# Contemporary Use of Dual Antiplatelet Therapy for Preventing Cardiovascular Events

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Adding clopidogrel to aspirin has well-established benefits in settings of acute coronary syndrome (ACS)[1,2] and percutaneous coronary intervention (PCI).[3,4] However, the role of dual antiplatelet therapy (DAPT) with aspirin and clopidogrel for secondary prevention of major adverse cardiovascular events (MACEs) in patients with chronic cardiovascular disease (CVD) in other settings remains controversial. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial[5] failed to demonstrate a benefit of DAPT in preventing MACEs in its overall study population, which consisted of both patients with established CVD and patients with multiple cardiovascular risk factors but without established CVD. However, a pre-specified subgroup analysis of CHARISMA demonstrated divergent results for the 2 study subgroups with decreased MACEs in patients with established CVD but significantly higher risk of death (both all-cause and cardiovascular) for patients with multiple risk factors.[5] Additional subgroup studies have reported that DAPT may confer benefit for specific cohorts within CHARISMA such as patients with prior myocardial infarction (MI), ischemic stroke, or symptomatic peripheral arterial disease (PAD),[6] or those exclusively with PAD.[7]

Editorial commentators have generally discounted the subgroup analyses and recommended against the use of DAPT in patients with either established CVD or multiple cardiovascular risk factors.[8,9] However, it is not clear how clinicians have applied the evidence from CHARISMA and its subgroup analyses to clinical prescription of DAPT. Accordingly, we analyzed data from a large registry of cardiovascular outpatient visits to examine prescription rates for DAPT among patients with characteristics similar to those in the CHARISMA trial.



## ABSTRACT

### Objectives

CHARISMA was a landmark randomized clinical trial that failed to demonstrate a benefit of dual antiplatelet therapy (DAPT) over aspirin alone for preventing cardiovascular events. However, subgroup analyses of the trial found fewer major adverse cardiovascular events (MACEs) for patients with established cardiovascular disease but more MACEs for patients with multiple risk factors without established cardiovascular disease. Our objective was to examine DAPT use in contemporary clinical practice after publication of CHARISMA results.

### Study Design

Retrospective analysis of a large clinical registry of outpatient cardiovascular visits to over 1000 physicians that collected data on patient clinical history, symptoms, vital signs, and medications.

### Methods

Clinical characteristics and prescription rates of aspirin and clopidogrel were compared for patients with established cardiovascular disease and for patients with only multiple cardiovascular risk factors. Prescription of DAPT by calendar quarter was evaluated from 2008 to 2011 using multivariable Poisson regression models.

### Results

Of 167,839 patients with established cardiovascular disease, 20.5% were prescribed both aspirin and clopidogrel. Of 20,478 patients with multiple risk factors but no known cardiovascular disease, 3.5% were prescribed both aspirin and clopidogrel. Across 14 calendar quarters, prescription rates of DAPT did not change significantly for patients with established CVD but decreased for patients with multiple risk factors with an incidence rate ratio of 0.77.

### Conclusions

Use of DAPT is modest in patients with established cardiovascular disease, for whom the CHARISMA trial suggested decreased MACEs, and prescription rates have remained stable over time. Use of DAPT in patients with multiple risk factors only, for whom CHARISMA suggested that DAPT may lead to increased MACE, was low and decreased over time.

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### Take-Away Points

An examination of contemporary use of dual antiplatelet therapy provides insight as to how physicians appear to have responded to subgroup analyses from a landmark randomized clinical trial.

- Dual antiplatelet therapy with aspirin and clopidogrel was prescribed in 20.5% of patients with established cardiovascular disease, a subgroup for whom a decrease in cardiovascular events was found.
- Among patients with multiple risk factors only, for whom dual antiplatelet therapy was associated with increased cardiovascular events in subgroup analyses, 3.5% of patients were prescribed aspirin and clopidogrel.

## METHODS

### Data

We used data from PINNACLE (Practice INNovation And CLinical Excellence),[10,11] a prospective registry administered by the American College of Cardiology National Cardiovascular Data Registry (ACC-NCDR). PINNACLE is the first national, office-based cardiac quality improvement registry in the United States, containing data on more than 2 million patient encounters submitted by more than 1000 participating physicians to date. Detailed information regarding the registry data collection has been published.[11] Briefly, physician practices collected longitudinal patient data including clinical history, symptoms, vital signs, and medications, either by paper forms or through electronic medical records, and regularly submitted them to PINNACLE. Selected data elements for this study include patient demographics (age, sex, race), cardiovascular risk factors (diabetes, hypertension, hyperlipidemia), prior cardiovascular procedures (percutaneous coronary intervention [PCI], coronary artery bypass surgery [CABG]), selected physical examination findings (systolic blood pressure), medications, and insurance status. Data quality was routinely monitored by Saint Luke's Mid America Heart Institute, the primary analytic center for the PINNACLE program.

### Study Cohort

We identified PINNACLE subjects meeting the inclusion criteria of the CHARISMA trial, both patients with established CVD and those with only multiple cardiovascular risk factors.[5] A total of 682,348 patients treated in 31 outpatient sites in PINNACLE were identified from April 2008 to September 2011; all were 45 years or older, as in the CHARISMA population. We selected the first outpatient record for each patient to avoid double counting. Because current clinical guidelines recommend DAPT for up to 12 months after PCI with stent implantation,[12] patients who underwent PCI within the year prior to the outpatient encounter (n = 61,193) were excluded from the study cohort. Subjects with acute myocardial infarction (AMI) within the year prior to the index outpatient visit (n = 45,460) were also excluded as, DAPT is also indicated for these patients.[1] In addition, because DAPT has been demonstrated to reduce stroke in patients with atrial fibrillation (AF) who are not candidates for warfarin anticoagulation,[13] patients with AF were excluded (n = 108,905). Patients prescribed warfarin for other indications (n = 22,621) were also excluded, similar to the CHARISMA trial. Of the remaining 435,795 patients, we excluded an additional 247,478 patients who did not meet the CHARISMA trial definitions of either established CVD or multiple cardiovascular risk factors without known CVD, resulting in a final cohort size of 188,317. Patients were categorized as having established CVD if they had a history of coronary artery disease (CAD; stable or unstable angina or previous MI), transient ischemic attack (TIA), stroke, PAD, or CABG. Similarly, patients were classified into the multiple cardiovascular risk factor group if they had 1 major risk factor (diabetes mellitus) and 2 of the following minor risk factors: systolic blood pressure ≥150 mm Hg despite medical therapy (beta-blocker, calcium channel blocker, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or diuretic), hyperlipidemia, current smoking, and aged ≥65 years for males or ≥70 years for females; or no major risk factor and 3 minor risk factors. As PINNACLE did not capture all the cardiovascular risk factors available in CHARISMA, the group definitions for our study were subsets of those in CHARISMA. Specifically, our study was not able to determine whether patients had the following major risk factors assessed in CHARISMA: diabetic nephropathy, ankle-brachial index <0.9, carotid stenosis ≥70%, or carotid plaque by intima-media thickness.

### Statistical Analysis

Analyses were conducted separately for the established CVD group and the multiple risk factor group. We calculated the proportion of patients prescribed antiplatelet medications: aspirin (A) only, clopidogrel (C) only, A+C, or neither A nor C. We compared differences in demographic and clinical characteristics across the 4 antiplatelet regimens using analysis of variance for continuous variables (age) and $\chi^2$ test for categorical variables. We then developed multivariable Poisson regression models to examine the number of antiplatelet medication pre-

scriptions by calendar quarter, adjusting for age, sex, cardiovascular risk factors, and insurance status. From these models, we calculated adjusted incidence rate ratios (IRRs) for each antiplatelet medication regimen from the second calendar quarter of 2008 (Q2 2008) to the third calendar quarter of 2011 (Q3 2011) using the initial calendar quarter as a baseline. For the adjusted models, approximately 7.7% of patients were excluded due to missing data, predominately insurance status. All statistical analyses were conducted using SAS 9.2 software (SAS Institute, Cary, North Carolina) and R (www.r-project.org).

## RESULTS

We identified a total of 188,317 patients meeting our modified CHARISMA classification criteria: 167,839 patients with established CVD and 20,478 patients with multiple cardiovascular risk factors. Patients in the established CVD group were slightly younger than those in the multiple cardiovascular risk factor group (aged 68.5 years vs 71.7 years, $P$ <.001). Patients in the established CVD group were predominately male (59.3%), while patients in the multiple risk factor group were predominately female (55.1%). A history of CAD was the most common reason (89.8%) for classification into the established CVD group; cerebrovascular disease (TIA or stroke) and PAD were less common reasons at 14.0% and 16.1%, respectively. Hyperlipidemia (93.6%) and hypertension (91.7%) were the most common cardiovascular risk factors. By design, no patients in the multiple risk factor group had known CVD, similar to the CHARISMA trial. Small differences in distribution across health insurance type were observed between the 2 groups, but consistent with national trends,[15] private insurance was the most common health insurance for both the established CVD and multiple risk factors groups, followed by fee-for-service Medicare (**Table 1**).

Patients with established CVD were more likely than those with multiple cardiovascular risk factors to be prescribed aspirin only (57.6% vs 56.5%, $P$ = .006), more likely to be treated with clopidogrel only (4.3% vs 2.2%, $P$ <.001), and more likely to be treated with A+C (20.5% vs 3.5%, $P$ <.001) (Table 1). Overall prescription rates of any antiplatelet therapy (aspirin, clopidogrel, or A+C) were 82.4% in the established CVD group and 62.2% in the multiple risk factor group. In established CVD patients prescribed A+C, the most common CVD diagnoses were previous myocardial infarction (29.5%), peripheral arterial disease (23.9%), and coronary artery disease (21.6%) (**Table 2**).

For the established CVD group, unadjusted prescription rates of A+C decreased slightly during the study period from 20.3% in Q2 2008 to 20.2% in Q3 2011 ($P$ for trend = .002) (**Table 3**). A decline in the prescription of aspirin only was observed from 60.0% in Q2 2008 to 53.9% in Q3 2011 in the established CVD group ($P$ for trend <.001). A+C use also decreased slightly in the multiple risk factor group (4.3% in Q2 2008 to 1.5% in Q3 2011, $P$ for trend <.001) (Table 3). The use of aspirin alone increased insignificantly during the study period (55.4% to 60.9%, $P$-for-trend = .967) in this group.

In multivariate Poisson regression models adjusting for age, sex, and comorbidities, prescription rates of A+C in the established CVD group did not change significantly over 14 calendar quarters (IRR = 0.90; 95% CI, 0.77-1.06; $P$ = .205). The prescription of aspirin alone also did not change significantly by calendar quarter (IRR 0.96; 95% CI, 0.8-1.08; $P$ = .474). In the multiple risk factor group, the adjusted rate of A+C prescription decreased (IRR = 0.77; 95% CI, 0.66-0.90, $P$ = .0012), but no significant change was observed in the prescription of aspirin (IRR = 1.01; 95% CI, 0.91-1.13, $P$ = .803) after multivariable adjustment.

## DISCUSSION

Our study revealed that DAPT was prescribed to approximately 1 out of 5 patients with established CVD, the CHARISMA subgroup in which DAPT may provide benefit. In the subgroup of patients with multiple risk factors for whom CHARISMA suggests that DAPT may be harmful, prescription rates were low. Across 14 calendar quarters, prescription rates of DAPT did not change significantly for patients with established CVD but decreased for patients with multiple risk factors. Our findings have the following implications:

***Adoption of DAPT in patients with established CVD appears modest.*** While the publication of the primary CHARISMA findings[5] and additional subgroup analyses[6,7] have suggested benefit from DAPT in patients with established CVD, its use has likely been tempered by the publication of several editorials expressing concern regarding the validity of subgroup analysis. The editorial accompanying the trial was unfavorable, recommending that "DAPT [be] avoided in these patients with stable disease."[9] A review by Drs Kaul and Diamond describes several methodological concerns regarding the positive results for the established CVD subgroup analyses.[8] The stroke literature also urges restraint in using DAPT for secondary prevention.[16,17] Overall, controversy over the

**Table 1.** Patient Characteristics

| Characteristics | Established CVD | Multiple Risk Factors |
|---|---|---|
| **n** | 167,839 | 20,478 |
| **Age, mean (standard deviation)** | 68.5 (11.0) | 71.7 (9.8) |
| **Gender** | | |
| Male | 99,549 (59.3%) | 9177 (44.8%) |
| Female | 67,811 (40.4%) | 11,282 (55.1%) |
| Missing | 497 (0.3%) | 19 (0.1%) |
| **Race** | | |
| White | 64,833 (38.6%) | 7546 (36.8%) |
| Black | 7586 (4.5%) | 1612 (7.9%) |
| Other | 917 (0.5%) | 135 (0.7%) |
| Missing | 94,503 (56.3%) | 11,185 (54.6%) |
| **BMI, median (interquartile range)** | 29.0 (25.5-33.1) | 29.7 (26.0-34.6) |
| **CVD risk factors** | | |
| Diabetes mellitus | 43,700 (26.0%) | 13,156 (64.2%) |
| Hypertension (systolic ≥150 mm Hg) | 128,310 (76.5%) | 18,784 (91.7%) |
| Hyperlipidemia | 126,287 (75.2%) | 19,160 (93.6%) |
| Current smoking | 24,570 (18.8%) | 6112 (33.4%) |
| **CVD** | | |
| Coronary artery disease | 150,682 (89.8%) | 0 (0.0%) |
| Stable angina | 17,368 (10.3%) | 0 (0.0%) |
| Unstable angina | 3657 (2.2%) | 0 (0.0%) |
| CABG surgery within 12 months | 9521 (6.1%) | 0 (0.0%) |
| Previous myocardial infarction | 33,079 (19.9%) | 0 (0.0%) |
| Transient ischemic sttack/stroke | 23,423 (14.0%) | 0 (0.0%) |
| Peripheral arterial disease | 27,069 (16.1%) | 0 (0.0%) |
| **Insurance** | | |
| None | 7625 (4.5%) | 862 (4.2%) |
| Private | 79,561 (47.4%) | 8697 (42.5%) |
| Medicare fee-for-service | 56,013 (33.4%) | 8938 (43.6%) |
| Medicare managed care | 5916 (3.5%) | 831 (4.1%) |
| Medicaid | 2052 (1.2%) | 246 (1.2%) |
| Other | 3748 (2.2%) | 348 (1.7%) |
| Missing | 12,924 (7.7%) | 556 (2.7%) |
| **Antiplatelet medications** | | |
| Aspirin only[a] | 96,610 (57.6%) | 11,580 (56.5%) |
| Clopidogrel only | 7282 (4.3%) | 460 (2.2%) |
| Aspirin and clopidogrel | 34,462 (20.5%) | 707 (3.5%) |
| Neither | 29,485 (17.6%) | 7731 (37.8%) |
| Either aspirin or clopidogrel | 138,354 (82.4%) | 12,747 (62.2%) |
| **Other medications** | | |
| Beta-blocker | 103,122 (61.4%) | 10,203 (49.8%) |
| ACE inhibitor/ARB | 97,822 (58.3%) | 13,863 (67.7%) |
| Statin | 122,326 (72.9%) | 13,908 (67.9%) |
| Nonstatin antidyslipidemic | 43,401 (25.9%) | 4604 (22.5%) |

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; CVD, cardiovascular disease.
[a] $P < .001$ for all comparisons except aspirin only ($P = .006$).

subgroup analysis and lack of robust findings in the primary study population likely explains the modest adoption of DAPT in patients with known CVD.

***Use of DAPT in patients with multiple risk factors who may be harmed by treatment was low and decreased.*** Given the increased risk of all-cause and cardiovascular mortality in this subgroup, the CHARISMA investigators concluded that there is no role for DAPT for primary prevention of CVD.[18] It is reassuring to note that DAPT prescription for primary prevention was low in our study, but for unclear reasons, 3.5% of these patients were still prescribed DAPT. While it is possible that there was misclassification of patients into the 2 study groups (eg, either patients met CHARISMA criteria for established CVD which were not recorded in the registry or patients met

**Table 2.** Dual Antiplatelet Prescription by CVD Diagnosis

| Diagnosis | % Prescribed A+C |
|---|---|
| Coronary artery disease | 21.6% |
| Previous myocardial infarction | 29.5% |
| Transient ischemic attack/stroke | 15.3% |
| CABG surgery within 12 months | 19.7% |
| Peripheral arterial disease | 23.9% |

A+C indicates aspirin plus clopidogrel; CABG, coronary artery bypass graft; CVD, cardiovascular disease.

**Table 3.** Antiplatelet Medication Prescription, by Calendar Quarter

| Calendar Quarter | n | Aspirin Only | Clopidogrel Only | Aspirin and Clopidogrel | Neither | Either Aspirin or Clopidogrel |
|---|---|---|---|---|---|---|
| **Established CVD** | | | | | | |
| Q2 2008 | 8534 | 60.0% | 5.1% | 20.3% | 14.6% | 85.4% |
| Q3 2008 | 9985 | 61.5% | 4.6% | 19.5% | 14.5% | 85.5% |
| Q4 2008 | 6607 | 62.9% | 4.2% | 19.5% | 13.5% | 86.5% |
| Q1 2009 | 5681 | 59.9% | 5.2% | 20.9% | 14.0% | 86.0% |
| Q2 2009 | 4739 | 59.7% | 5.1% | 21.7% | 13.5% | 86.5% |
| Q3 2009 | 6761 | 57.7% | 5.3% | 21.0% | 16.0% | 84.0% |
| Q4 2009 | 7967 | 58.7% | 4.4% | 21.3% | 15.7% | 84.3% |
| Q1 2010 | 27,866 | 54.9% | 4.3% | 22.2% | 18.5% | 81.5% |
| Q2 2010 | 23,223 | 54.6% | 4.8% | 22.3% | 18.3% | 81.7% |
| Q3 2010 | 20,121 | 59.7% | 3.7% | 18.9% | 17.7% | 82.3% |
| Q4 2010 | 17,978 | 59.9% | 3.7% | 19.5% | 17.0% | 83.0% |
| Q1 2011 | 11,604 | 55.6% | 4.0% | 20.2% | 20.1% | 79.9% |
| Q2 2011 | 8775 | 55.7% | 4.4% | 17.4% | 22.5% | 77.5% |
| Q3 2011 | 7998 | 53.9% | 3.4% | 20.2% | 22.5% | 77.5% |
| *P* for trend | | <.001 | <.001 | .002 | <.001 | <.001 |
| **Multiple risk factors** | | | | | | |
| Q2 2008 | 891 | 55.4% | 3.3% | 4.3% | 37.0% | 63.0% |
| Q3 2008 | 1187 | 57.0% | 3.1% | 5.3% | 34.6% | 65.4% |
| Q4 2008 | 834 | 57.7% | 2.4% | 4.1% | 35.9% | 64.1% |
| Q1 2009 | 771 | 59.9% | 2.6% | 3.4% | 34.1% | 65.9% |
| Q2 2009 | 715 | 58.0% | 2.5% | 6.3% | 33.1% | 66.9% |
| Q3 2009 | 830 | 57.2% | 2.9% | 3.5% | 36.4% | 63.6% |
| Q4 2009 | 932 | 55.5% | 2.6% | 3.6% | 38.3% | 61.7% |
| Q1 2010 | 2842 | 57.3% | 2.1% | 3.6% | 36.9% | 63.1% |
| Q2 2010 | 2421 | 54.2% | 2.8% | 4.4% | 38.7% | 61.3% |
| Q3 2010 | 2277 | 55.3% | 1.9% | 2.6% | 40.2% | 59.8% |
| Q4 2010 | 2136 | 54.3% | 1.8% | 2.9% | 41.0% | 59.0% |
| Q1 2011 | 1834 | 59.2% | 1.7% | 3.0% | 36.0% | 64.0% |
| Q2 2011 | 1409 | 54.2% | 1.7% | 2.3% | 41.9% | 58.1% |
| Q3 2011 | 1399 | 60.9% | 1.6% | 1.5% | 36.0% | 64.0% |
| *P* for trend | | .967 | <.001 | <.001 | <.001 | <.001 |

CVD indicates cardiovascular disease; Q2 2008, second calendar quarter 2008.

undocumented exclusion criteria such as AF or PCI), we cannot exclude the possibility that a small number of patients with multiple cardiovascular risk factors were prescribed both aspirin and clopidogrel, either unaware that or choosing not to believe that this regimen might cause harm. Overall, it appears that clinicians have largely avoided the use of clopidogrel for primary prevention in patients with multiple risk factors. Outpatient registries such as PINNACLE may prove useful for monitoring the extent to which patients continue to receive DAPT despite evidence suggesting potential harm.

Physicians apply the CHARISMA subgroup analyses' findings somewhat inconsistently, avoiding DAPT for the multiple risk factor subgroup but prescribing DAPT to a modest fraction of patients with established CVD. However, it is reasonable for clinicians to hold the findings of the 2 subgroup analyses to somewhat different standards. On one hand, because harm was suggested to be likely for patients with multiple risk factors, clinicians would demand a high burden of proof that DAPT is truly safe and efficacious, thus limiting its use. On the other hand, some patients with known CVD may be at such high risk for recurrent events that DAPT was prescribed, even though the evidence of benefit from subgroup analyses was weak, because harm was unlikely.

Given the divergent CHARISMA subgroup results, physicians must employ a clinical judgment approach to DAPT therapy, with the goal of minimizing harm while selectively offering treatment to high-risk individuals even though evidence of benefit is not conclusive. Ultimately, a prospective randomized trial of DAPT would be required to conclude that DAPT benefits patients with established CVD; however, such a trial is unlikely because US patent protection for clopidogrel expired in 2012.[17] In the absence of direct evidence from randomized clinical trials, comparative effectiveness studies may have to suffice for providing future evidence to guide optimal use of DAPT for patients with established CVD.

***Limitations.*** Our study should be interpreted in the context of the following limitations. First, PINNACLE did not record all the CVD and risk factor information collected by the CHARISMA trial, and our modified definitions did not fully replicate CHARISMA entry criteria. Our study had fewer patients in the multiple risk factor subgroup relative to the established CVD subgroup compared with CHARISMA. Second, we do not know how many patients prescribed DAPT underwent PCI greater than 1 year prior to registry entry, and some physicians may elect to prescribe DAPT for a prolonged period for patients at elevated risk of stent thrombosis. The optimal duration of DAPT following PCI remains a subject of debate,[12,18,20] and several large, controlled trials to investigate this issue are ongoing.[19] Lastly, our findings reflect the prescribing patterns of clinicians who report data to the PINNACLE registry. Data collection began in 2008, 2 years after the publication of CHARISMA; prescription patterns may differ at nonparticipating clinical practices, and our findings may not be generalizable.

## CONCLUSION

In a large, community-based registry of outpatients with cardiovascular disease, we found that prescription rates of dual antiplatelet therapy for secondary prevention of MACEs in patients with established CVD were modest and stable over time. DAPT for primary prevention in asymptomatic patients with multiple cardiovascular risk factors was low and decreased, but it was still prescribed to 1 out of 30 patients despite evidence suggesting increased MACEs in this subgroup.

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