National Essential Medicine List Medication Review Process
Adult Hospital Level
Component: Cardiovascular

Date: *25 July 2015*

Medication: *Thrombolytics – medicine class for STEMI*

Executive summary:
Prompt reperfusion improves myocardial salvage resulting in improved myocardial function, decreased arrhythmias and heart failure, and a reduction in mortality. Mortality rates can be reduced by up to 30% if fibrinolytic reperfusion therapy is administered within 6 hours of symptom onset in ST elevation myocardial infarction (STEMI) (Morse et al. 2009)[i]

Thrombolytic agents do not differ in their effect on mortality, but do differ in harm profile, with streptokinase resulting in more major bleeds and allergic reactions, compared to alteplase which results in greater numbers of strokes, including haemorrhagic strokes. The choice of agent will depend on availability, and patient profile, weighing up the risks and benefits of potential adverse effects of the different agents. Evidence from guidelines and systematic review provided below for the committee consideration.

Introduction:
Approximately 40% of patients with acute coronary syndrome (ACS) patients present with STEMIs (Cohen et al. 2010). Prompt coronary reperfusion using fibrinolysis or primary percutaneous coronary intervention (PCI) is globally accepted standard of care in STEMI. Prompt reperfusion improves myocardial salvage resulting in improved myocardial function, decreased arrhythmias and heart failure, and a reduction in mortality. Mortality rates can be reduced by up to 30% if fibrinolytic reperfusion therapy is administered within 6 hours of symptom onset[i].

Management of STEMI:
Primary PCI is the preferred method of reperfusion. However, the shortage of PCI-capable hospitals and related resources means fibrinolysis reperfusion in patients with STEMI who cannot have primary PCI within guideline-recommended time remains the cornerstone of treatment (Solhpour & Yusuf 2014) in South Africa and other middle to low income countries.

Pharmacological management:
Streptokinase, the first and most widely used thrombolytic agent in the treatment of STEMI in South Africa is currently the least expensive amongst thrombolytics. Streptokinase is a bacterial protein with no intrinsic enzymatic activity but forms a stable, noncovalent 1:1 complex with plasminogen. It is antigenic and has little fibrin specificity, and it has systemic lytic effects in clinical doses. Group C β-haemolytic streptococcus bacteria, a prevalent community acquired infection, produce streptokinase antibodies against streptococcal infections confer resistance to and reduce efficacy of streptokinase. Streptokinase is antigenic and results in the development of antibodies in those receiving streptokinase, which precludes its re-administration. Patients treated with streptokinase develop anti-streptococcal antibodies, which can inactivate the medicine if subsequent treatment is needed. The following thrombolytics are registered in South Africa: streptokinase, alteplase and tenecteplase.

Table 1. MCC registered and available fibrinolytics:

Fibrinolytic agent	Dose	Fibrin specificity	Antigenic
Fibrin specific			
tenecteplase (TNK-tPA)	Single IV weight based bolus	++++	No
Alteplase (tPA)	90 min weight based infusion	++	No
Non-fibrin-specific			
Streptokinase	1.5MU IV given over 30 – 60 min	No	Yes

Note: Activated drotrecogin alfa is a recombinant form of human activated protein C that has anti-thrombotic effects. It is used in sepsis and is not listed as a thrombolytic in the South African Medicines Formulary (SAMF 2014).

Purpose of this review

EDL Secondary Adult STGs recommend use of streptokinase for patients presenting with STEMI. However, there is a global shortage of stock of streptokinase, hence the purpose of this review is to consider the evidence base for thrombolytics for use in STEMI. This will inform committee deliberations for thrombolytic use for management of STEMI as a therapeutic class.

PICO framework

Are thrombolytics including alteplase and tenecteplase as efficacious and safe as streptokinase for adults presenting to hospital with STEMI to reduce mortality and morbidity?

P	Adults presenting to hospital with STEMI
I	Thrombolytics – specifically - alteplase, tenecteplase
C	Streptokinase
O	Mortality; morbidity (re-infarction, stroke); major bleeding; allergic reactions

SEARCH STRATEGY:

Part 1: Guidelines

With advice from Prof Commerford regarding key documents for consideration, we searched electronically (Google and PubMed) and found the following guidelines:

- National professional societies.
  - SA Heart Association
- International guidelines
  - European Society of Cardiology (ESC) guidelines
  - American College of Cardiology/American Heart (ACC/AHA) guidelines)
  - National Institute of Clinical Excellence (NICE) guidelines of the United Kingdom

Part 2: Systematic reviews and RCTs

Search strategy (Pubmed search strategy Appendix 1)

Selection of studies: Searches of Pubmed, Embase and CLIB were run in July 2015. We identified 179 records in the search for Systematic reviews, and 524 records for search for RCTs. One reviewer evaluated these and identified one eligible systematic review[ii] and 14 eligible trials[iiiivvviviiviiiixxxixiixiiixivxvxvixvii], no new trials found publication of systematic review.

Table 2. Search output results per database

	PUBMED	EMBASE	CENTRAL	TOTAL	NO. OF DUPLICATES	NO. OF RECORDS TO SCREEN
Systematic Reviews	12 (12)	173 (173)	-	185 (185)	5	**180**
RCTs	157 (157)	416 (415)	68 (70)	641 (642)	117	**524**

RESULTS OF EVIDENCE SYNTHESIS:

PART 1: GUIDELINES: All three guidelines described bellowed score well on AGREE II, with clearly described managed of conflicts of interest and the role of the funder (Table 3). All recommendations are referenced in the guideline. Only NICE refers to a HTA, including a systematic review of evidence that was conducted. The systematic review was subsequently published and is described below.

Table 3: External Guideline recommendations

Guideline	Recommendations
2012 ESC Guideline	Fibrinolytic therapy is recommended within 12 h of symptom onset in patients without contraindications if primary PCI cannot be performed by an experienced team within 120 min of FMC. (1A) In patients presenting early (<2 h after symptom onset) with a large infarct and low bleeding risk, fibrinolysis should be considered if time from FMC to balloon inflation is >90 min. (IIa B) A fibrin-specific agent (tenecteplase, alteplase, reteplase) is recommended (over non-fibrin specific agents). (I B)
2013 ACCF/AHA	In the absence of contraindications, fibrinolytic therapy should be given to patients with STEMI and onset of ischemic symptoms within the previous 12 hours when it is anticipated that primary PCI cannot be performed within 120 minutes of FMC. (I A) In the absence of contraindications and when PCI is not available, fibrinolytic therapy is reasonable for patients with STEMI if there is clinical and/or ECG evidence of ongoing ischemia within 12 to 24 hours of symptom onset and a large area of myocardium at risk or hemodynamic instability. (IIa C) Fibrinolytic therapy should not be administered to patients with ST depression except when a true posterior (inferobasal) MI is suspected or when associated with ST elevation in lead aVR. (III B)
***National Institute of Clinical Excellence (2006) https://www.nice.org.uk/guidance/ta52/chapter/4-Evidence**	Four thrombolytic agents which act by promoting the activity of circulating plasminogen are licensed and available to treat STEMI. The choice of thrombolytic agent (alteplase, reteplase, streptokinase or tenecteplase) should take account of the likely balance of benefit and harm (for example, stroke) to which each of the thrombolytic agents would expose the individual patient current UK clinical practice, in which it is accepted that patients who have previously received streptokinase should not be treated with it again, the hospital's arrangements for reducing delays in the administration of thrombolysis. *Note: In January 2006, following consultation, NICE guideline was made 'static.' This means that the evidence is not changing, guidance remains in force and has no scheduled review date.
SA Heart Association	South African Society of Cardiovascular Intervention (SASCI) as an official Special Interest Group of the South African Heart Association subscribe to the European

	Society of Cardiology (ESC) guidelines.

Comparing the guidelines with regards recommendations of agents:

Neither ESC nor NICE guidelines make specific recommendations on the choice of specific thrombolytics whereas the 2013 ACCH/AHA guidelines state that fibrin specific guidelines, when available, are more preferred than streptokinase. Tissue type plasminogen activator (tPA) and its derivatives reteplase (rPA) and tenecteplase (TNK-tPA) have better fibrin specificity. In terms of efficacy, tenecteplace and reteplase are equivalent to alteplase for 30-day mortality. Tenecteplase and reteplase boluses are however easier to administer even in pre-hospital situations.
Streptokinase is no longer available as a thrombolytic in America.

PART 2: SUMMARY OF SYSTEMATIC REVIEW

Table 4. Summary of published systematic review

Name of SR	Outcome information	SR quality*
Dundar 2003[ii]	*Question* directly relevant to EDL question √ *Search comprehensive*: Medline, Embase, Web of Science, Cochrane Library *Date of search*: 1980 to December 2001 *RCTs:* 14 *Study participants*: n = 142 907 Exclusion: age >70 or 75 *Thrombolytics:* streptokinase, alteplase, tenecteplase, reteplase *Settings:* Multi-centre - USA, Europe, Italy, Taiwan, New Zealand *Outcomes*: Mortality, bleeding, stroke, re-infarction, allergy and anaphylaxis.	Using AMSTAR, this review rated moderate quality 5/11 –gaps included quality of studies was assessed, but not reported in meta-analysis, and not considered when assessing results
Note: this review was commissioned and funded by (UK) NHS R&D HTA programme and informed the NICE guideline panel on use of thrombolysis in STEMI patients in hospital		

* we assessed the internal validity of systematic reviews using the AMSTAR 11 question critical appraisal tool for systematic reviews[xviii].

EVIDENCE SYNTHESIS FROM NICE GUIDANCE (2006), BASED ON DUNDAR (2003)[ii]

The NICE guideline team commissioned a systematic review. Fourteen randomised controlled trials (RCTs) comparing thrombolytic agents were included in the review. Overall the studies were considered to be of high quality. In total, the trials involved over 142,000 patients, and five of the trials included over 10,000 patients each. The trials had similar inclusion criteria in terms of age (usually <70 or <75 years), ECG changes, duration of symptoms, and presentation within 6 hours of symptom onset. Five of the trials included between 12% and 26% of patients aged over 70–75 years. Women were under-represented in all of the studies.

Primary endpoints included 30-day mortality, 90-minute artery patency/flow rates and left ventricular function. Secondary endpoints included bleeding, stroke, congestive heart failure, reinfarction, allergy and anaphylaxis. The results of the trials were also pooled in a meta-analysis.

A meta-analysis of eight comparisons of standard alteplase with streptokinase found no significant difference between the two agents in terms of mortality up to 35 days (odds ratio 1.0; 95% CI 0.94 to 1.06). A statistically significant difference in reinfarction rates in favour of alteplase was found (odds ratio 0.86; 95% CI 0.77 to 0.95). However, alteplase was associated with a statistically significant higher risk of stroke (odds ratio 1.37; 95% CI 1.16 to 1.62), due to a doubling in the risk of haemorrhagic stroke (odds ratio 2.13; 95% CI 1.04 to 4.36). However, streptokinase was associated

with a statistically significant higher risk of major bleeds (other than stroke) than alteplase (odds ratio 0.81; 95% CI 0.68 to 0.97).

No direct trial comparisons between tenecteplase and streptokinase or between tenecteplase and reteplase have been undertaken, and only cautious conclusions can be drawn from the indirect comparisons that can be deduced from other studies.

Streptokinase

Two placebo-controlled trials were instrumental in establishing the efficacy of streptokinase in reducing mortality. The GISSI trial (published in 1986) included 11,712 patients, and the ISIS-2 trial (published in 1988) included 17,187 patients. In the GISSI study, 21-day mortality was 10.7% in patients treated with streptokinase and 13% in those treated with placebo. This represents a statistically significant absolute reduction of 2.3% (risk ratio 0.81; 95% confidence ratio [CI] 0.72 to 0.9). In the ISIS-2 study, vascular mortality at 5 weeks was 9.2% in patients treated with streptokinase and 12% in those treated with placebo. This represents a statistically significant absolute reduction of 2.8%. These benefits were independent of those of early aspirin treatment.

Alteplase

A meta-analysis of eight comparisons of standard alteplase with streptokinase found no significant difference between the two agents in terms of mortality up to 35 days (odds ratio 1.0; 95% CI 0.94 to 1.06). A statistically significant difference in reinfarction rates in favour of alteplase was found (odds ratio 0.86; 95% CI 0.77 to 0.95). However, alteplase was associated with a statistically significant higher risk of stroke (odds ratio 1.37; 95% CI 1.16 to 1.62), due to a doubling in the risk of haemorrhagic stroke (odds ratio 2.13; 95% CI 1.04 to 4.36). However, streptokinase was associated with a statistically significant higher risk of major bleeds (other than stroke) than alteplase (odds ratio 0.81; 95% CI 0.68 to 0.97). The categorisation and reporting of major bleeding varied between the trials and so it is difficult to judge the clinical significance of these findings.

The studies included in this meta-analysis used the standard alteplase administration regimen, whereas the GUSTO-I trial used the accelerated regimen and is the only trial to have demonstrated superiority between different thrombolytic agents. The GUSTO-I trial included over 40,000 patients. It found an odds ratio of 0.85 (95% CI 0.78 to 0.94) for 30-day mortality for accelerated alteplase compared with streptokinase, and an absolute reduction in mortality at 30 days of 1.0% (6.3% versus 7.3%; 95% CI 0.4% to 1.6%) in favour of accelerated alteplase. However, this benefit was balanced by a statistically significantly higher incidence of haemorrhagic stroke (odds ratio 1.42; 95% CI 1.05 to 1.91). Using a combined outcome measure of mortality and disabling stroke, the absolute advantage of accelerated alteplase over streptokinase was lower (0.9%; p = 0.006). Rates of bleeds (moderate or worse), allergic reaction, anaphylaxis, congestive heart failure, and sustained hypotension were statistically significantly lower in the group treated with accelerated alteplase. A further meta-analysis of nine comparisons of alteplase with streptokinase, including the findings of GUSTO-I (i.e. accelerated alteplase), found no significant difference between the two agents in terms of mortality up to 35 days (odds ratio 0.94; 95% CI 0.85 to 1.04).

Tenecteplase

ASSENT-2, an equivalence trial of over 16,000 patients compared tenecteplase and accelerated alteplase. The study found that 30-day mortality was almost the same in the tenecteplase group (6.2%) and the accelerated alteplase (6.2%) group. The absolute difference of 0.03% in favour of accelerated alteplase was not statistically significant (95% CI -0.55% to 0.61%). Given the confidence limits, tenecteplase and accelerated alteplase can be considered equivalent in terms of mortality. However, there was a small but statistically significant reduction in the incidence of bleeding with

tenecteplase (26.4% compared with 28.9% in the accelerated alteplase group), resulting in fewer blood transfusions in the tenecteplase group (4.3% of patients compared with 5.5% in the accelerated alteplase group). Also, the rate of heart failure was statistically significantly lower in the tenecteplase group than in the accelerated alteplase group (6.1% vs 7.0%, p = 0.026).

Subgroups

None of the trials discussed was designed to investigate clinical subgroups, such as by age or site of infarct (anterior, inferior). It was concluded that there was no convincing evidence of relative differences in the effectiveness of the available agents in subgroups. The greater absolute benefit found in patients with anterior infarcts in GUSTO-I may simply be a reflection of the higher baseline risk in this group. The greater relative benefit in patients aged under 75 years was not reflected in their level of absolute risk reduction. None of the differences between the subgroups appeared to be statistically significant by interaction.

Summary

In summary, given the evidence on clinical effectiveness, it can be concluded that, in the hospital setting, in terms of mortality:

- standard alteplase is as effective as streptokinase
- reteplase is at least as effective as streptokinase, and
- tenecteplase is as effective as accelerated alteplase.

- If accelerated alteplase is believed to be superior to streptokinase, then indirectly tenecteplase would also be considered to be superior to streptokinase.

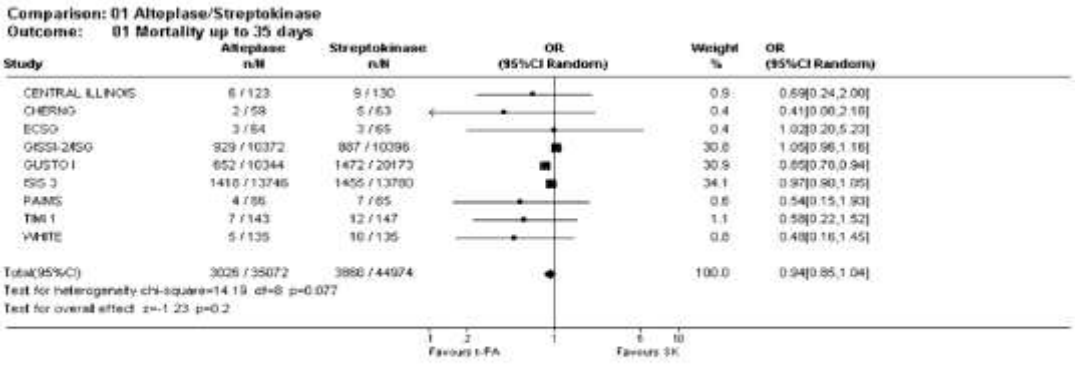
- Conclusions regarding the equivalence of reteplase compared with accelerated alteplase depend on the interpretation of GUSTO-III.

- Furthermore, if reteplase is considered to be equivalent to accelerated alteplase, then this indirectly implies that reteplase is as effective as tenecteplase.

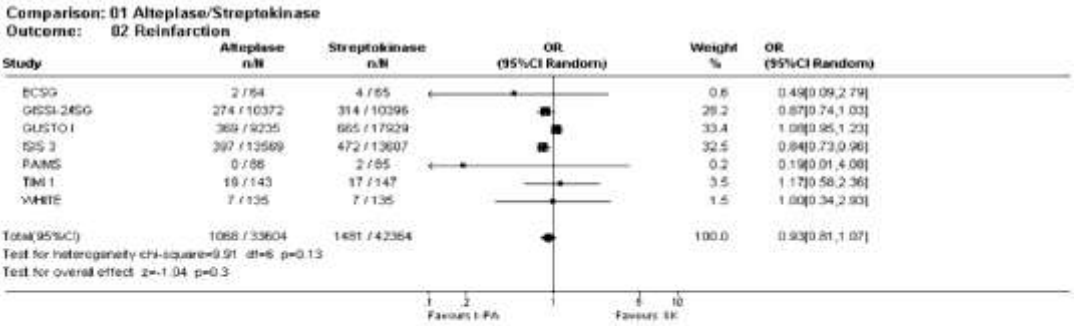
- Important differences in major adverse events between the thrombolytic agents are also apparent. The newer medicines are associated with a higher risk of haemorrhagic stroke compared with streptokinase, but there are no apparent differences in the frequency of haemorrhagic stroke between accelerated alteplase and reteplase (GUSTO-III), or between accelerated alteplase and tenecteplase (ASSENT-2). However, compared with streptokinase, the newer medicines may also be associated with a lower incidence of congestive heart failure. In addition, allergic reactions are more common with streptokinase than with the other medicines, and major bleeds (leading to transfusions) may also be more common with streptokinase, although the evidence on this is not consistent across the trials. There is also some evidence that tenecteplase may be associated with lower rates of major bleeds and heart failure than accelerated alteplase.

Figures 1 - 5: Forest plots of clinical endpoints alteplase vs streptokinase, including GUSTO 1 (accelerated alteplase)

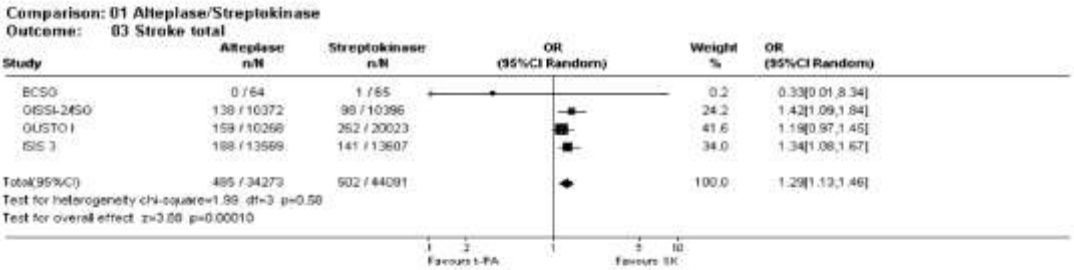
i. Mortality



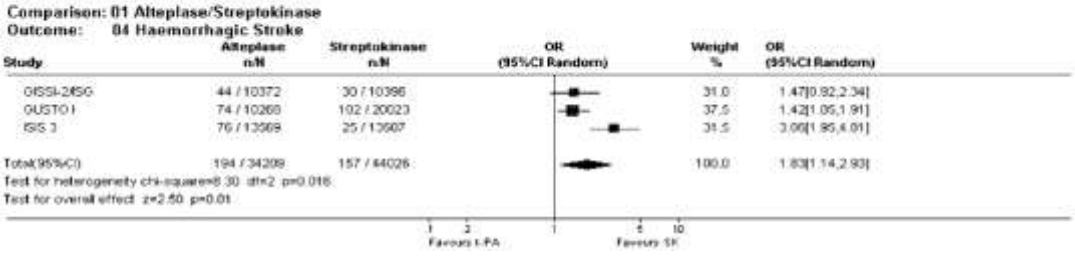
ii. Reinfarction



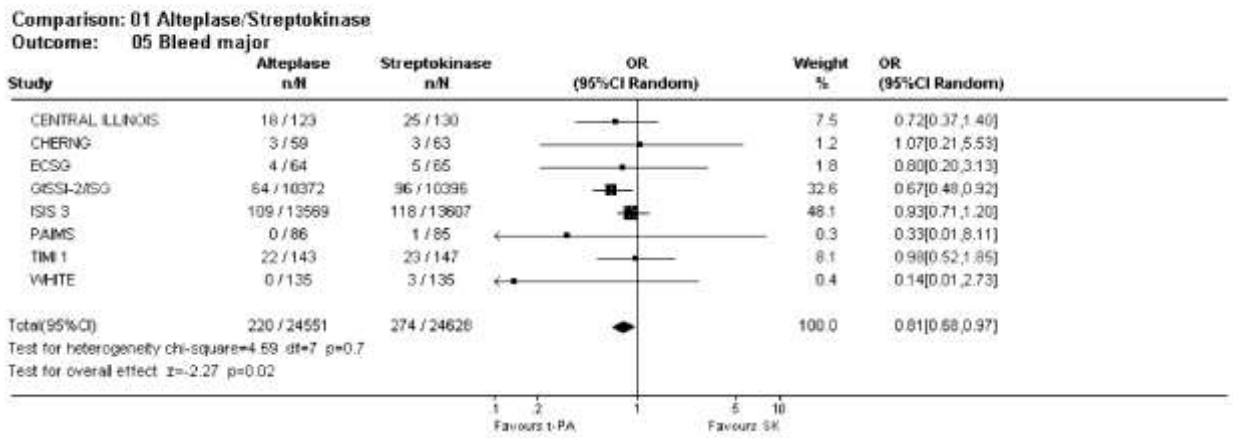
iii. Total stroke



iv. Haemorrhagic stroke



v. Major bleed



QUALITY OF THE EVIDENCE

SORT – Grade 1
Based on meta-analysis of high quality RCTs

The primary studies have not been reviewed and specific risks of bias has not been assessed that may change confidence in the results.

EVIDENCE TO DECISION FRAMEWORK

<table>
<tr><th></th><th>JUDGEMENT</th><th>SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>QUALITY OF EVIDENCE</td><td>What is the overall confidence in the evidence of effectiveness?

Confident [x] Not confident [ ] Uncertain [ ]</td><td>Summarised above</td></tr>
<tr><td>BENEFITS & HARMS</td><td>Do the desirable effects outweigh the undesirable effects?

Benefits outweigh harms [x] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]</td><td>For committee to advise
Benefits outweigh risks.
Major bleeds > Strep vs alteplase
Stroke is > in alteplase and reteplase
Allergic reactions > strep</td></tr>
<tr><td>VALES & PREFERENCES / ACCEPTABILITY</td><td>Is there important uncertainty or variability about how much people value the options?
Minor [ ] Major [ ] Uncertain [x]

Is the option acceptable to key stakeholders?
Yes [ ] No [ ] Uncertain [x]</td><td>For committee to advise

No data that I am aware of about values/ preferences and acceptability.

These issues could affect uptake, if health care providers not in favour or accustomed to newer agents</td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?

More intensive [ ] Less intensive [ ] Uncertain [x]</td><td>For the committee to advise

Cost of medicines/ month:
<table><tr><th>Medicine</th><th>Cost (ZAR)</th></tr><tr><td>Tenecteplase</td><td>13 431.10</td></tr><tr><td>Alteplase</td><td>5 984.83</td></tr><tr><td>Streptokinase</td><td>3 098.03</td></tr></table>
Additional resources:
Workforce training
Equipment
Costs of major bleeds (Strep) vs haemorrhagic stroke (Alt)</td></tr>
</table>

EQUITY	**What would be the impact on health inequity?** Yes: x No: Uncertain:	If no strep available, with no alternative available in public sector, significant impact on health inequity For committee to advise
FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes: No: Uncertain:	For the committee to advise

Type of recommendation	We recommend against the option or for the alternative ☐	We suggest not to use the option or to use the alternative ☐	We suggest using either the option or the alternative ☐	We suggest using the option ☐	We recommend the option ☐

Recommendation

Monitoring and evaluation considerations

Research priorities

RECOMMENDATION

Streptokinase be retained in the EML for STEMI.

Rationale:

- There is little difference in terms of safety and efficacy between streptokinase and fibrin-specific lytic agents.
- Streptokinase remains considerably cheaper and there is no reason to change current recommendations.
- If, as has been suggested, streptokinase becomes unavailable consideration will have to be given to selecting a fibrin-specific agent.
- It was noted that the newer fibrin-specific agents are more convenient to administer.
- All fibrin-specific agents require heparin administration and the cost of this need to be factored in to the evaluation.

Level of Evidence: I Meta-analysis of high quality RCTs

Appendix 1: Pubmed Search Strategies

Topic: **STEMI (randomized controlled trials)**
Database: **PubMed**
Date of search: **30 July 2015**

Search	Query	Items found
#11	Search ((#4 AND #7 AND #8 AND #10)	157
#10	Search (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mh] NOT humans[mh])	3124241
#9	Search (#4 AND #7 AND #8)	177
#8	Search (streptokinase[mh] OR streptokinase[tiab] OR streptodecase[tiab] OR avelizin[tiab] OR avelysin[tiab] OR awelysin[tiab] OR celiase[tiab] OR kabikinase[tiab] OR streptase[tiab] OR distreptase[tiab] OR kabivitrum[tiab])	11135
#7	Search (#5 OR #6)	2043
#6	Search (alteplase[tiab] OR actilyse[tiab] OR activase[tiab])	1745
#5	Search (tenecteplase[tiab] OR metalyse[tiab] OR TNK tPA[tiab] OR TNKase[tiab])	405
#4	Search (myocardial infarction[mh] OR myocardial infarct*[tiab] OR ST elevated [tiab] OR ST elevation [tiab] OR STEMI[tiab] OR st segment elevation[tiab] OR st segment elevated[tiab] OR heart infarct*[tiab])	211626

Topic: **STEMI (systematic reviews)**
Database: **PubMed**
Date of search: **30 July 2015**

Search	Query	Items found
#10	Search ((#4 AND #7 AND #8) AND (systematic[sb] OR systematic reviews[ti]))	12
#9	Search (#4 AND #7 AND #8)	177
#8	Search (streptokinase[mh] OR streptokinase[tiab] OR streptodecase[tiab] OR avelizin[tiab] OR avelysin[tiab] OR awelysin[tiab] OR celiase[tiab] OR kabikinase[tiab] OR streptase[tiab] OR distreptase[tiab] OR kabivitrum[tiab])	11135
#7	Search (#5 OR #6)	2043
#6	Search (alteplase[tiab] OR actilyse[tiab] OR activase[tiab])	1745
#5	Search (tenecteplase[tiab] OR metalyse[tiab] OR TNK tPA[tiab] OR TNKase[tiab])	405
#4	Search (myocardial infarction[mh] OR myocardial infarct*[tiab] OR ST elevated [tiab] OR ST elevation [tiab] OR STEMI[tiab] OR st segment elevation[tiab] OR st segment elevated[tiab] OR heart infarct*[tiab])	211626

References

[i] Morse MA, Todd JW, Stouffer GA et al. Optimizing the use of thrombolytics in ST-segment elevation myocardial infarction. *Drugs*, 2009 Oct 1; 69(14): 1945-66

[ii] Dundar Y, Hill R, Dickson R, Walley T. Comparative efficacy of thrombolytics in acute myocardial infarction: A systematic review. QJM - Monthly Journal of the Association of Physicians. 2003;96(2):103-13.

[iii] GUSTO. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. The GUSTO investigators. N Engl J Med 1993; 329:673–82. White HD, Rivers JT, Maslowski AH, Ormiston JA,

[iv] Taylor GJ, Moses HW, Koester D, Colliver JA, Katholi RE, Dove JT, et al. A difference between front-loaded streptokinase and standard-dose recombinant tissue-type plasminogen activator in preserving left ventricular function after acute myocardial infarction (the Central Illinois Thrombolytic Therapy Study). Am J Cardiol 1993; 72:1010–14.

[v] Cherng WJ, Chiang CW, Kuo CT, Lee CP, Lee YS. A comparison between intravenous streptokinase and tissue plasminogen activator with early intravenous heparin in acute myocardial infarction. Am Heart J 1992; 123:841–6.

[vi] Verstraete M, Bernard R, Bory M, Brower RW, Collen D, de Bono DP, et al. Randomised trial of intravenous recombinant tissue- plasminogen activator versus intravenous streptokinase in acute myocardial infarction. Report from the European Cooperative Study Group for Recombinant Tissue-type Plasminogen Activator. Lancet 1985; 1:842–7.

[vii] Feruglio GA, Lotto A, Rovelli F, Solinas P, Tavazzi L, Tognoni G, et al. GISSI-2: A factorial randomised trial of alteplase versus streptokinase and heparin versus no heparin among 12,490 patients with acute myocardial infarction. Lancet 1990; 336:65–71.

[viii] Van de Werf F, Wilcox RG, Barbash GI, Diaz R, Franzosi MG, Hampton JR, et al. In-hospital mortality and clinical course of 20,891 patients with suspected acute myocardial infarction randomised between alteplase and streptokinase with or without heparin. Lancet 1990; 336:71–5.

[ix] Hunt D, Varigos J, Dienstl F, Lechleitner P, Mauel C, Dienstl A, et al. ISIS-3: A randomised comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs. aspirin alone among 41,299 cases of suspected acute myocardial infarction. Lancet 1992;
339:753–770.

[x] Grines CL, Nissen SE, Booth DC, Gurley JC, Chelliah N, Wolf R, et al. A prospective, randomized trial comparing combination half-dose tissue-type plasminogen activator and streptokinase with full-dose tissue-type plasminogen activator. Circulation 1991; 84:540–9.

[xi] Magnani B. Plasminogen Activator Italian Multicenter Study (PAIMS): comparison of intravenous recombinant singlechain human tissue-type plasminogen activator (rt-PA) with intravenous streptokinase in acute myocardial infarction. J Am Coll Cardiol 1989; 13:19–26.

[xii] Chesebro JH, Knatterud G, Roberts R, Borer J, Cohen LS, Dalen J, et al. Thrombolysis in Myocardial Infarction (TIMI) Trial, Phase I: A comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. Circulation 1987; 76:142–54.

[xiii] Takayama M, Hart HH, et al. Effect of intravenous streptokinase as compared with that of tissue plasminogen activator on left ventricular function after first myocardial infarction. N Engl J Med 1989; 320:817–21.

[xiv] Van de Werf F, Adgey J, Ardissino D, Armstrong PW, Aylward P, Barbash G, et al. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. Lancet 1999; 354:716–22.

[xv] Topol EJ, Califf R, Ohman E, Skene A, Wilcox R, Grinfeld L, et al. A comparison of reteplase with alteplase for acute myocardial infarction. N Engl J Med 1997; 337:1118–23.

[xvi] Bode C, Smalling RW, Berg G, Burnett C, Lorch G, Kalbfleisch JM, et al. Randomized comparison of coronary thrombolysis achieved with double- bolus reteplase (recombinant plasminogen activator) and front-loaded, accelerated alteplase (recombinant tissue plasminogen
activator) in patients with acute myocardial infarction. Circulation 1996; 94:891–8.

[xvii] Hampton JR, Schroder R, Wilcox RG, Skene AM, Meyer-Sabellek W, Heikkila J, et al. Randomised, double-blind comparison of reteplase double-bolus administration with streptokinase in acute myocardial infarction (INJECT): trial to investigate equivalence. Lancet 1995; 346:329–36.

[xviii] Shea BJ, Hamela C, Wells GA, et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol 2009;62(10):1013-1020. [http://dx.doi.org/10.1016/j.jclinepi.2008.10.009]