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Atrial fibrillation prevalence and its management in aging, transfusion-dependent patients with thalassemia: the FATHAL study

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Key Points

- AF prevalence in β-TDT is 11.9%, reaching 31% in those aged 66 years.
- Cerebrovascular ischemic event prevalence is 7.9%, with 88% splenectomized, and one-third of the events occurring on anticoagulant therapy.

Atrial fibrillation (AF) represents an emerging challenge in thalassemia due to the increasing life expectancy. However, data are limited, and management relies on guidelines for the general population. We conducted a multicenter retrospective study to assess the prevalence of AF in transfusion-dependent beta-thalassemia (β-TDT). Nine centers, observing 1389 patients, participated in the study; 188 patients with a history of AF were included, 61% were male, and 73% splenectomized. The mean age at the first AF episode was 40 years. The prevalence of AF was 11.9%, reaching 31% in individuals aged >66 years. Among the known risk factors, the most common were diabetes, heart failure, and smoking. Regarding disease-specific factors, a history of cardiac iron overload was present in almost half of the patients before AF and in one-third at the time of the first event. Most patients exhibited left atrial dilatation, which can result from anemia. Transcatheter ablation was performed in 26.6% without any complications, and 74.4% reported improvement in symptoms, the primary aim of the procedure. The stroke prevalence was 5.5%, rising to 7.9% when including transient ischemic attacks, with 88% of patients being splenectomized. The CHA_2DS_2-VASc score was low in more than half of the patients, and 9 events occurred during anticoagulant therapy. This study is, to our knowledge, the first to evaluate AF prevalence in β-TDT, which is higher than in the general population. The CHA_2DS_2-VASc score has some limitations, and specific guidelines are necessary to provide optimal care for these patients.

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Data generated and analyzed during the current study are available from the corresponding author, Irene Motta (irene.motta@unimi.it), on reasonable request.

The full-text version of this article contains a data supplement.

Introduction

Beta-thalassemia is an autosomal recessive disorder characterized by a quantitative defect in the synthesis of β-globin chains that leads to an abnormal α-to-β-chain ratio, aggregation, and precipitation of excess α-chains, and subsequent ineffective erythropoiesis and hemolysis.[1] Patients are currently classified according to transfusion requirements in transfusion-dependent thalassemia (TDT) or non-TDT (NTDT).[2] Conventional therapy for patients with TDT involves treating chronic anemia with blood transfusions and, more recently, erythropoiesis-modulating agents,[3] as well as managing disease-related and treatment-induced complications, primarily iron overload (IO).[4,5] Despite significant improvement in the clinical management and survival,[6] cardiovascular disease remains the primary cause of mortality and one of the major causes of morbidity in TDT.[6,7] However, the main cardiac manifestations in TDT are shifting from heart failure to arrhythmias, particularly atrial fibrillation (AF).[8-10]

AF is an abnormal heart rhythm characterized by different impulses firing rapidly at once, resulting in a chaotic atrial rhythm. In the general population, AF is one of the most common conditions among the older adults, and its prevalence increases with age, reaching 10% in individuals aged >80 years.[11,12] AF prevalence in TDT is uncertain, ranging from 2% to 33% across evaluated populations.[9,13-16] Notably, most studies are in young cohorts with a mean age that does not reflect the increasing survival of patients with β-TDT. Indeed, in clinical practice, AF represents a constantly emerging issue, likely due to the longer survival of patients with β-TDT.[17] Regarding current AF management in TDT, it does not differ from that of the general population due to the lack of trials.[8,17] Nevertheless, special considerations apply to patients with TDT, including the increased risk of stroke,[18,19] especially in those who underwent splenectomy.[18-21]

In this retrospective, multicenter, national study from Italy, we aimed to assess AF prevalence in the adult β-TDT population, the characteristics and management of patients with AF, and to identify peculiar aspects to establish disease-specific recommendations.

Materials and methods

Study design and population

This is an observational, nonpharmacological, multicenter retrospective study in patients with β-TDT and AF/atrial flutter (AFL). Adults with TDT and AF/AFL followed at the coordinating or participating centers of the Società Italiana Talassemie e Emoglobinopatie network from 1 January 2003 to 31 December 2023 were enrolled in the study. The list of participating centers is available in the supplemental Materials (supplemental Table 1). "AF" in the text refers to both AF and atrial flutter unless otherwise specified. Clinical definitions outlining the criteria for TDT and NTDT, as well as for the diagnosis of AF[22,23] and cardiac IO,[15,24-27] are included in the supplemental Materials.

Data collection

Demographic, clinical, laboratory, and imaging parameters, AF characteristics, and management strategies were retrospectively collected using a dedicated electronic case report form, in accordance with national legislation, through REDCap (Research Electronic Data Capture).

Objective of the study

Clinical management indications for AF in TDT are the same as those in the general population, due to the lack of trials in TDT.[8,17] The primary objective of this project is to determine AF prevalence in patients with β-TDT in Italy. Secondary objectives include evaluating AF management and cerebrovascular events.

Statistical analysis

For descriptive analysis, quantitative variables are reported as the mean and standard deviation or the median and interquartile range (IQR; 25th-75th percentile), and categorical variables are expressed as absolute and relative frequencies. Data are reported as fractions and percentages of available data, which vary across variables. The overall point prevalence was calculated on 31 December 2023, as the ratio of alive patients with β-TDT with AF to the total number of alive patients with β-TDT at the participant centers at the data cutoff. The prevalence for age and sex subgroups was calculated in the same way. Comparison of the patient's characteristics at the first AF episode, according to the initial diagnosis of β-thalassemia (major vs intermedia), was analyzed using the χ^2 or Fisher exact test. Statistical analyses have been performed with the software R version 4.2.2 (R Core Team, 2022).

This study has been conducted according to Good Clinical Practice and the ethical principles originating in the Declaration of Helsinki, and in compliance with European clinical practice and all international guidelines and national regulations in Italy. The protocol has been approved by the ethics committee of the coordinating center Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (Milan) (ID 2878_SA_19.12.2023_P) and by the local ethics committees of the participating centers.

Results

Patients' characteristics

As of 31 December 2023, 9 Italian centers, which together managed a total of 1389 patients with β-TDT, participated in the study, all of which have dedicated cardiology services for thalassemia. A total of 188 patients were included, of whom 165 were alive at the time of data collection. Regarding the 23 patients who died during the study period, the average age at death was 47 years, and most of the patients died from heart-related causes (15/23; 65.2%) (supplemental Table 2).

Characteristics of patients are shown in Table 1. The mean age at the first AF episode was 40.3 years, with the most common comorbidities being hypothyroidism and diabetes mellitus. Additionally, 25% had a history of heart failure before their first AF episode of AF was reported in 1 of 4, and prior supraventricular arrhythmias. Almost all were White; most had β-thalassemia major, and 1 in 4 had thalassemia intermedia that became transfusion-dependent over time (Tables 1 and 3). More than two-thirds had undergone splenectomy. The mean age of surviving patients at the data cutoff was 51.9 years. At the data cutoff, ~12 years after the initial AF episode, we noted an increase in the burden of

Table 1. Patient characteristics and comorbidities at the first AF episode and in those alive at enrollment

	First AF episode	Alive at data cutoff
Male sex, n (%)	111/188 (59)	101/165 (61.2)
Age, mean ±SD, y	40.3 ± 11.5	51.9 ± 8.5
White, n (%)	184/188 (97.9)	162/165 (98.2)
Initial diagnosis of β-thalassemia, n (%)		
Major	144/188 (76.6)	125/165 (75.8)
Intermedia	44/188 (23.4)	40/165 (24.2)
Splenectomy, n (%)	119/179 (66.5)	121/165 (73.3)
Obesity, n (%)	6/182 (3.3)	6/159 (3.6)
Hypothyroidism, n (%)	44/171 (25.7)	64/164 (39.0)
Cancer, n (%)	8/185 (4.3)	12/163 (8.0)
Diabetes mellitus, n (%)	25/182 (13.7)	43/165 (26.1)
Kidney failure, n (%)	3/182 (1.6)	12/165 (7.3)
COPD, n (%)	1/83 (0.5)	5/164 (3.0)
Smoke, n (%)		
Active	24/140 (17.1)	27/146 (18.5)
Previous	18/140 (12.9)	26/146 (17.8)
Never	98/140 (70.0)	93/146 (64)
OSAS, n (%)	0/186 (0)	0/164 (0)
Cerebral ischemic event , n (%)	6/182 (3.3)	13/160 (8.1)
Venous thromboembolism, n (%)	10/180 (5.6)	14/162 (8.6)
Major bleeding, n (%)	1/185 (0.5)	2/162 (1.2)
Arterial hypertension, n (%)	5/174 (2.9)	27/165 (16.4)
Cardiovascular disease*, n (%)	0/181 (0)	3/161 (1.9)
Relevant valvular heart disease, n (%)	12/181 (6.6)	28/164 (17.1)
History of heart failure, n (%)	43/183 (23.5)	42/163 (25.8)
History of supraventricular arrhythmia, n (%)	28/179 (15.6)	34/162 (21.0)
History of ventricular arrhythmia, n (%)	14/181 (7.7)	18/163 (11.0)
Interatrial defect closure, n (%)	0/188 (0)	0/165 (0)
Patent foramen ovale closure, n (%)	0/184 (0)	0/165 (0)
CHA_2DS_2-VASc score†, n (%)		
Low risk	100/180 (55.6)	–
Intermediate risk	51/180 (28.3)	–
High risk	29/180 (16.1)	–

COPD, chronic obstructive pulmonary disease; OSAS, obstructive sleep apnea syndrome; SD, standard deviation.
*Includes coronary artery disease, previous myocardial infarction, peripheral arteriopathy, and aortic plaque.
†CHA_2DS_2-VASc score: low risk, 0 for males and 1 for females; intermediate risk, 1 for males and 2 for females; and high risk, ≥2 for males and ≥3 for females.

comorbidities, especially valvopathies (such as moderate or severe valve stenosis or insufficiency), whose prevalence tripled, and hypertension, which rose from 2.9% to 16.4% of patients, reflecting an aging population.

AF prevalence is higher in TDT than in the general population and increases with age

One thousand three hundred eighty-nine patients with β-TDT were regularly observed at the 9 participating centers at the time of data analysis; thus, the AF prevalence in this population is 11.9% (Table 2). When dividing the population by age groups, ~1 in 5 individuals over 50 years of age had at least 1 episode of AF in their lifetime, with a prevalence reaching 31% in those over 66. The overall prevalence was nearly twice as high in males compared to females (16.1% vs 8.4%), and this difference persisted when stratified by age groups (Table 2). Notably, the prevalence did not vary among the participating centers (supplemental Table 1).

AF diagnosis and management

Regarding the characteristics at diagnosis, most patients experienced their first arrhythmic episode as AF (161/184; 87.5%). In 12.5% (23/184), it was atrial flutter. The presentation was paroxysmal in 121 of 159 patients (76.1%). Most patients were symptomatic (129/172; 75.0%), mainly due to palpitations. Most patients had stage 3 on the European Heart Rhythm Association

Table 2. AF prevalence in the overall population, by sex and age groups

	All			Males			Females		
Age group, y	Cases (n)	Total (n)	Prevalence, % (95% CI)	Cases (n)	Total (n)	Prevalence, % (95% CI)	Cases (n)	Total (n)	Prevalence, % (95% CI)
18-35	5	226	2.2 (0.7-5.1)	5	123	4.1 (1.3-9.2)	0	103	0 (0-3.5)
36-50	63	735	8.6 (6.6-10.8)	44	337	13.1 (9.6-17.1)	19	398	4.8 (2.9-7.4)
51-65	88	399	22.1 (18.1-26.4)	48	159	30.2 (23.2-38.0)	40	240	16.7 (12.2-22)
≥66	9	29	31 (15.3-50.8)	4	9	44.4 (13.7-78.8)	5	20	25 (8.7-49.1)
Total	165	1389	11.9 (10.2-13.7)	101	628	16.1 (13.3-19.2)	64	761	8.4 (6.5-10.6)

symptom scale (46/12; 37.1%) (supplemental Figure 1), and ~15% (26/175) showed hemodynamic instability at diagnosis. Among those with 24-hour or 7-day continuous ECG monitoring or implantable devices, more than one-third (8/22; 36.4%) were asymptomatic.

Regarding AF management, in 16 of 185 patients (87.0%), at least 1 attempt of rhythm-control strategy (electrical or pharmacological cardioversion, chronic antiarrhythmic therapy, or transcatheter ablation) was performed during their lifetime (supplemental Table 3). The most widely used drug was amiodarone, but drugs

Table 3. Comparison of patient characteristics and comorbidities at the first AF episode according to initial diagnosis of β-thalassemia (major vs intermedia)

	Initial diagnosis of β-thalassemia intermedia n = 44	Initial diagnosis of β-thalassemia major n = 144	*P* value
Male sex, n (%)	25/44 (56.8%)	86/144 (59.7%)	.87
Age, mean ±SD, y	47.2 ± 13.8	38.2 ± 9.9	<.001
White, n (%)	41/44 (93%)	143/144 (99%)	.04
Splenectomy, n (%)	32/41 (78%)	87/138 (63%)	.11
Obesity, n (%)	1/43 (2.3%)	5/139 (3.6%)	1
Hypothyroidism, n (%)	1/40 (2.5%)	43/131 (32.8%)	<.001
Cancer, n (%)	3/43 (7%)	5/142 (3.5%)	.39
Diabetes mellitus, n (%)	3/42 (7.1%)	22/140 (15.7%)	.25
Kidney failure, n (%)	0/42 (0%)	3/140 (2.1%)	1
COPD, n (%)	0/42 (0%)	1/141 (0.7%)	1
Smoke, n (%)			
Active	2/36 (5.6%)	22/104 (21.2%)	
Previous	7/36 (19.4%)	11/104 (10.6%)	
Never	27/36 (75%)	71/104 (68.3%)	.04
OSAS, n (%)	0/44 (0%)	0/142 (0%)	-
Cerebral ischemic event, n (%)	0/42 (0%)	6/140 (4.3%)	.34
Venous thromboembolism, n (%)	6/41 (14.6%)	4/139 (2.9%)	.01
Major bleeding, n (%)	1/43 (2.3%)	0/142 (0%)	.23
Arterial hypertension, n (%)	3/41 (7.3%)	2/133 (1.5%)	.09
Cardiovascular disease, n (%)	0/41 (0%)	0/140 (0%)	-
Relevant valvular heart disease, n (%)	5/42 (11.9%)	7/139 (5.0%)	.15
History of heart failure, n (%)	5/43 (11.6%)	38/140 (27.1%)	.06
History of supraventricular arrhythmia, n (%)	6/39 (15.4%)	22/140 (15.7%)	1
History of ventricular arrhythmia, n (%)	1/42 (2.4%)	13/139 (9.4%)	.19
Interatrial defect closure, n (%)	0/44 (0%)	0/144 (0%)	-
Patent foramen ovale closure, n (%)	0/43 (0%)	0/141 (0%)	-
Atrial dilatation prior to AF, n (%)	18/23 (78.3%)	55/89 (61.8%)	.22
Cardiac IO before AF, n (%)*	2/21 (9.5%)	49/94 (52.1%)	<.001
Cardiac IO at first AF episode, n (%)*	2/26 (7.7%)	42/106 (39.6%)	.004
Cardiac IO at first ablation, n (%)*	0/5 (0%)	9/38 (23.7%)	.57

COPD, chronic obstructive pulmonary disease; OSAS, obstructive sleep apnea syndrome; SD, standard deviation.
Evaluated using T2 MRI.

Table 4. Prevalence of cardiac IO

Cardiac iron overload	History before AF	At the first AF episode	At the first ablation
T2* MRI only, n (%)	51/115 (44.3%)[a]	44/132 (33.3%)[a]	9/43 (20.9%)[a]
T2* MRI and SF, n (%)	60/140 (42.9%)[b]	48/157 (30.6%)[c]	9/46 (19.6%)[c]

IO was defined (a) considering T2* MRI <20 ms only; (b) considering T2* MRI <20 ms, irrespective of any provided ferritin levels, or ferritin >2500 μg/L when T2* MRI is not provided or when the elevated ferritin level provided refers to the period before the availability of T2* MRI (the year 2005 was considered the cutoff); and (c) considering T2* MRI <20 ms, irrespective of any provided ferritin levels, or ferritin >2500 μg/L when T2* MRI is not provided.

SF, serum ferritin.

considered proarrhythmic in patients with underlying cardiomyopathy were also used (eg, flecainide) (supplemental Table 4). In 35 patients, the rhythm-control strategy was discontinued in favor of rate control alone. At the last clinical evaluation available, which occurred a median of 9 years after the first AF episode, 146 of 184 (79.3%) were in sinus rhythm, irrespective of the chosen management.

Cardiac IO

Among the available data, a history of cardiac IO was observed in nearly half of the patients at some point before AF (Table 4). The proportion of patients with IO decreased over time. At the first occurrence of AF, only 1 of 3 patients had cardiac IO (Table 4), with 88 of 132 patients showing a normal cardiac T2* magnetic resonance imaging (MRI). The percentage of patients with cardiac IO among those who underwent transcatheter ablation was ~20%. Notably, a statistically significant difference was observed in the frequency of a history of cardiac IO between patients initially diagnosed with thalassemia major and those with thalassemia intermedia ($P < .001$) (Table 3). In the latter group, fewer than 10% had a documented history of cardiac IO. Consistently, IO-related complications (eg, hypothyroidism and heart failure) were less frequent in the originally thalassemia intermedia group. Cardiac IO was more prevalent in thalassemia major than in thalassemia intermedia, even during the first AF episode ($P = .004$) (Table 3). It is worth noting that all patients were transfusion-dependent at the time of data cutoff. Among patients with thalassemia intermedia, the first episode of AF occurred in 23 of 37 (62.2%) after starting a regular transfusion regimen, which began at a median age of 39.5 years (IQR, 22-51.5).

Atrial dilatation is present in two-thirds of the patients

Regarding echocardiographic parameters at the first AF episode, most patients had left atrial dilatation (73/112; 65.2%). Atrial dilatation, although not statistically significant, was more frequent in those initially diagnosed with thalassemia intermedia (Table 3). Only 12 of 181 (6.6%) had significant valvulopathy, mainly insufficiency, and no mechanical valves were reported at the time of the first AF event, suggesting that valvular AF does not account for a significant proportion of the arrhythmia in this population. Normal diastolic function was detected in most cases (69/99; 70%), and only 8 of 120 (6.7%) patients had an ejection fraction <40%. Considering those who were diagnosed through routine cardiac follow-up, namely those asymptomatic, >50% had left atrial dilatation.

Transcatheter ablation is safe and effective in improving symptoms in patients with β-TDT

Fifty of 188 (26.6%) patients underwent transcatheter ablation; their characteristics are presented in supplemental Table 5. Among them, 66% were male, and the mean age at the first procedure was 43.9 years. The indication was AF-related symptoms in 80% of cases (56/70 ablations). A total of 74 procedures were recorded in the study, with some patients undergoing multiple procedures (15 patients: 2 ablations; 3 patients: 3 ablations; and 1 patient: 4 ablations). Among centers with >10 AF cases (5 centers), the percentage of ablations is highly variable, ranging from 13.2% to 37.8% ($P = .04$). Interestingly, at the time of transcatheter ablation, the proportion of patients with IO was lower than at the first episode (Table 4), suggesting that intensive chelation therapy was used before the procedure. The outcomes of ablations were analyzed as the result of each procedure and as an improvement in arrhythmia-related symptoms after the last ablation. Regarding the outcome of each procedure, about one-third of ablations resulted in rhythm restoration without documented arrhythmia recurrence (Table 5). Most patients (32/43; 74%) reported improvement in symptoms after the last ablation, which had occurred with a median of 5.5 years before enrollment and 8.7 years after the first AF episode. In addition, the first ablation occurred at a median of 7.2 years from the first AF episode. No procedure-related complications were reported.

Prevalence and management of thromboembolic events

A survey revealed that 6 of 9 centers use the CHA_2DS_2-VASc score to assess stroke risk. CHA_2DS_2-VASc score at the first AF

Table 5. Outcome of the catheter ablation procedures (n = 74) in 50 patients

Procedure outcome	n = 74
a. Restoration of sinus rhythm without documented recurrence, n (%)	24 (32.4)
b. Absence of restoration of sinus rhythm, n (%)	2 (2.7)
c. Recurrence of arrhythmia within the first 3 months of ablation, n (%)	17 (23.0)
d. Recurrence of arrhythmia at least 3 months after ablation, n (%)	26 (35.1)
e. c and d, n (%)	1 (1.4)
f. NA, n (%)	4 (5.4)

NA, not available.

Table 6. Arterial thromboembolic events

Pt ID	Event	Type	Time from first AF episode (years)	Symptoms at the first AF episode	CHA_2DS_2-VASc score at the first AF episode (risk)	Ongoing anticoagulant (type)	Ongoing antiplatelet
1	1	Stroke	−25.5	N	Intermediate	N	N
2	2	TIA	−21.9	N	High	NA	NA
3*	3	Stroke	−13.6	Y	High	N	N
4*	4a	Stroke	−9.0	Y	High	N	N
	4b	Stroke	−4.0	Y		N	N
	4c	TIA	NA	Y		NA	NA
5*†	5a	TIA	−7.4	N	High	N	N
	5b	TIA	−3.9	N		N	Y
6*	6	Stroke	−0.45	NA	High	N	N
7	7	Stroke	2.0	NA	High	N	N
8†	8	TIA	4.1	Y	High	N	N
9	9	Stroke	6.5	Y	Low	N	N
10	10	Stroke	7.0	N	Intermediate	Warfarin	N
11	11a	Stroke	9.0	Y	Low	N	Y
	11b	Stroke	14.6	Y		Apixaban	N
12	12	Stroke	9.5	Y	High	N	N
13	13	TIA	9.8	Y	Low	N	N
14	14a	Stroke	13.1	Y	Intermediate	NA	NA
	14b	Stroke	16.4	Y		Apixaban	Y
15	15a	TIA	15	Y	Intermediate	N	Y
	15b	TIA	21	Y		Acenocoumarol	Y
	15c	TIA	22	Y		Acenocoumarol	Y
	15d	Stroke	23.0	Y		Acenocoumarol	Y
	15e	Stroke	24.6	Y		Acenocoumarol	Y
	15f	Stroke	25.1	Y		Acenocoumarol	Y
16	16	Stroke	21.7	Y	High	Rivaroxaban	N
17	17	TIA	NA	Y	High	N	N

CHA_2DS_2-VASc score at first AF episode: low risk = 0 for males and 1 for females; intermediate risk = 1 for males and 2 for females; high risk = ≥2 for males and ≥3 for females.
N, no; NA, not available; Pt, patient; TE, thromboembolism; TIA, transient ischemic attack; Y, yes.
*Dead.
†Not splenectomized.

episode resulted in a low risk of thromboembolism (0 for males, 1 for females) in more than half of the patients (100/180; 55.6%) and a high risk (≥2 for males; ≥3 for females[28]) in 29 of 180 (16.1%) patients (Table 1).

One hundred and forty-eight of 182 (81.3%) patients have been on anticoagulant therapy at any time in their lives, and in almost all of them (140/148; 95%), AF was the reason for the anticoagulation prescription. Among them, two-thirds (92/140; 66%) were naive to anticoagulant therapy at the time of the first AF episode and started anticoagulant therapy temporally close to the first AF episode. In these 92 patients, the CHA_2DS_2-VAS risk score at the first AF episode was high in 15, intermediate in 28, low in 48, and not available in 1 patient.

Seventeen of 188 (9.0%) patients, of whom 13 were alive at enrollment, experienced an arterial thromboembolic event (Table 6), with a prevalence of cerebral events of 7.9% (13/165; 95% confidence interval [CI], 4.4-13.4), and 5.5% (9/165; 95% CI, 2.7-10.4) when considering only stroke. The CHA_2DS_2-VASc score of these 17 patients was high in 10, intermediate in 4, and low in 3. The median age at the cerebral ischemic event was 37. None of the patients with thromboembolism had a mechanical mitral valve or moderate-to-severe mitral stenosis. Multiple events in a single patient were also reported (Table 6), with a total of 27 cerebral ischemic events reported in the study, of which 17 were strokes. Eight events occurred before the first episode of AF, 17 after, whereas the timing of 2 events is unknown. Notably, among the 17 events that occurred after the first documented episode of AF, only 4 of 10 patients (40%) had a high CHA_2DS_2-VASc. Even more interestingly, 9 events (in 5 patients) occurred during anticoagulant therapy, with only 1 having a high CHA_2DS_2-VASc score. Considering disease-specific prothrombotic risk factors, almost all the patients (15/17) underwent splenectomy before the occurrence of the thromboembolic event. Overall, the rate of cerebral ischemic events in the splenectomized population (15/131; 11.5%) was higher than in the nonsplenectomized

population (2/51; 3.9%), although this difference did not reach statistical significance. Regarding potential anticoagulation side effects, 3 major bleeds occurred (2%), 1 of which resulted in patient death.

Discussion

AF is an age-related condition and is becoming an emerging concern in patients with β-thalassemia, whose survival has significantly improved over recent decades due to optimized treatments. Besides age-related factors, disease-related factors may also increase the risk of AF in these individuals. However, due to limited evidence, there are no specific guidelines for AF management in TDT, and the current recommendation is to follow those established for the general population. Consequently, there is an urgent need to develop specific evidence-based recommendations. To our knowledge, this is the first study to evaluate AF prevalence and management in adult β-TDT. Our data show that AF management, especially regarding ablation and anticoagulation choices, varies significantly, even within specialized centers of the national health care system. The need for action is strongly supported by the high prevalence observed in our study. In fact, AF prevalence in Italian β-TDT is 11.9%, with ~1 in 5 individuals affected after the age of 50 years. According to a recent survey,[29] the number of living patients with TDT in Italy was 5205 in 2019, indicating that there are >500 individuals with TDT and AF in the country. These data align with a recent study on comorbidities in TDT in the United Kingdom by Jobanputra et al,[9] which reported a prevalence of 11.1% that increased after the age of 45 in a predominantly Asian population. In earlier studies conducted over a decade ago, prevalence ranged from 2.6% to 33.8% across different cohorts.[9,13-16] Notably, our study involves an older population, with enrolled participants being 20 years older on average, reflecting the aging thalassemia population. In a study published in 2024,[30] which partly overlaps with the population of this work, in a smaller and older sample, the prevalence was higher (29.3%). In comparing our cohort to the general population, we clearly observed a significantly higher prevalence than in age-matched groups. Indeed, in the general population, AF prevalence is ~2% to ~4%,[31] with a progressive increase with age,[11] reaching 5.9% in those aged >65 years.[32] For 2021, data from the Global Burden of Disease[33] estimate an AF prevalence in Italian adults of ~2.7% (95% CI, 2.0-3.4). This prevalence increases to 4.7% (95% CI, 3.6-6.0) when considering only patients aged ≥50 years, and reaches 14% (95% CI, 11-18) for those aged ≥85. Prevalence is expected to double in the next few decades, primarily due to the aging of the general population and new technologies for its detection.[22] Consistent with the general population, prevalence is higher in males,[11,34,35] although in our cohort, the difference between sexes is more pronounced.

Regarding recognized AF risk factors, the prevalence of diabetes mellitus is higher than in the general population (14.0% vs 5.6% according to the National Institute of Statistics,[36] 2021 report), likely due to iron-related damage. Our diabetes prevalence is also higher than in most previous studies of Italian patients with β-TDT (4.7%,[37] 8.6%,[38] 9.7%,[39] and 18%[40]), which could be attributed to the older cohort and to the fact that we enrolled participants who developed a potentially IO-related complication. The other most represented comorbidity is hypothyroidism (26%), which is more frequent in our cohort compared to other studies (19.8%[37] and 17.4%[38]). In addition to IO, this may also be related to the use of amiodarone, a drug commonly prescribed to these patients. A history of heart failure and supraventricular arrhythmias before the first episode of AF was reported in 23.5% and 15.6% of patients, respectively, suggesting the presence of prior heart disease in at least 1 of 5 patients.

Given the different prevalence and epidemiological features between TDT and the general population, some contributors to the pathophysiology of AF could be disease-related, namely IO and anemia, both of which lead to cardiac distress. IO is a known risk factor for arrhythmias.[10] A history of IO could have damaged the cardiac conduction system, leading to the development of AF. Our data show a decrease in the frequency of cardiac IO over time. This is likely related to the optimization of iron chelation therapy, the cornerstone of clinical management of TDT to prevent cardiac distress.[5] Some studies have shown that iron chelation is effective in reducing arrhythmic disorders,[41-44] but we demonstrate that arrhythmias can occur even in the absence of cardiac IO, as previously described.[45] These data highlight the importance of closely monitoring cardiac complications even when T2* MRI is normal. In this study, it is noteworthy that one-quarter of the patients had initially been diagnosed with β-thalassemia intermedia and that these patients are less prone to iron accumulation in the heart.[46] Nevertheless, the absence of myocardial IO at MRI does not imply the absence of atrial damage for several reasons: (1) T2* measured at the interventricular septum may not be an accurate indicator of iron at the atrial level, (2) atria myocardium is highly vulnerable to iron, (3) a prior IO could have damaged the atria, and (4) in the pre-MRI era it was more challenging to prove cardiac IO as the only parameter to suspect it was serum ferritin. However, aside from IO, atrial dilatation is another factor that predisposes patients to AF.[13,47] Atrial dilatation may be due to increased cardiac output resulting from anemia, and it may be involved in the genesis of the arrhythmia.[30] In our cohort, atrial dilatation was described in 65.2% of patients at the first AF episode, and it was more common in those initially diagnosed with thalassemia intermedia, although this difference was not statistically significant. Notably, according to the literature, the most common reason for starting a transfusion regimen in NTDT is low hemoglobin levels.[48] In line with this, recent studies underline the detrimental role of anemia.[49,50] Notably, the role of specific risk factors may vary depending on the initial thalassemia diagnosis (major vs intermedia). Thus, obtaining a comprehensive medical history, including a history of "phenoconversion,"[48] is essential for a personalized risk assessment and management strategy.

Regarding AF management, our data enlighten some pathophysiological aspects that represent a starting point for developing a disease-specific approach. The presence of symptoms is a crucial factor influencing treatment decisions (Figure 1). Although based on experience rather than evidence, it has been previously stated that patients with thalassemia are more symptomatic than those without thalassemia.[10,17] We herein show that 75% of patients were symptomatic at the first episode, a higher proportion than in the general population, where two-thirds report symptoms.[35,51] Notably, younger patients are more symptomatic, a factor that, combined with anemia, may contribute to this finding.[51] Consistent with the literature, the most prescribed antiarrhythmic drug was amiodarone.[10,17] However, a considerable proportion of patients

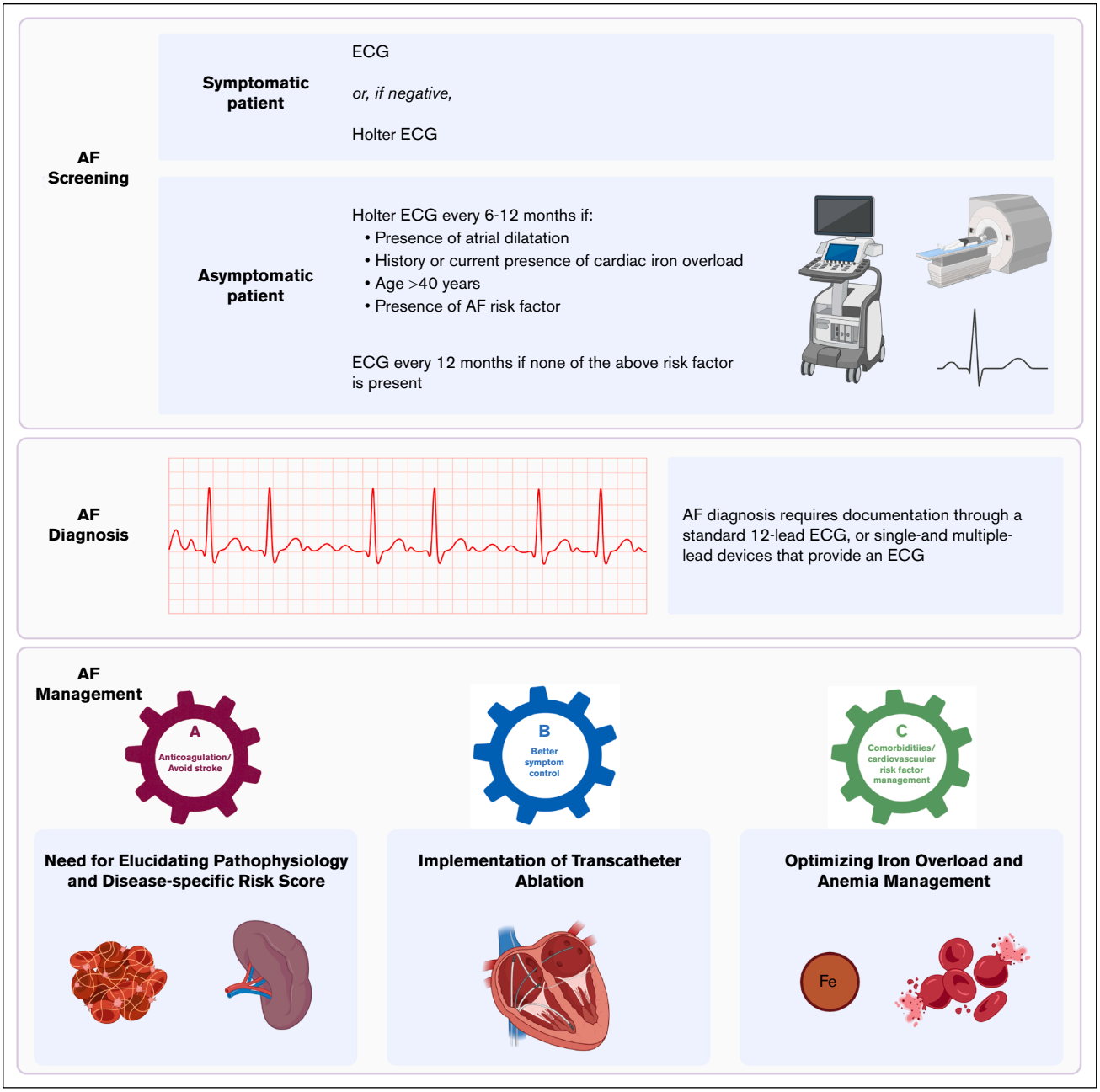

Figure 1. Screening, diagnosing, and managing AF in β-TDT. The AF screening approach depends on the presence or absence of symptoms: in patients with symptoms (eg, palpitations, fatigue, dyspnea, poor tolerance to effort, chest pain, syncope, dizziness, and sleep disorders), an ECG should be performed. If negative, a 24-hour or prolonged monitoring, including a 72-hour weekly Holter or loop recorder, is recommended. In asymptomatic patients, the approach depends on the presence or absence of at least 1 risk factor (ie, atrial dilatation, history, or current cardiac IO, or age >40 years). In those without any risk factor, an annual ECG is recommended. In those with at least 1 risk factor, Holter ECG every 6 to 12 months is advisable. AF diagnosis requires ECG documentation, which, in current practice, can include a standard 12-lead ECG or single- and multiple-lead devices that provide an ECG. AF management follows the approach of the European Society of Cardiology guidelines: A, avoid stroke/anticoagulation; B, better symptom control; C, comorbidities/cardiovascular risk factor management, taking into account pathophysiological peculiarities of the disease. ECG, electrocardiogram. Figure created with biorender.com Motta, I. (2025) https://BioRender.com/kale4w0.

have received other antiarrhythmic drugs, namely flecainide, propafenone, sotalol, and dronedarone, which require caution in the presence of underlying cardiac disease. Conversely, catheter ablation use, overall performed in more than 1 in 4 patients, was extremely heterogeneous despite the presence of highly symptomatic patients. Interestingly, ablation was safe and effective in improving symptoms. Despite the recommendation to perform catheter ablation as soon as possible, we observed a significant delay between the first AF episode and the procedure. This delay can result from several factors, including the fact that catheter

ablation is a relatively new procedure and the tendency to wait for cardiac IO to improve or resolve. It should be noted that, despite the delay, catheter ablation successfully improved symptoms.

In summary, according to recent AF European Society of Cardiology guidelines,[22] we recommend the following approach: a rhythm-control strategy is preferred for symptomatic patients to improve quality of life. We advise using ablation (Figure 1), which is safe and effective in ameliorating symptoms, and we recommend performing it in the absence of cardiac IO. Transcatheter ablation should be preferred whenever possible, also due to the complex polypharmacotherapy of these patients and the known side effects of antiarrhythmic drugs. Amiodarone is safe in the short term but can lead to multiple adverse effects if taken chronically, particularly hypothyroidism, whereas other antiarrhythmic drugs may have a proarrhythmic impact in patients with cardiac IO.[10,17]

It is known that in the general population AF increases by 5-fold the risk of stroke, the most alarming complication. Interestingly, the prevalence of stroke in our β-TDT cohort was more than 10-fold higher than the overall β-TDT population (5.5% vs 0.25%-0.46%[18-20]), although comparison should be cautious since the mean age in our study is higher than that of Taher and Karimi.[18,19] Consistent with previously published data,[18-20] we show that stroke was more frequent in those that underwent splenectomies, although not statistically significant, most likely due to the limited number of events. To assess stroke risk and evaluate the risk-benefit ratio of anticoagulant treatment in the general population with AF, the most commonly used score is the CHA_2DS_2-VASc.[28] Interestingly, although the centers reported using the CHA_2DS_2-VASc, our data suggest that in the real world, the decision to initiate anticoagulant treatment is not based on this score, as half (48/92) of those who started anticoagulant near the time of AF onset had a low risk. Additionally, it is noteworthy that half of the thromboembolic events occurred in individuals categorized as low to intermediate risk. Altogether, these data emphasized that the CHA_2DS_2-VASc score has limitations in these patients, given the significant role of age and its failure to account for potential disease-related risk factors, for example, splenectomy. However, the absence of a disease-specific score and the lack of evidence supporting a non–risk-free treatment (ie, anticoagulation), pose a challenge for clinicians. Even more interestingly, one-third of the patients experienced a thromboembolic event during anticoagulant therapy, raising further questions about the management of thromboembolic risk and its pathophysiology in this population.

Some limitations of our study should be acknowledged. First, it is a retrospective study; thus, we could not evaluate the outcomes of different treatments. Additionally, we lacked a control group, which limits our ability to identify potential risk factors. We also could not obtain hemoglobin levels due to the long observation period, and in the absence of T2* MRI, cardiac IO was assumed based on ferritin levels >2500 μg/L. A national, multicenter, prospective study has begun to confirm our findings and the proposed management strategy.

Conclusions

To our knowledge, this is the first study evaluating AF prevalence and management in β-TDT. AF is a significant complication in TDT, affecting 1 in 5 patients aged ≥50 years. IO and atrial dilation related to anemia are disease-specific factors that contribute to the arrhythmia pathophysiology. Transcatheter ablation was safe and effective in improving symptoms associated with AF. Moreover, we observed a high prevalence of thromboembolic events, with some occurring during anticoagulant therapy. Our findings highlight the need for a specific approach that accounts for the underlying pathophysiology of β-thalassemia.

Authorship

Contribution: V.D.S. and I.M. conceived and designed the study; V.D.S., V.O., F.L., A.B., M.C., A.R.D., S.C., F.F., I.F., F.M., A.P., P.R., and M.S. collected the data; V.D.S., B.G., M.R.M., R.O., M.B., and I.M. analyzed the data; V.D.S. and I.M. wrote the manuscript; and all authors revised the manuscript.

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