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ORIGINAL RESEARCH

Impact of Routine Platelet Reactivity Testing with VerifyNow Assay on Antiplatelet Choice After Percutaneous Coronary Intervention

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Fakilahyel S Mshelbwala
Daniel W Hugenberg
Rolf P Kreutz

Krannert Institute of Cardiology, Indiana University School of Medicine, Indianapolis, IN, USA

Background: High on-treatment ADP platelet reactivity (HPR) measured by VerifyNow P2Y12 assay (VN) is an established risk factor for ischemic events after percutaneous coronary intervention (PCI). We hypothesized that routine use of VN at time of PCI in clinical practice may affect choice of P2Y12 antiplatelet therapy at discharge.

Methods: In a single center retrospective analysis, we examined the influence of VN testing on choice of P2Y12 inhibitor post PCI in routine clinical practice. Assessment of HPR was used routinely in clinical care during the time period of analysis at discretion of clinical providers. Subjects with PRU>208 after the loading dose of clopidogrel or during clopidogrel steady state were switched to alternate P2Y12 inhibitors.

Results: We identified 1001 patients with PCI during the time period specified. A total of 252 subjects underwent VN testing. Among those, 43% were found to have HPR on clopidogrel and were switched to alternate therapies (prasugrel [n=60], ticagrelor [n=48]). Patients who had VN platelet function testing were more likely to be discharged on clopidogrel as compared to those who did not have VN assay done (57% vs. 50%, p=0.039). There was no significant difference in 1-year net-MACE (CVD, MI, stent thrombosis, BARC 2 or higher bleeding) using tailored antiplatelet therapy (VN testing) as compared to standard of care group (adjusted HR:0.92, 95% CI: 0.54–1.5, p=0.74).

Conclusion: Routine use of VN assay in personalized antiplatelet treatment decision-making after PCI is associated with lower likelihood of using novel P2Y12 inhibitors.

Keywords: clopidogrel, prasugrel, ticagrelor, myocardial infarction

Introduction

Among available P2Y12 platelet inhibitors, clopidogrel continues to be widely used because of the decreased risk of bleeding, lower cost, and less likelihood of side effects such as dyspnea. Clopidogrel bioactivation is in part determined by inter-individual differences in pharmacogenetics, predominantly cytochrome P450 *2C19* variants.[1,2] Inadequate platelet inhibition increases risk of stent thrombosis and other adverse cardiovascular events.[3]

High on treatment platelet reactivity (HPR) during treatment with clopidogrel has been consistently found to be strong risk factor for recurrent ischemic events after PCI.[4,5] In the landmark study by Stone et al, HPR defined as PRU>208 measured by the VN P2Y12 assay, was associated with 2.49 fold increased risk

Correspondence: Rolf P Kreutz
Krannert Institute of Cardiology, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN 46202, USA
Email rkreutz@iu.edu

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of stent thrombosis after PCI.[6] Insufficient P2Y12 receptor inhibition contributes to the HPR measured by the VN assay.[7] The superiority of prospective platelet reactivity testing and adaptation of antiplatelet therapy based on VN P2Y12 assay in comparison to standard has been questioned after negative clinical trial results.[8–10] However the TROPICAL-ACS study conducted by Sibbing et al demonstrated the benefit of antiplatelet testing to guide de-escalation of P2Y12 inhibition by reduction of combined bet ischemic and hemorrhagic endpoint (net-MACE).[11]

Applied in clinical practice, patients with HPR by VN assay are routinely switched to novel, more potent P2Y12 inhibitors prasugrel or ticagrelor due to concerns about increased risk of stent thrombosis due to inadequate platelet inhibition.

We intended to examine the impact of routine platelet monitoring with VN assay on choice of antiplatelet therapy in patients undergoing PCI, and hypothesized that the use of VN platelet function testing will result in higher use of clopidogrel compared to standard of care without the use of platelet function testing.

Materials and Methods

Study Objective

This was a retrospective, observational study to determine the influence of routine use of P2Y12 platelet function assay testing by VerifyNow (VN) on tailoring antiplatelet therapy in patients after PCI. Indiana University Institutional Review Board approval was obtained for the study. Requirement for individual written informed consent for participation in the research study was waived by the Indiana University Institutional Review Board due to the retrospective, observational design of the study. Confidentiality of patient level data was maintained and analysis was performed on a de-identified data set. The study was in compliance with the Declaration of Helsinki.

Patient Population

The study population consisted of 1001 patients who had undergone PCI with subsequent placement of at least 1 drug eluting (DES) or bare metal stent (BMS) between 2012 and 2018 at Eskenazi hospital in Indianapolis. Platelet reactivity testing with VN P2Y12 assay was available bedside in the cardiac catheterization laboratory at the discretion of the clinical provider at Eskenazi Health during this time period. When used, VN P2Y12 assay was completed after administration of clopidogrel (at least 4 hrs after 600mg loading dose if not loaded previously), usually at the time of PCI. Pharmacogenetic testing was not routinely performed in our institution during the study period.

Study Design

Platelet reactivity was assessed using VN P2Y12 assay according to the manufacturer's instructions. The VN point-of-care instrument measures platelet-induced aggregation of fibrinogen coated beads in response to 20μM ADP as an increase in light transmittance and uses a proprietary algorithm to report values in P2Y12 reaction units (PRU).[12] The assay also contains prostaglandin E1 to minimize contribution of P2Y1 to platelet aggregation. HPR was defined as PRU>208 to maintain consistency with previous studies.[6] Providers had been instructed on the use of the PRU cutoffs and were encouraged to continue patients on clopidogrel if they had low on treatment platelet reactivity. Patients identified with HPR (PRU>208) after administration of clopidogrel were switched to either prasugrel or ticagrelor. Percutaneous coronary interventions were performed according to established standards and guidelines.[13] Subjects who had VN testing done were compared to subjects who did not have a platelet assay performed during their hospital stay at Eskenazi Health between 2012 and 2018. During the time period analyzed, we did not follow a protocol of de-escalation as used in the TROPICAL-ACS study with repeat platelet testing on clopidogrel 1 week after switching from prasugrel.[11]

The primary outcome of the study was the prevalence of clopidogrel prescribed at hospital discharge. The main clinical endpoint was defined as combined net-MACE (cardiovascular death, MI, stent thrombosis, bleeding in Academic Research Consortium [BARC] 2 or higher bleeding) assessed at 1 year.[14–16] Endpoints were evaluated by review of electronic medical records. Patients with stent thrombosis and cardiovascular deaths were further adjudicated using original source documents and angiographic images when available. Death was considered non-cardiac when an unequivocal non-cardiac cause was documented.

Statistical Analysis

Baseline variables were compared between groups using Pearson-Chi Square test, and continuous data by Student's *t*-test. Binary outcome was compared by use of one-sided

Fisher's exact test. Survival analysis was performed using Kaplan-Meier estimates and the Log rank test was used to evaluate differences between groups. Cox proportional hazards model regression analysis was performed with forward multivariate adjustment of clinically significant baseline co-variates ($p<0.1$). Statistical analysis was performed with the use of SPSS software, version 25.0 (SPSS Inc., Chicago, Illinois).

Table 1 Clinical Variables

Characteristics	VerifyNow P2Y12 Platelet Assay Was Not Done (n = 749)	VerifyNow P2Y12 Platelet Assay Was Done (n = 252)	p value*
Age (years)	61.7 ± 11	60.9 ± 10	0.33
Gender			0.17
Female	264/749 (35%)	101/252(40%)	
Male	485/749 (65%)	151/252 (60%)	
Race			0.73
Black or African American	270/749 (36%)	93/252 (37%)	
White	400/749 (53%)	130/252 (52%)	
Unknown/Not reported	60/749 (8%)	24/252 (9%)	
Body mass index (kg/m2)	31.8 ± 8	32 ± 8	0.75
Angina			0.14
Stable	149/749 (20%)	65/252 (26%)	
Unstable	316/749 (42%)	100/252 (40%)	
Acute MI on Presentation			<0.001
STEMI	170/749 (23%)	16/252 (6%)	
NSTEMI	321/749 (43%)	173/252 (69%)	
Medical History			
Diabetes mellitus	343/749 (46%)	121/252 (48%)	0.54
Hypertension	563/749 (75%)	217/252 (86%)	<0.001
End stage renal disease	11/749 (1%)	6/252 (2%)	0.33
Hyperlipidemia	312/749 (42%)	130/252 (52%)	0.006
Peripheral vascular disease	53/749 (7%)	21/252 (8%)	0.51
Cerebrovascular accident	67/749 (9%)	32/252 (13%)	0.08
Prior myocardial infarction	107/749 (14%)	52/252 (21%)	0.17
Coronary artery bypass graft	79/749 (10%)	31/252 (12%)	0.44
Prior percutaneous coronary intervention	127/749 (17%)	69/252 (27%)	<0.001
Tobacco use	495/749 (66%)	177/252 (70%)	0.23
Stent Type			<0.001
Drug eluting stent	628/749 (84%)	234/252 (93%)	
Bare metal stent	121/749 (16%)	17/252 (7%)	
Medication at Discharge			
ACEi/ARB	585/749 (78%)	204/252 (81%)	0.34
Aspirin	729/749 (97%)	244/252 (97%)	0.67
Statin	724/749 (97%)	245/252 (97%)	0.66
Beta blocker	688/749 (92%)	240/252 (95%)	0.074
Proton pump inhibitor	145/749 (19%)	67/252 (27%)	0.015
P2Y12 Inhibitor Pre-VN			
Clopidogrel		241/252 (96%)	
Prasugrel		8/252 (3%)	
Ticagrelor		3/252 (1%)	

Notes: *t-test (continuous data), Chi-square (Binary data).

Results

A total of 1001 patients had PCI performed between 2012 and 2018. Among those, 252 had VN platelet function assay performed during their hospital stay. The majority of patients (96%) who had VN platelet testing performed had received pre-treatment with clopidogrel. Patients who did not have VN platelet reactivity testing performed were more likely to have presented with ST elevation myocardial infarction (STEMI) and to have a bare metal stent placed. Patients who did have VN platelet testing done were more likely to have a prior diagnosis of hypertension, hyperlipidemia, or prior PCI, present with a non-STEMI, and were more likely to be prescribed a proton-pump inhibitor (Table 1). Clinical baseline variables were otherwise well matched between groups.

Among patients who underwent platelet reactivity testing, 43% were found to be non-responders and were switched to alternate therapies (prasugrel [n=60], ticagrelor [n=48]). There was a wide range of on-treatment platelet reactivity (mean ± SD: 178 ± 88 PRU; range: 4–385 PRU).

Patients undergoing platelet function assay testing using VN were more likely to be discharged on clopidogrel vs. an alternate P2Y12 inhibitor in comparison to those who did not have this test done (57% vs. 50%, p=0.039) (Figure 1).

Use of VN in tailoring antiplatelet therapy after PCI compared to standard of care group was associated with no significant difference in risk of recurrent 1-year net-MACE (CVD, MI, stent thrombosis, BARC 2 or higher bleeding) (non-adjusted Hazard Ratio: 0.96 [95% CI: 0.57–1.6],[p=0.87]). There were no significant differences in clinical outcomes after multivariate adjustment comparing VN platelet reactivity testing group vs. standard of care (no VN) group (Table 2, Figure 2).

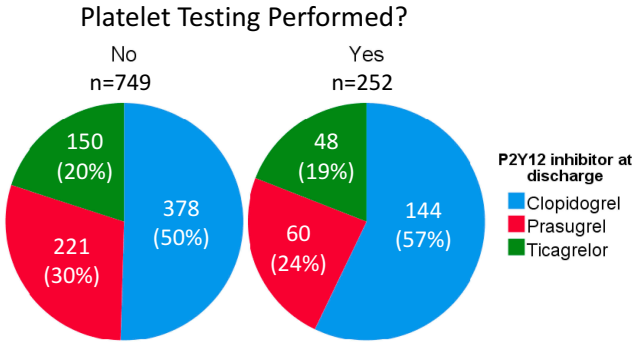

Figure 1 Distribution of different P2Y12 inhibitors prescribed at time of discharge for groups with and without VerifyNow (VN) platelet function testing.

Discussion

The results of our retrospective analysis demonstrate that routine use of VN assay in personalized antiplatelet treatment decision-making after PCI is associated with lower likelihood of using novel P2Y12 inhibitors as compared to standard treatment. Despite the higher prevalence of subjects with prior PCI and higher prevalence of NSTEMI in patients among the guided therapy group, there was no significant difference in clinical outcomes during 1-year follow up. Patients presenting with acute ST-elevation myocardial infarction were almost universally treated with either prasugrel or ticagrelor at time of primary PCI, making it unfeasible to use VN guidance for clopidogrel response at time of initial hospitalization. Upfront use of a novel P2Y12 inhibitor in our practice was routinely continued until discharge, and de-escalation of antiplatelet therapy using a platelet assay was not performed as a strategy in our institution.

Routine antiplatelet monitoring for high on-treatment platelet reactivity has been controversial due to lack of prospective trials showing superiority of such an approach compared to universal use of either prasugrel or ticagrelor.[8–10] However the main focus of use in our practice was to reduce the use of more expensive novel P2Y12 inhibitors while minimizing the risk of thrombotic events by screening for HPR on clopidogrel in the periprocedural period. More recently the TROPICAL-ACS trial showed benefit of guided antiplatelet de-escalation after PCI using the multiplate assay.[11] In that trial, patients who demonstrated low platelet reactivity after 7 days of clopidogrel 14 days post PCI, were switched to clopidogrel, whereas patients with HPR continued on prasugrel. The net-MACE benefit was driven mainly by a lower incidence of bleeding events, but also lower risk of combined ischemic endpoints.[11] In contrast, in the much smaller study by Cayla et al VN guided change of antiplatelet therapy in elderly patients who were initially prescribed low dose prasugrel was not superior to continued treatment with prasugrel 5mg daily.[17]

While clinical practice guidelines recommend the use of either ticagrelor or prasugrel over clopidogrel after PCI in patients presenting with ACS, more recent clinical trials have highlighted the increased risk of non-CABG bleeding with universal use of a potent P2Y12 inhibitor.[18–20] Avoidance of a potent P2Y12 inhibitor in patients who

Table 2 Clinical Events

Clinical Events (1-Year)	VerifyNow Done	No VerifyNow Done	Adj. Hazard Ratio (95% Confidence Interval)	p-value*
Net-MACE (combined death, myocardial infarction, stent thrombosis, BARC 2 or more bleeding)	19/252 (7.5%)	59/749 (7.9%)	0.92 (0.54–1.5)	0.74
Cardiovascular death	4/252 (1.6%)	14/749 (1.9%)	0.91 (0.29–2.9)	0.87
Myocardial infarction	14/252 (5.6%)	35/749 (4.7%)	1.31 (0.67–2.7)	0.42
BARC 2 or more bleeding	6/252 (2.4%)	14/749 (1.9%)	1.28 (0.49–3.3)	0.61

Note: *Cox proportional hazards model analysis with forward multivariate adjustment of clinically significant baseline co-variates (p<0.1).
Abbreviation: BARC, Bleeding in Academic Research Consortium.

have an acceptable pharmacodynamic response to clopidogrel and who may be at increased risk of bleeding may be a preferred strategy in post PCI dual antiplatelet therapy. Clinical risk scores have been developed to estimate bleeding risk on prolonged dual antiplatelet therapy, however they lack specificity and sensitivity and are less useful in assessing risk in regard to choice of potency of antiplatelet therapy. Clopidogrel bioactivation is dependent on activity of several cytochrome P450 (CYP) isoenzymes.[1,21] In particular, variation in CYP 2C19 isoenzyme activity due to common single nucleotide polymorphisms significantly affects clopidogrel response and on treatment platelet reactivity.[22] Several studies have demonstrated a reduction of net-MACE events by using pharmacogenetics guidance to tailor treatment with clopidogrel after PCI.[18,23-25] On treatment platelet reactivity to ADP by VN correlates with active clopidogrel metabolite concentration and is an established pharmacodynamic measure of clopidogrel response.[7] Thus, the use of VN assay to screen for HPR may be an alternative to a pharmacogenetic guided

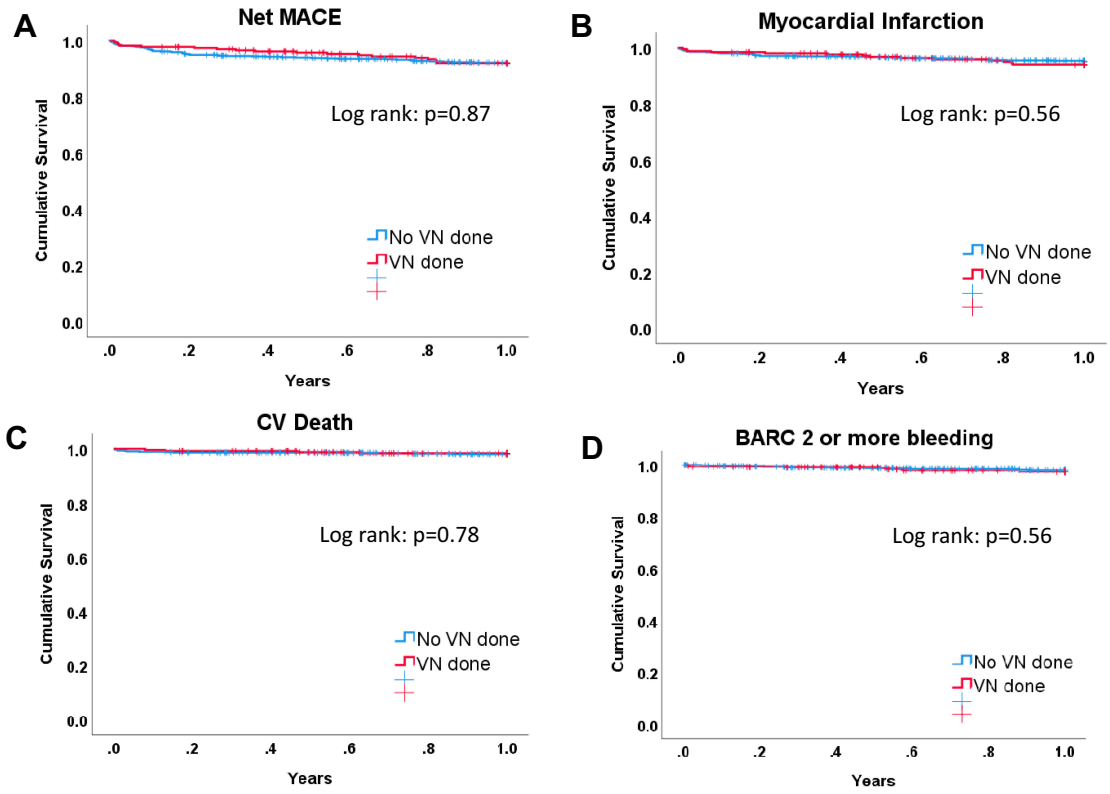

Figure 2 Clinical outcomes with Kaplan Meier cumulative survival curves for combined primary endpoint (Net-MACE: death, myocardial infarction, stent thrombosis, bleeding in Academic Research Consortium (BARC) 2 or more) (Panel [**A**]), myocardial infarction (Panel [**B**]), cardiovascular death (Panel [**C**]), and BARC 2 or more bleeding (Panel [**D**]). Analysis by log-rank model.

P2Y12 treatment strategy, and preferable in certain situations due to the ability to use the VN assay at the point-of-care with a very short turn-around time. In our study, there was no significant difference in occurrence of net-MACE or thrombotic events between groups post PCI, despite a higher prevalence of ACS in the VN guided group.

Limitations of our study include the retrospective, single center design of the study with a limited number of prescribers, and differences in baseline variables between patients with and without VN testing. The study was also not powered to evaluate clinical endpoints.

Conclusions

Tailoring of antiplatelet therapy by VN P2Y12 assay is feasible, and results in a lower likelihood of using a potent P2Y12 inhibitor post PCI in clinical practice. There was no significant association of VN P2Y12 assay use with clinical outcomes.

Disclosure

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