AN APPLICATION TO RECOMMEND THAT CLOPIDOGREL BE ADDED TO THE WHO MODEL LIST OF ESSENTIAL MEDICINES AS AN ANTITHROMBOTIC AGENT FOR THE TREATMENT OF CARDIOVASCULAR DISEASE (12.5)

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1. Executive Summary

Cardiovascular diseases (CVD), including ischemic heart disease and stroke, are the leading causes of mortality in the world with 80% of CVD-related deaths occurring in low- and middle-income countries (LMICs). Ischemic heart disease is the largest single cause of mortality and loss of disability-adjusted life years worldwide, with the largest burden occurring in LMICs. In November 2012, the World Health Organization (WHO) announced its target to reduce the risk of premature mortality related to non-communicable diseases (NCDs) by 25% by the year 2025. This goal is to be achieved, in part, through a health system target that assures availability of essential medicines and technologies to treat NCDs, including cardiovascular diseases (CVD), to at least 50% of eligible individuals (1).

The 18th Model List of Essential Medicines includes several drugs for the treatment and control of acute and chronic cardiovascular diseases, including aspirin, streptokinase, heparin, simvastatin, bisoprolol, and enalapril. These classes of drugs show independent mortality benefit and are highly recommended in clinical practice guidelines of major professional organizations for the treatment of acute coronary syndrome, including both ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI). These same clinical practice guidelines also highly recommend the use of dual antiplatelet therapy for the treatment of acute coronary syndrome. However, a second antiplatelet agent such as clopidogrel is not currently included in the Model List of Essential Medicines despite recently coming off patent and becoming more widely available. Clopidogrel is a thienopyridine antiplatelet drug that works by irreversibly inhibiting the P2Y_{12} adenosine diphosphate chemoreceptor on platelet cell membranes. Clopidogrel has been shown to be a safe and cost-effective way of reducing cardiovascular and total mortality in patients with acute coronary syndrome and following percutaneous coronary interventions. The quality of evidence supporting the use of clopidogrel is high not only for acute coronary syndrome but also for percutaneous coronary intervention, and the strength of recommendations is strong based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. We therefore propose that the Expert Committee consider:

1) Adding thienopyridines as a therapeutic class of antithrombotic medicines (Section 12.5 of the current List); and

2) Specifying clopidogrel as the representative of the thienopyridine class.

2. Name of the focal point in WHO submitting or supporting the application

N/A

3. Name of the organizations consulted and/or supporting the application

*Individuals on behalf of organizations supporting the application are listed below (in alphabetical order):*

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4. International Proprietary Name (INN)
Clopidogrel

5. Formulation proposed for inclusion
Clopidogrel bisulfate tablets (75 mg and 300 mg)

6. International availability
The U.S. Food & Drug Administration approved generic clopidogrel on May 17, 2012 (2). The generic pharmaceutical industry was spurred on by the $9 billion market that clopidogrel (Plavix®) constituted worldwide in 2011 (3).

Clopidogrel is registered for use in various countries including but not limited to Australia, Austria, Brazil, Bulgaria, Croatia, Denmark, Estonia, Finland, Germany, Hungary, India, Latvia, Lithuania, the Netherlands, Norway, Poland, Romania, Serbia, Slovakia, Slovenia, Sweden, the United Kingdom, and the United States of America.

Clopidogrel is manufactured by companies in a variety of countries (partial listing below):

Table 1. Partial list of countries where clopidogrel is manufactured.

<table>
<thead>
<tr>
<th>Country</th>
<th>Manufacturers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>Apotex</td>
</tr>
<tr>
<td>India</td>
<td>Aurobindo, Gate Pharmaceuticals, Dr. Reddy’s, Macleods Pharmaceuticals, Sun Pharmaceuticals, Torrent Pharmaceuticals, Wockhardt</td>
</tr>
<tr>
<td>Israel</td>
<td>Teva Pharmaceuticals</td>
</tr>
<tr>
<td>United States of America</td>
<td>Accord, Actavis, Macleods Pharmaceuticals, Mutual Pharmaceuticals, Mylan Pharmaceuticals, Roxane Pharmaceuticals, Sun Pharmaceuticals, Zydus</td>
</tr>
</tbody>
</table>
7. Listing as individual medicine or representative of therapeutic group
Representative of therapeutic group (thienopyridine)

8. Information Supporting the Public Health Relevance
Cardiovascular diseases (CVD), including ischemic heart disease and stroke, are the leading causes of mortality in the world with 80% of cardiovascular disease-related deaths occurring in low- and middle-income countries (LMICs) (4). The number of deaths due to CVD is projected to rise so that if current trends continue to the year 2030, then 85% of cardiovascular disease-related deaths will occur in LMICs (5, 6). Ischemic heart disease is the largest single cause of mortality and loss of disability-adjusted life years (DALYs) worldwide, accounting for roughly 7.3 million deaths and 129 million DALYs each year (4, 7, 8). Nearly two-thirds of all ischemic heart disease DALYs and more than half of these deaths occur in LMICs (7). Ischemic heart disease and its complications result in substantial microeconomic losses, including catastrophic health spending and distress financing, particularly among individuals in lower socioeconomic position than in individuals with higher socioeconomic position (9). It is estimated that, if current trends continue, then CVD will also account for one-third of a projected $47 trillion (or $15.6 trillion) in macroeconomic losses due to non-communicable, chronic diseases over the next 20 years (10).

Acute Coronary Syndrome
A frequent, acute manifestation of ischemic heart disease is acute coronary syndrome (also known as ACS), which includes ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina. Short-term case fatality rates for acute coronary syndrome, including acute myocardial infarction, have fallen dramatically from approximately 25% in the early 1980s to as low as 4% in the current era, due at least in part to a combination of medical therapy, reperfusion, and better overall intensive care, including availability of defibrillation (11-14). However, treatment of patients with acute coronary syndrome in LMICs is highly variable and often suboptimal (15), with increased symptom-to-presentation (pain-to-door) times and increased presentation-to-treatment (door-to-drug) times compared to high-income countries (HICs) and decreased adherence to evidence-based therapy for secondary prevention (16, 17). Antiplatelet medications, including aspirin and clopidogrel, have been well established to each have an independent mortality benefit in patients with acute coronary syndrome (18-21). However, use of clopidogrel is substantially lower in LMICs compared to HICs, with one study by Shimony et al. that compared two HICs to four LMICs demonstrating that 82% of patients in HICs with acute coronary syndrome received clopidogrel compared to only 34% of patients in LMICs (OR 9.1, 95% CI 5.6,14.8) (22).

Percutaneous Coronary Intervention
In patients with ST-segment elevation myocardial infarction, percutaneous coronary intervention is increasingly recommended as the reperfusion strategy of choice (19, 23). Percutaneous coronary intervention also provides faster angina relief than medical therapy alone in patients with stable ischemic heart disease and thus is recommended for
symptom relief in patients who are severely symptomatic (24-26). Based on these benefits and the increasing availability of cardiac catheterization laboratories, percutaneous coronary interventions have become more common globally, including in LMICs (27). For example, in 2011, over 152,000 percutaneous coronary interventions were performed in India with about 194,000 stents deployed, while in China, data from 2009 suggest that nearly 240,000 percutaneous coronary interventions were performed with at least 247,000 stents placed (28-30).

9. Treatment Details

Clopidogrel is an oral thienopyridine antiplatelet agent, and works by irreversibly inhibiting the P2Y₁₂, adenosine diphosphate chemoreceptor on platelet cell membranes. It is available in 75 mg and 300 mg tablets. The recommended dosage and duration of therapy with clopidogrel varies based on its indication (Table 1).

Table 2. Clopidogrel indications, dosing, and duration of therapy.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Loading dose</th>
<th>Maintenance dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute coronary syndromes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI</td>
<td>Yes – 600 mg</td>
<td>75 mg</td>
<td>12 months&lt;sup&gt;(19)&lt;/sup&gt;</td>
</tr>
<tr>
<td>STEMI with thrombolysis (&lt;75 years)</td>
<td>Yes – 300 mg</td>
<td>75 mg</td>
<td>≥14 days&lt;sup&gt;(19, 20, 31)&lt;/sup&gt;</td>
</tr>
<tr>
<td>STEMI with thrombolysis (&gt;75 years)</td>
<td>No</td>
<td>75 mg</td>
<td>≥14 days&lt;sup&gt;(19, 20, 31)&lt;/sup&gt;</td>
</tr>
<tr>
<td>UA/NSTEMI</td>
<td>Yes – 300 to 600 mg</td>
<td>75 mg</td>
<td>12 months&lt;sup&gt;(21, 32, 33)&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Percutaneous coronary intervention (non-ACS setting)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug eluting stent</td>
<td>Yes – 600 mg</td>
<td>75 mg</td>
<td>12 months&lt;sup&gt;(23)&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bare metal stent</td>
<td>Yes – 600 mg</td>
<td>75 mg</td>
<td>1-12 months&lt;sup&gt;(23, 34)&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

STEMI = ST-segment elevation myocardial infarction
UA = unstable angina
NSTEMI = non-ST-segment elevation myocardial infarction

10. Summary of comparative effectiveness in a variety of clinical settings

**Acute Coronary Syndromes**

**ST- Segment Elevation Myocardial Infarction (STEMI)**

In patients with ST-segment elevation myocardial infarction (STEMI), clopidogrel has demonstrated clinical efficacy in reduction of mortality and morbidity. In the pre-specified ST-segment elevation myocardial infarction subgroup analysis of a 2012 Cochrane systematic review, there was a significant association between clopidogrel pretreatment and a reduction of death (absolute risk 1.3% vs. 2.5%; OR 0.50, 95% CI 0.26, 0.96, p=0.04; number needed to treat (NNT), 79) compared to no pretreatment (35). Clopidogrel pretreatment in ST-segment elevation myocardial infarction was also
significantly associated with a reduction in major coronary events (a composite of death, myocardial infarction and urgent target vessel revascularization) (absolute risk 3.6% vs. 6.4%; OR 0.54, 95% CI 0.36, 0.81, p=0.003; NNT, 36) (35). Based on this review, patients with ST-segment elevation myocardial infarction gain more benefit from clopidogrel pretreatment compared to any other subclass (35).

The Percutaneous Coronary Intervention-Clopidogrel as Adjunctive Therapy (CLARITY-PCI) study evaluated 1,863 patients with ST-segment elevation myocardial infarction who underwent fibrinolysis (36). Following fibrinolysis, patients were either treated with clopidogrel (loading dose of 300 mg, followed by 75 mg daily) or placebo. At 30 days, patients with ST-segment elevation myocardial infarction undergoing secondary percutaneous coronary intervention after fibrinolysis had a significant decrease in cardiovascular death, myocardial infarction, or stroke with no increased risk of bleeding (7.5% vs. 12.0%; adjusted OR 0.59, 95% CI 0.43, 0.81, p=0.001; NNT, 23) compared to those in the placebo group (36). The authors concluded that in patients who have myocardial infarction with ST-segment elevation, clopidogrel pretreatment significantly reduces the incidence of cardiovascular death or ischemic complications both before and after percutaneous coronary intervention and without a significant increase in major or minor bleeding (36).

Unstable Angina (UA)/Non-ST-Segment Elevation Myocardial Infarction (NSTEMI)

Clopidogrel has demonstrated clinical efficacy in patients with unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI). A 2011 Cochrane systematic review found that in patients presenting with acute NSTEMI, the combination of clopidogrel and aspirin was associated with a lower risk of cardiovascular events (defined as death, myocardial infarction, unstable angina, heart failure, and ischemic stroke) (10.1% vs. 11.5%; OR 0.87, 95% CI 0.81, 0.94, p<0.01; NNT, 71) compared to aspirin alone (37). The authors concluded that this benefit outweighed the risk of increased bleeding events based on calculations that 13 cardiovascular events would be prevented for every 1000 patients treated with clopidogrel and aspirin, though 6 major bleeds would be caused (37). The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study was a randomized trial that enrolled 12,562 patients presenting with UA/NSTEMI (21). Patients were randomized to receive a loading dose of clopidogrel followed by maintenance clopidogrel and aspirin, or aspirin alone. Compared to the patients treated with aspirin alone, the patients treated with the dual antiplatelet therapy had a 20% reduction in the primary outcome defined as stroke, death from cardiovascular causes, or nonfatal myocardial infarction (9.3% vs. 11.4%; OR 0.80, 95% CI 0.72, 0.90, p<0.001; NNT, 48) (21).

The PCI-CURE study evaluated the 2,658 patients in the CURE study who underwent percutaneous coronary intervention (33). Following percutaneous coronary intervention, patients were either treated with clopidogrel and aspirin or aspirin and placebo for 3 to 12 months (mean 8 months). Within 30 days of percutaneous coronary intervention, the patients treated with both clopidogrel and aspirin had a significantly lower rate of the primary endpoint, which consisted of target vessel revascularization, death from cardiovascular etiologies, or nonfatal MI, compared to the group treated with aspirin
alone (4.5% vs. 6.4%); RR 0.70, 95% CI 0.50, 0.97, p=0.03; NNT, 53). Long-term treatment with aspirin and clopidogrel led to reductions in death, MI, or revascularization at 8-month follow-up, compared to patients treated with aspirin alone (21.7% in the clopidogrel and aspirin group vs. 18.3% in the aspirin alone group, RR 0.83, 95% CI 0.70, 0.99, p=0.03; NNT, 29) (33).

A 2008 systematic review and meta-analysis of eight randomized controlled trials, including CURE, PCI-CURE, and CLARITY mentioned above plus the Clopidogrel for the Reduction of Events During Observation (CREDO) and Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trials, found that patients with acute coronary syndrome who were treated with clopidogrel and aspirin had a 15% lower odds ratio of death, stroke, or reinfarction, compared to patients treated with aspirin alone (9.2% vs. 10.4%; OR 0.85, 95% CI: 0.23, 0.06) with mean follow-up of 28 days to 18 months (38). While the combination of clopidogrel and aspirin led to significant lowering in the odds of nonfatal and fatal reinfarction in patients with acute coronary syndrome and in those undergoing percutaneous coronary intervention, dual therapy did not lead to a significant reduction in all-cause mortality compared to patients treated with aspirin alone.

Application of the GRADE system classifies the recommendation of clopidogrel in patients with acute coronary syndrome as strong. The quality of evidence used to make these recommendations is high, given that the evidence was based on randomized controlled trials with low risk of bias. The findings are consistent, and the data show a favorable balance between desirable and undesirable effects (see Section 11 for a discussion of adverse effects).

Percutaneous Coronary Intervention

In combination with aspirin, clopidogrel is an effective antiplatelet drug to reduce morbidity and mortality in patients who undergo percutaneous coronary intervention (23, 35). A 2012 systematic review and meta-analysis of 7 randomized controlled trials including 8,608 patients reported that, among patients who undergo percutaneous coronary intervention, clopidogrel pretreatment was associated with a 23% lower odds of major coronary events (a composite of death, myocardial infarction and urgent target vessel revascularization) compared with no treatment (9.8% vs. 12.3%; OR 0.77, 95% CI 0.66, 0.89, p<0.001; NNT, 40) (35). There was evidence of lower mortality in patients who received clopidogrel (1.5% vs. 2.0%; OR 0.80, 95% CI 0.57, 1.11), but the event rates were low and the results were imprecise. There was evidence of an increased risk of bleeding associated with clopidogrel pre-treatment compared with no treatment (3.6% vs. 3.1%; OR 1.18, 95% CI 0.93, 1.50), but these results were also imprecise. The randomized controlled trials included in this systematic review had a low risk of bias across multiple domains with Jadad scores of 3 to 5.

A 2008 systematic review and meta-analysis by Bowry et al. found that patients undergoing percutaneous coronary intervention had a 34% lower odds ratio of death, stroke, or reinfarction when treated with clopidogrel and aspirin,
when compared to patients treated with aspirin alone (95% CI 44%, 22%). The authors also found that patients undergoing treatment with clopidogrel and aspirin were at a higher risk of bleeding when continued on both medications for greater than 1 month, when compared to patients treated with aspirin alone (OR 1.80, 95% CI 1.40, 2.30) (38).

Application of the GRADE system classifies the recommendation for clopidogrel to reduce major coronary events in patients undergoing percutaneous coronary intervention as strong. The quality of evidence used to make this recommendation is high because the evidence is based on randomized controlled trials with low risk of bias across multiple domains (including reporting bias), consistent results, and indirect evidence of benefit in other settings (acute coronary syndrome, e.g.). It is unlikely that additional studies would affect the confidence in the estimate of effect. The quality of evidence supporting the use of clopidogrel in reducing mortality in patients who undergo percutaneous coronary intervention is moderate based on the imprecision of the results for this outcome.

Aspirin Intolerance

Some patients with prior cardiovascular disease who take aspirin develop side effects or an allergic reaction that prohibits them from taking aspirin. In these patients who are considered intolerant to aspirin, clopidogrel may be an alternative. The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial was a randomized controlled trial that enrolled 19,185 patients with atherothrombotic disease, specifically prior myocardial infarction, ischemic stroke, or symptomatic peripheral artery disease and compared the effectiveness of either aspirin or clopidogrel in preventing death, myocardial infarction, or stroke. In the subgroup of the CAPRIE study population with a prior myocardial infarction, the patients who were treated with clopidogrel were found to have a similar primary outcome event rate per year compared to the aspirin group (5.0% vs. 4.8%, p=0.66) (39). Based on these results, the American Heart Association/American College of Cardiology Foundation cardiovascular disease secondary prevention guidelines recommend that in patients with ischemic heart disease who cannot tolerate aspirin, clopidogrel is as an effective alternative (AHA/ACCF Class of recommendation I, level of evidence B) (40).

The GRADE system classifies the recommendation for clopidogrel in patients with prior ischemic heart disease who cannot tolerate aspirin as strong. The quality of evidence used to make this recommendation is moderate because the evidence was based on one randomized controlled trial with low risk of bias. In addition, the data shows that there is little uncertainty regarding the balance between desirable and undesirable effects (see Section 11 for a discussion of adverse effects).
11. Summary of comparative evidence on safety

Adverse Events and Serious Adverse Events

Clopidogrel’s safety has been evaluated in a variety of contexts, specifically in comparison with aspirin, other thienopyridines (prasugrel, ticlopidine), and ticagrelor. In the CAPRIE study, which compared clopidogrel with aspirin, the following adverse effects were noted: hemorrhagic events, gastrointestinal disorders, rashes, neutropenia, or thrombocytopenia (39, 41).

Hemorrhagic events:

The CAPRIE study found more patients with validated nonfatal primary intracranial hemorrhage and hemorrhagic death in the aspirin-treated group compared to the clopidogrel-treated group (0.5% vs. 0.4%) (39, 41). Patients taking aspirin experienced more gastrointestinal hemorrhages than patients taking clopidogrel (2.7% vs. 2.0%, p<0.05), reflected by a 30% increase in hospitalizations in the aspirin group (39, 41).

In a 2007 meta-analysis including CURE, CREDO, CHARISMA, CLARITY, and COMMIT that compared clopidogrel plus aspirin to aspirin monotherapy, Bowry et al. report that in patients with acute coronary syndrome or post percutaneous coronary intervention, when dual antiplatelet therapy is continued beyond the immediate post–acute care period or beyond six months after drug-eluting stent implantation, the risk for bleeding increases substantially from 35-337% with the odds ratios and 95% CIs shown in Table 3 (38).

Table 3. Efficacy and bleeding outcomes with dual therapy vs. monotherapy in long-term and short-term trials.(38)

<table>
<thead>
<tr>
<th>Duration</th>
<th>Trial</th>
<th>OR for Major Bleeding (95%CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-term trials</td>
<td>CURE</td>
<td>1.76 (1.52-2.03)</td>
</tr>
<tr>
<td></td>
<td>CREDO</td>
<td>1.35 (0.98-1.87)</td>
</tr>
<tr>
<td></td>
<td>MATCH</td>
<td>3.37 (2.09-5.44)</td>
</tr>
<tr>
<td></td>
<td>CHARISMA</td>
<td>1.64 (1.27-2.10)</td>
</tr>
<tr>
<td></td>
<td>Combined effect</td>
<td>1.80 (1.41-2.30)</td>
</tr>
<tr>
<td>Short-term trials</td>
<td>COMMIT</td>
<td>1.07 (0.84-1.37)</td>
</tr>
<tr>
<td></td>
<td>CLARITY</td>
<td>1.09 (0.66-1.80)</td>
</tr>
</tbody>
</table>

* Data are presented as the ratio of the odds of the outcome in the dual-antiplatelet therapy group compared with the single-antiplatelet therapy group.

Gastrointestinal disorders:

In the CAPRIE study, patients in the clopidogrel-treated group were noted to have fewer gastrointestinal events, such as nausea, indigestion, and vomiting, as potential side effects of clopidogrel (39, 41). Patients in the clopidogrel-treated group were noted to have fewer gastrointestinal events, when compared to patients in the aspirin group (15.0% vs. 17.6%, p<0.05) (39, 41). Patients taking clopidogrel had a greater incidence of diarrhea, than the aspirin-treated group (4.5% vs. 3.4%, p<0.05) (39, 41). Severe diarrhea occurred more frequently in the clopidogrel group compared to the aspirin group (0.2% vs. 0.1%, p=0.08), but the number of these events was small (39, 41).
Rash:

The CAPRIE study noted that patients in the clopidogrel group had a modestly greater incidence of rash than the aspirin-treated group (6% vs. 5%, p<0.05) (39, 41). Severe rash occurred more frequently in the clopidogrel group as well, compared to the aspirin group (0.3% vs. 0.1%, p=0.02), but the number of these events was small (39, 41).

Hematologic events:

In the CAPRIE study, patients treated with clopidogrel were found to have similar rates of neutropenia (defined as 1.2x10^9/L neutrophils), when compared to patients treated with aspirin (0.1% vs. 0.2%) (39, 41). The CAPRIE study also found that patients treated with clopidogrel had similar rates of thrombocytopenia (defined as 100x10^9/L platelets), when compared to patients treated with aspirin (0.3% vs. 0.3%) (39).

Table 4. Adverse experiences associated with clopidogrel and aspirin use. (39)

<table>
<thead>
<tr>
<th>Adverse experience</th>
<th>Patients ever reporting</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>Clopidogrel</td>
<td>Aspirin</td>
</tr>
<tr>
<td></td>
<td>572 (6.62%)</td>
<td>402 (3.46%)*</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td></td>
<td>29 (0.26%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22 (0.23%)</td>
</tr>
<tr>
<td>Indigestion/nausea/vomiting</td>
<td>2141 (25.01%)</td>
<td>1096 (17.97)%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>93 (0.97%)</td>
</tr>
<tr>
<td>Any bleeding disorder</td>
<td>880 (10.27%)</td>
<td>322 (3.30)%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11 (0.11%)</td>
</tr>
<tr>
<td>Incidental haemorrhage</td>
<td>33 (0.35%)</td>
<td>23 (0.25%)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>Gastrointestinal haemorrhage</td>
<td>50 (0.51%)</td>
<td>47 (0.49%)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11 (0.11%)</td>
</tr>
<tr>
<td>Abnormal liver function</td>
<td>285 (3.27%)</td>
<td>302 (3.52)%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9 (0.09%)</td>
</tr>
</tbody>
</table>

*Statistically significant, p<0.05.

Monitoring

Laboratory monitoring is not required for patients taking clopidogrel. American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Intervention guidelines do not recommend routine platelet function testing (23). Clopidogrel is metabolized by CYP2C19 into its active form (23). However, the American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Intervention guidelines do not recommend routine genetic testing because of the lack of benefit seen in genotype-based dosing of clopidogrel (23).

Precautions

Proton Pump Inhibitors:

As described above, clopidogrel therapy can lead to an increased risk of gastrointestinal bleeding. Studies have evaluated the need for proton pump inhibitor therapy in patients requiring antiplatelet therapy (42). The American Heart Association/American College of Cardiology Foundation/American Gastroenterology Association 2010 Expert Consensus Statement recommends the use of proton pump inhibitors in patients with a history of gastrointestinal bleeding or with risk factors for bleeding (use of NSAIDs, steroids, anticoagulants; H. pylori infection), but no prophylactic use of proton pump inhibitors in patients with a low risk of gastrointestinal bleeding (42).

Medically-indicated withdrawal:

Withdrawal of clopidogrel is recommended 5 days prior to procedures that carry a high risk of bleeding and treatment of acute bleeding (23).
Contraindications
Clopidogrel is contraindicated in individuals with known clopidogrel hypersensitivity and/or active bleeding (intracranial hemorrhage, peptic ulcer) (43).

12. Summary of available data on cost and cost-effectiveness
Costs
According to the International Drug Price Indicator published by Management Sciences for Health in 2013, clopidogrel 75 mg has a median international cost of $0.0526/tablet, ranging from $0.0238 to $1.1078 (44). There are no other thienopyridine medications on the International Drug Price Indicator list for comparison.

Cost Effectiveness
Acute Coronary Syndrome
In the patients with ST-segment elevation myocardial infarction, European models based on the CLARITY and Clopidogrel and Metoprolol in Myocardial Infarction (COMMIT) trials have shown that in Sweden and France, one year of clopidogrel resulted in cost savings of €111 and €367, respectively. In a similar group of patients in Germany, the incremental cost-effectiveness ratio (ICER) for clopidogrel was €92 per life year gained (LYG) (45). For patients similar to those in the COMMIT study, the incremental cost of treatment with clopidogrel was €538 in Sweden, €798 in Germany and €545 in France per 0.194 LYG, with ICERS of €2,772, €4,144 and €2,786 per LYG, respectively. Based on this analysis, Berg et al. concluded that clopidogrel was cost-effective in the setting of ST-segment elevation myocardial infarction (45). In patients with ST-segment elevation myocardial infarction who receive thrombolysis rather than percutaneous coronary intervention, Zhang et al. evaluated the short- and long-term cost effectiveness of clopidogrel plus aspirin versus aspirin alone and found that a combination of clopidogrel and aspirin lowered event rates without an increase in cost ($7,791 vs. $7,797). Over a lifetime, treating for one year with clopidogrel plus aspirin produced a gain of 0.119 life years at an incremental cost of $1,269 compared to aspirin alone, resulting in an ICER of $10,691/LYG (46).

In patients with acute coronary syndrome without ST elevation, cost-effectiveness analysis from the CURE trial has shown that treatment with aspirin and clopidogrel compared with aspirin alone was cost-effective with an ICER of €3,113 per LYG in a German model and an ICER of <$4,000/LYG in a Canadian model (47).

Percutaneous Coronary Intervention
The cost-effectiveness of clopidogrel after elective percutaneous coronary intervention has been established based on findings of the CREDO trial. A cost effectiveness analysis in this setting yielded ICERs ranging from $3,685/LYG to $4,353/LYG based on a model using data from the Framingham Heart Study (48). The ICERs based on Saskatchewan data were $2,929/LYG to $3,460/LYG (48).

Cost-effectiveness data of clopidogrel in LMICs is limited. However, data from cost-effectiveness analysis in HICs suggest that clopidogrel treatment in LMICs will be cost-effective. According to the World Heart Organization threshold for cost-effectiveness, an
intervention should be considered cost-effective if a gain in a year of healthy life costs less than three times the per capita gross domestic product (49). The estimated ICER of approximately $3000 per year can be considered cost-effective in all nations with a per-capita gross domestic product greater than $1000.

13. Summary of regulatory status of the medicine

14. Availability of Pharmacopoeial Standards
International Pharmacopoeia: Not available.

15. Proposed (new/adapted) text for the WHO Model Formulary
We recommend that clopidogrel be added to the WHO Model Formulary as the representative of the thienopyridine class of antithrombotics for the treatment of acute coronary syndrome and post percutaneous coronary intervention. For the Formulary, we suggest, “Clopidogrel in addition to aspirin is useful for the treatment of acute coronary syndromes and for ischemic heart disease post percutaneous coronary intervention. It is also useful for patients needing antiplatelet therapy who have an intolerance to aspirin.”
REFERENCES:

15. Huffman MD, Prabhakaran D, Abraham AK, Krishnan MN, Nambiar AC, Mohanan PP. Optimal in-hospital and discharge medical therapy in acute


