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Case Report

Analysis of the Dilemma Involving Statins and Aspirin as Primary Prevention Alternatives in Cardiovascular Disease

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Cardiovascular disease is one of the deadliest diseases in the world. Nowadays, alongside the developments of various medical therapeutic strategies, there is a decreasing trend of cardiovascular mortality. However, this reduction is not adequate and needs to be supported by cardiovascular prevention approaches. Statins and aspirin are two of cardiovascular drugs that are believed to be beneficial in cardiovascular prevention. Their magnificent efficacies in the secondary prevention setting lead them to be used in the primary prevention. However, some safety issues associated with the drugs should be considered. For that reason, based on previous trials and studies, some recommendations regarding the efficacy-safety issues are developed.

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Keywords: aspirin, statins, cardiovascular, prevention

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Laporan Kasus

Dilema Penggunaan Statin dan Aspirin sebagai Alternatif Pencegahan Primer Penyakit Kardiovaskular

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Penyakit kardiovaskular adalah salah satu penyakit dengan angka kematian tertinggi di dunia. Saat ini, seiring dengan perkembangan berbagai metode penatalaksanaan medis penyakit kardiovaskular, didapatkan penurunan angka kematian yang diakibatkan oleh penyakit-penyakit tersebut. Namun, penurunan ini belum adekuat dan masih membutuhkan upaya pencegahan penyakit kardiovaskular sebagai intervensi penunjang. Statin dan aspirin adalah dua jenis obat kardiovaskular yang diyakini memiliki efek farmakologis mumpuni dalam pencegahan penyakit kardiovaskular. Efikasi kedua obat tersebut dalam pencegahan sekunder mengarahkan penggunaannya dalam lingkup yang lebih luas, yakni pencegahan primer penyakit kardiovaskular. Namun, beberapa masalah keamanan obat sering ditemui dan harus diperhatikan dalam penggunaannya. Dengan alasan inilah, berdasarkan penelitian dan eksperimen terkini, rekomendasi mengenai penggunaan kedua obat tersebut untuk penyakit kardiovaskular saat ini sedang dikembangkan.

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Kata kunci: aspirin, statin, kardiovaskular, pencegahan

Introduction

For many years, Cardiovascular Disease (CVD) has become a global burden and caused limitations in daily activities. It was the leading cause of death worldwide in 2013.[1] In the United Kingdom (UK), cardiovascular disease mortality was almost one-third of all-cause mortality across age and gender.[2] In 2014, cardiovascular diseases stood below cancer as the most common cause of death in the UK (**Figure 1**).[1,2]

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Various medical therapeutics strategies in cardiovascular medicine had been developed to overcome this problem. However, those developments were not enough to tackle the problem and cardiovascular disease remained challenging. For that reason, a few years ago, cardiovascular disease prevention was proposed as one of the breakout solutions. Nowadays, cardiovascular disease prevention is believed to be one of the best approaches to tackle cardiovascular disease and its complications.

Atherosclerotic CVD especially coronary artery disease is the deadliest of all cardiovascular disease group members.[1] It comprises a broad spectrum of disease pathology and clinical feature, from asymptomatic fatty streak to deadly ruptured plaque. For many years,

alongside the progression of therapeutic strategies developments, researchers and clinicians have tried to prevent this disease by modifying its risk factors. There are at least four major modifiable risk factors for Coronary Artery Disease (CAD), such as smoking, dyslipidemia, hypertension and diabetes mellitus. Furthermore, lifestyle modifications, such as exercise and healthy diet, are believed to be beneficial in tackling CAD. However, these lifestyle changes will not bring any favourable outcome unless there are interventions to those cardinal risk factors in the early stage of the disease. These interventions are not easy to be done because the initial stage of CAD and associated risk factors are usually asymptomatic and silent. For that reason, some experts recommend the use of several drugs, such as HMG-CoA Reductase Inhibitor (statin) and aspirin, as primary prevention modalities in Atherosclerotic Cardiovascular Disease (ASCVD), especially coronary artery disease.

Overview of pharmacological aspects of statins and aspirin

Statin acts as an inhibitor of hydroxymethyl glutaryl-CoA (HMG-CoA) reductase enzyme. Its role in the inhibition of sterol biosynthetic pathway makes statin a potent lipid-lowering drug. Statin is also proven to be beneficial in cardiovascular disease management and prevention. So far, statin family comprises of at

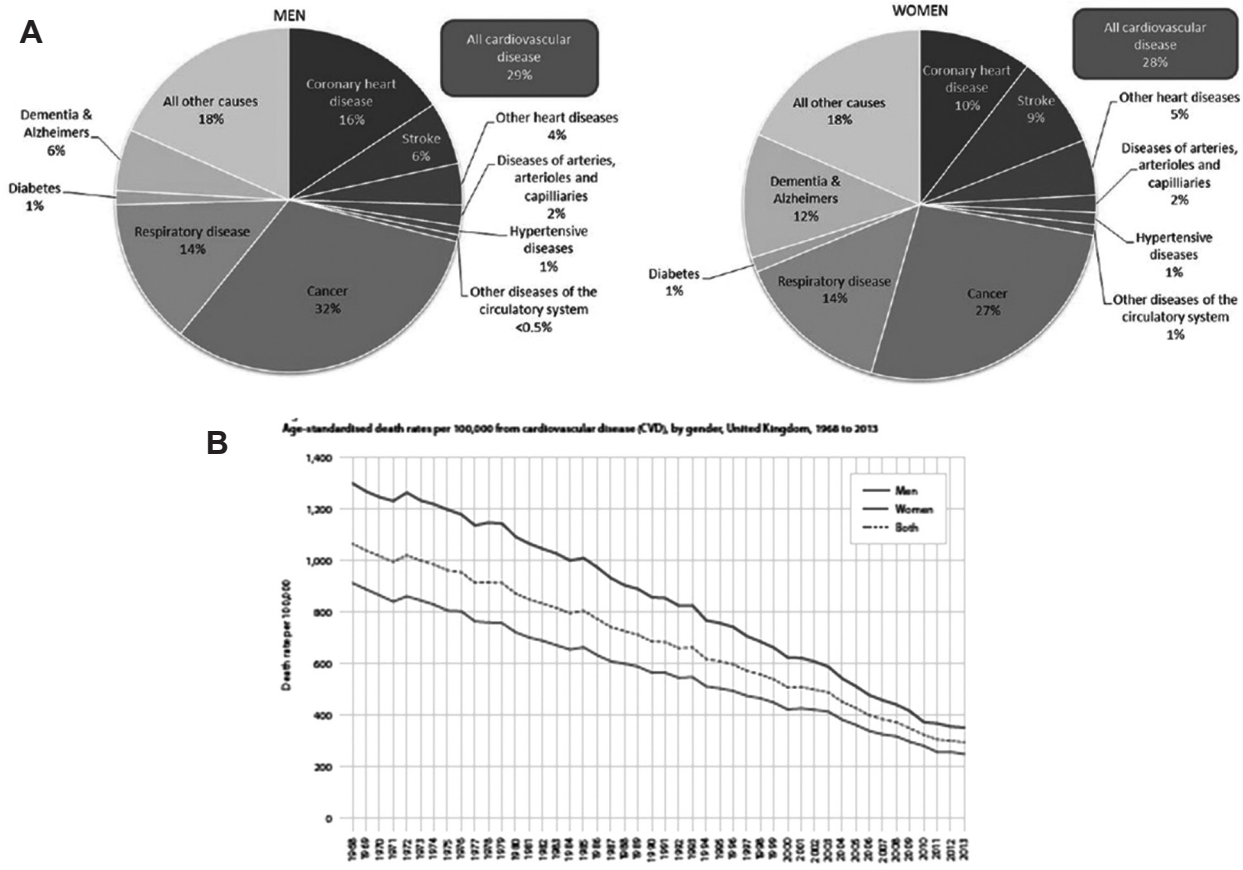

Figure 1. A) All-cause mortality in the UK classified by gender (2014). Cancer is the deadliest disease in both sexes (male and female) followed by cardiovascular disease at the second place. B) The Age-standardised death rate of CVD in 1968-2013. The mortality of CVD is decreasing with the improvement of CVD managements and prevention (cited from: Bhatnagar P, Wickramasinghe K, Williams J, et al. Heart. 2015;0:1-8 and Townsend N, Bhatnagar P, Wilkins E, et al. BHF. 2015).

least eight major members, including Pravastatin, Fluvastatin, Compactin, Atorvastatin, Lovastatin, Simvastatin, Pitavastatin, and Rosuvastatin.[3]

Those major types of statins have different potencies and characteristics depend on their molecular structures. Furthermore, they have different pharmacokinetic properties such as metabolism by cytochrome P-450, bioavailability, hydrophobicity, and cellular transport mechanisms. Despite the efficacy of statin in cardiovascular disease management, some side effects may appear, such as raised incidences of diabetes mellitus, ocular cataracts, a wide range of muscular disorders (from muscle pain to rhabdomyolysis). Additionally, some patients may also experience liver toxicity, proteinuria and haematuria as the effects of long-term statin therapy.[3]

Besides statins, there is another cardiovascular drug that also provides enormous benefits in cardiovascular disease management. It is named acetylsalicylic acid or aspirin. It was originated from willow bark and it used to be an analgesic in an ancient era.[4] Aspirin is categorised as a non-steroidal anti-inflammatory drug (NSAID). Now, it is occasionally used as an antipyretic drug, but the primary use of this drug is for cardiovascular disease.

As a cardiovascular drug, aspirin plays a role in platelet physiology.[5] Aspirin exerts its effect mainly by disrupting the biosynthesis of prostanoids, such as prostaglandin, prostacyclin and the most important one, Thromboxane A_2 (TxA_2).[4] Consequently, aspirin inhibits platelets aggregation that occurs during inflammation or haemostatic process.[4] In prolonged use, aspirin can cause gastrointestinal side effects such as gastritis, peptic ulcer and gastric bleeding. Furthermore, the disruption of the haemostatic process increases the bleeding risk and potentially leads to haemorrhagic stroke or other complications.[4]

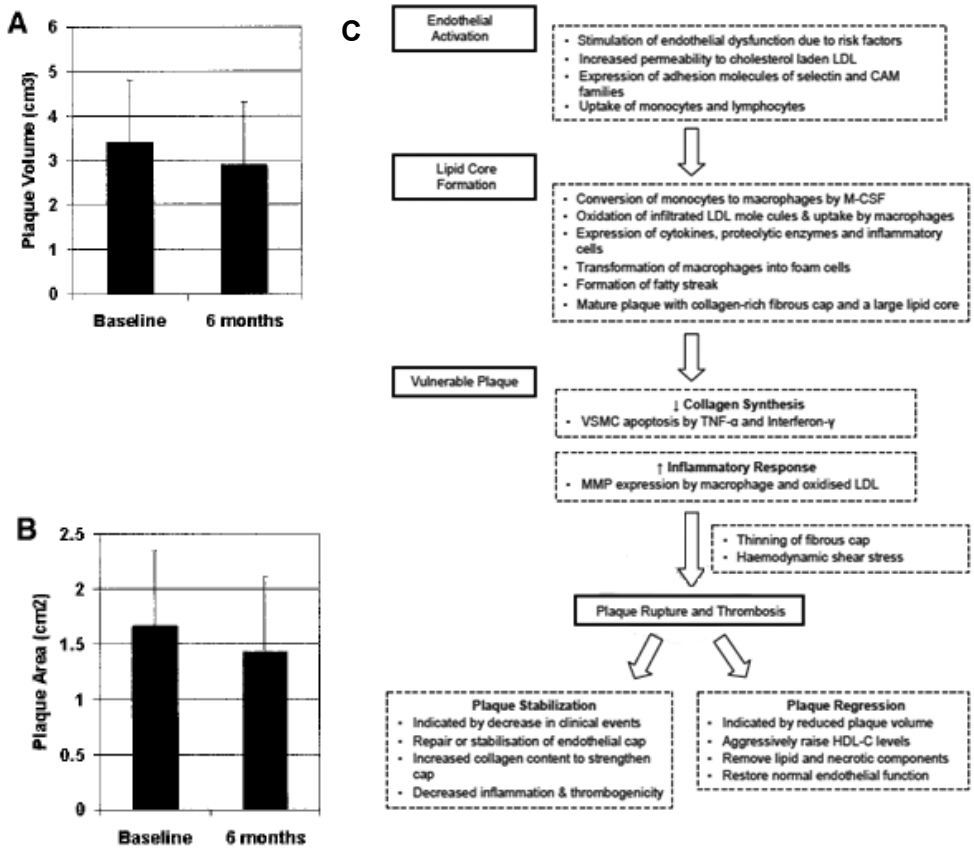

Figure 2. Plaque regression in an aortic atherosclerotic plaque 6-months after statin therapy. A) Reduction of the plaque volume B) Reduction of the plaque area C) Cellular pathway of plaque regression and stabilisation (cited from: Lima JAC, Desai MY, Steen H, et al. *Circulation*. 2004; 110:2336-2341 and Dave T, Ezhilan J, Vasnawala H, et al. IJEM. 2013;17(6):983-9).[32]

Roles of statins and aspirin in ASCVD management

Statins and aspirin are widely used as secondary prevention modalities in atherosclerotic cardiovascular diseases, especially coronary artery disease.[6] They provide tremendous benefits to patients who suffered from CAD. Statins, for example, have roles in lowering LDL-cholesterols level in the bloodstream and increasing LDL-cholesterols uptake from an atherosclerotic plaque. As the result, lipid depositions inside the atheroma are reduced and the plaque is stabilised. Additionally, statins have some pleiotropic effects, such as inflammation reduction, endothelial function improvement and plaque regression effects (**Figure 2**).[6-8] This plaque regression effect begins in the early phase of CAD and is associated with the reduction of the necrotic core.[9]

The Scandinavian Simvastatin Survival Study (4S)[10] reported a reduction in major cardiovascular events and mortality in patients with CAD and high cholesterol level. Furthermore, CARE trial reported that statins' cardio-protective effects were also present in myocardial infarction patients with average cholesterol levels.[11] Those two studies showed that the beneficial effects of statins in coronary artery disease were independent of the cholesterol levels. This evidence is supported by another study, Anglo-Scandinavian Cardiac Outcomes Trial Lipid-Lowering Arm (ASCOT-LLA),[12,13] which showed that the cardiovascular benefit of Atorvastatin was present in average and low cholesterol level. The follow-up of this trial also showed that statins' cardiovascular benefits are still present eleven years afterwards (**Figure 3**).

Aspirin, a non-steroidal anti-inflammatory drug, which acts as an anti-platelet in cardiovascular disease management, also plays a role in secondary prevention of atherosclerotic CVD. It is responsible for maintaining blood flow in CAD by inhibiting platelet aggregation process that occurs during and after a plaque rupture in myocardial infarction (MI) patients. In 2002, Anti-thrombotic Trialists Collaboration reported that aspirin reduced the risk of vascular events in patients with acute and prior CVDs (myocardial infarction and stroke).[4,14,15] Aspirin is also used routinely after revascularisation procedure because

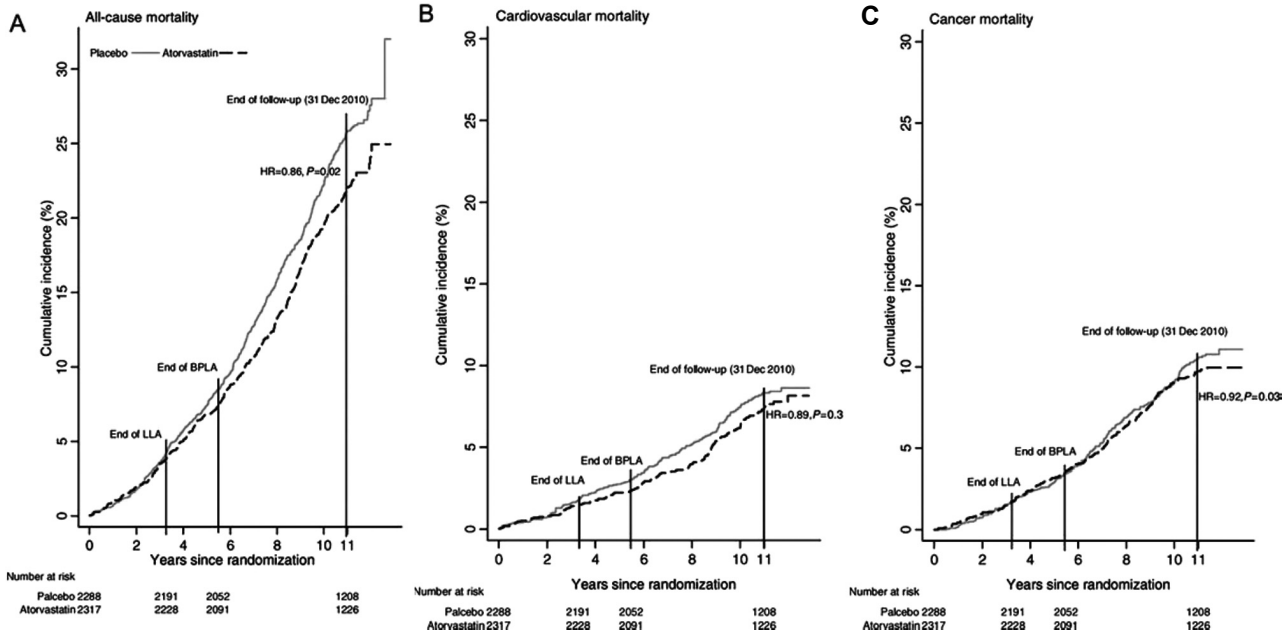

Figure 3. The result of ASCOT-LLA trial (11-year mortality follow-up). The effect of statin in the reduction of cardiovascular disease mortality is still present after 11 years (showed by reduction of all-cause and cardiovascular mortality – A&B). No increased cancer mortality due to statin administration (C) (cited from: Sever PS, Chang CL, Gupta AK, et al. *European Heart Journal*. 2011;-:1-8).

percutaneous coronary intervention (PCI) procedure often causes local vascular injuries that disrupt the endothelial layer and trigger the haemostatic process. These micro-injuries are prone to thrombosis and often results in myocardial ischemia post-PCI.[4] In PCI procedure; aspirin is usually combined with either secondary anti-platelet drugs (i.e., Ticlopidine, dipyridamole, clopidogrel) or anti-coagulants (i.e. warfarin). Regardless of the combinations of aspirin, there is a significant decrease in acute complications of PCI and reduction in thirty days mortality post-PCI.[4]

Moreover, the benefits of aspirin may also be achieved in patients post coronary bypass surgery (CABG).[4] The 5% to 15% risk of graft occlusion due to thrombosis at the anastomotic site can be prevented by aspirin administration immediate after the surgery. Continued aspirin administration for one year after bypass surgery reduces the rate of occlusive events more than 50%.[4] However, increased perioperative bleeding complications should be noticed and considered before aspirin administration in both PCI and CABG.

Role of statins and aspirin in primary prevention of ASCVD

As mentioned in the previous section, although the roles of statins and aspirin in secondary prevention of CVD are well established, ASCVD remains challenging. Now, the enthusiasm for statins and aspirin as primary prevention modalities has been developed.

Cardiovascular risk assessments in ASCVD

Nowadays, ASCVD risk assessment becomes an important issue because people want to predict their cardiovascular events risk in the next few years. Subsequently, this CV risk can be used as a basis for starting cardiovascular primary prevention programmes, including lifestyle modification, healthy diet and administration of certain drugs, such as statins and aspirin. Three most common CV risk calculators are QRISK2 from NICE, Framingham point scores from National Heart, Lung, and Blood Institute (NHLBI) and SCORE from European Society of Cardiology (ESC).[16,17,18-20] They use several parameters such as age, gender, body mass index (BMI), smoking behaviour, blood pressure and cholesterol level to measure the CV risk in the next ten years. It should be noted that not all medical conditions are suitable for CV risk assessment using these scores. For example, NICE did not recommend the use of CV risk calculator (QRISK2) in several conditions such as Type-1 Diabetes, people with eGFR less than 60 ml/min/1.73m^2 (chronic kidney disease/CKD) with/without albuminuria, familial hypercholesterolemia and pre-existing CVD.[29]

Statins in primary prevention of ASCVD

The role of statins in primary prevention of CVD is controversial. The Cholesterol Treatment Trialist (CTT) Collaboration evaluated data from 27 clinical studies of statins for primary and secondary prevention of CVD and reported that per 1 mmol/L reduction in LDL-C, there was approximately 20% risk reduction for major cardiovascular events. These advantageous effects were seen irrespective to the gender, cardiovascular disease risk, diabetic status, cholesterol level and age.[21,22] Additionally, a Cochrane systematic review of 18 trials of statins in primary prevention of CVD reported that statins lowered cardiovascular events risk by 27% even though in the group of patients with statins, the risk of getting type-2 diabetes is increased approximately 9%.[21]

Other large studies also showed the benefits of statins in primary prevention setting. They are ASCOT-LLA and JUPITER trial that reported a marked reduction in CV risk after administration of statins. As mentioned in the previous section, in ASCOT-LLA trial, there were reductions in CV risks in hypertensive patients without prior CV events regardless of the LDL cholesterol level.[12] In JUPITER trial, the trial was stopped after a median follow-up of 1.9 years (of maximum 5 years) because of a 44% reduction in all vascular events, 54% reduction in MI risk, 48% reduction in stroke and 20% reduction in all-cause mortality.[23,24]

In the JUPITER trial and most of other trials that evaluated the role of statins in the primary prevention setting of CVD, there were no significant differences between the treatment groups with placebo regarding the serious adverse events. Additionally, there was no difference among treatment groups with regards to the occurrence of muscle weakness, myopathy and

hepato-renal impairment. JUPITER trial also reported a significant reduction in cancer mortality in a short-term period of observation (1.9 years). However, as well as other studies (**Figure 4**), JUPITER trial also reported a few incidents of diabetes with a small increase in HbA1c.[23,24]

Aspirin in primary prevention of ASCVD

The benefits of aspirin in the primary prevention setting are also debatable. A few years ago, there were two large randomised trials of aspirin for primary prevention of CVD, Physician Health Study and British Physician Study.[4] The Physician Health Study randomised subject between 40 and 84 years and treated them with either aspirin 325 mg or placebo. This study was stopped after 5-years follow-up period because of significant results, such as 44% reduction in the risk of MI. However, there was no reduction in CV-related mortality.[4] In contrast, the British Physician study reported no difference in the incidence of MI. Additionally, it also reported that there was no difference in CV-related mortality after six years of aspirin treatment and there was an increase in the incidence of haemorrhagic stroke.[4]

In 1994, Antiplatelet Trialists Collaboration reported that there was a significant reduction in vascular and all-cause mortality in patients with increased risk of occlusive CVDs, such as patients with

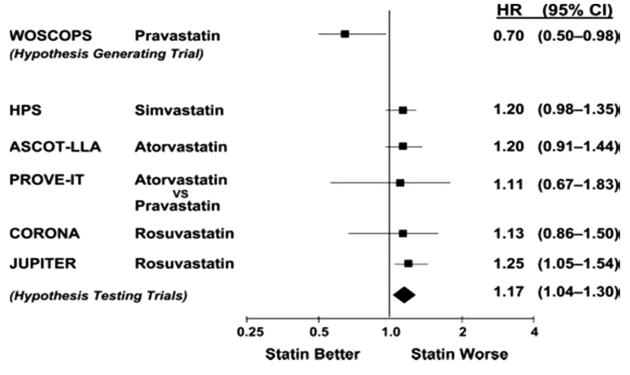

Figure 4. The Effects of statins therapy and incidence of diabetes in placebo-control trials. Almost all of the trials reported hazard ratio (HR) more than one regarding diabetes incidence in statin administration (cited from: Ridker PM, Pradhan A, MacFayden JG, et al. *Circ Cardiovasc Qual Outcomes*. 2009;2:279-85).

stable angina, valvular heart diseases, atrial fibrillation and peripheral artery diseases. Furthermore, compared to these benefits, the risk of major non-fatal and fatal bleeds was quite small.[4,14,25] Additionally, these results were significant in all groups of patients irrespective of gender, age and the presence of comorbidities such as hypertension and diabetes. In 1998, another study, the Thrombosis Prevention Trial, also tried to look up the effects of aspirin in high-risk individuals. The results were 20% reduction in ischemic heart disease events in aspirin-groups after 6-years follow-up without any significant effect on total mortality. However, aspirin alone did not cause any increase in the incidence of stroke.[26,27]

Older adults have a higher risk of getting CV events and may represent an age-group in which aspirin could provide the biggest benefits, but at the same time, older adults are very vulnerable to major haemorrhages, such as haemorrhagic stroke and gastrointestinal bleeding.[28] However, in the latest trial (AAA trial, 2010), it was reported that there was no CV benefit of using aspirin in primary prevention and there was an increasing trend of disabling stroke. Another study (ASPREE study) was commenced to resolve this issue and the result will be available in 2017. In this study, they evaluate the 5-years risk of having major CV events, dementia, cancer and cognitive impairment and measure the composite endpoint of disability in older population.[28]

Bleeding risks of aspirin, including haemorrhagic stroke, are important issues to be resolved. However, more importantly, the reason the latest aspirin prevention studies in high-risk populations did not show any CV-related events Relative Risk (RR) reduction is probably because of the attenuation of the effect of aspirin in these populations. Firstly, in high-risk populations, they often use statins and ACE-inhibitor that have already had some antithrombotic and anti-inflammatory effects. In this population, the effectiveness of aspirin as an antithrombotic agent is reduced. Secondly, diabetes in high-risk population is quite common and this condition may lead to the aspirin resistance. Thirdly, the hypothesis that the limited platelet inhibition by aspirin may be mediated by increasing weight, drug interactions and ageing process.[28] All of these complexities make the decision to use aspirin in the primary prevention setting even more challenging because the benefits of aspirin are likely to be outweighed by the harms.

Discussions

Statins and aspirin are two common drugs in cardiovascular disease management. Their roles in acute and secondary prevention setting are well established. Statins have a lipid lowering activity and some pleiotropic effects beyond it. Aspirin has a powerful anti-platelet activity that is beneficial in many major cardiovascular events. However, as mentioned in the previous section that the use of both drugs in primary prevention setting is controversial. Statins' controversy is more trivial than aspirins' because all of the studies reported the same benefit of statins in CV risk reduction. The dilemma of statins administration is mainly in diabetics and patients with chronic kidney disease. However, all studies of aspirin in primary prevention of cardiovascular disease did not report the same results. Some of them reported benefits without any harms, some of them reported benefits with a few incidents of harms and some of them reported no benefit at all with enormous potential harms (**Figure 5**).

Those complexities lead to difficulties in making recommendations for these drugs in primary prevention setting. In 2014, National Institute for Health and Care Excellence (NICE) published its new guideline about statins in primary prevention.[29] It recommended that the decision to start statin therapy should be made after a discussion about the risks and benefits of the treatment with regards to the potential benefits of lifestyle modifications and other modifiable risk factors managements. Regarding ineffective lifestyle modifications, statin treatment is initiated after the risk assessment. Atorvastatin 20 mg is administered to the person who has a 10% or greater 10-year risk of developing CVD (using QRISK2). Consequently, for people more than 85 years, statins may be beneficial in reducing nonfatal MI risk. In diabetic persons, NICE divided the recommendation according to the type of diabetes. In type-1 diabetes, statins are considered for all patients who are above 40 years old or have diabetes for more than a decade, have established nephropathy

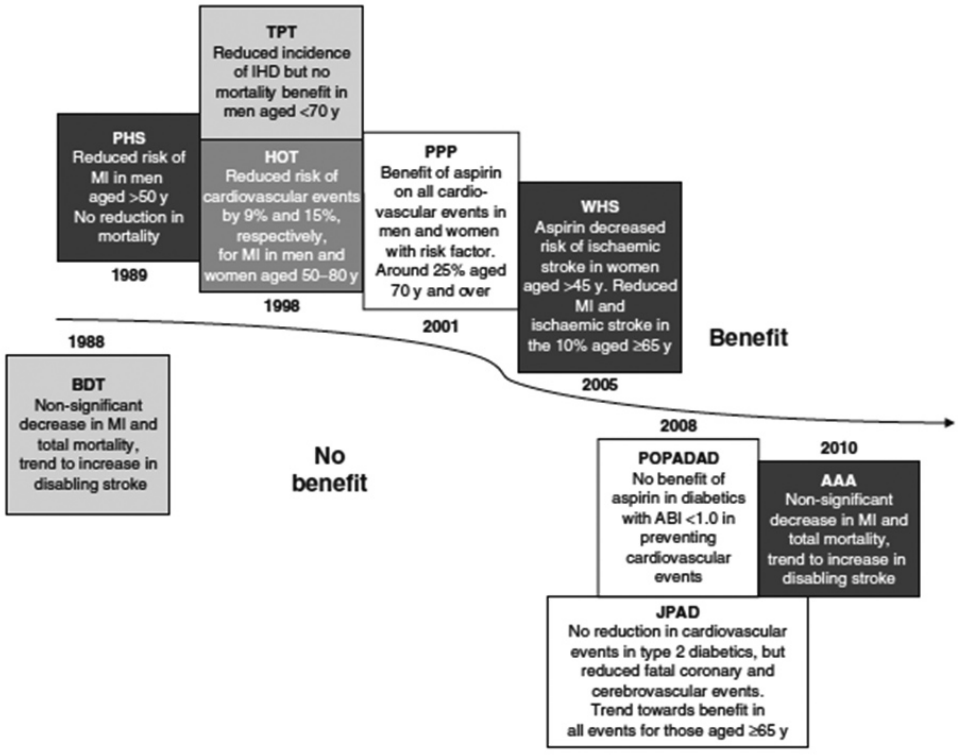

Figure 5. A timeline of trials of aspirin in primary prevention conducted between 1988-2010 (cited from: Ward SA, Demos L, Workman B, et al. Drugs Aging. 2012;29(4)).

or have other CVD risk factors. However, in type-2 diabetes, statins are limited only in patients with 10% or greater 10-year CVD risk. Additionally, there is a particular recommendation for CKD patients as well.[29] ESC evaluated this issue from a slightly different aspect. Its recommendation is based on two parameters, such as total CV risk (using SCORE) and LDL-C levels.[16-18] Despite the difference in the parameter; both recommendations agreed that statin therapy should be started in high-risk patients.

The recommendation of aspirin in primary prevention is more controversial than statins'. In 2015, NICE published a new guideline on this issue.[31] It did not recommend any routine prescription of antiplatelet drugs for primary prevention of CVD. However, some experts recommend treatment with aspirin for people with hypertension and have at least one of two conditions, such as people with age above 50 years with high cardiovascular disease risk (10-year cardiovascular disease risk more than 20%) or have an impaired renal function. In this group of patients, aspirin should not be started before the blood pressure is less than 150/90 mmHg to reduce the bleeding risk. In non-hypertensive patients with low CVD risk, aspirin is not recommended because there is evidence that aspirin increases the risk of severe bleeding. Recently, NICE recommendation of aspirin for diabetic patients was re-evaluated due to three meta-analyses that had reported no strong benefit of aspirin in primary prevention of cardiovascular disease in diabetes.[31]

In 2012, ESC also advised considering aspirin for primary prevention of cardiovascular disease in people with hypertension who have impaired renal function, or are at high CV risk (20-30% major CV events in the next ten years).[18,31] However, ESC did not recommend aspirin to be used in individuals without cardiovascular or cerebrovascular disease due to the increased risk of bleeding (Class III, LOE B).[18]

Conclusion

Statins and aspirin are very beneficial in cardiovascular disease managements. However, the use of these drugs in primary prevention setting still needs further research. So far, statins in primary prevention are recommended only under certain conditions (i.e. high-risk people). The use of aspirin in primary prevention is more limited and controversial because the potential harms outweigh the benefits of this drug. Finally, larger and more comprehensive clinical trials are needed to resolve these efficacy-safety related issues.

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Abbreviations

4S: Scandinavian Simvastatin Survival Study
ASCOT-LLA: Anglo-Scandinavian Cardiac Outcomes Trial Lipid-Lowering Arm
ASCVD: atherosclerotic cardiovascular disease
BMI: body mass index
CABG: coronary bypass surgery
CKD: chronic kidney disease
CTT: Cholesterol Treatment Trialist
CVD: cardiovascular disease
ESC: European Society of Cardiology
HMG-CoA: hydroxymethyl glutaryl-CoA
MI: myocardial infarction
NHLBI: National Heart, Lung, and Blood Institute
NICE: National Institute for Health and Care Excellence
NSAID: non-steroidal anti-inflammatory drug
PCI: percutaneous coronary intervention
RR: Relative Risk
TxA_2: Thromboxane
UK: United Kingdom

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