EFFICACY AND SAFETY OF IVABRADINE AS AN ADD-0N TO ATENOLOL IN PATIENTS WITH CHRONIC STABLE ISCHEMIC HEART DISEASE

DISSERTATION SUBMITTED TO

THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY

IN PARTIAL FULFILLMENT FOR THE AWARD OF THE DEGREE OF

DOCTOR OF MEDICINE

IN

PHARMACOLOGY

DEPARTMENT OF PHARMACOLOGY

TIRUNELVELI MEDICAL COLLEGE

TIRUNELVELI – 11

APRIL 2016

CERTIFICATE

This is to certify that the dissertation entitled "**EFFICACY AND SAFETY OF IVABRADINE AS AN ADD-0N TO ATENOLOL IN PATIENTS WITH CHRONIC STABLE ISCHEMIC HEART DISEASE"** presented herein by **DR.ELAVARASI.P** is an original work done by her in the Department of Pharmacology, Tirunelveli Medical College , Tirunelveli for the award of the Degree of Doctor of Medicine in Pharmacology during the academic period of 2013-2016.

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DECLARATION

I solemnly declare that the dissertation titled "**EFFICACY AND SAFETY OF IVABRADINE AS AN ADD-0N TO ATENOLOL IN PATIENTS WITH CHRONIC STABLE ISCHEMIC HEART DISEASE"** is done by me in the Department of Pharmacology , Tirunelveli Medical College, Tirunelveli.

The dissertation is submitted to The Tamilnadu Dr.M.G.R.Medical University in partial fulfillment for the award of the degree of Doctor of Medicine in Pharmacology.

Place: Tirunelveli

Date:

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ACKNOWLEDGEMENT

First of all, I am grateful to the Almighty for the good health and wellbeing that were necessary to complete this research work.

I am greatly indepted to **Dr.Sithy Athiya Munavarah MD**., Dean, Tirunelveli Medical College and **Dr. Kannan MD**.,Vice Principal.Tirunelveli Medical Collge ,Tirunelveli for their valuable support and generous permission for doing this research work.

I wish to thank with due respect and deep gratitude to **Dr. J.Ezhil Ramya M.D**.,Associate Professor and Head of the Department of Pharmacology for her inspiration, guidance and kind help rendered in completing this dissertation.

I would like to express my deepest thanks to **Dr.B.Meenakshi M.D**.,Associate Professor for giving kind advices, aspiring guidance ,motivation and encouragement throughout the research.

With deep sense of gratitude , I thank **Dr.R.Ravi Edwin M.D**., Professor and Head of the Department of Cardiology and other faculties of the department of cardiology for sharing their implicit knowledge, support and encouragement during the course of this research work.

I am immensely grateful to **Dr.Dulcie Celia M.D**.,Assistant Professor, **Dr.A.Geetha Rani M.D.,** Assistant Professor , **Dr. Vijay Sundar M.D**., Assistant Professor & **Dr.Shanthi M.D**., Assistant Professor for their support and advice provided during the research work.

I would like to thank the post graduates of Department of Pharmacology, for their friendly advice and sharing their illuminating views related to this study.

I also express my sincere thanks to my family members for their moral support ,encouragement and arranged all facilities to carry out this research successful as a postgraduate .

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CERTIFICATE OF REGISTRATION & APPROVAL OF THE TIREC REF NO: 513/PHARM/2014/20

PROTOCOL TITLE: EFFICACY AND SAFETY OF IVABRADINE AS AN ADD-ON TO ATENOLOL IN PATIENT WITH CHRONIC STABLE ISCHEMIC HEART DISEASE.

NAME OF PRINCIPAL INVESTIGATOR: Dr. P.Elavarasi, MBBS.,
DESIGNATION OF PRINCIPAL INVESTIGATOR: Post Graduate in MD Pharmacology
DEPARTMENT & INSTITUTION: Department of Pharmacology, Tirunelveli Medical College

Dear Dr. P.Elavarasi, *The Tirunelveli Medical College Institutional Ethics Committee (TIREC) reviewed and discussed your application during the IEC meeting held on 14.05.14.*

THE FOLLOWING DOCUMENTS WERE REVIEWED AND APPROVED

1.	TIREC Application Form	☐
2.	Study Protocol	☐
3.	Department Research Committee Approval	☐
4.	Patient Information Document and Consent Form in English and Vernacular Language	☐
5.	Investigator's Brochure	☐
6.	Proposed Methods for Patient Accrual Proposed	☐
7.	Curriculum Vitae of the Principal Investigator	☐
8.	Insurance /Compensation Policy	☐
9.	Investigator's Agreement with Sponsor	☐
10.	Investigator's Undertaking	☐
11.	DCGI/DGFT approval	☐
12.	Clinical Trial Agreement (CTA)	☐
13.	Memorandum of Understanding (MOU)/Material Transfer Agreement (MTA)	☐
14.	Clinical Trials Registry-India (CTRI) Registration	☐

THE PROTOCOL IS APPROVED IN ITS PRESENTED FORM ON THE FOLLOWING CONDITIONS

1. The approval is valid for a period of 2 year/s or duration of project whichever is later
2. The date of commencement of study should be informed
3. A written request should be submitted 3weeks before for renewal / extension of the validity
4. An annual status report should be submitted.
5. The TIREC will monitor the study
6. At the time of PI's retirement/leaving the institute, the study responsibility should be transferred to a person cleared by HOD
7. The PI should report to TIREC within 7 days of the occurrence of the SAE. If the SAE is Death, the Bioethics Cell should receive the SAE reporting form within 24 hours of the occurrence.
8. In the events of any protocol amendments, TIREC must be informed and the amendments should be highlighted in clear terms as follows:
   a. The exact alteration/amendment should be specified and indicated where the amendment occurred in the original project. (Page no. Clause no. etc.)
   b. The PI must comment how proposed amendment will affect the ongoing trial. Alteration in the budgetary status, staff requirement should be clearly indicated and the revised budget form should be submitted.
   c. If the amendments require a change in the consent form, the copy of revised Consent Form should be submitted to Ethics Committee for approval. If the amendment demands a re-look at the toxicity or side effects to patients, the same should be documented.
   d. If there are any amendments in the trial design, these must be incorporated in the protocol, and other study documents. These revised documents should be submitted for approval of the IEC, only then can they be implemented.
   e. Approval for amendment changes must be obtained prior to implementation of changes.
   f. The amendment is unlikely to be approved by the IEC unless all the above information is provided.
   g. Any deviation/violation/waiver in the protocol must be informed

STANDS APPROVED UNDER SEAL

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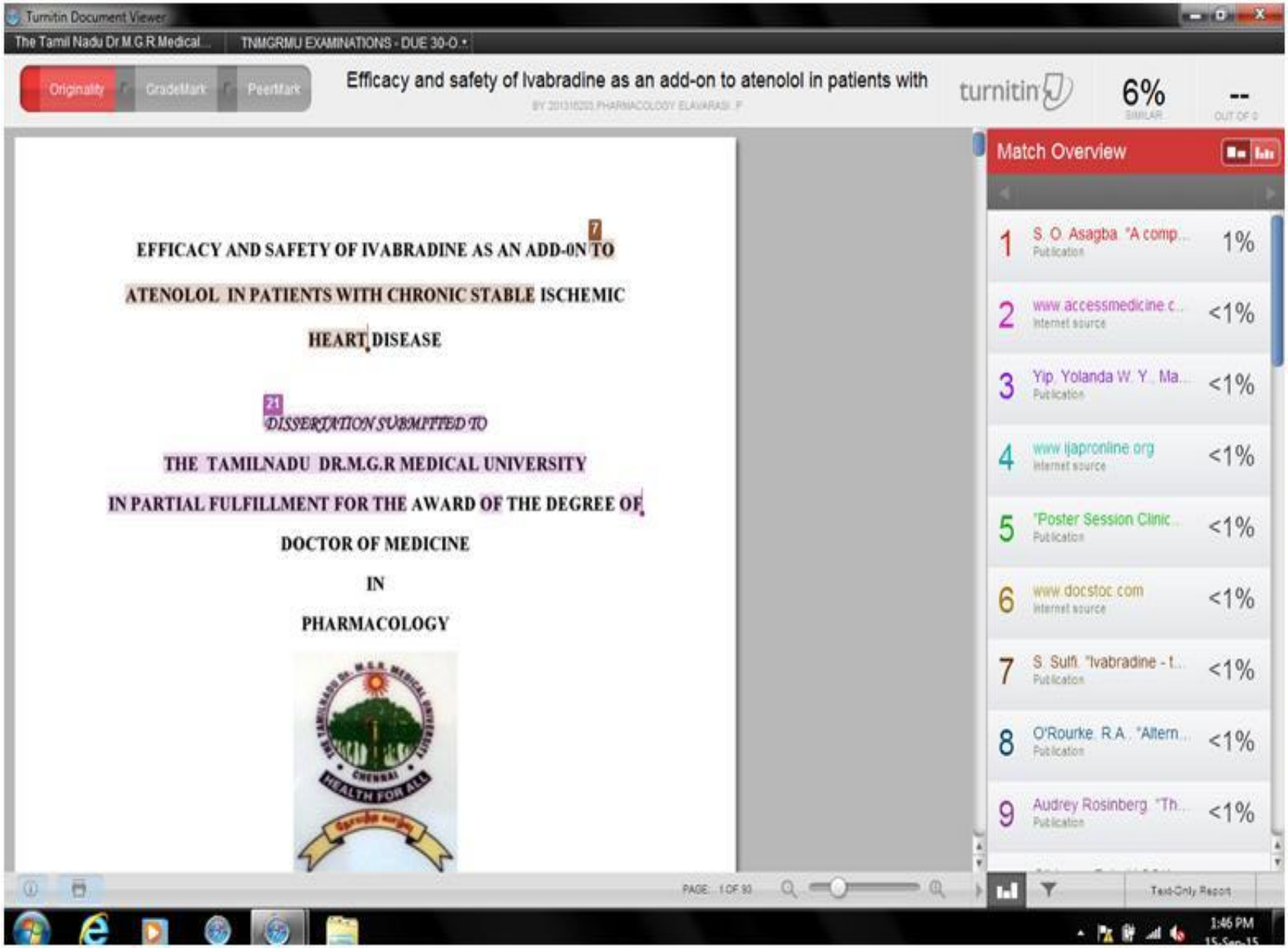
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CONTENTS

ABBREVIATIONS

CCB	- Calcium channel blockers
SA node	- Sino atrial node
AV node	- Atrio ventricular node
CAD	- Coronary artery disease
MI	- Myocardial Infarction
HF	- Heart failure
IHD	- Ischemic heart disease
VR- 1	- vanilloid receptor-1
ECG	- Electrocardiogram
CCS	- Canadian Cardiovascular Society
NYHA	- New York Heart Association
CRP	- C Reactive Protein
cGMP	- Cyclic guanosine monophosphate
LVEF	- Left Ventricular Ejection Fraction
EDHF	- Endothelium Dependent Hyperpolarizing Factor
HMG Co A	- 3-hydroxy-3-methylglutaryl-coenzyme A
ACE	- Angiotensin Converting Enzyme
FDA	- Food and Drug Administration
SPECT	- Single Photon Emission Computed Tomography
PDE	- Phosphodiesterase
CABG	- Coronary Artery Bypass Grafting
PCI	- Percutaneous Coronary Intervention

OPD - Out Patient Department

SAQ - Seattle Angina Questionnaire

PROACTIVE - Prospective Pioglitazone Clinical Trial in Macrovascular Events

INITIATIVE - International Trial on the Treatment of angina with Ivabradine vs. Atenolol.

BEAUTIFUL - The morBidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary artery disease and left-ventricULar dysfunction.

APPENDIX –I

INFORMED CONSENT FORM

Study Title :

Efficacy and safety of Ivabradine as an add-on to atenolol in patients with chronic stable ischemic heart disease-A prospective study.

Study Number _____

Subject's Full Name _____

Date of Birth/Age_____

Address

_____

1. I confirm that I have read and understood the information sheet dated for the above study and have had

the opportunity to ask questions.

OR I have been explained the nature of the study by the Investigator and had the opportunity to ask questions

2. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.

3. I understand that the sponsor of the clinical trial/project, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. However, I understand that my Identity will not be revealed in any information released to third parties or published.

4. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s)

5. I agree to take part in the above study

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:

_____

Signatory's Name _____ Date

_____

Signature of the Investigator _____ Date

_____

Study Investigator's Name _____

Signature of the Witness _____ Date

_____

Name of the Witness

நோயாளிகளுக்கு ஒப்புதல் மற்றும்

அறிவிப்பு படிவம்

ஆய்வு செய்யப்படும் தலைப்பு:

நீண்ட காலம் நிலையான மாரடைப்பு நோய்க்கு அட்டினலால் உடன் ஐவாபிராடின் (சேர்த்து பலன் மற்றும் பாதுகாப்பு குறித்து ஒரு ஆய்வு (மூன்று மாதங்கள்)

பங்கு றுபவரின் பெயர் :

பங்கு பெறுபவரின் வயது :

		பங்கு பெறுபவர் இதனை குறிக்கவும்
1	நான் மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்களை நான் படித்து புரிந்து கொண்டேன். என்னுடைய சந்தேகங்களை கேட்கவும் அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டுள்ளது என அறிந்து கொண்டேன்.	☐
2	நான் இவ்வாய்வில் தன்னிச்சையாக தான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும், எந்த சட்ட சிக்கலும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன்.	☐
3	இந்த ஆய்வு சம்பந்தமாகவோ. இதைச் சார்ந்து மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்கு பெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கையை பார்ப்பதற்கு என்னுடைய அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன்.	☐
4	இந்த அய்வின் மூலம் கிடைக்கும் தகவலையோ. முடிவையோ பயன்படுத்திக் கொள்ள மறுக்க மாட்டேன்.	☐
5	இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக் கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்து கொள்வதுடன் ஆய்வை மேற்கொள்ளும் மருத்து அணிக்கு உண்மையுடன் இருப்பேன் என உறுதியளிக்கிறேன். என் உடல் நலம் பாதிக்கப்பட்டாலோ. அல்லது எதிர்பாராத வழக்கத்திற்கு மாறான நோய்குறி தென்பட்டாலோ உடனே இதை மருத்துவ அணியிடம் தெரிவிப்பேன் என உறுதி அளிக்கிறேன்.	☐

பங்கேற்பவரின் கையொப்பம் /..... இடம் ..... தேதி .....
கட்டை விரல் ரேகை
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மையம் .....
கல்வியறிவு இல்லாதவற்கு (கைரேகை வைத்தவர்களுக்கு) இது அவசியம் தேவை
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பெயர் மற்றும் விலாசம் .....

APPENDIX – II

Canadian Cardiovascular Society Classification Class :

I “Ordinary physical activity does not cause angina,” such as walking or climbing stairs.Angina occurs with strenuous, rapid, or prolonged exertion at work or recreation.

II “Slight limitation of ordinary activity.”

Angina occurs on walking or climbing stairs rapidly; walking uphill ,under emotional stress; or only during the few hours after awakening. Angina occurs on walking >2 level blocks and climbing >1 flight of ordinary stairs at normal pace and under normal conditions.

III “Marked limitation of ordinary physical activity.”

Angina occurs on walking 1 to 2 level blocks and climbing 1 flight of ordinary stairs under normal conditions and at normal pace.

IV “Inability to carry on any physical activity” without discomfort anginal symptoms may be present at rest.

APPENDIX - III

The Seattle Angina Questionnaire

1. The following is a list of activities that people often do during the week. Although for some people with several medical problems it is difficult to determine what it is that limits them, please go over the activities listed below and indicate how much limitation you have had **due to chest pain, chest tightness, or angina over the past 4 weeks.**

Place an x in one box on each line.

Activity	Severely Limited	Moderately Limited	Somewhat Limited	A Little Limited	Not Limited	Limited, or did not do for other reasons
Dressing yourself	☐	☐	☐	☐	☐	☐
Walking indoors on level ground	☐	☐	☐	☐	☐	☐
Showering	☐	☐	☐	☐	☐	☐
Climbing a hill or a flight of stairs without stopping	☐	☐	☐	☐	☐	☐
Gardening, vacuuming, or carrying groceries	☐	☐	☐	☐	☐	☐
Walking more than a block at a brisk pace	☐	☐	☐	☐	☐	☐
Running or jogging	☐	☐	☐	☐	☐	☐
Lifting or moving heavy objects (e.g. furniture, children)	☐	☐	☐	☐	☐	☐
Participating in strenuous sports (e.g. swimming, tennis)	☐	☐	☐	☐	☐	☐

2. Compared with 4 weeks ago, how often do you have **chest pain, chest tightness, or angina** when doing your **most strenuous** level of activity?
I have had **chest pain, chest tightness,** or **angina**...

Much more often	**Slightly more** often	About **the same**	**Slightly less** often	**Much less** often
☐	☐	☐	☐	☐

3. Over the past 4 weeks, on average, how many times have you had **chest pain, chest tightness, or angina?**
I get **chest pain, chest tightness,** or **angina**...

4 or more times per day	1-3 times per day	3 or more times per week but not every day	1-2 times per week	Less than once a week	None over the past 4 weeks
☐	☐	☐	☐	☐	☐

4. Over the past 4 weeks, on average, how many times have you had to take nitros (nitroglycerin tablets) for your **chest pain, chest tightness,** or **angina?**
I take nitros...

4 or more times per day	1-3 times per day	3 or more times per week but not every day	1-2 times per week	Less than once a week	None over the past 4 weeks
❑	❑	❑	❑	❑	❑

5. How bothersome is it for you to take your pills for **chest pain, chest tightness or angina** as prescribed?

Very bothersome	**Moderately** bothersome	**Somewhat** bothersome	**A little** bothersome	**Not** bothersome at all	My doctor has **not prescribed** pills
❑	❑	❑	❑	❑	❑

6. How satisfied are you that everything possible is being done to treat your chest **pain, chest tightness, or angina**?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Highly satisfied
❑	❑	❑	❑	❑

7. How satisfied are you with the explanations your doctor has given you about your **chest pain, chest tightness, or angina**?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Highly satisfied
❑	❑	❑	❑	❑

8. Overall, how satisfied are you with the current treatment of your **chest pain, chest tightness, or angina**?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Highly satisfied
❑	❑	❑	❑	❑

9. Over the past 4 weeks, how much has your **chest pain, chest tightness, or angina** interfered with your enjoyment of life?

It has **severely** limited my enjoyment of life	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **barely** limited my enjoyment of life	It has **not** limited my enjoyment of life
❑	❑	❑	❑	❑

10. If you had to spend the rest of your life with your **chest pain, chest tightness, or angina** the way it is right now, how would you feel about this?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Highly satisfied
☐	☐	☐	☐	☐

11. How often do you worry that you may have a heart attack or die suddenly?

I can't stop worrying about it	I **often** think or worry about it	I **occasionally** worry about it	I **rarely** think or worry about it	I **never** think or worry about it
☐	☐	☐	☐	☐

சியாட்டல் நெஞ்சுவலி கேள்வித்தாள்

மக்களின் வாரந்தோறும் செய்யும் செயல்கள் கீழே கொடுக்கப்பட்டுள்ளது. நெஞ்சுவலி, மாரடைப்பு ஆகியவைகளால் கீழ்க்கண்ட செயல்கள் எந்த அளவிற்கு பாதிப்பு அடைந்துள்ளது என்று தெரிந்து கொள்ள விரும்புகிறோம். தயவு செய்து எல்லா கேள்விகளுக்கும் உங்களுக்கு மிகச் சிறப்பாக பொருந்தும் ஒரு பதிவை நீங்களே (✓) மூலம் பதிலளியுங்கள் இதில் சரியான (அ) தவறான பதில்கள் என்று எதுவும் இல்லை. நீங்கள் அளிக்கும் தகவல் ரகசியமாக வைக்கப்படும்.

பெயர் : _____ தேதி : _____

1.

செயல்கள்	தீவிரமான பாதிப்பு	மிதமான பாதிப்பு	ஓரளவு பாதிப்பு	சிறிதளவு பாதிப்பு	பாதிப்பு இல்லை	மற்ற காரணங்கள் கூட பாதிக்கவில்லை
சுயமாக உடை அணிதல்	☐	☐	☐	☐	☐	☐
சமதளத்தில் நடக்கும் போது	☐	☐	☐	☐	☐	☐
குளிக்கும் போது	☐	☐	☐	☐	☐	☐
மலை ஏறும்போது (அ) மாடிப்படி நிற்காமல் ஏறும்போது	☐	☐	☐	☐	☐	☐
தோட்டவேலை (அ) வீட்டுவேலைப் (அ) பளு தூக்குமும் போது	☐	☐	☐	☐	☐	☐
வேகமாக நடக்கும் போது	☐	☐	☐	☐	☐	☐
ஓடும்போது	☐	☐	☐	☐	☐	☐
எடை தூக்கும்போது (அ) தள்ளும்போது	☐	☐	☐	☐	☐	☐
கடின உடற்பயிற்சியில் பங்கு கொள்ளும்போது	☐	☐	☐	☐	☐	☐

2. கடந்த நான்கு வாரங்களுக்கு முன் ஒப்பிடும்போது நெஞ்சுவலி, நெஞ்சுபிடிப்பு (அ) மாரடைப்பு ஆகியவற்றை எத்தனை முறை கடின உடற்பயிற்சி மேற்கொள்ளும்போது உணர்ந்தீர்கள்.

மிகவும் அதிகமாக	கொஞ்சம் அதிகமாக	அதேபோல்	கொஞ்சம் குறைவாக	மிகவும் குறைவாக
☐	☐	☐	☐	☐

3. நான்கு வாரங்களாக தோராயமாக எத்தனை முறை நெஞ்சுவலி, நெஞ்சு பிடிப்பு (அ) மாரடைப்பு வந்துள்ளது?

ஒரு நாள்	1-3 முறை /ஒருநாள்	2-3/ ஒரு வாரம் (எல்லா நாட்களிலும் இல்லை)	1-2 முறை ஒருவாரம்	ஒரு வாரம்
☐	☐	☐	☐	☐

4. நான்கு வாரங்களாக தோராயமாக எத்தனை முறை நைட்ரஸ் (நைட்ரோகிளிசரின்) மாத்திரைகள் உங்களின் நெஞ்சுவலி, மாரடைப்பு (அ) நெஞ்சு பிடிப்புக்காக எடுத்துக்கொண்டீர்கள்?

4 முறை/ நாள்	1-3முறை / நாள்	3 வாரம் / எல்லா நாட்களிலும் இல்லை	1-2முறை / வாரம்	1 வாரம்
☐	☐	☐	☐	☐

5. உங்களின் நெஞ்சுவலி, மாரடைப்பு (அ) நெஞ்சு பிடிப்புக்காக மாத்திரை எடுத்துக்கொண்ட போது ஏதேனும் தொந்தரவுகள் ஏற்பட்டதா?

மிகவும் அதிகமாக	கொஞ்சம் அதிகமாக	ஓரளவு அதிகமாக	சிறிதளவு அதிகமாக	இல்லை	என்னுடைய மருத்துவர் மாத்திரைகளை பரிந்துரை செய்ய இல்லை?
☐	☐	☐	☐	☐	

6. உங்களின் நெஞ்சுவலி, நெஞ்சுபிடிப்பு (அ) மாரடைப்புக்கு செய்த சிகிச்சைகளால் தாங்கள் திருப்தி அடைந்தீர்களா?

கொஞ்சம்கூட திருப்தி அடையவில்லை	திருப்தி இல்லை	ஓரளவு திருப்தி	திருப்தி அடைந்துவிட்டேன்	மிகவும் திருப்தி அடைந்துவிட்டேன்
☐	☐	☐	☐	☐

7. உங்களின் நெஞ்சுவலி, நெஞ்சு பிடிப்பு (அ) மாரடைப்புக்காக உங்கள் மருத்துவர் கொடுத்த விளக்கம் உங்களுக்கு எவ்வளவு திருப்தி அளித்தது?

கொஞ்சம்கூட திருப்தி அடையவில்லை	ஓரளவு திருப்தி அடைந்துவிட்டேன்	மிகவும் திருப்தி அடைந்துவிட்டேன்
☐	☐ ☐ ☐	☐

8. இதுவரை தங்களின் நெஞ்சுவலி, மாரடைப்பு (அ) நெஞ்சு பிடிப்புக்காகக் கொடுத்துக்கொண்டு இருக்கும் சிகிச்சையில் எவ்வளவு திருப்தி அடைந்தீர்கள்?

கொஞ்சம்கூட திருப்தி அடையவில்லை	ஓரளவு திருப்தி அடைந்துவிட்டேன்	மிகவும் திருப்தி அடைந்துவிட்டேன்
☐	☐ ☐ ☐	☐

9. கடந்த நான்கு வாரங்களாக உங்களின் நெஞ்சுவலி, மாரடைப்பு (அ) நெஞ்சுபிடிப்பு உங்களின் மகிழ்ச்சியான வாழ்விற்கு எவ்வளவு இடையூறாக இருந்தது?

மிகவும் இடையூறாக	அதிகமாக இடையூறாக	கொஞ்சம் இடையூறாக	ஓரளவு இடையூறாக	இடையூறாக இல்லை
☐	☐	☐	☐	☐

10. இதுவரை உங்களுக்கு மாரடைப்பு, நெஞ்சுவலி (அ) நெஞ்சுபிடிப்பு இருந்ததைப்போல இனிமேலும் உங்களுக்கு அது இருக்கும் எனில் அதை எவ்வளவு உணர்கிறீர்கள்?

கொஞ்சம்கூட திருப்தி அடையவில்லை	ஓரளவு திருப்தி அடைந்துவிட்டேன்	மிகவும் திருப்தி அடைந்துவிட்டேன்
☐	☐ ☐ ☐	☐

11. மாரடைப்பு அல்லது திடீர் மரணம் குறித்த சிந்தனைகள் அடிக்கடி வருவது உண்டா?

நினைக்காமல் இருக்க முடியவில்லை	அடிக்கடி நினைப்பது உண்டு	அவ்வப்போது நினைப்பது உண்டு	அரிதாக நினைத்தது உண்டு	நினைத்ததே இல்லை
☐	☐	☐	☐	☐

APPENDIX - IV

PROFORMA

Name:

IP number:

Age:

Sex:

Weight:

Diagnosis :

Class of angina :

HISTORY:

Medical history:

1.Hypertension

2.Diabetes mellitus

3.Asthma

4. Seizure disorder

5.Bleeding diathesis.

Surgical history:

1.coronary angiography

2. CABS

3.Pacemaker implantation.

Drug history :

1. Aspirin/clopidogrel /statin
2. Beta blockers/ACE inhibitors / ARB / nitrates .

Other history :

Smoking/ alcohol and substance abuse .

Basic investigations:

	Hb%	TC	DC	ESR	BT	CT
Base line						
After 1 month						
After 3 months						

Liver Function Test :

	Direct bilirubin	Indirect bilirubin	Total bilirubin	ALT	AST	ALK PHOS
Base line						
After 1 month						
After 3 months						

Other investigations:

	Blood sugar	Blood urea	Serum creatinine	Serum electrolytes
Baseline				
After 1 month				
After 3 months				

ECG findings :

	HR	PR interval	QT interval
Baseline			
After 1 month			
After 3 months			

ECHO findings:

Class of angina :

Adverse effects :

1.Bradycardia

2. Severe hypotension

3.Heart Failure

4. Heart block 1/2/3 degree block.

5. Liver dysfunction.

EFFICACY AND SAFETY OF IVABRADINE AS AN ADD-ON TO ATENOLOL IN PATIENTS WITH CHRONIC STABLE ISCHEMIC HEART DISEASE

ABSTRACT:

INTRODUCTION:

Coronary artery disease is the leading cause of morbidity and mortality. Heart rate is the important key factor for determining the cardiac output ,myocardial oxygen demand and coronary blood flow . By the year 2020 , WHO predicts 13.2% death due to CAD . In india , 11% of urban population and 7% of the rural population had the prevalence of IHD. Reduction in heart rate is the main stay of treatment for preventing and treating the cardiovascular complications due to IHD. Pharmacotherapy of IHD are the conventional drugs like nitrates, beta blockers and calcium channel blockers . Due to the interactions with other drugs and adverse effects of the conventional drugs ,the management of IHD focused on novel targets . Ivabradine is a novel specific and selective If current inhibitor which slows the diastolic depolarization by acting on the SA node.

OBJECTIVE :

Efficacy and safety of Ivabradine as an add-on to atenolol in patients with chronic stable ischemic heart disease .

MATERIALS AND METHODS:

Interventional ,open label ,prospective clinical study was done over a period of 1 year (April 2014 to May 2015).Single centered study conducted in 50 patients in the Out patient Department of cardiology ,Tirunelveli Medical College Hospital , Tirunelveli.Primary endpoints noted were reduction in resting heart rate using 12 lead ECG and improvement in Canadian cardiovascular society (CCS)class of angina grading. Secondary end points were improvement in ejection fraction(EF) using echocardiography,improvement in left ventricular function(LVF) using echocardiography and improvement in quality of life score using SAQ .

RESULTS:

The demographic data concerning the patient's age, sex, weight, vitals, hemodynamic and laboratory parameters were statistically assessed at the baseline. Ivabradine in reducing the heart rate at the end of 1month (86.60±9.16) ($p<0.0001$) and at the end of 3 months (81.82±8.37)($p<0.0001$) when compared with baseline (93.08±11.67). CCS class of grade of angina also improved at the end of one month and 3 months compared with baseline .Grade IV (3►0►0), grade III(7►3►1) and grade II(40►8►9).

Study drug improved the LV dysfunction . After treatment with tab.Ivabradine , there were no patients with severe LV dysfunction at the end of 1 and 3 months when compared with 5 patients at the baseline.After treatment with study drug, moderate LV

dysfunction was reduced to 20 patients at the end of 1 month and 6 patients at the end of 3 months when compared with 35 patients at the baseline. After treatment with study drug the improvement in ejection fraction% was(45.48±5.03) ($p<0.001$) at the end of one month and (49.08±4.17) ($p<0.001$) three months compared with the baseline(41.36±6.23). Improvement in quality of life also assessed with SAQ questionnaire . Adverse drug reactions reported during the study was mild and no patients were withdrawn from the study due to adverse drug reactions and no patients experienced serious adverse drug reactions.

CONCLUSION :

Ivabradine is safe and effective in preventing and treating further anginal attacks in patients with chronic stable ischemic heart disease already on atenolol therapy.

KEYWORDS: Ivabradine, I_f current ,Ischemic Heart Disease, Heart Rate, Angina, Ejection fraction .

INTRODUCTION

Coronary heart disease is the leading cause of mortality and morbidity in developing countries and chronic stable angina pectoris is a primary symptom and the first clinical manifestation in upto 50% of patients[1]. Angina pectoris is characterized by substernal discomfort, heaviness, or a pressure-like feeling, which may radiate to the jaw, shoulder, back, or arm and which typically lasts several minutes[2] .Angina pectoris is caused by myocardial ischemia due to an imbalance between myocardial oxygen requirements and myocardial oxygen supply. The former may be elevated by increase in heart rate and contractility ,the latter is determined by coronary blood flow and coronary arterial oxygen content[3].

Heart rate is an important contributor in the pathophysiology of both coronary artery disease (CAD) and heart failure (HF).Heart rate is being recognised as a modifiable risk factor in patients with cardiovascular disease[4]. Elevated heart rate increases myocardial oxygen demand and limits tissue perfusion ,the latter by shortening the duration of diastole during which most myocardial perfusion occurs. [5]Pharmacotherapy for IHD is to reduce the frequency of anginal episodes, myocardial infarction, and coronary death. To achieve maximum benefit from medical therapy for IHD, it is necessary to combine agents from different classes and titrate the doses as guided by the individual profile of risk factors, symptoms, hemodynamic responses, and side effects. [6]In current clinical practice ,however many patients with chronic stable IHD require treatment with more than one anti-anginal drug in addition to nitrates, beta-blockers or calcium channel blockers(CCB)[7].

Ivabradine is a novel specific and selective heart rate lowering agent that acts in sino-atrial node(SA) cells by selectively inhibiting the cardiac pacemaker in a dose dependant manner.[8] I_f current has atypical or funny properties compared to other current systems such as a mixed Na^+-K^+ inward movement activated on hyperpolarization and modulated by autonomic nervous system. It is one of the most important ionic current for regulating the pacemaker activity in the SA node. Ivabradine reduces the slope of diastolic depolarization in these cells and lowers the heart rate at rest and during exercise.[2,9]

Beta blockers ,unlike ivabradine , reduce I_f activation by decreasing the sympathetic activity and cAMP formation, resulting in a lower HR. Left ventricular function and ventricular remodeling may be improved with I_f inhibition with beta blockers like atenolol . I_f inhibition with ivabradine does not alter myocardial inotropy or left ventricular function and reduces the remodeling process thus supporting cardiac output and coronary outflow during exercise.[6] Beta blockers have been used only in a limited manner because of hemodynamic or pulmonary intolerance. Beta blockers should be avoided in patients with reactive airway disease (asthma) or with SA or AV nodal dysfunction or in combination with other drugs that inhibit AV conduction like verapamil.[10]

CCBs bind to and inhibit L-type calcium channels, reducing calcium influx into cells. Intracellular calcium deprivation relaxes smooth muscle cells, causing vasodilation in the peripheral and coronary beds and increased coronary blood flow.[11]CCB s can produce negative chronotropic effect thereby reduce the heart rate .

However CCBs may cause reflex tachycardia, headache and edema and limit their usefulness in chronic stable angina[12].

There is still limited clinical trials related to Ivabradine and its combination with atenolol , which show its anti-anginal and anti-ischemic efficacy and safety in chronic stable ischemic heart disease. Thus the present study is aimed to evaluate the anti-anginal and anti-ischaemic efficacy and safety of the selective I_f current inhibitor ivabradine in patients with chronic stable angina pectoris already receiving atenolol, beta blocker therapy.

REVIEW OF LITERATURE

I. HISTORY OF ANGINA PECTORIS :

The concept of circulation was first presented to the Royal College of Physicians, London, and published in 1628 as *Exercitatio anatomica de motu cordis et sanguinis in animalibus (An anatomical disputation of the movement of the heart and blood in animals)* .Harvey stated that the blood is driven into a circular motion and that it moves perpetually and that this is the action or function of the heart which the heart performs by means of its pulse. On July 1768, William Heberden appropriated the term angina (Latin word meaning "strangling") and presented a seminar on "Some Account of a Disorder of the Breast" to the Royal College of Physicians, London, in which he stated that there was a disorder of the breast marked with strong and peculiar symptoms ,a sense of strangling and anxiety with which it was improperly be called angina pectoris. [13]

II. MAGNITUDE OF THE PROBLEM:

In many developed countries CHD is the largest public health problem. According to the global burden, by the year 2020 WHO predicts that among 65 million deaths 32% death due to cardiovascular complications and 13.2% death due to CHD .[14]In western countries the propotional mortality ratio is 30%death in males and 25% death in females due to CHD. According to a survey related to the prevalence of CAD and coronary risk factors ,prevalence of coronary artery disease in urban population is approximately 11% and rural population is around 7% across India.[15]

III. DEFINITION OF CHRONIC STABLE ANGINA:

Chronic stable angina pectoris refers to the predictable occurrence of a pressure or a choking sensation in the chest or adjacent areas caused by myocardial ischemia in association with physical or emotional stress and prompt relief of these symptoms with rest or sublingual nitroglycerin (glyceryl trinitrate). An imbalance between myocardial oxygen (O2) demand and supply is responsible for myocardial ischemia and anginal pain.In most patients who have chronic stable angina, the underlying lesion responsible for reduced myocardial blood flow(O2 supply) during periods of increased demand is severe atherosclerotic narrowing of one or more coronary arteries, which paradoxically constrict during exercise owing to endothelial dysfunction.[16]

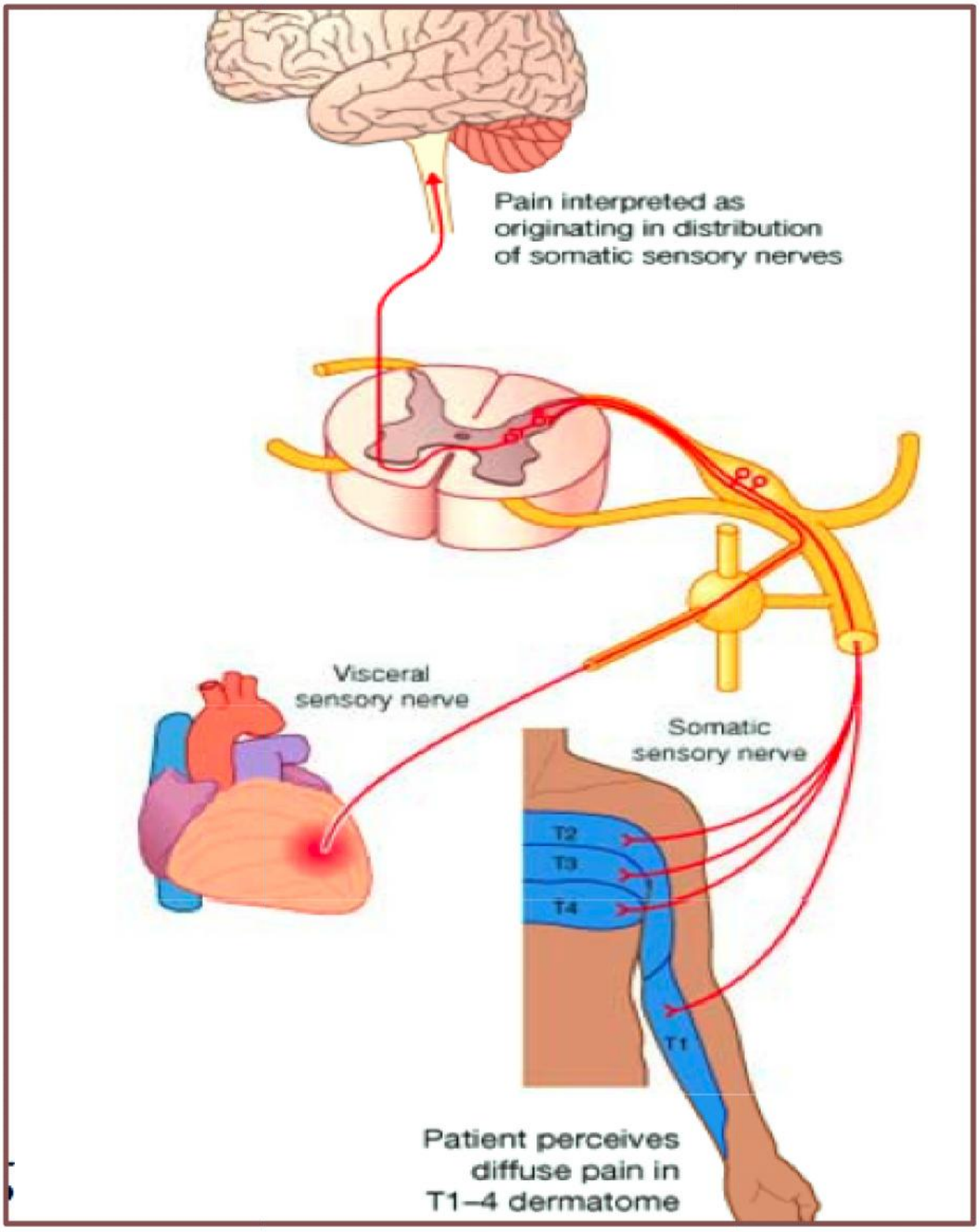
IV. NEUROMECHANISMS OF CARDIAC PAIN:

The mechanisms of cardiac pain and the neural pathways assumed that angina pectoris results from ischemic episodes that excite chemo-sensitive and mechano-sensitive receptors in the heart. Stimulation of both of these receptors results in the release of adenosine, bradykinin, and other substances that excite the sensory ends of the vagal afferent and sympathetic fibers. The afferent fibers traverse the nerves that connect to the upper five thoracic sympathetic ganglia and upper five distal thoracic roots of the spinal cord. Impulses are transmitted by the spinal cord to the thalamus and then to the neocortex. Data from murine vanilloid receptor-1 gene knockout model studies have identified the VR_1, an important sensor for somatic nociception situated on the sensory nerve endings of the heart and have suggested that VR_1 functions as a transducer of myocardial tissue ischemia.

Within the spinal cord, cardiac sympathetic afferent impulses may unite with impulses from somatic thoracic structures (T2 ,T3 and T4), which may be the basis for the pain referred to the chest. In addition, cardiac vagal afferent fibers synapse in the nucleus tractus solitarius of the medulla and then descend to excite the upper cervical spinothalamic tract cells, which may contribute to the anginal pain experienced in the neck and jaw.[17]

FIGURE 1

NEUROMECHANISM OF ANGINA [18]



V. DIFFERENT TYPES OF ANGINA:[19]

Five different kinds of angina have been identified:

- stable angina
- unstable angina
- Varient angina or primary angina
- microvascular angina or syndrome X
- silent angina and
- atypical angina

with the two most common being stable angina and unstable angina.

- **Stable angina (effort induced angina):**

Otherwise called classical angina or angina on exertion . This is the most common type of angina and it is either due to reduced oxygen supply or increased oxygen demand to myocardium.The ischemic attack occurs on exertion but there is no symptom at rest . These patients usually present with ST-segment depression on the electrocardiogram suggesting subendocardial ischemia.

- **Unstable angina** :

Otherwise called crescendo preinfarction or acute coronary syndrome.There is dislodging of a coronary plaque that triggers the local platelet aggregation and thrombosis which results in total or partial occlusion of coronary blood vessels. There is increased vascular tone leading to angina at rest . These patients are often prone to develop an acute myocardial infarction as a result of plaque rupture, thrombosis, and coronary vasoconstriction or spasm[20]. Less common kinds of angina include variant angina **,**microvascular angina, silent angina and atypical angina.

❖ **Variant Angina:**

Variant angina is otherwise called (Prinzmetal angina).Coronary spasm may lead to ST-segment elevation on the electrocardiogram. The exact mechanism responsible for coronary spasm has been due to number of vasoconstrictor substances including sympathomimetic amines such as norepinephrine or epinephrine, serotonin, histamine, endothelin, thromboxane A2 and acetylcholine act on G protein–coupled receptors will cause an increase in extracellular K+ or Ca2+ would result in membrane depolarization and vasoconstriction. This has also been implicated as causing coronary vasospasm.[21]

❖ **Microvascular angina :**

Some patients with angiographically normal coronary arteries have a positive exercise stress test with ST-segment depression on the electrocardiogram and perfusion defects indicative of myocardial ischemia and classical angina pectoris. This condition is often termed as “cardiac syndrome X” . The exact etiology of this syndrome is not certain. In this the symptoms of ischemia are absent but investigations like ECG ,echocardiography and other investigations show evidence of ischemia.

❖ **Silent angina:** Patients with CAD (particularly patients with diabetes) may have ischemia without symptoms. Ischemia is evidenced by transient asymptomatic ST-T abnormalities seen during 24-h Holter monitoring. Silent ischemia and angina pectoris may coexist, occurring at different times. Radionuclide studies can sometimes document asymptomatic myocardial ischemia during physical or mental stress. Prognosis depends on severity of CAD.

❖ **Atypical angina**

There may be a vague discomfort in the chest. Patient may experience shortness of breath, feel tired or nauseous, have indigestion or pain in the back or neck. Women are more likely than men to have feelings of vague chest discomfort.[22]

VI. GRADING OF ANGINA PECTORIS :

Canadian Cardiovascular Society Classification Class :[23]

I "Ordinary physical activity does not cause angina," such as walking or climbing stairs.Angina occurs with strenuous, rapid, or prolonged exertion at work or recreation.

II "Slight limitation of ordinary activity."

Angina occurs on walking or climbing stairs rapidly; walking uphill ,under emotional stress; or only during the few hours after awakening. Angina occurs on walking >2 level blocks and climbing >1 flight of ordinary stairs at normal pace and under normal conditions.

III "Marked limitation of ordinary physical activity."

Angina occurs on walking 1 to 2 level blocks and climbing 1 flight of ordinary stairs under normal conditions and at normal pace.

IV "Inability to carry on any physical activity" without discomfort anginal symptoms may be present at rest.

NYHA classification of angina:[21]

NYHA Class	Symptoms
I	No symptoms and no limitation with ordinary physical activity e.g. no shortness of breath when walking, climbing stairs etc.
II	Mild symptoms and slight limitation during ordinary activity
III	Marked limitation in activity due to symptoms. even less-than-ordinary activity
IV	Severe limitations in physical activity even at rest.

VII. PATHOPHYSIOLOGY OF CHRONIC STABLE ANGINA :

For an understanding the pathophysiology of myocardial ischemia is the balance between myocardial oxygen demand and blood supply . The major determinants of myocardial oxygen demand are heart rate, myocardial contractility, and myocardial wall tension. An adequate supply of oxygen is determined by the inspired level of oxygen, pulmonary function, and hemoglobin concentration. The myocardium requires a satisfactory level of oxygen-carrying capacity of the blood and an adequate level of coronary blood flow. In normal conditions ,the myocardium will control the supply of oxygen-rich blood to prevent underperfusion of myocytes. Thereby it will prevent the subsequent development of ischemia and infarction. Blood flows through the coronary arteries in a phasic fashion during diastole.[24]

a)Angina Caused by Increased Myocardial O_2 Requirements :

Also called demand angina .The myocardial O_2 requirement increases most commonly due to restricted O_2 supply. Hurrying, emotion and mental stress precipitate angina by increased hemodynamic and catecholamine responses to stress, increased adrenergic tone and reduced vagal activity. The combination of physical exertion and emotion in association with sexual activity may precipitate angina pectoris. Anger may produce constriction of coronary arteries with pre-existing narrowing, without necessarily affecting O_2 demand. Other precipitants of angina include physical exertion after a heavy meal and the excessive metabolic demands imposed by fever, thyrotoxicosis, tachycardia from any cause, and hypoglycemia.

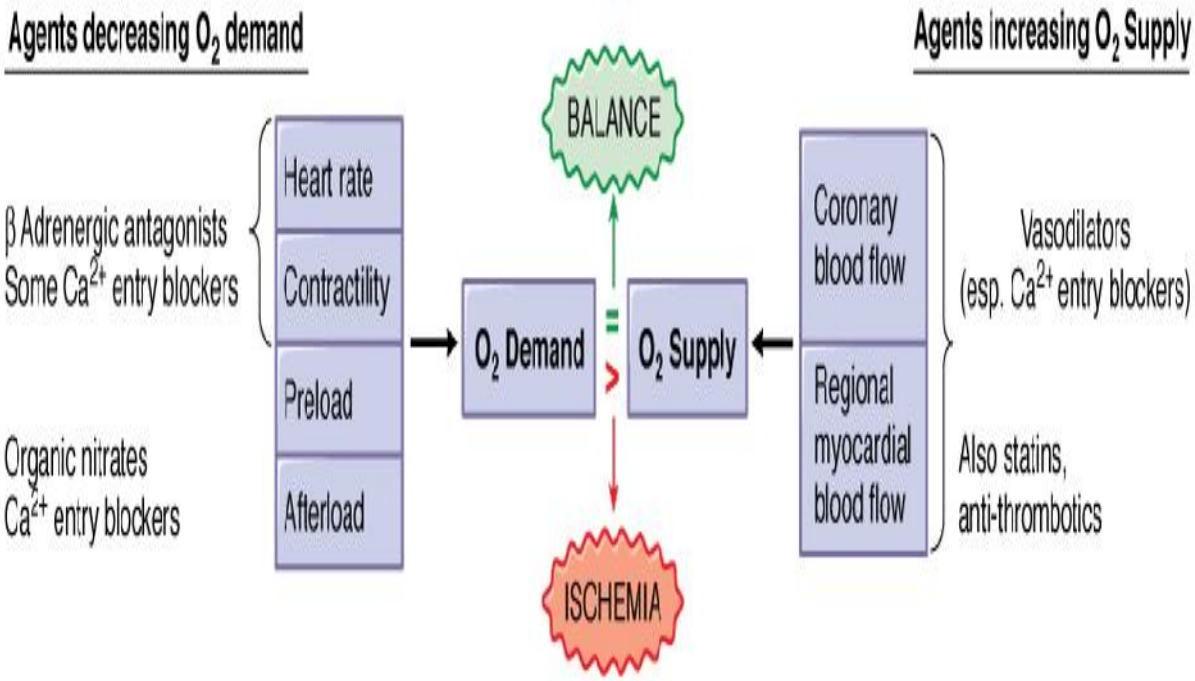
b)Angina Caused by Transiently Decreased O_2 Supply:

Also termed as supply angina . Transient reductions in O_2 supply has suggested that it occurs not only in unstable angina but also in chronic stable angina. In the presence of organic stenoses, platelet thrombi and leukocytes may elaborate vasoconstrictor substances, such as serotonin and thromboxane A_2. Also, endothelial damage in atherosclerotic coronary arteries decreases production of vasodilator substances and may result in an abnormal vasoconstrictor response to exercise and other stimuli.By reducing the lumen of the coronary arteries, atherosclerosis limits the perfusion when the demand for flow is augmented, as occurs during exertion or excitement. When the luminal reduction is severe, myocardial perfusion in the basal state is reduced. Coronary blood flow also can be limited by spasm ,arterial thrombi and coronary emboli as well as by ostial narrowing due to aortitis. Congenital abnormalities such as

the origin of the left anterior descending coronary artery from the pulmonary artery may rarely cause myocardial ischemia and infarction in adults.[25]

FIGURE 2

PATHOPHYSIOLOGY OF CHRONIC STABLE ANGINA[24]



VIII. CONTROL OF CORONARY BLOOD FLOW:

I. <u>Local Metabolic Feedback Control:</u>

An intrinsic local mechanism controls coronary blood flow to match changes in myocardial O2 consumption. The augmented O2 delivery restores myocardial O2 tension toward the normal operating point in a negative feedback manner. When myocardial O2 consumption increases, there is an incipient decrease in cardiac O2 tension, which results in a local vasodilator signal that increases coronary blood flow

and O2 delivery to the myocardium.. There have been several hypotheses about local metabolic control of coronary blood flow.

a. the adenosine hypothesis
b. the role of K^+ ATP channels; and
c. the role of O2 and carbon dioxide .

a)Adenosine Hypothesis:

The adenosine hypothesis proposes that adenosine is released from cardiac myocytes ,if myocardial O2 tension falls . Adenosine then crosses the interstitial space to act on adenosine receptors. It causes hyperpolarization of coronary vascular smooth muscle cells and causes dilatation of vascular smooth muscle.The resulting increases the coronary blood flow, which restores the balance between oxygen demand and supply.It is well established that ischemic or hypoxic myocardium releases adenosine, which acts as a pathophysiologic vasodilator.[26]

b)Role of K^+ATP Channels:

K^+ATP channels are found in the membranes of cardiac and coronary vascular smooth muscle cells . The experiments with hypoxia and ischemia interpreted as glibenclamide blunting the vasodilatory effects of adenosine . Therefore, blocking of K^+ATP channels with glibenclamide results in a decrease in coronary blood flow.

c)Role of Oxygen and Carbon Dioxide:

A hypothesis is that blood flow is primarily controlled by precapillary arterioles upstream from where the bulk of O2 and CO2 exchange occurs. Thus, the blood inside the arteriole has O2 and CO2 tensions that are close to the arterial level. Coronary

blood flow certainly responds to changes in arterial blood O2 content. A correlation between coronary blood flow and the synergistic effects of O2 and CO2 can be made when myocardial O2 consumption is increased by increase in coronary flow. For example, anemia increases coronary blood flow, but coronary venous O2 tension is little changed, demonstrating a good match between O2 delivery and myocardial O2 consumption by local metabolic control.[27]

II. Control of Flow by the Endothelium :

Endothelial cells lines the inner surface of the cardiovascular system .The endothelium produces vasoactive substances (eg, nitric oxide, prostacyclin, endothelin-1, epoxy eicosatrienoic acids) and responds to circulating factors (eg, epinephrine, serotonin). The overall function of the endothelium is to increase the blood flow through the arteries.Any damage to the endothelium resulted in vasoconstriction . Nitric oxide (NO) is the main mediator of vasodilation which is released physiologically through the parasympathetic neural stimulation. NO diffuses as a gas from the endothelium to the surrounding vascular smooth muscle cells where it induces a cyclic guanosine monophosphate (cGMP)– dependent muscular relaxation. In addition to NO, another potent vasodilator is prostacyclin, which is released by the endothelium involved in the normal vasodilation at rest .

III. Control by the Autonomic Nervous System:

i. Parasympathetic (Muscarinic) Receptor Control :

Vagal stimulation has a vasodilatory effect in the coronary bed by releasing NO . In addition to a direct effect on the coronary bed, increased parasympathetic tone reduces heart rate, arterial pressure, and inotropy. Altogether it reduces the oxygen demand of the myocardium . This effect is reproduced by administration of

acetylcholine and is blocked by atropine. It is well documented that parasympathetic system by releasing acetylcholine is responsible for coronary vasodilation .

ii. **Alpha Adrenergic Receptor Control** :

The stimulation of cardiac sympathetic nerves markedly increases coronary blood flow due to the increased metabolic demand induced by the increase in workload (heart rate, contractility and LV wall stress) resulting from catecholamine release. Similarly, direct stimulation of α1-adrenergic receptors with pharmacologic agonists can provoke vasoconstriction in coronary vessels. An important consequence of the α-adrenergic–mediated vasoconstriction in a context of increased workload is an increase in oxygen extraction which might be particularly relevant during exercise. The α-adrenergic tone of the coronary arteries can be activated by stimulation of reflex pathways, such as carotid baroreceptors upon carotid sinus hypotension, as well as by direct sympathomimetic stimulation. Similarly, stimulation of the carotid chemoreceptor, pulmonary inflation reflex, and arterial baroreceptor hypertension induce coronary vasodilation that results from a withdrawal of the α-adrenergic tone, potentially with a smaller vagal component contributing to the vasodilation.[28]

iii. Beta -Adrenergic Receptor Control :

Stimulation of the β-adrenergic receptors achieves coronary vasodilation through two mechanisms. First by Binding of the receptors in the coronary vessel itself will stimulate a Gs protein–mediated relaxation of the vascular smooth muscle cells. Second by binding of the receptors on the cardiac cells will stimulate a Gs protein–mediated increase in contractility, which, together with the increase in heart rate, will increase the metabolic demand and activate the recruitment of the coronary blood flow reserve through adenosine release. Patient treated with β-blockers will have reduced

coronary blood flow and exacerbated coronary vasospasm. However, the negative inotropy and reduction of heart rate following administration of β-blockers markedly reduce the risk of exercise-induced angina and provide protection following myocardial infarction and are used widely in patients with ischemic heart disease and hypertension.[29]

IV. Coronary Microcirculation:

Individual coronary resistance arteries are a longitudinally distributed network and the mechanisms controlling the resistance in these arteries is variable. These vessels dilate in co-ordinated manner so that they are able to meet the demands of the distal vascular bed . This is done by shear stress mediated control of the blood vessels or through myogenic control.

The resistance vessels are divided into resistance arteries and arterioles. The arteries are regulated by shear stress and myogenic response whereas the arterioles are mainly controlled by local metabolic factors and they regulate the perfusion of coronary capillary bed. Epicardial arteries with a diameter greater than 400 micron are mainly regulated by shear stress. The capillary density is considerably higher in the sub endocardium than the epicardium.

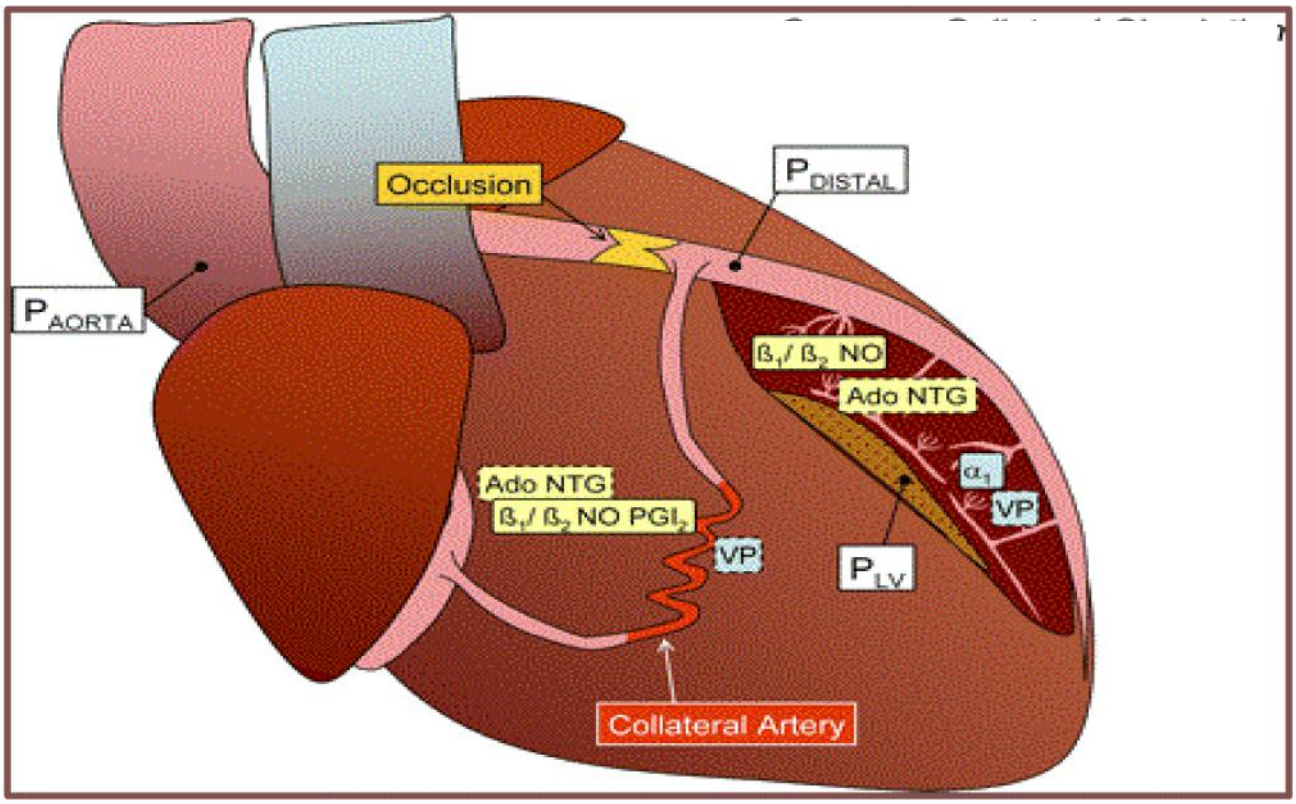
V. Myogenic Control:

This is a mechanism by which vessels dilate in response to decrease in pressure and constrict when the pressure increases. It is due to the tone of smooth muscle. It is believed to be due to the activation of the L type calcium channels.It occurs mainly in arterioles<100 micron diameter and is an important mechanism in coronary autoregulation.

Kuo and colleagues have shown flow-induced dilatation of coronary vessels[30]. This is mediated by NO and hence endothelium dependent. Endothelium Dependent Hyperpolarising factor ,an arachidonic acid metabolite primarily regulates epicardial conductance vessels.

FIGURE 3

CORONARY COLLATERAL CIRCULATION



The resistance vessels are controlled by Nitric oxide. EDHF may be upregulated during acquired disease states when Nitric oxide is deficient and serve as a compensatory mechanism assisting vasodilatation.

VI. CORONARY ATHEROSCLEROSIS:

Atherosclerosis is a chronic, lipid-driven inflammatory disease of the arterial wall leading to multifocal plaque development predominantly at predilection sites characterized by low and oscillatory endothelial shear stress (bifurcations, inner wall of curvatures) and preexisting intimal thickenings[31].

Epicardial coronary arteries are the major site of atherosclerotic disease. The major risk factors for atherosclerosis are high levels of plasma low-density lipoprotein (LDL), low plasma high-density lipoprotein (HDL),cigarette smoking, hypertension, and diabetes mellitus that disturb the normal functions of the vascular endothelium. Functional changes in the vascular milieu ultimately result in the subintimal collections of fat, smooth muscle cells, fibroblasts, and intercellular matrix that define the atherosclerotic plaque. This process develops at irregular rates in different segments of the epicardial coronary artery and leads eventually plaque formation.

There is also a predilection for atherosclerotic plaques to develop at sites of increased turbulence in coronary flow, such as at branch points in the epicardial arteries. When a stenosis reduces the diameter of an epicardial artery by 50%, there is a limitation of the ability to increase flow to meet increased myocardial demand. When the diameter is reduced by ~80%, blood flow at rest may be reduced, and further minor decreases in the stenotic orifice area can reduce coronary flow dramatically to cause myocardial ischemia at rest or with minimal stress .A thrombus composed of platelet aggregates and fibrin strands traps red blood cells and can reduce coronary blood flow, leading to the clinical manifestations of myocardial ischemia.

The location of the obstruction influences the quantity of myocardium. This determines the severity of the clinical manifestations. Thus, critical obstructions in vessels, such as the left main coronary artery and the proximal left anterior descending coronary artery, are particularly dangerous. Chronic severe coronary narrowing and myocardial ischemia frequently are accompanied by the development of collateral vessels, especially when the narrowing develops gradually. When well developed, such vessels can by themselves provide sufficient blood flow to sustain the viability of the myocardium at rest but not during conditions of increased demand.[32]

VII. **RISK FACTORS FOR IHD** :[33]

Major independent risk factors:

- Advancing age
- Cigarette smoking
- Diabetes mellitus
- Hypertension
- Elevated TC , LDL-C
- Low HDL-C

Conditional risk factors :

- Elevated serum lipoprotein (a)
- Elevated serum triglycerides
- Prothrombotic factors(fibrinogen)
- Elevated serum homocysteine

- Inflammatory markers (CRP)

Predisposing risk factors ;

- Ethnic characteristics
- Family history of premature coronary heart disease
- Physical inactivity
- Abdominal or central obesity
- Psychological factors.

VIII. SYMPTOMS OF ISCHEMIC HEART DISEASE :

The primary manifestation of ischemic heart disease is angina pectoris . It does not depend on the type of angina and the causal factors involved. Typically, the pain of angina occurs retrosternally and may manifest as a crushing, burning, or squeezing type of discomfort. The discomfort can be associated with shortness of breathe, nausea, diaphoresis, generalized weakness, and a fear of impending death.The pain may spread to the lower part of the neck and radiate down the left arm or either arm . The pain may be mild or intense and lasting for 5 to 10 minutes and is relieved rapidly by the administration of sublingual nitroglycerin . If nitroglycerin tablets do not relieve the pain, the pain is likely the result of an ongoing myocardial infarction or is from an extracardiac source. Chemical mediators such as adenosine, which is known to be released in large quantities during ischemia. Myocardial ischemia also appears to occur in cases without the symptoms of chest pain, known as silent ischemia. Anginal pain may occur in the absence of myocardial ischemia as a result of esophageal spasm or some other form of gastrointestinal disorder.

IX. EVALUATION OF IHD :

1. PHYSICAL EXAMINATION:

The physical examination in patients with stable angina are often asymptomatic. However, because of the increased risk of ischemic heart disease in patients with diabetes and/or peripheral arterial disease, clinicians should search for evidence of atherosclerotic disease at other sites, such as an abdominal aortic aneurysm, carotid arterial bruits, and diminished arterial pulses in the lower extremities. The physical examination also should include a search for evidence of risk factors for atherosclerosis such as xanthelasmas and xanthomas. Central obesity may indicate that the patient has the metabolic syndrome .There also may be signs of anemia, thyroid disease, and nicotine stains on the fingertips from cigarette smoking. Evidence for peripheral arterial disease should be sought by evaluating the pulse contour at multiple locations and comparing the blood pressure between the arms and between the arms and the legs (ankle-brachial index)

- ✓ Palpation may reveal cardiac enlargement and abnormal cardiac impulse .
- ✓ Auscultation of the chest can reveal arterial bruits, a third and/or fourth heart sound, and an apical systolic murmur due to mitral regurgitation. These auscultatory signs are best appreciated with the patient in the left lateral decubitus position .
- ✓ Examination of the fundi may reveal an evidence of hypertension as increased light reflex and arteriovenous nicking . Aortic stenosis, aortic regurgitation,pulmonary hypertension and hypertrophic cardiomyopathy must be excluded, since these disorders may cause angina in the absence of coronary

atherosclerosis. Examination during an anginal attack is useful, since ischemia can cause transient left ventricular failure with the appearance of a third and/or fourth heart sound, a dyskinetic cardiac apex, mitral regurgitation, and even pulmonary edema. Tenderness of the chest wall, localization of the discomfort with a single fingertip on the chest, or reproduction of the pain with palpation of the chest makes it unlikely that the pain is caused by myocardial ischemia.

2. NON INVASIVE TESTING :

a. Biochemical test :

Since the risk factors for stable IHD are hypercholesterolemia and other dyslipidemias , carbohydrate intolerance, and insulin resistance. All patients with established or suspected CAD can do the biochemical evaluation of total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, serum creatinine (estimated glomerular filtration), and fasting blood glucose levels. Measurement of lipoprotein (a) , lipoprotein-associated phospholipase A_2 (Lp-PLls A2) and homocysteine levels will provide information about the future events of ischemic heart disease.

Understanding the pathobiology of stable IHD have generated interest in inflammatory biomarkers as noninvasive indicators of underlying atherosclerosis and cardiovascular risk. The serum concentration of high-sensitivity C-reactive protein has shown a relationship to the risk of incident cardiovascular events. Other biomarkers of inflammation, such as myeloperoxidase, growth factors, and metalloproteinases are markers of underlying atherosclerosis remain under study.[34]

By assessing the blood levels of cardiac troponin as markers of necrosis are typically used to differentiate patients with acute MI from those with stable IHD.. Novel biomarkers of myocardial ischemia are the plasma concentration of brain natriuretic peptide (BNP) ,N-terminal pro-BNP are under study .Circulating biomarkers of myocyte injury have now been detected in patients with clinically stable IHD and shown to have a graded relationship with the subsequent risk of cardiovascular mortality and heart failure.

b. Resting Electrocardiography:

The most common electrocardiographic abnormalities in patients with chronic IHD are nonspecific ST-T wave changes, with or without abnormal Q waves. In addition to myocardial ischemia, other conditions that can produce ST-T wave abnormalities include LV hypertrophy and dilation, electrolyte abnormalities, neurogenic effects, and antiarrhythmic drugs . Various conduction disturbances, most frequently left bundle branch block and left anterior fascicular block, may occur in patients with stable IHD and are often associated with impairment of LV function and reflect multivessel CAD and previous myocardial damage. LV hypertrophy on the ECG is an indicator of worse prognosis in patients with chronic stable angina.[35]

c. Noninvasive Stress Testing:

Noninvasive stress testing can provide useful information to establish the diagnosis and estimate the prognosis in patients with chronic stable angina.

d. Exercise Electrocardiography:

The exercise ECG is particularly helpful for patients with angina pectoris who are considered to have a moderate probability of CAD provided they are capable of achieving an adequate workload and in whom the resting ECG is normal. Interpretation of the exercise test should include consideration of the exercise capacity , clinical, hemodynamic, and electrocardiographic responses. Antianginal pharmacologic therapy reduces the sensitivity of exercise testing as a screening tool. . Two or 3 days of interruption is required for patients receiving long-acting beta blockers.For long-acting nitrates, calcium antagonists, and short-acting beta blockers, discontinuing use of the medications the day before testing is required. Therefore, if the purpose of the exercise test is to diagnose ischemia, it should be performed in the absence of antianginal medications.

e. Stress Echocardiography

Stress echocardiography may be performed using exercise or pharmacologic stress and allows for the detection of regional ischemia by identifying areas of wall motion disorders. Two-dimensional echocardiography is useful for the evaluation of patients with chronic CAD because it can assess global and regional LV function under basal conditions and during ischemia, as well as detect LV hypertrophy and associated valve disease. Pharmacologic stress, such as with injection dobutamine, should be used for patients unable to exercise, those unable to achieve adequate heart rates with exercise, and those in whom the quality of the echocardiographic images during or immediately after exercise is poor.

f. Stress Myocardial Perfusion Imaging:

Stress testing should be performed only if there is no evidence of CAD in resting ECG .Perfusion imaging is also valuable for detecting myocardial viability in patients with regional or global LV dysfunction, with or without Q waves, and provides important information in regard to prognosis .Exercise perfusion imaging with simultaneous electrocardiographic testing is superior to exercise electrocardiography alone in detecting CAD, identifying multivessel CAD, localizing diseased vessels, and determining the magnitude of ischemic and infarcted myocardium. Exercise single-photon emission computed tomography (SPECT) provides higher sensitivity and specificity compared with exercise electrocardiography alone.

g. Chest Roentgenography :

The chest roentgenogram is usually within normal limits in patients with stable IHD. If cardiomegaly is present, it is indicative of severe CAD with previous MI, preexisting hypertension, or an associated nonischemic condition, such as concomitant valvular heart disease, pericardial effusion, or cardiomyopathy.

h. Computed Tomography :

Cardiac multidetector CT(MDCT) has made substantial advances as a noninvasive approach to imaging atherosclerosis . MDCT can also provide an angiogram of the coronary arterial tree. CT angiography may be reasonable for symptomatic patients at intermediate risk for coronary disease after initial evaluation in those with indeterminate results of stress testing. In addition to providing a highly

sensitive method for detecting coronary calcification which is diagnostic of coronary atherosclerosis.

i. Cardiac Magnetic Resonance Imaging :

Cardiac magnetic resonance imaging(CMR) is evolving as a versatile noninvasive cardiac imaging modality that has multiple applications for patients with IHD.It is established as a valuable clinical tool for imaging the aorta and cerebral and peripheral arterial vasculature. CMR is continuing to develop as a single approach to assessment of cardiac function, structure, blood flow, and viability without exposing the patient to ionizing radiation .it is useful to characterize congenital coronary anomalies and to detect stenoses in the proximal and middle segments of major epicardial vessels or surgical bypass grafts.

3. INVASIVE TESTING :

Catheterization and Coronary Arteriography:

The clinical examination and noninvasive techniques described are extremely valuable for establishing the diagnosis of CAD. Currently definitive diagnosis of CAD and precise assessment of its anatomic severity still require cardiac catheterization and coronary arteriography. Advanced invasive imaging techniques such as intravascular ultrasonography (IVUS) provide a cross-sectional view of the coronary artery and have substantially enhanced the detection and quantification of coronary atherosclerosis, as well as the potential to characterize the vulnerability of coronary atheroma. Angiography techniques provide information about reduced size of the coronary collaterals ,presence of myocardial bridging , defective LV wall

motion ,reduced coronary blood flow and abnormal myocardial metabolism suggestive of chronic IHD . The most serious limitation to the routine use of coronary angiography for prognosis in patients with stable IHD is its inability to identify which coronary lesions can be considered to be at high risk, or vulnerable, for future events, such as MI or sudden death.[36]

X. MEDICAL MANAGEMENT OF IHD :

Comprehensive management of stable IHD has five aspects: [37]

(1) identification and treatment of associated diseases that can precipitate angina and ischemia;

(2) reduction of coronary risk factors;

(3) application of pharmacologic and nonpharmacologic interventions for secondary prevention, with particular attention to adjustments in lifestyle;

(4) pharmacologic management of angina; and

1)TREATMENT OF ASSOCIATED DISEASES:

In patients with CAD or tachyarrhythmias can increase myocardial O_2 need with an increase in the frequency and severity of angina. Identification and treatment of these conditions are essential to the management of stable IHD. Several common medical conditions include anemia, marked weight gain, occult thyrotoxicosis, fever, infections and tachycardia. Cocaine, which can cause acute coronary spasm and MI . Therefore these conditions should be diagnosed early and managed accordingly.

2)REDUCTION OF CORONARY RISK FACTORS:

a) Cigarette Smoking :

- ✓ Smoking remains one of the most powerful risk factors for the development of CAD in all age groups. Cigarette smokers have a higher 5-year risk of sudden death, MI, and all-cause mortality than those who have stopped smoking in patients with angiographically documented CAD[38]. Moreover, smoking cessation lessens the risk of adverse coronary events in patients with established CAD. Cigarette smoking may be responsible for aggravating angina in addition to progression of atherosclerosis, it may increase myocardial O_2 demand and reduce coronary blood flow by an alpha-adrenergically mediated increase in coronary artery tone and thereby cause acute ischemia. . It causes vasoconstriction via activation of the sympathetic nervous system and platelet activation/aggregation with a consequent increase in thromboxane A2 biosynthesis Moreover, passive exposure to smoke has adverse cardiovascular effects that are almost as great as those of active smoking. Smoking cessation is one of the most effective and cost-effective approaches to the prevention of disease progression in native vessels and bypass grafts.
- ✓ **Nicotine(cigaretee)** is a potent drug of dependence. Withdrawal can lead to an "abstinence syndrome" consisting of craving, irritability and sometimes physical features (e.g. alimentary disturbances). A treatment programme should include medical , psychological and social support.
- ✓ **Bupropion** appears to reduce the desire to smoke and used as an adjunct to motivational support in smoking cessation. It is contraindicated in patients with

a history of seizures or of eating disorders, or who are experiencing acute alcohol or benzodiazepine withdrawal.

- ✓ **Varenicline**, a selective nicotinic receptor partial agonist, is an oral adjunct to smoking cessation. It is started 1–2 weeks before stopping smoking. It is contraindicated in pregnancy. Side effects include gastro-intestinal disturbances, headache, dizziness and sleep disorders.
- ✓ **Nicotine skin patches or nicotine gum** as part of a smoking cessation programme significantly increases success rates.[39]

b) Management of Dyslipidemia:

Most patients with dyslipidaemia have a combination of genetic and dietary factors. Secondary forms of dyslipidaemia are diabetes,hypothyroid,primary biliar cirrhosis and chronic kidney disease. Reducing the total plasma cholesterol concentration reduces the risk of coronary heart disease and can cause regression of atheroma.. In people without clinical evidence of atheromatous disease, the decision as to whether to initiate drug treatment at any given level of serum lipids should be informed by the risk of coronary events.

Lipid-lowering with statins (taken once daily at night) which is effective and has been shown to reduce in serum LDL cholesterol levels . In addition it would reduce circulating levels of hsCRP, decrease thrombogenicity, and favorably alter the collagen and inflammatory components of arterial atheroma and suggest antiatherothrombotic properties of statins. These properties may contribute to reduction in inducible myocardial ischemia, improvement in blood flow, and the reduction in coronary events in patients treated with statins. Also, in a large randomized, placebo-controlled trial in individuals with average LDL levels and no

known atherosclerosis but an increased risk of atherothrombosis identified with elevated hsCRP, statin therapy reduced the risk of first major cardiovascular events.

Mild and infrequent side effects of statins include nausea, constipation, diarrhoea, flatulence, fatigue, insomnia and rash. More serious adverse events are rhabdomyolysis, hepatitis and angioedema. Liver function tests should be performed before starting treatment and at intervals. HMG CoA reductase inhibitors should be avoided in alcoholics and patients with active liver disease, and are contraindicated during pregnancy. Statins are well absorbed, extracted by the liver and are subject to extensive presystemic metabolism by CYP3A4 or CYP2D6. The risk of rhabdomyolysis is increased by concurrent use of a fibrate or inhibitors of statin metabolism, e.g. azoles .[40]

c) Management of Diabetes Mellitus :

Patients with diabetes mellitus are at significantly higher risk of atherosclerotic vascular disease. A favorable impact of control of glycemia on microvascular complications of diabetes is well established. But the macrovascular complications on of diabetes on control of glycemia is not well established. In an analysis of a secondary endpoint of the PROACTIVE Trial, treatment of patients with type 2 diabetes with the oral hypoglycemic agent pioglitazone reduced the risk of death, nonfatal MI, or stroke.[41]According to the Diabetes Control and Complications Trial , during a mean follow-up of 17 years in patients with type 1 diabetes assigned to intensive glycemic therapy were at lower risk of cardiovascular complications.Several large trials evaluating the effects of oral hypoglycemic agents on cardiovascular outcomes are ongoing. Management of hypercholesterolemia and

hypertension are particularly important in patients with type 2 diabetes.

d) **Inflammation :**

Atherothrombosis has been recognized as an inflammatory disease.Markers of systemic inflammation, of which hsCRP is seen in patients with established vascular disease who are at higher risk for future ischemic events. Therefore, inflammation has been identified as a potential target for therapeutic intervention in patients with IHD. For example, in a number of studies, treatment with statins has lowered the serum concentration of hsCRP. In addition, lower levels of hsCRP achieved with statin therapy in patients 1 month after an ACS are associated with better long-term prognosis . Aspirin, ACE inhibitors, thiazolidinediones, thienopyridines, and fibric acid derivatives are among those agents that have been shown to exert anti-inflammatory or immunoregulatory actions .Other established preventive interventions, as well as novel therapeutic strategies, may also have anti-inflammatory effects that could target inflammation.

e) Obesity :

Obesity is an independent contributor to the risk for IHD and is associated with other risk factors, including hypertension, dyslipidemia, and abnormal glucose metabolism. Weight loss can improve or prevent many of the cardiovascular consequences of obesity.

3)ADDITIONAL DISEASE-MODIFYING PHARMACOTHERAPY FOR SECONDARY PREVENTION :

Antiplatelet drugs:

- **Aspirin:**

Aspirin blocks production of TxA_2 by acetylating a serine residue near the active site of platelet cyclooxygenase-1 (COX-1), the enzyme that produces the cyclic endoperoxide precursor of TxA_2.[42] According to antithrombotic trials low dose aspirin reduce the risk of MI by 87% during 5 yrs follow up. Low dose aspirin 75 to 162 mg daily is preferred for secondary prevention in the absence of recent intracoronary stenting.[43]

- **Clopidogrel :**

Clopidogrel, a thienopyridine derivative may be substituted for aspirin in patients with aspirin hypersensitivity or those who cannot tolerate aspirin. Clopidogrel is a prodrug with a slow onset of action .Clopidogrel is an irreversible inhibitor of platelet P_2Y_{12} receptors but is more potent and has a more favorable toxicity profile than ticlopidine, with thrombocytopenia and leukopenia occurring only rarely .The usual dose is 75 mg/day with or without an initial loading dose of 300 or 600 mg. The drug is somewhat better than aspirin in the secondary prevention of stroke, and the combination of clopidogrel plus aspirin is superior to aspirin alone for prevention of recurrent ischemia in patients with unstable angina. The superiority of the

combination suggests that the actions of the two drugs are synergistic, as might be expected from their distinct mechanisms of action. The FDA-approved indications for clopidogrel are to reduce the rate of stroke, myocardial infarction, and death in patients with recent myocardial infarction or stroke, established peripheral arterial disease, or acute coronary syndrome.[23] Ongoing studies are testing the hypothesis that more potent antiplatelet therapy than aspirin alone is useful for patients with stable IHD.[44]

i. Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers:

Although inhibitors of the renin-angiotensin-aldosterone system are not indicated for the treatment of angina, these drugs appear to have important benefits in reducing the risk of future ischemic events in some patients with cardiovascular disease.[24] The potentially beneficial effects of ACE inhibitors include reduction in LV hypertrophy, vascular hypertrophy, progression of atherosclerosis, plaque rupture, and thrombosis, in addition to a potentially favorable influence on myocardial O_2 supply and demand relationships, cardiac hemodynamics, sympathetic activity, and coronary endothelial vasomotor function. In addition, in vitro experiments have shown that angiotensin II induces inflammatory changes in human vascular smooth muscle cells, and treatment with ACE inhibitors can reduce signs of inflammation in animal models of atherosclerosis. ACE inhibitors may be considered for optional use in all other patients with stable IHD with normal LV ejection fraction and cardiovascular risk factors that are well controlled in whom revascularization has been performed.

ii. Antioxidants :

Oxidized LDL particles are strongly linked to the pathophysiology of atherogenesis. Descriptive, prospective cohort, and case-control studies have suggested that a high dietary intake of antioxidant vitamins (A, C, and beta-carotene) and flavonoids (polyphenolic antioxidants), naturally present in vegetables, fruits, tea, and wine is associated with a decrease in CAD events . Thus, based on current evidence, there is no basis for recommending that individuals take supplemental folate, vitamin E, vitamin C, or beta-carotene for the purpose of treating CAD. Additional investigation of other approaches to antioxidant therapy is ongoing.

ii. Counseling and Changes in Lifestyle:

- **Depression and angina** :

Depressive symptoms are associated with higher levels of circulating biomarkers of inflammation. In conjunction with counseling, treatment with a selective serotonin reuptake inhibitor appears to be safe and effective for managing depression in patients with IHD. Moreover, psychosocial stress at work, home, or both is associated with an increased risk of MI and may be a target for preventive interventions.Depressive symptoms are strongly associated with health status as reported by the patient, including the burden of symptoms and overall quality of life, independently of LV function and the presence of provokable ischemia. In addition, the association between depressive symptoms and IHD may reflect a causal relationship between the former and atherothrombosis.

- **Physical activity and angina :**

An important aspect of the physician's role is to counsel the patients with respect to dietary habits, goals for physical activity, the types of work they can do, and their leisure activities. Certain changes in lifestyle may be helpful, such as modifying strenuous activities if they constantly and repeatedly produce angina. However, isometric activities such as weightlifting expose the individual to the detrimental effects on the O_2 demand and supply relationship, and these activities should also be avoided whenever possible. Although it is desirable to minimize the number of bouts of angina, an occasional episode is not to be feared. Patients learn their usual threshold by trial and error. Eliminating or reducing the factors that precipitate anginal episodes is of obvious importace. Patients should avoid sudden bursts of activity, particularly after long periods of rest, after meals, and in cold weather. Both chronic and unstable angina exhibit a circadian rhythm characterized by a lower angina threshold shortly after arising. Therefore, morning activities such as showering, shaving, and dressing should be done at a slower pace and, if necessary, with the use of prophylactic nitroglycerin. The stress of sexual intercourse induces a heart rate of approximately 120 beats/min. With proper precautions (i.e., commencing more than 2 hours postprandially and taking an additional dose of a short-acting beta blocker 1 hour before and nitroglycerin 15 minutes before), most patients with stable angina are able to continue satisfactory sexual activity .

4)PHARMACOLOGICAL MANAGEMENT OF IHD:

I. NITRATES:

History of Nitrates:

Nitroglycerin was first synthesized in 1846 by Sobrero, who observed that a small quantity placed on the tongue elicited a severe headache. The explosive properties of nitroglycerin also were soon noted by Alfred Nobel.In 1857, T. Lauder Brunton of Edinburgh administered *amyl nitrite*, a known vasodepressor, by inhalation and noted that anginal pain was relieved within 30- 60 seconds.[45] The action of amyl nitrite was transitory, however, and the dosage was difficult to adjust. Subsequently, William Murrell established that sublingual nitroglycerin for relief of the acute anginal attack and as a prophylactic agent to be taken prior to exertion. In 1998 ,the importance of NO as a signaling molecule in the cardiovascular system and was recognized by the pharmacologists Robert Furchgott, Louis Ignarro, and Ferid Murad , awarding the Nobel Prize in medicine/physiology.[46]

Source and Synthesis :

The endogenous synthesis of NO in humans is catalyzed by a family of NO synthases that oxidize the amino acid L-arginine to form NO, plus L-citrulline as a co-product. There are three distinct mammalian NO synthase isoforms termed as *nNOS*, *eNOS*, and *iNOS* . They are involved in processes as diverse as neurotransmission, vasomotion, and immunomodulation.

Mechanism of Action:

The action of nitrate group of agents is to relax vascular smooth muscle. The vasodilator effects of nitrates are predominant in the venous circulation. The venodilator effect reduces ventricular preload, which in turn reduces myocardial wall tension and O_2 requirements. The action of nitrates in reducing preload and afterload makes them useful in the treatment of heart failure as well as angina. By reducing the cardiac mechanical activity, volume, and O_2 consumption, nitrates increase exercise capacity in patients with IHD, thereby allowing a greater total body workload to be achieved before the angina threshold is reached. Thus, in patients with stable angina, nitrates improve exercise tolerance and time to ST-segment depression during treadmill exercise tests. When used in combination with calcium channel blockers and/or beta blockers, the antianginal effects appear greater.

Effects on the Coronary Circulation:

Nitroglycerin causes dilation of epicardial arteries more than endocardial arteries . These stenoses are often eccentric lesions, and nitroglycerin causes relaxation of the smooth muscle in the wall of the coronary artery that is not encompassed by plaque. Even a small increase in a narrowed arterial lumen can produce a significant reduction in resistance to blood flow across obstructed regions. Nitrates may also exert a beneficial effect in patients with impaired coronary flow reserve by alleviating the vasoconstriction caused by endothelial dysfunction.

Redistribution of Blood Flow:

Nitroglycerin causes redistribution of blood flow from normally perfused to ischemic areas, particularly in the subendocardium. This redistribution may be mediated in part by an increase in collateral blood flow and in part by lowering of LV diastolic pressure, thereby reducing subendocardial compression. Nitroglycerin appears to reduce coronary vascular resistance preferentially in viable myocardium with ischemia, as detected by SPECT imaging. In patients with chronic stable angina responsive to nitroglycerin, topical nitroglycerin under resting conditions alters myocardial perfusion by preferentially increasing flow to areas of reduced perfusion, with little or no change in global myocardial perfusion.

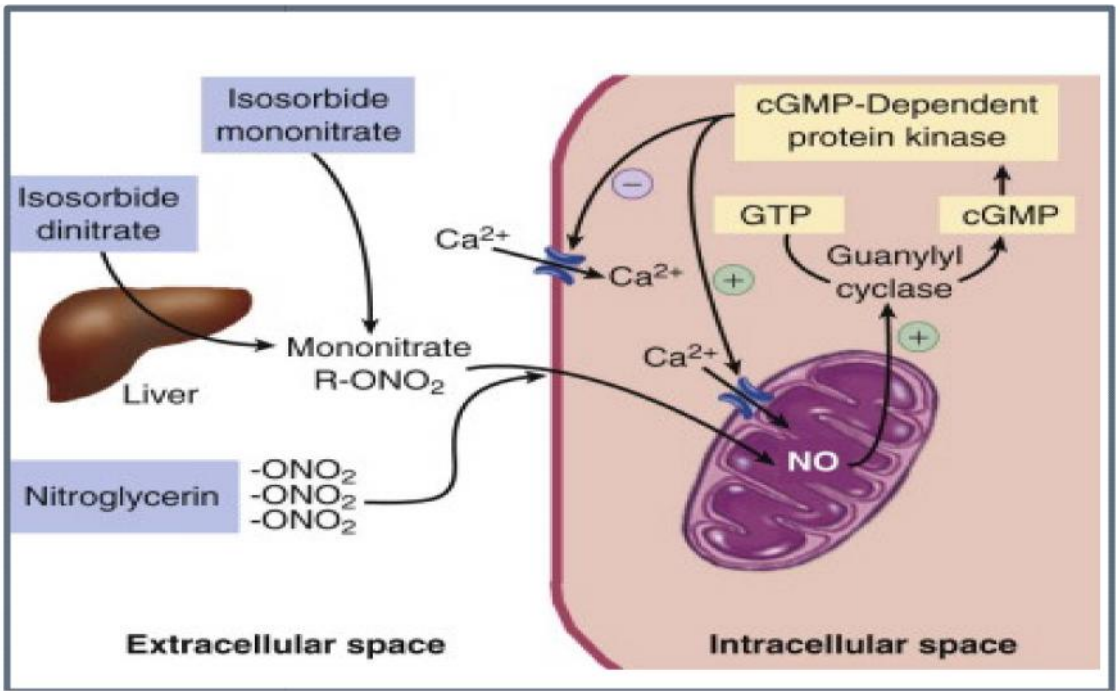
Cellular Mechanism of Action:

Nitrates have the ability to cause vasodilation, regardless of whether the endothelium is intact. After entering the vascular smooth muscle cell, nitrates are converted to reactive NO or *S*-nitrosothiols, which activate intracellular guanylate cyclase to produce cGMP, which in turn triggers smooth muscle relaxation and antiplatelet aggregator effects .Evidence now indicates that the biotransformation of nitroglycerin occurs via mitochondrial aldehyde dehydrogenase and inhibition of this enzyme may contribute to the development of tolerance. Although the aggregate evidence supports the release of NO as the major cellular mechanism of action of oral nitrates, experimental data have raised challenges to this conclusion. In particular, the arterial vasodilatory effects of nitroglycerin in vitro

depend at least in part on endothelial calcium-activated potassium channels.

FIGURE 4

MECHANISM OF ACTION OF NITRATE



Types of Preparations and Routes of Administration:

Nitroglycerin administered sublingually remains the drug of choice for the treatment of acute angina episodes and for the prevention of angina. Because sublingual administration avoids first-pass hepatic metabolism. The half-life of nitroglycerin itself is brief and it is readily converted to two inactive metabolites both of which are excreted in the urine. Within 30 to 60 minutes, hepatic breakdown has abolished the hemodynamic and clinical effects. The usual sublingual dose is 0.3 to 0.6 mg, and most patients respond within 5 minutes. If symptoms are not relieved by a single dose, additional doses of 0.3 mg may be taken at 5-minute intervals, but no more

than 1.2 mg should be used within a 15-minute period. The development of tolerance is rarely a problem with intermittent use. Sublingual nitroglycerin is especially useful when taken prophylactically shortly before undertaking physical activities that are likely to cause angina. When used for this purpose, it may prevent angina for up to 40 minutes. [47]

Preparations:

- ✓ **Nitroglycerin Tablets:**

Nitroglycerin tablets tend to lose their potency, especially if exposed to light, and should thus be kept in dark containers. An oral nitroglycerin spray that dispenses metered, aerosolized doses of 0.4 mg may be better absorbed than the sublingual form by patients with dry mucosal membranes. Other nitrate preparations are available in sublingual, buccal, oral, spray, and ointment forms .

- ✓ **Isosorbide Dinitrate**:

This drug is an effective antianginal agent but has low bioavailability after oral administration. It has two metabolites, one with potent vasodilator action, which are cleared less rapidly than the parent drug and excreted unchanged in the urine. It is available in tablets for sublingual use, in chewable form, in tablets for oral use, and in sustained-release capsules.

- ✓ **Isosorbide 5-Mononitrate:**

This active metabolite of the dinitrate is completely bioavailable with oral administration because it does not undergo first-pass hepatic metabolism; it is efficacious in the treatment of chronic stable angina. A single 20-mg tablet exhibits activity 8 hours after administration. The sustained-release preparation of isosorbide 5-mononitrate may be given once daily in a dosage of 30 to 240 mg.

- ✓ **Topical Nitroglycerin:**

1.*Ointment* : Nitroglycerin ointment (15 mg/inch) is efficacious when applied in strips of 0.5 to 2.0 inches. This form of the drug is effective for 4 to 6 hours, it is particularly useful for patients with severe angina or unstable angina who are confined to bed and chair. Skin permeability increases with increased hydration, and absorption is also enhanced if the paste is covered with plastic, with the edges taped to the skin.

2.Transdermal Patches. Application of silicone gel or polymer matrix impregnated with nitroglycerin results in absorption for 24 to 48 hours at a rate determined by various methods of preparation of the patch, including a semipermeable membrane placed between the drug reservoir and the skin. The release rate of the patches varies from 0.1 to 0.8 mg/hr.

Adverse Drug Reactions:

Adverse reactions are common and include headache, flushing, and hypotension. The last is rarely severe but, in some patients with volume depletion and in an upright posture, nitrate-induced hypotension is accompanied by a

paradoxical bradycardia, consistent with a vasovagal or vasodepressor response. This reaction is more common in older patients, who are less able to tolerate hypovolemia. Methemoglobinemia is a rare complication of very large doses of nitrates. Commonly used doses of nitrates cause small elevations of methemoglobin levels.

Nitrate Tolerance:

A major problem with the use of nitrates is the development of nitrate tolerance, which has been demonstrated with all forms of nitrate administration. Although nitrate tolerance is rapid in onset, renewed responsiveness is easily established after a short nitrate-free interval. The problem of tolerance applies to all nitrate preparations ,it is particularly important in patients with chronic angina, as opposed to those receiving short-acting courses of nitrates . Despite continuous administration of nitroglycerin for 48 hours nitrate tolerance appears to be limited to the capacitance and resistance vessels and has not been noted in the large conductance vessels, including the epicardial coronary arteries and radial arteries.

Mechanisms of nitrate tolerance :

Several mechanisms of nitrate tolerance have been proposed. Evidence has supported the hypothesis that increased generation of vascular superoxide anion ($?O_2^-$) is the central process. There are a number of consequences of increased superoxide anion formation; these include plausible links to many of the proposed mechanisms of nitrate tolerance:

(1) plasma volume expansion and neurohormonal activation;

(2) impaired biotransformation of nitrates to NO; and

(3) decreased end-organ responsiveness to NO.[48]

Management of nitrate tolerance:

The primary strategy to manage nitrate tolerance is to prevent it by providing a nitrate-free interval. The optimal interval is not known, but with patches or ointment of nitroglycerin or preparations of isosorbide dinitrate or isosorbide 5-mononitrate, a 12-hour off-period is recommended.

Nitrate Withdrawal:

A common form of nitrate withdrawal (rebound) is observed in patients whose angina is intensified after discontinuation of large doses of long-acting nitrates. In this situation, patients may also have heightened sensitivity to constrictor stimuli. The potential for rebound can be modified by adjusting the dose and timing of administration in addition to the use of other antianginal drugs.

Interaction with PDE5 Inhibitors:

Nitrate therapy is an absolute contraindication to the use of PDE5 inhibitors.The combination of nitrates and PDE5 inhibitors, such as sildenafil, may cause serious, prolonged, and potentially life-threatening hypotension. [49]

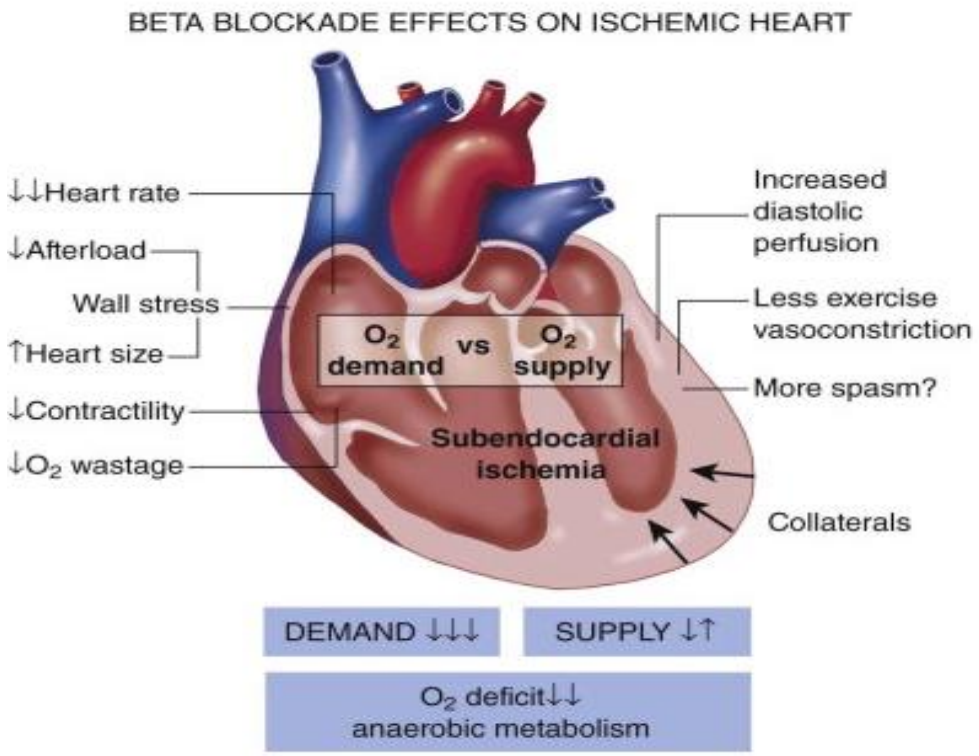
II. Beta-Adrenergic Blocking Agents:

Mechanism of action :

Beta-adrenergic blocking drugs constitute a cornerstone of therapy for angina. The beneficial actions of these drugs depend on their ability to cause competitive inhibition of the effects of neuronally released and circulating catecholamines on

beta adrenoceptors. In addition to their anti-ischemic properties, beta blockers are effective antihypertensives and antiarrhythmics . They have also been shown to reduce mortality and reinfarction in patients after MI and to reduce mortality in patients with heart failure . This combination of actions makes them extremely useful in the management of stable IHD.

FIGURE 5



Dosage:

For optimal results, the dosage of a beta blocker should be carefully adjusted.The usual effective dosage of atenolol is 50 to 100 mg daily up to a maximum of 200 mg daily. In the case of metoprolol, an extended-release formulation, which may be started at a dose of 100 mg once daily.Efficacy is determined by the effect on heart rate and symptoms and, the effect on exercise performance can be evaluated by treadmill exercise testing. The resting heart rate

should be reduced to between 50 and 60 beats/min, and an increase of less than 20 beats/min should occur with modest exercise (e.g., climbing one flight of stairs). Therapy with beta blockers needs to be individualized and requires repeated clinical evaluation during the initial period of drug administration.

Adverse Effects and Contraindications:

Most of the adverse effects of beta blockers occur as a consequence of the known properties of these drugs and include cardiac effects (e.g., severe sinus bradycardia, sinus arrest, AV block, reduced LV contractility), bronchoconstriction, fatigue, mental depression, nightmares, gastrointestinal upset, sexual dysfunction, intensification of insulin-induced hypoglycemia, and cutaneous reactions . Lethargy, weakness, and fatigue may be caused by reduced cardiac output or may arise from a direct effect on the central nervous system. Bronchoconstriction results from blockade of $beta_2$ receptors in the tracheobronchial tree. As a consequence, asthma and chronic obstructive lung disease may be considered as relative contraindications to beta blockers, even to $beta_1$-selective agents.

III. CALCIUM CHANNEL BLOCKERS:

The critical role of calcium ions in the normal contraction of cardiac and vascular smooth muscle . The calcium antagonists are a heterogeneous group of compounds that inhibit calcium ion movement through slow channels in cardiac and smooth muscle membranes by noncompetitive blockade of voltage-sensitive L-type calcium channels. The two predominant effects of calcium antagonists result from blocking the entry of calcium ions and slowing recovery of the channel.

The three major classes of calcium antagonists are the dihydropyridines (nifedipine is the prototype), the phenylalkylamines (verapamil is the prototype), and the modified benzothiazepines (diltiazem is the prototype).

Mechanism of Action:

The efficacy of calcium antagonists in patients with angina pectoris is related to the reduction in myocardial O_2 demand and the increase in O_2 supply. The latter effect is particularly important in patients with conditions in which a prominent vasospastic or vasoconstrictor component may be present, such as Prinzmetal (variant) angina , variable-threshold angina, and angina related to impaired vasodilator reserve of small coronary arteries. Calcium antagonists may be effective on their own or in combination with beta-adrenergic blockers and nitrates in patients with chronic stable angina. Several calcium antagonists are effective for the treatment of angina pectoris. Each relaxes vascular smooth muscle in the systemic arterial and coronary arterial beds. In addition, blockade of the entry of calcium into myocytes results in a negative inotropic effect, which is counteracted to some extent by peripheral vascular dilation and by activation of the sympathetic nervous system in response to drug-induced hypotension.However, the negative inotropic effect must be taken into consideration in patients with significant LV dysfunction.

Antiatherogenic Action:

Hyperlipidemia-induced changes in the permeability of smooth muscle cells to calcium may play a role in atherogenesis.More lipophilic second-generation agents such as amlodipine, have demonstrated improved endothelial function, inhibition of smooth muscle cell proliferation, migration, and ameliorated unfavorable membrane alterations.

Drug interactions :

CCBs inhibit the CYPA4 enzyme in the liver and, therefore, may raise levels of statinsand many other drugs, which may be overlooked. Cimetidine and grapefruit juice may raise the effective level of CCBs. Since magnesium is a calcium antagonist, magnesium supplements may enhance the actions of CCBs, particularly nifedipine.

Adverse Effects:

Common side effects of headache, dizziness, flushing, ankle edema are due to vasodilation. Interaction with other negative chronotropic or inotropic agents to produce bradycardia, heart block, or HF has been reported. CCBs may also suppress lower esophageal sphincter contraction and worsen symptoms of gastroesophageal reflux disease.

IV. **NEWER, NONTRADITIONAL ANTI-ISCHEMIC AGENTS**:

a. ***NICORANDIL****:*

Nicorandil is structurally a nicotinamide derivative with a nitrate moiety and

a dual mechanism of action. First, it increases potassium ion conductance by opening adenosine triphosphate (ATP)-sensitive potassium channels, in turn activating the enzyme guanylate cyclase. Second, nicorandil shares the smooth muscle-relaxing property of nitrates to vasodilate, lowering preload through venodilation. The drug also reduces afterload and promotes expression of endothelial NO synthase.Use is associated with improved myocardial function during ischemia-reperfusion,protection of myocardium during ischemia, shortened action potential duration, and prevention of intracellular calcium toxicity, of importance in modulating ischemic cell damage and death. [50] In addition to these effects, nicorandil may have cardioprotective actions mediated through the activation of potassium channels. Nicorandil has been associated with ulcerations of the gastrointestinal tract.

b. <u>TRIMETAZIDINE</u>:

Trimetazidine, a member of the class of "3-ketoacyl coenzyme A thiolase (3-KAT) inhibitors," is a metabolic modulator that improves myocardial energetics at several levels, partially inhibiting β-oxidation of fats by decreasing activity of mitochondrial enzyme 3-KAT.The drug raises myocardial glucose utilization, prevents a decrease in ATP and phosphocreatine levels in response to hypoxia or ischemia, preserves ionic pump function, minimizes free radical production, and protects against intracellular calcium overload and acidosis. It raises coronary flow reserve, lowers frequency of anginal episodes, improves exercise performance, and spares the use of nitrates without changes in heart rate, negative inotropic, or vasodilator actions.[51]

c. RANOLAZINE:

Ranolazine is a piperazine derivative that inhibits the late sodium channels, not only lowering total inward sodium flux but also the subsequent intracellular calcium overload.At therapeutic concentrations, fast inward sodium current is unchanged, and reduction of late inward sodium current is confined to ischemic or failing myocytes. By blunting the amount of excess sodium entering the cell, the total intracellular sodium concentration is restricted, thereby limiting the ischemia-associated calcium overload, the lethal component of events.The drug interrupts the positive feedback loop that perpetuates myocardial ischemia, sodium influx, loss of potassium, voltage gradient perturbations, and myocardial dysfunction. By preventing intracellular sodium overload, calcium accumulation is prevented, diastolic muscle relaxation is normalized, and myocardial oxygen balance and myocardial blood perfusion are preserved. Improvement in the dual changes in intracellular sodium and calcium promotes electrical stability, minimizing the pro arrhythmogenic effects of ischemia. Ranolazine also reduces the late inward calcium current, the inward Na+/Ca2+ exchange current, and the outward repolarizing, delayed rectifier potassium current. Ion channel changes induced by ranolazine resemble those of amiodarone.

The half-life of the sustained-release formulation of ranolazine is approximately 7 hours. A steady state is generally achieved within 3 days of dosing twice daily. Ranolazine is metabolized primarily through the cytochrome P-450 (CYP3A4) pathway and thus the plasma concentration is increased if administered in combination with moderate (e.g., diltiazem) or strong (e.g., ketoconazole and macrolide antibiotic) inhibitors of this system. Verapamil increases the absorption of

ranolazine by inhibition of P-glycoprotein. Plasma concentrations of simvastatin are increased approximately twofold after administration of ranolazine.[52]

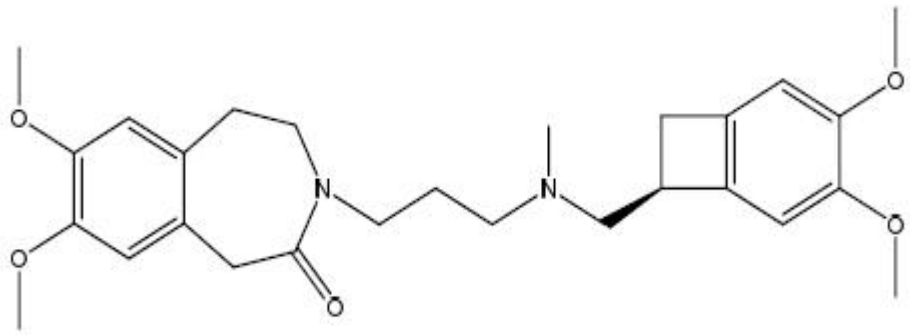
d. *FASUDIL* :

Rho kinase, or "ROCK", is an important intracellular enzyme which phosphorylates proteins to affect a number of cellular functions, among them phosphorylation of myosin, resulting in smooth muscle contraction and vasoconstriction. Fasudil is a rho-kinase inhibitor that has been used to prevent vasospasm, especially in the pulmonary and cerebral arterial beds, in addition to inhibiting production of vascular endothelial growth factor. [53]The drug is effective and safe in patients with stable angina who are already being treated with traditional agents.

e. ***IVABRADINE***:

Ivabradine is a new anti-ischemic antianginal agent which acts purely through heart rate reduction without affecting other cardiac functions. It is useful in maintaining myocardial contractility, atrioventricular conduction and ventricular repolarisation. Also there is no indirect alpha-stimulating activity which is responsible for the vasoconstriction seen with beta blockers. Ivabradine is now available as monotherapy for symptomatic treatment of patients with chronic stable angina and normal sinus rhythm but who are intolerant to beta blockers or have a contraindication to their use[54].

Figure 6 Structure of ivabradine.



Mechanism of action:

a)Selective sinus node If inhibition:

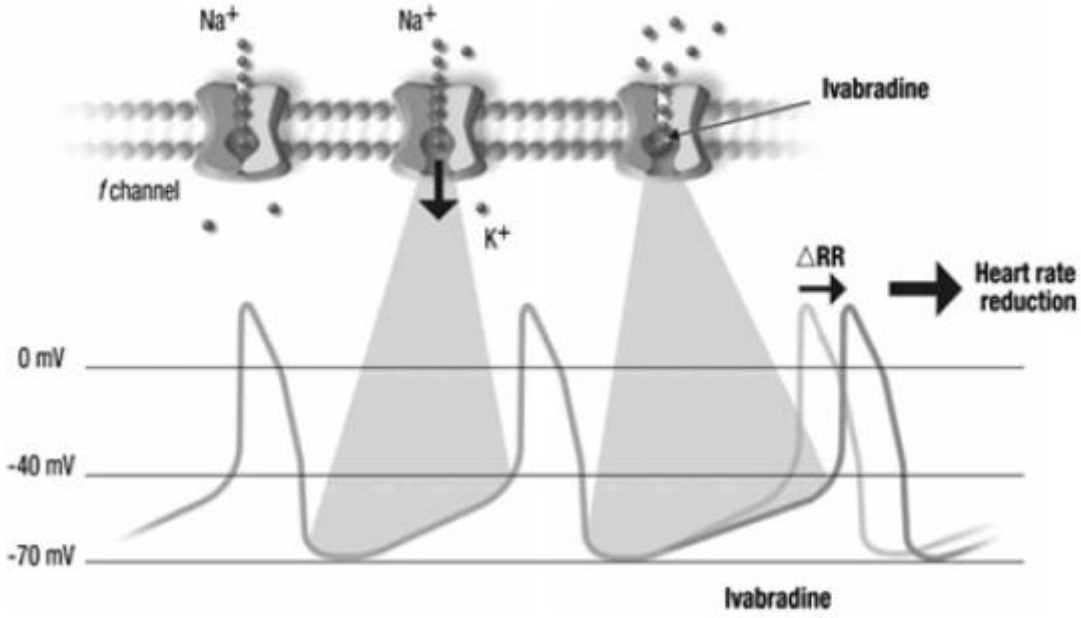
Heart rate is controlled by the sinoatrial node located in the right atrium. This is where the action potential is created and is conducted to the ventricles triggering ventricular contraction.

The sinoatrial myocytes are the heart's pacemaker cells. They generate an action potential by electrical depolarisation, which spreads from the sinus node through the cardiac conducting tissue in a controlled wave to coordinate cardiac contraction. This pacemaker activity controls heart rate and depends on interaction between several ionic currents involved in diastolic depolarisation. The f-channel (*funny* due to its unusual properties) allows sodium ions to move inwards and potassium ions to move outwards across the cell membrane through a hyperpolarisation activated, cyclic nucleotide-gated (HCN) channel so generating the *I*f current. This is the major determinant of the diastolic depolarization slope of the sinus node. The channels are open during the diastolic depolarisation phase and closed at the peak of the action potential. Therefore, targeting the f-channel can directly affect the

frequency of the action potential.[55] At therapeutic concentrations ivabradine had no significant effect on other cardiac ionic currents or cardiac action potential shape and therefore its action was found to be selective and specific .Ivabradine specifically binds to the f-channel on the intracellular side of sinoatrial pacemaker cell membrane and blocks the entry of sodium ions into the cell. This action causes selective inhibition of the *I*f current, in a dose dependent manner, which plateaus at higher concentrations. Blocking the *I*f current causes a reduction in the slow diastolic depolarisation slope, without affecting maximal diastolic potential or threshold activation potential, which exhibits a use-dependent effect on heart rate.

Figure 7

Pharmacodynamic I_f channel interaction and the effect on the sinoatrial action potential[56]



b)Pure heart rate reduction:

Heart rate reduction is a major determinant in maintaining myocardial oxygen supply. This is the common mechanism of action for beta-blockers and ivabradine in anti-anginal therapy, as heart rate reduction reduces exercise-induced ischemia by increasing diastolic perfusion time[57]. However these are distinct actions and other anti-anginal agents (ranolazine, trimetazidine) can reduce exercise-induced ischemia without having any effect on diastolic perfusion time. During exercise, increase in left ventricular (LV) filling rate depends on the ability of the left ventricle to relax and beta blockers alter this relaxation process by their intrinsic negative inotropic properties.[58]Ivabradine, unlike atenolol, reduced exercise-induced acceleration in heart rate without simultaneously exerting intrinsic depressant effects on of the rate of LV relaxation. Ivabradine was found to reduce heart rate both at rest and during exercise , without any inotropic effects or effect on left ventricular systolic function or coronary vasomotor activity. Ivabradine reduced heart rate in a dose-dependent manner when administered intravenously and orally.[59]

c)Improving the left ventricular function:

Ivabradine improved regional contractility in the stunned myocardium ,whereas with atenolol it deteriorated further due to negative inotropism. These results may have important clinical implications in LV systolic dysfunctions.[60]

Pharmacokinetics:

1.Absorption :

Ivabradine is rapidly and almost completely absorbed after oral administration .With a peak plasma level reached in about one hour under fasting conditions and an effective half life of 11 hours. The total clearance is around 400mL/min in patients

and the absolute bioavailability of the film-coated tablets is around 40%, due to first-pass effect in the gut and liver.[61]

2.Distribution :

Ivabradine is approximately 70% plasma protein bound.

3.Plasma half life :

Half life of ivabradine is about 2 hrs .

4.Metabolism :

The N-desmethylated derivative of ivabradine has been identified as the main active metabolite in humans. This active metabolite is responsible for the initial bradycardic effect, whereas the parent compound is responsible for the duration of action. Ivabradine is extensively metabolised by the liver and the gut, being oxidised by the cytochrome CYP3A4 and it is also a very weak inhibitor of this cytochrome.

5.Interactions :

CYP3A4 inhibitors and inducers may interact with ivabradine and influence its metabolism and pharmacokinetics to a clinically significant extent. Drug use with strong inhibitors of CYP3A4 (ketoconazole eryhthromycin, diltiazem or verapamil) is contraindicated as this may lead to a significant plasma exposure of ivabradine possibly resulting in risk of excessive bradycardia. The CYP3A4 inducer *Hypericum perforatum* was shown to reduce plasma concentration and availability of ivabradine and S18982 following co-administration with ivabradine in normal healthy volunteers. A short time was observed and lower apparent terminal half-life values, consistent with an induction of ivabradine metabolism.[62]

6.Excretion :

The total clearance is around 400mL/min.

- ✓ **Special populations:**

Ivabradine does not reliably slow heart rate during atrial fibrillation or other atrial tachycardia or in patients dependent on cardiac pacemakers. Therefore, it is only indicated for treatment in patients where heart rate is controlled by the sinus node. The use of ivabradine is contra-indicated in heart failure patients with NYHA functional classification III&IV and in patients with asymptomatic left ventricular dysfunction or stroke patients.[63]

- ✓ **Dosing and titration :**

Ivabradine is available in tablet form at 5 and 7.5mg. The usual recommended starting dose is 5 mg twice-daily, in the morning and evenings during meals. After three to four weeks of treatment, the dose may be increased to 7.5 mg twice-daily depending on the therapeutic response. If, during treatment, heart rate decreases persistently below 50 beats per minute (bpm) at rest or the patient experiences symptoms related to bradycardia such as dizziness, fatigue or hypotension, the dose must be titrated downward including the possible dose of 2.5 mg twice-daily (one half 5 mg tablet twice daily). Treatment must be discontinued if heart rate below 50 bpm or symptoms of bradycardia persist.[64]

- ✓ **Coadministration with other drugs:**

Concomitant use of ivabradine with heart rate reducing calcium channel blockers such as verapamil or diltiazem is not recommended. Ivabradine should also not be used in combination with QT prolonging agents. There is no contraindication in taking ivabradine in combination with other cardiovascular drugs, including anti-platelet agents , statins,angiotensin-converting enzymes and beta blockers.

- ✓ **Safety and tolerability:**

Ivabradine has a good safety profile and well tolerated.Sinus bradycardia is an expected pharmacological effect of ivabradine and is proportional to the resting heart rate. Slowing the heart rate by ivabradine is associated with prolongation of the QT interval in a dose-dependent manner .It occurs at rest and during exercise due to the slowing of the sinus node discharge by selective inhibition of the If current. There is no association of sinus bradycardia with aggravation of other arrhythmias. There is no rebound effect with drug cessation or pharmacological tolerance with long-term use.There is mild visual symptoms being the most widely reported side-effects.[65] The visual symptoms associated with ivabradine are due to the action of ivabradine on retinal ion channels (If current), which belong to the same family as those responsible for the If current in the sino-atrial node. In current clinical trials of ivabradine, visual symptoms (mainly phosphenes) are reported in a small proportion of patients. These symptoms are generally mild and resolved spontaneously during or after treatment.[47]

STUDIES RELATED TO IVABRADINE :

1. A meta-analysis conducted in Cardiovascular Division, King's College London, British Heart Foundation Centre, London identified Ivabradine significantly improves cardiac function in patients with ischemic heart disease . This was the first time to evaluate the benefits of Ivabradine in patients with IHD using meta-analysis. According to that study, Ivabradine can significantly improve the left ventricular function. More impressively, LVEF (WMD 2.669%; 95% CI 1.655 to 3.684; $p < 0.01$) was statistically improved no matter if patients were followed up for shorter or longer than

three months, enrolling in higher quality research or lower, and whether β-blockers were used concurrently or not .[66]

2. A 4-month, randomized, placebo-controlled trial conducted in Montreal and Danderyd Hospital, Stockholm, Sweden explained the efficacy of the I_f current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy. Ivabradine was superior to placebo for all exercise test criteria at 4 months (P . 0.001 for all) and 2 months (P-values between 0.001 and 0.018). Ivabradine in combination with atenolol was well tolerated.According to that study ,total exercise duration at 4 months was increased by (24.3+65.3 s) in the ivabradine group, compared with (7.7+63.8)with placebo (P < 0.001). [67]
3. Jean-Claude Tardif, Ian Ford conducted a study on efficacy of ivabradine, a new selective *I*f inhibitor, compared with atenolol in patients with chronic stable anginaDiseasePatients underwent treadmill exercise tests at randomization (M0) and after 4 (M1) and 16 (M4) weeks of therapy. Increases in total exercise duration(TED) at trough at M4 were 86.8+129.0 and 91.7+118.8 s with ivabradine 7.5 and 10 mg, respectively and 78.8+133.4 with atenolol 100 mg.[68]
4. A study conducted in Dubai Heart Center, Division of Cardiology identified the Short‐Term Effects of Ivabradine in Patients with Chronic Stable Ischemic Heart Disease .After 4 months of treatment, the heart rate was significantly reduced from an average of 82 ± 8 to 68 ± 6 bpm ($P < 0.001$). The reduction in heart rate was accompanied by a significant improvement in functional capacity (score 3.5 ± 0.9 to 4.7 ± 0.7, $P < 0.001$) and angina

classification.[69]

5. University of Medicine and Pharmacy, Bucharest Romania conducted a open –label, randomized trial on Ivabradine Versus Beta-Blockers in Patients with Conduction Abnormalities or Left Ventricular Dysfunction Undergoing Coronary Artery Bypass Grafting. The rates of 30-day mortality were lower in the combined therapy group (2.8%) versus metoprolol or ivabradine monotherapy groups (3.8% in each monotherapy group). The overall quality of life was better in ivabradine groups. Ivabradine-treated patients had shortened hospital stay.[70]

With the above extensive literature review , as there is handful of studies related to efficacy and safety of ivabradine and atenolol in patients with IHD, this study was designed to assess the anti-anginal and anti-ischemic efficacy and safety of ivabradine as an add-on to atenolol in patients with chronic stable ischemic heart disease.

AIM OF THE STUDY

To evaluate the efficacy and safety of Ivabradine as an add-on to atenolol in patients with chronic stable ischemic heart disease prospectively .

METHODOLOGY

STUDY TYPE:

Interventional study

STUDY DESIGN:

Open label ,prospective clinical study .

STUDY PERIOD:

April 2014 to May 2015.

STUDY DURATION :

Three months .

STUDY CENTRE:

Single centered study conducted in the Out patient Department of Cardiology ,Tirunelveli Medical College Hospital , Tirunelveli.

STUDY SAMPLE:

50 patients attending cardiology OPD receiving anti anginal medication for chronic stable ischemic heart disease.

INCLUSION CRITERIA:

- Patients with age of $\geq$18 to $\leq$80 years .
- Patients of both sexes.
- Patients with history of chronic stable ischemic heart disease

- Patients in Canadian Cardiac Society angina pectoris class 1,2,3 and 4.
- Patients with heart rate in sinus rhythm of atleast ≥ 80 beats per minute.
- Patients should be on oral tab. Atenolol for ischemic heart disease.

EXCLUSION CRITERIA:

- Patients with age group of below 18 yrs to more than 80 yrs .
- Patients with heart rate of < 80 beats per minute.
- Patients with H/O of hypotension , BP < 90/50 mmhg(in both the upper limbs either in the sitting or standing posture).
- Patients with recent or acute attack of myocardial infarction.
- Patients with signs and symptoms of acute decompensated heart failure .
- Patients with evidence of moderate to severe heart block.
- Patients not taking oral tab.Atenolol for ischemic heart disease.
- Patients with symptomatic liver dysfunction or renal impairment.
- Patients with H/O pregnancy and lactation.
- Known hypersensitivity to study drugs .
- Patients not on sinus rhythm /other types of arrhythmia
- Patients taking anti- arrhythmic drugs
- Patients taking drugs with enzyme inducing and inhibiting properties.

WITHDRAWAL CRITERIA:

- Non compliance with protocol
- Protocol deviation
- Request for withdrawal by the patients
- Heart rate <80 bpm while on medication.

- Adverse effects(decision about withdrawal from the study made either by patients or investigator).

ETHICAL CONSIDERATIONS :

Approval from Institutional Ethical Committee of Tirunelveli Medical College Hospital was obtained, before starting the clinical study. Written informed consent was obtained in local vernacular language from every patient before enrollment .

SCHEDULE OF STUDY VISIT :

a)Screening and recruitment:

The subjects were enrolled based on the inclusion criteria after screening. During enrollment clinical assessment and the following baseline investigations were done.

- Blood investigations: Hemoglobin,differential WBC count, ESR, bleeding time and clotting time were done in a blood sample using biochemical automated analyser.
- Blood sugar, urea and creatinine and serum electrolytes were measured in a blood sample using automated analyser.
- Liver function tests including ALT,AST ,total bilirubin ,direct and indirect bilirubin were measured in a blood sample.
- Baseline heart rate was measured by taking 12 lead electrocardiography.
- Baseline left ventricular ejection fraction (LVEF) (%)was assessed by echocardiogram.

$$\text{LVEF} = \frac{\text{Diastolic} - \text{systolic volume}}{\text{Diastolic volume}}$$

Normal >60% male &

>55% female.

- Baseline left ventricular systolic function was assessed by echocardiogram. Grading of left ventricular (LV)systolic dysfunction based on LVEF as follows:[71]

  No dysfunction = LVEF > 45%

  Mild dysfunction = LVEF 45-54%

  Moderate dysfunction = LVEF 44-30%

  Severe dysfunction = LVEF < 30%

- Baseline blood pressure was measured manually after 5 minutes of rest twice atleast 2 minutes apart in right arm in sitting posture with the cuff at heart level using sphygmomanometer.
- Baseline Canadian class of angina grading was assessed according to the clinical symptoms and signs.

b) Treatment protocol :

Patients received the drug as follows :

Tab.Ivabradine 5-7.5 mg OD for 3 months.

After screening, ivabradine 5 mg once daily was prescribed to all patients who were included in this clinical study . Patient's evaluation at baseline was used as the control. The study patients were reviewed every 2 weeks. Dose of ivabradine was titrated upto

7.5 mg once daily according to the heart rate(if still >100bpm) after 4 weeks of the study.Ivabradine was given orally once daily for a duration of 3 months for each patient. Also the patients were given a diary to note down the adverse events. The tablets were provided for 15 days only. Then the patients were instructed to report to the out patient department after 2 weeks along with the diary and empty strips to collect the drugs. During each visit heart rate was monitored by taking ECG. At the end of 1st and 3rd month ,left ventricular function and ejection fraction were measured by using echocardiogram. Ivabradine tablets(ivanode)5mg and 7.5 mg provided by pinnacle pharmaceuticals.

c)Quality of life assessed with SAQ:

For measuring specific quality of life, SAQ questionnaire[72] (Appendix)was used at the end of 3 months of study period. This questionnaire included (19 phrases) which measure five dimensions of coronary artery diseases:

- physical constraint (9 phrases)
- angina stability (1 question)
- angina severity (2 phrases)
- treatment satisfaction (4 phrases) and
- perceiving disease (3 questions).

The questions are in 5 and 6 Likert form. Scores on each scale range from 1 to 5 (or) 6. It is then converted from 0 to 100 using the following calculation.[73]

$$n = \frac{(z_{1-\alpha/2})^2 p(1-p)}{d^2}$$

Zero is the worst and one hundred is the best situation in the considered scale.

d) Follow up:

Follow up was done after 15,30,45,60,75 and 90 days ,clinical examinations including vital signs such as blood pressure, heart rate were measured .At the end of $1^{st}$and 3^{rd} month, laboratory investigations such as blood Hb gm%,total count ,ESR ,serum electrolytes,LFT ,blood sugar,urea and creatinine were performed. Also echocardiogram and Canadian class of angina grading based on clinical improvement in signs and symptoms was done .

EFFICACY PARAMETERS:

PRIMARY ENDPOINT:

- Reduction in resting heart rate using 12 lead ECG .
- Improvement in Canadian cardiovascular society (CCS)class of angina grading.

SECONDARY ENDPOINT:

- Improvement in ejection fraction(EF) using echocardiography.
- Improvement in left ventricular function(LVF) using echocardiography.
- Improvement in quality of life score using SAQ .

SAFETY ASSESSMENTS:

Any adverse events reported by the subject or noted by the clinician during each follow up visit was recorded .If continuation of the drug was considered harmful, the subject could be withdrawn from the study.Any adverse event was considered as serious if it was fatal, life threatening, disabling or if it prolonged hospitalization of the subject.

COMPLIANCE:

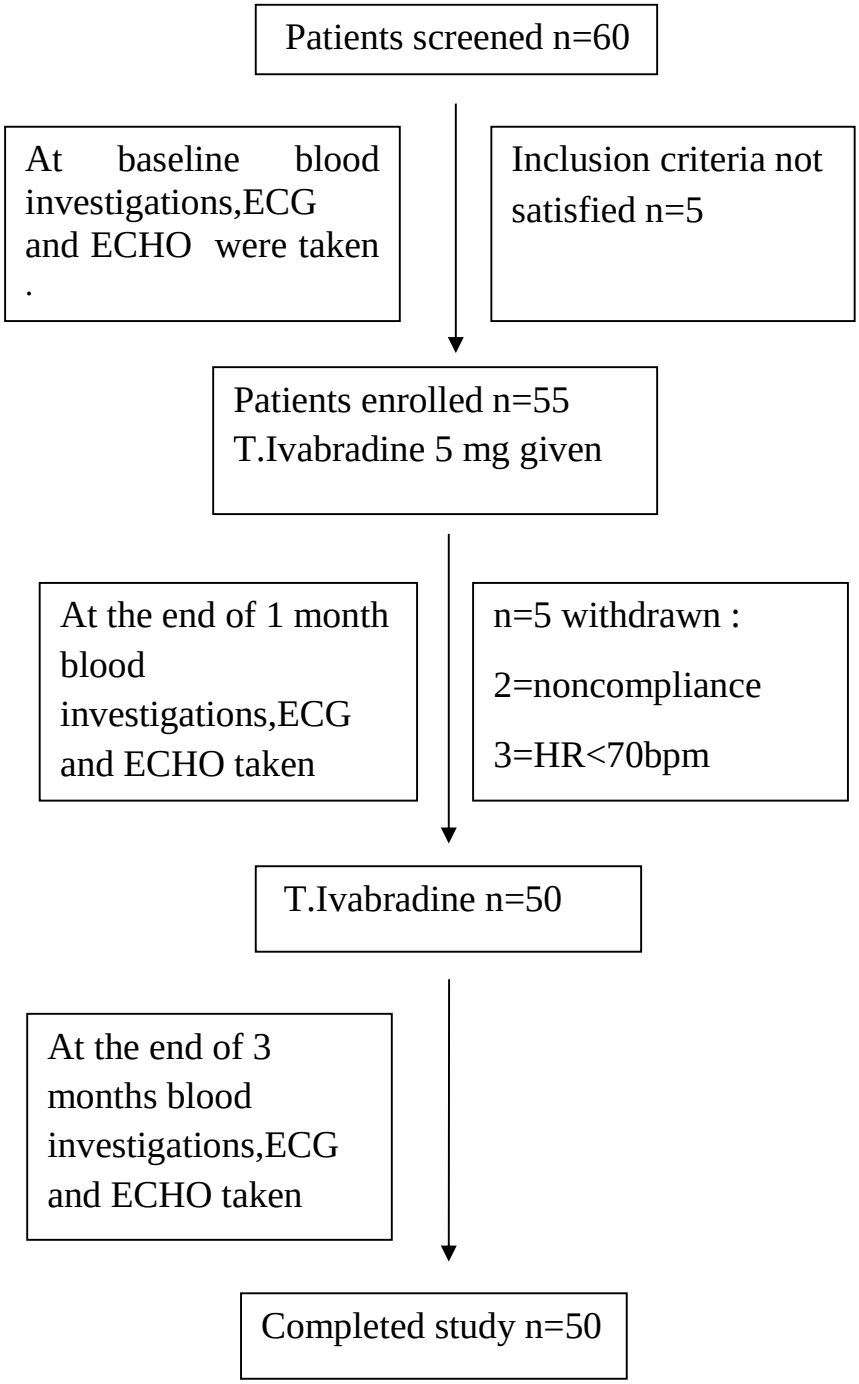
Compliance was assessed by reduction in heart rate and pill count methods.

STATISTICAL ANALYSIS:

Statistical analysis was performed with the help of statistical package SPSS(Statistical package analysis package for the social sciences)version 11.

- Baseline characteristics of the study patients were tabulated by descriptive statistics(mean and standard deviation) and frequency table .
- The analysis of primary parameters were done by using “Student paired t test” at the end of 1 and 3 months before and after giving Ivabradine.
- The analysis of secondary parameters like left ventricular function and ejection fraction improvement were done by using “Student paired t test” at the end of 1 and 3 months before and after giving Ivabradine
- The quality of life scoring was done by using SAQ questionnaire and compared with CCS class of grade of angina by using ANCOVA .
- The adverse drug reactions were tabulated and expressed in percentage.

CONSORT DIAGRAM



RESULTS

In the period of 1 year from April 2014 to May 2015 ,60 cases of chronic stable ischemic heart disease already on tab.atenolol ,attending the outpatient Department of Cardiology were screened for their eligibility based on the inclusion and exclusion criteria .Among the 60 patients , 55 patients were enrolled for the study and given tab.Ivabradine once daily orally and 5 patients were withdrawn from the study due to non compliance and reduction in heart rate below 70 bpm. At the end of 1 month, those 50 patients continued the study and completed the study.

The demographic data concerning the patient's age, sex, weight, vitals, hemodynamic and laboratory parameters were statistically assessed at the baseline.

TABLE -1

BASELINE CHARACTERISTICS

<table>
<tr><th colspan="2">BASELINE PARAMETERS</th><th colspan="4">TAB.IVABRADINE (n=50)</th></tr>
<tr><td colspan="2">Age(yrs) (mean/SD)</td><td colspan="4">56.06 ± 11.21</td></tr>
<tr><td rowspan="2">Gender (n)</td><td>Male</td><td colspan="4">38</td></tr>
<tr><td>Female</td><td colspan="4">12</td></tr>
<tr><td colspan="2">Heart Rate (bpm) (mean/SD)</td><td colspan="4">93.08± 11.67</td></tr>
<tr><td colspan="2">Ejection Fraction (%) (mean/SD)</td><td colspan="4">41.36±6.23</td></tr>
<tr><td colspan="2" rowspan="2">Canadian cardiovascular class(n)</td><td>0</td><td>1</td><td>2</td><td>3</td></tr>
<tr><td>0</td><td>80</td><td>14</td><td>6</td></tr>
<tr><td colspan="2" rowspan="2">Left ventricular dysfunction (n)</td><td>Mild</td><td colspan="2">Moderate</td><td>Severe</td></tr>
<tr><td>20</td><td colspan="2">70</td><td>10</td></tr>
<tr><td colspan="2">Hb (%) (mean/SD)

WBC (cells/cumm) (mean/SD)

ESR (mm/hr) (mean/SD)</td><td colspan="4">13.47 ± 1.95

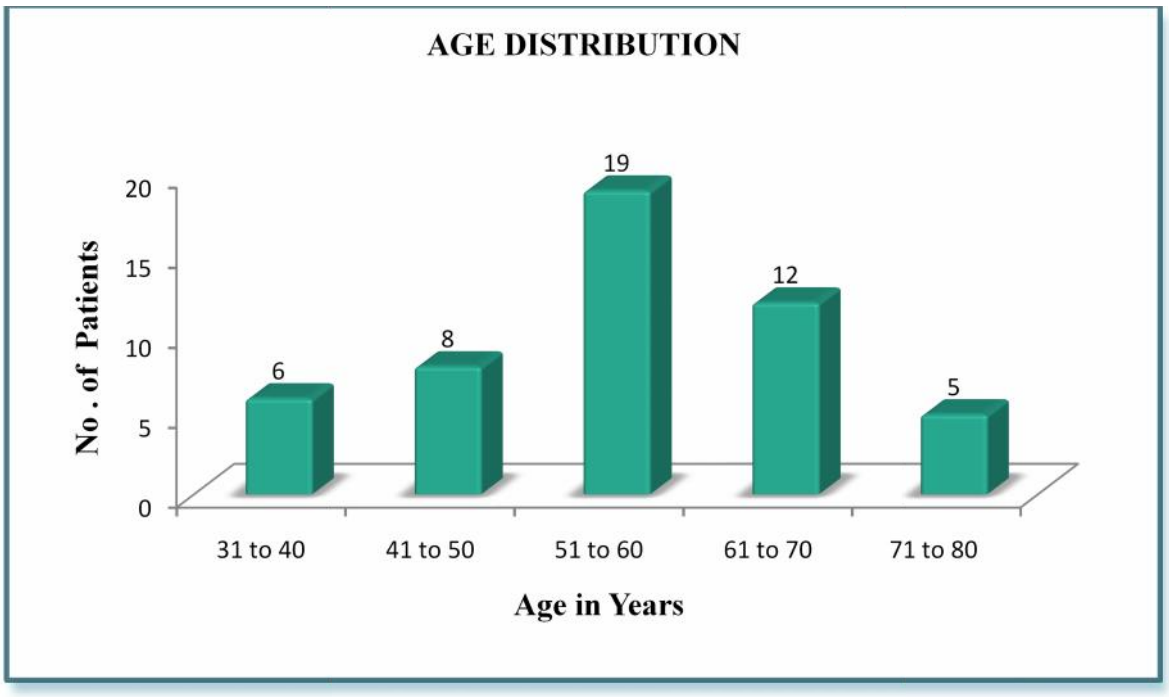
8873±1311.88

15.17±1.58</td></tr>
<tr><td colspan="2">Blood sugar (gms%) (mean/SD)</td><td colspan="4">168.6±64.5303</td></tr>
<tr><td colspan="2">serum Na+(meq/L) (mean/SD)</td><td colspan="4">139.18±3.29</td></tr>
<tr><td colspan="2">serum K+(meq/L) (mean/SD)</td><td colspan="4">4.2±0.3</td></tr>
<tr><td colspan="2">Alkaline phosphatase(IU/L) (mean/SD)</td><td colspan="4">74.24+30.81</td></tr>
</table>

Table 1 shows the baseline characteristics of the study population (mean/SD).

FIGURE 8

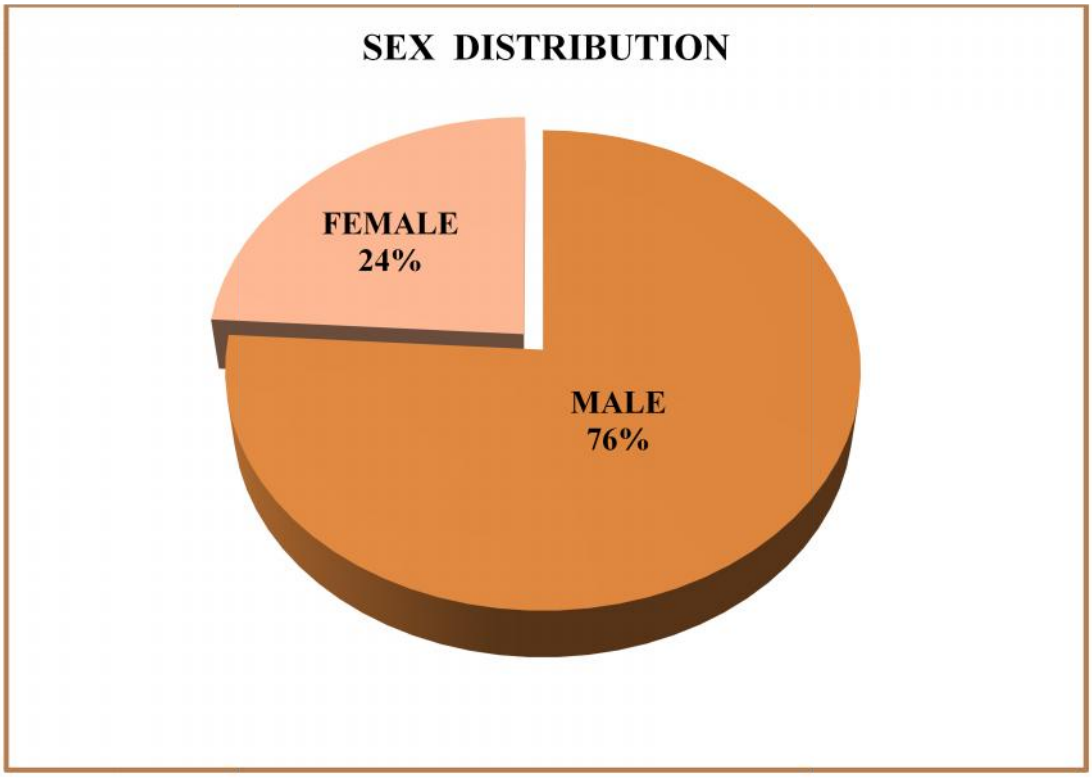
AGE DISTRIBUTION OF THE PATIENTS IN THE STUDY



- Figure 8 shows that the age distribution of chronic stable IHD patients involved in this study.
- Maximum number of patients (19 patients) were in the age group of 51- 60 yrs.

FIGURE 9

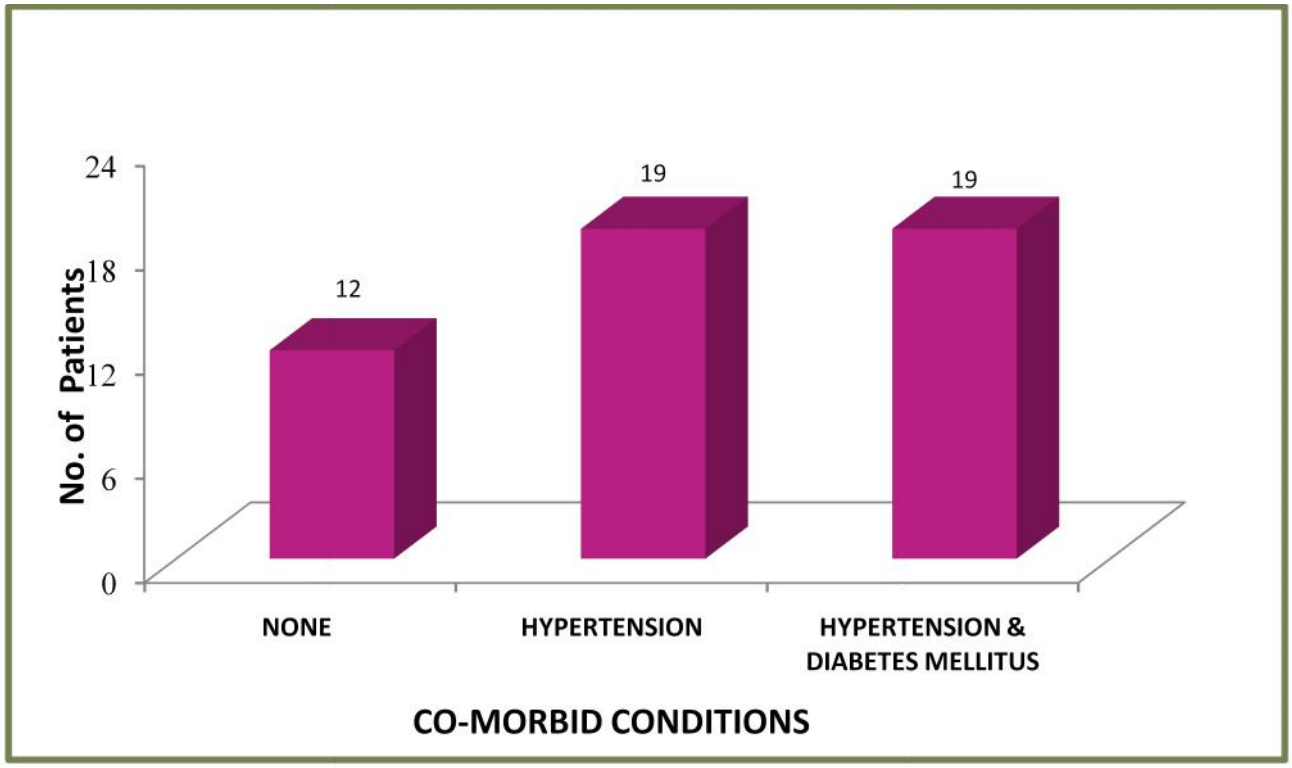
SEX DISTRIBUTION OF THE PATIENTS IN THE STUDY



- Figure 9 is a pictoral representation of sex distribution of study patients.
- 76% patients were male and 24% patients were female **.**

FIGURE 10

NUMBER OF STUDY PATIENTS WITH CO-MORBID MEDICAL CONDITIONS



- Figure 10 shows graphical representation no.of study patients with co- morbid medical conditions .
- Among 50 patients , 19 patients had hypertension and 19 patients had hypertension as well as diabetes .

PRIMARY EFFICACY PARAMETERS

TABLE 2

REDUCTION IN HEART RATE AT THE END OF 1 & 3 MONTHS COMPARED WITH BASELINE

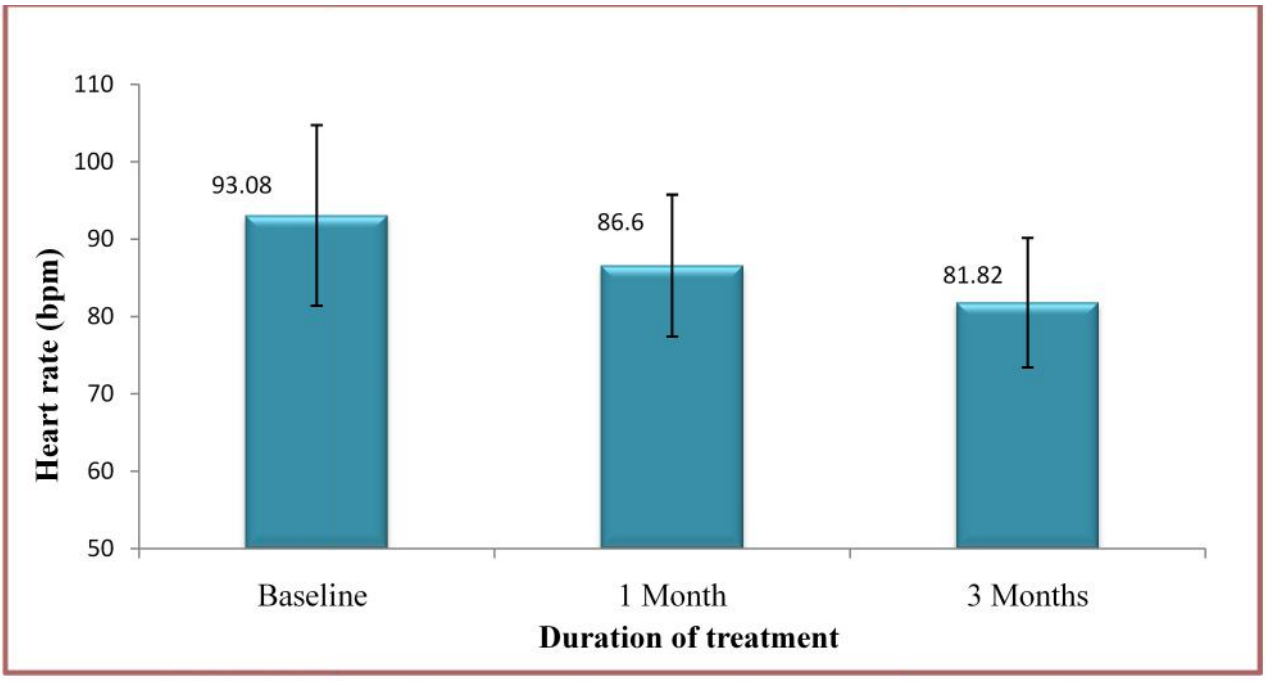
HEART RATE	MEAN	S.D	P VALUE
Base line	93.08	11.67	
1month	86.6	9.16	< 0.0001*
3months	81.82	8.37	< 0.0001*

*** p value <0.05, statistically significant at the end of first and third month.**

- Shown in Table 2 is efficacy of Ivabradine in reducing the heart rate at the end of 1month (86.60±9.16) and at the end of 3 months (81.82±8.37) when compared with baseline (93.08±11.67).
- Reduction in heart rate at the end of 1 and 3 months after taking Ivabradine was statistically significant ($p<0.0001$)

FIGURE 11

REDUCTION IN HEART RATE AT THE END OF 1 AND 3 MONTHS COMPARED WITH BASELINE



- Graphical representation of reduction in heart rate before and after taking tablet Ivabradine
- Reduction in heart rate from baseline (93.08±11.67) to end of the 1st month (86.60±9.16) and at the end of 3rd month (81.82±8.37).

TABLE 3

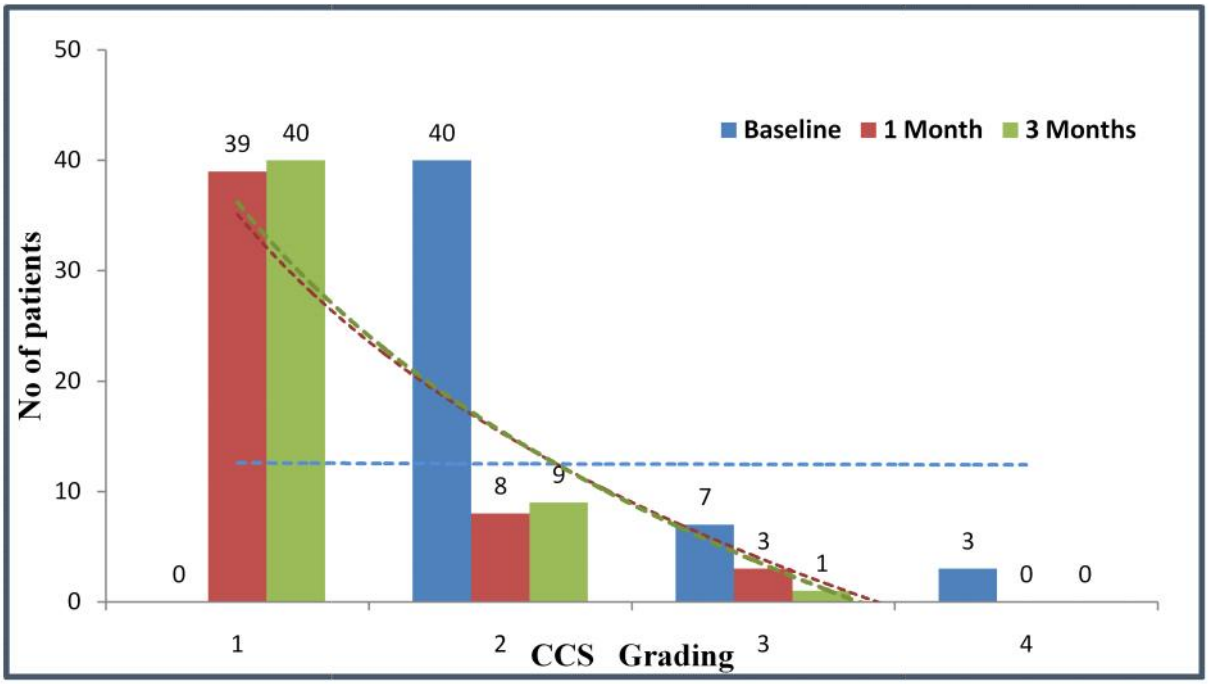
IMPROVEMENT IN CANADIAN CARDIOVASCULAR SOCIETY CLASS OF ANGINA GRADING

CCS class of angina grade		**1**	**2**	**3**	**4**
Number of Patients	Baseline	0	40	7	3
	1 Month	39	8	3	0
	3 Months	40	9	1	0

- Table 3 shows improvement in Canadian cardiovascular society class of angina pectoris grading based on the clinical signs and symptoms .
- At the baseline 3 patients were in the CCS class of angina grade IV. After treatment with Ivabradine , none of the patients were in the CCS class of angina grade IV at the end of 1 &3 months.
- At the baseline 7 patients were in the CCS class of angina grade III. After treatment with study drug ,patients with CCS class of angina grade III were 3 patients at the end of 1 month and 1 patient at the end of 3 months.
- At the baseline 40 patients were in the CCS class of angina grade II. After treatment with study drug ,patients with CCS class of angina grade II were 8 patients at the end of 1 month and 9 patients at the end of 3 months.

FIGURE 12

IMPROVEMENT IN CANADIAN CARDIOVASCULAR SOCIETY GRADING OF ANGINA PECTORIS



- Graphical representation of improvement of Canadian cardiovascular society grading (CCS)of angina at the end of 1 and 3 months compared with baseline .
- Blue dotted line in the above graph is the logarithmic trend line of baseline CCS compared with 1 st month (red dotted line) and 3 rd month (green dotted line) logarithmic trend lines .
- Based on the comparision of logarithmic trendline at the baseline with 1 and 3 months Ivabradine showed improvement in CCS class of grade of angina.

SECONDARY EFFICACY PARAMETERS

TABLE 4

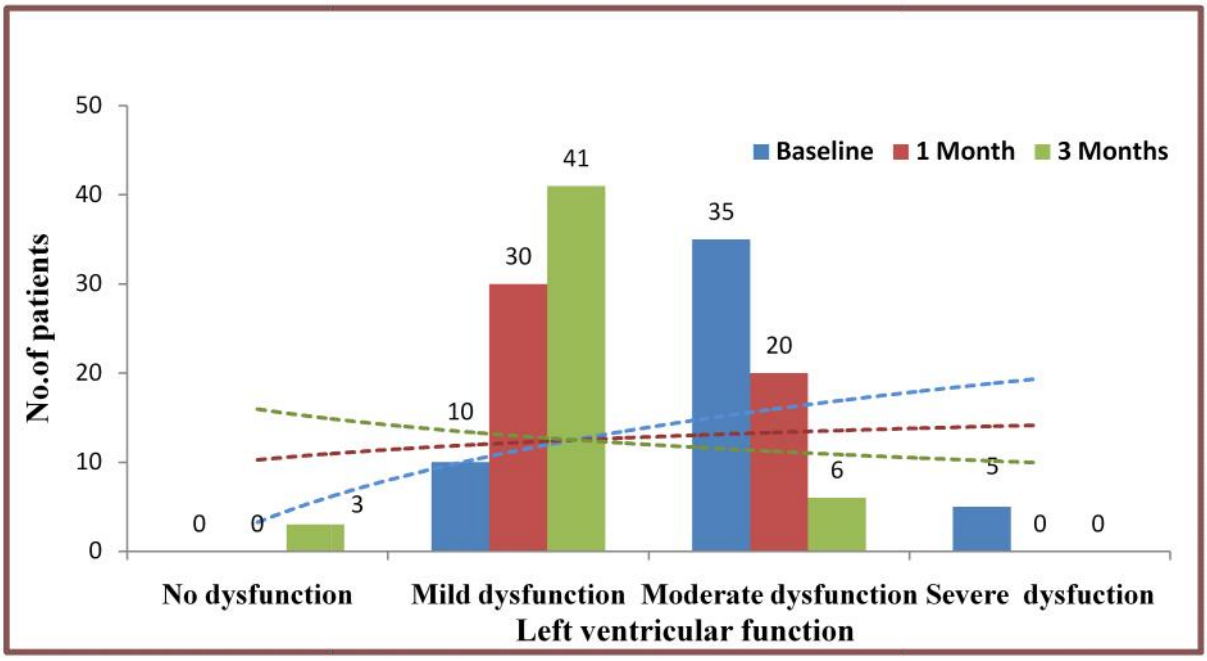
IMPROVEMENT IN LEFT VENTRICULAR FUNCTION

Left ventricular function		**No dysfunction**	**Mild dysfunction**	**Moderate dysfunction**	**Severe dysfunction**
Number of patients	Baseline	0	10	35	5
	1 Month	0	30	20	0
	3 Months	3	41	6	0

- Table 4 shows, study drug improved the left ventricular (LV)function at the end of 1 and 3 months of treatment when compared with baseline .
- At the baseline there were 5 patients with severe LV dysfunction ,35 patients with moderate LV dysfunction and 10 patients with mild LV dysfunction.
- After treatment with Ivabradine , there were no patients with severe LV dysfunction at the end of 1 and 3 months when compared with 5 patients at the baseline.After treatment with study drug patients with moderate LV dysfunction was reduced to 20 at the end of 1 month and 6 patients at the end of 3 months when compared with 35 patients at the baseline.

FIGURE 13

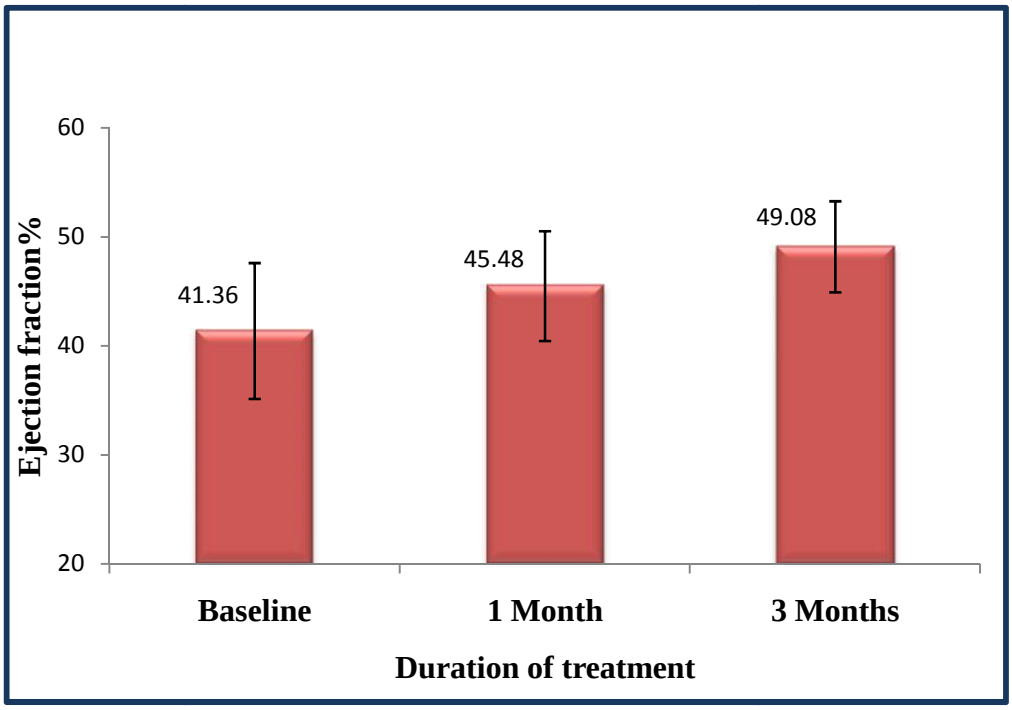
IMPROVEMENT IN LEFT VENTRICULAR FUNCTION AT THE END OF 1&3 MONTHS COMPARED WITH BASELINE



- Graphical representation of improvement in left ventricular function at the baseline ,at the end of 1 and 3 months.
- Blue dotted line in the graph shows logarithmic trend line of left ventricular function at the baseline .
- Red and green dotted lines show logarithmic trend line of left ventricular function at the end of 1 and 3 months respectively.

FIGURE 14

Improvement in ejection fraction %(mean/SD) at the end of 1 & 3 months of treatment compared with baseline



- Figure 14 shows ejection fraction % (mean and SD) at the end of 1&3 months compared with baseline .
- After treatment with study drug the improvement in ejection fraction% was (45.48±5.03) ($p<0.001$) at the end of one month and (49.08±4.17)($p<0.001$) three months compared with the baseline(41.36±6.23).

TABLE 5

Quality of life score based on SAQ . Five variables of angina are compared with CCclass of angina

VARIABLES	**CCS class 1**		**CCS class 2**		**CCS class 3**		**P value**
	Mean	S.D	Mean	S.D	Mean	S.D	
Physical Constraint	47.5	14.76	44.44	14.12	37.5	0	0.698
Angina Stability	37.5	18.77	47.22	29.16	25	0	0.368
Angina Severity	24.75	10.61	30	12.24	20	0	0.381
Treatment Satisfaction	42.85	9.22	39.11	12.57	29	0	0.258
Perceiving Disease	30.45	10.43	31.55	9.16	50	0	0.177

Table 5 shows the quality of life score based on SAQ . It contains five variables . Each variable(mean/SD) was compared with CCS class of angina and their p value was statistically not significant. It means all these variables were associated with highest score of quality of life and they did not show any significant differences in the different grades of CCS class of angina .

TABLE 6

LABORATORY PARAMETERS OF THE STUDY POPULATION

Parameters	Hemodynamic Parameters			RBS	Liver Function Tests	
	Hb%	WBC (cells/cumm)	ESR (mm/hr)	(mg%)	Total bilirubin(U/L)	AST (U/L)
At the baseline (Mean/SD)	13.47±1.95	8873±1311.88	15.17±1.58	168.6±64.5	0.81±0.28	74.24±30.81
At the end of 1 month (Mean/SD)	13.72±2.35	8806±1190.63	15.34±1.15	168.74±53.9	0.82±0.11	75.48±23.64
P value	0.318	0.364	0.307	0.967	0.719	0.644
At the end of 3 months(Mean/SD)	13.76±1.88	8782.5±1218.9	15.46±1.75	169.62±57.7	0.84±0.11	78.3±21.13
P value	0.196	0.359	0.164	0.766	0.419	0.329

- The above table shows the laboratory parameters of study patients at the baseline ,at the end of 1 month and at the end of 3 months .
- No significant changes were seen in hemodynamic parameters.
- No significant elevation in liver enzymes were found during the treatment period and follow up.

ADVERSE DRUG REACTIONS

No patients were withdrawn from the study due to adverse drug reactions during the study period. No serious adverse events were reported in study patients . The most common adverse drug reactions reported were tabulated .

TABLE 7:

Adverse drug reactions	**No. of patients** **n(%)**
Bradyarrythmia	2 (4%)
QT prolongation	1 (2%)
Blurring of vision	1 (2%)
Photopsia	1 (2%)

DISCUSSION :

Coronary artery disease is the leading cause of morbidity and mortality in world wide[1].Heart rate is a major determinant of cardiac output ,myocardial oxygen demand and coronary blood flow. High resting heart rate has emerged as a simple but relevant risk factor for coronary artery disease and heart failure. Pharmacotherapy for IHD is to reduce the angina attacks by reducing the heart rate. Evidence suggested that many patients maintain a resting HR ≥ 70/min despite optimal beta blocker therapy[74].

Conventional anti-anginal drugs like nitrates ,CCB and K + channel openers could interact with beta-blockers and in addition they have negative inotropic activity . So we need a better agent which will reduce the heart rate without having negative inotropic activity and other system involvement .

In recent years, a new drug to reduce HR, Ivabradine has been introduced for clinical practice by Euro Society of Cardiology .According to the results of the INITIATIVE trial which compared Ivabradine with atenolol over 4 months in 939 patients with stable angina pectoris and documented coronary artery disease , Ivabradine showed non-inferiority in reducing the total exercise duration and exercise performance and improved performance .[75]

The mean age of the subjects in our study was 56.06 ± 11.21(table 1). It clearly showed that ageing is an important non- modifiable risk factor for chronic stable ischemic heart disease .Similarly ,a prospective, follow-up study conducted in Finland concluded that in both sexes the CHD risk was largest in the oldest age (50-69yrs) group.[76]

According to our study, the majority of the study subjects were male patients 76%(figure 9)and males in the community were more prone for ischemic heart disease than females . In one study conducted by Peters and Woodwards showed that over a median follow-up of 6.7 years, 5695 IHD events were documented. Based on the major risk factors ,the age-adjusted prevalence was higher in males than females. The hazard ratio for IHD, comparing men with women, was 1.88 (95% CI 1.54-2.29) in Asia and 2.14 (95% CI 1.97-2.33) in Australian and New Zealand .[77]

In our study , significant reduction in heart rate was reported in patients with CHD during the treatment period was 81.82±8.37(table2) compared with baseline 93.08±11.67 and the p value was significant (<0.001) . Similarly a study conducted by Nicoline Jochmann and Franziska et al found a significant decrease in heart rate, both 4 hours after the intake of 7.5 mg of ivabradine (median −8 [interquartile range (IQR) -14 to −4] bpm) and after 4 weeks of twice daily intake (median −10 [IQR-17 to −5] bpm) ($p < 0.05$).[78]

Thus for preventing and treating the further anginal attacks reducing the heart rate is the important key factor without producing negative inotropic and lusitropic effect. Our study drug by acting on the novel specific and selective blocking of If current present in the SA node of the right atrial chamber showed significant reduction in heart rate(figure 11)

In this study , treatment with ivabradine improved the CCS class of angina grading compared with baseline.Those patients at the grade III and IV at baseline were moved to grade I and II over a period of 3 months. At the baseline 3 patients were in the CCS class of angina grade IV . After treatment with Ivabradine , none of the

patients in the CCS class of angina grade IV at the end of 1 &3 months. At the baseline 7 patients were in the CCS class of angina grade III. After treatment with study drug ,patients with CCS class of angina grade III were 3 patients at the end of 1 month and 1 patient at the end of 3 months.At the baseline 40 patients were in the CCS class of angina grade II. After treatment with study drug ,patients with CCS class of angina grade II were 8 patients at the end of 1 month and 9 patients at the end of 3 months. Similarly , in a post hoc analysis of BEAUTIFUL Trial suggested that the effect of adding Ivabradine to the conventional beta-blocker (90%) improved the CCS class of grade of angina .[79]

In this study , Ivabradine improved the left ventricular function based on LVEF compared with baseline . After treatment with Ivabradine , there were no patients with severe LV dysfunction at the end of 1 and 3 months when compared with 5 patients at the baseline. After treatment ,moderate LV dysfunction was reduced to 20 patients at the end of 1 month and 6 patients at the end of 3 months when compared with 35 patients at the baseline.

Like wise, after giving Ivabradine showed there was significant improvement ($p<0.001$) in ejection fraction%. It was 45.48±5.03 at the end of one month and 49.08±4.17 at the end of three months compared with the baseline(41.36±6.23).A SHIFT echocardiography substudy was conducted by Montreal Heart Institute which showed that LVEF was increased by (2.4 ± 7.7%) in the Ivabradine group but LVEF was unchanged in the placebo group (−0.1 ± 8.0%). More than a third (36%) of the patients in the ivabradine group had ≥5% increase in LVEF vs. less than a quarter (23%) of the placebo group (P= 0.003).[80]

In our study , Ivabradine improved the quality of life score and each variables in the SAQ was compared with CCS class of angina grade and showed that all these variables were associated with highest score of quality of life . Similar to this result , a study conducted by Taheri Kharame et al , which showed highest score regarding treatment satisfaction (66.34±17.32) and higher quality of life regarding angina stability and perceiving disease in patients who received Ivabradine.[81]

In our study ,Ivabradine did not influence the blood pressure. The routine hematological and biochemical evaluations did not show any significant difference in the pre–post values ($p>0.05$). A study conducted by Aditi Chaturvedi, Yogendra Singh et al. showed that Hb, LFTs, RFTs, serum electrolytes and RBS done at baseline and after 8 weeks of use of the Ivabradine did not show any significant difference $p>0.05$ (using the paired "*t*" test)[82].

In our study, Ivabradine related adverse drug reactions reported were bradyarrythmia, QT prolongation and visual disturbances like blurring of vision and photopsia. Study conducted by Borer et al.[83],Tardif et al.[84] and Ruzyllo et al.[85] showed similar adverse drug reactions.These reactions were considered to be mild and abated on its own after treatment period. But no patients were withdrawn from the study due to adverse drug reactions and no patients experienced serious adverse drug reactions .

Efficacy of Ivabradine by assessing the reduction in heart rate, left ventricular function and ejection fraction improvement in patients with chronic stable angina were the strength of this study . Small sample size and lack of long term follow up were the limitations of this study.

Thus the present study showed that Ivabradine causes reduction in HR, improvement in CCS class of angina grading , left ventricular dysfunction , ejection fraction and quality of life. Therefore the study drug, Ivabradine is safe and effective when given along with atenolol in treating chronic stable ischemic heart disease. Further studies are needed with larger sample size and long term follow up.

CONCLUSION

Based on the results of our study , we conclude that

Ivabradine is safe and effective in preventing and treating further anginal attacks in patients with chronic stable ischemic heart disease already on atenolol therapy.

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								Ivabradine 5mg/7.5mg for 3 months												
S.NO	Age	Sex	association	Dose mg	HR base	HR 1m	HR 3m	reduced	EF base	EF 1m	EF 3m	improved	LVF base	LVF 1m	LVF3m	improved	CCS base	CCS 1m	CCS 3m	improved
1	46	1	2	7.5	100	80	75	yes	36	44	46	yes	2	2	1	yes	2	2	1	yes
2	65	1	1	5	80	78	76	yes	44	48	54	yes	2	1	1	yes	2	1	1	yes
3	61	1	1	5	80	78	74	yes	34	36	47	yes	2	2	1	yes	3	2	2	yes
4	74	1	2	7.5	120	110	100	yes	44	47	49	yes	2	1	1	yes	2	1	1	yes
5	36	1	1	5	100	100	90	yes	44	48	50	yes	2	1	1	yes	2	1	1	yes
6	63	1	1	7.5	80	78	76	yes	45	50	52	yes	1	1	1	yes	2	1	1	yes
7	55	2	2	5	100	90	82	yes	38	42	47	yes	2	2	1	yes	2	1	1	yes
8	56	1	2	7.5	108	98	92	yes	40	46	54	yes	2	1	1	yes	2	1	1	yes
9	55	2	2	5	98	80	78	yes	38	40	45	yes	2	2	1	yes	2	1	1	yes
10	68	1	2	5	80	75	70	yes	44	48	50	yes	2	1	1	yes	2	1	1	yes
11	66	1	1	7.5	100	80	78	yes	38	40	45	yes	2	2	1	yes	3	2	2	yes
12	52	1	2	7.5	80	78	76	yes	35	44	48	yes	2	2	1	yes	3	2	2	yes
13	55	1	2	7.5	100	90	80	yes	44	50	52	yes	2	1	1	yes	2	1	1	yes
14	72	1	0	5	80	78	76	yes	42	48	50	yes	2	1	1	yes	2	1	1	yes
15	60	1	0	7.5	100	90	80	yes	44	48	52	yes	2	1	1	yes	2	1	1	yes
16	57	1	0	7.5	98	86	80	yes	48	50	50	yes	1	1	1	yes	2	1	1	yes
17	51	1	1	7.5	80	76	74	yes	44	48	50	yes	2	1	1	yes	2	1	1	yes
18	32	1	1	5	100	90	80	yes	44	46	48	yes	2	1	1	yes	2	1	1	yes
19	57	2	2	7.5	80	76	70	yes	46	48	50	yes	1	1	1	yes	2	1	1	yes
20	40	1	2	7.5	100	90	80	yes	53	54	56	yes	1	1	0	yes	2	1	1	yes
21	49	2	1	5	80	78	75	yes	30	38	44	yes	3	2	2	yes	3	2	2	yes
22	65	1	2	7.5	80	78	76	yes	37	44	46	yes	2	2	1	yes	2	1	1	yes
23	56	1	1	7.5	80	78	76	yes	30	40	44	yes	3	2	2	yes	3	2	2	yes
24	50	2	2	7.5	80	78	72	yes	53	54	55	yes	1	1	0	yes	2	1	1	yes
25	32	1	1	7.5	100	90	88	yes	20	34	44	yes	3	2	2	yes	3	2	2	yes
26	38	1	0	7.5	98	96	94	yes	50	52	54	yes	1	1	1	yes	2	1	1	yes
27	42	1	1	7.5	88	86	84	yes	44	48	50	yes	2	1	1	yes	2	1	1	yes
28	45	1	2	5	80	78	76	yes	44	46	48	yes	2	1	1	yes	2	1	1	yes
29	72	1	0	5	100	90	88	yes	43	46	48	yes	2	1	1	yes	2	1	1	yes
30	60	1	1	7.5	100	75	70	yes	40	50	54	yes	2	1	1	yes	2	1	1	yes
31	55	1	2	7.5	80	78	76	yes	43	44	46	yes	2	2	1	yes	2	1	1	yes
32	55	1	0	5	80	78	76	yes	40	43	45	yes	2	2	1	yes	2	1	1	yes
33	60	1	0	5	80	78	70	yes	44	46	48	yes	2	1	1	yes	2	1	1	yes
34	63	2	2	7.5	120	100	98	yes	39	44	50	yes	2	2	1	yes	3	2	2	yes
35	49	1	0	7.5	84	80	78	yes	42	44	48	yes	2	2	1	yes	2	1	1	yes
36	54	1	0	5	80	78	76	yes	44	48	50	yes	2	1	1	yes	2	1	1	yes
37	80	1	1	5	100	90	88	yes	28	32	38	yes	3	2	2	yes	4	3	2	yes
38	65	1	0	5	80	78	70	yes	45	48	62	yes	1	1	0	yes	2	1	1	yes
39	73	1	0	5	100	98	96	yes	30	32	40	yes	3	2	2	yes	4	3	2	yes
40	65	2	2	5	120	100	98	yes	40	44	48	yes	2	2	1	yes	2	1	1	yes
41	58	2	1	7.5	100	90	88	yes	50	52	54	yes	1	1	1	yes	2	1	1	yes
42	46	1	0	7.5	100	90	80	yes	42	46	48	yes	2	1	1	yes	2	1	1	yes
43	36	1	1	5	100	98	92	yes	37	40	45	yes	2	2	1	yes	2	1	1	yes
44	70	2	2	5	100	98	86	yes	44	50	52	yes	2	1	1	yes	4	3	3	yes
45	60	2	2	5	90	88	85	yes	44	50	54	yes	2	1	1	yes	2	1	1	yes
46	65	2	1	5	90	88	86	yes	45	48	50	yes	1	1	1	yes	2	1	1	yes
47	45	2	1	7.5	100	98	90	yes	40	44	46	yes	2	2	2	yes	2	1	1	yes
48	53	1	2	5	100	98	96	yes	44	46	48	yes	2	1	1	yes	2	1	1	yes
49	64	1	1	5	100	98	88	yes	47	50	52	yes	1	1	1	yes	2	1	1	yes
50	57	1	1	5	100	98	88	yes	44	46	48	yes	2	1	1	yes	2	1	1	yes

Laboratory investigations - Ivabradine 5/7.5mg

Hb(gm%)			TC (cells/cumm)			ESR (1mm/hr)			Platelet (lakh/cumm)			LFT	SGOT(IU/L)			SGPT(IU/L)			ALP(IU/L)			total bilirubin(mg%)			blood sugar(mg/dl)			electrolytes (Na+ meq/L)			electrolytes(K+ meq/L)		
b	1m	3m	b	1m	3m	b	1m	3m	b	1m	3m		b	1m	3m	b	1m	3m	b	1m	3m	b	1m	3m	b	1m	3m	b	1m	3m	b	1m	3m
14.3	14.5	13.2	7450.00	7300.00	7400.00	15	15	14.5		2.36	2.35		20	20	22	28	28	30	58	58	55	0.7	0.8	0.8	153	150	175	137	138	136	4.1	4.2	4.4
11.5	11	11.4	6900.00	6500.00	7000.00	14	15	15	2	2	2.5		40	35	40	35	35	30	100	120	80	0.5	0.8	0.8	115	120	125	141	140	140	4.8	4	5
11.5	11.6	12	7100.00	7200.00	8400.00	14	15.2	16	2.36	2.4	2.32		46	42	38	55	38	36	112	106	121	0.5	0.8	1	135	142	128	138	136	135	4.1	4.2	4
14.2	15	16	9800.00	9900.00	9700.00	12	12.2	12.8	2	2.5	2.5		40	40	40	40	35	35	60	65	80	0.8	0.8	1	144	150	150	141	140	138	4.8	5	1.3
10	15	12	6700.00	6800.00	7000.00	15	15.5	14.8	2	2	2.5		40	40	35	35	35	30	100	80	80	1.2	1	0.8	115	120	125	140	139	139	4.2	4	4
13.7	14	14	7500.00	7300.00	7200.00	18	17.8	17.6	2	1.5	1.75		40	35	40	35	30	35	60	80	100	0.8	1	0.8	119	120	130	139	138	140	4.4	4.3	4.2
12.4	13	13.6	7800.00	7700.00	7600.00	12.4	12.8	12.6	2.2	2.32	2.4		19	40	40	16	35	38	52	60	68	0.6	0.8	1	225	250	275	140	138	137	4	4.5	4
14.2	15.4	14.5	9850.00	9900.00	9800.00	13.2	13.8	13.6	2.4	1.75	2.2		42	41	43	24	26	28	121	101	132	0.8	1	0.9	112	102	98	138	140	139	4.2	4.4	4.2
12	12.5	13	6400.00	6450.00	6500.00	15.8	14	15.5	1.75	1.8	2		38	36	34	35	32	30	60	72	58	0.8	0.6	0.7	233	240	250	137	135	136	4.1	4.2	4
15.2	15	16	7800.00	7750.00	7825.00	20	18	18	1.5	1.5	2		40	40	35	49	35	30	80	60	75	1	0.8	0.8	190	200	225	138	140	140	4.3	4.2	4
14	14	15	8400.00	8450.00	8500.00	15.2	15	14.8	1.5	1.75	1.5		38	40	40	39	35	38	81	60	80	0.8	0.8	1	121	120	125	140	138	138	4.1	4	4.2
14.9	15	13.2	8700.00	8750.00	8800.00	15.4	15.2	15.4	1.75	1.8	2		40	42	34	45	35	30	48	50	60	1.5	1	1.2	102	150	175	140	140	142	4.1	4.2	4.2
15	16	16	10050.00	11000.00	11500.00	18.2	16	18	1.5	1.75	1.8		23	40	42	32	35	30	87	147	148	1.1	0.8	0.9	217	200	215	138	140	142	4	4.2	1
15	16	14.2	8500.00	8600.00	8400.00	17.8	16	17.5	1.75	1.8	1.7		33	42	48	40	35	30	54	60	80	1.3	1	0.9	181	189	200	138	140	142	4.2	4.2	4.4
9.3	10	12	8300.00	8400.00	8350.00	15.2	14.8	15.2	1.8	2	2		40	42	35	38	36	30	60	80	100	0.8	1	0.9	136	140	150	131	131	133	4.2	4.2	4.2
14	16	13.2	9000.00	10000.00	8000.00	15.5	15	15.2	1.75	1.8	2		50	40	35	38	35	30	91	90	100	0.6	0.8	0.8	113	150	115	138	140	142	4.2	4.2	4.4
17.4	18	18	8600.00	8400.00	8600.00	14.7	14.5	14.8	1.75	1.8	1.82		53	40	38	36	35	30	67	70	75	0.6	0.8	0.9	106	120	125	142	140	140	4.5	4.2	4.4
16.5	18	14.2	12600.00	12000.00	12500.00	17	18	17	1.75	1.8	2		40	42	38	37	38	35	60	80	67	1	1	0.8	178	176	200	138	140	139	4.2	4.1	4.2
13	14	14	10300.00	10250.00	10200.00	16.2	16	16	1.75	1.82	2.2		20	40	42	18	35	38	75	80	78	0.7	0.8	0.9	169	180	190	136	138	140	4.3	4.2	4.4
18	16	14	8600.00	8800.00	8700.00	17.5	16	17.2	1.75	1.8	2		40	38	39	38	36	35	80	100	112	0.8	0.8	0.9	150	175	200	140	138	140	4.2	4.3	4.2
11.6	12	12.2	8750.00	8700.00	8800.00	16.5	16	17	1.75	1.8	1.8		25	35	40	27	30	35	64	72	78	0.7	0.8	0.9	111	115	140	135	139	140	4.2	4.2	4.3
12.8	13	14	9900.00	9000.00	8400.00	16	16.2	15.8	1.75	1.8	2		37	40	42	20	36	38	52	60	58	0.4	0.8	0.6	200	126	158	138	140	142	4.3	4.2	4.4
14.6	15	14	11000.00	10000.00	10500.00	16.8	15.5	16.2	1.75	1.8	1.78		40	40	38	38	36	34	60	62	58	0.8	0.8	0.9	157	160	175	141	142	144	4.2	4.4	4.6
13.6	14	15	11200.00	10000.00	10250.00	14	15	16	1.75	1.8	2		48	45	40	35	40	38	85	86	78	0.9	0.8	0.7	183	180	200	139	138	140	4.3	4	4.2
14	15	15.2	11200.00	10200.00	11000.00	14	16	15.5	2	1.8	1.75		97	45	45	69	38	36	253	170	100	1	0.8	0.9	160	180	200	146	148	135	4.2	4.2	4
16.9	17	16	10000.00	9700.00	8600.00	14	16	16.2	1.5	1.5	1.75		40	38	37	38	36	30	64	70	72	0.8	0.9	0.8	164	180	174	138	140	142	4.2	4.2	5
12.3	13	14	11100.00	10000.00	9600.00	15	18	16	1.8	1.75	1.9		19	30	42	30	28	38	57	60	58	0.7	0.8	0.9	122	128	132	138	140	138	4.5	4.2	4.4
14.3	5	14.8	8300.00	9600.00	9800.00	16.8	16	17	1.75	1.8	1.82		20	40	42	10	38	36	62	64	70	1	0.8	0.9	178	180	182	138	140	142	4.3	4.2	4.2
15	16	18	9000.00	8600.00	9200.00	15.8	15	16	1.75	1.8	1.82		48	46	40	32	30	38	60	58	64	1.4	0.8	0.9	127	130	140	137	138	139	4.8	4.4	4.5
10.4	11	12	8200.00	8600.00	7800.00	17.6	16	17.2	1.8	2	2		40	42	38	38	39	36	60	58	62	0.8	0.6	0.9	166	170	180	134	138	139	4.9	4.6	4.4
12.9	13	12	9000.00	8900.00	9600.00	16.2	16	15	1.5	1.8	2		40	38	35	38	35	32	59	60	62	0.5	0.8	0.6	243	250	300	138	140	142	4.2	5	4.2
14	16	14	8800.00	8600.00	9000.00	14	14.5	14.2	1.5	1.75	1.8		45	44	40	38	40	39	60	58	72	0.8	1	0.9	130	150	160	138	136	138	4.2	4.4	4.5
14.9	15	15.2	8750.00	9000.00	8600.00	14	14.2	13.8	1.5	1.75	1.8		35	38	40	19	35	33	67	64	66	0.8	0.9	0.8	136	140	150	137	140	148	3.3	3.2	3.4
10.1	11	10	8800.00	8600.00	8500.00	14	13.8	14.1	1.5	1.85	2.2		21	40	42	38	38	36	66	64	62	0.6	0.8	0.7	118	120	130	137	140	138	4.6	4.6	4.8
14	14.2	14.4	9650.00	9600.00	9900.00	14	16	15.5	1.8	2	2		42	38	36	38	34	32	62	58	87	0.8	0.9	1	140	150	130	143	142	144	4.2	3.8	3.6
14	15	15.2	8400.00	8600.00	7800.00	14	14.6	15	1.75	1.8	2.1		40	42	38	36	38	36	62	58	54	0.7	0.8	0.9	130	140	138	140	138	136	4.2	4.2	4.4
10.9	12	14	7000.00	6400.00	7200.00	14	16	18	1.75	1.8	1.82		40	35	36	38	34	30	62	58	48	0.8	0.9	0.7	215	180	160	138	136	138	4.2	4.4	4.5
13.8	14	15	8800.00	9600.00	8600.00	15	16	17	1.8	1.75	1.8		44	40	38	24	38	32	105	98	96	2	0.8	0.9	170	180	200	152	148	150	4.4	4.2	4.6
13.5	14	15	9000.00	8600.00	7600.00	14	16	18	1.75	1.8	1.82		38	38	36	33	35	30	58	60	62	0.7	0.8	0.9	117	122	140	141	140	142	3.8	4.2	4.4
12.8	13	14	9300.00	8600.00	7600.00	14	15	8	1.75	1.5	2		40	42	34	35	35	32	62	58	80	0.8	1	0.9	230	280	320	140	138	140	4.2	4.4	4.6
12.7	13	13.2	6600.00	7200.00	8200.00	14	15	15	1.8	2	1.75		37	38	44	44	43	36	63	64	66	0.6	0.8	0.7	117	125	136	146	145	148	4.2	4.3	4.6
13.9	14	15	9900.00	9600.00	9800.00	15	14.8	15.2	1.8	2	1.75		38	39	34	26	29	30	62	58	66	0.8	0.9	0.8	176	140	160	141	138	139	3.2	4.2	4.4
16.2	15	14	9750.00	9800.00	9600.00	14	15	16	1.8	1.75	1.84		63	48	52	75	42	44	84	78	76	0.7	0.6	0.8	125	130	132	140	138	140	4.1	4.2	4.4
13.5	14	14.2	9200.00	9000.00	9200.00	17	15	17.2	1.8	1.75	2		40	38	35	23	35	28	93	80	78	0.8	0.6	0.8	326	350	345	141	142	144	4.2	4.4	4.8
9.5	10	11.2	7700.00	7800.00	7850.00	15	16	16.5	1.8	1.75	1.9		23	32	42	42	32	38	92	88	78	0.4	0.6	0.8	458	350	380	132	144	138	4.3	4.2	4.4
11.7	11.5	10	9900.00	9600.00	10000.00	14	14.5	14	1.75	1.8	1.84		44	42	40	36	38	30	64	112	124	0.8	1	0.9	287	298	320	140	144	134	3.8	3.6	4.2
14	12	10	9600.00	9500.00	9650.00	14	14.2	13.8	1.75	1.8	2		44	36	32	40	30	28	62	58	58	0.8	0.7	0.8	150	140	130	140	142	144	4.2	3.8	3.9
14.3	14.5	15.2	8000.00	8100.00	8200.00	15	14.8	14.9	1.8	2	2		43	34	36	41	30	30	79	80	82	0.8	0.8	0.9	254	280	286	140	142	135	4.2	4.4	4.5
14.8	15	13.2	7700.00	7750.00	7700.00	14	14.5	13.8	1.5	1.75	1.8		39	42	38	40	40	30	50	62	64	0.6	0.8	0.6	160	170	155	142	138	140	4.2	4.4	4.8
10.8	9	8.8	8800.00	9600.00	8600.00	15	16	14	1.8	2	1.75		48	35	30	38	25	32	77	79	82	0.5	0.8	0.6	166	180	200	139	140	142	3.8	4.2	4.4

						SAQ questionnaire score									
S.NO	Name	Age	Sex	CCS 3m	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11
1	shek	46	1	1	3.78	3	2	2	3	2	3	3	2	2	2
2	Ganesan	65	1	1	4	3	2	4	4	3	3	4	2	2	2
3	Srikrishna	61	1	2	4.444	2	3	2	3	3	2	2	2	2	2
4	Perumal	74	1	1	4.888	4	2	2	2	4	3	4	2	2	2
5	Peratchi	36	1	1	5.222	2	1	2	2	4	2	3	2	2	1
6	Natarajan	63	1	1	5.555	1	2	3	4	4	2	2	2	3	4
7	Radha	55	2	1	5.777	1	3	4	5	2	2	2	1	2	2
8	Sanniyasi	56	1	1	5.333	2	2	2	3	3	4	2	2	2	2
9	Savuriyam	55	2	1	4.888	3	2	3	3	3	4	2	2	2	2
10	Ganapathy	68	1	1	5.111	4	1	3	2	2	2	2	2	2	1
11	Natarajan	66	1	2	4.222	5	2	4	5	4	3	2	2	2	2
12	Uikattan	52	1	2	3.111	4	2	2	3	2	2	3	2	2	3
13	Mariappar	55	1	1	3	3	3	1	2	2	2	2	3	2	4
14	Gopal	72	1	1	3.333	2	2	2	3	2	3	3	2	2	4
15	Natarajan	60	1	1	5	2	1	2	4	3	3	3	2	2	3
16	Moosha	57	1	1	4.333	3	2	3	3	3	3	4	2	2	3
17	Isaki	51	1	1	4.444	3	2	4	3	3	3	4	4	2	2
18	Muthu	32	1	1	3.555	3	2	2	3	3	3	2	4	2	1
19	Vasantha	57	2	1	7.6	3	1	1	2	3	2	3	2	2	2
20	Kumarave	40	1	1	7.4	4	2	3	4	4	3	2	2	2	3
21	Rajakuma	49	2	2	5	2	2	0	2	2	2	3	2	2	3
22	Iyyapillai	65	1	1	5.222	2	3	2	2	4	2	3	3	2	3
23	Thangavel	56	1	2	5.555	2	2	3	3	4	3	3	2	3	3
24	Halima	50	2	1	5.666	2	2	2	2	4	3	2	2	3	2
25	Paramasiv	32	1	2	5.444	2	4	3	2	2	2	2	2	3	3
26	Charles	38	1	1	5.777	2	2	2	3	3	2	2	2	2	2
27	Arulvijaya	42	1	1	3.222	2	2	2	4	3	1	2	2	1	1
28	Velayudh	45	1	1	4.111	3	2	3	2	3	3	2	2	1	2
29	Kalasamy	72	1	1	4	3	3	1	2	2	2	2	2	2	2
30	Chelliah	60	1	1	4.333	2	2	2	3	3	4	2	1	3	3
31	Vaigundar	55	1	1	4.444	2	3	2	2	3	2	2	2	3	2
32	Muthiah	55	1	1	4.666	3	2	2	1	4	4	3	2	2	1
33	Joseph	60	1	1	4.888	2	3	2	2	2	3	4	3	1	1
34	Vadivu	63	2	2	5	3	3	2	4	2	3	4	2	1	2
35	Arunachal	49	1	1	4.111	3	3	4	5	3	4	2	2	2	2
36	Syed	54	1	1	5.222	2	2	3	4	3	2	2	1	2	3
37	Madasamy	80	1	2	5.777	4	3	3	3	2	2	2	2	2	2
38	Neelaiah	65	1	1	6	3	3	2	4	3	4	4	2	2	2
39	Ramasamy	73	1	2	3.222	2	1	3	2	4	2	2	3	3	2
40	Thirumala	65	2	1	3.111	2	2	2	3	4	3	2	2	2	2
41	Esakkiyam	58	2	1	3.333	2	1	1	2	4	3	2	2	2	2
42	Mahesh	46	1	1	3.555	3	3	3	2	2	3	2	2	3	2
43	Dharmara	36	1	1	4.111	3	2	3	5	3	2	2	3	3	2
44	Kanniyam	70	2	3	3.888	2	2	2	2	3	2	2	4	2	3
45	Annamala	60	2	1	4.666	2	1	3	3	4	3	2	3	2	3
46	Sornam	65	2	1	5.111	2	3	2	2	2	3	3	4	1	2
47	Kaasithai	45	2	1	5.333	3	2	2	3	3	3	2	4	2	2
48	Gnanasek	53	1	1	5.777	1	2	2	3	3	4	2	4	2	3
49	Chelliah	64	1	1	5.666	2	2	3	4	3	2	2	4	2	2
50	Sankar	57	1	1	5.777	3	2	2	4	3	2	2	4	2	2

EFFICACY AND SAFETY OF IVABRADINE AS AN ADD-ON TO ATENOLOL IN PATIENTS WITH CHRONIC STABLE ISCHEMIC HEART DISEASE

ABSTRACT:

INTRODUCTION:

Coronary artery disease is the leading cause of morbidity and mortality. Heart rate is the important key factor for determining the cardiac output ,myocardial oxygen demand and coronary blood flow . By the year 2020 , WHO predicts 13.2% death due to CAD . In india , 11% of urban population and 7% of the rural population had the prevalence of IHD. Reduction in heart rate is the main stay of treatment for preventing and treating the cardiovascular complications due to IHD. Pharmacotherapy of IHD are the conventional drugs like nitrates, beta blockers and calcium channel blockers . Due to the interactions with other drugs and adverse effects of the conventional drugs ,the management of IHD focused on novel targets . Ivabradine is a novel specific and selective If current inhibitor which slows the diastolic depolarization by acting on the SA node.

OBJECTIVE :

Efficacy and safety of Ivabradine as an add-on to atenolol in patients with chronic stable ischemic heart disease .

MATERIALS AND METHODS:

Interventional ,open label ,prospective clinical study was done over a period of 1 year (April 2014 to May 2015).Single centered study conducted in 50 patients in the Out patient Department of cardiology ,Tirunelveli Medical College Hospital , Tirunelveli.Primary endpoints noted were reduction in resting heart rate using 12 lead ECG and improvement in Canadian cardiovascular society (CCS)class of angina grading. Secondary end points were improvement in ejection fraction(EF) using echocardiography,improvement in left ventricular function(LVF) using echocardiography and improvement in quality of life score using SAQ .

RESULTS:

The demographic data concerning the patient's age, sex, weight, vitals, hemodynamic and laboratory parameters were statistically assessed at the baseline. Ivabradine in reducing the heart rate at the end of 1month (86.60±9.16) ($p<0.0001$) and at the end of 3 months (81.82±8.37)($p<0.0001$) when compared with baseline (93.08±11.67). CCS class of grade of angina also improved at the end of one month and 3 months compared with baseline .Grade IV (3►0►0), grade III(7►3►1) and grade II(40►8►9).

Study drug improved the LV dysfunction . After treatment with tab.Ivabradine , there were no patients with severe LV dysfunction at the end of 1 and 3 months when compared with 5 patients at the baseline.After treatment with study drug, moderate LV

dysfunction was reduced to 20 patients at the end of 1 month and 6 patients at the end of 3 months when compared with 35 patients at the baseline. After treatment with study drug the improvement in ejection fraction% was(45.48±5.03) ($p<0.001$) at the end of one month and (49.08±4.17) ($p<0.001$) three months compared with the baseline(41.36±6.23). Improvement in quality of life also assessed with SAQ questionnaire . Adverse drug reactions reported during the study was mild and no patients were withdrawn from the study due to adverse drug reactions and no patients experienced serious adverse drug reactions.

CONCLUSION :

Ivabradine is safe and effective in preventing and treating further anginal attacks in patients with chronic stable ischemic heart disease already on atenolol therapy.

KEYWORDS: Ivabradine, I_f current ,Ischemic Heart Disease, Heart Rate, Angina, Ejection fraction .

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