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Novel Potential Targets of Type 2 Myocardial Infarction

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Malik Usama[1], Prabhavalkar Kedar*[1]

[1]Dr Bhanuben Nanavati College of Pharmacy, Vile Parle, Mumbai, Maharashtra-400056 India.

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ABSTRACT

AMI type 2 is also referred to as NSTEMI. Type 2 myocardial infarction (T2MI) is caused by a myocardial oxygen demand /supply mismatch without the presence of an acute thromboembolic plaque rupture, and it has a poor short- and long-term prognosis. Individuals with T2MI have a significant mortality rate, which reaches over 50% after two years. Young people who suffer from type 2 MI have a greater long-term all-cause and myocardial death rate than type 1 MI patients. These findings highlight the importance of more active secondary prevention and possible treatment options for type 2 MI patients. The factors that contribute to T2MI are numerous and complicated. Release of reactive oxygen species, activation of myocardial cell death and myocardial stunning are involved. Further cardio protection is necessary in order to protect the heart from myocardial infarction, especially T2MI. In this review, the role of TRPV1, MicroRNA-497, TRPA1, Interleukin-6 antagonism, LRP1, Amyloid-β (1-40), lncRNA MEG3, PAD4, circMACF1, TNAP as a potential therapeutic target in T2MI will be thoroughly presented. Due to a wide variety of factors, their implementation into clinical practise has been largely unsatisfactory. With new evidence on cardio protection in NSTEMI accumulating over the last several years, it is critical to emphasise fresh therapeutic targets and assess the efficacy of "old" cardio protective strategies.

INTRODUCTION

T2MI is a disease condition in which myocardial cells die as a result of oxygen supply and demand imbalances. Which occurs in the absence of acute a theroembolic plaque disruption is called type 2 myocardial infarction (T2MI).This condition is mainly associated with adverse long-term and short-term prognoses. Because cardiac troponin tests are becoming more sensitive, this syndrome is becoming more common.[1]Coronary artery spasm, anaemia, hypotension or hypertension, arrhythmias, and coronary embolism are the major causes of type 2 myocardial infarction (T2MI).In individuals suspected of having a myocardial infarction, non-invasive imaging can help.[2]

Non-invasive imaging techniques include echocardiography, radionuclide imaging, magnetic resonance imaging, and X-ray computed tomography, which are helpful in the diagnosis of type 2 myocardial infarction (T2MI) and various cardio-vascular disorders. While high-sensitivity cardiac troponin testing is most commonly used. As per the Universal definition of Myocardial Infarction, the development of more sensitive cardiac troponin tests has resulted in an increase in the detection of myocardial damage in acute diseases other than acute coronary syndrome.[3]It might be hard to differentiate between type 2 and type 1 AMI in clinical practice. Because so many other non-ischemic diseases are linked to myocardial injury and troponin increases. Such non-ischemic diseases are septic shock and myocarditis. And much of the literature contains variations in the prevalence rate of type 2 myocardial infarction, which ranges from 1.6% to 29.6%.[4]Cardiac troponins are the most specific and sensitive biomarkers for non-ST-elevated acute coronary syndrome because they often rise within a few hours of the onset of symptoms and remain elevated for several days. Cardiac troponin T (cTnT) and cardiac troponin I (cTnI) have varied correlations with health outcomes, which mainly include particular cardiovascular disease outcomes. But it's unclear whether cardiac troponin I (cTnI) and cardiac troponin T (cTnT) are in this scenario, risk indicators are equivalent. Cardiac troponin I (cTnI) is a protein that is most commonly found in the heart, and it seems to be a more specific risk factor for composite CVD and coronary heart disease. Whereas cardiac troponin T has been more significantly linked to the risk of non-CVD mortality. Cardiovascular troponins I (cTnI) and T (cTnT) have both been linked to heart failure and cardiovascular mortality.[5]

T2MI is also known as non-ST elevated myocardial infarction (NSTEMI) because electrocardiogram results in type-2 AMI were found to be consistent with NSTEMI in 97

percent of patients. There is no potential cause for ST elevation. While STEMI has potent causes like myocarditis and many more other pathological conditions.[6] Non-traditional ECG characteristics such as QRS duration (QRSd) and QRS pattern are now being studied as prognostic indicators for myocardial infraction. In various pathological conditions, such as Non-ST Elevated Myocardial Infarction (NSTEMI), coronary artery disease (CAD), are shown some significant changes in the QRS pattern and QRS duration (QRSd) due to cardiac remodelling, which is done by the heart muscles to compensate for the myocardial loss after myocardial infarction. Cardiac remodelling leads to a lower left ventricular ejection fraction (LVEF).Various studies show that patients with lower left ventricular ejection factor (LVEF) had higher QRS duration (QSRd) at the time of non-ST elevated myocardial infarction (NSTEMI).So that involvement of the coronary artery and a decrease in the left ventricular factor are mainly predicted by the increase and decrease in the QRS duration (QRSD).The normal range of the QRS duration is QRSd≥ 90 ms at the time of non-ST elevated myocardial infarction. In further studies, during the measurement of the QRS duration its find that, at baseline the individuals with higher the rate of QRS duration at (27% vs. 18%; p b 0.045) had sever LV dysfunction.[7]In some cases, type 2 myocardial infarction (T2MI) is also associated with coronary heart disease having more mortality risk factors, and the absence and presence of coronary artery disease (CAD) may influence the outcomes of myocardial infarction, according to SWEDEHEART (Swedish MI Registry).The main mechanism behind the pure supply reduction is due to various pathological conditions like coronary spasm, coronary embolism, coronary endothelial dysfunction, and spontaneous coronary artery dissection, but these pathological conditions do not occur due to obstructive coronary artery disease. And there are some pathological conditions like tachyarrhythmia and severe hypertension that enhance the oxygen demand of myocardial tissue. On the other hand, reduced supply of oxygen to myocardial tissue is also associated with some pathological conditions, for example, severe anaemia, severe hypotension, severe hypoxia, and Brady arrhythmias. So, during the diagnosis of type 2 myocardial infarction (T2MI), it is found that the development of T2MI occurs due to heterogeneous causes.[8]In further studies, it has been shown that during the clinical diagnosis of type 1 myocardial infarction and type 2 myocardial infarction, some groups of patients having elevated troponin levels do not meet the diagnostic criteria of T1MI and type 2 myocardial infarction (T2MI).In such cases, those individuals who do not meet the diagnostic criteria are frequently discharged with a wide range of clinical diagnoses, including necrosis without MI, myocardial damage, and, moreover, their prognosis is unknown.[9]

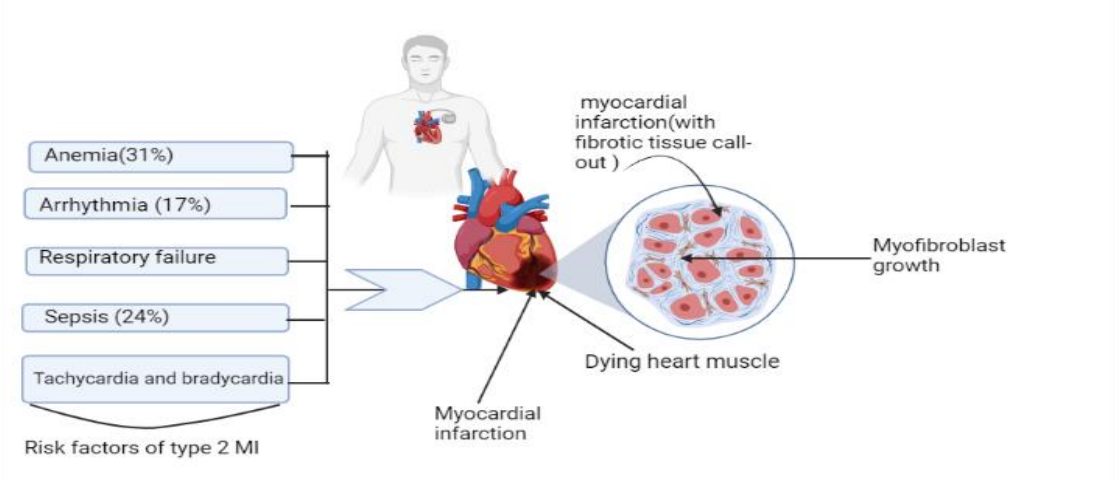

Fig. No. 1.risk factors and histopathological changes during T2MI

NOVEL POTENTIAL THERAPEUTIC TARGETS

a) TRPV-1(transient receptor potential cat ion subfamily V member 1):

After acute myocardial infarction (MI), a primary driver of ventricular arrhythmogenesis (VAs) is cardiac adrenergic stimulation (sympathoexcitation).The heart is innervated by the autonomic nerve, which is the sympathetic nerve by which cardiac sympathetic afferent reflexes (CSAR) are passed and which are involved in the transmission of nerve impulses and the sympathetic responses to acute myocardial infarction (MI).In particular, cardiac sympathetic afferent reflexes of the heart (CSAR) are primarily increased in a variety of chronic pathological conditions such as failing heart and myocardial infarction. CSAR's afferent limb is mediated in part by fibres that express the transient receptor potential cat ion subfamily V member 1 (TRPV1) channel. For example, some metabolites, such as capsaicin and bradykinin, are involved in TRPV1 activation. These metabolites are produced by ischemia and heat. Chronic pain is also linked to TRPV1 afferent signalling. While in rats, chronic heart sympathoexcitation induced by persistent TRPV1 afferent transmission causes negative remodelling.[10]Previous studies have shown that left stellate ganglions (LSG) are mostly found in front of the sixth and seventh cervical vertebrae and are involved in the regulation of the ventricular rhythm of the heart, as well as involvement and changes in the left stellate ganglions of the cervical vertebrae in the ventricular arrhythmias that result from myocardial infarction.[11] Left stellate ganglion (LSG) are considered a significant factor to malignant VAs in individuals with ischemia myocardial damage. Cardiac autonomic abnormalities include increased LSG activity, sympathetic hyper excitability, and parasympathetic degeneration. In the current investigation, Vanilloid 1 has a transient

receptor potential (TRPV-1) as cat ion channels are non-selective and are found in numerous neural tissues, and was shown to be abundantly expressed in the tyrosine hydroxylase (TH) positive neurons of LSG. So, using a suitable down regulator of transient receptor potential vanilloid 1 (TRPV-1) can protect the heart against non-ST elevated myocardial infarction by suppressing cardiac electrophysiological instability and cardiac autonomic imbalances.[12]TRPV1 may help prevent heart disease from myocardial damage by activating the PI3K/Akt signalling pathway, which has anti-apoptotic properties. Because several metabolites resulting from various physiological processes that accumulate after myocardial infarction may activate TRPV1.Early activation of TRPV1 may protect the heart from subsequent severe damage. Furthermore, During T2MI, TRPV1 activation enhances heart systolic and diastolic function recovery. Program cell death is also known as apoptosis, which has a crucial role in myocardial damage. Thus during T2MI, inhibiting apoptosis in myocardial cells may limit cell loss and reduce heart damage. Bcl-2 and Bax are important regulators of apoptosis. Because Bcl-2 and Bax are proteins linked to apoptosis. Furthermore, the ratio of both the proteins and their expression as a regulator in apoptosis.

According to a prior study, TRPV1 deficiency has been linked to an increased risk of death, an intensified inflammatory response, increased cardiac fibrosis, and accelerated LV remodelling seven days after myocardial infarction.[13]In animal studies using both pigs and rats, specific myocardial afferent denervation with a powerful TRPV1 agonist, reseniferitoxin (RTX), attenuated CSAR-evoked sympatho-excitation and mitigated the detrimental consequences following myocardial infarction. In these investigations, it shows that the TRPV1-positive myocardial impulses mostly go via the heart's superficial layer so that RTX is applied to the heart as a pericardial injection. Whereas this medication reduces the number of myocardial spinal afferent fibres in the heart. It also increases the chance of mild to severe epicardium injury if cardiomyocytes have TRPV1 receptors.[14]In general, TRPV1 can operate as a broad sensor for cellular stressors, especially hypoxia, in addition to the conventional activation by pain.[15]As per the pathophysiology of type 2 myocardial infarction (T2MI), which results from hypoxia or lack of oxygen supply to the heart muscle, hypoxia conditions lead to the generation of reactive oxygen species due to activation of various types of enzymes such as (NADPH).The generation of reactive oxygen species is responsible for the degeneration of cardiac muscles by damaging the genetic materials of the cell.[16]On the other hand, (TRPV1) uses calcium to modulate cellular responses to heat, noxious stimuli, and heat.TRPV1 is found in cardiomyocyte mitochondria and modulates mitochondrial

membrane potential via its interaction with calcineuri. Calcineurine is a serine/threonine protein phosphatase that is calmodulin-dependent.[17]Hypoxia causes myocardial damage due to the interaction of TRPV1 and calcineurin. So this interaction can be inhibited by using V-1 cal. By using these data to conclude that TRPV1 is a cardio-protective end-effector, and that altering the (TRPV1) protein's interaction with calcineurin reduces myocardial damage.

b) MicroRNA-497:

MiRNA is a form of non-coding RNA that has just recently been investigated but has the potential to govern a wide range of biological processes**.** According to various research papers, MiRNA is linked to a variety of cardiovascular disorders such as myocardial arrhythmia, myocardial infarction, myocardial fibrosis, hypertension, and myocardial hypertrophy.[18]Previous research found that miR-497 inhibited tumour growth in a variety of malignancies, including gastric cancer, cervical cancer, and lung cancer.[19]As per the studies, MiR-497 was shown to be abundant in heart tissue and MiR-497 up regulation increased myocardial apoptosis and hindered autophagy flow, while miR-497 silencing decreased myocardial apoptosis and boosted autophagic flux. So, inhibition of endogenous MiR-497 causes the suppression of myocardial cell apoptosis. A decrease in myocardial infarct size results from the suppression of myocardial cell apoptosis through targeting autophagy gene microtubule associated protein 1 light chain 3 B (LC3B) and g B cell lymphoma 2 (Bcl-2).[20]MiR-497 is sometimes used as a novel biomarker in the investigation of acute myocardial infarction because the expression level of MiR-497 and other biomarkers in the blood is elevated in acute myocardial infarction, indicating the presence of type 2 myocardial infarction.[21]Further research on the MiR-497, which is also commonly found in brain cells, is needed. And various experimental results in cerebral ischemia conditions also indicate that, increasing MiR-497 level may successfully attenuate CIS rats' brain injuries. Furthermore, in animal studies, reducing miR-497 can enhance functional outcomes after ischemia in rats by increasing neuronal autophagy.[22]As per the various research papers, it is found that, MiR-497most commonly exerts its activity by direct targeting the various therapeutic pathways such as the ERK signalling pathway (extracellular regulated protein kinase) and mitogen-activated protein kinase (MAPK) which are most commonly involved in the expression of the respective RNAs, and promotes cell apoptosis. Moreover In cells, overexpression of miR-497 significantly reduced ERK expression at both the mRNA and protein levels. There are various pathological conditions such as cardiac reperfusion injury and myocardial ischemia conditions that are also developed by MAPK/ERK pathways, and all these consequences

MiR-497 is responsible for.[23] In case of T2MI, apoptosis is one of the factor which involve in the apoptotic myocardial cell death. Which occurs due to oxygen demand mismatch. So by modulating MiR-497 is helpful in the decreasing myocardial cell death by mitogen-activated protein kinase (MAPK) pathways.[24-27] And MiR-497 serve as potential therapeutic target for T2MI.

c) TRPA1(transient receptor potential ankyrin 1):

Recent research has shown that transient receptor potential ankyrin 1 (TRPA1) has been shown to have a role in cardiovascular disorders**.** And as per the various research, TRPA1 is a nonselective calcium ion channel having a large conductance with high calcium permeability, and is found in many tissues of the cardiovascular system. Transient receptor ankyrin 1 (TRPA1) is most commonly present in sensory neurons, which are found throughout the body, and it mediates hyperalgesia and pain.[28] Furthermore, it is found that, the level of TRPA1 is also increased in the T2MI MI myocardial injury and using a suitable inhibitor of TRPA1 leads to improved cardiac function by reducing LVIDs and LVIDd and also improving LVFS and LVEF values in a dose dependent manner. Reduction in the infarct size and suppression of myocardial fibrosis is also done by inhibiting the (TRPA1) receptor present in the myocardial tissue.[29] Cardiac fibroblasts (CFs) are a kind of cell that maintains the homeostasis of the extracellular matrix of the heart, and CFs trans differentiate into cardiac myofibroblasts (CMFs) after being stimulated by myocardial infarction (MI) and play an important part in the fibrotic healing process. Cardiac myofibroblasts (CMFs) result from the differentiation of the cardiac fibroblasts, which requires cytokines, neurohumoral signals, and mechanical signals. Injured heart tissue contains a variety of signals that are helpful in the differentiation of cardiac fibroblasts. Furthermore, for the differentiation of the cardiac fibroblast, a suitable initiator is required. TGF- is a one-of-a-kind initiator of cardiac fibroblast differentiation.[30] Signalling pathways are grouped into two types: non canonical and canonical. And TGF- stimulates intracellular signalling via both canonical and noncanonical mechanisms, by which produces a protective effect on the heart from myocardial fibrosis through DYRK1A, which is required for the proper functioning of the CaN-NFAT, which results in cardiac fibroblast differentiation. Cardiac fibroblasts most commonly form after 3 to 6 hours of type 2 myocardial infarction T2MI.[31] According to the study, 33 TRP channel members are most commonly found in mammals and are classified based on the amino acid present on them. These members of TRP can be determined based on variations in amino acid sequence homology. TRPA, TRPV, TRPC, TRPP, TRPML, and

TRPN are the seven subfamilies of TPR channels.[32]Type 2 myocardial infarction is a multifactorial disease, and one of the factors which leads to the development of type 2 myocardial infarction is oxidative stress. The resultant component of the oxidative stress is reactive oxygen species, which leads to the degeneration of cell components of the heart. Some metabolites act as endogenous activators of TRPA1 in the heart. Endogenous agonists that are responsible for the TRPA1 activator are generated during lipid peroxidation.[33]TRPA1 is most commonly found in the pericardium, myocardium, and endocardium of murine cardiac muscles, where it colocalizes with TRPV1 at the z-disc, costameres, and intercalated disc in cardiomyocytes, according to previous research.[34]As per the various research studies, activation of both TRPA1 and TRPV1, which results in a transient increase in intracellular calcium [Ca^{2+}] level in a dose dependent manner, increases the contractile response via a CaMKII-dependent pathway.[35]As per the study, oxidative stress is a primary etiological factor involve in the T2MI. Activation of TRPA1 is done by oxidative stress.So that modulation of TRPA1 in T2MI might be helpful in the decreasing of myocardial fibrosis through Dual-specificity tyrosine phosphorylation-regulated kinase 1A(DYRK1A). Furthermore, TRPA1 serve as potential therapeutic target T2MI.

d) Interleukin-6(IL-6):

Despite contemporary treatments, Type 2 myocardial infarction (T2MI) is still the most common cause of heart failure, a condition that is linked with high morbidity and mortality worldwide.[36,37]Therefore, targeting the proinflammatory cytokine interleukin-6 (IL-6) is one such method, according to many lines of evidence. Furthermore, there are various interleukins that play various physiological and pathological roles in various pathological conditions. One of the interleukins that is known as cytokine interleukin-6 (IL-6) has been linked to vascular inflammation, the breakdown of the fibrous cap, and the onset and development of atherosclerosis, all of which contribute to plaque instability. As per the research, in the case of IL-6, it has been found to be elevated at the site of coronary blockage in individuals with ST-elevation MI (STEMI). It's also been claimed that IL-6 levels may be used to identify people with unstable coronary artery disease who would benefit more from an invasive procedure.[37,38] Various clinical trials were conducted to determine the role of interleukin-6 (IL-6) in the pathophysiology of non ST elevated myocardial infarction (NSTEMI). One of the clinical trials is based on, 117 individuals with non–ST-segment-elevation MI (NSTEMI), who were given a single dose of the human anti–IL-6 receptor (IL-6R) monoclonal antibody (Ab) tocilizumab (TCZ), which resulted in lower troponin-T levels

(Trop-T) and C-reactive protein. As a result, reductions in troponin-T (Trop-T) and C-reactive protein indicate cardio protection in type 2 myocardial infarction.[39]Troponin-T (Trop-T) and C-reactive protein levels are reduced by modulating interleukin-6 (IL-6) via two distinct signalling pathways, Trans signalling and classic signalling. In classic signalling, IL-6 initiates intracellular signalling by attaching to its membrane-bound a-receptor, which further binds with a dimer of the receptor b-subunit glycoprotein 130 (gp130). Only cells that express membrane-bound IL-6R, such as leukocytes and hepatocytes, are stimulated by traditional signalling.[40]While trans signalling is accomplished via IL-6 binding to a circulating soluble version of the receptor (sIL-6R), followed by the IL-6/sIL-6R complex attaching to a membrane-bound gp13 dimer, Because gp130 is widely expressed, IL-6 can stimulate all tissues regardless of whether or not they express membrane-bound IL-6R.Furthermore, tocilizumab medication reduces inflammation, in particular PCI-related troponin T release in patients with NSTEMI. In addition, tocilizumab's suppressive effect was accompanied by a substantial drop in TnT, which was inversely associated with changes in high-sensitivity C-reactive protein, indicating a relationship between inflammation and myocardial damage in these individuals. As per many research papers, the role of interleukin-6 is very critical in the development of cardiovascular diseases such as myocardial infarctions, coronary artery diseases, and sometimes as interleukin 6 (IL6) is an upstream inflammatory mediator that plays a critical role in the onset and advancement of the atherosclerotic process as a mediator propagating the inflammatory response. Furthermore, sometimes interleukin-6 is considered a biomarker along with various other biomarkers. Because of their elevation in various pathological conditions, So, interleukin-6 (IL-6) is also considered as an upstream inflammatory marker.[41]Furthermore, as per the research, the multifunctional cytokine interleukin-6 (IL-6) is generated by a variety of cells, including those in the cardiovascular system. So, binding of IL-6 to the membrane-bound form of the IL-6 receptor (IL-6R) causes the receptor subunit glycoprotein 130 (gp130) to homo dimerism, resulting in a high-affinity functional receptor complex comprising IL-6, IL-6R, and gp130.[42]Furthermore, IL-6 is a secondary downstream mediator of apical cytokines like IL-1 in inflammation. But in the case of non ST elevated myocardial infarction (NSTEMI), inhibition of interleukin-6 primarily leads to attenuating acute inflammatory responses and reducing troponin T (TnT) release as a secondary goal.[43]Certain drugs which are commonly used in the treatment of acute coronary syndrome (ACS) (e.g. gpIIb/IIIa-inhibitors) are also involved in attenuating IL-6 levels in type 2 myocardial infarction.[44]As a secondary goal, reduce troponin T (TnT) release. Tocilizumab does not interact with IL-6, but it prevents it

from interacting with its receptors by inhibiting both membrane-bound and soluble IL-6R. further In patients with autoimmune diseases, a comparable increase in IL-6 levels has been seen after the injection of tocilizumab, which appears to represent reduced IL-6 removal from the blood due to decreased IL-6R-mediated clearance produced by tocilizumab-mediated IL-6R blockage.[45]Furthermore, according to a randomised double-blind placebo-controlled trial In patients with non-ST-elevation myocardial infarction (NSTEMI), a single dose of tocilizumab reduced inflammatory response and percutaneous coronary intervention (PCI)-related troponin T (TnT) release.[46] So that by modulation ofIL-6 with suitable inhibitor are useful in the treatment of (T2MI) myocardial infarction. So that as per the above information, IL-6 is serve as potential therapeutic target for T2MI.

e) LRP1 (Low-Density Lipoprotein Receptor–Related Protein-1):

LRP1 (low-density lipoprotein receptor–related protein-1) is a ubiquitous membrane receptor that functions as both a scavenger and a regulator, activating anti-inflammatory and pro-survival signals.[47,48]While removal of cellular debris requires an inflammatory reaction as a result of tissue damage, Expression rises in response to hypoxia, ischemia, and tissue damage. Moreover, LRP1 is a nonselective plasma protein receptor that binds to a variety of proteins that are mainly found in heart muscles. LRP1 is also known as the A2MG receptor. Because LRP1 is a kind of receptor found in the body.[49]Cholesterol molecules make up about half of the lipid composition of the bilayer of the cell membrane. Despite the fact that all cells in the body have the biochemical machinery for cholesterol production. As per the varied research, the majority of the cholesterol requirements are met by the absorption of plasma lipoproteins by cellular membranes receptors such as low-density lipoprotein receptors (LDLR).Other receptors, such as scavenger receptor-class B type I and LDL receptor-related protein 1 (LRP1), also have the potential to absorb lipoprotein. Furthermore, increased demand for cholesterol in rapidly proliferating cells doubles all cell membranes. Mitochondrial, plasma, nuclear, and organelle membranes are known as rapidly dividing cells. These cells are provided by the overexpression of lipoprotein receptors, which allows for the absorption of greater levels of lipoprotein cholesterol.[50,51]As per some research papers, LRP1 is a multiligand-binding protein that is not selective for lipoproteins. LRP1 has a role in a variety of biological processes, such as regulation of signalling pathways and endocytosis. Activation of extracellular matrix metalloproteinase (MMP) is similarly influenced by LRP1.Under hypoxia conditions, LRP1 causes MMP-9 activation in human vascular smooth muscle cells and extracellular matrix components and is also involved in the modulation of

the extracellular signal-regulated kinase (ERK) pathway. These are all critical steps in the LV remodelling procedure.[52]As per the previous research, lipoprotein receptor expression was elevated in the infarcted region of infarcted rats with LV dysfunction. By demonstrating that in the ischemia region, the presence of three receptors indicates that lipoproteins are enhanced. In addition, the capacity of LRP1 to stimulate Akt and ERK1/2-dependent survival pathways protects cardiomyocytes against death. Cell viability is essential for LRP1 signalling. LRP1 has been identified as a major regulator of extracellular matrix remodelling, which is linked to increased morbidity and mortality following a heart attack. Furthermore, inflammatory mediators up regulate sterol regulatory element-binding protein (SREBP)-1, which lowers LRP1 levels in human macrophages. In mouse macrophages, inflammatory mediators have also been shown to have the ability to up-regulate SREBP-1 levels. In addition, Reduced LRP1 levels in neutrophils and macrophages may be due to the inflammatory state that characterises infarct sites one day after T2MI.Furthermore, macrophages with low LRP1 levels may contribute to the worsening of the inflammatory process, since LRP1 deficiency has been linked to increased MMP-9, MCP-1, and TNF-a production in atherosclerosis.[53]Previous studies have shown that myocardial LRP1 is considerably up-regulated in ischemic regions during the fibrotic phases of remodelling following MI, coinciding with increases in myocardial fibroblast proliferation. It is widely established that in response to particular stimuli, cardiac fibroblasts adopt a myofibroblast like phenotype and that this acquired phenotype plays a vital role in heart remodelling after MI.[54]

f) Amyloid-β (1-40) (Aβ40):

Protein conformational abnormalities are identified by abnormal peptide aggregation. Alzheimer's dementia (AD) is distinguished histopathologically by the presence of aggregated amyloid in the form of neurofibrillary tangles and senile plaques of the microtubule-binding protein tau. Amyloid b has two most common isoforms, Ab-40 and Ab-42, which present a possible therapeutic target for Alzheimer's disease (AD).[55]Various research papers state that in clinical cardiology, the risk classification of patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) remains a serious difficulty. In further studies, Amyloidb-(1-40) (Ab40) and (1-42) proteolytic components of a bigger protein are known as peptides. The amyloid precursor protein (APP), which is found in typical Alzheimer's disease brain amyloid deposits and is broken down by b- and gamma-secretases, is present in typical Alzheimer's disease brain amyloid deposits. Evidence

suggests that Ab40 a peptide with proinflammatory and prothrombotic characteristics, has a function in cardiovascular disease.[56]Endothelial cells in plaque microvasculature also included APP, although they did not display as much as neovessels in thrombi. In comparison to perivascular macrophages, there is immunoreactivity. Furthermore, expression of Ab and platelet phagocytosis are linked to cytokine production as evidenced by colocalization with iNOS and COX-2 activity in perivascular cells. In those with stable CAD, higher Ab40 concentrations in the body are connected to an increased risk of cardiovascular incidents and a combination of death or ACS.[57]Recent studies demonstrated that patients in the highest Abeta40 category had a risk of CV mortality that was more than three times higher and a risk of MACE that was much more than two times higher than individuals in the lowest category. Excitingly, A beta 40 showed a non-graded response in conjunction with CV events, with the biggest reaction in the upper percentile. It must have been recently discovered that when the myeloid scavenger receptor CD36 binds to fibrillar amyloid, it activates a signalling cascade that promotes the activation of microglia in the brain and the generation of inflammatory mediators. Because this receptor is important in the pathophysiology of T2MI and atherosclerosis.[58]Increased vascular stiffness in HF causes poor ventricular-vascular coordination and has been linked to mortality. High Ab40 levels may also have a role in the aetiology of atrial fibrillation, which affects about one-third of HF patients. Furthermore, the presence of HF and vascular disease raises Ab40 levels. Finally, Ab40 can operate as an inflammatory stimulator, activating monocytes and causing a significant rise in tumour necrosis factor and matrix metalloprotease-9 production, all of which are implicated in myocardial remodelling in T2MI. According to the New York Heart Association functional class, Ab40 levels rose as HF deteriorated. Reduced cerebral blood flow and neurohormonal stimulation might both contribute to neurovascular unit dysfunction. Resulting in an Ab40 build up in HF. However, blood levels of Ab40 in the current investigation seem to be more than three times greater than in individuals with stable coronary artery disease and T2MI.[59,60]

g) long non-coding RNA maternally expressed gene 3 (lncRNA MEG3):

In cardiac diseases, LncRNAs regulate vascular formation and modulate myocyte contraction phenotype, hypertrophy, mitochondrial activity, and apoptosis.[61]High-throughput sequencing methods have recently led to the discovery of multiple unique transcripts that are identical to mRNAs but are not translated into proteins. These transcripts are known as long non coding RNAs (lncRNAs).[62] Several lncRNAs, including, CARL, MIAT, APF, and MDRL, have been demonstrated to influence cardiomyocyte mortality following MI.[63]There are more than

200 nucleotides in their genomes. Meg3 was recently discovered to be a new regulator in cardiac tissue that regulates T2MI via direct interaction with the RNA-binding protein FUS (fused in sarcoma). Meg3 is substantially enriched in both the mouse and the human heart. Indicating that it may have a function in cardiovascular physiology and disease. (MEG3) is found on human chromosome 14q32 in a region having approximately 1.6 kb of nucleotides. ROS has also been shown to activate ERS, which is implicated in the CHOPWnt pathway. As long as there is persistent ischemia, ROS and ERS might establish a positive feedback loop, causing additional myocardial harm such as apoptotic induction. According to several studies, early repolarization syndrome is involved in the activation of myocardial apoptosis after a heart attack.[64]According to growing data, the abnormal expression of TRPV4 has been linked to the development of cardiac disorders. For example, TRPV4 was highly elevated in the (H/R) paradigm compared to normal groups cultivated in hypoxic conditions and accelerated cell damage in cardiac ischemia/reperfusion. According to the findings of this study, MEG3 modulated TRPV4 expression via miR3253p to prevent hypoxia-induced damage. The findings revealed that through sponging miR3253p, MEG3 may regulate TRPV4 to enhance hypoxia-induced damage in AMI. Despite the fact that the functions of MEG3 miR3253p and TRPV4 have already been established.[65]MEG3 Regulates gene expression in vascular endothelium, allowing it to govern cellular ageing and promote angiogenesis via interactions with EZH3 and JARID2. In addition, Meg3 modulates the production of matrix metalloproteinase-2 (MMP-2) in vitro in a P53-dependent way, and the lncRNA Meg3 displays significant expression in adult myocardial fibroblast.[66] In vivo, researchers discovered that inhibiting Meg3 preventively is cardio protective, resulting in lower MMP-2 expression and activity, reduced fibrosis and hypertrophy, and improved diastolic function. In addition to controlling Mmp-2 expression, Meg3 is thought to regulate the expression of additional genes associated with cardiac fibrosis growth and vascular disease. Furthermore, Meg3 knockdown has been shown to significantly enhance TGF-transcriptional activity in BT-549 human epithelial cells via epigenetic processes. In vitro suppression of Meg3 resulted in down regulation of TGF-isoforms in CFs, which was verified in in vivo research. This impact of Meg3 suppression on TGF expression might help to improve the preventative action against cardiac fibrosis.[67,68]

h) Peptidyl arginine deiminase4 (PAD4):

PAD4 is a 663-amino-acid protein found in human myeloid leukaemia HL-60 cells. PAD4 contains distinct N- and C-terminal domains, including two immunoglobulin-like components

in the N domain. Subdomain 1 (residues 1-118) has two calcium binding sites, whereas subdomain 2 (residues 119-300) has three.[69]Peptidyl arginine deiminases (PAD) are a family of enzymes that convert peptidyl arginines to peptidyl citrullines in target proteins. PAD4 can be found in the nucleus as well as the cytosol. It is mostly found in leukocytes. PAD4 citrullination of histone H3 (CitH3) is a post-translational nucleosome alteration essential for NET formation.[70,71]NET formation begins with the stimulation of the NOX complex, neutrophil elastase (NE), myeloperoxidase (MPO) and PAD4 follows the stimulation of neutrophils by recognising stimuli. PAD4 enhances chromatin proteolysis by catalysing the citrullination of histone proteins. ROS causes the nuclear membrane to gradually separate and lose its integrity, allowing extracellular chromatin to leak through the membrane holes and promoting nuclear fission. Extracellular traps are formed when cells are lysed and DNA, citrullinated histone (citH3), and some other intracellular components are liberated. According to several studies, NETs play a role in the development of autoimmune disorders, cancers, and other illnesses. Various members of the PAD group have been found, namely PAD1, PAD2, PAD3, PAD4, and PAD6, whose genes are grouped in the mouse and human genomes and have comparable sequences. Numerous studies have looked into PAD expression in various organs, both at the mRNA and protein levels. Each isotype is used to have a tissue-specific pattern of expression. In several investigations, PAD1 has been found in the uterus, pancreas, colon, and thymus. PAD2 appears to be widely expressed as it has been found in a variety of tissues, most notably leukocytes. PAD3 has been shown to be found in the skin, hair follicles, central nervous system, and intestine. PAD4 has been discovered in leukocytes (including lymphocytes), including the brain, colon, kidney, pancreas, spleen, and various tumours and hearts.[72, 73]Ischemia of the infarct region occurs immediately after a T2MI. Ischaemic tissue passes through a dynamic process that involves several biological processes and intricate histological alterations, such as inflammatory cell infiltration, cardiac destruction and apoptosis, and infarcted area growth.[74]In the current investigation, PAD4 expression is considerably increased in response to T2MI damage, and it can be decreased using the PAD4-specific inhibitor GSK484. Researchers found substantial penetration and deposition of leukocytes, especially neutrophils, inside the infarcted and adjacent regions after MI induction. Furthermore, in the infarcted region, there has been apparent vascular endothelium apoptosis as well as substantial disarray of heart muscle fibres. As demonstrated by substantial reductions in neutrophil infiltration, cardiomyocyte rectified liquefactive tissue damage, and heart muscle fibre disorganisation. GSK484 treatment significantly reduced neutrophil permeation, cardiomyocyte rectified liquefactive

tissue damage and heart muscle fibre disorganisation. PAD4 induction and stimulation is assumed to be a key facilitator of nuclear protein H3 citrullination, since citrullination of histone H3 is a critical step in NET production. PAD4 is now the only PAD enzyme found in the nucleus.[75,76]

i) circMACF1 (circMicrotubule Actin Crosslinking Factor 1):

Circular RNA (circRNA) is well acknowledged to play a role in cardiovascular and pulmonary disorders. Because the mammalian transcriptome contains a lot of circular RNA (circRNA). According to recent studies, CircRNA is involved in the control of transcriptional, translational, and post-transcriptional activities such as RNA processing, genetic rearrangement, chromosomal alteration, and X chromosome silencing.[77]In recent times, circular RNA (circRNA), a unique kind of endogenous noncoding RNA (ncRNA), has been a subject of great interest. CircRNAs are common and stable in living things, and they have chemically closed loop structures that distinguish them from linear RNAs. A growing number of researchers have discovered that circRNAs play an important role in gene regulation. They have also identified the processes of various circRNAs in diseases, implying clinical therapeutic potential.[78]CircMACF1 is a prominent lncRNA that has been recently found. CircumMACF1 has been demonstrated to be significantly down regulated in heart tissue and primary cardiomyocytes that have been damaged by ischemia. When circMACF1 was overexpressed, it decreased apoptosis and caspase-3 activity as compared to the NC group. According to in vivo investigations, overexpression of circMACF1 raised LVFS and LVEF, decreased LVEDd and LVESd, lowered CK-MB, LDH level, and myocardial infarct size, and prevented apoptosis. Myocardial apoptotic inhibition is seen as a critical treatment target for T2MI. This finding suggests that circMACF1 might help enhance cardiac performance after a T2MI by preventing apoptosis.[79]MiRNA is the most researched non-coding RNA type as a target of circRNA, and it can govern differentiation, cell proliferation, and death by suppressing target mRNA translation. In a vast number of studies, miRNA-133, miRNA-1, miRNA-499, and miRNA-208 have all been found to be useful indicators for myocardial damage in T2MI.[80]According to the research, circMACF1 has a target gene called miR500b-5p. Furthermore, Circulating miR-500b-5p and miR-500b-5p are co-transfected. When MACF1 was introduced, the protective action of circMACF1 on cardiomyocytes was virtually reduced. According to the findings, circMACF1 may reduce myocardial apoptosis by regulating miR-500b-5p.[81]The epithelial membrane protein 1 (EMP1) gene is found on chromosome 12's long arm and codes for a glycoprotein with four transmembrane areas.[82]It

participates in a variety of intercellular signalling pathways, including cell cycle control, proliferation, and differentiation. There has been little research on AMI. In primary cardiac myocytes overexpressing EMP1, miR-500b-5p expression has been drastically reduced, while overexpression of circMACF1 corrected the negative effects of miR-500b-5p overexpression on EMP1 expression. The protective impact of circMACF1 overexpression on myocardial apoptosis has been partially abolished when miR-500b-5p has been overexpressed or EMP1 has been down regulated. It implies that circMACF1 might have been a potential T2MI therapy gene.

j) Tissue nonspecific alkaline phosphatase (TNAP):

After a myocardial infarction, cardiac fibrosis is the most common aetiology that leads to cardiac remodelling and heart failure. Tissue nonspecific alkaline phosphatase (TNAP), a key regulator of bone and vascular calcification, is essential for cell differentiation and metabolism.[83]An excessive accumulation of extracellular matrix proteins inside the heart causes cardiac fibrosis, which leads to cardiac dysfunction. Cardiac fibroblasts (CFs) seem to be the main effector cells at this stage. CFs that express phenotypically α-smooth muscle actin (α-SMA) can proliferate, migrate, and transform into myofibroblasts.[84]Cardiovascular calcification (CVC) is linked to an increased risk of morbidity and death. It appears in a variety of disorders and sites, including the tunica intima of atherosclerotic plaques. It is also found in the tunica media of type 2 diabetes, chronic renal disease, and aortic valves. CVC is mostly caused by processes that are similar to those that arise during intramembranous ossification. TNAP is a good target for limiting CVC since that is the primary enzyme involved in skeletal and dental mineralization. TNAP has a role in the metabolism of pyridoxal phosphate. For example, the synthesis of neurotransmitters TNAP is also an anti-inflammatory kinase that can dephosphorylate adenosine nucleotides and lipopolysaccharide.[85,86]AMPK signalling is critical in the control of fibrosis. In CFs, inhibiting TNAP increased regulation of AMPK1/2 at Thr183/172. The AMP-hydrolysing function of TNAP, which has been validated in experiments in several types of cells and can be abolished by a TNAP pharmacological inhibitor, might represent the mechanism behind AMPK activation.[87]According to Gowans et al., AMP is a real physiological modulator of AMPK, activating it allosterically and increasing net phosphorylation.[88]Because TNAP hydrolyses AMP, inhibiting TNAP increased AMPK signalling in CFs, which was most likely mediated by a shift in AMP concentration. As per various studies, it also showed that inhibition of TNAP might be helpful in the treatment of myocardial fibrosis. TNAP inhibition

reduces cardiac fibrosis caused by type 2 myocardial infarction (T2MI) via activating P53 and deactivating TGF-1/Smads signalling pathways. TNAP suppression substantially reduced expression, migration, and differentiation of collagen-related genes. Furthermore, TGF-1/Smads signalling inhibition, as well as p-AMPK and p53 overexpression, were all engaged in the process. According to the various research papers, TNAP inhibition may be a new regulator in cardiac fibrosis after (T2MI), with anti fibrotic effects mediated mostly through AMPK-TGF-1/Smads and p53 signalling.[89-93]

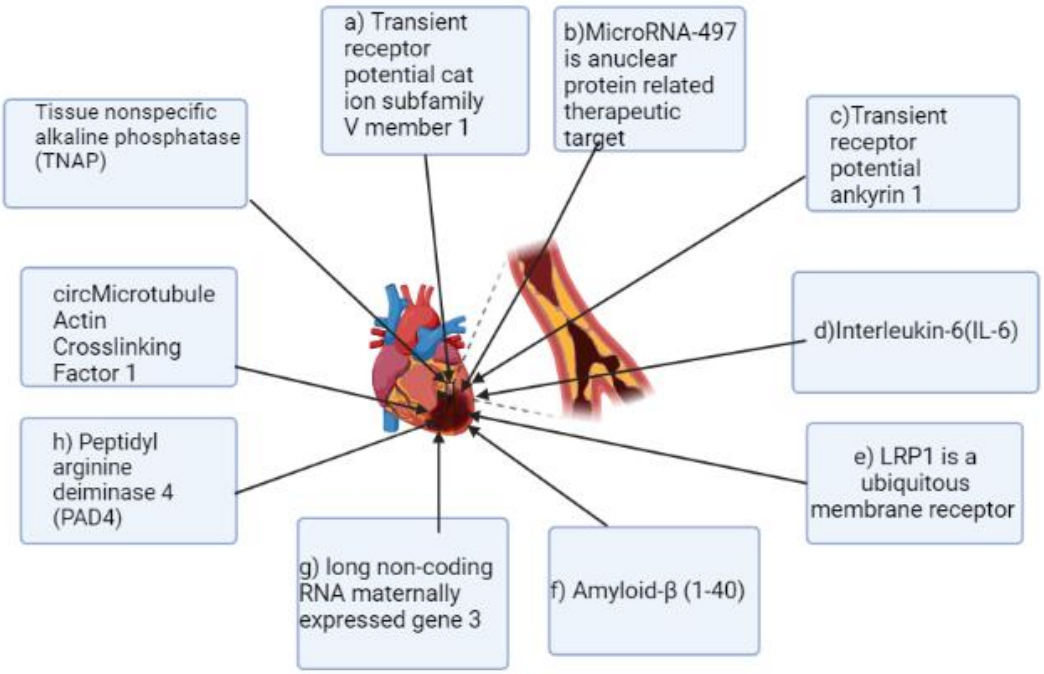

Fig. No. 2 Various potential therapeutic targets and infarcted heart.

CONCLUSION:

Accumulating evidence suggests that transient receptor potential cat ion subfamily V member 1,MicroRNA-497,Tissue nonspecific alkaline phosphatase, circMicrotubule Actin Cross linking Factor 1, Peptidyl arginine deiminase-4, long non-coding RNA maternally expressed gene 3, Amyloid-β (1-40), Low-Density Lipoprotein Receptor–Related Protein-1, Interleukin-6, transient receptor potential ankyrin 1are potential therapeutic targets for T2MI. Cardiovascular disorders are multifactorial, in which T2MI have high mortality rate worldwide. In this review, we discuss in detail fora better understanding of these targets and there pathways may leads to the design of new class of therapeutic agents. Which are helpful in the attenuating the progression of T2MI.

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