NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA52; Drugs for early thrombolysis in the treatment of acute myocardial infarction and review of TA230; Bivalirudin for the treatment of ST-segment elevation myocardial infarction (STEMI).

TA52 was issued in October 2002.

The review date for this guidance was October 2005.

In January 2006, following consultation, the Institute made this guidance 'static'.

TA230 was issued in July 2011.

The review date for this guidance is July 2014.

1. Recommendation

NICE has been asked to develop a clinical guideline on ‘the acute management of myocardial infarction with ST-segment-elevation’ and a related quality standard on the ‘management of acute coronary syndromes including myocardial infarction’. It is proposed that the recommendations of TA52 and TA230 are incorporated verbatim into the clinical guideline. The guideline developers may supplement the recommendations by placing them in the context of current clinical practice.

It is further proposed that TA230 is moved to the static list and TA52 remains on the static list until such time as the clinical guideline into which they are incorporated is updated. Both technology appraisals will remain extant alongside the clinical guideline. This has the consequence of preserving the funding direction for TA52 and TA230.

That we consult on this proposal.

2. Original remit(s)

TA52

Objective: To advise on the clinical and cost effectiveness of available drugs for early thrombolysis in acute myocardial infarction (AMI) in two settings: i) pre-hospital, and ii) hospital, and to produce guidance to the NHS in England and Wales.

TA230

To appraise the clinical and cost effectiveness of bivalirudin within its licensed indication for the treatment of ST-segment elevation myocardial infarction.

3. Current guidance

TA52

This guidance provides recommendations on the selection of thrombolytic drugs in patients with acute myocardial infarction (AMI). Recommendations are made in relation to the use of the drugs in hospital and pre-hospital settings. The guidance does not compare hospital and pre-hospital models of delivering thrombolysis.

1.1 It is recommended that, in hospital, the choice of thrombolytic drug (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.

1.2 Where pre-hospital delivery of thrombolytic drugs is considered a beneficial approach as part of an emergency-care pathway for AMI (for example, because of population geography or the accessibility of acute hospital facilities), the practicalities of administering thrombolytic drugs in pre-hospital settings mean that the bolus drugs (reteplase or tenecteplase) are recommended as the preferred option.

TA230

1.1 Bivalirudin in combination with aspirin and clopidogrel is recommended for the treatment of adults with ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention

4. Rationale[1]

There is no new evidence to suggest that either TA52 or TA230 require update. It is therefore appropriate to incorporate them into the ongoing, related clinical guideline.

5. Implications for other guidance producing programmes

Both TA52 and TA230 overlap with the ST-elevation myocardial infarction (STEMI) clinical guideline and acute coronary syndrome (including MI) quality standard. The STEMI guideline will incorporate these relevant TAs and may be used to inform the quality standards.

[1] A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

6. New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from September 2005 for TA52 and January 2011 for TA230 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

7. Summary of evidence and implications for review

TA52:

TA52 issued recommendations on the use of alteplase, reteplase, streptokinase or tenecteplase for early thrombolysis in acute myocardial infarction (AMI) in a pre-hospital and hospital setting. The guidance was put on the static list in January 2006 as no relevant additions to the evidence base that would have a material effect on the guidance were identified.

The marketing authorisation for streptokinase has been changed from 'treatment of acute myocardial infarction' to 'treatment of acute myocardial infarction within 12 hours of onset, with persistent ST-segment elevation or recent left bundle-branch block'. It is noted that streptokinase was indicated up to 12 hours after onset of symptoms even at the time of the original appraisal and the more explicit wording of the indication is not expected to have an impact on the recommendations in TA52. The manufacturers for all the drugs have confirmed that no extensions to the marketing authorisations are planned. The literature searches have not identified any new thrombolytics that have been launched or are likely to be launched in the UK in the near future. There have also not been any substantive price changes to the technologies that are likely to change the guidance.

The evidence for this appraisal was based on some very large comparative studies of thrombolytic drugs. No new trials of this nature have been found in the literature search and it appears that none is ongoing. The guidance recommended that opportunities for the evaluation of the administration of thrombolytic drugs in pre-hospital settings should be explored. However, no research has been identified to address this.

No new evidence has been identified that is likely to lead to a change in the recommendations of the original guidance.

TA230:

TA230 was published in July 2011 and it recommended bivalirudin in combination with aspirin and clopidogrel for the treatment of adults with STEMI undergoing primary PCI. The guidance did not issue any research recommendations. There has been no change to the marketing authorisation or the price of bivalirudin since the guidance was published.

Two trials, SAFARI-STEMI and MATRIX, have been identified that compare the impact of transradial access and transfemoral access using bivalirudin and these are expected to complete in 2014 and 2015. However, TA230 notes that the Committee discussed this issue and was aware that radial access is more common in UK practice than in the trial, and hence this could reduce the benefit of reduced access site bleeding with bivalirudin shown in the trial. However, in the trial bivalirudin was also shown to reduce bleeding not related to the access site in comparison with glycoprotein IIb/IIIa inhibitor plus heparin. The Committee accepted that similar outcomes for bleeding not related to access site could be expected in UK clinical practice as in the trial. In addition, the economic model assumed radial arterial access in 42.5% of cases, in line with UK practice. A sensitivity analysis from the manufacturer which increased the usage to 100% led to no changes in the results, with bivalirudin remaining the dominant treatment option. The Committee was satisfied that the model results were robust to changes in access site. Therefore, it is unlikely that the results of the trials that have been identified will have an impact on the recommendations.

The current literature search identified the EUROMAX trial which aims to show that the early administration of bivalirudin improves 30 day outcomes when compared to the current standard of care in patients with STE-ACS, with an onset of symptoms of >20 minutes and <12 hours, intended for a primary PCI management strategy, presenting either via ambulance or to centres where PCI is not performed. Given that TA230 issued a positive recommendation for the use of bivalirudin it is unlikely that the results from this trial would have an impact on the recommendations.

The current literature search also identified the phase IV BRAVE-4 trial which compares prasugrel plus bivalirudin versus clopidogrel plus heparin in patients with acute myocardial infarction undergoing emergency catheterization and coronary intervention. The trial is currently recruiting participants and is likely to complete in July 2013. This is potentially important as at the time of the original Guidance the clinical experts stated that a prasugrel/bivalirudin combination was likely to be better than a clopidogrel/bivalirudin combination because prasugrel reduces stent thrombosis. However, the marketing authorisation for bivalirudin is in combination with clopidogrel and the manufacturer has indicated that no extension to the marketing authorisation is planned.

In conclusion, no new evidence for TA52 or TA230 has been identified that is likely to lead to a change in the recommendations of the original guidance.

8. Implementation

TA52: A submission from Implementation on the trends in cost and volume of prescribing of the drugs in hospital pharmacies is included in Appendix 3.

9. Equality issues

TA52: No equality issues were raised in the original guidance.

TA230: No equalities issues were raised at any point in the appraisal.

GE paper sign off: Janet Robertson, 10 May 2012

Contributors to this paper:

Information Specialist:	Paul Levay
Technical Lead:	Raisa Sidhu
Implementation Analyst:	Rebecca Lea
Project Manager:	Andrew Kenyon

Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
A review of the guidance should be planned into the appraisal work programme.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	Yes

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline.	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	No

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

The technology falls within the scope of a clinical guideline (or public health guidance)

There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement

There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment

The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;

Spending on a treatment for the indication which was the subject of the appraisal continues to rise

There is evidence of unjustified variation across the country in access to a treatment

There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed

The treatment is excluded from the Payment by Results tariff

Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

Clinical Guidelines

Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. CG95. Published: March 2010

Unstable angina and NSTEMI: the early management of unstable angina and non-ST-segment-elevation myocardial infarction. CG94. Published: March 2010.

Note: CG94 replaces and updates TA80 Clopidogrel in the treatment of non-ST-segment-elevation acute coronary syndrome; and partly updates TA47 Glycoprotein IIb/IIIa inhibitors in the treatment of acute coronary syndromes.

Secondary prevention in primary and secondary care for patients following a myocardial infarction. CG48. May 2007.

Technology Appraisals

Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of technology appraisal guidance 90). TA210. Published: December 2010. Review: July 2013.

Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention.TA182. Published: October 2009. Review: September 2010. Review decision: deferred until January 2012.

Drug-eluting stents for the treatment of coronary artery disease (part review of TA71). TA152. Published: July 2008. Review: April 2009 (review deferred until June 2012).

Coronary imaging: Myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction. TA73. Published: November 2003. Review: partially updated by CG95 and CG126.

Ischaemic heart disease - coronary artery stents (review). TA71. Published: October 2003. Review: partly replaced by TA152.

Glycoprotein IIb/IIIa inhibitors in the treatment of acute coronary syndromes. TA47. Published: September 2002. Review: partly updated by CG94.

Medical Technologies

BRAHMS copeptin assay to rule out myocardial infarction in patients with acute chest pain. MTG4. June 2011.

Interventional Procedures

Percutaneous laser coronary angioplasty. IPG378. Published: January 2011.

Off-pump coronary artery bypass grafting. IPG377. Published: January 2011.

In progress

Clinical Guideline

Myocardial infarction with ST- segment elevation: the acute management of MI with ST-segment elevation. Status: in development (publication date TBC).

Note: this is being developed in conjunction with a Quality Standard called 'Management of acute coronary syndromes including myocardial infarction'.

Technology Appraisal

Ticagrelor for the treatment of acute coronary syndromes (ACS). Publication due: October 2011.

In topic selection[2]

[redacted]

[redacted]

[redacted]

[2] Information held by the NICE Topic Selection Team is treated as being potentially commercially sensitive by default. Details of the topics considered by NICE's Consideration Panels may be available on the NICE website, providing the manufacturers of the technologies under discussion have consented to the release of this information.

Details of changes to the indications of the technology

Indication considered in original appraisal	Proposed indication (for this appraisal)
Alteplase Can be delivered in a standard or accelerated regimen. The accelerated regimen, which is much more commonly used, is indicated up to 6 hours after symptom onset and is delivered by an initial IV bolus injection, followed by two IV infusions, the first given over 30 minutes and the second over 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. Costs £600 per patient (excluding VAT) (BNF 43, March 2002).	No change. 10 mg (5.8 million units)/vial, net price per vial (with diluent) = £120.00 20 mg (11.6 million units)/vial (with diluent and transfer device) = £180.00 50 mg (29 million units)/vial (with diluent, transfer device, and infusion bag) = £300.00 (BNF62, Sept 2011)
Reteplase Indicated up to 12 hours after symptom onset. It is given as two IV bolus injections 30 minutes apart. Costs £716 per patient (excluding VAT) (BNF 43, March 2002)	No change. 10 units/vial, net price pack of 2 vials (with 2 prefilled syringes of diluent and transfer device) = £627.97 (BNF62, Sept 2011)
Streptokinase Indicated up to 12 hours after onset of symptoms. It is administered as an IV infusion over 1 hour. In current UK practice, patients are usually treated with streptokinase only once. Costs £80 to £90 per patient (excluding VAT) (BNF 43, March 2002)	The description of the therapeutic indication has been changed from treatment of acute myocardial infarction to: Treatment of acute myocardial infarction within 12 hours of onset, with persistent ST-segment elevation or recent left bundle-branch block. (June 2008) Net price 250 000-unit vial = £15.91; 750 000-unit vial = £41.72; 1.5 million-unit vial = £83.44 (hosp. only) (BNF62, Sept 2011)

Indication considered in original appraisal	Proposed indication (for this appraisal)
Tenecteplase Indicated up to 6 hours after symptom onset. It is administered as a single (weight adjusted) IV bolus injection. Costs £700 to £770 per patient (excluding VAT) (BNF 43, March 2002)	No change Net price 40-mg (8000-unit) vial = £502.25; 50-mg (10 000-unit) vial = £502.25 (both with prefilled syringe of water for injection) (BNF62, Sept 2011)
Bivalrudin Has a marketing authorisation 'as an anticoagulant in adult patients undergoing percutaneous coronary intervention (PCI), including patients with ST-segment-elevation myocardial infarction (STEMI) undergoing primary PCI'. Should be administered with aspirin and clopidogrel. Administered by injection or infusion. The recommended dose is an IV bolus of 0.75 mg/kg body weight followed immediately by an IV infusion at a rate of 1.75 mg/kg body weight/hour for at least the duration of the procedure. May be continued for up to 4 hours after PCI according to clinical need. A reduced dose infusion of 0.25 mg/kg/hour may be continued for 4–12 hours as clinically needed. Assuming one 250 mg vial per patient, the acquisition cost is £310.00 (excluding VAT) (BNF 61, March 2011)	No change, (BNF62, Sept 2011)

Details of new products

Drug (manufacturer)	Details (phase of development, expected launch date,)
None identified	N/A

Bivalirudin

Trial name and registration number	Details
Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX MATRIX NCT01433627	Status: Not yet recruiting Method: randomised, single blind Expected completion: December 2015 Phase IV Purpose: to compare intended trans-radial versus trans-femoral intervention and bivalirudin monotherapy versus current European standard of care.
Femoral Versus Radial Access for Primary PCI SAFARI-STEMI NCT01398254	Status: recruiting Method: randomised, open label Expected completion: December 2014 Phase III Purpose: to address the bleeding differences between Transradial access (TRA) and Transfemoral access, using bivalirudin in the two groups

Trial name and registration number	Details
European Ambulance Acute Coronary Syndrome (ACS) Angiography Trial EUROMAX NCT01087723	Status: recruiting Method: randomised, open label Expected completion: December 2014 Phase III Purpose: To show that the early administration of bivalirudin improves 30 day outcomes when compared to the current standard of care in patients with ST segment elevation Acute Coronary Syndrome (STE-ACS), intended for a primary Percutaneous Coronary Intervention (PCI) management strategy, presenting either via ambulance or to centres where PCI is not performed.
Efficacy Study of Combined Prasugrel and Bivalirudin Versus Clopidogrel and Heparin in Myocardial Infarction (BRAVE-4 NCT00976092	Status: recruiting Method: randomised, parallel assignment, single blind Expected completion: July 2013 Phase IV Purpose: Randomized Trial of Prasugrel Plus Bivalirudin vs. Clopidogrel Plus Heparin in Patients With Acute STEMI

Additional information

TA52 (section 7.4) cited the ongoing Myocardial Infarction National Audit Project (MINAP). For up to date information see:

National Institute for Cardiovascular Outcomes Research (Sept 2011) Myocardial Ischaemia National Audit Project Tenth Public Report.

Appendix 3 – Implementation submission

Implementation feedback - review of technology appraisals: report for guidance executive

Technology Appraisal	**TA52; Myocardial infarction - thrombolysis**
Implementation input required by date	**12/09/2011**

1. Routine healthcare activity data

1.1 Hospital Pharmacy Audit Index (HPAI)

Data showing trends in prescribing cost and volume from hospital pharmacies are presented below in figures 1 and 2. Estimated costs are calculated by IMS using the drug tariff and other standard price lists. Many hospitals receive discounts from suppliers and this is not reflected in the estimated cost.

Figure 1 Trend in cost of prescribing alteplase, reteplase, streptokinase, tenecteplase in hospital pharmacies in England

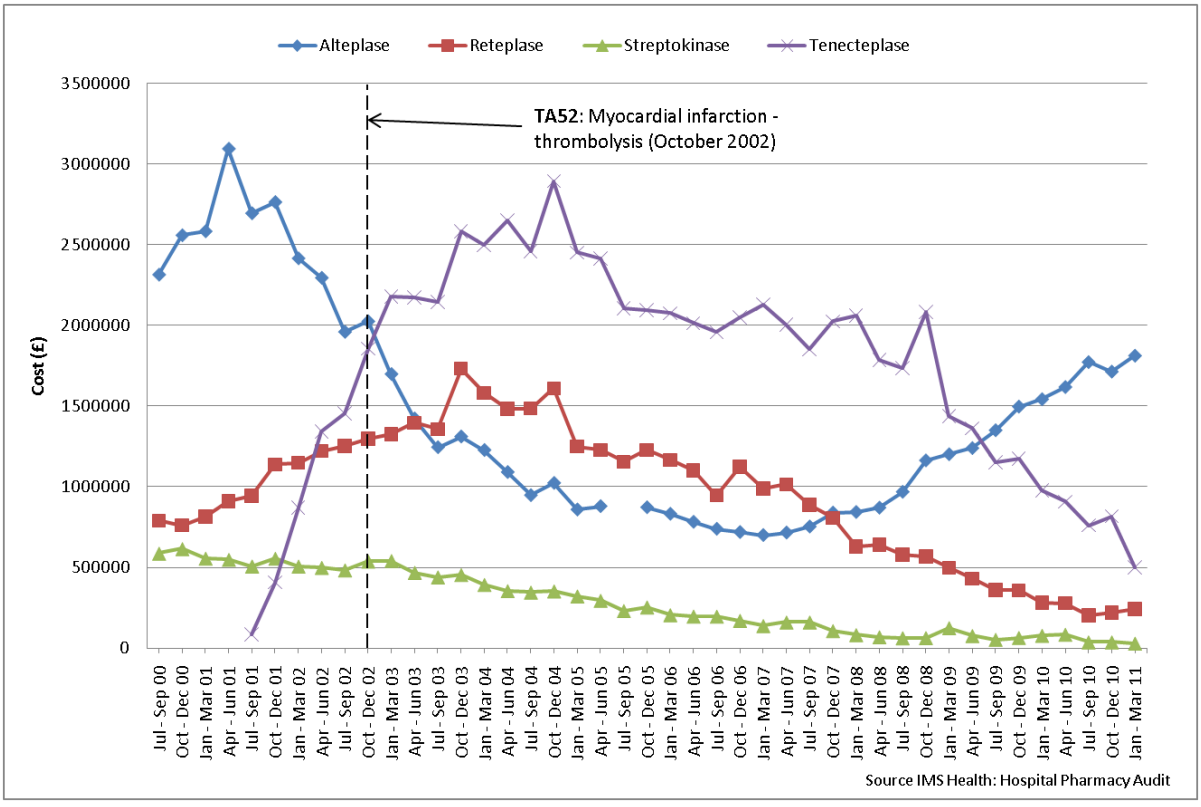
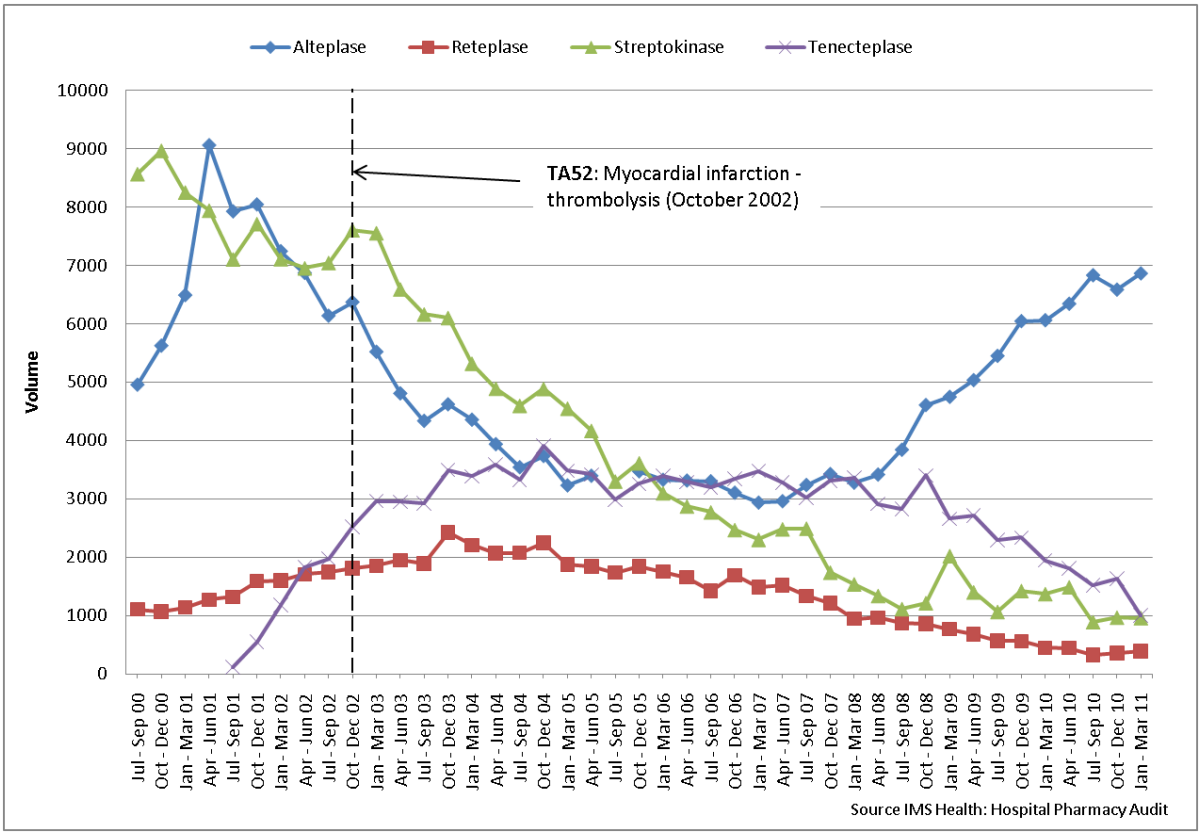


Figure 2 Trend in volume of prescribing alteplase, reteplase, streptokinase, tenecteplase in hospital pharmacies in England



2. Implementation studies from published literature

Information is taken from the ERNIE website.

Nothing to add at this time.

3. Qualitative input from the field team

The implementation field team have recorded the following feedback in relation to this guidance:

Nothing to add at this time.