Risk of MACE and MALE and Effects of Rivaroxaban after Revascularization in Patients with PAD and Chronic Kidney Disease: Insights from VOYAGER PAD

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BACKGROUND

VOYAGER-PAD was a randomized trial showing benefit of rivaroxaban versus placebo on a background of aspirin in patients with peripheral artery disease (PAD) following lower extremity revascularization (LER). However, the impact of chronic kidney disease (CKD) on the risk of major adverse cardiovascular (MACE) and limb events (MALE) and the treatment effect of rivaroxaban on limb outcomes has not been described.

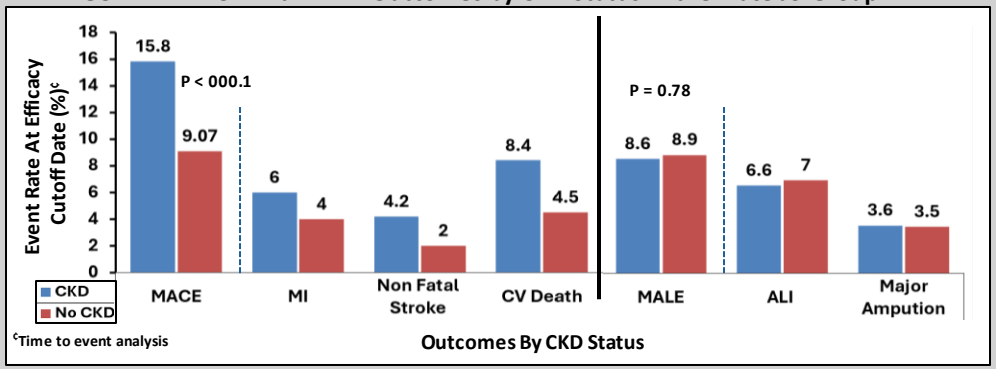
METHODS

VOYAGER-PAD randomized patients with PAD after LER to rivaroxaban 2.5 mg twice daily or placebo on a background of aspirin. CKD was defined as eGFR < 60 mL/min/1.73m^2 at baseline. Patients with eGFR <15 or on dialysis were excluded. The risk of MACE and MALE in those with and without CKD was evaluated in the placebo group to better understand natural history. The consistency of efficacy and safety of rivaroxaban by CKD group was examined.

Table 1. Baseline Characteristics By CKD

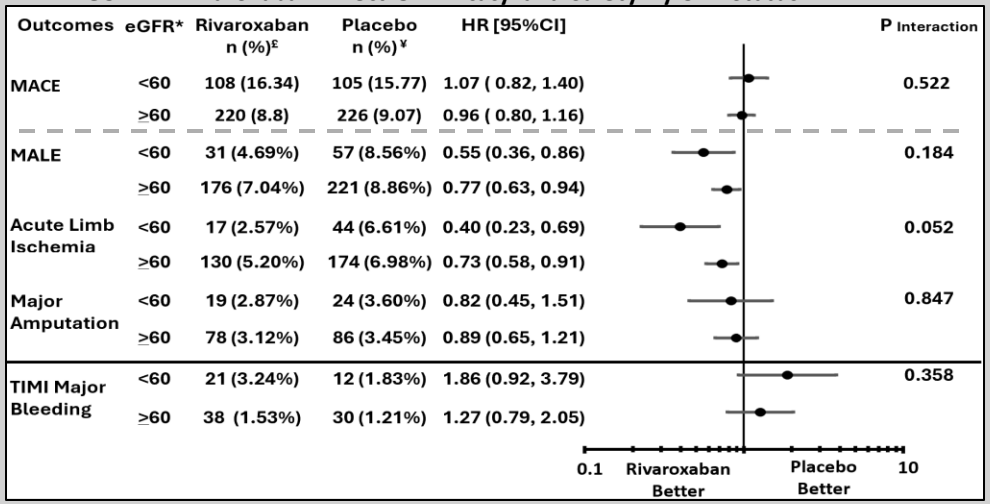
	eGFR < 60 ml/min/1.73m^2, n=1327	eGFR = or >60 ml/min/1.73 m^2, n=4992	p-value
Median age (IQR) - yr.	73.0(11.0)	65.0(11.0)	<0.0001
Female no. (%)	502 (37.83%)	1132 (22.68%)	<0.0001
Hypertension (%)	12 11 (91.26%)	3945 (79.03%)	<0.0001
Diabetes Mellitus (type 2) (%)	698 (52.60%)	1841 (36.88%)	<0.0001
Hyperlipidemia (%)	859 (64.73%)	2926 (58.61%)	<0.0001
Current smoking (%)	284 (21.40%)	1909 (38.24%)	<0.0001
Prior myocardial infarction (%)	190 (14.32%)	486 (9.74%)	<0.0001
History stroke/TIA	15 (1.13%)	55 (1.10%)	0.8835
Prior amputation (%)	103 (7.76%)	271 (5.43%)	0.0020
Prior peripheral percutaneous transluminal angioplasty	430 (32.40%)	1396 (27.96%)	0.0017
Chronic Limb-Threatening Ischemia (%)	360 (27.13%)	1131 (22.66%)	0.0008

FIGURE 1: MACE And MALE Outcomes by CKD Status In the Placebo Group



Events rates of MACE, MALE and their components at efficacy cutoff date (median follow up of 28 months) by CKD status (eGFR <, ≥ 60 mL/min/1.73m2) in the placebo group. CKD group, N = 666, No CKD group, N = 2493.

FIGURE 2: Rivaroxaban Effect On Efficacy and Safety By CKD Status



Hazard ratio (HR) and 95% confidence interval (CI) from stratified Cox proportional hazards models show consistent efficacy and safety of rivaroxaban by CKD. ITT analysis is shown for efficacy outcomes, on-treatment analysis for safety outcomes. ALI = acute limb ischemia; CV = cardiovascular; CKD = chronic kidney disease; MACE = major adverse cardiovascular events; MALE = major adverse limb events; MI = myocardial infarction * - eGFR units - mL/min/1.73m^2.

£ - Rivaroxaban group: ITT; eGFR < 60 N = 661, eGFR ≥ 60 N = 2499, On-Treatment; eGFR <60 N = 649, eGFR ≥ 60 N = 2483

¥ - Placebo Group: ITT; eGFR < 60 N = 666, eGFR ≥ 60 N = 2493, On-Treatment; eGFR < 60 N = 657, eGFR ≥ 60 N = 2474

RESULTS

Of 6564 randomized, baseline eGFR was available in 96.2% with 1327 (21%) having CKD. Patients with CKD were older (73 vs. 65 years, P <0.0001), and more often female (37.8% vs. 22.7% P<0.0001) and had higher prevalence cardiovascular risk factors as diabetes (52.6% vs. 36.9%) and hypertension (91.3% vs. 79.0%, P<0.0001 for both). Prior myocardial infarction was more prevalent in patients with CKD (14.3% vs. 9.7% P < 0.0001) but the prevalence of stroke was similar (1.1%% in both groups, P = 0.9). Patients with CKD were more likely to have prior endovascular intervention (32.4% vs 27.96% P = 0.0017), and prior amputation (7.76% vs. 5.43% P = 0.0020) and were more likely to present with chronic limb-threatening ischemia (27.1% vs. 22.7% P = 0.0008)(**Table 1**). In the placebo group, at a median follow up of 28 months, patients with vs without CKD had a higher risk of MACE (15.8% vs 9.1%, P <0.0001, **Figure 1**). In contrast, risk of MALE (8.6% vs. 8.9% P = 0.78, **Figure 1**) did not differ by CKD/No CKD. TIMI major bleeding was 1.83% in those with CKD and 1.21% in patients without CKD. The efficacy for MACE and MALE and safety of rivaroxaban was consistent in those with and without CKD (**Figure 2**).

CONCLUSIONS

- **In VOYAGER PAD, among patients with symptomatic PAD following lower extremity revascularization, participants with CKD and eGFR < 60 had a higher risk of MACE but similar risk of MALE, compared to patients with normal kidney function.**
- **The efficacy for MALE and safety of rivaroxaban was consistent in patients with and without CKD.**

DISCLOSURES

VOYAGER was designed and overseen by a collaborative group that included Colorado Prevention Center (CPC) Clinical Research (an academic research organization affiliated with the University of Colorado), the academic executive committee and the sponsors, Bayer and Janssen Pharmaceuticals. JH reports owning AstraZeneca stock and research funding to CPC Clinical Research from Arca Biopharma and Janssen. SA reports lecture fees from Bayer and Janssen. MRN, WHC, LD - no disclosure. MRP reports grant support, advisory board fees and consulting fees from AstraZeneca, grant support from Medtronic and Philips Healthcare, and grant support and advisory board fees from Heartflow. WRH reports grant support from Amgen and AstraZeneca. SD reports grant support from Cook and Terumo Aortic. CNH reports research funding to CPC Clinical Research from Merck, Bayer, and Amgen. SDB and EM are employed by Bayer. LPH is employed by Janssen Pharmaceuticals and owns stock in Johnson & Johnson RMB reports consulting fees and lecture fees from Bristol-Myers Squibb, Daiichi Sankyo. MPB reports research grants to CPC Clinical Research from Alnylam, Amgen, Arca, AstraZeneca, Bayer, CellResearch, Eidos, NovoNordisk, Osiris, Terumo

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