Occident to Orient Initiation

Optimizing DAPT for ACS-PCI Patients

A recent international symposium in Barcelona, bringing together worldwide experts focused on optimizing dual antiplatelet therapy (DAPT) for acute coronary syndrome patients requiring treatment with percutaneous coronary intervention (ACS-PCI). DAPT is now recognized as a mainstay of therapy in these patients; recent ESC guidelines help to provide a framework for physicians to ensure optimal regimens usage. Treatments may need to vary, however, individual patients should be managed according to their own specific requirements. Evidence-based guidelines generated from clinical trials should also be supplemented with data from real-world experience. With this in mind the first presentation was by Prof. Bolognese, who provided an in-depth overview of registry data from around the world. Prof. Silber then examined specific treatment regimens that provided clarity on the important role of specific P2Y12 inhibitors. Two interesting case presentations and discussion followed, from Dr. Chunhamaneewat, Thailand, and Dr. Abizaid, Brazil, highlighting the need to individualize treatment and the importance of understanding a patient' s health care system and access to the health care services.

Real-world Evidence of New P2Y12 inhibitors

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Therapeutic regimens based on clinical trials can be improved by utilizing data from real-world experience. National and international registries help illustrate the efficacy and safety of respective regimens in actual clinical practice. Prof. Bolognese used recent registry data to highlight the increasingly recognized role for the P2Y12 inhibitor prasugrel in optimizing dual antiplatelet therapy (DAPT) regimens.

Optimal guidelines for P2Y12 inhibitors were developed by real-world data from three patient cohorts – ST-elevation and non-ST-elevation myocardial infarctions (STEMI and NSTEMI) patients as well as those using switch regimens. Recently clinical registries (MULTIPRAC, ATACS, SCAAR, FAST-AMI, AMIS-PLUS) have reported results assessing prasugrel in STEMI patients.[1-6] Real-world evidence confirmed patients treated with prasugrel had improved survival and reduced incidence of major adverse cardiovascular events (MACE) compared to clopidogrel, resulting in an improvement in 30-day mortality, a benefit that remained observable at 1 year although not significant in clinical study data (Figure1).[1-6]

In 2014, the European Society of Cardiology launched the

Platelet Inhibition Registry in ACS Evaluation Study (PIRAEUS) to integrate data from European registries. Analysis showed a consistent pattern, confirming that STEMI patients treated with prasugrel have a lower all cause and cardiovascular death rate compared to ticagrelor, and to an even greater extent, those treated with clopidogrel.[7] Another important registry (UK-BCIS) has added data clarifying the use of P2Y12 inhibitors in STEMI patients treated with PCI. Multivariate analysis showed that prasugrel was associated with a lower mortality than clopidogrel at 30 days and 1 year. Compared with prasugrel, ticagrelor was linked to higher mortality at both time points and the odds of death did not differ between ticagrelor and clopidogrel.[8]

For NSTEMI patients, results from a US registry analyzed short-term outcome in terms of net adverse clinical event (NACE) and MACE.[9] NACE was 22% lower in prasugrel-treated patients and a 30-day adjusted MACE and major bleeding score was also lower in patients treated with prasugrel compared to ticagrelor. Further NSTEMI data, from the PIRAEUS project, revealed similar results, with a clear advantage for prasugrel compared to ticagrelor and clopidogrel.[10] Adding to this are results from the SCAAR registry, which found that ticagrelor was not superior to clopidogrel in ACS patients.[11]

PROMETHEUS, a multicenter US registry of ACS patients undergoing PCI analyzed patient comorbidities.[12] Their results demonstrated differences in MACE were attenuated and no longer statistically significant after adjusting for the propensity to receive prasugrel (HR 0.89, 95% CI: 0.76-1.05, P=0.16). However, at 1-year, reductions in MACE associated with prasugrel remained significant, even after propensity stratification. Prof. Bolognese stressed that these studies indicate ACS patients undergoing PCI fare better when treated with a more potent agent such as prasugrel compared to clopidogrel and this was also the case in complex PCI patients.[13]

Recent meta-analysis, COMFORTABLE and SPUM-ACS studies, have looked at switch therapy. They reported a trend in reducing ischemic events and MI when switching from a less potent (clopidogrel) to more potent (prasugrel) agent, which was not associated with an increase in bleeding.[14] An overview confirmed that among PCI patients, switching from clopidogrel to prasugrel was safe and should be encouraged.[15,16] Countering this was data from the SCOPE registry of PCI patients, which found that switching from an old to newer P2Y12 receptor inhibitor was safe, but downgrade switching from a newer to older agent was an independent predictor of NACE.[17]

Based on these findings it has been proposed that potent agents should be substituted with clopidogrel in the maintenance phase for ACS patients undergoing PCI. However some caveats are warranted due to concerns with the study design and the use of a higher than recommended dose of prasugrel in elderly patients. Prof. Bolognese noted that while this approach is interesting, it does not invalidate the superiority of prasugrel over clopidogrel as observed in the much larger, double-blind, multicenter trials and as a consequence shouldn't influence clinical practice and affect future guidelines. He concluded that prasugrel, and to a lesser degree, ticagrelor had substantially lower adverse event rates including mortality and that registry data is a key source of real-world information that can be used to further improve clinical management of specific patient cohorts.

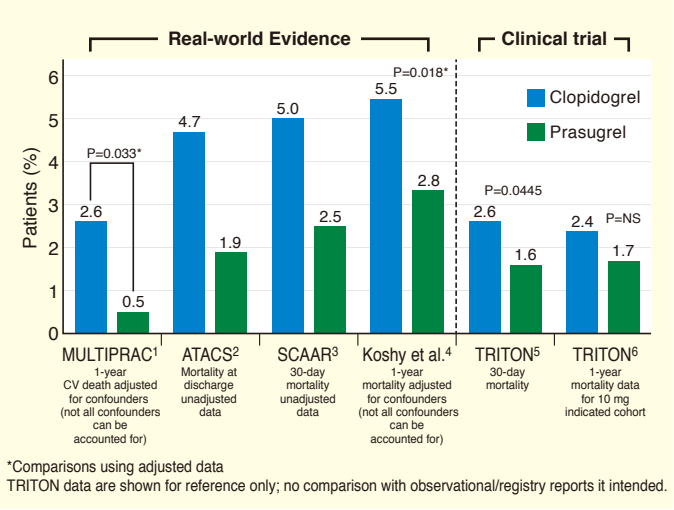

Figure1. Real-World Evidence: Mortality rates are lower with prasugrel than clopidogrel[1-6]

The New P2Y12 Inhibitors : Why, When and Duration of Prescription

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A comprehensive overview of the role of the P2Y12 inhibitors exemplified by prasugrel, clopidogrel, and ticagrelor was presented by Prof. Silber. He described the rationale for using these agents, looking at specific patient cohorts and treatment regimens, and providing clear therapeutic guidelines for optimal patient management.

Dual antiplatelet therapy (DAPT) has been beneficial in patients with cardiovascular disorders,[18-20] and this benefit has expanded with the development of newer more active P2Y12 inhibitors such as prasugrel and ticagrelor. Prof. Silber noted that choosing between prasugrel and ticagrelor is difficult due to differences in pivotal trial designs.[21,22] However primary combined endpoints from all patients in the TRITON and PLATO studies demonstrated the reduction in relative risk is similar (9.9% reduction for prasugrel vs. clopidogrel and 9.8% for ticagrelor vs. clopidogrel).

To clarify this issue, Prof. Silber examined different patient cohorts; first turning to stent thrombosis, a major problem associated with a 30-45% mortality rate.[23] Both prasugrel and ticagrelor provide significant benefits compared to clopidogrel in stent patients. However when specific stent types are analyzed, prasugrel significantly reduces thrombosis in both bare metal (BM) and drug eluting stents (DES) while ticagrelor did not significantly reduce thrombosis compared to clopidogrel in drug-eluting stents.

Further differentiation between the agents is possible by looking at patient characteristics. The TRITON study divided patients into those with prior stroke, ≥75 years and <60kg.

When patients with a prior stroke (4%), or elderly/low weight (16%) are excluded, prasugrel exerts a significant positive effect compared to clopidogrel with no significant difference in the incidence of major bleeding.[21] This is also true for patients with diabetes mellitus where prasugrel is associated with a highly significant positive effect.[24] In contrast the risk reduction in diabetes patients was not significant with ticagrelor compared to clopidogrel.

The effect of antiplatelet therapy on mortality has also been investigated. In PLATO, ticagrelor was associated with an improved mortality rate but this appears late in treatment and in patients on lipid lowering drugs.[22,25] Subgroup analysis comparing mortality in patients undergoing PCI found no difference between prasugrel and ticagrelor. Further investigation in STEMI patients has shown that prasugrel has a 50% reduction in mortality in those treated with PCI.[26] In contrast, the reduction of mortality in both STEMI and NSTEMI patients treated with ticagrelor was found in those who had PCI more than 10 hours after ticagrelor administration.

Prof. Silber noted that prasugrel and ticagrelor have similar PD features,[27] but the reversible binding of ticagrelor is not an advantage. This is because prasugrel-treated patients with severe bleeding can be given a platelet infusion, which is immediately effective, but such treatment in ticagrelor-treated patients has delayed efficacy. Ticagrelor is not just a $P2Y_{12}$ inhibitor but also an ENT-1 inhibitor, resulting in additional adverse effects, especially dyspnea, making it contraindicated in more patients than prasugrel **(Figure2)**.

Turning to guidelines, Prof. Silber noted that 2014 ESC/EACTS recommendation is for pretreatment prior to PCI in STEMI patients with either prasugrel or ticagrelor. Also, clopidogrel should only be given in STEMI when prasugrel or ticagrelor are not available or contraindicated.[28] The 2015 ESC Guideline recommend prasugrel in NSTEMI patients proceeding to PCI if there are no contraindications[29] and the latest 2017 guideline is also similar.[30]

The question of what is the minimum duration of DAPT after stenting in patients with ACS versus stable coronary artery disease (CAD) was then addressed. Prof. Silber stated that this has fluctuated over the past 20 years, but now ACS patients should be treated for at least 12 months. In stable patients after BM stenting 1 month treatment is recommended, with 6 months suggested for those with DES. Looking at the possible role of de-escalation in selected patients, he commented that convincing evidence demonstrating the validity of this approach is lacking and it is not recommended in guidelines. This is also true for triple therapy, as ticagrelor or prasugrel are not recommended as part of a triple therapy regimen.

Finally Prof. Silber noted that secondary prevention with prolonged DAPT is an interesting possibility; the TRILOGY trial indicated that prasugrel provides even greater benefit than clopidogrel after 360 days. This is supported by a subgroup analysis of the DAPT trial showing a significant positive effect on secondary prevention for prasugrel but not clopidogrel.[31]

	Prasugrel	Ticagrelor
Contraindications Brain	Prior Stroke, Prior TIA	Prior Cerebral Bleeding
Contraindications Liver	Severe Liver Dysfunction	Moderate or Severe Liver Dysfunction
Contraindications Metabolism	None	Co-administration of strong CYP3A4-inhibitors (e.g. Clarithromycine, Ketoconazole, Nefazodon and many others)
Warnings	Adjustment of Maintenance Dose (5mg) in Patients < 60 kg / ≥ 75 years	Bradycardia / AV-Block History of Asthma and/or COPD History of Hyperuricaemia Concomitant Use of ARBs Coadministration of some Statins or Digoxin

Figure2. Contraindications and Warnings

Discussion

The management of STEMI patients was discussed with Prof. Bolognese recommending the use of prasugrel rather than ticagrelor, especially in the first 30 days where a mortality benefit is also observed. He noted problems with ticagrelor in ACS patients treated by PCI. Dr. Silber agreed that prasugrel is recommended in STEMI, but also stressed that treatment needs to take individual characteristics into account. The physician needs to consider any contraindications against using the newer inhibitors. If none, for STEMI patients undergoing primary PCI, he recommended prasugrel or ticagrelor after pre-treatment. Prof. Silber agreed recommended prasugrel or ticagrelor after pretreatment. Prof. Silber agreed that for practical reasons prasugrel is easier to use because it has fewer contraindications. Dyspnea or a reduced ejection fraction may be caused by ticagrelor, which makes evaluation more difficult.

Prof. Bolognese noted that in NSTEMI the initial management approach should be conservative, depending on length of time before angiography. Prof. Silber agreed, noting that the major randomized trial demonstrated no difference between prasugrel and ticagrelor in NSTEMI, and that those physicians who treat these patients should consider whether there is an indication for long-term anticoagulation (for example, whether the patient have atrial fibrillation). If so, in those NSTEMI patients about to undergo PCI no pretreatment is required although he pretreats patients that cannot go directly for PCI. This highlights the need to individualize the treatment based upon the patient and the health care services available in each country.

As for the issue of de-escalation (prasugrel to clopidogrel), Prof. Bolognese noted that while one study showed non-inferiority for this strategy, limitations in the study design make this less clear. He cited two reasons for de-escalation; concern over bleeding and cost. However, downgrading from a more potent to less potent agent may be associated with risk due to changes in platelet reactivity. He believed that the key message is to develop regimens based on real-world registry data. Overall, in the registries, prasugrel, and to a lesser extent ticagrelor, have substantially lower event rates including mortality. More data is needed on this issue.

Clinical Case Discussion

Two interesting case histories, presented by Dr. Chunhamaneewat and Dr. Abizaid highlighted the importance of providing individualized treatment. Moderated by Prof. Silber, the lively discussion revealed that guidelines provide a useful therapeutic framework, yet they often need to be personalized to ensure optimal management.

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Dr. Chunhamaneewat reported the case of a 57-year-old male who presented to a community hospital with 3 days of chest pain, but discharged himself before having an angiogram. He developed dyspnea and returned to another hospital 2 days later, and diagnosed with severe heart failure from anteroseptal MI. He was managed with balloon angioplasty and the issue of whether he should receive immediate or deferred stenting was debated.

Guidelines recommend stenting as a primary strategy for STEMI cases, but because of the patient's late presentation when he had already developed myocardial edema, he was at high risk for no re-flow, which can be catastrophic. In these types of cases deferred stenting should be considered. As a poor complier it was better to treat him with a once daily regimen of aspirin and prasugrel. At follow-up 4 weeks later there was no residual thrombosis and some plaque in proximal LAD. The patient was then successfully treated with an Everolimus-eluting stent.

Dr. Silber commented that when a patient is at risk for no re-flow, there is a specific stent (MGuard), which helps prevent distal embolization. Dr. Abizaid agreed that in cases with a lot of thrombi and a relatively minor underlying lesion, deferred stenting is an acceptable approach and in some cases it is possible to use intracoronary thrombolytic therapy. Dr. Silber noted that if there is a small (20%) lesion with ruptured plaque causing thrombus, then it is possible to clean the vessel with antithrombolytic drug therapy. However, if there is an underlying lesion, with 50-60% stenosis, the likelihood of the patient returning with re-stenosis is very high.

The take-home message was that although routine use of deferred stenting is not recommended, it should be considered in some cases, especially in patients at high risk for developing no re-flow. While the optimal timing of the procedure is not clear, it is probably not within 48 hours and a strong $P2Y_{12}$ inhibitor like prasugrel is mandatory to prevent re-occlusion. One of the important features with this patient was his late presentation, which is very different from that in developed countries where patients tend to present shortly after developing chest pain. Therefore clinical practice depends on access to the health services and available health care options.

Dr. Abizaid presented the case of a 58 year old man with diabetes, hypertension, atypical chest pain and a normal ECG. He was followed for 3 weeks in which time he had 2-3 episodes of more typical exercise-induced chest pain. Repeat ECG and cardiac enzymes were normal. The best investigations to perform, including stress test, nuclear medicine, echo stress, angiography CT or immediate catheterization were debated. The patient underwent nuclear imaging which revealed lateral and inferior ischemia, followed by angiography illustrating diffuse disease in LAD, thrombus and slow flow. The patient was diagnosed as originally having non-Q wave MI and treatment options considered included immediate PCI plus aspirin and either clopidogrel, prasugrel or ticagrelor, or elective PCI with aspirin and a $P2Y_{12}$ inhibitor with low-molecular heparin for 72 hours.

Dr. Bolognese said GPI is another option, which he uses in 60% of STEMI patients. He also recommended immediate rather than elective management. The general consensus was the patient required PCI, but debate hinged on whether it should be done immediately or 2-3 days after preloading. Drs. Bolognese and Silber advocated immediate PCI, while Dr. Chunhamaneewat suggested to use a potent $P2Y_{12}$ inhibitor such as prasugrel and perform PCI later. If the patient was very stable this could be up to a month later, but in general should be within 3-5 days. Dr. Abizaid agreed, reporting that the patient was managed with 3 days prasugrel, aspirin and low molecular heparin achieving TIMI 3 flow, then PCI was performed. Another potential strategy was to do PCI for the right lesion immediately and repeat for the circumflex later. Dr. Abizaid commented that he wanted to have the benefits of the anti-thrombotic effects of prasugrel, aspirin and then potentially heparin first. This case again highlighted the need to deliver therapies based on the individual patient and that this is influenced by the health care options available.

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