Pharmacogenetic association of β1-adrenergic receptor Ser49Gly polymorphism with outcomes in the Secondary Prevention of Small Subcortical Strokes (SPS3) trial

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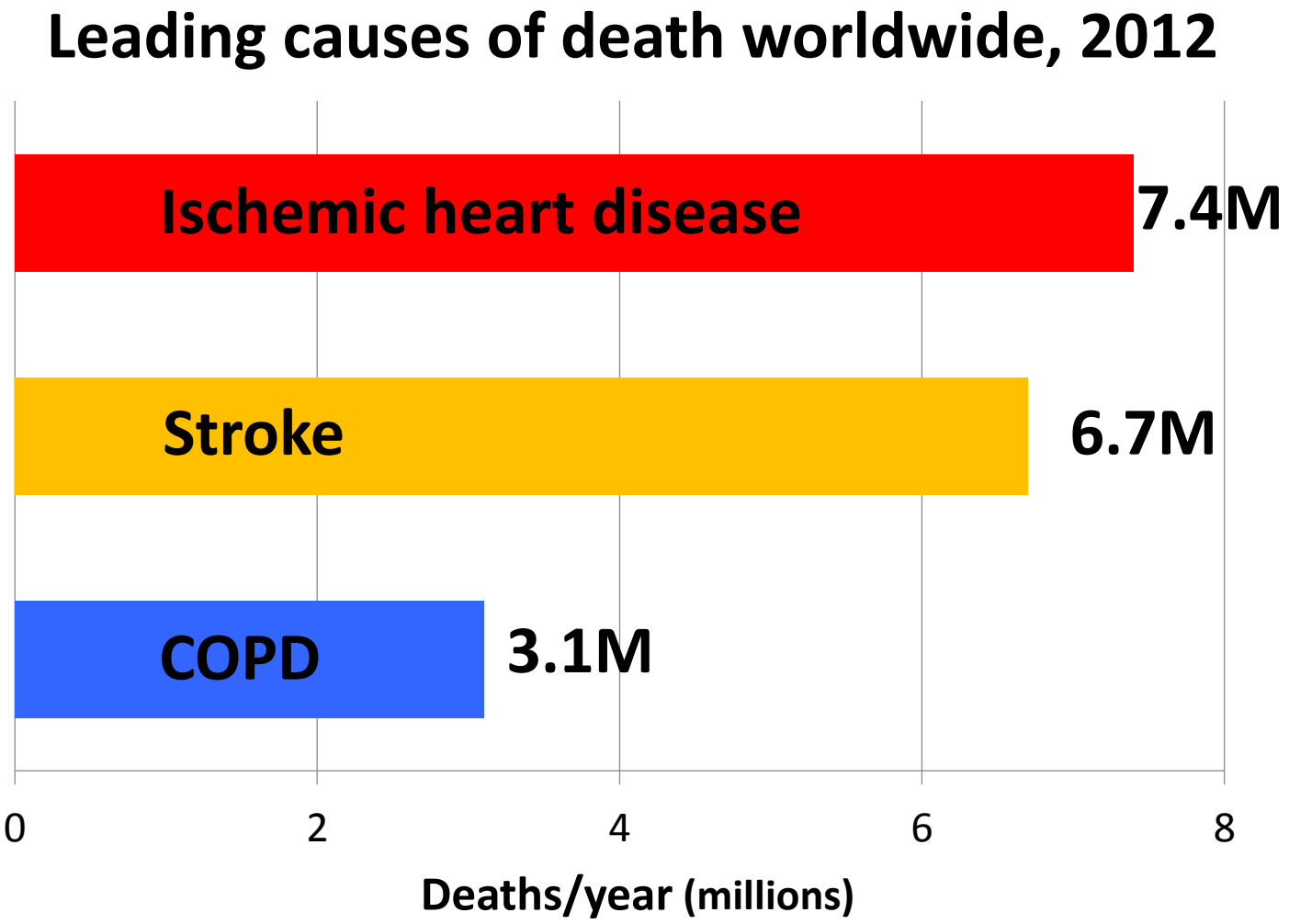
Background

- Cardiovascular diseases (CVD) are a leading cause of death worldwide (18M)
- Stroke accounts for a significant portion
- β-blockers widely used for management of CVD
  - Targets primarily cardiac β1- adrenergic receptors



WHO: Fact sheet, 2014; CDC: Stroke Statistics, 2015

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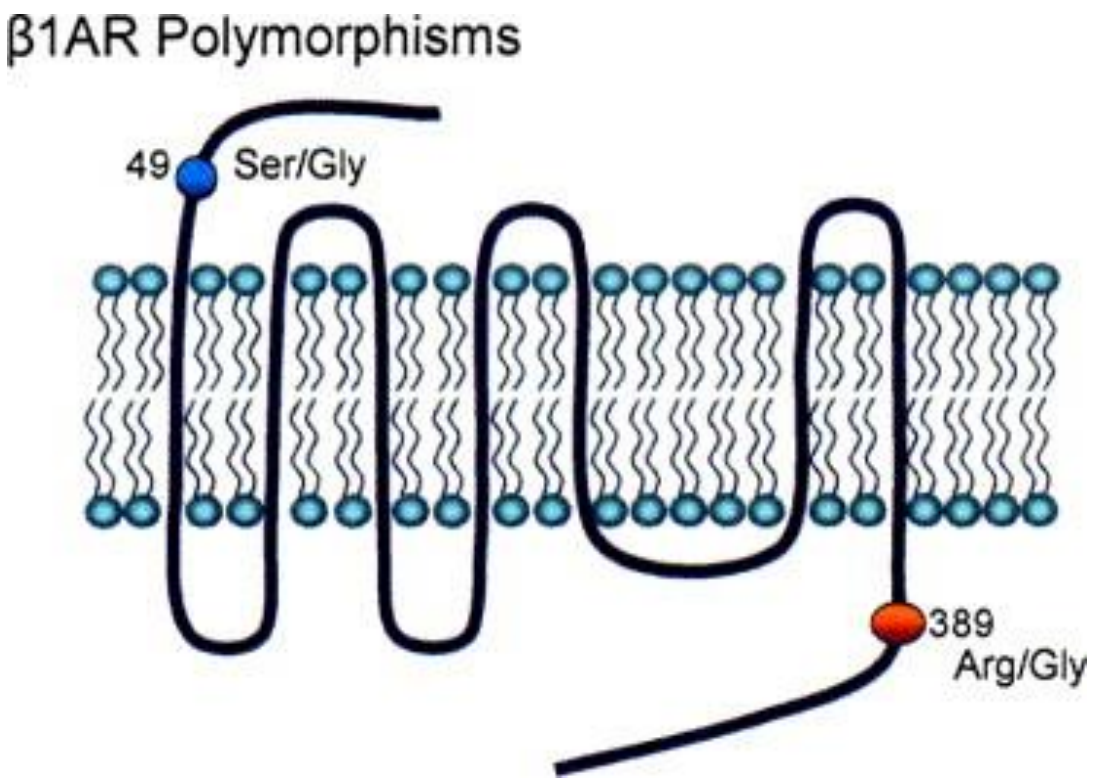
Background

- Two common polymorphisms associated with CVD risk and treatment response, Ser49Gly & Arg389Gly
(Liggett et al. PMID: 21289619)

- Gly49 allele associated with risk of ischemic stroke
(Kumar et al. PMID: 25510377)

- Its association with β-blocker use in the setting of stroke is unknown



Namath et al. Seminars in Anesthesia, Perioperative Medicine and Pain, Volume 26, Issue 1, 2007, 2–9

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Objective

- To examine whether Ser49Gly and Arg389Gly polymorphisms in *ADRB1* are associated with major adverse cardiovascular events (MACE), composed primarily of recurrent ischemic stroke

- To examine whether there is a pharmacogenetic association for β-blocker use and the Ser49Gly and Arg389Gly polymorphisms with risk of MACE

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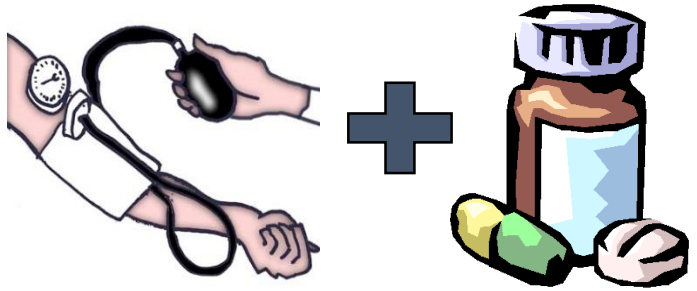
Study Population

- Secondary Prevention of Small Subcortical Strokes (SPS3) trial
  - RCT, 2x2 design: BP target & antiplatelet therapy
  - ≥ 30 years old; recent small artery stroke
  - Of 3,020 SPS3 participants, 1,139 in SPS3-GENES → 926 with DNA samples & hypertension at study entry
- Validation cohort: NINDS Stroke Genetics Network (SiGN); 30 cohorts: N=27,550 White participants with various stroke subtypes



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Methods

MACE: composite of all-cause stroke, CV death, myocardial infarction

Genotyping:

- SPS3: TaqMan assay-based on QuantStudio
- SiGN: Imputed data to 1000G Phase 3

Analysis:

- Main effects association (SPS3) between Ser49Gly or Arg389Gly and recurrent stroke
- Validation (SiGN): Association between Ser49Gly & incident stroke
- Pharmacogenetic associations (SPS3) for β-blocker use and Ser49Gly or Arg389Gly with MACE

- Kaplan-Meier/Cox regression (SPS3); logistic regression (SiGN)

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SPS3 Baseline Characteristics	MACE (n=67)	No MACE (n=859)	P-value
Age (years)	58 ± 9	63 ± 10	0.490
Male	40 (60)	521 (61)	0.897
BMI (kg/m^2)	30 ± 6	28 ± 5	0.250
SBP	147 ± 17	145 ± 18	0.363
DBP	80 ± 11	79 ± 10	0.639
Intensive BP control target	29 (43)	443 (52)	0.206
Current smoker	17 (25)	149 (17)	0.100
Medical history			
Diabetes	27 (40)	258 (30)	0.098
Myocardial infarction	6 (9)	32 (4)	0.050
PVD	5 (7)	19 (2)	0.025
Medications			
β-blocker	23 (34)	194 (23)	0.036
Ca+ channel blocker	24 (36)	240 (28)	0.205
Thiazide diuretic	25 (37)	318 (37)	1.000
ACE inhibitor	40 (60)	495 (58)	0.798
ARB	11 (16)	171 (20)	0.632

No (%) or Mean ± SD

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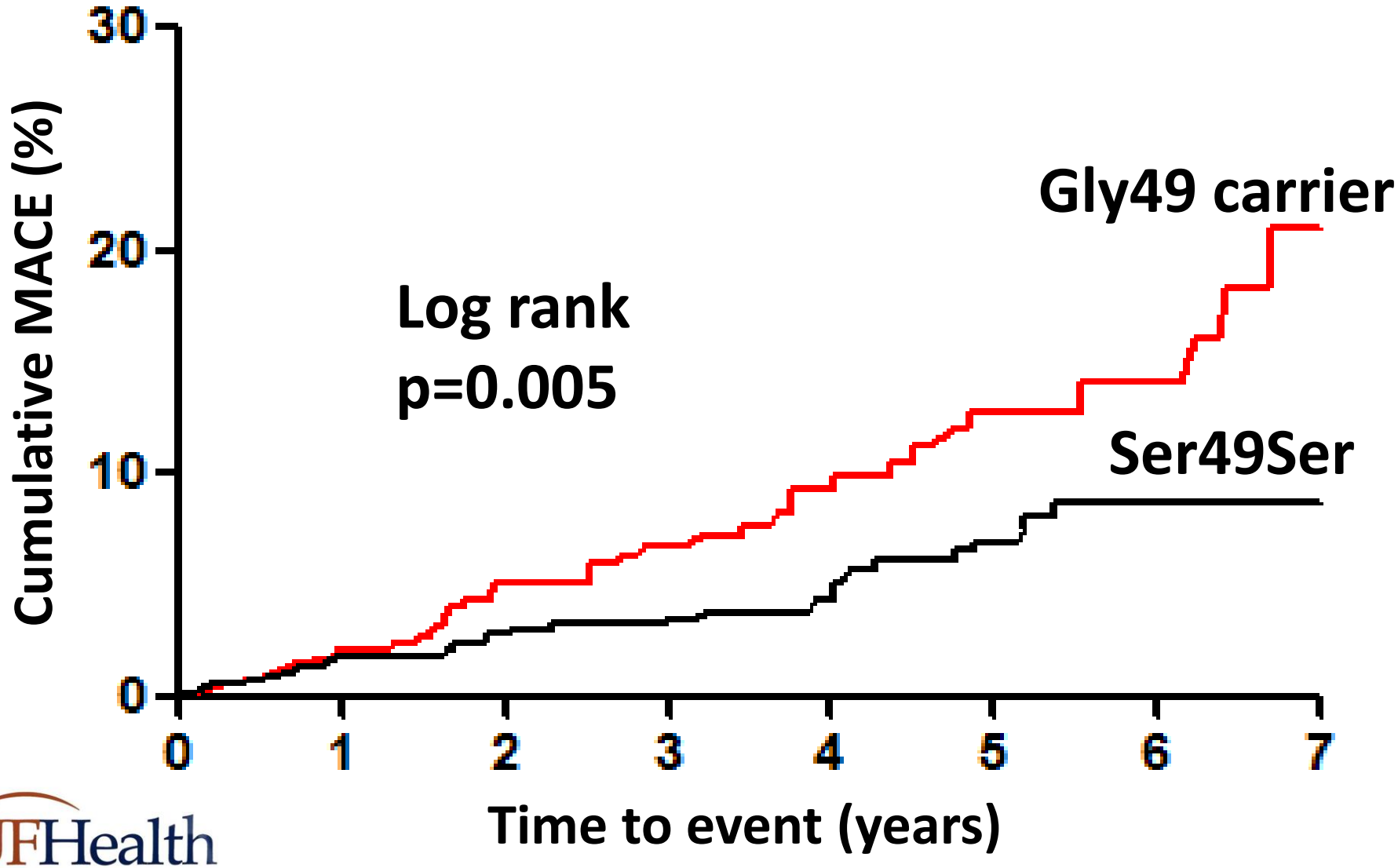
Kaplan-Meier survival analysis: Main effects



Event rate: 7%

- Gly49 carrier and MACE: **HR 1.75**, 95% CI 1.05-2.94, p=0.033
- SiGN: Gly49 carrier and small artery stroke: **OR 1.15**, 95% CI 1.04-1.27, p=0.005
- No association with Arg389Gly

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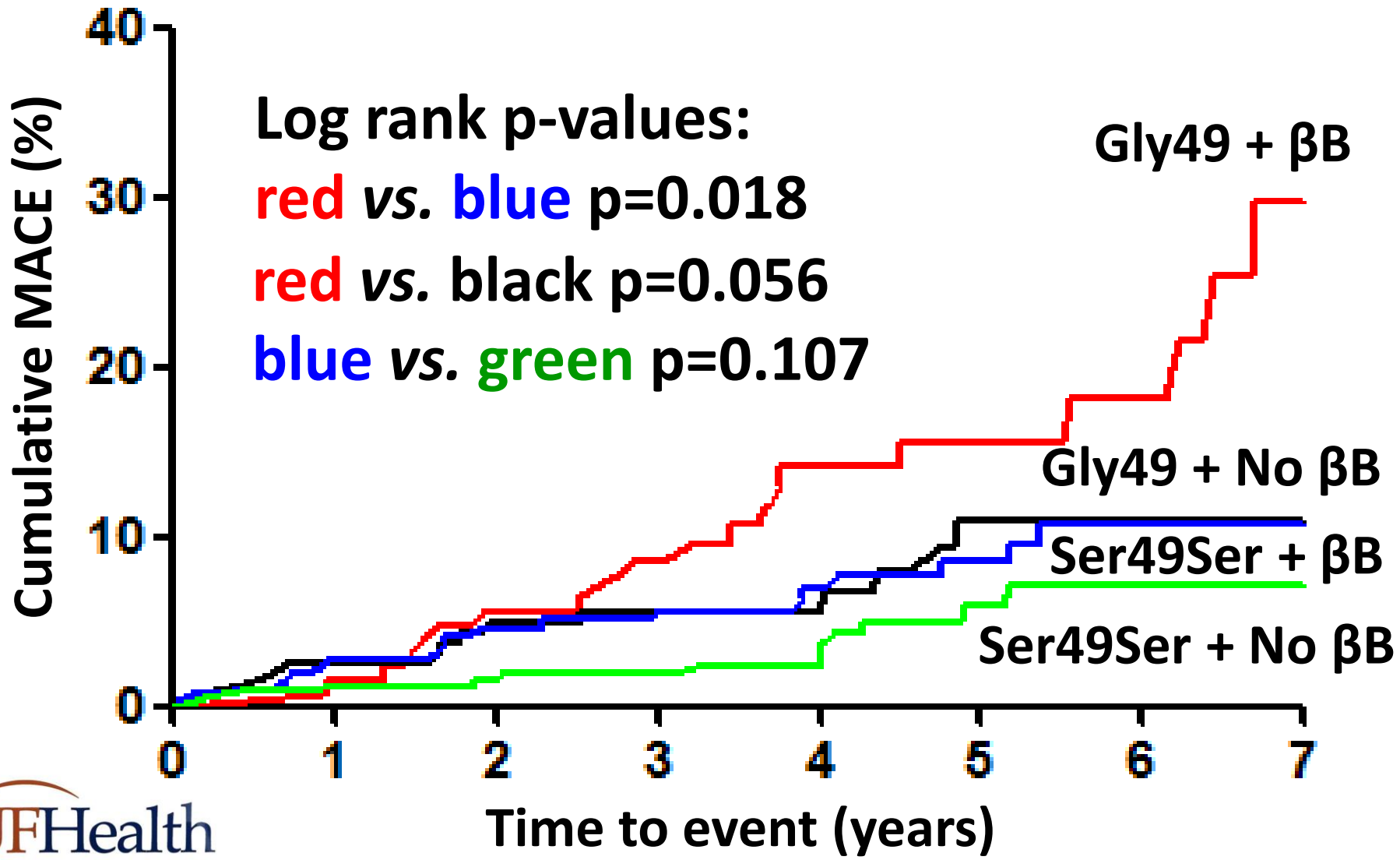
Kaplan-Meier survival analysis: PGx effects



Multivariable Cox model for MACE:

- Gly49+βB *vs.* others **HR 2.01**, 95% CI 1.22-3.63, p=0.007
- Gly49+βB *vs.* Ser49Ser+βB: **HR 1.76**, 95% CI 0.90-3.44, p=0.10
- No PGx associations for Arg389Gly

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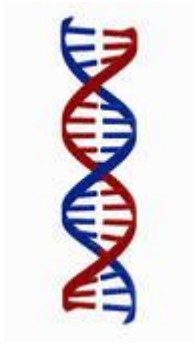
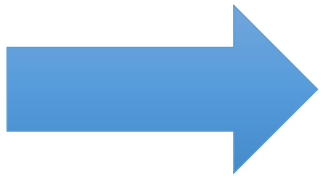
Conclusions

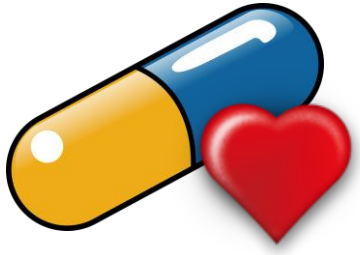


Gly49 carrier

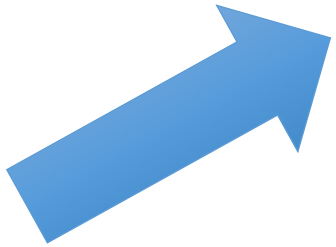


Ischemic stroke
-small artery

Gly49 carrier



β-blocker



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