Low-dose aspirin for the prevention of atherothrombosis across the cardiovascular risk continuum

Oriental Congress of Cardiology (OCC) 2021

Shanghai International Convention Centre and Virtual Access

The International Aspirin Foundation Symposium

Friday 28th May 2021 1-5pm

Introduction Professor Junbo Ge, Fudan University, Shanghai

Professor Junbo Ge welcomed speakers and attendees both present (25, 600) and virtual (120,000) to the International Aspirin Foundation (IAF) Symposium at the Oriental Congress of Cardiology (OCC). He introduced aspirin as the cornerstone of antiplatelet therapy with evidence for its efficacy and safety in cardiovascular disease (CVD) prevention accumulating since the 1970s.

Mechanistic insight into how aspirin prevents atherothrombosis.

Professor Carlo Patrono
Catholic University, Rome, Italy

Molecular target of aspirin's antiplatelet action and mechanism of its inactivation

Aspirin works by irreversibly inactivating the cyclooxygenase (COX) activity of the ubiquitous bifunctional enzyme, prostaglandin (PG)G/H-synthase, which catalyzes the conversion of arachidonic acid to PGG_2 (through its COX activity) and PGH_2 (through its peroxidase activity)[1]. PGH_2 is a common intermediate in the biosynthesis of different prostanoids (e.g., PGE_2, thromboxane [TX] A_2 and prostacyclin [PGI_2]), through the action of tissue-specific isomerases and synthases. Most human cells express two isoforms of the enzyme, PGG/H-synthase-1 and -2, colloquially referred to as COX-1 and COX-2[1]. While COX-1 is predominantly a constitutive enzyme, COX-2 is both constitutively expressed in some tissues (e.g., kidney and brain) and inducible, in response to inflammatory cytokines and growth factors[1]. Low-dose aspirin selectively inhibits the isoform COX-1, while higher doses of aspirin are required in order to also inhibit COX-2, which is expressed by vascular endothelial cells and can be induced in inflammatory cells.

Using a tridimensional model of COX-1 to explain the molecular details of aspirin interaction with key sites of the enzyme, Professor Carlo Patrono explained how aspirin irreversibly inactivates platelet COX-1 with two important consequences. Firstly, there is a long-lasting effect on platelet function meaning that a once-a-day regimen can be used despite the short half-life of aspirin (15-20 minutes) in the human circulation. Secondly, there is cumulative inhibition of platelet TXA_2 production resulting from repeated daily dosing with very low doses (i.e., 20-40 mg)[2].

Clinical pharmacology of platelet target inhibition

After single oral dosing in healthy subjects, there was a log-linear relationship between the aspirin dose and percentage inhibition of platelet TXA_2 production, with 100 mg achieving virtually complete suppression of platelet COX-1 activity[2]. In a four-week study of 30 mg of aspirin in healthy subjects, daily dosing achieved almost complete inhibition of platelet TXA_2 after one week and this remained stable over the 30 days of treatment. When aspirin was stopped at the end of the study, there was a time-dependent recovery of platelet function consistent with the platelet lifespan of 8-10 days[2].

Dose and dosing interval requirements for the clinical effect of aspirin

Professor Patrono discussed the vascular disorders where aspirin has been shown to be effective and the minimum effective daily dose ranging from 50 to 160 mg, with the higher dose used in trials involving patients with acute myocardial infarction or acute ischaemic stroke. Using data from the Antithrombotic Trialists' Collaboration[3], Professor Patrono showed that there is no further benefit to using higher aspirin doses than 75-150 mg daily in a chronic therapy setting. He concluded that the clinical benefit of aspirin appears to be saturable at relatively low doses, consistent with saturability of platelet COX-1 inactivation and TXA_2 suppression[4].

Does one size fit all?

The finding that inactivation of platelet COX-1 and subsequent suppression of thromboxane production are cumulative upon repeated daily dosing and saturable at doses as low as 30-40 mg daily means that a daily dose in the range of 75 to 100 mg should suit most people, and there is no convincing evidence that higher doses (e.g., 300-325 mg) are more effective than lower doses (75-100 mg). The CURRENT-OASIS 7 trial[5] is the single largest head-to-head comparison of a lower dose [75-100 mg] versus a higher dose [300-325 mg] in approx. 25,000 patients with acute coronary syndromes. The cumulative hazard ratio for the primary outcome (cardiovascular death, myocardial infarction, or stroke) at 30 days showed no difference between the two doses. Similarly, the ADAPTABLE trial was designed to test the hypothesis that a higher aspirin dose (325 mg daily) would result in a lower risk of death from any cause, hospitalization for myocardial infarction, or hospitalization for stroke (primary effectiveness endpoint) than a lower dose (81 mg daily) among approx. 15,000 patients with stable atherosclerotic cardiovascular disease (ASCVD)[6]. During a median

26-month follow-up, there was no statistically significant difference between the two aspirin doses in the risk of the primary effectiveness endpoint.

Therefore, any remaining uncertainty regarding the optimal dose of aspirin for the prevention and treatment of ASCVD, that prompted the CURRENT-OASIS 7 and ADAPTABLE investigators to randomize over 40,000 patients with acute and chronic coronary syndromes to a lower or higher dose, should now yield to a large body of evidence demonstrating saturability of the antithrombotic effect of aspirin at low doses, consistent with saturability of its molecular mechanism of action and clinical pharmacology of platelet TXA_2 inhibition[7].

Does one dosing regimen fit all?

Due to substantial interindividual variability in the rate of recovery of platelet COX-1 activity during the 24-hour dosing interval, one dosing regimen is probably not suitable for everyone. Patients who have an accelerated renewal of the drug target, because of faster platelet turnover, may require more frequent dosing (e.g., twice daily)[8]. The need for more frequent dosing has been clearly demonstrated in Essential Thrombocythemia (ET), a relatively rare myeloproliferative neoplasm with abnormal platelet production and accelerated renewal of platelet COX-1. A recent study showed that the currently recommended aspirin regimen of 75 to 100 once daily for cardiovascular prophylaxis is largely inadequate in reducing platelet activation in the vast majority of patients with ET. The antiplatelet response to low-dose aspirin can be markedly improved by shortening the dosing interval to 12 hours in this clinical setting[9].

References

1. Smith WL, Langenbach R. Why there are two cyclooxygenase isozymes. J Clin Invest 2001;107:1491-1495. doi: 10.1172/JCI13271.
2. Patrignani P, Filabozzi P, Patrono C. Selective cumulative inhibition of platelet thromboxane production by low-dose aspirin in healthy subjects. J Clin Invest 1982;69:1366-1372. doi: 10.1172/jci110576.
3. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71-86. http://dx.doi.org/10.1136/bmj.324.7329.71
4. Patrono C, García Rodríguez LA, Landolfi R, Baigent C. Low-dose aspirin for the prevention of atherothrombosis. N Engl J Med 2005;353:2373-2383. doi: 10.1056/NEJMra052717.
5. The CURRENT-OASIS 7 Investigators. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. N Engl J Med 2010;363:930-942. doi: 10.1056/NEJMoa0909475.
6. Jones WS, Mulder H, Wruck LM, et al; ADAPTABLE Team. Comparative effectiveness of aspirin dosing in cardiovascular disease. N Engl J Med 2021;384:1981–1990. doi:10.1056/NEJMoa2102137.
7. Liuzzo G, Patrono C. Are US cardiologists ADAPTABLE to considering low-dose aspirin for secondary prevention? Eur Heart J 2021; 42:2525-2526. doi:10.1093/eurheartj/ehab357.
8. Patrono C, Rocca B, De Stefano V. Platelet activation and inhibition in polycythemia vera and essential thrombocythemia. Blood 2013;121:1701-1711. doi:10.1182/blood-2012-10-429134.
9. Rocca B, Tosetto A, Betti S, et al on behalf of the ARES Investigators. A randomized double-blind trial of 3 aspirin regimens to optimize antiplatelet therapy in essential thrombocythemia. Blood 2020; 136:171-182. doi: 10.1182/blood. 2019004596.

Prevention of serious vascular events by low-dose aspirin across the cardiovascular continuum.

Professor J Michael Gaziano
Harvard University, Boston, USA

Professor Mike Gaziano reviewed three clinical case studies to illustrate his perspectives on aspirin's role in the prevention of cardiovascular events using data from both primary and secondary prevention trials.

For secondary prevention of CVD, in those with known atherosclerotic disease (e.g. prior myocardial infarction [MI] stroke, coronary artery disease [CAD], transient ischemic attack [TIA] or peripheral artery disease [PAD]) there are over 400 trials that have tested the hypothesis that platelet inhibition with aspirin lowers risk of CVD. The Antithrombotic Trialists' Collaboration (ATC)[1] reviewed 287 trials and found that compared with placebo, those assigned to aspirin or other antiplatelet agents had an approximately 22 percent reduction in the combined outcome of serious vascular thrombotic events (non-fatal MI, non-fatal stroke or vascular death) and had clear reductions in MI (34%), stroke (25%) and vascular death (15%). This was offset by a modest increased risk of bleeding. Antiplatelet therapy was protective in high-risk patients, including those with acute MI or stroke; previous MI, stroke, or transient cerebral ischemia; unstable or stable angina; PAD; or atrial fibrillation (AF) and indicated clear benefits for low-dose aspirin. Two of Professor Gaziano's case studies illustrated the types of people benefiting from aspirin for the secondary prevention of CVD.

Clinical trials showing primary prevention of cardiovascular events with aspirin are more difficult to carry out. They take longer because event rates are lower and compliance with medication is reduced over time. Prior to the more recent trials there were 12 large scale trials studying aspirin for primary CVD prevention. A meta-analysis of these studies showed a 12% reduction in vascular events[1,2] . Other subsequent meta-analyses have shown similar findings, and from an adverse event perspective there appeared to be ~ 30% increased risk in non-trivial bleeding. Cancer prevention benefits take longer to emerge. Guidelines in both the USA and Europe generally (but not consistently) recommend low-dose aspirin, with on average a class B evidence grade in higher risk individuals for primary CVD prevention. Recommendations for people with diabetes varied around the globe leading to the ASCEND trial[3] comparing CVD events prevented versus bleeding in this high-risk group. The technicalities of the analysis were difficult and showed large confidence intervals around the estimates, leading Professor Gaziano to question whether the individual sub-group analysis used within ASCEND was the best approach to assess events caused and prevented.

Low-dose aspirin in older individuals is another important area for debate. In 2009, the ATC[2] meta-analysis showed there was no difference in effect by age under or over 65. However, this study had a relatively modest number of older individuals with few over 70 years. This led the United States Preventative Services Task Force (USPSTF)[4] in 2016 to conclude that there was insufficient evidence in the 70-year and older age group to make recommendations. Providing individual patient information about the risks and benefits is important as some people may place a higher value on potential benefits and choose to take aspirin.

The ASPREE[5] trial in those ≥ 70 (or over 65 in minority groups in the US) had the composite primary end point of death, dementia or persistent physical disability and secondary endpoints of fatal and nonfatal CVD (including stroke and heart failure) Aspirin had not previously been studied for efficacy in heart failure, dementia or physical disability, with results showing no difference for the primary endpoint. The ASPREE findings are inconsistent with other trials, which may be due to the design. Results consistent with the other primary prevention studies were reductions in major adverse cardiovascular events in those taking aspirin (not statistically significant) and increased risk of bleeding.

ARRIVE[6] looked at higher risk individuals with primary outcomes including CVD death, MI, stroke, unstable angina and TIA, and safety outcomes including serious bleeding events. The study had a mean age of 64 with 70% of participants over 60 and good representation of women (approximately 30%). The CHD risk was around 14% using Framingham and the ASCVD risk score around 17%. However, the observed ASCVD event rate normalized to 10 years was around half that expected, with the likely explanation being modern medical management of other risk factors (such as lipids, blood pressure [BP]) and lifestyle advice helping reduce CVD

risk. Results showed early separation between aspirin and placebo arms, which then began to drift back leaving only a modest trend in the direction of a CVD prevention benefit with aspirin. It is suspected that many participants were non-compliant over time and people in the placebo arm were put on aspirin as their CVD risk grew. If we look at the individuals treated per protocol, we see results similar to earlier trials with a reduction in risk ~ 47% for MI.

In a meta-analysis data from these three trials were compiled with previous trials showing an 11% reduction in CVD, 6% reduction in total mortality and modest increase in bleeding events[7]. Results of this Zheng meta-analysis are strikingly similar to the USPSTF meta-analysis demonstrating that the new trials do not change the totality of evidence.

USPSTF Analyses vs. Zheng Meta-Analysis

Category	USPTF Outcome	RR (95% CI)	Zheng Outcome	RR (95% CI)
CVD	Nonfatal MI Nonfatal stroke	0.83 (0.74, 0.94) 0.86 (0.76, 0.98)	MI Stroke	0.85 (0.73-0.99) 0.81 (0.76-0.87)
Bleeding	Major extracranial Major GI Bleed Hemorrhagic stroke	1.54 (1.30, 1.82) 1.58 (1.29, 1.95) 1.27 (0.96, 1.68)	Major Bleeding Major GI Bleed ICH	1.43 (1.30-1.56) 1.56 (1.38-1.78) 1.34 (1.14-1.57)
Cancer	CRC after 10-year initiation Cancer death	0.60 (0.47, 0.76) 0.96 (0.87, 1.06)	No longterm cancer outcome data	Category
Mortality	All-cause mortality	0.95 (0.89, 1.01)	All-cause mortality	0.94 (0.88-1.01)

Bibbins-Domingo K. Ann Intern Med. 2016;164:836-845; Whitlock EP, et al. AHRQ Publication No. 13-05193-EF-1; 2015. Zheng and Roddick, JAMA. 2019;321(3):277-287

The International Polycap Study 3 (TIPS-3)[8], found low-dose aspirin plus polypill (statin and three BP-lowering medications) had the lowest number of primary events and an analysis of approx. 6000 patients comparing aspirin with placebo had results consistent with previous evidence.

Reviewing these trials, Professor Gaziano explained ASCEND shows aspirin works the same for people with diabetes, ASPREE shows aspirin does not prevent the combined outcome of dementia, disability or death and ARRIVE and the TIPS-3 suggest that aspirin does have an effect in primary disease prevention. Aspirin also appears to lose effect over time due to reduced compliance. Undertaking placebo-controlled trials in the 21st century is challenging, since many patients are placed on aspirin once they develop early signs of atherosclerosis even before they have events. These new data are consistent with previous primary prevention data. The ATT collaboration is starting an individual participant data meta-analysis that will include all 14 primary prevention trials.

In primary prevention, aspirin remains an important approach for preventing CVD. Along with other prevention strategies, benefit with aspirin can be increased by identifying accurate CV risk, with CT imaging employed when there is uncertainty. To decrease bleeding, it is important to accurately assess risk and consider using a proton pump inhibitor (PPI).

Aspirin in primary prevention

How to increase the benefit?

Pick right CVD risk level.
Consider CT imaging.
Need to accurately assess CVD risk.
Understand cancer risk

How to decrease the risk?

Accurately assess bleeding risk
PPI?

"In my assessment, aspirin remains a very important medication not only in secondary prevention, but it has an important role in primary prevention and the data has not changed materially with the addition of these four recent randomized trials and this very important drug can have a very important role to play in primary prevention. However, it does require careful discussion with the patient."

Professor Mike Gaziano OCC 2021

References

1. Antithrombotic Trialists' Collaboration (2002) Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002; 324: 71-86. http://dx.doi.org/10.1136/bmj.324.7329.71
2. Antithrombotic Trialists' Collaboration . Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomized trials. Lancet 2009; 373:1849-1860.
3. The ASCEND study Collaborative Group. Effects of aspirin for primary prevention in persons with diabetes mellitus. N Engl J Med 2018 Oct 18; 379:1529-1539. doi: 10.1056/NEjMoa1804988
4. USPSTF 2016 Aspirin use to prevent cardiovascular disease and colorectal cancer: Preventative Medicine. https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/aspirin-to-prevent-cardiovascular-disease-and-cancer
5. McNeil JJ, Nelson MR, Woods RL. Effects of aspirin on all-cause mortality in healthy elderly (ASPREE) N Engl J Med 2018; 379:1519-1528 doi:10.1056/NEJMoa1803955
6. Gaziano JM, Brotons C, Coppolecchia R et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE) : a randomized, double-blind, placebo-controlled trial. Lancet 2018 Sept 22; 392, (10152): 1036-1046. https://doi.org/10.1016/S0140-6736(18)31924-X
7. Zheng SL and Roddick AJ. Association of aspirin use for primary prevention with cardiovascular events and bleeding events. A systematic review and met-analysis. JAMA 2019, Jan 22; 321(3):277-287. doi:10.1001/jama.2018.20578
8. Yusuf S, Joseph P, Dans A et al. Polypil with or without aspirin in persons without cardiovascular disease. N Engl J Med 2021 Jan 21; 384:216-228. doi:10.1056/NEjMoa2028220

Prevention of serious vascular events by low-dose aspirin across the cardiovascular continuum in China.

Professor Xiaoying Li
Chinese PLA General Hospital, Beijing, China

Progress in CVD Epidemiology in China

Cardio-cerebral vascular disease represents the leading cause of death in the Chinese population over the last decade and its incidence in China is expected to continuously increase in the next decade.

China has a high incidence of CHD and stroke with the lifetime risk of stroke ranking first in the world. Data from the Blue Book[1] on the current situation of CVD and treatment in China shows the age-standardised incidence of CHD in 2016 was 228.1/100,000 and that the estimated number of new onset CHD cases 3.1 million. In the Chinese population over 25 years of age, the lifetime risk of having an ischaemic or haemorrhagic stroke was 39.3%, ranking first in the world[2].

The proportion of Chinese adults with a 10-year risk of fatal CVD ≥ 10% is among the highest in the world, with 33% of men and 28% of women falling into this high-risk group[3]. In the past five decades, except for a slight decrease in smoking rates, the prevalence of CVD risk factors (such as hypertension, diabetes, obesity and dyslipidaemia) has risen, increasing the number of CVD patients despite advances in medicine[4].

The role of aspirin in secondary prevention

Antiplatelet therapy strategies in the long-term secondary prevention for ASCVD are evolving. Professor Xiaoying Li provided an overview of antithrombotic treatments and trials for the secondary prevention of CHD demonstrating how long-term aspirin-based antiplatelet therapy is core, with a second anti-platelet drug added to cover the increased CVD risk period post percutaneous coronary intervention (PCI) or acute coronary syndrome (ACS) for 6-12 months. The duration of antiplatelet therapy should be reduced or prolonged after consideration of bleeding and ischaemic risk[5].

Previous evidence comparing aspirin with a $P2Y_{12}$ inhibitor is sparse with equivocal results. In 2020, a large meta-analysis in the Lancet reviewed nine RCT trials with 42,108 patients, 21,043 on a $P2Y_{12}$ inhibitor and 21,065 on aspirin. This is the first meta-analysis which uses data for ticagrelor. The results showed no significant difference between aspirin and the $P2Y_{12}$ inhibitor for all-cause death/vascular death and stroke. The risk of bleeding, major bleeding, fatal bleeding and intracranial bleeding was similar in both groups. The $P2Y_{12}$ inhibitors showed only a weak benefit in reducing MI, with a number needed to treat (NNT) of 244. These results support the use of aspirin in secondary prevention because there is better accessibility and compliance, fewer side effects (especially compared with ticagrelor, less variability in effect versus clopidogrel and superior cost effectiveness)[6,7].

In stroke or TIA, aspirin is also well established as a core therapy with more recent studies using dual antiplatelet therapy (DAPT) with clopidogrel and/or with the addition of the $P2Y_{12}$ inhibitor ticagrelor used in the acute phase and aspirin continued long-term[8-11]. Guidelines recommend that aspirin-based antiplatelet therapy should be given as early as possible in the acute phase of ischemic stroke[12-14].

Changes in the role and progress of aspirin in primary prevention

Whilst early trials showed benefits of low-dose aspirin in primary prevention for the general population, this has become the subject of debate due to improved prophylaxis in recent years. With better control of risk factors in Europe and the US, CVD in the general population has decreased. The ARRIVE[14], ASCEND[16] and ASPREE[17] trials in 2018 aroused new controversy on the role of aspirin in primary CVD prevention. However, a meta-analysis[18] which included 13 primary prevention randomised controlled trials (RCTs), as of November 2018, with 116,225 patients and a median follow up of 5 years and an average 10-year CV risk of 9.2%, showed that aspirin significantly reduced CV events by 11%, MI by 15% and ischemic stroke by 19%. This meta-analysis confirms that the net benefit remains in addition to other routine preventative measures, such as statins[18]. The 2019 guidelines on

primary prevention of ASCVD in the US and China have been updated to reflect this.

The TIPS-3 study[19], an international, randomised placebo-controlled trial, enrolled subjects with elevated INTERHEART risk scores, to one of four arms; 1) aspirin 75 mg daily, 2) polypill daily, 3) polypill and aspirin 75mg daily and 4) vitamin D 60000 IU monthly, with a median follow up of 4.4 years. The polypill consisted of atenolol 100 mg, ramipril 10 mg, hydrochlorothiazide 25 mg and simvastatin 40 mg. The primary endpoints of the study were cardiovascular death, MI, stroke, resuscitated cardiac arrest, heart failure or revascularisation. The results showed that in comparison to placebo the polypill reduced the cumulative incidence of first primary events by 21%, and polypill + low-dose aspirin by 31% [19].

Whilst aspirin compared with no aspirin does increase major bleeding by 50% (1.47% versus 1.02%; P<0.001), intracranial bleeding (including haemorrhagic stroke) by 32% (0.42% versus 0.32%; P=0.001) and major GI bleeding by 52% (0.80% versus 0.54%; P<0.001), it does not appear to increase fatal bleeding with a similar incidence of fatal bleeding seen in the five studies reporting it (0.23% versus 0.19% ;RR:1.09; 95% CI:0.78-1.55; P=0.6)[18].

The 2019 ACC/AHA guidelines on primary prevention of CVD identify seven major measures to prevent CVD[20]:

- Cholesterol management in those at risk with a statin,
- Exercise (150 minutes of moderate intensity or 75 minutes of vigorous intensity weekly),
- Hypertension – BP maintained below 130/80 mmHg,
- Type 2 diabetes mellitus (T2DM) – diet, exercise, metformin first line and SGLT-2 inhibitor or GLP-1 receptor agonist 2nd line
- Diet – emphasize the intake of vegetables, fruits, nuts, legumes, fish, and whole grains,
- Smoking cessation,
- Taking low-dose aspirin for high-risk patients.

Decision making about taking aspirin for primary CVD prevention should also include consideration of family history of a premature MI, inability to achieve lipid or BP targets, or a significant elevation in the coronary artery calcium score, as well as tailoring decisions to patient preferences. Aspirin is not routinely recommended for primary CVD prevention in those over 70 years or for those with increased bleeding risk[20].

In the last decade, multiple Chinese guidelines and expert consensus statements have recommended aspirin for the primary prevention of CVD. However, with increasing clinical evidence over recent years these recommendations no longer fully apply leaving some confusion among clinicians and patients. The 2019 Chinese guidelines on cardiovascular risk assessment and management recommend aspirin for primary prevention of ASCVD in clearly defined patient populations. The consensus statement includes measures to take before prescribing, and identifies the population recommended for and against primary aspirin prevention therapy[21].

The four measure to take before prescribing low-dose aspirin in primary prevention of CVD are:

- To assess the risk/benefit ratio and exclude those with a high risk of bleeding- reassess during usage and solve issues in a timely manner,
- To reduce risk by identifying and treating active pathological changes in advance (e.g. Helicobacter pylori and consider prophylactic PPI or H_2receptor agonists),
- To adhere to a healthy lifestyle and positively control BP, blood sugar and blood lipid levels,
- To communicate with patients and obtain their consent prior to prescribing.

In the Chinese guidelines the high-risk populations recommended to consider taking low-dose aspirin (75-100 mg/day) for primary CVD prevention are adults aged 40-69 years if the 10-year expected risk of ASCVD is 10% or more for their initial risk assessment and with three or more major risk factors that remain poorly controlled or difficult to change after active treatment intervention, e.g. family history of early onset CVD. According to the 2017 Chinese guidelines for CVD prevention[22], the main risk factors include – hypertension, diabetes, dyslipidaemia, smoking, family history of premature CVD in first degree relative < 50 years, obesity with a BMI >28 kg/m2, coronary artery calcification (CAC) score of 100 or more, or non-obstructive coronary artery stenosis (<50%) (N.B. coronary imaging examination of primary prevention subjects is not routinely recommended).

Populations not recommended for low-dose aspirin primary CVD prevention are those <40 years or ≥ 70 years, people whose bleeding risk is assessed as greater than their thrombosis risk, and those at higher risk of bleeding due to:

- Medication,
- GI bleeding, peptic ulcer or history of bleeding in other sites,
- Thrombocytopenia, coagulopathy,
- Severe liver disease,
- Chronic kidney disease (CKD) stage 4-5,
- Uneradicated *H. Pylori*,
- Uncontrollable hypertension.

It is important to note that the guidelines recommending treatment are regularly reviewed in order to continue to dynamically assess risk-benefit ratio.

CVD imposes a heavy burden in China and urgently needs to be prevented and treated. Aspirin is the cornerstone in the secondary prevention of ASCVD, while its role in primary prevention is controversial. The benefit of aspirin in the primary prevention of CVD is recognised in US and China with clear criteria. Aspirin is underused among high-risk populations in China, with the hope the 2019 Chinese expert consensus statement on aspirin application in primary prevention of CVD will promote uptake.

References

1. Yong H. China Cardiovascular Disease Prevention and Control Status Blue Book [M] Beijing People's Medical Publishing House 2019
2. The GBD 2016 Lifetime Risk of Stroke Collaborators. Global, Regional, and Country-Specific lifetime risks of stroke, 1990 and 2016. N Engl J Med 2018, Dec 20; 379(25):2429-2437. doi:10.1056/NejMoa1804492
3. Hajifathalian K, Ueda P, Lu Y et al. A novel risk score to predict cardiovascular disease risk in national populations (Globorisk): a polled analysis of prospective cohorts and health examination surveys. Lancet Diabetes Endocrinol 2015 May; 3(5):339-55. doi: 10.1016/S2213-85871(15)00081-9
4. Li H, Ge J. Cardiovascular disease in China: Current status and future perspectives. Int J Cardiol Heart Vasc.2014 Dec 30;6: 25-31. Dio:10.1016/j.ijcha2014.10.002
5. Steffel J, Verhamme P, Potpara T et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin k antagonist oral anticoagulants in patients with atrial fibrillation. European Heart Journal 2018;39:1330-1393. https://doi.org/10/1093/eurheartj/ehy136
6. Chiarito M, Sanz-Sánchez J, Cannata F et al. Monotherapy with a $P2Y_{12}$ inhibitor or aspirin for secondary prevention in patients with established atherosclerosis: a systematic review and meta-analysis. Lancet 2020 May 9;395(10235):1487-1495. https://doi.org/10.1016/S0140-6736(20)30315-9
7. Byrne RA and Colleran R. Aspirin for secondary prevention of cardiovascular disease. Lancet 2020 May 9; 395(10235):1462-1463. doi:10.1016/S0140-6736(20)30799-6
8. CHANCE Wang Y. Wang Y, Zhao X et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl j Med 2013;369:11-19
9. SOCRATES Johnston SC, Amarenco P, Albers GW et al. Ticagrelor versus aspirin in acute stroke or transient ischemic attack. N Engl j Med 2016; 375:35-43
10. POINT Johnston SC, Easton D, Farrant M et al. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. N Engl J Med 2018; 379:215-225
11. THALES Johnston SC, Amarenco P, Denison H et al. Ticagrelor and aspirin or aspirin alone in acute ischemic stroke or TIA. N Engl J Med 2020; 383:207-217
12. Royal College of Physicians Intercollegiate Stroke Working Party. National clinical guideline for stroke, October 2016. https://www.rcplondon.ac.uk/guidelines-policy/stroke-guidelines
13. National Institute of Clinical Excellent (NICE) Guideline NG128 (May 2019): Stroke and transient ischaemic attack in the over 16s: diagnosis and initial management. http://www.nice.org.uk/guidance/ng128
14. National Institute of Clinical Excellent (NICE) Intervention Evidence Review: Aspirin for suspected transient ischaemic attack (TIA): Review question: Should people with a suspected TIA be advised to take aspirin prior to assessment in a TIA clinic? https://www.nice.org.uk/guidance/ng128/evidence/a-aspirin-pdf-6777399566
15. Gaziano JM, Brotons C, Coppolecchia R et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE) : a randomized, double-blind, placebo-controlled trial. Lancet 2018 Sept 22; 392, (10152): 1036-1046. https://doi.org/10.1016/S0140-6736(18)31924-X
16. The ASCEND study Collaborative Group. Effects of aspirin for primary prevention in persons with diabetes mellitus. N Engl J Med 2018 Oct 18; 379:1529-1539. doi: 10.1056/NEjMoa1804988
17. McNeil JJ, Nelson MR, Woods RL. Effects of aspirin on all-cause mortality in healthy elderly (ASPREE) N Engl J Med 2018; 379:1519-1528 doi:10.1056/NEJMoa1803955
18. Zheng SL and Roddick AJ. Association of aspirin use for primary prevention with cardiovascular events and bleeding events. JAMA 2019; 321(3):277-287. doi:10.1001/jama.2018.20578
19. Yusuf S, Joseph P Dans A. Polypill with or without aspirin in persons without cardiovascular disease. N Engl J Med 2021; 384:216-228. doi:10.1056NEJMoa2028220
20. Arnett DK, Blumenthal RS, Albert MA et al. 2019 ACC/AHA Guideline on the primary prevention of cardiovascular disease: A report of the American college of cardiology/American heart association task force on clinical practice guidelines. J.Am.Coll. Cardiol 2019 Sept, 74(10)e177-e232. https://www.jacc.org/doi/full/10.1016/j.jacc.2019.03.010
21. Xiao-Ying Li, Zhong-Wei shi, Dong Zhao et al. 2019 Chinese expert consensus statement on aspirin application in primary prevention of cardiovascular disease. Chin Med J (Engl). 2020 May 20;133(10):1221-1223.
22. Writing Group of Chinese Cardiovascular Disease Prevention Guide (2017), Editorial Board of Chinese Journal of Cardiovascular Diseases. Chinese cardiovascular disease prevention guide (2017). Chin J Cardiovasc Dis 2018;46:10–25.

Discussion of the first three lectures

Professors Carlo Patrono and Mike Gaziano discussed the ADAPTABLE trial which they thought should settle a long debate on the optimal dose of aspirin for cardiovascular prevention. They agreed it is good to see large scale trials such as this being carried out for aspirin and interesting to note the pragmatic way this trial was conducted using electronic records.

Professor Patrono commented on the utility of Chinese guidelines, especially the four measures to take before prescribing aspirin for primary prevention of CVD. He noted differences between the most recent Chinese and US guidelines on primary CVD prevention in the way they define those not recommended for aspirin. In the 2019 Chinese guidelines, populations not recommended for low-dose aspirin primary CVD prevention are those <40 years or ≥ 70 years, because there is not enough evidence in these age groups. The US guidelines, however, state that low-dose aspirin could harm those older than 70. Professor Patrono questioned whether evidence from ASPREE, as a single study, was sufficient to justify this conclusion. An ongoing, individual-participant-data meta-analysis of the 14 primary prevention trials may provide an answer to this controversy.

Professor Gaziano replied that we need to rethink guidelines for many preventative strategies in older patients, including BP control and statin use. As we age our CVD risk rises dramatically making benefit from preventative strategies more important. Professor Gaziano said he considers evidence from ASPREE to be an outlier due to its unconventional primary outcome. Instead of age, it may be better to consider fitness versus frailty of individuals when planning CVD preventative strategies. The Chinese guidelines provide more emphasis on reassessing dynamically risk versus benefits to incorporate what happens as you age including an increased risk of both thrombotic and bleeding events. A frailty assessment is important, there are frail 65-year-olds with four-year life expectancies versus fit 85-year-olds with 10-year life expectancies. Age is no longer the only marker of future longevity, making it over-simplistic to simply switch off preventative strategies. Instead, it is important to consider the increased benefit of CVD prevention with increasing age and have meaningful discussions with individuals to help assess preventative strategies for a long and productive life.

Professor Rothwell agreed that past experience has shown each time it has been argued treatments do not work at older ages this has been proved incorrect. Although some treatments do become more hazardous with increasing age there are strategies to reduce this. Bleeding risk does increase with age and bleeding can become more severe and have more consequences. It is therefore important to prevent bleeding, with for example the use of a PPI. It is important not to dismiss treatment benefits just because there is the potential for some harm.

Following a question on aspirin resistance, Professor Patrono argued that this phenomenon does not really exist as it most likely reflects patient's non-compliance. If you witness aspirin administration and measure platelet thromboxane production 24 hours after dosing, he explained, you will not find any aspirin resistance. There may, however, be variation in the duration of the antiplatelet effect of aspirin due to differences in platelet turnover, but most individuals will show profound and persistent suppression of thromboxane production after aspirin administration. One notable exception to this rule is Essential Thrombocythemia, a rare myeloproliferative neoplasm, as he explained during his presentation.

Professor Gaziano added that the effect of aspirin is confined to the population taking it and disappearance of that effect occurs rapidly when participants stop.

> *'Resistance is not a mechanistic or physiological factor it is a resistance to opening the bottle and taking the pill that's the problem'*
>
> Professor Gaziano

Professor Rothwell in his trials noted a time-dependent loss of efficacy most likely reflecting a time-dependent reduction in drug compliance. Trials show most benefit occurs in the first few years, but when you tease out the effect in people remaining on aspirin this effect does not disappear. It is easy to forget how much impact non-compliance has overtime. Towards the end of some studies 60% of participants are no longer taking study treatment.

Professor Gaziano explained the actual effect of aspirin in primary prevention was similar to shorter higher compliance secondary prevention trials if time periods with good medication compliance were included. Due to non-compliance the actual effect of aspirin may be larger, he said, than currently seen in primary prevention trials, making it important to compare primary and secondary prevention trials based on same duration rather than events over a differing time frame.

Low-dose aspirin for the secondary prevention of stroke.

Professor Peter Rothwell
University of Oxford, Oxford, UK

There are over 13.7 million new strokes worldwide each year, with individuals having a lifetime risk of 20%. TIA and minor stroke comprise 70% of all acute cerebrovascular events and often herald an impending major stroke, with seven-day risk of major stroke as high as 10%[1,2]. However, urgent medical assessment and treatment are very effective in preventing early recurrent major stroke. The EXPRESS study showed urgent investigation/treatment after TIA and minor stroke reduced the 90-day risk of major recurrent stroke by about 80% - one of the most effective interventions in medicine[3,4]. This benefit was achieved by changing care from non-urgent general practice prescribing to urgent assessment and treatment using existing medications. Other studies show similar feasibility and results[5].

However, the EXPRESS Study intervention was multifactorial, including aspirin, other antiplatelet drugs in high-risk patients, BP-lowering drugs and statins, and it was uncertain which component had reduced stroke risk. Aspirin was given to all patients, but the effect of aspirin on recurrent stroke risk had long been considered modest, based on trials in acute major stroke and in long-term prevention after TIA/minor stroke. By detailed re-analysis of individual patient data from these trials, it was shown the acute benefits of aspirin in TIA/minor stroke had been considerably underestimated, showing that aspirin alone reduced 90-day risk of disabling recurrent stroke by 80% and of all stroke by 60%[6].

Despite education campaigns many patients do not seek help immediately, which is frustrating given the enormous benefits of aspirin. To help with this, Professor Rothwell has worked with guideline writers to recommend low-dose aspirin immediately after TIA and minor stroke, prior to specialist assessment/investigation[7-9]. First-line healthcare professional (e.g. paramedics, primary care physicians, and emergency physicians) should give aspirin and have adequate supplies in order to do so and recommendations for immediate use prior to specialist assessment/investigation is also now supported in online advice to the general public[9,10,11].

Aspirin is recommended after TIA and minor stroke in same way it is used after acute chest pain or suspected MI, with advice to call 999 and take an aspirin.

Patients with minor stroke and high-risk TIAs usually require a second antiplatelet drug for a few weeks in addition to aspirin. Benefits of short-term dual treatment have been demonstrated in several major international randomised trials[12,13,14,15]. Use of the ABCD2 score (2) to identify high-risk TIA patients for dual antiplatelet treatment is now recommended in most guidelines[9,16,17].

Aspirin is also recommended for life-long use in the secondary prevention of vascular events. However, benefits in trials of aspirin appear to diminish with increasing duration of follow-up[6]. Recent analysis of detailed individual patient data from secondary prevention aspirin trials after TIA or stroke[18,] showed that the diminishing effects on major vascular events on intention-to-treat analysis was mainly explained by cumulative withdrawal from allocated treatment. Benefit was evident in patients who remained on trial treatment. One trial having follow-up extended beyond three years[19], showed cumulative benefit to at least three years for patients who remained on allocated treatment, sustained to six years.

One study performing a time course analysis showed in the first six weeks aspirin use significantly (P<0.0001) reduced the risk and severity of early recurrent stroke after TIA attack and ischemic stroke compared with placebo[18]. In the 6-12-week period, a further significant reduction was seen (P<0.0001) but benefit was less easy to discern after 12 weeks (P<0.85). In fact, there was an acute effect with aspirin similar to the EXPRESS and SOS TIA study. Most events in the RCTs, however, occur after 12 weeks and by considering the data together the more dramatic impact of aspirin in the acute phase is masked. This early 12-week acute effect is highly consistent across all the trials (UKTIA, SALT, ESPS1, ESPS2 and eight small trials) and is statistically significant in every trial and highly significant in the pooled analysis (P<0.0001) with a greater than 50% relative risk reduction with aspirin versus control in the acute phase[18]. Professor Rothwell and his team also looked at the severity of recurrent ischaemic stroke for aspirin prophylaxis versus control in the first six and 12 weeks after randomisation in secondary prevention trials following TIA and ischaemic stroke. In the aspirin group they found fewer major strokes, less mortality and fewer very disabling strokes and more patients with very few or no symptoms after the event. Such findings suggest that not only was aspirin reducing the risk of stroke it also reduced severity in those first few weeks.

Aspirin shows a 70-80% reduction in risk of disabling stroke up to 12 weeks, benefits as dramatic as those found in acute treatment trials such as EXPRESS and SOSTIA. The effects are considered more likely to be due to aspirin rather than a statin or BP reduction in the acute phase[18].

Low-dose aspirin for secondary stoke prevention is highly effective in the acute phase, with a 60% reduction in 90-day incidence of recurrent ischaemic stroke, 70% reduction in 90-day disabling recurrent ischaemic stroke and even greater benefits when DAPT is used (a further 20% reduction). In the long-term, aspirin is moderately effective at reducing future events.

Guidelines tend to recommend antiplatelets for life due to evidence of a high long-term risk [20]. This long-term CVD versus bleeding risk has been investigated[21], in a population-based cohort study of age specific risk, severity, time-course and outcome of bleeding in people on long term antiplatelet treatment after vascular events. Results showed that risk of bleeding does increase with age and can be more disabling in elderly frail people. If aspirin is required long term in elderly frail individuals, consider reducing the bleeding risk with a co prescription of a PPI.

Looking at the three largest trials, - UKTIA, ESP2, SALT [19,23,24] - pooled data show a similar picture with initial benefit in the first six months on treatment and a longer-term benefit observed for those staying on treatment of 18-20% reduction in major vascular events, supporting long-term treatment.

Professor Rothwell concluded that long-term preventative treatment with low-dose aspirin is moderately effective giving a 20% long-term reduction in major vascular events, but that compliance is important, and individuals may require co prescription of a PPI if GI bleeding risk is increased. Aspirin is also highly effective in the acute phase. Current guidelines - to start aspirin immediately and continue lifelong - are correct.

References

1. Coull A, Lovett JK, Rothwell PM, on behalf of the Oxford Vascular Study. Population based study of early risk of stroke after a transient ischaemic attack or minor stroke: implications for public education and organisation of services. BMJ 2004; 328:326-328.
2. Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, Sidney S. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet 2007; 369:283-92.
3. Rothwell PM, Giles MF, Chandratheva A, Marquardt L, Geraghty O, Redgrave JNE, Lovelock CE, Binney LE, Bull LM, Cuthbertson FC, Welch SJV, Bosch S, Carasco-Alexander F, Silver LE, Gutnikov SA, Mehta Z, on behalf of the Early use of Existing PREventive Strategies for Stroke Study. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. Lancet 2007; 370:1432-42.
4. Luengo-Fernandez R, Gray AM, Rothwell PM. Effect of urgent treatment for transient ischaemic attack and minor stroke on disability and hospital costs (EXPRESS study): a prospective population-based sequential comparison. Lancet Neurol 2009;8:235-43.
5. Lavallée PC, Meseguer E, Abboud H et al. Transient ischaemic attack with round-the-clock access (SOS-TIA): feasibility and effects. Lancet Neurol. 2007;6:953-960.
6. Rothwell PM, Algra A, Chen Z, Diener HC, Norrving B, Mehta Z. Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials. Lancet 2016; 388: 365-75.
7. Royal College of Physicians Intercollegiate Stroke Working Party. National clinical guideline for stroke, October 2016. https://www.rcplondon.ac.uk/guidelines-policy/stroke-guidelines
8. National Institute of Clinical Excellent (NICE) Guideline NG128 (May 2019): Stroke and transient ischaemic attack in the over 16s: diagnosis and initial management. http://www.nice.org.uk/guidance/ng128
9. National Institute of Clinical Excellent (NICE) Intervention Evidence Review: Aspirin for suspected transient ischaemic attack (TIA): Review question: Should people with a suspected TIA be advised to take aspirin prior to assessment in a TIA clinic? https://www.nice.org.uk/guidance/ng128/evidence/a-aspirin-pdf-6777399566
10. Australian Stroke Foundation Guidelines (downloaded 8/10/2020) https://informme.org.au/en/Guidelines/Clinical-Guidelines-for-Stroke-Management
11. Patient information: NHS Website, Transient ischaemic attack (TIA) https://www.nhs.uk/conditions/transient-ischaemic-attack-tia
12. CHANCE Wang Y. Wang Y, Zhao X et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl j Med 2013;369:11-19

13. SOCRATES Johnston SC, Amarenco P, Albers GW et al. Ticagrelor versus aspirin in acute stroke or transient ischemic attack. N Engl j Med 2016; 375:35-43

14. POINT Johnston SC, Easton D, Farrant M et al. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. N Engl J Med 2018; 379:215-225

15. THALES Johnston SC, Amarenco P, Denison H et al. Ticagrelor and aspirin or aspirin alone in acute ischemic stroke or TIA. N Engl J Med 2020; 383:207-217

16. Clinical guidelines: Liu L, Chen W, Zhou H, et al. Chinese Stroke Association guidelines for clinical management of cerebrovascular disorders: executive summary and 2019 update of clinical management of ischaemic cerebrovascular diseases. Stroke & Vascular Neurology 2020; 5.

17. Fonseca AC, Merwick A, Dennis M et al. European Stroke Organisation (ESO) guidelines on management of transient ischaemic attack. European Stroke Journal (published online 16 March 2021).

18. Rothwell P. Algra A. Chen Z. et al. Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials. Lancet 2016, May 18; 388(10042): 365-375. https://doi.org/10.1016/S)140-6736(16)30468-8

19. Farrell B, Godwin J, Richards S et al The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. J Neurol Neurosurg Psychiatry. 1991 Dec;54(12):1044-54. doi:10.1136/jnnp.54.12.1044

20. Clark TG. Murphy MFG and Rothwell PM. Long term risk of stroke, myocardial infarction, and vascular death in 'low risk' patients with a non-recent transient ischaemic attack. J Neurol Neurosurg Psychiatry 2003; 74: 577-580.

21. Li L. Geraghty OC, Mehta Z., Rothwell PM et al. Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study. Lancet 2017, Jun 13, 390(10093): 490-499 doi:https://doi.org/10.1016/S0140-6736(17)30770-5

22. Diener HC, Cunha L, Forbes C European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurol Sci. 1996 Nov;143(1-2):1-13. doi:10.1016/s0022-510x(96)00308-5

23. The SALT Collaborative Group. Swedish Aspirin Low-Dose trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular events. Lancet 1991 Nov 30:338(8779):1345-9.

Discussion

Addressing dual antiplatelet therapy in the acute phase where risk of recurrent stroke is high, Professor Rothwell said the Chinese CHANCE trial - looking at aspirin plus clopidogrel versus aspirin alone - found the combination for a few weeks significantly reduced risk of recurrent stroke. Although adding a second drug to aspirin for three to four weeks after a TIA or minor stroke does increase risk of bleeding, overall benefit of dual therapy can be considered to outweigh risks.

In the US, a few years later, the POINT trial showed the same result. Professor Rothwell explained that if you 'tease out' time for hyper acute risk of CVD and risk of bleeding the optimal duration of dual treatment is about three weeks after TIA and minor stroke, beyond that risk of bleeding probably matches or exceeds benefit of dual versus monotherapy. When asked about considering the use of lower dose clopidogrel to reduce risk bleeding Professor Rothwell said he felt the best option is to offer a PPI.

Professor Patrono added that small asymptomatic lesions of the gastrointestinal mucosa are common and if patients take drugs interfering with haemostasis (such as any antiplatelet or anticoagulant drug) they increase risk of bleeding from those pre-existing lesions.

As yet, explained Professor Rothwell, there is no trial addressing when to stop aspirin after a TIA or stroke, although evidence suggests if patients continue aspirin they benefit from a continued reduction in the risk of CVD events which persists for the duration of trials. Stopping aspirin increases risk, evidenced from aspirin withdrawal in trial data.

Dual-pathway inhibition for secondary antithrombotic prevention in cardiovascular disease.

Professor Wei-Guo Fu
Fudan University, Shanghai, China

Current trends diagnosis and treatments of CAD+PAD

Over the past 30 years prevalence of CVDs in China has been on the rise. It is estimated that there were 93,808 million patients with CVDs in China in 2016. Among them 22,904 million suffered from ischaemic heart disease, 24,098 million from ischaemic stroke and 22,118 million from PAD. The mortality rate of patients with CVD in China was 307.9 per 100,000 in 2016 and the mortality rate for ischaemic heart disease has increased by 25.3% over the last 30 years[1].

CAD, cerebrovascular disease and PAD represent the same type of atherosclerotic disease manifested in different vascular beds. They have a common pathological basis; with increasing age the arteries develop fatty streaks followed by fibrous plaques then atherosclerotic plaques and finally plaque rupture/cleavage and thrombosis. During the plaque stage symptoms, such as stable angina pectoris and intermittent claudication, can occur.

Atherosclerotic disease of different vascular beds often coexists. The REACH registry showed[2] nearly 25% of patients with CAD also have arterial thrombotic lesions in other arterial regions, 61.5 % of patients with PAD had comorbidities of other vascular beds and 24.7 % of patients with CAD had comorbidities of other vascular beds. Patients with CAD and PAD have a higher risk of CV events and death versus CAD alone[3].

Patients with lower extremity artery disease (LEAD) are also at high risk of CV events with the risk of 10-year CVD events doubled with an ankle brachial index [ABI] ≥ 0.9[4]. Intermittent claudication (IC) is associated with a higher risk of five-year CVD events and death[5] and 20% of patients with IC had non-fatal MI or stroke within five years and 30% of patients died within five years[6].

PAD is a serious medical challenge, with global burden of PAD estimated at 236 million[7] and a 6.6% prevalence of PAD in Chinese subjects over the age of 35 years [Wang Z et al. 2019]. There is very low rates of awareness, revascularization and control in Chinese PAD patients[8] . Most PAD symptoms are insidious and easily overlooked, making disease screening important in high-risk groups. The 2017 ESC PAD treatment guidelines point out that only around 1/5-1/3 of patients with LEAD had IC or other symptoms of their lower extremity[6]. Imaging enables rapid screening and diagnosis of PAD.

Challenges and exploration of antithrombotic strategies for CAD + PAD

The long-term holistic management goal and strategy for patients with CAD and PAD is vascular protection. It is important to both reduce the risk of adverse CV events as well as improving limb symptoms and reducing risk of adverse limb events. Vascular protection strategies include healthy lifestyle, healthy diet, physical activity, weight control and psychosocial support, along with antithrombotic strategies, and lipid, BP and blood glucose control.

Single antiplatelet therapy is the primary antithrombotic strategy for prior chronic CAD/PAD[6,9,10].

New opportunities presented by DPI for antithrombotic strategies in patients with CAD + PAD

Dual-pathway inhibition (DPI) for antithrombotic strategies, anticoagulation and antiplatelet therapy, have synergistic effects in inhibition of atherothrombosis[11,12]. The COMPASS study determined the efficacy and safety of rivaroxaban 5 mg twice daily; rivaroxaban 2.5 mg twice daily and aspirin 100 mg once daily; or aspirin 100 mg alone in reducing risk of MI, stroke and CV death in patients with CAD or PAD. The study population had 91% CAD and 27% PAD. Due to the overwhelming efficacy shown in the rivaroxaban 2.5 mg twice daily and aspirin 100 mg once daily group the study was terminated one year earlier than expected in February 2017[13,14,15].

Rivaroxaban 2.5 mg twice daily combined with aspirin for chronic PAD reduces major adverse cardiac events

(MACE) by 28% and major adverse limb events (MALE) by 46%[16].

The safety endpoints for COMPASS did show increased bleeding events in the DPI antithrombotic group but no increases in fatal bleeding, vital organ bleeding or intracranial haemorrhage[13]. Also, the longer DPI antithrombotic therapy is administered the greater benefits seen, and MACE events reduced, with no increased risk of bleeding[17].

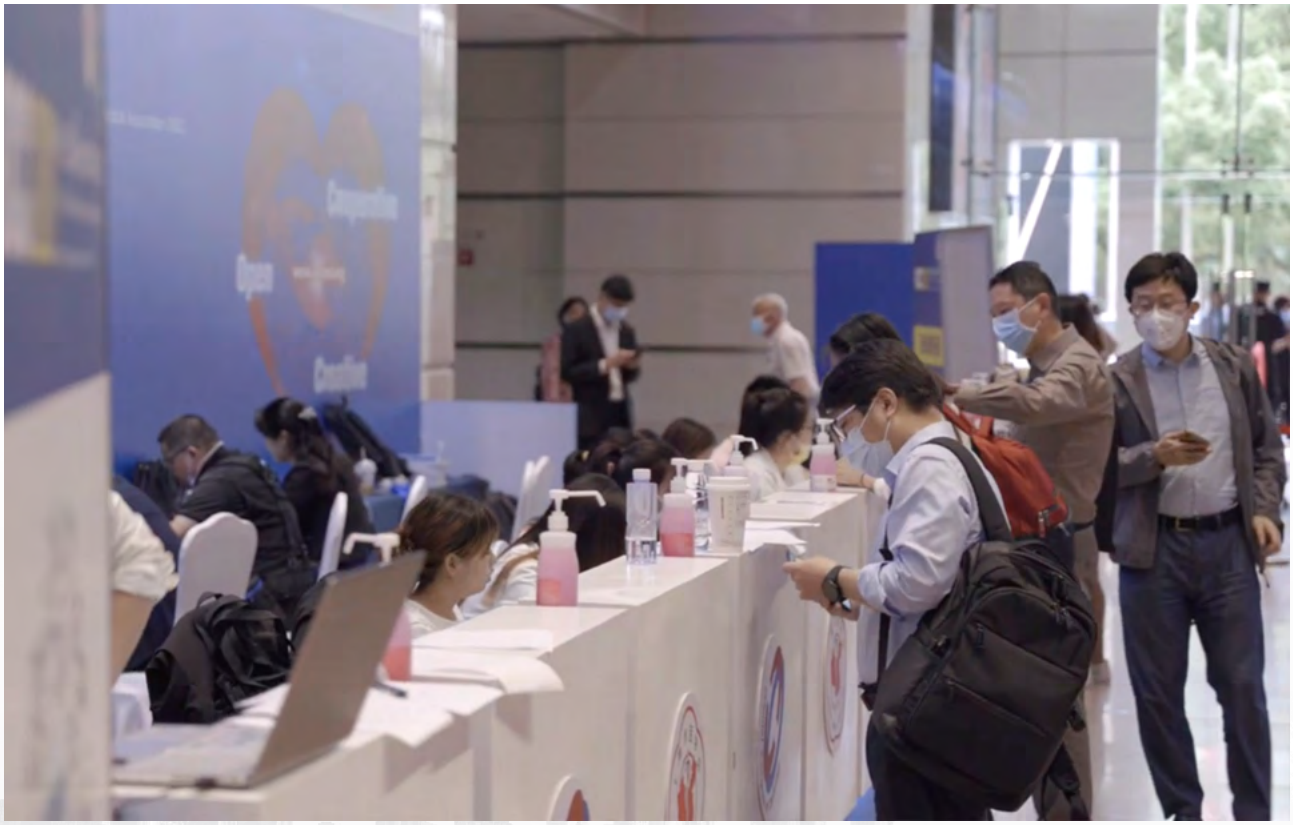
Rivaroxaban 2.5 mg twice daily combined with aspirin showed good efficacy and safety in CAD, which nearly halved ischaemic/cryptogenic stroke events. There were 1919 participants in this study with CAD defined as 50% or more carotid stenosis that is asymptomatic or required carotid endarterectomy/carotid stenting. Rivaroxaban combined with aspirin reduced ischemic/cryptogenic stroke events by nearly half compared with aspirin alone (68[0.7% per year] vs 132 [1.4% per year]); HR, 0.51; 95% CI (0.38 to 0.68); P<0.0001)[16,18].

An update in the 2019 ESC CCS guidelines on antithrombotic therapy based on the COMPASS study recommends rivaroxaban 2.5 mg twice daily with aspirin for secondary prevention in patients with diffuse multi vessel CAD + PAD if they were not at high risk of bleeding events[9].

Rivaroxaban 2.5 mg twice daily combined with aspirin for PAD after revascularization significantly reduces MACE/MALE by 15% without significantly increasing major bleeding according to the Thrombolysis in Myocardial Infarction (TIMI) classification (VOYAGER)[19]. The primary safety endpoint of incidence of TIMI major bleeding increased in the rivaroxaban 2.5 mg twice daily and aspirin group but not to the extent of showing a significant difference and there was no increase in incidence of intracranial haemorrhage or fatal bleeding in this dual therapy group[19].

The VOYAGER and COMPASS trials confirm the use of rivaroxaban 2.5 mg twice daily and aspirin for full PAD management whether there is symptomatic PAD or recent revascularisation (interventional or bypass). These two major RCTs both confirmed that rivaroxaban plus aspirin for full PAD management can consistently reduce the risk of MACE and MALE, without increasing intracranial haemorrhage or fatal bleeding.

In summary, the risk of CV events and death in patients with chronic CAD and PAD are increased and this requires urgent attention. PAD has an insidious onset and can easily escape diagnosis in patients. ABI and vascular ultrasound enable rapid PAD screening for high-risk patients. The COMPASS study demonstrated positive benefits for DPI in high-risk patients with chronic CAD, PAD and CAD with PAD. The latest published VOYAGER study provided new evidence for DPI antithrombotic therapy to help achieve effective management of PAD patients. Rivaroxaban 2.5 mg twice daily plus low-dose aspirin provides optimised DPI antithrombotic therapy for patients with high ischemic risk chronic CAD and PAD and this is recommended by latest CCS and PAD-related guidelines.



References

1. Liu S , Li Y , Zeng X et al. Burden of cardiovascular diseases in China, 1990-2016: Findings from the 2016 global burden of disease study. JAMA Cardiol. 2019 apr 1;4(4):342-352 .doi10.1001/jamacardio.2019.0295.Published online March 13, 2019
2. Bhatt DL, Steg G., Ohman M et al. International Prevalence, Recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis JAMA. 2006;295(2):180-189 doi:10.1001/jama.295.2.180 (REACH)
3. Steg PG, Bhatt DL, Wilson PWF et al. One-year cardiovascular event rates in outpatients with atherothrombosis. JAMA 2007; 297(11):1197-1206 doi:10.1001/jama.297.11.1197
4. Fowkes FGR, Murray GD, Butcher I et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. JAMA 2008 Jul 9; 300(2):197-208 doi:10.1001/jama.300.2.197
5. Weitz JI, Byrne J, Clagett GP et al. Diagnosis and treatment of chronic arterial insufficiency of the lower extremities: a critical review. Circulation 1996 Dec 1;94(11):3026-49 doi:10.1161/01.cir.94.11.3026
6. Aboyans V. Rico JB, Bartelink ML et al. 2017 ESC guideline on the diagnosis and treatment of peripheral artery disease, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of the extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries. Endorsed by: the European Stroke Organization (ESO) The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J. 2018 Mar1;39(9):763-816. Doi:10.1093/eurheartj/ehx095.
7. Song P, Rudan D, Zhu Y et al. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis. Lancet Glob Health. 2019 Aug 7(8):e1020-1030. DOI:10.1016/S2214-109X(19)30255-4
8. Wang Z, Wang Xin, Hao g et al. A national study of the prevalence and risk factors associated with peripheral arterial disease from China: The China Hypertension Survey, 2012-2015. Int J Cardiol. 2019 jan 15; 275:165-170. DOI: 10.1016/j.ijcard.2018.10.047.
9. Knuuti J, Wijns W, Saraste A et al . 2019 ESC Guidelines for the diagnosis and management of chromic coronary syndromes. Eur Heart J. 2020 jan 14;41(3):407-477. DOI:10.1093/eurheartj/ehz425
10. Gerhard-Herman MD, Gornik HL, Barrett C et al 2016 ACC/AHA Guideline on the management of patients with lower extremity peripheral artery disease. Circulation. 2017;135e726-e779. DOI:10.1161/CIR.0000000000000471
11. Angiolilo DJ. Capodanno D and Goto S. Platelet thrombin receptor antagonism and atherothrombosis. Eur Heart J. 2010 Jan 31(1): 17-28. DOI:10.1093/eurheart/ehp504.
12. Petzold T, Thienel M, Dannenberg L et al. Rivaroxaban reduces arterial thrombosis by inhibition of FXa-driven platelet activation via protease activated receptor-1. Circ Res. 2020 Feb 14; 126(4): 486-500. Doi:10.1161/CIRCRESAHA.119.315099.
13. Eikelboom JW, Connolly SJ, Bosch J et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. N Engl J Med 2017; 377:1319-1330. Doi:10.1056/NEjMoa1709118
14. Bosch J, Eikelboom JW, Connolly SJ et al. Rationale, design and baseline characteristics of participants in the cardiovascular outcomes for people using anticoagulation strategies (COMPASS) trial. Can J Cardiol 2017 Aug;33 (8): 1027-1035. Doi:10.1016/j.cjca.2017.06.001.
15. Connolly SJ, Eikelboom JW, Bosch J et al. rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet. 2018 Jan 20;391(10117): 205-218.
16. Anand SS, Bosch J, Eikelboom JW et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet 2018 Jan 20;391(10117) 219-229. Doi:10.1016/S0140-6736(17)32409-1
17. Eikelboom JW, Bosch J, Connolly S et al. major bleeding in patients with coronary or peripheral artery disease treated with rivaroxaban plus aspirin. J Am Coll Cardiol. 2019 Sep 24; 74(12): 1519-1528. Doi:10.1016/j.jacc.2019.07.065
18. Sharma M, Hart RG, Connolly SJ et al. Stroke outcomes in the COMPASS trial. Circulation. 2019 Jan 22; 139: 1134-1145. https://doi.org/10.1161/CIRCULATIONHA.118.035864
19. Bonaca MP, Bauersachs RM, Anand SS. Rivaroxaban in peripheral disease after revascularization. VOYAGER N Engl J Med 2020; 382:1994-2004. doi:10.1056/NEjMoa2000052

Discussion

In the discussion Professor Gaziano said that it is difficult to know where the 'sweet-spot' lies in regarding anticoagulation levels to add to aspirin in order to increase efficacy without increasing bleeding. Because patients experience increased bleeding with increased efficacy, it is best to reserve antiplatelet plus anticoagulant therapy for those with the highest risk of events, especially during high short-term risk. More studies are needed to understand optimum dosing.

Professor Patrono commented that in the COMPASS trial 5 mg twice daily of rivaroxaban alone was not shown to be significantly better for reducing major vascular events than low-dose aspirin alone. Moreover, he mentioned that platelet aggregates provide a surface for the assembly of clotting factors. When platelet aggregation is inhibited by aspirin, it is likely that a reduced platelet surface may decrease the requirement for the anticoagulant dose. This hypothesis may explain the additive beneficial effect of rivaroxaban 2.5 mg twice daily when combined with low-dose aspirin, as demonstrated by the COMPASS trial.

How to improve the gastrointestinal safety of low-dose aspirin.

Professor Andrew T Chan
Harvard University, Boston, USA

Aspirin has been shown to reduce the risk of cardiovascular disease (CVD) and increase the risk of bleeding including gastrointestinal (GI) bleeding in clinical trials and cohort studies[1]. As a result, the United States Preventative Task Force gave a grade B recommendation for taking low-dose aspirin for the primary prevention of CVD in adults aged 50 to 59 years at 10% risk for CVD over a ten years and low risk for bleeding[1-2]. Aspirin causes mucosal injury through prostaglandin-dependent topical and systemic mechanisms[3,4].

Recent trials, such as ASPREE, can better help quantify bleeding risk with low-dose aspirin[5] . In ASPREE, 19,114 participants ≥70 years in Australia or the USA [≥65 for US minority groups] with no CVD, dementia or physical disabilities were randomised to aspirin either 100mg per day [n=9525] or placebo [n=9589 i]. There was a median 4.7 years of aspirin therapy and primary outcomes were death from any cause, dementia or persistent physical disability. Whilst the trial did not show any benefit for this composite outcome, for the purposes of understanding bleeding risk the results showed that there were 162 major bleeding events in the aspirin arm compared with 102 in the placebo arm (HR 1.87 for upper GI bleeding and HR 1.36 for lower GI bleeding). The data is considered informative as it quantifies risk in older patients[6].

Another important trial which recently showed results for GI bleeding was ARRIVE, which studied the impact of low-dose aspirin in primary prevention for individuals at moderate CVD risk. Results in this study, where patients were followed for up to seven years, showed HR 2.1 for people randomised to aspirin versus placebo with GI bleeding in 0.97% of the aspirin group and 0.46% of the placebo group[7].

The bottom line from these studies is that across different risk factors and including older adults the risk of GI bleeding associated with aspirin is about one and a half to two-fold higher.

When we examine the evidence base for aspirin and GI bleeding we find regular aspirin use is associated with higher risk of GI ulcers and major bleeding[8,9]. Higher-dose rather than longer duration of use is the major determinant of tissue injury[10,11]. Low-dose aspirin has a better safety profile with most bleeding episodes occurring within the first six months of aspirin intake[12].

H.pylori infection is associated with an increased risk of gastroduodenal damage in low-dose aspirin users and the perceived higher risk of GI bleeding in Asian populations is likely due to a higher *H. pylori* prevalence[13].

The risk factors for aspirin/NSAID upper GI complications are [5,6,7,8]:

- Smoking,
- History of ulcer or ulcer complications,
- History of GI bleeding,
- Use of two or more NSAIDs,
- Concurrent use of corticosteroids or anticoagulants,
- Older age,
- Presence of severe disease,
- Larger waist circumference.

The initial RCT looking at $P2Y_{12}$ receptor antagonists and GI bleeding suggested that clopidogrel had a statistically lower bleeding risk (1.99% vs 2.66%)[14]. However, observational studies have indicated that clopidogrel has a similar risk of ulcer bleeding as aspirin[15,16]. An RCT undertaken in Hong Kong showed recurrent bleeding rates were higher in individuals taking clopidogrel compared with aspirin and esomeprazole (8.6% vs 0.7%) [17].

Non-aspirin anti-platelet agents $P2Y_{12}$ inhibitors, such as clopidogrel, ticagrelor, and prasugrel, have similar or higher risks for GI bleeding compared to aspirin[17, 18]. The use of both aspirin and $P2Y_{12}$ inhibitors synergistically increases the risk for GI bleeding[19]. Adding a PPI and eradication of *H. pylori* have been shown to reduce the risk of GI bleeding[20,21].

Most important for the current landscape is the fact that many individuals take the combination of DAPT with $P2Y_{12}$ inhibitors plus aspirin that magnifies risk of GI bleeding associated with aspirin. Data from the TWILIGHT study[19] showed a higher synergistic risk of bleeding when people take these agents in combination. The primary endpoint Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding was 7.1% for ticagrelor plus aspirin versus 4.0% for ticagrelor plus placebo.

There is a wealth of randomised trial data in different populations of patients showing there is probably no difference in GI bleeding risk between the various $P2Y_{12}$ agents and no difference compared to aspirin alone. However, there is clearly a magnified risk of GI bleeding when these agents are taken together compared to individually[19, 22-27].

There is clear meta-analysis data from 10 trials to show that GI bleeding can be reduced in patients requiring aspirin therapy by taking a PPI compared to not (OR 0.27 95% CI, 0.16, 0.43)[28]. Another meta-analysis showed that a PPI is better than H2 blockers in preventing GI bleeding (OR 2.10 95% CI, 1.01, 4.39)[29]. There is also convincing data that PPIs prevent upper GI bleeding in people taking DAPT following MI[30]. Across the board, with different safety and risk factor profiles, there is clearly substantial reduction in GI bleeding risk with concurrent PPI use. Eradication of *H. pylori* prevents aspirin associated GI bleeding to approximately the same magnitude as using a regular PPI[31].

Professor Chan explained that in his clinical practice he firstly considers individual risk factors for bleeding that may affect the patient such as: prior bleeding, other NSAIDs, use of other antiplatelet agents, *H. Pylori* infection, DAPT etc. and in people with one or more of these risk factors he strongly considers adding a PPIs for GI protection. Professor Chan also assesses whether patients may have *H. pylori* infection and then recommends eradication to reduce risk of GI bleeding. In this way, patients can be managed safely on aspirin or DAPT.

In conclusion, when considering low-dose aspirin for disease prevention, efforts should be made to examine the balance of risk versus benefit. Additional measures may be taken to lower risk of GI bleeding in low-dose aspirin users.

References

1. Zheng SL, Roddick AJ. Association of aspirin use for primary prevention with cardiovascular events and bleeding events: a systematic review and meta-analysis. JAMA. 2019;321(3):277. doi:10.1001/jama.2018.20578
2. Bibbins-Domingo K, on behalf of the U.S. Preventive Services Task Force. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2016;164(12):836. doi:10.7326/M16-0577
3. Penna G, Adorini L. 1α,25-dihydroxyvitamin D 3 inhibits differentiation, maturation, activation, and survival of dendritic cells leading to impaired alloreactive T cell activation. J Immunol. 2000;164(5):2405-2411. doi:10.4049/jimmunol.164.5.2405
4. van Oijen MGH, Dieleman JP, Laheij RJF, Sturkenboom MCJM, Jansen JBMJ, Verheugt FWA. Peptic ulcerations are related to systemic rather than local effects of low-dose aspirin. Clinical Gastroenterology and Hepatology. 2008;6(3):309-313. doi:10.1016/j.cgh.2007.12.018
5. McNeil JJ, Nelson MR, Woods RL. Effects of aspirin on all-cause mortality in healthy elderly (ASPREE) N Engl J Med 2018; 379:1519-1528 doi:10.1056/NEJMoa1803955
6. Mahady SE, Margolis KL, Chan A, et al. Major GI bleeding in older persons using aspirin: incidence and risk factors in the ASPREE randomised controlled trial. Gut. 2021;70(4):717-7.
7. Gaziano JM, Brotons C, Coppolecchia R et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE) : a randomized, double-blind, placebo-controlled trial. Lancet 2018 Sept 22; 392, (10152): 1036-1046. https://doi.org/10.1016/S0140-6736(18)31924-X
8. McQuaid K.R and Laine L. systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. Am J Med. 2006 Aug; 119(8) 624-38. Doi:10.1016/j.amjmed.2005.10.039.
9. Lanas A, Perez-Aisa MP, Feu F et al. A nationwide study of mortality associated with hospital admission due to severe gastrointestinal events and those associated with nonsteroidal anti-inflammatory drug use. Am J. Gastroenterol. 2005 Aug;100(8): 1685-1693. Doi:10.1111/j.1572-0241.2005.41833.x.
10. Huang ES, Strate LL, Ho WW et al. long-term use of aspirin and the risk of gastrointestinal bleeding. Am J Med.2011 May;124(5):426-433. Doi:10.1016/j.amjmed.2010.12.022.

11. Serebruany VL. Steinhubl SR, Berger PB et al. Analysis of risk of bleeding complications after different doses of aspirin in 192,036 patients enrolled in 31 randomised controlled trials. Am J Cardiol.2005 May 15; 95(10):1218-22 doi:10.1016/j.amjcard.2005.01.049
12. Slattery J, Warlow CP, Shorrock CJ et al. Risks of gastrointestinal bleeding during secondary prevention of vascular events with aspirin—analysis of gastrointestinal bleeding during the UK-TIA trial. Gut.1995 Oct;37(4):509-11. Doi:10.1136/gut.37.4.509
13. Lanas A, Fuentes J, Benito R et al. Helicobacter pylori increases the risk of upper gastrointestinal bleeding in patients taking low-dose aspirin. Ailment Pharmacol Ther 2002 Apr;16(4):779-86. doi:10.1046/j.1365-2036.2002.01230.x
14. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients as risk of ischaemic events (CAPRIE). Lancet 1996; 348 (9038)1329-1339. DOI: https://doi.org/10.1016/S0140-6736(96)09457-3
15. Ibáñez L, Vidal X, Vendrell L et al. Upper gastrointestinal bleeding associated with antiplatelet drugs. Ailment Pharmacol Ther. 2006 Jan 15; 23(2) 235-42. Doi:10.1111/j.1365-2036.2006.02759.x.
16. Lanas A, García-Rodríguez LA, Arroyo MT et al. Risk of upper gastrointestinal ulcer bleeding associated with selective cyclo-oxygenase-2 inhibitors, traditional non-aspirin non- steroidal anti-inflammatory drugs, aspirin and combinations. Gut. 2006 Dec; 55(12): 1731-1738. Doi:10.1136/gut.2005.080754.
17. Chan FKL, Ching JYL, Hung LCT, et al. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. N Engl J Med. 2005;352(3):238-244. doi:10.1056/NEJMoa042087
18. Guo C-G, Chen L, Chan EW, et al. Systematic review with meta-analysis: the risk of gastrointestinal bleeding in patients taking third-generation P2Y 12 inhibitors compared with clopidogrel. Aliment Pharmacol Ther. 2019;49(1):7-19. doi:10.1111/apt.15059
19. Mehran R, Baber U, Sharma SK, et al. Ticagrelor with or without aspirin in high-risk patients after PCI. N Engl J Med. 2019;381(21):2032-2042. doi:10.1056/NEJMoa1908419
20. Szabó IL, Mátics R, Hegyi P, et al. PPIs prevent aspirin-induced gastrointestinal bleeding better than H2RAs. A systematic review and meta-analysis. JGLD. 2017;26(4):395-402. doi:10.15403/jgld.2014.1121.264.hra
21. Moayyedi P, Eikelboom JW, Bosch J, et al. Pantoprazole to prevent gastroduodenal events in patients receiving rivaroxaban and/or aspirin in a randomized, double-blind, placebo-controlled trial. Gastroenterology. 2019;157(2):403-412.e5. doi:10.1053/j.gastro.2019.04.041
22. Wallentin L, Becker RC, Budaj A et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045-57. Doi:10.1056/NEjMoa0904327.
23. Johnston SC, Amarenco P, Albers GW et al. Ticagrelor versus aspirin in acute stroke or transient ischemic attack. N Engl j Med 2016; 375 35-43. Doi:10.1056/NEjMoa1603060
24. Hiatt WR, Fowkes GR, Heizer G et al. Ticagrelor versus clopidogrel in symptomatic peripheral artery disease. N Engl J Med 2017; 376:32-40. Doi:10.1056/NEjMoa1611688.
25. Bonaca MP, Bhatt DL, Cohen M et al. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med 2015; 372; 1791-800 doi:10.1056/NEjMoa1500857
26. Steg PG, Bhatt DL, Simon T et al. Ticagrelor in patients with stable coronary disease and diabetes. N Engl j Med 2019; 381:1309-20. Doi:10.1056/NEjMoa1908077
27. Dangas G, Baber U, Sharma S et al. ticagrelor with or without aspirin after complex PCI. J Am Coll Cardiol. 2020 May 19;75(19):2414-2424. Doi:10.1016/j.jacc.2020.03.011
28. Mo C, Sun G, Lu ML et al. proton pump inhibitors in prevention of low-dose aspirin-associated upper gastrointestinal injuries. World J Gastroenterol. 2015 May 7; 21(17): 5382-92. Doi:10.3748/wjg.v21.i17.5382.
29. Szabo IL, Mátics R, Hegyi P et al. PPIs prevent aspirin-induced gastrointestinal bleeding better than H2Ras. A systematic review and meta-analysis. Gastrointestinal Liver Dis. 2017 Dec;26(4):395-402. Doi.10.15403/jgld.2014.1121.264.hra
30. Sehested TSG, Carlson N, Hansen PW, et al. Reduced risk of gastrointestinal bleeding associated with proton pump inhibitor therapy in patients treated with dual antiplatelet therapy after myocardial infarction. European Heart Journal. 2019;40(24):1963-1970. doi:10.1093/eurheartj/ehz104
31. Chan FK, Chung SC, Suen By et al. preventing recurrent upper gastrointestinal bleeding in patients with helicobacter pylori infection who are taking low-dose aspirin or naproxen. N Engl j Med. 2001 Mar 29;344(13):967-73. Doi.10.1056/NEJM200103293441304.

Discussion

Professor Chan explained patients taking DAPT with a $P2Y_{12}$ inhibitors and aspirin long-term seem to remain at high risk of bleeding complications with a lack of data to support when to discontinue prophylaxis PPI therapy. As a result, Professor Chan keeps patients on PPI prophylaxis long-term even though there are some concerns of long-term complications. Theories suggest long-term use of a PPI can lead to osteoporosis or bone fracture and vascular complications. Evidence comes from long-term observation studies where it is unclear whether confounding issues have been controlled. More carefully constructed studies suggest complications from long-term PPI use are relatively small. On balance safety profiles are quite good for PPIs and it can therefore be considered appropriate to use them for GI protection in long-term antiplatelet use.

Where studies include endoscopic endpoints, a high prevalence of GI lesions occur caused by natural cyclical mucosal injury and repair seen within the GI tract. These studies can be difficult to interpret, making it better to look instead at clinical endpoints and clinically significant GI events.

Professor Chan was asked when it was safe to restart antiplatelet therapy after a GI bleed on low-dose aspirin. He explained there have been clinical studies and observational studies suggesting withholding aspirin therapy can be harmful as there is an increased risk of CVD and death caused from the action of keeping back aspirin after a GI bleed. Instead, Professor Chan, counsels colleagues to try to resume aspirin therapy as soon as possible. Once the patient is stabilised, GI bleeding controlled, and the ulcer has healed, it is important to restart aspirin. This is a situation where endoscopic investigation is useful in order to assess risk before restarting aspirin.

Summary

At the International Aspirin Foundation (IAF) Symposium, hosted at the Oriental Congress of Cardiology, experts from China, Europe and the USA reviewed use of low-dose aspirin for primary and secondary cardiovascular disease (CVD) prevention, with the aim of identifying similarities and differences between different geographical regions.

Professor Carlo Patrono (Catholic University, Rome, Italy) discussed the molecular mechanism of action of aspirin in preventing atherothrombosis. Irreversible inactivation of platelet cyclooxygenase-1 and suppression of thromboxane biosynthesis are necessary and sufficient to explain the clinical benefits of low-dose aspirin.

Professor Mike Gaziano (Harvard University, Boston, USA) considered aspirin use in primary and secondary CVD prevention. He highlighted the ASCEND study showing aspirin works the same for people with diabetes, and how due to non-compliance aspirin appears to lose effect with time. The presentation included strategies to increase the risk benefit ratio for individual patients' benefits, such as accurately identifying CVD risk and proton pump inhibitors (PPIs) to decrease bleeding.

Professor Xiaoying Li (Chinese PLA General Hospital, Beijing, China) explained how the 2019 Chinese consensus statement on aspirin application in primary prevention of CVD recommended introducing four measures before prescribing aspirin. The measures were assessing risk benefit ratio for individuals, treating active pathological changes (such as helicobacter pylori), positively controlling blood pressure, blood sugar and blood lipids, and obtaining patient consent. In the discussion it was felt Chinese guidelines place the greatest emphasis on individual reassessment of risk versus benefit as subjects' age.

Professor Peter Rothwell (University of Oxford, UK) considered low dose aspirin in secondary stroke prevention, exploring how multifactorial EXPRESS study interventions (including aspirin) reduce the 90-day risk of disabling stroke after TIA or minor stroke by 80% and all strokes by 60%. In secondary prevention, benefits appear to decrease with increased duration of follow-up, due to a cumulative withdrawal from allocated treatment. Evidence suggests that aspirin not only reduces the risk of stroke, but also reduces the severity of early recurrent stroke.

Professor Wei-Guo-Fu (Fudan University, Shanghai, China) reviewed how coronary artery disease (CAD), cerebrovascular disease (CVD) and peripheral artery disease (PAD) all have a common pathological basis, with the long-term holistic goal for all being vascular protection. The COMPASS trial in CAD and PAD patients showed the combination of rivaroxaban and aspirin reduced risk of MI, stroke, and CV death more than aspirin alone, with no increase in intracranial haemorrhage or fatal bleeding.

Professor Andrew Chan (Massachusetts General Hospital, Harvard Medical School, Boston) explored how to improve gastrointestinal (GI) safety of low dose aspirin, which causes mucosal injury through prostaglandin-dependent topical and systemic mechanisms. Higher doses of aspirin rather than longer duration of use appears to be the major determinant of tissue injury. The ASPREE trial in patients ≥ 70 years quantified bleeding risk for adults taking aspirin versus placebo - HR 1.87 for upper GI bleeding; HR 1.36 for lower GI bleeding. Adding a PPI and eradicating *H. pylori* have been shown to reduce risk of GI bleeding. Data from the TWILIGHT trial showed synergistic risks of bleeding for people taking combinations of dual antiplatelet therapy (DAPT), $P2Y_{12}$ inhibitors and aspirin. On balance, Chan felt safety profiles of PPIs were sufficient for GI protection for individuals requiring long-term antiplatelet use.

2021 Educational Symposium Programme

Prof. Xiaoying Li 

Prof. Junbo Ge and Prof. Carlo Patrono 

1.00pm - 1.05pm	Introduction Prof. Junbo Ge, Fudan University, Shanghai Prof. Carlo Patrono, Catholic University, Rome	
1.05pm - 1.25pm	Mechanistic insight into how aspirin prevents atherothrombosis Prof. Carlo Patrono, Catholic University, Rome	
1.25pm - 1.55pm	Prevention of serious vascular events by low-dose aspirin across the cardiovascular risk continuum Prof. Mike Gaziano, Harvard University, Boston	
1.55pm - 2.25pm	Prevention of serious vascular events by low-dose aspirin across the cardiovascular continuum in China Prof. Xiaoying Li, Chinese PLA General Hospital, Beijing	
2.25pm - 2.50pm	Discussion	
2.50pm - 3.20pm	Low-dose aspirin for the secondary prevention of stroke Prof. Peter Rothwell, University of Oxford, Oxford	
3.20pm - 3.30pm	Discussion	
3.30pm - 4.00pm	Dual-pathway inhibition for secondary antithrombotic prevention in cardiovascular disease Prof. Wei-Guo Fu, Fudan University, Shanghai	
4.00pm - 4.10pm	Discussion	
4.10pm - 4.40pm	How to improve the gastrointestinal safety of low-dose aspirin Prof. Andrew T Chan, Harvard University, Boston	
4.40pm - 4.50pm	Discussion	
4.50pm - 5.00pm	Summary/closing remarks Prof. Junbo Ge, Fudan University, Shanghai Prof. Carlo Patrono, Catholic University, Rome	

Increasing knowledge & understanding of aspirin

Founded in 1974, the International Aspirin Foundation shares information and stimulates research interest and discussion about all aspects of aspirin and acetylsalicylic acid.

www.aspirin-foundation.com

Event Supporter:

This Symposium kindly supported by Bayer AG

Disclaimers:

- Every effort is made by The Aspirin Foundation to see that no misleading or inaccurate data, statement or opinion appear in their publications or website, the International Aspirin Foundation cannot be held responsible for any errors or for any consequences arising from the use of the information contained in either their publications or website.
- The International Aspirin Foundation, its associates and the Scientific Advisory Board accept no liability whatsoever for the consequences of any such inaccurate or misleading data, information, opinion or statement.
- Any information involving drug usage, should only be followed in conjunction with the drug manufacturer's own published literature in their own country.
- Medical sciences evolve on a continual basis and therefore independent verification of the content should be made.
- The information, views, opinions and any other material provided should not be relied upon as a substitute to professional medical advice in relation to any medical condition. The International Aspirin Foundation, its associates and The Scientific Advisory Board accept no liability whatsoever for any consequences arising from any reliance placed on such information, views, opinions and other materials in lieu of professional medical advice.

For further information please contact

International Aspirin Foundation

Tel: +44(0) 1622 320118
Linkedin: www.linkedin.com/company/the-aspirin-foundation/
Twitter: @Aspirin1897
Email: aspirin@aspirin-foundation.com

www.aspirin-foundation.com