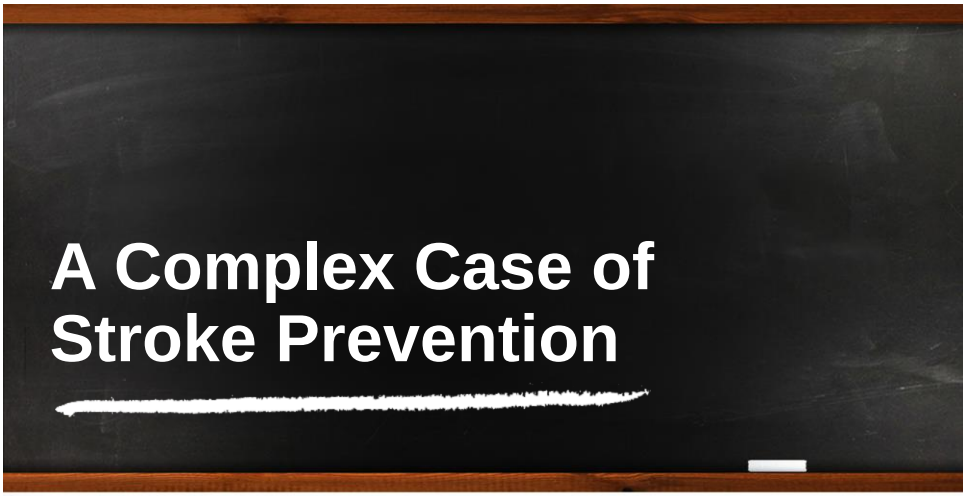



**Paul Dorian, MD, MSc, FRCP(C)**
Department Director, Division of Cardiology,
Staff Cardiac Electrophysiologist,
St. Michael's Hospital
Professor of Medicine, University of Toronto

## Disclosures

- Research support, honoraria from Bayer, BI, BMS, Pfizer, Servier

## Mr. MG (1)

- An 88-year-old retired businessman
- MI in 2006, LAD stent placed
- Developed persistent, then permanent AF in 2010
- Stroke with minimal deficit 2011; started on dabigatran 110 mg/day
- Hypertension, moderate LV dysfunction (EF 34%), dyslipidemia, sleep apnea, mild aortic stenosis (AVA 1.5 )

## Mr. MG (2)

- Treated with perindopril, bisoprolol, at max tolerated doses (hr 80 at rest), spironolactone, furosemide
- CrCl (eGFR) 45 ml/min
- Progressive decline in function—cognitive impairment, walks with a cane/walker, class 3 dyspnea
- **Admitted to hospital with CHF; O2 sat 80 on room air**

# Mr. MG (3)

- Treated with IV furosemide, improved
- BP 100/60; HR 75/min
- Hb 105; eGFR now 35; electrolytes N

- Any change in his DOAC?

# Please take out your mobile devices, and activate Sli.do

# Interactive Question 1

Would you make any of the following changes to Mr. MG's DOAC?

1. Stop dabigatran, start warfarin **(3%)**
2. Stop dabigatran, substitute ASA **(0%)**
3. Continue dabigatran **(14%)**
4. Switch to apixaban 2.5 mg BID **(66%)**
5. Switch to rivaroxaban 15 mg OD **(16%)**

# Mr. MG (4)

- No change to DOAC made
- That night, fall while going to bathroom
- X-ray shows fractured hip—risk of displacement, surgeon recommends OR within 24 hrs
- What to do about anticoagulation?

# Please take out your mobile devices, and activate Sli.do


# Interactive Question 2

What should be done about anticoagulation?

1. Measure aPTT; if normal, operate? **(20%)**
2. Administer PCC, operate? **(2%)**
3. Wait 72 hrs then operate? **(29%)**
4. Measure dilute thrombin time (Hemoclot test); if abnormal, administer idarucizimab? **(49%)**

## Measuring DOAC Effect


- aPTT may be normal even if thrombin inhibitor levels present
- PC unproven in reversing drug effect
- Half life of dabigatran may be 24 hrs and may take 3-5 days for complete loss of anticoagulant effect
- Hemoclot is an accurate measure of drug effect

## Mr. MG (5)

- Hemoclot test shows 150 ng/ml, 16 hrs after last dabigatran dose
- Idarucizimab administered
- Next morning, blood concentration = 0
- Taken to OR, successful surgery, post-op hypotension for 12 hrs
- Following day: eGFR 28 ml/min; no bleeding

- What to do about stroke prevention?

# Please take out your mobile devices, and activate Sli.do

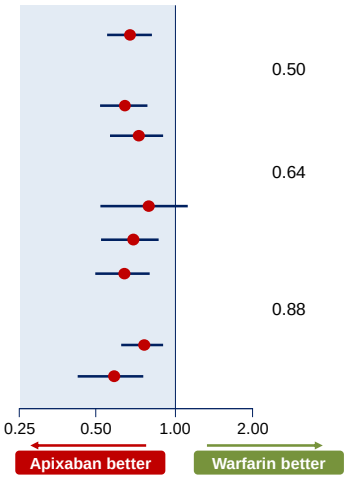

# Interactive Question 3

What should be done about stroke prevention?

1. Start heparin and warfarin? **(16%)**
2. Start ASA? **(0%)**
3. Restart dabigatran 110 mg BID? **(6%)**
4. Start apixaban 2.5 mg BID? **(68%)**
5. Start rivaroxaban 15 mg/day? **(9%)**

# Apixaban Major Bleeding Results Across Subgroups in ARISTOTLE

| CHARACTERISTICS | NO. OF PATIENTS | APIXABAN | WARFARIN | P VALUE FOR INTERACTION |
|---|---|---|---|---|
| | | *Number of events (%/yr)* | | |
| All patients | 18,140 | 327 (2.13) | 462 (3.09) | |
| **Prior warfarin/VKA** | | | | 0.50 |
| Yes | 10,376 | 185 (2.1) | 274 (3.2) | |
| No | 7,764 | 142 (2.2) | 188 (3.0) | |
| **Age** | | | | 0.64 |
| < 65 yrs | 5,455 | 56 (1.2) | 72 (1.5) | |
| 65 to < 75 yrs | 7,030 | 120 (2.0) | 166 (2.8) | |
| ≥ 75 yrs | 5,655 | 151 (3.3) | 224 (5.2) | |
| **Sex** | | | | 0.88 |
| Male | 11,747 | 225 (2.3) | 294 (3.0) | |
| Female | 6,393 | 102 (1.9) | 168 (3.3) | |

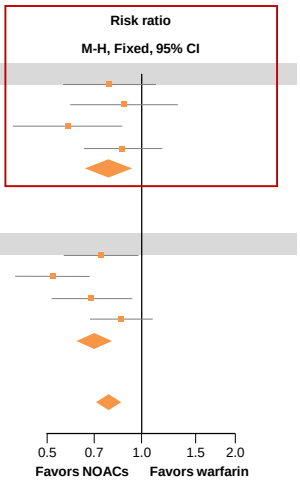



Adapted from Granger et al. N Engl J Med 2011; 365:981-92.

# Meta-Analysis of Renal Function on the Safety and Efficacy of Novel Oral Anticoagulants for AF (1)

## Risk of stroke or systemic embolism GFR <50 ml/min and use of NOACs versus warfarin in relation to renal function

| | NOACs | | Warfarin | | | Risk ratio |
|---|---|---|---|---|---|---|
| **Study or subgroup** | **Events** | **Total** | **Events** | **Total** | **Weight** | **M-H, Fixed, 95% CI** |
| **1.4.1 Stroke or systemic embolism GFR <50 ml/min** | | | | | | |
| ARISTOTLE | 54 | 1,502 | 69 | 1,515 | 6.9% | 0.79 (0.56, 1.12) |
| ENGAGE AF-TIMI 48 | 43 | 1,287 | 49 | 1,297 | 4.9% | 0.88 (0.59, 1.32) |
| RE-LY | 36 | 1,232 | 57 | 1,126 | 5.9% | 0.58 (0.38, 0.87) |
| ROCKET AF | 77 | 1,490 | 86 | 1,459 | 8.7% | 0.88 (0.65, 1.18) |
| Subtotal (95% CI) | | 5,511 | | 5,397 | 26.4% | 0.79 (0.66, 0.94) |
| **Total events** | **210** | | **261** | | | |
| Heterogeneity: $Chi^2 = 3.03$, df = 3 ($p = 0.39$); $I^2 = 1\%$. Test for overall effect: Z = 2.63 ($p = 0.008$) | | | | | | |
| **1.4.2 Stroke or systemic embolism GFR 50-80 ml/min** | | | | | | |
| ARISTOTLE | 87 | 3,817 | 116 | 3,770 | 11.7% | 0.74 (0.56, 0.97) |
| ENGAGE AF-TIMI 48 | 69 | 2,985 | 135 | 3,030 | 13.4% | 0.52 (0.39, 0.69) |
| RE-LY | 70 | 2,852 | 103 | 2,898 | 10.2% | 0.69 (0.51, 0.93) |
| ROCKET AF | 126 | 3,298 | 151 | 3,400 | 14.8% | 0.86 (0.68, 1.08) |
| Subtotal (95% CI) | | 12,952 | | 13,098 | 50.1% | 0.71 (0.62, 0.81) |
| **Total events** | **352** | | **505** | | | |
| Heterogeneity: $Chi^2 = 7.40$, df = 3 ($p = 0.06$); $I^2 = 59\%$. Test for overall effect: Z = 5.08 ($p < 0.00001$) | | | | | | |
| Total (95% CI) | | 29,066 | | 29,010 | 100.0% | 0.79 (0.72, 0.86) |
| **Total events** | **791** | | **1,001** | | | |
| Heterogeneity: $Ch^2 = 23.70$, df = 11 ($p = 0.01$); $I^2 = 54\%$. Test for overall effect: Z = 5.07 ($p < 0.00001$) | | | | | | |
| Test for subgroup differences: $Chi^2 = 7.39$, df = 2 ($p = 0.02$), $I^2 = 72.9\%$ | | | | | | |

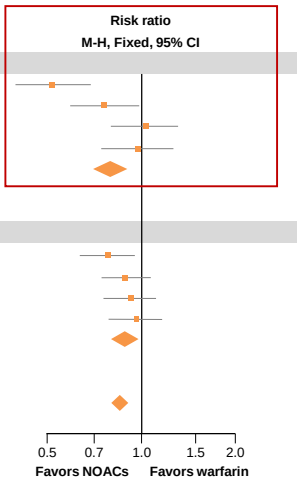



Munoz et al. Am J Cardiol 2016; 117(1):69-75.

# Meta-Analysis of Renal Function on the Safety and Efficacy of Novel Oral Anticoagulants for AF (2)

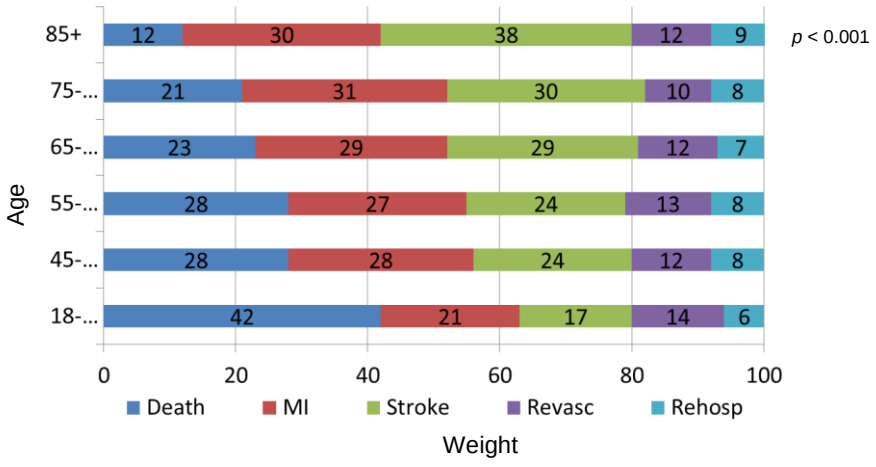
## Risk of major bleeding and use of NOACs versus warfarin in relation to renal function

| | NOACs | | Warfarin | | | Risk ratio |
|---|---|---|---|---|---|---|
| **Study or subgroup** | **Events** | **Total** | **Events** | **Total** | **Weight** | **M-H, Fixed, 95% CI** |
| **2.4.1 Major bleeding in GFR < 50 ml/min** | | | | | | |
| ARISTOTLE | 73 | 1,493 | 142 | 1,512 | 7.9% | 0.52 (0.40, 0.68) |
| ENGAGE AF-TIMI 48 | 96 | 1,287 | 128 | 1,297 | 7.1% | 0.76 (0.59, 0.97) |
| RE-LY | 129 | 1,232 | 116 | 1,126 | 6.8% | 1.02 (0.80, 1.29) |
| ROCKET AF | 99 | 1,502 | 100 | 1,476 | 5.7% | 0.97 (0.74, 1.27) |
| Subtotal (95% CI) | | 5,514 | | 5,411 | 27.5% | 0.80 (0.70, 0.91) |
| **Total events** | **397** | | **486** | | | |
| Heterogeneity: $Chi^2 = 15.66$, df = 3 ($p = 0.001$); $I^2 = 81\%$. Test for overall effect: Z = 3.49 ($p = 0.0005$) | | | | | | |
| **2.4.2 Major bleeding in GFR 50-80 ml/min** | | | | | | |
| ARISTOTLE | 157 | 3,807 | 199 | 3,758 | 11.2% | 0.78 (0.63, 0.96) |
| ENGAGE AF-TIMI 48 | 206 | 2,985 | 235 | 3,030 | 13.1% | 0.89 (0.74, 1.07) |
| RE-LY | 188 | 2,852 | 209 | 2,898 | 11.6% | 0.91 (0.76, 1.11) |
| ROCKET AF | 183 | 3,313 | 197 | 3,410 | 10.9% | 0.96 (0.79, 1.16) |
| Subtotal (95% CI) | | 12,957 | | 13,096 | 46.8% | 0.88 (0.80, 0.97) |
| **Total events** | **734** | | **840** | | | |
| Heterogeneity: $Chi^2 = 2.22$, df = 3 ($p = 0.53$); $I^2 = 0\%$. Test for overall effect: Z = 2.51 ($p = 0.01$) | | | | | | |
| Total (95% CI) | | 29,074 | | 29,019 | 100.0% | 0.85 (0.80, 0.91) |
| **Total events** | **1,528** | | **1,783** | | | |
| Heterogeneity: $Chi^2 = 28.85$, df = 11 ($p = 0.002$); $I^2 = 62\%$. Test for overall effect: Z = 4.66 ($p < 0.00001$) | | | | | | |
| Test for subgroup differences: $Chi^2 = 1.65$, df = 2 ($p = 0.44$), $I^2 = 0\%$ | | | | | | |

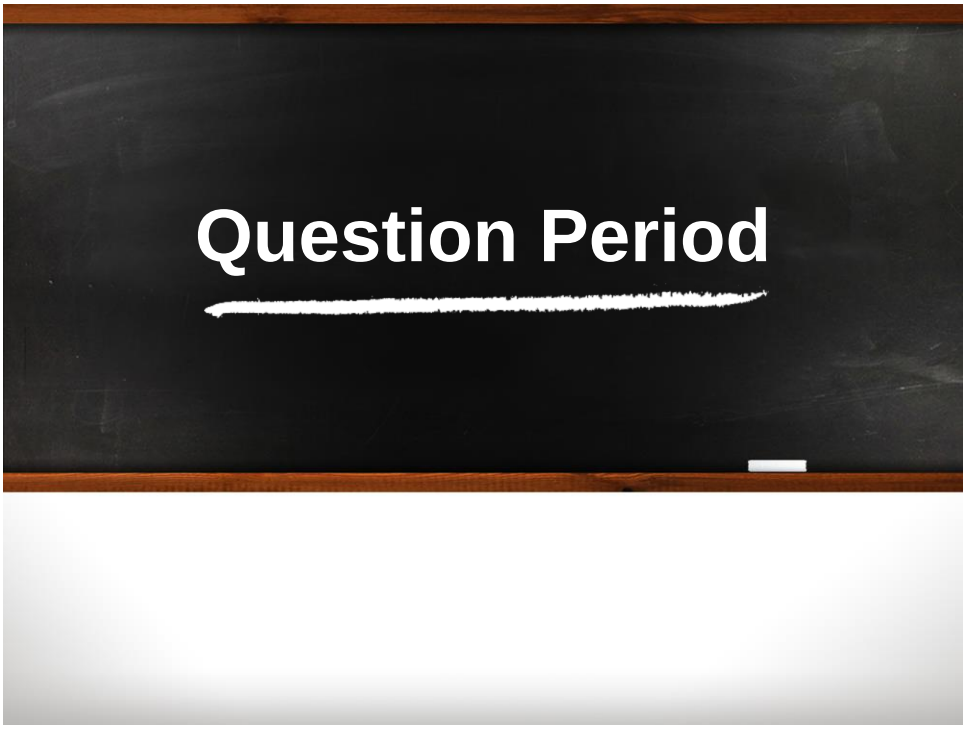



Munoz et al. Am J Cardiol 2016; 117(1):69-75.

# Older CV Patients Would Rather Prevent Stroke/MI than Death




No information on stroke outcomes/disability provided.
Relative (subjective) weight vs. death for stroke: Age > 75: 1.48, Age > 85: 3.64.
Stolker et al. Circulation 2014; 130(15):1254-61.


Question Period