INDICATIONS FOR ANTIPLATELETS CLINICAL GUIDELINES

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Indications for Antiplatelets Clinical Guidelines

ANCC Accredited NCPD Hours: 1.4 hrs

Target Audience: RN/APRN

Need Assessment

Antiplatelet therapy (APT) has become an important tool in the treatment and prevention of atherosclerotic events, particularly those associated with coronary artery disease. The choice of an antiplatelet agent depends on the clinical situation. The role of the nurse administering these medications in the acute setting involves monitoring for any acute adverse symptoms and patient education in regards to the same. Nurses are often the first healthcare provider to verify the therapeutic effectiveness of these agents and to monitor for adverse effects. Prompt communication by a nurse of an adverse reaction or a complication can significantly reduce patient morbidity and mortality. This role becomes crucial in patients receiving dual antiplatelet therapy, as is often the case for the prevention of stent thrombosis or after an acute coronary syndrome event. The nurse should communicate with the clinical provider and the pharmacist if noting any adverse reaction or if there is a concern for patient compliance with therapy so that alternative therapies can be considered. Antiplatelet drug therapy requires an inter-professional team approach, including clinicians, specialty-trained nurses, and pharmacists, all collaborating as an inter-professional team to achieve optimal patient results. An interprofessional approach, with a multifaceted and targetted approach to treatment, is necessary to improve patient outcomes with antiplatelet medications.

Objectives

- Describe the role of platelets in thrombosis
- Discuss the antiplatelet therapy indications, effects and side effects.
- Recognise the various types of antiplatelet drugs.
- Identify the guidelines on dual antiplatelet drug therapy in practice.
- Recognise the clinical guidelines of antiplatelet therapy on specific cardiac conditions.
- Adapt to the guidelines on safety and efficacy of antiplatelet therapy.

Goal

The goal of this article is to provide a contemporary state-of-the-art review of the clinical guidelines on indications for antiplatelet therapy based on the net clinical benefit for patients and its future perspectives.

Introduction

Antiplatelet therapy plays a fundamental role in reducing atherothrombotic events by several pathways. Research reviews available evidence on antiplatelet therapy both for primary prevention and in the presence of established peripheral, cerebral, or cardiac ischemic disease. Due to the importance of adherence to therapy to achieve optimal effects, special attention is given to the use of fixed-dose oral formulations in the clinical subset of patients in whom double antiplatelet therapy has proven indications.

The pivotal roles played by platelets in thrombosis at sites of vascular injury provide a strong rationale for blocking their function in the setting of coronary artery disease (CAD). Following adhesion at the site of arterial vascular injury in the presence of shear force, platelets undergo activation and release adenosine diphosphate (ADP) from dense granules and generate arachidonic acid from membrane phospholipids via the cyclooxygenase-1 (COX-1)/thromboxane synthase pathway and thrombin through the coagulation pathway on the surface of activated platelets.

Platelets and Thrombosis

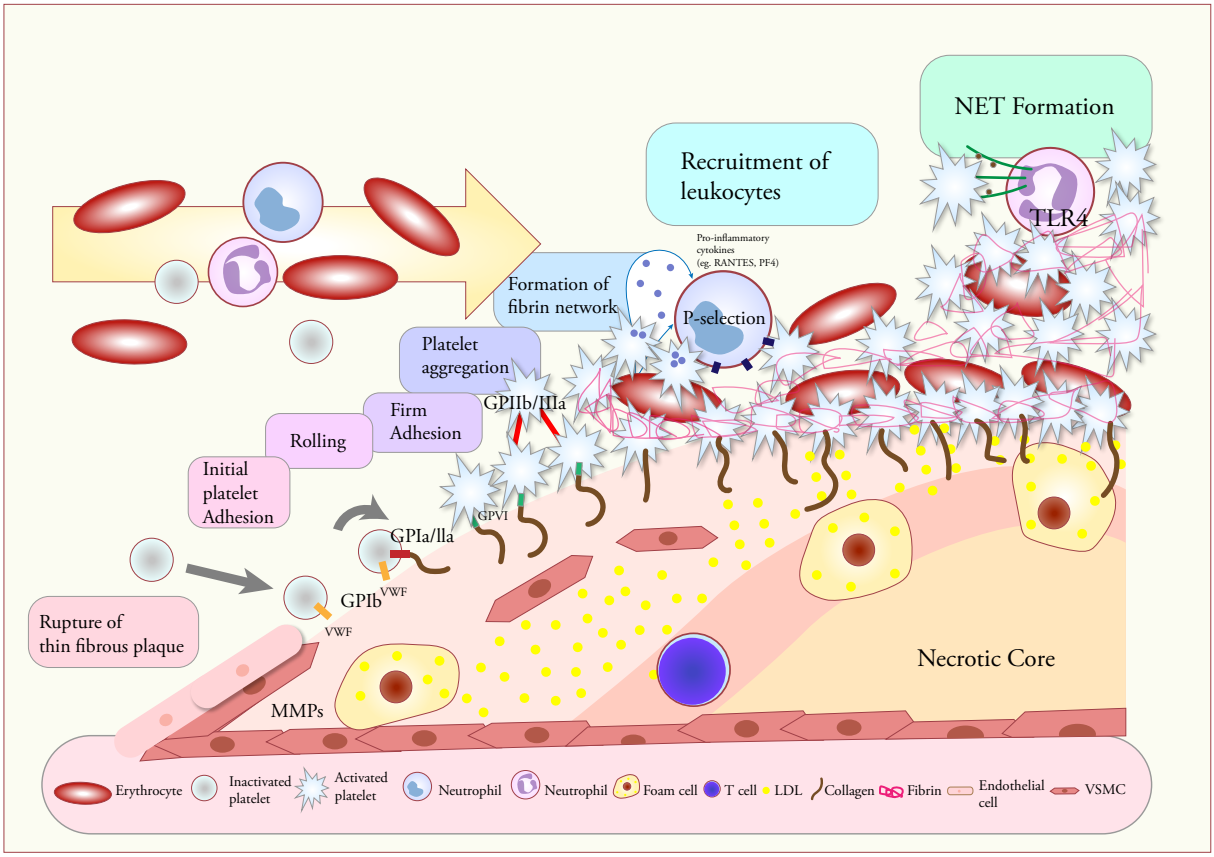

Figure 1: Role of platelets in Thrombosis

ADP, thromboxane A2, and thrombin act on three important G-protein-coupled receptors: P2Y12, TP, and protease-activated receptor (PAR)-1, respectively, and a cascade of intracellular signaling events culminate in the activation of the glycoprotein (GP) IIb/ IIIa receptor that then binds to the dimeric fibrinogen molecule to mediate platelet aggregation. The relative contributions of these upstream receptors to in vivo thrombosis remain incompletely defined. P2Y12, TP, and PAR-1 are associated with redundancy in their responses (signaling pathways). Therefore, targeting more than one of these receptor

pathways by oral agents is an attractive antithrombotic strategy for acute as well as long-term prevention of recurrent cardiovascular (CV) events in patients with CAD and has been extensively explored in clinical trials. [1, Rank 5]

Understanding the Problem

The prevalence of atrial fibrillation (AF) in the United States is approximately 6 million patients and is on the rise. More than 17 million patients have coronary artery disease (CAD), and over 6 and 8 million Americans, respectively, have suffered a stroke or have peripheral arterial disease. The prevalence of AF in patients with established atherothrombosis (11.7%) or risk factors for atherothrombosis (6.2%) is substantially higher compared with the general population (2.3%). Another challenging patient population is those with valvular heart disease who underwent mechanical valve replacement. Approximately 90000 valve substitutes are now implanted in the United States and 280 000 worldwide each year; approximately one fourth of the US valve replacements are mechanical valves requiring long term oral anticoagulants Venous thromboembolism (VTE) causes significant morbidity and mortality with an estimated annual incidence of 900,000 patients with clinically evident Venous thromboembolism in the U.S., resulting in an estimated 300,000 deaths from PE. Keeping in mind the burden of various diseases requiring long term oral anticoagulants, it is estimated that 5–7% of patients undergoing percutaneous coronary interventions (PCI) have indications for chronic oral anticoagulant therapy. [5, Rank 3]

The mechanisms of thrombus formation differ between that associated with thromboembolic diseases like AF and that of coronary artery disease and stent thrombosis. Plasma factors (i.e., coagulation factors) are more important in the development of thromboembolic events during

atrial fibrillation and cellular factors (i.e., platelets) are more important in the pathophysiology of atherothrombotic events. Consequently, oral anticoagulant therapies are mainstay of treatment for stroke prevention in atrial fibrillation (AF), as well as prevention of pulmonary embolism in the recent deep vein thrombosis or pulmonary embolism and antiplatelet agents are of greater benefit in the prevention of ischemic events, including stent thrombosis, in patients undergoing Percutaneous coronary intervention (PCI).

Atrial fibrillation is the most common cardiac arrhythmia and is associated with a small but significant incidence of stroke and systemic thromboembolism. It is well established that oral anticoagulants reduce the incidence of stroke and systemic embolism in these patients. A meta- analysis of 29 trials showed that warfarin reduced stroke by 64% as compared with placebo and by 39% as compared with aspirin in patients with non-valvular atrial fibrillation. Furthermore several trials including ACTIVE-W have confirmed the superiority of warfarin in reducing embolic events over dual antiplatelet therapy (DAPT) with aspirin and clopidogrel in patients with both paroxysmal and sustained atrial fibrillation and at least 1 additional stroke risk factor. [6, Rank 3]

Antiplatelet Therapy

Coronary heart diseases (CHD), particularly myocardial infarction (MI) is responsible for almost 1.8 million deaths annually in US. This mortality rate has decreased during the last three decades, owing to improvements in the acute treatment and secondary prevention of cardiovascular diseases (CVD). Nevertheless, death from Coronary heart diseases still constitutes 20% of all-cause mortality.

Antiplatelet drugs are given as acute treatment for acute coronary syndrome (ACS) and as secondary prevention for thrombotic events. Before 2002, only aspirin was used for secondary prevention. Since the publication of the European Society of Cardiology (ESC) guideline on the-management of myocardial infarction in 2002, aspirin in combination with a P2Y12-inhibiting drug is recommended for secondary prevention. Aspirin should be used indefinitely, while the P2Y12-inhibiting drug should be used for up to 1 year after a myocardial infarction. Since 2006, the cost of prescriptions of the P2Y12-inhibiting drug clopidogrel has been reimbursed by the public health-care system for 1 year after myocardial infarction.

Several studies have been carried out on the use of antiplatelet drugs. The

EuroAspire III survey on lifestyle, risk factors and drug use in patients with Coronary heart disease was conducted in selected areas in 22 countries, and the results showed a relatively wide range of proportions (73.6–98.4%) of patients who used antiplatelet drugs at 6 months after the index Coronary heart disease. The Antiplatelet Therapy Observational Registry (APTOR) study in acute coronary syndrome patients who underwent percutaneous coronary intervention (PCI) in several hospitals in 14 European countries reported 32–94% dual antiplatelet drug users at 1 year. [2, Rank 4]

Studies on antiplatelet drugs have seldom evaluated the persistence of drug use. The proportions of users reported have usually been based on antiplatelet drug use at a certain point in time, without providing information on the continuous use until that time point. Early discontinuation of antiplatelet drugs after Coronary heart diseases and percutaneous coronary intervention has been associated with an increased risk of stent thrombosis, recurrent myocardial infarction, ischaemic stroke and cardiac death. Therefore, persistence with antiplatelet treatment is critical in terms of the clinical outcome of these patients. Furthermore, none of the previous studies have followed the patients for a long period. Information on antiplatelet drug persistence after hospital discharge may be used to improve the secondary prevention of myocardial infarction, and eventually will improve the outcome of myocardial infarction patients. [3, Rank 3]

Indications for Antiplatelet Medications

Antiplatelet therapy represents the mainstay of the pharmacological treatment and secondary prevention of coronary artery disease (CAD).

Compared with placebo, antiplatelet therapy has been shown to reduce recurrent major adverse cardiovascular events (MACE) among patients with stable coronary artery disease or acute coronary syndrome (ACS). Dual antiplatelet therapy (DAPT) provides more intense platelet inhibition than single antiplatelet therapy resulting in incremental reductions in the risk of thrombotic events after percutaneous coronary intervention (PCI) or acute coronary syndrome, but it has been associated with an increased risk of major bleeding. The choice of optimal Dual antiplatelet therapy regimen and duration for patients with coronary artery disease requires a tailored approach based on the patient clinical presentation, baseline risk profile and management strategy. However, the

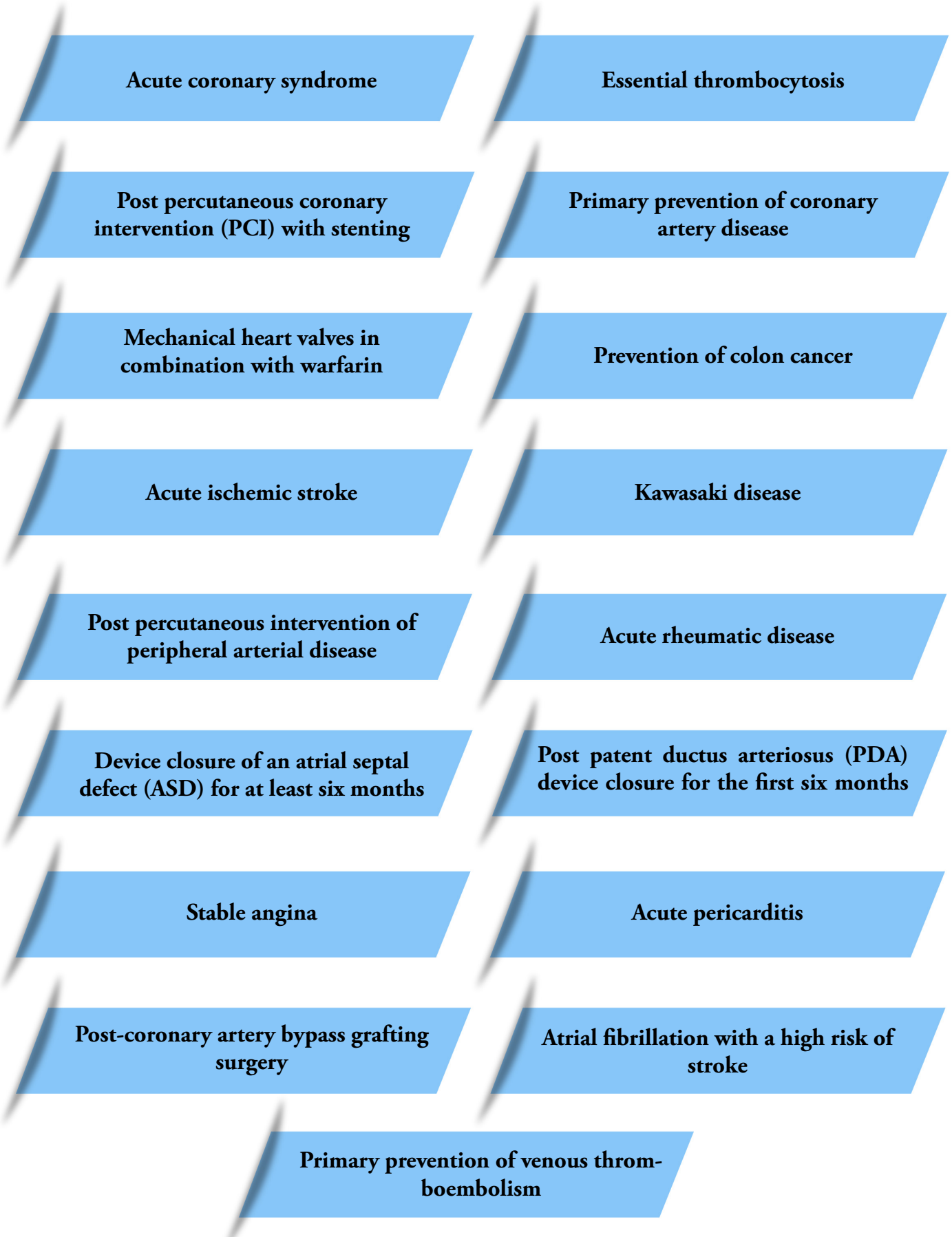

Figure 2: General indications for Antiplatelet therapy

selection of patients who might derive benefit from shorter or extended Dual antiplatelet therapy duration remains a matter of debate.

Antiplatelet Agents

Platelet inhibition plays a central role for treatment and prevention of short- and long-term atherothrombotic events in patients with coronary artery disease. Oral antiplatelet agents for secondary prevention of patients with coronary artery disease include the cyclo-oxygenase-1 inhibitor aspirin, and the platelet adenosine diphosphate P2Y12receptor inhibitors clopidogrel, prasugrel and ticagrelor. Aspirin and clopidogrel have been studied across the whole spectrum of coronary artery disease, whereas the more recent potent P2Y12 platelet receptor inhibitors prasugrel and ticagrelor have been evaluated in patients with acute coronary syndrome. Although there are several potential combinations of antiplatelet agents, Dual antiplatelet therapy refers to the therapy combining aspirin and a P2Y12 receptor inhibitor (clopidogrel, prasugrel or ticagrelor). Dual antiplatelet therapy has been shown to reduce recurrent major ischaemic events in patients with acute coronary syndrome or undergoing percutaneous coronary intervention, at the expense of an unavoidable increased risk of major bleeding compared with single antiplatelet therapy. A personalised approach based on the patient clinical presentation (stable CAD or ACS), baseline ischaemic and bleeding risk profiles, and management strategy (conservative treatment, percutaneous coronary interventions or coronary artery bypass graft (CABG)) is currently advocated. [4, Rank 4]

Classification of Antiplatelets	
Class	**Name**
Cyclooxygenase inhibitor	Aspirin Indobufen
Adenosine diphosphate (ADP) antagonists - Thienopyridines	Ticlopidine Clopidogrel Prasugrel
Adenosine diphosphate (ADP) antagonists- Non Thienopyridines	Cangrelor Ticagrelor Elinogrel
Glycoprotein IIb/ IIIa inhibitors	Abciximab, Tirofiban Eptifibatide, Defibrotide
Phosphodiesterase inhibitors	Dipyridamole Cilostazol NT 702
Protease activated receptor inhibitors	SCH530348 E5555 Terutroban ARC 1779
Nitric oxide releasing aspirin	NCX 4016
Collagen platelet interaction inhibitor	Monoclonal antibodies Aptamers Peptide inhibitors

Table 1: Types of Anticoagulants

Side effects

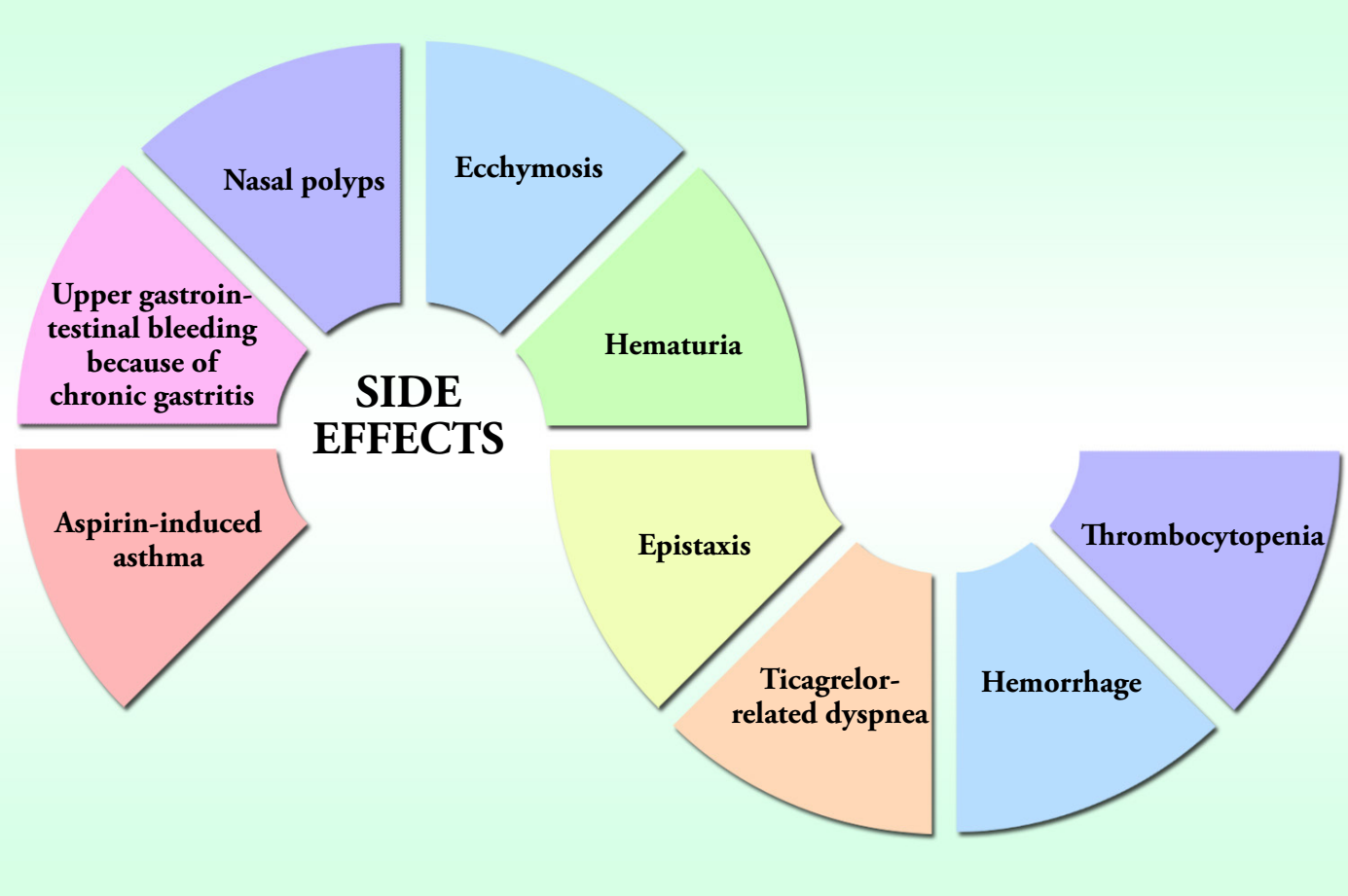

Figure 3: Side Effects of Antiplatelet drugs

Antiplatelet agent administration can be via oral, rectal, or intravenous routes. Oral medications include aspirin, clopidogrel, ticagrelor, cilostazol, and dipyridamole. Intravenous drugs include GpII-IIIA inhibitors and can be used for a short period, most commonly during acute coronary syndromes before or during PCI. Aspirin is available as a rectal suppository if the patient cannot take the drug orally.

Action of Aspirin

Aspirin remains the bedrock of antiplatelet therapy for acute and long-term treatment of patients with coronary and cerebrovascular diseases. After absorption in the upper gastrointestinal (GI) tract, it rapidly and irreversibly acetylates platelet COX-1 serine residue 529 in the prehepatic circulation. Acetylation prevents arachidonic acid from accessing the active site of the enzyme, thereby preventing subsequent

generation of TxA2 from thromboxane synthase and TxA2-induced platelet aggregation.

In most large-scale trials, novel antiplatelet agents have been administered as an adjunct to aspirin therapy. The net clinical benefit of aspirin for the secondary prevention of Cardio Vascular events is well demonstrated in multiple clinical trials, systematic reviews, and meta-analyses.

The antithrombotic trialists collaboration meta-analysis of 16 secondary prevention trials (N = 17,000 individuals with above-average risk) demonstrated that aspirin versus control therapy was associated with significant reduction in annual rates of serious vascular events (6.7% vs. 8.2%; P < 0.0001), total stroke (2.1% vs. 2.5%; P = 0.002), and major coronary events (4.3% vs. 5.3%; P < 0.0001). There was a non-significant increase in hemorrhagic stroke (risk ratio (RR), 1.67 (95% CI, 0.81–3.44)). However, in an aggregate of studies that included major bleeding as an endpoint, there was a significantly higher incidence of major bleeding in patients treated with aspirin versus controls (RR: 2.69 (95% CI, 1.25–5.76); P = 0.01). The net clinical benefit favoured aspirin therapy in the secondary prevention of serious vascular events. [12, Rank 2]

Many controversies exist regarding aspirin therapy. An optimal aspirin dose for secondary prevention has not truly been established. In the CURRENT OASIS-7 trial, in patients with acute coronary syndrome (ACS) and intended early percutaneous coronary intervention (PCI), there was no significant difference between low-dose aspirin (75–100mg/d) and high-dose aspirin (300–325mg/d) on 30-day MI, stroke, or CV mortality or major bleeding.

However, there was a trend toward higher rates of gastrointestinal bleeding in the high- versus low-dose aspirin group. These findings suggested that the low-dose aspirin regimens were as efficacious as high-dose aspirin regimens for secondary

> **"Aspirin is highly effective at blocking COX-1. In addition, non-COX-1-mediated effects of aspirin in platelets and other pleiotropic effects may also contribute antithrombotic properties. Aspirin monotherapy has been recommended for primary prevention in patients at high CV risk, defined as ≥2 major CV events (death, myocardial infarction, or stroke) projected per 100 person-years, who are not at increased risk of bleeding."**

prevention of cardiovascular disease, but exhibited a more favourable GI tolerability profile. The anti-ischemic benefit of long-term aspirin therapy has been shown to be similar for doses≥75mg/day in high-risk patients; however, increased bleeding events, particularly GI-related bleeding associated with ≥325mg/day dose.

Current guidelines for secondary prevention widely recommend indefinite 75–325 mg daily aspirin for all patients, and this has been generally implemented into current clinical practice. Whenever rapid and complete inhibition of TxA2-induced platelet aggregation is desired, a 150 - to 325-mg aspirin loading dose is favored. [13, Rank 3]

The stability of the antiplatelet effect over 24 h with widely used immediate-release aspirin in high-risk populations has been under scrutiny in recent years. Although, twice-daily dosing may provide improved antiplatelet activity coverage compared with once-daily dosing, the clinical significance and safety profile of twice-daily dosing have not been studied in a large-scale trial to date. To address the unmet medical need for 24-h antiplatelet coverage in high-risk populations, an extended-release aspirin was developed and approved in the United States in 2015. In addition, ongoing studies are now investigating the utility of deleting aspirin

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> "There are two types of COX enzymes, COX-1 and COX-2. Both enzymes produce prostaglandins that promote inflammation, pain, and fever; however, only COX-1 produces prostaglandins that activate platelets and protect the stomach and intestinal lining. NSAIDs block the COX enzymes and reduce production of prostaglandins."

therapy in the setting of potent P2Y12 receptor blockade with ticagrelor or replacing it with a new oral anticoagulant. [14, rank 4]

Clinical Guidelines

Before starting antiplatelet agents, the patient should undergo assessment for bleeding risk. Advanced age, female gender, and impaired renal function are important factors to consider. The patient should be aware of the risks, benefits, and alternatives of antiplatelet agents. If the antiplatelet is an essential therapy, such as in post-coronary stenting patients, the medications should be resumed as quickly as safely possible. The use of concomitant anticoagulant should be minimized as much as possible as it will increase the risk of bleeding by many times. Discontinuance of clopidogrel and ticagrelor should be at least five days and prasugrel at least seven days before major cardiac or non-cardiac surgery.

Monitoring during Therapy

Aspirin is the most commonly used of all antiplatelet drugs, so accidental intake is common. The effect can be life-threatening if taken over 150 mg/kg of the body weight. Supportive measure to decrease the absorption of the drug is achievable by using activated charcoal but only if administered within 4 hours of ingestion. The patient will need monitoring for signs and symptoms of bleeding and development of metabolic derangements, such as acidosis. If acidosis develops, immediate dialysis is indicated. [41, Rank 4]

> "Monitoring is generally not required for antiplatelet medications; however, if bleeding is present, bleeding time will be useful to determine if a platelet transfusion is needed or if the medication requires discontinuation. In life-threatening bleeding such as massive upper gastrointestinal bleed, the clinician should stop the drug as soon as possible."

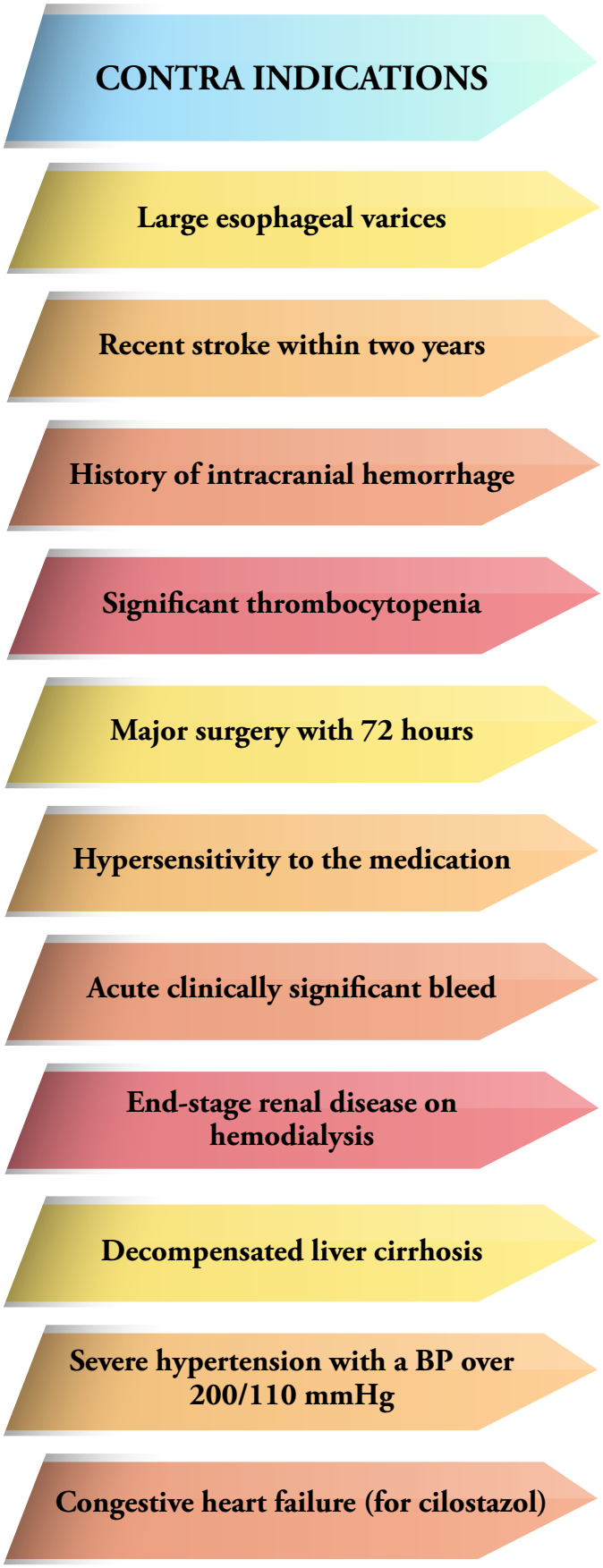

Figure 4: Contraindications of Antiplatelet drugs

Guidelines on Dual Antiplatelet Therapy (DAPT)

Dual antiplatelet therapy (DAPT), consisting of the combination of aspirin and a platelet P2Y12 inhibitor, is the cornerstone of pharmacological treatment aimed at preventing atherothrombotic complications in patients with a variety of coronary artery disease (CAD) manifestation The Dual Antiplatelet Therapy study randomly assigned 9961 patients who underwent

percutaneous coronary interventions with DES (drug-eluting stents) to continue thienopyridine therapy or to receive placebo for 18 months in addition to aspirin, after 12 months of dual antiplatelet therapy combining aspirin and a thienopyridine (clopidogrel or prasugrel).

Prolonged dual antiplatelet therapy (30 months) after drug-eluting stents significantly reduced rates of stent thrombosis and MI compared with 12-month dual antiplatelet therapy duration. Continued thienopyridine therapy beyond 12 months was associated with marginally increased rates of all-cause mortality and a significantly increased risk of moderate or severe bleeding compared with 12-month dual antiplatelet therapy.

Finally, there was an increased risk of stent thrombosis (ST) and MI in both

treatment groups during the 3 months period following discontinuation of thienopyridine treatment. In a posthoc analysis, extended dual antiplatelet therapy duration was associated with significantly increased non-Cardio Vascular (0.9% vs 0.5%, p=0.01) but not Cardio Vascular death (1.0% vs 1.0%, p=0.97) rates throughout the randomised period. The rates of fatal bleeding and death related to any prior bleeding were similar between both treatment arms. Cancer-related deaths were more frequent in patients with extended dual antiplatelet therapy treatment and were rarely related to bleeding. However, rates of cancer occurring over the randomised period or after exclusion of patients with cancer diagnosed before enrolment were similar between both treatment groups. Overall, findings of the dual antiplatelet therapy study suggest that continuation of dual antiplatelet therapy beyond 1 year after drug-eluting stents implantation might be considered in selected patients at low ischaemic and bleeding risks to reduce the rates of stent thrombosis and MI, at the expense of an increased risk of bleeding. [19, Rank 5]

The evidence derived from randomised control trails addressing different dual antiplatelet therapy strategies after newer generation drug-eluting stents implantation has been recently combined in several large meta-analyses. Shorter (3–6 months) DAPT courses have been associated with similar rates of MACE, all-cause death, cardio vascular death, MI, ST, or repeat revascularisation, but with reduced rates of major bleeding compared with 12-month DAPT. Although the dual antiplatelet therapy study and two subsequent meta-analyses showed that extended dual antiplatelet therapy duration beyond 1 year after drug-eluting stents may reduce the risk of stent thrombosis and MI, it has been associated with increased mortality due to increased risk of non-cardio vascular mortality not offset by a reduction in cardio vascular mortality. However, a recent large meta-analysis including 644 patients undergoing stent implantation did not demonstrate an association between extended dual antiplatelet therapy duration and all-cause, cardio vascular or non- cardio vascular mortality compared with aspirin alone or short dual antiplatelet therapy duration (≤6 months). [20, Rank 2]

A personalised approach considering the balance between the ischaemic benefit and the bleeding risk according to the patient's clinical profile is currently advocated. For most of patients with stable coronary artery disease receiving contemporary drug-eluting stents, a short-term dual antiplatelet therapy strategy (≤6 months) seems a reasonable approach, and may be

considered the default therapy in the absence of an increased ischaemic risk. The clinical decision to extend dual antiplatelet therapy duration beyond 1year (18–48 months) after stent implantation requires a personalised evaluation to weigh up ischaemic benefits - lower risk of myocardial infarction and Stent Thrombosis and risks (increased risk of major bleeding and non-cardio vascular death). However, further research is warranted to determine the optimal selection of patients who may derive benefit from extended dual antiplatelet therapy duration after stent implantation.Lifelong daily low-dose aspirin (75–150 mg) is currently recommended for secondary prevention of patients undergoing percutaneous coronary interventions for stable CAD (class I).

Clopidogrel (75 mg daily) is indicated as an alternative therapy in case of aspirin intolerance (class I). Due to the current lack of evidence in patients with stable CAD, the use of potent P2Y12 receptor antagonists, prasugrel or ticagrelor, is not recommended in low-risk elective percutaneous coronary interventions (class III), but may be considered in specific high-risk elective conditions, such as left main coronary artery percutaneous coronary interventions or patients at high risk of stent thrombosis or with diabetes (class IIb).

"Current European Society of Cardiology and American Heart Association/ American College of Cardiology guidelines recommend P2Y12 receptor inhibitor therapy with Clopidogrel (75 mg daily) for a minimum duration of 1 month after bare-metal stent (class I) and 6 months after drug-eluting stents implantation (class I) for patients with stable CAD undergoing percutaneous coronary interventions."

Premature discontinuation of P2Y12 receptor therapy after 3–6 months following drug-eluting stents implantation may be considered in patients deemed at high bleeding risk or who develop significant bleeding (class IIb). In patients at high ischaemic risk after bare-metal stent (BMS) or drug-eluting stents implantation who have tolerated dual antiplatelet therapy without bleeding and who are not at high bleeding risk, continuation of dual antiplatelet therapy with clopidogrel for longer than 1month in patients treated with bare-metal stent or longer than 6 months in patients treated with drug-eluting stents may be reasonable (class IIb). [21, Rank 3]

The concept of dual antiplatelet therapy will be challenged during the next years by several ongoing randomised control trials that will explore novel strategies using P2Y12 receptor inhibitors, clopidogrel (STOP DAPT-2 (NCT02619760), SMART-CHOICE (NCT02079194)) or ticagrelor (GLOBAL LEADERS (NCT01813435), TWILIGHT (NCT02270242)), as single antiplatelet therapy after a short-term (1 or 3 months) DAPT duration after newer generation drug-eluting stents.

GLOBAL LEADERS, the largest ongoing trial to date, is a multicentre, open-label, randomised study investigating the superiority of a 23-month ticagrelor monotherapy (after a 1-month DAPT course combining aspirin and ticagrelor) over a conventional 12-month dual antiplatelet therapy duration consisting of aspirin and clopidogrel - stable coronary artery disease or ticagrelor – Acute Coronary Syndrome followed by an additional 12-month course of aspirin monotherapy with respect to the composite endpoint of all-cause mortality or non-fatal MI at 2 years in all-comers patients undergoing percutaneous coronary interventions with the uniform use of a newer generation drug-eluting stents implantation.

Similarly, TWILIGHT is a large-scale randomised, double-blind, placebo-controlled trial that will assess the efficacy and safety of ticagrelor monotherapy (after a 3-month dual antiplatelet therapy course combining aspirin and ticagrelor) compared with standard 12-month dual antiplatelet therapy with aspirin and ticagrelor in up to 9000 high-risk patients with stable coronary artery disease or acute coronary syndrome undergoing percutaneous coronary interventions with drug-eluting stents The primary hypothesis of the trial is that ticagrelor monotherapy will be superior to dual antiplatelet therapy with respect to rates of major bleeding, while maintaining non-inferiority for the risk of ischaemic events. These trials will provide novel insights with respect to the potential role of ticagrelor monotherapy as an alternative for long-term platelet inhibition in a broad population of patients undergoing percutaneous coronary intervention with drug-eluting stents.

Additionally, large all-comers trials are currently evaluating the safety and efficacy of an abbreviated 1-month dual antiplatelet therapy duration compared with standard dual antiplatelet therapy duration (6–12 months) in high bleeding risk patients undergoing percutaneous coronary interventions with newer generation drug-eluting stents(SENIOR (NCT02099617), MASTER DAPT (NCT03023020)). The highly anticipated

results of these studies focused on patients who have been traditionally excluded from randomised trials on dual antiplatelet therapy may provide robust randomised evidence to support a short dual antiplatelet therapy regimen for high bleeding risk patients treated with newer generation drug-eluting stents in contemporary practice. [22, Rank 3]

Risk for bleeding and complications can be pre- analysed based on certain factors (as shown in Figure 5)

Risk characterization for ischemic or bleeding complications is an overriding concept in both the ACC/AHA and ESC updates, although it is recognized that many patients are at high risk for both types of event.

Risk Stratification in Dual Antiplatelet Therapy (DAPT)

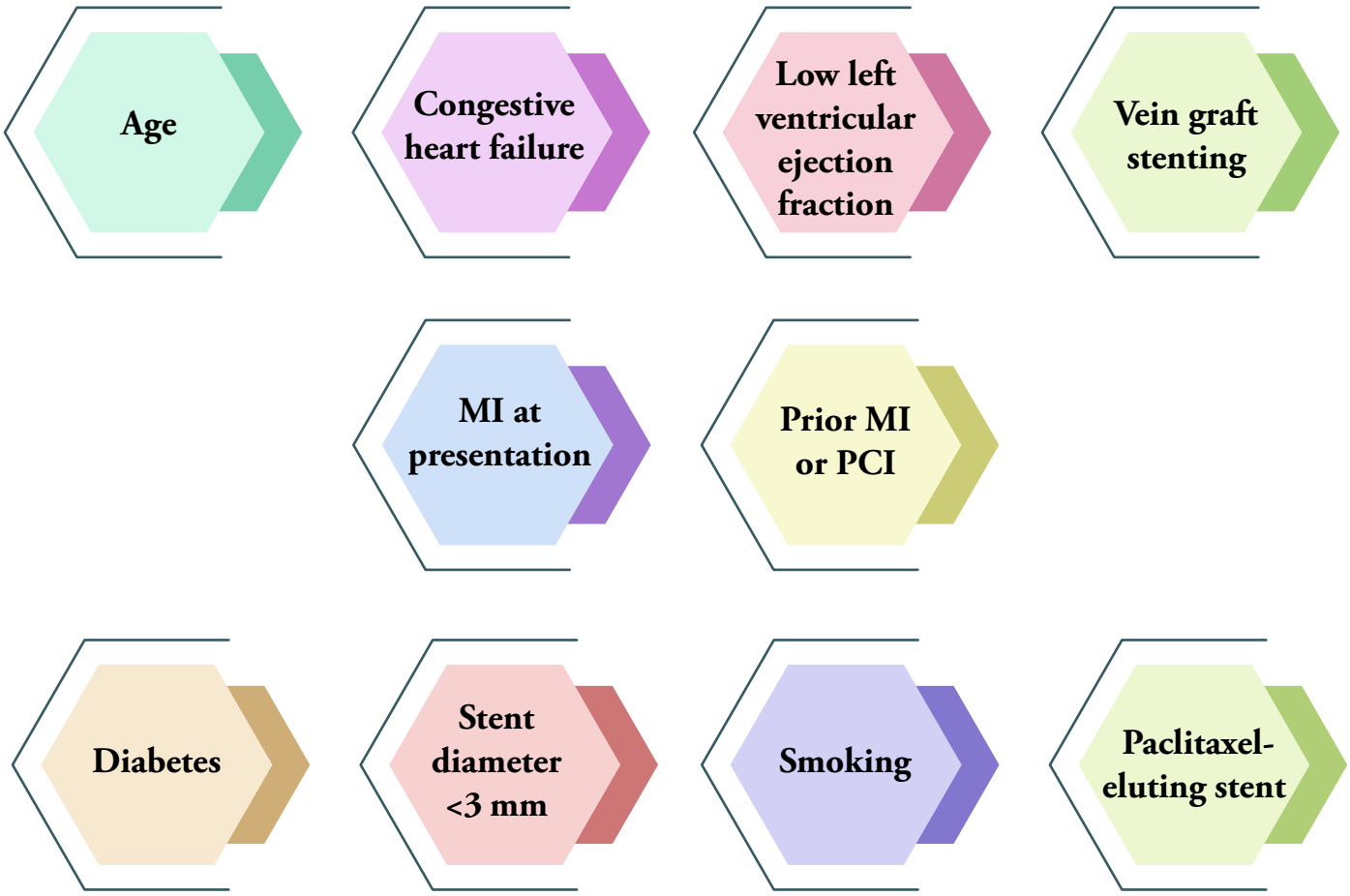

Figure 4: Contraindications of Antiplatelet drugs

The prediction rule assigns positive integer values to diabetes mellitus, current cigarette use, prior percutaneous coronary intervention or prior myocardial infarction congestive heart failure or left ventricular ejection fraction <30%, myocardial infarction at presentation, vein graft percutaneous coronary intervention, and stent diameter <3 mm. Conversely, it assigns negative integer values to older age categories.

With respect to specific bleeding risk prediction, the approach of the 2016 ACC/AHA update to risk stratification is essentially qualitative, with a focus on bleeding risk factors rather than an emphasis on predictive models.

Conservative Treatment

Data supporting the benefits of long-term Dual Antiplatelet Therapy in unselected patients with stable coronary artery disease are limited. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilisation, Management and Avoidance (CHARISMA) trial randomly assigned 603 patients with documented coronary artery diseases, peripheral artery disease, cerebro vascular disease or multiple athero-thrombotic risk factors to receive clopidogrel (75 mg daily) versus placebo in addition to low-dose aspirin. Overall, rates of the primary composite endpoint cardiovascular death, MI or stroke were similar in the clopidogrel plus aspirin and aspirin alone groups after a median follow-up of 28 months, despite a marginally increased risk of severe bleeding among patients treated with Dual antiplatelet therapy.

In the subgroup of patients with multiple risk factors, the rates of the primary endpoint and cardiovascular death were higher in clopidogrel treated patients (3.9% vs 2.2%, p=0.01). In the pre-specified subgroup of patients with clinically evident coronary artery diseases or peripheral artery disease or cerebro vascular disease, there was a marginally significant reduction in the primary ischaemic endpoint in the clopidogrel plus aspirin group whereas asymptomatic patients with multiple risk factors only (n=3284) assigned to

> **"The 2017 ESC update suggests using a 5-item bleeding risk score for the prediction of out-of-hospital bleeding hazard**
>
> - **Age**
> - **Creatinine Clearance**
> - **Haemoglobin**
> - **White Blood Cell Count**
> - **Prior Spontaneous Bleeding"**

clopidogrel plus aspirin experienced a 20% relative risk increase in the rate of primary ischaemic events (6.6% vs 5.5%, p=0.20) and a significant increase in rates of all-cause (5.4% vs 3.8%, p=0.04) and cardiovascular death (3.9% vs 2.2%, p=0.01), compared with those assigned to aspirin alone. In a posthoc subgroup analysis of 9478 patients with prior Myocardial infarction, ischaemic stroke or Peripheral Artery Disease, rates of the primary composite endpoint and hospitalisations for ischaemia were significantly lower in the clopidogrel plus aspirin arm than in the aspirin alone arm. In patients treated with Dual antiplatelet therapy, there was a significantly increased risk of moderate bleeding with no significant difference in rates of severe bleeding. [16, Rank 1]

Fixed Dose Antiplatelet Combinations

Keeping in mind the consequences induced by partial or complete suspension of double antiplatelet therapy, patient compliance plays a fundamental role. Researchers designed the nationwide REGINA survey to evaluate how the interruption of dual oral antiplatelet therapy is managed in "real world" practice. Over 2000 physicians were randomly selected to participate in a computer-assisted telephone interview. Knowledge about drug-eluting stents and dual oral antiplatelet therapy was appraised by multiple-choice questions. Based on data from the 93% of the responding practitioners who completed the interview, unjustified interruption of dual oral antiplatelet therapy was quite frequent (22%). Low-molecular-weight heparin was the substituted therapy in over two-thirds of cases (without available evidence) and was associated with longer periods of dual oral antiplatelet therapy interruption.

This evidence highlights the actual problem of therapy adherence, and the severe consequences related to lack of patient compliance with the prescribed treatment.

Treatment adherence is defined as "the extent to which patients take medications as prescribed by their health care providers". "Compliance" indicates passive patient obedience to doctor prescription, and "adherence" involves a major comprehension level by the patient. Although poor adherence depends on several factors, including provider–patient interaction and drug cost, the number of administrations per day, is indeed a non-negligible element.

In this context, in patients for whom double antiplatelet therapy has proven indications, fixed-dose formulations have a promising role. In patients at high

cardiovascular risk, who are often on multiple drug treatment, combining administration of two antiplatelet agents in a single pill, thereby reducing the number of administrations per day represents an excellent option to improve treatment adherence. [10, Rank 2]

The first fixed-dose combination available was Aggrenox (Boehringer Ingelheim, Ingelheim am Rhein, Germany) containing ASA 25 mg and extended-release dipyridamole 200 mg. Researchers evaluated the results of a combination of extended-release dipyridamole (ER-DP) and low-dose ASA compared with clopidogrel with or without ASA in diabetic patients. The study enrolled 60 patients aged over 40 years, with a diagnosis of type 2 diabetes and a history of transient ischemic attacks. Patients were allocated to receive ER-DP + ASA 200/ 25 mg twice daily, clopidogrel 75 mg/day, or a daily combination of clopidogrel 75 mg and ASA 81 mg. The primary endpoint was the change in platelet receptor expression at 30-day follow-up. ER-DP and ASA therapy was associated with a significant reduction in the glycoprotein IIb/IIIa receptor, clopidogrel monotherapy was associated with ADP-induced platelet aggregation, and the ASA and clopidogrel combination was associated with inhibition of collagen-induced platelet aggregation. These interesting data indeed clarified the molecular action of the best known antiplatelet therapy, but did not add information concerning clinical outcomes.

Knowledge regarding the association between clopidogrel and ASA is to date elementary. From a pharmacokinetic point of view, clopidogrel is rapidly absorbed, reaching peak plasma levels at approximately one hour following dosing. However, the active formulation is formed by oxidation to 2-oxo-clopidogrel and subsequent hydrolysis, regulated primarily by cytochrome P450. The active metabolite binds irreversibly to platelet receptors. Clopidogrel metabolites are then excreted 50% in the urine and 50% in the feces, with a half-life for the main circulating metabolite of about eight hours. On the other hand, ASA is rapidly hydrolyzed in plasma to salicylic acid, with a half-life of 20 minutes, and peak salicylic acid concentrations occur one hour after administration. Salicylic acid is then conjugated primarily in the liver to form salicyluric acid. The half-life of these molecules is about two hours and metabolites are excreted in the urine. [11, Rank 3]

Dual antiplatelet therapy (DAPT) is the standard of care to reduce recurrent ischemic events after acute coronary syndrome (ACS) and to prevent stent

thrombosis after percutaneous coronary intervention (PCI). Furthermore dual antiplatelet therapy has also been proven to be superior in terms of safety and efficacy when compared with anticoagulation with Warfarin following coronary stenting. Data from Stent Antithrombotic Regimen Study (STARS) trial, in which 1653 patients who had successful placement of the stent were randomly assigned to one of three regimens: aspirin alone (557 patients), aspirin and warfarin(550 patients), and dual antiplatelet therapy (DAPT) with aspirin and ticlopidine (546 patients), revealed that Dual antiplatelet therapy reduced the occurrence of death, target lesion revascularization, stent thrombosis, and recurrent MI at 30 days from 3.6% with aspirin alone and 2.7% for aspirin and warfarin compared to only 0.5% for aspirin and ticlopidine. Because clopidogrel, a second-generation thienopyridine, has fewer adverse effects than ticlopidine, such as thrombotic thrombocytopenic purpura and severe neutropenia, it rapidly became the thienopyridine of choice. Current ACC/AHA guidelines recommend Dual antiplatelet therapy in patients with an STEMI for at least 1 year for BMS and drug-eluting stents implantation. In patients with unstable angina or NSTEMI receiving a BMS, Dual antiplatelet therapy should be given for at least 1 month and preferably for 1 year. In patients who receive an elective drug-eluting stents implantation, the current recommendations are for one year of Dual antiplatelet therapy. [7, Rank 3]

Three antithrombotic drug combinations have been used most in practice: triple therapy (oral anticoagulation and dual antiplatelet therapy with aspirin and clopidogrel), oral anticoagulation, and 1 antiplatelet agent (aspirin or clopidogrel), or rarely, DAPT alone without oral anticoagulants. Although there are wide variations in type and duration of therapy in practice, triple therapy is the most common treatment regimen in this setting. Several studies demonstrate that the risk of bleeding rises with an increased number of antithrombotic agents. In one study of 21,443 elderly patients followed on average for 22 months after an acute MI, bleeding was 1.7 times more frequent with Dual antiplatelet therapy and 1.9 times more frequent with aspirin plus warfarin when compared with aspirin monotherapy. Patients taking combination of oral anticoagulants with aspirin and clopidogrel (“triple therapy”) pose a significant dilemma for the cardiologist because of the increased risk of major bleeding. [8, Rank 3]

In one study among patients on triple therapy with aspirin, clopidogrel, and

> "The ACC/AHA guidelines recommend oral anticoagulant therapy with warfarin for those patients with at least 1 additional risk factor for stroke and suggest the use of aspirin only for those at low risk for stroke such as patients without risk factors."

warfarin, major bleeding occurred in 4.7%, and approximately 50% of these patients died within 6 months. In a meta-analysis involving 13 retrospective studies and registries assessing antithrombotic regimens in patients with atrial fibrillation undergoing Percutaneous coronary intervention risk of major bleeding was 1.5% at 30 days and 5.2% at 1 year with triple AT (aspirin + warfarin + clopidogrel/ ticlopidine). Dual antiplatelet therapy (aspirin + clopidogrel/ ticlopidine) was associated with 2.4% annual risk of major bleeding. Similarly, in another meta-analysis involving 9 randomized controlled trials, patients with triple antithrombotic regimen had significant reduction in ischemic stroke as compared with dual antiplatelet therapy. While there was a two-fold increased risk of major bleeding associated with triple antithrombotic regime (OR 2.00, 95% CI 1.41 to 2.83; and $P < 0.0001$). The overall incidence of death (OR 1.20, 95% CI 0.63 to 2.27, and $P = 0.56$) and myocardial infarction (OR 0.84, 95% CI 0.57 to 1.23; and $P = 0.38$) was comparable between the two regimens. Both studies confirm the cardiovascular benefits of triple antithrombotic regimen by reducing ischemic stroke risk, but also demonstrated its increased risk of major bleeding.

Major bleeding is a serious complication that is associated with increased morbidity and mortality particularly when it occurs shortly after a stent procedure. Despite different bleeding definitions, both access site and non-access site bleeding has been observed across all the major trials in patients undergoing percutaneous coronary intervention. In fact, in one of a major meta-analysis using combined dataset from the REPLACE-2 - Randomized Evaluation in Percutaneous coronary intervention Linking Angiomax to Reduced Clinical Events-Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY), and HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trials in 17,393 Percutaneous coronary intervention patients, non-access site bleeding after Percutaneous coronary intervention was found to be common, representing approximately

two-thirds of all TIMI bleeding events, and was found to be associated with a 4-fold increase in 1-year mortality. Furthermore, similar results have been found in other studies indicating a strong relationship between early bleeding and 1 year mortality. Results from a major meta-analysis that included 5,384 patients from 4 randomized placebo-controlled trials: ISAR-REACT, SWEET, SMART-2, and REACT-2, revealed that the 30-day occurrence of bleeding independently predicted 1-year mortality by a Cox proportional hazards model, indicating a strong relationship between the 30-day frequency of bleeding and 1-year mortality after percutaneous coronary interventions. [9, Rank 1]

Antiplatelet therapy in Stable Coronary Artery Disease

Aspirin remains the cornerstone for secondary prevention of patients with stable CAD, irrespective of the management strategy. In a large meta-analysis including 16 secondary prevention trials and 17 000 high-risk patients, low-dose aspirin (75–150mg/day) was associated with a 20% relative risk reduction in MACE - cardiovascular death or non-fatal myocardial infarction and a 22% relative risk reduction in ischaemic stroke (RR 0.78, 95% CI 0.61 to 0.99), at the expense of an increased risk of haemorrhagic stroke (RR 1.67, 95% CI 0.97 to 2.90) and major extracranial bleeding (RR 2.69,95% CI 1.25 to 5.76).

Aspirin marginally reduced CV mortality (RR 0.91, 95%CI 0.82 to 1.00, p=0.06), resulting in a 10% relative risk reduction in all-cause mortality (RR 0.90, 95% CI 0.82 to 0.99, p=0.02). At variance of the antiplatelet effects, the gastrointestinal side effects of aspirin increase at higher doses. The optimal risk: benefit ratio appears to be achieved with an aspirin dosage of 75–150 mg daily.

The Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial compared antiplatelet therapy with clopidogrel (75 mg daily) versus aspirin (325 mg daily) in 185 patients with atherosclerotic cardiovascular disease (ACVD) (recent ischaemic stroke, recent MI or symptomatic peripheral arterial disease). Compared with aspirin, long-term administration of clopidogrel (median follow-up 2 years) was associated with significant risk reductions in the combined endpoint of CV death, MI or ischaemic stroke (5.32% per year vs 5.83% per year, relative risk reduction 8.7%, 95% CI 0.3 to 16.5, p=0.04) without significantly increased risk of severe intracranial (0.31%

vs 0.43%, p=0.23) and gastrointestinal bleedings (0.49% vs 0.71%, p=0.05). Importantly, the superiority of clopidogrel over aspirin was mainly driven by a reduction of events in the PAD, but not MI, subgroup. Although potent P2Y12 receptor inhibitors have shown superior efficacy than clopidogrel in patients with ACS, there is currently little evidence to support the use of prasugrel and ticagrelor in patients with stable CAD. [15, Rank 2]

Antiplatelet therapy in patients undergoing Percutaneous Coronary Intervention

The combination of aspirin and P2Y12 receptor inhibitor therapy remains the mainstay of pharmacological treatment for patients undergoing percutaneous coronary intervention with bare metal stents (BMS) or drug-eluting stents (DES). Among patients undergoing Percutaneous coronary intervention, Dual antiplatelet therapy with aspirin and a P2Y12 receptor antagonist (ticlopidine) during 4–6 weeks significantly reduced rates of MACE compared with combined aspirin and oral anticoagulation (OAC) therapy or aspirin single antiplatelet therapy, and decreased major bleeding rates compared with combination of aspirin and oral anticoagulants. However, prolonged Dual antiplatelet therapy duration increases the risk of major bleeding compared with aspirin alone, which has been strongly related to an increased risk of short and long-term mortality. The Clopidogrel for the Reduction of Events during Observation(CREDO) trial randomly assigned 2116 patients scheduled for elective Percutaneous coronary intervention or deemed at high likelihood of undergoing Percutaneous coronary intervention to receive clopidogrel for up to 1 year - preceded by a 300mg loading dose or for 1month - without loading dose, in addition to aspirin. At 1 year, long-term clopidogrel therapy was associated with a 27% relative risk reduction in the combined ischaemic endpoint (death, MI or stroke) (95% CI 3.9% to 44.4%, p=0.02; absolute reduction 3%) compared with a short clopidogrel regimen, at the expense of a marginally increased risk of major bleeding (8.8% vs 6.7%, p=0.07). [17, Rank 3]

While there is general consensus on 1-month Dual antiplatelet therapy duration after BMS implantation, the optimal duration of Dual antiplatelet therapy after drug-eluting stents implantation implantation remains a matter of debate. Newer generation drug-eluting stents implantation with thinner strut thickness, biocompatible or biodegradable polymer coatings, and reduced sirolimus-analogue

antiproliferative drug doses have been developed to improve arterial healing and reduce the risk of late thrombotic adverse events, which may potentially mitigate the need for prolonged intense platelet inhibition after drug-eluting stents implantation implantation. The conflicting evidence concerning optimal Dual antiplatelet therapy duration after drug-eluting stents implantation implantation is reflected in the contradictory results of 12 randomised controlled trials (RCT) performed to date to address this challenging and unsolved clinical issue. The inconsistent results may in part be explained by important differences in study designs, patient risk profiles, Dual antiplatelet therapy strategies, DES types implanted and study primary endpoints. Most of the trials have been characterised by slow enrolment, inclusion of low-risk patients and limited statistical power due to sample size estimates based on large event rates reductions or non-inferiority margins, coupled with lower than anticipated observed event rates. In addition, several study designs combined both efficacy and safety outcomes into a single primary endpoint, thus confusing the relative risks and benefits of individual ischaemic and bleeding outcomes.

Most of contemporary studies have compared either shorter (3–6 months) or longer (18–48 months) courses of Dual antiplatelet therapy versus 12-month Dual vantiplatelet therapy duration, which has traditionally been considered as the recommended Dual antiplatelet therapy duration for most patients after drug-eluting stents implantation implantation. Conversely, with the exception of the Dual antiplatelet therapy study, four RCTs have consistently failed to demonstrate a reduction in ischaemic events with Dual antiplatelet therapy prolongation beyond 12 months (up to 48 months), as compared with 12-month DAPT. [18, Rank 3]

Antiplatelet therapy after CABG (Coronary Artery Bypass Graft)

While aspirin administration remains a class I indication, the benefits of combined aspirin and clopidogrel therapy after CABG remain controversial. In a large meta-analysis including 728 patients after CABG, early saphenous vein graft occlusion and mortality rates were significantly reduced among patients receiving aspirin and clopidogrel compared with those treated with aspirin alone, whereas rates of perioperative angina or MI were similar between the two treatment groups. However, patients treated with DAPT showed a marginally increased risk of major bleeding,

> **"Antiplatelet therapy with aspirin, preferably when initiated within 24 hours after CABG, has been shown to significantly improve early postoperative saphenous vein graft patency and reduce major adverse ischaemic events in patients undergoing surgical revascularisation."**

compared with those treated with aspirin alone (RR 1.17, 95%CI 1.00 to 1.37, p=0.05).

In a pooled subgroup analysis of patients undergoing off-pump CABG, combined aspirin and clopidogrel therapy significantly reduced perioperative MI and saphenous vein graft occlusion rates by 68% and 55%, respectively. In another meta-analysis, antiplatelet monotherapy was associated with increased rates of early graft occlusion compared with Dual antiplatelet. These findings were mainly driven by significantly increased vein graft occlusion rates in patients treated with single antiplatelet therapy, whereas no beneficial effect was demonstrated on arterial graft occlusion rates in the Dual antiplatelet therapy group. These data might suggest the potential benefits of Dual antiplatelet therapy after CABG on vein graft, but not arterial graft, patency, at the expense of a marginally increased risk of bleeding events.

A prospective observational study compared short- (30 days) versus long-term (mean duration 34 months) administration of clopidogrel in addition to aspirin among 591 consecutive patients undergoing isolated off-pump CABG. After a mean follow-up of 38 months, postoperative clopidogrel administration was independently associated with reduced MACE (sudden cardiac death, MI or coronary reintervention) and symptom recurrence rates (p<0.0001 for both).

However, there was no significant difference in the incidence of individual ischaemic endpoints- all cause death, sudden cardiac death, MI, congestive heart failure, coronary reintervention or angina between short- and long-term clopidogrel administrations after multivariate analysis.

In the prevention of Coronary arteRY bypaSS occlusion After off-pump procedures (CRYSSA) single-centre RCT including 300 patients who underwent off-pump CABG, combined aspirin and clopidogrel therapy was shown to significantly reduce vein graft (7.4% vs 13.1%, p=0.04) but not arterial graft occlusion rates (4.9% vs 4.9%) and major adverse ischaemic events (death, MI, percutaneous

coronary interventions or stroke) (4.7% vs 9.3%, p=0.1), compared with aspirin alone. The rates of minor or major bleeding events (3.3% vs2.6%) were similar between the two treatment arms. [24, Rank 2]

For patients treated with Dual antiplatelet therapy after PCI who subsequently undergo CABG, P2Y12 receptor antagonist therapy should be resumed postoperatively to complete the recommended Dual antiplatelet therapy duration (class I). In patients with stable CAD undergoing CABG, Dual antiplatelet therapy with clopidogrel (initiated early in the postoperative period) for 12 months may be considered to improve vein graft patency (class IIb). Due to the lack of clinical evidence in patients with stable CAD, the use of potent P2Y12 receptor inhibitors (prasugrel or ticagrelor) is currently not recommended. Nevertheless, the efficacy and safety of an intensified platelet inhibition using ticagrelor after CABG are currently investigated in the Ticagrelor in CABG (TiCAB) trial (NCT01755520), an ongoing, multicentre, double-blind, double-dummy, randomised trial that will compare ticagrelor with aspirin for the prevention of MACE within 12 months after CABG. The study will randomise 3850 patients undergoing CABG in a 1:1 fashion to either ticagrelor 90 mg twice daily or aspirin 100 mg once daily. Of note, the study medication will be started within 24 hours after surgery and maintained for 12 months. The primary endpoint will be a composite of cardiovascular death, MI, stroke and repeat revascularisation at 12 months after CABG. [23, Rank 5]

Antiplatelet therapy in Acute Coronary Syndrome

Antiplatelet therapy with aspirin remains the cornerstone of pharmacological therapy for patients with ACS, irrespective of the clinical setting (non-ST-elevation ACS (NSTE-ACS), or ST-elevation myocardial infarction (STEMI)) and the patient management strategy (conservative treatment, percutaneous coronary interventions or CABG). In a meta-analysis of 16 secondary prevention trials comparing long-term aspirin versus control therapy in 17 000 high-risk patients, aspirin significantly reduced MACE by 20%, non-fatal stroke by 19% and cardiovascular mortality by 9%. However, there is ongoing debate regarding the optimal maintenance dose of aspirin for secondary prevention of cardiovascular events in patients with acute coronary syndrome. In the Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events-Seventh Organization to Assess Strategies in Ischemic Syndromes

(CURRENT-OASIS 7) trial including 2586 patients with acute coronary syndrome, no significant difference was observed between high-dose (300–325 mg daily) and low-dose (75–100mg daily) aspirin with regard to the composite endpoint of cardiovascular death, MI or stroke at 30 days, irrespective of the management strategy as a conservative treatment. Low-dose aspirin was associated with significant lower rates of major gastrointestinal bleeding, whereas high-dose aspirin showed no reduction in rates of the primary endpoint or major bleeding in the subgroup of patients undergoing percutaneous coronary interventions. Furthermore, a subanalysis of the Platelet Inhibition and Patient Outcomes (PLATO) trial has recently suggested a reduced efficacy of ticagrelor versus clopidogrel in acute coronary syndrome patients treated with high aspirin doses, whereas ticagrelor appeared to be more effective than clopidogrel in decreasing cardiovascular events in patients on low-dose aspirin.

Although the exact mechanism underlying the potential interaction between ticagrelor and higher aspirin doses remains unclear, a proposed hypothesis is linked to the level of P2Y12 inhibition and the potential prothrombotic effects of high-dose aspirin through the suppression of prostacyclin. Overall, data regarding the use of aspirin for secondary prevention of cardio vascular events in patients with acute coronary syndrome demonstrate a general lack of benefit of high maintenance doses of aspirin owing to the absence of a dose–response relationship between increasing aspirin dose and improved efficacy, and a higher incidence of gastrointestinal bleeding with increasing aspirin doses. [25, rank 4]

Guidelines for High On-Treatment Platelet Reactivity

High platelet reactivity in patients prescribed aspirin has been associated with an increased risk of thrombotic events. Therefore, this phenomenon has been used as one definition of aspirin resistance. Observational studies demonstrate that about one-third of patients treated with aspirin demonstrate less-than-expected inhibition of agonist-induced platelet aggregation and increased levels of urinary thromboxane.

Estimates of the prevalence of high on-treatment platelet reactivity are affected by differences among the studies in patient characteristics - age, female sex, diabetes, concomitant therapies particularly NSAIDs, eg, ibuprofen, the laboratory test used to measure the antiplatelet effects of aspirin light transmission or whole-blood aggregometry, shear stress-induced platelet

activation, expression of activation markers on the platelet surface as measured by flow cytometry, inhibition of thromboxane production, the cut-off used to define high on-treatment reactivity, and patient compliance with aspirin therapy. Despite these differences, high platelet reactivity in patients prescribed aspirin has been consistently associated with a twofold to fourfold higher risk of MI, stroke, or death. [26, rank 4]

If thrombotic events in aspirin-treated patients with high on-treatment platelet reactivity were solely attributable to reduced responsiveness to aspirin, strategies aimed at improving the response would be expected to reduce this risk. Observational studies suggest that aspirin inhibits platelet function and coagulation in a dose-dependent manner; a finding confirmed in a randomized dose comparison.

Thus, in a randomized, double-blind, crossover trial that included 125 patients with stable coronary artery disease, it was demonstrated that at doses of 81, 162, or 325 mg/d, aspirin inhibited adenosine diphosphate (ADP) and collagen-induced platelet aggregation, blocked shear-dependent platelet aggregation measured by the PFA-100 device, and reduced urinary thromboxane concentrations in a dose-dependent manner. Most of the patients included in this study demonstrated near-complete inhibition of arachidonic acid-induced platelet aggregation with the 81-mg/d dose of aspirin, but higher aspirin doses reduced the proportion of patients in whom arachidonic acid-induced aggregation exceeded a cut-off value of 20%.

The relationship between platelet reactivity and thrombotic risk is confounded by comorbidities, such as smoking or diabetes that affect both platelet function and cardiovascular risk. It is also possible that the laboratory tests used to measure platelet reactivity fail to monitor the mechanism by which aspirin reduces the risk of thrombotic events. Many of these tests use non-physiologic stimuli to induce platelet aggregation, and none assess platelet interaction with the vessel wall or the effect of aspirin on COX-2-dependent PGI2 production. Thromboxane production appears to be the most specific measure of the inhibitory effects of aspirin because thromboxane is the major biochemical end product of the platelet COX-1 biosynthetic pathway that is targeted by aspirin. However, serum thromboxane levels reflect the maximum capacity of platelets to produce thromboxane; urinary thromboxane is also produced from nonplatelet sources, and measures of thromboxane concentration do not capture the effect of aspirin on PGI2 production. [27, Rank 3]

Given the multifactorial triggers of atherothrombosis and the likelihood that platelet activation and subsequent aggregation are not the sole mediators of vascular events, it is not surprising that only a fraction usually one-fourth to one-third of all vascular complications can be prevented by aspirin alone. There is no evidence that patients who experience a thrombotic event despite aspirin therapy benefit from treatment with higher-dose aspirin. Concomitant administration of nonselective NSAIDs, such as ibuprofen, should be avoided because, as outlined previously, these drugs can interfere with the antiplatelet effect of aspirin.

A pharmacodynamic interaction between naproxen and aspirin has also been described, but this does not appear to occur with rofecoxib, celecoxib or diclofenac, drugs endowed with variable COX-2 selectivity. The US Food and Drug Administration (FDA) has issued a statement informing patients and health-care professionals that ibuprofen can interfere with the antiplatelet effect of low-dose aspirin (81 mg/d), potentially rendering aspirin less effective when used for cardioprotection or stroke prevention. [28, Rank 5]

Safety and Efficacy: Specific Guidelines

Prevention of Atherothrombosis

The efficacy and safety of aspirin are documented from analyses of > 100 randomized controlled trials that have included thousands of patients representing the entire spectrum of atherosclerosis, ranging from apparently healthy low-risk individuals to patients presenting with an acute MI or acute ischemic stroke. Trials have evaluated aspirin therapy of only a few weeks duration or as long as 10 years. Although aspirin has consistently been shown to be effective in preventing fatal and nonfatal vascular events in these trials, the absolute benefits depend on the clinical setting.

In Second International Study of Infarct Survival (ISIS-2), a single 162.5-mg tablet of aspirin started within 24 h of the onset of symptoms of a suspected MI and continued at the same dose daily for 5 weeks produced highly significant reductions in vascular mortality, nonfatal reinfarction, and nonfatal stroke (23%, 49%, and 46%, respectively). There was no associated increase in hemorrhagic stroke or gastro intestinal bleeding with aspirin, although there was a small increase in minor bleeding. Based on the results of this

study, a 5-week course of aspirin treatment in 1,000 patients with suspected acute MI will prevent 40 vascular events, a proportional odds reduction of 30%.

Two separate trials with a similar protocol tested the efficacy and safety of early aspirin use in acute ischemic stroke. The Chinese Acute Stroke Trial and the International Stroke Trial collectively randomized 40,000 patients within 48 h of the onset of stroke symptoms to 2 to 4 weeks of daily aspirin therapy at doses of 160 and 300 mg/d, respectively or to placebo. An overview analysis of the results of both trials indicated an absolute benefit of nine fewer deaths or nonfatal strokes per 1,000 patients in the first month of aspirin therapy. The proportional odds reduction in the risk of fatal or nonfatal vascular events was only 10% in this setting. Although the background risk of hemorrhagic stroke was threefold higher in the Chinese Acute Stroke Trial than in the International Stroke Trial, the absolute increase in this risk was similar in the two studies (an excess of 2/1,000 aspirin-treated patients). [29, Rank 3]

Long-term aspirin therapy confers a conclusive net benefit on the risk of subsequent MI, stroke, or vascular death among subjects with a high risk of vascular complications. These include patients with chronic stable angina, prior MI, unstable angina, history of transient ischemic attack or minor stroke, and other high-risk categories. The proportional reduction in vascular events with long-term aspirin therapy in these various clinical settings ranges from 20% to 25% based on an overview of all of the randomized trials. Estimates of relative benefits based on the results of individual trials vary from no statistically significant benefit in patients with peripheral arterial disease to an 50% risk reduction in patients with unstable angina. In terms of absolute benefit, the protective effects of aspirin translate into avoidance of a major vascular event in 50 of 1,000 patients with unstable angina treated with aspirin for 6 months to 36 of 1,000 patients with prior MI, stroke, or transient ischemic attack-treated with aspirin for 30 months.

> **"Compared with aspirin monotherapy, dual antiplatelets provide significant incremental reduction of cardiovascular events in patients with acute coronary syndrome and are considered the cornerstone of pharmacological treatment, irrespective of the management strategy."**

Primary Prevention

Among most high-risk patient groups, the expected number of individuals avoiding a serious vascular event by using aspirin substantially exceeds the number experiencing a major bleed. It is less certain, however, whether aspirin is of benefit in apparently healthy people who are at intermediate risk for serious vascular events because they have well-established cardiovascular risk factors. The Antithrombotic Trialists' Collaboration addressed this issue in an individual participant data meta-analysis of the results of large randomized trials of aspirin for primary prevention of vascular events. The analysis was based on the results of six primary prevention trials that included 95,456 subjects with a mean follow-up of 6.9 years and a median follow-up among survivors of 5.5 years, reflecting the fact that the Women's Health Study, which accounted for almost one-half of the participants, had a mean follow-up of 10 years. The effects of aspirin for primary prevention were compared with its effects in high-risk settings using the results of six trials among patients with a history of MI, nine trials among patients with a history of TIA or stroke, and one trial in patients with moderately severe diabetic retinopathy. [31, Rank 3]

Aspirin had no significant effect on the aggregate of all vascular causes of death, and there was no evidence of a protective effect on the two-thirds of vascular deaths due to coronary heart disease, the one-sixth due to stroke, or the remaining vascular causes of death. Aspirin had no significant effect on nonvascular mortality or unknown causes of death but increased the risk of major extracranial bleeds.

The absolute benefits of aspirin were summarized under the term "occlusive vascular events," that is, vascular events other than hemorrhagic stroke or fatal extracranial bleeds. Among low-risk individuals - annual risk of coronary heart disease ≤ 1%) allocation to aspirin resulted in the avoidance of four occlusive vascular events per 1,000 after 5 years, which was chiefly attributable to three fewer major coronary events. This benefit was offset by two additional major extracranial bleeds per 1,000 over the same 5-year period, but there was no significant excess risk of hemorrhagic stroke. Among the much smaller number of moderate-risk participants (yearly coronary heart disease risk > 1%), the net effect of aspirin over 5 years on occlusive vascular events was statistically uncertain because despite a definite reduction in major coronary events fewer per 1,000, there was no significant reduction in presumed ischemic

stroke and there was an excess of both haemorrhagic stroke and major bleeds. About one-half of the hemorrhagic strokes were fatal (and the remainder would be expected to result in moderate or severe disability), so this hazard substantially offsets any cardiac benefits in moderate-risk individuals. [32, Rank 4]

Previous meta-analyses of the effects of antiplatelet therapy in persons at high risk of occlusive vascular disease have shown that the benefits of aspirin far exceed the bleeding risks. By contrast, the majority (92%) of participants in the primary prevention trials was at low absolute risk of coronary disease; on average, the annual risk of a vascular event in the primary prevention trials was only about one-tenth of that in the high-risk trials. Although the proportional benefits of aspirin appeared broadly similar when used for primary or secondary prevention, the absolute benefits of aspirin in the primary prevention trials were very small. When used for primary prevention, fewer than one person of every 1,000 treated with aspirin would avoid an occlusive vascular event, whereas a comparably small number would experience a major extracranial bleed. Until the benefits of aspirin can be defined more precisely, therefore, the possibility of a benefit for vascular prevention does not seem to justify the potential for harms. However, these estimates do not take into account the benefits of aspirin for the prevention of cancer and cancer-related mortality, which might tip the balance in favour of aspirin use for primary prevention. [33, rank 5]

Atrial Fibrillation

Anticoagulant therapy with dose-adjusted warfarin international normalized ratio, 2.0-3.0), the direct thrombin inhibitor dabigatran etexilate, or the direct factor Xa inhibitors rivaroxaban and apixaban is very effective in reducing the risk of stroke in patients with nonvalvular atrial fibrillation. The efficacy of aspirin - in doses ranging from 75-1,200 mg/ d has been compared with that of placebo or no antiplatelet treatment in seven randomized trials that included 3,990 patients with nonvalvular atrial fibrillation. A pooled analysis revealed a relative risk reduction of 19% with aspirin compared with placebo or no treatment, which is consistent with the 22% relative risk reduction obtained when comparing any antiplatelet therapy with placebo or no antiplatelet therapy for stroke prevention in patients with nonvalvular atrial fibrillation. Pooled analysis of 10 trials involving 4,620 patients with nonvalvular atrial fibrillation revealed that dose-adjusted vitamin K antagonist therapy

was significantly more effective than aspirin, with a 39% relative risk reduction. Warfarin is also more effective than the combination of aspirin and clopidogrel.

The efficacy of antiplatelet therapy for stroke prevention in atrial fibrillation has been confirmed by the results of the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE) A trial, which compared the combination of aspirin plus clopidogrel with aspirin alone in 7,554 patients deemed ineligible for warfarin. Aspirin plus clopidogrel reduced the risk of major vascular events, comprising the composite of stroke, MI, non-CNS embolism, or death from vascular causes, by 11% compared with aspirin (95% CI, 2%-19%) primarily because of a 28% reduction in stroke (95% CI, 17%-38%). However, the combination of clopidogrel plus aspirin is less effective than warfarin and is associated with a similar risk of bleeding. [34, Rank 3]

Atrial Fibrillation

The Pulmonary Embolism Prevention (PEP) trial results demonstrated that aspirin is effective in preventing Venous Thrombo Embolism after major orthopedic surgery. This double-blind, multicenter study included 13,356 patients undergoing surgery for hip fracture and an additional 4,088 patients undergoing elective hip or knee arthroplasty. Patients were randomized to receive aspirin (160 mg/d) or placebo for 5 weeks, with the first dose administered prior to surgery. Other forms of prophylaxis were allowed, and either heparin or low-molecular-weight heparin was used in 40% of the patients. Among the 13,356 patients undergoing surgery for hip fracture, aspirin produced a 36% reduction in symptomatic deep vein thrombosis or pulmonary embolism. A similar relative risk reduction was observed in aspirin-treated patients who did or did not receive concomitant heparin or low-molecular-weight heparin. These results are consistent with those of meta-analyses performed by the Antiplatelet Trialists' Collaboration and by Sandercock and colleagues of antiplatelet trials in patients with stroke.

A large randomized controlled trial is required to compare the effectiveness of aspirin with that of anticoagulants for the prevention of fatal or symptomatic Venous Thrombo Embolism events. [35, Rank 3]

Placental Insufficiency

Preeclampsia and fetal growth restriction are believed to be related to reduce placental blood flow, which is believed to be caused by constriction,

thrombosis, or both of small placental arteries. The initial reports that low-dose aspirin therapy reduces the risk of severe low birth weight among newborns and lowers the need for cesarean section in mothers with pregnancy-induced hypertension led to the widespread use of prophylactic aspirin for prevention of preeclampsia. Subsequently, several larger trials reported no beneficial effects of aspirin. However, a systematic review of data from 59 trials in 37,560 women confirmed that antiplatelet therapy (mostly aspirin 60 mg/d) is beneficial.

Aspirin was associated with a 17% decrease in the risk of preeclampsia, an 8% reduction in the risk of preterm birth, a 14% reduction in the risk of fetal or neonatal death, and a 10% reduction in small-for-gestational age babies. An individual patient meta-analysis of 31 trials involving 32,217 patients who received antiplatelet therapy for primary prevention of preeclampsia revealed a consistent benefit of aspirin for the prevention of eclampsia (overall 10% relative risk reduction) in all of the subgroups studied (first pregnancy with or without any high risk factor; second pregnancy with or without high risk factors or history of hypertensive disorder of pregnancy; preexisting renal disease, diabetes, hypertension, or previous infant small for gestational age; maternal age; singleton or multiple pregnancy; and timing of starting of treatment or intended aspirin dose ≤ 75 mg/d or ≥ 75 mg/d). Aspirin given in doses ranging from 50 to 150 mg/d accounted for 98% of women included in this data set. [36, Rank 3]

Cancer Incidence and Mortality

There is compelling evidence from randomized controlled trials that aspirin reduces the incidence of colorectal cancer and cancer mortality. An individual patient meta-analysis of eight randomized controlled trials that included 25,570 subjects demonstrated that compared with no aspirin, daily aspirin for a scheduled mean treatment duration of at least 4 years reduced the odds of cancer deaths by 21% (95% CI, 8%-32%). The mortality benefit appeared to be unrelated to aspirin dose, only became apparent after 5 years of follow-up, and the absolute benefit increased over time. The greatest mortality benefit was seen with adenocarcinoma. Among patients aged ≥ 65 years at the start of the trials, the absolute reduction in cancer deaths over 20 years was 7.1% (95% CI, 2.4%-11.7%). Separate analyses based on individual patient data from four trials of 14,033 patients followed for a median of

18.3 years demonstrated that aspirin (at doses of 75-300 mg/d) also reduced the incidence of colorectal cancer. Furthermore, an analysis from the Transient ischaemic attack trial suggested that the risk of fatal colorectal cancer was higher with aspirin doses of 30 mg/d than it was with a dose of 283 mg/d. [37, Rank 3]

Conclusion

Antiplatelet therapies are effective for prevention of platelet-rich arterial thrombi that form under high-shear conditions. Antiplatelet therapies are also effective for the prevention of fibrin-rich thrombi that form under low-shear conditions, such as VTE and left atrial appendage thrombi that form in patients with atrial fibrillation, but for these indications, antiplatelet drugs are less effective than anticoagulants. The efficacy of antiplatelet drugs for thrombosis prevention is explained by their ability to block well-characterized pathways involved in platelet activation and aggregation. It is these actions that also lead to the major side effect of antiplatelet therapy, which is bleeding. The efficacy of antiplatelet therapy can be improved by increasing the intensity of therapy by using more-potent antiplatelet drugs or combinations of antiplatelet drugs but at the cost of an increase in bleeding. Under certain circumstances, efficacy can also be improved by using more rapidly acting drugs. [40, rank 5]

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