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Editorial

Choice of antithrombotics in acute coronary syndrome – A balance of efficacy versus safety

As to diseases, make a habit of two things—to help, or at least to do no harm.
— Hippocrates[1]

Thrombus is the main culprit in the pathogenesis of acute coronary syndrome (ACS). It forms through 2 mechanisms: first, the adhesion, activation, secretion, and aggregation of platelets; and the second, amplification of the coagulation cascade for the formation of thrombin. This requires an activated platelet surface. Antithrombotic agents are the mainstay of the therapy in ACS. The major goal of optimal antithrombotic therapy for patients with ACS is to minimize the risk of early- and long-term thrombotic adverse events, as well as to reduce risk of bleeding complications. Antithrombotic therapy consists of (a) anticoagulants or antithrombin agents and (b) antiplatelet agents. Aspirin is a cornerstone of therapy in the treatment of patients with ACS. However, dual antiplatelet therapy (DAPT) reduces the risk of stent thrombosis and cardiovascular events compared with aspirin alone in the treatment of patients with ACS.[2] For several years, clopidogrel plus aspirin has been the DAPT of choice for patients with ACS undergoing percutaneous coronary intervention (PCI) with stent implantation. More recently, prasugrel and ticagrelor have demonstrated greater efficacy than clopidogrel and are getting preference over the latter.[3,4] Amongst antithrombin agents, unfractionated heparin (UFH) dominated the scene for quite some time till it faced challenge from low-molecular weight heparins, fondaparinux, and bivalirudin. Recently, there has been a debate as to which of the several available anticoagulant agents should be used in the ACS treatment regimen even though all of these have class I recommendations in guidelines.[5,6] Bivalirudin has the advantage of lower bleeding and is often preferred over UFH. The latest guidelines have limited the use of GPIIb/IIIa antagonists in the management of ACS only in bailout situations and these no longer evoke much controversy.[5,6]

In this issue of the Indian Heart Journal, Wayangankar and colleagues[7] have presented interesting data from USA, on the patterns of use of antithrombotic therapy and its impact on outcome in 64,199 patients with non-ST elevation myocardial infarction (NSTEMI ACS) treated by PCI during 2007–2010 from The National Cardiovascular Data Registry's (NCDR) ACTION Registry®-GWTG™. The study noticed a significant increase in the use of UFH and bivalirudin coupled with a decrease in use of low-molecular weight heparins and GPIIb/IIIa receptor antagonists over a period of 4 years, which led to a significant decrease in major bleeding and use of blood products and a trend toward lower mortality attributed to lower bleeding risk. A matter of concern in this study was the underutilization of DAPT, statins, and antirenin agents, which was not highlighted. A very small number of patients were prescribed newer antiplatelets (prasugrel mainly), as this molecule was just getting recognition by interventional cardiologists in the period 2007–2010.

1. Antithrombin agents and ACS

The major debate in the mind of an interventional cardiologist is whether to use UFH (inexpensive, more familiar, subject to monitoring and a little more bleeding) or bivalirudin (expensive, less bleeding, a little more stent thrombosis). In this context, the recently published MATRIX trial[8] is of considerable interest. In this study of 7213 patients with ACS undergoing PCIs, the primary and the secondary endpoints of major cardiovascular events and net clinical benefit were similar for UFH and bivalirudin. Bivalirudin was associated with a significant risk of definite stent thrombosis but with considerably less major bleeding, leading to lower mortality. Our study also reported lower mortality in this setting.[9] From these data, it is apparent that bleeding risk algorithms should be the prime focus when a decision has to be made about the use of bivalirudin in the cardiac catheterization laboratory especially in the group with high risk of bleeding. Table 1 summarizes the advantages and disadvantages of various antithrombin agents used in management of ACS.

Each agent has strengths and weaknesses. The points of caution with UFH are the variable response and bleeding; with low-molecular weight heparin, it is the bleeding during inadvertent or intended switch-over; with bivalirudin, it is the cost and stent thrombosis, and with fondaparinux, it is the need for additional UFH during PCI.

Table 1 – Pros and cons of various antithrombins.

PROS	CONS
Unfractionated heparin	**Unfractionated heparin**
1. Inexpensive	1. Variable efficacy
2. Easily reversible	2. Needs dose monitoring
3. Proven efficacy	3. Thrombocytopenia
4. Rapid action	4. More bleeding
Bivalirudin	**Bivalirudin**
1. Linear dose–response curve	1. Expensive
2. No monitoring required	2. Often needs postprocedure infusion
3. Less bleeding	3. More stent thrombosis
4. Rapid reversibility	
5. Fixed dose	
Fondaparinux	**Fondaparinux**
1. Fixed single dose	1. Slow action
2. Less thrombocytopenia	2. Catheter thrombosis
3. Efficacy regardless of management strategy	3. Needs additional UFH during PCI
4. Favorable safety profile	4. Expensive
LMWH	**LMWH**
1. Linear dose–response curve	1. Expensive
2. Monitoring not required	2. Switch-over is messy
3. Thrombocytopenia uncommon	3. Bleeding risk

Table 2 – Pros and cons of P2Y12 inhibitors.

PROS	CONS
Clopidogrel	**Clopidogrel**
1. Inexpensive	1. Variable efficacy
2. Greater familiarity	2. Slow onset of action
3. Can be used in all cases of	3. Drug–drug interactions
4. Only agent with proven efficacy following thrombolysis	4. Genetic response variation
5. Once-daily dosing	
Prasugrel	**Prasugrel**
1. Rapid onset of action	1. Expensive*
2. Greater efficacy in STEMI/DM	2. Major bleeding higher
3. Less drug–drug interactions	3. Use only in PCI patients
4. More effective than clopidogrel	4. Cannot be preloaded
5. Single-daily dosing	5. Longer off-drug period before CABG
*Generics available are cheaper	
Ticagrelor	**Ticagrelor**
1. Rapid onset and offset of action	1. Expensive
2. Reversible platelet inhibition	2. Twice daily dosing
3. Greater efficacy than clopidogrel	3. Dyspnea and ventricular pauses
4. Bleeding risk comparable to clopidogrel	4. Higher non-CABG-related bleeding
5. Mortality benefit	5. Higher withdrawal rates
6. Can be used regardless of management strategy	

Aspirin and clopidogrel have been the standard partners of DAPT in ACS for more than a decade. Supremacy of clopidogrel has been challenged by the newer P2Y12 receptor inhibitors like prasugrel and ticagrelor. In ACS patients with planned PCI, in the TRITON-TIMI 38 study, prasugrel compared with clopidogrel resulted in a better clinical outcome.[10] The primary efficacy endpoint of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke occurred in 12.1% of patients receiving clopidogrel and 9.9% of patients receiving prasugrel (hazard ratio: 0.81; 95% CI: 0.73–0.90; $p < 0.001$), at a cost of higher rates of TIMI major bleeding. In the PLATO trial in ACS patients,[11] ticagrelor compared with clopidogrel reduced the primary endpoint of death from vascular causes, myocardial infarction, or stroke from 11.7% to 9.8% (hazard ratio: 0.84; 95% CI: 0.77–0.92; $p < 0.001$). Rates of major bleeding were similar between ticagrelor and clopidogrel, though major bleeding not related to coronary artery bypass grafting was more frequent in the ticagrelor-treated patients. No studies have yet compared prasugrel and ticagrelor in ACS patients; however, prasugrel and ticagrelor have different side effect profiles, and the choice of agent should be made either as a default choice and/or on an individual patient basis. In the absence of head-to-head clinical trials, network meta-analysis[12] suggests potentially relevant differences in efficacy and bleeding risk among novel antiplatelet treatments and may thereby help in understanding their differential therapeutic properties. Side effects, convenience, and cost can have a significant influence on drug selection. Bleeding constitutes the most common clinically significant safety concern of antiplatelet treatment. The goal with any antiplatelet regimen is to balance antithrombotic benefits with the inherent risk of bleeding. A comparison between clopidogrel, prasugrel, and ticagrelor is shown in Table 2.

In ACS patients undergoing PCI, a high on-treatment platelet reactivity while on clopidogrel is associated with adverse events.[13] The response to clopidogrel depends on a complex interplay of phenotypic (e.g. spontaneous platelet reactivity, inflammatory status, acuity of the clinical presentation, age, and renal function) as well as genetic variables. Genetic causes account for insignificant response variability to clopidogrel and hence looking for CYP2C19*2 allele to decide about using or not using the drug is not a cost-effective strategy.

Newer P2Y12 inhibitors, such as prasugrel and ticagrelor, are accompanied by a stronger and more consistent, antiplatelet action[14] when compared to clopidogrel resulting in better efficacy. In an adjusted indirect comparison meta-analysis of the TRITON-TIMI 38 and PLATO trials, a head-to-head comparison of prasugrel and ticagrelor showed no significant differences in overall death, myocardial infarction, stroke, or their composite.[11] Prasugrel appeared more protective from stent thrombosis, while causing more bleedings than ticagrelor.

Clopidogrel is known to be associated with issues such as nonresponsiveness, pharmacogenetics, drug–drug interactions, and questions regarding appropriate loading dose. Given its intrinsic limitations and inferior outcome data compared with newer antiplatelet agents, clopidogrel may not be an ideal drug for general use and, perhaps, should be reserved for those with low-risk ACS or patients who are unable to take ticagrelor or prasugrel.[6] The flexibility in usage and overall ischemic benefits of ticagrelor make it a very appealing drug for managing early stages of high-risk ACS patients. Like prasugrel, ticagrelor provides greater and more

consistent platelet inhibition than clopidogrel. Ticagrelor was associated with a 22% reduction in total mortality rate compared with clopidogrel.

It is uncommon to find pharmacologic interventions that result in a significant reduction in mortality. There is no clear explanation for the mortality benefit seen with ticagrelor, which may leave some skeptics to challenge this unexpected finding. Indirect comparison between prasugrel and ticagrelor showed that ticagrelor was superior in efficacy to prasugrel for chronic preventive use because of absolute mortality rate reduction, recurrent MI prevention, outcome benefit that continues to grow over time, fewer hemorrhagic fatalities, and potentially fewer CABG surgery-related bleeding event.[11]

2. Switch strategy

As ACS-related PCI increase in number and complexity, more patients must be treated with prolonged and intensified antiplatelet therapy. Objective view must be taken of each DAPT strategy. With clopidogrel, it is a variable response; with prasugrel, it is bleeding; and with ticagrelor, it is the cost. How do we determine which agent is best for a particular patient? There is no simple answer. Ticagrelor is a good compromise when balancing ischemic and bleeding risk with additional trump card of reduced mortality. Patients loaded initially with clopidogrel can be switched to ticagrelor with a loading dose.

Similarly, patients can be switched over to prasugrel from clopidogrel before PCI with a maintenance dose if clopidogrel loading dose had already been administered in the previous few days.

The agent ticagrelor or prasugrel needs to be continued uninterrupted for 1 year as per the most accepted protocols. Continuation of DAPT beyond one year is a matter of current interest as the benefits in ischemic events have been shown at the cost of increasing bleeding. Last word on this subject is still to come.

There also is a thought of switching back to clopidogrel after a period when ischemic risk has come down with reduction in costs and bleeding events. The concept can increase events in those patients who are clopidogrel resistant and hence platelet reactivity tests should be considered. We need more data in the form of randomized studies before recommending this strategy.

Ticagrelor binds reversibly to P2Y12 receptor. The reversible action makes it attractive for situations when DAPT needs to be interrupted. Prasugrel is a good alternative in those patients of ACS who undergo PCI with high ischemic risk and low bleeding risk. It is best suited for relatively young patients with ACS and diabetes and especially in those who have once experienced stent thrombosis or recurrence of ACS on clopidogrel therapy. Ticagrelor has the additional advantage of providing better efficacy even in those patients not going for PCI and continuing medical therapy unlike prasugrel, which is to be used only in patients undergoing PCI.

Clopidogrel is still the preferred drug in those with low ischemic burden and high bleeding risk. The special situations are in those patients who have received thrombolysis or those with deranged renal function or very elderly people. Prasugrel should not be used in patients with low body weight, very elderly, and with a history of stroke or transient ischemic attack. If ticagrelor is used, the dose of aspirin must be <100 mg daily. The use of GPIIb/IIIa blockers should be kept only for patients undergoing PCI for a bailout situation and their routine use should be discouraged. Intravenous Cangrelor if available is meant for patients who are antiplatelet drug naive and are being taken up for acute STEMI.

3. Conclusion

The use of newer agents like ticagralor and prasugrel in patients with intermediate- and high-risk ACS should be preferred given their proven superiority in robustly designed trials against clopidogrel. The indications for ticagrelor are wider in that it can be given before knowing coronary anatomy and also have a place in patients going on medical treatment alone unlike prasugrel, which has very specific indications during and after PCI for ACS. Cangrelor is the drug to bridge the gap between the onset of action of newer drugs, which can take up to a few hours after administration in sick patients with STEMI. In all situations, the clinical efficacy has to be balanced against bleeding.

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