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«Antithrombotic treatment after Coronary Stent Thrombosis»

by

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Abstract

Percutaneous coronary interventions (PCI) are the standard of care for patients with coronary artery disease (CAD) who are experiencing an acute coronary syndrome (ACS). Adjunctive medication, including antithrombotic medication, is essential for improving patient outcomes after PCI. Indeed, both acute and long-term ischemic episodes can occur in post-PCI patients. Antithrombotic medications, especially antiplatelet agents, are therefore essential for the management and avoidance of thrombotic problems that can occur locally as well as systemically. The antiplatelet therapy regimens utilized in post- PCI patients have evolved during the previous forty years. This can be attributed to several factors, including advancements in stent technologies that have resulted in safer, novel antiplatelet medications, and reduced thrombogenic stent technologies, and a better understanding of the prognostic significance of bleeding, which is the most concerning risk linked to the use of antiplatelet therapies. Additionally, a number of studies have contributed to the creation of a patient profile that highlights those who are more susceptible to ischemic and bleeding complications. These characteristics additionally created up opportunities for individualized treatment regimens, as we owe the knowledge that people may react differently to particular antiplatelet medications, aimed at optimizing both efficacy and safety. In this thesis, we present the rationale, review the

evidence, and summarize current trends, with a special view on oral antiplatelet therapeutic options.

Abbreviations

ACS: Acute coronary syndrome
AM: Acute Marginals
ARC: Academic Research Consortium
ASA: Acetylsalicylic acid
ASCVD: Atherosclerotic cardiovascular disease
BMS: Bare metal stents
CAD: Coronary artery disease
CABG: Coronary artery bypass grafting
DAPT: Dual antiplatelet therapy
DES: Drug Eluted Stents
ECG : Electrocardiogram
HPR: High platelet reactivity
hs-cTn: High-sensitivity cardiac troponin
LAD: Left Anterior Descending
LCX: Left circumflex
LDL: Low-density lipoprotein
MACCE: Major adverse cardiovascular and cerebrovascular events
MI: Myocardial Infarction
NSTEMI: Non ST-elevation MI
OM: Obtuse marginal
PAD: Peripheral artery disease
PCI : Percutaneous coronary interventions
RCA: Right coronary artery
SA: sinoatrial artery
SMCs: Smooth muscle cells
STEMI: ST-elevation MI
ST: Stent Thrombosis
SAPT: single antiplatelet therapy

TVR: target vessel revascularization

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Chapter 1: Introduction

1.1 Coronary network

The left main and the right coronary artery are the two main arteries that deliver blood to the myocardium (Figure 1). The base of the ascending aorta serves as the origin of both arteries. The left anterior descending (LAD) and left circumflex (LCx) arteries immediately separate out from the left main, which originates from the left coronary sinus of Valsalva. The LAD divides into three segments as it travels along the anterior epicardial ventricular septum: the proximal, mid, and distal segments. It then splits into several side branches. The proximal and mid portions of the larynx are divided by the first septal perforator. From proximal to distal, the number and diameter of the diagonal branches are named successively (e.g., D1, D2, etc.). The LCx divides into obtuse marginal (OM) branches, which are named similarly from proximal to distal, as it passes down the left atrioventricular sulcus. The right coronary sinus is the source of the right coronary artery (RCA), which is further divided into proximal, mid, and distal segments. The proximal segment is located from the ostium until the start of the first acute marginal (AM) artery. The proximal RCA branches off and proceeds posteriorly to become the sinoatrial (SA) artery, which is usually the second visible artery. The RCA splits further into a number of acute marginal branches, listed from proximal to distal, that differ in size and width as well. The term "dominance" describes whether the RCA, LCx, or both are the posterior descending artery's (PDA) original source. The coronary system forms the densest capillary network in the entire body, with each muscle fiber of the myocardium being accompanied by one capillary—approximately 2,500 capillaries per mm^3 of myocardium.

Furthermore, the amount of oxygen provided to the heart's tissues is more than twice that of any other part of the body. [1]

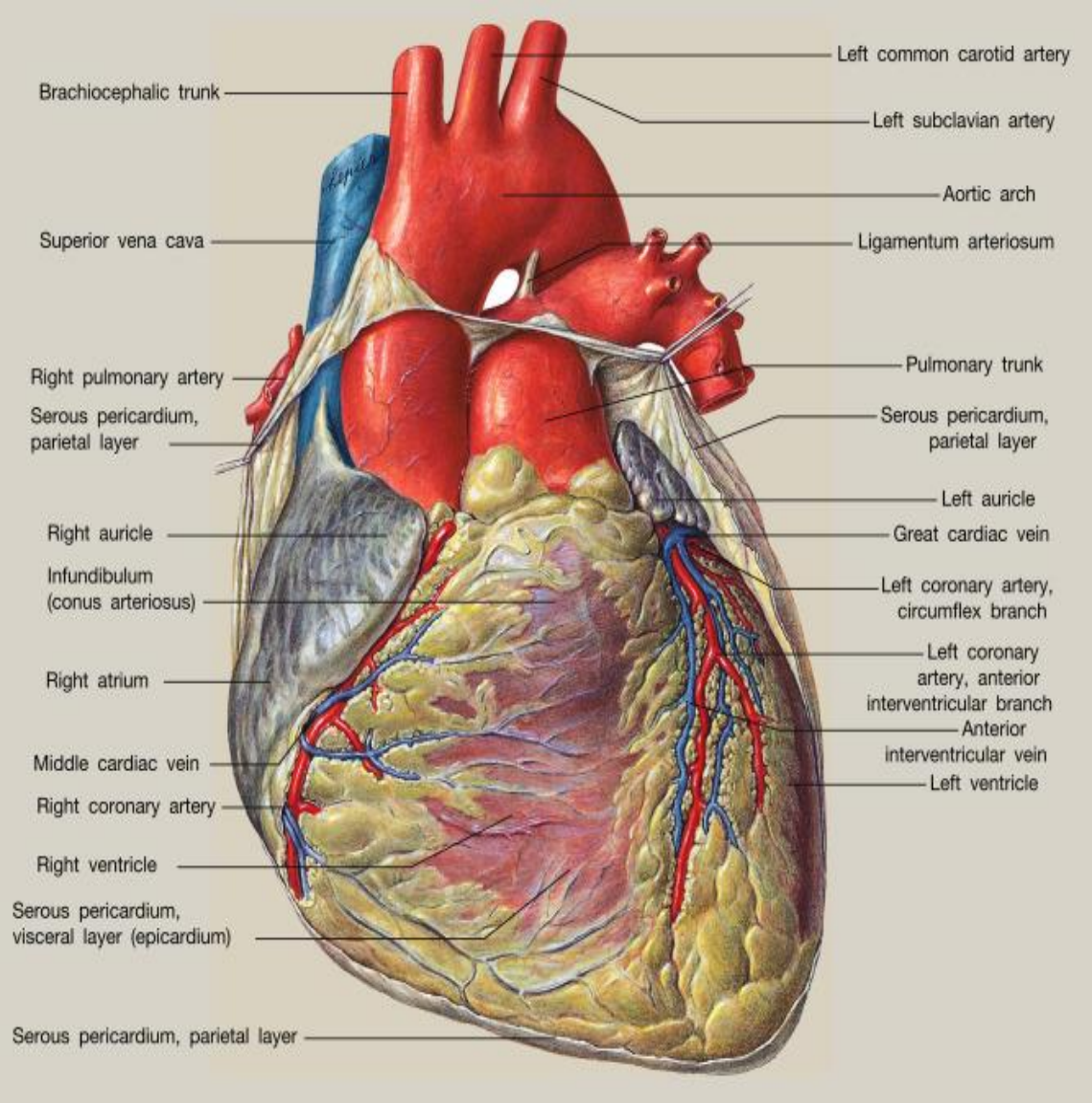


Figure 1: The coronary arteries [1]

1.2 Atherosclerosis

High levels of low-density lipoprotein (LDL) cholesterol are the main cause of atherosclerosis, a complicated inflammatory disease. It starts when lipids in the artery walls are retained and oxidized. This leads to persistent

inflammation and either thrombosis or stenosis of the vessel [2]. Atherosclerotic plaques frequently block the main arteries that provide blood to the whole body. The lesions usually start in the artery's intima layer and spread throughout the arterial wall. Hypercholesterolemia, tobacco, diabetes, obesity, hypertension, and genetic susceptibility are common risk factors that lead to the formation of these lesions. In humans, atherosclerosis has mostly been examined in great detail in the coronary arteries, carotid arteries, and aorta. Individual differences exist in the onset and course of atherosclerosis. The process occurs when lipids high in cholesterol build up in the artery wall, causing the arterial tissue to become inflamed. Extensive histopathological investigations in people and animals have elucidated the pattern of plaque progression in the coronary, carotid, and aortic arteries (Figure 2). Usually, the endothelium monolayer undergoes a qualitative alteration to initiate atherogenesis. Endothelial cells initially repress white blood cell attachment; but, in response to inflammatory stimuli, they start to release adhesion molecules, which allow leukocytes to adhere to their surfaces. Alternates in endothelial properties and modifications to the extracellular matrix composition underneath the endothelium are the two main mechanisms that allow LDL cholesterol to enter the arterial wall. Monocytes become macrophages once they enter and settle in the artery wall. In the growing atheroma, these mononuclear phagocytes evolve into foam cells. Smooth muscle cells (SMCs) go to the tunica intima from the middle layer of the artery, where they proliferate in response to growth factor generated from platelets, which is the process by which atheromas arises [3]. Subsequently, SMCs generate extracellular matrix molecules in the intima, creating a fibrous covering that envelops the plaque. A complex of foam cells produced from macrophages is covered by this cap; some of these cells die and release lipids that collect extracellularly. The atheromatous plaque may develop a lipid-rich pool, or necrotic core, as a result of this efferocytosis process. Often, plaque lesions result in the artery lumen narrowing, which obstructs blood flow and may induce tissue ischemia. Sometimes a plaque's fibrous cover might burst, causing thrombi to form.

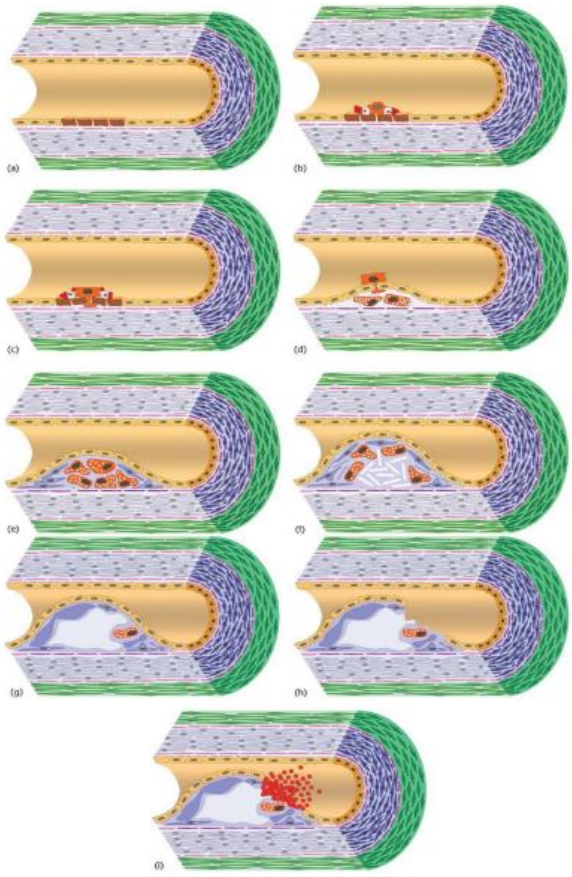


Figure 2: Pathogenesis of atherosclerosis. Endothelial dysfunction initiates the process by which blood leukocytes—specifically T lymphocytes (white) and monocytes (orange)—and thrombocytes adhere to the endothelial surface. Monocytes then migrate into the subendothelial space through diapedesis. Simultaneously, smooth muscle cells (light blue) migrate from the media into the subendothelial tissue, contributing to adaptive intimal thickening and foam cell formation, which marks the development of an atheroma. A synthetic phenotype (purple) is adopted by smooth muscle cells during this phase, which causes an increase in the deposition of purple extracellular matrix material in the subendothelial region.Increased foam cell development continuous transportation of SMCs, and additional deposition of extracellular matrix proteins (purple) are the reasons behind the thickening of the lesion. The lesion eventually develops a purple fibrous cap, and foamy macrophage death leads to the development of a necrotic lipid core. The manufacture of proteases by macrophages results in a thinner fibrous cap, which increases the plaque's susceptibility to rupture or erosion of the underlying endothelium. When this happens, blood exposure to subendothelial tissue triggers the clotting cascade, which results in the creation of a thrombus.

A number of risk factors, such as high blood pressure, smoking, angiotensin II, diabetes, and high cholesterol, have been linked to and have been shown to hasten the atherogenesis process (Table 1). Aneurysms frequently occur as a result of increased artery wall strain brought on by hypertension. By encouraging leukocyte adhesion, angiotensin II modifies endothelial function. Smoking and diabetes both have a major impact on blood vessel biology, which accelerates the process of atherogenesis. Many studies have been conducted on the function that cholesterol, especially LDL cholesterol, plays in this process. Lipids play a crucial function in the formation and advancement of atheromatic lesions, however a clear causal link in between lipids and atherogenesisas still not been established. Elevated LDL metrics are strongly related to an increased risk of cardiovascular disease and a greater individual susceptibility to atherosclerosis. Conversely, reducing LDL levels is directly linked to a lower likelihood of cardiovascular events. The cardiovascular risk is also heightened by monogenic disorders, which can exacerbate lipid imbalances. [4}

Category	Number	Risk Factor
Major	1	Unhealthy blood cholesterol and lipoprotein levels
	2	High blood pressure
	3	Smoking
	4	Insulin resistance
	5	Diabetes
	6	Overweight or Obesity
	7	Lack of physical activity
	8	Unhealthy diet
	9	Older age
	10	Family history of early heart disease
	11	Inflammation
Emerging Risk Factors	12	High levels of C-reactive protein (CRP)
	13	Triglycerides
	14	Sleep apnea
	15	Stress
	16	Alcohol

Table 1: The risk factors of Atherosclerosis. [5]

1.3 Coronary artery disease

Atherosclerotic plaque development in the vessel lumen is a frequent cardiac ailment known as coronary artery disease. When the coronary arteries occlude, the heart's supply and demand of oxygen are out of balance, which results in coronary artery disease (CAD). Usually, this disease is caused by plaques that build up in the coronary artery lumen and prevent blood circulation. The primary cause of death both internationally and in the US is CAD. At the arise of the 20th century, it was a relatively rare cause of death, but mortality rates peaked in the mid-1960s before declining. Despite this decrease, CAD remains the foremost cause of death worldwide. Many variables influence the development of CAD. Modifiable and non-modifiable factors are the two main categories of etiologic factors. Certain characteristics, such as age, gender, genetics, and family history, are immutable. It is possible to modify risk factors such as cholesterol levels, obesity, smoking, and psychosocial variables. The male gender is more predisposed than the female gender. Hypercholesterolemia remains a significant risk factor for coronary artery disease (CAD). Higher levels of high-density lipoproteins (HDL) are associated with a reduced incidence of CAD, while elevated low-density lipoproteins (LDL) increase the risk. To evaluate CAD, several diagnostic modalities are commonly used, including electrocardiograms (ECG), echocardiograms, chest X-rays (CXR), stress tests, cardiac catheterization, and blood tests. The choice of tests depends on the clinical setting in which patients present. Additionally, the Atherosclerotic Cardiovascular Disease (ASCVD) 10-year risk score can be computed online using the ASCVD equation available on the online portal. Acute Coronary Syndrome (ACS) and Stable Ischemic Heart Disease (SIHD) are the two primary forms of coronary artery disease.

1.4 Acute coronary syndromes and myocardial infarction

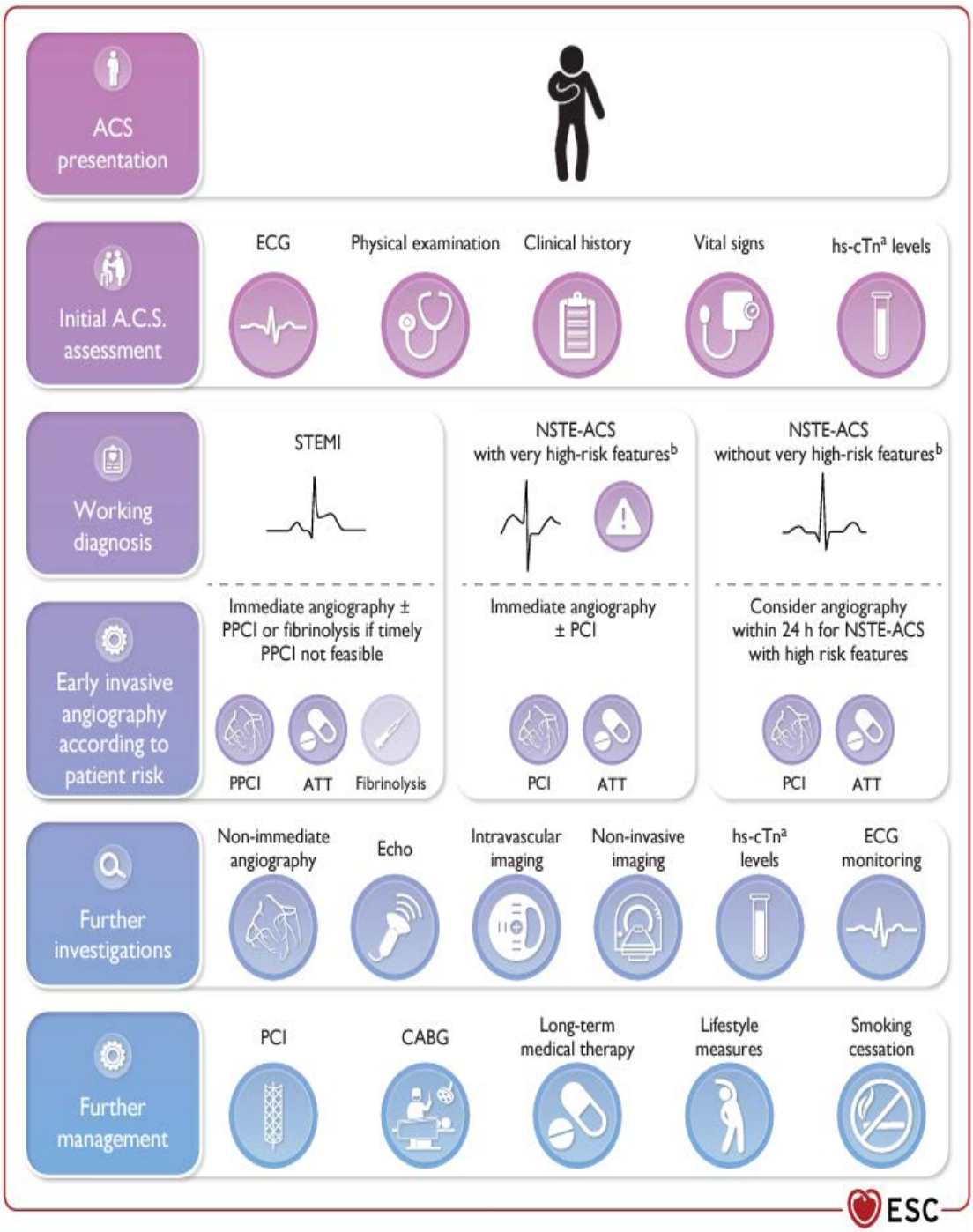


Figure 3: An overview of the preliminary diagnosis, course of care, and assessment for patients exhibiting symptoms and signs suggestive of acute coronary syndrome.[6]

1.5 Percutaneous Coronary Intervention (PCI)

Percutaneous coronary intervention (PCI), also known as coronary angioplasty, is a nonsurgical treatment for obstructive coronary artery disease, which includes unstable angina, acute myocardial infarction (MI), and multivessel coronary artery disease (CAD).

Clinical indications for PCI include the following:

- Stable and Unstable angina
- ST-elevation myocardial infarction (STEMI)
- Non–ST-elevation acute coronary syndrome (NSTE-ACS)
- Hemodynamically severe occlusion or high risk ischemia tests

1.6 Intracoronary Stents

1.6.1 First generation of DES

Initial stents were constructed of thick stainless steel and had a low radial force. They created a new issue with stent thrombosis but were successful in resolving the mechanical issue of acute artery closure following balloon angioplasty. Dual antiplatelet therapy was utilized to treat stent thrombosis that resulted from these novel devices. As time went on, a new issue with bare metal stents surfaced: in-stent stenosis, which was brought on by neo-intimal hyperplasia, which was brought on by inflammation and damage to the media and intima of the channel. In order to create intracoronary stents, a device that would lessen or cease this neo-intimal hyperplastic reaction had to

be developed. As a result first-generation drug-eluting stents were created. Antiproliferative agents, metal bases, and polymers to regulate medication release are the components of agent-eluting stents. The initial iteration of drug-eluting stents had a closed-cell architecture and were composed of stainless steel. First, sirolimus and paclitaxel were used with these stents. While paclitaxel damages the spindle apparatus during mitosis and targets tubulin in dividing cells, sirolimux, an analog of rapamycin, functions as a mTOR inhibitor. [7]

1.6.2 Second generation of DES

The issues with first-generation drug-eluting stents were attempted to be addressed by second-generation stents. With the use of thinner strut thickness therapy, the next generation of stents was created, resulting in reduced inflammation and damage to the media and quicker endothelialization and healing of the coronary culprit lesions. Rather than being made of stainless steel, second-generation drug-eluting stents are made of cobalt-chromium, which gives them greater malleability and delivery. These stents were thromboresistant and biocompatible due to the fluorinated polymers that made them up. Everolimus and zotarolimus were the medications used in these stents to prevent neointimal hyperplasia. [8]

1.6.3 Third generation of DES

The third generation of stents, which are presently in development, feature smaller struts and contain either bioabsorbable polymers or none at all. In certain cases, the stent is replaced by a scaffold that breaks down over time. Drug-coated, polymer-free stents are yet another potential advancement in third-generation stent technology. These are microstructured, 120-micron-thick stainless steel stents with an abluminal surface structure that contains the antiproliferative medication.

These polymer-free stents eliminate any chance of non-uniform medication elution from the polymer coating and may provide a shorter dual antiplatelet duration. Unlike sirolimus, everolimus, and zotarolimus, which are all 10-times less lipophilic than biolimus released by this specific stent, biolimus is able to remain in the upper layers of the cells and gradually self-elute. [9]

1.7 Antithrombotic drugs in patients undergoing percutaneous coronary intervention

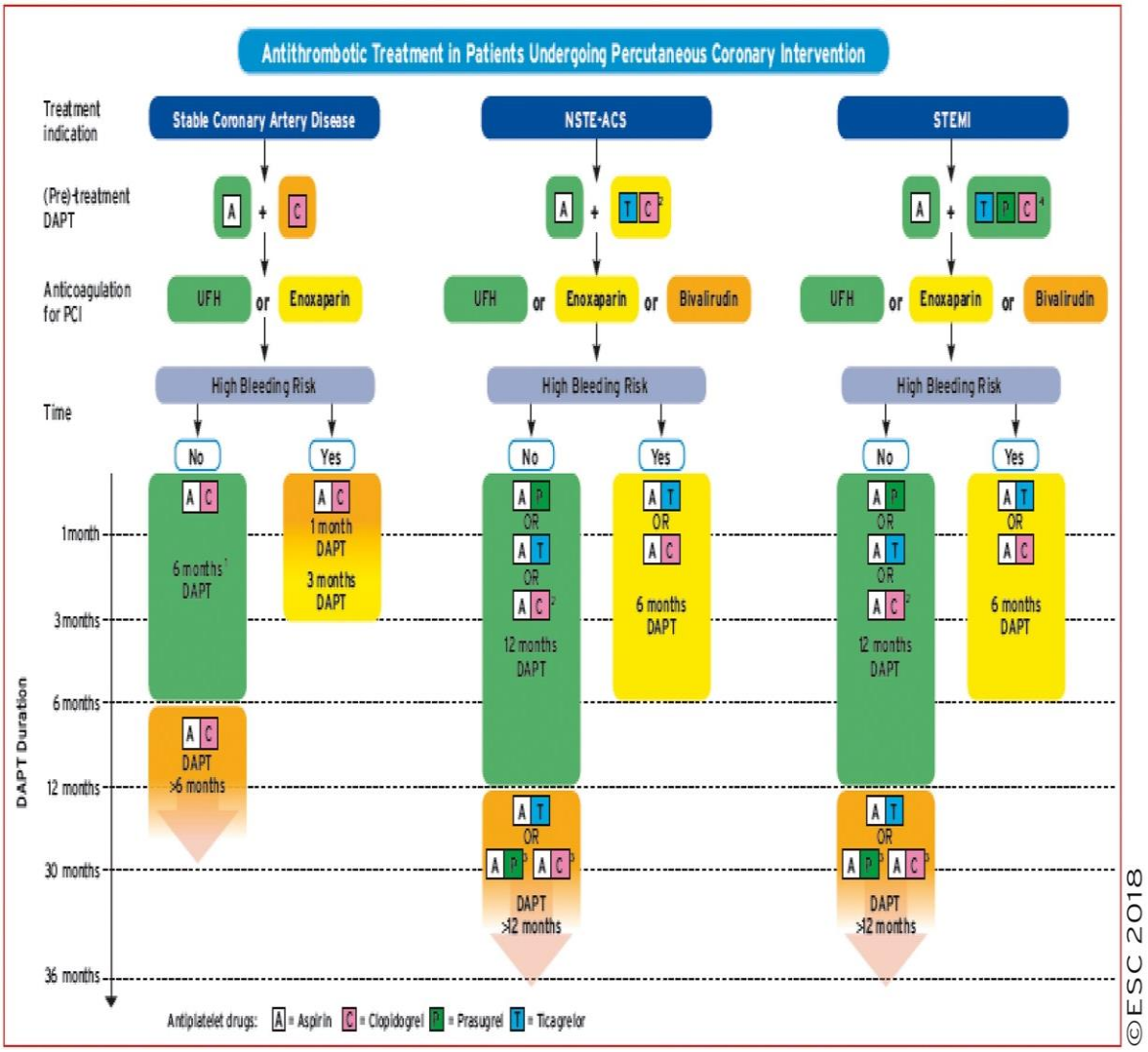


Figure 4: Guidelines for administering antithrombotic medications to patients undergoing percutaneous coronary intervention. [10]

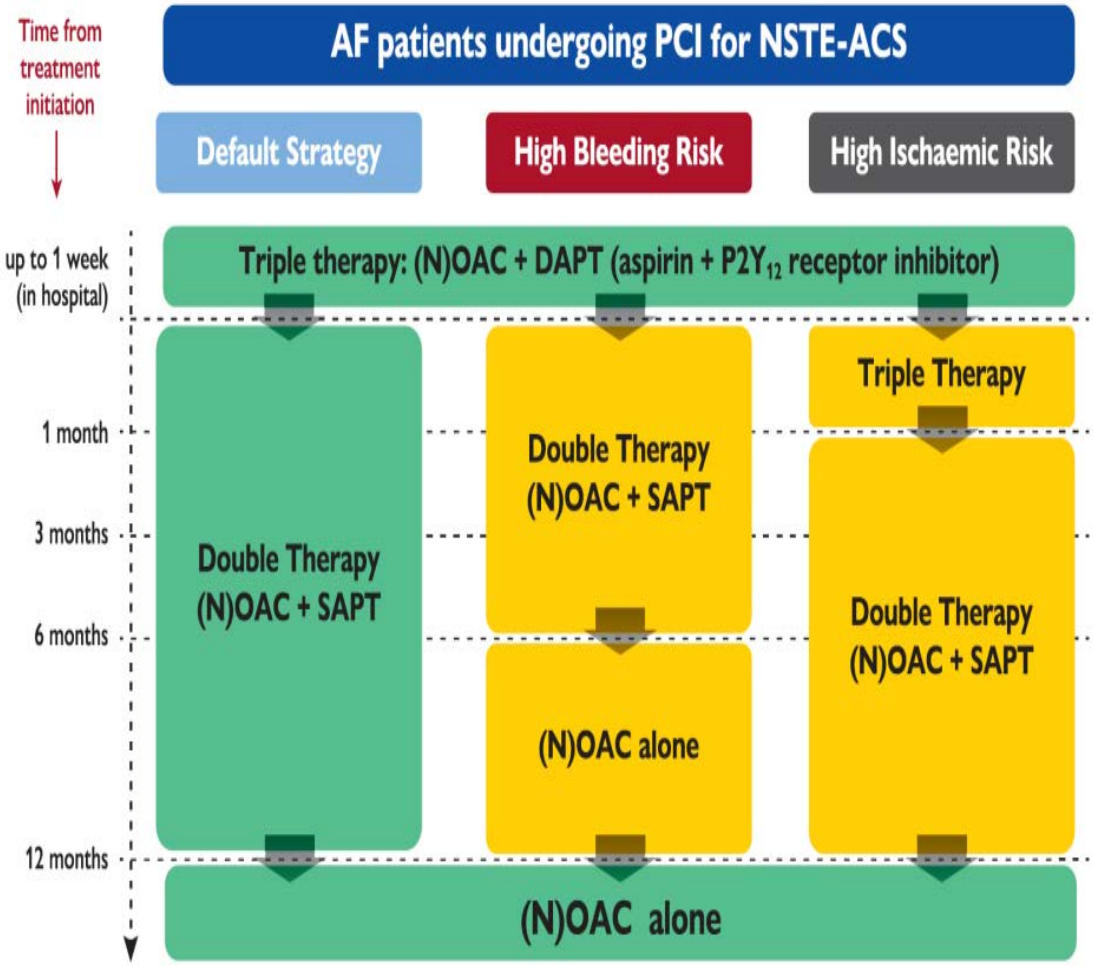


Figure 5: Algorithm for antithrombotic therapy in NSTEMI-ACS patients with atrial fibrillation undergoing PCI. [10]

1.8 Stent Thrombosis

1.8.1 Introduction

A medical emergency known as stent thrombosis (ST) is frequently linked to death (20%–40%), MI (50%–70%), or the need for immediate repeat revascularization.The extent alongside the condition of the myocardium that is at danger, and the promptness of emergency reperfusion therapy all influence the clinical outcomes of stent thrombosis [11]. When compared to bare metal

stents (BMS), drug-eluting stents (DES) decrease both angiographic and clinical restenosis and stent thrombosis; however, the incidence of stent thrombosis varies depending on the type of DES stent used, and the time course of stent thrombosis occurrence may also vary [12].

1.8.2 Stent Thrombosis definitions

TERM	DEFINITION
"Definite" ST	The highest level of certainty Either angiographic or post-mortem evidence of thrombotic stent occlusion
"Probable" ST	Any unanticipated death that occurs within 30 days following stent implantation, or any myocardial infarction that occurs in the area of the stent, regardless of when it occurs
"Possible" ST	Any death that remains unexplained after thirty days until the follow-up
"Early" ST	Acute: 0-24 hours Subacute: >24 hours-30 days
"Late" ST	>30 days-1 year
"Very late" ST (includes stent thrombosis occurring after target segment revascularisation)	>1 year

Figure 6: Academic Research Consortium (ARC) definitions for Stent Thrombosis

1.8.3 Risk factors related to stent thrombosis incidence

Several risk factors have been determined to serve a part in the development of stent thrombosis. These include residual target lesion thrombus, plaque prolapse, stent malapposition, undersizing and underexpansion, and noncompliance with DAPT. The etiology of both early and late ST has also been associated with a number of other parameters, such as smaller target artery diameter, overlapping stents, longer target lesion and/or stent length, and the severity of the clinical condition upon presentation. Lastly, smoking, multivessel disease, vein graft target lesion, and younger age are linked to late/very late stent thrombosis. [14] [15]

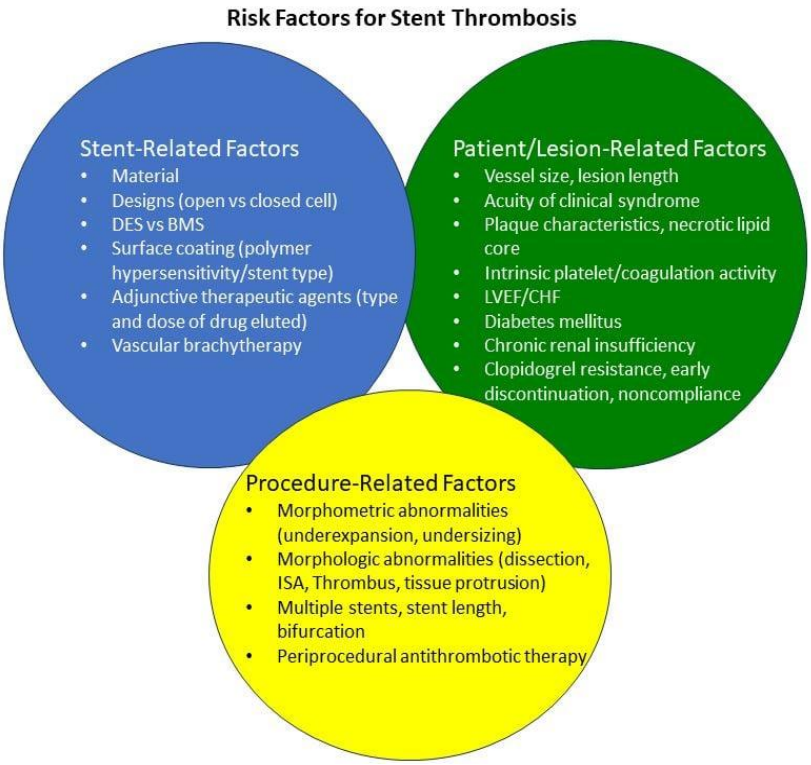


Figure 7: Parameters connected to stent thrombosis incidence [16]

1.8.4 Algorithmic approach to stent thrombosis

Both mechanical and pharmacologic treatments are vital when stent thrombosis occurs. The cornerstones of stent thrombosis treatment are anticoagulants and antiplatelet medications in particular. Due to distal embolization, glycoprotein IIb/IIIa antagonists may be taken into consideration to promote microvascular reperfusion; observational data suggests that prolonged infusions up to 72 hours can be beneficial. When post-intervention residual thrombus is detected, extended anticoagulation and antiplatelet therapy may be advantageous. A thorough assessment of drug resistance and compliance is necessary. Stronger antiplatelet medications such as ticagrelor, prasugrel, or aspirin should be taken into consideration. If there are available tests that calculate platelet aggregation and demonstrate inadequate (<50%) suppression of platelet aggregation with regular DAPT, then the continuous administration of 150 mg/d of clopidogrel may be taken into consideration. Rarely, warfarin or long-term non-vitamin K oral anticoagulants are indicated, however in certain situations of recurrent ST, they may be added. Angiographically evident thrombus should disappear after flow has resumed, and any angiographic or clinical signs of distant embolization should be investigated and treated. Despite the anecdotal use of mechanical and extraction thrombectomy, no extensive research has been done to evaluate their effectiveness or identify the subgroups that show the greatest or least potential. The cause of the stent closure should be investigated as soon as the patient has been stabilized. The stent should be evaluated by IVUS or OCT to evaluate its expansion, appropriateness of apposition, with the existence of intramural hematomas or edge dissections if DAPT has not been terminated. [17]

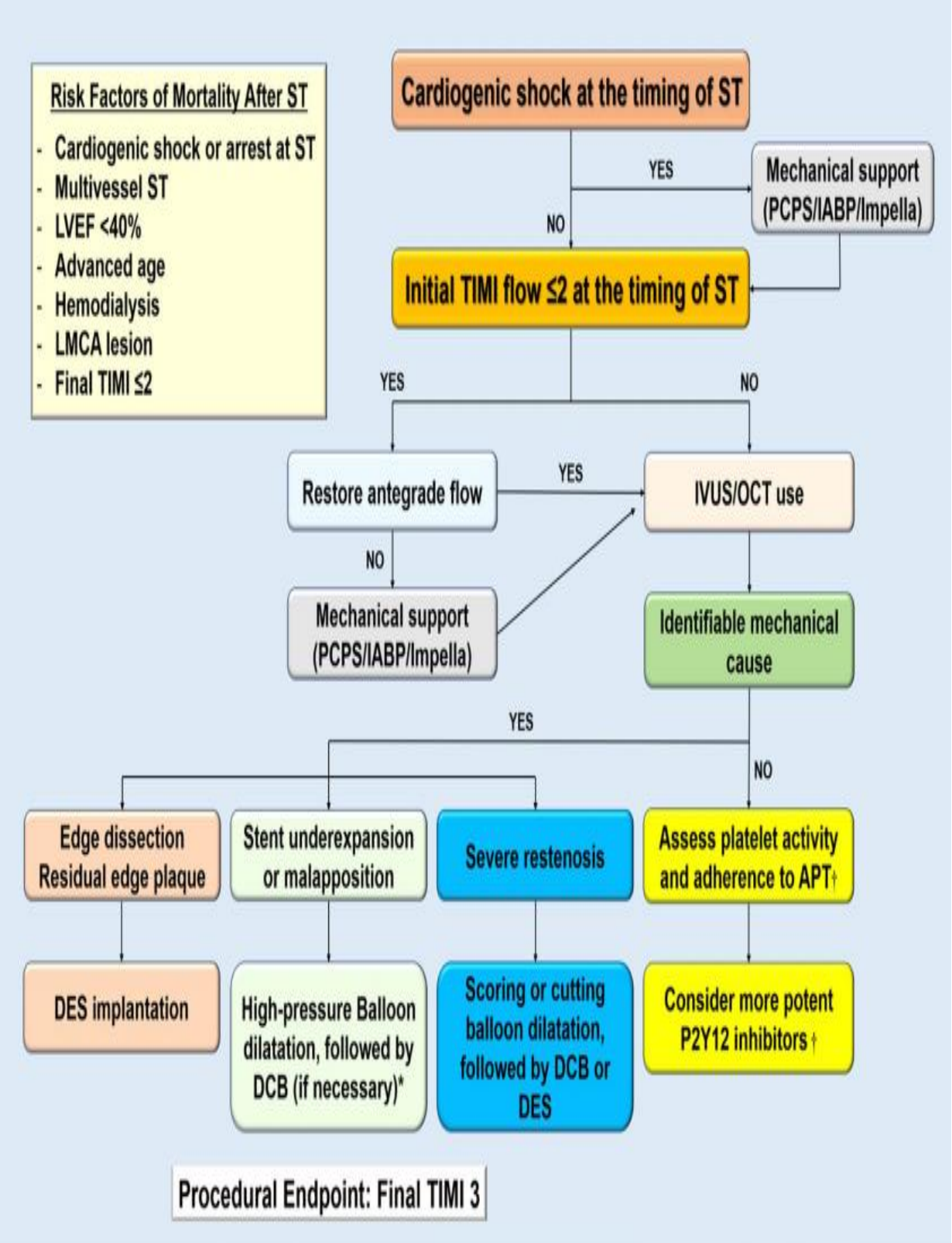


Figure 8: Algorithmic approach to stent thrombosis [17]

Chapter 2: Literature Overview

2.1 Objective

This current thesis aims to review and resume all the data available from the current literature on the subject “Stent thrombosis and antithrombotic therapy”. It takes place within the postgraduate program “Thrombosis and antithrombotic treatment”.

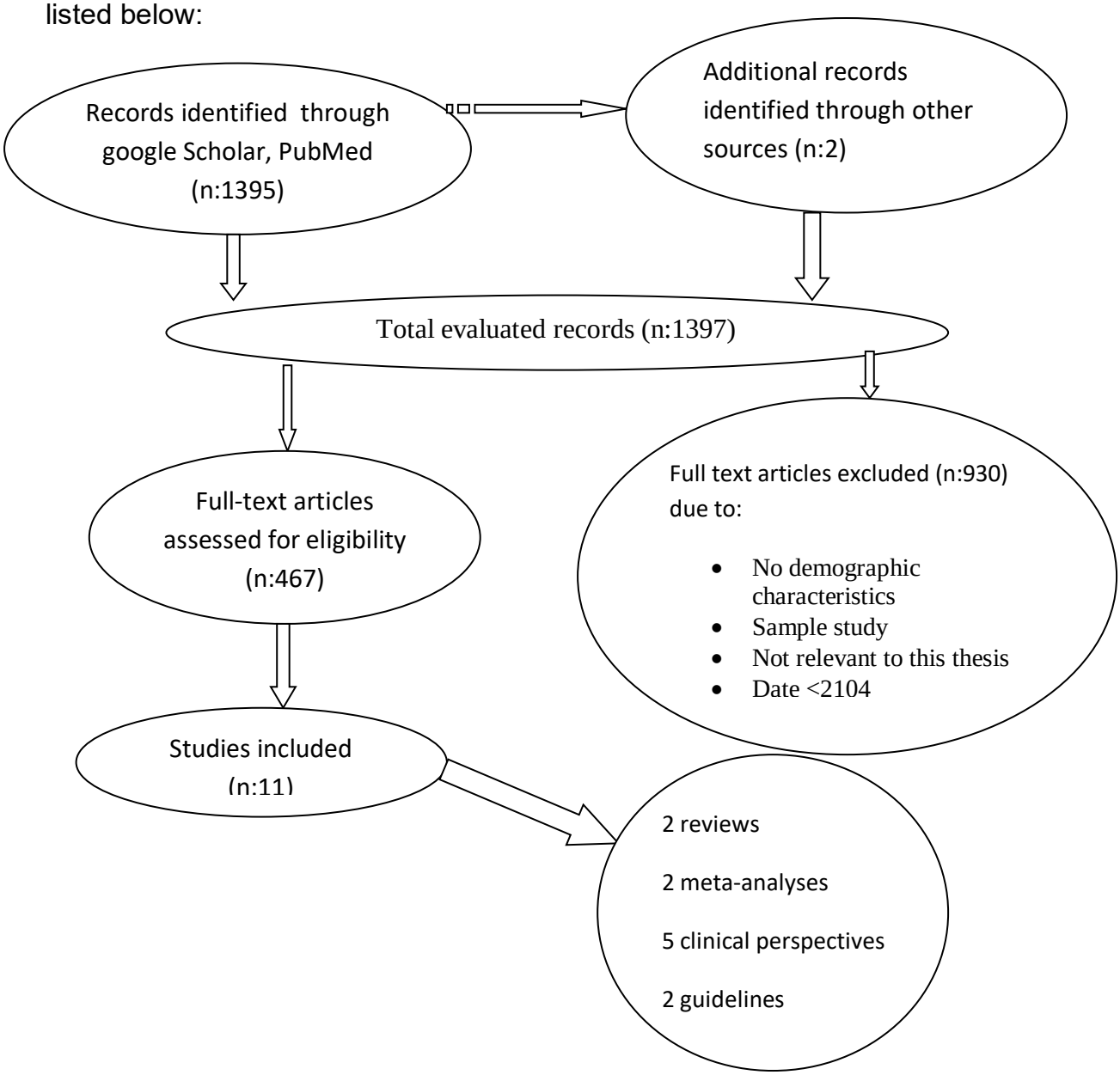
2.2 Methodology - Study inclusion criteria

The PICO model listed below was used to select the studies:

Population	Patients with Stent Thrombosis
Intervention	Antithrombotic Treatment
Comparison	(-)
Outcome	Myocardial Infarction, Death, Stent Thrombosis

Search strategy:

Studies were searched based on the PRISMA technique (flow chart) as listed below:



Searching Database keywords: << stent thrombosis>>, <<antiplatelet treatment>>, << antithrombotic treatment>>, <<DAPT>>, << resistance to clopidogrel>>,<<P2Y12 inhibitors>> , <<HPR>>.

Studies and articles after 2014 were selected and the search engine was PubMed and Google Scholar .The search language was English and animal studies and duplicates were removed

2.3 Results – Presentation of the outcome studies - Guidelines

2.3.1 Antiplatelet therapy

Preventing thrombosis after PCI requires a multifaceted approach which begins with patient risk stratification, fastidious procedural stent deployment and periprocedural adjunctive pharmacotherapy, and concludes with education and adherence to antiplatelet therapy. The optimal duration of dual antiplatelet therapy (DAPT) has evolved and more recently, strategies of short duration DAPT followed by single agent antiplatelet therapy (SAPT) or DAPT de-escalation from a high intensity P2Y12 inhibitor (ticagrelor or prasugrel) to clopidogrel have supplanted longer DAPT durations by reducing the risk for bleeding, with a similar or reduced risk of ischemic events when compared with longer durations of DAPT (enhanced net clinical benefit). Decisions regarding duration of DAPT as well as the type and duration of SAPT must be made in the context of the balance between a reduction in ischaemic event risk, for both stented and non-stented (secondary prevention) coronary segments, and an increase in bleeding event risk.

Study no.1

Zhang JJ et al, at their study in November 2016 made an effort to look at whether patients' clinical outcomes following the insertion of drug-eluting stents (DESs) are impacted by excessive platelet reactivity. PL-11 evaluated each enrolled patient who had DES implantation using a sequential platelet counting method. The primary result was the occurrence of stent thrombosis at two years, which was both confirmed and likely. The secondary goal was to prevent major adverse cardiovascular and cerebrovascular events (MACCE), such as ischemic stroke, TVR, spontaneous MI, and all cause mortality. In total, 1331 patients were enrolled in a row by the recommended center. Of the

patients on aspirin, 91 patients (6.8%) and 437 patients (32.9%) had high platelet reactivity (HPR). During the 2-year follow-up, patients with high reactivity on aspirin (9.9% vs. 0.4%, p < 0.001) and high platelet reactivity on clopidogrel (3.0% vs. 0.1%, p < 0.001) had a considerably greater incidence of stent thrombosis. The HPR on aspirin group had greater all cause death (7.7% vs. 1.6%, p = 0.002) and MI (9.9% vs. 1.9%, p < 0.001), which were the main causes of the elevated MACCE (16.5 % vs. 8.5 %, p = 0.021). In the same way, the HPR on clopidogrel group had a greater risk of MACCE (12.4 % vs. 7.4%, p = 0.004). There were no differences seen between hemorrhagic stroke and total hemorrhage. [18]

Conclusions: After DES implantation, the results of the current study revealed a relationship between higher platelet reactivity on aspirin and clopidogrel and incremental stent thrombosis.

Study no.2

In this research study (ADAPT-DES) Thomas D Stuckey et al, performed an independent comparison of the connections between the following results and platelet reactivity to clopidogrel and aspirin over a 2-year period. There is insufficient data on the association between platelet reactivity and long-term adverse outcomes after drug-eluting stent (DES) installation. After coronary intervention was performed, patients in the multicenter ADAPT-DES study underwent routine platelet function tests. Stent thrombosis (ST), either definite or probable, was the main research outcome. Other endpoints were MI, death of all cause and clinically significant bleeding. Between 2008 and 2010 the number of 8,582 patients were included in the study. Of these, 46.3% remained on DAPT for 2 years without interruption. At the 2-year mark, 92 patients (1.07%) experienced definite or probable stent thrombosis (ST). High platelet reactivity to clopidogrel was found to be positively correlated with increased risk of definite or probable ST (adjusted hazard ratio [HR]: 2.16; 95% confidence interval [CI]: 1.27 to 3.67; p = 0.003), clinically significant

bleeding (adjusted HR: 0.74; 95% CI: 0.62 to 0.90; p = 0.02), and increased all-cause mortality (adjusted HR: 1.36; 95% CI: 1.01 to 1.85; p = 0.04) among those receiving continuous dual antiplatelet therapy for a period of two years. Aspirin hyporesponsiveness in individuals receiving aspirin monotherapy was not linked to adverse events, nor was high platelet reactivity between years 1 and 2 connected with the very late ST. [19]

Conclusions: This study demonstrates the substantial correlation between 2-year ischemic and bleeding outcomes following DES and high platelet reactivity on clopidogrel. Most stent-related incidents happened in the first year.

Study no.3

Coronary stent thrombosis (ST) has a significant recurrence rate. On treatment, patients with ST frequently have high platelet reactivity (HPR). Patients with ST who are thought to be at high risk of atherothrombotic events may benefit from tailored antiplatelet treatment (APT). In comparison to a previous cohort of patients with ST who did not receive tailored APT, this study by Godschalk et al., assessed if tailored APT, based on platelet function testing, decreased the rate of cardiac mortality and/or recurrent ST at 1 year following ST. Our ST outpatient clinic saw patients with definite ST for customized APT and platelet function testing. These patients were matched exactly to a previous cohort of ST patients who received the then-recommended combination of aspirin and clopidogrel as treatment. The primary endpoint of the study was a composite measure of cardiac death and/or recurrent definite stent thrombosis (ST) after 1 year. The study comprised 113 participants in all who came to the outpatient clinic. Of the individuals taking clopidogrel, 6.7% had high platelet reactivity (HPR), whereas 0% had ticagrelor. 93% of patients with HPR showed normal platelet reactivity after receiving customized antiplatelet treatment (APT). Four patients from the outpatient clinic group and twenty-three individuals from the

history cohort experienced the primary endpoint. The customized APT effect on the primary endpoint had an odds ratio of 0.26 (95% confidence interval 0.11 to 0.64).p = 0.003), independent of potential confounders such as prior myocardial infarction and stent type. [20]

Conclusions: Following tailored APT, patients with ST had reduced HPR rates when they attended the outpatient ST clinic. Compared to a previous cohort of ST patients without customized APT, individuals attending the ST outpatient clinic had a lower risk of cardiac mortality or recurrent ST. Patients with ST who are on clopidogrel may take more advantage from the customized antiplatelet therapy approach due to their elevated HPR rate.

Study no.4

After literature research Biswas et al, presented the following meta-analysis:

There is ongoing debate and dispute regarding the best antiplatelet therapies for patients with ACS who have CYP2C19 loss-of-function (LoF) alleles and are undergoing percutaneous coronary intervention (PCI). The objective was to evaluate the effectiveness and safety outcomes of clopidogrel versus other P2Y12 receptor blockers, such as ticagrelor or prasugrel, for these individuals. Using either fixed-effects or random-effects models, RevMan software was used to evaluate the aggregated risk; two-sided P values less than 0.05 were deemed statistically significant. Nine studies totaling 16,132 patients with acute coronary syndrome (ACS) having percutaneous coronary intervention (PCI) were included in this analysis. Of these, 2,746 patients were assigned to the CYP2C19 loss-of-function (LoF) clopidogrel group, and 2,640 patients were assigned to the alternate therapy group. The findings indicated that patients treated with prasugrel or ticagrelor had a considerably lower risk of major adverse cardiovascular events (MACEs) (relative risk [RR] 0.59; 95% confidence interval [CI] 0.44-0.75; P < 0.0001) compared to those treated with clopidogrel, with both groups carrying CYP2C19 LoF alleles. According to subgroup analysis, the risk of myocardial infarction (MI) (RR

0.61; 95% CI: 0.45-0.82; P = 0.0008) and cardiovascular death (RR 0.43; 95% CI: 0.24-0.73; P = 0.001) was considerably lower with prasugrel or ticagrelor. Other clinical outcomes, such as stroke (RR 0.77; 95% CI: 0.43-1.38; P = 0.39), stent thrombosis (RR 0.66; 95% CI: 0.39-1.17; P = 0.18), unstable angina (RR 0.56; 95% CI: 0.14-2.36; P = 0.43), and revascularization (RR 0.77; 95% CI: 0.29-2.25; P = 0.67), however, did not demonstrate statistically significant differences between the two groups. Additionally, there was no discernible difference in bleeding incidents across the groups (RR 1.08; 95% CI: 0.89-1.29; P = 0.55). [21]

Conclusion: For ACS patients undergoing PCI, other antiplatelets (such as ticagrelor or prasugrel) may be a better therapy option than clopidogrel when it comes to efficacy and safety.

Study no.5

In a review published in 2022, Towashiraporn K, and Krittayaphong described the TRITON-TIMI randomized trial in which the efficacy of prasugrel, a more potent P2Y12 inhibitor, compared to clopidogrel was studied. In 2007, 13,608 patients were randomly categorized into two selected groups. Prasugrel was administered as a loading dose of 60 mg and a maintenance dose of 10 mg per day to one group, while clopidogrel was administered as a loading dose of 300 mg and a maintenance dose of 75 mg to the other group. It was found that in patients with ACS for whom PCI was planned, prasugrel was superior in reducing the incidence of ischemic events, including definite (DST) or probable (PST) stent thrombosis, recurrent myocardial infarction and recurrent cardiovascular events.

In addiiton this review presentd the efficacy of another potent P2Y12 inhibitor of ticagrelor studied in the PLATO trial; 18,624 patients with ACS were randomly divided into two groups. One group was given 180 mg of ticagrelor as a loading dosage, and then 90 mg twice a day after that. The second group

was administered a loading dosage of 300–600 mg of clopidogrel, with 75mg daily thereafter. Both groups were also given ASA with a loading dose of 325mg for those who had not previously received aspirin , followed by 75-100mg daily. The main efficacy endpoints were due to the lower rate of death from vascular causes and myocardial infarction. A sub-analysis in 61% of all participants undergoing PCI demonstrated that ticagrelor also reduced the rate of stent thrombosis. [22]

Conclusion: In the TRITON-TIMI trial, prasugrel was shown to be superior to clopidogrel on efficacy endpoints including stent thrombosis in patients with ACS undergoing PCI, with the disadvantage of increased bleeding events. As well as in the PLATO trial, ticagrelor appeared to be superior to clopidogrel with a lower rate of stent thrombosis, cardiovascular events, with fewer deaths and similar bleeding rates.

Study no.6

In 2019 Schüpke S. et al presented the results from a multicentre, randomised study ISAR-REACT 5 comparing two potent P2Y12 inhibitors, prasugrel and ticagrelor. This was a large, randomized study involving 4,018 patients with acute coronary syndrome undergoing PCI. The primary endpoint was death, myocardial infarction or stroke within 1 year. The secondary end point (the safety end point) was bleeding. Patients were divided into 2 groups where the first received aspirin 100mg along with ticagrelor at a loading dose of 180mg followed by a maintenance dose of 90mg twice daily and the second group prasugrel at a loading dose of 60mg and a maintenance dose of 10mg daily along with aspirin 100mg. In the ticagrelor group the primary endpoint was more frequent at 9.3% compared to 6.9% in the prasugrel group. More specifically in the ticagrelor group the death rate was 4.5% of infarction 4.8% and stroke 1.1%while in the prasugrel group it was 3.7%, 3.0%,1.0% respectively. Regarding stent thrombosis definite or probable ST occurred in 1.3% in the ticagrelor group versus 1.0% in the prasugrel group. While definite ST occurred 1.1% in the ticagrelor group and 0.6% in the group receiving

prasugrel. Also the secondary endpoint which was non-life-threatening bleeding occurred in the ticagrelor group in 5.4% and in the prasugrel group in 4.8%. [23]

Conclusion: When it comes to preventing stent thrombosis in patients with acute coronary syndrome who underwent PCI, prasugrel is more beneficial than ticagrelor.

Study no.7

In 2020 Sabouret,29 P.et al in a review they published presented the findings, including the DAPT study, on the ideal length of DAPT. In individuals with coronary artery disease who have had PCI, extended use of P2Y12 inhibitors for 30 versus 12 months in conjunction with aspirin may be advantageous for individuals with ischemia (9,961). This was investigated in an important randomized controlled trial. Sadly, excessive severe bleeding and a rise in non-cardiovascular mortality in that trial outweighed the positives (a decrease in stent and myocardial thrombosis), which were hotly debated and lacked a clear explanation.Patients who had experienced a myocardial infarction at baseline benefited the most. [24]

Conclusion. Prolonged DAPT >12 had the greatest benefit for ischemic patients at very high risk who had a medical history of atherothrombotic events.

2.3.2 Anticoagulation therapy in ACS

Anticoagulation and antiplatelet medication combined makes sense for treating individuals with acute coronary syndrome (ACS) acutely. The majority of acute coronary thrombosis events are caused primarily by breakdown of the atherosclerotic plaque. Both platelet aggregation and the coagulation

cascade are necessary for the formation of an acute thrombus. Despite advancements in revascularization and efficient antiplatelet treatment, the residual rates of recurrent thrombotic events within the first year following ACS remain at 5%–10%, showing no progress over the preceding 20 years. Evidence based data that a hypercoagulable condition might last long beyond the acute phase of ACS may contribute to this ongoing risk. It appears that using intensive antiplatelet medication along with oral anticoagulation should further lower the chance of recurring thrombotic episodes. The field of care for treating ACS patients in this manner is still developing, though. The effectiveness and safety of direct oral anticoagulants (DOACs) in the management of ACS have been examined in more recent research. The pharmacokinetics of DOACs are more stable and their administration is easier than that of warfarin. [25]

A Compass and an Atlas, But what is next?

ATLAS ACS 2 TIMI 51 (Anti Xa Therapy to Lower Cardiovascular Events in Addition to ASA with or without Thienopyridine Therapy in Subjects with Acute Coronary Syndrome—Thrombolysis in Myocardial Infarction) and APPRAISE 2 (Apixaban for Prevention of Acute Ischemic Events 2) are the only phase III clinical trials that aim at the use of direct oral anticoagulants (apixaban and rivaroxaban as well) in postacute treatment of ACS. Both trials demonstrated a statistically significant increase in significant bleeding while taking solitary Factor Xa inhibitors in comparison to dual antiplatelet therapy. In APPRAISE-2, apixaban 5 mg bid was associated with a higher incidence of thrombolysis in myocardial infarction (TIMI)-related serious bleeding (1.3%) compared to placebo (0.5%), which resulted in an early study termination. When comparing apixaban (7.5%) to placebo (7.9%), there was no discernible reduction in the composite of cardiovascular mortality, MI, or ischemic stroke. The study conducted in ATLAS ACS 2-TIMI 51 revealed that there was a dose-dependent increase in the incidence of TIMI major bleeding for both of the rivaroxaban doses that were investigated, 2.5 mg bid (1.8%) and 5 mg bid (2.4%), when compared to the placebo (0.6%). Additionally, rivaroxaban 2.5

mg bid (0.4%) and 5 mg bid (0.7%) increased intracranial bleeding in comparison to placebo (0.2%). In contrast to the results of APPRAISE-2, rivaroxaban (mixed dose arms) decreased the composite of cardiovascular mortality, MI, or stroke when compared to placebo (8.9% against 10.7%, respectively) in the primary analysis of the combination dosing arms. Subsequent investigation revealed that the composite of cardiovascular mortality, MI, or stroke was improved by both the 2.5 and 5 mg daily dosage regimes. While rivaroxaban proved successful in lowering these end goals, excessive bleeding has prevented it from being included into the routine care of post-ACS patients receiving dual antiplatelet therapy. [26]

COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial established a role for rivaroxaban in the treatment of patients with stable coronary artery disease or peripheral arterial disease, in contrast to the post-ACS population, in which the efficacy of rivaroxaban is countered by an excess of bleeding. COMPASS looked at patients with stable atherosclerotic vascular disease—of which 91% also had stable coronary artery disease—and compared the use of rivaroxaban + aspirin versus aspirin monotherapy. The trial did not include any patients who needed oral anticoagulation, nonaspirin antiplatelet medication, or dual antiplatelet therapy. Randomization was used to assign patients to receive aspirin alone, rivaroxaban 2.5 mg bid plus aspirin, or rivaroxaban 5 mg bid alone. When compared to aspirin alone, rivaroxaban 2.5 mg daily decreased the incidence of cardiovascular mortality, stroke, or MI by 24%. The combination of rivaroxaban 2.5 mg daily + aspirin was found to provide a greater net therapeutic benefit than aspirin alone because to the higher incidence of major bleeding in the rivaroxaban plus aspirin group. However, there was no difference in fatal or cerebral bleeding or bleeding into a vital organ. Rivaroxaban now has a US Food and Drug Administration indication for lowering cardiovascular events in patients with persistent coronary or peripheral artery disease, based on the results of COMPASS. [27]

A possible novel strategy for oral anticoagulation in post-ACS patients is suggested by recent studies. In patients with stable coronary disease, which

is often treated with aspirin monotherapy, the COMPASS trial demonstrated a potential for rivaroxaban in addition to aspirin. Rivaroxaban has the potential to lower residual thrombotic risk in the post-ACS scenario, as shown by the ATLAS ACS2 TIMI 51 study. However, its practical implementation has been limited due to excess bleeding that is associated with this medication. The current research identifies a subset of ACS patients (those with acute myocardial infarction treated noninvasively) for whom treatment with rivaroxaban with aspirin may be preferred due to the balance between safety and efficacy. However, unlike COMPASS, this technique should be compared to dual antiplatelet therapy in future research. This is because guidelines for post-ACS antithrombotic treatment now recommend this course of action.

2.3.3 Guidelines (Recommedations)

Whether or not to prolong dual antiplatelet therapy (DAPT) depends on the patient's high ischemic or bleeding risk. Whem the ischemic risk is high it is recommended (IIa) to prolong DAPT over 12 months or more according to the COMPAS, DAPT trials, PEGASUS TIMI-54. [28]

The assessment of ischemic risk is based on some criteria that the patient must have. In the 2018 guidelines these criteria are published. Diabetes mellitus under treatment, chronic kidney disease with eGFR15/19 ml/min,1.73m2, multivessel coronary artery disease,(CAD,PAD),coronary artery disease under 45 years of age and coexisting inflammatory diseases (lupus erythematosus rheumatoid arthritis) and the presence of stents, their number > 3, their length or any previous stent thrombosis under antiplatelet treatment. Depending on the number of criteria met, the patient is classified as high or moderate thrombotic risk. The antithrombotic treatment should be adjusted according to the profile of each patient. [29]

According to the 2020 European Society of Cardiology guidelines for the management of acute coronary syndrome without stent retraction, it is

recommended (IIA) that <<after stent implantation with a high risk of bleeding (PRECISE-DAPT ≥25), consideration should be given to discontinuation of P2Y12 inhibitor therapy after 3 months>34 The PRECISE-DAPT score consists of five factors: hematocrit , white blood cell count, patient age ,GFR and history of previous bleeding.If the PRECISE-DAPT score is above or equal to 25 it appears that there is an increased risk of bleeding and no more benefit from prolonging DAPT >12 months35If the PRECISE-DAPT score is above or equal to 25 it appears that there is an increased risk of bleeding and no more benefit from prolonging DAPT >12 months3If the PRECISE- DAPT score is above or equal to 25 there appears to be an increased risk of bleeding and no more benefit from prolonging DAPT >12 months. [30]

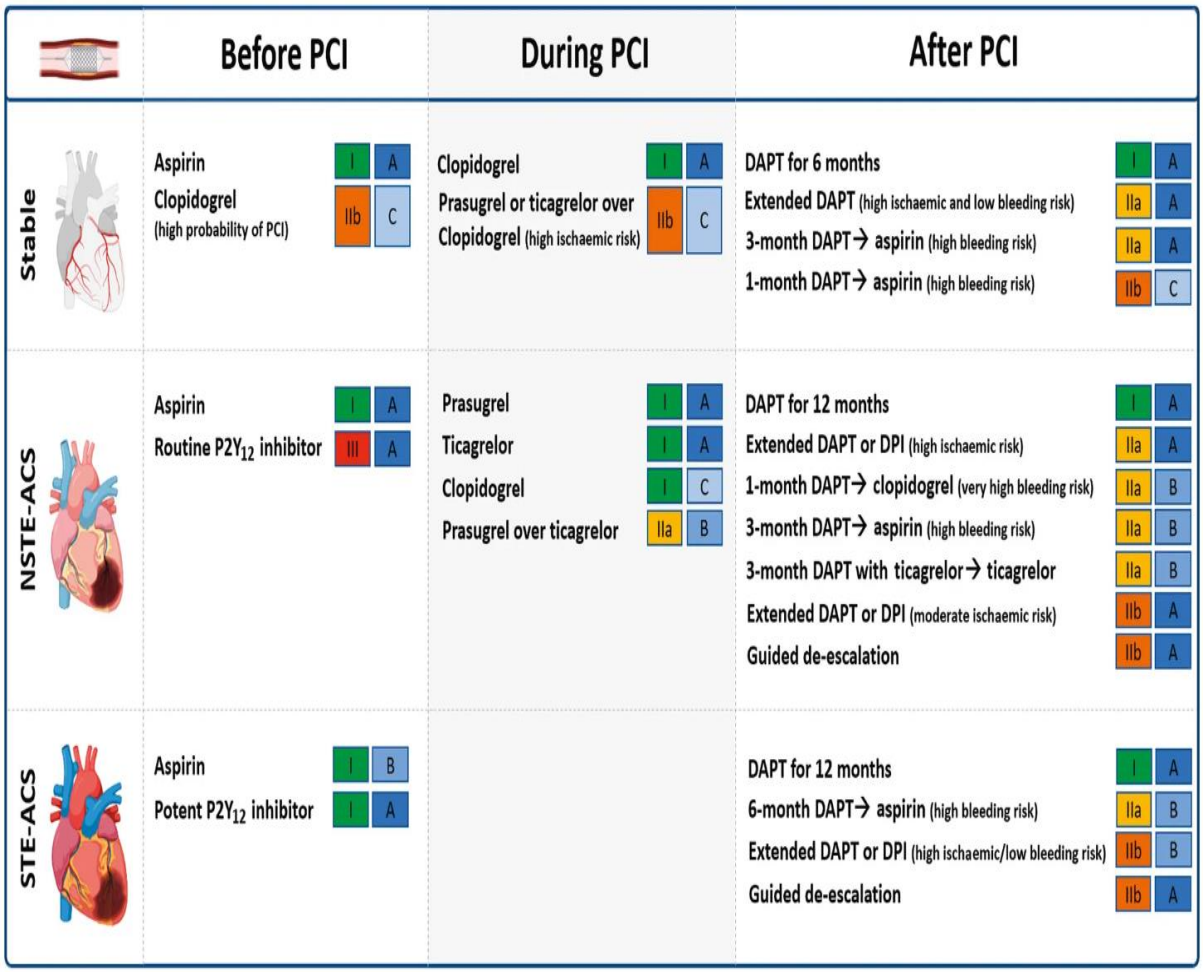


Figure 10: Recommendations for alternative antithrombotic therapy regimens. [30]

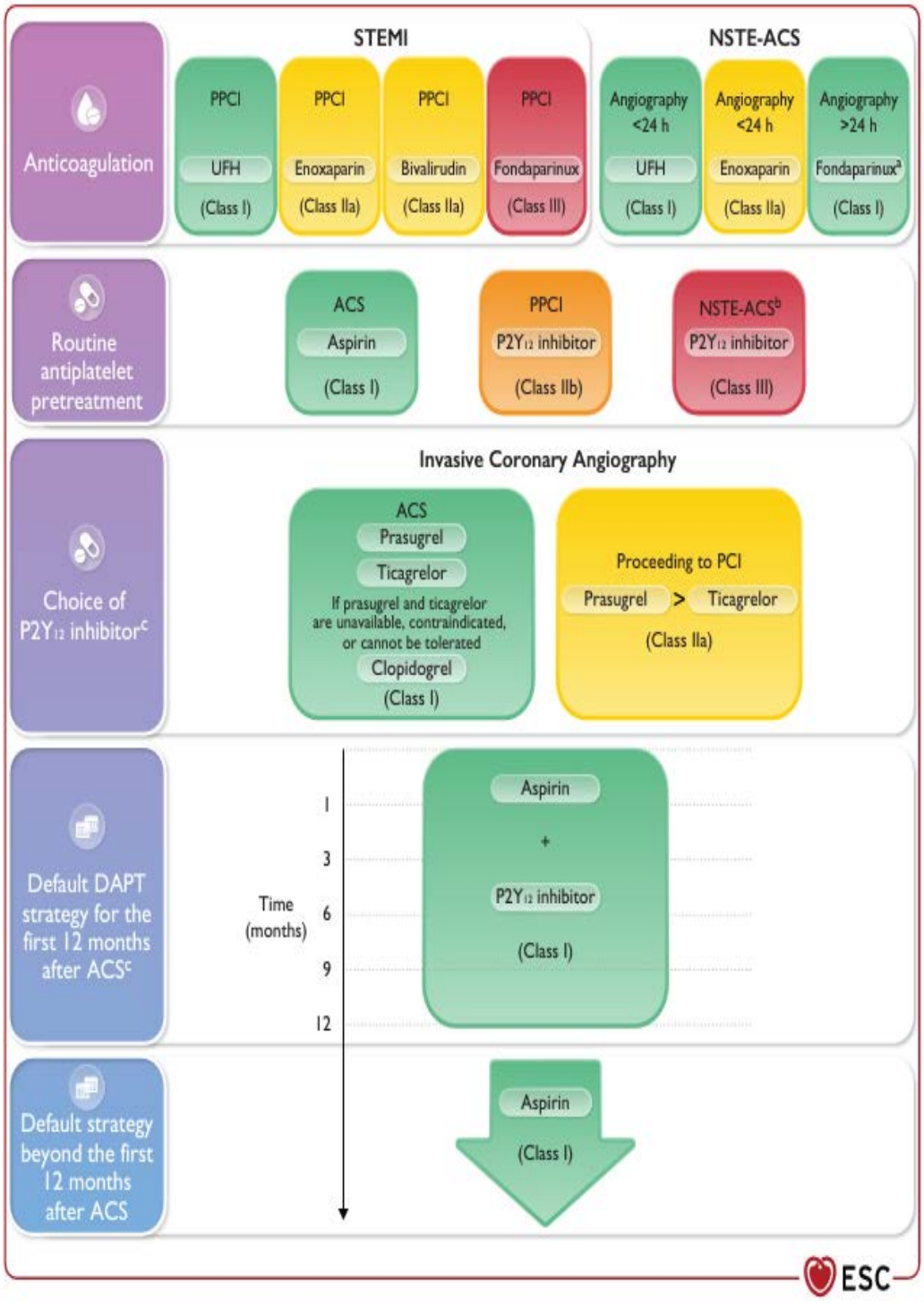


Figure 9: Recommended default antithrombotic therapy regimens in acute coronary syndrome patients without an indication for oral anticoagulation. [30]

2.4 Discussion

The aim of this thesis is to identify the optimal antithrombotic treatment for coronary stent thrombosis through the various studies of the last decade.

Stent thrombosis is a rare but very serious complication and several times fatal. Advances in stent technology and dual antiplatelet therapy have greatly reduced it. But the fact that in patients under treatment events of thrombosis occur has led researchers to conduct investigations to identify the cause.

Zhang JJ et al in the study they presented showed that of the subjects studied those who had the occurrence of stent thrombosis had 6.8% high reactivity to aspirin and 32.7% to clopidogrel.

And in the ADAPT-DES study Stuckey TD and his team confirms the strong association of high platelet reactivity with ischemic and thrombotic events after DES implantation.

In an older study Godschalk TC,e al observed that patients with stent thrombosis receiving customized antiplatelet therapy had low platelet reactivity, thus led to the conclusion that customized APT would benefit and prevent them from ischemic events. It is worth mentioning that the ARCTIC study which reports that after a study of 2240 patients, platelet reactivity is not a risk factor for ischemic events after percutaneous revascularization.

Resistance to clopidogrel appeared to be due to polymorphisms of the liver cytochrome P450 2C19. While CYP2C19 normally contributes to the conversion of clopidogrel to active drug, CYP2C19*2 mutation, is associated with reduced activation of clopidogrel, leading to more frequent ischemic events, such as stent thrombosis. Thus Biswas M,and colleagues were led to the conclusion by a meta-analysis conducted and published in 2021 that thienopyridines, prasugrel and ticagrelor are more effective and safer than

clopidogrel in the context of DAPT in patients with ACS undergoing PCI and carrying polymorphisms in the cytochrome genotype with loss of CYP2C19.

The safety and efficacy of prasugrel at a loading dose of 60mg once and then 10mg once daily in combination with aspirin 100mg versus clopidogrel in the context of DAPT after angioplasty was shown in the TRITON-TIMI study to be superior in preventing stent thrombosis. In the PLATO study also ticagrelor with a loading dose of 180mg once and 90mg twice along with aspirin 100mg per day had better results than clopidogrel in the context of DAPT as far as thrombotic events are concerned. Based on these studies the ISAR- REACT 5 study was conducted in 2019 where prasugrel showed a better efficacy and safety profile compared to ticagrelor.

The optimal duration of antiplatelet treatment was studied in several registries. One of them was the DAPT-study where it was shown that prolongation of DAPT > 12 months was mainly beneficial for very high-risk ischemic patients with a history of atherothrombotic events.

The use of anticoagulants seems to play an important role in the context of antithrombotic treatment after PCI. Although in the GEMINI-ACS-1 study there is no clear difference in bleeding and ischaemic events with the addition of rivaroxaban 2.5mg and P2Y12 compared with administration of aspirin with P2Y12,in the ATLAS ACS 2-TIMI 51 study the addition of rivaroxaban 2.5mg to antiplatelet treatment showed a reduction in thrombotic events as in the COMPASS study the the risk of major adverse cardiovascular events was significantly lower in stable cardiovascular disease with rivaroxaban 2.5mg together with aspirin.

Guided by the various studies, the 2017 guidelines suggest intensification of treatment with a more potent P2Y12 after an ST event, versus clopidogrel, and the duration of DAPT should be over 12 months when patients are at very high thrombotic risk, provided of course that no life-threatening bleeding has occurred during its administration.

2.5 Conclusion

For patients with CAD undergoing PCI, antithrombotic medication is the cornerstone of treatment for preventing local and systemic ischemic complications. Different antiplatelet regimens using P2Y12 inhibitors and aspirin have been developed and applied into clinical practice over the past few decades. The ideal regimen for each patient has been defined in large part by a greater understanding of the individual's reactivity to antiplatelet drugs, as well as the profile of bleeding and ischemic risk. To lower the risk of ischemic consequences while minimizing the danger of bleeding, adjustments should be made to the dosage and duration of aspirin and P2Y12 inhibitory treatment. The development of strategies aimed at reducing bleeding risk involves de-escalation, P2Y12 inhibitor monotherapy, and a shorter DAPT duration. Patients at elevated ischemic risk may think about prolonging their intensive antithrombotic therapy with DPI or DAPT if there is no significant bleeding risk. It has been shown that genetic testing and platelet function may assist in the P2Y12 inhibitor medication selection process. For a tailored selection of antiplatelet medicines among PCI patients, an integrated approach that incorporates procedural features, instruments to evaluate medication response, and scores/definitions to define bleeding and ischemic risk is the most promising method.

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