

World Journal of *Diabetes*

World J Diabetes 2019 May 15; 10(5): 269-323



**REVIEW**

- 269** Evolving spectrum of diabetic nephropathy
Kopel J, Pena-Hernandez C, Nugent K

MINIREVIEWS

- 280** Management of diabetic dyslipidemia: An update
Jialal I, Singh G
- 291** Novel pharmacological therapy in type 2 diabetes mellitus with established cardiovascular disease: Current evidence
Pozo L, Bello F, Suarez A, Ochoa-Martinez FE, Mendez Y, Chang CH, Surani S

ORIGINAL ARTICLE**Observational Study**

- 304** Association of hypoglycaemia in screening oral glucose tolerance test in pregnancy with low birth weight fetus
Nayak AU, Vijay AMA, Indusekhar R, Kalidindi S, Katreddy VM, Varadhan L

META-ANALYSIS

- 311** Association between sarcopenic obesity and higher risk of type 2 diabetes in adults: A systematic review and meta-analysis
Khadra D, Itani L, Tannir H, Kreidieh D, Masri DE, Ghoch ME

ABOUT COVER

Editorial Board Member of *World Journal of Diabetes*, Munmun Chattopadhyay, MSc, PhD, Assistant Professor, Research Scientist, Center of Emphasis in Diabetes and Metabolism, Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center, El Paso, TX 79905, United States

AIMS AND SCOPE

World Journal of Diabetes (*World J Diabetes*, *WJD*, online ISSN 1948-9358, DOI: 10.4239) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

The *WJD* covers topics concerning α , β , δ and PP cells of the pancreatic islet, the effect of insulin and insulinresistance, pancreatic islet transplantation, adipose cells, and obesity.

We encourage authors to submit their manuscripts to *WJD*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

The *WJD* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, Scopus, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: Yun-Xiaojuan Wu Proofing Editorial Office Director: Jin-Lei Wang

NAME OF JOURNAL

World Journal of Diabetes

ISSN

ISSN 1948-9358 (online)

LAUNCH DATE

June 15, 2010

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Timothy R Koch

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-9358/editorialboard.htm>

EDITORIAL OFFICE

Jin-Lei Wang, Director

PUBLICATION DATE

May 15, 2019

COPYRIGHT

© 2019 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Management of diabetic dyslipidemia: An update

Ishwarlal Jialal, Gurdeep Singh

ORCID number: Ishwarlal Jialal (0000-0001-9113-2604); Gurdeep Singh (0000-0001-6044-7419).

Author contributions: Jialal I and Singh G both contributed substantially to the work. Jialal I devised the format and edited to final submission. Singh G worked on the drafts and contributed significantly to the writing and referencing.

Conflict-of-interest statement: None of the authors have any conflict of interests.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Received: March 11, 2019

Peer-review started: March 12, 2019

First decision: May 8, 2019

Revised: May 13, 2019

Accepted: May 13, 2019

Article in press: May 14, 2019

Published online: May 15, 2019

P-Reviewer: Das U

S-Editor: Dou Y

L-Editor: A

Ishwarlal Jialal, California North-state University College of Medicine, VA Medical Center, Mather, CA 95757, United States

Gurdeep Singh, Lady of Lourdes Memorial Hospital, New York, NY 10041, United States

Corresponding author: Ishwarlal Jialal, MD, PhD, Professor, Assistant Dean, California North-state University College of Medicine, VA Medical Center, 9700 West Taron Drive, Elk Grove, Mather, CA 95757, United States. ishwarlal.jialal@cnsu.edu

Telephone: +1-530-7502859

Fax: +1-916-6867310

Abstract

Diabetic dyslipidemia is a cluster of lipoprotein abnormalities characterized by increased triglyceride level, decreased high-density lipoprotein-cholesterol levels and increase in small dense low-density lipoprotein (LDL) particles. It is extremely common in type 2 diabetes (T2DM) affecting around 70 % of patients. Diabetic is a significant risk factor for atherosclerotic cardiovascular disease (ASCVD) which is the most common cause of death in the United States and LDL-cholesterol is the number 1 predictor of ASCVD events in T2DM. The purpose of this review is to discuss the pathophysiology and treatment of diabetic dyslipidemia. In this review, we have discussed both non-pharmacological and pharmacological treatment modalities including major treatment trials which have impacted the cardiovascular outcomes in patients with diabetes. Statin therapy is the mainstay of treatment to reduce ASCVD by decreasing LDL-C by 30%-49% or at least 50% depending on risk level. Attractive adjunctive therapies include Ezetimibe which is more cost effective and PCSK9 inhibitors which display potent LDL-cholesterol lowering and ASCVD event reduction. For severe hypertriglyceridemia, to avert the risk of pancreatitis, both fish oil and fenofibrate in concert with diet is the best strategy.

Key words: Diabetes; Dyslipidemia; Statins; Atherosclerosis; Ezetimibe; PCSK9

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Atherosclerotic cardiovascular disease (ASCVD) is the major cause of mortality in diabetes. Low-density lipoprotein (LDL)-cholesterol lowering with statins reduce ASCVD and is the mainstay of therapy. Also, both ezetimibe and PCSK9 inhibitors are useful strategies when statins cannot be tolerated or the LDL-cholesterol goal is not achieved.

E-Editor: Wu YXJ



Citation: Jialal I, Singh G. Management of diabetic dyslipidemia: An update. *World J Diabetes* 2019; 10(5): 280-290

URL: <https://www.wjgnet.com/1948-9358/full/v10/i5/280.htm>

DOI: <https://dx.doi.org/10.4239/wjd.v10.i5.280>

INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) is the commonest cause of death in the United States and western world^[1]. It claims around 2300 lives in the United States every day^[2]. Diabetes is a significant risk factor for ASCVD and it is the leading cause of mortality. Diabetic patients are 2-4 times more likely to die from ASCVD as compared to non-diabetic patients. The rapidly increasing burden of diabetes from 108 million in 1980 to 442 million in 2014 poses a significant threat globally^[3].

Diabetes can cause microvascular complications (retinopathy, neuropathy, nephropathy) and macrovascular complications (ASCVD) manifesting as coronary artery disease, stroke and peripheral arterial disease^[4]. Dyslipidemia in diabetes is common and is characterized by hypertriglyceridemia (HTG) with decreased levels of high-density lipoprotein (HDL)-cholesterol. Whilst low-density lipoprotein (LDL)-cholesterol levels are usually not elevated there is a preponderance of small dense LDL particles which appear to be more atherogenic^[5-6]. Furthermore, there is an increase in particle number as evidenced by increased apolipoprotein B levels and non-HDL-cholesterol levels^[5-6].

The 2 major sequelae of diabetic dyslipidemia are premature ASCVD from the elevated apolipoprotein B carrying particles and pancreatitis with severe HTG > 1000 mg/dL.

PATHOPHYSIOLOGY

Dyslipidemia is very common in type 2 diabetes (T2DM) mellitus affecting around 72%-85% patients^[7].

The exact mechanism of lipoprotein abnormalities in diabetes is not very well understood. Insulin resistance, rather than hyperglycemia, has been implicated in the pathogenesis of diabetic dyslipidemia because lipoprotein changes including an increase in triglycerides (TG), increase in VLDL particles, small dense LDL particles and a decrease in HDL level have been shown in patients with impaired fasting glucose and impaired glucose tolerance and T2DM^[6-8].

Lipoprotein abnormalities in diabetes can be divided into quantitative and qualitative. Quantitative changes include an increased triglyceride level and decreased HDL-C level. Qualitative changes include an increase in small dense LDL particles and large very-LDL sub fraction (VLDL1) that predisposes to the formation of small dense LDL particles^[7].

HTG occurs due to both increased production and decreased clearance, and it is the most common abnormality of diabetic dyslipidemia.

Insulin resistance causes increased production of VLDL. VLDL can be further divided into large VLDL1 (triglyceride-rich) and small, dense VLDL2.

Insulin resistance causes an increase in VLDL1 levels which worsens HTG^[7,9].

In addition to increased secretion of VLDL, there is decreased clearance of VLDL due to decreased hepatic uptake and impaired activity of lipoprotein lipase^[7,9,10].

HTG increases the activity of cholesterol ester transfer protein which leads to transfer of triglyceride to HDL and LDL from triglyceride-rich lipoprotein^[11]. This causes an increase in the TG content of HDL and LDL.

Small dense LDL particles are more prone to post-secretory modifications such as glycation and oxidation and permeate the intima more easily where they are trapped by proteoglycans^[6,7]. Thus whilst the LDL-cholesterol level is not overly increased there is an increase in the more atherogenic small dense LDL particles. In addition there is an increase in chylomicron and VLDL remnant particles in T2DM which are also atherogenic^[7,12].

DIABETIC DYSLIPIDEMIA AND CARDIOVASCULAR DISEASE

Epidemiological studies have shown a correlation between increased TG level and cardiovascular disease (CVD), and recent studies have established a cause and effect relationship between TG rich lipoproteins and CVD *via* mutations in apolipoprotein C3^[13,14].

The role of HDL in CVD is unclear. Studies have shown an inverse relationship between HDL and CVD^[15]. However as will be discussed under therapy there is no benefit to raising HDL-cholesterol in T2DM with niacin therapy^[16].

LDL-cholesterol has been the primary predictor of CVD. Multiple studies have shown a strong relationship between LDL and CVD. In diabetes, LDL concentration may or may not be increased, but there is an increase in the concentration of small dense LDL particles which are considered more atherogenic than large LDL particles^[6,7,17]. Also, in the UKPDS study, Turner *et al*^[18] showed that LDL-cholesterol was the number 1 predictor of ASCVD risk in T2DM following adjustment for both age and sex^[18].

TREATMENT TARGETS BASED ON GUIDELINES

Treatment strategy has significantly changed over the last two decades, but LDL-cholesterol has remained the cornerstone of treatment.

In 2013 the American College of Cardiology (ACC)/American Heart Association (AHA) published guidelines for the management of cholesterol to reduce ASCVD. These guidelines recommended using high, moderate or low-intensity statins depending upon the 10-year CV risk score and presence or absence of ASCVD. These guidelines did not recommend specific cholesterol targets. The ACC/AHA recommended that any patient with diabetes mellitus type 1 or 2 aged 40-75 should be treated with moderate intensity statins with a goal reduction in LDL-C of 30%-49%. High-intensity statins were recommended if the 10- year CV risk score is $\geq 7.5\%$ or if ASCVD was present with a target LDL-C reduction of $>$ or equal to 50%^[19].

In 2017 American Association of Clinical Endocrinologists guidelines categorized diabetic patients as high, very high and extreme risk patients for CVD. It recommended that patients with high risk [≥ 2 risk factors and 10 year risk 10%-20%, or chronic kidney disease (CKD) stage 3-4 with no other risk factors], very high risk [established acute coronary syndrome (ACS) or recent hospitalization for ACS, peripheral arterial disease, carotid, coronary artery disease, 10-year risk $\geq 20\%$, CKD stage 3-4 with 1 or more risk factors, heterozygous familial hypercholesterolemia], extremely high risk (progressive ASCVD, coronary artery disease with CKD stage 3-4, diabetes or heterozygous familial hypercholesterolemia, history of premature ASCVD in female with age < 65 or males with age < 55 years) should be treated for LDL targets of < 100 , < 70 and < 55 mg/dL respectively^[20].

The American Diabetes Association 2019 guidelines recommend that all diabetic patients with ASCVD or patients with a 10-year atherosclerotic cardiovascular risk $> 20\%$ should be treated with high-intensity statins (goal of 50% reduction in LDL-cholesterol) in addition to lifestyle modification^[21]. Diabetic patients aged < 40 with additional atherosclerotic cardiovascular risk factors (LDL-C ≥ 100 mg/dL, hypertension, CKD, smoking, albuminuria and FH of premature ASCVD), diabetic patients age 40-75 years without ASCVD or 10 year ASCVD risk $< 20\%$ and diabetic patients > 75 years old should be treated with moderate intensity statins with a goal of 30%-49% LDL-C reduction^[21].

Most recently, the new ACC/AHA guidelines were published^[22]. Diabetes was defined as a high risk condition for ASCVD. In addition they provided diabetes specific Risk Enhancers which included: Diabetes duration of >10 years in T2DM and >20 years duration for T1DM, Albuminuria > 30 mg/G creatinine, an estimated GFR < 60 mL/min /1.73m², retinopathy, neuropathy and an ankle-brachial index (ABI) < 0.9 . In adults 40-75 years with diabetes regardless of 10-year risk initiate moderate intensity statin. In adults with diabetes with ASCVD or multiple ASCVD risk factors it is reasonable to prescribe high intensity statin to lower LDL-C by 50% or more. In adults > 75 years on a statin it is reasonable to continue statin therapy. In adults 40-75 years old with LDL-C between 70-189 mg/dL without ASCVD the 10-year risk should be assessed using the age and race based robust pooled cohort equation (PCE) which uses age, smoking, hypertension, serum cholesterol, HDL-C, and presence or absence of diabetes to compute the 10-year risk^[22]. If the risk is 20% or higher, then therapy should aim for an LDL-C reduction of 50% or greater. In diabetics between 20-39 years of age it is reasonable to institute moderate intensity statin therapy if the following are present: T2DM with duration $>$ or equal to 10 years, T1DM with duration $>$ or equal to 20 years, albuminuria > 30 mg/G creatinine, e-GFR < 60 mL/min, retinopathy, neuropathy, ABI < 0.9 ^[22].

Since the occurrence of a first ASCVD event in diabetic patients 40-75 years old is associated with increased morbidity and mortality compared to non-diabetic patients high intensity statin therapy is reasonable as they age (men > 50 and women > 60 years) or develop the risk modifiers including T2DM with duration > or equal to 10 years, T1DM with duration > or equal to 20 years, albuminuria > 30mg/G creatinine , e-GFR < 60 mL/min, retinopathy, neuropathy, ABI < 0.9^[22]. Also, it is prudent to consider statin therapy in diabetic patients > 75 years taking into account side effects and co-morbidities and the life span of the patient.

THERAPEUTIC STRATEGIES

Diabetic dyslipidemia treatments can be divided into non-pharmacological and pharmacological. Non-pharmacological treatment includes medical nutrition therapy, weight loss, and physical activity.

Diabetic patients should increase the intake of plant stanols/sterols, viscous fiber (legumes, citrus, oats), n-3 fatty acids and decrease the intake of saturated and trans-fatty acids. American Diabetes Association recommends the Mediterranean diet or DASH (Dietary Approaches to Stop Hypertension) diet^[21-23].

Tree nuts, peanuts, grains are a good source of unsaturated fat, and decrease cholesterol, blood pressure and risk of CVD and diabetes.

Consumption of a walnut-rich diet in a randomized study showed improvement of non-HDL cholesterol and apolipoprotein B^[24]. An epidemiological association between nut consumption and decrease death due to CVD and overall mortality has been shown but randomized clinical trial data is still lacking^[25].

Around a 5% reduction in body weight is associated with improvement in lipid profile, insulin resistance and glycemic control^[26]. Weight loss decreases triglyceride level, raises HDL-C levels and can also improve blood pressure^[27]. Even though weight loss was shown to improve multiple risk factors, such as hemoglobin A1C and blood pressure, the Look AHEAD study did not show improvement in the cardiovascular events (CVE) after long term weight loss with intensive lifestyle change^[28], indicating the need for pharmacotherapy along with lifestyle modification to reduce ASCVD^[23].

Pharmacological therapy includes statins, cholesterol absorption inhibitors, niacin, fibrates, bile acid sequestrants (BAS), PCSK9 inhibitors and omega-3 fatty acids^[22]. The drugs that effectively and safely lower LDL-cholesterol are depicted in [Table 1](#).

Statins

Statins inhibit 3-hydroxymethylglutaryl coenzyme A which is a rate-limiting step in the synthesis of cholesterol in the liver. Statins are used for primary and secondary prevention of CVD and stroke. Decreased cholesterol level in the liver leads to an upregulation of LDL receptors which leads to a decrease in plasma LDL cholesterol^[29]. In addition to the decrease in LDL cholesterol, statins lower the level of TG and increase the level of HDL-cholesterol^[30].

Statins also have pleiotropic effects and have been shown reduction of hsCRP and other markers of inflammation that help to stabilize plaque, improve endothelial function and decrease vascular inflammation and oxidative stress^[30,31]. Statins are divided into high-intensity (atorvastatin 40-80 mg, rosuvastatin 20-40 mg) which can decrease LDL-C by approximately 50% or more; moderate-intensity (Atorvastatin 10-20 mg, rosuvastatin 5-10 mg, simvastatin 20-40 mg, pravastatin 40 mg, lovastatin 40 mg, Fluvastatin 80 mg, pitavastatin 2-4 mg) which can decrease LDL-C by approximately 30%-50% ; and low-intensity (Simvastatin 10mg, Pravastatin 10-20 mg, Lovastatin 20 mg, Fluvastatin 20-40 mg, Pitavastatin 1 mg) which decrease LDL-C by < 30%^[19,22].

Trials have shown a reduction of CVE in diabetic patients with use of statins including the Heart Protection Study which reported a 22% reduction in CVE including ischemic stroke^[32] and The Collaborative Atorvastatin Diabetes Study^[33,34] which reported a 37% reduction in the primary end point of CVE also including ischemic stroke. Meta-analysis of 14 randomized clinical trials including over 18000 patients showed statin therapy reduced CVE by 21% and vascular mortality by 13% for every 39 mg/dL decrease in LDL-C during an average follow up of 4.3 years^[34,35].

Statins can cause side effects but are well tolerated in general. Myalgia is the most common side effect, affecting 5%-10% patients^[36]. Statin-induced necrotizing autoimmune myopathy and rhabdomyolysis are rare^[36]. Risk factors for myopathy include age, female sex, low BMI, high risk medications such as azole antifungals, macrolides, protease inhibitors, cyclosporine, fibrates, nicotinic acid, renal disease, Asian descent, excess alcohol intake, trauma^[19,22]. Statins can also cause new onset

Table 1 Summary of low-density lipoprotein-cholesterol lowering medications

Drug class	Mechanism of action	Clinical efficacy	Adverse reactions
Statins	Inhibition of HMG coenzyme A Reductase	Highly effective	Myalgia, myositis, rhabdomyolysis, elevation in liver enzymes, new onset diabetes
Ezetimibe	Decrease intestinal cholesterol absorption by binding to Niemann-Pick C1-like 1 protein	Moderately effective; Safe addition to statin therapy	Worsening of liver function, myopathy or rhabdomyolysis if added to statins; Nasopharyngitis, diarrhea, upper respiratory tract infection
PCSK9 inhibitors	Inhibition of Proprotein Convertase Subtilisin/Kexin Type 9	Very highly effective in combination with statin therapy	Injection site reaction including itching, swelling, erythema and pain
Bile acid sequestrants	Bind bile acids in the small intestine and prevent reabsorption	Moderately effective, safe addition to statin therapy, not desirable if triglycerides are > 300 mg/dL	Constipation, abdominal pain, bloating, drug malabsorption

HMG: Hydroxymethylglutaryl; PCSK9: Proprotein convertase subtilisin/kexin type 9.

diabetes; the exact underlying mechanism is not clear. The JUPITER (Justification for the use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) trial was the first trial to show an increased risk of diabetes. In this trial the risk of diabetes in the rosuvastatin group was increased by 0.6% compared to placebo group^[37]. The risk is higher with higher doses and in patients with Metabolic syndrome, BMI > 30 and A1c > 6%^[22]. The benefits of reducing CVE far outweigh the low risk for diabetes which can be prevented with diet and exercise.

Cholesterol absorption inhibitors (Ezetimibe)

Ezetimibe decreases cholesterol level by inhibiting intestinal absorption of cholesterol. It is used in combination with statins to achieve significant LDL-C reduction, or in patients who are not able to tolerate the required dose of statins.

In the IMPROVE-IT trial, 18144 patients with the ACS and LDL cholesterol between 50-125 mg/dL were randomized to simvastatin 40 mg with ezetimibe 10 mg or simvastatin 40 mg with placebo. During a median follow up of 6 years, patients who received simvastatin and ezetimibe had a significant reduction in LDL cholesterol compared to the simvastatin only group, 54 mg/dL *vs* 70 mg/dL respectively^[38]. There was 6.4% reduction in the primary composite endpoint (myocardial infarction, cardiovascular death, coronary revascularization in 30 d, hospitalization for unstable angina, and stroke) demonstrating the additional benefit of adding ezetimibe to a statin^[38]. More importantly in the patients with diabetes (27% of patients) there was a greater benefit on the primary end point with a 14% risk reduction. The combination of ezetimibe and simvastatin has been showed to decrease the risk of recurrent ischemic stroke when compared with simvastatin in patients with T2DM^[39] underscoring the importance of ezetimibe in diabetic patients with CVD.

Fibrates

Fibrates include bezafibrate, gemfibrozil, ciprofibrate, and fenofibrate. Fibrates activate nuclear peroxisome proliferator-activated receptor alpha which causes a reduction in triglyceride level by stimulating lipoprotein lipase activity. Fibrates can decrease fasting plasma triglyceride level by 30%-50% and can also decrease postprandial lipemia by decreasing the synthesis of fatty acids. Fibrates increase HDL level by upregulation of apoA-1 and A-II^[40]. Fibrates have also been shown to decrease small dense LDL level in some studies^[41].

In the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention trial, gemfibrozil compared to placebo resulted in a 31% reduction in TG, 4% reduction in cholesterol and a 6 % increase in HDL-cholesterol. Nonfatal myocardial infarction or death from coronary artery disease was decreased by 4.4%^[42] in these patients with ASCVD and low HDL-cholesterol. However, these patients did not have a high-risk LDL-C and did not appear to receive statin therapy.

The Fenofibrate Intervention and Even Lowering in Diabetes (FIELD) study evaluated the effect of treatment with fenofibrate in reducing macrovascular and microvascular complications in 9795 patients with T2DM. After 5-year follow-up period, treatment with fenofibrate was associated with no significant reduction in the primary end point^[43].

Also, in the ACCORD trial, a combination of simvastatin and fenofibrate in 5518 patients with T2DM, did not decrease the rate of nonfatal myocardial infarction, fatal

CVE or nonfatal stroke compared to simvastatin only group^[44].

Fibrates are metabolized in the kidney and should be avoided or used with caution in patients with CKD. The combination of gemfibrozil and statin predisposes to a greater risk for myopathy as is essentially contra-indicated.

The major indication of fibrates is to reduce TG in patients with very high TG at risk for pancreatitis. This diabetic HTG has been reviewed by the principal author^[45]. Briefly, in patients with severe HTG > 1000 mg/dL, secondary causes such as excess alcohol intake, drugs (steroids, oral estrogen, protease inhibitors *etc.*) and kidney disease should be ruled out. In these patients in addition to good glycemic control and reduction in fat and total calories in the diet, fibrates and or fish oils 4 g/d therapy needs to be initiated to lower TG levels < 500 mg/dL to avert the risk of pancreatitis.

Niacin

Niacin is a very potent drug for increasing HDL-cholesterol levels. Niacin also lower TG and LDL-cholesterol. However, the combination of statin and niacin did not show any additional cardiovascular benefit when compared with statin alone.

The AIM- HIGH trial did not show any cardiovascular benefit after adding niacin in high-risk patients who were already receiving simvastatin and ezetimibe^[46]. Heart Protection Study 2- Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) randomized 25673 patients with atherosclerotic vascular disease to receive niacin/laropiprant versus placebo. The treatment group did not show any cardiovascular benefit but there was a significant increase in new onset diabetes, bleeding and infections^[46]. No guidelines recommend niacin-statin combination therapy in patients with diabetes and patients with ASCVD since there is the potential for harm with no benefit.

Proprotein Convertase Subtilisin/Kexin Type 9 inhibitors

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK 9) inhibitors Alirocumab and Evolocumab are very potent drugs and can decrease LDL-C significantly when used as monotherapy or in combination with statins. PCSK9 inhibitors by binding PCSK9 prevents PCSK9 from binding LDL receptors and targeting them for intrahepatic lysosomal degradation. This leads to increased expression of LDL receptors causing a reduction in LDL-C level^[47]. These are given as subcutaneous injections every 2-4 wk.

PCSK9 inhibitors are indicated in patients with ASCVD who are on maximum tolerated statin therapy with or without ezetimibe but have LDL-C \geq 70 mg/dL or non-HDL-C \geq 100mg/dL. They are also indicated in patients with LDL \geq 190 mg/dL with underlying homozygous familial hypercholesterolemia or heterozygous familial hypercholesterolemia^[47].

In 2015, ODYSSEY long term trial enrolled 2341 adults who were at high risk for CVE due to history of established coronary artery disease or had presence of Heterozygous Familial Hypercholesterolemia, or coronary risk equivalent states (ischemic stroke, peripheral arterial disease, moderate CKD with GFR 30-59 or diabetes mellitus with two additional risk factors). These subjects had LDL-C level \geq 70 mg/dL despite being on maximum tolerated dose of statin and were randomized to receive alirocumab 150 mg or placebo. Alirocumab therapy decreased LDL-C from 122.8 mg/dL to 53 mg/dL at 48 mo^[48].

In ODYSSEY outcomes trial, use of alirocumab was studied in patients who have had ACS. This was a randomized, multicenter, double blind, placebo control trial of 18924 patients who had an episode of ACS within last 1-12 mo. These patients had an LDL-Cholesterol level of at least 70 mg/dL, an apolipoprotein B level of at least 80 mg/dL or a non-HDL cholesterol level of at least 100 mg/dL. These patients were already receiving maximum tolerated dose of statin or high intensity statin and were randomized to receive alirocumab 75 mg subcutaneously or placebo. After follow up 2.8 years there was a 15% reduction in the primary end point (composite of death from coronary heart disease, fatal or nonfatal ischemic stroke, nonfatal myocardial infarction or unstable angina requiring hospitalization), $P < 0.001$ ^[49]. Diabetic patients comprised 29% of the cohort and appear to have accrued a benefit but this was not detailed.

OSLER-1 and OSLER-2 evaluated the PCSK9 inhibitor Evolocumab. 4465 patients were randomly assigned in a 2:1 ratio to receive Evolocumab with standard therapy or standard therapy alone. Evolocumab decreased LDL-C from a median of 120 mg/dL to 48 mg/dL (61% reduction) as compared to standard therapy alone^[50].

PCSK9 inhibitors induce atheroma regression and decrease atheroma volume. In the Glagov randomized clinical trial, 968 patients were randomized to receive Evolocumab 420 mg subcutaneous injection monthly or placebo. Evolocumab decreased percent atheroma volume by 0.95% and total atheroma volume decreased by 5.8 mm³^[51].

In FOURIER trial 27564 patients with ASCVD and LDL level \geq 70 mg/dL while

being on maximally tolerated statin were randomized to evolocumab subcutaneous injection (140 mg every 2 wk or 420 mg every mo) or placebo. At 48 wk, the mean percent reduction in LDL-C was 59% in the treatment group compared to placebo with an achieved LDL-C of 30mg/dL. There was a 15 % relative risk reduction in the primary end -point (composite of cardiovascular death, stroke, myocardial infarction, coronary revascularization and hospitalization from unstable angina), $P < 0.001$ ^[52]. There was no increase in new onset diabetes. In a subsequent report in the 11031 diabetic patients they also showed a significant risk reduction in the above composite primary end point of 17%, $P = 0.0008$. There was no increase in new onset diabetes or any deleterious effect on glycaemia. However this was a study in diabetic patients with ASCVD so the role of PCSK9 inhibitors in primary prevention of ASCVD in diabetics remains unknown^[53].

PCSK9 inhibitors are very expensive with the annual cost of > \$14500^[54] which is more than 100 times higher than generic statin and can be a significant economic burden even in developed countries. These drugs are well tolerated, but the patient can develop an injection site reaction.

BAS

Bile acids are the end product of cholesterol catabolism. Cholestyramine, colestipol, and colesevelam are commonly used BAS. These bind to bile acid in the intestinal lumen and decrease their enterohepatic circulation which leads to increased production of bile acid in the liver causing a decrease in cholesterol level.

Use of cholestyramine in men over the long term has been shown to decrease total cholesterol and LDL cholesterol level by 13.4% and 20.3% respectively and also to decrease coronary heart disease by 19% when compared to placebo^[55]. Hence, they are a useful adjunct to statins in reducing LDL-C further. They are contra-indicated if TG levels are > 400 mg/dL since they can increase the risk of pancreatitis^[45].

Multiple studies have shown improved glycemic control with colesevelam in T2DM and hence they have the benefit of reducing both LDL-C and HbA1C levels, however there is no data to support further reduction in CVE^[56].

Omega-3 fatty acids

Omega-3 fatty acids are used as add on therapy to reduce triglyceride level. Omega-3 fatty acid formulations contain eicosapentaenoic acid (EPA) and docosahexaenoic acid.

Sub-analysis of the Japan EPA Lipid intervention trial showed that treatment with EPA of patients with impaired glucose metabolism and hypercholesterolemia resulted in a 22% reduction in coronary artery disease incidence compared to normoglycemic patients^[57]. However, in the ORIGIN trial, the use of omega-3 fatty acids (1.0 g/d) did not show cardiovascular benefit compared to placebo in patients with impaired glucose tolerance, diabetes or impaired fasting glucose^[58].

Recently, Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia (REDUCE-IT), double-blind, randomized multicenter, placebo control trial of 8179 patients with established CVD or diabetes and other risk factors was published. In this study, patients were already being treated with statins and had a fasting TG level of 135-499 mg/dL and LDL- cholesterol level between 41-100 mg/dL. They were randomized to receive either a total daily dose of 4 mg icosapent ethyl or placebo. The primary endpoint was a composite of cardiovascular death, nonfatal stroke, nonfatal myocardial infarction, coronary revascularization or unstable angina with a median follow-up of 4.9 years. There was a 25 % reduction in the primary end point with icosapent ethyl versus placebo, $P < 0.001$ ^[59]. Diabetics constituted around 58% of the patients and they appeared to accrue a similar benefit to non-diabetics. There was also a decrease in total mortality of 13% but an increase in hospitalizations for atrial fibrillation or flutter. However, before we can make any serious recommendations for diabetics, we need to see the publication in the diabetic sub-group but it could emerge as first line therapy for severe HTG and an adjunct to statins in patients with ASCVD and increased TG. Interestingly in the primary prevention cohort including diabetics there appears to be no significant benefit: Hazards Ratio of 0.88 (0.7-1.10).

CONCLUSION

Diabetic dyslipidemia is a prevalent condition and patients with diabetic dyslipidemia are at particularly high risk for ASCVD. For the majority of patients' statin therapy in concert with therapeutic life style changes remain first line. There are, however, many other lipid lowering medications available to treat individuals who do not attain LDL-C goals on statins such as ezetimibe and PCSK9 inhibitors.

EPA could also become another adjunctive therapy in diabetics with ASCVD.

REFERENCES

- 1 Heron M. Deaths: Leading Causes for 2016. *Natl Vital Stat Rep* 2018; **67**: 1-77 [PMID: [\[\[30248017\]\]](#)]
- 2 Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, Chiuve SE, Cushman M, Delling FN, Deo R, de Ferranti SD, Ferguson JF, Fornage M, Gillespie C, Isasi CR, Jiménez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Lutsey PL, Mackey JS, Matchar DB, Matsushita K, Mussolino ME, Nasir K, O'Flaherty M, Palaniappan LP, Pandey A, Pandey DK, Reeves MJ, Ritchey MD, Rodriguez CJ, Roth GA, Rosamond WD, Sampson UKA, Satou GM, Shah SH, Spartano NL, Tirschwell DL, Tsao CW, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. *Circulation* 2018; **137**: e67-e492 [PMID: [\[\[29386200\]\]](#) DOI: [10.1161/CIR.0000000000000558](#)]
- 3 World Health Organization. Global report on diabetes. 2016; Available from: <http://www.who.int/iris/handle/10665/204871>
- 4 Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000; **321**: 405-412 [PMID: [\[\[10938048\]\]](#)]
- 5 Jialal I, Bajaj M. Therapy and clinical trials: management of diabetic dyslipidemia. *Curr Opin Lipidol* 2009; **20**: 85-86 [PMID: [\[\[19106714\]\]](#) DOI: [10.1097/MOL.0b013e32832210b0](#)]
- 6 Mazzone T, Chait A, Plutzky J. Cardiovascular disease risk in type 2 diabetes mellitus: insights from mechanistic studies. *Lancet* 2008; **371**: 1800-1809 [PMID: [\[\[18502305\]\]](#) DOI: [10.1016/S0140-6736\(08\)60768-0](#)]
- 7 Vergès B. Pathophysiology of diabetic dyslipidaemia: where are we? *Diabetologia* 2015; **58**: 886-899 [PMID: [\[\[25725623\]\]](#) DOI: [10.1007/s00125-015-3525-8](#)]
- 8 Lorenzo C, Hartnett S, Hanley AJ, Rewers MJ, Wagenknecht LE, Karter AJ, Haffner SM. Impaired fasting glucose and impaired glucose tolerance have distinct lipoprotein and apolipoprotein changes: the insulin resistance atherosclerosis study. *J Clin Endocrinol Metab* 2013; **98**: 1622-1630 [PMID: [\[\[23450048\]\]](#) DOI: [10.1210/jc.2012-3185](#)]
- 9 Adiels M, Olofsson SO, Taskinen MR, Borén J. Overproduction of very low-density lipoproteins is the hallmark of the dyslipidemia in the metabolic syndrome. *Arterioscler Thromb Vasc Biol* 2008; **28**: 1225-1236 [PMID: [\[\[18565848\]\]](#) DOI: [10.1161/ATVBAHA.107.160192](#)]
- 10 Wu L, Parhofer KG. Diabetic dyslipidemia. *Metabolism* 2014; **63**: 1469-1479 [PMID: [\[\[25242435\]\]](#) DOI: [10.1016/j.metabol.2014.08.010](#)]
- 11 Guérin M, Le Goff W, Lassel TS, Van Tol A, Steiner G, Chapman MJ. Atherogenic role of elevated CE transfer from HDL to VLDL(1) and dense LDL in type 2 diabetes: impact of the degree of triglyceridemia. *Arterioscler Thromb Vasc Biol* 2001; **21**: 282-288 [PMID: [\[\[11156866\]\]](#)]
- 12 Hirany S, O'Byrne D, Devaraj S, Jialal I. Remnant-like particle-cholesterol concentrations in patients with type 2 diabetes mellitus and end-stage renal disease. *Clin Chem* 2000; **46**: 667-672 [PMID: [\[\[10794749\]\]](#)]
- 13 TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute. Crosby J, Peloso GM, Auer PL, Crosslin DR, Stitzel NO, Lange LA, Lu Y, Tang ZZ, Zhang H, Hindy G, Masca N, Stirrups K, Kanoni S, Do R, Jun G, Hu Y, Kang HM, Xue C, Goel A, Farrall M, Duga S, Merlini PA, Asselta R, Girelli D, Olivieri O, Martinelli N, Yin W, Reilly D, Speliotes E, Fox CS, Hveem K, Holmen OL, Nikpay M, Farlow DN, Assimes TL, Franceschini N, Robinson J, North KE, Martin LW, DePristo M, Gupta N, Escher SA, Jansson JH, Van Zuydam N, Palmer CN, Wareham N, Koch W, Meitinger T, Peters A, Lieb W, Erbel R, König IR, Kruppa J, Degenhardt F, Gottesman O, Bottinger EP, O'Donnell CJ, Psaty BM, Ballantyne CM, Abecasis G, Ordovas JM, Melander O, Watkins H, Orho-Melander M, Ardissino D, Loos RJ, McPherson R, Willer CJ, Erdmann J, Hall AS, Samani NJ, Deloukas P, Schunkert H, Wilson JG, Kooperberg C, Rich SS, Tracy RP, Lin DY, Altshuler D, Gabriel S, Nickerson DA, Jarvik GP, Cupples LA, Reiner AP, Boerwinkle E, Kathiresan S. Loss-of-function mutations in APOC3, triglycerides, and coronary disease. *N Engl J Med* 2014; **371**: 22-31 [PMID: [\[\[24941081\]\]](#) DOI: [10.1056/NEJMoa1307095](#)]
- 14 Do R, Willer CJ, Schmidt EM, Sengupta S, Gao C, Peloso GM, Gustafsson S, Kanoni S, Ganna A, Chen J, Buchkovich ML, Mora S, Beckmann JS, Bragg-Gresham JL, Chang HY, Demirkan A, Den Hertog HM, Donnelly LA, Ehret GB, Esko T, Feitosa MF, Ferreira T, Fischer K, Fontanillas P, Fraser RM, Freitag DF, Gurdasani D, Heikkilä K, Hyppönen E, Isaacs A, Jackson AU, Johansson A, Johnson T, Kaakinen M, Kettunen J, Kleber ME, Li X, Luan J, Lyytikäinen LP, Magnusson PK, Mangino M, Mihailov E, Montasser ME, Müller-Nurasyid M, Nolte IM, O'Connell JR, Palmer CD, Perola M, Petersen AK, Sanna S, Saxena R, Service SK, Shah S, Shungin D, Sidore C, Song C, Strawbridge RJ, Surakka I, Tanaka T, Teslovich TM, Thorleifsson G, Van den Herik EG, Voight BF, Volcik KA, Waite LL, Wong A, Wu Y, Zhang W, Absher D, Asiki G, Barroso I, Been LF, Bolton JL, Bonnycastle LL, Brambilla P, Burnett MS, Cesana G, Dimitriou M, Doney AS, Döring A, Elliott P, Epstein SE, Eyjolfsson GI, Gigante G, Goodarzi MO, Grallert H, Gravito ML, Groves CJ, Hallmans G, Hartikainen AL, Hayward C, Hernandez D, Hicks AA, Holm H, Hung YJ, Illig T, Jones MR, Kaleebu P, Kastelein JJ, Khaw KT, Kim E, Klopp N, Komulainen P, Kumari M, Langenberg C, Lehtimäki T, Lin SY, Lindström J, Loos RJ, Mach F, McArdle WL, Meisinger C, Mitchell BD, Müller G, Nagaraja R, Narisu N, Nieminen TV, Nsubuga RN, Olafsson I, Ong KK, Palotie A, Papamarkou T, Pomilla C, Pouta A, Rader DJ, Reilly MP, Ridker PM, Rivadeneira F, Rudan I, Ruokonen A, Samani N, Scharnagl H, Seeley J, Silander K, Stančáková A, Stirrups K, Uitterlinden AG, van Pelt LJ, Vedantam S, Wainwright N, Wijmenga C, Wild SH, Willemssen G, Wilsgaard T, Wilson JF, Young EH, Zhao JH, Adair LS, Arveiler D, Assimes TL, Bandinelli S, Bennett F, Bochud M, Boehm BO, Boomsma DI, Borecki IB, Bornstein SR, Bovet P, Burnier M, Campbell H, Chakravarti A, Chambers JC, Chen YD, Collins FS, Cooper RS, Danesh J, Dedoussis G, de Faire U, Feranil AB, Ferrières J, Ferrucci L, Freimer NB, Gieger C, Groop LC, Gudnason V, Gyllenstein U, Hamsten A, Harris TB, Hingorani A, Hirschhorn JN, Hofman A, Hovingh GK, Hsiung CA, Humphries SE, Hunt SC, Hveem K, Iribarren C, Järvelin MR, Jula A, Kähönen M, Kaprio J, Kesäniemi A, Kivimäki M, Koener JS, Koudstaal PJ, Krauss RM, Kuh D, Kuusisto J, Kyvik KO, Laakso M, Lakka TA, Lind L, Lindgren CM, Martin NG, März W, McCarthy MI, McKenzie CA, Meneton P, Metspalu A, Moilanen L,

- Morris AD, Munroe PB, Njolstad I, Pedersen NL, Power C, Pramstaller PP, Price JF, Psaty BM, Quertermous T, Rauramaa R, Saleheen D, Salomaa V, Sanghera DK, Saramies J, Schwarz PE, Sheu WH, Shuldiner AR, Siegbahn A, Spector TD, Stefansson K, Strachan DP, Tayo BO, Tremoli E, Tuomilehto J, Uusitupa M, van Duijn CM, Vollenweider P, Wallentin L, Wareham NJ, Whitfield JB, Wolffenbuttel BH, Altschuler D, Ordovas JM, Boerwinkle E, Palmer CN, Thorsteinsdottir U, Chasman DI, Rotter JI, Franks PW, Ripatti S, Cupples LA, Sandhu MS, Rich SS, Boehnke M, Deloukas P, Mohlke KL, Ingelsson E, Abecasis GR, Daly MJ, Neale BM, Kathiresan S. Common variants associated with plasma triglycerides and risk for coronary artery disease. *Nat Genet* 2013; **45**: 1345-4352 [PMID: [\[3773200\]](#)]
- 15 **Castelli WP**, Garrison RJ, Wilson PW, Abbott RD, Kalousdian S, Kannel WB. Incidence of coronary heart disease and lipoprotein cholesterol levels. The Framingham Study. *JAMA* 1986; **256**: 2835-2838 [PMID: [\[3773200\]](#)]
- 16 **AIM-HIGH Investigators**; Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K, McBride R, Teo K, Weintraub W. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 2011; **365**: 2255-2267 [PMID: [\[22085343\]](#) DOI: [10.1056/NEJMoa1107579](#)]
- 17 **Carmena R**, Duriez P, Fruchart JC. Atherogenic lipoprotein particles in atherosclerosis. *Circulation* 2004; **109**: III2-III7 [PMID: [\[15198959\]](#)]
- 18 **Turner RC**, Millns H, Neil HA, Stratton IM, Manley SE, Matthews DR, Holman RR. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). *BMJ* 1998; **316**: 823-828 [PMID: [\[9549452\]](#) DOI: [10.1136/bmj.316.7134.823](#)]
- 19 **Stone NJ**, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC, Watson K, Wilson PW; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; **63**: 2889-2934 [PMID: [\[24239923\]](#) DOI: [10.1016/j.jacc.2013.11.002](#)]
- 20 **Jellinger PS**, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA, Garber AJ, Grunberger G, Guerin CK, Bell DSH, Mechanick JI, Pessah-Pollack R, Wyne K, Smith D, Brinton EA, Fazio S, Davidson M. American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease. *Endocr Pract* 2017; **23**: 1-87 [PMID: [\[28437620\]](#) DOI: [10.4158/EP171764.APPGL](#)]
- 21 **American Diabetes Association**. 15. Diabetes Care in the Hospital: Standards of Medical Care in Diabetes-2019. *Diabetes Care* 2019; **42**: S173-S181 [PMID: [\[30559241\]](#) DOI: [10.2337/dc19-S016](#)]
- 22 **Grundy SM**, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC, Sperling L, Virani SS, Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol. *Circulation* 2018; CIR0000000000000625 [PMID: [\[30586774\]](#) DOI: [10.1161/CIR.0000000000000625](#)]
- 23 **Jialal I**, Vikram N. Nutrition therapy for diabetes: Implications for decreasing cardiovascular complications. *J Diabetes Complications* 2017; **31**: 1477-1480 [PMID: [\[28830659\]](#) DOI: [10.1016/j.jdiacomp.2017.07.008](#)]
- 24 **Wu L**, Piotrowski K, Rau T, Waldmann E, Broedl UC, Demmelmair H, Koletzko B, Stark RG, Nagel JM, Mantzoros CS, Parhofer KG. Walnut-enriched diet reduces fasting non-HDL-cholesterol and apolipoprotein B in healthy Caucasian subjects: a randomized controlled cross-over clinical trial. *Metabolism* 2014; **63**: 382-391 [PMID: [\[24360749\]](#) DOI: [10.1016/j.metabol.2013.11.005](#)]
- 25 **Bao Y**, Han J, Hu FB, Giovannucci EL, Stampfer MJ, Willett WC, Fuchs CS. Association of nut consumption with total and cause-specific mortality. *N Engl J Med* 2013; **369**: 2001-2011 [PMID: [\[24256379\]](#) DOI: [10.1056/NEJMoa1307352](#)]
- 26 **Klein S**, Sheard NF, Pi-Sunyer X, Daly A, Wylie-Rosett J, Kulkarni K, Clark NG; American Diabetes Association; North American Association for the Study of Obesity; American Society for Clinical Nutrition. Weight management through lifestyle modification for the prevention and management of type 2 diabetes: rationale and strategies: a statement of the American Diabetes Association, the North American Association for the Study of Obesity, and the American Society for Clinical Nutrition. *Diabetes Care* 2004; **27**: 2067-2073 [PMID: [\[15277443\]](#)]
- 27 **Wing RR**, Lang W, Wadden TA, Safford M, Knowler WC, Bertoni AG, Hill JO, Brancati FL, Peters A, Wagenknecht L; Look AHEAD Research Group. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. *Diabetes Care* 2011; **34**: 1481-1486 [PMID: [\[21593294\]](#) DOI: [10.2337/dc10-2415](#)]
- 28 **Look AHEAD Research Group**. Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, Coday M, Crow RS, Curtis JM, Egan CM, Espeland MA, Evans M, Foreyt JP, Ghazarian S, Gregg EW, Harrison B, Hazuda HP, Hill JO, Horton ES, Hubbard VS, Jakicic JM, Jeffery RW, Johnson KC, Kahn SE, Kitabchi AE, Knowler WC, Lewis CE, Maschak-Carey BJ, Montez MG, Murillo A, Nathan DM, Patricio J, Peters A, Pi-Sunyer X, Pownall H, Reboussin D, Regensteiner JG, Rickman AD, Ryan DH, Safford M, Wadden TA, Wagenknecht LE, West DS, Williamson DF, Yanovski SZ. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013; **369**: 145-154 [PMID: [\[23796131\]](#) DOI: [10.1056/NEJMoa1212914](#)]
- 29 **Stancu C**, Sima A. Statins: mechanism of action and effects. *J Cell Mol Med* 2001; **5**: 378-387 [PMID: [\[12067471\]](#)]
- 30 **Arrighoni E**, Del Re M, Fidilio L, Fogli S, Danesi R, Di Paolo A. Pharmacogenetic Foundations of Therapeutic Efficacy and Adverse Events of Statins. *Int J Mol Sci* 2017; **18** [PMID: [\[28067828\]](#) DOI: [10.3390/ijms18010104](#)]
- 31 **Devaraj S**, Rogers J, Jialal I. Statins and biomarkers of inflammation. *Curr Atheroscler Rep* 2007; **9**: 33-41 [PMID: [\[17169243\]](#)]
- 32 **Collins R**, Armitage J, Parish S, Sleight P, Peto R; Heart Protection Study Collaborative Group. 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 [PMID: [\[12814710\]](#)]
- 33 **Neil HA**, DeMicco DA, Luo D, Betteridge DJ, Colhoun HM, Durrington PN, Livingstone SJ, Fuller JH, Hitman GA; CARDS Study Investigators. Analysis of efficacy and safety in patients aged 65-75 years at randomization: Collaborative Atorvastatin Diabetes Study (CARDS). *Diabetes Care* 2006; **29**: 2378-2384

- [PMID: [\[17065671\]](#)]
- 34 **Diabetes Canada Clinical Practice Guidelines Expert Committee**; Mancini GBJ, Hegele RA, Leiter LA. Dyslipidemia. *Can J Diabetes* 2018; **42** Suppl 1: S178-S185 [PMID: [\[29650093\]](#) DOI: [10.1016/j.cjcd.2017.10.019](#)]
 - 35 **Cholesterol Treatment Trialists' (CTT) Collaborators**; Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Peto R, Armitage J, Baigent C. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet* 2008; **371**: 117-125 [PMID: [\[18191683\]](#) DOI: [10.1016/S0140-6736\(08\)60104-X](#)]
 - 36 **Thompson PD**, Panza G, Zaleski A, Taylor B. Statin-Associated Side Effects. *J Am Coll Cardiol* 2016; **67**: 2395-2410 [PMID: [\[27199064\]](#) DOI: [10.1016/j.jacc.2016.02.071](#)]
 - 37 **Ridker PM**, Danielson E, Fonseca FA, Genest J, Gotto AM, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008; **359**: 2195-2207 [PMID: [\[18997196\]](#) DOI: [10.1056/NEJMoa0807646](#)]
 - 38 **Cannon CP**, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM; IMPROVE-IT Investigators. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med* 2015; **372**: 2387-2397 [PMID: [\[26039521\]](#) DOI: [10.1056/NEJMoa1410489](#)]
 - 39 **Liu CH**, Chen TH, Lin MS, Hung MJ, Chung CM, Cherng WJ, Lee TH, Lin YS. Ezetimibe-Simvastatin Therapy Reduce Recurrent Ischemic Stroke Risks in Type 2 Diabetic Patients. *J Clin Endocrinol Metab* 2016; **101**: 2994-3001 [PMID: [\[27270238\]](#) DOI: [10.1210/jc.2016-1831](#)]
 - 40 **Staels B**, Auwerx J. Regulation of apo A-I gene expression by fibrates. *Atherosclerosis* 1998; **137** Suppl: S19-S23 [PMID: [\[9694537\]](#)]
 - 41 **Superko HR**, Berneis KK, Williams PT, Rizzo M, Wood PD. Gemfibrozil reduces small low-density lipoprotein more in normolipemic subjects classified as low-density lipoprotein pattern B compared with pattern A. *Am J Cardiol* 2005; **96**: 1266-1272 [PMID: [\[16253595\]](#) DOI: [10.1016/J.AMJCARD.2005.06.069](#)]
 - 42 **Rubins HB**, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, Faas FH, Linares E, Schaefer EJ, Schechtman G, Wilt TJ, Wittes J. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med* 1999; **341**: 410-418 [PMID: [\[10438259\]](#) DOI: [10.1056/NEJM199908053410604](#)]
 - 43 **Keech A**, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesäniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M; FIELD study investigators. 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 [PMID: [\[16310551\]](#) DOI: [10.1016/S0140-6736\(05\)67667-2](#)]
 - 44 **ACCORD Study Group**; Ginsberg HN, Elam MB, Lovato LC, Crouse JR 3rd, Leiter LA, Linz P, Friedewald WT, Buse JB, Gerstein HC, Probstfield J, Crouse RH, Ismail-Beigi F, Bigger JT, Goff DC Jr, Cushman WC, Simons-Morton DG, Byington RP. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med* 2010; **362**: 1563-1574 [PMID: [\[20228404\]](#) DOI: [10.1056/NEJMoa1001282](#)]
 - 45 **Jialal I**, Amess W, Kaur M. Management of hypertriglyceridemia in the diabetic patient. *Curr Diab Rep* 2010; **10**: 316-320 [PMID: [\[20532703\]](#) DOI: [10.1007/s11892-010-0124-4](#)]
 - 46 **HPS2-THRIVE Collaborative Group**. Landray MJ, Haynes R, Hopewell JC, Parish S, Aung T, Tomson J, Wallendszus K, Craig M, Jiang L, Collins R, Armitage J. Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med* 2014; **371**: 203-212 [PMID: [\[25014686\]](#) DOI: [10.1056/NEJMoa1300955](#)]
 - 47 **Orringer CE**, Jacobson TA, Saseen JJ, Brown AS, Gotto AM, Ross JL, Underberg JA. Update on the use of PCSK9 inhibitors in adults: Recommendations from an Expert Panel of the National Lipid Association. *J Clin Lipidol* 2017; **11**: 880-890 [PMID: [\[28532784\]](#) DOI: [10.1016/j.jacl.2017.05.001](#)]
 - 48 **Robinson JG**, Farnier M, Krempf M, Bergeron J, Luc G, Aversa M, Stroes ES, Langslet G, Raal FJ, El Shahawy M, Koren MJ, Lepor NE, Lorenzato C, Pordy R, Chaudhari U, Kastelein JJ; ODYSSEY LONG TERM Investigators. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015; **372**: 1489-1499 [PMID: [\[25773378\]](#) DOI: [10.1056/NEJMoa1501031](#)]
 - 49 **Schwartz GG**, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Lecroq G, Mahaffey KW, Moryusef A, Pordy R, Quintero K, Roe MT, Sasiela WJ, Tamby JF, Tricoci P, White HD, Zeiher AM; ODYSSEY OUTCOMES Committees and Investigators. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N Engl J Med* 2018; **379**: 2097-2107 [PMID: [\[30403574\]](#) DOI: [10.1056/NEJMoa1801174](#)]
 - 50 **Sabatine MS**, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J, Ballantyne CM, Somaratne R, Legg J, Wasserman SM, Scott R, Koren MJ, Stein EA; Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) Investigators. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015; **372**: 1500-1509 [PMID: [\[25773607\]](#) DOI: [10.1056/NEJMoa1500858](#)]
 - 51 **Nicholls SJ**, Puri R, Anderson T, Ballantyne CM, Cho L, Kastelein JJ, Koenig W, Somaratne R, Kassahun H, Yang J, Wasserman SM, Scott R, Ungi I, Podolec J, Ophuis AO, Cornel JH, Borgman M, Brennan DM, Nissen SE. Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients: The GLAGOV Randomized Clinical Trial. *JAMA* 2016; **316**: 2373-2384 [PMID: [\[27846344\]](#) DOI: [10.1001/jama.2016.16951](#)]
 - 52 **Sabatine MS**, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR; FOURIER Steering Committee and Investigators. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N Engl J Med* 2017; **376**: 1713-1722 [PMID: [\[28304224\]](#) DOI: [10.1056/NEJMoa1615664](#)]
 - 53 **Sabatine MS**, Leiter LA, Wiviott SD, Giugliano RP, Deedwania P, De Ferrari GM, Murphy SA, Kuder JF, Gouni-Berthold I, Lewis BS, Handelsman Y, Pineda AL, Honarpour N, Keech AC, Sever PS, Pedersen TR. Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial. *Lancet Diabetes Endocrinol* 2017; **5**: 941-950 [PMID: [\[28927706\]](#) DOI: [10.1016/S2213-8587\(17\)30313-3](#)]
 - 54 **Hlatky MA**, Kazi DS. PCSK9 Inhibitors: Economics and Policy. *J Am Coll Cardiol* 2017; **70**: 2677-2687

- [PMID: [\[\[29169476 DOI: 10.1016/j.jacc.2017.10.001\]\]](#)]
- 55 The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *JAMA* 1984; **251**: 351-364 [PMID: [\[\[6361299\]\]](#)]
 - 56 **Jialal I**, Abby SL, Misir S, Nagendran S. Concomitant reduction in low-density lipoprotein cholesterol and glycated hemoglobin with colessevelam hydrochloride in patients with type 2 diabetes: a pooled analysis. *Metab Syndr Relat Disord* 2009; **7**: 255-258 [PMID: [\[\[19344229 DOI: 10.1089/MET.2009.0007\]\]](#)]
 - 57 **Oikawa S**, Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K; JELIS Investigators, Japan. Suppressing effect of EPA on the incidence of coronary events in hypercholesterolemia with impaired glucose metabolism: Sub-analysis of the Japan EPA Lipid Intervention Study (JELIS). *Atherosclerosis* 2009; **206**: 535-539 [PMID: [\[\[19447387 DOI: 10.1016/j.atherosclerosis.2009.03.029\]\]](#)]
 - 58 **ORIGIN Trial Investigators**. Bosch J, Gerstein HC, Dagenais GR, Díaz R, Dyal L, Jung H, Maggiono AP, Probstfield J, Ramachandran A, Riddle MC, Rydén LE, Yusuf S. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. *N Engl J Med* 2012; **367**: 309-318 [PMID: [\[\[22686415 DOI: 10.1056/NEJMoa1203859\]\]](#)]
 - 59 **Bhatt DL**, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, Doyle RT, Juliano RA, Jiao L, Granowitz C, Tardif JC, Ballantyne CM; REDUCE-IT Investigators. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. *N Engl J Med* 2019; **380**: 11-22 [PMID: [\[\[30415628 DOI: 10.1056/NEJMoa1812792\]\]](#)]



Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: <https://www.f6publishing.com/helpdesk>
<https://www.wjgnet.com>

