

## Aspirin and Clopidogrel Resistance

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JS is a 52 year-old African-American male with a history of Crohn's disease, insulin-dependent diabetes mellitus, and hypertension who was ordered for a pharmacologic stress test as an outpatient for vague left shoulder pain with exertion. Although chest pain free, the nuclear study suggested a mild inferolateral reversibility defect with a preserved left ventricular ejection fraction.

Cardiac catheterization and coronary angiography demonstrated single-vessel right coronary artery (RCA) disease with an 80-90% mid to distal lesion. Three overlapping bare metal stents were placed and post-PCI angiography demonstrated TIMI 3 flow with 0% residual obstruction. The patient tolerated the procedure well and was discharged with aspirin 325mg and clopidogrel 75mg per day after completing 14 hours of eptifibatide.

On day 2 after PCI, the patient went to his local emergency room with crushing substernal chest pain, nausea and left arm pain along with acute ST elevations in the inferior leads. He was rushed back for catheterization and had an additional bare metal stent overlapping a prior stent as the clot was unable to be aspirated out. The result was successful TIMI 3 flow restoration with 0% residual. At this point, the concern for clopidogrel resistance was considered and after discussion with the patient regarding potential adverse effects, the decision was made to double the clopidogrel dose to 75mg twice daily. Resistance labs were sent.

Unfortunately, on day 5 after the initial catheterization, the patient had acute return of his thrombosis and had a repeat inferior myocardial infarction. Cardiac catheterization number 3 was performed and the thrombus was able to be dissolved and JS had resolution of his symptoms. In vitro labs demonstrated marked aspirin and clopidogrel "resistance".

### Introduction

Anti-platelet agents have proven effectiveness in preventing occlusive arterial events in patients at risk. Aspirin is used both in the primary and secondary prevention of ischemic cardiac events as well as in those who have undergone percutaneous coronary intervention (PCI) with stent placement. In a meta-analysis of 145 randomized studies in patients with coronary artery disease and cerebrovascular disease, 75-300 mg/day of aspirin therapy reduced the risk of non-fatal MI by 35% ( $p < 0.00001$ ) and the risk of vascular events 18% ( $p < 0.00001$ ) [1]. However, 10-20% of patients with an arterial thrombotic event who are treated with aspirin will have a recurrent thrombotic event [2]. The prevalence of aspirin resistance in various populations with cardiovascular disease is noted to be as high as 45% [1]. Given the high prevalence and mortality involved with atherothrombotic events, there is great importance in even small changes in platelet aggregation.

Clopidogrel has an FDA indication for its use post-PCI in preventing in-stent thrombosis and is also used in select patients for thrombotic event prevention. With the

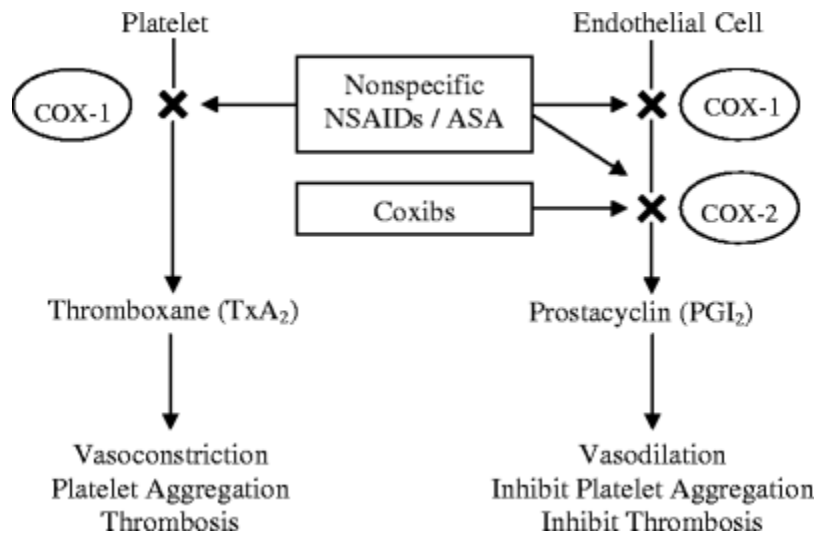
demonstration of patients who may be clinically “resistant” or “poor-responders” to anti-platelet agents, laboratory monitoring assays have been developed to predict who might be at higher risk of atherothrombotic events. In some studies the prevalence of clopidogrel resistance is as high as 30% [3]. Multiple large studies, including ISAR-CHOICE and OPTIMUS trials revealed significantly greater reductions in platelet aggregation with a 150mg dose of clopidogrel versus a 75mg daily maintenance dose. No large study has analyzed the clinical impact of such a change.

Ideally, we would have a test that was easy, cost-effective, accurate, and well standardized so that we could adequately define “resistance” and predict those at higher risk prior to clinical treatment failure (in this case, recurrent stent thrombosis). Once identified, we would need to find the correct dose or medication adjustment to circumvent this “resistance”. Currently the best treatment, if any, of aspirin or clopidogrel resistance is unknown and there is no consensus to convincingly address the clinical effectiveness of altering therapy [1]. There is clearly variability in the effects of aspirin and clopidogrel which may put certain patients at higher risk post-PCI, and this paper will discuss a case of such a patient and discuss relevant current thoughts in the literature.

Aspirin’s Mechanism of Action

Acetylsalicylic acid (ASA) or aspirin, was synthesized by Hoffman in 1897 and first used as an antipyretic and anti-inflammatory agent. In the late 1960s, aspirin emerged as an agent that prolonged bleeding time and inhibited platelet aggregation [4]. Aspirin acts by irreversibly acetylating a serine residue at position 529 in platelet cyclo-oxygenase-1 (COX-1), thereby inhibiting thromboxane A<sub>2</sub> synthesis which is a potent platelet aggregator (in a positive feedback mechanism) and vasoconstrictor (see table 1) [5].

Table 1



Aspirin is a non-selective COX inhibitor but it appears that at low levels in humans, aspirin is relatively selective for platelet COX-1. The irreversible nature of the COX-1 inhibition implies that no thromboxane is generated for the lifetime of the platelet (~10 days); platelets are anucleate and therefore return of TXA<sub>2</sub> parallels with the appearance of new platelets. TXA<sub>2</sub> is converted to the inactive TXB<sub>2</sub> which is then metabolized into a variety of products including 11 dehydro-TXB<sub>2</sub> (11 DTB<sub>2</sub>) and 2,3 dinor-TXB<sub>2</sub>, both of which are excreted in the urine. TXA<sub>2</sub> has been shown to be completely inhibited with a single dose of 100mg of ASA in normal healthy volunteers, but maintenance of this suppression of thromboxane requires doses as little as 30mg per day. Platelets may still aggregate to stronger agonists such as epinephrine or thrombin as they are less dependent on COX. The inhibition of COX-1 in vascular endothelial cells is replaced with functional enzymes and maintains the synthesis of prostacyclins, which are vasodilators and platelet inhibitors. Thus, the antiplatelet effects of ASA are a combination of both reducing the amount of available TXA<sub>2</sub> as well as increasing the amount of prostacyclin relative to TXA<sub>2</sub> [6].

### Aspirin Resistance

One of the major obstacles to using the term “aspirin resistance” and the reason for debate in much of the literature lies in its definition, or lack thereof. There can be a “clinical resistance” which might be defined as any situation where aspirin is unable to prevent atherothrombotic events, which most agree should more correctly be termed “treatment failure” [7]. True aspirin resistance implies a lack of COX-1 inhibition by the drug despite appropriate treatment, which is difficult to directly assess in vivo. Therefore, various laboratory tests have developed which attempt to predict who might be at decreased benefit from conventional therapy (see table 2).

Lordkipanidze et al. reported the results of a comprehensive study which compared six major tests for analyzing platelet function in patients with stable coronary artery disease; the correlation among the tests was poor [8]. None of these tests are felt to be sensitive or specific enough to be used as a screening test, especially as the laboratory threshold values for unsatisfactory platelet inhibition are often arbitrarily determined.

Andersen et al. found that aspirin treatment reduced thromboxane B<sub>2</sub> production to the same degree in patients who were aspirin resistant by PFA-100 as well as aspirin sensitive [9], thus raising question as to its utility.

Table 2: Methods of Assessing Aspirin Resistance [1,2,3]:

1. Bleeding Time
  - Involves inflating BP cuff to 40mmHg and inflicting a cut of 5-10mm length and 1mm depth on the volar surface of the forearm. The wound is gently blotted every 30 sec until bleeding stops.
  - In vivo test, but lacks sensitivity- varies with skin thickness, temperature
  - Highly inaccurate and poorly reproduced
2. Platelet Function Analyser (PFA)-100
  - Measures the time to cessation of flow (closure time) of blood through a capillary via a membrane coated with collagen and epinephrine or collagen and ADP. Like an in vitro bleeding time. Aspirin is expected to increase the closure time. Can also detect clopidogrel resistance.
  - Point of care method, reported to predict clinical resistance
  - Varies with VWF concentration.
3. Light Transmission Aggregometry
  - Spectrophotometric technique which looks at the changes of optical density due to platelet aggregation, using platelet rich plasma and various concentrations of ADP and Arachadonic acid
  - Technically difficult and arbitrary normals , reported to predict clinical ASA resistance
4. VerifyNow/ Ultegra rapid platelet funtion assay
  - Automated assay based on the ability of activated platelets to bind fibrinogen
  - Point of care method; reported to predict clinical ASA resistance
5. Serum Thromboxane B<sub>2</sub>
  - Breakdown product of TXA<sub>2</sub> → TXB<sub>2</sub>
  - Very low concentration, difficult to assess change
  - Some feel it is the most specific test for aspirin's effects
6. Urinary 11-dehydro thromboxane B<sub>2</sub>
  - Breakdown product of TXA<sub>2</sub> → TXB<sub>2</sub> → 11DTB<sub>2</sub>
  - Not solely derived from platelet TXB<sub>2</sub>
  - reported to predict clinical ASA resistance

### Does In-Vitro Aspirin Resistance Matter?

Several prospective studies show an association between biochemical aspirin resistance and clinical outcomes:

In a study of 180 patients with acute stroke, Grottemeyer et al. found that recurrent stroke, MI, or vascular death was more likely to occur in aspirin non-responders compared with responders (40% vs. 4.4%, respectively;  $P < .001$ ) [10].

In one of the more landmark studies, of 5529 patients enrolled in the Heart Outcomes Prevention Evaluation (HOPE) trial, the presence of platelet activation, as assessed by urinary thromboxane metabolite levels, despite aspirin therapy was associated with an increased risk of MI, stroke, or CV death (odds ratio for composite outcome, 1.8;  $p = .009$ ) [11]. Those patients in the upper quartile of urinary levels had a 2-times-higher risk of

myocardial infarction (OR, 2.0; 95% CI, 1.2 to 3.4; P=0.006) and a 3.5-times-higher risk of cardiovascular death (OR, 3.5; 95% CI, 1.7 to 7.4; P<0.001) than those in the lower quartile. Their conclusion was that patients with elevated urinary 11-dehydro thromboxane B2 levels are relatively resistant to aspirin and may benefit from additional antiplatelet therapies or treatments that more effectively block in vivo thromboxane production or activity.

Pamukcu et al. found that aspirin resistance was an independent predictor of major cardiac adverse events (MACE) in patients with stable coronary artery disease, using the PFA-100 [12]. Of the patients in this study, MACE in 12 months occurred in 45% with aspirin resistance vs. 11% in those found to be aspirin sensitive.

In a meta-analysis of 20 studies, Krasopoulos et al. found increased risk in those found to be aspirin resistant in MACE (OR 3.85), death (OR 5.99) and ACS (OR 4.06). Of those found to be aspirin resistant, they did not benefit from other antiplatelet (clopidogrel or ticlopidine) therapy [13].

In a meta-analysis of patients with prior vascular events, Hovens et al. found a prevalence of 1 in 4 patients with aspirin resistance, with a higher proportion in those using less than 100mg/day vs. those using greater than 300mg/day. Studies included used a variety of methods to assess resistance, including LTA (8%), point-of-care testing PFA-100 (26%) [14].

Others have questioned those findings and have been unable to reproduce a clinical correlation:

Barnes et al. looked at 3126 patients who were admitted with a diagnosis of ACS and divided them into cohorts by those with 1) no prior antiplatelet agents 2) prior aspirin use only 3) prior aspirin with clopidogrel (or ticlopidine). They found no significant differences in stroke, death or MACE at 6months in the groups, and felt that their data did not support the clinical entity of antiplatelet agent failure [15].

In 2005, the Working Group on Aspirin Resistance issued a position paper indicating that because the correct treatment of aspirin “resistance” is unknown, and due to the lack of convincing clinical correlation with laboratory testing, it is inappropriate to test for aspirin resistance or to change therapy based on such tests outside of research trials [2]. In effect, there probably is an entity of aspirin resistance, but we cannot accurately identify nor appropriately change our management to benefit these patients.

### Mechanisms of Aspirin Resistance

If we can establish that there are certain patients who derive a greater benefit from aspirin than others, the question then becomes why? Potential mechanisms are listed in the table below.

Table 3: Possible mechanisms of aspirin resistance [ 2]:

Bioavailability

Non-compliance  
 Underdosing  
 Poor absorption (enteric coated aspirin)  
 Interference: NSAID coadministration → competition for COX binding site

Platelet function

Incomplete suppression of thromboxane A2 generation  
 Accelerated platelet turnover, with introduction into bloodstream of newly formed, drug-unaffected platelets. ie. surgery, inflammation.  
 Stress-induced COX-2 expression in platelets  
 Increased platelet sensitivity to ADP and collagen

Single nucleotide polymorphisms

Receptors: GPIIb-IIIa, collagen receptor, thromboxane receptor, etc.  
 Enzymes: COX-1, COX-2, thromboxane A2 synthase, etc.

Platelet interactions with other blood cells

Endothelial cells and monocytes provide PGH2 to platelets (bypassing COX-1) and also synthesize their own thromboxane A2

Other factors

Smoking, hypercholesterolemia, exercise, stress, etc.

Rather than 'resistance' is it:

Aspirin response variability?  
 Platelet response variability?  
 Treatment failure (because arterial thrombosis is multifactorial)?

Aspirin has little or no effect on cigarette smoking, exercise [16] or catecholamine-induced platelet aggregability in vivo [1]. Ibuprofen and other reversible inhibitors may prevent aspirin from accessing the active site of COX-1, thus possibly negating the protective effects. Aspirin given 2 hours before a daily dose of ibuprofen successfully inhibits platelet aggregation, but ibuprofen given three times daily competitively prevents aspirin from accessing its target [17]. It is uncertain if this can be overcome by increased dosing.

Who might be at increased risk?

Studies have shown that among people with coronary artery disease, older individuals are more likely to be aspirin resistant ( $p=0.024$ ) as deemed by the PFA-100 [18].

A meta-analysis of 20 studies and 2930 patients with cardiovascular disease, found 28% of patients to be aspirin resistant with women more likely than men ( $p<0.001$ ) and those with renal insufficiency to be more likely than those with normal renal function ( $p<0.03$ ) [13]. No other characteristics were found to be significant, and other studies have not confirmed these findings.

In the ASPECT study, DiChiara et al. analyzed platelet aspirin responsiveness to various aspirin doses in diabetic and nondiabetic patients. Their results found that diabetic

patients with CAD who were taking 81mg/day aspirin demonstrated a higher prevalence of aspirin resistance by LTA, 11DTB<sub>2</sub> levels, and VerifyNow compared to their nondiabetic counterparts [19]. Higher doses of ASA significantly inhibited platelet function and decreased aspirin resistance in diabetic patients ( $p < 0.05$ ), raising the idea that diabetic patients may exhibit a global high platelet reactivity phenotype that may be overcome with higher doses. No resistance was observed in the 325mg groups regardless of diabetes status.

### Overcoming Resistance

Tirnaksiz et al. described an improvement in PFA-100 closure time in patients with known CAD deemed aspirin resistant after three months of 40mg/day of atorvastatin ( $p < 0.0001$ ) [20]. Though speculative, it is thought that LDL enhances platelet function, so lowering LDL may allow for improved COX-1 inhibition.

Clopidogrel is often used as there is in vivo evidence for improved platelet response for those who are aspirin resistant. However, a large meta-analysis did not find clinical benefit for the addition of clopidogrel therapy to aspirin resistant patients [13].

It is controversial as to whether increasing the dose of aspirin can overcome clinical or laboratory resistance. Large meta-analysis studies have not found any benefit in aspirin doses greater than 50mg/day [4], but these studies did not pull out patients who were deemed aspirin resistant. In theory, aspirin doses could be increased until a test (PFA-100) was found to reach its goal, but none of this has been found to have clinical significance yet. We have one small study which may support a higher dose of aspirin (325mg) in diabetics with stable CAD, but it is far from convincing. More studies are necessary and underway.

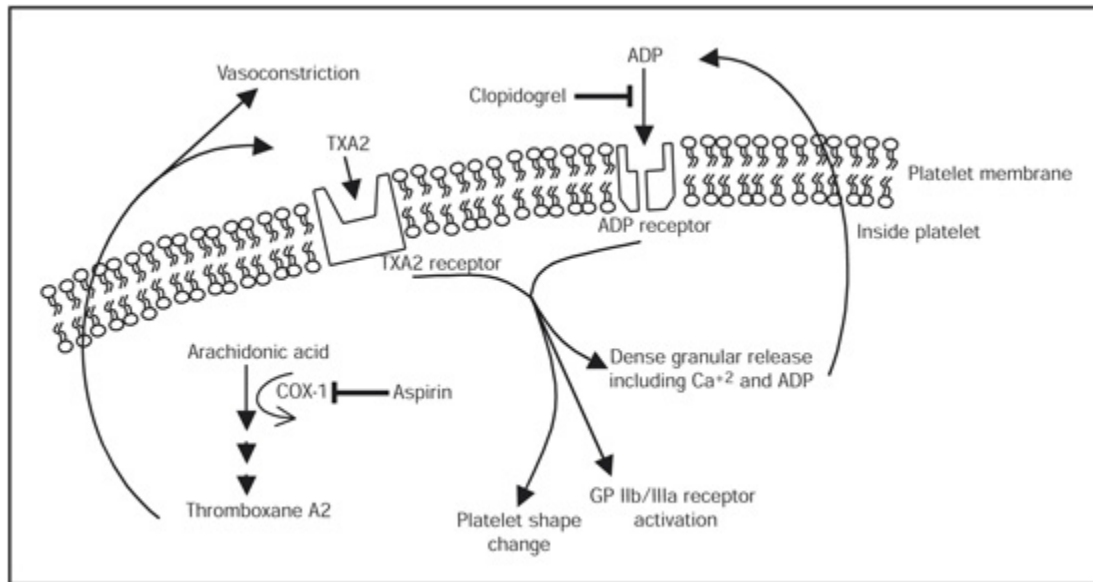
### Clopidogrel Post-PCI

Both the Clopidogrel for the Reduction of Events During Observation (CREDO) and PCI-CURE, a prospective substudy of the Clopidogrel in Unstable angina Recurrent Events trial, revealed a significantly reduced risk (27–31% relative risk reduction) of adverse ischemic events in favor of an extended dual antiplatelet regimen following coronary stenting. There is clearly a role for dual platelet inhibition in these patients.

### Pharmacology of Clopidogrel

The thienopyridines, clopidogrel and ticlopidine, irreversibly bind the platelet surface P2Y<sub>12</sub> ADP receptor, thereby inhibiting ADP-induced platelet activation. Although ticlopidine has proven superiority to aspirin in the prevention of atherothrombosis, clopidogrel is more widely used than ticlopidine because it offers better safety and tolerability with similar efficacy. Clopidogrel is a prodrug, and needs to be activated in

the liver to form an active metabolite that binds to the ADP receptor and disrupts the ability of platelets to activate in response to ADP as well as other factors. Strong agonists such as thrombin are unaffected by clopidogrel[22].



### Measuring Clopidogrel's Effect

Much like aspirin, assays have been developed to test platelet aggregation in response to ADP, which can then be used to interpret clopidogrel effect. At low concentrations of ADP, the response is highly dependent on the generation of thromboxane and is effectively inhibited by aspirin. Higher concentrations induce full and irreversible platelet aggregation that is insensitive to aspirin but can be overcome (up to 90%) by clopidogrel [22]. With an ADP cartridge, it would be expected that clopidogrel would prolong the closure time with a PFA-100-ADP test though the range of normal values is somewhat arbitrary. Using different concentrations of ADP (generally 5-20 micromol/L), light transmission aggregometry can separate out those who have higher platelet aggregation versus those who do not- generally broken up by quartiles.

### Clopidogrel Resistance / Clinical Significance

There is a variation and normal distribution in testing the effect of clopidogrel, with an average of 40-50% inhibition. Compliance, variable absorbance and variability on formation of the active metabolite all contribute to this variation in response. Clopidogrel is activated by CYP3A4, one of many cytochrome P450 enzymes. Activity of this enzyme is variable in the population, and platelet effect with the standard 75mg/day dose is therefore not completely predictable. In vitro testing finds that additional clopidogrel or its active metabolite can overcome reduced effect, suggesting that there is not a true resistance but a difference in bioavailability [22].

Drug interactions are also likely given the common cytochrome P450 enzyme: atorvastatin (which one study found increased aspirin sensitivity) has been implicated in interfering with clopidogrel's anti-platelet effect. The ability of clopidogrel to affect platelet aggregation was compared prospectively in a series of post-angioplasty patients taking atorvastatin, a CYP3A4 inhibitor, or pravastatin, which is not metabolized by CYP3A4. This study of 44 patients undergoing coronary artery stent implantation treated with clopidogrel demonstrated that the degree of platelet aggregation inhibition achieved 24 h after clopidogrel was significantly attenuated by atorvastatin as compared to the control ( $77 \pm 15$  versus  $34 \pm 23\%$ ;  $p < 0.0001$ ) [9]. Subsequent studies have not shown this effect and there has been no evidence of a clinically significant interaction in several studies of low-risk cohorts. Put in perspective, nearly half of prescribed medications (including amlodipine, nifedipine, prednisone which JS was on) are metabolized via CYP3A4 so it is difficult to truly implicate atorvastatin.

Gurbel and Bliden demonstrated that patients who were clopidogrel responders at 24 hours post-loading remained responsive at 30 days. Interestingly, half of the non-responders became responders at 30 days, possibly an induction of the cytochrome system to allow for better bioavailability of the active metabolite [17].

Buonamici et al. conducted a prospective cohort study in 804 patients who received a drug eluting stent. The 105 (13%) patients who were clopidogrel resistant (tested with 10 micromol/L ADP, with >70% platelet aggregation) were 3.8 times more likely to have stent thrombosis at 6 months. Nonresponders also were more likely to die (8.6% vs. 1.4%;  $p < 0.001$ ) or reach the secondary composite end point of death or stent thrombosis (10.5% vs. 2.7%;  $p < 0.001$ ). The results of multivariate analysis indicated that high residual platelet aggregability after dual antiplatelet therapy to be independently associated with ischemic events following PCI (hazard ratio 3.08, 95% confidence interval 1.32 to 7.16;  $p = 0.009$ ) [23].

The EXCELSIOR (Impact of Extent of Clopidogrel-Induced Platelet Inhibition During Elective Stent Implantation on Clinical Event Rate) study published in 2006 looked at 800 patients undergoing elective stent placement, and found that patients with higher platelet aggregation by LTA just prior to intervention were at higher risk of short term morbidity [24]. Quartiles of platelet aggregation were <4%, 4% to 14%, 15% to 32%, and >32%. Thirty-day MACE differed significantly ( $p = 0.034$ ) between quartiles of platelet aggregation. It was 0.5% in the first quartile, 0.5% in the second, 3.1% in the third, and 3.5% in the fourth. Platelet aggregation above the median carried a 6.7-fold risk (95% confidence interval 1.52 to 29.41;  $p = 0.003$ ) of 30-day MACE and was found to be an independent predictor [25]. Of note, prior to PCI these patients all received a 600mg loading dose of clopidogrel.

Rifampin and St. John's wort, inducers of CYP3A4, were found to improve clopidogrel induced platelet inhibition in a small study of healthy "non-responders" but the clinical implication is uncertain [17] and the potential for bleeding is likely to rise.

Many argue with clopidogrel “resistance” and find that the rate of noncompliance far outweighs the rate of adverse effects in those deemed resistant. Few studies measure clopidogrel metabolites to confirming compliance. The rate of in-stent thrombosis is less than 1.2% and clopidogrel resistance is as high as 30% , thus questioning the direct causality between clopidogrel resistance and in-stent thrombosis. Furthermore, if increasing the dose of clopidogrel was needed to overcome the resistance, you would not expect higher rates of bleeding because it would just be to get the same effect.

### Overcoming Resistance

Due to the concern of clopidogrel resistance, ACC/AHA guidelines on percutaneous coronary intervention recommend increasing the dose of clopidogrel to 150 mg in high-risk patients if <50% platelet inhibition is demonstrated (level of evidence C), though this testing is not routinely done [26]. This recommendation states:

In patients in whom stent thrombosis may be catastrophic or lethal, platelet aggregation studies may be considered and the dose of clopidogrel increased to 150 mg/day if <50% platelet inhibition is demonstrated.

Administration of a 150 mg oral maintenance dose of clopidogrel results in more intense inhibition of platelet aggregation at 30 days than administration of the currently recommended 75 mg maintenance dose [27], though this study looked at laboratory data and not clinical outcome.

In one recent study, laboratory clopidogrel nonresponsiveness can be found in approximately 1 in 5 patients undergoing PCI. Patients ex vivo labeled nonresponsive are likely to be also "clinically nonresponsive," as they exhibit increased risks of worsened cardiovascular outcomes. Results indicate that use of a 600-mg clopidogrel loading dose will reduce these risks, which needs to be confirmed in large prospective studies [28].

So, two issues are presented: immediate post-PCI antiplatelet dosing (most lead toward 600mg loading dose based on the ALBION study), and daily maintenance dose for long term prevention of ischemic events (less than convincing data to support testing if a patient “could not handle” in-stent thrombosis, and doubling maintenance dosing). Despite the observed benefit of upstream platelet inhibition, clopidogrel is generally not given prior to PCI (studies indicate a time to effect of least 2-12 hours), given the potential need for bypass surgery. For that reason, many are loaded *after* PCI and given GP 2B3A inhibitors during the immediate post-PCI period which have a short half life.

### Dual Therapy and Dual Resistance in PCI

Clopidogrel 75mg daily was found to be superior to aspirin 325mg daily in at risk patients (prior MI, CVA, PAD) in the CAPRIE trial, but the benefit was small and the number needed to treat was 115 which most find to not be cost-effective [29]. The

combination of aspirin and clopidogrel was found to benefit patients undergoing PCI (PCI-CURE substudy) and is the standard of care.

A study by Lev et al. used a cohort of 150 patients undergoing elective PCI, and sought the response of clopidogrel among aspirin-resistant versus aspirin-sensitive patients. Their results found that those deemed resistant to aspirin also had a reduced response to clopidogrel by in vitro studies [5]. Chen et al. observed an increase in procedure related myonecrosis in aspirin resistant patients despite clopidogrel pre-treatment [30].

In the PREPARE-POST STENTING trial, 192 non-emergent PCI patients were tested for platelet reactivity to adenosine diphosphate (ADP) by light transmittance aggregometry (LTA) in patients undergoing PCI. Most were on both clopidogrel and aspirin. Clot strength, a measure of thrombin-induced fibrin and platelet interactions, and the time to initial fibrin generation, a marker of thrombin activity, were measured by thrombelastography. Those at the highest quartiles of platelet reactivity and clot strength were more likely to have ischemic events over the next 6 months [31].

A Polish group published a nearly identical case as JS, with a patient who suffered two consecutive myocardial infarctions in a patient with suspected clopidogrel and aspirin resistance [32]. They changed clopidogrel to ticlopidine, the dose of aspirin was increased from 150mg to 300mg per day, and low molecular weight heparin was administered and the patient remained clinically stable. It should be noted that there is a black box warning in the United States on ticlopidine given the risk of neutropenia (2-4%) and thrombotic thrombocytopenic purpura.

### Potential Options/ Discussion

Some groups are supporting the use of a 600mg loading dose of clopidogrel which was shown to have a significant reduction in death, MI, need for revascularization in patients with unstable angina or NSTEMI (ARMYDA-2). Those given a 600mg loading dose were not shown to have had an increase in gastrointestinal bleeding, and 900mg did not show any additional benefit. Despite this evidence, the only FDA approved dose is 300mg as most clinical efficacy data has been done with that dose and many do not receive a pre-PCI loading dose.

Some have looked at cilostazol, a phosphodiesterase-3 inhibitor often used in intermittent claudication. In the Cilostazol for Restenosis Trial of 705 patients treated with aspirin and clopidogrel after successful bare-metal coronary stenting, the addition of cilostazol reduced the rate of restenosis by 36% compared with placebo therapy. In 100 post-PCI aspirin-treated patients randomized to cilostazol for 6 months or ticlopidine for 1 month, a 6-month composite outcome of adverse CV events favored cilostazol therapy (16% vs. 36%;  $P=.02$ ) [33]. Further studies are needed to determine whether aspirin and/or clopidogrel-resistant patients benefit from the addition of cilostazol. Of note, cilostazol is contraindicated in class 3 and 4 heart failure.

Potential new pharmacotherapeutic approaches to the aspirin-resistant patient being investigated include treatment with thromboxane synthase inhibitors, thromboxane receptor antagonists, and compounds that do both. Prasugrel (CS-747) ticagrelor, and cangrelor, are novel thienopyridines with a faster onset of action and 10 times the potency of clopidogrel, and are converted to its active metabolite in both hepatic and extrahepatic tissue, so resistance patterns may be different than clopidogrel [34]. The role of thrombin may deserve greater attention and thrombin inhibitors (SCH 520348) are also being tested in clinical trials [24].

We used low molecular weight heparin (as did the Polish group) for our patient, though there is no data to support such usage (aspirin and clopidogrel have previously been proven to be more effective than aspirin and warfarin), and it works in a mechanism other than platelet inhibition.

Aspirin and clopidogrel are currently the treatment of choice in acute coronary syndrome and prevention of thrombosis after coronary stent implantation. Recent evidence-based studies acknowledge that aspirin and/or clopidogrel resistance that can be linked to adverse cardiovascular events, though without standardization the results are difficult to interpret. One size probably does not fit all, but it is more likely to variations in bioavailability than true “resistance”. While new alternative treatment strategies to overcome aspirin and clopidogrel resistance are currently being sought, further investigations should focus on the development of a standardized methodological approach to detect individual aspirin and/or clopidogrel resistance to tailor individual antiplatelet therapy and make our decision-making proactive and not reactive.

Without a consensus on the proper management of a case as complicated and as rare as our patient, the therapeutic changes were speculative. By PFA-100 JS demonstrated aspirin and clopidogrel resistance. These were drawn both at the time of the third cardiac catheterization and confirmed one week later (due to use of eptifibatide). JS had aspirin discontinued (there is no evidence to support stopping this) had his clopidogrel increased to 300mg/day, and added low molecular weight heparin (no evidence to support this) for 6 weeks (the minimum duration of antiplatelet therapy for a bare metal stent) at a dose of 1mg/kg twice daily. His situation was more concerning given his known Crohn’s disease and the higher risk of gastrointestinal bleeding. Fortunately, he remained infarction free at 3 months out.

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