VANDERBILT UNIVERSITY MEDICAL CENTER

United States: The Good, the Bad, and the Future

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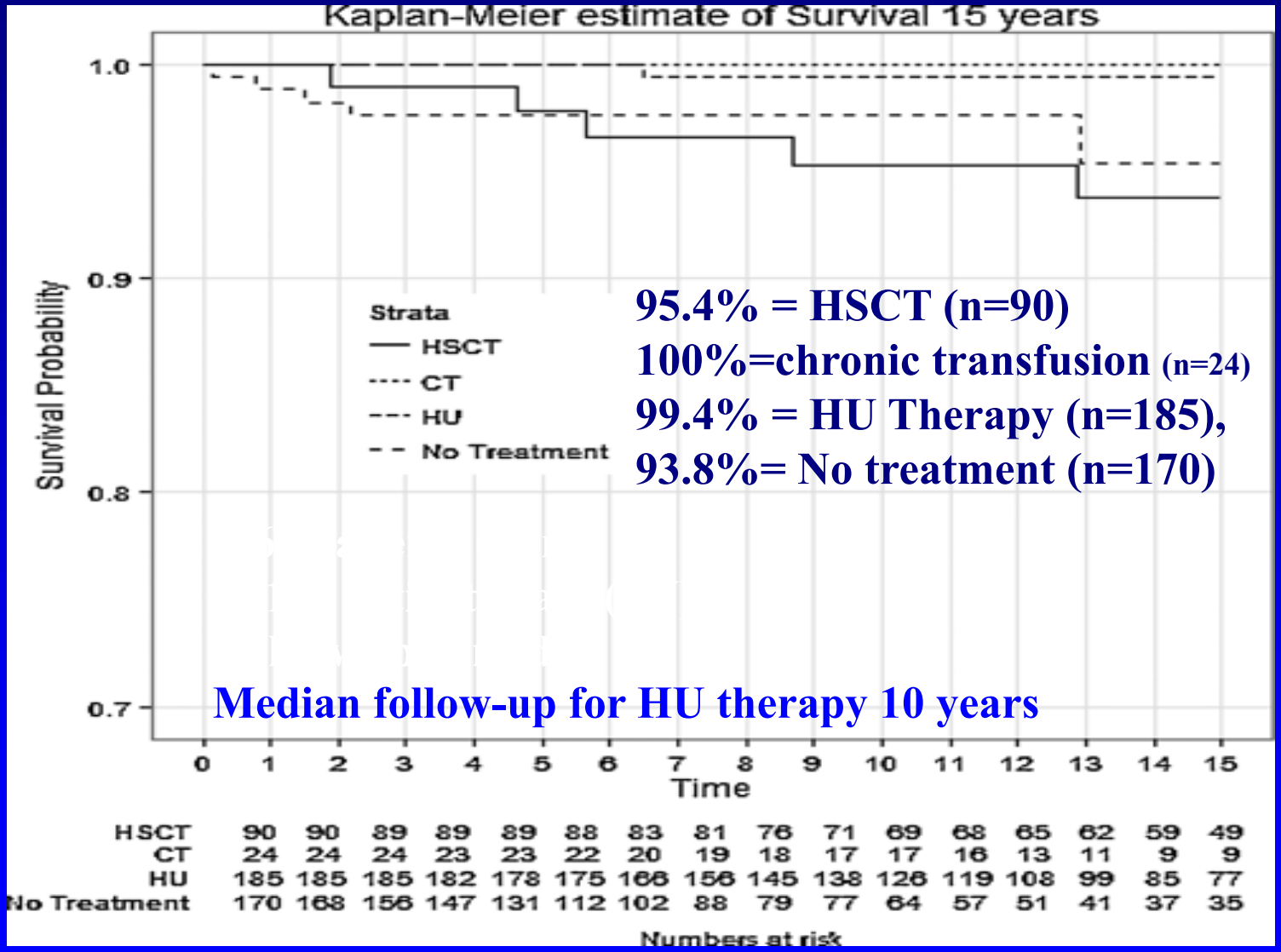
The Good!

Last 20 years: change in the clinical history of sickle cell disease in children

- Paradigm shift from an early life threatening condition to a chronic disease
- Strokes are the most common debilitating complications
  - 2% to 5% of children have overt strokes
  - 39% will have silent strokes
- Hydroxyurea therapy has decreased the rates of:
  - Pain
  - Acute chest syndrome
  - Blood transfusion therapy
  - Strokes in children (indirect evidence)

Dramatic benefit from hydroxyurea treatment Belgium cohort, 5,110 pt-yrs of follow-up period



Pediatric Blood & Cancer Volume 62 Issue 11 pages 1956-1961, 14 JUL 2015

Other experiences in children: SCD is no longer a life-threatening disease, but a disease with life-threatening events

1. East London cohort with 2,158 patient-years of observation
   - 16-year KM survival of 99% for infants followed at tertiary care medical center
2. Northern Paris region 6,776 patient-years of follow-up after providing electronic guidelines for management of SCD in children
   - 5 year KM survival rate was 99%
3. NIH funded prospective cohort study, DC Children's Hospital, 497 children and adolescents followed for 5 years
   - Estimated survival to 18 years was 99%

1. Haematologica. 2007;92:905-912
2. Br J Haematol. 2016;173:927-937
3. Am J Hematol. 2020;95:766-774

Pediatric research focused on preventing organ dysfunction and end-organ disease

- Most children, >98%, are expected to live to adulthood
- Main goal of therapy
  - preventing end organ dysfunction
  - improving quality of life
- To understand the determinants of end-organ dysfunction and disease

The NEW ENGLAND JOURNAL of MEDICINE

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Controlled Trial of Transfusions for Silent Cerebral Infarcts in Sickle Cell Anemia

M.R. DeBaun, M. Gordon, R.C. McKinstry, M.J. Noetzel, D.A. White, S.A. Sarnaik, E.R. Meier, T.H. Howard, S. Majumdar, B.P.D. Inusa, P.T. Telfer, M. Kirby-Allen, T.L. McCavit, A. Kamdem, G. Airewele, G.M. Woods, B. Berman, J.A. Panepinto, B.R. Fuh, J.L. Kwiatkowski, A.A. King, J.M. Fixler, M.M. Rhodes, A.A. Thompson, M.E. Heiny, R.C. Redding-Lallinger, F.J. Kirkham, N. Dixon, C.E. Gonzalez, K.A. Kalinyak, C.T. Quinn, J.J. Strouse, J.P. Miller, H. Lehmann, M.A. Kraut, W.S. Ball, Jr., D. Hirtz, and J.F. Casella

Snapshot about children with SCA in the USA

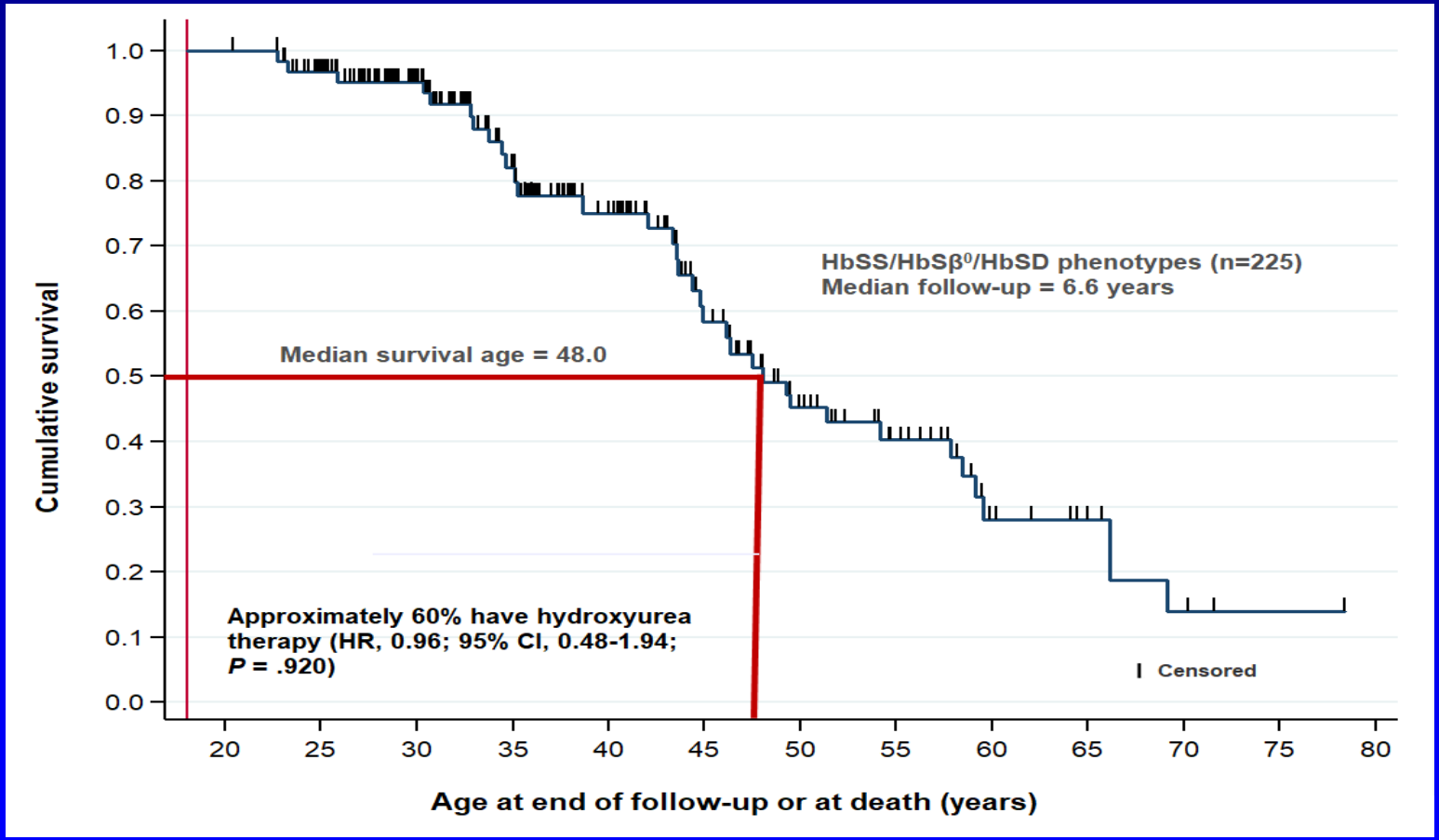
(yearly income per capita is $8,500)

- 86 % (169 of 196) patients completed all exit data required
  - Monthly transfusions for 3 years (90 participants)
  - 3-MRIs of the head
  - 4-Neurology evaluations
  - 3-Cognitive Test Evaluations-WASI, BRIEF
  - 2-Quality of life assessments
- 9% (18 of 196) patients completed partial exit data requirements
- 5 % (9 of 196) patients did not complete any exit data

The Bad!

What about adults with sickle cell disease?

Adults with sickle cell disease have a shortened life-span median survival for HbSS: 48.0 years with no change in 25 years

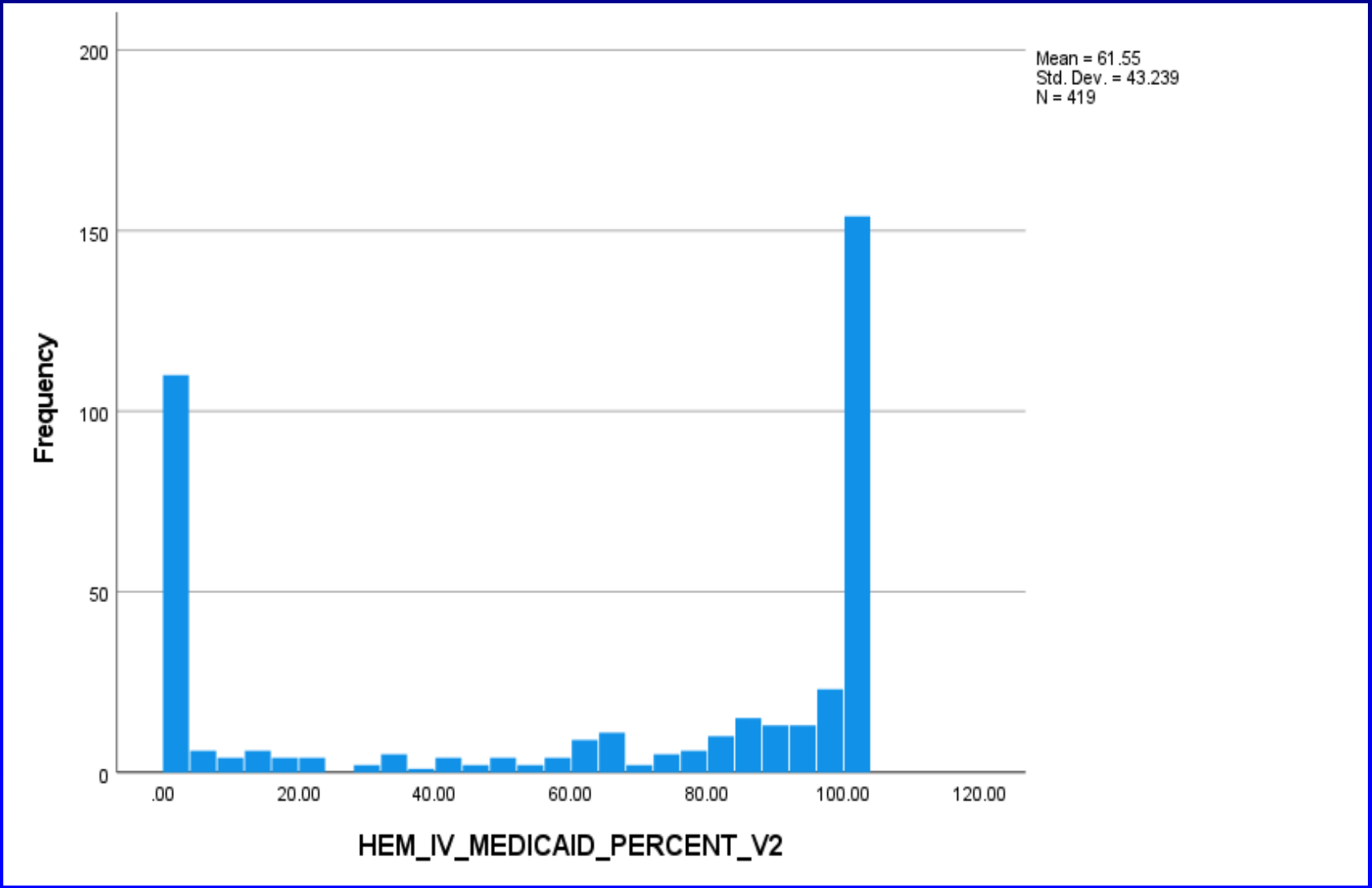


DeBaun M et al. Blood, 2019. 133(6): 615-617.

An Automated Contemporaneous Cohort in Adults with Sickle Cell Anemia to Predict Survival After Disease-Modifying Therapy
2014-2021- Vanderbilt University
(Cronin, Wuichet)

- Identified 419 children and adults
- Median follow-up of 7.4 years (IQR 3.6-13.5 years)
- A total of 98% (274 of 277) remained alive at age 18 years of age
- The median age of survival was 49.3 years of age
- The overall survival
  - hematopoietic transplants: 100% (22 of 22)
  - at least one year of hydroxyurea: 90.5% (220 of 243)nl
  - no treatment: 87.8% (86 of 98)
  - at least two years of transfusions: 78.6% (44 of 56).

Bimodal distribution of Medicaid in the Adult Vanderbilt Cohort



Poverty is the biggest risk factor for death in adults with SCA

	Sig.	Exp(B)	95.0% CI for Exp(B)	
			Lower	Upper
Age at the first visit	.000	1.086	1.065	1.107
Sex (male)	.133	1.610	.864	3.000
Hydroxyurea	.016	.379	.172	.834
Transfusion	.440	.705	.291	1.711
Transplant	.975	.000	.000	.
MEDICAID_1-99%	.038	3.052	1.063	8.763
MEDICAID_100%	.000	7.440	2.436	22.724

Why aren't more children and adults with Sickle Cell Disease Opting for Cure?

Two major challenges for curative therapy in children and adults with SCD

1. Small donor pool for children and adults with SCD for matched related donors
   - Less than 20% of patients with sickle cell disease
2. Myeloablative therapy curative therapy is too toxic for most adults because of pre-existing heart, lung and kidney disease
   - ~ 60% at least one major organ dysfunction
   - ~ 25% have two of three organ dysfunction

1.Am J Pediatr Hematol Oncol. 1994 Feb;16(1)

The Future!

Genetics to Guide Risks vs. Benefits of Therapies

New FDA-approved Therapies
- L-glutamine
- Crizanlizumab
- Voxelotor

Curative Therapies
- Allogeneic hematopoietic stem cell transplantation (HSCT)
- Gene therapy and Gene editing

HSCT & Gene Therapy Preparative Regimens

Fludarabine – neurotoxicity
Cyclophosphamide – cardiotoxicity, malignancy
Busulfan – pulmonary and liver toxicity, malignancy
Total body irradiation – cardiac, liver, pulmonary toxicity

Post-HSCT Immunosuppression

Tacrolimus – renal toxicity
Cyclosporine – renal toxicity
Sirolimus – renal and pulmonary toxicity

Conclusion USA: Social determinants of SCD is not associated with participation in rigorous clinical trials in children, but is associated with early death in adults

- A significant gap exist between evidence-based practice and usual care for children and adults with SCD
- New FDA approved therapies and curative therapies will continue to lag in uptake until the gap closes.