Management of patients with aspirin and clopidogrel impaired response

Aims: To determine the management of patients with impaired response to antiplatelet agents. **Methods:** We reviewed the records of 116 patients who had a response panel ordered between 1st January 2005 to 31st July 2007. Aspirin impaired response was defined as a mean platelet aggregation greater than or equal to 20% with 0.5% mg/ml arachidonic acid and/or greater than or equal to 70% with 10 µM adenosine diphosphate. Clopidogrel impaired response was defined as a mean platelet aggregation greater than or equal to 40% with 10 µM ADP. Management change was defined as any change occurring immediately after testing. **Results:** Of patients on aspirin (n = 112), 34% had an impaired response to aspirin leading to a management change in 58% of impaired response patients compared with 29% of responsive patients (p = 0.003). The aspirin impaired-response group was changed to higher dosages of aspirin and clopidogrel after testing. Clopidogrel impaired response occurred in 19.5% of patients on clopidogrel (n = 92). Management change was more frequent among patients with impaired response to clopidogrel compared with responsive patients (72 vs 31%; p = 0.001) and led to higher dosages of clopidogrel after testing. Patients with impaired response to both aspirin and clopidogrel (12%) were also changed to higher dosages of aspirin and clopidogrel. **Conclusions:** Patients with laboratory evidence of impaired response to either aspirin and/or clopidogrel are more likely to be changed to higher dosages of antiplatelet therapy. The efficacy and safety of this increasingly common strategy needs to be tested in prospective clinical trials.

KEYWORDS: antiplatelet ■ aspirin ■ clopidogrel ■ impaired response ■ platelet aggregation ■ resistance

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Antiplatelet therapy with aspirin and clopidogrel is a foundation in the therapeutic approach to acute coronary syndromes (ACS). Despite the appropriate use of aspirin or clopidogrel, patients continue to develop clinical events on antiplatelet therapy; better known as clinical 'resistance' or 'impaired response' [1]. The prevalence of aspirin or clopidogrel impaired response in the literature ranges from 0 to 65% and 4 to 58%, respectively [2–5]. Currently, no uniform definition or method for testing exists for aspirin or clopidogrel impaired response. What is not known is whether a laboratory finding of impaired response is correlated with true clinical impaired responsiveness [6]. Several studies have found an association between laboratory findings of impaired response and adverse clinical outcomes [7–12]. The exact mechanism(s) causing impaired response is not known [13]. This study examines the management of patients with laboratory evidence of aspirin and/or clopidogrel impaired response.

Methods

■ Patients

The study population consisted of any patient in whom an aspirin/clopidogrel response panel was ordered by a staff cardiologist at a single medical center between 1st January 2005 to 31st July 2007. The decision to order a response panel and strategies for treatment based upon the results were at the discretion of the physician. Patient information was obtained retrospectively using the EpicLink™ system electronic medical record. No patients were excluded from this study. Cleveland Clinic Institutional Review Board approval was obtained on 18th October 2007, with a waiver for informed consent (Protocol No. 07–887).

■ Data collection

Patient data were obtained through the electronic medical record system and/or paper charts and were independently verified by the authors. The last dosages of aspirin and/or clopidogrel taken by a patient on the day of testing and the day after testing were used for the purposes of this study. A change in the patient's management was defined as any pharmacologic or written change occurring after the response panel result was made available.

The aspirin/clopidogrel response panel measures optical platelet aggregation using a PAPS-4 platelet aggregometer (BioData) and exposing platelet-rich plasma to various

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aggregating agents, including ADP and arachidonic acid (AA). A platelet count was performed prior to aggregation testing. In platelet-poor plasma, platelet count was adjusted to 200 × 10^3/µl and 300 × 10^3/µl. For our study, aspirin impaired response was defined by a mean platelet aggregation greater than or equal to 20% aggregation with 0.5 mg/ml AA and/or greater than or equal to 70% aggregation with 10 µM ADP in a patient taking aspirin on the day of response panel testing. The definition of clopidogrel impaired response for this study was any patient taking clopidogrel on the day of response panel testing with a mean platelet aggregation of greater than or equal to 40% with 10 µM ADP.

Table 1. Baseline characteristics of study population*.

Clinical factors	**No. (%)**
Age (mean ± SD [years])	63.2 ± 13.8
Male (no. [%])	87 (75)
Weight (mean ± SD [lbs])	189.8 ± 37.9
BMI (mean ± SD)	29.5 ± 4.9
Smoking history (no. [%]):	
– Current	11 (10)
– Former	59 (52)
– Never	44 (38)
Inpatient (no. [%])	72 (62)
Diabetes (no. [%])	39 (34)
Hyperlipidemia (no. [%])	108 (93)
Hypertension (no. [%])	95 (82)
Renal insufficiency (no. [%])	15 (13)
Prior stroke (no. [%])	18 (15)
Prior MI (no. [%])	59 (51)
Prior PCI (no. [%])	73 (63)
Prior CABG (no. [%])	35 (30)
Medication use prior to testing	**No. (%)**
Aspirin	112 (96)
Clopidogrel	92 (79)
Aspirin and clopidogrel	90 (78)
GPIIb/IIIa inhibitors	10 (9)
Coumadin	6 (5)
ACE inhibitor or ARB	57 (49)
β-blocker	89 (77)
Calcium-channel blocker	32 (28)
Statin	107 (92)
Diuretic	24 (21)
Proton-pump inhibitor	52 (45)
NSAID	3 (2)
Laboratory values	**Median (IQR)**
White blood cell count (×10^3/µl)	6.8 (5.7–8.7)
Hemoglobin (g/dl)	12.8 (11.2–14.4)
Platelet count (×10^3/µl)	198 (168–257)
Creatinine (mg/dl)	1.0 (0.8–1.2)
Troponin T (ng/ml)	0.36 (0.08–1.95)
Ultra-sensitive CRP (mg/l)	4 (1.2–17.8)
BNP (pg/ml)	365 (162–761)

**Prior to response panel testing of 116 patients, 90 patients were on both aspirin and clopidogrel, 22 patients on aspirin only, two patients on clopidogrel only, and two patients on neither aspirin nor clopidogrel.*
ACE: Angiotensin-converting enzyme; ARB: Angiotensin-receptor blocker; BMI: Body mass index; BNP: B-type natriuretic peptide; CABG: Coronary artery bypass graft; CRP: C-reactive protein; GPIIb/IIIa: Glycoprotein IIb/IIIa; IQR: Interquartile range; MI: Myocardial infarction; NSAID: Nonsteroidal anti-inflammatory drug; PCI: Percutaneous coronary intervention; SD: Standard deviation.

■ Statistical analysis

We performed all statistical analysis using the JMP® 7.0 software. Categorical variables are presented as frequencies and percentages and were compared between patient cohorts using chi-square tests or Fisher's exact test if sample sizes were small. Continuous variables are presented as mean ± standard deviation or median and interquartile range. Student's t-test was used to compare continuous variables between two groups, where a p-value of less than 0.05 was considered to be statistically significant.

Results

Baseline characteristics of all 116 patients in the study are shown in Table 1. Prior to response panel testing, 90 patients were on both aspirin and clopidogrel, 22 patients on aspirin only, two patients on clopidogrel only, and two patients on neither aspirin nor clopidogrel. The diagnosis of each patient at the time of response panel testing is shown in Figure 1. ACS (40%), coronary artery disease (35%), and stable angina (15%) were the most common diagnoses. Table 2 summarizes the reasons for response panel testing. Testing after (24%) or before (13%) percutaneous coronary intervention (PCI) and patients termed 'prothrombotic' (13%) were the most common reasons for testing. Patients with stent thrombosis comprised 9.6% of the total population. The reason for testing was not clearly documented in 21% of patients, and thus is listed as unknown. Two patients tested for platelet response were not on aspirin or clopidogrel at the time of testing. One patient was tested in the setting of a ventricular assist device pre-operative work-up, and it was unclear why the other patient was tested.

Out of 112 patients on aspirin, 34% (n = 38) had an impaired response to aspirin. Clopidogrel-impaired response was observed in 19.5% of patients on clopidogrel (n = 92). Of the patients on both aspirin and clopidogrel (n = 90), 12% had an impaired response to both agents. After response panel testing, 38% (n = 44) had a change in management. The majority of changes in management were increases in doses of either aspirin and/or clopidogrel, yet 18% of management changes did not involve changing the dose and are listed in Box 1. The response panel was retested in 7% of patients with a change in management.

Patients with impaired response to aspirin were older, were more likely to be inpatients and had increased history of stroke, while clopidogrel impaired-response patients were more often female, diabetic, hypertensive and had higher mean platelet counts (Table 3). For unknown reasons, the clopidogrel-responsive group was nearly twice as likely to have prior myocardial infarction compared with the clopidogrel impaired-response group (Table 3). Patients with impaired response to both agents were older, female, diabetic, less likely to be on β-blockers, more anemic and with higher platelet counts (Table 4). As shown in Table 5, a change in management was observed more often in patients with impaired response to aspirin and/or clopidogrel compared with responsive patients. Patients with impaired response to aspirin and/or clopidogrel were more frequently changed to higher mean dosages of antiplatelet therapy (Table 6).

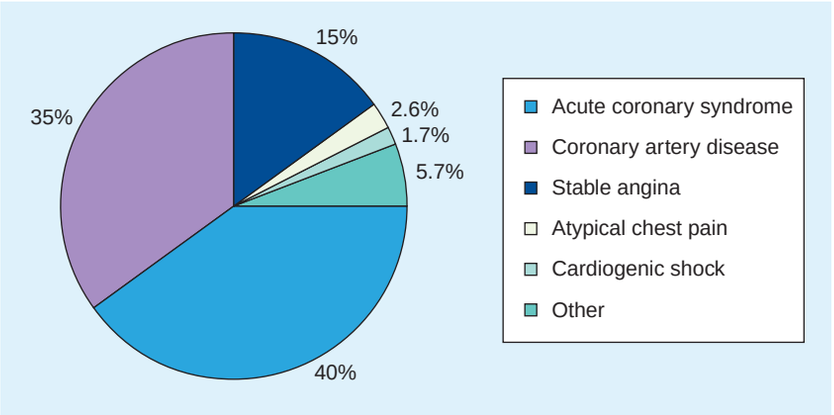

Figure 1. Diagnosis during response panel testing. The following diagnoses categorized as 'Other' were all documented once in the study: aortic stenosis after aortic valve replacement; family history of coronary artery disease; gastrointestinal bleeding in the setting of a drug-eluting stent; hematuria in the setting of a drug-eluting stent; incessant ventricular tachycardia; peripheral arterial disease; and recurrent stroke/transient ischemic attack.

Table 2. Documented reasons for response panel testing.

Reason	No. (%)
Follow-up after percutaneous intervention	28 (24)
Unknown	24 (21)
Prior to percutaneous intervention	15 (13)
Prothrombotic	15 (13)
Stent thrombosis	11 (9.6)
Secondary prevention failure	10 (8.6)
Primary prevention failure	3 (2.6)
Prior to clopidogrel discontinuation	3 (2.6)
In-stent restenosis	2 (1.7)
Risk for coronary artery disease	2 (1.7)
Patient desired testing	1 (0.9)
Possible risk factor for cardiac disease	1 (0.9)
Work-up for left ventricular assist device	1 (0.9)

Box 1. Other changes in management after response panel testing.

- Proceeded with bifurcation stenting (n = 2)
- Incorrectly referred to patient as having an impaired response to aspirin despite being responsive to aspirin and changed aspirin dose from 81 to 325 mg/day (n = 1)
- Extended duration of clopidogrel 150 mg/day from 1 to 3 months after percutaneous coronary intervention with a drug-eluting stent (n = 1)
- Started coumadin (n = 1)
- Allowed patient to return to exercising (n = 1)
- Discontinued clopidogrel based on adequate response to aspirin testing (n = 1)
- Referred patient for coronary artery bypass graft for recurrent in-stent restenosis (n = 1)

Discussion

We determined that a significant proportion of patients with laboratory evidence of aspirin and/or clopidogrel impaired response were changed to higher dosages of antiplatelet therapy compared with responsive patients. The prevalences of aspirin and clopidogrel impaired response in our patient population were 38% and 19.5%, respectively, which is within the range of previously reported data on prevalence [2–4]. The prevalence of combined aspirin and clopidogrel (i.e., dual drug) impaired response was 12% of patients on both agents. Prior studies on prevalence were in unselected patient populations, whereas the prevalence in our study may be elevated owing to a high index of suspicion for impaired response by the physician ordering the response panel.

Our study found several patient characteristics to be associated with nonresponse in patients on aspirin, clopidogrel, or both agents at the time of response panel testing. A number of these patient characteristics have been reported previously in the literature as possible mechanisms for platelet nonresponse [13]. We discovered that certain patient characteristics were associated with nonresponse with one antiplatelet agent, yet this association was not seen with the other antiplatelet agent (e.g., diabetic patients on aspirin or clopidogrel). It is unknown what clinical significance, if any, these differences represent. At present, the mechanism(s) for aspirin or clopidogrel nonresponse are unknown.

Our study assessed the reasons why a physician may order platelet function testing. Almost 90% of patients in the study had active signs and symptoms or a history of coronary artery disease. Platelet function testing in the setting of PCI accounted for nearly half of our patients. Patients termed 'prothrombotic' or who failed secondary prevention comprised 13 and 9% of the population, respectively. The data suggest that patients undergoing PCI or with signs of clinical impaired response were the most common reasons for ordering a response panel. Higher pre- or post-procedural platelet reactivity has been associated with increased ischemic events [14]. The 2006 American College of Cardiology/American Heart Association Task Force guidelines recommended platelet aggregation studies in patients with a risk for lethal thrombosis (e.g., unprotected left main) and to increase clopidogrel to 150 mg/day if inhibition of platelet aggregation is less than 50% [15]. Clopidogrel impaired responsiveness has been associated with higher rates of stent thrombosis [16]. Patients at risk for (i.e., high platelet reactivity) or presenting with stent thrombosis may represent a unique set of patients requiring aggressive antiplatelet therapies. Furthermore, these patients could benefit from more potent ADP antagonists (e.g., prasugrel) or adopt more aggressive therapeutic regimens with alternative antithrombotic agents in the setting of ACS [14,17].

The most striking result of our study is the response by physicians to patients who have laboratory evidence of impaired response. Patients with impaired response to aspirin had significant increases in the aspirin dosage after response panel testing. Some small studies have shown that higher doses of aspirin decrease platelet reactivity [18,19]. Despite these findings, lower dosages of aspirin have similar efficacy compared with higher dosages, but have been associated with higher bleeding complications [20–22]. Patients who are less responsive to aspirin have been shown to be more responsive to clopidogrel [23]. The addition of clopidogrel to aspirin in patients with impaired response to aspirin has not yet been demonstrated to improve clinical outcomes [10,24]. Further study is needed to determine if higher doses of aspirin or the addition of clopidogrel improves clinical outcome in patients with an impaired response to aspirin.

Both clopidogrel and dual drug impaired-response patients were changed to higher dosages of clopidogrel. Higher doses of clopidogrel

Table 3. Characteristics of patients tested for aspirin or clopidogrel response.

	Patients on aspirin at the time of response panel testing			Patients on clopidogrel at the time of response panel testing			
	Whole cohort (n = 112)	**Responsive (n = 74)**	**Impaired response (n = 38)**	**Whole cohort (n = 92)**	**Responsive (n = 74)**	**Impaired response (n = 18)**	**p-value**
Clinical factors							
Age (mean ± SD [years])	60.4 ± 12.8*	56.5 ± 13.5*	68.2 ± 11.1*	61.3 ± 13.7	60.5 ± 13.4	64.9 ± 15.2	*<0.0001
Male (%)	75.0	75.6	73.7	71.7‡	77.0‡	50.0‡	‡0.022
Weight (mean ± SD [kg])	86.5 ± 17.2	87.7 ± 18.7	84.3 ± 13.9	85.2 ± 17	85.3 ± 17.5	84.7 ± 14.7	
BMI (mean ± SD)	29.5 ± 5.0	29.3 ± 5.0	30.0 ± 4.9	29.1 ± 4.7	28.7 ± 4.6	30.7 ± 5.0	
Smoking history							
– Current (%)	9.9	12.2	5.4	11.0	12.2	5.9	
– Former (%)	50.5	51.4	48.7	49.4	48.7	52.9	
– Never (%)	39.6	36.5	46.0	39.6	39.2	41.1	
Inpatient (%)	62.5§	55.4§	76.3§	67.4	66.2	77.2	§0.03
Diabetes (%)	33.0	29.7	39.5	37.0¶	28.4¶	72.2¶	¶0.0005
Hyperlipidemia (%)	92.9	93.2	92.1	94.6	93.2	100	
Hypertension (%)	83.9	79.7	92.1	84.7#	81.1#	100#	#0.045
Renal insufficiency (%)	12.5	12.2	13.2	15.2	14.9	16.7	
Prior stroke (%)	16.1**	10.8**	26.3**	15.2	12.2	27.8	**0.034
Prior MI (%)	51.8	55.4	44.7	55.4‡‡	60.8‡‡	33.3‡‡	‡‡0.035
Prior PCI (%)	62.5	64.9	57.9	71.7	71.6	72.2	
Prior CABG (%)	29.5	35.1	18.4	32.6	35.1	22.2	
Medications prior to testing							
Aspirin (%)	100	100	100	97.8	97.3	100	
Clopidogrel (%)	80.4	85.1	71.0	100	100	100	
GPIIb/IIIa inhibitors (%)	8.9	10.8	5.3	9.8	12.2	0.0	
Coumadin (%)	4.5	5.4	2.6	4.4	2.7	11.1	
ACE inhibitor or ARB (%)	49.1	54.1	39.5	52.2	52.7	50.0	
β-blocker (%)	76.8	79.7	71.1	78.3	81.1	66.7	
Calcium-channel blocker (%)	28.6	25.7	34.2	27.2	23.0	44.4	
Statin (%)	92.9	94.6	89.5	93.5	94.6	88.9	
Diuretic (%)	20.5	17.6	26.3	21.7	21.6	22.2	
Proton-pump inhibitor (%)	46.0	41.1	55.3	46.7	45.9	50	
NSAID (%)	2.7	2.7	2.6	2.2	1.4	5.6	

Categorical variables are shown as percentages. Continuous variables are shown as mean ± SD. All missing p-values were nonsignificant.
**: p < 0.0001; ‡: p = 0.022; §: p = 0.03; ¶: p = 0.0005; #: p = 0.045; **: p = 0.034; ‡‡: p = 0.035; §§: p = 0.0198.*
AA: Arachidonic acid; ACE: Angiotensin-converting enzyme; ARB: Angiotensin-receptor blocker; BMI: Body mass index; BNP: B-type natriuretic peptide; CABG: Coronary artery bypass graft; CRP: C-reactive protein; GPIIb/IIIa: Glycoprotein IIb/IIIa; MI: Myocardial infarction; NSAID: Nonsteroidal anti-inflammatory drug; PCI: Percutaneous coronary intervention; SD: Standard deviation.

Table 3. Characteristics of patients tested for aspirin or clopidogrel response (cont.).

	Patients on aspirin at the time of response panel testing			Patients on clopidogrel at the time of response panel testing			
	Whole cohort (n = 112)	Responsive (n = 74)	Impaired response (n = 38)	Whole cohort (n = 92)	Responsive (n = 74)	Impaired response (n = 18)	p-value
Laboratory values (mean ± SD)							
White blood cell count (× 10^3/µl)	7.8 ± 3.4	7.7 ± 3.6	7.8 ± 3.0	7.9 ± 3.1	7.6 ± 3.1	9.0 ± 3.3	
Hemoglobin (g/dl)	12.7 ± 2.1	12.9 ± 2.1	12.3 ± 2.3	12.6 ± 2.1	12.7 ± 2.1	12.2 ± 2.3	
Platelet count (× 10^3/µl)	213 ± 77	214 ± 74	213 ± 83	223 ± 76[§§]	213 ± 72[§§]	263 ± 89[§§]	[§§]0.0198
Creatinine (mg/dl)	1.2 ± 1.0	1.2 ± 0.9	1.3 ± 1.1	1.2 ± 1.1	1.3 ± 1.2	0.99 ± 0.3	
Troponin T (ng/ml)	1.27 ± 1.64	1.37 ± 1.89	1.14 ± 1.19	1.34 ± 1.70	1.29 ± 1.67	1.55 ± 1.84	
Ultra-sensitive CRP (mg/l)	25.4 ± 50.9	23.6 ± 51.2	28.8 ± 50.4	27.5 ± 54.0	27.3 ± 55.7	28.1 ± 45.9	
BNP (pg/ml)	672 ± 894	629 ± 835	736 ± 979	709 ± 924	730 ± 988	618 ± 503	
Aggregation with AA (%)	18.4 ± 8.2	11.8 ± 5.2	31.2 ± 12.2	18.2 ± 11.8	16.4 ± 11.1	25.7 ± 14.4	Aspirin cohort = <0.0001 Clopidogrel cohort = 0.0033
Aggregation with ADP (%)	30.6 ± 18.3	24.2 ± 17.0	43.0 ± 20.8	25.7 ± 10.5	19.1 ± 10.9	52.9 ± 9.0	Both cohorts: <0.0001

Categorical variables are shown as percentages. Continuous variables are shown as mean ± SD. All missing p-values were nonsignificant.
**: $p < 0.0001$; [‡]: $p = 0.022$; [§]: $p = 0.03$; [¶]: $p = 0.0005$; [#]: $p = 0.045$; **: $p = 0.034$; [††]: $p = 0.035$; [§§]: $p = 0.0198$.*
AA: Arachidonic acid; ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blocker; BMI: Body mass index; BNP: B-type natriuretic peptide; CRP: C-reactive protein; CABG: Coronary artery bypass graft; GPIIb/IIIa: Glycoprotein IIb/IIIa; MI: Myocardial infarction; NSAID: Nonsteroidal anti-inflammatory drug; PCI: Percutaneous coronary intervention; SD: Standard deviation.

have been shown to improve platelet inhibition [25–28]. The Clopidogrel optimal loading dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Interventions trial (CURRENT/OASIS 7) will help to determine if higher loading and/or maintenance doses of clopidogrel provide benefit compared with standard dosing [101]. The newer ADP antagonists (e.g., prasugrel, ticagrelor and cangrelor) are potential therapeutic agents for use in patients with high platelet reactivity [14]. Prasugrel, ticagrelor and cangrelor are more potent inhibitors of platelet function than clopidogrel, yet, more potency may lead to increased bleeding complications [17,29–32]. Studies are needed to determine if these newer agents provide similar safety but improved efficacy in patients with higher platelet reactivity.

Study limitations

Our study is limited by its retrospective design. The lack of control for variables that alter platelet aggregation may affect the ability to detect true prevalence. Noncompliance was not assessed in our study and could account for differences in platelet responsiveness in patients tested in the outpatient setting. The response panel was only analyzed once for patients in our study and intra-individual variability could under- or over-estimate response in our population. The sample size was relatively small. The diagnosis, reasons for testing and changes in management were derived from the medical record. Our study is at a single, tertiary care medical center and the results may not be generalized to the entire population. The lack of any clinical outcomes in our study prevents analysis of the efficacy of management changes in our patients.

Conclusion

The study of aspirin and clopidogrel impaired response is an important concept. Noncompliance has been a confounder in the study of antiplatelet response and trials controlling for this factor are greatly needed. Despite the lack of a uniform definition and standard way to measure response, significant cardiovascular events have been reported with impaired inhibition of platelet function. The true correlation between laboratory findings of impaired response and clinical outcomes remains to be fully elucidated. Our study shows that physicians do regard persistent platelet reactivity despite antiplatelet

Table 4. Characteristics of patients tested for dual drug response.

	Whole cohort (%; = 90)	Responsive (%; = 79)	Resistant (%; = 11)	p-value
Clinical factors				
Age (mean ± SD [years])	61.2 ± 13.3	59.6 ± 13.7	72.3 ± 9.6	0.004
Male (%)	72.2	76.0	45.5	0.034
Weight (mean ± SD [kg])	85.2 ± 17.0	85.6 ± 17.2	82.0 ± 14.9	
BMI (mean ± SD)	29.1 ± 4.7	28.9 ± 4.6	30.4 ± 5.7	
Smoking history:				
– Current (%)	11.2	12.7	0.0	
– Former (%)	48.3	49.4	40.0	
– Never (%)	40.5	38.0	60.0	
Inpatient (%)	67.8	64.5	90.9	
Diabetes (%)	36.7	30.4	81.8	0.0009
Hyperlipidemia (%)	94.4	93.7	100.0	
Hypertension (%)	85.6	83.5	100.0	
Renal insufficiency (%)	14.4	12.7	27.3	
Prior stroke (%)	15.6	12.6	36.4	0.04
Prior MI (%)	56.6	60.8	27.3	0.04
Prior PCI (%)	71.1	70.9	72.7	
Prior CABG (%)	32.2	32.9	27.3	
Medication use prior to testing				
Aspirin (%)	100.0	100.0	100.0	
Clopidogrel (%)	100.0	100.0	100.0	
GPIIb/IIIa inhibitors (%)	10.0	11.4	0.0	
Coumadin (%)	3.3	2.5	9.1	
ACE inhibitor or ARB (%)	51.1	51.9	45.5	
β-blocker (%)	77.8	81.0	54.6	0.048
Calcium-channel blocker (%)	27.8	26.6	36.4	
Statin (%)	93.3	95.0	81.8	
Diuretic (%)	21.1	21.5	18.2	
Proton-pump inhibitor (%)	46.7	45.6	54.6	
NSAID (%)	2.3	1.3	9.1	
Laboratory values (mean ± SD)				
White blood cell count (×10^3/μl)	7.9 ± 3.1	7.7 ± 3.2	9.2 ± 2.9	
Hemoglobin (g/dl)	12.5 ± 2.1	12.7 ± 2.1	11.2 ± 2.3	0.03
Platelet count (×10^3/μl)	221 ± 77	216 ± 74	262 ± 97	
Creatinine (mg/dl)	1.3 ± 1.1	1.3 ± 1.1	1.1 ± 0.3	
Troponin T (ng/ml)	1.72 ± 1.41	1.44 ± 1.75	1.23 ± 1.43	
Ultra-sensitive CRP (mg/l)	28.2 ± 54.5	27.0 ± 54.8	35.5 ± 53.1	
BNP (pg/ml)	727 ± 936	727 ± 990	725 ± 481	
Aggregation with AA (%)	17.5 ± 8.9	15.2 ± 8.6	34.3 ± 11.3	< 0.0001
Aggregation with ADP (%)	25.6 ± 13.6	21.7 ± 14.0	54.0 ± 10.2	< 0.0001

Categorical variables are shown as percentages. Continuous variables are shown as mean ± SD. All missing p-values were nonsignificant.
AA: Arachidonic acid; ACE: Angiotensin-converting enzyme; ARB: Angiotensin-receptor blocker; BMI: Body mass index; BNP: B-type natriuretic peptide; CABG: Coronary artery bypass graft; CRP: C-reactive protein; GPIIb/IIIa: Glycoprotein IIb/IIIa; MI: Myocardial infarction; NSAID: Nonsteroidal anti-inflammatory drug; PCI: Percutaneous coronary intervention; SD: Standard deviation.

therapy as clinically significant and change management accordingly. The efficacy of these changes is not known. Clinical trials focusing on how to manage such patients are needed. As newer, more potent antiplatelet agents are discovered, the ability to inhibit platelet function will improve. Yet, clinical efficacy and more potent antiplatelet inhibition may not always be associated and potentially could lead to higher risks of bleeding. The future of antiplatelet therapy may involve platelet function testing that leads to individualized therapies that maximize efficacy and safety. While this practice appears to be increasingly

Table 5. Percentage of patients with a change in management after response panel testing.

	Whole cohort (%)	Responsive (%)	Impaired response (%)	p-value
Patients on aspirin (n = 112)	38.7	28.8	57.9	0.003
Patients on clopidogrel (n = 92)	39.1	31.1	72.2	0.0014
Patients on dual therapy (n = 90)*	38.9	32.9*	81.8*	0.0018

Responsive individuals were responsive to at least aspirin or clopidogrel while individuals with impaired response were not responsive to either agent. Prior to response panel testing, 90 patients were on both aspirin and clopidogrel, 22 patients on aspirin only, two patients on clopidogrel only, and two patients on neither aspirin nor clopidogrel.

common, randomized clinical trial data are needed before this approach becomes standard practice.

Financial & competing interests disclosure

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Table 6. Antiplatelet dosing of patients before and after response panel testing.

	Patients on aspirin at the time of response panel testing			Patients on clopidogrel at the time of response panel testing			Patients on aspirin and clopidogrel at the time of response panel testing		
	Whole cohort (n = 112)	Responsive (n = 74)	Impaired response (n = 38)	Whole cohort (n = 92)	Responsive (n = 74)	Impaired response (n = 18)	Whole cohort (n = 90)	Responsive to at least one agent (n = 79)	Impaired response to both (n = 11)
Aspirin dose									
Before testing:									
Mean ± SD	203 ± 125	212 ± 127	186 ± 121	213.± 125	210 ± 126	230 ± 122	214 ± 126	214 ± 126	214 ± 127
After testing:									
Mean ± SD	234 ± 118*	217 ± 126*	268 ± 130*	238 ± 119	230 ± 122	271 ± 104	240 ± 119	234 ± 121	281 ± 99
Clopidogrel dose									
Before testing:									
Mean ± SD	88 ± 35	88 ± 37	89 ± 30	88 ± 34	85 ± 26	100 ± 58	88 ± 35	88 ± 35	89 ± 30
After testing:									
Mean ± SD	105 ± 37‡	101 ± 36‡	115 ± 40‡	105 ± 36§	102 ± 36§	120 ± 38§	105 ± 36¶	102 ± 36¶	127 ± 36¶

*p = 0.035; ‡p = 0.045; §p = 0.081; ¶p = 0.036.
SD: Standard deviation.*

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