ACCADEMIA di FORMAZIONE

SIMTI

Emoglobinopatie: supporto trasfusionale e nuovi approcci terapeutici

La Diagnosi di Drepanocitosi

Lucia De Franceschi
Dept of Medicine, University of Verona & AOUI Verona

La sottoscritta, in qualità di Relatrice
dichiara che

nell'esercizio della Sua funzione e per l'evento in oggetto, NON È in alcun modo portatore di interessi commerciali propri o di terzi; e che gli eventuali rapporti avuti negli ultimi due anni con soggetti portatori di interessi commerciali non sono tali da permettere a tali soggetti di influenzare le mie funzioni al fine di trarne vantaggio.

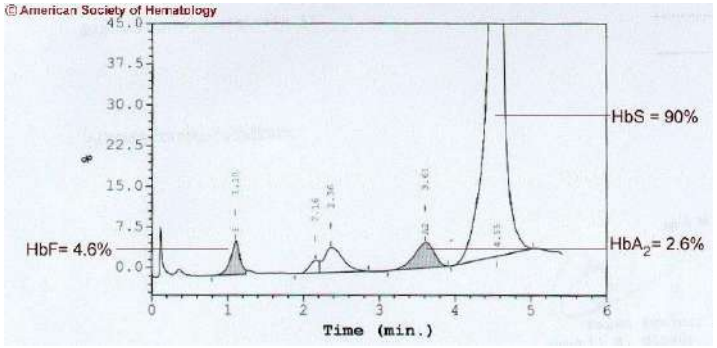

WHO
beta
Glu
Val
?
WHY
HOW

Diagnosis of SCD-I

- **IEF, CE, HPLC, mass spectrometry**
- **Molecular analysis**

Hb Electrophoresis

Hb HPLC



Diagnosis- II

Mass-spectrometric analysis: electro-spray coupled to tandem MS/MS

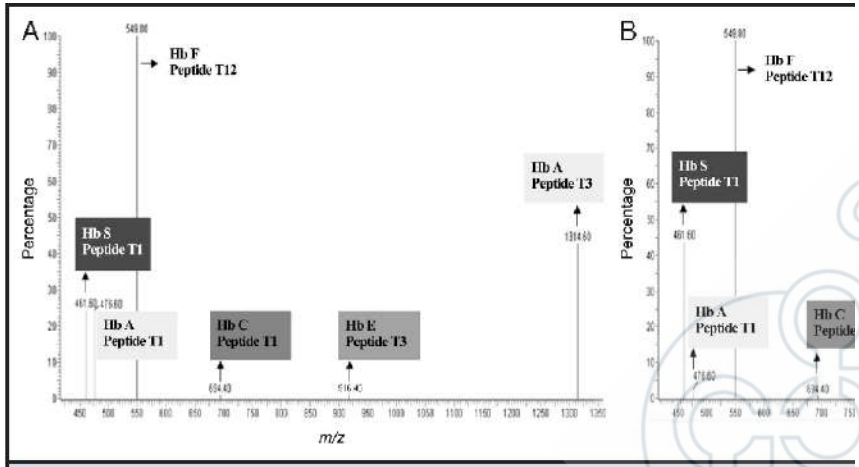


Fig. 1. MRM profile of b2-ions for patients with sickle cell trait (A) and sickle cell dise

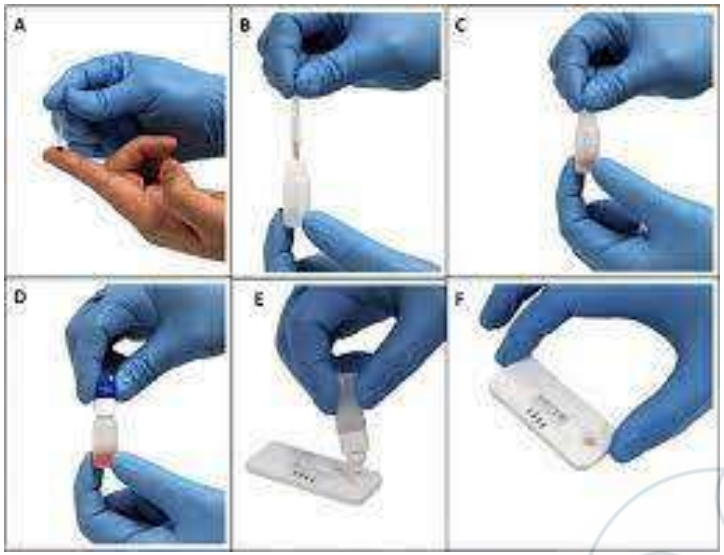
Table 4 Overview about studies on NBS for SCD in Germany

	Newborns screened	Affected babies	Reference
Berlin I	34,084	14	[17, 18]
Hamburg	17,018	7	[20]
Heidelberg	37,838	3	[19]
Berlin II	29,079	7	Present study
Total	118,019	31	

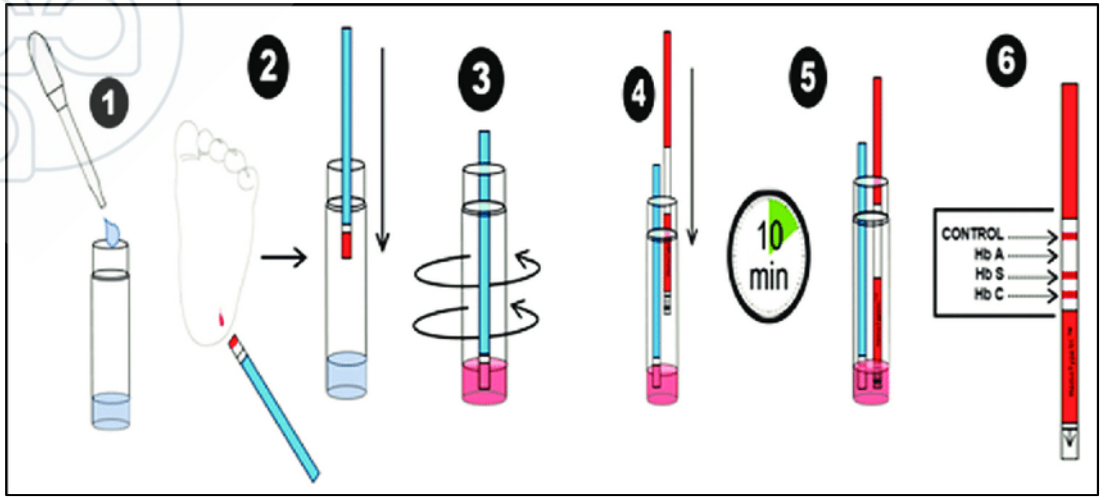
- 2.4/10.000 newborns-> costs: 3.00 euro MS/MS *vs* 3.58 euro CE
- Time consuming set-up compared to CE or HPLC- Advantages-> removing operator depending variability

Lobitz S et al Ann Hematol 98: 47, 2019; Daniel Y et al Int J Neon Screening 4: 35, 2018

Diagnosis-III



Rapid point of care (POC) test
SickleSCAN® or HemotypeSC™



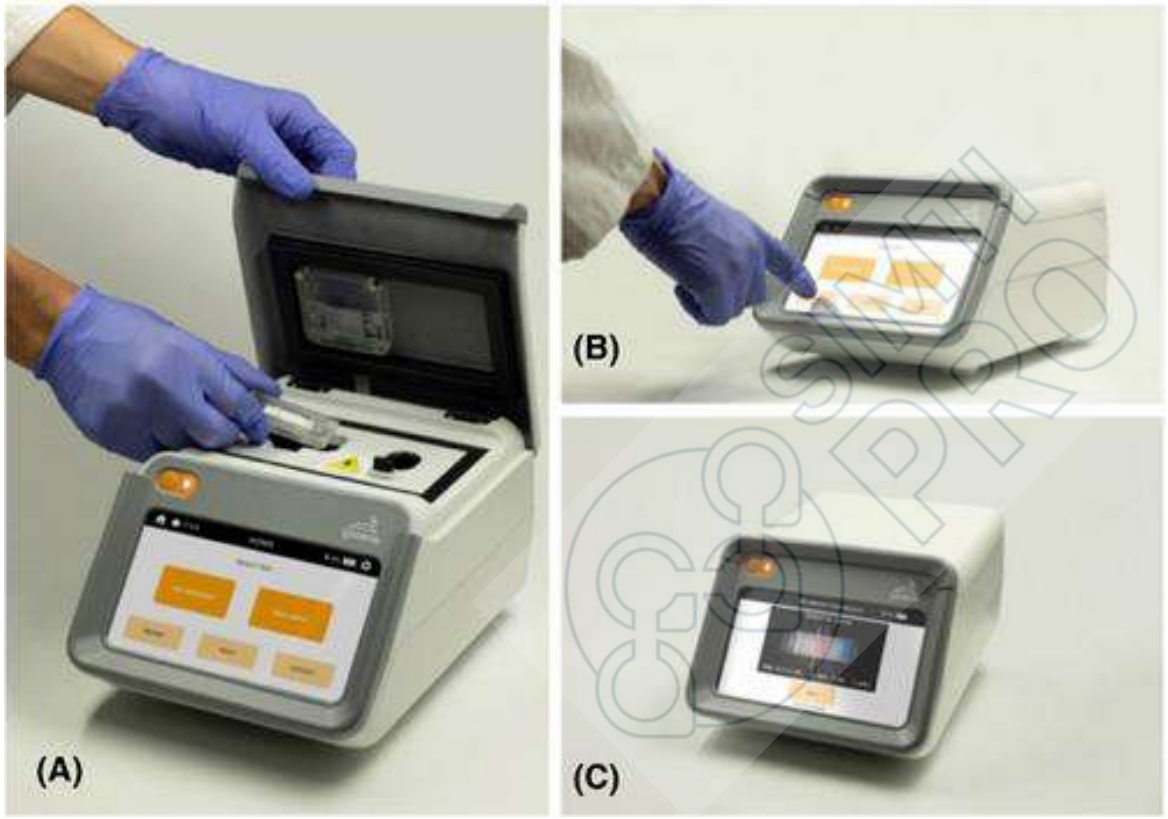
HemoTypeSC™ Detection Analysis by Hemoglobin Variant[a]

Location	Hb	Sensitivity[b]		Specificity[c]		PPV[d]		NPV[e]	
		TP/(TP+FN)	%	TN/(FP+TN)	%	TP/(TP+FP)	%	TN/(TN+FN)	%
Ghana	A	368/368	100.0	14/14	100.0	368/368	100.0	14/14	100.0
	S	49/50	98.0	331/332	99.7	49/50	98.0	331/332	99.7
	C	67/68	98.5	313/314	99.7	67/68	98.5	313/314	99.7
Martinique	A	45/45	100.0	1/1	100.0	45/45	100.0	1/1	100.0
	S	8/8	100.0	38/38	100.0	8/8	100.0	38/38	100.0
	C	5/5	100.0	41/41	100.0	5/5	100.0	41/41	100.0
USA	A	90/90	100.0	68/68	100.0	90/90	100.0	68/68	100.0
	S	95/95	100.0	63/63	100.0	95/95	100.0	63/63	100.0
	C	48/48	100.0	110/110	100.0	48/48	100.0	110/110	100.0
Total	**A**	**503/503**	**100.0**	**83/83**	**100.0**	**503/503**	**100.0**	**83/83**	**100.0**
	S	**152/153**	**99.3**	**432/433**	**99.8**	**152/153**	**99.3**	**432/433**	**99.8**
	C	**120/121**	**99.2**	**464/465**	**99.8**	**120/121**	**99.2**	**464/465**	**99.8**

Main Analysis Population = 587 Participants

Steele C et al Am J Hematol 94: 39, 2019

Diagnosis-IV



Gazelle Hb Variant. miniaturized micro-chip-based cellulose acetate electrophoresis HbS identification and other Hb variants in 8 min.

Hasan MN et al Analyst 145: 252,5 2020

Table II. Summary of currently available POCT for SCD.

	HemoTypeSC™	Sickle SCAN™	Gazelle Hb variant
Technology	LFIA – Monoclonal abs to HbA, S, C	LFIA – Polyclonal abs to HbA, S, C	Modified cellulose acetate electrophoresis detecting Hb A, F, S C, E, A2
Time	10 min	5 min	8 min
Equipment	None	None	Requires electrical supply.
Field Validation	**Ghana** (n = 384)[23] Sensitivity: 100% Specificity: 100% **Nigeria** (n = 1121)[21] Sensitivity: 93·4% Specificity: 99·1% **Nigeria** (n = 3603)[15] Sensitivity: 100% Specificity: 100% **India** (n = 1559)[33] Sensitivity: 98·1% Specificity: 99·1%	**Haiti** (n = 1372)[22] Sensitivity: 90% Specificity: 97% **Tanzania** (n = 652)[24] Sensitivity: 98·7% Specificity: 92·6% **Mali** (n = 80)[25] Sensitivity: 100% Specificity: 100% **Togo** (n = 209)[25] Sensitivity: 94·9–100% (genotype dependent) Specificity: > 99·2%	**Nigeria** (n = 315)[26] Sensitivity: 100% Specificity: 98% **Nigeria, Thailand, India, USA** (n = 768)[26] Overall diagnostic accuracy: 98·4%
Strengths	Accurate in young infants with high HbF Competitive against gold standard Low cost Validated within infant screening framework (Nigeria)	Accurate in young infants with high HbF Competitive against gold standard Low cost Validated within infant screening framework (Haiti) Easy, intuitive result interpretation	Accurate in infants Can detect non-HbS, HbC variants Quantitation of HbF, HbS Automated results Digital upload and data storage Possible linkage to malaria and haemoglobin testing with the same machine
Limitatio			ng

Costs:

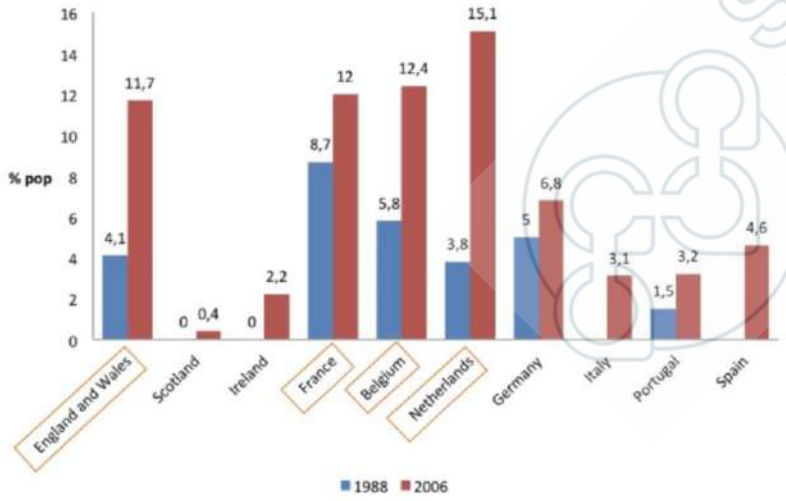
- **HemotypeSC®: 7.06 $**
- **SickleSCAN™: 4.60 $**
- **IEF: 9.90 $** (1.58$ reagents per test + equipment 20-30K$)

pply

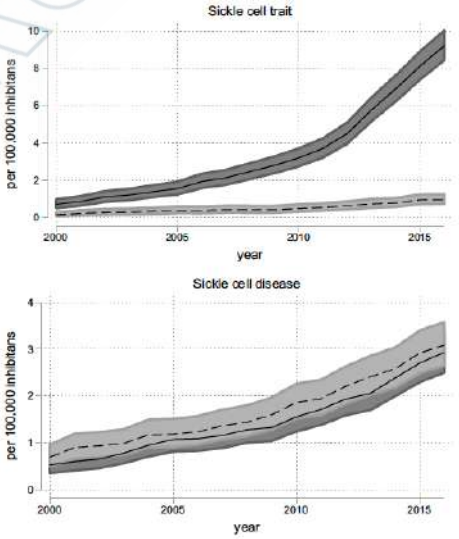
Heavenlight C et al Int J Lab Hematol 44:959, 2022; Kuznik A et al BMC Health Services Research 304, 2016; Dexter D et al BJH 196: 63, 2022; Olaniyan HS et al Blood Adv 7: 5860, 2023

SCD and EU-UK

Trends in at risk populations (%population: 1988-2006)

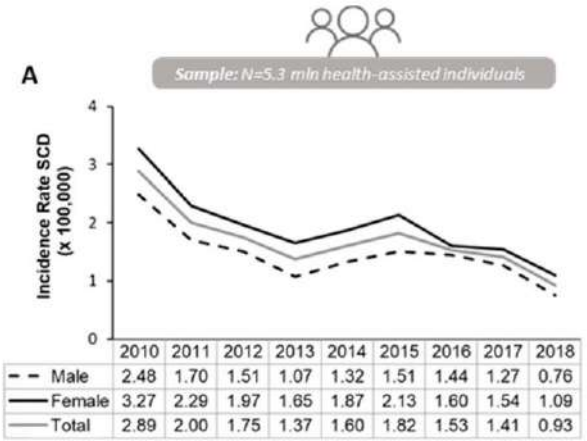


Prevalence of SCD showed fivefold increased in Danish population(2000-2015)

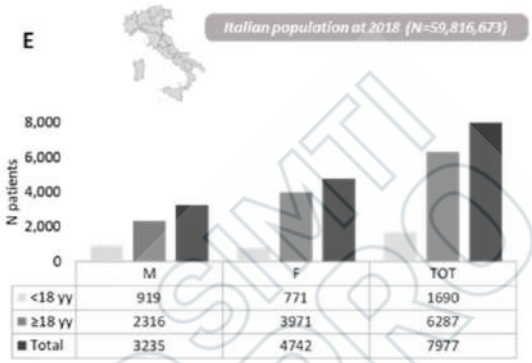


Modell et al Scand J Clin Lab Invest 67: 39, 2007; Hansen DL et al Clin Epidemiol 12: 485, 2020

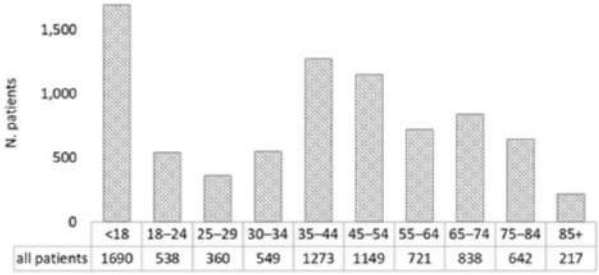
SCD in Italy



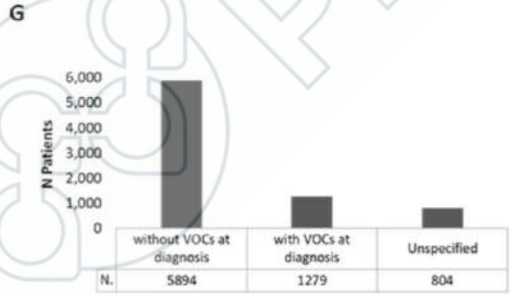
	2010	2011	2012	2013	2014	2015	2016	2017	2018
Male	2.48	1.70	1.51	1.07	1.32	1.51	1.44	1.27	0.76
Female	3.27	2.29	1.97	1.65	1.87	2.13	1.60	1.54	1.09
Total	2.89	2.00	1.75	1.37	1.60	1.82	1.53	1.41	0.93



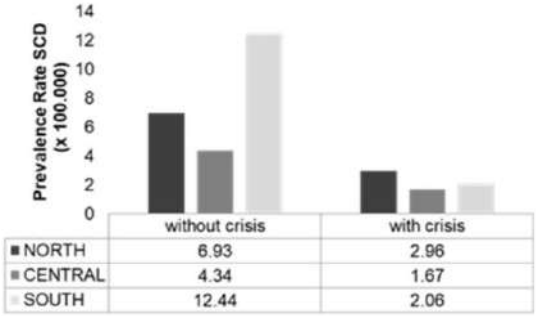
	M	F	TOT
<18 yy	919	771	1690
≥18 yy	2316	3971	6287
Total	3235	4742	7977



	<18	18–24	25–29	30–34	35–44	45–54	55–64	65–74	75–84	85+
all patients	1690	538	360	549	1273	1149	721	838	642	217



	without VOCs at diagnosis	with VOCs at diagnosis	Unspecified
N.	5894	1279	804



	without crisis	with crisis
NORTH	6.93	2.96
CENTRAL	4.34	1.67
SOUTH	12.44	2.06

De Franceschi L et al J Clin Med 12: 117, 2023;
Leleu H et al PlosOne 16: e0253986, 2021

Identification of patients with SCD

European SCD population:

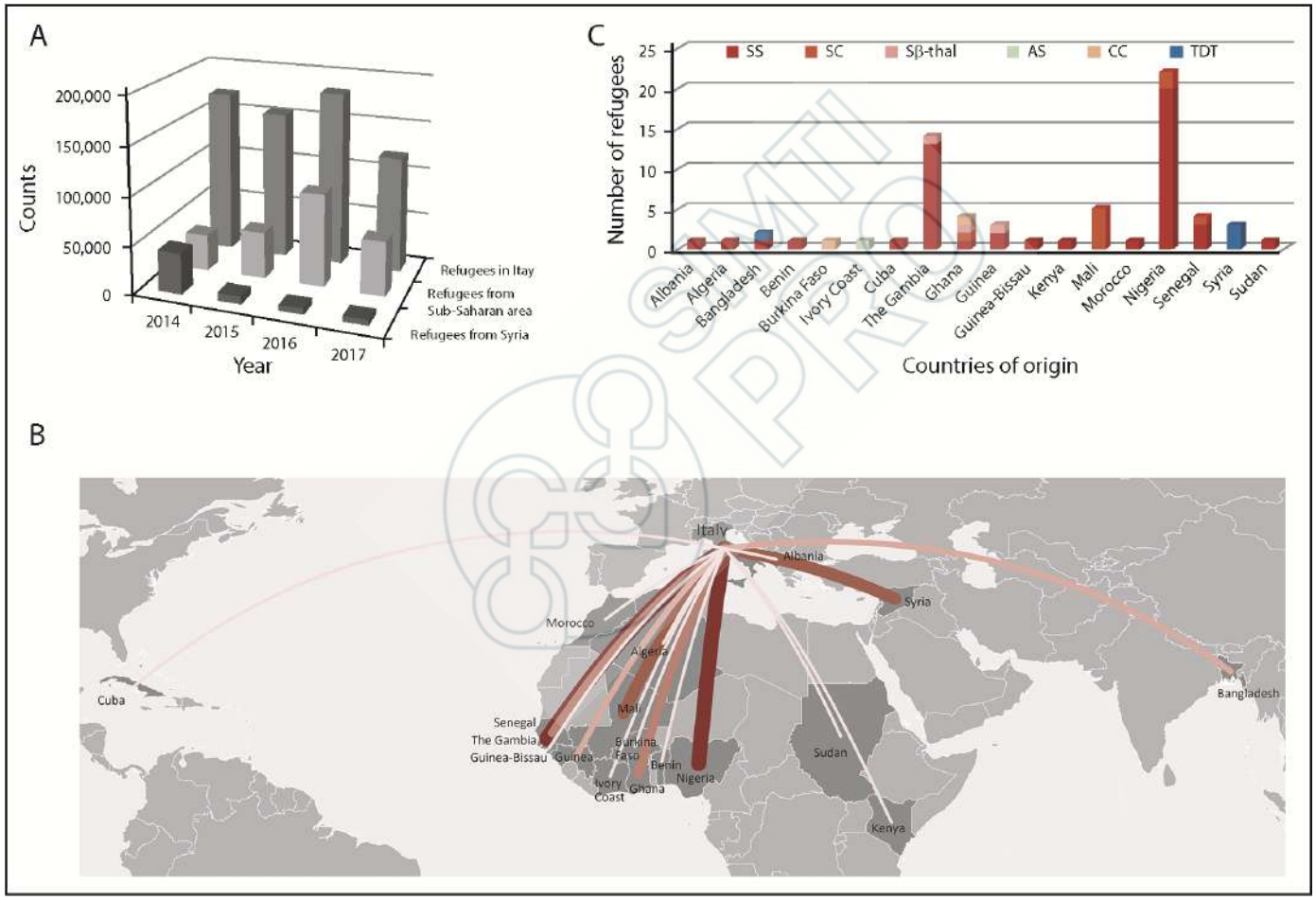
- **Endogenous:** Italy, Greece, Albania, Portugal
- **Exogenous:** **voluntary migration** (Afriacan Sub-sharan countries, South Amerca, Carabian areas, Middle East, Indian Sub-continent)

Identification strategies:

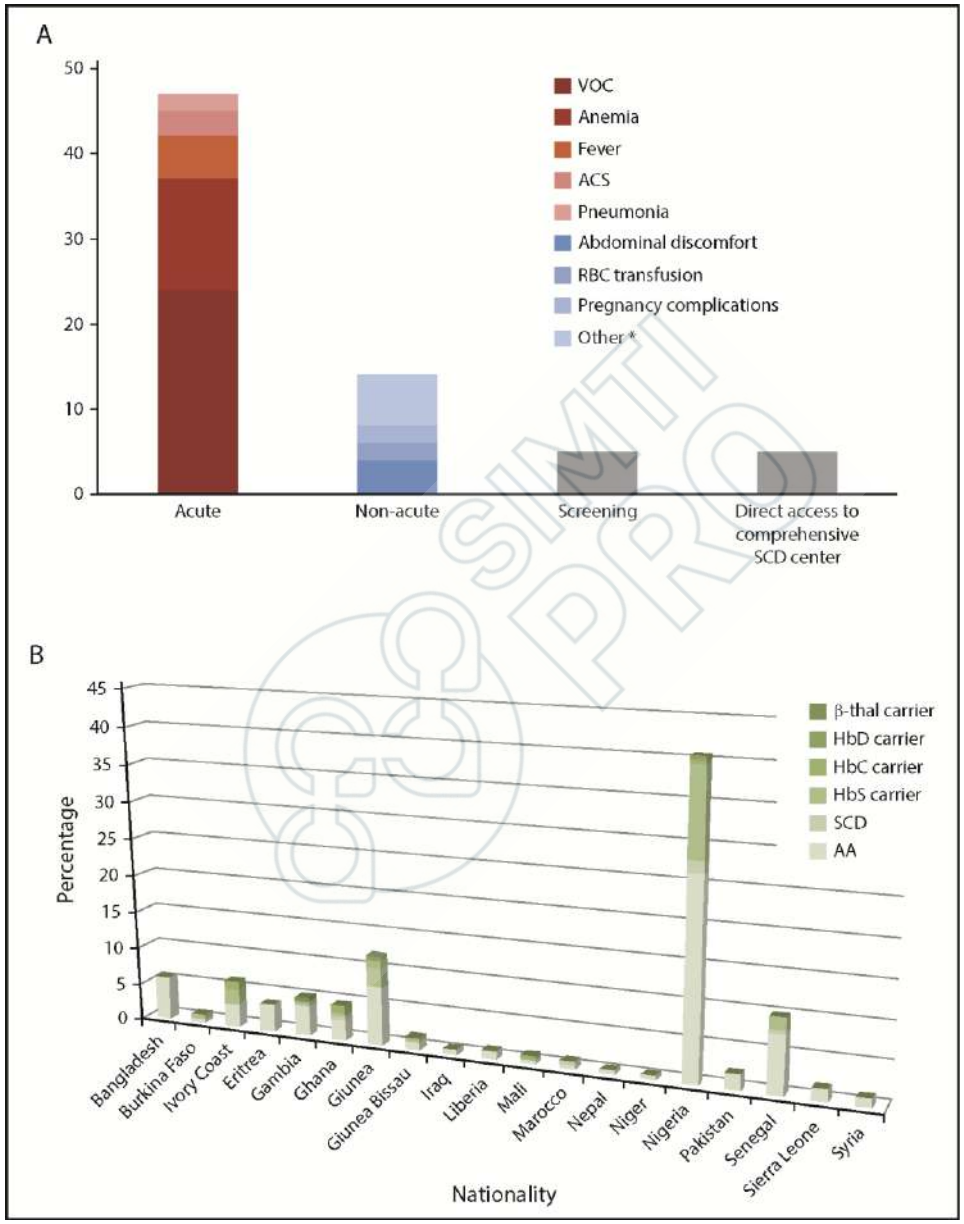
- **Neonatal screening-> not established in all EU countries**
- **Antenatal screening-> offered to couples**
- **Screening of refugees -> not established in all EU countries**

De Franceschi L et al Blood doi 10.1182/bloo-2018-09-876508

Access to emergency departments for acute events and identification of sickle cell disease in refugees



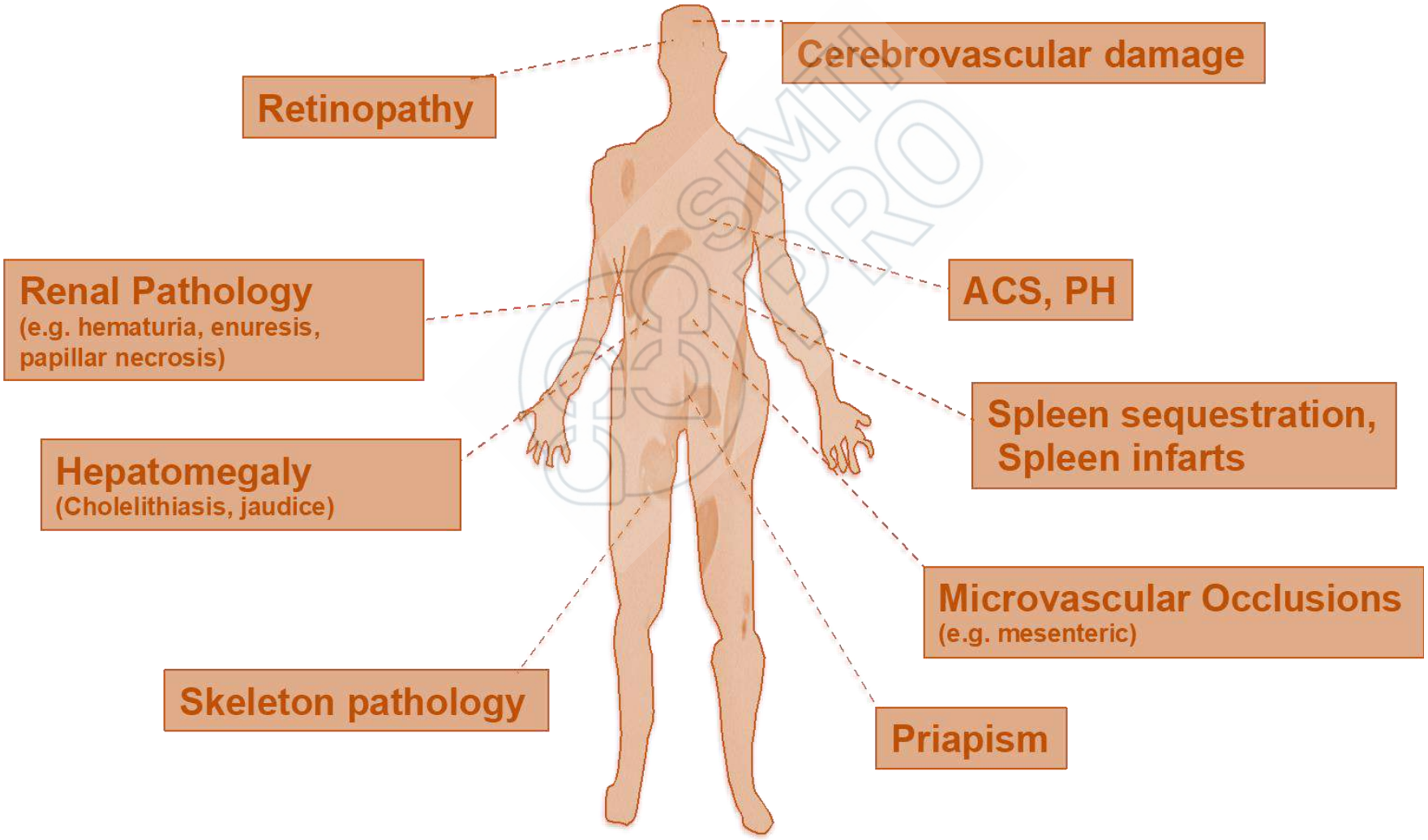
De Franceschi L et al Blood 133: 2100, 2019

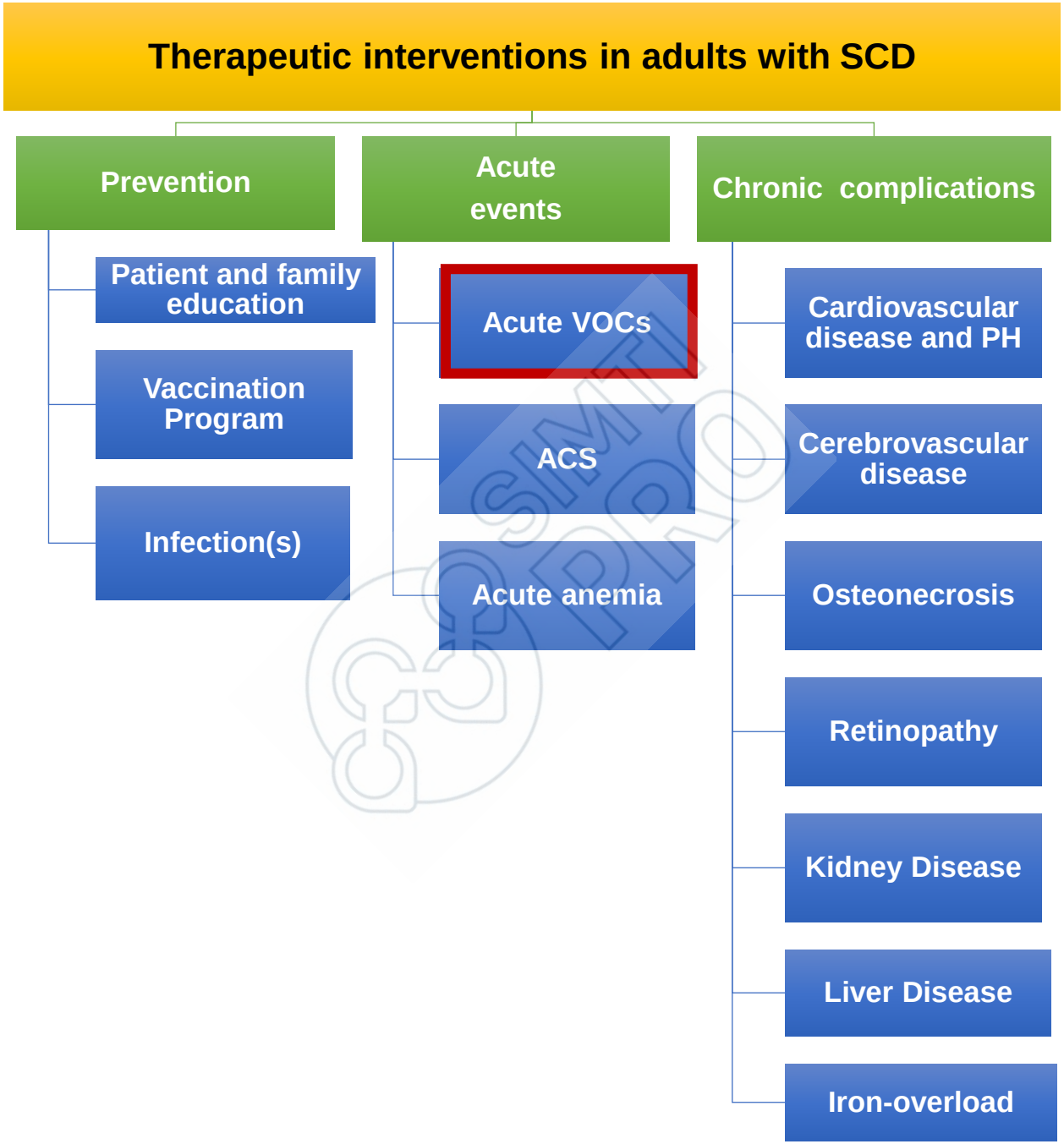


De Franceschi L et al Blood 133: 2100, 2019

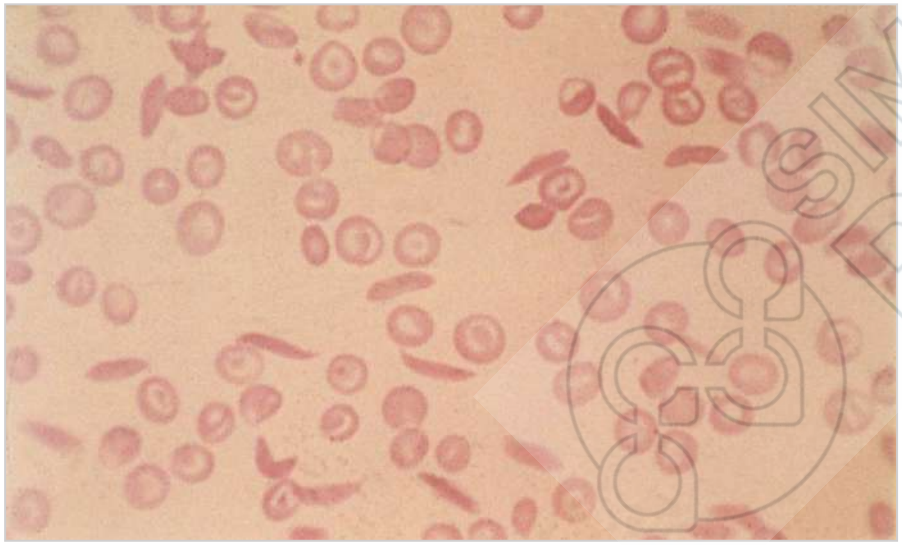

WHO
beta
Glu
Val
?
WHY
HOW

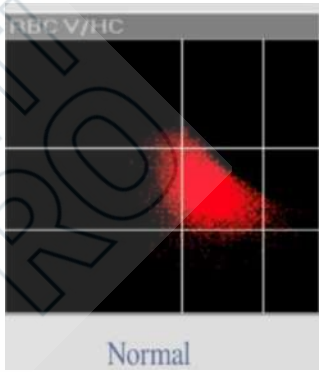
SCD is Monogenic disorder but multiorgan diseases

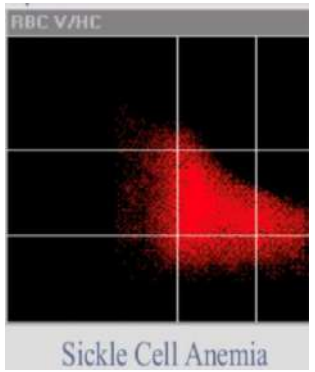


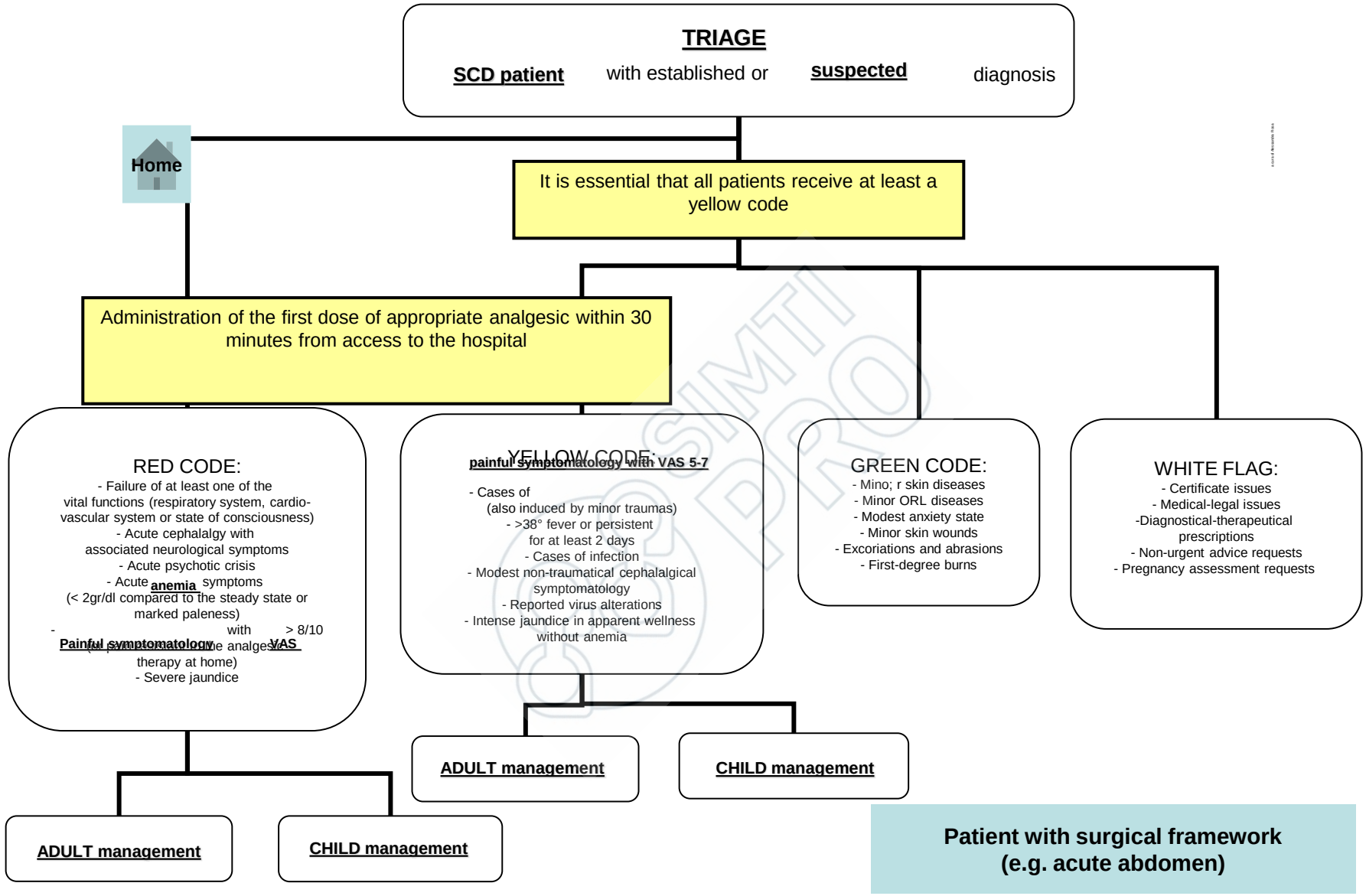

Therapeutic interventions in adults with SCD
Prevention
Acute events
Chronic complications
Patient and family education
Vaccination Program
Infection(s)
Acute VOCs
ACS
Acute anemia
Cardiovascular disease and PH
Cerebrovascular disease
Osteonecrosis
Retinopathy
Kidney Disease
Liver Disease
Iron-overload

Observe, Listen and Learn from Patients with Sickle Cell Disease (SCD)



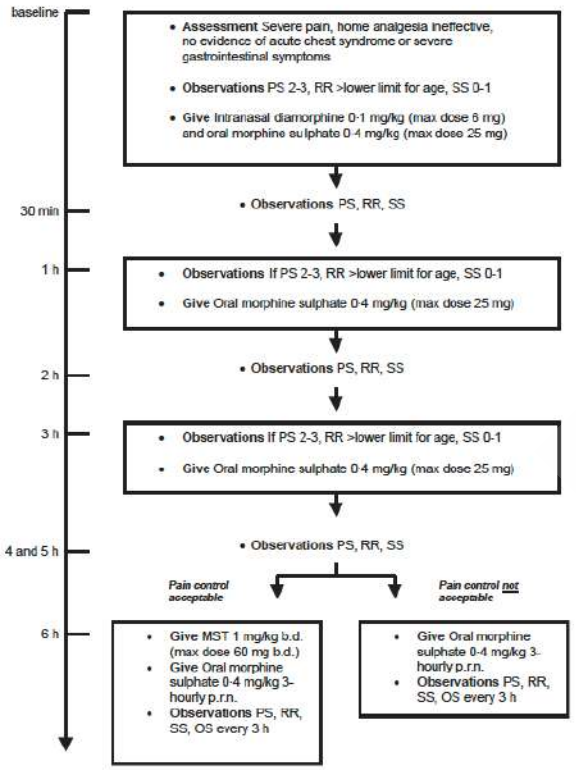


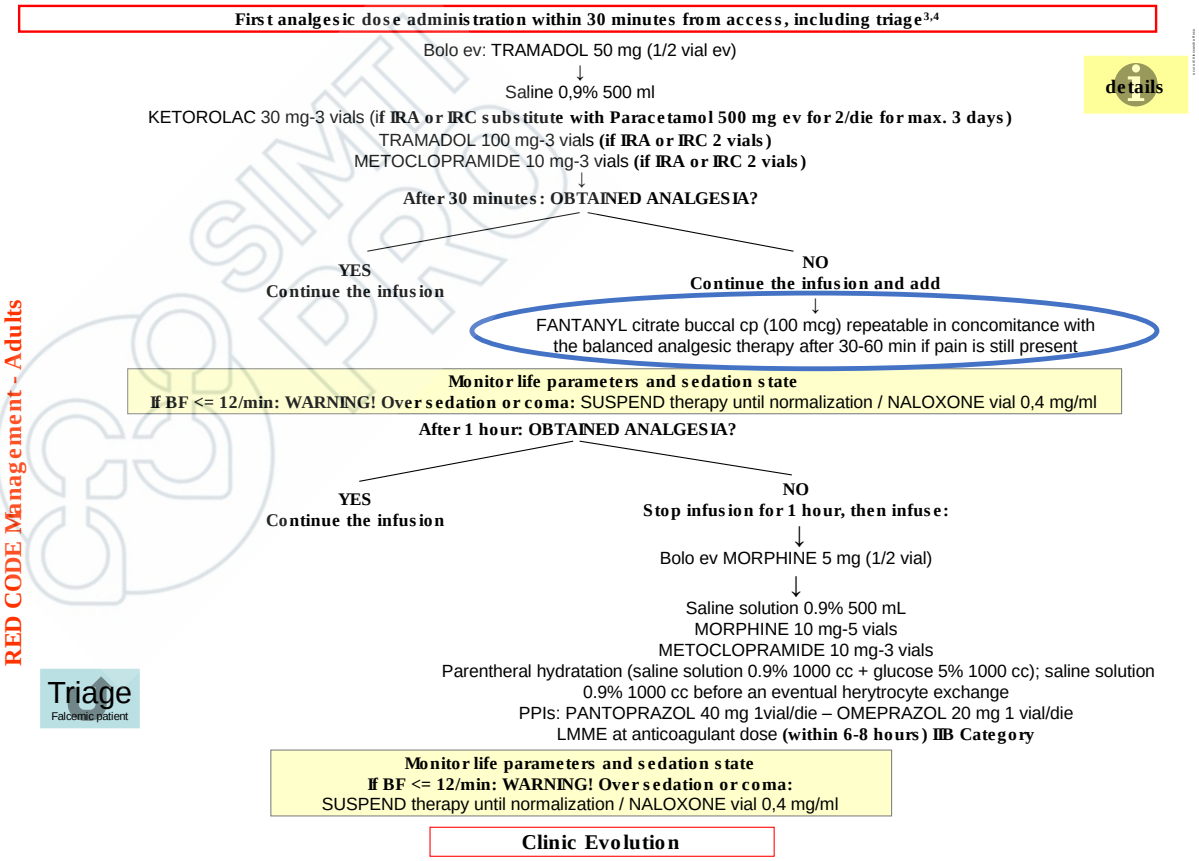




Forni GL et al Orphanet J Rare Dis 9: 91, 2014- www.site-italia.org

Management of sickle cell related pain in EU





Forni GL et al Orph J Rare Dis 9: 91, 2014; De Franceschi L et al Pain Practice 16: 680, 2016; Telfer P et al BJH 166: 157, 2014

Multimodal therapy for pain control related to SCD

- Based on the administration of drugs with different pharmacological mechanisms of action
- Multimodal modal therapy controls pain of different origins (vascular, somatic and neuropathic)
- Maximizes analgesia and minimizes adverse side effects
- Prevents the opioid induces post-synaptic morphological changes

Basbaum P, 1995; Kehlet H, 1993; Dellemijn PL 1997; Rowbotham MC, 2003; Forni GL et al Orph J Rare Dis 9: 91, 2014; De Franceschi L et al Pain Practice 16: 680, 2016

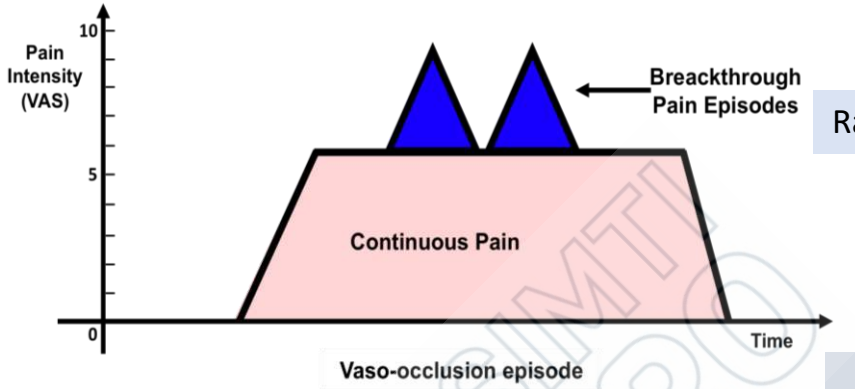
Balance Analgesia in SCD

- **Tramadol + Ketorolac in adult SCD patients** (continous infusion- max 72 hrs)
  - Tramadol 0.3 mg/Kg/hr
  - Ketorolac 0.86 mg/Kg/day (not more than 72 hours)/Praacetamol
  - Metoclopramide 0.57 mg/Kg/day

- **Tramadol + paracetamol or ketorolac in children with SCD** (continous infusion)
  - Tramadol 0.25 mg/Kg/hr
  - Paracetamol 40-60 mg/Kg/day/ Ketorolac 0.5-1 mg/Kg/day (not more than 72 hours)

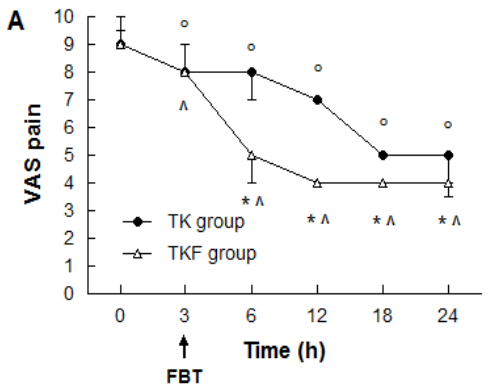
De Franceschi L, 2004; Erhan E 2007; Rees DC. Br J Haematol 120: 744, 2003; Forni GL et al Orph J Rare Dis 9: 91, 2014; De Franceschi L et al Pain Practice 16: 680, 2016

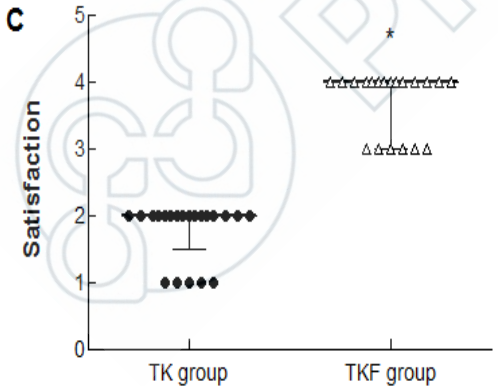
Buccal or nasal formulation for Fentanyl as pain breaking drug



Rapid-onset Fentanyl Formulations

Intranasal Fentanyl in children with SCD





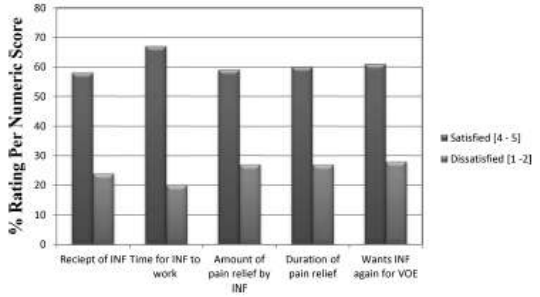


FIGURE 1 Patient/parent satisfaction data in children who received INF

Forni GL et al Orphanet J Rare Dis 9: 91, 2014; De Franceschi L et al Pain Practice 16: 680, 2016; De Franceschi L et al Haematologica 89: 1389, 2004; Ankisola B et al AJH doi 10.1002/ajh.25144, 2018; Kelly GS Am J Emerg Med 7:S0735, 2017; Anikasola B et al. AJH doi 10.1002/ajh.25144.2018; Payne J et al. Pediatr Blood Cancer 65: e27420, 2018

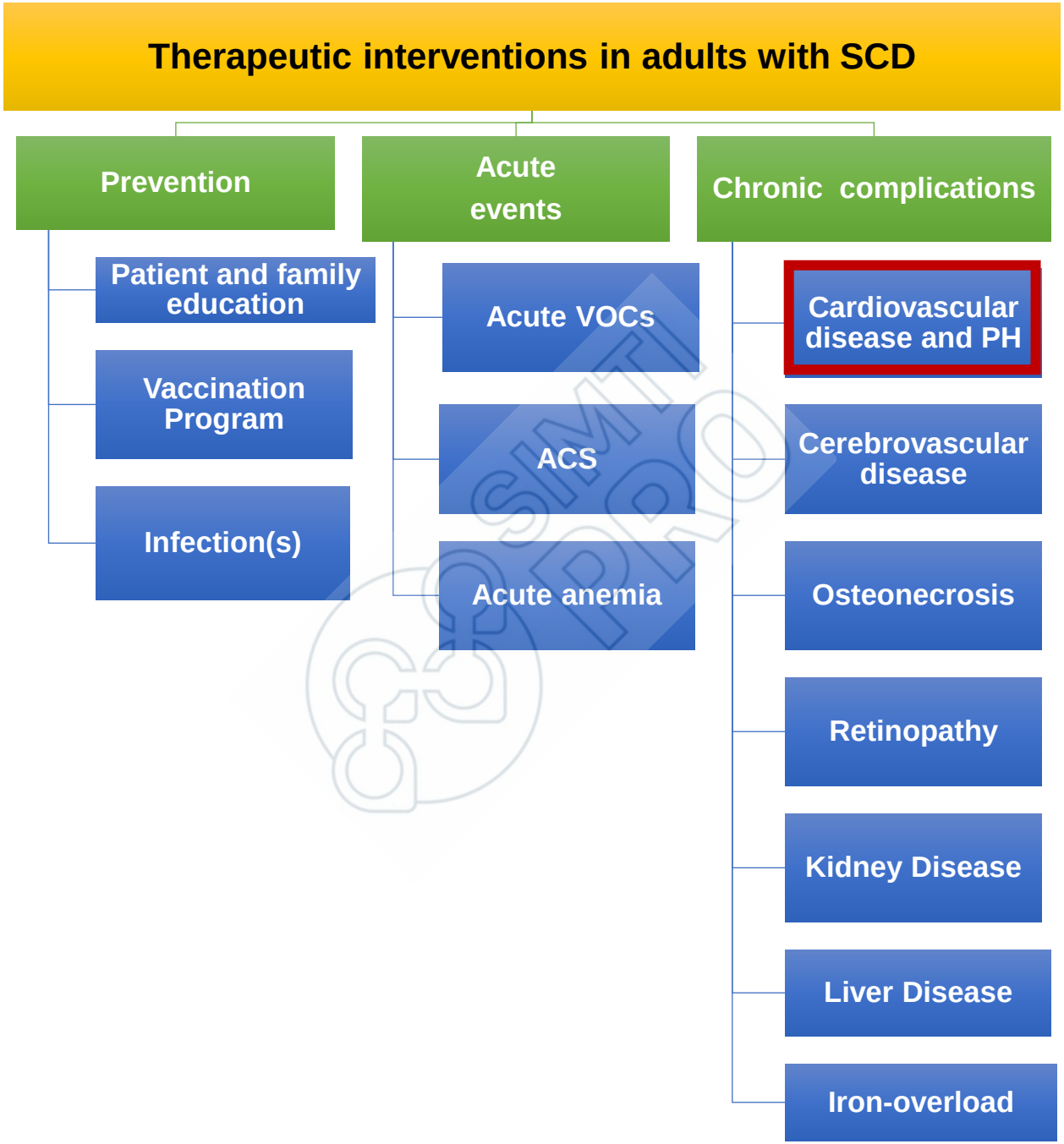
Re-hospitalization of SCD patients within 14–30 days of an acute event

Pneumonia | **Asthma** | **Heart failure**

- **The SCD population is more exposed to the risk of rehospitalization after acute events:**
  - **14 days to assess the quality of care related to hospitalization**
  - **30 days to assess the quality and accessibility to ambulatory care**

- **Young adults (18–30 years) are particularly at risk**
  - **Their disease worsens and the transition from paediatric to adult care may be complex**

Carroll CP *et al. Am J Hematol* 2009;84:666–670; Brousseau DC *et al. JAMA* 2010;303:1288–1294; van Such M *et al. Qual Saf Health Care* 2006;15:414–417; Ballas SK, Lusardi M. *Am J Hematol* 2005;79:17–25

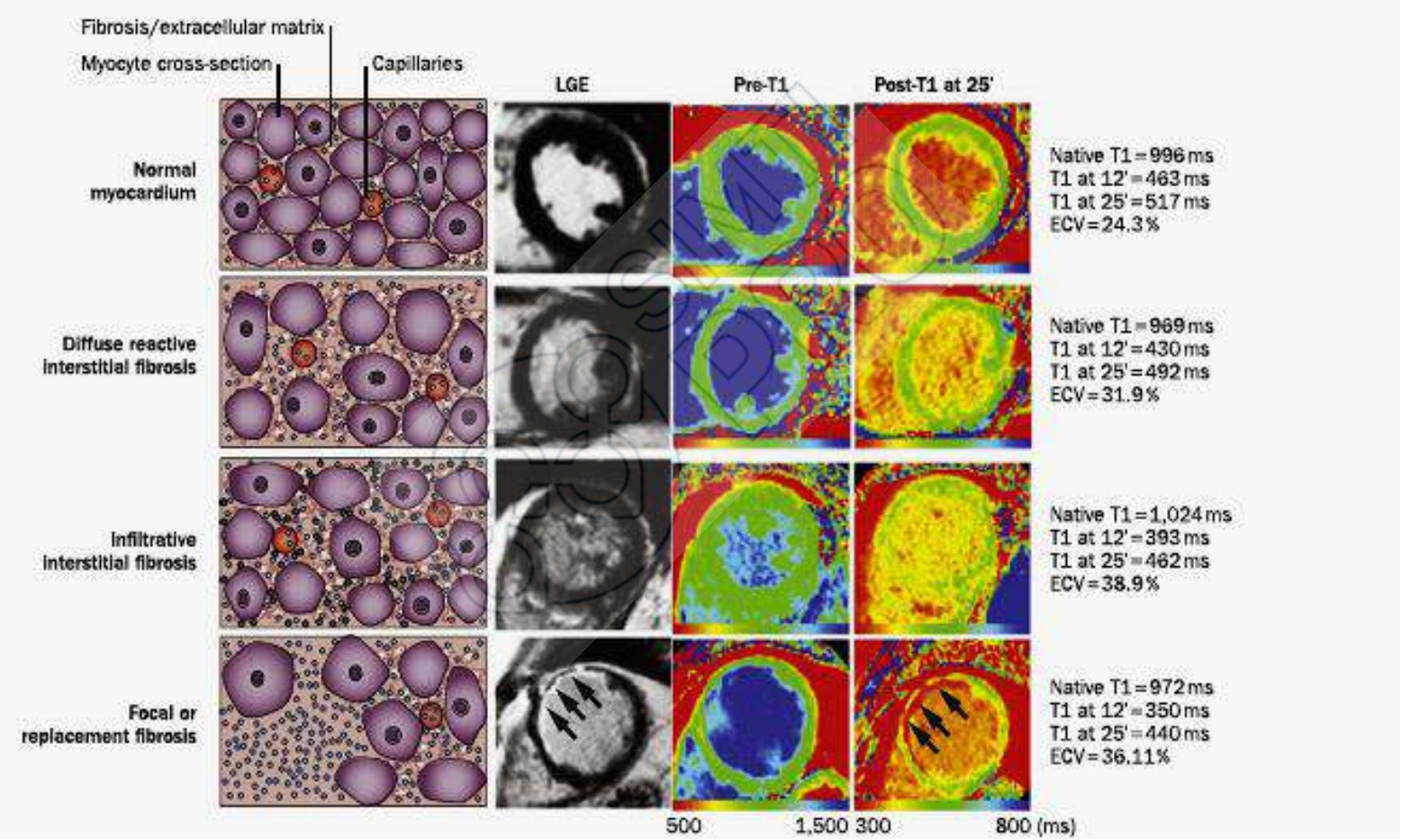

Therapeutic interventions in adults with SCD
Prevention
Acute events
Chronic complications
Patient and family education
Vaccination Program
Infection(s)
Acute VOCs
ACS
Acute anemia
Cardiovascular disease and PH
Cerebrovascular disease
Osteonecrosis
Retinopathy
Kidney Disease
Liver Disease
Iron-overload

Risk factors and Cardiovascular Disease in SCD Patients

- Tricuspidal regurgitant jet velocity (TRV)> 2.5 m/s by echo: independent risk factor for early mortality in adult with SCD
- Diastolic dysfunction (DD)
- Increased NT-proBNP, used as marker of myocardial wall stress and cardiac dysfunction
- Additional factors: LDH, Retics, % dense red blood cells

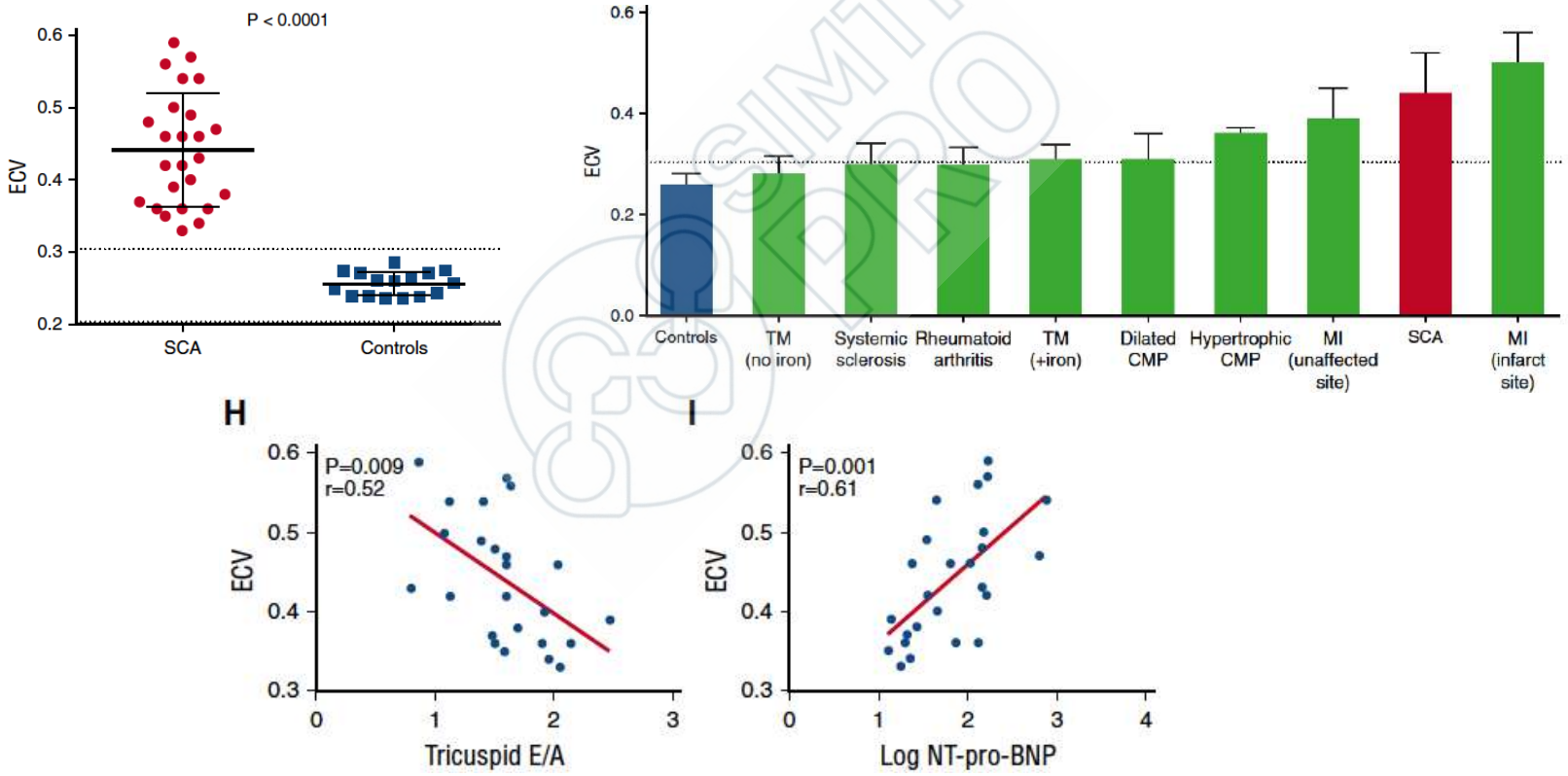
Bakeer N et al PNAS E5182-191, 2016; Damy T et al. Eur Heart J 37: 1158, 2016; Rai P et al Pediatr Blood Cancer 64: e26607, 2017; Niss O et al Blood cell Mol Dis 67: 126, 2017; Gladwin MT Lancet 387: 2565, 2016 Niss O et al Blood 130: 205, 2017.

MRI and SCD: Extracellular Volume Fraction (ECV) a marker of Heart Fibrosis



Rai P et al Pediatr Blood Cancer 64: e26607, 2017; Niss O et al Blood cell Mol Dis 67: 126, 2017;

In SCD, Increased ECV is Associated with 2 Markers of Early Mortality: Diastolic Dysfunction and NT-proBNP



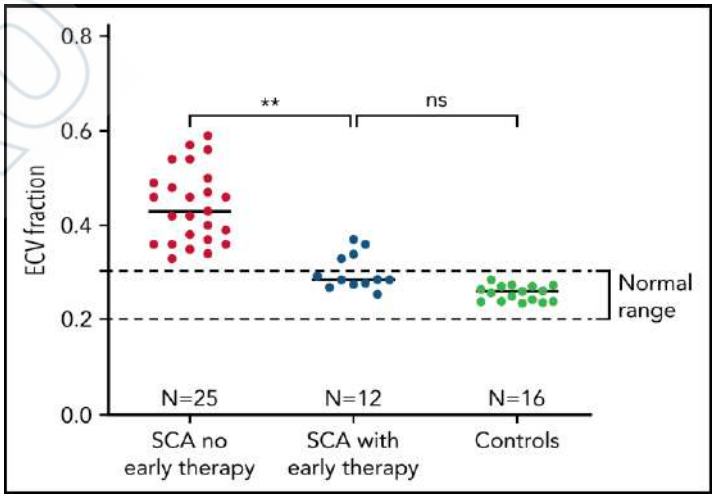
Niss O et al Blood 130: 205, 2017.

Early initiation of disease-modifying therapy can impede or prevent diffuse myocardial fibrosis in sickle cell anemia

Table 1. Characteristics of patients

ID	Age at start of therapy (y)	Age at evaluation (y)	Sex	Therapy	Duration of therapy (y)	ECV*	Diastolic classification
CCH01	2.3	11	Male	Chronic transfusions, hydroxyurea	8.9	0.29	No diastolic dysfunction
CCH02	2.7	17	Female	Chronic transfusions	14.6	0.27	No diastolic dysfunction
CCH03	1.7	8	Male	Chronic transfusions, hydroxyurea	6.6	0.26	Inconclusive
CCH04	1.9	7	Female	Chronic transfusions, hydroxyurea	5.9	0.29	No diastolic dysfunction
CCH05	1.1	7	Male	Chronic transfusions	6.5	0.34	No diastolic dysfunction
CHL01	3	28	Female	Chronic transfusions	24.9	0.37	No diastolic dysfunction
CHL02	3.4	24	Female	Hydroxyurea	20.9	0.28	No diastolic dysfunction
CHL03	3.2	19	Female	Chronic transfusions	15.8	0.28	No diastolic dysfunction
CHL04	4.5	22	Female	Hydroxyurea	17.4	0.28	No diastolic dysfunction
CHL05	5.4	21	Female	Chronic transfusions	11.7	0.36	Inconclusive
CHL06	5.5	23	Female	Hydroxyurea	17	0.33	No diastolic dysfunction
CHL07	2.4	16	Male	Hydroxyurea	13.7	0.29	No diastolic dysfunction

*ECV for normal controls: 0.26 ± 0.02; ECV for patients with untreated SCA: 0.44 ± 0.08.

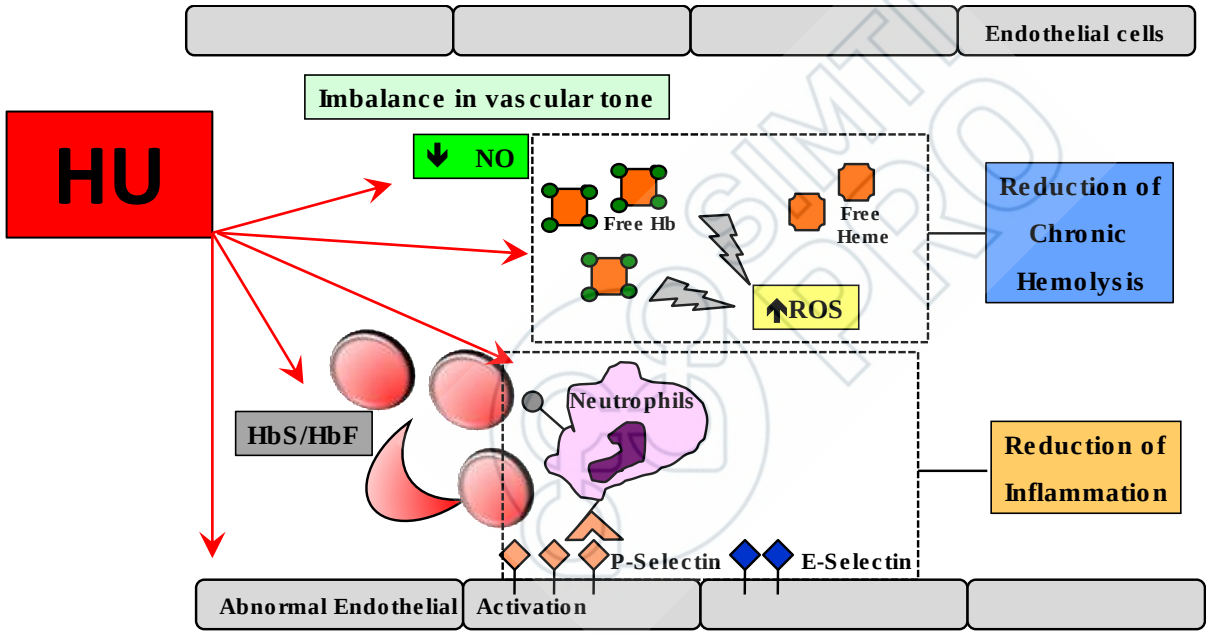


Niss O et al Blood 140: 1322, 2022.

Available Treatment for SCD in EU

- **Hydroxyurea**
- **Disease modifing agents:** voxelotor
- **Transfusion strategies:** acute or chronic regimens
- **Bone marrow transplantation**

HU is a Multimodal Therapy



Platt OS NEJM 358: 1362, 2008; Saleh AW et al. 102: 31, 1999; Charache S et al. 34: 15, 1997; Yarbro JW et al. 19: 1-10, 1992 ; Maier ER et al Pediatric Res doi 10/1038, 2016;

HU and SCD in EU

Start HU treatment 15-20 mg/kg/d		
United States	**Europe**	**UK**
Consensus After age 9 mo, regardless of clinical severity	No consensus Common selected indications: • Recurrent VOC and/or ACS • After a period of transfusion and normalization of TCD in patients who have had an abnormal TCD finding • Baseline Hb level <7 g/dL • Renal impairment • Chronic hypoxemia • Cerebral silent infarct • Conditional velocities on TCD	After age 9 mo, regardless of clinical severity

ACS, acute chest syndrome; Hb, hemoglobin; HU, hydroxyurea; TCD, transcranial Doppler ultrasonography; VOC, vaso-occlusive crisis.

de Montalembert M et al Hematology 490, 2019

Adherence to HU is a Challenge in SCD

- **35-50% SCD patients achieve high adherence to HU therapy;**

- **Multiple factors:**
  - Chronic medication
  - Socio-economic reasons
  - Adhesion barriers related to adolescence and transition from pediatric care to adult care.

Inoue S et al. Int J Hematol 104: 2000, 2016; Han J et al Pharmacotherapy doi 10.1002/phar.1834, 2016; Cerary S et al. JMIR Res Protoc 5: e193, 2016; Green S et al Pediatr. Blood Cancer 63: 2146, 2146; 2016; Green NS et al ASH poster #1310, 2016