	Title: White Paper: Platelet Function Testing 2019		Document: LBL-0072-A
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Revision Log

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1.0 INTRODUCTION

Platelets play an important role in thrombosis and hemostasis. Understanding and modulating their reactivity is central to the management of patients with certain pathologies. Toward this goal, Platelet Function Testing (PFT) has emerged as a valuable tool in personalized medicine to help stratify risk and individualize patient therapies to achieve the delicate balance between reducing thrombotic risk and maintaining hemostasis. Through numerous clinical studies, the perspective on PFT has evolved to “how and when” to utilize PFT rather than whether or not to utilize PFT in a variety of clinical situations such as cardiovascular, neurovascular, surgery, trauma, peripheral artery disease, etc.

2.0 CARDIOVASCULAR APPLICATIONS


In recent years the cardiovascular literature has progressively begun to embrace the use of PFT as improved clinical trial designs have clarified the appropriate utilization of PFT (1-4). In 2013 Dr Tracy Wang (Duke University) observed when commenting on the TRANSLATE-POP study that U.S physicians seem interested in PFT outcomes but at that time considered their own “clinical evaluations” to be sufficient for determining the appropriate medication for their patients(5). She then added that data was limited and additional clinical trials were needed.

In retrospect each of these observations was correct.

The subsequent development of the more potent P2Y12 inhibitors (ticagrelor and prasugrel) was a significant step forward in anti-platelet therapy. Since these potent drugs consistently inhibited platelet function, it was initially presumed that their advent might diminish the value of PFT (6).

However, each of these newer medications had higher risks for serious side effects; primarily bleeding (prasugrel, ticagrelor) and some disturbing pulmonary symptoms (ticagrelor). In addition although more powerful they were also considerably more expensive than the traditional clopidogrel.

As experience developed, the significant higher risk side effects of the new P2Y12 inhibitors as well as the socioeconomic considerations created new challenges for physicians in the management of anti-platelet medications. Thus the availability of three vs one P2Y12 inhibitors not only substantiated the need to individualize anti-platelet

	Title: White Paper: Platelet Function Testing 2019		Document:
	DCO: 19-0081	Date effective: 10/24/19	LBL-0072-A

therapy but created new venues where PFT was significant (7).

The SWAP trials, by Angiolillo, Franchi and colleagues, were a valuable series of publications that began in 2010 with SWAP-1(8). These trials continued through the SWAP-4 series which was published in 2018. (9-11).The latter study documented the value of PFT when “switching” anti-platelet medications, in this case De-escalating from the more powerful ticagrelor to clopidogrel (11)).

In 2017 the TROPICAL-ACS trial, was published in Lancet (3).This was a very significant multi-institution study that evaluated a large series of patients (n=2610), with Acute Coronary Syndrome (ACS) that underwent Percutaneous Coronary Intervention (PCI). Patients who were switched from prasugrel to clopidogrel after one week and were guided with PFT throughout treatment, at one year, had no increased risk for CV events and also had a lower incidence of bleeding than those who were kept on prasugrel for one year. The authors concluded that switching anti-platelet medication (De-escalation) guided by PFT did result in safer outcomes.


Furthermore PFT detected patients who were under-responsive or non-responsive to clopidogrel, and these patients were appropriately switched back to prasugrel

Dr D.J. Angiolillo, a known expert on PFT, commented favorably on the Tropical-ACS publication in Lancet. He emphasized that in real world practice, bleeding and socio-economic issues were primary contributors to De-escalation therapy, i.e. switching patients back to clopidogrel, guided by PFT (4).

In August 2019 a publication entitled “Updated Expert Consensus Statement on Platelet Function and Genetic Testing for Guided P2Y12 Receptor Inhibitor Treatment in PCI” in the Journal of the American College of Cardiology (JACC) was of great significance concerning utilization of PFT (1)

The authors represent the majority of current experts on the utilization of Platelet Function Testing. The discussion dealt primarily with post-PCI patients who were being treated with dual anti-platelet therapy (DAPT) and evaluated with PFT. Platelet function testing was considered to be of significant value in several areas including the following:

- 1.-High Platelet Reactivity (HPR)
- 2.-The determination of patients Post PCI adherence to anti-platelet treatment.
- 3.-Baseline HPR in certain patients.
- 4- Reducing waiting time pre-operatively on cardiac or non-cardiac surgery patients, with a prior history of PCI who were also on dual anti-platelet therapy

	Title: White Paper: Platelet Function Testing 2019		Document:
	DCO: 19-0081	Date effective: 10/24/19	LBL-0072-A

(DAPT).

5.-Escalation of P2Y12 inhibiting therapy in several clinical circumstances such as; left main coronary artery stenting; complex lesions; last patent vessel PCI; 2-stent bifurcation treatment; prior stent thrombosis all limited to only those patient not at risk for excessive bleeding.

6.-Escalation in high risk patients with HPR on clopidogrel with guided transition to prasugrel or ticagrelor.

7.-De-Escalation in patients on DAPT: i.e. consideration of stopping one of the drugs (ASA or clopidogrel) because of bleeding or risk of bleeding

8.-De-Escalation post PCI –from the more potent P2Y12 drugs to clopidogrel, to reduce bleeding risk, especially after 30 days.

As indicated in the title, the authors also discussed the potential value of genetic testing with respect to clopidogel resistance


In summary, it was concluded that PFT may be used as a tool for guiding Escalation or De-escalation of DAPT in post PCI patients.

3.0 NEUROVASCULAR APPLICATIONS

PFT is actively being used in neurovascular disciplines on patients being treated with DAPT (12-17). The following represent some of the clinical circumstances where PFT is included in patient management:

- Acute Ischemic Stroke management utilizing serial PFT (12).
- Pipeline Embolization (13).
- Titrating anti-platelet therapy with PFT in patients with cerebral thrombosis (14).
- Predicting post procedural “delayed hemorrhage” following flow diversion aneurysmal treatment with PFT by detecting the presence or absence of low platelet reactivity (LPR) (15).
- Management of delayed cerebral ischemia (DCI) after acute aneurysmal subarachnoid hemorrhage (16).

In each of these Neurovascular treatment areas PFT played a role in helping to avoid or minimize major complications of bleeding or thrombosis.

	Title: White Paper: Platelet Function Testing 2019		Document:
	DCO: 19-0081	Date effective: 10/24/19	LBL-0072-A

Interestingly the “skepticism implied in the title of Cheung’s recent Australian publication, (“PFT in Neurovascular Procedures, Tool or Gimmick?”) (17), was followed by a positive conclusion that elective neurological procedure outcomes and thromboembolic complication rates, -“may indeed”- be improved by identifying clopidogrel non-responders’ pre- procedure with PFT. Further, a meta-analysis by Ajadi et al. demonstrated that platelet hypo-response or hyper-response to dual antiplatelet therapy are associated with a higher risk of thrombotic and hemorrhagic events respectively in the treatment of cerebral aneurysms using flow diversion devices which underscores the importance of PFT (18).

4.0 SURGERY, TRAUMA, AND PERIPHERAL ARTERY DISEASE APPLICATIONS

Perioperative point of care in surgical patients represents another area for utilization of PFT. Its use can reduce waiting time for surgery in patients on DAPT as discussed previously (1) and to manage/reduce blood loss postoperatively (19-21). Ghadimi K et al discuss the value of PFT in conjunction with Thromboelastography(TEG) to manage bleeding in cardiac and coronary surgery as well as several other surgical theaters including trauma, liver transplantation and other complex surgical procedures (22).


Any area of surgery where blood loss can be significant is a potential arena for applying PFT, including Orthopedic Surgery. A recent report (23.) discusses the value of using PFT in the ER on patients with proximal femoral fractures who are also receiving anti-platelet therapy. Determining the degree of platelet inhibition in the ER on these patients, can result in earlier surgery and use of spinal anesthesia potentially reducing complications as well as shortening the hospital stay.

In addition, PFT has been used in conjunction with Spine Surgery to manage hemostatic function where the authors considered platelet aggregability an independent measure of the potential for bleeding (24).

It has also been noted that trauma patients can benefit from PFT to guide transfusion and to individualize blood product usage strategies for improved outcomes and reduce healthcare costs (25-27).

Aspirin and clopidogrel efficacy also vary in patients with peripheral artery disease PAD and may be associated with poor treatment outcomes (28-32). Further, it has been noted that the presence of PAD in conjunction with platelet hyper-reactivity despite clopidogrel usage is associated with adverse coronary disease outcomes (30). These observations highlight the potential utility of PFT in the PAD patient population.

In summary, current literature supports the application of Platelet Function Testing in a

	Title: White Paper: Platelet Function Testing 2019		Document: LBL-0072-A
	DCO: 19-0081	Date effective: 10/24/19	

variety of. in-patient and out-patient clinical circumstances It is a valuable and increasingly utilized test that can help to reduce the risks-of bleeding or thrombosis during the management of post-PCI patients, neurovascular patients as well as others on antiplatelet therapy including, surgical and non-surgical patients.


5.0 CONCLUSIONS

In summary, current literature supports the application of Platelet Function Testing in a variety of. in-patient and out-patient clinical circumstances It is a valuable and increasingly utilized test that can help to reduce the risks-of bleeding or thrombosis during the management of post-PCI patients, neurovascular patients as well as others on antiplatelet therapy including, surgical and non-surgical patients.


Note: The white paper was developed by AggreDyne, Inc. It is intended to provide general information. It is not intended to represent any specific platelet function testing product or its claims. Please see the product literature for specific information on AggreDyne products.

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	Title: White Paper: Platelet Function Testing 2019		Document: LBL-0072-A
	DCO: 19-0081	Date effective: 10/24/19	

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	Title: White Paper: Platelet Function Testing 2019		Document:
	DCO: 19-0081	Date effective: 10/24/19	LBL-0072-A

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	Title: White Paper: Platelet Function Testing 2019		Document:
	DCO: 19-0081	Date effective: 10/24/19	LBL-0072-A

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