

European Guidelines on Pericardial Diseases: a Focused Review of Novel Aspects

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Abstract Pericardial diseases are not uncommon in daily clinical practice. The spectrum of these syndromes includes acute and chronic pericarditis, pericardial effusion, constrictive pericarditis, congenital defects, and neoplasms. The extent of the high-quality evidence on pericardial diseases has expanded significantly since the first international guidelines on pericardial disease management were published by the European Society of Cardiology in 2004. The clinical practice guidelines provide a useful reference for physicians in selecting the best management strategy for an individual patient by summarizing the current state of knowledge in a particular field. The new clinical guidelines on the diagnosis and management of pericardial diseases that have been published by the European Society of Cardiology in 2015 represent such a tool and focus on assisting the physicians in their daily clinical practice. The aim of this review is to outline and emphasize the most clinically relevant new aspects of the current guidelines as compared with its previous version published in 2004.

Keywords European Society of Cardiology · Clinical practice guidelines · Pericarditis · Pericardial effusion · Constrictive pericarditis

Introduction

More than 10 years have elapsed since the first international guidelines [1] on the diagnosis and management of pericardial diseases endorsed by the European Society of Cardiology (ESC) were published. Since then, the knowledge on pericardial diseases has expanded significantly, due to randomized controlled trials (RCTs) and retrospective as well as prospective cohorts that were conducted during this time frame [2–17, 18•, 19••, 20, 21, 22••, 23••, 24••, 25, 26]. Additionally, only Spanish and Brazilian national societies of cardiology have so far published national guidelines on the management of pericardial diseases [27, 28•]. Therefore, an updated document has become mandatory in order to summarize all new data and translate them into a set of recommendations which could be implemented in clinical practice. For this purpose, the new guidelines, focused on clinical management of patients with pericardial diseases were issued by the ESC in 2015 [29].

The full text of the 2015 guidelines [29] contains nine sections (excluding web addenda, appendix, and references), near 30 second-level subsections and covers 44 pages. Several new chapters are introduced in the current guidelines, as compared with the previous version: a section on epidemiology of pericardial diseases with special emphasis on prevalence of tuberculous pericarditis, specific section on myopericarditis, a section on multimodality cardiovascular imaging and diagnostic workup, a section regarding age and gender issues, and a separate section on interventional techniques. The current

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guidelines state new definitions and clinical diagnostic criteria for pericarditis and postcardiac surgery syndromes. Triage-based approaches for the management of patients with pericarditis and pericardial effusion are proposed, and new treatment options for recurrent pericarditis are discussed. Finally, new sections “Perspective and unmet needs” and “To do and not to do messages from the pericardium guidelines” have been introduced and conclude the manuscript.

Epidemiology

Several epidemiological studies on pericardial diseases have been reported during the last decade [4, 11, 20, 21, 30]. Pericarditis is responsible for 5 % of emergency room admissions for chest pain and 0.1 % of all hospitalizations [31–33]. However, these data reflect hospitalized patients only, while many patients diagnosed with pericarditis are not admitted to a hospital [2, 8]. Boys, as well as adult men, are at higher risk for pericarditis development than girls and women [20, 21]. Recurrent episodes of pericarditis affect approximately one third of patients who are not treated with colchicine [5, 19••].

Aetiological and Duration-Related Classifications of Pericarditis

In the 2015 ESC guidelines, primary dichotomic aetiological classification for infectious and noninfectious causes has been proposed (Table 1). While viral infections are the most common etiologies for pericarditis in the developed countries, it is now evident that *Mycobacterium tuberculosis* is one of the most frequent causes of pericardial diseases in the world. In the endemic regions, coinfection with tuberculosis and human immunodeficiency virus (HIV) is common. The most prevalent noninfectious causes are secondary to autoimmune diseases or metastatic tumors, as well as postcardiac injury syndromes [26, 30, 31, 34, 35].

Inflammatory pericardial syndromes could be classified according to the time scale to acute, incessant, chronic, and recurrent pericarditis (Fig. 1). During the last decade, diagnostic definitions were proposed for acute pericarditis [5, 6, 16, 19••, 22••, 32, 34, 36•] and the ESC 2015 guidelines define diagnostic criteria that could be applied for clinical and epidemiological purposes (Table 2). Inflammatory markers (i.e., elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and white blood count) as well as imaging findings (evidence of pericardial inflammation on computed tomography (CT) or cardiac magnetic resonance (CMR) scan) were included in these criteria as a supportive evidence, confirming the pericardial inflammation. The diagnosis of recurrent pericarditis is made if a recurrent episode of pericarditis, defined

by the same criteria as a first occurrence, is documented after a symptom-free interval of at least 4–6 weeks.

Management and Treatment of Pericarditis

In the 2004 ESC guidelines, hospitalization and etiology workup were warranted for all patients, whether contemporary recommendations propose a triage-based approach (Fig. 2). Patients, for whom a particular underlying etiology (infectious nonviral or noninfectious nonidiopathic) of acute pericarditis is suspected, should be admitted and undergo diagnostic workup. Additionally, also patients who exhibit at least one high-risk prognostic factor are warranted to be hospitalized (class I, LOE B) [8, 37, 38]. These risk factors are divided into major (associated with poor prognosis on multivariable analysis) and minor (based on expert opinion) (Fig. 2). Major risk factors include high fever (>38 °C/100.4 °F), subacute onset, large pericardial effusion (diastolic free-space >20 mm on echocardiographic study), cardiac tamponade, and failure to respond within 7–10 days to nonsteroidal anti-inflammatory drugs (NSAIDs) [8]. Minor poor prognostic factors include myopericarditis, immunosuppression, trauma, and oral anticoagulant therapy. Patients without high-risk features and specific etiology could be managed as outpatient with empiric anti-inflammatory therapy and then followed after 1 week (class I, LOE B), based on their good prognosis and low rate of complications (cardiac tamponade, constrictive pericarditis, and recurrences) [2, 8, 15].

The current guidelines include, for the first time, nonpharmacological recommendations regarding patient’s management that are based, however, on expert opinion only. Physical activity restriction beyond sedentary life is advised until symptoms resolution and CRP, electrocardiographic (ECG), and echocardiographic features normalization for nonathletes (class IIA, LOE C). Athletes are suggested to avoid competitive activity for 3 months (arbitrary time frame that was defined according to experts consensus) at least, even if remission has been achieved earlier (class IIA, LOE C) [39, 40].

NSAIDs and aspirin are the first-line therapy for viral and idiopathic acute pericarditis [41, 42]. In the last decade, two RCTs addressed the efficacy of colchicine in treatment of acute pericarditis [5, 19••]. Colchicine, added to conventional therapy, was shown to be effective in reducing rates of treatment failure and halving the recurrences in patients with acute pericarditis comparing to anti-inflammatory therapy alone [5, 19••, 42, 43] and now is prescribed as an adjunctive first-line therapy (class I, LOE A). The loading dose of colchicine is not necessary, and weight-adjusted dosage treatment (0.5 mg twice daily in patients >70 kg or 0.5 mg once daily for patients <70 kg) is recommended for 3 months [19••].

Table 1 Etiology of pericardial disease

Infectious	Noninfectious
Viral (common)	Autoimmune (common)
Bacterial (<i>Mycobacterium tuberculosis</i> common)	Neoplastic (lung, breast, lymphoma common)
Fungal (very rare)	Traumatic and iatrogenic (postcardiac injury syndromes common)
Parasitic (very rare)	Drug-related (rare)
	Other

Corticosteroids were associated with severe adverse effects, more hospitalizations and higher rates of recurrences according to the results of a retrospective cohort of patients with recurrent pericarditis and systematic review on pericarditis therapy [10, 42]. Furthermore, in the COPE trial [5], corticosteroids were recognized as an independent predictor of recurrences in patients treated for acute pericarditis. Based on this evidence, the Task Force does not recommend corticosteroid treatment as a first-line approach (class III, LOE C). Corticosteroids are recommended only as a second-line therapy (after failure of NSAIDs and colchicine or when this therapy is contraindicated) or when a specific indication exists (e.g., rheumatologic disease, pregnancy). Moreover, low to moderate doses (0.2–0.5 mg/kg/day of prednisone or equivalent) are preferred in order to reduce side effects [10] (class IIA, LOE C).

To date, ideal treatment duration for acute pericarditis is unclear. Based on the single prospective cohort and several expert opinions, the ESC guidelines endorse therapy duration to be guided initially by symptoms severity and CRP levels with further dose tapering to reduce recurrence rates (class IIA, LOE C) [14, 33, 34].

Anti-inflammatory therapy with either NSAIDs or aspirin is a cornerstone of recurrent pericarditis therapy (class I, LOE A). Since the previous guidelines were published, several prospective trials have been conducted and proved the efficacy and safety of colchicine in treatment of recurrent pericarditis [6, 16, 22••]. Currently, a weight-adjusted dosage of

colchicine (0.5 mg twice daily in patients >70 kg or 0.5 mg once daily for patients <70 kg) is recommended as a first-line treatment, adjunctive to standard anti-inflammatory therapy, for as long as 6 months (class I, LOE A). Similarly to the recommendation on treatment of acute pericarditis, corticosteroids should not be used as a first-line therapy in recurrent episode of pericarditis (class III, LOE C). Furthermore, while preceding guidelines recommended a high-dose corticosteroid therapy in suitable recurrent episodes of pericarditis, the contemporary approach is to limit corticosteroid doses due to adverse effects, chronicity, and recurrences related to this treatment [10, 42]. However, a not negligible proportion of patients develop colchicine-resistant or corticosteroid-dependent recurrent pericarditis. In these cases, treatment with azathioprine, intravenous immunoglobulin (IVIg), or anakinra (a recombinant IL-1β receptor antagonist) may be considered (class IIB, LOE C), although the evidence regarding these agents is limited [44–46].

Myopericarditis (Pericarditis with Myocardial Involvement)

The current guidelines dedicate a new separate section for inflammatory syndromes that involve concurrently pericardial and myocardial tissue. The Task Force distinguishes between myopericarditis (predominant pericarditis with myocardial involvement) and perimyocarditis (predominant myocarditis with pericardial involvement), assuming that substantial myocardial pathology (perimyocarditis) will result in reduction of ventricular function [18•]. The authors recommend hospitalization for all patients with myocardial involvement for diagnosis and monitoring (class I, LOE C). Furthermore, coronary angiography and cardiac MRI are recommended to rule out acute coronary syndromes and confirm myocardial involvement (class I, LOE C). Empirical anti-inflammatory therapy is directed mainly to control chest pain (class IIA, LOE C). The lowest effective doses are recommended due to inflammation augmentation by NSAIDs in animal models of myocarditis [47•, 48]. Myocardial involvement may increase the risk of

Fig. 1 Classification of pericarditis according to the time scale

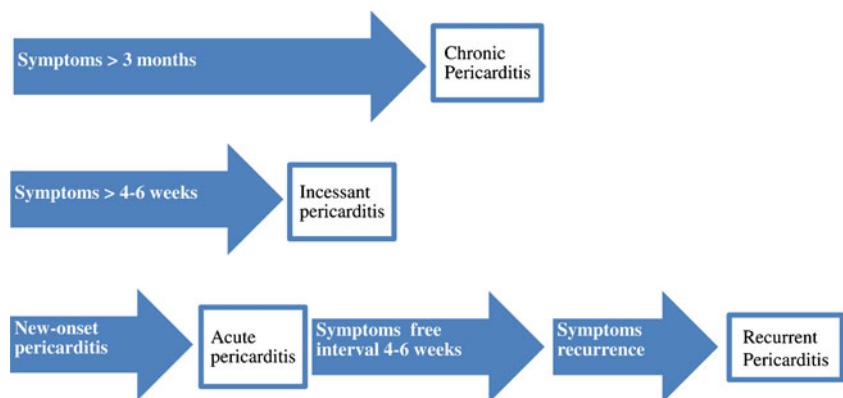


Table 2 Definitions and diagnostic criteria for pericarditis

Pericarditis	Definition and diagnostic criteria
Acute	Inflammatory pericardial syndrome to be diagnosed with at least 2 of the 4 following criteria: 1. Pericarditic chest pain 2. Pericardial rubs 3. New widespread ST-elevation or PR depression on ECG 4. Pericardial effusion (new or worsening) Additional supportive findings: - Elevation of markers of inflammation (i.e., C-reactive protein, erythrocyte sedimentation rate, and white blood count) - Evidence of pericardial inflammation by an imaging technique (CT, CMR)
Incessant	Pericarditis lasting for >4–6 weeks but <3 months without remission
Recurrent	Recurrence of pericarditis after a documented first episode of acute pericarditis and a symptom-free interval of 4–6 weeks or longer ^a
Chronic	Pericarditis lasting for >3 months

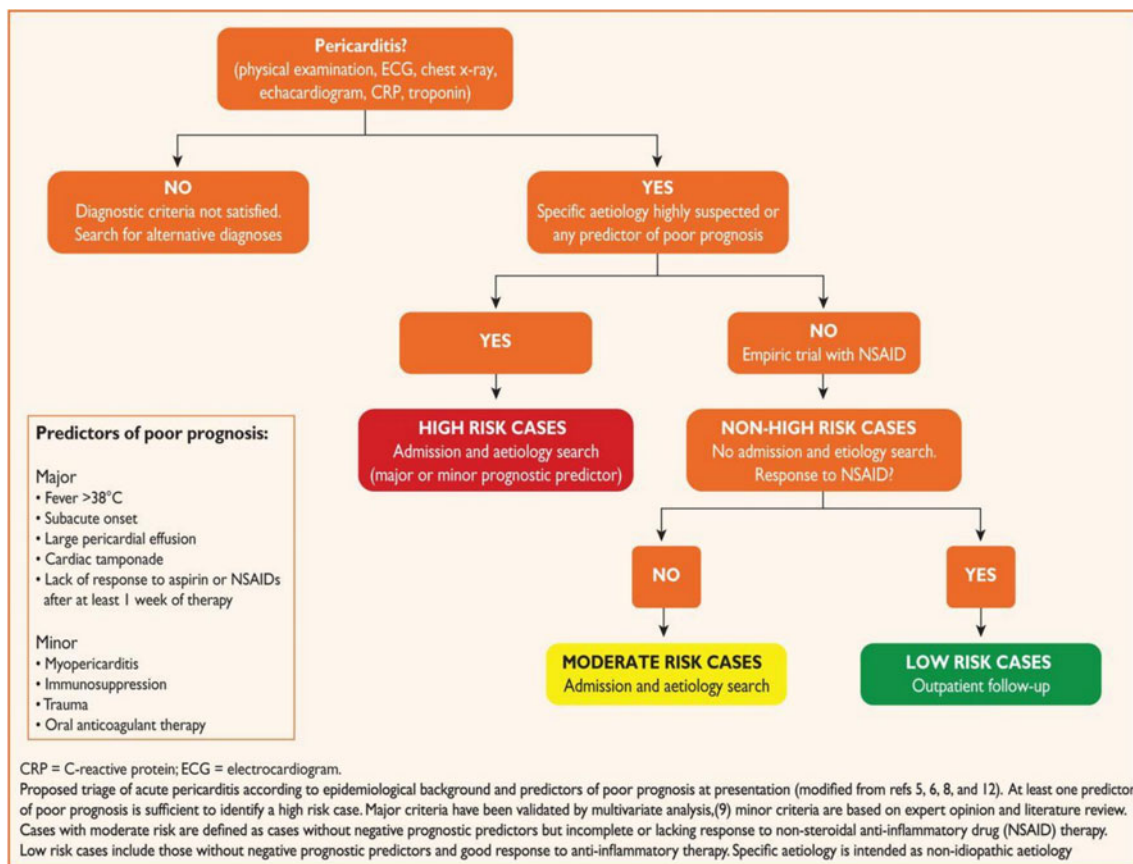
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CMR cardiac magnetic resonance, CT computed tomography, ECG electrocardiogram

^a Usually within 18–24 months but a precise upper limit of time has not been established

sudden cardiac death in patients with pericarditis, and therefore, restriction of physical activity is recommended for at least 6 months in all patients with suspected myocardial

involvement (class I, LOE C). Nevertheless, patients with myopericarditis have overall good prognosis also regarding myocardial function [18•, 48].



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Fig. 2 Proposed triage of pericarditis (from: Adler Y et al. Eur Heart J 2015;36:2921–2964; with permission of Oxford University Press (UK) © European Society of Cardiology, www.escardio.org/guidelines) [29]

Pericardial Effusion and Cardiac Tamponade

Pericardial effusion varies from small, asymptomatic to large and life-threatening cardiac tamponade. The main etiology of pericardial effusion in developed countries is idiopathic, while the predominant cause in developing countries remains *M. tuberculosis* [4, 9, 34, 49, 50]. An essential assessment of patient with suspected pericardial effusion includes chest X-ray, transthoracic echocardiography, and inflammatory markers (class I, LOE C). Once a diagnosis of pericardial effusion has been made, the Task Force endorses a triage-based approach (Fig. 3) (class I, LOE C): Hospital admission is recommended in high-risk patients (according to the decision tree of acute pericarditis). In patients with cardiac tamponade, suspected bacterial or neoplastic etiology, pericardiocentesis or cardiac surgery is indicated (class I, LOE C). Otherwise, and if elevated inflammatory markers are present, empirical treatment of pericarditis is suggested (class I, LOE C). In the majority of patients with pericardial effusion (in about 60 % of cases) another medical condition that could be associated with effusion development is present [50]. Consequently, and if inflammatory markers are absent, treatment of underlying disease is essential. In addition, in patients with large (>20 mm) and long-standing (>3 months) pericardial effusion, pericardiocentesis should be considered due to a reported high-risk of progression toward cardiac tamponade in these cases.

Constrictive Pericarditis

The probability of pericarditis evolution into a constrictive phase originates from its etiology. Bacterial pericarditis has the highest risk (20–30 %), immune-mediated and neoplastic have intermediate (2–5 %), and viral and idiopathic the lowest risk (<1 %) [15]. *M. tuberculosis* remains the main cause of constrictive pericarditis in developing countries, similarly to acute pericarditis and pleural effusion etiology [30]. The 2015 ESC guidelines do not refer to constrictive pericarditis as a sole condition but rather depict several subtypes that should be managed separately. A transient form of constrictive pericarditis may develop due to inflammatory component of acute pericarditis and responds well to the anti-inflammatory therapy [51]. Thus, an attempt of conservative management may be considered in newly diagnosed constrictive pericarditis with laboratory (i.e., elevated CRP) or imaging (pericardial enhancement after contrast administration on CT or CMR) evidence of pericardial inflammation, and without properties of chronicity (cachexia, atrial fibrillation, hepatic dysfunction, or pericardial calcification) (class IIB, LOE C). Effusive-constrictive pericarditis entity refers to the concomitant presence of pericardial effusion and constriction of visceral pericardium. Noninvasive imaging could be beneficial for diagnosis of effusive-constrictive pericarditis; however, frequently, it

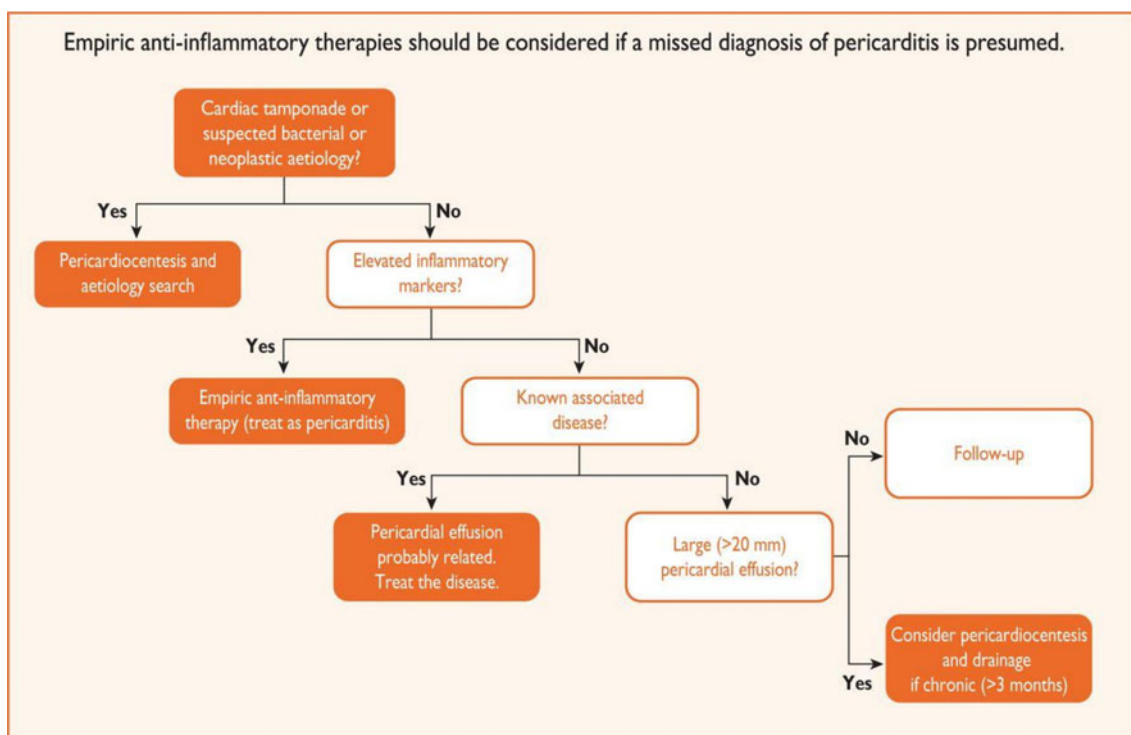
is discovered during pericardiocentesis only. Visceral pericardiectomy must be performed in patients with effusive-constrictive pericarditis, and therefore, referral of patient to an experienced center is essential [3, 52]. Once chronic constrictive pericarditis causing a congestive heart failure (NYHA class III or IV) has developed, pericardiectomy is the mainstay therapy (class I, LOE C). However, in patients with “end-stage” constrictive pericarditis, the benefit-risk ratio is low and surgery must be considered cautiously.

Multimodality Imaging of Pericardial Diseases

The 2015 ESC guidelines endorse integration of imaging modalities in the evaluation of patient with pericardial diseases. Selection of specific modality is driven by the clinical context or patient’s condition and should improve the diagnostic precision and clinical management of patients [36•, 53•]. Transthoracic echocardiography is the first-level imaging technique (class I, LOE C) due to its low costs and high availability, safety, and ability to assess expeditiously the size, location, and hemodynamic impact of pericardial effusion. Furthermore, echocardiography could guide efficiently pericardiocentesis procedure and provide re-assessment of patients during follow-up. However, the main disadvantages of this modality are operator and patient dependence (i.e., obese patients) and little usefulness in the diagnosis of loculated pericardial effusions, estimation of pericardial inflammation, thickness and calcifications, and characterization of pericardial effusion and masses.

Cardiac CT and CMR are second-level imaging modalities, complementary to echocardiography (class I, LOE C). CT provides excellent anatomical evaluation of the heart and pericardium and allows straightforward diagnosis of pericardial cysts. In addition, CT is the most accurate modality to depict pericardial calcifications, and therefore is an essential part of preoperative evaluation in patients with constrictive pericarditis. However, use of ionizing radiation and potential nephrotoxicity of contrast medium may guide a physician toward utilizing echocardiography or CMR in order to assess functional significance of pericardial disease [36•, 53•, 54]. CMR allows the most comprehensive approach to pericardial disease assessment. CMR shares the advantages of CT in the description of cardiac anatomy but offers better tissue characterization and evaluation of the functional consequences in patients with congenital pathology or malignant involvement of the pericardium [55, 56]. In addition, CMR could contribute the information regarding hemodynamical properties of the noncompliant pericardium [54]. Furthermore, CMR may be crucial in the diagnosis of atypical presentation of constrictive pericarditis [57].

Contemporary approach to pericardial diseases limits the role of cardiac catheterization to cases with unclear diagnosis despite a noninvasive evaluation, mainly in the assessment



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Fig. 3 A simplified algorithm for pericardial effusion triage and management (from: Adler Y et al. Eur Heart J 2015;36:2921–2964; with permission of Oxford University Press (UK) © European Society of Cardiology, www.escardio.org/guidelines) [29]

and differentiation of constrictive pericarditis from restrictive cardiomyopathy (class I, LOE C). The ratio of the right to left ventricular systolic pressure–time area during inspiration versus expiration is a novel parameter that showed high sensitivity and predictive accuracy in distinction between these two entities [58].

Specific Etiologies of Pericardial Diseases

Since the previous guidelines were published, several registries and clinical trials on tuberculous pericarditis have emerged [4, 7, 9, 23, 30, 59, 60]. The role of *M. tuberculosis* in pericardial disease is driven by its geographic distribution: while tuberculous pericarditis remains relatively uncommon (less than 4 %) in the Western countries, *M. tuberculosis* is the leading cause of pericardial diseases in developing world with a mortality rate of 25 % at 6 months after diagnosis [4, 35, 49, 59]. The diversity in *M. tuberculosis* prevalence guides treatment strategy: in endemic regions, empiric antituberculosis therapy is indicated once other etiology of pericarditis accompanied by exudative pericardial effusion has been excluded (class I, LOE C). In contrast, in nonendemic area, empiric therapy for tuberculous pericarditis is not suggested (class III, LOE C). A multidrug antituberculosis regimen for 6 months is indicated in proven tuberculous pericarditis in order to prevent progression to constriction

(class I, LOE C). If a deterioration or even no improvement of patient after 4–8 weeks under standard medical therapy is observed, pericardiectomy is advised (class I, LOE C). According to the 2015 ESC guidelines, corticosteroids may be considered as an adjunctive therapy in HIV-negative tuberculous pericarditis (class IIB, LOE C) in an attempt to prevent the evolution towards constrictive pericarditis. This recommendation is based on a randomized prospective trial which examined the role of high-dose prednisolone in tuberculous pericarditis [23]. In this trial, prednisolone failed to reduce an incidence of primary composite outcome of death, cardiac tamponade, or pericardiocentesis, as compared with placebo. Moreover, steroid therapy was associated with higher incidence of cancer, mainly in HIV-positive patients. However, a significant reduction in incidence of constrictive pericarditis and in hospitalization rate in prednisolone arm, as compared with placebo, was reported.

Postcardiac injury syndrome (PCIS) incorporates postpericardiectomy syndrome (PPS), postmyocardial infarction pericarditis, and posttraumatic pericarditis [61]. The 2015 ESC guidelines define clinical diagnostic criteria for PCIS: (1) fever without alternative causes; (2) pericarditic or pleuritic chest pain; (3) pericardial or pleural rubs; (4) evidence of pericardial effusion; and (5) pleural effusion with elevated CRP. At least two of five criteria should be fulfilled. Anti-inflammatory therapy is indicated in patients with PCIS

(class I, LOE B), but not in cases of asymptomatic postsurgical effusions due to side effects associated with NSAID therapy [12]. To date, several strategies regarding PPS prevention have been investigated including colchicine, acetylsalicylic acid, and corticosteroids [13, 24••, 62–64]. Of them, only colchicine was found to be consecutively effective in reduction of PPS incidence [13, 24••]. However, perioperative use of colchicine was associated with high rate of gastrointestinal adverse effects [24••]. Nevertheless, the 2015 guidelines propose to consider colchicine therapy after cardiac surgery in weight-adjusted doses (as previously described in the section on treatment of acute pericarditis) and without loading dose for 1 month to prevent PPS development (class IIA, LOE A).

Age and Gender Issues

Pericardial syndromes in children share similar etiology and diagnostic criteria with adults [20, 65]. An inflammatory reaction could be more prominent in pediatric patients, compared with adults. Therapy of acute pericarditis in children consists of NSAIDs at high doses (class I, LOE C) with adjunctive age-adjusted (0.5 mg once daily for age <5 years, 1–1.5 mg/day divided in 2–3 doses otherwise) colchicine (class IIA, LOE C). Aspirin and corticosteroids are not recommended in children due to associated Reye's syndrome and severity of side effects (e.g., especially growth impairment), accordingly (class III, LOE C). For patients with steroid-dependent recurrent pericarditis, anti-IL-1 β receptor agent (Anakinra) may be considered (class IIB, LOE C), based on promising results in small series of children and adults [66, 67].

Treatment of acute pericarditis in pregnant woman depends on gestational age: aspirin, NSAIDs, and corticosteroids may be considered until week 20 [68–70]. After week 20, a low dose of prednisone is the only therapy to be used, due to adverse effect of NSAIDs on the ductus arteriosus and fetal renal function [70]. Colchicine is contraindicated during both pregnancy, regardless of gestational age, and breastfeeding. During lactation, NSAIDs and prednisone therapy may be considered.

The main concerns in elderly patients are polypharmacy and renal impairment. Concomitant multidrug therapy could result in nonadherence and adverse drug interactions, while renal impairment related to age or comorbidities affects drug elimination. Dose-adjustment (e.g., halving colchicine dose), therefore should be applied in elderly patients.

Interventional Techniques

The surgical approach for biopsy and drainage of pericardial fluid, classically by subxiphoid incision, remains the gold standard. However, in clinical practice, pericardiocentesis guided either by fluoroscopy or echocardiography is generally used for aspiration of pericardial fluid. The complication rate

of pericardiocentesis is not negligible and ranges from 4 to 10 %, and therefore, this action should be performed by skillful operator. The most common complications are arrhythmias, puncture of coronary artery or cardiac chamber, hemothorax, pneumothorax, pneumopericardium, and hepatic injury. Pericardioscopy is another interventional technique which allows a combination of intrapericardial space visualization, targeted tissue sampling, and intrapericardial instillation of therapeutic agents. However, this technique could be performed only in a limited number of experienced centers [71].

Therapeutic surgical procedures for pericardial diseases include pericardial window and pericardiectomy. Pericardial window is less definitive procedure that could be indicated for the patients with large recurrent pericardial effusions who are not candidates for more complex operation or when patient's life expectancy is reduced. Pericardiectomy is the treatment for chronic permanent constrictive pericarditis (class I, LOE C). Recent evidence from a retrospective cohort suggests that pericardiectomy may be proposed also for patients with recurrent idiopathic pericarditis, as a last resort therapy and in experienced centers only [17].

Conclusions

The European Society of Cardiology pioneered the first international guidelines for the management and treatment of pericardial diseases in 2004. Since then, a significant advance has been made in this field including several randomized controlled trials and large cohort studies, and a demand for new updated guidelines was inevitable. In the current 2015 ESC guidelines, available evidence was summarized and transformed into a new set of recommendations regarding the management of patients with pericardial disease: from clear statement of diagnostic criteria, through triage and workup strategies till therapeutic options. An impact of tuberculosis on etiology of pericarditis and pericardial effusion, considerable progress in imaging modalities of pericardial diseases and a pivotal role of colchicine in treatment and prevention of pericarditis and postcardiac injury syndromes are only part of the take-home messages from the guidelines. Therefore, these guidelines provide a useful updated tool that should assist the physicians in improving the quality of clinical practice.

However, despite the progress that was made in pericardial diseases management, the number of prospective trials is relatively small and therefore, the majority of recommendations is based on the experts opinion (level of evidence C). The target of fully evidence-based management of patients with pericardial disease still was not reached and several issues await clarification. Prospective studies are required to better understand the etiology of pericardial diseases, risk factors, pathogenesis, optimal length of therapy, and novel therapeutic options for recurrent pericarditis, the role of invasive

diagnostic and treatment techniques in pericardial disease management, and long-term patient' outcomes. Furthermore, specific age, gender, and ethnic subgroups should be represented in future trials. Consequently, new basic and clinical trials, as well as registries and cohort studies are warranted to strengthen the evidence and provide better tools for patient management.

Compliance with Ethical Standards

Conflict of Interest Alexander Fardman, Philippe Charron, Massimo Imazio, and Yehuda Adler declare that they have no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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