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by Lynne Peterson and D. Woods

Quick Pulse

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Stephen Snyder, Publisher
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com
TrendsInMedicine@aol.com

Plavix-Resistance Testing Slow to Catch On

There is little enthusiasm among cardiologists – medical cardiologists or interventional cardiologists – about either aspirin resistance testing or Plavix (Sanofi-Aventis, clopidogrel) resistance testing. From interviews with a dozen cardiologists around the U.S. and with even more cardiologists at the recent European Society of Cardiology (ESC) meeting in Barcelona, it is clear that they do not see a need for the assays and/or are not convinced the test is sufficiently accurate. It is likely that changing practices to incorporate testing will be very slow and very difficult – if it happens at all.

Cardiologists generally agree that there is a percentage of patients who do not respond to Plavix, though estimates of how large this group is varies from 12%-35% of users. While platelet aggregation tests are available to test patients for Plavix resistance, those tests have not yet caught on. There is also new evidence that some of these non-responders are people with the CYP450 2C*19 allele. However, genetic testing has not caught on either, and experts do not expect that to change.

Current Plavix Use *

Patient population	Number of patients	Penetration	% of Plavix use
Acute coronary syndrome (ACS) – stent	1.5 million	90%	15%
ACS – non-stent	1.5 million	40%	10%
Other cardiovascular	28 million	25%	40%
Peripheral artery disease	8 million	15%	15%
Stroke and transient ischemic attack (TIA)	10 million	20%	20%

* Source: Bristol-Myers Squibb

The Arguments Against Testing

One reason for the apparent disinterest in Plavix-resistance testing has been that there has been no real option for Plavix for non-responders except perhaps increasing the dose – and there hasn't been good evidence that non-responders will respond to a higher dose of Plavix. The issue is not the cost of the test or reimbursement for it; it is simply that physicians don't want to do it, don't believe testing would be cost-effective, won't do it without data showing it makes a difference in patient outcomes, and/or aren't well educated on the available tests. Perhaps the best explanation of this was the comment by a doctor at ESC, "It has nothing to do with science or evidence, it has to do with belief."

The bottom line is that most cardiologists questioned do not expect use of platelet aggregate testing in general to become commonplace, at least not for the next 3-5 years.

CARDIOLOGIST ATTITUDES

Comments about the outlook for Plavix-resistance testing included:

- *Dr. Alfred Bove, president of the American College of Cardiology (ACC):* "It is behavioral habit…We have used aspirin for so long without considering aspirin resistance. That has been studied in the last 2-3 years and found significant in some populations…There are a lot of people urging testing of platelet response to aspirin or clopidogrel…and some day we will probably have a genetic pattern…(Plavix) testing is being done in the cath lab; they are beginning to look at clopidogrel sensitivity or resistance…But where you put the patient on clopidogrel for primary or secondary prevention, there are so many patients that **the cost would be excessive**…**Most physicians are not used to doing it**. It is not a routine thing available…I don't know for sure if someone doing primary prevention with aspirin or clopidogrel would be doing sensitivity testing routinely. The rule is everyone over age 40 should be on aspirin or, if they can't tolerate aspirin, clopidogrel. That is a lot of people. The logistics of doing a lot of people is one issue."

- *Dr. Michael Ezekowitz of Pennsylvania:* "It is very clear that Plavix, while very effective for a lot of patients, is not uniformly effective, and no one really knows why. There is a presumption there are genetic reasons, but to my mind that is not proven. We do not do genetic testing, and we do not look prophylatically for patients who may or may not respond…When you make a decision to initiate Plavix, it is usually made in an emergency situation, and the technology is not quite there yet. And prasugrel (Lilly's Effient) has only been recently approved, so **it takes time for physician practice to change**…But if there were a test where the testing could be done on a 24-hour a day, immediate response basis, like BNP or glucose…then I think with prasugrel being approved and other drugs coming, (testing) clearly is the way."

- *Dr. Clyde Yancy, president of the American Heart Association (AHA):* "(Plavix-resistance testing) is one algorithm we might happen upon, especially if clopidogrel were generic. It may be more reasonable to identify that someone is sensitive to clopidogrel and go with the less expensive drug, and if not sensitive, go with another drug. **We really need to wait to see (outcomes) data** on resistance testing…**Resistance testing is not catching on yet because there hadn't been another option until now**. There has either been the standard dose (Plavix) or a higher dose. Now, we may see physicians raising the question of platelet responsiveness to clopidogrel…but it is going to be an interesting thought process. If you go to another drug, and there is more bleeding risk, is that the right thing to do?…Or, do you go to Brilinta (AstraZeneca, ticagrelor) and know there are unintended side effects?"

- *Dr. Elliott Antman, Brigham & Women's Hospital, Boston, an AHA spokesman:* "We are frustrated that our lab hasn't provided (Plavix-resistance testing) in any quantitative way…and we got organized to institute that. **We are doing it in selected patients** – typically people who have had stent thrombosis already or who are considered high risk and have a high-risk lesion, maybe a diabetic with a proximal LAD stenosis that was stented… but **cost is an issue**…It comes down to a health economics analysis, to the availability and cost of resistance testing. And (for Accumetrics' VerifyNow) **whether we have confidence in a point-of-care test**. You have to test everyone – millions. The other option is to skip testing and give the new agent (Brilinta). The cost of testing may begin to approach the cost of the new agent. PBMs (pharmacy benefit managers) will be looking at cost…There is a paper in ***Circulation*** on the quality and outcomes of genetic testing for warfarin, which is $500 a test…It is important to know how to use clopidogrel more efficiently."

- *Dr. Spencer King of Emory University, past president of the ACC:* "We do know that with clopidogrel, a substantial number of patients do not have an adequate antiplatelet effect. Is it important to find that out? I don't know…(More potent agents) drive the idea of maybe identifying some of those patients at highest risk and seeing if they have adequate antiplatelet therapy. But **the current use of an agent that is not completely effective has not resulted in a great many problems**. The incidence of late stent thrombosis is small…and yet 30% of people are not getting adequate therapy from clopidogrel. It will take a while for people to become convinced that they have to put everyone on the more potent agents. The smart thing to do would be to develop clear evidence on who should and shouldn't get clopidogrel. Meanwhile, **it would be interesting and responsible to identify high-risk patients not having an antiplatelet effect and switch them to prasugrel or ticagrelor**."

- *Dr. Jonathan Halperin of Mt. Sinai Medical Center in New York, an AHA spokesman:* "Where (testing) will play in an era of alternative potent antiplatelet agents remains to be determined…We do (Plavix-resistance testing) in the lab on a selective basis, particularly where stents are deployed at critical anatomic sites, where we have concerns, and in patients who come back with stent thrombosis. **We do it selectively**…**A CLIA waiver is an important way to bring the test to the bedside, saving time and making it easier**."

- *Dr. Robert Bonow of Northwestern University, past president of the AHA:* "**Patients are asking about it more and more**. So, I think more physicians will be doing that testing in the future – unless another drug comes along…I think that (a CLIA waiver) will spur use...We are not doing this yet, but I think, as things evolve, we will."

- *Dr. Ralph Brindis, Kaiser Permanente Northern California, an ACC spokesman:* "We are still learning about (genetic testing for the allele)…The use of pharmacogenomics and better specifying therapy is in its infancy. It will be more important over time. **As the assay cost comes down, I think it will be important**…There is no doubt in my mind that in 5-10 years a lot of drug therapies will be detailed based on the risk profile and your ability to metabolize them…In our facility, we have done Plavix-resistance testing in patients who come back with stent thrombosis…We have looked at those as non-responders. In the past, we dealt with that with higher doses of Plavix. Now, there is an alternative drug (prasugrel). **Now that we have alternative drugs related to Plavix, there is no doubt that use of testing will come more into play** to allow physicians to make choices as to which thienopyridine to prescribe. But issues related to cost will come into play…When clopidogrel becomes generic, you could argue it would be very cost effective to figure out who are good candidates for generic clopidogrel and justify using more expensive drugs in non-responders. Then, we could argue that platelet or allele testing will be very wise ways of being cost effective."
- *Dr. Patrick Serruys of the Netherlands:* "With statins, myalgia occurs in 5% of patients, and you can genetically test for that, but no one does it because it is only 5% of patients. For 5%, we won't test 95%. Plavix resistance is 35%, but it isn't clear when you don't have to test… Testing could be interesting, and a company is developing a test that will take less than an hour. **The problem with testing is that there are so many alleles, so testing is not bulletproof**…Test and then give generic clopidogrel is one way to go…but Portola's elinogrel removes the need for testing."
- *ESC spokesman Dr. Freek Verheugt of the Netherlands:* "(With PLATO), **Plavix testing is over now – because resistance to new drugs is almost nil**. My thinking is testing will never be done. It's like ACE inhibitors. ACE polymorphisms never caught on, and we forgot about it and gave ACE inhibitors to everyone. We have two new standards of care – ticagrelor (Brilinta) and dabigatran (Boehringer Ingelheim's Pradaxa). Both will change the guidelines."
- *Dr. Martin Cowie of the U.K.:* "Physicians are not used to testing patients for drug resistance…The challenge is on Plavix (i.e., Sanofi-Aventis) to urge testing, but they are not interested in that because they are going generic. For me **it is easier to use one drug and not do sensitivity testing**."

What May Encourage Testing in the Future

Several factors might be expected to boost the use of platelet aggregation testing:

1. The recent approval of prasugrel.
2. The promising PLATO data presented at ESC on Brilinta, which looks at least as effective and safe as Plavix. If this gains FDA and EMEA approval, most doctors questioned predicted it would have a big impact on Plavix use and an even larger impact on prasugrel.
3. The results of the CURRENT-OASIS-7 trial which showed that double-dose Plavix is both safe and effective, resulting in a lower – but not non-existent – number of Plavix-resistant patients.
4. The upcoming availability of generic clopidogrel.
5. Outcomes data from ongoing – or future – clinical trials.

Specific Tests

For onsite testing there are several assays that could be considered, including:

- **Accumetrics' VerifyNow**, which may be the leader because it is point-of-care.
- **Diomed's Impact R** cone-plate analyzer.
- **Dynabyte's Multiplate.**
- **Haemoscope's Thromboelastogram.**
- **Helena Laboratories' ICHOR/Plateletworks.**
- **Siemen's PFA-100.**

Dr. John Eikelboom of McMaster University in Canada said he has three of these tests in his lab – VerifyNow, PFA-100, and Thromboelastogram – but all are used exclusively for research. At an ESC-sponsored (not industry-sponsored) session, Dr. Eikelboom reviewed the role of onsite (point-of-care) platelet function testing. The major points he made were:

- Vascular specialists and cardiologists are familiar with testing for risk factors for lipids, high blood pressure, and obesity, but platelet function testing has lagged.
- There are many current platelet function tests, but:
  - Unlike cholesterol, where measuring is simple, platelets are extremely difficult to measure. "To measure platelet function is much harder, and that is reflected by the huge array of tests."
  - The tests fall into different categories – those that test aggregation, those that test sheer-dependence, and those that test release of various substances.

Accumetrics sponsored a symposium on Plavix-resistance testing at ESC, and there was good (but not remarkable) attendance. Dr. Gilles Montalescot of France told the audience, "Is there a need (for assessing a patient's response to antiplatelet therapy? The short answer is yes. Clearly, we have the tools to do that. It is very attractive to measure what we are doing in our patients…What we have not yet done is demonstrated that changing the intervention, having a different approach based on this test, will improve (outcomes) …Do not forget the main limitation of aspirin is not resistance but compliance to treatment. We know aspirin has side effects, and many people just don't take it regularly…The prevalence of clopidogrel resistance in the literature ranges from 4% to 63%...What is the best test? What is the right number? Clearly we have a lot of work to do…VerifyNow can identify patients at risk of poor response to clopidogrel with a simple test that takes a couple of minutes…But we need studies to see if we can have an impact on the prognosis (by changing therapy based on the test)."

At the symposium, a doctor from Italy asked, "These tests give us a number, but that doesn't tell us what to do. With all these data on platelet aggregation tests, do we have a number that is biologically consistent? Shouldn't we switch based on individual patient numbers instead of population-based numbers?" Dr. Montalescot responded, "If we change the dose based on platelet function tests, will it have an effect? I don't know. No one knows (yet)."

Dr. J. W. van Werkum of the Netherlands, speaking at the same symposium, discussed the applicability of platelet function testing in clinical practice. He said, "Platelet reactivity now has been found to be a potential new marker for risk stratification of patients undergoing PCI (percutaneous coronary intervention). There is also marked inter-individual variability in baseline platelet reactivity. Is this clinically relevant? Yes. There is wide inter-individual variability in response to clopidogrel therapy. Clopidogrel is highly influenced by absorption, genetic, and clinical factors…There are a number of tests available…Which is best to use?...It depends on the purpose of the testing:

- **Light aggregation** is not standardized and not in whole blood. Moreover, it is very time and labor consuming. There is no point-of-care approach, and it takes 2-3 hours to get results, so it is not suitable for clinical practice.
- **VerifyNow** is standardized and easy to use."

Dr. van Werkum urged doctors to pay attention to the results of the POPular study to be presented at the American Heart Association meeting in November 2009. His conclusions were:

- There is high residual platelet reactivity in a substantial proportion of patients.
- There is a clear association between heightened platelet resistance and occurrence of atherothrombotic events (including stent thrombosis).

ACCUMETRICS' VERIFYNOW

Accumetrics' VerifyNow can be used to perform either aspirin-resistance or Plavix-resistance assays. The aspirin test is already CLIA-waived, and the whole blood, point-of-care P2Y12 test for Plavix resistance is expected to become CLIA-waived later this year. So far, more than 300 VerifyNow units have been placed in Europe – particularly in the U.K., Italy, and most recently, Spain – as well as about 700 in the U.S., with ~600 of the U.S. devices in hospitals and the remainder in doctors' offices.

Dr. Roxanna Mehran of Columbia University Medical Center, told an ESC audience that VerifyNow is being used ***routinely*** at her hospital because "it helps us make decisions on treatment." She predicted that Plavix-resistance testing will catch on, "(Clopidogrel) is going generic. It will be cheaper. And if we can choose therapies based on these measurements with aggregation studies and choose the right patient for the right drug, we will be better doctors."

Asked how long she waits to test patients after giving clopidogrel – since it takes 4-6 hours to reach maximum effect – Dr. Mehran said, "We don't wait and prolong our ACS patients. We do not stop and wait 4-6 hours for perfect measuring time to make a decision. We move ahead. We are giving 600 mg clopidogrel in all ACS patients undergoing PCI and then testing them."

Few of the other cardiologists questioned are currently using the VerifyNow P2Y12 test, and most were skeptical about its usefulness both now and in the future. Many doctors said that the number of patients who are Plavix resistant ***and*** who fail with Plavix therapy is very small.

- *Dr. James Slater, a New York interventional cardiologist who recently started to use the test but in a limited fashion:* "Our pathology lab sort of quarantined the machine for six months." He said that he doesn't know whether the test will be useful, "In a couple of months I should have a better sense, once we have done more extensive testing with the Accumetrics system."
- *Florida medical cardiologist:* "We don't use VerifyNow, but the real issue is that some people are resistant to Plavix. It doesn't work for some people. But failures from Plavix therapy are very few and far between. There is a very small percentage who don't respond. If you test people, maybe 30% have some resistance, but we don't see it clinically. It's more of a lab tool."
- *Dr. Bobby Khan, a medical cardiologist from Emory University School of Medicine:* "At this point neither my hospital/medical center nor I use VerifyNow for either aspirin or Plavix resistance. From interactions with my colleagues around the country, it is not widely used...The data so far are not sufficient…Do we need additional measurement to determine mechanisms of platelet function?"

- *Dr. Raoul Bonan, a Canadian interventional cardiologist:* "I don't think that it will be applied at large. Prospectively, we see fewer and fewer problems with a 600 mg Plavix-loading dose. Off the top of my head, no more than 5%-10% are Plavix resistant. Most of the time you would test afterwards, anyway, and not prospectively."
- *Dr. Steve Nissen of the Cleveland Clinic:* "We only do a little aspirin- and Plavix-resistance testing. Maybe we should do more. Why don't we do more? That is a good question. It has never caught on."
- *Dr. Jimmy Tcheng, Duke:* "We don't do Plavix-resistance testing routinely. We don't have VerifyNow. We just use the reference lab when we need it; they can do a formal platelet aggregation test, the old classic way, in a patient who returns with stent thrombosis to find out where they sit with regard to platelets…Probably two-thirds of stent thrombosis patients have aggregation problems."

THE ISSUES FOR VERIFYNOW

Is the outlook for VerifyNow like Cambridge Heart's T-wave alternans testing for ICD appropriateness – another test that works but has failed to catch on? An expert said no, "There are more questions about T-wave than Plavix resistance. There isn't an argument that Plavix resistance doesn't exist. It (is more) complacence or logistics."

So, why don't cardiologists use VerifyNow to test for Plavix resistance? Doctors cited a number of reasons, including lack of outcomes data, inaccuracy of the test, logistical reasons, etc. Explanations included:

Lack of evidence:

- "A little more ground work needs to be done on what the true incidence of Plavix non-resistance is and whether there are partial responders."
- "When the sales rep comes by and asks why we are not using it, we say show us the proof. You can do assays for P2Y12 resistance, but we don't know if an action based on that finding makes one iota of difference. So, at this point of time, absent clinical proof, we aren't doing it… But it does make complete sense. It allows you to assess the risk. But that is it. It doesn't tell you what you should do, and it hasn't proven that if you did something different, you changed someone's risk."

Numbers needed to treat don't justify use: "Although most of the patients who develop stent thrombosis have Plavix resistance, not all of them do. One-third don't. Just because they have Plavix resistance doesn't mean they will develop stent thrombosis. So, for every 20-30 patients who are Plavix resistant, 98% of them will do fine. If you assessed everyone, you would over-treat lots of patients to prevent 1-2 events with an off-label dose of Plavix, where you don't even know if you prevent the event…You are identifying the higher risk patients, but there isn't any innocuous behavior that you would change or a drug to prescribe…If you found 30% of patients Plavix resistant and doubled the dose in all those patients, out of those 30%, 10% would still be Plavix resistant, and all 30% would be taking more drug per month. And Plavix, in and of itself, causes more bleeds with a double dose."

Inaccuracy:

- "One thing I've noticed with VerifyNow is that sometimes it doesn't make a lot of sense. You test the patients and know they are loaded (with Plavix), and the test comes back zero. It is not completely believable."
- "Accumetrics curves from past devices have over-called whatever they are looking at. It is almost an artifact of the device methodology. If anything they are too sensitive."

Logistics: "You have to do it a few days after the patient gets the drug, which is one limitation. Most patients who come in today are in and out in 24 hours. That is one more test to do that slows things down…And the complications with Plavix are so low that it is hard to imagine how you could decrease that."

Reimbursement does ***not*** appear to be a big issue for most doctors. No source blamed poor reimbursement for a lack of interest in the test, but some concerns were raised. A Florida cardiologist said, "We don't do testing in the office. Testing is done at the hospital, and so we wouldn't do the test at all." A Maine cardiologist said, "Reimbursement is not an issue. It is not that expensive a test to begin with. It is neither a money maker or a money loser. Hospitals might complain about using it for inpatients because it does take away from the DRG (diagnosis-related group, the way Medicare pays hospitals). We haven't been approached to do it in our office, and I wouldn't want to invest in that." Another doctor pointed out that reimbursement and cost may become bigger issues when Plavix goes off patent.

Lack of outcomes data: Dr. Eikelboom said that outcomes data will be critical to adoption of VerifyNow or other Plavix-resistance tests, "The tests are getting better, and there are more of them, and we are getting closer to implementing them for prime time to test every patient, but we are not quite there yet. Some of the tests have some really neat characteristics, and VerifyNow is one of the leading contenders. But what we still have to do for patients is show that if we have a strategy where we routinely test, we will do more good than harm…but you might do more harm than good if you are not careful. It is not just the cost, but we may not be improving outcomes, just giving more intensive therapy without reducing ischemic events…It is frustrating for device manufacturers because science keeps saying we are not there yet…and we ***are not*** there yet, but we are getting a lot closer."

VERIFYNOW OUTCOMES DATA

Outcomes data on VerifyNow should be available in 2010 from the GRAVITAS trial, a double-blind, placebo-controlled, randomized study in PCI patients getting a drug-eluting stent. GRAVITAS reached the halfway mark in enrollment at the end of June 2009. The trial is testing all patients for Plavix resistance, then randomizing resistant patients to either standard (75 mg daily) or double-dose (150 mg daily) Plavix. The primary endpoint is MACE (major adverse cardiac events – CV death, non-fatal MI, or ARC definite/probable stent thrombosis) at 6 months.

Dr. Eikelboom said GRAVITAS will be very important, "We have to close the loop by completing the studies currently underway…Studies like that have really set the new standard. That could well provide the final set of information that will be needed to make recommendations to implement these tests routinely...The only other hope is the ticagrelor data – and higher dose clopidogrel. So, the need for testing for clopidogrel resistance may be somewhat diminished because in patients we are worried about, we may use prasugrel or ticagrelor (instead of Plavix)…but I don't think platelet testing will be eliminated (by those drugs). I still think it will take off …We want to improve platelet function, but we don't want to over-treat patients and cause more bleeding."

Accumetrics hopes to show that tailoring the dose of Plavix according to the resistance level shown with VerifyNow improves outcomes. The trial has taken a long time to get this far, but the company insists that enrollment is picking up.

The company's expectation is that GRAVITAS will show a 50% reduction in MACE in Plavix non-responders by boosting the dose. The trial is assuming a 5% event rate in non-responders on standard dose Plavix vs. 2% in responders. The trial will offer two comparisons: (1) boosted-dose non-responders vs. standard-dose non-responders and (2) standard-dose non-responders vs. responders.

On the outlook for the GRAVITAS trial, Dr. Eikelboom said, "I think GRAVITAS, as long as they pick people with disease will be positive…I would be willing to bet my house on that one – as long as the non-responders have disease and stick to the allocated treatment, I would be very, very surprised if higher dose clopidogrel didn't benefit."

However, other experts were less optimistic. An investigator said, "If GRAVITAS is positive, it would change things… (But) I would give it a 50/50 chance of being positive."

An interim analysis of GRAVITAS is planned later this year. There is a possibility that the company could decide to enlarge the trial at that point, but it would have to pay a statistical penalty to do that, and it would delay the final results by at least 6-8 months. If the trial is not enlarged, final results could be presented at TCT 2010.

Another factor that could impact the results of GRAVITAS is the number and distribution of patients in the trial who have the Cytochrome P450 2C19*2 genotype. A genome-wide association study by Dr. Alan Shuldiner of the University of Maryland School of Medicine and colleagues, published in the ***Journal of the American Medical Association*** (***JAMA***) in August 2009, found that people with the 2C19*2 allele have a diminished response to Plavix and poorer cardiovascular outcomes. The researchers looked at:

- 429 drug-naïve Old Order Amish patients (from the PAPI trial) who were given a baseline loading dose of 300 mg Plavix, followed by 75 mg daily for 6 days.
- 227 patients undergoing non-emergent PCI at Sinai Hospital of Baltimore who received either a 300 mg or 600 mg loading dose of Plavix followed by a 75 mg daily dose.

In both studies, the researchers found a strong link between 2C19*2 and Plavix resistance, which could not be explained away by other factors such as age, body mass index (BMI), diabetes, etc. And they noted that 24% of white people have at least one CYP2C19*2 allele, compared with ~18% of Mexican Americans, ~33% of African Americans, and ~51% of Asians, "Thus, clopidogrel resistance due to this variant may be particularly important in Asian and African American populations…Unfortunately, our sample size was not sufficient to examine ethnicity-specific differences in CYP2C19 genotype effects on clopidogrel response. Additional studies in diverse populations will be necessary."

VerifyNow was ***not*** used to measure platelet aggregation in either of these studies; all the measurements were done in laboratories, not point-of-care. While the findings emphasize the importance of knowing whether a patient is a responder or a non-responder, they also raise concerns that CYP2C19 status could confound the results in GRAVITAS.

*Will physicians start performing genotype testing, looking for patients with the CYP450 2C19*2 genotype and give them another therapy, such as Lilly's Effient (prasugrel) instead?* In an editorial in ***JAMA*** accompanying the allele article, Dr. Deepak Bhatt, chief of cardiology in the VA Boston Healthcare System and director of the integrated cardiovascular intervention program at Brigham and Women's Hospital, wrote, "This observation (the relationship of CYP2C19 and Plavix resistance) implies that even a future era of pharmacogenomic profiling could include a complementary role for point-of-care testing of platelet function." However, he cautioned that "this appealing concept" needs to be evaluated in prospective studies and in large, ethnically-diverse populations.

Dr. Bhatt concluded, "Additional work is needed before routine testing for this CYP2C19 polymorphism can be recommended…Polymorphisms that predict anticoagulation response to warfarin have already been identified, but testing is not widely used because of a lack of large randomized

outcome trials demonstrating that this approach actually reduces bleeding…Similarly, the lack of prospectively defined algorithms to react to the presence of clopidogrel-associated polymorphisms should limit such testing at present…(But) if such testing allowed use of a less expensive generic antiplatelet drug (i.e., generic clopidogrel), the test might essentially pay for itself."

Dr. Bhatt also suggested that newer antiplatelet agents may avoid or lessen the problem of Plavix resistance, though he warned this needs further study as well, "A strategy of increasing clopidogrel dose in carriers of CYP2C19*2 is time-consuming and largely ineffective at providing adequate platelet inhibition…This does not necessarily mean that all CYP2C19*2 carriers who are doing well clinically while taking clopidogrel would benefit from an alternative therapeutic approach – only a prospective, randomized trial could answer that tantalizing question."

*Asked if the CYP450 2C19*2 issue will skew the GRAVITAS results*, Dr. Eikelboom said, "That's true, but that is not completely clean. And CHARISMA is coming out. 2C19 is useful and important but not as important as it is made out to be."

Even if GRAVITAS is positive, doctors were dubious that there would be a significant increase in P2Y12 testing. They said that they might consider using VerifyNow if GRAVITAS shows an outcomes benefit, but most were dubious that the trial would have great results. Comments included:

- "The VerifyNow device is promising in that the machine is compact and results can be obtained in a few minutes… If the (GRAVITAS) data are positive…this will give real credibility and awareness to this testing device."
- "It (GRAVITAS) may (give use a boost), but it will take time for cardiologists to get their heads around it and learn to incorporate it into their routine."
- "(GRAVITAS) will probably provide some answers."
- Dr. Slater said that most patients on Plavix who get into trouble are those who prematurely stop the drug, "I see very few patients with subacute stent thrombosis (SAT) who were on the standard dose, so like most clinical trials, the event rate will probably determine whether there will be a treatment effect, and in my experience the event rate for SAT is low."
- "If there is an outcomes benefit, then (using the test) could make logical sense. If there is an outcomes benefit by testing, we would consider using it, but I'm doubtful."
- "It depends on how many people you would test and how much it costs. You have to look at the balance."

Two other trials are ongoing which could impact physician interest in VerifyNow:

1. **TRILOGY** – a 13,000-patient trial at 500 sites, with about half of these using VerifyNow. However, this trial is unlikely to have any major impact on VerifyNow usage because it is only testing reactivity and platelet function.
2. **TRIGGER-PCI** – an ~2,200-patient trial similar to GRAVITAS but only in Plavix non-responders. Drug-eluting stent (DES) patients are being randomized to 75 mg Plavix or 10 mg prasugrel, with VerifyNow used to make the choice between those drugs. This trial just recently started enrolling patients.

Perhaps yet another trial will be necessary. Dr. Eikelboom said, "We think there is scope for still another trial similar to GRAVITAS. GRAVITAS tests people, and those who are clopidogrel response get more aggressive treatment. The problem with that is, even without testing, if we give more aggressive treatment, then we will get better outcomes. We've seen that with OASIS (ticagrelor). The correct trial is to compare two groups: (1) standard treatment without testing, and (2) test everyone and adjust treatment appropriately."

The Impact of New Drugs on VerifyNow Use

Will the recent FDA approval of a second platelet inhibitor, Effient, increase the use of VerifyNow, perhaps to help doctors choose between Plavix and Effient? Probably not much.

A ***CRTonline*** poll asked cardiologists how often they will use Effient for patients with acute MI. Almost half (45%) said they would use it for <25% of AMI patients, while 29% said they would use it for >75% of patients, 9% plan to use it for 50%-75% of patients, and 16% expect to use it for 25%-49% of patients.

Most cardiologists questioned by ***Trends-in-Medicine*** said it is unlikely that they will use VerifyNow to determine which patients get Plavix and which get Effient. They pointed out that there is less resistance to Effient, and there are no data to show that patients who are resistant to Plavix have a better outcome on Effient.

- *Florida:* "There are other agents down the pipeline, like ADP (adenosine diphosphate) inhibitors, that may have shorter half-lives and less bleeding than Plavix or prasugrel."
- *New York:* "A logical way to use prasugrel would be to start it in patients who show Plavix resistance, but whether that will be standard procedure, I don't know."
- *Maine:* "I guess you could use VerifyNow to choose between Plavix and prasugrel. Maybe it will catch on. When prasugrel makes more inroads, then cardiologists will ask more questions about the right dose and what to do about drug-eluting stents."

- *North Carolina:* "It would be nice to say that (prasugrel) is the behavior you should encourage based on the assay results, but what needs to be done is to show that it makes a difference substituting prasugrel for Plavix, that prasugrel improves the outcome in patients who are clopidogrel resistant. I predict there will be ***some*** adoption, specifically for that purpose because absent good data – and there are no clinical data whatsoever – the next level of knowledge physicians use is pharmacology, and that makes complete sense…But I won't do that (absent data)."
- *Georgia:* "I think prescribing physicians will stay strictly on label (with prasugrel) for the time being. The indications are rather limiting. The initial TRITON studies with prasugrel have been encouraging, but the bleeding risk is of concern…I see no reason to use VerifyNow at this time to determine use of prasugrel vs. Plavix, but I believe this could change based on ongoing clinical trials and the GRAVITAS study."

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