References


‘I can see clearly now’: a new view on the use of IV GP IIb/IIIa inhibitors in acute coronary syndromes

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‘I can see clearly now the rain is gone
I can see all obstacles in my way . . .’
Johnny Nash

It has been several decades since the popular singer Johnny Nash used the above words in the opening lines of the popular song ‘I can see clearly now’. How apt they seem today as one reads the latest analysis of the use of intravenous glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors in patients presenting with an acute coronary syndrome (ACS) [1]. In this issue, Roffi et al. analyse the data from the PRISM, PRISM-PLUS, PARAGON-A, PURSUIT, PARAGON-B, and GUSTO IV ACS trials with two goals in mind: (1) to characterize the overall benefit of GP IIb/IIIa inhibitors and (2) to assess whether the reduction in ischemic endpoints varied with the revascularization strategy used [2–7].

The first objective of the Roffi analysis is not particularly novel and in one way or another has been touched on in prior publications. It is generally agreed that GP IIb/IIIa inhibitors represent an important advance in the management of patients with an ACS. In fact, reports on the effects of GP IIb/IIIa inhibitors have ‘rained down’ on the cardiology literature at such a rate that many practitioners find the data overload an ‘obstacle’ to a proper interpretation of how to use such agents. Clinicians ‘cannot see clearly’ what to do.

Trials such as those listed above as well as ‘pure’ trials of percutaneous coronary intervention (PCI) such as EPIC, EPILOG, CAPTURE, IMPACT II, RESTORE, and EPISTENT collectively form a database of about 40 000 patients [8–12]. From that database it has been reported that there is a significant 15–20% reduction in the proportion of patients who die or experience a myocardial infarction (MI) when they are treated with a GP IIb/IIIa inhibitor compared to placebo [13]. When we focus on just the PCI trials, we see a 30–40% reduction in death/MI, significantly favouring the use of GP IIb/IIIa inhibitors [13].

The strength of the evidence in favour of GP IIb/IIIa inhibitors, especially in patients undergoing PCI, formed the basis for the Class I recommendation (Level of Evidence A) in the current version of the ACC/AHA Guidelines for the Management of Patients with UA/NSTEMI that states: ‘A platelet GP IIb/IIIa antagonist should be administered, in addition to ASA and heparin, to patients in whom catheterization and
PCI are planned. The GP IIb/IIIa antagonist may also be administered just prior to PCI\textsuperscript{[13]}.

Perhaps the most interesting aspect of the Roffi et al. paper is the second objective. As noted above, there is approximately a two-fold greater treatment benefit of GP IIb/IIIa inhibitors if one focuses strictly on the PCI trials as compared to an analysis that includes both the PCI and mixed medical management/PCI trials. To explore this gradient of benefit further, Roffi et al. analysed the six trials where patients with an ACS were not routinely scheduled for an early revascularization. A similar approach was taken by Boersma et al. who also analysed the same six trials\textsuperscript{[14]}. Boersma et al. concluded that GP IIb/IIIa inhibitors were most effective in patients at greatest risk of thrombotic complications. Data contained in the Boersma et al. paper also show a smaller and non-significant treatment effect in patients treated only medically compared with those undergoing revascularization\textsuperscript{[14]}.

Roffi et al. excluded the 345 patients from PRISM-PLUS from the arm not containing heparin as well as the 1487 patients from the low dose eptifibatide arm of PURSUIT. That provided them with a total of 29 570 patients compared with the 31 402 included in the Boersma et al. meta-analysis. Of interest, among the 29 570 patients, 6337 (21%) underwent PCI, 2249 (7.6%) had the PCI performed while receiving the GP IIb/IIIa inhibitor, and 20 054 received only medical therapy for their ACS. The decision to perform a PCI or simply to manage the patient medically was not randomized, but instead was left to the discretion of the treating physician. Therein lies a limitation of such an analysis. However, the segregation of patients into three groups provides the opportunity to analyse the gradient of benefit of GP IIb/IIIa inhibitors.

Figure 6 in the Roffi paper plots the odds ratio and 95% CI for death/MI at 30 days among the patients medically managed, those undergoing a PCI after discontinuation of the study drug, and those undergoing PCI while on study drug. The point estimates for the treatment effect of GP IIb/IIIa inhibitors clearly define a progressively greater benefit that achieves statistical significance only for the group undergoing PCI on study drug. (As can be deduced from the text, the greatest contribution to the reduction in the composite endpoint was from a reduction in MI although there was a non-significant trend towards lower mortality favouring GP IIb/IIIa inhibitor use).

Also shown in their Figure 6 are the pooled estimates of the incidence of death/MI at 30 days for the placebo and GP IIb/IIIa inhibitor groups. From those data, one can calculate the events prevented per 1000 patients treated and the number of patients one needs to treat to prevent one event (see Fig. 1). These two calculations allow us to see the prior ‘obstacles’ in organizing our thinking about GP IIb/IIIa inhibitors and to ‘see clearly now’ how to use them in the most cost-effective manner. We can expect to prevent about 30 events for every 1000 patients who undergo PCI while on a GP IIb/IIIa inhibitor. However, we can prevent only about half as many events\textsuperscript{[14]} if the PCI is performed after the drug is discontinued, underscoring the importance of having the protective effect of a GP IIb/IIIa on board when endothelial disruption attendant to a PCI procedure occurs. If a patient with an ACS is treated only medically using a GP IIb/IIIa inhibitor, the number of events prevented per 1000 patients treated is less than a quarter of that attained when the GP IIb/IIIa inhibitor is used in association with PCI.
This gradient in anticipated benefit of GP IIb/IIIa inhibitors is reflected in the current ACC/AHA Guidelines for the Management of Patients with UA/NSTEMI. The guidelines include a lower level recommendation (Class IIa) that ‘Eptifibatide or tirofiban should be administered, in addition to ASA and LMWH or UFH, to patients with continuing ischemia, and elevated troponin or with other high-risk features in whom an invasive management strategy is not planned (Level of Evidence: A)”[13]. There is even a lower level of recommendation (Class IIb) regarding the administration of ‘Eptifibatide or tirofiban, in addition to ASA and LMWH or UFH, to patients without continuing ischemia who have no other high-risk features and in whom PCI is not planned. (Level of Evidence A)”[13].

Several issues emerge in the face of these new analyses: (1) While there is compelling evidence that use of GP IIb/IIIa inhibitors at the time of PCI reduces ischemic events, we do not have clear guidance on the optimum timing (upstream versus initiation in the cath lab) of their administration nor a clear answer as to whether they should be used universally for PCI procedures or more selectively in higher risk patients. Attempts to answer such questions by propensity scores and deductive reasoning from clinical trials is not sufficient to guide practice [15,16]. (2) Although the benefit of GP IIb/IIIa inhibitors is marginal in patients treated only medically, is it possible to identify high risk patients who may derive more benefit? It has been suggested that diabetic patients and those with a positive troponin test derive benefit from GP IIb/IIIa inhibitors[1,14]. But those are clearly the high risk patients who we now treat via an early invasive strategy[17]. Also, it is not clear that a dichotomous analysis of troponin tests is the best way to identify patients who benefit from GP IIb/IIIa inhibitors. There may well be a gradient of benefit of GP IIb/IIIa inhibitors stratified by the absolute level of troponin elevation[18]. Our treatment algorithms need further refinement. (3) Finally, in the face of very compelling independent evidence of benefit from clopidogrel[19] and enoxaparin[20] in patients with UA/NSTEMI largely in the absence of GP IIb/IIIa inhibitor use, what is the residual benefit of GP IIb/IIIa inhibitors in a contemporary mix of other pharmaco-therapeutic advances?

Our therapeutic options are rapidly changing as we plan the next stage of clinical trials. Papers such as that by Roffi et al. help us ‘see clearly’ as we move forward.[1].

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References


Percutaneous coronary intervention in diabetics with prior coronary artery bypass surgery: sweet or sour?

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There is a clear increase in the prevalence of diabetes mellitus in the western world and thus, a growing proportion of patient candidates for revascularization procedures suffer from diabetes. Following the results of trials such as BARI [1] the cardiology community has accepted that percutaneous revascularisation in diabetics, especially when they have multivessel disease, provides mediocre long-term results and that, when patients are amenable to coronary artery bypass grafting (CABG), the latter provides superior outcome, including reduced cardiac mortality (5-year cardiac mortality: 8.2% vs 23.4%). This has led to the recommendation that CABG be used for revascularization of diabetic patients and it has even been suggested that multivessel balloon angioplasty be abandoned in diabetics [2]. Yet, the picture of revascularization in these patients is not entirely black and white and data from the BARI registry show that in diabetic patients screened for randomization in the trial in whom physician or patient preference, based upon clinical and/or angiographic data, led to selection of percutaneous coronary intervention (PCI) or CABG rather than randomization, the outcomes of PCI and CABG appear similar (5-year cardiac mortality 7.5% and 6% for PCI and CABG, respectively) [3], suggesting the ability of physicians to discriminate ‘good candidates’ for either technique [4].

Thus, CABG is generally recommended for revascularization of diabetic patients with multivessel disease. However, over time, recurrent revascularization may become necessary in diabetic patients with prior CABG. There is little information on the outcomes of further revascularization at that stage.

In the present issue, Matthew et al. report on the outcomes of PCI in patients with prior CABG, and compare those outcomes in diabetic vs non-diabetic patients [5]. Using the Mayo Clinic coronary interventional registry, they were able to assemble a cohort of 1153 patients with prior CABG undergoing PCI of whom 326 are diabetics. Although the cohort is large, it must be stressed that it reflects the experience from a single American centre. Therefore, extrapolation of these results to other settings, especially in Europe where the use of CABG surgery is less widespread and where patients and procedural characteristics may be different is somewhat problematic. Still this is a very valuable registry because of its size, because of the detailed information available, including long-term follow-up in 96% of the patients, and because it reflects contemporary practice with use of stents in more than 80% of the patients and a substantial use of glycoprotein IIb/IIIa inhibitors (abciximab in approximately 40% of the patients). The information provided with respect to the outcomes of PCI in these patients is contrasted.

The good news is that in patients with prior CABG in whom PCI is attempted, procedural success and in-hospital outcomes were very similar among diabetic and non-diabetic patients. More importantly, in patients with ‘single territory’ coronary artery disease at the time of PCI, diabetes did not independently influence event-free survival. This observation, which should nevertheless be accepted with caution, given the relatively small sample size of that patient subset (99 diabetic and 240 non-diabetic patients), suggests that PCI is a very valid option for additional revascularization after CABG regardless of the diabetic status of patients. Another positive note is that diabetic status had no impact on long-term outcomes.