NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA210; Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of Technology Appraisal No. 90)

This guidance was issued in December 2010.

The review date for this guidance is July 2013.

1. Recommendation

The guidance should be transferred to the 'static guidance list'. That we consult on this proposal.

2. Original remit(s)

TA210: To review and update if necessary the Institute's guidance on the clinical and cost-effectiveness of clopidogrel and modified-release dipyridamole, within their licensed indications, for the prevention of occlusive vascular events in individuals with established peripheral arterial disease, or with a history of myocardial infarction, ischaemic stroke, or transient ischaemic attacks.

3. Current guidance

This guidance applies to people who have had an occlusive vascular event, or who have established peripheral arterial disease. For people who have had a myocardial infarction, this guidance follows on from the recommendations for clopidogrel in combination with low-dose aspirin in NICE clinical guidelines 48 and 94. This guidance does not apply to people who have had, or are at risk of, a stroke associated with atrial fibrillation, or who need treatment to prevent occlusive events after coronary revascularisation or carotid artery procedures.

1.1 Clopidogrel is recommended as an option to prevent occlusive vascular events:

- for people who have had an ischaemic stroke or who have peripheral arterial disease or multivascular disease **or**
- for people who have had a myocardial infarction only if aspirin is contraindicated or not tolerated.

1.2 Modified-release dipyridamole in combination with aspirin is recommended as an option to prevent occlusive vascular events:

- for people who have had a transient ischaemic attack **or**
- for people who have had an ischaemic stroke only if clopidogrel is contraindicated or not tolerated.

1.3 Modified-release dipyridamole alone is recommended as an option to prevent occlusive vascular events:

- for people who have had an ischaemic stroke only if aspirin and clopidogrel are contraindicated or not tolerated **or**

- for people who have had a transient ischaemic attack only if aspirin is contraindicated or not tolerated.

1.4 Treatment with clopidogrel to prevent occlusive vascular events should be started with the least costly licensed preparation.

1.5 People currently receiving clopidogrel or modified-release dipyridamole either with or without aspirin outside the criteria in 1.1, 1.2 and 1.3 should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

4. Rationale[1]

There is little new evidence for the treatments as specified in the recommendations and that which there is agrees with the evidence submitted as part of the TA210 appraisal. The new evidence identified will not lead to a change in the recommendations of the original guidance.

5. Implications for other guidance producing programmes

TA210 overlaps with the NICE clinical guideline 'secondary prevention in primary and secondary care for patients following a myocardial infarction'. This guideline is currently being updated and the new recommendations cross refer to TA210. CCP supports the suggestion that this is transferred to the static list.

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 February 2008 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.

6. Summary of evidence and implications for review

The manufacturers of clopidogrel and dipyridamole have not made any changes to the current marketing authorisations or indicated that they are planning to extend the current marketing authorisations. It does not appear that any relevant new interventions or comparators have come to market since the original guidance was issued.

[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

Literature searches identified a number of new studies which have been published since the original guidance, of which 5 were not relevant, a study of 2 Phase III studies (Uchiyama, 2009) did not use a comparator identified in the scope, but instead compared clopidogrel with ticlopidine, 1 study was a single blind pilot study (Serebruandy, 2008), 2 studies did not aim to assess efficacy of the interventions, the ASCET trial aimed to assess the affect of high on-aspirin residual platelet activity on patients receiving clopidogrel (Alf-Age, 2012) and 1 was a meta-analysis of 14 RCTs which aimed to evaluate the role of polymorphisms in patients receiving clopidogrel (Singh, 2012).

Studies comparing technologies (n=1)

In TA210 the Committee had evidence from 1RCT (The PRoFESS trial) comparing clopidogrel with dipyridamole and considered that it had not shown that clopidogrel provided greater benefits than modified-release dipyridamole plus aspirin or that modified-release dipyridamole plus aspirin provided greater benefits than clopidogrel. A new RCT (Sacco, 2008) published since the original guidance compared dipyridamole with clopidogrel, and also concluded that there is no evidence that either of the two treatments is superior to the other.

Studies evaluating clopidogrel (n=3)

A Cochrane review (Hankey, 2009) identified 1 RCT comparing clopidogrel with aspirin among people with high vascular risk. The study found clopidogrel was more effective than aspirin in preventing vascular events.

A systematic review (Palacio, 2012) of 12 RCTs evaluated the effect of clopidogrel on mortality in people with vascular disease or vascular risk. The study found the addition of clopidogrel to aspirin had no overall effect on mortality but reduced the incidence of myocardial infarction and increases fatal bleeding.

A systematic review and meta-analysis of 7 RCTs (Zhou, 2012) evaluating the effect of aspirin in combination with clopidogrel in people with vascular disease found clopidogrel plus aspirin reduced the risk of major cardiovascular events compared with aspirin or clopidogrel mono-therapy but increased the risk of major bleeding events.

Studies evaluating dipyridamole (n=2)

A meta-analysis (Halkes, 2008) of 5 RCTs in people who have had TIA or stroke found the combination of aspirin and dipyridamole was more efficacious than aspirin alone across all risk subgroups.

A meta-analysis (Verro, 2008) of RCTS in people with stroke and TIA, found the combination of aspirin and dipyridamole was more efficacious than aspirin alone.

Conclusion

The new evidence identified is not likely to lead to a change in the recommendations of the original guidance.

7. Implementation

A submission from Implementation is included in Appendix 3. Since the original guidance the published, it appears that NICE guidance is being adhered to and current practice has not significantly changed.

8. Equality issues

No equalities issues were raised in the original guidance

GE paper sign off: Frances Sutcliffe, Associate Director, 7 June 2013

Contributors to this paper:

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Project Manager: Andrew Kenyon

CPP input Phil Alderson

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.	No, as none of the ongoing CGs cover the full remit of this TA
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

Options	Consequence	Selected – 'Yes/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.	Yes

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

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

ii. 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

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

iv. 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

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

Appendix 2 – supporting information

Relevant Institute work

Published

Technology Appraisal TA80; Clopidogrel in the treatment of non-ST-segment-elevation acute coronary syndrome. Issued July 04. In April 2010 the review decision was as follows: "Recommendations 1.1 and 1.2 of this guidance have been updated by recommendations 1.3.4 to 1.3.8 in Unstable angina and NSTEMI: the early management of unstable angina and non-ST-segment-elevation myocardial infarction (NICE clinical guideline 94). … Recommendation 1.3 has been incorporated into NICE clinical guideline 94 and is classed as static guidance. This will preserve the funding direction associated with this recommendation in the technology appraisal."

Technology Appraisal TA94; Statins for the prevention of cardiovascular events in patients at increased risk of developing cardiovascular disease or those with established cardiovascular disease. Issued January 2006. Review decision October 2011: "the guidance should be updated within a review of the NICE guideline CG67; Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease"

Technology Appraisal TA223; Cilostazol, naftidrofyryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease. Issued May 2011.Review date: May 2014.

Clinical Guideline CG48; Secondary prevention in primary and secondary care for patients following a myocardial infarction. Issued May 2007. Review decision February 2011: update the guidance. Expected publication date: November 2013.

Clinical Guideline CG67; Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. Issued May 2008. An update is in progress, the expected date of issue is July 2014.

Clinical Guideline CG94; Unstable angina and NSTEMI: the early management of unstable angina and non-ST-segment-elevation myocardial infarction. Issued March 2010. Review decision March 2013: "It has been decided not to update this guideline at this stage. The guideline should cross refer to a new Technology Appraisal (TA236)."

Clinical Guideline CG127; Hypertension: clinical management of primary hypertension in adults. Issued August 2011.

NICE Pathway: Hypertension. Last updated March 2013.

NICE Quality Standard QS28; Hypertension. Issued March 2013.

Clinical Guideline CG147; Lower limb peripheral arterial disease: Diagnosis and management. Issued August 2012.

NICE Pathway: Lower limb peripheral arterial disease. Last updated February 2013.

NICE Quality Standard: Peripheral arterial disease. In progress. Expected date of issue: February 2014.

Clinical Guideline CG68; Diagnosis and initial management of acute stroke and transient ischaemic attack (TIA). Issued July 2008. Review decision July 2012: not to update at this time. However, a number of relevant recommendations were included in this review decision, including the following:

"One recent, updated Technology Appraisal was identified: TA 210 Vascular disease - clopidogrel and dipyridamole (2010). The guideline (CG68) should be amended to align it with the changes in the updated TA 210 that alter recommendations with regard to these pharmacological treatments."

NICE Pathway: Stroke. Last updated: January 2013.

NICE Quality Standard QS2 Stroke. Issued June 2010.

Details of changes to the indications of the technology

Indication considered in original appraisal	**Proposed indication (for this appraisal)**
"Clopidogrel … has a marketing authorisation 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'." (TA210)	Unchanged.
"Modified-release dipyridamole has a marketing authorisation for the 'secondary prevention of ischaemic stroke and transient ischaemic attacks either alone or in conjunction with aspirin'."	Unchanged.

Details of new products

Drug (manufacturer)	**Details (phase of development, expected launch date,)**
Ticagrelor (AstraZeneca) secondary prevention of thrombotic events.	[redacted]

Drug (manufacturer)	Details (phase of development, expected launch date,)
	[redacted]
Vorapaxar (Merck Sharp & Dohme) for secondary prevention of CV events.	Phase III trial is completed and published (TRA-2P-TIMI 50 study published in N Engl J Med 2012; 366:1404-1413). There have been two subgroup analyses published since then – see the ClinicalTrials.gov page for all three links.

Registered and unpublished trials

Trial name and registration number	Details
Randomized Controlled Trial to Explore Interaction Between Aspirin and Clopidogrel in Stable Patients With Previous Myocardial Infarction or Coronary Artery Stent. NCT01341964	Phase IV, currently recruiting. Enrollment: 300 Estimated primary completion date: April 2013.
A Randomized, Double-blind, Parallel Group, Multicentre Phase IIIb Study to Compare Ticagrelor With Clopidogrel Treatment on the Risk of Cardiovascular Death, Myocardial Infarction and Ischemic Stroke in Patients With Established Peripheral Artery Disease (EUCLID Examining Use of tiCagreLor In paD). NCT01732822	Phase III, currently recruiting. Enrollment: 11500 Estimated primary completion date: January 2016.
Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) Trial. NCT00991029	Phase III, currently recruiting. Enrollment: 4150 Estimated primary completion date: June 2016.
Stenting vs. Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis. NCT00576693	Phase III, ongoing not recruiting. Enrollment: 764 Estimated primary completion date: October 2013.

Trial name and registration number	Details
Is cessation of clopidogrel therapy associated with rebound of platelet activity in stable vascular disease patients? - a randomised double-blind placebo-controlled trial. ISRCTN77887299	Completion date is July 2011, but there is no trace of publication.

References

Alf- Age R (2012) High On-Aspirin Platelet Reactivity and Clinical Outcome in Patients With Stable Coronary Artery Disease: Results From ASCET (Aspirin Nonresponsiveness and Clopidogrel Endpoint Trial). *Journal of the American Heart Association. doi:10.1161/JAHA.;112.000703*

Halkes PH (2008) Dipyridamole plus aspirin versus aspirin alone in secondary prevention after TIA or stroke; a meta-analysis by risk. *Journal of Neurology, Neurosurgery and Psychiatry* 79(11); 1218-1223

Hankey GJ (2009) Thienopyridine derivatives (ticlopine, clopidogrel) versus aspirin for preventing stroke and other serious vascular events in high vascular risk patients. *Cochrane Database Syst Rev* 2009 (4); CD001246

Palacio S (2012) Effect of addition of clopidogrel to aspirin on mortality; systematic review of randomized trials, Stroke 43(8); 2157-62

Sacco RL (2008) Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med.359* (12); 1238-51

Serebruany VL (2008) Antiplatelet profiles of the fixed-dose combination of extended-release dipyridamole and low-dose aspirin compared with clopidogrel with or without aspirin in patients with type 2 diabetes and a history of transient ischemic attack: a randomized, single-blind, 30-day trial .*Clin Ther* 30 (2); 249-59

Singh M (2012) CYP2C19*2/ABCB1-C3435T polymorphism and risk of cardiovascular events in coronary artery disease patients on patients on clopidogrel: Is clinical testing helpful? *Indian Heart J* 64 (4); 341-52.

Uchiyama S (2009) The safety and efficacy of clopidogrel versus ticlopidine in Japanese stroke patients: combined results of two Phase III, multicenter, randomized clinical trials. *J Neuro*; 256 (6); 888-97

Verro P (2008) Aspirin plus dipyridamole versus aspirin for prevention of vascular events after stroke or TIA: a meta-analysis. *Stoke* 39 (4); 1358-63

Zhou YH (2012) Effects of combined aspirin and clopidogrel therapy on cardiovascular outcomes: a systematic review and meta-analysis. *PLoS One* 7(2); e31642

Appendix 3 – Implementation submission

Implementation feedback: review of NICE technology appraisal guidance 210

• NICE Technology Appraisal 210 Vascular disease - clopidogrel and dipyridamole
• Implementation input required by 17/04/2013
• Please contact Rebecca Lea regarding any queries rebecca.lea@nice.org.uk

Contents

Routine healthcare activity data

1.1 Hospital pharmacy audit index data

This section presents net ingredient cost (NIC) and volume of clopidogrel and dipyridamole prescribed and dispensed in hospitals in England.

Figure 1 Cost and volume of clopidogrel prescribed and dispensed in hospitals in England

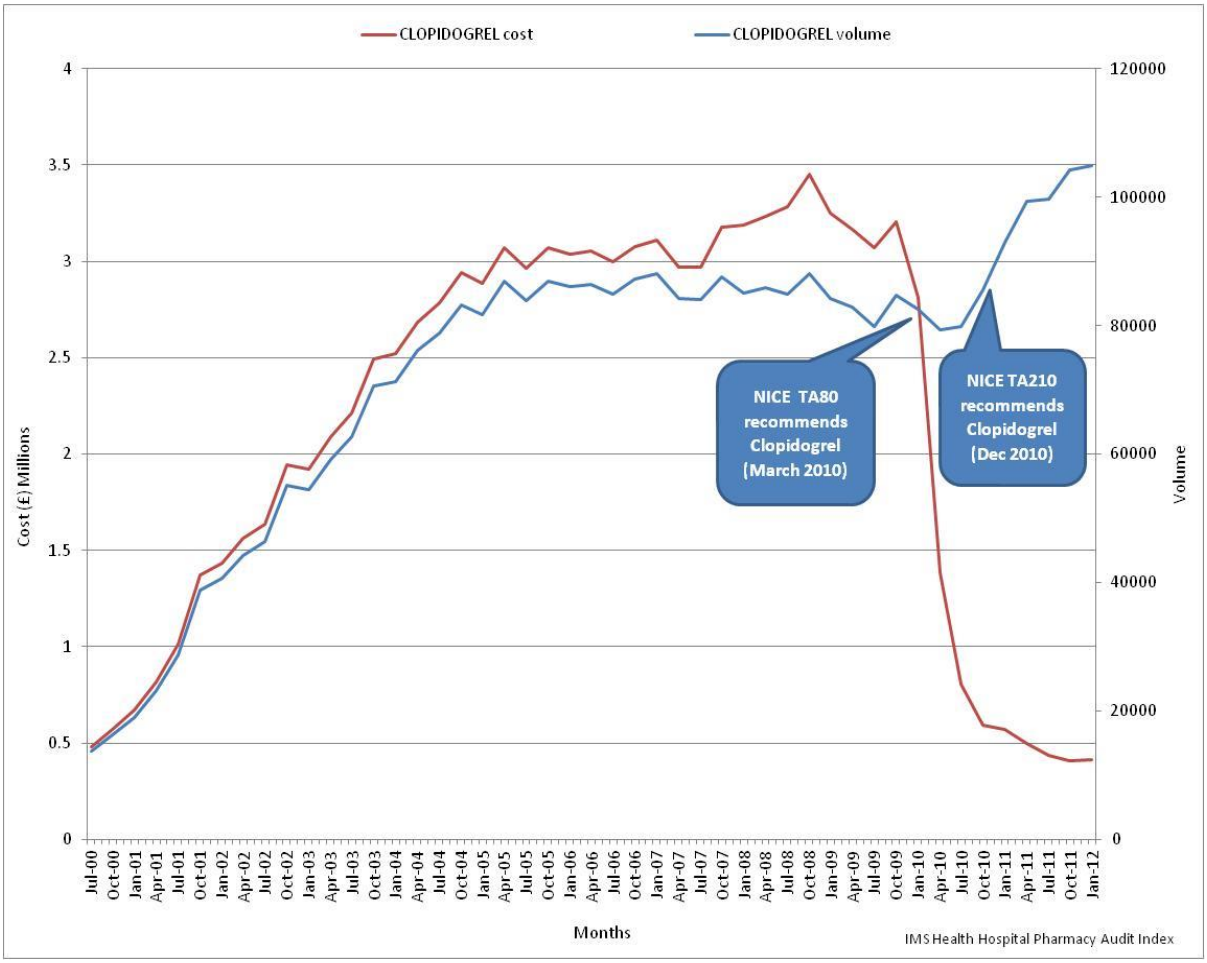
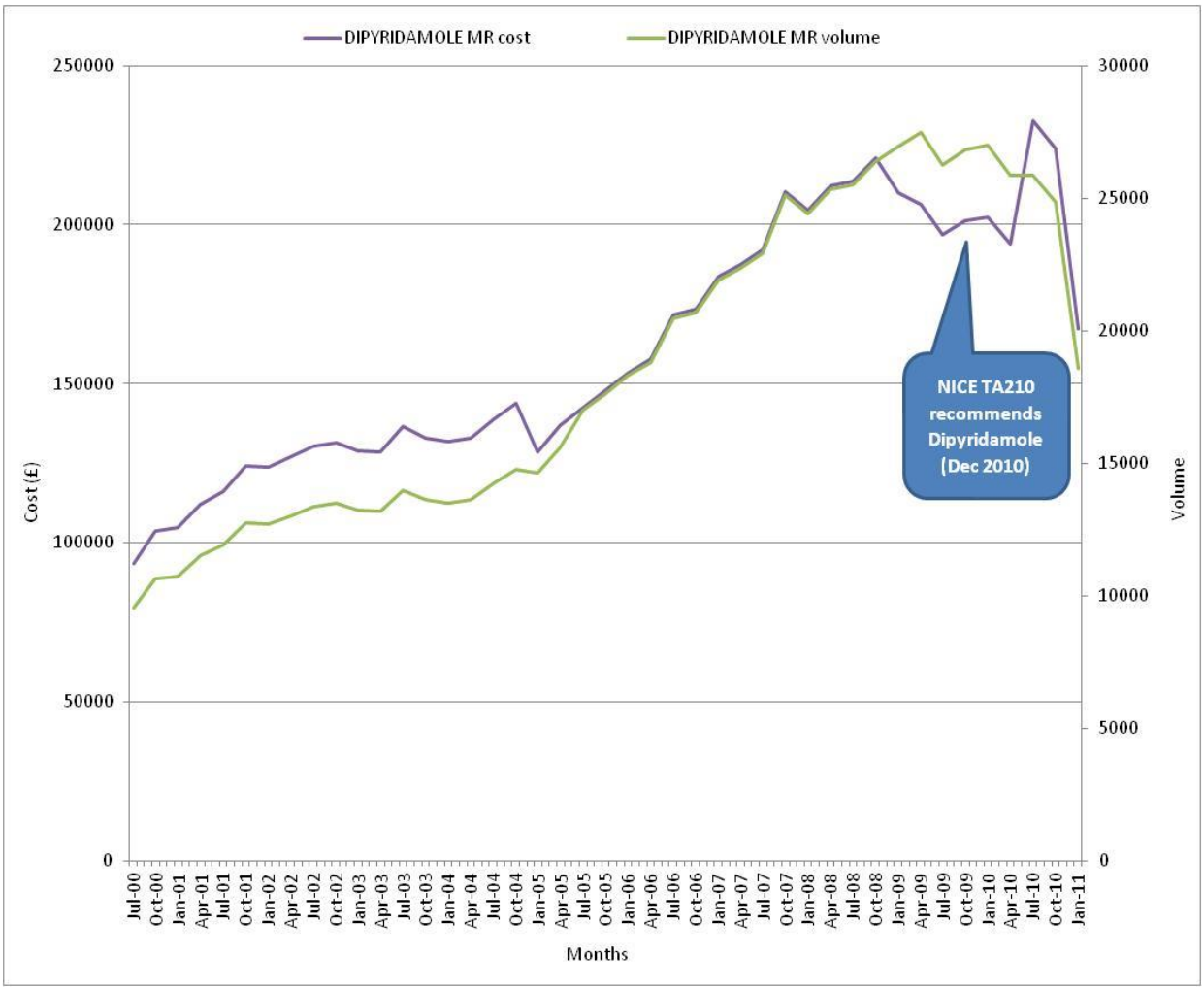


Figure 2 Cost and volume of dipyridmole prescribed and dispensed in hospitals in England

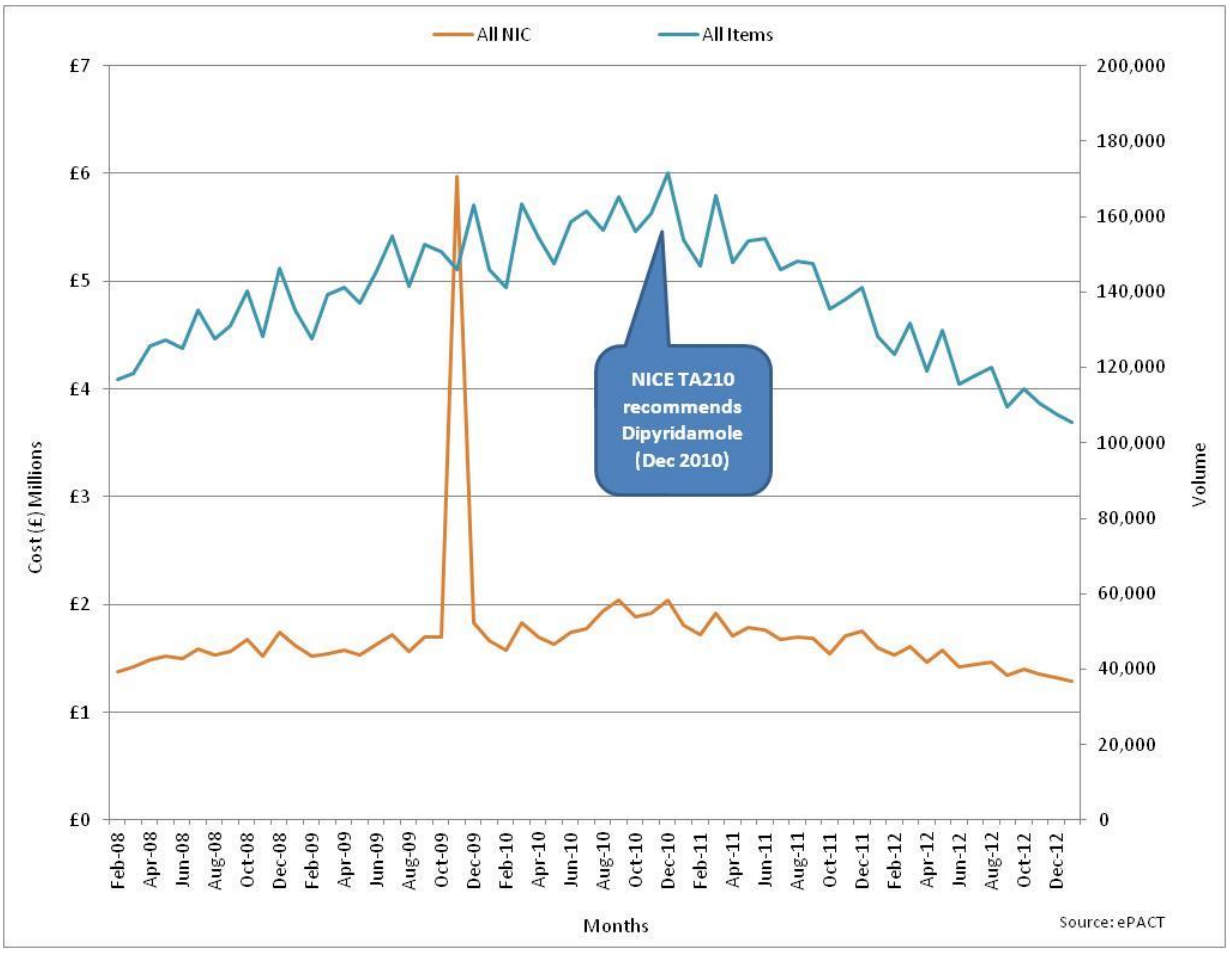


1.2 ePACT data

This section presents net ingredient cost and volume of Clopidogrel and Dipyridamole prescribed in primary care and in hospitals that have been dispensed in the community in England.

Figure 3 Cost and volume of clopidogrel prescribed in primary care and in hospitals that have been dispensed in the community in England

Figure 4 Cost and volume of dipyridamole prescribed in primary care and in hospitals that have been dispensed in the community in England



Implementation studies from published literature

Information is taken from the uptake database (ERNIE) website.
Nothing to add at this time.

Qualitative input from the field team

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

One person commented that they were champions of the guidance but were unclear of the process for development, and they felt there were individual interpretation and complexities of guidance such as clopidogrel 'from the last event'. Another person commented that regarding clopidogrel they had agreed a way of managing the 3 months treatment duration via one dispensing provider, but then the change to 12

month treatment made it more complex with primary care involved, and over prescribing with associated ill effects.
N.B. These comments are from 2006 and are likely to be of limited value.

Appendix A: Healthcare activity data definitions

Prescribing analysis and cost tool system

This information comes from the electronic prescribing analysis and cost tool (ePACT) system, which covers prescriptions by GPs and non-medical prescribers in England and dispensed in the community in the UK. The Prescription Services Division of the NHS Business Services Authority maintains the system. PACT data are used widely in the NHS to monitor prescribing at a local and national level. Prescriptions dispensed in hospitals or mental health units, and private prescriptions, are not included in PACT data.

Measures of prescribing

Prescription Items: Prescriptions are written on a prescription form. Each single item written on the form is counted as a prescription item. The number of items is a measure of how many times the drug has been prescribed.
Cost: The net ingredient cost (NIC) is the basic price of a drug listed in the drug tariff, or if not in the drug tariff, the manufacturer's list price.

Data limitations (national prescriptions)

PACT data do not link to demographic data or information on patient diagnosis. Therefore the data cannot be used to provide prescribing information by age and sex or prescribing for specific conditions where the same drug is licensed for more than one indication.

IMS HEALTH Hospital Pharmacy Audit Index (IMS HPAI)

IMS HEALTH collects information from pharmacies in hospital trusts in the UK. The section of this database relating to England is available for monitoring the overall usage in drugs appraised by NICE. The IMS HPAI database is based on issues of medicines recorded on hospital pharmacy systems. Issues refer to all medicines

supplied from hospital pharmacies: to wards; departments; clinics; theatres; satellite sites and to patients in outpatient clinics and on discharge.

Measures of prescribing

Volume: The HPAI database measures volume in packs and a drug may be available in different pack sizes and pack sizes can vary between medicines.
Cost: Estimated costs are also 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.
Costs based on the drug tariff provide a degree of standardization allowing comparisons of prescribing data from different sources to be made. The costs stated in this report do not represent the true price paid by the NHS on medicines. The estimated costs are used as a proxy for utilization and are not suitable for financial planning.

Data limitations

IMS HPAI data do not link to demographic or to diagnosis information on patients. Therefore, it cannot be used to provide prescribing information on age and sex or for prescribing of specific conditions where the same drug is licensed for more than one indication.