

The Social Cost of Suboptimal Medication Use and the Value of Pharmacogenomic Information:
Evidence from Geisinger

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Abstract

We utilize a cohort of 60,994 Geisinger patients, with linked clinical and genetic information to describe the potential value of pharmacogenomic information for the prevention and treatment of cardiovascular disease. Among 4073 patients the probability of a cerebrovascular accident and death was 63% and 40% higher among patients with a CYP2C19 genetic variant than it was among patients without the variant in the first 12 months after clopidogrel initiation. Among 7485 patients treated with statins, within the first decade of treatment, the probability of at least one myocardial infarction was 11% higher, and the probability of at least one cerebrovascular accident was 24% higher, among patients with a relevant genetic variant than it was among patients without the variant. Within a cohort of over 60,000 patients, genetic variations of two genes affecting the pharmacokinetics of commonly used cardiovascular medications are associated with higher cardiovascular risk and/or death. These events are potentially avoidable with pharmacogenomic testing and provide additional evidence support for routine pharmacogenomic testing in a generalized population.

Introduction

Pharmacogenomics has the potential to optimize clinical outcomes by streamlining the selection of medications to maximize benefit and minimize risk for an individual patient. This subsection of precision medicine has the capacity to significantly decrease medical expenditure by maximizing the clinical effectiveness of commonly prescribed medications while minimizing both medication nonadherence and adverse drug events. 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 [1, 2]. Prospective pharmacogenomic panel testing has been proposed as the most effective method of pharmacogenomic implementation – and the clinical benefit of such an approach has been estimated through epidemiological methods [3]. Prospective panel testing has been shown to be cost neutral as it relates to overall health expenditure in smaller studies of older adults. [4]

Despite the touted clinical benefits of pharmacogenomics, the adoption of this technology into routine practice has been limited by the dearth of real-world evidence on the clinical and economic benefits of pharmacogenomics-guided prescribing. Limited data linking patient-specific genomic and clinical information are available to inform clinical practice and coverage determinations [3,5].

Only a small number of health systems have integrated routine application of pharmacogenomics into their clinical workflows or pharmacogenomic test results into their medical records. [6] Even fewer data repositories tie economic information to genomic and clinically-linked patient outcomes. Much of the analyses concerning the value of pharmacogenomics-based prescribing have relied on modeling methods. These methodologies are limited by their assumptions, choice of comparator, and time frame, as well as their societal perspective. Assessing the value of pharmacogenomics-guided prescribing is further confounded in that these tests have historically been covered under prescription drug benefits, limiting the extent to which testing can be linked to total cost of care. These limitations have discouraged health systems from investing in implementation of pharmacogenomics.

Geisinger has made significant investments in MyCode[®], a community health initiative that links longitudinally collected biobank samples to initiatives aimed at leveraging genomic and phenotypic information. The MyCode[®] project currently has over 150,000 patients who have consented to participate, with approximately 1000 additional patients consenting each week. The goal is to enroll 250,000 patients in the next five years. Consent allows broad research use and recontact and includes whole exome sequencing (WES) of their genome facilitated by a partnership (DiscoverEHR[™]) with Regeneron Pharmaceuticals Inc. DiscoverEHR[™] has run and quality-controlled over 90,000 patients for WES.

Projects focusing on discovery and optimization of outcomes affected by genetic information are underway to capitalize on the growing reservoir of information.

WES is a genomic sequencing technology that focuses on the information contained in the 1% of human DNA that codes for proteins. 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 99% 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. Recent advances in database mining techniques however, enable extraction of PGx markers from Geisinger’s WES data allowing for real-world studies to assess the impact of variants on select outcomes for identified PGx variants. The results of this could then be imparted to theoretical PGx panel testing in a clinical use environment allowing for cost effectiveness estimates.

Some of the most frequently prescribed medications known to be affected by pharmacogenomic markers are utilized to prevent and treat cardiovascular conditions, most notably clopidogrel and statins. [8]

Clopidogrel is an antiplatelet medication that exerts its clinical effects through the inhibition of the P2Y₁₂ receptor. This medication is a prodrug that is activated in the body through the metabolic enzyme cytochrome P450 2C19 (CYP2C19). Genetic variation within CYP2C19 are common within the general population. Patients carrying decreased function variants of CYP2C19 are less able to transform clopidogrel to its active metabolite and are at a greater risk of serious adverse events due to thrombosis, while those carrying increased function alleles effectively receive a higher than expected dose of clopidogrel and are at risk for bleeding events. Clinical guidelines exist to guide the utilization of clopidogrel in the presence of pharmacogenomic information. [16] This pharmacogenomic test is reimbursable by many payers including CMS, though a very small percentage of patients receiving clopidogrel are genotyped.

Meta-analyses indicate that patients who carry a loss of function allele for the CYP2C19 gene are more likely to experience stent thrombosis (OR of 1.7-2.2.) or experience a subsequent cardiovascular (CV) event (OR 1.2-1.5) in the first 12 months of therapy due to insufficient formation of the active metabolite of clopidogrel [9-11]. A pooled analysis by the IGNITE investigators showed that in a cohort of 406 patients who were genotyped in response to PCI, 58 patients who carried a loss of function allele for CYP2C19 and received clopidogrel [8]. These patients suffered significantly higher rates of major

adverse cardiovascular events when compared to normal CYP2C19 metabolizers receiving clopidogrel or LOF carriers who were placed on an alternative therapy. [Circulation 2015: 132, suppl A11802].

Many models of the cost-effectiveness of CYP2C19-guided antiplatelet therapy have been published and reactively genotyping patients following percutaneous coronary intervention is suggested to have a positive economic impact by preventing bleeding and occlusive events.[REF] A large clinical trial evaluating outcomes with CYP2C19 genotype-guided antiplatelet therapy after PCI is on-going.[REF] 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.

The SLCO1B1 gene encodes the organic anion transporting polypeptide C (OATP1B1). This transporter is responsible for statin entry into the liver (hepatocytes) and is closely linked with both statin blood levels and rate of metabolism. A common variant within this gene (SLCO1B1 *5) is associated with lower transporter activity, decreased statin clearance and increased statin blood concentrations. This variant is also associated with an increased risk of statin induced myopathy – manifestations of which can range from mild myalgia to rhabdomyolysis. Clinical guidelines exist to guide the utilization of simvastatin in the presence of pharmacogenomic information in order to reduce the risk of adverse events associated with this genetic change. [CPIC 2014] Though clinical pharmacogenomic guidelines do not exist for atorvastatin and rosuvastatin – it has been hypothesized that similar associations exist for these medications. [CP&T 2007 82(6); 726]

Methods

Patient-participants of the Geisinger MyCode Community Health Initiative with a validated WES were selected for study in this analysis. To be eligible to enroll in the MyCode Community Health Initiative a patient must have an established relationship with Geisinger. All patients included in this analysis provided broad consent allowing for their clinical, financial and genetic information to be used for research as part of the MyCode Community Health Initiative. 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 was between January 1, 2006 and December 31, 2016. All available patient data during the study window was extracted including electronic health record data, GHP claims data, and GHP refill data.

Overview of Geisinger

Geisinger is one of the nation's largest health delivery systems and serves more than 3 million residents throughout 44 counties in central, south-central and northeast Pennsylvania, as well as 6 counties in southern New Jersey with the addition of AtlantiCare, a National Malcolm Baldrige Award recipient. The Clinic's patient population is very stable: census data indicate that except for two counties, the out-migration rate is less than 1% per year. The physician-led system is comprised of approximately 30,000 employees, including nearly 1,600 employed physicians, 12 hospital campuses, 83 primary and specialty clinic sites including 41 community-based primary care clinics, two research centers and a 510,000-member health plan.

Geisinger benefits 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. The Epic EHR is now fully implemented and integrated across all Geisinger ambulatory and inpatient sites of care

With initial funding from AHRQ, Geisinger has spearheaded the development of a regional health exchange, The Keystone Health Information Exchange (KeyHIE®). Linking hospitals, long-term care facilities, community health clinics, and healthcare professionals in more than 53 Pennsylvania counties, KeyHIE enables health information to follow patients across the care continuum. KeyHIE is one of the nation's largest and most advanced health information exchanges. Currently, there are 20 hospitals, 38 home health locations, 61 long term care facilities, more than 1,500 healthcare providers, and 3.7 million patients with health records in KeyHIE and more than 29,000 patient records are accessed monthly.

Data Sources

Clinical information

Geisinger's EHR, Epic has been in use since 1996 (fully implemented in 2001) in all outpatient clinics, and since 2007 in hospitals. To date, our EHR database contains information on more than 4 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.

Clinical data was extracted from the Geisinger's clinical data warehouse, Clinical Decision Intelligence System (CDIS). This database combines patient data from multiple sources – electronic medical record, patient registries, inpatient billing, outpatient billing, and Geisinger Health Plan data. Standardized Geisinger value sets were utilized to sort the electronic health record data to ensure capture of patients

with specific conditions. These sets comprised a set of inquiry codes based on groupings of ICD9, ICD10, diagnosis groups and CPT codes and were internally validated to reliably capture all patients with a given condition through utilization of the clinical record. Demographic information for this population can be found in the table 1.

Genetic Information

The pharmacogenomic variants of interest were extracted from research generated whole exome sequences utilizing bioinformatic methods. Prevalence of pharmacogenomic variants of interest can be found in table 2.

Financial and Prescription Refill Information

Approximately one third of Geisinger's patients are insured by the Geisinger Health Plan. For patients with GHP data during coverage was extracted on a per patient level in a PMPM fashion.

Clopidogrel Analysis:

Patients who had clinical record of an MI and/or PCI clinical event the study period were evaluated for inclusion in this sub-analysis. This population was queried for initiation of clopidogrel associated with this event. Clopidogrel initiation could be documented in either the clinical chart or prescription claims data. The goal was to evaluate the rate and timing of adverse events of interest in the patient population, stratifying by the presence or absence of a low function CYP2C19 variant in the 24 months following their qualifying event. Each patient was assigned an index date defined as the diagnosis date of the MI or PCI event, and each index date started a 24 month analysis window. For each patient – the medical record was queried for the presence or absence of the following events within 24 months of the index date: subsequent PCI, Subsequent MI, CABG, stroke, cerebrovascular accident, revascularization procedures, major bleeding events, death. Follow on MI and/or PCI events were only assigned their own index date if they occurred more than 24 months after the previously defined index date. Each patient's first index date and associated clinical adverse events were included in our analysis.

Statin Analysis:

Patients were included in this sub-analysis if they had record of an order for simvastatin, atorvastatin, or rosuvastatin during the study period. Statin use was defined as record in either the clinical chart or prescription claims data utilizing the generic medication identifier which also identified any associated combination products. For each patient – the medical record was queried for the presence or absence of the following events from the time of statin initiation to the end of the study period: Acute coronary syndrome, MI, cerebrovascular accident, stroke, myopathy, myalgia, rhabdomyolysis, death.

Statistical Analysis:

Time to event analysis was conducted for MI and PCI of interest weighted by the presence of one or more low function variants of CYP2C19. The presence or absence of each adverse outcome was examined as a function of the presence or absence of low function variants of CYP2C19.

Preliminary results

A. Patients treated with clopidogrel

To test the hypothesis that, among patients treated with clopidogrel, patients with a CYP2C19 variant were more likely to suffer adverse events within the first year of treatment than those without a CYP2C19 variant, we constructed contingency (cross-tabulation) tables and performed chi-square tests.¹ Rates of two types of adverse events were significantly (p -value $< .05$) higher for patients with a CYP2C19 variant than they were for patients without a CYP2C19 variant. As shown in panel A of Figure 1, the probability of dying within the first year of treatment was 40% higher among the 1234 patients with the variant than it was among the 2839 patients without the variant: 4.78% vs. 3.42%. As shown in panel B of Figure 1, the probability of a cerebrovascular accident within the first year of treatment was 63% higher among patients with the variant than it was among patients without the variant: 2.59% vs. 1.59%. As shown in panel C of Figure 1, the probability of a stroke was 25% higher among patients with the variant than it was for patients without the variant (7.46% vs. 5.95%); this difference was only marginally significant (p -value = .0719). Differences between 1-year probabilities of five other types of events (PCI treatment, myocardial infarction, CABG, bleed, and revascularization) were not statistically significant.

We also calculated event probabilities during longer (2-year) and shorter (30-day) time intervals after treatment initiation. For the 2-year time interval, the only significant difference was for the cerebrovascular accident rate (3.32% vs. 2.11%, p -value = .0228). For the 30-day time interval, none of the differences were statistically significant.

Of the 4,073 patients with an identifiable index date, 1468 had prescription coverage during the 24-month analysis window, 326 patients did not have a prescription claim for a P2Y₁₂ inhibitor (clopidogrel, prasugrel or ticagrelor).

B. Patients treated with statins

¹ Since CYP2C19 and other genetic variants are “randomly assigned,” it is not necessary to control for other potential determinants of adverse events.

We also sought to test the hypothesis that, among patients treated with statins, patients with an SLCO1B1 variant were more likely to suffer adverse events than those without an SLCO1B1 variant. These adverse events might occur during an extended period. Therefore, to maximize the length of the period of follow-up after treatment initiation, and to have a follow-up period of uniform length, we analyzed data on 7485 patients who began treatment with a statin in 2006.² For many of these patients, adverse events occurring until 2017 could be monitored.

As shown in panel A of Figure 2, the probability of at least one myocardial infarction was 11% higher among the 2175 patients with the variant than it was among the 5310 patients without the variant: 26.4% vs. 23.8%. As shown in panel B of Figure 2, the probability of at least one cerebrovascular accident was 24% higher among patients with the variant than it was among patients without the variant: 7.26% vs. 5.86%. Differences between probabilities of six other types of events (death, stroke, acute coronary syndrome, myalgia, myopathy, and rhabdomyolysis) were not statistically significant.

Ongoing Analyses

Clopidogrel Data Set

We will further refine our estimates of the clinical implications of CYP2C19 on outcomes in patients receiving clopidogrel following an MI and/or PCI by weighting our analysis by the number of days of clopidogrel or alternative P2Y12 inhibitor coverage during the 24-month analysis window. We also plan

² The following table shows the number of patients, by year of first statin rx:

year of first statin rx	No. of patients
2005	119
2006	7485
2007	3039
2008	2626
2009	2285
2010	1999
2011	1384
2012	1002
2013	837
2014	518
2015	374
2016	160

to analyze the role of CYP2C19 status in health care utilization following initiation of clopidogrel following an MI or PCI.

We will also evaluate the effect of CYP2C19 status on mean monthly overall expenditure following an index event with subsequent clopidogrel initiation.

Statin Data Set

We will refine our estimates of the clinical consequences of SLCO1B1 by looking only at patients with initial statin initiations.

Discussion

Our preliminary analysis over a ten year period in a real-world cohort, provides evidence of adverse effects following initiation of both clopidogrel and statins. The cost of pharmacogenomic panel testing, if done on a large population, can be estimated as costing \$250/patient. This information gathered on this one-time test could inform prescribing decisions across a patient's lifetime.

Strengths and Limitations

This is the first report of a large patient cohort with integrated clinical, economic and pharmacogenomic information.

Conclusions

Table 1. Demographic Table

	90 K cohort N = 60994	GHP subgroup, N = 37,461
Age (Mean, SD)	59.75 (17.73) Skewed right	59.08 (17.46) Skewed right
Age by Deciles		
<20	705 1.16%	11 0.03%
20-29	3080 5.05%	2251 6.01%
30-39	5729 9.39%	4167 11.12%
40-49	7114 11.66%	4630 12.36%
50-59	10796 17.70%	6525 17.42%
60-69	13607 22.31%	8217 21.93%
70-79	11471 18.81%	6677 17.82%
80-89 (includes >89)	8492 13.92%	4969 13.26%
>89	1888 3.10%	1068 2.85%
Male Sex, N, %	24,654 (40.42)	14487 (38.67%)
Time as GHS Patient (Mean, SD)	13.17 (4.41) Skewed right	13.60 (4.22) Skewed right
GHS PCP, N %	41474 (68.00%)	27454 (73.29%)
Charlson Comorbidity Index Score at end of study period	3.89 (3.38) Left Skewed	3.78 (3.36) Left Skewed
Conditions documented in chart at end of study period. N (%)		37461
Diabetes	18220 (29.87%)	11060 (29.52%)
Hyperlipidemia	36335 (59.57%)	22304 (59.54%)
Hypertension	34626 (56.77%)	21123 (56.39%)
Coronary Artery disease	13579 (22.26%)	7852 (20.96%)
Peripheral Vascular Disease	5587 (9.16%)	3337 (8.91%)
A-fib	7484 (12.29%)	4343 (11.59%)
Outcome of interest N (%)		
MI	7643 (12.53%)	4423 (11.81%)
PCI	5898 (9.67%)	3383 (9.03%)
Stroke	4658 (7.64%)	2845 (7.59%)
CABG	3741 (6.13%)	2204 (5.88%)
Cerebrovascular Accident	2309 (3.79%)	7846 (20.94%)
Bleed	8511 (13.95%)	5217 (13.93%)
Myalgia	12048 (19.75%)	7846 (20.94%)
Myopathy	839 (1.38%)	505 (1.35%)
Rhabdomyolysis	371 (0.61%)	221 (0.59%)
Death from any cause	5059 (8.29%)	2602 (6.95%)
Drug of interest		
Clopidogrel	9112 (14.94%)	5240 (13.99%)
Simvastatin	21133 (34.65%)	13231 (35.32%)
Atorvastatin	19520 (32.00%)	11910 (31.79%)
Rosuvastatin	6995 (11.47%)	4534 (12.10%)
Warfarin	10436 (17.11%)	6291 (16.79%)
Documented Smoker (ever)	24440 (40.07%)	14652 (39.11%)

Table 2. Genetic Findings

	All Patients (n=60994)	GHP Patients (n=37,461)
PGx Variation within cohort		
CYP2C19		
Poor	1474 (2.42%)	897 (2.39%)
Hetero inter	82 (0.13%)	45 (0.12%)
Inter	16332 (26.78%)	10111 (26.99%)
SLCO1B1		
2 Reduced	1663 (2.73%)	1006 (2.69%)
1 Reduced	16046 (26.31%)	9912 (26.46%)

Figure 1

1-year adverse event probabilities of clopidogrel patients with and without CYP2C19 variant

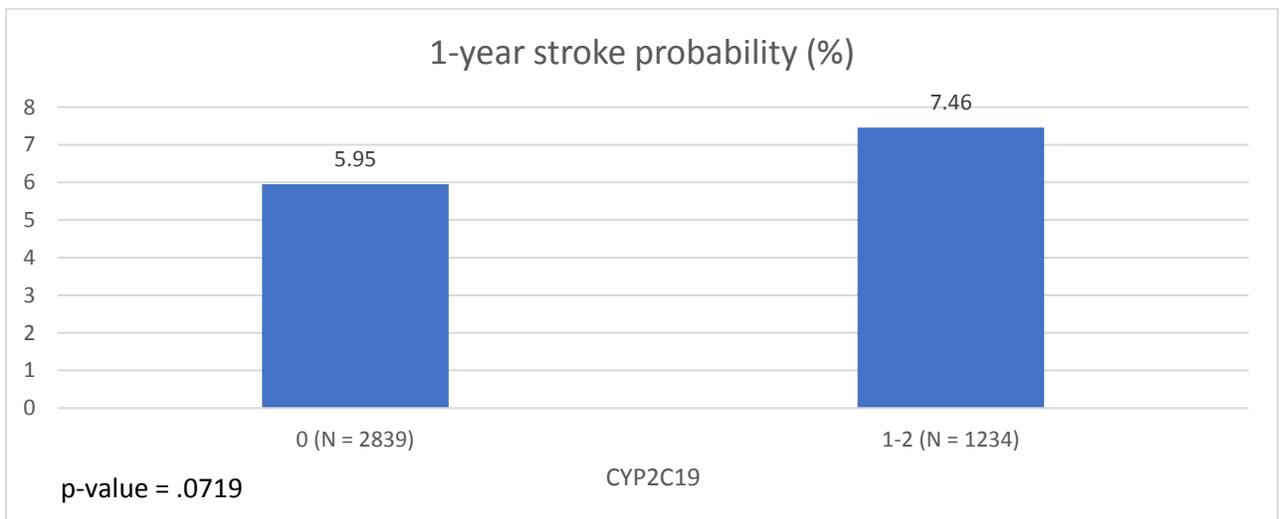
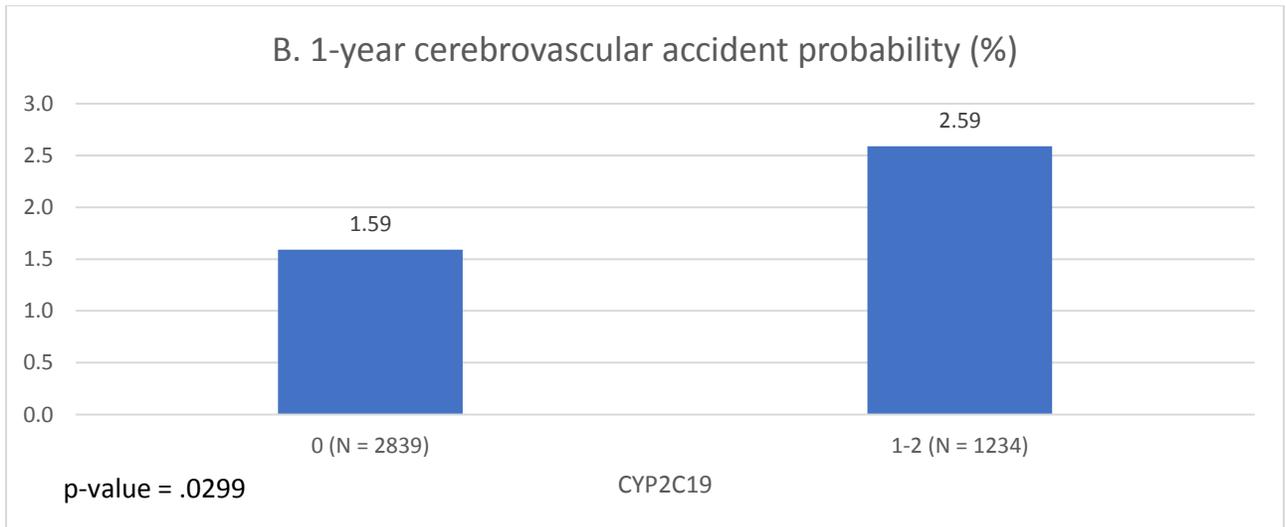
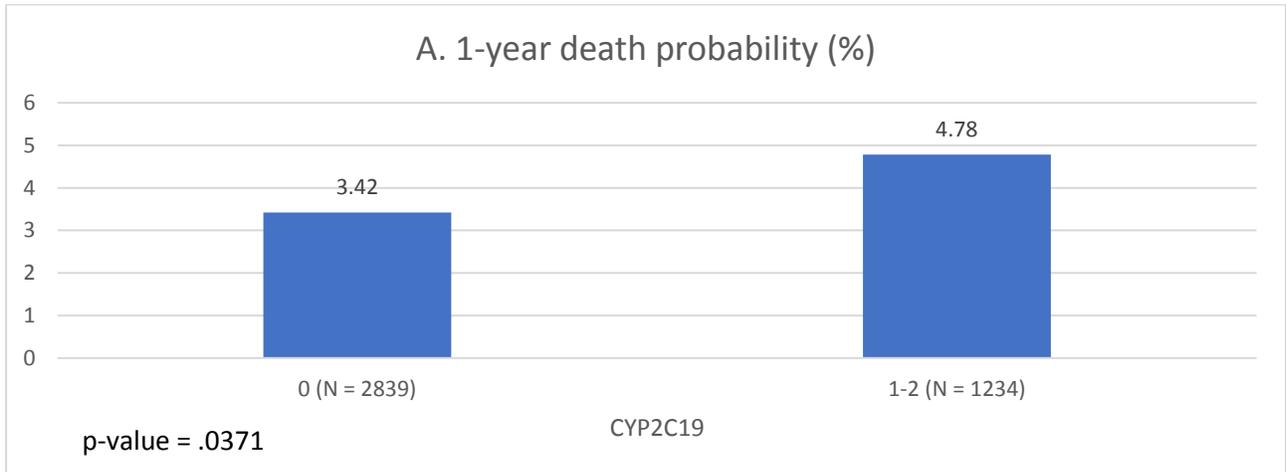
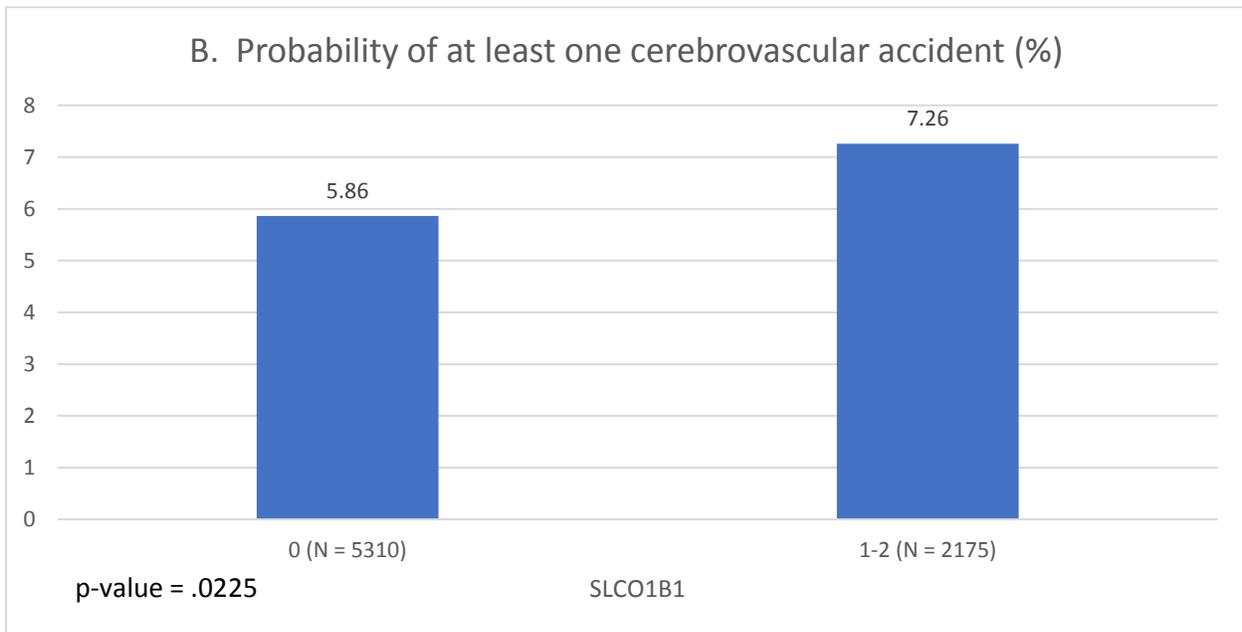
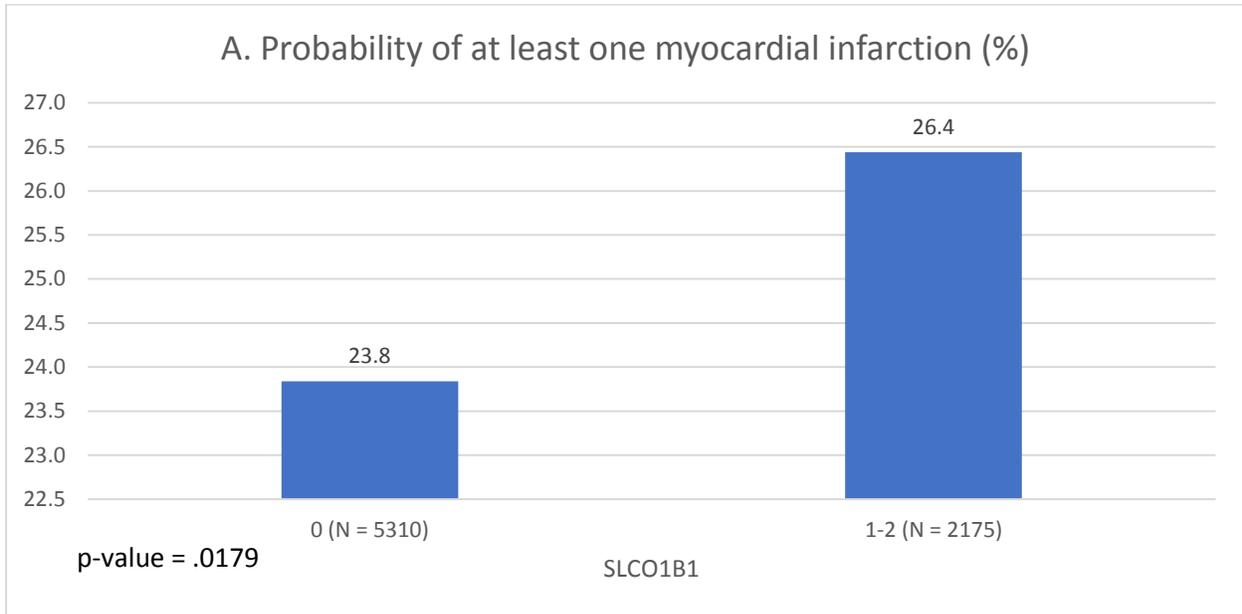


Figure 2

Post-treatment probabilities of events of patients with and without SLCO1B1 variant:
patients who initiated statin treatment in 2006



References:

- [1] Dosing Guidelines. Pharmacogenomics Knowledgebase (PharmGKB), Accessed August 29, 2017: <https://www.pharmgkb.org/view/dosing-guidelines.do>
- [2] Publications Clinical Practice Guidelines / Recommendations: Canadian Pharmacogenomics Network for Drug Safety, Accessed August 29, 2017 <http://cpnds.ubc.ca/about/projects>
- [3] Snyder SR, Mitropoulou C, Patrinos GP, Williams MS. Economic evaluation of pharmacogenomics: a value-based approach to pragmatic decision making in the face of complexity. Public Health Genomics. 2014;17(5-6):256-64. doi: 10.1159/000366177. Epub 2014 Sep 26.
- [4] Schildcrout JS, Denny JC, Bowton E, Gregg W, Pulley J, et. al. Optimizing drug outcomes through pharmacogenetics: A case for preemptive genotyping. Clinical Pharmacology & Therapeutics: 2012 92(2): 235-242
- [5] Brixner D., Biltaji E., Bress A., Unni S, et. al. The effect of pharmacogenetic profiling with a clinical decision support tool on healthcare resource utilization and estimated costs in the elderly exposed to polypharmacy. J Med Econ 2016 Mar; 19(3):213-28
- [6] Daneshi N, Hollifay E, Hancock S, Schneider J, et al. Prevalence of clinically actionable genotypes and medication exposure of older adults in the community. Pharmacogenomics and Personalized Medicine 2017: 10 17-27
- [7] Luzum J, Pakyz R, Elsey A, Haider C, et al. The Pharmacogenomics Research Network Translational Pharmacogenetics Program: Outcomes and Metrics of Pharmacogenomic Implementations Across Diverse Healthcare Systems. Clinical Pharmacology & Therapeutics 2017 102 (3) 502-510:
- [8] Mathias PC, Hendrix N, Wang WJ, Keyloun K, et al. Characterizing Pharmacogenomics-Guided Medication Use With a Clinical Data Repository. Pharmacology & Therapeutics; 2017 102(2) 340-348
- [9] Cavalari et al.. Circulation 2015: 132; suppl 3 A11802: Clinical benefit of preemptive pharmacogenomic testing for patients undergoing PCI was shown by the IGNITE network.
- [10] Jang et al. Am Cardiol2012;110:502-8;
- [11] Zabalza et al. Heart2012;98:100-8;
- [12] Holmes et al. JAMA 2011;306:2704-14;
- [13] Sorichet et al. CircCardiovascGenet 2014;7:895-903.

[14] Simvastatin: The Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for SLCO1B1 and simvastatin-induced myopathy: 2014 update. *Clinical pharmacology and therapeutics*. 2014. Ramsey Laura B, Johnson Samuel G, Caudle Kelly E, Haidar Cyrine E, Voora Deepak, Wilke Russell A, Maxwell Whitney D, McLeod Howard L, Krauss Ronald M, Roden Dan M, Feng Qiping, Cooper-DeHoff Rhonda M, Gong Li, Klein Teri E, Wadelius Mia, Niemi Mikko.

CP&T 2007 82(6); 726

[15] Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for cytochrome P450-2C19 (CYP2C19) genotype and clopidogrel therapy: 2013 Update. *Clinical pharmacology and therapeutics*. 2013. Scott Stuart A, Sangkuhl Katrin, Stein C Michael, Hulot Jean-Sébastien, Mega Jessica L, Roden Dan M, Klein Teri E, Sabatine Marc S, Johnson Julie A, Shuldiner Alan R

[16] Pharmacogenetics: From Bench to Byte- An Update of Guidelines. *Clinical pharmacology and therapeutics*. 2011. Swen J J, Nijenhuis M, de Boer A, Grandia L, Maitland-van der Zee A H, Mulder H, Rongen G A P J M, van Schaik R H N, Schalekamp T, Touw D J, van der Weide J, Wilffert B, Deneer V H M, Guchelaar H-J.