Baptist Health
HEART INSTITUTE

Cardiac Pharmacology

Session 1

Thomas D. Conley, MD FACC FSCAI

Disclosures: None

What's new in Cardiac Pharmacology?

- Coronary Disease
  - P2Y12 Antiplatelet therapy
    - Trials comparing P2Y12 Inhibitors after PCI
    - DAPT vs. Monotherapy after PCI
    - DAPT in Diabetics with Stable CAD
    - Antithrombotic/Antiplatelet therapy in A Fib with ACS/PCI
  - OAC in Stable Ischemic Heart Disease
- Anticoagulants with CKD
- Anti-inflammatory agents in AMI
- Lipid therapy
  - Positive and Negative Trial results
- Neprilysin inhibition in HFpEF

Antiplatelet therapy after AMI

- Randomized trials have shown both prasugrel and ticagrelor are superior to clopidogrel in patients with Acute Coronary Syndromes (reduced risk of CVD/MI/CVA)
  - TRITON-TIMI 38 Trial: prasugrel > clopidogrel
  - PLATO Trial: ticagrelor > clopidogrel
- Therefore, in patients with ACS in whom an invasive evaluation is planned, either ticagrelor or prasugrel is preferred over clopidogrel (Grade 1A - a strong recommendation based on high-quality evidence)
- However, the relative merits of ticagrelor vs. prasugrel in patients with ACS in whom an invasive evaluation is planned are uncertain…

ISAR-REACT Trial

Intracoronary **S**tenting and **A**ntithrombotic **R**egimen: **R**apid **E**arly **A**ction for **C**oronary **T**reatment

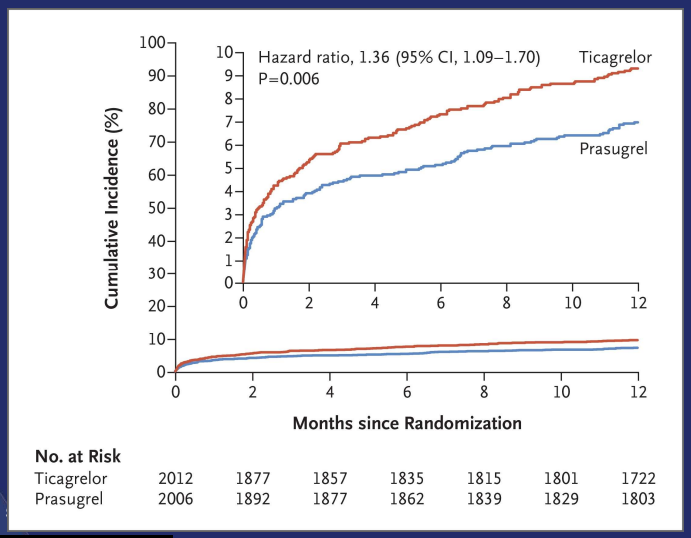
- Multicenter, randomized, open-label trial
- ACS (STEMI, NSTEMI or USA) with planned invasive strategy
- Ticagrelor vs. Prasugrel
- 1^0 End point: Composite of death, MI, or CVA at 1 year
- 2^0 End point: major bleeding (BARC type 3,4 or 5)

Bleeding Academic Research Consortium (BARC) Bleeding Scale

Type 0	No bleeding
Type 1	Bleeding that is not actionable and does not cause the patient to seek treatment
Type 2	Any clinically overt sign of hemorrhage that "is actionable" and requires diagnostic studies, hospitalization, or treatment by a health care professional
Type 3	a. Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL (provided hemoglobin drop is related to bleed); transfusion with overt bleeding b. Overt bleeding plus hemoglobin drop < 5 g/dL (provided hemoglobin drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control; bleeding requiring IV vasoactive agents c. Intracranial hemorrhage confirmed by autopsy, imaging, or lumbar puncture; intraocular bleed compromising vision
Type 4	CABG-related bleeding within 48 hours
Type 5	a. Probable fatal bleeding b. Definite fatal bleeding (overt or autopsy or imaging confirmation)

ISAR-REACT Trial

Primary End Point: Death/MI/CVA



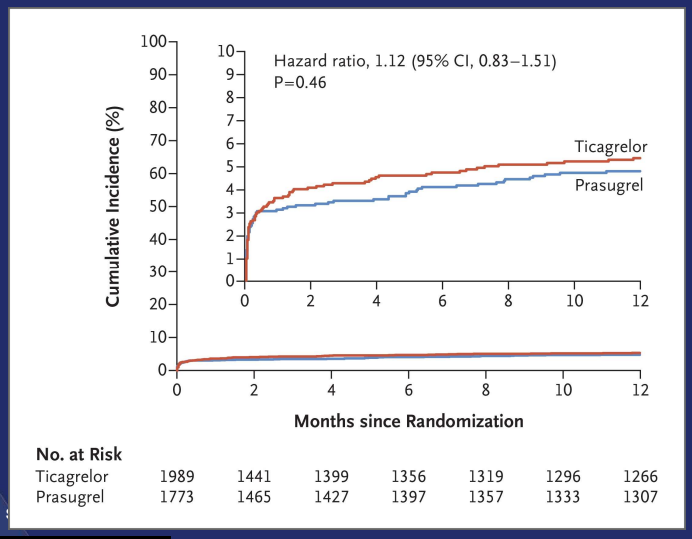
No. at Risk

Ticagrelor	2012	1877	1857	1835	1815	1801	1722
Prasugrel	2006	1892	1877	1862	1839	1829	1803

The NEW ENGLAND JOURNAL of MEDICINE

ISAR-REACT Trial

Major Bleeding



No. at Risk

Ticagrelor	1989	1441	1399	1356	1319	1296	1266
Prasugrel	1773	1465	1427	1397	1357	1333	1307

The NEW ENGLAND JOURNAL of MEDICINE

ISAR-REACT 5

- The ISAR-REACT 5 results (<risk of ischemic events with prasugrel compared with ticagrelor) were surprising and not predicted based on the results of existing randomized trials:
  - PLATO: ticagrelor superior to clopidogrel (ACS, either Invasive or Non-invasive).
  - TRITON-TIMI 38: prasugrel superior to clopidogrel (ACS-Invasive)
  - TRILOGY ACS: prasugrel not superior to clopidogrel (ACS-Non-invasive)
- Possible explanations include trial limitations
  - Open-label design (compared with the TRITON-TIMI 38 and PLATO trials)
  - Telephone follow-up in more than 90 percent of patients.
  - Different patient populations or co-interventions between TRITON-TIMI 38 and PLATO trials and ISAR-REACT 5.
- Until further evidence is available to support or refute the superiority of prasugrel, either prasugrel or ticagrelor is a reasonable choice for patients with ACS in whom a decision is made to proceed with diagnostic angiography within three hours.

DAPT vs. Monotherapy after PCI

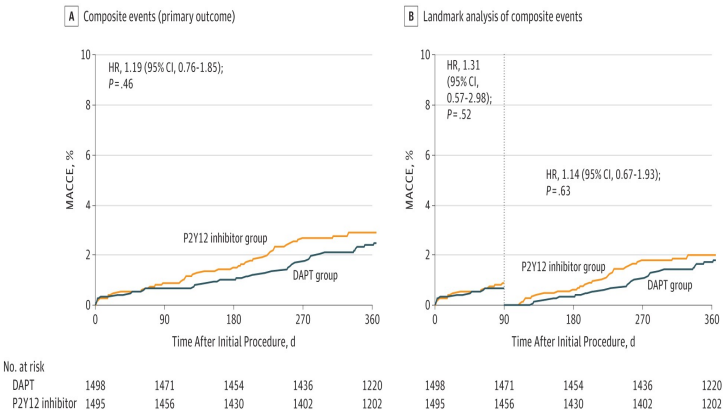
- SMARTCHOICE Trial
  - Smart Angioplasty Research Team: Comparison Between P2Y12 Antagonist Monotherapy vs Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents
  - Low risk patients, 3 months DAPT then randomized
- STOPDAPT-2 Trial
  - Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt Chromium Stent
  - Low risk patients, 1 month DAPT, then randomized
- TWILIGHT Trial
  - Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention
  - High risk patients, 3 months DAPT, then randomized

SMARTCHOICE Trial

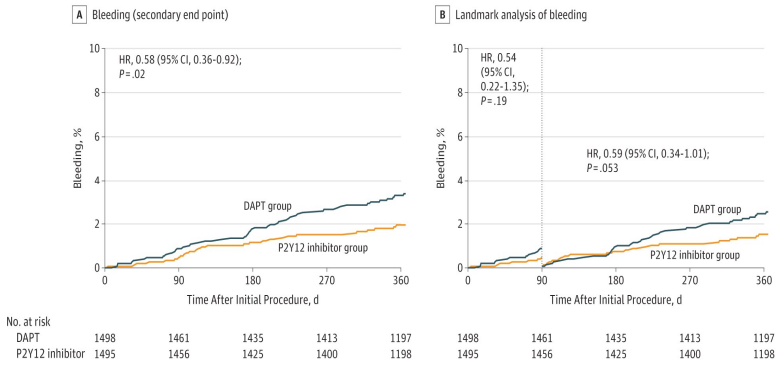
- Multicenter, open-label, randomized Noninferiority trial
- 2993 pts w/PCI at 33 hospitals in Korea
  - 3 mo DAPT followed by a P2Y12 inhibitor alone vs. 12 mo DAPT
    - Clopidogrel 76.9 vs. 77.6
    - Prasugrel 4.1 vs. 4.5
    - Ticagrelor 19.0 vs. 17.9
- 1^{O} End point: MACE - composite of All-cause death, MI or CVA

- RESULTS
  - No difference in MACE: Monotherapy 2.9% vs. DAPT 2.5% (*P* = .007 for noninferiority)
  - Bleeding was lower in the Monotherapy 2.0% vs. DAPT group 3.4%; HR = 0.58

SMART-CHOICE Cardiovascular Events



SMART-CHOICE
Bleeding Events

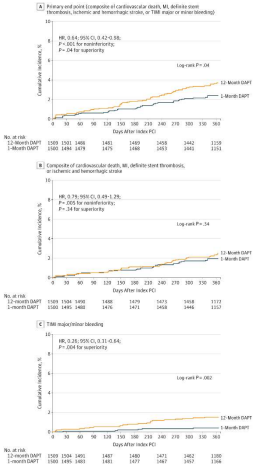


STOPDAPT-2 Trial

- Multicenter, open-label, randomized clinical trial
- 3045 Stable (not ACS) pts w/ PCI at 90 hospitals in Japan
  - 1 mo of DAPT followed by clopidogrel monotherapy for up to 5 years
  - 12 mos of DAPT followed by aspirin monotherapy for up to 5 years
  - For patients who had initially received prasugrel (~40%), prasugrel was switched to clopidogrel at 1 month in both groups
- 1^{O} End point: Composite of CVD, MI, CVA, Definite stent thrombosis, or major or minor bleeding

- RESULTS:
  - One-month DAPT was both noninferior ($P < .001$) and superior ($P = .04$) to 12-month DAPT for the primary end point (2.36% vs. 3.70%, HR = 0.64.

STOPDAPT-2
Cardiovascular and Bleeding Events



STOPDAPT-2
Cardiovascular and Bleeding Events

	No./Total (%)					
	1-Month DAPT (n = 1500)	12-Month DAPT (n = 1509)	HR (95% CI)	Favors 1-Month DAPT / Favors 12-Month DAPT	*P* Value	*P* Value for Interaction
Age, y						
≥75	10/448 (2.26)	25/499 (5.08)	0.44 (0.21-0.92)		.03	.20
<75	25/1052 (2.41)	30/1010 (3.02)	0.80 (0.47-1.36)		.41	
Acute coronary syndrome						
Yes	16/565 (2.88)	23/583 (4.02)	0.72 (0.38-1.36)		.44	.64
No	19/935 (2.05)	32/926 (3.49)	0.59 (0.33-1.03)		.06	
STEMI						
Yes	9/291 (3.15)	14/270 (5.26)	0.60 (0.26-1.38)		.23	.87
No	26/1209 (2.18)	41/1239 (3.36)	0.65 (0.40-1.06)		.08	
Severe chronic kidney disease						
Yes	9/82 (11.22)	5/84 (5.97)	1.93 (0.65-5.75)		.24	.03
No	26/1418 (1.86)	50/1425 (3.56)	0.52 (0.32-0.84)		.007	
Diabetes						
Yes	18/585 (3.12)	25/574 (4.45)	0.70 (0.38-1.29)		.26	.65
No	17/915 (1.88)	30/935 (3.24)	0.58 (0.32-1.05)		.07	
Total stent length ≥28 mm						
Yes	19/742 (2.60)	33/787 (4.23)	0.61 (0.35-1.07)		.08	.76
No	16/758 (2.14)	22/722 (3.12)	0.69 (0.36-1.32)		.26	
≥2 Target vessels						
Yes	4/100 (4.14)	8/116 (6.94)	0.58 (0.17-1.92)		.37	.85
No	31/1400 (2.24)	47/1393 (3.43)	0.66 (0.42-1.03)		.07	
PARIS thrombotic risk score						
High	9/211 (4.39)	19/215 (8.90)	0.47 (0.21-1.05)		.06	.39
Intermediate	17/560 (3.07)	18/536 (3.42)	0.91 (0.47-1.77)		.78	
Low	9/729 (1.24)	18/758 (2.40)	0.52 (0.23-1.15)		.11	
PARIS bleeding risk score						
High	13/302 (4.37)	25/291 (8.62)	0.49 (0.25-0.96)		.04	.61
Intermediate	17/757 (2.27)	23/801 (2.93)	0.78 (0.42-1.46)		.44	
Low	5/441 (1.15)	7/417 (1.72)	0.68 (0.21-2.13)		.50	
CREDO-Kyoto thrombotic risk score						
High	8/113 (7.24)	9/122 (7.41)	0.97 (0.37-2.51)		.95	.27
Intermediate	7/318 (2.25)	21/358 (5.94)	0.37 (0.16-0.87)		.02	
Low	20/1069 (1.89)	25/1029 (2.47)	0.77 (0.43-1.39)		.38	
CREDO-Kyoto bleeding risk score						
High	7/106 (6.70)	10/112 (8.93)	0.73 (0.28-1.91)		.52	.66
Intermediate	14/398 (3.58)	18/401 (4.57)	0.79 (0.39-1.59)		.51	
Low	14/996 (1.42)	27/996 (2.75)	0.52 (0.27-0.99)		.045	
Overall	35/1500 (2.36)	55/1509 (3.70)	0.64 (0.42-0.98)		.04	

TWILIGHT Trial

Ticagrelor with or without Aspirin in High-Risk Patients after PCI

(N Engl J Med Volume 381(21):2032-2042 November 21, 2019)

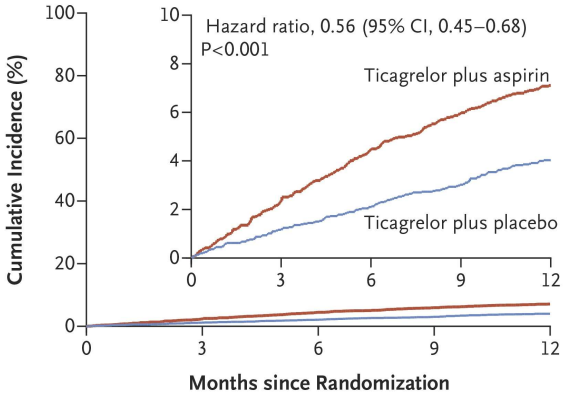
- Randomized, placebo-controlled, prospective trial of 7119 pts w/ successful PCI at high risk for ischemic or bleeding complications
  - At least one High Risk Clinical feature:
    - age >65, female, ACS, PAD, DM, CKD
  - At least one High Risk Angiographic feature:
    - MVD, long stent, thrombus, bifurcation stents, LM, Proximal LAD, Atherectomy
- DAPT for 3 mos with ticagrelor/ASA then randomized to either ticagrelor + ASA or ticagrelor + placebo for 12 additional months

TWILIGHT Trial

- 1^{O} End point: Bleeding between randomization and 1 year (BARC type 2, 3, or 5 bleeding)
- 2^{O} End point: Death from any cause, nonfatal MI or nonfatal stroke
- Other 2^{O} End points: CVD, MI, CVA, Stent thrombosis

TWILIGHT Trial

Primary Endpoints - BARC Type 2, 3, or 5 Bleeding



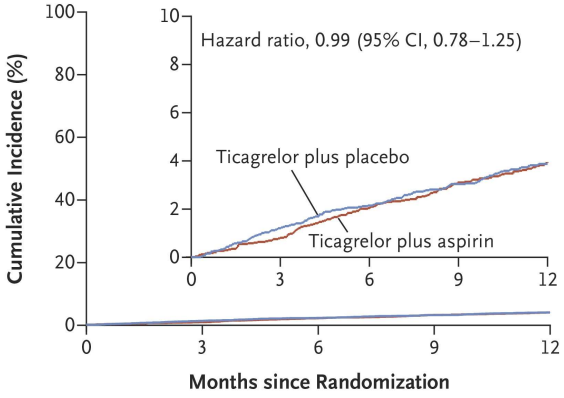
No. at Risk

Ticagrelor plus aspirin	3564	3454	3357	3277	3213
Ticagrelor plus placebo	3555	3474	3424	3366	3321

The NEW ENGLAND JOURNAL of MEDICINE

TWILIGHT Trial

Secondary Endpoints: Death/MI/CVA



No. at Risk

Ticagrelor plus aspirin	3515	3466	3415	3361	3320
Ticagrelor plus placebo	3524	3457	3412	3365	3330

The NEW ENGLAND JOURNAL of MEDICINE

TWILIGHT Trial Conclusions

- Among High-Risk patients who underwent PCI and completed 3 months of dual antiplatelet therapy, ticagrelor monotherapy was associated with a lower incidence of clinically relevant bleeding than ticagrelor plus aspirin, with no higher risk of death, myocardial infarction, or stroke.

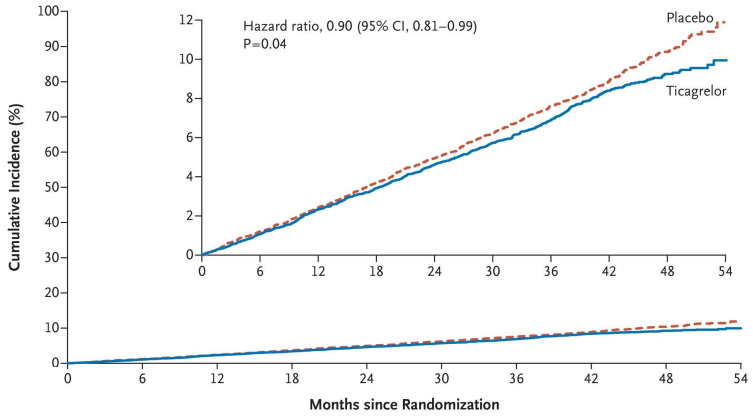
THEMIS Trial

Ticagrelor in Patients with Stable Coronary Disease and Diabetes

N Engl J Med Volume 381(14):1309-1320 October 3, 2019

- 19,220 pts randomized to receive either ticagrelor plus aspirin or placebo plus aspirin
  - Stable CAD (history of PCI, CABG or >50% stenosis of at least one coronary artery) and
  - Diabetes Mellitus
- 1^{O}efficacy outcome = composite of CVD, MI or CVA
- 1^{O}safety outcome = major bleeding,
- **Net Irreversible Harm** was prespecified as a composite of Death, MI, CVA, fatal bleeding, or ICH.

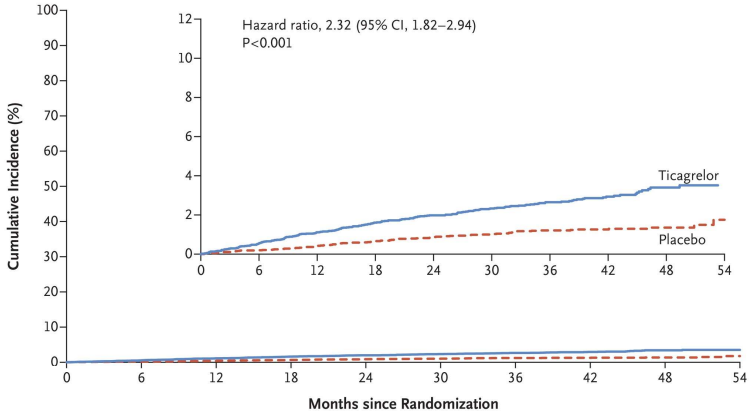
THEMIS Trial
Primary Composite Efficacy Outcome



No. at Risk										
Ticagrelor	9619	9416	9237	9074	8909	8692	5974	3664	1684	170
Placebo	9601	9414	9246	9076	8909	8692	5934	3682	1685	174

The NEW ENGLAND JOURNAL of MEDICINE

THEMIS Trial:
Primary Safety Outcome



No. at Risk										
Ticagrelor	9562	7928	7309	6826	6381	5997	4067	2464	1156	168
Placebo	9531	8665	8186	7767	7359	6967	4795	2952	1358	218

The NEW ENGLAND JOURNAL of MEDICINE

THEMIS-PCI Sub Study

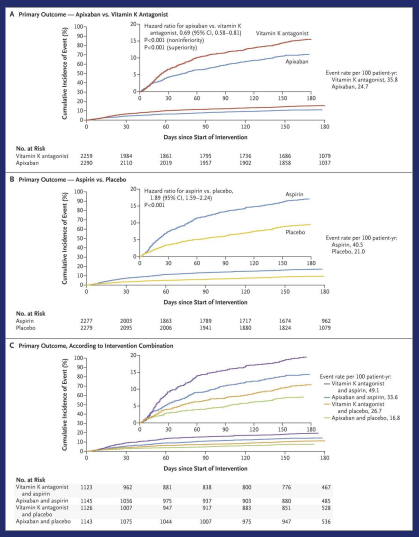
- THEMIS-PCI substudy –11,154 patients with Diabetes and a history of previous PCI
  - ticagrelor improved **Net Clinical Benefit** (9.3% vs. 11.0%)
  - the benefit was present irrespective of time from the most recent PCI
- Taken together, the THEMIS trial and the THEMIS-PCI subgroup analysis raise the possibility that patients with stable CAD and DM at very high ischemic risk and low bleeding risk may have a **net benefit** with long-term DAPT with aspirin and ticagrelor
- Based on these findings, long-term therapy with ticagrelor in addition to aspirin should be considered in patients with diabetes ***and a history of PCI*** who
  - have tolerated antiplatelet therapy
  - have high ischemic risk and
  - have a low bleeding risk

AUGUSTUS Trial
Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation

- Appropriate antithrombotic regimens for patients with atrial fibrillation who have an acute coronary syndrome or have undergone percutaneous coronary intervention (PCI) are unclear
- The AUGUSTUS Trial was a randomized trial of 4614 patients with atrial fibrillation who had an acute coronary syndrome or had undergone PCI and were planning to take a P2Y12 inhibitor
  - All patients received P2Y12 antagonist, and in a two-by-two factorial design also received either
    - Apixaban + ASA, or
    - Apixaban + placebo, or
    - VKA + ASA, or
    - VKA + placebo
- 1^{O} outcome = major or clinically relevant nonmajor bleeding
- 2^{O} outcomes = composite of death or hospitalization and the composite of death or ischemic events (CVA, MI, stent thrombosis or urgent revascularization).

AUGUSTUS Trial

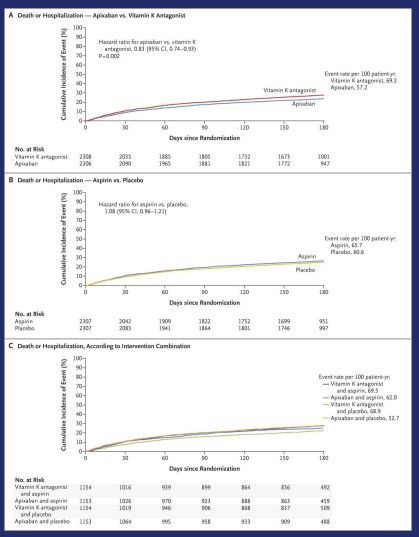
Primary Outcome of Major or Clinically Relevant Nonmajor Bleeding.



The NEW ENGLAND JOURNAL of MEDICINE

AUGUSTUS Trial

Composite of Death or Hospitalization.



The NEW ENGLAND JOURNAL of MEDICINE

AUGUSTUS Trial
Conclusions

- In patients with atrial fibrillation and a recent acute coronary syndrome or PCI treated with a $P2Y_{12}$ inhibitor, an antithrombotic regimen that included apixaban, without aspirin, resulted in less bleeding and fewer hospitalizations without significant differences in the incidence of ischemic events than regimens that included a vitamin K antagonist, aspirin, or both.

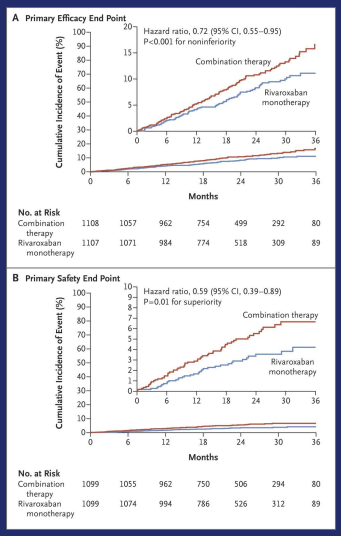
AFIRE Trial
Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease

- Noninferiority trial of 2236 patients with A Fib, remote PCI or CABG > 1 yr prior, or angiographically confirmed CAD not requiring revascularization
  - Randomized to receive monotherapy with rivaroxaban or combination therapy with rivaroxaban plus a single antiplatelet agent (~75% ASA, 25% clopidogrel).
- 1^{O} efficacy end point was a composite of CVA, systemic embolism, MI, unstable angina requiring revascularization, or death from any cause;
- 1^{O} safety end point was major bleeding

AFIRE Trial
Results

- The trial was stopped early because of increased mortality in the combination therapy group.
- Rivaroxaban monotherapy was noninferior (P<0.001) to combination therapy for the 1^{O} efficacy end point
- Rivaroxaban monotherapy was superior (P = 0.01) to combination therapy for the 1^{O} safety end point

AFIRE Trial
Primary Efficacy and Safety End Points.



The NEW ENGLAND JOURNAL of MEDICINE

AFIRE Trial
Conclusions

- As antithrombotic therapy, rivaroxaban monotherapy was noninferior to combination therapy for efficacy and superior for safety in patients with atrial fibrillation and stable coronary artery disease

The NEW ENGLAND JOURNAL of MEDICINE

SUMMARY

- The optimal P2Y12 antagonist in ACS is uncertain. The ISAR-REACT 5 Trial suggests prasugrel is superior to ticagrelor but until further studies are performed both are superior to and either is preferred over clopidogrel in ACS
- The optimal duration of DAPT after PCI is uncertain but monotherapy after 1-3 months appears to be safe and effective in both stable and high risk patients
- Prolonged DAPT in diabetics with CAD reduces ischemic complications at the expense of increased bleeding. The Net Clinical Benefit favors prolonged DAPT in patients with prior PCI, high ischemic risk and acceptable bleeding risk
- In patients with Atrial Fibrillation and recent PCI, treatment with a NOAC and $P2Y_{12}$ without ASA is safe and effective
- In patients with Atrial Fibrillation and stable CAD, monotherapy with rivaroxaban is as effective as and safer than rivaroxaban + antiplatelet therapy

YOUR PATIENTS

Patients with ACS following PCI:

Prasugrel or Ticagrelor >>> clopidogrel

Patients without ACS, @ Low Risk following PCI:

DAPT x 1-3 mos then prolonged P2Y12 without ASA

Patients with or without ACS, @ High Risk (clinical and angiographic), after PCI:

DAPT X 3 mos, then Ticagrelor alone x 12 mos

YOUR PATIENTS

Patients with Diabetes, CAD, no recent PCI but High Ischemic Risk & Low Bleeding Risk:

Prolonged DAPT with Ticagrelor + ASA

Patients with Chronic Atrial Fibrillation & CAD following PCI:

NOAC + P2Y12 but no ASA

Patients with Chronic Atrial Fibrillation & CAD but no recent PCI or CABG:

NOAC alone without antiplatelet

Thank You