

Impact of hemoglobin variants on Hb A1c interpretation –

Do we assume too much?



How true ?

Once there was a tiger which boasted that it can run faster than any one.

One day he chased a rabbit and failed to catch it.

“All right” said the tiger; “of course I failed on my boast.

But, remember the rabbit was running for its life and I, for my dinner.”

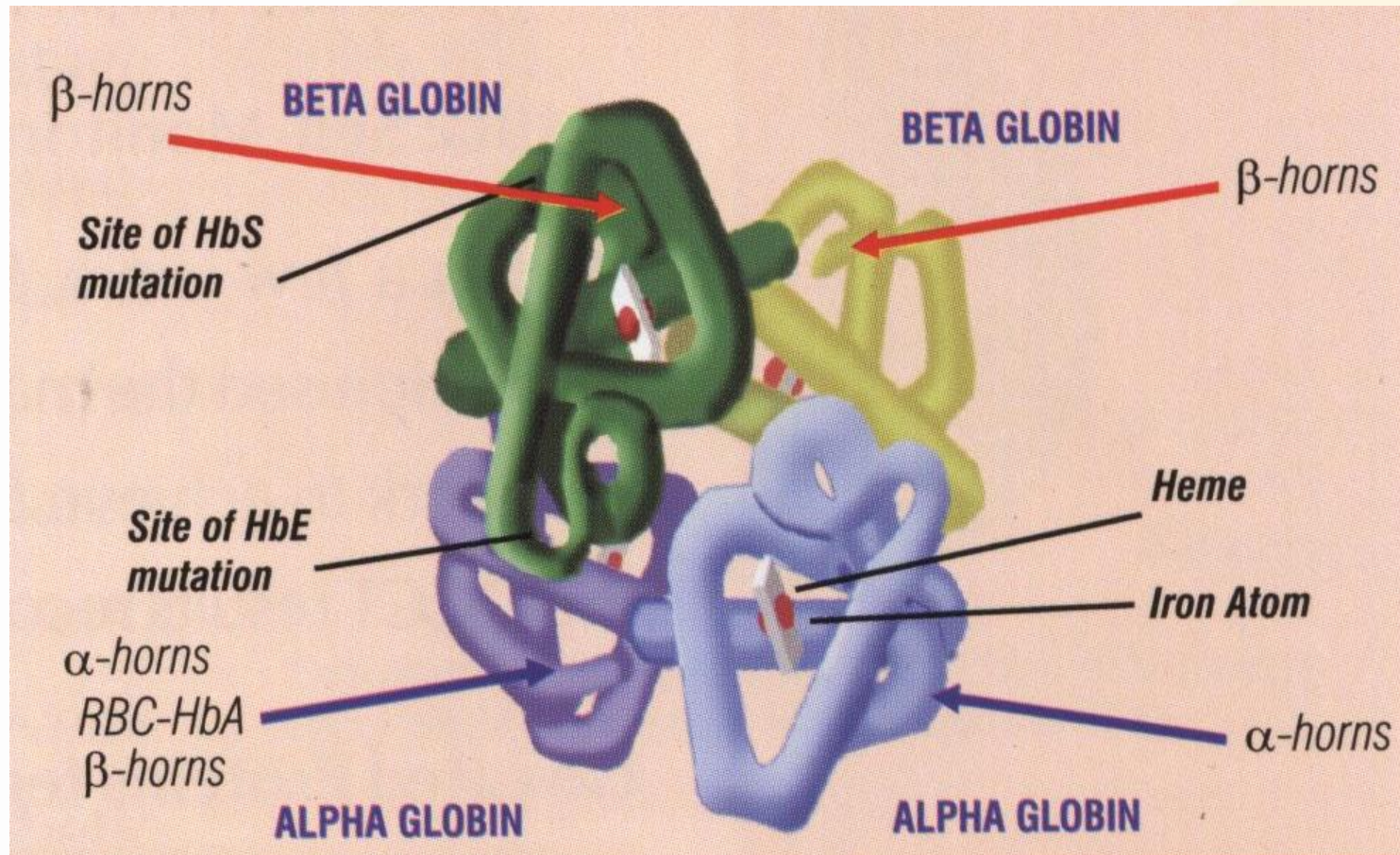
Now, decide who is the rabbit and who is the tiger - among we and our patient !

Alarming facts

- 7% of the world's population carries a Hb variant
- Most common monogenic diseases
- The effects range from clinically silent to life-threatening.
- Some Hb variants can lead to decreased red blood cell (RBC) survival.

Haemoglobin

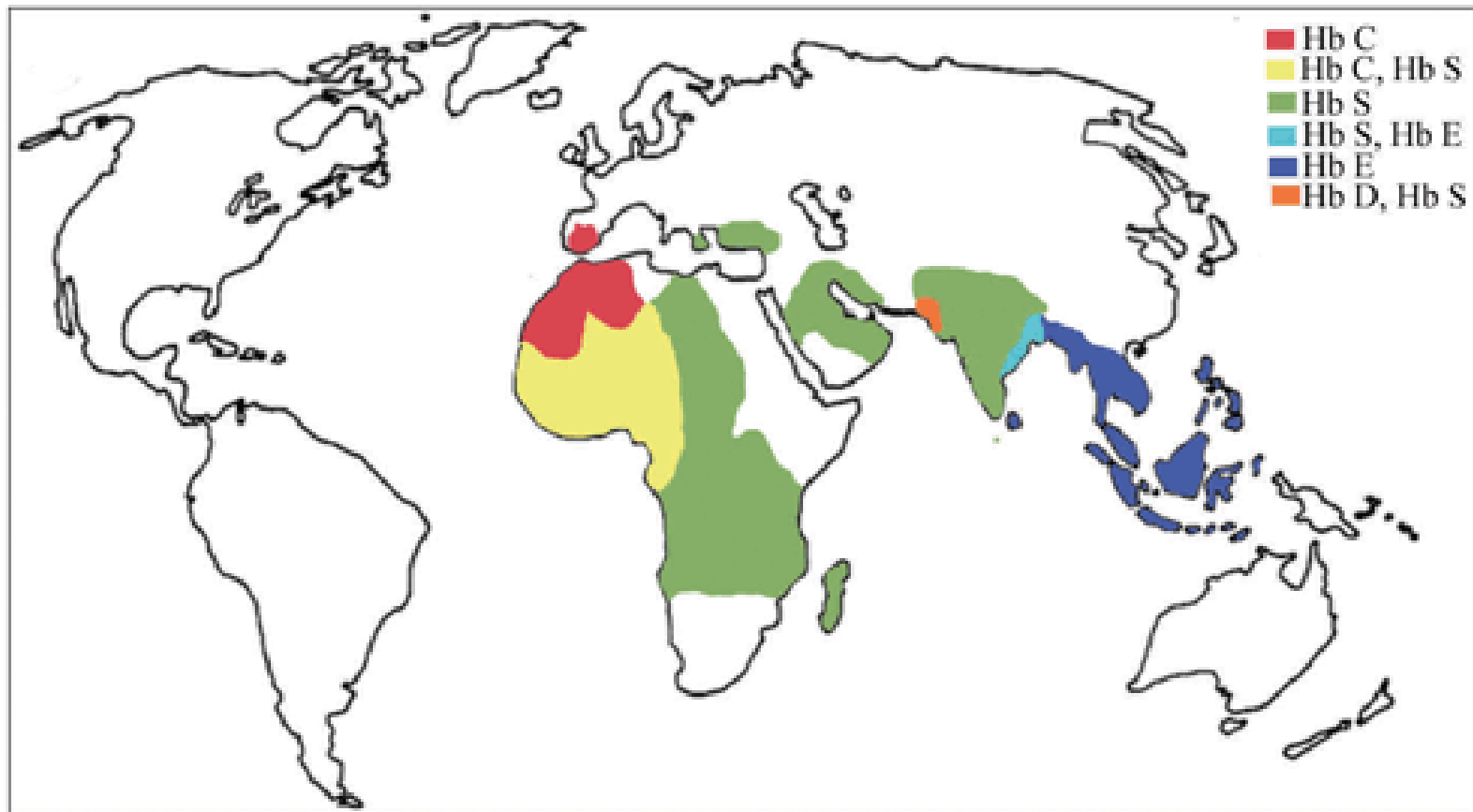
Structure of Hb



When should I Suspect?

- ✓ Results of blood glucose test or self-monitoring of blood glucose don't match the results of your A1C test
- ✓ A1C result is different than expected
- ✓ A1C result - is very high—above 15 percent
- ✓ Most recent A1C result is very different from your last A1C result
- ✓ members of pt family have sickle cell trait or sickle cell anemia

Distribution of Hb variants



Most common Hb variants worldwide in descending order of prevalence are

- ✓ **HbS,**
- ✓ **HbE,**
- ✓ **HbC,**
- ✓ **HbD**

Hb Variant	Prevalence in the U.S.
Hb S	8.3% of African Americans
Hb E	30% of Southeast Asians
Hb C	3% of African Americans
Hb D	2% of North Indians and descendants from Pakistan and Afghanistan

Average lifespan of RBCs from hematologically normal or Hb trait individuals

Hb	Average RBC Lifespan in Days (n)
Hb A	120
Hb S	93 (3) ²⁰
Hb E	No Data
Hb C	87 (6) ¹⁸
Hb D	115 (3) ¹⁹

Interference of Heterozygous Variants S, C, D, E, and Elevated HbF with Specific HbA1c Methods

- a** An ↑ or ↓ indicates an artificial increase or decrease in results.
- b** Not evaluated.
- c** HbF levels above 15% cause a clinically significant low bias.
- d** Offline manual recalculation must be performed if the HbF peak is mislabeled as labile HbA1c (LA1C)

Methods used most commonly

- Immunoassay,
- Ion-exchange High-Performance Liquid Chromatography (HPLC)
- Boronate affinity HPLC,
- Enzymatic assays

Interference of Heterozygous Variants S, C, D, E, and Elevated HbF with Specific HbA1c Methods

Manufacturer	Method	Interference from				
		HbAS	HbAC	HbAE	HbAD	↑ HbF
Immunoassay						
Abbott	Architect/Aeroset	Yes ↑	Yes ↑	_b	_b	_b
Bayer (Metrika)	A1cNOW	Yes ↑	Yes ↑	No	No	_b
Beckman	Synchron System	No	No	No	No	_b
Dade	Dimension	No	No	No	No	_b
Olympus	AU system	Yes ↑	Yes ↑	No	No	_b
Ortho-Clinical	Vitros	No	No	No	No	_b
Point Scientific	HbA1c on Modular P	No	No	No	No	_b
Roche	Cobas Integra	Yes ↑	Yes ↑	_b	_b	_b
Roche	Cobas Integra Gen.2 (Tina Quant)	No	No	No	No	_b
Roche/Hitachi	Hitachi (Tina Quant)	No	No	No	No	_b
Siemens (Bayer)	Advia	Yes ↑	Yes ↑	_b	_b	_b

Manufacturer	Method	Interference from				
		HbAS	HbAC	HbAE	HbAD	↑ HbF
Siemens (Bayer)	DCA 2000	No	No	No	No	Yes ^c
Ion-exchange HPLC						
Bio-Rad	D-10 (short)	No	No	No	No	_ ^b
Bio-Rad	D-10 (extended)	No	No	No	No	_ ^b
Bio-Rad	Variant A1c	No	No	No	Yes ↓	_ ^b
Bio-Rad	Variant II A1c	No	No	No	No	No
Bio-Rad	Variant II Turbo A1c	No	No	Yes ↑	Yes ↑	_ ^b
Menarini	HA8140 (diabetes mode)	Yes ↑	No	_ ^b	_ ^b	_ ^b
Menarini	HA8160 (diabetes mode)	No	No	Yes ↓	Yes ↓	_ ^b
Menarini	HA8160 (TP mode)	No	No	No	Not quantified	_ ^b
Tosoh	A1c 2.2 Plus	No	No	Yes ↓	No	Yes ^c
Tosoh	G7	No	No	Yes ↓	No	No ^d
Tosoh	G8	_ ^b	_ ^b	Yes ↓	No	_ ^b
Boronate affinity						
Axis-Shield	Afinion	No	No	No	No	_ ^b
Primus	Boronate affinity HPLC	No	No	No	No	Yes ^c

Summary -

- Hb variants can interfere with HbA1c methods for variety of reasons.
- All HbA1c methods are inappropriate for the assessment of glycemic control in pts homozygous for HbS or HbC, with HbSC disease
- Laboratorians should be aware of the limitations of their method with respect to interference from the most prevalent Hb variants.
- Select new methods that are less likely to have interference.
- If ion exchange HPLC method is used, then careful inspection of chromatograms may identify the presence of aberrant peaks produced by variants.
- **Any result that does not fit the clinical picture should be investigated further with the clinician**

Alternative for pts with Hb variant

- Alternative non-hemoglobin methods of measuring glycemic control
 - ✓ Fructosamine,
 - ✓ Glycated serum albumin
 - ✓ Self-monitoring of blood glucose

