Recent updates in antiplatelet therapy? End of an era for Aspirin

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ABSTRACT

Antiplatelet therapy is main stay of treatment of atherosclerotic cardiovascular disease. Aspirin is highly effective in the secondary prevention of cardiovascular events. The addition of P2Y12 inhibitors to aspirin further enhanced the efficacy of antiplatelet therapy but increasing bleeding risk. The search was always on to achieve perfect balance between ischemic risk and bleeding risk. The exclusion of aspirin was shown to reduce the bleeding risk without increasing the ischemic risk. Monotherapy with P2Y12 inhibitors was found to have encouraging results in recent trials. So the questions were raised if there is an end of aspirin role in primary or secondary prevention of ischemic events. This review is an attempt to address the role of aspirin in current era in light of recent trials.

Introduction :

Antiplatelet therapy is cornerstone of treatment of atherosclerotic vascular disease.[1] Antiplatelet therapy prevents ischemic events like myocardial infarction, stroke and stent thrombosis after percutaneous coronary intervention. Dual antiplatelet therapy (DAPT) is gold standard for the treatment of acute vascular events like acute coronary syndrome, acute cerebrovascular event or acute limb ischemia.[2] Also it is mandatory to administer dual antiplatelet therapy to all post angioplasty patients for a period of six to twelve months. It is recommended to continue dual antiplatelet therapy beyond one year depending upon the ischemic risk.[3] However prolonged antiplatelet therapy is associated with increased bleeding risk.[4] Also addition of anticoagulant drug in atrial fibrillation patients imposes further bleeding risk. The outcomes depend upon balancing the risk between the ischemic events and bleeding events.[5]

Aspirin is the first antiplatelet drug which was shown to reduce ischemic risk.[6] Aspirin was used for both primary and secondary prevention.[7] Addition of clopidogrel to aspirin further reduced the ischemic risk with some increase in bleeding risk.[8] Last decade saw the uprising of new potent P2Y12 inhibitor like Ticagrelor and Prasugrel.[9,10] Addition of these drugs further reduced ischemic risk with mild increase in bleeding risk. Then the trials were conducted to reduce the bleeding risk by omission of either drug of dual antiplatelet therapy, after varying period from index event of acute coronary syndrome or percutaneous coronary intervention (PCI).[11,12] The attempt to continue only aspirin was associated with both increased bleeding risk and reduced protection from ischemic events. Hence the multiple trials were conducted to use P2Y12 inhibitor as monotherapy to treat these subset of patients.[13,14] Last year 2019, results of multiple landmark trials were published which will have impact on current practice of using antiplatelet therapy for atherosclerotic vascular disease. This review aims to discuss these trials with respect to updates in dual antiplatelet therapy.

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Aspirin for primary prevention : negative results of trials

Recently the results of three primary prevention trials of aspirin were reported : the ASCEND (A Study of Cardiovascular Events in Diabetes) trial, which involved participants with diabetes; the ARRIVE (Aspirin to Reduce Risk of Initial Vascular Events) trial, which was intended to involve high-risk participants without diabetes; and the ASPREE (Aspirin in Reducing Events in the Elderly) trial, which involved older population.

The ASCEND trial evaluated aspirin as compared to placebo in diabetic patients without known cardiovascular disease.[15] Patients were followed up for mean duration of 7.4 years. The serious vascular

events occurred significantly less in the aspirin group than in the placebo group (P=0.01). However major bleeding events occurred in 4.1% in the aspirin group, as compared with 3.2% in the placebo group (P=0.003). The site of bleeding was more of gastrointestinal and other extracranial bleeding. Thus the trial showed that though the ischemic event rate was low, but there was absolute increase in major bleeding.[15]

The ARRIVE trial compared the Aspirin 100 mg daily with placebo for the primary prevention of cardiovascular events among high-risk participants without diabetes.[16] High risk was defined as presence of cardiovascular risk factors like dyslipidemia, current smoking, high blood pressure, positive family history of cardiovascular disease. Similar to previous trials, the use of aspirin offered no vascular benefit but resulted in a significant increase in the risk of bleeding complications. In the intention-to-treat analysis of the ARRIVE trial, the incidence of the composite primary outcome of myocardial infarction, stroke, unstable angina, transient ischemic attack, or death from cardiovascular causes was numerically less with aspirin than placebo (P = 0.60). The incidence of gastrointestinal bleeding events with aspirin was twice the incidence with placebo (hazard ratio, 2.1; 95% CI, 1.36 to 3.28; P<0.001). Thus among patients at moderate risk of coronary heart disease, the use of aspirin was not beneficial. Aspirin was not associated with a reduction in adverse cardiovascular events.[16]

The ASPREE trial involved 19,114 participants in Australia and the United States who were 70 years of age or older and were free from cardiovascular disease, dementia, and disability.[17] The participants were randomly assigned to receive 100 mg per day of enteric-coated aspirin or placebo and were followed for up to 5 years. At the end, the use of aspirin conferred no benefit with respect to the prespecified composite primary end point of death, dementia, or persistent physical disability, an issue of considerable importance in the elderly.[18] Of the primary end-point events that occurred, half were death, 30% dementia, and 20% persistent physical disability. Thus, the ASPREE trial showed no evidence of a cardiovascular benefit of aspirin, however aspirin increased the risk of major bleeding than with placebo (hazard ratio, 1.39; 95% CI, 1.18 to 1.62; P<0.001).[19]

Thus use of aspirin for primary prevention in all these trials showed little incremental benefit for prevention of cardiovascular event and was associated with the increased risk of bleeding. It will be prudent to use aspirin as a primary prevention in relatively younger population of age between 40 to 70 years and in patients who less bleeding risk or who have tolerated aspirin well.

Withdrawal of Aspirin from DAPT : Short duration of dual antiplatelet therapy

The current guidelines recommend 6 to 12 months of DAPT after PCI, at least 6 months in stable patients and 12 months in ACS patients. This year SMART-CHOICE trial, STOPDAPT-2 trial and TWILIGHT trial are published which were conducted to demonstrate the benefit of shorter duration of DAPT in high risk patients.

The SMART-CHOICE trial compared the safety and efficacy of short-duration DAPT (3 months) compared with longer duration DAPT (12 months) among patients undergoing PCI.[13] In the short duration DAPT arm, after 3 months, patients were continued on P2Y12 inhibitor monotherapy which predominantly included clopidogrel. Cumulative rates of major adverse cardiac and cerebrovascular events at 12 months were nearly similar in the P2Y12 inhibitor monotherapy group and DAPT group, meeting criteria for noninferiority of P2Y12 inhibitor monotherapy to DAPT (P?=?.007 for noninferiority). The short duration of DAPT did not increase the risk of stent thrombosis (0.2% in 3months DAPT vs. 0.1% in 12 months DAPT, p = 0.65). P2Y12 inhibitor monotherapy after 3 months of DAPT was noninferior to 12-month DAPT for the primary end point of major adverse cardiac and cerebrovascular events at 12 months after the index procedure, and was associated with a lower rate of bleeding (2.0% in 3 months DAPT vs. 3.4% in 12 months DAPT, p = 0.02). The important limitation of study was an open-label trial, not placebo

controlled, and was conducted in a low risk-population.

In the STOPDAPT-2 trial[14], patients undergoing PCI were randomized to 1 month of DAPT followed by clopidogrel monotherapy for 5 years (n = 1,523) versus 12 months of DAPT followed by aspirin monotherapy for 5 years (n = 1,522). One-month DAPT was both noninferior and superior to 12-month DAPT for the primary end point. The major secondary cardiovascular end point occurred less with 1-month DAPT than with 12-month DAPT, meeting criteria for noninferiority (P=0.005) but not for superiority (P=0.34). The major secondary bleeding end point occurred more with 12-month DAPT than with 1-month DAPT (P=0.004 for superiority). Authors concluded that 1 month of DAPT followed by clopidogrel monotherapy met criteria for noninferiority and also was associated with a net clinical benefit for the primary end point, a composite of cardiovascular and bleeding events, compared with 12 months of DAPT with aspirin and clopidogrel after CoCr-EES implantation. In addition, 1 month of DAPT was noninferior for the cardiovascular composite secondary end point and superior for the major secondary bleeding end point compared with 12 months of DAPT. Both these trials were modest in size and had chosen relatively low risk population for analysis, hence they could not make conclusive remark about abbreviating the duration of DAPT.

In the TWILIGHT trial, the effect of ticagrelor alone was compared with ticagrelor plus aspirin with regard to clinically relevant bleeding among patients who were at high risk for bleeding or an ischemic event and had undergone PCI.[20] The high risk for bleeding or an ischemic event was defined by either clinical or angiographic criteria. The clinical criteria for high risk were an age of at least 65 years, female sex, troponin-positive acute coronary syndrome, established vascular disease, diabetes mellitus that was being treated with medication, and chronic kidney disease. Angiographic criteria included multivessel coronary artery disease, a total stent length of more than 30 mm, a thrombotic target lesion, a bifurcation lesion treated with two stents, an obstructive left main or proximal left anterior descending lesion, and a calcified target lesion treated with atherectomy. The primary end point was Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding. Between randomization and 1 year, the incidence of the primary end point was less among patients randomly assigned to receive ticagrelor plus placebo than among patients assigned to receive ticagrelor plus aspirin (P<0.001). The incidence of death from any cause, nonfatal myocardial infarction, or nonfatal stroke was similar in both groups (P<0.001 for noninferiority). Thus authors concluded that among high-risk patients who underwent PCI and completed 3 months of dual antiplatelet therapy, ticagrelor monotherapy was associated with a lower incidence of clinically relevant bleeding than ticagrelor plus aspirin, without increasing the risk ischemic events like death, myocardial infarction, or stroke.[20] The most remarkable thing in these trials was that when aspirin is removed from the DAPT, it did not reduce the efficacy but lowered the bleeding risk.

Removal of Aspirin from triple therapy after PCI in atrial fibrillation patients

Post PCI, all the atrial fibrillation patients have to be on triple therapy. DAPT is prescribed to reduce the incidence of recurrent ischemic events and stent thrombosis and oral anticoagulants are prescribed to prevent stroke and systemic embolism. The current guidelines recommend at least 1 to 6 months of triple therapy.[3] However the triple therapy with oral anticoagulation and dual antiplatelet therapy have been shown to increase the risk of bleeding. Hence the search was on for perfect combination which will prevent both ischemic events as well as systemic embolism and also will not impose the additional bleeding risk. The two trials namely PIONEER AF-PCI[13] and RE-DUAL PCI[14] trials, had shown that combining lower dose of newer oral anticoagulants with P2Y12 inhibitor reduced the risk of bleeding without increasing the risk of ischemic events as compared to triple therapy. However these trials were not adequately powered to detect meaningful difference in incidence of ischemic events.

The idea to drop aspirin was derived from the WOEST (What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting) trial, which showed that discontinuation of aspirin leads to reduction in both bleeding and ischemic events in patients receiving oral anticoagulation with a vitamin K antagonist and undergoing PCI.[3]

In the PIONEER AF-PCI trial, the incidence of bleeding was significantly lower with the two rivaroxaban regimens than with a vitamin K antagonist, and there was no significant increase in the risk of ischemic events, stroke, or stent thrombosis.[13] Similarly in RE-DUAL PCI trial, rates of bleeding were significantly lower with each of the dabigatran-based regimens than with warfarin plus dual antiplatelet therapy, and the risk of ischemic events was not significantly higher.[14] However it was not clear whether the lower risk of bleeding that was seen in the new-oral-agent groups was due to the use of the new agent, the reduced dose of the agent, or the discontinuation of aspirin.

Recently published AUGUSTUS and AFIRE trial have favoured the combination of new oral anticoagulant with P2Y12 inhibitor without addition of Aspirin. The AUGUSTUS trial included patients who had an ACS or underwent PCI recently.[21] It compared standard-dose apixaban with a vitamin K antagonist and of low-dose aspirin with placebo, on a background of concomitant P2Y12 inhibitor therapy. In a 2 x 2 factorial design, patients with atrial fibrillation undergoing coronary revascularization were randomized in a 1:1 fashion to either apixaban 5 mg BID or vitamin K antagonist (VKA) with an internationalized ratio (INR) goal of 2-3, or aspirin 81 mg daily or matching placebo. Major or clinically relevant nonmajor bleeding was much less in the patients receiving apixabanas compared with those receiving a vitamin K antagonist ($P<0.001$ for both noninferiority and superiority). Similarly bleeding was less in placebo group than those patients receiving aspirin ($P<0.001$). Patients in the apixaban group had a lower incidence of death or hospitalization than those in the vitamin K antagonist group and a similar incidence of ischemic events. Overall, the risk of definite / probable / possible stent thrombosis was 1.6% within 6 months, with 80% occurring within 30 days. The number (proportion) of patients with definite or probable stent thrombosis at 6 months was 5 (0.57%) for apixaban plus aspirin, 8 (0.91%) for apixaban without aspirin, 6 (0.69%) for VKA plus aspirin, and 11 (1.26%) for VKA without aspirin groups.

Similar results were shown by the AFIRE (Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease) trial. It was, open-label trial involved patients with atrial fibrillation who had undergone percutaneous coronary intervention (PCI) or coronary-artery bypass grafting (CABG) more than 1 year earlier or who had angiographic coronary artery disease not leading to revascularization (i.e., stable coronary artery disease).[22] These patients were randomly assigned to receive rivaroxaban monotherapy or combination therapy with rivaroxaban plus a platelet inhibitor (aspirin or aP2Y12 receptor antagonist). The incidence of death from any cause was high in the combination-therapy group.The rate of the composite of death, stroke, systemic embolism, myocardial infarction, or unstable angina requiring revascularization (the primary efficacy end point) was less in the monotherapy group than in the combination-therapy group($P<0.001$ for noninferiority). Monotherapy was superior to combination therapy with respect to major bleeding (the primary safety endpoint) ($P=0.01$ for superiority).

The network meta-analysis of more than 10,000 patients compared with a regimen of a vitamin K antagonist plus dual antiplatelet therapy.[23] The odds ratios for TIMI (Thrombolysis in Myocardial Infarction) major bleeding were 0.58 for a vitamin K antagonist plus a P2Y12 inhibitor, 0.49 for the standard approved dose of a direct oral anticoagulant plus a P2Y12 inhibitor, and 0.70 for a direct oral anticoagulant plus dual antiplatelet therapy. As compared with a vitamin Kantagonist plus dual antiplatelet therapy, the odds ratios for a major adverse cardiovascular event were 0.96 for a vitamin Kantagonist plus a P2Y12 inhibitor, 1.02 for a direct oral anticoagulant plusa P2Y12 inhibitor,

and 0.94 for a direct oral anticoagulant plus dual antiplatelet therapy. The incidence of intracranial haemorrhage was higher with aspirin-containingregimens than with regimens that did not contain aspirin.[23] Therefore current guidelines recommend a short period of triple therapy (an oral anticoagulant plus aspirin and aP2Y12 inhibitor) followed by dual therapy with anoral anticoagulant plus a P2Y12 inhibitor for a period ranging from 1 to 12 months.

Conclusion :

Aspirin is most widely used drug for primary and secondary prevention of atherosclerotic cardiovascular disease. Recent trials showed use of aspirin is less efficacious and associate with increased bleeding risk. In contrast use of statins was associated with 25% decrease in the risk of major vascular events (rate ratio with statin vs. placebo, 0.75; 95% CI, 0.69 to 0.82)[24] without increasing the bleeding risk. Hence use of statin instead of aspirin in addition of lifestyle modification, diet control, exercise and smoking cessation is better strategy.[7] According to current guidelines, the duration of DAPT following intracoronary stent placement should be at least for minimum six to twelve months for most patients, with extension of up to an additional 18 to 24 months for those without bleeding events.[3,25] For stable post PCI patients with high ischemic and bleeding risk, the treatment with Ticagrelor plus aspirin for three months followed by Ticagrelor alone for at least an additional year is an option to long term dual antiplatelet therapy with aspirin and clopidogrel.[20] Prolonged DAPT should be considered for patients with high scores or patients with high risk factors like diabetes, long stent length, small diameter and low bleeding risk. Aspirin can be removed from triple therapy in patients with a low risk of thrombotic events (e.g., those undergoing elective PCI who do not have high-risk clinical or angiographic features) or a high risk of bleeding. They can be safely continued on direct oral anticoagulant plus clopidogrel. On the contrary, patients with complex, multivessel, or high-risk PCI or in those presenting with high-risk acute coronary syndrome, aspirin should be continued longer, depending on bleeding risk.

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