NOACs new data in cardiology, from trial to real world

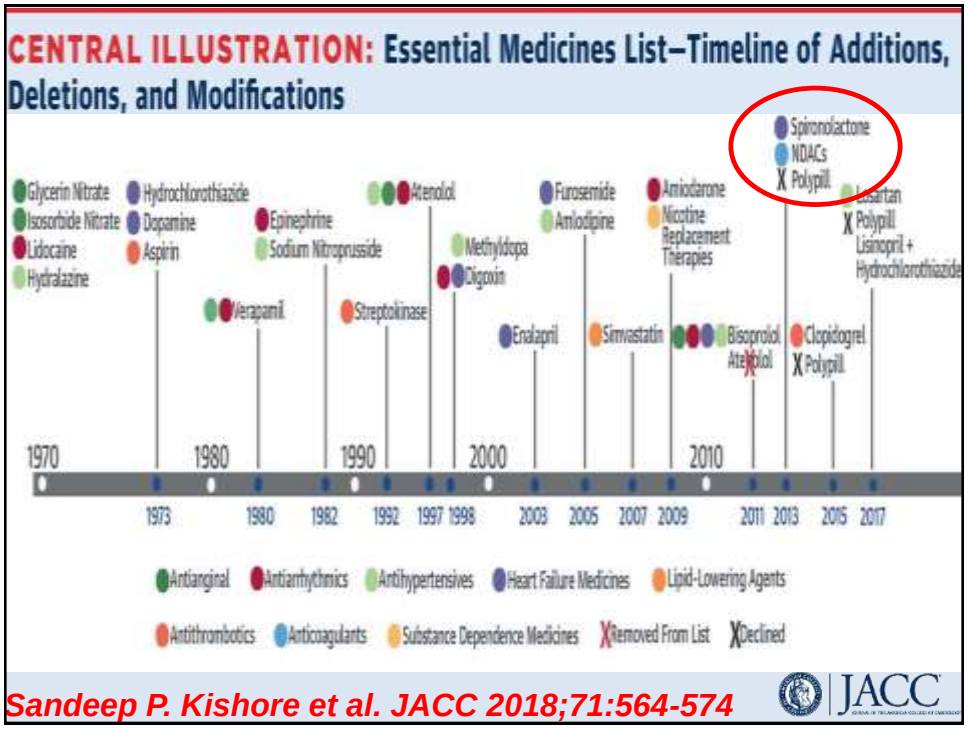
By

M.Wafaie aboleineen,MD,FACC

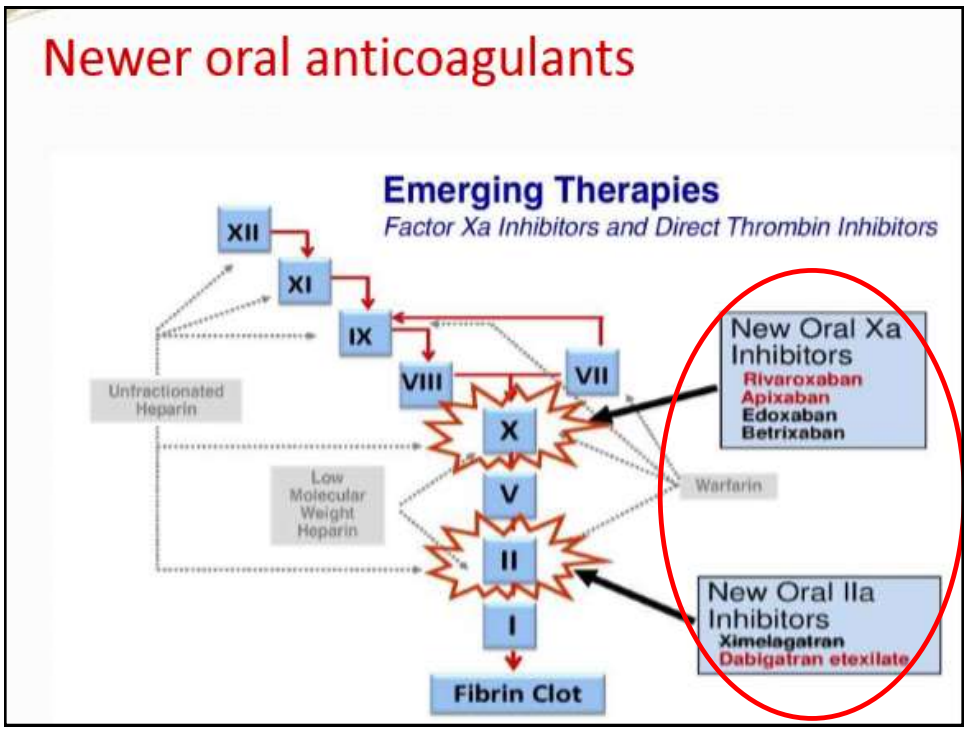
WARFARIN

almost 70 years old and still causing problems...

Still we have to stick with it...



Sandeep P. Kishore et al. JACC 2018;71:564-574



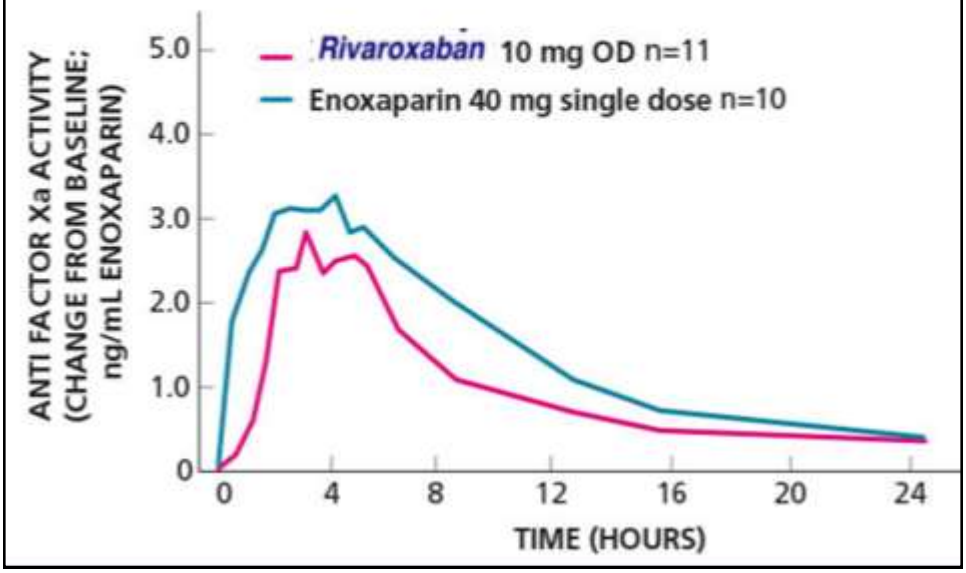
Ideal Anticoagulant?

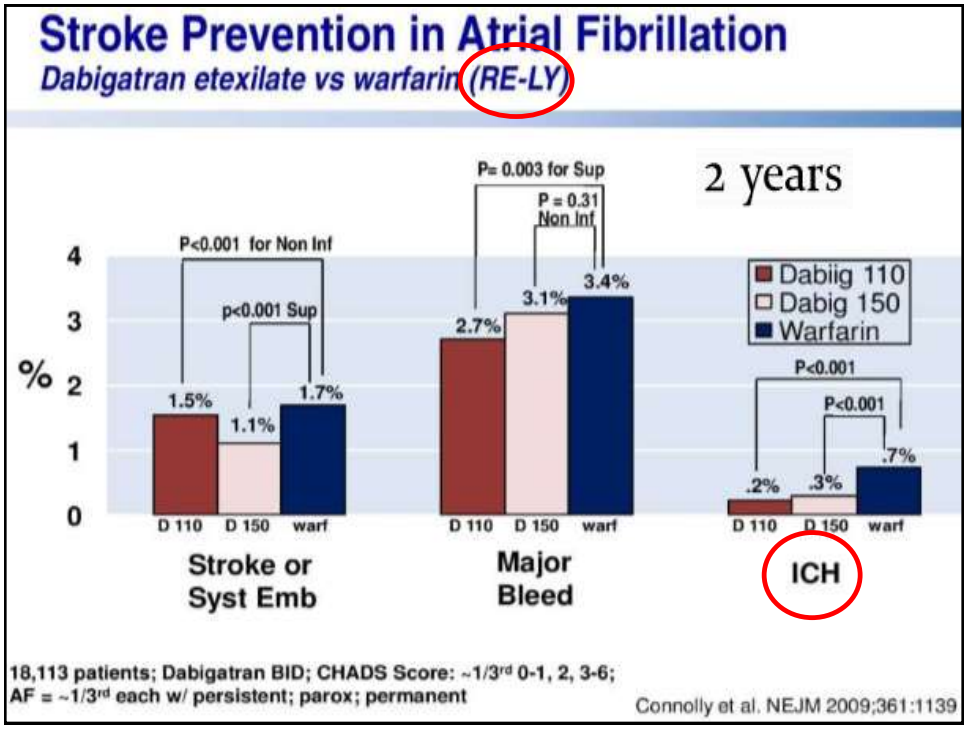
Table 2. Advantages of New Oral Anticoagulants

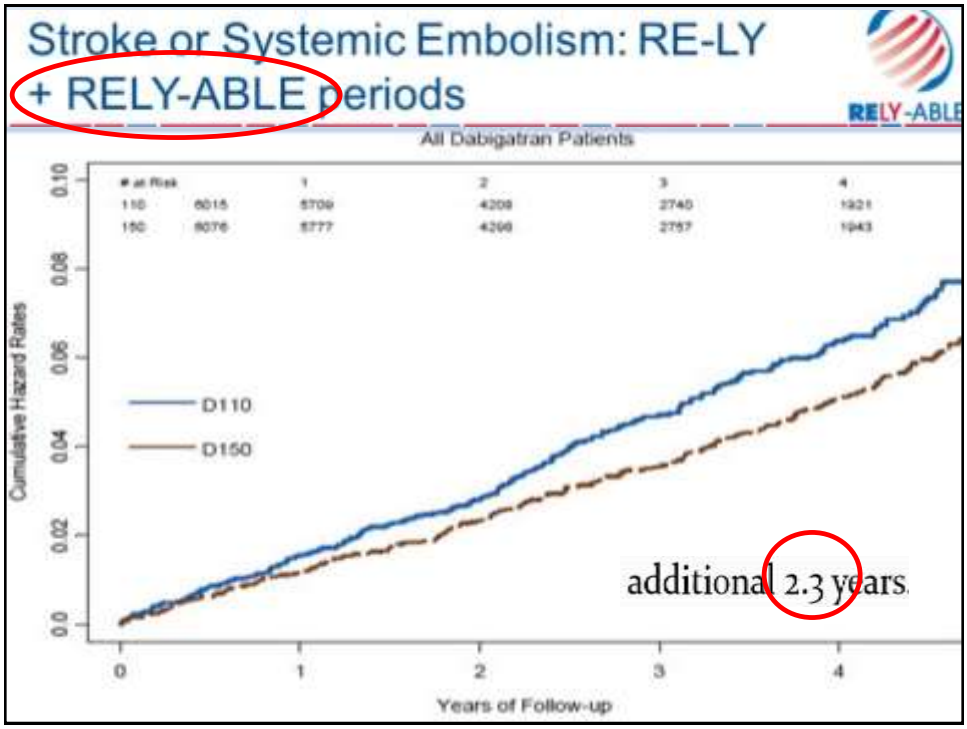
Advantage	Clinical Implications
Rapid onset of action	No need for bridging

	Once daily	No Food Interactions	Predictable response	No routine coagulation monitoring	Fixed dosing	Wide therapeutic window	Adaptable for compliance aids
OPTIMAL[1]	✓	✓	✓	✓	✓	✓	✓
Warfarin[1]	✓						
NOACs	+/-	✓ Taken with food	✓	✓	✓	✓	✓

Rivaroxaban Works as Fast as Enoxaparin[5]

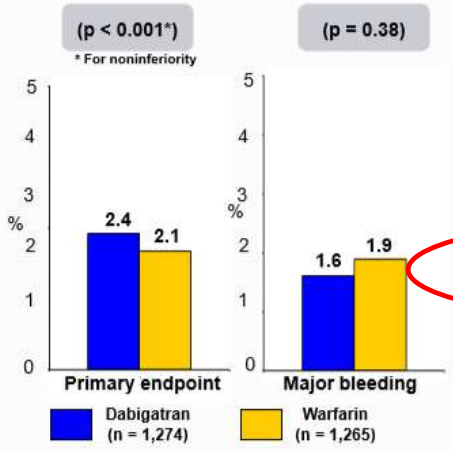



Stroke Prevention in Atrial Fibrillation
Dabigatran etexilate vs warfarin (RE-LY)
2 years
P= 0.003 for Sup
P = 0.31
Non Inf
P<0.001 for Non Inf
p<0.001 Sup
%
4
3
2
1
0
1.5%
1.1%
1.7%
2.7%
3.1%
3.4%
.2%
.3%
.7%
D 110
D 150
warf
Dabiig 110
Dabig 150
Warfarin
P<0.001
P<0.001
Stroke or Syst Emb
Major Bleed
ICH
18,113 patients; Dabigatran BID; CHADS Score: ~1/3rd 0-1, 2, 3-6;
AF = ~1/3rd each w/ persistent; parox; permanent
Connolly et al. NEJM 2009;361:1139


Stroke or Systemic Embolism: RE-LY
+ RELY-ABLE periods
RELY-ABLE
All Dabigatran Patients
Cumulative Hazard Rates
0.10
0.08
0.06
0.04
0.02
0.0
D110
D150
additional 2.3 years
0
1
2
3
4
Years of Follow-up

RE-COVER

Trial design: Evaluated the safety and efficacy of dabigatran 150 mg twice daily (n 1274) vs. warfarin (n 1265) for the treatment of acute VTE. Patients were followed for 6 months.



Results

- Primary outcome (recurrent VTE or death due to VTE): 2.4% vs. 2.1%
- Mortality: 1.6% vs. 1.7% (p > 0.05)
- Major bleeding: 1.6% vs. 1.9%; Major + clinically relevant bleeding: 5.6% vs. 8.8% (p = 0.002)

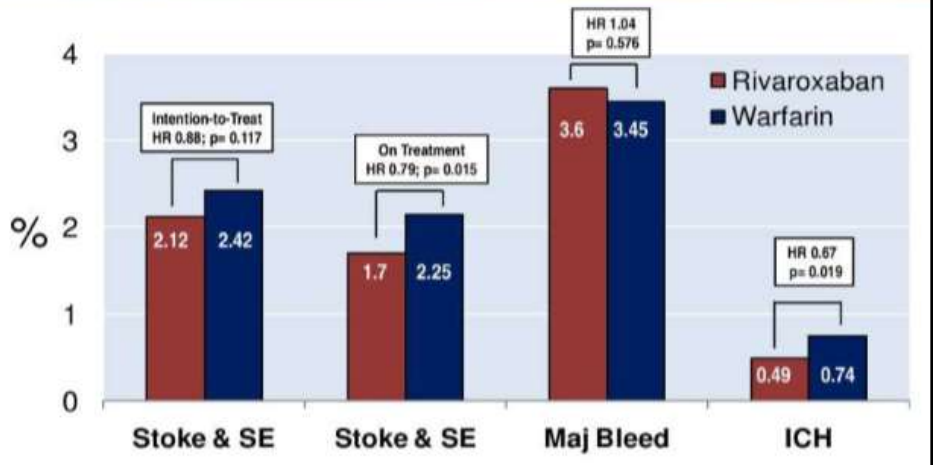
Conclusions

- Dabigatran 150 mg twice daily is noninferior to warfarin for the treatment of acute VTE, with a slightly better bleeding profile
- Complements other studies showing safety and efficacy of dabigatran, as compared with warfarin in other settings, such as AF

Schulman S, et al. N Engl J Med 2009;361:2342-52

Stroke prevention in Atrial Fibrillation

Rivaroxaban vs warfarin (ROCKET AF)



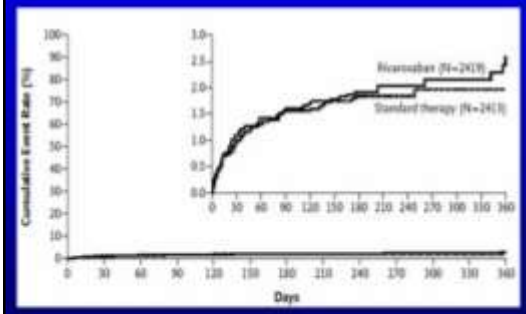
In contrast, ***bleeding from gastrointestinal sites, including upper, lower, and rectal sites, occurred more frequently in the rivaroxaban group****, as did bleeding that led to a drop in the hemoglobin level or bleeding that required transfusion*

Mahaffey et al. AHA , Nov 2010

Rivaroxaban for Pulmonary Embolism

The EINSTEIN-PE trial

Treatment	Recurrent VTE	Bleeding	Major Bleeding
Rivaroxaban	2.1%	10.3%	1.1%
Standard treatment	1.8%	11.4%	2.2%



Conclusion: rivaroxaban as effective as standard treatment for initial *and* extended treatment of pulmonary embolism, may be safer

NEJM 2012; 366: 1287

The NEW ENGLAND JOURNAL of MEDICINE

February 22, 2018
N Engl J Med 2018; 378:699-707

Aspirin or Rivaroxaban for VTE Prophylaxis after Hip or Knee Arthroplasty

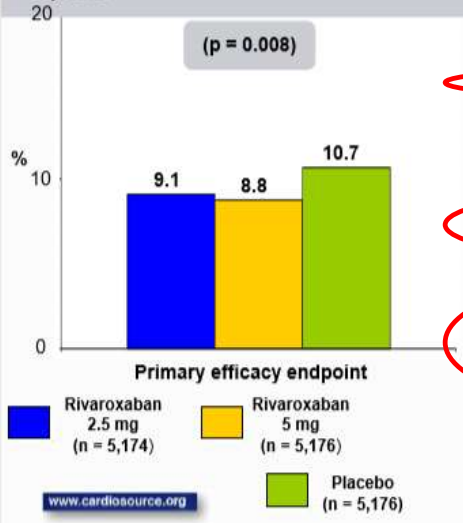
David R. Anderson, M.D., Michael Dunbar, M.D., John Murnaghan, M.D., Susan R. Kahn, M.D., Peter Gross, M.D., Michael Forsythe, M.D., Stephane Pelet, M.D., William Fisher, M.D., Etienne Belzile, M.D., Sean Dolan, M.D., Mark Crowther, M.D., Eric Bohm, M.D., Steven J. MacDonald, M.D., Wade Gofton, M.D., Paul Kim, M.D., David Zukor, M.D., Susan Pleasance, B.Sc.N., Pantelis Andreou, Ph.D., Steve Doucette, M.Sc., Chris Theriault, M.Sc., et al.

CONCLUSIONS

Among patients who received 5 days of rivaroxaban prophylaxis after total hip or total knee arthroplasty, extended prophylaxis with aspirin was not significantly different from rivaroxaban in the prevention of symptomatic

ATLAS ACS 2–TIMI 51

Trial design: Patients with recent ACS(<7 days) were randomized in a 1:1:1 fashion to rivaroxaban 2.5 mg twice daily, 5 mg twice daily, or placebo, in addition to dual antiplatelet therapy (DAPT) with aspirin and a thienopyridine in 93%. Patients were followed for 2 years.



Results

- Primary endpoint: CV death/MI/stroke for rivaroxaban vs. placebo: 8.9% vs.10.7%, p = 0.008. True for 2.5 mg (9.1%) and 5 mg (8.8%) doses individually. Greatest efficacy for ischemic endpoints with the 2.5 mg daily dose, including mortality (2.9% vs. 4.5%, p = 0.002)
- Non-CABG TIMI major bleeding: 2.1% vs. 0.6%, p < 0.001. Similar for 2.5 mg (1.8%) and 5 mg (2.4%)

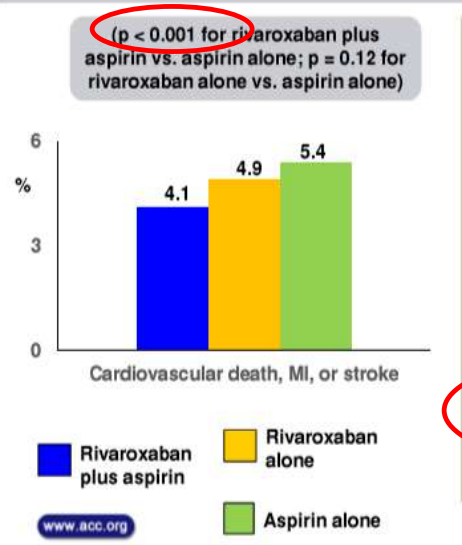
Conclusions

- Addition of very low dose rivaroxaban (2.5 mg twice daily) in patients with a recent ACS (most of whom were on DAPT) ↓ mortality, and ischemic events as compared with placebo. However, bleeding was simultaneously ↑
- First successful large trial with an oral anti-Xa agent in patients with ACS taking antiplatelet agents; use will require assessment of ischemia/bleeding risks

Mega JL, et al. N Engl J Med 2012;366:9-19

COMPASS

Trial design: Patients with stable atherosclerosis were randomized to rivaroxaban 2.5 mg twice daily plus aspirin (n = 9,152) vs. rivaroxaban alone (n = 9,117) vs. aspirin alone (n = 9,126).



Results

- Cardiovascular death, MI, or stroke: 4.1% of the rivaroxaban plus aspirin group vs. 4.9% of the rivaroxaban alone group vs. 5.4% of the aspirin alone group (p < 0.001 for rivaroxaban plus aspirin vs. aspirin alone; p = 0.12 for rivaroxaban alone vs. aspirin alone)

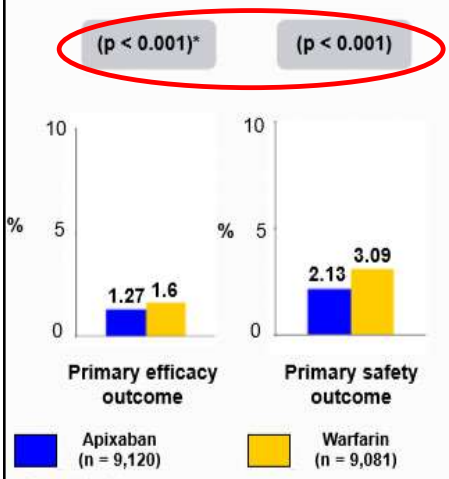
Conclusions

- Among patients with stable atherosclerosis, rivaroxaban plus aspirin was associated with fewer adverse cardiovascular events compared with aspirin alone

Eikelboom JW, et al. N Engl J Med 2017;Aug 27:[Epub]

ARISTOTLE

Trial design: Patients with atrial fibrillation (AF) and at least one additional risk factor for stroke were randomized to either apixaban 5 mg twice daily or dose-adjusted warfarin (titrated to a target INR of 2.0-3.0). Patients were followed for a median of 1.8 years.



Results

- Primary efficacy outcome (stroke/systemic embolism) for apixaban vs. warfarin: 1.27%/year vs. 1.6%/year; $p_{noninferiority} < 0.001$, $p_{superiority} = 0.01$
- All strokes:1.19%/year vs. 1.51%/year, p = 0.01; all-cause mortality: 3.52%/year vs. 3.94%/year, p = 0.047
- Primary safety outcome (ISTH major bleeding): 2.13%/year vs. 3.09%/year, p < 0.001

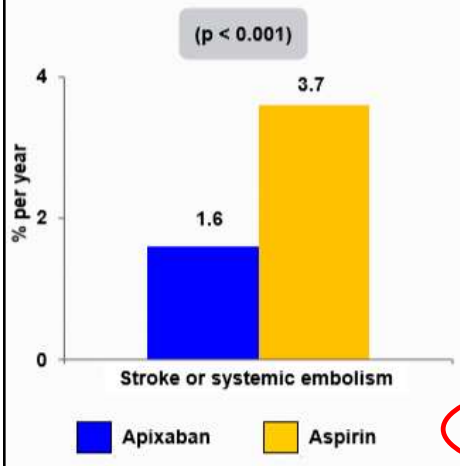
Conclusions

- Landmark trial, demonstrates superiority of apixaban over warfarin in patients with AF for efficacy, with a significant reduction in bleeding

Granger CB, et al. N Engl J Med 2011;365:981-92

AVERROES

Trial design: Patients with atrial fibrillation and elevated risk for stroke who were not suitable for warfarin therapy were randomized to apixaban 5 mg twice daily (n = 2,808) vs. aspirin 81-324 mg daily (n = 2,791).Median follow up was 1 yr



Results

- Stroke or systemic embolism: 1.6%/year with apixaban vs. 3.7%/year with aspirin (p < 0.001)
- Stroke: 1.6%/year vs. 3.4%/year (p < 0.001)
- Clinically relevant nonmajor bleeding: 3.1%/year vs. 2.7%/year (p = 0.35)
- Fatal bleeding: 0.1%/year vs. 0.2%/year (p = 0.53)

Conclusions

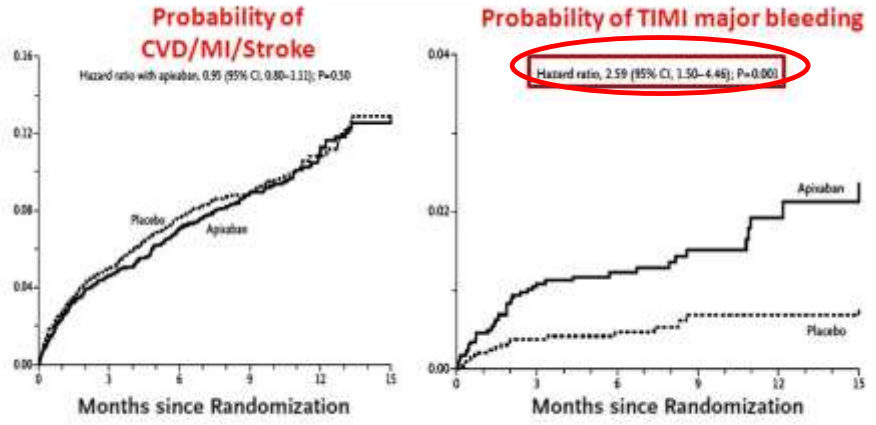
- Among patients with atrial fibrillation and elevated risk for stroke who were not suitable for warfarin therapy, apixaban was beneficial
- Apixaban reduced the risk for the primary outcome of stroke or systemic embolism compared with aspirin, without increasing the risk for major bleeding

Connolly SJ, et al. N Engl J Med 2011;364:806-17

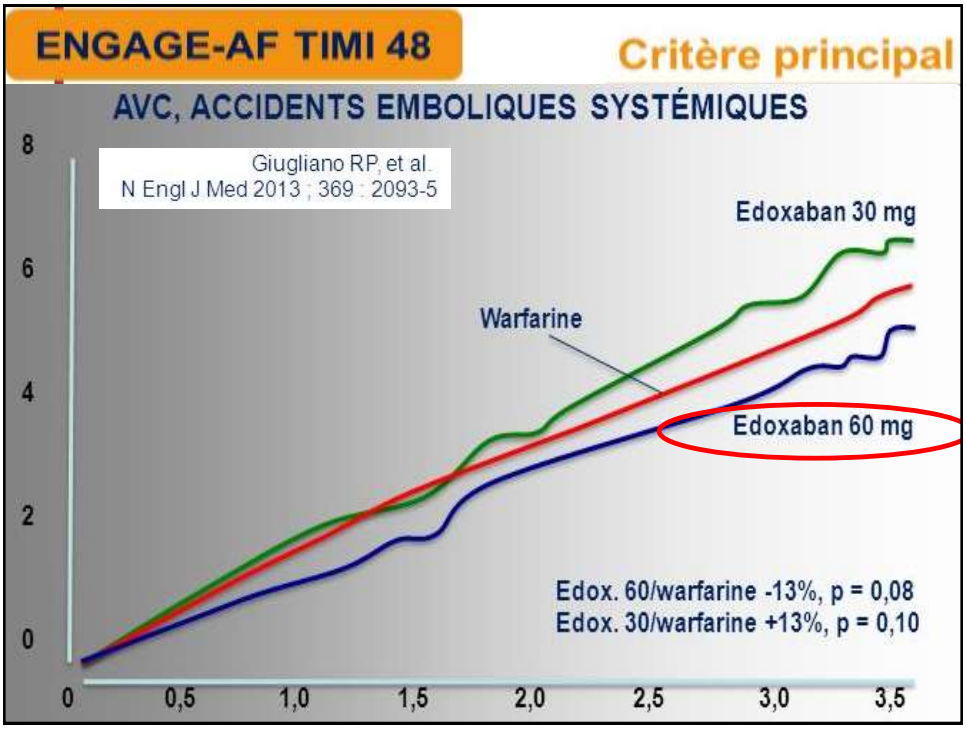
Apixaban with Antiplatelet therapy after Acute Coronary Syndrome (APPRAISE-2)

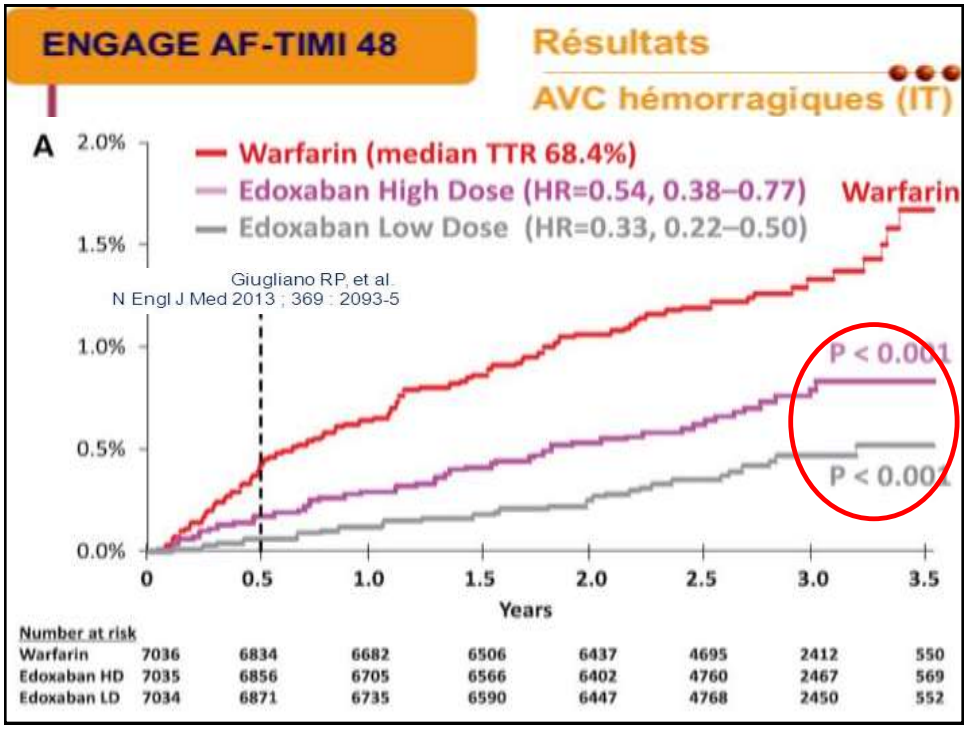
- Randomized, double-blind controlled clinical trial comparing apixaban, at dose of 5 mg twice daily with placebo in addition to standard antiplatelet therapy in pts with a recent ACS and at least 2 additional RF for recurrent ischemic events

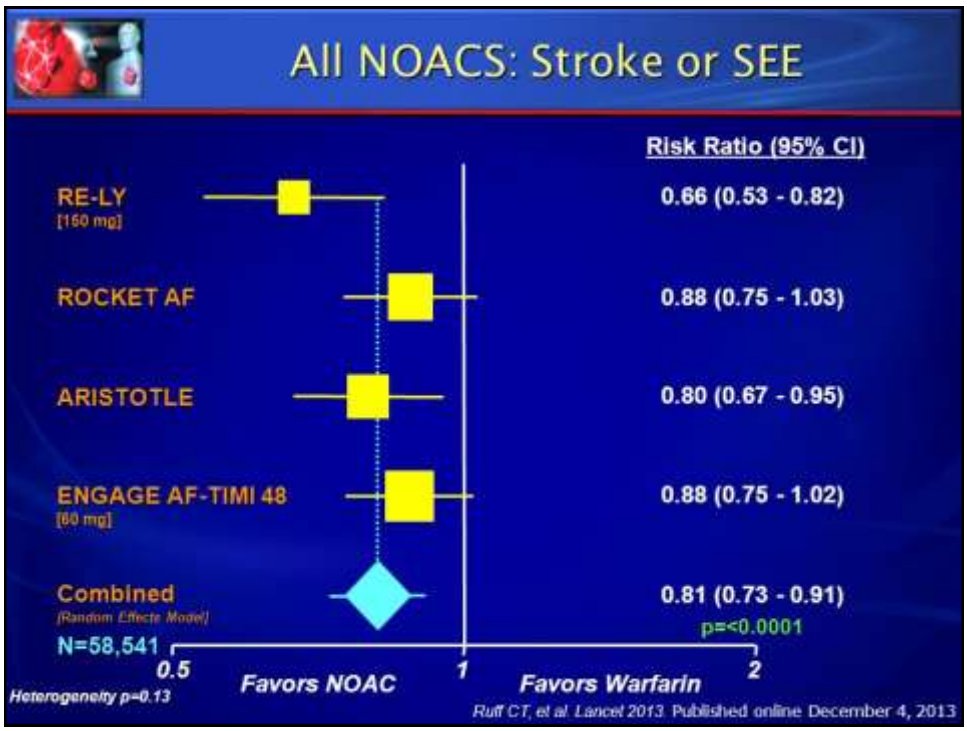
The trial was terminated prematurely after recruitment of 7392 patients because of an increase in major bleeding events with apixaban in the absence of a counterbalancing reduction in recurrent ischemic events. With a median follow-up of 241 days,

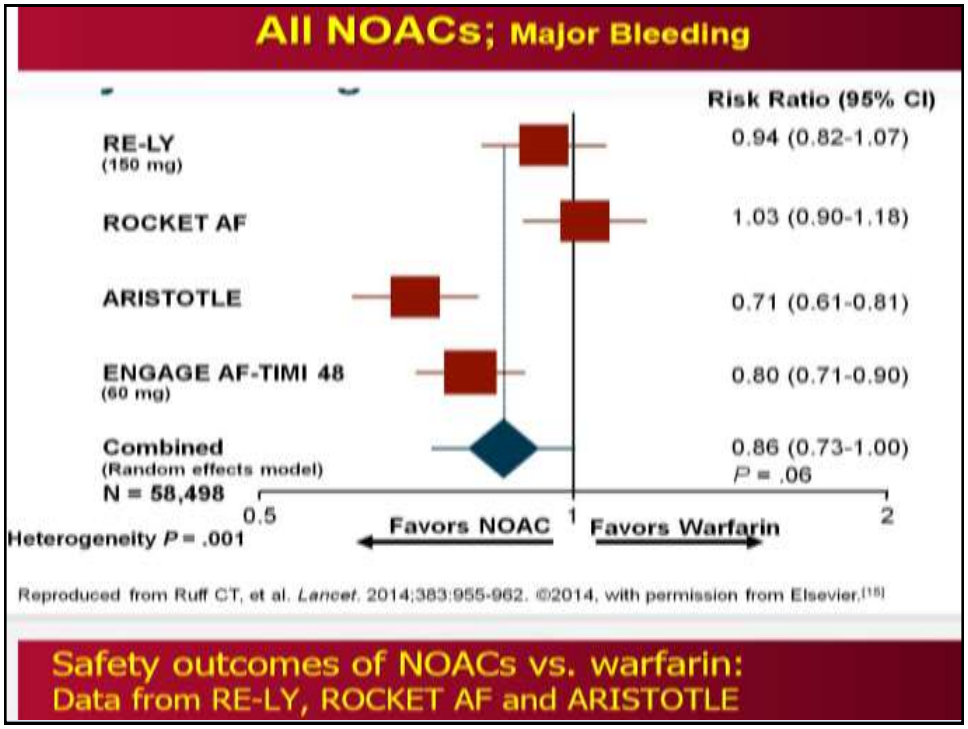


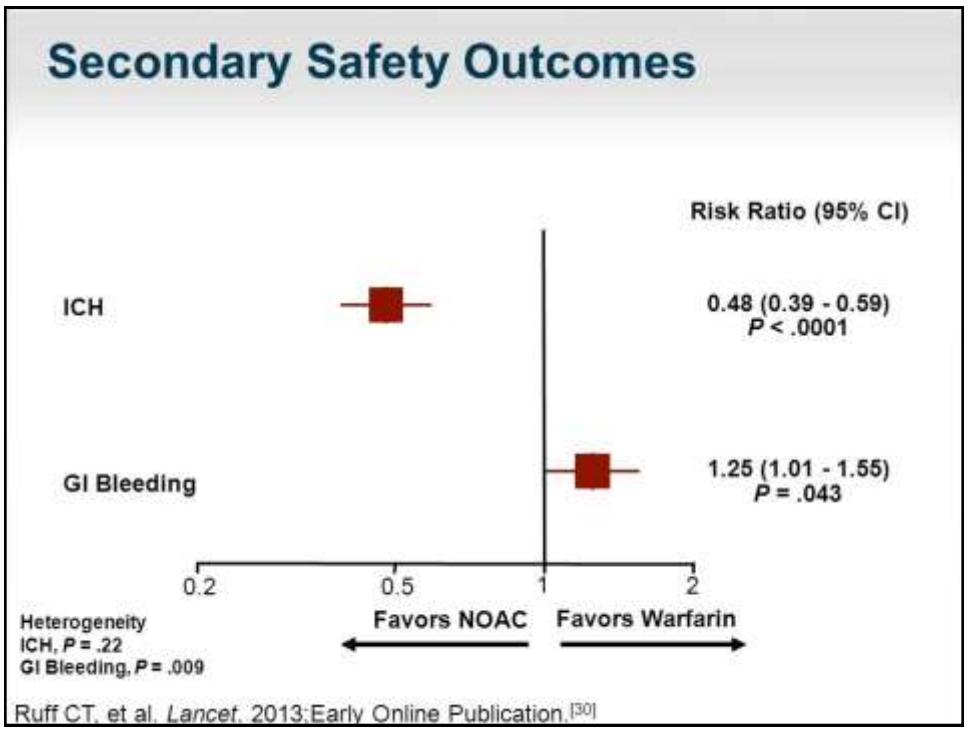
N Engl J Med 2011;365:699-708.




ENGAGE AF-TIMI 48
Résultats
AVC hémorragiques (IT)
A
Warfarin (median TTR 68.4%)
Edoxaban High Dose (HR=0.54, 0.38–0.77)
Edoxaban Low Dose (HR=0.33, 0.22–0.50)
Warfarin
Giugliano RP, et al.
N Engl J Med 2013 ; 369 : 2093-5
P < 0.001
P < 0.001
2.0%
1.5%
1.0%
0.5%
0.0%
0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
Years
Number at risk
Warfarin 7036 6834 6682 6506 6437 4695 2412 550
Edoxaban HD 7035 6856 6705 6566 6402 4760 2467 569
Edoxaban LD 7034 6871 6735 6590 6447 4768 2450 552


All NOACS: Stroke or SEE
Risk Ratio (95% CI)
RE-LY
[150 mg]
0.66 (0.53 - 0.82)
ROCKET AF
0.88 (0.75 - 1.03)
ARISTOTLE
0.80 (0.67 - 0.95)
ENGAGE AF-TIMI 48
[60 mg]
0.88 (0.75 - 1.02)
Combined
(Random Effects Model)
0.81 (0.73 - 0.91)
p=<0.0001
N=58,541
0.5
Favors NOAC
1
Favors Warfarin
2
Heterogeneity p=0.13
Ruff CT, et al. Lancet 2013. Published online December 4, 2013


All NOACs; Major Bleeding
Risk Ratio (95% CI)
RE-LY
(150 mg)
0.94 (0.82-1.07)
ROCKET AF
1.03 (0.90-1.18)
ARISTOTLE
0.71 (0.61-0.81)
ENGAGE AF-TIMI 48
(60 mg)
0.80 (0.71-0.90)
Combined
(Random effects model)
N = 58,498
0.86 (0.73-1.00)
P = .06
0.5
1
2
Favors NOAC
Favors Warfarin
Heterogeneity P = .001
Reproduced from Ruff CT, et al. Lancet. 2014;383:955-962. ©2014, with permission from Elsevier.[15]
Safety outcomes of NOACs vs. warfarin:
Data from RE-LY, ROCKET AF and ARISTOTLE


Secondary Safety Outcomes
Risk Ratio (95% CI)
ICH
0.48 (0.39 - 0.59)
P < .0001
GI Bleeding
1.25 (1.01 - 1.55)
P = .043
0.2
0.5
1
2
Favors NOAC
Favors Warfarin
Heterogeneity
ICH, P = .22
GI Bleeding, P = .009
Ruff CT, et al. Lancet. 2013;Early Online Publication.[30]

JAMA Cardiology | Original Investigation

Direct Oral Anticoagulants in Addition to Antiplatelet Therapy for Secondary Prevention After Acute Coronary Syndromes

A Systematic Review and Meta-analysis

Mauro Chiarito, MD; Davide Cao, MD; Francesco Cannata, MD; Cosmo Godino, MD; Corrado Lodigiani, MD; Giuseppe Ferrante, MD, PhD; Renato D. Lopes, MD, PhD; John H. Alexander, MD; Bernhard Reimers, MD; Gianluigi Condorelli, MD, PhD; Giulio G. Stefanini, MD, PhD

Results *Six trials (14 580 with STEMI and 15 036 with NSTE-ACS). The primary efficacy end point risk was significantly lower with DOAC (P < .001) , pronounced in STEMI (P < .001), no significant with NSTE-ACS (P = .36).*

DOACs associate[illegible] major bleeding (P <.001) .

JAMA Cardiol. doi:10.1001/jamacardio.2017.5306
Published online February 7, 2018.

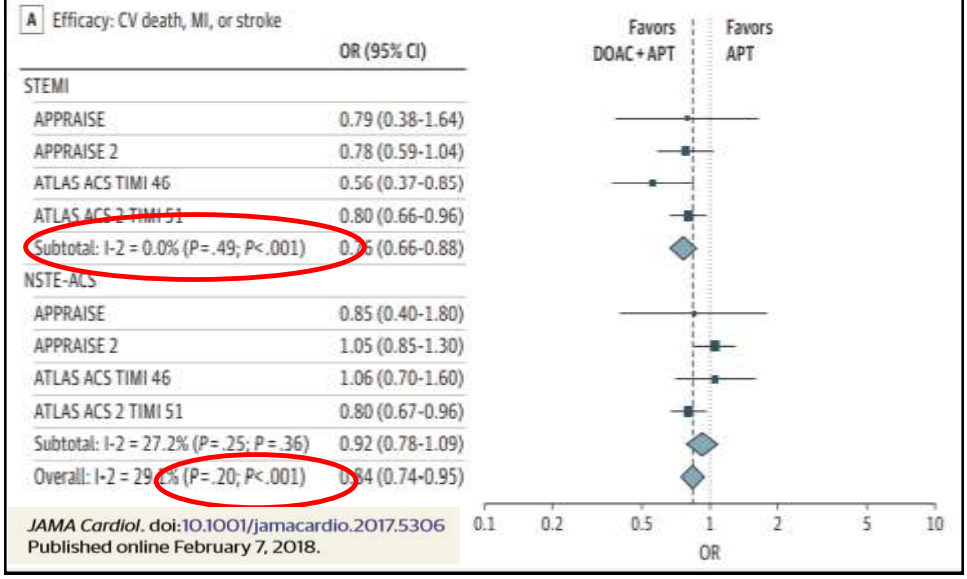
Table 1. Main Features of the Studies Included in the Meta-analysis

Source	Design	Study Population			Anticoagulant Dosages	Follow-up, mo
		Overall	DOAC Group	Control Group		
APPRAISE	RCT (phase II)	1715	1104	611	Apixaban, 2.5 mg BID, 10 mg QD	6
APPRAISE 2	RCT (phase III)	7392	3705	3687	Apixaban, 5 mg BID	8
APPRAISE J	RCT (phase II)	150	99	51	Apixaban, 2.5 mg BID, 10 mg QD	6
ATLAS ACS TIMI 46	RCT (phase II)	3491	2331	1160	Rivaroxaban, 5, 10, 15, and 20 mg QD	6
ATLAS ACS 2 TIMI 51	RCT (phase III)	15 526	10 350	5176	Rivaroxaban, 2.5 and 5 mg BID	13
REDEEM	RCT (phase II)	1861	1490	371	Dabigatran, 50, 75, and 110, 150 mg BID	6

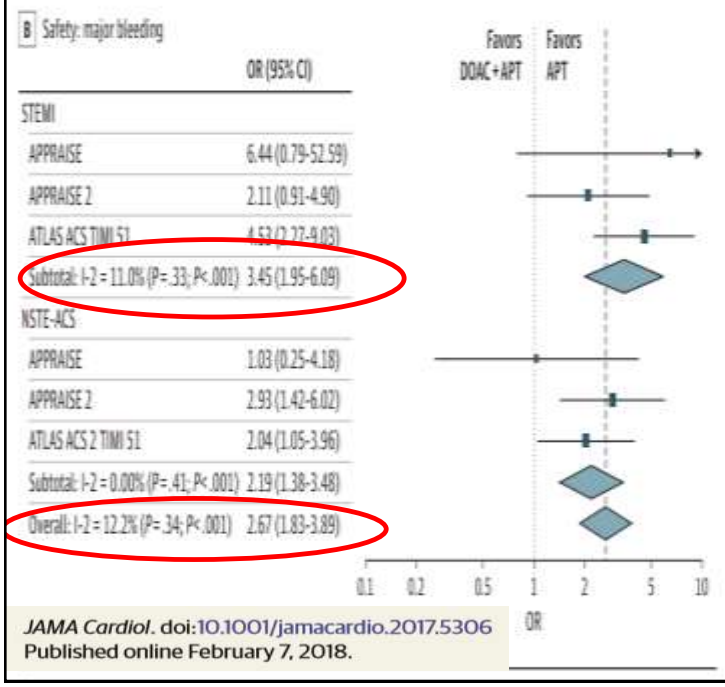
Abbreviations: APPRAISE, Apixaban for Prevention of Acute Ischemic Events; ATLAS ACS TIMI 46, Rivaroxaban versus Placebo in Patients With Acute Coronary Syndromes; BID, twice daily; DOAC, direct oral anticoagulant; QD, once daily; RCT, randomized clinical trial; REDEEM, Dose Finding Study for Dabigatran Etexilate in Patients With Acute Coronary Syndrome.

JAMA Cardiol. doi:10.1001/jamacardio.2017.5306
Published online February 7, 2018.

Figure 2. Risk of the Primary Efficacy End Point and the Primary Safety End Point With Direct Oral Anticoagulant (DOAC) in Addition to Antiplatelet Therapy (APT) as Compared With APT Alone, Overall and Stratified by Acute Coronary Syndrome Type



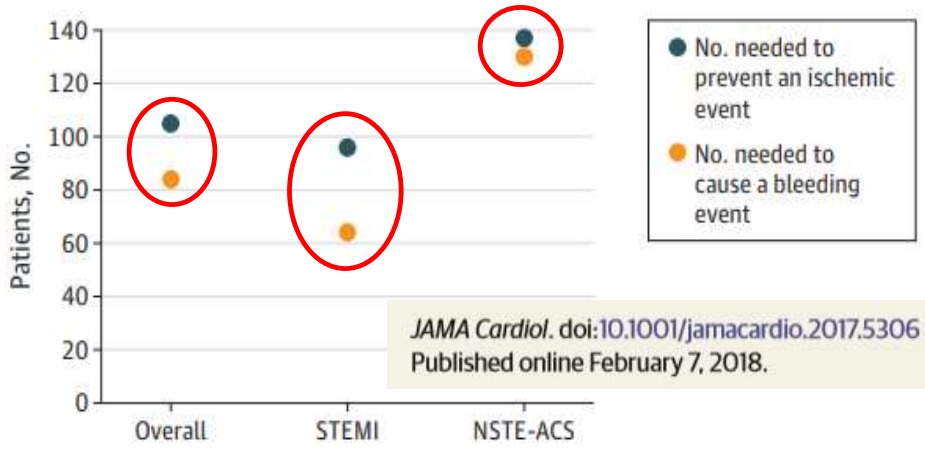
JAMA Cardiol. doi:10.1001/jamacardio.2017.5306
Published online February 7, 2018.



JAMA Cardiol. doi:10.1001/jamacardio.2017.5306
Published online February 7, 2018.

A, Efficacy end point. B, Safety end point. Only studies that reported outcomes stratified for the index event are included. Weights are from a random-effects analysis. APPRAISE indicates Apixaban for Prevention of Acute Ischemic Events; ATLAS ACS TIMI 46, Rivaroxaban versus Placebo in Patients With Acute Coronary Syndromes; CV death, cardiovascular death; MI, myocardial infarction; NSTE-ACS, non–ST-segment elevation myocardial infarction; OR, odds ratio; STEMI, ST-segment elevation myocardial infarction.

Figure 3. Number Needed to Prevent an Ischemic Event and Cause a Bleeding Event



JAMA Cardiol. doi:10.1001/jamacardio.2017.5306
Published online February 7, 2018.

Overall and in patients with ST-segment elevation myocardial infarction (STEMI) and non–ST-segment elevation acute coronary syndromes (NSTE-ACS).

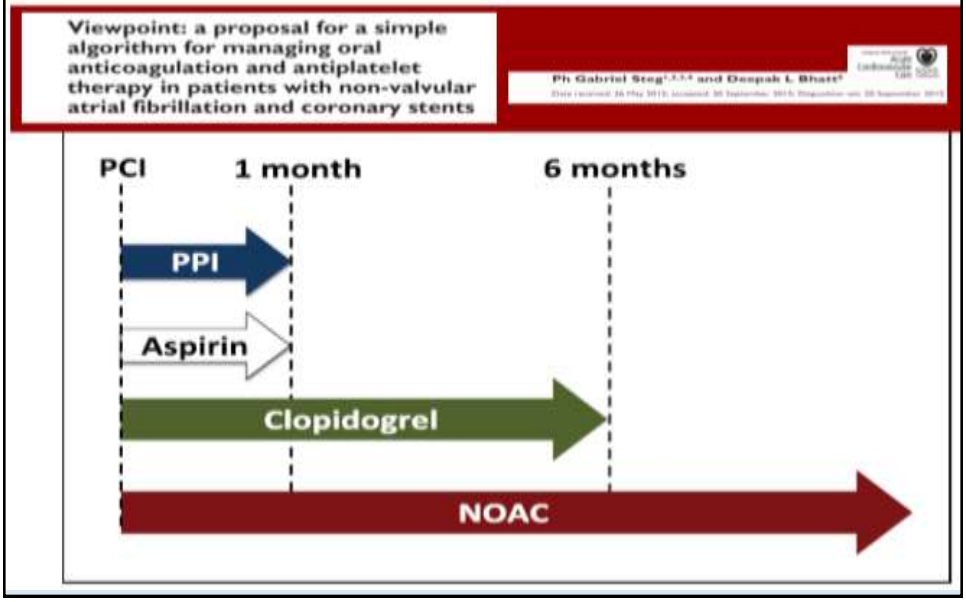
Chiarito M, et al. , . JAMA Cardiol 2018;Feb 7

Conclusions and Relevance ***To their knowledge, these findings are the first evidence to support differential treatment effects of DOAC in addition to APT in ACS . with NSTEI, the risk-benefit profile of DOAC appears unfavorable.***

DOAC in addition to APT might represent an attractive option for patients with STEMI

NOACS in Patient with Atrial Fibrillation & CAD

H. Heidbuchel et al. Updated EHRA practical guide for use of the non-VKA oral anticoagulants. Europace 8/2015



Specific antidotes to NOACs

	Idarucizumab	PER977	Andexanet alpha
Structure	Humanized Fab fragment	Synthetic small molecule	Human rXa variant
Target	Dabigatran	Universal	FXa inhibitors
Binding	Non-competit. High affinity	?	Competitive
Clinical studies	Rapid complete reversal	?	Rapid, near complete reversal

Lauw M, et al. *Can J Cardiol* 2014 (accepted).

Conclusions

NOACs minimize growing burden of thromboembolism (especially AF) and bleeding

Specific antidotes will provide reassurance to physicians .

Low doses are usefule for secondry prevention (in addition to DAPT)especially after STEMI.