A single nucleotide polymorphism in the p27^{kip1} gene is associated with primary patency of lower extremity vein bypass grafts


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Disclosures

• None
Vein Bypass Graft Failure

- 30-50% of infrainguinal vein grafts develop significant stenosis or occlusion within 5 years
- Adverse remodeling, hyperplasia
- No effective pharmacotherapy
Risk Factors for Vein Graft Failure

- Vein quality
- Critical ischemia vs claudication
- Redo surgery
- Smoking
- Non-white race/ethnicity
- Younger age
- Prothrombotic states
- Dyslipidemia

Genetics??
Implantation

0hr | 24hr | 1wk | 1mo | 3mo | 1yr

Pre-existing Vein Disease

Ischemia/Reperfusion
Platelets/thrombosis

EC Injury+Repair

SMC Migration/Proliferation

Matrix Accumulation

Lipid Accumulation/Fibrosis

Hemodynamic Adaptation

Overall incidence of primary trial endpoint: 25.4% at one year
Vein Graft Failure (≥ 75%)

Per Patient
- **Edifoligide**: 45% (436/965)
- **Placebo**: 46% (442/955)
  - P value = 0.660

Per Graft
- **Edifoligide**: 29% (601/2295)
- **Placebo**: 30% (597/2242)
  - *P value = 0.829*

*Adjusted for intra-pt graft correlation*
p27<sup>kip1</sup> is a cell cycle inhibitor

Nabel EG. *Nat Rev Drug Disc* 2002;1:587-598
p27\textsuperscript{kip1} in vascular injury

p27^{kip1} in vascular injury

p27kip1$^{\text{C} \rightarrow \text{A}}$ A Single Nucleotide Polymorphism Is Associated With Restenosis Risk After Coronary Stenting and Modulates p27kip1 Promoter Activity

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Methods

• Genetic association study in LEVB patients

• Two Cohorts
  – Boston, MA (N=204) prospective cohort study correlating inflammation with LEVB outcomes over time (HL 75771)
  – Seattle, WA (N=51) observational study correlating incidence of LEVB stenosis with biological factors

• Genomic DNA extracted from whole blood

• Genotyping for p27kip1 SNP rs36228499 (-838C>A) by PCR

• Genotypes correlated with graft events by univariate (log rank), then multivariable (Cox Proportional Hazards) analyses
## Covariate distribution by p27 genotype

<table>
<thead>
<tr>
<th>covariate</th>
<th>-838AA (n=35 17.2%)</th>
<th>-838CA (n=108 52.9%)</th>
<th>-838CC (n=61 29.9%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>67.3 (12.1)</td>
<td>66.8 (67.5)</td>
<td>67.8 (9.95)</td>
<td>.891</td>
</tr>
<tr>
<td>Male Gender, N (%)</td>
<td>26 (74.3)</td>
<td>81 (75.0)</td>
<td>40 (65.6)</td>
<td>.402</td>
</tr>
<tr>
<td>Caucasian race, N (%)</td>
<td>31 (88.6)</td>
<td>99 (91.7)</td>
<td>47 (77.1)</td>
<td>.025</td>
</tr>
<tr>
<td>DM, N (%)</td>
<td>19 (54.3)</td>
<td>53 (49.1)</td>
<td>35 (57.4)</td>
<td>.567</td>
</tr>
<tr>
<td>CAD, N (%)</td>
<td>14 (40.0)</td>
<td>56 (51.9)</td>
<td>41 (67.2)</td>
<td>.027</td>
</tr>
<tr>
<td>Current tobacco, N (%)</td>
<td>10 (28.6)</td>
<td>46 (42.6)</td>
<td>22 (36.1)</td>
<td>.305</td>
</tr>
<tr>
<td>CLI, N (%)</td>
<td>20 (57.1)</td>
<td>62 (57.4)</td>
<td>37 (60.7)</td>
<td>.908</td>
</tr>
<tr>
<td>Re-do LEVB, N (%)</td>
<td>3 (8.6)</td>
<td>11 (10.2)</td>
<td>6 (9.8)</td>
<td>.962</td>
</tr>
<tr>
<td>Conduit SSGSV, N (%)</td>
<td>32 (91.4)</td>
<td>91 (84.3)</td>
<td>46 (75.4)</td>
<td>.114</td>
</tr>
<tr>
<td>Infrapopliteal target, N (%)</td>
<td>17 (48.6)</td>
<td>47 (43.5)</td>
<td>36 (59.0)</td>
<td>.153</td>
</tr>
<tr>
<td>Statin use, N (%)</td>
<td>30 (85.7)</td>
<td>89 (82.4)</td>
<td>47 (77.1)</td>
<td>.532</td>
</tr>
<tr>
<td>Antiplatelet Rx, N (%)</td>
<td>29 (82.9)</td>
<td>86 (79.6)</td>
<td>49 (80.3)</td>
<td>.916</td>
</tr>
<tr>
<td>CRP &gt;5mg/L, N (%)</td>
<td>14 (40.0)</td>
<td>36 (33.3)</td>
<td>24 (39.3)</td>
<td>.650</td>
</tr>
</tbody>
</table>
Primary Patency by p27 genotype

Boston cohort

-838 CA Genotype

-838 CC Genotype

-838 AA Genotype
# Clinical Outcomes by p27 genotype

Boston cohort

<table>
<thead>
<tr>
<th>Outcome</th>
<th>AC/CC (n = 169)</th>
<th>AA (n = 35)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day graft failure: N (%)</td>
<td>5 (3.0)</td>
<td>2 (5.7)</td>
<td>0.91</td>
</tr>
<tr>
<td>30-day MACE: N(%)</td>
<td>5 (3.0)</td>
<td>2 (5.7)</td>
<td>0.91</td>
</tr>
<tr>
<td><strong>Primary Patency, 1 year: % (S.E.)</strong></td>
<td>66.5 (3.8)</td>
<td>84.6 (6.3)</td>
<td>0.029</td>
</tr>
<tr>
<td><strong>Primary Patency, 3 years: % (S.E.)</strong></td>
<td>60.7 (4.0)</td>
<td>80.7 (7.2)</td>
<td>0.029</td>
</tr>
<tr>
<td>Secondary Patency, 1 year: % (S.E.)</td>
<td>84.7 (2.9)</td>
<td>93.9 (4.2)</td>
<td>0.13</td>
</tr>
<tr>
<td>Secondary Patency, 3 years: % (S.E.)</td>
<td>81.9 (3.2)</td>
<td>93.9 (4.2)</td>
<td>0.13</td>
</tr>
<tr>
<td>Limb salvage rate, 3 years: % (S.E.)</td>
<td>92.3 (2.5)</td>
<td>91.1 (4.9)</td>
<td>0.71</td>
</tr>
<tr>
<td>Survival rate, 3 years: % (S.E.)</td>
<td>79.0 (3.5)</td>
<td>73.8 (8.9)</td>
<td>0.97</td>
</tr>
</tbody>
</table>
Primary Patency by p27 genotype

Kaplan-Meier bypass graft primary patency estimates

-838 AA
-838 AC/CC

p = .029 (log-rank test)
### Cox Model for Primary Patency

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.01 (0.99-1.03)</td>
<td>0.387</td>
</tr>
<tr>
<td>Non-white race</td>
<td>2.0 (1.12-3.60)</td>
<td>0.019</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.58 (0.95-2.62)</td>
<td>0.075</td>
</tr>
<tr>
<td>CLI</td>
<td>1.52 (0.86-2.69)</td>
<td>0.151</td>
</tr>
<tr>
<td>Re-do bypass</td>
<td>1.99 (1.03-3.84)</td>
<td>0.041</td>
</tr>
<tr>
<td>Baseline hs-CRP &gt;5mg/L</td>
<td>1.23 (0.77-2.16)</td>
<td>0.335</td>
</tr>
<tr>
<td>p27&lt;sup&gt;kip1&lt;/sup&gt; -838 AA</td>
<td>0.41 (0.18-0.97)</td>
<td>0.039</td>
</tr>
</tbody>
</table>
Secondary Patency by p27 genotype

Kaplan-Meier bypass grafts secondary patency estimates

-838 AA

-838 AC/CC

p = .13 (log-rank test)
Early graft remodeling by p27 genotype (N=56)

- Imaging substudy
- Lumen diameter by M-mode, intraop, 1 mo
- Homozygous CC genotype had less positive remodeling (univariate analysis)
- Small sample size
**$p27^{kip1}$ genotype frequencies and observed effect size**

Relative effects size of the AA genotype in three different cohorts.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Overall prevalence of stenosis (%)</th>
<th>Frequency of -838 AA genotype</th>
<th>Point estimate of effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boston Cohort, N=202</td>
<td>34.8%</td>
<td>17.2%</td>
<td>.41 (HR)</td>
</tr>
<tr>
<td>Seattle Cohort, N=51</td>
<td>37.3%</td>
<td>11.8%</td>
<td>.30 (OR)</td>
</tr>
<tr>
<td>Netherlands Cohort, N=598</td>
<td>18%</td>
<td>21.2%</td>
<td>.29 (HR)</td>
</tr>
</tbody>
</table>
Conclusions

• A common SNP in the \( p27^{kip1} \) gene promoter region is associated with primary patency of lower extremity vein bypass grafts.

• This SNP is also associated with outcomes of coronary stenting, suggesting a broadly important mechanism in vascular injury and healing.

• SNP frequencies and effect sizes observed were similar across three distinct geographic cohorts and two different vascular beds.
Limitations

• Modest sized study population limits ability to assess covariate effects (confounding)

• Requires prospective validation in another, larger multi-center cohort with greater racial and ethnic diversity

• Unclear if the observed SNP association is directly related to p27 gene expression

• Mechanism of effect (IH vs remodeling) unclear

• Only a single candidate SNP was examined
Acknowledgements

• Participating surgeons and clinical research staff at BWH, BIDMC, WRVA in Boston, VAMC-Seattle

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