IMPACT OF CLOPIDOGREL PRETREATMENT ON ISCHEMIC COMPLICATIONS OF PCI AMONG BIVALIRUDIN-TREATED PATIENTS: RESULTS FROM THE EVENT REGISTRY

Amit Amin, MD; Kevin F. Kennedy, MS; Michael Pencina PhD; Peter Berger MD; Robert N. Piana MD; John Lopez MD; Neal Kleiman MD; David J. Cohen, MD, MSc on Behalf of the EVENT Investigators

Saint Luke's Mid America Heart Institute, University of Missouri-Kansas City, Kansas City, MO; Harvard Clinical Research Institute, Boston MA.

Mid America Heart Institute
SAINT LUKE'S HEALTH SYSTEM
Directed by Cardiovascular Consultants, P.A.
saintlukeshealthsystem.org

BACKGROUND

- Pretreatment with clopidogrel is a class I indication in the current ACC/AHA/SCAI guidelines and is routinely administered prior to PCI, especially with unfractionated heparin.
- Bivalirudin, an active site-direct thrombin inhibitor, results in less bleeding and is not associated with increased platelet activation during PCI.
- The ACUITY trial in ACS pts showed a borderline interaction of bivalirudin with clopidogrel pretreatment, whereby clopidogrel pretreatment was needed in the bivalirudin monotherapy pts to prevent ischemic complications.
- The REPLACE-2 trial of bivalirudin in elective PCI patients, suggested no such effect of clopidogrel pretreatment with ischemic outcomes.
- Thus, the role of clopidogrel pretreatment to prevent ischemic complications in bivalirudin treated elective PCI patients has never been addressed in unselected registry patients outside of clinical trials, with long-term follow-up.

OBJECTIVES

- To describe the effect of clopidogrel pretreatment among elective PCI pts, when treated with bivalirudin.
- To describe the effect of timing of clopidogrel pretreatment on ischemic complications.

METHODS

Data Source

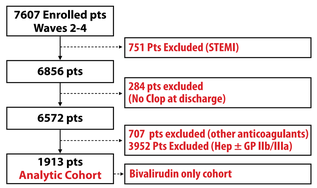
- The EVENT (Evaluation of Drug Eluting Stents and Ischemic Events) registry is a collaborative effort to assess the contemporary practice of PCI from 2004-07.
- Evaluates post-PCI outcomes in unselected PCI pts from 40 US centers.

Statistical Analysis

- Baseline differences analyzed by Chi-sqr test, and t-test as appropriate.
- Propensity score developed to model probability of clopidogrel pretreatment from age, gender, BMI, BP, DM, HTN, dyslipiemia, smoking status, dialysis, CHF, PAD, hxMI, prior PCI, ACS, hxCABG, number vessels intervened, SVG PCI, ACC/AHA lesion class, bifurcation PCI, total stent length, minimum stent diameter.
- Hierarchical logistic regression used to model outcomes adjusting for propensity score

Locations of Sites in EVENT

Study Inclusions and Exclusions



Efficacy Outcomes

- In-hospital Death
- In-hospital MI (CKMB > 3 X ULN)
- 1 Yr Death, MI, Stent Thrombosis

Safety Outcome

- Composite Bleeding (Defined as TIMI major or minor bleeding, vascular complication requiring intervention or need for transfusion

RESULTS

Table 1: Baseline Characteristics

	Clopidogrel Pretreatment n = 923	No Clopidogrel Pretreatment n = 990	p-value
Age	65.5 ± 10.8	65.5 ± 10.8	0.918
Male Gender	623 (67.5%)	686 (69.3%)	0.398
Insurance status			
Medicare	467 (50.6%)	486 (49.1%)	0.511
HMO	162 (17.6%)	191 (19.3%)	0.327
PPO	251 (27.2%)	259 (26.2%)	0.610
Diabetes	343 (37.2%)	361 (36.5%)	0.738
Hypertension (on treatment)	773 (83.8%)	791 (80.1%)	0.036
Hyperlipidemia (on treatment)	795 (86.3%)	739 (75.3%)	< 0.001
Current smoker / quit smoking < 1 year	194 (21.1%)	195 (19.9%)	0.505
Congestive heart failure	85 (9.2%)	75 (7.7%)	0.218
Peripheral arterial disease	136 (14.9%)	103 (10.5%)	0.004
Prior PCI	535 (58.3%)	278 (28.5%)	< 0.001
Prior bypass surgery	240 (26.1%)	214 (21.8%)	0.031
Canadian Cardiovascular Society Class			< 0.001
No Angina	131 (24.3%)	167 (26.6%)	
Not at ordinary activity	106 (19.6%)	122 (19.4%)	
Slight at ordinary activity	142 (26.3%)	217 (34.6%)	
Marked at ordinary activity	129 (23.9%)	96 (15.3%)	
Developed at ordinary activity	32 (5.9%)	26 (4.1%)	
GP IIb/IIIa Inhibitor given in hospital	22 (2.4%)	28 (2.8%)	0.542
Number of Vessels Treated			0.579
1	772 (84.0%)	846 (85.7%)	
2	137 (14.9%)	131 (13.3%)	
3	10 (1.1%)	10 (1.0%)	
Mean Number of Lesions Treated	1.41± 0.70	1.34 ± 0.61	0.018
Mean Number of Stents	1.57 ± 0.85	1.55 ± 0.89	0.670
Total Stent Length	26.7 ± 16.5	27.5 ± 18.2	0.310
Minimum Stent Diameter	2.9 ± 0.5	2.9 ± 0.4	0.344
Maximum Stent Diameter	3.0 ± 0.6	3.0 ± 0.5	0.581
Maximum stenosis	83.7 ± 9.9	84.2 ± 10.1	0.281
Bifurcation lesion PCI	102 (11.1%)	88 (8.9%)	0.112
In-stent restenosis PCI	99 (10.8%)	43 (4.4%)	< 0.001
Thrombus present	29 (3.2%)	31 (3.1%)	0.982
PCI successful (No complications during PCI)	869 (96.4%)	944 (96.2%)	0.800
ACC/AHA Lesion class			0.037
A	96 (10.6%)	109 (11.2%)	
B 1	339 (37.3%)	331 (34.0%)	
B 2	307 (33.8%)	385 (39.6%)	
C	166 (18.3%)	148 (15.2%)	
RCA PCI	322 (34.9%)	337 (34.0%)	0.697
LAD PCI	400 (43.3%)	428 (43.2%)	0.963
LCX PCI	257 (27.8%)	280 (28.3%)	0.831
Ramus Intermedius PCI	18 (2.0%)	25 (2.5%)	0.396
SVG PCI	76 (8.3%)	60 (6.1%)	0.063

Continuous variables compared using Student's T-test. Categorical variables compared using chi-square or Fisher's exact test.

Figure 1: Propensity Model Effectiveness

Distribution and overlap of propensity score in the two treatment groups

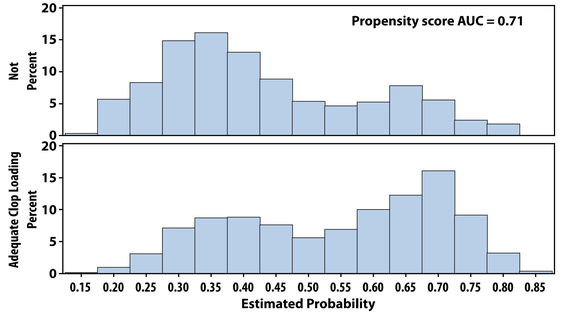


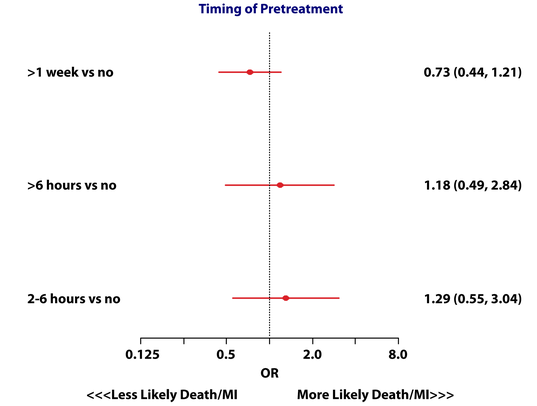
Table 2: Association of Clopidogrel Pretreatment with 30 day and 1 Year Outcomes

Outcome	Clopidogrel Pretreatment (n=923)	No Pretreatment (n=990)	Univariate p-value	Adjusted Odds Ratio (95% CI)	Multivariable p-value*
In-hospital Outcomes					
Death	0.3%	0.3%	1.00	**	
MI	5.2%	5.7%	0.66	0.93 (0.55-1.57)	0.78
Death or MI	5.5%	5.8%	0.83	0.97 (0.57-1.64)	0.90
Bleeding	1%	1%	0.94	1.17 (0.37-3.70)	0.79
1 Year Outcomes					
Death	1.4%	1.9%	0.38	0.56 (0.23-1.36)	0.20
MI	6.4%	6.6%	0.88	0.85 (0.54-1.34)	0.48
Death or MI	7.5%	8.3%	0.26	0.79 (0.52-1.19)	0.26
Definite or Probable Stent Thrombosis	0.3%	0.3%	1.00	**	

* Hierarchical models adjusted for derived propensity score. **Adjusted model not possible due to low event rate.

- Clopidogrel pretreatment was common – administered in 48 % of patients treated with bivalirudin.
- Most patients who received pretreatment, were on chronic clopidogrel therapy > 1 week duration.
- Multivariable, hierarchical modeling, adjusting for baseline clinical, and angiographic covariates and propensity to receive clopidogrel pretreatment revealed that clopidogrel pretreatment was not associated with the short- or long-term composite outcome of death or MI.
- Clopidogrel pretreatment was not associated with composite bleeding (OR 1.39 , 95% CI 0.49-3.91) nor with stent thrombosis.

Figure 2: Effect of Timing of Clopidogrel Pretreatment on 30 Day Death or MI (Adjusted Model)



- With regards to the timing of clopidogrel pretreatment – no differences in the composite ischemic end-point was observed in the >1 week; > 6 hours – 1 week and 2-6 hours pretreatment groups vs. no pretreatment.

SUMMARY

- Among 1913 unselected patients undergoing elective PCI and treated with bivalirudin anticoagulation, we found no evidence that pre-treatment with clopidogrel was associated with a reduction in either in-hospital or 1-year ischemic events (death, MI, or stent thrombosis) in either unadjusted or risk-adjusted analyses.
- There was also no evidence of increased bleeding among patients who received clopidogrel pre-treatment.

CONCLUSIONS

- Our finding suggest that for patients undergoing elective PCI in contemporary practice and receiving bivalirudin anticoagulation, clopidogrel pre-treatment does not appear necessary to reduce in-hospital or long-term ischemic events.
- These findings suggest that a strategy of withholding clopidogrel until after diagnostic angiography is reasonable for patients undergoing elective cardiac catheterization with bivalirudin as the planned anticoagulant, which should result in more streamlined care and avoidance of treatment delays among patients referred for bypass surgery.