High prevalence of intracardiac thrombi in cardiac amyloidosis

Ana Martinez-Naharro MD[a], Esther Gonzalez-Lopez MD[b], Andrej Corovic MD[a], Jesus G Mirelis MD, PhD[b], A. John Baksi, PhD[c], James C. Moon MD[d,e], Pablo Garcia-Pavia MD, PhD[b,f], Julian D. Gillmore MD, PhD[a], Philip N Hawkins PhD [a], Marianna Fontana MD, PhD[a]

[a] National Amyloidosis Centre, Division of Medicine, University College London, Royal Free Hospital, London, UK
[b] Department of Cardiology, Hospital Universitario Puerta de Hierro Majadahonda, CIBERCV, Madrid, Spain
[c] Royal Brompton Hospital, London, UK
[d] Institute of Cardiovascular Science, University College London, London, UK
[e] Barts Heart Centre, West Smithfield, London, UK
[f] University Francisco de Vitoria (UFV), Pozuelo de Alarcon, Madrid, Spain

Address for Correspondence
Dr Marianna Fontana MD, PhD
National Amyloidosis Centre, University College London, Royal Free Hospital
Rowland Hill Street
London. NW3 2PF, UK.
Telephone: +44 20 7433 2764
Fax: +44 20 7433 2803
E-mail: m.fontana@ucl.ac.uk

Dr Gonzalez-Lopez reports consulting and speaking fees from Pfizer. Dr Garcia-Pavia reports consulting fees from Akcea, Alnylam, Eidos, Neuroinmmune, Pfizer and Prothena; speaking fees from Akcea, Alnylam, Eidos, Pfizer and Prothena; and research funding from Alnylam, Pfizer and Prothena. This work was supported by the Instituto de Salud Carlos III (ISCIII) [PI17/01941, PI18/00765 and CB 16/11/00432]. Grants from ISCIII are supported by the Plan Estatal de I+D+I 2013-2016 – European Regional Development Fund (FEDER) "A way of making Europe". Professor Moon has received an unrestricted research grant from GSK. He has also been paid a consultancy fee for trial design. Dr Fontana is funded by the BHF FS/18/21/33447. Other authors have no conflict of interest relevant to this work to declare.

Cardiac amyloidosis can affect all cardiac chambers. The infiltrative process results in biventricular wall thickening, systolic and diastolic ventricular dysfunction and low cardiac output. In the atria leads to mechanical dysfunction and atrial enlargement, which cause blood stasis and risk of thrombus formation. High prevalence of intracardiac thrombi has been identified in patients with cardiac amyloidosis at autopsy and using transesophageal echocardiography (TEE)(1). However, the detection of intracardiac thrombi during TEE may reflect referral bias. CMR is a sensitive non-invasive method for detecting intracardiac thrombi; offering a comparable and equally specific alternative to TEE for evaluation of thrombus in the left atrial appendage (LAA) (2).

We assessed the prevalence of intracardiac thrombi using CMR in a consecutive cohort of patients with cardiac amyloidosis. 324 consecutive subjects were prospectively recruited at the National Amyloidosis Centre, London and at Puerta de Hierro University Hospital, Madrid. We excluded patients with contraindications to CMR including glomerular filtration rate <30 mL/min. All participants underwent CMR on 1.5T clinical scanners including a standard volumetric study with early gadolinium enhancement (EGE) and late gadolinium enhancement (LGE) as thrombus manifests an absence of contrast uptake due to its avascular composition. The absence of contrast enhancement can be used to distinguish thrombus from other masses such as neoplasm, which typically demonstrate contrast uptake. The gadolinium-based contrast agent used was 0.1 mmol/kg of gadoterate meglumine (Dotarem, Guerbet S.A., France). EGE of the LAA was acquired using a 5mm contiguous stack through the LAA and an inversion time of 440ms to confirm the presence or absence of thrombus (3) (Figure 1). LGE was acquired using magnitude and phase-sensitive inversion recovery reconstruction. In 300 patients, T1 mapping was acquired using the modified look-locker inversion recovery (MOLLI) sequence and

Extracellular volume (ECV) was calculated (4). EGE images were reviewed blind by two specialist CMR cardiologists (AMN and MF) who determined the presence/absence of thrombus.

Of 324 patients with cardiac amyloidosis (256 male, 79%; age 71 ± 11 years), 166 had cardiac ATTR, 155 had cardiac AL, 2 had Apolipoprotein A-I, and 1 had Apolipoprotein A-IV cardiac amyloidosis.

Two patterns of LGE were observed: subendocardial and transmural(4). Both patterns were present in AL and ATTR, being subendocardial more prevalent in AL (45.8% vs 27.1%, $p<0.01$) and transmural in ATTR (54.2% vs 72.9%, $p<0.01$). Average ECV was 0.51 in AL and 0.55 in ATTR ($p<0.01$).

The prevalence of AF was 29% and 1.5% had atrial flutter. The prevalence of AF was higher in ATTR than in AL (46.4% vs 14.2%, $p<0.001$). The prevalence of intracardiac thrombi was 6.2%, 95% CI [3.5, 8.8], in the overall population, 5.2%, 95% CI [1.6, 8.7] in AL and 7.2%, 95% CI [3.3, 11.2] in ATTR ($p=0.45$). Of the patients with intracardiac thrombi (20 patients), 13 patients were in AF and 7 in sinus rhythm.

Overall the prevalence of thrombi in patients in AF/flutter was high (13.1%), 9.1% in AL and 14.3% in ATTR ($p=0.52$). All the patients with intracardiac thrombi in AF were under long-term anticoagulation (46% with warfarin and 54% with DOACs). The prevalence of intracardiac thrombi in patients in sinus rhythm and AL amyloidosis was 4.5% whilst in ATTR was 1.1% ($p=0.11$). Most of the intracardiac thrombi were found in the LAA (90%), however, 6 patients had thrombi in other locations (30%); 2 of them in isolation (without thrombi in the LAA) and 4 patients had thrombi in other locations as well as in the LAA (2 patients in the right atrial appendage, one patient had multiple thrombi including thrombus right atrial wall and in the

proximal left and right pulmonary arteries and one patient had a thrombus in the left atrium). The longest diameter of the thrombi was 14.0mm ± 7.7.

The presence of intracardiac thrombi was significantly higher in patients with more severe biventricular systolic dysfunction (stroke volume, $p<0.01$; ejection fraction, $p<0.05$; MAPSE, $p<0.01$, TAPSE, $p<0.01$, and global longitudinal strain, $p<0.01$), atrial dilatation (LA $p<0.05$, RA $p<0.01$), and more severe degree of amyloid infiltration (ECV, $p< 0.01$). Intracardiac thrombi was associated with higher levels of NT pro-BNP ($p<0.01$) and AF ($p<0.05$).

This is the first study to report the prevalence of intracardiac thrombi in an unselected cohort of patients with cardiac amyloidosis. In contrast to the general anticoagulated AF population, in whom the prevalence of LAA thrombi has been reported to be <3% (5), we report a high prevalence of intracardiac thrombi in AF associated with cardiac amyloidosis despite anticoagulation (13.1%). Our results do not support the use of current recommendations for cardioversion after 3 weeks of anticoagulation in cardiac amyloidosis patients in AF rather we suggest the need for specific imaging to exclude intracardiac thrombi before undergoing cardioversion. Intracardiac thrombi were also found in a significant number of patients in sinus rhythm meriting further research to determine if these patients benefit of prophylactic anticoagulation.

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Figure 1. Stack through the LAA (A) planned in the short axis view typically at the aortic valve level. Left atrial appendage thrombus (red arrow, panel B).