Centre universitaire de santé McGill
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MINI HEALTH TECHNOLOGY ASSESSMENT

(Note: A mini HTA report consists of two parts. The first is completed by the applicant at the time the new technology is requested. The second consists of a commentary and possibly additional evidence provided by TAU)

Report number: 53
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Use of the VerifyNow point of care test to detect non-responsiveness to clopidogrel and aspirin.

PART I: Request for HTA (Completed by applicant)

REQUESTOR

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Technology (Name, Description, Purpose)
Name: VerifyNow

Description: VerifyNow is a point-of-care test that can evaluate a patient's response to several antiplatelet inhibitors, including aspirin and thienopyridines.

Purpose: Its purpose is to detect non-responders to antiplatelet medication so that by dose adjustment or change of medication a therapeutic response can be achieved.

Has it been used at the MUHC? What is the alternative?
It has not been used at the MUHC. The gold standard, laboratory-based Light Transmission Aggregometry (LTA) is available but cannot be used for this purpose because results are only available one week after ordering, making it too slow to influence the course of treatment.

Health benefits
Patients who do not achieve a full therapeutic response to aspirin and clopidogrel are at increased risk of atherothrombotic cardiovascular complications**.** Detecting

such patients and modifying their treatment so as to achieve therapeutic levels of antiplatelet therapy should reduce the incidence of such complications.

Risks/complications

There are no risks due to VerifyNow itself. However, agents that may be used to treat clopidogrel resistant cases, such as prasugel or ticagrelor, may increase the risk of bleeding.

Unit costs (Direct costs of items requested)

$70/test. The test would likely be used a second time in approximately 20% of cases to test the response to change in therapy. Thus, assume the average cost per patient would be $84.

Usage (Quantity of drugs/expendables or number of procedures per year)

The request is to use the VerifyNow test in approximately 100 selected patients per year. Selection criteria will be: patients presenting with stent thrombosis while on medication (approximately 2% of all stent placement procedures, or 32 patients per year), patients considered to be at very high risk of stent thrombosis due to such factors as long lesions in the presence of diabetes, and patients with lesions of the left main coronary artery in whom a subsequent thrombosis might have dire consequences. It is estimated that there will be approximately 70 such patients per year.

Impact on hospital services (Bed usage,OPD, Etc)

No major impact on hospital services. It will not be necessary to hire additional personnel to administer this test. Budget impact approximately $8,400 per year.

Resource Person/Expert at MUHC

Dr. Luc Bilodeau

References

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2) Varenhorst C, James S, Erlinge D, Braun OO, Brandt JT, Winters KJ et al. Assessment of P2Y(12) inhibition with the point-of-care device VerifyNow P2Y12 in patients treated with prasugrel or clopidogrel coadministered with aspirin. Am Heart J 2009; 157(3):562-569.

MINI HEALTH TECHNOLOGY ASSESSMENT

PART II: Additional comments of Technology Assessment Unit

Completed by: Mr. Xuanqian (Shawn) Xie
Dr. Maurice McGregor

Literature search

Methods: A literature review (non-systematic) was carried out using Pubmed and the HTA Database of the University of York, UK, using the key word "VerifyNow". No HTAs or systematic reviews on this subject were identified. Studies evaluating the reliability or validity of VerifyNow by comparison with Light Transmission Aggregometry (LTA) or studies of the relationship between Clopidogrel resistance and cardiovascular outcomes published since 2003 up to July 1, 2011 were retained.

Background

The placement of drug eluting stents (DES) can sometimes be followed in subsequent weeks by arterial thrombotic events including reocclusion of the stent, myocardial infarction, stroke, and death. The frequency of such events can be reduced by drugs such as aspirin and clopidogrel that inactivate platelet function, and it is currently routine practice to administer these drugs for at least one year after DES insertion.

However, approximately 20-25% of patients[1;2] are resistant to these medications so that platelets retain their function, placing the patients at increased risk of these thrombotic events. Studies have shown that laboratory detected clopidogrel resistance is significantly associated with increased risk of in-stent thrombosis and ischaemic events in patients undergoing PCI [1;3-10].

Platelet reactivity has until recently been measured in the laboratory by light transmittance aggregometry (LTA), but this procedure is slow, requires intensive sample preparation, and the results are not instantly available[11]. Recently introduced bedside tests such as VerifyNow can provide almost instantaneous results and allow for rapid decision-making.

Proposed intervention

The objective of the present application is to use the platelet reactivity test VerifyNow in selected patients believed to be at high risk of thrombotic events to detect clopidogrel resistance so that treatment can be adjusted to provide a therapeutic level of antiplatelet therapy.

As noted above, there is good evidence that resistance to Clopidogrel therapy is a strong predictor of in-stent thrombosis, stroke, myocardial infarction, and death. Two questions need to be considered:

1). Is VerifyNow a sufficiently accurate test of platelet reactivity to identify clopidogrel resistance and the associated increased risk of thrombotic events?

2). When Clopidogrel resistance has been identified, is there an accepted treatment that will abolish platelet reactivity and reduce the risk of thrombotic events?

1). Accuracy of VerifyNow.

The accuracy of this test can be considered in two ways: the extent to which it coincides with the results of the most accepted current test of platelet reactivity, in particular, Light Transmission Aggregometry (LTA), and the accuracy with which it predicts the vascular thrombotic effects in question.

Direct comparisons of VerifyNow with, the most accepted current test of platelet reactivity, Light Transmission Aggregometry (LTA), have shown significant but sometimes poor correlation[2;12-14], A recent reviewer concludes that the VerifyNow essay "has been well correlated with ADP-induced platelet aggregation by LT A"[15]. Using a different approach Lordkipanidze and colleagues[16], studied the extent of platelet inhibition resulting from Clopidogrel administration to 68 patients with coronary artery disease. They found that the percent inhibition according to the VerifyNow assay overestimated the inhibition of platelet activity calculated from the off-drug and on-drug ADP induced aggregation, by 8% (95%. CI 1-15%. P = 0.03). However, it has been observed that there is poor correlation between the several tests of platelet reactivity and it is still uncertain which is the best for evaluation of Clopidogrel resistance[10].

More relevant is the evidence that Clopidogrel resistance detected by VerifyNow is a predictor of subsequent short and longterm vascular thrombotic events. For example, Patti et al report a prospective study of the relationship between platelet reactivity measured by VerifyNow and the 30-day occurrence of major adverse cardiovascular events in 160 Clopidogrel treated patients undergoing PCI. Receiver Operating Curve (ROC) analysis of platelet reactivity (measured by VerifyNow) showed significant discrimination between patients with and without major adverse events (area under the curve = 0.69; P= 0.016)[17].

In a similar study platelet reactivity (VerifyNow) was capable of distinguishing between patients with and without events (cardiovascular death, non-fatal MI, and stent thrombosis) at a six-months follow-up of 380 patients on Clopidogrel following stent implantation (area under ROC curve = 0.720; P = 0.02)[15].The ability of VerifyNow to predict adverse thrombotic events through demonstration of Clopidogrel resistance has been shown in several studies[3;4;17-19], and in one of

these this assay was a better predictor of atherothrombotic events than LTA[18]. There is, therefore, sufficient evidence that VerifyNow is an appropriate test to use for the proposed intervention.

2). Management of clopidogrel resistant cases.

Attempts to overcome clopidogrel resistance by increasing dosage have not yet been successful. In a randomised controlled study study of post stent patients with clopidogrel resistance demonstrated by VerifyNow, 1105 patients were given standard dose clopidogrel (no loading dose with 75 mg daily) and 1109 high-dose (600 mg loading with 150 mg daily). At six months the event rate (cardiovascular death, non-fatal myocardial infarction, and stent thrombosis) was 2.3% in both groups[20]. However, other thienopyridine drugs might be effective in this situation.

Prasugrel, a third-generation thienopyridine, provides more complete platelet inhibition than clopidogrel. Thus, in a study of 101 aspirin treated patients with coronary artery disease who were randomly assigned to receive either clopidogrel or prasugel there was a 45% level of non-responders in the former compared to 0% in the latter[21]. When used to treat patients with acute coronary syndromes following coronary interventions, prasugel therapy was associated with modestly lower rates of myocardial infarction than clopidogrel (7.4% vs 9.7%, p<0.001). However, it was also associated with significantly more major bleeding events (2.4% vs 1.8%, p< 0.001)[22]. We found no reports of the specific use of prasugel for clopidogrel resistant patients.

Ticagrelor, another thienopyridine drug, was the subject of a12 month follow-up study of 18,624 patients on aspirin, receiving in addition either ticagrelor or clopidogrel. Ticagrelor was found to be associated with a modest reduction in the combined endpoint (death from vascular causes, myocardial infarction, and stroke), 9.8% versus 11.7%, p=<0.001 for those receiving clopidogrel. It was associated (non-significantly) with more haemorrhagic strokes 23 versus 13 (p=0.1)[23].

Ticagrelor has also been shown to effectively reduce platelet activity in clopidogrel resistant cases. In a crossover study of 98 patients made up of 41 non-responders and 57 responders to clopidogrel, tricagrelor was found to have an equivalent antiplatelet effect in responders and non-responders. The association with thrombotic events was not reported. One major and three minor bleeding episodes occurred in association with ticagrelor compared to none with clopidogrel[24].

It should be noted that an antiplatelet effect demonstrated by tests such as VerifyNow does not necessarily equate with a therapeutic effect. Thus, in a study of 960 patients receiving aspirin and clopidogrel for six months following DES insertion, 477 were randomly assigned to also receive c*ilostazo*l, a selective phosphodiesterase-3 inhibitor. In spite of a greater antiplatelet effect (as measured

by VerifyNow) in the latter group, there was no difference in the composite endpoint of cardiac death, non-fatal myocardial infarction, ischaemic stroke, and target lesion revascularization[25].

We found no study in which Clopidogrel resistance was managed by use of another antiplatelet agent, though a trial of this nature using prasugel is reported to be ongoing[26].

Conclusion

- **The applicant intends to use the VerifyNow test to detect those patients at increased risk of arterial thrombotic events due to Clopidogrel resistance. Patients found to be clopidogrel resistant will be treated with other thienopyridine drugs.**
- **The VerifyNow test is easy to use and is sufficiently accurate for this purpose.**
- **The cost of this intervention for approximately 100 selected patients per year will be approximately $8,400. There will be no increased use of beds or other hospital services.**
- **This intervention will probably result in improved patient outcomes. However, it is an intervention that has not previously been used and it's value is still unproven. It should therefore be considered an experimental intervention.**

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