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Update on NSTEMI and STEMI in the South African context

KEY MESSAGES

- As cardiologists we need to get involved early in the diagnosis of non-ST elevation myocardial infarction (NSTEMI), starting in the Emergency and Accident (EA) Unit
- Physicians should consider using clinical risk scores to help ensure a patient with cardiac-related pain is not sent home. I suggest you have the App on your phone (www.timi.org) or the GRACE ACS Risk Score 2.0 App
- The term NSTEMI is being replaced with non-ST elevation – acute coronary syndromes (NSTE-ACS) to include non-infarct syndromes, such as unstable angina
- Dual anti-platelet therapy should be continued for 12 months post-MI
- New European Society of Cardiology (ESC) recommendations for antithrombotic treatment in NSTE-ACS patients undergoing PCI are clear and provide evidence-led guidance to optimise therapy.[2]

"The value of following guidelines is that they set out optimal medical therapy for our patients", Dr David Kettles pointed out in his presentation at a special symposium, sponsored by Aspen Pharmacare, at the recent SA Heart Congress in Durban.

Dr Kettles noted that patients with NSTEMI often do better than those with STEMI during hospitalisation, but tend to have worse outcomes over time than successfully vascularised STEMI patients. This is evident also from the ACCESS (Acute Coronary Events – a Multinational Survey of Current Management Strategies) registry of South African patients, which shows one-year mortality among NSTEMI patients of 5%[3].This figure is comparable to those documented in other similar international studies of these patients who often also have a higher rate of both cardiac and noncardiac comorbidities.

"Expert advice encourages us to do early risk stratification in order to get the patient with chest pain at low risk of cardiac involvement out of the hospital, thereby saving costs. Interestingly, CT scans are being advocated in America for this purpose."

Echocardiographic assessment is also useful in NSTEMI to guide later therapy.

The guideline for contemporary standard medical therapy has also been reviewed by ESC.

"In this regard, it is important to note that the use of morphine in chest pain has now been lowered to a '2b' recommendation. Morphine reduces the early efficacy of antiplatelet therapy in both STEMI and NSTEMI patients", Dr Kettles pointed out.

Focus on antiplatelet and anticoagulation therapy in NSTEMI

For patients with acute coronary syndromes (ACS), the CURE Study[4] has clearly established the benefit of adding an additional anti-platelet agent to aspirin. This study of 1 000 patients treated with dual anti-platelet therapy (DAPT), showed that, if this clinical approach is used, there would be 21 fewer deaths, myocardial infarctions or strokes at a cost of 7 additional transfusions and 4 life-threatening bleeds. The benefit of DAPT is progressive with the curves separating over time, leading to the current

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guideline recommendation of continuing this therapy for 12 months post-MI."

The TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction 38) trial[5], showed that prasugrel can be used after coronary angiography in NSTEMI patients selected for revascularisation. It is however contraindicated in patients with a prior history of stroke, in the elderly (older than 75 years) and patients weighing less than 60kg. "The subsequent TRILOGY-ACS trial in which prasugrel was administered at the time of angiography to NSTE-ACS patients selected for medical management without revascularisation was essentially a negative trial showing no additional benefit when compared to clopidogrel.[6] Earlier use of prasugrel prior to angiography in the ACCOAST trial also did not show significant benefit, mainly due to the increased number of bleeds[7]", Dr Kettles said.

The experience with ticagrelor in the PLATO[8] series of studies has shown this reversible P_2Y_{12} inhibitor to be very effective. There was a significant reduction in the primary end point of time to mortality from vascular causes, myocardial infarction or stroke and a highly significant overall reduction in mortality.

At the most recent ESC Congress, ticagrelor use prior to coronary artery bypass graft (CABG) was shown to be associated with lower mortality (4.7% versus 9.7%) as compared to clopidogrel, also with fewer CABG-related bleeds. "The reason for this unexpected finding is still being sought."

Dr Kettles noted that geographical differences observed in clinical trials in the USA have resulted in guideline advice to use a daily dose of aspirin of 100 mg or less.

The newly issued American Guidelines on ACS[9] recommend the use of a P_2Y_{12} inhibitor plus aspirin for all ACS patients for up to 12 months post-MI. Additionally, these guidelines note that it is reasonable to replace clopidogrel with ticagrelor. In cases of early invasive therapy, GP IIb/IIIa antagonists can be considered. "GPIIb/IIIa inhibitors should, however, not be used routinely upstream in ACS patients already on DAPT and scheduled for angiography, as there is a uniform signal of increased bleeding from the clinical trials."

"GP IIb/IIIa inhibitors can be used selectively for high-risk percutaneous coronary intervention (PCI) patients with visible thrombi. They are not for use in patients being managed medically", Dr Kettles noted.

Dr Kettles stressed that it is not correct to withhold DAPT from ACS patients on the basis of the patient possibly undergoing bypass surgery. "It is clear that DAPT should be initiated early, as this is where the first benefit accrues, particularly if the patient is a high risk case. The surgeons can operate without an adverse effect on mortality; even in the face of increased bleeding and transfusions." He noted further that currently all patients scheduled for CABG bypass surgery should be on ticagrelor because of the mortality benefit that has recently been shown using this anti-platelet therapy.

Anticoagulant use in Acute Coronary Syndromes (ACS)

Anticoagulants are recommended for all patients regardless of which therapeutic route is selected – medical, PCI or bypass. The available agents in South Africa include unfractionated heparin, low molecular weight heparins (LMWH), such as enoxaparin, and fondaparinux.

In patients who are being medically managed, enoxaparin has been shown to be better than unfractionated heparin (UFH). "The uses of these agents do, however, come with an increase in in-hospital major bleeds when they are added to DAPT. In addition, there is evidence that switching between heparins is associated with higher risk of both events and bleeding. Switching heparins in an individual patient should be avoided", Dr Kettles noted.

Enoxaparin is much easier to use than UFH as it does not induce thrombocytopenia to the same extent, but it is perhaps not an optimal drug if PCI is intended unless the same drug is to be used in the cath lab.

Fondaparinux was compared to enoxaparin in the OASIS-5 Trial[10]. This study

included over 20 000 ACS patients, 60% of whom underwent angiography and 30% PCI. Catheter-induced thrombus formation was a problem early in the study, but was resolved by administration of the usual bolus dose of unfractionated heparin. In comparison to enoxaparin, the incidence of major bleeds was halved among patients who received fondaparinux, and this was also associated with a reduction in mortality. "This is because fondaparinux caused less anticoagulation than unfractionated heparin, but had sufficient effect as to prevent ischaemic events. The bolus dosage of heparin to be used is 85 units/kg decreased to 60 units/kg if GP IIb/IIIa inhibitors are being used", Dr Kettles noted.

The ESC guidelines on anticoagulant usage are provided in Table 1.[2]

Further important data on fondaparinux from two major registries was released at the recent ESC Congress. The Swedish Registry of 44 000 patients has shown that fondaparinux usage has increased from less than 1% in 2006 to 87% in 2010, with a resulting improvement in outcomes; 48% reduction in in-hospital bleeding events and 28% reduction in mortality[11]. A Portuguese registry of some 3 000 patients also confirmed the value of fondaparinux in ACS patients[12].

In summary and conclusion, Dr Kettles pointed out that fondaparinux was also more cost-effective than enoxaparin.

"NSTEMI is common and dangerous, but it can be effectively managed using available guidelines, which are aimed at optimising medical and interventional therapies."

Table 1. Recommendations for antithrombotic treatment in patients with NSTE-ACS undergoing PCI[2]

Recommendations	Class[a]	Level[b]
Antiplatelet therapy		
ASA is recommended for all patients without contraindications at an initial oral loading dose of 150–300 mg (or 80–150 mg i.v.), and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy	**I**	A
A P_2Y_{12} inhibitor is recommended in addition to ASA, and maintained over 12 months* unless there are contraindications such as excessive risk of bleeding. Options are:	**I**	A
* Prasugrel (60 mg loading dose, 10 mg daily dose) in patients in whom coronary anatomy is known and who are proceeding to PCI if no contraindication	**I**	B
* Ticagrelor (180 mg loading dose, 90 mg twice daily) for patients at moderate-to-high risk of ischaemic events, regardless of initial treatment strategy including those pre-treated with clopidogrel if no contraindication	**I**	B
* Clopidogrel (600 mg loading dose, 75 mg daily dose), only when prasugrel or ticagrelor are not available or are contraindicated	**I**	B
GP IIb/IIIa antagonists should be considered for bail-out situation or thrombotic complications	**IIa**	C
Pre-treatment with prasugrel in patients in whom coronary anatomy is not known, is not recommended.	**III**	B
Pre-treatment with GP IIb/IIIa antagonists in patients in whom coronary anatomy is not known, is not recommended.	**III**	A
Anticoagulant therapy		
Anticoagulation is recommended for all patients in addition to antiplatelet therapy during PCI.	**I**	A
The anticoagulation is selected according to both ischaemic and bleeding risks, and according to the efficacy–safety profile of the chosen agent.	**I**	C
Bivalirudin (0.75 mg/kg bolus, followed by 1.75 mg/kg/hour for up to 4 hours after the procedure) is recommended as alternative to UFH plus GP IIb/IIIa receptor inhibitor during PCI	**I**	A
UFH is recommended as anticoagulant for PCI if patients cannot receive bivalirudin	**I**	C
In patients on fondaparinux (2.5 mg daily s.c.), a single bolus UFH (85 IU/kg, or 60 IU/kg in the case of concomitant use of GP IIb/IIIa receptor inhibitors) is indicated during PCI	**I**	B
Enoxaparin should be considered as anticoagulant for PCI in patients pre-treated with subcutaneous enoxaparin.	**IIa**	B
Discontinuation of anticoagulation should be considered after an invasive procedure unless otherwise indicated	**IIa**	C
Crossover of UFH and LMWH is not recommended	**III**	B

*At the most recent American Heart Association meeting in November 2014, the DAPT study investigators found that using thienopyridine plus aspirin after drug-eluting stent procedures beyond 1 year further reduces the risk of stent thrombosis and MACE events as compared to aspirin only.

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Anticoagulant therapy in STEMI – the South African perspective

KEY MESSAGES

- Acute ST elevation myocardial infarction (STEMI) is a major and growing cause of death and morbidity in South Africa
- The therapeutic window to make a significant beneficial difference in outcomes with reperfusion to a STEMI patient is limited to the first 12 hours from onset of symptoms
- In South Africa, there is a clear need to build and strengthen health systems and networks to deal with STEMI in a structured coordinated way
- Education of at-risk patients is vital to reduce the time between MI and first medical contact (FMC)
- The use of thrombolytics (fibrinolytics, such as tenecteplase and streptokinase) early post-MI is often the only reperfusion option available for the majority of South African STEMI patients
- Anticoagulants as an adjunct to fibrinolytic therapy are recommended in South Africa for all patients, as they prevent new thrombus formation and halt propagation of thrombi, thereby preventing re-infarction and further ischaemic damage. The choice of anticoagulant depends on whether angiography is available within 24 hours
- Evidence suggests that fondaparinux is the safest, most efficacious and cost-effective anticoagulant option for the majority of South African patients who a] receive thrombolysis and do not go on to PCI within 24 hours; b] present outside of the therapeutic window for any reperfusion therapy. For those fortunate few who have access to early angiography and or PCI, low molecular weight heparins or unfractionated heparin are preferred
- It is time to advocate change in our networks and systems to ensure that the majority of patients get timely and prompt reperfusion therapy. For the majority this will mean thrombolysis and appropriate anticoagulation therapy, or thrombolysis followed by PCI or primary PCI when it is available.

"The optimal management of STEMI patients, even when the diagnosis is clear, can be confusing, because of the myriad of choices and decisions that the clinician in the Casualty Department must make. In South Africa, this is frequently complicated by late presentation, lack of clarity as to when effective PCI or thrombolysis is still

Table 2. A summary of important delays and treatment goals in the management of acute ST-segment elevation myocardial infarction (STEMI)[14]

Delay	Target
Preferred for FMC to ECG and diagnosis	≤10 min
Preferred for FMC to fibrinolysis (FMC to needle)	**≤30 min**
Preferred for FMC to primary PCI ('door to balloon') in primary PCI hospitals	≤60 min
Preferred for FMC to primary PCI	**≤90 min** (≤60 min if early presenter with large area at risk)
Acceptable for primary PCI rather than fibrinolysis	**≤120 min** (≤90 min if early presenter with large area at risk) if this target cannot be met, consider fibrinolysis.
Preferred for successful fibrinolysis to angiography	**3-24 h**

FMC: first medical contact; PCI: percutaneous coronary intervention

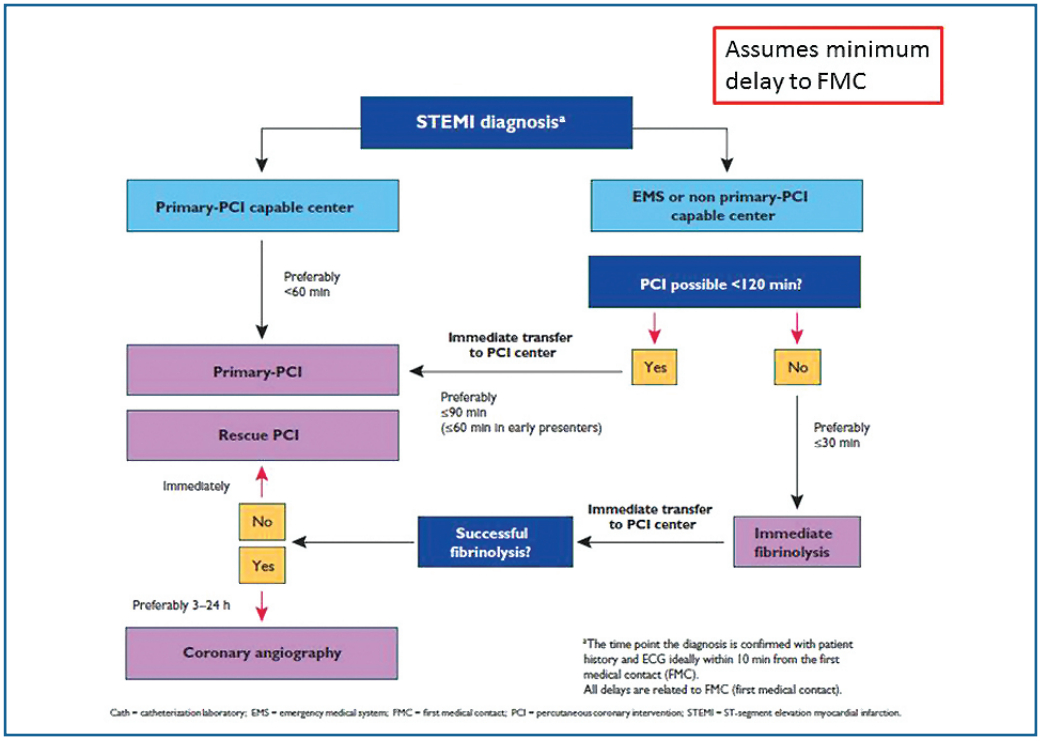

Figure 1. Prehospital and in-hospital management, and reperfusion strategies within 24 hours of FMC[14].

possible and uncertainty about the impact of individual patient characteristics, such as time since the event, age and renal function, on the various choices", Prof Mpiko Ntsekhe pointed out.

The time from the STEMI event to first medical contact (FMC) and subsequent successful revascularisation is critical regardless of whether PCI or thrombolytic therapy is the chosen route. "Reperfusion must be achieved within 6 hours to save myocardium and life. After 6 hours (6-12 hours) there is still an opportunity to reduce adverse remodelling of the left ventricle and related outcomes such as subsequent heart failure. Treatment 12-24 hours post-MI results in unpredictable outcomes, and interventions after a longer delay may in fact be harmful", Prof Ntsekhe noted[13].

The importance of time to intervention is reflected in the well-recognised algorithm for reperfusion strategies[14] (Figure 1) and the ESC summary of optimal time to interventions (Table 2).

An issue that is not often addressed in developed countries and in ESC debates around contemporary guidelines is the question of how to deal with late presenters, a frequent scenario in South Africa. "In patients who present late (24 hours post MI), the evidence suggests that neither PCI nor thrombolysis confer any benefits, especially in the absence of clinical, electrical and/or hemodynamic instability", Prof Ntsekhe said.[15]

Evaluating PCI opportunities in South Africa

The reality of South Africa is that there are only 55 cath labs in the country – 80% are in the larger cities (Cape Town, Johannesburg, Durban and Pretoria) with the remaining 20% spread through 3 other cities (Port Elizabeth, East London and Bloemfontein). "This means that the vast majority of South Africans with an MI will present to a non-PCI-capable hospital and will be managed by non-cardiologists." There are only 180 cardiologists in a country of 55 million people.

South African data on management of acute coronary syndromes

South African data is available from the ACCESS study[3] and the South African heart STEMI early reperfusion program (unpublished, personal communication Dr A Snyders).

How to optimally use anticoagulation in the South African context

Prof Ntsekhe pointed out that, in his view, two strategies are needed for the South African environment.

The first is for the minority of patients who will undergo PCI for STEMI (primary PCI, rescue PCI or pharmacoinvasive PCI <24 hours) where anticoagulation is needed to prevent abrupt stent/vessel thrombosis and clot formation on catheter/wires."

These anticoagulation choices are summarised in recent ESC guidelines (Table 3).

"Despite the fact that enoxaparin shows benefit over heparin in the cath lab situation, most surveys still show that cardiologists are more comfortable with heparin", Prof Ntsekhe said.

"In the second situation, which is the reality for most South African patients, STEMI patients will receive fibrinolytic therapy as the sole reperfusion strategy; anticoagulants are then required to prevent further thrombus formation and propagation and reinfarction."

Table 3. Periprocedural antithrombotic medication in primary percutaneous coronary intervention

Anticoagulants	Class[a]	Level[b]
An injectable anticoagulant must be used in primary PCI	I	C
Bivalirudin (with use of GP IIb/IIa blocker restricted to bailout) is recommended over unfractionated heparin and GP IIb/IIa blocker	I	B
Enoxaparin (with or without routine GP IIb/IIa blocker) may be preferred over unfractionated heparin	IIb	B
Unfractionated heparin with or without routine GP IIb/IIa blocker must be used in patients not receiving bivalirudin or enoxaparin	I	C
Fondaparinux is not recommended for primary PCI	III	B
The use of fibrinolysis before planned primary PCI is not recommended.	III	A

GP: glycoprotein; PCI: percutaneous coronary intervention; a: Class of recommendation; b: Level of evidence.

Choice of anticoagulant for STEMI patients receiving fibrinolysis or no reperfusion

Evidence in this group of patients has shown that unfractionated heparin (UFH) does not reduce death/reinfarction, but increases bleeding versus placebo or no treatment.[16]

In a robust study of 17 000 patients, low molecular weight heparin (LMWH) was shown to reduce mortality at 30 days compared to heparin and placebo, but at a cost of increased bleeding in comparison to placebo.[16]

Finally in the OASIS-6 trial, which included 12 000 patients[17], fondaparinux significantly reduced mortality and MI as compared to UFH or placebo. "Importantly, bleeding outcomes were reduced with fondaparinux, although this did not reach statistical significance", Prof Ntsekhe noted. "This reduced rate of bleeding seems to contribute to the overall benefit of fondaparinux, as various meta-analyses have shown that increased bleeding rates correlate with poorer outcomes in STEMI patients overall."

Additionally, for those patients presenting very late and who do not receive reperfusion therapy, in comparison to UFH and placebo, fondaparinux reduces the composite of death or myocardial infarction without an increase in severe bleeds or stroke.[18]

"Fondaparinux is the only agent with robust data in this patient group", Prof Ntsekhe pointed out.

In conclusion, with cardiovascular-related deaths outstripping HIV-deaths for the first time in South Africa in 2012, the time has come to ensure that more effective strategies are implemented to save the lives of people after myocardial infarction.

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