

Editorial

Comments on the 2014 ESC Guidelines on the Diagnosis and Treatment of Aortic Diseases

Comentarios a la guía de práctica clínica de la ESC 2014 sobre diagnóstico y tratamiento de la patología de la aorta

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INTRODUCTION

Since 2011, the Spanish Society of Cardiology has been putting into practice certain actions with respect to European Society of Cardiology (ESC) guidelines.¹ Together with the printing of the Spanish translation of the guidelines in *Revista Española de Cardiología*, these actions include the publication of a document prepared by a group of experts, coordinated by the Clinical Practice Guidelines Committee, in which they offer a critical review.^{2–4} The document corresponding to the comments on the 2014 ESC guidelines on aortic diseases⁵ is presented here.

METHODOLOGY

A working group was established to assemble experts in aortic diseases proposed by the Cardiac Imaging Working Group and the Guidelines Committee. The text of the guidelines was divided into several parts, which were sent to members of the working group for the analysis of the points that stood out as novel or controversial, or because they represented a change in current clinical practice. The resulting information was used to draw up an initial document with their comments, which was reevaluated by the original working group and sent to a second group of reviewers, proposed by the working groups on Ischemic Heart Disease and Acute Cardiovascular Care, Cardiac Imaging, and Clinical Cardiology of the Spanish Society of Cardiology and by the Spanish Society of Thoracic and Cardiovascular Surgery.

SUMMARY OF THE MAIN POINTS OF THE GUIDELINES

The most important new features of the guidelines are:

1. Improvement in the diagnosis and therapeutic management of aortic diseases will require a multidisciplinary approach and the

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creation of an “aorta team”. The complexity of certain surgical interventions suggests the need for the creation of reference centers in Europe.

2. Clinical decision making based on the measurement of the aortic diameters requires a painstaking methodology using the same imaging technique, the same method of measuring, and comparison with the measurements in the original images.

3. Inclusion of the complete study of the entire aorta (thoracic and abdominal) and its major branches (including the aortoiliac axis).

4. Utilization of the new surgical techniques in ascending aorta, with preservation of the aortic valve and established indications for endovascular treatment in descending aorta and aortic arch.

5. New diagnostic and therapeutic approach to acute aortic syndrome.

6. Diagnosis, follow-up, and surgical indication for hereditary aortic disease.

7. The definition of patient follow-up using imaging techniques after surgical or endovascular treatment.

NEW FEATURES OF THE 2014 EUROPEAN SOCIETY OF CARDIOLOGY GUIDELINES ON THE MANAGEMENT OF AORTIC DISEASES

Since the preceding ESC guidelines published in 2001,⁶ which focused on aortic dissection, there have been considerable changes in the diagnosis and management of aortic diseases. We need only to consider the important advances in imaging techniques, genetic diagnosis, surgical treatment of ascending aorta, or the introduction of endovascular treatment to understand the necessity of these new guidelines.

Evaluation of the Aorta

Regarding clinical evaluation, these guidelines point out the need to take special care to report any reference to a family history in the medical record. With respect to imaging techniques, the importance of measuring the aortic diameters in a plane perpendicular to the aortic flow is stressed. Special emphasis is also placed on the meticulous comparison of serial studies, using the same imaging technique and taking the measurements in the same way in the same anatomical segments. Thus, no clinical decision should be made on

the basis of the changes in diameters taken from a previous report. In principle, given the variability in the measurements, a progression on computed tomography (CT) of > 5 mm should be considered significant, although in ascending aorta and with electrocardiographic synchronization, changes > 3 mm are considered relevant in conditions like the Marfan syndrome and bicuspid valve.

The new guidelines focus more on the transthoracic echocardiogram (TTE) in the assessment of the aortic root and proximal ascending aorta due to the improvements in image quality. The transesophageal echocardiogram (TEE) is significantly superior in the rest of the thoracic aorta. Although the potential advantages of 3-dimensional echocardiography have been recognized, the guidelines caution that its incremental value in clinical practice has yet to be evaluated.

Ultrasound is indicated as the technique of choice for the initial study of the abdominal aorta. Although linear probes are more accurate, those used in echocardiography enable a correct assessment in most cases. The anteroposterior diameter of the abdominal aorta should be measured from outer edge to outer edge in a circular transverse image. Due to the variability in the measurement, it is recommended that variations of less than 5 mm be interpreted with caution.

Computed tomography plays a major role in the study of aortic diseases. The guidelines recommend acquisition with electrocardiographic gating, except in critical situations, to avoid motion artifacts. In the case of acute aortic syndrome (AAS), an initial acquisition should be carried out without contrast enhancement for the diagnosis of intramural hematoma, and studies of endovascular prostheses should include delayed acquisition. Moreover, the guidelines acknowledge the preferential use of CT when AAS is suspected because of its high sensitivity and specificity, its availability, and its speed.

Magnetic resonance is also considered to be valuable in the assessment of aortic diseases, especially in young patients and for follow-up studies that require frequent repetition, as it does not involve the use of radiation. Aortography is relegated to situations in which the findings with noninvasive techniques are ambiguous or incomplete. The new intravascular ultrasound techniques and intracardiac echocardiography could be useful during endovascular procedures. Another novel feature is the possibility of using positron emission tomography, or PET, with F-fluorodeoxyglucose, which aids in the diagnosis of inflammatory or infectious aortic diseases. Finally, the study of aortic stiffness, with the determination of carotid-femoral pulse wave velocity, is considered valuable for the early diagnosis of cardiovascular disease.

Medical Treatment

With respect to medical treatment in chronically ill patients, the guidelines stress general measures, including smoking cessation, blood pressure control (< 140/90 mmHg), and avoidance of competitive sports in patients with aortic dilation.

There are 2 novelties in terms of drug therapy. The first is the fact that treatment with losartan could reduce both the progression of aortic dilation and aneurysm formation in Marfan syndrome.⁷ The second is the observation that the use of statins could reduce the progression of aneurysms.⁸

Endovascular Treatment

The section on endovascular treatment highlights a number of recommendations for planning implantation and reducing complications. There are specific recommendations for thoracic aorta that refer to proximal and distal landing zones, which should be at least 2 cm long and less than 40 mm in diameter. In those patients with chronic aortic aneurysm, the guidelines recommend oversizing

of the stent diameter by 10% to 15% with respect to the landing zones. In aortic dissection, oversizing to any extent is advised against. During the procedure, the blood pressure should be lowered and preventive cerebrospinal fluid drainage should be performed in patients at high risk of paraplegia. A new aspect for cardiologists is the inclusion of endovascular treatment of abdominal aortic aneurysms.

Surgical Treatment

In aortic root surgery, techniques that preserve the aortic valve are recommended as the treatment of choice. However, in the presence of associated valve disease, the guidelines point out that these conservative techniques should only be performed in highly experienced centers. If there are doubts as to the durability of the repair, the decision should be made to replace the aortic valve. The authors recommend the utilization of either of the 2 standard techniques: the David operation (valve reimplantation) or the Yacoub procedure (aortic root remodeling) although, in this case, annuloplasty should also be performed to prevent future dilation of the aortic annulus. The David operation is the technique of choice in patients with connective tissue diseases.⁹

Mortality associated with isolated elective surgery of the aortic root and ascending aorta ranges between 1.6% and 4.8%,¹⁰ although in patients under 55 years of age, it is only 1.2%.¹¹ These results are in agreement with those documented in Spain in the first report corresponding to the Spanish project on quality in cardiovascular surgery in adults.¹² The authors point out the advances that have contributed to reducing the risk of interventions involving the aortic arch, especially the use of antegrade cerebral protection, utilization of the axillary artery as first choice for cannulation, and the development of new prostheses that include the supra-aortic trunks for total aortic arch replacement.

With respect to surgical treatment of aneurysms of descending aorta, the guidelines point out the importance of maintaining good perfusion of all the organs during aortic clamping and recommend left heart bypass as the perfusion technique of choice. To reduce the incidence of paraplegia in cases of thoracoabdominal aneurysm, the recommendations include the performance of the intervention with mild hypothermia (34 °C), the reimplantation of certain intercostal arteries between T8 and L1, and the utilization of cerebrospinal fluid drainage, which should be maintained for at least 72 hours.

Acute Aortic Syndrome

The guidelines maintain the standard Stanford and De Bakey classifications although, in general, they employ the Stanford classification, based on whether or not the ascending aorta is involved. What is truly novel is the definition of a new time-based classification that distinguishes among acute (< 14 days), subacute (up to 3 months), and chronic (more than 3 months) disease.

One of the important contributions of the guidelines is the assessment of the *a priori* probability of finding AAS in a given patient. The 3 sources of information (predisposing conditions, type of pain, and physical examination) are determining factors in the initial evaluation of the patient. The role of D-dimers during the early hours of aortic dissection is also pointed out, although the main limitation is that they are not elevated in intramural hematoma or penetrating aortic ulcer. Computed tomography is undoubtedly the most widely available and accurate technique for the diagnosis of AAS,¹³ and is especially useful for the study of the extension of the dissection and branch compromise. Nevertheless, TTE is included as the first-line diagnostic technique since, although it does not rule out AAS, a positive result helps to hasten the application of the therapeutic strategy. In unstable patients, the choice between TEE and CT depends on the availability of experts in the center. The latter would be indicated in stable patients.

Concerning surgical treatment of aortic dissection, the guidelines insist that it is indicated in all patients with type A AAS and stress that the aim should not only be to save the patient's life, but also to prevent late reinterventions. On the other hand, in the presence of organ malperfusion, a hybrid procedure (surgery and endovascular treatment or fenestration) may be the best option. The guidelines also recommend endovascular treatment in complicated type B aortic dissection (class I recommendation) and their advice is that this option be considered in uncomplicated dissections (class IIa recommendation).

Other Variants of Acute Aortic Syndrome

One of the aspects that have been well established in these guidelines is the diagnosis and management of intramural hematoma, in which unenhanced CT is the first-line diagnostic option. In type A intramural hematoma, either emergent or urgent (< 24 h) surgical treatment is indicated depending on the associated risk factors. The authors point out the dynamic component of the disease course in type B, a circumstance that makes close follow-up using imaging techniques indispensable. The same strategy should be employed in uncomplicated type B penetrating aortic ulcers.

In the case of contained aortic aneurysm rupture, the guidelines recommend CT as the diagnostic technique of choice and endovascular treatment (which is associated with lower perioperative morbidity and mortality rates, at the cost of a higher incidence of late complications) when the anatomy is favorable. In those patients with chest trauma in whom aortic injury is suspected, CT is the technique of choice, since it also facilitates the diagnosis of associated lesions. Cases of free rupture or periaortic hematoma should be considered surgical emergencies. In the remainder, treatment can be delayed 24 hours until the patient is stabilized. In agreement with published series, endovascular treatment is preferred to surgery due to both the associated survival benefit and the lower risk of paraplegia.

Thoracic Aortic Aneurysms

When an aortic aneurysm is diagnosed, it is important to perform CT or magnetic resonance imaging to assess the involvement of the rest of the aorta. Given that, in most cases, the diameter of the aneurysm is the parameter that is going to establish the indication for surgery, the guidelines stress the importance of taking the proper measurements, which should always be perpendicular to the longitudinal axis of the aorta. The indications for surgery in patients with ascending aortic aneurysm have not changed, except for the definition of this condition as a risk factor in patients with Marfan syndrome or bicuspid aortic valve having an increase in aortic diameter > 3 mm/year (in previous guidelines, a growth of > 2 mm/year was considered).¹⁴ Although in patients with Marfan syndrome the indication for surgery is established when the diameter is ≥ 50 mm, or ≥ 45 mm in the presence of risk factors, in those with bicuspid aortic valve, surgery is indicated when the diameter of the ascending aorta is ≥ 55 mm, or ≥ 50 mm in the presence of risk factors. The guidelines point out the importance of indexing the diameters in patients with a small body surface area, especially in those with Turner syndrome, and recommend surgery with indexed diameters > 27.5 mm/m². The indication for surgery in patients with aortic arch aneurysm remains similar to that of the United States guidelines; intervention is recommended for diameters of 55 mm or greater or when there are clinical signs of compression.

In patients with descending aortic aneurysm, endovascular treatment is established as the treatment of choice when the diameter is ≥ 55 mm. When the only treatment option is surgery, the procedure is considered to be indicated if the diameter is ≥ 60 mm.

The surgical option is recommended in patients with connective tissue diseases.

Abdominal Aortic Aneurysms

One of the contributions of these guidelines is the inclusion of the diagnosis and management of abdominal aortic aneurysm. The parameter most closely related to the risk of aneurysm rupture is its maximum diameter. For this reason, the diameter of the aneurysm is the reference used to establish the periodicity of follow-up visits and the indication for surgical treatment. The indications for elective surgery are a diameter > 55 mm, a growth rate of > 10 mm/year, or the development of symptoms. In smaller aneurysms, the conservative approach is a better option than surgery (open or endovascular). Whereas the mortality rate associated with endovascular treatment is 3-fold lower than that recorded in conventional surgery,¹⁵ this benefit is lost during follow-up because of the need for reinterventions. The indication for surgery in women is an especially complex decision. The rates of rupture for a given aortic diameter are 3 to 4 times higher in women than in men, and the aortic diameter at the time of rupture is, on average, 5 mm smaller.¹⁶ For this reason, the indication for surgery appears to be justified when the diameter is > 50 mm.

One interesting aspect is the screening of abdominal aortic aneurysms by means of abdominal ultrasound. The prevalence among men over 65 years of age has been calculated to be 5.5%. On the basis of recent studies,¹⁷ examination of the abdominal aorta with conventional echocardiography is recommended, as abdominal aortic aneurysms are diagnosed in 3.5% to 4% of men aged over 65 years in less than 1 minute.

Aortic Disease in Hereditary Syndromes

The guidelines recommend the performance of a genetic study in the first-degree relatives of patients with thoracic aortic aneurysm or aortic dissection and a diagnosis of familial aortic disease. Screening of the "healthy" relatives who are at risk should be carried out every 5 years as long as there is no clinical or genetic diagnosis of the disease. In families with nonsyndromic familial aortic disease, screening should cover the entire arterial tree, including the cerebral arteries.

Bicuspid Aortic Valve

There is a strong association between the presence of a bicuspid aortic valve and the progressive dilation of ascending aorta. The recommendations for elective surgical treatment of ascending aortic aneurysm in cases of bicuspid aortic valve differ from those of the North American guidelines for aortic diseases, but coincide with the recent European and North American guidelines for valve diseases.^{7,18} Surgery is considered to be indicated only with diameters > 50 mm in those cases in which there are associated risk factors, such as aortic coarctation or hypertension. These differences are based on recent publications that report a low incidence of AAS in the patient population with bicuspid aortic valve. The recommendations with respect to aortic surgery with a measurement > 45 mm if valve surgery is indicated remain unchanged.

Aortic Coarctation

Aortic coarctation is considered to be a diffuse involvement of the arterial vascular tree. Intervention is indicated when the pressure gradient between arms and legs is > 20 mmHg and is associated with hypertension (arterial blood pressure > 140/90 mmHg), an abnormal exercise response, or left ventricular hypertrophy. Intervention should also be considered when the diameter of the coarctation is < 50% of the aortic diameter at the level of the diaphragm.

Aortic Arteriosclerosis

Thoracic aortic arteriosclerosis is predominantly found in the aortic arch and descending aorta. The presence of atheromatous plaques ≥ 4 -mm thick has been identified as an independent risk factor of recurrent stroke.¹⁹ Transesophageal echocardiography is the test of choice in the diagnosis and quantification of the severity of these lesions. Antiplatelet or anticoagulation therapy should be considered in patients with cerebral or peripheral embolism. The choice of one or the other depends on the comorbidities and other indications for these treatments.

Long-term Follow-up of Aortic Diseases

In addition to strict arterial blood pressure control and restriction of competitive sports and isometric exercises, follow-up using imaging techniques to assess the disease course and development of complications is another important requirement. In patients with chronic type B dissection, the detection of progressive aortic growth (> 1 cm/year), total aortic diameter > 6 cm, malperfusion syndrome, or recurrent pain is considered an indication for endovascular or surgical treatment.

With respect to drug therapy, the experience reported in registries suggests the benefits of beta blockers in all types of dissection, and calcium channel blockers (no differentiation is made among types) in patients with type B dissection. Although renin-angiotensin system inhibitors are not associated with a survival benefit, angiotensin receptor blockers reduce aortic growth in patients with Marfan syndrome.

With regard to postintervention follow-up, the performance of imaging studies (CT or magnetic resonance) is recommended at 1, 6, and 12 months and, in the absence of complications, yearly or every 2 years thereafter.

CRITICAL ASSESSMENT OF THE MOST CONFLICTIVE ASPECTS

One of the major limitations to these guidelines is that there are very few randomized studies on aortic diseases. Thus, the level of evidence is low and the great majority of the recommendations are class C, the fruit of expert consensus.²⁰

Evaluation of the Aorta

The guidelines do not deal with the methodology employed in the measurement of the aorta using imaging techniques. This limitation appears to be justified as the recommendations for multimodality imaging are to be published in the near future. In the meantime, the current recommendations²¹ should be followed.

The explanation of the assessment of the size of the aneurysm is confusing. The authors specify that there is progression when the increase in the diameter is > 5 mm, but this is determined on the basis of the variability of CT measurements. Likewise, users of these guidelines would have appreciated a simplified table with the normal values for the diameters of the different aortic segments according to age and imaging technique and a more specific recommendation as to when aortic diameters should be indexed.

With respect to screening for abdominal aortic aneurysms, it is difficult to justify the class I recommendation in individuals over 65 years of age, and even more difficult to recommend that their management be different in women when the guidelines themselves recognize that abdominal aortic aneurysms are associated with higher risks in women. One important aspect is the recommendation that the abdominal aorta be studied during a conventional echocardiogram, as it would constitute a change with respect to routine clinical practice and would require formal, accredited training for all the cardiac sonographers.

Medical Treatment

The guidelines only underscore the general indication for treatment with beta-blockers to achieve strict arterial blood pressure control ($< 140/90$ mmHg) and allude to the possible benefit of angiotensin receptor blockers in the dilation of ascending aorta in patients with Marfan syndrome and of calcium channel blockers in descending aortic dissections. Statins are indicated in abdominal aortic aneurysms and when the etiology of the aortic disease is assumed to be arteriosclerotic, although there is no clear, objective numerical data.

Surgical Treatment

With respect to surgical treatment, the guidelines are quite descriptive when discussing the different techniques and options, but are somewhat vague when it comes to dealing with individual indications according to the patient or disease characteristics.

Acute Aortic Syndrome

The guidelines stress the role of CT in the diagnosis of AAS. However, they do not mention certain recent contributions attributable to echocardiographic techniques, such as 3-dimensional TEE or the use of contrast enhancement, which is an inexpensive and simple alternative that is useful in acute situations.²² They also fail to evaluate the importance of knowing the status of the supra-aortic vessels and left axillary artery (the cannulation site of choice) in surgical planning.

The management of patients in whom AAS is suspected is summarized in a diagnostic algorithm that leaves room for doubt regarding certain aspects. For example, in the group of stable patients with a high probability of AAS, in whom TTE results in a definitive diagnosis of type A dissection, the algorithm recommends that the patient be referred as soon as possible to the surgical team and that the study be completed with preoperative TEE. Interestingly, in addition to TTE, the same situation in an unstable patient calls for TEE or CT before the patient is sent to the operating room. The diagnostic role of D-dimers appears to be exaggerated, as testing for them can produce false positives and negatives and there is no evidence that this variable provides additional value to a reliable diagnostic approach based on imaging techniques. On the other hand, the diagram recommends the performance of chest X-ray only in patients in whom the probability is low, whereas it channels patients with a high probability directly to TTE. However, in high-risk patients, a portable X-ray system could provide rapid information on mediastinal widening, pleural effusion, cardiomegaly, signs of heart failure, or alternative diagnoses. This vagueness creates doubts as to the true applicability of the algorithm in clinical practice, especially when other simpler and more practical algorithms already exist.²

In addition, the text does not make it clear whether or not the indication for surgery in type A dissection should be urgent, in accordance with the table of recommendations, or emergent, as shown in the flow chart. Patients with acute type A dissection often require emergency surgery but, in certain uncomplicated cases, it might be reasonable to delay surgery for a few hours in order to intervene when the patient is in a more favorable situation and with a surgical team more suited to the situation. In the case of type A dissection, the guidelines tend to favor complex procedures, arguing that the long-term outcome is better; however, given the complexity of these patients, it will always be necessary to consider them on a case-by-case basis. The authors did differentiate between urgent and emergency surgery in their discussion of aortic intramural hematoma. In the case of penetrating aortic ulcer, the guidelines assign a similar diagnostic value to TTE and TEE, an assessment that is erroneous.

Most ulcers are located in descending thoracic aorta, a segment that is very difficult to examine with TTE. On the other hand, the recommendations for treatment of asymptomatic aortic ulcer are still quite controversial.

Aortic Disease in Hereditary Syndromes

The guidelines are too vague on several points concerning the management of patients with aortic disease in the context of a hereditary syndrome, although there is a lack of studies that provide information on the natural histories of rare diseases, aside from Marfan syndrome. We also note the absence of some recommendations on the specific panel of genes for use in the genetic study, information which, while provided in the North American guidelines,²⁴ is missing from these. Another important point is the omission by these guidelines of the changes introduced in 2010 (in the revised Ghent nosology) for the diagnosis of Marfan syndrome,²⁵ information that is transferred in its entirety to the guidelines on congenital heart disease published by the ESC 4 years ago. Finally, the guidelines suggest that Loeys-Dietz syndrome is associated with an especially high mortality rate, when the truth is that there is very little data on which to base clear recommendations.

Bicuspid Aortic Valve

There is not sufficient evidence to identify the groups of patients with bicuspid aortic valve who are at greater risk of developing aortic dilation. Thus, the recommendations for follow-up are based only on expert consensus and offer little detail. Among the issues to be resolved, it is necessary to point out the cost-effectiveness of familial screening, the virtual absence of reliable data on which to base recommendations for young women with bicuspid aortic valve who wants to become pregnant, or the most adequate threshold for dilation in surgery involving ascending aorta when the idea is to include the repair or preservation of the aortic valve. Repair stability is put forward as an argument to justify a more aggressive surgical intervention of the aorta under these circumstance, but we are still far from being able to determine this variable in surgical patients who do not belong to reference groups.

Aortic Coarctation

Decision making on the diagnosis and treatment of aortic coarctation with a pressure gradient > 20 mmHg is based on expert consensus. Nevertheless, a relationship between residual gradients of 15 mmHg and persistent hypertension has been reported and, thus, percutaneous treatment may be considered in patients with lower pressure gradients in the presence of hypertension. One unsolved problem is the follow-up strategy in these patients, who are at high risk for the development of aortic complications (in 10% to 15% of the cases), especially if they also have bicuspid aortic valve.²⁶

Aortic Arteriosclerosis

There is no objective evidence on which to base treatment recommendations. The guidelines also fail to provide a clear recommendation with respect to how to use imaging techniques in the assessment of aortic disease as a possible source of embolism.

Aortitis

The document does not define the diagnostic criteria in detail. Likewise, the discussion of imaging modalities is sketchy; the definition of specific classes of recommendations, taking into account possible clinical problems, would probably have been useful.

IMPLICATIONS FOR CLINICAL PRACTICE IN OUR PATIENT POPULATION

The application of these guidelines in our patient population implies the reinforcement of a series of strategies that were introduced some years ago, like the creation of multidisciplinary aortic disease units comprising cardiologists and radiologists (who often are experts in multimodality imaging), cardiac surgeons, and vascular surgeons, as well as the establishment of registries concerning the diagnosis and management of acute aortic disease, such as the RESA (*Registro Español del Síndrome Aórtico Agudo* [Spanish Acute Aortic Syndrome Registry]).⁶ The creation of national reference centers that would bring together an extensive body of experience to offer the best treatment in complex cases should probably be considered. Aortic disease units should not focus only on the diagnosis and treatment of these conditions, but should provide adequate clinical follow-up accompanied by imaging techniques. A fundamental aspect is the personalization of the recommendations of these guidelines, taking into account the characteristics and circumstances of each patient. Genetic studies should become more widespread to improve the diagnosis of familial aortic disease, and reference units offering excellence in the more sophisticated aspects of the diagnosis, medical management, and complex surgical techniques should be created.

CONCLUSIONS

The guidelines include the latest contributions associated with imaging techniques and surgical and endovascular treatment in aortic diseases. Using a multidisciplinary approach, they incorporate the recommendations resulting from recent studies or from expert consensus. With relative frequency, the guidelines do not carry level A or B evidence, nor do they provide a class I recommendation. Thus, for their application, it is important to consider the singularity of each patient and the experience and results of each center. The creation of multidisciplinary aortic disease units and reference centers with extensive experience should facilitate the achievement of the objectives of these guidelines and the proper management of the patients.

APPENDIX. AUTHORS

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CONFLICTS OF INTERESTS

None declared.

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