Statins in the Treatment of Type 2 Diabetes Mellitus: A Systematic Review.

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Citation

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Abstract

Globally, Type 2 diabetes mellitus (T2DM) continues to prove a huge challenge to patients and clinicians. Treatment of T2DM has traditionally been focused on the regulation of sugar in the blood with diet and drugs. Substantial epidemiological data has demonstrated since the 1970s that cardiovascular diseases (CVD) constitute the primary cause of morbidity and mortality in patients with diabetes. This systematic review was aimed at using clinical trials on published literature to pull out evidence - based medicine to support or discount the mortality benefits of statin therapy in T2DM patients. From the clinical trials reviewed, statin therapy in non diabetic and T2DM showed varying degrees of reduction in CHD events. Pravastatin therapy reduced the risk among all patients from 15.9 % to 12.3% (relative risk reduction (RRR) 24%). In diabetics, the RRR was 19%. Same therapy reduced the risk of stroke from 9.9% to 6.3% in diabetic group. Another study observed in their results a significant reduction in mortality (1328:12.9%) deaths among 10,269 patients in the simvastatin group versus 1507: 14.7% among 10,267 patients in the placebo group. Other studies also reported significant or near significant reduction in mortality or death rate. Artovastatin reduced acute CHD events by 36%, coronary revascularization by 31% and rate of stroke by 48%. Pravastatin on the other hand showed 25% reduction of risk of coronary events (CHD, death, non fatal myocardial Infarction (MI) and coronary artery by pass graft (CABG)). Another study showed that patients with T2DM and other risk factors of coronary artery disease or retinopathy had a 35% relative risk reduction in CVD when Atorvaststin 10mg was given daily which was similar to a 33% relative risk reduction in CVD with Simvastatin 40mg. Other clinical trials showed significant evidence that the pharmacological treatment with statins reduced mortality and morbidity associated with CVD especially those who are already at higher risk of CHD events, such as patients with T2DM while long term treatment is often necessary.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) continues to prove a huge challenge to patients and clinicians worldwide. In the U.S alone, diabetes is the 5th leading cause of death(American Diabetic Association, 2003) with economic burden costing an estimated $174 billion in medical expenses (American Diabetes Association, 2007) An estimated 20.8 million people (roughly 7% of U.S population) have diabetes, and with it's relatively high mortality, T2DM accounts for about 85-90% of all diabetes cases.1 T2DM increases the risk of cardiovascular disease (CVD) 2-4 times with outcomes especially worse after myocardial infarcation (MI) or stroke. Substantial epidemiological data has demonstrated since the 1970s that Cardiovascular diseases (CVD) constitute the primary cause of morbidity and mortality in patients with diabetes. (John Buse 2003)

Atherosclerosis accounts for about 80% of all mortality in patients who have diabetes, with estimates suggesting that about half of patients who have been recently diagnosed with T2DM have coronary heart disease (CHD) (Ginsberg,2006, Haffner et al,1998) Further studies have also suggested that high risk patients who have T2DM without a history of CHD have rates of new events similar to those of non-diabetic subjects with CHD. By implication, CVD is a major cause of morbidity and mortality in patients with T2DM, and the degree of CHD risk in patients with T2DM, without a prior history of CHD is similar to that of patients without T2DM but with existing CHD (Haffner et al, 1998).

Following results from studies suggesting this pattern of risk, the National Cholesterol Education Program classified T2DM as a cardiovascular disease equivalent, in its report (Stone et al, 2005). In order to reduce the risk of CVD and stroke in patients at significant risk, initiation of statin therapy is recommended.

The statins (3-Hydroxy-3-methyl glutaryl Coenzyme A reductase Inhibitors) or HMG CoA reductase Inhibitors, is a

group of drugs used widely in the treatment of hypercholesterolemia and other associated dyslipidemia. The statins exert their mechanism of action by the inhibition of HMG CoA reductase, a key enzyme that catalysis the conversion of HMG CoA to mevalonic acid, the rate limiting step in the in vivo production of cholesterol. The statins generally lower LDL-C while increasing HDL-C.

CLINICAL QUESTION

The review question arising from this therefore is “do we actually reduce end mortality (and morbidity) by placing T2DM patients on the statins, regardless of their cholesterol levels?” this systematic review seeks to pull the best possible evidence-based medicine, based on published literature, to support or discount the mortality benefits of statin therapy in patients with T2D

METHOD

A literature search was performed using MEDLINE ® 1966-week 3 of 2006, and Cochrane register of clinical trials published between 1966 and 2005. The initial search term used were “statin” or “HMG Co A reductase), combined with “type 2 diabetes”. The search was limited to English language, where full text available, and between 1990-2006. This produced only 14 total returns, thereby forcing a change in the search strategy, due to the narrow scope of hits. In order to produce more relevant returns, the search terms were changed slightly. The word “statin” or “HMG CoA reductase” was combined with simply “diabetes”, with the same limits. This produced a total of 424 returns from MEDLINE (R). A search of Cochrane register of clinical trials was performed using the same terms and limits. There were a total of 59 hits (limited to full text availability, between 1990-2005)

LITERATURE IDENTIFICATION

Inclusion into this systematic review was clinical trials published in English language, in which human subjects were used. There was no unpublished data. Studies with relatively large sample sizes were favored and thus included. Studies with relatively longer follow up years (>1 year) were also favored and thus included. In one study, the follow up period was 3 days, and the study drug, cerivastatin, had been withdrawn from the U.S market. This led to it’s exclusion. Studies that were done exclusively on Type 1 Diabetes Mellitus, or junevenile-onset diabetes, were also excluded. Studies that combined a statin with other non-statin antilipemic drugs , were also excluded. For the purpose of this project, only 10 clinical trials were selected.

RESULTS

Of the 10 clinical trials selected, 5 were identified as multicenter (ALLHAT, 2002, Sever ' et al 2003, Pyorala et al, 1998, Wanner et al, 2005). Only 1 study was identified as not being randomized with at no placebo control (Sever et al 2003). About 4 studies were identified as primary prevention studies (ALLHAT, 2002, Sever et al 2003, Colhoun et al, 2004 , Wanner et al, 2005) while 4 studies were identified as secondary prevention studies (Goldberg, et al,1998, Pyorala et al, 1998, Heart Protection Study Collaborative Group, 2002, Keech, et al.2003). A breakdown of drugs used in the 10 trials is shown below.

Figure 1

Table 1: Breakdown of therapy used in the major clinical trials as referenced in table 2

Treatment	N Studies
Torvastatin	4
Simvastatin	2
Pravastatin	4

Figure 2

Table 2: Examples of major clinical trials of therapy in patients with Type 2 Diabetes Mellitus

Trial	N-DM (Total)	Drug Treatment	mg/ day	Mean Follow (yrs)	% change from bln HDL LDL TG	Mjr CHD event% Trt Plcb	RRR% (PValue)	A RR (%)	NNT
CARDS[8]	2838 3 (2838 3)	Atorvastatin	10	3.9 median	-9 -31 -17	5.8 9.0	37(.001)	3.2	31
ALLHAT-LLT[9]	3738 (1035)	Pravastatin	20-40	4.8	+3 -28 -3	NR NR	11(NS)		
ASCOT-LLA[7]	2532 (1030)	Atorvastatin	10	3.3 median	0 -33 -22	3 3.6	16(.43)	0.6	167
CARE[9]	586 (4159)	Pravastatin	40	4.8	+4 -27 -13	17.7 20.4 28.7* 36.8*	13(NS) 25(0.005)	2.7 8.1	37 12
HPS[11]	5963 (2053)	Simvastatin	40	4.8	+1 -28 -11	9.4 12.6** 20.2** 25.1	27(<0.0001) 22(<0.0001)	4.9	20
4S[10]	202 (4444)	Simvastatin	20-40	5.4 median	+7 -36 -11	22.9 45.4	55(0.002)	22.5	4
Anti-inflamatory/Anti-coagulation Study[12]	50	Pravastatin	40	0.3	+1.2 -32 -10	4.9*** 6.3 27 4.0	<0.001		
Scheneider et al[13]	61	Atorvastatin	40	0.15	NS -45 NR		<0.001		
LIPIDS[15]	1077 (9014)	Pravastatin	40	6	–4 –28 –19	19.6 23.4	DM:19(0.11) IFG:36(0.009)	3.8	26
GDDS[14]	1255 (1255)	Atorvastatin	20	4 median	NR -42 NR	38**** 37****	8(0.37)		

ARR Absolute risk reduction, RRR relative risk reduction, IFG impaired fasting glucose (pre-diabetes), NR not reported
*Combined coronary death and non-fatal MI, ** combined major CHD events, coronary artery bypass graft and percutaneous transluminal coronary angioplasty, ***combined major CHD events, stroke and revascularization,
**** For overall population

DISCUSSION

EFFECT ON MORTALITY

In their study, Pyorala et al. in 1998 examined total mortality as a primary end point. Major CHD events (death) or non-fatal MI constituted the secondary end point. As their tertiary end point, they examined any CHD event, arteriosclerotic event (including death from hospital admission for such event), revascularization procedure, coronary artery bypass grafting or angioplasty. Mortality and occurrence of different forms of non fatal artherosclerotic events during follow-up were as follows: 578(27.2%) in non diabetics, 407 (19.25) in placebo group. In the simvastatin group: Diabetic patients 44(45.5%) in placebo group and 24 (22.9%) in the simvastatin group. Over the 5.4 year follow up period (median), the RR of main endpoints in simvastatin treatment –diabetic group were (total mortality) 0.57 (95% CI,0.30-1.08;P-0.087). Major CHD events 0.45(95% CI, 0.27-0.74; P<0.002) and for any artherosclerotic event 0.63 (95% CI, 0.43-0.92; P<0.018). The corresponding RR in non diabetic patients were as follows: 0.71 (95% CI, 0.58-0.87; P<0.001), 0.68(95% CI, 0.60-0.77; P<0.0001) and 0.74 (95% CI, 0.68-0.82; P<0.0001). Analysis of the 4S study suggests mortality benefit in lowering cholesterol in diabetics and also non-diabetics. Keech et al 2003 in their results observed that for the primary combined outcome of CHD death or non-fatal MI, Pravastatin therapy reduced the risk among all patients from 15.9 % to 12.3% (RRR 24%, P<0.001). In diabetics, the RRR was 19%. Also, Pravastatin reduced the risk of stroke from 9.9% to 6.3% in diabetic group. According to Collins et al in Heart Protection Study Collaborative Group, 2002, observation was made in their results of significant reduction of mortality (1328:12.9%) deaths among 10,269 patients in the simvastatin group versus 1507: 14.7% among 10,267 patients in the placebo group, P<0.003. Other studies (ALLHAT, 2002, Colhoun et al, 2004, Goldberg, et al, 1998, Sommeijer, et al, 2004) also reported significant or near significant reduction in mortality or death rate. Most studies reported mortality or death rate as a primary end point.

EFFECT ON CORONARY EVENTS-REVASCULARIZATION, STROKE, MI OR DIABETES.

Virtually all studies examined this as a secondary end point. Colhoun et al in 2004 believed that there is an association of a 2-4 fold increased risk of both CHD and stroke. In their study, acute CHD events were reduced 36% (-55 to -9), coronary revascularization by 31% (-59 to 16) and rate of stroke by 48% (-69 to -11), in the Artovastatin group. Goldberg et al,1998 reported reduction in relative risk for revascularization procedures by 32% (P< 0.04) in diabetic patients. However, when grouped together such as CHD, death, non fatal MI, CABG, Pravastatin group was associated with a 25% reduction of risk of coronary events. In CARDS, 2004, the investigators showed that patients with T2DM and other risk factor of coronary artery disease, or retinopathy, had a 35% relative risk reduction in CVD attributed to Atorvastatin 10 mg daily, which was similar to a 33% relative risk reduction in CVD with Simvastatin 40 mg. In the ALLHAT-LLT study 2002, Pravastatin did not reduce CHD significantly (or all cause mortality) compared with usual care in older participants with hypertension or moderately elevated LDL-C. Note: total T2DM population was about 35% of total participants. In the Heart Protection Study 2002, there was prepartial reduction in incidence rate of first stroke, following randomization 144, (4.3%) in Simvastatin versus 585(5.75%) in placebo; P<0.001 for revascularization. Overall, the simvastatin group produced a highly significant (24%, SE 4; 95% CI 17-30) proportional reduction in incidence rate of first revascularization procedure following randomization -939(9.1%) simvastatin versus 1205(11.7%) placebo, P<0.0001.

EFFECT ON OTHER OUTCOME-NEROPSYCHIATRIC,AND RESPIRATORY DISEASES AND CANCER.

The Heart Protection Study in 2002, specifically looked at the following outcomes:

Neropsychiatric: observational studies have suggested that lowering cholesterol might slow cognitive decline. However, no significant differences were found between treatment groups after being administered the well validated modified telephone interview for cognitive status (TICS-M) questionnaire.

On respiratory disease: Increased mortality from Chronic Obstructive Pulmonary disease (COPD) has been a concern for low cholesterol, an association sometimes linked to observational studies too. However, no significant differences were found in Forced Expiratory Volume (FEV1) 2.06L in the simvastatin group versus 2.05L in the placebo group.

On cancer; No significant difference occurred between the simvastatin group 814, 7.9% of new cancers versus 803, 7.8% in placebo.

EFFECT ON OTHER POPULATION - HEMODIALYSIS

Wanner et al in 2005, examined prospectively 1255 patients with T2DM, on maintenance hemodialysis, randomly assigned 20 mg Atorvastatin or placebo. With a primary end point of composite of death from cardiac causes, non-fatal MI or stroke, and a secondary endpoint of death from all causes-cardiac or cerebrovascular, they observed that Atorvastatin had no significant effect on individual components of primary end point, except the relative risk of fatal stroke among those receiving the drug (2.03) CI 95% (1.05-3.93), P<0.04. Atorvastatin reduced the rate of all cardiac events combined (RR 0.82, CI 95%, 10.68-0.99, P<0.03.

SAFETY CONCERNS

From results of more than 20000 patients, the statins seem to be relatively well tolerated, with slight or moderate increases in liver function enzymes (ALT and AST). Rises above three times the upper limit are considered high. Rhabdomyolysis remains rare in both diabetics and non diabetics regardless of lipid profile, receiving a statin therapy.

Biases to this review may emanate on selection of studies. Some studies selected, which contained sets of diabetic patients, may have actually contained non T2DM subjects. However, with T2DM constituting a huge majority of diabetics in general (85-90%) and with type 1 diabetes mellitus almost exclusively in juneveniles, it is assumed that subjects recruited for these studies were almost exclusively T2DM patients, since their average age was beyond 40 years. Also, some landmark studies involving statin therapy and T2DM may have been favorably recognized in the literature selection process.

There seem reasonable evidence to suggest that the statins have benefits beyond mere lowering of cholesterol, both in T2DM patients, and non diabetic patients. The evidence suggests mortality benefit in controlling diabetic dyslipidemia, or in the absence of dyslipidemia. This therefore, lends credence to an early treatment regimen in order to reduce long-term mortality. A question therefore arises “should we place all T2DM patients on statins regardless of their cholesterol level? The simple answer may not be easily comprehended, but good evidence suggest that even non-diabetics patients, with minimal CHD risk, may live longer with early statin therapy. T2DM patients being in a higher risk group of CHD events, it may be wise to initiate statin therapy as early as possible, in order to benefit from a greater long-term effect. Therapy should be encouraged in all T2DM patients above 40 years, and who can tolerate it. On going studies may hopefully explain better the benefits of statin therapy in all groups. Some studies have reported positive effects on Angiotensin 2 enzyme, as well as Thromboxane A2, suggesting a positive effect on hypertension and anticoagulation, respectively.

CONCLUSION

There is sufficient evidence based on randomized clinical trials to believe that statins do eventually “prolong” lives especially those who are already at higher risk of CHD events, such as patients with T2DM. However, as with all therapies, there is need to individualize each therapy, and to weigh the risks versus benefits before initiating treatment.

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