# Benefit Definition: ST-Elevation Myocardial Infarct

March 2015

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

## Contents

**Abbreviations**

| | | |
|---|---|---|
| ASA | – | acetylsalicylic acid |
| BMS | – | Bare metal stent |
| CABG | – | coronary artery bypass grafting |
| CAD | – | coronary artery disease |
| CDL | – | chronic disease list |
| CHF | – | chronic heart failure |
| CVD | – | cardiovascular disease |
| DAPT | – | Dual antiplatelet therapy |
| DES | – | Drug eluting stent |
| DSP | – | Designated Service Providers |
| ECG | – | electrocardiogram |
| FFR | – | fractional flow reserve |
| IVUS | – | Intravascular Ultrasound Imaging |
| LAD | – | left anterior descending |
| LV | – | left ventricle |
| MVD | – | multivessel disease |
| MRI | – | magnetic resonance imaging |
| NSTE-ACS | – | non-ST-segment elevation acute coronary syndrome |
| OCT | – | Optical Coherence Tomography |
| OMT | – | optimal medical therapy |
| PCI | – | percutaneous coronary intervention |
| PET | – | positron emission tomography |
| PMB | – | prescribed minimum benefit |
| PTCA | – | Percutaneous transluminal coronary angioplasty |
| SPECT | – | single photon emission computed tomography |
| STEMI | – | ST-segment elevation myocardial infarction |
| UA | – | Unstable angina |
| UFH | – | Unfractionated heparin |

## 1 Introduction

This benefit definition does not explicitly endorse one medicine/medical device within a particular therapeutic class over another. However due to the emergency nature of STEMI and to avoid delays associated with pre-authorisation and consultation with scheme formularies, this Benefit definition is highly specific on which treatment and classes may be used during ST elevation myocardial infarct (STEMI). This is to safe guard members against any possible co-payments that may arise from failure to use formularies and to protect the schemes of unplanned expenditure that may arise in a setting where it is impossible to obtain scheme authorisation.

Provision must be made for appropriate exceptions where this benefit definition has been ineffective, or causes, or would 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 should be developed and applied while taking into consideration evidence-based medicine, cost-effectiveness and affordability.

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 those stated here.

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

Alternatives must be made for patients in whom treatment stated here or in the scheme formulary may cause harm.

Due to high variability of clinical presentation and possible outcomes in patients with Ischaemic heart disease it was difficult to quantify frequency of tests and interventions in an acute setting.

***Procedure codes serve as a guideline for billing and may not include all relevant procedure codes.***

## 2 Scope

These benefit definitions include the management of ST-Elevation Myocardial Infarct (STEMI). The benefit definition covers out of hospital emergency care, in-hospital care and long term follow-up including secondary prevention. Coronary artery bypass graft is not included.

## 3 Burden of Disease

According to results of the INTERHEART study, the five most important risk factors for myocardial infarction operate similarly in different ethnic groups and geographical locations worldwide. These risk factors are smoking history, diabetes history, hypertension, abdominal obesity and the ratio of 74

apolipoprotein B to apolipoprotein A-1 (1). The emergence of risk factors for atherosclerotic vascular disease in South Africa has been noted for several decades (2). Population based surveys in the early 1990s showed that 13-31% of the population have at least one risk factor for atherosclerotic disease. Later in the 2000s, surveys confirmed high population prevalence of hypertension, diabetes, smoking as well as a high prevalence of obesity affecting about 50% of the female population in Limpopo and Mpumalanga provinces (2). Heart disease, diabetes and stroke together constitute the second most important cause of death in the adult population in South Africa (3). Cardiovascular disease is increasing amongst all age groups in South Africa and is predicted to become the prime contributor to overall morbidity and mortality in the over 50-year age group (4).

## 4 Emergency Diagnosis and Care for ST-Segment Elevation Myocardial Infarct

Patients may present with a history of chest pain for more than 20 minutes. The pain may radiate to the left arm, lower jaw and neck. Sometimes, patients may present with atypical symptoms such as fatigue, nausea and vomiting, palpitations or syncope. This atypical presentation is common in the elderly, women and diabetic patients.

The key to successful management is timely diagnosis of STEMI. ECG monitoring should be initiated as soon as possible in all patients with suspected STEMI to detect life-threatening arrhythmias and allow prompt defibrillation if indicated. A 12-lead ECG should be obtained and interpreted as soon as possible.

Management of STEMI; including diagnosis and treatment, start at the point of first medical contact. Point of first medical contact in South Africa includes general practice, emergency rooms, paramedics and other specialists other than physicians and cardiologists.

STEMI is typically diagnosed when there is ST-segment elevation in two consecutive leads on the ECG.

The highest priority in STEMI is to restore coronary blood flow as soon as possible. **Due to successful outcomes associated with early intervention** (5)**; pre-authorisation should not be a pre-requisite for initiating care.**

The aim of emergency medical care is

i. To establish diagnosis using ECG and blood sampling for cardiac enzymes
ii. Initiate management depending on the logistical arrangements (ability to refer to a specialist centre without delay, scope of practice of the first contact health provider, availability of resources etc).
iii. Reduce pain

## Table 1: Diagnostic and management codes in an emergency or out-of-hospital setting

| Item | Description | Codes | Additional comments |
|---|---|---|---|
| ECG | General Practitioner's fee for the taking of an ECG only: Without effort: ½ (item 1232) | 1228 | |
| | 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 | |
| | Physician's fee for interpreting an ECG: With and without effort | 1231 | |
| | 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/her for interpretation | | |
| | Electrocardiogram: Without effort | 1232 | |
| | Electrocardiogram: With and without effort | 1233 | |
| | ECG monitoring | | |
| Ambulance services | Ambulance code may include basic life support, intermediate or advanced life support as well as resuscitation | 100,103',125,127,111 ,112,129,130,131,133 ,141,142,152,153 | |
| Blood sampling | CKMB | 4152,4153,4138 | (Treatment should proceed without waiting for this results) |
| | Troponin (Treatment should proceed without waiting for this results) | 4161 | (Treatment should proceed without waiting for this results) |
| Oxygen | V03AN01 | | Indicated in patients with hypoxia (SaO2 < 95%) |
| Medication | N02 | IV OPIODS | |
| | B01 | Antiplatelets | |

| | | | |
|---|---|---|---|
| | B01 | Fibrinolytics | |
| | GTN | GTN | |
| | A04 | Antiemetics | |
| | | Anxiolytics | |
| Defibrillation and cardiac life support | | | |

## Table 2: Routine Investigations Management of STEMI

| *Type* | *Description of the test* | *Codes* | *Comments* |
|---|---|---|---|
| Pathology | CKMB | 4152,4153,4138 | |
| | Troponin | 4161 | |
| | Full Blood Count- | 3755<br>(Incl. 3739,3762,3783,3785,3791) | |
| | Platelet count | 3797 | |
| | Glucose-Hypo and hyperglycaemia affect treatment outcomes | 4057 | |
| | Lipogram-Lipid profile can change within 12-24 hours | 4025 | |
| | CRP | 3947 | |
| | ESR: Markers of inflammation | | |
| | U & E and Creatinine | 4171 | |
| | Creatinine-EGFR | 4032 | |
| | Pulse oximetry | | |
| Radiology | Chest X-Ray: assess the patient's heart size and the presence or absence of heart failure and pulmonary oedema. This may also assist in differential diagnosis | 30110,30100 | |
| 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 | is useful in patients with diagnostic uncertainty (ACCA) |

## 5 Logistical considerations for Management of Patients with STEMI

### a) Who should participate in care of patients with STEMI

All STEMI patients should undergo rapid evaluation for reperfusion and have reperfusion strategy implemented promptly after contact with medical system.

The goal is to facilitate rapid recognition and treatment of patients such that door to Needle time for fibrinolytic therapy is achieved within 30 minutes (door to needle) or that time for PCI can be kept under 90 -120 minutes. This goal may not be relevant for patients with diagnostic uncertainties, or co-morbidities such as respiratory failure.

Access to emergency treatment and prevention of delays is important in the management of STEMI. There is an understanding that the Cardiologist coverage in the country is insufficient, even in the private sector. There are provinces that do not have cardiologists and some small towns do not have a specialist physician.

***Due to these limitations, general practitioner, other specialist other than internal physicians or cardiologist, nurses and paramedics play an important role in the management and facilitation of care for patients with acute myocardial infarct***.

According to Regulation 8(6), a medical scheme may not prohibit or enter into arrangements or contracts that prohibit the initiation of an appropriate intervention by a health care provider prior to receiving authorisation from medical scheme or any other party, in respect of an emergency medical condition.

Therefore once a STEMI has been diagnosed, a first contact medical provider must initiate care which should include emergency transfer with a suitable mode of transport, to a facility and provider capable of providing treatment for acute myocardial infarct.

### b) Facilities for Diagnosis and treatment of STEMI

Initial diagnosis and emergency care can take place at home, in the ambulance, or at emergency rooms or general practitioner's (GP) rooms depending on where the member first presented.

Whenever possible patients must be transported or transferred to the nearest PCI facility. If a PCI facility is a non-designated service provider (DSP) these constitute involuntary use of a DSP.

If it is anticipated that delays will be longer than 2 hours due to distance, amongst other things, then the first medical contact personnel must provide pharmacological reperfusion treatment under the remote supervision of the cardiologist or physician if necessary in line with their registered scope of practice.

According to explanatory note to Annexure A: The objective of specifying a set of Prescribed Minimum Benefits within these regulations is two-fold:

(i) To avoid incidents where individuals lose their medical scheme cover in the event of serious illness and the consequent risk of unfunded utilisation of public hospitals.

(ii) To encourage improved efficiency in the allocation of private and public health care resources.

In view of point (ii), if state is the schemes DSP; and both the public and private PCI are equally accessible to the member; it is considered a prescribed minimum benefit that a patient who belongs to the medical scheme access the private facility as the use of the public sector will result in inaccessible care for indigent patients. It should be noted that PCI and interventional cardiologist coverage is far lower in the public sector as compared to private sector. Therefore, channelling patients to public sector will defeat objective (ii).

**c) Selection of Reperfusion Strategy**

Primary PCI without fibrinolytic therapy is the preferred reperfusion strategy in patients with STEMI, provided it can be performed expeditiously by an experienced team (5) (6)(7).

**d) Clinical presentation of the patient**

- ***Time from Onset of symptoms:***

Time from onset of symptoms to pharmacological reperfusions is an important predictor of clinical outcomes. The beneficial effect of pharmacological reperfusion is substantially higher in patients presenting within 2 hours after symptom onset compared to those presenting later (Boersman et al), but the effect is even greater when accessed earlier. There is, however, some benefit when the treatment is offered beyond this period.

- ***Risk of bleeding***

When both types of reperfusion are available, patients with high risk of bleeding with pharmacological reperfusion should receive PCI as reperfusion strategy.

**e) Availability and time required to transfer to PCI facility**

The availability and location of the interventional cardiology facility is a key determinant of whether PCI can be provided or not. If a patient presents in a PCI- capable facility or can be transferred to a PCI-capable facility within 2 hours, PCI approach remains superior to pharmacological reperfusion.

A decision must be made when a patient presents to a non-PCI facility to refer for PCI or initiate pharmacological reperfusion. Fibrinolytic agents can generally be provided sooner than PCI especially in provinces and towns where there is no interventional cardiologist. Fibrinolytic agents do not require a high skilled professional; can be provided by many health care professionals (in line with scope of practice as per regulatory bodies) and even more appropriate in South Africa where the coverage for PCI facilities and interventional cardiology is low.

## 6 Reperfusion Strategies

### 6.1 Percutaneous procedures

As this component of the treatment of the DTP 907E is not only specified in general terms i.e. “medical management” or “surgery”, but also in specific terms i.e. “percutaneous procedures”, the latter component it is not subject to the provision made in the explanatory note (2) to Annexure A in the regulations.

Percutaneous coronary interventions (PCIs) as prescribed minimum benefits are therefore not restricted to availability of this intervention in the public sector. A protocol should be developed on the basis of the

principles stated in Regulation 15D (b) and 15H namely, evidence based medicine, taking into account considerations of cost-effectiveness and affordability.

**i. Indications**

- PCI is the best preferred method of treatment if it can be provided within 90-120 minutes of first medical contact in patients with STEMI
- It can also be provided if the symptoms were within 3 hours and PCI can be done within an hour of diagnosis
- When fibrinolytic ineligible patient present within 12-24 hours
- Patients with a new LBBB within 12 hours of onset of symptoms
- Within 36 hours if a patient develops shock
- If patients has no contraindication to DAPT and is ***more likely to be compliant on DAPT***.
- A rescue PCI is indicated in patients with failed fibrinolytic therapy as indicated by residual ST element elevation post fibrinolysis

***In patients with multi vessel disease, only infarct related artery should be treated during initial intervention. The only exceptions when multi vessel PCI is indicated during STEMI is when patients are in cardiogenic shock with > 90% occlusion.*** (6) (5)

**ii. Contraindication**

- Inability to take or comply with DAPT
- Asymptomatic patients more than 12 hours after onset of STEMI
- Door to balloon delay of > 2hours. In this instance fibrinolytic therapy offers relatively better outcomes.

## Table 3: Percutaneous Cardiac Intervention and Procedure

| Item | Description | Procedure code | Discussion and conclusions |
|---|---|---|---|
| Catheter Laboratory | | | |
| Clinicians | Cardiologist<br>Anaesthetist (Only when unstable patient)<br>Physicians/2nd cardiologist (maybe required to assist in case of difficult anatomy)<br>Nurse<br>Radiographer<br>Technologist | 0190<br>0191<br>0192<br>0173-0175 | Anaesthetist sometimes required for PCI of unstable patients when airway management is anticipated.<br><br>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<br>Low molecular weight heparin or unfractionated heparin<br>Aspirin<br>Clopidogrel OR Prasugrel (Non-PMB)<br>Beta Blocker or calcium channel blocker when beta-blockers are contraindicated.<br>Prasugrel (Non-PMB) | | See Annexure A: Prasugrel not considered PMB level of care as it resulted in marginal benefit compared to Clopidogrel, yet it costs almost four times Clopidogrel |
| **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 | |
| | Use of balloon procedures including: First cardiologist: Atrial septostomy; Pulmonary valve valvuloplasty; Aortic valve valvuloplasty; Coarctation dilation; Mitral valve valvuloplasty | 1282 | |
| | Use of balloon procedure as in item 1282: Second cardiologist | 1283 | |
| 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 | |
| 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 twice 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 Pharmacological Reperfusion

#### i. Indications

In patients presenting with STEMI when PCI is inaccessible or contraindicated

#### ii. Absolute Contraindications

- History of intracranial bleeding
- Any significant head or face trauma in the previous 90 days
- Major trauma, surgery or gastrointestinal or genitourinary bleed in the last 6 weeks
- History of bleeding or clotting disorders
- Known structural CV lesion
- Suspected aortic dissection

#### iii. Relative contraindications

- CPR has been implemented for more than 10 minutes
- Pregnancy
- Active PUD
- Current use of anticoagulants: the higher the INR the higher the risk of bleeding.
- Previous exposure or allergies to certain thrombolytic

## Table 4: Procedure codes for Pharmacological Reperfusion

| Item | Description | Code | Comments |
|---|---|---|---|
| Professionals | Any health professional can provide pharmacological reperfusion in line with the registration status with the professional regulatory body scope of practise and local setting. | | Providing pharmacological reperfusion is essential to survival and should be provided as soon a possible to reduce mortality. This treatment should be widely available as part of emergency care at primary health care (General Practice) level as well. |
| Fibrinolytics | Streptokinase<br>Alteplase<br>Tenecteplase | B01AD | See Annexure B. Tenecteplase not considered PMB level of care as cost of treatment is higher than alteplase and streptokinase despite similar outcomes. |
| Anti-platelets | Clopidogrel<br>Prasugrel (Non-PMB) | B01AC | See Annexure A: Prasugrel not considered PMB level of care as it resulted in marginal benefit compared to Clopidogrel, yet it costs almost four times Clopidogrel. |
| | Aspirin | NO2BA01 | |
| Anticoagulant therapy | UFH<br>Low molecular weight heparins | B01AB | |
| | Bivalirudin | | Not registered with MCC and therefore not considered PMB level of care.(MSA explanatory note 2 of definitions to annexure A) |

### 6.3 Acute Phase Coronary By-Pass Graft

CABG may be performed as an emergency procedure in the context of an ST-segment elevation MI (STEMI) in cases where it has not been possible to perform percutaneous coronary intervention (PCI)

or where PCI has failed and there is persistent pain and ischemia threatening a significant area of myocardium despite medical therapy.

Coronary artery by graft surgery will include in-hospital admission, post-operative care which will include allied health care by physiotherapist and out-of hospital care.

At the time of publication, there was lack of industrial clarity on procedure codes regarding CABG, and the matter is undergoing judicial process. Therefore the entire care associated with CABG, is not discussed, although Council will continue adjudicating on a case by case basis.

## 7 Care post emergency reperfusion

All patients with STEMI undergoing reperfusion must be admitted in setting capable of monitoring the following:

a) Adverse events associated with puncture site.
b) Monitoring of chest pain and ECG.
c) Monitoring of adverse events associated with fibronylytic therapy
d) It may be necessary to refer unstable patients to a cardiologist.
e) In case of shock or unresponsive to pharmaceutical reperfusion, patients should be referred to a center with PCI should rescue of facilitated PCI be required.
f) Depending on the clinical circumstances and bed availability, patients can be admitted to cardiac unit, ICU, high care or general ward.
g) Radiological investigations:
    a. Echocardiography if complications are suspected
    b. Chest X-ray if cardiac failure is suspected
h) Blood tests
    i. Cardiac enzymes
    ii. U&E and creatinine
    iii. INR
    iv. Full Blood Count
    v. Baseline lipid profile in patient not previously diagnosed with hypercholestrolaemia
i) Intensive management of co-morbidities such as Diabetes, hypercholestrolaemia and hypertension.

## 8 Post discharge follow-up

Longer-term issues post-PCI are very patient-specific and variable but broadly involves detection and treatment of recurrent ischaemia, arrhythmias and heart failure, appropriate antiplatelet therapy and secondary prevention.

## Table 5: Procedure codes for investigations post-discharge

| | 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<br>In patients with positive finding during non-invasive testing<br>In patients who are persistently unstable<br>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.<br>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 | |
| | Cardiac examination + phonocardiography | 3626 | |
| Pharmacological stress testing | | | |

## 9 Secondary prevention for STEMI Patients

Secondary prevention is a prescribed minimum benefit and constitutes the following

### i. Lifestyle modification (7)

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 overweight patients, i.e. BMI > 25 kg/$m^2$
- Maintain ideal weight, i.e. BMI < 25 kg/m
- 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 LDL by at least 25%.

### 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. Clopidogrel must be used for at least a month if bare metal stents were used and for 6 to 12 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 blockers and angiotensin converting enzyme (ACE) inhibitors as a minimum benefit.

## 10 Bibliography

1. *Risk factors associated with myocardial infarct in Africa-The INTERHEART study.* Steyn, K, Silwa, K and Hawkins, S. 2005, Circulation, pp. 3554-61.

2. *Budern of non-communicable disease in South Africa.* Mayosi, B, et al. s.l. : Lancet, 2009, Vol. 374.

3. *Initial burden of disease estimates for South Africa. 2000.* Bradshaw, D, Groenewald, P and Laubscher, R. s.l. : S Afr Med J, 2003, Vol. 93.

4. *A hidden menace: Cardiovascular disease in South Africa and the costs of an inadequate policy response.* • Maredza M, Hofman KJ, Tollman SM. A hidden menace: Cardiovascular disease in South Africa and the costs of an inadequate policy response. SAHeart 2011, et al. : SAHeart, 20, Vol. 8.

5. *ESC Guidelines for the management of acute myocardial infarction in patients presentingwith ST-segment elevation .* The Task Force on the management of ST-segment elevation acute. s.l. : European Heart Journal, 2012, Vol. 33. doi:10.1093.

6. *Guidelines for the management of Patients with ST-Elevation Infarction-Executive summary: A reprot of the American Cardiology/American Heart Association Task Force on Practice guidelines.* American Heart Association. s.l. : Circulation, 2004, Vol. 110. doi:10.116/01.CIR00001347891.68010.FA.

7. Department of Health. Hospital Essential Drug List. 2012.

# 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<br>Clopidogrel | 17 months | Death from cardiovascular causes, nonfatal myocardial<br>infarction, or nonfatal stroke | | Fewer cardiovascular<br>deaths, myocardial<br>infarctions, or strokes in<br>the prasugrel group |
| **PRASFIT-ACS** | 1,363 patients with ACS undergoing PCI | Prasugrel<br>Clopidogrel | 14 days | MACE at 24 weeks, which was defined as a composite of<br>cardiovascular death, nonfatal myocardial infarction (MI), and<br>nonfatal ischemic stroke | Incidence of all-cause<br>death, myocardial ischemia requiring re-hospitalization, revascularization,<br>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<br>Clopidogrel | 30 days | Non–CABG-related “significant haemorrhage” at 30 days, all-cause mortality, myocardial infarction, stroke,<br>recurrent myocardial ischemia requiring hospitalization, and<br>clinical target vessel thrombosis | | Prasugrel and<br>clopidogrel both<br>resulted in low rates of<br>bleeding |
| **TRITON TIMI-38** | 13,608 patients with an ACS | Prasugrel<br>Clopidogrel | 30 days, 90 days | Cardiovascular causes, nonfatal myocardial infarction, or nonfatal<br>stroke | Composite<br>end point and a composite of death from cardiovascular | Overall mortality did not differ significantly<br>between treatment groups |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | causes, nonfatal myocardial infarction, or urgent target-vessel revascularization, stent thrombosis and a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or re-hospitalization due to a cardiac ischemic event. | 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 |
| **TRITON TIMI-38** | 13,608 patients with an ACS | Prasugrel<br>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<br>Excess major bleeding was observed with the use of prasugrel |
| **TRITON TIMI-38 substudy** | 13 608 undergoing PCI for ACS | Prasugrel<br>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 | Prasugrel therapy tended to reduce<br>clinical ischemic events and to increase bleeding events |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | with coronary artery bypass surgery (CABG), non–CABG-related TIMI life-threatening bleeding and non–CABG-related TIMI major or minor bleeding | |
| **TRITTON-TIMI 38 substudy** | 13 608 patients with acute coronary syndrome undergoing PCI | Prasugrel<br>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 but marginally 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 myocardial infarct.

## References


1. Harrington RA, Hodgson PK, Larsen RL: Cardiology patient page. Antiplatelet therapy. *Circulation* 2003, 108(7):e45-47.
2. Levine GN, Jeong YH, Goto S, Anderson JL, Huo Y, Mega JL, Taubert K, Smith SC, Jr.: Expert consensus document: World Heart Federation expert consensus statement on antiplatelet therapy in East Asian patients with ACS or undergoing PCI. *Nature reviews Cardiology* 2014, 11(10):597-606.
3. Thomas D, Giugliano RP: Antiplatelet therapy in percutaneous coronary intervention: integration of prasugrel into clinical practice. *Critical pathways in cardiology* 2009, 8(1):12-19.
4. Angiolillo DJ, Guzman LA, Bass TA: Current antiplatelet therapies: benefits and limitations. *American heart journal* 2008, 156(2 Suppl):S3-9.
5. NICE: Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events. In., December 2010 edn. UK: National Institute for Health and Care Excellence; 2010.
6. Wiviott S, White H, Ohman E, Fox K, Armstrong P, Prabhakaran D, Hafley G, Lokhnygina Y, Boden W, Hamm C *et al*: Prasugrel versus clopidogrel for patients with unstable angina or non-ST-segment elevation myocardial infarction with or without angiography: a secondary, prespecified analysis of the TRILOGY ACS trial. *Lancet* 2013, 382(9892):605-613.
7. Saito S, Isshiki T, Kimura T, Ogawa H, Yokoi H, Nanto S, Takayama M, Kitagawa K, Nishikawa M, Miyazaki S *et al*: Efficacy and Safety of Adjusted-Dose Prasugrel Compared With Clopidogrel in Japanese Patients With Acute Coronary Syndrome. *Circulation Journal* 2014, 78(7):1684-1692.
8. Wiviott SD, Antman EM, Winters KJ, Weerakkody G, Murphy SA, Behounek BD, Carney RJ, Lazzam C, McKay RG, McCabe CH *et al*: Randomized comparison of prasugrel (CS-747, LY640315), a novel thienopyridine P2Y12 antagonist, with clopidogrel in percutaneous coronary intervention: results of the Joint Utilization of Medications to Block Platelets Optimally (JUMBO)-TIMI 26 trial. *Circulation* 2005, 111(25):3366-3373.
9. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA *et al*: Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes. *The New England journal of medicine* 2007, 357(20).

10. Antman EM, Wiviott SD, Murphy SA, Voitk J, Hasin Y, Widimsky P, Chandna H, Macias W, McCabe CH, Braunwald E: Early and late benefits of prasugrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel-Thrombolysis In Myocardial Infarction) analysis. *Journal of the American College of Cardiology* 2008, 51(21):2028-2033.

11. Pride YB, Wiviott SD, Buros JL, Zorkun C, Tariq MU, Antman EM, Braunwald E, Gibson CM, Group TS: Effect of prasugrel versus clopidogrel on outcomes among patients with acute coronary syndrome undergoing percutaneous coronary intervention without stent implantation: a TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibitioN with prasugrel (TRITON)-Thrombolysis in Myocardial Infarction (TIMI) 38 substudy. *American heart journal* 2009, 158(3):e21-26.

12. Morrow DA, Wiviott SD, White HD, Nicolau JC, Bramucci E, Murphy SA, Bonaca MP, Ruff CT, Scirica BM, McCabe CH *et al*: Effect of the novel thienopyridine prasugrel compared with clopidogrel on spontaneous and procedural myocardial infarction in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38: an application of the classification system from the universal definition of myocardial infarction. *Circulation* 2009, 119(21):2758-2764.

# Annexure B

## Fibrinolytic therapy in the management of ST-segment Elevation Myocardial Infarction and Acute Coronary Syndromes

### 1. Introduction

Fibrinolytic therapy is still an important option for reperfusion in many ST-segment elevation myocardial infarction patients. Fibrinolytic agents are the preferred class because of their ability to achieve reperfusion and to restore blood flow when administered within 12 hours of symptom onset[1]. Currently, streptokinase, alteplase, reteplase and tenecteplase are used in the management of ST-segment elevation myocardial infarction [2]. In South Africa streptokinase, alteplase, and tenecteplase are approved for the treatment of coronary syndromes.

Streptokinase is administered as an intravenous infusion over 1 hour up to 12 hours after onset of symptoms[1]. Streptokinase is associated with hypotension, infrequent allergic reactions and sometimes anaphylaxis. Patients treated with streptokinase develop anti-streptococcal antibodies, which can inactivate the drug if subsequent treatment is needed. The use of streptokinase is contraindicated in patients with prior treatment with the previous 6 months [2]

Alteplase can be delivered in a standard or accelerated regimen. The accelerated regimen is indicated up to 6 hours after symptom onset and is delivered by an initial intravenous (IV) bolus injection, followed by two IV infusions between 30 and 60 minutes. The standard regimen is indicated between 6 and 12 hours after symptom onset and requires a bolus injection followed by five infusions over 3 hours. Unlike streptokinase, alteplase does not stimulate the production of antibodies, so it can be used repeatedly[1].

Reteplase is indicated up to 12 hours after symptom onset. It is given as two IV bolus injections over 30-60 minutes. Tenecteplase is indicated up to 6 hours after symptom onset. It is administered as a single weight-adjusted IV bolus injection[1].

### 2. Objective

The objective of this literature review is to compare the clinical effectiveness of Streptokinase, Alteplase, Reteplase and Tenecteplase in the management of myocardial infarction.

## 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 November 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 myocardial infarction undergoing thrombolytic therapy with a sample size larger than 50.
- Intervention: thrombolytic agents
- Comparator: other thrombolytic 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 included studies.

**Table 6: An overview of the included randomised clinical trials**

| Authors | Population | Intervention strategy | Follow-up period | End-point | Secondary End points | Results |
|---|---|---|---|---|---|---|
| **GISSI-2 Study** | 20768 patients with chest pain accompanied by (a) ST segment elevation of 1 mm or more in any limb lead of the ECG and/or of 2 mm or more in any precordial lead; (b) if they had been admitted to the coronary care unit (CCU) within 6 h of the onset of symptoms; and (c) if they had no clear contraindication to the fibrinolytic treatments or to heparin. No age restriction was imposed | Streptokinase<br>Alteplase | 6 months | Death, reinfarction, cerebrovascular accident | | Mortality rates, reinfarction and cerebrovascular accidents were similar in all treatment groups |
| **INJECT trial** | 6010 patients from 208 centres in 9 countries who were seen within 12 hours of the onset of symptoms | Reteplase<br>Streptokinase | 35 days | | Mortality | Mortality rates, bleeding events, recurrent myocardial infarction were similar in the two treatment groups |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Rapid-I** | 606 patients seen less than 6 hours after onset of symptoms at 38 centres in US, Germany, England and Austria | Alteplase<br>Reteplase | 5 days | 90 minute thrombolysis in myocardial infarction | TIMI grade 2 or 3 patency at 30 and 60 minutes and 5-14 days after initiation of thrombolytic therapy. Reocclusion within 5-14 days after administration of thrombolytic therapy, left ventricular ejection fraction and regional function at hospital admission and discharge | More rapid, complete, and sustained thrombolysis of the infarct-related artery than standard-dose by reteplase |
| **Rapid-II** | 324 patients within 6 and up to 12 hours of onset of acute myocardial infarction | Reteplase<br>Alteplase | 30 and 60 minutes<br>5 days | Patency of the infarct-related coronary artery 90 minutes after thrombolytic therapy | TIMI flow grade<br>Reocclusion<br>Left ventricular function<br>Coronary interventions | |
| **GUSTO-1** | 41 021 patients with evolving myocardial infarction, chest pains lasting at least 20 minutes and accompanied by electrocardiogram signs of ≥ 0.1 mV of St- Segment elevation in two or more limb leads or ≥0.2 in two or more contagious precordial leads | Streptokinase + subcutaneous heparin<br>Streptokinase + intravenous heparin<br>Alteplase + | 30 days | Death at 30 days from any cause | Combined end point of death and non fatal stroke, death and non-fatal hemorrhagic stroke, death and disabling stroke.<br>Bleeding: life threatening (severe), moderate o minor r | Reduction in mortality by 1.1% in alteplase group<br>Significant excess hemorrhagic strokes for accelerated alteplase<br>Combined end point of death or disabling stroke significantly lower in the accelerated alteplase |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | intravenous heparin<br>Streptokinase + Alteplase + intravenous heparin | | | | |
| **GUSTO-III** | 15,059 patients presented within 6 hours after the onset of symptoms with ST-segment elevation or bundle-branch block | Reteplase<br>Alteplase | | Mortality | Clinical benefit, defined as freedom from death or disabling stroke; death or nonfatal stroke; reinfarction; congestive heart failure; and mortality at 24 hours. | Death or nonfatal, disabling stroke, were similar for the two plasminogen activators |
| **ASSENT-2** | 16,949 patients with ST-elevation acute myocardial infarction. | Alteplase<br>Tenecteplase | 12 | Mortality | | Mortality rates remain similar in patients with acute myocardial infarction treated |

### 4.1 Streptokinase and Alteplase

*GISSI-2 trial*

The aim of the GISSI-2 study was to compare the effectiveness and safety of alteplase and streptokinase, and of heparin and no heparin, in patients with acute myocardial infarction in an open multicentre randomized trial with a 2x2 factorial study design. Six-months mortality rates of the study were similar for patients randomized to alteplase or streptokinase (12.3% vs. 11.7%, RR = 106, 95% CI 0.97-1.15). The rate of reinfarction was 3.1 for alteplase and 3.2 for streptokinase (CI: 0-89-1-25) with similar cerebrovascular accidents in all treatment groups (0.5 vs. 0.6 for alteplase and streptokinase with CI of 0.73-1.6. Adjusted analysis indicated that age and higher Killip class were the most important predictors of a poor prognosis. Previous myocardial infarction, female sex and longer delay from onset of symptoms were also indicators of poor prognosis[3].

*Gusto-I trial*

The Gusto trial randomly assigned 41 021 patients with ST-elevation myocardial infarct presenting within 6 hours of symptoms, to one or four treatment strategies consisting of streptokinase + subcutaneous heparin, streptokinase + intravenous heparin, accelerated Alteplase + intravenous heparin and streptokinase plus alteplase with intravenous heparin for reperfusion. The results of the four treatment groups for mortality we 7.2% for Streptokinase and subcutaneous heparin, 7.4% for Streptokinase and intravenous heparin, 6.3% for accelerated tPA and intravenous heparin and 7.0% for the combination of both thrombolytic and heparin. There was no difference in mortality between the streptokinase groups; however there was a significant reduction in mortality in the alteplase group compared to the two streptokinase strategies. The risk reduction was 1.1 % in the accelerated alteplase when compared to streptokinase plus heparin and 0.9% when compared to streptokinase plus subcutaneous heparin (p=0.001). Numbers needed to treat to prevent 1 death was 90. The rate of strokes was 1.22% for Streptokinase + subcutaneous heparin, 1.5%for Streptokinase and intravenous heparin, 1.55%for accelerated t-PA and intravenous heparin and 1.64 % for the combined thrombolytics and heparin. The rate of hemorrhagic stroke were 0.49% for Streptokinase + subcutaneous heparin, 0.54% for Streptokinase and intravenous heparin, 0.72% for accelerated t-PA and intravenous heparin and 0.94% for the combined thrombolytics and heparin (P=0.03). Compared to both streptokinase groups, alteplase caused a significantly high rate of hemorrhagic strokes. The rate of hemorrhagic, those converted to hemorrhagic and unknown strokes was similar in all 4 groups [4]. One-year mortality

rates were (9.1%) for alteplase and 10.1% for streptokinase with subcutaneous heparin (*P*=.011) and streptokinase 10.1% (*P*=.009) with intravenous heparin [5].

**4.2 Streptokinase Reteplase**

*Inject trial*

The INJECT trial was a randomized, double blind study designed to compare the effects of Reteplase and Streptokinase on survival of patients with acute myocardial infarction. The study involved 6010 patients from 208 centres in 9 countries who were seen within 12 hours of the onset of symptoms. Patients were randomized to receive either Reteplase as two boluses 10 U each given 30 minutes apart, or Streptokinase 1.5 MU given over 60 minutes. The thrombolytic drug was preceded by intravenous heparin 5000 U, followed by 1000 U hour for at least 24 hours, adjusted to maintain the activated partial thromboplastin time (aPTT) 1.5-2 times normal. Aspirin 250-320 mg was given initially and followed by 75-150 mg/day. Thirty five days mortality in patients receiving Reteplase was 9.02% while that of Streptokinase was 9.53%. The results were statistically significant (p=0.0003), however reteplase was equivalent to streptokinase the confidence interval includes zero (CI -1.74-0.73%).

Reteplase also significantly reduced mortality in patients with a previous acute myocardial infarction (11.3% vs. 17.3%) when compared to Streptokinase. Mortality at 6 months was not significantly different with Reteplase at 11.02% and Streptokinase at 12.05% (p =0.217, 95% CI -2.65, 0.59). Reteplase was associated with modest but significant (p<0.05) reductions in several categories of cardiovascular events, including heart failure (23.6 vs. 26.3%), hypotension (15.5 vs. 17.6%), and atrial fibrillation (7.2 vs. 8.8%). The total frequency of stroke was slightly but not significantly higher in the Reteplase group than in the Streptokinase group (1.23% vs. 1.00%). Bleeding events requiring transfusion were similar in the two groups Reteplase 0.7% and streptokinase 1.0% (p =0.0001)[6].

**4.3 Alteplase and Reteplase**

*RAPID-I trial*

The aim of the RAPID-1 study was to test the hypothesis that bolus administration of reteplase is superior to standard-dose alteplase administered 100 mg over 3 hours in achieving infarct-related artery at 90 minutes. Patients were randomized to alteplase or one of three dosages of reteplase: 15 U in a single bolus; 10 U followed by 5 U 30 minutes later (total 15 U); or 10 U followed by 10 U 30 minutes later (double bolus). A total dose of alteplase 100 mg was administered as 60 mg over the first hour (6-10 mg initial bolus) followed by 20 mg hour for an additional 2 hours to a total dose of 100 mg.

Aspirin 200-325 mg was given immediately before the thrombolytic drug and continued daily. Heparin was administered as a 5000-U bolus just before the thrombolytic drug and followed by 1000 U/hour for at least 24 hours.

Double-bolus reteplase achieved 90-minute TIMI grade 3 flow in 63% of patients, which was superior ($p<0.02$) to the 49% attained with the Alteplase 3-hour infusion. Reteplase was associated with a higher proportion of patients with TIMI grade 3 flow at 5-14 days than Alteplase (82% vs. 71%, $p<0.00l$). TIMI grade 3 flow at 60 minutes with double-bolus Reteplase was comparable to that of Alteplase at 90 minutes (51% vs. 49%). Left ventricular function **(**LVF) significantly improved with double-bolus reteplase compared with alteplase. Left ventricular ejection fraction at hospital discharge was 53% and 49%, respectively ($p<0.03$). Regional (infarct) zone revealed evidence of less impairment in the Reteplase group than in the Alteplase group at discharge (-2.19 vs. -2.61/cord, respectively; $p<0.02$). The effects on patency and left ventricular function of the other two regimens of Reteplase were similar to those of Alteplase and inferior to those of double-bolus Reteplase[7].

*RAPID-II*

The aim of the RAPID-II study was to assess angiographic patency after acute myocardial infarction following treatment with reteplase. Three hundred and twenty four patients were randomised to 10 MU+10MU double bolus regimen of reteplase and the accelerated regimen (90 min infusion) of alteplase. TIMI 3 flow was 60% for reteplase vs. 45% for alteplase ($P<005$)[8].

*Gusto III trial*

The GUSTO-III study randomly assigned in a 2:1 ratio patients to receive Reteplase, in two bolus doses of 10 MU each given 30 minutes apart, or an accelerated infusion of Alteplase, up to 100 mg infused over a period of 90 minutes. The mortality rate at 30 days was 7.47 percent for Reteplase and 7.24 percent for Alteplase (adjusted P= 0.54; odds ratio, 1.03; 95 percent confidence interval, 0.91 to 1.18). The 95 percent confidence interval for the absolute difference in mortality rates was 1.1 to 0.66 percent. Stroke occurred in 1.64 percent of patients treated with Reteplase and in 1.79 percent of those treated with Alteplase (P 0.50). The respective rates of the combined end point of death or nonfatal, disabling stroke were 7.89 percent and 7.91 percent (P 0.97; odds ratio, 1.0; 95% CI, 0.88 to 1.13)[9].

### 4.4 Alteplase and Tenecteplase

*ASSENT 2*

The second Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) trial randomised over 16 000 patients to compare Tenecteplase and Alteplase in patients with myocardial infarction. The study found that 30-day mortality was almost the same in the Tenecteplase group (6.18%) and the accelerated Alteplase (6.15%) group. Tenecteplase and accelerated alteplase were considered equivalent in terms of mortality due to the confidence interval. Rates of intracranial haemorrhage were similar (0·93% for tenecteplase and 0·94% for alteplase), but fewer non-cerebral bleeding complications (26·43 *vs.* 28·95%, p=0·0003) and less need for blood transfusion (4·25 *vs.* 5·49%, p=0·0002) were seen with tenecteplase. The rate of death or non-fatal stroke at 30 days was 7·11% with tenecteplase and 7·04% with alteplase (relative risk 1·01 [95% CI 0·91–1·13][10].

Mortality rates were 9.1% for alteplase and 9.2% for tenecteplase (RR, 1.01; 95% CI, 0.91-1.12) at one year. The mortality rate between 30 and 365 days after enrolment was 2.6% for alteplase and 2.8% for tenecteplase (RR, 1.07; 95% CI, 0.88-1.30). A lower 30-day mortality rate in patients treated with tenecteplase after 4 hours of symptom-onset persisted at 1-year follow-up (10.9% vs. 12.6% for alteplase), but was no longer statistically significant. There were also no significant differences in mortality rates between the 2 treatments in other major subgroups[11].

**5. Discussion**

The results of these trials provide important data on the clinical effectiveness of streptokinase, alteplase reteplase and tenecteplase in the treatment of acute coronary syndromes.

- The GISSI-2 study showed no statistically significant differences in mortality between patients randomized to alteplase and those randomized to streptokinase or for patients randomized to heparin and those randomized to no heparin. The rate of reinfarction and cerebrovascular accidents was also similar in all treatment groups.
- The results of the Gusto-I trial showed reduction in mortality and stroke and excess hemorrhagic stroke in the alteplase group.
- In the INJECT trial, reteplase was associated with lower rates of left ventricular dysfunction and several other adverse cardiovascular events than streptokinase.
- A double bolus of 10 + 10 MU of reteplase achieved more rapid, complete, and sustained thrombolysis of the infarct-related artery than standard-dose alteplase, without an apparent

increased risk of complications in the RAPID study. This was associated with improved global and regional left ventricular function at hospital discharge

- The results of the ASSENT study showed that one year after randomization, mortality rates remain similar in patients with acute myocardial infarction treated with an accelerated infusion of alteplase or a single bolus of tenecteplase. There is also some evidence that tenecteplase may be associated with lower rates of major bleeds and heart failure than accelerated alteplase.
- *The Gusto III study* showed that reteplase, although easier to administer, did not provide any additional survival benefit in the treatment of acute myocardial infarction. Other results, particularly for the combined end point of death or nonfatal, disabling stroke, were remarkably similar for the two plasminogen activators.

**6. Conclusion**

In conclusion, given the evidence of the trials on clinical effectiveness, it can be concluded that, in terms of mortality, standard alteplase is as effective as streptokinase while accelerated alteplase shows superiority to streptokinase. Reteplase was shown to be at least as effective as streptokinase, and tenecteplase as effective as accelerated alteplase. If accelerated alteplase is believed to be superior to streptokinase, it can be deduced that tenecteplase would also be superior to streptokinase. Although Streptokinase is on state EDL, it cannot be used if it has been previously utilised.

**6. References**


1. Hilleman, D.E., et al., *Fibrinolytic Agents for the Management of ST-Segment Elevation Myocardial Infarction.* Pharmacotherapy, 2007. 27(11): p. 1558-1570.
2. American College of Emergency, P., et al., *2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines.* J Am Coll Cardiol, 2013. 61(4): p. e78-140.
3. GISSI-2, *GISSI-2: a factorial randomised trial of alteplase versus streptokinase and heparin versus no heparin among 12,490 patients with acute myocardial infarction. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico.* Lancet, 1990. 336(8707): p. 65-71.
4. Gusto-I., *An International randomized trial comparing fout thrombolytic strategies for acute myocardial infarction.* The New England Journal of Medicine, 1993. 329(10): p. 673-682.
5. Gusto-I, *One-Year Results From the Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries (GUSTO-I) Trial.* Circulation Journal, 1996. 94: p. 1233-1238
6. INJECT, *Randomised, double-blind comparison of reteplase double-bolus administration with streptokinase in acute myocardial infarction (INJECT): trial to investigate equivalence.* Lancet, 1995. 346: p. 329-336.
7. Bode, C., R. Smalling, and G. Berg, *More rapid, complete, and stable coronary thrombolysis with bolus administration of reteplase compared with alteplase infusion in acute myocardial infarction. RAPID investigators.* Circulation, 1995. 91: p. 2725-2732.
8. Weaver, D.L., *Results of the RAPID 1 and RAPID 2 thrombolytic trials in acute myocardial infarction.* European Heart Journal, 1996. 17: p. 14-20.
9. III, G., *A COMPARISON OF RETEPLASE WITH ALTEPLASE FOR ACUTE MYOCARDIAL INFARCTION.* The New England Journal of Medicine, 1997. 337: p. 1118-1123.
10. ASSENT-2, *Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial.* Lancet, 1999. 354: p. 716–22.
11. Sinnaeve, P., et al., *One-year follow-up of the ASSENT-2 trial: a double-blind, randomized comparison of single-bolus tenecteplase and front-loaded alteplase in 16,949 patients with ST-elevation acute myocardial infarction.* Am Heart J, 2003. 146(1): p. 27-32.

# Annexure C

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

### 1. Introduction

The role of intravascular ultrasound (IVUS) in understanding the pathophysiology of coronary lesions, percutaneous diagnostics 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<br>ANGIO =142 | 284 patients with complex lesions (bifurcations, long lesions, chronic total occlusions or<br>Small vessels). | DES<br>Implantation | 1, 6, 9, 12, 24 | Post-procedure in<br>lesion minimal lumen<br>diameter | MACE, target lesion revascularization, target vessel revascularization, myocardial infarction (MI), and stent thrombosis | No statistical significant difference in MACE at 24 months<br>Benefit of IVUS in complex post-procedure minimal lumen diameter |
| **Opticus** | IVUS=273<br>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<br>coronary intervention) | Routine use of IVUS not supported by the study |
| **Reset** | IVUS =662<br>ANGIO =912 | 662 patients with clinical characteristics: diabetes mellitus, ACS, short and long lesion | DES<br>Implantation | 12 | | MACE | Routine IVUS guidance does not provide clinical benefits when performing short-length DES<br>implantation |
| **Resist** | IVUS<br>ANGIO | 164 patients with symptomatic ischemic heart disease | BMS Stent | | 6 months Restenosis<br>rate | | A non-significant 6.3% absolute reduction in the restenosis rate and a non-significant difference in MLD were observed |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Tulip** | IVUS =73<br>ANGIO=71 | Patients with de novo, nonostial stenosis 20 mm length in a native coronary artery with a reference diameter that permitted implantation of 3-mm stents without involvement of significant side branches (diameter 2.0 mm). | BMS Stent | 1, 6, 12 | Angiographic MLD at 6 months and the combined event rate of cardiac death, MI, and ischemia-driven target-lesion revascularization (TLR) within 6 months were the angiographic and clinical | Angiographic and procedural success, angiographic restenosis (_50% diameter stenosis) and percent diameter stenosis at 6 months, and combined event frequency at 12 months. | IVUS is superior to guidance by angiography up to 12 months after long stent placement guided by |
| **SIPS** | IVUS=166<br>ANGIO=190 | 269 patients with no chronic total occlusions or emergency procedures | Provisional 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<br>ANGIO=190 | | Provisional 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**

- 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**

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).

**References**


1. Bonello, L., et al., *Intravascular ultrasound-guided percutaneous coronary interventions in contemporary practice.* Arch Cardiovasc Dis, 2009. 102(2): p. 143-51.
2. Bourantas, C.V., et al., *Clinical indications for intravascular ultrasound imaging.* Echocardiography, 2010. 27(10): p. 1282-90.
3. Chieffo, A., et al., *A prospective, randomized trial of intravascular-ultrasound guided compared to angiography guided stent implantation in complex coronary lesions: the AVIO trial.* Am Heart J, 2013. 165(1): p. 65-72.
4. Harald Mudra, et al., *Randomized Comparison of Coronary Stent Implantation Under Ultrasound or Angiographic Guidance to Reduce Stent Restenosis (OPTICUS Study).* Circulation, 2001. 104: p. 1343-1349.
5. Yoon, Y.W., et al., *Usefulness of intravascular ultrasound to predict outcomes in short-length lesions treated with drug-eluting stents.* Am J Cardiol, 2013. 112(5): p. 642-6.
6. Schiele, F., et al., *Impact of intravascular ultrasound guidance in stent deployment on 6-month restenosis rate: a multicenter, randomized study comparing two strategies--with and without intravascular ultrasound guidance. RESIST Study Group. REStenosis after Ivus guided STenting.* J Am Coll Cardiol., 1998 32(2): p. 320-328.
7. Oemrawsingh, P.V., *Intravascular Ultrasound Guidance Improves Angiographic and Clinical Outcome of Stent Implantation for Long Coronary Artery Stenoses: Final Results of a Randomized Comparison With Angiographic Guidance (TULIP Study).* Circulation, 2002. 107(1): p. 62-67.
8. Frey, A.W., et al., *Ultrasound-Guided Strategy for Provisional Stenting With Focal Balloon Combination Catheter Results From the Randomized Strategy for Intracoronary Ultrasound-Guided PTCA and Stenting (SIPS) Trial.* Circulation 2000. 102: p. 2497-2502.
9. Muellera., C., et al., *Impact of intracoronary ultrasound guidance on long-term outcome of percutaneous coronary interventions in diabetics – insights from the randomised SIPS trial.* SWISS MED WKLY, 2002. 132: p. 2 7 9 – 2 8 4.