NOVEL ORAL ANTICOAGULANT (NOAC) USE AFTER LOWER EXTREMITY BYPASS IS ASSOCIATED WITH INCREASED GRAFT AND LIMB EVENTS AND RESULTS DO NOT LOOK BETTER THAN WITH WARFARIN

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William P. Robinson MD
Division of Vascular and Endovascular Surgery
University of Virginia School of Medicine
Charlottesville, VA

Anticoagulation after Lower Extremity Bypass (LEB)

- Veterans Affairs Cooperative study #362 (RCT) and a handful of retrospective studies have shown benefit to anticoagulation in patency of prosthetic or “high risk” vein LEB
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- Primary basis of common surgical practice:
  - ASA for standard vein bypass and prosthetic to AK pop
  - ASA and Warfarin for prosthetic bypass below the knee, “high risk” conduit, and poor outflow

Guidelines for Medical Therapy after LEB Weak and Highly Variable

- Recommend antiplatelet after LEB
- “Evidence inadequate to support a definitive recommendation” on anticoagulation

Bypass Patients have other Indications for Anticoagulation

25-30% of LEB patients are discharged on anticoagulation

Novel Oral Anticoagulants (NOACs)

Advantages
- No need for laboratory monitoring
- Lower food and drug interactions
- Broader therapeutic window
- Less bleeding risk?

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NOACs

- Novel Oral Anticoagulants (NOACs) approved for non-valvular atrial fibrillation, prophylaxis and treatment DVT/PE
  - dabigatran (2010)
  - rivaroxaban (2011)
  - Apixaban (2012)
  - Edoxaban (2015)
- Increasingly utilized “off-label” as anti-thrombotic therapy in PAD

Objective: assess the contemporary utilization of NOACs in patients undergoing infrainguinal bypass and the impact of NOACs on long-term graft and limb – related outcomes in comparison to Warfarin

Anticoagulation after LEB in the VQI

19,162 Infrainguinal Bypass VQI 2014-2017
9,398 with complete 1 year FU

Excluded:
- “asymptomatic” disease,
- bypasses on second limb
- unclear anticoagulation regimen
- Key graft variables

- 7,113 infrainguinal bypass
  - 248 (3.5%) NOAC
  - 1,475 (21%) Warfarin
  - 5,390 (76%) none

Results: NOAC Utilization after Lower Extremity Bypass

Results: Operative and Bypass Characteristics

<table>
<thead>
<tr>
<th>Distal Target</th>
<th>None</th>
<th>Warfarin</th>
<th>NOAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>↑ tibial bypass</td>
<td>↑ tibial bypass</td>
<td></td>
</tr>
<tr>
<td>NOAC</td>
<td>↑ prosthetic bypass</td>
<td>↑ prosthetic bypass</td>
<td></td>
</tr>
<tr>
<td>↑ operative time (30 minutes)</td>
<td>↑ operative time (30 minutes)</td>
<td></td>
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</tr>
</tbody>
</table>

Endarterectomy | 1,583 (29%) | 396 (27%) | 60 (24%) | 0.04
Suprainguinal Bypass | 122 (2%) | 49 (3%) | 7 (3%) | 0.008
Completion study | 1,342 (25%) | 443 (30%) | 60 (25%) | < 0.001
Arteriogram | 334 (6%) | 118 (8%) | 19 (8%) | 0.038
EBL (ml) mean (SD) | 257 (283) | 319 (395) | 304 (330) | < 0.001
Time (minutes) mean | 228 (104) | 265 (125) | 244 (118) | < 0.001

Results: Bypass Graft Patency

Results: Freedom from Major Adverse Limb Events
## Predictors of Graft Failure

<table>
<thead>
<tr>
<th>Variables</th>
<th>Failed Primary Patency</th>
<th>Failed Assisted Patency</th>
<th>Failed Secondary Patency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>HR (95% CI)</td>
<td>P-Value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>NOAC</td>
<td>1.3 (1.1-1.5)</td>
<td>1.3 (1.1-1.5)</td>
<td>1.5 (1.1-1.9)</td>
</tr>
</tbody>
</table>

Other predictors of Failed Graft Patency:
- Age < 60
- Prior PVI
- Hispanic
- Infrageniculate Target
- Real Pain vs. Claudication
- Prosthetic Conduit
- CHF
- Alternative Vein/Other
- Prior Bypass

## Predictors of Major Amputation and Major Adverse Limb Events

<table>
<thead>
<tr>
<th>Variables</th>
<th>Amputation</th>
<th>MALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>1.6 (1.3-2.0)</td>
<td>1.2 (1.1-1.3)</td>
</tr>
<tr>
<td>NOAC</td>
<td>-</td>
<td>1.4 (1.1-1.7)</td>
</tr>
</tbody>
</table>

Other predictors of MALE:
- Rest Pain
- CHF
- Tissue Loss
- Prior Ipsi Bypass
- Acute Ischemia
- Infrageniculate Target
- Dialysis
- Prosthetic Conduit

## Limitations
- Selection bias: VQI registry may not adequately capture important factors that influence selection of patients receive NOACs and outcomes
- Smaller sample size in NOAC population: underpowered to detect differences?
- Not all current NOACs captured in VQI
  - apixaban, edoxaban, and betrixaban
- Dosing regimens and compliance are not known
- Follow-up limited to 1 year

## NOACs, Warfarin, and LEB
- NOAC and Warfarin utilized after infrainguinal bypass with high-risk patient and graft characteristics
- NOAC utilization after infrainguinal bypass is increasing and Warfarin utilization decreasing
- At one year, NOACS and Warfarin were associated with worse mid-term graft patency and limb-related in comparison to no anticoagulation
- After controlling for multitude of patient, medical, operative, and post-operative characteristics
- No difference in graft-related and limb-related outcomes between NOACs and Coumadin

## Recent and Ongoing Study of NOACs
- COMPASS Trial: reduced MALE in 7000 patients with PAD randomized to low-dose Rivaroxaban + AS vs. ASA (27% underwent previous LE revascularization)
- Voyager-PAD: Low dose Rivaroxaban+ ASA vs. ASA in patients after LEb or endo. revasc.
- Outcomes: Thrombotic Vascular Events
- ALI, Amputation
- Ongoing study of the impact of NOACs on graft-related, limb-related, and cardiovascular outcomes in patients undergoing lower extremity bypass is warranted

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Thank you