Blutungs- und Thromboembolie-Risiko

8.3.2018, Schaan

JH Beer, Dept Medizin KS Baden,
Molekulare Kardiologie, Zürich

Disclosures JH Beer

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Astra Zeneca, Bayer, Bristol Myers Squibb / Pfizer, Inc.
Boehringer Ingelheim, Daiichi Sankyo, Sanofi

Bleeding and VTE-Risk

3 Cases:

1) *CAT: Cancer associated TE*

2) *ACS and afib: Triple therapy*

3) *Unprovoked VTE and Thrombophilia: Long-term treatment*


Editorial

«Park and Read!»

Update und individualisierte Medizin bei der Therapie thromboembolischer Erkrankungen

Jürg H. Beer[1,2]

[1]Departement Innere Medizin, Kantonsspital Baden
[2]Molekulare Kardiologie, Universitätsspital Zürich

Therapeutische Umschau (2016), 73(10), 545–549

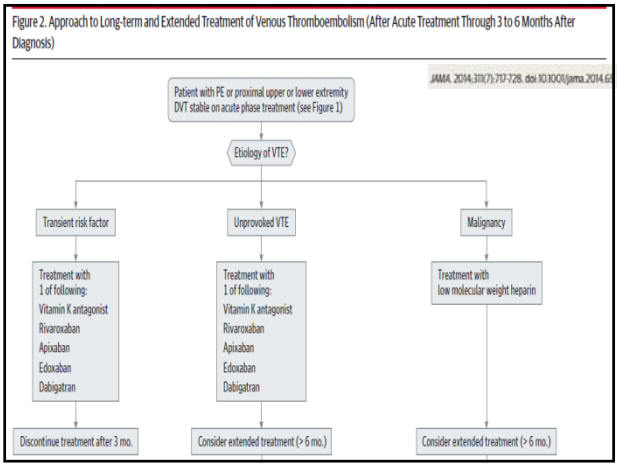
Bleeding and VTE-Risk

Case 1:

CAT: Cancer associated TE

70 yrs old male with colonic cancer T3N0M1 (liver)
Chemotherapy (folfox)
Fe deficiency anemia, recurrent colonic bleeds
Routine CT scan basal PE.

Anticoagulation at all?
Type of anticoagulant? (weight, kidney, plt count etc)
Dose of anticoagulant?
Timing?
Duration? Surgery?
Risk of VTE and Bleeding (GI, other, minor, major?
Patient preferences, doctors preferences



JAMA Clinical Guidelines Synopsis

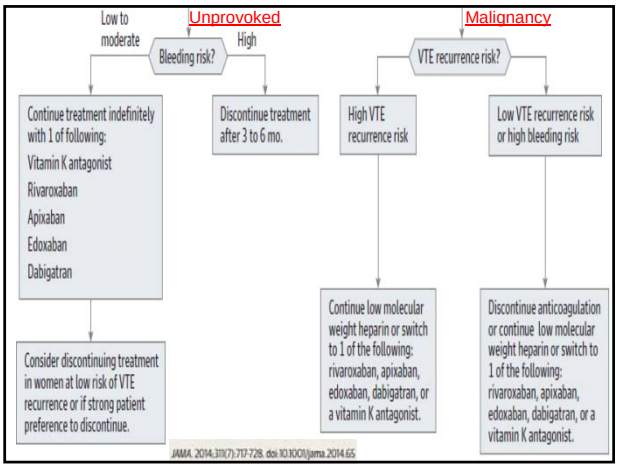
Antithrombotic Therapy for Venous Thromboembolic Disease

Atul Jain, MD, MS; Adam S. Cifu, MD

- In patients with cancer and DVT or PE (cancer-associated thrombosis), low-molecular-weight heparin (LMWH) is preferred over VKA therapy, dabigatran, rivaroxaban, apixaban, or edoxaban (grade 2C).
- In patients with an unprovoked DVT or PE who are stopping anticoagulant therapy and do not have a contraindication to aspirin, aspirin therapy is suggested (grade 2B).

(Reduced dose NOAC is more effective than ASA (Apixaban 2x2.5, Rivaroxaban 10mg)

JAMA May 16, 2017 Volume 317, Number 19



JAMA. 2014;311(7):717-728. doi:10.1001/jama.2014.65

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
Comments	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 label 'high risk of gastrointestinal bleeding' is imprecise. For example, patients with *H. pylori*-related ulcer haemorrhage may no longer be at high risk of bleeding once the infection has been eradicated. The gastrointestinal bleeding risk associated with any anticoagulant is increased by concurrent use of antiplatelet agents, including aspirin.[41]

European Heart Journal (2017) 38, 860–868

Gastrointestinal Safety of Direct Oral Anticoagulants: A Large Population-Based Study

Neena S. Abraham,[1,2,3] Peter A. Noseworthy,[2,4] Xiaoxi Yao,[2] Lindsey R. Sangaralingham,[2] and Nilay D. Shah[2,3,5]

Table 6. Stratified Analysis in Propensity Score–Matched Apixaban vs Rivaroxaban Users

	Apixaban (n = 6565)		Rivaroxaban (n = 6565)		Apixaban vs rivaroxaban (n = 13,130)	
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	0.38 (0.08–1.89)	.36
65–74 y	5	0.69	32	3.24	0.18*** (0.07–0.47)	
≥75 y	25	2.32	78	5.05	0.39*** (0.25–0.61)	

NOTE. *P* value in the table is for interaction; ***$P < .001$ indicates significance for the HR.
IR, incidence rate per 100 person-years.

Gastroenterology 2017;152:1014–1022

ORIGINAL ARTICLE

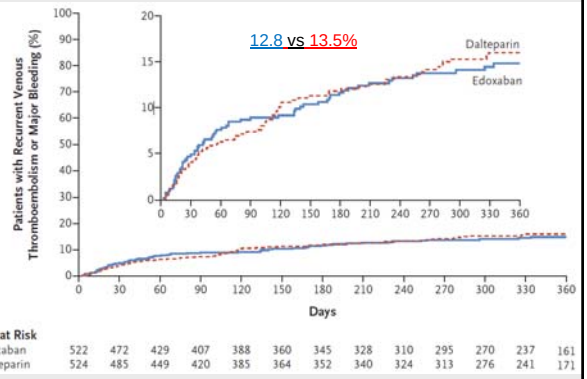
Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism

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*

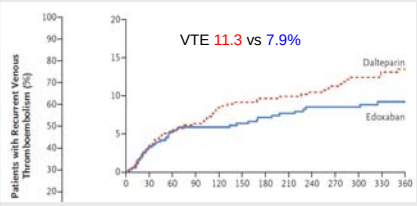
1050pts
Dalteparin 5d
Randomized to dalteparin 200U/kg/d
After 1m 150U/kg/d
Or
Edoxaban 60mg
For at least 6m up to 1y

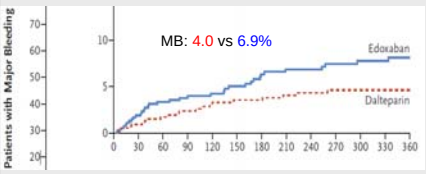
N ENGL J MED 378;7 NEJM.ORG FEBRUARY 15, 2018

Edoxaban in CAT



N ENGL J MED 378;7 NEJM.ORG FEBRUARY 15, 2018





N ENGL J MED 378;7 NEJM.ORG FEBRUARY 15, 2018

How do you treat this patient @home

CAT: Cancer associated TE

70 yrs old male with colonic cancer T3N0M1 (liver)
Chemotherapy (folfox)
Fe deficiency anemia, recurrent colonic bleeds
Routine CT scan large basal PE.

Anticoagulation at all?
Type of anticoagulant? (weight, kidney, plt count etc)
Dose of anticoagulant?
Timing?
Duration?
Risk of VTE and Bleeding (GI, other, minor, major?
Patient preferences, doctors preferences*
Follow up? What happened in real life?

Case 2:

Triple Therapy in atrial fibrillation and after ACS 6m ago

76y old woman, hypertension, afib CHADS Vasc 5, Has Bled 3, ACS & s-stent : Riva 15mg, ASA, Clopidogrel.
Fe deficiency anemia, occasional GI and chronic mucocutaneous bleeding

Anticoagulation at all?
Type of anticoagulant (weight, kidney, plt count etc)?
Dose of anticoagulant?
Timing?
Duration?
Risk of VTE and Bleeding (GI, other, minor, major?
Patient preferences, doctors preferences?*
Follow up? What happened in real life?

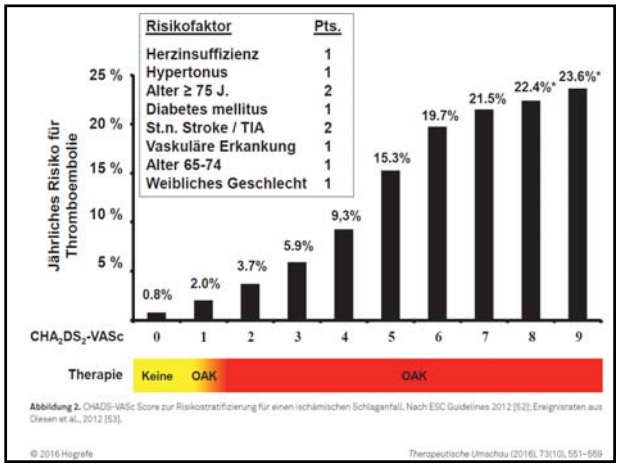
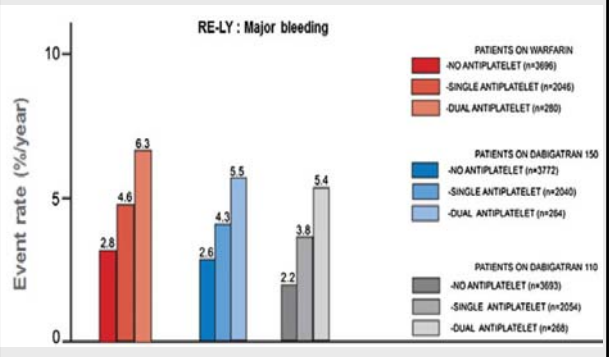


Abbildung 2. CHADS-VASc Score zur Risikostratifizierung für einen ischämischen Schlaganfall. Nach ESC Guidelines 2012 [52]; Ereignisraten aus Olesen et al., 2012 [53].

© 2016 Hogrefe Therapeutische Umschau (2016), 73(10), 551–559

Major Bleeds with DOACs in AF in Mono- Dual, or Triple Therapy



European Heart Journal (2017) **38**, 852–859

Table 2 Major haemorrhage by age subgroups

	No. of events (%/year)	No. of events (%/year)	Hazard ratio (95% CI)	P-value
ARISTOTLE	Apixaban 5 mg twice daily	Warfarin		
<65	56 (1.2)	72 (1.5)	0.78 (0.55–1.11)	0.63
65 to <75	120 (2.0)	166 (2.8)	0.71 (0.56–0.89)	
≥75	151 (3.3)	224 (5.2)	0.64 (0.52–0.79)	
RE-LY	Dabigatran 110 mg twice daily	Warfarin		
<75	138 (1.89)	215 (3.04)	0.62 (0.50–0.77)	0.0003
≥75	204 (4.43)	206 (4.37)	1.01 (0.83–1.23)	
	Dabigatran 150 mg	Warfarin		
<75	153 (2.12)	215 (3.04)	0.70 (0.57–0.86)	0.0001
≥75	246 (5.10)	206 (4.37)	1.18 (0.98–1.42)	
ROCKET AF	Rivaroxaban 20 mg once daily	Warfarin		
<65	59 (2.21)	59 (2.16)	1.02 (0.71–1.46)	0.59
65 to <75	113 (3.03)	123 (3.24)	0.94 (0.73–1.21)	
≥75	223 (4.86)	204 (4.40)	1.11 (0.92–1.34)	
ENGAGE AF-TIMI	Edoxaban 60 mg once daily	Warfarin		0.57
<75	(2.02)	(2.62)		
≥75	(4.01)	(4.83)		

The trials were different in the baseline risk for bleeding complications.

European Heart Journal (2017) **38**, 860–868

EHJ 2016

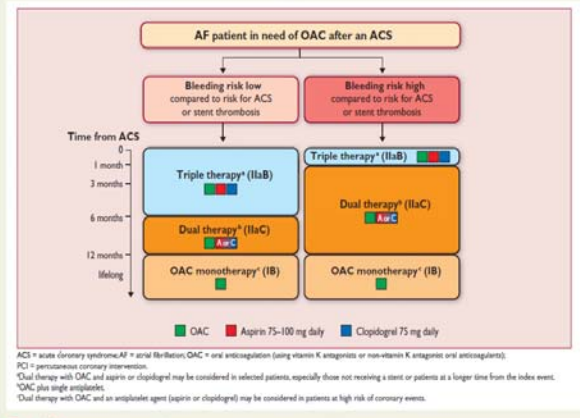


Figure 12 Antithrombotic therapy after an acute coronary syndrome in atrial fibrillation patients requiring anticoagulation.

Patients with stable coronary artery disease

First choice	Monotherapy with an NOAC is preferable for patients with AF and stable CAD. This suggestion is applicable to all NOACs
Second choice	In selected patients, addition of aspirin is still indicated in the long-term, based on individual risk assessment and coronary anatomy
Comment	In the absence of direct comparative studies, no particular NOAC can be favoured over another

European Heart Journal (2017) **38**, 852–859

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
Comments	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 label 'high risk of gastrointestinal bleeding' is imprecise. For example, patients with *H. pylori*-related ulcer haemorrhage may no longer be at high risk of bleeding once the infection has been eradicated. The gastrointestinal bleeding risk associated with any anticoagulant is increased by concurrent use of antiplatelet agents, including aspirin.[41]

European Heart Journal (2017) **38**, 860–868

Follow up and how do you do it @home

Case 2:

Triple Therapy in atrial fibrillation and after ACS 6m ago

76y old woman, hypertension, afib CHADS Vasc 5, Has Bled 3, ACS & s-stent

Fe deficiency anemia, occasional GI and chronic mucocutaneous bleeding

Anticoagulation at all?
Type of anticoagulant (weight, kidney, plt count etc)?
Dose of anticoagulant?
Duration/When to stop which medication?
Risk of VTE and Bleeding (GI, other, minor, major?
Patient preferences, doctors preferences?*
Follow up? ***What happened in real life?***

Europace (2016) **18**, 1609–1678
doi:10.1093/europace/euw295

ESC GUIDELINES

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)

Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC

Endorsed by the European Stroke Organisation (ESO)

European Heart Journal (2017) **38**, 852–859
doi:10.1093/eurheartj/ehv643

REVIEW

Prevention

Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 1

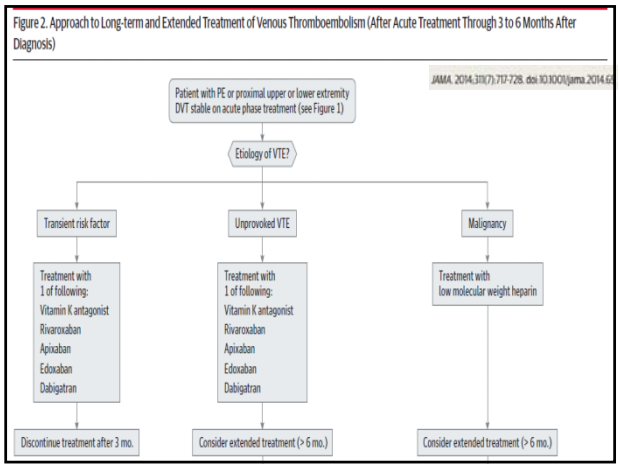
Hans-Christoph Diener[1*], James Aisenberg[2], Jack Ansell[3], Dan Atar[4], Günter Breithardt[5], John Eikelboom[6], Michael D. Ezekowitz[7,8,9], Christopher B. Granger[10], Jonathan L. Halperin[11], Stefan H. Hohnloser[12], Elaine M. Hylek[13], Paulus Kirchhof[14,15], Deirdre A. Lane[16], Freek W.A. Verheugt[17], Roland Veltkamp[18], and Gregory Y.H. Lip[19,20]

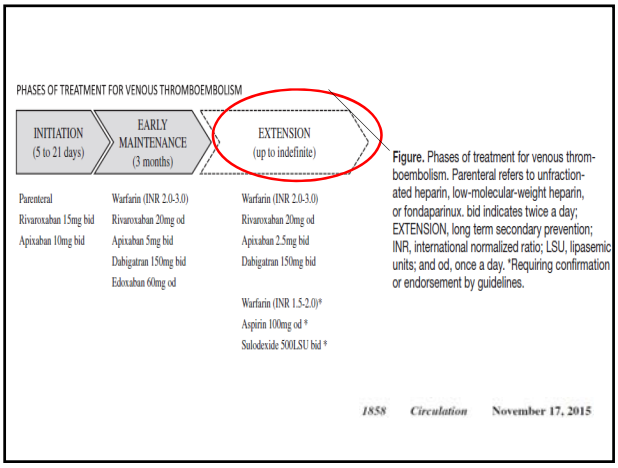
Bleeding and VTE-Risk

Case 3:

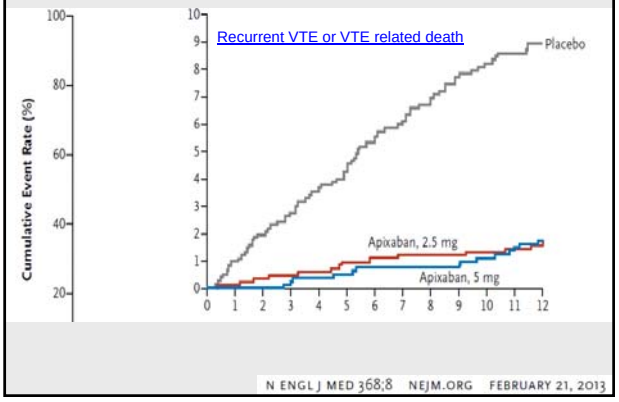
Pt, 65 yrs old woman with unprovoked VTE 3 months ago and ATIII (55%) deficiency wants to stop the therapy with rivaroxaban 20 mg because of frequent nose bleeding.
Second phase of history taking: Brother stroke with 27y.

Anticoagulation stop or longterm?
Local problem vs systemic factor (eg vWD)
Type of anticoagulant (weight, kidney, plt count etc)?
Dose of anticoagulant?
Duration?
Risk of VTE and Bleeding
Patient preferences - doctors preferences?*
Follow up? What happened in real life?





Treatment extension for VTE with Apixaban



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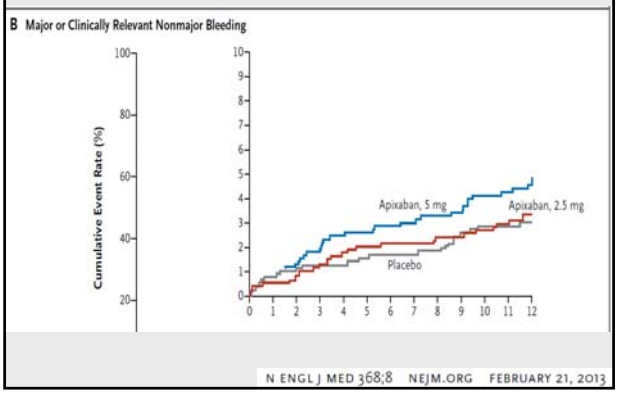
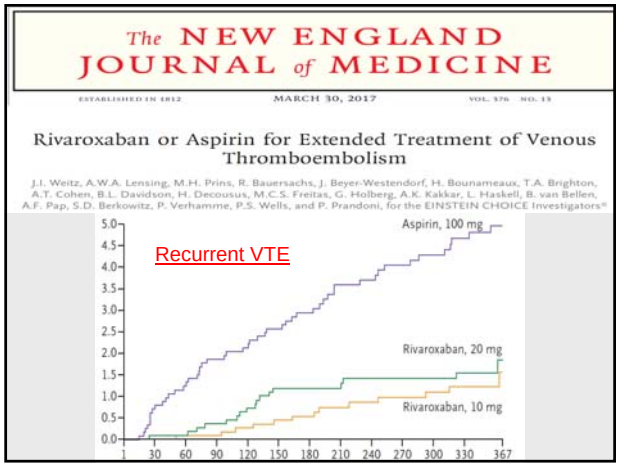




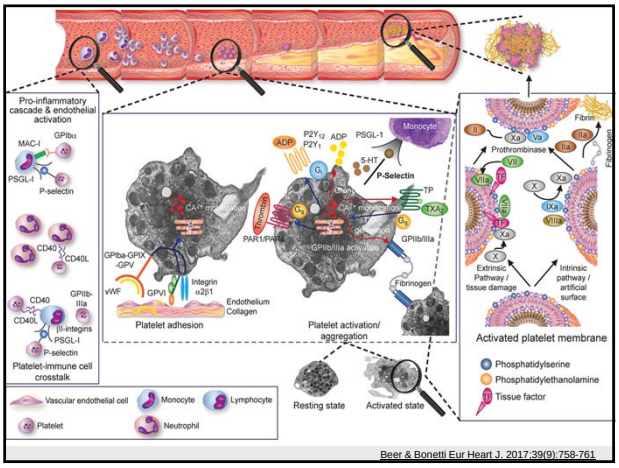
Case 3: Follow up and how I do it @ home

Pt, 65 yrs old woman with unprovoked VTE 3 months ago and ATIII (55%) deficiency wants to stop the therapy with rivaroxaban 20 mg because of frequent nose bleeding.
Second phase of history taking: Brother stroke with 27y.

Anticoagulation at all? Riva 20mg open ended
Local problem vs systemic factor (eg vWD); ORL Cons solved the problem
Type of anticoagulant (weight, kidney, plt count etc)?
Dose of anticoagulant?if not ATIII deficient: Riva 10mg/d or apix 2.5x2/d
Duration? Indefinitely with 3 monthly reconsideration
Risk of VTE and Bleeding
Patient preferences - doctors preferences?*
Follow up? What happened in real life?3 yrs well, no bleeds not VTE

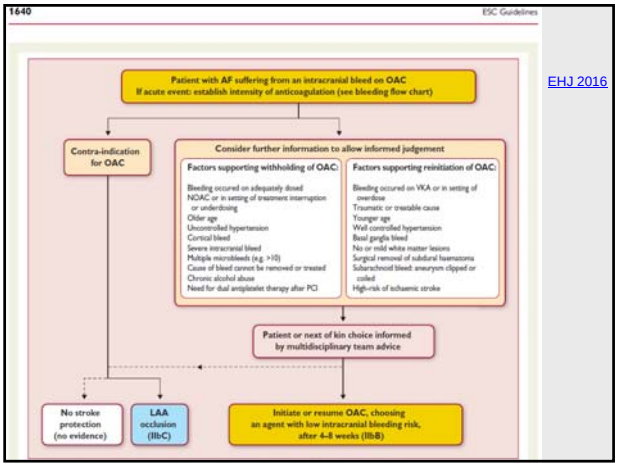
Take Home Messages: Risk assessment 3 Cases:

1) CAT: Cancer associated TE
LMWH, DOACs non inferior (Edoxaban), more GI bleeds
2) Afib and CA stenting: Triple trouble
Keep triple anticoagulation as short as possible after careful weighing risks and benefits
3) Unprovoked VTE with thrombophilia
Long term tx: Consider dose reduction in lower risk pts
4) Individualize therapy and consider pt preferences

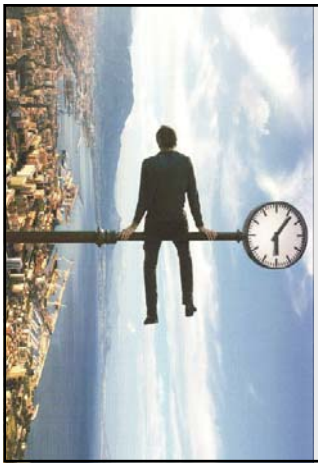


Beer & Bonetti Eur Heart J. 2017;39(9):758-761

Guideline vs individual pts

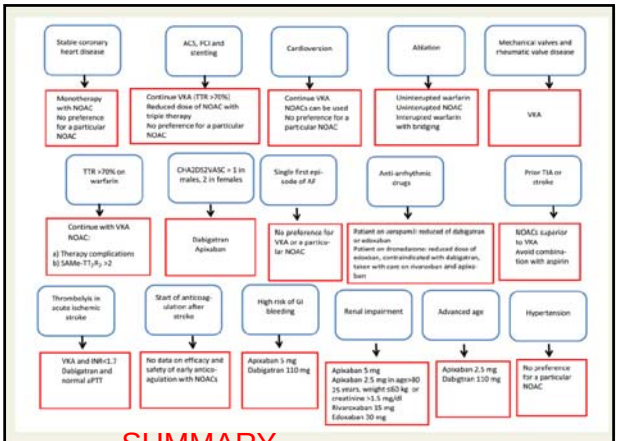


EHJ 2016



Guidelines vs Individual Management:

„No decision about the patient without the patient“!



SUMMARY

European Heart Journal (2017) **38**, 860–868

Patients with hypertension

Table 4 International Society of Thrombosis and Hemostasis[56] major bleeding (%/year) in relation to the presence or absence of hypertension in the four trials comparing non-vitamin K oral anticoagulants with warfarin in patients with atrial fibrillation

Trial	Drug and dose	Hypertension	No. of patients	NOAC	Warfarin	HR (95% CI)	P-interaction
ARISTOTLE[2]	Apixaban 5 mg twice daily[b]	Yes	15 916	2.07	3.00	0.69 (0.59–0.80)	
		No	2285	2.60	3.73	0.70 (0.48–1.00)	0.96
ENGAGE AF[4]	Edoxaban 60 mg once daily[b]	Yes	19 754	2.72	3.42	0.80[a]	
		No	1351	3.17	3.42	0.93[a]	0.68

European Heart Journal (2017) **38**, 860–868

The NEW ENGLAND JOURNAL of MEDICINE

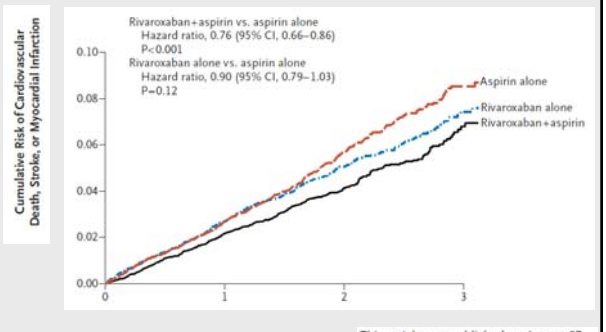
ORIGINAL ARTICLE

Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease

J.W. Eikelboom, S.J. Connolly, J. Bosch, G.R. Dagenais, R.G. Hart, O. Shestakovska, R. Diaz, M. Alings, E.M. Lonn, S.S. Anand, P. Widimsky, M. Hori, A. Avezum, L.S. Piegas, K.R.H. Branch, J. Probstfield, D.L. Bhatt, J. Zhu, Y. Liang, A.P. Maggioni, P. Lopez-Jaramillo, M. O'Donnell, A. Kakkar, K.A.A. Fox, A.N. Parkhomenko, G. Ertl, S. Störk, M. Keltai, L. Ryden, N. Pogosova, A.L. Dans, F. Lanas, P.J. Commerford, C. Torp-Pedersen, T.J. Guzik, P.B. Verhamme, D. Vinereanu, J.-H. Kim, A.M. Tonkin, B.S. Lewis, C. Felix, K. Yusoff, P.G. Steg, K.P. Metsarinne, N. Cook Bruns, F. Misselwitz, E. Chen, D. Leong, and S. Yusuf, for the COMPASS Investigators*

This article was published on August 27, 2017, at NEJM.org.

Compass Trial



This article was published on August 27, 2017, at NEJM.org.

CVD, Stroke, MI

R+A: 4.1%

R(5): 4.9%

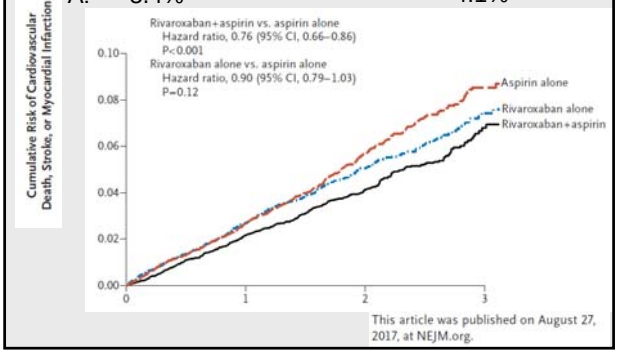
A: 5.4%

Death from any cause:

3.4%

4.0%

4.1%



This article was published on August 27, 2017, at NEJM.org.

Major Bleeds:

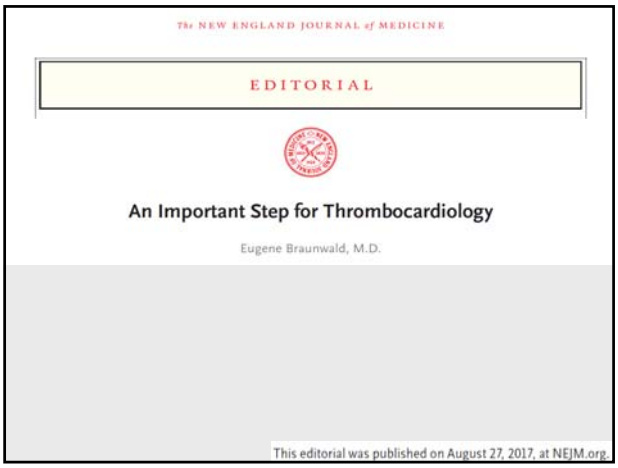
R&A: 3.1%

R (5): 2.8%

A : 1.9%

Table 3. Bleeding Events and Net Clinical Benefit.*

Outcome	Rivaroxaban plus Aspirin (N=9152)	Rivaroxaban Alone (N=9117)	Aspirin Alone (N=9126)	Rivaroxaban plus Aspirin vs. Aspirin Alone		Rivaroxaban Alone vs. Aspirin Alone	
				Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
	number (percent)						
Major and minor bleeding							
Major bleeding	288 (3.1)	255 (2.8)	170 (1.9)	1.70 (1.40–2.05)	<0.001	1.51 (1.25–1.84)	<0.001
Fatal bleeding†	15 (0.2)	14 (0.2)	10 (0.1)	1.49 (0.67–3.33)	0.32	1.40 (0.62–3.15)	0.41
Nonfatal symptomatic ICH†	21 (0.2)	32 (0.4)	19 (0.2)	1.10 (0.59–2.04)	0.77	1.69 (0.96–2.98)	0.07
Nonfatal, non-ICH, symptomatic bleeding into critical organ†	42 (0.5)	45 (0.5)	29 (0.3)	1.43 (0.89–2.29)	0.14	1.57 (0.98–2.50)	0.06
Other major bleeding†	210 (2.3)	164 (1.8)	112 (1.2)	1.88 (1.49–2.36)	<0.001	1.47 (1.16–1.87)	0.001
Fatal bleeding or symptomatic ICH	36 (0.4)	46 (0.5)	29 (0.3)	1.23 (0.76–2.01)	0.40	1.59 (1.00–2.53)	0.05
Fatal bleeding or symptomatic bleeding into critical organ	78 (0.9)	91 (1.0)	58 (0.6)	1.34 (0.95–1.88)	0.09	1.58 (1.13–2.19)	0.006
Major bleeding according to ISTH criteria	206 (2.3)	175 (1.9)	116 (1.3)	1.78 (1.41–2.23)	<0.001	1.52 (1.20–1.92)	<0.001
Transfusion within 48 hr after bleeding	87 (1.0)	66 (0.7)	44 (0.5)	1.97 (1.37–2.83)	<0.001	1.50 (1.03–2.20)	0.03
Minor bleeding	838 (9.2)	741 (8.1)	503 (5.5)	1.70 (1.52–1.90)	<0.001	1.50 (1.34–1.68)	<0.001



The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

An Important Step for Thrombocardiology

Eugene Braunwald, M.D.

This editorial was published on August 27, 2017, at NEJM.org.