Presenter Disclosures

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CAD + AF:
Difficult decisions when two diseases co-exist

Relationships with financial sponsors:

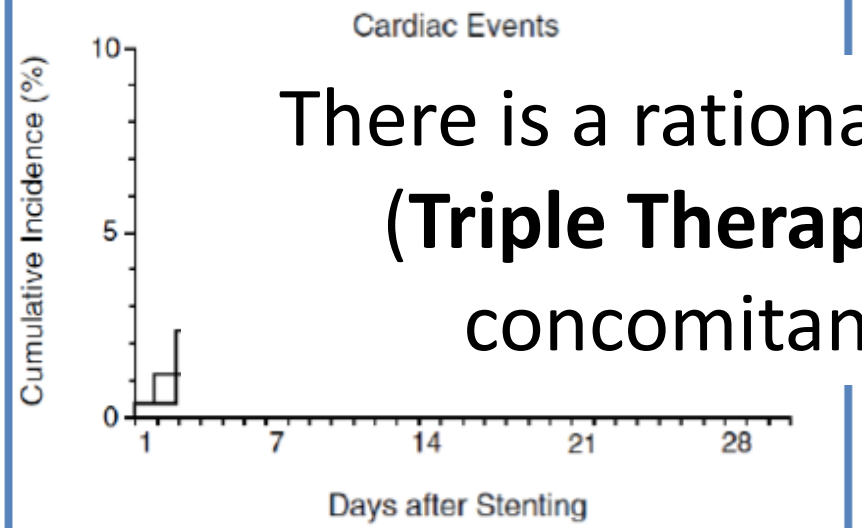
- **Grants/Research Support:** AstraZeneca, Bayer
- **Speakers Bureau/Honoraria:** AstraZeneca, BMS/Pfizer, Servier, Bayer Inc, Abbott vascular, Servier, Boehringer Ingelheim
- **Consulting Fees:** N/A
- **Patents:** N/A
- **Other:** N/A

Agenda

- Review Rationale for Dual Pathway
- Review Randomized Controlled Data Evidence in Support of Dual Pathway
  - PIONEER, REDUAL, AUGUSTUS, ENTRUST

Treatment for PCI and Atrial Fibrillation

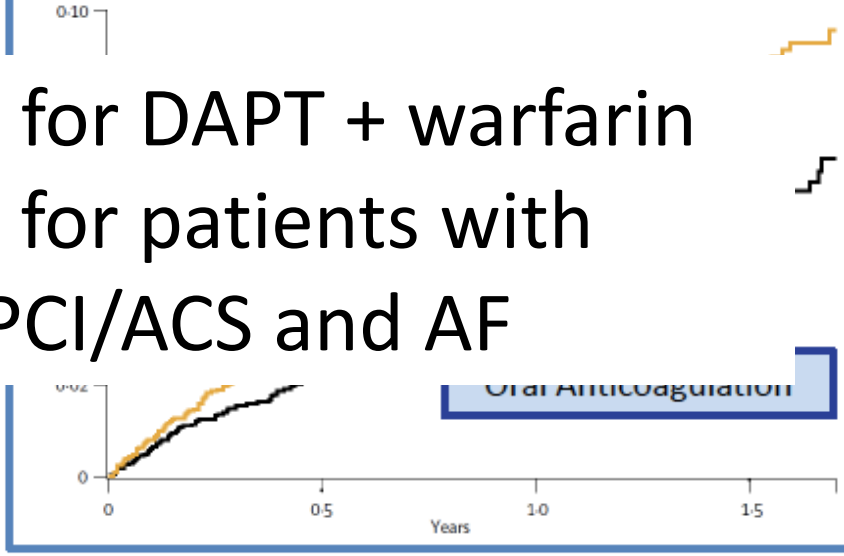
Coronary stent implantation



ISAR, NEJM 1996

+

Atrial fibrillation

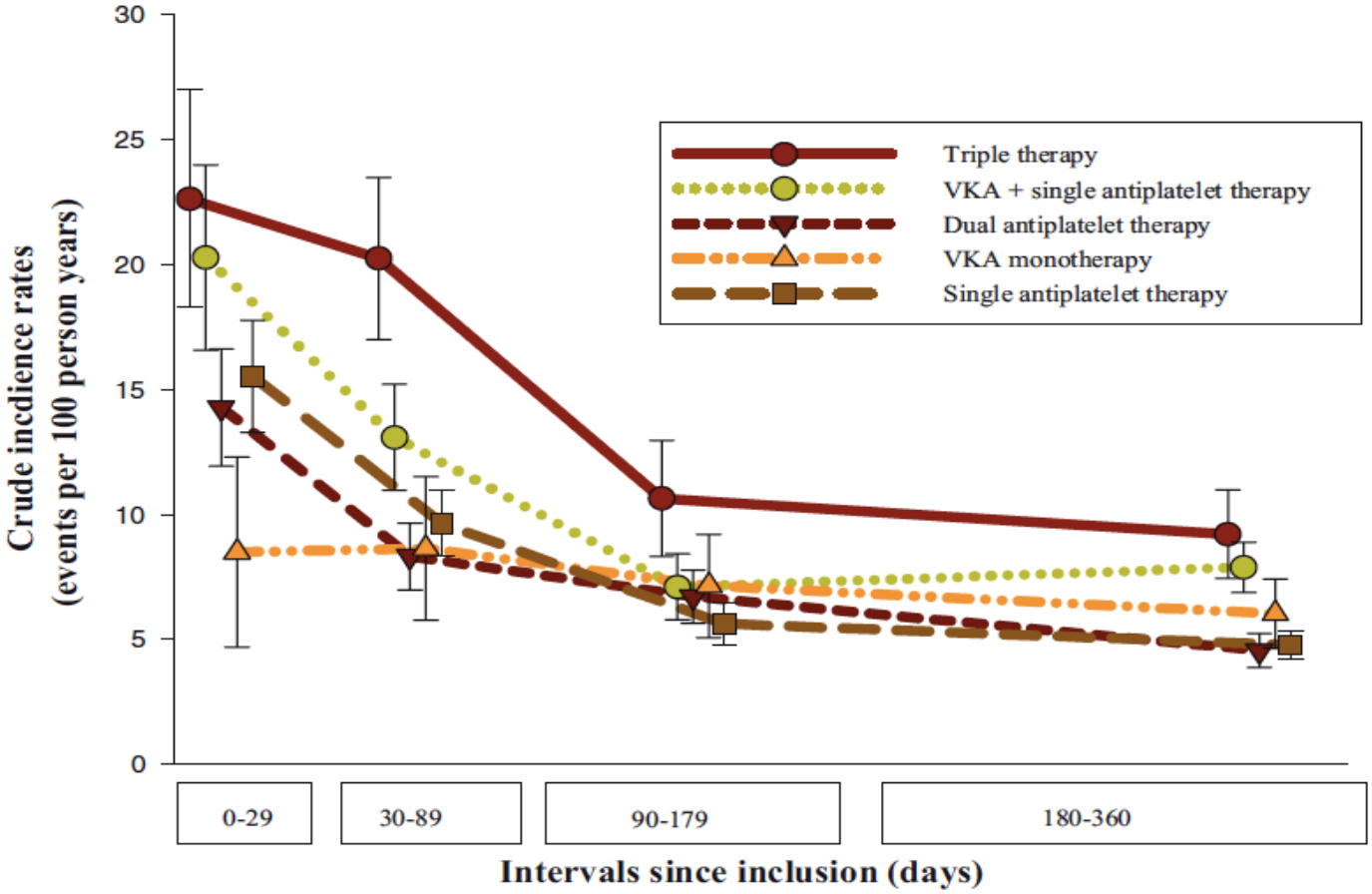


ACTIVE-W Lancet 2006

There is a rationale for DAPT + warfarin (**Triple Therapy**) for patients with concomitant PCI/ACS and AF

- DAPT refers to ASA + ticlopidine
- OAC refers to warfarin
- NOAC's not tested

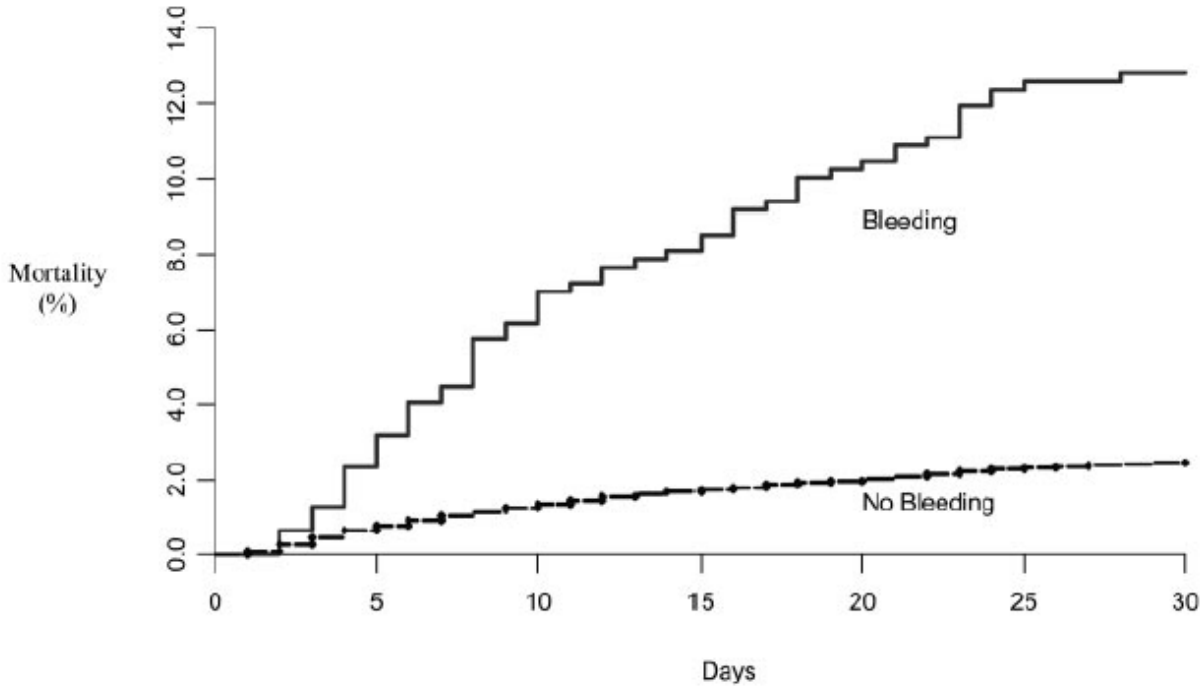
- DAPT refers to ASA + clopidogrel
- OAC refers to warfarin
- Novel ADPri's not tested



Lamberts et al JACC 2013

- Even prior to contemporary trials on dual pathway using DOACs, there was little doubt that <u>triple therapy is associated with greater bleeding than dual pathway</u>

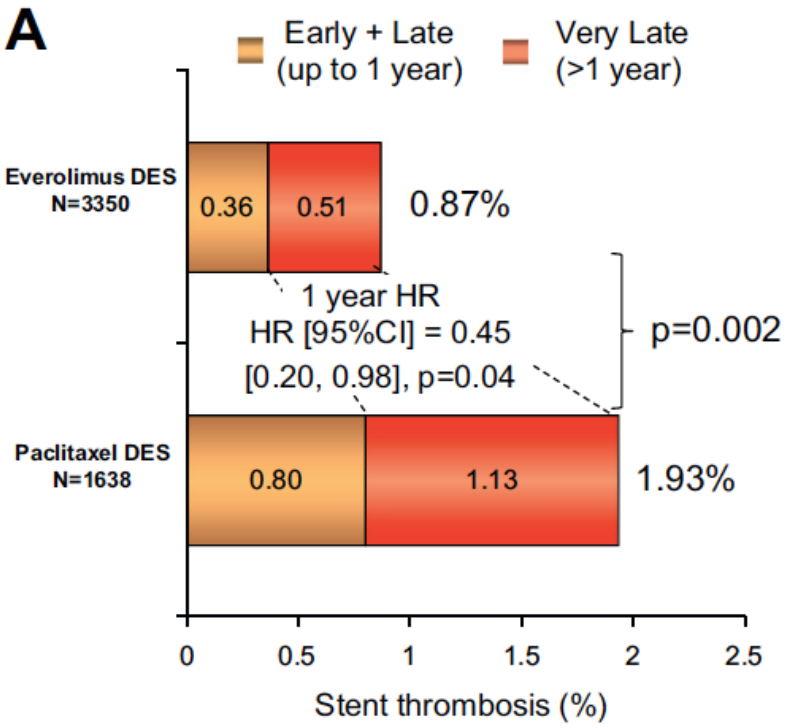
Bleeding is not as benign as previously thought



- Death due to bleeding itself, interruption of antiplatelet/antithrombotic therapy
- Reduction of bleeding worthwhile goal

Eikelboom et al. Circulation 2006

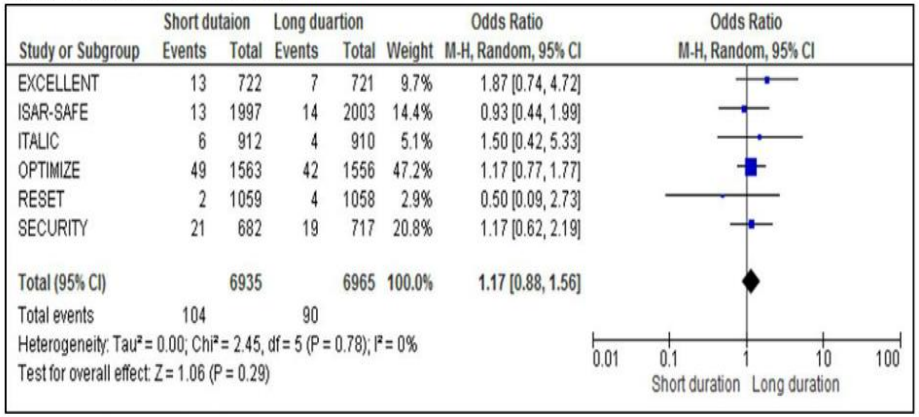
Risk of stent thrombosis significantly lower with current generation drug eluting stents



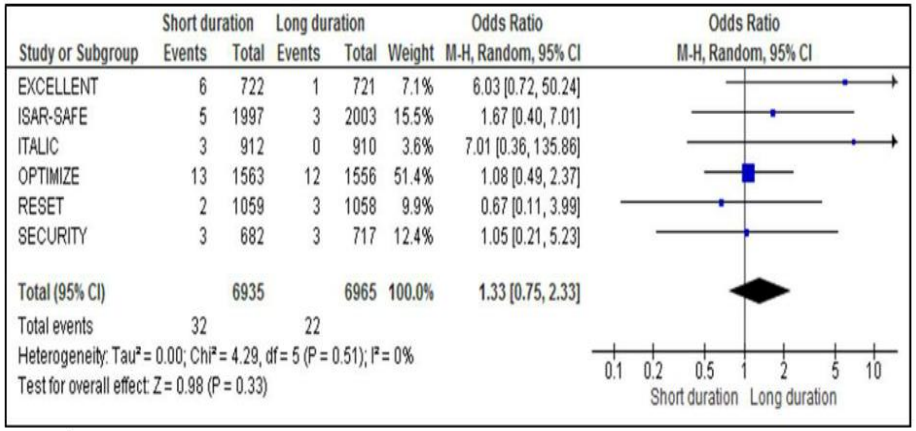
Dangas et al. JACC Int 2013

- Thinner stent struts; thrombus resistant polymer
- Improved vascular healing and endothelialization

Myocardial Infarction

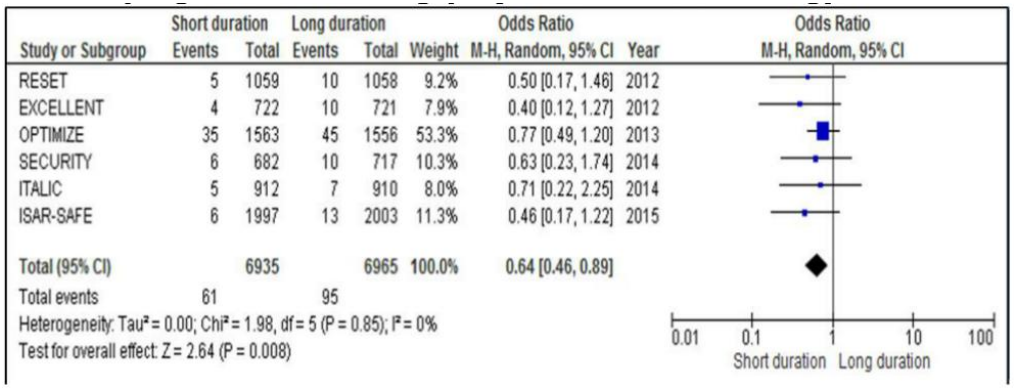


Stent Thrombosis



Duration of DAPT can be safely shortened in stable non-ACS patients undergoing PCI

Clinically significant bleeding



Wassef, Bagai et al. JIC 2016

“Dual Pathway”

- Since risk of stent thrombosis lower with current generation stents, can we stop aspirin early after stenting in patients on anticoagulation?

- Dual pathway: single antiplatelet (clopidogrel) + anticoagulant
  - Early omission of aspirin

Contemporary Trials of Dual Pathway using DOACs vs. Triple Therapy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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.

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*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation

Renato D. Lopes, M.D., Ph.D., Gretchen Heizer, M.S., Ronald Aronson, M.D., Amit N. Vora, M.D., M.P.H., Tyler Massaro, Ph.D., Roxana Mehran, M.D., Shaun G. Goodman, M.D., Stephan Windecker, M.D., Harald Darius, M.D., Jia Li, Ph.D., Oleg Averkov, M.D., Ph.D., M. Cecilia Bahit, M.D., Otavio Berwanger, M.D., Ph.D., Andrzej Budaj, M.D., Ph.D., Ziad Hijazi, M.D., Ph.D., Alexander Parkhomenko, M.D., Ph.D., Peter Sinnaeve, M.D., Ph.D., Robert F. Storey, M.D., Holger Thiele, M.D., Dragos Vinereanu, M.D., Ph.D., Christopher B. Granger, M.D., and John H. Alexander, M.D., M.H.S., for the AUGUSTUS Investigators*

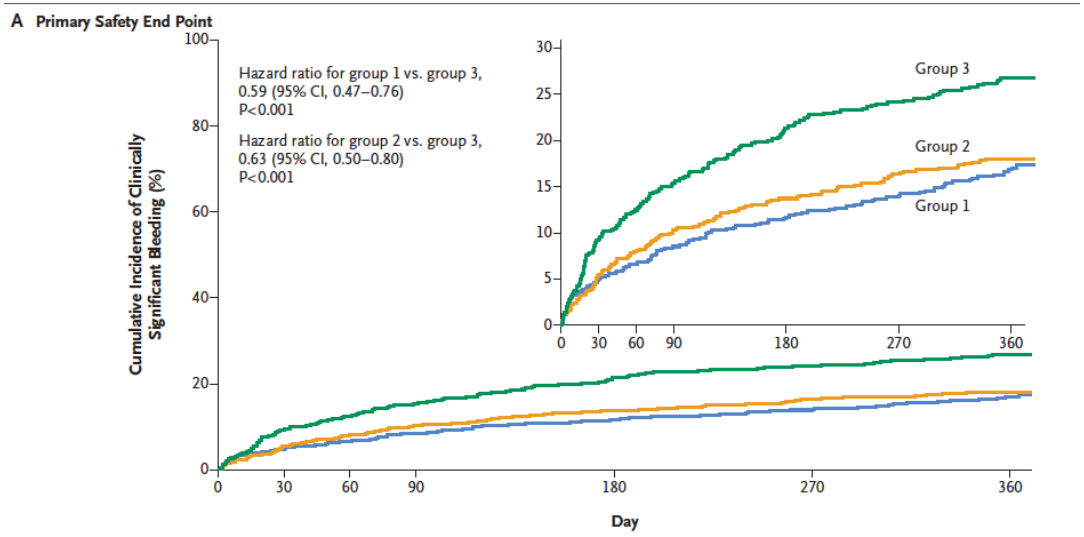
Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial

Pascal Vranckx, Marco Valgimigli, Lars Eckardt, Jan Tijssen, Thorsten Lewalter, Giuseppe Gargiulo, Valerii Batushkin, Gianluca Campo, Zoreslava Lysak, Igor Vakaliuk, Krzysztof Milewski, Petra Laeis, Paul-Egbert Reimitz, Rüdiger Smolnik, Wolfgang Zierhut, Andreas Goette

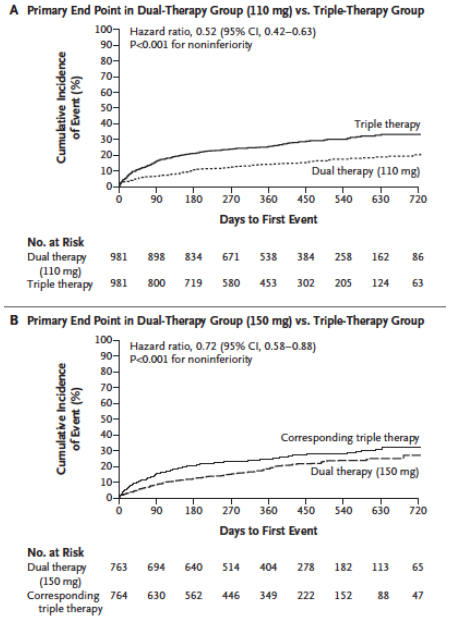
Study Characteristics

	PIONEER	REDUAL	AUGUSTUS	ENTRUST
n	2100	2725	4614	1506
DOAC	Rivaroxaban 15mg (*X% 10mg)	Dabigatran 110mg & 150mg	Apixaban 5mg (10% 2.5mg)	Edoxaban 60mg (20% 30mg)
Clopidogrel	95%	88%	93%	92%
Comparison	Vit K TT	Vit K TT	TT (Vit K + apixaban)	Vit K TT
ACS	50%	50%	61%	52%
Time to randomization after PCI/ACS	Within 72h	Within 120h	Median 6 days	Median 45h

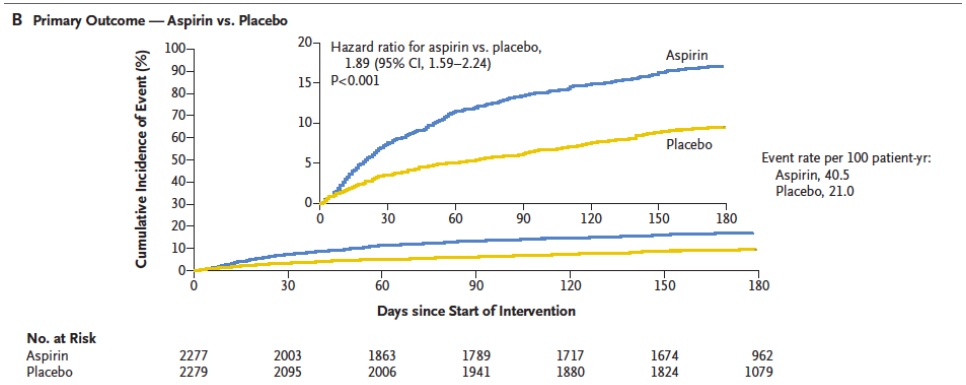
Contemporary trials confirm lower clinically relevant bleeding with Dual Pathway using DOACs vs. Triple therapy



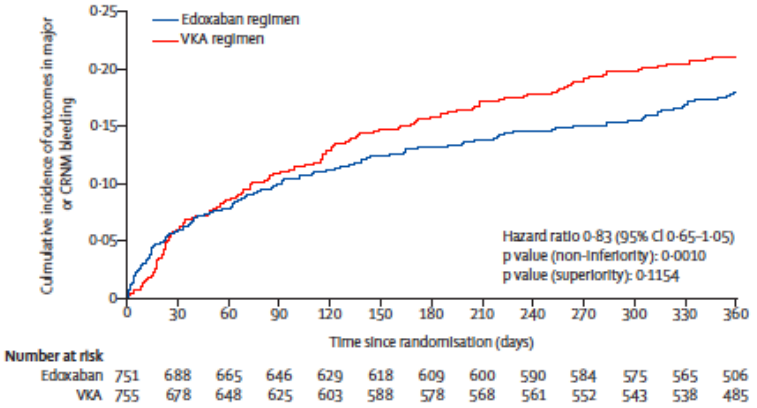
PIONEER (Rivaroxaban)



REDUAL (Dabigatran)

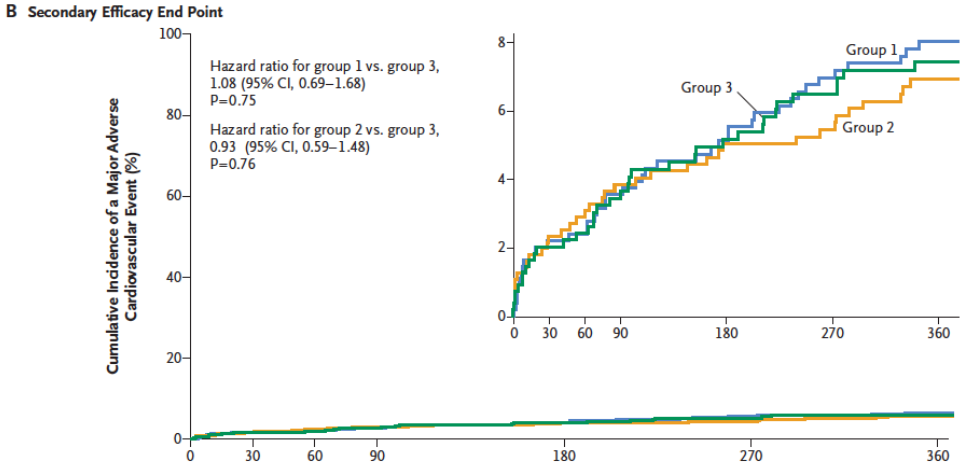


AUGUSTUS (Apixaban)

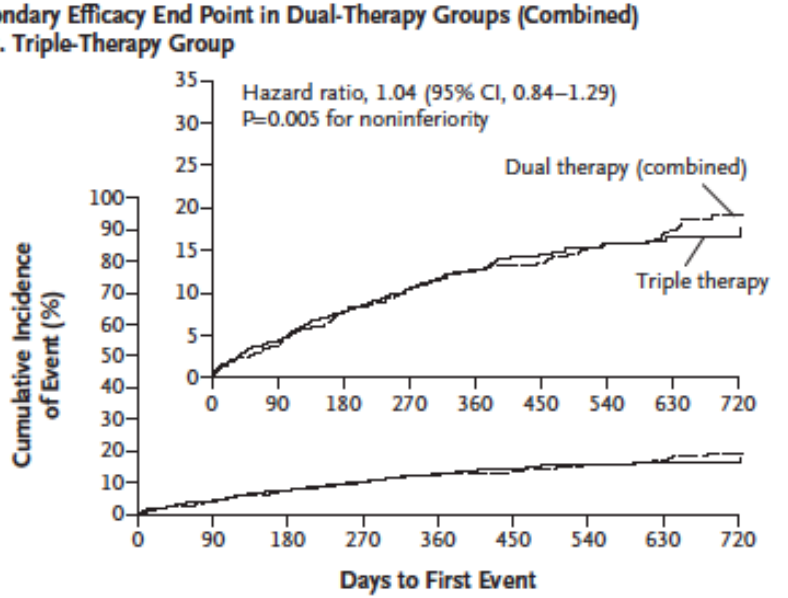


ENTRUST (Edoxaban)

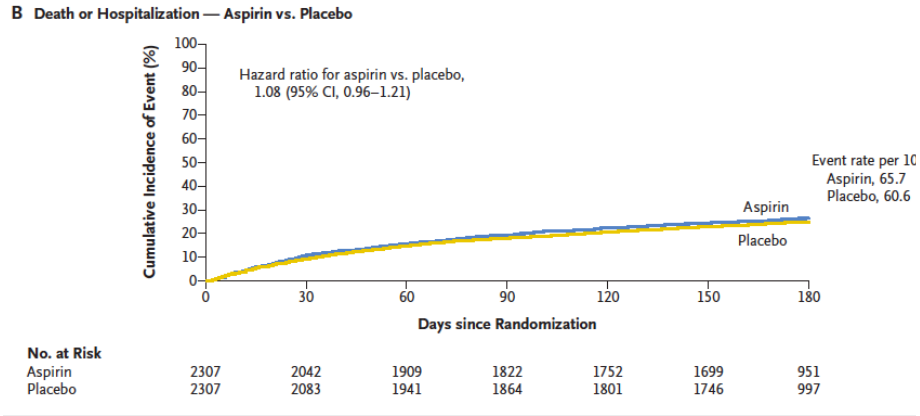
No increase in overall composite ischemic endpoints with Dual Pathway using DOACs vs. Triple Therapy



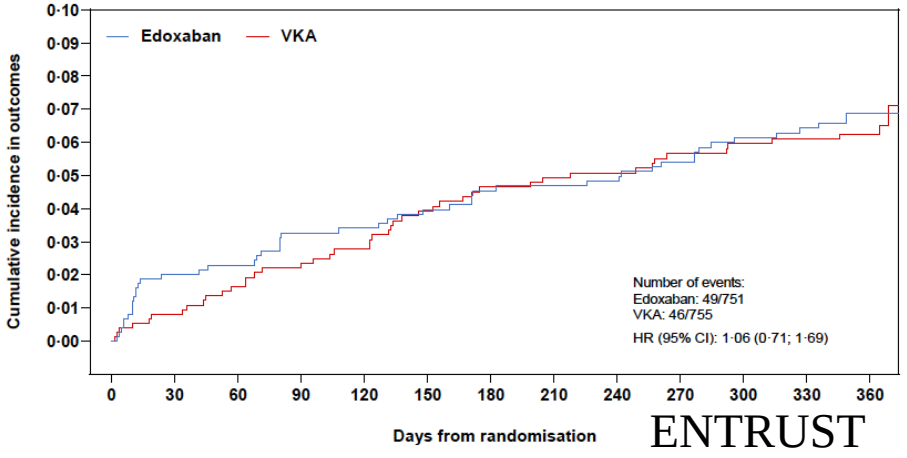
PIONEER



REDUAL



AUGUSTUS



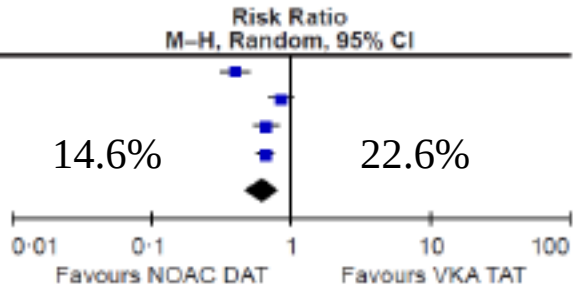
ENTRUST

Lower bleeding with Dual Pathway using DOACs vs. Triple therapy without increase in Ischemic Events

ISTH Major or Clinically Relevant Non-Major Bleeding

Study or Subgroup	NOAC DAT Events	Total	VKA TAT Events	Total	Weight	Risk Ratio M–H, Random, 95% CI
AUGUSTUS	84	1143	210	1123	23·7%	0·39 (0·31, 0·50)
ENTRUST AF-PCI	128	751	152	755	24·7%	0·85 (0·68, 1·05)
PIONEER AF-PCI	117	696	178	697	24·8%	0·66 (0·53, 0·81)
RE-DUAL PCI	305	1744	264	981	26·8%	0·65 (0·56, 0·75)
Total (95% CI)		**4334**		**3556**	**100·0%**	**0·62 (0·47, 0·81)**
Total events	634		804			

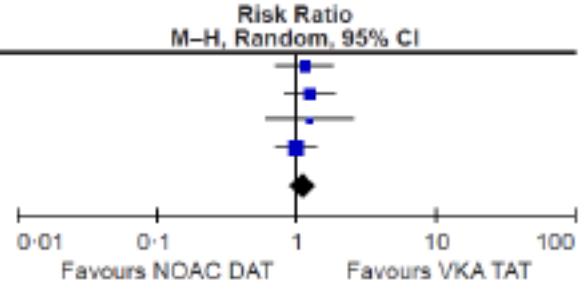
Heterogeneity: Tau² = 0·07; Chi² = 22·84, df = 3 (P <0·0001); I² = 87%
Test for overall effect: Z = 3·47 (P = 0·0005)



All-Cause Death

Study or Subgroup	NOAC DAT Events	Total	VKA TAT Events	Total	Weight	Risk Ratio M–H, Random, 95% CI
AUGUSTUS	39	1153	34	1154	23·4%	1·15 (0·73, 1·81)
ENTRUST AF-PCI	46	751	37	755	27·1%	1·25 (0·82, 1·90)
PIONEER AF-PCI	16	694	13	695	9·2%	1·23 (0·60, 2·54)
RE-DUAL PCI	85	1744	48	981	40·3%	1·00 (0·71, 1·41)
Total (95% CI)		**4342**		**3585**	**100·0%**	**1·12 (0·90, 1·39)**
Total events	186		132			

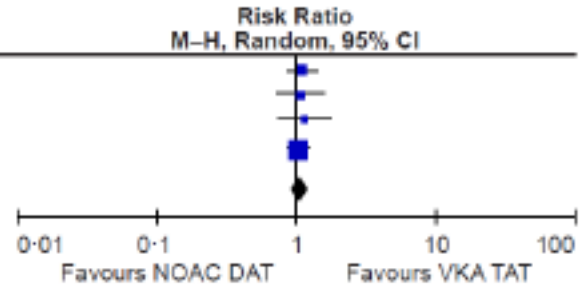
Heterogeneity: Tau² = 0·00; Chi² = 0·78, df = 3 (P = 0·85); I² = 0%
Test for overall effect: Z = 0·99 (P = 0·32)



Major Adverse Cardiovascular Events as Defined by Trials

Study or Subgroup	NOAC DAT Events	Total	VKA TAT Events	Total	Weight	Risk Ratio M–H, Random, 95% CI
AUGUSTUS	72	1153	66	1154	20·3%	1·09 (0·79, 1·51)
ENTRUST AF-PCI	49	751	46	755	14·1%	1·07 (0·73, 1·58)
PIONEER AF-PCI	41	694	36	695	11·3%	1·14 (0·74, 1·76)
RE-DUAL PCI	239	1744	131	981	54·3%	1·03 (0·84, 1·25)
Total (95% CI)		**4342**		**3585**	**100·0%**	**1·06 (0·91, 1·22)**
Total events	401		279			

Heterogeneity: Tau² = 0·00; Chi² = 0·25, df = 3 (P = 0·97); I² = 0%
Test for overall effect: Z = 0·76 (P = 0·45)



Vranckx et al. Lancet 2019

Adverse signal towards greater stent thrombosis with Dual Pathway

Event	Dabi 110 mg BID	Warfarin	HR (95% CI)	P Value
MI	44 (4.5)	29 (3.0)	1.51 (0.94–2.41)	0.09
Stent thrombosis	15 (1.5)	8 (0.8)	1.86 (0.79–4.40)	0.15

REDUAL

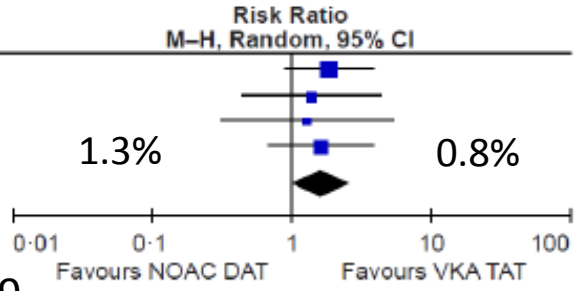
AUGUSTUS

Endpoint	Aspirin (N=2307)	Placebo (N=2307)	HR (95% CI)
Death / Ischemic Events (%)	**6.5**	**7.3**	0.89 (0.71–1.11)
Myocardial Infarction (%)	**2.9**	**3.6**	0.81 (0.59–1.12)
Definite or Probable Stent Thrombosis (%)	**0.5**	**0.9**	0.52 (0.25–1.08)

Stent Thrombosis

Study or Subgroup	NOAC DAT Events	Total	VKA TAT Events	Total	Weight	Risk Ratio M–H, Random, 95% CI
AUGUSTUS	21	1153	12	1154	40·0%	1·75 (0·87, 3·54)
ENTRUST AF-PCI	8	751	6	755	17·9%	1·34 (0·47, 3·84)
PIONEER AF-PCI	5	694	4	695	11·6%	1·25 (0·34, 4·64)
RE-DUAL PCI	22	1744	8	981	30·6%	1·55 (0·69, 3·46)
Total (95% CI)		**4342**		**3585**	**100·0%**	**1·55 (0·99, 2·41)**
Total events	56		30			

Heterogeneity: Tau² = 0·00; Chi² = 0·29, df = 3 (P = 0·96); I² = 0%
Test for overall effect: Z = 1·92 (P = 0·06)



Vranckx et al. Lancet 2019

Implications for ASA

- Highest risk period for stent thrombosis early within 1-2 weeks after PCI
- Clopidogrel the $P2Y_{12}$ inhibitor in 93%
  - Some uncertainty regarding its response variability and efficacy, particularly without aspirin
- Clinical decision making should be based on a balanced assessment of competing coronary ischemic and bleeding risk
- High risk of bleeding and low risk of thrombotic events → early omission of aspirin (within 1-2 weeks)
- Complex, multivessel PCI or high-risk ACS → greater duration of aspirin (2-4 weeks)

Implications for Anticoagulant

- Numerically lower bleeding with use of Dual Pathway irrespective of DOAC

- Dose adjustment based on individual drug dose reduction criteria
  - Rivaroxaban 15mg instead of 20mg

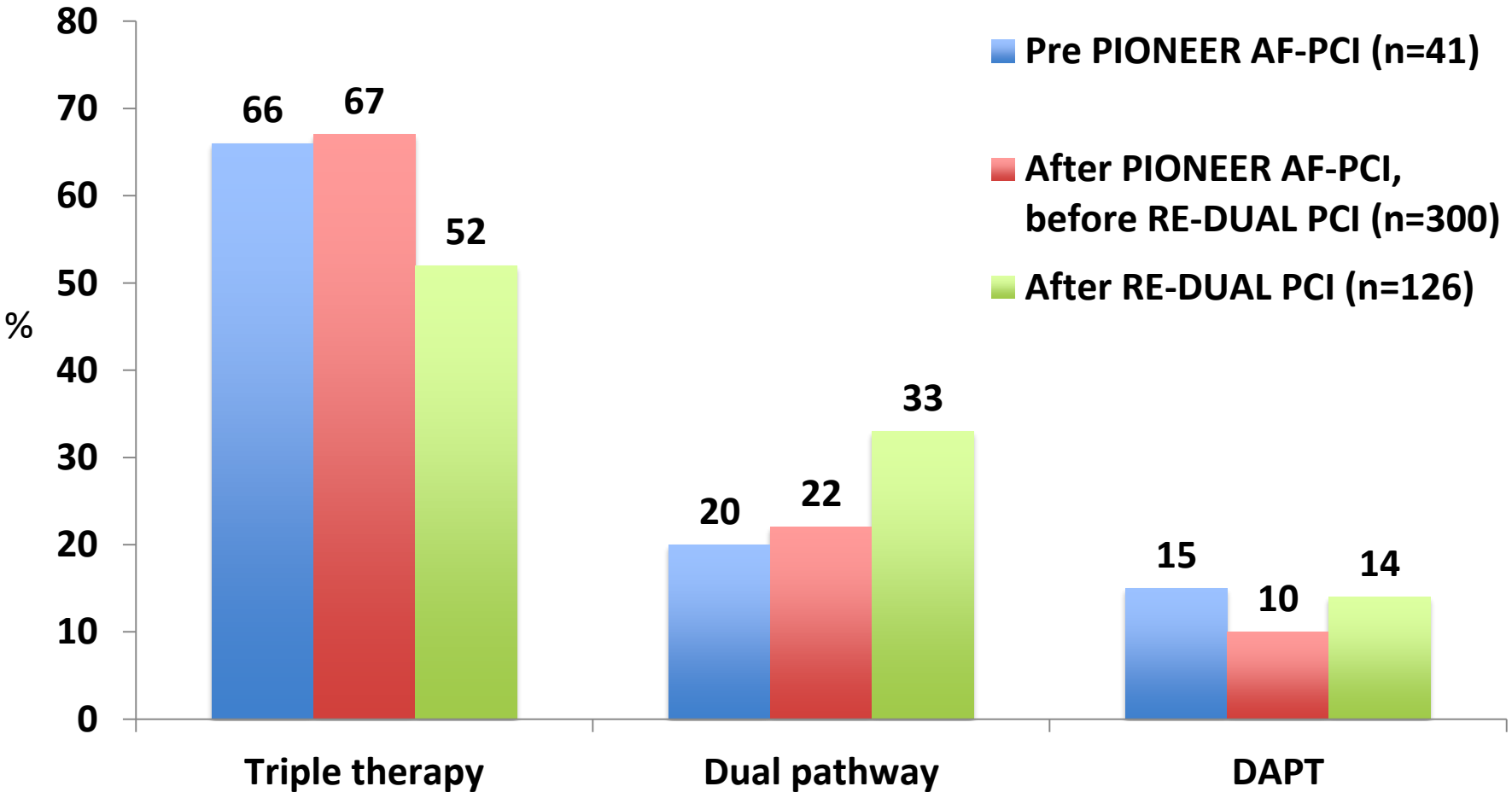
2018 CCS/CAIC Update APT Guidelines

AF and elective PCI without high-risk features

Age < 65 **and** CHADS2 = 0	Age ≥ 65 **or** CHADS2 ≥ 1
Strong recommendation	Strong recommendation
ASA + Clopidogrel up to 12 months • For BMS: at least 1 month • For DES: at least 3 months	**OAC + Clopidogrel up to 12 months** • For BMS: at least 1 month • For DES at least 3 months
Strong recommendation	Strong recommendation
For extended treatment: • ASA alone • Add $P2Y_{12}$ inhibitor if high thrombotic risk features develop, low bleed risk	**For extended treatment:** • OAC alone • Add $P2Y_{12}$ inhibitor or ASA if high thrombotic risk features develop, low bleed risk

2018 CCS/CAIC Focused Update of the Guidelines for the Use of Antiplatelet Therapy

CONNECT AF+PCI study



Bagai, Goodman et al. CCS 2018

Management of Patients with Atrial Fibrillation Undergoing PCI

- Evidence supports use of ”Dual Pathway”
- Regimens WILL differ between patients (science + art)
- Duration of Triple therapy individualized based upon ischemic, stroke and bleeding risk
- Reach out to interventional cardiologist if any questions/concerns

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