



## Assessment with Case Studies the Rational Use of Drugs among Patients with Ischemic Heart Disease at a Tertiary Hospital in South West Nigeria.

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**Abstract:** The requirement for rational use of drug (R U D) is that the right drug be used with the right dose at right interval and at right duration. These retrospective case studies were carried out at the University College Hospital (U.C.H) Ibadan to investigate factors that influence the selection of rational drug use in the treatment of ischemic heart disease among those admitted as in patients and outpatients in the hospital.

Four (4) case notes of 2 male adults consisting of one in-patient and one out-patient and 2 female adults consisting of one in-patient and one out-patient from medical out-patients records were randomly selected and thoroughly studied. Patient A was prescribed 8 drugs including Isosorbid dinitrate and Metoprolol as anti-ischemic drugs. Patient B was prescribed 10 drugs including Isosorbid dinitrate and metoprolol as anti ischemic drugs while patient C and D were prescribed the least number of drugs which was 7 with glyceryl trinitate and propranolol prescribed as anti ischemic drugs for patient C and Isosorbid dinitrate with propranolol for patient D. Propranolol was later changed to Atenolol. The ECGs indicated no change in QRS but indicated depressed ST segment and T wave flattened.

Although the patients were discharged and the pharmacotherapy individualized, anti-ischemics which were rationally used in the studies could be implicated by irrational use of drugs in the treatment of co-morbidities. Co-morbidities such as hypertension, obesity, diabetes and ulcer should be taken into consideration before anti-ischemics can be rationally prescribed.

**Key Words:** Rational drug use (RUD), Ischemic heart disease.

**Running Title:** Rational use of anti ischemic drugs.

### INTRODUCTION

The requirement for rational use of drug is that the right drug be used with the right dose at right interval and at right duration. The patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, at the lowest cost to them and their community. It implies proper management of the drugs with patient's involvement and balancing benefits against the risk and cost with the aim of maximizing patient's health status, minimize unwanted side effects and taking control of achieving effective health care. When the use of drugs is not in accordance with the above definition, there are often undesirable health and/or economic problems, such as insufficient therapeutic effect, adverse drug reactions, preventable side effects, interactions of drugs and increasing resistance of bacterial to antimicrobial medicines resulting in increased, prolonged or expensive hospital admissions<sup>(1)</sup>.

Essential drugs are among the most cost effective ways of saving lives and improving health. They constitute 20-40% of health budgets in many developing countries such as Nigeria. Increase in the cost of drugs often results in public health problems resulting in inability to procure sufficient drugs to meet patients demand. This often results in drug mismanagement, insufficient and irrational use of drugs. Irrational use of drugs can also be due to

inadequate training of health staff, lack of continuing education and supervision, lack of updated, reliable and unbiased drug information<sup>(2)</sup>.

Particular areas of inefficient and irrational drug use include poor selection of medicines without consideration for relative efficiency, cost ineffectiveness or local non availability, inefficient procurement practice resulting in non-availability of adequate drug quality. Furthermore there are wastage uses of unnecessarily expensive medicines, prescription not in accordance with standard treatment protocols, patient lack of knowledge about dosing schedules and patients not adhering to dosing schedules and treatment advice. Therefore anti ischemic drugs should be rationally selected to prevent these problems<sup>(2)</sup>

Ischemic heart disease is a condition with many underlying causes having in common the ability to impair the supply of oxygenated blood to cardiac tissue because the oxygen demand by cardiac tissue exceeds oxygen supply to the tissue. The most common situation in which oxygen demand exceeds supply occurs when the vascular supply to the heart is impeded by diseases such as arteroma, thrombosis or spasm of coronary arteries. Myocardial Ischemia can also arise if oxygen demand is abnormally increased as may occur in severe ventricular hypertrophy due to hypertension or where the oxygen-carrying capacity of blood is impaired as in iron-deficiency anemia<sup>(3)</sup>.

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Studies have shown that 25% of patients with heart attack die before medical intervention. This is why it is very important to modify the risk factors of ischemic heart disease such as family history, cigarette smoking, hypertension and raised serum cholesterol<sup>(3)</sup>. The assessment of these factors form the rationale behind the choice and use of anti-Ischemic drugs.

This study is set out to document the detail case histories of patients with ischemic heart disease from four (4) randomly selected case notes from medical outpatients department of the University College Hospital [UCH], Ibadan, assess the pharmacotherapeutic approach to the ischemic heart disease and discuss the rationale behind the choice of drugs for the management of ischemic heart disease.

**PATIENTS AND METHODS**

There was no patient admitted for ischemic heart disease at the university college hospital Ibadan during the time the study was conducted. As a result four case notes of ischemic heart disease patients were randomly selected from medical records department of University College Hospital (U.C.H) Ibadan.

The case notes of two male adults consisting of one in-patient and one out-patient and two female adults

consisting of one in-patient and one out-patient were randomly selected for the study. A detailed patient’s medication histories as well as detailed factors that influence rational drug use such as dosage form, dosage regimen, side effects, drug interactions and patient compliance were extracted from the case notes.

The case notes selected include general information which comprises of date of admission, age , race, sex, chief complaint, occupation, the type of ischemic heart disease, signs and symptoms, physical examination and laboratory findings as related to chief complaint.

Specific information in the case notes reviewed included the past medical history, patients’ family history, social history, review of system, drug history including present and past drug history with detail explanation of drug allergies and magnitude of patient’s complaint.

Electrocardiogram [ECG] chart was thoroughly studied to diagnose the underlying coronary heart disease of ischemic heart disease which were angina pectoris and silent myocardial infarction.

Physician impression, hospital course and discharge data were thoroughly studied to establish the rational behind the prescribed drugs. The data obtained were then analyzed to justify the rational drugs prescribed.

**RESULTS**

**CASE A**

A 74 year old man brought to the cardiology department was admitted few days by the renal unit on account generalized weakness of excessive sweating and vomiting

**Physical Examination**

GEN—Weak, appearing elderly man, afebrile, acyanosed but sweaty.

Vital signs

T	36.5	ABD	soft and non tender, active bowel sounds		
R.R	34/min	Hs	S <sub>4</sub> , S <sub>1</sub> , S <sub>2</sub>		
P.R	74/min	1/0	1450ml (oral)		
			1900ml (urine)		
B.P	124/85mmHg	Chest	clear		

**Laboratory Result**

Na <sup>+</sup>	139mEq/L	(135-152)	Uric acid	7.5mg/dl	(3.0-7.0)
K <sup>+</sup>	2.7mEq/L	(3.7-5.1)	BUN	15mg/dl	(8.25)
Cl	105mEq/L	(95-105)	CR	125ml/min	(125)
HCO <sub>3</sub>	18mM/L	(12)			

**Assessment** IHD with background pre- hypertension

**Medication History**

Tab. Ramipril 5mg daily	Tab. Metoprolol 50mg b.d
“ Lasix 20mg b.d	“ Augmentin 625mg b.d
“ A S A 75mg daily	“ Metronidazole 400mg tds
“ Isosorbide dinitrate 5mg b.d	SC Heparin 5000 I.V/ 12hrly

**CASE B**

A 77year old female diabetic patient was admitted on account of chest tightness, insomnia and headache for 3days. There was associated chest pain aggravated by

of 2 days duration. He developed excessive sweating in the evening. The sweating which was sudden on onset was not associated with exertion. There was associated breath difficulty and dizziness. There were episode of loss of consciousness but no history of abdominal pain.

**Physical Examination**

GEN well nourished old woman in distress

Vital signs:

PR	70/min regular thickened arterial wall	CNS	Grossly intact
B.P	148/78mmHg	Hs	S <sub>1</sub> ,S <sub>2</sub> no murmur clear

activities but revealed at rest. No history of vomiting or loss of consciousness. There was easy fatigability and not a known hypertensive patient.

ABD within normal limits

**Laboratory Result**

Na	140mEq/L (135-145)	Glu	150mg/dl (70-110)
K	51mEq/L (40-90)	HCO <sub>3</sub>	27mmol/L (24-30)
Cl	105mEq/L (100-106)	Ca	8.8mg/dl (9-11)

**Assessment** IHD with background of HBP (systolic) and diabetes mellitus

**Medication History**

I.V	Augmentin 1.2g stat: 600mg 8hourly	Tab.	Daonil 5mg daily
Tab.	Isosorbide dinitrate 5mg daily	”	Metformin 50mg b.d
”	A S A 150mg daily	”	Lisinopril 2.5mg daily
”	Lipitor 10mg daily	”	Lasix 40mg daily
”	Metoprolol tartarate 50mg daily	”	Aldactone 25mg daily

**CASE C**

A 40 year old woman was presented with 3 weeks history of chest pain and dyspnoea at the medical outpatient clinic. She also had a sudden retrosternal pain which radiated to all part of her body with associated weakness

and breathlessness but no loss of consciousness and no seizure. There was associated palpitation and progressive dyspnoea on exertion and associated polyuria nocturea and polydypsia but no cough and leg swelling. No family history of hypertension and diabetes.

**Physical examination**

GEN: Young woman not in distress.

Vital signs

B.P	140/90mmHg	HS	S <sub>1</sub> ,S <sub>2</sub> No murmur. Obese with striae
Chest	Bilateral rales and pleural rib	P.R	80/min, good vol. Reg.
ABD	Benign		

**Laboratory Results**

Na	136mEq/L (135-145)	Cl	98 mEq/L (100-106)
K	40mEq/L (40-90)	Ca	10mg/dl (9-11)
HCO <sub>3</sub>	26mM/L (24-30)	Phos	4mg/dl (3-3.5)
GLU	81 mg/dl (70-110)	Chol	140mg/dl (120-220)

**Assessment** No peripheral edema. Patient with IHD with obesity as a risk factor; hypertension, impaired glucose tolerance.

**Medication History**

Tab.	Propranolol 20mg b.d	Tab.	Aspirin 150mg daily
”	Paracetamol 1000mg daily	”	Glyceryltrinitrate 0.5mg PRN
”	Librium 10mg daily	”	Ternormin 50mg daily
”	Diazepam 5mg nocte		

**CASE D**

A 45 year old man was presented with 5 year history recurrent retrosternal discomfort, peppery sensation associated with late meal at the medical out-patient clinic. Pain not associated with exertion. No history of hematemesis. The peppery sensation usually radiate to the

upper limbs but not to the neck. No epigastric pain. No associated nausea, vomiting, paroxysmal dyspnoea or orthopnoea. No abdominal discomfort . Pain not reveal by change in position. He takes wine but not cigarette. No family history of hypertension and diabetes

**Physical Examination**

GEN- Restless, not sweaty. Afebrile, acyanosed, not pale, anoteric. No peripheral lymphadenopathy

Vital signs

P.R	110/min, regular normal	H.S	S <sub>4</sub> , S <sub>1</sub> and S <sub>2</sub>
B.P	160/110mmHg		Funduscopy normal, Normal muscle tone
ABD	Soft without masses		
CNS	Conscious and alert, well oriented, cranial nerves grossly intact.		

**Laboratory Results**

Na	140mEq/L (135-145)	Cl	105mEq/L (100-106)
K	50mEq/L (40-90)	Total cholesterol	190mg/dl (120-220)
Ca	11mg/dl (9-11)		

**Assessment** IHD associated with HBP (Hypertension)

**Medication history**

Tab	Isorsorbide dinitrate 5mg b.d	Tab	Propranolol 40mg b.d
”	ASA 300mg O.D	”	Ranitidine 150mg b.d
”	Diazepam 5mg nocte	Susp	MMT 300ml qds
”	Metchlorpramide 5mg b.d		

**DISCUSSION**

The professional career must appreciate that preventing Ischemic Heart Disease (IHD) is neither important instant, nor spectacular. It involves repeated sessions of counseling over many years to initiate and maintain healthy habits. It also involves persuasion of patients to continue taking medication for disorders such as hypertension or hyperlipidemia to prevent an outcome that “won’t happen to me”. Stable angina can be managed by a general practitioner or in an out patient clinic, but unstable angina should be treated in hospital.<sup>(3)</sup> In these studies the ECG charts indicated no change in QRS but

indicated ST segment depressed in figures 1 and 2 and wave flattened in figures 3 and 4. If angina occurs more frequently than two or three times per week, chronic prophylactic therapy is necessary. The three drug classes that can be used for this purpose are Nitrates, B-blockers and Calcium Channel Blockers.<sup>(4)</sup> Initial drug selection for chronic angina treatment should be based on the patient characteristics and concomitant conditions. Nitrates may reverse coronary vasospasm making them particularly useful in treating vasospastic angina. This effect may lead to increase in myocardial oxygen supply<sup>(5)</sup>.

**Table 1: Drugs prescribed for patient A**

Name of drug	Class of drug	Dose
Ramipril (tab.)	Angiotensin converting enzyme inhibitor (antihypertensive)	5mg daily
Lasix (tab.)	Loop diuretics	20mg daily
Acetylsalicylic acid Aspirin(tab.)	Non steroidal anti-inflammatory drugs (NSAIDs)	75mg daily
Isosorbid dinitrate (tab.)	Anti angina	5mg b.d
Heparin (sc)	Anti coagulant	5000 b.d
Metoprolol	B-Adrenoceptorblocker (Antihypertensive)	50mg b.d
Augmentin	B-lactum-antibiotics	625mg b.d
Metronidazole	Amoebicidal agent	400mg t.d.s

**Table 2: Drugs prescribed for patient B**

Name of drug	Class of drug	Dose
Augmentin cap.	B-lactam antibiotics	1.2g stat,600mg 8homly
Isosorbid dinitrate tab	Anti-angina	5mg daily
Acetylsalicylic acid [Aspirin] tab	Non-steroidal anti inflammatory drugs	150mg daily
Lipitor (Atorvastatin tab.)	Lipid regulating drugs	10mg daily
Metoprolol tartarate (tab.)	B-adrenoceptor blocker	50mg daily
Glibenclamide (tab.)	Anti diabetic drugs	5mg daily
Metformin (tab)	Anti diabetic drugs	500mg b.d
Lisinopril (tab)	Angiotension converting enzyme inhibitor	2.5mg daily
Lasix (furosemide)	Loop diuretics	40mg daily
Aldactone (tab) (spironolactone)	Potassium-sparing diuretics	25mg daily

Regardless of which nitrates is selected it should be started at low dosage to reduce the incidence of adverse effect early in therapy. Subsequent dosage adjustment can be based on incidence of adverse effect such as headache, dizziness and hypotension. Effectiveness of nitrate products can be assessed by decreased use of sublingual nitroglycerin for acute attack of angina, improvement in patient’s quality of life, that is, ability to perform normal activities without experiencing angina and objective assessment by exercise testing.<sup>(6,7)</sup> In the four (4) cases studied, nitrate products used were Isosorbid dinitrate 5mg two times daily in patient A, B and D (Table 1,2,4), while Glyceryl trinitrate 0.5mg PRN was used in patient C (Table 3). A decreased pharmacologic response in the

presence of continuously or frequently administered nitrate is well documented and is termed nitrate tolerance. Clinically, preventing nitrate tolerance involves the provision of a daily nitrate free interval (nitrate free period). The time of day for providing of a nitrate free interval is usually at night<sup>(7)</sup>. Problem with nitrate free period has therefore necessitated additional use of β-Blockers. β-Blockers are effective anti ischemic and anti angina agents that act to decrease myocardial oxygen demand by decreasing heart rate and contractility.<sup>(8,9)</sup> It is recommended that all patients with unstable angina receive β-Blocker therapy unless there are contraindications.

**Table 3: Drugs prescribed for patient C**

Name of drug	Class of drug	Dose
Propranolol (tab.)	B-adrenoceptor blockers	20mg b.d
Paracetamol (tab.)	Analgesic	1000mg t.d.s
Librium (tab.) [Chlordiazepoxide]	Benzodiazepine	10mg daily
Diazepam (tab.)	Benzodiazepine	5mg nocte
Acetylsalicylic acid. [tab] Aspirin	Non-steroidal anti inflammatory drugs	150mg daily
Glyceril trinitrate (tab.)	Anti-angina drugs	0.5mg PRN
Ternormin (tab.) (Atenolol)	B-adrenoceptor blockers	50mg daily

**Table 4: Drugs prescribed for patient D**

Name of Drugs	Class of drug	Dose
Isosorbide dinitrate (tab.)	Anti-angina drug	5mg b.d
Acetylsalicylic acid (tab.) Aspirin	Non-steroidal anti-inflammatory drugs	300mg O.D
Magnesium trisilicate (mix.)	Antacids	30ml qds
Propranolol (tab.)	B-adrenoceptor blocker	40mg b.d
Ranitidine (tab.)	Anti-ulcer drugs	150mg b.d
Diazepam (tab.)	Benzodiazepine	5mg nocte
Metochlor propamide (tab.)	Sulphonamide [sulphonylurea]	5mg b.d

In the four (4) cases studied,  $\beta$ -Blockers were rationally used as they were used to offset the problem associated with nitrates free period.  $\beta$ -Blockers have several beneficial effects in Ischemic heart disease.  $\beta$ -Blockers reduce heart rate mainly during time of sympathetic stimulation which results in reduced cardiac work and thus reduced myocardial oxygen demand. In addition to slowing heart rate,  $\beta$ -Blockers

increase diastolic filling time resulting in increased coronary perfusion and improved oxygen supply. In patient A and B, metoprolol 50mg b.d was used while in patient C & D Propranolol 20mg b.d and 40 mg b.d were used respectively. In patient D, Propranolol was changed to Atenolol the newer generation  $\beta$ -Blocker to offset the side effect of gastric disturbance of Propranolol.

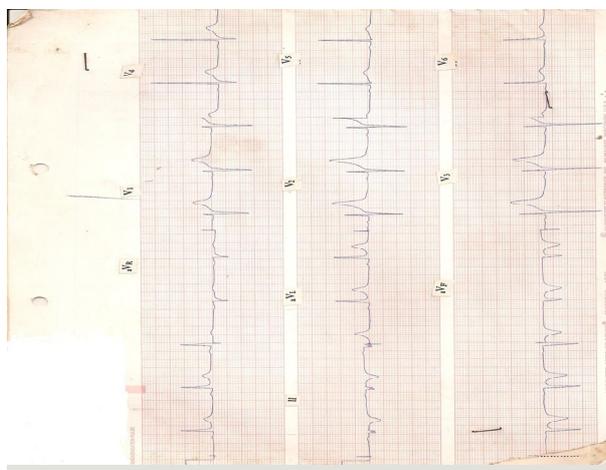


Fig 1.1-ECG of patient A

In contrast,  $\beta$ -Blockers reduce myocardial contractility and arterial blood pressure and thereby reduce myocardial oxygen demand. A potential problem with  $\beta$ -Blockers is that they may cause coronary vasoconstriction.<sup>(10,11)</sup> With blockade of  $B_2$  receptors which mediate vasodilatation, there is unopposed  $\alpha$ -receptor mediated coronary vasoconstriction. This is a particular concern in patients with rest or variant angina where  $\beta$ -Blockers could potentially precipitate an angina episode. This may necessitate the combination of Calcium Channel blockers with  $\beta$ -Blockers. However, Calcium channel blockers have five major physiologic effects: decreased systemic coronary vascular

resistance (peripheral vasodilatations), decreased myocardial contractility, slowing of sinus, reduced heart rate and AV nodal conduction. Reductions in systemic vascular resistance, heart rate and myocardial contractility result in decreased myocardial oxygen demand whereas decreased coronary vascular resistance increases myocardial oxygen supply.<sup>(12,13,14)</sup> Major adverse effect of Calcium channel blockers are headache, ankle edema, tachycardia, flushing and dizziness. Calcium channel blockers are effective in preventing angina. They are particularly useful in patient with contraindication to  $\beta$ -Blockers or patients with mainly variable threshold angina as well as with conditions such as Diabetes mellitus, prior

myocardial infarction, isolated systolic hypertension, systemic hypertension and left ventricular dysfunction. All calcium channel blockers appear to be effective in managing stable angina. (15,16,17)

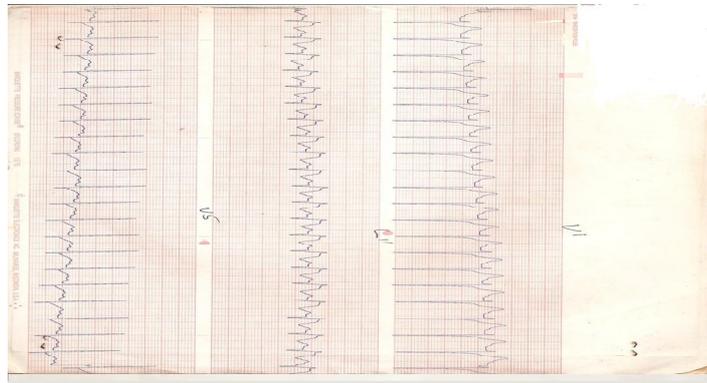


Fig 2.1-ECG of patient B

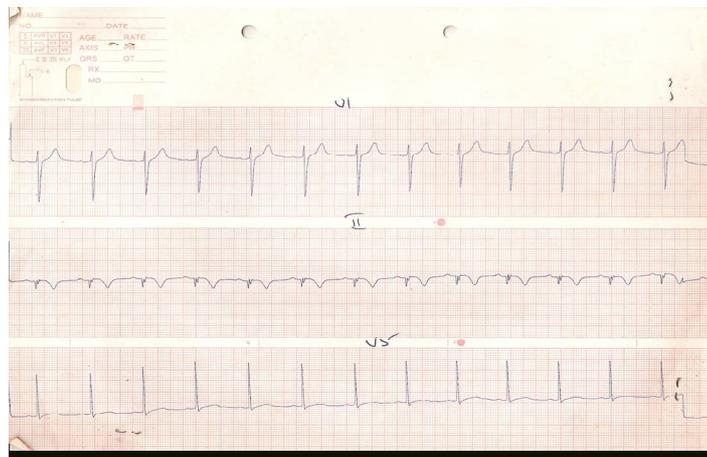


Fig 3.1-ECG patient C

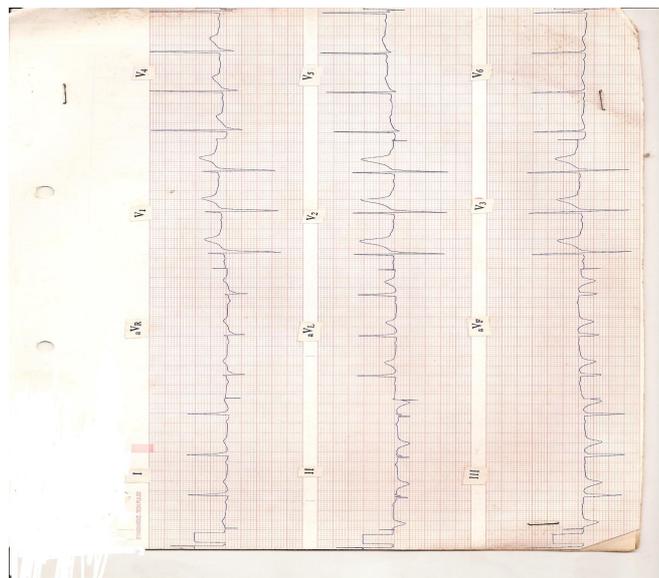


Fig 4.1-ECG patient D

In this study, there was no use of Calcium channel blockers as non of the four patients studied was contraindicated to

Beta-Blockers. In addition Calcium channel blockers may also cause gastrointestinal effect such as nausea and

constipation thus could not have been used in patient D where the patient was established to have gastrointestinal disturbance.

Aspirin as a prophylaxis of infarction at 75 mg to 300 mg daily have proved to be beneficial in all forms of IHD as administered in cases A,B,C and D. In case A, 75mg Aspirin was given daily. In cases B & C it was 150 mg daily and in case D, 300 mg Aspirin was given every other day. This is equivalent to 150 mg daily.<sup>(10)</sup> Patient suspected of having unstable angina or acute myocardial infarction should immediately be given aspirin 150mg to 300mg to chew or swallow except in case of a definite contraindication such as documented hypersensitivity or acute bleeding. Early administration of aspirin has been shown to be superior to placebo in preventing progression of unstable angina to acute myocardial infarction.<sup>(10)</sup> Dosage of 75-150mg/day seems to have efficacy similar to 300mg/day. Therefore it is recommended that patients with unstable angina take aspirin 75-300mg daily, the dosage based on clinician or patient preference.<sup>(10)</sup>

Heparin confers additional pharmacotherapeutic benefit in unstable angina and thus additional pharmacotherapeutic benefit is established in the rational use of Heparin 5,000 units every 12 hours in case A. The primary goal of anticoagulant such as Heparin is to prevent extension of the thrombus and thus prevent acute myocardial infarction. Although aspirin is superior to placebo in these patients, data suggest that unfractionated heparin alone may be superior to aspirin alone; interestingly some studies have not shown unfractionated heparin to be superior to aspirin or placebo.<sup>(18,19,20)</sup>

Nonetheless the expert panel that develops the clinical practice guideline recommended that unfractionated heparin should be administered immediately when the diagnosis of intermediate to high risk of unstable angina is made. In most patient, unfractionated heparin is given along with aspirin.<sup>(21)</sup>

In institutions not equipped to administer unfractionated heparin by continuous infusion, the recommended regimen is 5000U by intravenous bolus every 4 hours for 2 or 5 days. In patient-A, 5000U heparin was administered every 12 hours along with aspirin. This was rational administration of heparin since it was given along with aspirin. (Patient A, Table 1).

Because most patients with ischemic heart disease have underlying coronary artery disease, correcting and treating all modifiable cardiovascular risk factors is essential in an effort to reduce the risk of future vascular events. Risk factors reduction should focus on hypertension management and its risk factors such as diabetes management, smoking cessation, lipid lowering therapy, antiplatelet therapy and cardiac rehabilitation therapy exercise.<sup>(22,23,24)</sup> Lipid lowering drug therapy in patients with angina or prior myocardial infarction with average or elevated serum cholesterol concentrations has been shown to reduce cardiovascular morbidity and mortality.<sup>(25)</sup> Lipitor [atorvastatin] 10mg daily was given to patient B as lipid lowering agent [or lipid lowering drug]. This is rational as obesity and diabetes are

coronary risk factor and this patient is also diabetic. Diabetes and obesity as coronary risk factors may increase cardiovascular morbidity and mortality. Lipitor was rationally given to reduce cardiovascular morbidity and mortality which may result from ischemic heart disease.<sup>(25)</sup>

Hypertensive treatment reduces cardiovascular morbidity and mortality. Blood pressure reduction by antihypertensives also reduces myocardial oxygen demand thus, benefits patients with angina.<sup>(5)</sup>

Captopril Prevention Project (CAPP) trial found Captopril to be equal to diuretics and  $\beta$ -blockers in preventing cardiovascular morbidity and mortality.<sup>(26)</sup> ACEI are also additive with  $\beta$ -blockers.<sup>(22)</sup>

In patient A, Ramipril 5mg daily was used in combination with Lasix [frusemide] 20mg daily, a loop diuretic and in patient B, with spironolactone 25mg b.d which is a risk factor of ischemic heart disease. In patient C & D, there was no additional antihypertensive used apart from Propranolol, which was changed to Atenolol, a  $\beta$ -blocker. The use of  $\beta$ -blockers in these patients serves both as antihypertensive and antiischemic.

Metochlorpropamide, a derivative of chlorpropamide, a first generation sulphonylurea is associated with the highest incidence of adverse effects and drug interactions. Metochlorpropamide was used in patient D and there was no drug prescribed that interacted with it. Glibenclamide, a second generation sulphonylurea is a more potent antidiabetic agent. It tends to have fewer drug interactions because they bind nonionically and are present in much lower concentrations than the first generation agents such as Metochlorpropamide. In combination with Metformin, it is an additive therapy to lower hyperglycemia and to prevent the risk factors with diabetes in patient with ischemic heart disease.<sup>(27)</sup> Augmentin was rationally used in patient A & B as antibiotics and in patient A in combination with Metronidazole. There is no drug interaction reported with any of these drugs in these patients.<sup>(28)</sup>

For patient D, Ranitidine 150mg b.d for peptic ulcer was prescribed. Ranitidine minimally inhibits hepatic metabolism of drugs including Propranolol and Diazepam and it has fewer clinically significant drug interactions. There was a beneficial drug interaction in Patient D where Ranitidine was used only to increase the bioavailability of Propranolol or Atenolol and Diazepam.<sup>(28,29)</sup>

## CONCLUSION

Treatment of co-morbidities and risk factors such as hypertension, diabetes mellitus, obesity and ulcer should always be taken into consideration before anti ischemics can be rationally prescribed.

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