NUOVE TERAPIE: DREPANOCITOSI

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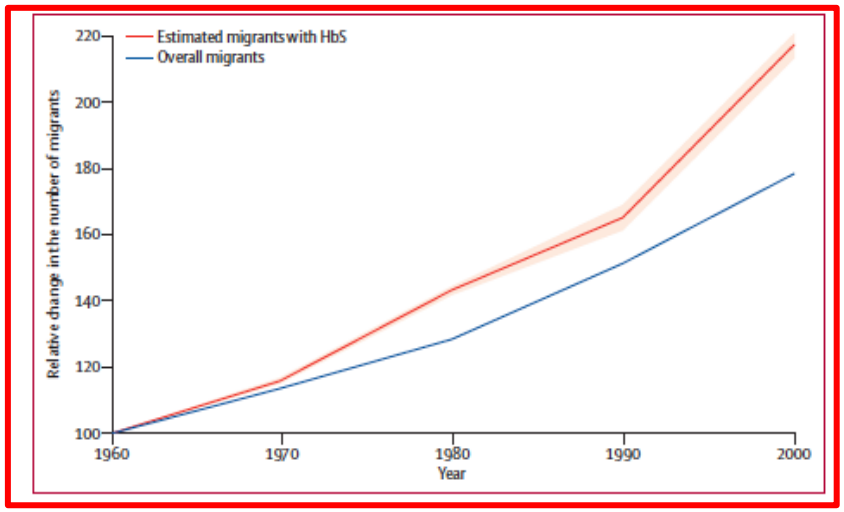
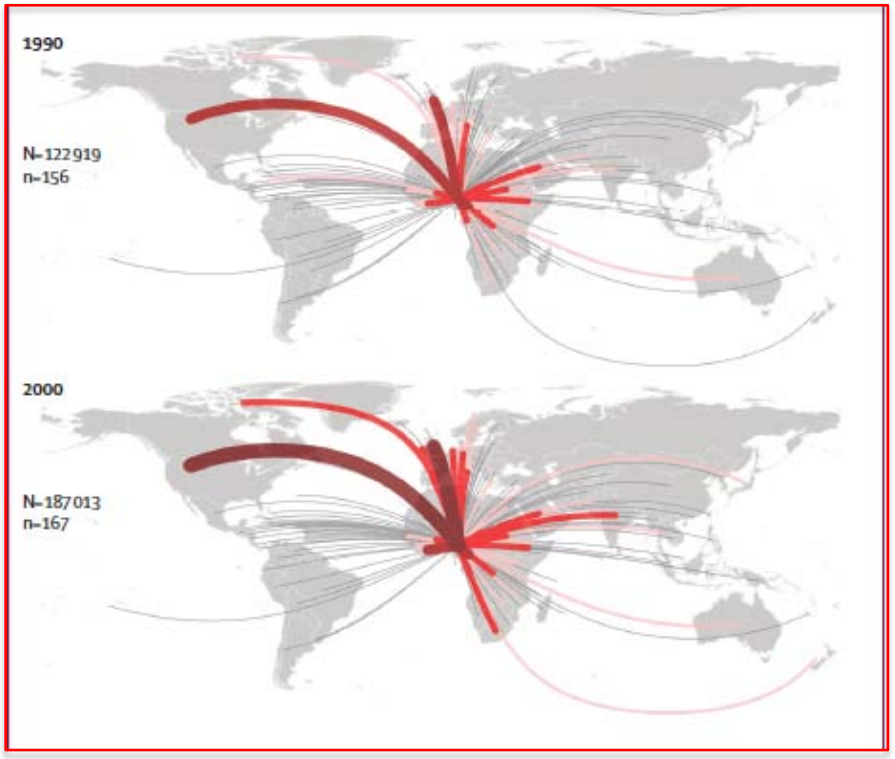
MILANO, 20 aprile, 2016- Rete Ematologica Lombarda-

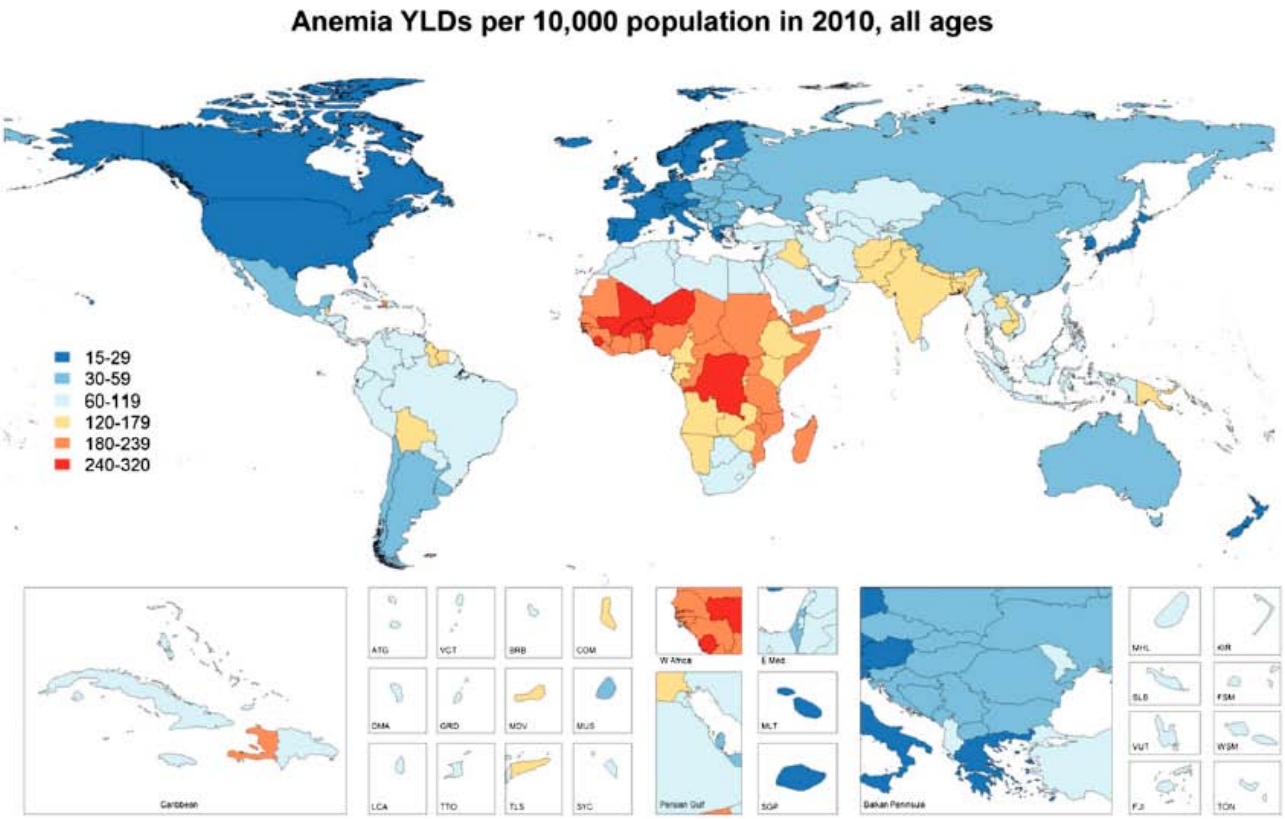
SCD is an Emerging Disoder in Non-Endemic Areas





Peil FB et al. Lancet Global Health 2: e80, 2014

Hemoglobinopathies are Emerging Problem of Public Health based on YLD and DALYs (1999-2010; 2010-2055)

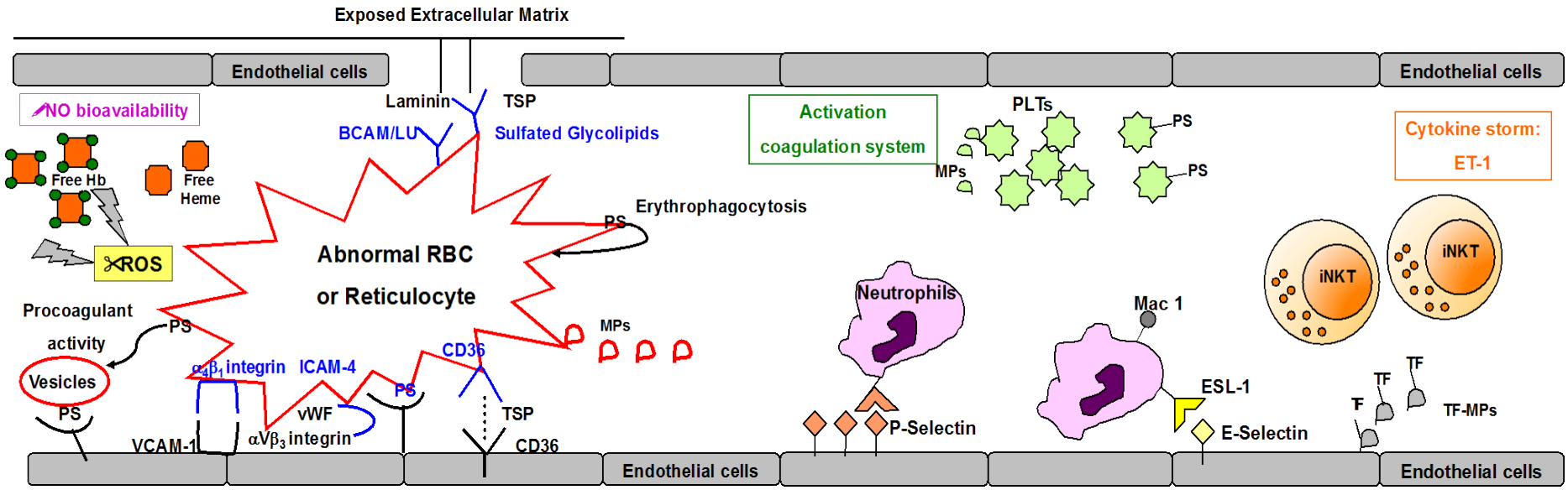


YLDs: years lived with disability for **hemoglobinopathies** (**β-thal and SCD**): **10.197** *vs* 21.342 cardiovascular disorders

DALYs: disability adjusted life years for **hemoglobinopathies** (**β-thal and SCD**): **15.640** *vs* 75.000 diabetes

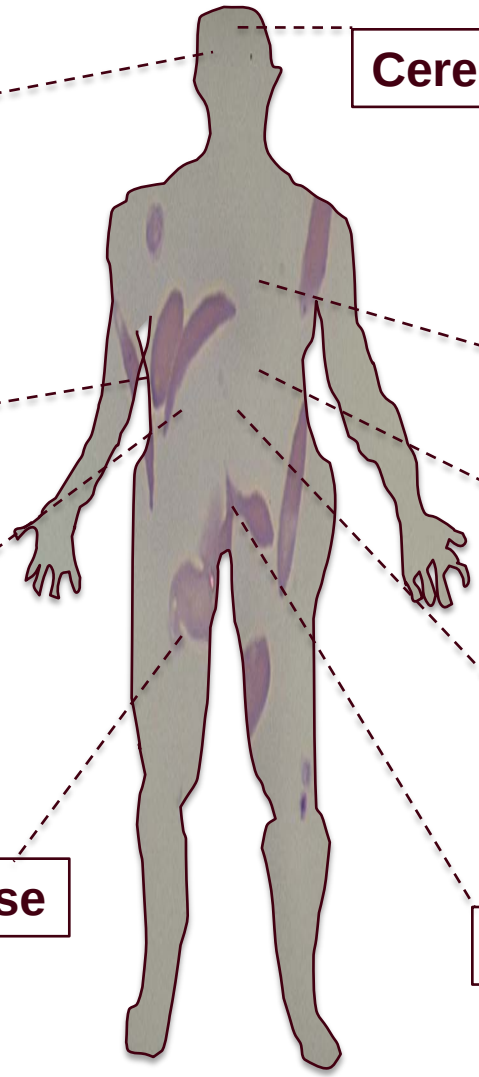
Murray CJ et al Lancet 380: 2197, 2012; Kassebaum NJ Blood 123: 615, 2014

The high Biocomplexity of SCD Substains Multi-Organ Damage



Modified from De Franceschi L *et al*. Seminars in Thrombosis, 37: 266; 2011

SCD is a Monogenic Disorder but a Multiorgan Disease



Cerebrovascular disease

Retinopathy

Renal Pathology
(e.g. hematuria, enuresis, papillar necrosis)

ACS, PH

Hepatomegaly
(Cholelithiasis, jaudice)

Spleen sequestration, Spleen infarts

Microvascular Occlusions
(e.g. mesenteric)

Bone disease

Priapism

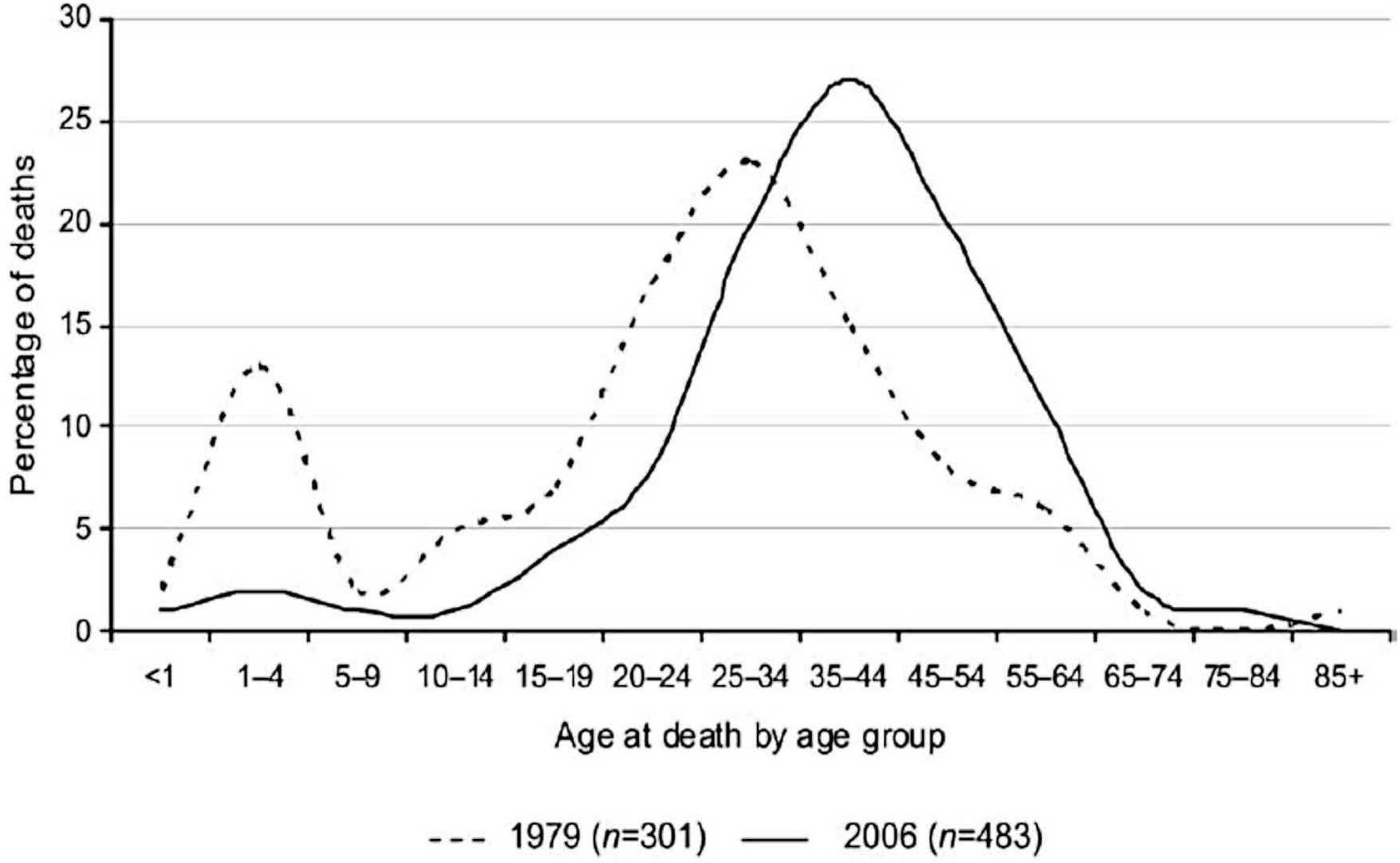


Figure 2. Age at death for individuals with SCD in 1979 and 2006
SCD, sickle cell disease

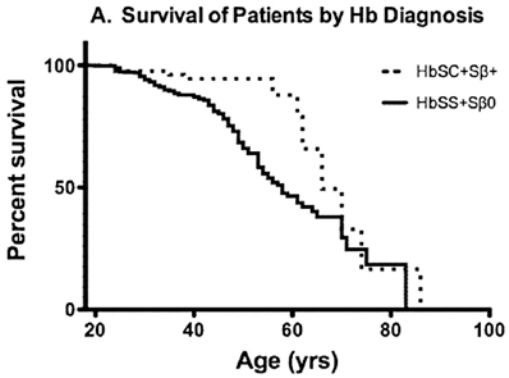
Hassel K et al. 38: 5512, 2010

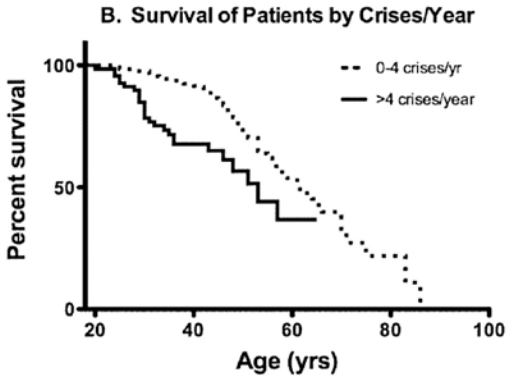
Risk Factor for Early Death in a Cohort of Adult SCD Patients

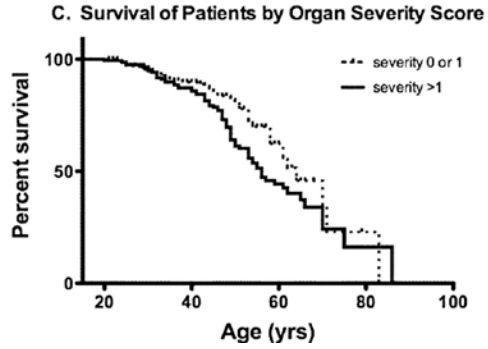
Trait	*N*	Hazard ratio	*P*-value
Hemoglobin (off HU)	362	1.21	**0.0043**
Hemoglobin (off HU) adjusted for GFR	319	0.93	0.3277
Hemoglobin (on HU)	168	1.36	**0.0107**
Hemoglobin (on HU) adjusted for GFR	157	0.83	0.1785
WBC (off HU)	351	1.06	**0.0419**
WBC (on HU)[a]	168	1.63	0.3181
Platelets (off HU)	350	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 Sβ^0 only.
Bold signifies statistical significance.

Elmariah H et al. AJH 89: 530, 2014





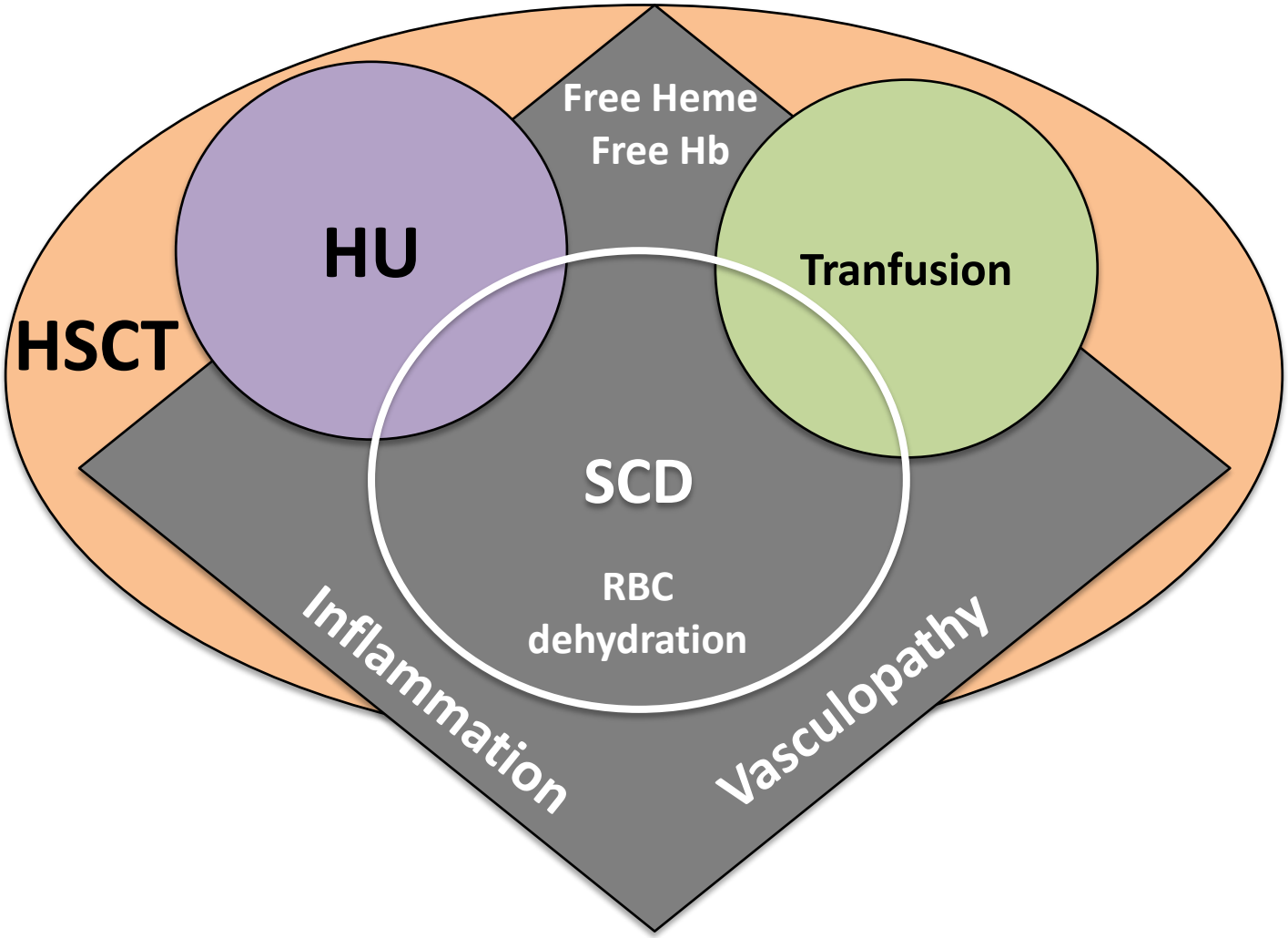


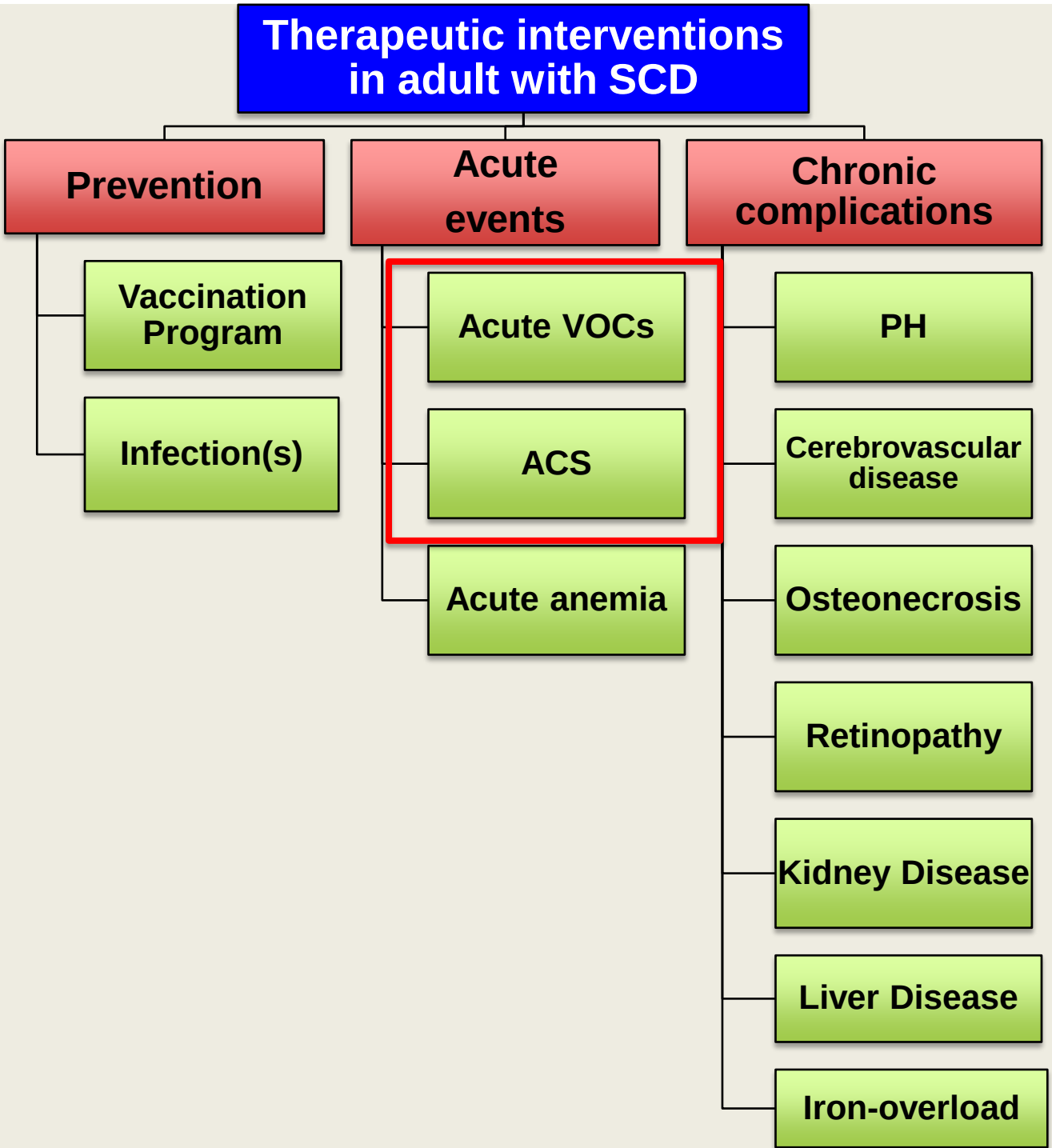
Association between patients survival:

- Pain frequency
- Hospitalization
- Narcotic use

Elmariah h et al. AJH 89: 530, 2014

Therapeutic Options in SCD




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

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

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 al: 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**

DOLORE nelle VOCs nella SCD

- **Dolore Nocicettivo**
  - **Danno infiammatorio tissutale** (VOC)
  - **Vasospasmo**
  - **Rilascio di citokine vaso-attive** (ET-1)
- **Dolore Neuropatico**
  - **Rilascio di molecole neuromodulattrici** (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

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 con molecole a differente target farmacologico

- **FANS che interferiscono con la trasduzione del segnale del dolore**

- **<u>Oppiodi maggiori</u> 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 2013

TRIAGE

Paziente falcemico con diagnosi accertata o sospetta

Si ritiene indispensabile che a tutti i pazienti venga attribuito almeno codice giallo

La somministrazione della prima dose di un analgesico appropriato entro 30 minuti dall'accesso in ospedale

CODICE ROSSO:
- Compromissione di almeno una della funzioni vitali (app. respiratorio, cardio-vascolare o stato di coscienza)
- Cefalea acuta con segni neurologici associati
- Crisi psicotica acuta
- Segni di anemizzazione acuta (< 2gr/dl rispetto allo steady state o pallore marcato)
- Sintomatologia dolorosa con VAS >8/10 (o dolore resistente alla terapia analgesica a domicilio)
- Ittero severo

CODICE GIALLO:
- Casi di sintomatologia dolorosa anche indotta da traumatologia minore
- Febbre > 38 o persistente da almeno 2 gg
- Casi di infezione
- Modesta sintomatologia cefalalgica non traumatica
- Riferite alterazioni del virus
- Ittero in apparente benessere senza anemizzazione

CODICE VERDE:
- Patologia cutanea minore
- Patologie ORL minori
- Modesto stato ansioso
- Ferite cutanee lievi
- Escorsioni ed abrasioni
- Ustioni di primo grado

CODICE BIANCO:
- Problematiche certificative
- Problematiche medico-legale
- Prescrizioni diagnostico-terapeutiche
- Richieste di consulenze non urgenti
- Richiesta di accertamento di stato gravidanza

Gestione ADULTI

Gestione BAMBINI

Gestione ADULTI

Gestione BAMBINI

Management Complicanze Acute

Paziente con quadro chirurgico (es. addome acuto)

ABBREVIAZIONI: AAII: 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-occlusive; ACS: Acute Chest Sindrome (ogni comparsa di un nuovo infiltrato polmonare)

Bibliografia

Somministrazione della prima dose di analgesico entro 30 minuti, incluso il tempo trascorso in Triage, dall'accesso in ospedale[3,4]

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

↓

Sol fisiologica 0,9% 500 ml
KETOROLAC 10 mg 3 fl (Se IRA o IRC sostituire con Paracetamolo 500 mg ev per 2/die)
TRAMADOLO100 mg 3 fl
METOCLOPRAMIDE 10 mg 3 fl (Se IRA o IRC: 2 fl)

↓

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.

dettagli

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

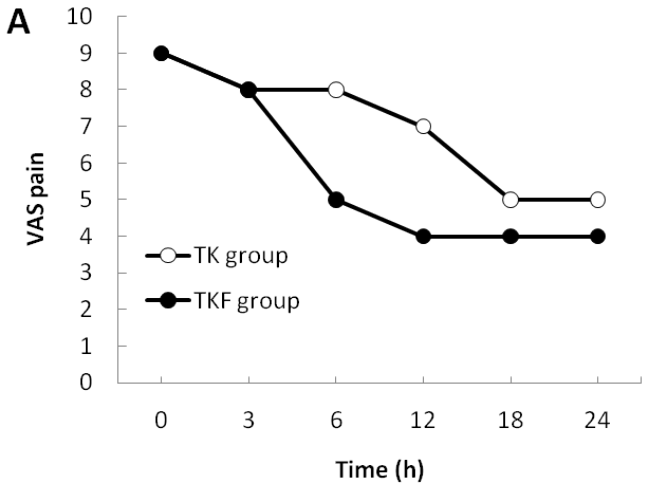
Monitorare parametri vitali e stato di sedazione
(se FR ≤ 12 atti/min: attenzione!) o eccessiva sedazione o coma
SOSPENDERE fino a normalizzazione / NARCAN 0,4 mg ev (Naloxone fl 0,4 mg/ml)

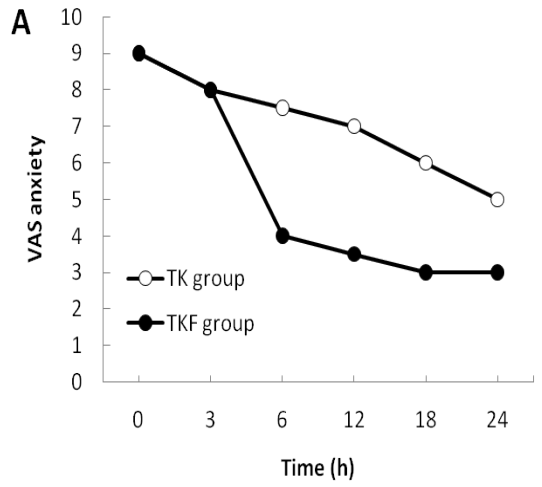
Gestione CODICE ROSSO - Adulti

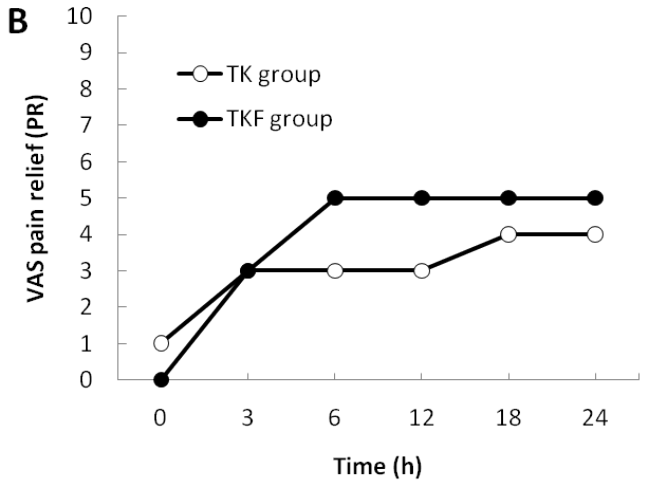
Triage
Paziente falcemico

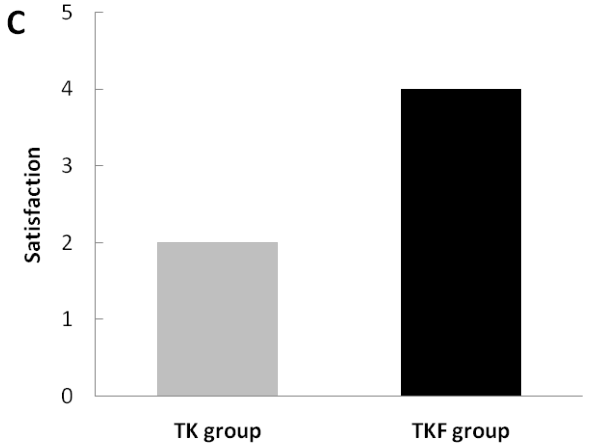
Evoluzione clinica: risoluzione dell'episodio/procedura trasfusionale: trasfusione di concentrati eritrocitari leucopleti; scambio eritrocitario automatizzato/ scambio eritrocitario manuale, exanguinotrasfusione

ORAL-FENTANYL AS PAIN-BREAKING DRUG DURING SEVERE ACUTE VOCs

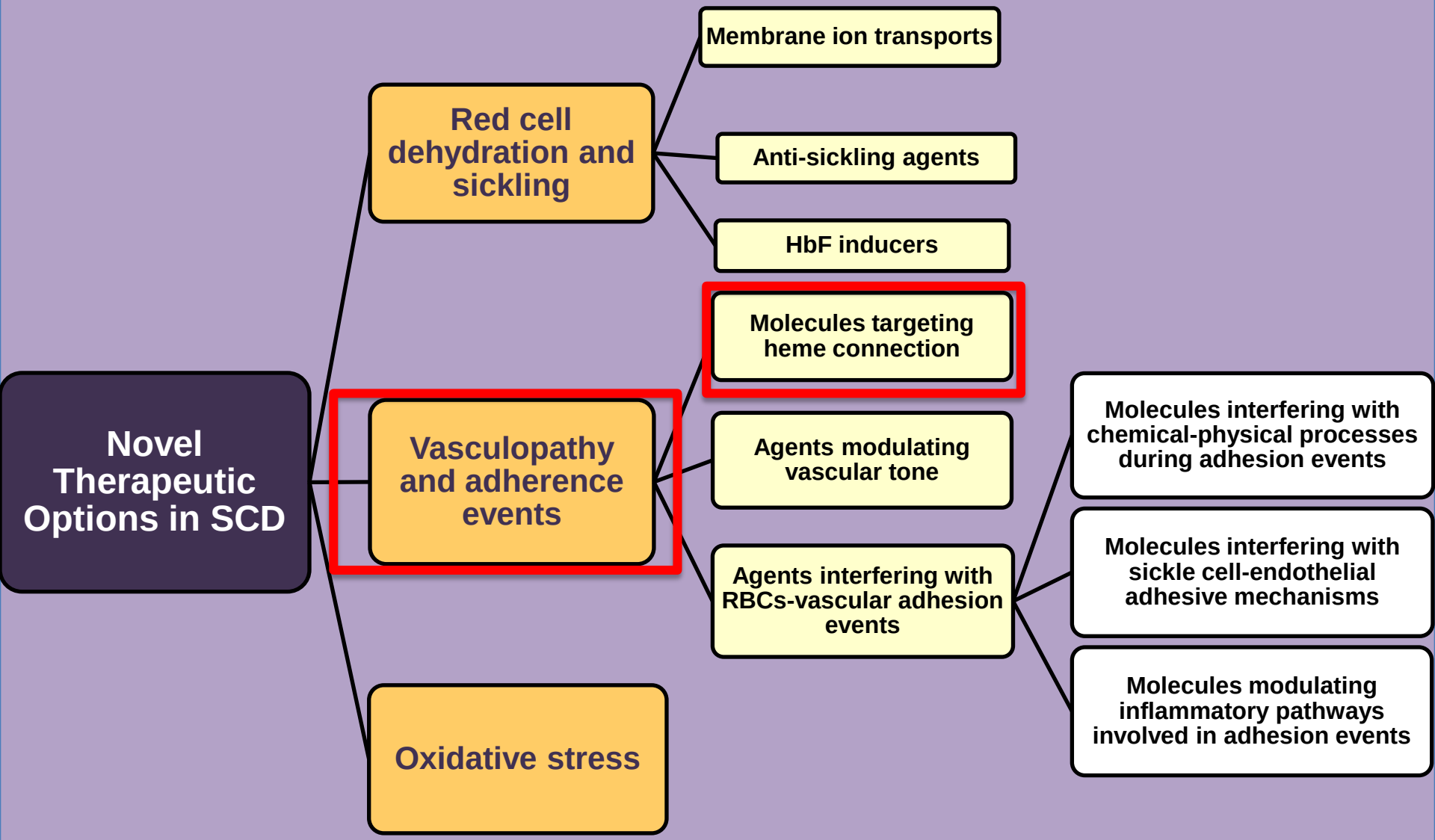








De Franceschi L et al Pain and Practice doi 10.111/papr.12313,;2015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Red cell dehydration and sickling
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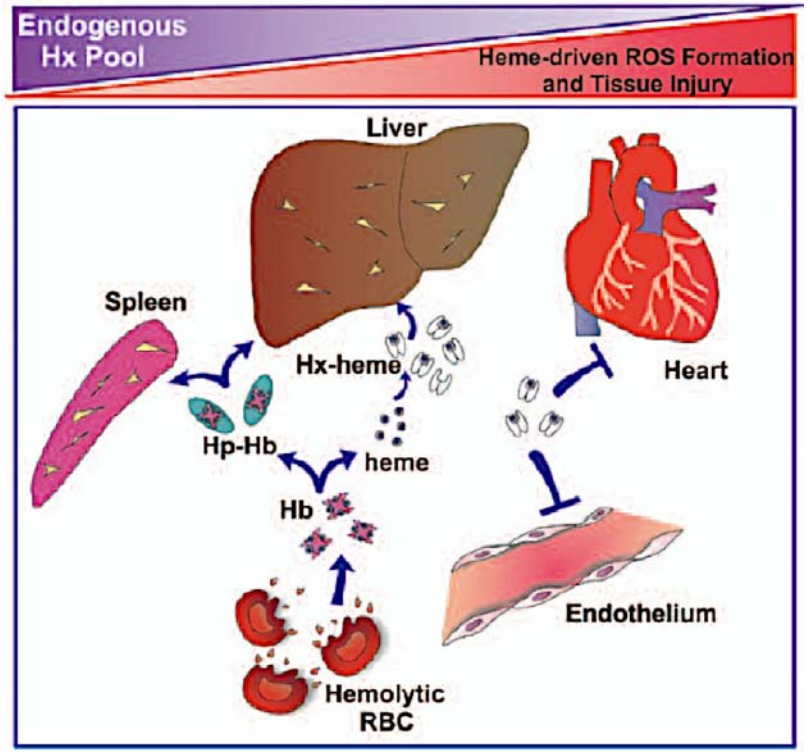
HbF inducers
Vasculopathy and adherence events
Molecules targeting heme connection
Agents modulating vascular tone
Agents interfering with RBCs-vascular adhesion events
Molecules interfering with chemical-physical processes during adhesion events
Molecules interfering with sickle cell-endothelial adhesive mechanisms
Molecules modulating inflammatory pathways involved in adhesion events
Oxidative stress

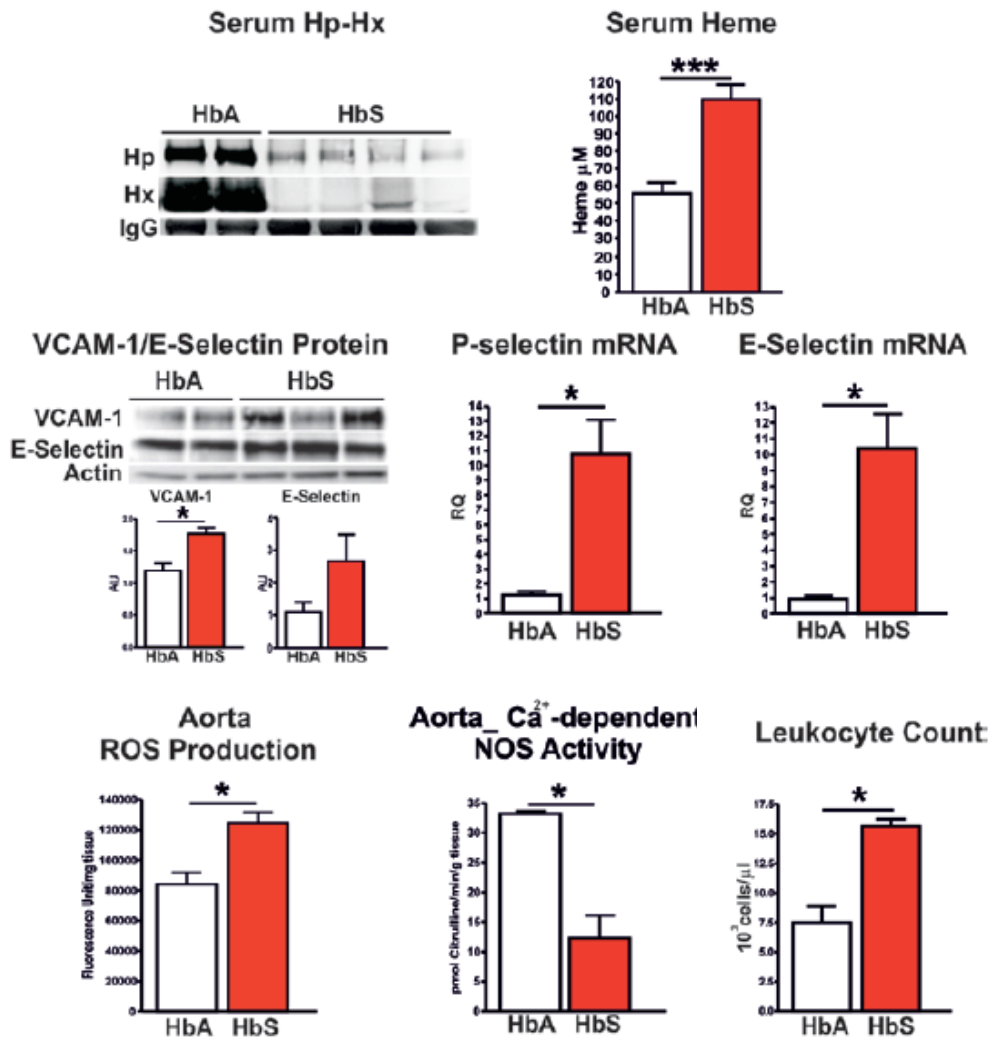
Heme Connection with SCD Vasculopathy

- In SCD, chronic hemolytic anemia is **1/3 intravascular hemolysis and 2/3 extravascular hemolysis**
- The saturation of physiological binding proteins such as **haptoglobin (Hb) and hemopexin (heme)**
- **Increased free Hb and free heme** promoting plasmatic pro-oxidant environment and **vascular endothelial activation**



Vinchi F et al. Circulation 127: 1317-29, 2013;
Vercellotti GM et al Frontiers in Pharmacology 5: 1; 2014
Hebbel RP Am J Hematol 86: 123, 2011

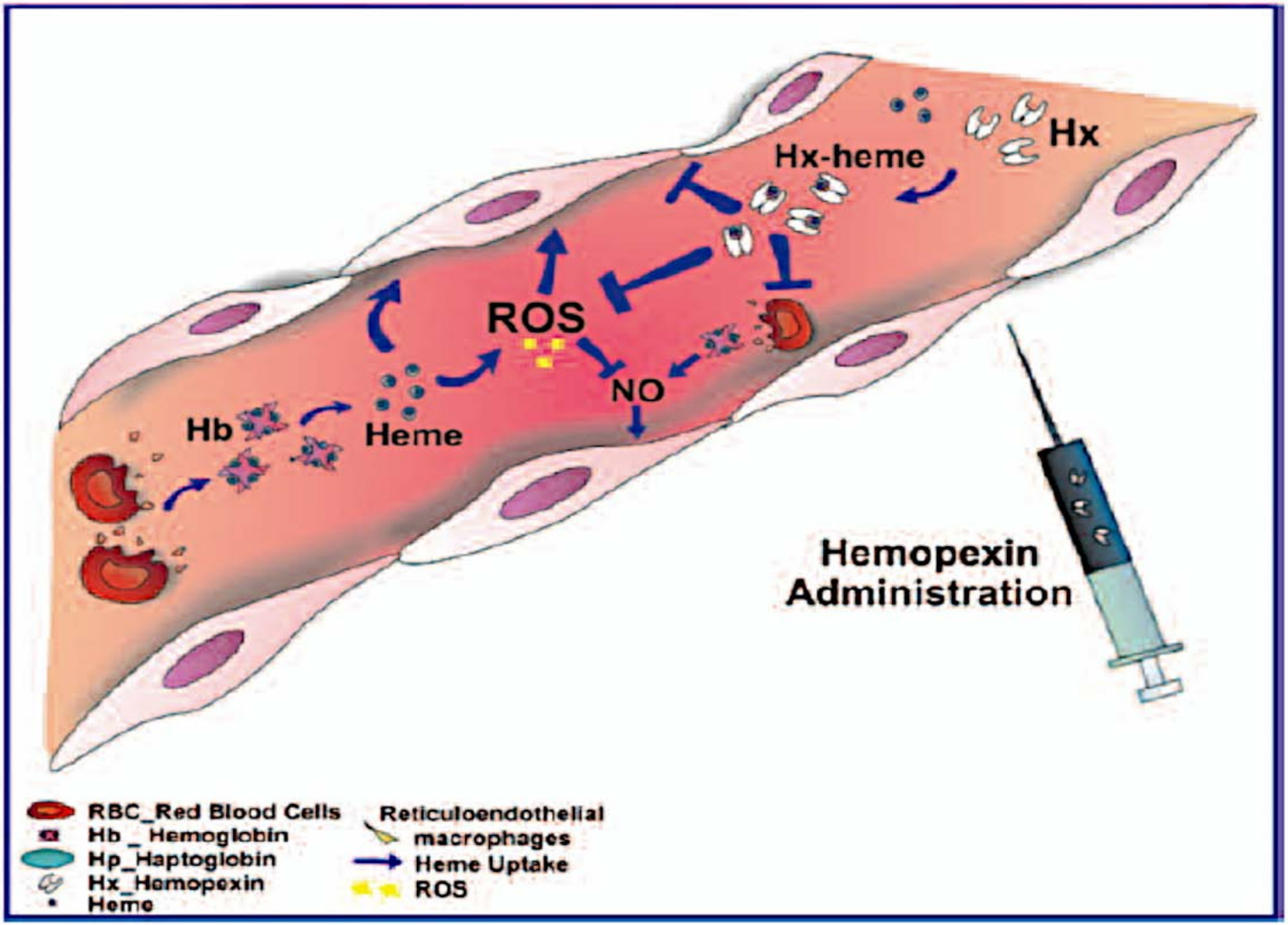
Hpx: Targeting Heme in SCD



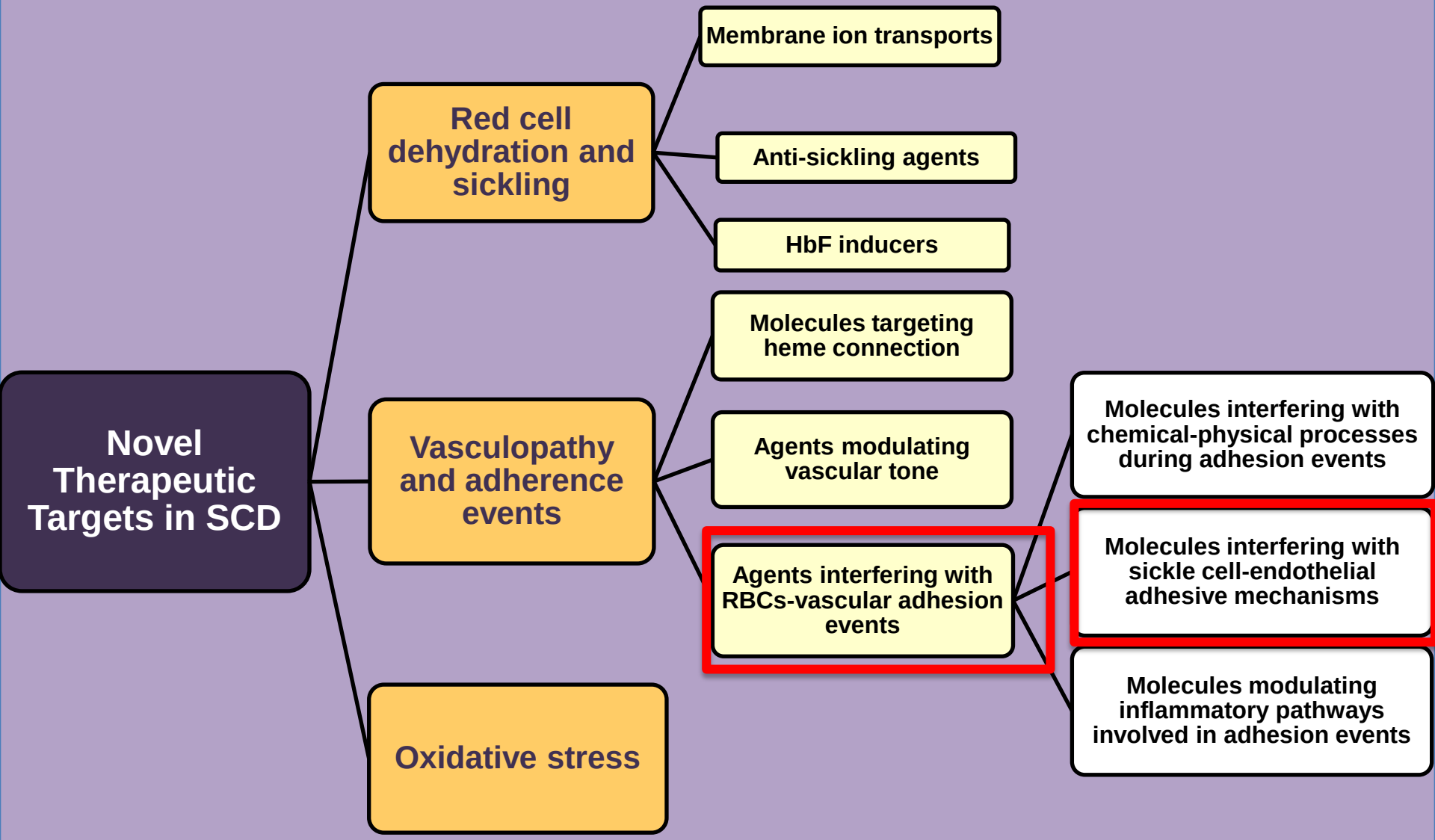
Vinchi F et al. Circulation 127: 1317-29, 2013

Cardiovascular Dysfunction Vasoconstriction

Therapeutical Hx administration



7-29, 2013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Molecules Interfering with Sickle-RBCs-Endothelial Adhesive Mechanisms: Selectin and SCD

- **Endothelial cell P-selectin is a member of the selectin family of cell adhesion molecules**
- **P-selectin plays a key role in leukocyte recruitment and sickle red cell adhesion to endothelium**
- **P-selectin levels are increased in 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

Therapeutic Strategies to Block Selectins in SCD

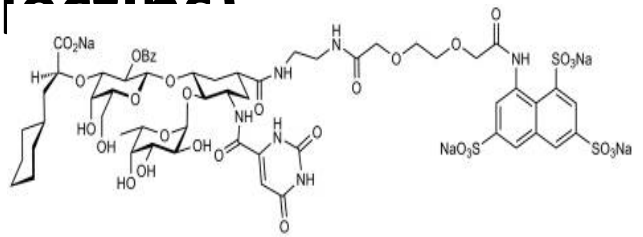
- **To block all selectins**:
  - Pan-Selectin antagosist (GMI-1070)

- **To target only P-selectin:**
  - Humanized anti-P-Selectin antibody
  - P-selectin aptamer
  - low molecular weight heparin, such as tinzaparin

Gutsaeva DR et al. Blood 117: 727, 2011; Kato G et al. 300: 2638, 2008; Kutlar A et al. 87: 536, 2012; Wun T et al. 9: e101301, 2014; Keefe AD 8: 147, 2008; Burmeister PE 16: 337, 2006; Burmeister PE 12: 25, 2005; De Souza EB 34: 142, 2009; Gustaeva DR 117: 727, 2011

Pan-Selectin Antagosist (GMI-1070) and SCD

- GMI-1070 is a glycomimetic pan-selectin antagonist (E, P and L-Selectins)



- In a mouse model for SCD, GMI-1070 inhibits selectin mediated leukocyte adhesion to vascular endothelium.

- In phase 1/2, GMI-1070 showed a safe profile and reduced E-Selectin levels in SCD patients during acute VOCs.

Chang J et al 116: 1779, 2010; Wun T et al 9: e101301, 2014

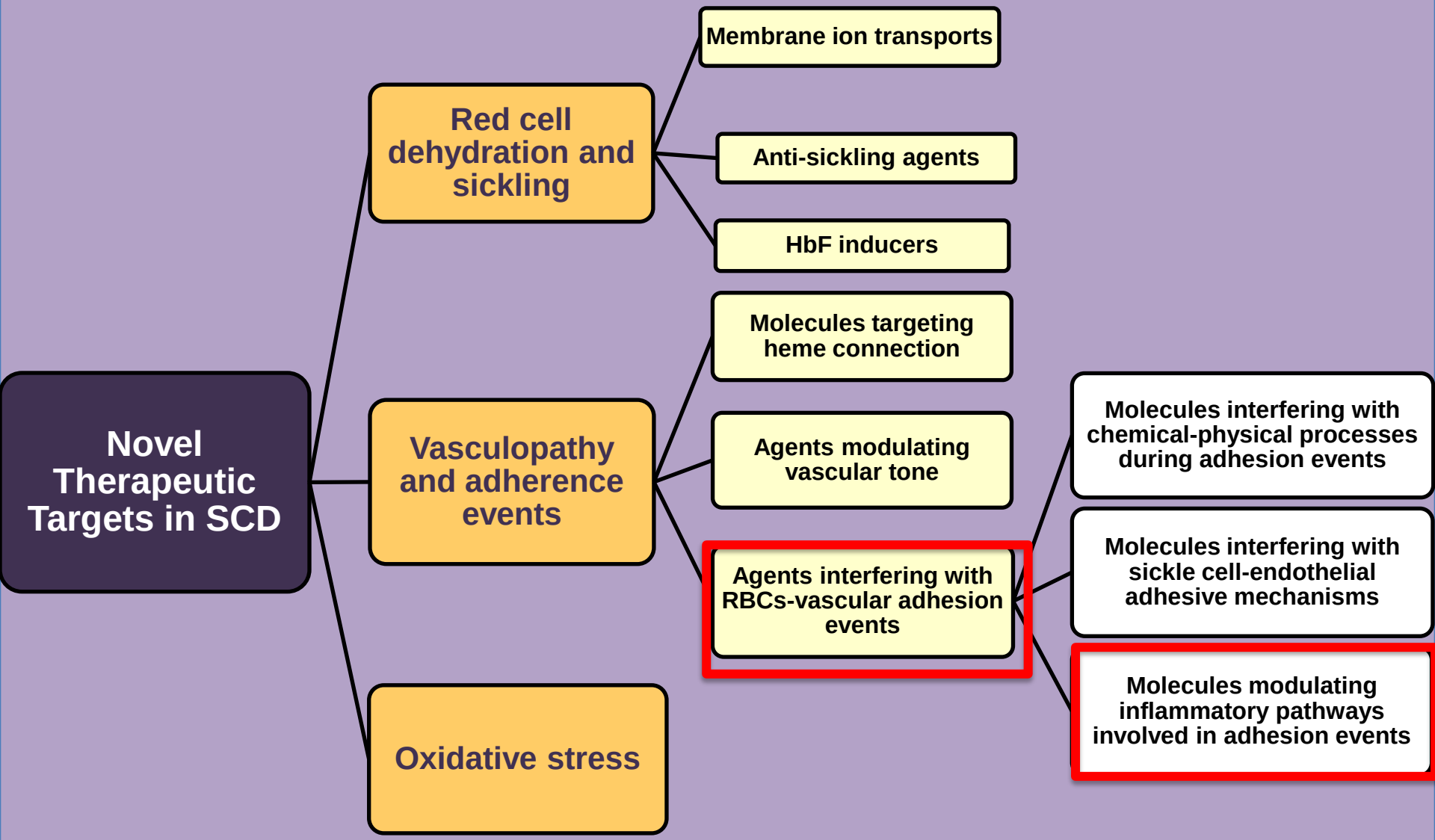
Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Randomized phase 2 study of GMI-1070 in SCD: reduction in time to resolution of vaso-occlusive events and decreased opioid use

Marilyn J. Telen,[1] Ted Wun,[2] Timothy L. McCavit,[3] Laura M. De Castro,[4] Lakshmanan Krishnamurti,[5] Sophie Lanzkron,[6] Lewis L. Hsu,[7] Wally R. Smith,[8] Seungshin Rhee,[9] John L. Magnani,[10] and Helen Thackray[10]

Archer J et al. Am J Hematol 90: 934, 2015;
Telen MJ et al. Blood 125: 2656; 2015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iNKT (invariant natural killer T cells) **and SCD**

- **iNKT are a subgroup of T cells that affects both innate and adaptive immunity partecipating to inflammatory cascade**

- **iNKT are increased in SCD on steady state and during acute VOCs**

Field JJ et al. Clin Immunol 140: 177, 2011; Field JJ et al Blood 121: 3329, 2013; Field JJ et al. Hematol Oncol Clin North Am 28: 287, 2014

iNKT activation is reduced by adenosine receptor antagonist-I

- During hypoxia/reoxygenation events adenosine is released from cells
- Adenosine interacts with A(1-3) receptors (AR), which are present on endothelial cells, leukocytes and iNKT cells
- NF-kB activity is modulated by A2AR

Field JJ et al. Clin Immunol 140: 177, 2011; Field JJ et al Blood 121: 3329, 2013;
Field JJ et al. Hematol Oncol Clin North Am 28: 287, 2014

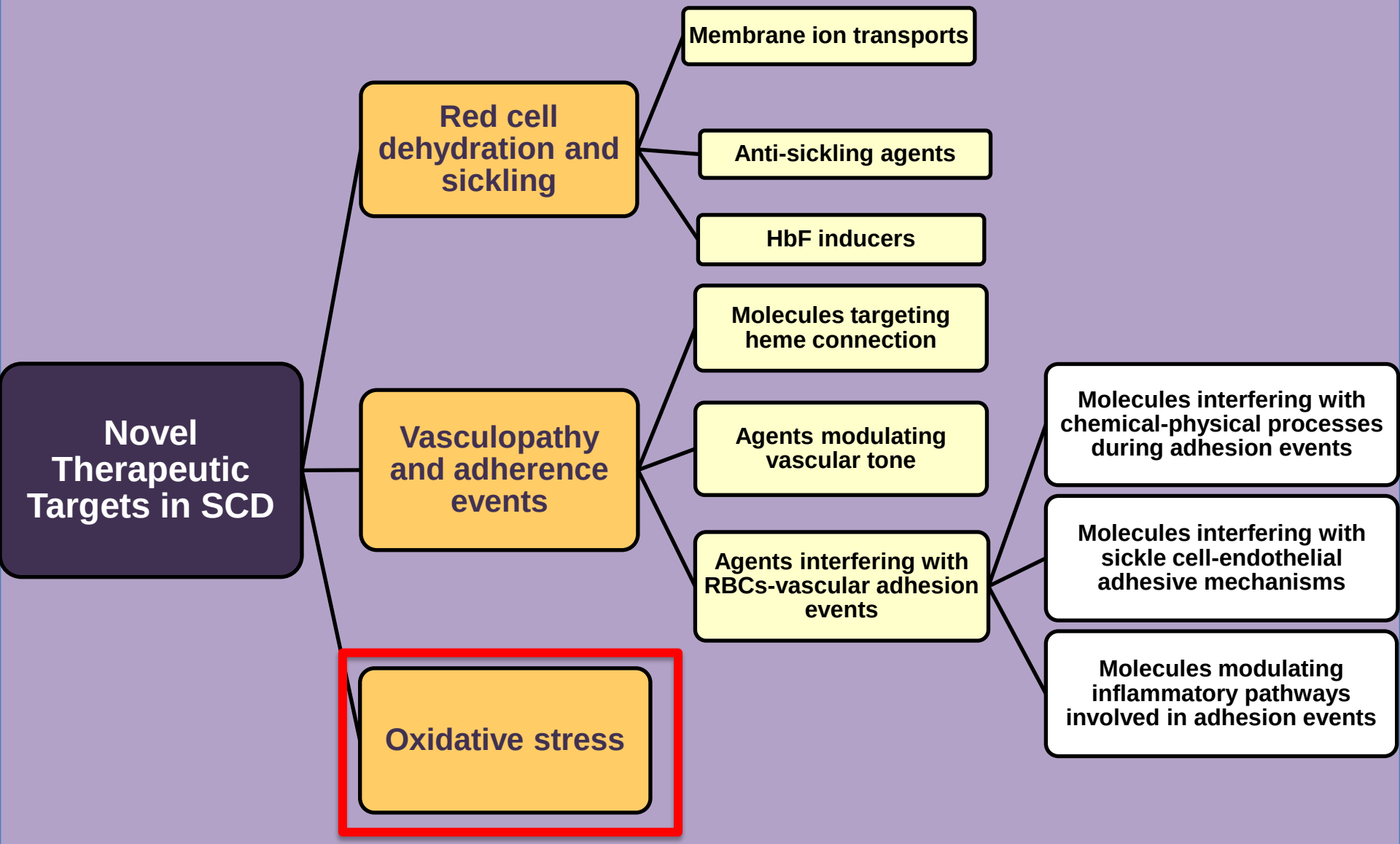
iNKT activation is reduced by adenosine receptor antagonist-II

- **A2AR agonist-regadenoson**- reduced iNKT activation in SCD mouse model

- **Phase 1 clinical trial with Regadenoson:**
  - 27 SCD patients (steady state and VOCs)
  - Reduced iNKT cells activation
  - **Major limitation of regadenoson: short life time (2 hrs)**

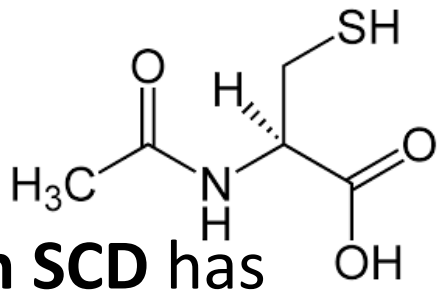
- **Phase 1 clinical trial with humanized monoclonal Ab to block iNKT (NKTT120)** for longer time compared to Regadenoson (#01783691)

Field JJ et al. Clin Immunol 140: 177, 2011; Field JJ et al Blood 121: 3329, 2013;
Field JJ et al. Hematol Oncol Clin North Am 28: 287, 2014


Novel Therapeutic Targets in SCD
Red cell dehydration and sickling
Membrane ion transports
Anti-sickling agents
HbF inducers
Vasculopathy and adherence events
Molecules targeting heme connection
Agents modulating vascular tone
Agents interfering with RBCs-vascular adhesion events
Molecules interfering with chemical-physical processes during adhesion events
Molecules interfering with sickle cell-endothelial adhesive mechanisms
Molecules modulating inflammatory pathways involved in adhesion events
Oxidative stress

Targeting Oxidative stress in SCD

- **SCD is** characterized by **high pro-oxidant environment, involving red cells and the vascular endothelial interface**



- **Targeting ROS as therapeutic strategy in SCD** has been addressed **by N-AcetylCysteine (NAC) studies**

- **NAC is an exogenous thiol donor and increases GSH levels**

Silva DG et al. FRBM 65:1101; 2013; Reid M et al. Am J Physiol Endocrinol Metab. 291: E73; 2006; Nagalla S et al. Cochrane Rev 7: CD003426; 2012; Pace BS et al Am J Hematol 73: 26; 2003; Nur E et al. Ann Hematol 91: 1097; 2012; Ozpolat T et al. Blood; 2014:4173.

In SCD patients:

- **Oral supplementation with NAC (1200 mg/d)**
  - reduces dense red cells
  - increases GSH levels
  - ameliorates hemolytic indices

  On going multicentric study on pain rate in NAC supplemented SCD patients (#01849016)

- **NAC infusion (150 mg/Kg bolus followed by 75 mg/Kg infusion for 7 hrs)**
  - reduces dense red cells
  - Decreases high molecular weight vWF, that contributes to vasculopathy and pro-thrombotic state of SCD patients (explorative study on 5 SCD patients)

Pace BS et al Am J Hematol 73: 26; 2003; Nur E et al. Ann Hematol 91: 1097; 2012; Ozpolat T et al. Blood; 2014:4173

CONCLUSIONI

- **La drepanocitosi e' una patologia ad elevata biocomplessita' che richiede una terapia multimodale**

- **Nuove opzioni terapeutiche per il trattamento degli eventi acuti nella drepanocitosi prevedono:**
  - **pain-breaking molecules per il controllare il dolore in modo efficace**
  - **Molecole che riducono la quota di heme libero e modulano la vasculopatia infiammatoria**
  - **Molecole che interferiscono con eventi adesivi tra endotelio e RBC-neutrofili attraverso la Selectina**
  - **Molecule che modulano la risposta infiammatoria ed il danno ossidativo**

- **Studi futuri di tipo clinico permetteranno di identificare nuove opzioni terapeutiche nella gestione degli eventi acuti e prevenire i danni d'organo relati alle VOCs.**

Table 1. Literature-cited clinical use of haptoglobin in Japan

Clinical condition	Subjects/controls	Haptoglobin dose	Primary finding (intention of treatment)	Reference
Cardiopulmonary bypass surgery	16/21	6 g	Prevention of acute renal failure	Hashimoto et al[87]
	14/0	4 g		Tanaka et al[88]
Coronary artery bypass grafting in a patient with β-thalassemia and severe hemolysis	Single case report			Horai et al[89]
Peripheral blood stem cell transplantation	Single case report	3 g	Prevention of acute renal failure	Tsuda et al[90]
Hemolytic transfusion reaction	Single case report	6 g	Prevention of acute renal failure	Homann et al[91]
Massive transfusion	16/34	6 g	Undetermined benefit	Gando et al[92]
Extracorporeal circulation	10/10	6 g	Prevention of acute renal failure	Kanamori et al[93]
HELLP syndrome	17/17	3 g	Prevention of acute renal failure	Yamamoto et al[94]
ABO-incompatible BM transplantation	Two patient case reports	11 g	Prevention of acute renal failure	Ito et al[95]
Thermal injury	Single case report (repeated, large-dose therapy)	> 20 g	Improved outcome Prevention of hemoglobinuria and acute renal failure	Imaizumi et al[96] Yoshioka et al[97]
Glucose-6-phosphate dehydrogenase deficiency	Single patient case report (24-mo-old boy)	8.5 g	Prevention of hemoglobinuria	Ohga et al[98]
Adult patent ductus arteriosus, coil embolization	Single patient case report	45 g	Prevention of hemoglobinuria	Eda et al[99]

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Perspectives

Hemolysis and free hemoglobin revisited: exploring hemoglobin and hemin scavengers as a novel class of therapeutic proteins

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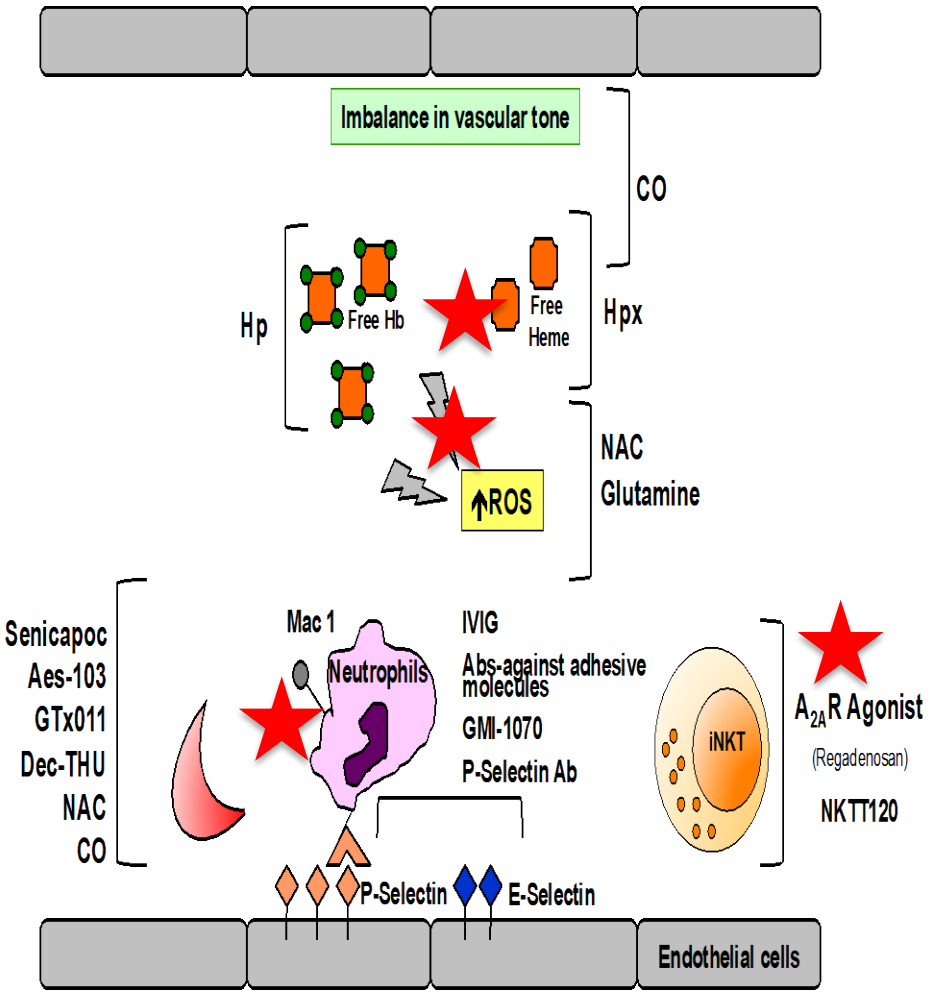
Imbalance in vascular tone
CO
Hp
Free Hb
Free Heme
Hpx
NAC
Glutamine
↑ROS
Senicapoc
Aes-103
GTx011
Dec-THU
NAC
CO
Mac 1
Neutrophils
IVIG
Abs-against adhesive molecules
GMI-1070
P-Selectin Ab
iNKT
A2AR Agonist
(Regadenosan)
NKTT120
P-Selectin
E-Selectin
Endothelial cells

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Abstract

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Clin Appl Thromb Hemost. 2016 Apr;22(3):230-8. doi: 10.1177/1076029614565880. Epub 2015 Jan 19.

Modulation of Sickle Red Blood Cell Adhesion and its Associated Changes in Biomarkers by Sulfated Nonanticoagulant Heparin Derivative.

Alshaiban A[1], Muralidharan-Chari V[1], Nepo A[2], Mousa SA[3].

Author information

Abstract

Abnormal cellular adhesion is one of the primary causes of vaso-occlusive crisis in **sickle cell disease** (SCD). Levels of intercellular adhesion molecule 1 (ICAM-1) and P-selectin are upregulated, resulting in increased adhesion of leukocytes and **sickle** red blood cells (RBCs) to endothelium. This study compares the inhibitory effect of a sulfated nonanticoagulant **heparin** (S-NACH) derivative with a low-molecular-weight **heparin**, tinzaparin, on the adhesion of **sickle** RBCs to endothelium. The S-NACH exhibits minimum effects on hemostasis and bleeding and interferes with the binding of pancreatic cancer cells to endothelial cells via P-selectin. We show by static binding assay that pretreatment of both erythrocytes and endothelial cells with S-NACH significantly inhibits the increased adhesion of **sickle** RBCs to endothelial cells. The S-NACH treatment also decreases the higher plasma levels of (adhesion biomarkers) ICAM-1 and P-selectin in SCD mice. This investigation signals further research into the potential use of S-NACH in treating vaso-occlusions with minimal bleeding events in patients with SCD.

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KEYWORDS: ICAM-1; adhesion molecules; endothelial cells; **heparin**; selectin; **sickle cell disease**; **sickle** red blood cells; sulfated nonanticoagulant **heparin**; tinzaparin

PMID: 25601897 [PubMed - in process]

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