3. Review of Literature

3.1 History and Philosophy of Pharmaceutical Care

The advent of modern medicine has a beginning in apothecaries of Europe, where in the health care provider worked as a one man army – diagnosing the disease, making the medicine, and administering to the patients. This type of arrangement became extremely difficult for health care provider, who divided the activity into different but coordinating professions like doctors, nurses and pharmacists. Doctors had to diagnose, nurses to give patient care and comfort and pharmacists to handle overall matters concerning drugs. On these lines, professional practice developed adopting, needed skills and knowledge. Further, it went on that, pharmacists should make the medicines and compound them as per the directions given by doctors. Doctor’s prescription has a $Rx$ symbol meaning, you take addressing to pharmacist. The pharmacists were nick named as compounders/chemist and druggists as they were doing all the activities pertaining to drugs. The entry of pharmaceutical industry into health care has an evolutionary impact on professional inter relationships and practice of professions. For example, compounding becomes obsolete, as readymade products are being available for use. The role of pharmacist became just dispensing the prescriptions. Further, the patients started asking the questions to pharmacists, while dispensing as they could not converse with the doctors due to lack of time. Hence, the pharmacists gradually started learning the skill of communication to satisfy the patients’ needs. It developed into a professional activity which is known as patient counseling. Due to availability of pharmacist at the dispensing counter and his expertise in the matters of drug and its usage, has achieved a unique status for the pharmacist as a confidential health care advisor for the patients.

The Phrase, pharmaceutical care is a new introduction to health care services. It is new because, it emerged naturally to fill the gap in health care service. The core health care
service team comprises of doctors, pharmacists and nurses along with their assistants. The dynamics and the pressure due to increased demand for the health care services have led to lack of time given to the patients. For example: doctors are spending less than a minute with patients. In that one minute, doctors are supposed to diagnose/write a prescription and educate the patient regarding the medication. This type of hustle bustle environment is a common scene in all hospitals, nursing homes and even private clinics. Further it should be realized that, the prime role of the doctors is to diagnose and prescribe. Due to non availability of trained pharmacists, the role and responsibility of pharmacists is shared by doctor and nurse.

The modern drugs became technically difficult to use, by the patients themselves. It was soon realized the drug effects can be influenced by timing they are administered, drug – food interactions, cryptic pharmacokinetics, and unpredictable adverse drug reactions. Each drug carries a huge burden of risk, if not used as per the guidelines. It became the role and responsibility of pharmacist to instruct patients, how to use the medicines in an intelligent manner, so that the benefits are maximized and risks were minimized. Looking at the complexity of each patient needs the need for personalized patient education became a necessity. Pharmacists were asked to supervise the overall outcome of treatments. So, the pharmacists work got transpired from dispensing to observe the therapeutic outcomes.

The over promotion of pharmaceutical products ignoring the patient interests, led to a product centric market. This had a negative effect on health care outcome and was considered unethical. Its wide spread practice, has made the World Health Organization, to promote patient centric health care, in which the patients are given priority rather than, products or procedures. There is a need for customized care plan to achieve the expected outcomes in a cost effective manner, by avoiding the risks arising due to wrong
medications and ignorance. The pharmaceutical care has emerged as a natural practice. The evolution of pharmacy practice has been taking place all across the globe simultaneously, in Northern America, Europe, Australia and Japan. Recently, the WHO and FIP, jointly worked together to bring out the guidelines for universal pharmaceutical care.

3.2 The emergence of Healthcare professionals – standards, ethics, inter professional collaborations, lifelong learning of practice through education and research

The profession is defined as “skillful art emerged by continuous practice through experiences along the changing times.” The profession gives an identity, dignified status and domains of practice. Here, a professional thoroughly understands his role and responsibility and develops a work culture which is acceptable to his clients and society. On these lines, the health care professionals have their own professional bodies, which documents and gives opportunities to excel in their professional practice. The professions, especially health care, are considered noble as they are primarily involved in dealing with health and suffering of the patients. The profession growth is dependent on individual’s professional dedication and contribution to the clients. For example, one of the earliest professions is of motherhood. A mother takes all the interest to learn and develop her child in the best possible way. Now the question is why mother takes a selfless profession to develop her child? The answer to this question lies in the nature, as it prompts her to develop a sense of belongingness to her child. She loves and endures all pain to see a smile on her child face. Her satisfaction is only achieved when, her child progress like other children. On the similar lines, HCPs are developed across the world. In ancient times in India, the Vaidyas, have learned the treatment of diseases and treated the patients without expecting the financial reward from the patients. Due to this service, they were honored by kings and taken care of their needs.
The pharmacy profession is also similar to motherhood. Here, the pharmacist take the patients as his own kith and kin, and tries to help them in all possible way, so that the suffering of the patients becomes bearable and hopes are raised for further living. The patients identify such traits and immediately recognizes. Thus, a professional identity gets established. This information gets spread across and leads to a unique status for a pharmacist in a healthcare settings.

The pharmacists should show empathy- a shared feeling, but not sympathy which is very much important in practice. However, the pharmacist should also think as far as neutral and should not be carried away by the feelings, thoughts, behavior of the patients. He should be able to dissociate himself and think with a calm mind what is good for the patient that he can do? The standards of professional practice are summarized as – code of ethics which forms the guidelines to take the decisions in dilemmas of practice. Hence, the thorough understanding of ethics is the foundations of good pharmacy practice. The quality of care is a ever demanding process, which improves upon self/peer examination of mistakes happened in practice, criticizing them and consolidating a protocol, how best to avoid it in future? The documentation of practice will act as an alarm for identifying the repetition of the errors and the resource to train future pharmacists.

In the course of practice, there are several instances, where the pharmacists have to disagree with fellow HCPs. In such instances, the pharmacist should be guided by the patient’s point of view and should be able to convince his professional idea. So that, the fellow HCPs gets convinced through discussions and appropriate course of action takes place. One should never forget, all the HCPs goal is to make patients comfortable, relief of tension and cure from disease. To achieve this common goal, all the HCPs need to
work as a team and never as competitors. Hence, it becomes individual’s responsibility to act and contribute without interfering with the practice of fellow HCPs.

To keep abreast with latest developments in professional practice, there is a need to participate in continuing education programs which are useful in exposing the latest professional practices which can modernize the services of profession. The research activities should also be the part of practice as one, who participates in research, gets an insight and broadens vision of the issue of the topic.

Provision of pharmaceutical care is advantageous to the individual patient, answer to the of ‘medication errors’ conception. Patient will be delighted with the improvement in his clinical and humanistic outcomes. Pharmaceutical care offers pharmacists’ a genuine possibility to be responsible healthcare professionals. In daily practice, structuring of the activities, cooperation with contemporaries and the Pharmaceutical associations might be desirable (1).

**3.3 Present scenario in Europe**

European Directorate for the Quality of Medicines and Health care (EDQM) conducted a survey about pharmaceutical care practices in the 17 countries of European Union and reported that, Pharmaceutical care is being considered as an vital goal but yet to be implemented in practice due to lack of awareness and cooperation among HCP. Only a few countries in Europe have a legal patronage for the implementation of pharmaceutical care (2).

There have been several pharmaceutical care initiatives taken place in Sweden. Documentation of drug related problems has been ahead and special campaigns are organized for specific patient groups (3).
Patient counseling by pharmacists is mandatory by law in Finland, and disease oriented pharmaceutical care initiatives such as care for elderly people, diabetes, heart disease and asthma patients and also initiated the projects like ask about your medicines (4). Community pharmacists are offering the services of monitoring of Hypertension, diabetes and dyslipidemia with the aid of documented data. To focus the action on local health issues, pharmacists are declaring a health topic of importance to draw the attention of the community and motivating the public to take up appropriate measures, to avoid a major future catastrophic calamity (5).

Pharmaceutical care leads to higher customer retention due to added benefits like patient comfort and minimization of drug related problems (6). National Health Service (NHS) of England is emphasizing on provision of pharmaceutical care for every prescription and has established instruments of quality assurance which is mandatory in healthcare delivery. It offers seven essential pharmaceutical care services along with smoking cessation program (7).

The concept of family or domiciliary pharmacies is a new development in Germany. These are community pharmacies with a focus on disease management and medication regimen reviews. Under this program, the patients choose their family pharmacy. All personal and medication data are maintained in the database and available for retrieval (8).

Provision of pharmaceutical care is regulated by law in Spain. Measurement of blood pressure, weight and testing of cholesterol were offered in the community pharmacies along with providing pharmaceutical care services (9). Areas such as networking, ADR monitoring or patient counseling have tremendous potential for pharmacist intervention (10).
Pharmaceutical care Network Europe (PCNE) was established by researchers in 1994 with the aim of developing pharmacy practice standards in European Union. It was started as the Therapeutic Outcome Monitoring (TOM) - a community based program, to detect, prevent and resolve drug related problems in asthma patients. The results were convincing as it improves the quality of medication therapy (11).

Elderly Medication Analysis, a randomized control trial (RCT) was conducted in seven European countries, showed the significant health related improvements and better controls in the sign and symptoms of the disease along with improvement in compliance to therapy and patient satisfaction (12).

3.4 Present scenario in Canada

After a decade of introduction of pharmaceutical care concept in Canada, 21.6% of pharmacists allotted more than four hours per day for the activities of pharmaceutical care. To overcome the obstacle of lack of time for the activities, reorganization of the technical functions to pharmacy assistants was prominent feature and changes were made in the layout of pharmacy by incorporating the private patient counseling area along with availability of education material was positive change occurred during the period (13).

3.5 Present scenario in America

In 2003, the US congress approves the Medicare prescription drug, Improvement, and Modernization act (MMA) (14). Legislation adds prescription drug benefits, via Medicare part D, administered by insurers. Insurers will provide the Medication Therapy Management Services (MTMS) to optimize therapeutic outcomes by improving medication adherence, and by reducing adverse drug reactions. To encourage the innovation and competition, MMA purposely left the enrolment criteria and details among insurers. To supervise these services, center for Medicare and Medicaid services (CMS) was established which will approve the services before the implementation (15).
Eleven national pharmacy organizations developed the definition of MTMS, which states that, “a distinct service, or group of services, that optimize the therapeutic outcomes, for individual patients, (that) are independent of, but can occur in conjunction with, the provision of drug product (16).”

MTM stipulates the eligibility criteria are the patients of age over 65 years, or suffering from End Stage Renal Disorders (without age limit), multiple chronic diseases (Diabetes, Hypertension, Dyslipidemia, Heart failure, Respiratory disease, Bone disease and Mental health disorder), multiple medications and high drug costs ($3000/year). Medicare provides hospital insurance (Medicare Part A), medical insurance (Medicare Part B) and prescription drug coverage (Medicare Part D) to those who qualify for benefits. Changes to the Medicare program were signed into law with the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA 2003). This legislation requires prescription drug plans to offer high-risk Medicare Part D beneficiaries Medication Therapy Management (MTM). For 2010, high-risk Medicare Part D beneficiaries included those with multiple chronic disease states, taking multiple Medicare Part D covered medications, and likely to incur an annual cost of US$3,000 for prescription medications.

Patient counseling provided at the time of dispensing is also made mandated by Omnibus Budget Reconciliation Act 1990, is typically one way communication with patient, explaining the purpose of the medication, its proper administration, length of the therapy, storage conditions, and refill information (17). It does not necessarily consider the other co-morbid conditions and medicines. In contrast, MTMS is much more time consuming, comprehensive and two way communications between patient and pharmacist. The advantage over patient counseling is the involvement of the patient in the decision making of their personal health.
CMS regulations established a general framework that allows for best practices in MTMS. Hence, 10 pharmacy organizations collaborated to develop the core elements of an MTM visit (18).

Medication Therapy Management Services provided by Medicare sponsors are comprehensive medication review and targeted medication review.

1. Comprehensive medication review: It is an annual medication review by pharmacist. The process involves interview with patient face to face when he visits the pharmacy. Further interviews can be done over the phone. It will essentially cover the medication action plan of the patient along with personal medication list to be followed.

2. Targeted medication review: It is a quarterly medication review by pharmacist. This process may be specific in nature, or whenever the patient experiencing the medication related problem or at high risk for developing medication related problem. However, this process can be done over phone and need not to be face to face.

There are several services were on offer for the beneficiaries which is provided by pharmacists, under the MTM Services. Here are the few examples;

a. Medication therapy reviews: Patient-specific information will be obtained by interview with patient and their caregiver. It includes assessing medication therapies of patients and identifying medication related problems, creating a plan to resolve them.

b. Pharmacotherapcy consultations: Patients of complex medical conditions will be included and identify patients experienced medication related problems or who are at high potential to develop them. Achieving desired therapeutic goals for patients by promoting safe, appropriate, and cost-effective use of medications.

c. Disease management support: It includes counseling about drug and non-drug therapies for the patients along with lifestyle modifications. Integrate programs to
manage their disease and medications to reduce healthcare costs and improve quality of life of patients.

d. Anticoagulation management: For the patients who were prescribed warfarin for Atrial fibrillation and for those who are at high risk of stroke were included in this service model. Patients were educated about self management, importance of adherence, follow-up tests, performing INR tests and adjustment in dosages by collaborative practice.

e. Medication safety surveillance: to prevent medication errors and adverse events. This program is for drugs or biologics that pose specific risk for patients, will optimize the balance of patient access and medication safety.

f. Health, wellness and public health: Screening programs for common disease states (Asthma, diabetes, cardiovascular disease) will be done. Weight loss counseling along with nutritional planning. Smoking cessation counseling will be conducted for the people who want to quit smoking.

g. Immunization services: Improve vaccination rates for vaccine preventable illnesses. Administer vaccines like seasonal flu vaccine, H1N1 vaccine, herpes zoster vaccine, travel vaccines etc., for the people.

h. Pharmacogenomics consultations: Pharmacogenomics is a new and emerging medication therapy management service, which provides the explanation and use of a patient’s genetic information to optimize a patient’s response to drug therapy. Pharmacists are comparing patient-specific treatments based on genetic markers, predicting patients’ response to therapy, dose calculations, predicting adverse reaction to selected therapies, and recommendations to prescribers on the individual patient, that maximize effectiveness while minimizing risk.
3.5.1 Published outcomes of MTMS

a. **Asheville project**: A community pharmacy project for patients ensured by two local employers in Asheville (19). Pharmacists were paid to provide MTM services to diabetic patients. Services included diabetes education, educate patient to monitor blood glucose at home, clinical assessment at follow up and referrals. Results were remarkable: Direct medical costs decreased by $1200, sick time days decreased every year. Also, increases in productivity were estimated at $18,000 per worker annually. An increase of $52 per patient per month because of pharmacy care service fees and it results in greater compliance with diabetes medications. However, there was a 29% decrease in non-diabetes related costs (hospital, doctor visits) and 16% decrease in all-diagnosis costs. Asheville project still going ahead. Another Asheville MTM program was started 2000-2005 for hypertension & Dyslipidemia.

b. **Iowa state Medicaid pharmaceutical case management program** (20): The medication appropriate index score was decreased from 9.4 to 8.3.

c. **Senior Pharm Assist program**: Patient’s knowledge about their medicines had been increased in first 6 months with no further improvement. Emergency room visits and self reported health status improved at the end of the study period (21).

d. **North Carolina state health plan employees MTMS**: Pharmacists were able to detect an average of 3.6 medication related problems. Potential underuse, treatment with most cost effective agent, and treatment with sub optimal drug were most commonly identified problems. 80% of the patients were satisfied with the services provided by pharmacists (22).

e. **Blue cross blue shield of Minnesota beneficiaries**: Therapeutic goals were achieved to the tune of 76% to 90% in the MTMS group. Total per person expenditure was decreased by 31.5%. Total cost of care decreased by US$ 3678 per person per year.
with return on investment of US$ 12.15 for every US$ 1 spent. Quality of life domains, physical role, social functioning and physical component scoring were improved significantly (23).

f. Impact of telephone MTM: The intervention group had significantly more medication and health related problems were resolved. Total drug costs were decreased by US$ 158 in intervention group compared with increase of US$ 118 in control group (24).

g. MTMS in community pharmacy: Estimated cost avoidance was US$93.78 and there is a shift from patient education and monitoring to cost efficacy management was observed. Acute medication management to long term chronic medication management was significant (25).

3.6 Myocardial Infarction – Pathology, treatment options- Angioplasty - brief history, procedure-general precautions- pharmacotherapy

Myocardial infarction (MI) occurs as a result of increased metabolic demand, decreased delivery of oxygen and nutrients to myocardium. An interruption in the supply of myocardial oxygen and nutrients occurs when a thrombus is superimposed on an ulcerated or unstable atherosclerotic plaque and results in coronary occlusion (26).

MI is classified (27) based on electrocardiographic (ECG) findings as means of distinguishing feature, ST elevation myocardial infarction (STEMI) and non –ST elevation myocardial infarction (NSTEMI).
3.6.1 Prevalence of Ischemic Heart Disease (IHD)

Disability adjusted life year (DALY) estimate for the year 2011 by WHO has summarized the Ischemic Heart Disease has 1,59,659,000 DALYs (5.8% total) and 43,851,000 DALYs (5.7% total) in South East Asian Region (SEAR). Next to Lower Respiratory Tract Infection, IHD was the major cause for DALY in the year 2011. It also estimated that, prevalence of 2301 DALYs per 100,000 populations in the year 2011 in
the age groups of 50 -69 years and above 70 years were more irrespective of gender difference. Whereas, the age group of 50-69 is more vulnerable for IHD in SEAR (28). Global Health Estimates Summary tables of WHO, projects mortality by cause, sex, age and region wise. In the Indian context, the models were used to project future health trends with cause specific mortality rates. It estimates that IHD will be leading cause of death (75, 94,000 with 13.2% of total death) in 2015, causing 105 deaths per 100,000 populations. The same trend is predicted for the year 2030, IHD will remain no.1 cause of death (92, 45,000 with 13.2% of total death). Age of 50-69 and above 70 years in male population will be affected more. Whereas, in female population the age group of above 70 years is more vulnerable to IHD (29).

3.6.2 Risk factors

Six primary risk factors have been identified for the MI, Hyperlipidemia, diabetes Mellitus, Hypertension, Tobacco use, Male gender and family history of atherosclerotic disease (26).

Hyperlipidemia: Elevated levels of Total Cholesterol, triglycerides and Low density lipids are associated with MI and atherosclerosis. Decreased levels of High density lipids (< 40 mg/dl) are also a risk factor (30).

Diabetes Mellitus: Patients with diabetes have greater risk of MI, as it increases the rate of atherosclerotic progression and adversely affects the lipid profile.

Hypertension: Increased risk of MI is significantly associated with Hypertension. Usage of anti hypertensive medications will reduce the risk of MI significantly (31).

Tobacco Use: Use of tobacco is known to cause blood vessel walls damage. It leads to the formation of atherosclerosis and its progression to MI.

Male gender: MI and atherosclerosis has more incidence rate in male gender. However, this gender difference will narrows with increasing age.
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Family History: Genetic components along with acquired general health practices like smoking and high fat diet may lead individual’s risk of atherosclerosis and MI.

3.6.3. Pathophysiology

The two primary characteristics of atherosclerotic plaque are fibro muscular cap and an underlying lipid rich core. Plaque erosion leads to disruption of the endothelium and fissuring of the fibro muscular cap. Disruption of endothelial surface leads to thrombus formation, which may occlude coronary blood flow leading to MI.

The death of myocardial cells first occurs at the endocardium. As the duration of occlusion increases, area of myocardial cell death enlarges to myocardium and to finally epicardium. If blood flow can be restored at the earliest, heart muscle can be saved from death.

STEMI is usually the result of complete coronary occlusion after plaque rupture and NSTEMI is with greater plaque burden without complete occlusion.

![Figure 4: Pathophysiology of Myocardial infarction (32)](image-url)
3.6.4 Signs and Symptoms (32)

Acute MI can have unique signs and symptoms in individual patients. However, asymptomatic MI is also possible in the patients of diabetes. Here are some characteristic symptoms are listed.

1. Chest pain described as a pressure sensation, fullness or squeezing in the mid portion of the thorax.
2. Radiation of chest pain into the jaw, shoulder, arm, and/or back
3. Associated dyspnea
4. Associated epigastric discomfort with/without nausea and vomiting
5. Sweating
6. Syncope or near syncope

![Myocardial infarction process](image)

Figure 5: Myocardial infarction process (32).
Most of the MI occurs at early hours of the morning or during physical activity or both. Creatine kinase, Troponin I and T, Myoglobin are released into blood stream, when a myocardial cell dies. Hence, the estimation of these enzymes will help to diagnose the MI.

![Cardiac enzyme markers released after the onset of MI (33).](image)

**Figure 6: Cardiac enzyme markers released after the onset of MI (33).**

### 3.6.5 Pharmacotherapy after MI

Anti Platelet agents: Aspirin 325mg should be administered immediately on recognition of MI signs and symptoms (34). Aspirin has shown to reduce mortality in the condition of MI beyond doubt. It irreversibly interferes with function of cyclooxygenase and inhibits the formation of thromboxane A2 (35). Aspirin prevents additional platelet activation and interferes with platelet adhesion and cohesion. Clopidogrel in combination with Aspirin has been demonstrated a benefit significantly in COMMIT-CCS 2 trials (36). Clopidogrel causes the irreversible blockade of the platelet P2Y12 receptor.

Nitrate: Nitroglycerin when administered sublingually or intravenously, which has rapid onset of action, metabolized into nitric oxide in vascular endothelium. Nitric oxide relaxes the smooth muscle and dilates the blood vessel lumen. Vasodilatation reduces the
cardiac preload and after load and decreases myocardial oxygen requirements needed for circulation. It also reverses the vasoconstriction associated with thrombosis and coronary occlusion.

Beta Blockers: Drugs like Metaprolol, Atenolol And Carvedilol were used within 12 hours of MI and continued indefinitely (33,34). These drugs decrease the rate and force of myocardial contraction and oxygen demand. Hence, it can minimize the myocardial injury and death.

Heparins: Unfractionated Heparin will be used with a bolus dose of 60 U/kg IV bolus and maintained at 12 U/kg/hr IV until ruptured plaque has completely resolved. The minimum duration of therapy is 48 hours. It has the added benefit of preventing thrombus formation.

Low molecular weight Heparins like, Dalteparin (120 U/Kg Subcutaneous, bid) or Enoxaparin (100 U/kg Subcutaneous, bid) can be administered to the patients, who are not treated with Fibrinolytics. These drugs have anti coagulant effect, proved effectiveness in both STEMI and NSTEMI conditions.

Fibrinolytics: Fibrinolytics therapy will be initiated for the patients with STEMI and have no immediate access to cath lab services for angioplasty procedure. These drugs have shown to restore coronary blood flow in STEMI patients and also provide survival benefit.

Angiotensin converting enzyme inhibitors: drugs like Ramipril were widely used in all the patients with STEMI and NSTEMI. These drugs decrease the myocardial after load through vasodilatation.

Glycoprotein IIb/IIIa antagonists: Drugs like Abciximab, Tirofiban and Eptifibatide were used in the patients of MI, acts by inhibiting the platelet aggregation. These drugs were extensively used in the Percutaneous Coronary Intervention procedure also.
Statins: Drugs like, Atorvastatin, Pravastatin are started as soon as patient is stabilized and its usage has been proven to reduce the level of LDL, Total Cholesterol and Triglyceride levels and improve the HDL levels, which is very much essential in the MI patients.

3.6.6 Other treatment options

Percutaneous Coronary Intervention: Ideally, all the patients of MI should undergo PCI within 48 hours of cardiac event. It consists of diagnostic angiography combined with stenting. Restoration of coronary blood flow is done by PCI method, which can restore the blood flow to coronary arteries in 95% patients of MI.

Coronary Artery bypass grafting: Surgical revascularization is warranted in the condition of re-stenosis conditions of PCI or complete coronary occlusion at Left Main Coronary Artery or multiple vessel disease comprising of occlusion at three or more coronary arteries.

3.6.6.1 Percutaneous Coronary Intervention

The percutaneous catheter techniques to treat coronary artery narrowing or occlusion have revolutionized the treatment of MI. The first procedure was performed in 1977 by Andreas Gruntzig. Technical advances, adjunctive therapy involving glycoprotein IIb/IIIa receptor antagonists and increased skills of interventional cardiologists made the management of MI by PCI, as safe and effective.

Technique: Access to vascular system is achieved by puncture of right femoral artery. Recently, radial artery approach has been used. This approach of right radial artery will allow quick mobilization of the patient. Basic tools for the performance of PCI are guiding catheter, the guide wire and balloon catheter and stent.

The guiding catheter is inserted through an introducer sheath via right femoral/ right radial artery. It has different diameters, ranging from 4 french (1.2mm) to 8 french
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(2.7mm) and has specific preshaped curve that makes easy engagement of ostium of right coronary artery or left main stem.

The guide wire is a long wire with soft, steerable and having a diameter of 0.36 mm. The wire is used as rail over which the balloon catheter slides into coronary vessel and placed across the lesion.

The balloon catheter consists of long catheter with an inflatatable balloon at its end. The balloons may vary in size; usually 2 cm, but available in the range of 1 to 6 cm. The balloon inflation pressure varies from 1 - 20 atmospheric pressure. Once the balloon is inflated, the diameter of the balloon will be 3- 3.5mm.

![Radio opaque markers](image)

*Figure 7: Balloon angioplasty catheter. Two radio opaque markers, indicating the lateral Balloon margins, aid in positioning of the balloon before inflation.*

Stent: Coronary artery stents are small mesh tubes that can help to reduce the blockage of artery. The stent is implanted into an artery and expanded to fit the size, shape and bend of the coronary artery. The stent is propped open to help prevent any more blockages. Once the stent is in place, it will remain the position. Over time, the artery wall will heal around the stent as it continues to support the artery.
There are two kinds of stents, bare metal and drug coated. Bare metal stents were made up of stainless steel and drug eluting stents are stents made up of stainless steel or cobalt chromium coated with polymer which carries and protects the drug before and during the procedure\textsuperscript{37}. Once the stent is implanted, it helps controlled drug release from the stent. Drug will be releasing for the period of six months. Sirolimus, Everolimus, Zotarolimus and Paclitaxel are widely used drugs in DES.

Figure 8: Stents mounted on balloon catheter. A- CYPHER Stent; B- TAXUS stent

Procedure of the angioplasty is involving the following steps:

1. Placement of guiding catheter and a radio opaque dye is injected through it to record the images of heart.

2. Introduction of the guiding wire and steer into coronary artery and crossing the lesion.

3. Introduction of the balloon catheter over the guide wire and precisely place across the lesion.

4. Inflation of the balloon for short period of 30 seconds.

5. Deflation of the balloon and removal of the balloon catheter.
6. Introduce the stent as in the step 3 and inflate the balloon mounted stent at 18 atmospheric pressure, so that stent and artery expand.

7. Balloon is removed and stent remains in the position.

8. Post dilation of the stent will be done by using the balloon.

9. Patient is shifted to cardiac intensive care unit, for observation by retaining the sheath in place. Removal of sheath done after 4 hours of the intervention.

Figure 9: Procedure of coronary angioplasty: (A) Guide catheter (B) Balloon catheter over Guide wire (c) Into the lesion area (37).

Mechanism: Once the balloon was inflated, it will dissect the intima and media and increase the total vessel circumference. But, it may cause excessive damage and abrupt coronary occlusion as a result of occlusive dissection occurs. The probability of having these problems is 4 -8% during procedure. The stent is an extremely useful device for scaffolding disrupted or friable atherosclerotic material and for eliminating acute and chronic recoil of the vessel wall (37).
Re-stenosis: Stent implantation exacerbates the neo-intimal proliferation response, resulting in 15% to 25% re-stenosis in bare metal stents. However, this problem is overcome by using drug eluting stents.

Figure 10: Angiographic images before, after and at late follow up after placing DES. The left anterior descending artery contains a tight stenosis (Arrow). After stent implantation, the stenosis is abolished. Follow up at 4 and 12 months shows no re-stenosis (37).
3.7 Quality of Life Measurement Instruments

Estimations are extremely imperative in all activities so as to separate and rank around themselves. Health care services provided by professionals received by patients who have different perceptions. Doctors are very nearly fulfilled with clinical outcomes. In actuality, the patients are more contented with the treatments if it makes a difference for them. They also would appreciate the treatments is economically priced. Traditionally health care was always valued from clinical perspective, and patient choices were of secondary importance. A broad definition of health implicates health as a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity (38). Hence patients’ opinion about health and its direct measurement has become vital among researchers. It will measure patients’ perception and the extent to which they can actually function in their daily activities. Even when the aim of treatment is to lower the incidence of direct outcomes like re-stenosis after percutaneous coronary intervention, evaluating the change in patients’ function and perception will provide valuable additional information.

The technique used to integrate effects of treatments and diseases from patients’ opinion is to use Health Related Quality of Life (HRQoL) measures. HRQoL is a broad theoretical construct developed to explain and organize measures concerned with the evaluation of health status, values and perceived levels of satisfaction and general well-being with respect to either specific health condition or life as a whole from individual’s perspective (39). Since many domains of HRQoL cannot be observed directly, HRQoL instruments are developed.

HRQoL instruments measure the broad perception of health (physical, mental, and social well-being) known as domains, by explaining the extent of difficulty with activities of daily living (including work, recreation, and household management) and how these
difficulties affect relationships with family, friends, and social groups. When measuring HRQoL it is important that the instrument selected measures the health dimensions relevant to that particular set of patients. For instance, an instrument intended for use with patients after myocardial infarction (MI) should take into account the individual's responses to living with the disease, in terms of recreational, occupational, social, personal and sexual relationships, as well as the acute and chronic physical consequences of the disease. This is because when someone is ill almost all aspects of his or her life may be affected (40).

HRQoL instruments often contain questions that measure body function (e.g., pain, depression, anxiety) and limitations with participation in the activities. HRQoL instruments are developed and evaluated according to psychometric principles of test theory. This involves the process of asking a series of questions indirectly. The answers to these questions are then assigned numerical values to yield ‘scale scores’. These scale scores are further combined to get domain scores or summary scores.

3.7.1 Role of HRQoL instruments in pharmacoeconomic evaluations

Scarce availability of resources in society compels decision-makers to balance the benefits and risks of treatment when they make decisions for patients. When the family resources are limited it has to give up other benefits, which demand the need for economic analysis to help informed decision making. The HRQoL instruments can be used to study benefit gained or perceived by the patients against the resources consumed, thus helping in economic evaluation.

The HRQoL instrument chosen will gives us values or utilities depending on the questions are asked. If the question is about certain outcomes it gives us values and if uncertain outcomes it gives us utilities.
3.7.2 Measurement of health status

Patient preferences for alternative health states can be measured either by Time Trade-Off Method or Standard Gamble Method. The Time Trade-Off measures values whereas Standard Gamble measures utilities (41).

3.7.3 Choosing the right HRQoL instruments

To provide an assessment of HRQoL, researchers can either select tools that focus on general health status using generic instruments, or they can choose disease-specific. The choice of right HRQoL instrument depends on the objectives of the researcher, which may be used to record treatment outcome, to make a distinction between patients according to disease severity and to record change in quality of life over a period of treatment.

Once the objectives are made clear, researcher should choose the required instrument is disease specific or generic. A disease-specific measure is designed to query specific aspects of health that are affected by the disease (Myocardial Infarction). In contrast, a generic instrument measures general health status, including physical symptoms, function, and emotional dimensions of health relevant to all health states, including healthy individuals (42).

Disease-specific instruments are more responsive to small but important changes in health than are generic measures (43). In some cases, disease-specific measures are so specific that comparisons between different populations within the same disease are not possible (e.g., pediatric versus adult populations in asthma). On the other hand, generic HRQoL instruments are useful when measuring the impact of a specific illness or injury across different diseases, severities, and interventions. For comprehensive picture of a patients’ HRQoL, it is often desirable to include combination of both, the generic health and
disease-specific instruments. Hence, we decided to use both disease specific and generic questionnaires.

The desirable instrument should be having the proof of Reliability (consistency in ratings), Validity (representation of theoretical constructs) and Responsiveness (detect even small changes.)

### 3.7.4 HRQoL instruments in MI- EQ 5D 5L and MacNew questionnaire

Major cardiovascular diseases include coronary heart disease, hypertension, heart failure and cerebrovascular disease. Cardiovascular disease impacts significantly on HRQoL of patients who survive coronary disease such as MI or stroke. HRQoL measures are particularly of great use while investigating treatment of CVD in three instances viz., when the survival analysis is intermediate but improves HRQoL, when mortality rate is reduced, but unacceptable side effects occur and when the patients were asymptomatic and have long duration of therapy (43).

Clinical trials conducted for cardiovascular diseases started to include the HRQoL measurements. These measures, alongside clinical measures of functionality, can help evaluate the physical, mental and emotional effects of cardiovascular disease as well as the effects of surgical and medical interventions. HRQoL measurement in CVD can be assessed using disease-specific instruments such as the Seattle Angina Questionnaire (SAQ)(44); MacNew Heart Disease Health-related Quality of Life Questionnaire; and the Minnesota Living with Heart Failure score (MLHF)(45). These questionnaires are particularly sensitive to changes in aspects of HRQoL directly related to cardiovascular disease. Alternatively, commonly used generic measures of HRQoL including the SF-36(46), Health Utilities Index (HUI)(47) and the EQ-5D (48)have also been used in cardiovascular disease studies. The main advantages of such generic multi-attribute health state classifiers are that they allow the calculation of Quality adjusted life years (QALYs)
within cost-utility analyses as well as allowing comparison of HRQoL across different conditions and against age-sex matched population norms.

3.7.5 EQ-5D-5L

EQ-5D-5L is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (49). Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys (48).

The EQ-5D-5L consists of 2 pages – the EQ-5D-5L descriptive system and the EQ visual Analogue scale (EQ VAS). It has 5 dimensions - mobility, self-care, usual activities, pain, and anxiety. However, each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondents are asked to indicate his/her health state by ticking in the box against the most appropriate statement in each of the 5 dimensions. The combined 5 digit number describes the respondent’s health state and it should not be used as a cardinal score (50).

A total of 3125 possible health states are defined in this way. Each state is referred to in terms of a 5 digit code. For example, state 11111 indicates no problems on any of the 5 dimensions, while state 12345 indicates no problems with mobility, slight problems with washing or dressing, moderate problems with doing usual activities, severe pain or discomfort and extreme anxiety or depression.17

The EQ VAS records the respondent’s self-rated health on a 20 cm vertical, visual analogue scale enables the patient to place their current health state on a range from 0 (worst imaginable health state) to 100 (best imaginable health state). It can be used as a quantitative measure of health as judged by the individual respondents(51).
EQ-5D 5L is designed for self-completion by respondents and is cognitively undemanding, taking only a few minutes to complete. EQ-5D-5L health states, may be converted into a single index value. The index values, presented in country specific value sets, are a major feature of the EQ-5D 5L instrument, facilitating the calculation of quality-adjusted life years (QALYs).

### 3.7.6 Validity of EQ-5D in cardiovascular diseases

In a study involving 106 consecutive patients with ACS completed the EQ-5D, the SF-36, and the MacNew questionnaire at admission, at discharge, and at three months follow up. Validity, reliability, responsiveness, and acceptance of the EQ-5D were tested. The results demonstrated that EQ-5D was highly accepted. The EQ-5D index showed substantial ceiling effects after rehabilitation. The EQ-5D visual analogue scale (VAS) score and EQ-5D index were significantly better for patients with myocardial infarction than for patients who underwent surgery (both \( p < 0.001 \)). The correlation with the MacNew sub scores and with the global score was significant. Hence, it was concluded that the EQ-5D has all qualities to be used in the condition of ACS (52).

In a study aimed to quantify the relationships between the EQ-5D index and commonly used cardiac measures, Canadian Cardiovascular Society (CCS) angina severity class, treadmill exercise time (ETT) and Seattle Angina Questionnaire (SAQ) were examined. This study concluded that EQ-5D index value decreases as severity of cardiac disease increases (53).

In another study done to confirm the contributions of different disease related, pathway related and demographic variables on patients` perceived HRQoL as a relevant and widely used outcome measure in cardiac populations using EQ-5D (54).
3.7.7 MacNew HRQoL Questionnaire

The main advantage of generic measures is that make comparisons between diseases, whereas disease-specific measures usually distinguish better between patients within a specific-disease category and are more responsive than generic ones (55). For this reason, it has been suggested to use both types of instruments in combination.

The MacNew Heart Disease Health-related Quality of Life questionnaire is a self-administered questionnaire to assess and evaluate HRQoL in patients with coronary heart disease which is established internationally. This questionnaire is a modification of Quality of life after Myocardial Infarction questionnaire. This questionnaire shown to be reliable, valid and responsive in patients with IHD; specifically in patients with MI, angina, Acute coronary syndrome and heart failure, and it is available in seven languages.

MacNew questionnaire consists of 26 items related to three domains of HRQoL, viz., physical (11 items), emotional (10 items), and social (7 items). Each of the items is rated on a 7-point Likert scale, where ‘1’ indicates poor and ‘7’ indicates good HRQoL. Scores are calculated by averaging the responses to the items of each domain, whereas averaging all items provides a global score (56).

Research article by Stan Maes et al., explains the methodology and validation procedure of MacNew in cardiac rehabilitation program. Internal consistencies were calculated by using cronbach alpha between baseline and at follow up leads to significant values for physical emotional, social and global domains. Hence it was concluded that, MacNew have high internal consistencies at both baseline and at follow up points and can discriminate well in all the diagnostic groups, sex and age. It also concludes that, MacNew subscales are responsive enough to capture changes over time period (57).

The minimal important difference of 0.5 on the 7 point scale is consistent with clinical improvement or deterioration (56).
Predictors of MacNew HRQoL have been identified and poor HRQoL is an independent predictor of later mortality and morbidity (58).

3.7.8 Quality of life after angioplasty

According to TRIUMPH registry, the registry of acute MI patients of United States, 4340 patients were subjected to detailed interview, and quality of life was assessed by Seattle Angina Questionnaire (disease specific) and EQ 5D and SF-12 (generic) questionnaires. About patient’s baseline independence was assessed by EQ 5D, 72.9% had no problems with mobility, 90.3% had no problems with self care and 66% had no problems with usual activities. Over the follow up period of one year, 43% experienced either independence or physical function decline. On subgroup analysis, decline in mobility (58.2%) and usual activities (65.5%) were more common that in self care group (21.4%). In patients with an improvement in angina, when compared to baseline- 21% experienced decline in physical function (59).

Benzer W and colleagues conducted a study to describe the impact of PCI, CABG or continued medical treatment on quality of life for the patients of coronary artery disease. MacNew questionnaire was used in the project. The association between MacNew scale at baseline and angina grade was significant along with moderate correlation for global, physical, emotional and social subscales. Mean Baseline scores for PCI are, 4.9, 5.1, 5.3, and 5.0 for physical, emotional, social and global score respectively. After a follow up period of one year, mean change (95% Confidence Interval) for PCI are, 0.8, 0.52, 0.59, 0.58 for physical, emotional, social and global score respectively. Global, Social and emotional scale significantly improved for PCI group of patients where as emotional and global scale improved in CABG group. Improvement in angina grade and each MacNew scale were moderately correlated (60).
Research group of Stent – PAMI trial, published the quality of life for the patients undergoing PCI or balloon angioplasty for the patients of acute MI. Research team used the SAQ and SF – 36 questionnaires to assess the quality of life. At one month of follow up, PCI group had reported the less bodily pain (76.3 to 80.8) than balloon angioplasty patients and at six months, PCI resulted in significant reduction in angina frequency 89.3 to (94.3) and bodily pain (76.3 to 78.9) and improved disease perception. At 12 months follow up, differences were not significant. These results favors the initial stenting will be beneficial for the acute MI patients (61).

Research group of RITA – 3, published an article on HRQoL after Interventional or conservation strategy with unstable angina or NSTEMI patients. Patients from England and Scotland who experience the UA or NSTEMI were randomized into Intervention strategy including PCI and conservation strategy involving pharmacotherapy. HRQoL was assessed by using EQ 5D and EQ VAS, SF-36, and SAQ questionnaires. Four month and One year follow up was conducted. The improvement in the intervention group at 4 months was significant (mean difference of 3.0). Results at one year showed, increase in mean VAS score favoring Intervention group. Larger percentage of patients in Conservation group had worsening HRQoL w.r.to, usual daily activities and anxiety. Global utility scores at one year were significantly better for the intervention group. SAQ domains were significantly better in all the domains for the intervention group, specifically with disease perception (62).

In a cross sectional study conducted at Australia, 202 patients who underwent PCI procedure answered the MacNew questionnaire after one year of the index PCI. Mean emotional score of 5.24 ± 1.2 along with mean physical score of 5.05 ± 1.3, mean social score of 5.43 ± 1.4 along with mean global score of 5.17 ± 1.2 were recorded. However, the trends of decline in the values were seen after 24 months in all the domains were seen.
Literature review

Overall HRQoL scores for all domains increased in patients at 15 to 17 months after the index PCI was observed (63).

Daniel Mark and his team for the Occluded Artery Trail, compared the PCI with Medical therapy alone in totally occluded infarct related MI. They assessed quality of life in 951 patients by Duke Activity Status Index (DASI) and SF – 36 at baseline, 4, 12 and 24 months. The mean difference between groups in the DASI score was 1.00 (p=0.36) at 12 months and 1.7 (p=0.29) at 24 months, with higher scores at PCI group. The difference in the percentages of patients reporting angina at 24 months was smaller for PCI group (11.9% in therapy and 7.1% in PCI. P=0.03). Score on Mental Health Inventory, the mean difference of 1.8 was observed in PCI group at 24 months (64).

The PCI patients treated with drug eluting stents were asked to participate in quality of life measurement study done at Netherlands. EQ 5D and EQ VAS were used as tool for assessment. EQ 5D levels were dichotomized into no problems and problems; VAS was dichotomized into using the 25th percentile (Cut off ≤ 60) indicating poor health status. Mobility (HR: 2.23), self care (HR: 3.09) and low health status (HR: 3.09) as per VAS were independent predictors of death (65).

In Austria, researchers were tried to observe the changes in HRQoL and mental distress after PCI procedure. MacNew and Hospital Anxiety and Depression Scale questionnaires were used at 1, 6, 12 and 24 months. Improvement of MacNew scale was found up to 6 month after PCI. Mental distress declined during the first month of the follow up period. MacNew global score increased significantly as improvement in all three subscales were improved at 1 month and 6 months. After 6 months up to the end of 24 months, scores were remained stable (66).

In a study conducted at Sweden, HRQoL was determined in the PCI patients using SF-36 and HADS questionnaires. An improvement in HRQoL at 1 year was noted for both men
and women, when compared with 5 months follow up after MI. Women reported scores on mental health (p<0.01) and men in physical health domain (67).

In a study conducted at Norway, the researchers were concluded that, the largest improvements were seen in scores related to physical functioning of SF-36 (mean overall change from baseline to follow-up was 6.9 points, p < 0.001) and lowest in the mental health domains (p<0.001)(68).

Study done by Kahler (69) et al., shows the improvement in the quality of life in both octogenarians and age group of 60-70, significantly in the physical abilities and decrease pain. In a study, assessing the dimension-specific burden of disease among cardiovascular diseases, problems with usual activities seems to be most common, followed by problems with mobility and pain (70).

Most of the researchers compared both CABG and PCI group of patients for HRQoL measurements. Hofer and colleagues reported that, the short and intermediate-term results revealed HRQoL differences between PCI and CABG in the month immediately after intervention despite the almost identical reduction in angina severity over the first month in both groups. PCI was associated with a relatively rapid increase in HRQoL in the first month, with little further change by 3 months (71).

Zhang et al reported that, both CABG and stent-assisted PCI resulted in significant improvement in angina-related health status at 6 months and 1 year after intervention (72).

Significant difference arises from better physical function for CABG patients than PCI patients. But, the mental health status remained similar in both groups (73).

HRQoL in both patients’ group was increased statistically significant by 6 months. No significant change in health-related quality of life took place in either group from 6 to 12 months (74).
In a multicentre study, patients with UA/NSTEMI and STEMI underwent percutaneous coronary intervention (PCI), along with evaluation of HRQoL. After PCI, both angina-specific and general HRQOL scores were improved, but improvement was much more frequent in angina-related HRQOL of patients with UA/NSTEMI than those with STEMI (44.2% v/s 36.8%, P < 0.001). At 30-days after PCI, angina-specific HRQOL of the patients with UA/NSTEMI was comparable to those with STEMI (P = 0.521), but general HRQOL was significantly lower after adjusting baseline characteristics (P < 0.001). The general health status of those with UA/NSTEMI was not good even after optimal PCI (75).
3.8 References


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