# Paziente con fibrillazione atriale e scompenso cardiaco

Dr Martino Pepe
Cardiologia Universitaria
Policlinico di Bari

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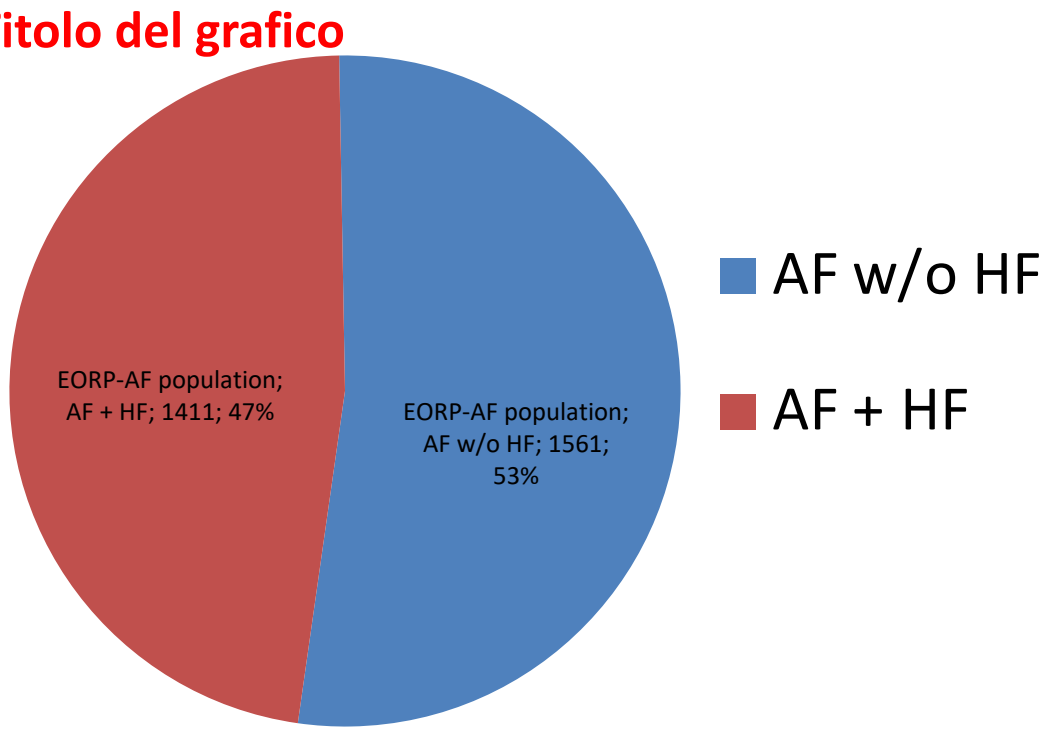
# Heart failure in patients with atrial fibrillation in Europe: a report from the EURObservational Research Programme Pilot survey on Atrial Fibrillation

Gregory Y.H. Lip[1]*, Cécile Laroche[2], Mircea I. Popescu[3], Lars H. Rasmussen[4], Laura Vitali-Serdoz[5], Gheorghe-Andrei Dan[6], Zbigniew Kalarus[7], Harry J.G.M. Crijns[8], Mario M. Oliveira[9], Luigi Tavazzi[10], Aldo P. Maggioni[2], and Giuseppe Boriani[11]



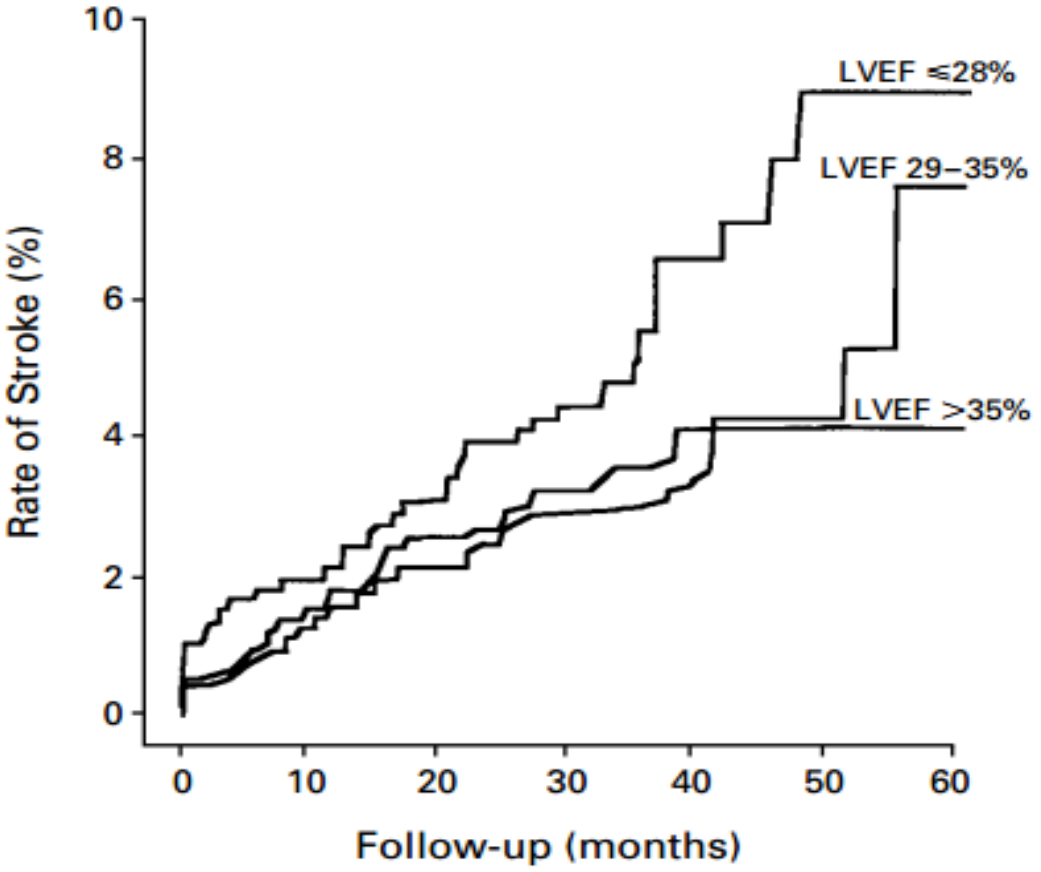

- In HF patients AF prevalence ranges from 12 to 41%
- Prevalence of AF increases with HF worsening

# VENTRICULAR DYSFUNCTION AND THE RISK OF STROKE AFTER MYOCARDIAL INFARCTION

EVAN LOH, M.D., MARTIN ST. JOHN SUTTON, M.D., CHUAN-CHUAN C. WUN, PH.D., JEAN L. ROULEAU, M.D., GREG C. FLAKER, M.D., STEPHEN S. GOTTLIEB, M.D., GERVASIO A. LAMAS, M.D., LEMUEL A. MOYÉ, PH.D., SAMUEL Z. GOLDHABER, M.D., AND MARC A. PFEFFER, M.D., PH.D.

**TABLE 2.** RISK FACTORS FOR STROKE IN THE MULTIVARIATE ANALYSIS.*

| RISK FACTOR | RELATIVE (95% |
|---|---|
| LVEF (for each decrease of 5 percentage points) | 1.18 (1.0 |
| Age (for each increase of 5 yr) | 1.18 (1.0 |
| Anticoagulant therapy during follow-up | 0.19 (0.1 |
| Aspirin use during follow-up | 0.44 (0.2 |
| Current smoking at randomization | 1.40 (0.8 |
| History of hypertension | 1.12 (0.7 |
| History of diabetes | 1.34 (0.8 |
| Previous myocardial infarction | 0.97 (0.6 |
| Recurrent myocardial infarction | 0.87 (0.4 |
| Assignment to captopril | 1.28 (0.8 |
| Atrial fibrillation or flutter before randomization | 1.62 (0.9 |
| Thrombolytic therapy | 0.62 (0.3 |




Loh et al, NEJM 1997

# Heart failure and thromboembolic risk

Hypotheses:

- deceleration of peripheral and intracardiac blood flow due to peripheral congestion and impaired cardiac contractility
- endothelial dysfunction (impaired NO response)
- prolonged bed rest in severely ill cases
- the presence of coagulation defects as, for example, in the case of ventricular assist devices

# VKA limitations

- Intra- and interpatient variability in dose response
- susceptibility to drug–drug and drug–food interactions
- narrow therapeutic index necessitating periodic monitoring of physiologic response to warfarin using the international normalized ratio (INR)

# HF and VKA: the bleeding risk

**Table 2** Unadjusted outcomes during 365-day follow-up period

| Characteristic | Stable group ($n$ = 533) | Comparator group ($n$ = 2555) |
|---|---|---|
| Received heparin* (%) | 1.1 | 7.1 |
| Deceased ($n$, %) | 2, 0.4 | 51, 2.0 |
| AC-related death ($n$, %) | 0, 0.0 | 2, 0.1 |
| AC-related thrombosis ($n$, %) | 1, 0.2 | 34, 1.3 |
| Arterial thromboembolism | 0, 0 | 1, 0.04 |
| Deep vein thrombosis | 0, 0 | 4, 0.2 |
| Pulmonary embolism | 0, 0 | 6, 0.2 |
| Stroke | 1, 0.2 | 14, 0.5 |
| Thrombophlebitis | 0, 0 | 1, 0.04 |
| Other | 0, 0 | 8, 0.3 |
| AC-related bleeding ($n$, %) | 11, 2.1 | 104, 4.1 |
| Epistaxis | 2, 0.4 | 24, 0.9 |
| Gastrointestinal | 5, 0.9 | 44, 1.7 |
| Hemarthrosis | 0, 0 | 3, 0.1 |
| Hematoma | 0, 0 | 6, 0.2 |
| Hematuria | 1, 0.2 | 10, 0.4 |
| Intracranial | 1, 0.2 | 8, 0.3 |
| Other | 2, 0.4 | 9, 0.4 |
| AC-related bleeding or thrombosis ($n$, %) | 12, 2.3 | 136, 5.3 |

**Table 3** Predictors of stable INR control status (c-statistic = 0.69)

| Predictor | Adjusted odds ratio | 95% CI |
|---|---|---|
| Age | | |
| > 70 years | 1.93 | 1.56–2.38 |
| ≤70 years | – | – |
| Sex | | |
| Female | – | – |
| Male | 1.44 | 1.16–1.78 |
| INR target | | |
| 2.0 | 2.80 | 1.83–4.28 |
| 2.5 | – | – |
| ≥3.0 | 0.28 | 0.17–0.47 |
| Primary indication for anticoagulation therapy | | |
| Atrial fibrillation | – | – |
| Venous thromboembolism | 0.81 | 0.63–1.04 |
| Heart valve disorder | 1.13 | 0.65–1.98 |
| Other | 1.01 | 0.77–1.31 |
| Risk factors | | |
| Diabetes mellitus | | |
| Yes | – | – |
| No | 1.69 | 0.93–3.08 |
| Hypertension | | |
| Yes | – | – |
| No | 0.98 | 0.77–1.24 |
| Heart failure | | |
| Yes | – | – |
| No | 2.08 | 1.36–3.17 |

Witt et al, J Thromb Haemost 2010

# Predictors of TTR<55%

Impact of demographics and co-morbidities on likelihood of lower time in therapeutic range

| Characteristic | OR (95% CI) | p |
|---|---|---|
| Age ≥75 (vs <75) (yrs) | 0.94 (0.88–1.01) | NS |
| Men (vs women) | 0.78 (0.73–0.83) | <0.001 |
| United States region | | |
| Northeast | 1.00 (Referent) | — |
| West | 1.39 (1.26–1.54) | <0.001 |
| South | 1.38 (1.26–1.52) | <0.001 |
| Midwest | 1.04 (0.95–1.14) | NS |
| Co-morbidities (vs not present) | | |
| Heart failure | 1.41 (1.28–1.56) | <0.001 |
| Diabetes | 1.28 (1.19–1.38) | <0.001 |
| Previous stroke | 1.15 (1.04–1.27) | 0.0075 |
| Hypertension | 0.86 (0.80–0.93) | <0.001 |

CI = confidence interval; OR = odds ratio.

Nelson et al, 2013 AmJCardiol

# HF and VKA: the bleeding risk

>4000 pts from the AFFIRM study

**Table I.** Baseline characteristics

| | All patients | No major bleeding | Major bleeding | P |
|---|---|---|---|---|
| n (%) | 4060 | 3800 | 260 | |
| Randomized to rhythm control | 2033 (50) | 1909 (50) | 124 (48) | .427 |
| Age (y) (mean ± SD) | 69.7 ± 9.0 | 69.6 ± 9.0 | 72.3 ± 8.2 | <.001* |
| Women | 1594 (39) | 1478 (39) | 116 (45) | .068 |
| Minority | 461 (11) | 428 (11) | 33 (13) | .482 |
| History of hypertension | 2876 (71) | 2686 (71) | 190 (73) | .412 |
| History of CAD | 1551 (38) | 1439 (38) | 112 (43) | .094 |
| History of CHF | 939 (23) | 857 (23) | 82 (32) | .001* |
| History of diabetes | 813 (20) | 748 (20) | 65 (25) | .038* |
| History of stroke or TIA | 542 (13) | 497 (13) | 45 (17) | .052 |
| History of hepatic or renal disease | 231 (6) | 205 (5) | 26 (10) | .002* |
| Recent history of smoking | 496 (12) | 471 (12) | 25 (10) | .186 |
| Qualifying episode of AF is first episode documented | 1391 (36) | 1291 (35) | 100 (40) | .113 |
| Left atrial enlargement (size >4.0 cm) | 2023 (65) | 1888 (65) | 135 (66) | .724 |
| Left ventricular dysfunction (ejection fraction <50%) | 788 (26) | 724 (26) | 64 (32) | .063 |
| Mitral regurgitation >2+ | 647 (20) | 603 (20) | 44 (21) | .799 |

Di Marco et al, Am Heart J 2005

# In summary:

## Disadvantages of HF patients in therapy with VKA

- Multiple drugs
- More frequent hepatic and renal dysfunction
- Greater INR lability

## HAS-BLED score

| Condition | Points |
|---|---|
| **H** - Hypertension | 1 |
| **A** - Abnormal renal or liver function (1 point each) | 1 or 2 |
| **S** - Stroke | 1 |
| **B** - Bleeding | 1 |
| **L** - Labile INRs | 1 |
| **E** - Elderly (> 65 years) | 1 |
| **D** - Drugs or alcohol (1 point each) | 1 or 2 |

# What about DOACs?

| | RE-LY | Rocket-AF | Aristotle | Engage AF TIMI |
|---|---|---|---|---|
| Agent (mechanism of action) | Dabigatran (direct thrombin inhibitor) | Rivaroxaban (direct inhibitor of activated factor X) | Apixaban (direct inhibitor of activated factor X) | Edoxaban (direct inhibitor of activated factor X) |
| NOAC dose | 150 mg or 110 mg twice daily | 20 mg once daily | 5 mg twice daily | 60 mg or 30 mg once daily<br>In both groups the dose was halved in patients who had any of the following criteria:estimated CrCl 30-50 ml/ min, body weight ≤60 kg or concomitant use of verapamil or quinidine |
| Patients (n) | 18,113 | 14,264 | 18,201 | 21,105 |
| Renal function exclusion CG criteria) | <30 ml/min/1.73 m2 | <30 ml/min/1.73 m2 | <25 ml/min/1.73 m2 | <30 ml/min/1.73 m2 |
| Safety and efficacy of NOAC in comparison to warfarin | 150 mg dose:lower rates of stroke and systemic embolism and similar rates of major haemorrhage<br>110 mg dose:similar rates of stroke and less major bleeding | Similar rates of stroke and major bleeding | Less stroke and major bleeding | Both doses:similar rates of stroke with less major bleeding |

# DOACs' registration trials

**Table 2:** Baseline characteristics of patients enrolled in major studies of FDA-approved direct-acting oral anticoagulants (DOACs)

| Drug | Dabigatran[46] | Rivaroxaban[45] | Apixaban[48] | Edoxaban[47] |
|---|---|---|---|---|
| HF subgroup, n (%) | 4904 (27) | 9033 (63) | 2736 (15) | 8076 (67) |
| HF definition | NYHA ≥II HF symptoms <6 months screening and prior HF admission | HF history, or LVEF <40% | LVEF <40% or moderate or severe LV dysfunction | current presence or history of clinical HF Class C or D |
| Mean LVEF | NR | | 35 (30-39) | NR |
| LVEF ≤ 40% | 44 | 34 | NR** | NR |
| Mean age | 68.3 ± 10.2 | 72 (65-78) | 68 (60-74) | NR |
| Male % | 67 | 61 | 79 | NR |
| Nonischemic HF% | 68 | 70 | 72 | NR |
| Hypertension% | 75 | 93 | 75 | NR |
| Diabetes mellitus% | 27 | 42 | 27 | NR |
| History of stroke/TIA% | 17 | 47 | 16 | NR |
| Vascular disease% | NR | 6.7 | NR | NR |
| Mean $CHADS_2$ | 2.6 (1.1) | 3.7(0.9) | 2.22 (1.2) | NR |

Zeitler et al, JAFIB 2015

# ROCKET AF-HF: impact of HF

Rivaroxaban vs VKA

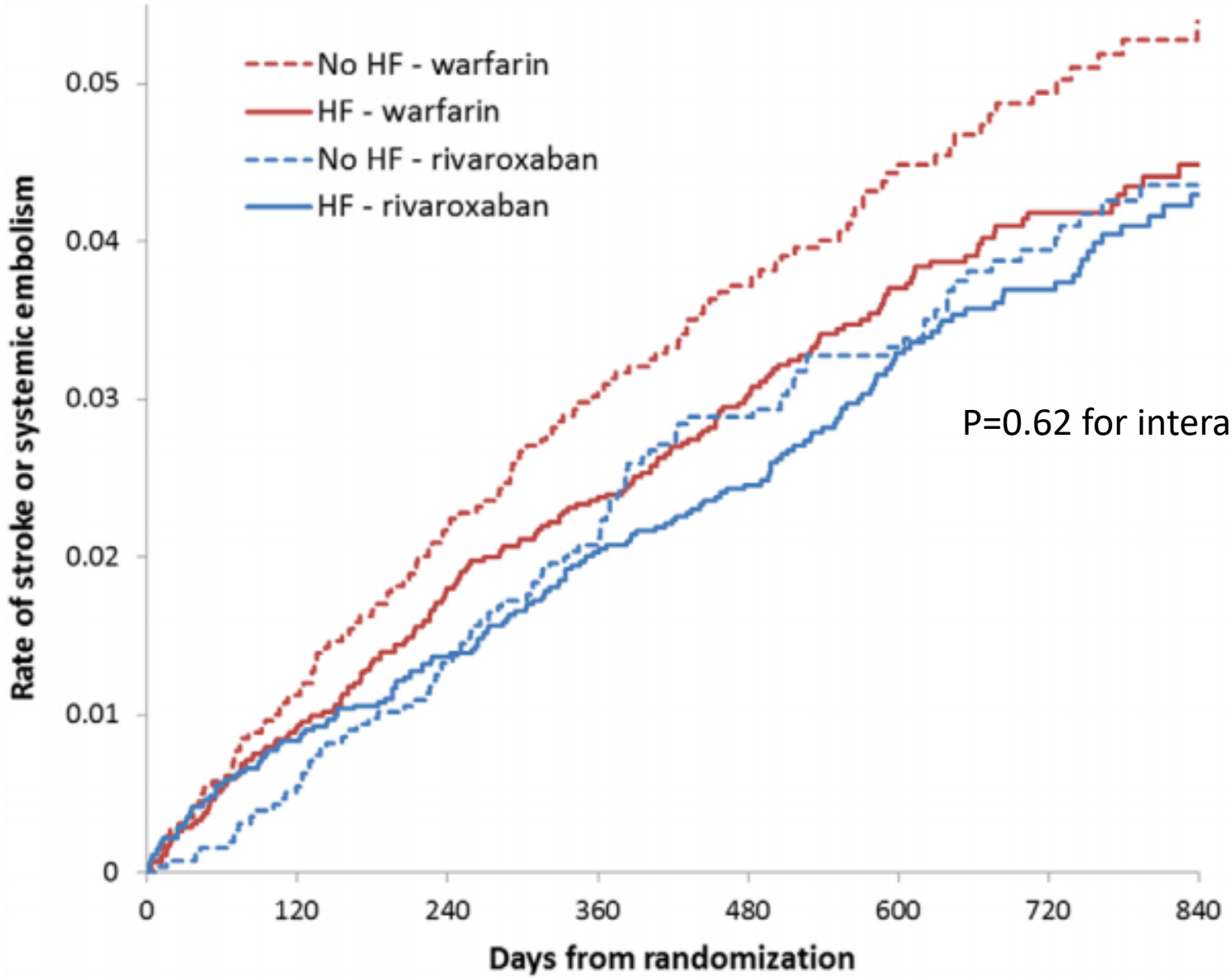
9033 pts with **HF history or LVEF<40%**

Mean $CHADS_2$ Score 3.5

| Outcomes | Heart Failure* | No Heart Failure* | Heart Failure vs No Heart Failure, HR (95% CI)† | *P* Value |
|---|---|---|---|---|
| Efficacy outcomes | | | | |
| Stroke or systemic embolization | 1.99 (343) | 2.32 (232) | 0.94 (0.78–1.13) | 0.51 |
| Stroke, systemic embolization, or vascular death | 5.00 (835) | 3.50 (346) | 1.28 (1.11–1.47) | 0.0006 |
| Stroke | 1.84 (317) | 2.16 (217) | 0.95 (0.78–1.15) | 0.57 |
| Systemic embolization | 0.17 (30) | 0.17 (17) | 0.93 (0.48–1.82) | 0.84 |
| All-cause death | 5.26 (879) | 3.37 (335) | 1.34 (1.17–1.55) | <0.0001 |
| Vascular death | 3.53 (600) | 1.75 (176) | 1.65 (1.37–1.98) | <0.0001 |
| Myocardial infarction | 1.15 (200) | 0.71 (72) | 1.20 (0.89–1.63) | 0.23 |
| Safety outcomes | | | | |
| Major or NMCR Bleeding | 14.12 (1766) | 15.73 (1158) | 1.00 (0.92–1.08) | 0.99 |
| Hemorrhagic stroke | 0.29 (41) | 0.45 (38) | 0.73 (0.45–1.20) | 0.22 |
| Intracranial hemorrhage | 0.53 (74) | 0.77 (65) | 0.84 (0.58–1.22) | 0.36 |

Van Diepen, Circ Heart Fail. 2013

# ROCKET AF-HF: outcomes by HF and therapy




P=0.62 for interaction

Van Diepen, Circ Heart Fail. 2013

# ROCKET AF-HF: outcomes by HF and therapy

| Outcomes | Heart Failure | | | No Heart Failure | | | *P* Value for Interaction‡ |
|---|---|---|---|---|---|---|---|
| | Rivaroxaban* | Warfarin* | Rivaroxaban vs Warfarin, HR (95% CI)† | Rivaroxaban* | Warfarin* | Rivaroxaban vs Warfarin, HR (95% CI)† | |
| Efficacy outcomes | (n=4530) | (n=4503) | | (n=2551) | (n=2587) | | |
| Stroke or systemic embolization | 1.90 (164) | 2.09 (179) | 0.91 (0.74–1.13) | 2.10 (105) | 2.54 (127) | 0.84 (0.65–1.09) | 0.62 |
| Stroke, systemic embolization, or vascular death | 4.88 (409) | 5.11 (426) | 0.97 (0.85–1.11) | 3.29 (163) | 3.71 (183) | 0.89 (0.72–1.10) | 0.52 |
| Stroke | 1.78 (154) | 1.89 (163) | 0.94 (0.76–1.17) | 1.97 (99) | 2.35 (118) | 0.85 (0.65–1.11) | 0.57 |
| Systemic embolization | 0.15 (13) | 0.19 (17) | 0.78 (0.38–1.61) | 0.14 (7) | 0.19 (10) | 0.72 (0.27–1.88) | 0.88 |
| All-cause death | 5.05 (423) | 5.46 (456) | 0.93 (0.82–1.07) | 3.20 (159) | 3.54 (176) | 0.89 (0.71–1.10) | 0.68 |
| Vascular death | 3.44 (292) | 3.63 (308) | 0.96 (0.82–1.13) | 1.65 (83) | 1.84 (93) | 0.89 (0.66–1.20) | 0.64 |
| Myocardial infarction | 1.09 (95) | 1.21 (105) | 0.94 (0.71–1.24) | 0.69 (35) | 0.72 (37) | 0.94 (0.59–1.49) | 0.99 |
| Safety outcomes | (n=4550) | (n=4527) | | (n=2561) | (n=2598) | | |
| Major or NMCR bleeding | 14.22 (888) | 14.02 (878) | 1.05 (0.95–1.15) | 16.12 (587) | 15.35 (571) | 1.05 (0.93–1.18) | 0.99 |
| Hemorrhagic stroke | 0.16 (11) | 0.43 (30) | 0.38 (0.19–0.76) | 0.43 (18) | 0.47 (20) | 0.91 (0.48–1.73) | 0.067 |
| Intracranial hemorrhage | 0.40 (28) | 0.65 (46) | 0.63 (0.40–1.02) | 0.64 (27) | 0.89 (38) | 0.72 (0.44–1.19) | 0.71 |

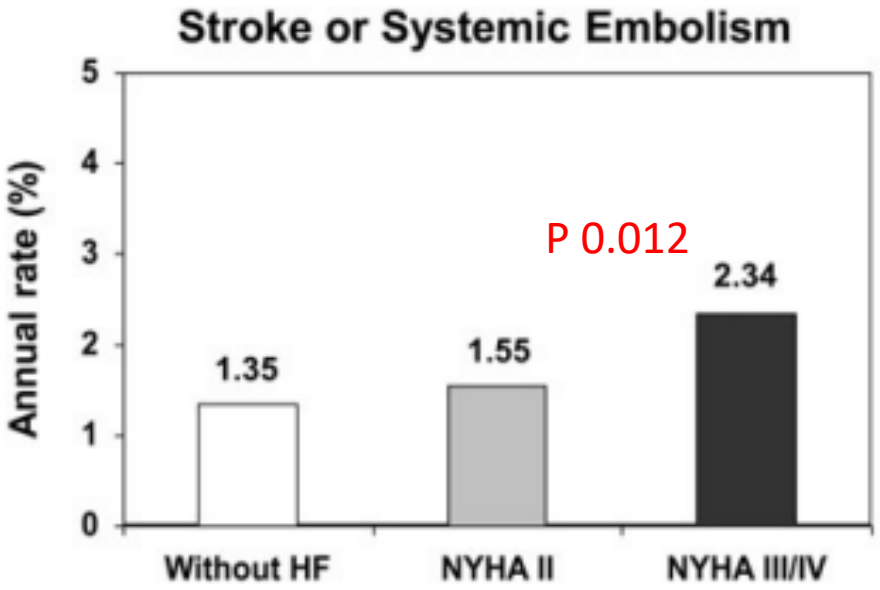
Van Diepen, Circ Heart Fail. 2013

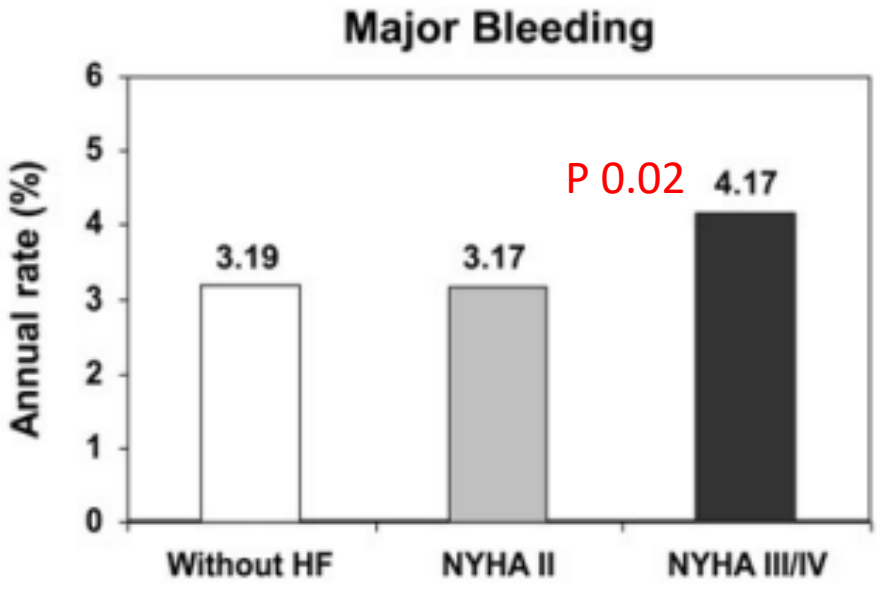
# RE-LY: HF subgroup analysis

Definition: NYHA ≥ 2 in the last 6 mo + history of HF

**Table 4 Total number and annual rates of outcomes in the study population with and without heart failure and multivariable adjusted hazard ratios**

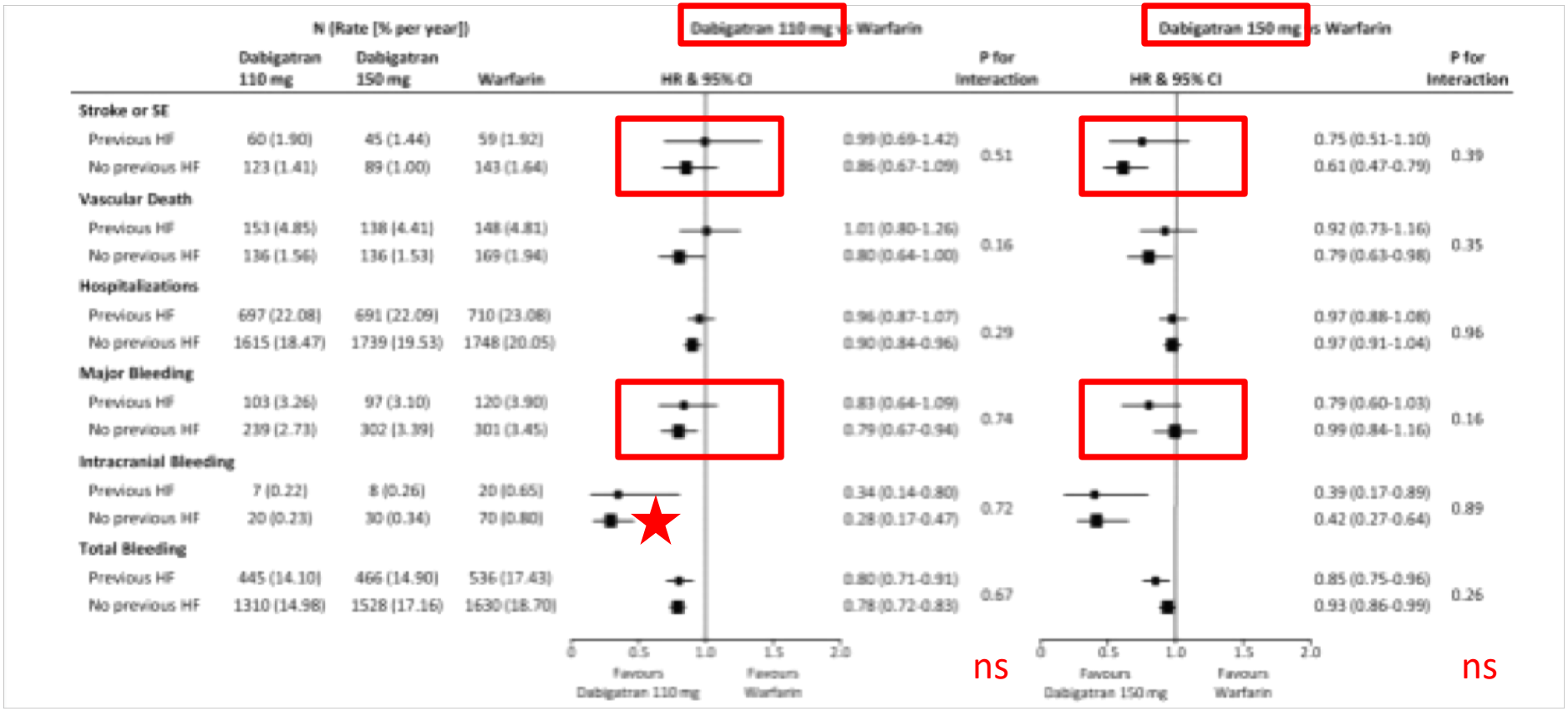
| Outcomes | With HF ($n$ = 4904) | Without HF ($n$ = 13 209) | Adjusted hazard ratio (95% CI) | $P$-value |
|---|---|---|---|---|
| Stroke or systemic embolism | 164 (1.75) | 355 (1.35) | 1.08 (0.89–1.31) | 0.46 |
| Vascular death | 439 (4.69) | 441 (1.67) | 2.26 (1.96–2.61) | <0.0001 |
| Hospitalization | 2098 (22.41) | 5102 (19.35) | 1.13 (1.07–1.20) | <0.0001 |
| Major bleeding | 320 (3.42) | 842 (3.19) | 0.96 (0.83–1.10) | 0.53 |
| Intracranial bleeding | 35 (0.37) | 120 (0.46) | 0.72 (0.49–1.06) | 0.10 |




Ferreira et al, Eur J Heart Fail 2013

# RE-LY HF: outcomes




Ferreira et al, Eur J Heart Fail 2013

# ARISTOTELE subanalysis

14671 pts

8728 patients

no symptomatic HF and an EF >40%

3207 patients

Symptomatic HF and an EF >40% (study definition of HF-PEF)

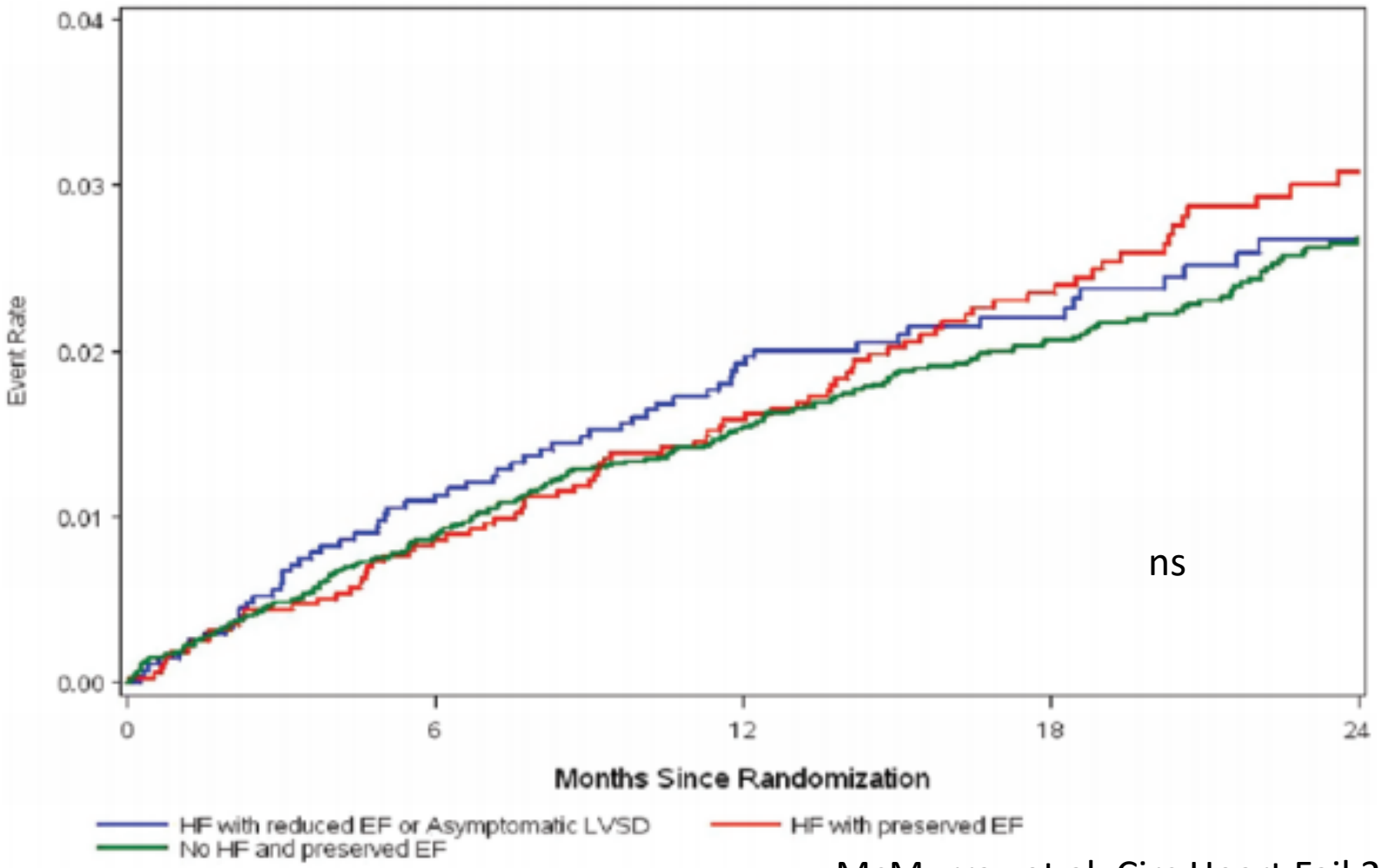
2736 patients

EF ≤40% (moderate or severe LV dysfunction)

McMurray et al, Circ Heart Fail 2013

# ARISTOTELE subanalysis

Composite primary outcome: stroke + SE




McMurray et al, Circ Heart Fail 2013

# Treatment effect by HF/LVSD: efficacy and safety endpoints

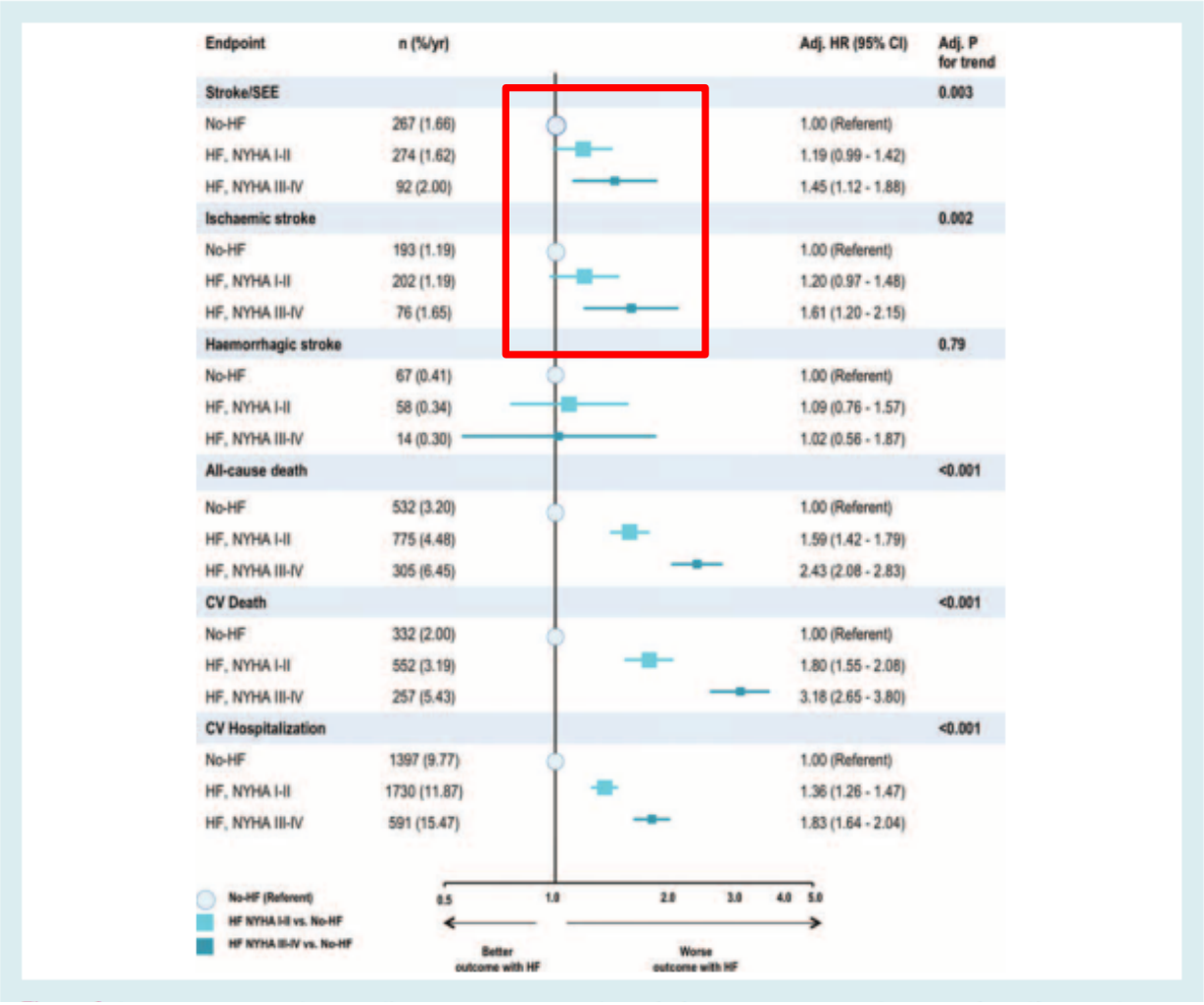
| | Rate (n) | | | |
|---|---|---|---|---|
| | Apixaban | Warfarin | HR (95% CI) | Interaction *P* Value |
| Stroke or systemic embolism* | | | | |
| LVSD | 0.99 (24) | 1.80 (43) | 0.55 (0.34–0.91) | 0.21 |
| HF-PEF | 1.51 (44) | 1.54 (45) | 0.98 (0.65–1.49) | |
| No LVSD/no HF | 1.16 (95) | 1.58 (129) | 0.74 (0.57–0.96) | |
| Stroke | | | | |
| LVSD | 0.91 (22) | 1.67 (40) | 0.54 (0.32–0.91) | 0.22 |
| HF-PEF | 1.37 (40) | 1.40 (41) | 0.98 (0.63–1.51) | |
| No LVSD/no HF | 1.09 (89) | 1.54 (125) | 0.71 (0.54–0.93) | |
| ISTH major bleeding | | | | |
| LVSD | 2.77 (61) | 3.41 (74) | 0.81 (0.58–1.14) | 0.50 |
| HF-PEF | 1.95 (52) | 3.17 (82) | 0.62 (0.44–0.88) | |
| No LVSD/no HF | 2.17 (162) | 2.83 (210) | 0.77 (0.62–0.94) | |
| ISTH major bleeding: intracranial | | | | |
| LVSD | 0.18 (4) | 0.73 (16) | 0.25 (0.08–0.73) | 0.23 |
| HF-PEF | 0.15 (4) | 0.76 (20) | 0.20 (0.07–0.58) | |
| No LVSD/no HF | 0.38 (29) | 0.81 (61) | 0.47 (0.30–0.73) | |

*"Apixaban was **superior** to warfarin with respect to both efficacy and safety outcomes in all patient groups, with the greatest absolute benefit in the highest risk patients with LVSD".*

McMurray et al, Circ Heart Fail 2013

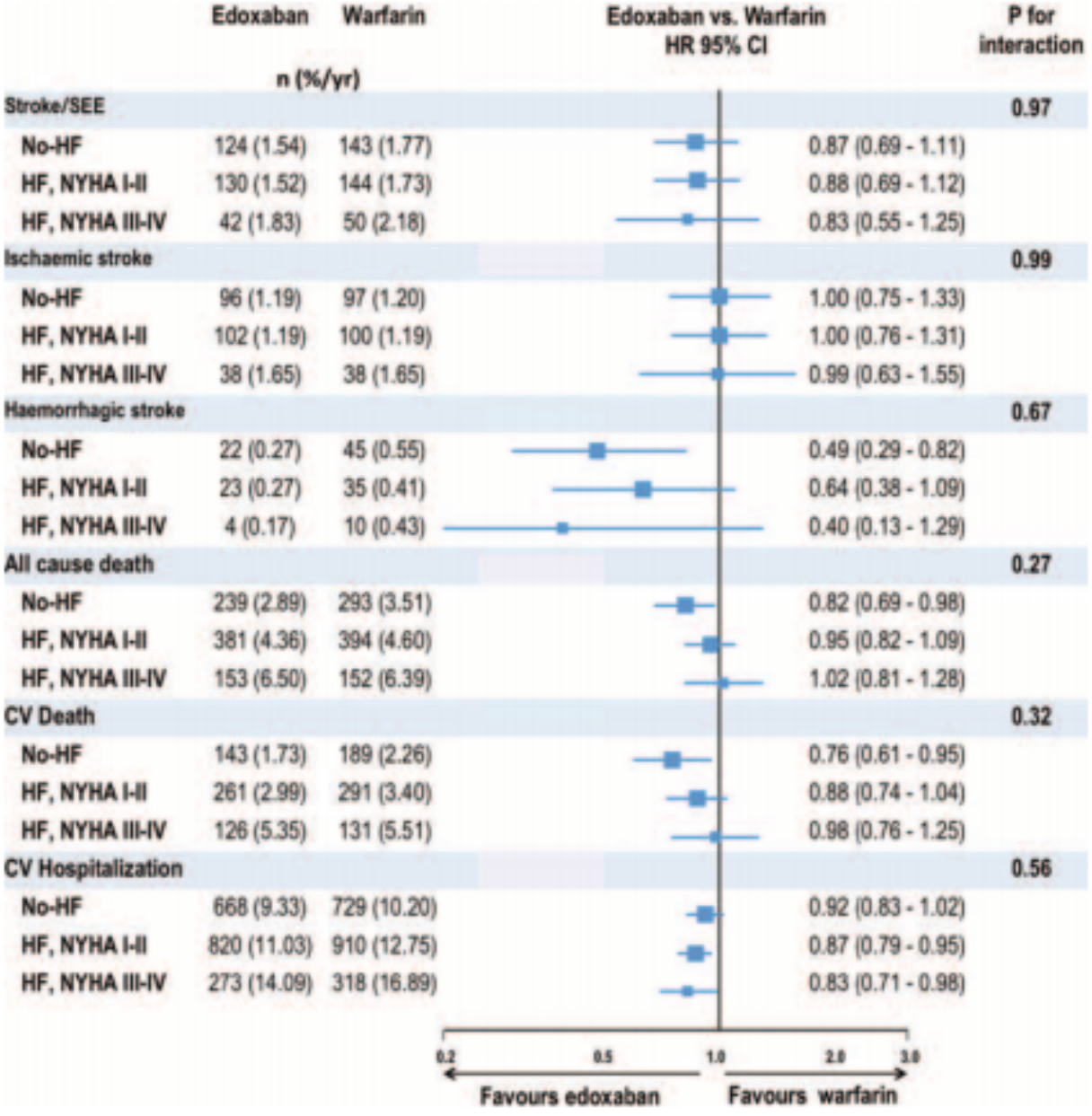
# ENGAGE AF-HF: outcomes by HF degree

HDER only!
Previous history or presence of HF stage C/D (ACC/AHA definition)




Magnani et al, European Journal of Heart Failure 2016

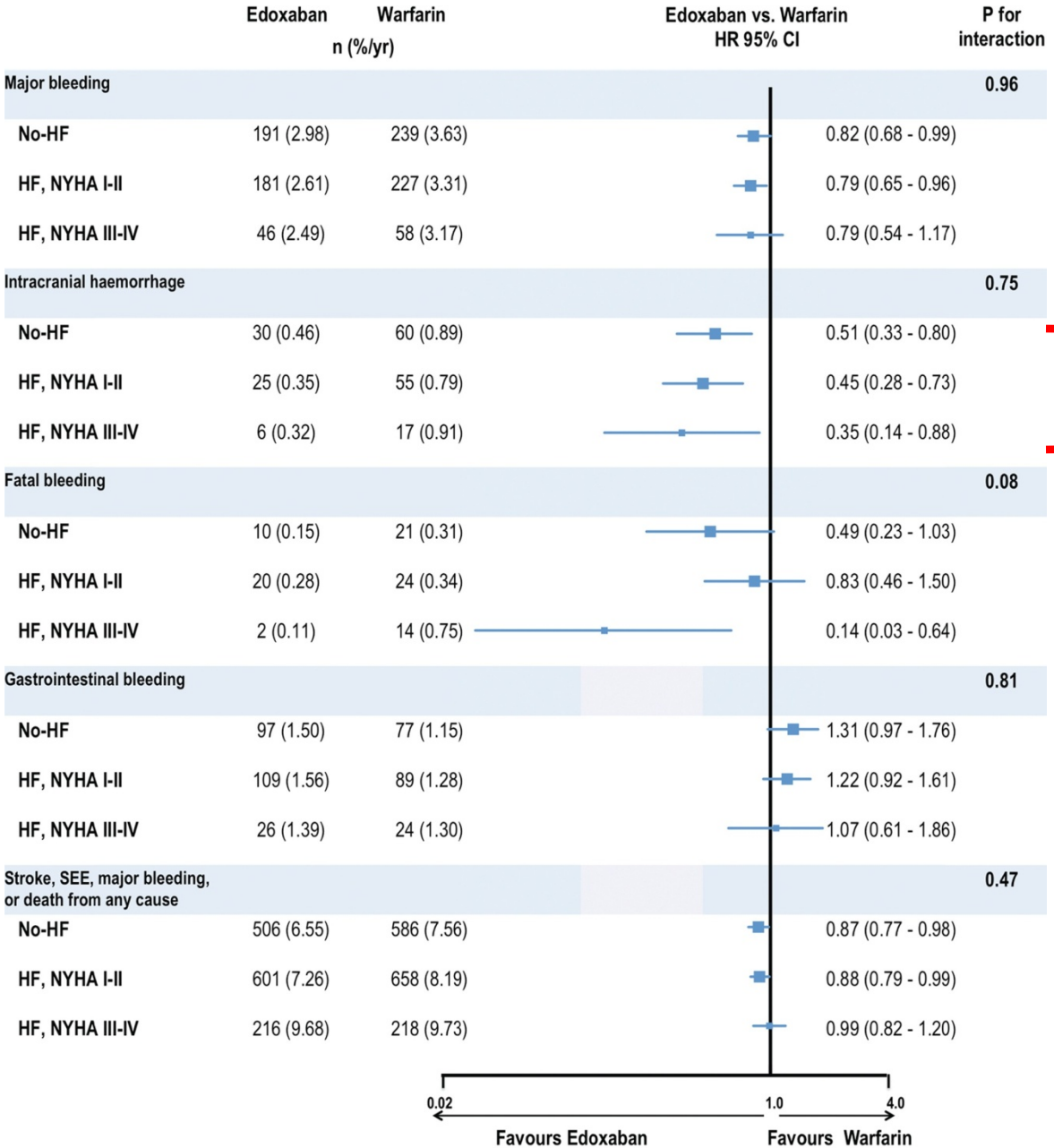
# ENGAGE AF-HF: outcomes by HF and therapy




All p<0.05

Magnani et al, European Journal of Heart Failure 2016

# ENGAGE AF-HF: outcomes by HF and therapy




p 0.04

p 0.02

All p<0.05

Magnani et al,
European Journal of Heart Failure 2016

# Overall results

**Table 2: Baseline characteristics of patients enrolled in major studies of FDA-approved direct-acting oral anticoagulants (DOACs)**

| Drug | Dabigatran[46] | Rivaroxaban[49] | Apixaban[48] | Edoxaban[47] |
|---|---|---|---|---|
| HF subgroup, n (%) | 4904 (27) | 9033 (63) | 2736 (15) | 8076 (67) |
| HF definition | NYHA ≥II HF | HF history, | LVEF <40% | current presence |
| Efficacy | No significant interaction between treatment effect of dabigatran (110mg or 150mg) and the presence of HF. | No significant interaction between the primary efficacy endpoint and the presence of heart failure for those taking rivaroxaban versus warfarin. | No evidence of treatment heterogeneity according to the presence of heart failure. | No interaction between reduction in stroke or systemic embolism and the presence of HF. |

Zeitler et al, JAFIB 2015

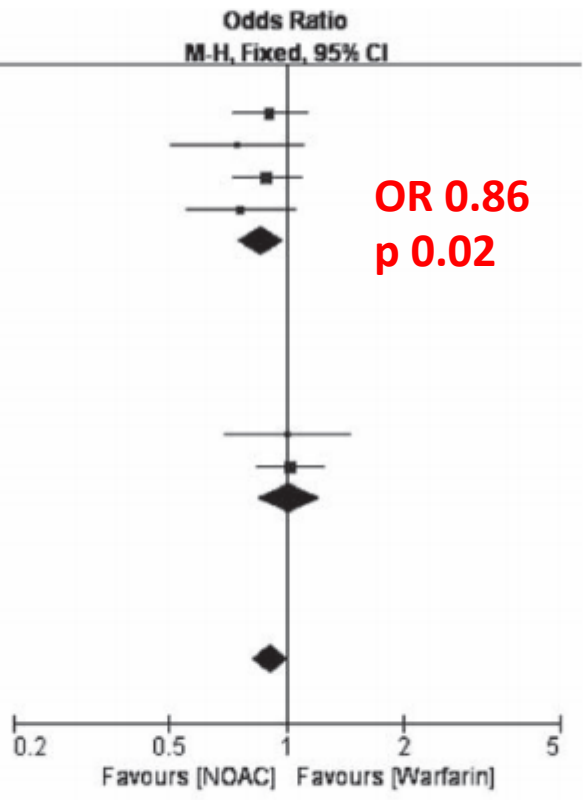
# AF +HF metanalysis

RCT: RE-LY, ARISTOTELE, ROCKET-AF, ENGAGE-AF

**Primary efficacy outcome: stroke/SE**

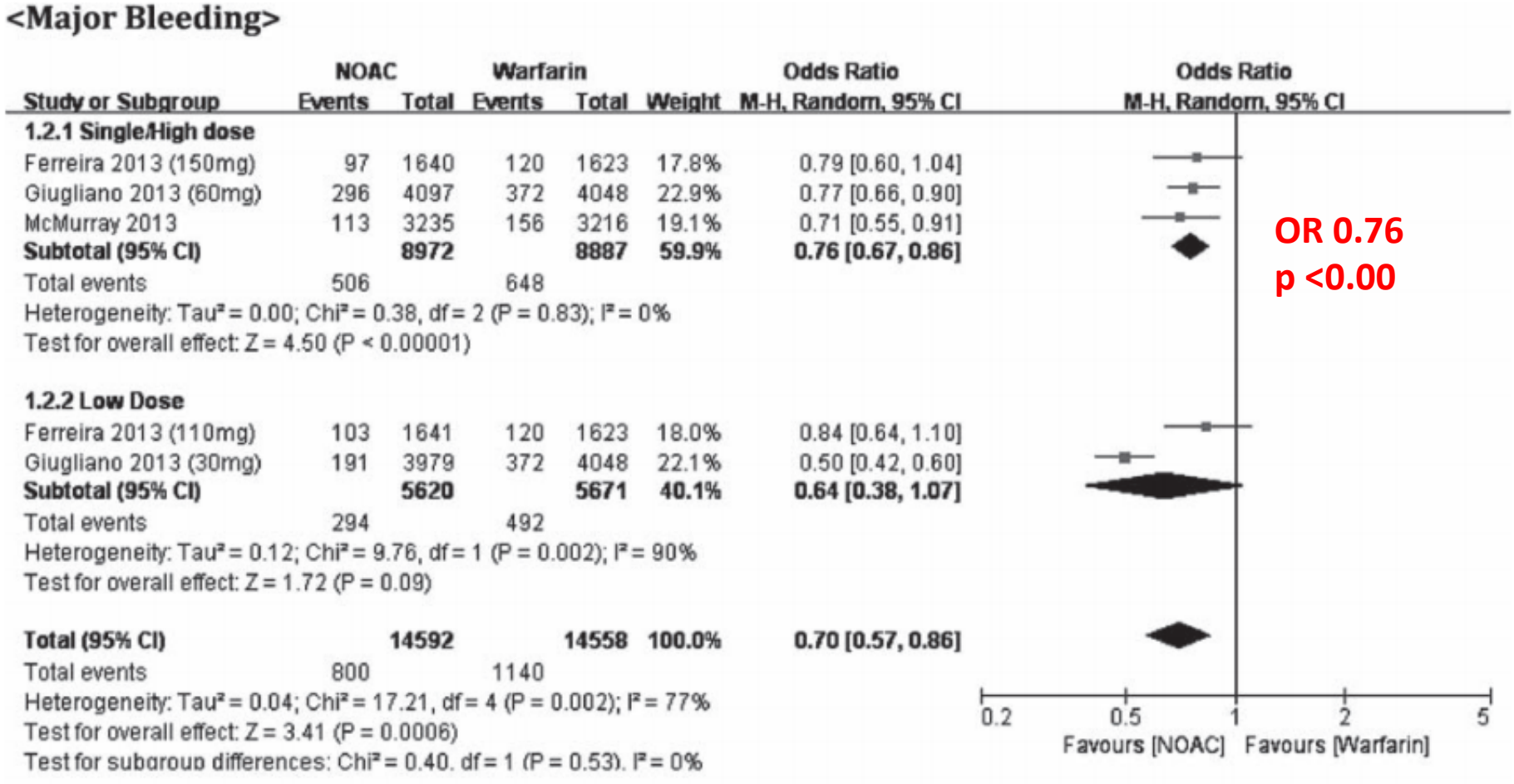
19122 NAO vs 13390 VKA

| Study or Subgroup | NOAC Events | NOAC Total | Warfarin Events | Warfarin Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **1.1.1 Single/High dose** | | | | | | |
| Diepen 2013 | 164 | 4530 | 179 | 4503 | 22.6% | 0.91 [0.73, 1.13] |
| Ferreira 2013 (150mg) | 45 | 1640 | 59 | 1623 | 7.5% | 0.75 [0.50, 1.11] |
| Giugliano 2013 (60mg) | 182 | 3979 | 206 | 4048 | 25.5% | 0.89 [0.73, 1.10] |
| McMurray 2013 | 68 | 3235 | 88 | 3216 | 11.3% | 0.76 [0.55, 1.05] |
| **Subtotal (95% CI)** | | **13384** | | **13390** | **66.9%** | **0.86 [0.76, 0.98]** |
| Total events | 459 | | 532 | | | |
| Heterogeneity: Chi² = 1.39, df = 3 (P = 0.71); I² = 0% | | | | | | |
| Test for overall effect: Z = 2.32 (P = 0.02) | | | | | | |
| **1.1.2 Low dose** | | | | | | |
| Ferreira 2013 (110mg) | 60 | 1641 | 59 | 1623 | 7.5% | 1.01 [0.70, 1.45] |
| Giugliano 2013 (30mg) | 213 | 4097 | 206 | 4048 | 25.7% | 1.02 [0.84, 1.25] |
| **Subtotal (95% CI)** | | **5738** | | **5671** | **33.1%** | **1.02 [0.86, 1.21]** |
| Total events | 273 | | 265 | | | |
| Heterogeneity: Chi² = 0.01, df = 1 (P = 0.94); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.21 (P = 0.83) | | | | | | |
| **Total (95% CI)** | | **19122** | | **19061** | **100.0%** | **0.91 [0.82, 1.01]** |
| Total events | 732 | | 797 | | | |
| Heterogeneity: Chi² = 3.78, df = 5 (P = 0.58); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.75 (P = 0.08) | | | | | | |
| Test for subgroup differences: Chi² = 2.39, df = 1 (P = 0.12), I² = 58.2% | | | | | | |




Xiong et al, European Journal of Heart Failure 2015

# AF +HF metanalysis: SAFETY



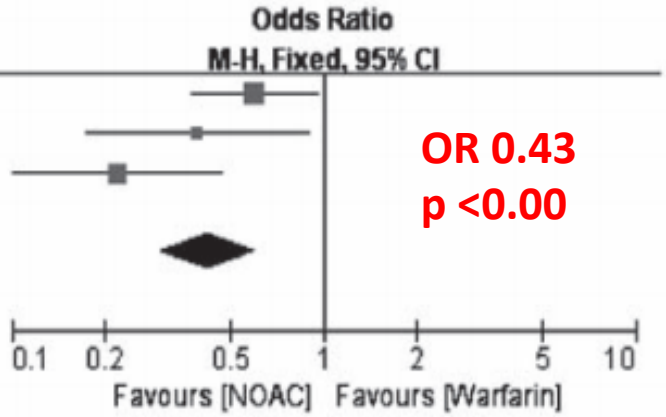

Xiong et al, European Journal of Heart Failure 2015

# AF +HF metanalysis: SAFETY

<Intracranial Haemorrhage>

| Study or Subgroup | NOAC Events | NOAC Total | Warfarin Events | Warfarin Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Diepen 2013 | 28 | 4530 | 46 | 4503 | 45.0% | 0.60 [0.38, 0.97] |
| Ferreira 2013 (150mg) | 8 | 1640 | 20 | 1623 | 19.6% | 0.39 [0.17, 0.89] |
| McMurray 2013 | 8 | 3235 | 36 | 3216 | 35.4% | 0.22 [0.10, 0.47] |
| **Total (95% CI)** | | **9405** | | **9342** | **100.0%** | **0.43 [0.30, 0.61]** |
| Total events | 44 | | 102 | | | |

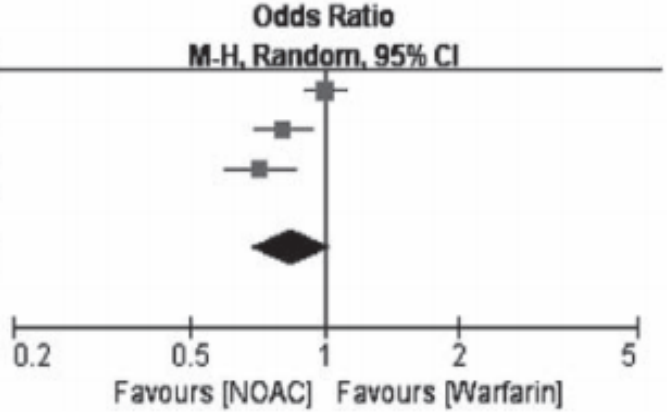
Heterogeneity: Chi² = 5.00, df = 2 (P = 0.08); I² = 60%
Test for overall effect: Z = 4.72 (P < 0.00001)




<All-bleeding>

| Study or Subgroup | NOAC Events | NOAC Total | Warfarin Events | Warfarin Total | Weight | Odds Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Diepen 2013 | 888 | 4530 | 878 | 4503 | 36.4% | 1.01 [0.91, 1.12] |
| Ferreira 2013 (150mg) | 466 | 1640 | 536 | 1623 | 33.2% | 0.80 [0.69, 0.93] |
| McMurray 2013 | 216 | 3235 | 292 | 3216 | 30.5% | 0.72 [0.60, 0.86] |
| **Total (95% CI)** | | **9405** | | **9342** | **100.0%** | **0.84 [0.69, 1.04]** |
| Total events | 1570 | | 1706 | | | |

Heterogeneity: Tau² = 0.03; Chi² = 12.52, df = 2 (P = 0.002); I² = 84%
Test for overall effect: Z = 1.62 (P = 0.10)



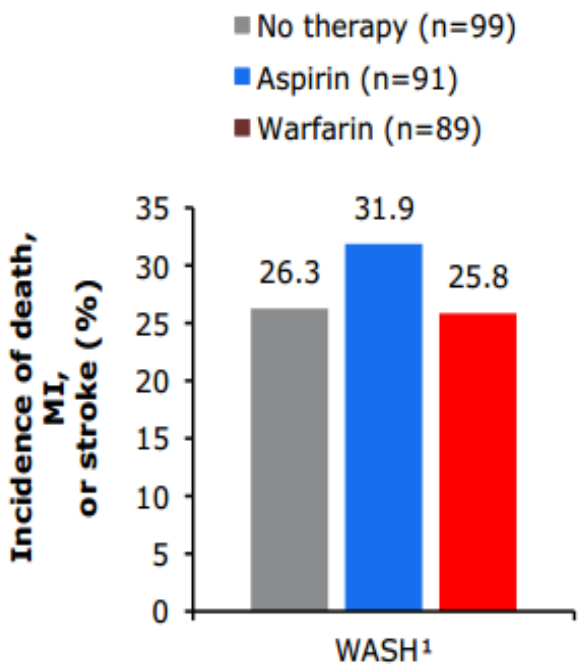

Xiong et al, European Journal of Heart Failure 2015

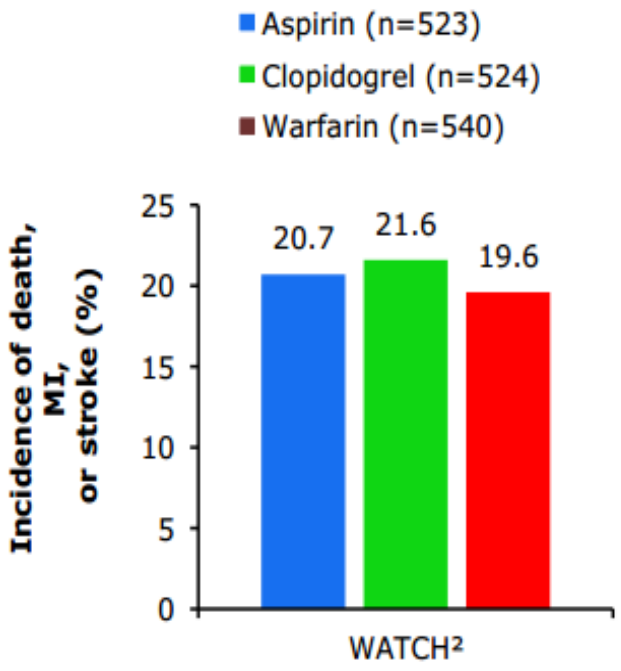
# Heart failure and sinus rhythm?

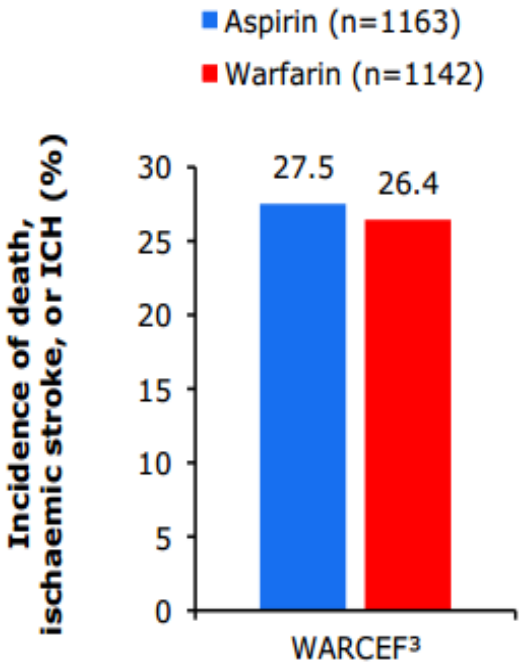
Rationale:

- deceleration of peripheral and intracardiac blood flow due to peripheral congestion and impaired cardiac contractility
- prolonged bed rest in severely ill cases
- endothelial dysfunction (impaired NO response)
- the presence of coagulation defects as, for example, in the case of ventricular assist devices
- **increased risk for misdiagnosed atrial fibrillation**

# Warfarin has failed to demonstrate improved outcomes in pts with HF and SR





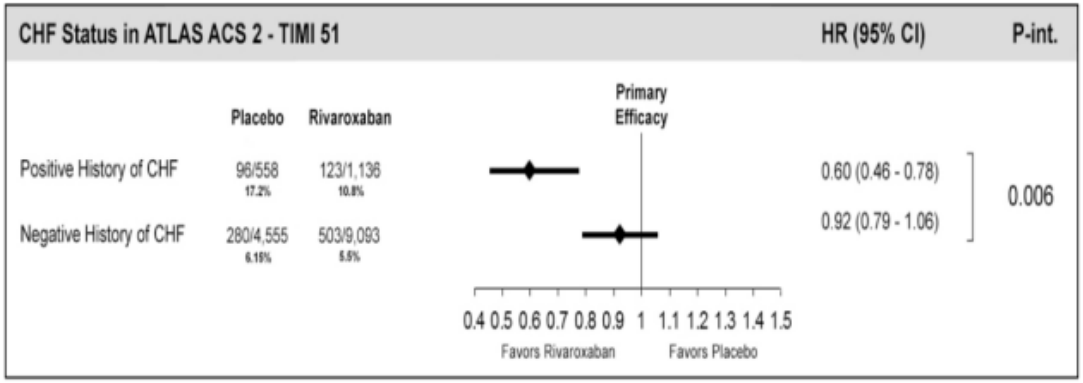
1. Cleland JGF, et al. *Am Heart J.* 2004.
2. Massie BM, et al. *Circulation.* 2009
3. Homma S *et al*, *N Engl J Med.* 2012.

# Rationale for the Commander HF design

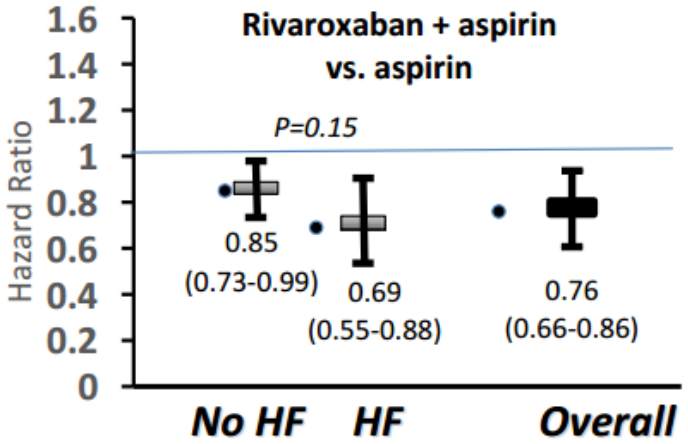
## ATLAS ACS 2-TIMI 51

Figure 1.

Primary Efficacy Endpoint among Subjects with History of CHF vs. Patient Without Prior History of CHF



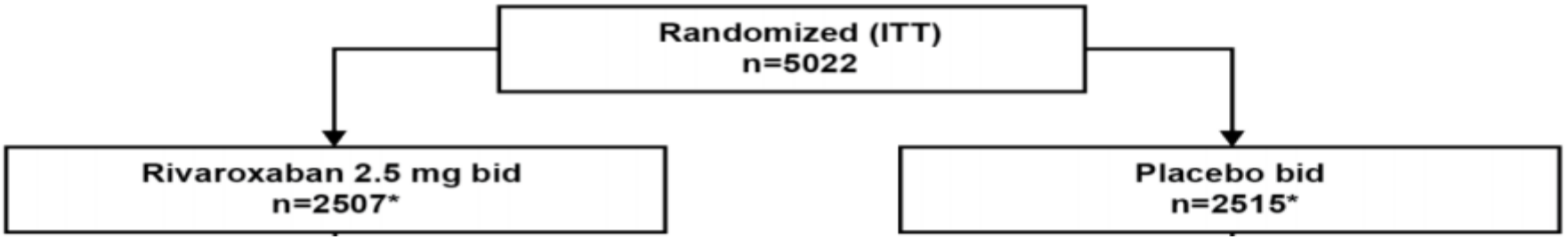

## COMPASS




Korjian et al, AJCC2018

Branch et al, Circulation 2019

# COMMANDER HF

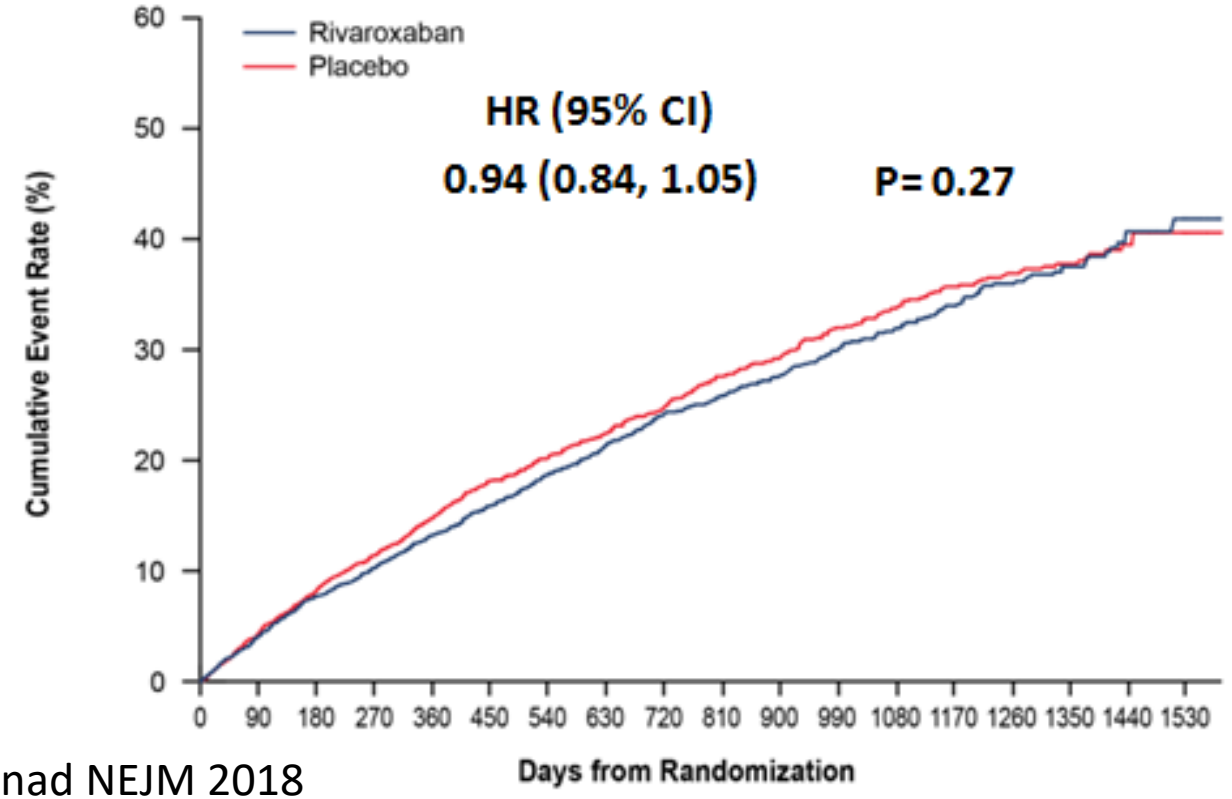



| Key Inclusion Criteria | Key Exclusion Criteria |
|---|---|
| • Chronic HF (>3mths) with reduced LVEF (≤40%) | Bleeding risk, AF, acute MI |
| • Within 21 days after an episode of hospitalization for worsening HF | • Planned cardiac surgery within 28 days (eg, PCIs and EP devices) |
| • Elevated plasma BNP (≥200 pg/mL) or NT-proBNP (≥800 pg/mL) during the index event | • History of severe valvular disease, chronic episodes of ventricular tachycardia, severe peptic ulcer disease, or HIV |
| • CAD (Hx MI, Revasc, angiogram, ECG+Echo) | • eGFR <20 mL/min |
| • Receiving appropriate guidelines medical treatment† | • Prior stroke (within 90 days) |
| • No anticoagulation | • Anemia (Hb<8 g/dL) or severe thrombocytopenia (platelets <50,000/μL) |

Zannad NEJM 2018

# COMMANDER HF

## Primary Efficacy Outcome
## (ITT, All-cause mortality, MI, or stroke)




Zannad NEJM 2018

# COMMANDER HF: safety outcomes

| | 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 |

*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*

# Take home messages

- Thromboembolic risk increases proportionally with HF stages
- In patients with both NVAF and HF all DOACs demonstrated the same efficacy/safety profile showed in the overall populations
- To date in patients with HF without AF the anticoagulation therapy did not prove benefit in prevention of ischemic events