

# Primary prevention of Cardiovascular Diseases among the Middle aged and the Elderly

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Received: December 2020; Accepted: January 2021; Published: February 1, 2021.

Citation: Naglaa Mohammed Ahmed Abdelrahim Omer, Wafaa Yousuf, Noof Mansouri. Primary prevention of Cardiovascular Diseases among the Middle aged and the Elderly. World Family Medicine. 2021; 19(1): 146-166 DOI: 10.5742/MEWFM.2021.93997

## Abstract

**Aim:** To define the best practice guidelines for primary prevention of cardiovascular diseases in middle age individuals as well as the elderly.

**Study design and Methodology:** Narrative review study for RCT, clinical trials and systematic review studies published in English language from 2003-2018; in middle age individuals as well as the elderly. Search was conducted in Pubmed and Google Chrome. Terms used for searching were (best practice guidelines) and (primary prevention of cardio-vascular disease).

**Results:** The total number of study search items was 2020 studies and after filtering them, the matching studies were 70: 38 studies were excluded whereas 32 studies were included. Six studies were about statins therapy in primary prevention of CVD in the elderly. Five studies were about statin benefits for primary prevention of cardiovascular disease in middle age individuals. Nine studies were about non-statin therapy. Five studies were about blood pressure control and primary prevention of cardiovascular disease. Seven studies were about aspirin for primary prevention of cardiovascular disease in diabetics.

**Conclusion:** Statins are beneficial for primary prevention of cardiovascular disease in middle age individuals as well as the elderly who had dyslipidemia or were diabetic aged 40-75 years, or 10-years CVD risk =>7.5% according to AHA/ACC, or =>10% in accordance with the guidelines for both NICE and USPSTF. There is no definite evidence for non-statin therapy benefit for primary prevention of CVD but it can be used in hypercholesterolemia patients or high CVD risk patients who do not tolerate statins or have not responded to the maximum dose of statins. There was no evidence for aspirin benefit in primary prevention of CVD in diabetics. Immediate blood pressure control is important in the primary prevention of CVD in hypertensive patients with high cardiovascular risk.

**Key words:** Cardiovascular diseases, middle aged, elderly, primary prevention

## Introduction

Cardiovascular disease (CVD), of which coronary heart disease (CHD) and stroke are the prevailing components, is by far the leading cause of death in most developed countries and is rapidly becoming the leading cause of death in the world (Lim et al., 2010). Indeed, the World Health Organization estimates that annual global mortality due to CVD will approach 25 million by 2030, of which about 80 % will occur in developing countries (World Heart Organization. Atlas of heart disease and stroke 2015). Not only is CVD a leading cause of mortality, but it is the leading cause of loss of disability-adjusted life years globally (Perk et al. 2012). Emelia et al (2017) stated that CVD and stroke accounted for 14% of total health expenditure in 2012 to 2013, more than any major diagnostic group. The annual direct and indirect cost of CVD and stroke in the United States was an estimated \$316.1 billion in 2012 to 2013. According to the same authors, taking into account nursing home care costs, the total direct medical costs of CVD between 2012 to 2030 are projected to increase from \$396 billion to \$918 billion. All these facts guide us to the importance of early detection of risk factors for CVD, so that we can identify and avoid these diseases. In addition, there is need to establish clear protocols and guidelines for primary prevention of CVD, of course, many countries do have them.

The INTERHEART study elucidated the effect of CVD risk factors including dyslipidemia, smoking, hypertension, diabetes, and abdominal obesity, whilst it demonstrated the protective effects of consumption of fruits and vegetables and regular physical activity. These risk factors were consistent throughout all populations and socioeconomic levels studied, helping to establish the viability of uniform approaches to CVD primary prevention worldwide (Yusuf et al., 2004).

Significant morbidity and mortality of CVD, in addition to its financial burden on health, led us to concentrate on the fundamental components of CVD primary prevention in the current study. The question remains what are the best practice guidelines for the primary prevention of CVD?

### Study Aim

The main aim of this study to define the best practice guidelines for primary prevention of cardiovascular disease. In addition the other study objectives are:

- 1-To improve the practice for primary prevention of cardiovascular disease through following evidence based best practice guidelines recommendations.
- 2-To control cardiovascular disease risk factors mainly hypertension, hypercholesterolemia and diabetes.
- 3-To check the role of aspirin in primary prevention of cardiovascular disease in diabetic patients.

### Study Hypothesis:

There is meaningful relationship between hypertension, hyperlipidemia, diabetes and cardiovascular disease so that the main hypothesis of the study is that the

management of these diseases plays a vital role in primary prevention of cardiovascular disease.

Other hypotheses include:

Aspirin has no benefit in primary prevention of cardiovascular disease in diabetic patients.

Best practice guidelines recommendations had an important role in primary prevention of cardiovascular disease.

## Methodology

The global burden of cardiovascular disease mortality, as it is classified as number one cause of mortality and the main reason for morbidity worldwide, requires the improvement of preventative strategies of cardiovascular disease and increased community and care provider awareness about best evidence strategies. Furthermore the World Health Organization (WHO) rating shows that above 75% of premature cardiovascular disease is preventable and improvement of risk factors is able to lower the increasing CVD load on both care providers and individuals (WHO 2016). While age is a recognized risk factor for CVD increase; autopsy evidence proposes that the process of CVD expansion in the last year is avoidable (Kannel et al 2020), so risk lowering is pivotal. Based on that the current study searched best practice guidelines for primary prevention of cardiovascular disease?

To answer this question properly, the study tried to review the most updated literature. The study used the RCT, systematic reviews and meta-analysis studies which have been published from 2003 to 2018 by using the Cochrane library, Pubmed, or Google Chrome.

The data did not use any studies with low evidence or old papers that were published more than 15 years. The study compared results of these studies with the current best practice guidelines mainly National Institute for Health and Care Excellence (NICE, 2016), American Heart Association (AHA) and American College of Cardiologists (ACC) (Eckel et al., 2013). The data reviewed a high number of studies around different aspects of CVD primary prevention and risk factors. The study formed a clear idea on the risk factors of CVD, the data then used the new-found knowledge to find a common reason why the cardiovascular system is susceptible to disease. Secondly, it reviewed the most relevant protocols used to modify CVD risk factors to avoid CVD. Then the study tried to find common links between the most common types of CVD and formulate the best recommendations that are used to avoid all types of CVD.

## Results

The total numbers of study search items were 2020 studies and after filtering them, the match studies were 70: 38 studies were excluded whereas 32 studies were included.

Six studies about statins therapy in primary prevention of CVD in the elderly.

Five studies about statin benefits for primary prevention of cardiovascular disease in middle age individuals.  
 Nine studies about non-statin therapy.  
 Five studies about blood pressure control and primary prevention of cardiovascular disease.  
 Seven studies about aspirin for primary prevention of cardiovascular disease in diabetic patients.

## Discussion

The main concept in primary prevention of cardiovascular disease is to control risk factors.

**Example:** hyperlipidemia /hypertension /diabetes/ smoking/sedentary life-style etc.

### Hyperlipidemia and primary prevention of cardiovascular disease:

#### Hyperlipidemia management in middle age individuals:

##### Statin therapy:

The Cholesterol Treatment Trialists' Collaboration provided evidence that statins are beneficial for primary prevention of ASCVD events. Meta-analyses of 27 studies (n = 174,149), using most of statin trials data as a source for participants, illustrated a reduction in main ASCVD events (e.g. stroke and non-fatal myocardial infarction).

Associated with the use of statins in patients with low risk (five-year risk of less than 10%). The authors found that for each reduction of 39 mg per dL (1.01 mmol per L) in LDL-C, there were 11 fewer major vascular events per 1,000 persons treated for five years. (Mihaylova et al., 2012). Secondary analysis aiming at identifying mortality reasons did not find any effectiveness for statin treatment in low-risk groups (i.e., 10-year risk less than 10%). (Abramson et al., 2014).

According to RCT (Yusuf et al., 2016), statins use in intermediate-risk persons without cardiovascular disease, reduced cardiovascular risk events with clinically and statistically significance.

Statin use in persons without evidence of cardiovascular disease leads to clinically significant reduction in CVD events and all-cause mortality, based on systematic review study (Taylor et al., 2013).

Diabetic patients are at high risk of ASCVD events during their life, so high rank of evidence level A recommended moderate-intensity statin therapy for diabetic patients at age 40-75 years old (Stone et al 2013). For those outside this range of age, statins therapy should be individualized depending on the benefits of statins, side effects, interaction, and patient priority.

**Table 1: Statins therapy for lowering lipid level in middle age individuals:**

Type of study	Sample size	Outcome	Type of patients.	Author/Year
Meta-analysis	174,149	reduction of major vascular event RR(0.79,95%CI 0.77-0.81)	low risk individuals	Mihaylova et al., 2012.
RCT	12,705	reduction of CVD related mortality HR (0.76, 95% CI 0.64-0.91) P0.002  Reduction of cardiovascular risk events HR (0.75, 95% CI 0.64-0.88) P0.001	Intermediate risk individuals	Yusuf et al., 2016.
Systematic review	56,934	Reduction of CVD related mortality OR (0.86, 95% 0.79-0.94), reduced combined fatal and non-fatal CVD RR0.75(95%0.70-.81)	People without evidence of cardiovascular disease Some with specific cases (hyperlipidemia, DM, Albuminuria, HTN)	Taylor, et al., 2013.
Meta-analysis Systematic review/RCT		Reduced CVD risk events And all cause mortality	Diabetics aged 40-75 years/at high CVD risk	Stone, 2013
RCT		Reduced CVD risk events And all related cause mortality	Adults aged 40-75 years With 10-years CVD risk of 7.5% or more.	Jones, 2016

Stone et al., (2013), demonstrated that high intensity statin therapy may be recommended (evidence level B) for primary prevention of cardiovascular events in patients with or without diabetes and a 10-year ASVD risk of at least 7.5% according to the ACC and AHA guidelines, or at least 10% in accordance with the guidelines for both NICE and USPSTF.

Almost every panel list for the 2004 ACC/AHA guidelines, joined with the National Heart, Lung, and Blood Institute, (Grundy et al., 2004) had industry ties. The ACC/AHA committee worked hard to eliminate industry impact for the 2013 guideline, but seven of the 15 committee members still had ties to industry (Ioannidis 2014).

Furthermore, there are worries that the 2013 guidelines (ACC/AHA), underestimate adverse effects of the statins. Main side effects of statins are myopathy (incidence of 0.5 per 1,000 more than in the general population over five years) and rhabdomyolysis (incidence of 0.1 per 1,000 more than in the general population over five years), (Taylor et al., 2013). In addition to the side effect of diabetes, 0.1, other studies mentioned higher percentages of diabetes as a side effect of statins.

The limitations of AHA/ACC guidelines are: bias due to industry ties, underestimation of risks associated with statins use, furthermore limitation is that some of the recommendations depend on expert opinions and some of these recommendations had a low level of evidence in addition to conflicts between guidelines members.

#### *CVD Risk calculation:*

ACC/AHA guidelines mentioned new Pooled Cohort Equations risk calculator that is available at <http://www.cvriskcalculator.com>. (Pursnani et al., 2015). The NICE panel, however, advised using QRISK2 calculator, which is available at <http://www.qrisk.org/> (Hippisley-Cox et al 2008). Physicians must use the Pooled Cohort Equations risk calculator, or QRISK2 calculator, or both to assess a patient's risk.

#### *Non –Statins lipid-lowering drugs:*

There is no potent evidence that routine use of non-statin lipid-lowering medications (i.e., fibrates omega-3 fatty acids, niacin and ezetimibe [Zetia]) are beneficial in the primary prevention of ASCVD (Sando and Knigh 2015). The addition of niacin demonstrated significant harm in a recent randomized controlled trial, and its use is no longer recommended (Landray et al., 2014).

Based on the SHARP study, a randomized double-blind control trial, enrolled 9270 patients with chronic kidney disease some 3023 on dialysis, with the rest no dialysis, without evidence of CVD. The patients were randomly assigned to simvastatin 20mg plus Ezetimibe 10mg versus placebo, and follow up for 5 years. The study found that simvastatin plus Ezetimibe group had clinically and statistically significant reduction in the incidence of atherosclerotic events versus placebo group.

According to IMPROVE-IT study, randomized double-blind control trial, including 18,144 acute coronary syndrome patients who had been hospitalized; randomly allocated them to either simvastatin 40mg and Ezetimibe 10mg or to simvastatin 40mg and placebo. They were followed for 6years. The results were a clinically significant reduction in LDL cholesterol with improving cardiovascular events outcome in Ezetimibe group compared to the placebo group.

Ezetimibe reduced atherosclerotic events in chronic kidney disease patients and lowering LDL and improved cardiovascular outcome in acute coronary syndrome as approved from above mentioned double-blind randomized control trials but no evidence about its role for primary prevention of cardiovascular disease.

Based on the systematic review study, involving 13,140 participants in the intervention group and 138,976 individuals in control group, comparing lipid-lowering intervention with placebo or diet/to assess Cardiac mortality, followed them for 6-months. The study found resins causes clinically significant reduction in cardiovascular mortality.

**Table 2:1 -Ezetimibe studies SHARP/IMPROVE-IT:**

Study type	Sample size	Outcome	Type of patients	Author/year
RCT (double-blind), (SHARPSTUDY)	9270	Reduced atherosclerotic events RR 0.83 95% CI 0.74-0.94 P0.0021	Patients with chronic kidney disease/no CVD	Baigent, 2011
RCT (double-blind) (IMPROVE-IT study)	18,144	Lowering LDL Improved cardiovascular events HR0.93,95%CI0.89-099/po. 016	Hospitalized patients for an acute coronary syndrome	Christopher, 2015

Table 3:2-Bile acid sequestrates:

Type of study	Sample size	Outcome	Type of patients	Author/year
Systematic review	137140 intervention group 138976 Control group	Reduced cardiac mortality for: Resins (RR0.70 , 95% CI 0.50-0.99)	>90% no CVD event <10% with CHD	Studer et al., 2005

Table 4:3-PCSK9 inhibitors:

Study type	Sample size	Outcome	Type of patients	Author/year
Systematic review/meta-analysis/RCT	10159	Significant lowering: of LDL Mean difference-47, 49% (95% CI-69.64 to-25.35%) Myocardial infarction rate OR0.94(95%CI0.26-039) p0.030 Serum creatinine kinase level increasing was reduced OR0.72 (95% CI 0.54 to 0.96)	Adult with hypercholesterolemia	Navarese 2015
Multicentre double-blind randomized control placebo trial (RUTHERFORD-2TRIAL)	329	Evolocumab 420mg once monthly reduced LDL-60 (95% CI-68to-52)	51 years (average) patients with heterozygous familial hypercholesterolemia	Oaks 2015 Raal et al., 2015
Multi-centre double-blind randomized control placebo trial (TESALA-B trial)	49	Mean reduction in LDL 31% (95% CI-44% to 18%) p<0.001	Homozygous hypercholesterolemia patients (aged 13-57 years)	Oaks 2015 Raal 2015

According to a systematic review and meta-analysis study Navarese et al., (2015), for randomized trials comparing proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9 inhibitors) versus non PCSK9 inhibitors, in total 10,159 participants of hypercholesterolemic adults. The study found PCSK9 inhibitors significantly reduced LDL. MI rate and no increase on side effects. Study limitation is that the data was extracted from previous RCT study, not directly from patients, and with their short duration of follow up 2 months to 2 years. They are expensive, need an injection to apply, and more research is needed about safety, effectiveness, and cost-effectiveness before recommended for CVD primary prevention.

Based on multi-centre randomized control placebo trial (RUTHERFORD-2TRIAL) Evolocumab 420mg once monthly for patients aged 51 years with heterozygous familial hypercholesterolemia reduced LDL significantly compared to the placebo group after 12 weeks follow up period.

TESALA-B trial, double-blind randomized trial, randomly assigned homozygous familial hypercholesterolemia patients aged 13 to 57 years, to Evolocumab 420mg monthly versus placebo. Evolocumab significantly reduced LDL in the intervention group after 12 weeks compared to the placebo group.

Based on Studer et al., (2005) systematic review study for randomized control trial, comparing the effect of a fibrate in the intervention group versus placebo group using random allocation/follow up at 6 months/reported mortality rate/fibrate associated with increased non-cardiovascular mortality.

According to Jun et al., 2010 systematic review for trials including 45,058 participants, found that fibrates reduced risk of cardiovascular disease events, as well as coronary events, reduced progression of albuminuria, but increased serum creatinine without significant increase in serious drug-related side effects.

Table 5:4-Fibrates:

Study type	Sample size	Outcome	Type of patient	Author/year
Systematic review/RCT	137140 intervention group 138976 control group	The risk ratio for overall mortality 1.0 (95% CI 0.91-1.11) The risk ratio for non-cardiovascular mortality 1.13 (95% CI 1.01 to 1.27)	Adult with hyperlipidemia >90% no CHD <10% with CHD event	Studer et al., 2005
Systematic review/meta-analysis	45058 participants Including 2870 major Cardiovascular events 4552 coronary events. 3880 deaths	Risk reduction: for major cardiovascular events 10% (95% CI 0-18) p0.048 For coronary events 13% (95% CI 7-12) p<0.0001 Risk reduction of albuminuria progression 14% (2-25, p0.028 A non-significant increase in serious drug-related side effects. RRL 2 (0.9-1.6) P0.19/Increase serum creatinine 1.9 (1.46-2.7) p<0.0001	Hyperlipidemia patients	Jun et al., 2010

**Table 6:5-Omega-3fatty acids:**

Study type	Sample size	Outcome	Type of patients	Author/year
Randomized open-label blinded endpoint analysis	18645	Relative reduction of 19% in major coronary events p0.011 LDL decreased by 25% Unstable angina/non fatal coronary events significantly reduced	Japanese hypercholesterolemia Patients.	Yokoyama et al., 2007

According to Yokoyama et al., 2007 randomized trial, involving 18,645 Japanese hypercholesterolemia patients, randomly allocated to statin plus omega-3fatty acid 1800mg or statin only. At follow up of 4.6 years' study found a 19% relative reduction in major coronary events. A significant reduction in unstable angina and non-fatal coronary events.

ACC in 2016 issued an Expert Consensus Decision Pathway (ECDP) on the action of non-statin medications in the treatment of ASCVD risk (Lloyd-Jones et al., 2016). The ECDP's target is to provide practical advice for physicians and patients in situations which are not covered by the ACC/AHA 2013 guidelines. The consensus recommends the non-statin medications for individuals at risk who did not achieve expected statin Response (50% or greater LDL-C reduction with a high-intensity statin or 30% to 49% LDL-C reduction with a moderate-intensity statin), or who cannot tolerate recommended statin dose. ECDP recommends ezetimibe as first-line medication or bile acid sequestrants as second-line therapy (e.g., if a patient cannot tolerate ezetimibe and the triglyceride level is less than 300 mg per dL) for primary prevention in patients with or without diabetes, a 10-year ASCVD risk of 10% or greater, and a baseline LDL-C level of 70 to 189 mg per dl (Lloyd-Jones et al., 2016). These recommendations also apply to patients with baseline LDL level of 190mg/dl or greater, without ASCVD.

#### **Management of hyperlipidemia in the elderly (past the age of 65 years): is not ideal due to many reasons:**

- 1- less potent statistical relationship between blood cholesterol level and cardiovascular disease, in comparison to middle-aged patients (Simons et al., 2003).
- 2- there are worries about the side effects of statins including myalgia and other side effects (Golomb 2005).
- 3- Calculators of cardiovascular disease risk are not accurate in the elderly, in whom clinicians may overestimate or underestimate the risk of cardiovascular disease (Yourman et al., 2012).

The risk of cardiovascular disease increases with age as demonstrated by previous epidemiological studies. Age is a crucial risk factor for cardiovascular disease, and the outcome of cardiovascular disease in the elderly is worse.

#### **CVD risk estimation in the elderly:**

Lately, the International Atherosclerosis Society (IAS), recommend using long term risk prediction; from age 50 years to 80 years for primary prevention through clinical intervention on atherogenic lipoproteins and low-density lipoproteins. Patients above the age of 80 years were not included due to deficiency of evidence and information. Long term risk for atherosclerotic CVD (age 50-80 years): <15 low, >45 high, in between is moderate risk.

Based on IAS/QRISK (for CVD prediction) seems to be credible for the UK and Western Europe (Hippisley-Cox et al., 2010). On the other hand, the IAS recommends for the general population the Framingham algorithm for calculating the absolute ASCVD risk (Berry et al., 2012). The calculated risk can be recalibrated established on coefficients specified by national arbitrage. If recalibration values are not available, then treatment should be individualized.

#### **Coronary Calcium Score:**

In the elderly, the Framingham equations overestimate CVD risk because they involve the age in the calculation. Numerous physicians do not use risk calculators, they use the impression of risk which they think is precise, and it is right to some limit (Jackson et al., 2013).

Coronary Calcium Score for mortality assessment in asymptomatic elderly individuals (age more than 75 years), has been established (Tota-Maharaj et al., 2012). A zero score is associated with 5.6 years' survival of 98%, similar to survival in other age groups with the same zero score, which is 99%. Participants in the study were 44,052 asymptomatic persons, in North America. High score predicted a high risk of all-cause mortality in all age groups. In the elderly (more than 75years), a score more than 400, was associated with 16 times mortality more than when the score is zero. The same study in North America, also CAC score, predicted all-cause mortality for those less than 45 years.

The CAC score is a vital predictor test for CAD and all-cause mortality, so based on this test some individuals will start treatment to reduce their CVD risk, while many of the elderly would not need medication treatment.

## Statin therapy:

Table 7: The benefit of Statins for the elderly:

Type of study	Sample size	Outcome	Type of patients	Author/year
Meta-analysis	50,000	Reduced total mortality of 15% Reduced CHD mortality 23% Fatal and non-fatal stroke 24% Fatal or non-fatal MI 26%	Elderly aged >60 years with hyperlipidemia	Roberts et al., (2007)
Meta-analysis CTTC (27 trials)	134537 in 22 trials 39612 in 5 trials	Reduced risk of major vascular events (RR 0.79, 99% CI 0.77-0.81). Reduced major coronary events (RR 0.57, 99% CI 0.36-0.89) p0.0021 and (RR 0.61 99% CI 0.50-0.74) p<0.0001	Low-risk vascular disease individuals 5-years risk of major vascular events <10%	Mihaylova et al., 2012
A multicentre randomized controlled trial ASCOT-LLA	19342	Atorvastatin 10mg reduced total cardiovascular events HR 0.79, 95% CI 0.69-0.90, p0.0005. Reduced total coronary events HR 0.71, 95% CI 0.59-0.86, p0.0005. Reduced fatal and non-fatal stroke HR 0.73 (95% CI 0.56-0.96), p0.024. Reduced death HR 0.87 (0.71-1.06), p0.16. Reduced primary endpoint (non-fatal MI, fatal CHD) HR 0.64 (95% CI 0.50-0.83), p0.0005	Hypertensive patients aged 40-79 years with at least three other cardiovascular risk factors. 10305 had total cholesterol non-fasting 6.5mmol/l or less	Sever et al., 2003
Multi centre randomized placebo controlled trial CARDS	2838	Atorvastatin 10mg reduced major cardiovascular events 37% (95% CI -52 to -17), p0.001. Reduced acute coronary Heart disease events RR 37% (95% CI -55 to -9). Reduced coronary revascularisation RR 31% (95% CI -59 to 16). Reduced death rate by 27% (-48 to 1) p0.059. Reduced stroke by 48% (-69 to -11)	Diabetics aged 40-75 years/without Cardiovascular disease/had LDL 4.1mmol/l or less fasting TG 6.78mmol/l or less, and at least one of HTN, retinopathy, albuminuria/current smoking	Colhoun et al., 2004
Randomized controlled trial (prospective) (MEGA study)	3966 randomly assigned to a diet 3866 to diet and 10-20mg pravastatin	Reduced coronary heart disease HR 0.67 95% CI 0.49-0.91, p0.01	Hypercholesteremic Japanese Patients/without CVD.	Nakamura et al., 2006



**Table 7: The benefit of Statins for the elderly:(continued)**

RCT (JUPITER)	17802	Reduced primary end point HR 0.56 (95% CI 0.46-0.69) p<0.00001. Reduced MI, HR0.46, 95% CI 0.30-0.70, p0.0002. Reduced stroke/HR 0.52 (95% CI0.34-0.79, p0.002. Reduced unstable angina HR0.53 (95% CI0.40-0.70, p0.00001. Reduced combined end point HR 0.53 (95% CI 0.40-0.69, p0.02.	Healthy men and women with normal LDL-C <3.4mmol/l, high sensitivity-C-reactive protein2mg/l or more	Ridker et al., 2008
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Roberts et al., (2007) demonstrated decreased total mortality (15% reduction), fatal or nonfatal myocardial infarction (MI) (26% reduction), coronary heart disease (CHD) mortality (23% reduction), and fatal or nonfatal stroke (24% reduction), in a meta-analysis study including more than 50,000 patients > 60 years old, treated with statins. (Roberts et al., 2007) consummated, "statin treatment should be given to high-risk elderly patients", and "statin therapy is associated with obviously decreased mortality risk of cardiovascular in the elderly patients aged 75 years or more".

The Cholesterol Treatment Trialists' Collaboration data highly recommended statins use in the elderly for cardiovascular disease risk reduction (Mihaylova et al., 2012).

As Mihaylova et al., (2012) meta-analysis (CTTC) study of 27 trials, involving 22 trials of statin versus control (participants 134537, follow them for 4.8 years)/5 trials of more versus less statin (n39612, follow them for 5.1 years)/participants in control group was divided into 5 categories based on 5 years major vascular event risk, study found statin reduced major vascular and coronary events significantly without harm, but regarding low risk individuals' statin use is not suitable.

Server et al., 2003 multicentre randomized controlled trial, involving 19342 hypertensive patients with at least three other risk factors for cardiovascular disease, were randomly assigned to one of two antihypertensive regimens of the Anglo-Scandinavian Cardiac test results, 10305 of the patients with total non-fasting cholesterol of 6.5mmol/L or less, randomly assigned to an additional atorvastatin 10mg or placebo. After 3.3 years, the study found atorvastatin group had clinically and statistically significant reduction in: the primary endpoint (non-fatal MI, fatal CHD), total cardiovascular events and total coronary events. In addition to a clinically significant reduction in fatal and non-fatal stroke but statistically not significant, versus the placebo group.

Colhoun et al., (2004) multicentre randomized placebo-controlled trial (CARDS), enrolled 2838 diabetics aged 40-75 years/without CVD, had LDL 4.1mmol/l or less/fasting TG6.78mmol/l, with at least one of: HTN, current smoking, albuminuria, retinopathy, randomly assigned to Lipitor 10mg daily or placebo, after 3.9 years, study found atorvastatin group had clinically significant reduction in first cardiovascular disease events and acute coronary events, compared to placebo group.

Nakamura et al., (2006) MEGA prospective randomized controlled trial, involving 3966 patients randomly assigned to diet group, 3866 to diet plus 10-20mg daily pravastatin. Japanese patients with hypercholesterolemia without CVD, after 5.3 years' study found significant risk reduction of coronary heart disease (HR0.67, 95% CI 0.49-0.91, p0.01) in diet plus pravastatin group compared to diet only group. A study limitation is withdrawal of some participants before the end of the study which leads to bias; also reduction of CHD is statistically insignificant.

Ridker et al., (2008) randomized trial (JUPITER), randomly allocated 17802 healthy women and men with normal LDL-C, but high Sensitivity-C-reactive protein to either rosuvastatin 20mg or placebo, after a 1.9-year study found clinically and statistically significant reduction in the incidence of major cardiovascular events in rosuvastatin group versus placebo group.

EPIC-Norfolk and Reykjavik studies for triglyceride as risk factors in the elderly aged from 70-74 years showed odds ratio (for the association of triglyceride with CHD) of 1.57 (95% CI, 1.10-2.24) and 1.76 (CI, 1.39-2.21) respectively, which is clinically significant. (Sarwar et al., 2007) meta-analyses of these, in addition to other studies, approve that triglycerides are distinct risk factors for cardiovascular disease. Fasting triglyceride level above 1.7mmol/l (150mg/dl) is associated with increased risk of CHD. About 33.3% of adults had the same range of previously mentioned fasting triglyceride (Kotseva et al., 2009). Lately meta-analysis of five prospective, randomized, placebo-controlled trials demonstrated the benefit of fibrates in reducing CHD events in elderly patients with elevated fasting triglycerides more than 2.3mmol/l (200mg/dl). OR =0.65 (0.54-0.78 [95% OR =0.65 (0.54-0.78 [95% CI]), (Jun et al., 2010) which is clinically significant.

The European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) Guidelines recommend medication therapy to reduce triglycerides if still fasting triglycerides remaining high more than 2.3 mmol/L (≈200mg/dl) despite lifestyle intervention (Catapano et al., 2011). Treatment is intended to be for patients considered at "high total CV risk". High total CV risk is defined as either significantly raised single risk factors such as severe hypertension and familial dyslipidemia, or a calculated 10-year risk of fatal CVD SCORE ≥5% and <10%.

The risk of pancreatitis is clinically significant with very high fasting triglycerides more than 10mmol/l (500mg/dl), (Catapano et al., 2011). The ESC/EAS guidelines warrant “actions to prevent acute pancreatitis are compulsory”.

ESC/EAS recommendations for medication therapy of high TGs are Class I/Level B for fibrates, Class IIa/Level B for n-3 fatty acids, Class IIb/Level B for fibrate and n-3 fatty acids and Class IIa/Level C for statin and fibrate (Catapano et al., 2011).

**Guidelines summary for lipid management in the elderly: REF. Noaman et al., (2014):**

1-Adult treatment panel III of national cholesterol education program recommended clinical judgment before using statins for primary prevention of CVD in the elderly due to unreliable CV risk calculators.

2-National collaborative centre for primary care recommended statin for primary prevention of CVD in the elderly aged 75 years and more/who are at high risk of CVD, put in consideration risk-benefit ratio.

3- European Society of Cardiology/European Atherosclerosis Society recommended clinical judgment in decision making for statin therapy in the very old >80-85 years.

American Heart Association/American College of Cardiology (AHA/ACC) recommend using pooled cohort equations for calculation of 10-year CVD risk which will help in treatment decision making in elderly patients aged from 76-79 years. (Stone et al., 2014) randomized control trials recommend continuing statins therapy in the elderly beyond 75years if they are already on statins and tolerating them. But we should consider the side effects of statins, safety, preferences of care and co-morbidities. AHA/ACC recommend discussion before starting statins for primary prevention in the elderly above 75 years, regarding side effects of statins, patient’s priorities, drug interactions, and the statins benefit in reducing cardiovascular disease risk (Stone et al., 2014).

Evidence for treatment in the elderly aged from 80-85 years is very limited due to sparse data, and the treatment decision is based on clinical judgment (Catapano et al., 2011).

National Institute for Clinical Excellence (NICE): NICE guidelines for lipid management in the elderly for primary prevention of cardiovascular disease in primary care, an organized strategy should be done to define people aged from 40-75 years who are at high risk of CVD. Those aged 75 years and more are already at high risk of CVD, so they are likely to benefit from statins therapy. But the treatment should be guided by benefits and risks of treatment, side effects, informed preference and co-morbidities which may make the treatment unsuitable (NICE, 2010).

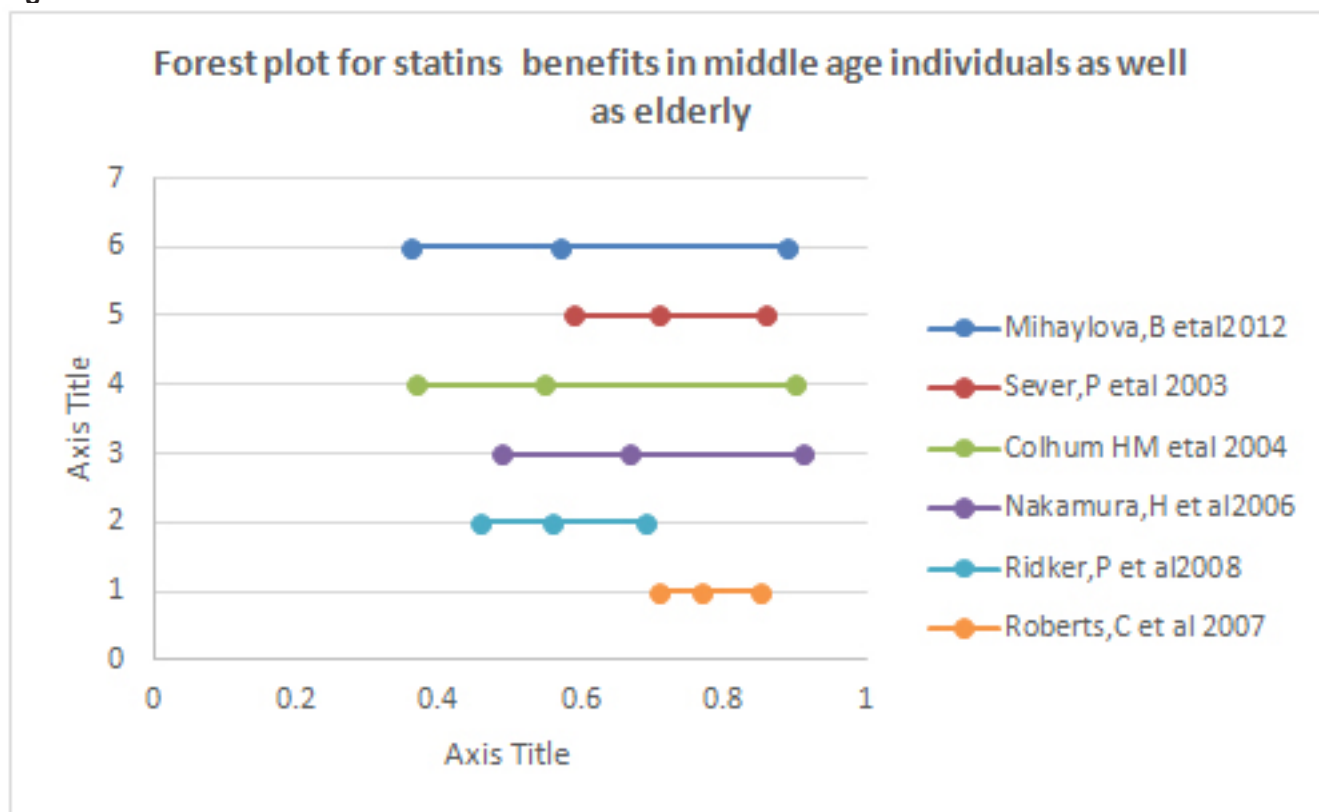
The International Atherosclerosis Society guidelines recommend calculating CHD risk in patients aged more than 65 years using Framingham scoring, recalibrated for country<sup>(1)</sup>. Total CVD can be calculated by adding the CHD risk by one-third, and the result should help in deciding on statin treatment.

Abelhafiz et al (2012) revised the relationship between cholesterol levels and outcomes in the elderly patients with specific consideration to body weight and fragility, pointing out that low body weight and fragility are substantial determinants of elevated CVD, which is associated with low cholesterol levels. Caution would seem suitable in considering therapy in fragile thin elderly patients (Abelhafiz et al., 2012).

(1) See the link: (<http://hp2010.nhlbihin.net/aptili/calculator.asp?usertype=prof>)

**Table 8: Statins benefits in middle age individuals as well as the elderly**

Author/year	Sample size	RR	CI lower	CI upper
Mihaylova et al 2012	174149	0.57	0.36	0.89
Sever et al 2003	19342	0.71	0.59	0.86
Colhum et al 2004	2838	0.37	0.55	0.90
Nakamura et al 2006	7832	0.67	0.49	0.91
Ridker et al 2008	17802	0.56	0.46	0.69
Roberts et al 2007	50000	0.77	0.71	0.85

**Figure**

### Blood pressure control and primary prevention of cardiovascular disease:

The Systolic Blood Pressure Intervention Trial (SPRINT), (Ambrosius et al 2014) which was a multi-centre randomized control trial included 9361 participants with a systolic blood pressure of at least 130mm Hg. The primary target of the trial was to assess if lowering systolic blood pressure to less than 120mm Hg, than the currently recommended less than 140mm Hg, will decrease the appearance of cardiovascular disease. Enrolled patients were 50 years or older with systolic blood pressure of at least 130mm Hg, with one of the other risk factors (example older than 75 years, intermediate to high risk for CVD) but without diabetes. The duration of the study was 3.26 years. The study found that reduction in both primary combined cardiovascular outcome and mortality, 25%, 27% respectively in the group randomized SBP to less than 120mm Hg (Ambrosius et al., 2014). The baseline mean blood pressure is 139.7 mm Hg for systolic blood pressure and 78.1 mm Hg for diastolic blood pressure.

One year later, mean systolic blood pressure was 121.4 mmHg in the intensive therapy group while 136.2 mmHg in the standard treatment group with marked reduction in the rate of the primary complex outcome in the intensive-treatment group compared to standard-treatment group (1.65% per year vs. 2.19% annually, the risk ratio with intensive treatment, 0.75; 95% confidence interval [CI], 0.64 to 0.89;  $P < 0.001$ ). All-cause mortality was also significantly reduced in the intensive-treatment group (hazard ratio, 0.73; 95% CI, 0.60 to 0.90;  $P = 0.003$ ). So reductions in the combined cardiovascular outcome and all-cause mortality were clinically significant but statistically not significant. On the other hand, there is bias as the interviewers knew about study group assignment in addition to dangerous side effects in the intensive treatment group. But still, the study is strong high evidence on the pyramid of evidence, with randomization, multi-centre, and minimizing the ascertainment bias by using the same format for interviewers, and a powerful study 88.7%. In addition participants were divided into subgroups which reduced confounders.

2-1 SPRINNT study  
**ACCORD study**

Table 9: SPRINT and ACCORD studies:

Study type	Sample size	Outcome	Patients type	Author/years
Multi centre randomized control trial (SPRINT)	9361	Reduced primary composite outcome HR0.75 (95% CI 0.64-0.89) p<0.001 Reduced all-cause mortality HR0.73(95%CI 0.60-0.90)p0.003	50 years or older patient with systolic<130 Or more/and increased cardiovascular risk/but no diabetes	Wright et al., 2015
Randomized trial (ACCORD)	4733	The annual rate of primary outcome HR0.88 (95% CI 0.73-1.06), p0.2 The annual rate of death HR1.07 (95% CI0.85-1.35), p0.55 The annual rate of stroke HR0.59(95% CI0.39-0.89) p0.01 Serious side effects 3.3%	Type 2 diabetes patients with a high risk of CVD events	William et al., 2010

**ASCOT-BPLA study.**

Table 10: Sever et al 2005 study:

Study type	Sample size	Outcome	Patients type	Author/year
A multicentre prospective randomized controlled trial	19257	Reduced fatal/non-fatal stroke RR0.77 (95% CI 0.66-0.89) p0.0003 Reduced all cardiovascular events and procedures RR0.84 (95% CI 0.78-0.90) p<0.0001 Reduced incidence of developing diabetes RR0.70 (95% CI0.63-0.78) p<0.0001	Hypertensive patients aged 40-79 years with at least 3 other CVD risk factors.	Sever et al., 2005.

William et al., (2010), randomized trial enrolled 4733 individuals with type 2 diabetes and randomly assigned them to intensive treatment, aiming at systolic blood pressure <120 mmHg and standard therapy, aiming at systolic blood pressure <140 mmHg. After one year the mean systolic blood pressure was 119.3 in the intensive treatment group, and 133.5mmHg in the standard therapy group. The annual rate of primary outcome and death were reduced, but was clinically and statistically insignificant. So intensive therapy to reduce systolic blood pressure <120mmHG in diabetics, compared to standard therapy aiming at systolic<140mmHG, did not reduce combined Cardiovascular events.

Sever et al., (2005), multicentre prospective randomized controlled trial, enrolled 19257 hypertensive patients aged 40-79 years with at least three other CVD risk factors, were randomly assigned either amlodipine 5-10mg, adding perindopril

4-8mg as needed (amlodipine regimen .n=9639), or atenolol adding Bendroflumethiazide 1.25-2.5mg and potassium as needed (atenolol regimen ,n=9618), after 5.5years study found clinically and statistically significant reduction in fatal, non-fatal stroke and all cardiovascular events and procedures in amlodipine regimen Group compared to atenolol regimen group and induced less diabetes than atenolol regimen, so new drugs had greater benefit for lowering blood pressure and preventing CVD than older drugs.

*2010 Canadian hypertension education program highly recommended (grade A) statins.*

Treatment in hypertensive patients older than 40 years with three or more cardiovascular risk factors or already atherosclerotic disease had been established regardless of the age (grade A).

If hypertensive patients have three or more of the following risk factors, statins should be considered. Derived from reference (Sever et al., 2003).

- 1- sex: male.
- 2- Age  $\geq$ 55 years
- 3- peripheral arterial disease. /
- 4- Microalbuminuria or proteinuria
- 5- Diabetes mellitus
- 6- Smoking
- 7- Family history of premature cardiovascular disease
- 8- Total cholesterol to high-density lipoprotein ratio  $\geq$ 6.

Julius et al., (2004), (VALUE), randomized double-blind trial, enrolled 15245 hypertensive patients aged 50 years or older, treated or untreated/had high cardiovascular risk. Randomly assigned Valsartan or amlodipine, after 4.2 years, the study found no difference between the two groups in primary Combined endpoint (HR 1.04, CI 0.94-1.15, p0.49). Based on the study the important issue is immediate Blood pressure control in hypertensive patients with increased CVD risk.

#### **VALUE study.**

Canadian Hypertension Education Program subgroup members for 2010 collaborated with Canadian Diabetes Association Guidelines Committee, Canadian Stroke Network and Canadian Society of Nephrology for 2010 recommendation methods. Conducting Medline search for systematic review and clinical trials in addition to all relevant articles each subgroup had national and international expert opinion reviewer. Actually, the recommendations are highly evidenced, had 80% or more approval, were based on high-quality evidence studies, conducting high sensitive search, and divided into subgroups leading to minimize confounders. Furthermore they had many independent expert opinion interviewers. No conflict between voting members.

#### **CHEP 2010 recommendation for hypertensive patients without indications:**

- 1-First therapy is monotherapy thiazide diuretics (grade A). Long-acting CCB (grade B), beta-blocker in patients younger than 60 years (grade B), ACEI (non-black patients grade B) or ARB (grade B).
- 2-Another antihypertensive drug can be added if goal blood pressure not achieved with standard-dose mono therapy (grade B).
- 3-Initial combination therapy for the treatment of hypertension (grade C) if systolic blood pressure is 20 mmHg exceeds goal or if diastolic blood pressure is 10 mmHg above goal.
- 4-If blood pressure is uncontrolled despite combination treatment with two or more first-line anti-hypertension medications, or there are side effects, other antihypertensive medications may be added (grade D).
- 5-Possible causes for poor response to medications should be investigated (Grade D).
- 6-Alpha-blockers are not recommended as first-line therapy for uncomplicated hypertension (grade A); beta-blockers are not recommended as first-line treatment for uncomplicated hypertension in patients aged 60 years or older (grade A), and ACE inhibitors are not recommended in black patients as first-line therapy for uncomplicated hypertension (grade A) while these medications may be used in patients with specific co-morbidities or in combination therapy.

#### **ESCAPE study.**

A randomized clinical trial of effects of a multifaceted intervention on cardiovascular risk factors in high-risk hypertensive patients: the ESCAPE trial, aimed to assess if multifaceted intervention concentrated on general practitioners (GPS), could raise markedly the proportion of high-risk hypertension patients in primary prevention who attained all their recommended curative goals. The trial enrolled 1,832 high-risk hypertensive patients; and

**Table 11: VALUE study:**

Study type	Sample size	Outcome	Patients type	Author/year
Randomized double-blind trial	15245	No difference in combined endpoint HR 1.04 (95% CI 0.94-1.15, P0.49)	Hypertensive patients aged 50 years or older Treated/or untreated/had high cardiovascular risk	Julius et al., 2004.

**Table 12: ESCAPE study:**

Study type	Sample size	Outcome	Patients type	Author/year
Randomized double-blind trial	15245	No difference in combined endpoint HR 1.04 (95% CI 0.94-1.15, P0.49)	Hypertensive patients aged 50 years or older Treated/or untreated/had high cardiovascular risk	Julius et al., 2004.

included 257 GPs randomized by region; GPs given training session, electronic Blood pressure measurement device and recommendation leaflet. Along with regular follow up for 2 years, localize one consultation on hypertension, and other cardiovascular risk factors every 6 months. Study after two years found a proportion of patients achieving their curative goals was markedly increased in both groups, but more significantly in the intervention group, OR 1.89 (95% confidence interval (CI) 1.09 to 3.27,  $P=0.02$ ), which is clinically significant but statistically insignificant. Blood pressure targets achievement are significantly more in the intervention group than regular care group OR 2.03 (95% CI 1.44 to 2.88,  $P<0.0001$ ), which is clinically and statistically significant. So trial summarized that multifaceted approach aimed at GP only, significantly increased proportion of high-risk hypertensive patients in primary prevention, attaining their recommended curative goals. The trial is a high rank of evidence, with randomization which increases the power of the study, in addition to a good sample size of participants (GPs and high-risk hypertensive patients); follow up period was sufficient. Furthermore, inclusion and exclusion criteria for patients were mentioned clearly, and ethical consent provided, statistical analysis was suitable for the study, with precise results clinically and statistically significant which made the study applicable to a practice.

#### **Diabetes and primary prevention of cardiovascular disease:**

Studies about the role of Aspirin in primary prevention of cardiovascular disease in diabetic patients was reviewed in nine trials which needed at least two years of follow up. Three of these trials exclusively studied patients with diabetes mellitus; the remaining trials enrolled general populations but included some patients with diabetes mellitus.

#### **Aspirin for primary prevention of cardio-vascular disease in diabetic patients:**

##### *Randomized controlled studies (RCT):*

Sacco et al., (2003), randomized trial, enrolled 1031 diabetics, aged 50 years or more/without CVD and 4495 individuals with one or more cardiovascular risk factors to compare effect of aspirin 100mg daily in two groups diabetics and non-diabetics in primary prevention of CVD versus Vit E 300mg daily. After 3.7 years, study found aspirin in diabetics patients non significantly reduced main endpoint and cardiovascular events, along with non-significant increase in cardiovascular death, while significantly reduced main endpoint, total cardiovascular events and cardiovascular death in non-diabetics. Vit E had no effect on any endpoints in both diabetics and non-diabetics. So based on study aspirin had low benefit in primary prevention of CVD in diabetics.

Ridker et al., (2005), randomized trial, involving 39876 initially healthy women aged 45 years and more, randomly assigned to 100mg daily aspirin each other day or placebo; followed them for 10 years, study found aspirin had significant reduction for ischemic stroke, but no significant reduction for major cardiovascular events, nor MI (fatal /non-fatal). For gastrointestinal bleeding, aspirin caused non clinically and statistically significant increase.

In 2008, Belch, et al, randomized, double-blind placebo-controlled trial, enrolled 1276 diabetics (type1 or2) aged 40years or >, had  $ABI=or<0.99$ , randomly assigned to aspirin 100mg daily, plus antioxidant capsule, aspirin plus placebo, placebo plus antioxidant or Placebo tablet plus placebo capsules, after 6, 7 years study demonstrated that aspirin caused non-significant reduction in primary event, non-clinically significant increase in death from CHD or stroke/same for antioxidant. Based on the study there are no recommendations for aspirin/or antioxidants for primary prevention of CVD. But the study had a bias due to the long duration of the study; some patients were lost to follow up or withdrew or died.

Ogawa, et al 2008, in a multicentre randomized blind trial involving 2539 type 2 diabetics without a history of CVD, were randomly assigned to aspirin versus non-aspirin, after 4.3 years, the study found aspirin caused no (clinically and statistically) significant reduction in atherosclerotic events, combined endpoint and cause mortality. So the study showed that low dose aspirin in type 2 diabetic patients did not reduce CVD events.

The trials that exclusively studied patients with diabetes mellitus were the Early Treatment of Diabetic Retinopathy (ETDRS), (ETDRS Investigators 1992), the Prevention of Progression of Arterial Disease and Diabetes (POPADAD), (Belch J, et al 2008) and the Japanese Prevention of Atherosclerosis with Aspirin in Diabetes (JPAD). These trials included a total of 7,526 patients with 38,275 patients–years of follow-up between them (Ogawa et al., 2008).

Aspirin therapy resulted in a 15% relative risk (RR) reduction in fatal plus nonfatal myocardial infarction in patients in the ETDRS (RR 0.85, 95% CI 0.73–1.00) which is clinically insignificant. In the JPAD study, (Ogawa, 2008) a similar reduction was observed for fatal plus nonfatal coronary heart disease events (RR 0.81, 95% CI 0.49–1.33) but the number of events was small (28 in the treatment group versus 35 in the control group) and the findings were statistically and clinically insignificant. Neither trial reduced the risk of stroke, although not many strokes occurred.

In January 2009, the American Diabetes Association (ADA) revised the strength of its recommendation for the use of aspirin for primary prevention of cardiovascular events in patients with diabetes mellitus, going from evidence level A (clear evidence from well-conducted, randomized trials) to level C (conflicting evidence with weight supporting recommendation) (ADA 2009). Canadian guidelines were similarly revised. (Canadian Diabetes Association, 2008). Others have suggested that aspirin should not be used for primary prevention in patients with diabetes mellitus because they consider the benefits to be unproven in the face of known deleterious effects (Barnett et al., 2010).

Ongoing trials such as ASCEND (British Heart Foundation 2010) and ACCEPT-D (De Berardis et al 2007) should help clarify the aspirin effect in primary prevention of

Table 13: Aspirin studies for primary prevention of Cardiovascular disease in diabetic patients:

Study type	Sample size	Outcome	Patients type	Author/ year
A randomized trial(PPP)	1031 diabetics 4495 with one or more major cardiovascular risk factors.	In diabetic patient aspirin non significantly reduced main endpoint (RR 0.90, 95% CI 0.50-1.62) Reduced (non significantly) total cardiovascular events (RR 0.89, 95% CI 0.62-1.26) Increased (non significantly) in cardiovascular death RR 1.23 (95% CI 0.69-2.19) In non-diabetics, aspirin reduced main endpoint, cardiovascular events, and death RRs 0.59 (0.37-0.94), 0.69(0.53-0.90), 0.32 (0.14-0.72)	1031 diabetics Aged 50 years or older. 4495 with one or more major cardiovascular Riskfactors.	Sacco et al., 2003
A randomized trial (WHS)	39876 (total) 1027(diabetics)	Aspirin reduced (non significantly) major cardiovascular events RR 0.91 (95% CI 0.80-1.03, p0.13) Reduced ischemic stroke RR 0.76 (95% CI 0.63-0.93, p0.009. No effect on fatal/non-fatal MI (RR 1.02, 95% CI 0.84-1.25, p0.83) Non significantly increased Gastrointestinal bleeding Requiring transfusion RR 1.40 (95% CI 1.07-1.83, p0.02)	Initially, healthy women aged 45 years or more	Ridker et al., 2005
Multi centre randomized double-blind placebo-controlled trial (POPADAD)	1276	Aspirin reduced (non significantly) primary event/HR 0.98 (95% CI 0.76-1.26) Increased (non significantly) death from coronary heart disease or stroke HR 1.23 (95% CI 0.79-1.93). Anti-oxidants no effect on Primary event HR 1.03 (95% CI 0.79-1.33). Non-significantly increased death from CHD and stroke HR 1.21(95% CI 0.78-1.89).	Diabetics (type 1 or 2) aged 40 years or more With ABI = or < 0.99/ no evidence of CVD.	Belch et al., 2008
Multi-centre prospective randomized blind trial (JPAD)	2539	Aspirin non significantly reduced atherosclerotic events HR 0.80 (95% CI 0.58-1.10), p0.16 Non significantly reduced combined endpoint HR 0.10 (95% CI 0.01-0.79, p0.0037. Non significantly reduced total cause mortality HR 0.90(95% CI 0.57-1.14, p0.67.	Patients with type 2 diabetes without a history of CVD.	Ogawa et al., 2008

cardiovascular disease in diabetic patients, in the future. The study considered aspirin as a suitable potential treatment at the current time for primary prevention of cardiovascular disease in diabetic patients and patient with high cardiovascular disease risk. But there was no definitive current evidence because we depend on very few events in trials to accurately assess their effects, and our results depend on analysis of subcategories of large trials which have a large possibility for bias.

#### Meta-analysis studies:

Xie et al., (2014) meta-analysis, showed a low dose of aspirin is beneficial for primary prevention of CVD. The effect differs by sex and diabetic status. The therapy should be individualized and more research is needed regarding primary prevention in diabetics. The study had also bias and confounders.

De Berardis et al., (2009) meta-analysis found that aspirin reduced cardiovascular events and mortality, beside all-cause mortality but it was non clinically significant while aspirin reduced MI in men significantly. So gender had an effect but there is still no evidence for benefit of aspirin for CVD primary prevention in diabetics.

Baigent et al., (2009), meta-analysis found aspirin reduced serious vascular events and non-fatal MI and was found to be statistically significant but it caused gastrointestinal and extra-cranial bleeding, so before aspirin is used for primary prevention, the risk benefit ratio needs to be weighed up.

The role of aspirin in ETDRS (TYPE1 or type 2 DM), JPAD (TYPE 2DM) and POPADAD (TYPE 1 and type 2 DM), studies which were exclusively for diabetic patients showed a reduction in CHD risk in both ETDRS and JPAD

**Table 14: Meta-Analysis studies for the effect of aspirin in CVD risk in diabetics:**

Study type	Sample size	Outcome	Patient type	Author/year
Meta-analysis	107686	Aspirin reduced: Major cardiovascular events RR 0.90 (95% CI 0.85-0.95), MI RR0.86 (95% CI 0.75-0.93), ischemic stroke RR0.86(0.75-0.98), all-cause mortality RR 0.94 (0.98-0.99) In subgroups, reduced MI among men RR 0.71(0.59-0.85) Reduced ischemic stroke among women RR 0.77(0.63-0.93) Reduced MI among diabetic men RR 0.65 (0.51-0.82)	Mixed men and women without CVD, some diabetics.	Xie et al., 2014
Meta-analysis	10117	Aspirin non statistically significant reduction on major cardiovascular events RR 0.90 (95% CI 0.81 -1.00), cardiovascular mortality RR 0.94 (95% CI 0.72-1.23, all-cause mortality 0.93 (0.82-1.05), significantly reduced the risk of MI in men RR0.57(0.34-0.94)	Diabetic patients with no pre-existing CVD event	De Berardis et al., 2009
Meta-analysis	95000 (low average risk) 660000 person-years 3554 serious vascular events	Reduced serious vascular events p0.0001, 0.51 Reduced non-fatal MI 0.18, p0.0001 Effect on stroke insignificant 0.20%, p0.4 Increased major gastrointestinal and extracranial bleeding 0.10% per year, p<0.0001	95000 (low average risk) 660000 person-years 3554 serious vascular events	Baigent et al., 2009



studies, but POPADAD had no effect on CHD risk. The overall effect of aspirin on CHD in 3 studies is clinically insignificant.

Primary prevention Trials found that low dose Aspirin in patients with/without diabetes is associated with an absolute risk of hemorrhagic stroke in around 1 in 10,000 people yearly (Blackwell et al., 2009).

A meta-analysis of six primary prevention trials found that aspirin is associated with a 54% increase in gastrointestinal risk bleeding (RR 1.54, 95% CI 1.30 to 1.82), which is clinically significant. Diabetics who used aspirin have 55% more risk for aspirin side effects (RR 1.55, 95%CI 1.13 to 2.14) than non-diabetics. So the risk for aspirin-related adverse effects is clinically significant in diabetics. Two trials mentioned the use of statins or other lipid-lowering medications; statin use in JPAD was 26%, while another lipid-lowering therapy in PPP was 13%.

#### Recommendations based on trials data:

1-Aspirin low dose (75-162 mg/day) in diabetics with high CVD risk (10-years CV risk is over 10%) and not at increased risk for bleeding. Diabetics at increased CVD risk include men over 50 years/women over 60 years, who had one or more of the following risk factors: dyslipidemia/hypertension/smoking/albumin urea, family history of premature CVD (ACCF/AHA class IIa, level of evidence: B) (ADA Level of evidence: C).

2-Aspirin should not be recommended for CVD primary prevention in diabetics with low CVD risk (men under 50/ women under 60/no additional major CVD risk factor-10-years CVD risk under 5%) As the risk overweight benefit (ACCF/AHA CLASS III, LEVEL of evidence: C), (ADA Level of evidence: C).

3-Aspirin low dose (75-162mg/day) might be deemed effective in diabetic with intermediate CVD risk (younger patients with one or more risk factors, or older patients with no risk factors or patients with a 10-year CVD risk of 5%-10%) till advanced research is obtainable (ACCF/AHA Class IIb, Level of Evidence: C), (ADALevel of Evidence: E).

#### Examples for sources for CVD risk assessment in diabetics:

American Diabetes Association Risk Assessment Tool, Diabetes PHD: <http://www.diabetes.org/phd>  
UKPDS Risk Engine: <http://www.dtu.ox.ac.uk/riskengine/index.php>

#### Limitation of Current study:

No two independent investigators, publication bias, confounders; in addition to language restriction furthermore it is difficult and time consuming.

#### Advantages of current study:

High level of evidence in hierarchy of evidence, rank one with meta-analysis study. The study design is suitable for aim of the study. Time of systematic review is sufficient. The sources of reviewed studies were comprehensive.

Statistical analysis is precise and suitable. Inclusion and exclusion criteria for recruited studies were clear.

## Conclusion

Statin is beneficial for primary prevention of cardiovascular disease in middle age individuals as well as the elderly, who have dyslipidemia or diabetics aged 40-75 years, or 10-years CVD risk =>7.5%. According to AHA/ACC or =>10% or according to NICE or USPSTF. Statin is effective for primary prevention of CVD in moderate and high risk individuals but no evidence for its benefit in low risk individuals. Caution would seem suitable in considering therapy in fragile thin elderly patients, who have substantial determinants of elevated CVD. No definite evidence for non-statin therapy benefit for primary prevention of CVD, but can be used in hypercholesterolemia patients or high CVD risk patients who did not tolerate statins or who had not responded to the maximum dose of statins. PCSK-9 inhibitors need more search about their safety, effectiveness and cost-effectiveness before they are recommended for primary prevention of cardiovascular disease. No evidence for aspirin benefit in primary prevention of CVD in diabetic patients; ongoing trials should help clarify their effect in primary prevention of CVD in the future. Immediate blood pressure control is important in the primary prevention of CVD in hypertensive patients with high cardiovascular risk.

## Recommendations

1-To control risk factors for CVD, mainly hyperlipidemia, hypertension and diabetes through pharmacological and non-pharmacological measurements.

2-To follow best practice guidelines recommendations for primary prevention of cardiovascular disease in hypercholesterolemia patients/hypertensive and diabetic patients, mainly AHA, ACC, NICE, USPSTF, adult treatment panel III (ATPIII) of national cholesterol education program national collaborated centre for primary care, European society of cardiology and European atherosclerosis society, American Diabetes Association (ADA), Canadian diabetes association and 2010 Canadian hypertension education program.

3-To lower systolic blood pressure to less than 120 than the currently recommended less than 140, will significantly reduce appearance of cardiovascular disease in hypertensive patients with other risk factors but without diabetes.

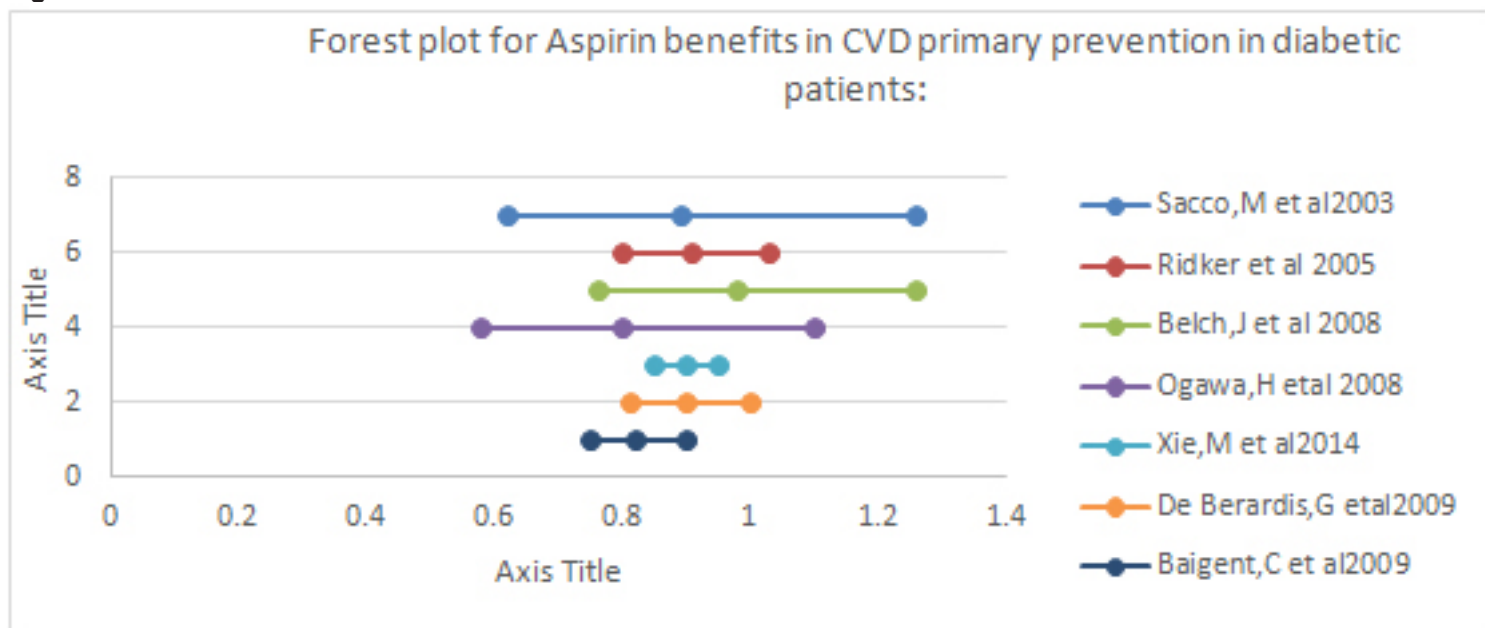
4-No need for intensive therapy to reduce systolic blood pressure less than 120 in diabetic patients because such will not reduce combined cardiovascular events.

5-To use new antihypertensive medications like amlodipine adding perindopril rather than to use old medications like atenolol adding flumethiazide and potassium, because the new medications had greater benefit for lowering blood pressure and preventing CVD than old medications.

6-To follow 2010 Canadian hypertension education program recommendation for statin therapy in

**Table 15: Aspirin benefits in CVD primary prevention in diabetic patients:**

Author/year	Sample size	RR	CI lower	CI upper
Sacco et al 2003	5526	0.89	0.62	1.26
Ridker et al 2005	39876	0.91	0.80	1.03
Belch et al 2008	1276	0.98	0.76	1.26
Ogawa et al 2008	2539	0.80	0.58	1.10
Xie et al 2014	107686	0.90	0.85	0.95
De Berardis et al 2009	10117	0.90	0.81	1.00
Baigent et al 2009	758554	0.82	0.75	0.90

**Figure**

hypertensive patients older than 40 years with 3 or more cardiovascular risk factors (grade A).

7-Immediate blood pressure control is important in hypertensive patients with increased CVD risk.

8-To follow Canadian hypertension education program 2010 recommendations of high grade evidence level A and B for hypertensive patients without indications.

9-Training sessions for general practitioners where required, with electronic blood pressure measurement device and recommendation leaflet are recommended.

10-No need for aspirin for primary prevention of CVD in diabetic patients.

11-To use statins for primary prevention of CVD in moderate and high risk individuals. No indication for its use in low risk individuals.

12-ADA recommendation for aspirin for primary prevention of CVD in diabetic patients is grade C (conflicting evidence).

13-Canadian diabetes association 2008, suggested that aspirin should not be used for primary prevention of CVD in diabetic patients as the benefit is unproven in the face of known deleterious effects.

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