



## TARDIS INVESTIGATORS' BROCHURE

Safety and efficacy of intensive versus guideline antiplatelet therapy in high risk patients with recent ischaemic stroke or transient ischaemic attack: a randomised controlled trial

<b>Short title:</b>	<u>T</u> riple <u>A</u> ntiplatelets for <u>R</u> educing <u>D</u> ependency after <u>I</u> schaemic <u>S</u> troke.
<b>Acronym:</b>	TARDIS
<b>EudraCT number:</b>	2007-006749-42
<b>ISRCTN:</b>	ISRCTN47823388
<b>REC reference:</b>	08/H1102/112
<b>Trial Sponsor:</b>	University of Nottingham
<b>Sponsor reference:</b>	31350 and 08093
<b>Funding Source:</b>	British Heart Foundation (start-up) Health and Technology Assessment Board (main)

## 1 BACKGROUND INFORMATION

Stroke is devastating to patients, carers and society through high mortality (~1-in-3 patients by 1 year), morbidity (dependency in ~1-in-3 patients often needing long-term care) and cost (6% of NHS spend). Both stroke incidence and prevalence will increase as the UK population ages. Following stroke or transient ischaemic attack (TIA), the risk of recurrence is high, especially immediately after the event (~10% over weeks) after which it falls (~40% by 5 years). Importantly, recurrent strokes are usually more severe than earlier events. The Government has emphasised stroke as a clinical 'marker' condition and has supported its research importance through funding the UK Stroke Research Network (Philip Bath is the Prevention Director, Tom Robinson and Hugh Markus are Local Research Network Directors for Trent and South-East respectively).

TIA ('mini stroke') is a sudden, focal neurologic deficit that lasts for less than 24 hours (typically 10 minutes to 1 hour), is presumed to be of vascular origin, and is confined to an area of the brain or eye perfused by a specific artery. (A tissue-based definition<sup>1</sup> is not used since MR scanning is not universally available around the world in the participating sites). TIAs are important because they are a key risk factor for subsequent stroke. Patients presenting with specific TIA features are at particularly high risk of a subsequent stroke, as assessed by the ABCD<sup>2</sup> score<sup>2</sup>: age  $\geq 60$  years (1 point); blood pressure  $\geq 140/90$  mmHg (1); clinical symptoms of unilateral weakness, (2) or speech impairment without weakness (1); duration  $\geq 60$  minutes (2), or  $\geq 10$  minutes (1); and diabetes (1)<sup>2</sup>. The score ranges from 0 to 7 and the risk of stroke over the next 90 days increases exponentially: score 0 - risk <1%, 1 - 2%, 2 - 4%, 3 - 4.5%, 4 - 8%, 5 - 12%, 6 - 17%, and 7 - 22%<sup>2</sup>. Other groups have now validated the score. An important caveat is that data for the training databases used to derive and validate the ABCD<sup>2</sup> score were collected up to 1998 and 2005 respectively so the absolute risk rates of stroke now are likely to be lower as enhanced secondary prophylaxis with antithrombotics, BP and lipid lowering are now standard practice.

The risk of recurrence can be reduced, but not abolished with life style changes, carotid endarterectomy (large artery stroke) and drug interventions: antihypertensives and statin therapy. While oral anticoagulants are established for cardioembolic stroke<sup>3</sup>, other patients with ischaemia (the majority) need antiplatelets<sup>4-5</sup>. These interventions are cost-effective. The archetypal antiplatelet, aspirin (inhibitor of cyclooxygenase), reduces recurrence (relative risk reduction, RRR) by 17% in patients with prior stroke or TIA<sup>6</sup>. Clopidogrel (adenosine diphosphate [ADP] receptor antagonist) was slightly more efficacious than aspirin in CAPRIE<sup>7</sup>. Importantly, the absolute difference in efficacy between A and C was highest in patients with prior stroke or MI<sup>8</sup>. Dipyridamole (inhibits red cell uptake of adenosine) reduced recurrence by 16% in comparison with placebo in ESPS II<sup>9</sup>. Evidence now suggests that stroke prevention is dependent on the number of antiplatelets, e.g. aspirin and dipyridamole reduces events by 23% in comparison to aspirin (or dipyridamole) alone without increasing the risk of bleeding, as seen in ESPS II and ESPRIT<sup>9-10</sup>. As with clopidogrel alone, the difference in efficacy between aspirin and dipyridamole versus aspirin alone was largest in patients with highest baseline risk<sup>11</sup>. Similarly, aspirin and dipyridamole was superior to aspirin in cardiac patients (CURE, CREDO)<sup>12-13</sup> but not in CHARISMA<sup>14</sup>, probably because the apparent benefit in those with prior stroke or MI (high risk of recurrence) was diluted by lack of efficacy in those with no previous vascular events (low risk). The risk of bleeding with aspirin and dipyridamole vs. aspirin was 30-40% higher in these 3 trials. The MATCH trial (aspirin and clopidogrel vs. clopidogrel) and SPS (aspirin + clopidogrel vs. aspirin) trial found that dual aspirin and clopidogrel therapy also increased bleeding<sup>15-16</sup>.

On the basis of this information and taking account of the prices of branded clopidogrel and dipyridamole-ER (£37 (UK price) and £10 per month respectively), UK NICE recommended

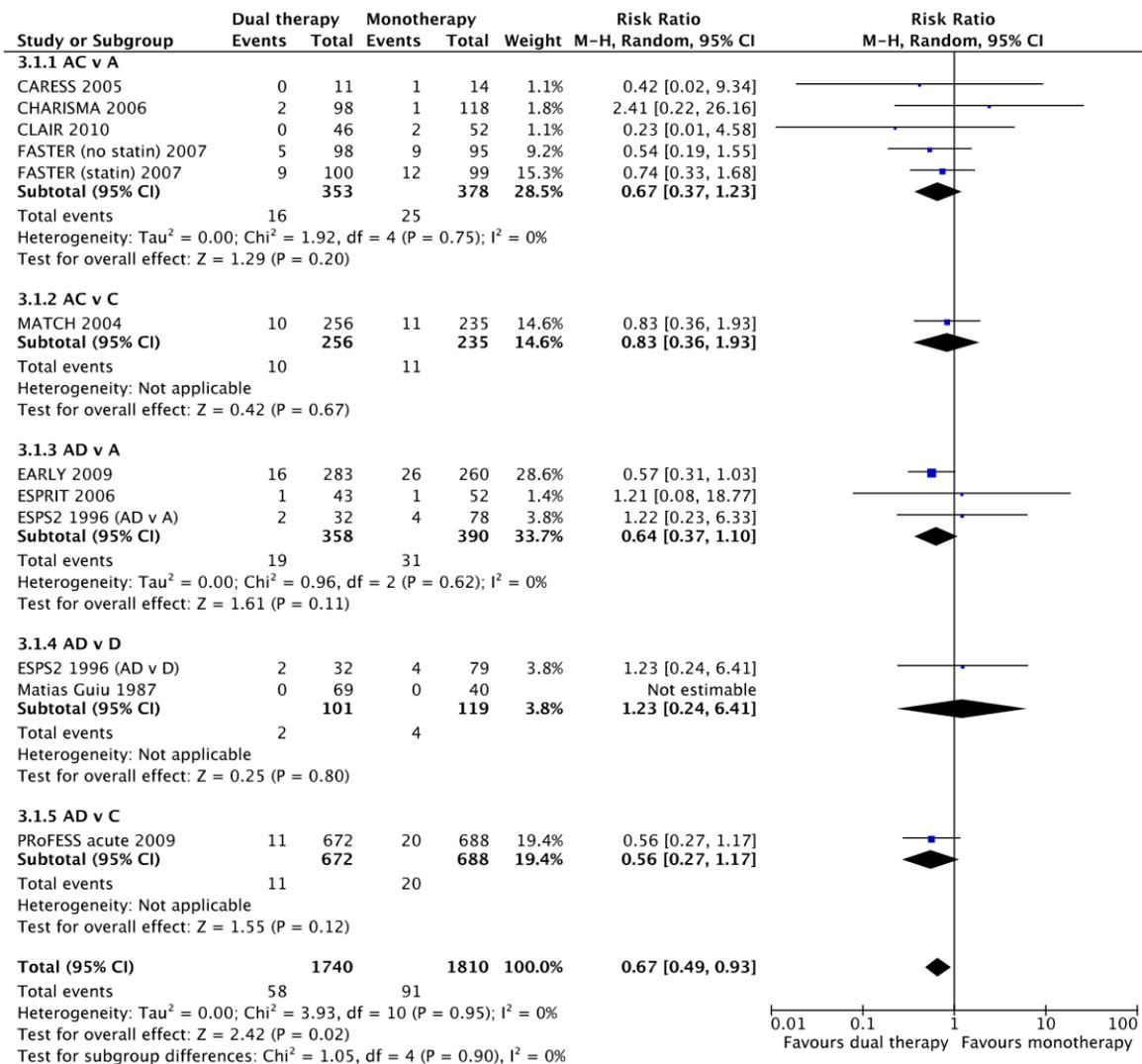
in 2005 that patients should take combined aspirin-dipyridamole after ischaemic stroke or TIA (TA90). In late 2010, NICE updated its recommendation to aspirin and dipyridamole for TIA, and clopidogrel for ischaemic stroke (TA210), this taking account of the massive drop in price of clopidogrel (£3.40, as a generic, British National Formulary [BNF] 61) but lack of significant randomised data and license for clopidogrel in patients with TIA. Former and current guidelines have not recommended dual aspirin and clopidogrel because of increased bleeding<sup>17-18</sup>. The preference for dual aspirin and dipyridamole or clopidogrel alone over aspirin alone is also recommended by the European Stroke Organisation in its 2008 guidelines (Bath was Co-Chair of the Prevention section)<sup>19</sup>. In contrast, the 2011 American Stroke Association secondary prevention guidelines still give equal recommendations for aspirin (50-325mg daily) alone, dual aspirin and dipyridamole, and clopidogrel (75mg daily) alone<sup>20</sup>, thereby ignoring the results of recent trials<sup>7, 9-10, 21</sup>.

The above data for stroke reflect long-term prophylaxis, a very different situation from the situation immediately after an event when the risk of recurrence is much higher. Conventional acute antiplatelet therapy is based on aspirin alone for ischaemic stroke reflecting the results of the IST-1 and CAST megatrials<sup>22-23</sup> but the effect size is small (absolute risk reduction ~1.1%); until recently the acute treatment of TIA had not been investigated. Since risk of recurrence falls quickly after stroke or TIA, intensive antiplatelet specific treatment is only likely to be needed for a short period so that the exposure-time to hazard (mainly bleeding) is limited. While clopidogrel-based dual therapy has not proved effective/safe in long-term stroke prophylaxis, early and short-term dual therapy may be useful, at least after TIA/minor stroke, as suggested by trials (FASTER, EARLY, PROfESS early<sup>24-26</sup>) and observational studies (EXPRESS, SOS<sup>27-28</sup>). In FASTER (n=392), 90 days of aspirin and clopidogrel (vs. aspirin) showed a trend to reduce stroke by absolute 3.7% (not significant [NS]) and increased symptomatic intracerebral haemorrhage (sICH) by absolute 1% (NS) leading to a net absolute benefit of 2.7%<sup>24</sup>. Similarly, EARLY (n=543, acute ischaemic stroke/TIA) found a trend to reduced vascular events at day 90 with aspirin and dipyridamole (vs. aspirin, NS) but no effect on functional outcome<sup>25</sup>, a pattern of observations also seen with aspirin and dipyridamole (vs. clopidogrel) in the PROfESS early subgroup (n=1,360, mild acute ischaemic stroke)<sup>26</sup>.

In a meta-analysis of all trials comparing dual with mono- antiplatelet therapy in acute patients with stroke or TIA (including CARESS, CHARISMA, CLAIR, FASTER, EARLY, ESPRIT, ESPS-2, MATCH and PROfESS early<sup>9-10, 14-15, 24-26, 29-30</sup>), acute dual therapy versus monotherapy within 3 days of ictus significantly reduced subsequent vascular events<sup>24</sup>, stroke (ischaemic and haemorrhagic, **figure 1**), and composite vascular events (trend) (Geeganage & Bath; published *Stroke*). No significant differences were seen for MI, sICH, major bleeding or death (but there were few events, **table 1**). No heterogeneity existed in any analysis, suggesting that the composition of dual and monotherapy was not of primary importance. None of the trials were large enough (each <1,400) to show individual significant differences in stroke or vascular events. Importantly, the magnitude of effect appeared to decline with time from ictus so trials recruiting early have greater reductions in their point estimates (albeit non-significant because of small sample size) than those recruiting later: range of odds ratio (OR) for stroke, early, OR 0.51 to 0.71 (EARLY, FASTER, PROfESS early); later, OR 0.83 to 2.44 (CHARISMA, MATCH).

	Stroke, MI, Vascular death	Stroke, TIA, ACS, all death	Stroke recurrence	MI	sICH	Major bleed	Death
Odds Ratio	0.75	<b>0.71</b>	<b>0.67</b>	0.71	1.39	2.09	1.34
95% Confidence intervals	0.56-0.99	<b>0.56-0.91</b>	<b>0.49-0.93</b>	0.25-2.03	0.22-8.75	0.86-5.06	0.76-2.34

**Table 1.** Meta-analysis of 12 trials of dual vs mono antiplatelets in patients with acute ischaemic stroke/TIA. Data were obtained from trialists for patients recruited within 72 hours of ictus (Geeganage & Bath; submitted *Stroke*).



**Figure 1.** Meta-analysis of effect of dual versus mono- antiplatelet therapy on stroke using data from 10 trials in patients with acute stroke or TIA. As compared with monotherapy, dual therapy reduced stroke: OR 0.67 (0.49-0.93). No heterogeneity was present suggesting that the composition of dual and monotherapy was less important than the number of antiplatelet agents (Geeganage and Bath; published *Stroke*).

Current stroke prevention is far from perfect: stroke is heterogeneous in type (ischaemic vs. haemorrhage; lacunar vs. cardioembolic vs. large artery), severity and outcome; treatments reduce, not abolish, events ('treatment failure'); and patients may be (relatively) insensitive to treatment ('treatment resistance', as identified for aspirin and clopidogrel<sup>31</sup>).

If aspirin and dipyridamole is superior to aspirin for long-term secondary prevention<sup>9-10, 32</sup>, and aspirin and clopidogrel is probably superior to aspirin in acute minor stroke/TIA<sup>24, 27</sup>, then triple antiplatelet therapy (aspirin+dipyridamole+clopidogrel) may be better still, providing the risk of recurrence is high and bleeding does not become excessive. In this respect, the risk of bleeding when adding clopidogrel to aspirin and dipyridamole is likely to be similar to that when adding clopidogrel to aspirin since dual aspirin and dipyridamole does not increase bleeding over aspirin<sup>9-10</sup>. We have performed a series of 'proof-of-concept' laboratory and clinical studies investigating this approach<sup>33-37</sup>. In-vitro

studies found that triple therapy was most effective in inhibiting aggregation, platelet-leucocyte conjugation, and leucocyte activation<sup>33-35</sup>. In multiway crossover phase I and II trials comparing short-term administration of mono, dual and triple antiplatelet therapies, the combination of aspirin and clopidogrel, with or without dipyridamole, was most potent in inhibiting platelet function ex-vivo in both normal volunteers (n=11) and patients with previous stroke/TIA (n=11)<sup>36-37</sup>.

In the only parallel group trial of triple therapy in patients with stroke, triple therapy was feasible to administer (vs. aspirin, phase II trial, n=17) for up to 24 months<sup>38</sup>. [The comparator of aspirin was chosen since this was the UK standard of care at trial start. The trial was stopped early on publication of ESPRIT<sup>10</sup> confirming the superiority of dual aspirin and dipyridamole over aspirin, i.e. it was unethical to continue patients on aspirin alone.] Predictably, there was a non-significant trend to increased bleeding with triple therapy vs. aspirin. Although unintended, the patients were at low risk of recurrence (young/recruited months after the event/many lacunar strokes), a problem also seen in MATCH and CHARISMA<sup>14-15</sup>. Future trials of triple antiplatelet therapy need to target patients at high risk of recurrence so that benefit is likely to outweigh hazard. We have also used chronic triple antiplatelet therapy in clinical practice in patients at high risk of recurrence, defined as recurrence on dual antiplatelet therapy<sup>39</sup>.

Short-term randomised controlled trials of triple antiplatelet therapy have been reported in patients with acute coronary syndromes or to cover stent insertion (25 studies, 17,383 patients). In our published meta-analysis and in comparison with dual antiplatelet therapy, GP IIb/IIIa based triple therapy reduced Myocardial Infarction (MI) in Non ST Elevation MI (NSTEMI) patients (OR 0.70, 95% CI 0.56-0.88) and ST Elevation MI (STEMI) (OR 0.26, 95% CI 0.17-0.38) patients, and vascular events in NSTEMI (OR 0.69, 95% CI 0.55-0.86) and STEMI (OR 0.39, 95% CI 0.30-0.51) patients<sup>40</sup>. Death was also reduced after STEMI; major bleeding and transfusions were non-significantly increased and were few in number such that benefit outweighed hazard in absolute numbers of patients. The number of stroke events were too few to assess any trends, and insufficient or zero data were available for other antiplatelets (cilostazol, clopidogrel, dipyridamole)<sup>40</sup>.

The proposed trial comes from members of the UK Stroke Research Network (SRN) Prevention Clinical Study Group (Philip Bath, Stan Heptinstall, Hugh Markus, Graham Venables) and is predicated on: (i) dual aspirin and dipyridamole is superior to aspirin after stroke; (ii) dual aspirin and dipyridamole or clopidogrel is the standard of care in the UK (NICE); (iii) dual aspirin and clopidogrel is superior to aspirin in patients with ischaemic heart disease; (iv) some patients still 'fail' on aspirin and dipyridamole; and (v) adding clopidogrel to aspirin may be useful in high-risk patients, i.e. immediately after TIA/minor stroke. The results of our experimental medicine research (laboratory, phase I/II trials) and routine clinical use support this approach<sup>33-37</sup>. Hence, triple therapy may be better still in high-risk patients provided benefit exceeds bleeding<sup>41</sup>.

## **1.1 DETAILS OF INVESTIGATIONAL MEDICINAL PRODUCTS (IMP)**

### **1.1.1 Description**

#### **1.1.1.1 Aspirin (Asp)**

International Non-Proprietary Name (INN): Aspirin

Chemical Abstracts Series (CAS) number: 50-78-2

Dose: Loading dose 300mg, then 75mg od.

Route: Enteral (including via nasogastric tube – dispersible or crushed tablets can be used) or rectal route.

For chemical and pharmacological properties, see summary of medical product characteristics (SmPC) at <http://www.medicines.org.uk/emc/>.

The IMP is defined by active substance only, so all authorised brands may be used.

### **1.1.1.2 Dipyridamole (Dip)**

INN: Dipyridamole

CAS number: 58-32-2

Dose: 200mg modified release (MR), bd. Dysphagic patients with enteral access will take dipyridamole suspension 75mg tds. Patients with a headache from dipyridamole will have the dose weaned up from daily MR 200mg or standard release 75mg od to MR 200mg bd. Fixed dose combinations of A and D can also be used, e.g. Asasantin Retard (Aspirin 25mg, Dipyridamole 200mg MR, bd)

Route: Enteral (including via nasogastric tube).

For chemical and pharmacological properties SmPC at <http://www.medicines.org.uk/emc/>. The IMP is defined by active substance only, so all authorised brands in the UK can be used.

### **1.1.1.3 Clopidogel (Clop)**

INN: Clopidogrel

CAS number: 113665-84-2

Dose: Loading dose 300mg, then 75mg od.

Route: Enteral (including via nasogastric tube – crushed tablets can be used) or rectal route.

For chemical and pharmacological properties see SmPC at <http://www.medicines.org.uk/emc/>.

The IMP is defined by active substance only, so all authorised brands in the UK can be used.

## **1.1.2 Packaging and labelling**

Standard pharmacy supplies should be used as all IMPs have marketing authorisation and are to be used in accordance with such authorisation. Hospitals/pharmacies should choose their own supplier for the IMPs and should be packaged according to local policy. All IMPs for the TARDIS trial should be labeled separately and pharmacies at the recruiting centre must have a written procedure in place for dispensing trial medications. The information on the label should include the trial name, EudraCT number, description of contents, batch number, expiry date, and quantity. There should be space for insertion of the trial number, name of the participant and the date of dispensing on the label (see appendix K). Under exceptional circumstances (e.g. out of hours) where labeled IMPs are not available, trial sites may choose to use ward stock without separate labeling if agreed locally and approved by the pharmacy.

## **1.1.3 Storage, dispensing and return**

The IMPs must be stored in a secure location at room temperature (20°C to 25°C) with excursions permitted within 15°C to 30°C. Depending on local arrangement, this may be at the local pharmacy, the research department or the ward. Following recruitment and randomisation into the trial, the study treatment should be prescribed on the drug chart and the IMPs dispensed by the principal investigator/qualified designee. An accountability log for all IMPs should be maintained by the pharmacy and/or the research team and should include the following information: hospital number, participant initials, trial number, date dispensed, brand manufacturer, batch number, expiry date, quantity dispensed, quantity returned and initials of personnel who dispense and check the log. This should be completed for every participant who is randomised into the study. Accountability logs must be available for inspection during trial monitoring and/or audit and open to regulatory authorities inspection at any time. A sample label is provided (Appendix K).

## **1.1.4 Known Side Effects**

### **1.1.4.1 Aspirin**

Adverse reactions

- i. Bleeding: Aspirin prolongs bleeding time, and bleeding disorders, such as epistaxis, haematuria, purpura, ecchymoses, haemoptysis, gastrointestinal bleeding, haematoma and cerebral haemorrhage have been reported.
- ii. Blood and lymphatic system disorders - anaemia, haemolytic anaemia, hypoprothrombinaemia, thrombocytopenia, aplastic anaemia, pancytopenia, prolonged bleeding time, occult blood loss, elevated transaminase levels, agranulocytosis.
- iii. Gastrointestinal disorders - gastrointestinal bleeding, erosions, perforations or ulceration, which can occasionally be major (may develop bloody or black tarry stools, severe stomach pain and vomiting blood), gastrointestinal irritation (mild stomach pain, heartburn, vomiting and nausea). Fatalities have occurred.
- iv. Hepatic disorders - hepatitis (particularly in patients with SLE or connective tissue disease)
- v. Renal and urinary disorders – disturbances of renal function
- vi. Ear and labyrinth disorders - tinnitus.
- vii. Hypersensitivity reactions - rhinitis, urticaria, purpura, Stevens-Johnson syndrome, angio-oedema, asthma, worsening of asthma, bronchospasm.

Interaction with other medicinal products:

- i. Salicylates may enhance the effect of oral hypoglycaemic agents, phenytoin and sodium valproate.
- ii. They inhibit the uricosuric effect of probenecid and may increase the toxicity of sulphonamides.
- iii. Aspirin may potentiate the effect of heparin and increases the risk of bleeding with oral anticoagulants, antiplatelet agents and fibrinolytics.
- iv. The risk of gastrointestinal ulceration and bleeding may be increased when aspirin and corticosteroids are co-administered.
- v. Concurrent use of aspirin and other Non Steroidal Anti Inflammatory Drugs (NSAID) should be avoided. Use of two or more NSAID preparations increases the risk of serious gastrointestinal haemorrhage.
- vi. Concurrent administration of carbonic anhydrase inhibitors such as acetazolamide and salicylates may result in severe acidosis and increased central nervous system toxicity.
- vii. Alcohol may enhance the gastro-intestinal side effects of aspirin.
- viii. Patients using enteric-coated aspirin should be advised against ingesting antacids simultaneously to avoid premature drug release.
- ix. Selective Serotonin Reuptake Inhibitors (SSRI) may increase risk of gastrointestinal bleeding if coadministered.

#### **1.1.4.2 Dipyridamole**

Adverse reactions at therapeutic doses are usually mild.

- i. Bleeding: In very rare cases, increased bleeding during or after surgery has been observed.
- ii. Blood and lymphatic system disorders: Isolated cases of thrombocytopenia have been reported in conjunction with treatment with Dipyridamole.
- iii. Gastrointestinal disorders: Vomiting, diarrhoea and symptoms such as nausea, dyspepsia. These tend to occur early after initiating treatment and may disappear with continued treatment.
- iv. Cardiovascular: As a result of its vasodilating properties, dipyridamole may cause hypotension, hot flushes and tachycardia. Worsening of the symptoms of coronary heart disease such as angina and arrhythmias may occur.
- v. Central Nervous System Disorders: Dizziness, headache and myalgia may occur early after initiating treatment and may disappear with continued treatment.
- vi. Hypersensitivity reactions such as rash, urticaria, severe bronchospasm and angio-oedema have been reported.

## Interaction with other medicinal products:

- i. Dipyridamole increases the plasma levels and cardiovascular effects of adenosine. Adjustment of adenosine dosage should therefore be considered if use with dipyridamole is unavoidable.
- ii. Dipyridamole may increase the hypotensive effect of blood pressure lowering drugs.
- iii. Dipyridamole may counteract the anticholinesterase effect of cholinesterase inhibitors thereby potentially aggravating myasthenia gravis.

**1.1.4.3 Clopidogrel**

## Adverse Reactions

- i. Bleeding is the most common reaction reported and is mostly reported during the first month of treatment. Bleeding: some cases were reported with fatal outcome (especially intracranial, gastrointestinal and retroperitoneal haemorrhage); serious cases of skin bleeding (purpura), musculo-skeletal bleeding (haemarthrosis, haematoma), eye bleeding (conjunctival, ocular, retinal), epistaxis, respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), haematuria and haemorrhage of operative wound have been reported; cases of serious haemorrhage have been reported in patients taking clopidogrel concomitantly with acetylsalicylic acid or clopidogrel with acetylsalicylic acid and heparin.

In addition to clinical studies experience, the following adverse reactions have been spontaneously reported. Within each system organ class (MedDRA classification), they are ranked under heading of frequency. "Very rare" corresponds to <1/10,000. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

- ii. Blood and lymphatic system disorders: very rare; Thrombotic Thrombocytopenic Purpura (TTP) (1/200,000 exposed patients), severe thrombocytopenia (platelet count  $30 \times 10^9/l$ ), agranulocytosis, granulocytopenia, aplastic anaemia/pancytopenia, anaemia.
- iii. Immune system disorders: very rare; anaphylactoid reactions, serum sickness
- iv. Psychiatric disorders: very rare: confusion, hallucinations
- v. Nervous system disorders: very rare; taste disturbances
- vi. Vascular disorders: very rare; vasculitis, hypotension
- vii. Respiratory, thoracic and mediastinal disorders: very rare; bronchospasm, interstitial pneumonitis
- viii. Gastrointestinal disorders: very rare; pancreatitis, colitis (including ulcerative or lymphocytic colitis), stomatitis
- ix. Hepato-biliary disorders: very rare; acute liver failure, hepatitis
- x. Skin and subcutaneous tissue disorders: very rare; angioedema, bullous dermatitis (erythema multiforme, Stevens Johnson Syndrome, toxic epidermal necrolysis), rash erythematous, urticaria, eczema and lichen planus
- xi. Musculoskeletal, connective tissue and bone disorders: very rare; arthralgia, arthritis, myalgia.
- xii. Renal and urinary disorders: very rare; glomerulonephritis.  
Investigations: very rare; abnormal liver function test, blood creatinine increase

## Interaction with other medicinal products:

- i. Clopidogrel should not be co-administered with warfarin due to increased bleeding risk. Caution should also be taken with corticosteroids, NSAIDs, heparin and thrombolytics.
- ii. Patients entered into clinical trials with clopidogrel have received a variety of concomitant medications including diuretics, beta blockers, ACEI, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents

(including insulin), antiepileptic agents, hormone replacement therapy and GPIIb/IIIa antagonists without evidence of clinically significant adverse interactions.

## REFERENCES

1. Albers GW, Caplan LR, Easton JD, Fayad PB, Mohr JP, Saver JL, et al. Transient ischemic attack--proposal for a new definition.[see comment]. *New England Journal of Medicine*. 2002;347:1713-1716
2. Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet*. 2007;369:283-292
3. EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fibrillation after tia or minor stroke. *Lancet*. 1993;342:1255-1262
4. Bath PMW, Zhao L, Heptinstall S. Current status of stroke prevention in patients with atrial fibrillation. *European Heart Journal*. 2005;7:C12-C18
5. Zhao L, Heptinstall S, Bath P. Antiplatelet therapy for stroke prevention. *British Journal of Cardiology*  
*Heart & Brain*. 2005;12:57-60
6. Antithrombotic Trialists Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002;324:71-86
7. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (caprie). *Lancet*. 1996;348:1329-1339
8. Ringleb PA, Bhatt DL, Hirsh AT, Topol EJ, Hacke W, for the CAPRIE Investigators. Benefit of clopidogrel over aspirin is amplified in patients with a history of ischemic events. *Stroke*. 2004;35:528-532
9. Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European stroke prevention study 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurological Sciences*. 1996;143:1-13
10. The ESPRIT Study Group. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (esprit): Randomised controlled trial. *Lancet*. 2006;367:1665-1673
11. Halkes PH, Gray LJ, Bath PM, Diener HC, Guiraud-Chaumeil B, Yatsu FM, et al. Dipyridamole plus aspirin versus aspirin alone in secondary prevention after tia or stroke: A meta-analysis by risk. *J Neurol Neurosurg Psychiatry*. 2008;79:1218-1223
12. Yusuf S, Fox KAA, Tognoni G, Mehta SR, Chrolavicius S, Anand S, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without st-segment elevation. *New England Journal of Medicine*. 2001;345:494-502
13. Steinhubl SR, Berger PB, Mann JT, Fry ETA, DeLago A, Wilmer C, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: A randomized controlled trial. *JAMA*. 2002;288:2411-2420
14. Bhatt DL, Fox KAA, Werner Hacke CB, Berger PB, Black HR, Boden WE, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *The New England Journal of Medicine*. 2006;354:1706-1717
15. Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (match): Randomised, double-blind, placebo-controlled trial. *Lancet*. 2004;364:331-337
16. Bath PMW. Role of aspirin in match. *Lancet*. 2004;364:1662
17. Intercollegiate Stroke Working Party. National clinical guidelines for stroke. 2004
18. Leys D, Kwiecinski H, Bogousslavsky J, Bath PMW, Brainin M, Diener H-C, et al. Prevention. European stroke initiative *Cerebrovasc Dis*. 2004;17:15-29
19. European Stroke Organisation (ESO) Executive Committee, Committee EW. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovascular Diseases*. 2008;25:457-507

20. Furie KL, Kasner SE, Adams RJ, Albers GW, Bush RL, Fagan SC, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;42:227-276
21. Sacco RL, Diener H-C, Yusuf S, Cotton D, Ounpuu S, Lawton W, et al. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *New England Journal of Medicine*. 2008;359:1238-1251
22. International Stroke Trial Collaborative Group. The international stroke trial (IST); a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. *Lancet*. 1997;349:1569-1581
23. CAST (Chinese Acute Stroke Trial) Collaborative Group. Cast: Randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. *Lancet*. 1997;349:1641-1649
24. Kennedy J, Hill MD, Ryckborst K, Eliasziw M, Demchuk AM, Buchan AM, et al. Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): A randomised controlled pilot trial. *Lancet Neurology*. 2007;6:961-969
25. Dengler R, Diener HC, Schwartz A, Grond M, Schumacher H, Machnig T, et al. Early treatment with aspirin plus extended-release dipyridamole for transient ischaemic attack or ischaemic stroke within 24 h of symptom onset (early trial): A randomised, open-label, blinded-endpoint trial. *Lancet Neurol*. 2010;9:159-166
26. Bath PM, Cotton D, Martin RH, Palesch Y, Yusuf S, Sacco R, et al. Effect of combined aspirin and extended-release dipyridamole versus clopidogrel on functional outcome and recurrence in acute, mild ischemic stroke: PROFESS subgroup analysis. *Stroke*. 2010;41:732-738
27. Rothwell PM, Giles MF, Chandratheva A, Marquardt L, Geraghty O, Redgrave JN, et al. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): A prospective population-based sequential comparison. *Lancet Neurology*. 2007;370:1432-1442
28. Lavalley PC, Meseguer E, Abboud H, Cabrejo L, Olivot J, Simon O, et al. A transient ischaemic attack clinic with round-the-clock access (SOS-TIA): Feasibility and effects. *Lancet Neurology*. 2007;6:953-960
29. Markus HS, Droste DW, Kaps M, Larrue V, Lees KR, Siebler M, et al. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using doppler embolic signal detection. The clopidogrel and aspirin for reduction of emboli in symptomatic carotid stenosis (CARESS) trial. *Circulation*. 2005;111:2233-2240
30. Wong KS, Chen C, Fu J, Chang HM, Suwanwela NC, Huang YN, et al. Clopidogrel plus aspirin versus aspirin alone for reducing embolisation in patients with acute symptomatic cerebral or carotid artery stenosis (CLAIR study): A randomised, open-label, blinded-endpoint trial. *Lancet Neurol*. 2010;9:489-497
31. Michelson AD, Cattaneo M, Eikelboom JW, Gurbel PA, Kottke-Marchant K, Kunicki TJ, et al. Aspirin resistance: Position paper of the working group on aspirin resistance. *Journal of Thrombosis and Haemostasis*. 2005;3:1309-1311
32. Leonardi-Bee J, Bath PM, Bousser MG, Davalos A, Diener H-C, Guiraud-Chaumeil B, et al. Dipyridamole for preventing recurrent ischemic stroke and other vascular events: A meta-analysis of individual patient data from randomized controlled trials. *Stroke*. 2005;36:162-168
33. Zhao L, Bath P, Heptinstall S. Effects of combining three different antiplatelet agents on platelets and leukocytes in whole blood in vitro. *British Journal Pharmacology*. 2001;134:353-358
34. Scholz T, Zhao L, Temmler U, Bath P, Heptinstall S, Losche W. The GPIIb/IIIa antagonist eptifibatid markedly potentiates platelet-leukocyte interaction and tissue factor expression following platelet activation in whole blood in vitro. *Platelets*. 2002;13:401-406
35. Zhao L, Bath PMW, Fox S, May J, Judge H, Losche W, et al. The effects of GPII-IIIa antagonists and a combination of three other antiplatelet agents on platelet-leukocyte interactions. *Current Medical Research Opinion*. 2003;19:178-186

36. Zhao L, Fletcher S, Weaver C, Leonardi-Bee J, May J, Fox S, et al. Effects of aspirin, clopidogrel and dipyridamole administered singly and in combination on platelet and leucocyte function in normal volunteers and patients with prior ischaemic stroke. *Thromb Haemost*. 2005;93:527-534
37. Zhao L, Gray LJ, Leonardi-Bee J, Weaver CS, Heptinstall S, Bath PM. Effect of aspirin, clopidogrel and dipyridamole on soluble markers of vascular function in normal volunteers and patients with prior ischaemic stroke. *Platelets*. 2006;17:100-104
38. Sprigg N, Gray LJ, England T, Willmot MR, Zhao L, Sare GM, et al. A randomised controlled trial of triple antiplatelet therapy (aspirin, clopidogrel and dipyridamole) in the secondary prevention of stroke: Safety, tolerability and feasibility. *PLoS ONE [Electronic Resource]*. 2008;3:e2852
39. Willmot M, Zhao L, Heptinstall S, Bath PMW. Triple antiplatelet therapy for secondary prevention of recurrent ischaemic stroke. *J Stroke Cerebrovasc Dis*. 2004;13:138-140
40. Geeganage C, Wilcox R, Bath PM. Triple antiplatelet therapy for preventing vascular events: A systematic review and meta-analysis. *BMC Med*. 2010;8:36
41. Hallas MJ, Dall M, Andries A, Andersen BS, Aalykke C, Hansen JM, et al. Use of single and combined antithrombotic therapy and risk of serious upper gastrointestinal bleeding: Population based case-control study. *British Medical Journal*. 2006;333:726
42. Bath PMW, Geeganage C, Gray LJ, Collier T, Pocock SJ. Optimising the analysis of stroke prevention trials: Converting dichotomous vascular outcomes into ordinal measures. *Stroke*. 2008;In press
43. Brooks R, with the EuroQol Group. Euroqol: The current state of play. *Health Policy*. 1996;37:53-72
44. Zung WWK. A self-rating depression scale. *Archives of General Psychiatry*. 1965;12:63-70
45. Schulman S, Kearon C, on behalf of the subcommittee on control of anticoagulation of the scientific and standardization committee of the international society on thrombosis and haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *Journal of Thrombosis and Haemostasis*. 2005;3:592-694
46. Weir CJ, Lees KR. Comparison of stratification and adaptive methods for treatment allocation in an acute stroke clinical trial. *Stat.Med*. 2003;22:705-726
47. Diener H-C, Sacco RL, Yusuf S, for the Steering Committee and PROFESS Study Group. Rationale, design and baseline data of a randomized, double-blind, controlled trial comparing two antithrombotic regimens (a fixed-dose combination of extended-release dipyridamole plus asa with clopidogrel) and telmisartan versus placebo in patients with strokes: The prevention regimen for effectively avoiding second strokes trial (profess). *Cerebrovascular Diseases*. 2007;23:368-380
48. Sung JJ. Combining aspirin with antithrombotic agents. *British Medical Journal*. 2006;333:726
49. Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. *Stroke*. 1993;24:35-41
50. Collet JP, Hulot JS, Pena A, Villard E, Esteve JB, Payo L, et al. Cytochrome p450 2c19 polymorphism in young patients treated with clopidogrel after myocardial infarction: A cohort study. *Lancet*. 2009;373:309-317
51. Simon T, Verstuyft C, Mary-Krause M, Quteineh L, Drouet E, Meneveau N, et al. Genetic determinants of response to clopidogrel and cardiovascular events. *New England Journal of Medicine*. 2009;360:363-375
52. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. *New England Journal of Medicine*. 2009;360:354-362
53. Abraha HD, Butterworth RJ, Bath PMW, Wassif WS, Garthwaite J, Sherwood RA. Serum s-100 protein, a prognostic marker of clinical outcome in acute stroke. *Annals of Clinical Biochemistry*. 1997;34:366-370

54. Weaver CS, Leonardi-Bee J, Bath-Hexall FJ, Bath PMW. Sample size calculations in acute stroke trials: A systematic review of their reporting, characteristics, and relationship with outcome. *Stroke*. 2004;35:1216-1224
55. Sprigg N, Gray LJ, England T, Willmot MR, Zhao L, Sare GM, et al. A randomised controlled trial of triple antiplatelet therapy (aspirin, clopidogrel and dipyridamole) in the secondary prevention of stroke: Safety, tolerability and feasibility (isrctn 83673558). *PLoS One*. 2008;submitted
56. DAMOCLES study group. A proposed charter for clinical trial data monitoring committees: Helping them to do their job well. *Lancet*. 2005;365:711-722
57. Grant AM, Altman D, G, Babiker AB, Campbell MK, Clemens FJ, Darbyshire JH, et al. Issues in data monitoring and interim analysis of trials. *Health Technology Assessment*. 2005;9:1-237
58. Hatano S. Experience from a multicentre stroke register: A preliminary report. *Bulletin of the World Health Organisation*. 1976;54:541-553
59. Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *New England Journal of Medicine*. 2008;359:1317-1329
60. Hacke W. European cooperative acute stroke trial (ecass) (abstract). *Stroke*. 1994;25:542
61. Hacke W, Markku K, Fieschi C, von Kummer R, Davalos A, Meier D, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ecass ii). *Lancet*. 1998;352:1245-1251
62. Rothwell PM, Giles MF, Flossmann E, Lowelock CE, Redgrave JNE, Warlow CP, et al. A simple score (abcd) to identify individuals at high early risk of stroke after transient ischaemic attack. *Lancet*. 2005;366:29-36
63. Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet*. 2007;369:283-292
64. Anonymous. Myocardial infarction redefined--a consensus document of the joint european society of cardiology/american college of cardiology committee for the redefinition of myocardial infarction. *European Heart Journal*. 2000;21:1502-1513
65. Brott T, Adams HP, Olinger CP, Marler JR, Barsan WG, Biller J, et al. Measurements of acute cerebral infarction: A clinical examination scale. *Stroke*. 1989;20:864-870
66. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet*. 1974;2:81-83
67. Rankin J. Cerebral vascular accidents in patients over the age of 60. 2. Prognosis. *Scottish Medical Journal*. 1957;2:200-215
68. Wade DT. *Measurement in neurological rehabilitation*. Oxford: Oxford University Press; 1992.
69. Mahoney FI, Barthel DW. Functional evaluation: The barthel index. *Maryland State Medical Journal*. 1965:61-65
70. Dorman PJ, Slattery J, Farrell B, Dennis MS, Sandercock PAG, United Kingdom Collaborators in the International Stroke Trial. A randomised comparison of the euroqol and short form-36 after stroke. *Br.Med.J*. 1997;315:461
71. de Jager CA, Budge MM, Clarke R. Utility of tics-m for the assessment of cognitive function in older adults. *International Journal of Geriatric Psychiatry*. 2003;18:318-324