

Coagulation and Thrombotic Risk in Thalassaemia Intermedia

Ali T. Taher, MD, FRCP
Associate Chair, Research
Department of Internal Medicine
American University of Beirut Medical Center
Consultant Hematologist, Chronic Care Center
Beirut - Lebanon

Clinical classification of β -thalassemia

<ul style="list-style-type: none">• Homozygous disorder• Significant imbalance of α / β globin chains• Severe anemia presenting early in life• Requires lifelong RBC transfusions & chelation• If untreated, leads to death usually in first decade	β-thalassemia major
<ul style="list-style-type: none">• Various genetic interactions• Globin chain production moderately impaired• Mild-moderate anemia, diagnosed usually in late childhood, alleviated by splenectomy• Blood transfusions and chelation not necessary	β-thalassemia intermedia
<ul style="list-style-type: none">• Heterozygous condition• Asymptomatic, mild anemia• Requires genetic counseling	β-thalassemia minor



β -Thalassemia intermedia

- “Highly diverse” group of β -thalassemia syndromes where red blood cells are sufficiently short-lived to cause anemia, without patients necessarily requiring regular blood transfusions
- The severity of the clinical phenotypes varies between those of β -thalassemia minor (TI) and β -thalassemia major (TM)
- TI arises from defective gene(s) leading to partial suppression of β -globin protein production

Mild

Severe



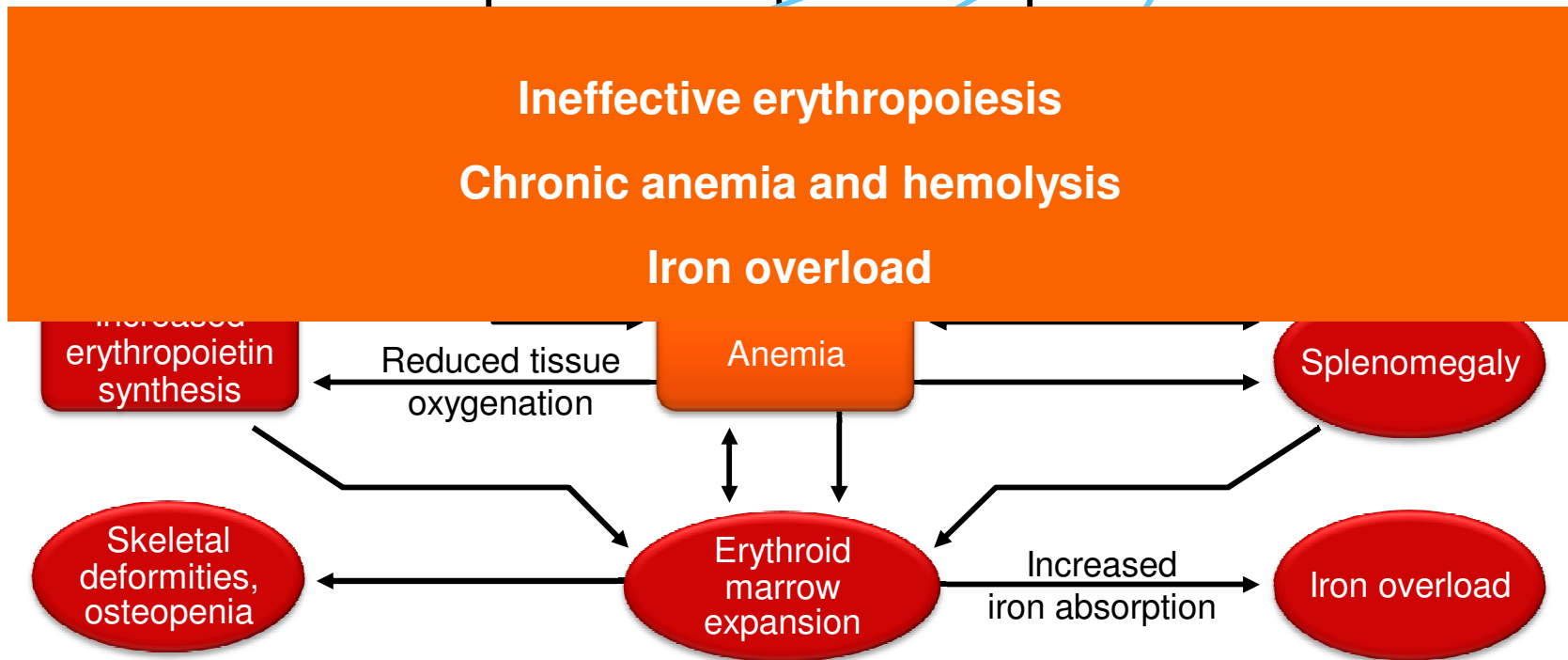
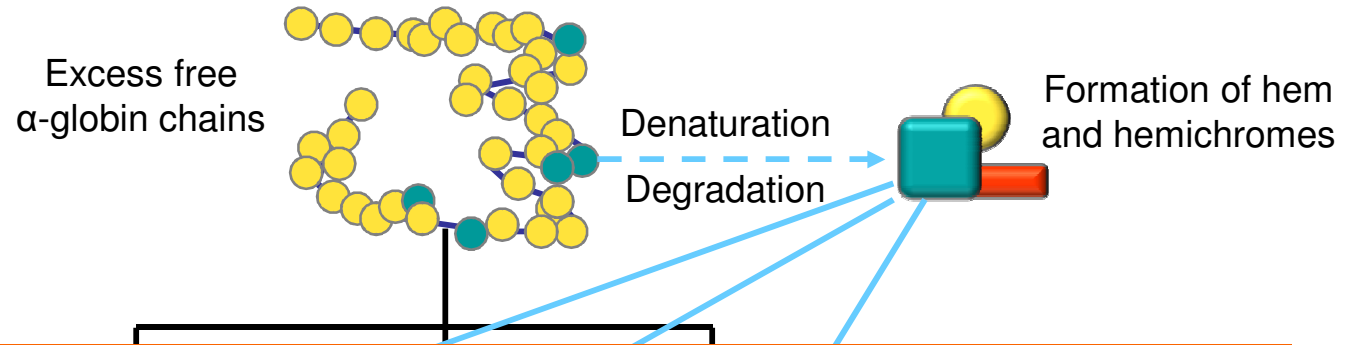
Completely asymptomatic
until adult life

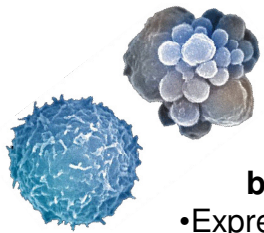
Presentation at age 2–6 years
Retarded growth and development

Determinants of disease severity

- Molecular factors
 - inheritance of a mild or silent β -chain mutation
 - presence of a polymorphism for the enzyme Xmn-1 in the $G\gamma$ -promoter region, associated with increased HbF
 - co-inheritance of α -thalassemia
 - increased production of α -globin chains by triplicated or quaduplicated α -genotype associated to β -heterozygosity; also from interaction of β - and $\delta\beta$ -thalassemia
- Environmental factors may influence severity of symptoms, e.g.
 - social conditions
 - nutrition
 - availability of medical care

Pathophysiology summarized





Peripheral blood elements

- Expression of endothelial adhesion molecules and tissue factor on endothelial cells
- Formation of microparticles



- Hallmark of hemolysis
- ↓ Levels leading to vasoconstriction



RBCs

- Formation of reactive oxygen species
- Expression of negatively charged phospholipids
- Enhanced cohesiveness and aggregability



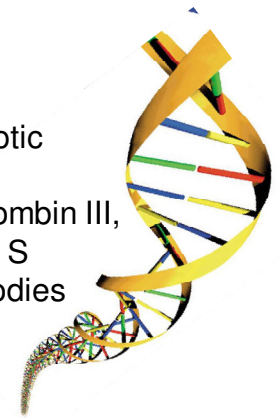
Platelets

- Increased platelet aggregation
- Increased expression of activation markers
- Presence of platelet morphologic abnormalities

Hypercoagulability

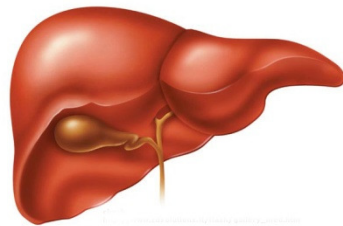
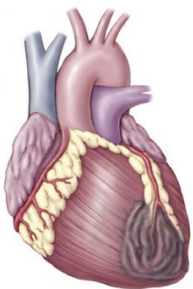
Thrombophilia

- No role for prothrombotic mutations
- Decreased levels of antithrombin III, protein C, and protein S
- Anti-phospholipid antibodies



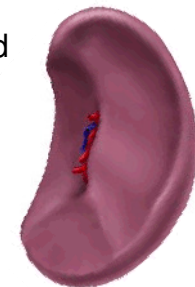
Other factors

- Cardiac dysfunction
- Hepatic dysfunction
- Endocrine dysfunction

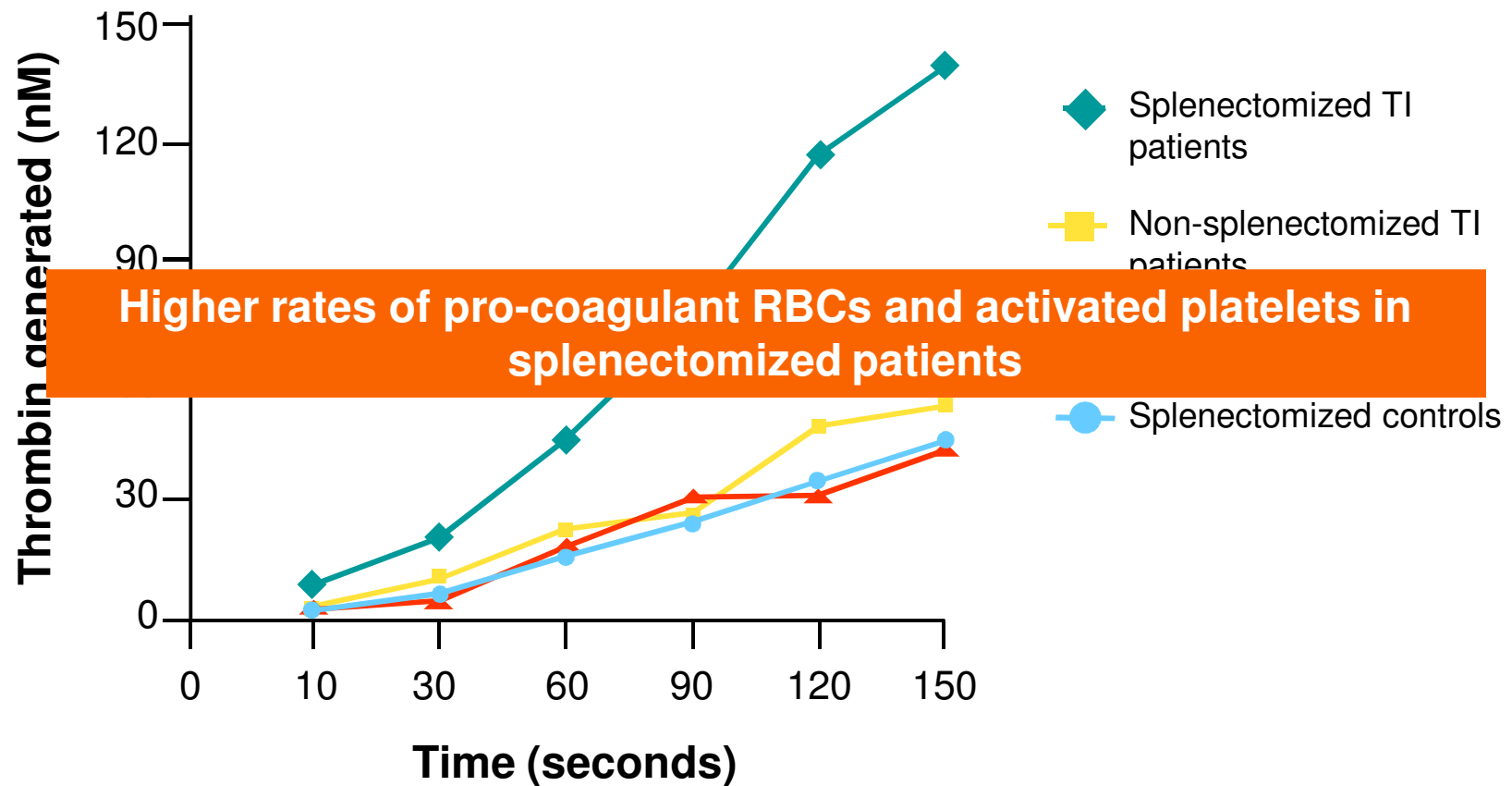


Splenectomy

- High platelet counts and hyperactivity
- High levels of negatively charged RBCs



Splenectomy associated with increased risk of hypercoagulability



Representative examples of time course of thrombin generation in the presence of erythroid thalassemic cells as a source of phospholipids

Thalassemia Intermedia

Excess free α -globin chains (due to decrease synthesis of β -globin)

Induce oxidative damage to both integral and cytoskeletal proteins of RBCs (indices of membrane damage: band 3, hemichromes, C3, are increased)

Damaged RBC membrane leads to alteration of the phospholipid "Flip-Flop" mechanism \Rightarrow exposure of negatively charged procoagulant phosphatidylserine

Adherence of RBCs of thalassemia intermedia to endothelin cells is increased

Thrombin generation

Thrombus formation

Fibrin/Platelets

Phosphatidylserine on damaged or senescent RBC leads to:

-recognition by phagocytes

removal from circulation

- apoptosis

Splenectomy favors persistence of these RBCs in the circulation

First attempt at understanding complications in TI vs TM

Complication (% of patients affected)	TI		TM	
	Lebanon (n = 37)	Italy (n = 63)	Lebanon (n = 40)	Italy (n = 60)
Splenectomy	90	67	95	83
Cholecystectomy	85	68	15	7
Gallstones	55	63	10	23
Extramedullary hemopoiesis	20	24	0	0
Leg ulcers	20	33	0	0
Thrombotic events	28	22	0	0
Cardiopathy*	3	5	10	25
Pulmonary hypertension†	50	17	10	11
Abnormal liver enzymes	20	22	55	68
HCV infection	7	33	7	98
Hypogonadism	5	3	80	93
Diabetes mellitus	3	2	12.5	10
Hypothyroidism	3	2	15	11

*Fractional shortening < 35%. †Defined as pulmonary artery systolic pressure > 30 mmHg; a well-enveloped tricuspid regurgitant jet velocity could be detected in only 20 patients, so frequency was assessed in these patients only.



Clinical Experience

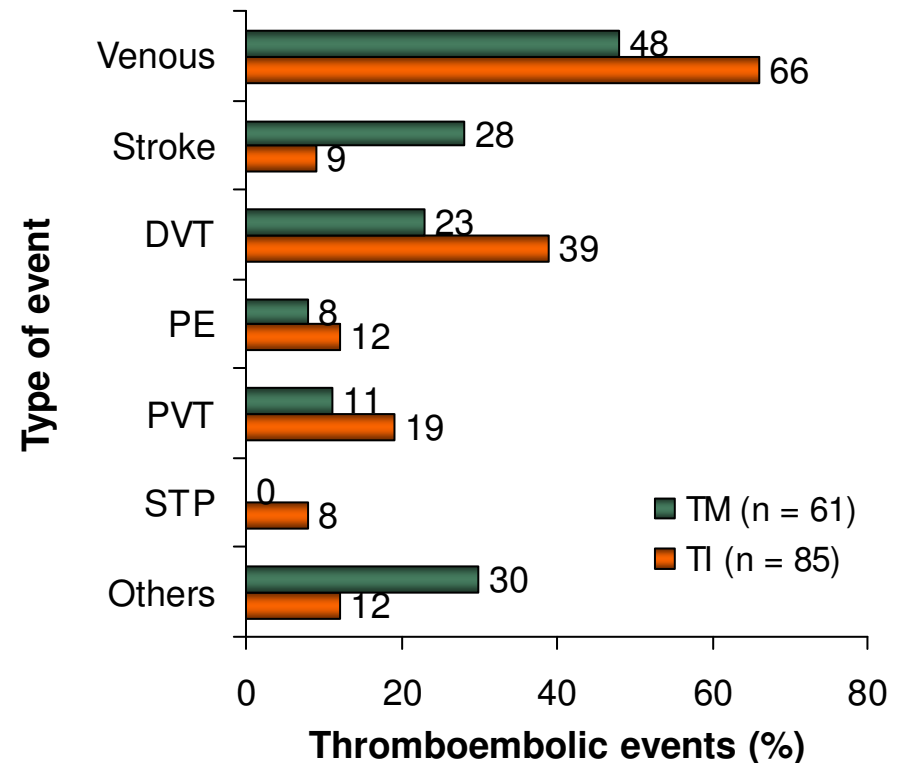
Epidemiology

Reference	TI n (%)	TM n (%)	Type of thrombosis			
			VT	PE	AT	Stroke
Zurlo et al, 1989	-	4/159 (2.5%)			N/A	
Michaeli et al, 1992	-	4/100 (4)	*	*	*	*
Aessopos J et al, 1997	3/5 (60)	3/5 (60)				*
Moratelli et al, 1998	12/74 (16.2)	14/421 (3.3)			N/A	
Borgna Pignatti et al, 1998	5/52 (9.6)	27/683 (4.0)	*	*	*	*
Cappellini et al, 2000	24/83 (29)	-	*	*	*	
Borgna Pignatti et al, 2004	-	8/720 (1.1)			N/A	

TI = thalassemia intermedia, TM = thalassemia major, VT = venous thrombosis, PE = pulmonary embolism, AT = arterial thrombosis, N/A = not available.

Thromboembolic events in a large cohort of TI patients

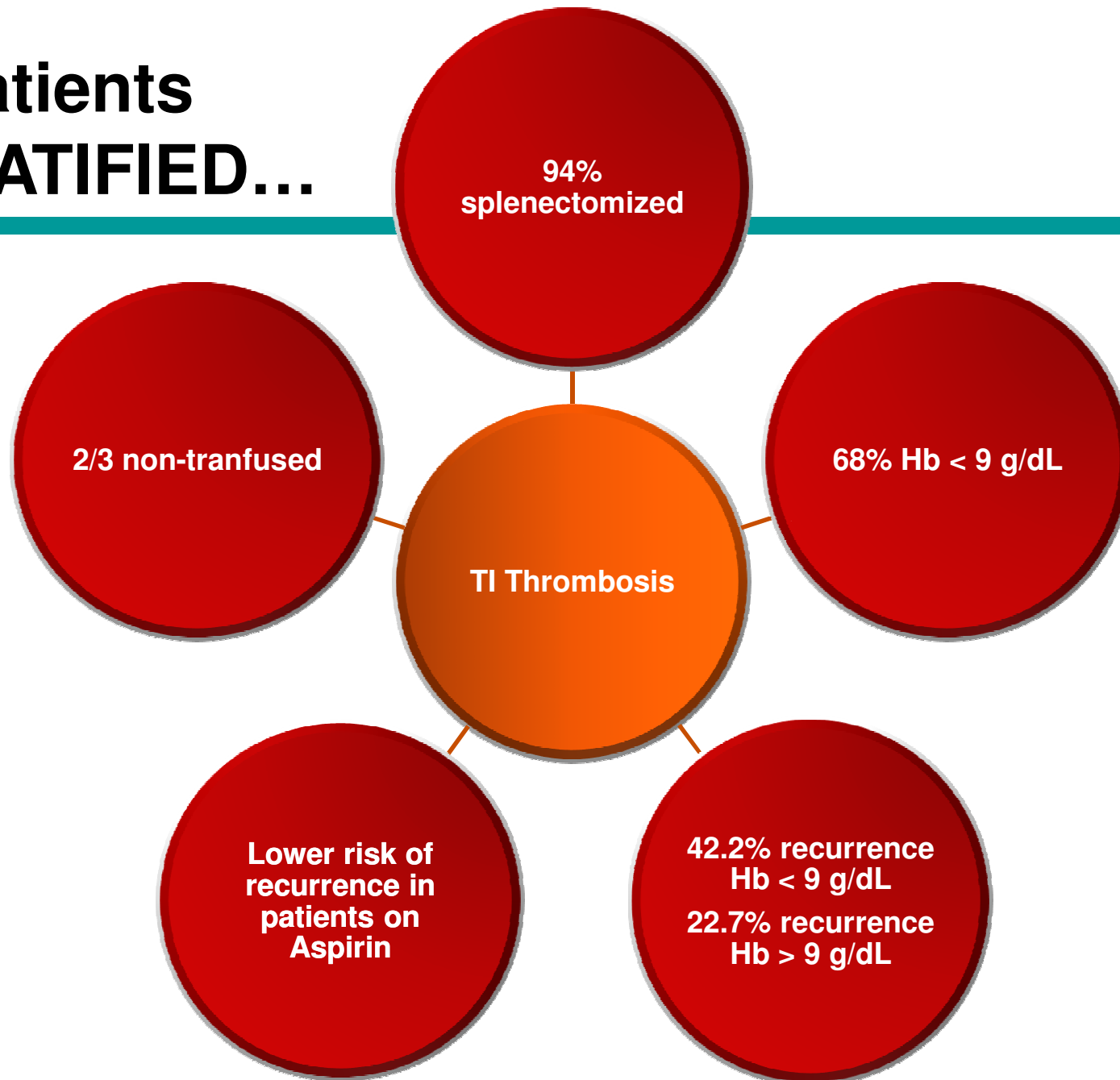
- Patients (N = 8,860)
 - 6,670 with TM
 - 2,190 with TI
- 146 (1.65%) thrombotic events
 - 61 (0.9%) with TM
 - 85 (3.9%) with TI
- Risk factors for developing thrombosis in TI were
 - age (> 20 years)
 - previous thromboembolic event
 - family history
 - splenectomy



DVT = deep vein thrombosis;

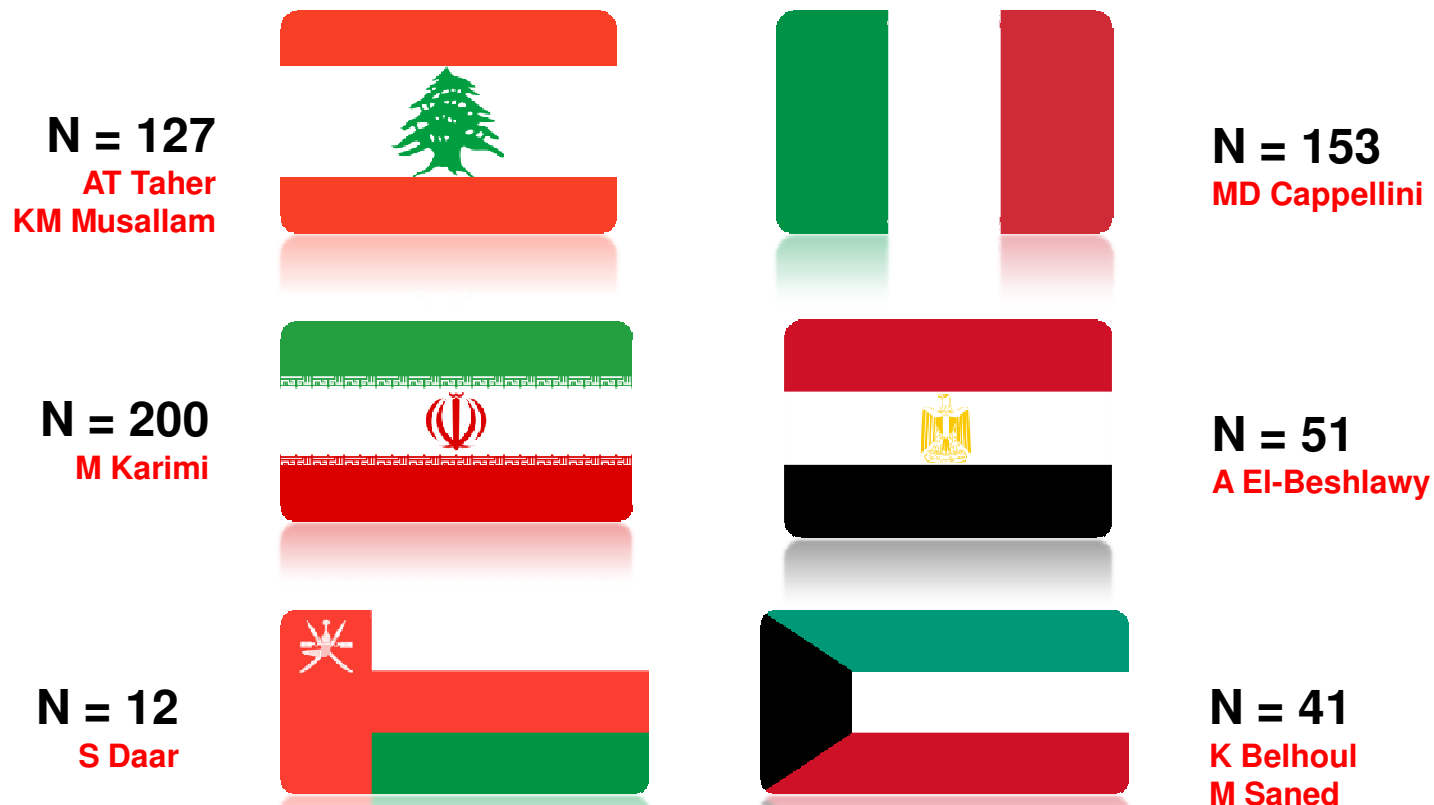
PVT = portal vein thrombosis; STP = superficial thrombophlebitis.

TI patients STRATIFIED...



Overview on Practices in Thalassemia Intermedia Management Aiming for Lowering Complication-rates Across a Region of Endemicity: the OPTIMAL CARE study

- Retrospective review of 584 TI patients from 6 comprehensive care centres in the Middle East and Italy



Taher AT, Musallam KM, Karimi M, et al. Blood. 2010;115:1886-92.

The OPTIMAL CARE study: overall study population

Parameter	Frequency n (%)
Age (years)	
< 18	172 (29.5)
18–35	288 (49.3)
> 35	124 (21.2)
Male:female	291 (49.8) : 293 (50.2)
Splenectomized	325 (55.7)
Serum ferritin (µg/L)	
< 1,000	376 (64.4)
1,000–2,500	179 (30.6)
> 2,500	29 (5)
Complications	
Osteoporosis	134 (22.9)
EMH	124 (21.2)
Hypogonadism	101 (17.3)
Cholelithiasis	100 (17.1)
Thrombosis	82 (14)
Pulmonary hypertension	64 (11)
Abnormal liver function	57 (9.8)
Leg ulcers	46 (7.9)
Hypothyroidism	33 (5.7)
Heart failure	25 (4.3)
Diabetes mellitus	10 (1.7)

Treatment	Frequency n (%)
Hydroxyurea	202 (34.6)
Transfusion	
Never	139 (23.8)
Occasional	143 (24.5)
Regular	302 (51.7)
Iron chelation	
None	248 (42.5)
Deferoxamine	300 (51.4)
Deferiprone	12 (2.1)
Deferiprone + deferoxamine	3 (0.5)
Deferasirox	21 (3.6)

EMH = extramedullary hematopoiesis.

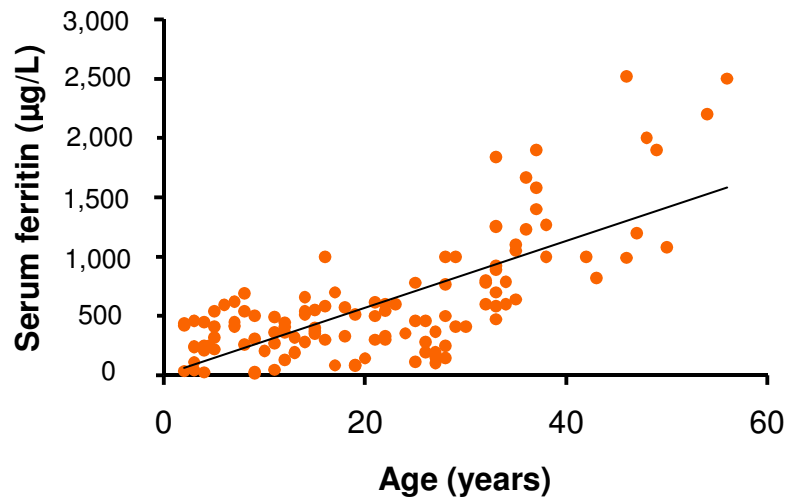
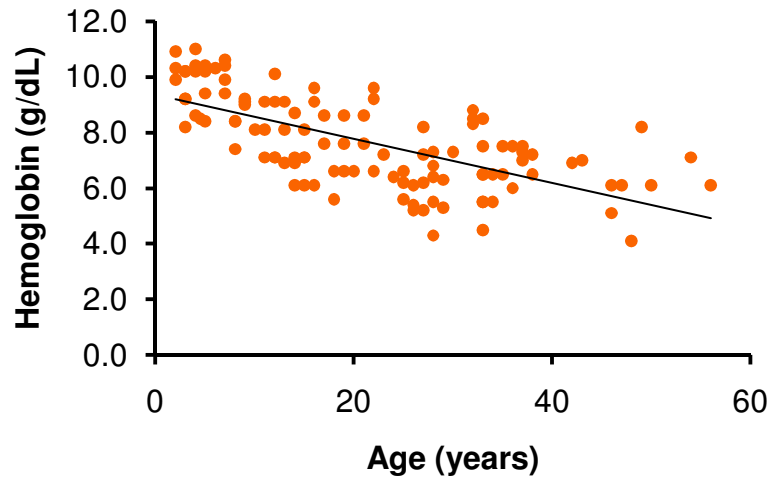
Taher AT, Musallam KM, Karimi M, et al. Blood. 2010;115:1886-92.

OPTIMAL CARE study: risk factors for thrombosis

Complication	Parameter	RR*	95% CI	p value
Thrombosis	Age > 35 years	2.60	1.39–4.87	0.003
	Hb ≥ 9 g/dL	0.41	0.23–0.71	0.001
	Serum ferritin ≥ 1,000 µg/L	1.86	1.09–3.16	0.023
	Splenectomy	6.59	3.09–14.05	< 0.001
	Transfusion	0.28	0.16–0.48	< 0.001

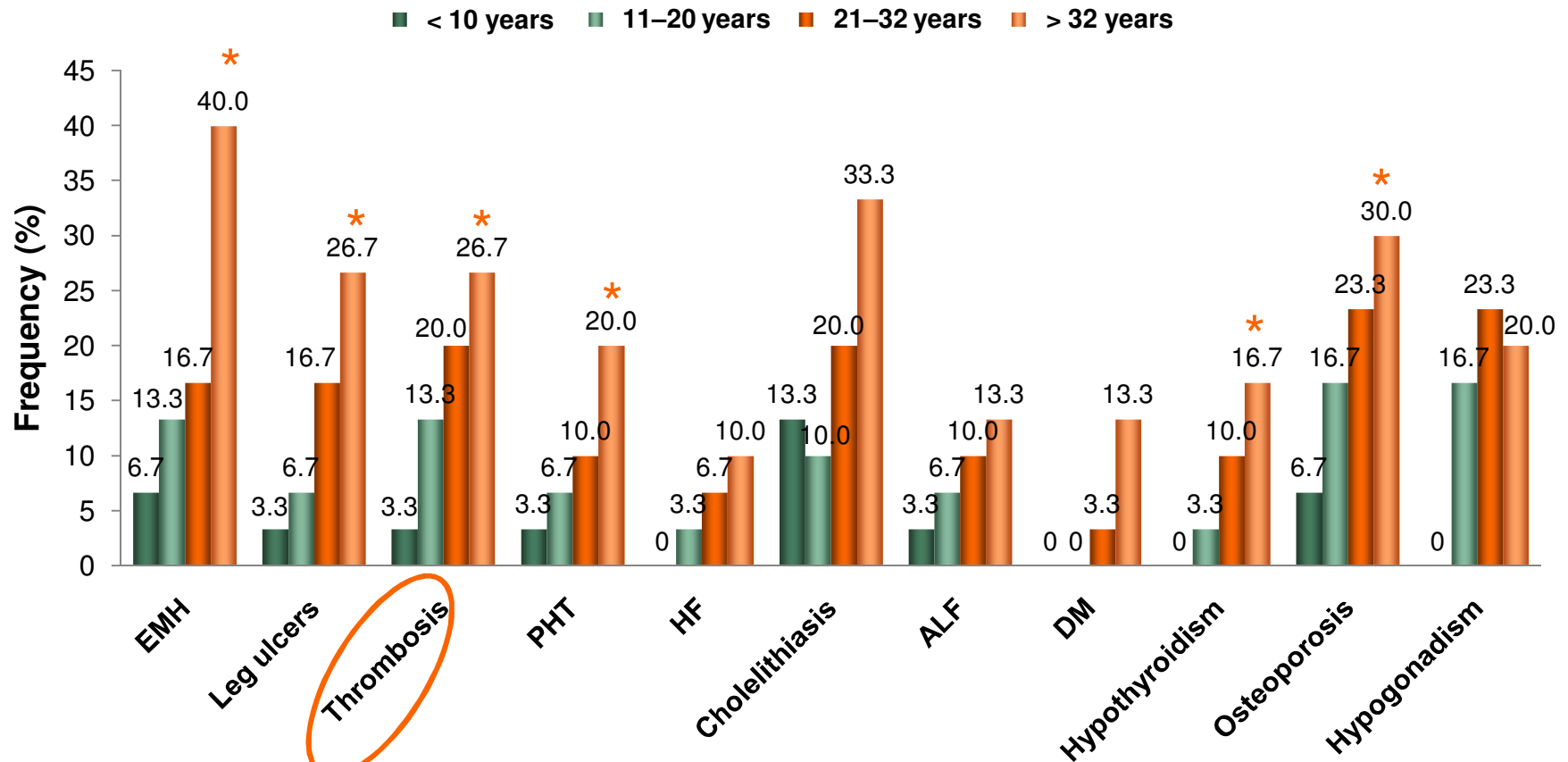
*RR indicates adjusted relative risk.

120 Treatment-naive patients



Complications vs age

Complications in 120 treatment-naive patients with TI



* = statistically significant trend.

PHT = pulmonary hypertension; HF = heart failure;

ALF = abnormal liver function; DM = diabetes mellitus. Taher A, Musallam KM, El-Beshlawy A, et al. Br J Haematol. 2010;150:486-9.

OPTIMAL CARE study: patient stratification according to splenectomy and TEE status

- Three groups of patients identified
 - **Group I**, splenectomized patients with a documented TEE (n = 73)
 - **Group II**, age- and sex-matched splenectomized patients without TEE (n = 73)
 - **Group III**, age- and sex-matched non-splenectomized patients without TEE (n = 73)

Type of thromboembolic event in splenectomized TI patients (Group I)	n (%)
DVT	46 (63.0)
PE*	13 (17.8)
STP	12 (16.4)
PVT	11 (15.1)
Stroke	4 (5.5)

*All patients who had PE had confirmed DVT.

OPTIMAL CARE study: patient stratification according to splenectomy and TEE status (cont.)

Parameter	Group I <i>Splenectomized with TEE</i> (n = 73)	Group II <i>Splenectomized without TEE</i> (n = 73)	Group III <i>Non-splenectomized</i> (n = 73)	p value
Mean age ± SD, years	33.1 ± 11.7	33.3 ± 11.9	33.4 ± 13.1	0.991
Male:female	33:40	35:38	34:39	0.946
Mean Hb ± SD, g/dL	9.0 ± 1.3	8.8 ± 1.2	8.7 ± 1.3	0.174
Mean HbF ± SD, %	45.9 ± 28.0	54.4 ± 32.8	44.2 ± 27.2	0.429
Mean NRBC count ± SD, x10 ⁶ /L	436.5 ± 205.5	279.0 ± 105.2	239.5 ± 128.7	< 0.001
Mean platelet count ± SD, x10 ⁹ /L	712.6 ± 192.5	506.3 ± 142.1	319.2 ± 122.0	< 0.001
PHT, n (%)	25 (34.2)	17 (23.3)	3 (4.1)	< 0.001
HF, n (%)	7 (9.6)	5 (6.8)	1 (1.4)	0.101
DM, n (%)	4 (5.5)	5 (6.8)	1 (1.4)	0.256
Abnormal liver function, n (%)	2 (2.7)	2 (2.7)	3 (4.1)	0.863
Family history of TEE	3 (4.7)	1 (1.4)	3 (4.7)	0.554
Thrombophilia, n (%)	3 (4.7)	2 (2.7)	2 (2.7)	0.863
Malignancy, n (%)	1 (1.4)	2 (2.7)	0 (0)	0.363
Transfused, n (%)	32 (43.8)	48 (65.8)	54 (74.0)	0.001
Antiplatelet or anticoagulant use, n (%)	1 (1.4)	3 (4.1)	2 (2.7)	0.598
Hydroxyurea use, n (%)	13 (17.8)	17 (23.3)	29 (27.4)	0.383

DM = diabetes mellitus; Hb = total hemoglobin; HbF = fetal hemoglobin;
 HF = heart failure; NRBC = nucleated red blood cell; PHT = pulmonary
 hypertension; TEE = thromboembolic events.

Taher A, Musallam KM, Karimi M, et al. J Thromb Haemost. 2010;8:2152-8.

OPTIMAL CARE study: multivariate analysis of the risk per patient group

Parameter	Group	OR	95% CI	p value
NRBC count $\geq 300 \times 10^6/L$	Group III	1.00	Referent	< 0.001
	Group II	5.35	2.31–12.35	
	Group I	11.11	3.85–32.26	
Platelet count ≥ 500	Group I had significantly higher NRBC, platelets, and PHT occurrence, and was mostly non-transfused			< 0.001
	Group II	4.00	0.99–16.13	
PHT	Group I	7.30	1.60–33.33	0.020
	Group II	4.00	0.99–16.13	
Transfusion naivety	Group III	1.00	Referent	0.001
	Group II	1.67	0.82–3.38	
	Group I	3.64	1.82–7.30	

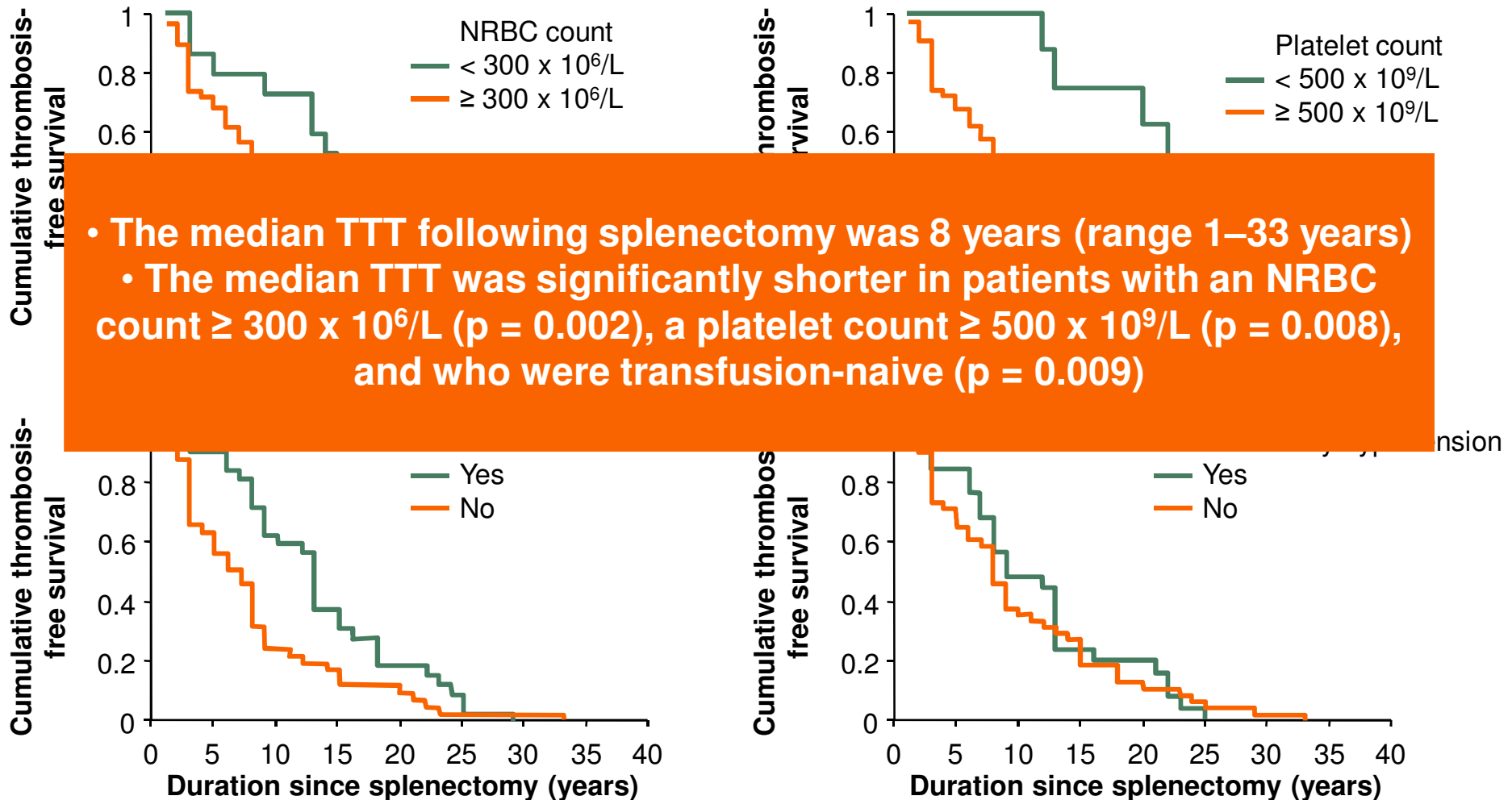
NRBC = nucleated red blood cell; PHT = pulmonary hypertension;

OR = adjusted odds ratio; CI = confidence interval.

Taher A, Musallam KM, Karimi M, et al. J Thromb Haemost. 2010;8:2152-8.

Time-to-thrombosis (TTT) since splenectomy

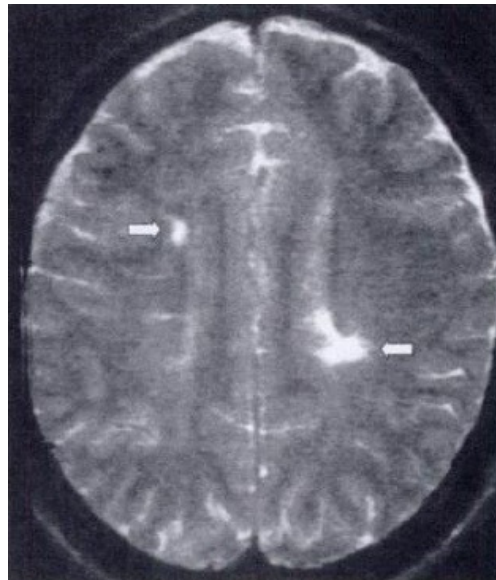
Time to thrombosis



- The median TTT following splenectomy was 8 years (range 1–33 years)
- The median TTT was significantly shorter in patients with an NRBC count $\geq 300 \times 10^6/L$ ($p = 0.002$), a platelet count $\geq 500 \times 10^9/L$ ($p = 0.008$), and who were transfusion-naive ($p = 0.009$)

Cerebral Thrombosis

- In 1972, Logothetis et al. described a “stroke syndrome” and neurological deficits compatible with **TIAs** in about 20% of 138 cases of **TM** in Greece¹
- In 1998, Borgna Pignatti et al. described **TIAs** accompanied by a clinical picture of headache, seizures, and hemiparesis in 2.2% of **TM** patients in Italy²
- In 16 patients with **TI**, Manfrè et al. found that **37.5%** showed evidence of asymptomatic brain damage including ischemic lesions³



Type of damage	n (%)
Atrophy	
Mild	5 (31)
Moderate	0 (0)
Severe	0 (0)
Infarcts	
Small (<0.5 cm)	4 (25)
Medium (0.5-1.5 cm)	1 (6.5)
Large (>1.5 cm)	1 (6.6)
Single	4 (25)
Multiple	2 (12.5)

TIA = transient ischemic attack.

¹Logothetis J, et al. Neurology 1972;22:294-304.

²Borgna Pignatti C, et al. Acta Haematol 1998;99:76-79.

³Manfrè L, et al. AJR Am J Roentgenol 1999;173:1477-1480.

Silent brain MRI findings in 30 splenectomized adults with TI

White matter lesions

Parameter	n (%)
Number	
Single	4 (22.2)
Multiple*	14 (77.8)
Location	
Frontal	17 (94.4)
Parietal	9 (50)
Temporal	1 (5.6)
Occipital	3 (16.7)
Internal capsule	1 (5.6)
External capsule	5 (27.8)
Size**	
Small (< 0.5 cm)	10 (55.5)
Medium (0.5–1.5 cm)	7 (38.9)
Large (> 1.5 cm) §	1 (5.6)

*Mean of 5 ± 10 lesions (range: 2 to > 40 lesions).

**For patients with multiple lesions, the largest lesion was used to define size.

§The possibility of misreading confluent multiple lesions was excluded radiologically based on lesion shape.

- **18** patients (**60%**) had evidence of one or more WMLs on brain MRI all involving the subcortical white matter
- **11** patients (**37%**) had evidence of mild cerebral atrophy, 10 of whom had associated WMLs

White matter lesions and brain atrophy are a common finding in adult, splenectomized, TI patients

Coronal and Axial FLAIR images showing multiple foci of high signal seen in the subcortical and periventricular white matter with one large lesion (1.7 cm) seen in the left parietal white matter.



Literature-based control

- Comparison with frequency data from **healthy** volunteers of similar **age**.

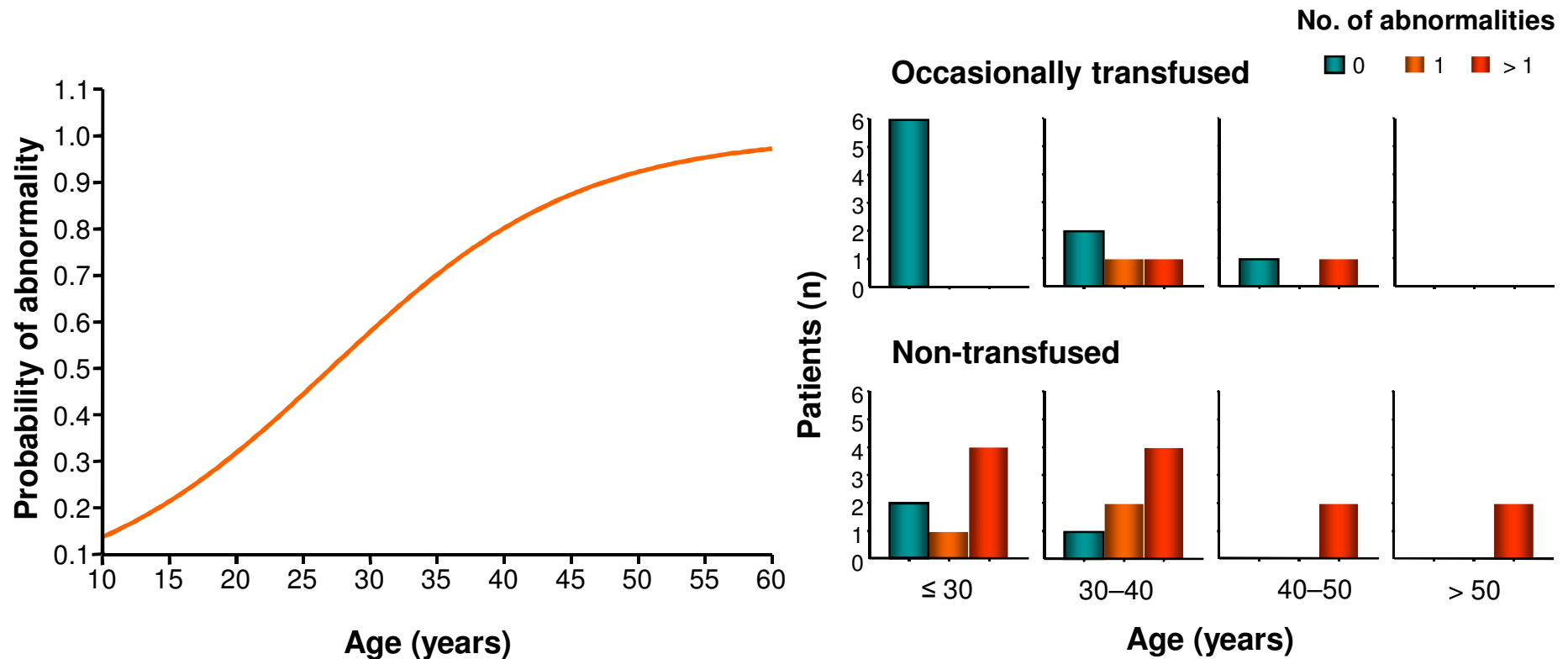
Reference	n	Mean age* (range),	Abnormality	Frequency (%)
Fazekas				lesions in 4 th
Saloner				
Katzman				
Hopkins 2006	243	(16-65)	WML	5.3
Weber 2006	750	(45-59)	WML	7.2
Vernooij 2007	2,536	20.5 (17-35)	Atrophy	0.43
Yamada 2008	16,206	70 (39-90)	WML	0.37

This highlights that the described changes are pathological rather than normal variations

WML = white matter lesions >0.5mm

*Where available.

Risk factors for white matter lesions



Increasing age and transfusion naivety are associated with a higher incidence and multiplicity of white matter lesions

Current and future directions in the prevention of thromboembolism

- A guarded approach to the need for splenectomy in TI is recommended with delay in initiating the procedure unless considered extremely necessary
- In already splenectomized TI, patients who will develop thrombosis may be identified early on by high **NRBC** and **platelet** counts, evidence of **PHT**, and **transfusion naivety**
- Attention should also be paid to the **aging** TI patient

Current and future directions in prevention of thromboembolism (cont.)

- The delayed type of thrombosis in splenectomized patients entails that any modality considered for prevention has to be evaluated for **long-term efficacy and safety**
- Prospective clinical trials that evaluate the efficacy, safety, and cost effectiveness of **transfusion** and **antiplatelet/anticoagulant** therapy in preventing thromboembolism in TI are called for.
- The role of **iron overload** and **chelation** therapy in vascular morbidity warrant further evaluation.