Review Article

Pharmacological Update: New Drugs in Cardiac Practice: A Critical Appraisal

Abstract

Cardiac practice involves the application of a range of pharmacological therapies. An anesthesiologist needs to keep pace with the rampant drug developments in the field of cardiovascular medicine for appropriate management in both perioperative and intensive care set-up, to strengthen his/her role as a perioperative physician in practice. The article reviews the changing trends and the future perspectives in major classes of cardiovascular medicine.

Keywords: *Cardiovascular medicine, new drugs, pharmacological therapies*

Rohan Magoon, Arindam Choudhury, Vishwas Malik, Ridhima Sharma[1], Poonam Malhotra Kapoor

From the Department of Cardiac Anaesthesia, CTC, AIIMS, [1]Department of Anaesthesia and Intensive Care, St. Stephen's Hospital, New Delhi, India

Address for correspondence:
Dr. Arindam Choudhury, CTC, AIIMS, New Delhi, India.
E-mail: archymd@gmail.com

Access this article online

Website: www.annals.in

DOI: 10.4103/0971-9784.197798

Quick Response Code:

Introduction

A cardiac patient receives a spectrum of medications for indications ranging from symptomatic relief, preoperative stabilization, rate and rhythm control, prevention of thrombosis, and metabolic modulation to optimization of systemic and pulmonary pressures. The pace of development of new drugs in the cardiovascular arena has been rapid. The impetus is driven by the need to improve the side effect profile of current drugs and to develop new agents that may treat the existing pathologies through novel mechanisms.

Knowledge of the new drug developments can help an anesthesiologist take better management decisions from the preanesthetic to the intensive care set-up. The effect of preoperative continuation or discontinuation of drugs, possible drug–drug interactions, electrolyte alterations, hemodynamic perturbations, and major metabolic pathways involved constitute invaluable information to the attending anesthesiologist.

Recent Trends in Cardiovascular Medicine

In addition to the approval of new drugs and synergistic combinations, other pharmacological developments include novel routes of administration, dosing regimen, and establishment of efficacy and safety of the existing drugs in a new patient cohort. The various classes of cardiovascular medicine that have seen major developments in the last decade have been discussed in Table 1.

Antiarrhythmics

Antiarrhythmic therapy is limited to a great extent by incomplete efficacy and narrow margin of safety with potential to cause cardiac and extracardiac toxicity. Amiodarone, though accepted as a valuable antiarrhythmic, the drug accumulates in tissues with prolonged therapy, resulting in significant organ toxicity. Several new compounds comparable in structure and electrophysiological effects to amiodarone have been developed recently.

Dronedarone, like amiodarone, is a de-iodinated benzofuranyl compound with reduced iodine-related toxicity. The side chain modification results in decreased lipophilicity and shorter half-life with reduced tissue accumulation compared to amiodarone.[1] The Food and Drug Administration (FDA) approved this moderately effective Vaughan William Class III drug for the treatment of paroxysmal or persistent atrial fibrillation (AF) or flutter in 2009 largely based on the results of ATHENA trial. The placebo-controlled trial evaluated dronedarone 400 mg twice a day in patients with AF or flutter, demonstrating a significant reduction in mortality.[2]

How to cite this article: Magoon R, Choudhury A, Malik V, Sharma R, Kapoor PM. Pharmacological update: New drugs in cardiac practice: A critical appraisal. Ann Card Anaesth 2017;20:S49-56.

Received: December, 2016. **Accepted:** December, 2016.

Table 1: The list of the cardiovascular drugs recently approved by the Food and Drug Association and the other pharmacological developments under investigation

Class	FDA approved drug in last decade/recently	Drugs/developments under investigation
Antiarrhythmics	Dronedarone for paroxysmal or persistent AF or flutter (2009)	Atrial-selective drugs (vernakalant) upstream therapy to hamper atrial remodeling (cause for AF) A_1 adenosine receptor agonists
Anticoagulants	Edoxaban (2015), apixaban-(2012), rivaroxaban (2011), and dabigatran-(2010) prevention of stroke/systemic embolism from AF idarucizumab-(2015) antibody against dabigatran	Antidotes against NOACs under development
Antiplatelets	Cangrelor (2015), vorapaxar (2014), ticagrelor (2011), and prasugrel (2009) reduction in thrombotic events	New agents investigated in various studies
Metabolic modulators	Ranolazine (antianginal, 2006 approved) acts as a metabolic modulator	Trimetazidine appears to be promising in studies
Antihypertensives	Azilsartan (2011) AT1 angiotensin II receptor antagonist, clevidipine (2008) IV CCB, aliskiren (2007) renin inhibitor, and nebivolol (2007) novel beta blocker	Many combinations of these drugs approved and investigated
Anti-HF	Entresto (sacubitril and valsartan) and ivabradine for the treatment of chronic HF, approved in 2015	Revised guidelines for defining the role in HF
Anti-pulmonary hypertension drugs	Selexipag (2015) riociguat, macitentan (2013) treprostinil, tadalafil (2009), and ambrisentan (2007)	Inhaled nitrite and inhibition of MRP4 being investigated

FDA: Food and Drug Association, HF: Heart failure, AF: Atrial fibrillation, NOACs: New oral anticoagulants, CCB: Calcium channel blocker, IV: Intravenous, MRP4: Multidrug resistance-associated protein 4

However, reports of liver toxicity highlight the importance of monitoring liver function tests with the therapy.[3] ANDROMEDA trial suggested worsening of congestive heart failure (CHF) with dronedarone in patients with moderate to severe CHF, contraindicating the drug in Class IV heart failure (HF) patients or in those with a recent decompensation.[4]

AF originates from the atrial tissue with altered structure or function. Thus, atrial-selective approaches represent promising options for management of AF, with several ionic currents (IKACh, IKur) and connexins (Cx-40) being the potential targets.[5] Vernakalant, an atrial-selective agent, is in advanced stages of investigation for the treatment of AF.[6] It is an atrial repolarization-delaying agent with major target being IKur (sustained outward potassium current). As IKur is present in higher proportion in the atria, the drug has a much greater effect in fibrillating atria and is much less likely to be proarrhythmogenic. Recently, efforts to develop "upstream" therapies for AF targeting atrial remodeling have gained interest.[7] Therapies altering RAS, as well as anti-inflammatory and antioxidative drugs, are being investigated alone and in combination with traditional antiarrhythmics.

Adenosine affects the termination of supraventricular tachycardia (SVT) in patient with AV nodal reentry by stimulating the A1 adenosine receptor. The concomitant stimulation of the A2A, A2B, and A3 adenosine receptors, in view of the nonselective action, leads to variety of side effects, including flushing, dyspnea, and chest pain. Thus, selective A1 receptor agonists have been developed for the termination of SVT and rate control in AF.[8] Tecadenoson, selodenoson, and PJ-875 are such agents under investigation.

Anticoagulants

Introduction of low-molecular-weight heparin and fondaparinux simplified the drug regime of arterial or venous thrombosis as these agents can be given subcutaneously without coagulation monitoring, with lower potential to cause heparin-induced thrombocytopenia (HIT).[9] The long-term use of these agents is limited by the potential for accumulation in renal failure, the lack of an antidote, and risk of catheter thrombosis. Bivalirudin can also be used in patients with HIT, thus representing a safe and effective alternative to heparin. Its short half-life precludes the need for an antidote though it can also accumulate in renal impairment.[10] The capacity to titrate the dose as per the results of point-of-care coagulation tests remains an important practical advantage of heparin and bivalirudin over fondaparinux or enoxaparin in setting of percutaneous coronary intervention.

Several new parenteral anticoagulants in advanced stages of development are AVE5026, idrabiotaparinux, and otamixaban selectively targeting factor Xa (FXa). RB006, an anticoagulant RNA aptamer, specifically targets factor IXa.[11,12] The new parenteral agents have a rapid onset of action with a predictable anticoagulant effect, which, in the case of idrabiotaparinux and RB006, can be rapidly neutralized by intravenous (IV) avidin or RB007, respectively.

The greatest unmet need in the present context is for oral anticoagulants which can replace Vitamin K

antagonists (VKAs). VKAs, such as warfarin, despite being the conventional orally active anticoagulants for long-term therapy, have numerous limitations. These include a slow onset of action, variable dose requirements, genetic metabolic polymorphisms, differences in dietary intake of Vitamin K, and numerous drug–drug interactions.[13] Therefore, routine coagulation monitoring is necessary to ensure a therapeutic international normalized ratio (INR).

The new oral anticoagulants (NOACs), target either thrombin or FXa, representing a viable alternative to the traditional VKAs and have gained recent attention in long-term anticoagulant therapy.

Oral Direct Factor Xa Inhibitors

Rivaroxaban

Rivaroxaban has a rapid onset of action and a half-life of 7–11 h with an oral bioavailability of 80%. With a dual mode of elimination, both kidneys and liver contribute along with CYP3A4-dependant pathways. The FDA approved the drug for the reduction in the risk of stroke and systemic embolism resulting from AF in 2011 (based on RECORD 1, 2, and 3 trials).[14] The recommended initial dose is 10 mg taken orally once daily.

Apixaban

Apixaban is absorbed rapidly with the maximal plasma concentrations achieved 3 h after oral administration. The drug is cleared with a half-life of 8–14 h and eliminated through multiple pathways, including hepatic metabolism and renal and intestinal excretion. Approved by FDA in 2012 to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF (NVAF) (based on two clinical trials, ARISTOTLE and AVERROES).[14] The recommended dose is 5 mg twice daily, with reduction to 2.5 mg twice daily in patients with any two of the characteristics: age >80 years, body weight <60 kg, and serum creatinine >1.5 mg/dL.

Edoxaban

An active drug that is rapidly absorbed, with a half-life of 9–11 h. Edoxaban has a dual mechanism of elimination; approximately, one-third is eliminated through the kidney, and the remainder is excreted in the feces. The FDA approved the drug in 2015 to reduce the risk of stroke and systemic embolism in patients with NVAF (based on the ENGAGE AF-TIMI 48 study).[14] The recommended dose is 60 mg taken orally once daily with reduction to 30 mg once daily in patients with CrCL 15–50 mL/min.

Oral direct thrombin inhibitors

Dabigatran etexilate (approved by FDA in 2010) is a prodrug of dabigatran which reversibly inhibits thrombin. NICE approved the drug for the prevention of stroke and systemic embolism in NVAF with: previous stroke, transient ischemic attack, or systemic embolism, left ventricular ejection fraction (LVEF) <40%, symptomatic HF (NYHA Class II or more), age 75 or older, age 65, or older with one of the following: Diabetes mellitus, coronary artery disease, or hypertension (HT). The drug is excreted renally with a half-life of 14–17 h. The recommended daily dose is 150 mg BD or 110 mg BD (>75 year) due to the increased risk of renal impairment.[14] Drugs that inhibit P-gp lead to a higher bioavailability of dabigatran, as a result, a lower dose recommended in patients taking P-gp inhibitors (e.g., verapamil or amiodarone).

The Randomized Evaluation of Long-term Anticoagulation Therapy trial compared 2 doses of dabigatran (110 mg and 150 mg twice a day) with warfarin for noninferiority in prevention of stroke or systemic embolus in AF. In comparison to the patients "warfarinized" to an INR of 2–3, both doses of dabigatran significantly decreased the annual rate of stroke or systemic embolus.[15]

The development of reversal agents against NOACs is the major breakthrough which can go a long way in expanding the application of NOACs, especially in emergency setting.

Idarucizumab is a humanized monoclonal antibody fragment (Fab) derived from an IgG1 isotype molecule, against dabigatran. The recommended dose of is 5 g. The FDA approval in 2015 was based on a single cohort case series trial with dabigatran-treated patients who had life-threatening or uncontrolled bleeding or who required an emergency surgery or urgent procedure (RE-VERSE AD).[16]

Aripazine: This is a synthetic small molecule (D-arginine compound) which has broad activity against old and NOACs.[17]

Andexanet: Recombinant, modified FXa molecule that is being developed as a direct reversal agent for patients receiving an FXa inhibitor who suffer major bleeding or who require an emergency surgery.[17]

Antiplatelets: Ticagrelor and prasugrel are antiplatelet drugs that are alternatives to clopidogrel in acute coronary syndrome. The major advantages include reduced rates of ischemia and stent thrombosis.[18] Table 2 compares the three antiplatelet agents with respect to their pharmacokinetic and pharmacodynamic profile.

Vorapaxar: New oral protease-activated receptor-1 antagonist inhibits thrombin-induced platelet activation. The drug has been approved by the FDA in 2014 for the reduction of thrombotic cardiovascular events.[21]

Cangrelor: Potent IV adenosine-diphosphate receptor antagonist acts rapidly with readily reversible effects. The drug has been approved by the FDA in 2015 for reducing periprocedural thrombotic events.[22]

Metabolic-modulators

Metabolic modulators represent a class of drugs that act through the optimization of cardiac substrate metabolism.

Table 2: A head-to-head comparison among the three antiplatelet agents

Attributes	Clopidogrel	Prasugrel	Ticagrelor
Class	Thienopyridine (second-generation)	Thienopyridine (third-generation)	Cyto-pentyl-triazolopyrimidine
Loading dose (mg)	300-600	60	180
Maintenance dose	75 mg OD	10 mg OD	90 mg BD
Pharmacokinetics	>52% oral BA	>76% oral BA	30%-40% oral BA
	CYP2C19 metabolism	CYP3A4, CYP2B6 metabolism	CYP3A4/5 metabolism
Pharmacodynamics	Inhibits $P2Y_{12}$, ADP receptor irreversibly	Inhibits $P2Y_{12}$, ADP receptor irreversibly	Modifies $P2Y_{12}$, ADP receptor reversibly
	Onset: 8 h (300 mg) 2 h (600 mg)	Onset: 30 min	Onset: 2 h
	Platelet function recovery time: 5 days	Platelet function recovery time: 7 days	Platelet function recovery time: 2-3 days
FDA approval	2002 approved by the FDA for the treatment of ACS	2009 for the prevention of thrombotic cardiovascular complications in ACS	2011 for the reduction of thrombotic events in patients with ACS
Major comparative trial with clopidogrel		TRITON-TIMI 38[19]	PLATO[20]

BA: Bio-availability, CYP: Cytochrome P enzyme, ADP: Adenosine diphosphate, ACS: Acute coronary syndrome, TRITON-TIMI: Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel, PLATO: Platelet Inhibition and Patient Outcomes Trial, FDA: Food and Drug Association

Ranolazine is approved for the drug treatment of chronic stable angina which reduces myocardial stunning and infarct size. It primarily acts through a subtle shift in myocardial energy metabolism from fatty acid b-oxidation toward the oxidation of glucose, thereby increasing adenosine triphosphate (ATP) generation and ultimately enhancing contractile function. The drug acts without reducing heart rate or blood pressure. It is contraindicated in patients with preexisting QT interval prolongation. The recommended initial dosing is 500 mg twice daily; this may be escalated to a maximum dose of 1000 mg twice daily. The FDA Approval in 2006 was based on a pair of clinical trials, ERICA, and CARISA.[23]

Trimetazidine (TMZ) is an inhibitor of free fatty acid oxidation that shifts cardiac and muscle metabolism from free fatty acids in favor of glucose utilization resulting into an increased generation of high-energy phosphates translating into an anti-ischemic effect. There has been growing supportive evidence that TMZ reduces ischemic injury and improves the cardiac function in humans. A randomized clinical trial further substantiated the role of TMZ in improving functional class, left ventricular end-systolic volume, and ejection fraction (EF) in patients with HF of various origins.[24]

Antihypertensives

The major drugs which have been approved by the FDA, as a monotherapy for the treatment of HT, include as follows:

Azilsartan medoxomil, a prodrug, is hydrolyzed to azilsartan, a selective AT1 subtype angiotensin II receptor antagonist. The drug is indicated for the treatment of HT, alone, or in combination with other antihypertensive agents.[25] The recommended initial dose in adults is 80 mg taken orally once daily.

Clevidipine is an IV short-acting dihydropyridine calcium channel antagonist acting by selectively relaxing smooth muscle cells lining the small arteries. This results in widening of the arterial lumen and effects the reduction of blood pressure since the small arterioles are the primary resistance vessel. The drug is specifically indicated for the reduction of blood pressure when oral therapy is not feasible or not desirable. The recommended initial dose of the drug is 1–2 mg/h until the optimal blood pressure reduction is achieved.[26] The desired therapeutic response for most patients occurs at doses of 4–6 mg/h.

Sanoski and Aliskiren[27] is an orally active potent renin inhibitor. The suppression of the Renin-Angiotensin System has been shown to treat HT and reduce cardiovascular events. It may be used alone or in combination with other antihypertensive agents. The recommended initial dose of the drug is 150 mg once daily increased up to 300 mg daily.

Nebivolol, a third-generation beta blocker, is a racemic mixture of d- and l-nebivolol. The drug exerts nitric oxide (NO)-mediated vasodilation in addition to conventional beta-blocking effects. The half-life of nebivolol varies from 10.3 h in extensive metabolizers to 31.9 h in poor metabolizers. The drug undergoes extensive first-pass metabolism through the CYP2D6 enzyme system with a variable bioavailability (12% for extensive metabolizers and 96% for poor metabolizers).[28] The recommended starting dose of nebivolol is 5 mg once daily, up to a maximum dose of 40 mg daily. In patients with renal or hepatic insufficiency, the starting dose is reduced to 2.5 mg once daily. The drug is not recommended for patients with severe hepatic impairment.

Numerous combinations involving the novel and old beta blockers, angiotensin-converting enzyme (ACE)-inhibitors, calcium channel blockers, thiazide diuretics, renin inhibitors, and angiotensin receptor blockers have been approved by the FDA in the last decade.

Anti-heart failure drugs

The latest update on pharmacological management in HF patients with reduced EF specifically addresses two new classes of drugs (in addition to ACE-inhibitors, beta-blockers, mineralocorticoid, or aldosterone receptor antagonists).

- A sinoatrial node modulator (Generic: Ivabradine, brand name: Corlanor)
- An angiotensin receptor neprilysin inhibitor (ARNI) (Generic: Valsartan/sacubitril, brand name: Entresto).

Ivabradine is a hyperpolarization-activated cyclic nucleotide-gated channel blocker. The drug reduces the spontaneous activity of the cardiac sinus node by selectively inhibiting the If-current (If), resulting in heart rate reduction with no negative impact on myocardial contractility. The drug reduces the risk of hospitalization in patients with chronic HF with LVEF ≤35%, in sinus rhythm with resting heart rate ≥70 beats/min, either on the maximally tolerated doses or having a contraindication to beta-blocker therapy.

The FDA approval of the drug was based on SHIFT (Systolic Heart failure treatment with the If inhibitor ivabradine).[29] The recommended starting dose is 5 mg twice daily, up to a maximum of 7.5 mg twice daily. The major side effects are bradycardia, HT, AF, and luminous phenomena.

Entresto (ARNI) is a combination of two compounds: Sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin II receptor blocker. The drug combination reduces the risk of cardiovascular death and hospitalization in patients with chronic HF (NYHA Class II–IV) and reduced EF. The recommended starting dose is 49/51 mg (sacubitril/valsartan) twice-daily, with the dose reduced to 24/26 mg (sacubitril/valsartan) twice-daily for patients with severe renal impairment and hepatic impairment. The major adverse effects include hypotension, hyperkalemia, cough, dizziness, or renal failure.

The FDA approval of the drug was based on PARADIGM-HF, a multinational, randomized, double-blind trial comparing Entresto and enalapril in 8442 adult patients with symptomatic chronic HF (NYHA Class II–IV) and systolic dysfunction (LVEF ≤40%). PARADIGM-HF demonstrated that Entresto was superior to enalapril in reducing the risk of cardiovascular death or hospitalization.[30]

Advances in Therapeutic Interventions for Patients with Pulmonary Arterial Hypertension

The armamentarium of drugs for the treatment of pulmonary arterial hypertension (PAH) traditionally relied on IV vasodilators that lacked the specificity for pulmonary circulation with the potential to cause undesirable systemic vasodilation. While the efficacy of inhaled NO for pulmonary-specific pulmonary hypertension treatment is well established, there has been interest among clinicians in developing less expensive inhaled and oral alternatives, which can be administered in a less cumbersome manner. The therapy against PAH targets one of the following pathways as depicted in Figure 1, many of which have been approved by the FDA [Table 3].

The therapy against PAH which is under recent investigation targets the following:

Nitrite - Nitric Oxide Pathway

NO is also generated through NO synthase-independent pathway involving nitrite. Nitrite (NO_2) is converted to NO by multiple enzymes with NO_2 reductase activity including xanthine oxidoreductase, aldehyde reductase, and

Table 3: The list of Food and Drug Association approved drugs for treatment of pulmonary arterial hypertension in the last decade

Drug	Selexipag[31]	Riociguat[32]	Macitentan[33]	Treprostinil[34]	Tadalafil[35]	Amberisentan[36]
MOA	Nonprostanoid IP receptor agonist	s-GC stimulator	Dual ET-1 receptor antagonist	Prostacyclin analog	PDE-5 inhibitor	Selective ETA receptor antagonist
Dose	200 mcg BD to max 1600 mcg BD	1 mg TDS upto 2.5 mg TDS	10 mg once daily	3 breaths 18 mcg/ session, QID	40 mg OD	5–10 mg OD
FDA	2015	2013	2013	2009	2009	2007
Indication	For the treatment of PAH	For CTEPH and PAH	For the treatment of PAH	For the treatment of PAH	For the treatment of PAH	For the treatment of PAH
Trial	GRIPHON	Chest-1 CTEPH Patent-1 PAH	SERAPHIN	TRIUMPH FREEDOM C	PHIRST	ARIES 1, 2
SE	Headache, diarrhea, jaw pain, nausea, myalgia, vomiting	Headache, dizziness, dyspepsia/gastritis, nausea, diarrhea, and hypotension	Anemia, pharyngitis, bronchitis, headache, influenza, urinary infection	Cough, headache, throat irritation nausea, flushing	Headache, dyspepsia, myalgia, nausea, back pain, nasopharyngitis	Peripheral edema Nasal congestion Sinusitis Flushing Palpitations

PAH: Pulmonary arterial hypertension, FDA: Food and Drug Association, s-GC: Soluble guanylyl cyclase, MOA: Mechanism of action, PDE: Phosphodiesterase, CTEPH: Chronic thromboembolic pulmonary hypertension, ET: Endothelin, ETA: Endothelin receptor A

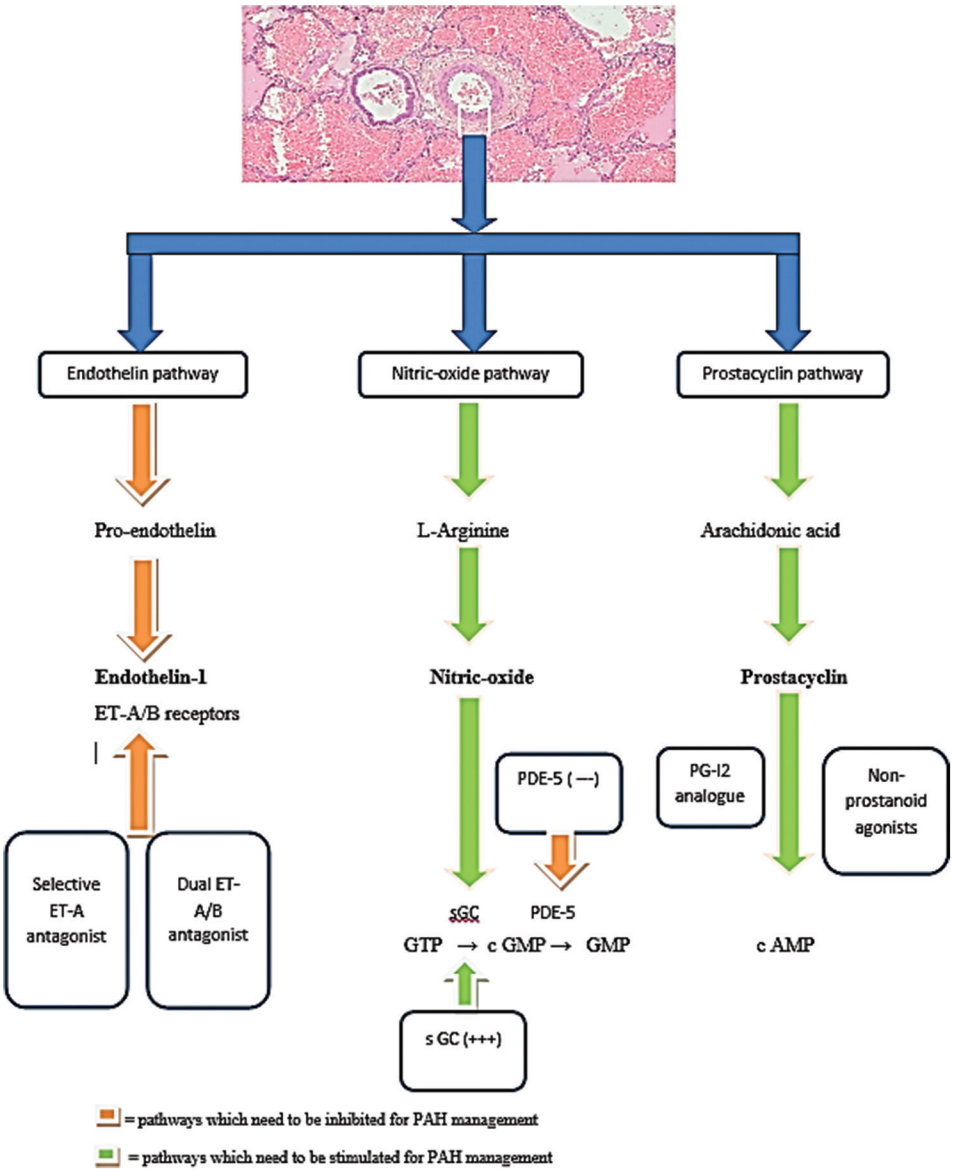

Figure 1: The three major pathways depicting the pathophysiology of the pulmonary arterial hypertension which forms the basis of novel therapeutics for pulmonary arterial hypertension (PDE: Phosphor diesterase E, s-GC: Soluble guanylyl cyclase, NO: Nitric oxide), ET: Endothelin, cGMP: Cyclic guanosine monophosphate, cAMP: Cyclic adenosine monophosphate. The green arrows represent the pathways which need to be inhibited for pulmonary arterial hypertension management. The orange arrows represent the pathways which need to be stimulated for pulmonary arterial hypertension management

deoxyhemoglobin. Thus, treatment with inhaled nitrite can theoretically reverse PAH. NO_2 is chemically more stable than NO with a half-life of 30 min, making intermittent dosing possible. The acute hemodynamic effects of inhaled nitrite are being currently investigated in human PAH.

Inhibition of Cyclic Nucleotides Metabolism

Cyclic guanine and adenine monophosphate play an important role in modulating the vasomotor tone. In addition to enzymatic degradation through phosphodiesterases, the cyclic nucleotides levels are also regulated by a transport system mediating active efflux. Multidrug resistance-associated protein 4 (MRP4), a member of ATP-binding cassette transporter family, mediates this efflux of the cyclic nucleotides. The recent research has demonstrated the overexpression of MRP4 in PAH patients. The inhibition of MRP4 thereby represents a potential target for treating PAH in humans.[37,38]

The following databases and electronic repositories were most useful for reviewing the current literature to evaluate the latest drug developments. PubMed Clinical Querries, CenterWatch, and FDA's Centre for Drug Evaluation and Research were extensively used. The authors recommend readers to visit www.centerwatch.com/drug-information for future FDA approved drugs and pharmacotherapies.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Tafreshi MJ, Rowles J. A review of the investigational antiarrhythmic agent dronedarone. J Cardiovasc Pharmacol Ther 2007;12:15-26.
2. Hohnloser SH, Crijns HJ, van Eickels M, Gaudin C, Page RL, Torp-Pedersen C, *et al.* Effect of dronedarone on cardiovascular events in atrial fibrillation. N Engl J Med 2009;360:668-78.
3. US Food and Drug Administration. FDA drug Safety Communication: Severe Liver Injury Associated with the Use of Dronedarone (Marketed as Multaq). Available from: http://www.fda.gov/drugs/drugsafety/ucm240011.htm. [Last accessed on 2016 Dec 17].
4. Køber L, Torp-Pedersen C, McMurray JJ, Gøtzsche O, Lévy S, Crijns H, *et al.* Increased mortality after dronedarone therapy for severe heart failure. N Engl J Med 2008;358:2678-87.
5. Ehrlich JR, Biliczki P, Hohnloser SH, Nattel S. Atrial-selective approaches for the treatment of atrial fibrillation. J Am Coll Cardiol 2008;51:787-92.
6. Cheng JW, Rybak I. Pharmacotherapy options in atrial fibrillation: Focus on vernakalant. Clin Med Ther 2009;1:215-30.
7. Burstein B, Nattel S. Atrial fibrosis: Mechanisms and clinical relevance in atrial fibrillation. J Am Coll Cardiol 2008;51:802-9.
8. Elzein E, Zablocki J. A1 adenosine receptor agonists and their potential therapeutic applications. Expert Opin Investig Drugs 2008;17:1901-10.
9. Weitz JI, Hirsh J, Samama MM; American College of Chest Physicians. New antithrombotic drugs: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133 6 Suppl: 234S-56S.
10. Stone GW, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, *et al.* Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med 2008;358:2218-30.
11. Savi P, Herault JP, Duchaussoy P, Millet L, Schaeffer P, Petitou M, *et al.* Reversible biotinylated oligosaccharides: A new approach for a better management of anticoagulant therapy. J Thromb Haemost 2008;6:1697-706.
12. Sabatine MS, Antman EM, Widimsky P, Ebrahim IO, Kiss RG, Saaiman A, *et al.* Otamixaban for the treatment of patients with non-ST-elevation acute coronary syndromes (SEPIA-ACS1 TIMI 42): A randomised, double-blind, active-controlled, phase 2 trial. Lancet 2009;374:787-95.
13. Hirsh J. Oral anticoagulant drugs. N Engl J Med 1991;324:1865-75.
14. Eriksson BI, Quinlan DJ, Weitz JI. Comparative pharmacodynamics and pharmacokinetics of oral direct thrombin and factor Xa inhibitors in development. Clin Pharmacokinet 2009;48:1-22.
15. Ezekowitz MD, Connolly S, Parekh A, Reilly PA, Varrone J, Wang S, *et al.* Rationale and design of RE-LY: Randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. Am Heart J 2009;157:805-10.
16. Schiele F, van Ryn J, Canada K, Newsome C, Sepulveda E, Park J, *et al.* A specific antidote for dabigatran: Functional and structural characterization. Blood 2013;121:3554-62.
17. Lu G, DeGuzman FR, Hollenbach SJ, Karbarz MJ, Abe K, Lee G, *et al.* A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa. Nat Med 2013;19:446-51.
18. Steg PG, Harrington RA, Emanuelsson H, Katus HA, Mahaffey KW, Meier B, *et al.* Stent thrombosis with ticagrelor versus clopidogrel in patients with acute coronary syndromes: An analysis from the prospective, randomized PLATO trial. Circulation 2013;128:1055-65.
19. Serebruany VL. Timing of thienopyridine loading and outcomes in the TRITON trial: The FDA Prasugrel Action Package outlook. Cardiovasc Revasc Med 2011;12:94-8.
20. Held C, Asenblad N, Bassand JP, Becker RC, Cannon CP, Claeys MJ, *et al.* Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: Results from the PLATO (Platelet Inhibition and Patient Outcomes) trial. J Am Coll Cardiol 2011;57:672-84.
21. Morrow DA, Braunwald E, Bonaca MP, Ameriso SF, Dalby AJ, Fish MP, *et al.* Vorapaxar in the secondary prevention of atherothrombotic events. N Engl J Med 2012;366:1404-13.
22. Bhatt DL, Stone GW, Mahaffey KW, Gibson CM, Steg PG, Hamm CW, *et al.* Effect of platelet inhibition with cangrelor during PCI on ischemic events. N Engl J Med 2013;368:1303-13.
23. Lopaschuk GD, Ussher JR, Folmes CD, Jaswal JS, Stanley WC. Myocardial fatty acid metabolism in health and disease. Physiol Rev 2010;90:207-58.
24. Fragasso G, Palloshi A, Puccetti P, Silipigni C, Rossodivita A, Pala M, *et al.* A randomized clinical trial of trimetazidine, a partial free fatty acid oxidation inhibitor, in patients with heart failure. J Am Coll Cardiol 2006;48:992-8.
25. Baker WL, White WB. Azilsartan medoxomil: A new angiotensin II receptor antagonist for treatment of hypertension. Ann Pharmacother 2011;45:1506-15.
26. Deeks ED, Keating GM, Keam SJ. Clevidipine: A review of its use in the management of acute hypertension. Am J Cardiovasc Drugs 2009;9:117-34.
27. Sanoski CA. Aliskiren: An oral direct renin inhibitor for the treatment of hypertension. Pharmacotherapy 2009;29:193-212.
28. Hilas O, Ezzo D. Nebivolol (bystolic), a novel Beta blocker for hypertension. P T 2009;34:188-92.
29. Chaudhary R, Garg J, Krishnamoorthy P, Shah N, Lanier G, Martinez MW, *et al.* Ivabradine: Heart failure and beyond. J Cardiovasc Pharmacol Ther 2016;21:335-43.
30. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, *et al.* Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993-1004.
31. Simonneau G, Torbicki A, Hoeper MM, Delcroix M, Karlócai K, Galiè N, *et al.* Selexipag: An oral, selective prostacyclin receptor agonist for the treatment of pulmonary arterial hypertension. Eur Respir J 2012;40:874-80.
32. Ghofrani HA, Galiè N, Grimminger F, Grünig E, Humbert M, Jing ZC, *et al.* Riociguat for the treatment of pulmonary arterial hypertension. N Engl J Med 2013;369:330-40.
33. Pulido T, Adzerikho I, Channick RN, Delcroix M, Galiè N, Ghofrani HA, *et al.* Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med 2013;369:809-18.
34. McLaughlin VV, Benza RL, Rubin LJ, Channick RN, Voswinckel R, Tapson VF, *et al.* Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: A randomized controlled clinical trial. J Am Coll Cardiol 2010;55:1915-22.
35. Galiè N, Brundage BH, Ghofrani HA, Oudiz RJ, Simonneau G, Safdar Z, *et al.* Tadalafil therapy for pulmonary arterial hypertension. Circulation 2009;119:2894-903.
36. Galiè N, Olschewski H, Oudiz RJ, Torres F, Frost A, Ghofrani HA, *et al.* Ambrisentan in Pulmonary Arterial

Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Studies (ARIES) Group. Ambrisentan for the treatment of pulmonary arterial hypertension: Results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo controlled, multicenter, efficacy (ARIES) study 1 and 2. Circulation 2008;117:3010-9.

37. Zuckerbraun BS, George P, Gladwin MT. Nitrite in pulmonary arterial hypertension: Therapeutic avenues in the setting of dysregulated arginine/nitric oxide synthase signalling. Cardiovasc Res 2011;89:542-52.
38. Wielinga PR, van der Heijden I, Reid G, Beijnen JH, Wijnholds J, Borst P. Characterization of the MRP4- and MRP5-mediated transport of cyclic nucleotides from intact cells. J Biol Chem 2003;278:17664-71.