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

Leading causes of death worldwide, 2012

- Ischemic heart disease: 7.4M
- Stroke: 6.7M
- COPD: 3.1M

• 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

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
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
**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)**
<table>
<thead>
<tr>
<th>SPS3 Baseline Characteristics</th>
<th>MACE (n=67)</th>
<th>No MACE (n=859)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58 ± 9</td>
<td>63 ± 10</td>
<td>0.490</td>
</tr>
<tr>
<td>Male</td>
<td>40 (60)</td>
<td>521 (61)</td>
<td>0.897</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30 ± 6</td>
<td>28 ± 5</td>
<td>0.250</td>
</tr>
<tr>
<td>SBP</td>
<td>147 ± 17</td>
<td>145 ± 18</td>
<td>0.363</td>
</tr>
<tr>
<td>DBP</td>
<td>80 ± 11</td>
<td>79 ± 10</td>
<td>0.639</td>
</tr>
<tr>
<td>Intensive BP control target</td>
<td>29 (43)</td>
<td>443 (52)</td>
<td>0.206</td>
</tr>
<tr>
<td>Current smoker</td>
<td>17 (25)</td>
<td>149 (17)</td>
<td>0.100</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>27 (40)</td>
<td>258 (30)</td>
<td>0.098</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>6 (9)</td>
<td>32 (4)</td>
<td>0.050</td>
</tr>
<tr>
<td>PVD</td>
<td>5 (7)</td>
<td>19 (2)</td>
<td>0.025</td>
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<tr>
<td>Medications</td>
<td></td>
<td></td>
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<tr>
<td>β-blocker</td>
<td>23 (34)</td>
<td>194 (23)</td>
<td>0.036</td>
</tr>
<tr>
<td>Ca+ channel blocker</td>
<td>24 (36)</td>
<td>240 (28)</td>
<td>0.205</td>
</tr>
<tr>
<td>Thiazide diuretic</td>
<td>25 (37)</td>
<td>318 (37)</td>
<td>1.000</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>40 (60)</td>
<td>495 (58)</td>
<td>0.798</td>
</tr>
<tr>
<td>ARB</td>
<td>11 (16)</td>
<td>171 (20)</td>
<td>0.632</td>
</tr>
</tbody>
</table>

No (%) or Mean ± SD
Kaplan-Meier survival analysis: Main effects

- Gly49 carrier and MACE: HR 1.75, 95% CI 1.05-2.94, p=0.033
  - Event rate: 7%
- SiGN: Gly49 carrier and small artery stroke: OR 1.15, 95% CI 1.04-1.27, p=0.005
- No association with Arg389Gly
Kaplan-Meier survival analysis: PGx effects

Log rank p-values:
- red vs. blue p=0.018
- red vs. black p=0.056
- blue vs. green p=0.107

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
Conclusions

Gly49 carrier

β-blocker

Ischemic stroke - small artery
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