CODEN [USA] : IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187
http://doi.org/10.5281/zenodo.4001420

Available online at: http://www.iajps.com *Review Article*

A REVIEW ON NOVEL AGENTS USED IN TREATMENT OF ANGINA PECTORIS.

Pratik Katare[1]*, Sanchita Dey[1], Priyanka Birhade[1], Gitesh Guthale[2], Hemant Dhakne[3], Sunil Mahajan[4].

[1]Pratik Katare, Final year B. Pharm, M. G. V's Pharmacy College, Panchavati, Nashik.
e-mail: katarepratik@gmail.com
[2]Sanchita Dey, Final year B. Pharm, M. G. V's Pharmacy College, Panchavati, Nashik.
e-mail: sanjibkumar.dey@rediffmail.com
[3]Priyanka Birhade, Final year B. Pharm, M. G. V's Pharmacy College, Panchavati, Nashik.
e-mail: priyankabirhade97@gmail.com
[4]Gitesh Guthale, M. Pharm (Pharmacology),
Department of Pharmacology, M. G. V's Pharmacy College, Panchavati, Nashik.
e-mail: monty.guthale99@gmail.com
[5]Hemant Dhakne, M. Pharm (Pharmaceutical Chemistry),
Department of Pharmaceutical Chemistry, Dr. L.H. Hiranandani College of Pharmacy, Ulhasnagar, Thane.
e-mail: dhaknehemant94@gmail.com
[6]Sunil Mahajan, Vice Principal and Professor,
Department of Pharmaceutical Chemistry, M. G. V's Pharmacy College, Panchavati, Nashik.
e-mail: skmahajan2010@rediffmail.com

Article Received: June 2020 **Accepted:** July 2020 **Published:** August 2020

Abstract:
Angina pectoris is the medical word for pain in chest or discomfort due to heart disease mainly coronary heart disease. It is observed when the muscle of heart doesn't get as sufficient blood. This usually occurs because of one or more of the arteries of heart is narrowed or blocked, this phenomenon is also known as ischemia. The present study focuses on novel drugs used in the treatment of angina pectoris along with their structural activity relationship and the pharmacological actions. The article provides a way to approach all the novel drugs used for the treatment of the disease.

Keywords: *Angina Pectoris, Anti anginal drugs, Pharmacological actions.*

Corresponding author:
Pratik Katare,
Final year B. Pharm,
M. G. V's Pharmacy College, Panchavati,
Nashik. e-mail: katarepratik@gmail.com

QR code

Please cite this article in press Pratik Katare et al, ***A Review On Novel Agents Used In Treatment Of Angina Pectoris.,*** *Indo Am. J. P. Sci, 2020; 07(08).*

INTRODUCTION

Angina Pectoris is a medical condition which involves severe chest pain which may be relieved after taking rest. The pain is generated due to the insufficient blood supply to the muscles of heart due to some obstacles like clot, shrinkage of supplying coronary arteries. The most common cause is shrinkage of coronary arteries due to gathering of fatty substance along with the inner wall of the coronary arteries. Angina pectoris can be of various dissimilar types depending on main cause, disease pattern of progression etc. These various dissimilar types are stable angina, (causes due to disproportionate increase in myocardial oxygen demand) unstable angina (chest pain occurs even after at rest) and variant angina (Prinzmetal's angina), (it is the result of coronary vasospasm), of these three types unstable angina is the most dangerous type as it may readily lead to cause heart attack. Treatment options include life style change, therapeutic agents like nitrates, calcium channel blockers, anticoagulants, antiplatelet drugs, low dose aspirin etc, angioplasty and stent implantation and coronary bypass surgery to bypass the blocked part inside of the coronary artery. Approximately 60% of the patients are suffering from severe degree angina and death occurs before 55 years of age. [1]

Anti-anginal agents

An antianginal agent is a therapeutic agent used to treat angina pectoris, an indication of ischaemic heart disease. Examples: Agents used to treat angina pectoris mainly includes nitrates, beta blockers, and calcium channel blockers.

1.Nitrates

Nitrates causes enlargement of the venous capacitance vessels by modulating the endothelium derived relaxing factor (EDRF). Nitrates are used to provide relief from both exertional and vasospastic anginas by causing venous pooling and decreasing the pressure in the ventricles thus reducing tension between wall and oxygen requirements in, the heart. Short-acting nitrates are used to avoid angina attacks that has been observed. Whereas longer-acting nitrates are used in management prophylactic condition. [2]

Therapeutic Uses

1. In angina pectoris to provide relief from chest pain.
2. In refractory biliary colic and bronchial asthma as antispasmodics.
3. In abdominal pain of lead colic.
4. In trigeminal neuralgia amyl nitrite inhalations may help in reducing the intensity and duration of pain.
5. In Raynaud's disease and trophic ulcers topical application of nitroglycerin is useful in vasodilation.
6. In cyanide poisoning agents such as nitroglycerin (glyceryl trinitrate) or pentaerythritol tetranitrate, isosorbide dinitrate and isosorbide mononitrate, triglycerol nitrate are used. [3]

2. Beta blockers

Beta blockers are used in the prevention of exertional angina by decreasing the myocardial oxygen demand below the level that would lead to provoke an angina attack. [4] They are not recommended in variant angina as they may lead for a heart failure. They are also to be avoided in severe asthmatic patients due to as it leads to cause bronchoconstriction, and should be used carefully in diabetic patients as they can prevent symptoms of hypoglycemia. Therapeutic agents mainly include cardioselectives such as acebutolol or metoprolol, or non-cardioselectives such as oxprenolol or sotalol.

Therapeutic Uses

1.Hypertension
2.Angina Pectoris
3.Cardiac Arrhythmia
4.Myocardial Infarction
5.Pheochromocytoma
6.Idiopathic hypertrophic Subaortic stenosis
7.Migraine
8.Hyperthyroidism
9.Parkinson's Disease
10.Glaucoma
11.Anxiety
12.Recurrent gastric bleeding. [3]

3. Calcium channel blockers

Calcium ion antagonists are used in the management of chronic stable angina, and mostly used in the treatment of variant angina (directly preventing coronary artery vasospasm). They are not used for treating of patients suffering from unstable angina. By acting *Invitro*, they enlarge the coronary and peripheral arteries and have negative inotropic and chronotropic effects by reducing afterload, improving myocardial functions, decreasing the rate of heart and improving blood flow in coronary artery. By acting *Invivo*, they cause vasodilation and hypotension and stimulates the baroreceptor reflex. Therefore, the main effect on direct and reflex actions.

1.Class I agents have the most potent negative inotropic effect and may cause heart failure.
2.Class II agents do not depress conduction or contractility of heart muscles.
3.Class III agent has very less inotropic effect and causes tachycardia.
Examples include Class I agents (e.g., verapamil), Class II agents (e.g., amlodipine, nifedipine), or the Class III agent diltiazam.

Nifedipine is more a active vasodilator and more useful to treat angina. It is in the class of dihydropyridines and do not affect refractory period on SA node conduction. [2]

Therapeutic uses of nitrates

1. Useful to treat angina pectoris due to coronary spasm.
2. Exertional angina pectoris.
3. Unstable angina.
4. Supraventricular tachyarrhythmia's
5. Hypertension emergencies
6. Raynaud's disease. [3]

Recent drugs approved in year 2015

1. **Corlanor (ivabradine)**

Company: Amgen
Approval status: Approved April 2015
Specific treatments: used in treatment of chronic heart failure.
Therapeutic Areas: Cardiology/Vascular Diseases (antianginal)

General Information

Corlanor (ivabradine) is a hyper polarization activated cyclic nucleotide gated channel blocker. This channel is responsible for the cardiac pacemaker of current, which regulates heart rate.
Corlanor dosage form- tablets for oral administration.
Dose- Starting dose - 5 mg twice daily.
After 2 weeks of treatment, the dose should be adjusted based on heart rate. The maximum dose is 7.5 mg twice daily.

Mechanism of action

Ivabradine lowers rate of heart by selective blocking of If channel. It shows its action at concentration dependent manner without affecting any other cardiac ion channels (calcium and potassium ion channels). Ivabradine enters into the channel pore and binds intracellularly, to disrupt If ion current flow. This results in prolonged diastolicrepolarization, hence decreases increased rate of heart. Sinoatrial node includes If channels which regulates cardiac pacemaker activity. Thus Ivabradine reduces pacemaker firing rate, decreases heart rate and myocardial oxygen demand. This leads to increase oxygen supply thus there is mitigation of ischemia as well as there is less chances of angina episode.

Structure

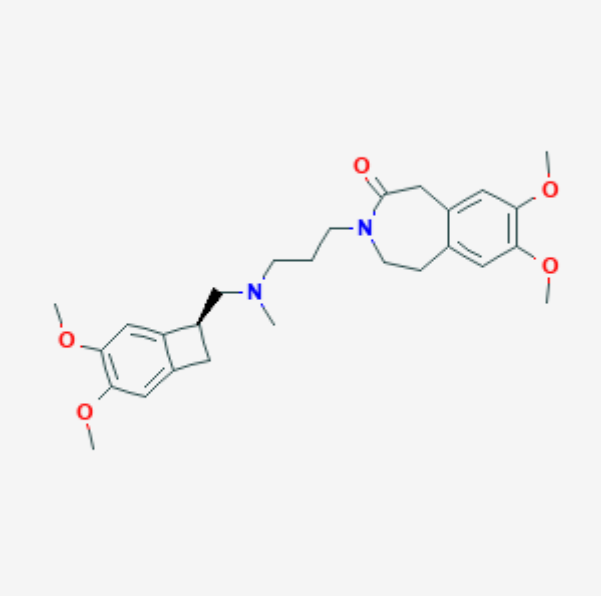

Fig 1 Ivabradine (IVA, Procoralan®, Corlentor®, Ivabid®)

IUPAC nomenclature-3-(3-{[((7S)-3,4-dimethoxybicyclo [4,2,0] octa1,3,5trien7yl) methyl] methyl amino} propyl)-1,3,4,5-tetrahydro-7,8-dimethoxy-2H-3-benzazepin-2-one hydrochloride

Structural activity relationship

Since 1980 agents having capacity of reducing diastolic depolarization rate have been developed having f-channel antagonizing property. The structural modifications with modified activity are as follows: Anilidine is an N-allyl derivative of clonidine with anti-anginal property. Falipalim and it's derivatives UL-FS49 and ZD7288 are having improved specificity of inhibition but reduced side effects. IV A is currently under clinical use.

Side effects
Adverse effects associated with the use of Corlanor may include, but are not limited to, the following:
1. Bradycardia
2. Hypertension
3. Atrial fibrillation
4. Luminous phenomena. [5]

2.Entresto (sacubitril and valsartan)
Company: Novartis

Approval Status: Approved in July 2015
Specific Treatments: chronic heart failure
Therapeutic Areas: Cardiology/Vascular Diseases.

General Information
Entresto is composed of sacubitril which is a inhibitor of neprilysin, and valsartan, it is a angiotensin II receptor antagonist. It minimizes the death rate in patients with chronic heart failure
Structure

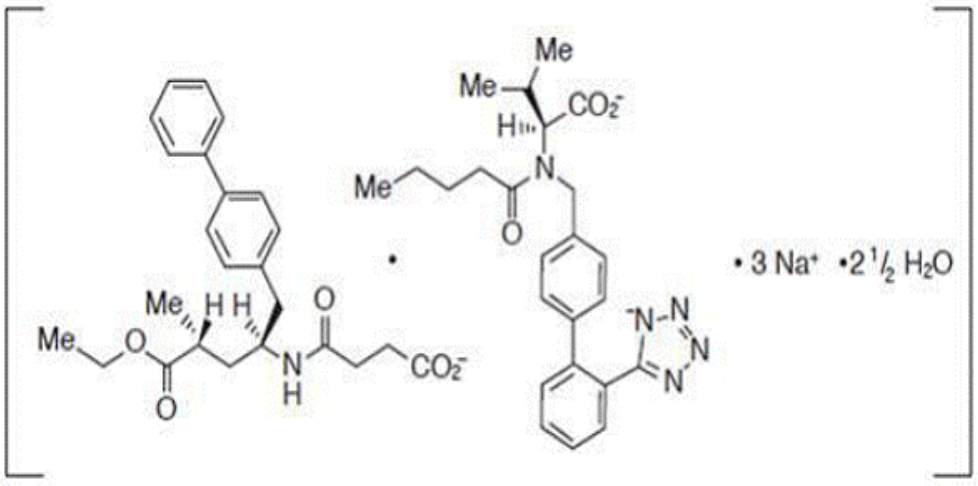

Fig 2. Entresto.

Octadecasodiumhexakis(4-{[(1S,3R)-1-([1,1´-biphenyl]-4-ylmethyl)-4-ethoxy-3-methyl-4-oxobutyl] amino}-4- oxobutanoate) hexakis(N-pentanoyl-N-{[2´-(1H-tetrazol-1-id-5-yl) [1,1´-biphenyl]-4-yl] methyl}-L-valinate). Its empirical formula (hemipentahydrate) is C48H55N6O8Na3 2.5 H2O. Its molecular mass is 957.99

ENTRESTO is available in market as film coated tablets for oral route of administration, it contains 24 mg of sacubitril and 26 mg, magnesium stearate (vegetable origin), talc, and colloidal silicon dioxide. The film of valsartan, 49 mg of sacubitril and 51 mg of valsartan; and 97 mg of sacubitril and 103 mg of valsartan. Inactive ingredients in tablet are microcrystalline cellulose, low-substituted hydroxypropylcellulose, crospovidone-coat inactive ingredients are hypromellose, titanium dioxide (E 171), Macrogol 4000, talc, and iron oxide red (E 172). The film-coat for the 24 mg of sacubitril and 26 mg of valsartan tablet and the 97 mg of sacubitril and 103 mg of valsartan tablet also contains iron oxide black (E 172). The film-coat for the 49 mg of sacubitril and 51 mg of valsartan tablet contains iron oxide yellow (E 172).

Side effects
Adverse effects associated with the use of Entresto are as follows
1. Hypotension
2. Hyperkalemia
3. Cough
4. Dizziness
5. Renal failure [6]

(NYHA Class II-IV) and it also leads to reduction in ejection fraction. Entresto is supplied as a tablet for oral route. The prescribed starting dose of Entresto is 49/51 mg (sacubitril/valsartan) two times a day. The dose of Entresto is doubled after 2 to 4 weeks to the achieve maintenance dose of 97/103 mg (sacubitril/valsartan) two times a day.

Mechanisms of action
Entresto antagonizes neprilysin (neutral endopeptidase; NEP) via LBQ657 which is active metabolite of the prodrug sacubitril, and blocks the angiotensin II type-1 (AT1) receptor via valsartan. The Entresto shows effect on cardiovascular as well as renal system which leads to increase in peptide levels, hence its natriuretic peptides become less effective by neprilysin with the help of LBQ657. Valsartan blocks the effects of angiotensin II by selectively antagonizing the AT1 receptor, and also blocks angiotensin II-dependent aldosterone release.

3.Nymalize (nimodipine)
Company: Arbor Pharmaceuticals
Approval Status: Approved in May 2013
Specific Treatments: decrease in incidence and severity of ischemic deficits following subarachnoid hemorrhage.

Therapeutic uses
1.It prevents cerebral vasospasm and resultant ischemia [7]
2.Head injury
3.Useful for treating ultradian bipolar cycling after brain injury and later, amygdalohippocampectomy. [8]

General Information
Nymalize (nimodipine) is an oral formulation of nimodipine available in solution form, a dihydropyridine calcium channel blocker. The mechanism of action of nimodipine is decreasing the incidence and severity of ischemic deficits in adult patients with SAH from ruptured intracranial berry aneurysms (Intracranial aneurysm, also known as brain aneurysm, is a cerebrovascular disorder in which weakness in the wall of a cerebral artery or vein causes a localized dilation or ballooning of the blood vessel) is unknown.

Nymalize is specially indicated for the improvement of neurological outcome by decreasing the incidence and severity of ischemic deficits in adult patients with subarachnoid hemorrhage (SAH) from ruptured intracranial berry aneurysms instead of their post-ictus neurological condition. Nymalize is supplied as a solution for oral administration. Nymalize should only be administered via the oral, nasogastric tube, or gastric tube route. The recommended oral dosage is 20 ml (60 mg) every 4 hours for 21 consecutive days.

Mechanism of action
Nimodipine is a dihydropyridine calcium channel blocker. The contraction of the smooth muscles is dependent upon the calcium ions, which enters in the cells of smooth muscles during depolarization's as slow ionic transmembrane currents. Thus, Nimodipine inhibits the entry of calcium ions into the smooth vascular cells which avoids or prevents the contraction of the vascular smooth muscles.
Structure

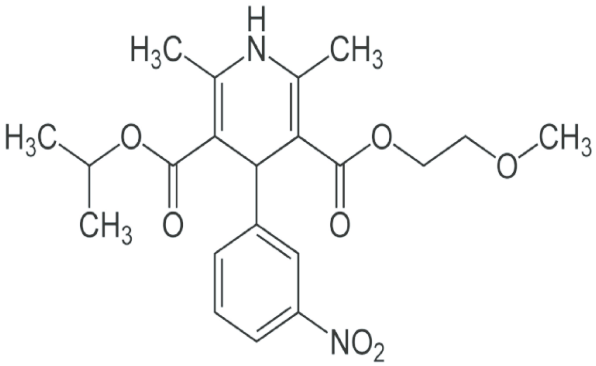

Fig 3. Nimodipine.

Nimodipine is isopropyl 2 - methoxyethyl 1, 4 - dihydro - 2, 6 - dimethyl - 4 - (m-nitrophenyl) - 3, 5 - pyridinedicarboxylate I
molecular weight -418.5, molecular formula - C21H26N2O7

Absorption
In humans, nimodipine is rapidly absorbed via oral route and maximum concentrations are generally achieved within one hour. Bioavailoability of nimodipine is 100% by intravenous administrations and 3 – 30% following by oral administration due to first pass metabolism.

Volume of Distribution: - Not available
Protein binding: - 95% binded to plasma protein.
Metabolism: - Hepatic metabolism via CYP 3A4

Bioavailability	Completely absorbed at around 5 hrs, steady state is reached by 60th hr.
Protein binding	Low (16%)
Metabolism	Minimal
Elimination – Half life	7 – 12 hrs
Excretion	Mainly renal (unchanged), exposure in increased in renal impairment on an average by 4 – folds in in subject with severe renal impairment (CrCl <30ml/min)

Route of elimination
Nimodipine is eliminated from systemic circulation almost exclusively in the form of metabolites and less than 1% is recovered in the urine as unchanged drug. Numerous metabolites, all of which are either inactive or considerably less active than the parent compound, have been identified.

Half-life :1.7 – 9 hrs

Clearance: Not available

Toxicity
Symptoms of over dosing would be related to cardiovascular effects such as excessive peripheral vasodilation with marked systemic hypotension.

Form	Route	Strength
Capsule	Oral	30 mg/l
Capsule liquid filled	Oral	30 mg/l
Capsule, gelatin coated	Oral	30 mg/l
Tablet	Oral	30 mg/l
Capsule	Oral	30 mg/l
Liquid	Intravenous	2 mg
Liquid	Intravenous	0.2 mg
Solution	Oral	30 mg/10Ml
Solution	Oral	60 g/ 20ml

Drugs approved in 2012
Trimetazidine
Trimetazidine is a drug for angina pectoris sold under many brand names. [17] Trimetazidine is described as the first cytoprotective anti-ischemic drug developed and marketed by Laboratories Servier (France). Trimetazidine is an anti-ischemic (anti-anginal) metabolic agent, which improves myocardial glucose utilization through inhibition of fatty acid metabolism, also known as fatty acid oxidation inhibitor.

Medical uses
Trimetazidine is used and prescribed for a long-term treatment of angina pectoris, and sometimes for tinnitus and dizziness. It is taken twice a day. The European Medicines Agency (EMA) explained the benefits and risks of trimetazidine and suggested for a restricted use of trimetazidine containing medicines. [18]

The study of trimetazidine shows a reverse in coronary flow reverse, hence, it delays the onset of ischemia related with exercise, rapid swings in blood pressure without changes rate of heart, significantly reduces the frequency of angina attacks and leads to cause drop in use of nitrates.

It leads to improve left ventricular function in diabetic patients with coronary heart disease. [19] [20]

Mechanism of action
By antagonizing long-chain 3-ketoacyl-CoA thiolase, which enhances glucose oxidation, Trimetazidine blocks beta-oxidation of fatty acids. [21] In an ischemic cell, the oxygen consumption required is less than that in beta oxidation process for glucose oxidation. Potentiation of glucose oxidation optimizes cellular energy processes, thus maintains proper energy metabolism during ischemia. By preserving energy metabolism in cells exposed to hypoxia or ischemia, trimetazidine prevents a decrease in intracellular ATP levels, thereby ensuring the proper functioning of ionic pumps and transmembrane sodium-potassium flow whilst maintaining cellular homeostasis. [22]

Structure

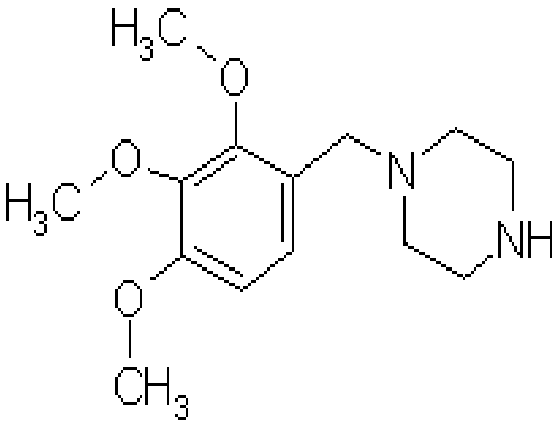

Fig 4. Trimetazidine
IUPAC name 1-(2,3,4-trimethoxybenzyl) piperazine, Formula:C14H22N2O3
Molar mass:266.336 g/mol g•mol−1

Adverse effects

Trimetazidine has been treated as a drug with a high safety and tolerability profile. [23] It interacts with monoamine oxidase inhibitors.

The recent EMA evaluation also revealed rare cases (3.6/1 000 000 patient years) of Parkinsonian (or extrapyramidal) symptoms (such as tremor, rigidity, akinesia, hypertonia), gait instability, restless leg syndrome, other related movement disorders, majority of patient recovered within 4 months after treatment discontinuation, thus, doctors are advised not to prescribe the medicine either to patients with Parkinson disease, parkinsonian symptoms, tremors, restless leg syndrome or other related movement disorders, nor to patients with severe renal impairment. [18]

Conventional Drugs

Nicorandil (1983)

Nicorandil is a vasodilator drug used to treat heart diseases specifically angina. There are many mechanisms which cause the increased smooth muscle contraction involved in coronary vasospasm, including raised Rho-kinase activity. Raised levels of Rho-kinase inhibit myosin phosphatase activity, leading to raising calcium sensitivity and hypercontraction. [9] Rho-kinase also reduces nitric oxide synthase activity, which causes reduction in nitric oxide concentrations. [10] Lower levels of nitric oxide are present in spastic coronary arteries. [11] L-type calcium channel expression increases in spastic vascular smooth muscle cells, which could result in excessive calcium influx, and hypercontraction. [12] It was patented in 1976 and approved for medical use in 1983. [13]

Mechanism of action

Nicorandil is an anti-anginal agent having dual properties of a nitrate and ATP-sensitive K+ channel agonist. In humans, the nitrate action of Nicorandil enlarges the large coronary arteries at low plasma concentrations. At high plasma concentrations Nicorandil reduces coronary vascular resistance, which is associated with increased ATP-sensitive K+ channel (KATP) opening. [14] Nicorandil modulates guanylate cyclase to increase formation of cyclic GMP (cGMP). cGMP activates protein kinase G (PKG), which phosphorylates and inhibits GTPase RhoA and reduces Rho-kinase activity. Reduced Rho-kinase activity allows an increment in myosin phosphatase activity, reducing the calcium sensitivity of the smooth muscle. [15]

PKG leads to stimulation of sarcolemma calcium pump to remove activating calcium. [16] PKG acts on K+ channels to promote K+ efflux and assuring hyperpolarization inhibits voltage-gated calcium channels. [14] Overall this causes relaxation of the smooth muscle and coronary vasodilation.

Structure

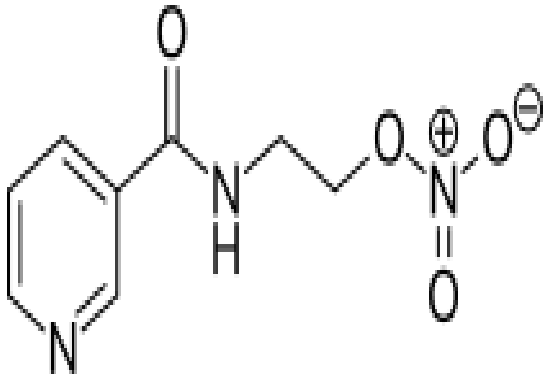

Fig 5. Nicorandil

IUPAC name 2-[(pyridin-3-ylcarbonyl) amino] ethyl nitrate

Mol formula- C8H9N304, Mol weight- 211.175g/mol

Side effects

1.Flushing, palpitations, weakness and vomiting.
2.perianal, ileal and peristomal ulceration.
3.Anal ulceration
4.Severe toothache, nasal congestion.

RECENT STUDIES

Experimental studies of ivabradine have shown independent reduction in heart rate without any effects on blood pressure, myocardial contractility and relaxation, ventricular repolarization or myocardial conduction Charles BB. et.al.2018. [24] It has been reported that based on a time-to-event analysis, Entresto was superior to enalapril in decreasing the risk for the combined end point of CV death or hospitalization in patients with heart failure, the treatment effect reflected a reduction in CV death and heart failure hospitalization. Overall, sacubitril plus valsartan reduced the risk for death from CV causes by 20%, reduced the risk for hospitalization for heart failure by 21%, and reduced heart failure–related symptoms and physical limitations compared with enalapril Loretta F.2015.[25] In case of trimetazidine, it was observed that, Trimetazidine 80 mg o.d. effectively reduced angina attacks and Short acting nitrates consumption, improved physical activity and adherence and was well tolerated in chronic Stable angina patients Glezer MG et.al 2018. [26]

CONCLUSION

Based on above information we can conclude that novel agents Ivabradine, Entresto, Trimetazidine are having therapeutic effects in the treatment of angina pectoris and other heart related diseases.

ACKNOWLEDGEMENT
The authors are grateful to principal Dr. R.S. Bhambar for their continuous support and encouragement.

CONFLICT OF INTEREST
The authors do not have any conflict of interest.

REFERENCES

1.http://www.medibiztv.com/articles/introduction-to-angina-pectoris.
2.Pfister M, Seiler C, Fleisch M, Göbel H, Lüscher T, Meier B. "Nitrate induced coronary vasodilatation: differential effects of sublingual application by capsule or spray". *Heart*. 80 (4): 365–9. October 1998.
3.BarrarF.S.K."Essentialsof Pharmacotherapeutics" S. Chand & Company Ltd., third edition 2000 Page no. 213, 269, 272, 273, reprint 2003,
4.O'Rourke ST "Antianginal actions of beta-adrenoceptor antagonists". *Am J Pharm Educ*. 71 (5): 95. (October 2007).
5.Ivabradine: An Intelligent Drug for the Treatment of Ischemic Heart Disease Graziano Riccioni Received: Published: 16 November 2012
6.https://www.pharma.us.novartis.com/product/pi/pdf/entresto.pdf
7."FDA approved Labelling text. Nimotop (nimodipine) Capsules for Oral Use" (PDF). Food and Drug Administration. December 2005. Retrieved 2009-07-21.
8. De León OA. "Response to nimodipine in ultradian bipolar cycling after amygdalohippocampectomy". J Clin Psychopharmacol. 32 (1):146–150. February 2012.
9.Kandabashi, T, Shimokawa, H, Miyata K, Kunihiro I, Kawano Y, Fukata, Y, Higo0 T, Egashira, K, Takahashi, S, Kaibuchi, K, Takeshita A "Inhibition of myosin phosphatase by upregulated rho-kinase plays a key role for coronary artery spasm in a porcine model with interleukin-1beta". *Circulation*. 101 (11), 1319–23, Mar 21, 2000.
10.Takemoto M, Sun J, Hiroki J, Shimokawa H, Liao JK. "Rho-kinase mediates hypoxia-induced downregulation of endothelial nitric oxide synthase". *Circulation*. 106 (1): 57–62Jul 2, 2002.
11.Kugiyama, K., Yasue H., Okumura K., etal. "Nitric oxide activity is deficient in spasm arteries of patients with coronary spastic angina". *Circulation*. 94 (3): 266–71. Aug 1, 1996.
12.Kuga T., Shimokawa H., Hirakawa Y. etal "Increased expression of L-type calcium channels in vascular smooth muscle cells at spastic site in a porcine model *Journal of cardiovascular pharmacology*. 35 (5): 822–8.
13.Fischer J., Ganellin C., etal. *Analogue-based Drug Discovery*. John Wiley & Sons. p. 454. 2006.
14.Nakae I, Matsumoto T, Horie, H, et al "Effects of intravenous nicorandil on coronary circulation in humans: plasma concentration and action mechanism". *Journal of cardiovascular pharmacology*. 35 (6): 919–25. June 2000.
15.Sauzeau V, Le Jeune H, Cario-Toumaniantz C.et al "Cyclic GMP-dependent protein kinase signalling pathway inhibits RhoA-induced Ca2+ sensitization of contraction in vascular smooth muscle". The Journal of Biological Chemistry. 275 (28): 21722, Jul 2000.
16.Vrolix M, Raeymaekers L, Wuytack F., et.al. "Cyclic GMP-dependent protein kinase stimulates the plasma lemma Ca2+ pump of smooth muscle via phosphorylation of phosphatidylinositol". *The Biochemical* Journal. 255 (3): 855–63, June 2000.
17."Trimetazidine – International brands". Drugs.com. Retrieved 7 May 2017.
18."European Medicines Agency recommends restricting use of trimetazidine-containing medicines" (pdf). *Press release*. European Medicines Agency. 2012..
19.Fragasso G, Palloshi A, Puccett P.et al. "A randomized clinical trial of trimetazidine, a partial free fatty acid oxidation inhibitor, in patients with heart failure". J. Am. Coll. Cardiol. 48 (5): 992–8. 2006.
20.Tuunanen H, Engblom E, Naum A, et al. "Trimetazidine, a metabolic modulator, has cardiac and extra cardiac benefits in idiopathic dilated cardiomyopathy". Circulation. 118 (12):12508, 2008.
21.Kantor PF, Lucien A, Kozak R, Lopaschuk GD. "The antianginal drug trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase". Circ.Res. 86 (5):580–8.2000.
22.Stanley WC, Marzilli M. "Metabolic therapy in the treatment of ischaemic heart disease: the pharmacology of trimetazidine". Fundam Clin Pharmacol. 17 (2):133-45,2003.
23.Ciapponi A, Pizarro R, Harrison J. "Trimetazidine for stable angina". Cochrane Database Syst Rev (4).2005
24. Charles BB., Robert J., Daniel H., "The therapeutic role of ivabradine in heart failure Ther Adv Chronic Dis, Vol. 9(11) 199–207,2018, DOI: 10.1177/2040622318784556
25.Loretta Fala., "Entresto (Sacubitril/Valsartan): First-in-Class Angiotensin Receptor Neprilysin Inhibitor FDA Approved for Patients with Heart Failure American Health & Drug Benefits, Vol 8, No 6,330-334 www.AHDBonline.com September 2015.

26. Maria GG., Vladimir AV., "Anti-Anginal Effectiveness and Tolerability of Trimetazidine Modified Release 80Mg Once Daily in Stable Angina Patients in Real-World Practice Adv Ther (2018) 35:1368–1377 https://doi.org/10.1007/s12325-018-0756-3