Benefit Definition: Unstable Angina/Non ST-elevation Myocardial Infarct (NSTEMI) - Acute Coronary Syndromes

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907E	Acute and sub-acute ischaemic heart disease including myocardial infarction and unstable angina.
Treatment:	Medical management; surgery; percutaneous procedures

Contents

1. Introduction

The legislation governing the provision of the prescribed minimum benefits (PMBs) is contained in regulations enacted under the Medical Schemes Act 131 of 1998. In respect of some of the diagnosis treatment pairs (DTPs), medical scheme beneficiaries find it difficult to know in advance what their entitlements are. In addition, medical schemes interpret these benefits differently resulting in a lack of uniformity of benefit entitlements.

The benefit definition project is coordinated by the Council for Medical Schemes and aims to define condition-specific treatment guidelines, which will serve to guide the interpretation of the PMB provisions by relevant stakeholders.

The benefit definition is based on the available evidence of clinical and cost effectiveness taking into consideration affordability constraints and financial viability of medical schemes in South Africa.

This benefit definition does not endorse explicitly one medicine/medical device within a particular therapeutic class over another. Provision must be made for appropriate exceptions where this benefit definition has been ineffective, causes, or will cause harm to a beneficiary, without penalty to that beneficiary. Health care providers must provide written documentation for exceptions.

All patients who are treated successfully in an emergency setting must register with their scheme for chronic management of Ischaemic heart disease. Scheme protocols and formularies developed taking into consideration evidence-based medicine, cost-effectiveness, affordability should then apply.

It should be noted that benefit definitions are a minimum set of benefits and schemes may enrich the benefits but not offer benefits less than stated here.

It should also be noted that management of ischaemic heart disease takes into consideration many clinical aspects of the patients. This benefit definition does not address specific circumstances of high risk and complicated patients who may need care more than specified here.

Acute coronary syndromes are considered an emergency, therefore use of a non-DSP must be considered in-voluntarily. Schemes may arrange for transfer to a designated service provider once the patient's condition has stabilised and transfer would not harm the member.

Alternatives must be made for patients where harm could be caused by treatment stated in the benefit definition, scheme formulary or protocol.

Please note: procedure codes serve as a guideline for billing and many not include all relevant procedure codes.

2. Definition

Acute coronary syndrome (ACS) represents a life-threatening manifestation of atherosclerosis. It is usually precipitated by acute thrombosis induced by a ruptured or eroded atherosclerotic coronary plaque, with or without concomitant vasoconstriction, causing a sudden and critical reduction in blood flow.

Among patients presenting with unstable angina, approximately 15% have one -vessel coronary artery disease (CAD), 35% have 2-vessel CAD, and 50% have 3-vessel CAD. The incidence of left main disease is roughly 5-10%. The rate of thrombus detected at coronary angiography varies widely, ranging from less than 10% among those with chest pain in the previous month to more than 50% among those with rest angina in the preceding 24 hours.(1)

Unstable angina is considered to be an ACS in which there is no detectable release of the enzymes and biomarkers of myocardial necrosis. N-STEMI is characterized by elevated cardiac enzymes, without ST-elevation on ECG. The other ECG changes may include ST-segment depression or T-wave inversion. It should be appreciated that a completely normal ECG does not exclude the possibility of NSTE-ACS.(2, 3)

3. Pathophysiology

Atherosclerosis is a chronic, multifocal immune-inflammatory disease of medium-sized and large arteries mainly driven by lipid accumulation.(4) NSTEMI usually occurs by developing a partial occlusion of a major coronary artery or a complete occlusion of a minor coronary artery previously affected by atherosclerosis.(5)

ACS represent a life-threatening manifestation of atherosclerosis usually precipitated by acute thrombosis, induced by a ruptured or eroded atherosclerotic plaque, with or without concomitant vasoconstriction, causing a sudden and critical reduction in blood flow. (6, 7)

4. Clinical Presentation and Diagnosis:

4.1 Clinical Presentation

Patients present mainly with the following symptoms:(2)

- Chest pain at rest that last longer than 20 minutes
- New onset severe angina
- Crescendo angina
- Post myocardial infarct angina

4.2 Diagnostic Tools

4.2.1 Physical examination

- Exclude non-cardiac and non-ischaemic causes of chest pain
- To assess complications of acute coronary syndrome
- To identify precipitating factors such as anaemia, fever, thyrotoxicosis etc.

4.2.2 Electrocardiogram

- Twelve Lead ECG must be done as soon as possible
- Continuous 12 – lead ECG monitoring must be done as 12 –ECG test may miss some cases especially in patients with silent ischaemia

4.2.3 Blood tests

- *Cardiac Enzymes*
  - Cardiac Troponins (cTnT or cTnI) are the preferred markers of myocardial injury, because they are more specific and more sensitive than the traditional cardiac enzymes.(8) Troponin is also a valuable prognostic test and useful in risk stratification.(9)
  - CKMB is important but limited by sensitivity
  - It should be noted that a single normal test may not be sufficient to exclude pathology in the presence of suggestive symptoms and therefore a series of tests need to be done.
- *Inflammatory markers*
  C-reactive protein (CRP), although it has no diagnostic value in ACS, is a good predictor of mortality.(2)
- *Novel biomarkers*
  Novel biomakers such as myeloperixodase are not considered to be at PMB level of care as there is insufficient data to confirm their ability to sensitively diagnose myocardial infarction.(2)

- *Other Blood test to assess baseline status and diagnose co-morbidities*
  - Full blood count: -anaemia may precipitate myocardial ischemia and low HB,
  - Urea, creatinine and electrolytes
  - Serum glucose (may need to do a serial during admission)
  - Lipid profile
  - Thyroid function tests when thyrotoxicosis is suspected
  - Natriuretic peptides, such as brain- type B-type natriuretic peptide (BNP)] or its N-terminal prohormone fragment (NT-proBNP) to detect left ventricular dysfunction. Although studies of natriuretic peptides were done in hypertensive population, the sensitivity of this test in diagnosing LVH is remains questionable. (10, 11) Therefore this tests are not considered to be at PMB level of care

4.2.4 Non- Invasive Imaging

- Chest-x ray; to exclude extra-cardiac causes of chest pain, detect heart failure and cardiomegaly
- Echocardiography -is used to exclude other non-cardiac causes of chest pain such as aortic dissection as well as diagnose ischaemia and detect complications of ischaemia such as left ventricular pathology
- MRI and Scintigraphy may be used when there is diagnostic uncertainty.

4.2.5 Invasive Imaging

- The gold standard remains angiography.
- Cardiac computed tomography (CT) cannot be recommended as the coronary imaging modality in NSTE-ACS, because of suboptimal diagnostic accuracy.(2)

Table 1: Possible codes for initial care of Acute Coronary Syndrome

Item	Description	Codes	Additional comments
Professionals	Paramedics		For initial assessment , stabilisation and transportation to suitable facility
	General practitioners and any other relevant health care provider in line scope of practice as per statutory body	0190-0192	For initial diagnosis and stabilisation
	Physicians and cardiologist	0190-0192	For initial diagnosis, in-hospital management, Interventions and follow-up
	Paramedics		
ECG	General Practitioner's fee for the taking of an ECG only: Without effort: ½ (item 1232)	1228	Serial ECG recording throughout assessment in Emergency room
	General Practitioner's fee for the taking of an ECG only: Without and with effort: ½ (item 1233)	1229	Note: Items 1228 and 1229 deal only with the fees for taking of the ECG, the consultation fee must still be added
	Physician's fee for interpreting an ECG: Without effort	1230	A specialist physician is entitled to the fees specified in item 1230 and 1231 for interpretation of an ECG tracing referred for interpretation. This applies also to a paediatrician when an ECG of a child is referred to him for interpretation
	Physician's fee for interpreting an ECG: With and without effort	1231	
	Electrocardiogram: Without effort	1232	
	Electrocardiogram: With and without effort	1233	For inducible ischaemia
Pathology	CKMB	4152,4153,4138	May be repeated every 6-8 hours
	Troponin	4161	
	Full Blood Count-	3755 (Incl. 3739,3762,3783,3785,3791)	To rule out anaemia as secondary cause of ACS
	Platelet count	3797	
	Glucose-Hypo and hyperglycaemia affect treatment outcomes	4057	
	Lipogram-Lipid profile can change within 12-24 hours	4025	

	CRP/ESR	3947/3743	
	U & E and Creatinine	4171	Creatinine useful as baseline especially when invasive strategy is considered. Potassium abnormality must be corrected.
	Creatinine-EGFR	4032	
	Magnesium	4094 or 4095	Low levels may predispose to arrhythmia

Non-invasive procedures	Single-photon emission computed tomography	This test should not be used to diagnose and will therefore not be funded as PMB	
	Echocardiogram	3620,3621,3622,3623,3624,3625	To evaluate LV function. Among non-invasive imaging techniques, echocardiography is the most important modality in the acute setting because it is rapidly and widely available. LV systolic function is an important prognostic variable in patients with CAD and can be easily and accurately assessed by echocardiography. In experienced hands, transient segmental hypokinesia or akinesia may be detected during ischaemia. Furthermore, differential diagnoses such as aortic dissection, pulmonaryembolism, aortic stenosis, hypertrophic cardiomyopathy, or pericardial effusion may be identified. (12) Therefore, echocardiography should be offered routinely in all patients.(3)
	Stress Imaging		In patients with non-diagnostic 12-lead ECGs and negative cardiac biomarkers but suspected ACS
	Coronary CT angiography		When troponin and ECG reading are non-conclusive
Invasive imaging (coronary angiograph	Fractional Flow Reserve (FFR)	FFR: First vessel. (add-on code)	1296
		FFR: Each additional vessels add-on code	1297
	Coronary angiography	1249-54	To determine extend of coronary artery disease or culprit lesion

Non-Invasive Radiology	Chest X-ray	1241, 30100,30110,30120	Evaluate patients for signs of congestive heart failure (CHF) and for other causes of chest symptoms, such as pneumothorax, pulmonary infection or masses, pulmonary hypertension, and mediastinal widening

5. Risk Stratification

Risk stratification should be performed as early as possible. Generally low risk patients will benefit from conservative and selective invasive approach and high risk patients should be rapidly referred for angiography and revascularization.

Tools for Risk Stratification

- Full clinical history and examination including history of MI and previous interventions
- The 12-lead ECG lies at the centre of the decision pathway for the evaluation and management of patients with ischemic discomfort. A recording made during an episode of the presenting symptoms is particularly valuable.
- CK-MB has until recently been the principal serum cardiac marker used in the evaluation of ACS. Despite its common use, CK-MB has several limitations (Loss of specificity in the presence of skeletal muscle disease or injury. Low sensitivity during very early or later after the symptoms) (1). Despite its limitations CK-MB remains a very useful marker for the detection of more than minor myocardial damage.
- The troponins offer greater diagnostic sensitivity due to their ability to identify patients with lesser amounts of myocardial damage.
- Various risk stratification tools are available however Global Registry of Acute Cardiac Events [GRACE] score or TIMI are commonly used.

In a Cochrane review studying early invasive versus conservative strategies for unstable angina and non-ST elevation myocardial infarction in the stent era, the invasive strategy did not reduce death on longer-term follow up. Invasive strategy was however associated with reduced rates of refractory angina and re-hospitalization in the shorter term and myocardial infarction in the longer term. The invasive strategy is associated with a doubled risk of procedure-related to heart attack and increased risk of bleeding. It is suggested that an invasive strategy may be particularly useful in those at high risk for recurrent events (1).

6. Treatment

Determination of the preferred strategy depends on the patient's clinical characteristics and clinical risk. In a Cochrane review studying early invasive versus conservative strategies for unstable angina and non-ST elevation myocardial infarction in the stent era, the invasive strategy did not reduce death on longer-term follow up. Invasive strategy was, however, associated with reduced rates of refractory angina and re-hospitalization in the shorter term and myocardial infarction in the longer term. The invasive strategy is associated with a doubled risk of procedure-related to heart attack and increased risk of bleeding. It is suggested that an invasive strategy may be particularly useful in those at high risk for recurrent events.(1)

Generally, the initial therapeutic approach is based on whether the patient is to be only medically treated, or in addition referred to angiography and revascularisation. Patients can be revascularised urgently or early (within 72 hours). Patient undergoing initial conservative management can be offered elective revascularisation. (2)

6.1 Initial Pharmacological Treatment and Conservative Management

Any Medical Practitioner in line with their scope of practice as regulated may initiate treatment. Patient must be referred to a physician or cardiologist as soon as possible, taking into consideration the limited number of cardiologists.

6.1.1 Anti-ischaemic agents (2)

- Beta-blockers are recommended in the absence of contraindications, particularly in patients with hypertension or tachycardia
- Intravenous or oral nitrates are effective for symptom relief in the acute management of anginal episodes
- Calcium channel blockers provide symptom relief in patients already receiving nitrates and beta-blockers; they are useful in patients with contraindications to nitrates and beta-blockers in the subgroup of patients with vasospastic angina
- Nifedipine, or other dihydropyridines, may be used in combination with beta-blockers

6.1.2 Anticoagulants

Anticoagulants are used in the treatment of NSTE-ACS to inhibit thrombin generation and/or activity, thereby reducing thrombus-related events. Anticoagulation is recommended for all patients in addition to antiplatelet therapy. Several anticoagulants are available; however the choice is dependent on the selected strategy.

6.1.3 Antiplatelets

Aspirin is recommended for all patients presenting with NSTE-ACS without contraindication at an initial loading dose of 160–325 mg (non-enteric) (I-A), and at a maintenance dose of 75–100 mg long-term.
All patients should receive a loading dose of Clopidogrel (or similar thienopyridine-class antiplatelet agent) and a maintenance dose of 75 mg for 12 months unless contraindicated.

6.1.4 Glycoprotein IIbIIIa inhibitors

These are recommended in intermediate to high risk patients. (1, 2)

Table 2: Pharmacological treatment of ACS

Type of drug	Names	Comments
Anti-ischaemic agents	Beta-blockers	
	Nitrates	
	Calcium channel blockers	In patients with persistent symptoms despite receiving adequate beta blockers and Nitrates and in patient with contraindications to either Nitrates or beta blockers.
	Angiotensin-converting enzyme inhibitors (ACEIs)	Recommended for high-risk patients, LV dysfunction, uncontrolled hypertension despite beta-blockers
Antiplatelet agents	Aspirin	This is the first choice and administered indefinitely
	Thienopyridine	Indicated for patients who are sensitive to aspirin due to hypersensitivity or major gastrointestinal disturbance. Patients who are at high risk when non-invasive strategy is considered.
	Ticagrelor	Not included as PMB level of care as it is not registered with MCC. Will be subject to cost-effectiveness analysis upon registration.
Anticoagulants	Unfractionated heparin	
	Low molecular weight heparins	Not recommended in patients with high risk of bleeding
	Vitamin K antagonists	
	Direct thrombin inhibitors	
Analgesia	Morphine Sulphate	Recommended in patients whose symptoms are not relieved after 3 serial sublingual NTG tablets or whose symptoms recur despite adequate anti-ischemic therapy

6.2 Invasive Strategy

Invasive strategy includes diagnostic catheterisation with instantaneous PCI or referral for coronary artery bypass graft.

Indications for invasive strategy

i. Cardiogenic shock
ii. Severe left ventricular dysfunction (<40%)
iii. Angina refractory to medical therapy
iv. Acute mitral regurgitation
v. New ventricular septal defect
vi. Unstable tachyarrhythmias
vii. Hemodynamic instability
viii. PCI within 6 months
ix. High-risk findings on non-invasive stress testing
x. New or presumably new ST-segment depression
xi. High-risk score (e.g., TIMI, GRACE)

There are no RCTs comparing PCI with CABG in patients with NSTE-ACS. In all trials comparing an early with a late strategy, or an invasive with a medical management strategy, the decision regarding whether to perform CABG or PCI is left to the discretion of the investigator. (2) In patients stabilized after an episode of ACS, the choice of revascularisation modality can be made as in stable CAD.

6.2.1 Percutaneous Coronary Intervention

It is suitable for patients with single vessel disease or low risk double vessel disease. The risk of bleeding complications should be balanced against the severity of ischaemia and the patient's risk profile. The choice of access site depends on operator expertise and local preference. Non-pharmacological strategies to reduce access site bleeding complications include the use of closure devices and the radial approach.

Both DES and bare metal stents can be used. However bare metal stents should be considered in patients who are likely to interrupt Clopidogrel or with Clopidogrel contraindications.

Table 3: Percutaneous Cardiac Intervention and Procedure Codes

Item	Description	Procedure code	Discussion and conclusions
Catheter Laboratory			
Clinicians	Cardiologist Anaesthetist (Only when patient unstable) Physicians/2nd cardiologist (maybe required to assist in case of difficult anatomy) Nurse Radiographer Technologist	0190 0191 0192 0173-0175	Anaesthetist sometimes required for PCI of unstable patients when airway management is anticipated. Assistant cardiologist is sometimes required in patients with difficult anatomy
Clinical Technologist	Preparation and operation of pre-operative, intra-operative or post operative physiological monitoring per patient, per admission	015	
	Cardiac catheterisation for the first hour.	063	
	Dilatation procedures and stents.	073	
Radiographers	Coronary angiogram per 30 minutes or part thereof provided that such part comprises 50% or more of the time	193	
	Stent procedure per 30 minutes or part thereof provided that such part comprises 50% or more of the time	197	
Ancillary Drugs	Glycoprotein IIb/IIIa inhibitor Low molecular weight heparin or unfractionated heparin Aspirin Clopidogrel or Prasugrel Beta Blocker or calcium channel blocker when beta-blockers are contraindicated. Prasugrel		Prasugrel not considered a PMB level of care
Percutaneous procedure			
PCI	Invasive cardiology: Percutaneous translumical angioplasty		
	Percutaneous transluminal angioplasty: First cardiologist: Single lesion	1276	
	Percutaneous transluminal angioplasty: Second cardiologist: Single lesion	1277	
	Percutaneous transluminal angioplasty: First cardiologist: Second lesion	1278	
	Percutaneous transluminal angioplasty: Second cardiologist: Second lesion	1279	
	Percutaneous transluminal angioplasty: First cardiologist: Third or subsequent lesions (each)	1280	
	Percutaneous transluminal angioplasty: Second cardiologist: Third or subsequent lesions (each)	1281	
Insertion of stents	Insertion of intravascular stent: First cardiologist	1286	The insertion of a stent(s) (item 1286 & 1267) may only be charged once per vessel regardless of the number of stents inserted in this vessel.
	Insertion of intravascular stent: Second cardiologist	1287	
Atherectomy	Atherectomy: Single lesion: First cardiologist	1284	
	Atherectomy: Single lesion: Second cardiologist	1285	

Item	Description	Procedure code	Discussion and conclusions
Stents	Bare metal stent		Drug eluting balloons and bioresorbable vascular scaffolds are currently not considered to be at PMB level of care due to lack of sufficient evidence on effectiveness and cost-effectiveness.
	DES		
	Drug Eluting Balloons		
	Bioresorbable vascular scaffolds		
Imaging			
IVUS	Diagnostic intravascular ultrasound (IVUS) imaging or wave wire mapping (without accompanying angioplasty). May be used only once per angiographic procedure.	5117	See Annexure C. The clinical evidence suggests that IVUS is not recommended to be used routinely in stents implantation. IVUS use has however been shown to be superior to angiography in the treatment of complex lesions (long lesions > 28 mm, chronic total occlusions or occlusion older than 3 months, lesions involving a bifurcation, vessels smaller than or equal to 2.5 mm and patients requiring more stents) and high risk patients (diabetes patients). Therefore this treatment is subject to motivation.
	Diagnostic intravascular ultrasound imaging or wave wire imaging (with accompanying angioplasty or accompanying intravascular ultrasound imaging or wave wire mapping in a different coronary artery [LAD (left anterior descending), Circumflex or Right coronary artery]). May be used a maximum of two per angiographic procedure	5118	
Fractional Flow Reserve (FFR)	FFR: First vessel. (add-on code)	1296	
	FFR: Each additional vessels (add-on code)	1297	

6.2.2 Coronary artery bypass surgery

Indications

- Left main coronary artery stenosis >50%
- Stenosis of proximal left anterior descending artery and proximal circumflex >70%
- Three vessel disease
- Three vessel disease with proximal LAD stenosis in patients with poor left ventricular (LV) function
- Two-vessel disease and a large area of viable myocardium in high-risk area in patients with stable angina
- More than 70% proximal LAD stenosis with either ejection fraction < 50% or demonstrable ischemia on non-invasive testing.

7. Post Discharge Care

All patients with NSTEMI-Unstable angina must have non-invasive stress testing. Echocardiogram must be done post-discharge or immediately before discharge to evaluate left ventricular functioning.

The risk of mortality increases few months down the line. For this reason patients with unstable angina must be followed more frequently than those with stable angina. Three monthly follow-ups are recommended.

Most of the patients with DES are also likely to default antiplatelet. These patients must be seen monthly for 3 months including post discharge follow-up between 4 and 6 weeks and there after 3 monthly. Stable patients can then be seen 6 monthly.

Table 4: Possible procedure codes post- discharge

Item	Description	Code	Comments
ECG	General Practitioner's fee for the taking of an ECG only: Without effort: ½ (item 1232)	1228	Serial ECG recording throughout assessment in Emergency room
	General Practitioner's fee for the taking of an ECG only: Without and with effort: ½ (item 1233)	1229	Note: Items 1228 and 1229 deal only with the fees for taking of the ECG, the consultation fee must still be added
	Physician's fee for interpreting an ECG: Without effort	1230	A specialist physician is entitled to the fees specified in item 1230 and 1231 for interpretation of an ECG tracing referred for interpretation. This applies also to a paediatrician when an ECG of a child is referred to him for interpretation
	Physician's fee for interpreting an ECG: With and without effort	1231	
	Electrocardiogram: Without effort	1232	
	Electrocardiogram: With and without effort	1233	For inducible ischaemia
Exercise testing	Effort electrocardiogram with the aid of a special bicycle ergometer, monitoring apparatus and availability of associated apparatus	1252	Can be considered in patients without contradiction to exercise before discharge or early after discharge to assess inducible ischemia; to evaluate functional significance of coronary lesion; risk stratify according to likelihood of coronary events, establish ability and to exercise for life style modification
	Multi-stage treadmill test	1234, 1235	
Angiography	Right and left cardiac catheterisation without coronary angiography (with or without biopsy)	1249	Indicated in patients with ECG changes of ischaemia post STEMI In patients with positive finding during non-invasive testing In patients who are persistently unstable For risk assessment in patients who had fibrinolytic therapy
	Left heart catheterisation with coronary angiography (with or without biopsy)	1252	
	Right heart catheterisation (with or without biopsy)	1253	
	Catheterisation of coronary artery bypass grafts and/or internal mammary grafts	1254	
Echocardiography	Cardiac examination plus Doppler colour mapping	3620	It is indicated in patients with STEMI when there is a negative change in clinical status. It is reasonable to repeat the procedure in 1 to 3 months time. It is used to assess and re-evaluate LV function and to evaluate suspected complications. It can be used in patient with suspected RV infarction and inferior STEMI.
	Cardiac examination (MMode)	3621	
	Cardiac examination: 2 Dimensional	3622	
	Cardiac examination + effort	3623	
	Cardiac examinations + contrast	3624	
	Cardiac examinations + doppler	3625	
Pharmacological stress testing	Cardiological supervision of Dobutamine magnetic resonance stress testing	1271	Indicated for patients who cannot exercise. Alternatives to dobutamine are adenosine and dipyridamole

8. Secondary prevention for N-STEMI Patients

i. Lifestyle modification(2, 13)

- All persons with risk factors for ischaemic heart disease should be encouraged to make the following lifestyle changes as appropriate:
- Smoking cessation.
- Weight reduction in the overweight patients, i.e. BMI > 25 kg/m^2
- Maintain ideal weight, i.e. BMI < 25 kg/m^2
- Reduce alcohol intake to no more than 2 standard drinks/day
- Follow a prudent eating plan i.e. Low saturated fat, high fibre and unrefined carbohydrates, with adequate fresh fruit and vegetables.
- Moderate aerobic exercise, e.g. 30 minutes brisk walking at least 3 times a week
- Members must be encouraged to participate in wellness and prevention activities as offered by the scheme in line with scheme rules.

ii. Lipid Lowering Agents

The 2012 Essential drug list recommends lipid lowering agents in all Ischaemic heart disease **irrespective of cholesterol and triglyceride plasma concentration**. The intention is to reduce the LDL by at least 25%. (13). The CDL algorithm recommends a target of 3mmol or a reduction in LDL by 45% in patients with established cardiovascular disease. The ESC guideline recommends a target LDL of 1.8 mmol for better outcomes. The current CDL algorithm was established in 2000 and is not in accordance with the CURRENT evidence-based medicine principles. Therefore, regardless of cholesterol levels, statin therapy must be implemented to achieve LDL reduction by 45%. However the schemes should consider reducing the LDL to 1.8 mmol as this may be cost-effective compared to funding a subsequent myocardial infarct.

iii. Control of diabetes

Maintain to HbA1 C < 7%

iv. Antiplatelets agents

Post STEMI patients must receive dual antiplatelet therapy. Aspirin must be continued indefinitely. Clpidogrel must be used for at least a month if bare metal stents were used and for at least 6 months if drug eluting stents were used.

v. Blood pressure control

The main aim is to maintain BP at < 140/90 or < 130/80 in patients with chronic kidney disease and diabetes mellitus.
Antihypertensive as per scheme's formulary and CDL algorithm must be used. However, this should include beta blocker and angiotensin converting enzyme inhibitors as a minimum benefit.(2)

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Annexure A

Review of Prasugrel versus Clopidogrel in the Management of Acute Coronary Syndrome

1. Introduction

Antiplatelets therapy remains the cornerstone for the treatment of patients with acute coronary syndromes (ACS) and patients undergoing percutaneous coronary interventions[1]. The use of dual antiplatelets therapy in the form of P2Y12 inhibitor combined with aspirin is well established[2]. Currently, clopidogrel, prasugrel and ticagrelor are used in the treatment of acute coronary syndromes[3].

Clopidogrel is an irreversible adenosine diphosphate-receptor antagonist that reduces the risk of vascular events when given with aspirin. Clopidogrel is indicated for the prevention of atherothrombotic events in patients suffering from myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease. Contraindications to clopidogrel include severe liver impairment and active pathological bleeding such as peptic ulcer or intracranial haemorrhage [4, 5].
Prasugrel is an oral antiplatelet drug that irreversibly blocks the P2Y12 platelet receptor. Prasugrel is indicated together with aspirin for the prevention of atherothrombotic events in adults with acute coronary syndrome [3].

2. Objective

The objective of this literature review is to compare the clinical effectiveness of clopidogrel versus prasugrel in the management of acute coronary syndromes.

3. Methods

A systematic review was performed by an electronic search of the PubMed and Science Direct databases and by a manual search of reference lists for randomized controlled trials published until December 2014. The database search was supplemented with bibliographies of relevant articles and reports. The databases of the major HTA institutions were also searched for related information and policies.

Inclusion criteria

Systematic reviews and randomized controlled trials were included in this study. The studies met the following description:

- Patients: Patients with acute coronary syndromes with a sample size larger than 50.
- Intervention: Anti-platelets agents
- Comparator: other anti-platelets agents
- Outcomes: Major adverse cardiac events
- Follow-up: hours to months

Exclusion criteria

Non-randomized studies, non-systematic reviews, editorials, letters, comments, case series and case reports were excluded.

4. *Results*

Six clinical trial studies were selected according to the inclusion criteria. Table 1 is an overview of the studies that were included.

Triology trial

The Triology ACS trial was a double-blind, randomized trial involving 7243 patients under the age of 75 years receiving aspirin. Patients were randomised to treatment with Prasugrel (10 mg daily) versus Clopidogrel (75 mg daily) and evaluated up to 30 months. The results of the study showed that treatment with prasugrel does not significantly reduce the frequency of the primary end point, as compared with clopidogrel. Similar risks of bleeding were observed amongst patients with unstable angina or myocardial infarction without ST-segment elevation.

Cardiovascular causes, myocardial infarction, or stroke among patients under the age of 75 years occurred in 13.9% of the prasugrel group and 16.0% of the Clopidogrel group. In the prasugrel group, 0.91; 95% confidence interval [CI], 0.79 to 1.05; P = 0.21). All components of the primary end point suggested a lower risk for prasugrel among patients under the age of 75 years (hazard ratio, 0.85; 95% CI, 0.72 to 1.00; P = 0.04). Rates of severe and intracranial bleeding were similar in the two groups in all age groups. There was no significant between-group difference in the frequency of non-hemorrhagic serious adverse events, except for a higher frequency of heart failure in the clopidogrel group[6].

Table1. Clinical trial of prasugrel versus clopidogrel in the management of acute coronary symptoms

Authors	Population	Intervention strategy	Follow-up period	End-point	Secondary End points	Results
TRIOLOGY ACS	7243 patients under the age of 75 years receiving aspirin	Prasugrel Clopidogrel	17 months	Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke		Fewer cardiovascular deaths, myocardial infarctions, or strokes in the prasugrel group
PRASFIT-ACS	1,363 patients with ACS undergoing PCI	Prasugrel Clopidogrel	14 days	MACE at 24 weeks, which was defined as a composite of cardiovascular death, nonfatal myocardial infarction (MI), and nonfatal ischemic stroke	Incidence of all-cause death, myocardial ischemia requiring re-hospitalization, revascularization, and stent thrombosis	Prasugrel was associated with a low incidence of ischemic events and low risk of clinically serious bleeding
JUMBO Trial	904 patients undergoing elective or urgent percutaneous coronary intervention	Prasugrel Clopidogrel	30 days	Non–CABG-related "significant haemorrhage" at 30 days, all-cause mortality, myocardial infarction, stroke, recurrent myocardial ischemia requiring hospitalization, and clinical target vessel thrombosis		Prasugrel and clopidogrel both resulted in low rates of bleeding
TRITON TIMI-38	13,608 patients with an ACS	Prasugrel Clopidogrel	30 days, 90 days	Cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	Composite end point and a composite of death from cardiovascular causes, nonfatal myocardial infarction, or urgent target-vessel revascularization, stent thrombosis and a composite of death	Overall mortality did not differ significantly between treatment groups Significantly reduced rates of ischemic events, including stent thrombosis, but with an increased risk of major

					from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or re-hospitalization due to a cardiac ischemic event.	bleeding, including fatal bleeding was reported in the prasugrel group
TRITON TIMI-38	13,608 patients with an ACS	Prasugrel Clopidogrel	30 days, 90 days	MI, urgent target vessel revascularization, stent thrombosis, TIMI major non–CABG-associated bleeding, and net clinical benefit as in the main trial.		Loading dose and maintenance dose of prasugrel were superior to clopidogrel for the reduction of ischemic events Excess major bleeding was observed with the use of prasugrel
TRITON TIMI-38 substudy	13 608 undergoing PCI for ACS	Prasugrel Clopidogrel	30 days	Composite of death from CV causes, nonfatal MI, or nonfatal stroke	Composite of the primary end point plus urgent target vessel revascularization and individual components of the primary end point. Safety end points included TIMI major bleeding not associated with coronary artery bypass surgery (CABG), non–CABG-related TIMI life-threatening bleeding and non–CABG-related TIMI major or minor bleeding	Prasugrel therapy tended to reduce clinical ischemic events and to increase bleeding events

TRITTON-TIMI 38 substudy	13 608 patients with acute coronary syndrome undergoing PCI	Prasugrel Clopidogrel	30 days	Cardiovascular Death, Nonfatal Myocardial Infarction (MI), or Nonfatal Stroke	Number of subjects reaching the composite endpoint of cardiovascular death, non-fatal myocardial infarction , or urgent target vessel revascularization	Prasugrel significantly reduces the risk of MIs that are procedure related and spontaneous and those that are small and large, including new MIs occurring during maintenance therapy

Prasfit ACS trial

The objective of the Prasfit ACS study was to confirm the efficacy and safety of prasugrel at loading dose of 20 mg and maintenance doses of 3.75 mg. Patients with acute coronary syndrome undergoing percutaneous coronary intervention (PCI) were randomized to either prasugrel (20/3.75 mg) or clopidogrel (300/75 mg) in combination with aspirin (81–330 mg for the first dose and 81–100 mg/day thereafter), for 24–48 weeks. The incidence of major acute cardiac events (MACE) at 24 weeks was 9.4% in the prasugrel group and 11.8% in the clopidogrel group (risk reduction 23%, hazard ratio 0.77, 95% confidence interval 0.56–1.07). The incidence of non-coronary artery bypass graft-related major bleeding was similar in both groups (1.9% vs. 2.2%). Prasugrel 20/3.75 mg was associated with a low incidence of ischemic events and with a low risk of clinically serious bleeding in ACS patients[7].

JUMBO-TIMI trial

JUMBO-TIMI 26 was a phase 2, randomized, dose-ranging, double-blind safety trial of prasugrel versus clopidogrel in 904 patients undergoing elective or urgent PCI. Patients were randomised to low (40-mg loading dose followed by 7.5 mg daily); intermediate (60-mg loading dose followed by 10 mg daily); high (60-mg loading dose followed by 15 mg daily) dose of Prasugrel or 300mg of Clopidogrel. All subjects received concomitant aspirin. Hemorrhagic complications were infrequent, with no significant difference between patients treated with prasugrel or clopidogrel in the rate of significant bleeding (1.7% versus 1.2%; hazard ratio, 1.42; 95% CI, 0.40, 5.08). Patients treated with prasugrel had lower incidences of MACE and of the secondary end points myocardial infarction, recurrent ischemia, and clinical target vessel thrombosis although the differences were not statistically significant. Prasugrel and clopidogrel both resulted in low rates of bleeding [8].

TRITON-TIMI trial 38

The objective of the phase 3 TRITON-TIMI trial 38 trial was to compare a regimen of prasugrel with the standard-dose regimen of clopidogrel in patients with acute coronary syndromes with scheduled PCI. 13,608 patients with moderate-to-high-risk acute coronary syndromes with scheduled percutaneous coronary intervention were randomly assigned to receive prasugrel (a 60-mg loading dose and a 10-mg daily maintenance dose) or clopidogrel (a 300-mg loading dose and a 75-mg daily maintenance dose), for 6 to 15 months. Cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke occurred in 12.1% of patients receiving clopidogrel and 9.9% of patients receiving prasugrel (HR for prasugrel vs. clopidogrel, 0.81; 95% CI, 0.73 to 0.90; P<0.001). Myocardial infarction (9.7% for clopidogrel vs. 7.4% for prasugrel; P<0.001), urgent target-vessel revascularization (TVR) (3.7% vs. 2.5%; P<0.001), and stent thrombosis (2.4% vs. 1.1%; P<0.001) was significantly reduced in the prasugrel group than in the clopidogrel group. Although the results are statistically significant, the benefits are marginal. Major bleeding was observed in 2.4% of patients receiving prasugrel and in 1.8% of patients receiving clopidogrel (HR, 1.32; 95% CI, 1.03 to 1.68; P = 0.03). Life-threatening bleeding (1.4%

vs. 0.9%; P = 0.01), including nonfatal bleeding (1.1% vs. 0.9%; hazard ratio, 1.25; P = 0.23) and fatal bleeding (0.4% vs. 0.1%; P = 0.002) was also observed in the prasugrel group than in the clopidogrel group[9].

TRITON-TIMI trial 38 (early and late complications substudy)

TRITON-TIMI 38 was a randomised trial that compared prasugrel with clopidogrel to determine which drug is better at reducing deaths, future heart attacks, or stroke. In this substudy of the trial a total of 13,608 patients with ACS were randomised to receive prasugrel or clopidogrel before PCI. Patients also received a daily dose of aspirin of 75 to 162 mg together with blinded drug during the maintenance phase. The rate of MI was 5.2% in the clopidogrel vs. 4.7%; (p=0.0008) in the prasugrel group 3 days post interventions. The risk difference was 0.5 % and NNT = 200. Three days after trial started, MI was 3.4 in the prasugrel vs. 4.7% in the clopidogrel group, p<0.001, stent thrombosis was 0.67 in the clopidogrel vs. 0.33% in the prasugrel group (p=0.047). Three days before the end of trial stent thrombosis was 2.97 % in the clopidogrel vs. 1.74 % in the prasugrel group (p=0.03). The use of prasugrel resulted in statistically significant but marginal reductions in ischemic events, including myocardial infarction, stent thrombosis, and urgent target vessel revascularization during the first 3 days and from 3 days to the end of the trial. [10].

TRITON –TIMI 38 trial (PCI without stent implantation substudy)

In the second sub study of the TRITON-TIMI 38 trial, patients undergoing PCI for ACS without stent implantation were randomized to aspirin plus clopidogrel or prasugrel. Amongst these patients, prasugrel reduced clinical ischemic events and increased bleeding events similar to patients who received stents. Patients who underwent PCI without stent implantation were older and had a higher incidence of hypertension, diabetes, prior myocardial infarction (MI), prior coronary artery bypass (CABG) surgery, and renal dysfunction than patients who underwent stent implantation. In the group that did not undergo stent implantation, baseline characteristics were similar between patients receiving clopidogrel and prasugrel. The composite of cardiovascular death, nonfatal MI, and nonfatal stroke occurred in 14.2% of patients receiving prasugrel and 17.1% of patients receiving clopidogrel (HR 0.82, P = 0.27), a risk reduction of 2.9 % with NNT equal to 34. There were significant reductions favouring prasugrel in the composite of any revascularization procedure (6.3% vs. 12.9%, HR 0.48, 95% CI 0.27-0.87, P =0.014). CABG-related TIMI major bleeding was more frequent among patients receiving prasugrel 12.5% vs. 19.4% in the clopidogrel group. There were no significant interactions between treatment and PCI type [11].

TRITON-TIMI 38 trial (spontaneous procedural myocardial infarction substudy)

In another TRITON-TIMI 38 study the effect of prasugrel compared with clopidogrel on myocardial Infarction was studied. Each MI underwent supplemental classification as spontaneous, secondary, or sudden cardiac death (types 1, 2, and 3) or procedure related (Types 4 and 5). Myocardial infarction events were fewer in patients treated with prasugrel (7.4% versus 9.7%; HR, 0.76; 95% CI, 0.67 - 0.85; *P*=0.0001). This reduction was observed in procedure-related MIs (4.9% versus 6.4%; HR, 0.76; 95% CI, 0.66 to 0.88; *P*=0.0002) and nonprocedural (type 1, 2, or 3) MIs (2.8% versus 3.7%; HR, 0.72; 95% CI, 0.59 to 0.88; *P*=0.0013) and

consistently across MI size, including MIs with a biomarker peak 5 times the reference limit (HR=0.74; 95% CI, 0.64 to 0.86; *P*=0.0001). At 30 days, patients treated with prasugrel had a lower risk of any MI (2.9% versus 3.7%; HR, 0.77; *P*=0.014), including nonprocedural MI (2.3% versus 3.1%; HR, 0.74; 95% CI, 0.60 to 0.92; *P* =0.0069). The risk reduction of any MI was 0.8 with NNT of 125.This study showed that treatment with prasugrel in patients with acute coronary syndrome undergoing percutaneous coronary intervention significantly reduces the risk of MIs that are procedure related and spontaneous and those that are small and large, including new MIs occurring during maintenance therapy[12].

5. Discussion

The results of the clinical trials have shown the benefits and limitations of using prasugrel and clopidogrel in the treatment of acute coronary syndromes.

- The results of the Triology study showed that prasugrel did not significantly reduce the frequency of the primary end point, as compared with clopidogrel. Similar risks of bleeding were observed amongst patients with unstable angina or myocardial infarction without ST-segment elevation
- Prasugrel was associated with a low incidence of ischemic events and with a low risk of clinically serious bleeding TIMI in the Prasfit trial. Although the benefit was marginal.
- In the phase 2 Jumbo study trial, prasugrel and clopidogrel both resulted in low rates of bleeding.
- Overall mortality did not differ significantly between treatment groups in the phase 3 TRITON-TIMI trial. Significantly reduced rates of ischemic events, including stent thrombosis, but with an increased risk of major bleeding, including fatal bleeding was reported in the prasugrel group
- Loading dose and maintenance dose of prasugrel were superior to clopidogrel for the reduction of ischemic events in the TRITON- TIMI trial. Excess major bleeding observed with the use of prasugrel occurred during the maintenance phase.
- From the TRITON-TIMI 38 trial, patients who underwent PCI without stent implantation had fewer clinical ischemic events and increased bleeding events to a similar magnitude as among patients who received stents in the prasugrel group
- Treatment with prasugrel compared with clopidogrel for up to 15 months in patients with acute coronary syndrome undergoing PCI significantly reduces the risk of myocardial infarctions that are procedure related and spontaneous and those that are small and large, including new MIs occurring during maintenance therapy.

6. Conclusion

The results of these clinical trials have shown that prasugrel is superior to clopidogrel with regards to reducing rates of ischemic events. Although prasugrel was statistically superior, the benefits were marginal. In addition, prasugrel resulted in excess major bleeding than clopidogrel. The results of these trials still leave uncertainty about whether prasugrel is clinically superior to clopidogrel in patients with unstable angina or NSTEMI.

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Annexure B

A review of intravascular ultrasound imaging and angiography to guide optimal stent placement in acute coronary syndromes

1. Introduction

The role of Intravascular ultrasound (IIVUS) in understanding the pathophysiology of coronary lesions, percutaneous diagnostic and therapeutic procedures is well established. IVUS is an invasive imaging modality that requires the insertion of a catheter with a transducer on its tip down the coronary artery to provide tomographic 2D cross-sectional images of the vessel. Several indications for IVUS have been identified such as assessing the severity of a lesion, identification of pseudo aneurysm, accurate assessment of the extent, morphology and constitution of plaque, selection of balloon's dimensions and inflation pressure, treatment of complex disease and the treatment of complex diseases[1][2]

Although IVUS use gives reliable data, the primary disadvantages of IVUS being used routinely in a cardiac catheterization laboratory are its expense, the increase in the time of the procedure, and the fact that it is considered an interventional procedure, and should only be performed by angiographers that are trained in interventional cardiology techniques[2].

2. Objectives

The objective of this review was to determine clinical outcomes for intravascular ultrasound imaging in guiding Percutaneous Coronary intervention (PCI).

3. Method

A systematic review was performed by an electronic search of the PubMed and Science Direct databases and by a manual search of reference lists for randomized controlled trials published until November 2014, with clinical outcomes and at least six months of clinical follow-up. The database search was supplemented with bibliographies of relevant articles and reports. The databases of the major Health Technology Assessment (HTA) institutions were also searched for related information and policies.

Inclusion criteria

Systematic reviews and randomized controlled trials were included in this study. The studies met the following description:

- Patients: Patients with coronary stenosis undergoing balloon dilatation, stent implantation (bare metal or drug-eluting stents) with a sample size larger than 50.
- Intervention: IVUS guidance in conjunction with angiographic guidance
- Comparator: Angiographic guidance
- Outcomes: Disease free progression
- Follow-up: At least 6 months

Exclusion criteria

Non-randomized studies, non-systematic reviews, editorials, letters, comments, case series and case reports were excluded.

4. Findings of literature review

Six studies were selected according to the inclusion criteria. Table 1 below gives an overview of the studies included in this review.

AVIO trial

The AVIO study evaluated if IVUS optimized DES implantation was superior to angiographic guidance alone in complex lesions. Complex lesions were defined as long lesions greater than 28 mm, chronic total occlusions or occlusion older than 3 months, lesions involving a bifurcation, vessels smaller than or equal to 2.5 mm and patients requiring more stents. The results of the study showed no significant differences in baseline characteristics. Minimal luminal diameter showed a statistically significant difference of 2.70 mm ± 0.46 mm for the IVUS group compared to 2.51 ± 0.46 mm for the angiography group (P = 0.0002).. No difference was observed in the occurrence of non-Q wave myocardial infarction (6.3% in IVUS vs. 7.0% in angio-guided group). No differences were observed in cumulative MACE (16.9%vs. 23.2 %), cardiac death (0%vs. 1.4%), MI (7.0%vs. 8.5%), target lesion revascularization (9.2% vs. 11.9%) or target vessel revascularization (9.8% vs. 15.5%), respectively in the IVUS vs. angio-guided groups after 24 months. Only one definite sub-acute stent thrombosis occurred in the IVUS group [3]. During hospitalization, no patient died, had repeated revascularization, or a Q-wave

Authors	Sample size	Population	Intervention strategy	Follow-up period (months)	Primary End-point	Secondary End points	Results
Avio Trial	IVUS =142 ANGIO =142	284 patients with complex lesions (bifurcations, long lesions, chronic total occlusions or Small vessels).	DES Implantation	1, 6, 9, 12, 24	Post-procedure in lesion minimal lumen diameter	MACE, target lesion revascularization, target vessel revascularization, myocardial infarction (MI), and stent thrombosis	No statistical significant difference in MACE at 24 months Benefit of IVUS in complex post-procedure minimal lumen diameter
Opticus	IVUS=273 ANGIO= 277	550 patients with a symptomatic coronary lesion or silent ischemia.	BMS stent	12	Incidence of angiographic restenosis (.50% lumen diameter reduction), minimal lumen diameter, and percent diameter stenosis after 6 months.	MACE during follow-up (death, myocardial infarction, bypass surgery, and repeat coronary intervention)	Routine use of IVUS not supported by the study
Reset	IVUS =662 ANGIO =912	662 patients with clinical characteristics: diabetes mellitus, ACS, short and long lesion	DES Implantation	12		MACE	Routine IVUS guidance does not provide clinical benefits when performing short-length DES implantation
Resist	IVUS ANGIO	164 patients with symptomatic ischemic heart disease	BMS Stent		6 months Restenosis rate		A non-significant 6.3% absolute reduction in the restenosis rate and a non-significant difference in MLD were observed
Tulip	IVUS =73 ANGIO=71	Patients with de novo, nonostial stenosis 20 mm length in a native coronary artery with a	BMS Stent	1, 6, 12	Angiographic MLD at 6 months and the combined event rate of cardiac death, MI, and	Angiographic and procedural success, angiographic restenosis (_50% diameter stenosis) and percent	IVUS is superior to guidance by angiography up to 12 months after long stent placement guided by

		reference diameter that permitted implantation of 3-mm stents without involvement of significant side branches (diameter 2.0 mm).			ischemia-driven target-lesion revascularization (TLR) within 6 months were the angiographic and clinical	diameter stenosis at 6 months, and combined event frequency at 12 months.	
SIPS	IVUS=166 ANGIO=190	269 patients with no chronic total occlusions or emergency procedures	Provinsional stenting	6	MLD	Acute MLD, acute chronic cost, quality of life, composite clinical event rates, clinically driven target lesion revascularization (TLR).	IVUS-guidance during provisional stenting slightly attenuates the negative effect of diabetes on long-term outcome. Re-stenosis rate remains very high.
SIPS	IVUS=166 ANGIO=190		Provinsional stenting	6, 18, 28	Death, non-fatal myocardial infarction and target vessel revascularisation	Re-stenosis rate at 6-month follow-up angiography	ICUS-guided provisional stenting improved 2-year clinical results after intervention

OPTICUS trial

The OPTICUS study randomised a total of 550 patients with a symptomatic coronary lesion or silent ischemia to either ultrasound-guided or angiography-guided implantation of 2 tubular stents. At 6 months, repeat angiography revealed no significant differences between the groups with ultrasound- or angiography-guided stent implantation with respect to dichotomous restenosis rate (24.5% versus 22.8%, *P*50.68), minimal lumen diameter (1.9560.72 mm versus 1.9160.68 mm, *P*=0.52), and percent diameter stenosis (34.8620.6% versus 36.8619.6%, *P*=0.29), respectively. At 12 months, neither major adverse cardiac events (relative risk, 1.07; 95% CI 0.75 to 1.52; *P*=0.71) nor repeat percutaneous interventions (RR= 1.04; 95% CI 0.64 to 1.67; *P*=0.87) were reduced in the ultrasound-guided group[4].

RESET trial

The RESET Investigators evaluated the usefulness of IVUS in predicting major adverse cardiac events (MACE), including cardiovascular death, myocardial infarction, or target vessel revascularization, at 1 year after DES implantation in short-length lesions. In the IVUS-guided group, adjuvant postdilation was more frequently performed (43.0% vs 34.6%, p <0.001), and the postintervention minimal lumen diameters were greater (2.88 – 0.44 mm vs 2.72 – 0.43 mm, p <0.001). MACE occurred in 15 IVUS-guided (2.3%) and 19 angiographically guided (2.1%) patients. In patients with diabetes mellitus, the MACE rate was 3.4% in the IVUS- and 1.7% in the angiographically guided patients (p = 0.384). The MACE rate in the IVUS- and angiographically guided patients with acute coronary syndrome was 1.1% and 2.7% respectively (p = 0.194) [5].

RESIST trial

The aim of the RESIST study group was to investigate the impact of intravascular ultrasound (IVUS)-guided stent implantation on the 6-month restenosis rate. After successful stent implantation, patients were randomized into two groups: Group A had no further dilation, and Group B had additional balloon dilation until achievement of IVUS criterion for stent expansion. Overdilation was carried out in 31 of 79 Group B patients, with the IVUS criterion being achieved in 63 of 79. The results of the study showed no significant difference in the MLD. The stent lumen cross-sectional area (CSA) was significantly larger in Group B (mean +/- SD) (7.16 +/- 2.48 vs. 7.95 +/- 2.21 mm2, p = 0.04). At 6 months, there was no significant difference in the restenosis rate, (28.8%) in Group A vs. 22.5% in Group B, (p = 0.25). The difference in MLD was also non significant (1.60 +/- 0.65 mm in Group A vs. 1.70 +/- 0.64 mm in Group B, p = 0.20), whereas the lumen cross-sectional area was 20% larger in the IVUS-guided group (4.47 +/- 2.59 vs. 5.36 +/- 2.81 mm2, p = 0.03)[6]. The power of the study was only 40% according to the observed difference in the restenosis rate.

TULIP trial

The TULIP study compared the 6-month outcome of stent implantation for long lesions in patients randomized to intravascular ultrasound or angiographic guidance. At 6 months, MLD in the IVUS group (1.82_0.53 mm) was

larger than in the angiography group (1.51_0.71 mm; *P*=0.042). Target-lesion revascularization (TLR) and combined end-point rates at 6 months were 4% and 6% in the IVUS group and 14% and 20% in the angiography group, respectively (*P*_0.037 for TLR and *P*_0.01 for combined events). Restenosis (50% diameter stenosis) was found in 23% of the IVUS group and 45% of the angiography group (*P*_0.008). At 12 months, TLR and the combined end point occurred in 10% and 12% of the IVUS group and 23% and 27% of the angiography group (*P*_0.018 and *P*_0.026), respectively[7].

SIPS trial

The aim of the Strategy for ICUS-Guided PTCA and Stenting (SIPS) was to test whether routine intracoronary ultrasound guidance of coronary interventions improves outcome. Consecutive patients with no chronic total occlusions or emergency procedures were randomized to intracoronary-guided provisional stenting or standard angiographic guidance. Six months follow-up showed no difference in MLD (1.7160.94 versus 1.5760.90, *P*=0.19) or binary restenosis rate (29% versus 35%, *P*=0.42). Clinical follow-up showed a significant decrease in clinically driven target lesion revascularization in the ultrasound group compared with the standard guidance group (17% versus 29%, respectively; *P*=0.02). Procedure success was recorded in the ultrasound-guided group (94.7%) than the standard group (87.4%) (*P*=0.033). The time for the procedure and contrast use was not significantly different with similar outcomes in the stenting rates (49.7% versus 49.5%, *P*=0.89)[8].

A subgroup was analysed to investigate whether routine IVUS-guidance during percutaneous intervention improves long-term outcome in diabetics. Primary endpoint occurred in 6 diabetic patients (31.6%) in the IVUS-group and 11 diabetic patients (45.8%) in the ANGIO-group (relative risk for IVUS, 0.83, 95% confidence interval 0.28–2.35, p = 0.83). The quantitative assessment of follow-up angiography revealed that the incidence of re-stenosis was high in both groups (IVUS: 53% versus ANGIO: 52%, p = 0.94). There was no difference in the mean duration of hospitalisation (11.8 days with IVUS versus 11.2 days with ANGIO, p = 0.83) or total cost ($ 16 725 with IVUS versus $ 16 230 with ANGIO, p = 0.83) during follow-up[9].

5. Discussion

The results of the seven clinical trial studies reviewed have shown that there is a moderate strength of evidence that the routine use of IVUS to guide optimal stent placement result in better outcomes when compared with standard angiography.

- In the Avio study, a benefit of IVUS optimized DES implantation was observed in complex lesions in the post-procedure minimal lumen diameter in. No statistically significant difference was found in MACE up to 24 months

- The OPTICUS study did not support the routine use of ultrasound guidance for coronary stenting. The study showed that angiography guided optimization of tubular stents can be performed with comparable angiographic and clinical long-term results.
- The clinical benefits of IVUS-guided DES implantation compared with angiographically guided DES implantation in short-length lesions could not be confirmed even in patients with clinically high-risk presentations (acute coronary syndrome and diabetes mellitus) in the RESET study. The study concluded that routine IVUS guidance does not provide clinical benefits when performing short-length DES implantation.
- A non significant 6.3% absolute reduction in the restenosis rate and a non significant difference in MLD were observed in the RESIST study. A significant increase was observed in immediate and 6-month lumen size, as detected by IVUS, indicating that ultrasound guidance in stent deployment may be beneficial.
- Angiographic and clinical outcome up to 12 months after long stent placement guided by IVUS was shown to be superior to guidance by angiography in the TULIP study
- In the SIPS study, angiographic MLD did not differ significantly after 6 months; however, ultrasound-guided provisional stenting improved 2-year clinical results after intervention.
- Routine IVUS-guidance during provisional stenting was shown to slightly attenuate the negative effect of diabetes on long-term outcome in the SIPS study. However, the re-stenosis rate remained very high.

6. Conclusion

In conclusion, given the evidence of the trials on clinical effectiveness, it can be concluded that IVUS is not recommended to be used routinely in stents implantation. IVUS use has however been shown to be superior to angiography in the treatment of complex lesions (long lesions > 28 mm, chronic total occlusions or occlusion older than 3 months, lesions involving a bifurcation, vessels smaller than or equal to 2.5 mm and patients requiring more stents) and high risk patients (diabetes patients).

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