Int J Pharma Res Health Sci. 2017; 5 (2): 1627-1631
DOI:10.21276/ijprhs.2017.02.04
MG Farnoud *et al*
CODEN (USA)-IJPRUR, e-ISSN: 2348-6465

PHS Scientific House
PHARMAHEALTHSCIENCES

International Journal of Pharma Research and Health Sciences

Available online at www.pharmahealthsciences.net

Review Article

Pharmacotherapeutic Benefits of Aspirin and Statins

Shekar HS [1], Maryam Ghanadi Farnoud [1,*], Anil Kumar KV [2], Beere Nagaraju [2], Ravindran M [3], Ravi CM [3]

[1]Department of Pharmacy Practice, Visveswarapura Institute of Pharmaceutical Sciences, KIMS Hospital and Research Centre, Bangalore 560002, India.
[2]Department of Pharmacology, Visveswarapura Institute of Pharmaceutical Sciences (under RGUHS), KIMS Hospital and Research Centre (Mentor Institute), Bangalore 560070, India.
[3]Chief Medical Superintendent, South Western Railway Divisional Hospital, Bangalore 560023, India.

ARTICLE INFO

Received: 20 Apr 2017
Accepted: 29 Apr 2017

ABSTRACT

Notwithstanding the high cardiovascular risk, facts of efficacy of preventive strategies in individuals with diabetes are limited. In particular, the recommendations in the use of aspirin in patients with diabetes mostly reflect an extrapolation from data deriving from other high risk populations. In addition, the supposed additive effects of aspirin and statins in diabetes remain to be investigated. This aspect is of particular interest in the light of the existing debate concerning the need of multiple interventions to reduce total cardiovascular risk, which has also lead to the proposal of a polypill. This review is to evaluate the efficacy of aspirin in the primary prevention of major cardiovascular events in diabetic patient's candidate for treatment of statins. These preventive strategies will be evaluated on the top of the other strategies aimed at optimizing the care of diabetic patients in terms of metabolic control and control of the other cardiovascular risk factors.

Keywords: aspirin, statins, cardiovascular.

1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) patients have high risk and recurrent cardiovascular events in addition to coronary, cerebrovascular, and peripheral arterial ischemia[1]. For more than 25 years, there has been thorough study and challenging demonstration that lowering low-density lipoprotein cholesterol with a potent statin therapy, and platelet inhibition with aspirin therapy, can reduce recurrent cardiovascular risk in these patients[2]. T2DM patients with

Corresponding author *
Dr Maryam Ghanadi Farnoud, Doctor of Pharmacy,
KIMS Hospital & Research Centre, Bangalore-560002
E-mail: maryam2016gf@gmail.com

additional cardiovascular risk factors are at high risk for incident ischemic events and statin therapy is also effective in this setting. As a result, there has been extensive clinical implementation of statin therapy in patients with T2DM. On the contrary, the additional benefit of aspirin therapy in patients without established cardiovascular disease, even those with T2DM, awaits definitive results[3].

One imperative field in which decisions and strategies for implementation of these therapies are critical is within cardiovascular outcomes trials studying new therapies in patients with T2DM[4]. A tested novel cardioprotective therapy is likely to be judged in the context of the trial patient's background treatment. In this review, it was discussed the use of aspirin and statins for the prevention of cardiovascular (CV) events in high-risk patients with T2DM. Existing guidelines separate patients into those with either established cardiovascular disease (secondary prevention) and those patients at high-risk for cardiovascular disease as a result of multiple risk factors (primary prevention) when discussing the evidence for these cardiovascular preventive therapies, and we discuss these therapies in that context.

In particular, the role of aspirin and statins for primary prevention therapy in high-risk patients with diabetes reviewed, considering recent results, potential controversy, and misconceptions of the benefits and risks of these medications in diabetic patients without a prior cardiovascular event[5]. It can be concluded that a summary of the scenery of milieu therapy in up to date cardiovascular outcomes trials of patients with T2DM, including trial recommendations for aspirin and statin treatment.

Cardiovascular Risk Reduction Important in Diabetes-Why?

T2DM patients are at 2 to 4 times increased risk of CV events compared with those without T2DM. In patients older than 65 years, the primary cause of death in 2 out of 3 diabetic patients is coronary heart disease, followed by stroke in 1 out of 6[6]. The risk of major vascular events may be lowered with lifestyle changes and medical therapy, but nevertheless the emphasis on prevention is important because a diabetic patient's first vascular event may be fatal[7]. The patients with established atherothrombosis (occlusive vascular disease) have a high risk of recurrent major vascular events (myocardial infarction [MI], stroke, or CV death)[8]. The highest risk group is those with prior ischemic events, followed by those with stable atherosclerosis, and those with T2DM and multiple risk factors without established cardiovascular disease (CVD).

Importance of CVD risk management in patients with T2DM

Type 2 diabetes mellitus (T2DM) is commonly accompanied by other cardiovascular disease (CVD) risk factors, such as hypertension, obesity, and dyslipidemia[7]. Furthermore, CVD is the most common cause of death in people with T2DM. It is therefore, the critical importance is to minimize the risk of macrovascular complications by carefully managing modifiable CVD risk factors in patients with T2DM. Therapeutic strategies should include lifestyle and pharmacological interventions targeting hyperglycemia, hypertension, dyslipidemia, obesity, cigarette smoking, physical inactivity, and prothrombotic factors. This article discusses the impact of modifying these CVD risk factors in the context of T2DM; the clinical evidence is summarized, and current guidelines are also discussed. The cardiovascular benefits of smoking cessation, increasing physical activity and reducing low-density lipoprotein cholesterol and blood pressure are well established.

For aspirin therapy, any cardiovascular benefits must be balanced against the associated bleeding risk, with current evidence supporting this strategy only in certain patients who are at increased CVD risk[7]. Although overweight, obesity, and hyperglycemia are clearly associated with increased cardiovascular risk, the effect of their modification on this risk is less well defined by available clinical trial evidence.

However, for hypoglycemic drugs, further evidence is expected from several ongoing cardiovascular outcome trials. Altogether, the evidence highlights the value of early intervention and targeting multiple risk factors with both lifestyle and pharmacological strategies to give the best chance of reducing macrovascular complications in the long term.

2. ASPIRIN THERAPY

Secondary prevention with Aspirin

The Antithrombotic Trialists' (ATT) Collaboration conducted a meta-analysis of the 195 randomized clinical trials that studied 135,640 patients with a wide range of atherothrombosis (including acute MI, prior MI, prior stroke or transient ischemic attack [TIA], peripheral artery disease, angina, coronary artery bypass surgery, or angioplasty)[9]. Aspirin therapy significantly lowered the risk of major vascular events (a composite of CV death, MI, or stroke) by 22% (events [%] in control arm, 13.2%, Vs events in antiplatelet arm, 10.7%; odds ratio [OR] 0.78 [95% CI, 0.75–0.81]; treating 1000 patients for 2 years will result in 25 [95% CI, 22–28] fewer major vascular events) regardless of prior type of athero-thrombosis, in those with and without T2DM, and among both men and women[9].

What Do the Guidelines Say?

Current guidelines recommend aspirin therapy (75-162 mg/d) for secondary prevention of recurrent CV events in diabetic patients with established coronary artery disease, cerebrovascular disease, and symptomatic peripheral arterial disease[10].

Primary prevention with Aspirin

Aspirin may also prevent a first vascular event in patients with T2DM and multiple risk factors without established atherosclerosis; however, definitive evidence of its benefit remains to be demonstrated. Among 4000 diabetic men and women without CVD studied in the ATT Collaboration, aspirin therapy lowered the risk of serious vascular events by 12%[11].

Important trials are ongoing to determine the contemporary benefits of aspirin for primary prevention of cardiovascular events in diabetic patients. Until the results of these studies are reported, it is reasonable to consider aspirin for patients with T2DM and multiple risk factors that who are not at high risk for bleeding. Although the absolute benefit may be small for aspirin in primary prevention, the effect is very meaningful on a population-wide perspective because millions of patients with T2DM have multiple risk factors without established atherosclerosis[12]. In addition, patients with diabetes who have more than 1 risk factor have an even higher baseline risk of incident CV events than the event rates reported in aspirin primary prevention studies and may derive even greater benefit from aspirin.

What Do the Guidelines Say?

Current guidelines encourage consideration of aspirin (75-162 mg/d) for the primary prevention of a first vascular event in high-risk men and women with T2DM[10]. Specifically, aspirin is appropriate in diabetic men aged ≥50 years or women aged ≥60 years with at least 1 additional CVD risk factor who are at low risk for major bleeding (i.e., no history of previous GI bleeding or peptic ulcer disease or concurrent use of other medications that increase bleeding risk, such as warfarin). These criteria fit the description of the high-risk patients with T2DM, and therefore we recommend that appropriately selected patients at low risk for bleeding be treated with low-dose aspirin for the primary prevention of CV events.

3. STATIN THERAPY

Secondary prevention with Statins

Diabetic patients commonly have dyslipidemia. Characteristic abnormalities in the lipid profile in T2DM include elevated triglycerides and apolipoprotein B, increased low-density lipoprotein (LDL) cholesterol, very low-density lipoprotein cholesterol (VLDL), and free fatty acids, as well as decreased atheroprotective high-density lipoprotein (HDL) cholesterol levels[13]. The lipid abnormalities that develop in T2DM promote atherogenesis and are strongly related to CVD risk. Therefore, dyslipidemia is an important therapeutic target.

Metabolic and lipid abnormalities improve with weight loss, exercise, smoking cessation, and dietary modification. It can be highlighted that the counseling of patients toward achieving these therapeutic lifestyle modifications[14] (see What Do the Guidelines Say?). Just as important is pharmacologic treatment with statins that have proven benefit in decreasing CVD risk in T2DM, especially in those patients with established atherosclerosis**.** Statins are safe, very well tolerated, and highly effective in reducing LDL cholesterol by increasing LDL clearance and decreasing VLDL secretion[15].

What Do the Guidelines Say?

Current guidelines recommend lifestyle modification to lower lipid levels by focusing on:

- Reducing saturated fat, trans fat, and cholesterol intake;
- Increasing omega-3 fatty acid, viscous fiber, and plant oil intake;
- Weight loss if indicated;
- Increased physical activity.

The guidelines also recommend statin therapy for secondary prevention of CVD in diabetic patients with established atherosclerosis regardless of baseline lipid levels. The primary goal of therapy is to achieve an LDL cholesterol (LDL-C) <100 mg/dL (<2.6 mmol/L) and ideally <70 mg/dL (<1.8 mmol/L) using higher-dose statins when lipid levels do not meet these targets on maximally tolerated statin therapy, the guidelines provide an alternative acceptable goal for a reduction in LDL-C of at least 30% below baseline[16]. In addition, desirable non–HDL-C levels in patients with T2DM are <130 mg/dL (<3.3 mmol/L) and ideally <100 mg/dL (<2.6 mmol/L) (or triglyceride levels <150 mg/dL (<1.7 mmol/L) and HDL cholesterol >40 mg/dL (>1 mmol/L) in men or >50mg/dL (>1.3 mmol/L) in women) and apolipoprotein-B (Apo-B) <100 mg/dL (1.0 g/L) and ideally <80 mg/dL (0.80 g/L). Nevertheless, LDL values remain the preferred lipid-lowering targets with statins.

Primary prevention with Statins

The benefits of statin therapy to prevent vascular events or vascular death in high-risk diabetic men and women without established CVD are also clear. There have been 14 major trials involving 18,686 T2DM patients (including the Heart Protection Study, Collaborative Atorvastatin Diabetes Study [CARDS], Anglo-Scandinavian Cardiac Outcomes Trial [ASCOT], and Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus [ASPEN]) that studied statins for primary prevention of CVD incorporated into the CTT meta-analysis[17]. Many trials enrolled a combination of diabetic patients with and without established atherosclerosis, but CARDS was one of the few trials that enrolled exclusively diabetic patients without established atherosclerosis.

What Do the Guidelines Say?

Present guidelines recommend lifestyle modification and then statin therapy for primary prevention of a first cardiovascular event in diabetic patients older than 40 years of age with multiple risk factors regardless of baseline lipid

levels[16]. The primary goal of therapy is to achieve an LDL cholesterol (LDL-C) <100 mg/dL (<2.6 mmol/L) and ideally <70 mg/dL (<1.8 mmol/L) using higher dose statins. When lipid levels do not meet these targets on maximally tolerated statin therapy, the guidelines again provide an alternative acceptable goal for an LDL-C reduction of at least 30%. The health benefit translates into 36 fewer (95% CI, 23–49) serious vascular events for every 1000 diabetic patients without established CVD who achieve an LDL cholesterol reduction of 40 mg/dL (1 mmol/L) with statin therapy over 5 years; additional reductions achieved in LDL cholesterol would translate into even more prevented events.

High-risk individuals, originally dogged from results of the Framingham Heart Study, are those without established CVD with an estimated 10% risk of developing an incident CV event over the ensuing 10 years due to the presence of multiple risk factors. This group includes diabetic men ≥50 years or women ≥60 years with at least 1 additional CVD risk factor (smoking, hypertension, hyperlipidemia, albuminuria, or family history of CVD). Therefore, it can be recommended that these high-risk diabetic patients receive statin therapy for primary prevention of CV events regardless of baseline lipid levels.

What the recommendations are for use of Statin and Aspirin Therapy in Contemporary Cardiovascular Outcomes Trials Studying Patients with T2DM?

A review of published contemporary major cardiovascular outcomes trials, cohort studies, and design papers in patients with T2DM revealed that the vast majority of studies stipulated that background risk factor preventive care be consistent with current guideline recommendations at the time of conduct[18]. The baseline use of aspirin and statin therapy, along with angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) use, and the concomitant use of antidiabetic medications within these studies[19]. Only 1 study reported in their main publication or methods paper that aspirin and statin therapy was expected to be prescribed to all participants unless contraindicated. Nevertheless, even under these ideal circumstances, contemporary cardiovascular outcomes trials studying secondary prevention in patients with T2DM enroll cohorts with approximately 75% statin use at baseline and approximately 60% use in mixed primary/secondary prevention cohorts, achieving only slight improvement over the course of the observation period[20]. Regarding aspirin therapy, a similar ceiling is seen; with baseline use of 50% to 70% in most trials that enroll mixed primary/secondary prevention cohorts from diverse international regions with varied access to background care.

4. CONCLUSION

Aspirin and statin therapy protect a wide range of patients with T2DM was established, or at high risk of developing atherothrombosis. These therapies, along with diet, exercise, and blood pressure control with medications such as ACE inhibitors, are currently considered the cornerstones of secondary and, in appropriately selected patients, primary cardiovascular therapy in high-risk diabetic patients. There remains considerable controversy regarding the balance of cardiovascular efficacy and potential bleeding with aspirin for primary prevention among younger or low-risk patients with T2DM. The results of ongoing large randomized clinical trials are therefore eagerly awaited to provide insight into this group of patients. In appropriately selected diabetic patients with multiple risk factors, the risk for incident or recurrent CV events is considered high enough to justify the protective therapy aspirin and statins afford.

5. REFERENCES

1. Todd Cade W. Diabetes-Related Microvascular and Macrovascular Diseases in the Physical Therapy Setting. Phys Ther. 2008; 88(11): 1322-35.
2. Enas A. Enas, Arun Kuruvila, Pravien Khanna, C.S. Pitchumoni, Viswanathan Mohan. Benefits & risks of statin therapy for primary prevention of cardiovascular disease in Asian Indians – A population with the highest risk of premature coronary artery disease & diabetes. Indian J Med Res. 2013; 138(4): 461-91.
3. Sang Yup Lim. Role of Statins in Coronary Artery Disease. Chonnam Med J. 2013; 49(1): 1-6.
4. Holman RR, Sourij H, Califf RM. Cardiovascular outcome trials of glucose-lowering drugs or strategies in type 2 diabetes. Lancet. 2014 7;383(9933):2008-17..
5. Antonio Nicolucci. Recommending Aspirin for Primary Prevention in Diabetic Patients: What May We Conclude from the Data? Ther Adv Chronic Dis. 2011; 2(3): 157-60.
6. Iciar Martin-Timon, Cristina Sevillano-Collantes, Amparo Segura-Galindo, and Francisco Javier del Canizo-Gomez. Type 2 diabetes and cardiovascular disease: Have all risk factors the same strength? World J Diabetes. 2014 Aug 15; 5(4): 444-70.
7. Daniel Lorber. Importance of cardiovascular disease risk management in patients with type 2 diabetes mellitus. Diabetes Metab Syndr Obes. 2014; 7: 169-83. Published online 2014 May 23. .
8. Harold P. Adams. Secondary Prevention of Atherothrombotic Events After Ischemic Stroke.Mayo Clin Proc. 2009 Jan; 84(1): 43-51.
9. Spinler SA, Rees C.Review of prasugrel for the secondary prevention of atherothrombosis. J Manag Care Pharm. 2009;15(5):383-95.
10. Jobert Richie N. Nansseu and Jean Jacques N. Noubiap. Aspirin for primary prevention of cardiovascular disease. Thromb J. 2015; 13: 38.
11. Antithrombotic Trialists (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular

disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009 30; 373(9678): 1849-60..
12. Jeremy B. Sussman, Robert Wood Johnson, Sandeep Vijan, HwaJung Choi, Rodney A. Hayward. Individual and Population Benefits of Daily Aspirin Therapy: A Proposal for Personalizing National Guidelines. Circ Cardiovasc Qual Outcomes. 2011; 4(3): 268-75.
13. Boudewijn Klop, Jan Willem F. Elte, Manuel Castro Cabezas. Dyslipidemia in Obesity: Mechanisms and Potential Targets. Nutrients. 2013; 5(4): 1218-40..
14. GS Mannu, MJS Zaman, A Gupta, Rehman HU, PK Myint. Evidence of Lifestyle Modification in the Management of Hypercholesterolemia. Curr Cardiol Rev. 2013; 9(1): 2-14.
15. Jaspinder Kaur. A Comprehensive Review on Metabolic Syndrome. Cardiol Res Pract. 2014; 2014: 943162..
16. Chad Raymond, Leslie Cho, Michael Rocco, Stanley L. Hazen. New guidelines for reduction of blood cholesterol: Was it worth the wait? Cleve Clin J Med. 2014; 81(1): 11-19.
17. Uchechukwu K. Sampson, Sergio Fazio, MacRae F. Linton. Residual Cardiovascular Risk Despite Optimal LDL-Cholesterol Reduction with Statins: The Evidence, Etiology, and Therapeutic Challenges. Curr Atheroscler Rep. 2012; 14(1): 1-10.
18. Lone Gale, Kavita Vedhara, Aidan Searle. Patients' perspectives on foot complications in type 2 diabetes: a qualitative study. Br J Gen Pract. 2008; 58(553): 555-63.
19. Pongwecharak J, Maila-ead C, Sakulthap J, Sripanitkulchai N. Evaluation of the uses of aspirin, statins and ACEIs/ARBs in a diabetes outpatient population in southern Thailand. J Eval Clin Pract. 2007 ;13(2):221-6.
20. Handrean Soran, Ricardo Dent, Paul Durrington. Evidence-based goals in LDL-C reduction. Clin Res Cardiol. 2017; 106(4): 237-48.

Conflict of Interest: None

Source of Funding: Nil