CHAPTER

49

How to Start Statins in Diabetes

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INTRODUCTION

Diabetes and cardiovascular diseases are major cause of illness and death world wide. Elevated blood cholesterol levels, specifically the low density lipoprotein {LDL} cholesterol is associated with a higher risk of myocardial infarction, stroke, and heart failure.

Diabetes is a significant cardiovascular risk factor (conferring a three time absolute adjusted risk of CVD death). Furthermore, in individuals with diabetes, a log linear relationship exists between cholesterol levels and CVD regardless of the baseline LDL. Thus, it is assumed, that regardless of the baseline cholesterol level, reducing the LDL will reduce the occurrence of CVD. This led to a number of primary cardiovascular prevention trials using statin therapy as the principal intervention. It has been clearly shown (and thus clearly incorporated into the ADA guidelines) that diabetic individuals with other risk factors should indeed be treated with a statin.

Diabetes mellitus (DM) is rapidly expanding pandemic (Figure 1) as per IDF (international Diabetes Federation) 2013 there are 382 million people suffering of (DM) all over the world and there will be an increase of 55% by year 2035. (Table 1) Thus the figure will be around 592 million. (Figure 2) Africa will have an increase 109 %, Europe will have a rise of 22.4 %. when we see these figures in India we will find more than 100 million DM patients by 2035 (68% increase vs 2013). 2 new countries i.e. Turkey & Pakistan will also appear in top ten list. (Table 2)

India is home to the second largest number of adults living with diabetes worldwide

At least 72% of persons with diabetes have concomitant dyslipidemia worldwide. But, In India, almost all diabetics have dyslipidemia Prevalence of Dyslipidemia (%) in Male T2 DM is 85.5 % & in Female T2DM is 97.8 % Iit's an alarming sign and is to be treated earliest possible as incidence of CAD is 3-5 times higher in DM pts.

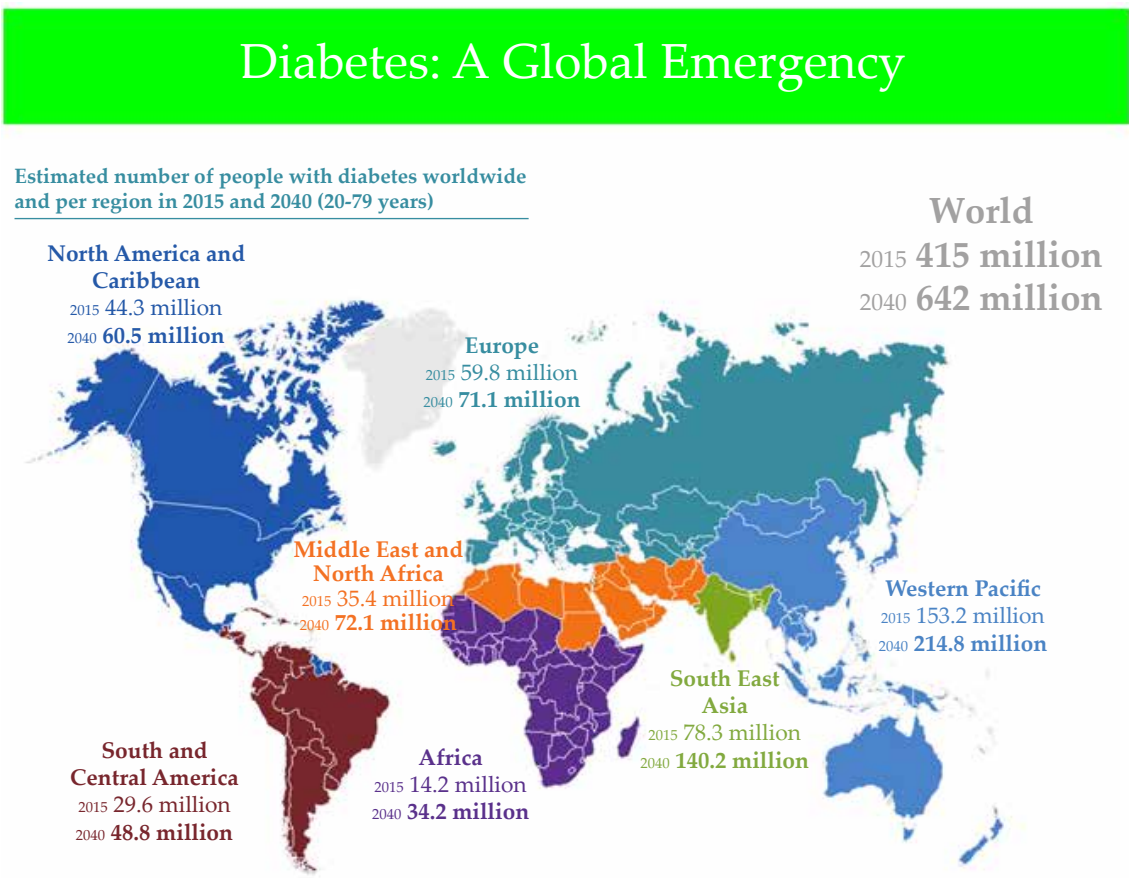

Fig. 1: Diabetes: A Global Emergency

HOW TO REDUCE RISK FACTORS?

i. Life-style management

ii. Blood sugar control

iii. Weight reduction in obese, by diet/excercise/drugs/ surgery.

iv. Management of hypertension.

v. Cessation of smoking

vi. Less alcohol consumption

vii. Lipid therapy which reduces long term damage to circulation

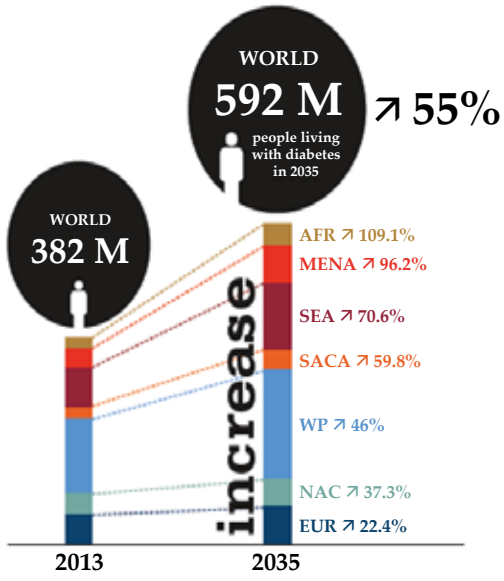

Fig. 2: Estimated Increase in Diabetes Globally

AFR: Africa, MENA: Middle East and North Africa, SACA: South and Central America, WP: Western Pacific, NAC: North America and Caribbean, SEA: South east Asia

WHAT ARE STATINS & THERE ROLE

- Statins are 3-Hydroxy-3-methyl glutaryl coA reductase inhibitors & cholesterol lowering drugs.
- They have complex relationship with diabetes (DM) & are basic focus of healthcare debate..
- Statins do reduce incidence of MI, stroke & also minimize risk of neuropathy,nephropathy&retino pathy.

We all know that 80 % of cholesterol (TC) is made by liver and 20 % is what, we get from the diet. Statins slow the action of HMG CoA reductase, which plays key role in manufacture of Cholesterol.They block a critical step in production of LDL. and also reduce inflammation and promote health of the lining of endothelium.

Table 1: Estimated Increase in Diabetes Countrywise

Country/ territory	2013 (Millions)	Country/ territory	2035 (Millions)
China	98.4	China	142.7
India	65.1	India	109.0
United States of America	24.4	United States of America	29.7
Brazil	11.9	Brazil	19.2
Russian Federation	10.9	Mexico	15.7
Mexico	8.7	Indonesia	14.1
Indonesia	8.5	Egypt	13.1
Germany	7.6	Pakistan	12.8
Egypt	7.5	Turkey	11.8
Japan	7.2	Russian Federation	11.2

Table 2: Comparison of Increase in People with Diabetes in 2015 with 2040

2015			2040		
Rank	Country/Territory	Number of People with Diabetes	Rank	Country/Territory	Number of People with Diabetes
1	China	109.6 million (99.6-133.4)	1	China	150.7 million (138.0-179.4)
2	India	69.2 million (56.2-84.8)	2	India	123.5 million (99.1-150.3)
3	United States of America	29.3 million (27.6-30.9)	3	United States of America	35.1 million (33.0-37.2)
4	Brazil	14.3 million (12.9-15.8)	4	Brazil	23.3 million (21.0-25.9)
5	Russian Federation	12.1 million (6.2-17.0)	5	Mexico	20.6 million (11.4-24.7)
6	Mexico	11.5 million (6.2-13.7)	6	Indonesia	16.2 million (14.3-17.7)
7	Indonesia	10.0 million (8.7-10.9)	7	Egypt	15.1 million (7.3-17.3)
8	Egypt	7.8 million (3.8-9.0)	8	Pakistan	14.4 million (10.6-20.4)
9	Japan	7.2 million (6.1-9.6)	9	Bangladesh	13.6 million (10.7-24.6)
10	Bangladesh	7.1 million (5.3-12.0)	10	Russian Federation	12.4 million (6.4-17.1)

International Diabetes Federation. IDF Diabetes Atlas, 7th edn. Brussels, Belgium. International Diabetes Federation. 2015 http://www.diabetesatlas.org

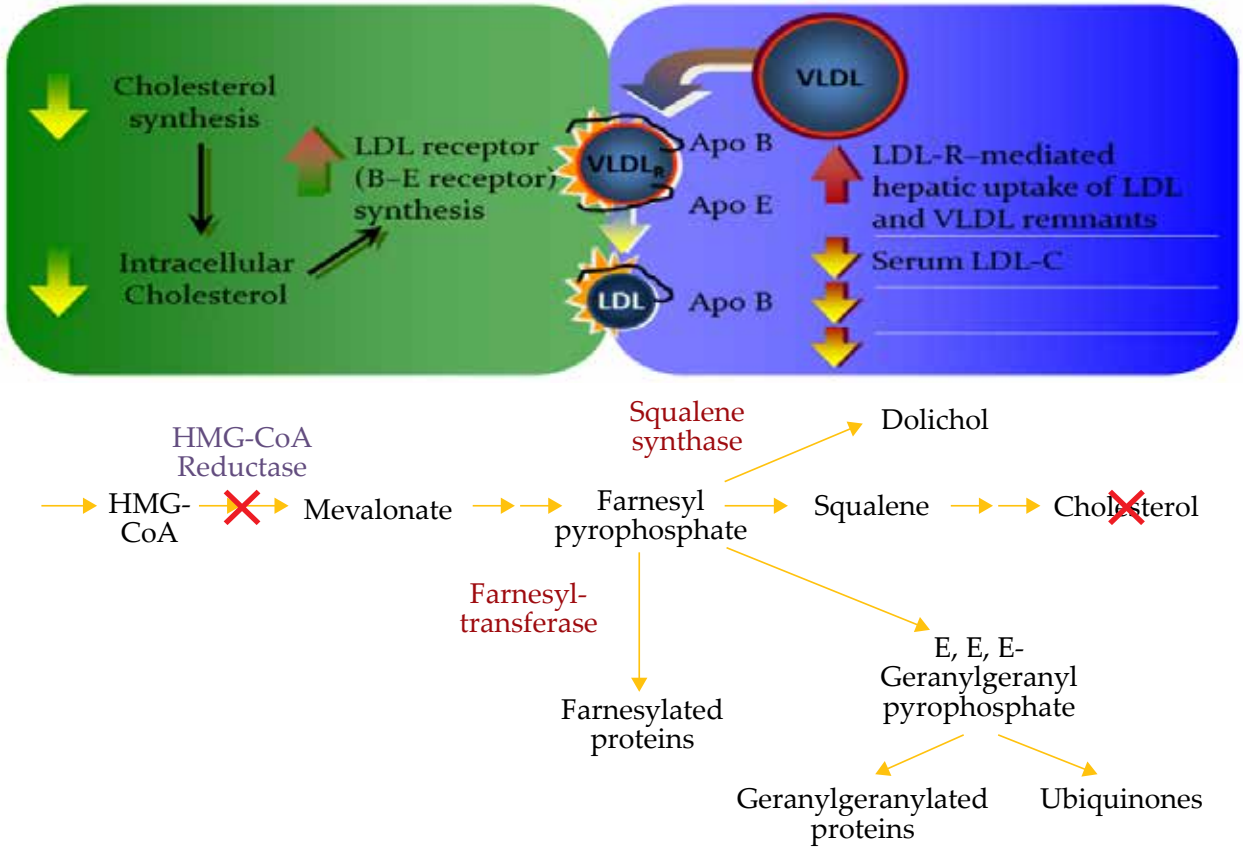

Fig. 3: Inhibition of the Cholesterol Biosynthetic Pathway

The reduction in hepatic cholesterol synthesis lowers intracellular cholesterol, which stimulates upregulation of the LDL receptor and increases uptake of non-HDL particles from the systemic circulation. (Figure 3)

Statin therapy in DM is advocated (regardless of baseline LDL-C)

a. When age is more than 40 yrs with micro/ macrovascular disease or DM of more than 15 yrs duration with age 40 years±, then it warrants lipid therapy(based on the 2012 Canadian Cardiovascular Society lipid guidelines).

b. Among women with childbearing potential, statins should only be used in the presence of proper preconception counseling & reliable contraception. Statins are to be stopped prior to conception.

Commonly used statins are atorvastatin, rosuvastatin, pitavastatin, simvastatin, pravastatin, fluvastatin.

Statins definitely lower lipids and reduces risk of CVA, CAD. Second- line agents are to be used if LDL-C target not reached with statin. We have to add bile acid sequestrants, cholesterol absorption inhibitors, fibrates or nicotinic acid/niacin. (Table 3)

Statin Therapy Should be concomitant with Lifestyle Therapy.

In the form of -

a. Smoking cessation

b. Energy-restricted diet

Table 3: Therapies to Lower LDL-C

Class	Drug(s)
3-Hydroxy-3-Methylglutaryl Coenzyme A (HMG-CoA) reductase inhibitors [Statins]	Simvastatin Atorvastatin Rosuvastatin Lovastatin Pitavastatin Fluvastatin
Bile acid sequestrants	Cholestyramine Colesevelam Colestipol
Cholesterol absorption inhibitor	Ezetimibe
Nicotinic acid	Niacin
Dietary Adjuncts	Soluble fiber Soy protein Stanol esters

i. Low cholesterol

ii. Low saturated and trans fatty acids

iii. Low refined carbohydrates

iv. Include viscous fibres, plant sterols, nuts, soy proteins

v. Alcohol in moderation, if necessary

vi. Physical activity (20-40 mts vigorous exercise, 5-7 days a week)

If triglycerides are more than 10.0 mmol/L… (180 mg %), fibrates are to be used to reduce the risk of pancreatitis

Table 4: Major secondary prevention studies on statin

Name	Study Drug Vs Comparator	Patients	Primary End Point	Duration	Results
CARE	Pravastatin 40 mg Vs Placebo	Post-MI 4159	Non-Fatal MI or CAD Death	5 yrs	24% risk reduction by pravastatin
Lipid	Pravastatin 40 mg Vs Placebo	9000 patients with Unstable angina / MI	CAD mortality	6.1 yrs	24% risk reduction by pravastatin
Prove IT TIMI 22	Atorvastatin 80 mg Vs Pravastatin 40 mg	4000 patients with ACS	Death, MI, Stroke, CABG/PCI	2 yrs	16% risk reduction by atorvastatin 80 mg
TNT	Atorvastatin 80 mg Vs 10 mg	10000 patients with Stable CAD, high LDL	MI, Stroke, Death	4.9 yrs	22% risk reduction by 80 mg Vs 10 mg atorvastatin
MIRACL	Atorvastatin 80 mg Vs Placebo	3000 patients with ACS (unstable angina/MI)	Death MI, resuscitated cardiac arrest, rehospitalisation for CAD	16 weeks	16% risk reduction by atorvastatin 80 mg
SPARCL	Atorvastatin 80 mg Vs Placebo	4700 patients with TIA/Stroke	Fatal/nonfatal stroke	5 yrs	16% risk reduction by atorvastatin 80 mg

Table 5: Drug Interactions with Statins

Statin	Contra-indicated or to be avoided with	Caution required	Dose limited
Atorvastatin	Cyclosporine, Tipranavir + Ritonavir, Telaprevir	Lopinavir + Ritonavir Digoxin, Niacin	**Upto 20 mg:/day:** Saquinavir / Darunavir / Fosamprenavir + Ritonavir, Clarithromycin, itraconazole **Upto 40 mg/day:** Boceprevir (Hepatitis C), Nelfinavir, Fenofibrate
Rosuvastatin	Gemfibrozil	Coumarin Anticoagulants, Niacin, Fenofibrate	**Upto 5 mg/day:** Cyclosporin **Upto 10 mg/day:** Gemfibrozil, Lopinavir or Atazanavir + Ritonavir

one has to optimize glycemic control and should not forget implementation of lifestyle management in form of weight reduction in obese, optimal dietary strategies and permission of alcohol in moderate quantity.

Certain dietary adjunts are also effective in reducing LDL-C they a include dietary soluble fiber, soy protein, stanol esters they reduce LDL-C 5-15 %.

Dietary soluble fiber, stanol esters are recommended in dose of 2-6 gms / day while soy protein is required 20-30gms / day in diet.

Atorvastatin dose response relationship in primary hypercholesterolemia is also very interesting. As we increase dose of atorvastatin from 10 mg to 80 mg / day, LDL-C fall is observed 30 -60 % after 6 wks. We should also have a Iook on vascular protection check list i.e. ABCDE

A. A1C – optimal glycemic control (usually ≤ 7%)

B. BP – optimal blood pressure control (<130/80)

C. Cholesterol – LDL ≤ 2.0 mmol/L if decided to treat

D. Drugs to protect the heart (regardless of baseline BP or LDL)

A - ACEi or ARB | S – Statin | A – ASA if indicated

E. Exercise / Eating healthily – regular physical activity, achieve and maintain healthy body weight.

There are two famous studies which recommend effect of statin in primary prevention in DM. They are CARDS (Collaborative Atorvastatin Diabetes Study) & HPS (Heart Protection Study). (Table 4)

CARDS was performed in 2838 no. of patients with age group of 40-75 years. They had no history of CVD. These T2DM patients were having one or more risk factors in form of retinopathy, albuminuria, hypertension, smoking. Intervention was done with atorvastatin 10 mg vs placebo. Significant results were observed in acute coronary events, coronary revascularisation (CABG), stroke and in acute cardiovascular disease event. the benefits were seen regardless of age, sex, or whether the cholesterol level was high or low. The trial's success meant, it was halted two years early.

HPS (study) was carried in 10269 pts vs 10267 pts. (placebo gp). Simvastatin40 mg/ day was given and beneficial effect among patients with DM were observed.

And both studies incidence of MI & Stroke were less as compared to control i.e. placebo group. CARDS showed reduction of events (MI 37 %, Stroke 48 %) while HPS results showed 33% reduction in MI & Stroke events.

On one hand statin therapy is quite useful in DM patients. They may increase risk of new DM. Various studies like HPS, ASCOT, CORONA, JUPITER showed risk of development of new DM by 10-13 %. Other side-effects of statin are occassional headache, abdominal pain, skin rashes, rarely memory problems which are reversible after dose adjustment / discontinuation if necessary. In few cases of DM patients on statin therapy elevated hepatic transaminases have been observed but it is dose dependent phenomenon and is usually reversible. There is some incidence of myalgias (15.4%), myositis (0.9%) & rhabdomyolysis (0.2%). Side-effects are observed with high doses of atorvastatin (80 mg / day) for more than 6 wks, If these patient are later put on low doses i.e. 5-10 mg of atorvastatin / day, there is regression in symptoms and SGOT,PT levels reach to normal.

It's not necessary that all DM patient have the same risk factors e.g. they may be normal weight individual, non smokers. While the studies show that statins are effective across the board. Their role starts even at less than 40 years age in young adults with T2DM.

RECOMMENDATIONS

Statins should be recommended as a part of treatment to reduce lipids & complications in DM pts. with addition of exercise, sensible eating, avoidance of excessive alcohol and good blood pressure control.

1. Statin therapy should be added to lifestyle therapy, regardless of baseline lipid levels, for diabetic patients with overt cardiovascular disease (CVD) level of evidence as described in the ADA evidence-grading system the primary goal is an LDL cholesterol <100 mg/dl (<2.6 mmol/l) a lower LDL cholesterol goal of 70 mg/dl (1.8 mmol/l), using a high dose of a statin, is an option and without CVD who are over the age of 40 years and have one or more other CVD risk factor. The primary goal is an LDL cholesterol <100 mg/dl (<2.6 mmol/l)
2. For lower-risk patients than those specified above (e.g., without overt CVD and under the age of 40 years), statin therapy should be considered in addition to lifestyle therapy if LDL cholesterol remains >100 mg/dl or in individuals with multiple CVD risk factors.
3. If drug-treated patients do not reach the above targets on maximal tolerated statin therapy, a reduction in LDL cholesterol of >40% from baseline is an alternative therapeutic goal.
4. Combination therapy using statins and other lipid-lowering agents may be considered to achieve lipid targets but has not been evaluated in outcome studies for either CVD outcomes or safety.
5. Statin therapy is contraindicated in pregnancy.

PRIMARY PREVENTION: IS THERE A DIABETIC INDIVIDUAL WHO SHOULD NOT GET A STATIN?

Diabetes is a significant cardiovascular risk factor (conferring a three time absolute adjusted risk of CVD death). Furthermore, in individuals with diabetes, a log linear relationship exists between cholesterol levels and CVD regardless of the baseline LDL. Thus, it was assumed, that regardless of the baseline cholesterol level, reducing the LDL will reduce the occurrence of CVD. This led to a number of primary cardiovascular prevention trials using statin therapy as the principal intervention. It has been clearly shown (and thus clearly incorporated into the ADA guidelines) that diabetic individuals with other risk factors should indeed be treated with a statin.

Yet only a few studies have included diabetic individuals without other CVD risk factors. In the Heart Protection Study (HPS), 5,963 individuals with diabetes were randomized to 40 mg simvastatin or placebo regardless of their baseline LDL or prior vascular disease status. A significant 22% reduction in the first event rate of major vascular outcomes (first major coronary event, stroke, or revascularization) was note. Based on the HPS data, an evaluation of the cost-effectiveness of lifetime simvastatin treatment found it to be cost saving even in patients as young as 35 years or with a 5-year risk of major vascular events as low as 5% (considered moderate CVD risk). These criteria include almost all of the diabetic individuals, including individuals with type 1 diabetes over the age of 30 years and individuals with type 2 diabetes over the age of 32 years for men and 38 years for women.

SECONDARY PREVENTION: HOW LOW SHOULD WE GO?

In patients with overt CVD, the guidelines state an optional goal LDL of 70 mg%. This recommendation is based on several recently published trials that examined the effect of aggressive LDL lowering therapy (i.e., high dose statin therapy) in high risk populations of patients. In the PROVE-IT TIMI 22 trial, 4,162 patients 10 days after an acute coronary syndrome (acute ST-segment elevation myocardial infarction [STEMI], non–ST-segment elevation myocardial infarction [NSTEMI], or high-risk unstable angina) were randomized to standard 40 mg pravastatin treatment or high dose/aggressive 80 mg atorvastatin treatment. Patients were followed for 18 to 36 months and achieved an average LDL cholesterol level of 62 mg% in the atorvastatin group and 95 mg% in the pravastatin group. In the aggressive therapy group versus the control group, a significant 16% reduction in the primary end point (a composite of death from any cause, myocardial infarction, unstable angina requiring re-hospitalization, revascularization and stroke) was noted. 18% of the ~1,600 patients in each treatment arm suffered from diabetes and showed similar risk reduction to that of the general cohort. A post hoc analysis of the PROVE-IT TIMI 22 trial data revealed a reduction not only in LDL cholesterol but also in CRP levels. This reduction in CRP was significantly associated with a reduction in cardiovascular events irrespective of the associated LDL reduction.

CONCLUSIONS & SUMMARY

Both in primary prevention and in the very-high-risk patients, it seems that statins reduce major cardiovascular

events irrespective (at least in part) of the baseline and post-therapy LDL levels achieved. Should statins be generally prescribed in a fixed-dose manner? We would not go so far as to suggest that, but indeed, in the diabetic individual whose LDL cholesterol is seemingly within normal limits, this should be considered. The indication for statin therapy in diabetic individuals should not rely solely on LDL levels but on the inherent cardiovascular risk that accompanies this disease (even if goal LDL levels are met).

We believe that the standards of care for individuals with diabetes should mirror the evidence. Replacing a fixed-dose statin trial scheme with a treat-to-target LDL guideline is controversial. This inherent problem of the current guidelines should be amended. Evidence based on "hard" outcome trials of statin use should guide our treatment goals and considerations, not epidemiologic or extrapolated LDL-based data.

REFERENCES

1. Stamler J, Wentworth D, Neaton JD : Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA* 1986; 256:2823-2828.
2. Cohen JC, Boerwinkle E, Mosley TH, Jr, Hobbs HH: Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med* 2006; 354:1264-1272.
3. Simons LA, Simons J, Friedlander Y, McCallum J : Cholesterol and other lipids predict coronary heart disease and ischaemic stroke in the elderly, but only in those below 70years. *Atherosclerosis* 2001; 159:201-208.
4. Ingelsson E, Schaefer EJ, Contois JH, McNamara JR, Sullivan L, Keyes MJ, Pencina MJ, Schoonmaker C, Wilson PW, D'Agostino RB, Vasan RS: Clinical utility of different lipid measures for prediction of coronary heart disease in men and women. *JAMA* 2007; 298:776-785.
5. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesaniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M : Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005; 366:1849-1861.
6. Kastelein JJ, Akdim F, Stroes ES, Zwinderman AH, Bots ML, Stalenhoef AF, Visseren FL, Sijbrands EJ, Trip MD, Stein EA, Gaudet D, Duivenvoorden R, Veltri EP, Marais AD, de Groot E: Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med* 2008; 358:1431-1443.
7. Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, Crowe T, Howard G, Cooper CJ, Brodie B, Grines CL, DeMaria AN : Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA* 2004; 291:1071-1080.
8. Ridker PM, Fonseca FA, Genest J, Gotto AM, Kastelein JJ, Khurmi NS, Koenig W, Libby P, Lorenzatti AJ, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ: Baseline characteristics of participants in the JUPITER trial, a randomized placebo-controlled primary prevention trial of statin therapy among individuals with low low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein. *Am J Cardiol* 2007; 100:1659-1664.
9. Davignon J, Leiter LA : Ongoing clinical trials of the pleiotropic effects of statins. *Vasc Health Risk Manag* 2005; 1:29-40.
10. Psaty BM, Furberg CD : Rosiglitazone and cardiovascular risk. *N Engl J Med* 2007; 356:2522-2524.
11. Skyler JS, Bergenstal R, Bonow RO, Buse J, Deedwania P, Gale EA, Howard BV, Kirkman MS, Kosiborod M, Reaven P, Sherwin RS : Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. *Diabetes Care* 2009;32:187-192.
12. Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, Pfeffer MA, Braunwald E : C-reactive protein levels and outcomes after statin therapy. *N Engl J Med* 2005; 352:20-28.
13. American Diabetes Association. Standards of medical care in diabetes: 2008. *Diabetes Care* 2008; 31:S12-S54.
14. Collins R, Armitage J, Parish S, Sleigh P, Peto R : MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003; 361:2005-2016.
15. Knopp RH, d'Emden M, Smilde JG, Pocock SJ : Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN). *Diabetes Care* 2006; 29:1478-1485.
16. Sever PS, Poulter NR, Dahlof B, Wedel H, Collins R, Beevers G, Caulfield M, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J: Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial–lipid-lowering arm (ASCOT-LLA). *Diabetes Care* 2005; 28:1151-1157.