

# The Evolving History of Anticoagulation: The DOAC Era?

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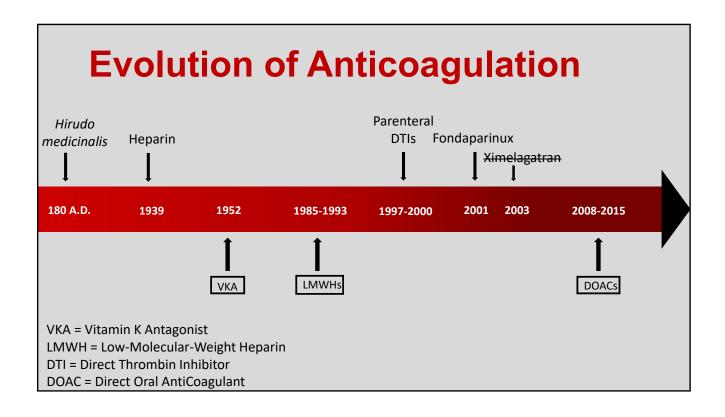
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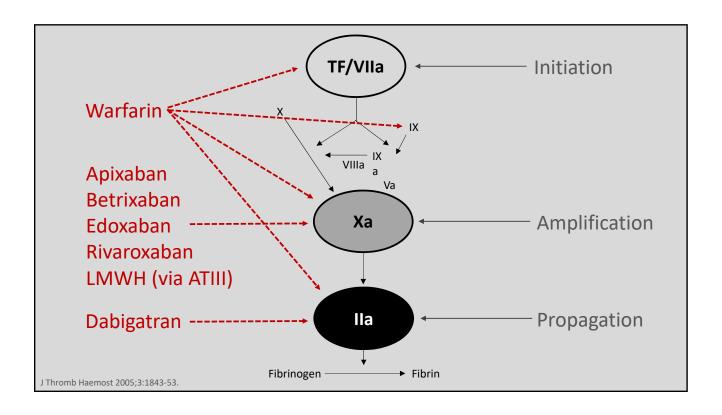
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# **Objectives**

- 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





FD.	A Ap	prov	ed O	ral An	ticoag	julant	S
	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®)	<b>√</b>	<b>√</b>	<b>√</b>	<b>√</b>	<b>√</b>	<b>√</b>	1
Dabigatran (Pradaxa®)	✓	✓	✓	✓			
Rivaroxaban (Xarelto®)	✓	✓	✓	✓	✓		<b>✓</b>
Apixaban (Eliquis®)	✓	✓	✓	✓			
Edoxaban (Savaysa™)	✓	✓	✓				
Betrixaban (Bevyxxa™)					✓		

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

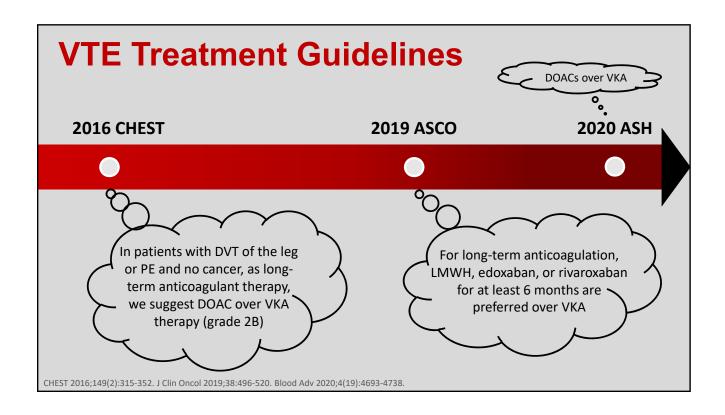
Oral	Antico	agulant	s Comp	arison	
Characteristics	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Half life	40 h	12-14 h	7-13 h	8-13 h	10-14 h
Peak effect	4-5 days	1.5-3 h	2–4 h	1-3 h	1-2 h
Renal elimination	None	80%	33%	25%	35-50%
VTE Initial Phase: Oral Only?	No	No	Yes	Yes	No
VTE Secondary Phase 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 20	016;41,15-31.				

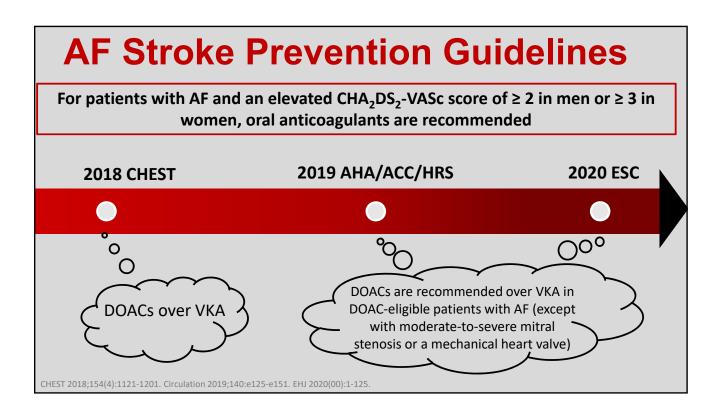
## **DOACs vs Warfarin for VTE**

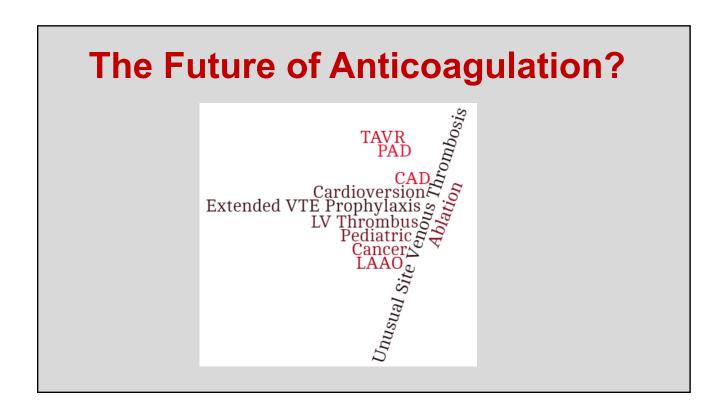
	Dabigatran (RE-COVER)	Rivaroxaban (EINSTEIN)	Apixaban (AMPLIFY)	Edoxaban (Hokusai-VTE)
Recurrent Symptomatic VTE or VTE-related Death	Equal	Equal*	Equal	Equal*
Major Bleeding	Equal	Ψ	Ψ	Equal
Major and Clinically Relevant Non-Major Bleeding	•	Equal	•	Ψ

\*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







## **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

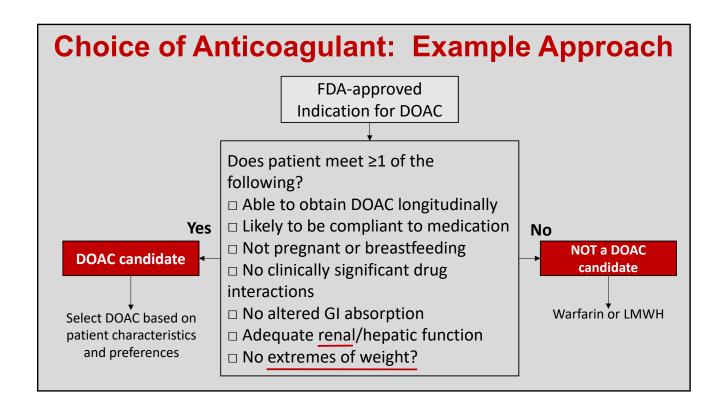
#### **FAERs Database**

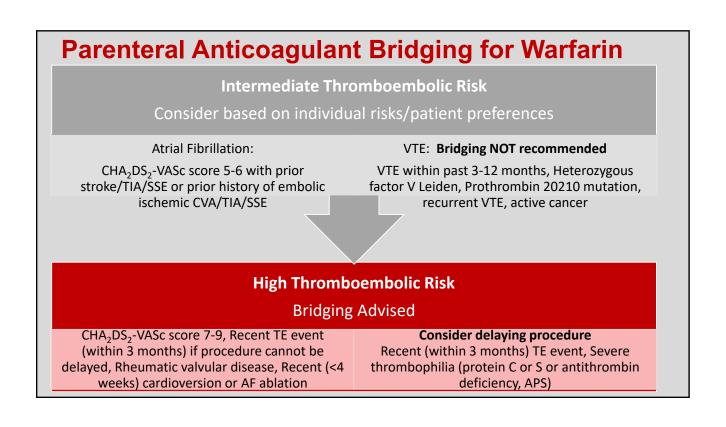
- 42 964 cases
- Rivaroxaban with highest rate per prescription for each ADR
- Dabigatran had the highest reported rates of ischemic stroke
- Warfarin with lowest rate per prescription for each ADR

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

## **Limitations of DOAC Use**

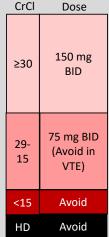
- Mechanical heart valves
- Antiphospholipid syndrome
- Pregnancy and breastfeeding
- Moderate or severe hepatic impairment (Child-Pugh B or C)
- CYP3A4 and P-gp strong inducers/inhibitors
  - Examples of P-gp inducers: carbamazepine, rifampin, St. John's Wort
  - Examples of P-gp inhibitors: amiodarone,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





# **DOACs in Renal Impairment**





CrCl in mL/min

Am J Med 2017;130:1015-1023

### 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

\*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

			Weight or BMI Cutoff	Proportion of Obese Patients (%)
Dabigatran	RE-COVER I/II	VTE	≥ 35 kg/m <sup>2</sup>	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/m <sup>2</sup>	28.5, 13.6
Apixaban	AMPLIFY ARISTOTLE	VTE AF	≥ 35 kg/m <sup>2</sup> > 30 kg/m <sup>2</sup>	13 40
Edoxaban	HOKUSAI VTE	VTE	> 100 kg	14.8
	ENGAGE AF-TIMI 48	AF	None	NR

## **DOACs in Morbidly Obese**

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

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

D = Dabigatran R = Rivaroxaban A = Apixaban

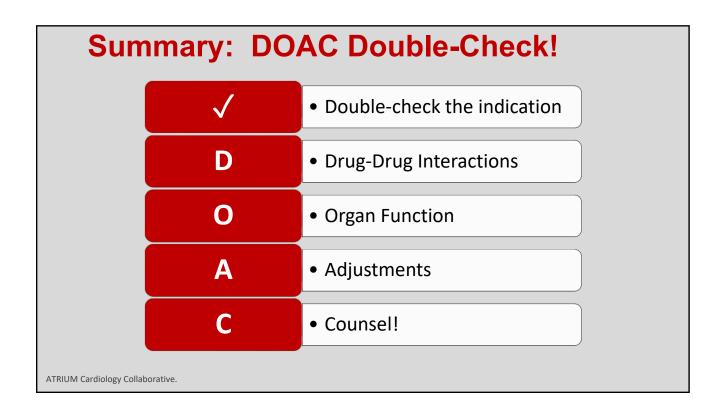
DOAC	Drug S	Selection		
Characteristics	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
All-oral therapy		<b>✓</b>	✓	
Dyspepsia or GI issues		<b>√</b>	<b>√</b>	<b>✓</b>
GI bleed			✓	√ (low dose)
Significant CAD		✓	✓	✓
Poor compliance with BID		<b>√</b>		<b>√</b>

dosing CrCl < 30

mL/min

Resource	Recommendation
European Heart Rhythm Association Non-valvular Atrial Fibrillation Guidelines (2015)	"Patients should return on a regular basis for ongoing reviewpreferably 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)	<ul> <li>For patients with a CrCl &gt; 50 ml/min receiving DOAC therapy, renal function should be monitored every 6-12 months</li> <li>For patients with a CrCl &lt; 50 ml/min receiving DOAC therapy, renal function should be monitored every 3 months</li> </ul>







### **Anticoagulant and Antiplatelet Update**

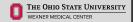
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## **Objectives**

- Describe the role of aspirin and oral P2Y<sub>12</sub> 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<sub>12</sub> 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 Gl workup
- STEMI alert
  - Acute thrombosis of <u>previous LAD stent</u>
  - Left heart catheterization with successful thrombectomy and balloon angioplasty

## **Case # 2**

57 YO M

Admitted for an <u>elective</u> urology procedure

#### **PMH**

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

#### PSH

Colonscopy

#### **Post Procedure**

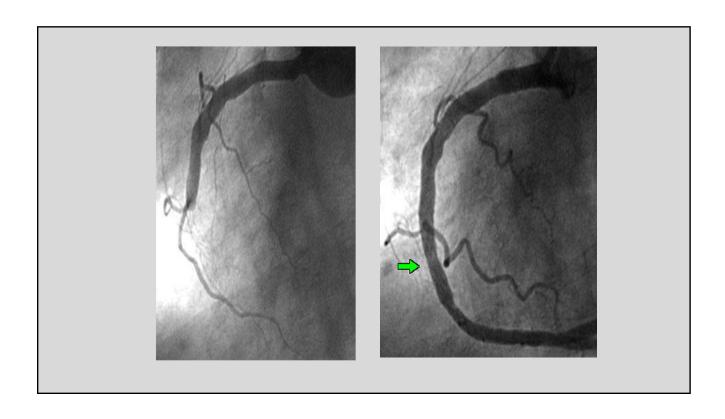
Chest Pain and diaphoresis

**EKG** showed ST-elevation

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

Patient instructed to discontinue aspirin for 10 days prior to procedure



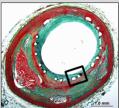


# Stent Evolution: Restenosis vs Stent Thrombosis

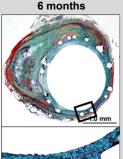
First Generation DES Restenosis 5 – 15% Second Generation DES Restesnosis ≤ 5 %

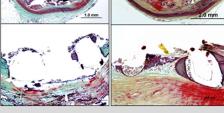
13 months





3 months





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

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CirculationVolume 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** 

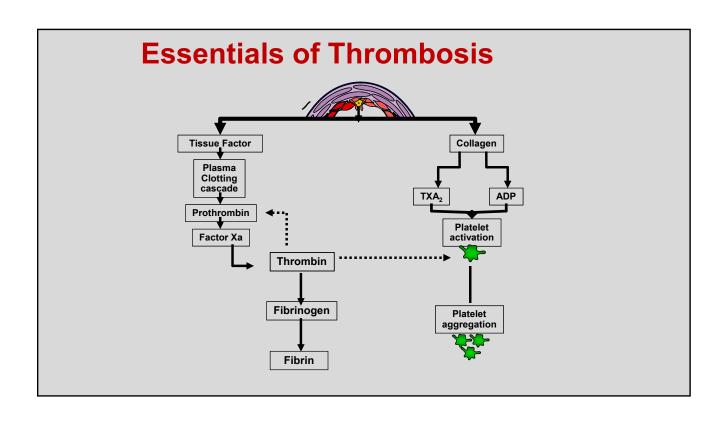
17 - 45%

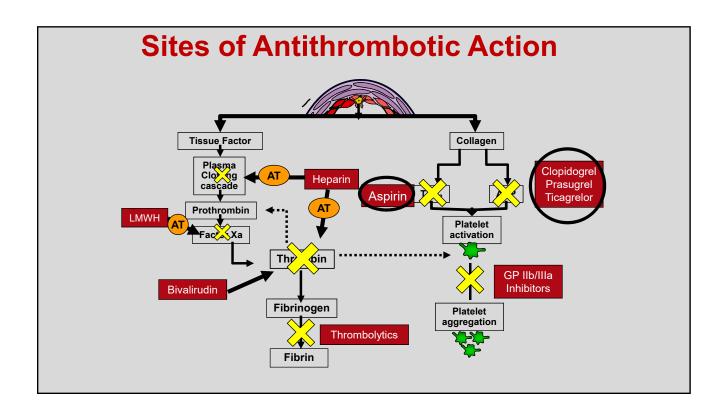
9 - 21%

Mortality associated with bleeding after PCI at 12-24 months

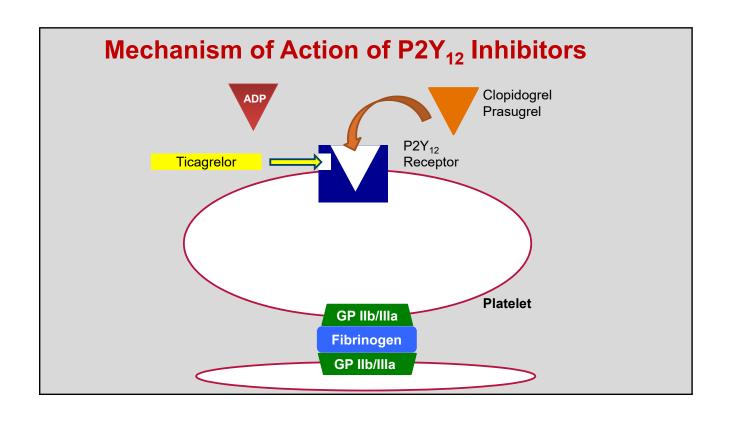
7.3 - 13%

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





	Clopidogrel	Prasugrel	Ticagrelor
oading 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
Fime to 50% Platelet Inhibition (min)	120-240 (600 mg)	60	30
Maximal Platelet Inhibition (%)	35	79	88



#### **Dual Antiplatelet Therapy (DAPT) Recommendations**

Bare metal stent for Acute Coronary Syndromes

Aspirin 81 mg by mouth daily uninterrupted lifelong

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

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)

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

**Increased Bleeding Risk** 

(May Favor Shorter-Duration DAPT)

- 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

	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 month vs Long DAPT (30 months)	,
Score calculator	HB	Age  z75 65 to <75 <65 Cigarette smoking Diabetes mellitus MI at presentation Prior PCI or prior MI Paclitaxel-eluting stent Stent diameter <3 mm CHF or LVEF <30% Vein graft stent	-2 pt -1 pt 0 pt +1 pt +1 pt +1 pt +1 pt +1 pt +1 pt +2 pt +2 pt
Score range	0 to 100 points	-2 to 10 points	
Decision making cut-off	$\geq$ 25 $\rightarrow$ 3-6 months of DAPT <25 $\rightarrow$ 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	<ul> <li>Clopidogrel 65%; prasugrel 35%</li> <li>Excluded prior bleeding/thromb events</li> <li>Excluded patients on long term anticoagulation</li> </ul>	

# **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 p=0.001 3.7
Triton- TIMI 38	ACS/PCI	15	Aspirin + Clopidogrel vs Aspirin + Prasugrel	1.8 p=0.03 2.4
PLATO	ACS	12	Aspirin + Clopidogrel vs Aspirin + Ticagrelor	2.2 p=0.03 2.8

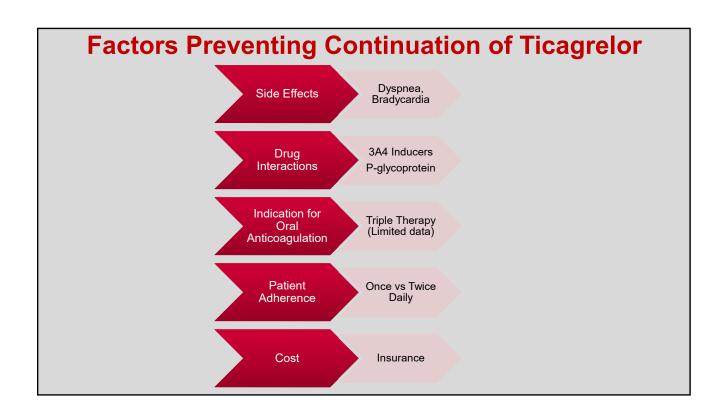
These rates are under the umbrella of a clinical trial **NOT** real world Patients who require oral anticoagulation are excluded

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<sub>12</sub> Recommendations** in Acute Coronary Syndromes

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

Levine GN. Circulation 2016;68:1082-1115



### **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**

1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1		Receptor Inhib	11010	
Loading Dose	Maintenance Dose	If converting to alternative P <sub>2</sub> Y12		
Clopidogrel	Clopidogrel	Prasugrel*	Ticagrelor**	
600 mg x 1	75 mg daily (start the next day)	10 mg daily (start the next day)	180 mg x 1 ( <u>24 hrs</u> after Last Clopidogrel Dose)	
			then	
			Ticagrelor 90 mg Q 12 hrs (12 hrs after the loading dose)	
Prasugrel	Prasugrel	Clopidogrel	Ticagrelor	
60 mg x 1	10 mg daily (start the next day)	75 mg daily (start the next day)	180 mg x 1 ( <u>24 hrs</u> after Last	
Contraindications: History of ICH, TIA/CVA, Thrombolytic use in the past 24 hours			Prasugrel Dose) then	
Relative contraindications; Age ≥75, Weight <60 kg. recent trauma/surgery, oral anticoagulant use			Ticagrelor 90 mg Q 12 hrs (12 hrs after the loading dose)	
Indicated for ACS patient who are managed with PCI			0.000-0.00	
Ticagrelor	Ticagrelor	Clopidogrel	Prasugrel	
180 mg x 1  Contraindications: History of ICH	90 mg Q 12 hrs (12 hrs after the loading dose)	600 mg x 1 ( <u>24 hrs</u> after Last Ticagrelor Dose)	60 mg x 1 ( <u>24 hrs</u> after Last Ticagrelor Dose)	
Relative contraindications: Risk for bradycardia, severe hepatic dysfunction, strong CYPSA4 inhibitor/inducer, severe dyspnea at baseline, oral anticoagulant use, Thrombolytic use in the past 24 hours		then Clopidogrel 75 mg daily (start the next day)	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,

## **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

<sup>\*</sup>In the setting of an ACS loading dose of prasugrel 60 mg can be given <u>during or after</u> the PCI.

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