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Review Article

Cardiac Biomarkers: A Beneficial Tool in the Diagnosis and Prognostification in Heart Failure- A Focus on Rheumatic Heart Disease

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Abstract

Globally, 26 million people are affected by Heart failure (HF). Greater number of morbidity and mortality due to cardiovascular diseases are reported as a growing problem worldwide.

A biomarker provides valuable information beyond the available clinical tools, as it reflects the pathophysiological mechanism involved and helps the clinicians in making decisions on patient management. Assessment of cardiac biomarkers has established its role in the routine evaluation and treatment of HF patients.

In the field of cardiology, biomarkers levels have a significant impact on the patient management, diagnosis, in assessing the degree of heart failure and to predict the developing cardiac dysfunction in Acute and Chronic Rheumatic Heart Disease. Despite the array of current biomarkers, technological advancement in molecular biology, cell biology and biochemistry, there remains a knowledge gap.

Ultimately, it is a combination of biomarkers and other parameters like Cardiac Imaging proves them as one of the most beneficial tool in diagnosis and risk stratification in Heart failure. A given biomarker can be a prognostic marker and should be more specific with improved calibration, discrimination and reclassification.

In this review article, the role of cardiac biomarkers like Galectin 3, Gelsolin, Matrix Metalloproteinase-9 (MMP-9), NT pro BNP (N-Terminal pro Brain Natriuretic Peptide), Procollagen Type I C Peptide (PICP), soluble Suppression of Tumorigenicity (sST2), Tenascin C (Tn C) in different cardiac conditions causing Heart Failure like Rheumatic Carditis, Rheumatic Heart diseases, Coronary Artery Diseases, Adults with Congenital Heart Diseases are enumerated in brief.

Keywords: *Cardiac biomarkers; Heart Failure; Rheumatic Heart Disease; PICP; Tenascin C; Soluble ST2; Predictive Marker*

Introduction

Globally, 26 million people have been affected by Heart Failure. Clinical history, symptoms and signs have limited value in diagnosing Heart Failure [1]. Greater number of morbidity and mortality due to cardiovascular diseases are reported as a growing problem worldwide, leading to Heart Failure [2].

Approximately one-third of deaths are due to cardiovascular diseases (CVD). Deaths before the average life expectancy are known as premature deaths and cardiovascular disease (CVD) are the leading cause of them. There is an expected increase in premature deaths from 5.9 million in 2013 to 7.8 million in 2025 and the global action plan is to reduce these premature deaths to 25% by 2025 [3]. Assessment of cardiac biomarkers has established its role in the routine evaluation and treatment of Heart Failure patients [4].

Acute myocardial infarction (AMI) may lead to Heart Failure [5]. Valvular Heart Disease (VHD) may be due to genetic, infectious, inflammatory, autoimmune and oxidative stress as a multifactorial process [6]. Measurement of sST2 early after AMI assists in the prediction of medium-term LV functional recovery [7].

Apart from CAD major healthcare problem is due to untreated Group A β-hemolytic streptococcal pharyngitis and it often occurs with the complication Acute Rheumatic Fever (ARF).Nearly 12 million people suffer from Acute rheumatic fever globally [6,8].

In developing countries, the most common cause of Valvular Heart Disease is Rheumatic**.** Significantly higher levels of N-Terminal pro-Brain Natriuretic Peptide (NT pro BNP) was found in children suffering from acute rheumatic carditis whereas Gelsolin plasma isoform levels were decreased in the patients of acute rheumatic carditis [6,9,10].

Rheumatic Heart Disease (RHD) leads to Heart Failure which can be chronic or acquired. Global prevalence of RHD is 15.6 million cases, documented with demanding deaths of 233,000 each year. Diagnosis of Rheumatic Carditis prior to pathological valve insufficiency is a clinical challenge [8,11]. Biomarkers helps to identify them at the earliest.

A Significantly high concentration of PICP was observed in RHD patient group when compared to Rheumatic Fever (RF) and pharyngitis. Increased MMP-9 activities may be possible diagnostic markers in RHD. The Tenascin C levels were significantly higher in Chronic Rheumatic Heart Disease group than the control group [11-13].

World Health Organization (WHO) Global Burden of Disease has recognized RHD as a Neglected Tropical Disease (NTD). In India, 30 - 40% of cardiovascular disease are due to RHD [8].

Approximately 1 in 100 births suffer from congenital heart defects and 1 in 500 births suffer from critical congenital heart defects (CCHDs) [14]. MMP-2, MMP-9 were increased in the circulation in conditions like TOF (Tetralogy of Fallot), post atrial switch operation and after Fontan procedure [15]. PICP levels also elevated in the TOF repair patients when comparing it with the control population [16].

Congestive Cardiac Failure is a major progressive health problem globally. Hence novel approaches for early diagnosis and treatment are needed**.** Heart Failure can be prevented by early interventions and modification of risk factors. Prediction of the onset of Heart Failure can be done with measurement of Galectin-3 [5,17].

Therefore, it is mandatory for identification of potential biomarkers. These biomarkers should help us to recognize the risk factors of HF onset, identify the HF at early pre-clinical stages and to advance the treatment protocol [5].

Though Noninvasive imaging technology like nuclear imaging like Single Photon Emission Computed Tomography (SPECT), MRI has come up in recent times, the biomarkers like N-Terminal -pro Brain Natriuretic Peptide (NT pro BNP), Cardiac Troponin I (cTn I) and Pro Brain Natriuretic Peptide (pro BNP)play a vital role in the diagnosis and prognosis of patients suffering from HF [1].

In this review article, the role of cardiac biomarkers like Galectin 3, Gelsolin, Matrix Metalloproteinase-9 (MMP-9), NT pro BNP (N-Terminal pro Brain Natriuretic Peptide), Procollagen Type I C Peptide (PICP), soluble Suppression of Tumorigenicity (sST2), Tenascin C (Tn C) in different cardiac conditions like Rheumatic Carditis, Rheumatic Heart diseases, Coronary Artery Diseases, Adults with Congenital Heart Diseases are enumerated in brief.

Galectin 3

Galectin-3 (Gal-3) is a galactosidase-binding protein. It is expressed in the epithelia of several organs, participates in profibrotic pathways and involved in many regulatory processes. They facilitate cell to matrix and cell to cell interaction [5,18].

It activates inflammatory cells such as dendritic cells, neutrophils, lymphocytes macrophages, Kupffer cells and mast cells. The expression during inflammation is increased and leads to the formation of human atherosclerotic plaques, thereby involving in atherogenesis. There is upregulation of lectin which increases the expression of Galectin-3. Galectin-3 helps in assessing the risk of development of HF and adverse effects of cardiac remodeling [5,18].

The plasma Gal 3 levels correlates significantly with the severity of Coronary Artery Disease. Gal 3 is a prognostic marker among the patients subjected for coronary angiography and chronic stable angina [18].

Prediction of onset of HF can be done with measurements of Gal-3 and sST2.Acute Heart Failure can be detected by combination of two biomarkers (Galectin-3 and NT-proBNP) which has high sensitivity and specificity [5,19].

Gelsolin

Gelsolin acts by regulating intracellular actin filaments and it is important in maintaining the cell morphology. It plays a vital role during migration and phagocytosis [20].

Plasma Gelsolin (pGSN) serves as a "extracellular actin-scavenging system" being released by injured cells. After being released, pGSN facilitates the removal of inflammatory actins by binding. Gelsolin reduce the inflammation by altering the macrophage function which inturn triggers the nitric oxide synthase [20,21].

Plasma GSN (pGSN) is a 93 kDa protein, calcium-dependent. The levels of pGSN in healthy individuals are noticeably high (about 200 ± 10 µg/mL) [21].

In certain pathological conditions, levels of pGSN decreases especially in case of myocardial infarction, rheumatoid arthritis, major trauma, lung and liver injury, Alzheimer's disease, sub arachnoid hemorrhage, sepsis and hemodialysis. Poor clinical outcomes have been associated with low levels of pGSN [21].

The beneficial effects of circulating GSN are proved in post-CPB (Cardiopulmonary bypass) patients. Adverse outcomes are associated in post-CPB (Cardiopulmonary bypass), AKI (Acute Kidney Injury) patients due to decrease in pGSN levels [15].

In menopausal women levels of Gelsolin (GS) and Estradiol (E2) are used as diagnostic markers of Coronary heart disease [20].

S. No	Author/Place of Study	Year	Biomarker	Disease	Predictive Value	Control	p value
1	Bastawesy RB., *et al.*/Egypt	2019	Galectin-3	CAD SVD (31) TVD (24) MVD (40)	 SVD-2.96 ± 0.95 (ng/mL) TVD-6.99 ± 1.78 (ng/mL) MVD-17.5 ± 3.93 (ng/mL)	Nil	<0.001**
2	Tymińska., *et al.*/ Poland	2019	Galectin-3	First-time STEMI treated by pPCI	Without HF at 1year (n = 54) 6.9 (4.6-8.0) (ng/mL) With HF at 1year (n = 50) 7.8 (6.5-10.0) (ng/mL)	Nil	0.002
3	Zhang H., *et al.*/ China	2018	Galectin-3	Acute Heart Failure	(n = 86) 19.42 ± 4.76 ug/L	(n = 26) 10.27 ± 1.89	0.004

4	Shi SS., *et al.*/ China	2018	Gelsolin	Acute kidney injury after cardiopulmonary bypass	AKI (n = 14)		Nil	0.03
					Before Operation 3.07 ± 0.68 (mg/L)	2.73 ± 0.91		
					6h post-op 1.80 ± 0.53 (mg/L)	2.23 ± 0.85		
					24h post-op 2.04 ± 0.65 (mg/L)	2.54 ± 1.61		
6	Al-Kraity WR., *et al.*/Iraq	2017	Gelsolin	Coronary Heart Disease in Menopausal Women	(n = 70) 179.827 ± 2.663 ng/ml		(n = 20) 336.740 ± 4.511	< 0.05
5	Argun., *et al.*/ Turkey	2014	Gelsolin	Acute Rheumatic Carditis	(n = 37) 197 ± 218 mg/L		(n = 24) 322 ± 255 mg/L	0.039

Table 1: *Significance of galectin-3 and gelsolin with cardiac function.*

Note: SVD: Single Vessel Disease; TVD: Two Vessel Disease; MVD: Multi Vessel Disease; STEMI: ST Segment Elevated Myocardial Infarction; pPCI: Primary Percutaneous Coronary Intervention; NT pro BNP: N Terminal Pro Brain Natriuretic Peptide; AKI: Acute Kidney Injury.

Matrix metalloproteinase-9 (MMP-9)

MMP-9 (Gelatinase B) belongs to the family of MMPs and subfamily of gelatinase. Gelatin, a denatured collagen is a main substrate of MMP-9. It is a multi-domain enzyme secreted and is responsible for the regulation of cell-matrix composition [22]. MMP-2 hydrolyse the collagens (Type I, IV, V, VII and XI), gelatins, laminin, aggrecans, large Tenascin C, fibronectin and elastin [23].

A pleiotropic cytokine, Transforming growth factor β1 (TGFβ1) is appearing in most tissues with a extensive range of the biological functions including senescence, differentiation, immunity, apoptosis, migration, tumor suppression, osteogenesis, cell proliferation, wound healing and adipogenesis. TGFβ1 plays a causative role in many pathophysiological conditions in the development of cardiovascular-renal complications [24].

MMP-9 is secreted by cells like macrophages, monocytes, keratinocytes, polymorphonuclear leukocytes and they are even secreted by malignant cells. MMP-2, MMP-9 and TGF-β1 (Transforming Growth Factor- β1) are raised and increased levels in the circulation are seen in conditions like TOF (Tetralogy of Fallot), post atrial switch operation and after Fontan procedure. MMP-9 increases in coronary artery stenosis and Ischemic Heart Disease (IHD) having a great predictor value in assessing the risk of progression [15,22,25].

The increase of MMP-9 cannot be used as a single marker for the diagnosis of developing HF in rheumatic heart diseases. It has to be done in combination with decreased Growth hormone (GH) and decreased Insulin like Growth Factor (IGF-I) [13].

N-terminal pro-B-type natriuretic peptide (NT pro BNP)

NT-proBNP is a hormone secreted in response to pressure and volume overload by ventricular cardiac myocytes. In acute conditions, it is an accurate marker in differentiating systemic diseases of the respiratory system and heart disease. It is a predictor of mortality and Heart failure events [26,27].

In stable CAD, cardiovascular death, MI (Myocardial Infarction), non-cardiovascular deaths, the N-terminal pro-brain natriuretic (NT-proBNP) and high sensitivity C-reactive protein (hs-CRP) levels in serum are increased and they are strong predictor markers [26].

In early stages of CAD, risk stratification can be detected by the elevated levels of high-sensitive cardiac troponin T (hs-cTnT), N-terminal pro-brain natriuretic peptide (NT-proBNP) and various other cardiac enzymes [28].

In children suffering from acute rheumatic carditis, NT-proBNP is elevated to a significant level. It is used as a prognostic marker in monitoring the therapeutic response during the first week of treatment of HF [1,9].

S. No	Author	Year	Biomarker	Disease	Predictive Value		Control	p value
1	Cheung YF., *et al.*/China	2019	MMP 9	Repaired Congenital Heart Disease	Repaired TOF (n = 46) 325.0 ± 151.0*		(n = 36) 196.3 ± 113.6	< 0.05
					TGA post ASO (n = 21) 163.1 ± 97.3			
					TGA post atrial switch (n = 15) 197.5 ± 71.0			
					Fontan (n = 27) 226.9 ± 193.4			
			MMP 2		Repaired TOF (n = 46) 234.0 ± 41.5*		(n = 36) 204.3 ± 33.2	
					TGA post ASO (n = 21) 219.2 ± 37.8			
					TGA post atrial switch (n = 15) 227.1 ± 36.0*			
					Fontan (n = 27) 261.7 ± 39.1*			
2	Januska R., *et al.*/Germany	2019	NT proBNP	Rheumatic Heart Disease	Before treatment 271 pg/mL		Nil	Nil
					After Treatment 115 pg/mL			
3	Kabi., *et al.*/ Odisha	2018	NT pro BNP	1st week in Heart Failure	IHD (n = 76)	9029 pg/dL	Nil	Nil
					DCM (n = 18)	3926 pg/dL		
					RHD (n = 6)	13583 pg/dL		
					Myocarditis (n = 18)	9176.77 pg/dL		
					Cor-pulmonale (n = 40)	3634.8 pg/dL		
					SBE (n = 2)	3340 pg/dL		

4	Zhang H., *et al.*/China	2018	NT pro BNP	Acute Heart Failure	(n = 86) 2044.86 ± 379.01 ug/L			(n = 26) 251.45 ± 95.47	0.006
5	Vasilez L., *et al.*/Russia	2018	MMP-9	Coronary heart disease associated with cardiac arrhythmias and arterial hypertension	IHD (n = 36)		107.6 ng /ml	Nil	0.0003
					IHD with AF (n = 23)		106.4 ng/ml		0.0003
					IHD, AH and AF (n = 49)		115.6 ng/ml		0.0001
6	Lee SD., *et al.*/Taiwan	2006	MMP 9	RHD	Age: <30	31~55	>56	(n = 30)	Nil
					RA (n = 36) 67.2 ± 5.7*	42.7 ± 2.0**	26.9 ± 1.6**	<30 100.0 ± 5.8	
								31~55 64.8 ± 3.8	
					RHD (n = 43) 117.9 ± 7.1	160.0 ± 9.5*	120.6 ± 7.9*	> 56 105.2 ± 5.4	

Table 2: *MMP 9, MMP 2, NT proBNP biomarkers in different cardiac conditions.*

Note: MMP: Matrix Metallo Proteinase; NT pro BNP: N-Terminal Pro Brain Natriuretic Peptide; TOF: Tetralogy of Fallot; TGA: Transposition of Great Arteries; ASO: Arterial Switch Operation; DCM: Dilated CardioMyopathy; SBE: Systemic Bacterial Endocarditis; RHD: Rheumatic Heart Disease; IHD: Ischemic Heart Disease; AF: Atrial Fibrillation; AH: Arterial Hypertension.

Procollagen type I C peptide (PICP)

PICP is released into the blood stream during the synthesis of Type I collagen. Carboxy terminal propeptide of PICP increases significantly in patients suffering from Mitral Stenosis (MS) and Mitral Regurgitation (MR) along with PIIINP (Procollagen type III amino-terminal propeptide) [8].

PIIINP is an extension peptide of procollagen type III, which is cleaved off stoichiometrically during conversion from type III procollagen to type III collagen. The collagen syntheses are increased in pathogenesis of mechanical dyssynchrony of LV, after TOF repair and in HF, thus enhancing the myocardial fibrosis [16,22].

PICP (Procollagen Type I C Peptide) is secreted by heart into the systemic circulation in case of hypertension**.** Hence the circulating levels of PICP and PIIINP are used as biomarkers. In Rheumatic Heart Disease patients, significantly high levels of PICP were seen when compared to the rheumatic fever and pharyngitis group [12,29].

MMP-2 and PICP levels in plasma are reliable biomarkers in diagnosis of Hypertrophic Cardiomyopathy patients with myocardial fibrosis [30].

Soluble suppression of tumorigenicity 2 (sST2)

ST2 ("suppression of tumorigenicity 2"), a interleukin 1 receptor-like 1 (IL1RL-1) is expressed by cardiac cells during myocardial stress (a novel Biomarker) and plays a vital role in the cardiovascular system [31,32].

ST2 is a protein which has two isoforms namely soluble ST2 (ST2) and transmembrane receptor form (ST2L). In HF, cardiomyocytes stretch leads to raised ST2 levels. Soluble ST2 lacks the intracellular and transmembrane domains. Both the isoforms have the same extracellular domain. ST2L is selectively expressed on Th2 T-cells, which is involved in Th2 cell-mediated immunological responses [2,33].

Sex-specific analyses showed that there is a strong association in women. The mortality due to HF and risk of HF is estimated with sST2. In patients with HFrEF (Heart Failure with reserved Ejection Fraction), sST2 values are associated with poor prognosis and vice - versa [34,35].

Measurement of sST2 after Acute Myocardial Infarction, used to predict medium-term LV functional recovery. Direct relationship between the infarct magnitude, infarct remodeling and sST2 exists [7].

ST2 is more sensitive predictive marker than NT pro BNP, as it predicts before the onset of severe LV dysfunction or Heart Failure. In clinical practice, ST2 is used as a prognostic marker [36,37].

S. No	Author	Year	Biomarker	Disease	Predictive Value	Control	p value
1	Januska., *et al.*/Germany	2019	Soluble ST2	Rheumatic Heart Disease	Before treatment 214 pg/ml After Treatment 16 pg/Ml	Nil	Nil
2	Tymińska., *et al.*/ Poland	2019	Soluble ST2	First-time STEMI treated by pPCI	Without HF at 1year (n = 54) 23.4 (17.0-29.9) (ng/mL) With HF at 1year (n = 50) 25.7 (20.1-34.5) (ng/mL)	Nil	0.04
3	Vasilez L., *et al.*/ Russia	2018	PICP	Coronary heart disease associated with cardiac arrhythmias and arterial hypertension	IHD (n = 36) 176.4 ng/ml IHD with AF (n = 23) 174.1 ng/ml IHD, AH and AF (n = 49) 163.2 ng/ml	Nil	<0.001 <0.001 <0.001
4	Sarkar S., *et al.*/ Chandigarh	2017	PICP	Rheumatic Fever and Rheumatic Heart Disease	Pharyngitis (n = 18) 520 ng/ml Rheumatic Fever (n = 23) 1000 ng/ml Rheumatic Heart Disease (n = 43) 1080 ng/ml	(n = 50) 530 ng/ml	0.05
5	Bahuleyan CG., *et al.*/ Kerala	2017	Soluble ST2	Heart failure patients with reduced ejection fraction	Without Adverse Outcome (n = 84) 48 ± 36.8 ng/ml With Adverse Outcome (n = 57) 106.6 ± 116.2 ng/ml Both 71.7 ± 83.9	Nil	<0.001

6	Bannerjee T., *et al.*/ Kolkata	2014	PICP	Rheumatic Mitral Valve Disease	(n = 77) MS (1265 ± 125 ng/ml) MR (848 ± 74 ng/ml)	(n = 41) 324 ± 18 ng/ml	<0.001
7	Lai CT., *et al.*/China	2011	PICP	After repair of tetralogy of Fallot	(n = 39) 363.4 ± 149.3 µg/L	(n = 25) 282.2 ± 83.6 µg/L	0.016
8	Weir RA., *et al.*/ Scotland	2010	Soluble ST2	Left Ventricular and infarct remodeling after acute myocardial infarction	(n = 100) Baseline At 12weeks 263.3 pg/ml At 24weeks 140.0 pg/ml	Nil	0.001

Table 3: *Association of PICP and sST2 in different types of cardiac conditions.*

Note: PICP: Pro-collagen Type I C Peptide; MS: Mitral Stenosis; MR: Mitral Regurgitation; IHD: Ischemic Heart Disease; AF: Atrial Fibrillation; AH: Arterial Hypertension; STEMI: ST Elevation Myocardial Infarction; pPCI: Primary Percutaneous Coronary Intervention; HF: Heart Failure.

Tenascin C

Tenascin-C (TNC), is a hexameric extracellular matrix (ECM) synthesized by interstitial fibroblasts. It is a multifunctional glycoprotein implicated in cell differentiation, its proliferation and migration. Tenascin-C expressions are induced during tissue repair, inflammation, cardiovascular disease and in malignancy [11,38].

Tenascin-C is also associated with progression and severity of pulmonary hypertension, acute pulmonary thromboembolism, Heart Failure and in myocardial infarction [39].

TNC is a useful biomarker in evaluating the acute aortic dissection. Significantly higher levels of the median of TNC (75.3 versus 141.1 pg/mL, $P < 0.001$) are seen in non-survivor group than the survivors of Type A Aortic Dissection [40]. In acute stage of Kawasaki Disease (KD), TNC expressions indicates the associated cardiovascular lesions [41].

Tenascin C levels significantly increases with the severity of atherosclerosis and indicates the risk of CAD. TNC can be used as a predictive marker for early assessment of CAD before angiography [42].

For diagnosing certain pathological conditions like inflammation, infection and rheumatic carditis this novel biochemical marker can be detected in serum. TnC levels can be a predictive marker in the differential diagnosis of Rheumatic Heart Disease in childhood and congenital HVD [11].

TNC is an independent predictor biomarker for mitral stenosis and dramatic decrease in their levels after Percutaneous Balloon Mitral Valvuloplasty (PBMV) have been documented [39].

S. No	Author	Year	Biomarker	Disease	Predictive Value		Control	p value
1	Celik., *et al.*/ Turkey	2013	Tenascin C	Rheumatic mitral stenosis and PBMV	(n = 40) Before BMV: 15.0 ± 3.8 ng/ml		(n = 20) 9.4 ± 2.9 ng/ml	<0.001
					After BMV: 10.9 ± 3.1 ng/ml			
2	Karatas., *et al.*/ Turkey	2013	Tenascin C	Rheumatic Carditis	Rheumatic Carditis (n = 25)		(n = 20) 5.56 ± 2.66 ng/ml	Carditis <0.01 CRHD <0.001
					1st analysis:	0.90 ng/ml		
					2nd analysis:	9.48 ng/ml		
					CRHD (n = 25)			
					Mild	12.95 ng/ml		
					Moderate	21.44 ng/ml		
					Severe	0.94 ng/ml		
					No insufficiency	5.56 ng/ml		
3	Guo., *et al.*/ China	2018	Tenascin C	Predicting in-hospital death in acute aortic dissection	(n = 109)		Nil	0.000
					Survivor	75.30 (58.30-99.30)		
					Non-Survivor	141.10 (112.40 -163.40)		
4	Gao., *et al.*/ China	2018	Tenascin C	Severity of Coronary Atherosclerosis	Non-CAD (n = 76)	67.87 ± 5.14	Nil	<0.001
					CAD (n = 81)	117.40 ± 9.32		

Table 4: *Significance of Tenascin C in various cardiac conditions.*

Note: BMV: Balloon Mitral Valvotomy; PBMV: Percutaneous Balloon Mitral Valvuloplasty; CRHD: Chronic Rheumatic Heart Disease; RHD: Rheumatic Heart Disease; CAD: Coronary Artery Disease.

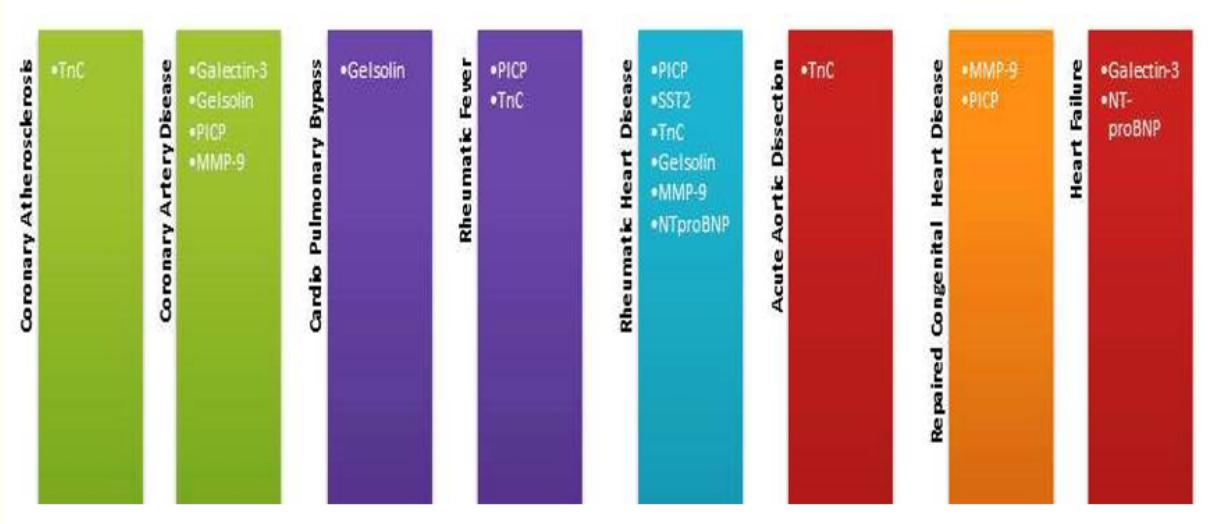

Figure 1: *Biomarkers used in different cardiac conditions.*

Conclusion

A biomarker provides information beyond the available clinical tools as it reflects the pathophysiological mechanism involved and helps the clinicians in making decisions on patient management**.** In the field of cardiology, biomarkers levels have significant impact in diagnosis, in assessing the degree of Heart Failure, to predict the developing cardiac dysfunction and in the patient management.

Myocardial degeneration determination may involve multiple processes. Combination of biomarkers may be more useful. Multiple biomarkers still remains an area for research. Elevated biomarker levels may have a stronger predictive and they represent diverse biological pathways. Despite the array of current Biomarkers, technological advancement in molecular biology, cell biology and biochemistry, there remains a knowledge gap.

Ultimately, it is combination of biomarkers and other parameters like Cardiac Imaging proves them as one of the most beneficial tool in diagnosis and risk stratification in Heart Failure.

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Conflicting Interest

None declared.

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