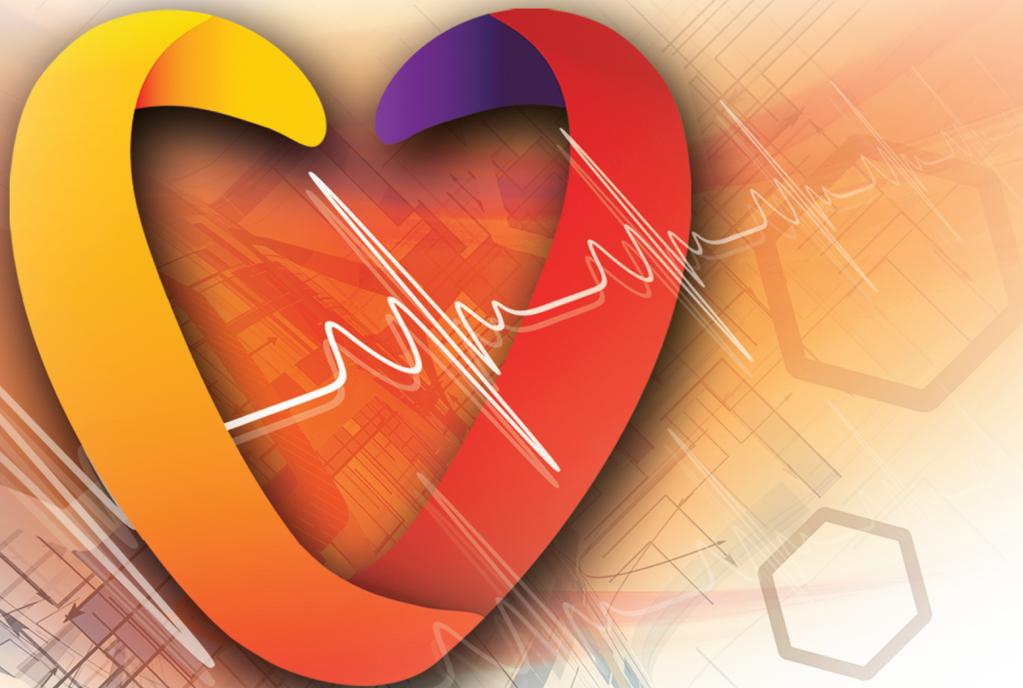


CME on Current Advances in

# Critical Cardiology



## Module 2

# Current Advances in **CRITICAL CARDIOLOGY**

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# Activity Information

## Description

The field of clinical cardiology, facilitated by the development of futuristic technologies, has grown by leaps and bounds. We are currently in the midst of a cardiovascular (CV) pandemic. CV diseases are major contributors of morbidity and mortality in both the developed and developing countries. The epidemiology and clinical presentation pattern of several CV disorders has changed with time, and so has their diagnostic and management protocols. Dyslipidemia is one of the most pre-eminent, yet a treatable, cause of CV diseases. Population-based studies have shown high global prevalence of dyslipidemia. The burden is equally high in India; moreover, Indian population has a characteristic pattern of lipid abnormalities, referred to as atherogenic dyslipidemia, which confers high risk of premature CHD to them. Several cardiology guidelines are currently available, outlining risk stratification approach, diagnoses and management of these CV disorders. On similar lines, many clinical practice guidelines have been developed to provide evidence-based recommendations on management of dyslipidemia; however, clinicians frequently encounter residual CV risk in their patients despite optimal statin therapy, and have difficulties deciding the choice of non-statin therapies to achieve target lipid goals in their patients. This CME program on "Current advances in critical cardiology" has been designed to provide its participants current updates and evidence-based recommendations on dyslipidemia and some other CV disorders of specific interest for clinicians and cardiologists. Module 1 of this CME will address issues related to dyslipidemia, its screening, risk stratification, and current management strategies. Module 2 will be focusing on other relevant topics in cardiology, such as heart failure, cardiomyopathy, infective endocarditis, interventional cardiology, pulmonary embolism, and antiplatelet resistance. Our objective is to enhance competence of the clinicians and cardiologists, improving treatment outcomes, thereby reducing the burden of CV diseases and their associated mortality.

## Activity

CME

## Learning objectives

1. To evaluate strength and weaknesses of different lipid markers of CV risk; and attempt to arrive at a consensus on whether LDL-cholesterol should remain or be replaced as the primary treatment target for lipid-lowering therapy
2. To familiarize readers with the current scenario of dyslipidemia in the Indian population and how to address the growing epidemic of dyslipidemia and its associated CV diseases in the Indian subcontinent
3. To update readers with current data pertinent to statin and non-statin therapies, including novel lipid-lowering therapies that have been recently introduced
4. To enhance competence in early detection and management of some cardiovascular disorders, such as heart failure, cardiomyopathy, pulmonary embolism, and infective endocarditis, and update readers on current advances in interventional cardiology

## Target participants

Physicians and Cardiologists

## Activity Director and Faculty

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## Activity length

2 hours

## Method of participation in the activity

Study all parts of the educational activity. Submit the final questionnaire along with answers, evaluation form and request for certificate. A CME certificate will be issued to activity participants who score 60% or better.

**Release date:** 1st April, 2018

**Expiration date:** 31st March, 2019

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# Table of Contents

## SECTION 1

Heart failure	4
---------------	---

## SECTION 2

Cardiomyopathy: Focus on dilated and hypertrophic cardiomyopathies	11
---	----

## SECTION 3

Pulmonary embolism	16
--------------------	----

## SECTION 4

Antiplatelet resistance	22
-------------------------	----

## SECTION 5

Advances in interventional cardiology	27
---------------------------------------	----

## SECTION 6

Infective endocarditis	29
------------------------	----

## SECTION 1

# Heart failure

### OVERVIEW

Heart failure is a complex cardiovascular (CV) disorder characterized by structural and/or functional defect of the myocardium, resulting in either impaired ventricular filling or reduced ventricular ejection.<sup>1</sup> It is recognized as a major public health problem given its association with high morbidity and mortality rates, increased hospitalizations, significant healthcare costs, and poor quality of life.<sup>2</sup> Risk of heart failure increases with advancing age; about 80% heart failure patients are elderly.<sup>3</sup> Several classifications of heart failure have been proposed. A widely accepted classification system divides it into two semi-discreet subtypes based on functional status of the heart: heart failure with reduced ejection fraction (HFrEF) [EF < 40%] and heart failure with preserved ejection fraction (HFpEF) [EF ≥ 50%].<sup>1,4,5</sup> Heart failure with EF between 40–49% is a ‘grey area’ that has remained unaddressed since a long time; the recent 2016 European Society of Cardiology (ESC) guidelines<sup>4</sup> now provides a nomenclature to this category, i.e. heart failure with mid-range ejection fraction (HFmrEF). Patients with HFmrEF predominantly have diastolic dysfunction, along with mild systolic dysfunction. They are often difficult to treat with standard heart failure therapies, similar to patients with HFpEF. ESC guidelines<sup>4</sup> have therefore combined management of HFmrEF with that of HFpEF.

### PATOPHYSIOLOGY OF HEART FAILURE

The pathophysiological mechanisms of heart failure are complex, regardless of the underlying etiological cause. Commonly implicated etiologies of heart failure include hypertension, diabetes, myocardial ischemia (MI), and cardiomyopathy (Table 1).<sup>6</sup> Cardiac injury from any of these causes initiates a complex immunoinflammatory response, triggered by increased production of inflammatory cytokines and chemokines.<sup>7,8</sup> As a downstream effect, several hemodynamic adaptive mechanisms are triggered to maintain tissue perfusion and homeostasis. They include activation of renin-angiotensin system (RAS) and

**Table 1: Important causes of heart failure**

- Hypertension
- Diabetes
- Myocardial ischemia
- Cardiomyopathy
- Valvular heart diseases
- Anemia
- Excess alcohol
- Pulmonary embolism
- Thyroid disorders (thyrotoxicosis)
- Pregnancy
- Cardiotoxic drugs

**Based on information from:** 1. Watson RD, Gibbs CR, Lip GY. ABC of heart failure: Clinical features and complications. *BMJ*. 2000 Jan 22; 320(7229): 236–239. 2. Kemp CD, Conte JV. The pathophysiology of heart failure. *Cardiovasc Pathol*. 2012 Sep-Oct;21(5):365-71.

sympathetic nervous system (SNS), different neurohumoral adjustments for maintaining tissue perfusion, renal sodium and water retention, and beta-1 adrenergic receptor activation; thereby increasing heart rate, inotropy and lusitropy. It is speculated that these compensatory mechanisms are maladaptive in heart failure, inducing counterproductive structural and molecular changes in the heart (remodeling), including myocyte hypertrophy, apoptosis, and fibrosis; eventually leading to myocardial dysfunction and reduced cardiac efficiency.<sup>8</sup>

Recently, natriuretic peptides have received considerable attention for their role in heart failure development. Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are synthesized primarily in the atrial myocytes, and released in response to atrial stretch. They are synthesized as large molecules (such as proBNP), and subsequently cleaved into active peptide hormone (BNP) and the biologically inactive N-terminal peptide fragment (NT-proBNP). Levels of natriuretic peptides are upregulated early in heart failure in response to volume and pressure overload. They are therefore deemed useful clinical markers of heart failure, particularly in patients

who present with acute dyspnea in the emergency department and there is uncertainty regarding their diagnosis.<sup>9</sup> Additionally, the role of natriuretic peptides in favorably modulating neurohormone levels in heart failure is also firmly established. Strategies involving either exogenous administration of a synthetic natriuretic peptide (nesiritide – a recombinant human BNP); or inhibitor of neprilysin – an endopeptidase involved in breakdown of natriuretic peptides, have been employed in heart failure management. The latter strategy, in particular, has been widely successful, and treatment outcomes appear to further improve by combining neprilysin inhibitor with an angiotensin receptor blocker (ARB), such as valsartan.<sup>10</sup>

### Gut hypothesis for heart failure development: An emerging concept

Recent reports have suggested possible role of altered gut flora in the development and progression of heart failure. The precise mechanism remains unknown. It is speculated that hemodynamic alterations in heart failure lead to gut wall ischemia, which compromises its integrity, allowing microbial endotoxins to percolate into the circulation, promoting systemic inflammation and adversely affecting cardiac function. Trimethylamine N-oxide (TMAO), a metabolite of phosphatidylcholine generated by gut microbiota, has been implicated as the principal driver of this association. Further research is currently undergoing in this field.<sup>11,12</sup>

### TWO PRINCIPAL PHENOTYPES OF HEART FAILURE: HFrEF VS HFpEF

Two principal phenotypes of heart failure based on left ventricular ejection fraction (LVEF) are HFrEF and HFpEF (Table 2). Their principal etiological causes and underlying mechanisms differ; although their clinical features frequently overlap. HFrEF commonly follows myocardial infarction (MI), diabetes, or dilated cardiomyopathy.<sup>5,13</sup> Ventricular remodeling in HFrEF characteristically involves eccentric hypertrophy with disproportionate increase in left ventricular size compared to its mass. Altered ventricular shape and geometry results in diffuse myocardial dysfunction, and reduced EF. It is the predominant type of heart failure seen in young individuals.<sup>13</sup> In contrast, HFpEF usually follows poorly-controlled hypertension, or in some cases, a valvular heart disease.<sup>5</sup> Myocardial fibrosis is the predominant structural abnormality.<sup>14</sup> It is primarily associated with concentric hypertrophy and resultant diastolic dysfunction. In HFpEF, increase in left ventricular wall mass is associated with little or no change in ventricular cavity size. There is

**Table 2: Principal differences between HFrEF and HFpEF**

HFrEF	HFpEF
EF < 40%	EF ≥ 50%
Primarily seen in young patients	Primarily seen in women and elderly
Etiologies – MI, diabetes, cardiomyopathy	Etiologies – Hypertension; less frequently valvular heart diseases
Characteristic remodeling – eccentric hypertrophy	Characteristic remodeling – Myocardial fibrosis; concentric hypertrophy
Increase in ventricular size to mass ratio	Increase in ventricular mass to size ratio
Evidence-based treatment available	No evidence-based treatment; difficult to manage

**Based on information from:** 1. Borlaug BA, Redfield MM. Diastolic and Systolic Heart Failure are Distinct Phenotypes of the Heart Failure Syndrome. *Circulation.* 2011 May 10; 123(18): 2006–2014. 2. Aziz F, Tk LA, Enweluzo C, Dutta S, Zaeem M. Diastolic heart failure: a concise review. *J Clin Med Res.* 2013 Oct;5(5):327-34.

therefore little or no change in ventricular shape, and EF is preserved. HFpEF is predominantly seen in the elderly population and women.<sup>13,15</sup> There is some recent evidence to suggest that in selected cases, HFpEF can progress to HFrEF, possibly indicating that they may be part of a continuum.<sup>13</sup>

### CLINICAL PRESENTATIONS

Heart failure can have variable clinical presentations. Patients can be asymptomatic, particularly in the initial stage of the disease. Cardinal symptoms of heart failure include exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, reduced exercise tolerance, and ankle swelling. Patients can also report with non-specific symptoms such as fatigue, abdominal pain, poor appetite, nocturnal cough, palpitations, dizziness, and confusion.<sup>14</sup> Raised jugular venous pressure (JVP) and displacement of apical impulse may be notable findings on examination, although these signs appear to have poor reproducibility.<sup>4</sup> Differentiating HFrEF from HFpEF based on signs and symptoms is challenging. A study<sup>16</sup> performed to explore clinical characteristics that could differentiate HFrEF from HFpEF in hospitalized patients with recent-onset heart failure showed that male gender, coronary heart disease (CHD), tachycardia, left bundle branch block (LBBB), and ischemic changes on ECG were suggestive of higher likelihood of HFrEF; while female gender, and atrial fibrillation (AF) at presentation were associated with higher odds of HFpEF.

Sudden worsening of signs and symptoms of heart failure requiring admission and/or emergency management is the characteristic presentation of acute decompensated heart failure (ADHF). Most patients have acute decompensation of a pre-existing chronic heart failure (CHF), while a subset of patients present with new-onset acute heart failure.<sup>17</sup> Precipitating causes of ADHF include non-adherence to medications, dietary indiscretion, poorly-controlled hypertension, diabetes, MI, arrhythmias, anemia, thyrotoxicosis and renal dysfunction. Medications, such as non-steroid anti-inflammatory drugs (NSAIDs), calcium-channel blockers, dipeptidyl peptidase-4 inhibitors and thiazolidinediones can also precipitate ADHF.<sup>18</sup>

The New York Heart Association (NYHA) categorizes heart failure into four categories based on degree of functional limitation (NYHA classes I-IV).<sup>1</sup> Patients with NYHA classes I and II heart failures (mild heart failure) are more susceptible to arrhythmias and sudden cardiac deaths (SCD); while those with NYHA classes III and IV heart failure can progress to end-stage ventricular dysfunction. Majority of deaths in heart failure result from cardiovascular (CV) causes.<sup>19</sup>

## DIAGNOSTIC WORK-UP

A detailed personal and family history and physical examination is essential in the initial diagnostic approach for all suspected heart failure patients. Baseline investigations include complete blood count (CBC), fasting blood sugar, HbA1c, lipid profile, serum electrolytes, liver function test, thyroid profile, urinalysis, and work-up for iron deficiency. A baseline 12-lead ECG is essential. Measurement of natriuretic peptides should also be considered for establishing an early diagnosis of heart failure.<sup>1</sup> The 2017 American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) update of the previous ACCF/AHA guidelines on heart failure management<sup>20</sup> strongly recommend baseline measurement of BNP or NT-proBNP in patients presenting with acute dyspnea to establish heart failure diagnosis (class I recommendation), as well as for prognosticating outpatients with CHF based on disease severity (class I recommendation). In hospitalized patients with ADHF, measurement of BNP or NT-proBNP and cardiac troponin at admission allows risk stratification (class IA recommendation). In contrast, the 2016 ESC guidelines<sup>4</sup> suggest measurement of natriuretic peptides for ruling-out heart failure rather than for establishing its diagnosis. These guidelines recommend that initial diagnostic approach in suspected heart failure should

be based on history, examination, and resting ECG. If at least one abnormal finding is present, natriuretic peptides should be evaluated to decide candidature for a subsequent echocardiography.

Non-invasive cardiac imaging is essential for evaluating all suspected heart failure cases. The 2013 ACCF/AHA guidelines on heart failure<sup>21</sup> recommend the following imaging tests for initial evaluation of heart failure; chest X ray and baseline transthoracic echocardiogram (TTE) with Doppler to assess cardiac structure and function, including LVEF (class I recommendation). Radionuclide ventriculography or cardiac magnetic resonance (CMR) is recommended as an alternative when echocardiography findings are inconsistent (class IIa recommendation). Similarly, the 2016 ESC guidelines<sup>4</sup> also recommend TTE as the initial imaging tool for evaluation of myocardial structure and function in heart failure. A CMR is recommended as an alternative diagnostic tool in patients with inadequate acoustic windows and those with complex congenital heart diseases. For assessment of myocardial ischemia and viability in patients with heart failure and coronary artery disease (CAD), non-invasive cardiac imaging (CMR, stress ECHO, SPECT, PET) should be considered.

## MANAGEMENT OF HEART FAILURE

Early detection and timely initiation of appropriate management is the key to improve outcomes in heart failure.<sup>1</sup>

### HFrEF

Hospitalized patients with HFrEF should be carefully assessed for hypoxemia ( $\text{SaO}_2 < 90\%$ ;  $\text{PaO}_2 < 60 \text{ mmHg}$ ).<sup>1</sup> If present, supplemental oxygen therapy should be promptly initiated. However, administering oxygen to all heart failure patients, including those with otherwise normoxemia, should be discouraged as it can have counterproductive effects due to hyperoxemia-induced vasoconstriction, resulting in reduced coronary and cerebral blood flow.<sup>22</sup>

### Diuretics

Fluid overload and pulmonary congestion are characteristic features of HFrEF. Diuretics reduce congestion and improve symptoms of dyspnea in heart failure. Loop diuretics (such as furosemide and torsemide) are currently considered an integral part of heart failure therapy. Although furosemide has traditionally been the most popular loop diuretic, recent evidence has emerged that shows potential benefits of torsemide in heart failure patients, including reduced hospitalizations, readmissions,

and mortality rates. However, these findings are still preliminary and need to be validated in larger clinical trials.<sup>23</sup>

In HFrEF, treatment with loop diuretic should be initiated in low doses (furosemide 40 mg; torsemide 20 mg daily) and escalated based on treatment response. In cases of sub-optimal response, a thiazide diuretic or a mineralocorticoid receptor antagonist (MRA) should be added to improve diuresis. Daily weights and electrolyte status should be monitored and sodium restriction is advisable. Restricting sodium intake is also advisable, especially if serum sodium concentration is < 130 mEq/L.<sup>24</sup>

### **RAS blockers and beta-blockers**

Renin-angiotensin system (RAS) blockers are an essential component of the treatment armamentarium of HFrEF. ACEI are most commonly utilized, but ARB may be substituted in intolerant patients. ACEI/ARB should be started in low doses, which should be up-titrated if tolerated to dosages utilized in randomized clinical trials. Rise in serum creatinine commonly follows treatment with ACEI/ARB, and a rise up to 30% is acceptable, not requiring treatment discontinuation. Renal function and serum potassium should be evaluated before initiating ACEI/ARB treatment; re-evaluation is necessary after 1-2 weeks of treatment initiation.<sup>24</sup> The 2016 ESC guidelines<sup>4</sup> on heart failure recommend preferential use of ACEI in asymptomatic patients with LV dysfunction and history of MI, and in symptomatic patients to reduce hospitalizations and deaths.

Beta-blockers are another currently established treatment option for HFrEF. Three beta-blockers (carvedilol, bisoprolol, and metoprolol succinate) have shown potential to improve symptoms, reduce hospitalizations and mortality rates in euvolemic heart failure patients.<sup>25</sup> Beta-blockers should be initiated in low doses; which can be up-titrated as per response till the target/maximal dose is reached.<sup>24</sup> Similar to ACEI, beta-blockers are also recommended by 2016 ESC guidelines,<sup>4</sup> both in asymptomatic patients with LV dysfunction and history of AMI, and in symptomatic HFrEF. The updated 2017 ACC/AHA/HFSA<sup>20</sup> heart failure guidelines recommend either ACEI or ARB (in patients intolerant to ACEI) along with beta-blockers in chronic HFrEF to reduce morbidity and mortality.

### **Mineralocorticoid receptor antagonists**

In patients with HFrEF, MRA (eplerenone and spironolactone) also have an established role in management. They are usually recommended as an add-

on to first-line therapy to maximize treatment outcomes, especially in those with serum creatinine < 2.5 mg/dL or an eGFR >30 mL/min/1.73 m<sup>2</sup> and stable serum potassium of < 5 Meq/L.<sup>24</sup> Three landmark studies, RALES,<sup>26</sup> EPHESUS,<sup>27</sup> and EPHESUS-HF<sup>28</sup> showed their benefits in reducing hospitalization and CV mortality rates across the complete spectrum, from mild to severe heart failure. A recent meta-analysis<sup>29</sup> confirmed these findings, emphasizing that MRA improve treatment outcomes in patients with HFrEF, independent of baseline LVEF or NYHA class. The ESC guidelines<sup>4</sup> on heart failure recommend MRA in all patients with HFrEF who remain symptomatic despite treatment with ACEI and beta-blockers. The 2017 updated ACC/AHA/HFSA<sup>20</sup> guidelines also recommend MRA along with a beta-blocker and either ACEI or ARB to reduce morbidity and mortality in HFrEF (class I recommendation). Patients initiated on MRA should have their K levels monitored.

### **Other pharmacological therapies for HFrEF**

An alternative treatment for HFrEF patients with either suboptimal response or poor tolerance to standard therapy is fixed-dose vasodilator combination of a nitrate (isosorbide dinitrate) with hydralazine. While isosorbide dinitrate is a potent vasodilator; hydralazine, in addition to being a vasodilator, also has antioxidant properties. The combination therefore favorably influences nitroso-redox balance, thereby addressing the fundamental biochemical derangement in heart failure. At present, this combination is recommended for patients with symptomatic HFrEF who do not respond to first-line therapy.<sup>24</sup>

The role of digoxin in heart failure management is controversial. There is some evidence to show that cardiac glycosides, such as digoxin, can reduce hospitalizations and improve prognosis in advanced heart failure (NYHA III-IV, LVEF <25%).<sup>30</sup> They are also suitable for patients with atrial fibrillations (AF) and rapid ventricular rate (> 110/minute).<sup>4</sup> However, their narrow therapeutic range necessitates caution when using them, particularly in women, elderly, and patients with renal failure.<sup>30</sup>

Neprilysin inhibitor combined with an ARB is a novel proven, treatment strategy for heart failure. The first member of this class is sacubitril-valsartan combination. While sacubitril is an inhibitor of neprilysin; valsartan is an ARB.<sup>31</sup> The PARADIGM-HF trial<sup>32</sup> randomly assigned heart failure patients with NYHA II-IV, and LVEF ≤ 40% to either LCZ696 (sacubitril-valsartan combination) or enalapril, in addition to standard therapy. Sacubitril-valsartan combination was superior to enalapril in reducing hospitalizations and deaths in the study subjects. This combination is currently recommended by 2016

ESC guidelines<sup>4</sup> in ambulatory patients with HFrEF as a replacement for ACEI in patients who remain symptomatic despite treatment with ACEI, beta-blockers, and MRA. The 2017 ACC/AHA/HFSA<sup>20</sup> heart failure update also recommends it as a replacement to ACEI or ARB in classes II-III HFrEF to reduce morbidity and mortality.

Another novel pharmacological treatment option which is being currently investigated in HFrEF is ivabradine. It lowers heart rate by selectively inhibiting the cardiac pacemaker current (If), a mixed sodium-potassium inward current that controls spontaneous diastolic depolarization in the sinoatrial (SA) node. Importantly, ivabradine does not have negative inotropic effects on cardiac conduction and contractility. It is recommended in patients with stable heart failure with LVEF  $\leq 35\%$ , who are in sinus rhythm with a resting heart rate of  $\geq 70$  bpm, despite being either on maximally-tolerated doses of beta-blocker or in those with contraindication to them.<sup>33</sup>

Additional treatment options include inotropic agents to improve tissue perfusion; anticoagulants to reduce thromboembolic risk; and antiarrhythmic agents to treat life-threatening arrhythmias. Diltiazem and verapamil are not recommended in HFrEF as they can worsen symptoms and increase risk of hospitalizations.<sup>14</sup>

### **Device therapies in HFrEF**

Sudden cardiac deaths (SCD) and progressive pump failure are the two leading causes of deaths in patients with HFrEF. In particular, SCD account for 30-50% of all cardiac deaths in this category. Implantable cardioverter-defibrillator (ICD) are effective in reducing risk of SCD in select heart failure patients, when used along with standard therapy. The US guidelines recommend placement of a primary prophylaxis ICD in select patients with ischemic ( $> 40$  days post MI) and non ischemic cardiomyopathy who have NYHA II/III heart failure despite optimal medical treatment with an LVEF  $< 35\%$ . Although they can also inadvertently increase risk of potential complications such as inappropriate shocks, device infections, and lead malfunctions, their benefits appear to outweigh the risks, establishing them as key treatment options of advanced HFrEF.<sup>34</sup> Cardiac resynchronization therapy should be considered in patient with a LBBB (QRS  $> 150$  msec) who manifest Class II-IV symptoms despite medical treatment.

### **HFpEF: A challenging heart failure to treat**

Evidence-based treatment options for HFpEF are scarce. Similar to HFrEF, diuretics can improve symptoms of

volume overload in HFpEF.<sup>1,35</sup> Although ACEI/ARB are established therapies in HFrEF, their benefit in HFpEF are uncertain.<sup>35</sup> Neither ACEI nor ARB have consistently shown mortality benefits in heart failure patients without systolic dysfunction. Recent results of the post-hoc analysis of I-PRESERVE trial<sup>36</sup> showed improved outcomes with irbesartan in low- but not high-risk patients with HFpEF. In the absence of other established evidence-based therapies, it is reasonable to consider ACEI or ARB in all patients with HFpEF, especially in the presence of hypertension.<sup>37</sup> Evidence-base for beta-blocker use in HFpEF is also weak. A recent meta-analysis<sup>38</sup> that evaluated effects of beta-blocker vs. non-beta-blocker therapy in patients with HFpEF (LVEF  $\geq 40\%$ ), showed that although beta-blocker therapy reduced all-cause mortality by 9%, it did not significantly affect hospitalization rates and composite outcomes (mortality and hospitalization). Calcium channel blockers (CCB), particularly nondihydropyridine CCB, are an alternative in HFpEF. Verapamil improves LV diastolic dysfunction in patients with HFpEF.<sup>39,40</sup> More studies are currently underway to establish their role in HFpEF with certainty. Aldosterone is a potent stimulator of myocardial fibrosis, a key abnormality in HFpEF. This forms the rational for MRA use in HFpEF. Indeed, eplerenone prevents progressive increase in collagen turnover and improves diastolic function in HFpEF.<sup>41</sup> Recently published results of the ALDO-DHF trial<sup>42</sup> showed that spironolactone improved LV diastolic function, but not symptoms, quality of life, or maximal exercise capacity in patients with HFpEF. These agents therefore need further evaluation for their role in HFpEF management.

Ivabradine is another potential treatment strategy in HFpEF, mainly due to its potential to reduce heart rate, improve vascular stiffness, and diastolic function.<sup>37</sup> However, results of the recently concluded EDIFY study<sup>43</sup> involving patients with HFpEF were disappointing, as heart rate reduction with ivabradine in these patients did not translate into improved outcomes. Ranolazine is a piperazine derivative and an antianginal drug with a novel mechanism of action. Through its action on the late activation of the inward sodium channel current ( $I_{NaL}$ ), ranolazine appears to improve myocardial contractility and diastolic tension, thereby showing promise in HFpEF management. In the recent RALI-DHF proof-of-concept study,<sup>44</sup> ranolazine improved hemodynamic parameters, but did not favorably influence relaxation parameters in HFpEF. Studies evaluating other novel treatment options in HFpEF are currently underway.

## CONCLUSION

Heart failure is a complex CV disorder resulting either from impaired ventricular filling or reduced ventricular ejection. Its prevalence increases with advancing age. Common etiological triggers of heart failure include

hypertension, diabetes, myocardial ischemia, and cardiomyopathy. Optimizing risk factor management, pharmacological therapy with or without device-based therapy is the current treatment approach for HFrEF. Evidence-based treatment options for HFpEF are limited, rendering its management challenging.

## POINTS TO REMEMBER

- Patients with HFmrEF (EF between 40-49%) predominantly have diastolic dysfunction, along with mild systolic dysfunction. The 2016 ESC heart failure guidelines have combined management of HFmrEF with that of HFpEF
- Important precipitating causes of ADHF include non-adherence to medications, dietary indiscretion, poorly-controlled hypertension, diabetes, MI, arrhythmias, anemia, and renal dysfunction
- Baseline chest X ray and TTE with Doppler should be the first-line imaging tools in all heart failure patients; CMR or radionuclide ventriculography may be considered when echocardiography findings are inconsistent
- Evidence-based early therapies for HFrEF include vasodilators, RAS blockers, and beta-blockers; additional therapies such as MRA and ivabradine should be considered in patients not responding to first-line treatment
- Sacubitril Valsartan combination has been proven superior to enalapril in reducing mortality and hospitalization for heart failure in Class II-IV subjects with LVEF  $\leq$  40%

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## SECTION 2

# Cardiomyopathy: Focus on dilated and hypertrophic cardiomyopathies

### OVERVIEW

Cardiomyopathy is a complex cardiovascular (CV) disorder associated with structural and/or functional abnormalities of the myocardium.<sup>1</sup> Both the definition and classification of cardiomyopathy has evolved considerably with time. In 1995, a Task Force of the World Health Organization (WHO) and International Society and Federation of Cardiology<sup>2</sup> defined cardiomyopathies as “diseases of the myocardium which cause cardiac dysfunction”. They classified cardiomyopathies into dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy. In 2006, an American Heart Association (AHA)<sup>3</sup> scientific statement defined cardiomyopathies as “a group of heterogeneous diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually, although not invariably, present with inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that are frequently genetic”. They, therefore, first introduced genetic basis for classification of cardiomyopathies. The AHA scientific statement further classified cardiomyopathies into two broad groups; primary cardiomyopathies, which are either exclusive or predominant disorders of the heart, and secondary cardiomyopathies, which are a part of a generalized systemic process. This was followed in 2008 by the publication of a position statement of the European Society of Cardiology (ESC) working group<sup>4</sup> which took a different approach to classification of cardiomyopathies, dividing them predominantly based on morphofunctional phenotypes (dilated, hypertrophic, restrictive, arrhythmogenic right ventricular cardiomyopathy, and unclassified variety), followed by division of each phenotype into familial and non-familial subtypes. More recently, in 2013, a MOGE(S) nosology system of cardiomyopathy classification was proposed and endorsed by World Heart Federation (WHF).<sup>5</sup> In this system, cardiomyopathies were described as “disorders characterized by morphologically and functionally

**Table 1. Important causes of DCM**

- Genetic factors
- Infections (adenoviruses, coxsackie viruses, diphtheria, brucellosis, fungal and protozoal infections)
- Endocrine disorders (Hypo- and hyperthyroidism, Cushing syndrome, Pheochromocytoma)
- Electrolyte disturbances
- Inflammatory/infiltrative diseases (inflammatory myocarditis, hemosiderosis, sarcoidosis)
- Vasculitis/autoimmune diseases (kawasaki disease, SLE, scleroderma)
- Neuromuscular diseases (dystrophinopathies, myotonic dystrophy, Friedreich's ataxia, limb-girdle muscular dystrophies)
- Miscellaneous (pregnancy, tachyarrhythmias)

**Based on information from:** Japp AG, Gulati A, Cook SA, Cowie MR, Prasad SK. The Diagnosis and Evaluation of Dilated Cardiomyopathy. *J Am Coll Cardiol.* 2016 Jun 28;67(25):2996-3010.

abnormal myocardium in the absence of any other disease that is sufficient, by itself, to cause the observed phenotype.” This system addresses five characteristic features while classifying cardiomyopathies: morphofunctional state (M), organ involvement (O), genetic inheritance (G), etiologic annotation (E) and functional state (S) as per ACC/AHA and NYHA staging systems. The two most common forms of cardiomyopathies, DCM and HCM, are discussed in detail below.

### DILATED CARDIOMYOPATHY

Dilated cardiomyopathy (DCM) is a disease of the myocardium characterized by dilatation and compromised function of left or both ventricles. It can affect any age, and is overall the most common type of cardiomyopathy worldwide, accounting for about 60% of all cases.<sup>1</sup> Several cardiac and systemic diseases are postulated as its etiological causes (Table 1).<sup>6,7</sup> However, in majority of cases the principal underlying cause remains unknown; this subtype is referred to as idiopathic DCM. Overall,

patients with idiopathic DCM have a better prognosis compared to other DCM.<sup>1</sup> Emerging evidence has shown a strong genetic basis for DCM.<sup>6,8</sup> Familial DCM constitutes approximately 40% of all cases. The diseased genes encode a wide range of structural proteins of the cardiomyocytes. Most cases have an autosomal dominant inheritance; however, autosomal recessive, X-linked, and mitochondrial inherited forms are also known. Since most inherited cardiomyopathies involve mutations in genes that are expressed in both heart and skeletal muscles, co-associated inherited skeletal myopathies, such as dystrophin-associated muscular dystrophies, limb-girdle muscular dystrophies, and myotonic dystrophies, are commonly seen.<sup>8</sup>

### Clinical presentation

Clinical presentation of DCM varies widely, and may differ even among closely-related members of the same family.<sup>8</sup> Most patients present in their third and fourth decades of life; risk of disease-related mortality increases with advancing age.<sup>7</sup> Heart failure is the most common presentation. In fact, DCM is one of the pre-eminent causes of heart failure worldwide.<sup>6</sup> Patients can also present with other CV complications, such as AV blocks, ventricular fibrillations (VF), thromboembolic episodes, and sudden cardiac death (SCD).<sup>1,9,10</sup> Prognosis worsens with reduced ejection fraction (EF) and increasing severity of diastolic dysfunction.<sup>9</sup>

### Diagnosis

Detailed history, including a three-generations family history, and patient examination should be included in the initial work-up of all patients with unexplained cardiomyopathy, particularly when EF < 50%.<sup>7</sup> Diagnosis of familial DCM is established if two or more closely-related members of the same family are affected.<sup>1</sup> A 2016 scientific statement of the AHA<sup>7</sup> on specific DCM recommends the following routine tests in the initial work-up: CBC, kidney function test, serum electrolytes, HbA1c, thyroid function test, and liver function test. A 12-lead ECG should be performed, which can either be normal or show signs of heart blocks, non-sustained or sustained ventricular tachycardias.<sup>1</sup> Echocardiography is the first-line imaging tool for confirming diagnosis of DCM, although it has limited value for detecting underlying etiology; LV dilation without significant ventricular wall thickening along with global hypokinesia are the typical findings.<sup>1,6,8</sup> All first-degree relatives of the index case should undergo screening evaluation (ECG/echocardiography) for DCM. Genetic testing is recommended for other members of the family of patient with familial DCM.<sup>1,6</sup>

Coronary angiography (invasive or CT coronary angiography) should be performed in all patients with DCM to rule out an underlying ischemic etiology. Traditionally, ischemic cardiomyopathy is characterized by presence of ≥ 75% stenosis in the left main stem, proximal left anterior descending coronary artery, or 2 or more epicardial coronary arteries.<sup>6</sup> CMR can evaluate ventricular structure and function with high degree of accuracy and reproducibility, particularly when echocardiographic findings are inconclusive. Late gadolinium enhancement (LGE) CMR enables the clinician to characterize the presence, extent and location of scarring which has both diagnostic and prognostic significance.<sup>1,8</sup> Diagnosis of inflammatory DCM following acute myocarditis can be established based on histopathological and immunohistological findings on endomyocardial biopsy (EMB) specimen. Routine genetic testing for diagnosis is only recommended in suspected familial DCM, i.e. when ≥ 2 family members are affected.<sup>6</sup>

### Treatment

There is no specific treatment of DCM. Patients with heart failure should be treated as per evidence-based recommendations, including beta-blocker, ACEI or ARB, and MRA, with or without diuretic therapy. Placement of ICD is acceptable for reducing risk of SCD, particularly in patients with severe systolic dysfunction, unexplained syncope, or in those with family history of SCD.<sup>1,8</sup> In selected patients with arrhythmias, ICD can be combined with CRT to further improve prognosis. Select patients refractory to treatment should be considered for advanced circulatory support options including left ventricular assist device (LVAD) cardiac transplantation.<sup>1</sup>

## HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy (HCM) is another common inherited cardiomyopathy associated with increased left ventricular thickness in the absence of an underlying cause of left ventricular hypertrophy (LVH), such as hypertension or aortic stenosis. It can develop at any age, although most patients present either in adolescence or as young adults.<sup>11</sup> It primarily has an autosomal dominant pattern of inheritance with variable penetrance. Genes primarily affected in HCM either encode sarcomere proteins or sarcomere-related proteins. While diastolic dysfunction with preserved EF is the rule in early stages of the disease due to myocardial hypertrophy and fibrosis; progression to end-stage “burnt out” phase characterized by both systolic and diastolic heart failure occurs in a subset of patients as the disease progresses.<sup>11,12</sup>

## Clinical presentation

Clinical presentation of HCM vary widely. About 70% patients with HCM have left ventricular outflow tract obstruction (HOCM), while remaining 30% patients have non-obstructive disease subtype (HNCM).<sup>12</sup> Left ventricular outflow tract (LVOT) obstruction involves asymmetrical septal hypertrophy and systolic anterior motion (SAM) of the mitral valve causing dynamic obstruction to the left ventricular outflow tract. Patients with HOCM can present with symptoms of poor exercise tolerance and exertional dyspnea, although 25-30% patients may have evidence of outflow tract obstruction even at rest. Recurrent syncopal attacks are common.<sup>13</sup> Patients with HCM can also have recurrent AF and resultant embolic complications (strokes); AF are the most common arrhythmias, seen in 20% of these patients.<sup>14</sup> Most deaths in HCM are attributed to progressive heart failure, AF, stroke, and SCD.<sup>13,14</sup>

## Diagnosis

A detailed history, including family history and clinical examination, should be included in the initial diagnostic approach for HCM. Evidence of LVOT obstruction at rest or provocation should be sought to categorize patients into HOCM and HNCM categories. A 12-lead ECG should be performed in all patients and can show findings of left axis deviation, LVH, abnormal Q waves simulating myocardial infarction, ST-segment and T-wave abnormalities.<sup>1,12</sup> The 2011 ACCF/AHA guidelines<sup>15</sup> on HCM additionally recommend a 24-hour ambulatory ECG to detect asymptomatic arrhythmias and decide candidature for ICD therapy (Class I recommendation). A TTE is necessary to establish diagnosis and should be used as the first-line imaging tool in patients with suspected symptoms (Class I recommendation). Evidence of LVH ( $\geq 15$  mm LV wall thickness in diastole) in the absence of an underlying cause is the mainstay of diagnosis.<sup>11</sup> Maximal wall thickness of  $> 30$  mm is a risk marker for SCD.<sup>15</sup> Similarly a drop in systolic BP of  $> 10$  mm Hg also contribute to risk stratification for SCD.

For evaluating LVH in atypical locations, such as the apical position and anterolateral free wall, CMR is superior to TTE. Additionally, CMR also provides better endocardial visualization and can reliably detect myocardial scars. It can also detect severity of myocardial fibrosis with LGE.<sup>14</sup> The 2011 ACCF/AHA guidelines<sup>15</sup> on HCM suggest use of CMR for diagnosis of HCM in case of inconclusive echocardiographic findings or when additional information is required that may impact invasive management (Class I recommendation). Coronary angiography, either invasive

or using CTA, should be performed in patients with chest discomfort and intermediate to high likelihood of CAD (Class I recommendation). Furthermore, in case of uncertainty regarding the diagnosis, endomyocardial biopsy (EMB) can be considered to rule out an alternative diagnosis.<sup>11,12</sup> Genetic testing is recommended in patients with atypical clinical presentation of HCM or when another genetic cause of LVH is suspected. All first-degree relatives should also be screened with or without genetic testing for HCM. If genetic status is unknown, screening using echocardiography (and ECG) should be performed every 12-18 months in individuals between 12 and 18-21 years of age, and at onset of symptoms or every five years in adults over 18-21 years of age.<sup>15</sup>

## Treatment

Patients with HCM should avoid strenuous exercises and taking part in high-intensity competitive sports.<sup>14</sup> Pharmacological treatment of asymptomatic patients with HCM is controversial. The ACCF/AHA guidelines<sup>15</sup> recommend beta-blocker therapy in both HOCM and HNCM as it reduces inotropy and chronotropy, thereby improving diastolic filling and reducing outflow gradient (Class I recommendation). In HOCM, non-vasodilating beta-blockers (such as metoprolol, atenolol, and bisoprolol) should be preferred.<sup>14</sup> In patients who do not respond to beta-blockers or have contraindications to it, an L-type calcium channel blocker (verapamil) is recommended (Class I recommendation). Diltiazem can be considered as an alternative. Disopyramide, a type I antiarrhythmic agent, has potent negative inotropic effect and potential to reduce outflow gradients but is often poorly tolerated due to its anti-cholinergic properties. The ACCF/AHA guidelines<sup>15</sup> recommend addition of disopyramide to either beta-blocker or verapamil therapy in patients with HOCM who do not respond to either of these drugs alone (Class IIa recommendation).

Arrhythmias, particularly AF, are important contributors to morbidity and mortality in HCM. Patients with AF who are hemodynamically unstable should be treated with direct current cardioversion. In stable patients, amiodarone and disopyramide can be considered for controlling AF. Disopyramide should be combined with a rate controlling agent (beta-blocker or non-dihydropyridine calcium channel blocker), especially in patients with HOCM (Class IIa recommendation).<sup>15</sup> In those with persistent or paroxysmal AF, oral anticoagulants should be used to reduce risk of embolic complications. The role of ACEI or ARB in patients with HCM is not currently well-established, particularly in those with HOCM.<sup>14,15</sup> ICD has a definitive role in secondary prevention of SCD and

is recommended in patients with previous history of VF, cardiac arrest, or hemodynamically significant VT (Class I recommendation). Their prophylactic application for primary prevention of SCD should also be considered in: patients with maximal LV thickness  $\geq$  30 mm;  $\geq$  1 recent unexplained syncopal episodes; patients with history of SCD in one or more first-degree relatives (Class IIa recommendations).<sup>15</sup>

Surgical septal myectomy at high volume centers with experience may be considered in severe HOCM and a gradient  $>$  50 mm Hg (rest or provocation), when patient does not respond to standard pharmacotherapy. Percutaneous alcohol septal ablation is a reasonable alternative to surgical septal myectomy for achieving LVOT gradient reduction.<sup>12,15</sup>

## CONCLUSION

Cardiomyopathies are complex diseases of the myocardium associated with its structural and/or functional abnormalities. Our knowledge of their etiopathogenesis has increased considerably over the last few years. Both definition and classification of cardiomyopathies has evolved with time. Two common types of cardiomyopathies encountered in cardiology practice are DCM and HCM. They have variable clinical presentations, although progressive heart failure, arrhythmias, and SCD are important causes of morbidity and mortality in both disorders. Early detection and evidence-based management can improve patient outcomes.

### POINTS TO REMEMBER

- The recent MOGE(S) nosology system defines cardiomyopathies as “disorders characterized by morphologically and functionally abnormal myocardium in the absence of any other disease that is sufficient, by itself, to cause the observed phenotype”
- DCM is overall the most common type of cardiomyopathy worldwide, accounting for about 60% of all cases; it usually presents in third and fourth decades of life. In contrast, HCM usually presents in adolescence or young adults
- All first-degree relatives of DCM should undergo screening evaluation (ECG/echocardiography). Genetic testing for other members of the family of patient with DCM is recommended
- Genetic testing is recommended in patients with HCM having atypical clinical presentation or when another genetic cause of LVH is suspected

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## SECTION 3

# Pulmonary embolism

### OVERVIEW

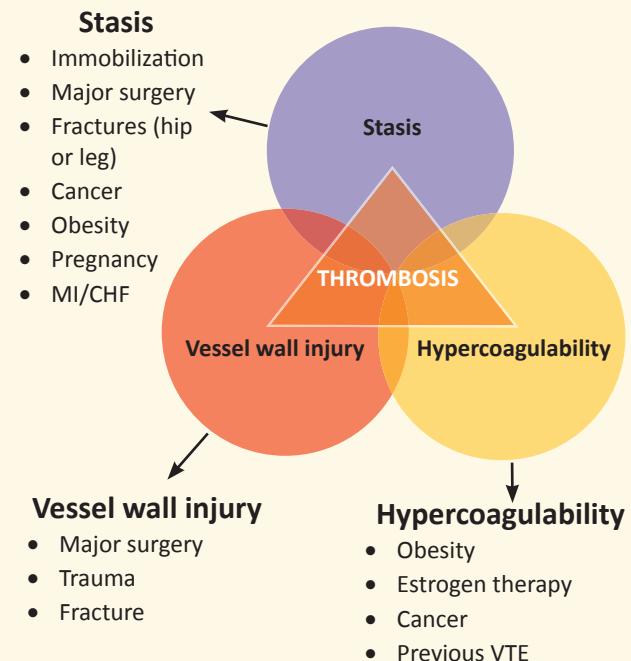
Pulmonary embolism (PE) is an acute, potentially life-threatening cardiovascular (CV) disorder, believed to be the third most common CV disorder worldwide after coronary artery diseases (CAD) and strokes.<sup>1</sup> Most patients have symptoms of sudden-onset dyspnea either at rest or after exertion, and/or chest pain at presentation. Fatal complications such as hypotension, shock, and sudden cardiac arrest can ensue.<sup>1,2</sup> PE is extremely rare in children; its prevalence rises markedly with advancing age. Recurrent PE episodes occur in 2.5-7% cases.<sup>3</sup> Overall prognosis of patients vary considerably, with 1-year survival rates of over 95% in low-risk patients, while 3-months mortality rates can be up to 40% in high-risk patients with hemodynamic instability.<sup>4</sup>

Most culprit emboli in PE arise from preexisting venous thromboembolism (VTE) of the lower extremities, and less frequently of the upper extremities.<sup>2</sup> Silent PE is reported in up to 40-50% patients.<sup>1</sup> Several inherited and acquired risk factors can predispose to PE. Due to wide variation in presentations and low diagnostic yield of symptoms, early detection of PE can be challenging. Timely detection, early and accurate risk stratification, followed by initiation of anticoagulant therapy, is the key to improve prognosis and reduce deaths in these patients.<sup>1,2</sup>

### PATHOPHYSIOLOGY AND RISK FACTORS

In 1856, Virchow proposed a triad of venous stasis, vessel wall injury, and hypercoagulability as the primary cause of venous thrombosis (Figure 1).<sup>5</sup> About 90% of PE originate from VTE of the lower extremities.<sup>6</sup> The primary sites of thrombus generation are incompetent venous valves, where stasis and hypoxia are common.<sup>5</sup> Detachment of an embolus, followed by its migration to the pulmonary vascular bed, and obstruction of the pulmonary artery or its peripheral branches can precipitate PE. Large emboli obstruct the main pulmonary trunk, while smaller emboli frequently occlude its peripheral branches, leading to pulmonary infarction and intra-alveolar hemorrhage.<sup>2,4</sup> Several factors, including size of the embolus (and therefore

Figure 1: Virchow's triad for venous thrombosis



Based on information from: Dalen JE. Pulmonary Embolism: What Have We Learned Since Virchow? Natural History, Pathophysiology, and Diagnosis. *Chest*. 2002; 122; 1440-56.

extent of obstruction) and co-existing cardiopulmonary disease(s) determine resultant hemodynamic response and time to onset of patients' symptoms.<sup>4,7</sup> Neurohormonal mediators such as serotonin and thromboxane are released, which trigger pulmonary vasoconstriction. Resultant increase in pulmonary vascular resistance promotes ventilation-perfusion mismatch, thereby impairing gas exchange and further aggravating hypoxia. The resultant increase in ventricular afterload results in right ventricular dilatation, and right-sided heart failure.<sup>2,4</sup> In the setting of a massive PE, circulatory collapse and sudden cardiac death can ensue.

Several risk factors for PE are known (Table 1). However, in about 30% patients, no antecedent risk

**Table 1. Some acquired risk factors for PE****Strong risk factors**

- Hip and knee replacement
- Fractures of hip or leg
- Major trauma or surgery

**Medium risk factors**

- Previous VTE
- Malignancy
- Hormone replacement therapy or oral contraceptives
- Chemotherapy
- Central venous lines
- CHF
- Respiratory failure
- Pregnancy/postpartum

**Weak risk factors**

- Advancing age (> 40 years)
- Immobilization (> 3 days)
- Obesity
- Varicose veins
- Pregnancy/antepartum
- Laparoscopic surgery

**Based on information from:** Tarbox AK, Swaroop M. Pulmonary embolism. *Int J Crit Illn Inj Sci.* 2013 Jan-Mar; 3(1): 69–72.

factor can be identified (idiopathic or unprovoked PE).<sup>1</sup> Prominent risk factors for PE include advancing age, immobilization, major surgery (particularly orthopedic and neurosurgeries), trauma, prior VTE episode, and comorbid conditions such as CHF or respiratory failure. Additionally, pregnancy, smoking, and hormone replacement therapy can also increase PE risk.<sup>1-3</sup> The presence of cancer can predispose to PE. Hematological cancers are associated with highest risk, followed by lung and gastrointestinal cancers.<sup>8</sup> Additionally, several inherited coagulation disorders such as deficiency of antithrombin III (AT III), protein C, protein S, and Factor V Leiden mutation are important, yet less recognized causes of PE.<sup>3,9</sup>

**CLINICAL PRESENTATION**

Patients with PE can be asymptomatic or develop acute-onset symptoms, with or without life-threatening complications. Sudden-onset dyspnea at rest or worsening of pre-existing dyspnea, and unexplained chest pain (usually pleuritic) are the two most common presenting symptoms of PE. Other non-specific symptoms include cough, hemoptysis, and syncopal episodes. Hypotension, shock, and SCD can occur.<sup>1</sup> One study<sup>10</sup> enrolled 800 patients of PE, obtained from two different settings and evaluated their symptoms at presentation. Sudden-onset

dyspnea was the most frequently reported symptom (81% and 78%); while chest pain (56% and 39%), fainting or syncopal episodes (26% and 22%), and hemoptysis (7% and 5%) were also encountered.

**DIAGNOSIS**

Diagnosis of PE is challenging due to wide variation in presentations and non-specificity of symptoms. Sudden-onset of dyspnea and/or chest pain in patients with known risk factors should arouse suspicion of this disorder. It is useful to determine the pre-test probability of PE through validated clinical prediction scores before proceeding to diagnostic testing. These clinical prediction scores are non-invasive and easy to apply. Common risk prediction scores for PE include the modified Wells score, revised Geneva score, and Pulmonary Embolism Rule Out (PERO) criteria (Tables 2,3,4).<sup>2,3</sup>

In low risk patients, diagnostic testing should start with measurement of D-dimer, an end-product of plasmin-mediated fibrin degradation. A negative D-dimer testing has a high negative predictive value and enables the clinician to “rule out” rather than “rule in” test for VTE and/or PE. Compression venous ultrasound can be performed to detect VTE of the lower extremities, which frequently presages a PE episode. However, normal venous ultrasound should not eliminate the possibility of a PE.<sup>4</sup> Ventilation/Perfusion (V/Q) scanning (lung scintigraphy) and multi-detector CT pulmonary angiography (CTPA) are imaging procedures that have been widely used for diagnosis of PE. Owing to its non-invasive nature, high sensitivity and potential to rule out other differentials in the chest cavity, CTPA has replaced V/Q scanning as the first-line imaging test for PE.<sup>2,11</sup> In the setting of renal failure or contrast allergy, a V/Q scan can be utilized. Recently,

**Table 2: Modified Wells Criteria**

Symptoms and signs of DVT	3.0
Heart rate > 100/minute	1.5
Immobilization or surgery in past 4 weeks	1.5
Previous PE or DVT	1.5
Hemoptysis	1.0
Malignancy	1.0
PE more likely than alternate diagnosis	3.0
Total score:	
≤ 4	PE unlikely
> 4	PE likely

**Based on information from:** Tarbox AK, Swaroop M. Pulmonary embolism. *Int J Crit Illn Inj Sci.* 2013 Jan-Mar; 3(1): 69–72.

**Table 3: Revised Geneva Score**

Previous DVT or PE	3
Heart rate of 75–94/min	3
Heart rate of $\geq 95/\text{min}$	5
Surgery or fracture within 1 month	2
Hemoptysis	2
Active cancer	2
Unilateral lower limb pain	3
Pain on lower limb deep venous palpation and unilateral edema	4
Age $> 65$ years	1
Total score:	
$\leq 5$	PE unlikely
$> 5$	PE likely

**Based on information from:** Tarbox AK, Swaroop M. Pulmonary embolism. *Int J Crit Illn Inj Sci.* 2013 Jan-Mar; 3(1): 69–72.

V/Q scans using modified pulmonary embolism diagnosis (PIOPED) and PISAPED criteria have been proposed which have increased their potential to accurately diagnose PE.<sup>12</sup> Estimation of cardiac biomarkers (troponin and natriuretic peptides) enable risk stratification of patients with PE. Similarly, echocardiography has risk-stratification potential in PE, and allows evaluation of impact of PE on right and/or left ventricular functions. It also provides information on the hemodynamic status of the patient.<sup>1</sup>

The 2014 ESC<sup>13</sup> guidelines on PE recommend that in all stable patients with suspected PE, pre-test probability of PE should be initially assessed. In patients with low or intermediate probability of PE (PE-unlikely), D-dimer testing should be performed to screen for PE; in case of negative results, PE is ruled out, and in case of positive results, further CTPA imaging should be performed to confirm diagnosis. However, in patients with high probability of PE, CTPA (without D-dimer testing) is directly recommended to establish diagnosis of PE. On the other hand, in patients with suspected PE who have hemodynamic instability, CTPA should be the first-line diagnostic testing. If unavailable, an echocardiography is recommended to detect cause of hemodynamic instability (Figure 2). Additionally, in sick patients with PE who have features of RV dysfunction but cannot undergo a CTPA, compression venous ultrasound testing can also be performed to look for thrombosis in veins of the extremities. V/Q scanning is only recommended when D-dimer levels are high and CTPA cannot be performed due to any reason.

In 2015, the Clinical Guidelines Committee of the

**Table 4: PE Rule-out Criteria**

- Age  $< 50$  years
- Heart rate  $< 100/\text{minute}$
- Oxyhemoglobin saturation  $> 94\%$  on room air
- No hemoptysis
- No estrogen use
- No prior DVT or PE
- No unilateral leg swelling
- No surgery or trauma requiring hospitalization within four weeks

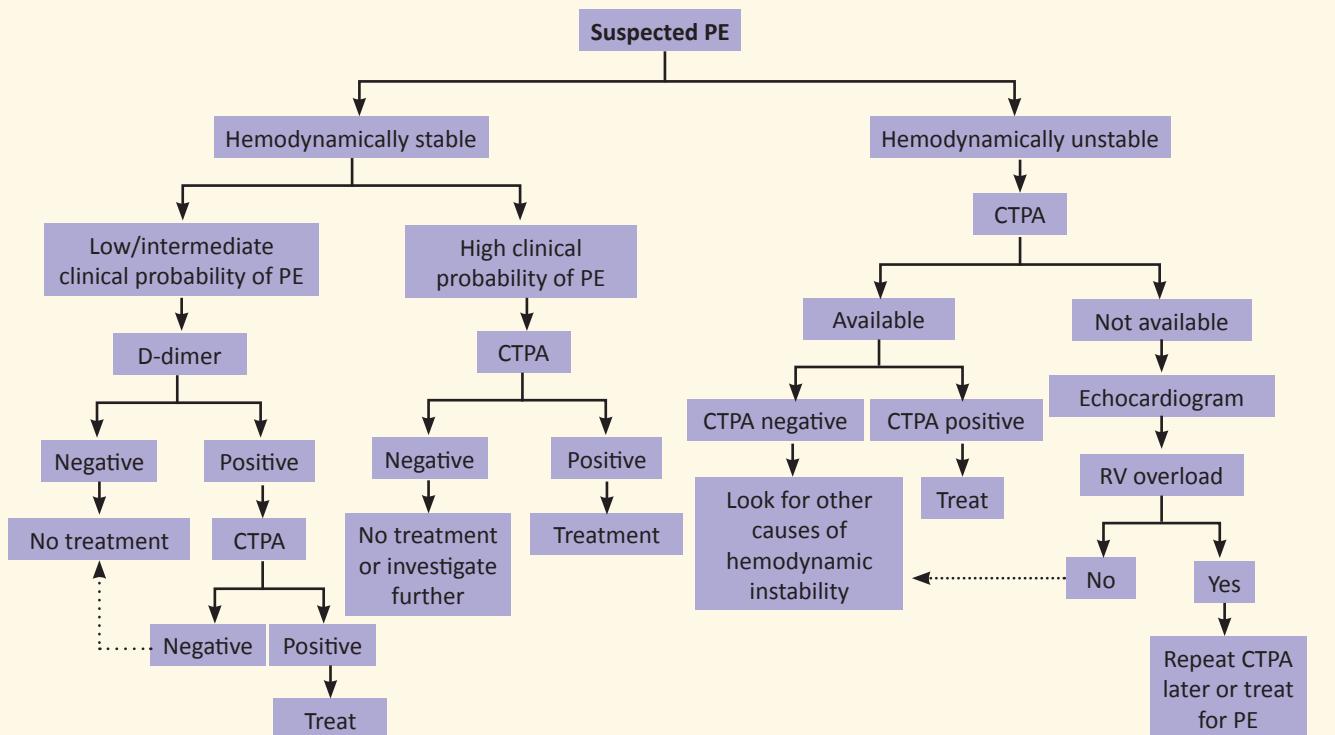
**Based on information from:** Tarbox AK, Swaroop M. Pulmonary embolism. *Int J Crit Illn Inj Sci.* 2013 Jan-Mar; 3(1): 69–72.

American College of Physicians (ACP)<sup>14</sup> published their recommendations on the evaluation of suspected PE. They also recommend use of validated clinical prediction scores, including the PERO criteria, for estimating pretest probability of PE. In patients with low probability of PE and those who meet all PERO criteria, neither D-dimer testing nor imaging is recommended. However, in patients with low probability of PE but who do not meet all PERO criteria, as well as in those with intermediate probability of PE, D-dimer testing should be performed. In patients with high pre-test probability of PE, imaging using CTPA (without D-dimer testing) is recommended. Routine use of V/Q scanning for diagnosing PE is not recommended by ACP guidelines, suggesting that it should be performed only when CTPA is not available or when patients have contraindications to it.

## STRATIFICATION AND MANAGEMENT

Stratifying patients of PE in different risk categories is essential as it guides treatment decisions. The 2014 ESC<sup>13</sup> guidelines on PE recommend a systematic risk-stratification approach in patients with suspected or definitive PE. All patients with hemodynamic instability (shock or persistent hypotension) should be categorized as high-risk patients. Remaining patients should undergo risk-stratification, preferably using Pulmonary Embolism Severity Index (PESI) or simplified PESI (sPESI) risk algorithms, and categorized into intermediate- and low-risk categories. The intermediate-risk category group should undergo further evaluation for RV function (using echocardiography or CT); and myocardial injury (using cardiac biomarker levels). Patients with RV dysfunction and elevated cardiac biomarker levels are stratified in intermediate-high-risk category; while those with normal RV function and normal biomarker levels are placed in intermediate-low-risk category.<sup>13</sup>

**Figure 2: Approach in suspected PE with and without hemodynamic instability (adapted from ESC guidelines)**



**Based on information from:** Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galie N, Gibbs JS, Huisman MV, Humbert M, Kucher N, Lang I, Lankeit M, Lekakis J, Maack C, Mayer E, Meneveau N, Perrier A, Pruszczak P, Rasmussen LH, Schindler TH, Svitil P, Vonk Noordegraaf A, Zamorano JL, Zompatori M; Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J.* 2014 Nov 14;35(43):3033-69.

The primary objectives of management in PE are: hemodynamic stabilization, restoration of pulmonary blood flow, and prevention of PE recurrence.<sup>3</sup> Priority should be given to stabilization of hemodynamically unstable patients using vasoressors (such as norepinephrine), inotropes (such as dopamine or dobutamine), and vasodilators (such as inhaled nitric oxide), although caution and meticulous monitoring is warranted when these agents are being administered.<sup>13,15</sup>

## Anticoagulants

Anticoagulants remain the cornerstone of PE management. Anticoagulant treatment should be initiated with parenteral anticoagulants; unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), or fondaparinux.<sup>13,15</sup> The 2014 ESC<sup>13</sup> guidelines on PE recommend preferential use of UFH in all high-risk patients with PE (those with shock or hypotension), while in all other patients without hemodynamic compromise, a choice between LMWH or fondaparinux should be made. Parenteral anticoagulation therapy should be given for 5-10 days.<sup>13</sup>

An oral vitamin K antagonist, such as warfarin, is recommended to be started in parallel in all patients on parenteral anticoagulation therapy, targeting an INR of 2-3 on two consecutive days; a ‘bridging’ period from parenteral to oral anticoagulation therapy is necessary during the acute phase of PE management.<sup>13,15</sup> Oral warfarin therapy should be given for at least 3 months. Prolonged oral anticoagulant treatment beyond 3 months can be considered after balancing recurrence risk of PE with risk of bleeding. Treatment with oral anticoagulant beyond 3 months should be considered in patients with first-episode of unprovoked PE; and is strongly recommended (preferably for indefinite period) in patients with recurrent unprovoked PE. If oral anticoagulants cannot be tolerated, aspirin is recommended for secondary VTE prophylaxis.<sup>13</sup>

In the last few years, many new oral anticoagulants were introduced in clinical practice. The direct FXa inhibitors (rivaroxaban and apixaban) are recommended as alternative to combined parenteral anticoagulation-warfarin therapy. On the other hand, edoxaban (another direct FXa inhibitor) or dabigatran (an antithrombin agent)

can be used as an alternative to oral warfarin therapy following acute-phase parenteral anticoagulation. Neither of these new anticoagulants should be administered in patients with severe renal impairment.<sup>13</sup>

## Thrombolysis

Systemic thrombolysis is recommended in all patients with PE having hemodynamic instability, unless they have a contraindication to it. Thromolytic (fibrinolytic) agents convert plasminogen to plasmin, which breaks down cross-links between fibrin molecules and hence, dissolve clots. First-generation thromolytic agents include streptokinase and urokinase; second-generation agent is alteplase (recombinant tissue plasminogen activator or rTPA); while third-generation advanced thrombolytics include reteplase (recombinant plasminogen activator) and tenecteplase; additional members have been recently added to the latter class of thrombolytics.<sup>16</sup> Streptokinase, urokinase and rTPA are primarily used in PE management.<sup>13</sup>

The 2014 ESC guidelines<sup>13</sup> recommend systemic thrombolysis in all high-risk patients with PE who present with shock and persistent hypotension. It should also be considered in intermediate-high-risk patients with hemodynamic decompensation. The role of thrombolysis in patients without hemodynamic compromise remains controversial and is currently not recommended. Major bleeding, particular intracranial bleeding, is its major side-effect. Risk of bleeding increases with advancing age and presence of co-morbidities.<sup>13</sup>

## Surgical embolectomy, catheter-directed interventions, and IVC filters

Surgical pulmonary embolectomy has traditionally been recommended as a treatment option for massive PE with hemodynamic compromise.<sup>17</sup> The ESC guidelines<sup>13</sup>

recommend it as a last resort in selective high- and intermediate-high-risk patients of PE, particularly when systemic thrombolysis cannot be performed due to high bleeding risk. Its early use in high-risk patients with massive PE before signs of hypotension and/or shock appear, improves outcomes.<sup>17</sup>

Percutaneous catheter-directed interventions (PCDI), such as catheter-directed clot fragmentation, suction thrombectomy, rheolytic thrombectomy, and rotational thrombectomy, are advanced treatment options for PE. The ESC guidelines<sup>13</sup> recommend PCDI as alternative to surgical embolectomy in all high-risk patients with PE when systemic thrombolysis is contraindicated. It can also be considered in intermediate-high-risk patients when anticipated risk of bleeding after thromolytic therapy is high. Finally, insertion of inferior vena caval (IVC) filters, designed to prevent migration of emboli from lower extremity veins to the pulmonary arteries, are indicated in select patients with absolute contraindication to anticoagulation or when PE recurs despite its use.<sup>13</sup>

## CONCLUSION

PE is a common CV disorder which can be associated with potentially fatal consequences. Several risk factors, such as prolonged immobilization, major surgeries, malignancy, and trauma can increase susceptibility to its development. Non-invasive clinical prediction scores should be used early to determine likelihood of PE, following which diagnostic testing is recommended. Risk stratification decides subsequent management strategies. Anticoagulants remain the mainstay of its treatment. Systemic thrombolysis with or without placement of IVC filters (in select patients with absolute contraindication to anticoagulants), surgical embolectomy, and catheter-directed interventions should be used as per evidence-based recommendations.

### POINTS TO REMEMBER

- Sudden-onset dyspnea and unexplained chest pain are the two most common presenting symptoms of PE
- Determining pre-test probability of PE through clinical prediction scores is recommended before diagnostic testing in suspected PE
- In PE, oral anticoagulation therapy should be given for minimum of 3 months; treatment beyond 3 months should be considered in patients with first-episode of unprovoked PE; and is strongly recommended in those with recurrent unprovoked PE
- Thromolytic therapy in patients without hemodynamic compromise is controversial and is currently not recommended

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## SECTION 4

# Antiplatelet resistance

### CONCEPT OF ANTIPLATELET RESISTANCE AND ITS CLINICAL SIGNIFICANCE

Antiplatelet agents are widely used in clinical practice for primary and secondary prevention of atherosclerotic events. There is clear evidence for their role in secondary cardiovascular (CV) prevention, leading to recommendations for their routine use in patients with acute coronary syndrome (ACS), ischemic strokes, and those undergoing PCI. In fact, they are currently considered the cornerstone in CV prevention. There are three primary classes of antiplatelet agents; thromboxane inhibitors (aspirin); P2Y12 inhibitors/ADP antagonists (clopidogrel, prasugrel, ticagrelor, cangrelor); and GPIIb/IIIa receptor antagonists (abciximab, tirofiban and eptifibatide).<sup>1,2</sup> Recently introduced antiplatelet drugs include protease-activated receptor (PAR) antagonists (vorapaxar and atropaxar). Antiplatelet potential of cilostazol has been utilized in the management of peripheral arterial disease (PAD).<sup>2</sup> Despite these growing benefits, recently emerging evidence has shown that a large number of patients continue to experience thrombotic events while on antiplatelet therapy, a concept loosely referred to as antiplatelet resistance.<sup>1</sup>

The term “resistance” to antiplatelet therapy has been shrouded in controversy ever since the time it was coined. Moreover, it has no clear “standard” definition, with some definitions based on laboratory results while others based on clinical outcomes.<sup>1,3</sup> Overall, antiplatelet resistance is an indicator of suboptimal or poor response to antiplatelet therapy. Several laboratory tests (Table 1) are available for measurement of platelet functions. Many of these laboratory assays are poorly sensitive, and lack reliability in accurately predicting ischemic events. Additionally, they are time-consuming, operator-dependent, and difficult to perform in clinical settings. Hence, despite their availability, they are still not used routinely for measurement of antiplatelet resistance in clinical practice.<sup>3</sup>

Antiplatelet agents towards which resistance is most commonly reported are aspirin and clopidogrel. Rates

**Table 1. Some laboratory tests currently available for measurement of antiplatelet resistance**

#### Laboratory tests

- Bleeding time
- Light transmittance aggregometry (gold-standard)
- Flow cytometry
- Serum and urinary thromboxane B2

#### Point-of-care assays

- Thromboelastography
- PFA-100
- VerifyNow
- Global thrombosis test

**Based on information from:** Saraf S, Bensalha I, Gorog DA. Antiplatelet Resistance—Does it Exist and How to Measure it? *Clin Med Cardiol.* 2009; 3: 77–91.

of aspirin resistance vary widely based on the laboratory test used; being low (< 1%) when measured by specific laboratory methods and high (20-60%) when non-specific assays are used. Rates of clopidogrel (thienopyridine) resistance measured by specific laboratory assays show considerable inter-individual variation; “poor responder” rates vary from 15-30%, while rates of “true resistance” are cited to be between 5-44%.<sup>1</sup>

### MECHANISMS OF ANTIPLATELET RESISTANCE

Mechanisms underlying antiplatelet resistance are poorly understood. Predominant causes of antiplatelet resistance can be grouped under the following broad categories; reduced bioavailability, genetic factors, increased platelet activation, alternate pathways of platelet activation, and disorders that predispose to poor platelet response (Table 2).<sup>3</sup> Patients with diabetes often show enhanced platelet reactivity, increasing their risk for ischemic events. Additionally, hypertension, dyslipidemia, obesity, and cigarette smoking are also associated with poor platelet response.<sup>4</sup> There is emerging evidence to show that proteinuria increases high-on-treatment-platelet-reactivity (HTPR), a measure of antiplatelet resistance, to

**Table 2. Broadly proposed mechanisms of antiplatelet resistance**

Reduced bioavailability	Genetic factors	Increased platelet activation	Alternate pathways of platelet activation	Disorders predisposing to poor platelet response
<ul style="list-style-type: none"> <li>Non-compliance</li> <li>Insufficient dose</li> <li>Poor absorption</li> <li>Drug interactions</li> <li>Increased metabolism</li> </ul>	<ul style="list-style-type: none"> <li>Mutations of COX-1 gene</li> <li>Polymorphisms in GPIIa</li> <li>Polymorphisms in CYP2C19 and CYP3As</li> </ul>	<ul style="list-style-type: none"> <li>Increased platelet production as in inflammatory disorders, ACS, and CABG</li> <li>Blood transfusion</li> <li>Cigarette smoking</li> </ul>	<ul style="list-style-type: none"> <li>Oxidative stress</li> <li>Excessive exercises (catecholamine-induced platelet activation)</li> </ul>	<ul style="list-style-type: none"> <li>Diabetes</li> <li>Hypertension</li> <li>Obesity</li> <li>Dyslipidemia</li> </ul>

Based on information from: References 3,4,7,8

both aspirin and clopidogrel.<sup>5</sup> Also, low vitamin D levels have been linked to HTPR to ADP antagonists, without influencing antiplatelet effects of aspirin.<sup>6</sup>

### Aspirin resistance

Non-compliance or non-adherence to treatment is firmly established as a pre-eminent cause of poor aspirin response. Increased platelet production associated with acute and chronic inflammatory disorders, ACS, and surgeries (CABG) can impair antiplatelet response of aspirin, particularly when it is used in low doses. Genetic causes, such as polymorphism of COX-1 gene, and a PIA1/A2 polymorphism of platelet glycoprotein receptor IIIa (GPIIIa) also appear to have a role in conditioning aspirin resistance.<sup>7,8</sup> Recently, altered activity or concentration of carbonic anhydrase II enzyme (which modulates acetylation of COX-1 enzyme by aspirin) has been postulated as a potential cause of aspirin resistance.<sup>9</sup>

Potential drug interactions of aspirin also appear to be relevant contributors to its suboptimal response. Many NSAIDs (particularly ibuprofen) compete with aspirin for COX-1 receptor site, thereby offsetting response to aspirin. Concomitant administration of a NSAID, such as ibuprofen, with aspirin should therefore be avoided.<sup>8</sup> Additionally, proton pump inhibitors (PPI) increase intragastric pH, and can thereby potentially reduce GI absorption of aspirin, adversely affecting its anti-aggregatory effects.<sup>4</sup>

### Clopidogrel resistance

Similar to aspirin, poor compliance and under-dosing are potential contributors to poor clopidogrel response. Clopidogrel is a prodrug and significant inter-individual variability in response has been shown, which appears to stem from disparate activities of its metabolizing enzymes, CYP2C19 and CYP3As among individuals. Polymorphic forms of both these P450 isoforms have been identified; carriers of variant CYP2C19 and CYP3A alleles

have impaired clopidogrel metabolism, and therefore demonstrate poor clopidogrel response.<sup>10</sup> Concomitant administration of other CYP2C19 and CYP3A4 substrates, such as PPI and statins (particularly lipophilic statins) with clopidogrel can competitively inhibit its activation, increasing propensity for clopidogrel resistance. The importance of this interaction in clinical practice is however not readily apparent. Recently, polymorphic variants of P2RY12 gene, which encodes its pertinent receptor, was associated with clopidogrel resistance; individuals with polymorphic variants of P2RY12 gene had enhanced risk for ischemic events following a PCI.<sup>11</sup>

### RESISTANCE TO NEW ANTIPLATELET THERAPIES: CURRENT EVIDENCE

In patients experiencing poor aspirin and/or clopidogrel response, switch to more potent antiplatelet agents, such as prasugrel and ticagrelor, is recommended as a treatment strategy to overcome resistance. However, sporadic reports citing poor response to these new antiplatelet therapies are also now beginning to emerge.<sup>12,13</sup> In an evaluation of STEMI patients undergoing PCI who were randomized to either ticagrelor or prasugrel, given as loading doses followed by maintenance doses for 5 days, both drugs exhibited similar HTPR at 2 hours (34.6% for prasugrel and 46.2% for ticagrelor), resulting in delay in onset of their antiplatelet effects.<sup>14</sup> Another recently published case series<sup>15</sup> cites three patients who developed stent thrombosis following insertion of drug-eluting stents, and had functional resistance to clopidogrel, prasugrel and ticagrelor.

### SHOULD PLATELET FUNCTION TESTING BE ROUTINELY PERFORMED?

Several platelet function tests are available (Table 1), and they have traditionally been used for diagnosing disorders of platelet function. However, their routine

use for screening antiplatelet resistance and quantifying need for starting or modifying antiplatelet therapy is not recommended, partly because most of the traditional laboratory assays are poorly standardized, labor-intensive, and require specialized instruments. Recent advances in laboratory medicine has facilitated development of many user-friendly, point-of-care tests (such as PFA-100 and VerifyNow System) that are more accurate, easy to perform, and provide faster results.

Since high platelet reactivity increases thrombotic risk while low platelet reactivity increases risk of bleeding, several clinicians have proposed merits of measuring platelet function for guiding choice and optimal dose of antiplatelet therapy.<sup>16</sup> This approach, although promising, has had little support in recent trials, and a large body of available evidence suggests no improvement in patient outcomes with individualization of antiplatelet treatment based on these tests' results.<sup>17</sup> Three large randomized trials (GRAVITAS, ARCTIC, ANTARCTIC)<sup>18-20</sup> have provided strong evidence against tailoring antiplatelet therapy based on platelet function testing, citing no benefits with this approach. These three clinical trials evaluated coronary artery disease (CAD) patients who underwent stenting, and showed that detection of HTPR followed by personalization of antiplatelet therapy neither reduced ischemic events nor improved clinical outcomes. However, results of these trials were challenged in the MADONNA study<sup>21</sup> which also evaluated patients with CAD who underwent PCI. In this study, detection of high platelet reactivity to clopidogrel, followed by treatment modification in non-responder group by either repeated loading doses of clopidogrel or switch to prasugrel, significantly reduced incidence of stent thrombosis and improved patient outcomes. These findings were in line with results of the ISAR-HPR registry<sup>22</sup> which included high-risk ACS patients showing HTPR to clopidogrel, and demonstrated significant reduction in risk of death and stent thrombosis in the tailored cohort that received either repeated loading doses of clopidogrel or switched to prasugrel compared to control cohort that was treated with conventional clopidogrel therapy.

Based on current evidence, the 2016 ACC/AHA guideline<sup>23</sup> on dual antiplatelet therapy in CAD advises against routine use of platelet function and genetic tests to guide therapy. Similarly, the 2017 ESC guidelines<sup>24</sup> on dual antiplatelet therapy in CAD do not recommend routine platelet function testing, both before and after stenting, except in specific situations when it can potentially change treatment strategy. They also suggest that platelet function testing can be considered to determine timing of cardiac surgery following withdrawal of a P2Y12 inhibitor.

## STRATEGIES TO OVERCOME ANTIPLATELET RESISTANCE

Antiplatelet resistance reflects poor response to antiplatelet therapy, and therefore increased risk of adverse CV outcomes. Identifying cause of antiplatelet resistance and addressing it through specific measures, such as treatment adherence, prevention of drug-drug interactions, and optimization of weight, blood pressure, and blood glucose are the primary steps to overcome resistance.<sup>3</sup>

### Proposed measures to overcome aspirin resistance

Aspirin-induced platelet inhibition is dose-dependent; use of higher doses (300 mg/day in place of 100 mg/day) has been proposed as a strategy to overcome sub-optimal response to low-dose aspirin. A recent study<sup>25</sup> showed that persistent platelet aggregation on low-dose aspirin (81 mg/day) could be treated by increasing its dose to 162 mg or more, daily. Higher doses of aspirin, however, increase bleeding risk.<sup>4</sup> It is therefore prudent to use lower doses, i.e. 75-100 mg/day of aspirin in patients undergoing PCI and receiving aspirin along with P2Y12 inhibitor therapy. Increasing frequency of aspirin dosing is another proposed strategy to improve aspirin response, although data in support for this strategy is currently limited.<sup>26</sup> Patients with poor or suboptimal aspirin response can also be managed by switching them to an alternate antiplatelet agent, or adding another antiplatelet agent to improve its anti-platelet effect.<sup>27</sup>

Aspirin is available in different formulations. Enteric-coated formulations of aspirin have lower bioavailability compared to regular/plain preparations. On the other hand, absorption rates of dispersible and chewable preparations of aspirin are comparable to its plain formulation. Correct choice of pharmaceutical preparation of aspirin can therefore improve its response.<sup>4</sup> Also, concomitant administration of an NSAID, which interferes with COX-1 activity, should be avoided with aspirin. If at all required, aspirin should either be administered before the NSAID; or alternatively, an NSAID which does not interfere with COX-1 activity (such as diclofenac) should be used.<sup>8</sup> Similarly, risks vs. benefits of using PPI along with aspirin should be weighed before decision to administer them concomitantly is taken.<sup>4</sup>

### Proposed measures to overcome clopidogrel resistance

Several strategies to overcome clopidogrel resistance have been proposed. One option is to use higher loading doses (600 mg in place of the usually recommended 300 mg),

and maintenance doses (150 mg/day in place of 75 mg/day) of clopidogrel. This strategy, although useful, has not been proven to be unequivocally effective in overcoming clopidogrel resistance. Another option is to switch from clopidogrel to more potent oral P2Y12 inhibitors (prasugrel and ticagrelor).<sup>28-30</sup> Recent study<sup>29</sup> showed that in patients undergoing carotid stenting, cilostazol-based dual antiplatelet therapy was superior to more commonly used aspirin-clopidogrel combination in reducing rates of clopidogrel resistance. Cilostazol added to aspirin-clopidogrel combination (triple antiplatelet therapy), when used in patients undergoing PCI with drug-eluting stents, also reduces clopidogrel resistance rates, although veracity of these findings require further validation.<sup>30</sup>

Although drug interactions of clopidogrel with PPI and lipophilic statins are known; their impact in real world clinical practice remains uncertain.<sup>4</sup>

## CONCLUSION

Antiplatelet therapies are being widely used in the management of thromboembolic disorders. In the recent past, several reports have cited occurrence of adverse CV events in patients despite being on antiplatelet therapy, a phenomenon loosely referred to as antiplatelet resistance. Most patients are reported to have resistance to aspirin and clopidogrel, although isolated reports of suboptimal response to newer antiplatelet agents (such as prasugrel and ticagrelor) are also beginning to emerge.

## POINTS TO REMEMBER

- Most of the traditional laboratory tests for measuring platelet function are poorly sensitive, time-consuming, labor-intensive, and lack reliability in accurately predicting ischemic events
- Predominant causes of antiplatelet resistance are grouped under the following broad categories; reduced bioavailability, genetic factors, increased platelet activation, alternate pathways of platelet activation, and disorders that predispose to poor platelet response
- A recent case series cites three patients who developed stent thrombosis following insertion of drug-eluting stents, and had functional resistance to clopidogrel, prasugrel and ticagrelor
- In patients with suspected antiplatelet resistance, optimal dosage, treatment adherence, and prevention of drug-drug interactions should be ensured; along with optimization of weight, blood pressure, and blood glucose

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## SECTION 5

# Advances in interventional cardiology

### ADVANCEMENTS IN STENT DEVELOPMENT

Andreas Gruentzig performed the first successful percutaneous transluminal coronary angioplasty in 1978. Since then, percutaneous coronary intervention (PCI) has undergone considerable advancements, facilitated by availability of improved guidewires, high-quality stents with drug-elution technologies, and novel antiproliferative agents, thereby increasing both efficacy and safety of this procedure in patients with stable and unstable CAD. Bare metal stents (BMS) for coronary intervention were first used in 1985. Although stenting using BMS reduced vessel restenosis rates, high rates of in-stent restenosis emerged as a major concern with their use. Search for superior stent options that could reduce restenosis rates, and therefore decrease need for revascularizations, lead to the development of drug-eluting stents (DES) in 2001.<sup>1,2</sup> First-generation DES, including sirolimus- and paclitaxel-eluting stents, were primarily composed of metal platforms with thick struts. Although first-generation DES were shown to be clearly superior to their predecessors (BMS), high rates of stent thrombosis (ST), particularly very late ST, were reported with their use.<sup>1,2</sup> Precise mechanisms for this phenomenon remains poorly understood, although excessive neointimal proliferation at site of vessel wall injury, delayed endothelialization of stent struts, and inflammatory response to polymer coating, were some of the plausible explanations provided. These observations laid the foundation for the development of second-generation DES, with superior metal frames (cobalt-chromium and platinum-chromium), thinner struts but preserved radial strength, and biocompatible-binding polymer coating.<sup>3</sup> It was postulated that thin strut platform of second-generation DES would reduce neointimal hyperplasia and enhance re-endothelialization rates, thereby reducing rates of ST.<sup>2</sup> Indeed, zotarolimus- and everolimus-eluting stents have shown lower rates of ST and better long-term post-PCI outcomes compared to their first-generation counterparts.<sup>1</sup>

Since hypersensitivity to the polymer coat is a recognized cause of very late ST, DES with biodegradable polymers have been developed. When first introduced, they were considered a major advancement over DES and were anticipated to further reduce risk of ST.<sup>3</sup> Currently

available data shows that biodegradable DES are indeed superior to BMS and first-generation DES; however, they do not appear to be superior to second-generation DES for reducing target vessel revascularizations, risk of ST, and cardiac deaths.<sup>3,4</sup> Development of non-polymer DES is another step towards progressive refinement in coronary intervention techniques. Recently developed drug-loaded non-polymer stents have been provided with innovative micro- and nanoporous surface coatings for controlling drug release at target site. Furthermore, evolution of microfabrication and nanotechnology strategies has paved the way for development of innovative stents with microfabricated reservoirs and microneedles to penetrate complex, advanced atherosclerotic plaques and deliver drugs deep within the vessel walls.<sup>5</sup> Gene-eluting stents are the most recent addition to the rapidly expanding series of next-generation endovascular stents. Additionally, multifunctional electronic stents fitted with temperature and flow sensors, and memory storage devices, are being designed to deliver drug- or genes based on physiological conditions.<sup>6</sup>

### DEFAULT ACCESS SITE FOR CARDIAC CATHETERIZATION

Transfemoral approach has been traditionally used for performing cardiac catheterization procedures. Its popularity stems from easy access of the puncture site, reduced contrast requirement, and lower risk of radiation exposure. Radial catheterization approach for PCI was first used in 1989. Since then, radial artery has been used as an alternative vascular access site for coronary angiography and PCI, although femoral approach continues to remain the “default approach” for these procedures in several parts of the world. Over the past decade, studies have consistently shown two major advantages of transradial approach; decrease in access-site complications and early return to mobility. However, this approach also prolongs procedural duration, fluoroscopic time, and therefore can predispose to higher radiation exposure, which is a major deterrent to its employment as the “standard” approach in catheterization labs.<sup>7</sup> The RADIAMI trial<sup>8</sup> was one of the first studies to compare transfemoral and transradial approaches for PCI in patients with acute MI. Its results showed that both approaches were associated with similar

efficacy, total procedural duration, contrast requirement, and radiation exposure. Subsequent studies, including a meta-analysis<sup>9</sup> and systematic review<sup>7</sup> of randomized controlled trials that compared these two interventional approaches, confirmed similar success rates with both approaches; however, radial approach was associated with lower bleeding and access-site complications, early ambulation, reduced hospital stay, and lower costs compared to transfemoral approach.

Bleeding is a major complication after PCI procedures; it is of particular concern in the elderly who frequently have co-morbidities and associated vascular problems which further aggravate their bleeding risk. Transradial approach, given its association with lower bleeding complications, should therefore be the preferred approach when performing coronary interventions in the elderly population. Moreover, contrary to popular belief, radial access is compatible with a wide range of coronary lesions,

including complicated cases, with lower requirement for crossover to femoral access.<sup>10</sup> Several catheterization labs worldwide are now shifting from femoral to radial approach for PCI due to its association with lower bleeding and access-site complications, early mobility, shortened hospital stays, and patient preferences. It is about time this procedure becomes the “default strategy” for performing angiography and PCI procedures worldwide.

## CONCLUSION

Coronary intervention techniques have undergone significant advancement in the management of CAD. Novel stent designs, with improved platforms, stent coatings, and drug reservoir systems have been developed. There is growing acceptance for transradial approach for angiography which stems from its association with lower bleeding and access-site complications, early mobility, and shortened hospital stays.

## POINTS TO REMEMBER

- Biodegradable DES are superior to BMS and first-generation DES; however, they do not appear to be superior to second-generation DES for reducing target vessel revascularizations and risk of ST
- Multifunctional electronic stents fitted with temperature and flow sensors, and memory storage devices, are being designed to deliver drugs- or genes based on physiological conditions
- Transradial approach is now being preferred to the traditional transfemoral approach by most cardiologists for coronary angiography due to its association with lower bleeding and access-site complications, early mobility, and shortened hospital stays

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## SECTION 6

# Infective endocarditis

### OVERVIEW

Infective endocarditis (IE) is an uncommon, yet a serious and often life-threatening multisystemic disease, which results from infection of the heart valves. In the developed world, the prevalence of IE has increased significantly over the past 30 years. Intravenous drug abuse, increasing utilization of indwelling catheters, pacemakers and intra-cardiac defibrillators, increase in the number of patients with heart valve replacement and residua of congenital heart disease as well as the aging population have all contributed to this finding. IE is associated with a high morbidity and mortality rates, with death rates approaching 25% despite treatment. Staphylococci and Streptococci (*S. aureus*, coagulase-negative staphylococci, and viridans-group streptococci [VGS]) account for about 80% of all etiological causes, followed by Enterococci. Gram-negative bacteria and non-bacterial agents, such as fungi, are other uncommon, yet known causes of IE.<sup>1</sup> The HACEK group (Haemophilus species, Aggregatibacter species, *Cardiobacterium hominis*, *Eikenella corrodens*, and Kingella species) includes fastidious Gram-negative bacteria; they contribute to < 5% of IE cases.<sup>2</sup> Overall, IE occurs more commonly in men than women, and its prevalence increases with advancing age.<sup>3</sup> Diagnosis of IE is based on modified Duke's criteria, results of blood culture and/or echocardiography. Management involves prolonged antimicrobial treatment, and in select cases, valvular surgery.<sup>1,3</sup>

### PATHOPHYSIOLOGY

Several factors, particularly turbulent blood flow within the heart and mechanical injury from intravascular catheters, can damage the endocardial surface. Transient bacteremia, which can follow injury to the oral cavity, genitourinary, and intestinal mucosa, allows seeding by bacteria, and its eventual growth through bacterial proliferation and additional fibrin deposition.<sup>3</sup> The response to bacterial seeding is species specific, with staphylococci and streptococci infections being aggressive with early tissue destruction and invasiveness secondary to the toxins and enzymes that are released. Organisms associated with IE also tend to produce a biofilm and this likely explains the failure of antibiotic therapy in large proportion of affected patients. With time, these vegetations grow, and their

eroded portions may enter systemic circulation, giving rise to multisystemic thromboembolic complications. Additionally, both cellular and humoral immunity are activated in IE, resulting in different types of antibodies.<sup>1</sup> Circulating antigen-antibody complexes have been documented in patients with IE, and their role in disease pathogenesis is known for more than five decades, particularly in the development of peripheral lesions (such as Osler nodes and Roth spots).<sup>1,4</sup>

Several risk factors for IE have been identified. About 75% patients of IE have pre-existing structural heart disease. While rheumatic heart disease (RHD) remains the most common cause of IE in areas of prevalence, IE cases are reported following other valvular defects, including degenerative mitral valve prolapse, aortic valvular defects; and congenital heart diseases.<sup>3</sup> Placement of prosthetic valves (risk with mechanical > bioprosthetic) and cardiac devices such as permanent pacemakers, also increases IE risk; risk is seemingly highest within 1 year of prosthetic valve implantation.<sup>1,3</sup> Additionally, prior episodes of IE and injection drug use also variably increase risk of IE.<sup>3</sup> A recent study<sup>5</sup> which explored epidemiological trends of patients diagnosed with IE from 1998 to 2014, confirmed underlying structural heart disease to be the most common risk factor, seen in 67% patients; other risk factors included prosthetic valve placement in 45%, and degenerative valve disease in 32% cases; mitral valve prolapse in 18% and bicuspid aortic valve in 8% cases; permanent pacemaker in 6% and congenital heart disease in 4.5% patients.

### CLINICAL PRESENTATION

Infective endocarditis can have both acute and subacute onset. Acute IE classically presents with sudden onset of high-grade fever, usually with rigors. Cardiac auscultation reveals a new-onset murmur in majority of patients. Occasionally, serious thromboembolic manifestations, such as myocardial infarction (MI) and ischemic strokes, can be seen. Septic emboli can obstruct peripheral vasculature in different organs, resulting in splenic, renal, and/or pulmonary infarcts. During the course of disease, visceral abscesses can also form at different locations, including the brain.<sup>1,3</sup> Serious CNS manifestations such as meningitis, cerebritis, encephalopathy, seizures, and brain abscess have been reported in patients with IE.<sup>6</sup> Skin manifestations

**Table 1. Modified Duke's criteria for infective endocarditis**

Major criteria	Minor criteria	Interpretation
<b>Positive blood culture for either of the following</b> <ul style="list-style-type: none"> <li>Typical microorganism (VGS, <i>S. gallolyticus</i>, HACEK organisms, <i>S. aureus</i>, community-acquired Enterococci in the absence of a primary focus) from 2 separate blood cultures</li> <li>Persistent bacteremia (two positive cultures &gt; 12 hours apart or three positive cultures or majority of ≥ 4 culture positive results &gt; 1 hour apart)</li> </ul>	<b>Predisposing condition</b> <ul style="list-style-type: none"> <li>Intravenous drug use</li> <li>Predisposing cardiac condition</li> </ul> <b>Vascular phenomenon</b> <ul style="list-style-type: none"> <li>Janeway's lesions</li> <li>Arterial embolism</li> <li>Septic pulmonary emboli</li> <li>Mycotic aneurysm</li> <li>Intracranial hemorrhage</li> <li>Conjunctival hemorrhages</li> </ul>	<b>Definite IE</b> <ul style="list-style-type: none"> <li>Pathologically proven IE</li> <li>Or</li> <li>Either two major criteria, one major and three minor criteria or five minor criteria</li> </ul> <b>Possible IE</b> <ul style="list-style-type: none"> <li>One major and one minor criterion or three minor criteria</li> </ul> <b>Rejected IE</b> <ul style="list-style-type: none"> <li>Firm alternative diagnosis</li> <li>Resolution of IE syndrome with antibiotic therapy for ≤ 4 days</li> <li>No pathologic evidence of IE at surgery or autopsy with antibiotic therapy ≤ 4 days</li> <li>Does not meet criteria for possible IE</li> </ul>
<b>Either of these evidences of endocardial involvement</b> <ul style="list-style-type: none"> <li>Echocardiographic findings of mobile mass attached to valve or valve apparatus, abscess, or new partial dehiscence of prosthetic valve</li> <li>New valvular regurgitation</li> </ul>		
<b>Serology</b> <ul style="list-style-type: none"> <li>Single positive blood culture for <i>C. burnetii</i> or antiphase 1 IgG antibody titre of ≥ 1:800</li> </ul>		

Based on information from: Holland TL, Baddour LM, Bayer AS, Hoen B, Miro JM, Fowler VG, Jr. Infective endocarditis. *Nat Rev Dis Primers.* 2016 Sep 1; 2: 16059.

include petechiae, Osler's nodes (tender lumps on finger and toes), and Janeway lesions (non-tender, often hemorrhagic lesions, mostly on the palms and soles); while ocular manifestations include Roth spots (splinter hemorrhages in retina).<sup>1</sup> In contrast to acute IE, subacute IE is often difficult to diagnose due to non-specific, and often subtle nature of constitutional symptoms.<sup>3</sup> Poor prognostic factors include older age, persistent bacteremia, *S. aureus* infection, heart failure, and septic shock.<sup>5</sup>

## DIAGNOSIS

A detailed clinical history, including history of previous IE, should be elicited, and thorough examination performed in all patients with suspected symptoms of IE. Modified Duke's criteria (Table 1) is considered the "gold standard" criteria for establishing its diagnosis. The 2015 AHA Scientific Statement<sup>7</sup> on IE in adults recommend obtaining at least 3 blood cultures for confirming diagnosis of IE, with the first and last blood samples obtained at least 1 hour apart. An echocardiography should also be performed for confirming diagnosis and assessing severity of IE (Class I recommendation). In all patients, a transesophageal echocardiography (TTE) should be first performed owing to its non-invasive nature; TEE, because of superior image quality and higher sensitivity, is subsequently recommended in the following settings: negative or inconsistent findings of initial TTE in patients with otherwise strong suspicion of IE; and when initial TTE is positive for IE and there is concern of intracardiac

complications (Class I recommendation). The 2015 AHA Scientific statement additionally recommends that in patients with high suspicion of IE but negative TEE, a repeat TEE should be performed within 3-5 days, or sooner if symptoms change (Class I recommendation). Further multimodality imaging, such as cardiac CT, MRI, are recommended only in select cases to better delineate valvular vegetations, and identify complications.<sup>7</sup> Patients with neurological findings should have imaging of the brain performed. Brain imaging may also be considered in the setting of left sided endocarditis when silent embolization is clinically suspected. If a cerebral mycotic aneurysm is suspected, cerebral angiography and neurosurgical evaluation, if indicated, should be considered.

## TREATMENT

Prolonged antimicrobial therapy is the cornerstone of management of IE.<sup>1,3</sup> Initial antimicrobial therapy is initiated empirically, and further treatment is guided by blood culture results. The 2015 AHA guidelines<sup>7</sup> on IE recommend that at least 2 blood cultures be obtained every 24-48 hours during antibiotic treatment, till cultures become negative. Duration of antimicrobial treatment is counted from the day on which blood cultures are negative, if initially they were positive (Class IIa recommendations). Choice of appropriate antimicrobial treatment targeting specific pathogens has been addressed in detail by the 2015 AHA guidelines.<sup>7</sup>

The AHA Scientific Statement<sup>7</sup> on IE recommends that antiplatelet therapy should not be used as an adjunct to antimicrobial treatment, except in cases where they are being used for other indications. Anticoagulation with heparin should be utilized with caution, and should be considered after weighing the risks and benefits only when there is an underlying indication like prosthetic mechanical valve, atrial fibrillation, deep vein thrombosis, or pulmonary embolism. In select cases of IE, early valvular surgery is recommended, primarily in patients with severe valvular dysfunction leading to heart failure, persistent infection not responding to antimicrobial therapy, and recurrent embolic events in high-risk patients.<sup>1</sup> Early surgery should be considered when left sided IE is caused by *S. aureus*, fungi or highly resistant organisms. Patients with aortic abscess, heart block and locally invasive lesions should undergo surgery. Given the catastrophic complications arising from embolization, surgery should also be considered in the setting of large mobile left sided vegetations that exceed 10 mm in length despite antibiotic treatment. When indicated, surgery should not be delayed to ensure bacterial clearance with antibiotic therapy. Intra-operative TEE is crucial during surgery. Early surgery should be considered in the setting of major cardiac indication even in the presence of a prior ischemic stroke. In the setting of a brain hemorrhage surgery should be delayed. Neurology and neurosurgical consultation and a team approach is key in making these decisions. All patients after discharge should undergo

short- and long-term follow-up, during which they should be evaluated for signs of recurrence, and development of complications, such as heart failure. Additionally, all patients of IE should undergo thorough dental evaluation (Class IIa recommendation), particularly if valvular surgery is contemplated. Prompt removal of intravenous catheters after completion of antimicrobial therapy is also recommended (Class I recommendation).<sup>7</sup>

Although widespread use of antibiotic prophylaxis for preventing IE relapse was the norm in the past, current mandate is to strongly discourage its routine use for all routine dental and non-dental invasive procedures. Current role of antimicrobial prophylaxis appears to be limited to high-risk individuals undergoing high-risk invasive dental procedures.<sup>8</sup>

## CONCLUSION

IE is a life-threatening disorder associated with infection of the heart valve, often with multisystemic manifestations. Several risk factors which increase susceptibility to IE have been identified. Most patients have acute-onset of symptoms, predominantly high-grade fever with rigors. Embolic complications are not uncommon, and account for deaths in majority of cases. Diagnosis is based on modified Duke's criteria, along with findings of blood culture, TTE (or TEE). Prolonged culture-guided antibiotic therapy and early surgery in select patients is cornerstone of its management.

## POINTS TO REMEMBER

- HACEK group includes fastidious Gram-negative bacteria; they contribute to < 5% of IE cases
- While RHD with mitral stenosis was the most common cause of IE in the past; recently, large number of IE cases are reported following other valvular defects, including rheumatic mitral regurgitation and aortic valvular defects
- Modified Duke's criteria is considered the "gold standard" criteria for establishing diagnosis of IE

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