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LETTER TO THE EDITOR

Estimating nuclear scanning capacity requirements for patients with suspected cardiac transthyretin amyloidosis

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a life-shortening disease, caused by the deposition of misfolded transthyretin amyloid fibrils in the extracellular space of the myocardium, leading to increased wall thickness and diastolic dysfunction that can result in heart failure (HF).[1]

Among patients with confirmed ATTR-CM, HF with a normal left ventricular ejection fraction (LVEF) is the predominant presentation, and an important clue to the underlying diagnosis is the presence of otherwise unexplained left ventricular hypertrophy.[2] Increased left ventricular wall thickness (LVWT) in patients with HF has been proposed as a red flag for cardiac amyloidosis that should prompt further investigations to confirm or exclude the diagnosis.[3]

The prevalence of ATTR-CM is uncertain, and, consequently, so is the number of patients that might be referred to an HF service with suspected ATTR-CM. The Hull LifeLab database, containing 20 years of data for patients who have been referred to a community HF clinic, offers a unique opportunity to investigate this issue.

The aim of this analysis was to understand the prevalence and characteristics of patients who should be considered for referral for nuclear scintigraphy to exclude or confirm a diagnosis of ATTR-CM, based on the presence of HF with a normal or mildly reduced ejection fraction and an increased LVWT.

Between August 2000 and January 2020, consecutive referrals to a community HF clinic were enrolled in a longitudinal epidemiological study at a single clinic (The Hull LifeLab). Patients consented for the use of their medical information prior to investigation. The study was approved by the Hull and East Yorkshire Local Research Ethics Committee. All patient identifiable information was anonymized before analysis.

For the present analysis, we focused only on patients with HF who had at their initial visit (i) a diagnosis of HF, based on symptoms and signs together with a raised N-terminal pro-brain natriuretic peptide (NT-proBNP) (≥400 ng/L)[4]; (ii) LVEF ≥45%, corresponding to mild or no evidence of LVSD, as determined by echocardiography; and (iii) measurements of LVWT. Patients were defined as being suitable for further investigations for a possible diagnosis of ATTR-CM if either the left ventricular posterior wall thickness or interventricular septal wall thickness was increased. An international position statement proposes an LVWT greater than or equal to 12 mm,[5] whereas another study suggests a cut-off of 14 mm.[3] Accordingly, we provide analyses using both criteria. We also present data for those with and without hypertension, defined as systolic blood pressure ≥140 mmHg.[6]

Of the original 7378 patients assessed in the clinic, 4788 had data available for NT-proBNP, LVEF, and LVWT, of whom 1735 had HF with normal or mildly reduced LVEF (*Figure 1*). Of these 1735, 884 (51%) had an LVWT ≥12 mm, and 282 (16%) had a LVWT ≥14 mm (*Figure 2*), which represents approximately 18% and 6%, respectively, of all patients for whom we had data on left ventricular systolic function, LVWT, and a contemporaneous NT-proBNP. Excluding patients with hypertension reduced the proportion who should be considered for nuclear scintigraphy to 7% those with a LVWT ≥12 mm and 2% of those with a LVWT ≥14 mm (*Figure 3*).

Patients with an LVWT ≥12 mm (*Table 1*) were more likely to have a history of hypertension or diabetes and a higher systolic blood pressure, were less likely to be treated with a beta blocker, and were more likely to be treated with a loop diuretic. Patients with greater wall thickness also had a longer QRS duration, had a higher NT-proBNP, and were more likely to have severe aortic valve disease. Left atrial size was not different between the two groups, but the left ventricular end-diastolic dimension indexed for body surface area (BSA) was slightly lower in the group with greater wall thickness. Similar findings were observed when comparing those with an LVWT ≥14 mm to those with a LVWT <14 mm (*Table 1*).

Epidemiologically, patients with HF and a normal LVEF are more likely to be women.[7] However, men are more likely to have increased LVWT, which could be due to myocardial hypertrophy or infiltration with ATTR and is consistent with the observation that ATTR-CM is much more common in men than women.[8]

Figure 1 Consort diagram describing selection for study groups. HF, heart failure; LVEF, left ventricular ejection fraction; LVWT, left ventricular wall thickness; NT-proBNP, N-terminal pro-brain natriuretic peptide.

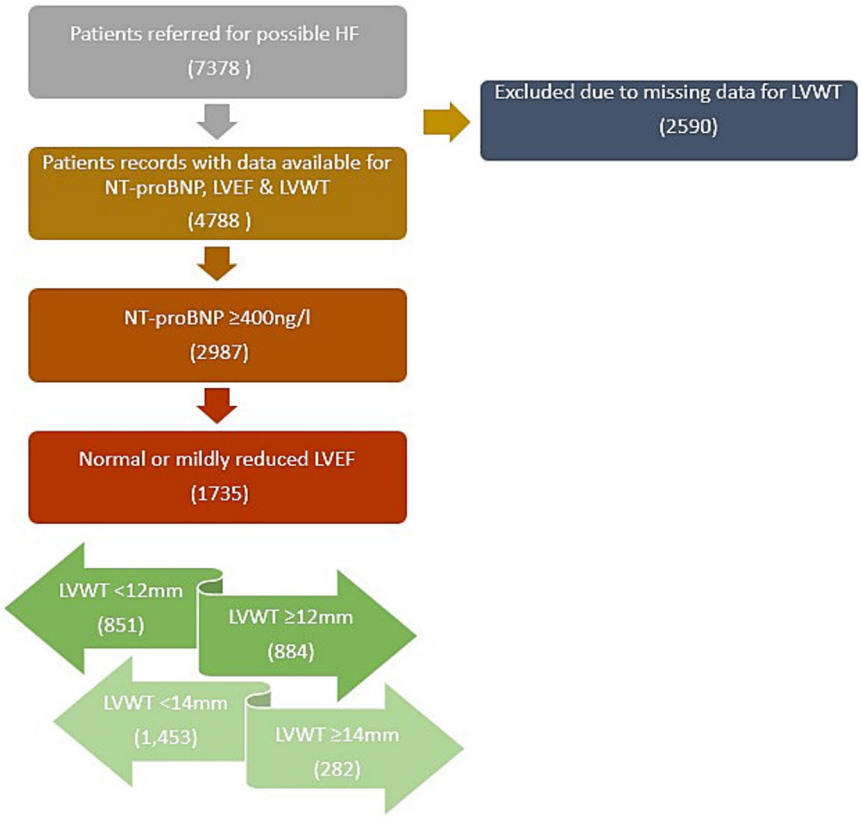

Figure 2 Proportion of patients presenting with LVWT ≥12 mm and ≥14 mmm by gender. Reported percentiles are based on total number of patients with an NT-proBNP ≥400 and normal to mildly reduced LVEF. HF, heart failure; LVEF, left ventricular ejection fraction; LVWT, left ventricular wall thickness; NT-proBNP, N-terminal pro-brain natriuretic peptide.

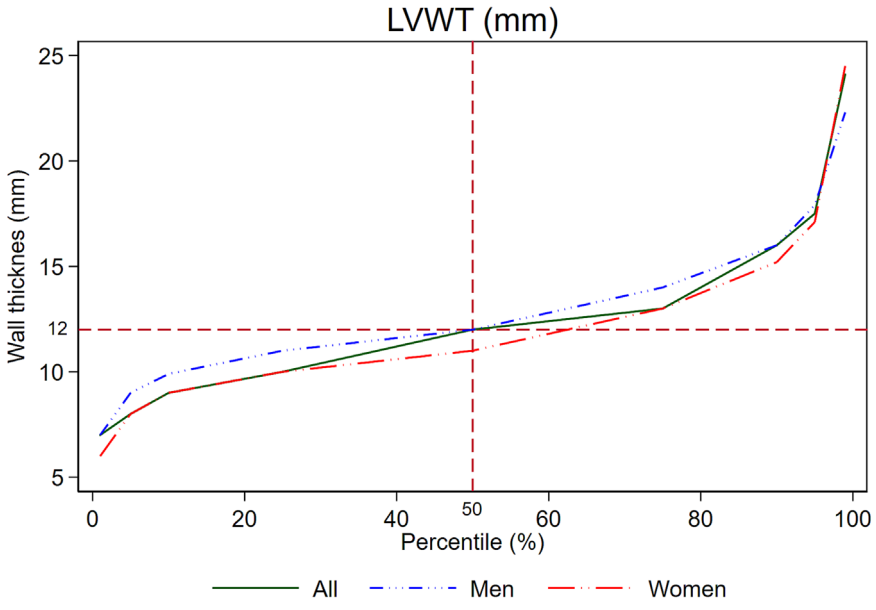

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Figure 3 Consort diagram describing the number of patients that should be considered for nuclear scintigraphy per 100 patients referred. HF, heart failure; LVEF, left ventricular ejection fraction; LVWT, left ventricular wall thickness; NT-proBNP, N-terminal pro-brain natriuretic peptide; SBP, systolic blood pressure.

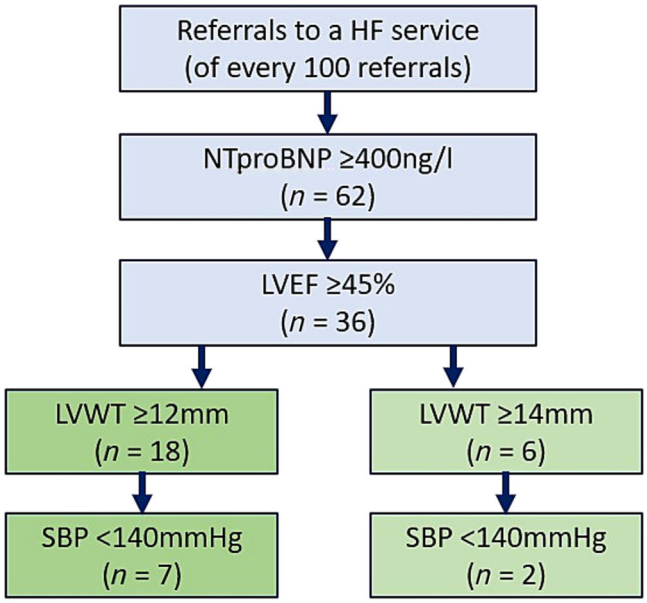

Table 1 Characteristics of patients with normal or mildly reduced LVEF, NT-proBNP ≥ 400 ng/L

	≥12 mm (*n* = 884)	<12 mm (*n* = 884)	*P* value (≥12 mm vs. <12 mm)	≥14 mm (*n* = 884)	<14 mm (*n* = 884)	*P* value (≥14 mm vs. <14 mm)
Age at referral (years)	78 (72, 83)	78 (72, 83)	0.54	77 (72, 82)	78 (72, 83)	0.03
Male (%)	56	45	<0.0001	59	49	0.004
BMI (kg/m^2)	28 (25, 33)	27 (24, 31)	0.003	28 (25, 32)	28 (24, 32)	0.11
SBP (mmHg)	148 (130, 167)	142 (126, 163)	0.001	148 (130, 171)	145 (128, 163)	0.057
SBP < 140 mmHg (%)	38	45	0.004	39	42	0.34
DBP (mmHg)	79 (69, 89)	77 (68, 89)	0.17	79 (69, 90)	78 (68, 89)	0.59
HR (BPM)	71 (60, 84)	72 (62, 84)	0.26	69 (60, 81)	72 (61, 84)	0.89
NYHA class III/IV	32	31	0.85	29	32	0.54
6MWT (m)	288 (120, 375)	300 (135, 360)	0.88	300 (147, 375)	288 (120, 375)	0.41
ECG						
Heart rate (bpm)	71 (60, 84)	72 (62, 84)	0.26	69 (60, 81)	71 (61, 8)	0.08
PR interval (ms)	172 (154, 198)	168 (151, 194)	0.04	169 (154, 202)	170 (152, 196)	0.63
QRS duration (ms)	98 (88, 116)	92 (84, 108)	<0.0001	100 (88, 119)	94 (84, 110)	0.0001
NT-proBNP (ng/L)	1386 (778, 2558)	1244 (776, 2256)	0.02	1497 (811, 2675)	1286 (773, 2325)	0.04
Co-morbidities						
AF (%)	44	48	0.13	41	47	0.08
IHD (%)	33	34	0.44	37	33	0.27
History of hypertension (%)	52	44	0.002	55	48	0.02
Diabetes (%)	27	22	0.04	32	24	0.005
COPD (%)	8	9	0.20	8	9	0.64
Treatment at referral						
Loop diuretics (%)	72	65	0.002	71	68	0.26
Thiazide diuretics (%)	8	8	0.93	7	8	0.63
ACEi/ARB (%)	63	61	0.44	61	63	0.68
Beta blockers (%)	56	61	0.03	51	60	0.007
MRA (%)	12	10	0.16	12	11	0.46
Echocardiography						
LVEF (%)	54 (48, 60)	55 (49, 60)	0.39	53 (47, 59)	55 (49, 61)	0.06
LVEDD (cm, BSA indexed)	2.5 (2.2, 2.8)	2.6 (2.3, 2.9)	<0.0001	2.5 (2.2, 2.8)	2.6 (2.3, 2.9)	0.001

(*Continues*)

Table 1 (continued)

	≥12 mm (n = 884)	<12 mm (n = 884)	P value (≥12 mm vs. <12 mm)	≥14 mm (n = 884)	<14 mm (n = 884)	P value (≥14 mm vs. <14 mm)
LVESD (cm, BSA indexed)	1.7 (1.5, 2.0)	1.8 (1.6, 2.1)	<0.01	1.8 (1.5, 2.1)	1.8 (1.5, 2.1)	0.35
LA diameter (cm, BSA indexed)	2.2 (1.8, 2.5)	2.1 (1.9, 2.4)	0.31	2.2 (1.9, 2.6)	2.2 (1.9, 2.4)	0.08
Any mitral regurgitation (%)	68	73	0.03	70	71	0.76
Mitral regurgitation >moderate (%)	10	11	0.75	12	10	0.33
Aortic root (cm)	3.3 (3.0, 3.6)	3.2 (2.9, 3.5)	<0.001	3.3 (3.0, 3.6)	3.2 (2.9, 3.6)	0.25
Aortic velocity (m/s)	1.4 (1.1, 1.8)	1.3 (1.1, 1.6)	<0.0001	1.4 (1.1, 1.8)	1.4 (1.1, 1.7)	0.24
Aortic velocity, <3 m/s (%)	94	96		94	95	
Aortic velocity, 3–4 m/s (%)	4	2	0.02	4	3	0.47
Aortic velocity, >4 m/s (%)	2	1		2	1	
Any aortic regurgitation (%)	34	33	0.68	34	33	0.75
Aortic regurgitation >moderate (%)	5	2	0.01	4	3	0.56

Continuous variables were analysed using a Mann–Whitney analysis and reported as median with 25th and 75th centiles. Categorical variables were analysed using Fisher's exact test and reported as percentages.
6MWT, 6-min walk test; ACEi, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin receptor blockers; BMI, body mass index; BPM, beats per minute; BPM, beats per minute; BSA, body surface area; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; HR, heart rate; IHD, ischaemic heart disease; LA, left atrial; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVSD, left ventricular systolic dysfunction; MRA, mineral corticoid receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Failure Association; SBP, systolic blood pressure.

These data have important service implications. A diagnosis of ATTR-CM should be considered for patients with HF, a normal or near-normal LVEF, and an unexplained increase in LVWT. Where active intervention rather than palliative care is being considered, further investigation should include bone scintigraphy (to detect ATTR-CM), a monoclonal protein screen (to support a diagnosis of AL amyloidosis), and, where appropriate, a fat biopsy to obtain a tissue diagnosis of AL amyloid.[3,5]

We acknowledge limitations of the data, which represent a single region in the UK and may not be representative of other HF services. Incomplete data may reduce the accuracy of our estimates. Routine measurement of NT-proBNP was only adopted in 2008. We also acknowledge that additional red flags for ATTR-CM such as a history of carpal tunnel syndrome were not routinely recorded.

This analysis shows that 51% of patients with HF and a normal or mildly reduced LVEF have an LVWT ≥12 mm and that 16% have an LVWT ≥14 mm. Such patients should be considered for further investigations to confirm or exclude ATTR-CM in the absence of alternative causes of LVH such as hypertension and aortic stenosis, although these diagnoses do not preclude concomitant ATTR-CM.[9] This analysis may help inform the planning of HF services and for the volume of nuclear scans required to investigate ATTR-CM.

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Vincenzo C. Leo
Pfizer Ltd, Walton Oaks, Dorking Rd, Tadworth, KT20 7NS, UK

Syed Kazmi
Hull University Teaching Hospitals Trust, Castle Hill Hospital, Castle Rd, Cottingham, HU16 5JQ, UK

Jack Brownrigg
Pfizer Ltd, Walton Oaks, Dorking Rd, Tadworth, KT20 7NS, UK

Marzieh Araghi
Pfizer Ltd, Walton Oaks, Dorking Rd, Tadworth, KT20 7NS, UK
E-mail: marzieh.araghi@pfizer.com

Harpreet S. Sarna
Pfizer Ltd, Walton Oaks, Dorking Rd, Tadworth, KT20 7NS, UK

Pierpaolo Pellicori
British Heart Foundation Cardiovascular Research Centre, School of Cardiovascular & Metabolic Health, University of Glasgow, Glasgow, UK, G12 8QQ

Joe Cuthbert
Hull York Medical School Castle Hill Hospital, Castle Rd, Cottingham, Kingston upon Hull, HU16 5JQ, UK

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John G.F. Cleland
British Heart Foundation Cardiovascular Research Centre, School of Cardiovascular & Metabolic Health, University of Glasgow, Glasgow, UK, G12 8QQ

Andrew L. Clark
Hull University Teaching Hospitals Trust, Castle Hill Hospital, Castle Rd, Cottingham, HU16 5JQ, UK

References

1. Halwani O, Delgado DH. Cardiac amyloidosis: an approach to diagnosis and management. *Expert Rev Cardiovasc Ther*. 2010; **8**: 1007–1013.
2. 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.
3. Witteles RM, Bokhari S, Damy T, Elliott PM, Falk RH, Fine NM, Gospodinova M, Obici L, Rapezzi C, Garcia-Pavia P. Screening for transthyretin amyloid cardiomyopathy in everyday practice. *JACC Heart Fail*. 2019; **7**: 709–716.
4. Al-Mohammad A, Mant J, Laramee P, Swain S. Diagnosis and management of adults with chronic heart failure: summary of updated NICE guidance. *BMJ*. 2018; **362**: k4080.
5. Garcia-Pavia P, Rapezzi C, Adler Y, Arad M, Basso C, Brucato A, Burazor I, Caforio ALP, Damy T, Eriksson U, Fontana M, Gillmore JD, Gonzalez-Lopez E, Grogan M, Heymans S, Imazio M, Kindermann I, Kristen AV, Maurer MS, Merlini G, Pantazis A, Pankuweit S, Rigopoulos AG, Linhart A. Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC working group on myocardial and pericardial diseases. *Eur Heart J*. 2021; **42**: 1554–1568.
6. NICE hypertension guideline |NICE guideline|guidelines (accessed: Dec 2022).
7. Duca F, Zotter-Tufaro C, Kammerlander AA, Aschauer S, Binder C, Mascherbauer J, Bonderman D. Gender-related differences in heart failure with preserved ejection fraction. *Sci Rep*. 2018; **8**: 1080.
8. Lauppe R, Liseth Hansen J, Fornwall A, Johansson K, Rozenbaum MH, Strand AM, Väkeväinen M, Kuusisto J, Gude E, Smith JG, Gustafsson F. Prevalence, characteristics, and mortality of patients with transthyretin amyloid cardiomyopathy in the Nordic countries. *ESC Heart Fail*. 2022; **9**: 2528–2537.
9. Ternacle J, Krapf L, Mohty D, Magne J, Nguyen A, Galat A, Gallet R, Teiger E, Côté N, Clavel MA, Tournoux F, Pibarot P, Damy T. Aortic stenosis and cardiac amyloidosis: JACC review topic of the week. *J Am Coll Cardiol*. 2019; **74**: 2638–2651.