

## Building the Case for Clopidogrel as a World Health Organization Essential Medicine

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### World Health Organization's Model List of Essential Medicines

The World Health Organization (WHO) defines essential medicines as medicines that satisfy the priority healthcare needs of the population.<sup>1</sup> These medicines are selected by the WHO based on their public health relevance, international availability, treatment details, efficacy and safety, comparative cost-effectiveness, the need for special requirements or training needed for the safe/appropriate use of the medicine, and regulatory status.<sup>1</sup> The medicines that are considered highest priority are included on the WHO Model List of Essential Medicines or Essential Medicines List (EML). The EML was first published in 1977 and is revised every 2 years by an expert committee. It serves as a catalog of critical medicines and informs purchasing decisions of low- and middle-income country (LMIC) governments.<sup>1,2</sup> Most individual nations align the WHO EML with the epidemiological profile and health priorities of their population to create a national EML.<sup>3</sup> Medicines on the national EML are then subsidized by the public sector, making them more affordable to the general population.<sup>4</sup> For example, in the national Mutuelle insurance system in Rwanda, members are eligible to receive national EML drugs for outpatient treatment with only a 10% copayment.<sup>3,5</sup>

In November 2012, the WHO announced its target to reduce the risk of premature mortality related to noncommunicable diseases by 25% by the year 2025.<sup>6</sup> This goal is to be achieved, in part, through a health system target that assures availability of essential medicines and technologies to treat noncommunicable diseases, including cardiovascular disease (CVD), to at least 50% of eligible individuals.

The 18th edition of the WHO EML includes several drugs for the treatment and control of acute and chronic CVDs, including aspirin, streptokinase, heparin, simvastatin, bisoprolol, and enalapril.<sup>7</sup> However, clopidogrel, a thienopyridine often used in conjunction with aspirin as a second antiplatelet agent for the treatment of acute coronary syndrome, post percutaneous intervention, and for the secondary prevention of stroke, was not included in the EML despite coming off patent in 2012 and becoming more widely available via generic

manufacturers (Figure). In November 2014, we submitted an application to the WHO Expert Committee on the Selection and Use of Essential Medicines to recommend the addition of clopidogrel to the EML. In this article, we describe (1) the social, political, and historical context of clopidogrel and (2) the rationale for adding clopidogrel to the EML to achieve global cardiovascular health targets.

### Social, Political, and Historical Context of Clopidogrel

Clopidogrel was first approved for use by the United States Food and Drug Administration in November 1997 and remained on patent until May 2012 (Figure).<sup>8</sup> In 2006, generic clopidogrel was briefly marketed by Apotex, a Canadian generic pharmaceutical company before a court order halted further production until resolution of a patent infringement case brought by Bristol-Myers Squibb.<sup>9</sup> The court ruled that Bristol-Myers Squibb's patent was valid and provided protection until November 2011.<sup>10</sup> The Food and Drug Administration extended the patent protection of clopidogrel by 6 months, giving exclusivity that expired on May 17, 2012. The Food and Drug Administration approved generic versions of clopidogrel on May 17, 2012.<sup>11</sup> In Europe, the European Medicines Agency gave authorization to 6 generic versions of clopidogrel bisulfate in June 2009.<sup>12</sup>

In 2006 and 2008, the government of Thailand decided to grant government use licenses to enable the import and local production of the generic versions of 7 medicines that were patent-protected in Thailand. Clopidogrel was the only cardiovascular medicine among this group, which otherwise included antiretrovirals for HIV and anticancer drugs.<sup>13</sup> The Thai government compulsory license was issued in January 2007, thus allowing the Thai government to over-ride Bristol-Myers Squibb's patent and produce and import generic versions of the medicine based on the country's public health need<sup>14</sup> (Figure). This decision was estimated to increase in the number of individuals with access to clopidogrel by 40947 during a 5-year period and result in 2435 quality-adjusted life years gained.<sup>15</sup> The Thailand experience demonstrates

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This article was handled independently by Karen E. Joynt, MD, MPH, as a Guest Editor. The editors had no role in the evaluation of the article or in the decision about its acceptance.

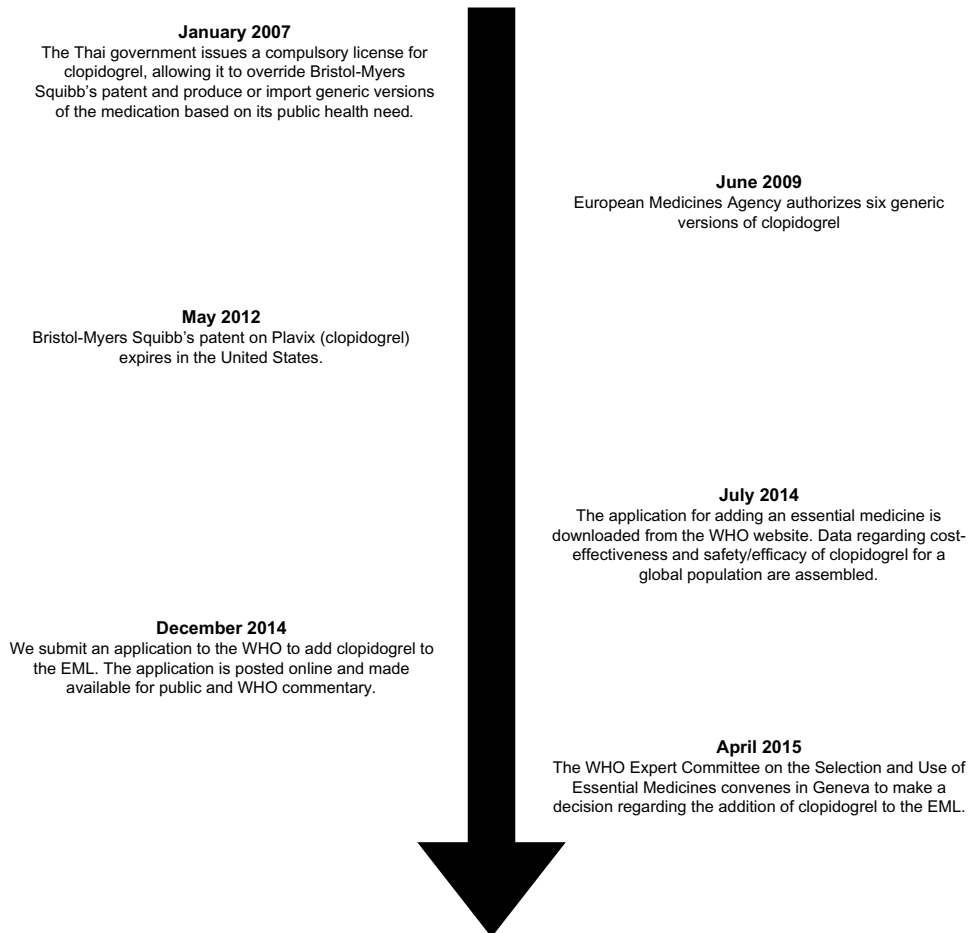
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(*Circ Cardiovasc Qual Outcomes*. 2015;8:447-451. DOI: 10.1161/CIRCOUTCOMES.115.001866.)

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*Circ Cardiovasc Qual Outcomes* is available at <http://circoutcomes.ahajournals.org>

DOI: 10.1161/CIRCOUTCOMES.115.001866



**Figure.** Timeline of the key events related to the application to add clopidogrel to the 19th World Health Organization (WHO) Model List of Essential Medicines. EML indicates Essential Medicines List.

the substantial impact of increasing access to clopidogrel in 1 country and serves as an example of the type of benefits that other LMICs can also experience.

## Rationale for Adding Clopidogrel to the Model List of Essential Medicines

### Public Health Relevance

CVDs, including ischemic heart disease and stroke, are the leading causes of mortality in the world with 80% of CVD-related deaths occurring in LMICs.<sup>16</sup> The number of deaths because of CVD is projected to rise so that if current trends continue to the year 2030, then 85% of CVD-related deaths will occur in LMICs.<sup>17,18</sup> At this rate, it is estimated that CVD will account for one-third of a projected \$47 trillion (or \$15.6 trillion) in macroeconomic losses because of noncommunicable, chronic diseases during the next 20 years.<sup>19</sup>

Although short-term case-fatality rates for acute coronary syndrome in high-income countries (HICs) have fallen dramatically in the current era because of a combination of medical therapy, reperfusion, and better overall intensive care,<sup>20–23</sup> treatment of patients with acute coronary syndrome in LMICs is highly variable and frequently suboptimal,<sup>24</sup> with increased symptom-to-presentation (pain-to-door) times and increased presentation-to-treatment (door-to-drug) times compared with

HICs and decreased adherence to evidence-based therapies, including clopidogrel.<sup>25,26</sup> Furthermore, the availability of cardiac catheterization laboratory services is increasing globally, including in LMICs.<sup>27</sup> In 2011, >152 000 percutaneous coronary interventions were performed in India with ≈194 000 stents deployed compared with 40 000 coronary interventions in 2005.<sup>28</sup> In China, data from 2009 suggest that ≈240 000 percutaneous coronary interventions were performed, with >247 000 stents deployed compared with only ≈16 000 percutaneous coronary interventions in 2001.<sup>28–30</sup> The number of people in whom dual antiplatelet therapy is indicated is thus similarly increasing.

Antiplatelet medications, including aspirin and clopidogrel, have been well established to each have an independent mortality benefit in patients with acute coronary syndrome.<sup>31–33</sup> However, the use of clopidogrel is substantially lower in LMICs than in HICs. For example, Shimony et al<sup>34</sup> demonstrated that 82% of patients in 2 HICs (Canada and the United States) with acute coronary syndrome received clopidogrel during hospitalization compared with only 34% of patients in 4 LMICs (Iran, India, Pakistan, and Tunisia; odds ratio [OR], 9.1; 95% confidence interval [CI], 5.6–14.8). Patients in these samples were somewhat dissimilar, with those in LMICs more often men, with a history of prior myocardial infarction and presenting with ST-segment–elevation myocardial

infarction (STEMI) compared with those in HICs, suggesting that patients in LMICs might derive even greater absolute benefit from clopidogrel than those in HICs. The clopidogrel treatment gap is because of a variety of reasons including the lack of access to health practitioners, high costs for healthcare services, lack of drug availability (stock-outs), poor adherence, unaffordable costs of even generic drugs compared with local incomes, and inadequate prescription of medicines.<sup>35</sup>

### Efficacy, Safety, and Cost-Effectiveness

Clopidogrel has been shown to be an efficacious, safe, and cost-effective way of reducing cardiovascular and total mortality in patients with acute coronary syndrome and in patients after percutaneous coronary interventions.<sup>36–39</sup> In the prespecified STEMI subgroup analysis of a 2012 systematic review on the effects of clopidogrel in patients with acute coronary syndrome, clopidogrel pretreatment was associated with a lower death rate compared with no pretreatment (1.3% versus 2.5%; OR, 0.50; 95% CI, 0.26–0.96).<sup>40</sup> Clopidogrel pretreatment in STEMI was also associated with a reduction in major coronary events, defined as a composite of death, myocardial infarction, and urgent target vessel revascularization (3.6% versus 6.4%; OR, 0.54; 95% CI, 0.36–0.81).<sup>40</sup> In patients with STEMI who undergo fibrinolysis, those treated with clopidogrel before undergoing facilitated percutaneous coronary intervention had a lower risk of cardiovascular death, myocardial infarction, or stroke (7.5% versus 12.0%; adjusted OR, 0.59; 95% CI, 0.43–0.81) with no increased risk of bleeding when compared with those randomized to the placebo group.<sup>41</sup> In patients with non–ST-segment–elevation myocardial infarction and unstable angina, patients treated with aspirin and clopidogrel had a 20% reduction in the primary outcome defined as death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (9.3% versus 11.4%; OR, 0.80; 95% CI, 0.72–0.90) compared with those treated with aspirin alone.<sup>42</sup>

Clopidogrel has also been shown to play an important role in the secondary prevention of stroke and can provide an alternative for patients who cannot take aspirin or aspirin and dipyridamole. The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial of 19 185 patients compared clopidogrel with aspirin in patients with a history of ischemic stroke and found that patients treated with clopidogrel had a relative risk reduction of recurrent ischemic stroke, myocardial infarction, or vascular death of 7.3% (95% CI, 5.7–18.7;  $P=0.26$ ).<sup>43</sup> Therefore, clopidogrel was shown to be as effective as aspirin for secondary prevention in patients with a history of a stroke or transient ischemic attack. We did not include this indication in our application to the WHO EML because current guidelines recommend single antiplatelet therapy for stroke prevention, and 1 antiplatelet agent (aspirin) is already included in the EML.<sup>7,44</sup>

Clopidogrel's safety has been evaluated in a variety of contexts, specifically in comparison with aspirin, other thienopyridines (prasugrel, ticlopidine), and ticagrelor. In subgroup analyses of a 2007 meta-analysis including 3 clinical trials of patients with acute coronary syndrome ( $n=61\,072$ ) and 3 clinical trials of patients after percutaneous coronary intervention ( $n=23\,164$ ), where clopidogrel plus aspirin was compared with aspirin monotherapy, Bowry et al<sup>37</sup> report that the use of dual

antiplatelet therapy beyond the immediate post-acute care period or beyond 6 months after drug-eluting stent implantation was not associated with a significant increase in the odds of major bleeding (OR, 1.31; 95% CI, 0.88–1.94 in acute coronary syndrome; OR, 1.24; 95% CI, 0.97–1.59 in post-percutaneous coronary intervention). When clopidogrel alone is compared with aspirin, as in the CAPRIE study, patients in the clopidogrel-treated group were noted to have less gastrointestinal irritation (nausea, vomiting, and indigestion) when compared with patients in the aspirin group (15.0% versus 17.6%;  $P<0.05$ ) and fewer episodes of gastrointestinal hemorrhage (2.0% versus 2.7%;  $P<0.05$ ).<sup>43,45</sup>

Although cost-effectiveness data of clopidogrel in LMICs are limited, data from HICs demonstrate that the addition of clopidogrel to aspirin for patients who have had an acute coronary syndrome or for patients after percutaneous coronary intervention is cost effective.<sup>36,38,39,46</sup> The WHO defines an intervention as being cost-effective if a gain in a year of healthy life costs  $<3\times$  the per capita gross domestic product of the country.<sup>47</sup> According to the International Drug Price Indicator published by the Management Sciences for Health in 2013, clopidogrel 75 mg has a median international cost of \$0.0526 per tablet.<sup>48</sup> The estimated incremental cost-effectiveness ratio of clopidogrel is  $\approx$ \$3000 per life year gained.<sup>36,38,46</sup> Thus, by WHO criteria, clopidogrel is cost-effective in nations with a per capita gross domestic product  $>$ \$1000, amounting to 182 of the 187 nations ranked by the International Monetary Fund in 2013.<sup>49</sup>

### Conclusions

To achieve the WHO's 25 $\times$ 25 goal and reduce inequities in CVD care on a global scale, there must be a mechanism in place to assure that those in LMICs have access to essential medicines and technologies. The approval of clopidogrel as a second antiplatelet agent in addition to aspirin has great potential to improve access and equity to treatment for CVDs by improving availability in LMICs, particularly as the burden of acute coronary syndrome and availability of percutaneous coronary stenting increase. Our application's approval by the Expert Committee is promising to address this growing need.<sup>50</sup> Overall, the EML serves as an important mechanism to facilitate access to critical medicines to reduce not only the global burden of CVD, but also other noncommunicable diseases to achieve the WHO's 25 $\times$ 25 goal. We authors encourage readers to submit applications for additions, deletions, and updates to future Model Lists to improve access to essential medicines. In summary, clopidogrel's safety, efficacy, and cost-effectiveness make it a powerful addition to the EML to reduce the burden of CVD worldwide.

### Acknowledgments

We would like to acknowledge Dr Kunal Karmali for his editorial advice.

### Sources of Funding

This work was in part supported by the National Institutes of Health/ National Heart, Lung, and Blood Institute through the Fogarty International Clinical Research Scholars and Fellows Program at Vanderbilt University (R24 TW007988) and the American Recovery and Reinvestment Act. Dr Vedanthan is supported by the Fogarty

International Center of the National Institutes of Health under award number K01 TW 009218-04. Dr Huffman is supported by a National Heart, Lung, and Blood Institute pathway to independence award (1 R00 HL107749). He has received grant support from the World Heart Federation's Emerging Leaders Program, which is supported by unrestricted educational grants from AstraZeneca, Boehringer Ingelheim, and Bupa Foundation. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

## Disclosures

None.

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KEY WORDS: clopidogrel ■ drugs, essential ■ World Health Organization

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*Circ Cardiovasc Qual Outcomes*. 2015;8:447-451; originally published online June 2, 2015;  
doi: 10.1161/CIRCOUTCOMES.115.001866

*Circulation: Cardiovascular Quality and Outcomes* is published by the American Heart Association, 7272  
Greenville Avenue, Dallas, TX 75231

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Print ISSN: 1941-7705. Online ISSN: 1941-7713

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