Noninvasive cardiovascular imaging for evaluating subclinical target organ damage in hypertensive patients: a consensus article from the European Association of Cardiovascular Imaging, the European Society of Cardiology Council on Hypertension and the European Society of Hypertension*

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Arterial hypertension accounts for the largest amount of attributable cardiovascular mortality worldwide, and risk stratification in hypertensive patients is of crucial importance to manage treatment and prevent adverse events. Asymptomatic involvement of different organs in patients affected by hypertension represents an independent determinant of cardiovascular risk, and the identification of target organ damage is recommended to further reclassify patients’ risk. Noninvasive cardiovascular imaging is progressively being used and continues to provide new technological opportunities to target organ damage evaluation at early stage. The aim of this article is to provide the community of cardiology with an update on appropriate and justified use of noninvasive imaging tests in the growing population of hypertensive patients.

**Keywords:** arterial hypertension, cardiovascular risk, noninvasive cardiovascular imaging, prognosis, target organ damage

**Abbreviations:** AAA, abdominal aorta aneurysm; AS, arterial stiffness; BP, blood pressure; CFR, coronary flow reserve; CV, cardiovascular; EF, ejection fraction; GLS, global longitudinal strain; HTN, hypertension; IMT, intima–media thickness; IVS, interventricular septal thickness; LA, left atrial; LAVi, left atrial volume index; LGE, late gadolinium enhancement; LV, left ventricular; LVFP, left ventricular filling pressure; LVID, left ventricular internal diameter; PWT, posterior wall thickness; RWT, relative wall thickness; TOD, target organ damage

INTRODUCTION

Relevance of hypertension (HTN) continues to rise, and HTN accounts for the largest proportion of attributable cardiovascular mortality worldwide [1,2]. Yet, cardiovascular risk substantially varies among patients with HTN, and current European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines recommend risk stratification in all patients with HTN to allow categorization into four groups of patients from low to very high cardiovascular risk [1]. Information on the level of risk of cardiovascular events may assist in the identification of the threshold for initiation of treatment and target blood pressure (BP) to reach. This possibility, reinforced by the recent SPRINT and HOPE 3 data [3,4], may be useful in the choice of initial treatment strategy (e.g. possible initial use of combination treatment) and may orient on the need for associated treatment (e.g. antiplatelet and lipid-lowering treatment). Subclinical, that is asymptomatic, involvement of different organs represents a key pathophysiological step along the...
continuum between HTN as risk factor and its impact on clinical outcome, being an independent determinant of cardiovascular risk. Thus, to further reclassify patients, especially those at moderate cardiovascular risk from SCORE risk charts, ESH/ESC guidelines recommend assessment of subclinical target organ damage (TOD) at different organ levels (Table 1), as it has been reported that TOD independently predicts cardiovascular outcomes and that multiorgan TOD carries a greater risk compared with single TOD [5,6] (Fig. 1). In addition, evidence of TOD may help to make the choice of the appropriate therapeutic pharmacological strategy in HTN patients. To this purpose, non-invasive cardiovascular imaging is increasingly being used and continues to provide new technological opportunities to assess TOD at increasingly early stage. In this context, information obtained from imaging techniques may be considered as risk modifiers to improve cardiovascular risk prediction and decision-making [7].

Yet, as addressed in HTN guidelines [1], much uncertainty remains on the overall clinical value of TOD assessment. In fact, the independent prognostic value of therapy-induced changes of TOD, assessed by imaging parameters, is still not definitively established mainly due to the retrospective nature of available evidence.

The purpose of the current document is to provide a joint opinion on behalf of the ESC European Association of Cardiovascular Imaging (EACVI), the ESH and the ESC Council on Hypertension that summarizes indications and gaps on the appropriate and justified use of cardiovascular imaging to assess TOD in HTN patients, based on pathophysiological, clinical and technical characteristics, as well as on strengths and limitations of each imaging modality.

IDENTIFICATION OF TARGET ORGAN DAMAGE USING NONINVASIVE CARDIOVASCULAR IMAGING

The identification of TOD through the use of cardiovascular imaging in hypertensive patients starts with a baseline evaluation that includes 12-lead ECG, renal function, urinary protein assessment and transthoracic echocardiography. Then, it continues with an advanced evaluation, including all the other components of the cardiovascular system, as illustrated in Fig. 2 and subsequently reported.

Heart

Echocardiography represents the first and most used imaging technique to assess TOD at the cardiac level. Standard echocardiography is currently used to measure left ventricular wall thickness and internal chamber diameters to quantify left ventricular mass (LVM), determine left atrial size and indexes of left ventricular diastolic function. Limitations of standard echocardiography in quantifying LVM and geometry are recognized as it relies on geometric assumptions and has suboptimal reproducibility. In particular, this disadvantage may prove problematic while obtaining accurate information on LVM changes in individual patients over time [8]. Echo-Doppler measurements of left atrial size and

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**TABLE 1. Subclinical target organ damage in the heart and cardiovascular system [1]**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Echocardiographic evidence of LVH (concentric LVH – RVWd &lt; 0.43 + increased LVM); eccentric LVH – RVWd &lt; 0.43 + increased LVM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>ECG evidence of LVH (Sokolow-Lyon index &gt; 3.5 mV, RavL &gt; 1.1 mV, Cornell voltage duration product &gt; 244 mV/ ms) Echocardiographic evidence of LVH (concentric LVH – RVWd &lt; 0.45 + increased LVM); eccentric LVH – RVWd &lt; 0.45 + increased LVM)</td>
</tr>
<tr>
<td>Cardiovascular system</td>
<td>Carotid wall thickening (IMT &gt; 0.9 mm) or plaque (IMT &gt; 1.5 mm or focal thickness increase of 0.5 mm or 50% of surrounding carotid IMT value)</td>
</tr>
<tr>
<td>Vessels</td>
<td>Carotid–femoral PWV &gt; 10 m/s Ankle–brachial index &lt; 0.9</td>
</tr>
<tr>
<td>Kidney</td>
<td>eGFR 30–60 ml/min per 1.73 m²/BSAa Microalbuminuria (30–300 mg/24h), or albumin–creatinine ratio (30–300 mg/g; 3.4–34 mg/mmol) (preferentially on morning spot urine)</td>
</tr>
<tr>
<td>Brain</td>
<td>Cerebral microvascular disease (lacunar infarcts and white matter hyperintensities at MRI)</td>
</tr>
<tr>
<td>Eye</td>
<td>Hypertensive retinopathy (grades I and II)</td>
</tr>
</tbody>
</table>

*Estimated by MDRD formula.

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**FIGURE 1** From risk factors for hypertension to end-stage hypertensive disease. Evolution from risk factors for hypertension to end-stage hypertensive conditions through the occurrence of different steps: uncomplicated hypertension, asymptomatic hypertensive disease and symptomatic hypertensive disease. "And other vessels abnormalities: carotid–femoral pulse wave velocity more than 10 ms, ankle–brachial index less than 0.9. "Estimated glomerular filtration rate 30–60 ml/min per 1.73 m². "Also with preserved systolic function. "Estimated glomerular filtration rate less than 30 ml/min per 1.72 m², proteinuria more than 300 mg/24 h. "Ischemic stroke, cerebral hemorrhage, transient ischemic attack. HTN, hypertension; LVH, left ventricular hypertrophy.
diastolic function have lower variability [8]. In general, however, the clinical use of all echo-Doppler parameters of cardiac damage in arterial HTN can be somewhat limited by the fact that they are influenced by physiologic and demographic factors including age, sex and ethnicity [9].

Cardiac MRI offers very high spatial resolution and tissue contrast and is considered the gold-standard technique for measurement of cardiac function. However, reduced availability, higher costs than echocardiography, patients’ claustrophobia (about 10% of all cases), and other specific CMR-related contraindications still limit MRI use in clinical practice [10].

Left ventricular mass and geometry

The identification of cardiac organ damage in arterial HTN corresponds traditionally to the identification of left ventricular hypertrophy (LVH) and concentric geometry, which are both caused by increased left ventricular stress due to chronic pressure overload and represent independent hallmarks of cardiovascular risk [1,11,12]. Despite some controversial opinions [13], echocardiography is in general considered to be more accurate than ECG in diagnosing LVH [14,15]. Linear measurements of septal and posterior wall thickness (PWT) and left ventricular internal end-diastolic diameter (by M-mode or direct two-dimensional parasternal long-axis view) allow to calculate LVM using the Devereux cube formula in which LVM = 0.8 × (1.04 × (IVS + LVID + PWT)3 – LVID3) + 0.6, where IVS, interventricular septal thickness and LVID, left ventricular internal diameter [16] (Fig. 3). LVM is commonly normalized for BSA, but this normalization makes it impossible to predict LVM in individuals who deviate from normal body weight, in particular in overweight/obese individuals [17]. The normalization for body height, a good surrogate of fat-free mass, appears to be more acceptable. However, as the relation between LVM (a three-dimensional variable generated by a cubic function) and height (a linear measure) cannot be linear [18], normalizations of LVM for height powered to 2.7 [18] and to 1.7 (in relation with possible

FIGURE 2 Diagnostic algorithm for the assessment of target organ damage [1]. The proposed diagnostic algorithm identifies two steps in the diagnostic evaluation of subclinical target organ damage in hypertensive patients: a baseline assessment (STEP 1), necessary in all hypertensive patients that includes ECG assessment, evaluation of renal function and presence of urinary protein excretion and transthoracic echocardiography (or MRI when echocardiography is technically not feasible). An advanced assessment (STEP 2) to be considered in presence of specific conditions that includes an integrated approach to all components of the cardiovascular system. *To be considered also if imaging of delayed enhancement would have therapeutic consequences. **Depending on costs and availability should be considered in all hypertensive patients, necessary in elderly and long standing hypertension. Examination of the retina is not recommended in mild-to-moderate hypertensive patients without diabetes, except in young patients. CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HTN, hypertension; PWV, pulse wave velocity; TOD, target organ damage.

FIGURE 3 Two-dimensional M-mode echocardiography of the left ventricle for the assessment of left ventricle mass and geometry. Example of M-mode parasternal long-axis view of the left ventricle that allows to measure left ventricle internal diameters and wall thickness and to calculate left ventricle mass and relative wall thickness to assess left ventricle geometry. In this case, both the indexations of left ventricle mass (BSA and height powered to 2.7) fulfill standardized cutoff point values for left ventricular hypertrophy. Relative wall thickness more than 0.43 indicates left ventricle concentric geometry. ASE, American Society of Echocardiography; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; FS, fractional shortening; IVSd/s, interventricular septum in diastole and systole; LV, left ventricle; LVIDd/s, mass ind left ventricular mass indexed for BSA; LVID, mass left ventricular mass; LVIDd, left ventricular internal diameter in diastole and systole; LVMHt, left ventricular mass indexed for height powered to 2.7; LVMHt/s, left ventricular posterior wall in diastole and systole; RWT, relative wall thickness; SV, stroke volume.
influence of sex) have been proposed [19]. Yet, the optimal
LVM indexation remains a controversial issue [19], although
the 2.7 power has more consolidated evidence, derived
from several studies by different research groups. Relative
wall thickness (RWTd = 2 * PWT/left ventricular end-
diastolic diameter) categorizes left ventricular geometry
(concentric or eccentric), being expression of wall-to-
radius ratio. By combining LVM and RWTd, concentric
LVH (RWTd ≥ 0.43 + increased LVM) and concentric remodeling
(RWTd ≥ 0.43 + normal LVM) can be differentiated from
normal left ventricular geometry (RWTd < 0.43 and normal
LVM). Because of a suboptimal categorization of dilated
ventricles, a novel classification, based on LVM, left
ventricular volume and RWTd or LVM/volume ratio, has
been proposed [20]. Using this approach, four distinct
patterns, nondilated ventricles (normal LVM and RWTd),
concentric remodeling or concentric LVH (RWTd ≥ 0.43 +
normal or increased LVM), eccentric remodeling (RWTd
< 0.43) and eccentric LVH (RWT < 0.43 + increased LVM)
can be identified, each with distinct functional and prog-
nostic value [20]. According to Laplace’s law, the first left
ventricular wall that becomes hypertrophic is the interven-
tricular septum. Sometimes, only the basal septum is hyper-
trophic, as the longitudinal fibers of the basal septum have
some of the largest radii among human heart fibers, thus
experiencing the greatest inward component of wall stress.
Moreover, the basal septum is the last part of the ventricle
to be electrically activated, suffering from a further increase
in wall stress due to the contraction of the other left ventricular
segments [21].

Great progress has been obtained by using real-time
three-dimensional echocardiography that provides very
accurate estimation of LVM and of LVM/volume ratio, an
index of concentric geometry primarily utilized by cardiac
MRI. The calculation of LVM by real-time three-dimensional
echocardiography has the advantage that it does not rely on
geometric formulas for calculating left ventricular myocardial
diameter but measures it directly. This allows a better accuracy
and reproducibility in comparison with standard echocar-
diography [22]. Three-dimensional-derived LVM has been
successfully validated with cardiac MRI, and three studies (on
390, 410 and 226 patients, respectively) reported reference
normal values for three-dimensional LVM including also
multiple ethnic groups (American, Japanese and European)
[23–25]. However, American Society of Echocardiography
(ASE)/EACVI does not recommend the clinical use of normal
reference values of three-dimensional LVM because little
information is available on its feasibility and prognostic value
in large population sample size [26]. Moreover, three-dimen-
sional echocardiography is not widely used in clinical prac-
tice and still remains a research tool.

The better cardiac MRI reproducibility in comparison
with echocardiography means that a population sample
size to detect a meaningful change in LVM can be substan-
tially lower (by over 80%) [27,28], allowing for a consider-
brable reduction in duration and costs savings of clinical trials
assessing LVH regression [29].

**Left ventricular diastolic dysfunction**

In early, mild HTN, LVH is usually absent, and the first
manifestation of cardiac organ damage may be left ven-
tricular diastolic dysfunction (LVDD) that is currently
assessed by echo-Doppler examination (Fig. 4). Using
echo-Doppler, LVDD can be detected as transmitral inflow
pattern of left ventricular abnormal relaxation (E/A ratio <1
and prolonged E velocity deceleration time) [30]. However,
over time and in parallel with LVH development, left
ventricular filling pressures (LVFP) can rise as an adaptive response to pressure overload and, before the onset of left ventricular chamber systolic dysfunction, induce symptoms/signs of heart failure (heart failure with preserved ejection fraction) [31]. Under these circumstances, the simple transmitral pattern is not sufficient to diagnose the clinical status but should be combined with further maneuvers (Valsalva) or additional Doppler parameters (pulsed tissue Doppler of mitral annulus and estimated pulmonary pressures by measuring the degree of tricuspid regurgitation by continuous wave Doppler) to detect LVFP increase [30] (Fig. 5). Limitations of this methodology correspond to the fact that Doppler-derived diastolic indices are strongly associated with age [32], a factor that can make it difficult to distinguish between abnormally increased LVFP and the physiological changes of myocardial relaxation due to aging. In addition, they are also influenced by changes in preload and afterload. However, according to the 2016 ASE/EACVI recommendations on diastolic function, in patients with normal ejection fraction, an increase of LVFP can be acknowledged when at least 50% of the following echo-Doppler parameters is above their normal limits: septal \( e' \) velocity less than 7 cm/s, lateral \( e' \) velocity less than 10 cm/s, average \( E/e' \) more than 14, tricuspid regurgitation retrograde velocity more than 2.8 m/s and left atrial volume index more than 34 ml/m\(^2\) [30]. In particular, tissue Doppler-derived \( e' \) velocity is an acceptable marker of myocardial relaxation, and \( E/e' \) ratio is less dependent on aging than other diastolic parameters [30]. Thus, this methodology should be applied to identify abnormally elevated LVFP also in the hypertensive clinical setting.

Cardiac MRI is not routinely used for detection of LVDD and requires a ‘cumbersome analysis’. However, due to its ability of noninvasive tissue characterization by late gadolinium contrast agent, which accumulates in extracellular matrix areas of cell death or increased interstitial space, late gadolinium enhancement (LGE)-cardiac MRI allows detection of myocardial fibrosis [33]. LGE, indicating myocardial fibrosis, is detectable in about half of the hypertensive patients, but LVDD can be present also in patients without LGE [34]. Moreover, T1 mapping, a novel developing parametric cardiac MRI technique that measures relaxation of tissues, appears more sensitive to detect myocardial fibrosis [35]. T1 mapping estimation of extracellular volume has recently shown greater diffuse fibrosis in hypertensive patients with LVH compared with non-LVH hypertensive and control patients [36]. Is it worthy to note that LVDD can be detected in many hypertensive patients without left ventricular concentric geometry [37] and that increased noninvasively estimated LVFP (i.e. high \( E/e' \) ratio) is well correlated with LGE-cardiac MRI extent of myocardial fibrosis.
fibrosis in absence of evident LVH [38]. The advanced speckle tracking echocardiography can also offer functional markers of myocardial fibrosis as serum tissue inhibitor of matrix metalloproteinases correlate with both impaired longitudinal strain rate and left ventricular twisting [39] and circulating biomarkers of collagen turnover are inversely correlated with left ventricular twisting and radial strain [40] in hypertensive patients with normal ejection fraction. These findings strongly suggest that alteration in collagen turnover due to myocardial fibrosis may affect early left ventricular myocardial active relaxation. A direct association between the extent of LGE-derived myocardial fibrosis and the degree of global longitudinal strain (GLS) has been also recently observed in uncomplicated hypertensive patients [38].

Left atrial dimension
Two-dimensional echocardiographic determination of LAVi provides further crucial information when the other echo-Doppler indices of diastolic function give uncertain results, as left atrial dilation (LAVi > 34 ml/m²) represents left atrial response to chronic LVFP increase in hypertensive individuals [30]. In fact, in HTN patients with suspected heart failure with preserved ejection fraction and increased natriuretic peptide levels, presence of left atrial enlargement may confirm the diagnosis, according to ESC guidelines on acute and chronic heart failure [42].

Left ventricular systolic function
Ejection fraction at rest may not identify subclinical systolic dysfunction in patients with HTN, and echocardiographic measurement of ejection fraction is subjected to substantial intraobserver and interobserver variability compared with cardiac MRI [10]. To assess systolic function, midwall fractional shortening, an estimate of myocardial mechanics of circumferential midwall fibers, obtainable by mathematical model from linear measures of left ventricular cavity size and wall thickness at end-diastole and end-systole, has been proposed [43]. However, this measurement is quite complex and not widely used in clinical practice. The new developed three-dimensional speckle tracking echocardiography represents a valuable tool for detection of HTN-related subclinical systolic dysfunction and allows estimating the different directional strain components in the beating heart. Speckle tracking echocardiography abnormalities of left ventricular longitudinal, circumferential and radial strain as well as twisting have been largely reported in uncomplicated hypertensive patients. However, due to its very high feasibility and excellent reproducibility [44], the quantification of GLS [45], that is the relative left ventricular length change between end-diastole and end-systole, should be preferred in this clinical setting (Fig. 6). GLS has been standardized in absolute values, and normal reference values of GLS have been identified (≥20%) [16,45]. GLS also showed superiority in comparison with ejection fraction to characterize left ventricular systolic dysfunction in a population of patients with heart failure preserved ejection fraction with a large proportion of arterial HTN [46]. Moreover, GLS is able to unmask early subclinical systolic dysfunction of newly diagnosed hypertensive patients without LVH [47], even in prehypertensive stages [48] when ejection fraction and other strain components are still normal. Thus, GLS measurement can detect asymptomatic subclinical left ventricular dysfunction in hypertensive [49] patients, although its routine clinical application may be in part limited by the intervendor variability of its measurements [44]. An additional parameter, global area strain, has also been proposed, comprehensive of both subendocardial and midwall function and potentially suitable to identify early cardiac organ damage in hypertensive heart [50]. However, three-dimensional speckle tracking echocardiography has been studied in populations of limited sample size. It represents, therefore, a research technique, currently far from routine clinical use.

To assess left ventricular function, and specifically to measure left ventricular ejection fraction, cardiac MRI provides better accuracy and reproducibility compared with echocardiography and should be preferentially used in patients with poor acoustic window [10].
Myocardial ischemia
ESC guidelines, among indications for TOD search, recommend the search of myocardial ischemia in hypertensive patients with suspected history of coronary artery disease. Diagnosis of myocardial ischemia in hypertensive patients is particularly challenging because HTN substantially lowers the specificity of exercise ECG and perfusion scintigraphy [51,52]. When exercise-EKG is either uninterpretable or ambiguous, an imaging test of inducible ischemia such as perfusion scintigraphy [53], stress echocardiography [54] or stress cardiac MRI [55] is warranted. Among imaging tests, stress echo has been shown to have higher specificity but reduced sensitivity compared with SPECT perfusion imaging [56]. In fact, stress-induced wall motion abnormalities are highly specific for angiographically detectable epicardial coronary artery stenosis, whereas myocardial perfusion abnormalities are frequently found in hypertensive patients with angiographically normal coronary arteries and coronary microvascular disease [1,10].

Table 2 summarizes the main echocardiographic parameters (and their cutoff values of abnormalcy) of cardiac damage in arterial hypertension.

Table 2. Echocardiographic parameters (and their cutoff values of abnormalcy) of cardiac damage in arterial hypertension

<table>
<thead>
<tr>
<th>Echo parameter</th>
<th>Type of cardiac damage</th>
<th>Abnormal if</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVM/BSA (g/m²)</td>
<td>LVH</td>
<td>≥95 W, &gt;115 M</td>
</tr>
<tr>
<td>LVM/Height (g/m²)²</td>
<td>LVH</td>
<td>≥47W, &gt;50M</td>
</tr>
<tr>
<td>RVWTd</td>
<td>LV concentric geometry</td>
<td>≥0.43</td>
</tr>
<tr>
<td>Septal annular e’ velocity (cm/s)</td>
<td>LVDD</td>
<td>&lt;7</td>
</tr>
<tr>
<td>Lateral annular e’ velocity (cm/s)</td>
<td>LVDD</td>
<td>&lt;10</td>
</tr>
<tr>
<td>E/e’ average ratio</td>
<td>Elevated LVFP</td>
<td>&gt;14</td>
</tr>
<tr>
<td>LAVi (ml/m²)</td>
<td>Elevated LVFP</td>
<td>&gt;34</td>
</tr>
<tr>
<td>GLS (%)</td>
<td>LV systolic dysfunction</td>
<td>&lt;20°</td>
</tr>
</tbody>
</table>

GLS = global longitudinal strain; LAVi, left atrial volume index; LV, left ventricular; LVDD, left ventricular diastolic dysfunction; LVFP, left ventricular filling pressure; LVH, left ventricular hypertrophy; LVM, left ventricular mass; M, men; RVWTd, relative diastolic wall thickness; W, women.

*Despite technically expressed by negative values, GLS is considered as “positive” (sign +) to strengthen its physiopathologic and clinical meaning: the higher the values, the better the strain deformation independent of the plus/minus sign (according to Lang et al. [6]).

Cardiovascular system

Vessels
The presence of vascular damage at subclinical, asymptomatic stages can identify a ‘vulnerable’ patient and help to improve prevention strategies. Increased intima–media thickness (IMT) of the common carotid artery (normal value <0.9 mm), easily measurable by vascular ultrasound, is a well known marker of HTN-induced vascular damage, whereas presence of plaque can be identified by an IMT at least 1.5 mm or by a focal thickness increase of 0.5 mm or 50% of surrounding carotid IMT value [1]. However, lack of standardization regarding the definition and measurement of IMT, its high variability and low intra-individual reproducibility have raised concerns regarding its clinical value. Arterial stiffness is one of the earliest detectable adverse structural and functional modifications of the vessel walls. Arterial stiffness results from a degenerative process affecting mainly the extracellular matrix of elastic arteries and is mainly influenced by aging and risk factors, particularly arterial HTN [58]. Moreover, arterial distensibility may be further impaired by functional factors, as observed in hypertensive current and ex-smokers [59]. Changes in extracellular matrix proteins and in vascular mechanical properties may activate several mechanisms also involved in the arterial microscismic process. Noninvasive methods to estimate large-vessel arterial stiffness include carotid–femoral pulse wave velocity (PWV), the reference for aortic stiffness estimate that can be determined as the time delay derived from either pressure (tonometry) or ultrasound (pulsed Doppler) techniques, and local distensibility measures of superficial arteries such as carotid and femoral [58]. Measures of arterial stiffness, such as aortic distensibility and PWV, can also be evaluated by phase-contrast MRI [60]. A meta-analysis showed that arterial stiffness predicts cardiovascular events and improves risk classification. However, the value of this conclusion was offset by evidence of substantial publication bias [61]. Abnormal vasoreactivity due to endothelial dysfunction is commonly observed in hypertensive patients, in whom it contributes, together with arteriolar remodeling, to microvascular dysfunction [62]. Vascular endothelial-derived nitric oxide function can be assessed either in the peripheral arteries by flow-mediated vasodilation [63] or in coronary vessels by vasodilator changes of CFR [54]. Several studies investigated markers of vascular disease in arterial HTN by ultrasound, whereas more data are needed to establish the clinical value of MRI for the evaluation of vessel damage in HTN. However, independently on the technique used, the clinical value of endothelial function assessment in hypertensive patients is not established, and, therefore, endothelial function assessment should not be routinely part of TOD assessment in HTN.

Elevated BP has been also associated with increased aortic wall thickness, aortic diameters and plaque extent in both thoracic and abdominal aorta [20]. HTN-induced aortic root dilatation predicts subsequent development of
Coronary artery calcium

Coronary artery calcium can be detected through multislice computed tomography and identifies subclinical coronary atherosclerosis. However, it must be emphasized that absence of coronary artery calcifications does not exclude atherosclerosis and that the presence of calcium does not correlate with the instability of the atherosclerotic lesions. Prevalence and severity of coronary calcium are higher in patients affected by HTN compared with normotensive patients [66]. In fact, high BP and its duration promote coronary calcium accumulation, in parallel with peripheral atherosclerosis [67].

Kidney

The evaluation of TOD at the kidney level is commonly obtained by the estimation of glomerular filtration rate (eGFR) and microalbuminuria in all hypertensive patients. Nuclear imaging techniques, that is renal sequential scintigraphy, can be used to assess renal function, whereas MRI is able to evaluate the gross morphology of the kidneys and renal arteries, enabling planning of renal denervation and identifying renal artery stenosis as a secondary cause of arterial HTN. However, none of them is currently recommended to assess subclinical kidney damage in hypertensive patients [1]. MRI T1 relaxation time to assess parenchymal structure [68] and MRI arterial spin labeling to measure renal tissue perfusion [69] are new promising techniques that may complement in the future the standard assessment of TOD at the kidney level.

Brain

HTN is associated with neurological deterioration, cognitive impairment and depression in the elderly. This association appears to be mediated in part by cerebral microvascular disease that is commonly detected by MRI (up to 40% of patients) in the form of lacunar infarcts (10–30% of patients) and white matter hyperintensities. These latter are seen in almost all elderly hypertensive patients and are predicted by the severity and duration of HTN [70,71]. More recently, microbleeds, representing an additional type of brain asymptomatic damage, have been identified in up to 5% of hypertensive patients. Adequate antihypertensive treatment may reduce the progression of white matter lesions [72], but the clinical value of this observation is uncertain. There is currently no indication for routine use of brain imaging to detect subclinical brain damage in hypertensive patients. However, MRI assessment of brain damage should be performed in elderly patients with neural deterioration, especially memory loss [1].

Eye

Hypertensive retinopathy refers to retinal microvascular signs that develop in response to increased BP. HTN is also a major risk factor for the development of other retinal vascular diseases, such as retinal vein and artery occlusion, and ischemic optic neuropathy [73]. The classification of hypertensive retinopathy is based on fundoscopy, and grade III (retinal hemorrhages, microaneurysms, hard exudates and cotton wool spots) and grade IV retinopathy (grade III signs and papilloedema and/or macular edema) are indicative of a severe form of retinopathy that predicts mortality [74]. HTN is known to be associated with an increase in the wall-to-lumen ratio of retinal arterioles [75]. Interestingly, it has been demonstrated that retinal arterioles wall-to-lumen ratio assessed noninvasively by scanning laser Doppler flowmetry is closely related to the media-to-lumen ratio measured with myography in vitro, which allows an invasive evaluation of the microvasculature, demonstrating that changes of the retinal arterioles mirror those of subcutaneous small arteries [76].

Key messages: identification of target organ damage using noninvasive cardiovascular imaging – heart

A comprehensive approach to cardiac TOD evaluation in patients with HTN should includes:

1. assessment of left ventricular geometry and left ventricular mass (LVM/BSA (g/m²) abnormal LVM > 95 W, > 115 M; LVM/height (g/m²) abnormal LVM > 47 W, > 50 M, especially when overweight is present; RWTd normal value, 0.43)
2. analysis of left ventricular diastolic function and LVFP
3. quantification of GLS (normal value >20%)
4. search for myocardial ischaemia in hypertensive patients with suspected history of coronary artery disease

Key messages: identification of target organ damage using noninvasive cardiovascular imaging – cardiovascular system

1. Ultrasound examination of carotid arteries is recommended to assess:
   a. carotid IMT (normal value <0.9 mm) as an early marker of vessel damage
   b. carotid plaque identified by an IMT ≥ 1.5 mm or by a focal thickness increase of 0.5 mm or 50% of surrounding carotid IMT value
2. HTN is associated with frequent asymptomatic brain damage and brain imaging by MRI should be considered in elderly patients with HTN and neural involvement
3. Fundoscopy should be performed in patients with severe and/or resistant HTN
4. Elevated BP is associated with increased aortic wall thickness, aortic diameters, and plaque burden in both thoracic and abdominal aorta and ultrasound evaluation of abdominal aorta should be performed in all severe long standing adult hypertensive patients
5. Coronary calcium score may be considered in patients at intermediate SCORE risk
6. No current indication for imaging of the kidney to detect subclinical damage

PROGNOSTIC IMPLICATIONS OF IMAGING-DETECTED TARGET ORGAN DAMAGE

As reported by Devereux and Alderman [77] about 20 years ago, presence of TOD attributable to HTN is a sign of ‘preclinical cardiovascular disease’ (Fig. 1) and can be considered as a bridge between exposure to cardiovascular risk factors and occurrence of cardiovascular events.
Heart

Cardiac morphologic adaptation

LVM is a predictor of adverse outcome in arterial HTN beyond SCORE prediction, evidence that has been produced with conventional standard two-dimensional echocardiography and confirmed with more accurate technologies [78,79]. In 2009, an appraisal document of the ESH reported evidence indicating that LVH is associated with a risk of cardiovascular events exceeding 20% in 10 years, thus identifying patients at high cardiovascular risk [80]. The integrated evaluation of LVM and geometry is useful to understand the surrounding hemodynamic pattern, but its utility in terms of improving risk profiling remains uncertain because the progressively increasing severity of the different left ventricular geometric patterns parallels a corresponding increase in LVM [78,79,81]. Thus, assessment of echocardiographic LVH may assist risk stratification beyond conventional risk assessment, mostly in patients at intermediate SCORE risk [6,80,82].

The recent recommendations of EACVI and ASE on the use of echocardiography in adult HTN [21] report a range of definitions of LVH from mild-to-severe degree, which would theoretically allow graduating risk prediction, though there is no evidence that this stratification helps risk assessment, compared with a clear-cut definition of LVH [78].

Left atrial dimension, assessed as anteroposterior diameter [83] or, better as left atrial volume, is an additional prognosticator of cardiovascular events [84]. However, because of the close dependence of left atrial size from diastolic function and the correlation with LVM, the independence of its prognostic impact remains uncertain [83].

Left ventricular systolic function

The dependency of ejection fraction on left ventricular geometry limits its value for the prediction of cardiovascular risk in hypertensive patients, especially in those exhibiting left ventricular concentric geometry [84]. Midwall shortening is an left ventricular geometry-independent estimate of wall mechanics and is significantly associated with adverse cardiovascular events [85,86]. GLS was associated with hospitalization for heart failure (HF) in the TOPCAT trial [87], a cohort with a very high prevalence of arterial HTN, yet its prognostic value for routine clinical use remains currently undefined. A very recent study has also observed that GLS deterioration is associated with major adverse cardiac events in asymptomatic hypertensive patients, a finding that warrants to assess in future studies the incorporation of GLS for predicting cardiovascular risk in hypertensive heart disease [88].

Left ventricular diastolic function

Left atrial dimension is an accurate marker of chronic diastolic dysfunction and can be used also as a prognosticator of diastolic function in the absence of mitral valve functional abnormalities [89]. The E/A ratio is associated with adverse cardiovascular events [90] and so is left atrial systolic force [91], but the associations are not linear. Low or high values (documenting prolonged left ventricular relaxation or increased late left ventricular stiffness) predict adverse outcome, and partition values have been proposed for the E/A ratio [90]. The limitation of this parameter relies on the close dependence on age and heart rate (HR) that should be accounted for [92].

Tissue Doppler imaging allows estimating LVFP, correlates with wedge pressure and is associated with cardiovascular fatal and nonfatal events [93,94]. In the ASCOT study, the ratio E/′ a has been reported to significantly add to predict prognosis beyond clinical risk factors and remained independently associated with prognosis when LVM and left atrial size were included in the model [95]. However, this finding needs confirmation in larger studies with sufficient statistical power.

In summary, despite the association between several echocardiography-derived parameters of cardiac morphology and function and cardiovascular events, LVH currently remains the only established cardiac imaging-derived risk modifier in patients with HTN.

Cardiovascular system

Vessels

BP is the most powerful determinant of carotid IMT, and the relationship is apparent from childhood and is related to several BP characteristics, especially SBP and pulse pressure [96]. The relationship between carotid IMT and cardiovascular risk is continuous, but for clinical purposes, a threshold value of more than 0.9 mm has been adopted by many as the value indicative of increased cardiovascular risk [97,98]. Carotid plaque represents evidence of vascular disease and is strongly predictive of cardiovascular events [6,95,99,100]. However, when increased carotid IMT is coexisting, then they seem to add little to each other in predicting cardiovascular events or in reclassifying the patient’s cardiovascular risk [100]. Furthermore, a recent meta-analysis concluded that the addition of IMT to conventional cardiovascular risk estimation using the Framingham risk score did not substantially affect reclassification of cardiovascular risk [101] nor was it associated with little improvement in 10-year risk prediction of first-time myocardial infarction or stroke [102].

Thus, the most useful setting for carotid screening and measurement of IMT in refining cardiovascular risk classification may come in patients at low or intermediate risk [103], or even more in young adults, that is less than 45 years, who are not yet eligible for standard cardiovascular risk screening [104].

Arterial stiffness has also been associated with increased cardiovascular risk [6,105]. A meta-analysis of 17 studies reported an almost two-fold increased risk of cardiovascular events, cardiovascular mortality and all-cause mortality in patients with increased aortic PWV, demonstrating a higher predictive ability of arterial stiffness as in patients with a higher baseline cardiovascular risk (coronary artery disease, renal disease, HTN and diabetes).

Coronary artery calcium is recognized as an independent predictor of cardiovascular events and mortality, whereas absence of coronary calcium is associated with a very high negative predictive value[66]. Yet, the role for risk stratification of uncomplicated HTN is not well defined. In fact, the inclusion of coronary calcium into prediction models mainly improves risk stratification of hypertensive patients at
null
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TABLE 3. Sensitivity to detect treatment-induced changes, time to change and prognostic value of asymptomatic target organ damage

<table>
<thead>
<tr>
<th>Method of TOD assessment</th>
<th>Sensitivity for changes</th>
<th>Time to change</th>
<th>Prognostic value of changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVH/echo</td>
<td>Moderate</td>
<td>Short-term (&gt;6 months)</td>
<td>Yes</td>
</tr>
<tr>
<td>LVH/cardiac MRI</td>
<td>High</td>
<td>Short-term (&gt;6 months)</td>
<td>Not available</td>
</tr>
<tr>
<td>Cardiovascular system</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carotid IMT</td>
<td>Very low</td>
<td>Long-term (years)</td>
<td>No</td>
</tr>
<tr>
<td>Carotid plaques</td>
<td>Very low</td>
<td>Long-term (years)</td>
<td>No</td>
</tr>
<tr>
<td>White matter lesions</td>
<td>Very low</td>
<td>Long-term (years)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

LVH, left ventricular hypertrophy; TOD, target organ damage.

normotensive patients (17%) [121]. Some data exist that favor use of ARBs, but the evidence is based on small studies. Beyond the established prognostic impact of TOD, the relationship between TOD modifications and prognosis represents a key issue in the management of patients with HTN. In fact, evidence that changes of TOD reflect the modification of cardiovascular risk status in individual patients would impact on several aspects of follow-up, including re-evaluation programing of diagnostic tests, therapeutic modifications driven by TOD sequential assessment and costs [1] (Table 3).

Changes in LVM and morphology assessed by echocardiography and induced by treatment are related to the effects on risk for cardiovascular events. Several studies have demonstrated a reduction in the risk of mortality, stroke, coronary events or congestive HF among hypertensive patients who reduce LVM [121]. However, intraoperator and interoperator variability of linear echocardiographic measurements needed to quantify LVM should be acknowledged, and, to be considered as a true change, LVM requires a variation of at least 10% or better 20%, which approximately equals 1 SD. In the echocardiographic substudy of the LIFE trial, there was decrease of about 20% of the primary end point for 1 SD of reduction of LVM (i.e. 25 g/m²). In that study, it was also shown that left atrial dimension paralleled the changes in LVM, suggesting the possible mechanism by which changes in LVM are associated with changing risk of developing atrial fibrillation. Moreover, it has been also shown that changes of left ventricular geometry during treatment may have additional prognostic significance in patients with and without LVH [122], being persistence or development of concentric hypertrophy the most adverse situation. Worthy of note, in the LIFE study, antihypertensive treatment in patients with HTN and ECG LVH resulted in significant improvement in transmitial flow patterns but was not associated with reduced cardiovascular morbidity and mortality; however, normal in-treatment left ventricular filling was strongly associated with a reduced risk for hospitalization for HF [123].

At variance with echocardiography, no cardiac MRI prognostic studies neither changes with treatment assessed with MRI are available in hypertensive patients free of coronary artery disease. Treatment-induced vascular changes in the carotid artery wall, thickness and plaques or other territories are less useful for follow-up as the changes over time are minimal and difficult to assess accurately. In fact, there is strong evidence that BP lowering reduces carotid IMT progression, but there is no evidence that regression of IMT is predictive of reduced risk of cardiovascular events [98]. Two large meta-regression analyses, one in patients enrolled in randomized clinical trials (and therefore subjected to most accurate evaluation of IMT changes) [124] and one in patients enrolled in longitudinal observational studies (PROG-IMT) [125], consistently reported that changes of IMT did not correlate with cardiovascular events in patients undergoing antihypertensive treatment, although baseline IMT values provided effective risk stratification [125]. Thus, serial evaluation of IMT should not be performed in HTN patients with the aim of monitoring their cardiovascular risk over time. Data on the prognostic value of carotid plaque modification induced by therapy are more scanty. Interestingly, in a study that followed up, for a median of 3.17 years, high-risk patients with evidence of carotid plaques at baseline, changes of total plaque volume but not of IMT at 1 year predicted subsequent major cardiovascular events [126].

The prognostic value of changes of hypertensive retinopathy assessed by fundoscopy has been assessed in a 15 years follow-up of 124 patients, in whom reduction in BP by 30 mmHg was accompanied by a regression of media-totolumen ratio of subcutaneous small arteries, and changes of arteriolar structure were associated with incidence of cardiovascular events [127]. Doppler flowmetry of retinal arterioles correlates with media-totolumen ratio of subcutaneous small arteries, but it is currently unknown whether noninvasively detected changes of microvasculature may predict changes of cardiovascular risk status in hypertensive patients.

GAPS IN EVIDENCE AND FUTURE PERSPECTIVES

Technical progress and growing biomedical data have made noninvasive bioimaging an effective approach to the identification and quantification of TOD in untreated and treated hypertensive patients, with a fundamental position in the modern management of this condition as well as of its sequelae. However, several aspects of imaging use remain insufficiently clarified and in need of future studies. First, the clinical value and cost-effectiveness of TOD assessment at different organ levels in a given patient remains undetermined. In fact, although a statistically significant correlation between damage of different organs has been reported, many patients develop, for unknown reasons, substantially different degrees of damage in different organs. Thus, it would be important to determine, via
prospective studies, the relationship among bioimaging-assessed cardiac, vascular and cerebral damage, and the value of multiorgan damage assessment for characterization and management of HTN patients. It would be also relevant to prospectively assess treatment-induced BP reductions at which their regression is maximal and normalization possibly achieved. In addition, following the initial disappointing results, studies should also be resumed on the possibility of an accurate bioimaging identification of the tissue components that accompany organ damages such as LVH and large artery wall thickening because the adverse prognostic consequences of either abnormality may importantly depend on the amount of fibrotic tissue growth. Finally, and most importantly, future studies are needed to dispose of a current major criticism, that is that evidence of the prognostic value of treatment-induced changes in TOD is inadequate because based on nonrandomized comparisons of patients with greater or lesser TOD regression, and thus open to the confounding of possible baseline inequalities. This will require outcome-based randomized trials in patients with LVH or other bioimaging-quantifiable damages in whom treatment is guided by their regression rather than on, or in addition to, BP reduction. In addition to improving knowledge on the effects of treatment on prognostically relevant organ damage, the results will provide strong evidence on whether and to what extent organ damage regression increases patient protection and reduces residual risk.

CONCLUSION
A thorough evaluation of TOD has become a key step in the initial management of patients with HTN. Presence of TOD identifies patients at high cardiovascular risk and has relevant impact on therapeutic strategies. Along this process, noninvasive cardiovascular imaging is being increasingly used, and innovative imaging techniques are on the way that might further refine risk stratification and provide opportunities to better target therapeutic strategies. Future research is warranted to assess the impact on outcome and the cost-effectiveness of noninvasive cardiovascular imaging in hypertensive patients.

ACKNOWLEDGEMENTS
The article was reviewed by members of the 2014–2016 EACVI Scientific Documents Committee.
EACVI reviewers included Dr Victoria Delgado, Prof Bernard Cosyns, Dr Massimo Lombardi, Prof Patrizio Lancellotti, Dr Denis Muraru, Dr Philipp Kauffmann, Prof Nuno Cardim, Prof Kristina Haugaa and Dr Andreas Hagendorff.

Conflicts of interest
There are no conflicts of interest.

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