The Evolving History of Anticoagulation: The DOAC Era?

Tiffany C. Ortman, PharmD, BCACP, CACP
Specialty Practice Pharmacist, Ambulatory Care
The Ohio State University Wexner Medical Center

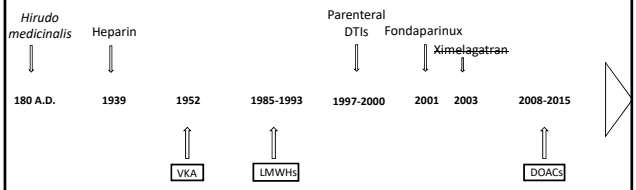
MedNet21
Center for Continuing Medical Education

The Ohio State University Wexner Medical Center

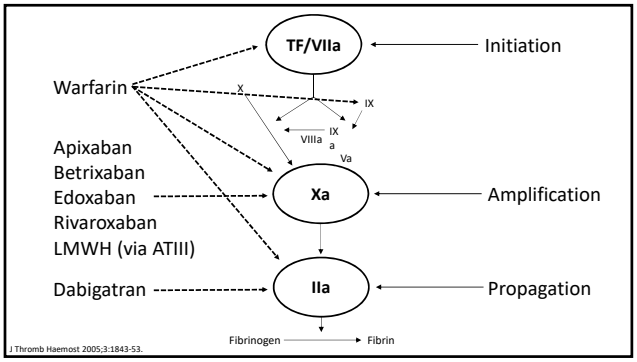
Objectives

- Discuss the evolution of anticoagulation therapy
- Compare and contrast the place in therapy for anticoagulants used in the outpatient setting
- Identify when parenteral anticoagulant bridge may be warranted in patients on warfarin with atrial fibrillation and/or venous thromboembolism
- Determine optimal oral anticoagulant based on patient-specific characteristics
- Recommend appropriate monitoring for direct oral anticoagulants

Evolution of Anticoagulation



VKA = Vitamin K Antagonist
LMWH = Low-Molecular-Weight Heparin
DTI = Direct Thrombin Inhibitor
DOAC = Direct Oral AntiCoagulant



J Thromb Haemost 2005;3:1843-53.

FDA Approved Oral Anticoagulants

	Prevent SSE in NVAF	VTE Treatment	VTE Secondary Prevention	VTE Prevention after hip or knee replacement	VTE Prevention in acutely ill medical patients	After Cardiac Valve Replacement	In CAD and PAD (with ASA)
Warfarin (Coumadin®, Jantoven®)	✓	✓	✓	✓	✓	✓	✓
Dabigatran (Pradaxa®)	✓	✓	✓	✓			
Rivaroxaban (Xarelto®)	✓	✓	✓	✓	✓		✓
Apixaban (Eliquis®)	✓	✓	✓	✓			
Edoxaban (Savaysa™)	✓	✓	✓				
Betrixaban (Bevyxxa™)					✓		

SSE = Stroke and Systemic Embolism, NVAF = Non-Valvular Atrial Fibrillation

Oral Anticoagulants Comparison

Characteristics	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Half life	40 h	12-14 h	7-13 h	8-13 h	10-14 h
Peak effect	4-5 days	1.5-3 h	2–4 h	1-3 h	1-2 h
Renal elimination	None	80%	33%	25%	35-50%
VTE Initial Phase: Oral Only?	No	No	Yes	Yes	No
VTE Secondary Phase Dosing	Once daily	BID	BID x21 days then Once daily	BID (reduced dose after 7 days)	Once daily
Antidote	Vitamin K	Idarucizumab	Andexanet alfa	Andexanet alfa	Andexanet alfa

J Thromb Thrombolysis 2016;41,15-31.

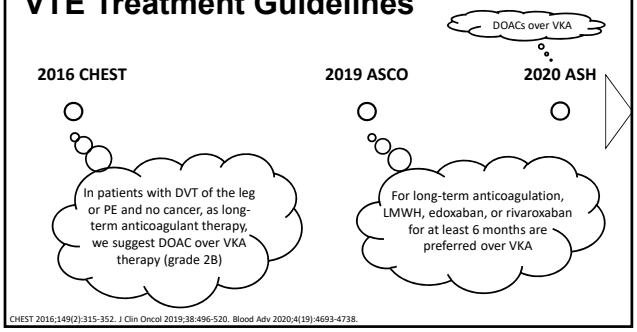
DOACs vs Warfarin for VTE

	Dabigatran (RE-COVER)	Rivaroxaban (EINSTEIN)	Apixaban (AMPLIFY)	Edoxaban (Hokusai-VTE)
Recurrent Symptomatic VTE or VTE-related Death	Equal	Equal*	Equal	Equal*
Major Bleeding	Equal	↓	↓	Equal
Major and Clinically Relevant Non-Major Bleeding	↓	Equal	↓	↓

*Did not include VTE-related death

- GI bleeding event rates were too low to draw definite conclusions (consider extrapolation from afib trials)
- Low rates of intracranial hemorrhage with DOACs compared to warfarin

VTE Treatment Guidelines



CHEST 2016;149(2):315-352. J Clin Oncol 2019;38:496-520. Blood Adv 2020;4(19):4693-4738.

AF Stroke Prevention Guidelines

For patients with AF and an elevated CHA_2DS_2-VASc score of ≥ 2 in men or ≥ 3 in women, oral anticoagulants are recommended

2018 CHEST

DOACs over VKA

2019 AHA/ACC/HRS

DOACs are recommended over VKA in DOAC-eligible patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve)

2020 ESC

CHEST 2018;154(4):1121-1201. Circulation 2019;140:e125-e151. EHJ 2020(00):1-125.

The Future of Anticoagulation?

Adverse Drug Reactions (ADRs)

WHO Database

- 39 972 reports in patients with NVAF
- 51% dabigatran, 28% warfarin, 19% rivaroxaban, 2% apixaban
- 204 ADRs with a reporting odds ratio > 1

FAERs Database

- 42 964 cases
- Rivaroxaban with highest rate per prescription for each ADR
- Dabigatran had the highest reported rates of ischemic stroke
- Warfarin with lowest rate per prescription for each ADR

Br J Clin Pharmacol 2017;83:1532-43. Eur J Haematol 2019;103:43-46.

Limitations of DOAC Use

- Mechanical heart valves
- Antiphospholipid syndrome
- Pregnancy and breastfeeding
- Moderate or severe hepatic impairment (Child-Pugh B or C)
- CYP3A4 and P-gp strong inducers/inhibitors
  - Examples of P-gp inducers: carbamazepine, rifampin, St. John's Wort
  - Examples of P-gp inhibitors: amiodarone, azithromycin, ketoconazole, ritonavir, verapamil

Choice of Anticoagulant: Example Approach

FDA-approved Indication for DOAC

Does patient meet ≥1 of the following?
- □ Able to obtain DOAC longitudinally
- □ Likely to be compliant to medication
- □ Not pregnant or breastfeeding
- □ No clinically significant drug interactions
- □ No altered GI absorption
- □ Adequate renal/hepatic function
- □ No extremes of weight?

Yes → **DOAC candidate** → Select DOAC based on patient characteristics and preferences

No → **NOT a DOAC candidate** → Warfarin or LMWH

Parenteral Anticoagulant Bridging for Warfarin

Intermediate Thromboembolic Risk

Consider based on individual risks/patient preferences

Atrial Fibrillation:	VTE: **Bridging NOT recommended**
CHA_2DS_2-VASc score 5-6 with prior stroke/TIA/SSE or prior history of embolic ischemic CVA/TIA/SSE	VTE within past 3-12 months, Heterozygous factor V Leiden, Prothrombin 20210 mutation, recurrent VTE, active cancer

High Thromboembolic Risk

Bridging Advised

CHA_2DS_2-VASc score 7-9, Recent TE event (within 3 months) if procedure cannot be delayed, Rheumatic valvular disease, Recent (<4 weeks) cardioversion or AF ablation	**Consider delaying procedure** Recent (within 3 months) TE event, Severe thrombophilia (protein C or S or antithrombin deficiency, APS)

DOACs in Renal Impairment

Dabigatran

CrCl	Dose
≥30	150 mg BID
29-15	75 mg BID (Avoid in VTE)
<15	Avoid
HD	Avoid

Rivaroxaban

>50	20 mg daily (VTE: 15 mg BID x21 day load)
50-15	15 mg daily (Avoid in VTE for <30)
<15	Avoid
HD	Avoid*

Apixaban

Standard dose	5 mg BID (VTE: 10 mg BID x7 day load)
2 of 3: ≥80 y, SCr > 1.5 mg/dL, Weight ≤60 kg	AF: 2.5 mg BID
HD	5 mg BID?

Edoxaban

>95	Avoid
50-95	60 mg daily (VTE weight ≤60 kg: 30 mg)
50-15	30 mg daily
<15	Avoid
HD	Avoid

CrCl in mL/min
Am J Med 2017;130:1015-1023.

*labeling suggests rivaroxaban may be administered to patients on HD at a dose of 15 mg, however, not adequately studied in large-scale clinical trial

Apixaban in Hemodialysis

Mavrakanas et al, 2017
- PK study
- N = 7
- At steady state, apixaban 5 mg BID increased exposure 2-5.7 times relative to 2.5 mg BID

Siontis et al, 2018
- Retrospective cohort study
- N = 25 523 with AF on HD or PD
- Apixaban 5 mg BID was associated with lower TE and major bleeding compared to warfarin

RENAL-AF, 2019
- Prospective randomized controlled trial (stopped early)
- N = 154 with AF on HD
- Apixaban 5 mg BID had similar rates of bleeding and stroke as warfarin (TTR ~44%) among patients with ESRD on HD

DOACs in Obesity

2016 ISTH SSC
We suggest that DOACs should not be used in patients with a BMI > 40 kg/m² or a weight > 120 kg

DOAC	Trial	Indication	Weight or BMI Cutoff	Proportion of Obese Patients (%)
Dabigatran	RE-COVER I/II	VTE	≥ 35 kg/m²	12.1
	RE-LY	AF	≥ 100 kg	17.1
Rivaroxaban	EINSTEIN DVT/PE	VTE	> 100 kg	14.3
	ROCKET-AF	AF	> 90 kg, ≥ 35 kg/m²	28.5, 13.6
Apixaban	AMPLIFY	VTE	≥ 35 kg/m²	13
	ARISTOTLE	AF	> 30 kg/m²	40
Edoxaban	HOKUSAI VTE	VTE	> 100 kg	14.8
	ENGAGE AF-TIMI 48	AF	None	NR

NR = Not Reported

DOACs in Morbidly Obese

Study, Year	N	Indication	Weight, kg	BMI, kg/m²	Anticoagulant	Efficacy Outcome	Safety Outcome
Kido et al, 2019	128	AF	> 120	> 40	DOAC (D, R, A) Warfarin	1.75%/y 2.07%/y p = 0.77	2.18%/y 4.97%/y p = 0.09
Kushnir et al, 2019	429	AF		> 40	DOAC (R, A) Warfarin	1.8% 1.3% p = 1.0	2.9% 7.9% p = 0.087
Kushnir et al, 2019	366	VTE		> 40	DOAC (R, A) Warfarin	2.0% 1.2% p = 0.69	1.5% 2.4% p = 0.60
Kalani et al, 2019	180	VTE and AF	≥ 120	≥ 40	DOAC (D, R, A) Warfarin	12.2% 11.1% p = 0.82	2.2% 3.3% p = 0.65
Coons et al, 2020	1840	VTE	100-300	(> 40 ~43-45%)	DOAC (D, R, A) Warfarin	6.5% 6.4% p = 0.93	1.7% 1.2% p = 0.31

Blood 2020;135(12):904-911. Pharmacotherapy 2020;40(3):204-210

D = Dabigatran R = Rivaroxaban A = Apixaban

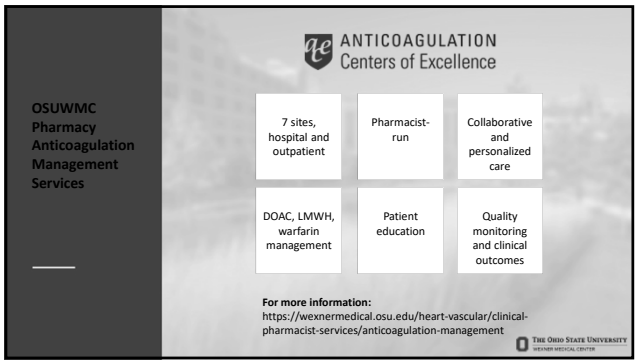
DOAC Drug Selection

Characteristics	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
All-oral therapy		✓	✓	
Dyspepsia or GI issues		✓	✓	✓
GI bleed			✓	✓ (low dose)
Significant CAD		✓	✓	✓
Poor compliance with BID dosing		✓		✓
CrCl < 30 mL/min			✓	

DOAC Monitoring

Resource	Recommendation
European Heart Rhythm Association Non-valvular Atrial Fibrillation Guidelines (2015)	"Patients should return on a regular basis for on-going review…preferably **after 1 month** initially and later **every 3 months**"
ACC/AHA/HRS Atrial Fibrillation Guidelines (2019)	"Renal function and hepatic function should be evaluated before initiation of a [DOAC] and should be re-evaluated **at least annually**"
ASH VTE Guidelines (2018)	• For patients with a **CrCl > 50 ml/min** receiving DOAC therapy, renal function should be monitored **every 6-12 months** • For patients with a **CrCl < 50 ml/min** receiving DOAC therapy, renal function should be monitored **every 3 months**

Joint Commission's National Patient Safety Goal 03.05.01
Reduce the likelihood of patient harm associated with the use of anticoagulant therapy



Summary: DOAC Double-Check!

✓	• Double-check the indication
D	• Drug-Drug Interactions
O	• Organ Function
A	• Adjustments
C	• Counsel!

ATRIUM Cardiology Collaborative.

Anticoagulant and Antiplatelet Update

Danielle Blais, PharmD, BCPS
Specialty Practice Pharmacist
Department of Pharmacy
The Ohio State University Wexner Medical Center

MedNet21
Center for Continuing Medical Education

The Ohio State University Wexner Medical Center

Objectives

- Describe the role of aspirin and oral $P2Y_{12}$ inhibitors for patients with stable ischemic heart disease (SIHD) or acute coronary syndromes (ACS) with or without percutaneous coronary intervention (PCI)
- Evaluate the advantages and disadvantages of the different $P2Y_{12}$ inhibitors

Epidemiology

- Chest discomfort most frequent reason for ED visits
- Coronary heart disease kills about 360,000 per year
- Each year ~ 112,000 people die of a myocardial infarction
- Estimated annual incidence is 605,000 for new heart attacks and 200,000 recurrent heart attacks. Of these ~ 170,000 silent attacks.
- Myocardial infarction ($12.1 billion) and coronary heart disease ($9 billion) are 2 of the 10 most expensive conditions treated in US hospitals in 2013
- About every 40 seconds an American will suffer a heart attack

Benjamin EJ. *Circulation 2019;139:e56-e528*

Case # 1

62 YO F admitted to the Emergency Department (ED)
- Abdominal pain and nausea. A couple of days before she took a test capsule for GI study.
- Sudden urge to have a bowel movement.
- In bathroom had sudden onset of severe chest pain
  - EKG showed ST-elevation

PMH:
CAD – LAD stent (unknown type) 2016
Hyperlipidemia
Chronic diarrhea

PSH:
Cholecystectomy 1992

Case # 1

- **Patient instructed to stop both clopidogrel (Plavix) and aspirin 9 days prior to GI workup**

- STEMI alert
  - Acute thrombosis of previous LAD stent
  - Left heart catheterization with successful thrombectomy and balloon angioplasty

Case # 2

57 YO M
– Admitted for an elective urology procedure

PMH
CAD with a history of 3 cardiac stents (unknown type) in 2017
Peyronie's and Erectile Dysfunction

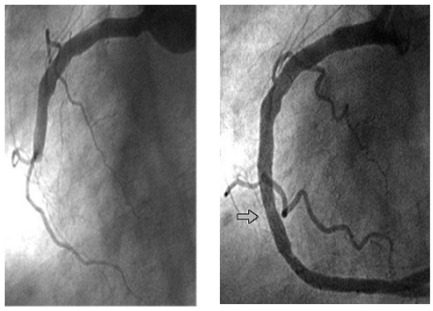
PSH
Colonscopy

Post Procedure
Chest Pain and diaphoresis

EKG showed ST-elevation

Emergent cath - 100% thrombotic occlusion of prox and mid RCA at site of previous stents
S/P thrombectomy and PCI with bare metal stent placement x 3

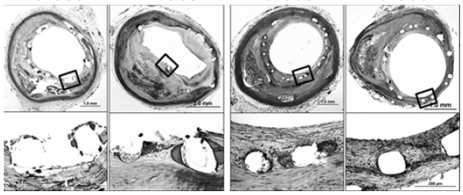
Patient instructed to discontinue aspirin for 10 days prior to procedure



Stent Evolution: Restenosis vs Stent Thrombosis

First Generation DES
Restenosis 5 – 15%

Second Generation DES
Restesnosis ≤ 5 %



American Heart Association. Pathology of Second-Generation Everolimus-Eluting Stents Versus First-Generation Sirolimus- and Paclitaxel-Eluting Stents in Humans
Fumiyuki Otsuka, MD, PhD, Marc Vorpahl, MD, Masataka Nakano, MD, Jason Foerst, MD, John B. Newell, AB, Kenichi Sakakura, MD, Robert Kutys, MS, Elena Ladich, MD, Aloke V. Finn, MD, Frank D. Kolodgie, PhD, and Renu Virmani, MD

Circulation Volume 129, Issue 2, 14 January 2014, Pages 211-223
https://doi.org/10.1161/CIRCULATIONAHA.113.001790

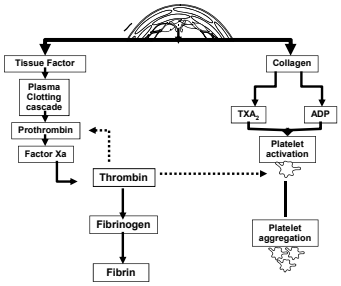
Risk of Mortality
Stent Thrombosis versus Bleeding

Mortality associated with stent thrombosis	
Drug Eluting Stents	Bare Metal Stents
17 - 45%	9 - 21%

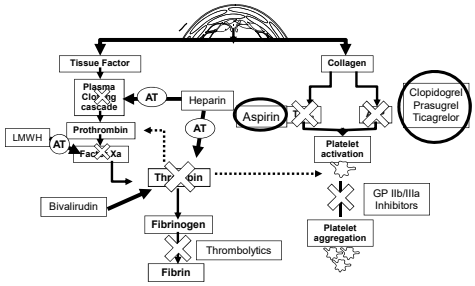
Mortality associated with bleeding after PCI at 12-24 months
7.3 - 13%

Thrombosis 2012:2012:956-962
JACC 2015;66:1036-45
Circ Cardiovasc Interv 2016;9:e003519
Circ Cardiovasc Interv 2010;3:140-7
JACC 2015;65:1411-20
JACC Cardiovasc Interv 2016;9:1450-7

Essentials of Thrombosis



Sites of Antithrombotic Action

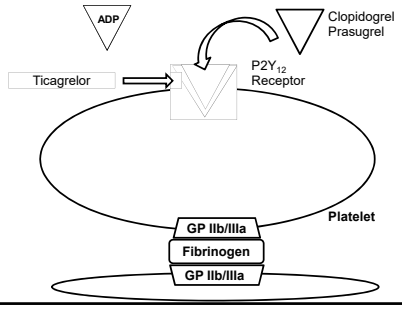


$P2Y_{12}$ Inhibitor Comparison

	Clopidogrel	Prasugrel	Ticagrelor
Loading Dose	300-600 mg	60 mg	180 mg
Maintenance Dose	75 mg daily	10 mg daily	90 mg BID
Prodrug	Yes	Yes	No
Reversible	No	No	Yes
Metabolism	CYP 2C19	CYP 3A, 2B6	CYP 3A
Time to 50% Platelet Inhibition (min)	120-240 (600 mg)	60	30
Maximal Platelet Inhibition (%)	35	79	88

Potency →

Mechanism of Action of $P2Y_{12}$ Inhibitors



Dual Antiplatelet Therapy (DAPT) Recommendations

Bare metal stent for Acute Coronary Syndromes
Aspirin 81 mg by mouth daily uninterrupted lifelong plus Clopidogrel 75mg daily or prasugrel 10mg daily or ticagrelor 90mg twice daily for a **minimum of 1 month** (Class II) **ideally at least 12 months** (Class I)
Drug eluting stent for Acute Coronary Syndromes
Aspirin 81 mg by mouth daily uninterrupted lifelong plus Clopidogrel 75mg daily or prasugrel 10mg daily or ticagrelor 90mg twice daily for a **minimum of 6 months** (Class II) **ideally at least 12 months** (Class1)
Bare metal stent for Stable Ischemic Heart Disease
Aspirin 81 mg by mouth daily uninterrupted lifelong plus Clopidogrel 75mg daily for a **minimum of 1 month** (Class 1) **consider up to 12 months** (Class II)
Drug-eluting stent for Stable Ischemic Heart Disease
Aspirin 81 mg by mouth daily uninterrupted lifelong plus Clopidogrel 75mg daily for a **minimum of 3-6 months** (Class 1) **consider up to 12 months** (Class II)
Medical management of Acute Coronary Syndromes
Aspirin 81 mg by mouth daily uninterrupted lifelong Plus Clopidogrel 75 mg daily or Ticagrelor 90 mg twice daily for **ideally at least 12 months** (Class I)

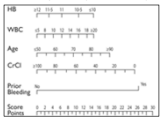
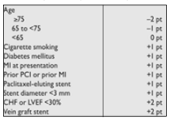
Levine GN. Circulation 2016;68:1082-1115

Find the Balance

Increased Ischemic Risk/Risk of Stent Thrombosis (May Favor Longer-Duration DAPT)	Increased Bleeding Risk (May Favor Shorter-Duration DAPT)
Advanced age Acute coronary syndrome presentation Extensive coronary artery disease Diabetes mellitus Chronic kidney disease Prior myocardial infarction Prior stent thrombosis Heart failure Current smoker	• Advanced age • Diabetes mellitus • History of prior bleeding • **Oral anticoagulant therapy** • Female sex • Low body weight Chronic kidney disease • Liver disease • Anemia • Chronic steroid or NSAID therapy
Multi-vessel disease Stent undersizing or underexpansion Small stent diameter Long stent length (>60 mm) Short stent length (<3mm) Bifurcation stents In-stent restenosis Multiple stents (≥ 3 stents) First-generation drug-eluting stent	

Levine GN. Circulation 2016;68:1082-1115
Boriani G. Eur J Intern Med 2020;77:27-29

Tools to find the balance

	PRECISE-DAPT Score	DAPT Score
Time of use	At time of coronary stenting	After 12 months of uneventful DAPT
DAPT duration strategies assessed	Short DAPT (3-6 months) vs Standard/long DAPT (12-24 months)	Standard DAPT (12 months) vs Long DAPT (30 months)
Score calculator		
Score range	0 to 100 points	-2 to 10 points
Decision making cut-off	≥ 25 → 3-6 months of DAPT <25 → 12-24 months of DAPT	≥2 → Long DAPT <2 → Standard DAPT
Limitations	• Clopidogrel 88% • Validated in PLATO cohort (Ticagrelor) • Excluded patients on long term anticoagulation	• Clopidogrel 65%; prasugrel 35% • Excluded prior bleeding/thrombotic events • Excluded patients on long term anticoagulation

Benefits of DAPT in Acute Coronary Syndromes

Study	Indication	Duration (months)	Antiplatelet Therapy	Incidence of Primary Composite Endpoint* (%)
CURE	ACS	12	Aspirin vs Aspirin + Clopidogrel	11.4 p<0.001 9.3
Triton-TIMI 38	ACS/PCI	15	Aspirin + Clopidogrel vs Aspirin + Prasugrel	12.1 p<0.001 9.9
PLATO	ACS	12	Aspirin + Clopidogrel vs Aspirin + Ticagrelor	11.7 p<0.001 9.8

***Primary Composite Endpoint** – Death from Cardiovascular (CV) Causes, Non-fatal myocardial infarction (MI) or Non-fatal stroke

N Engl J Med 2001;345:494-502
N Engl J Med 2007;357:2001-2015
N Engl J Med 2009;361:1045-1047

Risks of DAPT in Acute Coronary Syndromes

Study	Indication	Duration	Antiplatelet Therapy	Incidence of Major Bleeding (%)
CURE	ACS	12	Aspirin vs Aspirin + Clopidogrel	2.7 3.7 p=0.001
Triton-TIMI 38	ACS/PCI	15	Aspirin + Clopidogrel vs Aspirin + Prasugrel	1.8 2.4 p=0.03
PLATO	ACS	12	Aspirin + Clopidogrel vs Aspirin + Ticagrelor	2.2 2.8 p=0.03

These rates are under the umbrella of a clinical trial **NOT** real world
Patients who require oral anticoagulation are excluded

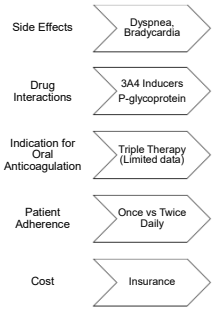
N Engl J Med 2001;345:494-502
N Engl J Med 2007;357:2001-2015
N Engl J Med 2009;361:1045-1047e

$P2Y_{12}$ Recommendations in Acute Coronary Syndromes

Recommendations	COR	LOE
It is reasonable to choose ticagrelor over clopidogrel in ACS patients treated with an early invasive strategy and/or PCI.	IIa	B-R
It is reasonable to choose prasugrel over clopidogrel in ACS patients who undergo PCI who are not at high risk for bleeding complications.	IIa	B-R
In ACS patients managed with medical therapy alone (without revascularization or fibrinolytic therapy) treated with DAPT, it is reasonable to use ticagrelor in preference to clopidogrel.	IIa	B-R
Prasugrel **should not** be administered to patients with a prior history of stroke or TIA.	III: Harm	B-R

Levine GN. Circulation 2016;68:1082-1115

Factors Preventing Continuation of Ticagrelor



Drug Interactions with Ticagrelor

- Ticagrelor is metabolized by CYP 3A
- Weak CYP 3A inhibitor

Strong CYP 3A inhibitors	CYP 3A inducers	CYP 3A substrates
Antiretrovirals	Carbamazepine	Cyclosporine
Clarithromycin	Rifampin	Tacrolimus
Ketoconazole	Phenytoin	Amlodipine
Itraconazole	Dexamethasone	Diltiazem, Verapamil
Voriconazole	Phenobarbital	Ator, simva, lovastatin

Simvastatin and lovastatin doses limited to no more than 40 mg

- Ticagrelor and active metabolite are P-glycoprotein (PgP) substrates and weak inhibitors PgP
  - Monitor digoxin levels
  - Dabigatran

Switching Between P2Y12 Inhibitors

Dosing for P_2Y12 Receptor Inhibitors

Loading Dose	Maintenance Dose	If converting to alternative P_2Y12	
Clopidogrel 600 mg x 1	Clopidogrel 75 mg daily (start the next day)	Prasugrel* 10 mg daily (start the next day)	Ticagrelor** 180 mg x 1 (24 hrs after Last Clopidogrel Dose) then Ticagrelor 90 mg Q 12 hrs (12 hrs after the loading dose)
Prasugrel 60 mg x 1 **Contraindications:** History of CVA, Thrombolytic use in the past 24 hours **Relative contraindications:** Age ≥75, Weight <60 kg, Active bleeding, surgery, oral anticoagulant use **Indicated for ACS patient who are managed with PCI**	Prasugrel 10 mg daily (start the next day)	Clopidogrel 75 mg daily (start the next day)	Ticagrelor 180 mg x 1 (24 hrs after Last Prasugrel Dose) then Ticagrelor 90 mg Q 12 hrs (12 hrs after the loading dose)
Ticagrelor 180 mg x 1 **Contraindications:** History of ICH **Relative contraindications:** Risk for bradycardia, severe hepatic dysfunction, strong CYP3A inhibitors, dyspnea at baseline, oral anticoagulant use, Thrombolytic use in the past 24 hours	Ticagrelor 90 mg Q 12 hrs (12 hrs after the loading dose)	Clopidogrel 600 mg x 1 (24 hrs after Last Ticagrelor Dose) then Clopidogrel 75 mg daily (start the next day)	Prasugrel 60 mg x 1 (24 hrs after Last Ticagrelor Dose) then Prasugrel 10 mg daily (start the next day)

ACS = Acute Coronary Syndrome, CVA = Cerebral Vascular Accident, ICH = Intracranial hemorrhage, PCI = Percutaneous Coronary Intervention, TIA = transient ischemic attack,

*In the setting of an ACS loading dose of prasugrel 60 mg can be given during or after the PCI.

**In the setting of an ACS a loading dose of ticagrelor 180 mg can be given immediately at the time of presentation, during or after the PCI.

Conclusions

- Understanding the current recommendations for DAPT is critically important
- Early discontinuation of DAPT is problematic
- Patients should remain on at least one antiplatelet medication following stent placement
- Patient education is key
  - Pharmacists can be instrumental in providing this education
- Work together with the patients cardiologist to ensure safe transitions of care