A Budget Impact Analysis of CYP2C19 Testing in Patients with Acute Coronary Syndromes (ACS) Receiving Percutaneous Coronary Intervention (PCI)

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Acute Coronary Syndrome

Acute coronary syndrome (ACS) is a collection of clinical diagnoses characterized by the sudden onset of myocardial ischemia. The subtypes of ACS include unstable angina, non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI).

ACS is responsible for nearly 1.4 million hospitalizations annually and represents nearly half of all deaths due to cardiovascular disease.

For patients who survive an initial ACS episode, to reduce the chance of a recurrent cardiovascular event, clinical guidelines call for dual anti-platelet therapy for at least 12 months. Clopidogrel is the most frequently prescribed anti-platelet agent along with aspirin; however, patients with loss-of-function variants for CYP2C19 have higher rates of adverse cardiac outcomes compared to prasugrel or ticagrelor.

Background

- Dual antiplatelet therapy is an established standard of care for patients with acute coronary syndromes (ACS) to reduce thrombotic risk.[1-3]
- Reduced CYP2C19 activity impairs clopidogrel bio-activation and increases risk of adverse clinical outcomes.[4-6]
- Poor and intermediate metabolizers treated with clopidogrel incur higher cardiovascular event rates, MI, stroke and stent thrombosis following ACS than patients with normal CYP2C19 function.
- Tests are available to identify a patient's CYP2C19 genotype and can be used to support a therapeutic strategy.
- In March 2010, the FDA introduced a black-box warning regarding availability of pharmacogenetic testing and diminished effectiveness for clopidogrel in CYP2C19 poor metabolizers.[7]
- Prasugrel & ticagrelor do not require activation by the CYP2C19 enzyme, but are more expensive and prasugrel has increased risk of bleeding.
- Despite this, CYP2C19 genotyping remains underutilized.[8]

Objective

- To estimate the financial impact of CYP2C19 genotyping in ACS patients (who receive PCI and coronary stents) treated with clopidogrel, prasugrel or ticagrelor in a managed care setting.

Methods

- A budget impact model with a one-year time horizon was developed to estimate differences in overall and average cost per patient based on the rate of CYP2C19 genotyping in a 1,000 patient cohort.
- Sensitivity analysis was carried out varying costs, adherence and the % of patients treated according to genotyping results. All costs were reported as 2012 US dollars.
- The budget impact model used rates from literature and publically available FDA advisory committee documents for:
  - prevalence of CYP2C19 metabolism status
  - cardiovascular events
  - bleeding events
  - costs of events
- Scenario analyses included:
  - Scenario A: no genotyping
  - Scenario B: 50% genotyping & appropriate treatment based on genotyping
  - Scenario C: 100% genotyping & appropriate treatment based on genotyping

Model Assumptions

The following probabilities are assumed within the budget impact framework:

- Managed Care ACS Population: n=1,000
- Initial Market Share (no genotyping):
  - Clopidogrel 93% (n=930)
  - Prasugrel 5% (n=50)
  - Ticagrelor 2% (n=20)
- CYP2C19 ultra-rapid or extensive metabolizer (UM/EM) = 73% [4]
- CYP2C19 intermediate or poor metabolizer (IM/PM) = 27% [4]

Event Rates by CYP2C19 Phenotype

Clopidogrel Adverse Event Probabilities

	EM/UM [4]*	IM/PM [4]**
Nonfatal MI	0.229	0.250
Nonfatal Stroke	0.006	0.022
Cardiovascular Death	0.017	0.017
Nonfatal Bleed	0.061	0.109
Bleed Death	0.001	0.001

*EM (*1A/*1A), UM (*17/*17, *1A/*17)
**IM (*1A/*2A, *1A/*3, *1A/*4, *1A/*8), PM (*2A/*2A, *2A/*3, *2A/*4, *2A/*5, *2A/*8)

Prasugrel Adverse Event Probabilities

	EM/UM [9]*	IM/PM [9]*
Nonfatal MI	0.204	0.133
Nonfatal Stroke	0.006	0.013
Cardiovascular Death	0.023	0.027
Nonfatal Bleed	0.126	0.039
Bleed Death	0.001	0.001

*Phenotype classifications identical to above

Ticagrelor Adverse Event Probabilities

	EM/UM [10]*	IM/PM [10]**
Nonfatal MI	0.058	0.058
Nonfatal Stroke	0.015	0.015
Cardiovascular Death	0.114	0.114
Nonfatal Bleed	0.04	0.04
Bleed Death	0.002	0.002

*EM (*1/*1), RM (*1/*17), UM (*17/*17)
**IM (*1/*2-*8), PM (*2-*8/*2-*8)

Estimated Costs

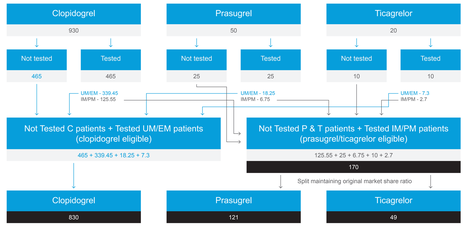
	2012 US Dollars
Nonfatal MI [11]	$26,086
Nonfatal Stroke [11]	$28,053
Cardiovascular Death [11]	$22,267
Nonfatal Bleed [11]	$24,829
Bleed Death [11]	$12,562
Clopidogrel per day*	$0.50
Prasugrel per day*	$8.00
Ticagrelor per day*	$8.71
CYP2C19 Testing	$315

* 2013 Wholesale drug prices, model assumes 80% adherence

Treatment Based on Testing

Scenario A (no testing)→ Scenario B (50% testing)

Distribution of patients:



Costs

Clopidogrel Costs = [(UM/EM clopidogrel patients * UM/EM clopidogrel AEs * AE Costs) + (IM/PM clopidogrel patients * IM/PM clopidogrel AEs * AE Costs) + clopidogrel costs + CYP testing]

Prasugrel Costs = [(UM/EM prasugrel patients * UM/EM prasugrel AEs * AE Costs) + (IM/PM prasugrel patients * IM/PM prasugrel AEs) + prasugrel costs + CYP testing]

Ticagrelor Costs = [(UM/EM ticagrelor patients * UM/EM ticagrelor AEs * AE Costs) + (IM/PM ticagrelor patients * IM/PM ticagrelor AEs * AE Costs) + ticagrelor costs + CYP testing]

Results

Scenario A – Base Case / No testing (n=1,000)
Scenario B – 50% testing (n=1,000)

- Clopidogrel 93%(A) → 83.0%(B)
- Prasugrel 5%(A) → 12.1%(B)
- Ticagrelor 2%(A) → 4.9%(B)

	Scenario A	Scenario B	Difference
Total Costs*	$8,866,274	$8,643,848	($222,426)
Cost per patient	$8,866	$8,644	($222)
CV Death	75	65	(10)
Nonfatal MI	229	213	(16)
Nonfatal Bleed	19	23	4

* Total costs = Drug Costs + AE Costs + Testing Costs

Scenario C – 100% testing (n=1,000)

- Clopidogrel 93%(A) → 73.0%(C)
- Prasugrel 5%(A) → 19.3%(C)
- Ticagrelor 2%(A) → 7.7%(C)

	Scenario A	Scenario C	Difference
Total Costs*	$8,866,274	$8,421,422	($444,852)
Cost per patient	$8,866	$8,421	($445)
CV Death	75	55	(20)
Nonfatal MI	229	197	(32)
Nonfatal Bleed	19	26	7

Sensitivity Analysis

- Varying all costs, adherence and cytochrome testing rates reduced overall costs, decreased mortality and increased nonfatal bleeds.
- AE rates and AE costs had the greatest impact on model results.
- Drug and CYP testing costs had a minimal impact on results (1/20th the impact relative to AE rates).

Discussion

Prasugrel and ticagrelor benefits of reduced nonfatal MI and fatal cardiovascular events are attenuated by higher risk of bleeding when compared with clopidogrel.

Using CYP2C19 genotype to guide treatment selection can reduce avoidable adverse clinical or drug effects associated with clopidogrel, prasugrel or ticagrelor use.

Important economic benefits may be realized by using a genotype-guided approach to reserve prasugrel or ticagreor use for patients with reduced-function CYP2C19 allele(s).

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