# Clopidogrel



ATC codes: B01AC04

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| **Indication** | Presence of coronary angioplasty implant or graft ICD11 code: QB50.4 |
| **INN** | Clopidogrel |
| **Medicine type** | Chemical agent |
| **List type** | Core |
| **Formulations** | **Oral > Solid:** 75 mg ; 300 mg |
| **EML status history** | First added in 2015 (TRS 994) |
| **Sex** | All |
| **Age** | Adolescents and adults |
| **Therapeutic alternatives** | The recommendation is for this specific medicine |
| **Patent information** | Patents have expired in most jurisdictions<br>Read more about patents. |
| **Wikipedia** | Clopidogrel |
| **DrugBank** | Clopidogrel |

## Summary of evidence and Expert Committee recommendations

An application was submitted by Drs Amisha Patel, Mahesh Vidula and Mark Huffman, Northwestern University Feinberg School of Medicine, Chicago, IL, USA, Dr Sandeep Kishore, Yale University School of Medicine, New Haven, CT, USA, and Dr Rajesh Vedanthan, Icahn School of Medicine at Mount Sinai, New York, USA, for the inclusion of the thienopyridine class of medicines on the Model List, with clopidogrel as representative of the class for the treatment of acute coronary syndrome and post-percutaneous coronary intervention. Reviews of the application were prepared by two members of the Expert Committee. Public comments in support of the application were received from Professor Valentin Fuster, past President of the American Heart Association and the World Heart Federation, Professor Bongani Mayosi, head of the Medicine Department at the University of Cape Town, South Africa, Dr D Prabhakaran, Executive Director of the Centre for Chronic Disease Control, New Delhi, India, and Professor Salim Yusuf, Population Health Research Institute, McMaster University, Hamilton, Canada. Ischaemic 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 (1-3). Acute coronary syndrome (ACS) is a frequent acute manifestation of ischaemic heart disease and includes ST-segment elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (NSTEMI) and unstable angina (UA). Treatment of patients with ACS in low- and middle-income countries (LMICs) is highly variable and often suboptimal (4). In well-resourced settings, a combination of medical therapy, reperfusion and better overall intensive care has led to dramatic reductions in case-fatality rates for ACS (5-8). Treatment outcomes in LMICs are worse and there is evidence of poor adherence to secondary prevention therapies. Antiplatelet medicines, including aspirin and clopidogrel, have been shown to have an independent mortality benefit in patients with ACS (9-12). The reperfusion strategy of choice in patients with STEMI is percutaneous coronary intervention (PCI) (10, 13); these procedures have become increasingly common with the growing availability of cardiac catheterization

laboratories, including in LMICs (14). A 2012 systematic review (15) reported a significant reduction in death associated with clopidogrel pretreatment compared with no pretreatment in a pre-specified subgroup of patients with STEMI (absolute risk 1.3% versus 2.5%; odds ratio (OR) 0.50; 95%: CI 0.26–0.96; number needed to treat (NNT) 79). Clopidogrel pretreatment was also associated with a reduction in major coronary events (composite outcome of death, MI and urgent target vessel revascularization; absolute risk 3.6% vs 6.4%; OR 0.54; 95% CI: 0.36–0.81; NNT 36). Among patients undergoing PCI, compared with no treatment, pretreatment with clopidogrel was associated with 23% lower odds of major coronary events (composite of death, MI and urgent target vessel revascularization) (9.8% vs 12.3%; OR 0.77: 95% CI: 0.66–0.89; NNT 40). Clopidogrel pretreatment was associated with an increased risk of bleeding compared with no treatment. The Percutaneous Coronary Intervention – Clopidogrel as Adjunctive Reperfusion Therapy (PCI-CLARITY) trial in patients with STEMI undergoing fibrinolysis concluded that clopidogrel pretreatment significantly reduced the incidence of death or ischaemic complications both before and after PCI, with no significant increased risk of major or minor bleeding (11). A 2011 Cochrane review (16) reported that, compared with aspirin alone, clopidogrel plus aspirin was associated with a small reduction in the risk of cardiovascular events (death, MI, UA, heart failure and ischaemic stroke) in patients with acute NSTEMI (absolute risk 10.1% vs 11.5%; OR 0.87; 95% CI: 0.81–0.94; NNT 71). Compared with aspirin alone, the risk of major bleeding was higher in the clopidogrel plus aspirin group (OR 1.34; 95% CI: 1.14–1.57; number needed to harm (NNH) 167). The review concluded that, in patients with acute non-ST coronary syndromes, combination treatment with clopidogrel and aspirin should be considered as the evidence suggests that the benefits of treatment outweigh the harms: for every 1000 patients treated, 13 cardiovascular events would be prevented while six major bleeds would be caused. The CURE trial randomized patients presenting with UA/NSTEMI to receive clopidogrel (loading dose followed by maintenance dose) or placebo in addition to aspirin for 3–12 months. Compared with patients treated with aspirin alone, patients treated with a clopidogrel and aspirin combination had a 20% reduction in the primary outcome of death from cardiovascular causes, nonfatal MI (absolute risk 9.3% vs 11.4%; OR 0.80: 95% CI: 0.72– 0.90; NNT 48) (958). The PCI-CURE trial evaluated a subset of patients from the CURE trial proceeding to PCI. In PCI-CURE, patients treated with both clopidogrel and aspirin had a significantly lower rate of the primary end-point (target vessel revascularization, death from cardiovascular etiologies, or nonfatal MI) at 30 days compared with those treated with aspirin alone (17). A 2008 systematic review and meta-analysis of eight trials including CLARITY, CURE and PCI-CURE concluded that, compared with aspirin monotherapy, combination treatment with clopidogrel and aspirin for patients with ACS or those undergoing PCI is associated with a reduction in the risk of major coronary events and fatal or nonfatal MI. However, dual antiplatelet therapy was not shown to be associated with a reduced risk of all-cause mortality but did increase the risk of major bleeding when administered for more than one year. On balance, the authors concluded that the benefits of dual therapy outweigh the harms for patients with ACS and those undergoing PCI but not for other patient subgroups (18). Overall, the applicants concluded that GRADE assessment found the evidence to be of high quality (RCTs with a low risk of bias and consistent findings) and this provided the basis for a strong recommendation for use of clopidogrel in patients with ACS and to reduce major coronary events in patients undergoing PCI. The evidence to support a claim of reduced mortality with clopidogrel in patients undergoing PCI was rated as being of moderate quality because of imprecision in the assessment of this outcome. The Expert Committee noted that no GRADE tables were included in the application to illustrate these conclusions. The CAPRIE study (clopidogrel versus aspirin in patients at risk of ischaemic events) found similar rates of validated nonfatal primary intracranial haemorrhage and haemorrhagic death in aspirin-treated patients compared with clopidogrel-treated patients (0.5% vs 0.4%) but higher rates of gastrointestinal haemorrhage in aspirin-treated patients (2.7% vs 2.0%), leading to more hospitalizations for gastrointestinal bleeding in the aspirin-treated group. Clopidogrel was associated with fewer gastrointestinal events such as nausea, indigestion and vomiting than aspirin (15% vs 17.6%). There were more rashes (6% vs 5%) and severe rashes (0.3% vs 0.1%) in the clopidogrel-treated patients. Rates of neutropenia (0.1% vs 0.2%) and thrombocytopenia (0.3% vs 0.3%) were broadly similar for the two groups (19). The 2008 meta-analysis by Bowry et al. concluded that there was a substantially increased risk of major bleeding with clopidogrel plus aspirin compared with aspirin alone when the combination was continued beyond the immediate post-acute care period or beyond six months after drug-eluting stent implantation. The increase in risk was 1.35–3.37 across the trials included in the analysis (18). Because of the increased risk of gastrointestinal bleeding associated with antiplatelet therapy, US consensus

recommendations suggest concomitant use of proton-pump inhibitors in patients with a history of gastrointestinal bleeding or risk factors for bleeding who require antiplatelet therapy (20). The Committee noted that, according to the 2013 International Drug Price Indicator, clopidogrel 75 mg has a median international cost of US$ 0.0526/ tablet (range US$ 0.0238–1.1078) (21). Based on the evidence presented, the Expert Committee recommended the addition of clopidogrel to the core list of the EML. The Committee did not agree with the request to list clopidogrel with a square box symbol as representative of the pharmacological class of thienopyridine agents, since no data were presented on other agents in the class. The Committee accepted that dual anti-platelet therapy with clopidogrel in combination with aspirin is effective treatment in reducing the risk of major cardiovascular events and is superior to aspirin monotherapy for patients with acute coronary syndromes or those undergoing PCI. The Committee considered that, in these patient populations, the benefits of dual therapy outweigh the potential harms. References: 1. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2197-223. 2. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095-128. 3. Vedanthan R, Seligman B, Fuster V. 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