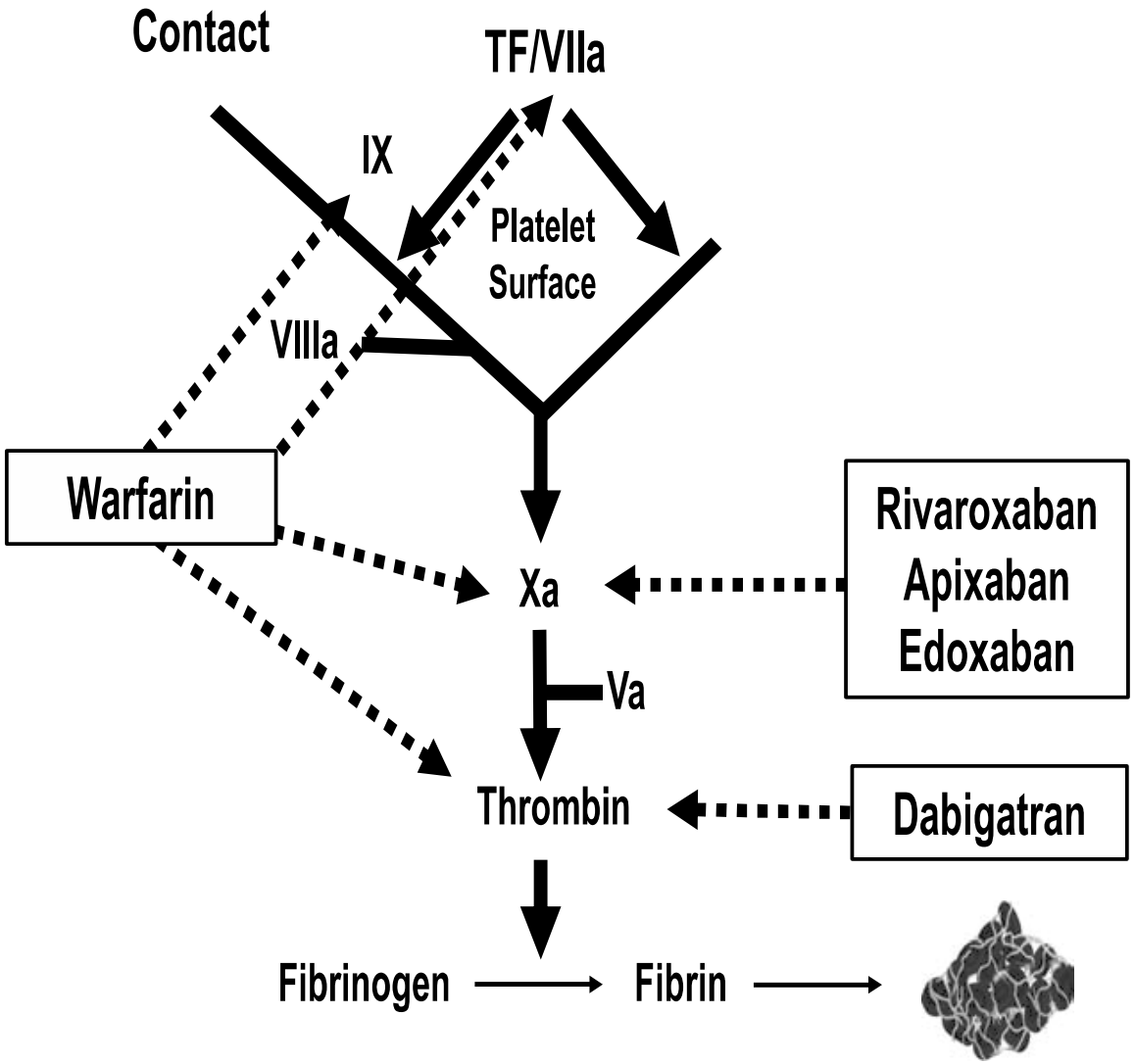
LA SCELTA DELLA TERAPIA ANTICOAGULANTE ORALE DIRETTA NEL PAZIENTE COMPLESSO

NEL PAZIENTE COMORBIDO

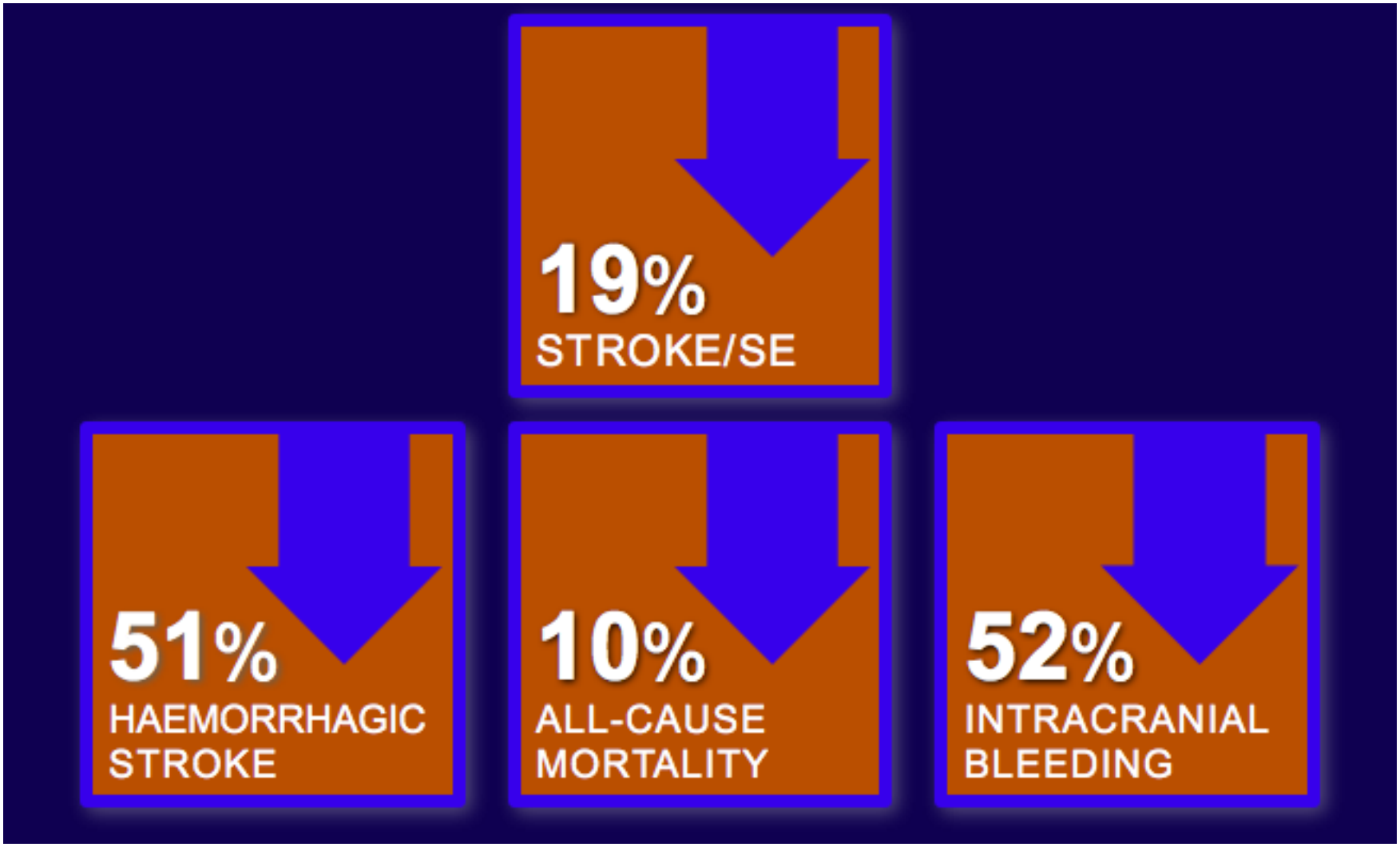
Dott. Fabio Marsico, MD,
Dipartimento di
Scienze Biomediche Avanzate
Sezione Cardiologia
Università degli Studi di Napoli "Federico II"

SITES OF ACTION OF WARFARIN AND THE NON-VITAMIN K ORAL ANTICOAGULANTS



Yeah et al. Arterioscler Thromb Vasc Biol. 2015;35:1056-1065

NOAC INNOVATION MEANS IMPROVED OUTCOMES ON KEY STROKE ENDPOINTS VS VKA THERAPIES



- **Meta-analysis of data from RE-LY®, ROCKET AF, ARISTOTLE, ENGAGE AF-TIMI 48**
- **Ruff et al. Lancet 2013**

ARISTOTLE POST-HOC SUBANALYSIS MULTIMORBIDITY

Multimorbidity Is Associated With Greater Risk of Thromboembolism and Bleeding in Patients With Atrial Fibrillation but a Constant Benefit of Apixaban: Results From ARISTOTLE

- Karen P. Alexander[1], Marc Brouwer[2], Hillary Mulder[1], Dragos Vinereanu[3], Renato D. Lopes[1], Sana M. Al-Khatib[1], Ziad Hijazi[4], Sigrun Halvorsen[5], Elaine M. Hylek[6], Freek W.A. Verheugt[7], John H. Alexander[1], Lars Wallentin[4], Christopher B. Granger[1]

- [1]Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC, [2]Radboud University Medical Center, Nijmegen, Netherlands, [3]University of Medicine and Pharmacy Carol Davila, University and Emergency Hospital of Bucharest, Bucharest, Romania, [4]Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden, [5]Oslo University Hospital, Oslo, Norway, [6]Boston University Medical Center, Boston, MA, [7]University Medical Center of Nijmegen, Nijmegen, Netherlands.

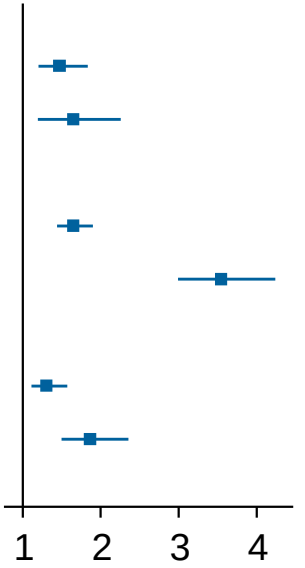
Alexander KP et al. Poster presentation at AHA 2017, 11-15 November, Anaheim, CA, USA, poster S3177

BACKGROUND

- Multimorbidity (MM), defined as ≥ 3 chronic conditions, is a marker of frailty based on the cumulative deficit model.
- This method of identifying increased risk counts comorbid conditions, and the sum of these is used to identify those with greater demands on homeostasis.
- MM increases the risk of polypharmacy which adds concerns about drug-drug and drug-disease interactions.
- MM is also a marker of increased risk for adverse events.
- For older patients with non-valvular atrial fibrillation, anticoagulation may be associated with different risks in the setting of MM.

RESULTS: ADJUSTED HAZARD RATIO OF ADVERSE EVENTS IN THOSE WITH MULTIMORBIDITY COMPARED TO THOSE WITH 0 TO 2 COMORBIDITIES

Outcome	Rate (Events)	HR (95% CI)
Stroke or Systemic Embolism		
3 to 5 comorbidities	1.63 (253)	1.47 (1.19 to 1.82)
6+ comorbidities	1.70 (65)	1.64 (1.20 to 2.24)
Death		
3 to 5 comorbidities	3.78 (602)	1.65 (1.43 to 1.90)
6+ comorbidities	7.44 (291)	3.54 (2.98 to 4.22)
Major Bleed		
3 to 5 comorbidities	2.81 (395)	1.31 (1.11 to 1.56)
6+ comorbidities	4.45 (145)	1.87 (1.49 to 2.34)

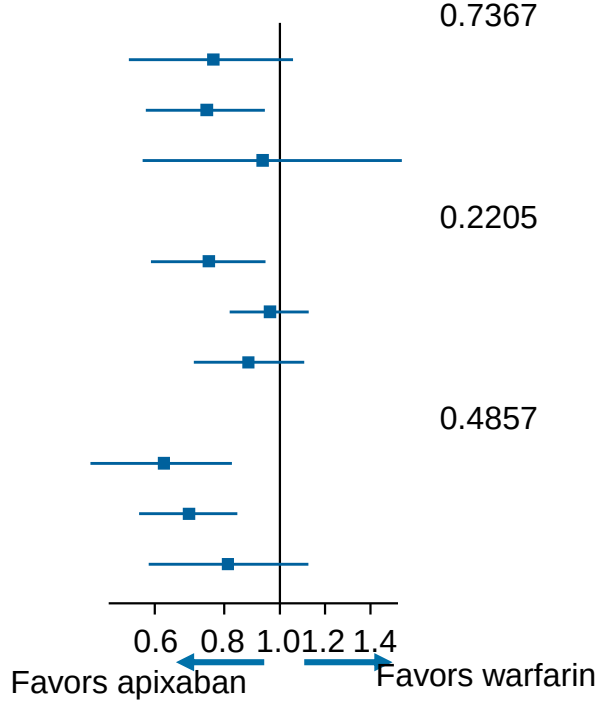


- Rates per 100 patient-years of stroke/systemic embolism, death, and major bleeding increased with MM, which was significant even after adjustment for age, sex, race, and region

Alexander KP et al. Poster presentation at AHA 2017, 11-15 November, Anaheim, CA, USA, poster S3177

RESULTS: HAZARD RATIO OF ADVERSE EVENTS IN EACH COMORBIDITY GROUP TREATED WITH APIXABAN VS. WARFARIN

Outcome	Apixaban Rate (Events)	Warfarin Rate (Events)	HR (95% CI)	*P*-Value
Stroke or Systemic Embolism				0.7367
0 to 2 comorbidities	1.03 (59)	1.36 (77)	0.76 (0.54 to 1.06)	
3 to 5 comorbidities	1.39 (109)	1.87 (144)	0.74 (0.58 to 0.95)	
6+ comorbidities	1.64 (31)	1.77 (34)	0.93 (0.57 to 1.51)	
Death				0.2205
0 to 2 comorbidities	2.21 (129)	2.96 (172)	0.75 (0.59 to 0.94)	
3 to 5 comorbidities	3.69 (297)	3.86 (305)	0.96 (0.81 to 1.12)	
6+ comorbidities	6.95 (135)	7.93 (156)	0.88 (0.70 to 1.11)	
Major Bleed				0.4857
0 to 2 comorbidities	1.61 (86)	2.58 (135)	0.62 (0.48 to 0.82)	
3 to 5 comorbidities	2.30 (164)	3.34 (231)	0.69 (0.56 to 0.84)	
6+ comorbidities	3.98 (66)	4.94 (79)	0.81 (0.58 to 1.12)	



- The safety and efficacy of apixaban and warfarin were consistent across the range of MM, with less bleeding with apixaban in all groups. Intracranial hemorrhage was significantly lower in patients randomized to apixaban across all MM groups; HR 0.28 (0.09 to 0.84) for apixaban vs. warfarin among 6+ comorbidities.

Alexander KP et al. Poster presentation at AHA 2017, 11-15 November, Anaheim, CA, USA, poster S3177

RESULTS: HAZARD RATIO OF ADVERSE EVENTS IN EACH COMORBIDITY GROUP TREATED WITH APIXABAN VS. WARFARIN

- MM (≥ 3 chronic conditions) is common, occurring in 63% of a contemporary trial population with AF. It is likely more common in a non-selected population.
- MM is associated with older age, polypharmacy, use of NSAIDs, gastric acid reducers, falls in the prior year, and increased CHA_2DS_2-VASc risk of stroke.
- Although MM is associated with greater risk of stroke/systemic embolism, death, and major bleeding, the efficacy and safety of apixaban versus warfarin was consistent even among patients with the greatest number of coexisting conditions.
- This supports the extension of trial results to community-treated patients with AF who often have greater MM than seen in clinical trials.

DRUG INTERACTION

	Via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Antiarrhythmic drugs:					
Amiodarone	moderate P-gp competition	+12-60%	No PK data[a]	+40%	Minor effect[a] (use with caution if CrCl <50 ml/min)
Digoxin	P-gp competition	No effect	No data yet	No effect	No effect
Diltiazem	P-gp competition and weak CYP3A4 inhibition	No effect	+40%	No data yet	Minor effect (use with caution if CrCl 15-50 ml/min)
Dronedarone	P-gp competition and CYP3A4 inhibition	+70-100% (US: 2 x 75 mg if CrCl 30-50 ml/min)	No PK or PD data: caution	+85% (Reduce NOAC dose by 50%)	Moderate effect but no PK or PD data: caution and try to avoid
Quinidine	P-gp competition	+53%	No data yet	+77% (No dose reduction required by label)	Extent of increase unknown
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12-180% (reduce NOAC dose and take simultaneously)	No PK data	+53% (SR) (No dose reduction required by label)	Minor effect (use with caution if CrCl 15-50 ml/min)
Other cardiovascular drugs					
Atorvastatin	P-gp competition and CYP3A4 inhibition	+18%	No data yet	No effect	No effect
Antibiotics					
Clarithromycin; Erythromycin	moderate P-gp competition and CYP3A4 inhibition	+15-20%	No data yet	+90% (reduce NOAC dose by 50%)	+30-54%
Rifampicin***	P-gp/ BCRP and CYP3A4/CYP2J 2 inducers	minus 66%	minus 54%	avoid if possible: minus 35%, but with compensatory increase of active metabolites	Up to minus 50%
Antiviral drugs					
HIV protease inhibitors (e.g. ritonavir)	P-gp and BCRP competition or inducer; CYP3A4 inhibition	No data yet	Strong increase	No data yet	Up to +153%

	Via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Fungostatics					
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% (if systemically administered)
Itraconazole; Ketoconazole; Posaconazole; Voriconazole;	potent P-gp and BCRP competition; CYP3A4 inhibition	+140-150% (US: 2 x 75 mg if CrCl 30-50 ml/min)	+100%	+87-95% (reduce NOAC dose by 50%)	Up to +160%
Immunosuppressive					
Cyclosporin; Tacrolimus	P-gp competition	Not recommended	No data yet	+73%	Extent of increase unknown
Antiphlogistics					
Naproxen	P-gp competition	No data yet	+55%	No effect (but pharmacodynamically increased bleeding time)	No data yet
Antacids					
H2B; PPI; Al-Mg-hydroxide	GI absorption	Minus 12-30%	No effect	No effect	No effect
Others					
Carbamazepine[b]; Phenobarbital[b]; Phenytoin[b]; St John's wort[b]	P-gp/ BCRP and CYP3A4/CYP2J 2 inducers	minus 66%	minus 54%	minus 35%	Up to minus 50%
Other factors:					
Age ≥ 80 years	Increased plasma level		b	d	
Age ≥75 years	Increased plasma level			d	
Weight ≤ 60 kg	Increased plasma level		b		
Renal function	Increased plasma level	See specific dose instructions according to renal function			
Other increased bleeding risk		Pharmacodynamic interactions (antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants); history of GI bleeding; recent surgery on critical organ (brain; eye); thrombocytopenia (e.g. chemotherapy); HAS-BLED ≥3			

EUROPACE 2015; 17: 1467-1507

SPECIAL POPULATIONS: FOCUS ON

- **GI bleeding**
- Extreme body weights
- Cancer
- Patients in therapy with antiaggregants

MAJOR BLEEDING IN CLINICAL TRIALS

	Dabigatran 150 mg twice daily[1]	Rivaroxaban 20 mg daily[1]	Apixaban 5 mg twice daily[1]	Edoxaban 60 mg daily[2]
Total patients (n)	6076	7131	9088	7012
Major GI bleeding (n)	223	224	105	232
Major GI bleeding (%/year)	**1.85**	**2.00**	**0.76**	**1.51**
Hazard ratio for major GI bleeding (vs. warfarin)	**1.49 [CI 1.21–1.84]**	**1.61 [CI 1.30–1.99]**	**0.89 [CI 0.70–1.15]**	**1.23 [CI 1.02–1.50]**

1. Modified by Desai J et al, Thromb Haemost 2013; 110: 205–212
2. Giugliano RP et al; ENGAGE AF-TIMI 48 Investigators. *N Engl J Med*. 2013; 369: 2093-2104

MAJOR GI BLEEDING IN REAL-LIFE

Abraham et al. Gastroenterology 2017

Rivaroxaban vs dabigatran — **HR 1.20**

Table 4. Stratified [...] Dabiga[...]

Variable	Events, n	IR	Events, n	IR	HR (95% CI)	*P* for interaction
Overall	222	2.74	215	2.02	1.20 (1.00–1.45)	
Age						
18–64 y	26	1.05	14	0.46	**HR 1.06**	.10
65–74 y	66	2.54	54	1.56		
≥75 y	130	4.29	147	3.54		

Apixaban vs dabigatran — **HR 0.39**

Table 5. Stratified [...] abigatra[...]

Variable	Events, n	IR	Events, n	IR	HR (95% CI)	*P* for interaction
Overall	33	1.38	121	2.73	0.39*** (0.27–0.58)	
Age						
18–64 y	2	0.34	7	0.73	[illegible]	.54
65–74 y	5	0.69	29	2.12	**HR 0.45**	
≥75 y	26	2.43	85	4.06		

Apixaban vs rivaroxaban — **HR 0.33**

Table 6. Stratified [...] Rivarox[...]

Variable	Events, n	IR	Events, n	IR	HR (95% CI)	*P* for interaction
Overall	32	1.34	116	3.54	0.33*** (0.22–0.49)	
Age						
18–64 y	2	0.34	6	0.81	**HR 0.39**	.36
65–74 y	5	0.69	32	3.24		
≥75 y	25	2.32	78	5.05	0.39*** (0.25–0.61)	

Patients with a high risk of gastrointestinal bleeding

First choice	For patients with a high risk of gastrointestinal bleeding, apixaban 5 mg twice daily or dabigatran 110 mg twice daily may be used
Second choice	Dabigatran 150 mg twice daily, edoxaban 60 mg once daily, or rivaroxaban 20 mg once daily

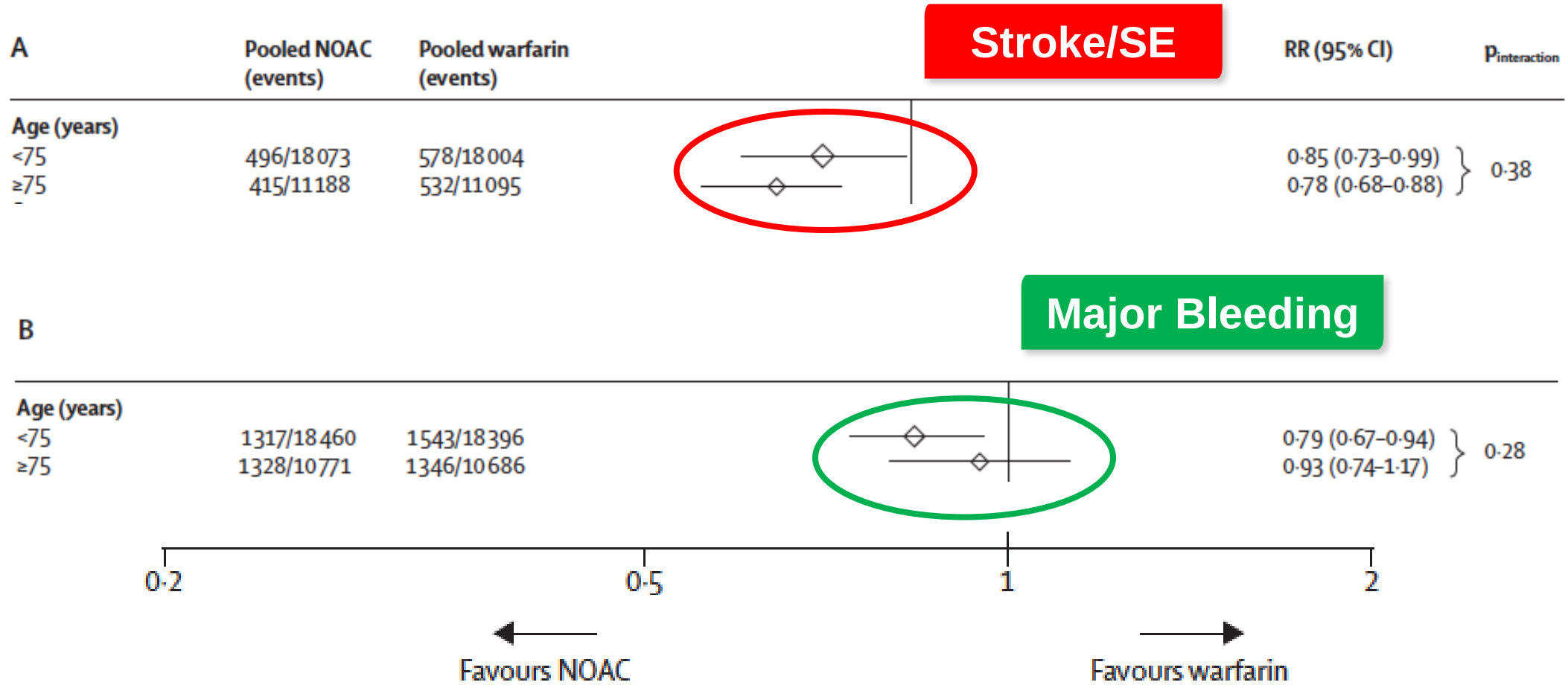
Gastrointestinal bleeding, even in the setting of anticoagulation, does usually not cause death or permanent major disability. Thus, the choice of OAC should be driven mainly by stroke prevention considerations.

The gastrointestinal bleeding risk of dabigatran and edoxaban are dose-dependent.

The increased gastrointestinal bleeding risk of dabigatran and rivaroxaban are most evident in patients ≥75 years old.

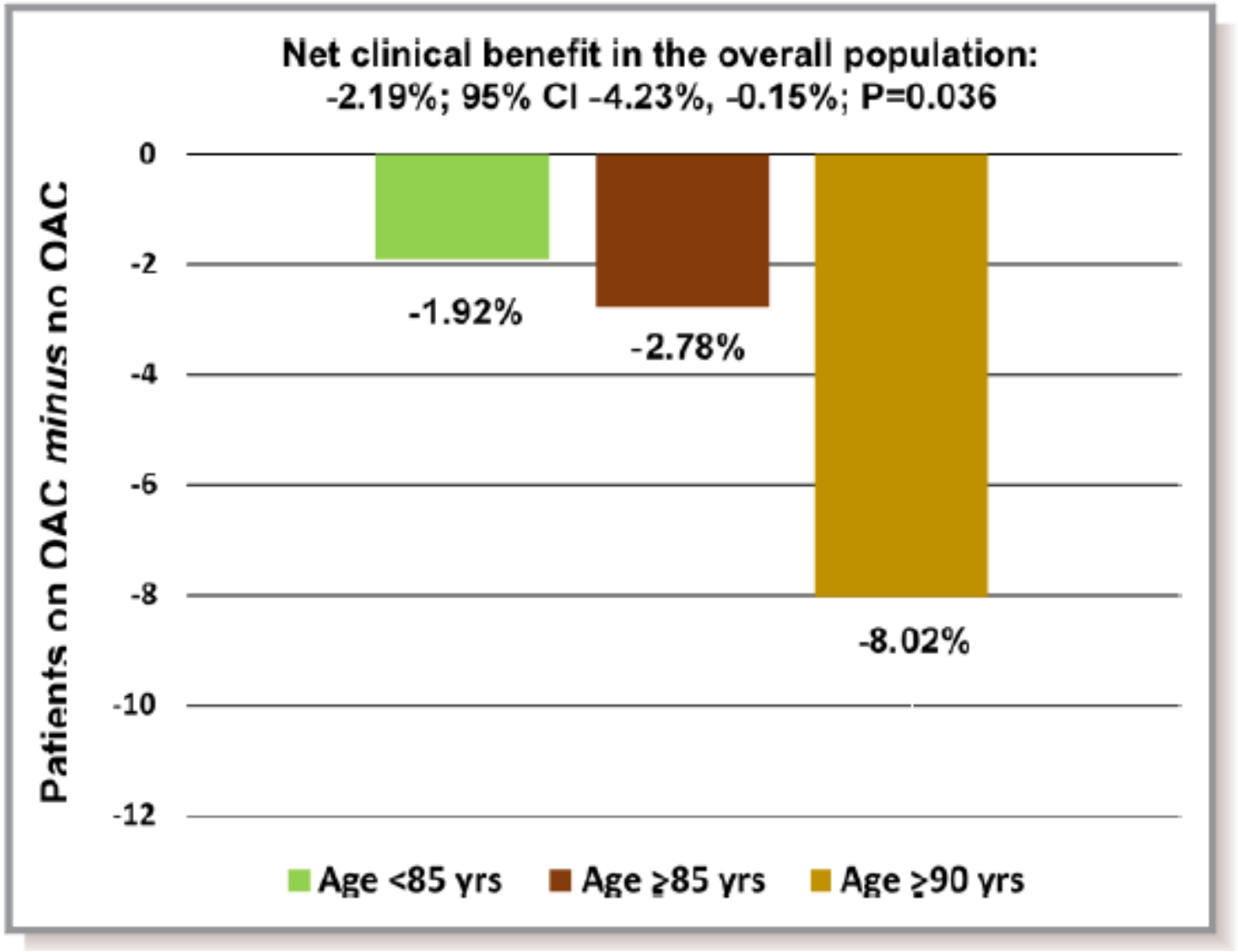
Diener et al. Eur Heart J 2017

ADVANCED AGE AND STROKE and/or BLEEDING RISK IN CLINICAL TRIAL



Ruff et al. Lancet 2014

NET CLINICAL BENEFIT OF OAC IN ELDERLY



Patti et al. J Am Heart Ass 2017

Non-vitamin K oral anticoagulants and age

First choice	In patients older than 75 years, we suggest apixaban 5 mg twice daily [2.5 mg if ≥2 of the following: age ≥80 years, body weight ≤60 kg, or creatinine ≥1.5 mg/dL (133 μmol/L)]
Second choice	Dabigatran 110 mg twice daily, rivaroxaban 20 mg once daily, or edoxaban 60 mg once daily

Diener et al. Eur Heart J 2017

SPECIAL POPULATIONS: FOCUS ON

- GI bleeding
- **Extreme body weights**
- Cancer
- Patients in therapy with antiaggregants

BACKGROUND

- Recent International Society on Thrombosis and Haemostasis (ISTH) guidelines caution against the use of non-vitamin K antagonists oral anticoagulants (NOACs) in patients with extremely high (> 120 kg) and low (≤ 60 kg) body weight due to lack of data in this population.
- The 2014 American College of Cardiology/American Heart Association guidelines suggest dose adjustment with extreme weights but do not provide guidance.

ARISTOTLE POST-HOC SUBANALYSIS MULTIMORBIDITY

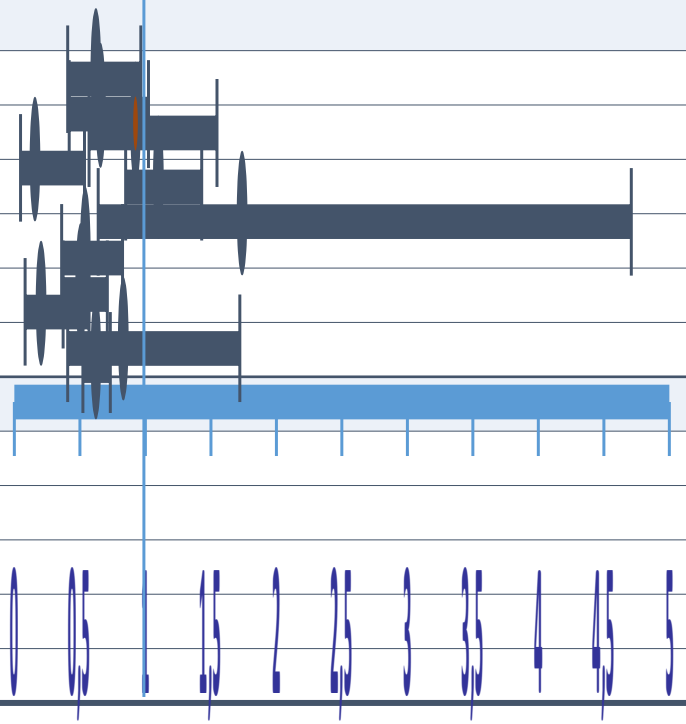
The Efficacy and Safety of Apixaban Versus Warfarin are Preserved in Patients With Atrial Fibrillation and Extreme Body Weights: Insights From the ARISTOTLE Study

- Marat Fudim[1], Renato D. Lopes[1], John H. Alexander[1], Daniel M. Wojdyla[1], Justin A. Ezekowitz[2], Michael Hanna[3]*, Dan Atar[4], Ziad Hijazi[5], M. Cecilia Bahit[6], Jose Lopez-Sendon[7], Lars Wallentin[5], Christopher B. Granger[1], Stefan H. Hohnloser.[8]

- [1]Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC, USA; [2]University of Alberta, Alberta, Canada; [3]Bristol-Myers Squibb, Princeton, NJ, USA; [4]University of Oslo, Oslo, Norway; [5]Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden; [6]Department of Cardiology, INECO Neurociencias Orono, Rosario, Santa Fe, Argentina; [7]Hospital Universitario La Paz, Madrid, Spain; [8]Johann Wolfgang Goethe University, Frankfurt, Germany.
*Employee of Bristol-Myers Squibb at the time of the study.

RESULTS: EFFICACY AND SAFETY OUTCOMES STRATIFIED BY WEIGHT CATEGORIES FOR APIXABAN VS WARFARIN USE – WEIGHT ≤ 60

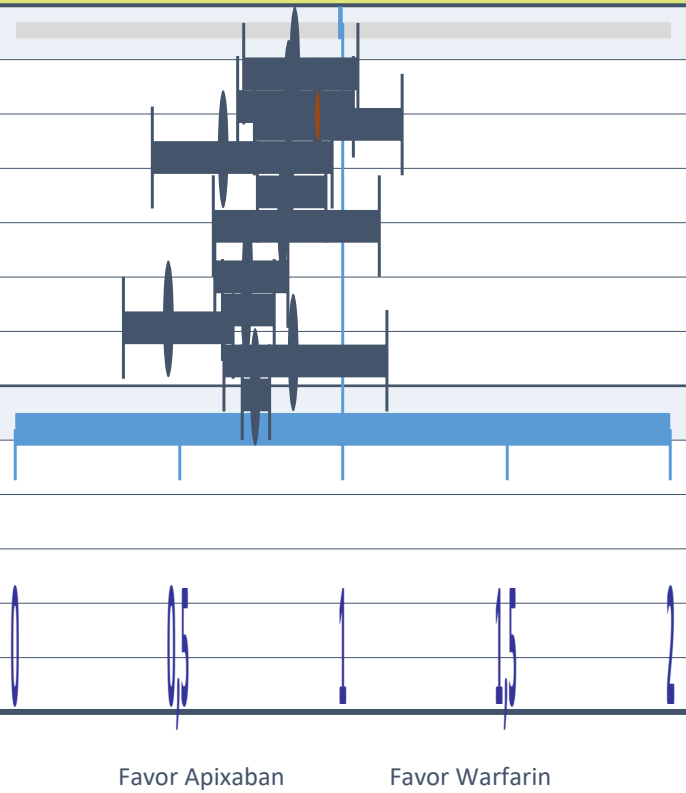
Weight ≤ 60 kg	Apixaban Rate (n)*	Warfarin Rate (n)*	Hazard Ratio (95% CI) Apixaban vs Warfarin
Efficacy Endpoints			
Stroke or systemic embolism	2.01 (34)	3.20 (52)	0.626 (0.406 to 0.964)
Stroke	1.95 (33)	2.95 (48)	0.658 (0.422 to 1.025)
Ischemic or uncertain stroke	1.77 (30)	1.90 (31)	0.933 (0.565 to 1.541)
Hemorrhagic stroke	0.18 (3)	1.10 (18)	0.158 (0.047 to 0.536)
All cause death	7.00 (122)	6.33 (107)	1.104 (0.852 to 1.431)
Myocardial infarction	0.64 (11)	0.36 (6)	1.741 (0.644 to 4.708)
Safety Endpoints			
Major bleeding	2.33 (36)	4.28 (62)	0.546 (0.362 to 0.823)
Major or CRNM bleeding	3.60 (55)	7.06 (101)	0.512 (0.369 to 0.711)
Intracranial bleeding	0.32 (5)	1.49 (22)	0.214 (0.081 to 0.565)
GI bleeding	0.90 (14)	1.09 (16)	0.838 (0.409 to 1.717)
Any bleeding	18.68 (244)	30.86 (344)	0.622 (0.528 to 0.733)



Fudim M et al. Poster presentation at ACC 2018, 10–12 March, Orlando, FL, USA, poster 1225M-09

RESULTS: EFFICACY AND SAFETY OUTCOMES STRATIFIED BY WEIGHT CATEGORIES FOR APIXABAN VS WARFARIN USE – > 60 to 120 kg

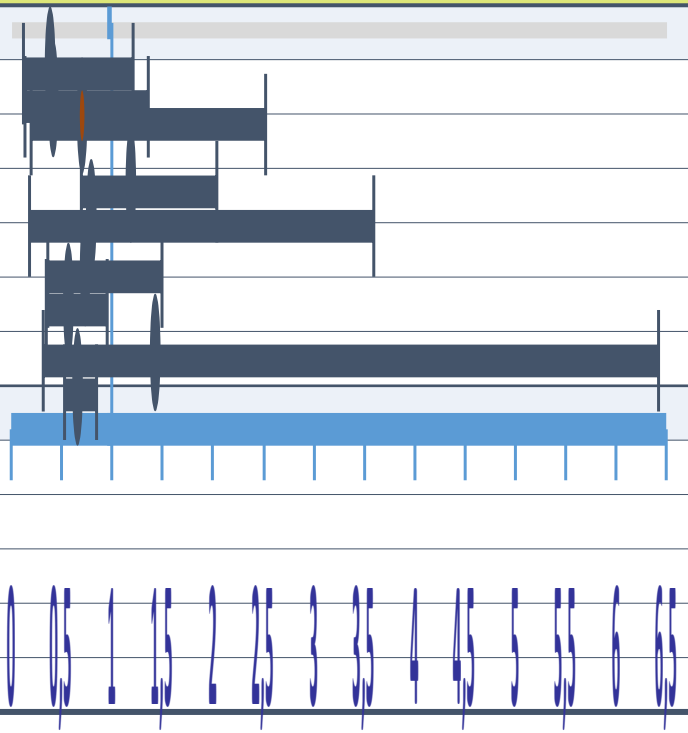
Weight > 60 to 120 kg	Apixaban Rate (n)*	Warfarin Rate (n)*	Hazard Ratio (95% CI) Apixaban vs Warfarin
Efficacy Endpoints			
Stroke or systemic embolism	1.23 (173)	1.44 (201)	0.853 (0.696 to 1.045)
Stroke	1.14 (161)	1.37 (191)	0.835 (0.677 to 1.030)
Ischemic or uncertain stroke	0.91 (128)	0.98 (137)	0.926 (0.728 to 1.179)
Hemorrhagic stroke	0.25 (36)	0.40 (56)	0.637 (0.419 to 0.968)
All cause death	3.14 (451)	3.75 (535)	0.836 (0.738 to 0.948)
Myocardial infarction	0.54 (76)	0.66 (92)	0.819 (0.604 to 1.110)
Safety Endpoints			
Major bleeding	2.15 (277)	3.02 (379)	0.713 (0.610 to 0.832)
Major or CRNM bleeding	4.20 (532)	5.97 (730)	0.707 (0.632 to 0.790)
Intracranial bleeding	0.35 (46)	0.75 (96)	0.468 (0.330 to 0.666)
GI bleeding	0.67 (87)	0.79 (100)	0.849 (0.637 to 1.132)
Any bleeding	18.15 (1987)	25.29 (2528)	0.732 (0.690 to 0.776)



Fudim M et al. Poster presentation at ACC 2018, 10–12 March, Orlando, FL, USA, poster 1225M-09

RESULTS: EFFICACY AND SAFETY OUTCOMES STRATIFIED BY WEIGHT CATEGORIES FOR APIXABAN VS WARFARIN USE – Weight > 120 kg

Weight > 120 kg	Apixaban Rate (n)*	Warfarin Rate (n)*	Hazard Ratio (95% CI) Apixaban vs Warfarin
Efficacy Endpoints			
Stroke or systemic embolism	0.44 (4)	1.13 (11)	0.387 (0.123 to 1.215)
Stroke	0.44 (4)	1.03 (10)	0.426 (0.134 to 1.357)
Ischemic or uncertain stroke	0.44 (4)	0.61 (6)	0.711 (0.201 to 2.521)
Hemorrhagic stroke	0.00 (0)	0.41 (4)	-
All cause death	3.00 (28)	2.52 (25)	1.190 (0.694 to 2.042)
Myocardial infarction	0.33 (3)	0.41 (4)	0.806 (0.180 to 3.600)
Safety Endpoints			
Major bleeding	1.55 (13)	2.08 (19)	0.742 (0.366 to 1.502)
Major or CRNM bleeding	2.77 (23)	4.83 (43)	0.575 (0.347 to 0.954)
Intracranial bleeding	0.00 (0)	0.43 (4)	-
GI bleeding	0.47 (4)	0.33 (3)	1.436 (0.321 to 6.416)
Any bleeding	16.44 (119)	25.13 (176)	0.670 (0.531 to 0.846)



Fudim M et al. Poster presentation at ACC 2018, 10–12 March, Orlando, FL, USA, poster 1225M-09

RESULTS: EFFICACY AND SAFETY OUTCOMES STRATIFIED BY WEIGHT CATEGORIES FOR APIXABAN VS WARFARIN USE – Weight > 120 kg

- This post-hoc analysis of the ARISTOTLE trial represents the largest study of NOACs in patients with AF allowing for analysis of efficacy and safety in patients within various weight categories.
- The efficacy and safety of apixaban versus warfarin appear to be similar in patients with very high or very low body weight when compared with those without extremes of body weight.

SPECIAL POPULATIONS: FOCUS ON

- GI bleeding
- Extreme body weights
- **Cancer**
- Patients in therapy with antiaggregants

CANCER PATIENTS IN FACTOR XA-INH TRIALS

RCT	Drug	Patients	Cancer
EINSTEIN-DVT	rivaroxaban	N = 3,449	6%
EINSTEIN-PE	rivaroxaban	N = 4,382	5%
AMPLIFY	apixaban	N = 5,395	3%
Hokusai-VTE	edoxaban	N = 8,240	10%
Total		N = 21,466	N = 1,366 (6%)

Hokusai VTE Cancer trial

The NEW ENGLAND JOURNAL of MEDICINE

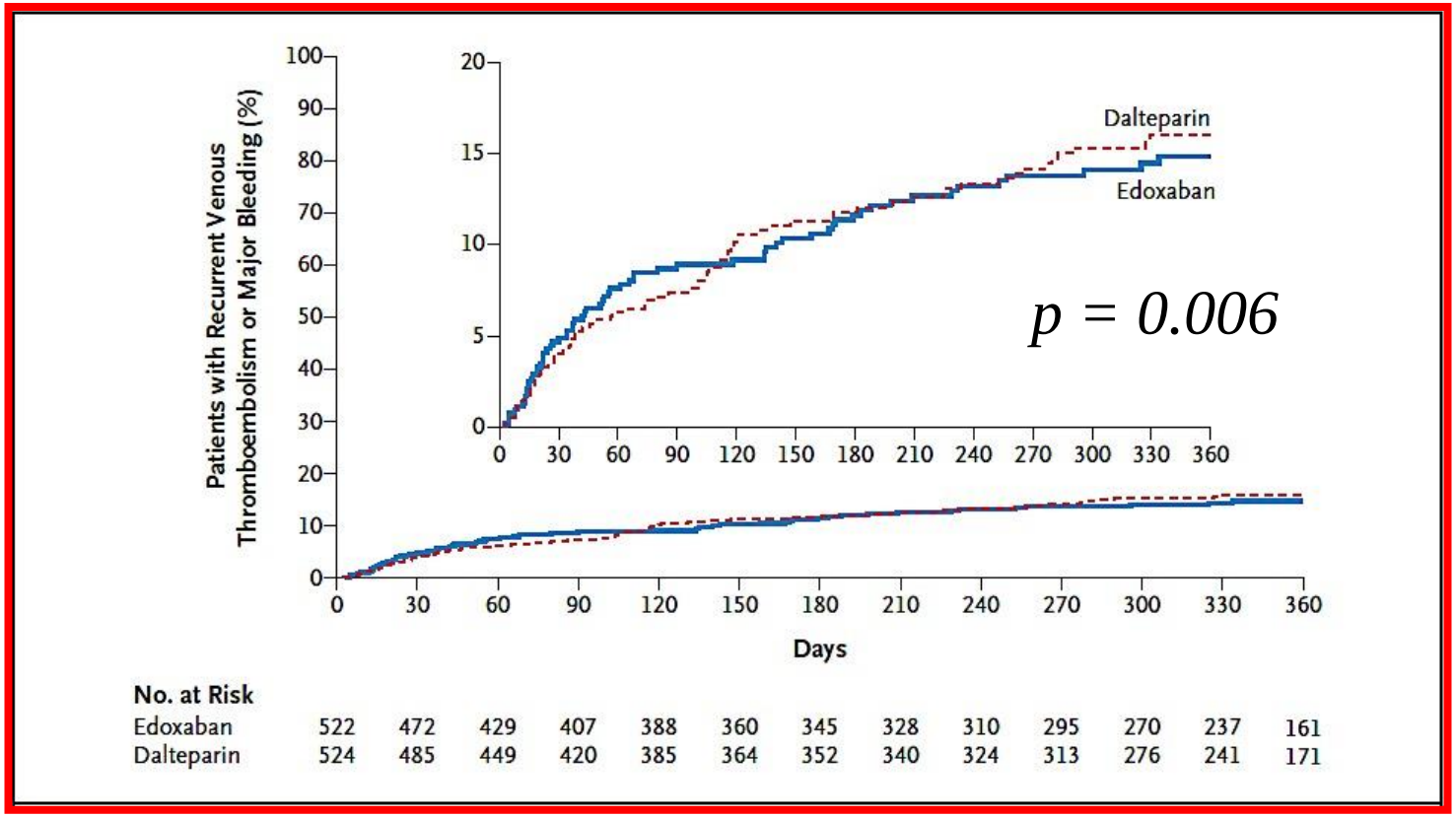
ORIGINAL ARTICLE

Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism

Gary E. Raskob, Ph.D., Nick van Es, M.D., Peter Verhamme, M.D., Marc Carrier, M.D., Marcello Di Nisio, M.D., David Garcia, M.D., Michael A. Grosso, M.D., Ajay K. Kakkar, M.B., B.S., Michael J. Kovacs, M.D., Michele F. Mercuri, M.D., Guy Meyer, M.D., Annelise Segers, M.D., Minggao Shi, Ph.D., Tzu-Fei Wang, M.D., Erik Yeo, M.D., George Zhang, Ph.D., Jeffrey I. Zwicker, M.D., Jeffrey I. Weitz, M.D., and Harry R. Büller, M.D., for the Hokusai VTE Cancer Investigators*

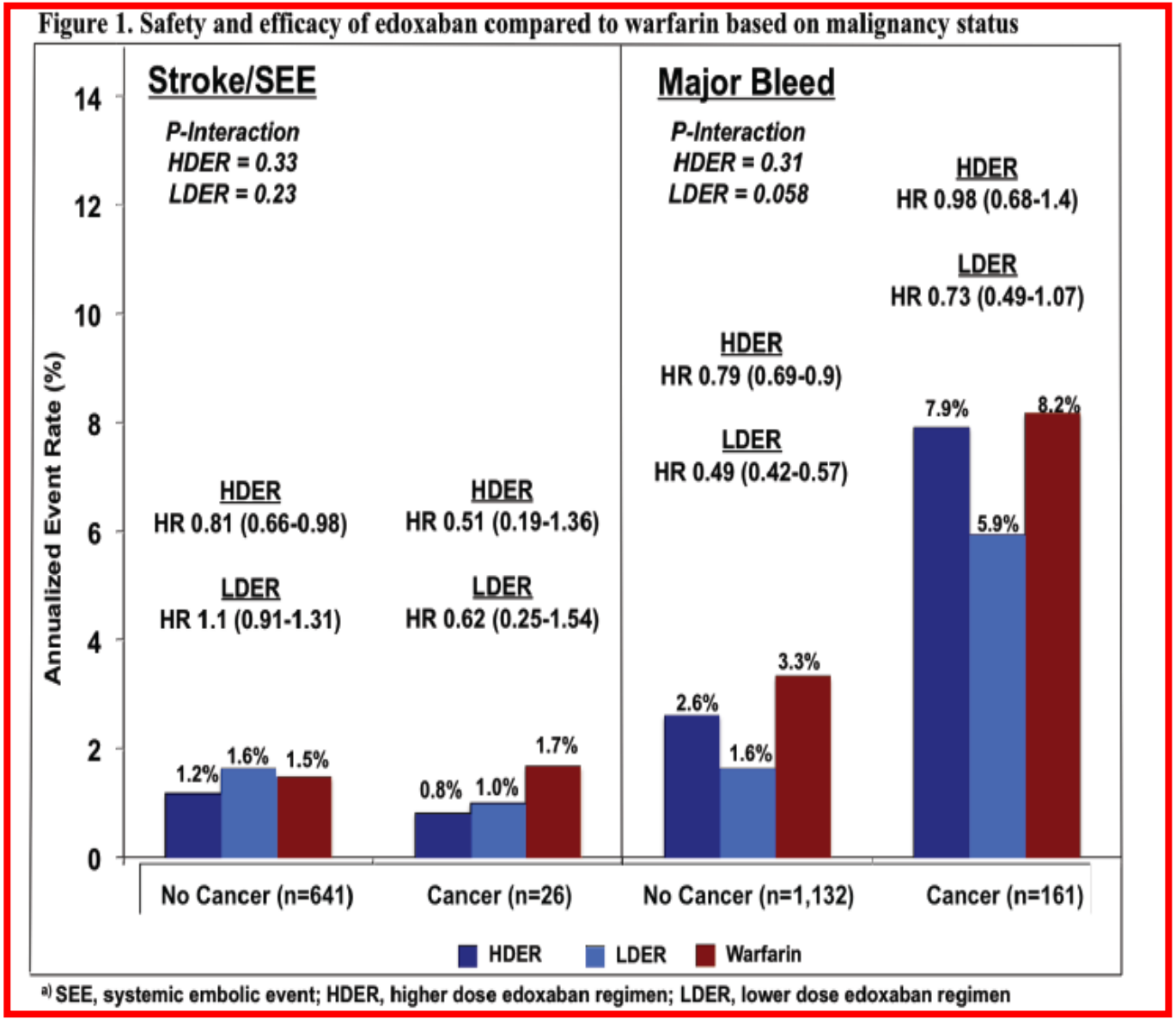
Raskob G.E. et al., NEJM, 2017

PRIMARY OUTCOME: RECURRENT VTE OR MAJOR BLEEDING



Raskob G.E. et al., NEJM, 2017

SAFETY AND EFFICAY COMPARED TO WARFARIN BASED ON MALIGNANCY STATUS



Fanola et al. JACC March 21, 2017 Volume 69,

VTE a common complication in cancer patients

Treatment of cancer-associated VTE challenging

- Risk of recurrent VTE and bleeding higher than in patients without cancer
- Both recurrent VTE and bleeding important
- Contribute to mortality/morbidity, interfere with cancer therapy

Guidelines (ACCP, ASCO, ESMO)* recommend LMWH for initial and long-term therapy

SC injections burdensome and limit adoption

*Kearon et al CHEST 2016; 149: 315 - 352
Lyman et al Journal of Clinical Oncology, 2013, 31:2189 - 2204
Mandala et al Ann Oncol 2011;22 (Suppl 6): 85 – 92
Farge et al JTH 2013; 11: 56 - 70

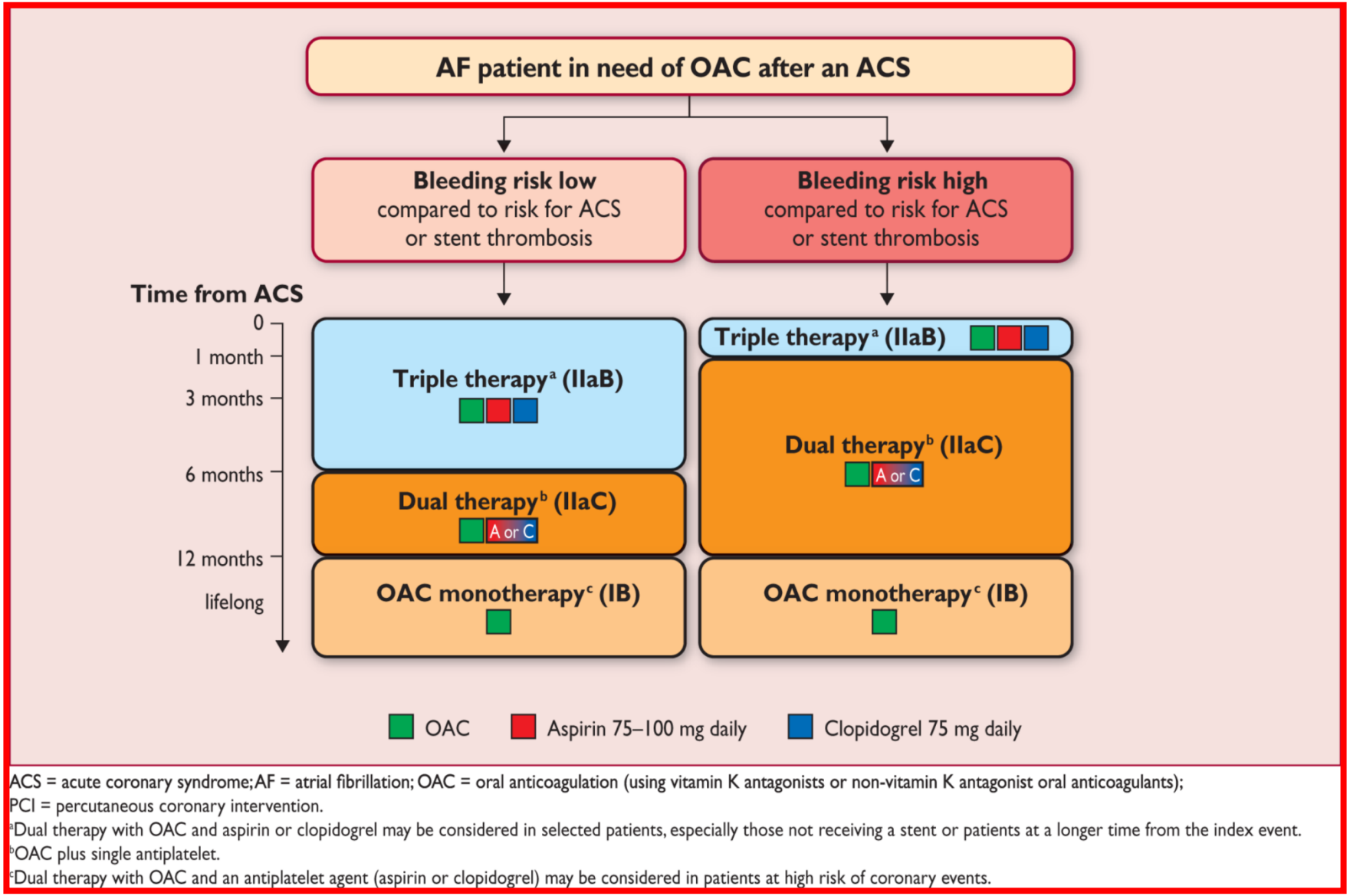
DOACs may be an attractive alternative for these patients, but…..

- Rate of severe major bleeding similar
- Survival free of recurrent VTE or major bleeding similar
- Limited data
- Active vs previous (???), type of cancer

SPECIAL POPULATIONS: FOCUS ON

- GI bleeding
- Extreme body weights
- Cancer
- **Patients in therapy with antiaggregants**

2016 ESC GUIDELINES FOR THE MANAGEMENT OF ATRIAL FIBRILLATION



ACS = acute coronary syndrome; AF = atrial fibrillation; OAC = oral anticoagulation (using vitamin K antagonists or non-vitamin K antagonist oral anticoagulants); PCI = percutaneous coronary intervention.

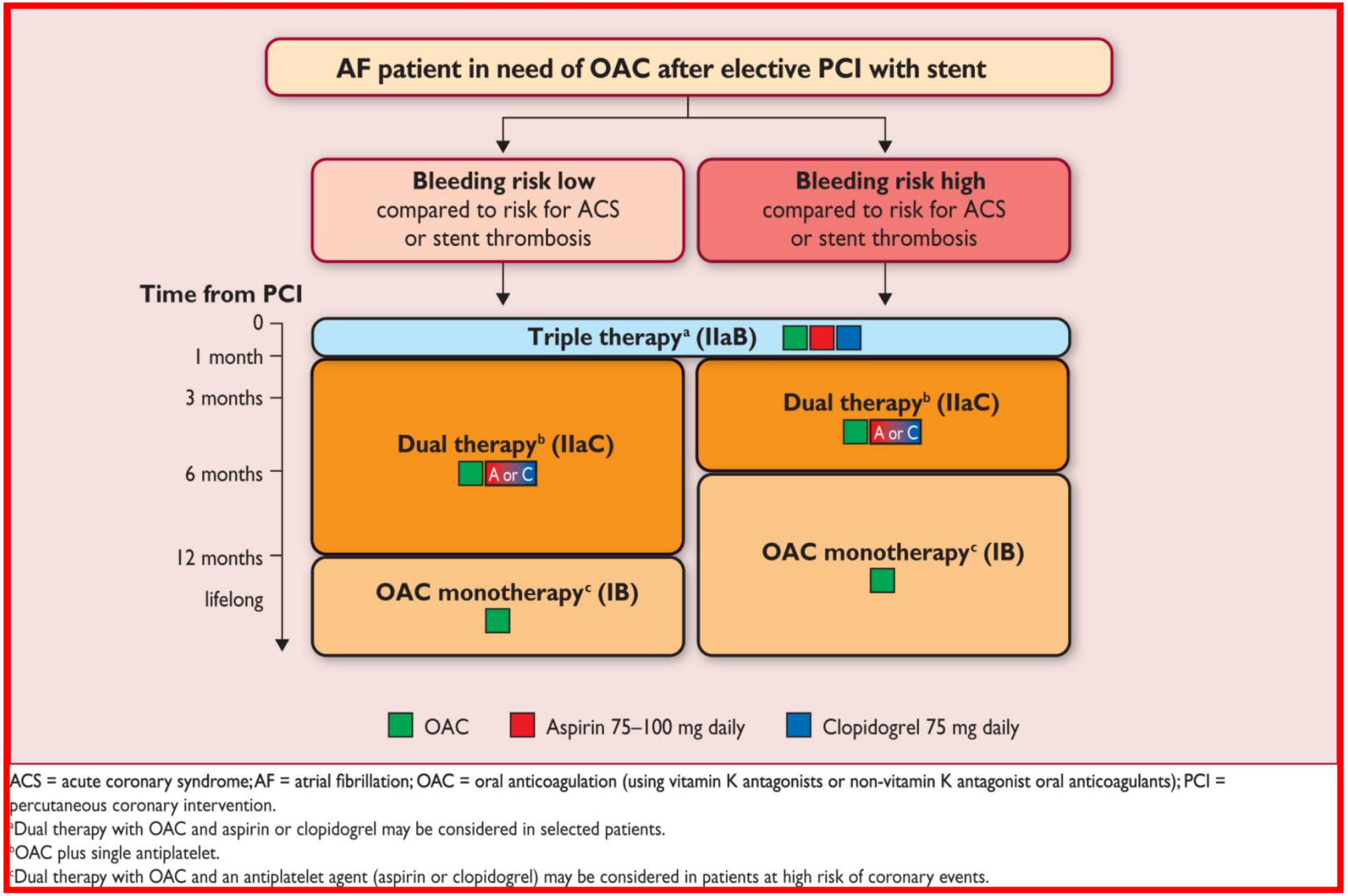
[a]Dual therapy with OAC and aspirin or clopidogrel may be considered in selected patients, especially those not receiving a stent or patients at a longer time from the index event.

[b]OAC plus single antiplatelet.

[c]Dual therapy with OAC and an antiplatelet agent (aspirin or clopidogrel) may be considered in patients at high risk of coronary events.

Eur Heart J. 2016;37(38):2893-2962.

2016 ESC GUIDELINES FOR THE MANAGEMENT OF ATRIAL FIBRILLATION



ACS = acute coronary syndrome; AF = atrial fibrillation; OAC = oral anticoagulation (using vitamin K antagonists or non-vitamin K antagonist oral anticoagulants); PCI = percutaneous coronary intervention.

[a]Dual therapy with OAC and aspirin or clopidogrel may be considered in selected patients.

[b]OAC plus single antiplatelet.

[c]Dual therapy with OAC and an antiplatelet agent (aspirin or clopidogrel) may be considered in patients at high risk of coronary events.

Eur Heart J. 2016;37(38):2893-2962.

WOEST trial

Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial

Lancet 2013; 381: 1107–15

Willem J M Dewilde, Tom Oirbans, Freek W A Verheugt, Johannes C Kelder, Bart J G L De Smet, Jean-Paul Herrman, Tom Adriaenssens, Mathias Vrolix, Antonius A C M Heestermans, Marije M Vis, Jan G P Tijsen, Arnoud W van 't Hof, Jurriën M ten Berg, for the WOEST study investigators

PRIMARY ENDPOINT AT 1 YEAR

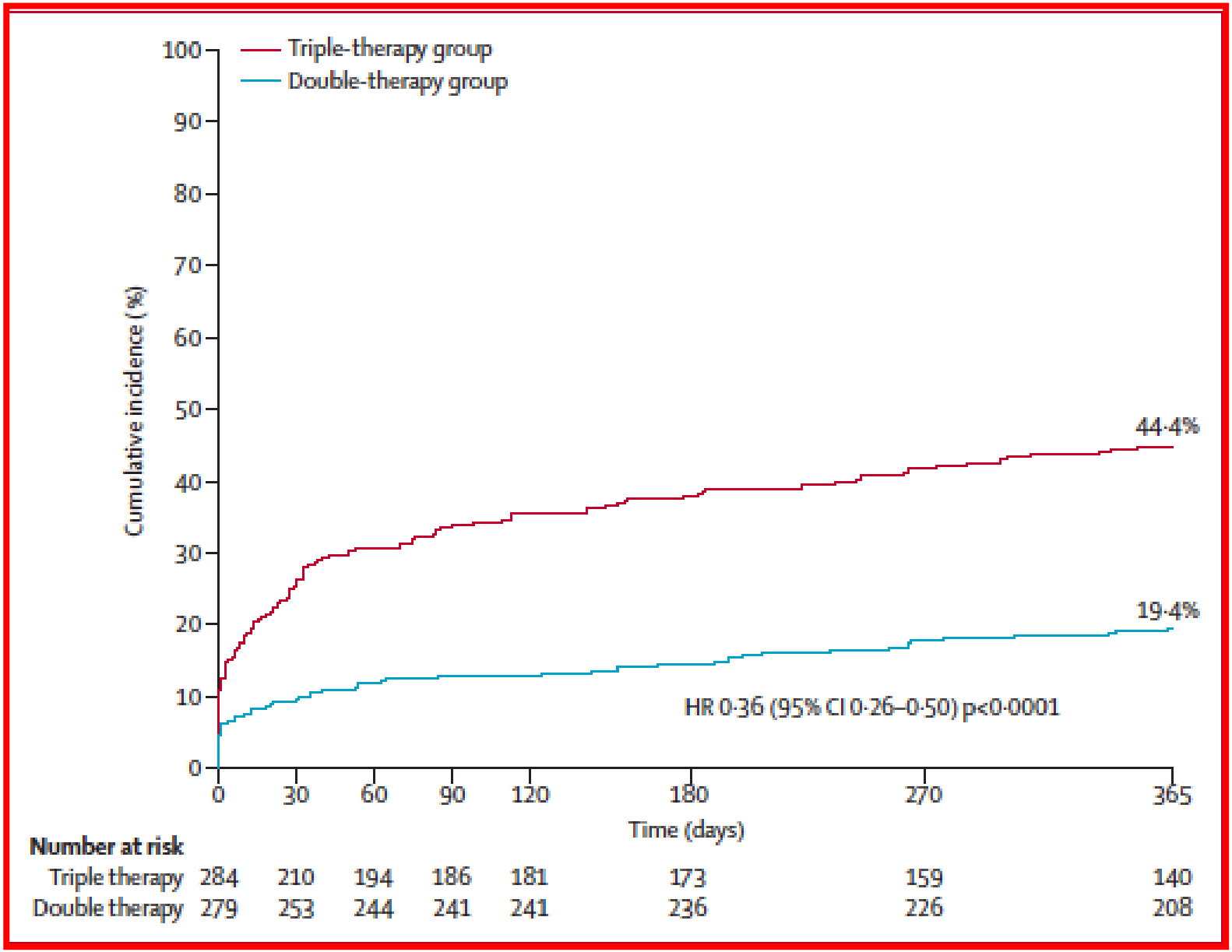
	Double therapy (n-279)	Triple therapy (n=284)	Hazard ratio (95% CI)	p value
Any bleeding event	54 (19·4%)	126 (44·4%)	0·36 (0·26–0·50)	<0·0001
TIMI bleeding				
Major	9 (3·2%)	16 (5·6%)	0·56 (0·25–1·27)	0·159
Major and minor	39 (14·0%)	89 (31·3%)	0·40 (0·27–0·58)	<0·0001
GUSTO bleeding				
Severe	4 (1·4)	10 (3·5%)	0·40 (0·12–1·27)	0·119
Severe and moderate	15 (5·4%)	35 (12·3%)	0·42 (0·23–0·76)	0·003
BARC bleeding				
3	18 (6·5%)	36 (12·7%)	0·49 (0·28–0·86)	0·011
3c	3 (1·1%)	3 (1·1%)	1·00 (0·20–4·90)	0·996
3b	6 (2·2%)	14 (5·0%)	0·43 (0·17–1·10)	0·074
3a	9 (3·2%)	19 (6·7%)	0·47 (0·21–1·00)	0·054·
2	23 (8·2%)	59 (20·8%)	0·36 (0·23–0·59)	<0·0001
2+3	40 (14·3%)	90 (31·7%)	0·40 (0·28–0·58)	<0·0001
1	18 (6·5%)	45 (15·8%)	0·38 (0·22–0·66)	0·0004
Any blood transfusion	11 (3·9%)	27 (9·5%)	0·39* (0·17–0·84)	0·011

Percentages are calculated from the Kaplan-Meier curve. TIMI= Thrombolysis in Myocardial Infarction criteria. GUSTO=Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries criteria. BARC=Bleeding Academic Research Consortium criteria. *Odds ratio.

Table 3: **Results for the primary endpoint at 1 year**

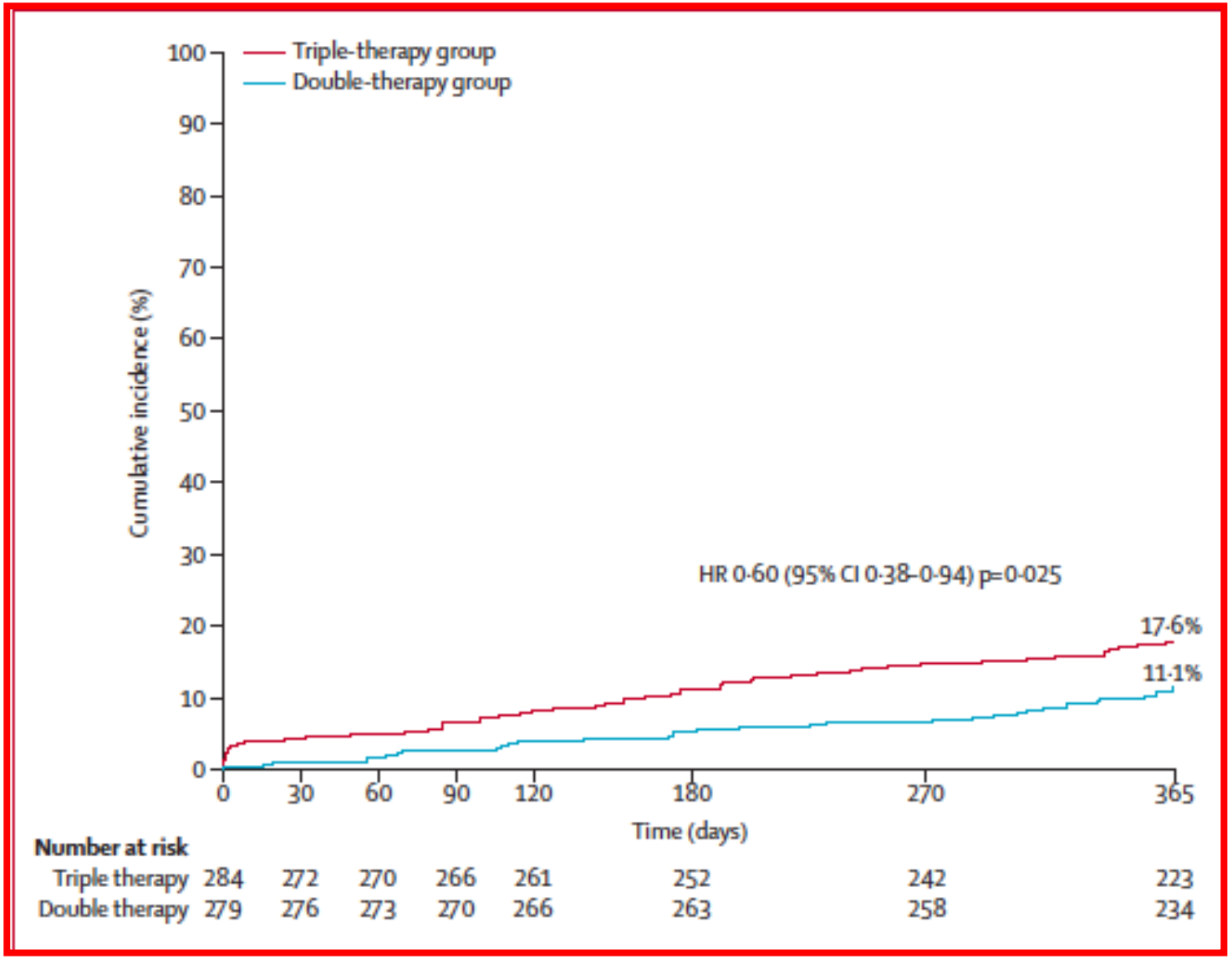
Dewilde WJM et al. Lancet 2013; 381: 1107–15

INCIDENCE OF THE PRIMARY ENDPOINT (ANY BLEEDING)



Dewilde WJM et al. Lancet 2013; 381: 1107–15

CUMULATIVE INCIDENCE OF THE SECONDARY ENDPOINT (DEATH, MYOCARDIAL INFARCTION, STROKE, TARGET-VESSEL REVASCULARISATION, AND STENT THROMBOSIS)



Dewilde WJM et al. Lancet 2013; 381: 1107–15

SECONDARY AND SAFETY ENDPOINTS AT 1 YEAR

	Double therapy (n=297)	Triple therapy (n=284)	Hazard ratio (95% CI)	p value
Combined secondary endpoint	31 (11·1%)	50 (17·6%)	0·60 (0·38–0·94)	0·025
Death				
All-cause	7 (2·5%)	18 (6·3%)	0·39 (0·16–0·93)	0·027
Cardiac	3 (1·1%)	7 (2·5%)	0·43 (0·11–1·66)	0·207
Non-cardiac	4 (1·4%)	11 (3·9%)	0·36 (0·11–1·13)	0·069
Myocardial infarction				
Any	9 (3·2%)	13 (4·6%)	0·69 (0·29–1·60)	0·382
STEMI	1 (0·4%)	3 (1·1%)	0·34 (0·04–3·25)	0·325
Non-STEMI	8 (2·9%)	10 (3·5%)	0·79 (0·31–2·01)	0·625
Target-vessel revascularisation				
PCI or CABG	20 (7·2%)	19 (6·7%)	1·05 (0·56–1·97)	0·876
PCI	17 (6·1%)	16 (5·6%)	1·06 (0·54–2·10)	0·869
CABG	3 (1·1%)	3 (1·1%)	1·00 (0·20–4·90)	0·998
Stroke				
Any	3 (1·1%)	8 (2·8%)	0·37 (0·10–1·40)	0·128
Ischaemic	2 (0·7%)	8 (2·8%)	0·25 (0·05–1·17)	0·056
Haemorrhagic	1 (0·4%)	0	NA	0·321
Disabling	2 (0·7%)	2 (0·7%)	0·99 (0·14–6·99)	0·988
Non-disabling	1 (0·4%)	7 (2·5%)	0·14 (0·02–1·16)	0·034
Stent thrombosis				
Any	4 (1·4%)	9 (3·2%)	0·44 (0·14–1·44)	0·165
Definite	1 (0·4%)	3 (1·1%)	0·33 (0·03–3·22)	0·319
Probable	0	2 (0·7%)	NA	0·161
Possible	3 (1·1%)	4 (1·4%)	0·75 (0·17–3·30)	0·708

Percentages are calculated from the Kaplan-Meier curve. STEMI=ST-elevation myocardial infarction. PCI=percutaneous coronary intervention. CABG=coronary artery bypass graft. NA=not applicable.

Dewilde WJM et al. Lancet 2013; 381: 1107–15

The NEW ENGLAND JOURNAL of MEDICINE

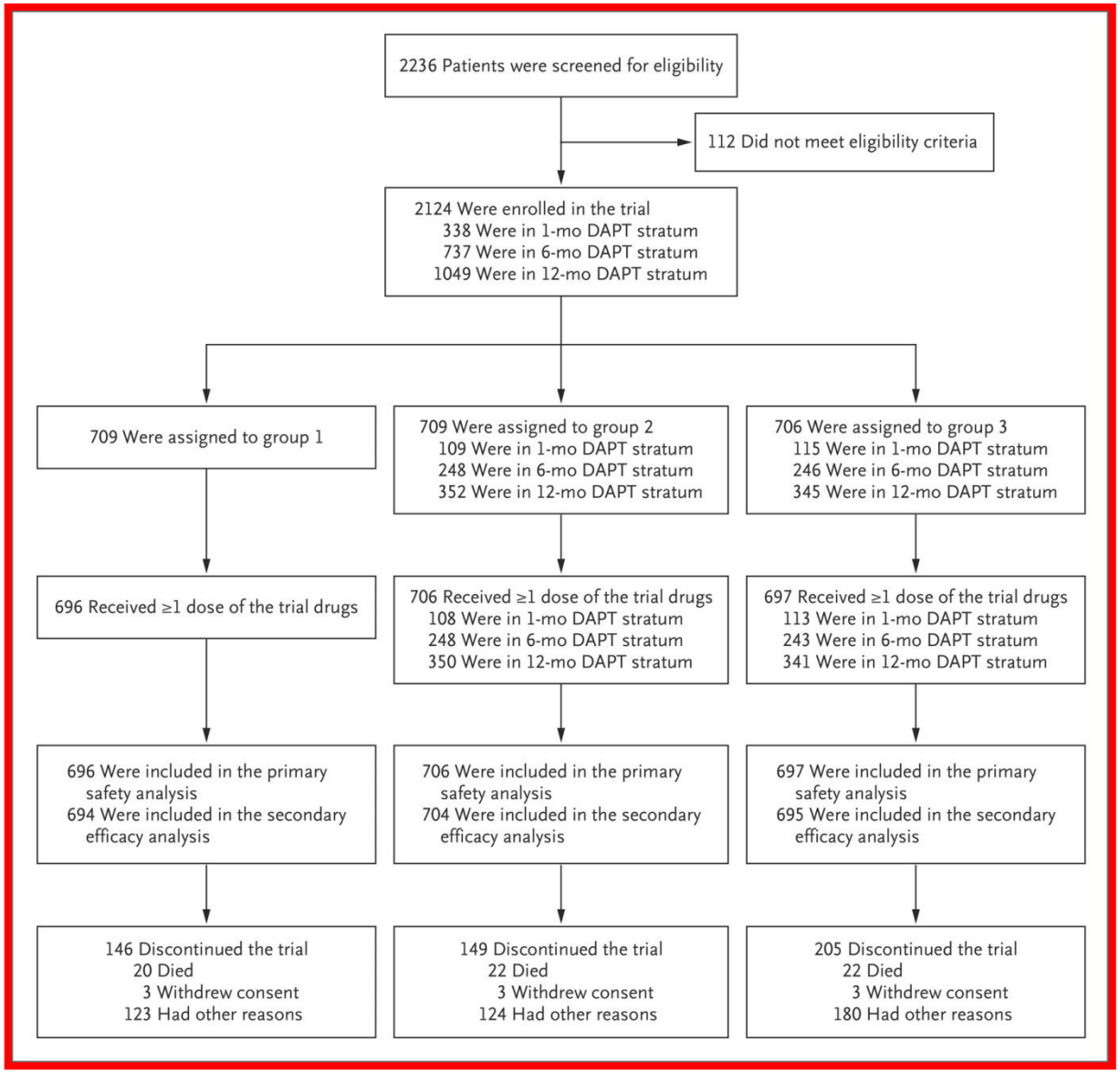
ESTABLISHED IN 1812 DECEMBER 22, 2016 VOL. 375 NO. 25

Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI

C. Michael Gibson, M.D., Roxana Mehran, M.D., Christoph Bode, M.D., Jonathan Halperin, M.D., Freek W. Verheugt, M.D., Peter Wildgoose, Ph.D., Mary Birmingham, Pharm.D., Juliana Ianus, Ph.D., Paul Burton, M.D., Ph.D., Martin van Eickels, M.D., Serge Korjian, M.D., Yazan Daaboul, M.D., Gregory Y.H. Lip, M.D., Marc Cohen, M.D., Steen Husted, M.D., Eric D. Peterson, M.D., M.P.H., and Keith A. Fox, M.B., Ch.B.

STRATIFICATION, RANDOMIZATION, AND FOLLOW-UP.

group 1 rivaroxaban (15 mg once daily) plus a $P2Y_{12}$ inhibitor for 12 months
group 2 rivaroxaban (2.5 mg twice daily) plus DAPT for 1, 6, or 12 months
group 3 standard therapy with a dose-adjusted vitamin K antagonist (once daily) plus DAPT for 1, 6, or 12 months.



Gibson CM et al. N Engl J Med 2016;375:2423-2434

BASELINE CHARACTERISTICS OF THE PARTICIPANTS

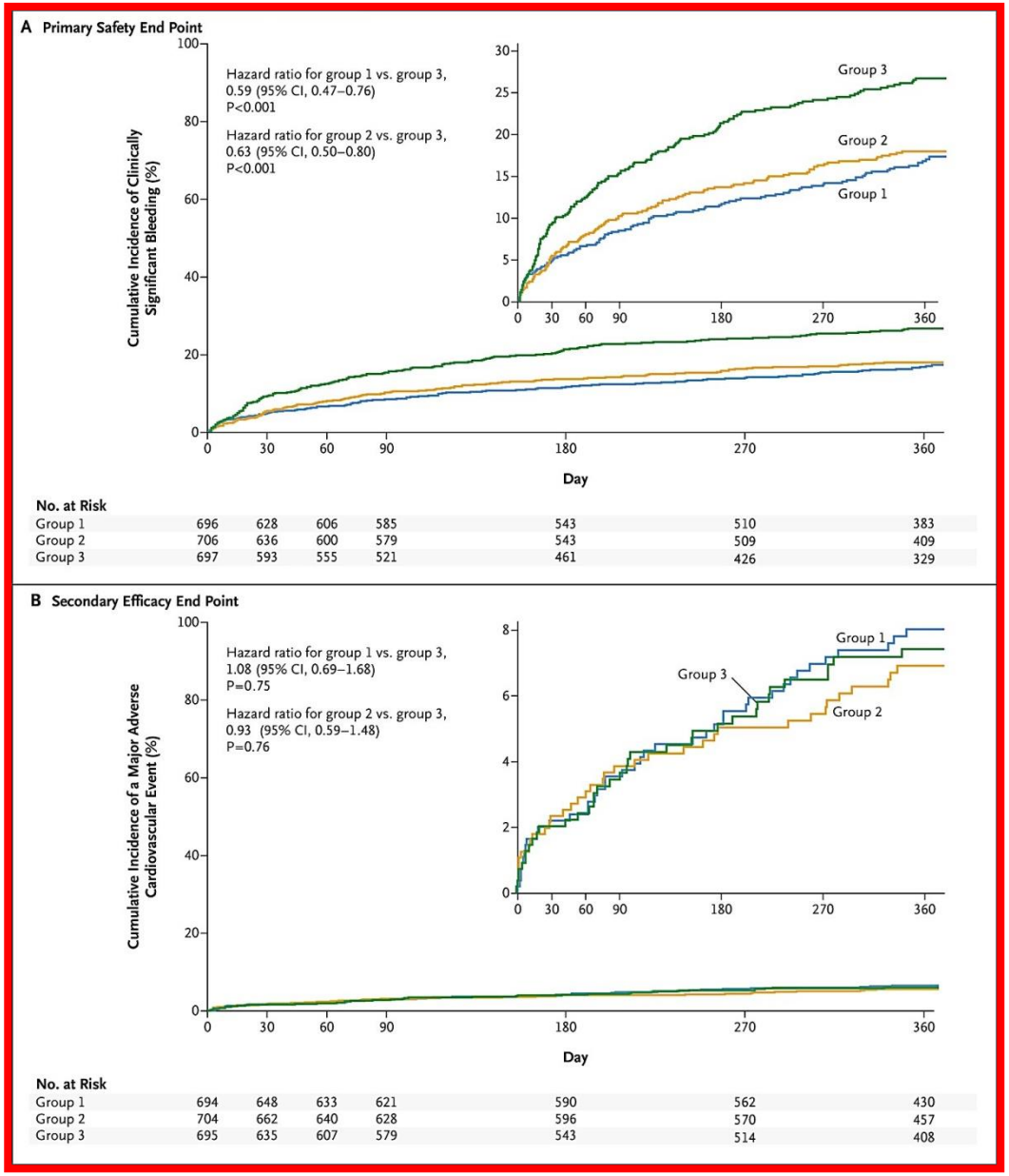
Table 1. Baseline Characteristics of the Participants.*

Characteristic	Group 1 (N=709)	Group 2 (N=709)	Group 3 (N=706)
Age — yr	70.4±9.1	70.0±9.1	69.9±8.7
≥65 Yr of age — no. (%)	523 (73.8)	516 (72.8)	526 (74.5)
≥75 Yr of age — no. (%)	254 (35.8)	245 (34.6)	230 (32.6)
Female sex — no. (%)	181 (25.5)	174 (24.5)	188 (26.6)
Race or ethnic group — no. (%)†			
White	662 (93.4)	671 (94.6)	664 (94.1)
Black	7 (1.0)	3 (0.4)	1 (0.1)
Asian	25 (3.5)	28 (3.9)	33 (4.7)
American Indian or Alaska Native	1 (0.1)	0	0
Other or unknown	14 (2.0)	7 (1.0)	8 (1.1)
Current smoker — no. (%)	37 (5.2)	56 (7.9)	48 (6.8)
Creatinine clearance — ml/min‡	78.3±31.3	77.5±31.8	80.7±30.0
Creatinine clearance of 30 to <60 ml/min — no./total no. (%)‡	194/674 (28.8)	196/680 (28.8)	175/668 (26.2)
Creatinine clearance of <30 ml/min — no./total no. (%)‡	8/674 (1.2)	7/660 (1.1)	2/668 (0.3)
$P2Y_{12}$ inhibitor at baseline — no. (%)			
Clopidogrel	660 (93.1)	664 (93.7)	680 (96.3)
Prasugrel	12 (1.7)	11 (1.6)	5 (0.7)
Ticagrelor	37 (5.2)	34 (4.8)	21 (3.0)
Type of index event — no./total no. (%)§			
NSTEMI	130/701 (18.5)	129/703 (18.3)	123/691 (17.8)
STEMI	86/701 (12.3)	97/703 (13.8)	74/691 (10.7)
Unstable angina	145/701 (20.7)	148/703 (21.1)	164/691 (23.7)
Type of stent — no./total no. (%)			
Drug-eluting stent	464/709 (65.4)	471/705 (66.8)	468/704 (66.5)
Bare-metal stent	231/709 (32.6)	220/705 (31.2)	224/704 (31.8)
Drug-eluting and bare-metal stents	14/709 (2.0)	14/705 (2.0)	12/704 (1.7)
Type of atrial fibrillation — no./total no. (%)			
Persistent	146/708 (20.6)	146/709 (20.6)	149/705 (21.1)
Permanent	262/708 (37.0)	238/709 (33.6)	243/705 (34.5)
Paroxysmal	300/708 (42.4)	325/709 (45.8)	313/705 (44.4)
CHA_2DS_2-VASc score — no. (%)¶			
0	11 (1.6)	10 (1.4)	7 (1.0)
1	66 (9.3)	65 (9.2)	44 (6.2)
2	112 (15.8)	93 (13.1)	96 (13.6)
3	125 (17.6)	122 (17.2)	148 (21.0)
4	138 (19.5)	153 (21.6)	174 (24.6)
5	140 (19.7)	163 (23.0)	125 (17.7)
6	93 (13.1)	85 (12.0)	91 (12.9)
7	24 (3.4)	18 (2.5)	21 (3.0)

* Plus–minus values are means ±SD. Participants in group 1 were assigned to receive low-dose rivaroxaban (15 mg once daily) plus a $P2Y_{12}$ inhibitor for 12 months, those in group 2 were assigned to receive very-low-dose rivaroxaban (2.5 mg twice daily) plus dual antiplatelet therapy (DAPT) for 1, 6, or 12 months, and those in group 3 were assigned to receive standard therapy with a dose-adjusted vitamin K antagonist (once daily) plus DAPT for 1, 6, or 12 months. There were no significant differences among the three groups.
† Race or ethnic group was self-reported.
‡ Creatinine clearance was calculated with the use of the Cockcroft–Gault equation.
§ NSTEMI denotes non–ST-segment elevation myocardial infarction, and STEMI ST-segment elevation myocardial infarction.
¶ A higher CHA_2DS_2-VASc score indicates a higher risk of stroke.

Gibson CM et al. N Engl J Med 2016;375:2423-2434

CUMULATIVE INCIDENCE OF THE PRIMARY SAFETY END POINT AND A SECONDARY EFFICACY ENDPOINT



Gibson CM et al. N Engl J Med 2016;375:2423-2434

CUMULATIVE INCIDENCE OF THE PRIMARY SAFETY END POINT AND ITS COMPONENTS, WITH STRATIFICATION ACCORDING TO INTENDED DURATION OF DAPT

Table 2. Cumulative Incidence of the Primary Safety End Point and Its Components, with Stratification According to Intended Duration of DAPT.*

Cohort and End Point	Group 1	Group 2	Groups 1 and 2	Group 3	Group 1 vs. Group 3		Group 2 vs. Group 3		Groups 1 and 2 vs. Group 3	
	No. of Participants with Events (Kaplan–Meier Event Rate)				Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
All participants — no.	696	706	1402	697						
Clinically significant bleeding	109 (16.8)	117 (18.0)	226 (17.4)	167 (26.7)	0.59 (0.47–0.76)	<0.001	0.63 (0.50–0.80)	<0.001	0.61 (0.50–0.75)	<0.001
Major bleeding	14 (2.1)	12 (1.9)	26 (2.0)	20 (3.3)	0.66 (0.33–1.31)	0.23	0.57 (0.28–1.16)	0.11	0.61 (0.34–1.09)	0.09
Minor bleeding	7 (1.1)	7 (1.1)	14 (1.1)	13 (2.2)	0.51 (0.20–1.28)	0.14	0.50 (0.20–1.26)	0.13	0.51 (0.24–1.08)	0.07
Bleeding requiring medical attention	93 (14.6)	102 (15.8)	195 (15.2)	139 (22.6)	0.61 (0.47–0.80)	<0.001	0.67 (0.52–0.86)	0.002	0.64 (0.51–0.80)	<0.001
Participants assigned to DAPT for 1 mo — no.		108		113						
Clinically significant bleeding		19 (19.4)		27 (25.7)			0.68 (0.38–1.23)	0.20		
Major bleeding		1 (1.1)		5 (5.0)			0.19 (0.02–1.66)	0.10		
Minor bleeding		1 (1.2)		2 (2.0)			0.48 (0.04–5.27)	0.54		
Bleeding requiring medical attention		18 (18.4)		21 (20.4)			0.85 (0.45–1.59)	0.60		
Participants assigned to DAPT for 6 mo — no.		248		243						
Clinically significant bleeding		39 (17.5)		68 (31.2)			0.51 (0.34–0.75)	<0.001		
Major bleeding		7 (3.3)		9 (4.4)			0.74 (0.28–2.00)	0.56		
Minor bleeding		1 (0.5)		6 (2.9)			0.16 (0.02–1.32)	0.05		
Bleeding requiring medical attention		32 (14.5)		56 (26.0)			0.51 (0.33–0.79)	0.002		
Participants assigned to DAPT for 12 mo — no.		350		341						
Clinically significant bleeding		59 (17.9)		72 (23.9)			0.74 (0.52–1.04)	0.08		
Major bleeding		4 (1.3)		6 (2.1)			0.60 (0.17–2.14)	0.43		
Minor bleeding		5 (1.5)		5 (1.8)			0.91 (0.26–3.14)	0.88		
Bleeding requiring medical attention		52 (15.9)		62 (20.9)			0.75 (0.52–1.09)	0.13		

* Data are for all participants who underwent randomization and received at least one dose of the trial regimen during the treatment period. Participants in group 1 were assigned to receive low-dose rivaroxaban (15 mg once daily) plus a $P2Y_{12}$ inhibitor for 12 months, those in group 2 were assigned to receive very-low-dose rivaroxaban (2.5 mg twice daily) plus DAPT for 1, 6, or 12 months, and those in group 3 were assigned to receive standard therapy with a dose-adjusted vitamin K antagonist (once daily) plus DAPT for 1, 6, or 12 months. The primary safety end point of clinically significant bleeding was a composite of major bleeding or minor bleeding, defined according to Thrombolysis in Myocardial Infarction (TIMI) criteria, or bleeding requiring medical attention. Only one event for each participant could be included in the analysis of the composite end point and in the analyses of each component of the composite end point. If a participant had more than one type of event, the first event that occurred is the event that was included in the analysis of the composite end point, but the first occurrence of each type of event was included in the analyses for each component of the composite end point. Cumulative event rates were estimated with the use of the Kaplan–Meier method, hazard ratios and 95% confidence intervals were calculated with the use of the Cox proportional-hazards model, and P values were calculated with the use of the two-sided log-rank test.

CUMULATIVE INCIDENCE OF SECONDARY EFFICACY END POINTS, WITH STRATIFICATION ACCORDING TO INTENDED DURATION OF DAPT.

Table 3. Cumulative Incidence of Secondary Efficacy End Points, with Stratification According to Intended Duration of DAPT.*

Cohort and End Point	Group 1	Group 2	Group 3	Group 1 vs. Group 3		Group 2 vs. Group 3	
	No. of Participants with Events (Kaplan–Meier Event Rate)			Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
All participants — no.	694	704	695				
Major adverse cardiovascular event	41 (6.5)	36 (5.6)	36 (6.0)	1.08 (0.69–1.68)	0.75	0.93 (0.59–1.48)	0.76
Death from cardiovascular causes	15 (2.4)	14 (2.2)	11 (1.9)	1.29 (0.59–2.80)	0.52	1.19 (0.54–2.62)	0.66
Myocardial infarction	19 (3.0)	17 (2.7)	21 (3.5)	0.86 (0.46–1.59)	0.62	0.75 (0.40–1.42)	0.37
Stroke	8 (1.3)	10 (1.5)	7 (1.2)	1.07 (0.39–2.96)	0.89	1.36 (0.52–3.58)	0.53
Stent thrombosis	5 (0.8)	6 (0.9)	4 (0.7)	1.20 (0.32–4.45)	0.79	1.44 (0.40–5.09)	0.57
Major adverse cardiovascular event or stent thrombosis	41 (6.5)	36 (5.6)	36 (6.0)	1.08 (0.69–1.68)	0.75	0.93 (0.59–1.48)	0.76
Participants assigned to DAPT for 1 mo — no.		108	112				
Major adverse cardiovascular event		6 (5.8)	5 (5.2)			1.17 (0.36–3.84)	0.79
Death from cardiovascular causes		2 (2.1)	2 (2.2)			0.96 (0.13–6.80)	0.97
Myocardial infarction		3 (2.9)	1 (1.1)			2.93 (0.30–28.16)	0.33
Stroke		2 (1.9)	3 (3.1)			0.65 (0.11–3.91)	0.64
Stent thrombosis		2 (1.9)	1 (1.1)			1.97 (0.18–21.74)	0.57
Major adverse cardiovascular event or stent thrombosis		6 (5.9)	5 (5.2)			1.17 (0.36–3.84)	0.79
Participants assigned to DAPT for 6 mo — no.		248	243				
Major adverse cardiovascular event		16 (7.0)	9 (4.3)			1.72 (0.76–3.88)	0.19
Death from cardiovascular causes		6 (2.8)	4 (1.9)			1.45 (0.41–5.12)	0.57
Myocardial infarction		7 (3.0)	6 (2.9)			1.13 (0.38–3.37)	0.82
Stroke		6 (2.7)	0				0.02
Stent thrombosis		4 (1.7)	1 (0.4)			3.91 (0.44–35.02)	0.19
Major adverse cardiovascular event or stent thrombosis		16 (7.0)	9 (4.3)			1.72 (0.76–3.40)	0.19
Participants assigned to DAPT for 12 mo — no.		348	340				
Major adverse cardiovascular event		14 (4.5)	22 (7.4)			0.57 (0.29–1.11)	0.10
Death from cardiovascular causes		6 (1.9)	5 (1.7)			1.08 (0.33–3.55)	0.89
Myocardial infarction		7 (2.3)	14 (4.8)			0.44 (0.18–1.10)	0.07
Stroke		2 (0.6)	4 (1.3)			0.46 (0.08–2.51)	0.36
Stent thrombosis		0	2 (0.8)				0.10
Major adverse cardiovascular event or stent thrombosis		14 (4.5)	22 (7.4)			0.57 (0.29–1.11)	0.10

* Data are for all participants who underwent randomization and received at least one dose of the trial regimen during the treatment period; six participants from one site (two in each group) were excluded from all secondary efficacy analyses because of violations of Good Clinical Practice guidelines. Participants in group 1 were assigned to receive low-dose rivaroxaban (15 mg once daily) plus a $P2Y_{12}$ inhibitor for 12 months, those in group 2 were assigned to receive very-low-dose rivaroxaban (2.5 mg twice daily) plus DAPT for 1, 6, or 12 months, and those in group 3 were assigned to receive standard therapy with a dose-adjusted vitamin K antagonist (once daily) plus DAPT for 1, 6, or 12 months. The end point of a major adverse cardiovascular event was a composite of death from cardiovascular causes, myocardial infarction, or stroke. Only one event for each participant could be included in the analysis of the composite end point and in the analyses of each component of the composite end point. If a participant had more than one type of event, the first event that occurred is the event that was included in the analysis of the composite end point, but the first occurrence of each type of event was included in the analyses for each component of the composite end point. Cumulative event rates were estimated with the use of the Kaplan–Meier method, hazard ratios and 95% confidence intervals were calculated with the use of the Cox proportional-hazards model, and P values were calculated with the use of the two-sided log-rank test.

Gibson CM et al. N Engl J Med 2016;375:2423-2434

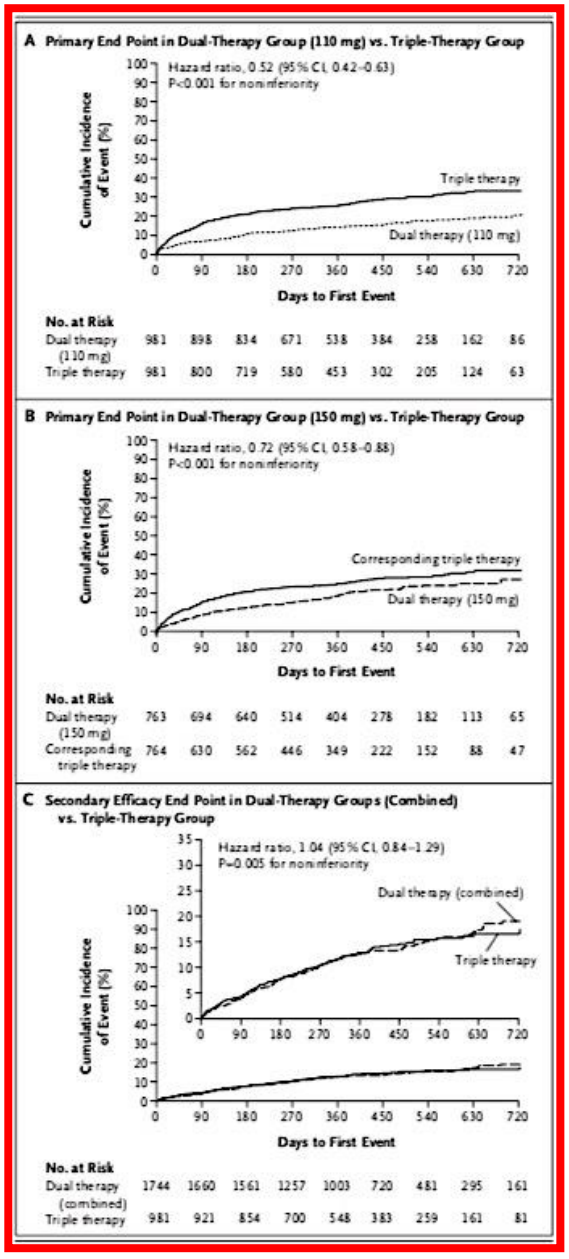
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 19, 2017 VOL. 377 NO. 16

Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation

Christopher P. Cannon, M.D., Deepak L. Bhatt, M.D., M.P.H., Jonas Oldgren, M.D., Ph.D., Gregory Y.H. Lip, M.D., Stephen G. Ellis, M.D., Takeshi Kimura, M.D., Michael Maeng, M.D., Ph.D., Bela Merkely, M.D., Uwe Zeymer, M.D., Savion Gropper, M.D., Ph.D., Matias Nordaby, M.D., Eva Kleine, M.Sc., Ruth Harper, Ph.D., Jenny Manassie, B.Med.Sc., James L. Januzzi, M.D., Jurrien M. ten Berg, M.D., Ph.D., P. Gabriel Steg, M.D., and Stefan H. Hohnloser, M.D., for the RE-DUAL PCI Steering Committee and Investigators*

PRIMARY END POINT SAFETY AND SECONDARY EFFICACY ENDPOINT



SAFETY ENDPOINTS

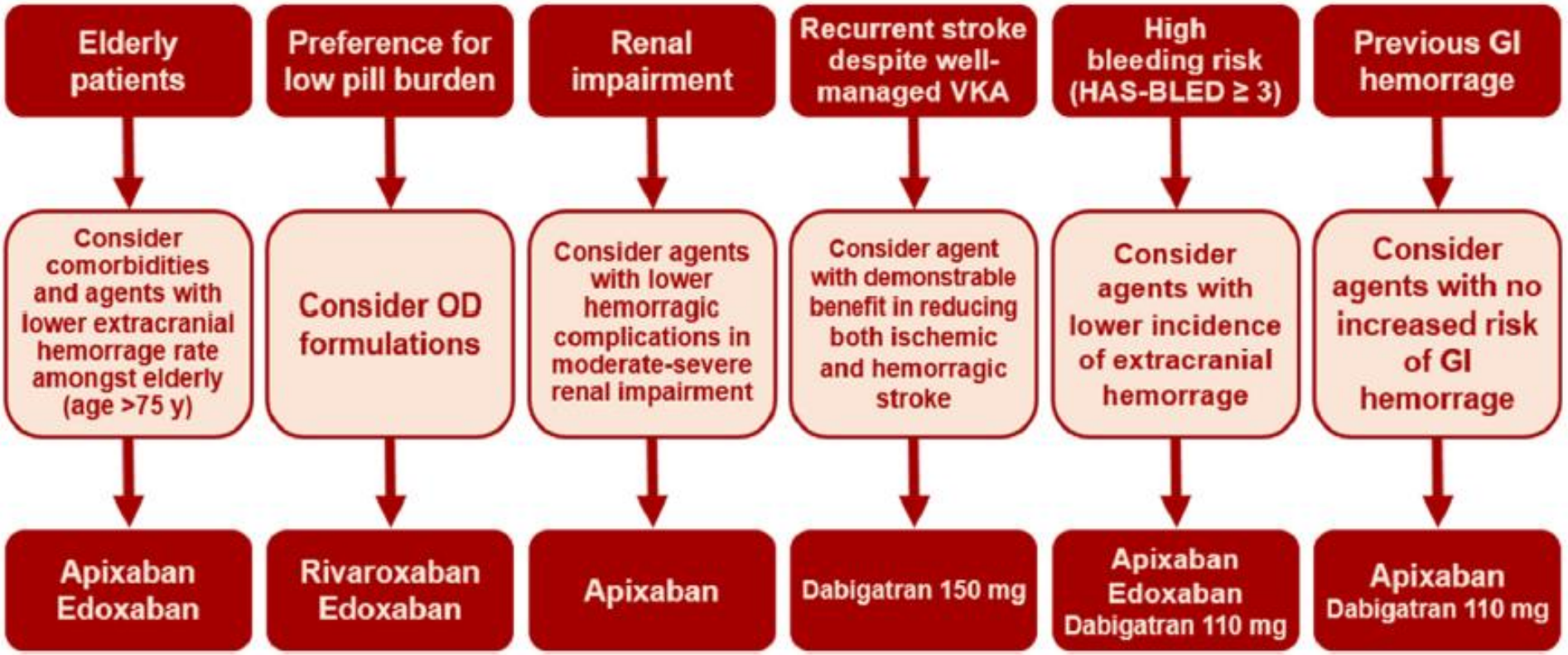
End Point	Dual Therapy with Dabigatran, 110 mg (N=981)	Triple Therapy with Warfarin (N=981)	Hazard Ratio (95% CI)	P Value†	Dual Therapy with Dabigatran, 150 mg (N=763)	Corresponding Triple Therapy with Warfarin (N=764)	Hazard Ratio (95% CI)	P Value†
	no. (%)				*no. (%)*			
Primary end point: ISTH major or clinically relevant nonmajor bleeding	151 (15.4)	264 (26.9)	0.52 (0.42–0.63)	<0.001 (<0.001 for noninferiority)	154 (20.2)	196 (25.7)	0.72 (0.58–0.88)	0.002 (<0.001 for noninferiority)
ISTH major bleeding	49 (5.0)	90 (9.2)	0.52 (0.37–0.74)	<0.001	43 (5.6)	64 (8.4)	0.64 (0.43–0.94)	0.02
Total bleeding	266 (27.1)	421 (42.9)	0.54 (0.46–0.63)	<0.001	254 (33.3)	316 (41.4)	0.72 (0.61–0.84)	<0.001
Intracranial hemorrhage	3 (0.3)	10 (1.0)	0.30 (0.08–1.07)	0.06	1 (0.1)	8 (1.0)	0.12 (0.02–0.98)	0.047
TIMI major bleeding	14 (1.4)	37 (3.8)	0.37 (0.20–0.68)	0.002	16 (2.1)	30 (3.9)	0.51 (0.28–0.93)	0.03
TIMI major or minor bleeding	29 (3.0)	69 (7.0)	0.41 (0.26–0.63)	<0.001	27 (3.5)	48 (6.3)	0.53 (0.33–0.85)	0.009

Cannon et al. N Engl J Med 2017;377:1513-24

EFFICACY ENDPOINTS

End Point	Dual Therapy with Dabigatran (Combined) vs. Triple Therapy with Warfarin				Dual Therapy with Dabigatran (110 mg) vs. Triple Therapy with Warfarin				Dual Therapy with Dabigatran (150 mg) vs. Triple Therapy with Warfarin			
	Combined Dual-Therapy Groups (N=1744)	Triple-Therapy Group (N=981)	Hazard Ratio (95% CI)	P Value†	110-mg Dual-Therapy Group (N=981)	Triple-Therapy Group (N=981)	Hazard Ratio (95% CI)	P Value†	150-mg Dual-Therapy Group (N=763)	Corresponding Triple-Therapy Group (N=764)	Hazard Ratio (95% CI)	P Value†
	no. (%)				*no. (%)*				*no. (%)*			
Composite efficacy end point: thromboembolic events, death, or unplanned revascularization	239 (13.7)	131 (13.4)	1.04 (0.84–1.29)	0.74 (0.005 for noninferiority)	149 (15.2)	131 (13.4)	1.13 (0.90–1.43)	0.30	90 (11.8)	98 (12.8)	0.89 (0.67–1.19)	0.44
Thromboembolic events or death	168 (9.6)	83 (8.5)	1.17 (0.90–1.53)	0.25 (0.11 for noninferiority)	108 (11.0)	83 (8.5)	1.30 (0.98–1.73)	0.07	60 (7.9)	60 (7.9)	0.97 (0.68–1.39)	0.88
Death					55 (5.6)	48 (4.9)	1.12 (0.76–1.65)	0.56	30 (3.9)	35 (4.6)	0.83 (0.51–1.34)	0.44
Myocardial infarction					44 (4.5)	29 (3.0)	1.51 (0.94–2.41)	0.09	26 (3.4)	22 (2.9)	1.16 (0.66–2.04)	0.61
Stroke					17 (1.7)	13 (1.3)	1.30 (0.63–2.67)	0.48	9 (1.2)	8 (1.0)	1.09 (0.42–2.83)	0.85
Definite stent thrombosis					15 (1.5)	8 (0.8)	1.86 (0.79–4.40)	0.15	7 (0.9)	7 (0.9)	0.99 (0.35–2.81)	0.98

Guida pratica alla scelta dei NOAC



Bo et al. Eur J Itern Med 2017

Grazie per l'attenzione