



Efficacy of Standard and Intensive Statin Treatment for the Secondary Prevention of Cardiovascular and Cerebrovascular Events in Diabetes Patients: A Meta-Analysis

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Abstract

Aims: To estimate the efficacy of standard and intensive statin treatment in the secondary prevention of major cardiovascular and cerebrovascular events in diabetes patients.

Methods: A systematic search was conducted in Medline over the years 1990 to September 2013. Randomized, double-blind, clinical trials comparing a standard-dose statin with placebo or a standard-dose statin with an intensive-dose statin for the secondary prevention of cardiovascular and cerebrovascular events in diabetes patients were selected. Trial and patient characteristics were extracted independently by two researchers. The combined effect on the composite primary endpoint was measured with a fixed-effect model. Potential publication bias was examined with a funnel plot.

Results: Five trials were included in the analysis comparing standard-dose statins with placebo with a total of 4 351 participants. Four trials were included for comparing standard-dose with intensive-dose statins, including 4 805 participants. Compared with placebo, standard-dose statin treatment resulted in a significant relative risk (RR) reduction of 15% in the occurrence of any major cardiovascular or cerebrovascular event (RR 0.85, 95% CI 0.79–0.91). Compared with standard-dose statin treatment, intensive-dose statin treatment resulted in an additional 9% relative risk reduction (RR 0.91, 95% CI 0.84–0.98).

Conclusion: Treatment with standard-dose statins to prevent cardiovascular or cerebrovascular events in diabetes patients with manifest cardiovascular disease results in an estimated 15% relative risk reduction and intensive-dose statin treatment adds 9%. If proven cost-effective, more intensive statin treatment should be recommended for diabetes patients at high cardiovascular risk.

Citation: de Vries FM, Kolthof J, Postma MJ, Denig P, Hak E (2014) Efficacy of Standard and Intensive Statin Treatment for the Secondary Prevention of Cardiovascular and Cerebrovascular Events in Diabetes Patients: A Meta-Analysis. PLoS ONE 9(11): e111247. doi:10.1371/journal.pone.0111247

Editor: Michael Lipinski, Washington Hospital Center, United States of America

Received: July 2, 2014; **Accepted:** September 21, 2014; **Published:** November 5, 2014

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Data Availability: The authors confirm that all data underlying the findings are fully available without restriction. All relevant data are within the paper and its Supporting Information files.

Funding: The authors have no support or funding to report.

Competing Interests: The authors of this manuscript have read the journal's policy and have the following competing interests: MJP received grants, honoraria, and travel stipends from various pharmaceutical industries, inclusive of those potentially interested in the subject matter of this paper. FMdV, JK, PD, and EH have no conflicts of interest that are directly relevant to the content of this meta-analysis. This does not alter the authors' adherence to PLOS ONE policies on sharing data and materials.

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Background

Cardio- and cerebrovascular diseases are ranked among the major causes of mortality worldwide [1]. Patients with diabetes have a two- to four-fold higher risk of cardiovascular events than age-matched non-diabetes patients [2]. Especially those diabetes patients with a history of cardio- or cerebrovascular disease are at increased risk for recurrent events [3]. Hence, cardiovascular risk management is an essential part of the management of diabetes [4].

The need for statin treatment for secondary prevention of cardiovascular events is widely recognized. Significant benefits of

statin treatment were reported in two meta-analyses, leading to the conclusion that statin therapy reduces the occurrence of major vascular events in diabetes patients with and without vascular disease [5,6]. These analyses did not include the ASPEN study, which did not show significant results with a standard-dose statin in diabetes patients [7]. Recently Chang et al. [8] performed a meta-analysis and came to the conclusion that there is still uncertainty regarding the benefits of statins in diabetes patients. When focusing on high quality trials for secondary prevention in diabetic patients only, being the ASPEN trial and the 4D trial [9], no significant benefits of statin treatment were seen [8]. In these previous meta-analyses several studies with selective subgroups,

such as patients on hemodialysis, were included and a significant heterogeneity was seen. Moreover, most trials included in the previous meta-analyses were limited to interventions with standard-dose statins. Baigent et al. reported, however, that more intensive treatment is associated with even further reductions in the risk for major vascular events in secondary prevention patients [10]. As LDL cholesterol targets have been set at lower levels, targets are not met in at least a third of these patients and more intensive treatment may be needed [11,12]. Randomized clinical trials comparing standard with intensive statin treatment reported partly significant and partly insignificant effects of intensive treatment on reducing the occurrence of major cardiovascular or cerebrovascular complications within the diabetes subgroup [13,14,15,16]. For clinical decision making and cost-effectiveness analysis it is important to have precise effect estimates of standard and intensive statin treatment for secondary prevention diabetes patients.

We aimed to perform two meta-analyses: (1) to assess the effect of standard-dose statins over placebo and (2) to assess the additional effect of intensive-dose statins over standard-dose statins, both for the secondary prevention of major cardiovascular and cerebrovascular events in a non-restrictive diabetes population. Only high-quality and double-blinded studies were eligible for inclusion.

Methods

Search strategy

We searched the Medline and Embase databases and Clinical-Trials.gov for randomized clinical trials that either compared statin treatment to placebo or standard to intensive statin treatment for the secondary prevention of cardiovascular and cerebrovascular events (1990 to September 2013) reported in the English-language. Trials were identified with the use of the medical subject heading (MeSH) terms 'statins', 'HMG-CoA reductase inhibitor', 'randomized controlled trial', 'secondary prevention', 'intensive', 'moderate', 'diabetes', 'coronary heart disease', 'myocardial infarction' and 'stroke'. Reference lists of reviews and meta-analysis related to the study were examined. The search was independently performed by two researchers (FV and JK).

Study selection

Inclusion criteria for both meta-analyses were: randomized clinical trials (1); including a non-restrictive secondary prevention diabetes population with previous coronary heart disease, cerebrovascular disease, myocardial infarction or unstable angina pectoris (2); and reporting major cardiovascular and cerebrovascular events as endpoint (3). For the first meta-analysis studies were required to include a standard-dose statin arm and a placebo arm, for the second meta-analysis studies were included which compared standard-dose with intensive-dose statin arm. Standard-dose refers to commonly prescribed daily doses of atorvastatin ≤ 20 mg, simvastatin ≤ 60 mg, rosuvastatin ≤ 10 mg and any dosing of pravastatin, lovastatin and fluvastatin [17,18,19]. Higher daily doses were categorized as intensive-dose statin treatment. The quality of selected studies was scored with the Jadad score [20]. The Jadad score evaluates on a scale from 0–5 the appropriateness of the randomization technique (1), the method for double-blinding (2) and the description of withdrawals and dropouts (3). Two researchers (JK, FV) individually extracted the trial and patient characteristics and the outcome results.

Endpoints

The primary endpoint for both meta-analyses was a composite of major cardiovascular and cerebrovascular events, including the first occurrence of fatal and non-fatal myocardial infarction (MI), fatal and non-fatal stroke, revascularization and hospitalization for unstable angina. The meta-analysis comparing standard-dose statins with placebo also assessed the secondary endpoints: fatal and non-fatal MI (a); fatal and non-fatal stroke (b); and all-cause mortality (c).

Data analysis and statistical methods

For each endpoint, the relative risk (RR) with corresponding 95% confidence interval (CI) and the number needed to treat (NNT) with 95% CI were calculated [21]. The results of the separate studies were pooled with the fixed-effect model and the random-effect model in the computer program RevMan from the Cochrane Collaboration [22,23]. The fixed-effect model assumes that differences in effects between studies are due to sampling error whereas the random-effect model assumes that the separate studies are measuring different effects. Model selection was based on heterogeneity testing which was assessed by calculating the Q statistic, that tests the homogeneity hypothesis, and the I^2 index [24], that calculates the percentage of variability in the effect estimates that is due to heterogeneity rather than chance. Based on the heterogeneity testing the fixed-effect model was used for all endpoints. Evidence for potential publication bias was examined by visually studying funnel plots.

Results

Description of included randomized clinical trials

Data from nine randomized clinical trials were included in the current meta-analyses (Fig. 1): the 4S [25], the ASPEN [7], the CARE [26], the HPS [27] and the LIPID [28] trial for the comparison of a standard-dose statin with placebo and the A to Z [13], the PROVE-IT TIMI [14], the SEARCH [15] and the TNT [16] trials for the comparison of standard-dose statin treatment with intensive-dose statin treatment (see Table 1 for full trial names). The study and patient characteristics of the included studies can be found in Table 2 and Table 3. In total, 4 351 (2 153 standard-dose statin/2 198 placebo) participants were included in the standard-dose statin/placebo analysis and 4 805 (2 409 intensive-dose statin/2 396 standard-dose statin) participants were included for the comparison intensive-dose statin/standard-dose statin treatment. Within the standard-dose statin/placebo analysis participants were treated with pravastatin 40 mg, atorvastatin 10 mg or simvastatin in the dosage of 20 or 40 mg daily. Within the analysis comparing standard-dose statin treatment with intensive-dose statin treatment, patients in the standard-dose statin group were treated with simvastatin 20 mg, pravastatin 40 mg or atorvastatin 10 mg and patients in the intensive-dose statin group were treated with simvastatin 80 mg or atorvastatin 80 mg.

The weighted mean follow-up was 5.3 years (ranging from 4.0 in the ASPEN trial [7] and 6.0 in the LIPID trial [28]) in the standard-dose statin/placebo analysis and 4.6 years (ranging from 2.0 years in the A to Z trial [13] and the PROVE-IT TIMI trial [14] to 6.7 years in the SEARCH trial [15]) in the standard-dose statin/intensive-dose statin analysis. Participants in both analyses did not differ according to age and gender.

The definition for secondary prevention patients was slightly different for the individual trials included in both meta-analyses (Table 2). Some studies included patients with previous unstable angina or cerebrovascular disease, while others did not. Furthermore, some slight differences in inclusion criteria were made in

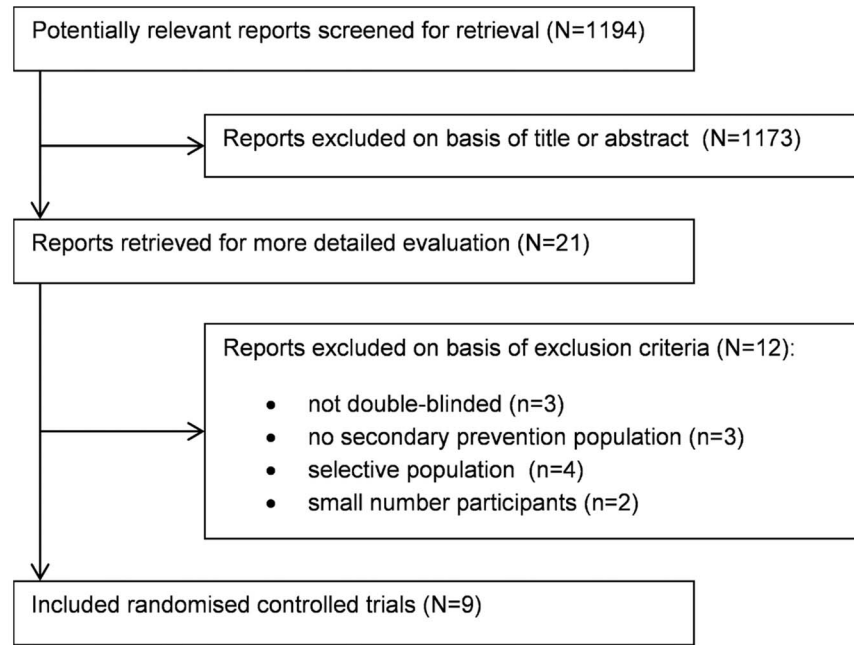


Figure 1. Flow diagram of study selection.

doi:10.1371/journal.pone.0111247.g001

age, cholesterol and triglyceride levels. Small differences were also present in the definition of endpoints that were included in the composite endpoint of major cardiovascular and cerebrovascular events.

Relative risk of standard-dose statin versus placebo

Within a hypothetical high risk population with a 10-year risk for cardiovascular disease of 50%, 27 patients need to be treated for 5 years with a standard-dose statin to prevent one major cardiovascular or cerebrovascular event. Standard-dose statin treatment was associated with a significant relative risk (RR) reduction of 15% for major cardiovascular or cerebrovascular events (RR 0.85, 95% CI 0.79–0.91) (Fig. 2, Fig. 3). In the statin treatment group, 35.2% of subjects had a major cardiovascular or

cerebrovascular event (763/2153), whereas 41.4% of those in the placebo group experienced such an event (914/2198). There was no observed publication bias and non-significant heterogeneity in the individual effect estimates.

In Table 4, participant and event numbers and outcome results for secondary endpoints are presented. For fatal and non-fatal stroke, there was a significant 33% relative risk reduction (RR 0.67, 95% CI 0.49–0.90). Non-significant relative risk reductions of 27% for fatal and non-fatal MI (RR 0.73, 95% CI 0.53–1.00) and 22% for all-cause mortality (RR 0.78, 95% CI 0.53–1.14) were found.

Table 1. Full trial name of study acronyms.

Study acronyms	Trial name
4D [9]	Die Deutsche Diabetes Dialyse Studie
4S [25]	Scandinavian Simvastatin Survival Study
ASPEN [7]	Atorvastatin Study of Prevention of coronary heart disease Endpoints in Non-insulin-dependent diabetes mellitus
A to Z [13]	Phase Z of the A to Z trial
CARE [26]	Cholesterol And Recurrent Events
GISSI [30]	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Prevenzione trial
HPS [27]	Heart Protection Study of cholesterol-lowering with simvastatin in people with diabetes
LIPID [28]	Long-Term Intervention with Pravastatin in Ischemic Disease
LIPS [31]	The Lescol Intervention Prevention Study
Post CABG [29]	Post Coronary Artery Bypass Graft Trial
PROVE IT TIMI [14]	The Pravastatin or Atorvastatin Evaluation and Infection Therapy Thrombolysis in Myocardial Infarction trial
SEARCH [15]	Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine
TNT [16]	Treating to New Targets

doi:10.1371/journal.pone.0111247.t001

Table 2. Patient and trial characteristics of the included studies.

Trial	Intervention	Patients	Drugs	DM type	Outcome used for primary endpoint	Jadad [20] #
4S, ¹⁹⁹⁷ [25]	SDS/Placebo	MI or AP	Sim 20 mg	T1/T2	CHD death, MI, revascularization, stroke, PVE	5
ASPEN, ²⁰⁰⁶ [7]	SDS/Placebo	MI or IP	Ato 10 mg	T2	CHD death, MI, stroke, revascularization, UAP	4*
CARE, ¹⁹⁹⁸ [26]	SDS/Placebo	MI	Pra 40 mg	T1/T2	CHD death, MI, revascularization	5
HPS, ²⁰⁰³ [27]	SDS/Placebo	CVD	Sim 40 mg	T1/T2	CHD death, MI, stroke, revascularization	5
LIPID, ²⁰⁰³ [28]	SDS/Placebo	MI or UAP	Pra 40 mg	T1/T2	CHD death, MI, stroke, revascularization, UAP	5
A to Z, ²⁰⁰⁴ [13]	SDS/IDS	ACS	Sim 20 mg/Sim 80 mg	T1/T2	CHD death, MI, stroke, AP	5
PROVE-IT TIMI, ²⁰⁰⁶ [14]	SDS/IDS	ACS	Pra 40 mg/Ato 80 mg	T1/T2	CHD death, MI, stroke, AP, revascularization	4*
SEARCH, ²⁰¹⁰ [15]	SDS/IDS	MI	Sim 20 mg/Sim 80 mg	T1/T2	CHD death, MI, stroke, revascularization	5
TNT, ²⁰⁰⁶ [16]	SDS/IDS	CHD	Ato 10 mg/Ato 80 mg	T1/T2	CHD death, MI, stroke, revascularization, AP, CHF	4*

score ranging 1–5; * method of randomization not described.

ACS: acute coronary syndrome; **AP:** angina pectoris; **Ato:** atorvastatin; **CHD:** coronary heart disease; **CVD:** cardiovascular disease; **CHF:** congestive heart failure; **DM:** diabetes mellitus; **IDS:** intensive-dose statin; **IP:** interventional procedures; **LDLC:** low-density lipoprotein cholesterol; **MI:** myocardial infarction; **Pra:** pravastatin; **PVE:** peripheral vascular event; **SDS:** standard-dose statin; **Sim:** simvastatin; **T1:** Type 1 diabetes; **T2:** Type 2 diabetes; **UAP:** unstable angina pectoris.

doi:10.1371/journal.pone.0111247.t002

Relative risk of intensive-dose statin versus standard-dose statin

To prevent one major cardiovascular or cerebrovascular event, 17 patients need to be treated with an intensive-dose statin for 5 years in a hypothetical high risk population with a 10-year risk for cardiovascular disease of 50%. Compared to treatment with standard-dose statins, treatment with intensive-dose statins resulted in an additional 9% relative risk reduction (RR 0.91, 95% CI 0.84–0.98) (Fig. 4, Fig. 5, Table 4). In the intensive-dose statin treatment group, 31.7% of subjects had a major cardiovascular or cerebrovascular event (764/2409), whereas 34.9% of those in the standard-dose statin treatment group experienced such an event (837/2396).

Discussion

The results of this study show that treatment with standard-dose statins for the secondary prevention of major cardiovascular or cerebrovascular events in diabetes patients is associated with a 15% significant relative risk reduction. Treating patients with an intensive-dose statin instead of a standard-dose statin will reduce the relative risk for such events with an additional 9%. Within a hypothetical high risk population with a 10-year risk for cardiovascular events of 50% this will reduce the number needed

to treat for 5 years to prevent one major cardiovascular and cerebrovascular event from 27 to 17.

Secondary endpoints in the analysis of a standard-dose statin compared to placebo also achieved a significant relative risk reduction of 33% for fatal and non-fatal stroke and non-significant relative risk reductions of 27% for fatal and non-fatal MI and 22% for all-cause mortality. The number of participants for these analyses were small, however, leading to wide confidence intervals. Due to lack of data we were not able to compare standard-dose statin treatment and intensive-dose statin treatment for secondary endpoints in a meta-analysis. The TNT [16] and PROVE-IT TIMI [14] trials, however, did report results on some of these endpoints. In the TNT trial there was a non-significant risk reduction of 33% (RR 0.67, 95% CI 0.43–1.04) for stroke. The PROVE-IT TIMI trial reported a non-significant difference in stroke event rate of 2.6% for diabetes patients on intensive-dose statin treatment vs 2.2% on standard-dose statin treatment. Also, regarding event rates for MI and all-cause mortality, only non-significant differences were observed [14,16].

Previous meta-analyses comparing standard-dose statin treatment with placebo for secondary prevention in diabetes patients reported risk reductions of 20% [5] and 21% [6] as well as a non-significant reduction of 11% [8], whereas our estimate was 15%. These differences can be explained by differences in study

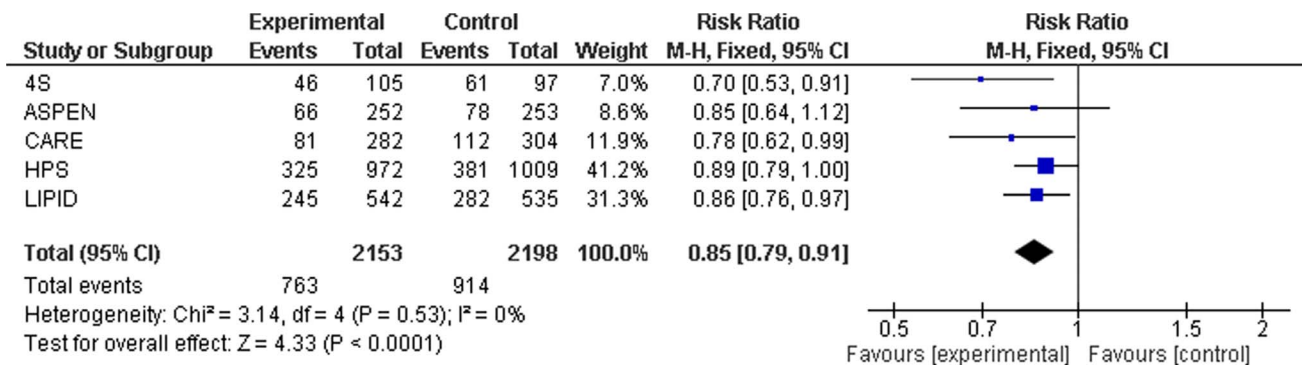


Figure 2. Results of the primary endpoint of major cardiovascular and cerebrovascular events comparing standard-dose statins with placebo.

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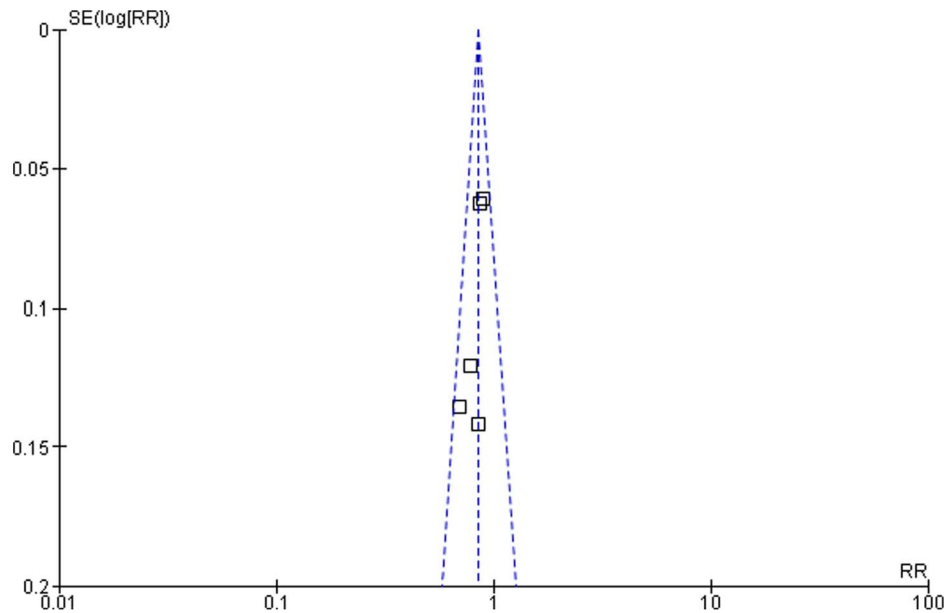


Figure 3. Funnel plot of the meta-analysis comparing placebo with standard-dose statin treatment.
doi:10.1371/journal.pone.0111247.g003

inclusion criteria. The estimates of 20% and 21% included non-blinded studies, such as the Post-CABG [29] in the analysis of Costa et al. [6] and the GISSI [30] in the analysis of Kearney et al. [5]. Furthermore, Chang et al. included studies in restrictive subpopulations, such as patients with heart failure or on hemodialysis [8]. Analyses of Chang et al. showed that including these studies resulted in higher risk reductions than when including only double-blinded studies in diabetes patients [8]. All previous analyses included the LIPS [31] which was conducted in patients after a successful percutaneous coronary intervention. We did not include non-blinded studies nor studies in restrictive subpopulations.

On the other hand, we did include the ASPEN trial that was not included by Kearney et al. [5] and Costa et al. [6]. The non-significant results from the ASPEN trial caused conflicting evidence from the randomized clinical trials regarding the efficacy of statins [7] but contributed to our risk reduction estimate of 15%.

In addition to the previous meta-analyses comparing standard-dose statins with placebo, we conducted a meta-analysis compar-

ing standard-dose with intensive-dose statins including all diabetes patients from relevant studies. Through using similar inclusion criteria for both comparisons, we were able to determine the estimate of the overall effect of statins in a general secondary prevention population with diabetes and the effect of intensive-dose over standard-dose statins.

There are some limitations to our study. There were small differences in the definition for secondary prevention in the separate studies, which could have resulted in differences in the baseline risk of the populations. Also, the diagnostic criteria for diabetes differed among the studies. Where most used the World Health Organization definition for diabetes, CARE [26] interviewed the patients and asked whether they had diabetes. Most included type 1 and type 2 diabetes patients. Furthermore, the events included in the primary endpoint were not exactly similar. The differences especially concern the inclusion of unstable angina, congestive heart failure or peripheral vascular events in addition to CHD death, MI and stroke in some studies. Including additional events in a composite endpoint may lead to larger or

Table 3. Patient characteristics of the included studies.

Trial	No. DM patients (exp/con)	Age (yr.)	Men (%)	Baseline TC (mmol/l)	Baseline LDLC (mmol/l)	Follow-up (yr.)
4S, ¹⁹⁹⁷ [25]	202 (105/97)	60	72	6.7	4.8	5.4
ASPEN, ²⁰⁰⁶ [7]	505 (252/253)	63	82	4.9	2.9	4.0
CARE, ¹⁹⁹⁸ [26]	586 (282/304)	61	80	5.3	3.6	5.0
HPS, ²⁰⁰³ [27]	1981 (972/1009)	NA	NA	NA	NA	5.0
LIPID, ²⁰⁰³ [28]	1077 (542/535)	64	81	5.6	3.7	6.0
A to Z, ²⁰⁰⁴ [13]	1059 (529/530)	NA	NA	NA	NA	2
PROVE-IT TIMI, ²⁰⁰⁶ [14]	978 (499/479)	60	72	4.6	2.6	2
SEARCH, ²⁰¹⁰ [15]	1267 (633/634)	NA	NA	NA	NA	6.7
TNT, ²⁰⁰⁶ [16]	1501 (748/753)	63	72	4.5	2.5	5

Con: controls; **DM:** diabetes mellitus; **Exp:** experimental; **LDLC:** low-density lipoprotein cholesterol; **TC:** total cholesterol.

doi:10.1371/journal.pone.0111247.t003

Table 4. Overall results of the primary and secondary endpoints in the meta-analysis comparing standard-dose statins with placebo and intensive-dose statins with standard-dose statins.

	No. of patients (statin/control)	No. of events (statin/control)	RR (95% CI)	I ²	Q	NNT (95% CI)
Standard-dose vs. placebo:						
MCCE	2153/2198	763/914	0.85 (0.79–0.91)	0%	3.14	16 (11–30)
F/NF stroke	1181/1189	65/98	0.67 (0.49–0.90)	0%	2.0	37 (21–142)
F/NF MI	534/557	56/81	0.73 (0.53–1.0)	0%	0.22	25 (13–711)
All-cause mortality	357/350	41/51	0.78 (0.53–1.14)	41%	1.70	32 (12–∞)
Intensive-dose vs. standard-dose:						
MCCE	2409/2396	764/837	0.91(0.84–0.98)	0%	0.04	31 (17–180)

F: fatal; **MCCE:** Major cardiovascular and cerebrovascular events; **MI:** myocardial infarction; **NF:** non-fatal.

doi:10.1371/journal.pone.0111247.t004

smaller risk reductions depending on the effect of statins on such events. The larger risk reductions seen for our secondary endpoints MI and stroke may suggest that we have underestimated the overall risk reduction for the major events. Furthermore, not all patients who were prescribed statins were still taking them at the end of follow-up, and some patients in the placebo group may also receive statins during follow-up, which will lead to lower risk reductions. In the analysis comparing standard-dose with intensive-dose statin treatment, patients could also have changed treatment intensity over time. For the ASPEN [7], HPS [27], TNT [16], PROVE-IT TIMI [14], A to Z [13] and SEARCH [15] trials, we used subgroup results which can cause bias. However, these trials used minimization randomization techniques we do not expect that this will have a high impact on the meta-analysis results.

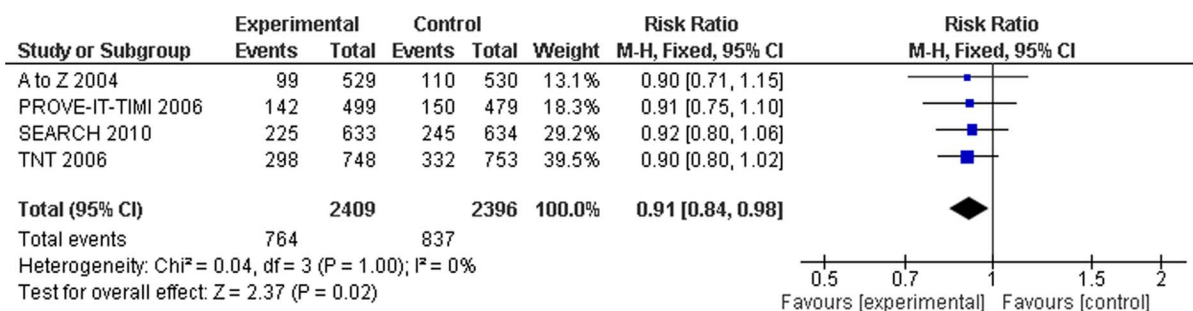
Cardiovascular risk management is an important part of diabetes treatment. The Dutch and European guidelines [32,33], for example, recommend statin treatment in almost all diabetes patients, and especially in those patients with a history of cardiovascular disease. LDL-cholesterol targets are lowered for these high risk patients, therefore reaching targets is more difficult and intensive-dose statin treatment may be needed [11,12,34]. Our analysis shows that intensive-dose statin treatment has a significant effect in reducing major cardiovascular and cerebrovascular events compared to standard-dose statin treatment for the secondary prevention in diabetes patients. We should acknowledge, however, that these reductions are not confirmed yet by analyzing individual endpoints. While the 2012 ESC guidelines just recommend statin treatment [33], the recent ACC/AHA guideline recommends intensive-dose statin treatment for all

secondary prevention patients [35]. In contrast, the current Dutch guidelines recommend to start with a standard-dose statin, such as simvastatin 40 mg. This choice is largely driven by economic considerations [32]. Now that the patent for atorvastatin has expired, however, the cost-effectiveness needs to be reassessed.

Besides the reductions in cardiovascular events, there are adverse events associated with statins, among which muscle toxicity and effects on liver enzymes are well acknowledged [36]. With higher doses there is an increased risk for statin-induced adverse events, especially regarding their effect on liver enzymes [36,37,38]. The risk of myopathy remains low at high doses, with an estimated incidence of 0.5% for simvastatin 80 mg and 1.5% for atorvastatin 80 mg [37,38]. The incidence of rhabdomyolysis was found to be too low to detect significant differences between standard and intensive dose statin treatment [36,37,38].

The efficacy of statins as shown here is based on clinical trials in which patients usually form a more selective population than patients included in observational studies. A few observational studies have been conducted in secondary prevention patients. These studies show similar results as found in the clinical trials. Significant risk reductions for repeat hospitalization for acute coronary syndrome and for mortality were reported in observational studies comparing standard-dose with intensive-dose statins [39,40].

Translation of trial evidence into guideline recommendations and of guideline recommendations into practice is subject to interpretation of the evidence. Meta-analyses can support and strengthen this process. Some guidelines now recommend intensive-dose statin treatment for all secondary prevention patients, whereas others recommend to start statin treatment on

**Figure 4.** Results of the primary end point of major cardiovascular and cerebrovascular events comparing standard-dose statins with intensive-dose statins.

doi:10.1371/journal.pone.0111247.g004

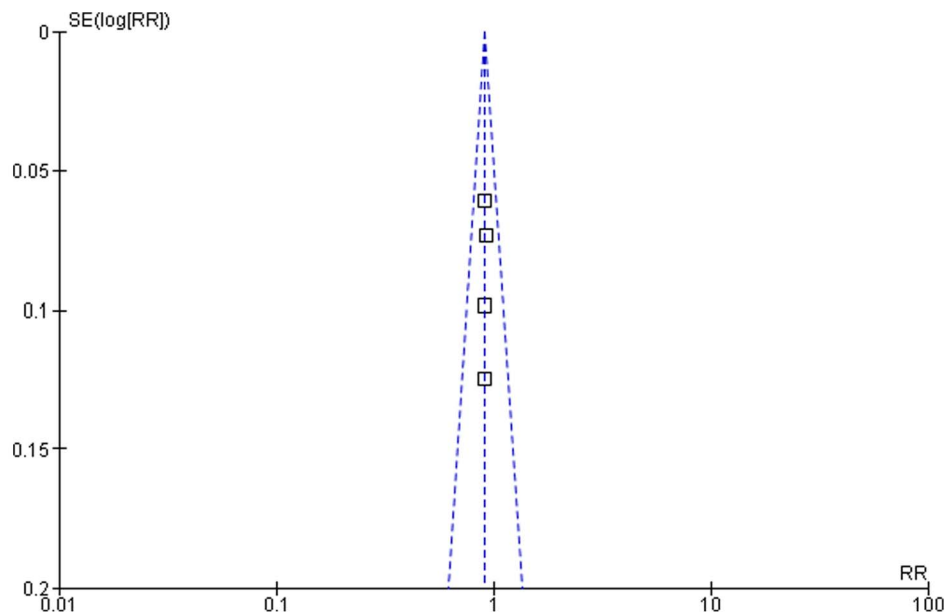


Figure 5. Funnel plot of the meta-analysis comparing standard-dose with intensive-dose statin treatment.
doi:10.1371/journal.pone.0111247.g005

a standard-dose and to switch to an intensive-dose if LDL cholesterol targets are not reached. Our meta-analyses show that standard-dose statin treatment is associated with a 15% relative risk reduction of cardiovascular and cerebrovascular events and that the use of intensive-dose statins results in a reduction of 9% compared to standard-dose statin treatment in a secondary prevention diabetes population. These estimates are useful for further cost-effectiveness analyses. If proven cost-effective, a more differentiated advice can be given, where more intensive treatment is recommended for diabetes patients at high cardiovascular risk.

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Supporting Information

Checklist S1 PRISMA 2009 checklist.
(DOC)

Author Contributions

Conceived and designed the experiments: FMV JK MJP PD EH. Performed the experiments: FMV JK. Analyzed the data: FMV JK MJP PD EH. Contributed reagents/materials/analysis tools: FMV JK MJP PD EH. Contributed to the writing of the manuscript: FMV JK MJP PD EH.

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