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# MARINER & COMMANDER HF CLINICAL TRIAL RESULTS REVIEW

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# Presenters

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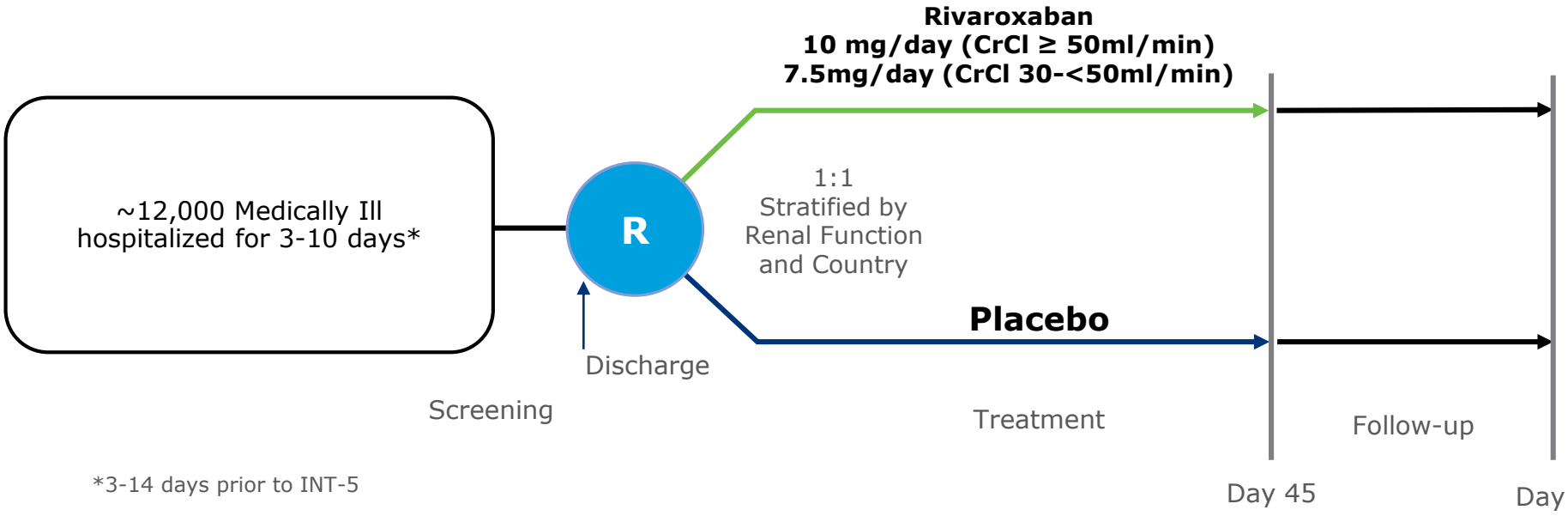
# MARINER

# MARINER - Study Design

**Design:** Randomized, double-blind placebo-controlled, event driven trial




*3-14 days prior to INT-5

Power: 90%, Two sided alpha 0.05 to target 161 events (Pb 2.5%, 40% RRR)

# Baseline Characteristics (1)

| Characteristic | Rivaroxaban (n=6007) | Placebo (n=6012) |
|---|---|---|
| Age (Mean-yr) | 69.7 | 69.7 |
| ≥ 75 yr (%) | 35.9 | 35.6 |
| Male Sex (%) | 52.1 | 52.5 |
| Race (% White) | 96.3 | 96.6 |
| Weight (mean kg) | 80.8 | 80.6 |
| Creatinine Clearance (ml/min) | | |
| 30 - < 50 (%); 7.5mg Dose Stratum | 18.3 | 18.3 |
| ≥50 (%); 10mg Dose Stratum | 81.7 | 81.7 |
| Diabetes (%) | 29.1 | 27.9 |
| History of Cancer (%) | 8.1 | 8.9 |
| Baseline aspirin use (%) | 52.6 | 50.7 |

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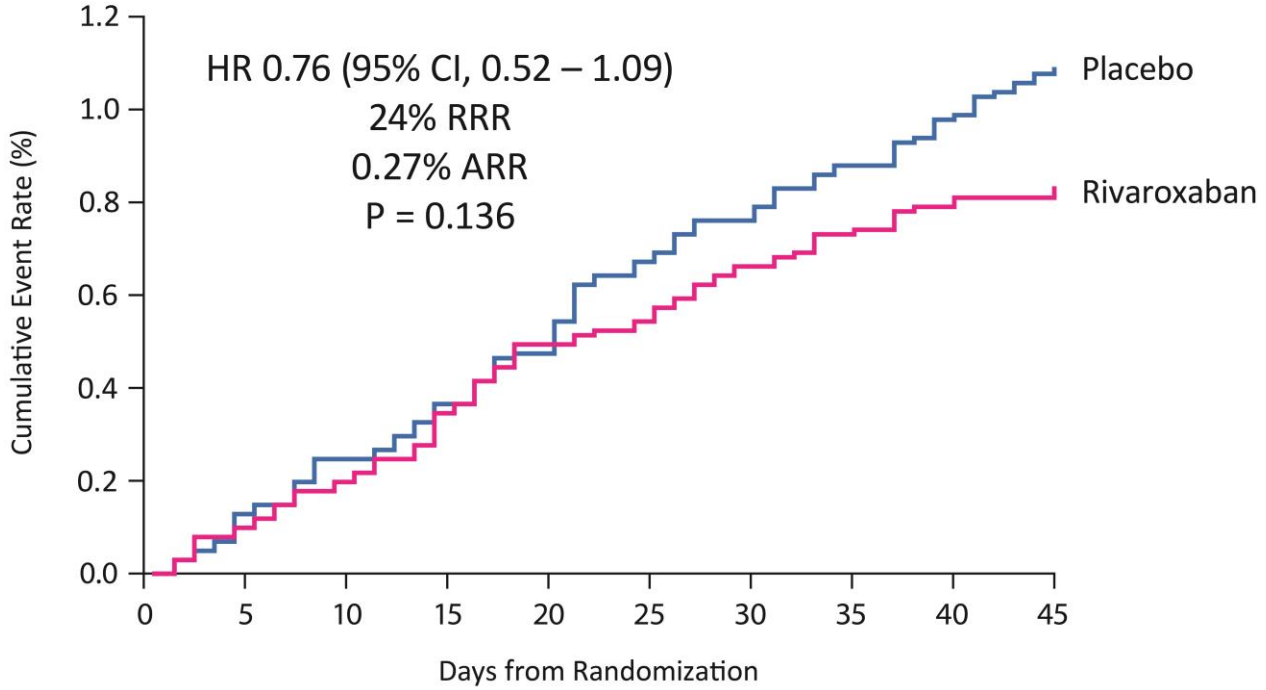
# Primary Efficacy Outcome up to Day 45




No. at risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Placebo | 6012 | 5989 | 5970 | 5959 | 5943 | 5922 | 5910 | 5902 | 5890 | 0 |
| Rivaroxaban | 6007 | 5989 | 5972 | 5962 | 5948 | 5934 | 5927 | 5919 | 5913 | 0 |

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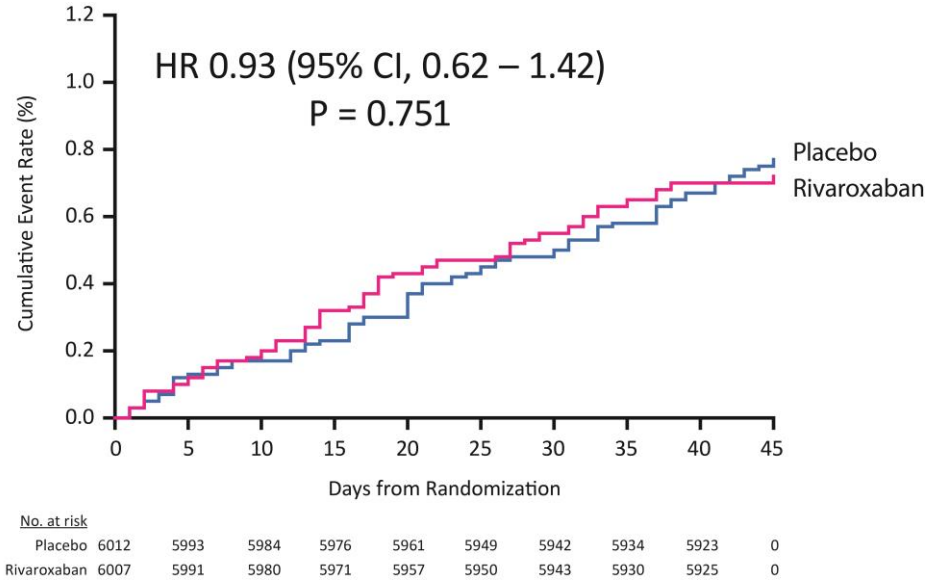
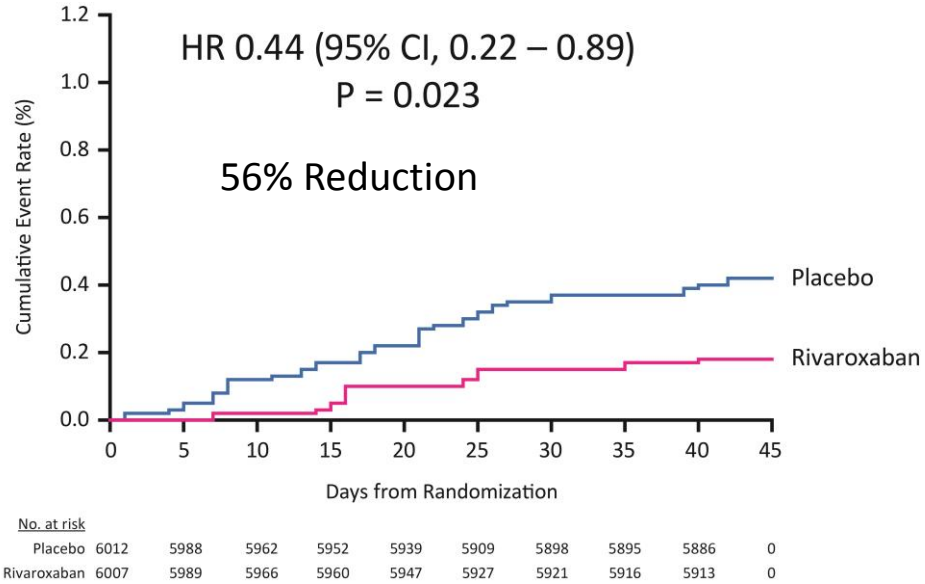
# Secondary Efficacy Outcomes up to Day 45

## VTE-related Death




| No. at risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 6012 | 5993 | 5984 | 5976 | 5961 | 5949 | 5942 | 5934 | 5923 | 0 |
| Rivaroxaban | 6007 | 5991 | 5980 | 5971 | 5957 | 5950 | 5943 | 5930 | 5925 | 0 |

## Symptomatic VTE




| No. at risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 6012 | 5988 | 5962 | 5952 | 5939 | 5909 | 5898 | 5895 | 5886 | 0 |
| Rivaroxaban | 6007 | 5989 | 5966 | 5960 | 5947 | 5927 | 5921 | 5916 | 5913 | 0 |

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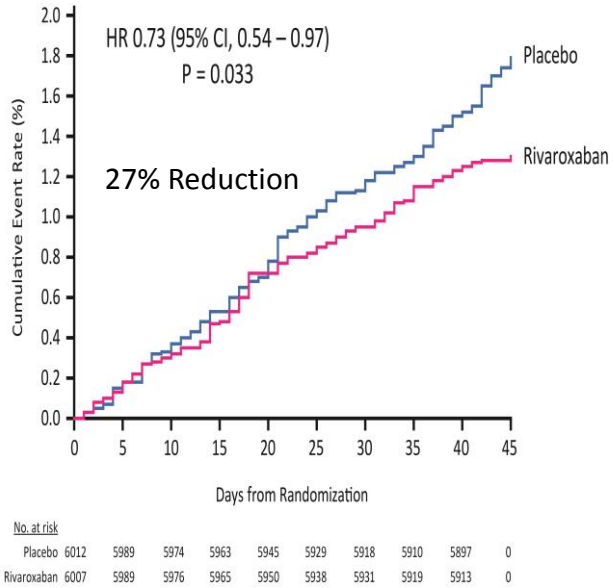
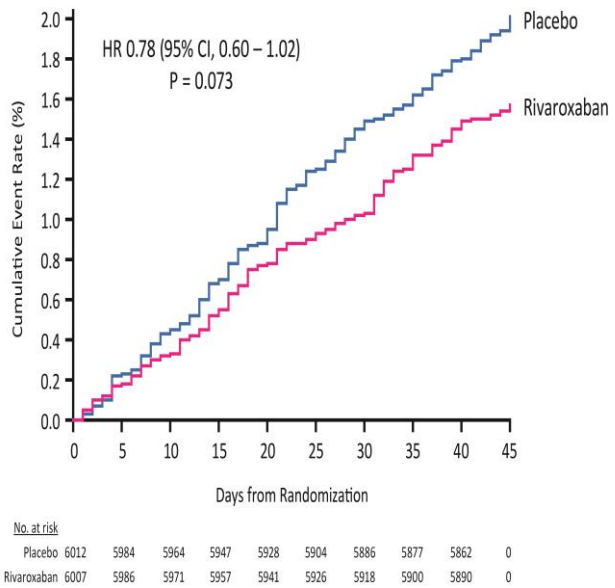
# Secondary Efficacy Outcomes up to Day 45

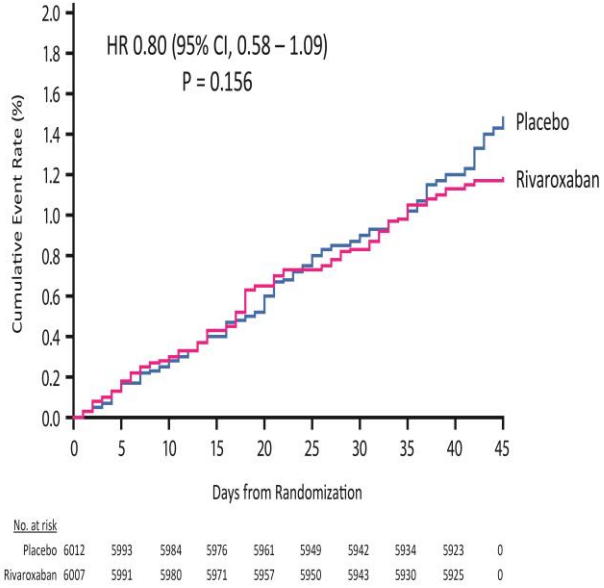
## Symptomatic VTE and All-Cause Mortality




## Symptomatic VTE, MI, Ischemic Stroke and CV Death




## All-Cause Mortality



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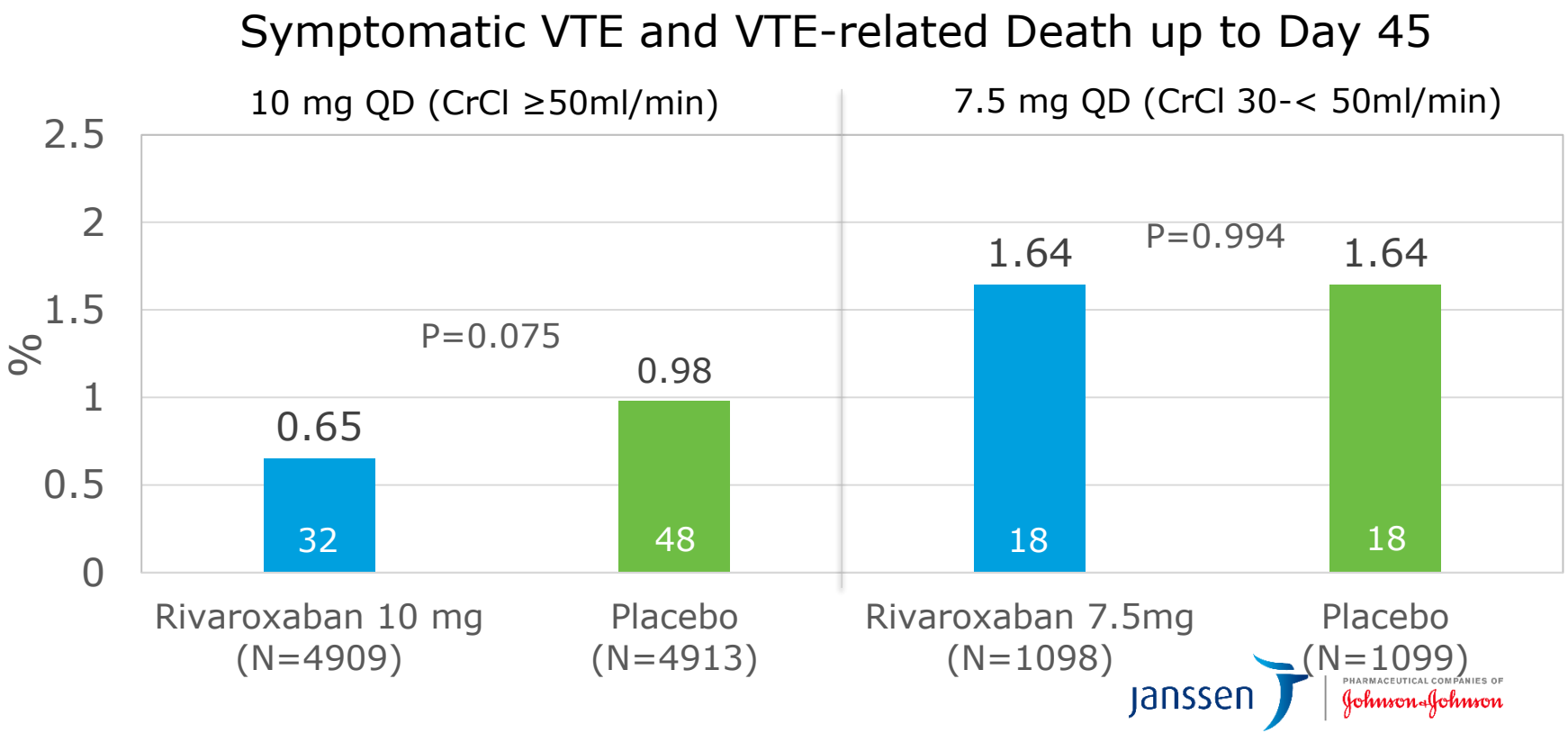
# Primary Efficacy Outcome: By Dose Stratum/Baseline Renal Function

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# Bleeding Outcomes (On Treatment + 2 Days)

| | Rivaroxaban (N=5982) | Placebo (N=5980) | Rivaroxaban vs Placebo | |
|---|---|---|---|---|
| | n (%) | n (%) | Hazard Ratio (95% CI) [1] | p-value [2] |
| **Major bleeding** | **17 (0.28)** | **9 (0.15)** | **1.88 (0.84, 4.23)** | **0.124** |
| A fall in hemoglobin of >=2g/dL | 14 (0.23) | 6 (0.10) | 2.33 (0.89, 6.05) | 0.084 |
| A transfusion of >=2 units of packed RBC | 11 (0.18) | 3 (0.05) | 3.66 (1.02, 13.10) | 0.047 |
| A critical site | 3 (0.05) | 2 (0.03) | 1.50 (0.25, 8.97) | 0.657 |
| A fatal outcome | 2 (0.03) | 0 (0.0) | NA (NA, NA) | |
| **Non-major clinically relevant bleeding** | **85 (1.42)** | **51 (0.85)** | **1.66 (1.17, 2.35)** | **0.004** |

[1] Hazard ratio (95% CI) and p-value are from the Cox proportional hazard model, stratified by baseline CrCl (30-<50 mL/min vs. >=50 mL/min), with treatment as the only covariate.
[2] P-value (two-sided) for superiority of rivaroxaban versus placebo from the Cox proportional hazard model.

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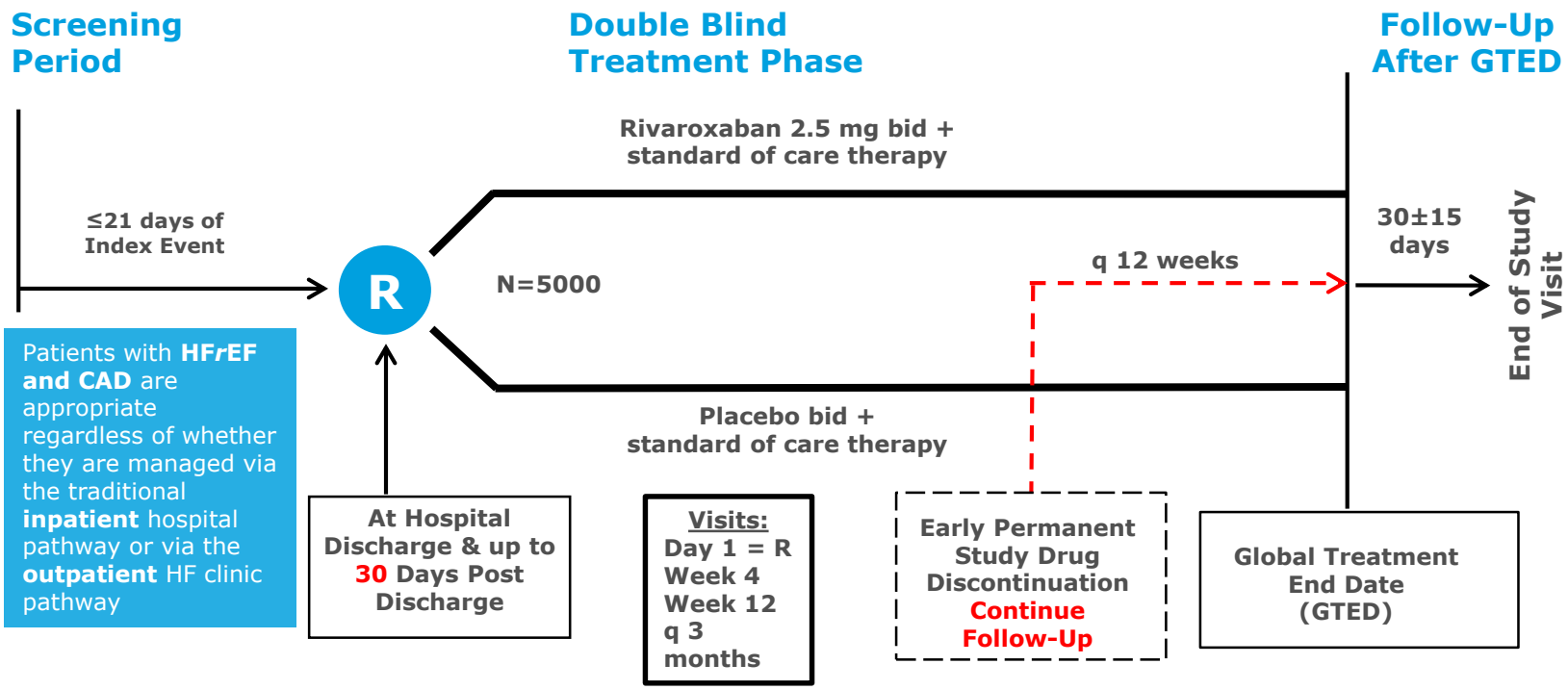
# Conclusions – MARINER

- Rivaroxaban did not significantly reduce the composite of symptomatic VTE and VTE-related death in an at-risk medically ill population post-hospital discharge (ARR=0.27%)
  - There appeared to be no effect on VTE-related death
- Secondary outcomes revealed:
  - A 56% reduction in symptomatic VTE
  - A 27% reduction in symptomatic VTE and all-cause mortality
- Rivaroxaban 10mg in subjects without significant renal impairment (CrCL ≥ 50ml/min) appeared more effective than reduced dose in subjects with moderate renal impairment
- The incidence of major bleeding with rivaroxaban was low (0.28%) with no significant increase in major, critical, or fatal bleeding
- We believe there is a filing pathway forward for approval

# COMMANDER HF

# COMMANDER HF – Study Design




Zannad F, et al. *Eur J Heart Fail*. 2015:17(7):735-742.

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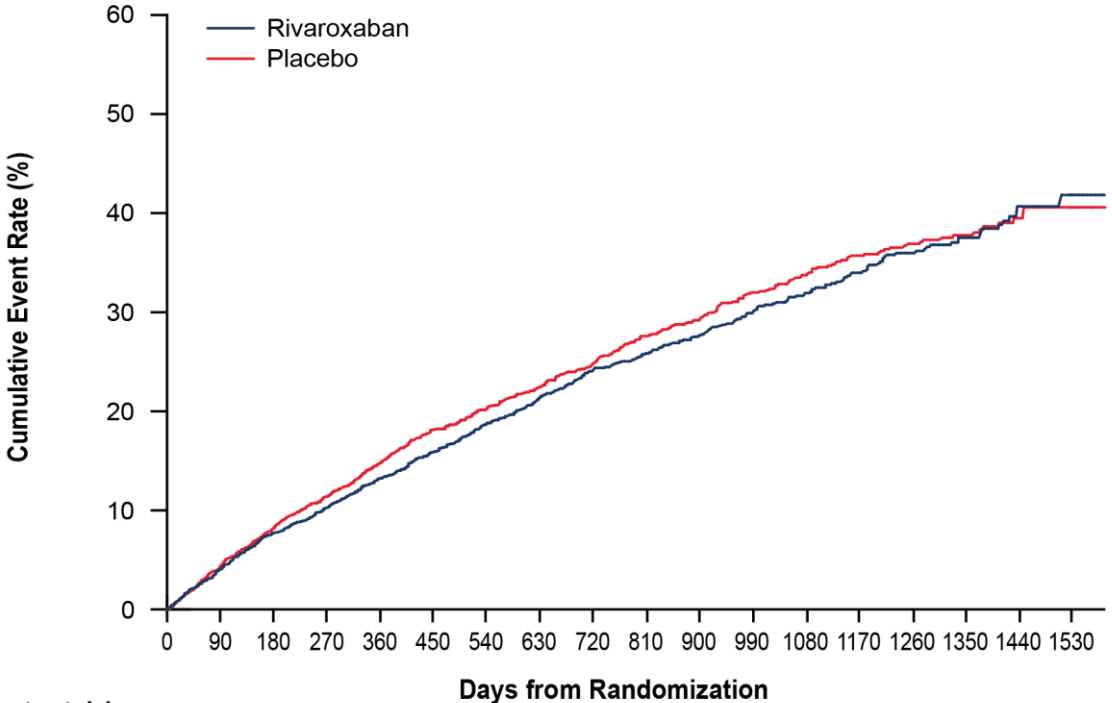
# Key Baseline Characteristics (ITT)

| Characteristic | Rivaroxaban (N=2507) | Placebo (N=2515) |
|---|---|---|
| Age, yr | 66.5±10.1 | 66.3±10.3 |
| Female sex, n (%) | 551 (22.0) | 599 (23.8) |
| Race, n (%) | | |
| White | 2063 (82.3) | 2065 (82.1) |
| Black or African American | 29 (1.2) | 36 (1.4) |
| Asian | 362 (14.4) | 365 (14.5) |
| Other | 53 (2.1) | 49 (1.9) |
| Region, n (%) | | |
| Eastern Europe | 1610 (64.2) | 1614 (64.2) |
| North America | 74 (3.0) | 75 (3.0) |
| Asia Pacific | 367 (14.6) | 366 (14.6) |
| Latin America | 229 (9.1) | 229 (9.1) |
| Western Europe and South Africa | 227 (9.1) | 231 (9.2) |
| Body mass index (kg/m2) | 27.6±5.1 | 27.8±5.3 |
| eGFR (mL/min/1.73 m2), n (%) | | |
| <30 | 81 (3.2) | 82 (3.3) |
| 30 to <60 | 884 (35.3) | 898 (35.7) |
| 60 to <90 | 1101 (43.9) | 1137 (45.2) |
| ≥90 | 441 (17.6) | 398 (15.8) |

# Primary Efficacy Outcome (ITT)




**Subjects at risk**

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Rivaroxaban | 2507 | 2404 | 2308 | 2159 | 1883 | 1637 | 1384 | 1189 | 974 | 817 | 668 | 588 | 505 | 423 | 327 | 239 | 121 | 46 |
| Placebo | 2515 | 2407 | 2303 | 2145 | 1851 | 1589 | 1353 | 1169 | 960 | 804 | 661 | 582 | 502 | 426 | 330 | 236 | 127 | 43 |

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# Primary Efficacy Outcome & Components (ITT)

| | Rivaroxaban (N=2507) | | Placebo (N=2515) | | Rivaroxaban vs. Placebo | |
|---|---|---|---|---|---|---|
| **Outcomes** | **n (%)** | **Event Rate/ (100 pt-yr)** | **n (%)** | **Event Rate/ (100 pt-yr)** | **HR (95% CI)** | **Log-rank P value** |
| Primary efficacy (composite) | 626 (25.0) | 13.44 | 658 (26.2) | 14.27 | 0.94 (0.84, 1.05) | 0.27 |
| All-cause mortality | 546 (21.8) | 11.41 | 556 (22.1) | 11.63 | 0.98 (0.87, 1.10) | - |
| MI | 98 (3.9) | 2.08 | 118 (4.7) | 2.52 | 0.83 (0.63, 1.08) | - |
| Stroke | 51 (2.0) | 1.08 | 76 (3.0) | 1.62 | 0.66 (0.47, 0.95) | - |

# Secondary and Exploratory Efficacy Outcomes (ITT)

| | Rivaroxaban | | Placebo | | Rivaroxaban vs Placebo |
|---|---|---|---|---|---|
| **Outcomes** | **n (%)** | **Event Rate/ (100 pt-yr)** | **n (%)** | **Event Rate/ (100 pt-yr)** | **HR (95% CI)** |
| CV death or RHHF | 932 (37.2) | 23.32 | 929 (36.9) | 23.46 | 0.99 (0.91, 1.09) |
| CV death | 453 (18.1) | 9.46 | 476 (18.9) | 9.96 | 0.95 (0.84, 1.08) |
| RHHF | 689 (27.5) | 17.24 | 691 (27.5) | 17.45 | 0.98 (0.89, 1.09) |
| RHCV | 543 (21.7) | 13.30 | 572 (22.7) | 14.04 | 0.95 (0.84, 1.07) |
| | | | | | |
| All-cause mortality or RHHF (composite) | 993 (39.6) | 24.84 | 973 (38.7) | 24.57 | 1.01 (0.92, 1.10) |
| | | | | | |
| Symptomatic deep vein thrombosis | 5 (0.2) | 0.10 | 7 (0.3) | 0.15 | 0.71 (0.23, 2.24) |
| Symptomatic pulmonary embolism | 11 (0.4) | 0.23 | 9 (0.4) | 0.19 | 1.23 (0.51, 2.96) |

# Principal Safety Outcome (Safety, On-Treatment)

| | Rivaroxaban | (N=2499) | Placebo | (N=2509) | Rivaroxaban vs. Placebo | P value |
|---|---|---|---|---|---|---|
| **Outcomes** | **n (%)** | **Event Rate/ (100 pt-yr)** | **n (%)** | **Event Rate/ (100 pt-yr)** | **HR (95% CI)** | **Log-rank P value** |
| Principal safety (composite) | 18 (0.7) | 0.44 | 23 (0.9) | 0.55 | 0.80 (0.43, 1.49) | 0.484 |
| Fatal bleeding | 9 (0.4) | 0.22 | 9 (0.4) | 0.22 | 1.03 (0.41, 2.59) | 0.951 |
| Bleeding in critical space with potential for permanent disability | 13 (0.5) | 0.32 | 20 (0.8) | 0.48 | 0.67 (0.33, 1.34) | 0.253 |
| **ISTH major bleeding** | **82 (3.3)** | **2.04** | **50 (2.0)** | **1.21** | **1.68 (1.18, 2.39)** | **0.003** |
| ISTH: HGB decreases ≥2g/dL | 55 (2.2) | 1.37 | 30 (1.2) | 0.73 | 1.87 (1.20, 2.91) | 0.005 |
| ISTH: transfusions ≥2 Units | 31 (1.2) | 0.77 | 18 (0.7) | 0.43 | 1.74 (0.98, 3.12) | 0.058 |
| ISTH: critical bleeding sites | 25 (1.0) | 0.62 | 23 (0.9) | 0.56 | 1.12 (0.63, 1.97) | 0.699 |
| ISTH: fatal outcome | 3 (0.1) | 0.07 | 7 (0.3) | 0.17 | 0.45 (0.12, 1.72) | 0.228 |
| Bleeding requiring hospitalization | 61 (2.4) | 1.52 | 48 (1.9) | 1.16 | 1.30 (0.89, 1.90) | 0.170 |

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# Conclusions – COMMANDER HF

In patients with recent worsening of chronic HF and reduced ejection fraction who also have underlying CAD and are not in AF, low-dose rivaroxaban, when added to guideline-based therapy, does not improve the composite of all-cause mortality, MI, or stroke, nor does it favorably influence HF rehospitalization

# Q&A

# Contact

For Investor Relations Inquiries call 800-950-5089,
or contact Chris DelOrefice, 732-524-2955 or Lesley Fishman, 732-524-3922.

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