International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 1 Jan-Feb 2024, pp: 1041-1048 www.ijprajournal.com ISSN: 2249-7781

Novel- Antiplatelet Therapies for Atherothrombotic Diseases

k.Malleswari[1], D.Rama Bramha Reddy[2],A.Karthikeya sharma[3]
[1]*Professor,Department of pharmaceutics, Nalanda Institute Of Pharmaceutical Sciences.*
[2] *Principal And Professor,Department of Depatment of Pharmaceutical Chemistry, Nalanda Institute Of Pharmaceutical Sciences.*
[3]*Student, Nalanda Institute Of Pharmaceutical Sciences.*

Submitted: 25-01-2024 Accepted: 03-02-2024

ABSTRACT
Over The Last Decades, Antiplatelet Agents, Mainly Aspirin And P2Y12 Receptor Antagonists, Have Significantly Reduced Morbidity And Mortality Associated With Arterial Thrombosis.Their Pharmacological Characteristics, Including Pharmacokinetic/Pharmacodynamics Profiles, Have Been Extensively Studied, And A Significant Number Of Clinical Trials Assessing Their Efficacy And Safety In Various Clinical Settings Have Established Antithrombotic Efficacy. Notwithstanding, Antiplatelet Agents Carry An Inherent Risk Of Bleeding. Given That Bleeding Is Associated With Adverse Cardiovascular Outcomes And Mortality, There Is An Unmet Clinical Need To Develop Novel Antiplatelet Therapies That Inhibit Thrombosis While Maintaining Hemostasis. In This Review, We Present The Currently Available Antiplatelet Agents, With A Particular Focus On Their Targets, Pharmacological Characteristics, And Patterns Of Use. We Will Further Discuss The Novel Antiplatelet Therapies In The Pipeline, With The Goal Of Improved Clinical Outcomes Among Patients With Atherothrombotic Diseases.

Keywords : Antiplatelet Therapy, Cardiovascular Disease, Targets Acute Coronary Syndrome; Aspirin; Atherothrombosis; Bleeding; Cardiovascular Disease; Dual Antiplatelet Therapy; P2Y12 Receptor Antagonists; Platelets.

I. INTRODUCTION

Antiplatelet Therapy, Mainly Including Aspirin (Acetylsalicylic Acid, ASA) And P2Y12 Receptor Antagonists, Is One Of The Most Prescribed Therapies In Medicine Due To The Worldwide High Prevalence Of Cardiovascular Diseases (CVD) . Antiplatelet Agents Have Significantly Improved Patient Clinical Outcomes During The Last Century, Thus Preventing A Substantial Number Of Atherothrombotic Events And Decreasing Cardiovascular Mortality Rates. However, Secondary Bleeding Complications Remain Relatively Frequent. Substantial Efforts Have Been Made To Develop Tools To Predict Individual Ischemic And Bleeding Risks, To Minimize Antiplatelet Exposure Among Patients With High Bleeding Risk And/Or Low Ischemic Risk, And To Improve Percutaneous Stent Technologies Reducing Late Thrombotic Risks. This Manuscript Provides An Overview Of The Antiplatelet Agents Currently Available, Details Their Management In Clinical Scenarios Such As Surgeries And Bleeding Complications, Discusses The Consequences Of Residual High Ontreatment Platelet Reactivity (HTPR), And Summarizes The Current Trends Toward Patient-Centered Precision Medicine.

II. PLATELET PHYSIOLOGY

Platelets Are The Major Cell Components Of The Hemostatic System That Aim To Minimize Blood Loss By Forming Together With Crosslinked Fibrin A Hemostatic Plug Following Vascular Injury. They Are Small Anucleate Cells (2–4 μm In Diameter) Produced By Megakaryocytes Mainly In The Bone Marrow And In The Lung And Are Released Into Blood, Where They Circulate For 7–10 Days In Humans, After Which They Are Eliminated In The Spleen And Liver . Approximately 1 × 1011 Platelets Are Released Into The Circulation Every Day, Where Their RNA Content Progressively Reduces Along With The Loss Of Surface Glycoproteins (Gps) Sialic Acid Residues Promoting Their Clearance . Physiologically, The Vascular Endothelium Inhibits Platelet Activation In The Circulation Via (I) The Release Of Nitric Oxide (NO) And Prostaglandin I2 (PGI2, Prostacyclin), (Ii) The Expression Of Ectonucleotidases, Which Degrade Adenosine Tri- And Di- Phosphate (ATP And ADP, Respectively) Leading To The Production Of Adenosine, And (Iii) The Expression Of Thrombomodulin, Which Binds Thrombin And Inhibits Its Prothrombotic Effects . PGI2 And NO Activate Adenylyl And Guanylyl Cyclases Within

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 1 Jan-Feb 2024, pp: 1041-1048 www.ijprajournal.com ISSN: 2249-7781

Platelets, Respectively, Thus Increasing Intra-Platelet Cyclic Adenosine 30 ,50 -Monophosphate (Camp) And Cyclic Guanosine 30 ,50 -Monophosphate (Cgmp). Both Camp And Cgmp Activate Protein Kinases (PKA And PKG) That Phosphorylate Specific Substrates (I.E., Phosphodiesterases (PDE) 3A And 5A, Rap1b, IP3 Receptor, Filamin, Vasodilator-Stimulated Phosphoprotein, Etc.), Thus Interfering With Their Own Synthesis. Accumulation Of Camp And Cgmp Also Hinders Signaling Induced By Platelet Receptor Agonists, Through Among Other Factors, Impaired Cytosolic Ca2+ Elevation And Cytoskeletal Reorganization . Three PDE Isoforms, Namely, PDE2, PDE3, And PDE5, Catalyze The Hydrolysis Of Camp And Cgmp To Inactive 50 -AMP And 50 -GMP, Thereby Limiting The Intracellular Levels Of Cyclic Nucleotides (Figure 1) . Following Vascular Injury, Platelets Roll On The Sub-Endothelium Via The Interaction Between The Gpib-V-IX Integrin And The High-Molecular-Weight Von Willebrand Factor (VWF) Of The Sub-Endothelium . Platelets Are Stabilized As They Adhere To VWF Via A Second Receptor, Gpiibiiia (Also Called Integrin Aiibβ3), And To Collagen Receptors Gpiaiia (Also Called Integrin A2β1) And GPVI. Signaling Through These Receptors, Which Involves Multiple Small G-Protein Regulators, SRC-Family Kinases, And Serine/Threonine Protein Kinases, Leads To The Activation Of Phosphoinositide 3-Kinase (PI3K) And Plcγ Followed By Ca2+ Release Into The Cytoplasm . Ca2+ And Protein Kinase-Dependent Activation Of Cytosolic Phospholipase A2 (PLA2) Within Activated Platelets Leads To The Synthesis And Secretion Of Thromboxane A2 (TXA2) Through The Release Of Arachidonic Acid (AA) From Membrane Glycerophospholipids And Transformation Into TXA2 By The Sequential Action Of Cyclooxygenase-1 (COX-1) And TXA2 Synthase. TXA2, In Turn, Activates Platelets In An Autocrine And Paracrine Fashion Via The Thromboxane Receptor (TP). Activation Of The TP Stimulates Plcβ Via Gαq Proteins, Inducing Ca2+ Release Into The Cytoplasm, PKC Activation, And Its Interaction With Gα12/13 Proteins. It Also Triggers Rho-Associated Protein Kinase (ROCK) Activation, Which Is Involved In Platelet Shape Change And Spreading. Besides Being A Potent Platelet Activator, TXA2 Exerts A Significant Vasoconstrictor Effect . Human Platelets Contain Three Types Of Storage Granules: A-Granules, Dense Granules, And Lysosomes. Dense Granules Contain Small Molecules Such As ADP, ATP, Serotonin, Ca2+ , Pyrophosphate, And Polyphosphate As Well As The Lysosomal Membrane Proteins CD63 And Lysosome-Associated Membrane Protein (LAMP) 1 And 2 . Following Activation, Platelets Secrete Their Granular Content Including ADP, Which Acts As A Soluble Agonist Binding To Two Purinergic Receptors On Platelets Consisting Of A Single Polypeptide Chain Of Seven Transmembrane A Helices, P2Y1 And P2Y12. P2Y1 Associates With Gαq To Regulate Platelet Shape Change And Induce An Initial Weak Transient Phase Of Aggregation . P2Y12 Is A Gi -Protein-Coupled Receptor. Its Activation Inhibits Gαi, Adenylate Cyclase-Mediated Signaling, Thus Decreasing The Camp Level, And Stimulates PI3K Via The Gβγ Protein Complex, Resulting In Akt Stimulation, Which Activates A Number Of Downstream Substrate Proteins, Ultimately Leading To Platelet Activation . ADP Is Hydrolyzed To AMP By CD39 Present On The Endothelial Cell Surface And Then To Adenosine By CD73. Adenosine Stimulates A2A And A2B Platelet Surface Receptors That Activate Adenylyl Cyclase, Increasing The Intra-Platelet Camp Level, Which Leads To Platelet Inhibition . A Part Of Extracellular Adenosine Is Internalized Into Red Blood Cells And Platelets Via A Membrane- Platelet Activation Results In A Conformational Change Of Gpiibiiia (Or Integrin Aiibβ3), From A Low-Affinity To A High-Affinity State For Fibrinogen, But Also For VWF And Fibronectin, Facilitating Platelet Aggregation And Activation. This Pathway Involves Caldag– GEFI (Ca2+- And Diacylglycerol-Regulated Guanine Nucleotide-Exchange Factor And Rap1b) And Cytoskeleton-Linked Signaling Molecules (Kindlin, Talin, And Filamin). Ligand-Bound Gpiibiiia Generates Outside-In Signaling Events That Mediate Cytoskeletal Reorganization And Platelet Spreading. It Is Also Critical For Platelet-Mediated Clot Retraction, A Process That Helps Seal The Injury Site And Initiates Wound Healing [1-2] .

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 1 Jan-Feb 2024, pp: 1041-1048 www.ijprajournal.com ISSN: 2249-7781

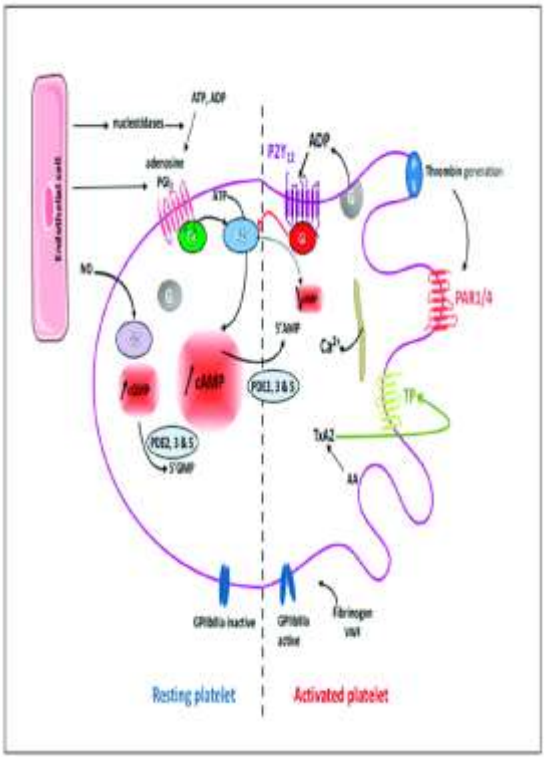

Figure 1. Major Signaling Events And Responses In Resting And Activated Platelets. Under Physiological Conditions, Endothelial Cells Release Nucleotidases That Degrade Adenosine Di- And Tri-Phosphate (ADP And ATP, Respectively) To Adenosine.

III. CURRENT ARSENALOF ANTIPLATELET AGENTS

Antiplatelet Drugs Represent Key Components Of Antithrombotic Agents, Mainly Prescribed For The Treatment And Prevention Of Atherothrombotic Diseases Including Acute Coronary Syndromes (ACS), Stable Coronary Artery Disease (CAD), Peripheral Artery Disease (PAD), Ischemic Stroke, And Transient Ischemic Attack (TIA). Antiplatelet Agents Act Either By Preventing The Formation Of Second Messengers, By Interacting With Intracellular Signaling Pathways, By Blocking Membrane Receptors,Or By Inhibiting Platelet Aggregation Per Se (Figure 2)[3].

Aspirin

ASA Reduces The Formation Of Thrombi Via Irreversible Cyclooxygenase (COX)-1 Inhibition, Thereby Suppressing Platelet Thromboxane A2 (TXA2) Synthesis . It Can Be Administered Intravenously (In Europe) Or As An Oral Loading Dose (Usually With Chewable Tablets In North America), In The First Phase Of ACS Treatment, Followed By Daily Maintenance Dose, Usually With Enteric-Coated Tablets That May Be Absorbed More Slowly And Less Efficiently In Some Patients. Lysine Acetylsalicylate Is The Only Formulation Available In Some Countries That Can Be Administered Intravenously. Intravenous Lysine Acetylsalicylate Provided More Rapid And Consistent Platelet Inhibition (Evaluated By Arachidonic Acid-Induced Platelet Aggregation Measured Using Light Transmission Aggregometry) Than Oral ASA Within The First Hour After Dosing In Healthy Volunteers. In The ECCLIPSE Trial, A Loading Dose Of Intravenous Lysine Acetylsalicylate Achieved An Earlier Platelet Inhibition With Less Inter-Individual Variability Than The Oral Loading Dose Of ASA . However, It Has Been Suggested By Some Investigators That IV Administration Of Lysine Acetylsalicylate May Have An Acutely Negative Effect On Endothelial Vasodilatory Prostaglandin Production; The Clinical Impact Of This Potential Endothelial Inhibition Has Not Been Directly Studied In Clinical Studies. Lysine Acetylsalicylate Can Also Be Given Orally, And Was Shown To Induce Fewer Gastrointestinal Adverse Effects Than ASA With Similar Or Higher Inhibitory Effect On Light Transmission Platelet Aggregometry In Healthy Volunteers And CAD Patients. Considering The Limited Evidence Comparing The Effects Of Intravenous Lysine Acetylsalicylate And Oral ASA On Platelet Inhibition And Endothelial Prostacyclin Biosynthesis In Humans, This Remains To Be More Extensively Explored In Future Clinical Studies. In ACS Setting, ASA Is Indicated In Association With A P2Y12 Receptor Antagonist For 6–12 Months Depending On The Balance Between Bleeding And Ischemic Risks . Dual Antiplatelet Therapy (DAPT) Duration Can Be Extended For Up To 3 Years In Patients At High Risk Of Ischemic Events. Afterwards, ASA Is Recommended Indefinitely As A Single Antiplatelet Therapy (SAPT). ASA Is Also Commonly Prescribed In Patients With Stable CAD. It Can Be Associated With Clopidogrel For Up To 12 Months In Patients Undergoing Elective Coronary Percutaneous Intervention (PCI). In Patients With Chronic Symptomatic PAD, ASA Is Commonly Prescribed As A Long-Term SAPT Its Efficacy Is Counterbalanced By Concerns Of Safety Thus It Is Not Recommended Routinely In Primary Prevention, But Can Be Considered For Higher-Risk Patients On A Case-By-Case Basis .

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 1 Jan-Feb 2024, pp: 1041-1048 www.ijprajournal.com ISSN: 2249-7781

ASA Can Also Be Prescribed In Combination To Clopidogrel For Up To 90 Days In Patients With Recent (Within 30 Days) TIA Or Stroke. It Can Also Be Prescribed For The Secondary Longterm Prevention Of Stroke And TIA As A Single Therapy Or In Combination With Dipyridamole[4].

Glycoprotein Iib/Iiia Inhibitors

Glycoprotein Iib/Iiia Receptor Antagonists Are Ligand-Mimetic Molecules That Prevent The Binding Of Fibrinogen To Activated Platelets And Thereby Directly Inhibit Platelet Aggregation.Three Gpiib/Iiia Inhibitors Are Currently Approved: Abciximab, Tirofiban, And Eptifibatide. Abciximab Is A Humanized Antigenbinding Fragment Of A Mouse Monoclonal Antibody. Eptifibatide Is A Cyclic Heptapeptide And Tirofiban A Nonpeptidic Small Molecule, Both Mimicking The Fibrinogen-Binding Sequence Within Gpiib/Iiia.4 All 3 Agents Are Administered Intravenously, And Due To Their High Bleeding Risk, Their Clinical Us Is Restricted To Patients With ACS With A High Thrombus Burden Or No-Reflow Syndrome Following PCI[4].

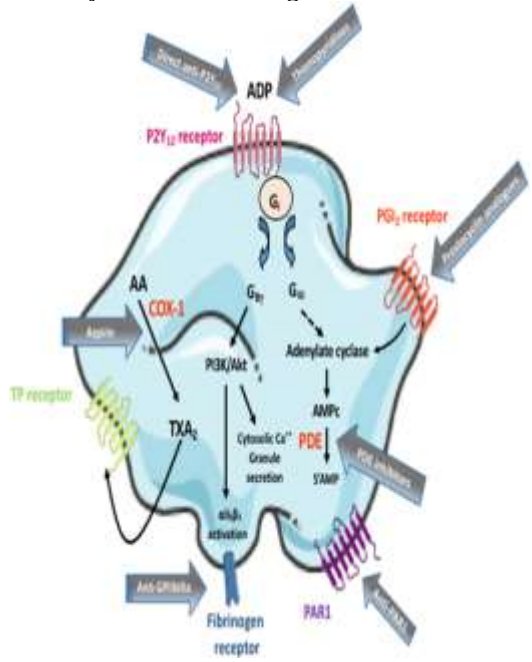

Figure 2 :- Targets Of The Commercialized Antiplatelet Agents. Arachidonic Acid (AA) Is Produced By Membrane Phospholipids Upon The Action Of Phospholipase A2.

P2Y12 Antagonists

P2Y12 Is A G-Protein-Coupled Receptor That Binds ADP And Thereby Enhances Sustained Platelet Aggregation Through Intracellular Signal Activation And Conformational Changes Of The Gpiib/Iiia Receptor Augmenting The Affinity For Its Major Ligand, Soluble Fibrinogen. The Currently Available P2Y12 Inhibitors Comprise 2 Families: The Thienopyridines, That Is, Ticlopidine, Clopidogrel, And Prasugrel, And The Nucleoside–Nucleotide Derivatives, That Is, Ticagrelor And Cangrelor.All Thienopyridines Are Prodrugs Which Need To Be Converted To Active Metabolites By The Hepatic Cytochrome (CYP) P450 Enzyme System Before Irreversibly Binding To The P2Y12 Receptor. Ticlopidine Is Usually Not Used In Clinical Practice Anymore Due To Its Multiple Side Effects And Is Not Recommended In The Current Guidelines. Clopidogrel On Top Of Aspirin Is The State-Of-Theart Dual Antiplatelet Therapy (DAPT) Regimen Following Elective Percutaneous Coronary Intervention (PCI) Or Peripheral Angioplasty With Stenting.Moreover, Clopidogrel Has Been The Preferred P2Y12 Inhibitor In The Acute Setting For Many Years. However, It Is Characterized By A Delayed Onset Of Action, A Significant Response Variability, And Insufficient Antithrombotic Activity In Some Patients, Also Known As High-On Treatment Residual Platelet Reactivity. These Characteristics Prompted The Development Of More Potent And Reliable Drugs Targeting The P2Y12 Receptor: The Third Thienopyridine Prasugrel Exhibits Greater Bioavailability, A More Potent Antiplatelet Effect, And Less Interindividual Response Variability Than Clopidogrel. Furthermore, It Was Superior To Clopidogrel In Reducing Ischemic Outcomes In Patients With Acute Coronary Syndrome (ACS) Undergoing PCI But Not In Medically Managed Patients With ACS.Recent Data Also Suggest A Benefit Of Prasugrel Over The Fourth P2Y12 Inhibitor Ticagrelor In Patients With ACS. In Contrast To The Thienopyridines, The Nucleoside– Nucleotide Antagonists Ticagrelor And Cangrelor Do Not Require CYP450-Mediated Biotransformation In Order To Reversibly Bind To The P2Y12 Receptor And Inhibit ADP-Induced Platelet Aggregation. Similar To Prasugrel, Ticagrelor Shows Greater Bioavailability And Less Response Variability Compared To Clopidogrel. Furthermore, Ticagrelor Was Superior To Clopidogrel In Medically Managed Patients With ACS And Patients With ACS Undergoing PCI. The Adenosine Triphosphate (ATP) Analogue Cangrelor Is The Only Intravenously Available P2Y12 Inhibitor. It Directly And Reversibly Blocks P2Y12 Receptors With A Rapid Onset Of Action Of 2 Minutes And

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 1 Jan-Feb 2024, pp: 1041-1048 www.ijprajournal.com ISSN: 2249-7781

A Short Halflife Of 3 To 5 Minutes. The Administration Of Cangrelor Together With Aspirin Is Approved For Patients With PCI Without Prior P2Y12 Inhibitor Treatment[5].

Protease-Activated Receptor 1 Antagonists

Protease-Activated Receptor 1 (PAR-1) Is A Major Binding Site For Thrombin On Human Platelets Allowing Strong And Persistent Platelet Activation. Vorapaxar Is A Competitive PAR-1 Antagonist And May Be Used On Top Of Standard Antiplatelet Therapy In The Secondary Prophylaxis Of Ischemic Events In Patients With A History Of Myocardial Infarction (MI) Or Symptomatic Peripheral Artery Disease. Of Note, Vorapaxar Was Associated With An Increase In Intracranial Bleeding Events In 2 Large Phase 3 Clinical Trials And Is Contraindicated In Patients With A History Of Stroke Or Transient Ischemic Attack[5].

IV. OTHER AGENTS: PHOSPHODIESTERASE INHIBITORS AND ANALOG OF PROSTACYCLIN

Iloprost Is A Stable Analog Of Prostacyclin (PGI2) That Activates Adelylate Cyclase To Increase Intraplatelet Camp Level. It Is Also An Arterial Vasodilator Which Increases Its Therapeutic Value For Systemic Administration In Patients With Severe PAD But Increases The Risk Of Hypotension . Dipyridamole Is Another Antiplatelet Agent That Increases Camp Level Within Platelets By Inhibiting Its Degradation By Phosphodiesterase (PDE)3 And PDE5 . It Also Induces Endothelial Synthesis And Release Of PGI2 And Raises The Extracellular Levels Of Adenosine By Inhibiting Its Reuptake By Red Blood Cells And Scavenges Peroxy Radicals, Thus Preventing Vascular And Tissue Damage . It Is Worth Mentioning That Anticipated Pharmacodynamics Of Both Iloprost And Dipyridamole Should Strictly Match Their Pharmacokinetics. Dipyridamole Is Usually Used In Association With ASA For The Secondary Long-Term Prevention Of Stroke And TIA As Previously Mentioned. Cilostazol Is A Selective Inhibitor Of PDE3A (The Main Subtype Of PDE3 Expressed In Platelets) Preventing The Degradation Of Cyclic Adenosine 3′ ,5 ′ -Monophosphate (Camp) And To A Lesser Degree Of Cyclic Guanosine 3′ ,5 ′ -Monophosphate (Cgmp) Thus Resulting In An Increase In The Active Forms Of Protein Kinase A (PKA) And PKG. It Also Inhibits Adenosine Uptake And Has A Vasodilatory Effect By Relaxing The Vascular Smooth Muscle Cells . Cilostazol Is Recommended For The Treatment Of Patients With Intermittent Claudication In The Absence Of Tissue Necrosis Or Rest Pain . In The Light Of CSPS, CSPS2 And CASISP Trials , It May Also Be Used For Secondary Stroke Prevention, Particularly In Asian Patients . Randomized Trials Are Still Needed To Determine Its Usefulness For The Secondary Stroke Prevention In Non-Asian Populations[6].

V. INDICATIONS OF THE CURRENTLY AVAILABLE ANTIPLATELET AGENTS

Antiplatelet Agents Are Mainly Indicated For The Treatment And Prevention Of Atherothrombotic Diseases Including ACS, Stable Coronary Artery Disease (CAD), PAD, Ischemic Stroke, And Transient Ischemic Attack (TIA). Somewhat Less Frequently, They Can Also Be Used In Other Pathologies Such As Pre-Eclampsia And Myeloproliferative Syndromes. Globally, Aspirin (The COX-1 Inhibitor) And P2Y12 Receptor Antagonists Are By Far The Most Commonly Prescribed. Needless To Say, Treatment Strategies May Vary Across Countries, Particularly With Regard To The Choice Of Molecules, Dosage, And Treatment Duration[7].

Acute Coronary Syndrome

In The Setting Of ACS, Aspirin Is Indicated In Association With A P2Y12 Receptor Antagonist For Secondary Prevention Of Major Adverse Cardiovascular Events For 6–12 Months Depending On Patient's Bleeding Risk. This Duration Can Be Extended Beyond 12 Months (Up To Three Years) In Patients At High Risk Of Ischemic Events Who Have Tolerated DAPT Well. In Medically-Managed ACS Patients, Ticagrelor Is Indicated As A P2Y12 Receptor Antagonist In Association To Aspirin, Whereas In ACS Patients Undergoing PCI Without Any History Of Stroke (Either Ischemic Or Hemorrhagic), Prasugrel Or Ticagrelor May Be Prescribed With No Preference For One Over The Other. Prasugrel May Be Preferred Over Ticagrelor Post PCI In Patients With Non-ST-Elevation (NSTE) ACS , And Clopidogrel May Be A Favorable Alternative To Ticagrelor Or Prasugrel In Patients Aged 70 Years Or Older Presenting With NSTE-ACS, As Fewer Bleeding Events And No Increase In The Combined Endpoint Of All-Cause Death, Myocardial Infarction, Stroke, And Bleeding Were Recorded In The Popular AGE Trial . It Is Worth

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 1 Jan-Feb 2024, pp: 1041-1048 www.ijprajournal.com ISSN: 2249-7781

Mentioning That Clopidogrel Is Currently The Commonly Used P2Y12 Receptor Antagonist In ACS Patients Who Have Undergone Thrombolysis. Gpiibiiia Inhibitors Are Very Rarely Prescribed In An ACS Context Owing To Concerns Regarding Bleeding And The Introduction Of Potent Oral P2Y12 Receptor Antagonists. They Can Still Be Considered As A Bailout Therapy In The Event Of Angiographic Evidence Of A Large Thrombus, Slow Or No Reflow, And Other Thrombotic Complications In Patients With ST-Segment Elevation Myocardial Infarction (STEMI) Undergoing PCI Or In Patients With NSTE-ACS Undergoing High-Risk PCI Without Pre-Treatment With Oral P2Y12 Receptor Antagonists.Following DAPT, Aspirin Is Recommended As A Single Antiplatelet Therapy Indefinitely As It Is Affordable And Widely Available Even In Low-Income Countries. Special Attention Should Be Given To Some Patients' Population Having A High Ischemic Risk. Clopidogrel Is The Only P2Y12 Receptor Antagonist That Can Be Prescribed As Part Of The Triple Antithrombotic Therapy (In Association To Aspirin And Oral Anticoagulant)]In Patients With Atrial Fibrillation (AF) Suffering From ACS. Triple Therapy Should Be As Short As Possible: During Index Hospitalization Or Up To One Or Six Months (Depending On The Patient's Ischemic And Bleeding Risk). This Is Followed By Dual Antithrombotic Therapy (Single Antiplatelet Agent Plus Oral Anticoagulant) For One Year After Coronary Stenting And Then By Oral Anticoagulation Indefinitely. As Part Of Dual Antithrombotic Therapy, Prasugrel Is Allowed In The Japanese Guidelines Whereas Ticagrelor May Be An Alternative To Clopidogrel In Patients With High Ischemic And Low Bleeding Risk According To The American And European Guidelines. In Patients With Mechanical Heart Valves Undergoing PCI, A Daily Dose Of Clopidogrel In Addition To Vitamin K Antagonist Is Indicated Following A 1-Month Triple Therapy That Could Be Prolonged Up To Six Months In Patients With High Ischemic Risk . Beyond One Year Of Dual Therapy, Oral Anticoagulation Is Currently Recommended With Subsequent Withdrawal Of Antiplatelet Agents. Another Particular Population Is That Of Patient Suffering From DM Due To Increased Platelet Reactivity Seen At Baseline And On-Treatment In Diabetic Patients. Prasugrel And Ticagrelor Are Thus Preferred In These Patients In Association With Aspirin[8-9] .

VI. ANTIPLATELET AGENTS UNDER PRECLINICAL/CLINICAL DEVELOPMENT

Recurrent Thrombotic Events Occur In One In 10 Patients In The First Year Following ACS Despite Treatment With The Most Potent Antiplatelet Therapy. Currently Available Antiplatelet Drugs Have Some Practical Challenges In A Real-World Setting, Especially The Significantly Increased Bleeding Risk. These Limitations Have Stimulated Research Interest To Identify New Antiplatelet Targets. Following The Latest Advances In The Understanding Of Thrombus Formation, It Is Now Known That The Thrombotic Response That Regulates The Growth Of A Propagating Outer Layer Of The Thrombus Primarily Involves Platelets In Lower Activation States, The Recruitment Of Which Is Less Sensitive To Standard Antiplatelet Therapy . However, Platelets Located Close To The Site Of Arterial Injury Are Fully Activated By SoluBle Agonists Such As TXA2, ADP, And Thrombin And Are Thus More Sensitive To Currently Available Antiplatelet Agents. The Challenge Is That Although New Antiplatelet Agents Are Expected To Cause Less Bleeding, They Should Not Exhibit Reduced Antithrombotic Potency. Unlike Most Of The Currently Available Antiplatelet Drugs That Suppress Autocrine Events InVolved In Platelet Aggregation, Novel Drugs In Development Are Frequently Directed Against Other Platelet Activation Processes, Such As Adhesion, Signaling, And Pro-Coagulant Activity . Here, We Highlight New Antiplatelet Agents That Are In Advanced Preclinical Development Or Have Already Entered Into The Clinical Development Phase . How These Potential New Therapeutics Will Fit Within The Current Paradigm Of Antiplatelet Therapy And Whether They Will Lead To Safer Combinations In The Clinical Practice Remain To Be Determined[10].

Novel Gpiibiiia Inhibitors

The Major Disadvantage Of The Currently Available Gpiibiiia Inhibitors Is The Increased Risk Of Bleeding. Moreover, Ligand-Mimetic Gpiibiiia Inhibitors May Induce Conformational Changes After Binding To Their Target, Thus Potentially Causing Severe Thrombocytopenia And Paradoxical Platelet Activation . Unlike With The Long-Term Use Of Gpiibiiia Inhibitors, The Aforementioned Limitation May Be Superseded By The Short-Term Blockade Of This GP. RUC-4 Binds To The Metal Ion-Binding Site On Gpiiia,

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 1 Jan-Feb 2024, pp: 1041-1048 www.ijprajournal.com ISSN: 2249-7781

Thereby Inhibiting Ligand Binding Without Inducing A Conformational Change And Thus Paradoxical Platelet Activation. In Preclinical Studies, RUC-4 Showed High Antithrombotic Efficacy . It Can Be Administered By Intramuscular Injection, Which Raises The Prospect Of Administration In Pre-Hospital Settings. However, It Inhibits Both Non-Activated And Activated Gpiibiiia And Therefore, All Circulating Platelets. The Bleeding Risk Profile Of This Agent Is Yet To Be Established. Another Promising Strategy For Targeting Gpiibiiia Is To Inhibit Only The Activated Isoform Of This Glycoprotein. Single-Chain Variable Fragments (Scfvs) Directed Against The Active Conformation Of Gpiibiiia Were Coupled With The ADP-Hydrolyzing Enzyme CD39 , The Potent Factor Xa Inhibitor Tick Anticoagulant Peptide, Or The Fibrinolytic Agent Urokinase . All These Compounds Have Displayed Potent Antithrombotic Effects In Preclinical Models Without Affecting Hemostasis. Clinical Studies Are Eagerly Awaited. Another Interesting Approach Could Be To Specifically Inhibit The Early Phases Of This Integrin Outside-In Signaling, Such As The Interaction Between The Intracellular Domain Of The B3 Subunit And Gα13 With A Myristoylated Peptide Exe Peptide Motif (Mp6). Further Studies Are Required To Confirm The Efficacy And Safety Of Such A Novel Antiplatelet Approach [10].

Novel P2Y12 And P2Y1 Receptors Antagonists

Selatogrel, A Novel P2Y12 Receptor Antagonist, Was Recently Evaluated In Patients With Chronic Coronary Syndrome. It Was Rapidly Absorbed Following Subcutaneous AdminisTration And Attained A Peak Plasma Concentration 30 Min After A Single Injection, Thus Providing Prompt, Potent, And Consistent Platelet P2Y12 Inhibition Sustained For ≥8 H And Reversible Within 24 H. It Was Assessed In A Small-Sized Trial (N = 47) That Included Acute NSTEMI And STEMI Patients. In Total, 90% Of The Patients With Acute Myocardial Infarction Had A Profound P2Y12-Mediated Platelet Inhibition (Measured By Verifynow®) 30 Min After The Injection Of Selatogrel 8 Or 16 Mg . This Subcutaneously Administered Drug May Open Up A Promising New Avenue Of Self-Administration Of An Anti-P2Y12 Receptor Antagonist In Patients Early After The Onset Of Myocardial Infarction Symptoms, Which Aims To Reduce The Ischemic Time And Thus To Limit The Size Of Irreversible Myocardial Damage. Further Studies Are Warranted To Evaluate The Clinical Efficacy And Safety Of Such A Novel Approach In Acute Settings Where Rapid Platelet Inhibition Is Desirable, As For Example In ACS Patients . Two Other Novel Highly Potent Inhibitors Of P2Y12 Are Under DevelOpment, AZD1283 And SAR216471, The Latter Being In The Most Advanced Stage Of Development. It Was Associated With Less Bleeding, Higher Selectivity, And Equivalent Antithrombotic Efficacy Compared To Ticagrelor In A Rat Model And Is Currently Undergoing A Phase II Study (NCT03384966). The Potential Of P2Y1 Inhibition As An Antiplatelet Strategy That Does Not Significantly InCrease The Bleeding Risk Has Also Been Explored. The Compound BMS-884775 Demonstrated Similar Efficacy With Less Bleeding Compared To Prasugrel In A Rabbit Model . Another P2Y1 Receptor Antagonist, MRS2500, Was Shown To Prevent Carotid Artery Thrombosis In Cynomolgus Monkeys . Moreover, Combining P2Y1 And P2Y12 Receptors Inhibition Is Also Of Interest And Has Led To The Development Of Diadenosine Tetraphosphate And Other Derivative Compounds . Of These, GLS-409 Improved Coronary Blood Flow Recovery In A Canine Model Of Unstable Angina, With Minimal Increase In Bleeding Time . No Clinical Trials Assessing The Efficacy And Safety Of These Novel P2Y1 Receptor Antagonists Have Yet Been Started[11].

12-Lipoxygenase Inhibitor

Platelet 12-Lipoxygenase Is An Oxygenase Predominantly Expressed In Human Platelets. It Metabolizes AA To Form Bioactive Metabolites (12-(S)-Hydroperoxyeicosatetraenoic Acid And 12-(S)-Hydroxyeicosatetraenoic Acid [12-HETE]) That Activate Platelets And Induce Granule Secretion. The First Identified Inhibitor Of 12-Lipoxygenase, ML355, Was Evaluated In A Mouse Arteriole Thrombus Model. ML355 Impaired Thrombus Formation And Vessel Occlusion With Minimal Effects On Hemostasis. Further Studies Are Required To Verify The Efficacy And Safety Of This Novel Antiplatelet Target[12].

VII. CONCLUSIONS

Major Advances In Antiplatelet Therapy Have Been Accomplished Over The Last Few Decades. However, Atherothrombotic Events Remain A Leading Cause Of Death Worldwide. Incomplete Protection And Bleeding Complications Associated With The Use Of The Currently Available Antiplatelet Agents Represent Areas Of

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 1 Jan-Feb 2024, pp: 1041-1048 www.ijprajournal.com ISSN: 2249-7781

Development And Deserve Further InvestigaTion In Order To Appropriately Manage CVD Patients And Provide Better Guidance In The Search For New Antiplatelet Targets. Substantial Research Progress Has Been Undoubtedly Achieved, Nevertheless, Much Remains To Be Done.

REFERENCES

[1]. Capodanno, D.; Ingala, S.; Calderone, D.; Angiolillo, M.J. Aspirin For The Primary Prevention Of Cardiovascular Disease: Latest Evidence. Expert Rev. Cardiovasc. Ther. 2019, 17, 633–643.

[2]. Lefrancais, E.; Ortiz-Muñoz, G.; Caudrillier, A.; Mallavia, B.; Liu, F.; Sayah, D.M.; Thornton, E.E.; Headley, M.; David, T.; Coughlin, T.D.S.R.; Et Al. The Lung Is A Site Of Platelet Biogenesis And A Reservoir For Haematopoietic Progenitors. Nature 2017, 544, 105–109.

[3]. Van Der Meijden, P.E.J.; Heemskerk, J.W.M. Platelet Biology And Functions: New Concepts And Clinical Perspectives. Nat. Rev. Cardiol. 2019, 16, 166–179.

[4]. Stefanini, L.; Bergmeier, W. Negative Regulators Of Platelet Activation And Adhesion. J. Thromb. Haemost. JTH 2018, 16, 220–230.

[5]. Nagy, Z.; Smolenski, A. Cyclic Nucleotide-Dependent Inhibitory Signaling Interweaves With Activating Pathways To Determine Platelet Responses. Res. Pract. Thromb. Haemost. 2018, 2, 558–571.

[6]. Voors-Pette C, Lebozec K, Dogterom P, Jullien L, Billiald P, Ferlan P, Et Al. Safety And Tolerability, Pharmacokinetics, And Pharmacodynamics Of ACT017, An Antiplatelet GPVI (Glycoprotein VI) Fab. Arterioscler Thromb Vasc Biol. (2019) 39:956–64.

[7]. Schüpke S, Hein-Rothweiler R, Mayer K, Janisch M, Sibbing D, Ndrepepa G, Et Al. Revacept, A Novel Inhibitor Of Platelet Adhesion, In Patients Undergoing Elective PCI-Design And Rationale Of The Randomized ISAR-PLASTER Trial. Thromb Haemost. (2019) 119:1539–45.

[8]. Jourdi G, Lordkipanidzé M, Philippe A, Bachelot-Loza C, Gaussem P. Current And Novel Antiplatelet Therapies For The Treatment Of Cardiovascular Diseases. Int J Mol Sci. (2021) 22:13079.

[9]. Baharoglu MI, Cordonnier C, Al-Shahi Salman R, De Gans K, Koopman MM, Brand A, Et Al. Platelet Transfusion Versus Standard Care After Acute Stroke Due To Spontaneous Cerebral Haemorrhage Associated With Antiplatelet Therapy (PATCH): A Randomised, Open-Label, Phase 3 Trial. Lancet Lond Engl. (2016) 387:2605–13.

[10]. Spahn DR, Bouillon B, Cerny V, Duranteau J, Filipescu D, Hunt BJ, Et Al. The European Guideline On Management Of Major Bleeding And Coagulopathy Following Trauma: Fifth Edition. Crit Care Lond Engl. (2019) 23:98.

[11]. T, Kitamura T, Ishihara J, Onishi H, Nojima T, Yamamoto K, Et Al. Early Predictors For Massive Transfusion In Older Adult Severe Trauma Patients. Injury. (2017) 48:1006–12.

[12]. Levine GN, Jeong Y-H, Goto S, Anderson JL, Huo Y, Mega JL, Et Al. Expert Consensus Document: World Heart Federation Expert Consensus Statement On Antiplatelet Therapy In East Asian Patients With ACS Or Undergoing PCI. Nat Rev Cardiol. (2014) 11:597–606.