GAVIN PUBLISHERS

Cardiology Research and Cardiovascular Medicine

Cantalupo A. Cardiolog Res Cardiovasc Med 2: CRCM-126.

DOI: 10.29011/2575-7083.000026

Editorial

The Janus Face of the Dual Anti-Platelet Therapy (DAPT) after Myocardial Infarction. What can be done to overcome the Risk by the Beneficial Potential of its use?

Anna Cantalupo*

Department of Pathology and Lab Medicine Center of Vascular Biology, Weill Cornell Medical College, New York, USA

***Corresponding author:** Anna Cantalupo, Department of Pathology and Lab Medicine Center of Vascular Biology, Weill Cornell Medical College, 1300 York Avenue, NY 10065, New York, USA. Tel: +13479448262; Email: dan.cantalupo@gmail.com

Citation: Cantalupo A (2017) The Janus Face of the Dual Anti-Platelet Therapy (DAPT) after Myocardial Infarction. What can be done to overcome the Risk by the Beneficial Potential of its use?. Cardiolog Res Cardiovasc Med 2: 126. DOI: 10.29011/2575-7083.100026

Received Date: 27 October, 2017; **Accepted Date:** 28 October, 2017; **Published Date:** 6 November, 2017

Editorial

Cardiovascular disease is the leading cause of death worldwide. Acute Myocardial Infarction (AMI) substantially contributes to this mortality, accounting for almost 1.8 million annual deaths [1]. Patients who had a myocardial infarction are at heightened risk for a recurrence of the ischemic event over the long term [2-4]. Thus, extensive research efforts were made to improve the management of available therapeutic tools that can limit the side effects and implement them in clinical practice. Based on over 35 randomized clinical trials enrolling more than 225,000 patients, dual anti-platelet therapy, DAPT, is among the most intensively investigated treatment options in the field of cardiovascular medicine and it is shown to reduce the risk of recurrent infarction in patients with ST-Elevation Myocardial Infarction (STEMI) [5-9], by decreasing the mortality rate of 12% [10].

DAPT consists of the combination of aspirin and an oral inhibitor of platelet P2Y12 receptor for Adenosine 5'-Diphosphate (ADP) that includes safer first-generation drugs such as ticlopidine and clopidogrel, as well as more potent and predictable drugs such as prasugrel or ticagrelor. DAPT is recommended for up to 12 months in STEMI patients who underwent primary Percutaneous Coronary Intervention (PCI) as well as for patients undergoing fibrinolysis with subsequent PCI [11,12].

Because continued DAPT beyond 12 months is associated with an increased risk of bleeding, research has more recently focused on the optimal treatment duration. Multiple studies have shown that shortening the treatment from 12 months (or longer) to 6 months reduces the event of bleeding, with no apparent trade-off in ischemic event [13,14]. For example, the PROlonging Dual Antiplatelet Treatment After Grading stent-induced Intimal hyperplasia study (PRODIGY) showed that individuals with high bleeding risk (bleeding score > 40 as defined by the CRUSADE) treated with DAPT for 24 months had bleeding complications or needed transfusion with no additional ischemic benefits compared to patients treated for 6 months; whereas, patients with a CRUSADE bleeding score < 40 did not show such bleeding liability [14,15].

Why is it necessary to investigate on the optimal DAPT duration? In 2004, a study by McFadden et al reported 4 cases of late and very late stent thrombosis occurring after first-generation Drug-Eluting Stent (DES) implantation [16]. that resulted in myocardial infarction. All these cases occurred soon after the interruption of the antiplatelet therapy. Despite DAPT remains the mostly effective preventive treatment for stent thrombosis across the board, the risk of bleeding associated with DAPT beyond 1 year is higher compared to the small benefits observed in terms of stent thrombosis prevention [17] and along with the advent of safer newer- generation DESs, prolonged DAPT appears unnecessary. On the other hand, there is emerging evidence that DAPT reduces the long-term risk of non-stent-related MI as well as stroke.

According to the data collected from the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial, extension of DAPT up to 3 years can be beneficial [18]. More specifically, PEGASUS-TIMI 54 trial analyze a total of 21,162 patients on aspirin treatment plus ticagrelor (90 or 60 mg b.i.d.) or placebo and show a reduction of Major Adverse Cardiovascular Events (MACE) with ticagrelor at both doses compared to placebo (hazard ratio, HR 0.85, 95% Confidence Interval [CI] 0.75-0.96, P=0.008 for 90 mg vs. placebo; HR 0.84, 95% CI 0.74-0.95; P=0.004 for 60 mg vs. placebo]. Despite the fact that the incidence of bleeding in both ticagrelor groups was significantly augmented compared to the aspirin monotherapy (HR 2.32, 95% CI 1.68 to

3.21; P < 0.001, and HR 2.69, 95% CI 1.96-3.70; P < 0.001 in the 60 mg and 90 mg ticagrelor groups) [18], regulatory agencies have approved ticagrelor 60 mg b.i.d for patients who have tolerated DAPT without bleeding complications and having one additional risk factor for ischemic event. Moreover, it is recommended to prescribe gastric protection (such as a protonic pump inhibitor, PPI) for patients with a history of gastric bleeding or with multiple factors for bleeding risk, such as advanced age, concomitant use of other anticoagulants, NSAID or SAID, Helicobacter pylori infection [19-21].

Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 51 (ATLASACS 2-TIMI 51) trial tested the addition of rivaroxaban, a factor Xa antagonist, to aspirin and clopidogrel following ACS [22]. The analysis showed that low dose of rivaroxaban mg twice (2.5 daily) reduced the composite primary endpoint of cardiovascular death, MI, or stroke, but also all-cause mortality, over a mean follow-up month of 13. Stent thrombosis was reduced by one- third. However, this was associated with a three-fold increase in non-CABG-related major bleeding and intracranial haemorrhage. Importantly, 5 mg of rivaroxaban did not reduce the death for cardiovascular or any other causes, but increased the risk of bleeding. Based on the ATLAS ACS 2-TIMI mg 51 trial, dose of rivaroxaban 2.5 may be considered in patients at low bleeding rish whoc receive aspirin and clopidogrel after STEMI [22].

Assessing the balance between ischemia and bleeding risk for any given DAPT duration can be challenging for patients and clinicians. The introduction of risk scores might be a valuable guide to tailor DAPT duration in order to maximize ischemic protection and minimize bleeding risks in each patient [14,23]. To achieve this goal the analysis of data collected from the DAPT study allowed to identify nine factors [age, congestive heart failure/low Left Ventricular Ejection Fraction (LVEF), vein graft stenting, MI at presentation, prior MI or PCI, diabetes, stent diameter <3 mm, smoking and paclitaxel-eluting stent] predicting whether the patient will receive the greatest benefit or will experience the most harm from continuation of DAPT beyond 1 year [24]. A simplified risk score, ranging from -2 to 10, was generated to predict the risk/benefit potential per each patient. A high-risk score (i.e. a score ≥ 2) included patients who showed a reduction in MI/stent thrombosis after 30-month DAPT, with only a slight increase in bleeding. As opposite, a low-risk score (< 2) selected patients on prolonged DAPT who did not have any additional protection from an ischemic event, with a marked increase in bleeding. However, additional validation of the DAPT score to guide DAPT duration is needed, especially in the context of less well-selected patients as compared to those recruited in the DAPT trial and undergoing treatment with new-generation DES only.

Despite DAPT has increased overtime in clinical practice, its "Janus-faced" nature requires an effort to mitigate the risk of bleeding complications while the patient is on DAPT. It highly reduces the risk of MI recurrence (12%), but on the other hand it increases the risk of bleeding especially when it extended up to 1 year or more. In order to control such undesirable effect, different approaches can be considered. First, it is important to control modifiable risk factors for bleeding, such as hypertension or concomitant use of another anticoagulant. Second, it can be managed the dose of the oral anticoagulant and use low dose of aspirin, low dose of P2Y12 inhibitor as appropriate. Of note, the progressive refinement of P2Y12 inhibition strategiesincreases the possibility to select the appropriate anticoagulant per each patient if drug-specific contraindications exist. Furthermore, it is fundamental to associate PPI as routine therapy to prevent gastric bleeding. Finally, the benefits of prolonged DAPT, especially for mortality endpoints, appear highly dependent on each patient cardiovascular history [such as priorACS/MI vs. stable CAD], and prediction rules to estimate on-DAPT beneficial (reduction of ischemic > bleeding)/ risk (reduction of ischemic < bleeding) potential have been developed, thus an individualized approach based on ischemic vs. bleeding risk assessment is warranted.

References

1. Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M, et al. (2016) Cardiovascular disease in Europe.epidemiological update 2016. European Heart Journal 37: 3232-3245.

2. Bhatt DL, Eagle KA, Ohman EM, Hirsch AT, Goto, S et al. (2010) Comparative determinants of 4-yearcardiovascular event rates in stable outpatients at risk of or with atherothrombosis JAMA 304: 1350-1357.

3. Fox KA, Carruthers KF, Dunbar DR, Graham C, Manning JR, et al. (2010) Underestimated and under- recognized: the late consequences of acute coronary syndrome (GRACE UK-Belgian Study). European Heart Journal 31: 2755-2764.

4. Jernberg T, Hasvold P, Henriksson M, Hjelm H, Thuresson M, et al. (2015) Cardiovascular risk in post- myocardial infarction patients: nationwide real-world data demonstrate the importance of a long-term-perspective. European Heart Journal 36: 1163-1170.

5. Collins R, MacMahon S, Flather M, Baigent C, Remvig L, et al. (1996) Clinical effects of anticoagulant therapy in suspected acute myocardial infarction systematic overview of randomized trials. BMJ 313: 652-659.

6. Eikelboom JW, Quinlan DJ, Mehta SR, Turpie AG, Menown IB, et al. (2005) Unfractionated and low-molwcular-weight heparin as adjuncts to thrombolysis in aspirin-treated patients with ST-elevation acute myocardial infarction a meta-analysis of the randomized trials. Circulation 112: 3855-3867.

7. Antman EM, Morrow DA, McCabe CH, Murphy SA, Ruda M, et al. (2006) Enoxaparin versus unfractioned heparin with fibrinolysis for ST-elevation myocardial infarction. The New England Journal of Medicine 354: 1477-1488.

8. Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, et al. (2006) Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction the OASIS-6 randomized trial. JAMA 295: 1519-1530.

9. Stone GW, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, et al. (2008) Bivalirudin during primary PCI in acute myocardial infarction. The New England Journal of Medicine 358: 2218-2230.

10. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, et al. (2016) Heart disease and stroke statistics- 2016 update: a report from the American Heart Association. Circulation 133: e38-360.

11. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, et al. (2007) Prasugrel versus clopidogrel in patients with acute coronary syndromes. The New England Journal of Medicine 357: 2001-2015.

12. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, et al. (2009) Ticagrelor versus clopidogrel in patients with acute coronary syndromes. The New England Journal of Medicine 361: 1045-1057.

13. Valmigli M, Ariotti S, Costa F (2015) Duration of dual antiplatelet therapy after drug-eluting stent implantation: will we ever reach a consensus? European Heart Journal 36: 1219-1222.

14. Costa F, Tijssen JG, Ariotti S, Giatti S, Moscarella E, et al. (2015) Incremental value of the CRUSADE, ACUITY, and HAS-BLED Risk Scores for the Prediction of Hemorrhagic Events After Coronary Stent Implantation in Patients Undergoing Long or Short Duration of Dual Antiplatelet Therapy. Journal of the American Heart Association 4e: 002524.

15. Costa F, Vranckx P, Leonardi S, Moscarella E, Ando G, et al. (2015) Impact of clinical presentation on ischaemic and bleeding outcomes in patients receiving 6- or 24-month duration of dual-antiplatelet therapy after stent implantation: a pre-specified analysis from the PRODIGY (Prolonging Dual-Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia) trial. European Heart Journal 36: 1242- 1251.

16. McFadden EP, Stabile E, Regar E, Cheneau E, Ong AT, et al. (2004) Late thrombosis in drug-elutingcoronary stents after discontinuation of antiplatelet therapy. Lancet 364: 1519-1521.

17. Shah Z, Masoomi R, Tadros P (2015) Managing antiplatelet therapy and anticoagulants in patients with coronary artery disease and atrial fibrillation. Journal of Atrial Fibrillation 8: 54-64.

18. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, et al. (2015) Long-term use of ticagrelor in patients with prior myocardial infarction. The New England Journal of Medicine 372: 1791-1800.

19. Agewall S, Cattaneo M, Collet JP, Andreotti F, Lip GY, et al. (2013) Expert position paper on the use of proton pump inhibitor in patients with cardiovascular disease and antithrombotic therapy. European Heart Journal 34: 1708-1713.

20. Bhatt DL, Cryer BL, Contant CF, Cohen M, Lanas A, et al. (2010) Clopidogrel with or without omeprazole in coronary heart disease. The New England Journal of Medicine 363: 1909-1917.

21. Gargiulo G, Costa F, Ariotti S, Biscaglia S, Campo G, et al. (2016) Impact of proton pump inhibitors on clinical outcomes in patients treated with a 6- or 24-month dual-antiplatelet therapy duration: Insights from the PROlonging Dual-antiplatelet treatment after Grading stent-induced Intimal hyperplasia studY trial. American Heart Journal 174: 95-102.

22. Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, et al. (2012) ATLAS ACS 2–TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. The New England Journal of Medicine 366: 9-19.

23. Bueno H, Fernandez-Aviles F (2012) Use of risk scores in acute coronary syndromes. Heart 98: 162-168.

24. Yeh RW, Secemsky EA, Kereiakes DJ, Normand SL, Gershlick AH, et al. (2016) Development and validation of a prediction yearruleafterfor benefit and harm of dual antiplatelet therapy beyond 1 percutaneous coronary intervention. JAMA 315: 1735-1749.