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Review Article

Myocardial Infarction: Background, Recent Advances, and Interventions Supported by Clinical Trial and Patent Landscape

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ABSTRACT

A total of 805,000 myocardial infarctions (MI)-related deaths occurred in the United States between 2005 and 2014, indicating that heart disease is still the country's leading cause of death. In quality review audits, gender and racial/ethnic discrepancies in MI diagnosis are becoming more pronounced. Even though recent modifications to diagnostic codes have improved the framework, it is still difficult to clinically distinguish between different forms of MI. Negative results in cardiac medicine are largely due to MI misdiagnoses and health inequities. We did a review of the relevant biomedical literature on the classification of MI and MI treatment approaches. Additionally, data from academic journals were gathered, and the clinical trials website was used to gain information about clinical studies. Utilizing databases from the USPTO (United States Patent and Trademark Office), EPO (European Patent Office), WIPO (World Intellectual Property Organization), and others, a thorough patent search was carried out. With a current worldwide prediction, the analysis validates the general progression and untapped areas of research on MI treatment techniques.

Keywords: Myocardial Infraction; Patent Database; Clinical trial.

INTRODUCTION

Infarction of the heart is one of the main causes of mortality and disability on a global scale. A heart attack is often referred to as a myocardial infarction (abbreviated as MI) or an acute myocardial infarction (abbreviated as AMI)[1]. It derives from the Latin phrase "infarctus myocardial," which translates to "heart attack." An MI happens when there is an obstruction in blood flow to a section of the heart, which results in damage to the heart muscle due to insufficiency of oxygen. One of the coronary arteries, which supplies blood to the heart, becomes clogged as a result of an unstable accumulation of plaques, fat, cholesterol, and white blood cells[2] When the condition becomes life-threatening, medical professionals refer to it as an "acute" myocardial infarction, or "acute" AMI for short. Myocardial infarction is known to be one of the five primary types of coronary heart disease (MI)[3]. In epidemiological studies, the incidence of coronary heart disease in a community can serve as a proxy for evaluating the burden of coronary heart disease in those people[4].

2. BACKGROUND- MI

2.1. Epidemiology

From an epidemiological point of view, the rate of MI that occurs within a community can serve as a stand-in for coronary artery disease prevalence within that population. In the world today, cardiovascular disease is the main cause of mortality, which accounts for 30% of all mortalities and 10% of all disease burden. This makes it a significant challenge to the public's health[5].

The prevalence of MI was reported to be 6.4 lakhs in men and 2.75 lakhs in females, for a total of around 9.15 lakh people in the United Kingdom who had suffered from MI, as per a self-reported nationwide survey that was done in 2014. This study was carried out in 2014. In 2013, the incidence of MI in males was approximately threefold higher in the United Kingdom[16]. According to Figure 1, the age-specific MI prevalence ranges from 0.06% in males under the age of 45 to 2.46% in men who were seventy-five years or more[6].

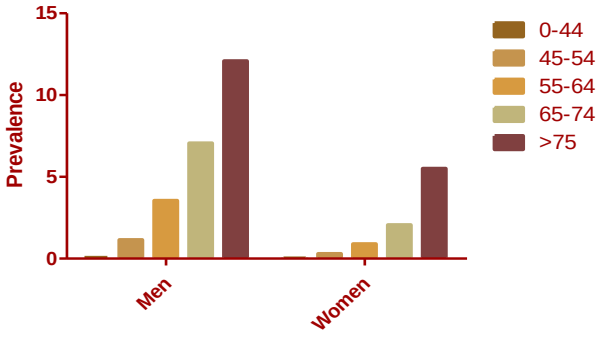

Figure 1: Prevalence of MI in Men and Women in comparison to age.

The percentage of adults in the UK who had an MI was based on their age in 2014. Datalink for Clinical Practice Research (CPRD) 2014. The evaluations are based on data collected from a representative sample of general practices located in each of the countries that make up the United Kingdom. In contrast to these affluent nations, South Asian nations (including India, Sri Lanka, Pakistan Bangladesh, and Nepal) have the largest proportion of MI in people under the age of 45 in comparison to people over the age of 60.

In the Mozaffarian Study, the occurrence of myocardial infarction was examined and contrasted between white men and women, black men and women, and black males and white women. The study found that the rate of myocardial infarction was significantly greater among black men in the age category of 75 to 84 years old (12.9/100,000 males) compared to white men (9.1/per 100,000 males) and women (7.8/per 100,000 females). Similar patterns can be seen across other age categories and their respective equivalents (Figure 2).

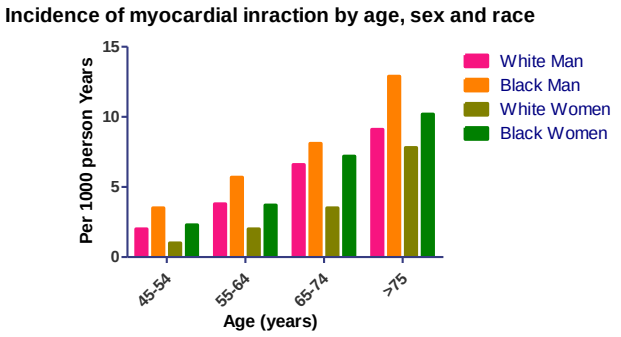

Figure 2: Incidence of MI by age, sex, and race.

The incidence of an MI in the USA in 2015, was broken down by age, gender, and race[7]. Statistics on heart disease and stroke, modified from the most recent version published in 2015: A report has been made available by the American Heart Association. It was hypothesized that the incidence rates of STEMI (per 100,000) would decrease greatly (from 121 to 77), and the incidence rates of NSTEMI (from 126 to 132) would decrease only a little[7]. According to the findings of a significant study, there was no significant difference in the overall mortality rate between STEMI and NSTEMI during the follow-up period of six months to four years. Individuals diagnosed with STEMI, on the other hand, had a worse long-term prognosis compared to patients diagnosed with NSTEMI [7]. According to the findings of other pieces of research[8], people suffering from NSTEMI have a greater 7-year fatality rate than STEMI patients[8]

2.2. Etiology

MI, more commonly known as a heart attack, happens due to constriction and obstruction of the coronary arteries by plaques, cholesterol, and fat deposits. This results in the formation of blood clots, which in turn restricts the flow of blood to the hear[9]t. The hardening of the artery walls is a symptom of atherosclerosis, a disease that can affect anyone. The accumulation of fatty substances in the coronary arteries is the primary cause of heart attacks[10]. A family history of heart disease, a spasm of the muscles that line the arterial walls, the narrowing of the arteries, emotional stress, strenuous activity or workouts, such as shovelling snow and being exposed to extremely cold weather or air, lifting heavy goods upstairs, or the misuse of drugs (cocaine or amphetamines) are also potential causes of a heart attack[11,12]

2.3. Types

There are typically two forms of MI: STEMI (where the ST-segment is elevated) and NSTEMI (non-ST-segment elevation MI). This type of myocardial infarction can be identified on an electrocardiogram (ECG). This classification is used quite frequently for patient populations who have chest ischemic symptoms to ensure that they receive immediate care, which may involve reperfusion therapy. On the other hand, there is a different categorization that is based on a global consensus and is divided into five categories[13]. This classification is more commonly used.

Type 1 (Spontaneous MI)-This type of MI is caused by a rupture, degradation, fissuring, or fragmentation of an atherosclerotic plaque. Intraluminal thrombosis and distal emboli can worsen it[14]. Plaque rupture can cause intraplaque hemorrhage[15].

Type 2 (Ischemic-related MI)- This MI is due to an imbalance in supply and demand for O2 to heart muscle shock, anemia, respiratory failure, bradycardia, arrhythmia, coronary artery spasm, and atherosclerosis[15]. Increased demand occurs in circumstances such as tachycardia lasting more than 20 minutes and systolic pressure over 160 mm Hg associated with ventricular hypertrophy[16].

Type 3 (Sudden unexpected cardiac death without cardiac biomarkers evidence.)- In this form, unexpected mortality, including cardiac arrest, occurs before a rise in cardiac biomarkers[17]. There are myocardial infarction symptoms, but no evidence[18].

Type 4 (Percutaneous coronary procedure-related MI)- This type of MI is linked to medical interference and can manifest in two distinct forms: type 4a, which manifests itself after percutaneous coronary intervention (PCI), and type 4b, which manifests itself after the placement of a coronary stent[19] This can happen during the surgery or at a later time; either way, it is an indication of a complication with the stent or device, such as stent thrombosis or restenosis[20]. Postmortem angiography or an autopsy can both be used to locate it[21].

Type 5 (Cardiac surgery-related MI.)- This kind of myocardial infarction is commonly seen after coronary artery bypass grafting[14]. According to research, CABG has a higher mortality rate than percutaneous coronary intervention (PCI)[22].

2.4. Risk Factors

Hypertension, Smoking, Dyslipidemia, Age, Gender, Angina, Gout, Physical activity, Social and economic circumstances, Alcohol consumption, Diabetes mellitus, and Family history[20,23–31].

2.5. Clinical Presentation

Pain in the chest and angina, especially in the absence of any other warning indications, are common symptoms of a heart attack. The term "silent heart attack" refers to a

situation in which a person has a small heart attack but no one notices it. The following are some of the signs that you may be having a heart attack:

Pain in the chest or high BP, a feeling of tightness, burning, squeezing, or chest heaviness that lasts for greater than 10 minutes, left shoulder or arm pain; pain that travels up into the neck or along the jawline; and shortness of breath[32–35].

Sweating and dizziness, weakness in the muscles, nausea or vomiting, difficulty breathing due to smoke inhalation, worry or stress, and sadness are among the symptoms of second hand smoke exposure[36,37].

On the other side, a silent heart attack does not present with any symptoms[11].

2.6. Pathophysiology

Myocardial infarction is caused by chronic ischemia. Coagulation and contraction band necrosis are pathological terminology for cell death, which usually results from oncosis but sometimes from apoptosis[38–41]. To identify these things, an expert must examine histological sections[42]. After cardiac ischemia begins, cell death occurs over time (as little as 20 min or less in some animal models)[43]. Myocardial necrosis isn't detectable until many hours after death. Necrosis of all at-risk myocardial cells takes 2-4 hours or longer, depending on collateral circulation to the ischaemic zone, persistent or intermittent coronary arterial occlusion, the myocytes' sensitivity to ischemia, pre-conditioning, and/or individual demand for myocardial oxygen and nutrients[43]. Microscopic (focal necrosis), small (10% of the left ventricular [LV] myocardium), moderate (10-30% of the LV myocardium), and large (30% of the LV myocardium) myocardial infarctions are common[16,21,44–47].

2.7. Diagnosis

Patients with a myocardial infarction or heart attack are treated at the emergency department. Myocardial infarction is diagnosed by risk factors, clinical characteristics, ECG abnormalities, and cardiac enzymes or biomarkers[11].

ECG or EKG measures the heart's beat or rhythms to identify improper blood flow to the heart. ECG shows MI presence and location. ST-segment elevation, aberrant Q wave, and T-wave inversion are ECG signs of MI[16]. Blood tests measure the number of proteins and lipids that could affect cardiac muscles[48]. Different proteins secreted by damaged myocytes, such as myoglobin, cardiac troponin T and I, CK, LDH, and others, can identify myocardial cell death. Higher levels of cardiac enzymes or biomarkers such as plasma troponin (T or I) are selective and sensitive. Elevated cardiac troponin levels indicate MI[49].

2.8. Complications

Unexpected death, Rate, rhythm, and conduction problems, Rupture of the heart, Failure of the heart, Angina Pectoris, Thromboembolism, pulmonary embolism, deep vein thrombosis, Pericarditis, Ventricular septal defect, Aneurysm of the vena cava, Papillary muscles ruptured, Dressler's syndrome, Depression and psychological difficulties[24,50].

2.9. Treatment

When someone is having a heart attack, the best course of action is to call an ambulance and get to the closest hospital as quickly as possible. If the person's heart rate has slowed down or stopped completely, cardiopulmonary resuscitation (CPR) or an electrical defibrillator should be delivered as soon as possible to start the heartbeat back up again[11]. Restoring and maintaining blood flow to the heart should start as soon as possible to reduce the risk of further injury to the heart's muscles.

The following treatments are among the most common ones used for people with MI:

1. Aspirin: The intake of aspirin as soon as possible is good since it will help in the process of breaking up the blood clot. The recommended dose is around 325 milligrams, and for optimal absorption, a chewable form is recommended. If it is not possible to give the medication orally, rectal suppositories could be used instead. If the patient has an allergy to aspirin, clopidogrel monotherapy is an alternative treatment option. It has been hypothesized that the use of a combination of aspirin and clopidogrel for the prevention of ischemic stroke is just as risk-free as the use of aspirin on its own. On the other hand, the combination has a lower risk, but it is connected to a higher risk of bleeding over three months when compared to taking aspirin by itself[51].

2. Oxygen therapy: Oxygen therapy should be administered to everyone suspected of having AMI (O2). You can either use a face mask or an endotracheal tube to deliver it to the patient. Because ischemic heart illness is brought on by a persistent disruption in the oxygen supply that is delivered to the myocardium, oxygen therapy is advised in situations of acute myocardial infarction (AMI). O2 supplementation has the potential to enhance myocardial oxygenation, hence reducing discomfort, shrinking the size of infarctions, and, as a consequence, lowering mortality rates.

3. Analgesics: Morphine is recommended for use and is commonly used to alleviate chest pain that is produced by the death of myocardial tissue. It is also utilized to minimize sympathetic activity that is linked with AMI. This particular kind of sympathetic activity is capable of causing myocardial overload in addition to vasoconstriction. Pethidine is still another painkiller that may be utilized for AMI patients. It is also known by the name meperidine, and it is a type of synthetic opioid. Within administering it intramuscularly, the analgesic effect begins to take effect after only 15 minutes[52].

4. Nitro-glycerine: Nitro-glycerine, also known as glyceryl trinitrate, is the medication that is prescribed most frequently to patients who have been diagnosed with angina or AMI. It accomplishes this by expanding blood

vessels, which leads to an increase in coronary blood flow. It is effective in restoring oxygenation to the area of the myocardium that has been damaged by ischemia[53,54].

5. Platelet P2Y12 receptor antagonists: Platelet P2Y12 receptor helps with haemostasis and thrombosis. It represents for adenosine diphosphate (ADP) chemoreceptor. STSMI is treated with platelet P2Y12 antagonists. Prasugrel, clopidogrel, and ticagrelor are antiplatelet medicines advised in this condition; the first two are irreversible receptor inhibitors[55]. Clinically, clopidogrel is the most common P2Y12 antagonist. Before or during percutaneous coronary intervention, 600 mg clopidogrel is suggested. Prasugrel and ticagrelor are more effective than clopidogrel in preventing cardiac events[56].

6. Anticoagulants: All STEMI patients should get antithrombotic treatment unless contraindicated. UFH is administered as a single bolus of 60 U/kg with a maximum dose of 4,000 U, followed by a 12-U/kg/h infusion with a maximum of 1,000 U/h. The goal is for the partial thromboplastin time (PTT) to be between 45 and 65 seconds. low molecular weight heparin (LMWH) is a suitable alternative to UFH for fibrinolysis[57].

It has higher bioavailability, a more constant dosage, better thrombin inhibition, less heparin-induced thrombocytopenia, and lower cost because seria Activated Partial Thromboplastin Time monitoring (aPTT) monitoring is not required. Other anticoagulants are used to prevent a recurrence, not to treat the condition. Dabigatran, a direct thrombin inhibitor, and anti-Xa treatments are among them (rivaroxaban, apixaban, and apixaban)[58]

7. Thrombolytic or clot-dissolving medications: In the first three hours after the onset of a heart attack, some drugs, including tissue plasminogen activator (tPA), streptokinase, and urokinase, are infused into the bloodstream to dissolve arterial blockages.

8. Antihypertensive medicines Medications such as beta-blockers, ACE inhibitors, and calcium channel blockers may be taken to bring down the patient's blood pressure and minimize the oxygen demand placed on the heart. The effects of these drugs may be amplified when used with diuretics.

9. Digitalis glycosides, such as digoxin, may be administered to improve heart muscle contraction in some circumstances.

10. Dopamine, which is also known by its chemical name dobutamine, is administered to patients to enhance blood flow to the heart and to strengthen the heartbeat.

Angioplasty: An angioplasty is a type of treatment that includes inserting a catheter, which is a long, thin tube with a deflated balloon at its tip, into the restricted part of the artery while the patient is under the influence of a local anaesthetic. Following this step, the balloon will be inflated, which will result in the plaque being compressed and the inner diameter of the blood vessel being increased. This will result in the blood being able to flow freely. This will result in blood being able to flow freely.

Coronary bypass surgery can be used to bypass clogged blood arteries and restore proper heart blood flow.

Electronic implants: To maintain powerful and regular contractions of the heart muscle, electronic implants like pacemakers and defibrillators are frequently inserted in the chest or the abdomen of the patient.

In extreme circumstances, when the cardiac tissues have been extensively damaged, a heart transplant may be required.

Reperfusion therapy:

Reperfusion therapy infuses blood. It restores coronary blood flow after AMI by passing through or around the occluded vesse[24]. It includes drugs and surgery. Medications include fibrinolytics, and surgery includes PCI and coronary bypass surgery. Reperfusion should be resumed quickly. Reperfusion interference at the proper moment can decrease myocardial damage and infarct size, reducing morbidity and death (McCoy et al, 2013). Fibrinolysis or PCI could be utilized to perfuse. PCI is desirable if angiography and PCI facilities are within 90 minutes of medical contact.

Alternatively, fibrinolysis could be utilized. Patients who have not been diagnosed with non-ST elevation myocardial infarction, on the other hand, should not be given the most recent fibrinolysis treatments. In this particular scenario, antifibrinolytics ought to be administered within the first half an hour of medical contact unless doing so would be unsafe. However, preparations for PCI could be made if they are deemed unsafe to use. The fibrinolytic enzymes alteplase, streptokinase, reteplase, and tenecteplase are a few examples. In conjunction with the usage of these medications, heparin treatment should be administered. Treatment with antiplatelet medications and anticoagulants given intravenously is recommended in every scenario. Before being released from the hospital, patients who have been diagnosed with AMI could be given prescriptions for aspirin, beta-blockers, high-dose statins, and/or an ACE inhibitor.

2.10. Prognosis and prevention

Even with treatment, there is always the possibility of dying from a myocardial infarction. Approximately 5–10 percent of people who have MI die within the first year after the occurrence of the circumstances that caused the MI. In addition to that, around half of them will require re-hospitalization within the same calendar year.

Two fundamental pillars support the approach to primary prevention of MI that is widely advocated and utilized. The first component is handled by healthcare systems, and it consists of living in a healthy environment and making healthy lifestyle choices. The second personal factor comes from the individuals themselves, and it consists of avoiding potential risk factors. These include refraining from

smoking and excessive drinking, adopting a new healthy dietary pattern, avoiding obesity, and treating underlying causes such as diabetes and hypertension[59].

A person can ward against a heart attack by keeping a close eye on their blood pressure, getting at least 30 minutes of activity every day, and working to reduce their overall body fat percentage[59]. If you are experiencing chest pain, take an aspirin tablet, and if you are experiencing anxiety or tension, go to a physician. Treatment with cardioprotective estrogens is recommended for women who are going through menopause[24,59].

3. CLINICAL TRIALS

3.1. Summary of clinical trials data

There is still no precise therapy or treatment for a full recovery from MI as of this writing. As a result, scientists are always coming up with novel medication molecules or technological advancements. Approximately 183 therapies are now undergoing various stages of clinical trials in response to the requirement [start date: 01/08/2002 to 05/10/2022]. Phase I studies included 9 trials, but Phase II studies included 50 interventions. The remaining 51 and 34 interventions were participating in Phase 3 and Phase 4 investigations, respectively, at the same time. Nearly 152 interventions have been finished, and more are in the recruiting stage. Nearly half of the clinical trials were funded by businesses, and the remaining half was split between institutions, groups, and people. Table 1 depicts a thorough summary of a few completed clinical trials.

Clinical Trial 1: Vorapaxar in Patients with Prior Myocardial Infarction Treated with Prasugrel and Ticagrelor.

Dual antiplatelet treatment with aspirin and a P2Y12 receptor inhibitor is crucial to preventing atherothrombotic events in MI patients. Ischemia recurrence rates remain elevated, which might be related to active platelet signaling pathways such as thrombin-induced platelet aggregation. Vorapaxar inhibits thrombin-mediated platelet aggregation by inhibiting PAR-1. FDA-approved for reducing thrombotic cardiovascular events in MI or PAD patients. Vorapaxar clinical trial experience has been virtually exclusively with clopidogrel, where vorapaxar effects with ticagrelor or prasugrel are mainly unknown. Vorapaxar is involved in an antithrombotic therapy regimen with a new P2Y12 receptor blocker and withdrawal of aspirin is another area of clinical interest since it can maximize ischemia protection while lowering bleeding risk. The proposed prospective, randomized, parallel-design, open-label trial investigated vorapaxar's pharmacodynamic effects along with antiplatelet therapy with a new P2Y12 receptor blocker (ticagrelor or prasugrel) with and without aspirin. This interventional phase 4 randomized study was started in February 2016 and was completed in January 2020. It included 130 participants with inclusion criteria which considered patients with a prior myocardial infarction within the previous two weeks to one year aged between 18 to 75 years who were free from bleeding and ischemic events. This study has concluded[60].

Clinical Trial 2: Antiplatelet Therapy Effect on Extracellular Vesicles in Acute Myocardial Infarction.

Myocardial infarction is caused by platelet activation and aggregation. The activation of platelets requires the presence of platelet P2Y12 receptors. Unknown anti-inflammatory effects are produced by blockers against the receptor P2Y12, which are well-known in secondary prevention of MI. Comparing ticagrelor, a new P2Y12 receptor antagonist, to clopidogrel, the prior standard of care for myocardial infarction patients, infection-related mortality was reduced. Pro-inflammatory and procoagulant platelet extracellular vesicles are released by activated platelets. The researchers believe that ticagrelor's stronger suppression of platelet vesicle release as compared to clopidogrel may account for the decrease in infection-related mortality in people receiving the medication. This investigation uncovered another way that ticagrelor works that could explain the reported clinical advantages in ticagrelor-treated patients. The research project was started on December 30, 2017, and continued until it was completed on December 30, 2019. The inclusion criteria were patients who were aged above 18 and underwent Percutaneous coronary intervention(PCI) with implantation of the stent due to first STEMI, or first NSTEMI, and those who were administered with a loading dose of clopidogrel. It was an interventional phase 4 randomized study wherein 60 participants took part. The research project has been finished[61].

Clinical Trial 3: Affordability and Real-world Antiplatelet Treatment Effectiveness After Myocardial Infarction Study

By balancing co-payments for clopidogrel and ticagrelor, the ARTEMIS study will evaluate the effects of co-payments reduction in a realistic multicentre, cluster-randomized clinical setting. ARTEMIS evaluated clinical outcomes, patient medication adherence, and prescribing trends. It was predicted that better adherence would result from lower out-of-pocket expenses for P2Y12 receptor inhibitors. Additionally, lowering the co-payments for both brand-name and generic antiplatelet medications may lower the risk of MACE. Greater adherence to a secondary preventative medicine based on evidence is part of the reason for this. Additionally, the decrease in MACE might be attributable to the use of more potent antiplatelet agents, which have been shown in randomized clinical trials to lower MACE, as provider decision-making regarding antiplatelet treatment will be primarily influenced by risk-benefit analysis rather than patient financial burden.

Table 1. Description of a few completed clinical trials on MI.

Rank	NCT Number	Title	Conditions	Interventions	Outcome Measures
1.	NCT02545933	Vorapaxar in Patients With Prior Myocardial Infarction Treated With Prasugrel and Ticagrelor	Myocardial Infarction	Drug: Prasugrel|Drug: Vorapaxar|Drug: Aspirin|Drug: Ticagrelor	Maximal Platelet Aggregation
2.	NCT01863134	Clinical Effects of Eptifibatide Administration in High-Risk Patients Presenting With Non-ST Segment Elevation Acute Coronary Syndrome (NSTE-ACS) Requiring Urgent Coronary Artery Bypass Graft Surgery in Short- and Long-Term Follow-up	Non-ST Elevation Myocardial Infarction	Drug: Eptifibatide|Drug: Placebo	Major Adverse Cardiac and Cerebrovascular Events (MACCE)
3.	NCT02931045	Antiplatelet Therapy Effect on Extracellular Vesicles in Acute Myocardial Infarction	Myocardial Infarction	Drug: Ticagrelor|Drug: Clopidogrel	Concentration of Platelet Extracellular Vesicles/ml|Concentration of Extracellular Vesicles Exposing Fibrinogen|Concentration of Extracellular Vesicles Exposing Phosphatidylserine|Concentration of Extracellular Vesicles From Endothelial Cells|Concentration of Extracellular Vesicles From Leukocytes
4.	NCT01519518	How Effective Are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention	Acute ST Elevation Myocardial Infarction	Drug: unfractionated heparin|Drug: Bivalirudin	Major Adverse Cardiac Events (MACE) in Terms of the Incidence of All-Cause Mortality, Cerebrovascular Accident, Re-infarction, and Additional Unplanned Target Lesion Revascularization|Type 3-5 Bleeding According to BARC (Bleeding Academic Research Consortium)Definition|CKMB Release Following Index Revascularisation Measured With a Single Estimation 12-18 Hours After the Procedure|Minor Bleeding: Type 2 Bleeding According to BARC (Bleeding Academic Research Consortium) Definition|Stent Thrombosis Rate (ARC Definite or Probable)|For Illustration, and to Allow Comparison With Existing Trials the Rate of Net Adverse Clinical Events (NACE), Combining the Primary Safety and Efficacy Outcomes|All Cause Mortality|Development of Thrombocytopenia|Door-to-first Device Time
5.	NCT02406677	Affordability and Real-world Antiplatelet Treatment Effectiveness After Myocardial Infarction Study	Cost Sharing, Acute Coronary Syndrome	Other: Study voucher card	Kaplan-Meier Cumulative Incidence Rate of Major Adverse Cardiovascular Events|Percentage of Patients With Long Term Non-persistence to P2Y12 Receptor Inhibitor|P2Y12 Receptor Inhibitor Selection
6.	NCT02548650	Vorapaxar as an Add-On Antiplatelet Therapy in Patients With and Without Diabetes Mellitus	Myocardial Infarction|Diabetes Mellitus|Peripheral Arterial Disease	Drug: Vorapaxar|Drug: Clopidogrel|Drug: Aspirin	Maximal Platelet Aggregation in DM|Maximal Platelet Aggregation in Non-DM

7.	NCT02224274	Antiplatelet Therapy After Cardiac Arrest	Cardiac Arrest|Postresuscitation Syndrome|Myocardial Infarction (ST-Elevation Myocardial Infarction and Non-ST-Elevation Myocardial Infarction)	Drug: Clopidogrel|Drug: Ticagrelor	VerifyNow P2Y12Test - Platelet Reactivity|VerifyNow P2Y12Test - % Inhibition|Multiplate ADP Test
8.	NCT01347580	A 30-Day Study to Evaluate Efficacy and Safety of Pre-hospital vs. In-hospital Initiation of Ticagrelor Therapy in STEMI Patients Planned for Percutaneous Coronary Intervention (PCI)	Myocardial Infarction|Segment Elevation Myocardial Infarction (STEMI)	Drug: Ticagrelor|Drug: Placebo	Thrombolysis In Myocardial Infarction (TIMI) Flow Grade 3 of MI Culprit Vessel at Initial Angiography (Co-primary Endpoint)|ST-segment Elevation Resolution Pre PCI â‰¥70% (Co-primary Endpoint)|1st Composite Clinical Endpoint|2nd Composite Clinical Endpoint|Definite Stent Thrombosis|TIMI Flow Grade 3 Post -PCI|ST Segment Elevation Resolution Post-PCI >= 70%|Thrombotic Bail-out With GPIIb/IIIa Inhibitors at Initial PCI|Major Bleeds Within 48 Hours|Minor and Major Bleedings Within 48 Hours|Major Bleeds After 48 Hours|Minor and Major Bleeds After 48 Hours
9.	NCT00257309	Thrombolysis Versus Primary Angioplasty for AMI in Elderly Patients	Acute Myocardial Infarction	Drug: Tenecteplase + UFH (+ clopidogrel, since 01/97)|Procedure: Primary angioplasty	Incidence of Death or Reinfarction or Disabling Stroke|Death/Reinfarction/Disabling Stroke at 30 Days
10.	NCT03207451	Vorapaxar on Thrombin Generation and Coagulability	Coronary Artery Disease|Peripheral Vascular Disease|Myocardial Infarction	Drug: Vorapaxar|Drug: Vorapaxar and Aspirin|Drug: Vorapaxar and Clopidogrel|Drug: Vorapaxar, Aspirin, and Clopidogrel	Effects of Vorapaxar on 15 Î¼mol/L SFLLRN (PAR-1 Activating Peptide) Induced Platelet Aggregation|Effects of Vorapaxar on Thrombin Induced Platelet-fibrin Clot Strength (TIP-FCS)|Effects of Vorapaxar on Von Willebrand Factor (vWF).
11.	NCT02212028	Pharmacological Effects of Crushing Prasugrel in STEMI Patients	Coronary Artery Disease	Drug: prasugrel	P2Y12 Reaction Units (PRU)|Platelet Reactivity Index (PRI)
12.	NCT00138034	APRICOT-3: Antithrombotics in the Prevention of Reocclusion In COronary Thrombolysis -3	Myocardial Infarction	Procedure: Percutaneous coronary intervention (PCI)	6-month Reocclusion|Composite of Death, Reinfarction, Stroke, and Revascularization at the Time of Follow-up Angiography
13.	NCT00736229	Intravenous Exenatide in Coronary Intensive Care Unit (ICU) Patients	Hyperglycemia|Acute Coronary Syndromes|Myocardial Infarction	Drug: Exenatide	Median Glucose Values From Steady State Through 48 Hours or Until Discharge.|Time to Steady State|Rates of Hypoglycemia and Severe Hypoglycemia|Serious Adverse Events (Death, Non-fatal Myocardial Infarction, and Non-fatal Stroke Through 30 Days)
14.	NCT03247738	Platelet Inhibition With Cangrelor and Crushed Ticagrelor in STEMI	ST-Segment Elevation Myocardial Infarction|Percutaneous Coronary Intervention	Drug: Cangrelor|Other: Placebo	Platelet Reactivity Measured by VerifyNow PRU|Platelet Reactivity Measured by Vasodilator-stimulated Phosphoprotein (VASP)

The interventional phase 4 randomized open-labeled trial was started on the 5th of June 2015 and included 11001 participants aged 18 years and above who were diagnosed with S T elevation myocardial infarction or non-S T elevation MI during hospitalization and the ones who were treated with a P2Y12 receptor blocker when enrolling having U.S. based health insurance coverage with prescription drug benefit. The study ended on October 23, 2017, and it was completed[62].

Clinical Trial 4: Influence of Morphine on Pharmacokinetics and Pharmacodynamics of Ticagrelor in Patients with Acute Myocardial Infarction.

The interventional phase 4 randomized parallel designed study aimed to determine whether or not the IV administration of morphine before administering ticagrelor in patients with STEMI and patients with NSTEMI altered ticagrelor and its active metabolite's plasma concentrations, and if or not it was related to any pessimistic impact on ticagrelor's antiplatelet effect. The number of participants involved in the study was 74. It began in August 2014 and ended in June 2015. The participants who could take part in the study were males or females who were not pregnant aged 18-80 years with a diagnosis of acute STEMI or acute NSTEMI. The study was completed as proposed[63].

Clinical Trial 5: Alirocumab in Patients With Acute Myocardial Infarction.

Alirocumab is an inhibitor of proprotein convertase subtilisin / kexin (PCSK9), and this Phase IV clinical trial is comparing its efficacy to that of a placebo when added to atorvastatin 80 mg, which is a high-intensity statin, to reduce levels of LDL cholesterol in patients who suffered an NSTEMI. This interventional phase 4, randomized, parallel-design trial was started in January 2017 and was completed in August 2018. The study was performed on 20 participants.

The inclusion criteria were patients with Acute type I (spontaneous) NSTEMI with an onset of symptoms within 12 hours of presentation, a duration of >15 minutes, and elevated cardiac troponin I levels, with or without electrocardiographic changes with the exclusion of ST elevation and those on treatment with high-intensity statin before admission with known LDL cholesterol ≥70 mg/dL within 12 months. The study was completed[64].

4. PATENT ANALYSIS

After the reclamation of publications, a search was continued for patent-related information on drug repurposing. Various jurisdiction's patent websites were utilized to excavate patent portfolios. Search the database with Title: (myocardial AND (infraction AND treatment)) OR (Abstract: (myocardial AND (infraction AND treatment)) OR Claims: (myocardial AND (infraction AND treatment))) and the Filters: Published Date = (*2002-08-01 - 2022-12-12.* A total of 124 patents were recorded and a few were mentioned in Table 2.

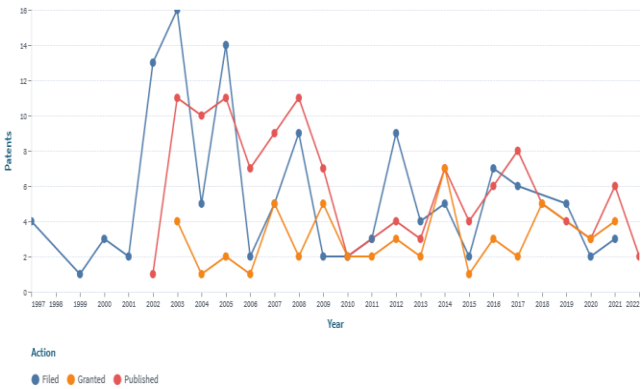

Figure 3: Patent documents by published, granted, and filed concerning year.

The total no of patent documents filed has increased enormously since 2002, owing to their applicability, but surprisingly, this followed a zigzag pattern after 2014 [Figure 3]. However, after 2017, a positive slope was observed to date. In a specific look at granted patents, both postie and negative slope was observed from 2013 to 2022. Country-wide sharing of these patents is given in Figure 4. United States ranked 1 with 51 patents followed by WO-WIPO with 30.

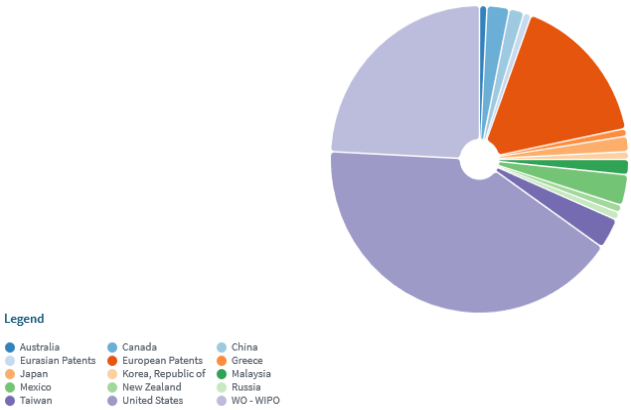

Figure 4: Patent documents by jurisdiction

The process of classifying patents according to their technical properties is known as patent classification. Earlier, this was only employed for document sorting. Through their technical classification, patents can be found in the most precise and best way possible. There are many different classifications in use across the globe, which may be related to each nation's unique or independent patent laws. Therefore, all the nations joined together and created a uniform code to consolidate patents. CPC (Cooperative patent categorization) and IPC were mostly used to categorize these (International patent classification). As an extension of IPC that is governed by the USPTO and EPO, CPC went into effect in Q4 of 2010 [10] [Figure 5].

Table 2: Summary of a few patents filed related to MI.

#	Jurisdiction	Publication date	Application number	Applicants	Title
1	Wo	05-06-2014	Kr 2012010353 w	Nat univ gyeongsang iacf	A composition comprising peroxisome proliferator-activated receptor delta agonist, as the active ingredient, for promoting the treatment of myocardial injury after myocardial infarction
2	Wo	18-08-2005	Us 2005/0003312 w	Decode genetics ehf;;helgadottir anna;;hakonarson Hakon;;gulcher jeffrey r;;gurney mark e	Susceptibility gene for myocardial infarction, stroke, and paod; methods of treatment
3	Wo	20-04-2017	Ep 2016066936 w	Pasteur institut;;univ paris descartes;;centre hospitalier sainte-anne paris	5-hydroxytryptamine 1b receptor-stimulating agent for the treatment of myocardial infarction
4	Us	25-10-2018	Us 201615768001 a	Pasteur institut;;univ paris descartes;;centre hospitalier sainte anne paris	5-hydroxytryptamine 1b receptor-stimulating agent for the treatment of myocardial infarction
5	Ep	20-08-2014	Ep 08703408 a	Mochida Pharm co ltd	Composition for prevention or treatment of disease associated with thrombus or embolus
6	Mx	19-04-2005	Mx pa02012316 a	Lotus Pharmaceutical co ltd	Uses of thaliporphine or its derivatives in the treatment of cardiac diseases and preparation of same.
7	Us	07-02-2008	Us 70189807 a	Univ edinburgh	Treatment of myocardial infarction with 11hsd1 inhibitors
8	Ep	30-07-2003	Ep 00915328 a	Hadasit med res service	Supar stimulating activity of tcupa-mediated fibrinolysis and different uses thereof
9	Us	23-11-2006	Us 36762806 a	Jacoby douglas b; dinsmore jonathan h	Catheter-based delivery of skeletal myoblasts to the myocardium of damaged hearts
10	Ep	20-07-2016	Ep 12761998 a	Tecnologias avanzadas inspiralia s l;;univ manchester;;inst chimii macromolecular;;ustav ex mediciny akademie ved ceske republiky v v i	New scaffold for cardiac patch
11	Us	12-08-2021	Us 201917264411 a	Diffusion pharmaceuticals llc	Diffusion-enhancing compounds and their use with thrombectomy embolectomy and other vascular disease procedures

12	Wo	31-03-2022	Us 2021/0052396 w	Georgia Tech res inst	Use of cystine and derivatives thereof as anti-thrombotic and thrombolytic agents
13	Kr	10-01-2019	Kr 20170083057 a	Univ ewha ind collaboration; univ inje ind acad coop found	Formulation of human-derived cardiac stem cell spheroids and application thereof
14	Ep	20-10-2021	Ep 20305372 a	Hopitaux paris assist publique;;inst nat sante rech med;;univ paris	Method of prognosis of left ventricular remodeling
15	Tw	01-04-2008	Tw 96144624 a	Arena pharm inc	Human g protein-coupled receptor and modulators thereof for the treatment of ischemic heart disease and congestive heart failure
16	Tw	01-01-2008	Tw 96125738 a	Arena pharm inc	Human g protein-coupled receptor and modulators thereof for the treatment of ischemic heart disease and congestive heart failure
17	Wo	21-10-2021	Ep 2021059878 w	Hopitaux paris assist publique;;inst nat sante rech med;;univ paris	Method of prognosis of left ventricular remodeling
18	Tw	21-12-2007	Tw 92120775 a	Arena pharm inc	Human g protein-coupled receptor and modulators thereof for the treatment of ischemic heart disease and congestive heart failure
19	Tw	01-07-2004	Tw 92120775 a	Arena pharm inc	Human g protein-coupled receptor and modulators thereof for the treatment of ischemic heart disease and congestive heart failure
20	Wo	27-03-2014	Ep 2012068648 w	Tecnologias avanzadas inspiralia s l 25;;univ manchester 25;;inst chimii macromolecular;;ustav ex mediciny akademie ved ceske republiky verejna vyzkumna instituce	New scaffold for cardiac patch

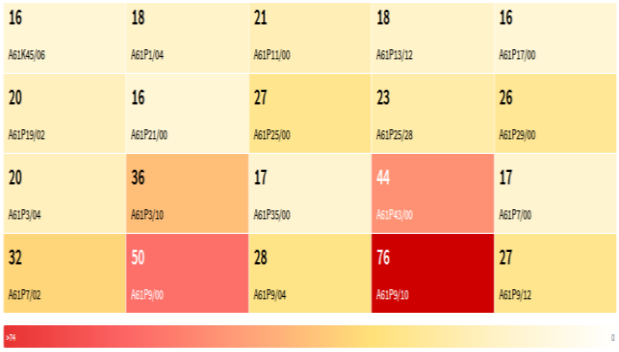

Figure 5: Top CPC classification codes with heat map.

A61K45/06 class has the highest number of patents [76] related to treating ischaemic or atherosclerotic diseases, e.g. antianginal drugs, coronary vasodilators, drugs for myocardial infarction, retinopathy, cerebrovascular insufficiency, renal arteriosclerosis. This was followed by A61P9/00, Drugs for disorders of the cardiovascular system. Drugs for specific purposes, not provided for in groups were patented along with A61P1/00 - A61P41/00.

4.1. Exploration of a few patents

5-Hydroxytryptamine 1b Receptor - Stimulating Agent for The Treatment of Myocardial Infarction.

Chretien Fabrice Bruno et al., invented 5 - Hydroxytryptamine 1b Receptor - Stimulating Agent For The Treatment Of MI, and this invention was patented with EP, WO, US jurisdictions[US 2018/0303772 A1]. It was published on October 25, 2018. The invention was related to MI. It was more particularly related to an agent stimulating, the 5-hydroxytryptamine 1B receptor, and to a composition comprising said agent, for use in the treatment of a patient having a myocardial infarction (MI). The invention also includes diagnostic and screening procedures. A pharmaceutical composition for treating a patient with myocardial infarction includes at least one 5-hydroxytryptamine 1B receptor (5-HT1 BR)-stimulating agent chosen from the class of antidepressants and migraine medications, as well as combinations and at least one pharmaceutically acceptable derivative, analog, isomer, metabolite, salt, solvate, clathrate, polymorph, and co-crystal thereof beta-blockers, antithrombotics, trinitrine, vasodilators, angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers, L-carnitine, lidocaine, calcium channel inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), therapeutic cells, and growth factors, as well as combinations of these substances and at least one pharmaceutically acceptable excipient. Pasteur Institut FR, Univ Paris Descartes FR, Centre Hospitalier Sainte Anne Paris filed the patent[65].

2. Treatment of myocardial infarction with 11 HSD1 inhibitors.

The patent titled 'Treatment of myocardial infarction with 11 HSD1 inhibitors' was published on February 7, 2008. The invention was patented with EP, GB, US, WO jurisdictions[US 2008/0033046 A1] with the inventors being Walker Brian R et al., The invention was related to the MI treatment utilizing blockers of a particular enzyme involved in the metabolism of glucocorticoid. A composition comprising, preferably consisting of, an inhibitor of 11HSD1 and one or more agents used in the routine MI treatment (Thrombolytic agents; Glycoprotein Iib0IIIa platelet inhibitors, calcium channel blockers, Antiarrhythmics: Amiodarone and Lidocaine, Unfractionated heparin (UFH) or LMWH, Nitrates, Angiotensin receptor blockers, ACE inhibitors, etc) and a pharmaceutically acceptable carrier, diluent and/or excipient is used for the treatment of myocardial infarction. This increases the left ventricular ejection fraction[66].

3. Traditional Chinese medicine for treating acute myocardial infarction combined with shock and preparation methods.

Guan Wenwen et al., invented. Traditional Chinese medicine for treating acute MI along with shock and preparation methods for treatment of myocardial infarction. This invention was patented with CN jurisdictions [CN 105748931 A] and was published on July 13, 2016. The invention provided traditional Chinese medicine for treating acute MI along with shock and a preparation method. The traditional Chinese medicine comprised of Phlomis likiangensis, nodding chrysanthemum, daphniphyllum root, Herba pimpinellae, phytolacca flower, Indian abutilon root, abutilon, borneolum, combined spicebush fruit, bisagra, limax, Tetracera asiatica, Argyreia osyrensis, trachycarpus root, Polygonum senticosum, Hibiscus llutabilis, decumbent bugle herb, Cremanthodium hookerii clarke, granolithic, Lysimachia insignis, Radix spiranthis lanceae, and Chinese forgetmenot herb. Traditional Chinese medicine has had the advantages of being capable of cooperating with conventional comprehensive methods of Western medicine to treat acute myocardial infarction combined with shock, better in treatment effect, free of toxic and side effects and adverse reactions, and simple in preparation process[67].

4. Use of Glp-1 Or Analogs in Treatment of Myocardial Infraction.

The patent titled. The use of Glp-1 or analogs in the treatment of MI was invented by Efendic Suad and published on September 28, 2007. That invention was patented with CN, EP, AT, IL, EA, MY, DK, CA, NZ, WO, NO, HU, AU, CZ, RS, DE, PT, KR, YU, BR, JP, US, HK, ES, PL jurisdictions[MY 131796 A]. With the help of this invention, myocardial infarction mortality and morbidity can be decreased. A dose of glp-1, a glp-1 analog, or glp-1 derivative, is given to help normalize blood sugar levels. Lilly Co Eli filed the patent[68].

5. Method and Pharmaceutical Composition for Use in The Treatment And Prediction Of Myocardial Infraction.

Mallat Ziad *et al., invented* a Method and pharmaceutical composition for use in the treatment and prediction of MI and published it in May 2014. This invention was patented with WO jurisdictions[WO 2014/064192 A1]. The method according to the invention comprises the steps of I

determining the expression level of MCP-3 in a sample from the patient, ii) comparing said expression level with a predetermined reference value, and iii) providing a good prognosis of the survival time or of the recurrence of a MI of a patient who had previously suffered from a myocardial infarction. The substance used in the invention also prevented MCP-3 from binding to CCR2, CCR1, or CCR3, or it inhibited the gene expression or signaling pathways for MCP-3, CCR2, CCR1, or CCR3 to be used in the treatment of myocardial infarction[69].

6. Susceptibility gene for myocardial infarction, stroke, and PAOD; methods of treatment.

The patent titled ' Susceptibility gene for MI, stroke, and PAOD; methods of treatment was invented by Gurney Mark E et al., and was published on the 18th of August 2005. The invention was patented with AU, WO, CA, JP, EP jurisdictions [AU 2005/210657 A1]. Decode Genetics Ehf filed a patent on January 31, 2005. A region on chromosome 13q12 was linked to myocardial infarction (MI). In particular, a genetic association study revealed that the FLAP gene at this locus is a susceptibility gene for MI, ACS, stroke, and PAOD. Particularly, pathway targeting for therapeutic and diagnostic purposes in determining those who were at risk of developing MI, ACS, stroke, or PAOD was outlined. The innovation also included leukotriene synthesis inhibitor-containing formulations, as well as instructions on how to use them to lower C-reactive protein in people who are at risk for MI, ACS, stroke, and/or PAOD [70].

7. Uses of Thaliporphine Or Its Derivatives In Treatment Of Cardiac Diseases And Preparation Of Same.

Lee Shoeisheng et al. invented the patent titled 'Uses of Thaliporphine or its derivatives In the treatment of cardiac diseases and preparation of same which was patented with RU, CA, IL, AU, MX, BR, HU, CN, EP, PT, DE, DK, WO, ZA, AT, KR, JP, ES jurisdictions [MX PA02012316 A]. This was published on April 19, 2005. The innovation made thaliporphine and its derivatives available for the treatment and/or prevention of cardiac disorders, such as cardiac arrhythmia, myocardial ischemia or infarction, and sudden cardiac death brought on by an acute myocardial infarction or cardiac arrhythmia. On February 28, 2001, Lotus Pharmaceutical Co LTD submitted a patent [71].

8. Catheter-based delivery of Skeletal Myoblasts to the Myocardium of Damaged Hearts.

The patent titled 'Catheter-based delivery of skeletal myoblasts to the myocardium of damaged hearts' was invented by Jacoby Douglas B et al., and was published on November 23, 2006. The invention was patented in US jurisdictions. [US 2006/0263338 A1]. The innovation offered better systems and techniques for treating heart tissue loss, damage, and/or deficiency minimally invasively, particularly in patients with illnesses marked by inadequate cardiac function, such as CHF or MI. Preferably, the cell transplantation was performed after identifying a region of the subject's myocardium in need of treatment. The inventive procedure, which can be repeated several times over time, results in improved structural and/or functional properties of the region treated, as well as improved overall cardiac function. In particular, inventive therapeutic methods may be performed on patients who have previously undergone CABG or LVAD implantation[72].

9. New Scaffold for Cardiac Patch.

Saint-Pierre Guillaume et al. invented a New Scaffold for a Cardiac Patch and the invention was patented with EP, PL, WO, US, JP, ES Jurisdictions [WO 2014/044321 A1]. In their invention, they created a biocompatible and biodegradable medical device patch made of natural and synthetic polymers, with the natural polymer chosen from chitosan, sodium alginate, and cellulose, and the synthetic polymer chosen from a group including polylactic acid, glycolic acid, lactone, polyglicerol sebacate, and copolymers of synthetic polymers and combinations thereof. It featured a layered construction, with the first layer acting as a suturing layer and mechanical support for a thick porous scaffold that could be covered in an extracellular matrix that mimicked a tissue (ECM). The end-user was able to receive services from this device in the form of separate layers that could be cut and put together according to their requirements. The layers were put together without the use of any tools. No adhesive was required for the layer assembly. Completely hemocompatible and acts better than polytetrafluoroethylene, which is utilized to repair any soft tissue. Cardiovascular therapy is one use of this technology, but it shouldn't be restricted to that discipline. Tecnologias Avanzadas Inspiralia S L 25 filed a patent on and published on July 20th,2016[73].

10. Use of Cystine and Derivatives Thereof as Anti-Thrombotic and Thrombolytic Agents.

Kim Dongjune et al. invented the patent titled 'Use of cystine and derivatives thereof as Anti-Thrombotic and Thrombolytic agents'. This invention was patented with WO jurisdictions [WO 2022/067248 A1] and was published on the 31st of March 2022. the patent was filed by Georgia Tech Res Inst on September 28, 2021. The invention provided compositions that have had anti-thrombotic and thrombolytic activity. These compositions were useful in the disease treatment or disorders associated with thrombus formation, such as stroke and myocardial infarction, and for other uses. The treatment required cystine, or a pharmaceutically acceptable salt or derivative thereof, in a quantity effective to induce thrombolysis in patients. The cystine is N, N'-diacetyl-L- cystine which is substantially pure and free of N- acetylcysteine. It was available in tablets, and liquid dosage form, and was normally administered through oral or IV route. Cystine was administered in combination with a lytic agent.[74].

5. CONCLUSION

To summarize the current manuscript, we have reviewed the different drugs/compositions, scholarly articles, and patent data for MI. Treatments under various phases of clinical trials were elaborated with a particular focus on

Phase 4. Owing to the high market value of MI drugs (US$ 1,816.8 Mn in 2021), considerable interest was attained to grab the opportunities. Several research groups and industries have made great efforts in inventing various technologies/therapies to treat MI. This can be evident from the significant number of patents filed from 2002 to date. Many inventions were filed on methods/devices to improve the effectiveness of MI treatment. Many of these inventions were granted, as they were proven as efficient models in treating MI. Even though many of these are still unable to gain public acceptance because of many unanswered issues. Hence, there will always be substantial scope to work on MI-related research/inventions

6. CONFLICTS OF INTEREST:

The authors declare no conflict of interest.

8. FUNDING:

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