High Risk PCI in Women
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Abstract:
Percutaneous Coronary Intervention (PCI) has been venturing into the population of high-risk which includes a large fraction of women. Cardiogenic Shock and acute myocardial infarction along with multiple other conditions have been presently included in the high-risk category for PCI. In the past, there had been no decline in post-myocardial infarction mortality. Women had been treated less aggressively and lacked involvement in multiple clinical trials regarding the use of interventional devices. It was also seen that treatment on women lacked following strict protocols. As a result, in-hospital mortality is higher in women in various conditions. Of those women classified as high-risk, CABG (regarded as the therapy providing complete revascularization) was often denied although eligible. Female sex was an independent risk factor for post-CABG mortality. Despite having a higher age-adjusted risk, they are equally likely as men to survive unto hospital discharge after PCI. High-risk PCI involving the use of Mechanical Circulatory support systems demonstrated higher rates of complications in women such as ‘transfusion-requiring-bleeding’ and earlier neurological events. Although, devices such as the Impella was shown to lower risk of repeat revascularization and provide better 90-day survival in non-emergent high-risk PCI, it also had a higher risk of bleeding events compared with the Intra-aortic balloon pump. Since women tend to have a higher rate of renal insufficiency, Impella allowed the support of the hemodynamics providing a renoprotective effect along with the leeway for higher rates of complete revascularization with PCI. Thus, in turn projected better survival.

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Key words: high risk PCI; women; interventional cardiology

Introduction:
Percutaneous coronary intervention (PCI) has advanced much in the recent ages with respects to techniques and devices that enable interventional cardiologists to operate not only on lower risk patients but also has ventured into patients at high-risk. The advancements in technology has progressed to an extent where Mechanical Circulatory Support (MCS) devices which once used to be a bridge-to-transplant, now is also a preferred destination therapy. The definition of ‘high-risk’ has also evolved to include clinical, hemodynamic and/or anatomic complexities. Complex high-risk indicated patients (CHIP) in commonness may include cases such as unprotected left main disease, last patent coronary conduit, patients of old-age, multi-vessel disease, severe coronary calcification, coronary vessel supplying a large myocardial territory with depressed ejection fraction (EF), concomitant cardiac, pulmonary or nephrological comorbidities.

Ischemic heart disease is the leading cause for both mortality and morbidity irrespective of gender. On the other hand, cardiogenic shock (CS) implies a state of hypotension due to low cardiac output resulting in tissue hypoxia and hypoperfusion. The two most common causes of CS are acute myocardial infarction (AMI - approximately 80% with acute left ventricular failure) and cardiac arrest (CA). Patients with cardiogenic shock suffer from high mortality and survivors have high morbidity. Patients with high risk, especially those with cardiogenic shock, require the use of mechanical circulatory support (MCS) so as to maximally normalize hemodynamics. There are 3 types of MCS devices-LVADs (Impella, Tandem Heart, HeartMate) IABP and...
ECMO. Their main function is to maintain or improve cardiac output in patients undergoing PCI. Of these, the Impella and IABP has been scrutinized in the past with the hope of improving mortality. Clinical trials and various studies have shown highly variable results over time, which also would be focused in this article.

**Background:**
In the past, amongst the patients with acute coronary syndromes (ACS) - which is 625,000 people per year - about 262,000 were women (2017). There has been no decline in post-Myocardial infarction mortality in women when comparing the period 2001-2003 and 2007-2009. Women have been treated less aggressively compared to men in the treatment of acute coronary syndromes. In 2005, the CRUSADE study, it was shown that women who experience NSTEMI, have taken longer time from symptom onset to presentation, and are less likely to perform the first electrocardiogram within 10 minutes of presentation.

Also, compared to men, there is evidence that women have higher unadjusted mortality, early intervention, reperfusion therapy and are provided lesser thienopyridines and glycoprotein inhibitors use. Today, in-hospital mortality is higher in women presenting with both STEMI and N-STEMI. Female sex is known to have higher mortality, lesser guideline-directed care and eligible reperfusion rates. Ventricular assist devices are far less likely used or included in trials on women compared to men, despite the similar prevalence of eligibility. Over the years, it can be assumed that it has been negated with improved ischemia to door to balloon times. Hence it is of great significance to magnify and review the impact of PCI in women categorized as high-risk.

**Mechanical Circulatory Support (MCS) devices:**
Technological development, increasing operator skill, ease of use, exploring the boundaries of indications of patients have expanded the use of MCS devices in PCI. Due to this, there has been an increasing trend with the use of MCS. The use of mechanical circulatory systems increased from 2.5% of all PCI procedures in 2008, to about 3.5% in 2016. And along with it, in-hospital mortality with LVAD implantation decreased significantly from 47.2% to 12.7% in the period 2005 to 2011. Despite the high rates of debilitation caused by CS as a successor of MI, in 2011 it was shown that there is a paucity of sex-specific safety, effectiveness, and outcomes data for mechanical support in the setting of CS, particularly prior to FDA approval. Most studies lack female participants.

Prior reports from registries concerning use of LVADs from 2015 INTERMACS had demonstrated a higher mortality in the female sex. Recent studies, 2019 INTERMACS has no such evidence demonstrating gender-disparity in mortality rates - thus hinting better outcomes with newer LVAD utilization. Although with promising results, the European Registry for Patients with Mechanical Circulatory Support (EUROMACS) noted that significantly more male patients received MCS compared to women. In the EUROMACS Registry (2011 to 2014) the need for right ventricular support was significantly more in women than men. There was significantly inferior survival rate in women vs. men in 1-year, 2-year and 3-year survival. This urges the need for better implementation of appropriate management protocols for women.

**Devices:**

**Impella:**

**Mechanism**
Impella (Abiomed Inc., Danvers, Massachusetts) is a device that is positioned across the aortic valve. During diastole, it flushes out the blood from the left ventricle so as to reduce diastolic wall stress, increasing the aortic and coronary pressures, simultaneously reducing coronary microvascular resistance. This allows recovery of stunned or hibernating myocardium. There are multiple variants of the device - Impella 2.5™
(pumps 2.5 l/min), Impella 5.0™ (pumps 2.5 l/min), Impella CP™ (pumps 4.0 l/min)\textsuperscript{16}.

**Intra-aortic balloon pump:**

*Mechanism*

There are two principles by which IABP allows assistance to the left ventricular functioning by alternating inflation and deflation situated inside the aorta - diastolic augmentation and systolic unloading\textsuperscript{17-18}. There occurs an increase in the aorto-coronary pressure gradient which allows higher flow of blood into the coronaries. Multiple studies have demonstrated highly variable results, such as no increase in coronary blood flow (CBF)\textsuperscript{19} in opposition to some studies demonstrating increase in distal blood flow\textsuperscript{20}. This works by inflation of balloon in the aorta during aortic valve closure, thus propelling blood into coronaries and distal aorta. Consequential active deflation of the balloon during isovolumetric contraction such as to assist the ventricle by reducing the oxygen demand\textsuperscript{15}.

**Tandem heart:**

*Mechanism*

The Tandem Heart is a percutaneously placed device where one end is penetrated into the femoral vein, passed via a transseptal perforation to the left atrium. The other end is placed into the aortic bifurcation via the femoral artery. This allows a bypass for blood from the left heart to the circulatory system hence reducing the workload and thus reducing oxygen demand of the myocardium. The flow rate achieved by this device of about ~4 l/min improves cardiac index, mean arterial pressure, reduces pulmonary capillary wedge pressure by the reduced filling of both ventricles\textsuperscript{15,21}.

**Extracorporeal membrane oxygenation:**

*Mechanism*

Extracorporeal membrane oxygenation (ECMO) takes blood from the venous circulation and oxygenates it to deliver the blood to the arterial circulation. It is the only type of MCS which oxygenates the blood. Contrastingly, it causes an increase in LV after load and thus raising the myocardial oxygen requirements. One of the pre-requisites is the necessity for anti-coagulation with heparin while setting up the ECMO\textsuperscript{15}. Conditions such as severe aortic stenosis, bleeding diathesis, stroke, recent hemorrhage, and uncontrolled sepsis contraindicates against ECMO\textsuperscript{22}.

**Review:**

*High-Risk PCI:*

The definition of high-risk PCI is ever-evolving and is yet to obtain a concrete form. At present, many parameters are set to form an inclusive criterion by a consensus by American College of Cardiology 2015. There are many reasons why women have a higher cardiac mortality compared to men of the same age. They include - smaller coronary arteries\textsuperscript{23-24}, abnormal coronary reactivity, microvascular dysfunction, predisposition to plaque erosion and distal embolization. A study by Campbell et al showed that women had higher arteriolar wall thickness and diffusion radius\textsuperscript{25}.

Women classified under high-risk have higher co-morbidities and hence higher mortality with CABG when compared to males with the same STS (Society of Thoracic Surgeons) scores\textsuperscript{26}. In a study to analyze sexual dimorphism in outcomes of those undergoing coronary angiography and percutaneous coronary intervention by the German Society of Cardiology, 2017, demonstrated that women have a 20% higher age-adjusted risk of death and of ischemic cardiac and cerebrovascular events. Women who have MI more often sustain a cardiac arrest compared to men. Higher rates of arrhythmias and peripheral artery embolisms are seen in women.

Despite such complications, and seeding high in the high-risk category, they are equally likely as men to survive unto hospital discharge after PCI\textsuperscript{27}. Earlier in 2004, that was not the case, as women with MI had higher in-hospital mortality compared to men\textsuperscript{28-39}. Exploring the reasons, women with STEMI developed more CS compared to men. Despite that, intervention with protected PCI using Impella, women demonstrated an equal likelihood of survival compared to men when instituted early in the treatment. It is also seen that women also were more often in cardiogenic shock at the time of MCS implantation compared to men, although, contrastingly studies show highly variable results both with lower or similar survival to males\textsuperscript{30}.

**Procedural Bleeding**

Women tend to have a higher chance of developing ‘transfusion-requiring-bleed’ after PCI, when compared to males\textsuperscript{11}. In a study in 2015, women were seen to have higher re-operations for bleeding complications\textsuperscript{16}. In a meta-analysis done recently, it was seen that LVADs resulted in increased bleeding complications.
compared to IABP. This is speculated due to their larger sheaths and more complex operations. Hence DAPT or anticoagulation after PCI must be monitored well to prevent such complications.

Metaanalysis and Other Studies Equating Impella to Iabp

A recent meta-analysis by Wenhai et al. (2019) from Baltimore demonstrates that neither IABP nor LVADs used in patient undergoing high-risk PCI, improved survival of patients over 30 days and 6 months (RR 0.96 95% CI 0.71–1.29; RR 1.23 95% CI 0.88–1.72) respectively [31]. Although, LVADs does reduce repeat revascularization (RR 0.26 95% CI 0.08–0.83), there was an increased risk of bleeding events compared to IABP (RR 2.85 95% CI 1.72–4.73). The PROTECT II Trial (2012) demonstrated that there is no mortality difference between Impella 2.5 and IABP during high-risk PCI in 30-day or 90-day mortality. On the contrary, in 90-day survival, Impella 2.5 outshone IABP depicting better survival trends when applied in non-emergent high-risk PCI. There were fewer rates of irreversible MACCE, death/stroke/MI/repeat revascularization the Impella 2.5 arm vs. that of IABP. This is essential to know, as LVADs demonstrate a higher risk in women to develop the first neurological event (1.44; 95% CI, 1.05–1.96; P=0.020) [30]. In 2013, use of IABP has been downgraded from Class I to a Class IIa recommendation due to no mortality benefit in early (30-day) post-infarct period in the Intra-aortic Balloon Pump Support for Myocardial Infarction with Cardiogenic Shock (IABP-SHOCK II) Trial.

No-Difference In Genders - Impella

A study was conducted in 2017 on 160 patients who were not in cardiogenic shock - with Impella 2.5 or Impella CP as the device of choice - for patients who were having an EF <35% additionally with another criteria of inclusion which included the use of atherectomy device, unprotected left main disease or multi-vessel disease. It was seen that there is no difference in clinical outcomes between the genders. A study on the cVAD registry with 180 patients showed that women were better beneficiaries than men to the use of the Impella 2.5 as pre-PCI. It was associated with a greater survival benefit to hospital discharge in women compared to men, despite a higher predicted risk of mortality and a greater revascularization failure rate for women. Overall, pre-PCI use of Impella produced lesser mortality rates than those who received a post-PCI support. This supported early initiation of hemodynamic support prior to PCI with Impella 2.5, in the setting of AMI complicated by CS. With the knowledge that women are at a higher risk of developing CS than men after STEMI, this evidence affirms to funnel the guidelines to the use of Impella 2.5 in women prior to PCI to obtain better survival. A study of 19,278 all comer patients including 5456 women in whom Impella was used showed that women suffered higher morbidity and mortality in high-risk group but not in the cardiogenic shock group. Weighing it with the evidence that women have higher bleeding risk compared to men with Impella use, the interventionist must decide between Impella and the IABP when considering bleeding, as it is one of the common causes of re-operation in women.

Significance Of Revascularization:

Complete revascularization is best achieved with CABG, that provides the most long-term mortality benefits when done in eligible patients. Unfortunately, complex high-risk indicated patients are more likely excluded from the CABG procedure due to other associated comorbidities, CAD severity and low ventricular function. Protected PCI is considered equally as safe as CABG. The female gender as such is an independent risk factor for mortality post-PCI. Considering gender, it is seen that more of the female sex was turned down from proceeding into CABG due to the higher prevalence of comorbidities. These patients would require hemodynamic support at the time of PCI. Thus, from the meta-analysis by Wenhai et al., the hemodynamic support using LVADs would be advisable to prevent revascularization in those women opting CABG.

Moreover, with the use of Impella, it was observed that more vessels were able to be treated, more stents used and enabled the use of atherectomy for plaque modification. This is enabled by their powerful hemodynamic support. In eventuality, this function of the Impella in turn accommodates the leeway to perform complete revascularization through PCI. Complete revascularization has shown to have better clinical outcomes than incomplete revascularization. Historically, success rate of revascularization as such is lower in women. There is no difference in clinical outcomes between males and women in in-hospital mortality and 30-day survival rates when performing revascularization in the setting of LVADs. In view of complete revascularization,
CvLPRIT, ACUITY and PRIMULTI trials supported complete revascularization for improved outcomes. A meta-analysis by Gaffar et al. done also suggests the use of single setting complete revascularization in acute coronary syndrome.

Renal
Women generally tend to have a higher rate of renal insufficiency compared to males-with-high-risk at baseline. The use of Impella allows to maintain appropriate perfusion to coronary and renal vessels, thus supporting hemodynamics. This helps to reduce the incidence of acute kidney injury. It will sustain its renoprotective effect inclusive in the presence of an underlying chronic kidney disease or reducing ejection fraction.

Device disparity: Impella vs. IABP
IABP counter pulsation and Impella has been compared and contrasted in various trials in the past. A higher cardiac index was seen in the Impella Group vs. the IABP group in the ISAR-SHOCK trial (2008). The SHOCK Trial registry depicted that cardiac power (i.e., the rate of energy input the systemic vasculature receives from the heart at the level of the aortic root, which represents the energy available to perfuse vital organs) must considered to the most important predictors for the outcome for patients with CS undergoing PCI.

Tandem Heart demonstrated no mortality benefit seen in the 30-day mortality when patients with CS were randomized to Tandem Heart and IABP.

Conclusion:
With the under-representation of women in clinical studies and lack of adherence to strict treatment protocols when deployed on female patients, it calls for the need to shed light on the advances in interventions among them in High-risk PCI. As women have higher age-adjusted risk and are often deferred from CABG, PCI stand the most opted route of treatment for most of them. The use of MCS shows better outcomes in women when compared to males. The use of Impella not only allows for compensating the hemodynamic chasm, but also allows higher rates of complete revascularization with PCI, hence offering better survival. Bleeding and neurological events do pose a risk higher in women than men. IABP offers a lesser risk of post-procedural bleeding when compared to Impella. Lastly, predictors such as cardiac power must be used in high-risk patients with cardiogenic shock prior to PCI for better outcomes.

References:


