Efficacy of apixaban as compared with warfarin in relation to renal function in patients with atrial fibrillation - Insights from the ARISTOTLE Trial

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Conflicts of interest

S.H.H. has served as a consultant, member of the steering committee, or speaker for: Bayer Healthcare, BMS, Boehringer Ingelheim, Boston Scientific, Cardiome, Forest RI, J&J, Medtronic, Pfizer, Portola, Sanofi aventis, St. Jude Medical

Aristotle: Study Design

Inclusion risk factors:
- Age ≥ 75 years
- Prior stroke, TIA, or SE
- HF or LVEF ≤ 40%
- Diabetes mellitus
- Hypertension

Randomize
double blind,
double dummy
(n = 18,201)

Major exclusion criteria:
- Mechanical prosthetic valve
- Severe renal insufficiency
- Need for aspirin plus thienopyridin

Apixaban 5 mg oral twice daily
(2.5 mg BID in selected patients)

Warfarin
(target INR 2-3)

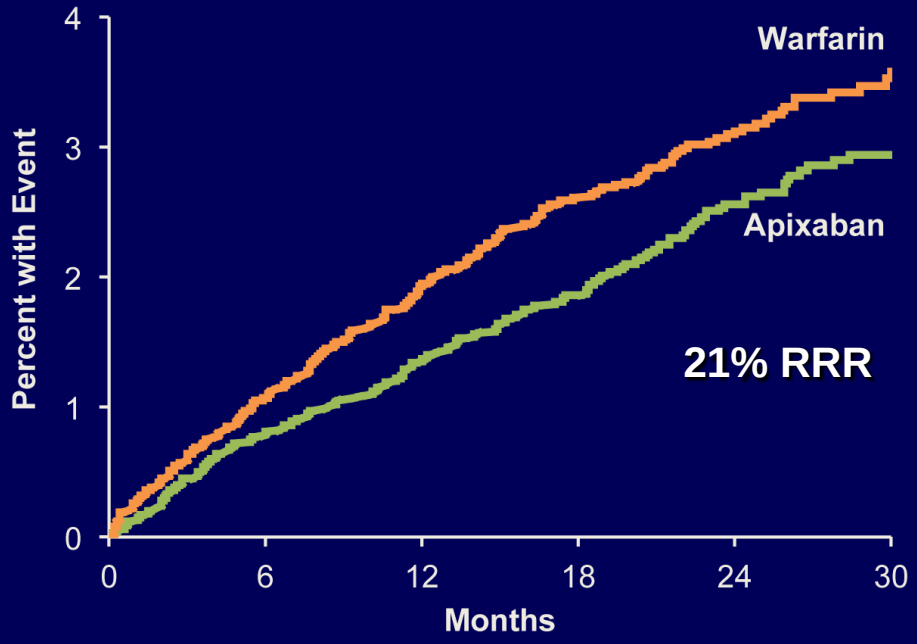
Warfarin/warfarin placebo adjusted by INR/sham INR
based on encrypted point-of-care testing device

Primary outcome: stroke or systemic embolism

Hierarchical testing: non-inferiority for primary outcome, superiority for primary outcome, major bleeding, death

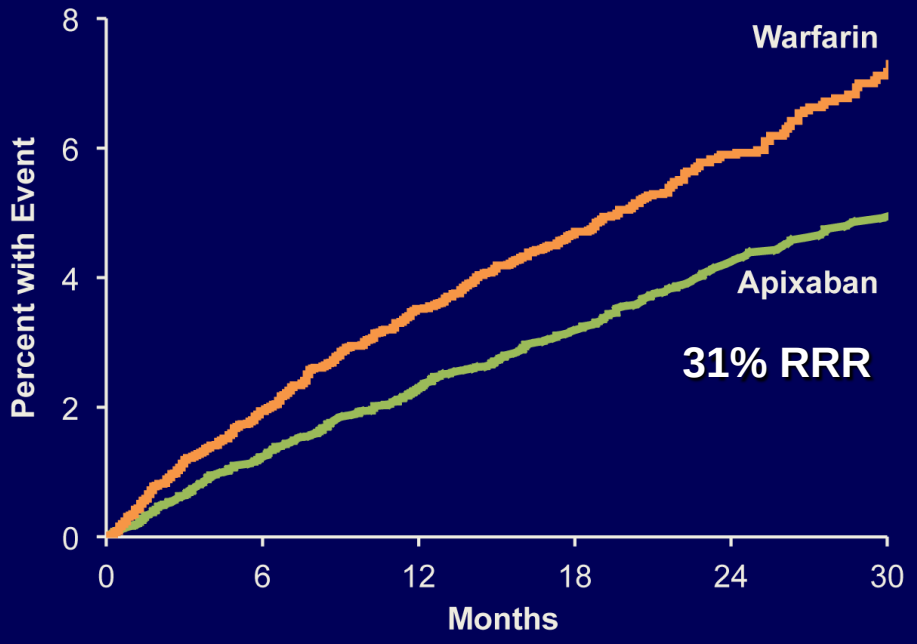
ARISTOTLE Main Trial Results

Stroke or systemic embolism



Apixaban 212 patients, 1.27% per year
Warfarin 265 patients, 1.60% per year
HR 0.79 (95% CI, 0.66–0.95); P=0.011

ISTH major bleeding



Apixaban 327 patients, 2.13% per year
Warfarin 462 patients, 3.09% per year
HR 0.69 (95% CI, 0.60–0.80); P<0.001

Median TTR 66%

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Purpose of the Study

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To evaluate the efficacy and safety of apixaban relative to warfarin in AF patients according to renal function (as estimated by three different methods)

Methods

- Primary efficacy endpoint: Stroke & SEE
- Primary safety endpoint: Major bleeding

- Determination of renal function based on estimation of creatinine clearance by Cockgroft Gault and CKD-EPI[(1)] formula as well as based on cystatin C determination[(2)] at baseline

- Patients excluded from ARISTOTLE if
  - serum creatinine > 2.5 mg/dl, or
  - creatinine clearance < 25 ml/min

- Statistics:
  - GFR estimated by CrCl, CKD-EPI, and based on cystatin C
  - outcome analysis per pre-specified GFR cut-offs > 80, >50-80, ≤ 50 ml/min
  - sensitivity analysis based on continuous GFR values

(1) Levey AS et al, Ann Int Med 2009;150:604
(2) Newman DJ et al, Kidney Int 1995;47:312

Clinical characteristics at baseline according to renal function by Cockroft-Gault

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Characteristic	80 ml/min (N=7518)	>50-80 ml/min (N=7587)	≤50 ml/min (N=2747)	P-Value
Age (mean, SD	62.9 (8.6)	71.8 (7.5.)	77.3 (7.0)	<0.0001
Age ≥ 75	597 (7.9%)	2922 (38.5%)	1906 (69.4%)	<0.0001
Female sex	1938 (25.8%)	2837 (37.4%)	1446 (52.6%)	<0.0001
Systolic blood pressure (mean, SD)	131.8 (15.7)	131.6 (16.8)	129.6 (16.9)	<0.0001
Diastolic blood pressure (mean, SD)	81.0 (10.0)	78.7 (10.5)	75.9 (10.8)	<0.0001
Prior Myocardial Infarction	958 (12.7%)	1106 (14.6%)	457 (16.7%)	<0.0001
Congestive Herat Failure	2300 (30.6%)	2236 (29.5%)	872 (31.7%)	<0.0001
Prior Stroke, TIA or Systemic Embolism	1124 (15.0%)	1639 (21.6%)	683 (24.9%)	<0.0001
Diabetes	2157 (28.7%)	1738 (22.9%)	578 (21.0%)	<0.0001
Hypertension	6739 (89.6%)	6555 (86.4%)	2322 (84.5%)	<0.0001
Prior clinically relevant or spont. bleeding	1177 (15.7%)	1257 (16.6%)	548 (19.9%)	<0.0001
Type of atrial fibrillation				0.0003
Paroxysmal	1235 (16.4%)	1142 (15.1%)	361 (13.1%)	
Persistant or permanent	6281 (83.6%)	6444 (84.9%)	2386 (86.9%)	
CHADS (mean, SD)	1.9 (1.0)	2.2. (1.1)	2.6 (1.2)	<0.0001
CHADS Score 1	3262 (43.4%)	2391 (31.5%)	478 (17.4%)	<0.0001
CHADS Score 2	2662 (35.4%)	2678 (35.3%)	1057 (38.5%)	<0.0001
CHADS Score ≥ 3	1594 (21.%)	2518 (33.2%)	1212 (44.1%)	<0.0001

Medications at baseline according to renal function by Cockroft-Gault

Characteristic	80 ml/min (N=7518)	>50-80 ml/min (N=7587)	≤ 0 ml/min (N=2747)	P-Value
ACE inhibitor or ARB	5510 (74.5%)	5258 (70.4%)	1841 (67.9%)	<0.0001
Amiodarone	818 (11.1%)	840 (11.3%)	360 (13.3%)	0.0158
Beta-Blocker	4986 (67.4%)	4694 (62.9%)	1624 (59.9%)	<0.0001
Aspirin	2266 (30.1%)	2369 (31.2%)	878 (32.0%)	0.0458
Clopidogrel	98 (1.3%)	150 (2.0%)	84 (3.1%)	<0.0001
Digoxin	2372 (32.1%)	2359 (31.6%)	975 (36.0%)	0.0002
Calcium blocker	2308 (31.2%)	2315 (31.0%)	831 (30.7%)	0.7203
Lipid lowering agents	3397 (45.9%)	3416 (45.8%)	1230 (45.4%)	0.9098
Nonsteroidal anti-inflammatory agent	640 (8.7%)	596 (8.0%)	245 (9.0%)	0.0277

Outcome Events in Relation to Kidney Function

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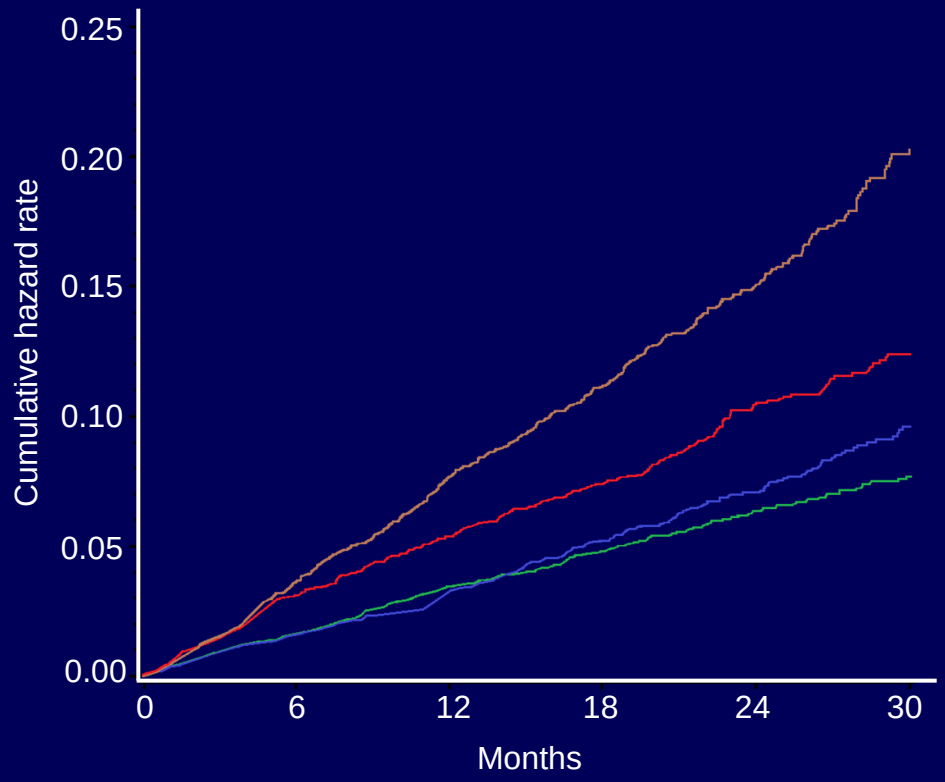
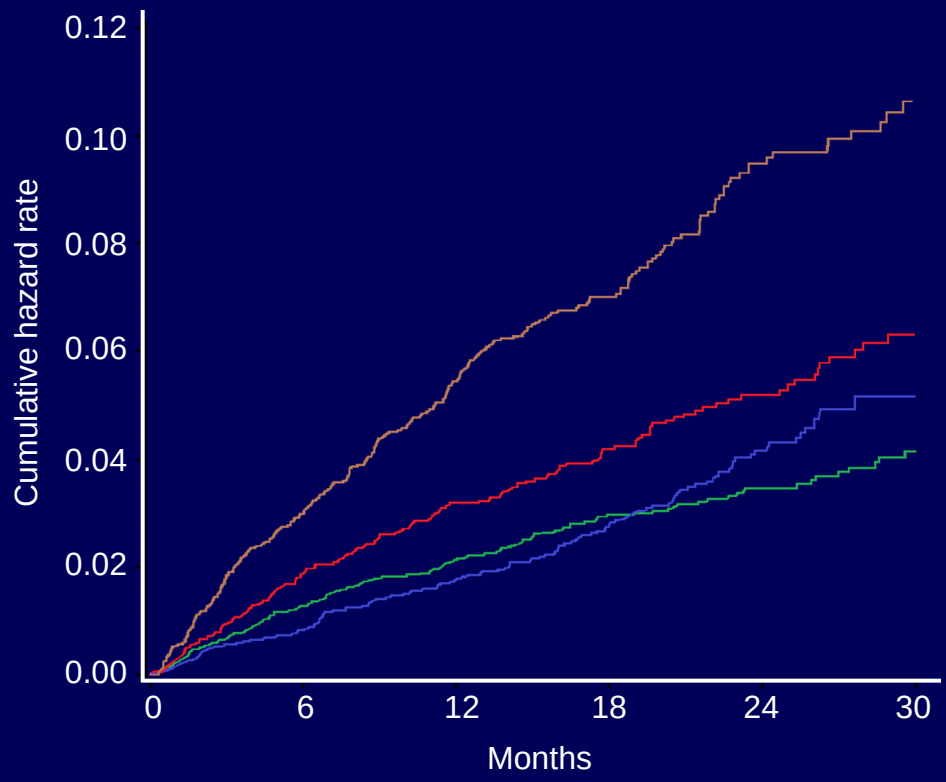
Stroke, SEE, Death



Major Bleeding



Quartiles of cystatin C

- Group: 1<0.86
- Group: 2 0.86-1.02
- Group: 3 1.03-1.23
- Group: 4>1.23

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Apixaban versus Warfarin: Effect on Stroke/SEE According to Kidney Function

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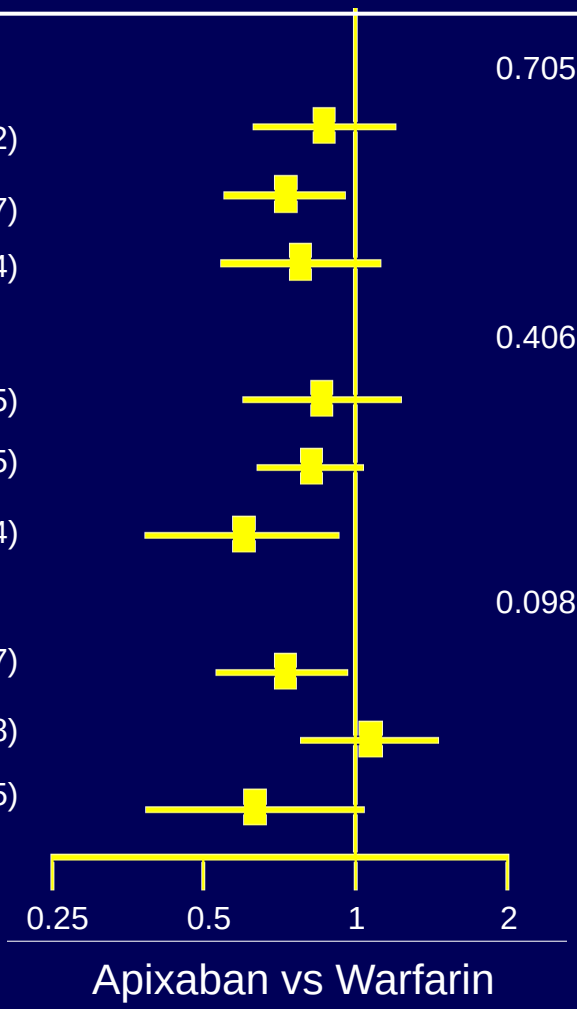
	Apixaban %/yr (n)	Warfarin %/yr (n)	Hazard Ratio (95% CI)	P Value for interaction
Cockcroft-Gault eGFR ml/min				0.705
>80	0.99 (70)	1.12 (79)	0.88 (0.64, 1.22)	
>50-80	1.24 (87)	1.69 (116)	0.74 (0.56, 0.97)	
≤50	2.11 (54)	2.67 (69)	0.79 (0.55, 1.14)	
CKD-EPI eGFR ml/min				0.406
>80	1.16 (56)	1.33 (63)	0.87 (0.61, 1.25)	
>50-80	1.31 (123)	1.59 (149)	0.83 (0.65, 1.05)	
≤50	1.30 (33)	2.13 (53)	0.61 (0.39, 0.94)	
Cystatin C eGFR ml/min				0.098
>80	0.99 (73)	1.38 (100)	0.72 (0.53, 0.97)	
>50-80	1.65 (81)	1.52 (76)	1.08 (0.79, 1.48)	
≤50	1.41 (27)	2.19 (40)	0.64 (0.39, 1.05)	



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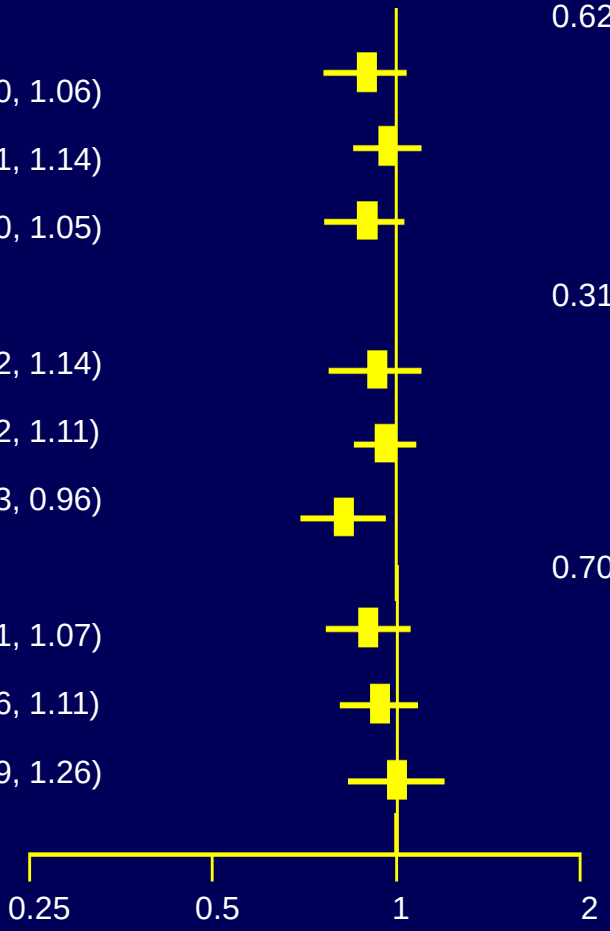
Apixaban versus Warfarin: Effect on Mortality According to Kidney Function

	Apixaban %/yr (n)	Warfarin %/yr (n)	Hazard Ratio (95% CI)	P Value for interaction
Cockcroft-Gault eGFR ml/min				0.627
>80	2.33 (169)	2.71 (195)	0.86 (0.70, 1.06)	
>50-80	3.41 (244)	3.56 (251)	0.96 (0.81, 1.14)	
≤50	7.12 (188)	8.30 (221)	0.86 (0.70, 1.05)	
CKD-EPI eGFR ml/min				0.319
>80	2.82 (139)	3.11 (151)	0.91 (0.72, 1.14)	
>50-80	3.26 (312)	3.42 (327)	0.95 (0.82, 1.11)	
≤50	5.83 (152)	7.48 (191)	0.78 (0.63, 0.96)	
Cystatin C eGFR ml/min				0.706
>80	2.20 (165)	2.53 (188)	0.87 (0.71, 1.07)	
>50-80	4.14 (208)	4.50 (230)	0.92 (0.76, 1.11)	
≤50	7.19 (142)	7.21 (135)	1.00 (0.79, 1.26)	



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Primary Study Endpoint by Continuous Renal Function and Treatment

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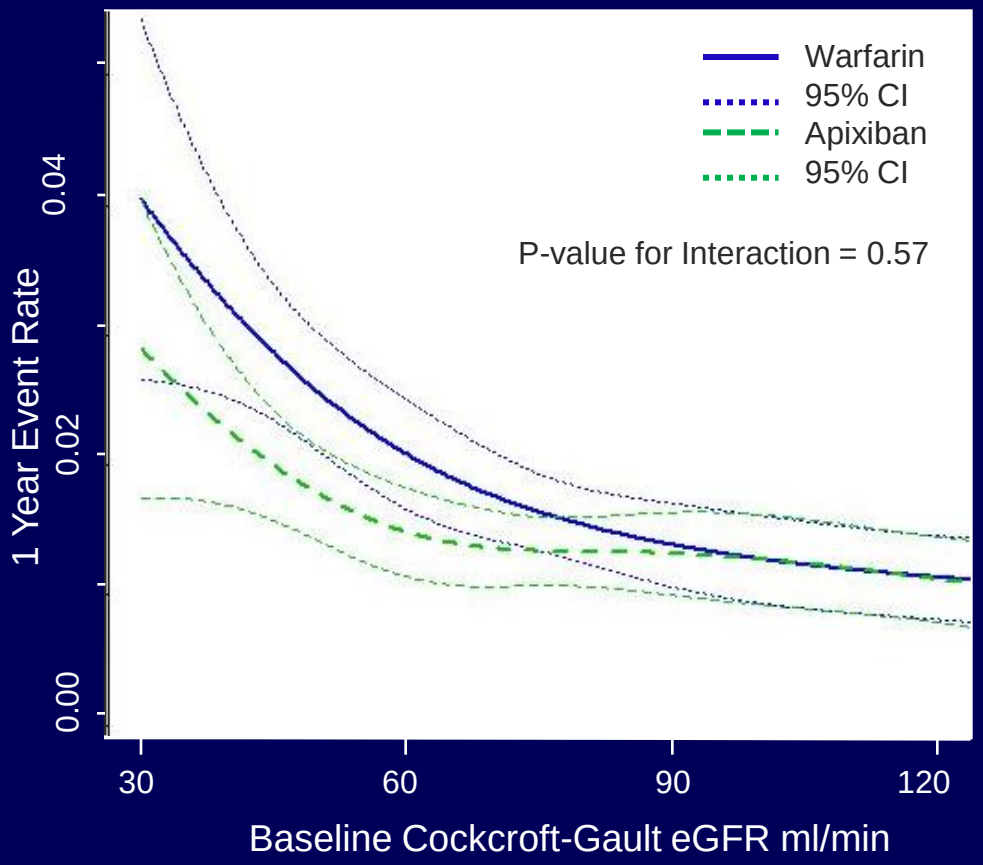
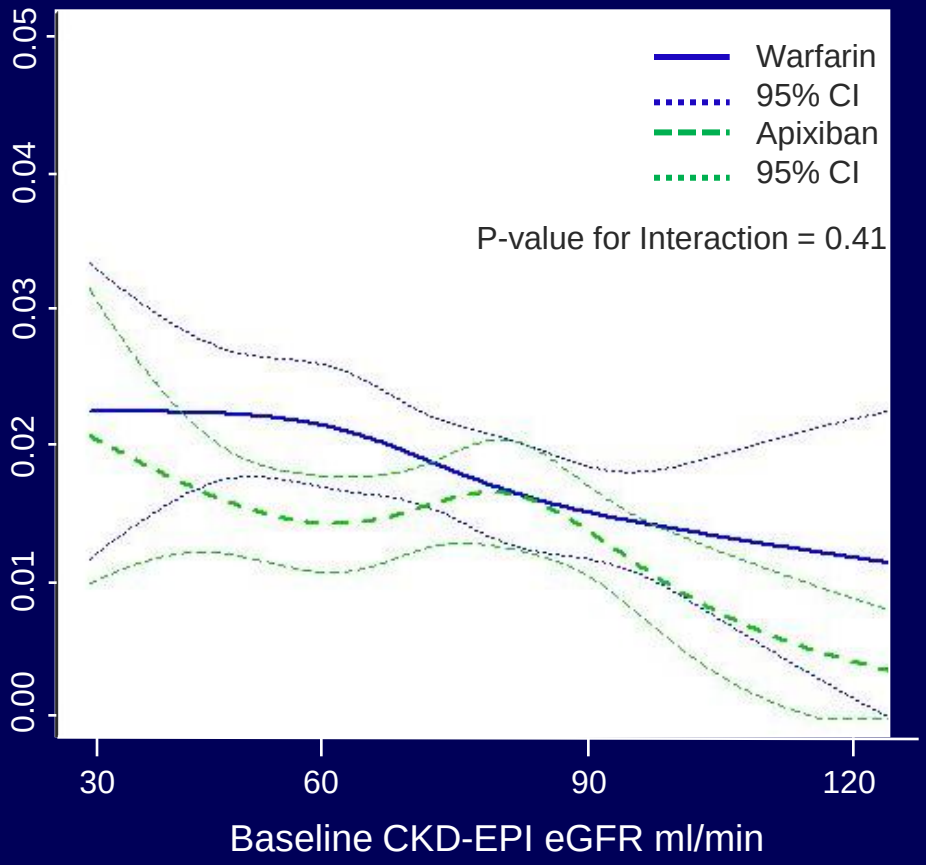
Stroke or Systemic Embolism





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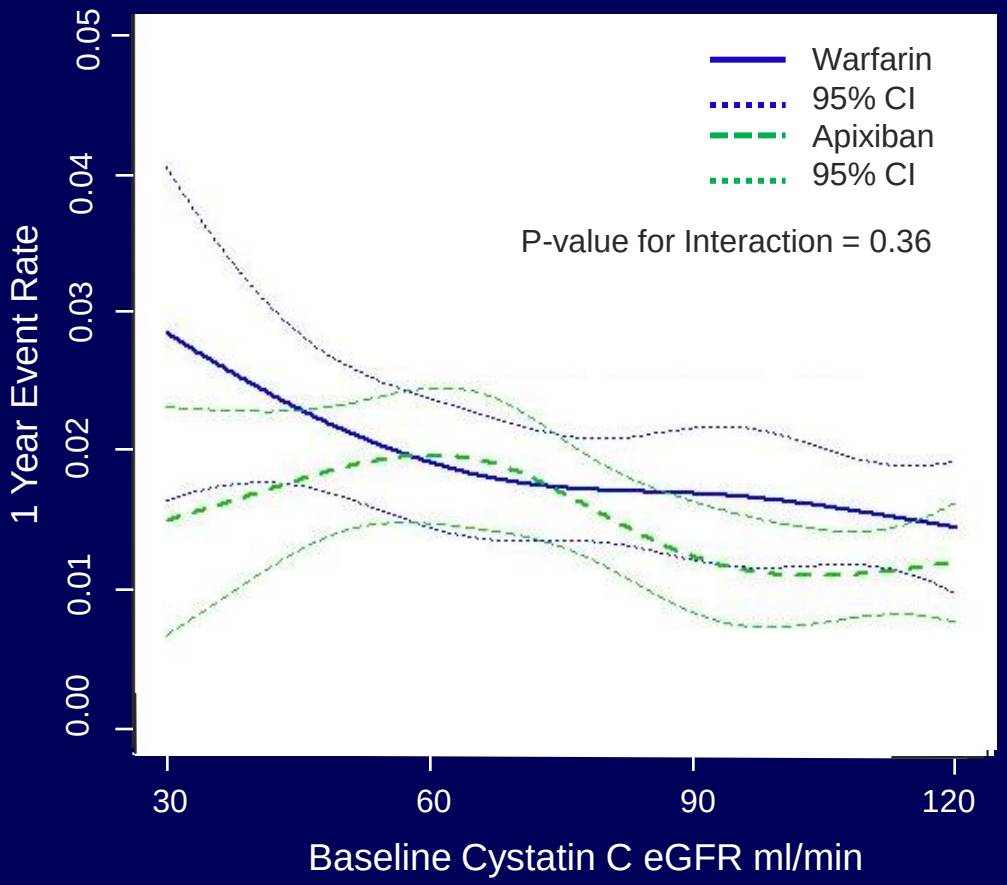

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Apixaban versus Warfarin: Effect on Major Bleeding According to Kidney Function

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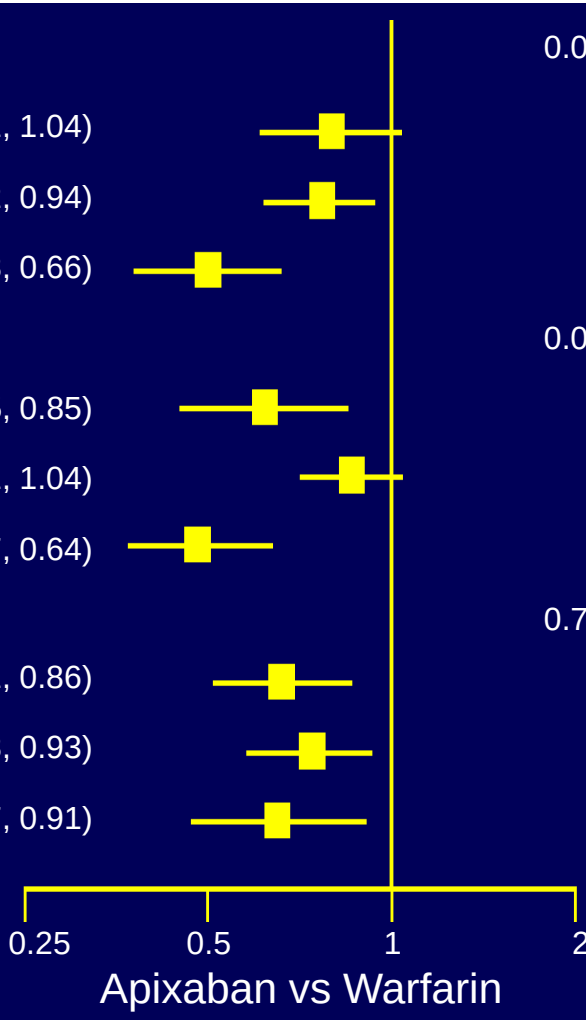
	Apixaban %/yr (n)	Warfarin %/yr (n)	Hazard Ratio (95% CI)	P Value for interaction
Cockcroft-Gault eGFR ml/min				0.030
>80	1.46 (96)	1.84 (119)	0.80 (0.61, 1.04)	
>50-80	2.45 (157)	3.21 (199)	0.77 (0.62, 0.94)	
≤50	3.21 (73)	6.44 (142)	0.50 (0.38, 0.66)	
CKD-EPI eGFR ml/min				0.004
>80	1.42 (64)	2.30 (100)	0.62 (0.45, 0.85)	
>50-80	2.21 (190)	2.58 (219)	0.86 (0.71, 1.04)	
≤50	3.28 (73)	6.78 (143)	0.48 (0.37, 0.64)	
Cystatin C eGFR ml/min				0.775
>80	1.45 (99)	2.19 (146)	0.66 (0.51, 0.86)	
>50-80	2.67 (120)	3.62 (162)	0.74 (0.58, 0.93)	
≤50	3.56 (60)	5.47 (84)	0.65 (0.47, 0.91)	



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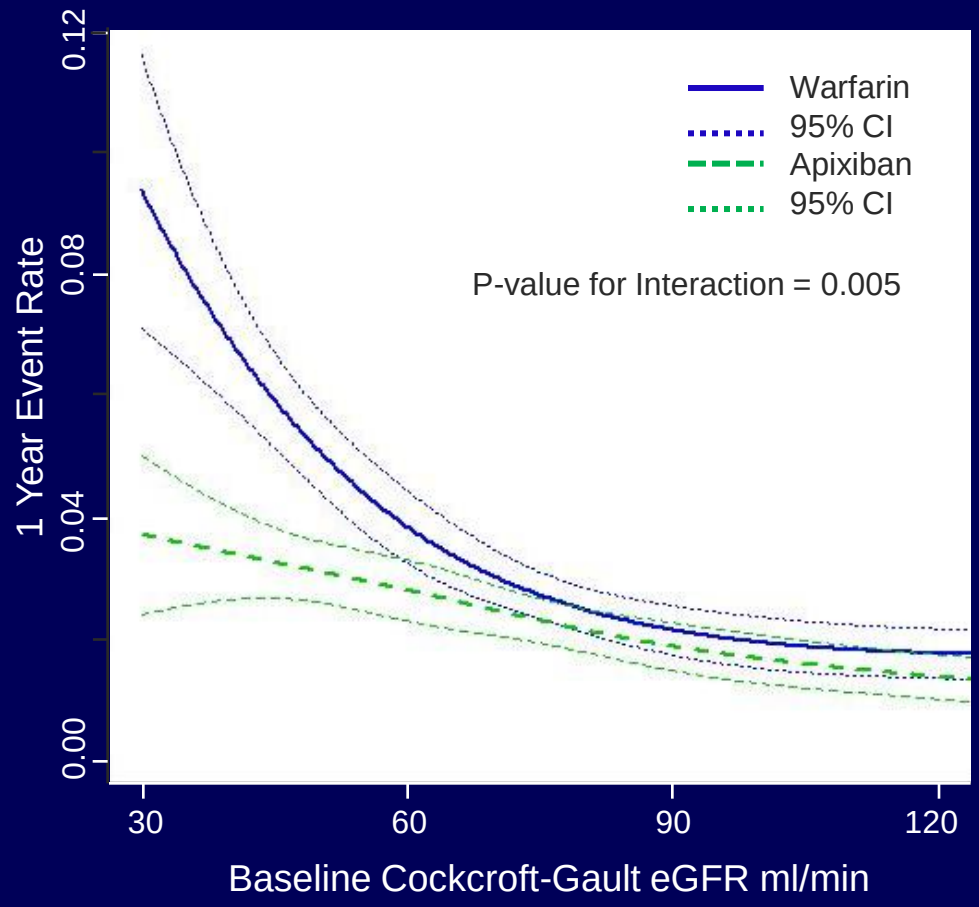
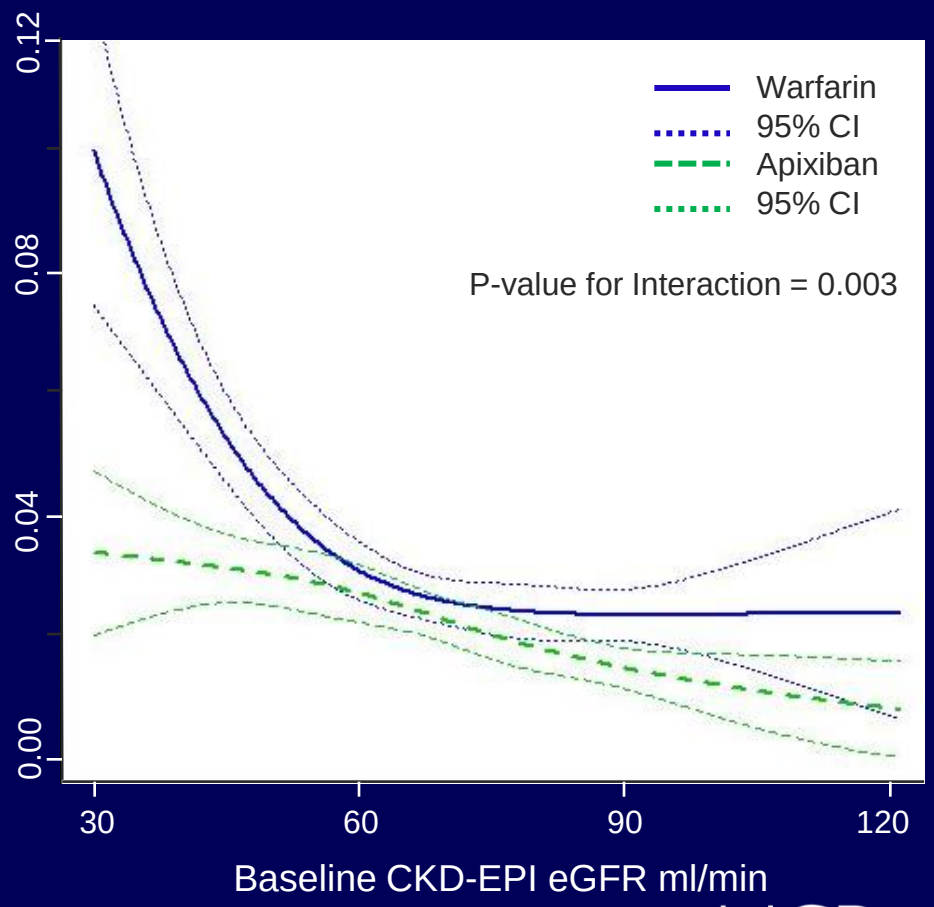
Primary Safety Endpoint by Continuous Renal Function and Treatment

Major Bleeding





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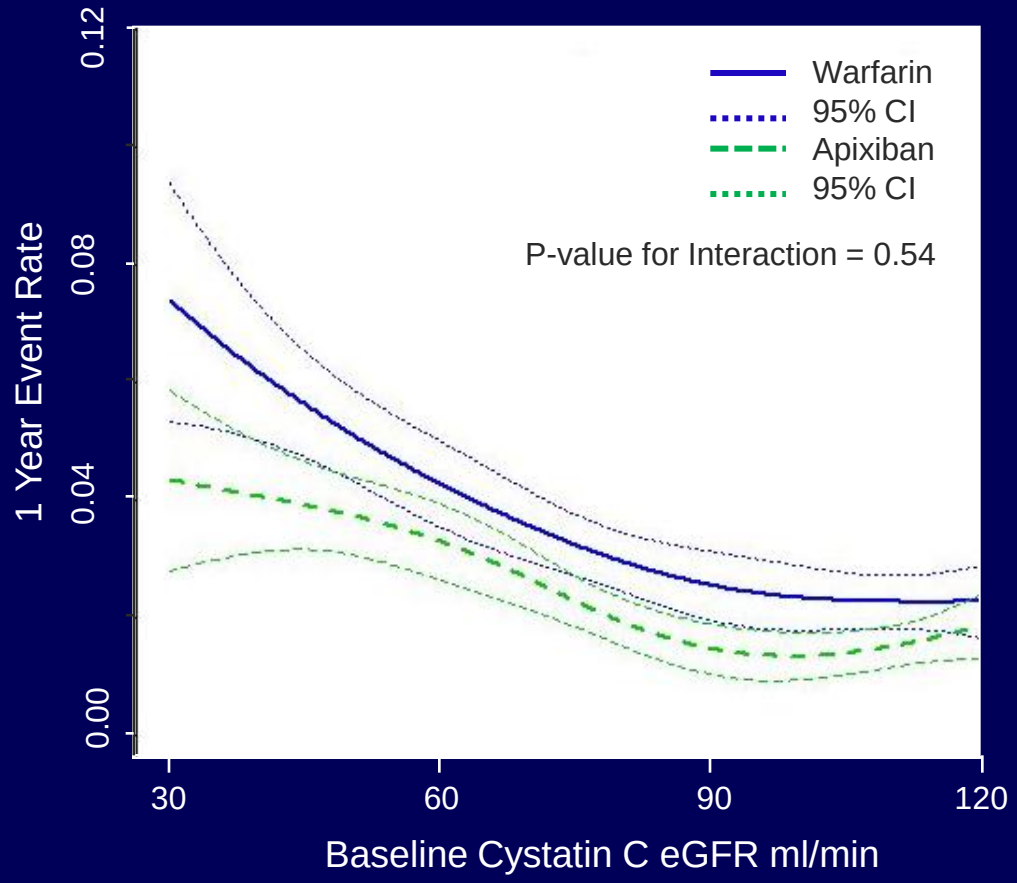
Primary Safety Endpoint by Continuous Renal Function and Treatment

Major Bleeding



Summary

- AF patients with impaired renal function have higher rates of stroke/SEE, mortality and major bleeding events than those with preserved renal function.
- Apixaban is more effective than warfarin in reducing stroke/SEE, mortality and bleeding irrespective of renal function and its method of assessment.
- Patients with impaired renal function seemed to have the greatest reduction in major bleeding with apixaban as compared with warfarin.

Conclusion

Our findings suggest that apixaban may be particularly suited to address the unmet need for more effective and safe stroke prevention in patients with AF and renal dysfunction.

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Link to our ESC article
will be provided as last slide

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