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Keywords

patient-reported outcome, coronary artery disease, oral anticoagulation therapy, treatment burden

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Material and methods

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Patients with CAD could have a lower TBN in comparison to patients with other chronic medical conditions.

Preprint

Assessment of patient-reported treatment burden in patients with coronary artery disease

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Introduction

Coronary artery disease (CAD) remains the third cause of death among individuals aged ≥ 35 years globally.¹ Patient-reported treatment burden (TBN) refers to the patient's time and effort invested in the management of their chronic health conditions and the impact of that effort on their overall functioning and well-being.² High TBN is associated with various unfavourable outcomes, such as non-adherence, higher hospitalisation rates, exacerbation of chronic health conditions, and higher mortality.^{3,4} It has been shown that TBN of ≥ 59 points, as assessed using the Treatment Burden Questionnaire (TBNQ), is indicative of an unacceptably high TBN for patients.⁵ We have previously reported that patients with atrial fibrillation (AF) had a significantly higher TBN in comparison to those without AF.⁶ In addition, we found that female patients with AF might experience a higher TBN compared to male patients,⁷ and observed that CAD was a positive predictor of the higher TBN in AF patients, especially in females.^{6,7} The possible explanation could be in the fact that when CV disease is revealed the prognosis is significantly worse in females compared to males.⁸ Nevertheless, data are lacking regarding specific features of TBN in patients with CAD. In this exploratory analysis we aimed to address this research gap by exploring and characterising TBN in patients with CAD.

Methods

The rationale and design of the study have been previously reported.^{6,7} Briefly, consecutive adult patients were invited to voluntarily fill out the study questionnaires during the enrolment period from April to June 2019, during their clinical visit to the University Clinical Centre of Serbia. Only the patients who had been taking therapy for one or more chronic medical conditions for a

minimum of six months before enrolment in this study were eligible for inclusion in the research. The TBN questionnaire has been developed and validated for assessing TBN in patients undergoing treatment for various chronic health conditions and cardiovascular diseases.⁹ The TBN questionnaire comprises 13 items that examine the burden associated with taking medicine, self-monitoring, organisational and administrative requirements, following medical advice regarding diet and physical activity, as well as the social repercussions of the treatment. The question regarding the financial burden of treatment was excluded from the questionnaire due to the availability of a comprehensive national public health insurance program for all Serbian citizens. In addition, participants completed the EQ-5D questionnaire.

Statistical analysis

Continuous variables were expressed as means with standard deviations (SD) and analysed using the Students' t-test, while the categorical variables were represented as frequencies and corresponding percentages and analysed using the Chi-Square test.

The TBNQ score represents the sum of the points assigned by patients to each question, ranging from 1 (indicating minimal burden) to 10 (reflecting the highest burden). Responses to questions "I don't know" or unanswered questions were assigned 0 points, signifying the absence of perceived burden for the patient. The TBNQ score ranged from 0 to 170 points.

The TBNQ score was analysed as a continuous variable using linear regression analysis and presented as the Standard Coefficient Beta with a corresponding 95% confidence interval (CI). Moreover, the TBNQ score was stratified into quartiles, with the lowest quartile defined as TBNQ of ≤ 26 points and the highest quartile as TBNQ of ≥ 59 points. The lowest and the highest quartile

were analysed using Binary Logistic Regression and presented as Odds ratio (OR) with 95% CI. The variables (presented in Supplementary S3) which exhibited statistical significance ($p < 0.05$) on univariate regression analysis were used in building the multivariable models.

Statistical analyses were performed employing the SPSS Statistics software for Windows (version 26), and a two-sided P-value threshold of <0.05 was considered statistically significant.

Results

Out of 514 patients (mean age 64.9 ± 11.27 years; 41.1% female) enrolled in the study, 116 patients (22.6 %) had CAD. The differences between patients with and without CAD in demographics, social characteristics, concomitant comorbidities, and therapy are shown in Supplementary Table S1. Patients with CAD were significantly older, more commonly males, with an elementary level of education, retired, former smokers, and more often had functional mobility with help compared to non-CAD controls (all P-values ≤ 0.014). Furthermore, patients with CAD had a significantly higher prevalence of hypertension, heart failure, type 2 diabetes mellitus, and hyperlipoproteinemia compared to non-CAD patients, while the diagnosis of AF was significantly more common in non-CAD patients (all $P \leq 0.009$).

Self-reported treatment burden

The mean self-reported TBN score was 40.49 ± 21.54 points for patients with CAD and 46.17 ± 21.44 points for patients without CAD, $p=0.023$; While there was no difference in the prevalence of TBN score of ≥ 59 points between the two groups (19.0% vs. 25.1%, respectively, $p=0.170$). With respect to individual components of the TBN, patients with CAD reported significantly lower scores in relation to questions concerning laboratory tests, arranging

appointments, and doctor visits, as well as first, third, and fourth question about taking an OAC compared to non-CAD controls (all P-values ≤ 0.008), Figure and Supplementary Table S2.

Multivariable regression analysis

Univariate regression analysis within CAD and Non-CAD group were presented in the Supplementary Table S3 and S4. On multivariable analysis of TBN questionnaire score as continuous variable within CAD group, the OAC treatment duration of ≥ 1 year was associated with an increased likelihood of having higher TBN (beta -0.316, 95% CI -21.79-(-3.20), P= 0.009), while the use of spironolactone was associated with an increased likelihood of having lower TBN (beta 0.297, 95% CI 2.75-23.89, P= 0.014) Table. On multivariable analysis of the TBN score quartiles within CAD group, OAC treatment duration ≥ 2 years was a significant predictor of the highest TBN score quartile (OR 5.870, 95% CI 1.17-29.57, P= 0.032).

The overall self-rated health status score was positively associated with the lowest TBN quartile (OR 1.029, 95% CI 1.01-1.05, P= 0.011), while the Q5 of the EQ-5D questionnaire regarding anxiety/depression and a CHA₂DS₂-VASc score of ≥ 4 points were inversely associated with the lowest TBN quartile (OR 0.490, 95% CI 0.30-0.80, P= 0.005 and OR 0.388, 95% CI 0.16-0.93, P= 0.035, respectively) within CAD group.

Notably, the variables "diabetes mellitus," "insulin therapy," and the "number of parenteral applications daily," which demonstrated significance in univariate analysis, did not retain significance in the multivariable analysis. In comparison to CAD patients multivariable factors were different among non-CAD patients, presented in the Supplementary Table S5.

Discussion

To our knowledge, this is the first study to measure TBN in CAD patients. Our study shows the following: *i)* patients with CAD had a significantly lower TBN score in comparison to patients without CAD, *ii)* 1 in 5 CAD patients reported a TBN of ≥ 59 points, deemed to be unacceptably high from the patients' perspective, and *iii)* using OAC for one year or longer was a positive predictor of higher TBN in patients with CAD, while an OAC treatment duration of two years or longer was a positive predictor of the highest TBN of ≥ 59 points.

In the present analysis, the mean TBN score in patients with CAD was 40 points, which is lower than the previously reported mean TBN score in patients with AF of 47 points.⁶ Indeed, AF is a specific chronic disease which could burden patients with, for instance, frequent highly symptomatic episodes of AF that require doctor and/or hospital visits, changes in antiarrhythmic drug therapy, comprehensive concomitant risk factors and comorbidity management, and so forth. On the other hand, patients with CAD rarely have more than several episodes of acute coronary syndromes in their lifetime.

Regarding specific domains of the TBN questionnaire, the greatest contributors to the TBN score in patients with CAD were questions regarding doctor visits, administrative aspects, diet, and physical recommendations, which aligns with previous studies in patients with other chronic health conditions.^{6,7,9}

In the present analysis, 19% of patients with CAD reported unacceptably high TBN (≥ 59 points), in line with a large study from France of 2413 patients with various chronic medical conditions, which reported that a total of 28% of participants declared an unacceptably high TBN, ranging from 19% of patients with cardiac conditions to 50% of those with asthma.⁵

In our study, patients with CAD reported significantly lower TBN in comparison to patients without CAD. However, patients with CAD reported a significantly lower quality of life and more commonly had multimorbidity and polypharmacy compared to those without CAD, which is apparently paradoxical. A possible explanation could be because patients without CAD had a significantly higher prevalence of AF and female sex. **We found that in non-CAD patient's atrial fibrillation was multivariable predictors of higher TBN, see Supplementary Table S5.** Our previous research has indicated that patients with AF (especially females) have significantly higher TBN compared to those without AF.^{6,7} Furthermore, patients with CAD reported significantly lower scores for questions regarding laboratory analysis and other exams, arranged appointments and scheduled doctor visits compared to patients without CAD. This finding could be explained with better coordination of diagnosis and treatment pathways for patients with CAD, including the establishment of ST-elevation myocardial infarction (STEMI) networks.¹⁰ Furthermore, the initial manifestation of CAD is often characterised by specific symptoms in most patients, while in other cardiac diseases such as AF, the clinical presentation could be nonspecific, and a patient may go through examinations by various specialities before being seen by a cardiologist for definitive diagnosis and treatment of AF, which could impose a significant burden on patients.

The OAC is associated with a higher bleeding risk and dietary modification, which could affect the patient's TBN over time. As a consequence, and perhaps not unexpectedly, in multivariable regression analysis we found that longer use of OAC was an independent positive predictor of higher TBN and unacceptably high TBN in patients with CAD. Additionally, we found that the utilization of spironolactone therapy was an independent predictor of lower TBN, and the possible explanation could be that spironolactone therapy is commonly employed in the management of

heart failure, contributing to heart failure symptom regulation and potentially reducing the necessity for repeated medical consultations.

Limitations

This study was a pilot, cross-sectional, single-centre study with a relatively small cohort, which could have influenced the results. Additionally, we did not capture data regarding other factors that could have impacted the results, such as health literacy, cognitive function, etc. Given that the vast majority of citizens of Serbia have extensive public health insurance, we excluded question regarding financial burden, which could have influenced the results of TBN in other countries.

Conclusion

This was the first study that specifically addressed TBN in patients with CAD. Our findings suggest that patients with CAD could have a lower TBN in comparison to patients with other chronic medical conditions, possibly owing to a better-structured diagnosis and management pathways pertinent to CAD. Nevertheless, one in five patients with CAD experienced an unacceptably high TBN, thus indicating that optimisation in the long-term management of patients with CAD is still needed. Further research is needed to comprehensively characterise the patient-reported TBN and its implications in patients with CAD.

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Conclusion

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Table. Multivariable linear and logistic regression analyses of treatment burden in patients with coronary artery disease.

Multivariable Linear Regression analysis			
Variable	Beta	95% CI	P value
Spiroglactone	-0.316	-21.79-(-3.20)	0.009
OAC treatment duration ≥1 year	0.297	2.75-23.89	0.014
Multivariable Logistic Regression analysis of the highest TBNQ score quartile (≥59)			
Variable	OR	95% CI	P value
OAC treatment duration ≥2 years	5.870	1.17-28.57	0.032
Multivariable Logistic Regression analysis of the lowest TBNQ score quartile (≤26)			
Variable	OR	95% CI	P value
Q 5 -Anxiety/Depression	0.490	0.30-0.80	0.005
CHA ₂ DS ₂ -VASc score ≥4 points	0.388	0.16-0.93	0.033
Overall self-rated health status	1.029	1.01-1.05	0.011

OAC, Oral Anticoagulant; Q, Question; TBNQ, Treatment Burden Questionnaire.

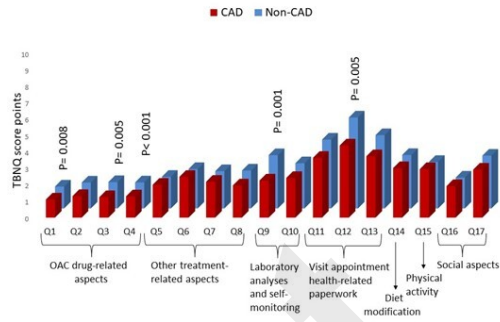


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Table S1. Socio-demographic characteristics of the study cohort, concomitant comorbidity, and current medication.

Variable	All n=514 (%)	CAD¹ n= 116 (22.6%)	Non-CAD n=398 (77.4%)	P value
Age (mean)	64.9 ±11.27	69.3 ±8.04	62.8 ±11.66	<0.001
Age≤50 years	63 (12.3)	0 (0.0)	63 (15.8)	<0.001
Age≥65 years	292 (56.8)	87 (75.0)	205 (51.5)	<0.001
Age≥75 years	83 (16.1)	28 (24.1)	55 (13.8)	0.008
Female sex	211 (41.1)	32 (27.6)	179 (45.0)	0.001
<i>Education degree</i>				
Elementary school	67 (13.0)	23 (19.8)	44 (11.1)	0.014
High school	268 (52.1)	46 (39.7)	222 (55.8)	0.002
College	69 (13.4)	22 (19.0)	47 (11.8)	0.047
University	109 (21.2)	24 (20.7)	85 (21.4)	0.877
<i>Employment status</i>				
Employed	143 (27.8)	13 (11.2)	130 (32.7)	<0.001
Unemployed	45 (8.8)	6 (5.2)	39 (9.8)	0.121
Retired	326 (63.4)	97 (83.6)	229 (57.5)	<0.001
<i>Marital status</i>				
Married/living with a partner	376 (73.2)	83 (71.6)	293 (73.6)	0.659
Alone/divorced	55 (10.7)	7 (6.0)	48 (12.1)	0.065
Widow(er)	83 (16.1)	26 (22.4)	57 (14.3)	0.037

<i>Cigarette smoking</i>				
Smoker	94 (18.3)	20 (17.2)	74 (18.6)	0.740
Former smoker	150 (29.2)	52 (44.8)	98 (24.6)	<0.001
Non-smoker	270 (52.5)	44 (37.9)	226 (56.8)	<0.001
<i>Functional mobility</i>				
Fully mobile	483 (94.0)	102 (87.9)	381 (95.7)	0.002
Mobile with help	31 (6.0)	14 (12.1)	17 (4.3)	0.002
Immobile	0 (0.0)	---	---	---
<i>AF characteristics</i>				
AF	331 (64.4)	58 (50.0)	273 (68.6)	<0.001
Total AF history (years)	6.41 ±6.63	6.47 ±8.00	6.40 ±6.32	0.948
Duration of AF ≤1 year	55 (10.7)	12 (21.4)	43 (16.0)	0.323
Duration of AF ≤2 years	103 (20.0)	20 (35.7)	83 (30.9)	0.477
Duration of AF ≤3 years	145 (28.2)	26 (46.4)	119 (44.2)	0.764
Permanent AF	97 (18.9)	21 (36.2)	76 (27.8)	0.204
<i>Comorbid conditions</i>				
Hypertension	418 (81.3)	104 (89.7)	314 (78.9)	0.009
Heart failure	51 (9.9)	24 (20.7)	27 (6.8)	<0.001
LVEF <50%	72 (14.0)	36 (31.0)	36 (9.0)	<0.001
Cardiomyopathy	34 (6.6)	5 (4.3)	29 (7.3)	0.256
Valvular disease	42 (8.2)	12 (10.3)	30 (7.5)	0.331
Supraventricular arrhythmias	84 (16.3)	16 (13.8)	68 (17.1)	0.399
Ventricular arrhythmias	69 (13.4)	19 (16.4)	50 (12.6)	0.289

CIEDs ²	32 (6.2)	7 (6.0)	25 (6.3)	0.923
Peripheral artery disease	12 (2.3)	6 (5.2)	6 (1.5)	0.021
Diabetes mellitus type II	122 (23.7)	39 (33.6)	83 (20.9)	0.004
Prior stroke/TIA	23 (4.5)	7 (6.0)	16 (4.0)	0.356
CKD	52 (10.1)	24 (20.7)	28 (7.0)	<0.001
COPD	43 (8.4)	14 (12.1)	29 (7.3)	0.102
Malignancy	27 (5.3)	8 (6.9)	19 (4.8)	0.367
Thyroid dysfunction ³	94 (18.2)	20 (17.2)	74 (18.6)	0.740
Hyperlipoproteinemia	208 (40.5)	80 (69.0)	128 (32.2)	<0.001
Other diseases	91 (17.7)	17 (14.7)	74 (18.6)	0.407
CHA ₂ DS ₂ -VASc score (mean)	2.71 ±1.51 (Range: 0-7)	4.00 ±1.21	2.33 ±1.37	<0.001
CHA ₂ DS ₂ -VASc score ≥2 points	401 (78.0)	115 (99.1)	286 (71.9)	<0.001
CHA ₂ DS ₂ -VASc score ≥4 points	157 (30.5)	77 (66.4)	80 (20.1)	<0.001
<i>Current medication</i>				
OAC	320 (62.3)	62 (57.8)	253 (63.6)	0.277
OAC treatment duration (years)	3.71 ±3.91	3.79 ±4.57	3.69 ±3.73	0.854
OAC treatment duration ≤1 year	100 (19.5)	24 (38.7)	76 (31.1)	0.257

OAC treatment duration ≤ 2 years	154 (30.0)	32 (51.6)	122 (50.0)	0.821
OAC treatment duration ≤ 3 years	194 (37.7)	39 (62.9)	155 (63.5)	0.928
OAC treatment duration ≥ 1 year	233 (76.1)	46 (74.2)	187 (76.6)	0.687
OAC treatment duration ≥ 2 years	193 (63.1)	33 (53.2)	160 (65.6)	0.072
OAC treatment duration ≥ 3 years	152 (49.7)	30 (48.4)	122 (50.0)	0.821
VKA	206 (40.1)	51 (44)	155 (38.9)	0.332
NOAC	114 (22.2)	16 (13.8)	98 (24.6)	0.013
LMWH	8 (1.6)	5 (4.7)	3 (0.8)	0.017
Aspirin	118 (23.0)	69 (59.5)	49 (12.3)	<0.001
P2Y12 inhibitor	69 (13.4)	56 (48.3)	13 (3.3)	<0.001
Beta blocker	396 (77.0)	98 (84.5)	298 (74.9)	0.030
Non-DHP Ca blocker	11 (2.1)	0 (0.0)	11 (2.8)	0.070
Digitalis	17 (3.3)	5 (4.3)	12 (3.0)	0.492
Antiarrhythmic drugs	235 (45.7)	43 (37.1)	192 (48.2)	0.034
Mexiletine	4 (0.8)	0 (0.0)	4 (1.0)	0.278
Propafenone	51 (9.9)	2 (1.7)	49 (12.3)	0.001
Flecainide	32 (6.2)	0 (0.0)	32 (8.0)	0.002
Sotalol	6 (0.9)	2 (1.7)	4 (1.0)	0.526

Amiodarone	145 (61.7)	39 (33.6)	106 (26.6)	0.141
DHP Ca blocker	160 (31.1)	37 (31.9)	123 (30.9)	0.839
ACEI/ARB	359 (69.8)	93 (80.2)	266 (66.8)	0.006
Diuretic	277 (53.9)	79 (68.1)	198 (49.7)	<0.001
Spirolactone	110 (21.4)	41 (35.3)	69 (17.3)	<0.001
Statin	226 (44.0)	97 (83.6)	129 (32.4)	<0.001
Nitrates	45 (8.8)	36 (31.0)	9 (2.3)	<0.001
Trimetazidine	78 (15.2)	51 (44.0)	27 (6.8)	<0.001
Sedative	72 (14.0)	21 (18.1)	51 (12.8)	0.149
PPI	147 (28.6)	63 (54.3)	84 (21.1)	<0.001
Thyroid hormone	56 (10.9)	15 (12.9)	41 (10.3)	0.424
Thyroid suppression therapy	14 (2.7)	1 (0.9)	13 (3.3)	0.162
Insulin	43 (8.4)	19 (16.4)	24 (6.0)	<0.001
Oral antidiabetic drug	95 (18.5)	27 (23.3)	68 (17.1)	0.131
Other medications	234 (45.5)	85 (73.3)	149 (37.4)	<0.001
<i>Non-pharmacological treatment</i>				
Ablation/ECV	141 (27.4)	10 (8.6)	131 (32.9)	<0.001
ECV AF	96 (18.7)	6 (5.2)	90 (22.6)	<0.001
ECV AFL	5 (1.0)	0 (0.0)	5 (1.3)	0.225
Ablation AF	55 (10.7)	3 (2.6)	52 (13.1)	0.001
Ablation AFL	12 (2.3)	3 (2.6)	9 (2.3)	0.838
Ablation other arrhythmias	4 (0.8)	0 (0.0)	4 (1.0)	0.278

<i>Multimorbidity and polypharmacy</i>				
Polypharmacy	353 (68.7)	112 (96.6)	241 (60.6)	<0.001
N of drugs	6.20 ±2.94	8.91 ±2-84	5.41 ±2.46	<0.001
N of pills	7.13 ±3.47	10.18 ±3.51	6.24 ±2.91	<0.001
Parenteral drugs use	50 (9.7)	23 (19.8)	27 (6.8)	<0.001
N of parenteral applications daily	0.27 ±0.91	9.61 ±3.51	5.61 ±2.83	<0.001
N of comorbidities	3.59 ±1.67	4.92 ±1.38	3.20 ±1.54	<0.001
Multimorbidity (without SA/VA)	462 (89.9)	116 (100.0)	346 (86.9)	<0.001
QoL EQ-5D questionnaire				
Q 1 –Mobility	0.83 ±1.10	1.22 ±1.20	0.71 ±1.05	<0.001
Q 2 -Self-care	0.19 ±0.66	0.31 ±0.88	0.16 ±0.58	0.076
Q 3 -Usual activities	0.45 ±0.96	0.66 ±1.11	0.39 ±0.90	0.018
Q 4 -Pain/Discomfort	0.71 ±0.98	0.78 ±1.09	0.69 ±0.95	0.355
Q 5 -Anxiety/Depression	0.93 ±1.07	0.93 ±1.09	0.93 ±1.06	0.974
QoL EQ-5D total score	3.11 ±3.29	3.90 ±3.72	2.88 ±3.12	0.003
Overall self-rated health status today (Range: 0-100)	61.73 ±20.56	55.28 ±21.59	63.61 ±18.88	<0.001

ACS, Acute coronary syndrome; MI, Myocardial infarction; CAD, Coronary artery disease; LVEF, Left ventricular ejection fraction; TIA, Transient ischemic attack; COPD, Chronic

obstructive pulmonary disease; CKD, Chronic kidney disease; PAD, Peripheral artery disease; OAC, Oral anticoagulant therapy; VKA, Vitamin K antagonist; NOAC, Non-vitamin K antagonist oral anticoagulant; DHP, Dihydropyridine; ACEi, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor inhibitor; PPI, Proton pump inhibitor; Q, question.

¹Coronary artery disease: Acute coronary syndrome, n= 13, Prior myocardial infarction, n= 61, Percutaneous coronary intervention/balloon angioplasty, n= 66, Coronary artery bypass grafting, n= 20, Chronic stable CAD, n= 28.

²CIED: cardiac implantable electronic devices (Antybradycardia PM: n=20, ICD: n=7, CRT: n=5).

³Thyroid dysfunction: HYPOthyroidism, n= 65, HYPERrthyroidism, n=29.

Table S2. Treatment burden questionnaire (TBNQ) score values in CAD and non-CAD patients.

Questions	CAD n= 116 (22.6%)	Non-CAD n=398 (77.4%)	P value
<i>Questions about OAC-related treatment burden</i>			
1. The taste, shape or size of your tablets and/or the inconvenience caused by your injections (for example, pain, bleeding, scars)	1.10 ±0.64	1.33 ±1.22	0.008

2. The number of times you have to take your medication every day	1.31 ±1.33	1.57 ±1.73	0.090
3. The things you do to remind yourself to take your daily medication and/or to manage your treatment when you are not at home	1.24 ±0.96	1.60 ±1.80	0.005
4. The specific conditions when taking your medication (for example, taking it at a specific time of the day or meal, not being able to do certain things after taking them like driving or lying down)	1.13 ±0.70	1.58 ±1.74	<0.001
<i>Questions about other drugs-related treatment burden</i>			
5. The taste, shape or size of your tablets and/or the inconvenience caused by your injections (for example, pain, bleeding, scars)	1.99 ±2.25	1.92 ±2.16	0.772
6. The number of times you have to take your medication every day	2.47 ±2.80	2.39 ±2.53	0.750
7. The things you do to remind yourself to take your daily medication and/or to manage your treatment when you are not at home	2.17 ±2.43	2.26 ±2.46	0.732

8. The specific conditions when taking your medication (for example, taking it at a specific time of the day or meal, not being able to do certain things after taking them like driving or lying down)	1.95 ±2.41	2.30 ±2.56	0.179
<i>Questions about other aspects of treatment burden</i>			
9. Lab tests and other exams (frequency, time spent and inconvenience of these exams)	2.25 ±2.62	3.23 ±3.10	0.001
10. Self-monitoring (for example, INR controls, taking your blood pressure or measuring your blood sugar yourself: frequency, time spent and inconvenience of this surveillance)	2.40 ±2.67	2.74 ±2.83	0.250
11. Doctor visits (frequency and time spent for the visits)	3.62 3.53	4.17 ±3.45	0.131
12. Arrange appointments and schedule doctor visits and laboratory tests?	4.37 ±3.77	5.51 ±3.84	0.005
13. How would you rate the burden associated with taking care of paperwork from health insurance agencies, welfare organisations, hospitals and/or social care?	3.72 ±3.76	4.44 ±3.78	0.069

14. How would you rate the constraints associated with your diet (for example, not being allowed to eat certain foods)?	3.01 ±3.08	3.24 ±3.11	0.483
15. How would you rate the burden associated with the recommendations from your doctors to practice regular physical exercises?	2.94 ±3.02	2.82 ±2.96	0.695
16. What is the impact of your healthcare on your social relationships (for example, need for assistance, being ashamed to take your medication in front of people)?	1.91 ±2.35	1.87 ±2.25	0.881
17. 'Frequent healthcare reminds me of my health problems.'	2.91 ±2.97	3.20 ±3.06	0.367
Total treatment burden score	40.49	46.17	0.023
Mean ±SD;	±21.54;	±24.11;	
Median, IQR	35.50, 22.50-51.75	40.00, 27.75-59.00	
Total TBN ≤26 points	41 (35.3)	93 (23.4)	0.010
Total TBN ≥59 points	22 (19.0)	100 (25.1)	0.170

CAD: Coronary Artery Disease; TBN: Treatment Burden; SD: Standard Deviation; IQR: Interquartile Range.

Table S3. Univariate analyses of treatment burden in patients with coronary artery disease.

Variable	CAD n= 116 (22.6%) TOTAL TBN			CAD n= 116 (22.6%) TBN ≥59 points			CAD n= 116 (22.6%) TBN ≤26 points		
	beta	95%CI	P value	OR	95%CI	P value	OR	95% CI	P value
Age (years)	-0.025	-.057-0.43	0.787	0.989	0.93-1.05	0.713	0.999	0.95-1.05	0.961
Age≤40 years	---	---	---	---	---	---	---	---	---
Age≤45 years	---	---	---	---	---	---	---	---	---
Age≤47 years	---	---	---	---	---	---	---	---	---
Age≤48 years	---	---	---	---	---	---	---	---	---
Age≤49 years	---	---	---	---	---	---	---	---	---
Age≤50 years	---	---	---	---	---	---	---	---	---
Age≤64 years	0.029	-7.77-10.60	0.761	1.158	0.41-3.31	0.785	1.161	0.49-2.77	0.737
Age≥65 years	-0.029	-10.60-7.77	0.761	0.864	0.30-2.47	0.785	0.861	0.36-2.06	0.737
Age 65-74 years	-0.006	-8.2-7.72	0.952	1.200	0.47-3.05	0.701	0.879	0.41-1.88	0.740
Age≥75 years	-0.022	-10.41-8.18	0.812	0.648	0.20-2.11	0.471	1.022	0.42-2.48	0.963

Age \geq 80 years	0.001	-13.52- 13.64	0.993	0.944	0.19- 4.71	0.944	0.661	0.166 -2.64	0.588
Female sex	0.123	-2.91-14.76	0.187	1.667	0.62- 4.46	0.309	0.636	0.26- 1.55	0.317
<i>Education degree</i>									
Elementary	-0.055	-12.91-7.02	0.559	0.877	0.27- 2.90	0.830	0.970	0.37- 2.53	0.950
High school	-0.003	-8.26-8.00	0.975	0.842	0.32- 2.20	0.726	1.535	0.71- 3.33	0.278
College	-0.018	-11.15-9.15	0.846	1.332	0.43- 4.11	0.618	1.056	0.40- 2.78	0.912
University	0.085	-5.31-14.26	0.367	1.161	0.38- 3.55	0.793	0.543	0.20- 1.50	0.238
<i>Employment status</i>									
Employed	0.056	-8.81-16.37	0.553	1.326	0.33- 5.29	0.689	0.793	0.23- 2.75	0.715
Unemployed	0.044	-13.72- 22.17	0.642	2.250	0.39- 13.15	0.368	0.910	0.16- 5.20	0.916
Retired	-0.074	-14.98-6.46	0.433	0.595	0.19- 1.87	0.375	1.223	0.43- 3.50	0.708
<i>Marital status</i>									
Married/living with a partner	-0.177	-17.10-0.26	0.057	0.495	0.19- 1.30	0.155	1.673	0.69- 4.05	0.254

Alone/divorced	0.173	-086-32.05	0.063	3.553	0.73- 17.19	0.115	0.718	0.13- 3.88	0.700
	0.093	-4.73-14.27	0.322	1.387	0.48- 4.01	0.545	0.607	0.23- 1.59	0.311
<i>Cigarette smoking</i>									
Smoker	0.012	-9.86-11.1	0.899	2.143	0.72- 6.42	0.173	1.273	0.47- 3.42	0.633
Former smoker	0.084	-4.33-11.61	0.367	0.821	0.32- 2.11	0.682	0.810	0.38- 1.75	0.590
Non-smoker	-0.096	-12.40-3.93	0.306	0.719	0.27- 1.93	0.513	1.074	0.49- 2.35	0.858
<i>Functional mobility</i>									
Fully mobile	0.111	-19.46-4.82	0.235	0.536	0.15- 1.90	0.334	3.714	0.79- 17.49	0.097
Mobile with help	0.111	-4.82-19.46	0.235	1.867	0.53- 6.62	0.334	0.269	0.06- 1.27	0.097
Immobile	---	---	---	---	---	---	---	---	---
<i>AF characteristics</i>									
AF	0.006	-7.70-8.22	0.949	1.000	0.40- 2.53	1.000	0.587	0.27- 1.27	0.176
Total AF history (years)	0.045	-0.58-0.81	0.739	0.983	0.90- 1.08	0.714	0.973	0.89- 1.06	0.541

Duration of AF \leq 1 year	-0.217	-23.66-2.44	0.109	---	---	---	1.500	0.38- 5.97	0.565
Duration of AF \leq 2 years	-0.215	-20.19-2.17	0.112	0.137	0.02- 1.16	0.068	1.885	0.56- 6.31	0.304
Duration of AF \leq 3 years	-0.180	-18.06-3.58	0.185	0.359	0.08- 1.53	0.166	1.460	0.45- 4.79	0.532
Permanent AF	0.187	-3.18-18.85	0.160	2.560	0.67- 9.74	0.168	0.434	0.12- 1.56	0.202
<i>Comorbid conditions</i>									
Hypertension	0.014	-12.05- 14.08	0.878	1.190	0.24- 5.87	0.830	0.741	0.22- 2.50	0.629
Heart failure	-0.052	-12.58-7.03	0.576	1.161	0.38- 3.55	0.793	1.125	0.44- 2.86	0.804
LVEF <50%	-0.139	-14.95-2.08	0.137	1.046	0.39- 2.84	0.930	1.484	0.66- 3.34	0.341
<i>Ischaemic heart disease</i>									
Recent ACS	-0.050	-16.57-9.52	0.594	0.840	0.17- 4.14	0.830	1.971	0.59- 6.56	0.269
Prior MI	-0.018	-8.76-7.17	0.844	0.880	0.35- 2.23	0.787	1.450	0.67- 3.13	0.344
Chronic stable CAD	-0.020	-10.44-8.39	0.829	0.686	0.21- 2.24	0.532	0.891	0.36- 2.21	0.803

PCI/Balloon angioplasty	0.084	-4.36-11.65	0.370	1.413	0.54-3.69	0.479	1.109	0.51-2.40	0.792
CABG	-0.003	-10.70-10.36	0.974	1.549	0.50-4.84	0.452	2.097	0.79-5.56	0.137
Cardiomyopathy	-0.082	-28.19-10.86	0.381	---	---	---	2.882	0.46-17.99	0.257
Valvular disease	-0.009	-13.70-12.42	0.923	1.491	0.37-6.04	0.575	1.971	0.59-6.56	0.269
Supraventricular arrhythmias (SA+AFL)	-0.163	-21.52-1.24	0.080	---	---	---	1.510	0.52-4.41	0.451
Ventricular arrhythmias	-0.095	-16.20-5.20	0.311	0.453	0.10-2.12	0.315	1.081	0.39-3.00	0.881
<i>CIEDs</i>	-0.080	-23.87-9.44	0.393	0.698	0.08-6.12	0.746	1.401	0.30-6.59	0.669
Anti-bradycardia pacemaker	0.034	-20.42-29.68	0.715	2.190	0.19-25.30	0.530	---	---	---
ICD	-0.120	-50.17-10.51	0.198	---	---	---	---	---	---
CRT	-0.068	-41.68-19.31	0.469	---	---	---	1.850	0.11-30.37	0.667
Peripheral artery disease	-0.005	-18.48-17.45	0.955	0.848	0.09-7.64	0.883	0.350	0.04-3.10	0.346

Diabetes mellitus type II	0.331	7.07-22.97	< 0.001	3.778	1.44-9.89	0.007	0.344	0.14-0.85	0.020
Prior stroke/TIA	-0.158	-30.70-2.29	0.091	---	---	---	2.595	0.55-12.21	0.228
Chronic kidney disease	-0.088	-14.45-5.12	0.347	0.822	0.25-2.71	0.747	1.749	0.70-4.36	0.231
COPD	0.012	-11.39-13.03	0.894	0.683	0.14-3.30	0.636	0.703	0.21-2.40	0.573
Malignancy	0.130	-4.55-26.59	0.164	2.811	0.62-12.78	0.181	---	---	---
Thyroid dysfunction	0.001	-10.46-10.60	0.989	1.083	0.32-3.63	0.897	0.982	0.36-2.70	0.972
Hyperlipoproteinemia	0.095	-4.14-12.98	0.309	1.250	0.45-3.51	0.672	0.953	0.42-2.17	0.908
Other conditions	0.083	-6.20-16.22	0.378	3.920	1.29-11.91	0.016	1.338	0.47-3.83	0.587
CHA ₂ DS ₂ -VASc score	0.064	-2.16-4.42	0.496	1.156	0.79-1.69	0.456	0.869	0.63-1.20	0.391
CHA ₂ DS ₂ -VASc score ≥1 point	---	---	---	---	---	---	---	---	---
CHA ₂ DS ₂ -VASc score ≥2 points	0.085	-23.22-62.54	0.366	---	---	---	---	---	---

CHA ₂ DS ₂ -VASc score ≥ 3 points	0.006	-13.14- 14.02	0.949	1.059	0.21- 5.29	0.944	1.512	0.38- 6.04	0.558
CHA ₂ DS ₂ -VASc score ≥ 4 points	0.181	-0.087- 16.48	0.052	2.669	0.84- 8.53	0.097	0.356	0.16- 0.80	0.012
CHA ₂ DS ₂ -VASc score ≥ 5 points	0.028	-7.29-9.90	0.765	1.347	0.51- 3.57	0.549	0.608	0.26- 1.43	0.255
CHA ₂ DS ₂ -VASc score ≥ 6 points	-0.009	-13.70- 12.42	0.923	0.840	0.17- 4.14	0.830	1.971	0.59- 6.56	0.269
<i>Current medication</i>									
OAC	-0.022	-9.00-7.10	0.815	0.851	0.33- 2.17	0.735	0.567	0.26- 1.23	0.149
OAC treatment duration (years)	-0.079	-1.46-0.77	0.540	1.010	0.88- 1.16	0.888	1.089	0.97- 1.22	0.147
OAC treatment duration ≤ 1 year	-0.066	-13.06-7.75	0.612	0.255	0.05- 1.28	0.097	0.722	0.23- 2.28	0.579
OAC treatment duration ≤ 2 years	-0.121	-14.85-5.33	0.349	0.133	0.03- 0.67	0.015	0.667	0.22- 2.01	0.471
OAC treatment duration ≤ 3 years	-0.032	-11.80-9.22	0.807	0.515	0.14- 1.84	0.307	0.647	0.21- 1.98	0.445
OAC treatment duration ≥ 1 year	0.291	1.99-24.19	0.022	---	---	---	0.588	0.18- 1.97	0.389
OAC treatment duration ≥ 2 years	0.141	-4.53-15.62	0.275	5.870	1.17- 29.57	0.032	1.141	0.38- 3.44	0.814

Sotalol	0.040	-23.92- 37.16	0.668	4.429	0.27- 73.70	0.300	1.850	0.11- 30.37	0.667
Amiodarone	-0.164	-15.73-0.89	0.079	0.519	0.18- 1.53	0.235	1.447	0.65- 3.21	0.363
DHP Ca blocker	-0.073	-11.85-5.17	0.439	0.411	0.13- 1.32	0.134	1.172	0.52- 2.64	0.701
ACEI/ARB	0.072	-6.09-13.82	0.443	1.712	0.46- 6.37	0.423	1.317	0.49- 3.52	0.583
Diuretic	-0.106	-1336-3.61	0.258	0.613	0.24- 1.60	0.316	1.208	0.53- 2.76	0.654
Spironolactone	-0.241	-18.87-(- 2.72)	0.009	0.342	0.11- 1.09	0.070	1.769	0.80- 3.89	0.156
Statin	0.062	-7.12-14.34	0.507	1.299	0.34- 4.92	0.700	0.925	0.33- 2.57	0.881
Nitrates	0.112	-3.34-13.75	0.230	2.179	0.84- 5.65	0.109	1.050	0.46- 2.39	0.908
Trimetazidine	0.143	-1.74-14.12	0.125	3.452	1.28- 9.28	0.014	0.854	0.40- 1.85	0.688
Sedative	0.230	2.78-22.89	0.013	4.731	1.67- 13.43	0.004	0.897	0.33- 2.44	0.831
PPI	0.066	-5.12-10.82	0.480	2.054	0.77- 5.49	0.152	0.960	0.45- 2.06	0.917

Thyroid hormone	0.071	-7.26-16.39	0.446	1.677	0.48- 5.87	0.419	0.903	0.29- 2.85	0.861
Thyroid suppression therapy	-0.102	-66.50- 19.11	0.275	---	---	---	---	---	---
Insulin	0.281	5.96-26.60	0.002	4.312	1.48- 12.60	0.008	0.291	0.08- 1.07	0.063
Oral antidiabetic drug	0.133	-2.59-16.08	0.155	1.727	0.62- 4.81	0.296	0.441	0.16- 1.20	0.109
Other medications	0.063	-5.93-12.02	0.502	1.813	0.56- 5.85	0.320	0.992	0.42- 2.34	0.985
<i>Non-pharmacological treatment</i>									
Ablation/ECV	-0.162	-26.34-1.63	0.083	---	---	---	3.043	0.81- 11.49	0.101
ECV AF	-0.096	-27.19-8.57	0.305	---	---	---	1.895	0.37- 9.85	0.447
ECV AFL	---	---	---	---	---	---	---	---	---
Ablation AF	-0.179	-48.78-0.55	0.055	---	---	---	---	---	---
Ablation AFL	-0.092	-37.44- 12.48	0.324	---	---	---	3.795	0.33- 43.17	0.282
Ablation other arrhythmias	---	---	---	---	---	---	---	---	---
<i>Multimorbidity and polypharmacy</i>									

Polypharmacy	0.055	-15.31- 28.23	0.558	---	---	---	0.5 34	0.07- 3.94	0.539
N of drugs	0.075	-0.84-1.97	0.426	1.137	0.96- 1.35	0.135	0.950	0.83- 1.09	0.459
N of pills	-0.022	-1.27-1.00	0.817	1.060	0.93- 1.21	0.390	0.998	0.90- 1.11	0.975
N of drugs without OAC	0.043	-1.12-1.78	0.649	1.115	0.94- 1.33	0.220	0.983	0.86- 1.13	0.810
N of pills without OAC	-0.019	-1.25-1.02	0.842	1.063	0.93- 1.21	0.365	1.010	0.91- 1.13	0.863
Parenteral drugs use	0.184	0.10-19.72	0.048	3.010	1.08- 8.42	0.036	0.585	0.21- 1.62	0.303
N of parenteral applications daily	0.203	0.36-6.64	0.029	1.384	1.01- 1.90	0.046	0.765	0.53- 1.11	0.160
N of comorbidities	0.043	-2.22-3.57	0.645	1.147	0.82- 1.60	0.418	0.907	0.68- 1.20	0.496
Multimorbidity (without SA/VA)	---	---	---	---	---	---	---	---	---
QoL EQ-5D questionnaire									
Q 1 –Mobility	0.146	-0.68-5.91	0.119	1.179	0.80- 1.73	0.400	0.640	0.45- 0.91	0.012
Q 2 -Self-care	0.195	0.33-9.25	0.036	1.593	1.03- 2.47	0.038	---	---	---

Q 3 -Usual activities	0.144	-0.77-6.35	0.123	1.466	1.01- 2.14	0.046	0.711	0.48- 1.06	0.091
Q 4 -Pain/Discomfort	0.085	-1.97-5.31	0.364	1.340	0.90- 1.99	0.148	0.873	0.61- 1.25	0.459
Q 5 - Anxiety/Depression	0.381	4.16-10.97	< 0.00 1	1.822	1.20- 2.77	0.005	0.463	0.29- 0.74	0.001
QoL EQ-5D total score	0.272	0.54-2.61	0.003	1.161	1.04- 1.30	0.011	0.788	0.68- 0.92	0.003
Overall self-rated health status today (Range: 0-100)	-0.188	-0.37-(- 0.01)	0.043	0.990	0.97- 1.01	0.372	1.032	1.01- 1.05	0.003

AF: Atrial fibrillation; LVEF: Left ventricular ejection fraction; ACS: Acute coronary syndrome; MI: Myocardial infarction; CAD: Coronary artery disease; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; AFL: Atrial flutter; CIED: Cardiac implantable electronic devices; ICD: Implantable cardioverter defibrillator; CRT: Cardiac resynchronisation therapy; TIA: Transient ischemic attack, COPD: Chronic obstructive pulmonary disease; OAC: Oral anticoagulant therapy; VKA: Vitamin K antagonist; NOAC: Non-vitamin K antagonist oral anticoagulant; ASA: Acetylsalicylic acid; DHP: Dihydropyridine; ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor inhibitor; PPI: Proton pump inhibitor; ECV: electrical cardioversion; SA: Supraventricular arrhythmias; VA: Ventricular arrhythmias; N: number.

Table S4. Univariate analyses of treatment burden in patients without coronary artery disease.

	Non-CAD								
	TOTAL TBN			TBN ≥59 points			TBN ≤26 points		
Variable	beta	95%CI	P value	OR	95%CI	P value	OR	95% CI	P value
Age (years)	-0.112	-0.44-(-0.03)	0.025	0.981	0.96-0.999	0.044	1.018	0.97-1.04	0.092
Age≤40 years	0.101	0.31-22.0	0.044	2.072	0.82-5.23	0.123	0.350	0.08-1.54	0.165
Age≤45 years	0.103	0.40-16.50	0.040	2.390	1.20-4.76	0.013	0.588	0.24-1.45	0.251
Age≤47 years	0.111	0.96-16.04	0.027	2.561	1.34-4.89	0.004	0.703	0.32-1.57	0.391
Age≤48 years	0.086	-0.87-13.43	0.085	2.233	1.20-4.15	0.011	0.798	0.38-1.67	0.548
Age≤49 years	0.073	-1.78-11.86	0.147	1.819	0.997-3.32	0.051	0.678	0.33-1.40	0.296
Age≤50 years	0.175	-2.01-11.00	0.175	1.768	0.993-3.15	0.053	0.573	0.28-1.18	0.129
Age≤64 years	0.061	-1.81-7.69	0.224	1.273	0.81-2.00	0.298	0.750	0.47-1.20	0.228

Age \geq 65 years	-0.061	-7.69-1.81	0.224	0.786	0.50- 1.24	0.298	1.334	0.84- 2.13	0.228
Age 65-74 years	-0.025	-6.17-3.64	0.612	0.908	0.57- 1.45	0.687	1.262	0.79- 2.03	0.335
Age \geq 75 years	-0.053	-10.56-3.21	0.294	0.713	0.35- 1.44	0.347	1.141	0.59- 2.20	0.694
Age \geq 80 years	-0.005	-10.69-9.69	0.923	1.055	0.40- 2.75	0.913	1.168	0.45- 3.06	0.751
Female sex	0.189	4.46-13.85	<0.00 1	2.256	1.42- 3.58	0.001	0.675	0.42- 1.09	0.105
<i>Education degree</i>									
Elementary	-0.066	-12.64-2.50	0.189	0.633	0.28- 1.41	0.264	1.830	0.94- 3.58	0.078
High school	0.057	-1.99-7.57	0.252	1.668	1.04- 2.67	0.033	1.066	0.67- 1.70	0.788
College	0.098	1.00-14.67	0.050	1.307	0.67- 2.56	0.434	0.642	0.29- 1.43	0.277
University	-0.097	-11.45-0.10	0.054	0.469	0.25- 0.89	0.020	0.780	0.43- 1.41	0.409
<i>Employment status</i>									
Employed	-0.050	-7.66-2.47	0.315	0.903	0.56- 1.47	0.682	0.915	0.56- 1.51	0.728

Immobile	---	---	---	---	---	---	---	---	---
<i>AF characteristics</i>									
AF	0.124	1.37-11.54	0.013	2.017	1.18-3.45	0.010	0.614	0.38-0.995	0.048
Total AF history (years)	0.042	-0.31-0.65	0.489	1.033	0.99-1.08	0.118	0.977	0.93-1.03	0.383
Duration of AF \leq 1 year	-0.060	-12.44-4.18	0.329	0.442	0.19-1.04	0.062	2.115	1.03-4.35	0.042
Duration of AF \leq 2 years	-0.023	-7.89-5.32	0.702	0.737	0.41-1.33	0.313	1.612	0.87-2.98	0.127
Duration of AF \leq 3 years	-0.040	-8.16-4.12	0.517	0.605	0.35-1.05	0.072	1.341	0.74-2.42	0.330
Permanent AF	-0.022	-8.00-5.49	0.715	0.835	0.46-1.51	0.553	0.365	0.16-0.81	0.014
<i>Comorbid conditions</i>									
Hypertension	-0.044	-8.45-3.20	0.376	0.688	0.40-1.17	0.167	0.823	0.47-1.43	0.492
Heart failure	-0.040	-13.29-5.62	0.425	0.842	0.33-2.15	0.719	1.708	0.74-3.94	0.209
LVEF <50%	-0.090	-15.83-0.68	0.072	0.570	0.23-1.41	0.225	1.293	0.60-2.79	0.513
Cardiomyopathy	-0.012	-10.26-8.04	0.811	1.147	0.49-2.68	0.751	0.946	0.33-2.14	0.724

Valvular disease	0.023	-6.95-11.06	0.654	1.815	0.83- 3.96	0.134	1.449	0.64- 3.28	0.374
Supraventricular arrhythmias (SA+AFL)	-0.092	-12.17-0.41	0.067	0.523	0.26- 1.04	0.065	1.898	1.08- 3.35	0.027
Ventricular arrhythmias	-0.105	-14.74-(- 0.47)	0.037	0.530	0.24- 1.17	0.117	1.844	0.97- 3.49	0.060
<i>CIEDs</i>	0.111	1.30-20.79	0.026	2.507	1.10- 5.72	0.029	0.429	0.13- 1.47	0.177
Anti-bradycardia pacemaker	0.095	-0.39-23.00	0.058	2.792	1.05- 7.45	0.040	0.196	0.03- 1.50	0.117
ICD	0.050	-10.56- 32.10	0.322	0.742	0.08- 6.72	0.791	0.818	0.09- 7.410	0.858
CRT	0.026	-20.27- 34.71	0.606	6.061	0.54- 67.57	0.143	1.647	0.15- 18.37	0.685
Peripheral artery disease	0.021	-15.46- 23.57	0.683	0.592	0.07- 5.13	0.634	0.652	0.08- 5.65	0.698
Diabetes mellitus type II	0.084	-0.87-10.80	0.095	1.486	0.87- 2.53	0.145	0.738	0.40- 1.35	0.324
Prior stroke/TIA	-0.039	-16.83-7.37	0.442	0.678	0.19- 2.43	0.551	0.749	0.21- 2.69	0.657
Chronic kidney disease	0.019	-7.52-11.08	0.707	0.993	0.41- 2.41	0.987	0.526	0.18- 1.56	0.246

COPD	0.142	4.11-22.23	0.004	2.634	122-5.69	0.014	0.665	0.25- 1.80	0.421
Malignancy	0.042	-6.35-15.94	0.398	1.068	0.78- 3.04	0.902	0.602	0.17- 2.11	0.428
Thyroid dysfunction	0.065	-2.07-10.13	0.195	1.229	0.70- 2.16	0.475	0.802	0.43- 1.49	0.486
Hyperlipoproteinemia	-0.042	-7.26-2.92	0.402	0.931	0.57- 1.52	0.774	1.216	0.75- 1.98	0.434
Other conditions	0.022	-5.02-7.85	0.665	1.172	0.65- 2.13	0.602	0.791	0.41- 1.53	0.484
CHA ₂ DS ₂ -VASc score	0.021	-1.3-2.10	0.680	1.024	0.67- 1.21	0.778	0.960	0.81- 1.14	0.642
CHA ₂ DS ₂ -VASc score ≥ 1 point	0.035	-4.79-9.95	0.492	1.112	0.54- 2.28	0.772	0.772	0.39- 1.53	0.460
CHA ₂ DS ₂ -VASc score ≥ 2 points	-0.090	-9.22-0.42	0.073	0.611	0.39- 0.96	0.034	1.130	0.70- 1.82	0.615
CHA ₂ DS ₂ -VASc score ≥ 3 points	-0.078	-9.32-1.06	0.119	0.735	0.44- 1.23	0.241	1.516	0.93- 2.48	0.097
CHA ₂ DS ₂ -VASc score ≥ 4 points	-0.020	-10.56-6.93	0.684	0.822	0.34- 1.96	0.659	0.445	0.15- 1.30	0.139
CHA ₂ DS ₂ -VASc score ≥ 5 points	0.045	-8.28-22.09	0.372	2.028	0.56- 7.34	0.281	0.357	0.05- 2.86	0.332

CHA ₂ DS ₂ -VASc score ≥ 6 points	0.033	-31.61- 63.36	0.511	---	---	---	---	---	---
<i>Current medication</i>									
OAC	0.098	-0.02-9.82	0.051	1.560	0.96- 2.55	0.076	0.696	0.43- 1.12	0.133
OAC treatment duration (years)	0.119	-0.04-1.68	0.063	1.073	0.998- 1.15	0.055	0.892	0.80- 0.99	0.037
OAC treatment duration ≤ 1 year	-0.096	-12.24-1.67	0.136	0.549	0.29- 1.05	0.071	1.953	1.03- 3.69	0.039
OAC treatment duration ≤ 2 years	-0.097	-11.43-1.46	0.129	0.583	0.33- 1.03	0.064	1.927	1.02- 3.63	0.043
OAC treatment duration ≤ 3 years	-0.088	-11.37-2.03	0.171	0.617	0.35- 1.10	0.099	1.899	0.95- 3.80	0.070
OAC treatment duration ≥ 1 year	0.108	-1.08-14.13	0.092	2.061	0.97- 4.36	0.059	0.464	0.24- 0.91	0.026
OAC treatment duration ≥ 2 years	0.092	-1.83-11.73	0.152	1.619	0.87- 3.01	0.128	0.508	0.27- 0.95	0.034
OAC treatment duration ≥ 3 years	0.097	-1.46-11.43	0.129	1.716	0.97- 3.04	0.064	0.519	0.28- 0.98	0.043
VKA	0.175	3.83-13.44	<0.00 1	2.051	1.30- 3.25	0.002	0.689	0.42- 1.12	0.132
NOAC	-0.089	-10.45-0.55	0.078	0.650	0.37- 1.14	0.133	1.008	0.59- 1.73	0.978

LMWH	-0.040	-38.73- 16.22	0.421	1.495	0.13- 16.67	0.744	1.647	0.15- 18.37	0.685
ASA	-0.017	-8.45-6.02	0.741	0.846	0.42- 1.73	0.645	1.533	0.79- 2.96	0.203
P ₂ Y ₁₂ inhibitor	0.072	-3.66-23.03	0.154	1.338	0.40- 4.44	0.634	0.587	0.13- 2.70	0.494
Beta blocker	-0.053	-8.42-2.54	0.292	0.940	0.56- 1.58	0.816	1.408	0.80- 2.48	0.234
Non-DHP Ca blocker	0.069	-4.36-24.59	0.170	1.732	0.50- 6.05	0.389	---	---	---
Digitalis	0.044	-7.71-20.08	0.382	2.188	0.68- 7.06	0.190	0.291	0.04- 2.28	0.240
Antiarrhythmic drugs	0.048	-2.43-7.08	0.338	1.290	0.82- 2.03	0.272	1.066	0.67- 1.70	0.788
Mexiletine	0.012	-20.98- 26.70	0.814	0.993	0.10- 9.56	0.995	10.13 3	1.04- 98.61	0.046
Propafenone	-0.041	-10.24-4.23	0.414	0.638	0.30- 1.37	0.247	1.713	0.90- 3.28	0.104
Flecainide	0.047	-4.61-12.87	0.353	1.394	0.64- 3.05	0.407	0.912	0.38- 2.18	0.835
Sotalol	0.043	-13.39- 34.26	0.390	0.993	0.10- 9.66	0.995	---	---	---

Amiodarone	0.053	-2.49-8.26	0.292	1.518	0.93- 2.49	0.097	0.815	0.48- 1.40	0.459
DHP Ca blocker	0.052	-2.42-7.86	0.299	1.006	0.62- 1.64	0.981	0.626	0.37- 1.07	0.086
ACEI/ARB	0.017	-4.18-5.93	0.734	0.951	0.59- 1.54	0.838	0.725 7	0.45- 1.18	0.196
Diuretic	-0.038	-6.57-2.94	0.454	0.863	0.55- 1.36	0.525	0.985	0.62- 1.57	0.950
Spironolactone	0.053	-2.92-9.63	0.294	1506	0.96- 2.65	0.156	0.894	0.48- 1.67	0.725
Statin	0.038	-3.14-7.02	0.453	1.315	0.82- 2.11	0.258	0.814	0.49- 1.35	0.427
Nitrates	-0.010	-17.65- 14.35	0.839	0.366	0.05- 2.96	0.346	0.404	0.05- 3.27	0.395
Trimetazidine	-0.002	-9.64-9.28	0.970	1.277	0.54- 3.01	0.577	1.417	0.60- 3.35	0.428
Sedative	0.057	-3.00-11.21	0.257	1.022	0.52- 2.01	0.949	0.889	0.44- 1.81	0.745
PPI	0.116	1.04-12.62	0.021	1.681	0.995- 2.84	0.052	0.595	0.32- 1.12	0.105
Thyroid hormone	0.019	-6.33-9.32	0.707	1.265	0.62- 2.58	0.519	0.914	0.42- 1.99	0.821

Thyroid suppression therapy	0.100	0.19-26.82	0.047	1.908	0.61-5.97	0.267	0.587	0.13-2.70	0.494
Insulin	0.058	-4.12-15.83	0.250	1.866	0.79-4.41	0.155	1.379	0.55-3.43	0.490
Oral antidiabetic drug	0.043	-3.55-9.07	0.391	1.192	0.66-2.14	0.557	0.824	0.43-1.56	0.553
Other medications	0.081	-0.89-8.91	0.108	1.526	0.96-2.42	0.072	0.744	0.46-1.22	0.239
<i>Non-pharmacological treatment</i>									
Ablation/ECV	-0.077	-8.97-1.12	0.127	0.690	0.42-1.14	0.147	0.845	0.51-1.40	0.511
ECV AF	-0.116	-12.34-(-1.05)	0.020	0.577	0.32-1.05	0.070	0.998	0.57-1.74	0.993
ECV AFL	-0.016	-24.76-17.94	0.754	---	---	---	---	---	---
Ablation AF	-0.003	-7.30-6.82	0.947	0.992	0.51-1.95	0.982	1.108	0.56-2.18	0.765
Ablation AFL	-0.112	-34.03-(-2.24)	0.025	---	---	---	4.276	1.12-16.26	0.033
Ablation other arrhythmias	-0.008	-25.78-21.91	0.873	0.993	0.10-9.66	0.995	---	---	---
<i>Multimorbidity and polypharmacy</i>									

Polypharmacy	0.080	-0.90-8.80	0.110	1.287	0.80- 2.06	0.294	0.694	0.43- 1.11	0.127
N of drugs	0.135	0.37-2.33	0.007	1.107	1.01- 1.22	0.032	0.912	0.83- 1.01	0.076
N of pills	0.111	0.11-1.74	0.027	1.071	0.99- 1.16	0.078	0.922	0.85- 1.00	0.058
N of drugs without OAC	0.119	0.21-2.24	0.018	1.094	0.99- 1.20	0.065	0.922	0.83- 1.02	0.128
N of pills without OAC	0.097	-0.01-1.67	0.052	1.062	0.98- 1.15	0.131	0.928	0.85- 1.01	0.090
Parenteral drugs use	0.041	-5.54-13.36	0.416	1.837	0.81- 4.16	0.144	1.417	0.60- 3.35	0.428
N of parenteral applications daily	0.087	-0.37-5.86	0.084	1.326	1.02- 1.73	0.036	0.933	0.73- 1.35	0.964
N of comorbidities	0.018	-1.27-1.82	0.725	1.026	0.89- 1.19	0.727	0.977	0.84- 1.14	0.762
Multimorbidity (without SA/VA)	0.064	-2.47-11.62	0.202	1.291	0.64- 2.62	0.480	0.803	0.41- 1.56	0.516
QoL EQ-5D questionnaire									
Q 1 –Mobility	0.166	1.58-6.07	0.001	1.283	1.04- 1.58	0.018	0.845	0.67- 1.07	0.163
Q 2 -Self-care	0.114	0.68-8.88	0.022	1.389	0.98- 1.97	0.066	0.757	0.46- 1.24	0.268

Q 3 -Usual activities	0.112	0.37-5.63	0.026	1.276	1.01- 1.61	0.039	0.783	0.58- 1.07	0.119
Q 4 -Pain/Discomfort	0.194	2.47-7.40	<0.00 1	1.400	1.12- 1.76	0.004	0.731	0.55- 0.96	0.026
Q 5 - Anxiety/Depression	0.320	5.15-9.41	<0.00 1	1.639	1.33- 2.02	<0.00 1	0.663	0.51- 0.85	0.001
QoL EQ-5D total score	0.277	1.40-2.87	<0.00 1	1.156	1.08- 1.24	<0.00 1	0.876	0.80- 0.96	0.004
Overall self-rated health status today (Range: 0-100)	-0.187	-0.34-(- 0.11)	<0.00 1	0.980	0.67- 0.99	0.001	1.012	1.00- 102	0.059

AF: Atrial fibrillation; LVEF: Left ventricular ejection fraction; ACS: Acute coronary syndrome; MI: Myocardial infarction; CAD: Coronary artery disease; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; AFL: Atrial flutter; CIED: Cardiac implantable electronic devices; ICD: Implantable cardioverter defibrillator; CRT: Cardiac resynchronisation therapy; TIA: Transient ischemic attack, COPD: Chronic obstructive pulmonary disease; OAC: Oral anticoagulant therapy; VKA: Vitamin K antagonist; NOAC: Non-vitamin K antagonist oral anticoagulant; ASA: Acetylsalicylic acid; DHP: Dihydropyridine; ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor inhibitor; PPI: Proton pump inhibitor; ECV: electrical cardioversion; SA: Supraventricular arrhythmias; VA: Ventricular arrhythmias; N: number.

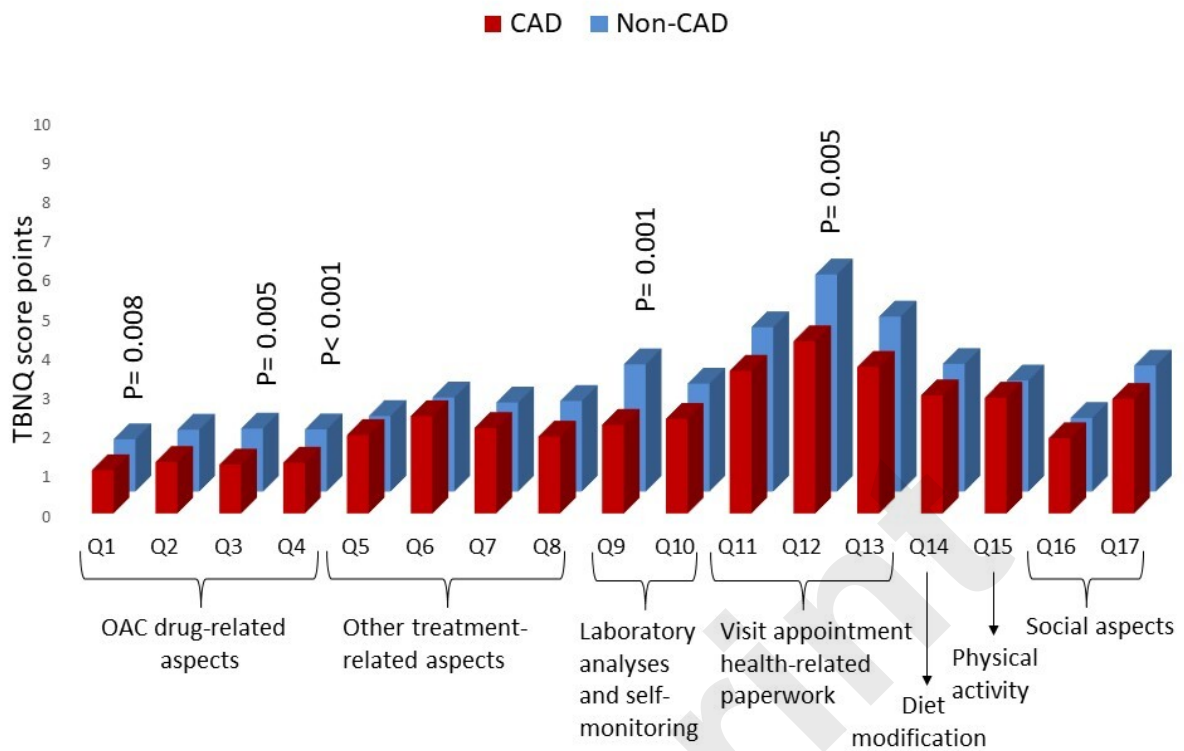
Table S5. Multivariable linear and logistic regression analyses of treatment burden in patients without coronary artery disease.

Multivariable Linear Regression analysis			
Variable	Beta	95% CI	P value
Q 5 -Anxiety/Depression	0.264	3.95-8.11	<0.001
VKA therapy	0.136	1.71-11.69	0.009
Age	-0.215	-0.64-(-0.25)	<0.001
Female sex	0.146	2.52-11.63	0.002
Number of drugs	0.107	0.13-2.01	0.026
Atrial fibrillation	0.126	0.86-12.25	0.024
Multivariable Logistic Regression analysis of the highest TBNQ score quartile (≥59)			
Variable	OR	95% CI	P value
Age ≤47 years	4.232	1.91-9.36	<0.001
Female sex	2.601	1.53-4.41	<0.001
Atrial fibrillation	2.171	1.10-4.29	0.026
CHA ₂ DS ₂ -VASc score ≥2 male, ≥3 female	0.427	0.24-0.78	0.005
VKA therapy	1.899	1.07-3.38	0.029
Number of drugs	1.168	1.04-1.30	0.007
Q 5 -Anxiety/Depression	1.513	1.20-1.90	<0.001
Multivariable Logistic Regression analysis of the lowest TBNQ score quartile (≤26)			
Variable	OR	95% CI	P value
Q 5 -Anxiety/Depression	0.695	0.50-0.97	0.033

Permanent atrial fibrillation	0.345	0.15-0.79	0.011
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VKA, Vitamin K Antagonist; Q, Question; TBNQ, Treatment Burden Questionnaire.

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CAD, Coronary artery disease; OAC, Oral anticoagulants; Q, Question; TBNQ, Treatment burden questionnaire.