

The economic consequences of non-evidence-based clopidogrel use

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Background Clinical trials have helped clarify the efficacy of clopidogrel for the treatment and prevention of vascular disease. Costs for its use exceeded \$5.9 billion in 2005, making it the second greatest source of drug expenditure in the world. However, little is known about the appropriateness of that use. Overuse of clopidogrel could have important implications for health care quality and drug expenditures.

Methods We conducted a retrospective cohort study linking all filled prescriptions to all clinical encounter data for Medicare beneficiaries enrolled in a large state-wide pharmacy assistance program. We identified all patients newly prescribed clopidogrel during a recent 2-year period and determined the proportion who had indications for clopidogrel, the mean number of tablets filled by patients with and without apparent indications in the year after starting therapy, and the costs associated with the observed patterns of clopidogrel use.

Results We identified 4977 patients who were newly prescribed clopidogrel. Of these patients, only 47% had ≥ 1 documented indications for clopidogrel according to clinical trial findings. Using looser criteria, the number of patients with appropriate indications was 56%. During the first year of therapy, 43% (\$2.05 million) of total clopidogrel expenditures for the patients studied was spent on patients without an indication that this agent was required, using the extended criteria for evidence-based use.

Conclusions More than 40% of the clopidogrel used in this population appears to have been prescribed to patients for whom the drug had no documented advantage over aspirin or no antiplatelet therapy. If the same proportion applies nationally, in 2005, it would represent almost \$1.5 billion of potentially unnecessary health care expenditure. (*Am Heart J* 2008;155:904-9.)

Numerous large-scale randomized trials have clarified the role of clopidogrel (Plavix, Bristol-Myers Squibb, New York, NY) for the treatment and prevention of vascular disease.¹⁻⁶ The combination of clopidogrel and aspirin has been shown to be superior to aspirin alone for patients who have had an acute coronary syndrome (ACS)²⁻⁴ or who have undergone percutaneous coronary intervention.^{7,8} Similarly, clopidogrel monotherapy is more effective than aspirin alone for patients with peripheral

arterial disease, recent stroke, or recent myocardial infarction (MI).¹ This study also found that clopidogrel caused less gastrointestinal toxicity than aspirin, although it was compared with 325 mg daily of aspirin rather than the 81 to 162 mg daily more commonly used at present for cardioprotection. In contrast, a combined regimen of clopidogrel plus aspirin in patients with less acute vascular disease or those without known vascular disease but with multiple atherothrombotic risk factors was not found to provide any incremental benefit over aspirin alone and increased the risk of bleeding.⁶

The use of clopidogrel has risen sharply since its introduction in 1997 (see [Figure 1](#)), spurred in part by a very active program of promotion to both physicians and patients, with an estimated \$110 million spent in 2005 for print and broadcast advertising to patients alone.⁹ Despite this, the underuse of clopidogrel is common,¹⁰ occurs to an extent that is similar to that observed for other cardiovascular drugs, and may have important effects on patient outcomes.¹¹⁻¹⁴

In contrast, it is likely that some proportion of clopidogrel prescribing occurs in the absence of published literature supporting its use. Because a daily dose of Plavix in 2006 cost approximately \$4, whereas the daily cost of aspirin is just 3 cents,¹⁵ the overuse of clopidogrel

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The author contributions are as follows: study concept and design by Choudhry and Avorn; acquisition of data by Choudhry, Levin, and Avorn; analysis and interpretation of data by Choudhry, Levin, and Avorn; drafting of the manuscript by Choudhry; critical revision of the manuscript for important intellectual content by Choudhry and Avorn; statistical expertise by Choudhry, Levin, and Avorn; administrative, technical, or material support by Levin; and study supervision by Choudhry. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Submitted June 21, 2007; accepted November 30, 2007.

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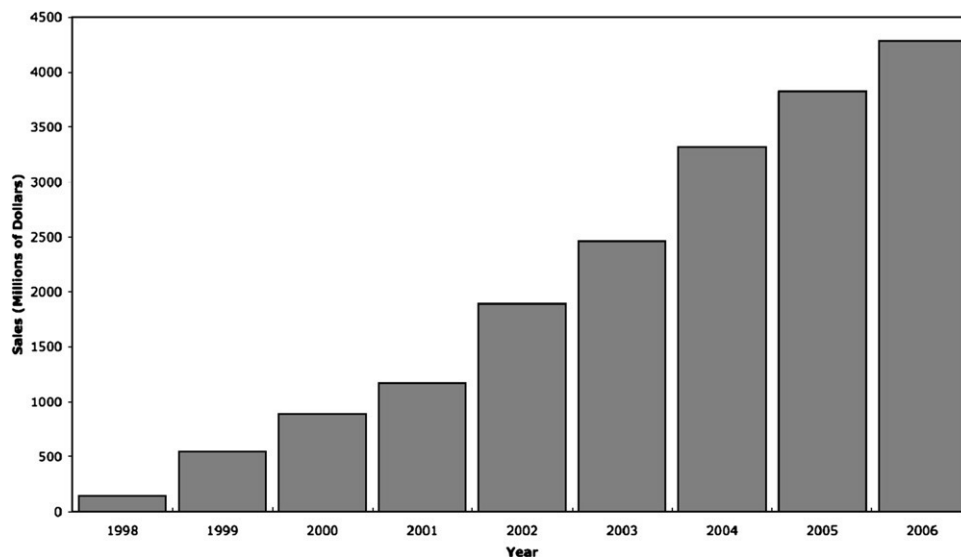
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0002-8703/\$ - see front matter

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doi:10.1016/j.ahj.2007.11.039

Figure 1



Increasing use of Plavix in the United States. Figures represent Plavix sales by Bristol-Myers Squibb since its introduction in 1997. Data obtained from Securities and Exchange Commission filings by Bristol-Myers Squibb (available at www.sec.gov). Annual 2006 figures extrapolated from first quarter sales (assuming a 12% growth rate compared with 2005).

may have significant clinical and economic implications when used in patients for whom aspirin has been shown to be equally effective. Accordingly, clopidogrel represents an increasingly common problem in pharmacotherapy: a newer, costly branded product that is equivalent to an older, far less expensive agent for many patients but more effective for a well-defined subset of patients. With the advent of Medicare drug coverage and the availability and much wider use of costly medications supported by public funding, this problem has gained added importance.

We sought to determine what proportion of patients newly prescribed clopidogrel had evidence-based indications for this therapy and to evaluate the economic implications of the observed patterns of clopidogrel use.

Methods

Setting and design

We assembled a retrospective cohort of Medicare patients newly prescribed clopidogrel between January 1, 2003, and December 31, 2004, by linking Medicare files to data from the Pennsylvania Pharmaceutical Assistance Contract for the Elderly (PACE)¹⁶ program. During the period studied, PACE provided prescription drug benefits to lower-middle-income individuals aged ≥ 65 whose yearly earnings were above the threshold to qualify them for Medicaid. Participants paid copayments between \$5 and \$10 per prescription without any deductibles, and the program covered all medications that require a prescription, with no restrictions on which medications can be prescribed (ie, no formularies, preferred drug lists, or prior authorization requirements).

We combined filled prescription data from PACE with complete paid claims data (Medicare parts A and B) describing all clinical encounters for these individuals, including all recorded diagnoses. The data were assembled into a relational database consisting of data for all filled prescriptions, procedures, inpatient and outpatient physician encounters, hospitalizations, long-term care admissions, and deaths for the patients in our cohort. These data sources have been used extensively to study population-based health outcomes.^{12,17,18} All traceable person-specific identifying factors were transformed into anonymous coded study numbers to protect subjects' privacy. The institutional review board of Brigham and Women's Hospital, Boston, MA, approved the study.

We defined each patient's index date as the date of the first filled clopidogrel prescription. To ensure complete ascertainment of indications for clopidogrel use and the economic implications of the observed patterns of prescribing, we also excluded patients who were not active users of Medicare and PACE throughout the 3 years before and 1 year after their index date. We identified patients newly prescribed clopidogrel by restricting our analysis to patients who had not taken clopidogrel at any point in the 3 years before their index date. Patient comorbidities were determined by searching physician service claims and hospitalization records for relevant diagnostic codes in the 1-year period before their index date.

Indications for clopidogrel use

We determined whether patients had possible indications for clopidogrel by searching all recorded diagnoses from all ambulatory care visits and hospitalizations (Table D). Indications for clopidogrel approved by the US Food and Drug Administration (FDA) and that appear on the official prescription drug label for Plavix were obtained from the FDA web site.²⁰ Literature-

Table I. Indications for clopidogrel

Indication type	Criteria
FDA approved	<ol style="list-style-type: none"> 1. Hospitalization for ACS ≤ 35 d* before being prescribed clopidogrel 2. Hospitalization for stroke ≤ 6 m before being prescribed clopidogrel 3. Diagnosis of peripheral artery disease † ≤ 3 y before being prescribed clopidogrel
Literature based	<ol style="list-style-type: none"> 1. Hospitalization for ACS ‡ or PCI § ≤ 35 d before being prescribed clopidogrel 2. Hospitalization for stroke ≤ 6 m before being prescribed clopidogrel 3. Diagnosis of peripheral artery disease b ≤ 3 y before being prescribed clopidogrel e 4. Hospitalization for upper GI ≤ 3 y before being prescribed clopidogrel ¶
Extended	<ol style="list-style-type: none"> 1. Any of the following at any point within 3 y before being prescribed CABG: hospitalization for ACS, hospitalization for stroke, coronary revascularization (either PCI or CABG), diagnosis of peripheral artery disease, or hospitalization for upper GI bleed 2. Any of the following in 30 d after first being prescribed clopidogrel #: hospitalization for ACS or stroke, undergoing PCI or CABG, or being diagnosed with peripheral artery disease

GI, Gastrointestinal; CABG, coronary artery bypass graft surgery; PCI, percutaneous coronary intervention (coronary stent insertion or angioplasty).

*The official FDA drug label lists "recent MI, recent stroke or established peripheral artery disease" and "acute coronary syndrome" as indications for clopidogrel. We assigned time windows for "recent" and "established" events based on the trials cited in the labeling documentation.

†Using outpatient or inpatient diagnostic codes or procedure codes for lower limb revascularization (including stent insertion) or amputation.

‡Based on the CAPRIE,¹ CURE,² CLARITY,³ and COMMIT⁴ trials.

§Based on the PCI-CURE⁷ and CREDO⁸ trials. Although clopidogrel use after PCI should be initiated acutely, we chose this period to allow patients sufficient time after their procedure to fill their prescription.

||Based on the CAPRIE trial.

¶Based on the CAPRIE trial results and the current American Heart Association/American College of Cardiology guidelines for the management of patients with ST-segment elevation MI.¹⁹

#To allow for the possibility that clopidogrel was initiated to treat newly developing ("crescendo-ing") vascular events not yet captured in recorded diagnoses.

based indications were based on the inclusion criteria from randomized controlled trials of clopidogrel. A looser definition of "extended" indications for clopidogrel used less stringent criteria. The primary analyses were based on these extended indications because they provide more forgiving estimates of the need for clopidogrel use.

Economic analysis

To estimate the economic impact of the observed patterns of clopidogrel use, we determined the mean number of clopidogrel doses that were filled by patients with an extended indication or with no apparent evidence-based indication in the year after the first prescription. We then calculated the cost for clopidogrel paid by the PACE program by multiplying the mean number of clopidogrel tablets consumed by the daily cost of clopidogrel. The daily cost of clopidogrel was calculated by reducing the 2005 mean wholesale price of clopidogrel (\$4.67/d)²¹ by the mean rebate that PACE receives from manufacturers (16%).²²

Results

The final study cohort consisted of 4977 patients who had been newly prescribed clopidogrel. Of these patients, 56% had at least 1 extended indication for clopidogrel (Figure 2). Using literature-based definitions and FDA-approved indications decreased the number of patients with appropriate indications to 47% and 39%, respectively.

The general characteristics of patients with and without evidence of an extended indication requiring clopidogrel are presented in Table II. Patients with such indications were more likely to be male, reside in a nursing home, have comorbid medical conditions, and use other prescription medications. Most patients studied, including those with and without extended indications for clopidogrel, had ≥ 1 cardiac risk factors; all would be at sufficient risk to receive some form of antiplatelet prophylaxis by virtue of age alone.

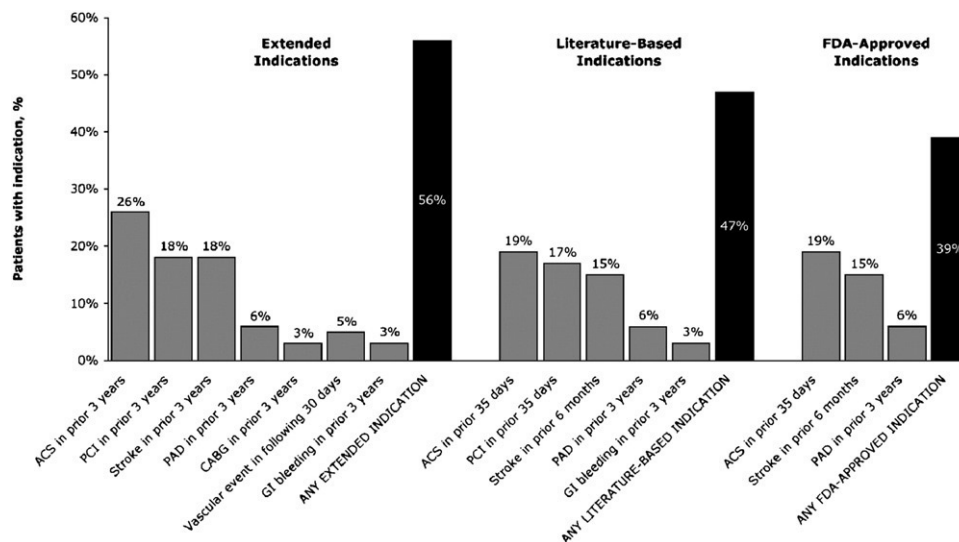
Patients without an extended indication requiring clopidogrel consumed a mean of 239 clopidogrel tablets in the 365 days after starting therapy (Table III). This means that during the first year after these patients were started on clopidogrel, the PACE program spent a mean of \$937 per patient and a total of almost \$2.05 million (43% of total PACE spending on clopidogrel among new users) to provide clopidogrel to patients without clear extended evidence-based indications for that drug. Using literature-based appropriateness criteria, the PACE program spent \$2.46 million (51% of total clopidogrel spending for new users) to provide clopidogrel to patients who did not have a literature-based indication for its use. Assessing appropriateness based on official drug label, the PACE program spent \$2.87 million (60% of total clopidogrel spending for new users) to provide clopidogrel for patients without FDA-approved indications.

Discussion

In a cohort of Medicare patients newly prescribed clopidogrel, we found that only 56% had documented diagnoses, indicating that this drug was necessary (as opposed to aspirin). Using more stringent criteria, even fewer patients (47%) received this agent in concordance with the results of published clinical trials. Only 39% of patients had indications approved by the FDA for the use of this drug.

Our results should be interpreted in light of several limitations. We relied on diagnoses recorded in utilization data to identify indications for clopidogrel, and although we only studied patients who had complete health records for 3 years before starting clopidogrel, and we used accurate and well-validated algorithms to identify relevant conditions, it is possible that we misclassified patients with appropriate indications for therapy. For example, some patients may have had peripheral artery

Figure 2



Clopidogrel use by indication. The bars represent the proportion of patients prescribed clopidogrel who have extended, literature-based, and FDA-approved indications. CABG, Coronary artery bypass graft; GI, gastrointestinal; PAD, peripheral artery disease; PCI, percutaneous coronary intervention.

disease and appropriately started on clopidogrel, but their physicians may not have recorded this condition at any medical encounter. It is possible that some of the patients we studied had an allergic reaction to aspirin and may have been appropriately prescribed clopidogrel on this basis. Although the accuracy of utilization data for identifying aspirin allergy is unknown, this diagnosis is unlikely to be reliably captured. Nevertheless, aspirin-related asthma, the most common form of aspirin hypersensitivity, occurs in <0.2% of the general population,²³ and thus, this condition is unlikely to explain the extent of clopidogrel overuse that we observed.

Our analysis of clopidogrel overuse relied on a set of extended indications for clopidogrel use that were purposefully broad. For example, the CAPRIE trial only enrolled patients with MI who had their events within the prior 35 days,¹ yet we considered an MI at any point during the 3-year period before a patient's first filled clopidogrel prescription to be an appropriate extended indication for clopidogrel. Similarly, the prespecified subgroup analysis of patients with MI enrolled in CAPRIE did not demonstrate the superiority of clopidogrel over aspirin, yet we considered MI to be an appropriate indication for clopidogrel in the current analysis, consistent with the overall trial results. Similarly, gastrointestinal bleeding may not be as clear an indication for clopidogrel as believed, especially because the dose of aspirin used in CAPRIE was 325 mg/d, and there is no evidence that clopidogrel is less gastrotoxic than the currently recommended 81 to 162 mg/d. Furthermore,

recent evidence suggests that the combination of aspirin and a proton pump inhibitor is superior to clopidogrel for prevention of recurrent aspirin-induced gastrointestinal bleeding.²⁴ Nonetheless, for the purpose of our analysis, we considered even remote gastrointestinal bleeding to be an appropriate indication for clopidogrel.

Our study did not address the underuse of clopidogrel. This drug has clear benefits for some patients, and its underuse in these circumstances may have significant clinical consequences. For example, in a contemporary cohort of patients with non-ST-segment elevation ACS, only 56% received clopidogrel at hospital discharge.¹⁰ Moreover, prematurely discontinuing clopidogrel after drug-eluting stent insertion is significantly associated with subsequent mortality.¹⁴

These results are based on a cohort of modest-income elderly patients and may not be generalizable to other groups of patients or other jurisdictions. However, by virtue of age alone, the population we evaluated would be expected to have a higher burden of vascular disease and may in fact have more indications for clopidogrel than younger, healthier patients. Accordingly, we may be underestimating the extent of clopidogrel overuse in the general population, where even more patients may be receiving clopidogrel for primary prevention.

Notwithstanding these limitations, our results have important implications for health care quality. Patients we classified as not having indications requiring clopidogrel were very likely prescribed this therapy for primary prevention, either as an alternative or an adjunct to

Table II. Characteristics of patients with and without primary indications for clopidogrel

Characteristic	Patients with extended indication for clopidogrel (n = 2788)	Patients without extended indication requiring clopidogrel (n = 2189)
Age, y, mean (SD)	80.8 (6.4)	81.8 (6.4)
Male, n (%)	536 (19.2)	330 (15.1)
Nursing home residence, n (%)	520 (18.7)	266 (12.2)
Comorbid conditions, n (%)		
Hypertension	2503 (89.8)	1655 (75.6)
Diabetes	1182 (42.4)	646 (29.5)
Congestive heart failure	881 (31.6)	386 (17.6)
Renal disease	1020 (36.6)	591 (27.0)
Atrial fibrillation	600 (21.5)	334 (15.3)
Concurrent medication use, n (%)		
ACEI or ARB	1351 (48.5)	955 (43.6)
β -Blocker	1530 (54.9)	1027 (46.9)
Statin	1212 (43.5)	830 (37.9)
Proton pump inhibitor or H ₂ blocker	993 (35.6)	678 (31.0)
Warfarin	332 (11.9)	234 (10.7)

ACEI, Angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

aspirin. Although we are unable to assess over-the-counter aspirin use with our administrative data sources, there is no evidence supporting the use of clopidogrel for patients without documented vascular disease. The CHARISMA trial⁶ demonstrated the lack of benefit of adding clopidogrel to aspirin as well as an increase in the risk of bleeding with this combination. Similarly, the use of clopidogrel as a substitute for aspirin has been evaluated only for secondary prevention,¹ whereas the value of aspirin for primary prevention has been extensively documented.²⁵ Therefore, although the use of clopidogrel may appear reasonable in this context, the burden of evidence does not support this practice.

Our findings also have important implications for health expenditure. In 2005, clopidogrel was the second best-selling drug in the world,²⁶ with the United States spending \$3.5 billion on this medication.²⁷ If our analysis of overuse can be extrapolated to nationwide spending on clopidogrel, this would mean that health care payors and individuals in the United States spent almost \$1.5 billion in 2005 for clopidogrel in instances in which it has not been demonstrated to be superior to aspirin. Using most stringent criteria based on the best available trial evidence as the appropriateness standard would increase the estimated amount of money spent on clopidogrel in the absence of literature-based indications to almost \$1.8 billion annually. With per

Table III. Clopidogrel use and spending in first year after starting therapy, based on whether patients had an extended indication requiring therapy

	Patients with extended indication for clopidogrel (n = 2788)	Patients without extended indication requiring clopidogrel (n = 2189)
Mean no. of tablets filled by patients in year after starting clopidogrel	254	239
Mean PACE program spending on clopidogrel in year after patients started clopidogrel (\$)	996	937
Total PACE program spending on clopidogrel in year after patients started clopidogrel (\$)	2775532	2050835

capita spending on prescription drugs higher in the United States than in nearly every other nation²⁸ and with such costs continuing to rise both in the United States and abroad, these results suggest that substantial savings could be achieved if scarce health care resources were used instead to increase the use of therapies of proven necessity.

Many factors contribute to physicians' decisions to prescribe a drug in the absence of scientific evidence justifying its use.^{29,30} Patients' expectations about receiving medications³¹ and their requests for them,³² physicians' perceptions of risk,³³ and pharmaceutical marketing to both patients³⁴ and physicians³⁵ all may have contributed to the patterns of clopidogrel use that we observed. Some patients may have had atrial fibrillation and received clopidogrel for stroke prophylaxis, although very limited data were available to support this practice during the period of our study, and a subsequent large scale trial clarified the relative lack of utility of clopidogrel combined with aspirin compared with warfarin in this patient population.³⁶ Widely disseminated concerns about "aspirin resistance" may also have motivated clopidogrel use in some cases.^{37,38} Although cellular factors and genetic polymorphisms do appear to affect the efficacy of aspirin (and of clopidogrel), their therapeutic significance is unclear. Therefore, using clopidogrel for patients who have not truly "failed" aspirin, regardless of their laboratory results, is not currently recommended.^{37,39}

In summary, this analysis of a very large population of typical older patients suggests that >40% of the patients treated with clopidogrel may not have required this very costly drug according to the best available clinical trial

data and would have had clinical outcomes identical or better with aspirin alone, at a fraction of the cost.

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