Recent advances in antiplatelet therapy

Introduction

- Acute coronary syndrome (ACS) describes the range of ischemic states that includes unstable angina (UA), non-ST elevated myocardial infarction (NSTEMI), or ST-elevated myocardial infarction (STEMI).
- The diagnosis is based on a thorough review of clinical features, including electrocardiogram (ECG) findings and biochemical markers of myocardial necrosis.
- Acute coronary syndrome continues to be a significant cause of morbidity and mortality.

Smith JN et al. J Am Board Fam Med. 2015 Mar-Apr;28(2):283-93.
Khaled S et al. Indian Heart J. 2018 Jan - Feb;70(1):45-49.

Introduction

- Activation of platelets on a ruptured or eroded atherosclerotic plaque is a key event in atherothrombosis, including acute coronary syndromes
- Activated platelets trigger and disseminate vascular inflammation by exposure and release of pro-inflammatory molecules, contributing to the progression of atherosclerosis.
- Platelet P2Y12 receptors for adenosine diphosphate (ADP) are essential for platelet activation.

Kubisa MJ et al. Ther Clin Risk Manag. 2018 Jan 17;14:129-140

Burden of ACS worldwide

- It is the greatest single cause of mortality and loss of disability-adjusted life years (DALYs) worldwide, accounting for seven million deaths and 129 million DALYs annually
- High income countries (HICs) continue to deal with significant ischemic heart disease (IHD) mortality, nearly two-thirds of all IHD DALYs and over half of deaths occur in low and middle-income countries (LMICs).
- In addition, the age-standardized mortality rates from IHD are higher in many LMICs than in HICs, thus indicating more individuals are dying at a younger age from IHD in LMICs

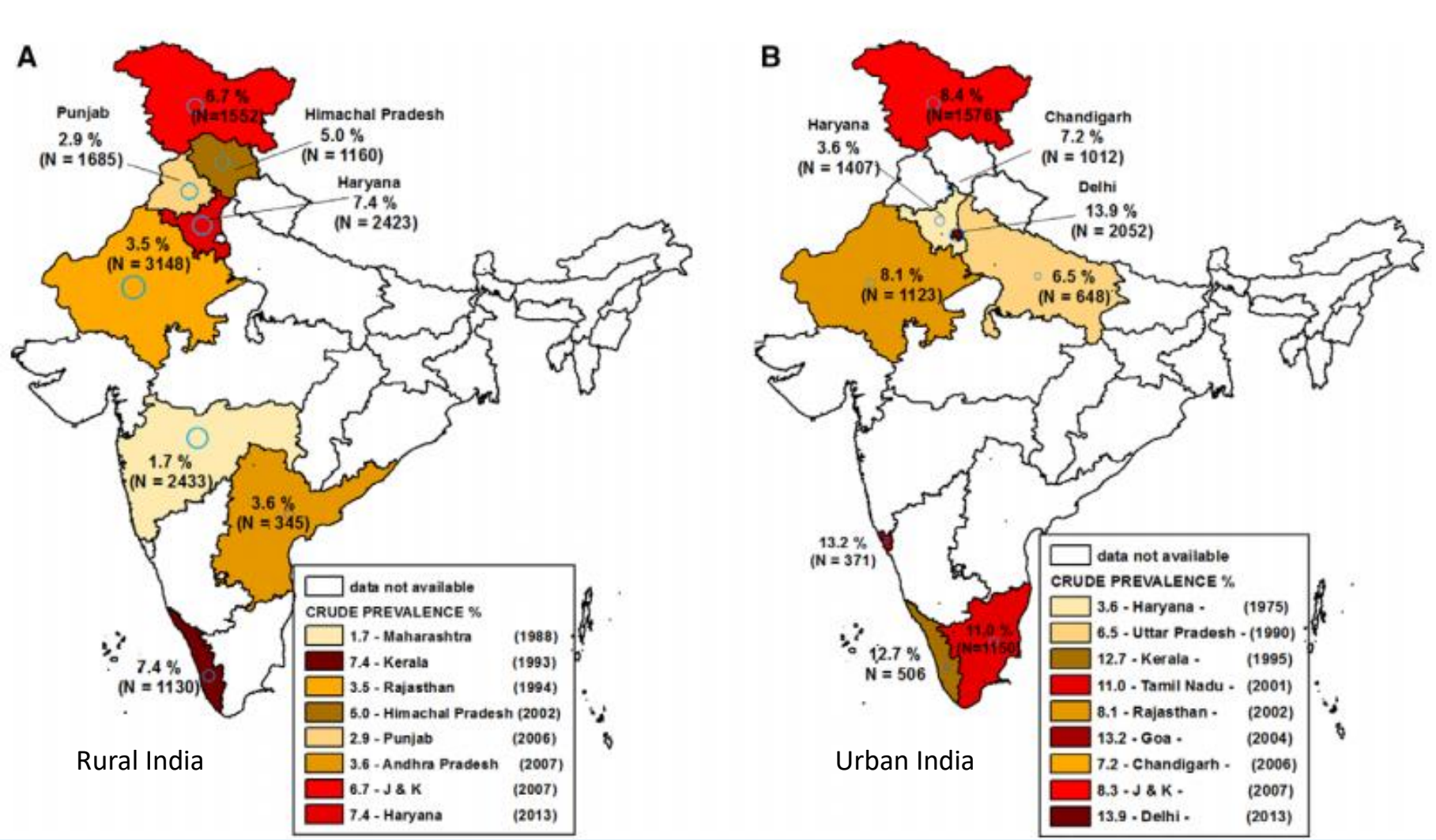
Vedanthan R et al. Circ Res. 2014 Jun 6; 114(12): 1959–1975.

ACS in india

- As per World Health Organisation (WHO) data, the Coronary Artery Disease (CAD) prevalence continues to rise in India with rapid ‘epidemiological transition’.
- The rising incidence of CAD in young Indians is of particular concern.
- The incidence of CAD in young population in Western countries is 2–5%, whereas it is 11–16% in Asian Indians.
- The Global Burden of Disease study estimate age-standardized CVD death rate is 272 per 100 000 in Indian population, higher than the global average of 235 per 100 000 population.

Guha S et al. Indian Heart J. 2017 Apr;69 Suppl 1:S63-S97.

Prevalence of ischemic heart disease in india



Prabhakaran D et al. Circulation. 2016;133(16):1605-20

Decreasing the burden of ACS

- First, similarly to other diseases , lifestyle risk factors may have synergistic and multiplicative health effects rather than an additive effect in ACS patients.
- Second, evidence of varying degrees of co-occurrence of lifestyle risk factors may better direct more effective behavioral change interventions for the secondary prevention of ACS.
- Cardiac rehabilitation for secondary prevention of ACS mainly focuses on the promotion of healthy behavioral change in terms of quitting smoking, adopting healthy eating habits and being physically active.

Kalra K et al. Curr Atheroscler Rep. 2013 ;15(12):371.

Decreasing the burden of ACS

- Management of ACS is determined by the patient's risk.
- In the case of ACS, to complete coronary occlusion, STEMI, the goal is for immediate revascularization to salvage myocardium.
- For NSTEMI and unstable angina (UA), treatment is to mitigate the changes of recurrent infarction and/or to reduce the size of infarction.
- Medical therapy is guided by the degree of patient risk for ischemic complications and balanced against the risk for bleeding or other complications from these treatments.

Kalra K et al. Curr Atheroscler Rep. 2013;15(12):371.
Hyun KK et al.BMC Health Serv Res. 2016;16(1):636

Antiplatelet therapy and ACS

- Antiplatelet therapy has formed the backbone of ACS management for decades
- This drug class continues to evolve as novel agents with increasingly efficacious antiplatelet actions are identified.
- The main risk associated with all antiplatelet therapies is bleeding.
- There is a need to carefully weigh the possible adverse effects against the benefits of prescribing these drugs to patients with ACS.

Layne K et al. European Cardiology Review 2017;**12**(1):33–7.

Dual Antiplatelet therapy

- Dual antiplatelet therapy (DAPT) is combining aspirin and a P2Y12 receptor inhibitor.
- It has been consistently shown to reduce recurrent major adverse cardiovascular events (MACE) in patients with ACS or undergoing percutaneous coronary intervention (PCI) for stable CAD
- Dual antiplatelet therapy (DAPT) provides more intense platelet inhibition resulting in incremental reductions in the risk of thrombotic events after PCI or ACS, but with risk of bleeding.
- The choice of optimal DAPT regimen and duration for patients with CAD requires a tailored approach based on the patient clinical presentation, baseline risk profile and management strategy.

Degrauwe S et al. Open Heart. 2017;4(2):e000651.

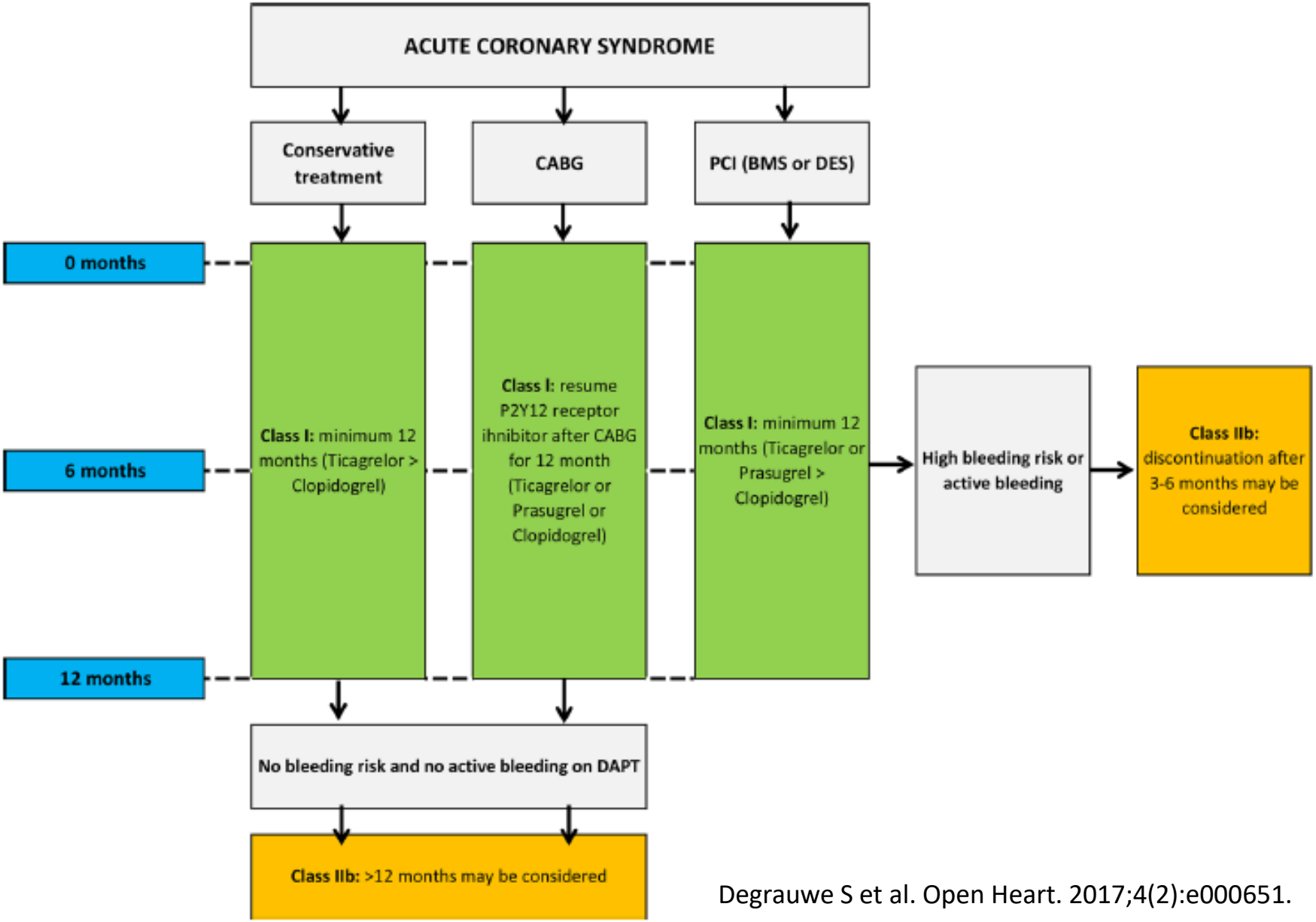
Anti platelet therapy in acute coronary syndrome

	Aspirin	Clopidogrel	Prasugrel	Ticagrelor
Molecule chemical class	Acetylsalicylic acid	Thienopyridine	Thienopyridine	Cyclopentyl-triazolo-pyrimidine
Route of administration	Oral	Oral	Oral	Oral
Mechanism of action	Cyclo-oxygenase-1 inhibition	$P2Y_{12}$ receptor inhibition	$P2Y_{12}$ receptor inhibition	$P2Y_{12}$ receptor inhibition
Loading dose	150–300 mg (80–150 mg intravenously)	300–600 mg	60 mg	180 mg
Maintenance dose	75–150 daily	75 mg daily	10 (5) mg daily	90 mg twice daily
Activation	Prodrug, hydrolysis by an esterase	Prodrug, variable hepatic metabolism	Prodrug, predictable hepatic metabolism	Active drug with additional active metabolite
Action	Irreversible	Irreversible	Irreversible	Reversible
Action onset	30–40 min	2–6 hours	30 min	30 min
Action duration	5 days	3–10 days	7–10 days	3–5 days
Interruption before surgery	No interruption when possible (5 days if high bleeding risk surgery)	5 days	7 days	5 days
Plasmatic half-life of prodrug	2–3 hours	30–60 min	30–60 min	6–12 hours
Inhibition of adenosine reuptake	No	No	No	Yes
Indications	► Stable CAD ► ACS	► Stable CAD ► ACS	► ACS scheduled for PCI	► ACS ► Stable CAD after MI
Contraindications	► Active bleeding ► Hypersensibility to aspirin ► Severe hepatic failure	► Active bleeding ► Severe hepatic failure	► Active bleeding ► History of stroke or TIA ► Severe hepatic failure (Child-Pugh C)	► Active bleeding ► History of intracranial bleeding ► Moderate to severe hepatic failure ► Coadministration with potent cytochrome CYP3A4 inhibitors

ACS, acute coronary syndrome; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack.

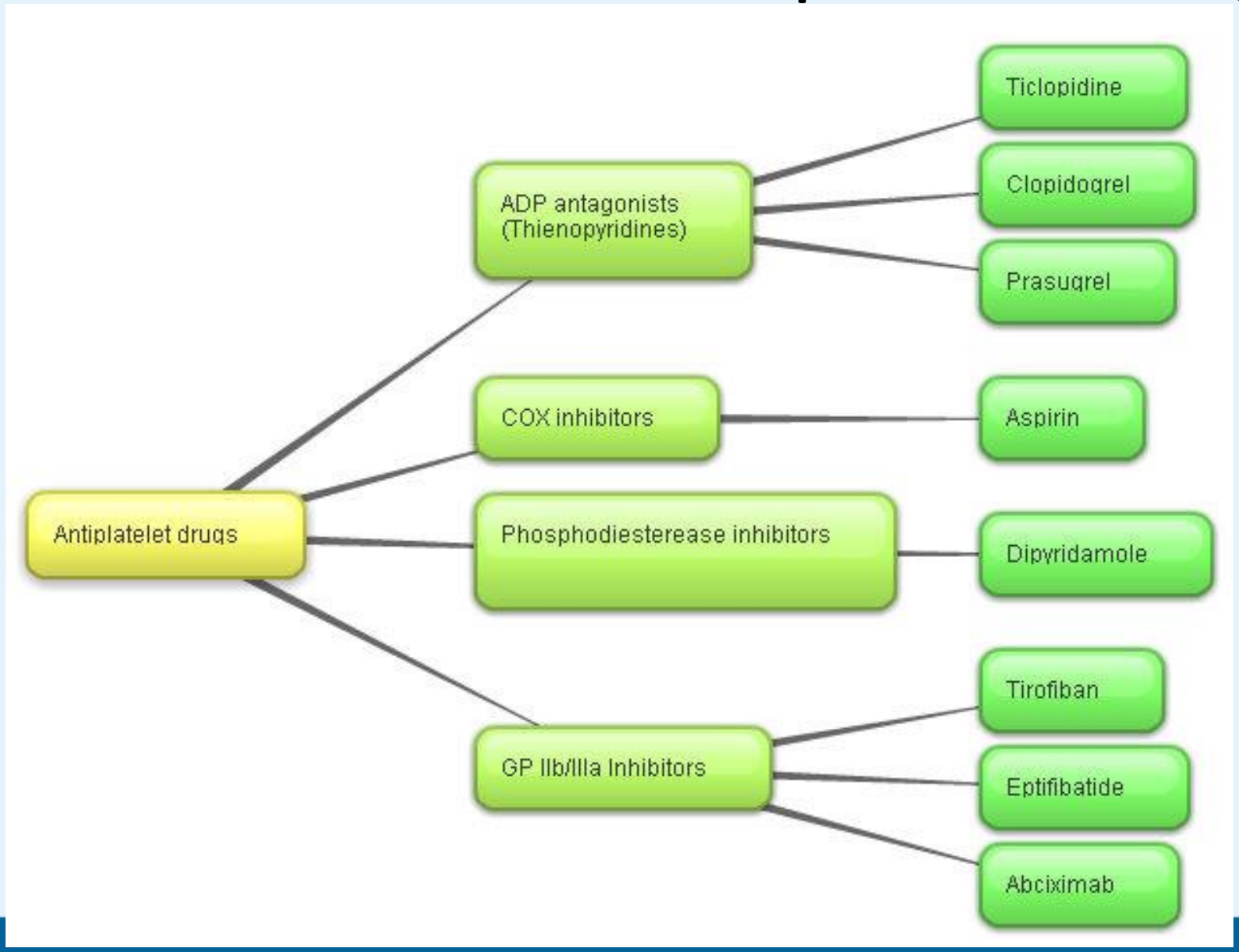
Degrauwe S et al. Open Heart. 2017;4(2):e000651.

P2Y12 receptor inhibitor therapy for secondary prevention of patients with ACS

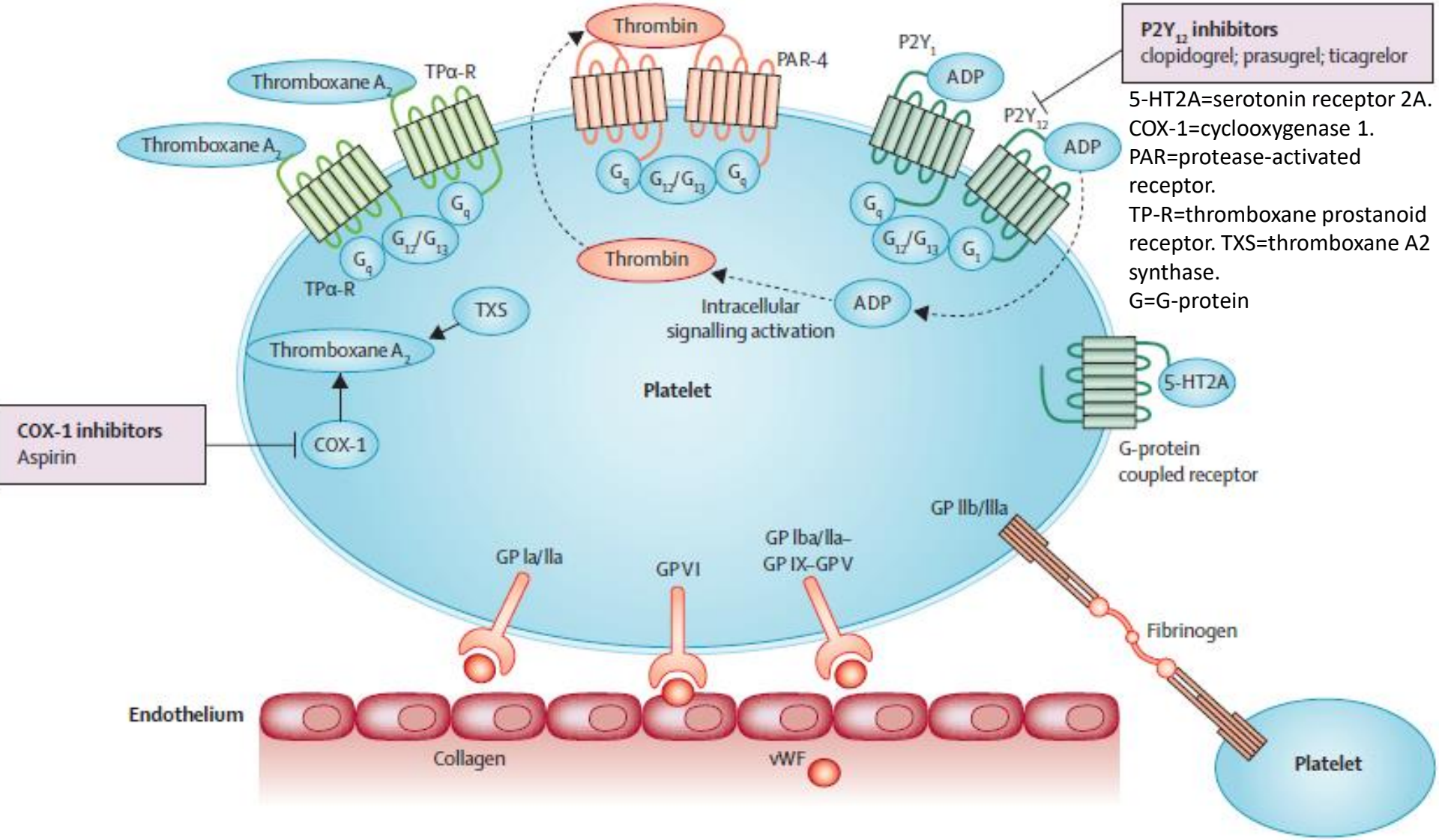


Degrauwe S et al. Open Heart. 2017;4(2):e000651.

Classification of anti platelet drugs



Platelet pathways and antiplatelet therapies



5-HT2A=serotonin receptor 2A.
COX-1=cyclooxygenase 1.
PAR=protease-activated receptor.
TP-R=thromboxane prostanoid receptor. TXS=thromboxane A2 synthase.
G=G-protein

Mega JL et al. Lancet. 2015 ;386(9990):281-91.

Unmet need

- Clopidogrel, the most widely used P2Y12 inhibitor, has a number of limitations.
- Despite the widespread use of clopidogrel, there is a rate of recurrent cardiovascular (CV) events of at least 10% within 1 year of an ACS event. These events are related to the irreversible inhibition of platelets that persists throughout the lifetime of the platelet.
- This complicates management in patients who might require surgery and would therefore be at increased risk of bleeding.
- Clopidogrel requires hepatic conversion to an active metabolite (a thienopyridine characteristic), resulting in delayed onset of effect and posing the potential for variable interindividual platelet effects associated with variable metabolism.

Dobesh PP et al. Pharmacotherapy. 2014 ;34(10):1077-90.
Husted S et al Cardiovasc Ther. 2009 Winter;27(4):259-74.

Unmet need

- The P2Y12- receptor inhibitor prasugrel overcame a number of limitations of clopidogrel but has a similar chemical structure (thienopyridine).
- Prasugrel must be activated through metabolism to provide antiplatelet effects.
- Prasugrel has good inhibitory effect on platelets and lower risk of myocardial infarction and stent thrombosis, but it is associated with a higher risk of major bleeding in patients.

Dobesh PP et al. Pharmacotherapy. 2014 ;34(10):1077-90.
Husted S et al Cardiovasc Ther. 2009 Winter;27(4):259-74.

Unmet need

- Clopidogrel effects are modest and responses to this agent are variable, including hyporesponsiveness that has been associated with increased risk of adverse clinical outcomes.
- These drawbacks may be partly overcome with prasugrel, a new thienopyridine agent that is more efficiently metabolized to its active form and whose magnitude and consistency of platelet ADP inhibition is greater than clopidogrel.
- Hence the need arises for a drug which has distinct pharmacologic properties compared with those of the thienopyridines which is effective and well tolerable

Dobesh PP et al. Pharmacotherapy. 2014 ;34(10):1077-90.
Husted S et al Cardiovasc Ther. 2009 Winter;27(4):259-74.

The Need for the Novel Antiplatelet

- Oral antiplatelet therapy is a cornerstone of antithrombotic treatment in patients with acute coronary syndromes (ACS)

- However, Clopidogrel, the most widely used P2Y12 inhibitor, has a number of limitations. Despite the widespread use of clopidogrel, there is high rate of recurrent cardiovascular (CV) events within 1 year of an ACS event.

- Clopidogrel has irreversible inhibition of platelets (a thienopyridine characteristic) that persists throughout the lifetime of the platelet.

- This may complicate management in patients who might require surgery and would therefore be at increased risk of bleeding.

- Clopidogrel requires hepatic conversion to an active metabolite (a thienopyridine characteristic), resulting in delayed onset of effect

The Need for the Novel Antiplatelet

- Prasugrel overcame a number of limitations of clopidogrel, but Prasugrel must be activated through metabolism to provide antiplatelet effects.

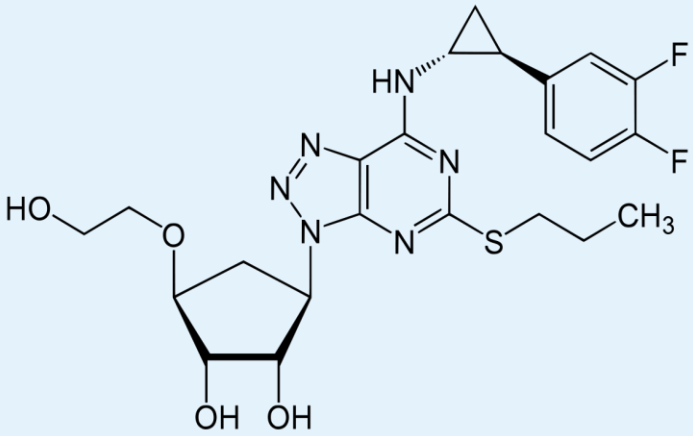
- Prasugrel has good inhibitory effect on platelets and lower risk of myocardial infarction and stent thrombosis, but it is associated with a higher risk of major bleeding in patients

- Hence the need arises for an antiplatelet drug which has distinct pharmacologic properties compared with those of the thienopyridines which is effective and well tolerable.

Ticagrelor

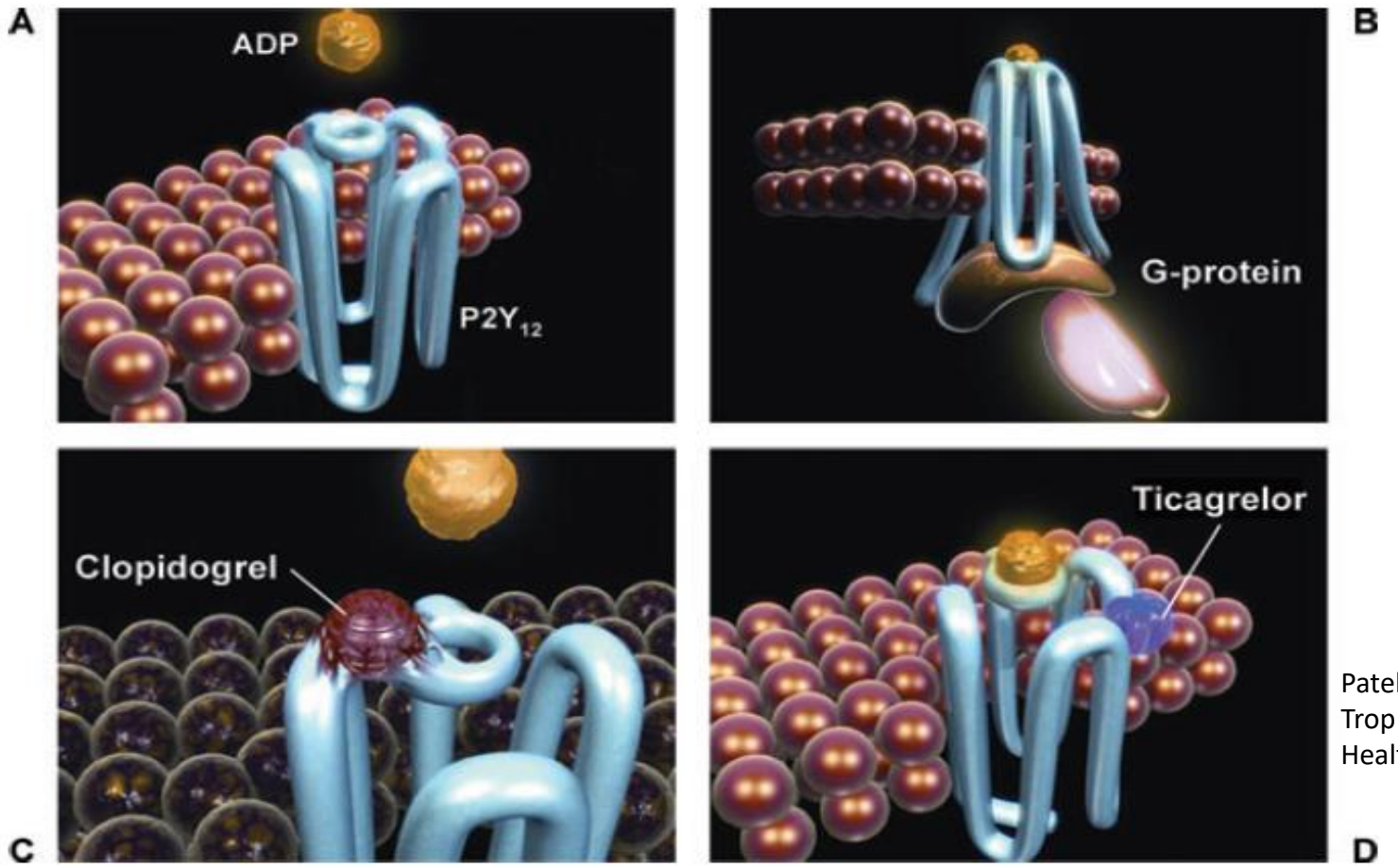
Ticagrelor

- **Ticagrelor is a cyclopentyl-triazolo-pyrimidine (CPTP), a class of antiplatelet agents that differs from both thienopyridines and adenosine triphosphate (ATP) analogs.**
- **Ticagrelor is the first reversibly binding oral P2Y12 receptor antagonist that blocks ADP-induced platelet aggregation.**
- **Ticagrelor addressed many of the limitations of thienopyridine therapy**



Al-Salama ZT et al.Drugs. 2017;77(18):2025-2036.

Mechanism of action



Patel TV et al. Ann Trop Med Public Health 2013;6:14-9

(A and B) ADP binds to the P2Y12 receptor, resulting in conformational change and G-protein activation. **(C)** Binding of the clopidogrel active metabolite to the P2Y12 receptor is irreversible, rendering the receptor nonfunctional for the life of the platelet. **(D)** Ticagrelor binds reversibly to P2Y12 at a site distinct from the ADP-binding site and inhibits ADP signaling and receptor conformational change by “locking” the receptor in an inactive state; the receptor is functional after dissociation of the ticagrelor molecule. ADP can still bind at its binding site, and the degree of receptor inhibition is dependent on the concentration of Ticagrelor.

INDICATIONS

- Indicated for the prevention of thrombotic events (cardiovascular death, myocardial infarction and stroke) in patients with Acute coronary syndromes (ACS) unstable angina, non ST elevation Myocardial infarction (STEMI) including patients managed medically.
- Also indicated in those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG).

https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022433s020lbl.pdf. Accessed on 07-11-19.

DOSAGE AND ADMINISTRATION

- In the management of ACS, initiate Ticagrelor treatment with a 180 mg (Two 90 mg tablets) of loading dose. Administer 90 mg twice daily during the first year after an ACS event.
- Ticagrelor can be administered with or without food.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022433s020lbl.pdf. Accessed on 07-11-19.

WARNINGS AND PRECAUTIONS

- Like other antiplatelet agents, ticagrelor increases the risk of bleeding.
- Dyspnea was reported more frequently with Ticagrelor. Dyspnea is self-limiting.
- **Severe Hepatic Impairment:** Avoid use of ticagrelor in patients with severe hepatic impairment.
- **Concomitant Aspirin Maintenance Dose:** Use ticagrelor with a maintenance dose of aspirin of 75-100 mg and not to exceed it.
- **Bradyarrhythmias** – AV block have been reported.
- **Renal Impairment:** No dosage adjustment is needed in patients with renal impairment. Patients receiving dialysis have not been studied

https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022433s020lbl.pdf. Accessed on 07-11-19.

ADVERSE EFFECTS

Most common adverse reactions are:

- Bleeding
- Dyspnea
- Dizziness
- Diarrhea

CONTRAINDICATIONS

- Active Bleeding
- Contraindicated in patients with known Hypersensitivity to the active substance, or to any of the excipients.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022433s020lbl.pdf. Accessed on 07-11-19.

DRUG INTERACTIONS

CYP3A inhibitors and inducers: Avoid use of strong inhibitors of CYP3A (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, ritonavir, indinavir) and inducers (e.g, rifampin, dexamethasone, phenytoin, carbamazepine and Phenobarbital).

Other Concomitant Therapy: Ticagrelor can be administered with unfractionated or low-molecular-weight heparin, GPIIb/IIIa inhibitors, proton pump inhibitors, beta-blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022433s020lbl.pdf. Accessed on 07-11-19.

Use in Special Populations

- **Pregnancy:** There are no adequate and well-controlled studies of ticagrelor use in pregnant women.
- **Lactation:** Ticagrelor is not indicated for use in nursing mothers.
- **Pediatric Use:** The safety and effectiveness of ticagrelor in pediatric patients have not been established.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022433s020lbl.pdf. Accessed on 07-11-19.

PHARMACOKINETICS

Absorption of Ticagrelor (t_{max})	**1.5 h**
Bioavailability	36%
Relation to food	Can be taken with or without food
Plasma proteins binding	>99%
Metabolism	CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of its major active metabolite.
Half Life (t ½)	Approximately 7 hours
Excretion	Approximately 84% (58% in feces, 26% in urine)

https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022433s020lbl.pdf. Accessed on 07-11-19.

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Indications	► Stable CAD ► ACS	► Stable CAD ► ACS	► ACS scheduled for PCI	► ACS ► Stable CAD after MI
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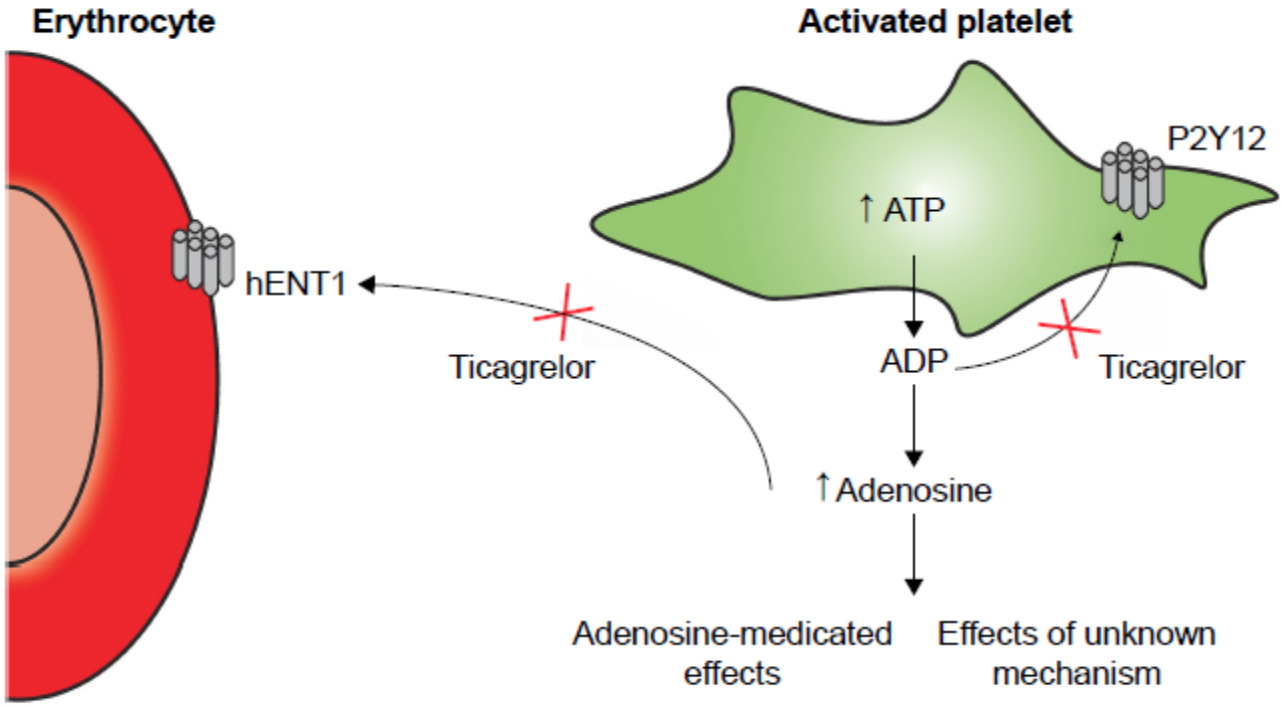
ACS, acute coronary syndrome; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack.

Degrauwe S et al. Open Heart. 2017;4(2):e000651.

Summary of key characteristics			
	Ticagrelor	**Clopidogrel**	**Prasugrel**
Class	Cyclopentyl triazolo pyrimidine	Thienopyridines	Thienopyridines
Metabolic activation required	No	Yes	Yes
Reversibility of binding to ADP receptor	Reversible	Irreversible	Irreversible
Onset of inhibition of platelet aggregation (IPA)			
•40–50 % IPA	30 min	2–4 h	1 h
•Maximum IPA	2 h	8 h	3 h
•Duration of IPA	3–5 days	7–10 days	5–10 days
Onset	Faster	Slow (prodrug)	Slow (prodrug)
Offset	Reversible; wears off faster	Irreversible	Irreversible
Stop before surgery	5 days	5 days	7 days
Drug interactions	CYP3A4 inhibitors	CYP2C19 omeprazole	—
Pharmacogenetics	Does not seem to be affected	Genetic variation	Does not seem to be affected

Pleotropic effects of Ticagrelor



ICaL- L-type Ca(2+) currents in cardiomyocytes;
PAI- plasminogen activation inhibitor;
EGF- endothelial growth factor;
IL-10 - interleukin 10;
hENT1- human equilibrative nucleoside transporter 1;
ATP -adenosine triphosphate;
ADP-adenosine diphosphate;
VSMC- vascular smooth muscle cells

Endothelium	Endothelial progenitor cells	Cardiomyocytes	Leukocytes	VSMC	Osteoclasts	Osteoblasts	Vagal C fibers
↓ PAI ↑ EGF ↑ Angiopoietin	↑ Migration ↑ Serum concentration	↑ Ventricular pauses ↓ Infarct size ↓ ICaL density ↓ Contractility	↑ IL-10 ↓ Inflammatory markers ↑/↓ Chemotaxis ↑/↓ Phagocytosis ↓ Degranulation	↑ Coronary blood flow	↑ Differentiation	↑ Depletion	↑ Bronchoconstriction ↑ Bradycardia

Kubisa MJ et al. Ther Clin Risk Manag. 2018;14:129-140

Advantage of Ticagrelor in ACS

Adenosine receptors	Ticagrelor-relevant role	Impact on cell cAMP	Concentration of adenosine required for activation
A1	• Coronary vessel spasm • Promotion of neutrophil chemotaxis and phagocytosis • Negative chronotropic effect • Dyspnea • GFR decrease	Decrease	Low
A2a	• Coronary vessel dilation • EPC migration • Inhibition of platelet activation • Dyspnea • Inhibition of neutrophil trafficking, granule release, and production of inflammatory mediators	Increase	Low
A2b	• Coronary vessel dilation • Inhibition of platelet activation • Inhibition of neutrophil trafficking, granule release • Inhibition of production of inflammatory mediators	Increase	High
A3	• Coronary vessel spasm • EPC migration • Promotion of neutrophil chemotaxis and phagocytosis	Decrease	Low

Abbreviations: cAMP, cyclic adenosine monophosphate; GFR, glomerular filtration rate; EPC, endothelial progenitor cell.

Kubisa MJ et al. Ther Clin Risk Manag. 2018;14:129-140

Current guidelines for the treatment

According to the **European Cardiac Society and European Association of Cardio-Thoracic Surgery (ECS/EACTS):**

- Ticagrelor is recommended for prevention of stent thrombosis in patients undergoing myocardial revascularization.
- Ticagrelor is preferred over clopidogrel for patients with nonST-segment elevation acute coronary syndromes (NSTE-ACS) and STEMI .

Newest guidelines by the **American College of Cardiology and American Heart Association (ACC/AHA)** suggests :

- Ticagrelor is preferred over clopidogrel in patients with ACS

•Windecker S et al. Eur Heart J. 2014; 35: 2541–2619.
•Valgimigli M et al. Eur Heart J. 2018 Jan 14;39(3):213-260.
•Levine GN et al.. J Am Coll Cardiol. 2016;68:1082–1115.

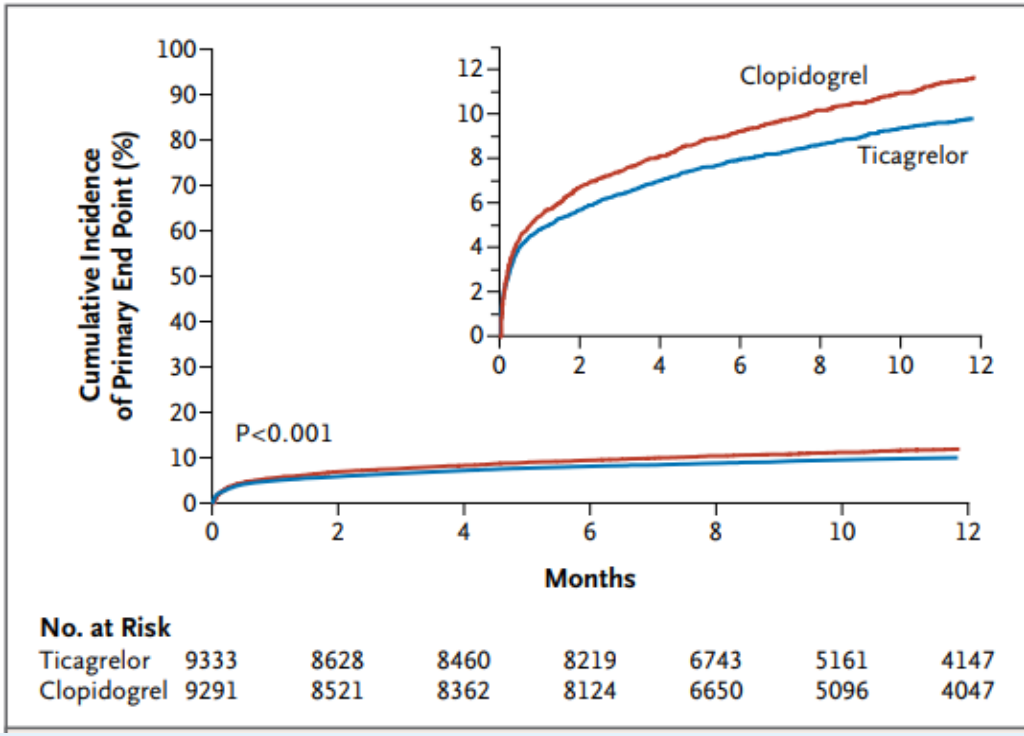

CLINICAL
TRIAL

PLATelet inhibition and patient Outcomes (PLATO) Trial

Objective	To compare ticagrelor (180-mg loading dose, 90 mg twice daily thereafter) and clopidogrel (300-to-600-mg loading dose, 75 mg daily thereafter) for the prevention of cardiovascular events		
Study Design	Multicenter, double-blind, randomized trial involving 18,624 patients from 862 centers in 43 countries.		
Study Methodology	Outcome	The primary end point--a composite of death from vascular causes, myocardial infarction, or stroke	
	No. of patients	Ticagrelor (n=9333)	Clopidogrel (n=9291)
	Intervention	180-mg loading dose, 90 mg twice daily thereafter	300-to-600-mg loading dose, 75 mg daily thereafter
	Median Age group	62 years	62 years
	Gender: Female,N (%)	2655/9333 (28.4%)	2633/9291 (28.3%)
	Duration	12 months	

PLATelet inhibition and patient Outcomes (PLATO) Trial

- Results: At 12 months, the primary end point* - 9.8% of patients receiving ticagrelor as compared with 11.7% of those receiving clopidogrel P<0.001).
- The secondary end points showed myocardial infarction alone (5.8% in the ticagrelor group vs. 6.9% in the clopidogrel group, P=0.005) and death from vascular causes (P=0.001).

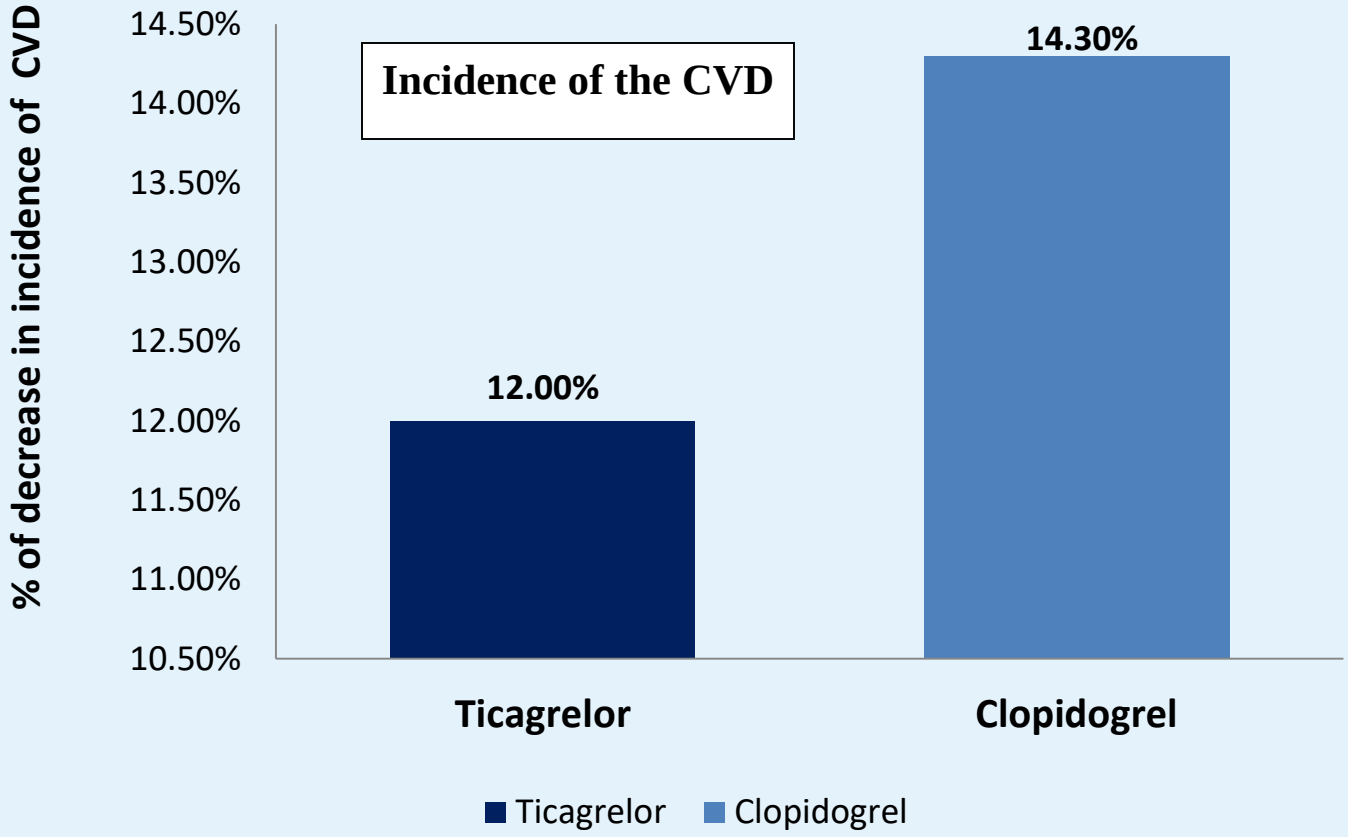


*primary end point — a composite of death from vascular causes, myocardial infarction, or stroke — occurred significantly less often in the ticagrelor group than in the clopidogrel group

PLATO Trial: Results

RESULTS:

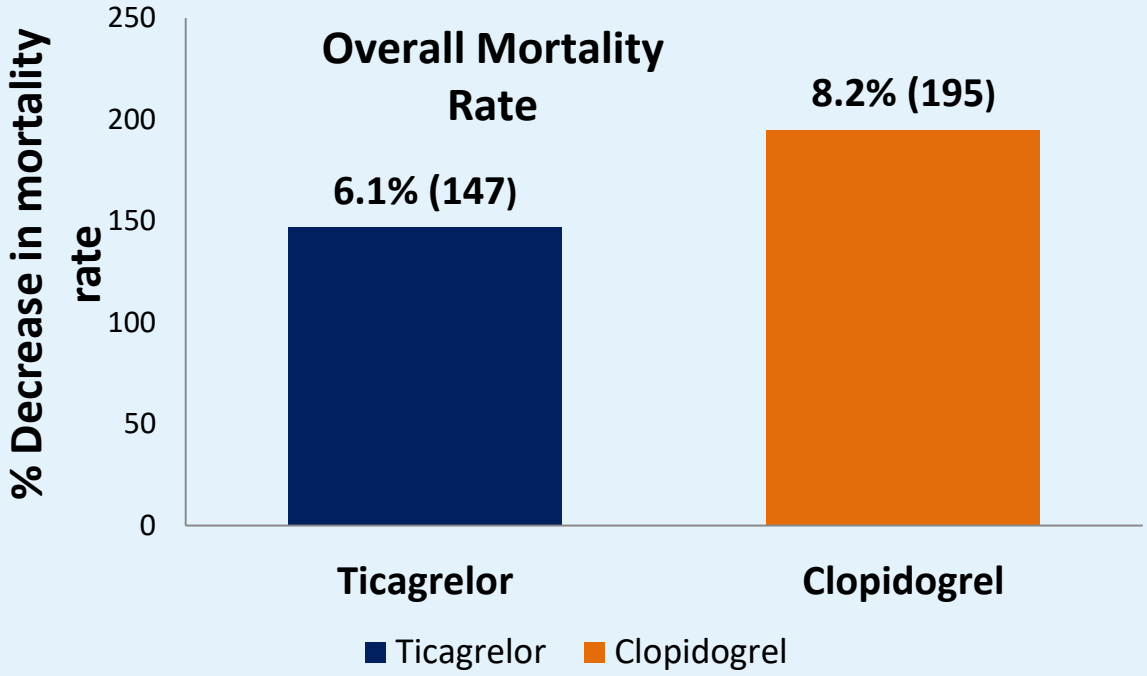
- The incidence of the CVD was lower with ticagrelor than with clopidogrel (12.0% vs 14.3%).



James SK et al. BMJ. 2011; 342: d3527.

PLATO Trial: Results

- Mortality rate was also lower (6.1% (147) v 8.2% (195)) with ticagrelor compared to Clopidogrel.



CONCLUSION:

In patients with ACS the benefits of ticagrelor over clopidogrel were consistent indicating the broad benefits of P2Y12 inhibition with ticagrelor .

James SK et al. BMJ. 2011; 342: d3527.

RESPOND Study

Response to ticagrelor in clopidogrel nonresponders and responders and effect of switching therapies

METHODS

- Patients with coronary artery disease on aspirin therapy received-300 mg clopidogrel load.
- Nonresponders and responders received clopidogrel (600 mg/75 mg once daily) or ticagrelor (180 mg/90 mg twice daily) for 14 days during period 1(Day 1-14).
- In period 2 (Day 15-28), all nonresponders switched treatment; half of the responders continued the same treatment, whereas the others switched treatment.

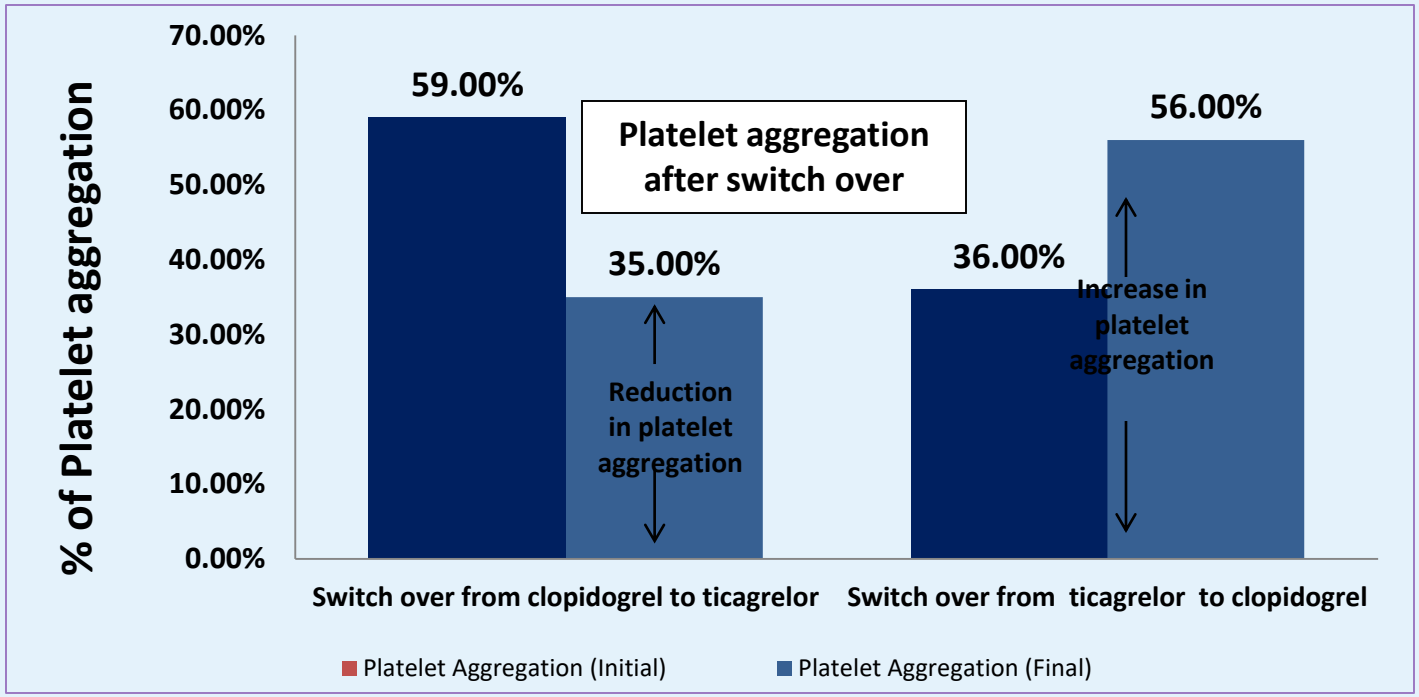
RESULTS

- Inhibition of platelet aggregation was higher in non-responders treated with ticagrelor compared with clopidogrel.

Gurbel PA et al.. Circulation. 2010 Mar 16;121(10):1188-99.

The RESPOND study: Results

- **Switchover from clopidogrel to ticagrelor-** Platelet aggregation fell from 59% to 35%.
- **Switchover from ticagrelor to clopidogrel-** Platelet aggregation increased from 36% to 56%.



CONCLUSION:

Ticagrelor therapy overcomes non-responsiveness to clopidogrel, and its antiplatelet effect is the same in responders and non-responders.

Gurbel PA et al. Response to ticagrelor in clopidogrel nonresponders and responders and effect of switching therapies: the RESPOND study. Circulation. 2010 Mar 16;121(10):1188-99.

The ONSET/OFFSET study

Assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor *vs* clopidogrel in patients with stable coronary artery disease

METHODS:

- 123 patients with stable coronary artery disease
- Given aspirin therapy (75 to 100 mg/d), ticagrelor (180-mg load, 90-mg BID maintenance dose), clopidogrel (600-mg load, 75-mg/d maintenance dose), or placebo for 6 weeks.

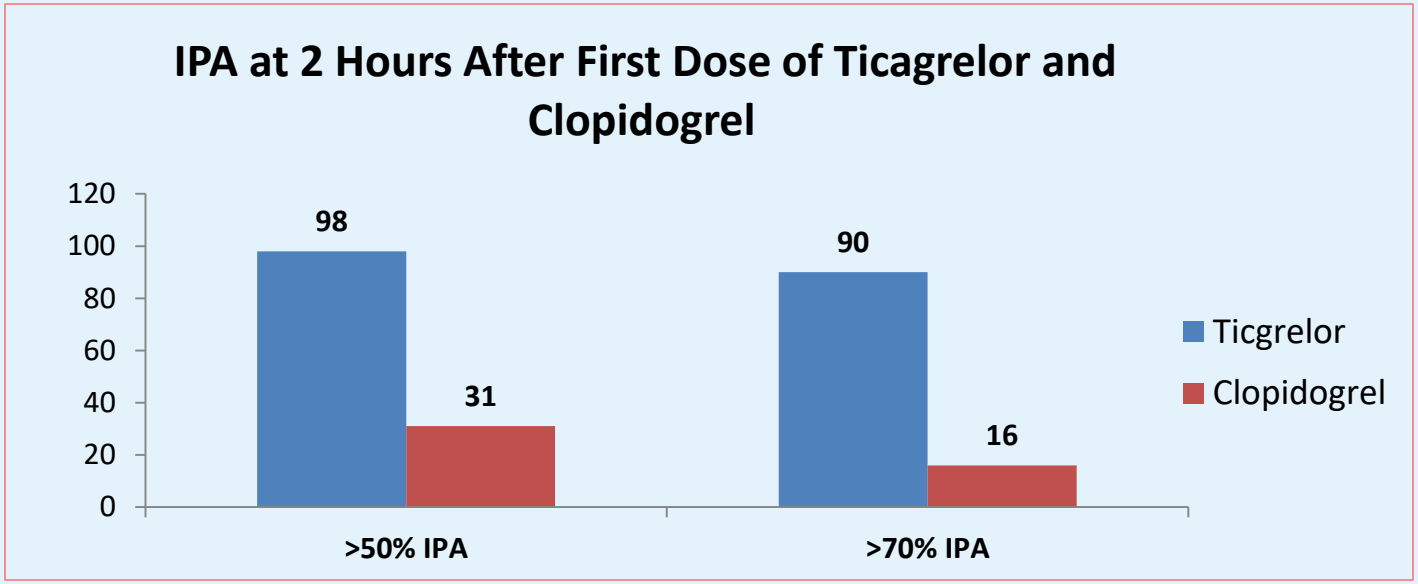
RESULTS:

- Greater platelet inhibition (IPA) occurred with ticagrelor than with clopidogrel at 0.5, 1, 2, 4, 8, and 24 hours after loading and at 6 weeks.

Gurbel PA et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. Circulation. 2009 Dec 22;120(25):2577-85.

ONSET/OFFSET Study: Results contd..

- At 24 hours after the last dose, mean IPA was 58% for ticagrelor versus 52% for clopidogrel.



CONCLUSION:

Ticagrelor achieved more rapid and greater platelet inhibition than clopidogrel.

Gurbel PA et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. Circulation. 2009 Dec 22;120(25):2577-85.

PEGASUS-TIMI 54 trial

Efficacy and safety of ticagrelor for long-term secondary prevention of atherothrombotic events in relation to renal function:

METHODS:

- 20,898 Patients with a history of MI for 1-3 years.

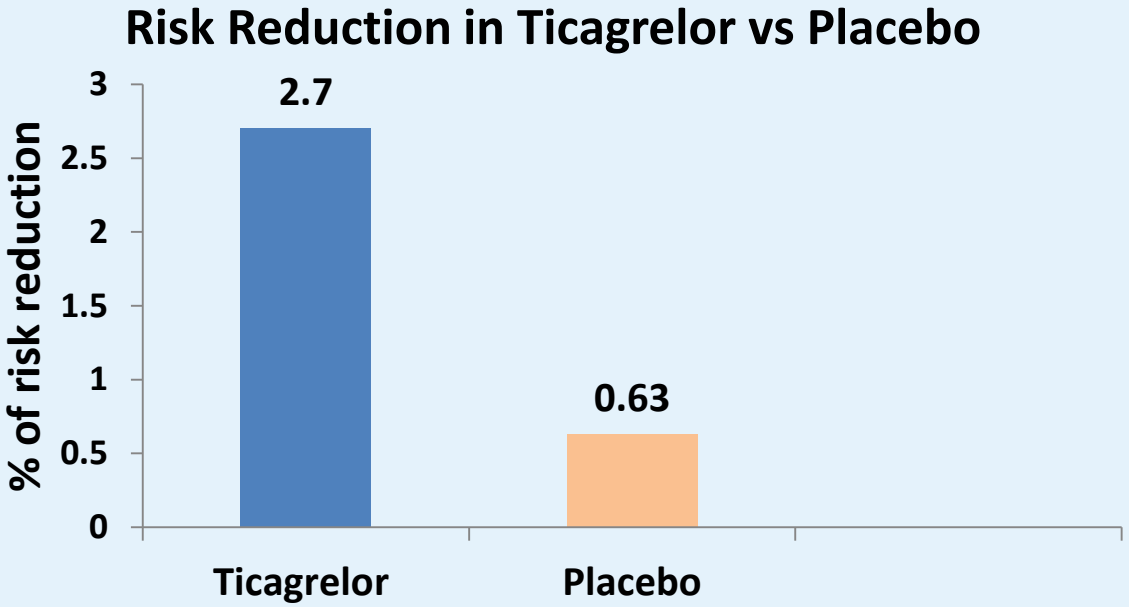
RESULTS:

- Of 20,898 patients, those with estimated glomerular filtration rate (eGFR) <60 had a greater risk of major adverse cardiovascular events (MACE) at 3 years.
- The relative risk reduction in MACE was seen with ticagrelor.

Magnani G et al. Efficacy and safety of ticagrelor for long-term secondary prevention of atherothrombotic events in relation to renal function: insights from the PEGASUS-TIMI 54 trial. Eur Heart J. 2016 Jan 21;37(4):400-8.

PEGASUS-TIMI 54 trial- Results Continued

- The risk reduction with ticagrelor was higher: 2.7 vs. 0.63%.



CONCLUSION:

In patients with a history of MI, patients with renal dysfunction are at increased risk of MACE and absolute risk reduction with long-term treatment with ticagrelor.

Magnani G et al. Efficacy and safety of ticagrelor for long-term secondary prevention of atherothrombotic events in relation to renal function: insights from the PEGASUS-TIMI 54 trial. Eur Heart J. 2016 Jan 21;37(4):400-8.

Ticagrelor versus clopidogrel in type-2 diabetic patients with cardiovascular disease.

METHODS:

- 20 T2DM patients received a loading-dose [LD] + 1week of daily therapy [DT] of clopidogrel or ticagrelor.
- Treatment effects were assessed by measuring thrombus formation and platelet aggregation at 2- and 6-hour post-LD and on Day-7 of DT.

RESULTS:

- Ticagrelor significantly reduced thrombus formation versus baseline at 2- and 6-hour post-LD and Day-7 of DT (33 %, 40 % and 31 %, respectively)
- Thrombus reductions with clopidogrel much lower and significant at 6-hour post-LD (16 %, 20 % and 17 %, respectively).

CONCLUSION:

Ticagrelor exhibits a faster and more potent antithrombotic effect than clopidogrel in T2DM patients with cardiovascular disease.

Zafar MU et al. Thromb Haemost. 2017 Oct 5;117(10):1981-1988.

Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes.

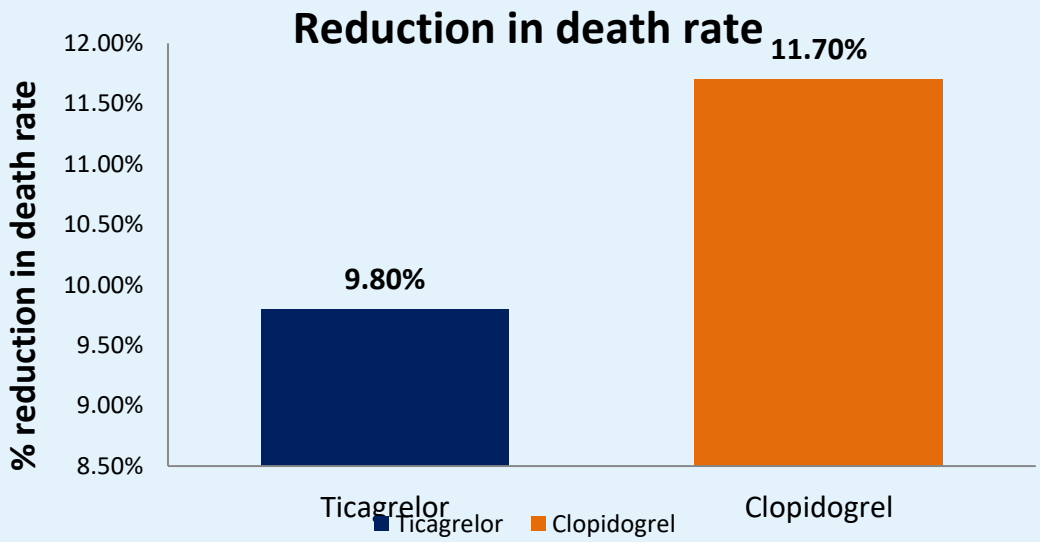
METHODS:

- 18,624 patients with ACS, with or without ST-segment elevation were treated.
- Ticagrelor- 180-mg loading dose, 90 mg twice daily thereafter compared with clopidogrel- 300-to-600-mg loading dose, 75 mg daily thereafter.

Wallentin L et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009 Sep 10;361(11):1045-57.

RESULTS:

- Less deaths at 12 months from MI, or stroke of patients receiving ticagrelor than clopidogrel (9.8% vs 11.7%).



CONCLUSION:

Treatment with ticagrelor as compared with clopidogrel significantly reduced the rate of death from vascular causes, myocardial infarction, or stroke.

Wallentin L et al.. N Engl J Med. 2009 Sep 10;361(11):1045-57.

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

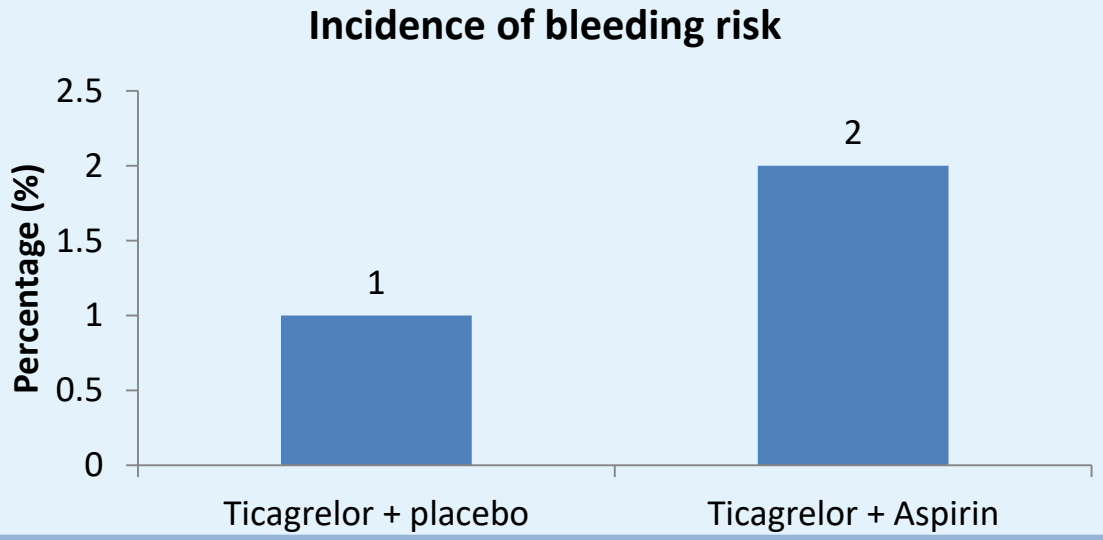
METHODS:

- Patients who were at high risk for bleeding or an ischemic event and had undergone PCI
  - 3555 patients in Ticagrelor + placebo group and
  - 3564 patients in Ticagrelor + Aspirin received treatment for 1 year.

TWILIGHT study

RESULTS:

- The incidence of bleeding risk was 1.0% among patients receiving ticagrelor plus placebo and 2.0% among patients receiving ticagrelor plus aspirin.



Ticagrelor monotherapy was associated with a lower incidence of clinically relevant bleeding than ticagrelor plus aspirin.

Mehran R et al. N Engl J Med. 2019 Sep 26. doi: 10.1056/NEJMoa1908419. [Epub ahead of print]

Ticagrelor Landmark Studies

Landmark Study	Study Groups and No.	Results
The PLATO Study Platelet Inhibition and Patient Outcomes (PLATO) Study	• Ticagrelor (n=9333) • Clopidogrel (n=9291)	Ticagrelor as compared with clopidogrel significantly reduced the rate of death from vascular causes, myocardial infarction, or stroke without an increase in the rate of overall major bleeding
The PEGASUS-TIMI 54 trial Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction	• Ticagrelor, 90 mg (N = 7050) • Ticagrelor, 60 mg (N = 7045) • Placebo (N = 7067)	In patients with a MI more than 1 year previously, treatment with ticagrelor significantly reduced the risk of cardiovascular death, myocardial infarction, or stroke and increased the risk of major bleeding
The RESPOND Study Response to Ticagrelor in Clopidogrel Nonresponders and Responders and Effect of Switching Therapies	• Nonresponders (n=41) • Responders (n=57)	Ticagrelor therapy overcomes nonresponsiveness to clopidogrel, and its antiplatelet effect is the same in responders and nonresponders

Ticagrelor Landmark Studies

Landmark Study	Study Groups and No.	Results
DISPERSE Study Dose confIrmation Study assessing anti- Platelet Effects of AZD6140 vs. clopidogRel in non–STsegment Elevation myocardial infarction-2	• Clopidogrel 75 mg (N=327) • Ticagrelor 180 mg (N=324) Ticagrelor 90 mg (N=323)	There was no difference in major bleeding but an increase in minor bleeding at the higher dose with encouraging results on the secondary end point of MI
The ONSET/OFFSET Study	• Ticagrelor (n=57) • Clopidogrel (n=54) • Placebo (n=12)	Ticagrelor achieved more rapid and greater platelet inhibition than high-loading-dose clopidogrel and was faster in offset after drug discontinuation
TWILIGHT Study Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention	• Ticagrelor + placebo N= 3555 • Ticagrelor + Aspirin N=3564	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.

Salient Features:

- Ticagrelor, is an orally active, reversible, and selective adenosine diphosphate (ADP) receptor antagonist
- Unlike the thienopyridines, ticagrelor is not a prodrug. Hence, Ticagrelor does not require metabolic activation.
- It binds reversibly to the receptor and exhibits rapid onset and offset of action
- The action mechanism of ticagrelor facilitates the rapid recovery of platelet function after drug withdrawal.
- National and International guidelines recommend Ticagrelor in patients with ACS
- **Several landmark studies viz., PLATO , PEGASUS, RESPOND, DISPERSE, ONSET/OFFSET, TWILIGHT Studies have demonstrated the benefit of Ticagrelor.**


Thank You!