Title
Contemporary use of dual antiplatelet therapy for preventing cardiovascular events.

Journal
The American Journal of Managed Care, 20(8)

ISSN
1088-0224

Authors
Goldsweig, Andrew M
Reid, Kimberly J
Gosch, Kensey
et al.

Publication Date
2014-08-01

Peer reviewed

HHS Public Access

Author manuscript

Am J Manag Care. Author manuscript; available in PMC 2015 August 17.

Published in final edited form as:

Am J Manag Care. 2014 August ; 20(8): 659–665.

Contemporary Use of Dual Anti-Platelet Therapy for Preventing Cardiovascular Events

Andrew M. Goldsweig, M.D[a], **Kimberly Reid**[b], **Fengming Tang**[b], **Margaret Fang, M.D.**[c], **Thomas M. Maddox, M.D. M.Sc**[d], **Paul S. Chan, M.D, M.Sc.**[b], **David J. Cohen, M.D., M.Sc.**[b], and **Jersey Chen, M.D. M.P.H**[e]

[a]Department of Internal Medicine, Yale University School of Medicine, New Haven CT and Yale-New Haven Hospital, New Haven, CT

[b]Saint Luke's Mid-America Heart Institute, University of Missouri-Kansas City, Kansas City, MO

[c]Department of Internal Medicine, University of San Francisco, San Francisco, CA

[d]Veterans Administration Eastern Colorado Health Care System and Department of Medicine (Cardiology), University of Colorado ,Denver, CO

[e]Section of Cardiovascular Medicine, Department of Internal Medicine, Yale University School of Medicine, New Haven, CT

Abstract

Objective—CHARISMA was a landmark randomized clinical trial that failed to demonstrate a benefit of dual anti-platelet therapy (DAPT) in preventing cardiovascular events in the overall study population, but subgroup analyses suggested benefit for patients with established cardiovascular disease and harm for asymptomatic patients with multiple risk factors. The use of DAPT following CHARISMA in contemporary clinical practice is unknown.

Study design—Retrospective analysis of a large clinical registry of outpatients with established cardiovascular disease or risk factors.

Methods—Clinical characteristics and prescription rates of aspirin and clopidogrel were compared for patients with established cardiovascular disease, and for patients with only multiple risk factors. Prescription of DAPT by calendar quarter was evaluated from 2008 to 2009 using multivariable Poisson regression models.

Results—Of 41,131 patients with established cardiovascular disease, 20.4% were prescribed both aspirin and clopidogrel. Of 5,100 patients with multiple risk factors but no known cardiovascular disease, 4.6% were prescribed both aspirin and clopidogrel. Rates of prescription of DAPT did not change significantly over seven calendar quarters in either group.

Conclusions—Use of DAPT is modest in patients with established cardiovascular disease for whom the CHARISMA trial suggested benefit, and prescription rates have remained stable over time. Use of DAPT in patients with risk factors only for whom DAPT may lead to harm is low but

CORRESPONDING AUTHOR: Jersey Chen, Yale University School of Medicine, Section of Cardiovascular Medicine, P.O. Box 208017, 333 Cedar St., New Haven, CT 06520-8056. Telephone: (203) 785-4127. Fax: (203) 483-8314, jersey.chen@yale.edu.

not zero; further investigation is warranted as to why these patients are prescribed both aspirin and clopidogrel.

Keywords

aspirin; clopidogrel; cardiovascular disease; CHARISMA

INTRODUCTION

Adding clopidogrel to aspirin has well-established benefits in settings of acute coronary syndrome (ACS)[1] and percutaneous coronary intervention (PCI).[2,3] However, the role of dual anti-platelet therapy (DAPT) with aspirin and clopidogrel for secondary prevention of cardiovascular (CV) events 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 failed to demonstrate a benefit of DAPT in preventing CV events in its overall study population, which consisted of patients with established CVD or patients with multiple CV risk factors but without established CVD. However, a pre-specified subgroup analysis of CHARISMA demonstrated divergent results for the two study subgroups: fewer CV events in patients with established CVD, but more CV events for patients with multiple risk factors.[4,5]

Editorial commentators generally discounted the subgroup analysis and recommended against the use of DAPT among patients with either established CVD or multiple cardiovascular risk factors. However, the use of DAPT in contemporary clinical practice is unknown. Accordingly, we analyzed data from a large registry of cardiovascular outpatient visits to examine prescription rates and trends over time for DAPT among patients represented by CHARISMA.

METHODS

Data

We used data from PINNACLE (Practice INNovation And CLinical Excellence),[6,7] a registry administered by the American College of Cardiology National Cardiovascular Data Registry (ACC-NCDR). PINNACLE contains data on nearly 1,000,000 patient records submitted by more than 1000 participating physicians to date. Data elements include patient demographics (age, sex, race), cardiovascular risk factors (diabetes, hypertension, hyperlipidemia), prior cardiovascular procedures (PCI, coronary artery bypass surgery [CABG]), selected physical examination findings (systolic blood pressure), medications and insurance status.

Study Cohort

We identified PINNACLE subjects meeting the inclusion criteria of the CHARISMA trial, both patients with established CVD and with only multiple CV risk factors.[8] A total of 155,060 patients in PINNACLE were identified from July 2008 to December 2009 who were age 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 12 months after PCI,[9] patients who underwent PCI within the year prior to the outpatient encounter were excluded from the study cohort (n=7841). Subjects with AMI within the year prior to the index outpatient visit were also excluded as DAPT is also indicated for these patients.

In addition, because A+C has been demonstrated to reduce stroke in patients with atrial fibrillation who are not candidates for warfarin anticoagulation[10], patients with atrial fibrillation were excluded (n=26,713). Patients prescribed warfarin were also excluded, similar to the CHARISMA trial (n=17,144). Our final cohort was comprised of 46,231 patients.

Consistent with the CHARISMA trial, we classified patients in the study cohort into those with established CVD and those without CVD but multiple cardiovascular risk factors. Patients were categorized as having established CVD if they had a history of CAD (stable or unstable angina or previous MI), transient ischemic attack (TIA), stroke, peripheral arterial disease (PAD), or history of coronary artery bypass surgery (CABG). PCI prior to 12 months of index visit was not recorded but these patients were presumably captured by the data element recording history of CAD. Similarly, patients were classified into the multiple CV risk factor group if they had diabetes mellitus and two of the following risk factors, or at least three of the following risk factors: systolic blood pressure ≥150 mmHg with medical therapy (beta-blocker, calcium channel blocker, angiotensin-converting enzyme inhibitor, angiotensin receptor blockers or diuretics), hyperlipidemia, current smoking and age ≥65 years for males or ≥70 years for females. As PINNACLE did not capture all of the CVD entities and CV risk factors available in CHARISMA, the group definitions for our study were subsets of those for CHARISMA.

Statistical Analysis

Analyses were conducted separately for the established CVD group and the multiple CV risk factor group. We calculated the proportion of patients prescribed anti-platelet medications: aspirin (A) only, clopidogrel (C) only, A+C or neither A nor C. We compared differences in demographic and clinical characteristics across the four anti-platelet regimens using analysis of variance for continuous variables (age) and χ^2-tests for categorical variables. We then developed multivariable Poisson regression models to examine the number of anti-platelet medication prescriptions by calendar quarter, adjusting for age, sex, CV risk factors and insurance status. From these models, we calculated adjusted incidence rate ratios (IRRs) for each anti-platelet medication regimen from the second calendar quarter of 2008 (Q2 2008) to the fourth calendar quarter of 2009 (Q4 2009) using the initial calendar quarter as a baseline. 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 46,231 patients meeting our modified CHARISMA classification criteria: 41,131 patients with established CVD and 5,100 patients with multiple CV risk factors. Patients in the established CVD group were slightly younger than those in the multiple CV risk factor group (68.4 vs. 71.6 years, p<0.001). Patients in the established

CVD group were predominately male (62.6%), while patients in the multiple CV risk factor group were predominately female (57.3%). A history of CAD was the most common reason (90.1%) for classification into the established CVD group; cerebrovascular disease (TIA or stroke) and PAD were less common reasons at 6.8% and 9.0% respectively. Hyperlipidemia (94.8%) and hypertension (92.0%) were the most common CV 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 two groups, but private insurance was the most common health insurance for both established CVD and multiple risk factors groups, followed by fee-for-service Medicare.

Patients with established CVD were more likely than those with multiple CV risk factors to be prescribed aspirin only (61.2% vs. 57.3%, p<0.001), more likely to be treated with clopidogrel only (4.8% vs. 2.8%, p<0.001) and more likely to be treated with DAPT (20.4% vs. 4.6%, p<0.001) (Table 1). Overall prescription rates with any anti-platelet therapy (aspirin or clopidogrel or both) were 86.4% in the established CVD group and 64.6% in the multiple risk factor group.

Unadjusted DAPT treatment rates rose modestly in both study populations. For the established CVD group, unadjusted prescription rates of A+C increased during the study period from 19.0% in Q2 2008 to 25.0% in Q4 2009 (p<0.001) (Table 2). A decline in the prescription of aspirin only was observed from 61.6% in Q2008 to 56.4% in Q4 2009 in the established CVD group (p<0.001). DAPT use also increased in the multiple risk factor group, but the absolute increase was much smaller than for the CVD group. (4.2% in Q2 2008 to 5.1% in Q4 2009; p<0.001) (see Table 2). The use of aspirin only was unchanged during the study period (55.1% to 55.1%, p=0.67) in this group.

In Poisson regression models adjusting for age, sex and insurance status, the prescription rates of A+C in the established CVD group did not change significantly over seven calendar quarters (IRR=1.03, 95% confidence interval [95% CI] 0.98 to 1.09, *P*=0.25). The prescription of aspirin alone significantly increased by calendar quarter (IRR 1.34, 95% CI 1.05 to 1.72, *P*=0.02), and the prescription of clopidogrel alone remained unchanged (IRR=1.01 95% CI, 0.96 to 1.05, *P*=0.80). In the multiple risk factor group, no significant changes over time were observed in the prescription of aspirin (IRR 1.03, 95% CI 0.98–1.08, *P*=0.21), clopidogrel (IRR 1.03, 95% CI 0.93–1.14, *P*=0.56) or both (IRR 1.03, 95% CI 0.92–1.15, *P*=0.57) after multivariable adjustment.

DISCUSSION

Our study demonstrated DAPT was prescribed in approximately one out of four patients with established CVD, the subgroup in which DAPT may provide benefit. In the subgroup of patients with multiple CV risk factors for whom current evidence suggests that DAPT may be harmful, prescription rates were low, but not neglible. Prescription rates of A+C did not change significantly across seven calendar quarters for either subgroup. Our findings have the following implications:

Adoption of DAPT in patients with established CVD appears modest

While subgroup analyses 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, warning that "extracting favorable p values from subgroups should be resisted and DAPT avoided in these patients with stable disease".[11] A Letter to the Editor in the Journal of the American College of Cardiology concurred, comparing the subgroup analysis of CHARISMA to similar analysis in the CAPRIE trial[12] and stating that, "positive subgroups within negative trials such as the CHARISMA trial are virtually always the result of confounding or bias, especially post hoc defined subgroups".[13] A review by Drs. Kaul and Diamond cites three major problems with interpreting CHARISMA subgroup analyses: 1) the overall analysis was not statistically significant; 2) the two sub groups yielded opposite treatment effects as opposed to similar effects of differing degree; and 3) no Bonferroni correction was performed to account for the multiple comparisons.[14] The stroke literature also urges restraint in using DAPT for secondary prevention.[15,16] Overall, controversy over the subgroup analysis and lack of robust findings in the primary study population likely explains the modest adoption of DAPT in patients with known CVD.

Subsequent subgroup analyses of CHARISMA appear to have had limited impact on prescription rates of DAPT

Following the main CHARISMA trial results, several additional subgroup analyses have been published that suggest that A+C may confer benefit for particular populations. One such analysis limited to established CVD subjects with prior MI, ischemic stroke or symptomatic PAD demonstrated a significant reduction in the primary trial endpoint (hazard ratio HR=0.83, 95% CI 0.72 to 0.96, p=0.01).[5] Another substudy focused exclusively on PAD patients and found a significantly lower rate of MI (HR 0.63, 95% CI 0.42 to 0.96) and hospitalization for ischemic events (HR 0.81, 95% CI 0.68 to 0.95) for those treated with A +C compared with aspirin alone.[17] However, publication of these reports during our study period did not appear to have significantly increased the prescription of A+C for patients with established CVD.

Use of DAPT in patients with multiple risk factor who may be harmed by treatment was low but not zero

Given the increased risk of mortality in this subgroup of patients, the CHARISMA investigators concluded that there is no role for A+C for primary prevention of CVD.[19] It is reassuring to note that DAPT for primary prevention in these patients was low in our study, but for unclear reasons, approximately 5% of these patients were still prescribed A+C. While it is possible that there was misclassification of patients in the 2 study groups (e.g., patients met CHARISMA criteria for established CVD but which was not recorded in the registry), we cannot exclude the possibility that a small number of patients with multiple CV risk factors were prescribed both aspirin and clopidogrel in spite of evidence that this regimen may cause harm. For such patients receiving treatments inconsistent with evidence-based practice, outpatient registries such as PINNACLE may prove useful for improving quality.

Overall there appears to be a slight inconsistency on the part of physicians with respect their response to use of DAPT in each subgroup— clinicians have shied away from DAPT for the multiple risk factor subgroup where harm was suggested, but have engaged in modest prescription of DAPT for patients with established CVD where benefit was suggested. However, it would be reasonable for clinicians to hold the findings of the two subgroup analyses to different standards when deciding on the use of DAPT. On the one hand, once harm was suggested for asymptomatic patients with multiple risk factors, many clinicians would demand a high burden of proof that DAPT was 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 could be considered, even though evidence of benefit from subgroup analyses was weak,. Ultimately, a prospective randomized trial of DAPT would be required to conclude that DAPT benefits patients with established CVD; however, this is unlikely given that the patent protection for clopidogrel in the U.S. will expire in 2012. {Amiel, January 25`, 2011 #61} In the absence of direct evidence from randomized clinical trials, comparative effectiveness studies may provide 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 of the CVD and CV risk factor information collected by the CHARISMA trial, and our modified definitions of CVD and CV risk factors did not perfectly replicate CHARISMA entry criteria. Second, we do not know how many patients prescribed A+C underwent PCI more than one year prior to registry entry, and some physicians may have elected to prescribe DAPT for a prolonged period for patients at elevated risk of stent thrombosis. This is because the optimal duration of A+C following PCI remains a subject of debate[9,20,21] and several large, randomized controlled trials to investigate this issue are ongoing[22]. Lastly, our findings reflect the prescribing patterns of clinicians who report data to the PINNACLE registry; therefore, prescription patterns may differ at non-participating 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 anti-platelet therapy for secondary prevention of CV events in patients with established CVD was modest and stable over time. However, dual anti-platelet therapy for primary prevention in patients with multiple CV risk factors was prescribed in 1 of out 20 patients, despite evidence suggesting harm in this subgroup.

Acknowledgments

PINNACLE Registry® is an initiative of the American College of Cardiology Foundation and MedAxiom. The Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership is a Founding Sponsor of the PINNACLE Registry. Bristol-Myers Squibb and Sanofi are manufacturers of clopidogrel, but have neither reviewed or approved this manuscript.

SOURCE OF FUNDING

This research was supported by the American College of Cardiology Foundation’s National Cardiovascular Data Registry (NCDR). The views expressed in this manuscript represent those of the authors, and do not necessarily represent the official views of the NCDR or its associated professional societies identified at www.ncdr.com

Dr. Chen is supported by an Agency for Healthcare Research and Quality (AHRQ) Career Development Award (1K08HS018781-01). Dr. Chan is supported by a Career Development Grant Award (K23HL102224) from the NHLBI.

References

1. Yusuf S, Zhao F, Mehta S, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. Aug; 2001 345(7):494–502. [PubMed: 11519503]
2. Steinhubl S, Berger P, Mann, et al. Early and sustained dual oral anti-platelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA. Nov; 2002 288(19): 2411–2420. [PubMed: 12435254]
3. Mehta S, Yusuf S, Peters R, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet. Aug; 2001 358(9281):527–533. [PubMed: 11520521]
4. Wang T, Bhatt D, Fox K, et al. An analysis of mortality rates with dual-anti-platelet therapy in the primary prevention population of the CHARISMA trial. Eur Heart J. Sep; 2007 28(18):2200–2207. [PubMed: 17673448]
5. Bhatt D, Flather M, Hacke W, et al. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. J Am Coll Cardiol. May; 2007 49(19):1982–1988. [PubMed: 17498584]
6. PINNACLE Registry. National Cardiovascular Data Registry. www.pinnacleregistry.org. Available at: www.pinnacleregistry.org
7. Chan PS, Oetgen WJ, Buchanan D, et al. Cardiac performance measure compliance in outpatients: the American College of Cardiology and National Cardiovascular Data Registry's PINNACLE (Practice Innovation And Clinical Excellence) program. J Am Coll Cardiol. Jun; 2010 56(1):8–14. [PubMed: 20620710]
8. Bhatt D, Fox K, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med. Apr; 2006 354(16):1706–1717. [PubMed: 16531616]
9. King SB, Smith SC, Hirshfeld JW, et al. 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines. J Am Coll Cardiol. Jan; 2008 51(2):172–209. [PubMed: 18191745]
10. Connolly S, Pogue J, Hart R, et al. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med. May; 2009 360(20):2066–2078. [PubMed: 19336502]
11. Pfeffer M, Jarcho J. The charisma of subgroups and the subgroups of CHARISMA. N Engl J Med. Apr; 2006 354(16):1744–1746. [PubMed: 16531617]
12. Toplak H, Bahadori B, Wascher T. CAPRIE trial. Lancet. Feb.1997 349(9048):354. author reply 356. [PubMed: 9024394]
13. Gebel JJ. The CAPRIE-like subgroups of CHARISMA: a CAPRIEciously biased analysis of an unCHARISMAtic truth. J Am Coll Cardiol. Oct.2007 50(17):1704. author reply 1704–1705. [PubMed: 17950155]
14. Kaul S, Diamond GA. Trial and error. How to avoid commonly encountered limitations of published clinical trials. J Am Coll Cardiol. Feb; 2010 55(5):415–427. [PubMed: 20117454]
15. Alberts M. CHARISMA revisited: is the glass half full or just empty? Int J Stroke. Feb; 2008 3(1): 16–19. [PubMed: 18705911]
16. Bousser M. Life after CHARISMA. Int J Stroke. Aug; 2006 1(3):167–168. [PubMed: 18706041]
17. Cacoub P, Bhatt D, Steg P, Topol E, Creager M, Investigators C. Patients with peripheral arterial disease in the CHARISMA trial. Eur Heart J. Jan; 2009 30(2):192–201. [PubMed: 19136484]
18. Collet J, Montalescot G, Steg P, et al. Clinical outcomes according to permanent discontinuation of clopidogrel or placebo in the CHARISMA trial. Arch Cardiovasc Dis. Jun-Jul;2009 102(6–7):485–496. [PubMed: 19664568]
19. Berger P, Bhatt D, Fuster V, et al. Bleeding complications with dual anti-platelet therapy among patients with stable vascular disease or risk factors for vascular disease: results from the

Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial. Circulation. Jun; 2010 121(23):2575–2583. [PubMed: 20516378]

20. Park SJ, Park DW, Kim YH, et al. Duration of dual anti-platelet therapy after implantation of drug-eluting stents. N Engl J Med. Apr; 2010 362(15):1374–1382. [PubMed: 20231231]
21. Tanzilli G, Greco C, Pelliccia F, et al. Effectiveness of two-year clopidogrel + aspirin in abolishing the risk of very late thrombosis after drug-eluting stent implantation (from the TYCOON [two-year ClOpidOgrel need] study). Am J Cardiol. Nov; 2009 104(10):1357–1361. [PubMed: 19892050]
22. Mauri L, Kereiakes DJ, Normand SL, et al. Rationale and design of the dual anti-platelet therapy study, a prospective, multicenter, randomized, double-blind trial to assess the effectiveness and safety of 12 versus 30 months of dual anti-platelet therapy in subjects undergoing percutaneous coronary intervention with either drug-eluting stent or bare metal stent placement for the treatment of coronary artery lesions. Am Heart J. Dec; 2010 160(6):1035–1041.e1031. [PubMed: 21146655]

TAKE-AWAY POINTS

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

- Dual anti-platelet therapy with aspirin and clopidogrel was prescribed in 20.4% of patients with established cardiovascular disease, a subgroup for whom benefit was found.
- Among patients with multiple risk factors only for whom dual anti-platelet therapy was associated with harm in subgroup analyses, 4.6% of patients were prescribed aspirin and clopidogrel; this may represent an area for quality improvement efforts.

Table 1

Patient Characteristics

	Established CVD	Multiple Risk Factor
n	41131	5100
Age, mean (standard deviation)	68.4 (10.9)	71.6 (9.8)
Gender		
Male	62.6%	42.7%
Female	37.4%	57.3%
CVD Risk Factors		
Diabetes mellitus	28.6%	66.9%
Hypertension (Systolic Blood Pressure 150)	77.9%	92.0%
Hyperlipidemia	78.2%	94.8%
Current Smoking	14.4%	25.9%
CVD		
Coronary Artery Disease	90.1%	0.0%
Stable Angina	7.9%	0.0%
Unstable Angina	1.9%	0.0%
CABG Surgery Within 12 Months	4.0%	0.0%
Previous Myocardial Infarction	20.9%	0.0%
Transient Ischemic Attack/Stroke	6.8%	0.0%
Peripheral Arterial Disease	9.0%	0.0%
Insurance		
None	4.5%	6.3%
Private	59.1%	50.2%
Medicare fee-for-service	30.9%	36.9%
Medicare managed care	2.6%	3.6%
Medicaid	1.6%	1.7%
Other	1.3%	1.3%
Medications		
Aspirin Only	61.2%	57.3%
Clopidogrel Only	4.8%	2.8%
Aspirin and Clopidogrel	20.4%	4.6%

Am J Manag Care. Author manuscript; available in PMC 2015 August 17.

	Established CVD	Multiple Risk Factor
Neither	13.6%	35.4%
Either Aspirin or Clopidogrel	86.4%	64.6%

$P < 0.001$ for all comparisons

Abbreviations: CABG, coronary artery bypass graft; CVD, cardiovascular disease

Table 2

Anti-platelet Medication Prescription, by Calendar Quarter

Established CVD								
	Q2 2008	**Q3 2008**	**Q4 2008**	**Q1 2009**	**Q2 2009**	**Q3 2009**	**Q4 2009**	***P* for trend**
n	8191	9964	6579	5724	4598	3232	2843	
Aspirin Only	61.6%	62.6%	63.8%	60.3%	60.0%	58.4%	56.4%	<0.001
Clopidogrel Only	5.3%	4.6%	4.2%	5.1%	5.1%	4.6%	4.4%	0.33
Aspirin and Clopidogrel	19.0%	19.2%	19.3%	21.2%	21.9%	21.9%	25.0%	<0.001
Neither	14.2%	13.6%	12.7%	13.3%	13.0%	15.1%	14.1%	0.78
Either Aspirin or Clopidogrel	85.8%	86.4%	87.3%	86.7%	87.0%	84.9%	85.9%	86.1%

Multiple Risk Factors								
	Q2 2008	**Q3 2008**	**Q4 2008**	**Q1 2009**	**Q2 2009**	**Q3 2009**	**Q4 2009**	***P* for trend**
n	851	1154	816	753	692	478	356	
Aspirin Only	55.1%	57.5%	57.4%	59.5%	58.8%	56.3%	55.1%	0.67
Clopidogrel Only	3.1%	3.1%	2.5%	2.5%	2.6%	2.5%	2.8%	0.45
Aspirin and Clopidogrel	4.2%	5.3%	3.9%	3.5%	6.1%	3.8%	5.1%	0.85
Neither	37.6%	34.1%	36.3%	34.5%	32.5%	37.5%	37.1%	0.79
Either Aspirin or Clopidogrel	62.4%	65.9%	63.7%	65.5%	67.5%	62.6%	62.9%	0.79

Abbreviations: CVD, cardiovascular disease