Sex-Based Differences in Outcomes Following Peripheral Artery Revascularization: Insights from VOYAGER PAD

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Peripheral Artery Disease in Women

- >200 million people with PAD globally
- Patients with PAD are at high risk of major adverse cardiovascular events and major adverse limb events
  - Dominant morbidity in PAD related to limb outcomes, including lower extremity revascularization (LER)
- Prevalence of PAD in women as high or higher than in men
- Coronary studies suggest outcomes may differ on the basis of sex

Risk profile and outcomes after LER in women with symptomatic PAD are not well understood

Hirsch A, et al. Circulation 2012
Kosmidou I, et al. JACC 2020
• 6,564 symptomatic PAD patients
• Surgical or endovascular LER
• Rivaroxaban 2.5 mg twice daily or placebo
• ASA 100 mg daily
• Clopidogrel (<6 mos) per operator discretion

Primary Endpoint*
ITT - HR 0.85
(0.76 – 0.96)
P=0.0085
ARR 2.6%, NNT 39

TIMI Major Bleeding
On Treatment - HR 1.43
(0.97 – 2.10)
P=0.0695
ARI 0.8%, NNH 125

*Composite of acute limb ischemia, major amputation of a vascular cause, myocardial infarction, ischemic stroke, cardiovascular death
Objectives and Methods

• To examine sex-based differences in:
  – Trial metrics (recruitment and adherence)
  – Cardiovascular and limb outcomes
  – Efficacy and safety of rivaroxaban

• Prespecified subgroup analysis of VOYAGER PAD

• Outcomes prospectively ascertained and independently adjudicated by a blinded committee

• Associations between sex and outcomes and effects of rivaroxaban estimated with adjusted Cox proportional hazards models
  – Intention-to-treat and on-treatment analyses performed
Female Participation in VOYAGER PAD
6,564 patients enrolled at 542 sites in 34 countries

- 87% male
- 13% female

Subjects Enrolled
- Female: 26%
- Male: 74%

Site Investigators
- Female: 13%
- Male: 87%

Female enrollment
- Female Investigators: 25
- Male Investigators: 25
- p = 0.89

Overall enrollment
- Female Investigators: 10
- Male Investigators: 8
- p = 0.02
## Baseline Characteristics

| Characteristic at Randomization | Women N=1704 % | Men N=4860 % | P-value |
|---------------------------------|----------------|--------------|---------|
| Age, years median (IQR)         | 69 (63-76)     | 66 (60-72)   | <0.0001 |
| BMI, kg/m², median (IQR)        | 26 (23-29)     | 26 (24-29)   | NS      |
| Caucasian                       | 80             | 81           | NS      |
| Hypertension                    | 86             | 80           | <0.0001 |
| Diabetes mellitus               | 42             | 41           | NS      |
| Hyperlipidemia                  | 63             | 59           | 0.005   |
| eGFR < 60 ml/min/1.73m²         | 30             | 17           | <0.0001 |
| Current smoking                 | 26             | 38           | <0.0001 |
| Coronary artery disease         | 27             | 33           | <0.0001 |
| Baseline clopidogrel use        | 55             | 49           | <0.0001 |
| Baseline statin use             | 80             | 80           | NS      |

NS = not significant
## PAD & Procedural Characteristics

|                          | Women N= 1704 | Men N= 4860 | P-value |
|--------------------------|---------------|-------------|---------|
| **Peripheral Artery Disease History** |               |             |         |
| Prior lower extremity revascularization | 35 %          | 36 %        | NS      |
| Prior amputation         | 5             | 6           | NS      |
| Baseline ABI ≤0.50       | 40 %          | 41 %        | NS      |
| **Index Revascularization** |               |             |         |
| Performed for critical limb ischemia | 26            | 23          | 0.006   |
| Long (≥15 cm) target lesion | 33            | 35          | NS      |
| Endovascular (including hybrid) | 74            | 64          | <0.0001 |
| Atherectomy*             | 9.1           | 6.3         | 0.002   |
| Drug-coated device*      | 31            | 31          | NS      |

*among patients undergoing endovascular revascularization

NS = not significant
Outcomes in Placebo Patients by Sex

Primary outcome

KM Rate (%) vs Years

Male
Female

HR 0.90 (95% CI 0.74-1.09)

p=0.29

Number at Risk

Female 857 756 577 180
Male 2421 2126 1576 468

HR reflects stratification for endovascular vs surgical index revascularization

*Additionally adjusted for age, BMI, hypertension, hyperlipidemia, diabetes, CAD, eGFR<60 ml/min/1.73m², current smoking
# Effect of Rivaroxaban on the Primary Outcome by Sex (Intention-to-Treat)

|                | Rivaroxaban | Placebo | HR (95% CI)       | P-interaction |
|----------------|-------------|---------|-------------------|---------------|
| **Overall**    | 6.8         | 8.0     | 0.85 (0.76, 0.96) |               |
| N=6564         |             |         |                   |               |
| **Females**    | 7.0         | 7.2     | 0.97 (0.77, 1.23) | 0.22          |
| N=1704         |             |         |                   |               |
| **Males**      | 6.8         | 8.3     | 0.82 (0.71, 0.94) |               |
| N=4860         |             |         |                   |               |
Effect of Rivaroxaban on Unplanned Index Limb Revascularization by Sex

Overall

Events per 100 patient-years

| Group       | Events per 100 patient-years | HR (95% CI)       |
|-------------|------------------------------|-------------------|
| Rivaroxaban  | 8.4                          | 0.88 (0.79-0.99)  |
| Placebo     | 9.5                          | 0.92 (0.75-1.13)  |

HR 0.88 (0.79-0.99)
Women More Frequently Discontinued Study Medication

**Premature Treatment Discontinuation (%)**

- **Female**: 40.0%
- **Male**: 35.7%

**HR 1.13 (95% CI 1.03-1.25) p = 0.0099**

**Reasons for treatment discontinuation**

- **Female**: N = 588
- **Male**: N = 1503

**Pattern of d/c (rivaroxaban or placebo) similar for females and males**

**D/C at sites with female Pls 29.4% versus male Pls 32.7% (p=0.0375)**

*for this category vs all others*

PI, Principal Investigator
Effect of Rivaroxaban on the Primary Outcome by Sex (On-Treatment)

|               | Rivaroxaban Events / 100 p-y | Placebo Events / 100 p-y | HR (95% CI)   | P-interaction |
|---------------|-----------------------------|--------------------------|---------------|---------------|
| Overall       | 5.3                         | 7.1                      | 0.75 (0.65, 0.86) |               |
| N=6504        |                             |                          |               |               |
| Females       | 5.2                         | 6.6                      | 0.80 (0.60, 1.06) | 0.64          |
| N=1687        |                             |                          |               |               |
| Males         | 5.3                         | 7.3                      | 0.74 (0.63, 0.87) |               |
| N=4817        |                             |                          |               |               |

Rivaroxaban better Placebo better

An affiliate of:
Safety of Rivaroxaban by Sex

**Events per 100 patient-years**

**Females**
- Placebo: 0.9
- Rivaroxaban: 1.0

**Males**
- Placebo: 0.5
- Rivaroxaban: 0.7

**TIMI Major**
- Females: 0.2
- Males: 0.3

**ICH or Fatal**
- Females: 0.3
- Males: 0.3

**ISTH Major**
- Females: 2.3
- Males: 2.1

**HR**
- Females: **1.73** (0.76 – 3.95)
- Males: **1.35** (0.87 – 2.09)

**P-interaction**
- 0.61

**HR**
- Females: **1.04** (0.21 – 5.15)
- Males: **0.88** (0.43 – 1.80)

**P-interaction**
- 0.85

**HR**
- Females: **1.38** (0.84 – 2.25)
- Males: **1.44** (1.07 – 1.95)

**P-interaction**
- 0.88
Summary and Conclusions

• >1,700 women in VOYAGER PAD → one of the largest experiences of post-LER outcomes in women
  – ~1/4 of patients female

• Compared with men, women were enriched for risk factors, presented with more severe PAD, underwent more endovascular LER, and had greater risk of unplanned index limb revascularization

• Efficacy and safety of rivaroxaban were consistent irrespective of sex
  – Study treatment discontinuation more common in women than men

• Efforts to understand sex-based differences in outcomes after LER and clinical trial participation and treatment adherence are needed
  – Prospective data collection and studies on the impact of women in site and leadership roles