

# Recommendations for echocardiography use in the diagnosis and management of cardiac sources of embolism

## European Association of Echocardiography (EAE) (a registered branch of the ESC)

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Embolicism of cardiac origin accounts for around 15–30% of ischaemic strokes. Strokes due to cardioembolism are generally severe and early and long-term recurrence and mortality are high. The diagnosis of a cardioembolic source of stroke is frequently uncertain and relies on the identification of a potential cardiac source of embolism in the absence of significant autochthone cerebrovascular occlusive disease. In this respect, echocardiography (both transthoracic and/or transoesophageal) serves as a cornerstone in the evaluation, diagnosis, and management of these patients. A clear understanding of the various types of cardiac conditions associated with cardioembolic stroke and their intrinsic risk is therefore very important. This article reviews potential cardiac sources of embolism and discusses the role of echocardiography in clinical practice. Recommendations for the use of echocardiography in the diagnosis of cardiac sources of embolism are given including major and minor conditions associated with the risk of embolism.

### Keywords

Cardioembolic stroke • Transthoracic echocardiography • Transoesophageal echocardiography

## Introduction

### Why do we need recommendations for the echocardiographic diagnosis and management of cardiac sources of embolism?

Echocardiography is commonly used for the investigation of patients with acute stroke, transient ischaemic attack (TIA) or

peripheral embolism. Stroke is the third leading cause of death in several industrial countries and cardiogenic embolism accounts for 15–30% of ischaemic strokes.<sup>1–3</sup> The diagnosis of a cardioembolic source of stroke is frequently uncertain and relies on the identification of a potential cardiac source of embolism in the absence of significant autochthonous cerebrovascular occlusive disease. In this regard, echocardiography [both transthoracic (TTE) and/or transoesophageal (TOE)] serves as a cornerstone in the evaluation and diagnosis of these patients. However,

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cardioembolic stroke is a heterogeneous entity, since a variety of cardiac conditions can predispose to cerebral embolism. These cardiac conditions may be classified as major, minor, or uncertain risk (Table 1). The indications for and role of ultrasound techniques in these diseases are not well defined. Moreover, from a pathological point of view cardioembolic sources of embolism may be classified into three distinct categories: cardiac lesions that have a propensity for thrombus formation [i.e. thrombus formation in the left atrial appendage (LAA) in patients with atrial fibrillation (AF)], cardiac masses (i.e. cardiac tumours, vegetations, thrombi, aortic atherosclerotic plaques), and passageways within the heart serving as conduits for paradoxical embolization (i.e. PFO, patent foramen ovale).

Recommendations are important in this field for several reasons.

- (1) The clinical diagnosis is now dominated by echocardiography which has become the standard to evaluate these patients; however, better transducers and new ultrasound modalities (i.e. second harmonic imaging, Doppler tissue imaging, contrast echocardiography, 3D, and others) have further improved and expanded diagnostic capabilities. Consequently, the complementary or alternative role of TTE and TOE may be further defined.
- (2) Treatment of these conditions and of ischaemic stroke has not only developed through the continuous advances in understanding of the disease, but has also been reoriented by the development of new strategies and the advent of interventional techniques.
- (3) The today's patient population has changed due to ageing, and increase of patients with heart failure with a significant decline in both rheumatic fever and rheumatic valve disease.
- (4) The aim of these recommendations is to provide a consensus document for the echocardiographic screening and diagnosis of cardiac sources of embolism. Evidence for indications to recommend echocardiography in patients with stroke, TIA, or peripheral embolism is reviewed in detail.

**Table 1** Potential cardioembolic sources

Major risk sources	Minor or unclear risk sources
Atrial fibrillation	Mitral valve prolapse
Recent myocardial infarction	Mitral annulus calcification
Previous myocardial infarction (LV aneurysm)	
Cardiomyopathies	Calcified aortic stenosis
Cardiac masses	
Intracardiac thrombus	Atrial septal aneurysm
Intracardiac tumours	
Fibroelastoma	Patent foramen ovale
Marantic vegetations	
Rheumatic valve disease (mitral stenosis)	Giant Lambli's excrescences
Aortic arch atheromatous plaques	
Endocarditis	
Mechanical valve prosthesis	

## Method of article and definition of levels of recommendations

This consensus document is based on a literature review conducted using Medline (PubMed) for peer-reviewed publications and focuses on the studies published mainly in the last 10 years. Publications on appropriateness reflect an ongoing effort by the authors to critically and systematically create, review, and categorize clinical conditions and situations, where diagnostic tests are used by physicians caring for patients with a suspected of cardiac source of embolism. Although not intended to be entirely comprehensive, the indications are meant to identify common scenarios encompassing the major part of contemporary practice in this field. The ultimate aim of this document is to improve patient care and health outcomes in a cost-effective manner (whenever possible) linked to clinical decision making. Availability or quality of equipment or personnel may influence the choice of appropriate imaging procedures. These criteria are also associated with clinical judgement and practice experience. Because of the diverse nature of the topics and the absence of objective rating levels of evidence (mainly due to gaps in current knowledge in several fields), it was not possible to provide a systematic uniform summary of recommendations in all chapters. On the basis of all these considerations, the writing group decided to avoid levels of recommendations and maintain only the term 'Recommendation'. This implies an appropriate method recommended for all patients with a suspected of cardiac source of embolism.

## General comments

### Patient evaluation

Ischaemic stroke or TIA may be caused by several factors such as systemic hypoperfusion, *in situ* thrombosis or vascular or cardiogenic embolism. Since embolism from a cardiac source accounts for 15–30% approximately of these cerebral events, a very detailed neurological and cardiac evaluation should first include the patient's clinical presentation, even though there are several limitations in making this clinical diagnosis. Several neurological and cardiac features (detailed information on the characteristics of the clinical event, history of the patients, clinical evaluation) may suggest a cardioembolic origin. Moreover, evidence of embolism to other organs suggests that a cardioembolic source is likely.

### Neurological and cardiac evaluation

A number of cardiac conditions have been proposed as potential sources of embolism and an accurate clinical evaluation may easily raise the suspicion of a cardioembolic even in the presence of known structural heart disease or of clinical signs of cardiac diseases (i.e. arrhythmias, heart murmurs). However, the presence of a potential cardioembolic source of embolism does not itself justify the diagnosis of cardioembolic stroke or TIA, since atherosclerotic cerebrovascular disease and cardiac disease often co-exist. The most frequent causes of cardiogenic stroke are AF, left ventricular (LV) dysfunction (congestive heart failure), valve disease and prosthetic valves, intracardiac right-to-left shunts (PFO, particularly in conjunction with atrial septum aneurysm), and atheromatous

thrombosis of the ascending aortic arch. From an epidemiological point of view,<sup>1,4</sup> there is a history of AF in around one half of cases, of valvular heart disease in one-fourth, and of LV mural thrombus in almost a third. The presence of a potential cause of embolism or signs and symptoms of heart failure, increase stroke risk by a factor of 2–3.<sup>5–7</sup> All these considerations strongly suggest the importance of an accurate clinical evaluation in conjunction with the diagnostic imaging approach. This is particularly important with respect to the correct medical treatment for the patient with cardiogenic embolism according to the Guidelines for Prevention of Stroke.<sup>3</sup>

TOE has revolutionized the search for cardiac sources of embolism because of its (near) non-invasive nature and its relatively good sensitivity and high specificity.<sup>8</sup> In current clinical practice, echocardiography is used in over 80% of patients with acute stroke (particularly in stroke units) as a major cornerstone in the diagnostic work-up with a 1:3 ratio of TTE alone vs. TOE. This careful cardiodiagnostic approach appears to be justified even in patients with already known cerebral small vessel disease or artery-to-artery brain embolism from extracranial occlusive disease of the neck arteries because of the frequently found ‘competing’ stroke aetiologies in the same patient. Owing to the tremendous increase in morbidity in the elderly, monocausal strokes are becoming less frequent, and patients with multiple stroke aetiologies are tending to become the rule.

Stroke and cardiac disease are also linked to mortality risk. Whereas in the first 6 months after a first-ever stroke the cause of death is mostly stroke related, this changes within the subsequent 4–5 years in the sense that cardiovascular disorders assume the role of a major killer, particularly due to myocardial infarction and congestive heart failure.<sup>9</sup> As opposed to lacunar or atherothrombotic stroke, the outcome after cardiogenic stroke is particularly poor<sup>10,11</sup> with a 50% mortality after 3 years.<sup>12</sup> This is another important reason why cardiogenic sources of emboli must be identified whenever possible.

Clinically, the most important cause of cardiogenic brain embolism is AF both paroxysmal and chronic.<sup>13</sup> Any history of bouts of tachycardia or of periods of arrhythmia may suggest intermittent AF. The TOAST criteria are the most frequently used classification of stroke in epidemiological or genetic studies and refer to (i) large-artery atherosclerosis (artery-to-artery embolus, large artery atherothrombosis), (ii) cardiac embolism, (iii) cerebral small artery occlusion (lacunar stroke), (iv) stroke of another determined aetiology (rare aetiologies), and (v) stroke of undetermined aetiology.<sup>14</sup> The latter category refers to cryptogenic strokes, but is also chosen if two or more causes of stroke can be identified in the same patient, or—even more questionably—if the patient has a negative or incomplete evaluation. Categories 2 and 5 are of particular interest for echocardiography. Echocardiography in patients with AF enables risk stratification with respect to recurrent stroke by measuring the size of the atrium. The annual risk of stroke is 1.5% in cases with a normal left atrial diameter, but raises significantly in patients with an enlarged atrium.<sup>1–4</sup>

The extension and site of the infarct on computed tomography (CT) or magnetic resonance imaging (MRI) can deliver important clues towards a cardiogenic embolic stroke mechanism. This is the case if the infarct shows a cortical extension, multiplicity, or

**Table 2** Clinical and imaging findings indicating cardioembolic stroke mechanism

Abrupt onset of stroke symptoms, particularly in AF with lack of preceding TIA and severe first-ever stroke.
Striking stroke severity in the elderly (NIH-Stroke Scale $\geq 10$ ; age $\geq 70$ years)
Previous infarctions in various arterial distributions
Multiplicity in space (=infarct in both the anterior and posterior circulation, or bilateral)
Multiplicity in time (=infarct of different age)
Other signs of systemic thromboembolism (e.g. edge-shaped infarctions of kidney or spleen; Osler splits; Blue toe-syndrome)
Territorial distribution of the infarcts involving cortex, or subcortical ‘large lenticulostriate infarct’ (see Figures 1 and 2)
Hyperdense MCA sign (as long as without severe ipsilateral internal carotid stenosis)
Rapid recanalization of occluded major brain artery (to be evaluated by repetitive neurovascular ultrasound)

AF, atrial fibrillation; TIA, transient ischemic attack; MCA, middle cerebral artery.

bilaterality.<sup>15</sup> But there is also a specific type of subcortical infarct, the ‘large lenticulostriate infarct’ which typically indicates an embolic stroke mechanism.<sup>16</sup> Further characteristic clinical and imaging indicators of a cardioembolic stroke mechanism are listed in Table 2. In the individual patient, classification of pathological echocardiographic findings as incidental or causal can be difficult or even impossible. If no clear cardiac embolic source can be detected, it is essential that indirect clues for cardiogenic embolism (according to Table 2) such as reduced LV function in conjunction with ‘no better explanation’ for the brain infarct be recognized. This constellation would argue in favour of cardiogenic embolism. After having identified a potential or highly suspicious source of cardiac brain embolism, neurologists have to estimate the probability of cardiogenic stroke by also considering other competing causes of stroke. Echo findings and the pattern of infarction on brain imaging may help in this regard. In cardiac embolism, the pattern of infarct is territorial in type and distribution (Figures 1 and 2). Multiplicity of lesions involving both the anterior and posterior circulation and/or both hemispheres is highly suggestive of cardiogenic embolism.<sup>15</sup>

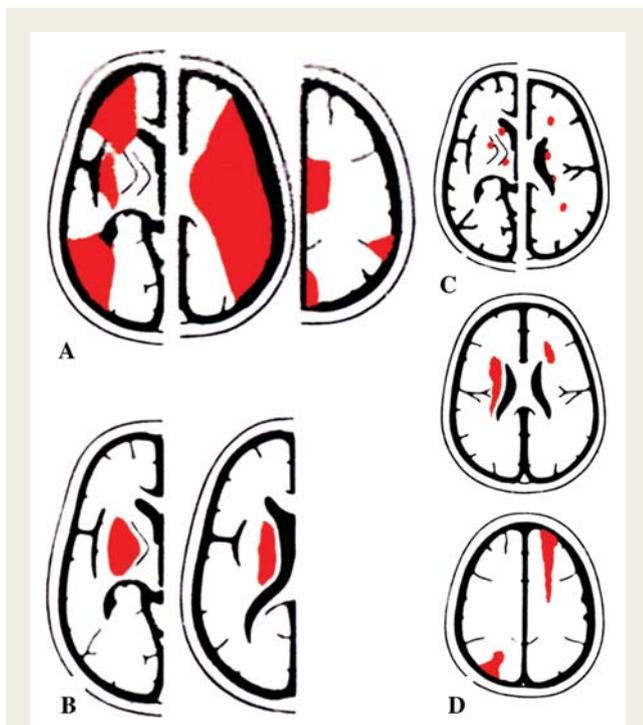
## General recommendations

TTE and TOE are recommended when symptoms potentially due to a suspected cardiac aetiology including syncope, TIA, and cerebrovascular events are present.

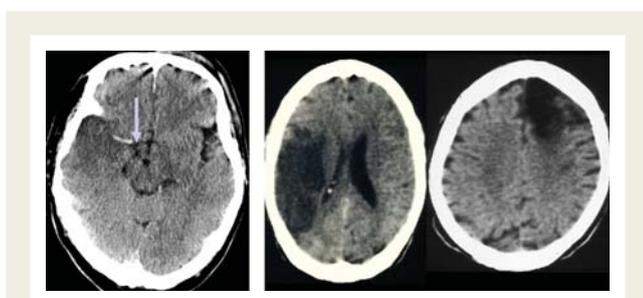
## Specific recommendations in diseases related to cardioembolic events

### Myocardial infarction and heart failure

Thromboembolism is a severe complication in patients with heart failure. Although the detection of an intracardiac thrombus may be



**Figure 1** Schematic drawings of patterns of brain infarctions signalling different stroke mechanisms. (A) In cortical infarcts with territorial distribution, cardioembolic stroke is probable. (B) The same holds true for large striatocapsular infarcts. (C) This is not the case in lacunar infarctions by definition located subcortically. (D) Low flow infarct can be located subcortical (upper panel) or cortical (lower panel), but their distribution is not territorial but interterritorial.



**Figure 2** Left panel: hyperdense middle cerebral artery-sign (dense artery sign; arrow): embolic occlusion of middle cerebral artery in a 70-year-old patient with intermittent atrial fibrillation. Right panel: territorial type of bilateral old infarcts in right middle cerebral artery and left anterior cerebral artery distribution in atrial fibrillation.

the primary culprit for a thromboembolic event, a variety of factors are also associated with heart failure and predispose to thrombosis. These include vascular disease, procoagulative status and impaired flow. It is accepted that the single most useful diagnostic test in the evaluation of patients with heart failure is the comprehensive TTE coupled with Doppler flow studies to determine

whether abnormalities of myocardium, heart valves, or pericardium are present and which chambers are involved.<sup>17</sup> The role of echocardiography is therefore to assess the size and function of the LV (global and regional), estimate the LV ejection fraction (LVEF) quantitatively, and assess other structural abnormalities such as valvular, pericardial, or right ventricular abnormalities that could account for the clinical presentation. Finally, echocardiography allows us to look for intracardiac masses that may be related with systemic embolization risk.

Aetiologies of LV dysfunction leading to heart failure may be ischaemic or non-ischaemic. Both lead to heart failure and can provide the anatomical substrate for LV thrombus formation. Left atrial thrombus may also lead to thromboembolic events; however, this is mainly the result of AF or significant mitral stenosis.

### Prevalence of intracardiac thrombus in myocardial infarction

Intracardiac thrombus is a common finding in patients with ischaemic stroke and may represent an indication for long-term anticoagulation to reduce the threat of further stroke and possibly to dissolve the thrombus.<sup>18</sup> Echocardiography plays an important role in its detection and is considered to be the first-line imaging modality in such patients and should be performed early. In a recent study of patients with ischaemic stroke, 26% of patients presenting with cerebrovascular events had an intracardiac thrombus, 70% of which were located in the LAA. Of the cardiac variables, only AF and LV systolic dysfunction manifested by wall motion abnormality on TOE were correlated with intracardiac thrombus.<sup>19</sup> In that study, LV systolic dysfunction was an independent predictor of intracardiac thrombus. A contributing causal link might be the higher incidence of AF in patients with coronary artery disease, which could explain the higher prevalence of left atrial thrombus in that study. Whereas a hypercoagulable status may also contribute to the formation of an intracardiac thrombus, no haematological or coagulation variables were correlated with the presence of intracardiac thrombus.

Thrombus formation following myocardial infarction is now rare, since the majority of patients with acute myocardial infarction undergo prompt thrombolysis and revascularization. The exact incidence of LV thrombus following acute myocardial infarction is not known as studies have been performed over several chronological periods, while treatment of acute myocardial infarction was changing. Early data suggest that in the setting of acute myocardial infarction, LV thrombus may be present in 7–20% of patients, most frequently in acute anterior or apical myocardial infarction. With chronic ventricular aneurysm, the prevalence of LV thrombus may increase up to 50%.<sup>20</sup> In one study, LV mural thrombus was visualized between 2 and 11 days (median 6) after the clinical onset of myocardial infarction in 40% of patients with anterior infarction. Despite this rather high incidence of post-myocardial infarction thrombus formation, the prevalence of thromboembolic events was low.<sup>20</sup> In a more recent study, Weinsaft et al.<sup>21</sup> used cardiac MRI in a large non-homogeneous cohort of patients with LV systolic dysfunction (LVEF < 50%) predominantly of ischaemic aetiology and found the prevalence of thrombus to be 7% in this heart failure

cohort. Patients with thrombus were more likely to have previous myocardial infarction, more advanced systolic dysfunction, and more extensive myocardial scarring by delayed enhanced MRI. In these patients, however, the overall prevalence of prior cerebrovascular events was just 12%.

## Echocardiography and left ventricular thrombus

LV thrombus is defined as a discrete echo dense mass in the LV with defined margins that are distinct from the endocardium and seen throughout systole and diastole. It should be located adjacent to an area of the LV wall which is hypokinetic or akinetic and seen from at least two views (usually apical and short axis). Care must be taken to exclude false tendons and trabeculae and of course rule-out artefacts, which constitute the most common false diagnosis of a thrombus. Sensitivity and specificity of the echocardiographic diagnosis of LV thrombus are in the range of 95 and 86%, respectively. However, very often the LV apex cannot be clearly defined and the presence or absence of a thrombus may be very difficult to establish. It is therefore useful to use a contrast ultrasound agent injected intravenously, which will then clearly identify the presence or absence of a thrombus.<sup>22</sup> The use of contrast improves image quality and allows for a more accurate assessment of LV volumes and LVEF, thrombus detection, and a decrease in both intraobserver and interobserver variability.<sup>23</sup> Having a low threshold of using ultrasound contrast agents effectively eliminates one of the earlier limitations of echocardiography, that of 'technically difficult' studies. Patients who are difficult to image with echocardiography are often referred for additional testing to obtain accurate information. Although other imaging modalities can provide accurate information, they may be associated with additional risks, time delays, and costs. Thus, in these technically difficult to image patients, a rapid, simple, inexpensive, and safe test that results in accurate information is desirable.<sup>23</sup> Contrast echocardiography therefore not only eliminates the technically difficult studies but it is also cost-effective.<sup>22,23</sup> TOE has little to offer in the detection of LV apical thrombus. Although it is the technique of choice for detecting atrial masses and thrombi in the LAA, it is not always helpful for detecting LV thrombus as the apex is often foreshortened or not well visualized.

Several echocardiographic features of the thrombus also need to be evaluated, including the presence or absence of an adjacent LV aneurysm defined as a localized area of akinesis or dyskinesis that deforms the LV chamber during both systole and diastole, often with a thin myocardial wall. The presence or absence of mitral annular calcification also needs to be noted.

## Thrombus characteristics

### Shape

LV thrombus may be flat (mural), lying along the LV wall or protruding within the cavity. It may be homogeneously echogenic, or present a heterogeneous texture often with central lucency. As an estimate of thrombus size, a one-dimensional measurement of maximal thrombus thickness may be made perpendicular to the myocardium from the epicardial–pericardial interface to the innermost border of the thrombus–blood interface.

### Motion

Thrombi may be fixed along LV wall or present an independent motion to a variable extent. Motion may involve the entire thrombus or more commonly a portion of the thrombus. Motion is independent of the underlying myocardium and that characteristic clearly distinguishes a true thrombus from an artefact. Colour Doppler tissue imaging may further facilitate this differential diagnosis.

### Follow-up

The long-term fate of LV thrombi that are present months to years after myocardial infarction is largely unknown. Approximately 20% of thrombi resolve spontaneously after acute infarction without therapy,<sup>20</sup> whereas others are prevented or treated with heparin or warfarin therapy. A significant number of patients continue to have an LV thrombus long after acute myocardial infarction. The risk of embolization decreases over time, likely as a result of organization of the thrombus, which include thrombus neovascularization.

## Left ventricular thrombus and anticoagulation

The effects of anticoagulants on the risk of embolization are debated. A number of studies showed a low embolic risk in patients without anticoagulant therapy,<sup>20</sup> but others with documented thrombus following acute anterior myocardial infarction showed a 27% prevalence of systemic embolization in untreated patients. Patients with chronic heart failure are at increased risk of thromboembolic events due to stasis of blood in dilated and hypokinetic cardiac chambers and in peripheral blood vessels; an increased activity of procoagulant factors may also be involved in this increased risk. However, in large-scale studies, the risk of thromboembolism in clinically stable patients has been low (1–3% per year), even in those with very depressed LVEF and echocardiographic evidence of intracardiac thrombi.<sup>24,25</sup> These rates are sufficiently low to limit the detectable benefit of anticoagulation in these patients.

## Predictors of embolization

The risk of embolization from LV thrombi in acute anterior myocardial infarction may be assessed from patient age and echocardiographic features. The risk of peripheral emboli is probably higher in patients with larger thrombus size, those with protruding and mobile LV thrombi and in the older patients.<sup>26</sup>

## Recommendations

- (1) Echocardiography is acknowledged to be the single most useful diagnostic test in the evaluation of patients following acute myocardial infarction to determine the extent of LV and right ventricular systolic dysfunction, the status of heart valves, and pericardium and should be performed as the first-line imaging investigation.
- (2) Echocardiography should be used in identifying LV thrombus, and the addition of contrast may increase diagnostic accuracy.
- (3) TOE has little to offer in the detection of LV thrombus.
- (4) It is recommended that patients with large, mobile thrombus protruding into the LV cavity should be anticoagulated.

## Cardiomyopathies

Patients with dilated cardiomyopathy, either primary or secondary,<sup>27</sup> are at increased risk of LV thrombus formation. Echocardiography plays a pivotal role in describing the size and extent of LV dysfunction but also to look for possible intracavitary thrombus in a similar way to in the post-myocardial infarction patient. Similar to the coronary artery disease patients, the presence of LV thrombus is related to an adjacent hypokinetic myocardial segment. It is extremely rare to have an LV thrombus on the top of a normally contracting LV wall; in the advent of such situation the first possible differential diagnosis should be an artefact. One exception, however, is in patients with endomyocardial fibrosis where the left or indeed right ventricular thrombus may be found in normally contracting ventricular walls. Another cardiomyopathy that presents several diagnostic challenges is idiopathic LV non-compaction (LVNC).<sup>28</sup> Complications such as arrhythmias, LV failure, and cardioembolic events arising as a result of non-compaction will need to be treated promptly upon diagnosis. TTE is the imaging modality of choice for LVNC where diagnosis is based on the identification of multiple prominent ventricular trabeculations with intertrabecular spaces communicating within the ventricular cavity.<sup>29</sup> Cardioembolic complications may result either from AF or thrombus formation within the myopathic LV. This latter mechanism is supported by necropsy reports of mural thrombi within the deep intertrabecular recesses. Echocardiography plays an important role in the diagnosis but cardiac MRI may also complement the diagnosis, particularly for detecting LV thrombus within the deep myocardial recesses. Three-dimensional echocardiography may supersede two-dimensional imaging by allowing for more detailed characterization of the non-compacted myocardium. Contrast echocardiography enhances endocardial border definition after opacification of the LV cavity unmasking the deep intertrabecular recesses and may therefore serve as a valuable adjunct to conventional two-dimensional imaging. TOE permits excellent visualization of the LV free walls, but the apex is not optimally visualized. During follow-up, as in patients with previous myocardial infarction, patients with dilated cardiomyopathy show either no change in thrombus size or thrombus resolution in the vast majority of cases. Warfarin therapy may increase the rate of thrombus resolution by approximately two-fold. In view of the increased embolic risk associated with chronic LV thrombi and because warfarin is probably effective in thrombus resolution, chronic anticoagulation may be helpful in both the dilated and the non-compacted LV.

As in coronary artery disease patients, optimal imaging with echocardiography is crucial in identifying or ruling out the presence of an LV thrombus. The use of intravenous contrast agents is strongly recommended since the cardiac apex is frequently not well visualized.<sup>22</sup>

No controlled study of long-term anticoagulation in patients with congestive heart failure due to dilated cardiomyopathy has been conducted and reports on the incidence of thromboembolic events in this population show widely variable results. Fuster et al.<sup>30</sup> reported an 18% frequency of thromboembolic events and an incidence of 3.5 clinically apparent events/100 patient-years in a retrospective study of 104 patients with non-ischæmic dilated

cardiomyopathy. In 1993, Katz et al.<sup>31</sup> prospectively followed 264 patients with dilated cardiomyopathy and reported that the incidence of stroke was 1.7/100 patient-years. Finally, in 1995, Natterson et al.<sup>32</sup> retrospectively studied 224 patients awaiting heart transplantation (mean LVEF 20%) and found that only six (3%, or 3.2/100 patient-years) had an episode of arterial embolization over a mean follow-up period of almost 1 year. There are a number of factors that may predispose to thromboembolic events in cardiomyopathy patients, including low cardiac output, very dilated ventricles, extensive wall motion abnormalities but also AF, particularly for atrial thrombus formation. It is therefore recommended that the only clear indications for anticoagulation in most patients with dilated cardiomyopathy are AF, a previous thromboembolic event or LV thrombus.

## Recommendations

- (1) It is recommended that echocardiography should be performed as the first-line imaging test in patients with known or suspected cardiomyopathy to determine the extent of LV and/or RV dysfunction.
- (2) Echocardiography must be used to identify LV thrombus and the use of contrast may increase its diagnostic accuracy.
- (3) Patients with dilated, poorly contracting ventricles, AF, a previous thromboembolic event or LV thrombus should be anticoagulated.

## Atrial fibrillation

The link between AF and cerebral or systemic embolism is important and complex. Its importance derives from the high prevalence of AF (0.4–1% in the general population, increasing to 9% in persons aged 80 years or older)<sup>33</sup> and from the frequent occurrence of stroke and embolism, ranging from 1 (low risk) up to 15% event/year (high-risk patients) among patients with AF. The causality complexity derives from the pathogenesis of thromboembolism which, despite being usually attributed to the migration of thrombi from the LAA, can also be caused (in up to 25% of cases) by intrinsic cerebrovascular diseases, proximal aortic plaques, or other cardiac sources of embolism. Moreover, most of patients with AF are older than 75 years, hypertensive, diabetics and have carotid artery stenosis factors all considered to be independent major risk factors for stroke or systemic embolism.

Owing to its widespread use, low cost, and bed-side availability, echocardiography has routinely become established in guidelines<sup>34</sup> for management of AF. This is particularly true for TOE to guide cardioversion and/or to detect cardiac sources of embolism.

In fact, the aetiological diagnosis of stroke is often achieved with an adequate clinical history and echocardiography, allowing for beginning anticoagulation and potentially treating AF with invasive therapeutic approaches.

TTE has great importance in identifying aetiological causes underlying AF such as:

- (1) Valvular heart disease;
- (2) Left and right atrial dimensions (diameters, area, and volume);
- (3) LV dimensions and thickness;

- (4) LV systolic and diastolic function;
- (5) Right ventricular dimensions and function;
- (6) Tricuspid regurgitation with right ventricular systolic pressure estimate;
- (7) Pericardial disease.

Finally, with the increasing use of procedures of radiofrequency ablation and of LAA closure, the echocardiography has gained an important role in the selection, guidance, and follow-up of percutaneous and surgical interventions.

## Echocardiography to identify the presence of thrombi

The presence of thrombi in left atrium (LA) or LV can be detected with TTE, but the most common location for thrombi in patients with AF is the LAA, which cannot be regularly examined by TTE. Thrombi formation in the cardiac cavities is mainly due to blood stasis, since the other aspects of the Virchow triad (vascular wall damage and hypercoagulability) have less importance in AF patients. During sinus rhythm the contractile activity of LAA with its vigorous emptying of blood flow, usually prevents the formation of thrombi in the LAA, despite its *cul-de-sac* shape and its plurilobate anatomical structure. The onset of atrial dysfunction, due to a variety of pathophysiological conditions increasing LA pressure<sup>35</sup> (systemic hypertension, AF, mitral valvulopathy, post-cardioversion atrial stunning), renders the LA prone to the formation of thrombi within its cavity and consequently a potential source of systemic embolization. In this setting, TOE is the gold-standard technique, with a great sensitivity and specificity to detect LAA thrombi. These thrombi are seen as echo reflecting masses in the atrial body or in the LAA (often in its apex), distinct from the underlying endocardium, observed in more than one imaging plane, and not related to pectinate muscles.<sup>36</sup> TOE is also able to detect signs of LAA dysfunction, often associated with or preceding the thrombus formation, such as low LAA emptying velocities and spontaneous echo contrast. Low LAA emptying velocities are well depicted with pulsed Doppler TOE, when the maximum peak of emptying velocity at TOE is lower than 30–40 cm/s.<sup>36</sup> Recent studies using the second harmonic TTE (with M-mode or PW Doppler)<sup>37,38</sup> demonstrated that TTE can be also effective to study the LAA function in a large number of patients, both in AF and in sinus rhythm. Also spontaneous echo contrast seen as a high density flow due to low-flow conditions, which remains stable with changes in gain settings, is well depicted on TOE.

## Echocardiography in the evaluation of embolic risk

The assessment of embolic risk in AF is crucial to indicate anticoagulant therapy in each patient, counterbalancing the haemorrhagic risk and the patient's preference. The risk stratification of patients with AF is based on clinical predictive factors according to a validated scheme named CHADS2.<sup>39</sup> The CHADS2 is a simple scheme, which assigns one point for each of the following: history of congestive heart failure, hypertension, age >75, or diabetes (the initials of the acronym CHAD) and two points for a history of stroke or TIA (S2). Whereas the antithrombotic

**Table 3** Echocardiographic predictors of embolic risk in patients with atrial fibrillation

### Echocardiographic risk factors

Left ventricular systolic dysfunction (EF < 35%)
Complex aortic plaques <sup>a</sup>
LAA thrombi or spontaneous echo contrast <sup>a</sup>
LAA dysfunction (emptying blood flow velocities $\leq 20$ cm/s and/or reduced contraction at M-mode)

<sup>a</sup>Identified only at TOE.

therapy is well defined for patients with no CHADS2 risk factors (aspirin) and for those with  $\geq 2$  CHADS2 risk factors (warfarin), the selection of the best antithrombotic agent is left to the personal choice of the physician for patients at intermediate risk (CHADS = 1).<sup>34</sup> It is also difficult the selection of antithrombotic therapy in patients at high haemorrhagic risk.<sup>40</sup> In the difficult decision to indicate lifelong anticoagulation in these patients, several echocardiographic factors can help in predicting the thromboembolic risk (Table 3). The linkage between clinical risk factors (hypertension, old age, LV dysfunction) and LAA thrombi is perhaps mediated by the ventricular diastolic dysfunction with effects on LA dynamics and pressure. Accordingly, LAA dysfunction is very often the ultimate pathophysiological link between clinical risk factors and thromboembolic event. Fortunately, the contractile function of the LAA, both in SR and in AF, can be evaluated directly (calculating the 2D fractional area change, the M-mode fractional shortening, or the Doppler LAA emptying velocity) or indirectly (looking for LAA thrombi or spontaneous echocontrast) with TTE and TOE. All the data coming from the specific multivariate analysis of echocardiographic risk factors for thromboembolic events in the Stroke Prevention in Atrial Fibrillation (SPAF) III<sup>35</sup> and other trials, showed the only factors independently associated with increased thromboembolic risk to be LAA thrombi [relative risk (RR) 2.5,  $P < 0.04$ ], dense SEC (RR 3.7,  $P < 0.001$ ), LAA peak flow velocities  $\leq 20$  cm/s (RR 1.7,  $P < 0.008$ ), and complex aortic plaques (RR 2.1,  $P < 0.001$ ). Therefore, echocardiographic data on LAA are independent predictors of thromboembolism<sup>41</sup> and can offer additional information, mostly in the subgroup of patients at intermediate risk and in all cases with doubts on the risk/benefit ratio for the therapeutic choice.

## TOE to guide cardioversion

The most important role of TOE in AF is to guide short-term anticoagulation for cardioversion. In patients with AF lasting more than 48 h, it is now unanimously agreed that besides the 'conventional approach' with oral anticoagulation for at least 3 weeks pre-cardioversion a 'short-term TOE-guided approach' can be used. This 'TOE-guided approach', based mainly on the results of the ACUTE study<sup>42</sup> avoids the 3 weeks of pre-cardioversion anticoagulation in patients with no evidence of thrombi in the LA or in the LAA at TOE. In patients with no identifiable thrombus at TOE, the cardioversion is performed after few hours of anticoagulation (with unfractionated or low-molecular weight heparin<sup>43,44</sup> and

soon after TOE). In patients with thrombus identified at TOE, oral anticoagulation is usually performed lifelong, and the rhythm-control therapy is often changed to a rate-control strategy, abolishing the cardioversion because of the high-thromboembolic risk. When the physician decides to attempt AF cardioversion despite the identification of LAA thrombi, TOE is usually repeated after at least 3 weeks of anticoagulation, immediately before attempting the cardioversion. An advantage of the 'TOE-guided approach' is related to the lower incidence of haemorrhage.<sup>42</sup> In fact nearly twice as many haemorrhagic events (major and minor haemorrhages) have been observed in the conventional-treatment approach when compared with the TOE guided one over an 8-week period.<sup>42,45</sup> This difference is probably due to the longer duration of anticoagulant therapy required by the conventional strategy, which is almost double that with the other approach, with higher incidence of bleeding. This increase in haemorrhages also causes higher costs when compared with conventional strategy.<sup>46</sup> Moreover, a greater overall rate of success in achieving sinus rhythm and a reduction of time in AF has been described with the TOE guided strategy.<sup>45</sup> It is still debated whether an improvement in SR persistence can be maintained during follow-up. There is a consensus on 4 weeks of oral anticoagulation after cardioversion with either strategy because of the possible occurrence of thromboembolism in the early post-cardioversion period even in the absence of thrombi in the pre-cardioversion TOE. These rare embolic events are due to the post-cardioversion LAA dysfunction (the so called 'atrial stunning'), which causes atrial stasis and provide a milieu for the formation of new thrombi. Atrial stunning is visible as a low (<20 cm/s) emptying velocity in the LAA, calculated with PW Doppler TOE. Most of the atrial stunning resolves in 48–72 h after cardioversion and almost always in 7 days. A complete normal LAA function observed at TOE 7 days after cardioversion indicates patients with low embolic risk, in whom the withdrawal of the anticoagulation therapy has been demonstrated to be safe.<sup>43</sup> The presence of a good LAA function (high velocities of emptying flow from the LAA at TOE) is also an independent predictor of absence of AF recurrences post-cardioversion, both in the short and long term. The great limitation of the LAA study is due to the semi-invasive nature of TOE, particularly if this examination has to be repeated during follow-up. In order to overcome this limitation, the TOE has been used in conjunction with contrast echocardiography<sup>47</sup> or with a second harmonic M-mode technique.<sup>37</sup> Other independent predictors of recurrences of AF after cardioversion are atrial volumes and deformation properties of the LA.<sup>48–51</sup>

## Recommendations

TTE is clinically indicated in patients with AF

- (1) to detect an underlying pathology affecting management or therapeutic decisions (ischaemic heart disease, valvulopathy, cardiomyopathy, or reduced ventricular function);
- (2) before cardioversion of atrial flutter (since this arrhythmia is often a marker of severe heart disease);
- (3) to indicate, guide and follow-up invasive surgical procedures, such as substrate AF ablation (RF or surgical) or LAA closure.

The addition of TOE in patients with AF is indicated:

- (1) in guiding short-term anticoagulated cardioversion.
- (2) in clinically selected cases (pre-ablation of AF and pre-closure LAA, suspected aortic arch atherosclerosis, recurrence of embolism during correct anticoagulation);
- (3) in determining the risk for future embolism (study of LAA function);

## Patent foramen ovale

### Detection of PFO

PFO, the remnant of an embryologic circulatory bypass of the lungs, is present in approximately one-fourth to one-third of all adults. The foramen ovale is a slit-like communication between the left and right atrium bounded by two thin septal membranes representing the septum secundum (on the right atrial side) and the septum primum (on the left atrial side), in the cranial portion of the fossa ovalis, the thin part of the atrial septum. Most of the time, the PFO is kept closed by a positive left-to-right atrial pressure gradient which holds the two septal membranes together. Therefore, in most cases, there is no spontaneous left to right shunt across a PFO. If right atrial pressure exceeds left atrial pressure, however, as in the Valsalva manoeuvre or due to right atrial pressure increase (e.g. in acute or chronic pulmonary hypertension), a right-to-left shunt flow through the PFO ensues. There is a wide anatomic range in size and functional significance of PFO, from the described frequent minimal variant to rarer forms, where there is a permanent open communication between the atria, leading to a predominant left-to-right shunt with occasional shunt reversal. In some cases, dilatation of the atria or an abnormal redundancy of the septal membranes, as in atrial septal aneurysm, generates a true atrial septal defect between septum primum and secundum, with spontaneous left-to-right shunt. Such defects have also been described as 'fenestrations' of the fossa ovalis. An atrial septal aneurysm is diagnosed if there is a fixed displacement or a mobile excursion of the fossa ovalis region of the atrial septum towards the right atrium or LA, or both, exceeding 10 mm from the mid-line (a line from the basal part of the interventricular septum to the insertion of the septum secundum in the atrial wall). The potential mechanism may be that the aneurysm may act as like a net capturing thrombi and conveying them to the PFO.

The association of PFO and otherwise unexplained neurological ischaemic insults has been intensively studied over the last decades since the seminal papers of Lechat *et al.*<sup>52</sup> and Webster *et al.*<sup>53</sup> that showed a significantly increased PFO incidence in young patients with unexplained stroke.<sup>54</sup> The underlying concept of paradoxical embolism of venous thrombi through the PFO has been well documented in the context of acute pulmonary embolism. However, while many authors have confirmed the statistical association between PFO and unexplained neurological events in young patients, the causality has not been conclusively established. This is an area of clinical uncertainty and ongoing debate, rendering it difficult to give firm recommendations.<sup>55–62</sup> We believe that the following statements are fair in view of the available evidence.

- (1) Paradoxical embolism through a PFO is a rare cause of neurological ischaemic events, except in the context of acute pulmonary embolism with a rise in right atrial pressure.

(2) In the absence of a demonstrable elevation of right atrial pressure, caution should be exercised to incriminate PFO in unexplained neurological events. However, in the absence of more likely causes, paradoxical embolism through a PFO may be assumed in the following circumstances.

- (a) Young age. Over the age of 55 years, the likelihood of atherosclerotic disease or occult paroxysmal AF as a source of embolism is far higher than that of paradoxical embolism through a PFO. Two population-based study of subjects over 39 years of age found no excess ischaemic neurological events in subjects with vs. subjects without PFO,<sup>62,63</sup> although some controversy over this issue continues.<sup>64</sup>
- (b) The presence of an atrial septal aneurysm additional to a PFO is associated with a marked increase in recurrent unexplained neurologic events.<sup>65</sup>
- (c) Large provokable right-to-left shunts have shown a stronger association with unexplained neurological events than small shunts.<sup>66</sup> Shunt quantification is difficult, but the number of bubbles crossing the septum either spontaneously or after a Valsalva manoeuvre gives a rough idea of shunt size. More than 20 bubbles have been cited to indicate a 'large PFO'.

These points should be integrated into the decisions on patient management. If PFO emerges as the most likely cause of an unexplained neurological event, the therapeutic options are either anticoagulation or device closure of the PFO. Anticoagulation is also appropriate secondary prevention of venous thrombosis and many other potential embolic sources such as AF and (probably) aortic atheroma. The best duration of anticoagulation is unclear and not necessarily lifelong.

### Technical points of PFO detection

Transcranial Doppler performed in the neurological department often provides the first clue to the existence of a right to left shunt by detecting microbubbles in the mid-cerebral artery after intravenous fluid injection. A PFO is diagnosed if intravenous microbubbles (agitated infusion solutions, right heart contrast agents, or saline–blood mixtures) passing from the right atrium into the LA, either spontaneously or after a Valsalva manoeuvre are directly observed.<sup>67</sup> If passage through the PFO is not clearly visualized, only very early (within three heart cycles from appearance of contrast in the right atrium) LA contrast bubble detection should be counted as proof of PFO, because bubbles may cross the lung and subsequently be detected in the LA. A right-to-left or left-to-right shunt on colour Doppler clearly originating from a passage between the two septa in the fossa ovalis is also diagnostic. The number of bubbles crossing the atrial septum is a rough indicator of the magnitude of the shunt. In many patients, a PFO will open transiently only immediately after release of the strain phase of the Valsalva manoeuvre. It is therefore important especially when performing a TOE to detect PFO to explain the Valsalva manoeuvre to the patient prior to starting the TOE. Alternatively or additionally, coughing may be used for provocation, but many patients fail to cough strongly enough, especially during TOE. Although TOE is still regarded as the gold standard for PFO detection, current echo machines equipped with harmonic imaging have

an equivalent sensitivity to visualize right-to-left shunt through a PFO if overall image quality is reasonable or good.<sup>68</sup>

### Recommendations

- (1) TOE is traditionally the gold standard for the detection of PFO, however in the presence of good image quality, trans-thoracic echo is sufficient to detect the presence of a PFO. Performance of a valid Valsalva manoeuvre or strong cough must be ensured with both methods.
- (2) The aetiological role of paradoxical embolism through a PFO in unexplained stroke should be assumed with great caution and discussed with the neurologist. Factors that argue in favour of this mechanism and that would suggest an indication for either anticoagulation or PFO closure are:
  - (a) temporal relationship of the neurological event with venous thrombosis
  - (b) young age (typically <55 years) and absence of other potential causes
  - (c) presence of an atrial septal aneurysm
  - (d) presence of a large spontaneous or provokable right-to-left shunt.

### Aortic atherosclerosis

Aortic atherosclerosis is well known to increase with advancing age and is related to traditional cardiovascular risk factors such as hypertension, hypercholesterolaemia, diabetes mellitus, and smoking. The prevalence of aortic atheromas on TOE varies depending on the population studied. In a community study, aortic atheromas were present in 51% of randomly selected residents aged 45 years or older, with a greater prevalence in descending aorta.<sup>69</sup> Complex atheromas were present in 7.6%. In patients with known significant carotid artery disease, the prevalence of aortic atheromas was 38%, and 92% in those with significant coronary artery disease.<sup>69</sup> On the other hand, several studies have shown the association between aortic atheromas and embolic disease, stroke, or peripheral embolism.<sup>70</sup> Aortic arch atherosclerosis is found in 60% of patients 60 years or older who had cerebral infarction.<sup>71</sup> Furthermore, complicated aortic atherosclerosis has been considered independent of other risk factors for stroke such as carotid disease or AF. In the SPAF,<sup>72</sup> investigators reported that 35% of patients with 'high risk' non-valvular AF had complex aortic plaque (mobile, ulcerated size >4 mm). During 13 months of follow-up, patients with complex aortic atheromatous plaque had a four-fold increased rate of stroke, compared with plaque-free patients (RR 4.0). However, although some studies suggested that aortic atherosclerosis is a high-risk factor for the development of vascular events, other studies showed that after adjustment for age and other risk factors, aortic atherosclerosis was not an independent predictor.<sup>73</sup> A possible explanation of these disparities is that most studies included the high-risk patient population referred for stroke or heart disease, and hence, may have a referral bias.

Mobile thromboses of the aorta are infrequent causes of systemic emboli and appear to be a complication of atherosclerosis. Clots floating in the aorta frequently become inserted to atherosclerotic plaque and have a high embolic risk. Another complication of

aortic atherosclerosis is cholesterol embolization syndrome, spontaneous or secondary to an invasive vascular procedure such as cardiac catheterization or placement of an intra-aortic balloon pump.<sup>74</sup> Similarly, ascending aorta and arch atheromas proved to be a highly significant risk factor for intra-operative stroke.<sup>75</sup>

### Aortic atherosclerosis diagnosis

Aortic atheromas are characterized by irregular intimal thickening of at least 2 mm. On the basis of their morphology, aortic atheromas are classified as either simple or complex plaques. The latter are atheromatous plaques that ulcerate and disrupt the elastic internal lamina, burrowing deeply into the aortic media and beyond.

Although the usefulness of TTE is limited for assessing aortic atherosclerosis, it has been shown to play a role in the diagnosis of aortic arch atheromas using suprasternal harmonic imaging. Schwammenthal *et al.*<sup>76</sup> showed that with adequate image quality the diagnosis was achieved in 84% of cases. TTE may be a useful test when it clearly visualizes atheromatous plaques. On the other hand, it provides complementary views of regions which may be blind spots on TOE. Both anatomical orientation and the location of detected atheromas with respect to the origin of the major aortic branches are more readily seen with TTE than TOE.

TOE is the imaging modality of choice for diagnosing aortic atheromas. It provides higher-resolution images than TTE and has good interobserver reproducibility. TOE characterises the plaque by measuring plaque thickness, ulceration, calcification, and superimposed mobile thrombi, thereby determining the embolic potential of each plaque. The advantages of TOE over other non-invasive modalities (CT and MRI) include its ability to assess the mobility of plaque in real time. The French Aortic Plaque in Stroke group showed that increasing plaque thickness of  $\geq 4$  mm imparted a greater embolic risk.<sup>72</sup> Mobile lesions (thrombi) superimposed on aortic atheromas are also known to increase the risk of embolism. Other characteristics of the lesions seen on TOE, such as ulceration  $\geq 2$  mm in aortic plaques and non-calcified plaques, are also associated with a higher risk of stroke. The following grading system, is used to classify aortic atherosclerosis: Grade I: intimal thickening  $< 4$  mm; Grade II: diffuse intimal thickening  $\geq 4$  mm; Grade III: atheroma  $< 5$  mm; Grade IV: atheromas  $> 5$  mm; and Grade V: any mobile atheroma (modified from Montgomery *et al.*<sup>77</sup>).

Large mobile thromboses of the aorta are infrequent causes of systemic emboli and appears to be a complication of atherosclerosis. TOE is the best technique for the diagnosis and evolution of these large thrombi.<sup>78</sup> The optimal management of this complication remains to be defined; anticoagulation and statin therapy appear to be a logical approach, although surgical removal has been performed in the cases of recurrent embolic events.

Ascending aorta dissection may be a rare cause of stroke of ischaemic more than embolic origin; Because of the vital prognostic and therapeutic consequences, the detection of a double lumen, floating membrane, initial flap, or aortic dilatation by means of TOE can be extremely valid.

### Recommendations

(1) In patients with stroke, the use of suprasternal TTE may help to identify arch atheromas. TOE may be indicated when image

quality is inadequate to reliably rule out atheromas or define plaque characteristics so that specific therapies can be considered.

(2) In patients with peripheral embolism, when TTE fails to identify the source of embolism, TOE is the technique of choice for the detection of mobile lesions superimposed on aortic atheromas or to rule out the presence of large, mobile, or pedunculated thrombi.

### Cardiac masses

Cardiologists evaluate cardiac masses after clinical symptoms lead to a positive imaging study, or because of an incidental mass found at imaging, usually echocardiography. Echocardiography has the best spatial and temporal resolution among the different cardiac imaging modalities, providing excellent anatomical and functional information, is useful to identify conditions in which masses may develop, is an accurate technique to detect and characterize masses once they are present, provides a non-invasive means for surveillance after treatment or removal, and is the optimal imaging modality for imaging small masses  $< 1$  cm or masses arising from valves. It is generally the only imaging modality required preoperatively, although MRI or CT may also be indicated in selected cases. Cardiac masses range from non-neoplasms lesions to high-grade malignancies and occur over a wide range of ages.<sup>79–81</sup> Ninety percent of primary cardiac tumours are either myxomas, which are cured by resection, or sarcomas, which have a dismal prognosis regardless of treatment. Normal variants and artefacts may be distinguished from pathological structures and tumours. In this regard, *Table 4* shows main normal variants and artefacts to be considered when evaluating cardiac masses.

### Cardiac myxoma

Cardiac myxoma is the most common benign primary tumour of the heart, accounting for  $\sim 30$ – $50\%$  of all primary cardiac tumours. Almost  $90\%$  of myxomas occur in the LA as polypoid lesions attached to the oval fossa, sometimes they involve the right atrium ( $15\%$ ) or the left or right ventricle ( $5\%$  each), in  $5\%$

**Table 4** Normal variants and artefacts not related to embolic events and distinct from cardiac masses

Right atrium	Chiari network, Eustachian valve, crista terminalis, catheters/pacemaker leads, lipomatous hypertrophy of interatrial septum, pectinate muscles, fatty material (surrounding the tricuspid annulus)
Left atrium	Lipomatous hypertrophy of interatrial septum, fossa ovalis, transverse sinus, calcified mitral annulus, coronary sinus, ridge between left upper pulmonary vein and LAA, suture line following transplant, pectinate muscles
Left ventricle	Trabeculations, false chords, papillary muscles
Right ventricle	Catheters and pacemaker leads, muscle bundles/trabeculations, moderator band.

of case they show multiple locations. In over 50% of patients LA myxomas cause symptoms of mitral valve stenosis (dyspnoea and orthopnoea from pulmonary oedema or heart failure). Right atrial myxomas may obstruct the tricuspid valve and cause symptoms of right-sided heart failure. Embolic phenomena occur in 30–40% of patients. Smooth surfaced tumours are more likely to produce valvular obstruction, while polypoid and myxoid ones are more likely to embolize. At echocardiography<sup>82,83</sup> cardiac myxomas typically appear as a mobile mass attached to the endocardial surface by a stalk, usually arising from the fossa ovalis. TTE imaging is usually sufficient, although small tumours or those that involve the right heart may require TOE for diagnosis. Three-dimensional echocardiography has also been used to more fully characterize atrial myxomas. If the narrow stalk is not visible, the diagnosis cannot be made by echocardiography and further imaging, MRI or CT, is necessary to show the tumour's margins and to exclude tumour infiltration. The major complication of myxoma is embolization, especially of myxoid, friable, familial ones. Myxomas are often confused with thrombi, although their characteristic location and attachment site is generally helpful in the differential diagnosis.

### Papillary fibroelastoma

Fibroelastomas are by far the most common valve-associated tumours, accounting for more than 85–90% of them. Myxomas and fibromas account for the remainder, whereas malignant tumours involving the valves are very rare. Papillary fibroelastomas are small, generally 0.5–2.0 cm in diameter and are often confused with vegetations. Making this distinction is difficult because of the similarity in the echocardiographic appearance. A correct diagnosis therefore depends on the clinical setting, and the presence or absence of signs of infection. These tumours are usually attached to the downstream side of the valve by a small pedicle and are irregularly shaped with delicate frond-like surfaces; tumour mobility is the independent predictor of death or non-fatal embolization and significant valvular regurgitation is rare. Asymptomatic patients with non-mobile lesions can be followed up closely. Differential diagnosis with Lambl's excrescences is difficult and controversial; generally Lambl's excrescences are smaller and frequently seen on an otherwise normal valve in elderly patients. Whether the two pathologies represent different entities remains controversial.

### Recommendations

Echocardiography is recommended for:

- (1) Evaluation of patients with clinical syndromes and events suggesting an underlying cardiac mass.
- (2) Evaluation of patients with underlying cardiac disease known to predispose to mass formation for whom a therapeutic decision regarding surgery or anticoagulation will depend on the results of echocardiography.
- (3) Follow-up or surveillance studies after surgical removal of masses known to have a high likelihood of recurrence (i.e. myxoma).
- (4) Patients with known primary malignancies when echocardiographic surveillance for cardiac involvement is part of the disease staging process.

## Endocarditis

Embolic events represent one of the most severe complications of infective endocarditis (IE),<sup>84,85</sup> particularly in case of cerebral embolism which is associated with an increased morbidity and mortality.<sup>86</sup> Echocardiography plays a key role in the management of patients with IE and may be useful both for the diagnosis of IE in patients with unexplained embolism, and for the prediction of risk of embolism in patients with known IE.<sup>87</sup>

### Endocarditis as a source of embolism

The rate of systemic embolism in IE is very high. It has been estimated to be 10–50% of IE. However, its exact incidence is unknown, with a large number of embolic events being clinically silent.<sup>88</sup> In the majority of cases, IE is clinically suspected because of fever and/or other clinical findings suggestive of IE. However, in some situations, these features are absent and IE is diagnosed on a systematic TOE performed because of unexplained embolic event. In addition, embolism may be the first clinical manifestation of IE, and the majority of embolic events occur before the initiation of antibiotic therapy.<sup>89</sup>

Three echocardiographic findings are considered as major criteria for endocarditis, including vegetation, abscess, and new dehiscence of a prosthetic valve.<sup>90</sup> Among them, the presence of vegetation is a hallmark of IE. Vegetation typically appears as a chaotic mass with acoustic properties different from that of the underlying cardiac structure, adherent to a valve leaflet and with mobility independent to the associated valve. Less frequently, vegetations are localized on mural endocardium, or papillary muscles.

Echocardiography must be performed in all cases of suspected IE.<sup>91</sup> It combines the advantages of diagnosing IE and assessing the severity of valve damage, detecting cardiac complications, and predicting prognosis and embolic risk.<sup>88</sup> TTE must be performed first and has sensitivity of about 60% for the diagnosis of vegetation. TOE is mandatory in cases of doubtful TTE, in prosthetic and pacemaker IE, and when an abscess is suspected. TOE enhances the sensitivity of TTE to about 85–90% for the diagnosis of vegetation and the additive value of TOE is even more important for the diagnosis of abscess and other forms of perivalvular extension.<sup>92</sup>

However, the sensitivity of echocardiography is lower in patients with a prosthetic valve or an intracardiac device, even with the use of TOE. Similarly, identification of vegetations may be difficult in the presence of mitral valve prolapse (MVP) with valve thickening, if vegetations are very small (<2 mm) or already embolized. For these reasons, TTE/TOE must be repeated after a few days delay after an initially negative echocardiographic examination, if the clinical suspicion remains high. Conversely, it may be frequently difficult to differentiate a vegetation from a thrombus, a fibroelastoma, or a non-bacterial thrombotic endocarditis.

### Recommendations

- (1) TTE must be performed first in suspected IE.
- (2) Given to its better sensitivity, TOE must be performed in cases of initially negative TTE with a high level of clinical suspicion, in suspected prosthetic valve endocarditis, and when TTE provides inadequate imaging.

- (3) Repeated TTE/TOE within 7–10 days is recommended in cases of initially negative examination when clinical suspicion of IE remains high.

## Echocardiography to predict the risk of embolism in IE

In addition to its role in diagnosing IE, echocardiography plays a major role in predicting embolic events,<sup>89,93–96</sup> although this prediction remains difficult in the individual patient. Both the presence and the size and mobility of the vegetation have been associated with an increased risk of embolism. Location of the vegetation on the mitral valve<sup>95</sup> and the increasing or decreasing size of the vegetation under antibiotic therapy<sup>94</sup> have also been associated with an increased embolic risk. Among these factors, the size and mobility of the vegetations are the most potent independent predictors of a new embolic event in patients with IE.<sup>89</sup> The risk of new embolism increases with the increasing size of the vegetation, with patients with very large (>15 mm) and mobile vegetations having the highest risk, especially in staphylococcal mitral valve endocarditis.<sup>89</sup> The risk of a new embolism is highest during the first days following the initiation of antibiotic therapy and decreases after 2 weeks,<sup>86,89,97</sup> although some degree of risk persists indefinitely in the presence of a vegetation.<sup>94,95–98</sup> For this reason, the benefit of surgery to prevent embolization would be greatest during the first week of antibiotic therapy, when the embolic rate is highest.

## Recommendations

- (1) The risk of embolism is related to the size, and mobility of vegetation, risk is increased in large (>10 mm) vegetations and particularly high with very mobile and large (>15 mm) vegetations.
- (2) The risk of new embolism is highest during the first days following initiation of antibiotic therapy and decreases after 2 weeks.

## Prosthetic valves/intracardiac devices

Intracardiac devices and prosthetic valves represent a major source of embolism. The presence of an intracardiac material in the setting of an embolic event raises a high level of suspicion of a cardioembolic source.

### Prosthetic valves

Two complications of prosthetic valve replacement must be suspected when an embolic event occurs in a patient with a prosthetic valve: prosthetic valve IE (see endocarditis) and prosthetic thrombosis. Prosthetic thrombosis is one of the most severe complications of mechanical heart valve replacement, although it may be observed less frequently in other types of valve substitutes. Situations at risk include early postoperative period, interruption of anticoagulant therapy, and pregnancy.<sup>99</sup> Both TTE and TOE must be performed in suspected prosthetic valve thrombosis. Two different clinical

and echocardiographic presentations may occur. In severely obstructive thrombosis, TTE is the first-line examination and may evidence an abnormal transprosthetic colour flow jet, an elevated Doppler transprosthetic gradient and a reduced effective orifice area. A high transvalvular gradient is of great value for the diagnosis of prosthetic thrombosis, especially when comparison with a reference value is available. Although direct evidence of valve thrombus may be obtained by TTE, TOE is the method of choice to diagnose the main signs of prosthetic thrombosis,<sup>99</sup> e.g. restricted leaflet or disc motion, abnormal central regurgitation, loss of physiological regurgitant jets in mechanical valves, and direct visualization of thrombus or pannus formation. Cinefluoroscopy may also be useful in this setting. TOE is also very helpful for the assessment of the extent of thrombus formation. The risk of embolism and complications in prosthetic thrombosis has been related to the size of the thrombus, with a large thrombus (>0.8 cm<sup>2</sup>) being a major risk factor for complications of thrombolytic treatment.<sup>100</sup> Thus, TOE may help in the choice between surgery and anticoagulant or thrombolytic therapy.<sup>99,100</sup> TTE and TOE must also be used for the follow-up of patients with prosthetic thrombosis after initiation of specific therapy.<sup>101</sup>

Diagnosis of partial prosthetic thrombosis is more difficult, especially when obstruction is mild or absent. TTE is of limited value in this setting and TOE is the method of choice for the diagnosis of small prosthetic thrombosis.<sup>99</sup> However, the diagnosis of prosthetic thrombosis, even with TOE, suffers from some limitations. First, small abnormal echoes around the prosthesis may also be observed in prosthetic endocarditis, and it may be difficult to differentiate between thrombus formation and vegetation. Moreover, examination of aortic prostheses is often difficult when a mitral prosthesis is also present, owing to attenuation of the ultrasound beam. Care must be taken to differentiate a prosthetic thrombus or vegetation from a suture line or fibrin strands.

## Recommendations

- (1) TTE must be performed in patients with a prosthetic valve and an embolic event.
- (2) Owing to its better sensitivity, TOE must be performed in patients with a prosthetic valve and an embolic event, even if TTE is negative.
- (3) TOE plays an important role in guiding therapeutic strategy in prosthetic thrombosis, the presence of a large thrombus favouring surgery.
- (4) Repeated TTE/TOE is recommended for follow-up after thrombolytic therapy or anticoagulant therapy of a prosthetic valve thrombosis.

### Intracardiac devices

A right-sided cardiac source of embolism must be suspected when an embolic event, particularly a pulmonary embolism occurs in a patient with an intracardiac device, including permanent pacemaker, implantable cardioverter defibrillators, or other intracardiac device, or when a paradoxical embolism is suspected. Both TTE and TOE are useful for the diagnosis of device thrombosis and/or IE.

Transcatheter closure of PFO is frequently used to prevent new embolism in patients with PFO and presumed paradoxical emboli.

However, recurrent embolic events may occur after this procedure.<sup>102</sup> Echocardiography may be used for guidance of the transcatheter closure procedure and must be performed in case of new embolic event.

## Minor conditions

### Mitral valve prolapse

MVP is a very common cardiac condition estimated to occur (mainly in young women) in 2% of the general population.<sup>103,104</sup> While in the past (also due to overestimation of the disease for echocardiographic technical reasons) several studies identified MVP in approximately one-third of patients under 45 years with cerebral ischaemia, the most recent cohort and case–control studies have cast doubt on the role of uncomplicated MVP in stroke.<sup>105</sup> Other studies identified the presence of myxomatous degeneration (with thickened or redundant leaflets) and supra-ventricular arrhythmias as risk factors for stroke. In a prospective study of 343 patients with MVP stroke occurred only in two (0.6%)<sup>106</sup> and currently the risk of thromboembolic complications in MVP is in general felt to be quite low (estimated at 1 per 6000 patient-years).<sup>107</sup>

The mechanism of stroke in MVP is not clearly understood; one of the postulated aetiological causes is that platelet–fibrin thrombi may form on the surface of the redundant leaflet tissue and embolize. More recently, an association between MVP and interatrial septal aneurysms has been clearly demonstrated and consequently the potential of paradoxical emboli is present.<sup>108</sup>

### Mitral annulus calcification

Mitral annulus calcification (MAC) is a very common degenerative process. It refers to a chronic non-inflammatory fibrous-calcification degeneration of the mitral annulus. Even though the Framingham heart study demonstrated a two-fold increase in the risk of stroke in these patients, no causal relationship between stroke and MAC has been established. Since MAC is a marker for generalized atherosclerosis or other cardiovascular disease it may not be a specific cause of stroke.<sup>109</sup> However, occasionally mobile plaques may be clearly identified at the level of the calcified annulus by echocardiography (both TTE or TOE) and in those cases the probability of an embolic source is much higher.

### Calcific aortic stenosis

Calcific aortic stenosis is a very common disease including degenerative calcification, rheumatic, or congenital pathology. Embolic complications are very uncommon in these patients and the majority of cases neurological events are occult or minor. Rarely larger emboli have been associated with calcific aortic stenosis, mainly in procedural setting such as cardiac catheterization and percutaneous valvuloplasty or percutaneous valve implantation. TTE or TOE may rarely visualize small debris or mobile plaques at the level of the valve leaflets or annulus, further reinforcing the potential for an embolic event.

## Recommendations

(1) No certain casual relationships between minor conditions and stroke have been established.

- (2) In patients with embolic events, the coexistence of MVP, MAC, or aortic stenosis may be an incidental finding on echocardiography.
- (3) Echocardiography is recommended in patients with known MVP, MAC, or aortic stenosis and an embolic event.

## Neurologist's perspective

Every stroke patient should initially be investigated by a 12-lead ECG to rule out myocardial infarction and to check for severe arrhythmias. In essence, during history taking and by thorough clinical checking, the stroke neurologist focuses on the detection of AF, history, and presence of prosthetic valves or valvular disorders, and history or signs of congestive heart failure and deep vein thrombosis, or lung embolism.

Both echocardiography and transcranial Doppler sonography are reliable diagnostic test for the detection of potential pathways for paradoxical brain embolism (so called 'shunt tests'). TOE and TTE are best for the imaging of an LV thrombus or aneurysm, but less reliable for aortic arch atherothrombosis. Colour-coded duplex imaging of the neck arteries and intracranial large arteries, in conjunction with cervical fat-suppressed MRI and CT arteriography or MR arteriography are optimal to check for cervical artery occlusive disease, including cervical artery dissection, respectively, and for direct or indirect indicators of large or small vessel occlusive disease. It also helps to define the time and degree of spontaneous or thrombolytic-induced recanalization of embolically occluded major brain arteries. These findings could be helpful to identify a cerebral artery occlusion as cardioembolic in origin, prompting a meticulous echocardiographic work-up.

An unsolved, yet urgent problem is the detection of paroxysmal AF. The patient's history of palpitation, intermittent tachycardia, or irregular heart beat is the one source of information; the other one is the immediate ECG in every stroke patient on admission. If the ECG does not show AF, a 24-h Holter ECG is the next step in the diagnostic escalation. Unfortunately, 24-h ECG can detect intermittent AF in only 1.2–8% of these patients.<sup>5</sup> Schaer *et al.*<sup>110</sup> could prove intermittent AF by 24-h Holter ECG in only 2.1% of their stroke patients with a normal ECG on admission. From this point of view, it appears questionable whether 24-h Holter ECG is worthwhile at all. In a similar setting, however, the study by Vandenbrouke and Thijs<sup>111</sup> revealed positive Holter ECG finding in 5.1 and 4.4%, respectively. Even in patients with already proven paroxysmal AF, repetitive 24-h ECG monitoring is not sufficiently reliable for clinical purposes. If a Holter ECG were performed in these patients once every month over a period of 1 year, and if all these ECGs were normal, the negative predictive value for AF would only be as high as 30%.<sup>112</sup> A 7-day ambulatory ECG monitoring in 149 stroke patients with the help of an event-loop recorder revealed only limited success. Event-loop recorder application is recommended as the third escalation step in stroke patients with presumed cardioembolism in case of normal standard ECGs and normal Holter ECG.<sup>113</sup> TOE is also a key procedure in these patients since in the presence of AF or intermittent AF, an LAA thrombus can be visualized.<sup>35</sup>

## Conclusions

During the past two decades, enormous progress has been made in the non-invasive diagnosis of cardioembolic events. A potential cardiac source of embolism should be considered in all patients presenting with stroke or TIA. In this regard, echocardiography is not only a powerful tool for the evaluation of cardioembolic sources of stroke, but also to establish recommendations for the primary and secondary prevention of cardioembolic stroke.

This article reports in detail conditions associated with the risk of embolism and the role of echocardiography in this field.

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