ESC European Society of Cardiology

Europace (2020) **22**, 1788–1797
doi:10.1093/europace/euaa210

CLINICAL RESEARCH
Atrial fibrillation

Self-reported treatment burden in patients with atrial fibrillation: quantification, major determinants, and implications for integrated holistic management of the arrhythmia

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Received 12 March 2020; editorial decision 1 July 2020; accepted after revision 4 July 2020; online publish-ahead-of-print 10 October 2020

Aims Treatment burden (TB) refers to self-perceived cumulative work patients do to manage their health. Using validated tools, TB has been documented in several chronic conditions, but not atrial fibrillation (AF). We measured TB and analysed its determinants and impact on quality of life (QoL) in an AF cohort.

Methods and results A single-centre study prospectively included consecutive adult AF patients and non-AF controls managed from 1 April to 21 June 2019, who voluntarily and anonymously answered the TB questionnaire (TBQ) and 5-item EQ-5D QoL questionnaire; TB was calculated as a sum of TBQ points (maximum 170) and expressed as proportion of the maximum value. Of 514 participants, 331 (64.4%) had AF. The mean self-reported TB was 27.6% among AF patients and 24.3% among controls, $P = 0.011$. The mean TB was significantly higher in patients taking vitamin K antagonists (VKAs) vs. those taking non-VKA antagonist oral anticoagulants (NOAC; 29.5% vs. 24.7%, $P = 0.006$). The highest item-specific TB was reported for healthcare system organization-related items (e.g. visit appointment), diet, and physical activity modifications. On multivariable analyses, female sex, younger age, and permanent AF were associated with a higher TB, whereas NOACs and electrical AF cardioversion exhibited an inverse association; TB was an independent predictor of decreased QoL (all $P < 0.05$).

Conclusion Our study provided clinically relevant insights into self-perceived TB among AF patients. Approximately one in four patients with AF have a high TB. Specific AF treatments and optimization of healthcare system-required patient activities may reduce the self-perceived TB in AF patients.

Keywords Treatment burden • Atrial fibrillation • Patient-reported outcome • Quality of life • Non-vitamin K antagonist oral anticoagulant

Introduction

Treatment burden (TB) refers to patients' perception of cumulative work they do to manage their health, including learning about their condition(s) and treatment(s), attending medical appointments, getting prescriptions, taking medications, monitoring their health (e.g. blood pressure or glucose blood levels), implementing lifestyle and/or behavioural changes (e.g. exercise, smoking cessation, diet), maintaining their medical equipment/devices (e.g. changing batteries, cleaning the device), etc.[1,2]

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What's new?

- This study is the first to measure self-perceived treatment burden (TB) in patients with atrial fibrillation (AF). Our findings suggest that TB in AF patients may be higher compared with other chronic conditions.
- In our study, one in four patients with AF had a high TB that could be considered unsustainable in a long term.
- The greatest share of self-reported TB was most commonly attributed to the healthcare system organization-relates items (e.g. frequency of visits to physician, visit appointment, other paperwork).
- Our study also suggests that lifestyle change requirements (e.g. diet modification, weight loss, physical activity, etc.) often pose a considerable burden to patients, who could perhaps benefit from additional counselling and support during the process.
- Specific treatments (i.e. using a non-vitamin K antagonist oral anticoagulant, electrical AF cardioversion) were significantly associated with a lower likelihood of having the highest TB.
- Measurement of self-reported TB should be considered as a component of integrated management of AF patients, informing physicians and healthcare policy makers of the patient-perceived barriers that need to be addressed.

The perception of TB is patient-specific (e.g. a diet modification requirement may be embraced by one and perceived as a great difficulty by another patient) and often underappreciated by health professionals,[3] who may hence overestimate the patient's capacity to sustain more interventions.[1] Independently of the illness-related burden, patient-perceived TB is significantly associated with lower adherence to treatment,[4,5] impaired quality of life (QoL),[6] and increased hospitalization and mortality rates.[7]

Minimally disruptive medicine aims to tailor treatment to the context of individual patients, their daily lives and their specific goals.[8] Understanding patient-perceived TB is highly relevant to shared, informed decision-making and selection of treatment strategies that are both effective and acceptable for the patient (and carer). Future guidelines should implement patient-perceived burden and explicitly describe the burden associated with specific recommendations (at least the quantifiable workload and potential effect on patient's life), but data informing such approach are scarce.[1]

Using various validated tools,[9] several studies have documented TB in specific or multiple chronic conditions. In a recent large study in France ($n = 2413$ patients with one or more self-reported conditions), for example, the median TB scored 41 points.[10] A TB scoring ≥59 points was considered unacceptable by the participants, and as many as 38% of participants had a TB score of ≥59 points in that study.[10]

Treatment burden in patients with atrial fibrillation (AF) is unknown. The arrhythmia is a global epidemic associated with significant morbidity and mortality, and contemporary integrated holistic AF management includes active continuous patient involvement.[11] Given the multiplicity of main treatment goals in AF management (i.e. stroke prevention, symptom control, and management of concomitant conditions/risk factors), the information about self-perceived TB in AF patients is very much needed.

In this study, we measured patient-perceived TB in patients with AF and explored multiple aspects of TB in AF and non-AF patients in a prospectively collected cohort.

Methods

Study population

This single-centre, non-interventional study prospectively included consecutive adult patients with established diagnosis of AF, seen in the centre from 1 April to 21 June 2019. During the last 3 weeks of the enrolment period, consecutive patients without known AF but with other cardiovascular disease(s) were included as control group. No formal calculation of the sample size has been performed, because none of previously published studies could inform the calculation (none of the studies had specifically measured the TB among AF patients, but all included patients with various chronic conditions, including cardiovascular and pulmonary diseases, diabetes mellitus, etc.). Nevertheless, it has been pre-specified that the control group should enrol ~50% of the number of patients enrolled in the AF group. The enrolment of control group was restricted to the 3-week period given the large volume of our centre, serving the whole country.

Only patients who have been treated for at least 6 months before enrolment were included, to diminish the risk of under- or overestimation of self-reported TB with recently prescribed therapy. All patients voluntarily and anonymously answered the TB questionnaire (TBQ; Supplementary material online, *Table S1* for the full TBQ content), which has been previously developed[12] and validated[13] among patients with various chronic conditions, including cardiovascular diseases, but not specifically AF. The first four questions in the original TBQ address several aspects of oral and parenteral medication, and in our study, these questions were asked separately for oral anticoagulant therapy (OAC) and all other medication. Another 9 TBQ questions address the healthcare system-related requirements (e.g. arranging visit appointments, taking care of the paperwork) and lifestyle changes requested from the patient within the treatment process (e.g. diet restrictions). We excluded the question about healthcare costs since all Serbian citizens utilize the same state-funded health insurance plan [albeit non-vitamin K antagonist oral anticoagulants (NOACs) are not reimbursed].

In addition to the TBQ, participants answered the 5-item EQ-5D QoL questionnaire. Patient demographics, disease-related data, and all current therapy were recorded by the study investigator recruiting the patient. Only the established diagnoses noted in patient's medical records using the International Classification of Diseases 10 were included. Multimorbidity was defined as the presence of two or more comorbid conditions[14] in addition to AF. Polypharmacy was defined as taking five or more medications daily.[15]

All patients signed the written consent for participation, and the study was approved by the ethics committee of School of Medicine, Belgrade University.

Statistical analysis

Continuous variables were shown as mean value with standard deviation (SD) or median with interquartile range (IQR), and dichotomous variables as numbers and percentages. Continuous variables were compared using the Student's *t*-test, whereas the difference between categorical variables was analysed using the χ^2 test.

Treatment burden was calculated as a sum of TBQ points (range 0–10 per each question, 0 for 'I do not know', 1 for low burden, and 10 for the highest burden), with a maximum possible score value of 170, and expressed as proportion of the maximum value.

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Treatment burden was analysed as a continuous variable (i.e. the TBQ score value) as well as a categorical variable across the TBQ score quartiles, using the Linear Regression and Binary Logistic Regression method, respectively. Results were expressed as the Standardized Coefficient Beta with 95% confidence interval (CI) and odds ratio (OR) with 95% CI, respectively. On univariate analyses, all variables listed in *Table 1* (i.e. patient demographics, comorbidity, and treatment) were examined relative to TB (the dependent variable). Multivariable models were constructed using the variables which were statistically significantly associated with TB on univariate analyses.

The analyses of predictors of QoL were restricted to patients with AF and conducted using the same principles as in the analyses of TB.

All analyses were conducted using the SPSS software version 26. Two-sided *P*-values of <0.05 were considered statistically significant.

Results

Study population

Of 530 consecutive patients invited to complete the study questionnaires, 16 (3.0%) declined participation owing to a lack of time or interest. Of 514 patients who completed the questionnaires, 331 (64.4%) had AF, while the control group included 183 non-AF patients (35.6%) with an actively managed cardiovascular condition (*Figure 1*).

Socio-demographic characteristics, concomitant comorbidity, and current therapy are shown in *Table 1*. There were 480 patients (93.4%) with multimorbidity and 353 patients (68.7%) with polypharmacy.

Patients with AF were older and more commonly retired, or non-smokers compared with non-AF controls (all $P < 0.01$). The prevalence of hypertension and heart failure was similar in both groups. Patients with AF were more commonly taking OAC, and less often aspirin. The mean number of concomitant comorbidities was higher among AF patients compared to non-AF controls, but the difference was of borderline statistical significance. There was no difference in multimorbidity, drug treatment, or polypharmacy between the groups (*Table 1*).

Self-reported treatment burden

The mean self-reported TB was 27.6% among patients with AF and 24.3% among controls, $P = 0.011$ (*Table 2* and *Figure 2*; see also Supplementary material online, *Table S1*).

The distribution of study cohort per quartiles of TB is shown in *Table 2*. Notably, a TB within the highest quartile of TBQ was reported by 27.2% of patients with AF and 17.5% of non-AF controls ($P = 0.013$), *Table 2*.

On the analysis including only patients not taking OAC, there was no significant difference in the mean TB between AF patients and controls (26.2% vs. 24.8%, $P = 0.578$), *Figure 2*. On another sensitivity analysis of the whole study cohort, the mean TB was non-significantly higher in patients taking OAC ($n = 320$) compared with 194 non-OAC patients (27.2% vs. 25.0%, $P = 0.081$), *Figure 2*.

Among on-OAC patients, TB was significantly higher in those taking a vitamin K antagonist (VKA; $n = 206$) than in 114 patients taking a NOAC (28.7% vs. 24.6%, $P = 0.014$). Patients taking a NOAC had a similar TB as non-OAC patients ($P = 0.759$), whereas in patients taking a VKA TB was significantly higher than in non-OAC patients ($P = 0.011$), *Figure 2*.

On the analysis restricted to AF patients, the mean TB was similar in those taking OAC and in patients not on OAC (27.7% vs. 26.2%, $P = 0.574$). However, the mean TB was significantly higher in VKA vs. NOAC patients with AF (29.5% vs. 24.7%, $P = 0.006$), *Figure 2*. A detailed comparison of demographics, clinical features, comorbidity, and concomitant therapies between AF patients taking a NOAC and those taking a VKA is shown in Supplementary material online, *Table S2*. Patients taking a VKA less commonly had a university degree education, more commonly were retired, with permanent AF, longer duration of oral anticoagulant therapy, a higher mean CHA_2DS_2-VASc score, and more comorbidities (all $P < 0.05$).

The TBQ item-specific TB is shown in *Figure 3*. The highest TB in both AF and non-AF patients was reported for the frequency of visits to physician, administrative aspects of health management (i.e. visit appointment, health insurance, and other paperwork), diet modifications, physical activity requirements and any treatment-related activities reminding the patient on his/her health problems (Supplementary material online, *Table S1*).

Univariate and multivariable linear regression analyses of the association of demographic, disease-related, and treatment-related variables with self-reported TB (considered as a continuous variable or the highest and lowest TBQ quartile) in the whole study cohort and separately in patients with AF and non-AF control group are shown in Supplementary material online, *Tables S3–S6*. Notably, on univariate analyses, there was no significant association between multimorbidity or polypharmacy with self-reported TB, but female sex and younger age were significantly associated with increased likelihood of reporting a TB within the highest TBQ quartile (both $P < 0.05$; Supplementary material online, *Table S4*).

On multivariable analysis restricted to patients with AF, female sex was associated with increased likelihood of having a TB within the highest TBQ quartile (OR 2.23, 95% CI 1.27–3.91; $P = 0.005$), whereas NOAC therapy (OR 0.42, 95% CI 0.23–0.77; $P = 0.005$), electrical cardioversion of AF (OR 0.48, 95% CI 0.24–0.97; $P = 0.041$), or having a supraventricular arrhythmia in addition to AF (OR 0.29, 95% CI 0.11–0.80; $P = 0.016$) were inversely associated with the highest TB. Age <50 years (OR 0.11, 95% CI 0.01–0.87; $P = 0.037$) and permanent AF (OR 0.48, 95% CI 0.24–0.98; $P = 0.043$) were multivariable predictors of decreased likelihood of having a TB within the lowest TBQ quartile (Supplementary material online, *Table S6*).

Relationship of treatment burden with quality of life

The lowest EQ-5D score (i.e. the score value of 0) reflects the highest QoL, whereas the lowest QoL would score 20 points.

The mean EQ-5D QoL score in the whole study cohort was 3.11 ± 3.29. The score was significantly higher in patients with multimorbidity (3.22 ± 3.35) than in those without (2.13 ± 2.54), $P = 0.024$, and in patients with polypharmacy (3.61 ± 3.59) vs. those without (2.00 ± 2.14), $P < 0.001$. There was no significant difference between the mean EQ-5D QoL score value in patients taking OAC and those not on OAC (3.18 ± 3.39 vs. 2.99 ± 3.13, $P = 0.541$), but the mean

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Table 1 Socio-demographic characteristics of the study cohort, concomitant comorbidity, and current medication

Variables	All, *n* = 514 (%)	AF, *n* = 331 (64.4%)	Non-AF, *n* = 183 (35.6%)	*P*-value
Age (mean ± SD)	64.9 ± 11.27	65.4 ± 10.32	62.2 ± 12.59	0.002
Age ≤47	44 (8.6)	19 (5.7)	25 (13.7)	0.003
Female sex	211 (41.1)	127 (38.4)	84 (45.9)	0.097
Education degree				
Elementary school	67 (13.0)	44 (13.3)	23 (12.6)	0.815
High school	268 (52.1)	165 (49.8)	103 (56.3)	0.162
College	69 (13.4)	47 (14.2)	22 (12.0)	0.489
University	109 (21.2)	75 (22.7)	34 (18.6)	0.279
Employment status				
Employed	143 (27.8)	83 (25.1)	60 (32.8)	0.062
Unemployed	45 (8.8)	23 (6.9)	22 (12.0)	0.054
Retired	326 (63.4)	225 (68.0)	101 (55.2)	0.004
Marital status				
Married/living with a partner	376 (73.2)	250 (75.5)	126 (68.9)	0.103
Alone/divorced	55 (10.7)	32 (9.7)	23 (12.6)	0.310
Widow(er)	83 (16.1)	49 (14.8)	34 (18.6)	0.266
Cigarette smoking				
Smoker	94 (18.3)	49 (14.8)	45 (24.6)	0.006
Former smoker	150 (29.2)	93 (28.1)	57 (31.1)	0.466
Non-smoker	270 (52.5)	189 (57.1)	81 (44.3)	0.005
Functional mobility				
Fully mobile	483 (94.0)	313 (94.6)	170 (92.9)	0.449
Mobile with help	31 (6.0)	18 (5.4)	13 (7.1)	0.449
Immobile	0 (0.0)	0 (0.0)	0 (0.0)	–
AF characteristics				
Total AF history (years), mean ± SD	–	6.41 ± 6.62	–	–
Permanent AF	–	97 (29.3)	–	–
Comorbid conditions				
Hypertension	418 (81.3)	271 (81.9)	147 (80.3)	0.667
Heart failure	51 (9.9)	34 (10.3)	17 (9.3)	0.721
LVEF <50%	72 (14.0)	50 (15.1)	22 (12.0)	0.336
Ischaemic heart disease	116 (22.6)	58 (17.5)	58 (31.7)	<0.001
Recent ACS	13 (2.5)	2 (0.6)	11 (6.0)	0.002
Prior MI	61 (11.9)	29 (8.8)	32 (17.5)	0.004
Chronic stable CAD	28 (5.4)	16 (4.8)	12 (6.6)	0.411
PCI/balloon angioplasty	66 (12.8)	30 (9.1)	39 (19.7)	0.001
CABG	20 (3.9)	8 (2.4)	12 (6.6)	0.025
Cardiomyopathy	34 (6.6)	30 (9.1)	4 (2.2)	0.006
Valvular disease	42 (8.2)	25 (7.6)	17 (9.3)	0.492
Supraventricular arrhythmias	84 (16.3)	52 (15.7)	32 (17.5)	0.602
Ventricular arrhythmias	69 (13.4)	30 (9.1)	39 (21.3)	<0.001
CIEDs[a]	32 (6.2)	25 (7.6)	7 (3.8)	0.100
Peripheral artery disease	12 (2.3)	4 (1.2)	8 (4.4)	0.033
Diabetes mellitus type II	122 (23.7)	64 (19.3)	58 (31.7)	0.002
Prior stroke/TIA	23 (4.5)	13 (3.9)	10 (5.5)	0.422
CKD	52 (10.1)	28 (8.5)	24 (13.1)	0.096
COPD	43 (8.4)	24 (7.3)	19 (10.4)	0.222
Malignancy	27 (5.3)	17 (5.1)	10 (5.5)	0.873
Thyroid dysfunction[b]	94 (18.2)	70 (21.2)	24 (13.1)	0.025
Hyperlipoproteinaemia	208 (40.5)	114 (34.4)	94 (51.4)	<0.001
Other diseases	91 (17.7)	46 (13.9)	45 (24.6)	0.003
CHA_2DS_2-VASc score (mean; range 0–7)	2.71 ± 1.51	2.63 ± 1.50	2.85 ± 1.53	0.117

Continued

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Table 1 *Continued*

Variables	All, *n* = 514 (%)	AF, *n* = 331 (64.4%)	Non-AF, *n* = 183 (35.6%)	*P*-value
≥1 non-sex-related CHA_2DS_2-VASc risk factors	467 (90.9)	300 (90.6)	167 (91.3)	0.815
Current medication				
OAC	320 (62.3)	299 (90.3)	21 (11.5)	<0.001
VKA	206 (40.1)	189 (57.1)	17 (9.3)	<0.001
NOAC	114 (22.2)	110 (33.2)	4 (2.2)	<0.001
OAC treatment duration (years)	3.71 ± 3.91	3.69 ± 3.82	4.24 ± 5.76	0.620
Aspirin	118 (23.0)	35 (10.6)	83 (45.4)	<0.001
P_2Y12 inhibitor	69 (13.4)	27 (8.2)	42 (23.0)	<0.001
Beta blocker	396 (77.0)	264 (79.8)	132 (72.1)	0.062
Non-DHP Ca blocker	11 (2.1)	8 (2.4)	3 (1.6)	0.754
Digitalis	17 (3.3)	14 (4.2)	3 (1.6)	0.130
Antiarrhythmic drugs	235 (45.7)	195 (58.9)	40 (21.9)	<0.001
Mexiletine	4 (0.8)	0 (0.0)	4 (2.2)	0.999
Propafenone	51 (9.9)	36 (10.3)	15 (8.2)	0.332
Flecainide	32 (6.2)	27 (8.2)	5 (2.7)	0.020
Sotalol	6 (0.9)	3 (0.9)	3 (1.6)	0.465
Amiodarone	145 (61.7)	129 (39.0)	16 (8.7)	<0.001
ACEI/ARB	359 (69.8)	232 (70.1)	127 (69.4)	0.920
Diuretic	277 (53.9)	188 (56.8)	89 (48.6)	0.080
Spironolactone	110 (21.4)	81 (24.5)	29 (15.0)	0.025
Statin	226 (44.0)	135 (40.8)	91 (49.7)	0.052
Sedative	72 (14.0)	35 (10.6)	37 (20.2)	0.003
PPI	147 (28.6)	95 (28.7)	52 (28.4)	1.000
Insulin	43 (8.4)	13 (3.9)	30 (16.4)	<0.001
Oral antidiabetic drug	95 (18.5)	50 (15.1)	45 (24.6)	0.009
Other medications	234 (45.5)	127 (38.4)	107 (58.5)	<0.001
Electrical cardioversion of AF	–	96 (29.0%)	–	–
Catheter ablation of AF	–	55 (16.5%)	–	–
Multimorbidity and polypharmacy				
Number of comorbidities, mean ± SD (range)	3.59 ± 1.67 (1–14)	3.70 ± 1.76 (1–14)	3.40 ± 1.46 (1–8)	0.051
Patients with multimorbidity	480 (93.4)	313 (94.6)	167 (91.3)	0.152
Number of drugs, mean (range)	6.20 ± 2.94 (1–15)	6.18 ± 2.74 (1–15)	6.22 ± 3.27 (1–15)	0.895
Number of pills, mean ± SD (range)	7.13 ± 3.47 (0–20)	7.21 ± 3.27 (1–20)	6.98 ± 3.80 (0–17.5)	0.475
Patients on parenteral drugs	50 (9.7)	16 (4.8)	34 (18.6)	0.480
Number of parenteral applications daily, mean ± SD (range)	0.27 ± 0.91 (0–6)	0.12 ± 0.59 (0–4)	0.53 ± 1.26 (0–6)	0.115
Patients with polypharmacy	353 (68.7)	237 (71.6)	116 (63.4)	0.060
Quality of life				
Self-estimated health status today, mean ± SD (range 0–100)	61.73 ± 20.56	61.98 ± 20.39	61.25 ± 20.89	0.700
Total EQ-5D QoL score (mean ± SD)	3.11 ± 3.29	2.95 ± 3.25	3.39 ± 3.35	0.153
Mobility	0.83 ± 1.10	0.75 ± 1.06	0.96 ± 2.17	0.039
Self-care	0.19 ± 0.66	0.18 ± 0.63	0.21 ± 0.72	0.665
Usual activities	0.45 ± 0.96	0.42 ± 0.92	0.50 ± 1.02	0.381
Pain/discomfort	0.71 ± 0.98	0.69 ± 0.95	0.74 ± 1.04	0.637
Anxiety/depression	0.93 ± 1.07	0.91 ± 1.06	0.98 ± 1.08	0.431

ACEi, angiotensin-converting-enzyme inhibitor; ACS, acute coronary syndrome; AF, atrial fibrillation; ARB, angiotensin receptor inhibitor; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DHP, dihydropyridine; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant therapy; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; SD, standard deviation; TIA, transient ischaemic attack; VKA, vitamin K antagonist.

[a]CIED: cardiac implantable electronic devices (anti-bradycardia PM: *n* = 20, ICD: *n* = 7, CRT: *n* = 5).

[b]Thyroid disfunction: hypothyroidism, *n* = 65 and hyperthyroidism, *n* = 29.

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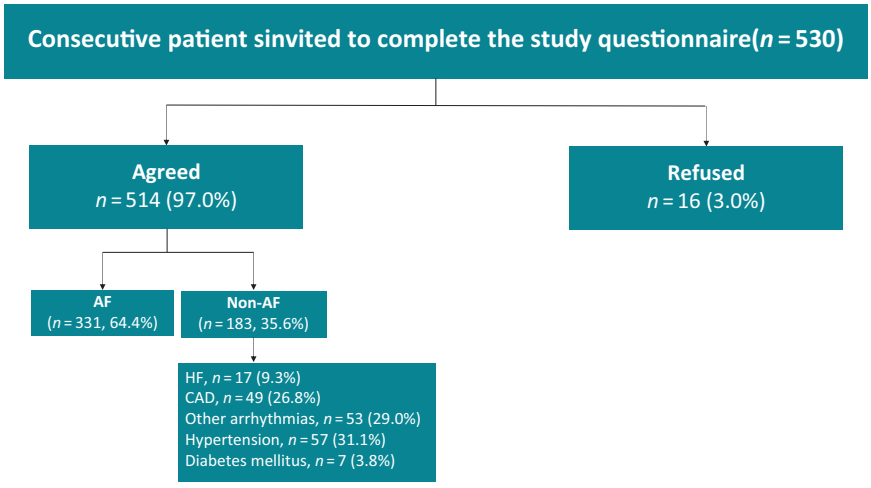

Figure 1 Study flowchart. AF, atrial fibrillation; CAD, coronary artery disease; HF, heart failure.

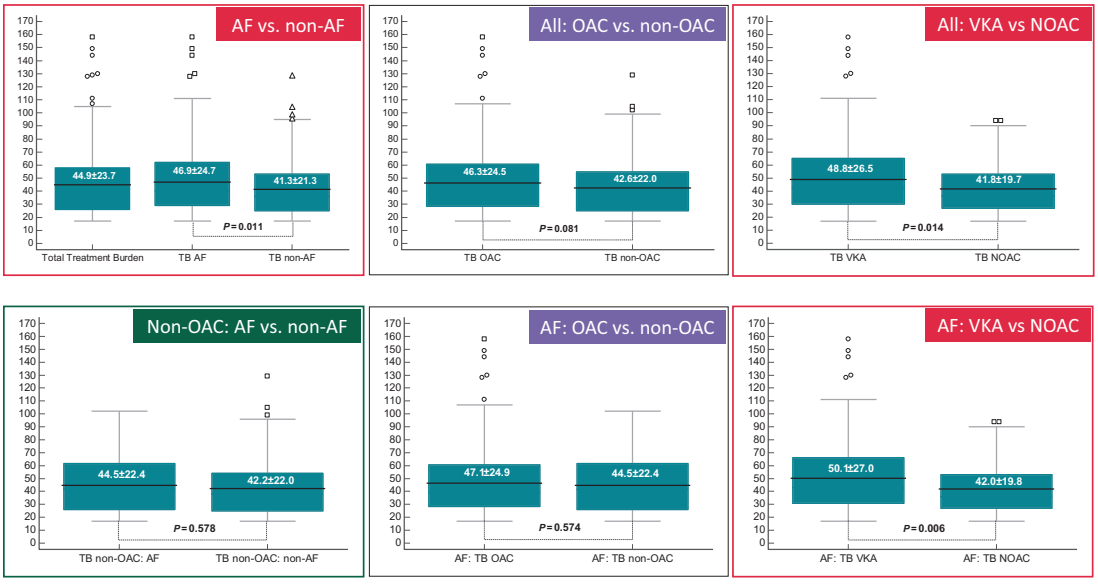

Figure 2 Treatment burden per specific sub-groups of patients. *Y*-axis shows the treatment burden questionnaire points. AF, atrial fibrillation; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant therapy; TB, treatment burden.

score was significantly higher in patients taking a VKA (3.50 ± 3.52) compared with those taking a NOAC (2.59 ± 3.09), $P = 0.020$.

The mean EQ-5D QoL score value was numerically lower in AF patients (2.95 ± 3.25) than in non-AF controls (3.39 ± 3.35), $P = 0.157$. In both groups, the mean total EQ-5D QoL score values significantly increased with increasing TB (*Figure 4*, upper panel). Among AF patients, mobility, usual activities, pain/discomfort, and anxiety/depression scores significantly increased with increasing TB (*Figure 4*, upper panel).

Treatment burden was an independent predictor of the highest quartile of the EQ-5D score among patients with AF (see *Table 3* and Supplementary material online, *Tables S7–S10*).

The mean self-estimated health status rating in the whole study cohort was 61.73 + 20.56 (out of the maximum 100 points), with no

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Table 2 The distribution of study cohort per quartiles of treatment burden

	All patients, *N* (%)	AF patients, *N* (%)	Non-AF patients, *N* (%)	*P*-value
Treatment burden				
Mean value	44.89	46.87	41.31	0.011
95% CI	42.84–46.94	44.20–49.53	38.20–44.41	
Range	17.00–158.00	17.00–158.00	17.00–129.00	
SD	23.65	24.66	21.30	
Median	39.00	40.00	36.00	
IQR	32.00	33.00	28.00	
Proportion of the maximum 170 points	26.4%	27.6%	24.3%	
TB quartiles				
TB ≤26 points	134 (26.1)	73 (22.1)	61 (33.3)	0.006
TB 27–39 points	127 (24.7)	89 (26.9)	38 (20.8)	0.135
TB 40–58 points	131 (25.5)	79 (23.9)	52 (28.4)	0.291
TB ≥59 points	122 (23.7)	90 (27.2)	32 (17.5)	0.013
Total	514	331	183	

AF, atrial fibrillation; CI, confidence interval; IQR, interquartile range; *N*, number; SD, standard deviation; TB, treatment burden.

Figure 3 Specific management aspect-related treatment burden in patients with and without atrial fibrillation. AF, atrial fibrillation; OAC, oral anticoagulants; Q, question; TB, treatment burden.

significant difference between the AF and control group (*Table 1*). The self-estimated health status rating significantly decreased with increasing TB in AF patients, whereas in non-AF controls the numerical increase did not reach statistical significance (Beta −0.200, 95% CI −0.253 to −0.077; $P < 0.001$ and Beta −0.105, 95% CI −0.246 to 0.041; $P = 0.159$, respectively), *Figure 4*, lower panel.

Discussion

Our study was the first to quantify TB among patients with AF and explore its major determinants and impact on QoL in AF patients. Our study provided clinically relevant insights into patient-perceived TB that may inform future guidelines on the management of AF patients. In addition, measurement of TB in patients with AF may serve as a patient-reported quality indicator highlighting the most burdensome treatment-related and/or healthcare system-related items that need to be addressed to improve the care of AF patients.

Our main findings were as follows: (i) TB among patients with AF was slightly but significantly higher than in patients with other chronic conditions, (ii) younger age and female sex were multivariable predictors of a higher TB, (iii) specific AF-related treatments (i.e. using a NOAC for stroke prevention or electrical cardioversion of AF for

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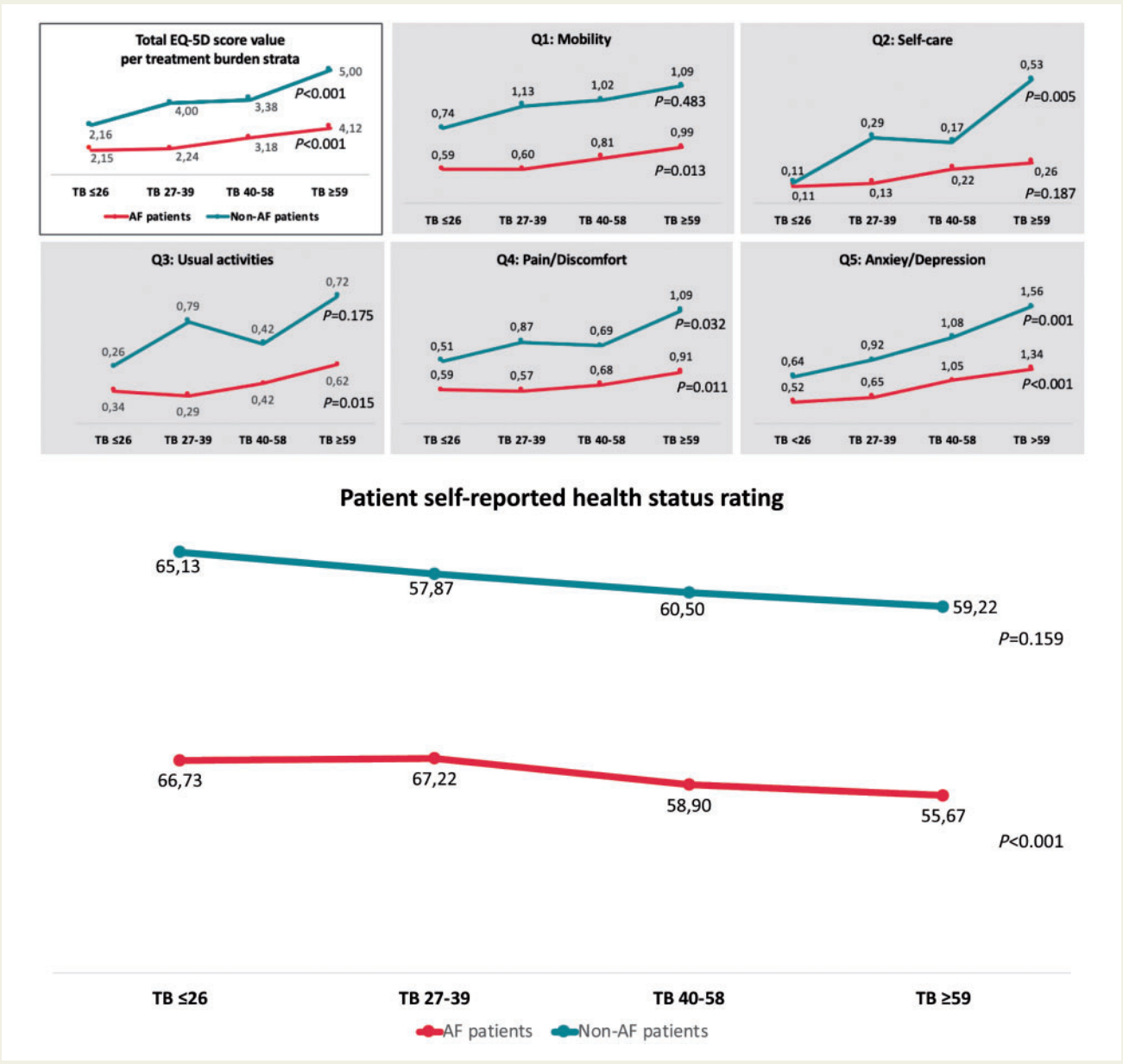

Figure 4 Self-reported health rating and the EQ-5D score values across treatment burden quartiles in patients with AF and non-AF control group (the higher EQ-5D score value, the lower QoL). *Y*-axis shows the EQ-5D score points. AF, atrial fibrillation; TB, treatment burden.

rhythm control) were significantly associated with a lower likelihood of having the highest TB, (iv) the greatest share of self-reported TB was most commonly attributed to the frequency of visits to physician, administrative aspects of health management (i.e. visit appointment, health insurance, and other paperwork), diet modification, physical activity requirements and any treatment-related activities reminding the patient on his/her health problems, and (v) TB was an independent predictor of impaired QoL in patients with AF.

Patients with AF were older than controls in our study. The age difference is not surprising, as the prevalence of AF increases with ageing, whereas other conditions (e.g. diabetes mellitus) occur earlier in life. To the best of our knowledge, no study has previously assessed the TB among AF patients. A recent study of non-AF patients showed that those with a TB of ≥59 points considered their TB unsustainable[10]. Given that 27% of AF patients in our study had a TB score of ≥59 points, around 1 in 4 AF patients could perhaps not adhere to their treatment owing to an unacceptably high TB. Notably, our findings suggest that using specific treatments for stroke prevention (i.e. a NOAC rather than a VKA) and rhythm control could influence the TB among AF patients. Indeed, the TB in AF patients taking a NOAC was similar to that among AF patients not taking OAC therapy in our study.

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In addition, our study highlighted the important unmet needs related to the healthcare system organization, suggesting that planning an adequate visit schedule and facilitating the access to healthcare providers would likely positively impact the AF patients' self-perception of TB.

In an international study quantifying TB among 610 multimorbid patients from 26 countries (mostly from the USA, UK, Canada, and Australia/New Zealand)[13], the greatest proportion of total TB has been assigned to the healthcare system-related issues (e.g. blood tests and other diagnostic procedures, doctor visits and other appointments), requirements for diet and physical activity changes and social aspects of treatment (e.g. the need for regular medication intake with a strict schedule). The mean self-reported TB values per specific TBQ items their share in the total TB in our study (*Figure 3*) were broadly similar to the aforementioned study. Indeed, the only significant inter-country variability seen in that study was related to the financial burden of healthcare, which is country-specific and varies among countries worldwide—hence was not investigated in our study, owing to the nationwide health insurance system utilized by all citizens.

Our study cohort included mostly patients with two or more chronic conditions (>90%). The self-reported TB among our patients was broadly comparable to TB in other studies reporting a quantified TB in multimorbid patients.[10,12,13]

Given that self-perception of TB is highly individual, it is not surprising that we identified only a few independent predictors of TB severity (e.g. female sex and younger age). Nevertheless, healthcare system-related barriers consistently appear to be burdensome for patients, in our study, as well as in other reports including patients with various chronic conditions from different countries. Our study also suggests that lifestyle change requirements (e.g. weight loss, physical activity, etc.) often pose a considerable burden to patients, who could perhaps benefit from counselling and additional support during the process.

Treatment burden significantly affected the QoL in AF patients in our study, as also reported in earlier studies of non-AF patients.[6] In addition, our study provided insight into the relationship of TB with specific aspects of QoL included in the EG-5D questionnaire, showing that all EQ-5D domains except self-care were negatively influenced by increased TB.

Given the observed impact of self-perceived TB on patient's QoL, our study suggests that the improvement in QoL observed after specific rhythm control intervention treatments[16] perhaps could have been partly mediated by the reduction in self-reported TB associated with specific rhythm control therapies, but this observation needs further investigation.

Limitations

The single-centre study findings may not be generalizable to other AF cohorts. However, we have previously reported that the overall cardiovascular and AF-related risk profile of AF patients from the Balkan countries including Serbia was broadly similar to AF patients from other European regions, excluding the younger mean age in patients from the Balkans.[17] The management of patients with AF in our tertiary healthcare centre is adherent to current European Society of Cardiology AF Guidelines.[18]

Table 3 The EQ-5D score quartiles and multivariable predictors of the highest EQ-5D score quartile among patients with atrial fibrillation

The EQ-5D quartiles in AF patients ($n = 321$)			
EQ-5D ≤ 1 point, *N* (%)	**EQ-5D = 2 points, *N* (%)**	**EQ-5D 3–5 points, *N* (%)**	**EQ-5D ≥ 6 points, *N* (%)**
150 (45.3)	**39 (11.8)**	**83 (25.1)**	**59 (17.8)**
Multivariable predictors of EQ-5D ≥ 6			
Variables	**OR**	**95% CI**	***P*-value**
Low education level[a]	2.47	1.03–5.94	0.043
Widow(er)	2.61	1.12–6.06	0.026
Fully mobile	4.72	2.16–10.31	<0.001
CHA_2DS_2-VASc score	1.32	1.02–1.71	0.036
Polypharmacy	4.86	1.54–15.41	0.007
TBQ score	1.03	1.01–1.04	<0.001

TBQ, treatment burden questionnaire.
[a]Elementary school.

The healthcare system-related factors relevant to the overall patient-perceived TB in our study may be country-specific, but such differences are likely present across many European countries. A modest size of our cohort could have influenced the results, but we included consecutive patients and their distribution across the TB quartiles was broadly even.

We have not included the psychological aspects (e.g. patient personality, mental status, and cognitive function assessment) in our analysis of TB, and we have not collected data on patients' adherence to treatments. In addition, we have not investigated patient knowledge about AF, which could be significantly associated with patient perception of TB. However, although no formal structured education about AF is available to patients in our centre, they are regularly informed about their disease and treatment on every clinical visit.

Owing to a single time period sampling of participants, the results of our study should be interpreted with caution. However, we have prospectively included consecutive patients, and this approach is being used in observational studies (e.g. the latest European Cardiology Society-led EurObservational Research Programme registries).

As with any other patient-related feature, self-perceived TB may change over time, which was not evaluated in the present study, but the follow-up measurement of TB in patients with AF is ongoing in our centre.

Conclusions

Our study provided clinically relevant insights into self-perceived TB among patients with AF. Approximately one in four patients with AF have a high TB that could be considered unsustainable in a long term. Stroke prevention using a NOAC, electrical cardioversion of AF for rhythm control, optimized clinical visit schedule, and rationalization

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of healthcare system-required patient activities may reduce the self-perceived TB in AF patients and improve their QoL.

Measurement of self-reported TB should be considered as a component of integrated management of AF patients, informing physicians and healthcare policy makers of the patient-perceived barriers that need to be addressed. Itemized analysis of the patient's self-reported TB may help better balancing of the workload that patient needs to sustain during the long-term treatment of AF against the patient's overall capacity, thus potentially improving the adherence to treatment and ultimate outcome.

More research is needed to elucidate the association of psychological factors with self-perceived TB and characterize the dynamic changes in self-perceived TB over time, with new comorbidities and treatment changes.

Supplementary material

Supplementary material is available at *Europace* online.

Acknowledgements

The authors thank the head nurse Zlatiborka Mijatovic for her valuable assistance during patient recruitment and scheduling for study questionnaires.

Conflict of interest: T.P.: Consultant for Bayer and Pfizer (no fees). The other authors have no conflict of interest relevant to this work.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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