Review Article

High Bleeding Risk (HBR) patients Percutaneous Coronary Intervention-a Challenge to Deal with

AHM Waliul Islam[1], AQM Reza[2], Sham Munwar[3], Shahabuddin Talukder[4]

Abstract:

Coronary artery disease (CAD) is one of the leading causes of death in our patient population. In the era of cardiovascular intervention, Percutaneous coronary intervention (PCI) is one of the most important modalities in treating these group of patients. Several CAD risks factors and co-morbid conditions are key responsible factor of procedural success. High bleeding risk (HBR) patients undergoing PCI is not an uncommon phenomenon. Incidences and prevalence of HBR patients with CAD and their management by PCI is not well addressed in our literature. PCI in HBR patients carries potential risk of intracranial hemorrhage (ICH) and life-threatening bleeding. Therefore, careful pre-PCI assessment of possible risk or threats of post-PCI complications in patients with HBR are deem necessitate to understand. We recommend forming multicenter common consensus and to form a guideline in treating HBR patient by PCI. Thus, to reduce post procedural complication and subsequent improvement of mortality and morbidity in HBR patients undergoing PCI in both ST segment elevated myocardial infarction (STEMI) and as well as non-STEMI.

Key word: *CAD, HBR, PCI, ICH and STEMI*

(Bangladesh Heart Journal 2021; 36(2): 133-138)

Percutaneous Coronary intervention (PCI) is an important and popular treating modality in patients with CAD in the settings of ST segment elevated myocardial infarction (STEMI) and non-(STEMI). With the available facilities and advent of interventional procedures, enrichment of well experienced interventionist, PCI in Bangladesh, has reached its level high in national and international arena of interventional cardiology. Patients with acute STEMI are posing potential risk of sudden cardiac arrest and death. Primary PCI is a lifesaving modality in treating acute STEMI patients by primary PCI within 6hrs of MI and provides better myocardial salvages.[1] Many of the big city and district level hospital has cardiac Cath lab, where Primary PCI can be offered. Thus, these subsets of patient are preventing from the major adverse cardiac events like LVF, death, cardiac arrhythmia, and recurrent hospitalization.

Over two and half decades, since our journey towards cardiovascular intervention, many of the centers providing state of the art ACC/AHA and ESC guideline recommended therapy by PCI, in treating STEMI patients and patients with CAD.[2-3] Post PCI stent thrombosis and ischemic stroke and bleeding has not been well addressed or not well known in our patient perspective. Exact data on post PCI bleeding in our population, especially in High bleeding risk (HBR) is not available in the literature.

Patients with high bleeding risk (HBR) are in potential threat to successful PCI and complications. Possible untoward effects with Intra-cranial hemorrhage (ICH) or bleeding might complicate the post procedural survival outcome, along with, the increase of mortality and

1. Consultant, Interventional Cardiology, Evercare Hospital Dhaka, Bangladesh.
2. Sr. Consultant, Interventional Cardiology, Evercare Hospital, Bangladesh.
3. Sr. Consultant, Interventional Cardiology, Evercare Hospital, Bangladesh.
4. Sr. Consultant, Interventional Cardiology, Evercare Hospital, Bangladesh.

Address for Correspondence: Prof. Dr. AHM Waliul Islam, Consultant Interventional Cardiology, Evercare Hospital Dhaka, Bangladesh. Mobile: +8801713228884, Email: waliull.islam@evercarebd.com

DOI: https://doi.org/10.3329/bhj.v36i2.56039

morbidity. Academic consortium for HBR consensus recommend[4] *major criteria* are anticipated use of long term oral anticoagulants (OAC), Severe or End stage CKD (eGFR, <30mL/min, Anemia (Hb <11gm/dl), Spontaneous bleeding requiring hospitalization or transfusion in the past 6 month or anytime , if recurrent, moderate or severe baseline thrombocytopenia <100,000cmm3), Chronic bleeding diathesis, Liver cirrhosis with portal HTN, Active malignancy previous spontaneous ICH at any time, previous traumatic ICH within past 12 month, presence of bAVM, moderate to severe ischemic stroke within past 6 month, nondeferrable major surgery on DAPT, recent major surgery or major trauma within 30 day prior PCI. Among the *Minor criteria* Age>75yrs, moderate CKD (eGFR 30-59mL/min), Hemoglobin 11-12.9g/dl), spontaneous bleeding requiring hospitalization or transfusion within the past 12 month not meeting the major criterion, long-term uses of NSAIDS or Steroids, any ischemic stroke at any time not meeting the major criterion.[4]

Patients with ST-elevation Myocardial infarction (STEMI) who are undergoing primary percutaneous coronary intervention (PCI) are at high risk of ischemic and bleeding events, both of which strongly affect subsequent morbidity and mortality.[5-6] Therefore the selection of optimal antithrombotic in STEMI patients after PCI may requires careful evaluation and offsetting risk of ischemia and bleeding .[7] Usually, highest rate of ischemic events occurs in first few days or weeks after STEMI, a less potent antiplatelet regimen could offer a favorable balance of ischemic protection versus bleeding avoidance.[8-9] Therefore, Identification and managements of patients at high bleeding risk undergoing PCI are of major concern. The academic research consortium for high bleeding risk (ARC-HBR) developed a consensus definition of high bleeding risk. The proposed ARC-HBR consensus definition of HBR in clinical trials evaluating the safety and effectiveness of drugs and devices for patient undergoing percutaneous coronary intervention (PCI).[4]

High bleeding Risk (HBR) is defined as a bleeding academic consortium (BARC) 3 or 5 bleeding risk of >4% at 1 year or a risk of an intracranial hemorrhage (ICH) of >1% at 1 year. Thus, a major criterion for ARC-HBR is defined as any criterion, that in isolation is considered to confer a BARC 3 or 5 bleeding risk of >4% at 1 year or any criterion considered to be associated with a risk of ICH of >1% at 1 year. A minor criterion is defined as any criterion that in isolation is considered to confer increased bleeding risk, with BARC 3 or 5 bleeding rate of <4% at 1 year. The cut-off value of 4% for BARC 3 or 5 bleeding was based on consensus of the participants taking into account that 1 year major bleeding rates in trials of DAPT use after PCI which largely excluded patients at HBR, were <3% and that in DES trial enrolling patients at HBR , 1 year BARC 3 to 5 bleeding rates were 7.2% in LEADERS FREE trial[10] and 4.2% in ZEUS-HBR[11] despite 1 moth uses of DAPT after PCI and in SENIOR trial[12] was 3.5% in which age >75 were only inclusion criteria. The 2017 ESC guideline focused update on DAPT in coronary artery disease (CAD) recommended (class IIb level of evidence A) that uses of scores PRCISE-DAPT (predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy) and DAPT scores may be considered to guide antiplatelet therapy after PCI.[13]

In our patient perspective, it is not well known about exact number of HBR patients undergoing PCI. Almost 30% of the PCI of all-comers who participated in BIO-RESORT trial were in HBR. They also have an increased risk of ischemic events and thus represents a population with an overall high risk of adverse clinical outcome.[14] Many PCI patients might have an increased bleeding risk, but exact proportion depends on HBR criteria, and many be higher in patients with acute coronary syndrome.[15]

The evolution of percutaneous coronary intervention (PCI) over the last several decades has facilitated treatment for extremely complex patients. Ischemic events after coronary stenting declined over the years with the advent of newer drug eluting thin struts stents. DAPT plays a very important role in preventing post PCI stent thrombosis and In-stent restenosis. Uses of DAPT types and duration is important in this subset of HBR patient with both STEMI and non-STEMI. However, prolong uses of DAPT to have stronger and longer inhibition of platelets, the coincident of bleeding complication is increased specially in patient with HBR. To reduce this complication, optimal patient identification is required before pharmacological and interventional approach. In the early, uses of first-generation DES, DAPT recommended for 3-6 months.[16-18] Later, DAPT extended to 12 months due to possibility of stent thrombosis (ST).[19] Randomized trials comparing DES and BMS with DAPT of 1 month in patients perceived to be increased bleeding risk showed superior safety and efficacy with DES.[10-12] The European Antiplatelet Therapy Guide paved the way for one-month DAPT in patients with stable coronary artery disease and HBR ; and 6 months for ACS (class IIb and II c recommendation).[13] Similarly, the 2016 American

College of Cardiology/ American Heart Association (ACC / AHA) Recommendations consider it reasonable to discontinue DAPT after 6 months for patients with ACS after PCI and HBR (Class IIb recommendation, C-LD level of evidence).[20-22]

Most patients after PCI treated with DES that elute an antiproliferative drug from the polymer coating. Life-long presence of durable polymers may induce vessel wall inflammation, delaying arterial healing with subsequent stent thrombosis or MI.[23] To overcome this thin-strut biodegradable polymer DES. Although guideline recommended contemporary uses of DES over first-generation DES and BMS in patients going PCI.[24] meta-analysis of clinical trials showed no unequivocal benefit of BP-DES over DP-DES, but there might be advantage of BP-DES in high-risk patients.[25] Patients with High bleeding risk who undergo percutaneous coronary intervention also have increased risk of ischemic events and represents an overall high-risk population. In clinical practice, a substantial proportion of PCI patients are at HBR.[26-27]

The absolute risk of ischemic events was highest in early after the PCI, then it exponentially decayed overtime. Thus, it emphasized that the uses of most potent antiplatelet may have greatest utility in improving prognosis. On the other hand, absolute rate of bleeding was high in early after PCI, more potent agent may harm at this time. Literature has documented that procedural and post procedural uses of Bivalirudin rather than unfractionated heparin and GP Inhibitor may results in greater risk for ST but less bleeding. These offsetting risk can be avoided by routine uses of bivalirudin infusion at 1.75mg/kg/h for 3-to-4-hour post PCI, which may eliminate excess acute risk of ST without increasing bleeding.[28,13] Intensification of P2Y12-receptor inhibition by uses of intravenous cangrelor compared with clopidogrel during the PCI procedure and first 2 to 4 hour thereafter favorably reduces the acute and 48-hours rate of MI and stent thrombosis without affecting increasing major bleeding.[29]

Although the uses of prasugrel rather than the clopidogrel in patients with acute coronary syndrome was highly effective in reducing adverse ischemic events early after PCI, the excessive bleeding complication with irreversible agents offset much of its benefit.[30] In the PLATO (Platelet inhibition and patients' outcome) trial, both STEMI and Non-STEMI patients were treated with Aspirin plus Ticagrelor rather than Aspirin with Clopidogrel, experienced a 1-year reduction of stent thrombosis, MI, cardiac mortality and noncardiac mortality, despite a modest increase in non-CABG related major bleeding.[22]

In the HORIZON AMI trial, in patients with STEMI treated with primary PCI on a background of aspirin and clopidogrel for 1 year, the risk for adverse ischemic and bleeding events was highest after the procedure and declined overtime.[31-32]

Coronary stenting in patients who need long-term oral anticoagulant (OAC), poses potential challenges regarding the best antithrombotic strategy. Coronary stenting requires an initial period of DAPT with aspirin and P2Y12 inhibitor to prevent stent thrombosis.[33,13] Yet high risk patient with atrial fibrillation needs OAC to mitigate the risk of stroke or systemic embolism, further amplifying the bleeding risk of DAPT.[34] In fact, called Triple antithrombotic therapy, has been associated with to a greater risk of major bleeding.[35] undergoing coronary intervention is at higher bleeding risk due to the concomitant need for oral anticoagulant and antiplatelet therapy. RE-DUAL PCI trial demonstrated better safety with dual antithrombotic therapy (Dabigatran and Clopidogrel) compared to triple antithrombotic therapy (warfarin, Clopidogrel or Ticagrelor and aspirin).[36]

Therefore, optimum balance of ischemia suppression and implementation of bleeding avoidance strategies also essential, especially in the acute and sub-acute phase of primary PCI. Several risk stratification systems (score) have emerged in HBR patients with increasing data and information on the adverse impact of hemorrhagic incidents on post PCI outcomes. Among them, CRUSADE score, ACTION score, ACUITY / HORIZON MI score and HORIZON-MI score are mentionable. [37] In the PORECISE-DAPT study showed prolong DAPT >6 months post PCI in HBR patients increased bleeding without reducing ischemic events.[38] PLATO-a study of platelet inhibition and patient outcome-Ticagrelor associated with 20% higher risk of non-cardiac bleeding and 30% higher incidence of ICH compared with clopidogrel.[39] I TIMI TRITON-8 prasugrel is associated with 30% higher incidence of major bleeding in patients >75yrs age, with a history of stroke or weight <60kg.[40] Combination of aspirin and clopidogrel or ticagrelor for 6 months after PCI is recommended in ESC guideline for patients with HBR (class IIa, level of evidence B, in the year 2016, ACC/AHA recommendations, use of ticagrelor instead of clopidogrel in this case is class IIa level of evidence B-R.[22]

Since, the journey of PCI to manage both STEMI and non-STEMI patients begun two and half decade ago, interventional cardiology reaches its level high in national and international arena in treating STEMI, non-0STEMI,

CTO lesion, Complex PCI, LM Bifurcation PCI, Retrograde CTO PCI- both ipsi-lateral and contralateral approach. Many of the Center doing round the clock PCI for STEMI. In pandemic, pharmaco-invasive therapy replaces primary PCI, since, in our country covid dedicated Cath lab not available.[41] Treating HBR patient especially post-CABG with background end stage renal disease with or without hemodialysis are presenting with more complex, calcified disease, which are in potential high risk of post PCI bleeding. Treating AF with CAD or patient of post AVR or MVR CAD also in high risk of bleeding due to OAC, is not uncommon in our routine interventional procedure.

To avoid post procedural bleeding or intracranial hemorrhage, in these subsets of population, needs to address well before proceeding to PCI. It is mandatory, to examine HBR patients by careful history taking, assessment of potential threat and preparedness to deal the complication prior to proceed to PCI. Potential risk of ICH or life-threatening bleeding might jeopardize the success of PCI.

In the literature, exact percentage of Bangladeshi patient with HBR going for PCI is not well addressed or known. Therefore, we recommend forming a common consensus to develop a national guideline through cardiovascular and interventional society, if possible, to categorize Bangladeshi HBR patients prior PCI. Also, need randomized multicenter comparative study to assess better survival outcome with reduction of major adverse cardiac events after PCI in this subset of Bangladeshi patients. No doubt, this will help to take care of HBR patient in a safer way to intervene when needed without any potential life-threatening complication. Also, need to set the DAPT protocol with or without OAC with possible shorter duration, thus, to avoid ICH or bleeding after PCI.

References:

1. O'Gara PT, Kushner FG, Ascheim DD, et all. 2013 ACCF/ AHA guideline for the management of ST segment elevation myocardial infarction: a report of the American college of cardiology foundation/ American Heart Association Task Force on Practice guideline. J Am Coll Cardiol 2013; 61: e78-e140.'
2. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial in patients presenting ST segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018; 39(2): 119-177.
3. Kushner FG, Hand M, Smith SC Jr, et al. 2019 focused updates: ACC/AHA guidelines for the management of patients of STEMI and ACC/AHA/ SCAI guidelines on percutaneous coronary intervention. A report of the American College of Cardiology Foundation/ American Heart Association task force on practice guidelines. J Am Coll Cardiol. 2009; 54:2205-2241.
4. Islam AHMW, Munwar S, Talukder S, et al. Primary Percutaneous Coronary Intervention of ST-segment Elevated Myocardial Infarction-Experiences in a Tertiary Care Hospital Cardiovasc j 2021; 13(2): 154-163
4. Urban P, Roxana M, Colleran R, et al. Defining High Bleeding Risk in Patients Undergoing Percutaneous Coronary Intervention-A Consensus Document from the Academic Research Consortium for High Bleeding Risk. Circulation 2019; 140:240–261
5. Mehran R, Pocock S, Nikolsky E, eta al. Impact of bleeding on mortality after percutaneous coronary intervention results from a patient level pooled analysis of the REPLACE-2 and ACUITY and HORIZONS-MI trials. J Am Coll Cardiol Intv 2011; 4:654-64
6. Generux P, Glustino G, Witzenblchler B et al. Incidence, predictors, and impact of post discharge bleeding after percutaneous coronary intervention. J Am Coll Cardiol 2015; 66:1036-45
7. Gutierrez A, Bhatt DL, et al. Balancing the risk of stent thrombosis and major bleeding during primary percutaneous coronary intervention. Rur Heart J 2014; 35:2448-51
8. Steg PG, James S, Harrington RA, et al., Ticagrelor versus clopidogrel in patients with ST elevated acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: a platelet inhibition and patients' outcome (PLATO) trial subgroup analysis. Circulation 2010; 122:2131-41
9. Montalescot G, Wiviott SD, Braunwald E, et al. Prasugrel compared with Clopidogrel in patients undergoing percutaneous coronary intervention for ST Elevation myocardial infarction (TRITON TMI 38): double blind, randomized controlled trial Lancet 2009;373:723-31
10. Urban P, Meredith IT, Abizaid A, et al. Polymer-free drug-coated coronary stents in patient at high bleeding risk. N Eng J Med 2015,3173:2038-47

11. Ariotti S, Adamo M, Costa F, et al. ZEUS Investigators (2016) Is bare-metal stent implantation still justifiable in high bleeding risk patients undergoing percutaneous coronary intervention? A pre-specified analysis from the ZEUS trial. JACC Cardiovascular Interventions 9(5): 426–436

12. Varenne O, Cook S, Sideris G, et al. SENIOR investigators (2018) Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomized single-blind trial. The Lancet 391(10115): 41–50.

13. Valgimigli M, Bueano H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the task force for dual antiplatelet therapy in coronary artery disease of the European society of cardiology and the European association of Cardio-thoracic Surgery (EACTS). EHJ 2018;39;213-260

14. Byme RA, Stone GW, Ormiston J et al. Coronary balloon angioplasty, stents, and scaffolds. Lancet 2017; 390:781-92

15. von Birgelen C, Kok MM, van der Heijden LC, et al. Comparison of 3 biodegradable polymer and durable polymer everolimus-eluting and sirolimus eluting stents versus durable polymer zotarolimus eluting stents in allcomers with coronary artery disease (BIO_RESORT): a three-arm randomized non-inferiority trial. Lancet 2016; 388:2607-17

16. Stone GW, Midei M, Newman W, et al. SPIRIT III Investigators (2008) Comparison of an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease: a randomized trial. JAMA 299: 1903–1913.

17. Moses JW, Leon MB, Popma JJ, et al. SIRIUS Investigators (2003) Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. The New England Journal of Medicine 349(14): 1315– 1323. H

18. Kandzari DE, Leon MB, Popma JJ, et al. ENDEAVOR III Investigators (2006) Comparison of zotarolimus-eluting and sirolimus-eluting stents in patients with native coronary artery disease: a randomized controlled trial. Journal of the American College of Cardiology 48: 2440–2447

19. King SB, Hannan EL. Mounting Evidence for Safety and Improved Outcomes of Drug-Eluting Stenting but Is It the Stent? Circulation. 2008; 118:1783-1784.)

20. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, Malmberg K, Rupprecht H, Zhao F, Chrolavicius S, Copland I, Fox KA, Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) Investigators (2001) Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. The Lancet 358(9281): 527–533

21. Yusuf S, Zhao F, Mehta SR, et al. (2001) Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation [published correction appears in The New England Journal of Medicine 2001 Dec 6;345(23):1716] [published correction appears in The New England Journal of Medicine 2001 Nov 15;345(20):1506]. The New England Journal of Medicine 345(7): 494–502.

22. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients with Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2016. 134(10): e123–e155.

23. Joner M, Finn AV, Farb et al. Pathology of drug eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 2006; 48: 193-202

24. Windecker S, Kolh P, Alfonso F et al. 2014 ESC/EACTS guidelines on myocardial revascularization: the task force on myocardial revascularization of the European Society of Cardiology (ESC) and European

25. Palmerini T, Biondi-Zoccai G, Della Riva D et al. Clinical outcomes with bioabsorbable polymer versus durable polymer-based drug eluting and bare-metal stents: evidence from comprehensive meta-analysis. J Am Coll Cardiol 2014; 63:299-307Short- versus long-term dual antiplatelet therapy after drug-eluting stent implantation: an individual patient data pairwise and network meta-analysis

26. Zocca P, Kok MM, van der Heijden LC et al. High bleeding risk patients with acute coronary syndromes treated with contemporary drug-eluting

stents and clopidogrel or Ticagrelor: insights from CHANGE DAPT. Int J card 2018; 268:11-17

27. Alraies MC, Lee SY, Deng M et al. Effect of bleeding risk on type of stent used in patients presenting with acute coronary syndrome. Am J Cardiol. 2017; 120:1272-8 AJC 2017
28. Han Y, Guo J, Zheng Y,et al. Bivalirudin vs heparin with or without tirofiban during primary percutaneous coronary intervention in acute myocardial infarction: the BRIGHT randomized clinical trial. JAMA. 2015 Apr 7;313(13):1336-46
29. Bhatt DL, Stone GW, Mahaffey KW et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. N Eng J Med 2013; 368:1303-13
30. Wiviott SD, Braunwald E, Mccabe CH et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Eng J Med 2007; 357:2001-15
31. Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction, N Engl J Med. 2008 May 22;358(21): 2218-30.
32. Stone GW, Lansky AJ, Pocock SJ, et al. Paclitaxel eluting stents versus bare metal stents in acute myocardial infarction. N Eng J Med 2009; 360: 1946-59
33. Angiolillo DJ< Goodman SG, Bhatt DL et al. Antithrombotic therapy in patients with atrial fibrillation treated with oral anticoagulation undergoing percutaneous coronary intervention. Circulation 2018; 138:527-536
34. Capodanno D, Huber K, Mehran R et al. Management of antithrombotic therapy in atrial fibrillation patients undergoing PCI: JACC state of the art of Review. J Am Coll cardiol 2019:74:83-99
35. Van Rein N, Heide-jorgensen U, Lifering WM, et al. Major bleeding rates in atrial fibrillation patients on single, dual, or triple antithrombotic therapy. Circulation 2019; 139:775-786
36. Benjamin E. Peterson, Deepak L. Bhatt DL, et al. Evaluation of Dual Versus Triple Therapy by Landmark Analysis in the RE-DUAL PCI Trial J Am Coll Cardiol Intv. 2021 Apr, 14 (7) 768–780
37. Mehran R, Pocock SJ, Nikolsky E, et al.A Risk Score to Predict Bleeding in Patients With Acute Coronary Syndromes2010; 55(23):2567–9
38. Costa F, van Klaveren D, James S, et al. PRECISE-DAPT Study Investigators (2017) Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. The Lancet 389(10073): 1025–1034
39. Wallentin L, Becker RC, Budaj A, et al. for the PLATO Investigators (2009) Ticagrelor versus clopidogrel in patients with acute coronary syndromes. The New England Journal of Medicine 361(11): 1045–1057.
40. Wiviott SD, Braunwald E, McCabe CH, et al. TRITON–TIMI 38 Investigators (2007) Prasugrel versus clopidogrel in patients with acute coronary syndromes. The New England Journal of Medicine 357(20): 2001–2015
41. Islam AHM, Munwar S, Reza AQM et al. Pharmacoinvasive therapy to treat STEMI patient in Covid 19-Bangladesh Perspective. J Inv Clin Card 2019;1(2):75-81