

2017



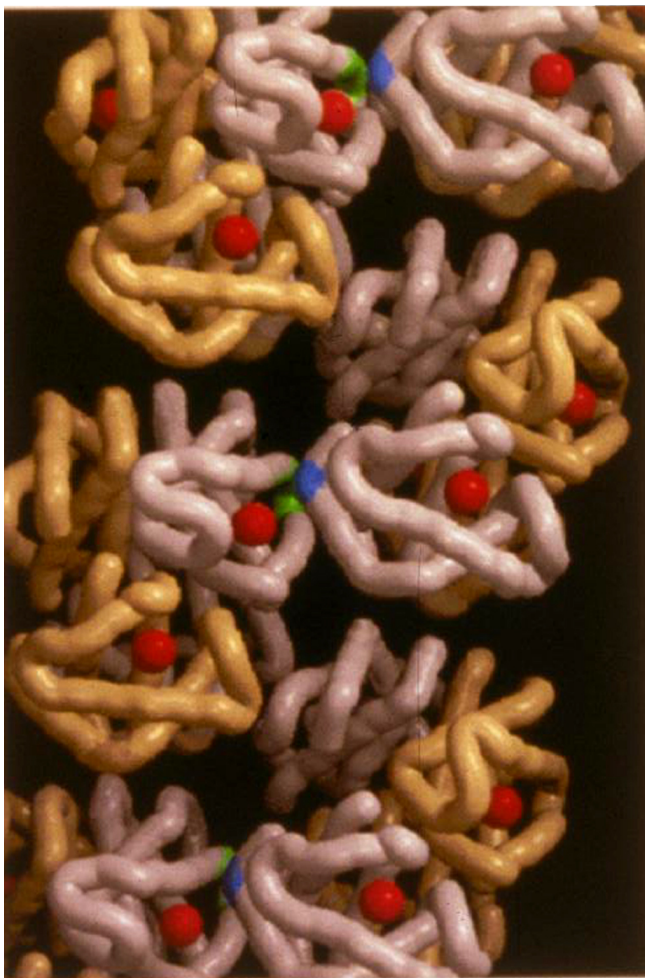
Progetto Ematologia Romagna

Le Anemie Congenite del Migrante: Anemia Falciforme

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2017



MOLECULES

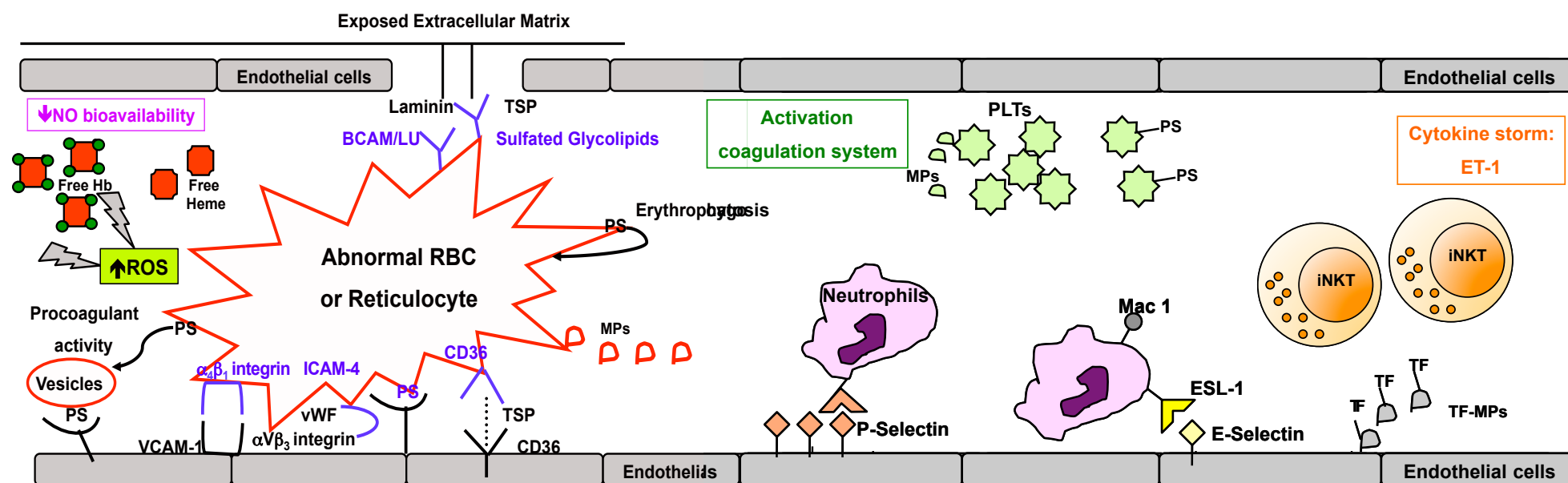


POLYMER



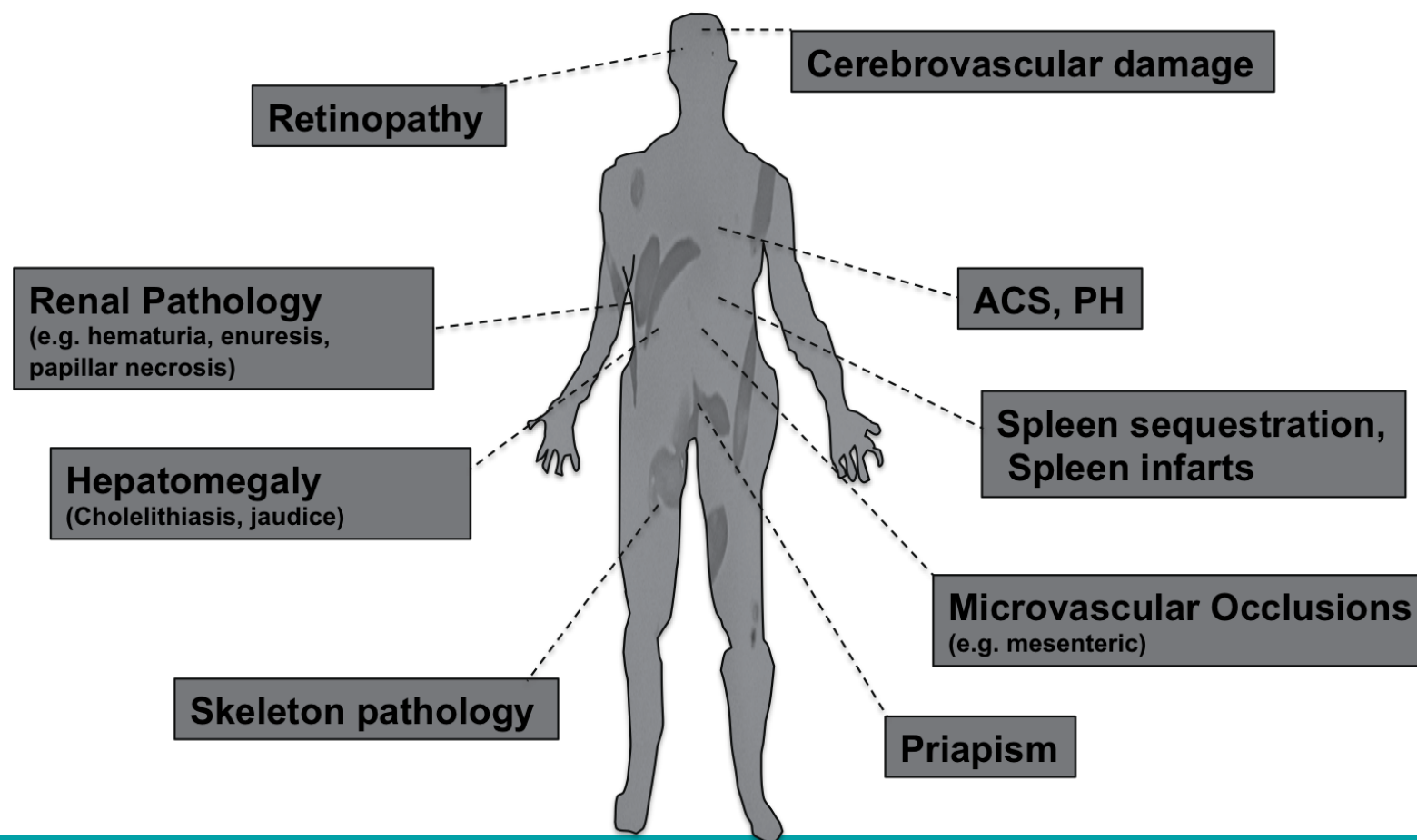
CELLS

The High Biocomplexity of SCD Substains Multi-Organ Damage



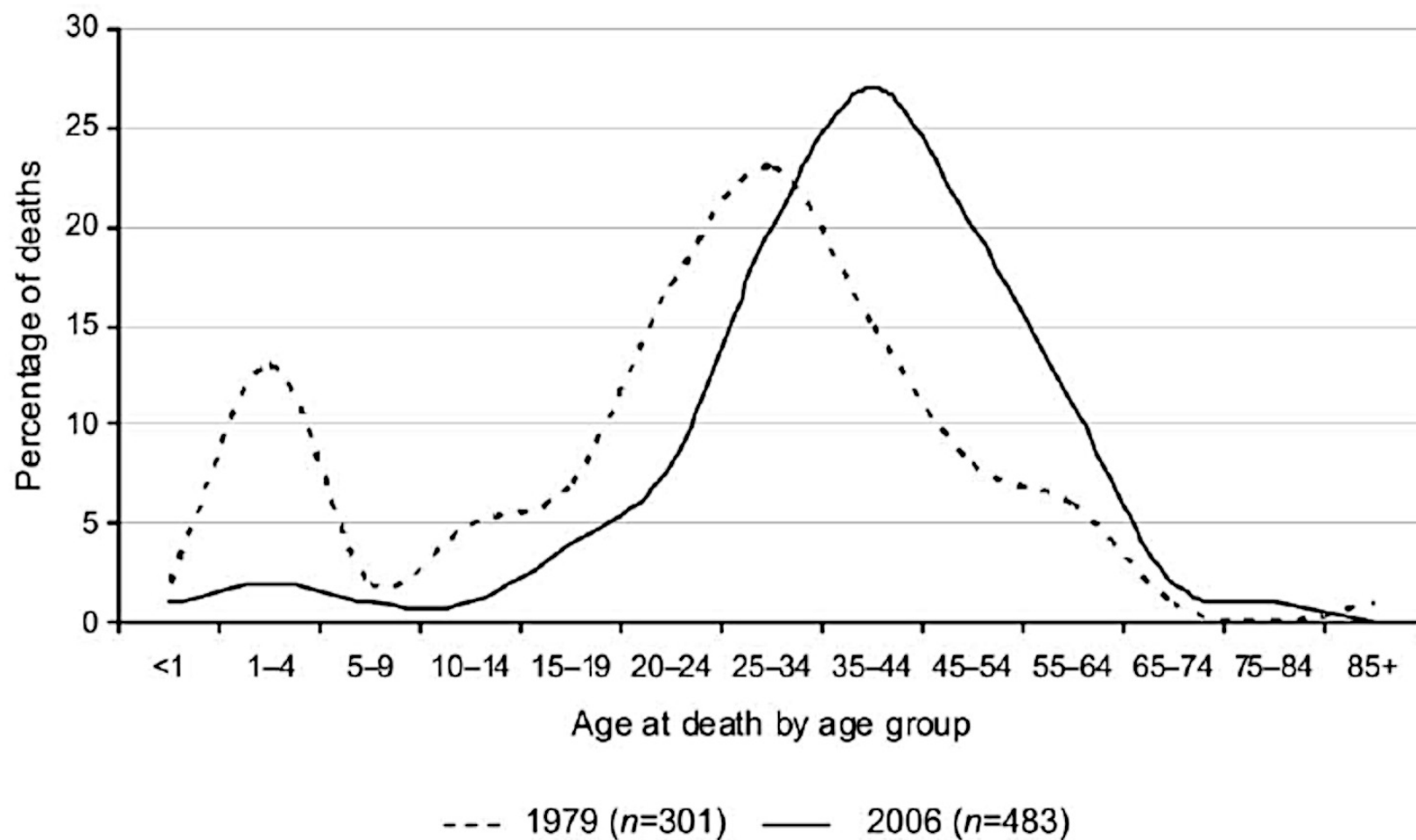
Modified from De Franceschi L et al. *Seminars in Thrombosis*, 37: 266; 2011; De Franceschi L *Haematologica* 100 (S3): 195-7, 2015

SCD is a Monogenic Disorder but Multiorgan Disease





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Hassel K et al. 38: 5512, 2010; Ngo S et al Blood 124: abstract 2715; 2015

Risk Factor for Early Death in a Cohort of Adult SCD Patients

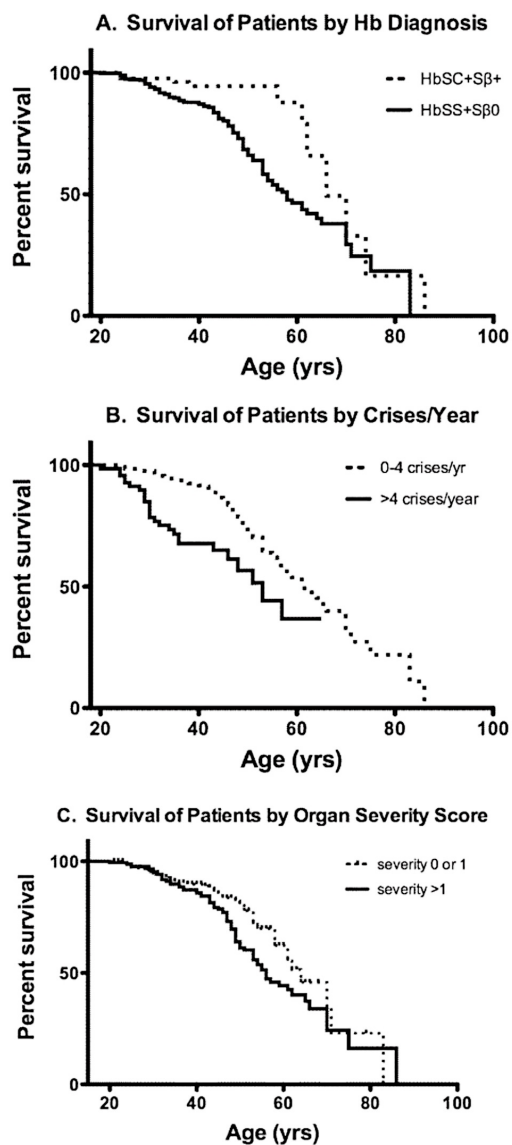
Trait	N	Hazard ratio	P-value
Hemoglobin (off HU)	362	1.21	0.0043
Hemoglobin (off HU) adjusted for GFR	319	0.93	0.3277
Hemoglobin (on HU)	168	1.36	0.0107
Hemoglobin (on HU) adjusted for GFR	157	0.83	0.1785
WBC (off HU)	351	1.06	0.0419
WBC (on HU) ^a	168	1.63	0.3181
Platelets (off HU)	350	1.00	0.9402
Platelets (on HU) ^a	167	0.65	0.3066
Fetal hemoglobin (off HU) ^a	180	1.00	0.9954
Fetal hemoglobin (on HU) ^a	124	0.79	0.3199
Ferritin ^a	153	1.27	0.0628
Mean corpuscular volume (off HU)	361	1.01	0.5220
Mean corpuscular volume (on HU)	168	1.02	0.2582
Lactate dehydrogenase ^a	382	0.82	0.1621
Reticulocytes (off HU) ^a	313	1.01	0.9663
Hemolytic index ^b	313	1.10	0.3206
Total bilirubin	410	1.01	0.8887
GFR	414	1.07	<0.0001
Body mass index	343	0.98	0.3138
Body mass index adjusted for HU	317	0.98	0.2711
NT-pro-BNP ^a	87	1.62	0.0004
sICAM-1	87		0.1376
sVCAM-1	87	2.03	0.0003
E-Selectin	87		0.1513
P-Selectin	87		0.8673
sCD40L	87		0.8235
IL-6	87		0.6459
IL-8	87		0.9505
IL-10	87		0.5447
TNF- α	87		0.5876

Abbreviation: HU, hydroxyurea.

^a Variables converted to logarithmic scale.

^b Calculated in subjects with Hb SS and Hb S β^0 only.

Elmariah H et al. AJH 89: 530, 2014



Association between patients survival:

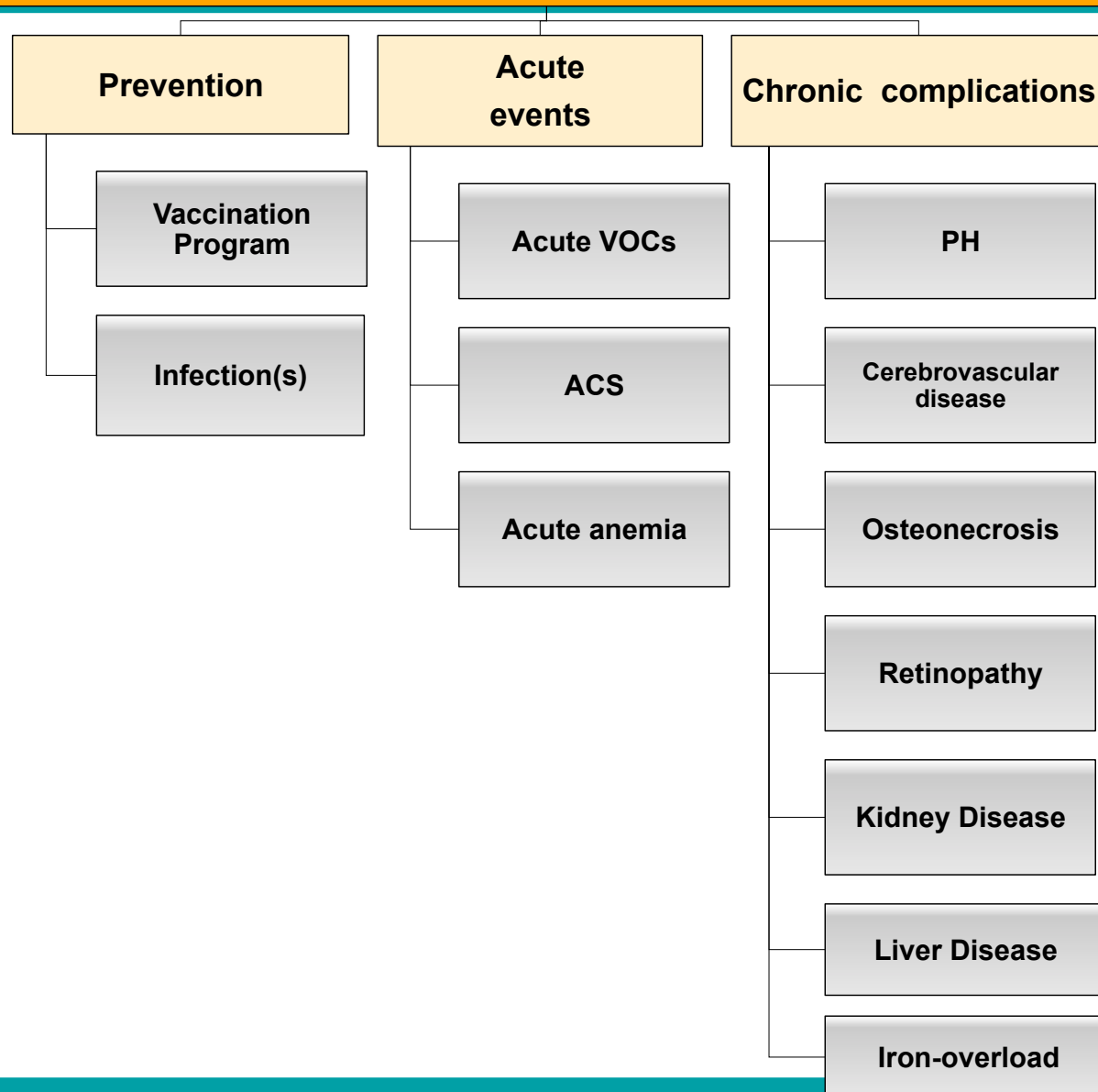
- Pain frequency
- Hospitalization
- Narcotic use

Elmariah h et al. AJH 89: 530, 2014



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Therapeutic Interventions in Adult with SCD



**Gli eventi vaso-occlusivi acuti rendono i pazienti affetti da SCD
i piu' grandi utilizzatori dei Dipartimenti di Emergenza
rispetto ad altre emoglobinopatie con gravi manifestazioni
d'organo .**

Carroll CP Am J Hematol 84: 666, 2009; Brousseau DC JAMA 303: 1288, 2010



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Acute Events Responsible For Admission Of Sickle Cell Patients To The Emergency Department

<i>Acute Events</i>
Acute painful crisis
Acute chest syndrome (ACS)
Acute abdominal pain
Pneumonia
Septicemia
Priapism

Caroll CP et al Am J Hematol 84: 666, 2009; Miller ST Blood 117: 5297, 2011; Vichinsky EP et al NEJM 342: 1855, 2000; Brousseau DC et al. JAMA 303: 1288, 2010; Brodsky MA et al. Am J Med doi: 10.1016/j.amjmed.2016.12.0101, 2017



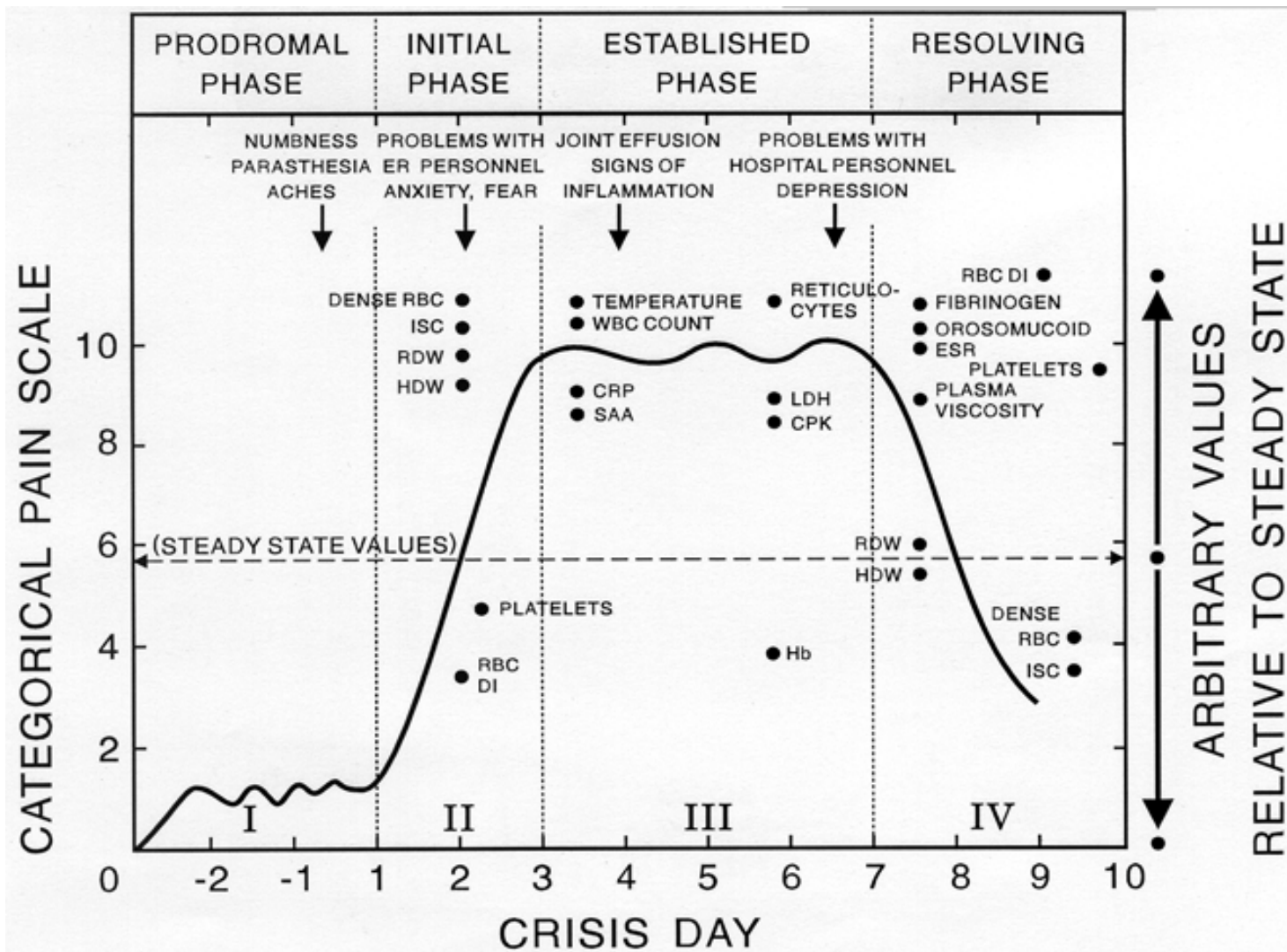
Crisi Vaso-occlusive acute (VOCs) o crisi dolorose in SCD

**Le VOCs sono le complicanze acute piu' frequenti nella SCD -->
*rate di 0.8 episodi/anno.***

•Gli elementi trigger sono:

- **Esposizione a:** freddo, altitudine, sbalzi rapidi di temperatura (caldo-freddo), alcol, tabacco, droghe (cocaina, anfetamine), esercizio fisico
- **Malattie respiratorie:** asma, tonsillite ostruttiva, rinite allergica, sindrome delle apnee notturne
- **Trigger vascolari:** compressione arteriosa involontaria, ipertensione arteriosa, esposizione ad agenti con azione adrenergica, disidratazione
- **Altri fattori:** eventi emotivi intensi, stress psico-emozionali, lavoro eccessivo, infezioni acute, chirurgia addominale

•Nella maggior parte delle VOCs non si riconosce peraltro il trigger iniziale e si sviluppa gradualmente



Ballas SK (ASH meeting) Hematology 97, 2007

Il Dolore In Corso Di VOCs

- **Dolore Nocicettivo**

- Danno infiammatorio tissutale (VOC)
- Vasospasmo
- Rilascio di citokine vaso-attive (ET-1)

- **Dolore Neuropatico**

- Rilascio di molecole neuromodulatrici (PGE2, serotonin)
- Danno diretto del distretto nervoso (nerve ischemia from VOC, nerve compression, nerve injury)

- **Dolore Idiopatico**

- Dolore senza causa riconosciuta

Francis & Johnson, 1991; Song & Carr, 1999; Brandow AM et al Pain 158, S79, 2017



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The PiSCES Study: Pain in Sickle Cell Epidemiology Study

- The mean pain did not differ by: gender, age or genotype
- Pain crisis are more frequent in SCD subjects: depressed or older than 45 years of age
- The number of pain sites only moderately correlates with pain intensity
- The most common pain sites are: lower back, knee/shin and hip.

McClish DR et al. Pain 145: 246, 2009;
Taylor ELV et al. J Pain symptom Manage 40: 416, 2010



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Strategie per il Controllo del Dolore nella SCD

- Pazienti con SCD e dolore toracico hanno un *aumento della frequenza respiratoria con bassi volumi di ventilazione alveolare*. Questo quadro respiratorio e' migliorato da un'efficace analgesia
- *Il management efficiente del dolore durante una VOC e' l'obiettivo primario* da raggiungere per ridurre l'incidenza di manifestazioni cliniche acute piu' gravi come l'ACS

Needleman JP et al. Chest 122: 43, 2002; Darbaris DS et al J. Pain 12: 531, 2011



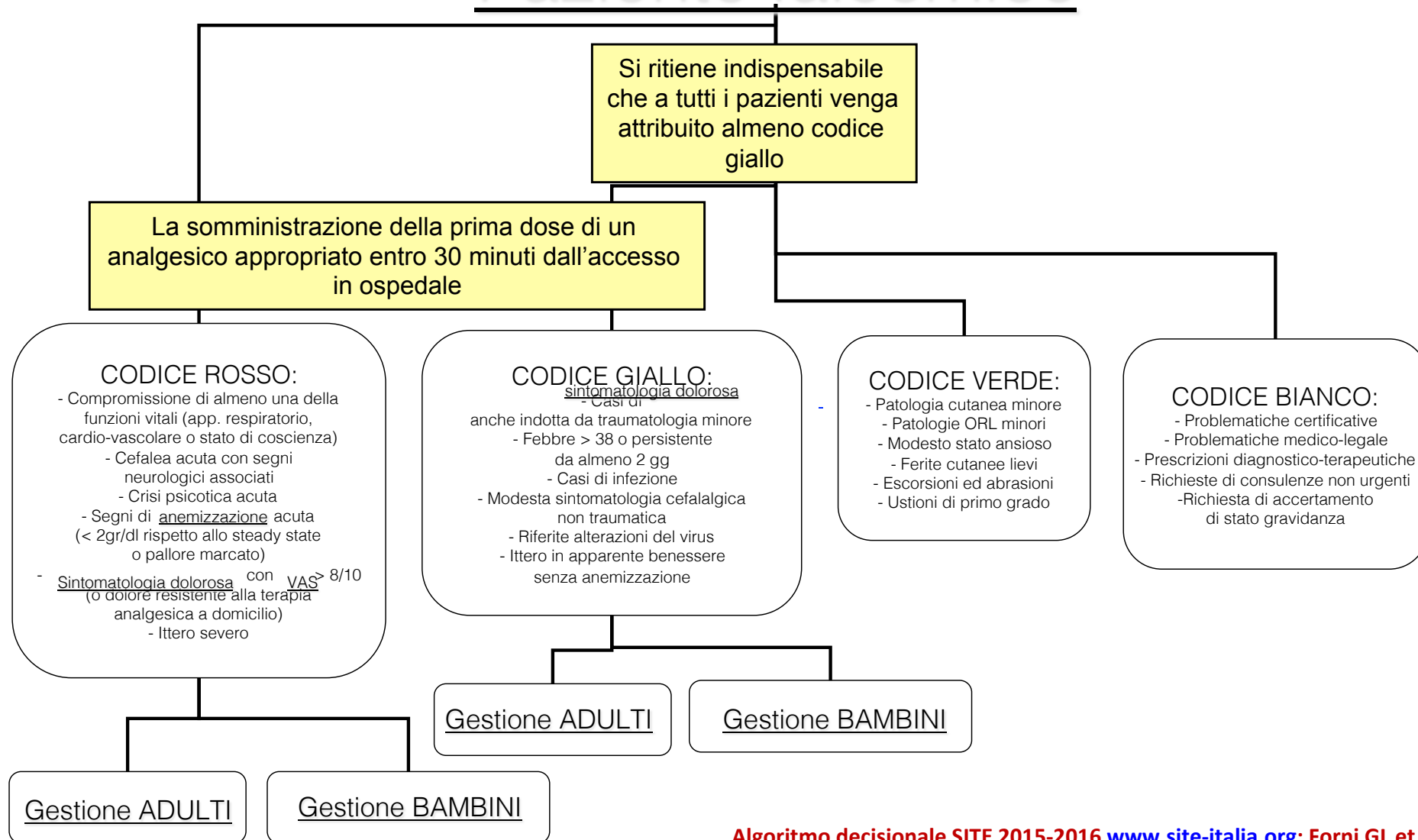
Strategie Per Il Controllo Del Dolore: Trattamento Combinato (Co-administration)

- **FANS che interferiscono con la trasduzione del segnale del dolore**
- **Oppioidi maggiori che influenzano la trasmissione e la modulazione nocicettiva e se usati in forma sistemica la percezione del dolore .**

Linee guida ENERCA 2013; Linee Guida SITE 2015- Algoritmo decisionale SITE 2015-2016
www.site-italia.org; De Franceschi L et al. Pain and Practice 16: 680, 2016;
De Franceschi L et al. Haematologica 89: 1389, 2004

TRIAGE

Paziente falcemico



Algoritmo decisionale SITE 2015-2016 www.site-italia.org; Forni GL et al
Orphanet J Rare Dis 9: 91, 2014

ABBREVIAZIONI: AAIL: arti inferiori; AASS: arti superiori; AF: Anemia Falciforme; EBPM: Eparina a basso peso molecolare; ECG: elettrocardiogramma; EEX: scambio eritrocitario; FC: frequenza cardiaca; FR: Frequenza respiratoria; Hb: Emoglobina; HbS Emoglobina S; IRA: insufficienza renale acuta; IRC: insufficienza renale cronica; ORL: otorinolaringoiatra; PA: pressione arteriosa; PCR: Proteina C Reattiva; PPI: inibitori pompa protonica; PLS: Pediatra di Libera Scelta; SPO2: saturazione parziale ossigeno; T.C.: Temperatura Corporea; VAS: scala del dolore; VOC: Sindrome vaso-occlusiva; ACS: Acute Chest Syndrome (ogni comparsa di un nuovo infiltrato polmonare)

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Somministrazione della prima dose di analgesico entro 30 minuti,
incluso il tempo trascorso in Triage, dall'accesso in ospedale

Bolo ev :TRAMADOLO 50 mg (1/2 fl ev)

dettagli

Peso in Kg.	Velocità d'infusione (cc/h)*
40 Kg	20 cc/h
50 Kg	30 cc/h
60 Kg	35 cc/h
70 Kg	40 cc/h

*velocità massima calcolata in base al dosaggio massimo giornaliero del tramadolo.

Sol fisiologica 0,9% 500 ml
KETOROLAC 10 mg 3 fl (Se IRA o IRC sostituire con Paracetamolo 500 mg ev per 2/die)
TRAMADOLO 100 mg 3 fl
METOCLOPRAMIDE 10 mg 3 fl (Se IRA o IRC: 2 fl)

DOPO 30 Minuti: ANALGESIA OTTENUTA?

SI
continuare l'infusione

NO
sospendere l'infusione per un'ora, poi infondere

MORFINA 5 mg ev in bolo (1/2 fiala da 10 mg)

Sol fisiologica 0,9% 500 ml

MORFINA 10mg 5 fl

METOCLOPRAMIDE 10mg 3 fl

Idratazione per via parenterale (soluzione fisiologica 0,9% 1000 cc +
glucosata 5% 1000 cc); almeno 1000 cc di idratazione con soluzione
fisiologica 0,9% prima dell'eventuale scambio eritrocitario

PPI: Pantoprazolo 1 fiala/die

EBPM a dose anticoagulante (entro 6-8 ore)

DOPO un'ora: ANALGESIA OTTENUTA

SI
continuare l'infusione

NO
continuare l'infusione e aggiungere

FENTORA cp orosolubile (Fentanyl citrato 100 mcg)
ripetibile dopo 30-60 min se ancora dolore in concomitanza all'infusione con terapia
antalgica bilanciata

Monitorare parametri vitali e stato di sedazione

(se FR $\leq$ 12 atti/min: attenzione!) o eccessiva sedazione o coma

SOSPENDERE fino a normalizzazione / NARCAN 0,4 mg ev (Naloxone fl 0,4 mg/ml)

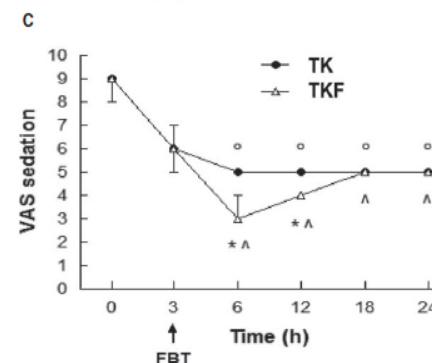
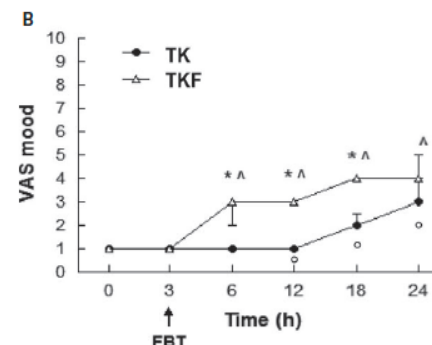
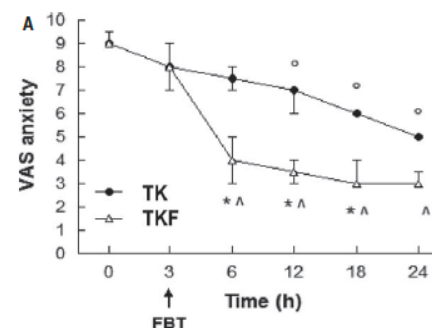
Gestione
CODICE
ROSSO - Adulti

Triage

Paziente falcemico

PROGETTO EMATOLOGIA – ROMAGNA

Ravenna, 25 marzo 2017



De Franceschi L et al. Pain and Practice 16: 680-687, 2016



Possible Causes of Acute Pain Interesting Bone-Muscle District(s)

- Bone infarction
- Aseptic necrosis of bone: ephiphyseal segments of the humeri and especially of the femora
- Osteoporosis/ vertebral collapse
- Osteomyelitis
- Pain interesting a joint, associated with fever and local signs of arthritis-> *consider septic arthritis*

De Franceschi L et al Haematologica 89: 1389, 2004; De Franceschi L et al. Haematologica 88 (suppl. 6) 59, 2003; De Franceschi L. et al. Pain and Practice 16: 680, 2016

Transfusion Strategy and Acute Pain Crisis

- In severe acute SCD pain crisis transfusion strategy is crucial and might be offered as:
 - Partial manual red cell exchange,
 - erythrocytoapheresis
 - simple red cell transfusion
- The goal is to rapidly reduce HbS levels and to restore patients hemoglobin levels -> not more than 10-11 g/dL to avoid complications related to blood hyperviscosity
- Exchange trasfusional strategy should always be considered in patients with Hb > 9 g/dL

Raphael JL et al. *Pediatr Blood Cancer* 51: 82, 2008; Ware MA et al 104: 93, 1999; Benjamin LJ et al. *Blood* 95: 1130, 2000; Wright J et al. *Br J Haematol* 126: 878, 2004; Delville M et al. *Am J Hematol* 92: 136, 2017; Sarode R et al. *J Clin Apher* doi: 10.1002/jca.21511, 2016; Kelly S et al *Transfusion* 56: 2877, 2016



Treatment of Uncomplicated Pain Crisis in Day-Hospital

- SCD children or adult patients with pain VAS < 7
- Two-Three consecutive days treatment with hydration intensive pain management supported by home treatment overnight with oral analgesic and anti-inflammatory agents
- This approach is well accepted by patients and represents an interesting alternative cost-effective care delivery system

Scmalezer EA 41, 1987; Lottenberg R 58, 2005; Vichinsky EP 333, 1995; Haberken CM 89, 1997; Neumayr L 57, 1998; Vichinsky EP 2010

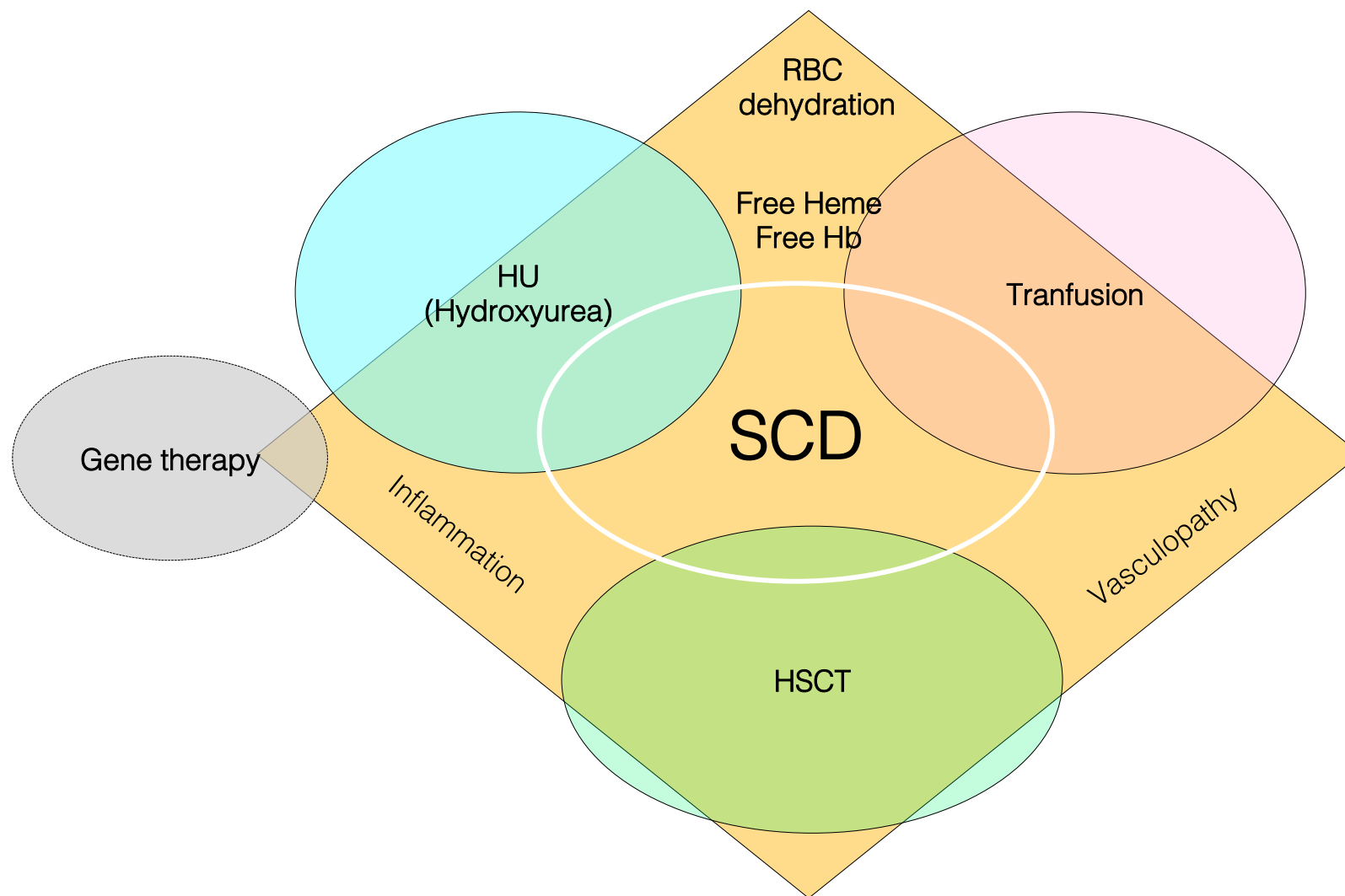
Risk Factors For 30-day Readmission In Adults With SCD After an Acute Event

Pneumonia
Asthma
Heart failure
Diabetes mellitus

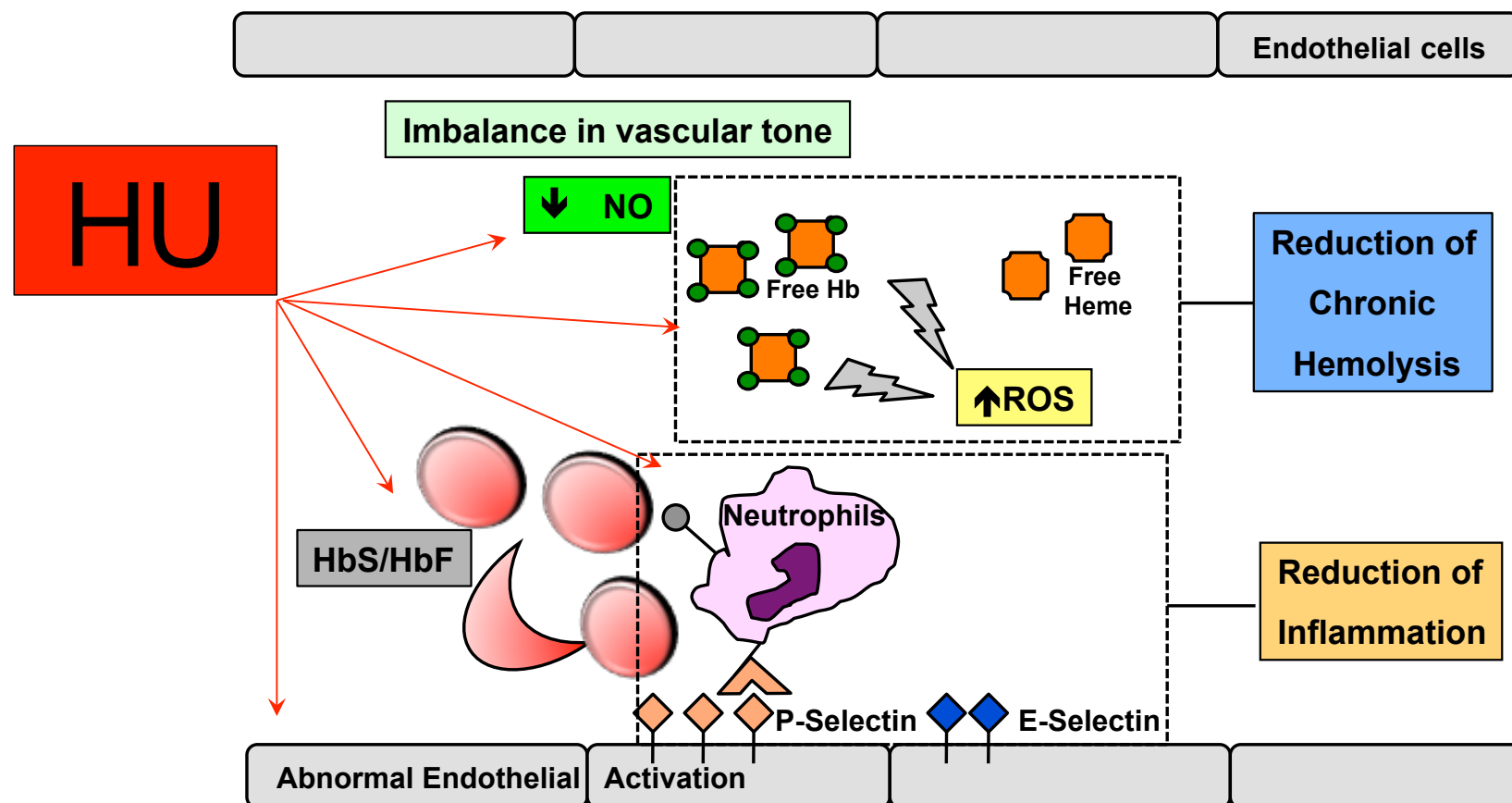
- **Indicators:** *14 d* to assess the quality of care related to hospitalization; *30 d* to assess the quality and access to ambulatory care
- 1: 3 patients is rehospitalized in 30 days: 50% SCD adult and 30% SCD children
- **Risk factors:** # of VOCs requiring hospitalization in the prior year.
- The young adult 18-30 years old are particularly at risk-> *their disease worsens and the transition from pediatric to adult care*

Carroll CP et al Am J Hematol 84: 666, 2009; Brousseau DC et al. JAMA 303: 1288, 2010; van Such M et al 15: 2006; Ballas SK et al. 79: 17, 2005; Brosky MA et al Am J Med pii: S0002-9343, 2017

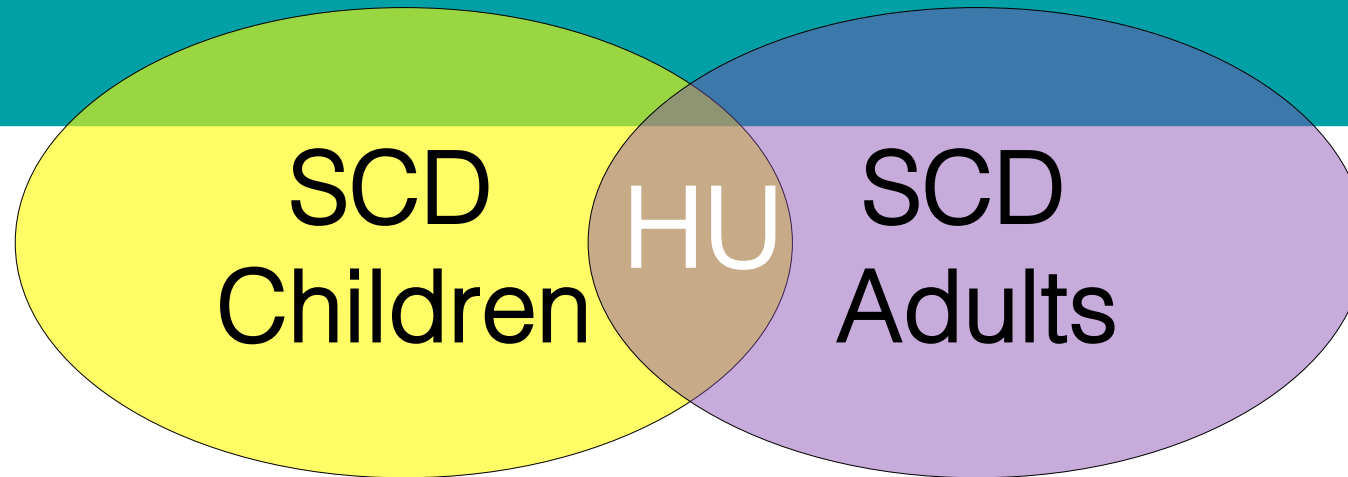
Available Treatments for SCD



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; Yarbrow JW et al. 19: 1-10, 1992 ;
Maier ER et al Pediatric Res doi 10/1038, 2016



In SCD, HU ameliorates mortality and morbidity and reduces

- Frequency of VOC and rate of hospitalization
- ACS
- Transfusion requirements
- Severe dactylitis in SCD pediatric population

Wong TE et al Blood Epub Oct 2014; Crosby LE et al. Pediatr Blood Cancer Epub 2014; Voskaridou E et al. Blood 115: 2354, 2010; Wang WC et al. The Lancet 377: 1663, 2011; Yawn BP et al JAMA 312: 1033, 2014.



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HU as Acceptable Alternative to Chronic Transfusion in SCD Children with History of TCD Abnormalities

- In SCD children under chronic transfusion regime, a careful transition to HU might be considered with normal TCD, maintaining every 3 months TCD follow-up;
- Identified predictive factors for reversion to abnormal TCD velocities:
 - Before HU: High retic count ($> 400 \times 10^9$ cells/uL)
 - After HU: WBC.

Bernaudin F et al Blood 127: 1814, 2016; Helton KJ et al Blood 124: 891; 2014 ; Ware RE Blood 119: 3925; 2012; Ware RE et al Lancet 387: 661-70, 2016



Adherence to HU is a Challenge in SCD

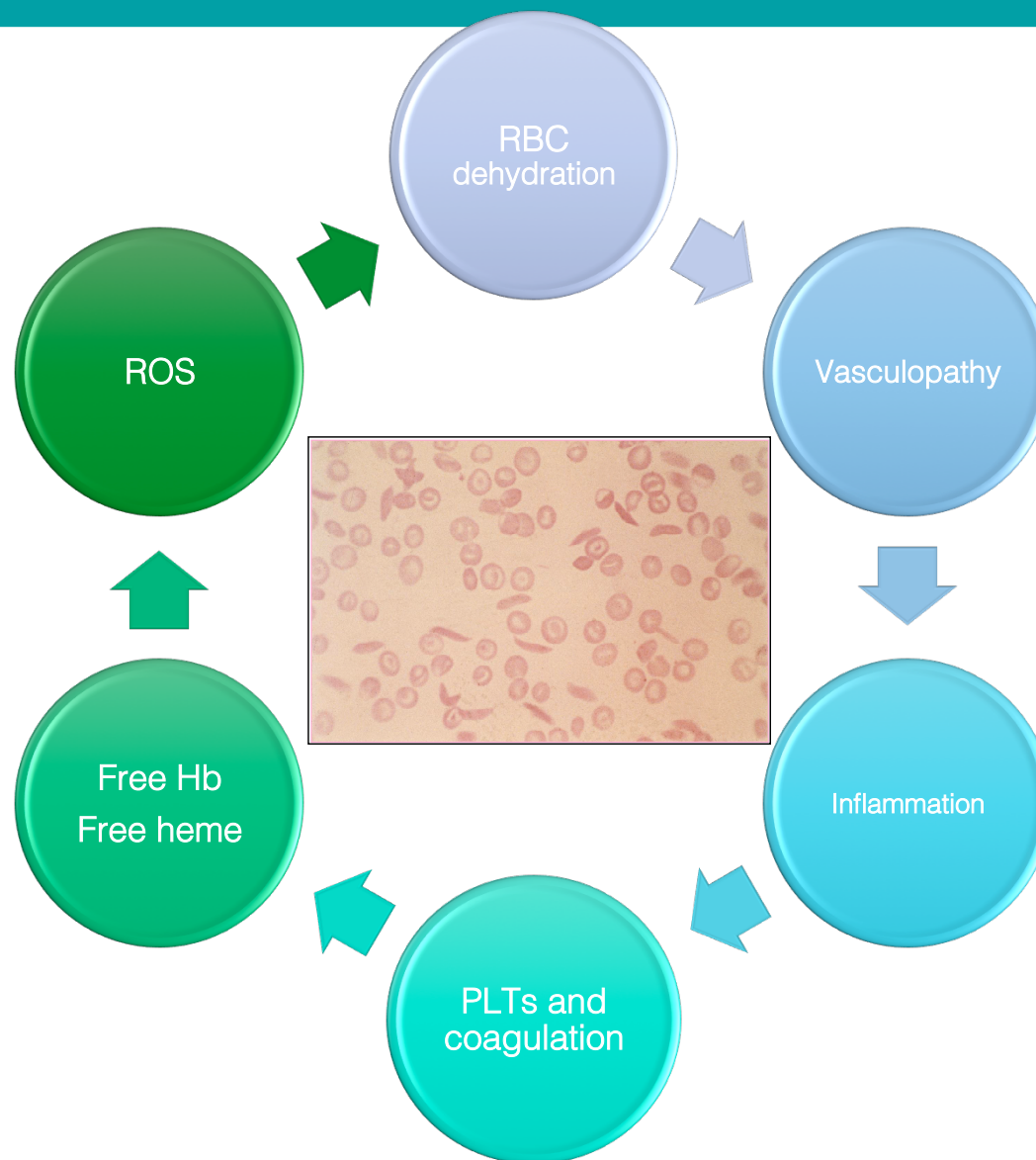
- 35-50% SCD patients achieve high adherence to HU therapy;
- Multiple factors:
 - Chronic medication
 - Socio-economic reasons
 - Adhesion barriers: adolescence and transition from pediatric to adult care
- Ongoing studies on adherence to HU therapy:
 - Implementation of pharmacy service
 - Glowcap device
 - HABIT study: home visits by CHN and text messaging seem to be effective

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



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SCD Requires Multitarget Treatment





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Emerging New Treatments in SCD: Block of Selectins

- **Endothelial cell P-selectins are cell adhesion molecules**
- **P-selectins play a key role in leukocyte recruitment and sickle red cell adhesion to endothelium**
- **P-selectin values are increased in plasma of SCD patients**

Pan J JBC 273: 10058, 1998; Matsui NM Blood 98: 1955, 2001; Turhan A PNAS 99: 3047, 2002; Kato GJ Br J Haematol 130: 943, 2005; Blann AD J Thromb Thrombolysis 25: 185, 2008.

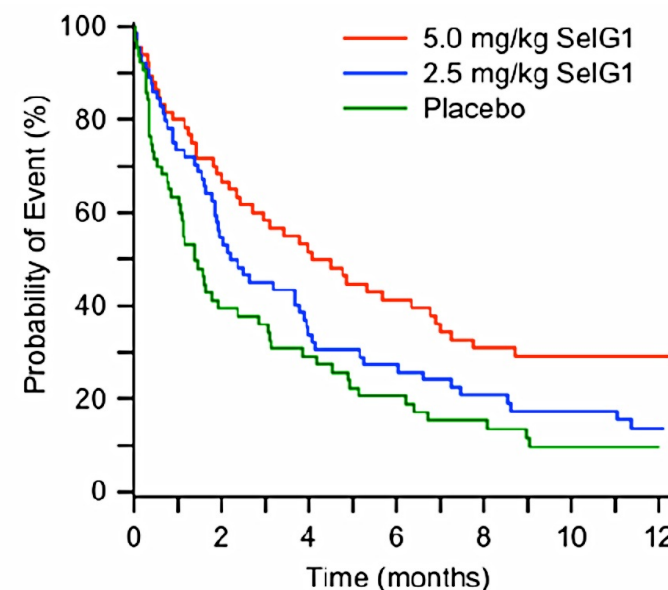


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Humanized Monoclonal Ab against P-selectin (SelG1-Crizanlizumab)

In a double blind placebo-controlled multinational trial, **SelG1**:

- was safe and well tolerated
- Induced a 1 month P-selectin block
- Reduced pain crisis
- Increased the time between pain crisis



Mandarino D et al Blood 122: abstract 970, 2013; Telen MJ Blood 127: 810-19, 2016; Ataga KI et al abstract 1, 2016; Ataga KI et al. NEJM 376: 429, 2017



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CONCLUSIONS

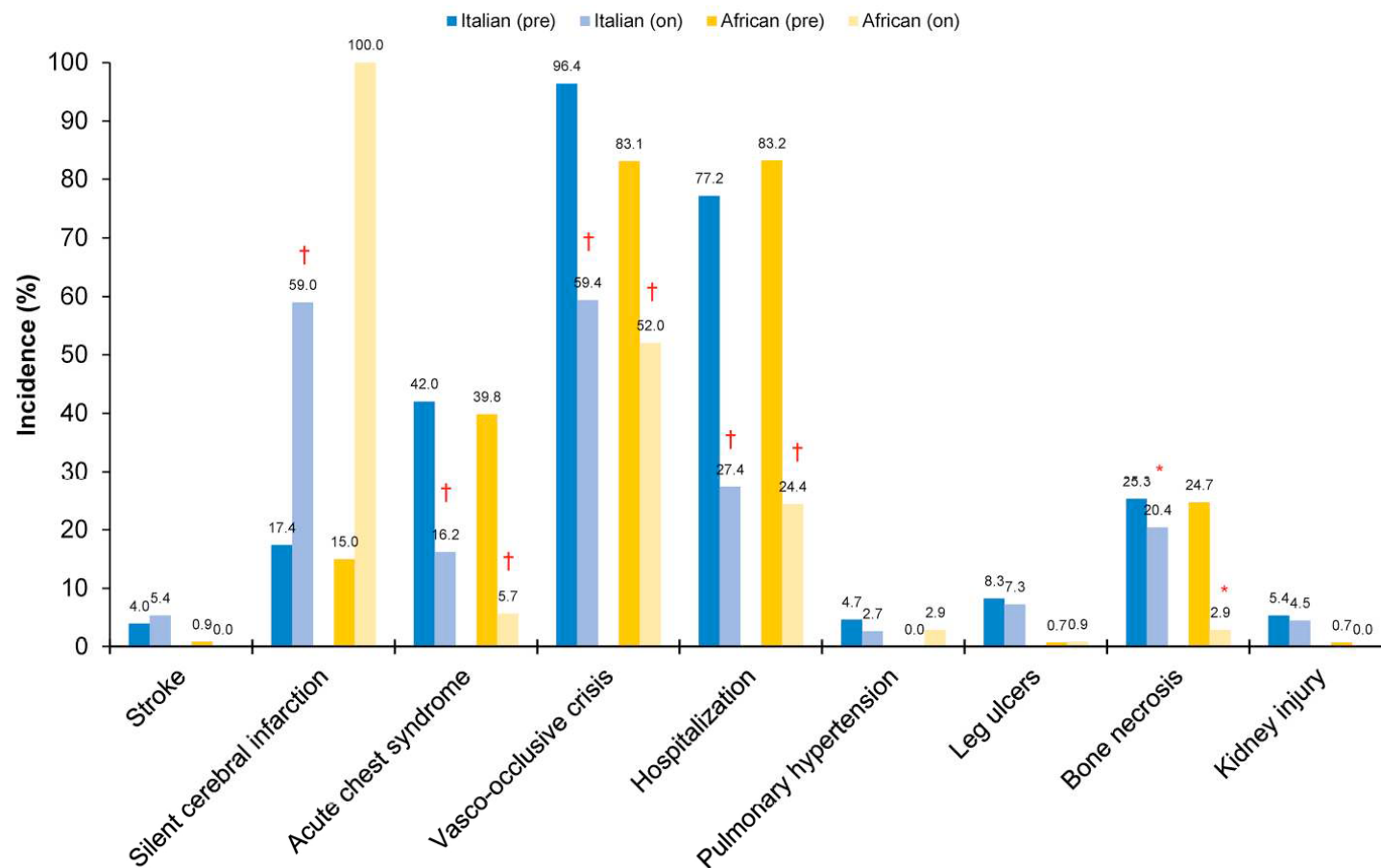


PROGETTO EMATOLOGIA – ROMAGNA

Ravenna, 25 marzo 2017

Table I. Patients' characteristics (n=628).

Parameter	Value
Age in years, mean $\pm$ SD, median (range)	24.5 $\pm$ 15, 24.0 (range: 1.0-67.0)
Age category in years, n/N (%)	
<18	209/554 (32.7)
$\geq$ 18	345/554 (67.3)
Male, n/N (%)	320/622 (51.4)
Origin, n/N (%)	
Italy	354/621 (57.0)
Africa	215/621 (34.6)
Other	52/621 (8.4)
Genotype, n/N (%)	
β S/ β S	277/594 (46.6)
β^0 / β S	167/594 (28.1)
β^+ / β S	131/594 (22.1)
Other	19/594 (3.2)
SD, standard deviation.	



Incidence for post- compared with on-hydroxyurea: * $p < 0.05$; ** $p < 0.01$; † $p < 0.001$

Rigano P et al. submitted 2017
SITE & AIEOP study