27. Coronary Intervention: What a Physician Should Know?  
   Nihar Mehta, Harish Surwade

28. Current Status of Management of Rheumatic Heart Disease in India  
   Kunal Mahajan, Prakash Chand Negi, Sachin Sondhi

29. Role of Stress ECG in Preoperative Evaluation for Non-Cardiac Surgery  
   Neelima Singh, Sushma Trikha

30. Screening for Atrial Fibrillation for Stroke Prevention: Clinical Perspective  
   SB Gupta

31. Prevention of CVD in Diabetes: Taming the Dragon  
   Prabhash Chand Manoria, Pankaj Manoria, Sharad Kumar Parashar

32. Heart Failure 2021  
   Amal Kumar Banerjee

33. Asymptomatic Left Ventricular Dysfunction  
   Asha Mahilmaran

34. Cardiovascular Risk Assessment Tools  
   Ravikeerthy M

35. ARMOR—Arati’s Regime for Management of Rheumatic Fever—Against Rheumatic Heart Disease—A Great Milestone  
   Arati Lalchandani, Prem Singh, Arvind Kumar, Taruni Lalchandani

36. Evaluation and Management of Chronic Stable Angina: Physicians Perspective  
   Vibhu Khanna, Ankush Gupta, Sanya Chhikara

37. Optimal Therapy in ST-elevation Myocardial Infarction Patients Presenting after 24 hours  
   Gaurav Singhal, Dinesh Gautam, Sanjiv Maheshwari, Shekhar Kunal, Shyam Sunder

38. Management of Heart Failure in 2021—What Physician Must Know?  
   Alok Kumar Singh

39. Atherosclerotic Cardiovascular Prevention in 2020: Consideration of Gray Areas and Ways to Remedy It  
   Amarendra Kumar Sinha, Ashish Sinha, Nitin Kumar Sinha

40. SGLT2 Inhibitors in Heart Failure  
   NS Prasad

41. Dual Antiplatelet Therapy: Current Status  
   Sudha Vidyasagar

42. Novel Oral Anticoagulants: Which, When, and Where?  
   Vishwanath Krishnamurthy

43. Recent Practice Changing Landmark Trials of Cardiology  
   Gurbhej Singh, Ashish Kumar, Gurpreet S Wander

44. Iron Deficiency and Iron Deficiency Anemia in Chronic Heart Failure: A High Risk  
   Pramod Kumar Sinha

45. Peripartum Cardiomyopathy  
   Monika Maheshwari, Sneha Garg
Coronary Intervention is a continuously evolving field. Over the last four decades, the innovations in this field have made coronary intervention a safer, more effective, and widely available procedure. A combination of physiological and anatomical evaluation is possible for detailed objective evaluation of the coronary tree. The refinement in the hardware and stent technology as well as the imaging modalities have lead to better outcomes in even complex coronary anatomies. As physicians, it is essential to know the basics of coronary anatomy and hardware along with the indications and options of revascularization, individualized to every patient.

**Introduction**

The use of coronary interventions has grown rapidly over the last few years. New improvements in techniques, hardware, operator experience, pharmacology, and safety as shown by clinical studies have expanded the use of coronary interventions. First Percutaneous Transcatheter Coronary Angioplasty (PTCA) was performed by Dr Andreas Gruntzig on 16 September 1977 in Zurich, Switzerland, with a balloon catheter. Since then use of PTCA has grown leaps and bounds. Balloon angioplasty was replaced by Bare Metal Stent implantation to reduce the incidence of recoil, restenosis, and complications like dissections. Drug eluting stents (DES) were the next innovation, which have replaced the bare metal stents (BMS) since 2003. The DES consisted of an antiproliferative drug, which was slowly released into the vessel to further reduce the rate of restenosis. Over the last two decades, several refinements have been made to DES such as reduction of stent strut size, use of newer anti-proliferative drugs, bioabsorbable stents, etc. This has led to improved outcomes of PTCA over the years. The indications have expanded to more complex coronary lesions, which were previously treated by surgery as a default.

**Epidemiology**

The problem of coronary artery disease (CAD) or atherosclerotic lesions in coronary arteries has grown fourfold in India during last 40 years. Current epidemiological studies estimate its prevalence to be between 7% and 13% in urban and 2% and 7% in rural regions. According to epidemiological studies over 30 million cases of CAD are present in India. Of more than 10.5 million deaths reported in India annually, cardiovascular disease (CVD) led to 20.3% deaths in males and 16.9% deaths in females. As per 2010–2013 data, the proportionate mortality from CVD increased to 23% of deaths. The mortality varies from less than 10% in rural locations in less developed states to more than 35% in more developed urban locations. A study by Gajalakshmi et al. during 1995–1997 showed that CVD deaths are the highest (38.6%) in urban Chennai. Similar data are published by Joshi et al. from Andhra Pradesh.
Indications

See Table 1.

Relative Contraindications

- Congestive cardiac failure
- Acute or chronic renal failure (unless dialysis is planned)
- Acute stroke
- Active gastrointestinal bleeding
- Electrolyte imbalances
- Bleeding diathesis
- History of allergic reaction to iodinated contrast agent
- History of allergy or bronchospasm to aspirin
- Bacteremia

Coronary Angiography and Percutaneous Coronary Intervention

Preprocedure

Preprocedural wearing of a lead apron, thyroid shield, lead goggles, and a lead cap protects against potential radiation hazard. A preprocedural evaluation should include a note of the last oral intake, a history of drug and a history of previous experience with sedative or contrast agents.

The patient should be kept fasting for at least 3–4 hours before the start of the procedure. For diabetic patients, medications should be adjusted. Metformin should be stopped 48 hours before and after PCI to reduce the likelihood of lactic acidosis. Adequate hydration with IV fluids and N-Acetyl cysteine starting 12 hours before procedure in patients with mild renal dysfunction is advised for nephroprotection.

Strict aseptic precautions and cleaning and draping of the access sites should be done. The procedure is performed under local anesthesia in most cases with or without mild sedation.

Vascular Access

The procedure is usually preformed via the femoral or radial artery approach. Femoral artery access has a fairly straight course to the descending aorta, is larger and gives better catheter support during the procedure. However, complications like bleeding, pseudoaneurysms, retroperitoneal hematomas, or arteriovenous fistula are possible in 3–7% of cases. The radial artery is increasing in popularity as an access site due to early patient mobilization, reduced complications rates and fairly direct access into ascending aorta. Smaller sheath and catheter sizes (4F, 5F) have replaced the larger catheters (8F), which lead to lower access site complications.

Coronary Angiography/Arteriography

Once the vascular access has been secured by modified Seldinger technique, especially shaped coronary catheters are advanced up to the ascending aorta. They are engaged

TABLE 1

<table>
<thead>
<tr>
<th>Indications for coronary angiography</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coronary artery disease:</strong></td>
</tr>
<tr>
<td>• Asymptomatic:</td>
</tr>
<tr>
<td>- At high risk of coronary event based on noninvasive testing</td>
</tr>
<tr>
<td>• Symptomatic:</td>
</tr>
<tr>
<td>- Stable Angina with Canadian Cardiac Society Class II, III, or IV symptoms</td>
</tr>
<tr>
<td>- Unstable angina or Non-ST Elevation Myocardial Infarction (Acute Coronary Syndrome)</td>
</tr>
<tr>
<td>• ST Elevation Myocardial Infarction (STEMI): Reperfusion with a primary percutaneous coronary intervention (direct intervention without thrombolysis) or pharmaco-invasive approach (within 2–24 hours after thrombolysis) or Rescue PCI (in case of failed thrombolysis)</td>
</tr>
<tr>
<td>• Complications of STEMI: Acute pulmonary edema, Cardiogenic shock, Mechanical complications (Ventricular septal defect or Mitral regurgitation)</td>
</tr>
<tr>
<td><strong>Valvular heart disease:</strong></td>
</tr>
<tr>
<td>• Prior to valve replacement surgery in patients suspected of having coronary artery disease</td>
</tr>
<tr>
<td><strong>Cardiomyopathy:</strong></td>
</tr>
<tr>
<td>• Newly diagnosed cardiomyopathy suspected to be due to coronary artery disease</td>
</tr>
<tr>
<td>• Hypertrophic cardiomyopathy with angina</td>
</tr>
<tr>
<td><strong>Congestive cardiac failure:</strong></td>
</tr>
<tr>
<td>• New onset angina suspected to be due to coronary artery disease</td>
</tr>
<tr>
<td><strong>Congenital heart disease:</strong></td>
</tr>
<tr>
<td>• Suspected associated coronary artery anomalies</td>
</tr>
<tr>
<td><strong>Cardiac transplantation:</strong></td>
</tr>
<tr>
<td>• Preoperatively and post-transplant to detect coronary artery vasculopathy</td>
</tr>
<tr>
<td><strong>Others:</strong></td>
</tr>
<tr>
<td>• Survivors of sudden cardiac arrest</td>
</tr>
<tr>
<td>• Sustained monomorphic ventricular tachycardia or non-sustained polymorphic tachycardia</td>
</tr>
</tbody>
</table>
into the left or right coronary artery (RCA) and hand injections are made using a radiopaque contrast material. The radiographic images (cine angiography) are recorded in several different orthogonal views. The anatomy of the epicardial coronary arteries and coronary bypass grafts can be outlined.

**Normal Coronary Anatomy and Coronary Artery Disease**

Although coronary anatomy can be variable between individuals, in general there are two coronary ostia—the left and right. The left main coronary artery divides into the left anterior descending (LAD) and the left circumflex artery (LCx). The LAD gives septal and diagonal branches whereas the LCx gives obtuse marginal branches (Fig. 1A). In about 1–2% of individuals, a ramus intermedius branch directly arising from the left main coronary artery, between the LAD and the LCx.

The RCA divides distally into the posterior descending artery (PDA) and the posterior lateral artery/posterior left ventricular artery (PLV). This anatomy is called the right dominant circulation and is found in 85% of individuals (Fig. 1B). In about 5% of individuals, the PDA arises from the LCx, which is defined as left dominant circulation. The remaining 10% have a codominant circulation.

Coronary artery stenoses are visualized by coronary angiography as luminal narrowing and the degree of narrowing is referred to as percentage stenosis. The percentage stenosis is determined visually by comparing the most severely diseased area to the distal normal artery segment. A coronary stenosis of 40–70% is considered intermediate and more than 70% is considered significant.

Coronary calcification can be visualized during angiography before injecting the radiocontrast material. Collateral blood vessels can also be seen between one vessel and the distal part of a severely stenosed vessel. Other abnormalities like dissections, thrombus, coronary ectasia, and myocardial bridges can also be visualized during coronary angiography.1

**Patient Selection for Percutaneous Coronary Intervention (PCI)**

Patients with significant CAD can be revascularized by percutaneous transluminal coronary angioplasty (PTCA/PCI) or coronary artery bypass graft (CABG) surgery. The choice between PCI and CABG vary depending on the type of presentation and characteristics of coronary anatomy.

- Chronic stable angina: The main aim of treatment is to improve symptoms or reduce mortality:
  - In asymptomatic or mildly symptomatic patients, revascularization can be deferred if procedural risks/bleeding risks are high. PCI is warranted only if symptoms worsen or there is evidence of severe ischemia on noninvasive testing in spite of optimal medical therapy.
- Moderate to severely symptomatic patients should undergo ischemia-guided revascularization.
- Left main CAD, triple vessel disease or diabetic patients have better outcomes with CAGB surgery.
- Less severe multi-vessel disease with or without diabetes have equal outcomes with PCI and CAGB.

- Acute coronary syndromes: PCI is superior to optimal medical management due to high risk of mortality. PCI is preferred over CAGB surgery except in case of severe multi-vessel disease or anatomical factors which are not amenable to successful treatment.
- ST elevation myocardial infarction (STEMI):
  - Primary PCI (Primary angioplasty in Myocardial Infarction—PAMI) is a preferred strategy (direct intervention without thrombolysis).
  - In the pharmaco-invasive approach, patients are thrombolysed followed by PCI within 2–24 hours after thrombolysis.
  - In case of failed thrombolytic therapy (patients in whom there is ongoing angina 90 minutes after fibrinolysis and/or ECG persistently shows ST elevation), Rescue PCI should be performed.

- In patients presenting with cardiogenic shock or heart failure (HF), PCI is class I indication that increases survival.
- Several coronary arterial anatomical factors influence success and safety of PCI such as location of the lesion (proximal or distal), tortuosity, calcification, length of lesion, size of vessel, thrombus, or chronic total occlusion (>3 months in duration). Patients with unfavorable anatomy are candidates for CAGB surgery.
- Conversely, some patients are inoperable for CAGB surgery due to comorbidities such as advanced age, frailty, chronic obstructive pulmonary disease (COPD), or poor LV function.

### PTCA Procedure (Figs. 2 and 3)

Prior to the procedure, patients are given a loading dose of dual antiplatelet medications: aspirin (325 mg) and a P2Y12 inhibitor (clopidogrel 300–600 mg or prasugrel 60 mg or ticagrelor 180 mg) to prevent thrombotic complications.

The procedure is carried out under local anesthesia with or without mild sedation. Vascular access is obtained in the same way as outlined earlier using Seldingers technique. During the procedure, anticoagulation is achieved by using unfractionated heparin or bivalirudin (direct thrombin inhibitor). In the case of STEMI or large thrombus in the coronary arteries, intravenous glycoprotein IIb/IIIa inhibitors (abciximab, tirofiban, or eptifibatide) is used.

The most commonly used PCI equipment consists of four basic elements: a guiding catheter, a balloon catheter, a coronary guidewire, and a stent (Fig. 4).

Via the introducer sheath at the vascular access site, a guiding catheter is used to selectively cannulate the culprit coronary artery. All subsequent coronary hardware is passed into the coronary artery through the guiding catheter. A flexible guidewire is passed into the coronary artery across the stenosis and is positioned in the distal coronary artery. The guidewire acts as a guiding “rail” for all subsequent hardware to be passed in and out of the coronary arterial tree.

A balloon catheter is passed over the guidewire, positioned across the stenosis, and then dilated to stretch the coronary artery and displace the plaque to enlarge the coronary lumen thus improving blood flow. The balloon catheter is then removed over the guidewire, maintaining the position of the guidewire in the coronary artery.

A coronary stent is a stainless-steel mesh/scaffold which is available in a compressed state over a balloon catheter. It is passed over the guidewire, positioned across the stenosis and deployed by inflating the balloon. When the balloon is deflated, the stent stays in place in the coronary artery and the balloon catheter is removed. Normal blood flow is restored to the coronary artery. The guidewire, guiding catheter, and introducer sheath are subsequently removed. Hemostasis is achieved using manual pressure or vascular closure devices.

The patient is then transferred to a recovery area and then to the patient’s room. If no complications occur, the patient is discharged the next morning. The patient usually returns to work shortly (<7 days) thereafter.

### Mechanism of Angioplasty and Stenting and Stent Composition

**Mechanism of balloon angioplasty:** The inflated balloon exerts pressure against the plaque and the arterial wall, causing fracturing and splitting. Concentric (round or circumferential) lesions fracture and split at the thinnest and weakest points. Eccentric lesions split at the junction of the plaque and the normal arterial wall. Dissection
or separation of the plaque from the vessel wall releases the restraining effect caused by the lesion and results in a larger lumen.

**Mechanisms of stenting:** Placing a stent in the coronary artery leads to disruption and fracture of atheromatous plaque. The scaffold prevents elastic recoil of artery and leads to longitudinal compression of plaque material against the wall. The anti-proliferative drug inhibits the intimal proliferation and reduces the restenosis rates.

DES are made of a stainless-steel mesh/scaffold. They have a thin polymer coating, which holds an anti-proliferative drug, which is released into the atherosclerotic plaque slowly for 1-3 months. This reduces the rate of restenosis. The anti-proliferative drugs used are paclitaxel, sirolimus, everolimus, zotarolimus, or biolimus. Bioabsorbable vascular scaffold (BVS) stents were initially available, which gradually degraded over 2 years; however, the BVS stents were withdrawn due to late stent thrombosis.9

**Additional Interventional Devices**
Several other interventional devices are available such as thrombus aspiration catheters (to aspirate thrombus
in case of a STEMI), distal embolic protection devices (to protect the distal vasculature from embolization in case of heavy thrombus burden in STEMI or degenerated saphenous vein graft intervention), rotational atherectomy or directional atherectomy or orbital atherectomy (devices used in heavily calcified lesions, which are resistant to balloon dilatation), among others.

**IVUS, OCT, and FFR**

In the case of intermediate stenoses (40–70%) additional modalities are to be used to determine if the stenosis is flow limiting. Intravascular Ultrasound and Optical Coherence Tomography provide an anatomical assessment of the coronary arteries, whereas fractional flow reserve (FFR) provides a physiological assessment of the coronary flow.9

Intravascular ultrasound (IVUS) is an ultrasound device mounted catheter that is advanced into lumen of diseased artery. It gives atherosclerotic plaque burden, reference vessel diameter and area, and morphology of stenosis (Figs. 5A and B). IVUS can also be used after angioplasty to determine the adequacy of the stent placement.

Optical coherence tomography (OCT) is infrared-based imaging technique that has a higher resolution than IVUS, but has limited penetration (depth of visualization) (Figs. 6A and B).

FFR is a ratio of pressure distal and proximal to the stenosis respectively when there is maximal vasodilation of the coronary microvasculature. It gives the physiologic significance of a borderline stenosis and can guide PCI

**Figs. 3A to D:** (A and B) Primary angioplasty (PAMI) of right coronary artery (RCA) and (C and D) obtuse marginal (OM) branch of the left circumflex artery. Black arrows in A and C show thrombotically occluded RCA and OM arteries, respectively. Black arrows in B and D show final result after stenting the respective arteries.
Fig. 4: PCI equipment

Fig. 5A and B: Intravascular ultrasound (IVUS) images: (A) Normal coronary artery with three layers: the intima, media, and the adventitia. The lumen is the dark central area within the intima. (B) Coronary artery with an atherosclerotic plaque encroaching into the lumen from 12 o’clock to 6 o’clock position.

Fig. 6A and B: Optical coherence tomography images: (A) Normal coronary artery with three layers, the intima, media, and adventitia. The lumen is the inner black central area within the intima. (B) Coronary artery with a calcified atherosclerotic plaque from 7 o’clock to 1 o’clock position.

Complications and Risks
- Vascular complications: Bleeding, hematoma, pseudoaneurysm formation
- Contrast induced nephropathy: Rise in the serum creatinine by 0.5 mg/dL or by 25% above the baseline that occurs 48–72 hours after the procedure
- Contrast allergy: Severe anaphylactoid reaction, urticarial, nausea, vomiting
- Acute myocardial infarction: Due to stent thrombosis, dissections, distal embolization or side branch closure
**Figs. 7A and B:** Fractional flow reserve (FFR): (A) Right coronary artery with an intermediate stenosis (black arrow). (B) Pressure tracing from the pressure wire across the lesion. FFR is ratio of the mean distal pressure (Pd)/mean pressure in aorta (Pa) at maximal hyperemia. In this case the Pd/Pa = 0.79, which shows that the lesion is flow limiting and should be revascularized.

**TABLE 2** High-risk PCI

<table>
<thead>
<tr>
<th>Anatomic</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left main coronary artery disease</td>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td>Triple vessel disease</td>
<td>Cardiogenic shock/Hemodynamic instability</td>
</tr>
<tr>
<td>Associated valvular disease (especially severe aortic stenosis)</td>
<td>Atrial/Ventricular arrhythmias</td>
</tr>
<tr>
<td>Left ventricular dysfunction (EF &lt;40%)</td>
<td>Poorly controlled hypertension</td>
</tr>
<tr>
<td>Severe peripheral vascular disease</td>
<td>Decompensated heart failure</td>
</tr>
<tr>
<td>Post CABG—Saphenous vein graft/Arterial graft interventions</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Past PCI</td>
<td>Renal dysfunction</td>
</tr>
<tr>
<td>Complex subsets: Chronic total occlusions/Calcified lesions/ Tortuous lesions</td>
<td>Pulmonary disease (COPD/Asthma/OSA)</td>
</tr>
<tr>
<td></td>
<td>Bleeding diathesis/Anemia/Thrombocytopenia/Deranged INR</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td></td>
<td>Contrast allergy</td>
</tr>
<tr>
<td></td>
<td>Elderly/Frail</td>
</tr>
<tr>
<td></td>
<td>Medications: Oral anticoagulants/Insulin/Diuretics</td>
</tr>
<tr>
<td></td>
<td>Emergent procedures</td>
</tr>
</tbody>
</table>
Cerebrovascular accident: Acute or delayed stroke
Stent thrombosis
Restenosis due to neointimal hyperplasia
Tachy- or bradyarrhythmias: Requiring pharmacotherapy, cardioversion or pacing
Death: Relatively low risk

The risks associated with coronary angiographies are relatively low when performed electively. The risks are higher in certain subsets such as when done in an emergency or in hemodynamically unstable patients (Table 2).

Considering the multiple factors in an individual patient, which dictate the decision of PCI versus CABG in multi-vessel CAD, it is ideal to have a heart team approach involving the interventional cardiologist, cardiac surgeon and physician while decision-making.

Conclusion

With the continuous innovations in the field of interventional cardiology, we have come a long way in the last four decades to make PTCA a safer and more effective procedure. The refinement in the hardware and stent technology has led to higher success rate in more complex anatomies with better long-term outcomes. As a physician, the decision to intervene is essential as well as offering the ideal mode of revascularization keeping in mind the risks, clinical and anatomical factors, individualized for every patient.

References

Abstract

Rheumatic heart disease continues to be a significant cause of cardiovascular morbidity and mortality in India and other low-middle income countries. In most endemic regions, the disease is often neglected and diagnosed late, with majority of the affected patients presenting for the first time with complications like heart failure, atrial fibrillation, and cardio-embolism. Echocardiography screening based on World Heart Federation echocardiographic criteria holds promise to identify patients earlier, when prophylaxis is more likely to be effective. This review focuses on the diagnostic and management approach to the patients with acute rheumatic fever and rheumatic heart disease based on the available literature and guidelines.

Introduction

Rheumatic heart disease (RHD) is a neglected disease which leads to significant cardiovascular morbidity and mortality in India and other low-middle income countries. RHD occurs in response to rheumatic carditis either due to initial or recurrent episodes of acute rheumatic fever (ARF) and seen in 60% of patients with ARF. ARF is a nonsuppurative sequelae of group A beta-hemolytic streptococcus (GAS) pharyngitis. ARF occurs in 0.3–3% of patients after a streptococcal sore throat. Therefore, early detection and management of ARF is pivotal in the prevention of RHD. Once it occurs, RHD causes significant morbidity and results in various long-term complications like stroke, peripheral embolism, heart failure, and premature death. This review will highlight the diagnostic and management approach to the ARF/RHD patients based on the available literature and guidelines.

Epidemiology of RF/RHD

Despite a global decline in the incidence of RHD, it remains endemic in regions with overcrowded living conditions and inadequate health-care services. Worldwide, there is a gross disparity in the incidence rates in endemic versus non-endemic areas. The incidence rate varies from 3.4 per 100,000 population in the non-endemic countries to as high as 444 per 100,000 population in the endemic countries. Unfortunately, India is the “RHD Capital” of the world, with nearly 40% of the global RHD burden. However, in India, gross disparities exist in the socioeconomic statuses and the availability of healthcare facilities across different states, within the states, and between the urban and the rural areas. As a result, the burden of RHD in India is likely to differ widely within and across the states. Unfortunately, there are hardly any data from the worst affected states like Uttar Pradesh, Bihar, Jharkhand, West Bengal, and Odisha.

Diagnosis and Management of Rheumatic Carditis

The ARF is most frequent in the age group of 5–15 years. The diagnosis of ARF is based on Jones criteria, which were last revised in the year 2015 (Table 1). Carditis is the most severe manifestation of ARF because it may lead
to chronic RHD with its attendant complications of heart failure, atrial fibrillation, thromboembolism, infective endocarditis, and death. Clinical features depend on whether there is the involvement of the pericardium, myocardium, or heart valves. Myocarditis always occurs in presence of valvulitis, and isolated myocardial involvement in absence of valvular involvement, should raise doubts over the diagnosis of rheumatic carditis. The mitral regurgitation is a dominant valvular lesion in 90% of ARF cases, causing an apical pansystolic murmur. It may be accompanied by aortic regurgitation (AR). Isolated AR is seen in less than 5% of cases. Stenotic lesions occur in the late stages of the disease. Among patients with previously diagnosed RHD, recurrence of acute rheumatic carditis is clinically suggested by a new murmur or a change in the character of the previously heard murmur. Nevertheless, echocardiography is strongly recommended in all patients with definite/suspected acute rheumatic carditis since it is more specific and sensitive than cardiac auscultation.

The aim of treatment in ARF is:

- to suppress the inflammatory response and thus minimize the effects of inflammation on the heart and joints
- to provide symptomatic relief
- to eradicate the GAS harboring the pharynx
- to commence secondary prophylaxis.

The management of carditis during an episode of ARF aims at diagnosing and assessing the severity of cardiac involvement using echocardiography, and management of cardiac manifestations like congestive heart failure, and heart blocks. Available literature does not suggest that anti-inflammatory treatment improves cardiac outcomes; however, glucocorticoids may prove beneficial in patients with acute cardiac failure secondary to severe carditis. Prednisolone is preferred with an initial dose of 1–2 mg/kg/day, given for 2–3 weeks followed by gradual tapering and the total duration of therapy should be 8–12 weeks. Some recommend the introduction of salicylates as the dose of steroids is reduced to prevent rebound.

In patients with clinical signs and symptoms of heart

---

**TABLE 1** The 2015 revised Jones criteria for the diagnosis of acute rheumatic fever

<table>
<thead>
<tr>
<th>2015 Revised Jones criteria for the diagnosis of ARF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>For all patient population with evidence of preceding GAS infection</strong></td>
</tr>
<tr>
<td><strong>Diagnosis of initial ARF – 2 major or 1 major plus 2 minor manifestations</strong></td>
</tr>
<tr>
<td><strong>Diagnosis of recurrent ARF – 2 major or 1 major plus 2 minor manifestations or 3 minor</strong></td>
</tr>
<tr>
<td><strong>Low-risk population:</strong> ARF incidence ≤2 per 100,000 school-aged children or all-age RHD prevalence of ≤1 per 1,000 population year</td>
</tr>
<tr>
<td><strong>Major criteria</strong></td>
</tr>
<tr>
<td>Carditis</td>
</tr>
<tr>
<td>Arthritis</td>
</tr>
<tr>
<td>Chorea</td>
</tr>
<tr>
<td>Erythema marginatum</td>
</tr>
<tr>
<td>Subcutaneous nodules</td>
</tr>
<tr>
<td><strong>Minor criteria</strong></td>
</tr>
<tr>
<td>Carditis</td>
</tr>
<tr>
<td>Arthralgia</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Markers of inflammation</td>
</tr>
</tbody>
</table>

*Subclinical carditis: Seen only on echocardiography without auscultatory findings. #Accounting for age variability and only if carditis NOT counted as a major criteria.

ARF, acute rheumatic fever; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GAS, group A beta hemolytic Streptococcus; RHD, rheumatic heart disease.
failure, conventional treatment that includes diuretics and renin-angiotensin system blockers should be initiated. Valve surgery is rarely necessary in acute setting, and is usually reserved for patients with valve leaflet or chordae tendineae rupture where surgery can be lifesaving.7

The eradication of GAS from pharynx can be done by penicillin, which can be administered as a single intramuscular dose of benzathine penicillin or oral penicillin for 10 days.7 Once the diagnosis of ARF/definite RHD is established, penicillin (preferably in form of 3 weekly intramuscular injections of benzathine penicillin) is recommended for secondary prevention (Table 2). The benzathine penicillin can cause allergy and/or anaphylaxis in 3% and 0.3% of cases, respectively. There are few concerns with the use of intramuscular injections of penicillin, like difficulty in ensuring round-the-year availability in remote areas, fear associated with allergy/anaphylaxis, pain at the local site, and the long duration for which injections have to be administered on the 3–4 weekly basis. Azithromycin (once a week orally) and other oral drugs like erythromycin and sulfonamide are potential substitutes but are less effective.8

**Diagnosis of Chronic RHD**

Chronic RHD usually affects the patients in their most prime and productive years. In one of the most extensive contemporary Indian data on RHD patients, the HP-RHD (Himachal Pradesh rheumatic heart disease) registry, the mean age of patients was 40±14 years, and 70% of affected patients were females, and multivalvular disease was present in 67% of patients.1 Early diagnosis of RHD, before the symptoms/manifestations become overt, along with early initiation of penicillin prophylaxis, can halt the disease progression and improve the outcomes. Criteria have been developed by “World Heart Federation (WHF) 2012” for echocardiographic diagnosis of RHD and to differentiate it from normal physiological variants (Table 3).9

### Table 2: Secondary prophylaxis for rheumatic fever (drugs and duration of therapy)7

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Route</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzathine benzylpenicillin</td>
<td>Single deep intramuscular</td>
<td>If weight &gt;30 kg then 1,200,000 IU If weight &lt;30 kg then 600,000 IU</td>
</tr>
<tr>
<td></td>
<td>injections every 3–4 weeks</td>
<td></td>
</tr>
<tr>
<td>Penicillin V</td>
<td>Oral</td>
<td>250 mg twice daily</td>
</tr>
<tr>
<td>Sulfonamides (sulfadiazine, sulfisoxazole, sulfadoxine)</td>
<td>Oral</td>
<td>If weight &gt;30 kg them 1 gm daily, if weight &lt;30 kg then 500 mg daily</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Oral</td>
<td>250 mg twice daily</td>
</tr>
</tbody>
</table>

**Duration of secondary prophylaxis for rheumatic fever**

| In patients with no cardiac involvement | For 5 years after last attack or until 21 years of age (whichever is longer) |
| In patients with preceding carditis and mild residual mitral regurgitation or valve lesion which resolved completely | For 10 years after last attack or until 21 years of age (whichever is longer) |
| In patients with preceding carditis with moderate to severe valve damage | For 10 years after last attack or until 40 years of age (whichever is longer); Lifelong in high-risk patients |
| In patients with relapses or high risk of infection | Lifelong |
| After valve surgery | Lifelong |

### Management of Individual Valve Lesions

#### Mitral Stenosis

**Medical Management**

The medical management of mitral stenosis (MS) is directed at

- the prevention of recurrent rheumatic fever
- management of complications like atrial fibrillation, embolic complications, infective endocarditis, pulmonary artery hypertension (PAH) and right heart failure
- monitoring disease progression and allows intervention at an optimal time.

Asymptomatic patients with mild-moderate MS should be monitored annually. The management of severe
disease includes the use of diuretics, beta-blockers, and/or digoxin for rate control. The anticoagulation with warfarin should be given to patients of MS having atrial fibrillation, LA/LAA (left atrium/left atrial appendage) clot, history of embolization, and if LA is grossly dilated (LA >55 mm). The target INR (international normalized ratio) should be maintained between 2–3. The role of newer oral anticoagulants in the management of MS is controversial and needs further evaluation. The factors responsible for acute worsening like anemia, pregnancy, infection, infective endocarditis, and ARF recurrence also need consideration while managing mitral stenosis.

Mitral Valvotomy

The older techniques of closed mitral valvotomy (CMV) and open mitral valvotomy (OMV) have now been replaced by percutaneous balloon mitral valvotomy (BMV), also known as percutaneous transvenous mitral commissurotomy (PTMC). BMV is strongly recommended in symptomatic and suitable patients with moderate to severe MS (i.e., valve area <1 cm²/m² of BSA or <1.5 cm² in normal-sized adults with pliable noncalcified valves, no more than mild MR and with no evidence of LA/LAA thrombus). Besides, BMV is a favorable option for asymptomatic patients with valve area less than 1 cm² or when MS results in the development of AF. BMV is done through the femoral vein approach, and after doing trans-septal puncture, the “Inoue balloon” is inflated across the orifice of mitral valve, which results in the fracture of nodular calcium, and separation of the mitral commissures, and as a result, increase in the orifice area of the mitral valve. BMV is, however, contraindicated in the presence of persistent left atrial or LAA thrombus, more than mild (moderate to severe) mitral regurgitation, and severe or bicommissural calcification. A meta-analysis comparing BMV with surgical commissurotomy suggested that, compared with surgical commissurotomy, BMV results in slightly smaller mitral valve area, a comparatively higher risk of developing MR, and an approximately threefold risk of reintervention. However, with an increase in operator experience and familiarity, refined hardware, relative procedural ease, and perhaps being a cheaper option compared with surgical options, BMV remains the preferred treatment option for rheumatic MS. The possible complications of BMV include cardiac perforation (1%), cerebral emboli (1%), development of MR (15% develop MR out of which 2% require surgery), and even death in 1–2% of patients.

Mitral Valve Replacement

Valve replacement may be needed if the valve is severely calcific and non-pliable with echocardiography based Wilkins score greater than 8 (Wilkins score is based on leaflet mobility, leaflet calcification, leaflet thickening, and

### TABLE 3

<table>
<thead>
<tr>
<th>A. Morphological features of RHD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Features in the MV:</strong></td>
</tr>
<tr>
<td>• AMVL thickening* ≥3 mm (age-specific)</td>
</tr>
<tr>
<td>• Chordal thickening</td>
</tr>
<tr>
<td>• Restricted leaflet motion</td>
</tr>
<tr>
<td>• Excessive leaflet tip motion during systole</td>
</tr>
<tr>
<td><strong>Features in the AV:</strong></td>
</tr>
<tr>
<td>• Irregular or focal thickening</td>
</tr>
<tr>
<td>• Coaptation defect</td>
</tr>
<tr>
<td>• Restricted leaflet motion</td>
</tr>
<tr>
<td>• Prolapse</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Criteria for pathological regurgitation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pathological mitral regurgitation</strong> (all four Doppler echocardiographic criteria must be met):</td>
</tr>
<tr>
<td>• Seen in two views</td>
</tr>
<tr>
<td>• In at least one view, jet length ≥2 cm*</td>
</tr>
<tr>
<td>• Velocity ≥3 m/s for one complete envelope</td>
</tr>
<tr>
<td>• Pan-systolic jet in at least one envelope</td>
</tr>
<tr>
<td><strong>Pathological aortic regurgitation:</strong> (all four Doppler echocardiographic criteria must be met)</td>
</tr>
<tr>
<td>• Seen in two views</td>
</tr>
<tr>
<td>• In at least one view, jet length ≥1 cm*</td>
</tr>
<tr>
<td>• Velocity ≥3 m/s in early diastole</td>
</tr>
<tr>
<td>• Pan-diastolic jet in at least one envelope</td>
</tr>
</tbody>
</table>

*A regurgitant jet length should be measured from the vena contracta to the last pixel of regurgitant color (blue or red).

AMVL, anterior mitral valve leaflet; AV, aortic valve; MV, mitral valve; RHD, rheumatic heart disease.
subvalvular deformity), and also in the presence of more than grade 2 MR, and/or persistent LA/LAA clot. 12

Mitral Regurgitation

The chronic mitral regurgitation (MR) has a long asymptomatic course, and usually symptoms appear after two decades of an ARF unless complicated by infective endocarditis or recurrent rheumatic fever. 12 The most common symptom of chronic MR is exertional fatigue due to low effectual cardiac output. However, acute MR causes a sudden increase in LA pressure and pulmonary venous hypertension, which requires treatment with afterload reducing agents and urgent surgical intervention. The mild to moderate degree of MR requires an annual follow-up with echocardiography to assess the progression of the disease, whereas the management of chronic severe MR is done based on the patient’s symptom status. The drugs like beta-blockers and renin-angiotensin system blockers are recommended only once left ventricular dysfunction ensues, and their role in mild to moderate MR is controversial. The indications of surgical interventions in chronic severe mitral regurgitation are following: 12

- Presence of symptoms with LVEF >30% [Class 1]
- Asymptomatic chronic severe MR with LVESD (left ventricular end-systolic diameter) ≥40 mm and or LVEF ≤60% [Class 2a]
- Asymptomatic chronic severe MR with either new-onset atrial fibrillation and/or pulmonary hypertension with pulmonary artery systolic pressure >50 mm Hg [Class 2a]

The decision to replace or repair the valve is of critical importance. Although repair is better than replacement, it maintains “annular-chordal-papillary muscle continuity” and prevents LV remodeling; however, it requires a steep learning curve. Furthermore, the repair is less successful in older patients with rigid, calcified and deformed valves due to RHD. 12 Furthermore, in countries with poor resources like India, where re-do surgeries are seldom performed, valve replacement is often the preferred option compared with valve repair, despite the possible consequences associated with prosthetic valves in the presence of inadequate INR monitoring and irregular warfarin supplies. The repair of primary degenerative MR is most often successful in

- Children’s and adolescents with pliable valves
- Adults with MR secondary to MVP

- Cases of annular dilatation, chordal rupture, and leaflet perforation secondary to infective endocarditis. 12

Aortic Stenosis

Unlike degenerative aortic stenosis (AS), isolated rheumatic AS occurs rarely. 7 The cardinal symptoms of AS are exertional angina, exertional dyspnea, syncope, and, ultimately, heart failure. Overall, the average survival without aortic valve replacement (AVR) is only 1–3 years after symptom onset. 12 Symptomatic AS is an indication for valve replacement. Patients undergoing concomitant surgery for other indication, and having associated moderate to severe AS should also undergo AVR. Patients with severe AS and left ventricular dysfunction and an EF (ejection fraction) of less than 50% can also be taken up for AVR. Patients with an abnormal response to stress testing should also undergo AVR. Aortic valve repair is not consistently possible with rheumatic AS, and replacement is needed. Over the last decade, transcather AVR (TAVR) has revolutionized the treatment of degenerative AS. However, the use of TAVR in RHD does not look promising, since AS in RHD seldom occurs as an isolated lesion and secondly because AS in RHD occurs at younger age compared with degenerative AS. 4

Aortic Regurgitation

The isolated involvement of the aortic valve is rare and often accompanied by rheumatic mitral valve involvement. 6 There is a long latent period of the disease, and patients may only complain of uncomfortable awareness of heartbeat, especially on lying down. The exertional dyspnea and paroxysmal nocturnal dyspnea are only noticed when there is an onset of LV dysfunction or simultaneous mitral valve involvement. The mild to moderate degree of AR requires to follow-up by echocardiography, whereas severe AR requires treatment with renin-angiotensin system inhibitors to decrease the regurgitant fraction of AR and beta-blockers and diuretics in case of LV dysfunction. 12 The indications of AVR are following:

- Severe symptomatic AR [Class 1]
- Severe asymptomatic AR with LVEF <50% [Class 1]
- Severe asymptomatic AR with other cardiac surgery [Class 1]
- Severe asymptomatic AR with LVEF >50% with LVESD (LV end-systolic dimensions) >50 mm [Class 2a]
Current Status of Management of Rheumatic Heart Disease in India

###CHAPTER 28

####Major highlights and implications from the HP-RHD (Himachal Pradesh Rheumatic Heart Disease) Registry and the REMEDY registry

<table>
<thead>
<tr>
<th>HP-RHD registry</th>
<th>REMEDY registry</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study population</td>
<td>2,005 patients (All Indian patients from the state of Himachal Pradesh)</td>
<td>3,343 patients (293 patients were Indians). This comparison includes patients from low-middle income countries (n=1,370)</td>
</tr>
<tr>
<td>Age</td>
<td>Mean age = 40.3±14.3 years</td>
<td>Median age = 28 years</td>
</tr>
<tr>
<td>Female sex</td>
<td>72.3%</td>
<td>63%</td>
</tr>
<tr>
<td>Schooling up to primary level only</td>
<td>40.4%</td>
<td>27.4%</td>
</tr>
<tr>
<td>Past history of ARF</td>
<td>25.1%</td>
<td>44.3%</td>
</tr>
<tr>
<td>CHF</td>
<td>15.7%</td>
<td>21%</td>
</tr>
<tr>
<td>PAH</td>
<td>30.5%</td>
<td>34.2%</td>
</tr>
<tr>
<td>AF</td>
<td>24.4%</td>
<td>22%</td>
</tr>
<tr>
<td>Stroke</td>
<td>3.9%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Peripheral embolism</td>
<td>4.1%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Multivalvular heart disease</td>
<td>43.2%</td>
<td>NA</td>
</tr>
<tr>
<td>Moderate to severe valvular involvement</td>
<td>69.3%</td>
<td>63.9%</td>
</tr>
<tr>
<td>Use of secondary prophylaxis</td>
<td>28.5%</td>
<td>59.7%</td>
</tr>
<tr>
<td>Use of OAC in high risk patients</td>
<td>77.8%</td>
<td>69.5%</td>
</tr>
<tr>
<td>Use of valvuloplasty</td>
<td>16%</td>
<td>4%</td>
</tr>
<tr>
<td>Use of valve surgery</td>
<td>9.7%</td>
<td>28%</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; ARF, acute rheumatic fever; CHF, congestive heart failure; OAC, oral anticoagulant; PAH, pulmonary artery hypertension; RHD, rheumatic heart disease.

- Severe asymptomatic AR with LVEDD (LV end-diastolic dimensions) >65 mm [Class 2b]
  
  If AVR is needed for stenosis or regurgitation, concurrent aortic root replacement is recommended if a maximum aortic dimension exceeds 45 mm.

**Management of Tricuspid Valve Disease**

The involvement of the tricuspid valve in RHD is most common due to PAH secondary to left-sided valve lesions (hypertensive tricuspid regurgitation). It has been increasingly recognized that the concept that "correcting
the left-sided lesion” will restore the tricuspid competence in hypertensive tricuspid regurgitation (TR) is not always true since, in the majority of patients, TR recurs in short/medium term follow-up and usually requires another intervention. Therefore, it is recommended to do tricuspid annulus repair using various anuloplasty techniques among patients undergoing left valve surgery in the presence of:
- Severe TR
- Mild to moderate TR with annular dimensions >40 mm or 21 mm/m²

Patients with normotensive TR (without PAH), organic tricuspid valve disease, and associated with tricuspid stenosis need to have their valves repaired or replacement (if repair not possible) preferably with a bioprosthetic valve. Patients with organic tricuspid stenosis and right heart failure should undergo tricuspid valvotomy at the time of their surgery. Isolated tricuspid stenosis should undergo balloon valvotomy if feasible.³

**Current Situation in India**

The available data suggests that the major reasons for high morbidity and mortality associated with RF/RHD include inadequate adherence to secondary prophylaxis, insufficient use and monitoring of oral anticoagulant therapy, and the limited access to surgical/percutaneous interventions.¹ Despite being home to 40% of the world’s RHD burden, there are limited contemporary Indian data on
- RF/RHD mortality
- Complications of RHD (atrial fibrillation, cardioembolism, heart failure, infective endocarditis, pregnancy morbidity)
- Treatment practices
- Long-term outcomes among RF/RHD patients.¹²

This is hugely disappointing since there is enough evidence that the existing preventive and therapeutic strategies can decrease the morbidity and mortality secondary to RHD. The focus of cardiovascular research has unfortunately shifted from RHD to coronary artery disease, despite India losing more than 100,000 patients to RHD every year.¹ The HP-RHD registry provides the most extensive published contemporary Indian data on the clinical characteristics, treatment practices, and outcomes in patients with RHD.¹ The other significant contemporary data comes from the REMEDY registry which included RHD patients from 25 hospitals across 12 African Countries, India, and Yemen.¹⁴ Indian patients constituted 8.8% (293 patients) of the study population in REMEDY registry. The salient features of both the registries have been highlighted in the Table 4.¹³⁴

**Conclusion**

Despite being one of the major causes of cardiovascular morbidity and mortality in low- and middle-income countries like India, RHD is often neglected cardiovascular disease, which causes significant morbidity and mortality. It primarily affects young patients in their most prime and reproductive ages. Although strategies for preventing RHD are proven, simple, cheap, and cost-effective, they are, unfortunately, adequately implemented. Furthermore, there is a gross inadequacy of data, especially from the worst affected regions. Percutaneous and surgical valve interventions are not available to the majority of the patients. There is a gross inadequacy in the availability and use of optimal preventive and therapeutic drugs and strategies. Patients are often not detected early and usually present to tertiary care centers when their disease is advanced and severe. The reasons for ARF and RHD remaining a burning problem in India are poor socioeconomic conditions, lack of hygiene and awareness, inadequate use of secondary prophylaxis, lack of vaccine, and absence of a national program to control RF/RHD in our country. These issues need to be addressed along with the encouragement of RF/RHD related research to make informed policies and programs to make India “RF/RHD free.”

**References**


8. Bank R. Secondary prophylaxis to control rheumatic heart disease in developing countries: put into a cage if can’t be killed. Indian Heart J. 2018;70(6):907-10.


CHAPTER 29
Role of Stress ECG in Preoperative Evaluation for Non-Cardiac Surgery

Neelima Singh, Sushma Trikha

Abstract

Acute coronary events lead to high risk period from few weeks to months before performing non-cardiac surgery. Exercise Stress test helps to estimate functional capacity and has prognostic implications. The aim of this review is to offer an approach in the preoperative evaluation of patients undergoing non-cardiac surgery and to stress the importance and indications of stress testing in patients with heart diseases.

Introduction

Perioperative cardiac mortality and morbidity are increased in adults and elderly population undergoing major surgery. Preoperative evaluation provides assessment of both short-term and long-term cardiac risks in addition to evaluation of current medical status. Acute coronary events lead to a high-risk period from few weeks to months before performing non-cardiac surgery.1

Multidisciplinary team should ideally be involved for assessing perioperative cardiac risks.2 Cardiac stress testing is an important tool for diagnosis and management of patients with known or suspected heart disease. While stress testing can be performed in many ways, the most commonly used stress testing modalities are exercise electrocardiography (TMT non-imaging) and exercise or pharmacologic stress test combined with imaging [stress echocardiography or stress radionuclide myocardial perfusion imaging (MPI)].

The aim of this review is to offer an approach in the assessment of patients undergoing non cardiac surgery and stress the importance and indications of stress testing in preoperative patients with heart disease.

Cardiac Stress Tests (Stress ECG) for those who can Exercise

Stress Testing (TMT)

It is a simple and widely available tool. For those who can exercise. Noninvasive tests, Exercise stress test, Tread Mill Test (TMT) also called Stress ECG or Exercise ECG is a preferred component of stress testing in most patients.

Exercise capacity is a very important determinant of prognosis particularly in elderly. The ability to achieve 4 METs (metabolic equivalent of tasks) of activity without symptoms is thought to be a good prognostic indicator.

The onset of myocardial ischemic response at low exercise is associated with increased risk of perioperative and long-term cardiac events. In contrast, myocardial ischemia at high workload is associated with only a minor risk increase.

With normal baseline ECG, an exercise ECG test is able to produce a reliable and reproducible result almost comparable to Technetium 99m sestamibi perfusion— imaging.

Exercise ECG test is economical with reliable disease interpretation.3 Stress testing is not a routine test for
preoperative patient. However, some clinicians prefer preoperative stress imaging in patients who are scheduled for major vascular surgery.

**Exercise Stress Echocardiography**

It is usually advised in patients scheduled for intermediate or high-risk surgical procedure. The choice of stress testing modality depends on many factors, including ability to perform adequate exercise.

**Cardiac Stress Tests for those who cannot Exercise**

- Stress echocardiography
- Myocardial perfusion studies

In patients with indications for stress testing who are unable to exercise, pharmacological stress testing with either DSE (Dobutamine Stress Echo) or MPI (Myocardial Perfusion Studies) may be appropriate. Intravenous dipyridamole and adenosine should be avoided in patients with heart block, bronchospasm, critical carotid occlusive disease.

Dobutamine should be avoided in patients with serious arrhythmias or severe hypertension. All stress agents should be avoided in unstable patients.4 Imaging stress testing is generally not recommended before low-risk surgery.5

**Stress Echocardiography**

Stress echocardiography is 2D echocardiography with a physical, pharmacological, or electrical stress. Stress echocardiography is today the most cost-effective and risk-effective imaging technique for diagnosis of coronary artery disease.6 Other advantages are low cost, wide availability, and lack of radiation exposure.7

Objectives of exercise stress echocardiography are diagnosis of CAD, assessment of residual myocardial ischemia after a revascularization and relationship with chest symptoms on exertion.8 Cardiac magnetic resonance perfusion stress testing may be appropriate for the testing patients with intermediate probability of coronary artery disease.9

**Myocardial Perfusion Studies**

Often called nuclear stress test is a noninvasive imaging technique that examines perfusion of heart muscles during exercise or at rest. There are two techniques for MPI, single-photon emission computerized tomography (SPECT), and positron emission tomography (PET).

**Cardiac Nuclear Stress Test**

Stress/Rest MPI uses PET or SPECT imaging of patient’s heart before and after exercise to determine the effect of physical stress on blood flow through coronary arteries. MPI is the most appropriate test for diagnosing coronary artery disease early in patients at risk for MI. It also offers improved diagnostic accuracy over exercise. TMT, myocardial perfusion studies can be done in combination with exercise or with a pharmacologically induced stressor. Once the target heart rate is reached, the radionuclide is injected intravenously. The difference in the uptake of the radionuclide is then assessed either by SPECT or PET. Myocardial perfusion study can detect areas of ischemia or myocardial infarction.

Normal heart will have a normal uptake of radiotracer and a rapid wash-out time. Ischemic areas or reversible lesions will have a slow uptake of tracer, as well as a prolonged wash-out time. An infarcted region will not take up the tracer either at rest or during stress.10

**Systematic Approach for Preoperative Evaluation**

**Issues Related to Cardiac Evaluation**

- What are the underlying cardiac risk factors?
- Will such evaluation change the management plan of the patient?
- Will it postpone surgery?
- What will be the management in the postoperative period?

**Determine the Cardiac Risk Factors**

*Valvular Heart Disease:* Patient with severe aortic stenosis due to fixed cardiac output do not tolerate either spinal or general anesthesia because of associated vasodilatation. Patients having moderate to severe mitral stenosis do not tolerate surgery well. Patients with aortic and mitral regurgitation having preserved left ventricular function are less likely to have an adverse cardiac event.

*Congestive Heart Failure:* Preoperative congestive heart failure (CHF) increases the risk of pulmonary edema from
3% in New York Heart Association (NYHA) Class 1–25% in patients with NYHA Class IV CHF. Elective surgery should be deferred for at least a week after the signs of heart failure have settled.

Arrhythmias: Patients with arrhythmias may not tolerate surgery well. In supraventricular arrhythmias, rate needs to be controlled prior to surgery. Patients with ventricular arrhythmias should be evaluated by a cardiologist prior to surgery. Those with first-degree heart block and Mobitz type I heart block may tolerate surgery well, while patients with Mobitz type II and third degree heart block might require intraoperative pacing.

Major Clinical Predictor of Cardiac Risks: They include decompensated heart failure, acute coronary syndrome, arrhythmias, and severe valvular heart disease.

Intermediate Clinical Predictor of Cardiac Risks: Angina, heart failure, history of myocardial infarction, diabetes mellitus, and renal insufficiency.

Minor Clinical Predictor of Cardiac Risks: Advanced age, ECG changes, reduced functional capacity, history of cardiovascular accident, high blood pressure.

Revised Cardiac Risk Index (RCRI): For assessing preoperative cardiac risks—two models are often used. The RCRI is also called Lee index or the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) risk model. The RCRI is simple and has been widely used. The NSQIP calculator is more complex.

Evaluation of Surgical Patients and Different Categories of Surgery

Evaluation starts with history taking and clinical examination. An essential skill is the identification of high-risk patients, whose pre-existing condition need to be optimized prior to surgery.

Emergent Surgery—Where little or no time for clinical evaluation, e.g., life saving limb surgery.

Urgent Surgery—Limited time for clinical assessment prior to life saving or limb saving procedure (6–24) hours.

Time sensitive Surgery—A delay of 1–6 weeks is acceptable, e.g., oncologic surgeries.

Elective Surgery—Procedure were delay up to 1 year is acceptable.

Surgeries on the Basis of Risk

High Risk Surgeries: The American Society of Anesthesiologist (ASA) have stratified the surgical risk based on patient’s functional state, comorbid diseases, and urgency of surgery.

High cardiac risks surgeries include emergency surgeries which are major in elderly, aortic and vascular surgeries, and peripheral arterial procedures.

Intermediate Risk Surgeries: They include head and neck surgery, carotid endarterectomy, abdominal surgery, intrathoracic surgeries, prostate surgery, and orthopedic surgery.

Low Risk Surgeries: They include endoscopic procedures, breast surgery, cataract surgeries, and superficial procedures.

Functional Status

Energy expenditures for following activities such as eating, dressing, walking around the house, and dishwashing range from 1 to 4 METs, scrubbing floors, climbing a flight of stairs, running a short distance, walking on level ground at 6.4 km per hour represents 4–10 METs.

Strenuous sports such as singles tennis and football often exceed 10 METs. Every operation elicits a stress response triggered by tissue injury. Surgery also causes change in balance between prothrombotic and fibrinolytic factors leading to increased thrombogenicity.

The mortality rate overall of all surgeries is 0.3%. The mortality rate is less than 1% for major surgical procedures in patients younger than 65 years, but 5% for patients between 65 and 80 years. The incidence of myocardial infarction in postoperative general surgery patients over 50 years is 0.7%, and is 3.1% in those undergoing vascular surgery.

Death in the first 48 hours in the postoperative period is mainly due to cardiac causes, while death between 48 hours and 6 weeks is often due to pneumonia, sepsis, pulmonary embolism, renal failure.

Stress testing is not a routine test for pre operative patient. However, some experts routinely obtain preoperative stress imaging in patients who are scheduled for major vascular surgery.
Role of Stress ECG in Preoperative Evaluation for Non-Cardiac Surgery

**Stepwise Approach**

**Step 1: Decide the Urgency of Surgery**

In emergent situation, where little or no time for clinical assessment proceed directly to surgery. If surgery is not urgent proceed to Step 2.

**Step 2: Assess for Unstable Cardiac Condition**

If high cardiac risk predictors, e.g., acute coronary syndrome or MI, CCF, etc., present, cardiological evaluation is required. In unstable cardiac condition, patients can proceed for coronary artery intervention in addition to dual-antiplatelet therapy if the surgical procedure can be postponed, or may go directly for surgery if delay is impossible. If there is no unstable cardiac condition proceed to Step 3.

**Step 3: In Cardiac Stable Patients Determine the Risk of Surgical Procedure**

Procedure for (Major Adverse Cardiac Event (MACE) which includes MI or death).

- **For Low Risk Procedure**: Proceed to surgery. In patients with ischemic heart disease low dose beta-blocker may be advised before surgery. In patients with heart failure ACE inhibitors should be given before surgeries.

- **For intermediate or high risk procedure**: assess functional capacity of the patient proceed to Step 4.

**Step 4: Assess Functional Capacity of the Patient**

If patient’s functional capacity is good or more than 4 METs, in intermediate risk surgeries with one or more risk factors, it is appropriate to go for surgery. If the functional capacity is less than 4 METS proceed to Step 5.

**Step 5: Consider the Risk of Surgical Procedure**

- **Intermediate Risk Surgeries**: Noninvasive stress testing may be considered in those with one or more risk factors. These patients can be taken for surgery. Baseline ECG is required to monitor changes during surgical procedure.

- **High Risk Surgeries**: Assess RCRI.

  Proceed to Step 6.

**Step 6: Assess Revised Cardiac Risk Index (RCRI)**

- Ischemic Heart Disease like previous MI or angina
- Heart failure
- Stroke or TIA
- Renal dysfunction serum creatinine 2 mg/dL or above
- Diabetes mellitus requiring insulin therapy.

  If two risk factors and patient scheduled for high risk surgery consider non invasive testing. If three risk factors proceed to Step 7.

**Step 7: Consider Noninvasive Testing**

If no, mild, or moderate stress induced ischemia proceed with planned surgery. If extensive stress induced ischemia is present, an individualized perioperative management is indicated considering the potential benefit of the recommended surgical procedure compared with the predicted adverse outcome, and the effect of conservative management and/or coronary revascularization.

**When to Perform Stress Tests in Preoperative Cases**

Noninvasive (stress test) is indicated in those with major clinical predictors, or those with intermediate clinical predictors and poor functional capacity (4 METs) scheduled for high surgical risk procedures.

  OR, in cases with minor clinical predictors and poor functional capacity undergoing high risk procedure.

**Conclusion**

Clinical risk factors should form the basis of risk assessment. Exercise stress test helps to estimate functional capacity and has prognostic implications. Thus, cardiac stress testing can be a valuable tool in determining whether a patient can safely proceed to surgery or a further consultation with cardiologist is needed before proceeding with intermediate or high risk surgery.

  Acute coronary events, like new onset ischemia, infarction, or revascularization, lead to a high-risk period of 6 weeks, and an intermediate-risk period of 3 months before performing non-cardiac surgery.
References

Abstract

Atrial fibrillation, an important risk factor for stroke, is quiet prevalent in general population, especially in the elderly group. It remains silent, therefore remains undiagnosed and not treated adequately. Screening general population for silent atrial fibrillation is not feasible because of cost constraints and treating all silent atrial fibrillation patients may cause more harm than benefits. However, identifying atrial fibrillation in high-risk individuals and elderly population is a viable option. Various screening tools are available and proper utilization of such assets is the key to success.

Introduction

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia and affects 1–4% of the general population and is important risk factor for stroke. Prevalence of AF is predicted to double over the next 30 years and is associated with a fivefold increased risk of ischemic stroke. People with ischemic stroke, approximately one-third die within a year and approximately one-third of the survivors have some type of permanent disability. Prevalence of AF keeps on rising as age advances and is about 3% in men and 2% in women of age 65–69 years and is about 10% of adults of age 85 years or above. Unfortunately, AF is diagnosed in 20% of the cases of ischemic stroke at the first presentation of stroke.

Further, if AF detected early and treated with anticoagulants in eligible patients, the risk of stroke is reduced by around 65%. Unfortunately, AF in many people goes undetected and therefore untreated because either such patients are asymptomatic or have paroxysmal AF.

Screening is logical one such approach to detect AF early and thereby initiating anticoagulant therapy early to reduce the incidence of ischemic stroke. However, the current recommendations of various international task forces are against mass screening, mainly because of the cost implications and the uncertainty of the benefits of the systematic screening vis-à-vis usual care. US Preventive Services Task Force (USPSTF) in their latest recommendations have concluded that the current evidence is insufficient to assess the balance of benefits and harms of screening for AF with ECG. In high-risk individuals, screening has been recommended as the strategy to detect AF early and start anticoagulant therapy at the earliest. European Society of Cardiology (ESC) and National Institute for Health and Care Excellence (NICE) have recommended the screening for AF by opportunistic pulse palpation and/or electrocardiogram in all patients above the age of 65 years and who have symptoms suggestive of AF, respectively, based on the landmark SAFE trial, showing 60% improvement in AF detection compared to routine care over a period of 12 months.

Currently, AF remains undiagnosed in a vast population and, if detected, at least 75% of such individuals will be eligible for anticoagulation. In general population above the age of 65 years, systematic review of AF screening found the incidence of 1.4% of previously undiagnosed AF.
Repeat serial ECGs over 2 weeks improved the detection rates by fourfold. Detection rate of asymptomatic AF may go up to 50% if patients having pacemakers or implantable cardiac devices where prolonged ECG monitoring happens (Fig. 2). Detection of asymptomatic AF depends upon the definition of AF and duration of screening. 2,455 participants aged more than 65 years in the ASSERT study who have received either a dual-chamber pacemaker or internal cardioverter-defibrillator (ICD) with no prior history of AF showed asymptomatic AF in 18.8% when followed up for 2.5 years and in 11% of the patients had an episode of AF lasting for more than 24 hours in a 3-year follow-up (Fig. 3).

Patients with asymptomatic AF compared with no AF showed 2.5-fold increased risk of stroke or systemic thromboembolism over a mean of 2.5 years follow-up.

There appears no doubt that asymptomatic AF carry increased stroke and mortality risk as compared to the persons having sinus rhythm. But whether the risk will be higher in the persons with silent AF, detected on screening in the general population, remains to be seen.

As compared to sustained AF, approximately 25% of the people have paroxysmal AF and persons with persistent and permanent AF are at higher risk of thromboembolism and all-cause mortality as compared to the persons with paroxysmal AF. In the ASSERT study, a significant increased risk of stroke and thromboembolism was noted in persons with asymptomatic AF of more than 24 hours duration as compared to those without AF and there was no increased risk with asymptomatic AF of less than 24 hours.

Currently, if AF lasts for more than 30 seconds, the diagnosis of AF is established. And if treatment guidelines for treating AF will be followed, then people with low burden of AF will be put on anticoagulants and under these circumstances, then the bleeding risk from anticoagulants will outweigh stroke risk reduction.

AF is not only linked to higher risk for ischemic stroke, but also for the cognitive decline. One such study from Korea, of 10,435 people diagnosed with AF, showed that anticoagulation was associated with a 39% reduction in the incidence of dementia.

**Screening Tools**

A range of electronic devices are available to screen for AF. And the detection rate of silent AF improves as the duration of screening increases.

Following is the list of devices currently available:

- ECG
- Serial ECGs
- Holter monitoring (24–72 hours)
- Patch ECG monitors (external loop recorders)
Fig. 2: Prevalence of asymptomatic atrial fibrillation by screening method and stroke risk score

Fig. 3: Atrial fibrillation in patients with cryptogenic stroke

- Implantable cardiac loop recorder
- Pacemakers/ICDs
- Smartphone compatible ECG recorder
- Hand-held devices
- BP monitors
- Apple watch
mHealth devices have been categorized into the following three groups:

- App based, using Smartphone or tablet app, either by direct or indirect photoplethysmography (PPG). “Cardio Rhythm” is one of the most common Smartphone apps.
- “Wrist-Worn Wearables” like Apple Watch or HUAWEI Band 2.
- Hand-held devices like “AliveCor”

mHealth devices are convenient and have a high accuracy. However, after detection of AF by such devices, AF needs to be confirmed by standard 12-lead ECG Holter monitoring.15

Smartphones and smart watches have the sensitivity and specificity of above 90% for detection of AF.16,17 Recently, the data of Apple Watch study, of nearly 420,000 people with no prior history of AF or on current anticoagulation was presented. Approximately 3% of the people above the age of 65 years received irregular pulse notification. The people who received the notification were advised to wear an ECG patch, 450 participants wore the patch and returned. Of which, 153 (34%) had AF detected showing the positive predictive value of 84% for irregular pulse notification.18

However, there are no randomized studies to compare the harm of systematic screening to no screening, but potential harms do exist from population screening.19 Screening method which may have 95% specificity for AF diagnosis, can result in 50,000 false positive cases per million screened.20 Unnecessary investigations, anxiety related to health, and the increased bleeding risk because of guideline directed anticoagulant therapy are the potential hazards. Further, cost-effectiveness by systematic population screening programs is always an area of big concern, hence systematic opportunistic screening has been recommended as the best strategy as on date.7 All over the world, it has been noticed that anticoagulation has always remained suboptimal in large numbers of cases. The Risk-Stroke registry, having 94,000 people who suffered ischemic stroke, with over 22% AF population, only 16% received anticoagulation, 6 months prior to their stroke.21 Cost-effectiveness of anticoagulation vis-à-vis economic impact of suboptimal anticoagulation in reducing stroke risk is burning issue and will be the area of future research. Changes in the stroke rates, major bleeding, and mortality are the areas of interest in the upcoming studies which are duly powered.22

Obesity, physical inactivity, and hypertension are preventable risk factors and control of hypertension and lifestyle modification shall be advised regarding maintaining ideal body weight and doing regular exercise in general.

A large number of uncertainties have been pointed out and remain to be sorted:3

- Prevalence of undiagnosed AF
- Which population to screen and how to screen?
- Stroke risk for people with AF detected via screening.
- Is screening the most effective way to reduce AF stroke incidence?
- What burden of AF is associated with significant stroke risk?
- Duration and frequency of screening
- Which screening device?
- What are the harms of screening?

Several ongoing trials, STROKESTOP, SCREEN-AF, IDEAL-MD, and D2AF, in future will definitely be enlightening the physicians to deal with the issue of screening for asymptomatic AF and then the treatment strategy.

**Conclusion**

Atrial fibrillation is quite a common arrhythmia and asymptomatic AF (subclinical AF) is also common and both AF and subclinical AF (SCAF) remain important risk factor for stroke and other thromboembolic complications and are growing health problem. Highly specific treatment strategies like anticoagulants are available, which can reduce this risk. Need to identify and treat SCAF to reduce the stroke risk and subsequent disability and death is logical, but with so many uncertainties, currently systemic population screening is not recommended. However, systematic opportunistic screening and screening of high-risk individuals need to be done. Large scale randomized trials are needed to understand the evidence gaps and cost-effective strategies to address SCAF management.

**References**


Abstract

With better control of infective and metabolic complications, diabetes has become a cardiovascular disease (CVD). About 52–80% of diabetics die because of CVD and acute myocardial infarction accounts for 70% of deaths. The conventional anti-diabetic medications do not provide cardiovascular risk reduction but the two new blockbusters GLP-1 RAs and SGLT2 inhibitors are powered to improve cardiovascular and renal outcomes. The GLP-1 RA decreases atherosclerotic cardiovascular disease (ASCVD) but has no impact on heart failure. The SGLT2 inhibitors improve heart failure and renal outcomes. Besides this attention should be focused on lipid control with statins, ezetimibe, PCSK9 inhibitors, icosapent ethyl, etc., tight BP control, antiplatelet drugs in patients with high ASCVD risk, cessation of smoking, bariatric procedures, and lifestyle modification. A multipronged approach must be followed and this provides improvement in the outcomes on a long-term basis as shown STENO-2 trial and its extension follow-up.

Introduction

Diabetes is a den of cardiovascular disease (CVD). Globally, CVD occurs 10–15 years earlier in diabetics, is two times more common than non diabetics and a major chunk of diabetics succumb to CVD mainly acute myocardial infarction. Cardiovascular risk reduction (CVRR) is therefore of paramount importance and we are running a race against CVD for several decades. The conventional anti-diabetic agents do not provide CVRR but the two new anti-diabetic medications sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonist (GLP-1 RA) has shown improved CV outcomes in several dedicated trials. The conventional antidiabetic medications only provide glycemic control and do not offer cardiac protection. Among the new antidiabetic medications SGLT2 inhibitors and GLP-1 receptor agonist have shown cardio renal protection in various cardiovascular outcome trials (CVOTs).

New Antidiabetic Medications and Cardiovascular Risk Reduction

The SGLT2 Inhibitors

These drugs are very useful in providing benefit to patients of heart failure (HF). They have been used in several subsets of patients.

High CV Risk Patients at Risk of Heart Failure

The three landmark trials EMPA-REG, CANVAS, and DECLARE TIMI-58 have shown decreased hospitalization for HF in patients at high risk both in the primary prevention group and in patients with preexisting CVD.
(EMAPREG OUTCOME trial). The EMPAREG OUTCOME trial carried out in patients with preexisting CVD also showed decrease in cardiovascular mortality and all cause mortality. This was also shown in the subgroup analysis in patients with preexisting CVD in the CANVAS and the DECLARE TIMI-58.

**Heart Failure with Reduced Ejection Fraction (HFrEF)**

The DAPA HF trial conducted in patients of HFrEF has shown improved CV outcomes. Patients with symptomatic HFrEF LVEF <40%, mean age 66 years, both diabetic (45%) as well as non diabetics were randomized to dapagliflozin 10 mg daily (n=2,373) versus placebo (n=2,371) with a follow-up 18.2 months. The N-terminal pro-B-type natriuretic peptide was ≥600 pg/mL. The trial showed a relative risk reduction of 26% (hazard ratio [HR] 0.74; 95% confidence interval [CI] 0.65-0.85), p<0.001 in the composite primary end point of CV death or hHF or an urgent HF visit. The CV death was reduced by 18% (HR 0.82, CI 0.69-0.98, p=0.029) and worsening HF component decreased by 30% (HR 0.70, CI 0.59-0.83, p=0.00003). The primary outcome was same in diabetic subset (HR 0.75, CI 0.63-0.90) compared to non-diabetic subset (HR 0.73, CI 0.60-0.88). Dapagliflozin also produced benefit on top of ARNI (HR 0.75, CI 0.50-1.13, without ARNI HR 0.74, CI 0.65-0.86), which was utilized in about 11% of patients in the trial. Several other trials with these agents in HFrEF are ongoing like EMPEROR-R and EMPIRE HF, CANDLE, etc.

Several trials of SGLT2 inhibitors are also ongoing in the subset of HFpEF like DELIVER, PRESERVED HF, EMPEROR-P, EMPERIAL-P, but none of them have been completed as yet.

**Renoprotection with SGLT2 Inhibitors**

All SGLT2 inhibitors have shown renoprotection. Canagliflozin was tested in the dedicated chronic kidney disease (CKD) trial CANVAS. The trial was carried out in 4,401 patients with canagliflozin compared to placebo in patients of T2D and established CKD. Half of them were put on canagliflozin and the remainder served as control. The duration of follow-up was 2.62 years. The trial was prematurely terminated because of immense benefit. The primary end point was end stage, kidney disease, doubling of serum creatinine, renal, or CV death.

The DAPA CKD trial with dapagliflozin was carried out in diabetic as well non-diabetic subset and has been terminated prematurely because of immense benefit. The top line results show that both diabetic and non-diabetic patient benefited from it. The EMPA CKD trial with empagliflozin is ongoing.

**GLP-1 RAs Trials**

Of the six completed CVOTs with GLP-1 RAs, four trials have shown positive results, that is, LEADER, SUSTAIN-6, HARMONY, and REWIND in terms of reduction of primary point of atherosclerotic MACE, that is, cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. The EXSCEL trial narrowly missed the primary end point while the ELIXA trial was negative.

The oral semaglutide was tested for its CV safety in a small trial in a dose 14 mg orally versus placebo. The trial was found to be non inferior in terms of atherosclerotic MACE. However, there was strong signal of reduction in cardiovascular death was by 51% (HR, 0.49; 95% CI, 0.27-0.92) and all cause mortality by 49% (HR, 0.1; 95% CI, 0.31-0.84). The oral semaglutide showed similar reduction in weight and HbA1c like the injectable semaglutide. The drug has been approved by FDA for treatment of diabetes and also going to be launched in India in near future. The CV OUTCOME trial SOUL with oral semaglutide is ongoing and is expected to complete by 2023/2024.

**Lipid Control**

Statins are the corner stone of treatment for diabetic dyslipidemia. All type 2 diabetics should be on moderate intensity statins. For high-risk patient the LDL-C goal is less than 70 mg/dL and he/she requires high intensity statins like atorva 80 mg or rosuva 40 gm. For the very high-risk patient the LDL-C goal is less than 55 mg/dL. If the goal is not achieved with high intensity statins than ezetimbe 10 mg/day can be added. If still the goal are not achieved PCSK9 inhibitors should be utilized. Bempedoic acid is not yet available in India but this can also be tried prior to initiation of PCSK9 inhibitors.

**PCSK9 Inhibition**

Monoclonal antibodies to PCSK9 have been tried in two CV OUTCOME trials. The PCSK9 inhibitors produce an additional reduction of LDL-C by 40–60%, LP(a) is reduced by approximately 25% and other lipoprotein are also favorable altered. Both these molecules have been
approved for clinical use. Evolocumab is commercially available in India.

**Evolocumab**

This molecule was evaluated in FOURIER trial, which compared evolocumab with placebo in 27,564 patients with ASCVD having an LDL-C of more than 70 mg/dL with a median follow-up of 2.2 years. There was a 15% relative risk reduction in the primary end point of CV death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization (HR, 0.85; 95% CI, 0.79-0.92; P<0.001).

In FOURIER study, LDL-C decreased from median baseline value of 92 mg/dL to 30 mg/dL, i.e., approximately by 60% (P<0.001), 42% had LDL-C <25 mg/dL. Despite such low levels of LDL-C there was no evidence of muscle or liver toxicity, diabetogenesis or neurocognitive decline. The dedicated sub-study, EBBINGHAUS also confirmed lack of neurocognitive decline with its use. The only side effect which was more common with evolocumab was injection site reactions, 2.1% (evolocumab) versus 1.6% (placebo). The study therefore demonstrated incredible safety on top of statins. The benefit was seen across the range of LDL up to 20–25 mg/dL. All quartiles benefitted, highest as well as lowest. There was no J curve so lower is better is also validated for super low LDL-C. The FOURIER trial showed reduction in MI by 27% p≤0.001, stroke by 21%, p=0.01, and coronary revascularization by 22%, P≤0.001. There was no significant decrease in all cause or CV mortality.

It is available as 1 mL pen containing 140 mg. It is given in doses of 140 mg biweekly/420 mg monthly sc.

**Alirocumab**

The ODYSSEY OUTCOMES alirocumab with placebo in post ACS patients 1–12 months after the acute event in 18,924 having LDL-C level of more than 70 mg/dL. The median duration of follow-up was 2.8 years. The composite primary end-point of ischemic event showed a relative risk reduction of 15% (hazard ratio, 0.85; 95% CI, 0.78-0.93; P<0.001). There was no statically significant decrease in CHD mortality or all cause of mortality. Patients with LDL-C >100 mg/dL benefited more and also showed decrease in all cause mortality.

This is approved for clinical use and is commercially available as 1 mL pen containing 75 mg, which is given every 2 weeks or 150 mg, which is given monthly.

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**BOX 1** Indications of PCSK9 inhibitors

- Failure to achieve LDL-C goals despite optimal doses of statins in patients with ASCVD
- Statin intolerance
- Familial hypercholesterolemia

The SPIRE 1 and 2 trial with bococizumab was prematurely terminated because of presence of neutralizing antibody in 29% and antidrug antibodies in 48% of patients taking the drug. This is because bococizumab is partially murine monoclonal antibody unlike evolocumab and alirocumab which are fully humanized monoclonal antibodies.

Although both SPIRE I and SPIRE II trials were prematurely terminated, the SPIRE II, which had LDL-C >100 mg/dL showed a reduction in CV events by 21% at 12 months hinting that the drug is also useful for primary prevention. The SPIRE I trial which enrolled cooperatively lower risk population (LDL-C >70) did not showed any benefit.

The current indications PCSK9 MoAbs are outline in Box 1.

Given the lack of long-term safety and efficacy data on these agents, they are not recommended for use for primary prevention except in patients with familial hypercholesterolemia. The data of PCSK9 for primary prevention like high-risk diabetics is yet to evolve out.

**Role of Triglyceride (TG)**

TG is commonly elevated in diabetes. All randomized trial of TG lowering with fibrates on top of statins has failed to show any CV benefit. The ACCORD LLA trial did not show benefit of fibrates on top of statins. The subgroup analysis of TG more 204 mg/dL and HDL-C <34 mg/dL has shown reduction in the CV events. This is hypothesis generating but is not yet tested in any randomized control trial. A meta-analysis of fibrates has shown benefit but all trials in this meta analysis were not done on top of statins. The REDUCE IT Trial® evaluated patients with established CVD or with diabetes and other risk factor who have been on statins with LDL-C levels of 41–100 mg/dL and TG levels were between 135 and 499 mg/dL. Icosapent ethyl 2 gm twice daily was compared with placebo over a period of 4.9 years and showed reduction of 25% in the composite primary end point of ischemic events (HR, 0.75; 95% CI,
Atrial fibrillation was more often seen with icosapent ethyl compared to placebo (3.1% vs. 2.1%, P=0.004). Serious bleeding was also observed in more number of patients with icosapent ethyl compared to placebo, 2.7 versus 2.1 (P=0.06). The trial was positive but subgroup analysis showed that the benefit was similar in groups with TG<150 mg/dL and >150 mg/dL indicating the mechanism of benefit is not related lowering of TG.

Saroglitazar in dose of 4 mg/day has been used to treat hypertriglyceridemia, but there is no outcome data with it.

**Newer Agents for Lipid Management**

Besides PCSK9 inhibitors bempedoic acid is also approved for clinical use by US FDA and is likely to be available in our country in near future. It decrease LDL by 15–20% and is not associated with muscle toxicity. Inclisiran a small interfering RNA inhibits synthesis of PCSK9 and single injection of 300 mg decreases LDL-C levels by 50% and this remains there for 6 months. It is emerging as an important competitor for PCSK9 monoclonal antibodies but it is still undergoing evaluation. A single injection of PCSK9 vaccine decreases LDL-C by 50% which lasts for 12 months. If the human trial comes to out to be positive a yearly booster dose of this vaccine will be the new modality to target atherosclerotic cardiovascular disease (ASCVD).

**Blood Pressure Control**

The target for blood pressure control as per all current guideline is 130/80 mm Hg. RAAS blockers are the preferred agents but most of the diabetics in the long run require multiple drugs.

**Antiplatelet Drugs**

Currently antiplatelet drug are not recommended for primary prevention group unless the patient belongs to a very high risk group, that is, the 10-year ASCVD risk more than 10%. The three major trials released in 2018 have not shown any benefit in primary prevention of cardiovascular events.

**Lifestyle Modification**

All patients of diabetes must strictly adhere to lifestyle modification including cessation of smoking. The LOOK AHEAD Trial carried out with intensive lifestyle intervention, focused on weight loss, improved CV risk factors in T2D did not improve CV risk in T2D.

**Bariatric Procedures**

Bariatric surgery is recommended in obese diabetics and produces significant decrease in weight and blood glucose along with improvement in other concomitant risk factors. Currently great advances have been made in endoscopic bariatric procedure like intragastric balloon, endoscopic bypass, endoscopic gastroplasty, etc. The advantage of these procedures is that they are safe and have fewer complications than bariatric surgery.

**Multipronged Approach**

The STENO-2 trial carried out a multipronged approach in T2DM patient and showed marked benefit in the long run. The composite endpoint of ischemic events decreased by 53% in this study and on follow-up after 5 year the benefit escalated to 59%. A 21-year follow-up of the trial showed a survival benefit of 7.9 years and CVD-free survival of 8.1 years.

**Conclusion**

Prevention of CVD in diabetes requires a multidisciplinary approach targeting all risk factors for ASCVD coupled with optimum glycemic control and increasing use of new antidiabetic medication like SGLT2 inhibitors and GLP-1 RA. Endoscopic bariatric procedures are also making their way in the treatment of obese diabetics and helps in CV risk reduction.

**References**

CHAPTER
32
Heart Failure 2021
Amal Kumar Banerjee

Abstract
As we progress into 2021, health-care delivery, particularly for heart failure patients, becomes even more complicated and challenging. However, this poses opportunities in the path of an uncertain future. There has been remarkable progress in the science and management of heart failure recently. A key emerging theme in the science and medicine of heart failure is the need to identify and target specific causes of heart failure, defined by phenotype or genotype, which will respond to a particular intervention. QRS duration (a marker of cardiac dyssynchrony), mitral regurgitation, iron deficiency, and amyloidosis each identifies patients that will respond to a specific intervention. Although the evidence base for the treatment of HFrEF has expanded substantially, much work remains for the other forms of HF. New therapies for HF with preserved EF are under exploration, and the evidence base addressing HF with improved EF is just emerging. Adherence to recommendations can be enhanced by shared decision-making between health-care providers and patients, with patient engagement in selecting interventions based on individual values, preferences, and associated conditions and comorbidities.

Introduction
Heart failure (HF) can be defined in several ways, viz., ischemic and nonischemic cardiomyopathy based on the underlying cause and to determine outcomes. Of late, genetic information has been employed to subclassify different forms of nonischemic cardiomyopathy. Iatrogenic forms of HF have also been recognized in patients undergoing cancer therapy.

However, the simplest and most widely used classification is based on left ventricular ejection fraction (LVEF) and, notably, it provides important diagnostic and prognostic information.

The usual HF is a condition with reduced ejection fraction (HFrEF), but it has been noted that patients with near normal or normal ejection fraction could also present with symptoms of HF, and this is known as HF with preserved ejection fraction or HFpEF, which remains an enigma and a challenge for clinicians. In between there is a gap, and this has been filled in the recent ESC Guidelines on Acute and Chronic HF with the introduction of a novel category, that is, HFmrEF or HF with mid-range ejection fraction. Possibly, mild HFrEF may be much more appropriate terminology than HFmrEF.

As we progress into 2021, health-care delivery, particularly for HF patients, becomes even more complicated and challenging. HF has recently undergone major changes, while HFrEF is declining due to effective revascularization of patients with acute coronary syndromes, the prevalence and incidence of HFpEF, mainly characterized by diastolic dysfunction, is increasing due to ageing Indian societies.

Initiating Therapy
Established therapies for chronic HFrEF include angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers, loop diuretics, aldosterone antagonists, and hydralazine/isosorbide dinitrate (HYD/ISDN), with the exception
of loop diuretics, all have been shown in randomized controlled trials to improve symptoms, reduce burden of hospitalization, and/or provide survival benefit. Recently, in addition to established guideline directed medical therapy (GDMT), an angiotensin receptor-neprilysin inhibitor (ARNI) and the hyperpolarization channel blocker ivabradine have been added to the treatment guidelines for HFrEF.

ACEI or ARB initiation is usually better tolerated when patient is congested whereas beta-blockers may be better tolerated when patient is relatively dry with adequate resting heart rate. Only beta-blockers with evidence of benefit in HF should be used in HFrEF. In selected patients with HFrEF, low dose of a beta-blocker and an ACEI/ARB may be started; while in persistently symptomatic patients who tolerate an ACEI or ARB, switching to ARNI, would be recommended.

In one recent study, LVEF increased and cardiovascular mortality improved with beta-blockers in all groups in sinus rhythm except in those with a value of ≥50%. In patients with atrial fibrillation, beta-blockers increased LVEF when <50% at baseline, but did not improve prognosis. The data are most robust in HFrEF, but similar benefit was observed in HFmrHF. These relevant findings reinforce that HFrEF and HFmrHF are part of the same spectrum of HFrEF.

Mineralocorticoid receptor antagonists (MRAs) also improve HFrEF prognosis and possibly of HFpEF. The role of MRAs in reducing inflammation and fibrosis, which cause progression of HF, is currently under investigation.

Angiotensin Receptor-Neprilysin Inhibition

Neprilysin, also known as neutral endopeptidase, is a zinc-dependent metalloprotease that inactivates several vasoactive peptides, including the natriuretic peptides, adrenomedullin, bradykinin, and substance P, each of which has an important role in the pathogenesis and progression of HF. Because angiotensin II is also a substrate for neprilysin, neprilysin inhibitors raise angiotensin levels, which explains the rationale for coadministration of ARB. Neprilysin inhibitors are not combined with ACEI due to a higher risk of angioedema. When making the transition from an ACEI to ARNI, a 36-hour washout period should be strictly observed to avoid angioedema, a delay that is not required when switching from an ARB to ARNI. Starting dose of sacubitril/valsartan: 24/6 mg to 49/51 mg twice daily and target dose is 97/103 mg twice daily.

With accumulating clinical and research experience, there is a strong argument to consider them as first-line agents, in place of ACEI/ARB for the treatment of HFrEF. The benefits of sacubitril/valsartan are severely attenuated at LVEF above 60%, and therefore ARNI should not be used in HFpEF.

Sodium Glucose Cotransporter 2 (SGLT2) Inhibitors

Although sodium glucose cotransporter 2 (SGLT2) inhibitors were developed for control of glycemia, but their cardiovascular benefits have caught the clinicians’ attention. Dapagliflozin, reduced the combined risk of cardiovascular death and hospitalization for HF by 26% and the risk of cardiovascular death alone by 18% in the DAPA-HF trial. SGLT2 inhibitors are presently being explored to treat HFrEF regardless of diabetic status of a subject in ongoing clinical trials. It is almost sure that, another drug would be added to the portfolio of cardioprotective agents. These disease-modifying drugs target important, but distinct, pathways that promote cardiomyocyte dysfunction and death.

Ivabradine

Ivabradine is a specific inhibitor of the If current involved in sinoatrial nodal activity and reduces the heart rate of patients in normal sinus rhythm without lowering blood pressure. In the SHIFT (Systolic HF Treatment with the If Inhibitor Ivabradine Trial) study, ivabradine therapy, when added to GDMT, resulted in a significant reduction in HF hospitalizations in stable, chronic, and HFrEF patients predominantly in NYHA class II and III.

Ivabradine is recommended to reduce the risk of HF hospitalization in patients with HFrEF (LVEF < 35%) already receiving GDMT (including a beta-blocker at maximally tolerated dose), and who are in sinus rhythm with a heart rate greater than 70 bpm at rest.

Biomarkers—When to Order Natriuretic Peptides

B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are the most studied biomarkers in HF. They play a role in diagnosis and prognostication. Higher concentrations of BNP or NT-proBNP in an ambulatory patient with HFrEF inform high risk, particularly when the concentrations...
are rising. Current clinical practice guidelines give a Class I recommendation to measure NT-proBNP or BNP to support a clinical diagnosis of HF, to assess disease severity, or to establish prognosis.²

More recently, biomarkers have been examined for their role as a marker of clinical responsiveness to GDMT. This is, in part, due to the fact that a wide range of GDMT may reduce BNP and NT-proBNP concentrations, in parallel with the benefits of these therapies. Patients whose natriuretic peptide concentrations do not fall with GDMT (nonresponders) have a worse prognosis and more deleterious LV remodeling.⁹ Therefore, measurement of BNP or NT-proBNP is useful to monitor risk, to assist in decision-making regarding the ordering of imaging studies to evaluate LV remodeling, to support clinical judgment with respect to prescription of GDMT, and to provide helpful objective data regarding decision-making for referral to advanced HF therapies. In the setting of worsening symptoms, the reassessment of BNP or NT-proBNP may be informative. However, serial assessment of BNP or NT-proBNP to guide aggressive titration of GDMT is not indicated and not warranted.¹⁰ Severe renal dysfunction may interfere with the interpretation of natriuretic peptide concentrations.

While rising natriuretic peptide concentrations are correlated with adverse outcomes, this relationship can be confounded with the use of sacubitril/valsartan. Due to neprilysin inhibition, concentrations of BNP rise in patients treated with sacubitril/valsartan and tend not to return to baseline despite chronic therapy. In contrast, NT-proBNP concentrations typically decrease, as NT-proBNP is not a substrate for neprilysin.¹¹ Therefore, it may be more prudent to check only NT-proBNP in patients on ARNI. Also, transient increases in natriuretic peptide levels have been documented in the initial phases of beta-blocker initiation; such changes should not preclude up-titration of beta-blocker therapy, which should be guided by patient tolerance instead of asymptomatic change in natriuretic peptide levels.

**Functional Mitral Regurgitation in Chronic Heart Failure**

Left ventricular (LV) remodeling and subsequent papillary muscle displacement resulting in mitral valve (MV) leaflet tethering, dilatation, and flattening of the mitral annulus and reduced closing forces can lead to functional mitral regurgitation (FMR)¹² in cases of chronic HF.

FMR is associated with HF symptoms, increased hospitalization rates and worse long-term prognosis of patients with chronic HF. However, it remains debated whether FMR is a central driving force of HF progression or rather a bystander, reflecting the severity of the disease. Nevertheless, driven by recent advances in percutaneous MV repair (PMVR), significant efforts are currently undertaken to reduce FMR in patients with HF in the hope to improve prognosis.¹³ Similar to HF patients without FMR, it is recommended to prescribe optimized guideline-directed HF therapy (OMT) targeting LV dysfunction including cardiac resynchronization therapy.

However, whether OMT is able to counterbalance maladaptive processes and the adverse effects of FMR on long-term survival remain unknown.¹⁴ Likewise, the impact of MV repair on outcome in HF patients with severe FMR by interruption of the presumed maladaptive effects is unknown.

The COAPT trial¹⁵ suggested that a percutaneously delivered mitral clip could reduce functional (secondary) regurgitation with a subsequent substantial improvement in morbidity and mortality, while two-year follow-up of MITRA-FR suggested no benefit.¹⁶

Periodic longitudinal follow-up of patient populations with FMR will be needed to have a deeper understanding of its relation to long-term mortality in patients with various stages of HF, which in turn will help identify those that will benefit most from MV repair.
Left Ventricular Dysfunction in Cancer Treatment

Cancer therapies today have significantly improved survival but at the cost of treatment-related cardiovascular toxicity, including LV systolic dysfunction. Anthracyclines and radiation therapy were the only known cancer treatments with significant cardiotoxicity earlier. However, modern targeted cancer therapies, including HER2 inhibitors, tyrosine kinase inhibitors (TKIs), proteasome inhibitors, and immune checkpoint inhibitors, are known to have adverse cardiovascular events.

People with cardiomyopathy-related gene mutations may be more prone (7.5% compared to 1.1% of those without a titin gene mutation) to develop ventricular dysfunction after the administration of chemotherapy.17 Normal LVEF is a prerequisite for antineoplastic therapies, but it has limitations for risk prediction, and has prompted investigation of serum and imaging biomarkers in patients receiving cardiotoxic therapies. In patients receiving high-dose chemotherapy, early elevations in cardiac troponin I (cTnI)-predicted cardiac events at 3 years,18 and troponin-guided initiation of enalapril in a similar cohort was associated with reduced risk of LVEF decline.19 Decreases in global longitudinal strain (GLS), an echocardiographic marker investigated in breast cancer patients receiving doxorubicin and trastuzumab, have also been shown to predict subsequent LV dysfunction in combination with ultrasensitive cTnI.20 In a systematic review, a 10–15% reduction in GLS predicted subsequent LV systolic dysfunction,21 supporting the American Society of Echocardiography (ASE) recommendations to include GLS and cTnI in risk stratification of patients before and during treatment with anthracyclines or trastuzumab.22

Beta-blockers, ACEI, and ARBs have been mostly investigated in patients receiving lower anthracycline doses and overall have demonstrated feasibility, safety, and varying degree of LVEF decline attenuation, which has been the most common endpoint.

Conclusion

The prevalence of HF is escalating rapidly. Compounding this, HF is an illness that consumes significant health-care resources, inflicts significant morbidity and mortality, and greatly impacts quality of life. Important breakthroughs have redefined opportunities to change the natural history of the disease with a broad range of medical therapies, devices, percutaneous interventions along with different implants and care strategies, including readmission reduction programs and ambulatory outpatient disease management for those with more advanced disease.

References


Asymptomatic left ventricular dysfunction (ASLVD) is more widely prevalent than overt clinical heart failure. ASLVD represents a huge opportunity but is under diagnosed and there are no clear cut trial data or guidelines for management. Symptomatic heart failure carries high morbidity and mortality and appropriate interventions to prevent or delay overt heart failure at the stage of ASLVD is critical in improving the prognosis.

Introduction
Heart failure is increasing in incidence as there is an increase of diabetes, hypertension, coronary artery disease and people surviving to advanced age. Heart failure continues to remain a major threat, an important cause of hospitalizations due to cardiac causes and mortality worse than many cancers despite advances in medical, interventional, and device therapy. The economic and social burden of the disease is immense and it is worthwhile to dwell upon early diagnosis at the asymptomatic stage of left ventricular dysfunction and if it is possible to prevent progression to overt heart failure.

Definition
Asymptomatic left ventricular dysfunction (ASLVD) is defined as depressed left ventricular dysfunction in the absence of overt symptoms and signs of heart failure. The ejection fraction used as cut-off have varied in different studies, but we would use a left ventricular ejection fraction (LVEF) less than 50\% as used in definition of heart failure reduced ejection fraction (HFREF).

American Heart Association Classification of Heart Failure
Stage A: At risk for heart failure like obesity, diabetes, hypertension, CAD, but no evidence of structural disease.
Stage B: Asymptomatic, but having structural abnormalities such as left ventricular dysfunction, left ventricular hypertrophy, and valvular lesions.
Stage C: Symptomatic heart failure.
Stage D: End stage heart failure.
ASLVD is classified as stage B heart failure and has the risk of progression to stage C or D heart failure.

Prevalence
The prevalence of ASLVD ranges from 7.3\% to 23\%. The heterogeneity is compounded by different cut-offs of LVEF used in various studies. The prevalence of ASLVD was 6.0\% in men and 0.8\% in women in the Framingham sub-study of 4,257 subjects who were followed for up to 12 years. Mild ASLVD-EF-40–50\% was present in 61\%, moderate
EF 30–39% in 33%, and only 6% had severe ASLVD with EF less than 30% (Table 1).

The risk of progression to overt heart failure was greater in patients with LVEF less than 40% as compared to mid-range ejection fraction of 40–50%. The relative risk of progression to clinical heart failure was 4.6 in patients with ASLVD in a meta-analysis of 11 studies comprising of 25,369 patients. The risk of progression was 1.7% in patients with asymptomatic left ventricular diastolic dysfunction (ALVDD). The major factors predicting an increased risk of progression from an asymptomatic stage were age, sex, blood pressure, diabetes, and body mass index. In the David-Berg study, patients with mild ASLVD had higher risk of overt HF on follow-up when there was associated diastolic dysfunction in patients with LVEF 40–52%. The HR for HF was 3.3 for patients with mild ASLVD (EF 40–50%), and HR of 7.8 for patients with moderate-to-severe ASLVD (EF < 40%) in the Framingham sub-study. The median survival of ASLVD was 7.1 years in this study (Fig. 1).

**Etiology of Heart Failure**

The major underlying causes of heart failure include hypertension, CAD, diabetes, obesity, and rheumatic heart disease (RHD). Quantitatively hypertension plays the most important contributing factor in isolation or alongside of CAD and RHD. A tight control of blood pressure is therefore one of the important early preventive intervention (Fig. 2).

**Neuroendocrine Activation in ASLVD**

Neuroendocrine activation has been shown to occur much earlier than symptomatic HF. In the SOLVD prevention arm, patients with asymptomatic LVEF less than 35% had higher plasma nor epinephrine levels than normal people, but lower than patients with clinical heart failure, the extent of nor epinephrine elevation correlated with future death, overt heart failure development and ischemic events. Plasma atrial natriuretic peptide, plasma arginine vasopressin levels were also increased but not plasma renin activity, suggestive that sympathetic activation occurs earlier than renin angiotensin system. This may help us plan strategy of treatment in ASLVD (Fig. 3).

In the SAVE trial in patients with LVEF less than 40% following acute myocardial infarction (AMI), all neurohormones (PNE, PRA, AVP, and ANF) were all increased in asymptomatic patients, hence suggestion of benefit from early targeted therapy in ASLVD. Neurohormonal modulation preemptively in the stage of ASLVD may prevent progression to overt heart failure.

**Prognostic Significance of Preoperative ASLVSD and ASLVDD**

In a study of 1,005 patients undergoing vascular surgery, both asymptomatic LV systolic dysfunction and diastolic dysfunction were associated with increased 30-day morbidity and long-term mortality. There was 17% incidence of non-fatal MI at 30 days, 10% in patients with normal LV function, 18% in ASLVDD, 23% in ASLVSD, and 49% in patients with symptomatic heart failure. Long-term follow-up revealed decreased survival in overt HF, HR 10.3, followed by ASLVSD HR 4.6, then ASLVDD, HR 3.0 as compared to normal LV function (Fig. 4).
**Fig. 2:** Etiology of heart failure
HCVD, hypertensive heart disease; CHD, coronary heart disease; RHD, rheumatic heart disease

**Fig. 3:** Plasma norepinephrine levels and correlation to mortality and CV outcomes
Screening for ASLVD

Tests

**ECG:** Presence of Q-waves, old MI, left atrial enlargement, LVH, Conduction blocks, IVCD, and AF should prompt an evaluation of left ventricular function.

**Chest X-ray:** Presence of cardiomegaly, pleural effusion, pulmonary congestion, aortic calcification, posterior mitral annular calcification, aortic valve calcification merit further evaluation.

**NT-ProBNP:** Patients with elevation of NT-ProBNP had ASLVD in 6.6% of screened population in the SCREEN-HF study in a cohort of 3,550 patients with high risk for HF (AGE > 60 years with one other added risk factor for HF). In the David-Berg study, prevalence of ALSVD increased with age and CV risk. The prevalence was 5.3% and NT-ProBNP was more predictive than a combination of Framingham heart failure risk score (FHFRS) and ECG abnormalities.10-12

**ECHO:** ECHO screening should be done for patients with prior myocardial infarction, long standing DM, CKD, uncontrolled hypertension, presence of LVH, elderly patients above 60 years.

*Global longitudinal strain (GLS):* GLS is a more sensitive modality to diagnose early left ventricular function, it is load independent and less inter-observer variability is present. It is calculated by speckle tracking and GLS is the sum of peak longitudinal strain of 18 LV segments calculated from three standard two-dimensional ECHO views, apical long axis, Apical 4 chamber and Apical 2 chamber views. The normal value is -21 and a low value is ≤17. It is especially valuable in patients undergoing cancer chemotherapy as early detection may enable change of drug regime, initiation of early heart failure therapy. A decrease of 10–15% GLS is a reliable predictor of cancer chemotherapy induced cardiotoxicity. Low GLS has been noted in patients with uncontrolled hypertension, uncontrolled DM, obesity, hypercholesterolemia even with preserved LVEF. The low GLS is a predictor of future HF in these patients.13

**Treatment of ASLVD**

ACEI are the cornerstone of therapy of ASLVD. SOLVD prevention trial in patients with LVEF less than 35% had decreased HF hospitalization and overt HF when treated with enalapril as compared to placebo. SOLVD 12 year follow-up study showed decreased mortality in ASLVD patients on enalapril.14 The SAVE trial, captopril in patients with ASLVD following AMI and in the TRACE trial following AMI, ASLVD patients on trandolapril were shown to have reduced CV events, HF, and mortality.

**Angiotensin receptor blockers (ARB):** ARB can be used in ACEI intolerant patients as shown in OPTIMAAL trial with losartan versus captopril and VALIANT trial with valsartan to be non-inferior to captopril in patients with LV dysfunction following AMI, a subset of whom were asymptomatic.

Beta blockers have been shown in the retrospective analysis of SOLVD and SAVE trials to have synergistic benefits when used with ACEI in ASLVD patients. In ANZ study and CAPRICORN trial, carvedilol has been shown to benefit post MI patients with LVEF less than 40%. In the REVERT trial, metoprolol has been shown to result in improvement in ejection fraction and ventricular remodeling in LV dysfunction of ischemic and non-ischemic etiology. Hence, beta blockers should be used in ASLVD to decrease the sympathetic over activation and slow progression of HF in both ischemic and non-ischemic etiologies.
Statin has been shown to reduce heart failure in patients with ischemia in the 4S study.

Diabetic patients with ASLVD had a higher risk of overt HF (HR-1.53) and HF hospitalization (HR-2.04) in the sub-analysis of SOLVD prevention trial patients with DM who developed HF had a mortality of 37% versus 29% in patients without DM. Sodium-glucose cotransporter inhibitor 2 (SGLT2) is the new class of diabetic drug, which prevents heart failure by 23% in a meta-analysis even in patients without pre-existing heart failure. The mechanism of benefit in heart is due to multiple modalities of action. They act by inhibiting glucose and sodium reabsorption in the proximal convoluted tubule causing glucosuria and natriuresis. The diuretic action of SGLT2 inhibitors is more on the interstitial fluid rather than intravascular fluid, so that there is no sympathetic activation and preload to heart is maintained. There is an increase in hematocrit by stimulation of erythropoietin, there is a uricosuric effect as well. The reduction in uric acid contributes to reduced oxidative stress. They inhibit Na\(^+\)-H\(^+\) ion exchanger in the heart resulting in prevention of cytosolic calcium excess which leads to apoptosis, shift the heart energy substrate to energy efficient ketone bodies instead of glucose. They also prevent cardiac fibrosis and hypertrophy and prevent adverse ventricular remodeling, which leads to progression of heart failure (Flowchart 1).

In addition, by increasing the sodium delivery in the distal tubule due to decreased proximal tubule reabsorption of sodium, through a tubule glomerular feedback, SGLT2 inhibitors lead to decreased glomerular pressure and have a renal protective effect as well, they also reduce renal fibrosis and hypoxia, which have favorable effects on the cardio renal syndrome in HFREF (Table 2). 

SGLT2 inhibitors have been shown to decrease HF hospitalization and CV mortality in the EMPAREG,
CANA\textsc{vas}, CRE\textsc{DENCE}, and DAPA-HF trials. The DAPA-HF trial showed benefit in HFREF patients with or without DM. SGLT2 inhibitors added at the stage of A, B, or C has shown benefit and should be included for all diabetic patients with LV dysfunction with or without symptoms. It is probably worthwhile to explore their use in all patients with ASLVD with or without DM.\textsuperscript{15,16}

**Device Therapy**

Patients with LVEF less than 30% for more than 1 month after an AMI have been shown to have survival benefit as shown in the MADIT II trial which included 40% of asymptomatic patients.

Cardiac resynchronization therapy (CRT) has been shown to reverse ventricular remodeling in REVERSE trial in patients with NYHA class II and III, but data not strongly showing benefit in NYHA class I patients.

The PACE trial showed better outcomes in patients with atrioventricular sequential pacing as compared to RV pacing in patients with LVEF less than 45%. Biventricular pacing has been shown to be superior to right ventricular pacing in patients with LVEF less than 50% in the BLOCK HF trial in patients with atrioventricular block with decreased combined end point of mortality, HF hospitalization or more than 15% increase in LV end systolic volume index.

His Bundle Pacing (HBP) is a new pacing strategy, which avoids the adverse consequences of RV pacing and ensures atrioventricular and intraventricular synchrony. It has been found to preserve left ventricular function and reduce mitral regurgitation in patients with heart failure and pacing indication. HBP is also being explored as an alternative to CRT in patients with LBBB and CRT indication.\textsuperscript{15-18}

**Conclusion**

Asymptomatic left ventricular dysfunction occurs twice as common as overt heart failure. ASLVD carries a good prognosis until the development of overt HF and presents with a huge window of opportunity to implement therapy and mitigate the progression and adverse consequences of overt HF. Early screening with ECHO, GLS, and NT-ProBNP will help catching the patients early. RAAS inhibitors, Beta blockers, SGLT2 inhibitors, statins in patients with CAD prevent progression of heart failure and should be initiated in this stage. Avoidance of RV pacing, use of His bundle pacing in patients with left ventricular dysfunction improves LVEF.\textsuperscript{19}

AICD prevents sudden death and decreases mortality in patients with LVEF less than 30% irrespective of their symptom status.

CRT and HBP are useful in patients with LBBB, broad QRS, and mitral regurgitation with LV dysfunction with stage C HF, but data not adequate in ASLVD. The use of ARNI also needs to be explored in ASLVD and if it is superior to ACEI in preventing adverse LV remodeling.
References

CHAPTER

34

Cardiovascular Risk Assessment Tools

Ravikeerthy M

Abstract

Cardiovascular disease is the major non-communicable disease in both developed and developing countries. Its prevalence is increasing with the change in lifestyle factors. It is one of the preventable conditions. The disease remains asymptomatic till advanced stages in majority of the population. Early intervention with lifestyle changes and medication can prevent these cardiovascular events, need tools to identify the people at risk, and these tools are used to calculate an individual’s risk of developing a CV event from risk factors obtained from history, physical examination, or investigations. There are several tools available for the risk assessment but very few tools like JBS3 identify the risk more accurately and this is applicable for Indian population also.

Introduction

Cardiovascular disease (CVD) has overtaken infection as a leading cause of death all over the world. It is the leading cause of not only mortality but also the morbidity, and is a major economic burden. With changing life styles and increased life span, the burden of disease is also increasing. India is no different from this because of the increase in its prevalence and that of CVD risk factors. The Global Burden of Disease study estimates suggest higher age-standardized CVD death rate of 272 per 100,000 population in India compared to the global average of 235 per 100,000 population.

CVDs include coronary heart disease, cerebrovascular disease, peripheral artery disease, aortic atherosclerosis, and aneurysm of aorta (thoracic or abdominal).

Cardiovascular risk factors are divided into modifiable and non-modifiable risk factors. Modifiable risk factors are further classified as health conditions and lifestyle factors (Table 1).

Various studies have shown that early intervention with lifestyle changes and medication can prevent these cardiovascular events. So accurate estimation of CV risk is important as it affects health behavior and medical decision-making, and helps improve patient compliance to the treatment. As per the world health organization prevention is classified into the following type:

- Primordial prevention
- Primary prevention
- Secondary prevention
- Tertiary prevention
- Quaternary prevention

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<th>Table 1</th>
<th>Classification of CV risk factors</th>
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<td>Non-modifiable risk factors</td>
<td>Modifiable risk factors</td>
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<td>Health conditions</td>
<td>Lifestyle factors</td>
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<td>Age</td>
<td>Hypertension</td>
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<td>Sex</td>
<td>Dyslipidemia</td>
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<td>Diabetes mellitus</td>
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The main aim should focus on Primordial or Primary prevention.5

**Definition**
Cardiovascular risk stratification by definition is the assessment to estimate the risk of developing cardiovascular event or estimating the risk of developing cardiovascular event during noncardiac surgery by perioperative risk assessment.

So we need tools to identify the people at risk and these tools are used to calculate an individual’s risk of developing a CV event from risk factors obtained from history, physical examination, or investigations. Most guidelines recommend the use of risk scores to predict global risk rather than focusing on single risk modification. Studies from different parts of the world have reported that the rates of use of CV risk scores range from 17% to 65%. A study conducted in the United States, showed that 92% of physicians were aware of risk stratification tools; however, it was used in only 41% of patients, with only a part of the latter being used to guide the subsequent treatment decisions.

Studies have shown that subjective estimation of CV risk by doctors is inaccurate. Patients and doctors generally estimate risk by risk factor profile or risk factor counting as opposed to absolute risk calculation. However, focusing on individual risk factors or risk factor counting tends to underestimate risk in those who may have slightly elevated level of multiple risk factors that synergistically increase the overall absolute CV risk.4,6

Another study in primary care physicians in Canada demonstrated that almost one-third were not aware of the defining point for high CV risk (>20% 10-year FRS CV risk) which leads to misclassification of risk and underestimation of truly high-risk patients.

**Risk Stratification Tools**
There are many different tools available. Most important are listed below:
- Framingham Risk Score (FRS)
- Prospective Cardiovascular Munster Score (PROCAM)
- World Health Organization/International Society of Hypertension (WHO/ISH) CVD risk prediction charts
- Systemic Coronary Risk Evaluation (SCORE)
- American College of Cardiology/American Heart Association (ACC/AHA) pooled cohort equations
- 3rd Joint British Societies (JBS3) risk calculator
- Reynolds score
- Assign risk score
- Qrisk risk score
- Adult Treatment Panel III

**Framingham Risk Score**
It is the landmark study especially for the assessment of 10 years risk and most widely adapted. This is also used to assess the composite of all atherosclerotic cardiovascular events like angina, stroke, peripheral vascular disease, and heart failure. Paramaters used for assessment are age, sex, diabetes, smoking, hypertension, total and HDL cholesterol.

Limitations—does not predict the true values in European and Asian people. Some important risk factors like family history of cardiovascular events, chronic kidney disease and body mass index are not included. Analysis of the study show both overprediction in low risk population and underprediction in high risk population. The study relies greatly on age as a predictor of cardiovascular risk; hence, in a young individual, the estimated 10-year CV risk is invariably low, even in the presence of multiple cardiovascular risk factors.

**Systemic Coronary Risk Evaluation**
This study was derived from 12 cohort studied involving more than 200,000 people in Europe and accuracy for European population is good. One major plus point of this study is its prediction of first fatal cardiovascular event.

**Reynolds Risk Score**
This was initially developed to assess the risk in healthy women and later applied to male population with slight modifications.7 Around 25,000 healthy health professionals were involved in the initial study to assess the composite events like myocardial infarction, stroke, coronary revascularization, and cardiovascular death. Compare FRS and score tools, inclusion of HS CRP and parenteral premature cardiac events in this gives a better predictive value.

**JBS3 Risk Calculator**
The joint British societies released this risk score in 2014, and end points assessed are cardiovascular death, nonfatal MI, angina, stroke, TIA, and intermittent claudication.
This score estimates both 10-year risk and lifetime risk of CVD and also the “Heart Age.” This is a more extensive risk assessment tool compared to others. It includes several additional risk factors such as obesity and family history of premature CVD. This study also includes data on ethnic Indians and is more suitable for Indian population for the CV risk assessment.

**Assign Risk Score**

Assessing cardiovascular risk to Scottish Intercollegiate Guidelines Network is developed in Scotland. The study group involved the asymptomatic CVD subjects aged between 30–74, both men and women. The study included most of the parameters as in other studies and a new risk factor that is social deprivation. One of the limitations of the study in not including obesity as a risk factor. This score predicted the 10-year risk of cardiovascular disease. It included all the discharges with the diagnosis of CVD and death.

**QRISK Risk Score**

QRESEARCH cardiovascular risk algorithm a cohort of 1.3 million subjects, aged between 35–74 years and were free from diabetes and CVD. The following risk factors were considered in the study-age, sex, smoking status, systolic blood pressure, ratio of total to HDL-C, body mass index, family history of CHD, social deprivation, and antihypertensive treatment. The above score predicts the 10-year risk of CVD such as MI and also stroke, transient ischemic attack. Major limitation of the study is that it was validated on the same study subjects.

The risk of CVD is classified into borderline (5–7.5%), intermediate risk (7.5–20%), and high risk (>20%) based on the different risk score. ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease-2019 recommends Cardiac Risk Assessment. By using the pooled cohort equations (PCEs), the physician should regularly assess cardiovascular risk factors and calculate 10-year risk of ASCVD of adults of age group 40–75 years.

For adults 20–39 years of age, it is rational to assess traditional ASCVD risk factors at least once in 4–6 years. In adults at borderline risk (5% to <7.5% 10-year ASCVD risk) or intermediate risk (≥7.5% to <20% 10-year ASCVD risk), it is rational to use additional risk-enhancing factors to guide decisions about preventive interventions (e.g., statin therapy). In adults at intermediate risk (≥7.5% to <20% 10-year ASCVD risk) or selected adults at borderline risk (5% to <7.5% 10-year ASCVD risk), if risk-based decisions for preventive interventions (e.g., statin therapy) remain uncertain, it is rational to measure a coronary artery calcium score to guide clinician–patient risk discussion. For adults 20–39 years of age and for those 40–59 years of age who have <7.5% 10-year ASCVD risk, estimating lifetime or 30-year ASCVD risk may be considered.

The present understanding of the 10-year risk for atherosclerotic CVD identifies patients in higher-risk groups who are likely to have greater net benefit and lower number needed to treat for both statins and antihypertensive therapy. Lifetime CVD risk estimation, which measures the cumulative risk of developing the disease during the rest of an individual’s lifespan, could provide a more accurate assessment of future risk of CVD than short-term risk estimates, more so in younger individuals who have low short-term risks. The guidelines now recommend stepwise stratification of disease-free and asymptomatic individuals into high short-term, low short-term/high lifetime, and low short-term/low lifetime CHD risk groups for targeting primary prevention strategies in all eligible individuals.

**Subclinical Atherosclerosis Assessment**

Risk-scoring tools can improve the prediction of risk but their adoption in clinical practice is poor. Risk factor based approach estimate CV risk at population level and not at individual level. Hence, it is desirable to develop tools which could accurately identify individuals who are truly at risk. For example, 20% risk of cardiovascular events over 10 years means that out of 100 such individuals, 20 will develop a vascular event over 10 years; however, it is impossible to predict who are those 20 who might develop the event. Hence, all 100 patients need treatment.

Hence, inclusion of noninvasive tests that can identify subclinical atherosclerosis is required in improving the risk assessment.

Imaging techniques for sub-clinical atherosclerosis not only shows the evidence of sub-clinical atherosclerosis but also increases the probability of developing CVD later on, irrespective of cardiovascular risk factors and also helps benefit the patient by providing suitable preventive strategies and helps improving patient’s treatment compliance.
The following is the list of tools available for the assessment of subclinical atherosclerosis:
- Carotid plaque assessment
- Carotid intima-media thickness (CIMT)
- Brachial artery flow-mediated dilatation
- Coronary calcium score (CCS)
- Ankle-brachial index
- Pulse wave velocity (PWV)
- Stress test/TMT

Coronary calcium score, carotid ultrasound imaging, and PWV are studied extensively in clinical practice. CCS is a computed tomography test which helps detect and quantify the amount of calcium in the coronary arteries. Presence of coronary calcium provides direct evidence of ongoing coronary atherosclerosis. CCS also provides prognostic information. CCS correlates with the extent of coronary artery disease in Indian subjects as well. The presence of atherosclerosis in carotid arteries shows high risk of coronary events also (since atherosclerosis is a generalized process). It can evaluate both intima-media thickness (CIMT) and carotid plaques. CIMT is associated with greater risk of vascular events, independent of common CV risk factors or FRS. CIMT is related to CV risk factors, presence of CAD, and the extent of CAD on angiography in Indian patients also. Aortic pulse wave velocity (PWV) is an indicator of arterial stiffness. It has greater value in the evaluation of pathophysiologically states associated with arteriosclerosis, such as hypertension, ageing, and end-stage renal disease. A significant relationship between PWV and CV risk factors and incident CVD is shown in Indian subjects.

Other Markers of CV Risk Assessment
- High-sensitive c-reactive protein
- Lipoprotein a [Lp(a)]
- Apolipoproteins
- Inflammatory cytokines
- Fibrinogen

Indian Scenario
Indians are at a greater risk of CV disease as compared to other populations probably due to genetic make-up and early onset of conventional CV risk factors. A calibration method has been proposed to optimize cardiovascular risk estimates for Indians. A 10-year risk based on FRS can be recalibrated by multiplying the calculated risk with a correction factor. For rural Indians, the suggested correction factor is 0.8 for women and 1.0 for men, whereas for urban Indians it is 1.54 for women and 1.81 for men.11

WHO published series of risk prediction charts, which might be the only option available for populations for which prospective studies are not available. Another option is JBS3 risk calculator that allows separate risk assessment for people with Indian ethnicity. JBS3 risk calculator seems to have greater accuracy in Indian patients as it includes data on ethnic Indians and takes into consideration of many other risk factors such as obesity and family history of premature CVD. So it is more comprehensive risk assessment tool.12

Conclusion
Assessment of the risk of occurrence of future CV events is an important step in the management of the patients requiring primary prevention of CV disease. Using various risk assessment tools, people at high risk of CVD can be recognized. However, in clinical practice, cardiovascular risk assessment by primary care physicians frequently involves subjective evaluation rather than the use of risk assessment tools. Most of the cardiovascular risk assessment tools are not suitable for use in the Indian population. Therefore, there is a need for an optimal cardiovascular risk assessment tool in the Indian population. Although Framingham risk score is most widely used and accepted it is not suitable for the Indian population. Among the various risk assessment tools, the Joint British Societies (JBS3) risk calculator has been reported to provide a more accurate estimation of the cardiovascular risk in Indian population. Assessment of subclinical atherosclerosis enables more accurate identification of individuals who are at increased risk of CVD.

References
Abstract
Rheumatic heart disease is a disease for which no significant progress has taken place as regards the diagnosis and the management for seven long decades; therefore, we find that physicians are struggling with the same dilemma in diagnosis and the age-old painful and ineffective prophylaxis with parenteral penicillin.

The ARMOR, i.e., Arati’s Regime for Management of Rheumatic Fever – Against RHD will prove to be a great milestone in the management of Rheumatic Fever. The practice of ARMOR shall simplify and increase the sensitivity of diagnosis of RHD and make the treatment and prophylaxis of RHD safe, effective, and popular.

Introduction
ARMOR consists of:

I. Diagnostic criteria for rheumatic fever (RF) rheumatic heart disease (RHD)—arthralgia or arthritis, cardiac involvement typical of RF, Echo-Doppler findings typical of RF RHD, with history of sore throat.

II. Use of newer anti-inflammatory drugs for arthritis of RF—aceclofenac 200 mg BD or any NSAID for 5 days or longer.

III. Primary prevention, treatment, and secondary prophylaxis of RF RHD with tablet azithromycin 500 mg 1 daily for 5 days followed by 1 tablet once a week for 1 year only.

Azithromycin must be started with 500 mg/day each time even when changing over from other drugs.

Since more than five decades physicians have been struggling with the very same weapons against RF/RHD although there have been great strides in management of infections especially over past two decades.

RHD is no doubt a heart disease, but it is well established that it begins as an infection of the tonsils/sore throat which later, by still largely unexplained mechanism, destroys the heart valves irrevocably thus shortening the life span of the individual.

Since 1940s though several attempts were made to bring about changes to Jones Criteria for diagnosis and management of RF RHD, the dire changes needed were not made.

The Major Problems with Application of Jones Criteria

I. Very complicated confusing criteria for diagnosis: RHD is a simple disease with very typical symptoms and consistency of clinical features; therefore, should be very easy to diagnose by any practitioner. Moreover, since the introduction of Echocardiography Doppler study, a very definite diagnosis can be made by viewing the heart under direct vision.

The ARMOR regime therefore in its diagnostic limb only includes typical migratory arthritis affecting the medium and large joints, transient, recovering completely, endocarditis of heart valves resulting in regurgitant or stenotic valves, pericarditis with minimal fluid with full recovery, myocarditis with MR TR, cardiomegaly, heart failure, very often even...
irreversible heart valve damage—mitral stenosis, mitral regurgitation, aortic regurgitation, aortic stenosis, tricuspid regurgitation.

The heart lesions typical of RF RHD can be easily and definitively confirmed by Echo Doppler study, which is now available as easily as X-ray of yesteryears.

The other clinical features of RF RHD viz chorea, subcutaneous nodules, and erythema marginatum have been given too much importance as major Jones criteria.

In a study of 200 patients of RF by Lalchandani et al. it was shown that out of all the Jones criteria only arthritis, arthralgia, and carditis were found in the majority of patients whereas there were no patients with chorea, erythema marginatum, or subcutaneous nodules.¹

Since it is well known that chorea in RF occurs as an isolated feature and almost never with cardiac involvement; therefore, it should not be a major diagnostic criterion for RF. Also a patient of chorea does not have the evidence of Streptococcal infection; therefore, chorea could very well be a separate entity called Sydenham’s chorea.²,³

The incidence of chorea has been very low in western literature and very rare in Indian patients. A patient of chorea who does not have other features of RF should not be labeled as patient of ARF as there are many other causes of chorea.

According to Jones criteria only one major and two minor criteria along with essential association of GABHS is required for diagnosis so subcutaneous nodules and erythema marginatum, which have so many other causes cannot be considered as major criteria.

The clinical profile of 550 cases of RF RHD was studied by Ravisha et al. in India where arthritis and carditis was found in 169 (67.6%) and 105 cases (42%) chorea in 47 (18.8%) and erythema marginatum in 4 only.⁴

As regards minor criteria of Jones they are mostly the features of infection and inflammation, which are common to many other diseases.

By thus simplifying the diagnosis of RF RHD sensitivity of ARMOR would be high compared to Jones and would help in starting early prophylaxis and curing the cases before serious organic heart disease.

It is pointed out here that even ARF can be picked up on echocardiography-echocardiographic criteria for diagnosis of RF by Dr Anita Saxena and Dr IB Vijaylaxmi.⁵,⁶

II. A majority of literature on RF RHD advocate an extremely dangerous drug—Aspirin as the drug of choice for rheumatic arthritis: It is really flummoxing that even after the discovery of an array of anti-inflammatory analgesic drugs with excellent safety profile and availability the textbooks continue to advocate Aspirin. Aspirin is a very toxic drug causing peptic ulcer, hemorrhage from gastric and other sites, rhinitis, bronchial asthma, Reye’s syndrome and even death.

Aspirin has been recommended in a very high dose of 8–12 g/d for 6 weeks to 6 months and needs to be tapered over weeks to avoid rebound relapse.

Therefore, Aspirin should be replaced with the newer anti-inflammatory aceclofenac 200 mg twice a day or Nimesulide 200 mg twice a day, which needs to be given only for 5 days or more according to discretion of physician. These are very safe effective easily available and can be given for very short duration without rebound or relapse.⁷

III. The antibiotic of choice till today continues to be the age-old BPG (Benzathine Penicillin): The mainstay of prevention and treatment of RHD is an antibiotic effective against GABHS. BPG the gold standard is given as a stat dose IM AST in a dose of 1.2 m units for treatment. For secondary prophylaxis BPG 1.2 m units is given IM AST every 21 days.

Today the best drug for GABHS is azithromycin which if started within 9 days of symptom of sore throat, almost all cases of RF can be prevented.

Azithromycin can be used for primary prevention treatment and also to prevent recurrent attacks of ARF as well as secondary prevention because of its accessibility safety, efficacy, affordability, tolerability, and oral mode of dispensation.

All cases of sore throat whether of viral or bacterial etiology resolve in 3–5 days but full course of azithromycin 500 mg or 12 mg/kg once daily for 5 days must be given to all cases to prevent RF RHD in the developing countries.⁸

BPG must be replaced with azithromycin due to the following reasons:

- Severe fatal reaction may occur with BPG in as many as 1:10000 patients, which is a considerable number
as 20 million people may be having RHD in the world today. Only a well-equipped emergency setup can deal with anaphylaxis due to BPG.

- The demand of BPG hugely outruns the supply.
- BPG has to be given AST each time.
- After an injection BPG the patient suffers from same features of RHD like pains, aches, and fever.
- BPG is an oily injection given deep IM 2–5 mL in quantity to cachectic patients of RHD.
- Patients have transient valvulitis of MV AV after BPG so that benefit of BPG is not seen.
- Commonly co-prescribed drugs like warfarin, aspirin, diuretics interact with penicillin.
- Accidental IV can cause cardiac arrest and death.
- Severe allergic reactions are common.
- Pseudomembranous colitis can occur.
- Clostridium difficile associated diarrhea increases mortality and morbidity.

Many studies have shown that relapse and recurrence and progression of RHD is not much influenced by regular administration of BPG as substantiated in Pediatric Cardiology 2010 Division of Cardiology, University of Virginia in retrospective review of patients of ARF less than 21 years, which showed recurrence rate of 38% in 144 patients of RHD, compliance with BPG 59% and recurrence of ARF in 57%.

The recurrence rate of RF from various studies is 3–8% over 5–6 years with BPG and consistently less than 3% with azithromycin.

Penicillin concentration in serum of more than 0.02 µgm/mL is required to prevent recurrence compared to azithromycin, which persists in therapeutic concentration in tissues.

**Azithromycin is the drug of choice in ARMOR due to the following reasons:**

- Azithromycin is an azalide, chemical name is 9-deoxy-9-za9-a-methyl-9-a homoerythromycin, Molecular weight 749.
- Azithromycin if started with 500 mg OD for 5 days has to be given only weekly thereafter as its persistence in the tissues continues for about 6 days, therefore, needs to be given on the 7th day, that is, weekly dose.
- It has autoimmune suppressant and anti-inflammatory effect.
- It is acid stable so oral dose is well absorbed and is readily absorbed.
- Time to peak concentration is 2.1–3.2 hours.
- The drug is concentrated in phagocytes and actively transported to infection site thereafter released at the site of infection in large quantities.
- Concentration of azithromycin is 50 times higher in tissues than in plasma due to ion trapping and high solubility of drug. Concentration in lung and tonsils exceeds MIC 90 even after a single dose. A single large dose can eradicate the bacteria completely.
- It acts by binding to 50s ribosomal subunits and prevents translocation of peptides thus inhibiting bacterial protein synthesis.
- After single dose of 500 mg of azithromycin its concentration in plasma declines in polyphasic pattern with a plasma clearance rate of 630 mL/minute and terminal elimination half-life 68 hours due to property of large uptake and sustained slow release of drug from tissues.
- It is freely available, safe, cost-effective with excellent antistreptococcal activity.
- Has to be given with caution in renal impairment.
- Safe in hepatic impairment.
- Safe in pregnancy.

Azithromycin discovered in 1991 is extensively used for GAS with great results by physicians and ENT surgeons.

In a systematic review of 21 RCTs azithromycin 20 mg/kg/day for 3 days achieved GABHS eradication in 95% cases in streptococcal tonsillopharyngitis.

In a study by Lalchandani et al., 730 patients were given azithromycin for ARF in dose 500 mg once daily for 5 days followed by 500 mg on 2 consecutive days in a week. No patient had relapse or reinfection or worsening of cardiac valve disease. Compliance was 100% and patients who had no new problem attributable to RF were given prophylaxis for 1 year only.

In a correspondence with Prof A Lalchandani, Dr Stephen Marko of World Heart Federation, University of Connecticut, expressed concern over use of BPG due to alarming issues of quality and quantity of drug stating that treatment guidelines be modified by individual circumstances.

After detailed deliberations over the GABHS infection, its persistence in the bloodstream, sensitivity to the drug, a possible time-interval for causation of autoimmune
damage, the time gap between infection and carditis progressing to organic heart valve disease, conclusion is that there is no basis for RHD prophylaxis for greater than 1 year after sore throat, recurrence, or relapse or ARA. In a study by Dr BL Agarwal in 1986 the mean duration of symptoms before admission to hospital in a series of 100 cases of initial attack was 6.47±3.4 weeks, in children without carditis it was 5.0±4.03 weeks after onset of illness while in those with uncomplicated carditis it was 5.95±5.26 weeks.

In view of the above facts RHD prophylaxis exceeding 1 year seems devoid of reasoning. Even in poststreptococcal reactive arthritis VHD patients should be given appropriate prophylaxis for up to 1 year (Class IIb, LOE C-AHA Scientific Statement).

Conclusion

In anticipation of infection lifelong prophylaxis with antibiotic is not only absurd but extremely harmful; that too with a drug which has to be tested each time for sensitivity, the risk incurred being greater than benefit reaped. With azithromycin prophylaxis for 1 year the disease progression is checked and even reversed.

For the past more than 12 years azithromycin is being given exclusively for treatment and prophylaxis of RF RHD in GSVM Medical College, Kanpur, with excellent miraculous results which have been documented in theses of PG students over several years. Many studies have shown azithromycin to be a much superior drug to BPG when GABHS is culprit organism of RF.

References

17. Azithromycin (ARMOR) must replace benzathine penicillin for treatment. Available from https://www.omicsonline.org/.../azithromycin-armor-must-replace-benzathine_penicillin
Abstract

Chronic stable angina, while being a widely used term, is part of a much wider spectrum of chronic coronary syndromes (CCS). This spectrum consists of a dynamic and progressive disease course rather than a stable one, and hence requires thorough risk stratification and management. Risk stratification includes analyzing the demographics and clinical presentation of the patient to decide further management and testing. While ECG is the first step in making the diagnosis, there are several other modalities available to us today that supplement the ECG. These include both functional and anatomical imaging techniques like Echocardiography, Cardiac Magnetic Resonance Imaging, Coronary CT Angiography and various stress tests as well as invasive techniques like Percutaneous Coronary Angiography. The mainstay of treatment for CSA and CCS remains medical treatment. There are a variety of drug classes available that can be tailored depending on individual patient requirements. In addition to medical management, myocardial revascularization can also be attempted in specific cases using percutaneous coronary intervention or surgery.

Introduction

Coronary artery disease (CAD) or ischemic heart disease (IHD) covers a wide spectrum of syndromes that occur due to imbalance between myocardial oxygen demand and supply. The underlying pathology is most often the atherosclerotic involvement of the epicardial vessels, with varying degrees of obstruction. While the disease itself is chronic and progressive, presentation varies widely. Patients may be asymptomatic, present with a chronic stable course, or present acutely.

The most widely accepted classification of symptomatic patients includes stable coronary artery disease (SCAD) and acute coronary syndrome (ACS). Recent literature has recommended the use of the term chronic coronary syndrome (CCS) as an alternative to SCAD so as to retire the use of “Stable” and emphasize the progressive nature of the condition. The 2019 guidelines on CCS by the European Society of Cardiology (ESC) provide a comprehensive outlook on this new terminology as well as clinical practical guidelines on the approach and management of CCS. The ACS spectrum includes unstable angina, non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI). SCAD/CCS also includes a variety of presentations, one of which is chronic stable angina (CSA). This is an episodic clinical syndrome caused due to transient myocardial ischemia. CSA occurs due to gradual progression of atherosclerosis in the epicardial vessels or due to supply/demand mismatch caused increased myocardial oxygen demand.

Presentation

Angina refers to chest pain/discomfort attributable to myocardial ischemia. Elements of history that are critical to making the diagnosis of angina include four main categories as shown in Table 1.
Symptomology can be classified on the basis of history taking into typical, atypical, or noncardiac chest pain (Table 2). Atypical presentation is often seen in women and elderly.

Angina can be graded into various classes depending on severity (Table 3).

**Evaluation**

In addition to laboratory investigations and biochemical tests to identify possible causes of ischemia and risk factors, the diagnosis of CAD can be made with the help of the several modalities. The choice of diagnostic tests should made after giving due consideration to pretest probability and the patients be stratified as high-, intermediate-, and low-risk groups. For example, a young woman presenting with atypical angina would be classified as a low-risk patient and does not warrant additional testing for CAD if the baseline ECG is normal.

**Resting Electrocardiography**

While a normal ECG is often recorded, ongoing angina may be accompanied by dynamic ST segment changes making this modality crucial for diagnosis of CAD. Other findings that may be indicative of underlying pathology include evidence of previous infarction (Q waves or an R wave in V1 or persistent ST-T wave inversions), conduction blocks (LBBB, AV blocks), and LV hypertrophy.

**Resting Echocardiography**

Echocardiography utilizes ultrasound waves to assess cardiac function and structure. In patients with CAD, ischemic myocardial damage can be correlated with LV ejection fraction (LVEF) as well as regional wall motion abnormalities (RWMA). It may also help in identifying alternative causes of chest pain like heart failure, valvular abnormalities (like aortic stenosis) or cardiomyopathies. CMR is a relatively new alternative to echocardiography and can be helpful in defining cardiac anatomy and function, especially in patients with poor acoustic windows.
Exercise Electrocardiography

Exercise ECG (Ex-ECG) is a widely utilized initial diagnostic test for SCAD and CSA. It is often conducted using a Treadmill test (TMT). The presence of exercise induced ST-T changes or chest pain is an indicator of coronary obstruction. The Duke Treadmill Score can also be of valuable diagnostic and prognostic importance, and combines multiple predictors into one composite index. Ex-ECG has a sensitivity and specificity of 68% and 77% respectively, for detection of CAD. However, the diagnostic performance of Ex-ECG is inferior as compared to diagnostic imaging tests. Hence, there may be limited benefit of doing Ex-ECG testing without the addition of imaging. Other limiting factors to its use include patients who are unable to reach target heart rate and the existence of baseline ECG abnormalities that might interfere with the interpretation of ST-T changes, for example, LBBB, paced rhythm, WPW syndrome, or baseline ST depression. Nevertheless, careful interpretation of Ex-ECG in selected patients may be of considerable benefit in resource limited conditions and non-availability of imaging.

Stress Echocardiography/Stress CMR

New or worsening RWMA or LV function during, immediately before, and after stress are the diagnostic outcomes in stress echo. This stress, that is, reaching a target heart rate, can be achieved using either exercise or pharmacologic agents. In patients who have difficulty in exercising, stress can be induced by pharmacological agents, of which dobutamine is most commonly used. Alternatives are vasodilators like adenosine, dipyridamole, and regadenoson. Stress echocardiography has a sensitivity of 70–85% for exercise and 85–90% with pharmacological agents and specificity of 77–89% for exercise and 79–90% with pharmacological agents.

Nuclear Myocardial Perfusion Imaging (MPI)

Nuclear MPI is an excellent noninvasive modality that provides assessment of stress induced reversible perfusion defect (RPD) in the myocardium. RPD refers to decrease in myocardial perfusion after stress, which may be exercise or pharmacologically induced. The sensitivity of stress nuclear MPI ranges from 82% to 88% for exercise and 88% to 91% for pharmacological MPI, whereas the specificity ranges from 70% to 88% for exercise and 75% to 90% for pharmacological stress nuclear MPI. Stress CMR MPI can also be used to assess MPI.

Coronary CT Angiography (CCTA)

CCTA is a noninvasive diagnostic test using intravenous contrast to provide a highly accurate definition of coronary artery lumen. CCTA, along with functional noninvasive imaging like nuclear MPI or Stress Echo, is recommended as the initial diagnostic test for diagnosing CAD by guidelines. CCTA’s high sensitivity (values ranging 93–97%) and negative predictive value make it an excellent modality to rule out CAD.

Invasive Testing

Invasive coronary angiography is considered the “gold standard” for diagnosis of CAD and may be used in cases where noninvasive tests are either inconclusive or indicate a high likelihood of severe IHD. It may also be used as an initial diagnostic test in patients with high clinical likelihood of CAD or angina with minimal exertion or symptoms unresponsive to medical therapy.

Treatment

Management of CSA involves a multidisciplinary approach using general measures like lifestyle management, promotion of medical adherence, and support for managing lifestyle risk factors in conjunction with medical or interventional management. Lifestyle recommendations include smoking cessation, dietary changes, regular physical activity, maintaining a healthy weight, as well as management of risk factors like hypertension, diabetes, and hypercholesterolemia.

Medical Management

This is the mainstay of treatment in CSA for both symptomatic relief and coronary event prevention. The drugs used are mentioned in Table 4.

Revascularisation: Myocardial revascularization should be considered in patients of CSA who are symptomatic despite medical therapy. While there is no mortality benefit of revascularization in CSA, some patients continue to be symptomatic despite optimal medical treatment. Such patients may benefit from revascularization, leading to improvement in quality of life and endurance with
### TABLE 4  
**Medical management of chronic stable angina**¹

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<td>Irreversible COX-1 inhibition</td>
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<td>Patients in whom DAPT is recommended (e.g., Post-PCI, history of PAD/TIA/Ischemic stroke) in combination with aspirin</td>
<td>Block the platelet P2Y₁₉ receptor, thus inhibiting platelet activation and preventing the development and propagation of arterial thrombus</td>
</tr>
<tr>
<td>- Prasugrel</td>
<td></td>
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<tr>
<td>- Ticagrelor</td>
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<tr>
<td><strong>Anti-anginal drugs</strong></td>
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<td><strong>Beta-blockers</strong></td>
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<tr>
<td>β, selective: Metoprolol</td>
<td>Patients with recent MI or chronic heart failure</td>
<td>Reduce heart rate, contractility, and atrioventricular conduction, thus reducing myocardial oxygen demand and time-to-angina onset during exercise</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td></td>
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<tr>
<td>Atenolol</td>
<td></td>
<td></td>
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<tr>
<td>Non β, selective: Carvedilol</td>
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<td></td>
</tr>
<tr>
<td><strong>Calcium Channel Blockers</strong></td>
<td></td>
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</tr>
<tr>
<td>DHP: Nifedipine</td>
<td>• Hypertensive patients with angina usually with a beta-blocker</td>
<td>DHP: Reduction in peripheral vascular resistance due to arterial vasodilation</td>
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<tr>
<td>Amlodipine</td>
<td>• Exercise induced ischemia</td>
<td></td>
</tr>
<tr>
<td>Non-DHP: Verapamil</td>
<td>All types of angina (exercise, vasospastic, or unstable), SVTs, and hypertension. Avoided in heart failure or in patients on beta-blockers</td>
<td>Decrease heart rate and myocardial inotropism</td>
</tr>
<tr>
<td>Diltiazem</td>
<td></td>
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<tr>
<td><strong>Nitrates</strong></td>
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</tr>
<tr>
<td>Short acting: Sublingual/Spray nitroglycerin</td>
<td>• Acute effort angina</td>
<td>Dilatation of peripheral veins, with corresponding reductions in systemic vascular resistance, coronary blood flow redistribution, and preload</td>
</tr>
<tr>
<td>Long acting: Isosorbide mononitrate</td>
<td>• Prophylaxis before physical activities</td>
<td></td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>Angina prophylaxis in cases where beta-blockers or non-DHP CCBs are contraindicated, poorly tolerated or provide insufficient symptom control</td>
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<tr>
<td><strong>Lipid lowering drugs</strong></td>
<td></td>
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<tr>
<td><strong>Statins:</strong></td>
<td>Moderate to high dose statin therapy is indicated in all patients irrespective of LDL/Cholesterol levels</td>
<td>HMG-CoA reductase inhibition</td>
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<tr>
<td>Atorvastatin</td>
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<tr>
<td>Rosuvastatin</td>
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<tr>
<td>Simvastatin</td>
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¹ Contd...
reduced pharmacological and mental burden on the patients. Other indications of revascularization include multivessel disease, reduced ejection fraction, significant coronary artery stenosis, and large area of ischemia (>10% of LV). Revascularization may be achieved percutaneously or with CABG.

Conclusion

A patient with history of chest pain presents a diagnostic challenge for physicians because of the wide variety of causes and variability in presentation. Therefore, careful history taking and guideline dictated testing is essential for identifying possible cardiac causes without subjecting the patient to unnecessary testing and monetary burden.

While chronic stable angina often presents as a "stable" disease, it is important to carefully evaluate patients for progressive disease or risk of imminent ischemic event. Lifestyle modification and medical therapy are the mainstay of treatment of CSA. Revascularization may be considered in addition to these in selected patients with careful consideration.

References


CHAPTER

Evaluation and Management of Chronic Stable Angina: Physicians Perspective

Vibhu Khanna, Ankush Gupta, Sanya Chhikara

Abstract

Chronic stable angina, while being a widely used term, is part of a much wider spectrum of chronic coronary syndromes (CCS). This spectrum consists of a dynamic and progressive disease course rather than a stable one, and hence requires thorough risk stratification and management. Risk stratification includes analyzing the demographics and clinical presentation of the patient to decide further management and testing. While ECG is the first step in making the diagnosis, there are several other modalities available to us today that supplement the ECG. These include both functional and anatomical imaging techniques like Echocardiography, Cardiac Magnetic Resonance Imaging, Coronary CT Angiography and various stress tests as well as invasive techniques like Percutaneous Coronary Angiography. The mainstay of treatment for CSA and CCS remains medical treatment. There are a variety of drug classes available that can be tailored depending on individual patient requirements. In addition to medical management, myocardial revascularization can also be attempted in specific cases using percutaneous coronary intervention or surgery.

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The ACS spectrum includes unstable angina, non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI). SCAD/CCS also includes a variety of presentations, one of which is chronic stable angina (CSA). This is an episodic clinical syndrome caused due to transient myocardial ischemia. CSA occurs due to gradual progression of atherosclerosis in the epicardial vessels or due to supply/demand mismatch caused increased myocardial oxygen demand.2

Presentation

Angina refers to chest pain/discomfort attributable to myocardial ischemia. Elements of history that are critical to making the diagnosis of angina include four main categories as shown in Table 1.
TABLE 1  Anginal chest pain

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Chest pain, often retrosternal, with radiation to the epigastrium, arms, shoulders, neck and throat, jaw, and rarely interscapular Levine sign: Placing a clenched fist over the precordium to describe the pain</td>
</tr>
<tr>
<td>Quality</td>
<td>Often described as: squeezing, pressure, constricting, strangling, burning, chest fullness, band-like sensation, ache, heavy weight on chest</td>
</tr>
<tr>
<td>Duration</td>
<td>Classically for 2–5 minutes but usually lasts not more than 20–30 minutes</td>
</tr>
<tr>
<td>Other exacerbating or relieving factors</td>
<td>Provoking factors: Increased myocardial oxygen demand due to exercise, cold, emotional stress, sexual intercourse, meals, or lying down Relieving factors: termination of the provoking factor or administration of nitroglycerin</td>
</tr>
</tbody>
</table>

TABLE 2  Clinical classification of angina

<table>
<thead>
<tr>
<th>Type</th>
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</tr>
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<tbody>
<tr>
<td>Typical</td>
<td>Substernal chest discomfort with characteristic quality and duration Relieved by rest or nitroglycerin</td>
</tr>
<tr>
<td>Atypical</td>
<td>Meets two of the above characteristics</td>
</tr>
<tr>
<td>Non-cardiac</td>
<td>Meets one or none of the typical angina characteristics</td>
</tr>
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Source: Knuuti, J. et al.¹

Symptomology can be classified on the basis of history taking into typical, atypical, or noncardiac chest pain (Table 2). Atypical presentation is often seen in women and elderly.

Angina can be graded into various classes depending on severity (Table 3).

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</tr>
<tr>
<td>Non-DHP: Verapamil, Diltiazem</td>
<td>Exercise induced ischemia</td>
<td>Decrease heart rate and myocardial inotropism</td>
</tr>
<tr>
<td><strong>Nitrates</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short acting: Sublingual/Spray nitroglycerin</td>
<td>Acute effort angina, Prophylaxis before physical activities</td>
<td>Dilatation of peripheral veins, with corresponding reductions in systemic vascular resistance, coronary blood flow redistribution, and preload</td>
</tr>
<tr>
<td>Long acting: Isosorbide mononitrate, Isosorbide dinitrate</td>
<td>Angina prophylaxis in cases where beta-blockers or non-DHP CCBs are contraindicated, poorly tolerated or provide insufficient symptom control</td>
<td></td>
</tr>
<tr>
<td>Ivabradine</td>
<td>2nd line drug</td>
<td>Decreases heart rate and consequently myocardial oxygen demand. No effect on contractility or BP</td>
</tr>
<tr>
<td>Nicorandil</td>
<td>2nd line drug</td>
<td>Stimulates the ATP-sensitive potassium channels of the vascular smooth muscle resulting in systemic venous and coronary vasodilation</td>
</tr>
<tr>
<td>Ranolazine</td>
<td>2nd line drug in patients with refractory angina</td>
<td>Inhibition of calcium overload in cardiomyocytes, without substantial changes in heart rate or BP</td>
</tr>
<tr>
<td>Trimetazidine</td>
<td>2nd line drug</td>
<td>Targets deranged cellular energetics, particularly in ischemic myocardial tissue. Improves HbA1c and glycemia in diabetics</td>
</tr>
<tr>
<td><strong>Lipid lowering drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins: Atorvastatin, Rosuvastatin, Simvastatin</td>
<td>Moderate to high dose statin therapy is indicated in all patients irrespective of LDL/Cholesterol levels</td>
<td>HMG-CoA reductase inhibition</td>
</tr>
</tbody>
</table>

*Contd*...
Contd...

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>MoA</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAAS blockers</td>
<td>Patients with coexisting hypertension, LVEF ≤40%, diabetes, or CKD</td>
<td>Reduce mortality, MI, stroke, and HF</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Post-MI patients who:</td>
<td>Aldosterone receptor blockers</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>• Are on an ACEI/ARB plus beta-blocker,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• EF ≤35%, and</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• DM or HF</td>
<td></td>
</tr>
</tbody>
</table>

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; BP, blood pressure; DAPT, dual anti-platelet therapy; DHP, dihydropyridine; DM, diabetes mellitus; EF, ejection fraction; HF, heart failure; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

reduced pharmacological and mental burden on the patients. Other indications of revascularization include multivessel disease, reduced ejection fraction, significant coronary artery stenosis, and large area of ischemia (>10% of LV). Revascularization may be achieved percutaneously or with CABG.

**Conclusion**

A patient with history of chest pain presents a diagnostic challenge for physicians because of the wide variety of causes and variability in presentation. Therefore, careful history taking and guideline dictated testing is essential for identifying possible cardiac causes without subjecting the patient to unnecessary testing and monetary burden.

While chronic stable angina often presents as a “stable” disease, it is important to carefully evaluate patients for progressive disease or risk of imminent ischemic event. Lifestyle modification and medical therapy are the mainstay of treatment of CSA. Revascularization may be considered in addition to these in selected patients with careful consideration.

**References**

Abstract

The management of ST-elevation myocardial infarction (STEMI) has undergone a paradigm shift from the initial days of thrombolysis to balloon angioplasty and percutaneous coronary intervention (PCI) along with stenting. Patients with STEMI have a time dependent myocardial injury leading to grim outcomes in delayed presenters. It has been clearly demonstrated that there is a remarkable benefit in opening of the infarct-related artery in order to salvage the ischemic myocardium within 12 hours of chest pain. There are also evidences that patients do not get benefit who present after 12 hours of STEMI. However, if patient presented with ongoing chest pain, signs of cardiogenic shock, or persistent ST-elevation, patient should be managed actively by PCI and stenting.

Guidelines also say about routine pharmacoinvasive therapy in 3–24 hours of STEMI. Most of the clinical trials either based on fibrinolysis or PCI and stenting showed suboptimal outcome after 24 hours of STEMI. Asymptomatic and stable patients do not get benefit by any reperfusion intervention after 24 hours.

Case Scenario

Case 1: A 64-year-old never smoker diabetic female presented to the cardiology outpatient emergency with complaints of a single episode of retrosternal chest pain lasting for 15 minutes a day prior to her presentation. She had initially consulted a local physician who after a thorough evaluation had got an ECG done which he interpreted to be abnormal, and hence referred her to a cardiologist. However, since the patient thought her symptoms had abated, she planned a routine visit to a cardiologist in the nearby city the day later. On evaluation, the patient was pain free, hemodynamically stable with a 12-lead ECG showing anterior wall myocardial infarction. The Cardiologist now has to make a decision regarding the treatment of this late presenter of STEMI.

Case 2: A 59-year-old former smoker hypertensive male presented in the emergency department with symptoms of chest pain (angina in character) for the past 2 days. On examination, the patient was drowsy but arousable, with tachycardia (pulse: 120/min, regular), blood pressure of 80/50 mm Hg with bibasilar crepitations. ECG on presentation was suggestive of an extensive ST-segment elevation MI. 2D echocardiogram reported severely depressed left ventricular ejection fraction with akinesia of the anterior wall with mild mitral regurgitation and no evidence of pericardial effusion. The emergency physician consulted the cardiologist on call who has to decide the further treatment plan in this patient with STEMI, cardiogenic shock, and delayed presentation.

Both the clinical scenarios presented above are not something new but reflects the problems faced by clinicians in everyday practice.
CHAPTER 37
Optimal Therapy in ST-elevation Myocardial Infarction Patients Presenting after 24 hours

Introduction

Management of ST-elevation myocardial infarction (STEMI) is based on timely reperfusion of the occluded vasculature in order to salvage the ischemic myocardium. However, a significant number of patients present late (beyond 12–24 hours) and constitute what we know as “late presenters.” Data from the Western countries reveal that nearly 11% patients in the GRACE registry were classified as late presenters. However, the data from India is somewhat limited and showed that one third to half of STEMI patients presented to non percutaneous coronary intervention (PCI) centers and managed there conservatively and then referred to higher center. A study from Lucknow (single center) is showing nearly a third of their cases were late presenters. Patients presented after 24 hours of STEMI has different spectrum of presentation including totally asymptomatic to mild symptoms to cardiogenic shock (CS). Late presenters with CS constitute a subset of patients with extensive myocardial damage and poor clinical outcomes. In a another single center study from India, the in-hospital mortality rates of late presenters with CS was as high as 42.9%. Hence, prompt identification of STEMI followed by urgent revascularization should be the goal of therapy. These late presenters may have completed occluded artery or may have patent infract-related artery (IRA) or severe stenosis in one, two, and three vessel disease. They can present with mechanical complication like rupture chordae, ventricular septal perforation, acute mitral regurgitation (MR), etc.

So the management of such a spectrum of presentation cannot be done in one way. Treatment strategy in such cases should be individualized with use of existing, but limited guidelines and experience. Many studies have suggested to perform primary PCI in late presenters with hemodynamic or electrical instability irrespective of time of presentation. But guidelines are not clear regarding the management of stable late presenters and there is an unmet need for well-planned clinical trials in order to have a clear understanding of the treatment algorithm in these patients. In this chapter we have discussed about management of patients presented after 24 hours of STEMI.

Reasons for Late Presentation

Multiple reasons can be laid down for late presentation in STEMI patients, which include:

- Lack of awareness or denial of the symptoms or presence of atypical symptoms
- Failure to or refusal to seek medical attention or use of alternative system of medicine
- Poor access to health care
- Incorrect diagnosis including atypical presentation
- Presentation in a non-PCI hospital
- Financial issues

Proposed mechanism underlying the beneficial effects of late reperfusion: Clinical trials and meta-analysis showed the beneficial effects of reperfusion up to 12 hours from the onset of MI. After that there is no benefit to open the artery because of formation of mature thrombus and myocardial necrosis. However, this is not applicable to every patient.

There are some factors like presence of collaterals, ischemic preconditioning, subtotal occlusion, and spontaneous reperfusion, which delay the progression of infract size and prevent ventricular dysfunction.

Therapy in patients with STEMI presented after 24 hours:

The goal of early management of STEMI by thrombolysis or by PCI with stent is to restore the myocardial perfusion, reduce microvascular damage, to limit infract size, and reduce mortality. It has been seen that spontaneous recanalization of occluded IRA occur in one third of patients started at 12–24 hours. This delayed spontaneous reperfusion may enhance left ventricular function because it reduces infract size, prevents ventricular remodeling. In addition, interventions like thrombolysis or PCI accelerates the healing of infract. The efficacy of pharmacological agents decreases as coronary thrombus mature overtime. For every 30 minute delay in reperfusion, there is increase 8% relative risk of mortality per year.

Thrombolysis in patients presented after 24 hours of STEMI: Thrombolysis is based on clot lysis and establishment of the patency of the IRA leading to the salvage of the ischemic myocardium. Most of the landmark trials on fibrinolysis in STEMI revealed that a majority of benefit is seen in patients who present early and the role of thrombolysis is limited to patients presenting within 12 hours. The meta-analysis of nine major trials evaluated the role of fibrinolysis in 58,600 patients presenting with STEMI. The authors reported a significant decrease in mortality among patients
presenting early (up to 12 hours) post-STEMI, but no benefit in late presenters.

- **Reperfusion PCI in patients beyond 24 hours of STEMI:** Primary PCI is considered as the treatment of choice in patients with STEMI presenting within 12 hours of symptom onset. However, if patients have ongoing pain, persistent ST elevation, CS, decision of either thrombolysis or PCI should be taken accordingly and it is case dependent. A multi-centric RCT Occluded Artery Trial (OAT)\(^{12}\)—involving 2,166 stable patients with total occlusion of the IRA 3–28 days post an episode of acute MI along with the presence of a high-risk criterion (i.e., LVEF <50% or a proximal occlusion of a coronary artery). The primary outcome was a composite of death, re-infarction or NYHA class IV heart failure (HF) with the exclusion criteria being (a) CS, (b) NYHA class III/IV HF; and (c) severe ischemia or left main involvement or triple vessel disease. The primary endpoint was achieved among 17.2% patients in the PCI group as compared to 15.6% of the medical therapy group with a higher re-infarction rate in the PCI group. In addition, there was no difference in event-free survival between groups with a median follow-up of 3.2 years. This trial showed no benefit of routine PCI in stable late presenters with STEMI.

Barve II study\(^{13}\) enrolled patients who were presented more than 12 hours but without any chest pain. There was significant reduction in infract size in the invasive group compared to medical therapy group but no mortality benefit. Four-year results of this study showed mortality benefit in PCI group but results of this study cannot be applied to all patients because of limitations of this study. A meta-analysis (Abbate et al.\(^{14}\)) evaluated 10 RCTs comparing PCI of IRA with medical therapy in patients with delayed presentation (>12 hours–60 days) following acute MI. The PCI arm had significantly lower mortality as compared to the medical therapy arm [PCI arm: 112 (6.3%) vs. medical therapy: 149 (8.4%); OR: 0.49; P=0.03]. In addition, favorable benefits were reported in terms of significantly improved LVEF in PCI arm (4.4% increase post PCI; P=0.009).

**Risk Stratification in Late Presenters after STEMI**

- **Clinical:** In patients with late presentation following STEMI, clinical parameters pointing to a high risk include hemodynamic or electrical instability, and hence prompt revascularization should be performed in these patients.

- **LV ejection fraction (LVEF):** Most of the guidelines recommend assessment of resting LVEF as an integral component of risk stratification in late presenters.\(^{15}\) Multiple imaging modalities including echocardiogram or cardiac MRI can be used to determine the LVEF. There is an increased cardiac mortality in patients with LVEF below 40%.\(^{16}\)

- **Myocardial viability:** In clinically stable late (>72 hours) presenters myocardial viability should be assessed before a decision to revascularize is taken. A spectrum of imaging modalities, such as Thallium-201 or Technetium-99m SPECT, FDG-PET, Dobutamine stress echo (DSE), Contrast-enhanced cardiac MRI, and Dobutamine stress cardiac MRI, can be used to assess myocardial viability. The Viability-Guided Angioplasty after Acute Myocardial Infarction (VIAMI)\(^{17}\) trial showed that PCI was associated with a significant reduction in ischemic event rates in patients with viability reported on low-dose DSE performed 48–72 hours post-STEMI. A decision to revascularize the ischemic myocardium should be made based on the presence of viability. CMR can very well characterize acute myocardial injury and determine the infarct size, hence has become the imaging modality of choice for the assessment of patients post-STEMI.

- **Stress testing:** Exercise testing in late presenters of STEMI is useful in determining the exercise capacity, identifying persistent ischemia as well as for future risk stratification. This has been proven in the DANAMI-\(I^{18}\) and the SWISSI-II\(^{19}\) trials where a beneficial effect was seen post PCI in late presenters with evidence of ischemia on stress testing. Stress testing can be combined with an imaging modality to identify high-risk patients who would benefit from delayed revascularization.

**Recommendations for management of “unstable” late presenters:** This subgroup of patients (clinical scenario: Case B) present with ongoing angina, CS or electrical instability following acute MI. These subgroup of patients requires the highest attention and timely revascularization in these patients, often alter the natural course of the disease.\(^{20}\) Most of the guidelines\(^{20,21}\) are in unison regarding the recommendations in these group of patients.
Recommendations for management of “stable” late presenters: The clinical scenario in the initial part of the chapter regarding Case A reflects the problems faced by clinicians and interventionalists in deciding the tricky approach regarding revascularization in these asymptomatic/“clinically stable” late presenters following STEMI. The 2013 ACCF/AHA STEMI guidelines clearly state that “Delayed PCI of a totally occluded infarct artery greater than 24 hours after STEMI should not be performed in asymptomatic patients with 1- or 2-vessel disease, if they are hemodynamically and electrically stable and do not have evidence of severe ischemia” (Class: III, LOE: B). The guidelines defined clinical stability as “absence of low cardiac output or hypotension, persistent tachycardia, apparent shock, high-grade ventricular or supraventricular tachyarrhythmias, and spontaneous recurrent ischemia.”

The 2017 ESC guidelines on STEMI management states that “In asymptomatic patients, routine PCI of an occluded IRA >48 hours after onset of STEMI is not indicated” (Class: III, LOE: A). A more practical approach in this subgroup of patients would be coronary angiogram with an intent to revascularize in clinically stable early “late presenters” (<48 hours), while in patients presenting beyond 48 hours, stress or viability testing should be performed followed by a decision to revascularize.

Indian Guidelines: The 2017 Cardiological Society of India position statement for the management of STEMI in India states that in late presenters of STEMI (>24 hours) with evidence of shock, pulmonary edema, electrical instability or ongoing ischemia, coronary angiogram with an intent to revascularize should be done as soon as possible. In addition, clinically stable patients with diabetes and LVEF below 40% should undergo a coronary angiogram with PCI if subtotal occlusion is there. In cases of total occlusion, myocardial viability needs to be established prior to PCI. Hemodynamically stable patients without high-risk features should undergo a stress test prior to discharge based on which a decision to revascularize should be made. Very late presenters (>72 hours) with a total occlusion and clinically stable do not have significant improvement following revascularization as seen in the OAT trial.

Conclusion

Asymptomatic STEMI patients after 24 hours should be managed conservatively, and intervention can only be done when signs and symptoms of ischemia appears. If there are complications like CS, ongoing pain, and other signs of ischemia, then intervention should be done to restore the flow. Further availability of various stress tests and myocardial viability tests would help in management of such late presenters.

References


**Abstract**

Heart failure (HF) is the final common pathway for many diseases that affect the cardiovascular system, if left untreated in the early course of disease. The lifetime risk for developing HF is about 20% for both men and women. Increasing prevalence of cardiac risk factors, such as hypertension, diabetes, and dyslipidemia as well as improved survival of patients with acute cardiovascular diseases, have resulted in HF becoming a major public health problem, across the world. The fundamental hemodynamic changes present in HF are increased pulmonary capillary wedge pressure, increased central venous pressure, and reduced cardiac output. Fluid and salt restriction (<5 gm) is indicated in congested symptomatic HF patients in spite of diuretic therapy. RAS inhibition, beta blockade, and mineralocorticoid receptor antagonists (MRAs) are the main pillars of medical therapy of HF. At present angiotensin receptor nepriylisin inhibitor (ARNI) (sacubitril/valsartan) is preferred over isolated RAS inhibition. Cardiac resynchronization therapy (CRT) and implantable cardiac defibrillator (ICD) should be utilized judicially at proper time in the disease course of HF. LV-assist devices should be considered in refractory heart failure as bridge to transplantation or as destination therapy.

**Introduction**

Heart failure (HF) is the final common pathway for many diseases that affect the cardiovascular system, if left untreated in the early course of disease. The lifetime risk for developing HF is about 20% for both men and women. Increasing prevalence of cardiac risk factors, such as hypertension, diabetes, and dyslipidemia, as well as improved survival of patients with acute cardiovascular diseases, have resulted in HF becoming a major public health problem, across the world. There is no exact data on HF burden in India is available at present, because of the absence of disease surveillance systems in India. A rough estimate on the community-level prevalence of HF in the adult population in India is about 1%. As per the European Society of Cardiology, HF is best defined as “A clinical syndrome characterized by typical symptoms that may be accompanied by signs caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.” In this chapter we restrict our discussion in the context of chronic HF only.

**Pathophysiological Basis of Heart Failure**

The three fundamental hemodynamic changes present in HF are increased pulmonary capillary wedge pressure, increased central venous pressure, and reduced cardiac output. Lung congestion, secondary to increase left sided cardiac filling pressure, responsible for breathlessness at rest or exertion, paroxysmal nocturnal dyspnea, orthopnea, or rales in lung during chest examination. Increased CVP secondary to left sided heart disease, or isolated right heart disease, leads to systemic congestion, leads to
clinical features such as ascites, anorexia (secondary to gut congestion), elevation of liver enzyme (sometimes can mimic viral hepatitis) and generalized body swelling. Reduced forward cardiac output secondary to ventricular dysfunction occurs relatively late in the natural history of chronic HF, although in acute HF it may occur in minute to hours. In chronic HF, as the ejection fraction decreases, heart increases stroke volume by increasing end diastolic volume of the left ventricle, until or unless ejection fraction very low (<20%), so this may be the reason, why some patients are relatively asymptomatic for longer time in chronic HF with left ventricular with systolic dysfunction.

Chronic maladaptive activation of sympathetic nervous system (SNS) and renin angiotensin system (RAS) in HF leads to ventricular remodeling. The complex alterations in the ventricle in response to various mechanical and neurohormonal stressors on the heart, resulting in alterations in volume, wall thickness and/or shape (from ellipsoid to spherical in case of left ventricle) is defined as ventricular remodeling. As a result of myocardial stretch in HF, the gene coding for brain natriuretic peptide (BNP) is activated and the prohormone pro-BNP is produced. This is cleaved to the biologically active BNP and the biologically inert but stable NT-proBNP. BNP induces natriuresis, vasodilatation, and vascular smooth muscle relaxation, because of their sympatho-inhibitory action. These three systems (SNS, RAS, and NP) are the targets of modern medical therapy, which have changed the natural history of HF by inducing reverse remodeling.

**Classification of Heart Failure**

HF can be classified in multiple ways, depending on left ventricular ejection fraction (Table 1), depending on presentation (Table 2), and functional class (Table 3). These classifications are important for management strategies as well as prognostic point of view. The NYHA functional classification has been used to describe the severity of symptoms and exercise intolerance. The symptom stages are clearly related survival, yet they correlate poorly with LV function. The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) classification describes stages of HF development based on structural changes and symptoms have been described in Table 4. The ACC/AHA staging is invaluable in holistic management of HF, from prevention to appropriate intervention at appropriate time.

### Table 1: The classification of heart failure based on LVEF

<table>
<thead>
<tr>
<th>Type of HF</th>
<th>Characteristics</th>
</tr>
</thead>
</table>
| Heart failure with reduced ejection fraction (HFrEF) | • Symptom ± sign of heart failure  
• LVEF < 40% |
| Heart failure with preserved ejection fraction (HFpEF) | • Symptom ± sign of heart failure  
• LVEF > 49%  
• Elevated level of natriuretic peptide*  
• Minimum one additional echo criteria  
  - Relevant structural heart disease such as LVH and LAE  
  - Evidence of diastolic dysfunction |
| Heart failure with midrange ejection fraction (HFmrEF) | • Symptom ± sign of heart failure  
• LVEF 40–49%  
• Elevated level of natriuretic peptide*  
• Minimum one additional echo criteria  
  - Relevant structural heart disease such as LVH and LAE  
  - Evidence of diastolic dysfunction |

*BNP—35 pg/mL or NT-proBNP > 125 pg/mL.

### Table 2: The classification of heart failure based on time course

<table>
<thead>
<tr>
<th>Type of heart failure</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute decompensated heart failure (ADHF)</td>
<td>Term for patients presenting acutely with HF, which can be defined as “the sudden onset of the signs or symptoms of heart failure requiring unplanned hospitalization, or emergency room visits, or unplanned office consultation”</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>Term for patients presenting with insidious onset of symptom and signs of heart failure</td>
</tr>
<tr>
<td>A new-onset/de novo HF</td>
<td>Term used for HF patients, presenting with symptoms of heart failure in an acute or sub-acute (gradual) fashion for the first time</td>
</tr>
<tr>
<td>Stable heart failure</td>
<td>A treated patient of heart failure with unchanged symptomatic status for at least 1 month is said to be “stable”</td>
</tr>
<tr>
<td>Advanced HF</td>
<td>Term refers to patients with severe cardiac dysfunction, recurrent decompensation, and severe symptoms despite optimal standard medical therapy</td>
</tr>
<tr>
<td>Asymptomatic LV systolic dysfunction</td>
<td>Term used for an asymptomatic patient with reduced LVEF who never exhibited typical signs and symptoms of HF</td>
</tr>
</tbody>
</table>
**Diagnosis of Heart Failure**

**Clinical Features**

Breathlessness on exertion or at rest, orthopnea, and paroxysmal nocturnal dyspnea may be the presenting symptom of HF. Anorexia, generalized swelling of body, fatigue, oliguria, and altered sensorium may be the presenting feature of advanced HF. S3, S4, and murmur on cardiac auscultation may be present in HF patients. Presence of rales (usually absent in chronic HF) may be present on lung examination. Presence of raised jugular venous pressure, hepatomegaly, anasarca, and ascites may point toward the diagnosis of HF. ECG is must in all cases of HF. ECG may give clue to the etiology of HF. Perfectly normal ECG is highly unlikely in HF, although some time may be present. If history, physical examination, and ECG are suggestive of HF, then echo should be done to establish the diagnosis and classification of HF. If echo is not available at site, then assessment of cardiac biomarker followed by echocardiography can be done. For patients presenting with chronic HF, the optimum exclusion cut-off point is 125 pg/mL for NT-proBNP and 35 pg/mL for BNP, whereas for patients presenting with acute HF, the ideal exclusion cut-off point is proposed to be 300 pg/mL for NT-proBNP and 100 pg/mL for BNP. It needs to be understand that the negative predictive value of BNP/NT-pro-BNP is very high (0.94–0.98), while the positive predictive value is low (0.64–0.67), making them a good test to rule out HF but a poor tool to establish diagnosis.

Echo is invaluable in diagnosing specific valvular pathologies, pericardial diseases, and specific type of cardiomyopathies. Assessment of diastolic dysfunction (E/A ratio, E/e, Left Atrial volume, LV mass) is must for establishing the diagnosis of HFmrEF and HFpEF.

Presence of pulmonary artery hypertension is indicative of poor prognosis in HF, so it should be looked for in every case of HF.

In select cases CT or invasive coronary angiography is recommended for ruling in or out coronary artery disease. Magnetic resonance imaging is also having important role in establishing the diagnosis of specific cardiomyopathies and determining the viability in ischemic cardiomyopathy before proceeding to revascularization. Complete blood count (Hb, TC, DLC, and ESR), serum electrolyte, and serum creatinine, liver function test, and thyroid profile should be done in all cases of HF.

**Treatment of Heart Failure**

Fluid and salt restriction (<5 gm) is indicated in congested symptomatic HF patients, in spite of diuretic therapy. Exercise should be encouraged in early phases of HF, but in
advance stage it may not be advised. If any specific etiology is responsible for HF should be treated accordingly, such as valvular heart diseases by valvular intervention, ischemic heart disease by revascularization and pericardectomy for constrictive pericarditis. Diuretics are recommended to relieve lung as well as systemic congestion and symptomatic benefit only. No specific therapy have been found to change the natural history of HF in HFP EF population till date, so only symptomatic treatment and associated comorbidities such as hypertension, diabetes, dyslipidemia, chronic obstructive pulmonary disease (COPD), and rhythm disorders such as atrial fibrillation should be treated. The major objective of therapy in HFrEF is to improve functional class, symptomatic status, and prevent recurrent hospitalizations and reduce mortality. It is recommended to treat HFrEF patients with ACE inhibitor [or angiotensin receptor blocker (ARB)] and beta blockers to the maximum tolerated dosages. If patient is still symptomatic and LVEF less than 35%, then mineralocorticoid receptor antagonists (MRAs) should be added. Once MRAs and angiotensin converting enzyme) inhibitors (ACEIs) or ARB are combined, then close monitoring of serum potassium and creatinine

### TABLE 5

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Number needed to treat (For 5 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta blocker</td>
<td>8</td>
</tr>
<tr>
<td>ARNI</td>
<td>11 (compared to placebo), 21 (compared to ACEI)</td>
</tr>
<tr>
<td>MRA</td>
<td>15</td>
</tr>
<tr>
<td>ACE</td>
<td>18</td>
</tr>
<tr>
<td>ARB</td>
<td>24</td>
</tr>
<tr>
<td>ICD</td>
<td>14</td>
</tr>
<tr>
<td>CRT</td>
<td>14</td>
</tr>
</tbody>
</table>

### TABLE 6

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Dosages</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta blockers</td>
<td>Metoprolol succinate (12.5–200 mg od) Carvedilol (3.125–25 mg bd) Bisoprolol (1.25–10 mg od)</td>
<td>Hypotension, Bradycardia, AV-block, Fatigue</td>
</tr>
<tr>
<td>ACEIs</td>
<td>Enalapril (2.5–20 mg bd) Ramipril (2.5–10 mg od) Captopril (6.25–50 mg tds) Lisinopril (2.5–35 mg od)</td>
<td>Cough, dizziness, angioedema, hypotension, renal impairment, and hyperkalemia</td>
</tr>
<tr>
<td>ARBs</td>
<td>Losartan (50–150 mg od) Valsartan (40–160 mg bd) Candesartan (4–32 mg od)</td>
<td>Same as above</td>
</tr>
<tr>
<td>ARNI</td>
<td>Sacubitril/Valsartan (49/51–97/103 mg bd)</td>
<td>Same as above</td>
</tr>
<tr>
<td>MRAs</td>
<td>Spironolactone (25–50 mg od) Eplerenone (25–50 mg od)</td>
<td>Hyperkalemia, Gynecomastia (more common with spironolactone)</td>
</tr>
<tr>
<td>If channel inhibitor</td>
<td>Ivabradine (5–7.5 mg bd)</td>
<td>Bradycardia, development of AF and rarely torsade ds pointes, visual symptoms (phosphenes)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>(125 mg od to .25 mg od)</td>
<td>Nausea, vomiting, anorexia, arrhythmias (ectopic and re-entrant tachycardias with AV block), visual disturbances, disorientation, and confusion</td>
</tr>
<tr>
<td>Hydralazine and isosorbide dinitrate</td>
<td>(25/20–75/40 mg tds)</td>
<td>Headache, dizziness, and non-specific gastrointestinal complaints</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>Furosemide (20–240 mg od) Bumetanide (0.5–5 mg od) Torsemide (5–200 mg od)</td>
<td>Hypokalemia, fluid depletion, azotemia, ototoxicity</td>
</tr>
<tr>
<td>Thiazides</td>
<td>Hydrochlorothiazide (12.5–100 mg od) Metolazone (2.5–10 mg od) Indapamide (2.5–5 mg od)</td>
<td>Hyperuricemia, hyponatremia, hypokalemia, hypomagnesemia, hypercalcemia, and fatigue</td>
</tr>
</tbody>
</table>
is recommended, because both can increase serum potassium. If HF patient able to tolerate ACEIs or ARB, and still symptomatic and LVEF less than 35%, then ACEIs or ARB should be replaced with angiotensin receptor neprilysin inhibitor (ARNI) (Sacubitril/valsartan). ARNI should be started after 36 hour of stopping ACEIs because of increased risk of angioedema, if both are combined together. If patient is still not improving and in sinus rhythm and heart rate greater than 70, then channel current inhibitor (ivabradine) should be added. After all pharmacological treatment exhausted (3–6 months of optimal medical therapy), patient still symptomatic, LVEF less than 35%, QRS duration greater than 130 milisecond and LBB morphology, then cardiac resynchronization therapy (CRT) is recommended. If there is a history of ventricular tachycardia or fibrillation or patient LVEF is less than 35% despite optimal medical therapy, then implantation of implantable cardiac defibrillator (ICD) is recommended to prevent sudden cardiac death. As evidenced by recent analysis, among all guideline directed therapies, beta blockers are most effective in reducing mortality and promoting reverse remodeling in HF (Table 5). The dosages and side effect of drugs recommended in HF are summarized in Table 6. If patient is still symptomatic and refractory to all described therapies, then patient should be referred to specialized center for ventricular-assist devices or cardiac transplantation. Based on the result of DAPA-HF trial of the US FDA dapagliflozin (SGLT-2 inhibitor) approved for the treatment symptomatic HF of LVEF 40%. Drugs known to adversely affect the clinical status of patients of HFrEF should be avoided, whenever possible (e.g., most antiarrhythmic drugs), most calcium channel blocking drugs (except amlodipine), NSAIDs, or TZDs (pioglitazones).

**Conclusion**

HF is the final common destination of untreated cardiovascular diseases. As the population is aging worldwide, prevalence of HF is increasing. RAS inhibition and beta blockade is the main pillar of medical therapy of HF. At present ARNI is preferred over isolated RAS inhibition. CRT and ICD should be utilized judiciously at proper time in the disease course of HF. LV-assist devices should be considered in refractory heart failure as bridge to transplantation or as destination therapy.

**References**

Abstract
The most important way to prevent atherosclerotic vascular disease, heart failure, and atrial fibrillation is to promote healthy lifestyle throughout life. Coronary artery disease (CAD) risk equivalents, like atherosclerotic changes in carotid artery, peripheral artery, and abdominal aortic aneurysm, should receive serious attention to prevent established atherosclerotic cardiovascular disease. A diligent search should be made to detect apparent risk and silent risk factors like coronary artery calcium (CAC) and inflammatory status (increased hs-CRP, IL-6, especially associated with visceral adiposity, etc.). Guidelines should be shorter, crisp, and user friendly. A team-based care approach is an effective strategy for prevention of cardiovascular disease. Health literacy is essential for implementation of guideline.

Introduction
In the developed nations and to some extent also in developing nation, coronary artery disease (CAD) is a major cause of death and disability. Although mortality rates related to CAD have continued to decline over past years, CAD remains accountable for about one third of all deaths over the age of 35 years. Majority of CAD are due to atherosclerosis (ASCVD), which involves other major large arteries like cerebral and peripheral artery. Obviously it has huge impact on finances and health care system.

Most Americans, who have had myocardial infarction (MI), had unfavorable level of at least 1 Cardiovascular (CV) risk factor before their ASVCD event. In 2010, American Heart Association (AHA) defined “ideal CV health” and referred to as “Life’s simple 7”.

Risk Factors and CAD Risk Equivalents

CAD Risk Equivalents
Some individuals without known CAD have risk of major CV events that is equivalent to that of patient with established CAD. They should be managed aggressively like patient of established CAD. They are:

- Atherosclerotic disease status in carotid artery, peripheral artery, abdominal aortic aneurysm. In such situation 10 years risk of developing CAD exceeds 20%.
- Diabetes mellitus (DM), insulin resistance, hyperinsulinemia, and elevated blood sugar are associated with ASCVD. The all-cause mortality risk associate with DM is comparable to all-cause mortality risk associated with prior MI.
- Hyperglycemia without overt DM correlates with CV risk.
- Chronic kidney disease (CKD) even with mild to moderate renal dysfunction is associated with substantial increase in CAD risk.

Traditional Risk Factors for Atherosclerosis

- High blood pressure
- High total cholesterol
- High LDL cholesterol
Low HDL cholesterol
Hypertriglyceridemia
Increased non-HDL cholesterol
Increased lipoprotein (a)
Increased apolipoprotein-B
Increased apolipoprotein C-III
Small dense LDL particles
Glucose intolerance
Smoking
Family history of premature CAD
High BMI
Age
Physical inactivity
Obesity
Psychosocial factors, (depression, anger, stress, and other factors). They lead to premature CAD, acute coronary syndrome (ACS), and sudden cardiac death (SCD).

Novel and Emerging Risk Factors
- High Hs-CRP (high-sensitivity C-reactive protein)
- High IL-6 (interleukin) and membrane bound IL-6
- Increased level of leukocyte enzyme myeloperoxidase
- HIV-positive status
- Mediastinal and chest wall radiation
- Metabolic syndrome
- Microalbuminuria
- Remnant lipoproteins

Novel risk factors like Hs-CRP, IL-6, leukocyte enzyme myeloperoxidase denote inflammatory changes in atheroma formation and progression. They have opened new pathway for treatment. The association of microalbuminuria and CAD is established but mechanism remains unclear.

Genetic susceptibility to CAD is seen in 40-60% cases. Currently 33 genetic variants have been identified, which increase patients risk for CAD.

Borderline CAD Risk
Among adults with 10 years borderline risk (5% to <7.5%) and intermediate risk (>7.5% to <20%) risk, one may consider searching additional individual risk-enhancing clinical factors. This will help to revise the 10 years ASCVD risk estimate.

Risk-enhancing Factors
- Family history of premature ASCVD (male: <55 years; female: <65 years)
- Primary hypercholesterolemia
- Metabolic syndrome (MS)
- Chronic kidney disease (CKD)—eGFR 15–59 mL/min/1.73 m²
- Chronic inflammatory conditions. Example, psoriasis, RA (rheumatoid arthritis), lupus, or HIV/AIDS
- History of premature menopause (before 40 years) or preeclampsia
- High-risk ethnicity. Example, South Asian Ancestry

Lipid/Biomarkers associated with increased ASCVD risk
- Persistently elevated LDL > 160 mg/dL
- Persistently elevated primary hypertriglyceridemia >175 mg%—non fasting
- High Hs-CRP (≥2.0 mg/L)
- High lipoprotein (a) (≥50 mg/dL)
- Elevated apolipoprotein B (≥130 mg/dL)
- ABI (<0.9)

Risk Assessment and Detection of Asymptomatic Atherosclerosis

Status of CAC
Coronary artery calcium (CAC) detection by high-resolution computer tomography (CT) or CT angiography. CT angiography is burning topic, as these have additional power of treating ASCVD.

Recent evidences support that measurement of CAC is predictive of coronary heart disease death or MI at 3–5 years. Current evidence also suggests that use of CAC is independently predictive of outcome over and above traditional cardiac risk factors.

CAC scoring has been evaluated as noninvasive diagnostic technique for detecting obstructive CAD. CAC may be used as an effective filter before undertaking invasive diagnostic procedure. Score less than 100 are associated with low probability. No calcium means zero score.

Use of CAC score are not recommended for follow-up of lesion due to cost and radiation hazard.
Atheroma Progression, Regression, Vulnerable Plaque: Impact of Serial CAC and Statin

A trend toward increasing atheroma calcification following statins use has been reported. Aside from lipid regression within plaques following long-term potent statin therapy, statin mediated atheroma calcification may improve plaque stability.

Recent research suggests that plaques containing low proportion of microcalcifications actually rupture. With more confluent and dense plaque calcification, plaque stability is improved due to low-wall stress. Cardiac CT angiography (CCTA) provides direct visualization of vessel wall, thus providing good assessment of the atherosclerotic burden. The goal is to identify vulnerable plaque, responsible for most ACS. Plaque measured by wall component is classified in Hounsfield Units (HU), as soft or lipid rich (30–60 HU), fibrous (70–120 HU), or calcified (>350 HU).

In a study of 1,059 patients, who underwent CCTA, the investigators found that those with plaques showing positive remodeling and low attenuation on CCTA were at higher risk for ACS during 27-month mean follow-up compared with patients without these characteristic.

Atherosclerosis, Inflammation, and Thrombosis

Inflammation most likely plays a causal role in plaque rupture. Vulnerable plaque has thin cap fibroatheroma (TCFA). These have very high density of macrophages (approximately 14%) in contrast to stable fibroatheroma (approximately 2.0% macrophages). These can be assessed by CCTA.

Detection of inflammatory markers as discussed earlier has opened a new avenue for treating atherosclerosis and preventing impending thrombosis. Two trials are worth mentioning:

- **Colcot Trial:** Efficacy and safety of low dose colchicines after MI. A small dose of 0.5 mg daily was used in recent MI. Endpoint was composite death from CVS cause, MI, stroke, angina, cardiac arrest. Result was 5.5% in treated group versus 7.1% in placebo, with hazard ratio of 0.77.

How should we Approach Preventing ASCVD?

ACC/AHA guideline (2019) on the primary prevention of CVD aims to promote the delivery of patient-centered care:

- Team based care approach for control of risk factors associated with ASCVD. (COR:1).
- Shared decision, after discussion about best strategy to reduce ASCVD risk (COR:1).
- Social determinants of health will guide better implementation of plan for prevention of ASCVD.

Assessment of Cardiovascular Risk

Tool is available online at ACC/AHA site:

- For adult 40–75 years—should routinely assess traditional CV risk factor and calculate 10 years risk of ASCVD.
- For adults 20–39 years—Assess risk every 4–6 years.
- In adult at borderline risk (5% to <7.5%) or in intermediate risk (≥7.5% to <20% 10 years risk) assess risk enhancing factors to guide about preventive therapy (like statin).
- In adult with intermediate risk or in borderline risk, if decision about statin remains uncertain, measure CAC for clarification (Class IIa).

Assessment of Risk Factors

- One should look for all traditional and emerging risk factors in each cases but the clinical scenario will guide the situation.
- At the same time risk-enhancing factors should be searched and assessed.

Assessment of Social Determinants of Health

This will guide us about implementation of preventive strategy in each case at grass root level:

- Psychological stressors
Health literacy
Social barriers of heart healthy diets
Neighborhood environment. Facility of exercise
Concept about health, body weight, and obesity
Concept of lifestyle counseling for weight loss, sleep, psychosocial stressors
Job status, family life, and mutual relation, history of depression
Personal habits, viz. tobacco, alcohol
Diabetes mellitus—controlled on diet, exercise of drugs? Education to maintain sugar level
Hypertension—controlled on drug? Does he understand benefit of low-sodium diet, exercise, and proper sleep
It cannot be overemphasized that health literacy will go long way to prevent ASCVD.

Detection of Inflammatory Status and Asymptomatic Cases of ASCVD
This has already been discussed earlier in this chapter. It is very important to prevent ACS. This concept is the need of hour and is oriented toward saving life of patient. This involves detection of inflammatory marker and study by CCA or CCTA for vulnerable plaque.

Management Issues
All risk factors should be dealt with as per guideline. Few very relevant points will be discussed here:
- Diet
- Exercise and physical activity (PA)
- Cholesterol management (lipids)
- Hypertension (HTN)
- Diabetes mellitus
- Tobacco abstinence
- Prophylactic ASA (aspirin) therapy

Diet: It should be followed as per guideline. Salient points are:
- Encourage vegetables, fruits, legumes, nuts, whole grain and fish
- Replacement of saturated fat with dietary monounsaturated and polyunsaturated fats
- Low in cholesterol and sodium
- Avoid processed meats, refined carbohydrate, and sweetened beverages
- Red meat should be eliminated. It increases systemic levels of TMAO (Trimethylamine N Oxide) a microbiome-dependent metabolite. It has been associated with increase CV risk
- Trans fats should be avoided

Exercise and physical activity:
- Should be routinely counseled in health care visits about need of active lifestyle
- Adult should engage in at least 150 minutes per week of moderate exercise or 75 minutes per week of vigorous-intensity aerobic exercise
- Even less than ideal goal is beneficial

Definitions of different intensity of physical activity:
- Sedentary, 1–1.5 mets—sitting, lying, watching TV
- Light, 1.6–2.9—walking slowly, cooking, light household work
- Moderate, 3.0–5.9—brisk walking (3.8–6 km/hr), biking (8–14 km/hr), active yoga
- Vigorous ≥6—jogging, running, biking >16 km/hr, single tennis, swimming laps

Cholesterol management: Few accepted facts as per 2018 cholesterol guidelines:
- Adults with intermediate (7.5% to <20%) risk of 10 years ASCVD—moderate intensity statin.
- In intermediate risk LDL-C should be reduced by 30% or more.
- In high risk 10 years group (20% or more)—LDL-C should be reduced by 50% or more.
- In adult, 40–75 years of age with diabetes, regardless of estimated 10 years risk, moderate intensity statin is indicated.
- In patients of 20–75 years age with LDL-C level 190 mg/all maximum tolerated dose of statin should be given.
- In DM with multiple ASCVD risk factors. High intensity statin should be prescribed. Goal should be to reduce LCL-C by 50% or more.
- In intermediate risk (≥7.5% to <20%) presence of risk enhancing factors favor initiation or intensification of statin therapy.
- In intermediate or borderline risk, if CAC is measured—CAC is zero—hold statin.
- CAC is 1–99—start statin in 55 years age or more.
- CAC is 100 or higher—initiate statin.
In borderline risk (5% to <7.5%), presence of risk enhancing factors justify statin.

**Hypertension:** Principles of management as per guideline:
- Non-pharmacological interventions:
  - Weight loss
  - Heart healthy dietary pattern
  - Sodium restriction
  - Dietary potassium supplementation
  - Increased physical activity and exercise
  - Limited alcohol (1–2 drink daily) (1 drink means 14 gm pure alcohol)

- BP target of less than 130/80 mm Hg
- In CKD and DM, treatment initiated at 130/80
- If ASCVD 10 years risk is less than 10%, antihypertensive drugs are initiated at 140/90 or more choice of drug as per guidelines.

**Diabetes mellitus (T2DM):**
- One should look for diabetes specific risk enhances in DM (T2DM). These are independent of other risk factors:
  - Long duration—more than 10 years in T2DM, more than 20 years in T1DM.
  - Albuminuria + >30 mcg albumin/mg of creatinine.
  - eGFR <60 mL/min/1.73 m²
  - Retinopathy
  - Neuropathy
  - ABI <0.9

Such patients required high-intensity statin therapy.
- After appropriate diet therapy and exercise cum physical activity plan, one should proceed to drug therapy:
  - Metformin is a first-line drug. It reduces 32% reduction in micro and moreover vascular DM related outcome, 39% reduction in MI, and 36% reduction in all-cause mortality rate.
  - In addition two class of drug: SGLT-2 inhibitors reduce incidence of heart failure. GLP-1R agonist reduces ASCVD events.

Drug management of DM should be done as per guideline protocol.

**Achieve tobacco abstinence:** It should be firmly emphasized. It is important to encourage patients to seek help from trained staff. All adult and adolescents should avoid secondhand smoke exposure to reduce ASCVD risk.

**Prophylactic aspirin:**
- In primary prevention:
  - Benefit seen in DM. Major vascular events decreased by 12%.
  - Between age 40 and 70 years only Class IIb recommendation. Individual approach by clinician and risk of bleeding to be considered.
  - Beyond 70 years, not recommended.
- In secondary prevention:
  - Prophylactic ASA (aspirin) is recommended in setting of elevated ASCVD risk.
  - ASA suggested when risk is more than 10% at 10 years ASCVD risk.
  - Recent clinical trials also allow us to use low dose ASA among patient with high ASCVD risk.
  - Dose of ASA can be adjusted as per body weight.

**Conclusion**

- ASCVD events are avoidable through primordial prevention (i.e., prevention of risk factor development) and control of traditional CV risk factors.
- Tobacco avoidance is critically important for ASCVD prevention.
- Exercise and physical activity along with dietary management are absolutely essential.
- All these factors are better implemented with basic health education and how best dedicated persons are involved in counseling. Without these, it will go waste.
- The intensity of preventive efforts should match with individual’s absolute risk of future ASCVD event.
- The clinician must balance the benefit and risk.
- Assessing appropriateness of pharmacotherapy may require search of “Risk enhancing factors” in borderline situation.
- At this point, use of “CAC” measurement can help in decision-making for cholesterol lowering or antihypertensive medication use in intermediate risk individuals.
- CCTA or CAC is now the most accurate in invasive tool for the assessment of ASCVD with highest concordance to invasive coronary angiography (CAG). CCTA is widely utilized in accurate and rapid assessment in cases of chest pain in emergency department (ED). The visualization of subclinical atherosclerosis (on either coronary calcium scanning or seeing non-obstructed plaques on CCTA) allows for targeted anti-atherosclerotic treatment strategies and improved adherence to these treatment. Possible diagnosis of vulnerable plaque is another achievement to prevent ACS.

*Contd...*
Inflammatory markers should also be taken care of to halt atherosclerosis progress and possibly prevent ACS. There are additional challenges specific to prevention realm. 

AHA in 2011 in their policy statement described about value of primordial and primary prevention in CVD:

“Assessing the value of prevention in apparently healthy patients is generally more difficult than evaluating therapy for established disease because the time horizon to the clinical manifestation of disease is generally long, many decades in the young. Thus, it is difficult, perhaps impossible, to assess long-term effectiveness in terms of survival or quality-adjusted life-years (QALYs) or associated costs because of increasing uncertainty about outcome, the further one tries to look into the future.”

References

CHAPTER

SGLT2 Inhibitors in Heart Failure

NS Prasad

Abstract

The occurrence of heart failure (HF) is on the increase globally and in India. The coexistence of diabetes (DM) and HF increases the mortality risk. Various CVOT trials have proven SGLT inhibitors to reduce the hospitalization for heart failure (HHF) and CV mortality. SGLT inhibitors have proven to be useful in heart failure regardless of diabetic status.

Introduction

Patients with coexisting conditions of type 2 diabetes mellitus (T2DM) and heart failure (HF) tend to have increased mortality risk when compared to people who do not have either DM or HF. This association of DM and HF is mainly due to mistimed and asynchronous handling of glucose and free fatty acids by the cardiac system. Another hypothesis is that the effect on heart and blood vessels, caused directly by the metabolic derangements seen in patients with diabetes mellitus (DM) may also play a vital role in this coexistence. Also, use of certain anti-diabetic agents (mainly DPP-4 inhibitors and pioglitazone) can potentiate hospitalization for HF.

As high as 20% of the population is expected to develop HF at some point during their lifetime. It is a global pandemic affecting an estimated 26–37.7 million people worldwide. The burden of HF in India has become an important public health concern because of very high mortality. HF exerts a high-economic burden mostly due to hospitalizations. India is the highest spending country on HF in South Asia with a total expenditure amounting to 1.7% of total health expenditure of India.

Recent studies have clearly shown that the prevalence of HF with preserved ejection fraction (HFrEF) is mounting significantly when compared to that of HF with reduced ejection fraction (HFrEF). Available statistics further suggest that in the year 2020, only 35% of patients with HF have reduced EF<40%, and over 65% have a preserved EF>40%. Atherogenesis and endothelial damage play a very crucial role in pathophysiology of HF in DM. Insulin resistance and hyperinsulinemia cause left ventricular hypertrophy which is frequently linked to T2DM. Hyperglycemia results in cardiac muscle stiffness and leading to non-compliance of the myocardium. Therefore, drugs decreasing insulin resistance and aggressively controlling the hyperglycemia should be part of therapy in order to reduce the incidence of HF in T2DM. T2DM could potentially cause cardiomyopathy independent of atherosclerotic ischemia, and there is evidence of cardiomegaly in T2DM patients. Hence, therapy targeting such pathology, for example, sodium/glucose cotransporter-2 inhibitors (SGLT2i), might be useful.

Cardiorenal Association

Heart and kidney are closely related when it concerns the physiological functions and pathological conditions of both systems. Acute or chronic disorders of one of these organ systems are capable of having a deleterious effect on the other. This closely linked interplay is often called as the cardiorenal association. Studies have indicated that...
anywhere between 20% and 67% of patients with HF will also have chronic renal impairment as an association. \(^{17,18}\) HF can also directly or indirectly lead to renal impairment or CKD. This may be due to a low cardiac output and increased venous pressure. On the other hand, renal impairment may also worsen HF. This can happen via enhanced water and sodium retention, potentiated atherosclerosis, anemia, inflammation, uremic toxins, and activation of the neurohormonal pathways. \(^{19,20}\)

### Evidence for Use of SGLT2i in HF Prophylaxis

SGLT2i have shown positive results when it comes to hospitalization for the sake of heart failure (HHF) and CV or overall mortality across several cardiovascular outcome trials. These favorable results have been demonstrated both in patients with and without history of pre-existing cardiac ailment. A meta-analysis has confirmed robust advantages with SGLT2i on HHF and CV mortality even in patients without CVD or HF, indicating benefits in the early HF stages as well.\(^{21}\)

Empagliflozin in the EMPAREG OUTCOME study\(^{22}\) and dapagliflozin in DECLARE-TIMI 58\(^{23}\) study revealed a significant reduction in HHF. Analysis of the CANVAS trial\(^{24}\) also exhibited a significant fall in HHF rates in both prevention groups—primary and secondary. In line with these results, the US regulatory authority has approved empagliflozin for lowering CV mortality and canagliflozin for lowering major adverse cardiac events—MACE in patients with DM who also have coexisting cardiac disease. The results of DECLARE-TIMI 58 have proven significantly lower rates of cardiovascular mortality or HHF. Further, they also mildly suggested that it may apply to primary prevention also, since clinical mortality benefits were seen in patients who did not have cardiac disease or HF at the baseline. DECLARE TIMI results when stratified by cardiac ejection fractions showed an HHF reduction.\(^{25}\) Patients with previous cardiac disease had a greater absolute relative risk in DECLARE-TIMI 58.\(^{26-30}\) DAPA HF trial\(^{33}\) results have also shown significant fall of mortality with the use of dapagliflozin (both with and without DM). Dapagliflozin\(^{27}\) significantly reduced the overall composite endpoints of CV mortality/HHF/urgent HF visit, when compared with standard arm (both with and without DM). The quality of life was also significantly improved as measured by KCCQ score.\(^{32}\)

Major trials that are currently underway (such as the EMPEROR employing the use of empagliflozin) may further show the path toward SGLT2i use in patients with or without DM for HF treatment or prevention.

### Safety of SGLT2i

One of the most common side effects of SGLT2i is genital infections.\(^{22,23,33,34}\) DKA can also typically occur in patients treated with SGLT2i, although rare.\(^{22,23,33,34}\) Current recommendations suggest that treatment should be discontinued as soon as DKA sets in.\(^{35,36}\) CANVAS trial showed that lower limb amputation frequency was significantly greater in the arm with canagliflozin.\(^{33}\) Accordingly, regulators have highlighted practicing doctors’ need for caution when they use SGLT2i. This is more so pertinent in patients who have a history of or high risk of amputation.\(^{27}\) Another major concern with canagliflozin was the higher risk of fractures in CANVAS. However, this was not replicated in the trials with other SGLT2i.\(^{22,23,33}\)

### Can SGLT2i be Beneficial in the Treatment of HF?

Efficacy in HF prevention need not mean that SGLT2i are also useful in HF treatment.\(^{38,39}\) Dapagliflozin significantly lowered primary composite end point of CV mortality or HHF. This was more evident in patients with HFrEF than in HfPEF.\(^{25}\) Patients who had reduced EF (EF<30%) had significantly higher benefit.\(^{25}\) Also, CV mortality benefits in patients with HFrEF were seen in those treated with ARBs, ACEIs, and beta-blockers.\(^{25}\)

### Role of SGLT2i in Patients without DM

As mentioned earlier, SGLT2i might serve to be useful regardless of DM status and EF percent. While several mechanisms have been hypothesized for their cardiac benefits, the following are backed with considerable evidences:

- **Reduction of cardiac preload leading to an improvement in ventricular loading** (facilitated predominantly due to increased osmotic diuresis and sodium loss in urine).\(^{40}\)
- **Sodium/hydrogen (Na⁺/H) exchanger inhibitor in the myocardial tissues.**\(^{41}\)
As all these mechanisms have been elucidated both in patients with and without DM, SGLT2i may benefit all groups of patients.45-48

Future Directions
Impending results of the currently progressing trials on SGLT2i in HF are required to fully analyze and study the treatment/preventive ability. This will apply to all patients, irrespective of DM status and EF percent. DAPA-HF, DELIVER, EMPEROR-Reduced and EMPEROR-Preserved may help in this regard. The EMPA-HEART study showed that empagliflozin causes a significant decrease in LV mass regression, which probably suggests potential reverse cardiac remodelling.49 SOLOIST-WHF trial, which is testing sotagliflozin (a dual SGLT1/SGLT2i), may reveal drug-specific effects due to the difference in receptor selectivity and specificity. If this class of drugs sees clinical efficacy, then there is a likelihood of moving from a multidrug-containing polypill to a single pill that will be able to target multiple pathways at the same time.50

Conclusion
HF and T2DM are major public health threats across the globe. SGLT2i have emerged as a potential drug group for the prophylaxis of HF in individuals with DM. Accumulating evidence suggests that SGLT2i may produce coupled renal and cardiac effects, thus ensuring promise for the treatment of HF in patients irrespective of DM status and EF percent. We will have to play the waiting game to see if this promise turns into reality in the coming times, with the results of ongoing trials in these categories.

References


49. Verma S, Mazer CD, Yan AT, et al. EMPA-HEART Cardiolink-6: A Randomized Trial Evaluating the Effect of Empagliflozin on Left Ventricular Structure, Function and Biomarkers in People With Type 2 Diabetes (T2D) and Coronary Heart Disease. American Heart Association Scientific Sessions 2019. Chicago, IL, November 10-12, 2018; Abst 19332.

Abstract
The role of dual antiplatelet therapy (DAPT) has come into vogue, in the last two decades, after several clinical trials proved their superiority to aspirin alone, in the prevention of vascular events, especially in the coronary and cerebral circulations. In the heart, their use has been extensive, especially after the use of drug eluting stents for acute coronary events. In the brain, their efficacy has to be balanced against their tendency to cause dangerous intracranial hemorrhage. Several scoring systems have been devised to address this risk benefit ratio. Judicious use of these combination therapies for the appropriate duration will prevent a significant number of recurrent vascular events, without dangerous bleeding risk.

Introduction
Atherosclerosis leading to vascular complications of heart and brain are important causes of morbidity and mortality. Platelet activation has a very important role in the occurrence of ischemic events in atherosclerosis. This makes antiplatelet drugs an essential part of the armamentarium the physician has to reduce these events. Currently they are being used in cardiology for acute coronary syndromes and vascular pathologies, and in neurology for the prevention of stroke and transient ischemic attacks (TIAs). In addition, their role in the management of prevention of thromboembolism in atrial fibrillation is also to be defined.

In this chapter we will review the current status of dual antiplatelet therapy (DAPT), in cardiac and cerebral events, keeping in mind the data available on this subject, and the current guidelines on the use of DAPT.

Review of Literature on DAPT
Brief History
The concept of using DAPT therapy began when it was shown two decades ago, that they decreased vascular events, especially in the context of coronary intervention. The choice of anti-platelet therapy has also changed from ticlopidine to the safer clopidogrel and more potent drugs like ticagrelor and prasugrel.

Role in Acute Coronary Syndrome
ST-Elevation Myocardial Infarction (STEMI)
In STEMI, the aim of antiplatelet therapy is to reduce the thrombotic tendency at the site of plaque rupture, and also prevent further thrombosis due the intervention in the coronaries. This has to be efficient and fast in order to serve this purpose. Hence, the combination of heparin, aspirin (325 mg, non-enteric coated, crushed or chewed for early action) and a second antiplatelet drug like prasugrel or ticagrelor is recommended. The concept of preloading before stenting is not recommended any more, based on the results of the ATLANTIC trial, which did not show any advantage in patients who received anti platelet therapy in the ambulance.

The current focused update of European Society of Cardiology (ECS) recommends that ticagrelor 90 mg BD be used, along with aspirin in all patients undergoing
percutaneous coronary angioplasty (PCI). If the patient has been on clopidogrel, it is recommended to stop it and switch to ticagrelor because of its superior efficacy.\(^3\) In STEMI patients who undergo thrombolysis, clopidogrel 300 mg loading, with 75 mg OD should be continued. In patients whom bypass surgery is anticipated early, DAPT is avoided, and only aspirin is given.

**In Unstable Angina**

In NSTEMI, the need for antiplatelet therapy is to stabilize the ruptured plaque. The patient is usually taken up for intervention over the next 1–2 days. When they undergo PCI, it is advised to give DAPT, preferably ticagrelor or prasugrel with aspirin. These need not be given upfront, as the ACCOAST trial,\(^4\) did not find any advantage in using the second antiplatelet at arrival, and in fact showed that it increased chances of bleeding.

In patients who need only medical management for acute coronary syndrome (ACS), it is advised to give ticagrelor along with aspirin for a period of 1 year. Clopidogrel is a second choice.

**In Stable Angina**

For stable angina patients, who are managed medically, DAPT is not needed, as shown by the CHARISMA trial.\(^5\) For those who undergo coronary stenting, clopidogrel can be added to aspirin and continued further for 6 months. The loading dose would be 600 mg, followed by 75 mg OD along with aspirin. If they have a high risk of bleeding, DAPT can be brought down to single drug at 1 month.

**Role of DAPT after Stenting**

The problem of prevention of stent thrombosis encouraged the use of DAPT. The change from bare metal stents to the use of drug eluting stents further increased the danger of stent thrombosis, which led to the usage of more potent drugs. However, here, DAPT has a dual role. It serves to prevent stent thrombosis, but also prevented atherosclerotic events as a whole in the body. Ticagrelor fitted the bill adequately and is hence recommended for prevention of stent induced thrombosis.

**Duration of DAPT after Stenting**

The fear of stent thrombosis with DES has also come down as the stents now have thinner struts and are more biodegradable. Hence, the duration of DAPT therapy has also come down from 12 months to 6 months and even 3 months in suitable patients. The TWILIGHT trial found that 3 months of DAPT followed by ticagrelor monotherapy for 1 year, is non inferior to 1 year of DAPT.\(^6\)

The duration of therapy needed after stenting is a delicate balance between the risk of thrombosis and recurrence of ACS, versus the danger of bleeding. The current ECS recommendations are for 6 months in patients with drug eluting stents, if they are stable. However, for patients with ACS, the risk of recurrence is higher, and hence DAPT is extended for 1 year. This can be reduced to 6 months if bleeding risk is high.

To balance the ischemic and bleeding risk, various scores have been put forth. The ischemic risk is calculated by patient characteristics and what is defined as the complexity for the coronary lesion as given below, using the DAPT score. If this score is more than 2, a longer duration of DAPT is advised.

The PRECISE-DAPT score assesses the bleeding risk. A PRECISE-DAPT score of more than 25 would indicate a high bleeding risk and may call for shortening duration of DAPT (Table 1).\(^7\)

In a meta-analysis of 9,000 patients, the PCI complexity was assessed by six interventional factors: three-vessel PCI, implantation of three or more stents, three or more complex coronary lesions, bifurcation stenting, total stent length more than 60 mm, and treatment of a chronic total coronary occlusion.\(^8\) Further, if the LAD is involved, the duration of therapy is extended even beyond 12 months keeping in mind the recurrence risk.\(^9\)

The bleeding risk can also be calculated by the CRUSADE score and the HAS-BleD scores to decide on duration of therapy. Treatment will have to be individualized, as has been recommended by all major guidelines.\(^10\) In addition, all patients who require DAPT for any indication, and have a high bleeding risk, should be given proton pump inhibitors along with them. Table 2 summarizes current recommendations.

**DAPT in Patients with AF**

Between 6–8% of patients who are on anticoagulation may need PCI. In such patients, the duration of DAPT plus an anticoagulant can be given up to 6 months if their bleeding risk is low and shortened to 1 month if it is high. However, prasugrel and ticagrelor are best avoided, as they...
TABLE 1  Risk scores validated for dual antiplatelet therapy duration decision-making

<table>
<thead>
<tr>
<th>PRECISE-DAPT score</th>
<th>DAPT score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of use</td>
<td>At the time of coronary stenting</td>
</tr>
<tr>
<td>DAPT duration strategies assessed</td>
<td>Short DAPT (3–6 months) vs. Standard/long DAPT (12–24 months)</td>
</tr>
<tr>
<td>Score calculation</td>
<td></td>
</tr>
<tr>
<td>HB</td>
<td>≥12</td>
</tr>
<tr>
<td>WBC</td>
<td>≤5</td>
</tr>
<tr>
<td>Age</td>
<td>≤50</td>
</tr>
<tr>
<td>CrCl</td>
<td>≥100</td>
</tr>
<tr>
<td>Prior bleeding</td>
<td>No</td>
</tr>
<tr>
<td>Score points</td>
<td>0</td>
</tr>
<tr>
<td>Score range</td>
<td>0 to 100 points</td>
</tr>
<tr>
<td>Decision-making cut-off suggested</td>
<td>Score ≥25 → Short DAPT</td>
</tr>
<tr>
<td>Calculator</td>
<td><a href="http://www.precisedeptscore.com">www.precisedeptscore.com</a></td>
</tr>
</tbody>
</table>

TABLE 2  Drug of choice and duration of treatment for various vascular conditions

<table>
<thead>
<tr>
<th>Clinical condition</th>
<th>DAPT-aspirin + Drug of choice</th>
<th>Duration of DAPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI with PCI</td>
<td>Prasugrel/ticagrelor</td>
<td>1 year</td>
</tr>
<tr>
<td>MI with thrombolysis</td>
<td>Clopidogrel</td>
<td>1 year</td>
</tr>
<tr>
<td>NSTEMI with PCI</td>
<td>Prasugrel/ticagrelor</td>
<td>1 year</td>
</tr>
<tr>
<td>NSTEMI with medical treatment</td>
<td>Ticagrelor</td>
<td>1 year</td>
</tr>
<tr>
<td>Stable angina with PCI</td>
<td>Clopidogrel</td>
<td>6 months</td>
</tr>
<tr>
<td>Stable angina with medical management</td>
<td>Only aspirin</td>
<td>Lifelong single drug</td>
</tr>
</tbody>
</table>

If aspirin can be continued, stopping DAPT for few days will not be difficult. If aspirin is discontinued, bridging with tirofiban or eptifibatide may be needed.

**Intervention on DAPT:** If a patient needs PCI on DAPT, radial access is preferred over femoral one, and aspirin can be continued. The additional use of a PPI is recommended.

**DAPT in Neurology Practice**

**DAPT in Transient Ischemic Attacks**

TIAs are the forerunners of strokes but leave no permanent neurological deficit. They give an opportunity to give antiplatelet therapy to prevent further vascular events. The risk of stroke increases with the characteristics of the TIA, which can be categorized by clinical features. Patients with TIA are risk stratified according to ABCD² score (age, blood pressure, clinical features, duration of TIA, and presence of diabetes). A score of more than or equal to 4 denotes a high-risk TIA and such patients are prone for recurrent stroke of up to 8%, especially in the first 48 hours.

Two major trials addressed the question of DAPT and its duration in high risk TIAs and minor strokes with National Institutes of Health Stroke Scale (NIHSS) score of

**Surgery on DAPT**

Stopping DAPT for elective surgery should be a collective decision between departments involved and cardiologist. It is unpredictable and cause major bleeding along with anticoagulants. There is some data, that using NOACs like apixaban and rivaroxaban may cause less bleeding risk; however, treatment is best individualized.⁵
less than or equal to 3. The CHANCE (Clopidogrel in High-Risk Patients with Acute Non-Disabling Cerebrovascular Events) trial done in China, showed for the first time, that aspirin and clopidogrel for 21 days, and then only clopidogrel until 90 days decreased the subsequent ischemic events. However, the POINT trial, which was conducted in North America, Australia, and other countries, did not find lesser ischemic events with DAPT, and had more bleeding events.

This difference has been attributed to the different patient populations used and the varying causes of ischemic events in these groups. The POINT showed more risk of bleeding, which could be due to the longer duration of DAPT used (90 days as opposed to 21 days in CHANCE). Further the Asian population in CHANCE did have genetic differences which could account for the lesser bleeding risk. The absorption of clopidogrel depends on the presence of a transporter in gut called ABCB1, which affects its efficacy but not bleeding risk. Hence, the different results may be due to ethnic variation.

However, most analysis recommend the use of DAPT in high risk TIA with aspirin (160–325 mg loading dose, followed by 50–100 mg daily) plus clopidogrel (300–600 mg loading dose, followed by 75 mg daily) in the first 21 days of therapy, as this is the most vulnerable period for recurrent ischemic events. From day 22 to 90 days, the ischemic events were less, and the bleeding risk was unnecessarily increased as seen in a meta-analysis including CHANCE and POINT trials. In fact, the first 10 days after TIA are crucial to prevent recurrence, though most guidelines recommend DAPT up to 21 days. The bleeding risk with DAPT is minimal till 21 days, and this does not compromise the benefits of prevention of stroke. If the TIA happens on a single antiplatelet drug, the second one can be added up to 21 days as advised.

The choice of the antiplatelet drug, which should be continued after day 21, till 90 days, has been clopidogrel in most studies, anticipating aspirin resistance. However, the Indian guidelines on stroke do not specify this, and mention that either aspirin or clopidogrel can be continued based on the choice of the physician, as aspirin resistance is not well documented in the Indian population. There is also a small improvement in functional scores after DAPT in minor strokes, which may recommend their use.

Further triple therapy (aspirin, dipyridamole, and clopidogrel) was also tried in the TARDIS trial and given up, as it gave rise to more bleeding and less advantage with ischemic events. Of late, newer DAPT therapy using ticagrelor and prasugrel are also undergoing trials to check their efficacy and safety. The SOCRATES trial compared the efficacy of clopidogrel to ticagrelor, and found it is non inferior, but caused more bleeding risks in the ticagrelor arm.

**DAPT in Secondary Prevention of Strokes**

The CAPPRIE trial was the first to demonstrate the efficacy of additional clopidogrel in secondary prevention of strokes. This was followed by the MATCH trial, which actually showed higher bleeding risk in patients on DAPT. Following this the CHARISMA trial used aspirin, versus aspirin with clopidogrel, and found DAPT to be useful in preventing ischemic events though with increase in bleeding. So DAPT is recommended for patients with acute ischemic stroke with an NIHSS score of less than 3. As of now, there is no role for DAPT in acute ischemic stroke with a higher score. In these patients, a single antiplatelet, which is aspirin in a dose of 325 mg stat, followed by 75 mg daily after that is given lifelong.

As of now, there is no evidence for continuing DAPT beyond 90 days, in any neurological situation as it results in more bleeding and less efficacy for prevention.

**DAPT in Lacunar Strokes**

Antiplatelet therapy has no major role in lacunar strokes. However, in high risk TIAs and those with early neurological deterioration in lacunar infarcts, a study showed better functional outcomes of short duration DAPT for 5 days.

**DAPT in Intracranial Large Artery Thrombosis**

DAPT decreases stroke and death in patients in this subgroup, if aspirin and clopidogrel are given in the first 90 days in symptomatic patients with 70–99% stenosis as shown in the SAMMPRIS trial. But this is useful only when the NIHSS score is less than 3. Beyond this, there is a fear of hemorrhagic transformation and aspirin alone is recommended.

**DAPT in Vascular Disease**

DAPT has been used in symptomatic carotid stenosis, which is severe, for the prevention of stroke for at least 3 months. In patients with asymptomatic intracranial stenosis, DAPT can be given for 1 month, followed by single antiplatelet, if patients have TIA and minor stroke.
TABLE 3  Summary of indication on antiplatelet treatment from ESC guidelines, 2017

<table>
<thead>
<tr>
<th>District</th>
<th>Monotherapy (aspirin or clopidogrel)</th>
<th>DAPT (aspirin plus clopidogrel)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LEAD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>Class III A</td>
<td>–</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>Class IA</td>
<td>–</td>
</tr>
<tr>
<td>Endovascular revascularization</td>
<td>From 1 month after procedure: class IIA C</td>
<td>For 1 month after procedure: class IIA C</td>
</tr>
<tr>
<td>Surgical revascularization</td>
<td>Class IIB B</td>
<td>–</td>
</tr>
<tr>
<td><strong>Carotid artery disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic (&gt;50% carotid artery stenosis, low bleeding risk)</td>
<td>Class IIA C</td>
<td>–</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>Class IA</td>
<td>–</td>
</tr>
<tr>
<td>Endovascular revascularization</td>
<td>From 1 month after procedure: class I A</td>
<td>For 1 month after procedure: class I A</td>
</tr>
<tr>
<td>Surgical revascularization</td>
<td>Class IIA</td>
<td>–</td>
</tr>
</tbody>
</table>

ESC, European Society of Cardiology; LEAD, lower extremity

TABLE 4  Antiplatelet reversal recommendations

<table>
<thead>
<tr>
<th>Reversibility</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irreversible binding agents</td>
<td>Platelet transfusion</td>
</tr>
<tr>
<td></td>
<td>Intracranial hemorrhage: Platelet transfusion for patients NOT undergoing a neurosurgical procedure is associated with worse functional outcome and death with no change in volume growth</td>
</tr>
<tr>
<td></td>
<td>Desmopressin 0.4 µg/kg IV for 1 dose</td>
</tr>
<tr>
<td></td>
<td>Desmopressin can be considered for patients on antiplatelet therapy that binds irreversibly. For those undergoing a neurosurgical procedure DDAVP can be used in addition to platelet transfusion.</td>
</tr>
<tr>
<td>Reversible binding agents</td>
<td>Platelet transfusion</td>
</tr>
<tr>
<td></td>
<td>Neurosurgical procedure: Allow 3–5 half-lives from the last administration of the antiplatelet agent before administering platelet transfusion to prevent inhibition of infusing platelets</td>
</tr>
<tr>
<td></td>
<td>Desmopressin 0.4 µg/kg IV for 1 dose</td>
</tr>
<tr>
<td></td>
<td>When used in combination with platelet transfusion, desmopressin may be beneficial prior to emergent procedures</td>
</tr>
</tbody>
</table>

In the CASPAR (Clopidogrel and Acetylsalicylic Acid in Bypass Surgery for Peripheral Artery Disease) study, subjects underwent below-knee femoropopliteal bypass received either DAPT or aspirin alone. This study showed that the patients with prosthetic grafts on DAPT did benefit.20

Currently, DAPT is advised for both carotid stenosis and peripheral vascular disease, for 1 month, after revascularization. If asymptomatic, there is no indication for DAPT in lower extremity atherosclerotic disease or mild to moderate carotid stenosis (Table 3).

In patients with cardioembolic stroke with contraindication to anticoagulants, DAPT has been tried as an alternative, with some success, though this is not the first choice.

**DAPT and Correction of Bleeding**

There is always a danger of bleeding during any neurosurgical procedure for patients on DAPT for any indication. In this instance, platelet transfusion and desmopressin can be used as summarized in Table 4.

**Conclusion**

To conclude, DAPT has a definite role to play in the prevention of ischemic events in the coronary and cerebral circulation. Their efficacy in decreasing mortality and morbidity is evident from results from various trials. However, they must be used judiciously to avoid bleeding risks, for the minimum period of time, to be useful and safe.
References


Abstract

The new oral anticoagulants (NOACs) developed to address these limitations are backed by good trials. Beginning with Dabigatran in 2010, currently two classes of NOACs are available, the oral direct thrombin inhibitors (e.g., dabigatran) and direct factor Xa inhibitors. They have a distinct advantage of having rapid onset of action, fixed dosing, and absence of need of regular monitoring compared to VKA. Prediction tools like SAMe TTR2 score can be used in the decision-making between NOAC and VKA. In this chapter a brief description of different NOACs and its use in several situations have been highlighted. With the correct knowledge about these drugs, choosing the right patient and following the principle of therapeutic humility the benefits of these novel drugs can be passed on to the patients for better efficacy.

Introduction

Vitamin K antagonists (VKAs) have been the main treatment modality for the prevention of thrombotic episodes in atrial fibrillation (AF). Despite its significant impact to prevent strokes, there have been many limitations in its use from benign one to more serious ones. In the last several years, the new oral anticoagulants (NOACs) developed to address these limitations are backed by good trials. Beginning with Dabigatran in 2010 leads to creation of another novel oral anticoagulant rivaroxaban. Further with development of apixaban, edoxaban they changed the name to direct oral anticoagulants and is currently the term used by ISTH (International Society of Thrombosis and Hemostasis).1

There are several advantages and disadvantages of NOAC Vs VKA (Table 1), with the correct knowledge and decision making the right NOACs can be given to the right patient.

Mechanism of Action

Currently two classes of NOACs are available, the oral direct thrombin inhibitors (e.g., dabigatran), which directly bind to thrombin, thus prevent cleaving of fibrinogen to fibrin and direct factor Xa inhibitors (e.g., rivaroxaban, apixaban, and edoxaban), which prevent factor Xa from cleaving prothrombin to thrombin. Unlike VKAs, which block the formation of vitamin K-dependent coagulation factors (factors II, VII, IX, and X), these drugs block a particular step in coagulation cascade.

Approved Indications for NOAC3,4

- Reduce risk of embolization events (e.g., stroke) in patients with non-valvular AF.
- Treatment of DVT and pulmonary embolism (PE).
- Reduction in risk of recurrent DVT, PE in patients at risk after initial treatment.
- Prophylaxis of DVT.
**TABLE 1** Advantages and disadvantages of NOAC over warfarin

<table>
<thead>
<tr>
<th>Feature</th>
<th>Warfarin</th>
<th>NOAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of action</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Dosing schedule</td>
<td>Variable</td>
<td>Fixed</td>
</tr>
<tr>
<td>Food interaction</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Interactions</td>
<td>Many</td>
<td>Fewer</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Offset</td>
<td>Long</td>
<td>Shorter</td>
</tr>
<tr>
<td>Frequency</td>
<td>Once daily</td>
<td>Once/Twice</td>
</tr>
<tr>
<td>Monitoring</td>
<td>INR</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Clearance</td>
<td>Non renal</td>
<td>Renal (25–80%)</td>
</tr>
<tr>
<td>Antidote</td>
<td>Vit K</td>
<td>Idaricuzumab/Andexanet alpha/?Dialysis</td>
</tr>
<tr>
<td>Familiarity</td>
<td>Extensive</td>
<td>Minimal</td>
</tr>
</tbody>
</table>

**TABLE 2** Table showing SAMeTTR2 score

<table>
<thead>
<tr>
<th>Factor</th>
<th>Point</th>
<th>Score</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (Female)</td>
<td>1</td>
<td>0–2</td>
<td>Patients likely to achieve a high TTR VKA may be beneficial</td>
</tr>
<tr>
<td>Age (&lt;60 years)</td>
<td>1</td>
<td>0–2</td>
<td>Patients likely to achieve a high TTR VKA may be beneficial</td>
</tr>
<tr>
<td>Medical history (H/O more than two of the following: HTN, Diabetes, CAD, PAD, Heart failure, Stroke, Pulmonary hepatic, or Renal disease)</td>
<td>1</td>
<td>≥2</td>
<td>NOAC would be better initial option</td>
</tr>
<tr>
<td>Treatment (Interacting medications, e.g., amiodarone)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobacco Use (within 2 years)</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race (non-caucasian)</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Emerging Indications**

- Use of NOACs before and after cardioversion and catheter ablation in AF.
- Prevention of further cardiovascular events in patients after ACS.
- NVAF undergoing PCI.
- In stable CV disease and peripheral vascular disease.
- Prevention of venous thromboembolism (VTE) in acutely ill medical patients.

Considerations when starting/choosing a NOAC—think ABCDE:

A—Low weight (dose reduction might be needed)
B—Bleeding risk (GI bleeding)
C—Creatinine clearance (renal function)
D—Drug interactions (p-glycoprotein, CYP450, e.g., reduced verapamil dose with dabigatran)
E—Elderly (dose reduction might be necessary)

**SAMe-TT2R2 Score (Table 2)**

It is a prediction tool that predicts the quality of vitamin K antagonist anticoagulation therapy as measured by time in therapeutic INR range (TTR). It can be used in the decision-making between NOAC and VKA. It can be used in patients with CHA2DS2VASc score ≥1 where oral anticoagulation is recommended.

**Brief Description of NOACs**

**Dabigatran**

Dabigatran belongs to group of direct thrombin inhibition, after oral ingestion inactive drug is converted to active form and reaches peak plasma levels within 2–3 hours. Onset of action is 1–2 hours, with a half-life of 12–17 hours, and is predominantly excreted by the kidneys (80%)
RE-LY trial compared dabigatran 110 mg BID or 150 mg BID with warfarin in 18,113 patients with AF with a mean CHADS score of 2.1. The primary endpoints assessed were occurrence of stroke and systemic embolism. However, GI bleeding was found to be more with dabigatran (150 mg BID). Dabigatran 110 mg BID was non-inferior to warfarin for the primary endpoint, with a reduction of 20% in major bleedings.

An extension of RE-LY study called the RELY-ABLE study was conducted where the cases enrolled in the earlier RE-LY study were further followed up for another 2 years and 3 months from the original study period. This study confirmed the results of RE-LY and gave information on the long-term effects of dabigatran use in both the doses.

Another two studies (RE-COVER) and RE-COVER II, which were a comparison of dabigatran and warfarin in venous thromboembolism showed that dabigatran was non-inferior to standard treatment of VTE with reduced bleeding risk (1.4%) with no differences in major bleeding.

### Rivaroxaban

It is a dose-dependent direct inhibitor of factor Xa and the second NOAC approved by the FDA based on the ROCKET AF study.

Rivaroxaban in comparison to warfarin is effective in prevention of stroke in AF, and also in treatment and prevention of DVT with reduced risk of serious bleeding complications.

The ROCKET AF was a double-blinded study which showed noninferiority of rivaroxaban to warfarin in the prevention of stroke or systemic embolism; however, rivaroxaban failed to show superiority over warfarin in the intention to treat analysis. Fatal bleeding occurred less frequently in the rivaroxaban group, with no differences in the risk of major bleeding. GI bleeding and transfusion requirements were greater with rivaroxaban. The EINSTEIN DVT trial showed rivaroxaban was noninferior to warfarin for DVT with similar bleeding risk among both.

### Apixaban

It is a direct, reversible, competitive, and selective inhibitor of factor Xa in patients of AF. It is approved for stroke prevention. Among the NOACs, apixaban is least cleared from the kidneys and is metabolized predominantly by the liver, and hence its use in renal failure patients.

The ARISTOTLE study showed apixaban was better than warfarin, with fewer primary outcomes (overall strokes and systemic emboli). Apixaban was compared with aspirin in the AVERROES study. But after a mean follow-up of 1.1 years, the study was prematurely stopped as there was a clear benefit of apixaban. The primary outcome of stroke or systemic embolism was significantly lower in the apixaban group versus aspirin, with similar bleeding risk (major bleeding and intracranial bleeding) between the two. The APPRAISE study assessed the effect of apixaban with placebo in addition to antiplatelets following ACS. It was stopped as it was found to have more risk of bleeding with less benefit after 8 months.

### Edoxaban

It is once daily dosing drug. In comparison with warfarin, once daily Edoxaban had similar efficacy to warfarin in stroke prevention and treatment of DVT AND PE with lesser risk of bleeding complications. ENGAGE AF TIMI 48 trial showed that both low dose (30 mg) and high dose (60 mg) were noninferior to warfarin and a dose-related reduction in bleeding as compared to warfarin.

### Bleeding while Using an NOAC

Unlike in VKA, fresh frozen plasma cannot be used when there is serious bleeding for reversal, instead can be used only for volume expansion. Drugs like andexanet alfa (a recombinant human FXa analogue that competes for the FXa inhibitors with FXa), idarucizumab, (humanized antibody fragment that specifically binds dabigatran) prothrombin concentrates, can be used depending on the availability and latest evidence. More importantly we have to inquire about the dosing regimen, the time of last dose as it is expected that after stopping the treatment, haemostasis is expected within 12–24 h after the last taken dose, as plasma half-life is around 12 h for most NOACs. Thus in most non serious bleeding conditions a wait and watch principle can be used.

### Switching from Heparin/VKA to NOAC

While Changing from heparin to NOAC, in case of conventional heparin they can be started after stopping the conventional heparin, in case of LMWH it has tob
### TABLE 3: NOAC in renal disease\(^{22}\)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Criteria</th>
<th>Dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Creatinine clearance &lt;50 mL/min &lt;30 mL/min</td>
<td>110 mg BD &amp; as per ESC guidelines should not be used</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Creatinine clearance &lt;50 mL/min</td>
<td>15 mg OD</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Two of these factors: Age &gt;80, creatinine &gt;1.5, weight &lt;60</td>
<td>2.5 mg BD</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Creatinine clearance &lt;50 mL/min</td>
<td>30 mg OD</td>
</tr>
</tbody>
</table>

### TABLE 4: NOAC before surgery\(^{23}\)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renal function</th>
<th>Minor surgery</th>
<th>Major surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CrCl &gt;50</td>
<td>PREOP</td>
<td>POST-OP</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Stop 2 days</td>
<td>Restart 1 day</td>
<td>Stop 3 days</td>
</tr>
<tr>
<td></td>
<td>before surgery</td>
<td>after surgery</td>
<td>before surgery</td>
</tr>
<tr>
<td></td>
<td>CrCl &lt;50</td>
<td>Stop 3 days</td>
<td>Restart 1 day</td>
</tr>
<tr>
<td></td>
<td>before surgery</td>
<td>after surgery</td>
<td>after surgery</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Stop 2 days</td>
<td>Restart 24 h</td>
<td>Stop 3 days</td>
</tr>
<tr>
<td></td>
<td>before surgery</td>
<td>post-surgery</td>
<td>before surgery</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Stop 2 days</td>
<td>Restart 24 h</td>
<td>Stop 3 days</td>
</tr>
<tr>
<td></td>
<td>before surgery</td>
<td>post-surgery</td>
<td>before surgery</td>
</tr>
</tbody>
</table>

### TABLE 5: Coagulation profile and NOAC\(^{24}\)

<table>
<thead>
<tr>
<th>Test</th>
<th>Factor Xa inhibitors</th>
<th>Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qualitative (Present/Absent)</td>
<td>PT (Riva&gt;Edoxa&gt;Apixaban)</td>
<td>TT&gt;aPTT</td>
</tr>
<tr>
<td>Quantitative test</td>
<td>Chromogenic Anti Xa levels (Requires specific calibration to drug)</td>
<td>Dilute TT, Anti IIa (specific calibration)</td>
</tr>
</tbody>
</table>

### Flowchart 1: NOAC in stroke\(^{25}\)

- **Ischemic Stroke**
  - TIA
    - After 1 day
  - Mild stroke (NIHSS < 8)
    - After 3 days
  - Moderate stroke (NIHSS 8 to 16)
    - Exclude hemorrhagic transformation by CT or MRI at day 6
    - Start after 6 days
  - Severe stroke (NIHSS > 16)
    - Exclude hemorrhagic transformation by CT or MRI at day 12
    - Start after 12 days
started 2 hours prior to stopping LMWH. When it has to be changed back from NOAC to parental anticoagulants we can start 12 h after Apixaban or Dabigatran dose and after 24 hrs of last Rivaroxaban dose. From warfarin to NOAC depending on the INR (Dabigatran/Apixaban if INR <2.0 , Rivaroxaban when INR <2.5) it can be started after stopping warfarin.27

NOAC in Special Situations

Refer Tables 3 and 4, Flowchart 1.

NOAC in Asian Population

A meta-analysis which included 5 NOAC trials, 21 observational Cohort showed that NOAC were associated with decreased rates of systemic embolization, ischemic stroke, myocardial infarction, major bleeding among Asian population with consideration of rivaroxaban for myocardial infarction.28,31

Coagulation Profile and NOAC24

NOAC does not require routine monitoring of coagulation profile. However, they can significantly be affected and pose a difficulty in presence of acute overdose or significant bleeding.

Normal PT or aPTT does not guarantee absence of anticoagulant activity. Quantitative tests are not standardised or approved. Depending on the clinical situations decision on switching between anticoagulants have to be taken (Table 5).

Conclusion

With increase in the armamentarium of drugs used for antithrombotic effect, it is imperative that as clinicians we need to know the mechanism of action, adverse events, studies backing the NOAC, and importantly the situation where these drugs have to be used and when are they contraindicated. We should never forget the important third dimension in the treatment which is the financial consideration as it is one of the important aspects in our setup. As most of these drugs’ costs are higher compared to VKA with the correct knowledge and use of these drugs also taking into the economic aspects the benefit can be passed on to the patients for better efficacy and better compliance.

References

Abstract

Human medicine has always evolved as evident by the literature available. This change has come from scientific evidence accumulated from numerous clinical trials and studies. Cardiovascular diseases are one of the most important causes for morbidity and mortality. Most of the guidelines for management of the diseases come from the scientific data which gives us direction and insight into understanding of the disease and treatment. Hence, it becomes vital for the physicians to be updated with recently evolving scientific data in the form of clinical trials and studies. Here, we discuss briefly the recently published literature in the field of cardiology.

Introduction

Human medicine is a dynamic and ever-evolving field guided by new evidence derived from clinical studies. Cardiovascular disease is a major cause of morbidity and mortality in humans, hence it is crucial to explore this segment of medicine further to advance the aspects of diagnosis and management. Most of the clinical practice is dependent on evidence-based medicine. This evidence comes from the scientific data generated as a result of clinical trials, clinical studies, and experience of the scientific community. A clinical trial is a scientifically conducted investigation of a treatment or drug involving healthy people and patients. Clinical trials are needed to determine the correct dose of new drugs, to determine whether the drug will treat the disease effectively in humans, the safety of new drugs alone and in combination with other drugs, and to determine whether an intervention is better than the standard treatment. There are lots of trials being conducted every year and evidence-based guidelines also change, depending on the trial results. In this chapter, we discuss the recent scientific data on cardiology in the form of published landmark trials which are likely to have a significant impact on our clinical practice (Table 1).

Heart Failure

Heart failure (HF) is an important cause of mortality and morbidity in patients with cardiac disease. Different treatment options exist ranging from drugs to various cardiac interventions. Sacubitril–valsartan has been studied in these patients and has shown good results. This drug was evaluated in acute decompensated HF patients.

PIONEER-HF (Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure) Trial

Sacubitril–valsartan therapy is now widely used in chronic HF. In this trial, patients with HF with reduced ejection fraction who were admitted for acute decompensated HF were included after hemodynamic stabilization. The patients either received sacubitril–valsartan to a target dose of 200 mg (97 mg of sacubitril with 103 mg of valsartan) twice daily or enalapril to a target dose (10 mg)
### TABLE 1
Summary of recently published clinical trials in cardiology

<table>
<thead>
<tr>
<th>Trial Description</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIONEER-HF (Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure) trial</td>
<td>HFrEF patients getting hospitalized for acute decompensated HF, sacubitril–valsartan therapy causes reduction in the NT-proBNP than the enalapril therapy without an increase in worsening renal function, hyperkalemia, symptomatic hypotension, or angioedema</td>
</tr>
<tr>
<td>AUGUSTUS (Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation) trial</td>
<td>In patients with AF and a recent ACS or PCI on a P2Y12 inhibitor, addition of apixaban, without aspirin, resulted in lesser bleeding events, and hospitalizations without significant differences in the incidence of ischemic events than regimens that include a vitamin K antagonist, aspirin, or both</td>
</tr>
<tr>
<td>ISAR-REACT-5 (Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes) trial</td>
<td>In ACS patients undergoing invasive strategy, the incidence of death, MI, or stroke was significantly lower with prasugrel than ticagrelor, with no major difference in the incidence of major bleed</td>
</tr>
<tr>
<td>COLCOT (Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction) trial</td>
<td>Colchicine at a dose of 0.5 mg daily reduces the risk of ischemic cardiovascular events than placebo in patients with a recent MI</td>
</tr>
<tr>
<td>COMPLETE (Complete Revascularization with Multivessel PCI for Myocardial Infarction) trial</td>
<td>A complete revascularization strategy in STEMI but with multivessel coronary artery disease was seen to lower the risk of CV death or MI, or composite of CV death, MI or ischemia-driven revascularization</td>
</tr>
<tr>
<td>REDUCE-IT (Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia) trial</td>
<td>In metabolic syndrome with elevated triglyceride levels, the risk of ischemic events is found to be significantly lower among patients taking 2 gm of icosapent ethyl twice daily with statins as compared to statin therapy alone</td>
</tr>
<tr>
<td>CLEAR Harmony (Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol) trial</td>
<td>Addition of bempedoic acid to maximally tolerated statin therapy reduced the LDL cholesterol levels without an increase in adverse events</td>
</tr>
<tr>
<td>AFIRE (Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease) trial</td>
<td>In patients with AF and stable coronary artery disease, rivaroxaban monotherapy when compared to rivaroxaban and aspirin was seen to be similar in efficacy and superior for safety</td>
</tr>
<tr>
<td>THEMIS (Ticagrelor in Patients with Stable Coronary Disease and Diabetes) trial</td>
<td>In diabetic patients with stable CAD without prior ACS or stroke, ticagrelor plus aspirin was seen to have lower incidence of ischemic cardiovascular events but at a cost of higher major bleeding events than those who received placebo plus aspirin</td>
</tr>
<tr>
<td>TWILIGHT (Ticagrelor with or without Aspirin in High-Risk Patients after PCI) trial</td>
<td>Double blind trial. Conducted in high risk patients undergoing PCI, ticagrelor alone when compared to combination of ticagrelor and aspirin after 3 months of dual antiplatelet therapy was seen to have similar risk of death, MI, or stroke and a lower incidence of clinically important bleed</td>
</tr>
<tr>
<td>STOP DAPT-2 (Effect of 1 month dual antiplatelet therapy (DAPT) followed by clopidogrel versus 12 month DAPT on CV and bleeding events in patients receiving PCI)</td>
<td>Multi-center, open label, randomized trial, tested a very short-term DAPT versus 12 DAPT, and found a lower rate of CV and bleeding events</td>
</tr>
<tr>
<td>DAPA-HF (Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction) trial</td>
<td>Phase-3 placebo controlled trial. In HFrEF, dapagliflozin reduced the risk of worsening of HF or CV death irrespective of diabetic status</td>
</tr>
<tr>
<td>EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) trial</td>
<td>Type 2 diabetic patients who are at high risk for CV events were found to have reduced CV events and mortality when they received empagliflozin as compared with placebo</td>
</tr>
<tr>
<td>ISCHAEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial</td>
<td>Among patients with stable CAD and moderate to severe ischemia on stress testing, routine invasive therapy failed to reduce major adverse cardiac events compared with optimal medical therapy. Routine invasive therapy was associated with harm at 6 months (increase in perioperative MIs) and associated with benefit at 4 years (reduction in spontaneous MI)</td>
</tr>
<tr>
<td>POET (Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis) trial</td>
<td>Left sided infective endocarditis patients in stable condition had similar outcomes with a shift to oral antibiotics after 10 days of intravenous antibiotics as compared to continued intravenous antibiotics</td>
</tr>
<tr>
<td>PARTNER-3 (Transcatheter aortic valve replacement with a balloon expandable valve in low risk patients)</td>
<td>In severe aortic stenosis patients with low surgical risk, transcatheter aortic valve replacement with balloon expandable valve had lower risk of composite of death, stroke, or rehospitalization at the end of 1 year</td>
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</table>
twice daily. Patients on sacubitril-valsartan had a greater reduction in the N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels than the enalapril group from baseline till weeks 4 and 8. It was interesting to see that there was a decrease in the NT-proBNP levels as early as week 1. There was no significant difference noted in incidence of worsening renal function, angioedema, symptomatic hypotension, and hyperkalemia in the two groups.

**Acute Coronary Syndrome**

Acute coronary syndrome (ACS) comprises patients with angina and evidence of characteristic electrocardiographic changes and/or evidence of myocardial damage with biochemical markers. Patients may present with unstable angina, non-ST-elevation myocardial infarction (NSTEMI), or ST-elevation myocardial infarction (STEMI). Its management comprises of antiplatelet drugs and evaluation of coronaries by coronary angiogram according to clinical presentation.

**AUGUSTUS (Antithrombotic Therapy after ACS or PCI in Atrial Fibrillation) Trial**

Patients with atrial fibrillation (AF) with an ACS or who undergo percutaneous coronary intervention (PCI) require an appropriate antithrombotic regimen requiring anticoagulants in addition to the antiplatelets. This trial evaluated such patients who need to be on a P2Y12 inhibitor, and was randomized to either apixaban or a vitamin K antagonist and to receive aspirin or matching placebo for a duration of 6 months. This trial concluded that patients with AF and ACS or post PCI who are planned for a P2Y12 inhibitor, apixaban, without aspirin, resulted in lesser bleeding events and hospitalizations, however, in the absence of significant differences in ischemic events as compared to the patients on vitamin K antagonist, aspirin, or both.

**ISAR-REACT-5 (Ticagrelor or Prasugrel in Patients with ACSs) Trial**

In this randomized trial patients with ACS who were planned for invasive evaluation received either ticagrelor or prasugrel. The primary end-point was defined as composite of death, myocardial infarction (MI), or stroke at 12 months was seen in lesser patients on prasugrel as compared to ticagrelor (HR, 1.36; P=0.006). Bleeding event rates were similar in both the groups. Further, it was noted that the incidence of death, MI, or stroke was significantly lower in the patients receiving prasugrel than those with ticagrelor.

**COLDOT (Efficacy and Safety of Low-Dose Colchicine after MI) Trial**

Colchicine is a mainstay therapy for hyperuricemia and is used frequently for management of pericarditis. This study tested effect of colchicine in patients with MI. Within 30 days, patients with MI were randomized to colchicines (0.5 mg once daily) or placebo. The composite of cardiovascular death, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization requiring revascularization was significantly lower in the colchicine group than the placebo (P=0.02). Thus, colchicine was seen to significantly lower the risk of ischemic cardiovascular events than placebo.

**Revascularization in ACS**

PCI of the culprit lesion in STEMI is shown to lower risk of cardiovascular morbidity and mortality.

**COMPLETE (Complete Revascularization with Multivessel PCI for MI) Trial**

STEMI patients with multivessel coronary artery disease undergoing PCI of the culprit lesion were randomized to complete revascularization with PCI or no further revascularization. Further, these patients according to planned timing of non-culprit PCI (either during or after the index hospitalization) were randomized in groups. It was seen that at 3-year median follow-up, the composite of MI and CV death, or composite MI, CV death, and ischemia driven revascularization was lower in the complete revascularization group. This was irrespective of the timing of the complete revascularization.

**Cardiovascular Drugs**

**Drugs for Dyslipidemias**

**REDUCE-IT (Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia) Trial**

In patients with known cardiovascular disease or who are at risk of CVD, this trial evaluated the effect of Icosapent ethyl (IPE) on cardiovascular events as compared to
placebo. Elevated triglyceride levels are an independent marker for ischemic events. IPE, a highly purified and stable eicosapentaenoic acid (EPA) when used as an adjunct to the diet in patients with triglyceride levels at least 500 mg/dL, lowers the triglyceride levels and in addition has been seen to have anti-inflammatory, plaque stabilizing, and also membrane stabilizing properties. Patients were started on 2 gm of IPE in addition to statins with fasting triglyceride level of 135–499 mg/dL and an LDL (low-density lipoprotein) cholesterol level of 41–100 mg/dL were randomized to receive 2 gm of IPE twice daily (total daily dose, 4 gm) or placebo. The primary outcome of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina was seen less in the drug group as compared to the placebo group (P<0.001). Additionally, the secondary outcome of cardiovascular death, nonfatal MI, or nonfatal stroke occurred in 11.2% in icosapent group and in 14.8% of patients in the placebo group (P<0.001). Hence, it was seen that IPE added with statins lowers the risk of ischemic events.

**CLEAR Harmony (Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol) Trial**

Bempedoic acid is a prodrug, acts liver-specific, and lowers LDL cholesterol by inhibiting ATP citrate lyase, an enzyme which acts upstream of HMG-CoA reductase (3-hydroxy-3-methylglutaryl coenzyme A). This was a phase 3 randomized, double blind placebo controlled trial done in patients on highest tolerated doses of statins (alone or in combination with other drugs) with evidence of atherosclerotic cardiovascular disease, heterozygous familial hypercholesterolemia, or both. These patients were enrolled if LDL cholesterol level was at least 70 mg/dL and then were randomized to either bempedoic acid or placebo. There was reduction at 12 weeks in the LDL levels (19.2 mg/dL) translating to a change of 16.5% from baseline. The adverse events did not differ substantially between the two groups; however, more patients discontinued treatment due to adverse events in the bempedoic acid. The safety and efficacy was similar irrespective of the dose of statins used.

**Antiplatelet Drugs**

Antiplatelet drugs form the cornerstone of treatment in patients with coronary artery disease and patients undergoing percutaneous coronary interventions. Here, we describe the important trials evaluating the antiplatelet drugs in stable coronary artery disease, ACSs, and post PCI patients.

**AFIRE (Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease) Trial**

In this trial, patients with AF undergoing PCI or coronary artery bypass grafting (CABG) more than a year back or who had evidence of insignificant coronary artery disease as documented by an angiogram were randomized to either rivaroxaban alone or a combination therapy with rivaroxaban plus a single antiplatelet agent. The primary (efficacy) end-point was a composite of MI, stroke, systemic embolism, unstable angina needing revascularization, or death from any cause. The primary end-point (safety) was major bleeding. It was decided to stop this trial early due to increased mortality noted in the combination therapy group. It was seen that rivaroxaban when given alone showed non-inferiority as compared to the combination therapy for the primary efficacy end-point. For the safety end-point, rivaroxaban alone was superior to combination therapy. Hence, to summarize rivaroxaban when given alone showed non-inferiority as compared to the combination therapy for the primary efficacy end-point. For the safety end-point, rivaroxaban alone was superior to combination therapy. Hence, to summarize rivaroxaban when given alone showed non-inferiority as compared to the combination therapy for the primary efficacy end-point. For the safety end-point, rivaroxaban alone was superior to combination therapy. Hence, to summarize rivaroxaban when given alone showed non-inferiority as compared to the combination therapy for the primary efficacy end-point. For the safety end-point, rivaroxaban alone was superior to combination therapy.

**THEMIS (Ticagrelor in Patients with Stable Coronary Disease and Diabetes) Trial**

Patients with diabetes and stable coronary artery disease have a higher risk of cardiovascular events as compared to non-diabetics. This trial tested whether addition of ticagrelor to aspirin in diabetics with a stable coronary artery disease with no previous history of MI or stroke, improves ischemic outcomes. Ticagrelor proved to reduce the incidence of ischemic events group (7.7% vs. 8.5%; P=0.04), but was associated with a higher bleeding events (2.2% vs. 1.0%; P<0.001). Further, it is to be noted that although the risk of intracranial bleed was higher (0.7% vs. 0.5%; P=0.005), but the incidence of fatal bleed was not different as compared to the placebo (0.2% vs. 0.1%; P=0.11). Hence, addition of ticagrelor to aspirin reduced the ischemic events but simultaneously increased major bleeding rates.
TWILIGHT (Ticagrelor with or without Aspirin in High-Risk Patients after PCI) Trial

Post PCIs, after a period of dual antiplatelet therapy, most patients are preferably shifted to a single antiplatelet drug. This dual antiplatelet therapy is given to reduce thrombotic risk in patients undergoing PCI, which is higher in case of certain clinical factors like diabetes or angiographic factors. Antiplatelet therapy is prescribed to maintain a balance between antithrombotic activity and risk of bleed. P2Y12 inhibitors alone have been evaluated in such patients in order to decrease the risk of bleed while maintaining safety after dual antiplatelet therapy. Here in this study, ticagrelor alone was compared to ticagrelor with aspirin after 3 months of dual antiplatelet (ticagrelor + aspirin) therapy for clinically important bleeding events or ischemic events in patients who were post PCI and had a higher risk of bleed. These patients were randomized to receive either aspirin or placebo after 3 months till 1 year. The bleeding events as defined by Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding was the primary outcome. The primary end-point was 4% in ticagrelor group versus 7.1% in ticagrelor plus aspirin group (P<0.001).

The incidence of death from any cause, nonfatal MI or nonfatal stroke, was 3.9% in both groups (P<0.001 for non-inferiority). Hence, ticagrelor monotherapy after 3 months of dual antiplatelet therapy was seen to reduce clinically relevant bleeding events without an increase in death, MI, or stroke.

STOPDAPT-2 (Effect of 1-Month Dual Antiplatelet Therapy Followed by Clopidogrel vs. 12-Month Dual Antiplatelet Therapy on Cardiovascular and Bleeding Events in Patients Receiving PCI) Trial

Current guidelines recommend a 12-month dual antiplatelet therapy for patients undergoing PCI. This trial evaluated a very short-term (1 month) dual antiplatelet therapy (DAPT) after PCI with a cobalt-chromium everolimus eluting (Co-Cr EES) stent in patients with high bleeding risk. Patients receiving 1-month DAPT followed by clopidogrel monotherapy were compared to 12 months of DAPT (aspirin and clopidogrel). The investigators found that very short duration of DAPT followed by clopidogrel monotherapy, compared with 12 months of DAPT, led to a significantly lower rate of a composite of cardiovascular and bleeding events, fulfilling the criteria for both non-inferiority and superiority. These findings suggest that a shorter duration of DAPT may provide benefits in patients undergoing Co-Cr EES, however, needs further testing in a larger trial involving other populations.

Diabetes and Cardiovascular Disease

DAPA-HF (Dapagliflozin in Patients with HF and Reduced Ejection Fraction) Trial

Patients with diabetes mellitus type 2 have increased risk of cardiovascular disease and HF. The newer addition to diabetes treatment includes the inhibitors of sodium-glucose cotransporter 2 (SGLT2). These have been seen to reduce the rate of hospitalization for HF in diabetic patients. Whether SGLT2 inhibitors will reduce the risk of first hospitalization for HF with reduced ejection fraction irrespective of diabetic status is unknown and was studied in this trial. Patients with New York Heart Association (NYHA) class II, III, or IV HF and an ejection fraction ≤40% on recommended therapy were randomized to either dapagliflozin (10 mg once daily) or placebo. The primary outcome of composite of worsening HF (hospitalization or a visit needing an intravenous therapy for HF) was seen in lesser patients on dapagliflozin than in placebo group (16.3% vs. 21.2%, P<0.001). Death from cardiovascular causes were also less frequent in dapagliflozin group as compared to placebo (hazard ratio, 0.82; 95% CI, 0.69–0.98). These findings were similar in diabetics and non-diabetics. The frequency of adverse events also did not differ. Hence, it was concluded that in HF and a reduced ejection fraction, addition of dapagliflozin to guideline directed therapy reduced the risk of worsening HF or CV death, regardless of the presence or absence of diabetes.

EMPA-REG Outcome (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) Trial

Empagliflozin, an inhibitor of sodium–glucose cotransporter 2, was studied in this trial and its effect on cardiovascular morbidity and mortality in patients with type 2 diabetes at high cardiovascular risk was evaluated. EMPA-REG outcome trial was done in patients with cardiovascular disease (10% had HF) and showed favorable outcome in terms of nonfatal MI, cardiovascular death, and nonfatal stroke. Further, a reduction in risk of hospitalization was seen, in addition to an improved renal
outcome. Among patients receiving empagliflozin, there was an increased rate of genital infection noted without an increase in other adverse events.

**Trials for Stable Coronary Artery Disease**

**ISCHAEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) Trial**

Various studies have been done in the past comparing the different treatment strategies in patients with stable coronary artery disease. However, quantification of ischemia and relation to outcomes in such subset of patients has not been evaluated. In ISCHEMIA trial, these patients were tested with stress testing and a blinded computed tomographic evaluation of coronaries was done in those with moderate to severe ischemia. Patients having significant unprotected left main disease and non-significant CAD were excluded. Subsequently, these patients were randomized to two groups, one group underwent cardiac catheterization and revascularization plus optimized medical therapy (OMT), and the other group being optimized medical therapy alone. It is worth noting that patients who failed on OMT underwent an invasive strategy. It was interesting to find that composite of CV death, MI, or hospitalization for unstable angina, HF, or resuscitated cardiac arrest was not different significantly in both the groups. Both the groups had lower incidence of death from any cause. Further, an improvement in symptoms was noted with invasive strategy more so in patients who had angina more frequently which was seen till 12 and 36 months. There are certain limitations which need to be seen, first being the power of the study which was reduced with lesser patients than was planned. Secondly, the effect of complete revascularization has not been reported as of now. Moreover, effect on left main disease, left ventricular dysfunction, ACS patients, and more symptomatic patients needs to be analyzed further.

**Valvular Heart Disease**

**POET (Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis) Trial**

Infective endocarditis (IE) is managed with a prolonged course of intravenous antibiotics, the duration depends on the pathogen cultured. This trial evaluated the safety and efficacy of shift to oral antibiotics from intravenous antibiotics in stable patients with left sided IE caused by streptococcus, Enterococcus faecalis, Staphylococcus aureus, or coagulase-negative staphylococci. These patients who were stable and treated with intravenous antibiotics were randomized to continue intravenous treatment or to switch to oral antibiotic treatment. All patients received intravenous antibiotics for at least 10 days. If found stable, patients in the orally treated group were discharged and followed in outpatient department. There was no significant difference noticed in the primary outcome of all-cause mortality, embolism, unplanned cardiac surgery, or relapse of bacteremia with the primary pathogen [12.1% (I/V) vs. 9.0% (oral), P=0.40], till 6 months after completion of antibiotic treatment. Hence, in stable patients of left sided IE, a shift to oral antibiotics was seen to be non-inferior than continued intravenous antibiotic therapy.

**PARTNER-3 (Transcatheter Aortic Valve Replacement with a Balloon Expandable Valve in Low Risk Patients)**

Transcatheter aortic valve replacement (TAVR) is widely being done for high and intermediate surgical risk patients with severe aortic stenosis. In low surgical risk patients, the benefit of balloon expandable TAVR was evaluated in this randomized trial. One thousand patients were randomized to transfemoral TAVR or surgery. At the end of 1 year the primary outcome, a composite of death, stroke, or rehospitalization was less with TAVR as compared to surgery. However, this needs to be individualized after a heart team meeting as durability, and TAVR in younger age groups need further evaluation.

**Conclusion**

Cardiovascular science is a vital part of medicine and is being investigated aggressively. For physicians, being updated in this period of evidence-based medicine is important. In this chapter, we have summarized the recent key trials that were published and presented in the field of cardiology. Many of these studies will help guide clinical practice and guideline updates. Others have shown encouraging early data to guide further research development.
References

Iron deficiency with or without anemia in chronic heart failure remains a very important issue and is associated with increase in morbidity and mortality. Various studies and trials have convincingly proved that management of deficiency of iron by intravenous iron therapy scores over oral iron therapy in improving the different parameters of exercise capacity, morbidity, and in decreasing the overall incidence of mortality. Thus, proper evaluation and management of iron deficiency in chronic heart failure needs utmost care and attention.

Introduction

Heart failure (HF) is one of the major public health problems, overall, about 2% of adult population suffers, the prevalence increases with rising age affecting 6–10% of people over age 65. Despite many advancement and advent of newer therapeutic approaches, prognosis of symptomatic HF remains poor. This sad scenario is compounded by the occurrence of anemia in general and iron deficiency anemia or only iron deficiency in particular. Iron deficiency (ID) is detected to be a frequent association with chronic heart failure (CHF) and is an important factor for reduced quality of life (QoL), diminished exercise ability and poor prognosis including recurrent hospitalization and mortality whether present with anemia or no anemia. Management with IV iron has been convincingly shown to improve the situation in different trials. Despite these facts, looking for ID in HF is not in the priority list of physicians leading to underdiagnosis and consequently undertreatment of deficiency of iron. Thus, as per evidence from many trials, ID needs to be recognized as high-risk factor in respect to consequences of CHF and evaluation of deficiency of iron requires to be included in the routine workup for CHF with proper management.

Prevalence of ID in CHF

Thirty-five to fifty percent of patients with HF found to suffer from ID and it remains the most significant cause of anemia in HF; however, ID without anemia is found to be associated with 46% of systolic HF. An international cohort of 1,506 patients with CHF observed presence of ID to be closely associated with severity of HF with reduced ejection fraction assessed by New York Heart Association (NYHA) functional class or NT-pro BNP level. Similar association of ID and severity of HF is also observed by Okonko et al. and Jankowska et al. Women found to have higher prevalence of ID in CHF.

However, the study done for prevalence of ID in HF with preserved ejection fraction (HFpEF) is comparatively much less but then similar rate of ID is reported in HFpEF compared to HF with reduced ejection fraction (HFrEF). A small observational study showed the prevalence of 57% in HFpEF.
Etiology of Anemia and Iron Deficiency in Heart Failure

The development of anemia with HF can result from various etiologies such as a dilutional anemia, anemia of chronic disease, and blunted erythropoietin response with ID being the most significant cause.5,6

The causes of ID in CHF are multifactorial. In general, less dietary intake, disturbed absorption, and chronic blood loss cause ID. But besides these, increase in hepcidin level due to the inflammatory state induced by HF and liver congestion in CHF leads to diminished iron absorption and increased reticuloendothelial block of releasing iron for utilization resulting in ID and anemia.7

Definition of Iron Deficiency in HF

Iron deficiency is classified as absolute and functional and patients with CHF are prone to suffer from both forms. Absolute ID represents decline in total body iron store that is reduced or absent storage iron in bone marrow, liver, and spleen caused by improper dietary intake, disturbed gastrointestinal absorption, and prolonged blood loss whereas functional ID refers to impaired iron delivery to target cells despite normal or overly abundant iron stores due to chronic inflammation via increase in hepcidin production resulting in inhibition of iron exporter ferroportin leading to impaired iron absorption and utilization.

Diagnosis of ID in HF

Diagnosis of ID in CHF based on serum ferritin level warrants consideration of HF associated inflammatory state. The standard cut-off value of serum ferritin for diagnosis of ID in general is less than 30 mcg/L. But then this value does not apply in case of CHF as serum ferritin is an acute phase reactant and CHF underlies an inflammatory state.6

Presently based on landmark FAIR-HF study6 and thereafter inclusion of the very criteria in 2012 ESC Guidelines on diagnosis and treatment of HF, serum ferritin level less than 100 mcg/L defines absolute ID, and serum ferritin level between 100–299/L combined with a transferrin saturation (TSAT) less than 20% defines functional ID.

Iron Deficiency and Cardiac Function

Iron deficiency leads to well-known derangement of erythropoiesis resulting in ID anemia affecting oxygen carrying capacity of blood with its effect on cardiac function. Besides this iron is incorporated in enzymes like cytochromes, peroxidases, and others subserving important and critical role in body metabolism including cellular immunity and so chronic deficiency of iron on its own leads to derangement of cellular energy mechanism including oxidative metabolism and immunity related activity resulting in impairment of functional and structural quality of myocardium culminating in LV dysfunction.

Clinical Outcome of ID in CHF

A number of studies have convincingly shown that ID impairs exercise capacity, causes poor QoL and leads to poor prognosis with recurrent hospitalization and enhanced mortality independent of anemia and left ventricular ejection fraction.

Okonko et al.2 and Jankowska et al.9 found that patients with CHF and ID suffer poor exercise capacity irrespective of hemoglobin level and severity of heart disease. Iron deficiency independent of anemia has been shown to be accompanied by suboptimal QoL as measured by Minnesota Living with Heart Failure Questionnaire (MLHFQ), lower the TSAT lower is the QoL.9,10 In a post-hoc analysis of CHF patients showed that patients with ID presented with poorer QoL compared with those having no ID.4

Several studies revealed that ID is an independent and strong predictor of poor prognosis in HF. In a large study of 1,506 CHF patients by Klip,1 patients having ID showed remarkably higher rates of mortality at 6 months (8.7% vs. 3.6%) persisting throughout the study duration. Okonko et al.2 in their study on 157 CHF patients found ID to be prognostically more ominous than anemia. In a big cohort of CHF patients, Jankowska et al.3 observed that ID is a strong predictor of poor prognosis related to hospitalization and mortality with 3 years survival of 59% for patients suffering ID compared to 71% without having ID.

A cross-sectional study of 447 patients of HFpEF, iron deficient patients showed worse performance in the 6-minute walk test and poor QoL on MLHFQ compared to patients with normal iron status.11
Thus, ID with or without anemia represents a high-risk factor for worsening of symptoms of HF including poor QoL, diminished exercise ability, and increased hospitalization and mortality.

**Treatment**

Obvious clinical importance of ID and its high prevalence in CHF make restoration of iron status essential together with care of the cause of ID.

Use of oral iron is not favored because of its poor absorption due to CHF induced edema and congestion of gut mucosa together with high hepcidin level besides interaction with diet or drug, and because of need of much prolonged duration of treatment needed with oral iron to achieve the target. Clinical trial also does not support oral iron therapy. IRONOUT trial\(^\text{12}\) using oral iron did not found betterment of exercise capacity over 16 weeks and also no change observed in iron biomarker. IRON-HF trial comparing oral iron versus IV iron showed clinically relevant difference in improvement of exercise capacity favoring IV iron; however, it lacks statistical power.

IV iron proves to be effective and its use is well supported by different clinical trials. It is cost effective as it saves expenditure by cutting down the given recurrent hospitalization in ID patients and by improving the survival.

FAIR-HF trial\(^\text{8}\) comparing ferric carboxy maltose (FCM) versus placebo showed unexpected significant improvement in QoL, symptoms, and exercise capacity accessed by 6-minute walk distance test on IV iron arm in patients of CHF and ID with or without anemia. All patient’s subgroup based on hemoglobin level, renal function, sex, and ejection fraction showed the improvement. NYHA functional class and global assessment of patient also showed betterment with IV FCM.

CONFIRM-HF trial\(^\text{13}\) using FCM in symptomatic HF showed significant improvement in exercise capacity accessed by 6-minute walk distance at 24th week, also led to diminished risk of hospitalization for worsening HF at week 52.

Bolger et al.,\(^\text{14}\) Tolle et al.\(^\text{15}\) Usmanov et al.,\(^\text{16}\) and Ferric-HF trial\(^\text{17}\) used IV iron sucrose supplementation in patients of CHF with ID and/or anemia and observed improvement in markers of iron status and also in exercise capacity, NYHA functional class, 6-minute walk distance and QoL.

Data relating to IV Iron treatment for ID in HFpEF is limited. Ongoing FAIR-HFpEF Study and PREFER-HF trial addressing the issue of benefit of IV iron treatment in patients with HFpEF and ID will resolve the query.

Nunes data\(^\text{18}\) revealed that FCM therapy in 459 HF outpatient with ID resulted in increase in hemoglobin and TSAT and also found FCM to be well tolerated; moreover, higher doses of FCM (1,000 mg) showed a significant higher efficacy compared with lower dose (500 mg).

Thus, IV iron needs to be used for CHF with ID with or without anemia. However, comparative data for the different IV iron compounds are not available. But then FCM provides the advantage of high dose (500 mg) formulation and is well tolerated. The therapeutic target may be achieved with one or two injections only.

**Guidelines for Treatment of ID in CHF Patients**

2016 ESC guidelines for the diagnosis and treatment of acute and CHF\(^\text{19}\) recommended to include serum ferritin and TSAT evaluation to screen ID for initial assessment of newly diagnosed HF (Class 1, Level C) and also recommends IV FCM for treatment of ID-Class IIA, Level A (Table 1).

2017 ACC/AHA/HAS focused update of the 2013 ACCF/AHA guideline for management of HF\(^\text{20}\) also recommends that in NYHA Class II to III patients with ID (Class II, Level B), IV iron might be reasonable to improve QoL and functional status (Table 2).

**Present Scenario in Clinical Workup/Management for ID in CHF**

PReP prospective registry\(^\text{21}\) revealed that ID and anemia many a times remain unappreciated in CHF ambulatory patients by physicians despite its well-known high prevalence and clinical implication.

In a substudy of RAID-F registry,\(^\text{22}\) it is observed that screening for ID in CHF and IV iron therapy for treating ID in CHF is much under practiced; oral iron found to preferred to be the first choice despite the fact that evidence favors use of IV iron.
TABLE 1  2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure

| Recommendations for the treatment of other comorbidities in patients with heart failure |
|-----------------------------------------------|-------------------|-------------------|
| **Iron deficiency**                           | **Class** | **Level**         |
| IV FCM should be considered in symptomatic patients with HFrEF and ID (serum ferritin < 100 mcg/L, or ferritin between 100-299 mcg/L and transferrin saturation <20%) in order to alleviate HF symptoms, and improve exercise capacity and quality of life. | IIa        | A                 |

TABLE 2  2017 ACC/AHA/HAS focused update of the 2013 ACCF/AHA guideline for management of HF

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
<th>Comment/Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb</td>
<td>B-R</td>
<td>In patients with NYHA CLASS II and III HF and ID (ferritin &lt;100 ng/L or 100-300 ng/L if transferrin saturation is &lt;20%). IV iron replacement might be reasonable to improve functional status and QoL.</td>
<td>NEW: New evidence consistent with therapeutic benefit.</td>
</tr>
<tr>
<td>III: No Benefit</td>
<td>B-R</td>
<td>In patients with HF and anemia, erythropoietin – stimulating agents should not be used to improve morbidity and mortality.</td>
<td>NEW: Current recommendation reflects new evidence demonstrating absence of therapeutic benefit.</td>
</tr>
</tbody>
</table>

**Conclusion**

Iron deficiency with or without anemia is one of the most common and important comorbidities of CHF and evidences reveal that ID is a high-risk factor for poor consequences of CHF in terms of increased morbidity and mortality. IV iron therapy proved to improve HF symptoms, QoL, 6-minute walk distance, New York Heart Association (NYHA) functional class, and results in better survival with decrease in recurrent hospitalization for worsening HF symptoms. Oral iron is not found to have comparable efficacy.

Thus, as per the evidences and so also as suggested by guidelines, screening for ID should be included in routine workup of all cases of HF and IV iron must be considered for its treatment.

**References**

Abstract

Peripartum cardiomyopathy is defined as symptomatic heart failure with reduced ejection fraction in last month of pregnancy and up to 5 months postpartum. Common risk factors include older maternal age, multiparity, and preeclampsia. Suggested etiopathogenesis includes nutritional deficiencies, viral myocarditis, and autoimmune process. Treatment in acute decompensated heart failure includes intravenous vasodilators, diuretics, digitalis. Data regarding use of vasopressors and bromocriptine is limited. Prognosis is variable. Between 50–60% of women completely recover normal heart size and function usually within 6 months of delivery. Patient with severe cardiac dysfunction should be considered for heart transplantation.

Introduction

Peripartum cardiomyopathy (PPCM) that affects women of childbearing age is a type of heart failure (HF) with reduced ejection fraction (systolic heart failure). Usually PPCM affects women during pregnancy or in early postpartum period. In 1930, PPCM was recognized a distinct entity although it was first described as early as in the 18th century. Demakis et al. described the syndrome as "The peripartum cardiomyopathy" in 1971.

The symptoms of PPCM are like the normal findings of late pregnancy. Thus, there is a delay in diagnosis usually. The severity and mortality vary from patient to patient. It is a relatively rare disease and the exact incidence in India is not documented, but a study from a tertiary care hospital from South India reports an incidence of 1 case per 1,374 live births.

Definition

In women presenting with HFrEF, PPCM is a diagnosis of exclusion. It was earlier defined as symptomatic HF in the last month of pregnancy and up to 5 months postpartum.

Now, the 2010 Heart Failure Association of the European Society of Cardiology Working Group revised the definition of PPCM to “an idiopathic cardiomyopathy presenting with HF secondary to LV systolic dysfunction toward the end of pregnancy or in the months following delivery, where no other cause of heart failure is found.” This diagnostic criterion indicates that EF is less than 45% and there may/may not be ventricular dilatation. Outcomes can be complete recovery or rapid deterioration, persistent myocardial dysfunction, and HF leading to urgent mechanical circulatory support and cardiac transplantation.

Risk Factors

Many risk factors like African ancestry, older maternal age, hypertension, etc. have been associated with PPCM. The risk factors are summarized in Box 1.

Pathophysiology

The etiology of PPCM is multifactorial. Suggested etiopathogenesis of PPCM includes nutritional
deficiencies, viral myocarditis, and autoimmune process. Two vascular-hormonal models of pregnancy-associated cardiomyopathy were developed. These models suggested novel mechanisms for PPCM in humans. The 1st model—a STAT3 knockout mouse. In this model oxidative stress led to cleavage of the prolactin. This 16-kDa prolactin fragment was vasculo-toxic and pro-apoptotic, leading to vascular and myocardial dysfunction. Treatment with bromocriptine, a suppressor of prolactin secretion, had complete reversal of the condition in mice. Human prolactin has been more resistant to cleavage than prolactin in mice.

The 2nd model—cardiac-specific genetic deletion of proliferator-activated receptor gamma coactivator-1a (PGC-1a). This led to vasculo-toxicity by activation of prolactin fragment and decreased expression of proangiogenic vascular endothelial growth factor (VEGF). In this case there is only partial reversal with bromocriptine. For complete recovery addition of VEGF is required. In pre-eclampsia the levels of soluble Fms-like tyrosine kinase-1 (sFlt1), an antagonist of VEGF and placental growth factor are elevated markedly. Elevated sFlt1 levels also have been found in women with worse outcomes in PPCM.

Genetics
Observations suggest familial clustering of PPCM. Genetic contribution can be suggested by 6% co-occurrence with idiopathic dilated cardiomyopathy (DCM). A GWAS identified a single-nucleotide polymorphism near the PTHLH gene, which regulates vascular homeostasis. Rare pedigree evaluation suggests that both PPCM and DCM had likely pathogenic variants in genes, which were known to contribute to DCM-TTN and BAG3. But more than 90% subjects with TTN truncating variants do not develop DCM or PPCM suggesting that additional environmental genetic or epigenetic factors play a role. Incompletely penetrant genetic origin and role of additional factors is suggested by the fact that most women with PPCM do not have a family history of cardiomyopathy and it does not always recur with a subsequent pregnancy.

Clinical Features
The presentation of PPCM is indistinguishable from non-pregnant patients with systolic dysfunction or DCM. New/rapid onset of symptoms requires urgent evaluation. Most women are diagnosed typically in the 1st month postpartum. The symptoms are cough, fatigue, palpitations, orthopnea, chest pain, hemoptysis, weight gain, and unexplained abdominal pain. Signs of PPCM are enlarged heart, tachycardia, decreased SpO₂, elevated JVP, presence of S₃, and loud P₂. Mitral and Tricuspid regurgitation and pulmonary rales are noted. Worsening of peripheral edema, hepatomegaly and ascites may be seen. Arrhythmias are commonly found, which may lead to embolic phenomenon either peripheral or pulmonary. Moderate pericardial effusion may be seen. Findings of pre-eclampsia must be evaluated. High output cardiac failure has also been reported in some patients.

Diagnosis
Various cardiac diagnostic modality including imaging and biochemical investigations are used to identify PPCM. The investigations recommended and findings associated with PPCM are:

- **Chest X-ray**: Findings suggestive of PPCM are cardiomegaly. Also pulmonary venous congestion with interstitial/alveolar edema. Pleural effusion may be found. Chest X-ray should be avoided in pregnancy as findings are not specific and if needed an abdominal shield is used.
- **Electrocardiography**: Heart rate is usually normal. Sinus tachycardia, atrial fibrillation, other conduction abnormalities with nonspecific ST segment changes may be present.
- **Echocardiography**: This is the most important tool for evaluation and follow-up for women with PPCM.
Overall features of PPCM are like primary non-ischemic DCM. The findings on echocardiography are a decrease in myocardial systolic function, as manifested by reduction in left ventricular ejection fraction (LVEF) or fractional shortening. In women presenting late, left ventricular dilatation is frequently evident. Mild compensatory left ventricular hypertrophy can be seen. In early and immediate postpartum period a small pericardial effusion is found on echocardiography. Mitral insufficiency secondary to annular dilatation is seen when there is marked LV enlargement. Other reported findings are tricuspid/pulmonary regurgitation, left atrial/biatrial enlargement and intracardiac thrombus.

- **Endomyocardial biopsy:** The usual findings are features of myocarditis. Biopsies in patients with PPCM when performed earlier after symptom onset have the highest yield. Endomyocardial biopsy is not routinely recommended yet.

- **Viral and bacterial titer & cultures:** In selected cases antibody titer of virus like Coxsackie B should be considered. This approach is more useful for research than diagnosis.

- **Cardiac MRI (CMR):** Nowadays a highly studied and used entity at higher centers. CMR can characterize the myocardium and is used to measure global and myocardial contraction. Delayed gadolinium contrast enhancement can differentiate myocarditis from ischemia as a mechanism of myocyte necrosis. Myocarditis has a subepicardial nonvascular distribution with a nodular/band-like pattern while ischemia has a subendocardial or transmural vascular distribution. Chamber measurements can also be done. CMR can also be used as a guide for biopsy. It is a useful prognostic tool as well.5

- **Right heart catheterization:** Used for assessment of the filling pressure and cardiac output in patients with persistent HF; hemodynamic instability/evidence of an organ dysfunction. Enlargement of atria and ventricles will also be demonstrated.

- **Biochemical evaluation:** Creatine kinase and cardiac troponin evaluation is usually not significant in diagnosis. Brain natriuretic peptide (BNP)&N-terminal pro-BNP levels are elevated in PPCM patients. Differential diagnosis of HF in pregnancy has been listed in **Box 2.**

### Management

The most important concern for medical treatment in PPCM is fetal safety. To prevent thromboembolic complications in PPCM superimposed by the hypercoagulable state of pregnancy, anticoagulation is required especially in severely decreased LVEF during late pregnancy and 6–8 weeks postpartum. American Heart Association recommends anticoagulation when the EF is less than 30%,6 while European Society of Cardiology when EF less than 35% as the threshold.7 Warfarin is avoided during pregnancy. Low-molecular-weight heparin can be used. During lactation warfarin and low-molecular-weight heparin are safe. Novel anticoagulants are not studied widely in this context and not recommended as of now.

### Experimental Treatment

Bromocriptine (dopamine agonist and inhibitor of release of prolactin) has been tried in PPCM based on the research that in mouse model PPCM is caused by the antiangiogenic and proapoptotic 16-kDa form of prolactin. Many studies have been done on this approach but still evidence is lacking. Implications on breast feeding also discourage its use. REBIRTH study—a randomized double-blind, placebo control (Randomized Evaluation of Bromocriptine in Myocardial Recovery Therapy) to investigate the effect of bromocriptine on myocardial

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**BOX 2** Diffential diagnosis of heart failure in pregnancy

- Takotsubo cardiomyopathy
- Familial cardiomyopathy
- Pre-existing cardiomyopathy
- Recurrent peripartum cardiomyopathy
- Pre-eclampsia
- Hypertrophic cardiomyopathy
- Myocarditis consider
- Arrhythmogenic right ventricular cardiomyopathy
- Left ventricular noncompaction
- Valvular heart disease
- Congenital heart disease
- Tachycardia-arrhythmia mediated cardiomyopathy
- Hypertensive heart disease
- Ischemic heart disease
- Cardiomyopathy related to other systemic medical diseases and acute conditions
- Pulmonary embolism
recovery and clinical outcome in PPCM with 200 women in the USA and Canada has been proposed by the IPAC group and is under evaluation. The 2018 ESC guidelines include a Class IIb recommendation for the use of bromocriptine. Its use is also associated with thrombotic complications.

**Treatment of Severe PPCM**

In acute decompensated HF, intravenous vasodilators like nitroglycerin may be needed during pregnancy. Inotrope Dobutamine has adverse effects and Levosimendan was not shown to improve outcomes in PPCM. Milrinone and Levosimendan showed comparable hemodynamic improvement.

*Advanced therapies* for cardiogenic shock during/shortly after pregnancy are mechanical circulatory support with intra-aortic balloon pump (IABP), percutaneous left ventricular assist device therapy, and extracorporeal membrane oxygenation (ECMO). These should be used early in women with hemodynamic instability in PPCM.

Cardiac transplant has been shown to have higher chances of complications.

**Labor and Delivery**

A combined effort of cardio-obstetrics team is required to minimize maternal and fetal mortality. Timing and mode of delivery should be discussed with experts. To avoid prematurity and associated fetal complications stabilization of mother should be done. Early delivery is prompted in the setting of hemodynamic instability despite medical therapy. Vaginal delivery is recommended in stable patients except for obstetric cesarean section indications. Invasive hemodynamic optimization before delivery and strict monitoring is beneficial in unstable patients. After delivery relieving of caval compression, autotransfusion due to uterine contractions and fluid mobilization contribute to increase in preload. Thus, risk of fluid overload and pulmonary edema must be taken care of.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Subsequent pregnancies in PPCM: counseling and management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subsequent pregnancy</strong></td>
<td><strong>Recovered (LVEF ≥50%)</strong></td>
</tr>
<tr>
<td>Preconception/First Visit</td>
<td>• Risk counseling</td>
</tr>
<tr>
<td></td>
<td>• Follow-up planning</td>
</tr>
<tr>
<td></td>
<td>• Clinical &amp; EF reassessment of RAAS blocking agents for 3 months</td>
</tr>
<tr>
<td></td>
<td>• Baseline Echo &amp; BNP/NT-proBNP level</td>
</tr>
<tr>
<td>Maternal Risks</td>
<td>• Relapse in ~20%</td>
</tr>
<tr>
<td></td>
<td>• Rare severe deterioration</td>
</tr>
<tr>
<td></td>
<td>• Mortality unlikely</td>
</tr>
<tr>
<td></td>
<td>• High rate of subsequent recovery</td>
</tr>
<tr>
<td>Medications</td>
<td>• Continue beta blocker</td>
</tr>
<tr>
<td></td>
<td>• Diuretics &amp; hydralazine/ISDN in case of clinical/LV functional deterioration</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Labor and Delivery</td>
<td>• Multidisciplinary planning</td>
</tr>
<tr>
<td></td>
<td>• Spontaneous vaginal delivery preferred</td>
</tr>
<tr>
<td></td>
<td>• Monitoring for fluid overload in the first 48 hours after delivery, esp. in cases of recurrent LV dysfunction</td>
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<tr>
<td></td>
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<tr>
<td></td>
<td></td>
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<tr>
<td>Follow-up</td>
<td>• Close monitoring of symptoms</td>
</tr>
<tr>
<td></td>
<td>• Echocardiographic reassessment of LV function &amp; BNP/NT-proBNP level at the end of the 1st &amp; 2nd trimesters, 1 month before delivery, after delivery prior to discharge, 1 month postpartum &amp; at any time if symptoms develop</td>
</tr>
</tbody>
</table>
Prior to Hospital Discharge

**Lactation:** Earlier some studies and 2010 ESC advised against lactation in PPCM. But recent IPAC data showed that breastfeeding did not lead to adverse outcomes, persistent myocardial dysfunction, or inflammatory markers. This suggests that continued stimulation of prolactin secretion might not be harmful. Most HF medications can be given safely with breastfeeding (Table 1) and should not be a reason to advise women against lactation.

**Contraception:** Due to increased risk of thromboembolism, it is recommended to defer the use of estrogen-containing contraceptives. Subcutaneous progesterone-releasing implants/the Mirena IUDs are safe and effective choices. Second-line consideration can be given to injectable depot medroxyprogesterone. Tubal ligation and vasectomy are other options. In patients with persistent LV dysfunction, the risk of a subsequent pregnancy is more than any risk associated with contraception. Thus, contraception must be encouraged by both cardiologist and obstetrician.

Subsequent Pregnancies

The subsequent pregnancies and their management are the most important area of consideration in a patient treated for PPCM. This is elaborated in Table 1.

Conclusion

In all pregnant and postpartum women, the diagnosis of PPCM should be considered. Echocardiography gives an assessment of systolic dysfunction. Prompt treatment prevents adverse outcomes. Multidisciplinary team management with optimal HF management is rewarding. The optimal duration of medications after recovery is not yet known. Women considering subsequent pregnancy must be counseled and monitored. Long-term follow-up of patients of PPCM is essential.

References