Case Report

Stent Thrombosis Patients with Hyporesponsiveness to Clopidogrel, Prasugrel, and Ticagrelor: A Case Series Using Short Thromboelastography

Bartosz Olechowski, Alexander Ashby, Nalyaka Sambu, Michael Mahmoudi, and Nick Curzen

Wessex Cardiothoracic Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK

Correspondence should be addressed to Bartosz Olechowski; drolechowski@gmail.com

Received 20 June 2016; Revised 24 August 2016; Accepted 28 August 2016

Academic Editor: Michael S. Firstenberg

Copyright © 2016 Bartosz Olechowski et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

1. Introduction

Stent thrombosis (ST) is a major complication of percutaneous coronary intervention (PCI), occurring in 2.0–2.9% of patients within 22 months [1]. Although uncommon, ST is associated with significant mortality of up to 45% [2]. Dual antiplatelet therapy (APT) with aspirin and P2Y12 inhibitor has become the default strategy in patients undergoing coronary stent implantation to reduce the risk of ST. However, a cohort of patients may have an inadequate functional response to P2Y12 [3, 4] and are more likely to sustain ischaemic events including ST [5].

There is particular concern about clopidogrel in this regard [6, 7]. The established link between functional hyporesponsiveness to clopidogrel and ischaemic events, including ST, in patients receiving coronary stents has triggered the development of more potent and faster-acting P2Y12 inhibitors. Two large randomised trials have demonstrated reduction in ischaemic endpoints for prasugrel and ticagrelor when compared to clopidogrel in acute coronary syndrome (ACS) patients undergoing PCI, albeit at the price of increased bleeding [8, 9]. In response to these data and earlier studies demonstrating quicker onset and more potent and more homogeneous responses of healthy volunteers and stable patients to prasugrel and ticagrelor compared to clopidogrel, many PCI centres in the UK have switched from clopidogrel to either prasugrel or ticagrelor as their default. Interestingly the incidence of prasugrel hyporesponsiveness is estimated to be 25% using flow cytometric analysis of intraplatelet vasodilator-stimulated phosphoprotein (VASP) phosphorylation in ACS patients [10, 11]. In the CREST registry, out of 6 patients who were found to be hyporesponsive to prasugrel, only 3 responded adequately to ticagrelor [6].

We present for the first time 3 cases in which patients who had had ST exhibit hyporesponsiveness to clopidogrel, prasugrel, and ticagrelor.

We present for the first time 3 cases in which patients who had experienced definite ST after drug eluting stent (DES) implantation who demonstrated functional hyporesponsiveness to clopidogrel, prasugrel, and ticagrelor, using a previously well validated test, short thromboelastography (sTEG) [12–15]. sTEG uses a novel parameter, percentage clotting inhibition (%CI) in the AA or ADP channel for clotting inhibition by aspirin or P2Y12 inhibitors, respectively. The formula for %CI by aspirin is 100 – (AUC15(AA)/AUC15(Thrombin) × 100) and for %CI by P2Y12 inhibitors is 100 – (AUC15(ADP)/AUC15(Thrombin) × 100) [14]. Threshold %CI of <50 in
the AA channel and <30 in the ADP channel was used to
define hyporesponsiveness to aspirin and P₂Y₁₂ inhibitors,
respectively.

2. Case Report

Patient 1 is a 74-year-old male with type 2 diabetes mellitus
and previous anterior ST elevation myocardial infarction
(STEMI) treated with a single drug eluting stent (DES) in
the circumflex artery. He presented with proximal stent occlusion
2043 days after his index PCI while on aspirin 75 mg once
daily. He was successfully treated with plain old balloon
angioplasty (POBA) and bare metal stent (BMS) insertion.
Subsequently he underwent platelet function testing using
sTEG. Initially our patient was started on aspirin 150 mg daily
and clopidogrel 75 mg daily. Forty-two days later, the assay
revealed an inadequate response to aspirin (%CI 71) but subopt-
imal response to clopidogrel (%CI 17). Therefore, prasugrel
5 mg daily was commenced as patient was borderline for
age group with no initial loading. Once more the reading
showed inadequate response to prasugrel 5 mg daily (%CI
−7) after 63 days of treatment and the dose was uptitrated
to 10 mg daily. Subsequent test, 105 days later, revealed sub-
optimal response again (%CI 9). As a result, the patient was
commenced on ticagrelor 90 mg twice daily without initial
loading and retested after 85 days of treatment. Similarly, his
reading revealed hyporesponsiveness (%CI 1) (Figure 1). Due
to development of dyspnoea while on ticagrelor, the patient was
finally left on prasugrel 10 mg daily for life. After this episode,
he was treated with cardiac resynchronisation therapy and
defibrillation due to severe ischaemic cardiomyopathy but
is currently alive, having suffered no further ST or other
ischaemic events.

Patient 2 is a 62-year-old male smoker with hyperlipi-
daemia and positive family history for premature coronary
artery disease who originally presented with a non-ST-
elevation myocardial infarction (NSTEMI) for which he had
three DES implanted in the left anterior descending artery
(LAD). He represented with anterior STEMI due to ST
elevation myocardial infarction (NSTEMI) for which he had
ischaemic events.

Our case series demonstrate three cases of patients with
acute stent thrombosis who were found to be hyporesponsive
to all three commonly available P₂Y₁₂ receptor inhibitors. To
the best of our knowledge, this is the first time that a series
of such cases has been described. Two previously published
case reports have illustrated patients with dual thienopyridine
resistance to clopidogrel and prasugrel [16, 17]. In both cases,
the patient was subsequently shown to have an adequate
response to the ticagrelor. Orban et al. suggested that the
response to ticagrelor may be due to its properties as an active
drug, compared with prasugrel and clopidogrel which are
prodrugs requiring hepatic cytochrome bioactivation prior to
P₂Y₁₂ inhibition [17].

Based upon both early studies reporting superior potency,
speed of onset and consistency of responses to prasugrel and
ticagrelor versus clopidogrel in both volunteers and stable
patients [18, 19], and subsequent large scale randomised trials,
in many PCI centres, prasugrel and ticagrelor have become
the default P₂Y₁₂ agent. The assumption from some interven-
tionalists is that prasugrel and ticagrelor are not associated
with functional hyporesponsiveness (also known as “resist-
ance”). However, recent data suggest that functional resis-
tance does indeed occur in association with these agents
[11, 20].

Our case series describe for the first time the concept of
functional resistance to all three commonly available P₂Y₁₂
inhibitors. These data were obtained using short TEG, a well
described and validated modification of TEG platelet map-
ning assay [10–13]. Our group has previously described the
reproducibility of sTEG and has demonstrated the value
of comparing the ADP-induced clotting response to that
achieved using kaolin stimulation. This method has the
advantage that there is a built-in reference, both numerical
and visual, of the strength of the clot in response to ADP com-
pared to the maximum clot strength achieved by kaolin. We
have also used sTEG to describe discrepancies between these
results from Verify Now assay [21, 22].

One limitation of our case series is that we were not able
to objectively prove patients’ compliance with medications,
although we appreciate that it might have implications on
final management strategy. In addition to this, no other

3. Discussion

Our case series demonstrates three cases of patients with
acute stent thrombosis who were found to be hyporesponsive
to all three commonly available P₂Y₁₂ receptor inhibitors. To
the best of our knowledge, this is the first time that a series
of such cases has been described. Two previously published
case reports have illustrated patients with dual thienopyridine
resistance to clopidogrel and prasugrel [16, 17]. In both cases,
the patient was subsequently shown to have an adequate
response to the ticagrelor. Orban et al. suggested that the
response to ticagrelor may be due to its properties as an active
drug, compared with prasugrel and clopidogrel which are
prodrugs requiring hepatic cytochrome bioactivation prior to
P₂Y₁₂ inhibition [17].
Figure 1: Short thromboelastography traces showing adequate response to aspirin 150 mg daily and hyporesponse to $P_2Y_{12}$ inhibitors in first patient. (a) Patient 1 clotting response to AA when on 150 mg daily aspirin, producing a %CI(AA) of 71, an adequate response to aspirin. (b) Patient 1 clotting response to ADP when on 75 mg clopidogrel daily, producing a %CI(ADP) of 17 (nonresponse to clopidogrel). (c) Patient 1 clotting response to ADP when on 10 mg prasugrel daily, producing a %CI(ADP) of 9 (nonresponse to prasugrel). (d) Patient 1 clotting response to ADP when on 90 mg ticagrelor twice daily, producing a %CI(ADP) of 1 (nonresponse to ticagrelor).

Platelet function assays (i.e., Verify Now) were used to confirm our results.

These cases suggest that some patients experiencing ST may exhibit functional resistance to all 3 of the currently available oral $P_2Y_{12}$ inhibitors. As well as adding weight to the argument in favour of measuring individual responses to $P_2Y_{12}$ inhibitors, with the intention of possibly avoiding stents in patients who do not respond to them, it also raises interesting questions about the mechanism of hyporesponsiveness.
Further data are required to investigate whether this observation in such patients could be due to a paucity of receptor numbers, a functional flaw in the receptor activation, or perhaps even a lack of availability of such drugs at the receptor.

**Competing Interests**
Bartosz Olechowski, Alexander Ashby, Nalyaka Sambu, and Michael Mahmoudi declare that they have no competing interests. Nick Curzen received unrestricted research grants.
from Boston Scientific, Haemonetics; Heartflow, St. Jude Medical, and Medtronic; speaker fees/consultancy from Haemonetics, St. Jude Medical, Abbott Vascular, and Heartflow; and travel sponsorship from Biosensors, Abbott, and Lilly/D-S.

References


