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Toward Personalized DAPT: Is There an Inter-Manufacturer Difference in Generic Clopidogrel Response?

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Abstract

Objective.—To compare rates of clopidogrel response among patients receiving medication produced by 2 different manufacturers after acute coronary syndrome (ACS) and/or percutaneous coronary intervention.

Methods.—This quality-improvement project included 515 adult patients receiving clopidogrel for ACS or ischemic heart disease and referred for coronary angiography/percutaneous coronary intervention. The project was divided into 2 phases: (1) retrospective collection of baseline data (April 2019-October 2020); and (2) two 12-week, prospective phases in which all clopidogrel in the hospital was restricted to a single manufacturer at a time (November 2020-May 2021). The primary outcome was clopidogrel response measured by platelet function testing, defined as adenosine diphosphate (ADP) response <40% on light transmission aggregometry.

Results.—Of 515 total patients included in both phases (mean age, 64.5 ± 11.4 years; 351 men [68.2%]; 450 with ACS [87.4%]), 52% were found to be clopidogrel responders based on results of platelet function testing. Among 135 patients in the prospective phase, there was a significantly lower proportion of patients who were clopidogrel responders in the Manufacturer 1 group compared with the Manufacturer 2 group (34.8% vs 55.1%, respectively; P=.03). After adjustment for age, sex, body mass index, aspirin response, therapeutic hypothermia, left heart catheterization indication, clopidogrel loading dose, time between loading dose and lab measurement, and manufacturer, aspirin response (odds ratio 0.96; 95% confidence interval, 0.95–0.97; P<.001) and manufacturer (odds ratio, 2.45; 95% confidence interval, 1.18–5.22; P=.02) were associated with clopidogrel response.

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Conclusions.—In a large public hospital, we observed that pharmacodynamic response to clopidogrel varied by drug manufacturer. Further investigation and/or regulation is needed to minimize inter-manufacturer variability.

Keywords

antiplatelet therapy; clopidogrel; coronary artery disease; generics; platelet function

Antiplatelet therapy with a $P2Y_{12}$ receptor inhibitor is an essential component of treatment after acute coronary syndrome (ACS) and/or coronary stent placement. Clopidogrel, the least potent of the 3 available oral agents, still remains widely utilized. While it is well established that clopidogrel has variable inter-individual response,[1] the use of platelet function testing (PFT) to tailor therapy remains controversial. Initial randomized trials of PFT were indeterminate as the event rates achieved after trial completion were significantly lower than the projected rates, rendering the trials underpowered; nevertheless, they have been inappropriately inferred as providing robust evidence against routine PFTs. However, in a recent meta-analysis that included 11 trials, guided selection of antiplatelet therapy reduced ischemic and bleeding events when compared with standard therapy.[2] Although many factors contribute to clopidogrel hyporesponse, whether there is inter-manufacturer variability in generic clopidogrel response has not been explored in the United States.

Methods

This quality improvement project had 2 phases. First, we retrospectively identified all patients who had PFTs since April 2019 (the date of EPIC adoption at our institution). Patients were included if they had at least 1 light transmission aggregometry (LTA) PFT (AggRAM Analyzer, Helena Laboratories) and were on clopidogrel for a coronary indication. During this time period, the pharmacy department purchased generic clopidogrel from several manufacturers and it was not possible to link a patient's clopidogrel to the manufacturer. The second phase was to prospectively create 2 separate 12-week periods in which all clopidogrel in the hospital was restricted to 1 of 2 manufacturers (Manufacturer 1 group: 300 mg manufactured in Canada, 75 mg manufactured in India; Manufacturer 2 group: 300 mg and 75 mg manufactured in United States). The primary outcome was clopidogrel response defined as ADP ≤40%.[3] We also collected data on aspirin response defined as arachidonic acid ≤20%.[4] This was an internal quality-improvement project and thus did not require institutional review board approval.

Statistical analysis.

Multivariable logistic regression analysis was performed to assess the predictors of clopidogrel response, adjusting for demographics, clinical characteristics, and laboratory values. Variables with *P*-values of <.20 in univariate analyses, as well as variables that are clinically important, were selected as candidate predictors for entry. A 2-sided *P*-value <.05 was considered to be statistically significant.

Results

Five-hundred and fifteen patients with PFTs were included in this study (Table 1, Part 1 and Table 1, Part 2). The majority of patients (87%) underwent left heart catheterization (LHC) for an ACS and 91% received coronary stents. Over the 2-year period, 52% were clopidogrel responders. Clopidogrel responders were more likely to be men, showed more complete platelet inhibition with aspirin, and were more likely to be aspirin responders (80.6% vs 49%; $P<.001$). Overall, 42% were both clopidogrel and aspirin responders, 24% were clopidogrel responders but aspirin hypo-responders, 24% were aspirin responders but clopidogrel hypo-responders, and 10% were both clopidogrel and aspirin hypo-responders.

One hundred and thirty-five patients were included in the prospective phase; 66 patients received clopidogrel from Manufacturer 1 and 69 patients received clopidogrel from Manufacturer 2. There was no difference in baseline characteristics or clopidogrel load factors between the groups (Table 2). A significantly lower proportion of patients in the Manufacturer 1 group were clopidogrel responders compared with the Manufacturer 2 group (34.8% vs 55.1%; $P=.03$). Additionally, a significant difference in distribution of ADP values between the 2 groups was observed (34.8% ADP ≤40%, 18.2% ADP 41%−50%, and 47% ADP >50% in the Manufacturer 1 group vs 55.1%, 5.8%, and 39.1% in the Manufacturer 2 group, respectively; $P=.02$) (Table 2). There was no difference in aspirin response between the 2 groups. Multivariable analysis showed that the odds of being a clopidogrel responder were 2.5 times higher among patients in the Manufacturer 2 group vs those in the Manufacturer 1 group (odds ratio, 2.45; 95% confidence interval, 1.18–5.22; $P=.02$) (Table 3).

Discussion

Inter-individual variability in response to clopidogrel has been well documented, but little has been to done to describe variability between generic manufacturers. In this prospective study from a large public hospital, we found a significant difference in clopidogrel response based on manufacturer, with a response rate of 35% with Manufacturer 1 vs 55% with Manufacturer 2 even after multivariable adjustment.

Given the need to balance ischemic benefit and bleed risk for patients on antiplatelets, the use of PFTs to tailor therapy has been the subject of great interest. In a recent meta-analysis, Galli et al found a significant decrease in thrombotic and bleeding events among patients treated with a guided antiplatelet strategy (by PFTs or genotyping) compared with standard care.[2] Among studies testing escalation of therapy (ie, clopidogrel to prasugrel or ticagrelor), there was a significant reduction in ischemic events and among studies testing de-escalation of therapy there was a significant reduction in bleeding. Moreover, analyses grouping studies by testing type (PFT vs genotyping) were consistent with the primary findings. Yet, current guidelines and expert statements, which predate this large meta-analysis, recommend testing be considered an optional tool to guide treatment de-escalation and tailor therapy among selected patients.[5,6]

At our large public hospital with a significant proportion of under- or uninsured patients, clopidogrel, which is exponentially cheaper with the additional benefit of once daily dosing and a better safety profile, is an appealing agent especially among patients with complex social, economic, and health statuses. Additionally, while large trials have shown prasugrel and ticagrelor to be superior to clopidogrel in the setting of ACS, advancements in stent technology have decreased the risk of stent thrombosis,[7,8] shifting attention toward the bleeding risk of antiplatelet therapy.

Since the expiration of the Plavix brand in 2012, many have questioned the safety and efficacy of utilizing generic formulations. In a systematic review of 72 studies with over 1,000,000 patients, the crude risk of hospital visits was higher for patients exposed to generic compared with brand-name cardiovascular drugs. However, the evidence was heterogeneous and insufficient to draw any firm conclusion.[9] In an analysis from the United States Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS), the overall adverse event profile suggested potentially better safety of branded clopidogrel over generic clopidogrel.[10] To the contrary, several studies outside of the United States compared generic formulations of clopidogrel with branded clopidogrel and have largely shown no difference in outcomes including platelet inhibition, thrombotic, and bleeding events.[11–15] Conversely, a single center in the United States reported an increase in the rate of stent thrombosis from 0.14% to 0.38% after the substitution of generic clopidogrel.[16]

None of the above studies assessed whether or not differences exist between generic formulations of medications. To our knowledge, ours is the first description of differences between generic manufacturers in the United States. Our results raise questions about the interchangeability of generic drugs. All clopidogrel products available in the United States are deemed therapeutic equivalents—meaning they contain the same active ingredient and demonstrate bioequivalence determined by studies of drug absorption in healthy adults.[17] While therapeutic equivalence provides theoretic and legal justification for generic substitutions, concerns have been raised regarding interchangeability of drugs based on clinician observations and postmarketing data. Based on the inter-manufacturer variability we observed, further investigation regarding the safety of interchanging clopidogrel may be warranted.

Study limitations.

This study was not randomized. However, we used an all-comers design with a prospective component in which the clinicians were unaware of the clopidogrel manufacturer used at any time point. The study did not assess clinical outcomes and given the sample size would have been underpowered to detect a difference in hard endpoints. Finally, the study assessed differences in clopidogrel response among 2 manufacturers and it is not known whether this variability will extend to other manufacturers.

Conclusion

We found that rates of clopidogrel response varied between 2 manufacturer groups. On a macro level, institutions may consider performing quality checks to eliminate additional response variability, while on a micro level providers may define high-risk patient groups

in which to test. Furthermore, these findings suggest that therapeutic equivalence does not necessarily confer clinical equivalence and that generic substitutions should be used with caution.

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Table 1.

Patient characteristics by clopidogrel response.

Characteristics	All Patients (n = 515)	Responders (n = 268)	Non-Responders (n = 247)	*P*-Value[a]
Age (years)	64.5 ± 11.4	64.7 ± 11.2	64.3 ± 11.7	.70
Male, No. (%)	351 (68.2%)	194 (72.4%)	157 (63.6%)	.04
Weight (kg)	78.4 ± 20.0	76.9 ± 18.1	80.0 ± 21.8	.08
Body mass index (kg/m^2)	28.1 ±6.3	27.6 ± 5.9	28.6 ±6.7	.09
Body mass index group				.74
<18.5 kg/m^2	16 (3.1%)	10 (3.7%)	6 (2.4%)	
18.5–24.9 kg/m^2	153 (29.8%)	83 (31.0%)	70 (28.5%)	
25–29.9 kg/m^2	180 (35.0%)	95 (35.4%)	85 (34.6%)	
30–34.9 kg/m^2	103 (20.0%)	52 (19.4%)	51 (20.7%)	
35–39.9 kg/m^2	37 (7.2%)	18 (6.7%)	19 (7.7%)	
≥40 kg/m^2	25 (4.9%)	10 (3.7%)	15 (6.1%)	
Race				.67
Black or African American	161 (31.3%)	83 (31.0%)	78 (31.6%)	
White	52 (10.1%)	31 (11.6%)	21 (8.5%)	
Asian	64 (12.4%)	34 (12.7%)	30 (12.1%)	
American Indian or Alaska Native	4 (0.8%)	3 (1.1%)	1 (0.4%)	
Native Hawaiian or other Pacific Islander	1 (0.2%)	1 (0.4%)	0 (0.0%)	
Unknown	233 (45.2%)	116 (43.3%)	117 (47.4%)	
Ethnicity				.72
Non-Hispanic	299 (58.1%)	156 (58.2%)	143 (57.9%)	
Hispanic	185 (35.9%)	98 (36.6%)	87 (35.2%)	
Unknown	31 (6.0%)	14 (5.2%)	17 (6.9%)	
History of diabetes	259 (50.3%)	128 (47.8%)	131 (53.0%)	.27
Left heart catheterization indication				.20
Acute coronary syndrome	450 (87.4%)	229 (85.4%)	221 (89.5%)	
Stable ischemic heart disease	58 (11.3%)	35 (13.1%)	23 (9.3%)	
Arrythmia etiology	4 (0.8%)	3 (1.1%)	1 (0.4%)	
Staged percutaneous coronary intervention	1 (0.2%)	1 (0.4%)	0 (0.0%)	
No left heart catheterization	2 (0.4%)	0 (0.0%)	2 (0.8%)	
Intervention type				.29
Stent	467 (90.7%)	248 (92.5%)	219 (88.7%)	
Median number of stents (n)	2.0 (1.0–2.0)	2.0 (1.0–2.0)	2.0 (1.0–3.0)	
Medical management	27 (5.2%)	12 (4.5%)	15 (6.1%)	
Other	21 (4.1%)	8 (3.0%)	13 (5.3%)	
Clopidogrel responder	268 (52.0%)			

Characteristics	All Patients (n = 515)	Responders (n = 268)	Non-Responders (n = 247)	*P*-Value[a]
Adenosine diphosphate (%)	39.0 (26.0–56.0)	26.0 (17.0–34.0)	56.0 (50.0–64.0)	<.001

Table 1.

Patient characteristics by clopidogrel response.

Characteristics	All Patients (n = 515)	Responders (n = 268)	Non-Responders (n = 247)	*P*-Value[a]
Adenosine diphosphate group				
≤40%	268 (52.0%)	268 (100%)	0 (0.0%)	<.001
40%–50%	68 (13.2%)	0 (0.0%)	68 (27.5%)	
>50%	179 (34.8%)	0 (0.0%)	179 (72.5%)	
Arachidonic acid (%)	15.0 (9.0–27.0)	11.0 (7.0–17.0)	21.0 (13.0–30.0)	<.001
Arachidonic acid ≤20%	337 (65.4%)	216 (80.6%)	121 (49.0%)	<.001
Time from clopidogrel load to lab measurement (hours)	32.0 (20.7–64.6)	32.0 (21.1–66.3)	29.7 (20.4–63.0)	.64
Time from clopidogrel load to lab measurement by group				
<24 hours	183 (38.0%)	92 (36.1%)	91 (40.1%)	.64
24–48 hours	161 (33.4%)	74 (29.0%)	64 (28.2%)	
>48 hours	138 (28.6%)	89 (34.9%)	72 (31.7%)	
Clopidogrel load strength				
300 mg	172 (33.5%)	93 (34.8%)	79 (32.0%)	.23
600 mg	310 (60.3%)	162 (60.7%)	148 (59.9%)	
No load	32 (6.2%)	12 (4.5%)	20 (8.1%)	
Targeted temperature management when loaded	9 (1.8%)	2 (0.7%)	7 (2.8%)	—
Clopidogrel manufacturer				
Manufacturer 1	—	23 (8.6%)	43 (17.4%)	.01
Manufacturer 2	—	38 (14.2%)	31 (12.6%)	
Unknown manufacturer	—	206 (77.2%)	173 (70.0%)	

Data presented as mean ± standard deviation, median (interquartile range), or number (%).

[a] *P*-values for comparison between responders and non-responders.

Table 2.

Patient characteristics by manufacturer group.

Characteristics	MG 1 (n = 66)	MG 2 (n = 69)	*P*-Value
Age (years)	65.1 ± 11.3	63.0 ± 10.9	.28
Male	44 (66.7%)	44.0 (63.8%)	.86
Weight (kg)	75.9 ± 15.5	80.6 ± 23.5	.17
Body mass index (kg/m^2)	27.0 ± 5.3	29.2 ± 7.4	.05
Body mass index group			.31
<18.5 kg/m^2	3 (4.5%)	1 (1.4%)	
18.5–24.9 kg/m^2	22 (33.3%)	22 (31.9%)	
25–29.9 kg/m^2	23 (34.8%)	20 (29.0%)	
30–34.9 kg/m^2	14 (21.2%)	14 (20.3%)	
35–39.9 kg/m^2	3 (4.5%)	5 (7.2%)	
≥40 kg/m^2	1 (1.5%)	7 (10.1%)	
Race			.69
Black or African American	21 (31.8%)	28 (40.6%)	
White	7 (10.6%)	7 (10.1%)	
Asian	6 (9.1%)	7 (10.1%)	
American Indian or Alaska Native	1 (1.5%)	0 (0.0%)	
Native Hawaiian or other Pacific Islander	0 (0.0%)	1 (1.4%)	
Unknown	31 (47.0%)	26 (37.7%)	
Ethnicity			.80
Non-Hispanic	38 (57.6%)	44 (63.8%)	
Hispanic	25 (37.9%)	22 (31.9%)	
Unknown	3 (4.5%)	3 (4.3%)	
History of diabetes	35 (53.0%)	38 (55.1%)	.95
LHC indication			.58
Acute coronary syndrome	59 (89.4%)	61 (88.4%)	
Stable ischemic heart disease	6 (9.1%)	6 (8.7%)	
VT/PVC etiology	1 (1.5%)	0 (0.0%)	
Staged PCI	0 (0.0%)	0 (0.0%)	
No LHC	0 (0.0%)	2 (2.9%)	
Intervention			.02
Stent	65 (98.5%)	59 (85.5%)	
Number of stents (n)	1.0 (1.0–2.0)	2.0 (1.0–2.0)	
Medical management	0 (0.0%)	5 (7.2%)	
Other	1 (1.5%)	5 (7.2%)	
Clopidogrel responder	23 (34.8%)	38 (55.1%)	.03
Adenosine diphosphate (%)	46.5 (27.3–56.0)	39.0 (25.0–55.0)	.24

Characteristics	MG 1 (n = 66)	MG 2 (n = 69)	*P*-Value
Adenosine diphosphate group			
≤40%	23 (34.8%)	38 (55.1%)	.02
40%−50%	12 (18.2%)	4 (5.8%)	
>50%	31 (47.0%)	27 (39.1%)	
Arachidonic acid (%)	16.5 (10.0–28.8)	14.0 (7.0–27.0)	.30
Arachidonic acid ≤20%	38 (57.6%)	44 (63.8%)	.58
Time from clopidogrel load to lab measurement (hours)	25.5 (19.2–64.2)	23.4 (17.0–48.3)	.23
Time from clopidogrel load to lab measurement by group			
<24 hours	30 (47.6%)	36 (55.4%)	.63
24–48 hours	12 (19.0%)	12 (18.5%)	
>48 hours	21 (33.3%)	17 (26.2%)	
Clopidogrel load strength			
300 mg	24 (36.4%)	22 (31.9%)	.84
600 mg	39 (59.1%)	43 (62.3%)	
No load	3 (4.5%)	4 (5.8%)	
Targeted temperature management when loaded	2 (3.0%)	0 (0.0%)	.24

Data presented as mean ± standard deviation, median (interquartile range), or number (%).

ADP = adenosine diphosphate; LHC = left heart catheterization; PCI = percutaneous coronary intervention; MG = manufacturer group.

Table 3.

Predictors of clopidogrel response.

Predictors	OR (95% CI)	*P*-Value
Age	1.00 (0.96–1.03)	.92
Manufacturer group, 2 vs 1	2.45 (1.18–5.22)	.02
ACS, yes vs no	0.86 (0.26–2.91)	.81
Load, load vs no load	1.12 (0.20–6.72)	.89
Sex, male vs female	1.18 (0.54–2.59)	.68
Body mass index	0.99 (0.93–1.05)	.83
Arachidonic acid	0.96 (0.93–0.98)	<.01
Estimates for interaction term: no need to report the OR (95% CI) for interaction		
Days between load and PFT:load	1.10 (0.84–1.43)	.45

ACS = acute coronary syndrome; CI = confidence interval; OR = odds ratio; PFT = platelet function test.