Intervention on Anticoagulation – real life evidence on NOAC use and periprocedural management

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DISCLOSURES

BAYER

COOK
PAD Pandemic:
Over 200 Million PAD Patients Worldwide

LMIC: low or middle income countries; HIC: high income countries

Fowkes GR et al. Lancet 2013 early online publication, 1 Aug 2013
doi:10.1016/S0140-6736(13)61249-0
Primary Goals of PAD Therapy

• Reduce the risk of cardiovascular events
  • Patients with PAD are at an increased risk of CV events – estimated at 4% per year which is similar to patients with a history of an ACS event

• Preserve limb health
  • Patients with PAD are at increased risk of acute limb ischemia (ALI) with contemporary event rates of 1% per year
  • PAD patients with a recent ALI event and PAD with more severe ischemic disease are at increased risk of major amputation

• Stop disease progression

• Improve functionality
  • Treat the reduced walking ability and exercise limitation
Risk in Patients with PAD – A Complex Calculus

- Antithrombotic therapies for patients with PAD have only targeted reduction of systemic CV risk
- Treatment options for PAD are been limited
- Guideline recommendations are based on limited subgroup analyses from CV trials
- Acute limb ischemia and major vascular amputation are of similar clinical severity as non-fatal MI and stroke

Thrombotic vascular risk has not been adequately addressed, with few therapies to improve cardiac and limb outcomes

Courtesy of Marc Bonaca
Natural History of Peripheral Artery Disease

Initial clinical presentation

- Asymptomatic P.A.D. 20%-50%
- Atypical leg pain 40%-50%

Possible progressive functional impairment

Claudication 10%-35%

Critical limb ischemia 1%-2%

5-year outcomes

- Stable claudication 70%
- Worsening claudication 10%-20%
- Critical limb ischemia 1%-2%
- Nonfatal CV event 20%
- Mortality 15%-30%

CV mortality 25%
Amputation 25%

1-year outcomes

Violi et al. In Antiplatelet Agents (2012); Adapted from JACC (2006) 47:1239-1312
Fatal: Acute Limb Ischemia (ALI)

• Results from arterial thrombosis, arterial embolus, or bypass graft-in stent thrombosis

• Remains one of the most common vascular surgery emergencies

• The post-procedure rates of mortality are as high as 20% to 40% and limb loss as high as 12% to 50%

30 Day Outcomes for ALI vs. CLI

Patients Requiring Amputation

- Above Knee Amputation: ALI 60%, CLI 31%
- Below Knee Amputation: ALI 40%, CLI 69%

Need for Surgical Revision
- ALI 15%, CLI 11%

Mortality
- ALI 25%, CLI 19%

Campbell et al. Cardiovascular Surgery. 2003
Current State of Care in High-Risk Vascular Disease

- Revascularization reduces the risk of amputation but the clinical benefits are highly variable depending on location
- Increasing rates of endovascular revascularization, particularly in an outpatient setting
- Potentially significant underuse of anti-thrombotic therapies
- Patients with high-risk vascular disease continue to have poor outcomes despite a wide array of approved, evidence-based therapies
Guideline Recommendations
Management of Antithrombotics in the setting of revascularization

• ACC-AHA 2011 update. **Aspirin** or **Clopidogrel** for reduction of ischemic risk; silent on the optimal antithrombotic approach to revascularization

• TASC 2007 - Aspirin or clopidogrel for reduction of ischemic risk; silent on the optimal antithrombotic approach to revascularization

• Chest 2012 - For patients undergoing peripheral artery angioplasty recommend long term aspirin (75-100 mg/day) or clopidogrel (75 mg/day) (Grade 1A). For patients undergoing peripheral artery PTA with stenting, suggest single rather than dual antiplatelet therapy (Grade 2C)

• ESC – DAPT for 1 month after infrainguinal BMS (1C)

• ESC – Aspirin ± dipyridamole after infrainguinal bypass (1A)
CAPRIE: Superior Efficacy of Clopidogrel versus ASA?

Patients with recent ischemic stroke, recent MI or symptomatic PAD


*MI, ischemic stroke or vascular death
†Intent-to-treat analysis (n=19,185)
CAPRIE Outcomes by Subgroup

Mean & 95% CI

Aspirin Better
Clopidogrel Better

Stroke
MI
PAD
All patients

Warfarin Antiplatelet Vascular Evaluation Trial (WAVE)

Antiplatelet alone vs. antiplatelet and oral anticoagulant

Warfarin increases life threatening bleeding
Unmet Need In PAD

The optimal antithrombotic management of patients with PAD undergoing revascularization is unknown

• Use of dual antiplatelet therapy (aspirin plus clopidogrel) after endovascular interventions is common but without any direct clinical trial evidence to assess the risks and benefits
• Ischemic risk of MACE events remains high in PAD despite the use of antiplatelet drugs

Trial Rationale VoyagerPAD:
• The direct acting factor Xa inhibitor rivaroxaban has shown benefit in ACS
• Will rivaroxaban in combination with aspirin improve outcomes in PAD undergoing revascularization?
Rivaroxaban is a potent and selective oral direct factor Xa inhibitor which blocks initiation of the final common coagulation pathway.

Gibson CM, AHA 2008
Clinically Significant Bleeding Dose Dependent

(TIMI Major, TIMI Minor, Bleed Requiring Medical Attn.)

Kaplan-Meier estimates for cumulative events, HR(CI), for bleeding rates during the 180 day period; HR=Hazard Ratio; CI=Confidence Interval

*p<0.01 for placebo Vs Riva 5mg. p<0.001 for Riva 10,15,20mg vs placebo

Mega JL et al. Lancet 2009
Rivaroxaban at 5 mg PO BID was associated with a numerical but not statistically significant reduction in mortality.

* First occurrence of cardiovascular death, MI, stroke (ischemic, hemorrhagic, and uncertain) as adjudicated by the CEC
Two year Kaplan-Meier estimates, HR and 95% confidence interval estimates from Cox model stratified by thienopyridine use are provided per mITT approach; Stratified log-rank p-values are provided for both mITT and ITT approaches.

Mega JL et al. NEJM 2012
PAD – Rivaroxaban Dose: 2.5 mg bid

• Combination of 2.5 mg rivaroxaban with ASA 100 mg is based on confirmed experience in ATLAS 2 and regimen under investigation in the COMPASS (stable CAD and PAD)

• As shown in the pooled ATLAS 1 and 2 results, the combination of 2.5 mg rivaroxaban with ASA was associated with benefit along with an acceptable bleeding profile

• No dose adjustment for moderate renal impairment is required, consistent with current label.

Mega JL et al. NEJM 2012
# Voyager Executive Committee

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Voyager PAD: Study Design

- International, Multicenter
- Randomized
  - Placebo-controlled, double-blind (1:1 rivaroxaban vs. placebo)
  - Randomization stratified by procedure and clopidogrel use
  - Treatment will be balanced within a country
- Phase 3
- Event-driven (~1015 endpoint events)
- ITT (intention-to-treat)
- 6,500 subjects
- Enrollment period: ~18 months
- Mean treatment duration: ~30 months
- Total study duration: ~42 months
**Study Design**

Multicenter, randomized, double-blind, placebo-controlled, event-driven phase III study

**Patients age ≥ 50 years of age with:**
- Documented moderate to severe PAD with ABI <0.90 and angiographic or imaging evidence of occlusive PAD
- Any vascular surgical bypass to the lower extremity including aorto-iliac, infra-inguinal, and extra-anatomic bypass for symptomatic PAD
- Clinical indication to treat symptomatic PAD with peripheral revascularization to restore limb perfusion

**Primary efficacy outcome:** Thrombotic Vascular Events of CV death, myocardial infarction, ischemic stroke, acute limb ischemia, and major amputation
**Principal safety outcome:** TIMI Major Bleeding

**Exclusion criteria:**
- Rutherford category 0, 1, & 6
- Endovascular revascularization of the aorto-iliac segment without any additional revascularization below the inguinal ligament
- General criteria based on known rivaroxaban contraindication such as allergy, known bleeding diathesis, etc.

**Screening Phase**

**Treatment Phase**
(mean treatment duration of 30 months, maximum 42 month)

Rivaroxaban 2.5 mg bid + ASA 100 mg od

1:1 randomization*

T0, Day 1

1 month post study drug observation period
RE-LY® Peri-procedural outcomes subgroup analysis: background

• **Aim:**
  - To assess outcomes in patients undergoing surgery/invasive procedure

• **Approach:**
  - Bleeding and thromboembolic events assessed
  - Primary analysis limited to the first surgery/procedure per patient
  - Peri-procedural period: 7 days before to day 30 post-procedure

• **4591 patients included in the subanalysis**
  - Even distribution of patients and surgery types across treatment arms
  - Common surgeries/procedures included dental, pacemaker/ICD, cataract removal (all ~10%)

ICD = implantable cardioverter defibrillator;
Healey JS et al. Circulation 2012 doi:10.1161/CIRCULATIONAHA.111.090464

Disclaimer: Dabigatran etexilate is now approved for clinical use in stroke prevention in atrial fibrillation in certain countries. Please check local prescribing information for further details.
Peri-procedural outcomes subgroup analysis: anticoagulation management

- Warfarin managed according to local practice
- Dabigatran withheld prior to procedure:
  - Dec 2005 – Aug 2008: 24 hours for all patients
  - Aug 2008 – Mar 2009: 2–5 days (based on CrCl) for high-risk procedures
- Dabigatran restarted post-procedure after achieving adequate haemostasis
- Time from last anticoagulant dose to procedure:
  - Dabigatran: 49 (35–85) hours
  - Warfarin: 114 (87–144) hours
- Peri-procedural bridging with heparin used in 15.3% (D110), 17.0% (D150), and 28.5% (warfarin) of patients (P<0.001)

CrCl = creatinine clearance; D110 = dabigatran 110 mg twice daily; D150 = dabigatran 150 twice daily

Healey JS et al. Circulation 2012 doi:10.1161/CIRCULATIONAHA.111.090464

Disclaimer: Dabigatran etexilate is now approved for clinical use in stroke prevention in atrial fibrillation in certain countries. Please check local prescribing information for further details
Peri-procedural outcomes subgroup analysis

• Compared with warfarin, both doses of dabigatran (D110, D150) associated with similar rates of:
  – Peri-procedural* bleeding (including major and fatal bleeding)
  – Thrombotic complications

• No significant difference in rates of major bleeding in patients who underwent urgent surgery

• For patients who underwent procedure within 48 hours of stopping anticoagulation:
  – Dabigatran significantly reduced bleeding risk vs warfarin

*Peri-procedural period defined as 7 days before to day 30 post-procedure

Healey JS et al. Circulation 2012 doi:10.1161/CIRCULATIONAHA.111.090464

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RESULTS

In total, 1884 patients were enrolled, with 950 assigned to receive no bridging therapy and 934 assigned to receive bridging therapy. The incidence of arterial thromboembolism was 0.4% in the no-bridging group and 0.3% in the bridging group (risk difference, 0.1 percentage points; 95% confidence interval [CI], −0.6 to 0.8; \( P=0.01 \) for noninferiority). The incidence of major bleeding was 1.3% in the no-bridging group and 3.2% in the bridging group (relative risk, 0.41; 95% CI, 0.20 to 0.78; \( P=0.005 \) for superiority).
Overdose

Guidance

- Due to limited absorption, a ceiling effect with no further increase in average plasma exposure is expected at supra-therapeutic doses of 50 mg rivaroxaban and above

- A specific antidote antagonising the pharmacodynamic effect of rivaroxaban is not available

- Activated charcoal to reduce absorption may be considered within the first hours after intake

- Due to the high plasma protein binding rivaroxaban is not expected to be dialyzable

Evidence

- PK/PD data support the observed ceiling effect

Xarelto® (rivaroxaban). Summary of Product Characteristics as approved by the European Commission
Bleeding management

**Guidance**

- Should a bleeding complication arise in a patient on Xarelto, next dose should be delayed or treatment be interrupted as felt appropriate\(^1\)
- Individualized bleeding management may include:\(^1\)
  - Symptomatic treatment (such as mechanical compression, surgical intervention, fluid replacement)
  - Hemodynamic support (such as blood products or blood components)
- For life threatening bleeding, use of specific procoagulant agents should be considered such as:\(^1\)
  - Prothrombin complex concentrate (PCC)
  - aPCC
  - Factor VIIa

**Evidence**

- Further details in the SmPC\(^1\)
- Clinical studies published\(^2,3\)

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note: there is currently limited clinical experience with these measures

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