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Abstract: Atherothrombosis describes the formation of a thrombus on a disrupted atherosclerotic plaque, and is the primary cause of acute ischaemic events. Atherothrombosis is a generalised and progressive process with an inflammatory component. Patients with disease in one vascular bed are at risk of disease in another. Platelet adhesion, activation, and aggregation in the final stage of atherothrombosis are responsible for arterial occlusion and consequent ischaemia. Therefore antiplatelet therapy is an effective treatment choice for secondary prevention. Clopidogrel, an adenosine diphosphate receptor antagonist, given alone or in combination with aspirin, may benefit secondary prevention of ischaemic events. Current treatment guidelines suggest the use of combination of these two agents for secondary prevention where appropriate. However, data conflict regarding the efficacy of antiplatelet therapy for primary prevention. A recent meta-analysis demonstrated that aspirin significantly reduces the risk of first myocardial infarction in both men and women. The recent Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization Management, and Avoidance trial, (CHARISMA) which evaluated the effects of clopidogrel plus aspirin compared with aspirin alone, seems to support the use of dual antiplatelet therapy in secondary prevention, but suggests that it may not be more effective than aspirin alone in primary prevention.

Key Words: atherothrombosis, aspirin, clopidogrel, antiplatelets, cardiovascular disease

Atherothrombosis, the unhealthy coupling of atherosclerosis and thrombosis, is the most common cause of acute ischaemic events. The underlying atherosclerotic process is diffuse, generalised, and progressive, affecting multiple vascular beds. This leads to a number of clinical manifestations, the natures of which are influenced by the target organ and specific vascular bed involved. Ischaemic events related to atherothrombosis include coronary, cerebral, and peripheral arterial disease (PAD).

Disease in one vascular bed increases the risk of disease in other, a concept known as "cross-risk."2-3 In the Reduction of Atherothrombosis for Continued Health (REACH) Registry, which included a total of 67,888 patients from 44 countries, 15.9% of the 55,499 with symptomatic atherothrombosis had polyvascular disease, defined as at least 2 of the following: coronary artery disease (CAD), PAD, and cerebrovascular disease.4 These patients, who tend to be older and have more comorbidities, had higher rates of cardiovascular outcomes after 1 year of follow-up compared with patients with vascular disease in a single bed.5 Patients with one ischaemic event have an increased likelihood of experiencing another event in the future. A 7-year population-based study showed that, compared with patients who had no history of myocardial infarction (MI), those who had experienced a prior MI had significantly increased risks of stroke (1.9 % versus 7.2 %) and death from cardiovascular causes (2.1 % versus 15.9 %), in addition to an increased risk of recurrent MI (3.5 % versus 18.8 %).6 Similarly, a community-based study of patients with a first stroke demonstrated that among those who survived the first 30 days after the initial events, other cardiovascular events accounted for approximately the same proportion of deaths (26 %) as the initial stroke (27%) during the following 10 years.7 Secondary prevention is therefore necessary in all patients with a history of ischaemic events.

Management of ischaemic risk factors, through a combination of lifestyle modifications and pharmacotherapy, reduces the incidence of ischaemic events.8 There are a number of pharmacological agents useful for primary and secondary prevention; this review will focus on the role of antiplatelet agents in the prevention of atherothrombotic events in patients at high risk.

Pathophysiology of Atherothrombosis

The pathogenesis of atherothrombosis is a complex process that can be divided into 5 phases, with inflammation playing a key role.1,9,10 Indeed, atherosclerosis and atherothrombosis are currently viewed as inflammatory disorders.11 Atherosclerotic plaque rupture heralds the activation of haemostasis, involving platelets and the coagulation system. Under the high shear flow of a ruptured plaque, platelets may adhere directly to von Willebrand factor (vWF) and the activated endothelium, initiating the process of platelet activation. Platelets undergo a series of important events during activation, including: (1) shape change from a tiny disc to sphere with extending filopodia; (2) activation of the surface glycoprotein IIb/IIIa receptor, the ultimate path to platelet aggregation; and (3) the release of vasoactive (eg, thromboxane A2, serotonin, platelet-activating factor), pro-aggregant [eg, adenosine diphosphate (ADP), vWF], and pro-coagulant (e.g. thrombin, tissue factor) substances from platelet granules. After initial activation, potent amplification...
mechanisms, such as platelet-to-platelet aggregation and fibrin formation ensue, leading to a growing thrombus at the site of plaque rupture.

Despite this complex response, most plaque ruptures remain clinically silent, as the fibrous cap of the plaque is constantly undergoing remodelling, rupture, thrombosis, and healing. Clinically manifested ischaemic events occur when acute thrombosis arises on top of plaque rupture, bringing along the ominous consequences of acute flow impairment. In the case of coronary heart disease, the type and severity of the syndrome seem to be related to the extent of vessel obstruction (whether total or partial) and the duration and severity of critical ischaemia over the threshold of myocardial sensitivity.

Identification of High-Risk Patients

Individuals with evidence of atherosclerotic lesions are at risk for clinically manifested atherothrombotic events. Symptomatic patients with established coronary, cerebrovascular, or PAD are particularly at high risk for recurrent events. We have learned in recent years that individuals with silent atherosclerosis and multiple risk factors such as hypercholesterolaemia, diabetes, cigarette smoking, or uncontrolled hypertension are also at risk for clinically manifested ischaemic syndromes. A study which compared the 7-year incidence of MI in patients with type 2 diabetes mellitus (DM) and nondiabetic subjects indicated that diabetic patients without prior history of MI are at equivalent risk of an event as nondiabetic patients with previous MI history. Diabetic patients with no prior MI and nondiabetic subjects who had a history of MI at baseline had similar rates of MI (20.2% versus 18.8%), stroke (10.3% versus 7.2%), and death from cardiovascular causes (15.4% versus 15.9%) during the follow-up period. These and other high-risk groups need to be identified early, as they may be candidates for aggressive medical therapy in addition to lifestyle modification.

Oral antiplatelet Agents and Impact on Ischaemic risk Reduction

Given the central role of platelets in atherothrombosis, antiplatelet agents are an important armament in the management of atherothrombotic syndromes, whether in acute treatment or for secondary prevention.

Aspirin (N-acetylsalicylic acid) is a time-honoured, inexpensive antiplatelet agent, the most extensively studied drug of its class. Aspirin binds to and irreversibly inhibits cyclo-oxygenase (COX), the first step enzyme in the biosynthesis of prostaglandins in platelets. Pharmacologic inhibition of COX in platelets blocks the arachidonic pathway of platelet activation, effectively shutting down the formation of thromboxane (Tx) A2, its end terminal product. Tx A2 is a potent platelet agonist and vasoconstricting substance. The irreversible inhibition of COX stems from the fact that platelets are anuclear cells, hence devoid of protein synthesis and unable to replete its pool of enzymes. The end result is a shutdown of Tx A2 production for the remaining life of the platelet, i.e., its physiologic lifespan of 10 days.

Dipyridamole is thought to inhibit phosphodiesterase, which acts as a catalyst for cyclic adenosine monophosphate (cAMP) in platelets. Increased cAMP activity diminishes calcium mobilisation from the platelet cytosol, an important step for platelet activation.

Clopidogrel and ticlopidine block the ADP receptor on platelets, key to another important pathway for platelet activation and aggregation. ADP is an important constituent of the platelet granules, released during ADP-induced platelet activation. The situation is further compounded by the reduced activities of enzymes (endothelial ecto-ADPases) responsible for ADP degradation under physiologic conditions. Experimental models of arterial thrombosis under high shear flow conditions have underscored the salient role of ADP-induced platelet activation.

Secondary Prevention

Antiplatelet Class

In its latest meta-analysis update, the Antithrombotic Trialists’ Collaboration (ATC) group reported on the cumulative effectiveness and safety of antiplatelet agents in more than 135,000 patients from 195 trials. These studies enrolled patients at high risk for vascular events due to preexisting disease or a recent vascular event.

The pooled analysis of the general antiplatelet class, with all agents combined, yielded a highly significant 2.5% absolute reduction in the number of major vascular events (i.e., nonfatal MI or stroke, or vascular death) during the observation period (10.7% versus 13.2%; P = 0.0001). For specific outcomes, the absolute risk reductions were 1.2% (2.46% versus 3.66%) for nonfatal MI, 0.89% (2.99% versus 3.88%) for nonfatal stroke, and 1.05% for vascular mortality. Antiplatelet therapy significantly reduced the risk of vascular events in patients with stroke or transient ischaemic attack (TIA), PAD, and unstable angina (UA), underscoring once again the systemic nature of atherothrombosis.

Although the analysis showed that antiplatelet therapy was associated with an absolute 0.42% excess of serious (fatal or nonfatal requiring transfusion) extracranial bleeding (1.13% versus 0.71%), this was offset by a reduction in vascular events, with an overall positive net benefit.

Aspirin Alone

Aspirin alone yielded an absolute 3.1% reduction in vascular event rates versus control (12.9% versus 16.0%). The size of the cumulative patient cohort available in the ATC meta-analysis update allowed for comparisons amongst aspirin doses, a subject of debate during the last
2 decades. Aspirin dose comparisons for 75 to 150 mg, 160 to 325 mg, and 500 to 1500 mg yielded absolute reductions of 4.3%, 3.3%, and 2.7%, respectively. There is no evidence to support improved efficacy for aspirin doses > 1500 mg. Doses < 75 mg yielded an absolute reduction of 2.1%. However, results for the < 75 mg versus > 75 mg subgroups were not statistically significant. The risk of serious extracranial bleeding was fairly constant amongst aspirin dose < 325 mg. Overall, a daily dose of 75 to 150 mg aspirin seems to provide the best benefit-to-risk ratio.

**Dipyridamole**

For dipyridamole, the meta-analysis included 25 non-confounded studies which compared dipyridamole plus aspirin with aspirin alone. The addition of dipyridamole to aspirin yielded a nonsignificant 0.6% absolute reduction in vascular events (11.8% versus 12.4%). Results from the second European Stroke Prevention Study (ESPS-2), which enrolled patients with a history of stroke or TIA, demonstrated that although extended-release dipyridamole did not reduce the rate of recurrent stroke compared with aspirin alone, the combination was associated with an approximately 3% absolute decrease in the rate of recurrent stroke compared with either agent alone (9.5% for extended-release dipyridamole plus aspirin versus 12.8% for extended-release dipyridamole alone versus 12.5% for aspirin alone; P < 0.001). The efficacy of the combination of extended-release dipyridamole and aspirin in reducing recurrent stroke was confirmed in the European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT).

**ADP-Receptor Antagonists**

Ticlopidine and clopidogrel are prodrugs, inactive in vitro, activated in vivo upon hepatic conversion. Both agents inhibit ADP-induced platelet aggregation.

The proof of concept for clopidogrel was established in the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial, a randomised comparison of clopidogrel 75 mg and aspirin 325 mg. CAPRIE assessed the relative efficacy and safety of clopidogrel in the secondary prevention of vascular events (i.e., vascular death, nonfatal MI, ischaemic stroke, leg amputation) in 19,185 patients with a prior MI or ischaemic stroke, or with symptomatic PAD, all of which are manifestations of diffuse atherothrombotic disease.

Clopidogrel was associated with a significant absolute reduction of 0.51% in the rate of the primary composite endpoint of MI, ischaemic stroke or vascular death compared with aspirin (5.32% versus 5.83%; P = 0.043). Clopidogrel was associated with significantly less gastrointestinal bleeding and ulcers when compared with aspirin.

The aim of the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study was to evaluate the role of long-term therapy with aspirin and clopidogrel in patients at high risk for secondary cardiovascular events. Patients who presented within 24 hours with UA/non-ST segment elevation (NSTE) MI were randomly assigned to receive clopidogrel (300 mg loading dose followed by 75 mg/d) or placebo in addition to aspirin (75-325 mg/d) for 3 to 12 months. Clopidogrel plus aspirin was associated with a significant 2.1% absolute reduction in the rate of the primary composite endpoint of MI, stroke, or cardiovascular death compared with placebo plus aspirin (9.3% versus 11.4%; P < 0.001), with benefits demonstrated as early as the first day. There was no significant difference in life-threatening bleeding between groups; however, significantly more patients receiving clopidogrel plus aspirin experienced major bleeding (3.7% versus 2.7%; P = 0.001), and the risk of minor bleeding was also significantly higher among clopidogrel recipients (5.1% versus 2.4%; P < 0.001). Major bleeding rates in CURE were dependent on aspirin dose. Current American College of Cardiology/American Heart Association guidelines recommend at least 1 month, and ideally up to 1 year, of treatment with clopidogrel plus aspirin for patients with UA/NSTEMI.

Findings from 2 major randomised trials highlight the clinical benefits to be gained from sustained dual antiplatelet therapy after percutaneous coronary intervention (PCI). The PCI-CURE study compared the effects of pretreatment and long-term therapy with clopidogrel versus placebo in 2,658 aspirin-treated patients from the CURE population who underwent PCI. The primary composite endpoint of cardiovascular death, MI or urgent target vessel revascularisation with significantly less frequent in the clopidogrel group than the placebo group (4.5% versus 6.4%; P = 0.03). Furthermore, long-term administration of clopidogrel post-PCI was associated with a lower rate of cardiovascular death or MI between PCI and the end of follow-up compared with placebo (6.0% versus 8.0%; P = 0.047). There was no significant difference in the rates of major bleeding, including life-threatening major bleeding, within 30 days of PCI between the clopidogrel and placebo groups (1.6% versus 1.4%; P = 0.69). The Clopidogrel for the Reduction of Events During Observation (CREDO) study compared the effects of long-term (12 months) clopidogrel versus placebo therapy in aspirin-treated patients undergoing elective PCI. At 12 months' follow-up, the dual antiplatelet regimen was associated with a significant 3% absolute reduction, relative to aspirin alone, in the composite endpoint of death, MI, or stroke (8.5% versus 11.5%; P = 0.02). There was no significant difference in the risk of major bleeding between the 2 groups.

Currently, evidence-based guidelines recommend that patients implanted with bare metal stents receive dual antiplatelet therapy for at least 1 month, whereas patients implanted with a sirolimus or paclitaxel drug-eluting stent (DES) receive dual antiplatelet therapy for at least 3 and 6 months, respectively. The guidelines also recommend that ideally, dual therapy should be maintained for 1 year. Based on the finding that premature discontinuation of dual antiplatelet therapy is a predictor of late stent thrombosis, a recently published Science Advisory recommends that all patients implanted with a DES should receive 12 months of dual antiplatelet therapy. It is further recommended that if a patient is unlikely to complete a 12-month dual antiplatelet regimen, regardless of the
reason, strong consideration should be given to implanting a bare metal stent instead.

The benefits of dual treatment can also be extended to the management of ST-segment elevation (STE) MI patients.27-28 The question of whether the addition of clopidogrel is beneficial in patients with STEMI who are receiving a standard fibrinolytic regimen, including aspirin, was addressed in the Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis In Myocardial Infarction Study 28 (CLARITY-TIMI 28).28 A total of 3,491 patients who presented within 12 hours of the onset of STEMI were randomised to receive clopidogrel 75 mg/d (after a loading dose of 300mg) or placebo; all patients received fibrinolytic therapy and aspirin. The primary endpoint was a composite of an occluded infarct-related artery on angiography, or death, or recurrent MI before angiography. The rates of the primary endpoint were significantly lower in the clopidogrel than placebo group (15% versus 21.7%; P < 0.001). At 30 days, the rate of occurrence of the composite endpoint of cardiovascular death, recurrent MI or recurrent ischaemia requiring urgent revascularisation was reduced by 2.5% (from 14.1% to 11.6%; P = 0.03) in the group receiving clopidogrel. The rates of major bleeding were similar in the clopidogrel and placebo groups (1.3% versus 1.1%; P = 0.64). The PCI-CLARITY study, a prospective analysis of the 1,863 patients from CLARITY-TIMI 28 who underwent PCI, showed that pretreatment with clopidogrel significantly reduced the incidence of cardiovascular death, MI or stroke during the 30-day period after PCI compared with placebo (3.6% versus 6.2%; P = 0.008).29 There were no significant differences in TIMI major or minor bleeding events between clopidogrel and placebo (2.0% versus 1.9%; P > 0.09).

The Clopidogrel and Metoprolol in Myocardial Infarction Trial/Chinese Cardiac Study (COMMIT/CCS) was designed to assess the effect of clopidogrel (75 mg/d) versus placebo in STEMI patients who were also receiving aspirin therapy (162 mg/d), for a mean treatment period of 15 days.27 The composite primary endpoint of death, reinfarction, or stroke was significantly less frequent in clopidogrel than placebo recipients (9.2% versus 10.1%; P = 0.002). A significant reduction in the second primary endpoint of death from any cause was also achieved in clopidogrel recipients (7.5% versus 8.1%; P = 0.03). There was no significant difference in the rate of major bleeding events between the 2 groups; however, minor bleeding was significantly more common in the clopidogrel arm than the placebo arm (3.6% versus 3.1%; P = 0.005).

Clopidogrel is significantly more expensive than aspirin. However, a review of several pharmacoeconomic analyses revealed that dual antiplatelet therapy with aspirin and clopidogrel is cost-effective when used for up to 12 months by patients with UA/NSTEMI or coronary stents.30

Evidence for the efficacy of dual antiplatelet therapy in secondary prevention in high-risk patients with recent ischaemic stroke is limited. The results of the Clopidogrel and Aspirin for Reduction of Emboli in symptomatic carotid Stenosis (CARESS) trial showed that the combination of clopidogrel and aspirin was more effective than aspirin alone in reducing asymptomatic embolisation in patients with recent symptomatic carotid stenosis.31 However, in the Management of Atherothrombosis with Clopidogrel in High-risk patients (MATCH) trial, the addition of aspirin to clopidogrel administered for up to 18 months in high-risk stroke and TIA patients conferred no extra efficacy advantage, but increased the risk of life-threatening or major bleeding compared with clopidogrel alone.32

Primary Prevention

The efficacy of antiplatelet therapy for primary prevention of atherothrombosis is unclear. In 1988, the US Physicians’ Health Study showed that aspirin (325 mg on alternate days) reduced the absolute risk of first MI in supposedly healthy men by 0.9% (1.3% versus 2.2%; P < 0.000001), but did not reduce cardiovascular mortality in subjects aged > 50 years.33 Conversely, results from the British Doctors’ Trial of male subjects did not show any significant benefit of aspirin (500 mg/d) on the incidences of and mortality from stroke, MI, or other vascular conditions.34

A meta-analysis of 5 randomised trials of aspirin in the primary prevention of cardiovascular disease (including both US Physicians’ Health Study and the British Doctors’ Trial) published in 2003 showed that aspirin does significantly reduce the risk of a first MI in both men and women.35 Among the 55,580 subjects included in this meta-analysis, aspirin was associated with a statistically significant 0.70% reduction in the rate of first MI (1.65% versus 2.35%) and a significant 0.37% reduction in the rate of all important vascular events, defined as a composite of nonfatal MI, nonfatal stroke, and vascular death (4.14% versus 4.51%). However, aspirin did not have a significant effect on the risk of either nonfatal stroke or vascular death alone. Conversely, the Women’s Health Study, a large primary prevention trial in 39,876 women published in 2005, showed that aspirin 100 mg on alternate days reduced the risk of stroke without affecting the risk of MI or cardiovascular death.36 A subsequent sex-specific meta-analysis, showed that aspirin had different effects in men and women.40 Although aspirin therapy was found to significantly reduce the risk of major cardiovascular events (composite of stroke, MI, cardiovascular death) in both sexes, in women this was through a reduction in the rate of ischaemic stroke (0.84% versus 1.08%; P = 0.008), whereas in men this was due to reduction in MI (1.91% versus 2.76%; P = 0.001). Aspirin had no significant effect on the risk of MI in women or stroke in men, and did not significantly reduce cardiovascular mortality rates in either sex. An increased rate of major bleeding (predominantly gastrointestinal) was observed in both women (0.71% versus 0.46%; P = 0.01) and men (0.081% versus 0.48%; P < 0.001).

The US Preventive Services Task Force (USPSTF)41 found good evidence that aspirin reduces the incidence of CAD in adults who are at increased risk. The USPSTF concluded that for asymptomatic individuals whose 5-year ischaemic risk is > 3%, the benefits of long-term aspirin therapy are likely to outweigh any associated risks. However, there is currently no clear consensus on the use of aspirin or other antiplatelets for primary
prevention. Critical evaluation of the literature and use of the Framingham coronary heart disease risk prediction score sheets are, for the moment, the best tools for clinical practitioners to assess patient risk and decide upon treatment for individual patients.42

CHARISMA: Dual Antiplatelet Therapy for Primary and Secondary Prevention

The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial43-45 evaluated the effects of dual antiplatelet therapy with clopidogrel and aspirin in a broad population of high-risk patients. The study included a total of 15,603 patients who were followed to a fixed study end date that allowed for at least 1,040 primary endpoint events (cardiovascular death, MI, or stroke) to occur. In addition to the overall population, CHARISMA evaluated the efficacy and safety of dual antiplatelet therapy for secondary prevention in 12,153 symptomatic patients with established CAD, cerebrovascular disease, or PAD, and for primary prevention in 3,284 asymptomatic patients considered to be at high risk of atherothrombotic events. To qualify as a high-risk primary prevention candidate, patients were required to have 2 major, 3 minor, or 1 major and 2 minor atherothrombotic risk factors.

Results of the CHARISMA study44-45 suggested mixed benefits for dual antiplatelet therapy. Among the overall population, treatment with clopidogrel plus aspirin did not significantly reduce the incidence of the primary endpoint, i.e., a composite of MI, stroke, or death from cardiovascular causes (6.8% versus 7.3%; P = 0.22), but did reduce the risk of the principal secondary endpoint of first MI, stroke, cardiovascular death, or hospitalisation for UA, TIA, or revascularisation (16.7% versus 17.9%; P = 0.04).44 There was no significant difference in the rates of GUSTO-defined severe bleeding between the groups receiving clopidogrel plus aspirin or aspirin alone (1.7% versus 1.3%; P = 0.09), but moderate bleeding was more frequent with dual antiplatelet therapy (2.1% versus 1.3%; P < 0.001). Subgroup analysis of patients enrolled with a history of MI, stroke, or symptomatic PAD seems to support the use of dual antiplatelet therapy for secondary prevention in these patients as the rates of the primary endpoint decreased by 1.5% in patients taking dual therapy (7.3% versus 8.8%; P = 0.010).45 The absolute risk reductions were similar for patients enrolled with a history of MI (6.6% versus 8.3%; P = 0.031), stroke (8.4% versus 10.7%; P = 0.029), and PAD (7.65 versus 8.7%; P = 0.285). There was also no significant difference in severe bleeding between groups (1.75 versus 1.5%; P = 0.509). In contrast, among asymptomatic patients evaluated for primary prevention, treatment with clopidogrel plus aspirin did not produce a significant reduction in primary endpoint events compared with aspirin alone (6.6% versus 5.5%; P = 0.20), and a significant increase in cardiovascular death was observed with dual antiplatelet therapy in this subgroup (3.9% versus 2.2%; P = 0.01). A nonsignificant difference in the rate of severe bleeding was reported between the clopidogrel plus aspirin group and the group receiving aspirin alone (2.0% versus 1.2%; P = 0.07). Precise reasons for the difference in efficacy in the asymptomatic and symptomatic populations have yet to be elucidated.

Conclusion

Atherothrombosis is the most common cause of ischaemic events. Individuals with a history of atherothrombotic events are at high risk of recurrence and are at risk for ischaemic disease in multiple vascular beds. Many individuals with asymptomatic, clinically silent atherothrombosis are also at high risk of ischaemic events. As the platelets play a pivotal role in the process of atherothrombosis, antiplatelet agents are effective and have become well established for the secondary prevention of ischaemic events in at-risk patients. The benefits of antiplatelet therapy in the primary prevention setting are less clear. Primary prevention was explored further in the CHARISMA study, which investigated the relative efficacy of aspirin monotherapy versus dual antiplatelet therapy with clopidogrel plus aspirin for primary prevention in patients at high risk for atherothrombosis and for secondary prevention in patients with established MI, stroke or PAD. Although results of this trial suggested that dual antiplatelet therapy may be beneficial in the secondary prevention setting and concur with major studies such as CURE and COMMIT, a similar benefit was not observed for primary prevention in asymptomatic patients. Further study of dual antiplatelet therapy is therefore warranted in symptomatic patients only.

References


