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ABOUT COVER

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Diagnostic and prognostic value of cardiac imaging in amyloidosis

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Abstract

Amyloidosis is an infiltrative disease caused by extracellular protein deposition that has accumulated a lot of scientific production in recent years. Different types of amyloidosis can affect the heart. Transthyretin amyloidosis and light chain amyloidosis are the two most common types of cardiac amyloidosis. These entities have a poor prognosis, so accurate diagnostic techniques are imperative for determining an early therapeutic approach. Recent advances in cardiac imaging and diagnostic strategies show that these tools are safe and can avoid the use of invasive diagnostic techniques to histological confirmation, such as endomyocardial biopsy. We performed a review on the diagnostic and prognostic implications of different cardiac imaging techniques in cardiac amyloidosis. We mainly focus on reviewing echocardiography, cardiac magnetic resonance, computed tomography and nuclear imaging techniques and the different safety measurements that can be done with each of them.

Key Words: Cardiac imaging techniques; Transthyretin cardiac amyloidosis; Immunoglobulin light-chain amyloidosis; Echocardiography; Magnetic resonance imaging; Nuclear imaging

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Core Tip: Cardiac amyloidosis is a disease with a poor prognosis. However, in recent years, specific therapies have been developed. When implemented in the early stages of the disease, they are associated with an improvement in the quality of life and survival. The use of cardiac magnetic resonance, echocardiography, computed tomography and nuclear imaging techniques allows an early diagnosis. In this review, we define in detail the implication of each imaging technique in cardiac amyloidosis.

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INTRODUCTION

Amyloidosis is a systemic infiltrative disease characterized by extracellular amyloid deposition, which causes a structural and functional alteration at different organs. Amyloid comes from up to 30 different types of misfolded precursor proteins. Only five directly affect the heart: Light chain, transthyretin, apolipoprotein A, fibrinogen and serum amyloid-protein A; Although, most cases of cardiac amyloidosis (CA) will be caused by the first two proteins^[1]. The different proteins involved allow classifying the different types of amyloidosis, which have different clinical expression, prognosis and treatment.

Light chain amyloidosis (AL) is a plasma cell dyscrasia characterized by inappropriate production of only one type of light chain. Deposition of these proteins can be evidenced not only in the heart but also in the kidneys, nervous system, gastrointestinal system and soft tissues^[2].

Transthyretin amyloidosis (ATTR) originates from the accumulation of transthyretin (a transporter molecule for thyroxine and retinol-bound protein) that mainly comes from the liver and whose principal deposit is limited to cardiac tissue, soft tissues and the nervous system^[3]. Within this type of amyloidosis, two subtypes are classified based on the presence or absence of a mutation in the transthyretin gene: Variant transthyretin amyloidosis (ATTRv) and wild-type transthyretin amyloidosis (ATTRwt).

The early diagnosis of this pathology is essential due to its worse prognosis when it affects the heart and the existence of treatments that can modify the evolution of these patients^[4].

This review aims to describe the different imaging tools for CA diagnosis and the prognostic value of the different approaches.

EPIDEMIOLOGY

For years, AL has been considered the most frequent subtype of amyloidosis. However, an increase in ATTR diagnoses has been evidenced recently. The incidence of AL is estimated to be around three to five patients per million per year^[5]. The overall prevalence of ATTRv is around 5000-10000 persons, although it is endemic in areas such as Portugal, Sweden or specific areas of Japan^[6]. The controversy started when trying to define the prevalence of ATTRwt. Classically it was considered a rare disease; however, a prevalence of 16% has been observed in patients with severe aortic stenosis undergoing transcatheter aortic valve replacement^[7], 13.3% in patients hospitalized with heart failure with preserved ejection fraction and left ventricular hypertrophy (LVH) greater than or equal to 12 mm^[8] and up to 25% in autopsies of patients > 85 years^[9]. These results imply that it is an underdiagnosed disease, especially in older people.

Both subtypes show high morbidity and mortality in the short term. For ATTR-CA,

the TRACS study found a median survival from diagnosis of 25.6 mo for ATTRv and 43.0 mo for ATTRwt^[10]. Likewise, cardiac involvement in AL (found in up to 50%-70% of patients^[11]) determines a worse prognosis with a median survival of 6 mo in patients with heart failure and untreated disease^[12,13].

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Amyloid can infiltrate any cardiac structure. Mainly, the deposit occurs in both ventricular walls increasing wall thickness, progressively altering the ventricular compliance and generating diastolic dysfunction. Also, amyloid can infiltrate the atrial walls, heart valves and conduction tissue. Clinically it can manifest as heart failure, cardiac conduction alteration, valve dysfunctions or with supraventricular arrhythmias such as atrial fibrillation.

As previously exposed, CA is a systemic disease that can involve multiple organs. ATTR-CA can cause glaucoma due to eye protein deposition. In the nervous system it causes varying degrees of ascending symmetric sensory-motor polyneuropathy (mainly ATTRv) and sometimes affecting the autonomic nervous system causing dysautonomia with orthostatic hypotension, erectile dysfunction, urinary incontinence and gastrointestinal symptoms. A greater predisposition to deposit protein in soft tissues frequently causing carpal tunnel syndrome (even bilateral), lumbar canal stenosis due to deposit in the yellow ligament, atraumatic rupture of the biceps tendon (Popeye's sign on physical examination), quadriceps tendon rupture and Dupuytren's contracture^[1,3] has been observed in ATTRwt.

The deposits of the monoclonal protein in LA can affect not only the organs previously described but also the kidney. It causes monoclonal gammopathies of renal significance that leads from the development of a nephrotic syndrome to kidney failure. In 5% of patients, gastrointestinal deposits cause clinical manifestations of gastrointestinal malabsorption, and in 15% of patients the deposit is in the liver with the development of hepatomegaly/splenomegaly and different grades of organ dysfunction^[2].

Classically, diagnosis of CA required pathological confirmation of amyloid deposition in the myocardium obtained through endomyocardial biopsy. However, thanks to the algorithm published in 2016 that joins the determination of monoclonal proteins in blood and urine together with the performance of a ^{99m}Tc-labeled phosphate scintigraphy, it is possible to perform the noninvasive diagnosis of patients with ATTR-CA^[8,14]. Nowadays, different hospital protocols have adapted the algorithm published by an expert consensus in order to reduce the invasive approach (Figure 1).

CARDIAC IMAGING

Cardiac imaging is playing an increasingly important diagnostic and prognostic role in amyloidosis. It allows reducing the invasive approach thus decreasing the number of endomyocardial biopsies performed to confirm the diagnosis. In this review we analyze the different cardiac imaging tools.

ECHOCARDIOGRAPHY

Transthoracic echocardiography (TTE) is an accessible and harmless technique for the patients, so it is usually the first study performed to rule out cardiac involvement in amyloidosis.

As previously described, amyloid deposition causes thickening of both ventricles. The characteristic pattern was defined as concentric; however, in several studies different patterns such as the asymmetric septal were observed^[15]. Multiple studies suggest that the measurement of 12 mm or more in the long parasternal axis at the level of the interventricular septum, in the absence of alternative causes of LVH, is the cut-off point for suspecting CA^[16]. The appearance of the left ventricle (LV) wall has been classically described with the term "sparkling." However, it is not diagnostic of CA because multiple situations can simulate this appearance.

Other findings that can be observed in CA are valve or interatrial septum thickening, biatrial dilatation and mild pericardial effusion. Valve involvement, objectified in the mitral and tricuspid valves in 50% of patients and in the aortic valve

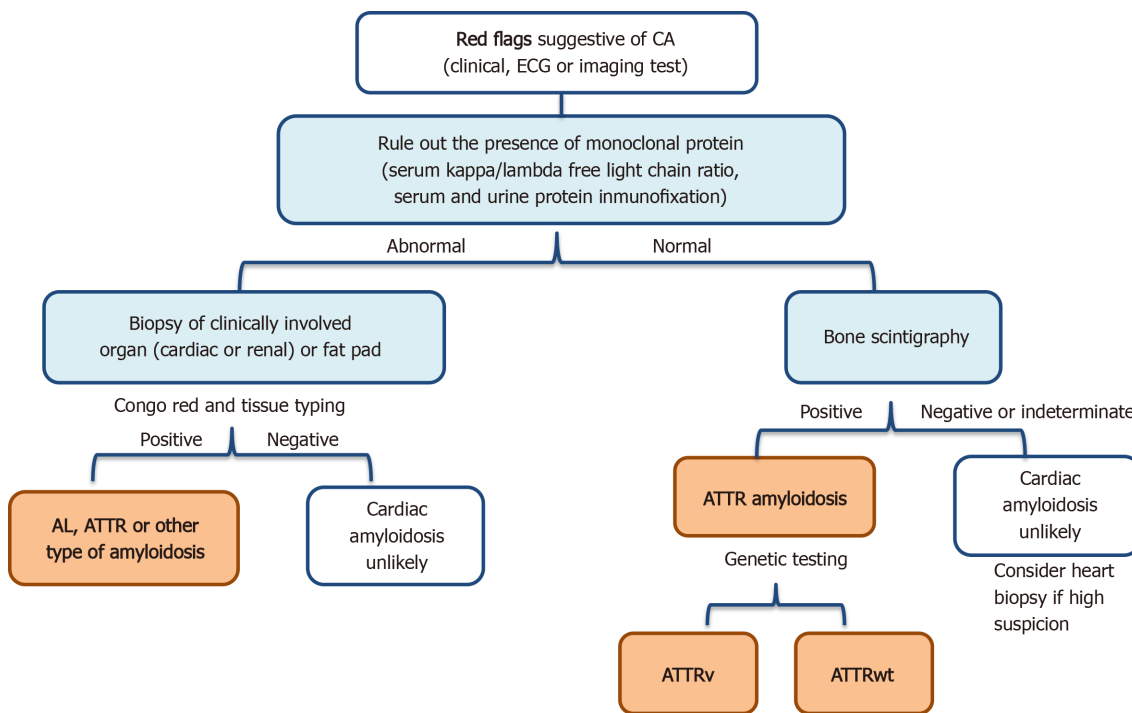


Figure 1 Algorithm for diagnostic patients with suspected cardiac amyloidosis^[78]. AL: Light chain amyloidosis; ATTR: Transthyretin amyloidosis; ATTRv: Variant transthyretin amyloidosis; ATTRwt: Wild-type transthyretin amyloidosis; CA: Cardiac amyloidosis; ECG: Electrocardiogram.

in 25%, has been related to a more advanced New York Heart Association functional class, lower left ventricular ejection fraction (LVEF) and was associated with reduced 5-year survival^[17].

At first, it is important to use conventional ultrasonography. It allows us to obtain a high suspicion of amyloidosis. With conventional TTE, there are parameters that guide the differentiation between CA and hypertrophic cardiomyopathy (HCM). For example, in HCM, LVH is usually severe and asymmetric, generating an obstructive gradient in the outflow tract. However in CA, LVH is usually concentric, not so severe, without an obstructive gradient and sometimes with sparkling. Likewise, interatrial, pericardial involvement and the apical sparing are usually rare in HCM unlike in CA^[18].

Diastolic function is impaired and in the advanced stages it presents a restrictive filling pattern. The deceleration time of transmitral E wave, E/A ratio of transmitral flow and D/S ratio of pulmonary venous flow were independent predictors of overall death^[19].

Functional assessment of the LV can be carried out in different ways. CA predominantly affects diastolic function; thus it was traditionally related to normal or slightly depressed LVEF values. However, it has recently been observed in different series that up to 50% of patients with ATTRwt-CA had LVEF < 50%^[20]. Small variations in LVEF may imply large myocardial amyloid deposits. For this reason, other parameters have been evaluated to detect early alterations in the correct functioning of the LV with low cardiac amyloid burden. In AL-CA patients with normal LVEF but symptomatic and with high cardiac biomarker values, parameters such as stroke volume index < 33 mL/min, myocardial contraction fraction (MCF) (calculated as a ratio between LV stroke volume and LV myocardial volume) < 34% and cardiac-index < 2.4 L/min/m² determine a higher mortality. Moreover, these measurements are altered before LVEF, so they provide earlier information^[21]. Myocardial dysfunction from amyloidosis can prolong pre-ejection period leading to reduced ejection time, and its measurement has shown an important prognostic implication. The cut-off ≤ 240 ms had a specificity of around 90% in predicting 1-year cardiac mortality in AL-CA patients^[22,23].

Right ventricle (RV) involvement has been studied as a prognostic factor in the evolution of the disease. It was observed that a ventricular area ratio ≤ 2 predicts survival in AL-CA patients^[24]. In both AL-CA and ATTR-CA, reductions in RV fractional shortening, tricuspid annular plane systolic excursion (TAPSE), tissue Doppler systolic velocity and global RV longitudinal strain have been described. Of them, only TAPSE < 14 independently predicted 6 mo major adverse cardiac events^[25].

Therefore, a simple technique such as measuring TAPSE is particularly useful in the prognostic evaluation of the disease.

Diastolic dysfunction progressively generates biatrial dilation, and it has been shown that patients with higher N-terminal pro b-type natriuretic peptide (NT-proBNP) and troponin values presented larger indexed 3D left atrial volumes and lower 3D left atrial total emptying fraction. A cut-off of 3D left atrial total emptying fraction < 34% combined with worse 3D peak atrial longitudinal strain had significantly lower 2-year survival^[26].

Longitudinal (LS) and radial strain total values are reduced in CA. Phelan *et al*^[27] described the regional variations in LS from base to apex in CA patients. Patients with CA typically present a marked decrease in longitudinal strain in the basal and midwall segments and a relative apical sparing (Figure 2). The relative apical longitudinal strain [average apical longitudinal strain/(average basal + mid longitudinal strain)] greater than 1 could differentiate CA from hypertrophic cardiomyopathy and aortic stenosis with high diagnostic precision (sensitivity 93%, specificity 82%). Along the same lines, Koyama *et al*^[28] showed that the reduction of LV basal strain was an independent predictor of both cardiac and overall deaths. Different articles published later, defined other relevant diagnostic and prognostic strain measurements. Speckle-tracking-imaging derived global longitudinal early diastolic strain rate was superior to conventional diastolic parameters for predicting mortality in CA patients with preserved LVEF, increasing the risk of death fourfold with a cut-off value of 0.85^[29]. RV strain analysis brings more prognostic information. Free-wall right ventricular longitudinal strain worse than 21.2% distinguishes between CA and other etiologies of cardiac hypertrophy^[30].

LS and 2D-global LS provided incremental value to the combination of NT-proBNP, troponin and clinical parameters on survival in AL amyloidosis, and LS correlated strongly with the amyloid deposition measured histologically^[31,32]. Strain is especially useful in early stages of the disease and could set up groups with a worse prognosis.

In summary, echocardiography can objectify cardiac infiltration in all its stages. The effect of strain and E/e' have high probabilities of being abnormal at low cardiac amyloid burden. However, indexed stroke volume, MCF and TAPSE are abnormal more gradually with the progressive amyloid infiltration. Finally, at high levels of cardiac infiltration, biatrial areas and biventricular ejection fraction are altered^[33]. Echocardiography is an important resource to objectify cardiac involvement. The advantages of the use of conventional TTE are: Rapid and instantaneous diagnostic tool; technically simple and easily interpretable; high availability; and does not require radiation of the patient. Completing the study with the strain test can slightly prolong the duration of the procedure, but it has a greater interpretive difficulty and the availability of the software is lower, which limits its use. The combination of structural parameters such as the biventricular hypertrophy pattern, biatrial dilation, pericardial effusion, interseptal and valve thickening associated with functional parameters such as conventional diastolic function measurement, MCF and the strain parameters allow clinicians to perform a first diagnostic approach and provide prognostic data on the evolution of the disease.

CARDIAC MAGNETIC RESONANCE

Cardiac magnetic resonance (CMR) is a widely used technique today. It is a noninvasive tool that permits the evaluation of cardiac structure and function as well as characterization of the composition of interstitial tissue. To this aim, certain sequences are used, and it can be grouped into three categories: Functional/cine imaging; Noncontrast tissue imaging; and Postcontrast tissue imaging^[34].

Cine sequences or functional assessment in patients with CA allow visualizing the morphology of the infiltrated myocardium (*i.e.* biventricular hypertrophy, valvular or interatrial septum thickening, pericardial effusion or biatrial dilation) and accurately assessing systolic and diastolic function. It is particularly important for the evaluation of the LV and the rest of the cardiac chambers. RV involvement is a predictor of mortality in CMR, as it had been shown previously in TTE^[35]. With the disease progression towards advanced stages, there is an increase in the atrium volume and an alteration of their functioning. It occurs by direct infiltration of the amyloid fibrils in the atrium and indirectly by the increase in filling pressures secondary to diastolic dysfunction. Mohty *et al*^[36] observed in patients with AL-CA that the reduction of the total left atrial emptying fraction was not only related to more advanced stages of the disease and with a worse functional class but also with an increase in 2-year mortality

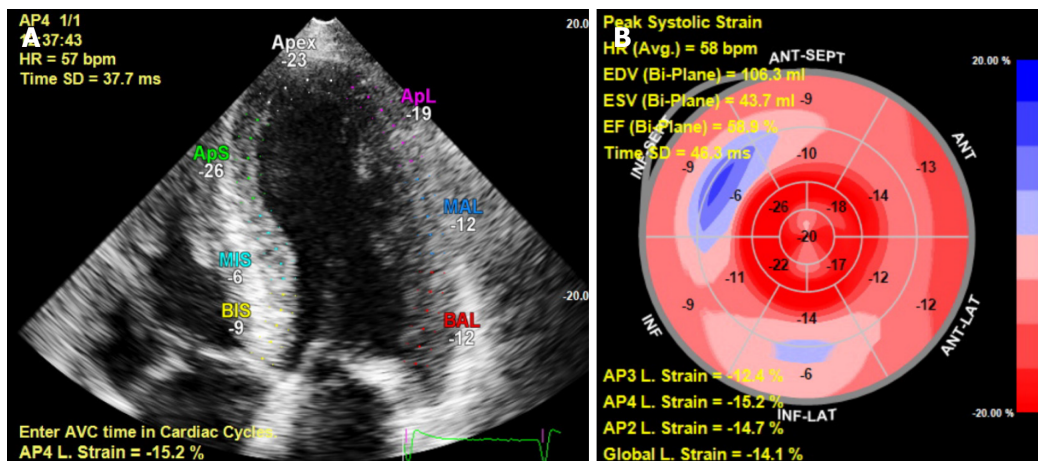


Figure 2 Transthoracic echocardiography imaging from a patient with transthyretin amyloidosis-cardiac amyloidosis. A: Strain imaging by transthoracic echocardiography; B: Reduced mid and basal values with apical sparing.

if its value decreased below 16%. In addition, the CMR also allows us to measure less frequently used parameters such as MCF and long axis strain. These new determinations can further stratify the risk in AL-CA patients with late gadolinium enhancement (LGE) uptake if the value of long axis strain exceeds 7% and the MCF value decreases below 52.6%. This subgroup of patients will have the greatest risk of death and heart transplantation^[37].

Unlike TTE, CMR usually provides high image quality that allows differentiation of the endocardial border and greater definition of small displacements. Ochs *et al*^[38] evaluated the prognostic value of different valve plane displacements. Traditionally, this measurement is reduced to TAPSE and inferoseptal mitral plane systolic excursion. However, it was found that the anterior aortic plane systolic excursion was the valve displacement that provided the best predictive value for transplant-free survival in AL patients. Therefore, cine sequences provide a global assessment with important prognostic and diagnostic information. It can even objectify the alteration of different parameters at low cardiac amyloid burden^[39].

The strain can be analyzed by CMR to complete a deep study. Wan *et al*^[40] noticed that the strain correlates well with the level of LGE uptake, and it may be an alternative to LGE in the group of patients where contrast should not be used (Table 1). They found that global longitudinal strain and global circumferential strain were significantly lower in the subendocardial and transmural than in no or nonspecific LGE group. They also found that the impaired global longitudinal strain was a robust predictor of all-cause mortality. Furthermore, they emphasized the utility of this tool in the early stage of the disease because in AL patients without cardiac involvement, basal segmental circumferential strain and radial strain were significantly impaired compared with those in healthy subjects.

One of the most worthwhile uses of CMR is the possibility of characterizing the tissue in a noninvasive way, for which the pre-contrast (native) T1 mapping, the postcontrast imaging-LGE and T1 mapping are used. In amyloidosis, the deposition of amyloid fibrils in the extracellular level causes an increase in the interstitial volume and a greater accumulation of gadolinium in that level.

The significant amyloid deposit alters the gadolinium kinetics. The gadolinium presents a rapid clearance from the intravascular space into the extracellular space. Thus the myocardial signal becomes hyperintense before the blood pool signal, unlike healthy patients. It is difficult to acquire and correctly interpret LGE images. Therefore, in the imaging acquisition of LGE the inversion time on the scanner needs to be adjusted to make the normal myocardium appear dark and the abnormal tissue bright. If the amyloid infiltration is diffusely distributed, then it is even more difficult to identify the optimal inversion time because of little or no normal tissue available to null the myocardium. There are some tools to overtake this issue like phase correction inversion recovery LGE imaging or quantitative T1 mapping. It has prognostic implications because there is an increased risk of death if it is impossible to obtain a normal myocardial signal on LGE using the look locker sequence (T1 sequence with different inversion times) with inversion time over 300 ms^[41].

The typical pattern of LGE in amyloidosis is a diffuse subendocardial uptake, and it was described a transmural pattern enhancement and less frequently a focal patchy

Table 1 Early imaging tool for cardiac amyloidosis diagnosis

	Patients with renal impairment	Patients without renal impairment
TTE	MCF, cardiac-index, strain parameters, E/A ratio of transmitral flow	MCF, cardiac-index, strain parameters, E/A ratio of transmitral flow
CMR	Stroke volume index, global longitudinal and circumferential strain, T1 native	Stroke volume index, global longitudinal and circumferential strain, T1 native and ECV
CCT		ECV
Nuclear imaging		^{99m} Tc-DPD myocardial uptake, MIBG uptake

^{99m}Tc-DPD: ^{99m}Tc-labeled 3,3-diphosphono-1,2-propanodicarboxylic acid; CCT: Cardiac computed tomography; CMR: Cardiac magnetic resonance; ECV: Extracellular volume; MCF: Myocardial contraction fraction; MIBG: 123-iodine metaiodobenzylguanidine; TTE: Transthoracic echocardiography.

one. The gadolinium deposits usually involve the RV and the atrial walls. Controversy exists regarding the prognostic implication of gadolinium uptake in the myocardium. Maceira *et al*^[42] noticed that the presence of LGE was not a robust predictor of death but they described a new method to measure gadolinium kinetics: The difference post-gadolinium intramyocardial T1 between subepicardium and subendocardium. If there is less difference between the subepicardium uptake and the subendocardium uptake, it implies that the amyloid infiltration is more diffuse. These patients had a worse survival when that difference was lower than 23 ms. Ruberg *et al*^[35] founded in 28 AL patients with suspected heart disease that the LGE is highly sensitive and specific (86% and 86% respectively) for the identification of CA, and it correlated with high values of brain natriuretic peptide but did not predict survival. A clear correlation with high NT-proBNP values and the extent of LGE was observed without showing a direct relationship with survival^[43]. However, multiple subsequent studies demonstrated a relevant prognostic implication of LGE in this disease. Diffuse subendocardial uptake detected using a modified LGE-CMR protocol with visual T1 assessment had high diagnostic precision (positive predictive value 93%, negative predictive value 90%), and it was significantly associated with 2-year mortality^[44,45]. Fontana *et al*^[46] observed the presence of a transmural pattern in ATTR and AL patients that predicted high risk of death in a follow-up period of 24 + 13 mo. All of this information was tested in a meta-analysis where it was found that in patients with known or suspected CA, LGE was associated with an odds ratio of 4.96 (95% confidence interval: 1.90 to 12.93) for all-cause mortality, without differences between both types of CA^[47].

Wan *et al*^[48] studied the RV gadolinium uptake in AL patients, and they showed that it was an independent predictor of survival during a period of 6 mo follow-up. Afterwards, the same investigation group^[49] proposed a new CMR parameter, the query amyloid late enhancement score. It is a semiquantified measurement of LGE in both LV and RV, where higher values imply greater involvement. The query amyloid late enhancement score above 9 predicted worse survival, and it was especially useful in patients with a subendocardial LGE pattern because the query amyloid late enhancement score value above 9 defined a subgroup with a higher risk of death.

In patients with AL-CA, the diffuse pattern provides incremental prognosis over biomarker stage^[50]. In patients with multiple myeloma the presence of LGE patterns included diffuse subendocardial, transmural and focal or patchy, and suboptimal nulling provides incremental prognosis for mortality prediction over biomarker stage, clinical and echocardiographic variables^[51]. In patients with ATTR-CA, the presence of LGE increases the prognostic power over the functional New York Heart Association class^[52]. This information suggests that the combination of conventional LGE images with clinical, biomarker and echocardiographic findings has an important prognostic role, and it improves the diagnostic accuracy in CA.

Noncontrast T1-mapping has the potential to detect and quantify cardiac involvement and could become a clinically useful diagnostic and prognostic tool, especially for impaired renal patients where the use of contrast has deleterious effects. The amyloid infiltration alters cardiac native signal. In ATTR and AL patients, it involves greater myocardial T1 native values. The increase of T1 values is not only due to interstitial expansion but also cellular hypertrophy. It could limit the ability of myocardial T1 values to distinguish CA from other cardiac hypertrophy etiologies, especially in early stages where there is little interstitial expansion^[34]. Despite that, Karamitsos *et al*^[53] proved that myocardial T1 was increased in AL amyloidosis even when cardiac involvement was uncertain or absent, showing that this tool could allow an early diagnosis of CA. The cut-off value of 1020 ms had high sensitivity and

specificity (around 90%) for identifying amyloid patients with possible or definite cardiac involvement. Higher T1 values were well correlated with decreased LVEF, decreased LV mass index and with worse diastolic function suggesting that T1 changes could reflect more severe cardiac involvement. At that time, there was still no clear information about the prognostic implication of native T1.

T1 mapping (Figure 3) with native T1 and extracellular volume (ECV) are recently developed quantitative parameters. Patients with AL and suspected cardiac involvement had increased values of native T1 and ECV, even in early stages where no LGE was demonstrated^[54]. It emphasized that native T1 and ECV are more useful tools than LGE in early cardiac diagnosis. However, only the ECV had a significant prognostic implication with greater mortality if its value was above 44%. This tool was especially useful in subgroups with the same LGE pattern where the ECV could distinguish a high risk group^[54]. Basal, mild and apical level of native T1 and ECV were quantified in a Wan *et al*^[55] report. Basal ECV had the best prognostic value amongst myocardial T1 mapping parameters, and it increased in patients without LGE uptake, strengthening the concept that this tool is very useful in early disease stages. Later, relative to ATTR-CA, Martinez-Naharro *et al*^[56] observed that both native T1 and ECV provided excellent diagnostic accuracy for identification of ATTR-CA, without difference between the two types of ATTR. Similar to AL, only ECV was an independently predictor of mortality. Both native T1 and ECV correlated with cardiac function parameters and with increasing cardiac uptake (assessed by bone scintigraphy). They noticed that due to the different biological information provided by native T1 and ECV measurements (ECV measures extracellular volume and native T1 measures the interstitial expansion and the cellular hypertrophy) that there were discrepancies in measurements depending on the level of cardiac infiltration. When amyloid burden was moderate or severe, there were discrepancies between the results of ECV and native T1. However at low level infiltration assessed by nondiagnostic ^{99m}Tc-labeled 3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) grade 1 uptake, there were consistent abnormal values of both myocardial T1 and ECV, proving that they had greater precision at low amyloid burden. Using these measurements, CMR could detect a phenotype of early amyloid infiltration. Unless the patient had impaired renal function, the ECV was a better T1 mapping parameter than native T1^[54].

Another sequence that it could be used in the diagnosis of CA is the T2-weighted imaging, and it is attractive because no gadolinium administration is needed. A decreased myocardial signal intensity compared with skeletal muscle in T2 images was associated with shortened survival. However, for a T2 ratio value less than 1.36 it had a weak sensitivity and specificity (63% and 73%, respectively) to predict cardiac involvement^[57,58].

In conclusion, CMR would be a second step to complete the diagnostic study of a patient with suspected CA. It is an imaging technique that is not available in many hospitals, and the long duration of each study limits the number of studies that can be performed per day. Likewise, increasing the number of sequences further prolongs the duration of the test, which hinders accessibility. Another drawback is that it does not provide instant information as with TTE, and postprocessing is required to complete the entire test. However, the great advantage of this technique, in addition to the anatomical and functional cardiac characterization, is the tissue characterization and the absence of ionizing radiation on the patient. The use of contrast for gadolinium uptake sequences would cause kidney damage, but as previously exposed, it seems that the use of strain presents an adequate correlation with gadolinium uptake, which obviate this sequence in patients at risk of impaired kidney function. Therefore, the use of CMR establishes an early and accurate diagnostic approach in CA through measurement of MCF, strain parameters, native T1 and ECV. These measurements associated with an adequate assessment of the RV, atrial function and in non-contraindicated cases the pattern of LGE uptake have shown implications in the prognosis and mortality of the patient. Therefore, it is a fundamental tool in the diagnosis of CA.

CARDIAC COMPUTED TOMOGRAPHY

The usefulness of cardiac computed tomography (CCT) for the diagnosis of CA is unknown due to few trials. Nevertheless, it is commonly used to rule out the presence of other concomitant diseases. This tool, despite being more accessible than performing a CMR or a scintigraphy, has deleterious effects on the patient, such as the use of contrast and radiation exposure^[34].

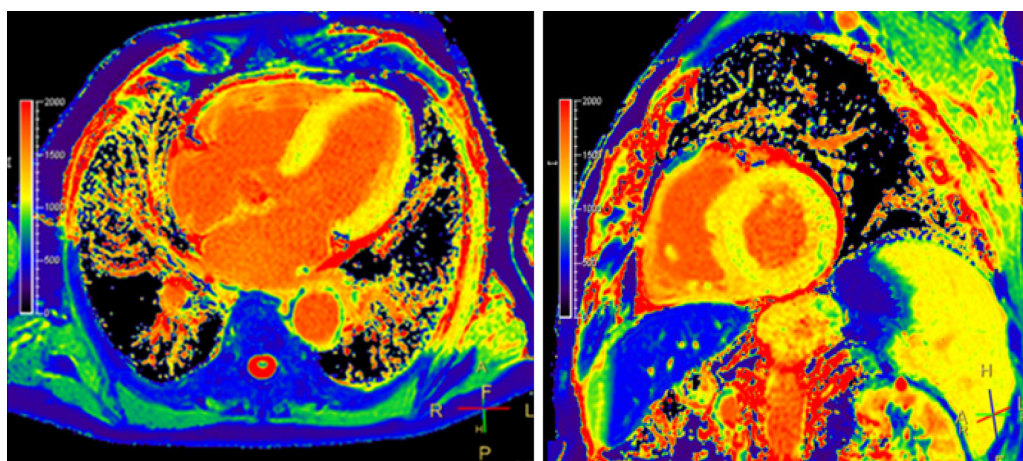


Figure 3 Native T1-mapping images. Abnormally elevated values of T1 native (1120 ms) in a patient with amyloidosis-cardiac amyloidosis.

Few studies have been published about the diagnosis of CA by CCT. Treibel *et al*^[59] compared a small sample of 26 patients with AL and ATTR-CA with patients with severe aortic stenosis by quantifying the contrast distribution in the extracellular volume by CCT. They underwent a dynamic equilibrium CCT protocol with rapid contrast administration to quantify the ECV. The authors observed an adequate correlation between the ECV measured by CCT in the first 5 min and the ECV measured by CMR, with high diagnostic accuracy of CA and a great correlation with clinical and biochemical markers of disease severity. Furthermore, CCT had good results and was easier, quicker and more accessible than CMR.

To quantify the ECV by CCT it is necessary to obtain a combination of the hematocrit, pre- and postcontrast measurements. Treibel *et al*^[60] simplified this technique to not require blood extraction, further facilitating the use of this method.

Despite the disadvantages of this technique with respect to ionizing radiation and the need to use contrast, the greater availability of this tool and the capacity of tissue characterization with the ECV measurement, makes the CCT an alternative to CMR in the diagnosis of cardiac infiltration by amyloid.

NUCLEAR IMAGING

None of the previous cardiac imaging tools gives us great information with regard to the type of CA. The main utility of the scintigraphy is to precisely differentiate the types of amyloidosis.

^{99m}Tc-DPD, ^{99m}Tc-labeled pyrophosphate (^{99m}Tc-PYP) and ^{99m}Tc-labeled hydroxymethylene diphosphonate were the different bone avid radiotracers used for ATTR-CA diagnosis^[14]. Fibril deposits are composed of the precursor protein, heparin sulfate proteoglycan and a calcium dependent P-component. It is thought that the use of calcium for binding amyloid P and fibrils explains the uptake of ^{99m}Tc-bone avid tracers. Stats *et al*^[61] histologically showed that hearts affected by ATTR-CA have higher microcalcification density compared to hearts with AL-CA, which may explain the higher uptake in the ATTR subgroup. This binding allows a semiquantitative (visual) scoring and a quantitative (heart to contralateral ratio) assessment of amyloid protein deposition.

The use of ^{99m}Tc-labeled hydroxymethylene diphosphonate allows us to distinguish cardiac involvement by transthyretin from other nonamyloid left ventricle hypertrophy, and it predicts acute heart failure and/or death^[62]. However, the ability to differentiate between the two subtypes is limited, and its diagnostic utility compared to ^{99m}Tc-PYP and DPD is likely suboptimal.

In Europe, ^{99m}Tc-DPD is the only radiotracer approved for clinical use. Perugini *et al*^[63] documented the high accuracy (around 100%) of ^{99m}Tc-DPD scintigraphy for distinction of AL and ATTR etiology (Figure 4). Subsequently, in patients with ATTR-CA, the ^{99m}Tc-DPD myocardial uptake proved to be a determinant of cardiac outcome, and it could also detect the myocardial involvement before visualization of morphological abnormalities by echocardiogram, which is very relevant in the early diagnosis of CA^[64]. Regarding the different degrees of uptake in the semiquantitative

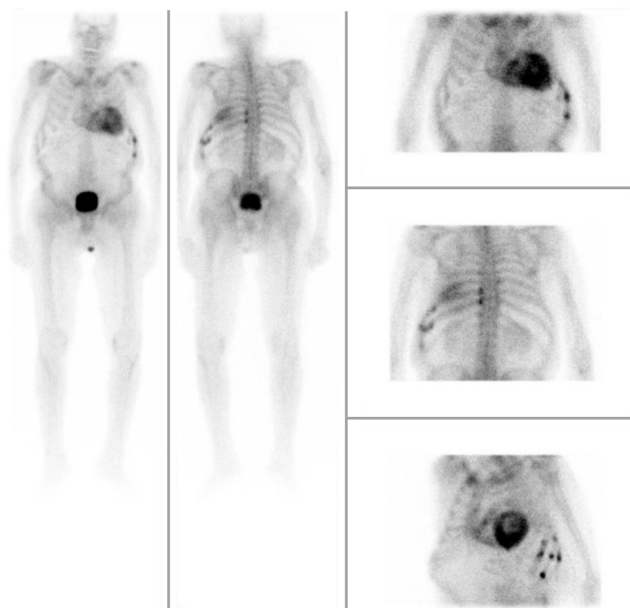


Figure 4 Planar scintigraphy showing intense cardiac uptake of ^{99m}Tc -labeled 3,3-diphosphono-1,2-propanodicarboxylic acid corresponding to a grade 3 in a patient diagnosed with cardiac amyloidosis-transthyretin amyloidosis.

measurement of the uptake of ^{99m}Tc -DPD, Hutt *et al*^[65] showed a better survival in patients with grade 0 compared to grades 1, 2 and 3 with no differences in nonzero degrees.

^{99m}Tc -PYP is the other tracer available in North America. Bokhari *et al*^[66] proved that patients with ATTR-CA had a significantly higher uptake of ^{99m}Tc -PYP than AL-CA patients evaluated both semiquantitatively and quantitatively, and the elevated cardiac uptake was associated with an increase of all-cause mortality^[14]. The heart to contralateral ratio > 1.5 had a sensitivity of 97% and a specificity of 100% for the diagnosis of ATTR-CA. In a period of 5 years, a heart to contralateral ratio of 1.6 or greater was associated with a significantly worse survival^[67]. In relation to this tracer, Sperry *et al*^[68] described an apical-sparing pattern and an increase in mortality dependent on regional distribution of LV ^{99m}Tc -PYP uptake. Patients with diffuse infiltration had more apical uptake and as a result a worse survival.

Gillmore *et al*^[14] studied the uptake of these radiotracers in patients with suspected CA, and they found that a visual scoring of a radiotracer uptake grade ≥ 2 without monoclonal proteins on serum and urine analysis had a specificity and positive predictive value of 100% for ATTR-CA. As we explained previously, this information revolutionized the noninvasive diagnosis of CA, avoiding a large number of invasive procedures in these patients.

Positron emission tomography tracers are being investigated for the diagnosis of CA. The advantage over single-photon emission computed tomography tracers is that they allow quantification of the amyloid burden. To date the different tracers evaluated are 18F-florbetapir, 18F-florbetaben and 11C-Pittsburgh Compound-B in which a higher uptake has been observed in patients with amyloidosis compared to other types of cardiomyopathies. Regarding 18F-florbetapir the retention index and the uptake values in the LV myocardium was greater in patients with amyloidosis, and higher values have been observed in AL compared to ATTR hearts without significant differences^[69]. Likewise, the increased uptake correlated with deterioration of biventricular function^[70]. However, its prognostic involvement in the survival of these patients has not yet been demonstrated in multicenter studies, and it is a future research field.

In patients with amyloidosis, myocardial sympathetic denervation often precedes the neurological and cardiac manifestations, especially in ATTRv. Therefore, the detection of this situation could anticipate cardiac involvement^[71]. 123-iodine metaiodobenzylguanidine (MIBG) imaging assesses myocardial sympathetic denervation, and the reduction of the myocardial uptake previously occurs before morphologic alterations visualized by TTE. An increased 5-year mortality rate in ATTR patients with a heart to mediastinum MIBG uptake ratio below 1.6^[72] and worse liver transplant survival outcomes in ATTRv with a ratio lower than 1.43^[73] has been observed. Even, cardiac sympathetic denervation documented by decreased MIBG

uptake is detected earlier than amyloid burden demonstrated by ^{99m}Tc -DPD scintigraphy in ATTRv patients, highlighting the importance of this tool for an early diagnosis in this subgroup of patients^[74].

The disadvantage of scintigraphy, as well as CCT, is that it requires exposure to ionizing radiation. Advantages of this tool are the early diagnosis, even before the anatomical alterations are evident, and the ability to distinguish the different types of amyloidosis. Due to the advances in this technique, an algorithm has been developed that allows the diagnosis of ATTR-CA without the need for endomyocardial biopsy. Currently, it has positioned itself as one of the imaging techniques that contributes the most in the precise diagnosis of ATTR-CA.

MACHINE LEARNING

Before ending this review, we want to highlight the growth of machine learning and artificial intelligence in medicine in general and in diagnostic imaging in particular. It consists of using algorithms that learn from previous studies, identifying complex image patterns and later apply them in the diagnosis of different pathologies. In this way, we can shorten the duration of the different imaging techniques and increase diagnostic precision by reducing the interobserver variability of the tests^[75,76].

The machine learning-based radiomics technique has been studied in different imaging tools (TTE, CCT, CMR and scintigraphy) with high diagnostic precision in acute myocardial infarction, HCM and RV abnormalities. However, the data about its applicability in the diagnosis of CA are limited. There was a study conducted by Zhang *et al*^[77] that used automated cardiac image interpretation in patients diagnosed with CA. They evaluated myocardial structure, ventricular function and LS measured by TTE and compared it with segmentation and manual measurement. Using the cases with confirmed CA and matched controls, they found high diagnostic precision with an area under the curve of 0.87 (95% confidence interval: 0.83–0.91). It provides promising data that could revolutionize routine clinical practice. However, to implement the use of machine learning in CA, it is necessary to obtain more data about the diagnostic precision of the other imaging techniques as well as several studies to evaluate the ability of this technique to distinguish different cardiomyopathies.

CONCLUSION

Advances in cardiac imaging techniques not only allow for an accurate and early diagnosis, but also provides relevant prognostic information of patients. Given a clinical suspicion of cardiac involvement due to amyloidosis, initially an approximation study should be performed using TTE because it is the fastest and safest technique. TTE should evaluate simple measurements, such as TAPSE, whose alterations are relevant to patient mortality. Likewise, more complex measurements should be studied such as strain and MCF. They are altered in patients with low levels of myocardial infiltration, and it could modify their prognosis with the early establishment of treatment.

Subsequently, depending on the availability of the hospital, it would be advisable to perform a tissue characterization through CMR or CCT. The use of native T1 and ECV have a high diagnostic precision for CA and their alteration have already been observed in early stages of the disease. If renal function allows, then the use of the LGE imaging provides additional information on the prognosis, although it could be substituted for the strain analysis.

The noninvasive differentiation of amyloidosis types can be carried out with high precision through the ^{99m}Tc -DPD scintigraphy, and the detection of sympathetic denervation with decreased MIBG uptake anticipates the diagnosis of cardiac infiltration even before ^{99m}Tc -DPD myocardial uptake.

Finally, we hypothesize that cardiac imaging could replace invasive techniques in the CA diagnosis. Depending on the accessibility to the imaging techniques in the different hospital centers, multiple measurements with important prognostic implications in these patients can be selected.

REFERENCES

- 1 **González-López E**, López-Sainz Á, García-Pavia P. Diagnosis and Treatment of Transthyretin Cardiac Amyloidosis. Progress and Hope. *Rev Esp Cardiol (Engl Ed)* 2017; **70**: 991-1004 [PMID: 28870641 DOI: 10.1016/j.rec.2017.05.036]
- 2 **Palladini G**, Merlini G. What is new in diagnosis and management of light chain amyloidosis? *Blood* 2016; **128**: 159-168 [PMID: 27053535 DOI: 10.1182/blood-2016-01-629790]
- 3 **Barge-Caballero G**, Barriales-Villa R, Crespo-Leiro MG. Cambio de paradigma en el diagnóstico y tratamiento de la amiloidosis cardiaca por transtirretina. *REC: CardioClinics* 2019; **54**: 9-12 [DOI: 10.1016/j.rcccl.2018.12.007]
- 4 **Siddiqi OK**, Ruberg FL. Cardiac amyloidosis: An update on pathophysiology, diagnosis, and treatment. *Trends Cardiovasc Med* 2018; **28**: 10-21 [PMID: 28739313 DOI: 10.1016/j.tcm.2017.07.004]
- 5 **Gertz MA**. Immunoglobulin light chain amyloidosis diagnosis and treatment algorithm 2018. *Blood Cancer J* 2018; **8**: 44 [PMID: 29795248 DOI: 10.1038/s41408-018-0080-9]
- 6 **Schmidt HH**, Waddington-Cruz M, Botteman MF, Carter JA, Chopra AS, Hopps M, Stewart M, Fallet S, Amass L. Estimating the global prevalence of transthyretin familial amyloid polyneuropathy. *Muscle Nerve* 2018; **57**: 829-837 [PMID: 29211930 DOI: 10.1002/mus.26034]
- 7 **Castañó A**, Narotsky DL, Hamid N, Khaliq OK, Morgenstern R, DeLuca A, Rubin J, Chiuzaan C, Nazif T, Vahl T, George I, Kodali S, Leon MB, Hahn R, Bokhari S, Maurer MS. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. *Eur Heart J* 2017; **38**: 2879-2887 [PMID: 29019612 DOI: 10.1093/eurheartj/ehx350]
- 8 **González-López E**, Gallego-Delgado M, Guzzo-Merello G, de Haro-Del Moral FJ, Cobo-Marcos M, Robles C, Bornstein B, Salas C, Lara-Pezzi E, Alonso-Pulpon L, Garcia-Pavia P. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. *Eur Heart J* 2015; **36**: 2585-2594 [PMID: 26224076 DOI: 10.1093/eurheartj/ehv338]
- 9 **Tanskanen M**, Peuralinna T, Polvikoski T, Notkola IL, Sulkava R, Hardy J, Singleton A, Kiuru-Enari S, Paetau A, Tienari PJ, Myllykangas L. Senile systemic amyloidosis affects 25% of the very aged and associates with genetic variation in alpha2-macroglobulin and tau: a population-based autopsy study. *Ann Med* 2008; **40**: 232-239 [PMID: 18382889 DOI: 10.1080/07853890701842988]
- 10 **Ruberg FL**, Maurer MS, Judge DP, Zeldenrust S, Skinner M, Kim AY, Falk RH, Cheung KN, Patel AR, Pano A, Packman J, Grogan DR. Prospective evaluation of the morbidity and mortality of wild-type and V122I mutant transthyretin amyloid cardiomyopathy: the Transthyretin Amyloidosis Cardiac Study (TRACS). *Am Heart J* 2012; **164**: 222-228. e1 [PMID: 22877808 DOI: 10.1016/j.ahj.2012.04.015]
- 11 **Merlini G**, Bellotti V. Molecular mechanisms of amyloidosis. *N Engl J Med* 2003; **349**: 583-596 [PMID: 12904524 DOI: 10.1056/NEJMra023144]
- 12 **Kyle RA**, Linos A, Beard CM, Linke RP, Gertz MA, O'Fallon WM, Kurland LT. Incidence and natural history of primary systemic amyloidosis in Olmsted County, Minnesota, 1950 through 1989. *Blood* 1992; **79**: 1817-1822 [PMID: 1558973 DOI: 10.1182/blood.V79.7.1817.1817]
- 13 **Kyle RA**, Gertz MA. Primary systemic amyloidosis: clinical and laboratory features in 474 cases. *Semin Hematol* 1995; **32**: 45-59 [PMID: 7878478]
- 14 **Gillmore JD**, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, Wechalekar AD, Berk JL, Quarta CC, Grogan M, Lachmann HJ, Bokhari S, Castano A, Dorbala S, Johnson GB, Glaudemans AW, Rezk T, Fontana M, Palladini G, Milani P, Guidalotti PL, Flatman K, Lane T, Vonberg FW, Whelan CJ, Moon JC, Ruberg FL, Miller EJ, Hutt DF, Hazenberg BP, Rapezzi C, Hawkins PN. Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. *Circulation* 2016; **133**: 2404-2412 [PMID: 27143678 DOI: 10.1161/CIRCULATIONAHA.116.021612]
- 15 **González-López E**, Gagliardi C, Dominguez F, Quarta CC, de Haro-Del Moral FJ, Milandri A, Salas C, Cinelli M, Cobo-Marcos M, Lorenzini M, Lara-Pezzi E, Foffi S, Alonso-Pulpon L, Rapezzi C, Garcia-Pavia P. Clinical characteristics of wild-type transthyretin cardiac amyloidosis: disproving myths. *Eur Heart J* 2017; **38**: 1895-1904 [PMID: 28329248 DOI: 10.1093/eurheartj/ehx043]
- 16 **Barros-Gomes S**, Williams B, Nhola LF, Grogan M, Maalouf JF, Dispenzieri A, Pellikka PA, Villarraga HR. Prognosis of Light Chain Amyloidosis With Preserved LVEF: Added Value of 2D Speckle-Tracking Echocardiography to the Current Prognostic Staging System. *JACC Cardiovasc Imaging* 2017; **10**: 398-407 [PMID: 27639764 DOI: 10.1016/j.jcmg.2016.04.008]
- 17 **Mohty D**, Pradel S, Magne J, Fadel B, Boulogne C, Petitalot V, Raboukhi S, Darodes N, Damy T, Aboyans V, Jaccard A. Prevalence and prognostic impact of left-sided valve thickening in systemic light-chain amyloidosis. *Clin Res Cardiol* 2017; **106**: 331-340 [PMID: 27933393 DOI: 10.1007/s00392-016-1058-x]
- 18 **Cardim N**, Galderisi M, Edvardsen T, Plein S, Popescu BA, D'Andrea A, Bruder O, Cosyns B, Davin L, Donal E, Freitas A, Habib G, Kitsiou A, Petersen SE, Schroeder S, Lancellotti P, Camici P, Dulgheru R, Hagendorff A, Lombardi M, Muraru D, Sicari R. Role of multimodality cardiac imaging in the management of patients with hypertrophic cardiomyopathy: an expert consensus of the European Association of Cardiovascular Imaging Endorsed by the Saudi Heart Association. *Eur Heart J Cardiovasc Imaging* 2015; **16**: 280 [PMID: 25650407 DOI: 10.1093/ehjci/jeu291]
- 19 **Koyama J**, Ray-Sequin PA, Falk RH. Prognostic significance of ultrasound myocardial tissue characterization in patients with cardiac amyloidosis. *Circulation* 2002; **106**: 556-561 [PMID: 12000000]

- 12147536 DOI: [10.1161/01.cir.0000023530.86718.b0](https://doi.org/10.1161/01.cir.0000023530.86718.b0)]
- 20 **Grogan M**, Scott CG, Kyle RA, Zeldenrust SR, Gertz MA, Lin G, Klarich KW, Miller WL, Maleszewski JJ, Dispenzieri A. Natural History of Wild-Type Transthyretin Cardiac Amyloidosis and Risk Stratification Using a Novel Staging System. *J Am Coll Cardiol* 2016; **68**: 1014-1020 [PMID: [27585505](https://pubmed.ncbi.nlm.nih.gov/27585505/) DOI: [10.1016/j.jacc.2016.06.033](https://doi.org/10.1016/j.jacc.2016.06.033)]
 - 21 **Milani P**, Dispenzieri A, Scott CG, Gertz MA, Perlini S, Mussinelli R, Lacy MQ, Buadi FK, Kumar S, Maurer MS, Merlini G, Hayman SR, Leung N, Dingli D, Klarich KW, Lust JA, Lin Y, Kapoor P, Go RS, Pellikka PA, Hwa YL, Zeldenrust SR, Kyle RA, Rajkumar SV, Grogan M. Independent Prognostic Value of Stroke Volume Index in Patients With Immunoglobulin Light Chain Amyloidosis. *Circ Cardiovasc Imaging* 2018; **11**: e006588 [PMID: [29752392](https://pubmed.ncbi.nlm.nih.gov/29752392/) DOI: [10.1161/CIRCIMAGING.117.006588](https://doi.org/10.1161/CIRCIMAGING.117.006588)]
 - 22 **Migrino RQ**, Mareedu RK, Eastwood D, Bowers M, Harmann L, Hari P. Left ventricular ejection time on echocardiography predicts long-term mortality in light chain amyloidosis. *J Am Soc Echocardiogr* 2009; **22**: 1396-1402 [PMID: [19880277](https://pubmed.ncbi.nlm.nih.gov/19880277/) DOI: [10.1016/j.echo.2009.09.012](https://doi.org/10.1016/j.echo.2009.09.012)]
 - 23 **Bellavia D**, Pellikka PA, Al-Zahrani GB, Abraham TP, Dispenzieri A, Miyazaki C, Lacy M, Scott CG, Oh JK, Miller FA Jr. Independent predictors of survival in primary systemic (AL) amyloidosis, including cardiac biomarkers and left ventricular strain imaging: an observational cohort study. *J Am Soc Echocardiogr* 2010; **23**: 643-652 [PMID: [20434879](https://pubmed.ncbi.nlm.nih.gov/20434879/) DOI: [10.1016/j.echo.2010.03.027](https://doi.org/10.1016/j.echo.2010.03.027)]
 - 24 **Patel AR**, Dubrey SW, Mendes LA, Skinner M, Cupples A, Falk RH, Davidoff R. Right ventricular dilation in primary amyloidosis: an independent predictor of survival. *Am J Cardiol* 1997; **80**: 486-492 [PMID: [9285663](https://pubmed.ncbi.nlm.nih.gov/9285663/) DOI: [10.1016/s0002-9149\(97\)00400-1](https://doi.org/10.1016/s0002-9149(97)00400-1)]
 - 25 **Bodez D**, Ternacle J, Guellich A, Galat A, Lim P, Radu C, Guendouz S, Bergoend E, Couetil JP, Hittinger L, Dubois-Randé JL, Plante-Bordeneuve V, Deux JF, Mohty D, Damy T. Prognostic value of right ventricular systolic function in cardiac amyloidosis. *Amyloid* 2016; **23**: 158-167 [PMID: [27348696](https://pubmed.ncbi.nlm.nih.gov/27348696/) DOI: [10.1080/13506129.2016.1194264](https://doi.org/10.1080/13506129.2016.1194264)]
 - 26 **Mohty D**, Petitalot V, Magne J, Fadel BM, Boulogne C, Rouabhia D, ElHamel C, Laverigne D, Damy T, Aboyans V, Jaccard A. Left atrial function in patients with light chain amyloidosis: A transthoracic 3D speckle tracking imaging study. *J Cardiol* 2018; **71**: 419-427 [PMID: [29153741](https://pubmed.ncbi.nlm.nih.gov/29153741/) DOI: [10.1016/j.jjcc.2017.10.007](https://doi.org/10.1016/j.jjcc.2017.10.007)]
 - 27 **Phelan D**, Collier P, Thavendiranathan P, Popović ZB, Hanna M, Plana JC, Marwick TH, Thomas JD. Relative apical sparing of longitudinal strain using two-dimensional speckle-tracking echocardiography is both sensitive and specific for the diagnosis of cardiac amyloidosis. *Heart* 2012; **98**: 1442-1448 [PMID: [22865865](https://pubmed.ncbi.nlm.nih.gov/22865865/) DOI: [10.1136/heartjnl-2012-302353](https://doi.org/10.1136/heartjnl-2012-302353)]
 - 28 **Koyama J**, Falk RH. Prognostic significance of strain Doppler imaging in light-chain amyloidosis. *JACC Cardiovasc Imaging* 2010; **3**: 333-342 [PMID: [20394893](https://pubmed.ncbi.nlm.nih.gov/20394893/) DOI: [10.1016/j.jcmg.2009.11.013](https://doi.org/10.1016/j.jcmg.2009.11.013)]
 - 29 **Liu D**, Hu K, Störk S, Herrmann S, Kramer B, Cikes M, Gaudron PD, Knop S, Ertl G, Bijnsens B, Weidemann F. Predictive value of assessing diastolic strain rate on survival in cardiac amyloidosis patients with preserved ejection fraction. *PLoS One* 2014; **9**: e115910 [PMID: [25542015](https://pubmed.ncbi.nlm.nih.gov/25542015/) DOI: [10.1371/journal.pone.0115910](https://doi.org/10.1371/journal.pone.0115910)]
 - 30 **Uzan C**, Lairez O, Raud-Raynier P, Garcia R, Degand B, Christiaens LP, Rehman MB. Right ventricular longitudinal strain: a tool for diagnosis and prognosis in light-chain amyloidosis. *Amyloid* 2018; **25**: 18-25 [PMID: [29260587](https://pubmed.ncbi.nlm.nih.gov/29260587/) DOI: [10.1080/13506129.2017.1417121](https://doi.org/10.1080/13506129.2017.1417121)]
 - 31 **Buss SJ**, Emami M, Mereles D, Korosoglou G, Kristen AV, Voss A, Schellberg D, Zugck C, Galuschky C, Giannitsis E, Hegenbart U, Ho AD, Katus HA, Schonland SO, Hardt SE. Longitudinal left ventricular function for prediction of survival in systemic light-chain amyloidosis: incremental value compared with clinical and biochemical markers. *J Am Coll Cardiol* 2012; **60**: 1067-1076 [PMID: [22883634](https://pubmed.ncbi.nlm.nih.gov/22883634/) DOI: [10.1016/j.jacc.2012.04.043](https://doi.org/10.1016/j.jacc.2012.04.043)]
 - 32 **Ternacle J**, Bodez D, Guellich A, Audureau E, Rappeneau S, Lim P, Radu C, Guendouz S, Couetil JP, Benhaïem N, Hittinger L, Dubois-Randé JL, Plante-Bordeneuve V, Mohty D, Deux JF, Damy T. Causes and Consequences of Longitudinal LV Dysfunction Assessed by 2D Strain Echocardiography in Cardiac Amyloidosis. *JACC Cardiovasc Imaging* 2016; **9**: 126-138 [PMID: [26777222](https://pubmed.ncbi.nlm.nih.gov/26777222/) DOI: [10.1016/j.jcmg.2015.05.014](https://doi.org/10.1016/j.jcmg.2015.05.014)]
 - 33 **Knight DS**, Zumbo G, Barcella W, Steeden JA, Muthurangu V, Martinez-Naharro A, Treibel TA, Abdel-Gadir A, Bulluck H, Kotecha T, Francis R, Rezk T, Quarta CC, Whelan CJ, Lachmann HJ, Wechalekar AD, Gillmore JD, Moon JC, Hawkins PN, Fontana M. Cardiac Structural and Functional Consequences of Amyloid Deposition by Cardiac Magnetic Resonance and Echocardiography and Their Prognostic Roles. *JACC Cardiovasc Imaging* 2019; **12**: 823-833 [PMID: [29680336](https://pubmed.ncbi.nlm.nih.gov/29680336/) DOI: [10.1016/j.jcmg.2018.02.016](https://doi.org/10.1016/j.jcmg.2018.02.016)]
 - 34 **White JA**, Fine NM. Recent Advances in Cardiovascular Imaging Relevant to the Management of Patients with Suspected Cardiac Amyloidosis. *Curr Cardiol Rep* 2016; **18**: 77 [PMID: [27319007](https://pubmed.ncbi.nlm.nih.gov/27319007/) DOI: [10.1007/s11886-016-0752-7](https://doi.org/10.1007/s11886-016-0752-7)]
 - 35 **Ruberg FL**, Appelbaum E, Davidoff R, Ozonoff A, Kissinger KV, Harrigan C, Skinner M, Manning WJ. Diagnostic and prognostic utility of cardiovascular magnetic resonance imaging in light-chain cardiac amyloidosis. *Am J Cardiol* 2009; **103**: 544-549 [PMID: [19195518](https://pubmed.ncbi.nlm.nih.gov/19195518/) DOI: [10.1016/j.amjcard.2008.09.105](https://doi.org/10.1016/j.amjcard.2008.09.105)]
 - 36 **Mohty D**, Boulogne C, Magne J, Varroud-Vial N, Martin S, Ettaïf H, Fadel BM, Bridoux F, Aboyans V, Damy T, Jaccard A. Prognostic value of left atrial function in systemic light-chain amyloidosis: a cardiac magnetic resonance study. *Eur Heart J Cardiovasc Imaging* 2016; **17**: 961-969 [PMID: [27194782](https://pubmed.ncbi.nlm.nih.gov/27194782/) DOI: [10.1093/ehjci/ewj100](https://doi.org/10.1093/ehjci/ewj100)]

- 37 **Arenja N**, Andre F, Riffel JH, Siepen FAD, Hegenbart U, Schönland S, Kristen AV, Katus HA, Buss SJ. Prognostic value of novel imaging parameters derived from standard cardiovascular magnetic resonance in high risk patients with systemic light chain amyloidosis. *J Cardiovasc Magn Reson* 2019; **21**: 53 [PMID: [31434577](#) DOI: [10.1186/s12968-019-0564-1](#)]
- 38 **Ochs MM**, Fritz T, Arenja N, Riffel J, Andre F, Mereles D, Siepen FAD, Hegenbart U, Schönland S, Katus HA, Friedrich MGW, Buss SJ. Regional differences in prognostic value of cardiac valve plane displacement in systemic light-chain amyloidosis. *J Cardiovasc Magn Reson* 2017; **19**: 87 [PMID: [29121956](#) DOI: [10.1186/s12968-017-0402-2](#)]
- 39 **Fontana M**, Ćorović A, Scully P, Moon JC. Myocardial Amyloidosis: The Exemplar Interstitial Disease. *JACC Cardiovasc Imaging* 2019; **12**: 2345-2356 [PMID: [31422120](#) DOI: [10.1016/j.jcmg.2019.06.023](#)]
- 40 **Wan K**, Sun J, Yang D, Liu H, Wang J, Cheng W, Zhang Q, Zeng Z, Zhang T, Greiser A, Jolly MP, Han Y, Chen Y. Left Ventricular Myocardial Deformation on Cine MR Images: Relationship to Severity of Disease and Prognosis in Light-Chain Amyloidosis. *Radiology* 2018; **288**: 73-80 [PMID: [29664336](#) DOI: [10.1148/radiol.2018172435](#)]
- 41 **Mekinian A**, Lions C, Leleu X, Duhamel A, Lamblin N, Coiteux V, De Groote P, Hatron PY, Facon T, Beregi JP, Hachulla E, Launay D; Lille Amyloidosis Study Group. Prognosis assessment of cardiac involvement in systemic AL amyloidosis by magnetic resonance imaging. *Am J Med* 2010; **123**: 864-868 [PMID: [20800158](#) DOI: [10.1016/j.amjmed.2010.03.022](#)]
- 42 **Maceira AM**, Prasad SK, Hawkins PN, Roughton M, Pennell DJ. Cardiovascular magnetic resonance and prognosis in cardiac amyloidosis. *J Cardiovasc Magn Reson* 2008; **10**: 54 [PMID: [19032744](#) DOI: [10.1186/1532-429X-10-54](#)]
- 43 **Lehrke S**, Steen H, Kristen AV, Merten C, Lossnitzer D, Dengler TJ, Katus HA, Giannitsis E. Serum levels of NT-proBNP as surrogate for cardiac amyloid burden: new evidence from gadolinium-enhanced cardiac magnetic resonance imaging in patients with amyloidosis. *Amyloid* 2009; **16**: 187-195 [PMID: [19922329](#) DOI: [10.3109/13506120903421538](#)]
- 44 **Austin BA**, Tang WH, Rodriguez ER, Tan C, Flamm SD, Taylor DO, Starling RC, Desai MY. Delayed hyper-enhancement magnetic resonance imaging provides incremental diagnostic and prognostic utility in suspected cardiac amyloidosis. *JACC Cardiovasc Imaging* 2009; **2**: 1369-1377 [PMID: [20083070](#) DOI: [10.1016/j.jcmg.2009.08.008](#)]
- 45 **White JA**, Kim HW, Shah D, Fine N, Kim KY, Wendell DC, Al-Jaroudi W, Parker M, Patel M, Gwady-Sridhar F, Judd RM, Kim RJ. CMR imaging with rapid visual T1 assessment predicts mortality in patients suspected of cardiac amyloidosis. *JACC Cardiovasc Imaging* 2014; **7**: 143-156 [PMID: [24412191](#) DOI: [10.1016/j.jcmg.2013.09.019](#)]
- 46 **Fontana M**, Pica S, Reant P, Abdel-Gadir A, Treibel TA, Banyersad SM, Maestrini V, Barcella W, Rosmini S, Bulluck H, Sayed RH, Patel K, Mamhood S, Bucciarelli-Ducci C, Whelan CJ, Herrey AS, Lachmann HJ, Wechalekar AD, Manisty CH, Schelbert EB, Kellman P, Gillmore JD, Hawkins PN, Moon JC. Prognostic Value of Late Gadolinium Enhancement Cardiovascular Magnetic Resonance in Cardiac Amyloidosis. *Circulation* 2015; **132**: 1570-1579 [PMID: [26362631](#) DOI: [10.1161/CIRCULATIONAHA.115.016567](#)]
- 47 **Raina S**, Lensing SY, Nairouz RS, Pothineni NV, Hakeem A, Bhatti S, Pandey T. Prognostic Value of Late Gadolinium Enhancement CMR in Systemic Amyloidosis. *JACC Cardiovasc Imaging* 2016; **9**: 1267-1277 [PMID: [27568115](#) DOI: [10.1016/j.jcmg.2016.01.036](#)]
- 48 **Wan K**, Sun J, Han Y, Luo Y, Liu H, Yang D, Cheng W, Zhang Q, Zeng Z, Chen Y. Right ventricular involvement evaluated by cardiac magnetic resonance imaging predicts mortality in patients with light chain amyloidosis. *Heart Vessels* 2018; **33**: 170-179 [PMID: [28840397](#) DOI: [10.1007/s00380-017-1043-y](#)]
- 49 **Wan K**, Sun J, Han Y, Liu H, Yang D, Li W, Wang J, Cheng W, Zhang Q, Zeng Z, Chen Y. Increased Prognostic Value of Query Amyloid Late Enhancement Score in Light-Chain Cardiac Amyloidosis. *Circ J* 2018; **82**: 739-746 [PMID: [29093431](#) DOI: [10.1253/circj.CJ-17-0464](#)]
- 50 **Boynton SJ**, Geske JB, Dispenzieri A, Syed IS, Hanson TJ, Grogan M, Araoz PA. LGE Provides Incremental Prognostic Information Over Serum Biomarkers in AL Cardiac Amyloidosis. *JACC Cardiovasc Imaging* 2016; **9**: 680-686 [PMID: [27209101](#) DOI: [10.1016/j.jcmg.2015.10.027](#)]
- 51 **Bhatti S**, Watts E, Syed F, Vallurupalli S, Pandey T, Jambekar K, Mazur W, Hakeem A. Clinical and prognostic utility of cardiovascular magnetic resonance imaging in myeloma patients with suspected cardiac amyloidosis. *Eur Heart J Cardiovasc Imaging* 2016; **17**: 970-977 [PMID: [27225804](#) DOI: [10.1093/ehjci/jew101](#)]
- 52 **Migrino RQ**, Christenson R, Szabo A, Bright M, Truran S, Hari P. Prognostic implication of late gadolinium enhancement on cardiac MRI in light chain (AL) amyloidosis on long term follow up. *BMC Med Phys* 2009; **9**: 5 [PMID: [19416541](#) DOI: [10.1186/1756-6649-9-5](#)]
- 53 **Karamitsos TD**, Piechnik SK, Banyersad SM, Fontana M, Ntusi NB, Ferreira VM, Whelan CJ, Myerson SG, Robson MD, Hawkins PN, Neubauer S, Moon JC. Noncontrast T1 mapping for the diagnosis of cardiac amyloidosis. *JACC Cardiovasc Imaging* 2013; **6**: 488-497 [PMID: [23498672](#) DOI: [10.1016/j.jcmg.2012.11.013](#)]
- 54 **Lin L**, Li X, Feng J, Shen KN, Tian Z, Sun J, Mao YY, Cao J, Jin ZY, Li J, Selvanayagam JB, Wang YN. The prognostic value of T1 mapping and late gadolinium enhancement cardiovascular magnetic resonance imaging in patients with light chain amyloidosis. *J Cardiovasc Magn Reson* 2018; **20**: 2 [PMID: [29298704](#) DOI: [10.1186/s12968-017-0419-6](#)]
- 55 **Wan K**, Li W, Sun J, Xu Y, Wang J, Liu H, Dong Y, Cheng W, Zhang Q, Zeng Z, Zhou X, Han Y,

- Chen Y. Regional amyloid distribution and impact on mortality in light-chain amyloidosis: a T1 mapping cardiac magnetic resonance study. *Amyloid* 2019; **26**: 45-51 [PMID: [30931628](#) DOI: [10.1080/13506129.2019.1578742](#)]
- 56 **Martinez-Naharro A**, Kotecha T, Norrington K, Boldrini M, Rezk T, Quarta C, Treibel TA, Whelan CJ, Knight DS, Kellman P, Ruberg FL, Gillmore JD, Moon JC, Hawkins PN, Fontana M. Native T1 and Extracellular Volume in Transthyretin Amyloidosis. *JACC Cardiovasc Imaging* 2019; **12**: 810-819 [PMID: [29550324](#) DOI: [10.1016/j.jcmg.2018.02.006](#)]
- 57 **Wassmuth R**, Abdel-Aty H, Bohl S, Schulz-Menger J. Prognostic impact of T2-weighted CMR imaging for cardiac amyloidosis. *Eur Radiol* 2011; **21**: 1643-1650 [PMID: [21720941](#) DOI: [10.1007/s00330-011-2109-3](#)]
- 58 **Legou F**, Tacher V, Damy T, Planté-Bordeneuve V, Rappeneau S, Benhaïem N, Rosso J, Itti E, Luciani A, Kobeiter H, Rahmouni A, Deux JF. Usefulness of T2 ratio in the diagnosis and prognosis of cardiac amyloidosis using cardiac MR imaging. *Diagn Interv Imaging* 2017; **98**: 125-132 [PMID: [27692958](#) DOI: [10.1016/j.diii.2016.08.007](#)]
- 59 **Treibel TA**, Bandula S, Fontana M, White SK, Gilbertson JA, Herrey AS, Gillmore JD, Punwani S, Hawkins PN, Taylor SA, Moon JC. Extracellular volume quantification by dynamic equilibrium cardiac computed tomography in cardiac amyloidosis. *J Cardiovasc Comput Tomogr* 2015; **9**: 585-592 [PMID: [26209459](#) DOI: [10.1016/j.jcct.2015.07.001](#)]
- 60 **Treibel TA**, Fontana M, Steeden JA, Nasis A, Yeung J, White SK, Sivarajan S, Punwani S, Pugliese F, Taylor SA, Moon JC, Bandula S. Automatic quantification of the myocardial extracellular volume by cardiac computed tomography: Synthetic ECV by CCT. *J Cardiovasc Comput Tomogr* 2017; **11**: 221-226 [PMID: [28268091](#) DOI: [10.1016/j.jcct.2017.02.006](#)]
- 61 **Stats MA**, Stone JR. Varying levels of small microcalcifications and macrophages in ATTR and AL cardiac amyloidosis: implications for utilizing nuclear medicine studies to subtype amyloidosis. *Cardiovasc Pathol* 2016; **25**: 413-417 [PMID: [27469499](#) DOI: [10.1016/j.carpath.2016.07.001](#)]
- 62 **Galat A**, Rosso J, Guellich A, Van Der Gucht A, Rappeneau S, Bodez D, Guendouz S, Tissot CM, Hittinger L, Dubois-Randé JL, Plante-Bordeneuve V, Itti E, Meignan M, Damy T. Usefulness of (99m)Tc-HMDP scintigraphy for the etiologic diagnosis and prognosis of cardiac amyloidosis. *Amyloid* 2015; **22**: 210-220 [PMID: [26465835](#) DOI: [10.3109/13506129.2015.1072089](#)]
- 63 **Perugini E**, Guidalotti PL, Salvi F, Cooke RM, Pettinato C, Riva L, Leone O, Farsad M, Ciliberti P, Bacchi-Reggiani L, Fallani F, Branzi A, Rapezzi C. Noninvasive etiologic diagnosis of cardiac amyloidosis using 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy. *J Am Coll Cardiol* 2005; **46**: 1076-1084 [PMID: [16168294](#) DOI: [10.1016/j.jacc.2005.05.073](#)]
- 64 **Rapezzi C**, Quarta CC, Guidalotti PL, Pettinato C, Fanti S, Leone O, Ferlini A, Longhi S, Lorenzini M, Reggiani LB, Gagliardi C, Gallo P, Villani C, Salvi F. Role of (99m)Tc-DPD scintigraphy in diagnosis and prognosis of hereditary transthyretin-related cardiac amyloidosis. *JACC Cardiovasc Imaging* 2011; **4**: 659-670 [PMID: [21679902](#) DOI: [10.1016/j.jcmg.2011.03.016](#)]
- 65 **Hutt DF**, Fontana M, Burniston M, Quigley AM, Petrie A, Ross JC, Page J, Martinez-Naharro A, Wechalekar AD, Lachmann HJ, Quarta CC, Rezk T, Mahmood S, Sachchithanatham S, Youngstein T, Whelan CJ, Lane T, Gilbertson JA, Rowczenio D, Hawkins PN, Gillmore JD. Prognostic utility of the Perugini grading of 99mTc-DPD scintigraphy in transthyretin (ATTR) amyloidosis and its relationship with skeletal muscle and soft tissue amyloid. *Eur Heart J Cardiovasc Imaging* 2017; **18**: 1344-1350 [PMID: [28159995](#) DOI: [10.1093/ehjci/ehw325](#)]
- 66 **Bokhari S**, Castaño A, Pozniakoff T, Deslisle S, Latif F, Maurer MS. (99m)Tc-pyrophosphate scintigraphy for differentiating light-chain cardiac amyloidosis from the transthyretin-related familial and senile cardiac amyloidoses. *Circ Cardiovasc Imaging* 2013; **6**: 195-201 [PMID: [23400849](#) DOI: [10.1161/CIRCIMAGING.112.000132](#)]
- 67 **Castano A**, Haq M, Narotsky DL, Goldsmith J, Weinberg RL, Morgenstern R, Pozniakoff T, Ruberg FL, Miller EJ, Berk JL, Dispenzieri A, Grogan M, Johnson G, Bokhari S, Maurer MS. Multicenter Study of Planar Technetium 99m Pyrophosphate Cardiac Imaging: Predicting Survival for Patients With ATTR Cardiac Amyloidosis. *JAMA Cardiol* 2016; **1**: 880-889 [PMID: [27557400](#) DOI: [10.1001/jamacardio.2016.2839](#)]
- 68 **Sperry BW**, Vranian MN, Tower-Rader A, Hachamovitch R, Hanna M, Brunken R, Phelan D, Cerqueira MD, Jaber WA. Regional Variation in Technetium Pyrophosphate Uptake in Transthyretin Cardiac Amyloidosis and Impact on Mortality. *JACC Cardiovasc Imaging* 2018; **11**: 234-242 [PMID: [28917675](#) DOI: [10.1016/j.jcmg.2017.06.020](#)]
- 69 **Dorbala S**, Vangala D, Semer J, Strader C, Bruyere JR Jr, Di Carli MF, Moore SC, Falk RH. Imaging cardiac amyloidosis: a pilot study using ¹⁸F-florbetapir positron emission tomography. *Eur J Nucl Med Mol Imaging* 2014; **41**: 1652-1662 [PMID: [24841414](#) DOI: [10.1007/s00259-014-2787-6](#)]
- 70 **Law WP**, Wang W, Moore P, Mollee P, Ng A. Cardiac amyloid imaging with ¹⁸F-florbetaben positron emission tomography: a pilot study. *Amyloid* 2017; **24**: 162 [PMID: [28434374](#) DOI: [10.1080/13506129.2017.1281120](#)]
- 71 **Tanaka M**, Hongo M, Kinoshita O, Takabayashi Y, Fujii T, Yazaki Y, Isobe M, Sekiguchi M. Iodine-123 metaiodobenzylguanidine scintigraphic assessment of myocardial sympathetic innervation in patients with familial amyloid polyneuropathy. *J Am Coll Cardiol* 1997; **29**: 168-174 [PMID: [8996310](#) DOI: [10.1016/s0735-1097\(96\)00438-x](#)]
- 72 **Coutinho MC**, Cortez-Dias N, Cantinho G, Conceição I, Oliveira A, Bordalo e Sá A, Gonçalves S, Almeida AG, de Carvalho M, Diogo AN. Reduced myocardial 123-iodine metaiodobenzylguanidine uptake: a prognostic marker in familial amyloid polyneuropathy. *Circ Cardiovasc Imaging* 2013; **6**:

- 627-636 [PMID: [23833285](#) DOI: [10.1161/CIRCIMAGING.112.000367](#)]
- 73 **Algalarrondo V**, Antonini T, Théaudin M, Chemla D, Benmalek A, Lacroix C, Castaing D, Cauquil C, Dinanian S, Eliahou L, Samuel D, Adams D, Le Guludec D, Slama MS, Rouzet F. Cardiac Dysautonomia Predicts Long-Term Survival in Hereditary Transthyretin Amyloidosis After Liver Transplantation. *JACC Cardiovasc Imaging* 2016; **9**: 1432-1441 [PMID: [27838303](#) DOI: [10.1016/j.jcmg.2016.07.008](#)]
- 74 **Piekarski E**, Chequer R, Algalarrondo V, Eliahou L, Mahida B, Vigne J, Adams D, Slama MS, Le Guludec D, Rouzet F. Cardiac denervation evidenced by MIBG occurs earlier than amyloid deposits detection by diphosphonate scintigraphy in TTR mutation carriers. *Eur J Nucl Med Mol Imaging* 2018; **45**: 1108-1118 [PMID: [29511839](#) DOI: [10.1007/s00259-018-3963-x](#)]
- 75 **Martin-Isla C**, Campello VM, Izquierdo C, Raisi-Estabragh Z, Baeßler B, Petersen SE, Lekadir K. Image-Based Cardiac Diagnosis With Machine Learning: A Review. *Front Cardiovasc Med* 2020; **7**: 1 [PMID: [32039241](#) DOI: [10.3389/fcvm.2020.00001](#)]
- 76 **Leiner T**, Rueckert D, Suinesiaputra A, Baeßler B, Nezafat R, Išgum I, Young AA. Machine learning in cardiovascular magnetic resonance: basic concepts and applications. *J Cardiovasc Magn Reson* 2019; **21**: 61 [PMID: [31590664](#) DOI: [10.1186/s12968-019-0575-y](#)]
- 77 **Zhang J**, Gajjala S, Agrawal P, Tison GH, Hallock LA, Beussink-Nelson L, Lassen MH, Fan E, Aras MA, Jordan C, Fleischmann KE, Melisko M, Qasim A, Shah SJ, Bajcsy R, Deo RC. Fully Automated Echocardiogram Interpretation in Clinical Practice. *Circulation* 2018; **138**: 1623-1635 [PMID: [30354459](#) DOI: [10.1161/CIRCULATIONAHA.118.034338](#)]
- 78 **Maurer MS**, Bokhari S, Damy T, Dorbala S, Drachman BM, Fontana M, Grogan M, Kristen AV, Lousada I, Nativi-Nicolau J, Cristina Quarta C, Rapezzi C, Ruberg FL, Witteles R, Merlini G. Expert Consensus Recommendations for the Suspicion and Diagnosis of Transthyretin Cardiac Amyloidosis. *Circ Heart Fail* 2019; **12**: e006075 [PMID: [31480867](#) DOI: [10.1161/CIRCHEARTFAILURE.119.006075](#)]

Retrospective Cohort Study

Safety and performance of the EverPro™ everolimus-eluting coronary stent system with biodegradable polymer in a real-world scenario

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Abstract

BACKGROUND

The EverPro™ (Sahajanand Laser Technology Ltd., India) everolimus-eluting coronary stent system (EES) is a second-generation drug-eluting stent with a biodegradable polymer.

AIM

To determine the safety and performance of the EverPro™ EES in patients with coronary artery disease (CAD) during a 1-year clinical follow-up.

METHODS

This observational, retrospective, single-center study enrolled patients who had been implanted with the EverPro™ stent between June 1, 2018 and January 31, 2019, and had completed a 1-year follow-up period after the index procedure. The primary clinical endpoint was major adverse cardiac events (MACE) at 6 mo defined as the composite of cardiac death, myocardial infarction (MI), and target lesion revascularization (TLR). Secondary endpoints were the incidence of TLR at 1, 6 and 12 mo follow-up, MACE at 1 and 12 mo follow-up, and stent thrombosis up to 1 year after the index procedure.

RESULTS

The study population comprised 77 patients (98 lesions). A total of 37 (48.1%) patients had comorbid hypertension. In total, 26 (33.8%) patients presented with ST segment elevation MI and 10.4% patients with non-ST segment elevation MI. Treated lesions were located mainly in the left anterior descending artery (49%)

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followed by the right coronary artery (29.6%), left circumflex (12.2%) and obtuse marginal (9.2%) arteries. The majority of patients were with single-vessel disease (79%), 22.2% of lesions had a mild to severe thrombus load, and 94.9% were American College of Cardiology/American Heart Association type B or C. *De novo* stenting was performed in 96.9% of patients and 3% were treated for in-stent restenosis. Procedural success was attained in all patients. In-hospital or follow-up MACE and stent thrombosis were not reported during the 1-year follow-up period.

CONCLUSION

These findings suggest that the EverPro™ EES is a safe and effective treatment option with no MACE or stent thrombosis reported during the 1-year study period in patients with CAD.

Key Words: Coronary artery disease; Everolimus; Major adverse cardiac event; Retrospective, EverPro™, Myocardial infarction

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Core Tip: New-generation drug-eluting stents (DES) reduce the risk of stent thrombosis. However, the everolimus-eluting coronary stent system (EES) exerts higher interaction with rapamycin complex 2, higher bioavailability, shorter half-life than sirolimus, decreases vascular inflammation and promotes rapid endothelialization; therefore, outperforms paclitaxel DES in safety and efficacy. EverPro™, a second-generation EES with a biodegradable polymer and a 60 µm cobalt-chromium platform design, facilitates reduction in intra-arterial injury. This observational study enrolled 77 patients with coronary artery disease (CAD), implanted with the EverPro™ stent who completed a 1-year follow-up period after the index procedure. Our findings suggested that EverPro™ EES is safe and effective with no major adverse cardiac events/stent thrombosis during the 1 year follow-up period in patients with CAD.

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INTRODUCTION

The incidence of coronary artery disease (CAD) has been increasing, causing significant morbidity and mortality worldwide^[1]. Percutaneous coronary intervention is an increasingly performed revascularization modality for the treatment of CAD. It aims to restore blood supply to myocardial tissues with poor blood supply due to coronary stenosis or vessel occlusion.

Bare-metal stents (BMS) have demonstrated superior clinical outcomes over balloon angioplasty, but neointimal hyperplasia and restenosis are the major challenges in BMS technology. Evidence suggests that revascularization rates have markedly decreased with the use of drug-eluting stents (DES) compared to BMS^[2-4], but the risk of late stent thrombosis was the major limitation of the first-generation of DES. Second-generation DES were designed to reduce stent thrombosis and maintain good acute and long-term results. Advances in DES technology, such as new polymers, novel platform material and structure, alteration in coating distribution or additional coating and better antiproliferative drugs, have resulted in the development of new generations of DES.

Polymer composition and stent strut thickness are important factors affecting the clinical outcomes of DES. First-generation DES were manufactured from durable polymer and had thick struts which trigger the inflammatory process and induce stent thrombosis, while the new-generation DES employ biocompatible polymers that will be fully resorbed by hydrolysis after drug release. The strut thickness greatly differs

among the available biodegradable polymer DES and thinner struts reduce vessel wall injury, decrease inflammation and promote faster endothelialization^[5]. The strut thickness of new-generation biodegradable polymer stents is half of that in the first-generation biodegradable polymer DES^[6]. Therefore, new-generation DES reduce the risk of stent thrombosis compared with first-generation DES, particularly very late stent thrombosis that can occur after discontinuation of dual antiplatelet agents^[4]. Coronary stent systems with metal alloys and biodegradable polymers show similar clinical outcomes compared with durable polymer DES^[7-9].

Antiproliferative drugs in the second-generation DES belong to the “limus family” (sirolimus, everolimus, zotarolimus) that inhibit mammalian target of rapamycin, and everolimus is known to exert much higher interaction with rapamycin complex 2. This interaction blocks protein synthesis and arrests cell cycle progression, inhibits smooth muscle cell proliferation and reduces stent restenosis. Everolimus has higher bioavailability and a shorter half-life than sirolimus; it decreases vascular inflammation and promotes rapid endothelialization. Everolimus-eluting stents have outperformed paclitaxel DES, and outcomes are comparable with zotarolimus- and sirolimus-eluting stents in terms of safety and efficacy as shown in various clinical studies^[10-12]. The EverPro™ everolimus-eluting coronary stent system (EES) is an approved coronary stent system with a biodegradable polymer. It has an ultra-thin (60 µm) cobalt-chromium platform design that facilitates a reduction in intra-arterial injury. The present post-marketing surveillance study aimed to determine the safety and performance of the EverPro™ EES in patients with CAD during the 1-year clinical follow-up.

MATERIALS AND METHODS

Study design

In this single-center, observational study, consecutive patients who were implanted with the EverPro™ stent between June 1, 2018 and January 31, 2019 at The Atma Malik Hospital, Maharashtra, India, and who completed 1-year follow-up were retrospectively selected from June 2019 to January 2020. The study protocol was approved by an independent ethics committee (Sangini Hospital Ethics Committee on June 8, 2020), and a waiver of informed consent was obtained. The study was conducted in accordance with the Declaration of Helsinki and the principles of good clinical practice, CTRI/2020/07/026564.

Patient selection

All patients aged > 18 years and implanted with EverPro™ stents to treat CAD were included. Patients treated with stents other than the EverPro™ stent during the index procedure, pregnant/lactating women, and those with grade III renal insufficiency, left ventricular ejection fraction < 30%, history of cardiac failure, structural heart disease, cardiomyopathies, or arrhythmia were excluded. A detailed description of the inclusion and exclusion criteria is provided in [Figure 1](#).

Device description

The EverPro™ (Sahajanand Laser Technologies Ltd., India) EES is an approved DES comprising a biodegradable polymer and surgical grade cobalt-chromium L605 alloy, everolimus as the active pharmaceutical ingredient and poly-L-lactide (PLLA) and poly-DL-lactide-co-glycolide (PLGA) as the drug carrier. PLLA and PLGA in the EverPro™ EES slowly and gradually erode within six months into small molecules, and are metabolized and excreted as carbon dioxide and water. The design of the everolimus-eluting coronary stent is an 8-crown laser cut hybrid design that provides uniform vessel scaffolding and drug distribution ([Figure 2](#)).

Study procedure and data collection

The indications for the angioplasty procedure and stent implantation were at the discretion of the treating physicians per the standard treatment guidelines. Baseline patient data, including age, gender, medical history, angina status, and clinical presentation were collected retrospectively from inpatient and outpatient clinical notes, angiogram reports, and procedural angiographic images and discharge summaries. Routine laboratory data including cardiac biomarkers, blood chemistry, and 12-lead electrocardiogram were also collected. The data from the paper case report forms were translated to a central database that was used for the final analysis. The

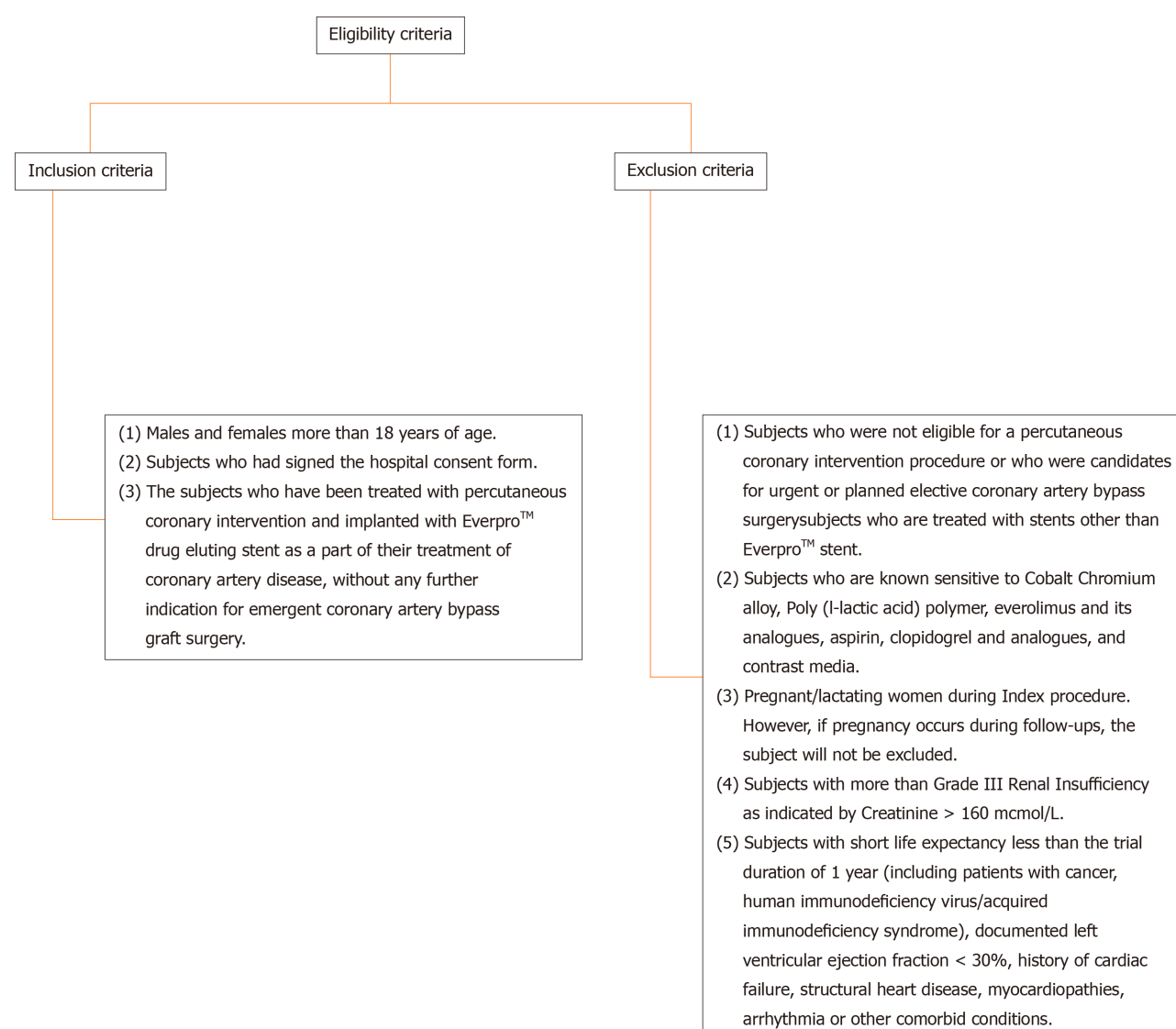


Figure 1 Eligibility criteria for the study.

follow-up data of patients attending the clinic were extracted from their medical records. A few patients were followed up by telephone and asked a list of questions from a structured questionnaire to determine the exact status of the endpoint. We excluded patients with incomplete medical notes or those who did not respond to telephonic follow-ups.

Study endpoints and definitions

The primary clinical endpoint of this study was major adverse cardiac events (MACE) at 6-mo follow-up. MACE was defined as a composite of cardiac death, myocardial infarction (MI), and target lesion revascularization (TLR). The secondary endpoints consisted of TLR at 1, 6 and 12 mo follow-up, MACE at 1, and 12 mo follow-up, and the frequency of stent thrombosis up to 1 year after the date of stent implantation. The outcomes of stent thrombosis were further divided into definite, probable, and possible stent thrombosis, as defined by The Academic Research Consortium^[13,14]. Cardiac death was considered in the case of any death owing to cardiac cause (MI, low output failure and lethal arrhythmia), unobserved death, death due to unknown reasons, and all procedure-related deaths, including those associated with concomitant treatment. MI was defined as an increase in cardiac troponin values [$> 5 \times 99^{\text{th}}$ percentile upper reference limit (URL)] in patients with normal baseline values ($\leq 99^{\text{th}}$ percentile URL) or an increase in cardiac troponin values of $> 20\%$ when the baseline values were elevated and stable, or declining. Pathological Q waves were defined as per amplitude, location, and depth if they were present in at least two contiguous leads. Restenosis within the stent or in the 5-mm distal or proximal to the stent was considered to require TLR. Stenosis in any segment of the treated vessel was defined

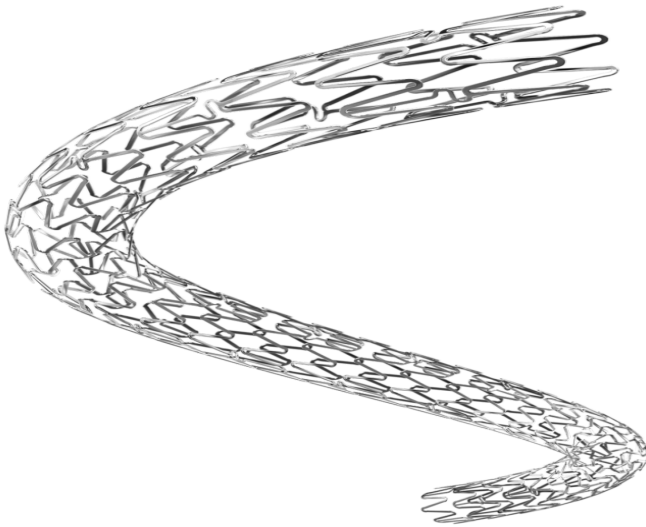


Figure 2 Design of the everolimus-eluting coronary stent.

as target vessel revascularization. The incidence of stent thrombosis was considered acute if it occurred within 24 h, sub-acute if it occurred between 1 and 30 d, and late if it took place after 30 d. Any symptoms suggestive of an acute coronary syndrome and angiographic or pathological confirmation were termed as definite stent thrombosis. Any unexplained death within 30 d or target vessel MI without angiographic confirmation of stent thrombosis was described as probable stent thrombosis. Unexplained death after 30 d was described as possible stent thrombosis.

Statistical analysis

All calculations were based on the available data and missing data were excluded from the calculations. Categorical data are presented as frequency and percentages. Continuous variables are presented as the mean \pm standard deviation (SD). The data were analyzed using the Statistical Package for Social Sciences program (SPSS Inc., Chicago, IL, United States), version 23.

As no hypothesis was tested in the study, we did not perform formal sample size calculation and included patients who met the eligibility criteria during the stipulated time.

RESULTS

Baseline demographic and clinical characteristics

The total study population comprised 77 patients (98 lesions). Baseline demographic and clinical characteristics are shown in [Table 1](#). The mean (SD) age of patients was 55 ± 11.8 years, and 77% were men. A total of 48% of patients had comorbid hypertension, 19.4% had diabetes, and 31% were smokers. The majority of patients presented with MI (44.2%) followed by stable angina in 39%. The majority of patients had single-vessel disease (79%).

Procedural and lesion characteristics

A total of 102 lesions were detected in these patients, and 98 lesions were treated by implantation of the EverPro™ stent. Treated lesions were located mainly in the left anterior descending artery (49%), followed by the right coronary artery (29.6%), left circumflex (12.2%) and obtuse marginal (9.2%) arteries. Approximately 22.2% of lesions had a mild to severe thrombus load and 94.9% lesions were American College of Cardiology/American Heart Association type B or C. *De novo* stenting was performed in 96.9% of patients and 3% were treated for in-stent restenosis. Procedure-related details are shown in [Table 2](#). Procedural success was attained in all patients with no in-hospital MACE. All patients were prescribed antiplatelet agents at discharge ([Table 2](#)).

Table 1 Baseline demographics and clinical characteristics

Characteristics	<i>n</i> = 77
Age (mean ± SD), yr	55 ± 11.8
Men, <i>n</i> (%)	59 (76.6)
Medical history, <i>n</i> (%)	
Hypertension	37 (48.1)
Diabetes	15 (19.48)
Smoking	24 (31.2)
Consumption of alcohol	9 (11.7)
Stroke	2 (2.6)
Previous coronary intervention	4 (5.2)
Previous myocardial infarction	34 (44.2)
Cardiac status, <i>n</i> (%)	
Stable angina	30 (39)
Unstable angina	13 (16.9)
STEMI	26 (33.8)
NSTEMI	8 (10.4)
Coronary angiogram finding, <i>n</i> (%)	
Single-vessel disease	61 (79.2)
Double-vessel disease	16 (20.8)
Triple-vessel disease	0 (0.0)
Heart rate (mean ± SD), bpm	81.26 ± 12.08
Systolic blood pressure (mean ± SD), mmHg	134.91 ± 27.51
Diastolic blood pressure (mean ± SD), mmHg	83.19 ± 13.57
Serum creatinine (mean ± SD), mg/dL	1.13 ± 0.23
LVEF (mean ± SD), %	46.38 ± 8.19

LVEF: Left ventricular ejection fraction; NSTEMI: Non-stent thrombosis segment elevation myocardial infarction; SD: Standard deviation; STEMI: Stent thrombosis segment elevation myocardial infarction; bpm: Beats per minute.

Clinical outcomes during follow-up

MACE and stent thrombosis were not observed in any patient throughout the 1-year follow-up period.

DISCUSSION

This post-marketing surveillance study was performed to determine the safety and performance of EverPro™ stents for the treatment of CAD in a real-world clinical setting. The results of this study show that the EverPro™ stent was not associated with MACE or TLR. In addition, stent thrombosis was not observed during the 1-year follow-up period.

The clinical performance and safety of everolimus-eluting stents in the treatment of CAD have been well documented. The series of SPIRIT clinical trials demonstrated the superior efficacy of EES over BMS and paclitaxel-eluting stents^[10]. Furthermore, a meta-analysis of the final results of SPIRIT II, III, and IV clinical trials demonstrated that EES was superior to paclitaxel-eluting stents in reducing target lesion failure (8.9% *vs* 12.5%, *P* = 0.0002), all-cause mortality (3.2% *vs* 5.1%, *P* = 0.003), MI (3.2% *vs* 5.1%, *P* = 0.002), cardiac death or MI (4.4% *vs* 6.3%, *P* = 0.005), ischemia-driven TLR (6.0% *vs* 8.2%, *P* = 0.004), stent thrombosis (0.7% *vs* 1.7%, *P* = 0.003), and MACE (9.4% *vs* 13.0%,

Table 2 Procedural and lesion characteristics

Characteristics	n = 77
Access site approach, n (%)	
Femoral	20 (26)
Radial	57 (74)
Total number of lesions	102
Total number of lesions treated with EverPro™	98
Lesions per patient	1.32
Stents per patient	1.27
Lesion location, n (%)	
Right carotid artery	29 (29.6)
Left anterior descending artery	48 (49)
Left circumflex artery	12 (12.2)
Obtuse marginal artery	9 (9.2)
Stenosis type, n (%)	
<i>De novo</i>	95 (96.9)
In-stent	3 (3.1)
Thrombus load, n (%)	
None	76 (77.6)
Mild	10 (10.2)
Moderate	5 (5.1)
Severe	7 (7.1)
ACC/AHA lesion type, n (%)	
A	5 (5.1)
B1	30 (30.6)
B2	38 (38.8)
C	25 (25.5)
Percent stenosis (mean ± SD)	88.39 ± 9.30
Stent length (mean ± SD), mm	18.20 ± 4.34
Stent diameter (mean ± SD), mm	2.89 ± 0.36
TIMI flow post-procedure, n (%)	
TIMI 3	98 (100)
Discharge medications, n (%)	
Aspirin	77 (100)
Clopidogrel	44 (57.1)
Ticlopidine	2 (2.6)
Prasugrel	3 (3.9)
Ticagrelor	27 (35.1)

ACC: American College of Cardiology; AHA: American Heart Association; SD: Standard deviation; TIMI: Thrombolysis in myocardial infarction.

$P = 0.0002$)^[11]. The safety and efficacy of EES have also been demonstrated in selected high-risk patients in real-world studies. The XIENCE V United States trial evaluated 5054 participants, and 98.1% reached the 1-year follow-up. No stent thrombosis was observed in standard-risk and high-risk patients even after discontinuation of dual antiplatelet therapy after 6 mo^[15]. EES have been compared with sirolimus-eluting stents, and at 5 years, MACE (14.0% *vs* 17.4%, respectively) and stent thrombosis (0.4% *vs* 2.0%, respectively) rates were found to be lower in the EES group than in the SES group^[16]. Clinical studies comparing zotarolimus-eluting stents (ZES) to EES have shown that ZES are non-inferior to EES with regard to death from cardiac causes, MI, or clinically indicated TLR within 1 year. However, the rate of stent thrombosis was higher with ZES than with EES (2.3% *vs* 1.5%)^[17]. In a meta-analysis, compared to paclitaxel and sirolimus, EES were also found to be more efficacious and safe in patients with concomitant diabetes, resulting in a reduction in MACE by 18%, MI by 43%, and stent thrombosis by 46%^[18].

The 12-mo MACE rate following implantation of EES ranged from 0.3% to 6.2% for diverse clinical presentations in randomized trials, and real-world studies^[19-24]. The 1-year incidence of MACE following treatment with another indigenous biodegradable polymer DEC ranged from 0.9% to 4.2%^[25-27]. No MACE was reported during the 1-year follow-up period in our study. The EverPro™ stent has a very thin strut (60 µm) and it is built on a cobalt-chromium L605 alloy platform with SCHIFFSORB polymer technology. The biodegradable polymers PLLA and PLGA degrade entirely and reduce the risk of thrombosis. The stent has an innovative “S”- and alternate “C”-linked 8-crown design that enhances flexibility and provides high radial strength. With foreshortening of < 0.2%, it is ideal for all lesion locations, including ostial lesions. Additionally, the utilization of electropolishing technology results in an ultra-smooth stent surface that reduces the risk of edge dissection and very late stent thrombosis. These properties may have contributed to the procedural success and good clinical outcomes observed in this study.

While these data on the use of the EverPro™ stent in the treatment of CAD are very promising, this study is limited by its observational design, retrospective analysis of data, small sample size, and a short follow-up period. Therefore, the results need to be substantiated in well-designed studies with a longer follow-up duration.

CONCLUSION

The findings of this study support the favorable safety and performance of the EverPro™ EES. Product characteristics, such as the conformal coating of everolimus and ultra-smooth stent surface, which provides high radial strength with minimal foreshortening, may be responsible for the results. The EverPro™ EES could be an effective alternative to other contemporary DES for the treatment of CAD.

ARTICLE HIGHLIGHTS

Research background

The increasing prevalence of coronary artery disease (CAD) has caused significantly higher rates of morbidity and mortality worldwide. Thus, percutaneous coronary intervention, a revascularization modality to treat CAD, restores blood supply to myocardial tissues. Antiproliferative drugs in second-generation drug-eluting stents (DES) inhibit mammalian target of rapamycin and affect stent restenosis. However, EverPro™, an approved second-generation everolimus-eluting coronary stent system (EES) with a biodegradable polymer facilitates a reduction in intra-arterial injury.

Research motivation

Sirolimus has a longer half-life, lower bioavailability and does not directly affect stent restenosis. However, everolimus outperforms sirolimus and can decrease vascular inflammation and promote rapid endothelialization. These findings indicate the potential of EES to replace second-generation DES and impart benefits to patients with CAD.

Research objectives

The objectives of this study were to determine the safety and performance of EverPro™ EES in a real-world scenario and to translate its use in the real world as an

effective alternative to DES for the treatment of CAD. The EverPro™ EES could offer various benefits in addition to reduced stent restenosis and rapid endothelialization.

Research methods

This single-center, observational study enrolled patients who completed a 1-year follow-up period after being implanted with the EverPro™ stent (between June 1, 2018 and January 31, 2019). As no hypothesis was tested in the study, we did not perform a formal sample size calculation and included patients who met the eligibility criteria during the stipulated time.

Research results

Of the 102 lesions detected in the included patients, 98 lesions were treated by implantation of the EverPro™ stent. *De novo* stenting was performed in 96.9% of patients and 3% were treated for in-stent restenosis. Procedural success was attained in all patients with no in-hospital major adverse cardiac events (MACE) or stent thrombosis observed throughout the follow-up period. However, the results were limited by the study's observational nature, retrospective data analysis and a shorter follow-up period.

Research conclusions

The results showed that EverPro™ EES is a safe and effective treatment alternative as no MACE or stent thrombosis was observed during the 1-year study period in patients with CAD.

Research perspectives

The data on the use of the EverPro™ stent in the treatment of CAD are very promising. However, if future studies can overcome the study limitation by conducting well-designed studies with a larger sample size and a longer follow-up duration, EverPro™ EES can be used as an alternative to contemporary DES for treating CAD.

REFERENCES

- 1 **Jayashree S**, Arindam M, Vijay KV. Genetic epidemiology of coronary artery disease: an Asian Indian perspective. *J Genet* 2015; **94**: 539-549 [PMID: 26440097 DOI: 10.1007/s12041-015-0547-4]
- 2 **Drachman DE**. Clinical experience with drug-eluting stents. *Rev Cardiovasc Med* 2002; **3** Suppl 5: S31-S37 [PMID: 12478233]
- 3 **Morice MC**, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico R; RAVEL Study Group. Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002; **346**: 1773-1780 [PMID: 12050336 DOI: 10.1056/NEJMoa012843]
- 4 **Daemen J**, Wenaweser P, Tsuchida K, Abrecht L, Vaina S, Morger C, Kukreja N, Jüni P, Sianos G, Hellige G, van Domburg RT, Hess OM, Boersma E, Meier B, Windecker S, Serruys PW. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institution cohort study. *Lancet* 2007; **369**: 667-678 [PMID: 17321312 DOI: 10.1016/S0140-6736(07)60314-6]
- 5 **Kang SH**, Park KW, Kang DY, Lim WH, Park KT, Han JK, Kang HJ, Koo BK, Oh BH, Park YB, Kandzari DE, Cohen DJ, Hwang SS, Kim HS. Biodegradable-polymer drug-eluting stents vs. bare metal stents vs. durable-polymer drug-eluting stents: a systematic review and Bayesian approach network meta-analysis. *Eur Heart J* 2014; **35**: 1147-1158 [PMID: 24459196 DOI: 10.1093/eurheartj/ehu570]
- 6 **Byrne RA**, Stone GW, Ormiston J, Kastrati A. Coronary balloon angioplasty, stents, and scaffolds. *Lancet* 2017; **390**: 781-792 [PMID: 28831994 DOI: 10.1016/S0140-6736(17)31927-X]
- 7 **Zhang Y**, Tian N, Dong S, Ye F, Li M, Bourantas CV, Iqbal J, Onuma Y, Muramatsu T, Diletti R, Garcia-Garcia HM, Xu B, Serruys PW, Chen S. Impact of biodegradable versus durable polymer drug-eluting stents on clinical outcomes in patients with coronary artery disease: a meta-analysis of 15 randomized trials. *Chin Med J (Engl)* 2014; **127**: 2159-2166 [PMID: 24890171]
- 8 **Picard F**, Pighi M, de Hemptinne Q, Airaksinen J, Vinco G, de Pommereau A, Biancari F, Varenne O. Comparison of the biodegradable polymer everolimus-eluting stent with contemporary drug-eluting stents: A systematic review and meta-analysis. *Int J Cardiol* 2019; **278**: 51-56 [PMID: 30503189 DOI: 10.1016/j.ijcard.2018.11.113]
- 9 **Kufner S**, Joner M, Thannheimer A, Hoppmann P, Ibrahim T, Mayer K, Cassese S, Laugwitz KL, Schunkert H, Kastrati A, Byrne RA; ISAR-TEST 4 (Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents) Investigators. Ten-Year Clinical Outcomes From a

- Trial of Three Limus-Eluting Stents With Different Polymer Coatings in Patients With Coronary Artery Disease. *Circulation* 2019; **139**: 325-333 [PMID: 30586724 DOI: 10.1161/CIRCULATIONAHA.118.038065]
- 10 **Townsend JC**, Rideout P, Steinberg DH. Everolimus-eluting stents in interventional cardiology. *Vasc Health Risk Manag* 2012; **8**: 393-404 [PMID: 22910420 DOI: 10.2147/VHRM.S23388]
- 11 **Dangas GD**, Serruys PW, Kereiakes DJ, Hermiller J, Rizvi A, Newman W, Sudhir K, Smith RS Jr, Cao S, Theodoropoulos K, Cutlip DE, Lansky AJ, Stone GW. Meta-analysis of everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease: final 3-year results of the SPIRIT clinical trials program (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions). *JACC Cardiovasc Interv* 2013; **6**: 914-922 [PMID: 24050859 DOI: 10.1016/j.jcin.2013.05.005]
- 12 **Piccolo R**, Stefanini GG, Franzone A, Spitzer E, Blöchliger S, Heg D, Jüni P, Windecker S. Safety and efficacy of resolute zotarolimus-eluting stents compared with everolimus-eluting stents: a meta-analysis. *Circ Cardiovasc Interv* 2015; **8** [PMID: 25858975 DOI: 10.1161/CIRCINTERVENTIONS.114.002223]
- 13 **Cutlip DE**, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW; Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007; **115**: 2344-2351 [PMID: 17470709 DOI: 10.1161/CIRCULATIONAHA.106.685313]
- 14 **Thygesen K**, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD; Joint ESC/ACCF/AHA/WHF Task Force for Universal Definition of Myocardial Infarction; Authors/Task Force Members Chairpersons, Thygesen K, Alpert JS, White HD; Biomarker Subcommittee, Jaffe AS, Katus HA, Apple FS, Lindahl B, Morrow DA; ECG Subcommittee, Chaitman BR, Clemmensen PM, Johanson P, Hod H; Imaging Subcommittee, Underwood R, Bax JJ, Bonow JJ, Pinto F, Gibbons RJ; Classification Subcommittee, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW; Intervention Subcommittee, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasche P, Ravkilde J; Trials & Registries Subcommittee, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML; Trials & Registries Subcommittee, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G; Trials & Registries Subcommittee, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D; Trials & Registries Subcommittee, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S; ESC Committee for Practice Guidelines (CPG), Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S; Document Reviewers, Morais J, Aguiar C, Almahmeed W, Armar DO, Barili F, Bloch KD, Bolger AF, Botker HE, Bozkurt B, Bugiardini R, Cannon C, de Lemos J, Eberli FR, Escobar E, Hlatky M, James S, Kern KB, Moliterno DJ, Mueller C, Neskovic AN, Pieske BM, Schulman SP, Storey RF, Taubert KA, Vranckx P, Wagner DR. Third universal definition of myocardial infarction. *J Am Coll Cardiol* 2012; **60**: 1581-1598 [PMID: 22958960 DOI: 10.1016/j.jacc.2012.08.001]
- 15 **Krucoff MW**, Rutledge DR, Gruberg L, Jonnavithula L, Katopodis JN, Lombardi W, Mao VW, Sharma SK, Simonton CA, Tamboli HP, Wang J, Wilburn O, Zhao W, Sudhir K, Hermiller JB. A new era of prospective real-world safety evaluation primary report of XIENCE V USA (XIENCE V Everolimus Eluting Coronary Stent System condition-of-approval post-market study). *JACC Cardiovasc Interv* 2011; **4**: 1298-1309 [PMID: 22192371 DOI: 10.1016/j.jcin.2011.08.010]
- 16 **Jensen LO**, Thayssen P, Christiansen EH, Maeng M, Ravkilde J, Hansen KN, Hansen HS, Krusell L, Kaltoft A, Tilsted HH, Berencsi K, Junker A, Lassen JF; SORT OUT IV Investigators. Safety and Efficacy of Everolimus- Versus Sirolimus-Eluting Stents: 5-Year Results From SORT OUT IV. *J Am Coll Cardiol* 2016; **67**: 751-762 [PMID: 26892409 DOI: 10.1016/j.jacc.2015.11.051]
- 17 **Serruys PW**, Silber S, Garg S, van Geuns RJ, Richardt G, Buszman PE, Kelbaek H, van Boven AJ, Hofma SH, Linke A, Klauss V, Wijns W, Macaya C, Garot P, DiMario C, Manoharan G, Kornowski R, Ischinger T, Bartorelli A, Ronden J, Bressers M, Gobbens P, Negoita M, van Leeuwen F, Windecker S. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. *N Engl J Med* 2010; **363**: 136-146 [PMID: 20554978 DOI: 10.1056/NEJMoa1004130]
- 18 **Bavishi C**, Baber U, Panwar S, Pirrotta S, Dangas GD, Moreno P, Tamis-Holland J, Kini AS, Sharma SK. Efficacy and safety of everolimus and zotarolimus-eluting stents versus first-generation drug-eluting stents in patients with diabetes: A meta-analysis of randomized trials. *Int J Cardiol* 2017; **230**: 310-318 [PMID: 28062139 DOI: 10.1016/j.ijcard.2016.12.116]
- 19 **Park KW**, Chae IH, Lim DS, Han KR, Yang HM, Lee HY, Kang HJ, Koo BK, Ahn T, Yoon JH, Jeong MH, Hong TJ, Chung WY, Jo SH, Choi YJ, Hur SH, Kwon HM, Jeon DW, Kim BO, Park SH, Lee NH, Jeon HK, Gwon HC, Jang YS, Kim HS. Everolimus-eluting versus sirolimus-eluting stents in patients undergoing percutaneous coronary intervention: the EXCELLENT (Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting) randomized trial. *J Am Coll Cardiol* 2011; **58**: 1844-1854 [PMID: 22018294 DOI: 10.1016/j.jacc.2011.07.031]
- 20 **Kim WJ**, Lee SW, Park SW, Kim YH, Yun SC, Lee JY, Park DW, Kang SJ, Lee CW, Lee JH, Choi SW, Seong IW, Lee BK, Lee NH, Cho YH, Shin WY, Lee SJ, Lee SW, Hyon MS, Bang DW, Park WJ, Kim HS, Chae JK, Lee K, Park HK, Park CB, Lee SG, Kim MK, Park KH, Choi YJ, Cheong SS, Yang TH, Jang JS, Her SH, Park SJ; ESSENCE-DIABETES Study Investigators. Randomized comparison of everolimus-eluting stent versus sirolimus-eluting stent implantation for de novo

- coronary artery disease in patients with diabetes mellitus (ESSENCE-DIABETES): results from the ESSENCE-DIABETES trial. *Circulation* 2011; **124**: 886-892 [PMID: [21810659](#) DOI: [10.1161/CIRCULATIONAHA.110.015453](#)]
- 21 **Kimura T**, Morimoto T, Natsuaki M, Shiomi H, Igarashi K, Kadota K, Tanabe K, Morino Y, Akasaka T, Takatsu Y, Nishikawa H, Yamamoto Y, Nakagawa Y, Hayashi Y, Iwabuchi M, Umeda H, Kawai K, Okada H, Kimura K, Simonton CA, Kozuma K; RESET Investigators. Comparison of everolimus-eluting and sirolimus-eluting coronary stents: 1-year outcomes from the Randomized Evaluation of Sirolimus-eluting Versus Everolimus-eluting stent Trial (RESET). *Circulation* 2012; **126**: 1225-1236 [PMID: [22824435](#) DOI: [10.1161/CIRCULATIONAHA.112.104059](#)]
 - 22 **Hofma SH**, Brouwer J, Velders MA, van't Hof AW, Smits PC, Quéré M, de Vries CJ, van Boven AJ. Second-generation everolimus-eluting stents *versus* first-generation sirolimus-eluting stents in acute myocardial infarction. 1-year results of the randomized XAMI (XienceV Stent vs. Cypher Stent in Primary PCI for Acute Myocardial Infarction) trial. *J Am Coll Cardiol* 2012; **60**: 381-387 [PMID: [22835668](#) DOI: [10.1016/j.jacc.2012.01.073](#)]
 - 23 **Kasturi S**. Safety and efficacy of a novel everolimus eluting stent system in real world patients with coronary artery disease, a report of 1 year outcomes from ongoing see-real registry. *Eur Heart J* 2018; **39**: 1340
 - 24 **Alidoosti M**, Sharifnia V, Kassaian SE, Hajizeinali A, Poorhosseini H, Salarifar M, Nozari Y, Hakki Kazazi E. One-Year Outcome of Everolimus-Eluting Stents Versus Biolimus-Eluting Stents in Patients Undergoing Percutaneous Coronary Intervention. *J Tehran Heart Cent* 2016; **11**: 62-67 [PMID: [27928256](#)]
 - 25 **Abhyankar A**, Sandhu MS, Polavarapu RS. Twelve-month comparative analysis of clinical outcomes using biodegradable polymer-coated everolimus-eluting stents *versus* durable polymer-coated everolimus-eluting stents in all-comer patients. *Indian Heart J* 2019; **71**: 149-154 [PMID: [31280828](#) DOI: [10.1016/j.ihj.2019.04.013](#)]
 - 26 **Durgaprasad R**, Velam V, Kasala L, Gajjala OR, Kanavat SN. Comparison of 1-year Outcomes of Biodegradable Polymer (Everoflex) Versus Permanent Polymer (Xience Pro) Coated Everolimus-eluting Coronary Stent Systems in All-comers Patient Population at a Tertiary Care Hospital. *J Am Coll Cardiol* 2017; **69**: S81 [DOI: [10.1016/j.jacc.2017.03.193](#)]
 - 27 **Gupta M**, Batra V, Girish MP, Bansal A, Tyagi S. TCT-304 1-Year Clinical Outcomes in Patients Implanted With Biodegradable Polymer Coated Ultrathin Strut Sirolimus-Eluting Coronary Stent System for the Treatment of Very Long (≥ 40 -mm) Lesions. *J Am Coll Cardiol* 2019; **74**: B302 [DOI: [10.1016/j.jacc.2019.08.380](#)]



Observational Study

Psychological stress and long-term blood pressure variability of military young males: The cardiorespiratory fitness and hospitalization events in armed forces study

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Abstract

BACKGROUND

Acute stress might increase short-term heart rate variability and blood pressure variability (BPV); however, chronic stress would not alter short-term BPV in animal models.

AIM

To examine the association of psychological stress with long-term BPV in young male humans.

METHODS

We prospectively examined the association of chronic psychological stress with long-term BPV in 1112 healthy military males, averaged 32.2 years from the cardiorespiratory fitness and hospitalization events in armed forces study in Taiwan. Psychological stress was quantitatively evaluated with the Brief Symptom Rating Scale (BSRS-5), from the least symptom of 0 to the most severe of

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20, and the five components of anxiety, insomnia, depression, interpersonal sensitivity, and hostility (the severity score in each component from 0 to 4). Long-term BPV was assessed by standard deviation (SD) for systolic and diastolic blood pressure (SBP and DBP), and average real variability (ARV), defined as the average absolute difference between successive measurements of SBP or DBP, across four visits in the study period from 2012 to 2018 (2012-14, 2014-15, 2015-16, and 2016-18).

RESULTS

The results of multivariable linear regressions showed that there were no correlations of the BSRS-5 score with SD_{SBP} , SD_{DBP} , ARV_{SBP} , and ARV_{DBP} after adjusting for all the covariates [β (SE): -0.022 (0.024), -0.023 (0.026), -0.001 (0.018), and 0.001 (0.020), respectively; $P > 0.05$ for all]. In addition, there were also no correlations between each component of the BSRS score and the long-term BPV indexes.

CONCLUSION

Our findings suggest that chronic psychological stress might not be associated with long-term BPV in military young male humans.

Key Words: Long-term blood pressure variability; Military; Psychological stress; Young males; Brief Symptom Rating Scale; Average real variability

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Core Tip: This study investigated the relationship of psychological stress evaluated using the Brief Symptom Rating Scale (BSRS-5) with long-term blood pressure variability (BPV) in 1112 military young male adults across four visits during a 7-year period. We found that there were no correlations of the BSRS-5 score and related components with systolic and diastolic BPV indexes in the fully adjusted model. Although previous studies have demonstrated that there was an association between psychological stress and elevated blood pressure, our study suggested no association of psychological stress and long-term BPV in young male adults.

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INTRODUCTION

Psychological stress is related to activation of the sympathetic nervous system and production of norepinephrine and epinephrine from the adrenal glands, leading to elevated blood pressure. Previous studies have shown that psychological stress, particularly chronic stress, may cause the development of hypertension^[1]. To our knowledge, psychological stress is subjective and complicated in human beings. An experiment in mice demonstrated that acute stress might result in increased short-term heart rate variability and blood pressure variability (BPV); however, chronic stress would not alter short-term BPV^[2]. Whether chronic mental stress is associated with long-term BPV remains unclear in human beings. Therefore, we investigated such association in a military cohort of young male adults.

MATERIALS AND METHODS

Study population

We prospectively examined the association of chronic psychological stress with long-

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term BPV in 1112 healthy military males aged 18–40 years (32 years on average) from the cardiorespiratory fitness and hospitalization events in armed forces study in Taiwan^[3–10]. All participants visited the Hualien Armed Forces General Hospital for a comprehensive health examination including the survey of demographics, anthropometrics, hemodynamics, mental stress, and behaviors and laboratory studies at least at two-year intervals from 2012 to 2018 (2012–14, 2014–15, 2015–16, and 2016–18).

Psychological stress measurements

The chronic psychological stress severity of military males in Taiwan was assessed using the Brief Symptom Rating Scale (BSRS-5) in the past 3 mo. There were five psychological domains included in BSRS-5, *i.e.*, depression (feeling blue), anxiety (feeling tense), interpersonal sensitivity (feeling inferior to others), hostility (feeling easily annoyed or irritated), and insomnia (trouble falling asleep). The scoring scale of each domain is Likert-type, ranging from 0 to 4 in severity: 0, nothing; 1, a little; 2, moderately; 3, quite a bit; 4, extremely^[11,12]. The BSRS-5 scores ≤ 5 , 6–9, and ≥ 10 were defined as normal, slight, and great stress, respectively^[11]. The test-retest reliability coefficient of the BSRS-5 score was 0.82, and the internal consistency (Cronbach alpha) coefficients ranged from 0.77 to 0.90^[12,13].

BPV measurements

Caffeine or theophylline-containing materials were banned for all participants in a 12-h fast before each hospital visit. Systolic and diastolic blood pressure (SBP and DBP, respectively) was measured with an automated blood pressure monitor (FT-201; Parama-Tech Co. Ltd., Fukuoka, Japan), once over right upper arm of each participant in a sitting position after a rest for 15 min or more at each visit. Long-term BPV was assessed across four visits in the study period by standard deviation (SD) and average real variability (ARV) for SBP and DBP variability. For instance, SD and ARV for SBP variability denoted as SD_{SBP} and ARV_{SBP} are respectively presented by dotted and solid lines in Figure 1. ARV was defined as the average absolute difference between successive measurements of blood pressure, and it takes the order of measurements into account $[(|\Delta 1| + |\Delta 2| + |\Delta 3|)/3]$ ^[14].

Statistical analysis

The characteristics of those who had a BSRS-5 score ≤ 5 and BSRS-5 score > 5 are expressed as the mean \pm SD for continuous data, and categorical data are expressed as numbers and percentages. In model 1, a multivariable linear regression model adjusted for age, body mass index, baseline SBP and DBP, alcohol intake status, and physical activity (exercise frequency) was used to determine the relationship. The statistic power calculated was 0.85. A value of $P < 0.05$ was considered significant. SAS statistical software (SAS version 9.4; SAS Institute, Cary, NC, United States) was used for all statistical analyses.

RESULTS

Table 1 shows the baseline profiles of the study participants. The age, body stature, hemodynamic status, and serum lipid profiles were similar between the normal subjects and those with stress. Those who had chronic mental stress were found with a lower level of physical activity and higher prevalence of alcohol drinking. Table 2 shows the results of multivariable linear regressions. In the unadjusted model, there were no correlations between the BSRS score and each component with SD and ARV for SBP and DBP variability, except that interpersonal sensitivity was borderline significantly and negatively correlated with SD_{SBP} [β (SE): -0.010 (0.005), $P = 0.07$]. After adjusting for the covariates in model 1, the associations of the BSRS score and each component with the long-term BPV indexes did not change a lot and remained insignificant. The correlation between interpersonal sensitivity and SD_{SBP} was just mildly reduced [β (SE): -0.009 (0.005), $P = 0.09$].

DISCUSSION

We found that young military male adults with chronic psychological stress had a higher prevalence of alcohol drinking and less physical activity, reflecting that the

Table 1 Baseline characteristics of the study cohort (n = 1112)

Characteristic	BSRS ≤ 5 (n = 983)	BSRS > 5 (n = 129)	P value
Age (yr)	32.21 ± 3.87	32.22 ± 4.02	0.99
Body mass index (kg/m ²)	25.14 ± 2.93	25.18 ± 2.71	0.89
SBP (mmHg)	118.45 ± 13.45	117.60 ± 12.98	0.49
DBP (mmHg)	71.58 ± 10.12	71.83 ± 9.95	0.78
Heart rate (beats per min)	74.96 ± 10.48	75.51 ± 11.54	0.58
Fasting plasma glucose (mg/dL)	94.42 ± 13.17	95.09 ± 15.33	0.59
Total cholesterol (mg/dL)	180.27 ± 36.62	179.30 ± 34.01	0.75
High-density lipoprotein (mg/dL)	47.97 ± 9.78	48.30 ± 11.15	0.72
Physical activity			
Never or occasionally	147 (15.0)	38 (29.5)	< 0.01
1-2 times/wk	365 (37.1)	62 (48.1)	
≥ 3-5 times/wk	471 (47.9)	29 (22.5)	
Current drinkers (%)	441 (44.9)	76 (58.9)	< 0.01
Current smokers (%)	376 (38.3)	55 (42.5)	

Continuous variables are expressed as the mean ± SD, and categorical variables as *n* (%). BSRS: Brief Symptom Rating Scale; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

BSRS score may be reliable for the evaluation of mental stress^[15,16]. The principal finding was that there was no association of chronic psychological stress and its pivotal domains with long-term BPV in young military male adults. A prior study in mice has revealed that acute stress but not chronic stress was associated with short-term BPV (within an hour measurement)^[2]. In addition, acute stressors on human beings could lead to an elevation of blood pressure levels and the effect persisted for a while^[17]. This finding may make short-term BPV less sensitive to stress as compared with heart rate variability in human beings and similarly in the mouse model^[2,18]. Notably, this study was the first one providing the evidence for a null association between chronic psychological stress and long-term BPV.

The results from the mouse experiment also demonstrated that acute stress could increase short-term BPV, which was likely due to sympathetic nervous system activation and baroreflex control impairment^[2]. On the contrary, chronic stress might reduce short-term BPV due to the coordination of sympathetic activation and physiological response to the vascular alterations in hypertension^[19,20]. Our findings also revealed that the BSRS-5 score was inversely correlated to almost all of the long-term BPV indexes in young male adults despite insignificance. This tendency of inverse association might differ by the components of BSRS-5 score, which was in line with anxiety, depression, and interpersonal sensitivity but contradicted to insomnia.

There were some strengths in this study. First, the questionnaire for BSRS-5, physical examinations, and blood pressure measurements were all performed standardly and in a strict manner at the clinic visit. Second, many unmeasured confounders had been controlled at baseline since daily life of the military such as deployment, physical activity, and stress sources were similar across troops. On the contrary, there were several limitations in this study. First, the results were obtained from the male subjects and might be inappropriately applied for the female subjects. Second, the study had a follow-up period for merely 7 years when the prevalence of hypertension remained low, possibly reducing the degree of association between psychological stress and BPV. Third, we used only a single measurement of blood pressure on each visit, which might be susceptible to change by cigarettes, coffee, and indoor temperature. Although the objective environment and the detailed preparations for blood pressure assessment have been regulated, other confounders such as white coat hypertension might be present in some subjects, possibly resulting in a bias. Lastly, there were only four occasions (every two years in interval) for blood pressure measurement, which would cause wide variations of SD and ARV, resulting in reduced associations for psychological stress. The interval of blood pressure

Table 2 Association of the Brief Symptom Rating Scale score and the components with the long-term blood pressure variability indexes in multivariable liner regressions

	Unadjusted			Model 1		
	β (SE)	P value	R ² , %	β (SE)	P value	R ² , %
BSRS scores						
ARV _{SBP}	-0.005 (0.019)	0.80	0.0	-0.001 (0.018)	0.94	7.2
ARV _{DBP}	-0.003 (0.020)	0.88	0.0	0.001 (0.020)	0.96	7.2
SD _{SBP}	-0.028 (0.025)	0.26	0.1	-0.022 (0.024)	0.36	7.2
SD _{DBP}	-0.032 (0.027)	0.23	0.1	-0.023 (0.026)	0.38	7.2
Anxiety						
ARV _{SBP}	-0.005 (0.005)	0.31	0.1	-0.003 (0.005)	0.51	6.2
ARV _{DBP}	-0.003 (0.005)	0.53	0.0	-0.001 (0.005)	0.83	6.1
SD _{SBP}	-0.009 (0.006)	0.17	0.2	-0.006 (0.006)	0.32	6.2
SD _{DBP}	-0.007 (0.007)	0.29	0.1	-0.003 (0.007)	0.66	6.1
Depression						
ARV _{SBP}	-0.002 (0.004)	0.62	0.0	-0.001 (0.004)	0.71	5.6
ARV _{DBP}	0.000 (0.004)	0.93	0.0	0.000 (0.004)	0.93	5.6
SD _{SBP}	-0.007 (0.005)	0.16	0.2	-0.006 (0.005)	0.21	5.7
SD _{DBP}	-0.005 (0.006)	0.40	0.1	-0.003 (0.006)	0.58	5.6
Hostility						
ARV _{SBP}	0.002 (0.004)	0.66	0.0	0.003 (0.004)	0.55	6.1
ARV _{DBP}	0.001 (0.005)	0.88	0.0	0.001 (0.005)	0.83	6.0
SD _{SBP}	-0.003 (0.006)	0.54	0.0	-0.002 (0.006)	0.67	6.1
SD _{DBP}	-0.006 (0.006)	0.31	0.1	-0.005 (0.006)	0.40	6.1
Interpersonal sensitivity						
ARV _{SBP}	-0.002 (0.004)	0.55	0.0	-0.002 (0.004)	0.60	6.1
ARV _{DBP}	-0.001 (0.004)	0.76	0.0	0.000 (0.004)	0.90	6.1
SD _{SBP}	-0.010 (0.005)	0.07	0.3	-0.009 (0.005)	0.09	6.3
SD _{DBP}	-0.008 (0.006)	0.18	0.2	-0.006 (0.006)	0.29	6.2
Insomnia						
ARV _{SBP}	0.003 (0.004)	0.49	0.0	0.003 (0.004)	0.41	3.9
ARV _{DBP}	0.001 (0.004)	0.80	0.0	0.001 (0.004)	0.74	3.8
SD _{SBP}	0.001 (0.005)	0.84	0.0	0.002 (0.005)	0.72	3.8
SD _{DBP}	-0.003 (0.005)	0.58	0.0	-0.002 (0.005)	0.71	3.8

β means standardized regression coefficient; R² means a measure for model prediction. The covariates adjusted in model 2 include age, systolic and diastolic blood pressure, physical activity, and current alcohol intake. BSRS: Brief Symptom Rating Scale; ARV_{SBP}: Average real variability for systolic blood pressure variability; ARV_{DBP}: Average real variability for diastolic blood pressure variability; SD_{SBP}: Standard deviation for systolic blood pressure variability; SD_{DBP}: Standard deviation for diastolic blood pressure variability.

measurement had a long time scale (years instead of months). Therefore, it may promote further studies to either confirm or dispute the conclusions.

CONCLUSION

In conclusion, our findings suggest that chronic psychological stress is not associated

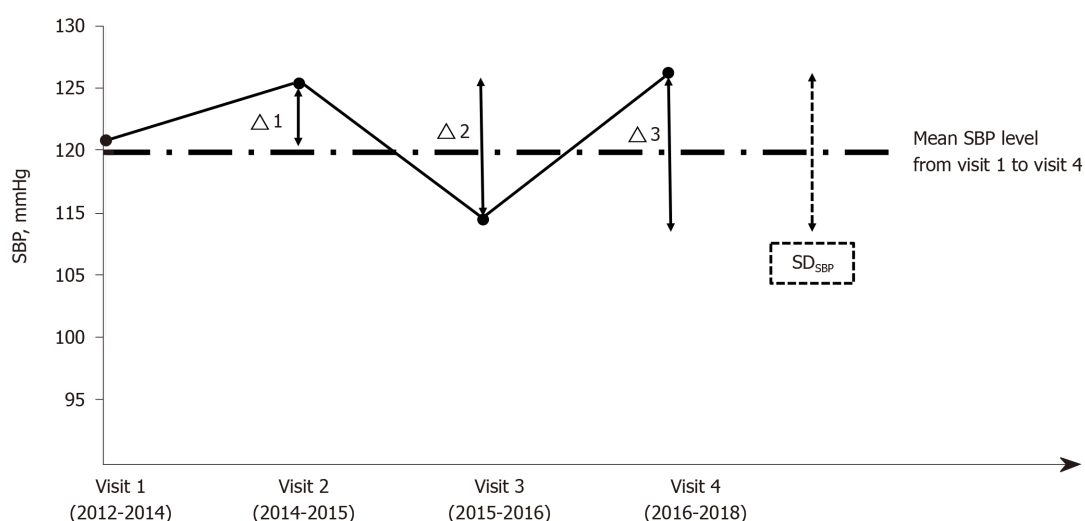


Figure 1 Standard deviation and average real variability for systolic blood pressure variability denoted as SD_{SBP} and ARV_{SBP} respectively presented by dotted and solid lines. Average real variability was defined as the average absolute difference between successive measurements of blood pressure, and it takes the order of measurements into account $[(|\Delta 1| + |\Delta 2| + |\Delta 3|)/3]$. SBP: Systolic blood pressure; SD_{SBP} : Standard deviation for systolic blood pressure variability.

with long-term BPV in young males. In addition, this study is the first one revealing a null association between each chronic stress component and long-term BPV in human beings. It is necessary to see whether there might be a change for the relationship with long-term BPV in a longer follow-up when the prevalence of hypertension increases with ageing.

ARTICLE HIGHLIGHTS

Research background

An experiment in mice demonstrated that acute stress might result in increased short-term heart rate variability and blood pressure variability (BPV); however, chronic stress would not alter short-term BPV.

Research motivation

Whether chronic mental stress is associated with long-term BPV remains unclear in human beings.

Research objectives

To examine the association of psychological stress with long-term BPV in young male adults.

Research methods

The association between chronic psychological stress and long-term BPV was examined in 1112 healthy military males, averaged 32.2 years in Taiwan. Psychological stress was quantitatively evaluated using the Brief Symptom Rating Scale (BSRS-5), from the least symptom of 0 to the most severe of 20, and the five components of anxiety, insomnia, depression, interpersonal sensitivity, and hostility (the severity score in each component from 0 to 4). Long-term BPV was assessed by standard deviation (SD) for systolic and diastolic blood pressure (SBP and DBP), and average real variability (ARV), defined as the average absolute difference between successive measurements of SBP or DBP, across four visits in the study period from 2012 to 2018 (2012-14, 2014-15, 2015-16, and 2016-18).

Research results

The results of multivariable linear regressions showed that there were no correlations of the BSRS-5 score with SD_{SBP} , SD_{DBP} , ARV_{SBP} , and ARV_{DBP} after adjusting for all the covariates [β (SE): -0.022 (0.024), -0.023 (0.026), -0.001 (0.018), and 0.001 (0.020), respectively; $P > 0.05$ for all]. In addition, there were also no correlations between each

component of the BSRS score and the long-term BPV indexes.

Research conclusions

Our findings suggest that chronic psychological stress might not be associated with long-term BPV in military young males.

Research perspectives

Future studies should focus on the association between chronic mental stress and long-term BPV which is assessed by a smaller interval of blood pressure measurement (*i.e.*, from years to months).

REFERENCES

- 1 **Liu MY**, Li N, Li WA, Khan H. Association between psychosocial stress and hypertension: a systematic review and meta-analysis. *Neurol Res* 2017; **39**: 573-580 [PMID: [28415916](#) DOI: [10.1080/01616412.2017.1317904](#)]
- 2 **Farah VM**, Joaquim LF, Bernatova I, Morris M. Acute and chronic stress influence blood pressure variability in mice. *Physiol Behav* 2004; **83**: 135-142 [PMID: [15501500](#) DOI: [10.1016/j.physbeh.2004.08.004](#)]
- 3 **Lin GM**, Li YH, Lee CJ, Shiang JC, Lin KH, Chen KW, Chen YJ, Wu CF, Lin BS, Yu YS, Lin F, Su FY, Wang CH. Rationale and design of the cardiorespiratory fitness and hospitalization events in armed forces study in Eastern Taiwan. *World J Cardiol* 2016; **8**: 464-471 [PMID: [27621774](#) DOI: [10.4330/wjc.v8.i8.464](#)]
- 4 **Chen YJ**, Chen KW, Shih YL, Su FY, Lin YP, Meng FC, Lin F, Yu YS, Han CL, Wang CH, Lin JW, Hsieh TY, Li YH, Lin GM. Chronic hepatitis B, nonalcoholic steatohepatitis and physical fitness of military males: CHIEF study. *World J Gastroenterol* 2017; **23**: 4587-4594 [PMID: [28740347](#) DOI: [10.3748/wjg.v23.i25.4587](#)]
- 5 **Tsai KZ**, Lin JW, Lin F, Su FY, Li YH, Lin YP, Lin YK, Han CL, Hsieh CB, Lin GM. Association of betel nut chewing with exercise performance in a military male cohort: the CHIEF study. *J R Army Med Corps* 2018; **164**: 399-404 [PMID: [30012664](#) DOI: [10.1136/jramc-2017-000899](#)]
- 6 **Tsai KZ**, Lai SW, Hsieh CJ, Lin CS, Lin YP, Tsai SC, Chung PS, Lin YK, Lin TC, Ho CL, Han CL, Kwon Y, Hsieh CB, Lin GM. Association between mild anemia and physical fitness in a military male cohort: The CHIEF study. *Sci Rep* 2019; **9**: 11165 [PMID: [31371766](#) DOI: [10.1038/s41598-019-47625-3](#)]
- 7 **Chao WH**, Su FY, Lin F, Yu YS, Lin GM. Association of electrocardiographic left and right ventricular hypertrophy with physical fitness of military males: The CHIEF study. *Eur J Sport Sci* 2019; **19**: 1214-1220 [PMID: [30955480](#) DOI: [10.1080/17461391.2019.1595741](#)]
- 8 **Liu PY**, Lin YK, Chen KW, Tsai KZ, Lin YP, Takimoto E, Lin GM. Association of Liver Transaminase Levels and Long-Term Blood Pressure Variability in Military Young Males: The CHIEF Study. *Int J Environ Res Public Health* 2020; **17** [PMID: [32825751](#) DOI: [10.3390/ijerph17176094](#)]
- 9 **Lin GM**, Lu HH. A 12-Lead ECG-Based System With Physiological Parameters and Machine Learning to Identify Right Ventricular Hypertrophy in Young Adults. *IEEE J Transl Eng Health Med* 2020; **8**: 1900510 [PMID: [32509473](#) DOI: [10.1109/JTEHM.2020.2996370](#)]
- 10 **Lin GM**, Liu K. An Electrocardiographic System With Anthropometrics via Machine Learning to Screen Left Ventricular Hypertrophy among Young Adults. *IEEE J Transl Eng Health Med* 2020; **8**: 1800111 [PMID: [32419990](#) DOI: [10.1109/JTEHM.2020.2990073](#)]
- 11 **Lee MB**, Liao SC, Lee YJ, Wu CH, Tseng MC, Gau SF, Rau CL. Development and verification of validity and reliability of a short screening instrument to identify psychiatric morbidity. *J Formos Med Assoc* 2003; **102**: 687-694 [PMID: [14691593](#)]
- 12 **Chen HC**, Wu CH, Lee YJ, Liao SC, Lee MB. Validity of the five-item Brief Symptom Rating Scale among subjects admitted for general health screening. *J Formos Med Assoc* 2005; **104**: 824-829 [PMID: [16496062](#)]
- 13 **Lu IC**, Yen Jean MC, Lei SM, Cheng HH, Wang JD. BSRS-5 (5-item Brief Symptom Rating Scale) scores affect every aspect of quality of life measured by WHOQOL-BREF in healthy workers. *Qual Life Res* 2011; **20**: 1469-1475 [PMID: [21431460](#) DOI: [10.1007/s11136-011-9889-4](#)]
- 14 **Hastie CE**, Jeemon P, Coleman H, McCallum L, Patel R, Dawson J, Sloan W, Meredith P, Jones GC, Muir S, Walters M, Dominiczak AF, Morrison D, McInnes GT, Padmanabhan S. Long-term and ultra long-term blood pressure variability during follow-up and mortality in 14,522 patients with hypertension. *Hypertension* 2013; **62**: 698-705 [PMID: [23959561](#) DOI: [10.1161/HYPERTENSIONAHA.113.01343](#)]
- 15 **Lin KH**, Chen YJ, Yang SN, Liu MW, Kao CC, Nagamine M, Vermetten E, Lin GM. Association of Psychological Stress with Physical Fitness in a Military Cohort: The CHIEF Study. *Mil Med* 2020; **185**: e1240-e1246 [PMID: [32239167](#) DOI: [10.1093/milmed/usz469](#)]
- 16 **Lin GM**, Nagamine M, Yang SN, Tai YM, Lin C, Sato H. Machine Learning Based Suicide Ideation Prediction for Military Personnel. *IEEE J Biomed Health Inform* 2020; **24**: 1907-1916 [PMID: [32324581](#) DOI: [10.1109/JBHI.2020.2988393](#)]

- 17 **Hjortskov N**, Rissén D, Blangsted AK, Fallentin N, Lundberg U, Søgaard K. The effect of mental stress on heart rate variability and blood pressure during computer work. *Eur J Appl Physiol* 2004; **92**: 84-89 [PMID: [14991326](#) DOI: [10.1007/s00421-004-1055-z](#)]
- 18 **Fredrikson M**, Blumenthal JA, Evans DD, Sherwood A, Light KC. Cardiovascular responses in the laboratory and in the natural environment: is blood pressure reactivity to laboratory-induced mental stress related to ambulatory blood pressure during everyday life? *J Psychosom Res* 1989; **33**: 753-762 [PMID: [2621677](#) DOI: [10.1016/0022-3999\(89\)90091-3](#)]
- 19 **Grippe AJ**, Beltz TG, Johnson AK. Behavioral and cardiovascular changes in the chronic mild stress model of depression. *Physiol Behav* 2003; **78**: 703-710 [PMID: [12782226](#) DOI: [10.1016/s0031-9384\(03\)00050-7](#)]
- 20 **Pagani M**, Rimoldi O, Pizzinelli P, Furlan R, Crivellaro W, Liberati D, Cerutti S, Malliani A. Assessment of the neural control of the circulation during psychological stress. *J Auton Nerv Syst* 1991; **35**: 33-41 [PMID: [1940025](#) DOI: [10.1016/0165-1838\(91\)90036-3](#)]

Heparin-induced thrombocytopenia in renal insufficiency undergoing dialysis and percutaneous coronary intervention after acute myocardial infarction: A case report

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Abstract

BACKGROUND

Heparin-induced thrombocytopenia (HIT) is a rare complication of heparin therapy, and is characterized by arteriovenous thrombosis and bleeding events. The incidence of HIT after percutaneous coronary intervention (PCI) in patients with myocardial infarction complicated with renal failure is rarely reported.

CASE SUMMARY

We report a 73-year-old man with acute myocardial infarction and renal failure who underwent hemodialysis and PCI, and developed a progressive decline in platelets and subcutaneous hemorrhage of both upper limbs after heparin treatment. In addition to a gradual decrease in platelets, the patient's 4T's score was 7, and HIT antibody was positive, confirming the diagnosis of HIT.

CONCLUSION

Patients receiving heparin combined with antiplatelet therapy should be monitored closely, especially for their platelet count. In the case of thrombocytopenia, HIT should be highly suspected. When the diagnosis of HIT is confirmed, timely individualized treatment should be delivered.

Key Words: Thrombocytopenia; Heparin; Percutaneous coronary intervention; Myocardial infarction; Chronic renal insufficiency; Case report

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Core Tip: Heparin-induced thrombocytopenia (HIT) is a rare complication of heparin

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therapy. Its pathogenesis includes thrombotic events that can rarely affect the coronary arteries. We report a 73-year-old man who presented with extensive lower extremities deep venous thrombosis. After being treated with heparin, he developed ST-elevation myocardial infarction secondary to acute thrombus formation. The patient's platelets dropped within 6 d, and heparin-platelet factor 4 immunoglobulin G antibody and serotonin release assay were positive, confirming the diagnosis of HIT. HIT is associated with an increased risk for coronary thrombosis and ischaemia. HIT can cause coronary complications usually in previously disrupted coronary vessels and bypass grafts.

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INTRODUCTION

Heparin-induced thrombocytopenia (HIT) refers to thrombocytopenia occurs following therapy with heparins including unfractionated heparin (UFH) and heparin derivatives, such as low-molecular weight heparin (LMWH). During HIT, immune antibodies mediated by platelets play an important role, and cause a reduction in platelet count. This can lead to arteriovenous thrombosis and bleeding events, and may even cause death in severe cases^[1,2]. With an increasing number of patients undergoing dialysis or coronary intervention treatment, HIT has gradually gained more and more attention. Timely detection and treatment significantly improve the prognosis of these patients. We report a case of HIT in a patient with chronic renal insufficiency and acute myocardial infarction (AMI) following percutaneous coronary intervention (PCI).

CASE PRESENTATION

Chief complaints

A 73-year-old man was admitted to a regional hospital because of AMI occurring 1 wk before admission to our hospital.

History of present illness

During his stay in the regional hospital, a coronary angiogram (CAG) was obtained, in which 3000 units of UFH was administered, and CAG revealed the presence of trunk and 3-vessel disease. The patient was transferred to our department (November 7, 2018) for further treatment.

History of past illness

The patient had a history of chronic kidney disease for 5 years and hypertension for 4 years. He received hemodialysis treatment four times before being transferring to our hospital.

Personal and family history

This patient had no specific personal and family history.

Physical examination

On initial presentation to our hospital, he was hemodynamically stable with a heart rate of 76 bpm, and blood pressure of 156/74 mmHg. A small amount of moist rales was heard at the bottom of both lungs on auscultation. His heart boundary size was critical on percussion and rhythm was regular on auscultation. A grade-III systolic murmur was heard in the aortic valve area.

Laboratory examinations

Laboratory studies were significant for a cardiac troponin T level of 7.670 µg/L (normal 0.000-0.100 µg/L), pro-brain natriuretic peptide of 46034 pg/mL (normal 0.00-125.00 pg/mL), creatinine of 580.5 µmol/L, glomerular filtration rate (GFR) of 7.6 mL/L, hemoglobin of 90 g/L (normal 130-175 g/L), and platelet (PLT) count of 121×10^9 /L (normal $100-300 \times 10^9$ /L).

Imaging examinations

Cardiac ultrasound showed that the left atrium and left ventricle were enlarged, and the aorta and pulmonary arteries were widened. Severe aortic insufficiency with moderate stenosis, and moderate mitral valve insufficiency were also found by ultrasound. Left ventricular systolic and diastolic function was reduced. The bedside electrocardiogram (Figure 1) after admission showed sinus rhythm, T wave inversion in leads I, aVL, and V3-V6, and the QRS wave in leads V1 and V2 was QS type.

FINAL DIAGNOSIS

After admission, the patient was initially diagnosed with AMI, chronic renal failure, renal anemia, and hypertension. His GRACE score was 183, and CRUSADE score was 53. Thus, the ischemic risk and hemorrhagic risk were both high in this patient. He received standard treatment for secondary prevention of coronary heart disease, including dual-antiplatelet (aspirin 100 mg/d and Plavix 75 mg/d) and lipid-lowering (rosuvastatin 10 mg/d) therapies. Simultaneously, intravascular ultrasound (IVUS) examination and CAG were performed (November 9, 2018), which revealed left main coronary artery (LMT) and 3-vessel disease. Following a team discussion, the patient underwent PCI, with one stent placed in the LMT-LAD (Xience Xpedition 2.75 mm × 38 mm) and two overlapping stents placed in the mid-left circumflex (LCx) (Firehawk 2.5 mm × 13 mm) and proximal LCx (Xience Xpedition 3.5 mm × 33 mm) (Figure 2). During the operation, bivalirudin was administered for anticoagulation. The day before and after the angiogram, the patient was treated with hemodialysis, in which 8700 IU of LMWH calcium was used in total. The second day after CAG, he developed a fever with a temperature of 37.8 °C after hemodialysis, without chills, chest pain, or other discomfort. Routine blood examination was performed, which showed a hemoglobin level of 77 g/L, and a PLT count of 45×10^9 /L. There was no clinical bleeding at that time. The patient's fever resolved the following day, but both upper limbs showed signs of skin necrosis (Figure 3). His PLT count decreased to 23×10^9 /L. HIT was then considered. Calculation of the 4T's score revealed a count of 7, which indicated a high probability of HIT.

TREATMENT

Hence, all heparin agents were stopped. At the same time, platelet factor 4 (PF4) antibody was determined. In order to prevent stent thrombosis, bivalirudin was administered (0.20 mg/kg per hour, activated clotting time approximately 200 s). Due to a high risk of bleeding, aspirin was stopped, and antiplatelet therapy with clopidogrel was continued. After 4 d, the PLT count rose to 70×10^9 /L, and the PF4 antibody result was reported as 7.1 U/mL (normal 0-0.1 U/mL), which confirmed the diagnosis of HIT. Due to renal insufficiency, the use of a new oral anticoagulant and fondaparinux was limited. In addition, as the PLT count did not reach 300×10^9 /L, the patient did not receive warfarin. Following treatment, the patient's condition was stable, and there were no more embolism events. Bivalirudin was discontinued on November 16, 2018, and dual-antiplatelet therapy with aspirin and clopidogrel was resumed. The next day, a sudden deviation of the patient's mouth was observed. Brain magnetic resonance imaging confirmed acute cerebral infarction at the right ventricle and upper insular lobe (Figure 4). No special adjustments were made to the treatment regimen. His symptoms improved gradually. The PLT count recovered to 110×10^9 /L on November 19, 2018.

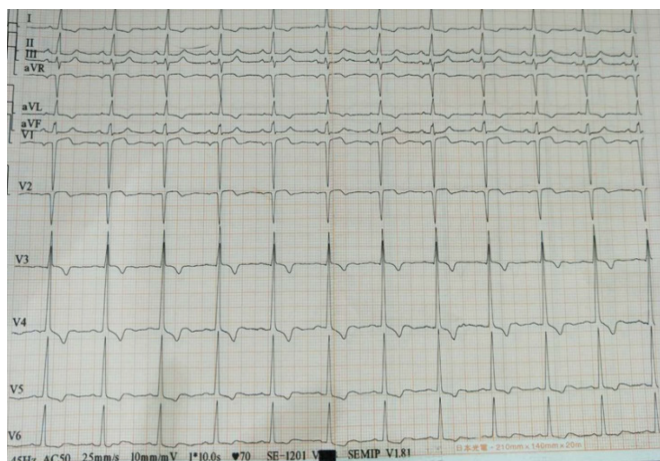


Figure 1 Bedside electrocardiogram after admission.

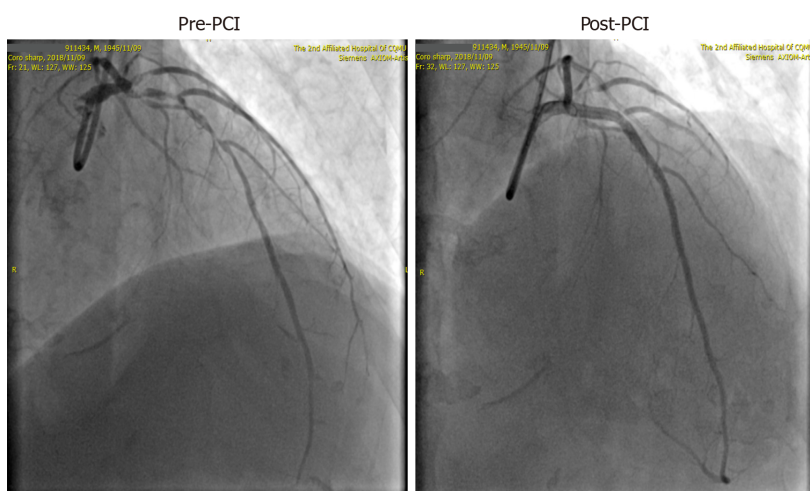


Figure 2 Angiogram showing pre- and post-percutaneous coronary intervention of the left main coronary artery-LAD and left circumflex. PCI: Percutaneous coronary intervention.



Figure 3 Photograph showing skin necrosis of the right and left upper extremities.

OUTCOME AND FOLLOW-UP

No emboli or bleeding events occurred during the 18-mo follow-up period.

DISCUSSION

Reports of HIT in patients with renal failure undergoing dialysis and PCI after AMI are rare. According to statistics, the risk of HIT after exposure to UFH is 2.6%^[3,4]. In addition to clinical manifestations and dynamic monitoring of the PLT count, the diagnosis of HIT is mainly based on the 4T's scoring system combined with HIT antibody detection and PLT function examination^[5]. HIT is divided into type I and type II^[1,6]. Our patient's PLT count decreased significantly after 1 wk of heparin therapy, to $23 \times 10^9/L$ at the lowest value. He presented additional symptoms of a general reaction and skin necrosis. His 4T's score was 7 points, which showed a high clinical probability of HIT. The HIT antibody test was positive, and his PLT count recovered gradually following heparin discontinuation. This patient was diagnosed with type II HIT^[6,7].

When the patient's history was traced back, his PLT count showed a progressive decline after heparin administration during the initial dialysis and CAG (Figure 5). HIT was diagnosed when the patient developed general reactions and skin necrosis with an obvious decrease in PLT count after heparin therapy after the patient received dialysis again. During diagnosis and treatment, the drugs administered and the autoimmune factor may be responsible for thrombocytopenia. In this patient, indicators of autoimmune diseases were negative, such as immunoglobulin and complement, β_2 glycoprotein I antibody, platelet antibody, and other tests. Therefore, we were able to exclude thrombocytopenia caused by autoimmune factors. Medications that could have led to a decrease in PLT count in this patient included aspirin, clopidogrel, and heparins. Low-dose aspirin can reduce the production of thromboxane A2 (TXA2), thus inhibiting platelet aggregation induced by TXA2. The incidence of thrombocytopenia caused by aspirin is 0.1%. In addition, the incidence of thrombocytopenia caused by clopidogrel is approximately 0.2%, which mostly occurs within 2-3 mo after taking medication, and thrombotic thrombocytopenia purpura is more common with clopidogrel. The patient had been taking clopidogrel since the onset of his disease, and the PLT count gradually rebounded after discontinuation of heparin. Thus, decreased PLT count caused by clopidogrel was excluded. In addition, his PLT count did not decrease again when aspirin was taken orally but increased to more than $60 \times 10^9/L$; thus, thrombocytopenia caused by aspirin was also excluded.

When HIT is diagnosed or highly suspected, heparin should be discontinued immediately and an alternative anticoagulant should be given. Argatroban, a recombinant hirudin, and bivalirudin have been approved by the FDA as anticoagulants in patients with HIT who require PCI, and both bivalirudin and argatroban have been recommended by the American College of Chest Physicians (ACCP)^[1,8]. This was based on multiple randomized trials (> 19000 patients without HIT) that proved the efficacy and safety of anticoagulant therapy using bivalirudin in patients undergoing PCI. Compared with UFH, bivalirudin showed a similar incidence of ischemic complications and was able to reduce the rate of bleeding events^[9-14]. Although recent clinical trials have also shown that the risk of bleeding was similar to or lower than UFH, the stent thrombosis rate increased. In view of these new data, the clinical efficacy and cost-effectiveness of bivalirudin in patients not undergoing PCI have been questioned^[15-17]. However, in patients with HIT, bivalirudin was still the best choice^[1]. Fondaparinux, a new oral anticoagulant, and warfarin could also be used as alternative therapies, but the evidence for these agents is relatively weak. Our patient with AMI and chronic renal insufficiency developed HIT after PCI with a CRUSADE score of 53 points. Thus, the bleeding risk was high. However, considering the risk of coronary stent thrombosis and other emboli, stopping one type of antiplatelet and adding another anticoagulant at the same time was necessary. Bivalirudin was the preferred alternative anticoagulant in this patient because of his renal function. After 5 d of bivalirudin treatment, no new bleeding or thromboembolic events occurred. Bivalirudin was suspended in view of the financial situation of the patient's family. Considering the patient's renal function, new oral anticoagulants and fondaparinux could not be used to replace bivalirudin. Warfarin was not added as the PLT count was below $300 \times 10^9/L$. After the recovery of the PLT count, dual-antiplatelet therapy was resumed, but acute cerebral infarction occurred after the withdrawal of bivalirudin. At present, there is no consensus on the course of

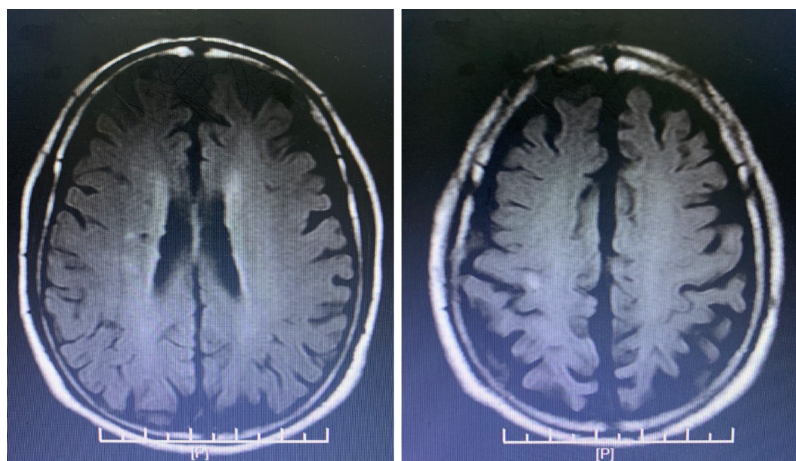


Figure 4 Magnetic resonance imaging showing cerebral infarction.

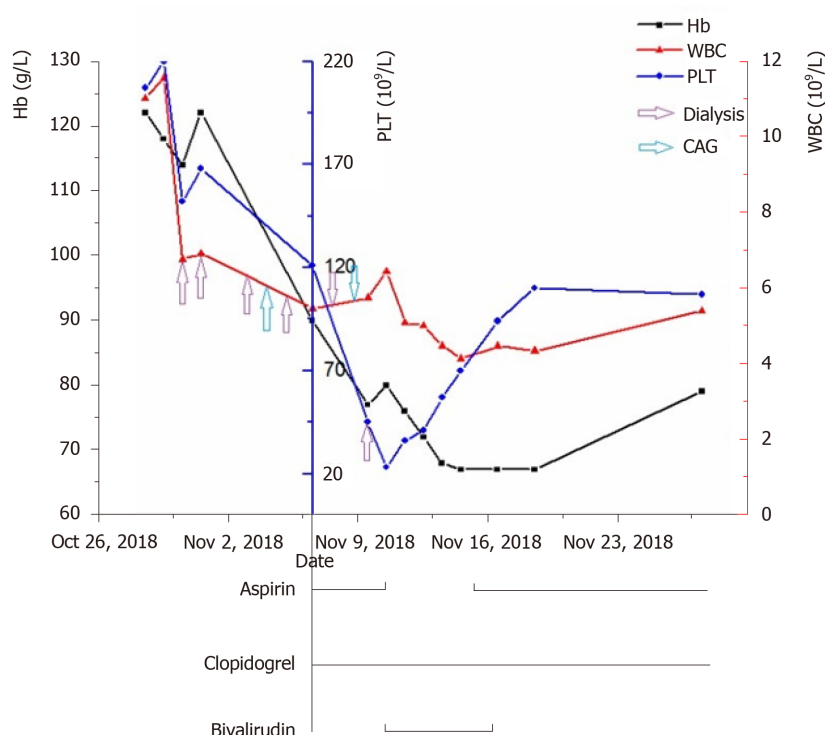


Figure 5 Trends in hemoglobin, white blood cells, and platelets during the patient's disease course. Hb: Hemoglobin; WBC: White blood cell; PLT: Platelet; CAG: Coronary angiogram.

anticoagulant therapy for HIT patients. The 2012 ACCP guidelines for HIT diagnosis and treatment do not clearly indicate the best alternative anticoagulant therapy. In 2018, the HIT treatment guidelines of the American Society of Hematology^[6] proposed that alternative anticoagulation could be sustained until the PLT count returned to normal. According to the 2017 Chinese expert consensus on HIT^[18], alternative anticoagulants should be used for at least 1 mo in patients with simple thrombocytopenia. For HIT patients with thrombus formation, anticoagulation therapy should continue for no less than 3 mo. The optimal course of alternative anticoagulation therapy still requires further research. Our patient was elderly and receiving dialysis for renal failure, which had an effect on the treatment process for HIT. Individualized treatment plans should be developed for special populations, in order to achieve satisfactory treatment effects.

CONCLUSION

HIT is a rare complication of heparin therapy. Due to its high mortality, it is important to diagnose this disease in a timely manner. Thrombocytopenia can be considered an early warning sign. When a patient is assessed as having a high clinical likelihood of HIT, the use of heparin should be discontinued as soon as possible and further tests should be carried out to identify or exclude HIT. With vigilance and suspicion, HIT can be diagnosed in the early stage, and individualized alternative anticoagulant therapy can reduce the mortality rate.

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REFERENCES

- 1 **Linkins LA**, Dans AL, Moores LK, Bona R, Davidson BL, Schulman S, Crowther M. Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; **141**: e495S-e530S [PMID: [22315270](#) DOI: [10.1378/chest.11-2303](#)]
- 2 **Arepally GM**, Ortel TL. Clinical practice. Heparin-induced thrombocytopenia. *N Engl J Med* 2006; **355**: 809-817 [PMID: [16928996](#) DOI: [10.1056/NEJMcp052967](#)]
- 3 **Martel N**, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. *Blood* 2005; **106**: 2710-2715 [PMID: [15985543](#) DOI: [10.1182/blood-2005-04-1546](#)]
- 4 **Girolami B**, Prandoni P, Stefani PM, Tanduo C, Sabbion P, Eichler P, Ramon R, Baggio G, Fabris F, Girolami A. The incidence of heparin-induced thrombocytopenia in hospitalized medical patients treated with subcutaneous unfractionated heparin: a prospective cohort study. *Blood* 2003; **101**: 2955-2959 [PMID: [12480713](#) DOI: [10.1182/blood-2002-07-2201](#)]
- 5 **Almeqdadi M**, Aoun J, Carrozza J. Native coronary artery thrombosis in the setting of heparin-induced thrombocytopenia: a case report. *Eur Heart J Case Rep* 2018; **2**: yty138 [PMID: [31020214](#) DOI: [10.1093/ehjcr/yty138](#)]
- 6 **Cuker A**, Arepally GM, Chong BH, Cines DB, Greinacher A, Gruel Y, Linkins LA, Rodner SB, Selleng S, Warkentin TE, Wex A, Mustafa RA, Morgan RL, Santesso N. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. *Blood Adv* 2018; **2**: 3360-3392 [PMID: [30482768](#) DOI: [10.1182/bloodadvances.2018024489](#)]
- 7 **Lovecchio F**. Heparin-induced thrombocytopenia. *Clin Toxicol (Phila)* 2014; **52**: 579-583 [PMID: [24844576](#) DOI: [10.3109/15563650.2014.917181](#)]
- 8 **Lanzarotti S**, Weigelt JA. Heparin-induced thrombocytopenia. *Surg Clin North Am* 2012; **92**: 1559-1572 [PMID: [23153884](#) DOI: [10.1016/j.suc.2012.08.015](#)]
- 9 **Bittl JA**, Strony J, Brinker JA, Ahmed WH, Meckel CR, Chaitman BR, Maraganore J, Deutsch E, Adelman B. Treatment with bivalirudin (Hirulog) as compared with heparin during coronary angioplasty for unstable or postinfarction angina. Hirulog Angioplasty Study Investigators. *N Engl J Med* 1995; **333**: 764-769 [PMID: [7643883](#) DOI: [10.1056/NEJM199509213331204](#)]
- 10 **Bittl JA**, Feit F. A randomized comparison of bivalirudin and heparin in patients undergoing coronary angioplasty for postinfarction angina. Hirulog Angioplasty Study Investigators. *Am J Cardiol* 1998; **82**: 43P-49P [PMID: [9809891](#) DOI: [10.1016/s0002-9149\(98\)00766-8](#)]
- 11 **Lincoff AM**, Bittl JA, Harrington RA, Feit F, Kleiman NS, Jackman JD, Sarembock IJ, Cohen DJ, Spriggs D, Ebrahimi R, Keren G, Carr J, Cohen EA, Betriu A, Desmet W, Kereiakes DJ, Rutsch W, Wilcox RG, de Feyter PJ, Vahanian A, Topol EJ; REPLACE-2 Investigators. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *JAMA* 2003; **289**: 853-863 [PMID: [12588269](#) DOI: [10.1001/jama.289.7.853](#)]
- 12 **Lincoff AM**, Bittl JA, Kleiman NS, Sarembock IJ, Jackman JD, Mehta S, Tannenbaum MA, Niederman AL, Bachinsky WB, Tift-Mann J 3rd, Parker HG, Kereiakes DJ, Harrington RA, Feit F, Maier ES, Chew DP, Topol EJ; REPLACE-1 Investigators. Comparison of bivalirudin vs heparin during percutaneous coronary intervention (the Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events [REPLACE]-1 trial). *Am J Cardiol* 2004; **93**: 1092-1096 [PMID: [15110198](#) DOI: [10.1016/j.amjcard.2004.01.033](#)]
- 13 **Gurm HS**, Bhatt DL. Thrombin, an ideal target for pharmacological inhibition: a review of direct

- thrombin inhibitors. *Am Heart J* 2005; **149**: S43-S53 [PMID: [15644793](#) DOI: [10.1016/j.ahj.2004.10.022](#)]
- 14 **Lee MS**, Liao H, Yang T, Dhoot J, Tobis J, Fonarow G, Mahmud E. Comparison of bivalirudin vs heparin plus glycoprotein IIb/IIIa inhibitors in patients undergoing an invasive strategy: a meta-analysis of randomized clinical trials. *Int J Cardiol* 2011; **152**: 369-374 [PMID: [20843568](#) DOI: [10.1016/j.ijcard.2010.08.007](#)]
 - 15 **Stone GW**, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, Kornowski R, Hartmann F, Gersh BJ, Pocock SJ, Dangas G, Wong SC, Kirtane AJ, Parise H, Mehran R; HORIZONS-AMI Trial Investigators. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med* 2008; **358**: 2218-2230 [PMID: [18499566](#) DOI: [10.1056/NEJMoa0708191](#)]
 - 16 **Steg PG**, van 't Hof A, Hamm CW, Clemmensen P, Lapostolle F, Coste P, Ten Berg J, Van Grunsven P, Eggink GJ, Nibbe L, Zeymer U, Campo dell'Orto M, Nef H, Steinmetz J, Soulat L, Huber K, Deliargyris EN, Bernstein D, Schuette D, Prats J, Clayton T, Pocock S, Hamon M, Goldstein P; EUROMAX Investigators. Bivalirudin started during emergency transport for primary PCI. *N Engl J Med* 2013; **369**: 2207-2217 [PMID: [24171490](#) DOI: [10.1056/NEJMoa1311096](#)]
 - 17 **Shahzad A**, Kemp I, Mars C, Wilson K, Roome C, Cooper R, Andron M, Appleby C, Fisher M, Khand A, Kunadian B, Mills JD, Morris JL, Morrison WL, Munir S, Palmer ND, Perry RA, Ramsdale DR, Velavan P, Stables RH; HEAT-PPCI trial investigators. Unfractionated heparin vs bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. *Lancet* 2014; **384**: 1849-1858 [PMID: [25002178](#) DOI: [10.1016/S0140-6736\(14\)60924-7](#)]
 - 18 **Committee on thrombosis prevention and treatment**, Internal Medicine Branch of Cardiovascular Diseases, Chinese Physicians' Association, Xu JT, Li WM, Men JL, Zhao X, Li Y. Chinese expert consensus on heparin-induced thrombocytopenia. *Zhonghua Yixue Zazhi* 2018; **98**: 408-417 [DOI: [10.3760/cma.j.issn.0376-2491.2018.06.003](#)]



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