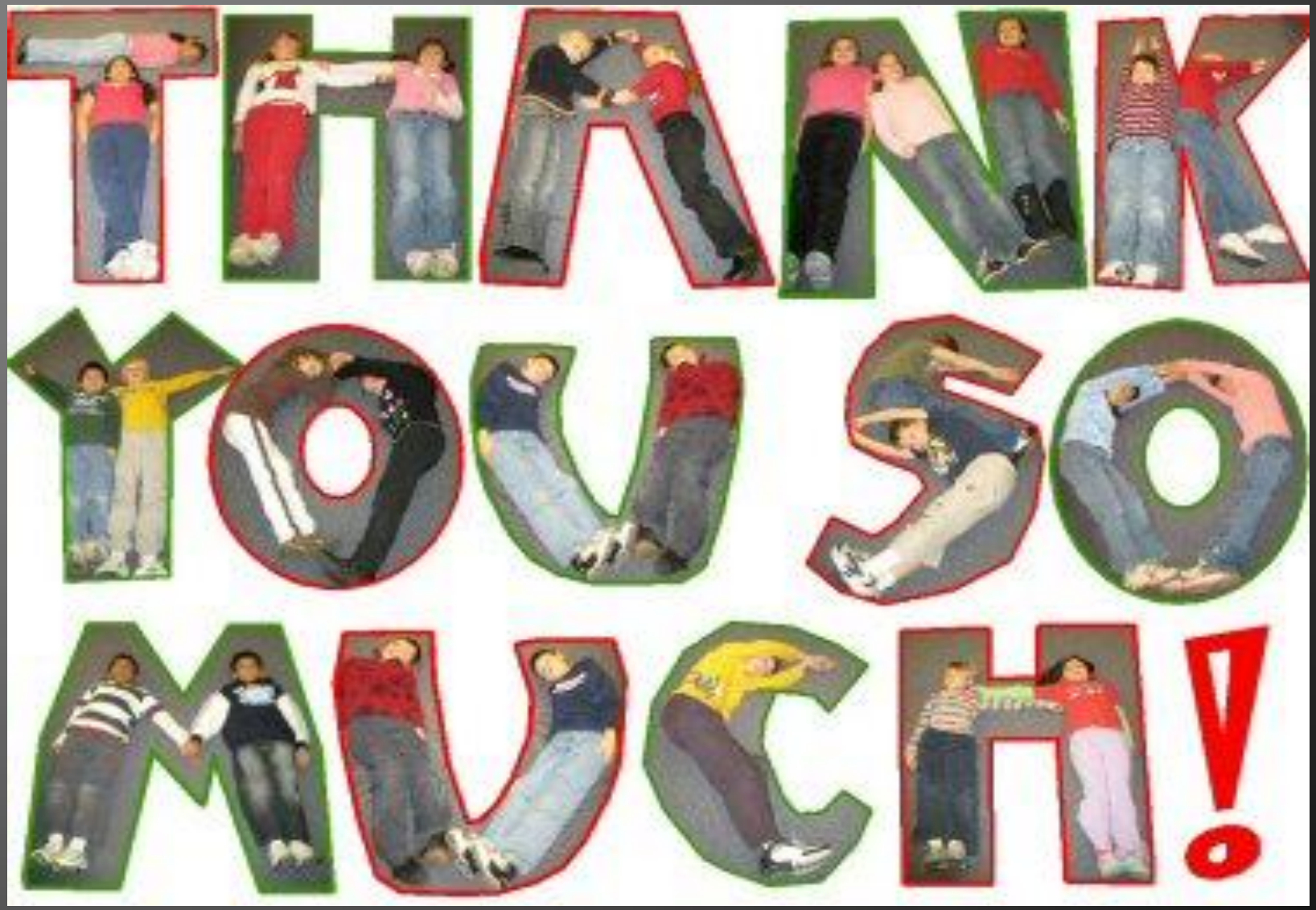
5- Detection bias due to the possibility that intensive statin therapy may have caused more adverse effects and therefore lead to differences in routine clinical care between those treated with intensive- and moderate-dose regimens

Conclusion

- This meta-analysis extends earlier findings of an increased incidence of diabetes with statin therapy by providing evidence of a **Dose dependent association**

Conflict of Interest

- **Conflict of interest Disclosure was declared and most of the authors received consulting and lecturing fees from several pharmaceutical companies**


THANK
YOU SO
MUCH!