No cover image available

Economic Dimensions of Personalized and Precision Medicine

Ernst R. Berndt (ed.) et al.

https://doi.org/10.7208/chicago/9780226611235.001.0001

Published: 2019 **Online ISBN:** 9780226611235 **Print ISBN:** 9780226611068

CHAPTER

10 The Value of Cytochrome P450 2C19 Pharmacogenomic Information for Patients Receiving Clopidogrel Therapy Following a Major Cardiovascular Event: Evidence from Geisinger

Rebecca A. Pulk, Jove Graham, Frank R. Lichtenberg, Daniel Maeng, Marc S. Williams, Eric Wright

https://doi.org/10.7208/chicago/9780226611235.003.0011 Pages 273–304

Published: April 2019

Abstract

Dual antiplatelet therapy, combining a P2Y12 inhibitor and aspirin, is central to management of patients with acute coronary syndromes. Clopidogrel is a commonly prescribed thienopyridine P2Y12 inhibitor used to prevent secondary events following a myocardial infarction/percutaneous coronary intervention. Clopidogrel effectiveness has been linked to proper function of metabolic enzyme cytochrome P450 2C19 (CYP2C19). Testing for CYP2C19 genetic changes that result in decreased activity has been proposed as a mechanism by which to identify clopidogrel non-responders a priori. Robust real-world studies evaluating the impact of genotype-guided antiplatelet selection on clinical, utilization and outcome metrics are lacking. We linked clinical and financial data on 2,595 Geisinger patients prescribed antiplatelet therapy without pharmacogenomic insight. Leveraging post-hoc, research-generated pharmacogenomic information, we describe the potential value of pharmacogenomic information in the selection of clopidogrel as the P2Y12 inhibitor therapy. Among patients examined, CYP2C19 loss of function did not predict the probability of later adverse events, clinical utilization or total medical costs within the 12 months after clopidogrel initiation. Universal CYP2C19 pharmacogenomic testing to inform P2Y12 selection following an MI/PCI index event within the Geisinger patient population studied would not have led to improved clinical outcomes, decreased health care utilization or lower total medical cost.

Keywords: pharmacogenomics, cost-effectiveness, Clopidogrel

Subject: Microeconomics

10.1 Introduction

Pharmacogenomics has the potential to improve clinical outcomes by optimizing the selection of medications to maximize benefit and minimize risk for an individual patient. This subset of precision medicine could decrease medical expenditure by increasing the clinical effectiveness of commonly prescribed medications while minimizing adverse drug events (Snyder et al. 2014; Schildcrout et al. 2012). The potential clinical utility of pharmacogenomics can be observed by the steady increase in the number of practice guidelines published to direct the use of medications based on genetic markers (Pharmacogenomics Knowledgebase, various; Canadian Pharmacogenomics Network for Drug Safety, various).

One of the most popular applications of pharmacogenomic information surrounds the use of genotype-guided antiplatelet therapy (Mathias et al. 2017; Luzum et al. 2017; Cavalari 2015). Antiplatelet agents are commonly used to prevent platelet adhesion and secondary occlusive events following an acute coronary syndrome event including myocardial infarction (MI) or percutaneous coronary intervention (PCI)
p. 274 (Sabouret and Taiel-Sartral ↳ 2014). Following MI and PCI, medical management consists of a combination of aspirin (an irreversible inhibitor of platelets), and a P2Y12 inhibitor (currently approved agents include clopidogrel, ticagrelor, prasugrel, and cangrelor, IV only; Levine et al. [2016]).

Clopidogrel is a prodrug that is activated in the body through the metabolic enzyme cytochrome P450 2C19 (CYP2C19). Genetic variation within *CYP2C19*, the gene that encodes CYP2C19, is common within the general population; available estimates of variants leading to loss of enzyme function within a Caucasian population are between 12 and 14 percent (Scott et al. 2013). Patients carrying variants that decrease the function of CYP2C19 are less able to transform clopidogrel to its active metabolite and are at a greater risk of thrombosis, while those carrying variants that increase function receive a higher than expected dose of clopidogrel and are at risk for bleeding events (Swen et al. 2011). Clinical guidelines exist to guide the utilization of clopidogrel in the presence of pharmacogenomic information, but routine use in clinical care is limited, due in part to time to receive testing results, reimbursement challenges, and implementation lag (Jang et al. 2012). Other P2Y12 inhibitors are not dependent upon CYP2C19 for activation, and biological activity is not influenced by *CYP2C19* genetic variations that affect enzyme activity. However, clopidogrel remains a highly utilized agent due to its "first in class" status and earlier generic availability (May 2012 in the United States).

Available evidence suggests that the conversion of clopidogrel to its active form is necessary to reduce subsequent thrombotic events. Several studies have sought to associate genomic makeup with clinical endpoints. A meta-analysis of sixteen cohort studies including 7,035 patients with at least one loss of function (LOF) allele for *CYP2C19* and 13,750 with normal enzyme function (NF), found that patients who carry at least one LOF allele for the *CYP2C19* gene are more likely to experience cardiac death (OR 2.18, 95 percent CI 1.37-3.47), stent thrombosis (OR of 2.41, 95 percent CI 1.763.30), or experience a subsequent MI (OR 1.42, 95 percent CI 1.12-1.81) in the first twelve months of therapy due to insufficient formation of the active metabolite of clopidogrel (Zabalza et al. 2012). In a stratified a priori analysis, the OR for composite adverse outcomes was more pronounced in the Asian population with LOF than Western populations with LOF (OR 1.89 vs. 1.28), suggesting a less pronounced effect among a Western (Caucasian) population. A second systematic review and meta-analysis published by Zabalza and colleagues included thirteen studies and over 16,000 individuals evaluating both LOF (*CYP2C19*2*) and gain of function (*CYP2C19*17*) on the incidence of cardiovascular outcomes and major bleeding risk (Notaran-gelo, Bontardelli, and Merlini 2013). Despite noting a significant increase in stent thrombosis (HR 2.24, 95 percent CI 1.52-3.30) among LOF allele carriers, there was no significant increased risk of cardiovascular events with LOF alleles (HR 1.23, 95 percent CI 0.97-1.55). Additional work has suggested that *CYP2C19* LOF genotype is responsible for as little as 12 percent of a patient's clinical response to clopidogrel (Borse et al. 2017).

p. 275 Though second generation antiplatelet therapies carry a higher acquisition cost, it is believed that, for patients carrying a LOF change in *CYP2C19*, this increased front-end cost of the therapeutic is offset by lower rates of follow-on occlusive events.

Many papers testing models of the cost effectiveness of *CYP2C19*-guided antiplatelet therapy have been published, and reactively genotyping patients following PCI is suggested to have a positive economic impact by preventing bleeding and occlusive events (Johnson et al. 2015; Jiang and You 2017; Mayo Clinic 2013). A large clinical trial evaluating outcomes with *CYP2C19* genotype-guided antiplatelet therapy after PCI is ongoing (University of Florida, various). Data from pragmatic and observational studies and smaller trials support improved outcomes with genotyping after PCI and use of alternative antiplatelet therapy in patients with a *CYP2C19* genotype associated with reduced clopidogrel effectiveness. One observational cohort trial focused on the demonstration of the potential benefit of *CYP2C19* genotyping in the selection of P2Y12 inhibitor is underway at the University of Florida (Deneer 2013); it is designed as an implementation-effectiveness trial measuring both the ability to genotype patients within forty-eight hours of heart catherization, as well as the clinical outcomes of patients following genotype-guided P2Y12 selection. A prospective cost-effectiveness trial of genotype-guided treatment with antiplatelet drug selection is being conducted in Europe and is examining clinical, safety, and economic outcomes (Carey et al. 2016).

There are many limitations to the available clinical data linking *CYP2C19* genotype to patient outcomes associated with clopidogrel treatment. Much of the research supporting the clinical benefit of *CYP2C19* genotyping in antiplatelet selection has utilized data from clinical trials from which patients with high medical complexity, advanced age, previous cardiovascular disease, or serious comorbidities have been excluded. In addition, although economic models exist, data on the actual impact of *CYP2C19* testing on the costs of care in a real-world environment are lacking (Johnson et al. 2015). Additionally, though current clinical guidelines specify that any patient carrying a LOF change within *CYP2C19* be considered for alternative antiplatelet therapy, the evidence for this shift in treatment is much stronger for those with two LOF alleles (Pharmacogenomics Knowledgebase, various; Scott et al. 2013).

Geisinger has made significant investments in the MyCode Community Health Initiative, which links longitudinal electronic health record data with collected biobank samples to support initiatives aimed at leveraging genomic and phenotypic information (Dewey, Murray, et al. 2016). The MyCode project currently has over 190,000 patients who have consented to participate, with approximately 1,000 additional patients consenting each week. Consent allows broad research use, re-contact, and return of medically actionable results. Whole exome sequencing (WES), high-density genotyping and HLA-typing for MyCode participants is done in partnership with Regeneron Pharmaceuticals, Inc., (the DiscovEHR cohort) (Haggerty et al. 2017).
p. 276 Sequencing has been completed and quality controlled for over ↳ 92,000 MyCode participants. Projects focusing on discovery and optimization of outcomes affected by genetic information are underway to capitalize on the growing reservoir of information. The MyCode 90,000 cohort is noted to have an average age of 55.4 years and an average Charlson Comorbidity Index of 3.4. This cohort is 60.54 percent female, and 97.57 percent self-identified as Caucasian (Abul-Husn et al. 2016; Dewey, Gusarova, et al. 2016; Centers for Disease Control and Prevention 2015).

Whole exome sequencing is a genomic sequencing technology that focuses on the information contained in the 1–1.5 percent of human DNA that codes for proteins, with inclusion of some of the gene regulatory regions (promoters and enhancers). This technology, while very powerful for detecting single nucleotide variants and small insertions and deletions (indels), is limited in its ability to detect larger copy number variants and areas of the exome that have repetitive motifs. It does not capture variation for the remainder of the genome outside of these target regions. An exome done as part of a research project or for a diagnostic indication has the potential to yield pharmacogenomic (PGx) data "for free." To date, it has been difficult to directly extract actionable PGx information from WES data, thus literature assessing the cost effectiveness of WES in directing pharmacotherapy is unavailable. However, recent advances in bioinformatics enable extraction of PGx variants from Geisinger's WES data, allowing for real-world studies to assess the impact of variants on selected health outcomes. These advances could potentially be implemented in a clinical environment, allowing for both clinical-and cost-effectiveness estimates.

Despite Geisinger's embrace of genomic research, to date PGx-guided medication selection has not been implemented within our health care system, and monitoring of platelet aggregation is also not routinely performed.

The aim of our analysis is to determine whether clinical endpoints (e.g., recurrent MI), health care utilization (e.g., hospitalizations, emergency visits), or medical costs of care differ among patients with varying *CYP2C19* genotype status prescribed clopidogrel following an acute hospitalization for index MI or PCI within a nine-year window (January 1, 2007–December 31, 2015) within an integrated health delivery system.

10.2 Methods

We conducted a retrospective cohort study using electronic health information combined with administrative claims of incident users of clopidogrel therapy from January 1, 2007–December 31, 2015, who have also consented to the MyCode Community Health Initiative and had completed WES. Our goal was to compare clinical and economic outcomes following initial clopidogrel usage among *CYP2C19* variant populations.

10.2.1 Setting

Geisinger is one of the nation's largest health delivery systems and serves forty-four counties in central,
p. 277 south-central, and northeast Pennsylvania, as ↳ well as six counties in southern New Jersey. The clinic's patient population is very stable: census data indicate that except for two counties, the outmigration rate is less than 1 percent per year.

Geisinger has benefited from an early investment in electronic health records. Geisinger is one of the country's "most wired" health care systems, with an electronic health record (EHR) in all outpatient clinics, patient portal, and other digital means of delivering care. Geisinger began implementation of the Epic Corporation (Verona, WI) EHR in 1996. To date, our EHR database contains information on more than four million patients, with over 600,000 unique patients having encounters in the health system each year. Information from the electronic health record and medical/pharmacy claims are stored in data warehouses accessible to both the clinical and research enterprises. The Epic EHR is now fully implemented and integrated across all Geisinger ambulatory and inpatient sites of care. Participants in the DiscovEHR cohort have a median of twelve years of electronic health record data.

As noted, Geisinger has invested in the MyCode Community Health Initiative centered around a repository of blood DNA and genomic analysis through WES and the DiscovEHR cohort. The WES results are electronically stored and used for query for research purposes and clinical confirmation under protocol. Using the Pharmacogenomics Clinical Annotation Tool or PharmCAT developed from a bioinformatics collaborative, we have the capacity to extract pharmacogenomic gene variants from the WES capture regions, interpret the variant alleles, and generate a report listing these genetic variations for each patient.

10.2.2 Data Sources

All available patient data during the study window were extracted, including EHR, medical claims from our health plan (Geisinger Health Plan [GHP]), and GHP prescription claims. For this study, we used PharmCAT to retrieve LOF variations of CYP2C19 among the MyCode Community Health Initiative participants with WES results.

Clinical Information

Clinical data were extracted from Geisinger's clinical data warehouse, the Clinical Decision Intelligence System (CDIS). This database combines patient information from multiple sources: electronic medical records, patient registries, inpatient billing, outpatient billing, and GHP claims data. Standardized Geisinger value sets were utilized to sort the EHR data to ensure capture of patients with specific conditions. These value sets are comprised of inquiry codes based on ICD-9 and ICD-10 codes, diagnosis groups, and Current Procedural Terminology (CPT) codes, and have been internally validated to reliably capture all Geisinger patients with a given condition through utilization of CDIS. Demographic information for this population
p. 278 can be found in table 10.1. ↳

Table 10.1 Demographics of patients with MI/PCI associated with a hospitalization and P2Y12 inhibitor use

	PCI/MI while hospitalized with P2Y12 use *N*= 3,010	Clopidogrel cohort *N*= 2,595	Clopidogrel cohort, no prior MI/PCI/P2Y12 *N*= 1,578	Clopidogrel cohort patients included in financial analysis *N*= 1,093
Age by deciles (%)				
20-29	3 (0.10)	3(0.12)	3(0.19)	0(0)
30-39	61 (2.03)	49(1.89)	32 (2.03)	11(1.01)
40-49	306(10.17)	242 (9.33)	155(9.82)	93(8.51)
50-59	778 (25.85)	651 (25.09)	400 (25.35)	244 (22.32)
60-69	990 (32.89)	831 (32.02)	498(31.56)	332 (30.38)
70-79	746 (24.78)	694 (26.74)	421 (26.68)	341 (31.20)
80-89 (includes > 89)	126(4.19)	125 (4.82)	69 (4.37)	72 (6.59)
"89"	1 (0.03)	0(0)	0(0)	0(0)
Male sex, *N (%)*	2,018(67.04)	1,719 (66.24)	1,034(65.53)	729 (66.70)
Time as GHS patient (%)				
0-5	82 (2.72)	64 (2.47)	44 (2.79)	29 (2.65)
6-10	400(13.29)	331 (12.76)	180(11.41)	99 (9.06)
11-15	1,149(38.17)	984 (37.92)	624 (39.73)	380 (34.77)
15<	1,379(45.81)	1,216(46.86)	727 (46.07)	585 (53.52)
GHSPCP,iV(%)	1,852(61.53)	1,591(61.31)	1,000 (63.37)	737 (67.43)
Charlson Comorbidity Index at end of study (%)				
0-5	1,386(46.05)	1,120(43.16)	829 (52.53)	465 (42.54)
6-10	1246(41.40)	1116(43.01)	602(38.15)	467 (42.73)
11-15	329 (10.93)	311(11.95)	125 (7.92)	143 (13.08)
15<	49(1.63)	48(1.85)	22(1.39)	18(1.65)
↳ Conditions documented in EHR *N* (%)				
Diabetes	1,566(52.03)	1,370 (52.79)	749 (47.47)	570(52.157)
Hyperlipidemia	2,876 (95.55)	2,483 (95.68)	1,490(94.42)	1,043 (95.43)
Hypertension	2,762(91.76)	2,397 (92.37)	1,416(89.73)	1,007(92.13)
Coronary artery disease	2,975 (98.84)	2,565 (98.84)	1,552(98.32)	1,085 (99.27)
Peripheral vascular disease	726(24.12)	660 (2543)	299(18.95)	263 (24.06)
A-fib	896 (29.77)	815(31.41)	402 (25.48)	351(32.11)

Documented smoker (ever) (%)	1,520(50.50)	1,306(50.33)	770 (48.80)	535 (48.95)
Outcome of interest, ever *N ("As)*				
MI	2,161(71.79)	1,893 (72.95)	1,032 (65.40)	768 (70.27)
PCI	2,842 (94.42)	2,433 (93.76)	1,500 (95.06)	1,045(95.61)
Stroke	512(17.01)	473 (18.23)	212(13.43)	186(17.02)
CABG	798 (26.35)	711(27.40)	304(19.26)	322 (29.46)
Bleed	854 (28.37)	774 (29.83)	374 (23.70)	313(28.64)
Death from any cause	600 (19.93)	561(21.62)	269(17.05)	207 (18.94)
P2Y12 inhibitor use, ever (%)				
Clopidogrel	2,963 (98.44)[b]	2,593 (99.92)[b]	1,578(100)	1,092 (99.91)[b]
Prasugrel	687 (22.82)	324 (12.49)	230(14.58)	203(18.57)
Ticagrelor	126(4.19)	59 (2.27)	30(1.90)	33 (3.02)
PGx variation, CYP2C19 (%)				
Poor	79 (2.62)	67(2.58)	43 (2.72)	24 (2.20)
Hetero inter[a]	4(0.13)	4(0.19)	2(0.13)	2(0.19)
Inter	832 (27.64)	709 (27.32)	440 (27.88)	288 (26.35)
Normal	2,095 (69.60)	1,815(69.94)	1,093(69.26)	779(71.27)

a This group of patients was included in the intermediate metabolizer group for outcome and financial analysis.

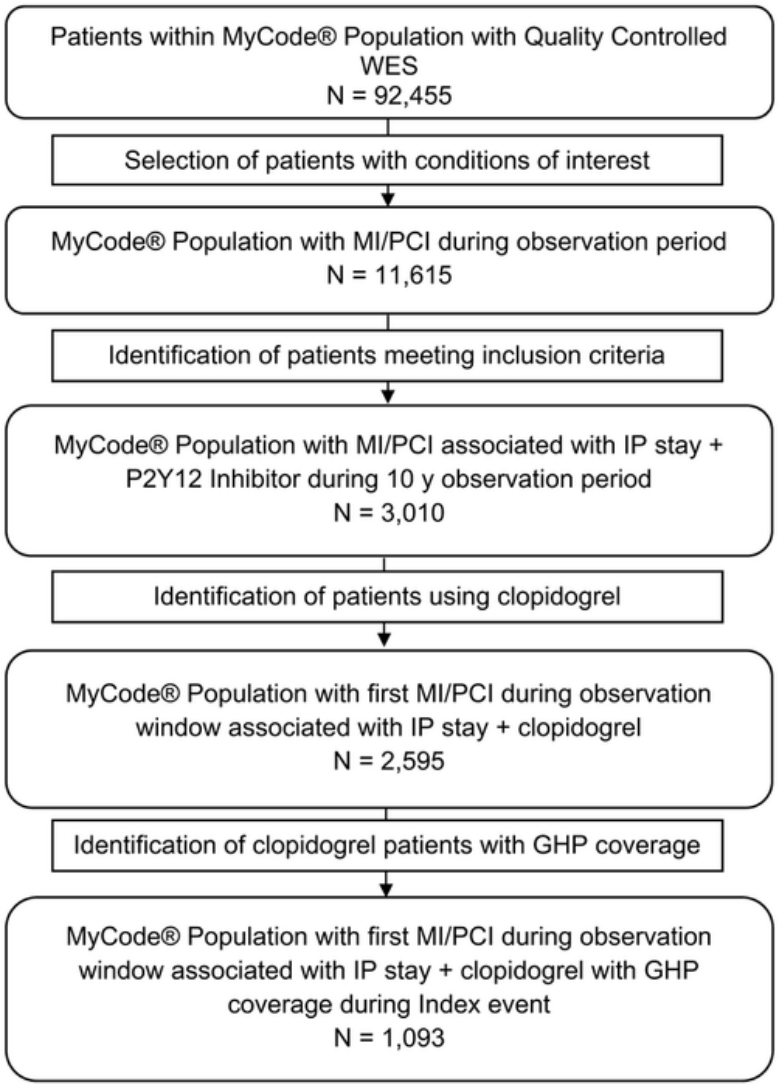
b Medication discrepancy between clinical record and prescription claims data.

p. 280

Population Selection

Patient-participants from the Geisinger MyCode Community Health Initiative with a validated WES were evaluated for inclusion in this analysis (90,000 cohort, *N* = 92,455 patients). (See figure 10.1.) This study was reviewed and approved by the Geisinger Institutional Review Board (IRB), along with additional approval from the MyCode Governing Board. The study period of January 1, 2007–December 31, 2015, was chosen to maximize the availability of electronic health-record information within the inpatient setting, as well as to allow for one year of clinical and claims data following the index event.

Fig. 10.1



Population selection

We queried the MyCode 90,000 cohort for any mention of a myocardial infarction (MI) or percutaneous coronary intervention (PCI) as defined by Geisinger value sets—as these events are associated with the utilization of

p. 281 clopidogrel. From this population of 11,615 patients, we further refined our inclusion criteria to include only patients who had a documented MI/PCI on their active problem list during an inpatient hospitalization within a Geisinger facility and were prescribed a P2Y12 inhibitor (clopidogrel, ticagrelor, or prasugrel) at the time of discharge (*N* = 3,010). The first-ever occurrence of an MI/PCI during our study period was defined as the index date for this evaluation. Patients whose index event was associated with clopidogrel (through discharge medication order or for the subgroup of patients with GHP coverage, verified use by administrative prescription claims) were defined as our clopidogrel cohort for this study (*N* = 2,595). As Geisinger as a health system does not perform pharmacogenomic screening, it is assumed that patients within this cohort were not stratified to specific antiplatelet agents based on their *CYP2C19* genotype.

The goal of our analysis was to evaluate the rate and timing of clinical adverse events of interest, utilization costs in the clopidogrel patient population in the twelve months following their qualifying index event, and stratifying by the presence or absence of low-function *CYP2C19* variants. For each patient, the medical record was queried using Geisinger value sets for the presence or absence of the following events within twelve months of index: subsequent PCI, subsequent MI, coronary artery bypass grafting (CABG), stroke, cerebrovascular accident, other revascularization procedures, major bleeding events, and death by any cause. All dates were collected (shifted +/−ten days to de-identify) and used in subsequent time-to-event analysis. We also examined the frequency of emergency room visits and inpatient hospitalizations within the twelve months following the defined index event.

Financial and Prescription Refill Information

Approximately 42 percent of patients within the clopidogrel cohort were insured by GHP at the time of their index event. Patient-level medical costs were also acquired from GHP administrative claims among a cohort of 1,093 patients with GHP coverage before and after index event. For patients with prescription coverage and a paid prescription claim within thirty days of their index, all prescription claims for the 365 days following index were extracted and analyzed. All collected medical and prescription claims gathered for this population underwent the same patient-specific date shift utilized in the clinical event blinding. To determine the impact of CYP2C19 variants on cost of care, total medical cost of care for the twelve months after the index event was compared to the total medical cost of care for the twelve months leading up to the index event. For patients within the clopidogrel cohort who had GHP coverage at the time of their index event (N = 1,093), the total medical cost of care for the twelve months after the index event was compared with the total medical cost of care for the twelve months leading up to the index event.

Genetic Information

CYP2C19 status was assigned utilizing bioinformatic methods to extract PGx information from research-generated whole exome sequences. Variants of *CYP2C19* included in this analysis include *2, *3, *4, *5, *6, *7, *8; all of these are associated with decreased enzyme activity (Swen et al. 2011). Prevalence of PGx variants of interest can be found in table 10.1. Due to the low frequency of the *CYP2C19* poor metabolizer phenotype (patients with two loss of function alleles) and comparable event distributions across *CYP2C19* groups, analyses were conducted grouping patients both by LOF variant count (0, 1, 2) as well as by normal function (NF)/loss of function (LOF) bifurcation. (See table 10.2.)

Table 10.2 Clopidogrel cohort descriptive analysis by CYP2C19 status

	Entire clopidogrel cohort	***CYP2C19* NF**	***CYP2C19* LOF, 1 copy**	***CYP2C19* LOF, 2 copies**	***CYP2C19* LOF (all)**	***p-value* (NF vs. LOF)**	**OR (NFvs. LOF)**	**95% CI of OR**
N included in analysis (%)	2,595	1,815(69.94)	713(27.49)	67 (2.58)	780 (30.06)			
Prior MI (%)	497(19.15)	362 (19.94)	125(17.53)	10 (14.92)	135(17.31)	0.118	0.840	0.6753-1.0451
Prior PCI (%)	551 (21.23)	403 (22.20)	137(19.21)	11(16.42)	148(18.97)	0.065	0.821	0.665-1.013
Prior clopidogrel (%)	838 (32.29)	598 (32.95)	220 (30.86)	20 (29.85)	240 (30.77)	0.277	0.905	0.755-1.084
Prior prasugrel (%)	7 (0.27)	7 (0.39)	0(0)	0(0)	0(0)	0.082	0.155	0.009-2.708
Prior ticagrelor (%)	3(0.12)	2(0.11)	1 (0.04)	0(0)	1 (0.13)	0.902	1.164	0.105-12.85
Prior MI/PCI/P2Y12 (%)	1,017(39.19)	722 (39.78)	271 (38.01)	24 (35.82)	295 (37.82)	0.349	0.921	0.775-1.094
CCI (%)								
0-5	1,120(43.16)	777 (42.81)	311(43.62)	32 (47.76)	343 (43.97)			
6-10	111(43.01)	766 (42.20)	323 (45.30)	27 (40.30)	350 (44.87)	0.076		
11-15	31(11.98)	236 (13.00)	67 (9.40)	8(11.94)	75 (9.62)			
15<	48(1.85)	36(1.98)	12(1.68)	0(0)	12(1.54)			
Documented PPI use[a]	1,396(53.80)	967 (53.28)	395 (55.40)	34 (50.75)	429 (55.00)	0.42	1.072	0.91-1.3
Age decile (%)								
20-29	3(0.12)	1 (0.06)	2 (0.28)	0(0)	2 (0.26)			
30-39	49(1.89)	34(1.87)	13(1.82)	2 (2.99)	15 (1.92)			
40-49	242 (9.33)	161 (8.87)	73 (10.24)	8(11.94)	81 (10.38)			
50-59	651 (25.09)	453 (24.96)	177 (24.82)	21 (31.34)	198 (25.38)			
60-69	831 (32.02)	589 (32.45)	222(31.14)	20 (29.85)	242(31.03)			
70-79	694 (26.74)	490 (27.00)	189(26.51)	15 (22.39)	204(36.15)			
80-89+	125 (4.82)	87 (4.79)	37(5.19)	1 (1.49)	38 (4.87)			
Index below the age of sixty (%)	945 (36.42)	649 (35.76)	265(37.17)	31 (46.27)	296 (37.95)	0.288	1.099	0.924-1.307
GHP coverage (%)	1,093(42.12)	779 (42.92)	290 (40.67)	24 (35.82)	314(40.26)			

Clop PDC calculated (%)	931 (35.88)	653 (35.98)	253 (35.48)	22 (32.84)	275 (35.26)	0.800	0.978	0.821-1.165
Clopidogrel PDC (out of 931) (%)						*p-value* PDC > 0.8		
>80	581 (62.41)	401 (61.40)	166(65.61)	14 (63.64)	180 (65.45)			
40-79.9	158(16.97)	110(16.85)	43 (17.00)	5 (22.73)	48 (17.45)	0.25	1.191	
Below 40	189 (20.30)	142(21.75)	44(17.39)	3(13.63)	47 (17.10)			0.887-1.598

[a] Given PPIs inhibit CYP2C19 and these medications were available without a prescription during our observation window—we feel this figure is an underestimation. Due to the limitations of capturing true exposure to PPIs, we are unable to adjust our analysis by this factor.

10.2.3 Statistical Analysis

Clinical Utilization

Clinical utilization events in the twelve months following index date—specifically subsequent MI, subsequent PCI, CABG, revascularization, stroke, bleed, emergency department (ED) visits, and inpatient hospitalizations—were examined in three ways. First, chi-squared tests were used to compare the percentages of patients with versus without each event as a function of *CYP2C19* metabolizer status, history of MI, history of PCI, previous clopidogrel exposure, age at index event (grouped by deciles), and Charlson Comorbidity Index (CCI). Next, the number of those events per patient during the twelve months following index date were compared between patients with and without CYP2C19 function, using a zero-inflated Poisson model. These models were run with and without adjusting for CCI (categorized as 0–5, 6–10, 11–15 or >15). Finally, survival analysis was used to compare time-to-first event for each category of event, stratified by *CYP2C19* status. All-cause mortality in the twelve months following index date was also compared between patients with and without *CYP2C19* function using a logistic regression model, unadjusted and adjusting for CCI.

Medication Adherence

Of the 2,595 patients within the clopidogrel cohort, we identified 931 patients who had pharmacy benefit coverage and pharmacy claims within thirty days of their index event. For this population, we examined adjudicated prescription claims to identify paid claims for clopidogrel, prasugrel, and ticagrelor. For each P2Y12 inhibitor, medication adherence was calculated using the proportion of days covered (PDC) (Bristol-Myers Squibb 2017). Using the pharmacy claim dates when prescriptions were filled and the days' supply of medication obtained on each of those dates, we determined whether a patient was "covered" (i.e., supplied)
p. 283 with medication on each day of the period of interest, from which we calculated the percentage ↳
p. 284 of covered days (PDC). The PDC was calculated for the twelve months following index date, or until death, or until disenrollment from the insurance plan, whichever occurred first. A combined therapeutic class PDC was derived by combining the individual clopidogrel, prasugrel, and ticagrelor PDCs.

We used a logistic regression model to compare the risk of each clinical follow-on event described above (e.g., subsequent MI, ED visit) as a function of *CYP2C19* status, PDC adherence, and the interaction between the two, to test whether adherence had a different impact on clinical utilization for patients with *CYP2C19* LOF or if *CYP2C19* LOF impacted adherence.

Total Medical Costs

We also used a difference-in-difference method to compare changes in total medical costs before and after index date between the patients with *CYP2C19* LOF and NF. Total cost of care was defined as total GHP medical "allowed" amounts (i.e., the sum of all GHP's payments to providers for the care covered under the patients' medical benefits) plus all patient out-of-pocket expenses such as copays, deductibles, and coinsurance. Total costs were summed for the twelve months before and twelve months after index, and the estimated difference-in-differences for the two groups were obtained via a generalized linear model with log link and gamma distribution, adjusting for CCI and PDC adherence.

Sensitivity Analysis

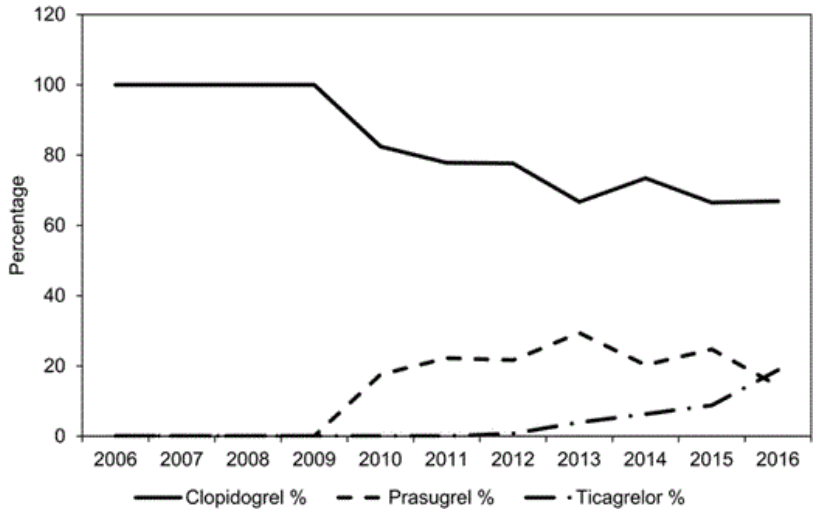
Finally, we performed sensitivity analyses to aid in the interpretation of results. First, we used chi-squared tests to examine whether the patients with *CYP2C19* LOF were either more or less likely than those with NF to have a prior instance of MI or PCI, or prior utilization of a P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor) more than seven days prior to the index date. A seven-day cutoff was used to eliminate events that triggered the inpatient hospitalization associated with the index event (e.g., MI upon presentation to ED, PCI for this MI performed within seven days during same IP hospitalization.). Second, we flagged patients if there was any documentation of proton pump inhibitor (PPI) use within the medical record during the twelve months after the index event,[1] and used logistic regression to test for relationships between PPI use and the presence or absence of subsequent follow-on clinical events, and the interaction of this factor with *CYP2C19* LOF and adherence. Third, we repeated the analysis of the effect of *CYP2C19* LOF status on the presence or absence of clinical events in patients with a CCI between 0 and 5. Finally, we
p. 285 analyzed the effect of ↳ *CYP2C19* LOF variant count on the presence or absence of clinical events in patients with *CYP2C19* LOF.

10.3 Results

10.3.1 Clopidogrel Use within Geisinger

A total of 3,010 patients were identified with an MI/PCI event and associated initiation of a P2Y12 inhibitor during an inpatient hospitalization from January 1, 2007, through December 31, 2015. Clopidogrel was ordered as the P2Y12 inhibitor for 2,408 patients (80.0 percent), prasugrel for 529 patients (17.6 percent), and ticagrelor for 73 patients (2.4 percent). (See table 10.1.) Of the 213 GHP patients with claims data who were indicated as having a prasugrel or ticagrelor prescription associated with their index event, we found that 159 (74.65 percent) of them utilized clopidogrel as a P2Y12 inhibitor during the twelve months following index per claims records. A breakdown of the prescribing of P2Y12 inhibitors over time denotes less clopidogrel use following introduction of prasugrel (July 2009) followed by tigagrelor (July 2011) in the United States market, but continued high prevalent use of clopidogrel through 2016 (figure 10.2). For the most recent full year available (2016), the utilization mix was 66.83 percent clopidogrel, 14.32 percent prasugrel, and 18.84 percent ticagrelor as the ordered drug at discharge.

Fig. 10.2



P2Y12 use over time; P2Y12 medication mix during study period

10.3.2 Clopidogrel Cohort Definition

We defined our clopidogrel population as anyone whose index event was associated with a clopidogrel order (*N* = 2,408), or whose prescription claims

p. 286 information indicated that clopidogrel was used as a P2Y12 inhibitor in the twelve months following index (*N* = 159). The clopidogrel cohort had an average index age of 64.2 years and average Charlson Comorbidity Index of 6.6. This cohort was 66.27 percent male, and 99.46 percent self-identified as Caucasian. (See table 10.1.)

CYP2C19 Function within the Clopidogrel Cohort

For patients within the clopidogrel cohort (*N* = 2,595), 1,815 (69.9 percent) did not carry the LOF marker for *CYP2C19*, 713 (27.5 percent) carried a single copy of a mutation associated with *CYP2C19* LOF, and 67 (2.6 percent) carried two copies of a LOF mutation. Patients with no LOF markers were categorized as *CYP2C19* normal function (NF) for this analysis. (See table 10.2.)

10.3.3 Outcome Analysis

In our unadjusted analysis, *CYP2C19* LOF was not a statistically significant predictor of the presence or absence of any follow-on events or utilization outcome examined in the twelve-month period following the index event (see table 10.3).

Table 10.3 Binary outcomes by CYP2C19 status

	***CYP2C19* NF event rate**	***CYP2C19* LOF event rate**	***p*-value**	**Odds ratio**	**95% CI of OR**
MI (%)	280 (15.42)	110 (14.10)	0.39	0.90	0.71–1.14
PCI (%)	442 (24.35)	177 (22.69)	0.36	0.91	0.75–1.13
Stroke (%)	38 (2.09)	15 (1.92)	0.78	0.92	0.50–1.68
CABG (%)	158 (8.71)	52 (6.67)	0.08	0.75	0.54–1.04
Bleed (%)	115 (6.34)	48 (6.15)	0.86	0.97	0.68–1.37
Death (%)	87 (4.79)	46 (5.90)	0.24	1.24	0.86–1.80
MI/stroke/death (%)	354 (19.50)	144 (18.46)	0.54	0.93	0.75–1.16
ED visits (%)	522 (28.76)	217 (27.82)	0.63	0.95	0.79–1.15
IP visits (%)	553 (30.47)	225 (28.85)	0.41	0.93	0.77–1.11

CYP2C19 LOF was not found to be a statistically significant predictor of the aggregate count of any adverse or outcome events during the twelve months following index event (see table 10.4).

Table 10.4 Unadjusted analysis of count of adverse outcomes within twelve months of index event

			***CYP2C19* normal metabolizer *N*= 1,815**	***CYP2C19* LOF (poor or intermediate) N = 780**	**Relative ratio (no. events expected LOF/no. events expected NF)**	**P-value**	**95% CI**
Reported as modeled no. events	Aggregate events (all cause death + MI + stroke)		0.289	0.269	0.917	0.39	0.736-1.162
	Subsequent MI		0.215	0.188	0.887	0.28	0.694-1.120
	Subsequent PCI		0.337	0.333	1.001	0.99	0.849-1.180
	Subsequent CABG		0.122	0.103	0.886	0.52	0.591-1.249
	Subsequent stroke		0.026	0.022	0.840	0.64	0.403-1.612
	Bleed		0.074	0.068	0.932	0.68	0.637-1.302
	Reported as modeled no. admissions/visits	ED utilization (index + 365 days)	0.562	0.547	0.893	0.28	0.699-1.146
IP utilization (index + 365 days)			0.574	0.524	0.946	0.37	0.778-1.101

CYP2C19 LOF was not found to be a statistically significant predictor of the aggregate count of any adverse or outcome events during the twelve months following index event when the model was adjusted for CCI group (see table 10.5).

Table 10.5 Adjusted analysis of count of adverse outcomes within twelve months of index event

		***CYP2C19* normal metabolizer *N*= 1,815**	***CYP2C19* LOF (poor or intermediate) N = 780**	**Relative ratio (no. events expected in patient with LOF/ no. events expected in patient with NF)**	***p*-value**	**95% CI**
Reported as modeled no. events	Agg. event					
	0-5	0.153	0.147	0.950	0.56	0.767-1.1514
	5-10	0.321	0.310			
	10-15	0.615	0.597			
	15<	0.462	0.449			
	Subsequent MI					
	0-5	0.121	0.110	0.896	0.37	0.684-1.130
	5-10	0.238	0.215			
	10-15	0.431	0.390			
	15<	0.363	0.329			
	Subsequent PCI					

	0-5	0.289	0.287	0.982	0.85	0.812-1.157
	5-10	0.347	0.347			
	10-15	0.451	0.458			
	15<	0.415	0.413			
	Subsequent CABG					
	0-5	0.069	0.058	0.829	0.33	0.575-1.234
	5-10	0.143	0.124			
↳	10-15	0.223	0.193			
	15<	0.189	0.179			
	Subsequent stroke					
	0-5	0.010	0.009	0.778	0.63	0.217-1.536
	5-10	0.029	0.026			
	10-15	0.070	0.060			
	15<	0.044	0.035			
	Bleed					

	0-5	0.032	0.034	1.077	0.82	0.573-1.912
	5-10	0.087	0.083			
	10-15	0.159	0.140			
	15<	0.150	0.131			
Reported as modeled no. admissions/visits	ED utilization					
	0-5	0.473	0.476	1.005	0.95	0.814-1.231
	5-10	0.486	0.489			
	10-15	1.067	1.080			
	15<	0.832	0.839			
	IP utilization					
	0-5	0.266	0.255	0.950	0.62	0.794-1.162
	5-10	0.607	0.583			
	10-15	1.402	1.345			
	15<	1.184	1.136			

Note: Adjusted for CCI grouping (0-5, 6-10, 111-15, 15<).

Neither *CYP2C19* LOF, P2Y12 inhibitor PDC, nor the interaction of these factors had statistically significant effects on the presence or absence of follow-on events in the twelve-month period following the index event (see table 10.6).

Table 10.6 Binomial regression—PDC, *CYP2C19* LOF, and the interaction of these factors on adverse outcomes in the twelve months post index event

	When examining only patients with PDC > = 0.8			**When examining only patients with *CYP2C19* NF (expect high PDC patients to have better outcomes)**		
	***CYP2C19* LOF versus NF OR**	***p*-value**	**95% CI**	**PDC > = 0.8 versus PDC < 0.8 odds ratio**	***p*-value**	**of OR**
MI	1.03	0.90	0.62–1.73	0.70	0.10	0.45–1.08
PCI	1.03	0.89	0.68–1.57	0.76	0.13	0.52–1.09
Stroke	3.45	0.18	0.57–20.82	0.17	0.03	0.03–0.81
Death	1.95	0.13	0.83–4.59	0.89	0.81	0.36–2.21
CVAgg	1.16	0.54	0.72–1.89	0.63	0.03	0.41–0.95

We did identify CCI grouping to be significant in predicting all follow-on

p. 280 adverse events examined (see table 10.7). Age was also found to be a statistically significant predictor of MI, stroke, or death from any cause, but not of PCI or the aggregate CV outcome. Since age is included in the CCI score, and CCI was the most significant variable in the presence or absence of follow-on events, we chose to adjust only for CCI.

Table 10.7 Binary outcomes by CCI grouping

	CCI 0-5	**CCI 6-10**	**CCI 11-15**	**CCI 15+**		
	***N*= 1,120 event rate**	***N*= 1,116 event rate**	**N=311 event rate**	**N=48 event rate**	***p-value* (for chi-square analysis)**	
MI (%)	103	190	84	13	<0.0001	6-10
	(9.20)	(17.03)	(27.01)	(27.08)		11-15
						15+
PCI (%)	239	273	94	13	0.01	6-10
	(21.34)	(24.46)	(30.23)	(27.08)		11-15
Stroke (%)	10	23	18	2	0.0001	15+ 6-10
	(0.89)	(2.06)	(5.79)	(4.17)		11-15
						15+
CABG (%)	55	109	39	7	0.0001	6-10
	(4.91)	(9.77)	(12.54)	(14.58)		11-15
						15+
Bleed (%)	31	84	42	6	0.0001	6-10
	(2.77)	(7.53)	(13.50)	(12.50)		11-15
						15+

Death (%)	26	66	38	3	0.0001	6-10
	(2.32)	(5.91)	(12.22)	(6.25)		11-15
						15+
Ml/stroke/death (%)	129	244	110	15	0.0001	6-10
	(11.52)	(21.86)	(35.37)	(31.25)		11-15
						15+
ED visits (%)	295	286	131	12	0.0001	6-10
	(26.34)	(26.52)	(42.12)	(25.42)		11-15
						15+
IP visits (%)	215	371	169	23	0.0001	6-10
	(19.20)	(33.20)	(54.34)	(47.92)		11-15 15+

10.3.4 All-Cause Mortality Analysis

CYP2C19 LOF was not found to be a statistically significant predictor of death during the twelve months following index event (OR: 1.245, 95 percent CI: 0.862-1.798). (See table 10.3.) However, when stratified by CCI groupings, mortality was found to be significantly higher among patients with *CYP2C19* LOF and a CCI between 0–5 (mortality rate in LOF: 3.79 percent, OR: 2.3152, 95 percent CI: 1.062-5.048). (See table 10.8.)

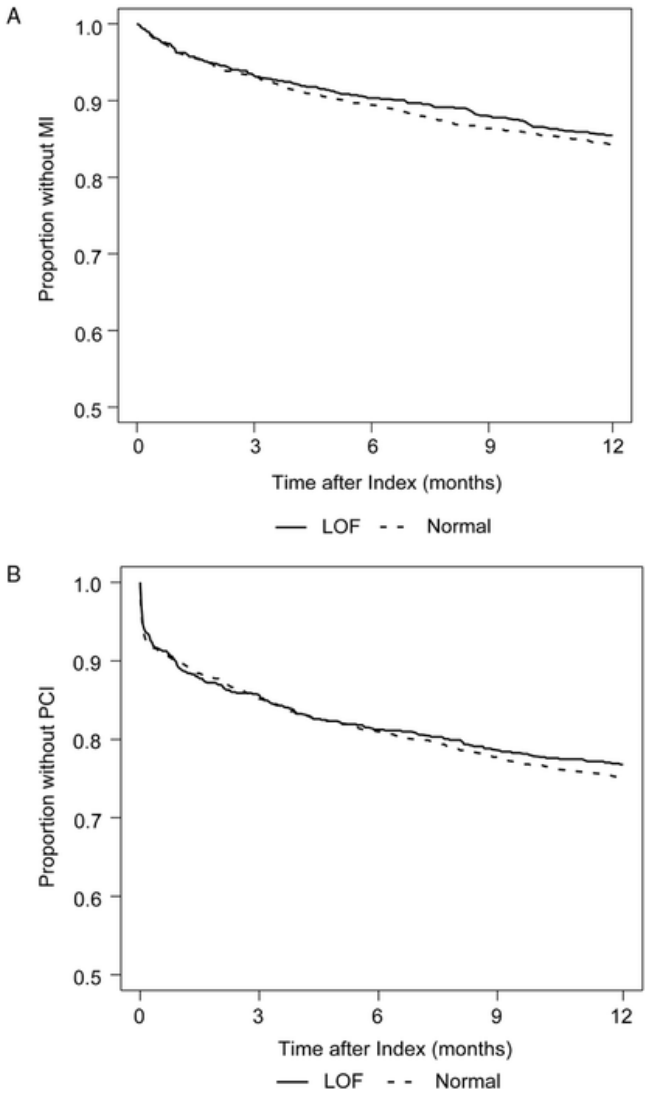
Table 10.8 Mortality analysis by CCI grouping

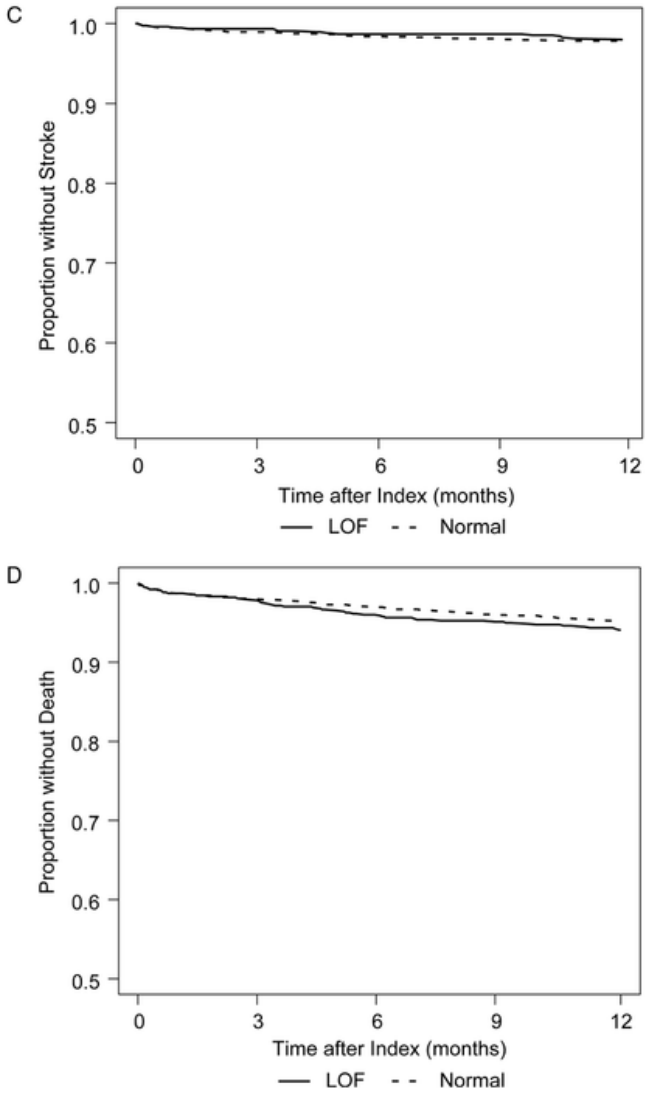
		***CYP2C19* NF**	***CYP2C19* LOF**			
	No. patients	***N* = 1,815 (%)**	***N* = 780 (%)**	**OR**	***p*-value**	**95% CI**
CCI 0–5	1,120	13 (1.67)	13 (3.79)	2.315	0.035	1.062–5.048
CCI 6–10	1,016	46 (6.01)	20 (5.71)	0.949	0.848	0.552–1.629
CCI 11–15	311	27 (11.44)	11 (14.67)	1.330	0.459	0.625–2.831
CCI 15+	48	1 (2.78)	2 (16.67)	5.996	0.127	0.574–85.385

10.3.5 Time to Event Analysis

CYP2C19 metabolic status was not found to influence the time to occurrence for any adverse or utilization event analyzed (MI *p*-value = 0.2712; PCI *p*-value = 0.3382; stroke *p*-value = 0.337; death *p*-value = 0.2413). (See figure 10.3.)

Fig. 10.3





Time to event curves

10.3.6 Financial Results

Total allowed claim amounts for patients within the clopidogrel cohort were higher in the 365-day period following index event compared to the allowed claims for 365 days leading up to the index event regardless of *CYP2C19* status (average twelve-month cost increase = $7,395; table 10.9). *CYP2C19* LOF was not a significant predictor of the pre-versus postindex change in total allowed claim amounts when the model was adjusted for CCI group and clopidogrel PDC (difference-in-difference: $613; 95 percent, CI−$2,039—
p. 291 $3,264; table 10.10). ↳

Table 10.9 Unadjusted financial analyses among patients with GHP coverage during first event

	Entire cohort (*N* = 1,093) ($)	CYP2C19 NF (*N* = 779) ($)	CYP2C19 LOF (*N* = 314) ($)	*p*-value (NF vs. LOF)[a]
Average allowed claim total 12				
months prior to index event	21,064	21,542	19,873	0.280
Average allowed claims total for				
30 days following index event	11,695	11,428	12,358	0.258
Average allowed claim total 12				
months following index event	28,459	28,916	27,326	0.468

a *P*-value is based on linear comparison of log-transformed dollar values (obtained via GLM with log link and gamma distribution).

Table 10.10 Adjusted financial analyses—clopidogrel cohort with GHP coverage

	CYP2C19 NF (normal metabolizer; *N* =779)	*CYP2C19* LOF (poor or intermediate; *N* =314)	Difference- in-difference	95% CI
Preindex ($)	19,285	17,775	613	–2,039—3,264
Postindex ($)	24,985	24,088		

Note: Year, CCI groupings: 0–5, 6–10, >10, and total PDC where available.

p. 293

10.3.7 Sensitivity Analysis

CYP2C19 metabolic status was not found to be a statistically significant predictor of prior MI/PCI events or prior clopidogrel use. For patients who had no previous mention of an MI or PCI, *CYP2C19* LOF status was not found to be associated with the age at which index event occurred, CCI, or patient sex. The presence or absence of subsequent follow-on events was not found to be influenced by the clinical factors of patient sex or smoking history. (See table 10.11.) ↳

p. 294

Table 10.11 Binary analyses—prior MI/PCI or clopidogrel by clinical feature

		Male sex versus female	Hx of smoking versus never	CCI above 5 versus below 5	Age over 60 versus under 60	*CYP2C19* LOF versus NF
Prior MI	OR	0.738	0.862	2.685	1.024	0.90
	p-value	0.006	0.138	<0.0001	0.825	0.39
	95% CI	0.60–0.92	0.709–1.049	2.154–3.345	0.831–1.261	0.71–1.14
Prior PCI	OR	0.862	0.898	1.662	1.166	0.91
	p-value	0.138	0.261	<0.0001	0.127	0.36
	95% CI	0.709–1.049	0.744–1.084	1.365–2.023	0.957–1.420	0.75–1.13
Prior clopidogrel	OR	0.979	0.819	2.460	1.046	0.92
	p-value	0.810	0.018	<0.0001	0.616	0.78
	95% CI	0.822–1.166	0.695–0.966	2.063–2.934	0.878–1.245	0.5–1.68

In a regression model incorporating *CYP2C19* LOF, PPI use, and the interaction of these factors, patients with documented PPI use during clopidogrel therapy were significantly more likely to experience an adverse outcome within the twelve months following their index event. (See table 10.12.)

Table 10.12 Binomial regression—PPI and *CYP2C19* LOF on adverse outcomes in the twelve months postindex event

	When examining only patients with a PPI exposure			**When examining only patients with *CYP2C19* NF(expect PPI patients to have worse outcomes)**		
	***CYP2C19* LOF vs. NF OR**	***p*-value**	**95% CI**	**PPI yes vs. no OR**	***p*-value**	**95% CI**
MI	0.876	0.366	0.657–1.167	2.661	<0.0001	2.001–3.523
PCI	0.971	0.819	0.754–1.251	1.600	<0.0001	1.285–1.993
Stroke	1.042	0.909	0.521–2.084	1.925	0.063	0.965–3.84
Death	1.063	0.786	0.683–1.656	2.885	<0.0001	1.750–4.756
MI/stroke/death	0.894	0.401	0.687–1.162	2.710	<0.0001	2.102–3.492

In the 1,120 patients with a CCI between 0 and 5, *CYP2C19* LOF status was associated with a *decrease* risk of
p. 295 MI in the twelve months ↳

postindex, but was not found to be a predictor of other follow-on events. (See table 10.13; MI OR:0.615, CI: 0.361-0.961.)

Table 10.13 Binary outcomes by CYP2C19 status in patients with CCI between 0 and 5

	***CYP2C19* NF event rate (%)**	***CYP2C19* LOF event rate (%)**	***p*-value**	**Odds ratio**	**95% CI of OR**
MI	81 (10.42)	22 (6.41)	0.032	0.615	0.361–0.961
PCI	175 (22.52)	64 (18.66)	0.146	0.789	0.573–1.086
Stroke	8 (1.03)	2 (0.58)	0.470	0.564	0.119–2.669
CABG	39 (5.02)	16 (4.66)	0.800	0.926	0.510–1.681
MI/stroke/death	96 (12.36)	33 (9.62)	0.188	0.755	0.497–1.147

In the 780 patients with *CYP2C19* LOF, LOF variant count was not found to be a predictor of follow-on events. (See table 10.14.)

Table 10.14 Binary outcomes by CYP2C19 LOF variant count

	CYP2C19 1 LOF variant *N* = 713 event rate (%)	*CYP2C19* 2 LOF variants *N* = 67 event rate (%)	*p*-value	Odds ratio	95% CI of OR
MI	97 (13.60)	13 (19.40)	0.192	1.529	0.804–2.906
PCI	165 (23.14)	12 (17.91)	0.328	0.725	0.379–1.386
Stroke	14 (1.96)	1 (01.49)	0.788	0.757	0.098–5.844
CABG	50 (7.01)	2 (2.99)	0.207	0.408	0.097–1.715
DEATH	42 (5.89)	4 (5.97)	0.979	1.014	0.352–2.921
MI/stroke/death	130 (18.23)	14 (20.90)	0.591	1.185	0.638–2.200

10.4 Discussion

Our analysis of a real-world cohort of Geisinger patients treated with clopidogrel following an index MI/PCI
p. 296 event over nine years showed that ↳ patients with *CYP2C19* LOF generally fared no worse than those without these genetic variants. This finding was consistent when looking at the count of follow-on adverse events or the time to the first instance of these events, in adjusted and unadjusted models.

These results are unexpected. The clopidogrel package insert has a black box warning stating that the effectiveness of clopidogrel is dependent upon functional *CYP2C19*, and that patients who carry two copies of LOF mutations should not receive this medication (P&T Community 2003). Additionally, the CPIC guidelines for clopidogrel dosing in patients with *CYP2C19* LOF recommend that an alternative P2Y12 inhibitor be used in the context of dual antiplatelet therapy following acute coronary syndrome for any patients who carry either at least one copy of a *CYP2C19* LOF variant (Scott et al. 2013).

We believe our findings point out the importance of factors beyond *CYP2C19* LOF in real-world patient response to clopidogrel. Despite in vitro evidence of the paramount influence of *CYP2C19* in the conversion of clopidogrel to its active metabolite, *CYP2C19* genetic status has been shown to explain only 12 percent of the interpatient variability in the clinical response to clopidogrel (Zhu et al. 2011). Patient age and complexity, additional genetic markers, stent selection, medication adherence, and concomitant medication use are all known to affect clopidogrel efficacy. Although most of our analysis compared patients with normal function *CYP2C19* to those that carried any loss of function change, we also analyzed the influence of *CYP2C19* LOF variant count on clinical outcomes, and did not find it to be statistically significant. As expected from previously conducted population studies, only 2 percent of patients carried two LOF variants for *CYP2C19* (classified as poor metabolizers). These patients would be expected to be most impacted if clopidogrel is used; a larger sample of patients with two LOF variants would be needed to adequately power an analysis of poor metabolizers. Therefore, no conclusions can be drawn from this study about the impact of poor metabolizer status on the outcomes of interest.

Genetic variants beyond those associated with *CYP2C19* LOF have been shown to play a role in clopidogrel clinical efficacy. The *CYP2C19* *17 allele, a common gain of function mutation, is associated with increased enzymatic function. Since the genetic change associated for the *17 allele lies outside of the WES capture region in the MyCode population, we were unable to identify patients who carried *CYP2C19* gain of function. This limitation confounds the assignment of intermediate metabolizers, as compound heterozygotes (i.e., *17/*2) are expected to have enzymatic function similar to that of normal metabolizers. Interestingly, among the three pooled studies that evaluated gain of function (*CYP2C19*17*), which included 6,584 patients, those with the gain of function allele had a lower risk of cardiovascular outcomes (HR 0.75, 95% CI: 0.66-0.87), but a higher risk of major bleeding among 7,660 patients (HR 1.26, 95% CI: 1.05-1.50). Hence, despite ↳ a mechanism suggesting little clinical effect with LOF allele and higher function among

gain of function (GOF) allele status, questions remain concerning the overall impact that LOF or GOF has on clinical endpoints within large Western population cohorts. Further, little is known about how these allele variants affect costs of care or utilization patterns in a real-world setting. Genetic changes within the *ABC* gene coding for a P-glycoprotein intestinal transporter have also been shown to affect clopidogrel, but were not considered in this analysis.

We attempted to measure clopidogrel adherence by calculating the proportion of days covered (PDC) for all patients with Geisinger Health Plan (GHP) coverage and paid prescription claims during the 365 days following index. Unfortunately, this information was available for only 931 patients. Of these patients, over 62 percent had a clopidogrel PDC above 80 percent, a common standard for good adherence. This number is in line with other population-based studies of medication-taking behavior; given the demographic alignment between the GHP population with PDC data and the overall clopidogrel cohort metrics (table 10.1) we believe that the population for which PDC was calculated was representative of the patients within our system (Khalili et al. 2016; Siller-Matula et al. 2009).

Use of clopidogrel at the same time as a proton pump inhibitor (PPI) is known to decrease clopidogrel response through the inhibition of CYP2C19 enzymatic function by the PPI (Momary and Dorsch 2010). Clinical studies examining the effect of this drug interaction have shown increased rates of platelet aggregation, as well as higher rates of adverse cardiovascular events (Siller-Matula et al. 2009). Patients who have been identified as CYP2C19 normal metabolizers could be expected to experience a decrease in enzymatic function with use of a PPI, dropping their enzymatic function to that of an intermediate metabolizer. Likewise, patients who have been identified as CYP2C19 intermediate metabolizers taking a PPI could be expected to experience a decrease in enzymatic function to that of a poor metabolizer. Fifty-three percent of patients within our clopidogrel cohort had EHR documentation of PPI administration during clopidogrel treatment in the twelve months following their index event. Since PPIs inhibit CYP2C19, only patients with functional CYP2C19 activity would be affected by the interaction; we may underestimate the impact of genetic *CYP2C19* LOF on clinical outcomes. Due to the over-the-counter availability of PPIs since 2003, we expect our definition of patients exposed to PPIs to be an underrepresentation of the patients prone to diminished clopidogrel effectiveness (Momary and Dorsch 2010; Siller-Matula et al. 2009).

Clopidogrel was first approved and marketed within the United States in March 2003. As our observation period did not begin until January 1, 2007, and electronic medical records were not fully deployed within the inpatient setting throughout the Geisinger system until this time, it is possible that patients with previous
p. 298 MI/PCI events and clopidogrel exposure ↳ were included in our clopidogrel population. In our sensitivity analysis, we queried the medical record of each patient for the presence or absence of MI/PCI events or previous mention of clopidogrel prior to the study index date. One potential explanation of the nonsignificance of *CYP2C219* status on clinical outcomes would be selection of clopidogrel for patients who had a history of preferential response to this agent following a prior MI/PCI event, resulting in those with NF surviving longer or with less disease following a prior event treated with clopidogrel. However, we found no evidence of this "survivorship advantage": presence or absence of prior MI, prior PCI, prior clopidogrel use, prior prasugrel use, or prior ticagrelor use was not correlated with CYP2C19 functional status. Although this analysis is limited incomplete data on prior events, this analysis suggests that our findings are unlikely to be due to an underlying nonrandom NF/LOF distribution resulting in selection bias from a theoretical "survivorship benefit."

Two published meta-analyses of the impact of *CYP2C19* genotype on clinical outcomes in patients taking clopidogrel presented conflicting conclusions of the importance of *CYP2C19* LOF (Zabalza et al. 2012; Notarangelo, Bontardelli, and Merlini 2013). A closer examination of published studies associating *CYP2C19* LOF with clinical cardiovascular outcome, grouped by study size, shows that the only pooled analyses with < 500 patients per study had significantly higher cardiovascular outcomes among LOF allele carriers. Our findings of *CYP2C19* LOF not being a statistically significant predictor of follow-on clinical events is therefore in line with previous reports of large populations.

10.4.1 Continued Importance of Clopidogrel

Though practice trends within Geisinger and across the United States have shown a shift toward P2Y12 inhibitors that are not affected by *CYP2C19* LOF (prasugrel and ticagrelor), we expect clopidogrel to remain the P2Y12 selected in dual antiplatelet regimens for a significant proportion of patients. Due to reduced frequency of bleeding effects, clopidogrel is still a good option for patients with high risk of bleeding. Though generic availability of prasugrel is expected by the end of 2018, clopidogrel is expected to remain the lowest price P2Y12 inhibitor. A 2017 year-to-date analysis of P2Y12 prescribing in patients hospitalized for an MI/PCI shows that clopidogrel is still the P2Y12 inhibitor of record in 66 percent of index events. An examination of prescription claims records for the subset of this cohort with coverage through Geisinger Health Plan revealed that 75 percent of patients prescribed a next generation P2Y12 inhibitor proceeded to fill clopidogrel during the twelve months following their index event.

10.4.2 What Our Results Mean to the Practice of Genomic-Guided P2Y12 Inhibitor Selection

CYP2C19 testing to guide antiplatelet selection following an MI/PCI is the most commonly ordered and
p. 299 applied pharmacogenomic test within the ↳ United States (Momary and Dorsch 2010). Much effort and expense has been invested in genotype-guided antiplatelet therapy, yet our results indicate that in a real-world setting, pharmacogenomic testing would not have improved clinical outcomes. Though guidelines for clopidogrel selection when pharmacogenomic information is available have been established, our results suggest that *CYP2C19* testing for all patients initiating clopidogrel therapy following an MI/PCI event would have incurred additional costs and not have improved clinical outcomes.

Our results suggest that there may be a place for *CYP2C19* testing for P2Y12 inhibitor selection in patients with a lower Charlson Comorbidity Index. When we repeat the binary analysis for all outcomes in the low CCI group (CCI = 0–5), the only findings that are statistically significant are death and MI within twelve months of index. Though this binary analysis was conducted post hoc, these findings are intriguing. While we are unable to fully explain this observation at this time, we hypothesize that those with *CYP2C19* LOF are suffering from more severe occlusion due to inadequate platelet inhibition, leading to death and not a survivable MI. We also believe that while there may be a true clinical effect of *CYP2C19* LOF, this effect on clinical outcomes is overpowered by stronger effects of clinical factors such as CCI and PPI use. Why this is more differentially seen in the lower CCI grouping is yet unknown, or perhaps a random effect. Additional evaluation of these lower comorbid patients is warranted.

If we assume that switching a *CYP2C19* LOF patient from clopidogrel to an alternative P2Y12 agent reduces his or her twelve-month mortality rate from 3.79 percent to 1.67 percent (what is seen in patients with *CYP2C19* NF on clopidogrel), we would estimate that seven lives could have been saved by testing the 1,120 low CCI patients in this study population. Since the cost of one *CYP2C19* test is approximately $100, the estimated cost incurred by single-gene testing for this population would be $112,000. If we assume that genome-guided antiplatelet selection in low-comorbidity patients is indeed lifesaving, the cost incurred from genetic testing per life saved would be $16,000. As both prasugrel and ticagrelor are more costly than generic clopidogrel, the total cost-of-care impact of a genome-guided antiplatelet selection strategy would be higher than this figure.

Unfortunately, a true mortality estimate for patients on next generation P2Y12 inhibitors is not available from this data set. Since almost three-fourths of patients with a prasugrel or ticagrelor prescription at index event within the GHP population we observe proceed to utilize clopidogrel as the P2Y12 inhibitor component of antiplatelet therapy, we are unable to calculate a true twelve-month mortality rate for low CCI patients receiving these medications. Consequently, further exploration of the utility of genome-guided antiplatelet selection in patients with low CCI is needed, particularly if pharmacogenomic information can be captured during other genomic analysis.

p. 300

10.4.3 Financial Considerations of CYP2C19 Testing

Though genomic testing for *CYP2C19* can be used to validate the use of clopidogrel therapy after stent placement, it is acknowledged that identification of LOF in this enzyme might shift patients from the relatively inexpensive, generically available treatment (clopidogrel) to more expensive P2Y12 inhibitors such as prasugrel and ticagrelor.

Despite the fact that CYP2C19 pharmacogenomic testing is reimbursable by many payers, including the Center for Medicare Services, when ordered in conjunction with clopidogrel initiation, only a very small percentage of patients receiving clopidogrel are genotyped. Direct reimbursement for *CYP2C19* testing is only available when conducted in an outpatient setting, and inpatient testing is only reimbursable through diagnosis-related group (DRG) billing, which lumps all payments for a particular diagnosis/procedure into one payment.

Given the current payment landscape for pharmacogenomic testing, initiation of antiplatelet therapy with a next generation P2Y12 inhibitor at discharge with subsequent pharmacogenomic testing only for patients with low comorbidity in the outpatient setting (to guide potential de-escalation to clopidogrel) may allow for improved patient outcomes while maximizing the investment in pharmacogenomic testing.

10.4.4 Implications for Precision Medicine

Our results highlight the inherent complexity of precision medicine. Small percentages of patients will fall in the most extreme phenotype classifications. In the real world, patient factors such as medication compliance and use of interfering medications can override the influence of genetic-based effects on medical outcomes. Our inability to capture reliable measures of these patient-specific factors will limit our ability to detect genetically mediated effects in pragmatic trials.

Though research initiatives, such as the All of Us Research Program, propose to link clinical and genetic information for a very large cohort, it is important to note the exponential decrease in cohort size that occurs upon stratification to address a particular research question.

Our experience also highlights the need to invest in multigene testing whenever clinically feasible. As the costs of next-generation sequencing and genomic array testing rapidly decrease, the differential in price between single-gene and panel testing is closing. Panel pharmacogenomic testing has the potential to provide a patient with a number of clinically actionable results that will not change over the course of his or her lifetime. When pharmacogenomic information is indicated (e.g., for evaluating *CYP2C19* genotype), complete pharmacogenomic panel testing may be more cost effective than single-gene testing.

Additionally, we suggest revisiting the use of pharmacogenomic information generated in a research setting
p. 301 within patient care to further our ↳ understanding of the genetic influence on medical outcomes. This would be particularly important for research-generated results for which the accuracy/validity of pharmacogenomic findings can be estimated. The prevailing policy interpretation is that CLIA-validated confirmation is required before this information is used to inform medication selection. However, resource constraints may preclude confirmatory testing of pharmacogenomic variants that have been identified in a large number of patients, creating the potential for individuals to be denied the benefits of this information and/or to experience avoidable medication-related harms.

Strengths of our analysis include:

- This is the first report of a large, single-system patient cohort with integrated clinical, economic, and pharmacogenomic information.
- Our findings are based on a real-world population wherein all patients with a qualifying event and P2Y12 inhibitor prescription were included in the analysis.
- Pharmacogenomic testing and other assessments of platelet reactivity were not in use during the time frame of interest, eliminating knowledge of genetic status as a confounder of the results.

Limitations of our analysis include:

- There were only a small number of individuals who carried two loss of function variants for *CYP2C19* (classified as poor metabolizers). These patients would be expected to be most impacted if clopidogrel is used. Combining the intermediate and poor metabolizers may have obscured a signal from the poor metabolizers. Therefore, no conclusions can be drawn from this study about the impact of poor metabolizer status on the outcomes of interest.
- As this retrospective analysis was conducted utilizing previously collected patient information in a real-world health care setting, we were unable to account for factors that could affect the outcomes of patients prescribed clopidogrel, including any concomitant use of proton pump inhibitors, which are known to interfere with the function of CYP2C19.
- We were only able to extract all-cause mortality, so we could not isolate deaths that occurred in our study population that were due to cardiovascular causes.
- Our EHR data did not enable us to measure a commonly utilized marker of "stent occlusion" as a factor of *CYP2C19* LOF.
- Financial analysis was performed on medical costs only (medication costs not included).

10.5 Conclusions

Universal *CYP2C19* pharmacogenomic testing to inform P2Y12 selection following an MI/PCI index event within the Geisinger patient population studied would not have led to improved clinical outcomes, decreased ↳ health care utilization, or lower total medical cost. These results counter prevailing movements to test for *CYP2C19* function among all candidates for clopidogrel therapy, suggesting no value in the indiscriminate *CYP2C19* variant testing in this population. Use of clopidogrel is still a viable option in patients post-MI/PCI, although caution should be taken in applying these findings in more diverse (and Eastern) populations.

p. 302

We have identified several potential explanations for why our conclusions are at odds with much of the published literature. First and foremost, we acknowledge that patients in our cohort are older, with a higher degree of medical complexity than patients enrolled in previous studies. Additional genetic markers, stent selection, medication adherence, and concomitant medication use are all known to affect clopidogrel efficacy and may have influenced our findings.

Despite these limitations, availability of *CYP2C19* genotype at the time of an MI/PCI provides an opportunity to apply precision medicine. Our results suggest that while use of these results in patients with less medical complexity may decrease all-cause one-year mortality, further study is needed. Additionally, awareness of complete loss of CYP2C19 enzyme function could direct therapy selection in accordance with the clopidogrel package insert. Increasing availability of preemptive pharmacogenomic testing and WES may provide *CYP2C19* genotype information at a nominal cost.

References

Abul-Husn, N. S., K. Manickam, L. K. Jones, E. A. Wright, D. N. Hartzel, C. Gonzaga-Jauregui, C. T. O'Dushlaine, et al. 2016. "Genetic Identification of Familial Hypercholesterolemia within a Single U.S. Health Care System." *Science* 354 (6319). https://www.doi.org/10.1126/science.aaf7000.
Google Scholar WorldCat

Borse, M. S., O. M. Dong, M. J. Polasek, J. F. Farley, G. A. Stouffer, and C. R. Lee. 2017. "CYP2C19-Guided Antiplatelet Therapy: A Cost-Effectiveness Analysis of 30-Day and 1-Year Outcomes following Percutaneous Coronary Intervention." *Pharmacogenomics* 18 (12): 1155–66.
Google Scholar WorldCat

Bristol-Myers Squibb. 2017. *PLAVIX (clopidogrel bisulfate)* [package insert]. Bridgewater, NJ.
Google Scholar Google Preview WorldCat COPAC

Canadian Pharmacogenomics Network for Drug Safety. Various. Publications Clinical Practice Guidelines/Recommendations. Accessed Aug. 29, 2017. http://cpnds.ubc.ca/about/projects.
WorldCat

Carey, D. J., S. N. Fetterolf, F. D. Davis, W. A. Faucett, M. L. Kirchner, U. Mirshahi, M. F. Murray, D. T. Smelser, G. S. Gerhardt, and D. H. Ledbetter. 2016. "The Geisinger MyCode Community Health Initiative: An Electronic Health Record-Linked Biobank for Precision Medicine Research." *Genetics in Medicine* 18 (9): 906–13.
Google Scholar WorldCat

Cavalari, L. 2015. "Clinical Benefit of Preemptive Pharmacogenomic Testing for Patients Undergoing PCI Was Shown by the IGNITE Network." *Circulation* 132 (suppl. 3): A11802.
Google Scholar WorldCat

p. 303 Centers for Disease Control and Prevention. 2015. "Calculating Proportion of Days Covered (PDC) for Antihypertensive and Antidiabetic Medications: An Evaluation Guide for Grantees." Accessed Nov. 20, 2017. https://www.cdc.gov/dhdsp/docs/med-adherence-evaluation-tool.pdf.
WorldCat

Deneer, Vera H. M. 2013. "Cost-Effectiveness of Genotype Guided Treatment with Antiplatelet Drugs in STEMI Patients: Optimization of Treatment (POPular Genetics)." Accessed Aug. 29, 2017. NLM identifier: NCT01761786. https://clinicaltrials.gov/ct2/show/NCT01761786?draw=1.
WorldCat

Dewey, F. E., V. Gusarova, C. O'Dushlaine, O. Gottesman, J. Trejos, C. Hunt, C. V. Van Hout, et al. 2016. "Inactivating Variants in ANGPTL4 and Risk of Coronary Artery Disease." *New England Journal of Medicine* 374 (12): 1123–33.
Google Scholar WorldCat

Dewey, F. E., M. F. Murray, J. D. Overton, L. Habegger, J. B. Leader, S. N. Fetterolf, C. O'Dushlaine, et al. 2016. "Distribution and Clinical Impact of Functional Variants in 50,726 Whole-Exome Sequences from the DiscovEHR Study." *Science* 354 (6319). http://www.doi.org/10.1126/science.aaf6814.
Google Scholar WorldCat

Haggerty, C. M., C. A. James, H. Calkins, C. Tichnell, J. B. Leader, D. N. Hartzel, C. D. Nevius, et al. 2017. "Electronic Health Record Phenotype in Subjects with Genetic Variants Associated with Arrhythmogenic Right Ventricular Cardiomy-opathy: A Study of 30,716 Subjects with Exome Sequencing." *Genetics in Medicine* 19 (11): 1245–52.
Google Scholar WorldCat

Jang, J. S., K. I. Cho, H. Y. Jin, J. S. Seo, T. H. Yang, D. K. Kim, S. H. Seol, et al. 2012. "Meta-Analysis of Cytochrome P450 2C19 Polymorphism and Risk of Adverse Clinical Outcomes among Coronary Artery Disease Patients of Different Ethnic Groups

Treated with Clopidogrel." *American Journal of Cardiology* 110 (4): 502–08.
Google Scholar WorldCat

Jiang, M., and J. H. You. 2017. "CYP2C19 LOF and GOF-Guided Antiplatelet Therapy in Patients with Acute Coronary Syndrome: A Cost-Effectiveness Analysis." *Cardiovascular Drugs and Therapy* 31 (1): 39–49.
Google Scholar WorldCat

Johnson, S. G., D. Gruntowicz, T. Chua, and R. J. Morlock. 2015. "Financial Analysis of CYP2C19 Genotyping in Patients Receiving Dual Antiplatelet Therapy following Acute Coronary Syndrome and Percutaneous Coronary Intervention." *Journal of Managed Care & Specialty Pharmacy* 21 (7): 552–57.
Google Scholar WorldCat

Khalili, H., R. Singh, M. Wood, A. Edwards, M. Cooper, C. Ayers, E. Moss, J. D. Berry, W. Vongpatanasin, J. A. de Lemos, and S. R. Das. 2016. "Premature Clopidogrel Discontinuation after Drug-Eluting Stent Placement in a Large Urban Safety-Net Hospital." *American Journal of Cardiology* 117 (4): 522–25.
Google Scholar WorldCat

Levine, G. N., E. R. Bates, J. A. Bittl, R. G. Brindis, S. D. Fihn, L. A. Fleisher, C. B. Granger, et al. 2016. "ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients with Coronary Artery Disease." *Journal of the American College of Cardiology* 68 (10): 1082–115.
Google Scholar WorldCat

Luzum, J., R. Pakyz, A. Elsey, C. Haider, J. F. Peterson, M. Whirl-Carillo, S. K. Handelman, et al. 2017. "The Pharmacogenomics Research Network Translational Pharmacogenetics Program: Outcomes and Metrics of Pharmacogenomic Implementations across Diverse Healthcare Systems." *Clinical Pharmacology & Therapeutics* 102 (3): 502–10.
Google Scholar WorldCat

Mathias, P. C., N. Hendrix, W. J. Wang, K. Keyloun, M. Khelifi, P. Tarczy-Hornoch, and B. Devine. 2017. "Characterizing Pharmacogenomic-Guided Medication Use with a Clinical Data Repository." *Clinical Pharmacology & Therapeutics*. 102 (2): 340–48.
Google Scholar WorldCat

Mayo Clinic. 2013. "Tailored Antiplatelet Therapy following PCI (TAILOR-PCI)." Accessed Aug. 29, 2017. NLM identifier: NCT01742117. https://clinicaltrials.gov/ct2/show/NCT01742117.
WorldCat

Momary, K. M., and M. P. Dorsch. 2010. "Factors Associated with Clopidogrel Nonresponsiveness." *Future Cardiology* 6 (2): 195–201.
Google Scholar WorldCat

Notarangelo, M. F., F. Bontardelli, and P. A. Merlini. 2013. "Genetic and Nongenetic Factors Influencing the Response to Clopidogrel." *Journal of Cardiovascular Medicine* 14 (suppl. 1): S1–S7.
Google Scholar WorldCat

P&T Community. 2003. "Over-the-Counter Prilosec Approved." P&T Community, June 23. Accessed Nov. 20, 2017. https://www.ptcommunity.com/news/20170421/over-counter-prilosec-approved.
WorldCat

Pharmacogenomics Knowledgebase (PharmGKB). Various. Dosing Guidelines. Accessed Aug. 29, 2017. https://www.pharmgkb.org/view/dosing-guidelines.do.
WorldCat

Sabouret, P., and M. Taiel-Sartral. 2014. "New Antiplatelet Agents in the Treatment of Acute Coronary Syndromes." *Archives of Cardiovascular Disease* 107 (3): 178–87.
Google Scholar WorldCat

Schildcrout, J. S., J. C. Denny, E. Bowton, W. Gregg, J. M. Pulley, M. A. Basford, J. D. Cowan, et al. 2012. “Optimizing Drug Outcomes through Pharmacogenet-ics: A Case for Preemptive Genotyping.” *Clinical Pharmacology & Therapeutics* 92 (2): 235–42.
Google Scholar WorldCat

Scott, S. A., K. Sangkuhl, C. M. Stein, J. S. Hulot, J. L. Mega, D. M. Roden, T. E. Klein, M. S. Sabatine, J. A. Johnson, and A. R. Shuldiner. 2013. “Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for *CYP2C19* Genotype and Clopidogrel Therapy: 2013 Update.” *Clinical Pharmacology & Therapeutics* 94 (3): 317–23.

Siller-Matula, J. M., A. O. Spiel, I. M. Lang, G. Kreiner, G. Christ, and B. Jilma. 2009. “Effects of Pantoprazole and Esomeprazole on Platelet Inhibition by Clopidogrel.” *American Heart Journal* 157 (1): 148.e1-5.
Google Scholar WorldCat

Snyder, S. R., C. Mitropoulou, G. P. Patrinos, and M.S. Williams. 2014. “Economic Evaluation of Pharmacogenomics: A Value-Based Approach to Pragmatic Decision Making in the Face of Complexity.” *Public Health Genomics* 17 (5-6): 256–64.
Google Scholar WorldCat

Swen, J. J., M. Nijenhuis, A. de Boer, L. Grandia, A. H. Maitland-van der Zee, H. Mulder, G. A. Rongen, et al. 2011. “Pharmacogenetics: From Bench to Byte—An Update of Guidelines.” *Clinical Pharmacology & Therapeutics* 89 (5): 662–73.
Google Scholar WorldCat

University of Florida. Various. “Implementation of CYP2C19 Genotyping to Guide Antiplatelet Therapy.” Accessed Aug. 29, 2017. NLM identifier: NCT02704319. https://clinicaltrials.gov/ct2/show/NCT02724319?recrs=ab&cond=CYP2C19&draw = 1.
WorldCat

Zabalza, M., I. Subirana, J. Sala, C. Lluis-Ganella, G. Lucas, M. Tomás, R. Masiá, J. Marrugat, R. Brugada, and R. Elosua. 2012. “Meta-Analyses of the Association between Cytochrome CYP2C19 Loss-and Gain-of-Function Polymorphisms and Cardiovascular Outcomes in Patients with Coronary Artery Disease Treated with Clopidogrel.” *Heart* 98 (2): 100–08.
Google Scholar WorldCat

Zhu, B., Z. Zhao, P. McCollam, J. Anderson, J. P. Bae, H. Fu, M. Zettler, and L. Lenarz. 2011. “Factors Associated with Clopidogrel Use, Adherence, and Persistence in Patients with Acute Coronary Syndromes Undergoing Percutaneous Coronary Intervention.” *Current Medical Research and Opinions* 27 (3): 633–41.
Google Scholar WorldCat

Notes

Rebecca A. Pulk was a postdoctoral fellow at Geisinger Health System when this chapter was written and is currently serving as the Clinical Coordinator of Pharmacogenomics at Yale New Haven Health System. Jove Graham is a researcher in the Center for Pharmacy Innovation and Outcomes at Geisinger Health System. Frank R. Lichtenberg is the Courtney C. Brown Professor of Business at Columbia University Graduate School of Business and a research associate of the National Bureau of Economic Research. Daniel Maeng is an assistant professor in the department of epidemiology and health services research at Geisinger. Marc S. Williams is director of the Genomic Medicine Institute at Geisinger Health System. Eric Wright is a professor and codirector within the Center for Pharmacy Innovation and Outcomes at Geisinger and an adjunct professor in the department of pharmacy at Wilkes University.
For acknowledgments, sources of research support, and disclosure of the authors’ material financial relationships, if any, please see http://www.nber.org/chapters/c13993.ack.

1. Proton pump inhibitors are known inhibitors of the CYP2C19 enzyme and can override the effects of a normal CYP2C19 genotype, making a patient unable to activate clopidogrel (Zhu et al. 2011).