Primary stroke prevention in children with sickle anemia living in Africa: the false choice between patient-oriented research and humanitarian service

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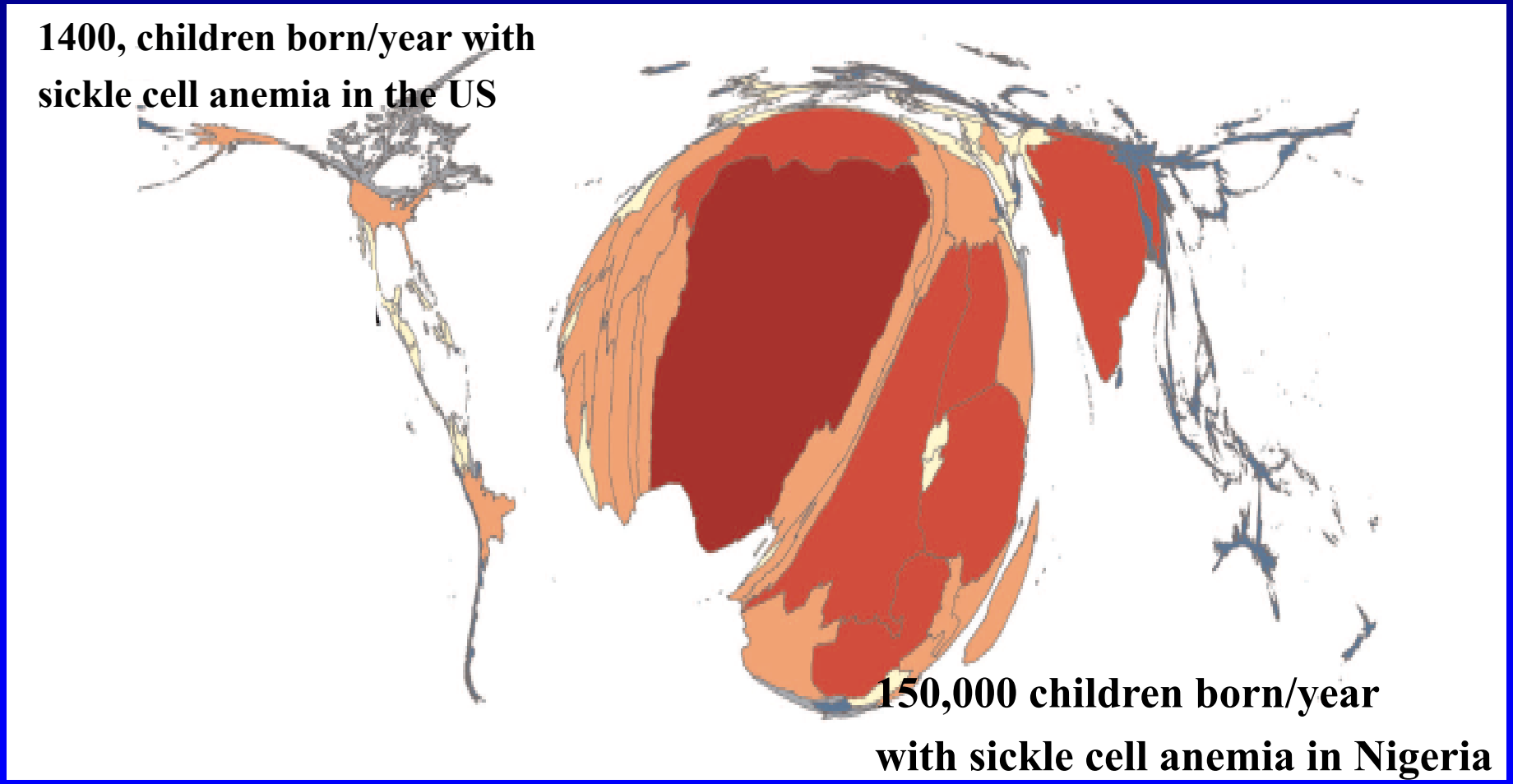
Cartograms of the estimated number of newborns with sickle cell anemia based on demographics, excess mortality, and interventions



PLoS Med. 2013;10(7):e1001484

Summer of 2011 co-sponsored retreat for young girls with SCD living in Katsina, Nigeria
6 of 42 girls had new diagnosis of stroke

The critical question:

Can we prevent strokes in children living in Nigeria?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prevention of a First Stroke by Transfusions in Children with Sickle Cell Anemia and Abnormal Results on Transcranial Doppler Ultrasonography

Robert J. Adams, M.D., Virgil C. McKie, M.D., Lewis Hsu, M.D., Ph.D., Beatrice Files, M.D., Elliott Vichinsky, M.D., Charles Pegelow, M.D., Miguel Abboud, M.D., Dianne Gallagher, M.S., Abdullah Kutlar, M.D., Fenwick T. Nichols, M.D., Duane R. Bonds, M.D., Donald Brambilla, Ph.D., et al.

N Engl J Med. 1998 Jul 2;339(1):5-11.

- Abnormal TCD velocities (> 200 cm/sec) randomly allocated
  - Treatment arm (monthly transfusions)
  - Observation arm (no transfusions)
    - **a 92 percent relative risk reduction (P<0.001)**
  - Subsequently
    - Up to a 10-fold-decrease in strokes occurring in children with sickle cell anemia living in the USA

Challenges of regular blood transfusion therapy in sub-Saharan Africa

- Include, but are not limited to:
  - Inadequate blood supply
  - Cost of monthly blood transfusions
  - Unsafe transfusion practices
  - High probability of blood borne infections

Additional challenge: extreme poverty for most children with sickle cell anemia living in northern Nigeria

- 40% of the population, 83 million Nigerians, live on approximately $1.00/day
- Cost of CBC to assess hydroxyurea toxicity, a chemotherapy agent, is $5.00 (March 2022)
- Cost of European produced hydroxyurea is $0.50 to $1.00 per 500 mg capsule

NINDS R01 2015-2021

SPRING Trial: Primary Hypothesis

Daily hydroxyurea at a fixed moderate-dose (~20 mg/kg) will result in a 66% relative risk reduction for primary strokes (9 to 3 events per 100 person-years) in children with abnormal transcranial doppler velocities compared to a daily fixed low-dose (~10 mg/kg).

The hypothesis was selected to address the sustainability of stroke prevention after the trial completion

- If 20 mg/kg/day was superior to 10 mg/kg/day, we know the minimum hydroxyurea dose needed to prevent stroke recurrence in children with SCA in Africa

- If 20 mg/kg/day was no better than 10 mg/kg/day, the government can treat twice as many children with SCA to prevent strokes for the same cost
  - no prior arrangement was established for the state government to assume the strategy for securing hydroxyurea for primary stroke prevention
- Maximum tolerated hydroxyurea dose ~ 25 to 35 mg/kg/day, was never an option because of the prohibitive laboratory costs for the majority of families and lack of clinical expertise

2015- 2022

THE LANCET
Haematology

Hydroxyurea for primary stroke prevention in children with sickle cell anaemia in Nigeria (SPRING): a double-blind, multicentre, randomised, phase 3 trial

Shehu U Abdullahi, Binta W Jibir, Halima Bello-Manga, Safiya Gambo, Hauwa Inuwa, Aliyu G Tijjani, Nura Idris, Aisha Galadanci, Mustapha S Hikima, Najibah Galadanci, Awwal Borodo, Abdulkadir M Tabari, Lawal Haliru, Aisha Suleiman, Jamila Ibrahim, Brittany C Greene, Djamila L Ghafuri, Mark Rodeghier, James C Slaughter, Fenella J Kirkham, Kathleen Neville, Adetola Kassim, Edwin Trevathan, Lori C Jordan, Muktar H Aliyu, Michael R DeBaun

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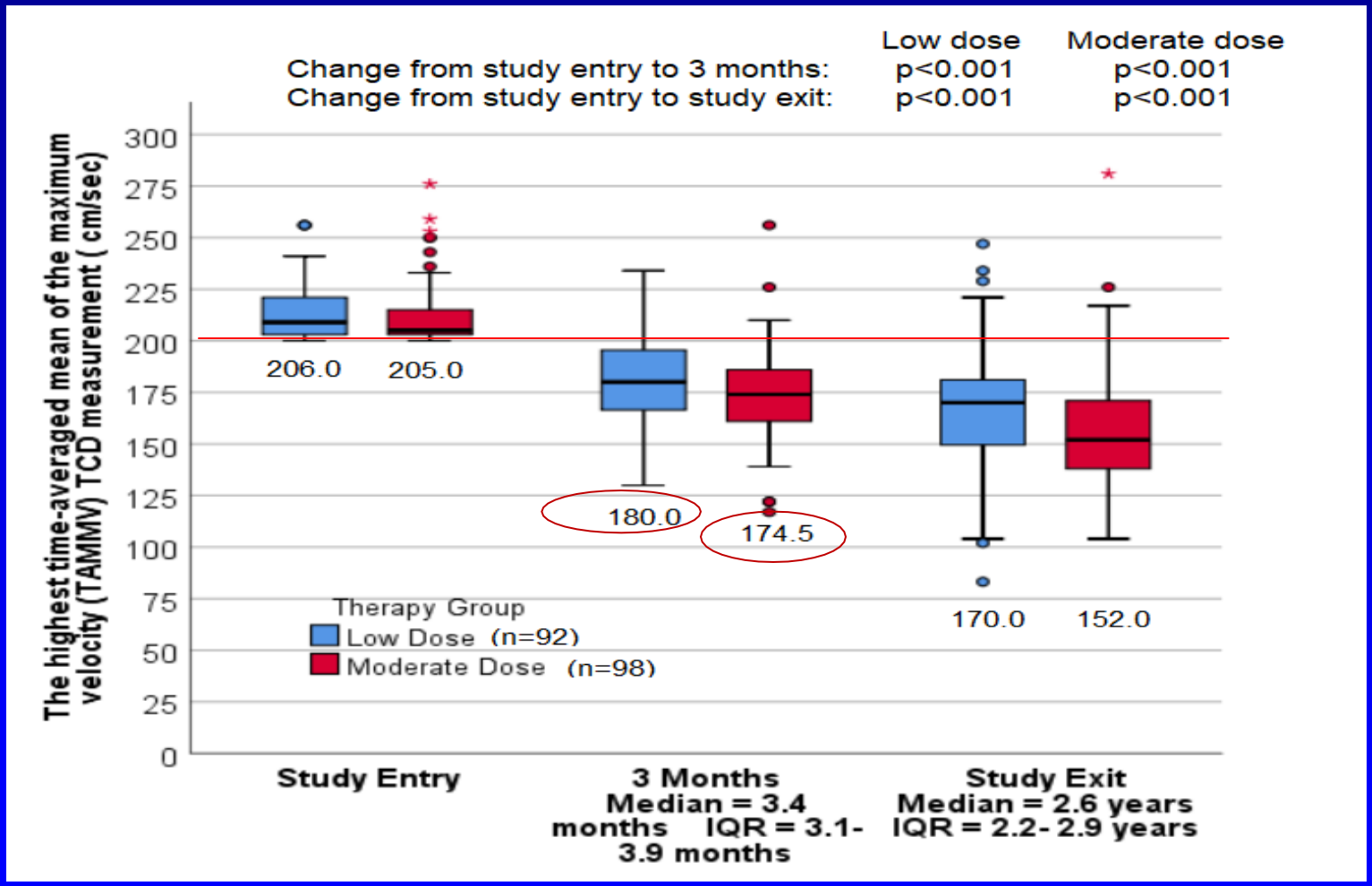
Hydroxyurea was associated with reductions in TCD velocities (TAMMV) over time



Low-dose and moderate-dose hydroxyurea therapy had similar primary stroke incidence rates

Event	Therapy group	Incidence rate per 100 pt./years (95% CI)	Incidence rate ratio (95% CI)	P Value
Primary Stroke	Low dose	1.19 (0.25 – 2.49)	1.60 (0.31 – 10.33)	0.768
	Moderate dose	1.92 (0.62 – 4.47)		

STOP Trial expected stroke rate for children with abnormal TCD velocities
-observation arm 10.7 events per 100 person- years
-regular blood transfusion 0.9 events per 100 persons- years

* All participants had monthly evaluations for 2.4 years and all strokes were determined locally and neurology adjudication committee confirmed all strokes with a video sent to committee.

Conclusion from the SPRING Trial

- For children with abnormal TCD velocities, no difference in the incidence rate of ischemic strokes between low-dose and moderate dose hydroxyurea
  - Approximately 1.5 event per 100 person years
    - If transfused, we expect approximately 1.0 events per 100 person years

- Standard care for primary stroke prevention for 40,000 children with sickle cell disease in three states of northwestern Nigeria (three states) NOW include:
  - free TCD measurements in 9 clinics across three states.
  - free state government sponsored hydroxyurea therapy starting at 10mg/kg/day
  - routine biannual CBC

- Hydroxyurea was suppled by a Nigeria pharmaceutical company at a subsidized case of $0.15 per 500 mg capsule

After the trial is over and the funding is gone, now what?

Public-Research Partnership
Kano, Katsina, Kaduna states- 40,000 children with SCA (> USA)
Memorandum of Understanding
Stroke prevention clinics with TCD performed without charge (n=9)
Free hydroxyurea for primary stroke prevention

	Date of Commencement	Total number of TCD performed	Total number of abnormal TCD	Percent positive abnormal TCD	Percent started on hydroxyurea
SITE					
Aminu Kano Teaching Hospital	April, 2016	1,484	147	9.91	98.61
Hasiya Bayero Paediatric Hsptl.	Nov. 2017	1,154	60	5.2	100
Muhammad Abdullahi Wase Teaching Hsptl.	Nov. 2017	371	21	5.66	100
Murtala Muhammad Specialist Hsptl.	April 2016	5,198	412	7.93	100
Barau Dikko Teaching Hsptl.	Dec. 2017	2,037	103	5.07	100
TOTAL		10,244	743	7.3%	99.0%

Nigeria team capacity building efforts

- Three mentees have advanced their careers as physician-scientists
  1. Najibah-PhD in epidemiology 2021 UAB
  2. Halima- K43 (mentored award) implementation science and stroke prevention in Kaduna, Nigeria
  3. Ibrahim- ASH Global Research Award, RCT preventing priapism in men with SCD in Kano Nigeria- Dr. Burnett is a co-mentor

- Six research staff are SOCRA trained and have an active SOCRA chapter

- Over $5.5 million in NIH and foundation funding
  - Three stroke prevention trials in SCA

- Partnership with St. Jude and the teaching hospital in Kano, Nigeria
  - Newborn screening program with pre-marital genetic counseling
  - Under 7 clinic for children with SCA to decrease mortality and morbidity

- First NIH RCT for treatment of malnutrition in children between 5 and 12 years of age

Stroke Sickle Cell Disease Team

+ 1 (Dr. Arthur Burnett JHU urologist working with the team on preventing priapism in Nigeria)

August 2019

Thank You!