Dual Antiplatelet Therapy Plus Systemic Anticoagulation: Bleeding Risk and Management

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Financial Disclosure Information

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None

76 year old male

- On routine examination, he is noted to have an irregular rhythm. ECG confirms new onset atrial fibrillation. His rate is adequately controlled.
- Coronary Disease
  - Recent DES (n=2) to LAD
- PMHx:
  - Diabetes mellitus,
  - Hyperlipidemia,
  - Carotid disease (2 prior TIAs; s/p endarterectomy),
  - "Smoldering" Waldenstrom's macroglobulinemia.

LINGO

TOAT: triple oral antithrombotic therapy
DAPT: dual antiplatelet therapy
OAC: oral anticoagulant therapy

Question

What antithrombotic cocktail should be used for this patient?

1. Aspirin
2. Clopidogrel (or other P2Y12 antagonist)
3. DAPT
4. OAC
5. TOAT

Question

If you offer him TOAT, what will you quote his anxious daughter regarding annual risk of major bleeding?

1. 3%
2. 6%
3. 9%
4. 15%
5. 25%

Learning Objectives

To Understand

- The magnitude of the problem
- The relative magnitude of the bleeding risk
- The comparable risk if novel anticoagulants are employed
- The utility of online tools in the bleeding risk prediction
- Recommendations for management

Resources

- *Reed GW, Cannon CP. Triple Oral Antithrombotic Therapy in Atrial Fibrillation and Coronary Artery Stenting. Clin Cardiol. 2013 Jul 19.*
- Lamberts M, et al. Bleeding after initiation of multiple antithrombotic drugs, including triple therapy, in atrial fibrillation following MI and coronary intervention: a nationwide cohort study. Circulation. 2012;126:1185-93.
- ACCP Guidelines: Antithrombotic Therapy for Atrial Fibrillation. Chest. 2012;141:e531S-e575S.

Magnitude of the Problem
(Combining OAC with DAPT)

U.S. disease prevalence

- Atrial fibrillation: 4.4 million
  30% have known CAD
- Coronary disease: 16 million
  >1 million coronary interventions/year
  70% include use of DES
  1 in 10 subjects with acute MI have Afib
- 250,000 patients/year with TOAT indication

Circulation 2012;125:E2-220
JACC 2012;60:2017-31

What is the risk of major bleeding for patients taking TOAT relative to other antithrombotic combinations?

Risk of Bleeding with Single, Dual, or Triple Therapy in Patients with Atrial Fibrillation

- Nationwide Danish registry
- 118,606 patients with AF
  - Warfarin (n = 50,919)
  - Aspirin (n = 47,541)
  - Clopidogrel (n = 3,717)
  - ASA/Clop (n = 2,859)
  - Warfarin + aspirin (n = 18,345)
  - Warfarin + aspirin + clopidogrel (n = 1,261)
- 1° end point: ***nonfatal bleeding requiring hospitalization*** or ***fatal bleeding.***

Arch Intern Med. 2010;170:1433-1441

Risk of Bleeding with Single, Dual, or Triple Therapy in Patients with Atrial Fibrillation

Bleeding rates*	Non fatal	Fatal	Both
Warf	3.6	0.2	3.9
ASA	3.3	0.4	3.7
Clop	4.8	0.8	5.6
ASA/Clop	***7.0***	***0.6***	***7.4***
Warf/ASA	***6.4***	***0.4***	***6.8***
Warf/clop	***13.3***	***0.6***	***13.9***
Warf/ASA/clop	***15.4***	***0.2***	***15.7***

*Incidence rate: % per patient-year

Arch Intern Med. 2010;170:1433-1441

Registry Studies

Study	N	DAPT	OAC	TOAT
Buresly	21,443	6.8%	5.9%	8.5%
Sorensen	40,812	3.7%	4.3%	12.0%
Lamberts	11,480	7.0%	7.0%	14.2%
Hansen	118,606	7.4%	3.9%	15.7%

TOAT increases risk
- 2 fold relative to DAPT
- 3 fold relative to OAC or antiplatelet mono-therapy

Clin Cardiol 2013; July

Is TOAT more effective than OAC plus clopidogrel for thromboembolic event reduction?

Clopidogrel ± aspirin in patients taking OAC undergoing PCI
WOEST Trial

Patients: Patients undergoing PCI with an OAC indication*
Exclusions: ICH hx, shock, PUD, tpenia, major bleed hx

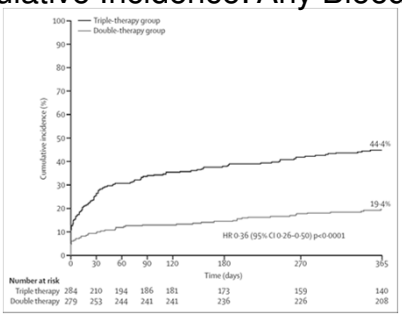
573 patients → TOAT
573 patients → Warfarin plus clopidogrel

Primary endpoint: any bleeding episode within 1st year
Secondary endpoint: death, MI, stroke, TVR, stent thrombosis

*Afib 69%, MHV 11%, Other 20%

Lancet 2013; 381: 1107–15

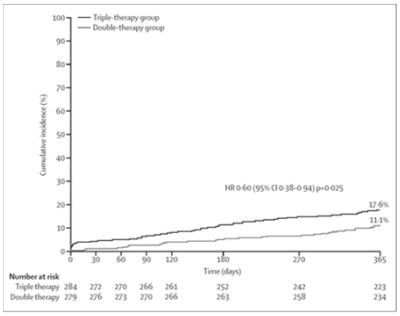
Cumulative Incidence: Any Bleeding



HR 0.36, 95%CI 0.26 – 0.50 P<0.0001
Major bleeding (TIMI, GUSTO, BARC): NS

Lancet 2013; 381: 1107–15

Cumulative Incidence: MACE



HR 0.60, 95% CI 0.38 – 0.94 P<0.025
Major bleeding (TIMI, GUSTO, BARC): NS

Lancet 2013; 381: 1107–15

TOAT vs. OAC plus clopidogrel

- These results suggest that OAC/ clopidogrel carries lower bleeding risk without increased thromboembolism.
- Further RCTs are warranted

Chest. 2012;141:e531S-e575S

What is the risk of TOAT when a novel anticoagulant is used?

Apixaban with Antiplatelet Therapy in ACS
APPRAISE-2

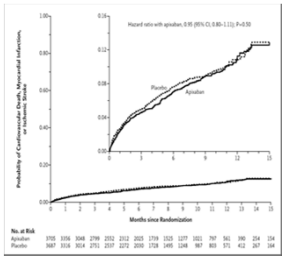
Patients: Patients suffering high risk ACS*
≥ 2 risk factors: age > 65, DM, rec MI, CVD, PAD, HF, EF<40%, CKD

7392 patients → Apixaban 5 mg BID
7392 patients → Placebo

STEMI 40%, NSTEMI 42%
ASA use 97%; P2Y12 use 81%

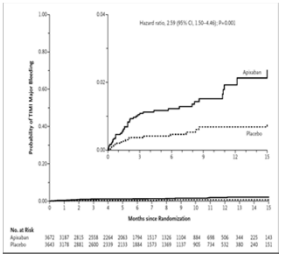
NEJM 2011;365:699

Efficacy



HR, 0.95 (95% CI, 0.80–1.11); P=0.50

Safety



HR, 2.59 (95% CI, 1.50–4.46); P=0.001

NEJM 2011;365:699

Apixaban with Antiplatelet Therapy in ACS
APPRAISE-2

Bleeding

per 100 pt-yrs	Apixaban/ DAPT	Placebo/ DAPT
Major*	2.4	0.9
Fatal*	0.3	0
Intracranial*	0.6	0.2

*p<0.05

NEJM 2011;365:699

Rivaroxaban in Patients with ACS
ATLAS ACS-2 TIMI 51

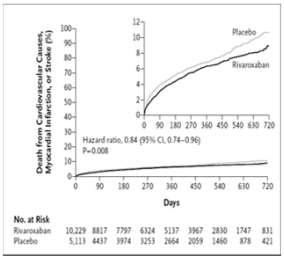
Patients: Patients suffering ACS

15526 patients → Rivaroxaban 2.5 mg BID
15526 patients → Rivaroxaban 5 mg BID
15526 patients → Placebo

STEMI 50%, NSTEMI 25%
ASA use 99%; P2Y12 use 93%

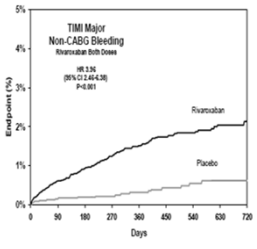
NEJM 2012;366:9

Efficacy



HR 0.84 (95% CI, 0.74–0.96)
P=0.008

Safety



HR 3.96 (95% CI 2.46-6.38)
P<0.001

NEJM 2012;366:9

Rivaroxaban in Patients with ACS

ATLAS ACS-2 TIMI 51

Bleeding

per 100 pt-yrs	Riva 2.5 DAPT	Riva 5 DAPT	Placebo DAPT
Major*	1.8	2.4	0.6
Fatal	0.1	0.4	0.2
Intracranial*	0.4	0.7	0.2

*p<0.05

NEJM 2012;366:9

Bottom Line: NoACs with TOAT

- Bleeding rates are increased relative to DAPT.
- Absolute bleeding rates however are modest relative to warfarin/TOAT.
- Caution is advised but concept is attractive.

What are the Guideline recommendations regarding TOAT?

Guideline Statements: TOAT

- For AF patients at ***low to intermediate risk*** of stroke ($CHADS_2 < 2$) with DES, we suggest DAPT over TOAT (Gr 2C).
- For AF patients at ***high risk*** of stroke ($CHADS_2 \geq 2$) with DES, we suggest triple therapy rather than DAPT (Gr 2C).

Chest. 2012;141:e531S-e575S

Guideline Statements: TOAT

- For patients who have an OAC indication, adding warfarin to DAPT is reasonable. *(Class IIb LoE B)*
- Targeting a lower INR (2.0 – 2.5) is reasonable in patients requiring DAPT (Class IIb; LoE C).

Circulation. 2012;126:875-910

What are some practical recommendations regarding TOAT?

Practical Points to Ponder

1. Lower INR target (2.0 -2.5)
2. Consider employing BMS
3. Proton pump inhibitor if GI bleed history
4. If low $CHADS_2$ score (0-1), consider DAPT alone
5. Consider OAC plus clopidogrel
6. Reduce aspirin dose (81 mg/day)
7. Avoid NSAIDs
8. Consider Factor Xa inhibitor instead of warfarin

Question

What antithrombotic cocktail should be used for this patient?

1. Aspirin
2. Clopidogrel (or other P2Y12 antagonist)
3. DAPT
4. OAC
5. TOAT
6. ***OAC plus clopidogrel***

Question

If you offer him TOAT, what will you quote his anxious daughter regarding annual risk of major bleeding?

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