Drug Corner

Positioning of the fixed dose combination of Rosuvastatin + Clopidogrel + Aspirin in the Treatment of Cardiovascular Diseases

Vilas Magarkar[1], Akshay Bafna[2], Ankur Gupta[3], Nikhil Motiramani[4], Shweta Sharma[5], Kumar Gaurav[6]

Dual anti-platelet therapy (DAPT) and statins are recommended by guidelines for the management of cardiovascular diseases (CVDs), even though the duration of treatment is guided by ischemic and bleeding risk. Clopidogrel and aspirin are the most commonly used DAPT in CVDs. Adding a statin to DAPT is helpful in reducing the thrombosis risk. Fixed-dose combination (FDC) therapy in CVD can help to address the factors of convenience, compliance, control, cost, and complication better than free drug combinations. Therefore, the FDC of rosuvastatin (10 mg or 20 mg) + clopidogrel (75 mg) + aspirin (75 mg) is likely to improve compliance in CVD patients, thereby reducing adverse cardiovascular outcomes and cost of treatment. There is lack of awareness on long term benefits of this FDC in Indian patients.

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Cardiovascular diseases (CVD) are the leading cause of mortality in India accounting for 30%-42% of all deaths[1]. More than 80% of CVD deaths are due to acute coronary syndrome (ACS), coronary artery disease (CAD) and stroke[1]. Peripheral artery disease (PAD) is another CVD of high prevalence in India[2].

Dual Anti-platelet Therapy (DAPT) and statins are usually prescribed for long periods in the management of CVD,although the duration of treatment is guided by ischemic and bleeding risk. Continued treatment with DAPT and statins in high risk patients is important to prevent further adverse cardiovascular events, however, adherence to these medications decreases over time[3,4]. This results in further complications and re-admissions, thereby increasing cost of treatment.[4]Therefore,the FDC of rosuvastatin (10 mg or 20 mg) + clopidogrel (75 mg) + aspirin (75 mg) is likely toaddress these concerns.

This position paper was formed through a series of virtual advisory board meetings held in 2021. The main objective of the advisory boards was to understand the positioning of the FDC of Rosuvastatin (10 and 20 mg) + clopidogrel (75 mg) + aspirin (75 mg) in post ACS/CAD and PAD patients. The advisory boards were attended by eminent cardiologists and cardio-thoracic surgeons across India. The panels deliberated extensively on available literature, guideline recommendations and their own clinical experience to formulate this position paper. Points endorsed by majority of panelists were considered for the positioning.

(1) Rationale of the FDC use in post ACS/CAD/PAD:

1A. Panel discussion based on available literature

i) Rationale based on efficacy, safety and mechanism of action

The FDC contains a DAPT (clopidogrel and aspirin) combined with a statin (rosuvastatin). The concomitant use of clopidogrel and aspirin is universally accepted as an effective and safe DAPT therapy in post ACS/CAD/PAD setting[5]. Rosuvastatin is a reversible competitive inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductaseand plays a strong

[1]MBBS, MD (Medicine), DM (Cardiology), Senior Consultant & Head of Department of Cardiology, Seth Nandlal Dhoot Hospital, Aurangabad, Maharashtra 431210

[2]MBBS, MD (Medicine), DM (Cardiology), DGM (Geriatric Medicine), Head of Department of Cardiology, CPRH Kolhapur, Maharashtra 416002

[3]MBBS, MD (Medicine), DM (Cardiology), Consultant & Interventional Cardiologist, Meditrina Heart Centre, Panchkula, Haryana

[4]MBBS (Gold Medalist), MD (Medicine), DM (Cardiology), Consultant & Interventional Cardiologist, Shri Medishine Hospital, Raipur, Chattisgarh 492015

[5]MBBS, MD, Medical Affairs, Dr Reddy's Laboratories Pvt Ltd, Hyderabad 500049 and Corresponding Author

[6]MBBS, MD, Medical Affairs, Dr Reddy's Laboratories Pvt Ltd, Hyderabad 500049

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role in plaque regression[6,7]. Rosuvastatin is highly potent in decreasing low density lipoprotein cholesterol (LDL-C), triglycerides (TG) and increasing high density lipoprotein cholesterol (HDL-C); thereby decreasing the cardiovascular risk[6,8]. The metabolism of clopidogrel plus rosuvastatin show synergism. Clopidogrel is a prodrug and requires CYP3A4 to form its active metabolite[9]. Rosuvastatin is not metabolized by CYP3A4, and therefore does not compete with clopidogrel for CYP3A4.

All the three drugs have proven clinical efficacy in primary and secondary prevention of thrombosis and thromboembolic events[5,10-12]. The R-GOLD study from India on the use of the FDC of clopidogrel, aspirin and rosuvastatin in stable ACS patients (N=13,410), suggested that this FDC is non-inferior to the free drug combinations of the three drugs[13]. However, further evidences are needed on long term benefits of this FDC in Indian patients even though individually these drugs are recommended in high risk ACS/CAD patients.

ii) Rationale based on compliance and adherence

Patients with ACS/CAD/PAD usually experience high pill burden due to long-termtherapies and comorbidities.[3,14]Adherence to medications in CVD is highest at one month, declines by 12 months, and further reduces to about 3% at 5-years post CVD[4,15]. Non-adherence leads to adverse outcomes, hospitalreadmissions and increase risk of mortality.[14,15] FDC reduces pill burden, increases compliance and is also cost-effective[3,4,15].

1B. Positioning of the FDC based on the rationale of use

- FDCs reduce pill burden, cost of treatment and thus, improve patient adherence, satisfaction, and outcomes.
- Factors associated with non-adherence include bleeding, poor education status, and lack of information regarding the importance of continued adherence to DAPT. Patient should be clearly explained about the consequences of missing a FDC dose which increases ischemic risk.
- It is preferable to initiate with free drug combinations especially in patients with high bleeding risk (HBR) as dose titration becomes easy. However, in HBR patients with poor compliance to free-drug combinations, FDCs can be used with strict monitoring of bleeding risk. The FDC can be safely given in patients with high ischemic risk and low bleeding risk (LBR).

(2) Role of the FDC post ACS/CAD :

2A. Panel discussion

Points to be considered while deciding the ideal patient profile and duration of FDC – Is it ACS or stable CAD? Secondly, is the patient being managed conservatively or through intervention (PCI or CABG)? Lastly, how much is the bleeding risk, high or low?

i) FDC in conservative management of ACS and chronic stable CAD

The ACC/AHA and the ESC guidelines state that clopidogrel and ticagrelor is preferred (class I recommendation) for DAPT with aspirin in patients with ACS managed with conservative therapy. DAPT can be effectively and safely combined with statins to reduce thrombosis risk.[13] The FDC is not indicated in chronic stable CAD as DAPT is not indicated in this situation.

ii) Role of FDC post PCI

Most patients with ACS/CAD are prescribed DAPT, for secondary prevention of athero-thrombotic complications, and this usually includes aspirin and a platelet P2Y12 inhibitor.[5]

a) Stable CAD undergoing PCI : All three clopidogrel, ticagrelor and prasugrel have class I recommendation in these patients.[5,13,16]The FDC is not indicated in PCI for chronic stable CAD as DAPT is not indicated in this situation.

b) Patients with ACS undergoing PCI : In patients with non-ST elevation (NSTE) and STEMI undergoing PCI, all three drugs have a class I recommendation[5,16]. Though DAPT with clopidogrel 75 mg and aspirin 75 mg is effective and safe in post ACS/CAD/PAD cases[5,13], some patients, especially those who underwent complex PCIs, have high ischemic risk and LBR, require a stronger antiplatelet like ticagrelor or prasugrel[5]. Patients who are intolerant to ticagrelor can be switched to clopidogrel without affecting the clinical outcomes[17]. Alternatively, patients with resistance to clopidogrel can be effectively and safely switched to ticagrelor[17]. The PCI-CURE study in NSTE ACSpatients showed that pre-treatment and long term post PCI treatment with clopidogrel in patients receiving aspirin significantly reduced cardiovascular outcomes[18].

c) Choice of drugs based on bleeding risk and ischemic (thrombosis) risk :

Post-ACS when risk of thrombosis is high, DAPT is given with prasugrel or ticagrelor, and thereaftercan be de-escalated to clopidogrel + aspirin if HBR persists. Non-ACS patients with HBR and are usually started with clopidogrel with aspirin.

Affordability alsomajorly affects the choice of drug; clopidogrel + aspirin is preferred in non-affording patients. However, use of prasugrel or ticagrelor is associated with better cardiovascular outcomes and lower readmission rates than clopidogrel[19]. This cost

benefit needs to be explained to the patients who need a stronger antiplatelet due to high ischemic risk.

In HBR patients, DAPT can be effectively and safely combined with statins to reduce thrombosis risk[13]. In high ASCVD risk, guidelines recommend high intensity statin to reduce LDL cholesterol by ≥50%[20]. Rosuvastatin is effective and can be used in patients with Chronic Kidney Disease (CKD), elderly, patients with risk of calcification and patients at HBR[20]. High risk patients need to be continued on high intensity statins.

d) Treatment in patients who are already bleeding:

Treatment depends on the type(major/minor) and area of bleed. In patients with minor bleeds, ticagrelor or prasugrel are stopped as bleeding risk is high with these drugs. DAPT with clopidogrel is associated with lower bleeding risk. DAPT may be initiated after the minor bleed is appropriately controlled[21]. No change is made in the P2g12 inhibitor. In case of a major bleed, all antiplatelets, anticoagulants and antithrombotics need to be stopped[21].

e) Duration of DAPT: Depends on risk of thrombosis, risk of bleeding and on whether the disease is acute or chronic stable.[21] Risk of thrombosis further depends on the complexity of procedure (type, length, diameter of stent, presence of dissection), previous history of CAD, diffuse disease etc. Bleeding is a risk factor for thrombosis as it activates whole thrombotic system.

In ACS patients with LBR undergoing PCI, DAPT is recommended for a year whereas in HBR itis recommendedfor 6 months followed by antiplatelet monotherapy.[5] In patients with chronic coronary syndrome undergoing PCI, DAPT is recommended for 6 months followed by antiplatelet monotherapy.[5] In HBR patients it is recommended for 3 months.

DAPT is recommended for one month after bare metal stent (BMS) followed by antiplatelet monotherapy[5]. The latest generation ultra-thin drug eluting stent (DES) are at lower risk of thrombosis.[22] The benefit of short-DAPT is also seen in Asian population.[23] The STOPDAPT-2 trial showed that ultra-short DAPT (1 month) with clopidogrel + aspirin followed by clopidogrel monotherapy (11 months) significantly reduced major bleeding and cardiovascular events, especially in HBR patients.[24]

iii) Role of FDC post CABG

The guidelines state that P2g12 inhibitor should be resumed early (class I recommendation)[5]. However, time to resume DAPT depends on post-surgical bleeding and patient's bleeding risk. Ticagrelor is usually preferred in LBR and clopidogrel in HBR patients. The DAPT combination with rosuvastatin will be effective in these patients.Patients undergoing CABG for chronic stable CAD require only aspirin.

Usually, aspirin is started within the first 24 hours. DAPT is started after 24 hours to one week. Some surgeons prefer to start DAPT after surgical drain is removed.

The recommended duration of DAPT post CABG is one year followed by monotherapy with aspirin usually[5,16]. In case of multiple risk factors, like diabetes, PAD, cerebrovascular disease, high intensity statins like Rosuvastatin is started along with DAPT for minimum one year and maybe even more if there are no contraindications. The FDC can be given for a year in these patients.

2B. Positioning of the FDC in post ACS/CAD:

- Clopidogrel (75 mg) is a universal antiplatelet with low bleeding risk that can be safely given with aspirin (75 mg) and rosuvastatin in post ACS/CAD patients.
- In patients being managed conservatively:
  - In ACS patients: The FDC with the 20 mg rosuvastatin dose can be given or an additional 20 mg rosuvastatin pill can be given along with the FDC for aggressive LDL and CV risk reduction
  - In chronic stable CAD patients: The FDC is not indicated as DAPT is not indicated in this situation.
- The FDC may be indicated for the duration DAPT is given. The duration depends on the bleeding and ischemic risk. Post ACS: risk of ischemia is high in first 3 months.
  - Standard guidelines should be followed: DAPT to be given for at least a year. The duration can be extended up to 30 months.
  - Clinicians can use short DAPT (<6 months) and ultra-short DAPT (1 month) based on patient's bleeding and ischemic risk. So individualization of DAPT is important.
- *Positioning of FDC in patients requiring DAPT + statin for a year*:

Most clinicians initially prefer to give aspirin, clopidogrel and rosuvastatin, as free drug combinations for 3-6 months. After 3-6 months, FDC can be started in patients with HBR and low ischemic risk who need to be continued on DAPT + statin for a year. The FDC serves the purpose of improving compliance, which is a major issue in these patients. The FDC may not be indicated in patients with LBR and high ischemic risk as usually ticagrelor or prasugrel is preferred in these patients.

- *Positioning of FDC in patients requiring DAPT + statin for longer duration (>24 months)*:
  - Patients with previous ACS/MI, chronic smokers, with renal dysfunction, diabetes, left ventricular ejection fraction <30%, stent diameter <3 mm, vein graft PCI, complex procedures, high CAD burden, and diffuse thrombosis (CAD+PAD) benefit from extended duration DAPT (>1 year).[22]
  - The FDC can be given to patients with high ischemic risk but LBR who require DAPT up to 6-12 months. The following set of patients are considered to high ischemic burden and increased risk for in-stent thrombosis/restenosis: Patients in whom multiple and long stents are deployed (total length is >60 mm), angioplasty is performed in left main PCA, bifurcation PCA, venous graft PCA, single remaining vessel, >3 vessels or chronic total occlusions (CTOs); angioplasty attempted in patients with in-stent thrombosis, CKD or diabetes.[25] In such patients this FDC can be continued for as long as 30-36 months especially in patients who are on clopidogrel + aspirin because of HBR.[25]
- In young patients (< 40 years) with MI: High intensity rosuvastatin (40 mg) with DAPT or FDC with additional 20 mg of rosuvastatin can be given up to 1 year followed by single antiplatelet therapy with statins.
- In patients who are bleeding:
  - FDC may be indicated if DAPT is initiated after the minor bleed is appropriately controlled. However, usually these patients are switched to antiplatelet monotherapy.
  - FDC is not indicated in patients with major bleeds as all antiplatelets, anticoagulants and antithrombotic drugs are stopped
- The FDC is not indicated in chronic stable CAD (either post PCI or CABG) as DAPT is not indicated in this situation.
- Post ACS/CAD patients are at high risk of thrombosis. Hence, high dose rosuvastatin is required.Most panelists recommended initial one-year use of this FDC that contains 20mg of rosuvastatin. If LDL goals not achieved in 4-6 weeks, additional 20 mg can be added as a separate pill to achieve LDL goal. FDC with lower dose rosuvastatin should be used in patients who are intolerant to higher statin dose.

(3) Role of FDC in patients with non-coronary artery disease :

3A. Panel discussion

The ESC guidelines on PAD[26]recommend a narrow window of one month of DAPT (clopidogrel + aspirin - class I recommendation) in patients undergoing carotid artery stenting. In patients with lower extremity artery disease undergoing percutaneous revascularization, DAPT (clopidogrel+aspirin) is again recommendedfor one month but recommendation is class IIA.[26]

However, in patients with CAD with PAD/or poly-vascular disease who have LBR, dual inhibition pathways (anticoagulant + antiplatelet) are preferred over DAPT.[27]In patients with PAD with HBR or thosebeing managed medically, monotherapy with either anticoagulant or antiplatelet agent can be used.[28] On the other hand, in patients with HBR undergoing stenting for ACS and/or PAD, the standard DAPT guidelines for ACS with clopidogrel + aspirin[5]can be followed easily.

3B. Positioning of the FDC in non-coronary artery disease

- The FDC can be used in patients with non-coronary artery disease (Carotid/PAD), especially in LBR patients
- In patients with both PAD/CAD undergoing PCI, the recommendation for ACS/chronic coronary syndrome should be followed.

(4) Role of platelet reactivity in positioning the FDC in post ACS/CAD/PAD :

4A. Panel discussion

Platelet reactivity is highest in ACS patients with diabetes, and hence these patients have high ischemic risk compared to ACS patients without diabetes[29]. However, platelet reactivity is found to be not clinically useful in assessing thrombosis risk.The ACCEL-STATIN study showed that ACS patients treated with clopidogrel and a CYP3A4 metabolized statin (atorvastatin) after PCI demonstrated high platelet reactivity (HPR) butwhen switched to non- CYP3A4 metabolized statin (rosuvastatin) resulted in significant decrease in the platelet reactivity and HPR prevalence was reduced by 24%[30]. There is no recommendation in guidelines to choose an antiplatelet drug based on platelet reactivity

4B. Role of platelet reactivity in positioning the FDC

- Routine assessment of platelet reactivity is not required while choosing the antiplatelet therapy and statin.
- Platelet reactivity is of importance in a patient with diabetes; patient who has developed stent thrombosis; patient who has a single surviving vessel which has been stented; patient with left main bifurcation stenting. It may be assessed in these patients to avoid adverse outcomes.
- Clinical trials are required to assess the role of HPR in assessing the choice of drugs and duration of the FDC.

(5) Bleeding risk calculator for monitoring FDC post ACS/CAD/PAD :

5A. Panel discussion

Many tools are available to calculate the bleeding risk[31]. However, most of these risk scores have been validated in western population.

5B. Role of bleeding risk calculators in monitoring the FDC

- In clinical practice, clinicians can rely on their experience and patient profile to assess bleeding risk of the patient.Patients with HBR include elderly, thin and frail, low weight, patients with ESRD/renal failure, patient who had previous bleeding, patients with moderate or severe liver diseases, patients already on anticoagulants.
- No bleeding risk calculator has been validated in Indian population. Hence, clinicians may use a bleeding risk calculator they are comfortable with and have the experience to assess the bleeding risk profile of the patient.

Table 1 — *Key Summary points in positioning of FDC*

Indications	Contraindications
FDC can be universally used in all patients post ACS/CAD as clopidogrel is safe to use irrespective of bleeding profile. The FDC may be indicated for the duration DAPT is given.	The FDC is not indicated in patients with complex PCIs or high ischemic risk as they will require a stronger antiplatelet like ticagrelor or prasugrel and higher statin dose than available in the FDC.
The FDC can be the combination of choice in HBR patients, both after PCI and after CABG: Can be given safely in patients with high bleeding risk, very elderly patients, frail patients, patients with ESRD or renal replacement therapy or when the patient is intolerant to prasugrel or ticagrelor.	The FDC is unlikely to be used in LBR patients with high ischemic risk as ticagrelor or prasugrel are preferred in these patients.
FDC can also be given in ACS/CAD patients with low bleeding and low ischemic risk.	The FDC is not indicated in chronic stable CAD (either post PCI or CABG) as DAPT is not indicated in this situation.
The FDC may be continued in adequately treated patients with minor bleeds but with strict monitoring. Usually a monotherapy is preferred in a patient who has developed a bleed.	The FDC needs to be stopped immediately in patients who develop major bleed
The FDC can be used in patients with non-coronary artery disease (Carotid/PAD), especially in LBR patients	

Abbreviations: CABG, coronary artery bypass graft;ESRD, end stage renal disease; PCI, percutaneous coronary intervention

Way Forward

The position paper is attempted to help clinicians understand the positioning of the FDC of rosuvstatin (10 or 20 mg) + clopidogrel (75 mg) + aspirin (75 mg) in post ACS/CAD and PAD patients. There is a felt need to disseminate this knowledge among clinicians to help them better manage their patients. There is also a need for prospective observation real-world study to observe how doctors are currently practicing use of DAPT + statin (FDC/free drug combinations) to understand the long-term outcomes. Also, it is important to assess which bleeding score is best for use in Indian population. Hopefully, the information in the position paper and the knowledge gaps identified in patient management will set the path forward for better management of these patients.

Ethics Compliance : This is a position statement based on consensus through a series of advisory board meetings. Hence, there are no issues of ethical compliance.

Conflicts of Interests : This study represents original work and has not been published elsewhere. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work, and have given final approval for the version to be published. Dr Shweta Sharma and Dr Kumar Gaurav declare that they work in the Medical Affairs Department in Dr. Reddy's Laboratories Ltd, Hyderabad, India.

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