Novel Biomarkers for Prediction of Cardiovascular Morbidity

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ABSTRACT

Cardiovascular diseases are still one of the most common causes of deaths in the world .The changing demographics of fatal cardiovascular events is a significant indicator to consider new approaches in risk prediction and risk stratification. This article aims to address a few probable bio markers which may help determine the probability of an underlying cardiovascular condition much before the onset of acute symptoms.

Keywords: Sudden Cardiac Death, Ventricular Tachyarrthmia, sST2, Galectin-3, GEH

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INTRODUCTION

Sudden cardiac death (SCD) still remains a major cause of mortality (estimated 15–20% of all deaths worldwide) even though advanced preventive and therapeutic strategies are available now. Of all the reported sudden cardiac deaths, the majority (70-80%) is still due to coronary artery disease.[1-5]

Although anecdotal evidence suggests an increasing trend in the incidence of SCD in young adults of India, only one study[6] was conducted in our country recently, exploring the incidence of SCD in rural India. This study identified the prevalence as 17% in a South Indian rural population. In comparison to other cardiac deaths including those due to CAD, in India, the proportion of SCD events and the risk factor profile of the individuals at risk for SCD still remains largely unknown.

Sudden cardiac death (SCD) is defined, as sudden unexpected death occurring within 1 hour of onset of cardiac symptoms,[7] most often due to ventricular arrhythmias induced by coronary artery disease or cardiomyopathy.[8] Most of the SCD s are seen in individuals without any symptoms nor an increased blood levels of classical biomarkers of cardiac arrest.[9]

PATHOPHYSIOLOGY

The causes for Ventricular tachyarrhythmias vary between enhanced automaticity, triggered activity and/or reentry.[10,11] The increased myocardial automaticity is due an acceleration of the spontaneous firing in cardiac myocyte. As a consequence, this leads to irregular activation patterns in the heart. Triggered activity is characterized by calcium-mediated premature action potentials that arise from early or delayed afterdepolarizations.

One of the most common mechanisms of cardiac reentry involves multiple excitation wave that moves around myocardial areas with impaired conduction and refractory tissue.

Most often this arrhythmogenic effect is a consequence of the electrophysiological remodelling processes in the heart, which induces changes in cardiac ion channel expression and function in the heart. These, indeed are due to the fibrotic processes progressing in the myocardium thus affecting the cardiac conduction.[9,10]

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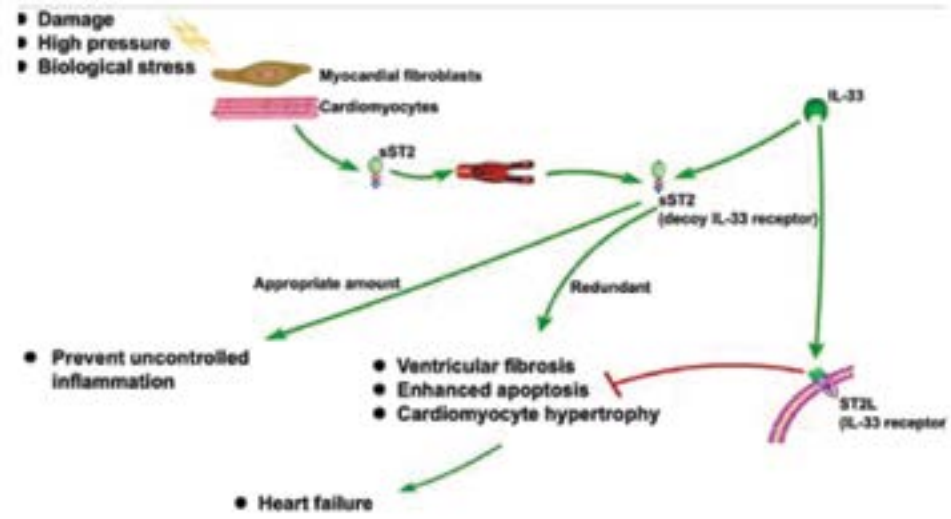

Figure 1. **ST2 pathway in CVD**

These mechanisms are often modulated or/and induced by different processes like myocardial necrosis, inflammation, myocardial stress or neurohormonal activation with the involvement of various biological signal proteins. While these proteins are often released during signalling processes, their levels can be measured in patient serum as indicator of signalling activation. Consequently, they can be useful for characterization of normal or pathogenic processes of the heart including electrophysiological remodelling. Indeed, biomarkers have become a useful tool, which refers to a broad subcategory of quantifiable and reproducible characteristics of biological signs. Therefore, their potential as a useful marker for cardiac risk stratification needs to be discussed.[12]

One interesting fact is that, other than the "classic" cardiac biomarkers like BNP or troponin, inflammatory biomarkers like C-reactive protein (CRP) or high-sensitive (hsCRP), also have been useful in diagnosing cardiac diseases.[12]

The novel or emerging biomarkers being studied are probably the bye products of myocardial injury like myocardial necrosis, inflammation, plaque instability, platelet activation, myocardial stress and neurohormonal activation. Indeed, one of the "novel" cardiac biomarkers, soluble suppression of tumorigenicity 2 (sST2) protein, is gaining steady significance as a good prognostic marker for heart failure.[13]

In this review we will describe few cardiac Biomarkers which might help to predict the risk of ventricular cardiac arrhythmias . The need and the potential clinical implications of new cardiac Biomarkers also needs attention. In this article we discuss three "novel" cardiac biomarkers as potential predictors of fatal ventricular arrhythmias.

Novel and Alternative' Biomarkers as Potential Predictors of Ventricular Arrhythmias

Soluble suppression of tumorigenicity 2 (sST2)

A number of Recent studies have demonstrated that blood levels of the molecule 'suppression of tumorigenicity 2' (ST2) is remarkably associated with risk for cardiac diseases.[14,15, 23-25]

ST2 is a member of the interleukin 1 receptor family and was discovered in 1989 as an inflammatory mediator in autoimmune conditions.[16,17,40] The biological activity of ST2 is mediated by its interaction with its ligand, IL-33.[18] Soluble ST2(sST2) is seen to be released from myocardial fibroblasts and cardiomyocytes under stress.[26,27] When cardiomyocytes stretch due to any stress, this molecule gets released.[19,20] It is also associated with inflammation during the MI and HF.[21] During normal response, Il-33 binds to the ST2 receptor has a cardioprotective ability but when bound with sST2, Il-33 is unable to progress on its usual cellular pathways, resulting in the potential loss of cardioprotective characteristics.[34] Consequently, higher levels of sST2 are linked to more severe stress responses in the heart[39] as it suggests significant inhibition of signal transduction by Il-33/ST2 pathways.[22] The ST2 pathway in CVD is shown in **Figure 1.**

The biomechanics of the IL-33/ST2 signalling pathway has been well established and has been found that it plays a significant role in cardiomyocyte hypertrophy and cardiac fibrosis.[28] As mentioned earlier, sST2 release as a result of myocyte stretch, neutralises its ligand IL-33, which is a key component in preventing myocardial fibrosis and hypertrophy.[33,34] Any change in the geometry or load conditions of the heart, such as MI, hypertension, and valvular heart disease, may change the mechanical strain imposed on a single cardiomyocyte, leading to cardiomyocyte hypertrophy, enhanced extracellular protein deposition (ventricular fibrosis), and eventually HF.[29,30,31] Cardiomyocyte hypertrophy is the most important of the pathophysiological changes in the heart, eventually contributing to ventricular wall thickening and stiffening.[32] Therefore, both cardiomyocyte hypertrophy and cardiac fibrosis contribute to elevated serum sST2 levels in HF patients, which was corroborated by the recent researches.

During conditions of myocardial damage, either by high pressure or any other biological strain IL-33 is released from the fibroblasts, which in turn prevents apoptosis of the myocardial cells.[35,36] This cardio protective effects are mediated via the membrane receptor for IL-33, ST2. The protective effects of IL-33 is lost in the presence of sST2 because sST2 acts as a competitive inhibitor of ST2L.[22] In fact, elevated blood sST2 concentrations denotes apoptosis, cardiomyocyte hypertrophy, and cardiac fibrosis, which denotes irreversible damage after MI, leading to HF.

We speculate that higher serum sST2 concentrations after MI may cause a worse prognosis because sST2 blocks the beneficial effects of IL-33, such as reducing fibrosis and hypertrophy, preventing apoptosis, preserving ventricular function, and improving survival.[35] Therefore, sST2 may be used to evaluate risk of death after MI.

One meta-analysis result indicated that the sST2 level was not correlated with ischemic heart disease or Myocardial infarction but was significantly associated with Heart Failure. sST2 levels did not differ significantly between patients with IHD or MI and healthy individuals. But it is a potential tool as an additional aid for the diagnosis of HF.[38,41]

Another study, The ARTEMIS study,[43] also concluded that Elevated sST2 and hs-TnT predict the occurrence of Sudden cardiac deaths among patients with Coronary artery disease. This study also suggested that Combination of elevated sST2 and hs-TnT is the most useful predictor on the risk of SCD. These two biomarkers obviously reflect partly different aspects of cardiovascular stress and tissue damage leading to untoward cardiac events, either progressive heart failure or occurrence of SCD even without prior evidence of left ventricular systolic dysfunction. It can be hypothesized that elevated hs-TnT is a marker of ongoing myocyte loss and elevated sST2 reflects the consequent cardiac replacement fibrosis as a result of cell death, which eventually creates a substrate for fatal arrhythmia. Fibrotic scarring has been shown to correlate strongly with an increased incidence of arrhythmias and SCD.[44]

Galectin-3

Galectins are a family of proteins defined by two characteristics: functionally a beta-galactoside affinity and structurally a conserved carbohydrate recognition domain (CRD). Tissue damage activates this molecule[45] and inside the cell it activates messenger ribonucleic acid (mRNA) splicing which in turn promotes anti-apoptotic signalling. This becomes particularly relevant in fibroblasts as it promotes mitogenesis in these cells.[49] Therefore, we can consider that galectin -3 is representative of fibrotic processes in the damaged heart, including in heart failure.[21] Infact, one study elicited that , elevated levels of galectin -3 in general population was associated with not only more incidence of heart diseases , but also with an increased risk of all-cause mortality.[46] It is to be noted that galectin-3 has proven to be a useful complementary biomarker in prognosis and risk stratification of patients with cardiac failure.[47]

Recent evidence also suggests galectin-3 to be a good tool to predict the onset of Ventricular tachycardia as well as Ventricular Fibrillation. They investigated a possible association with risk prediction of sudden cardiac death in Hypertrophic cardiomyopathy. The authors observed a positive correlation between the estimated five-year risk of SCD and serum levels of galectin-3, thus indicating a possible association between sudden cardiac deaths and this protein.[48]

ECG biomarkers

An electrocardiogram (ECG) can denote the presence and properties of the electrophysiological pathology of SCD. One study recently showed that global electrical heterogeneity (GEH), as measured by five metrics [spatial QRS-T angle, spatial ventricular gradient (SVG) azimuth, elevation, and magnitude, and sum absolute QRST integral (SAI QRST)] is independently (after comprehensive adjustment for time-updated CVD events and their risk factors) associated with SCD, probably denoting the cause of SCD . They also developed a competing risk score of SCD and showed that the addition of GEH measures to clinical risk factors significantly improves the reclassification of SCD risk.[50]

They proved that a parameters like wide QRS-T angle, SVG vector pointing backward (towards LV), wide QRS, prolonged QTc, and increased heart rate points to a non-SCD structural heart disease. While increased chances of SCD was seen in ECG s characterized by SVG vector pointing upward (towards the outflow tract). Dynamic predictive accuracy of ECG and VCG biomarkers of SCD should be taken into account for development of dynamic and life-long prediction of SCD and non- SCD.[51,52]

Other Biomarkers

Heart-Type Fatty Acid Binding Protein (H-FABP)

Heart fatty acid-binding protein (H-FABP) is present on the myocyte cell membrane, during injury gets released in the bloodstream.[53] Three hours after myocardial infarction, the level rises to a maximum.[54] It may be established as a marker of ongoing myocardial membrane damage and has been reported to be a useful indicator for future cardiovascular events.[55]

Metalloproteinases (MMP) and Procollagens

Metalloproteinases (MMPs) are enzymes mainly concerned with the turnover of extracellular matrix. These enzymes regulate the inflammatory and fibrotic components of myocardial wound healing.[56] In hypertrophic cardiomyopathy which is characterised by cardiac remodelling, MMP-3 levels were significantly higher especially in patients prone to ventricular arrhythmias.[57]

Endothelin

As one of the most potent vasoconstrictive peptides, the endothelium-derived factor endothelin is still relevant as a predictor of sudden cardiac death.[58] Endothelin 1 (ET 1) increases platelet aggregation. In animal models, endothelin is associated with increased incidence of ventricular arrhythmias.[59-61] In addition, endothelin was linked to ischemia induced ventricular arrhythmias[62] and arrhythmogenic responses during myocardial reperfusion.[63]

Uric acid is the final product of the purine metabolism. In recent years, serum uric acid has gained interest as a determinant of cardiovascular risk. Indeed, patients with hyperuricemia are at higher risk of cardiovascular events.[64] It has been suggested that high serum levels are a strong, independent marker of poor prognosis in HF.[65]

Fibrinogen is a glycoprotein involved in clotting processes. Furthermore, it is a known regulator of revascularization and wound healing, but also acts as an acute-phase protein, which is secreted in response to systemic inflammation and tissue injury.[66] Consequently, fibrinogen plasma levels were shown to be higher in patients suffering from CVD, as indicated by a subgroup analysis of the Framingham population.[67]

CONCLUSION

Classical Biomarkers such as cardiac troponin (cTn), and CK-MB are still considered as the main indicators of any cardiac event.A Biomarker which is predictive of an acute cardiac event causing SCD is still not evident.Much evidence suggests elevated ST2 as a probable indicator to fit into the role of a marker for SCD in patients with heart failure.

It has been shown that an increase in ST2 levels show poor prognosis in patients with acute MI.[68] Blood levels of sST2 early after AMI predicts left ventricle (LV) function and recovery after AMI, which may interlink the RAAS and IL- 33/sST2 pathways.[69]

sST2 is in vogue as a promising prognostic indicator for Heart failure and a useful tool for risk stratification.[37] as per the results of one meta-analysis of serum sST2 levels in different CVDs. It demonstrated that serum sST2 levels in HF patients are remarkably higher than those in healthy individuals. However, serum sST2 levels did not differ significantly between IHD or MI patients and healthy individuals. Therefore, ST2 may be used as an additional diagnostic biomarker of Heart Failure.[26,27,41]

The dynamic changes in electrical activity of heart due to the progressive myocardial inflammatory and fibrotic changes is another hopeful discovery in predicting the SCD. One study investigated the dynamic predictive accuracy of GEH and traditional ECG biomarkers of SCD within a survival framework in comparison with competing non-sudden cardiac death (non-SCD) in the Atherosclerosis Risk in Community (ARIC) study participants.[42]

Despite multiple advances in the strategies for SCD risk stratification, the current available techniques have limitations related to sensitivity, specificity, and cost-effectiveness. The goal of developing effective, low-cost, and noninvasive risk stratification tools for SCD still remains elusive.[9] When we take into consideration of the fact that risk of SCD is not based on a single myocardial strain but a continuous and dynamic process, the current risk models fails in accurate prediction of SCD. The current methods used to predict SCD are based on using baseline risk factors measured at a single point in time. Therefore, innovative and accurate predictions of these dynamic cardiac changes is necessary for understanding the temporal relationship between substrate and events more better. The next generation of medical devices would probably evolve to incorporate a continuous cardiac electrical monitoring and instantaneous predictive abilities of SCD way before the actual event happens. Further investigations in this exciting field is imperative to generate novel risk assessment approaches in the future for predicting and preventing SCDs.

END NOTE

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REFERENCES

1. Wong CX, Brown A, Lau DH, Chugh SS, Albert CM, Kalman JM, et al. Epidemiology of sudden cardiac death: Global and regional perspectives. Heart Lung Circ. 2019;28:6–14.
2. Albert CM, Chae CU, Gradstein F, Rose LM, Rexrode KM, Ruskin JN, et al. Prospective study of sudden cardiac death among women in the United States. Circulation. 2003;107:2096–101.
3. Chugh SS, Reinier K, Teodorescu C, Evanado A, Kahr E, Al Samara M, et al. Epidemiology of sudden cardiac death: Clinical and research implications. Prog Cardiovasc Dis. 2008;51:213–28.
4. Huikuri HV, Castellanos A, Myer burg RJ. Sudden death due to cardiac arrhythmias. N Engl J Med. 2001;345:1473–82.
5. Katritsis DG, Gersh BJ, Camm AJ. A clinical perspective on sudden cardiac death. Arrhythm Electrophysiol Rev. 2016;5:177–82.
6. Madhavan SR, Reddy S, Panuganti PK, Joshi R, Mallidi J, Raju K, et al. Epidemiology of sudden cardiac death in rural South India-insights from the Andhra Pradesh rural health initiative. Indian Pacing Electrophysiol J. 2011;11:93–102.
7. Greenberg H, et al. Analysis of mortality events in the Multicenter Automatic Defibrillator Implantation Trial (MADIT-II) J Am Coll. Cardiol. 2004;21:1459
8. Greene, H.L. Sudden arrhythmic cardiac death—Mechanisms, resuscitation and classification: The Seattle perspective. Am. J. Cardiol. 1990, 65, 4B–12B.
9. Shenasa M, Estes NAM, Tomaselli GF. Sudden Cardiac Death: Contemporary Challenges. Cardiac Electrophysiology Clinics. 2017 Dec 1;9(4):xvii–xviii.
10. Lane, R.E.; Cowie, M.R.; Chow, A.W. Prediction and prevention of sudden cardiac death in heart failure. Heart 2005, 91, 674–680.
11. Motloch, L.J.; Akar, F.G. Gene therapy to restore electrophysiological function in heart failure. Expert Opin. Biol. Ther. 2015, 15, 803–817.
12. Paar, V.; Jirak, P.; Larbig, R.; Zagidullin, N.S.; Brandt, M.C.; Lichtenauer, M.; Hoppe, U.C.; Motloch, L.J. Pathophysiology of Calcium Mediated Ventricular Arrhythmias and Novel Therapeutic Options with Focus on Gene Therapy. Int. J. Mol. Sci. 2019, 20.
13. Shaw, R.M.; Rudy, Y. The vulnerable window for unidirectional block in cardiac tissue: Characterization and dependence on membrane excitability and intercellular coupling. J. Cardiovasc. Electrophysiol. 1995, 6, 115–131.
14. Yancy, C.W.; Jessup, M.; Bozkurt, B.; Butler, J.; Casey, D.E., Jr.; Drazner, M.H.; Fonarow, G.C.; Geraci, S.A.; Horwich, T.; Januzzi, J.L.; et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J. Am. Coll. Cardiol. 2013, 62, e147–e239.
15. Najjar E, Faxén UL, Hage C, Donal E, Daubert J-C, Linde C, et al. ST2 in heart failure with preserved and reduced ejection fraction. Scand Cardiovasc J. (2019) 53:21–7.
16. Tominaga S. A putative protein of a growth specific cDNA from BALB/c- 3T3 cells is highly similar to the extracellular portion of mouse interleukin 1 receptor. FEBS Lett. (1989) 258:301–4.
17. Klemenz R, Hoffmann S, Werenskiold AK. Serum- and oncoprotein- mediated induction of a gene with sequence similarity to the gene encoding carcinoembryonic antigen. Proc Natl Acad Sci U S A. (1989) 86:5708– 12.
18. Oshikawa K, Kuroiwa K, Tago K, Iwahana H, Yanagisawa K, Ohno S, et al. Elevated soluble ST2 protein levels in sera of patients with asthma with an acute exacerbation. Am J Respir Crit Care Med. (2001) 164:277– 81.
19. Dieplinger B, Mueller T. Soluble ST2 in heart failure. Clin Chim Acta. (2015) 443:57–70.
20. Weinberg EO, Shimpo M, De Keulenaer GW, MacGillivray C, Tominaga S, Solomon SD, et al. Expression and regulation of ST2, an interleukin-1 receptor family member, in cardiomyocytes and myocardial infarction. Circulation. (2002) 106:2961–6.
21. Parikh RH, Seliger SL, Christenson R, Gottdiener JS, Psaty BM, deFilippi CR. Soluble ST2 for prediction of heart failure and cardiovascular death in an elderly, community-dwelling population. J Am Heart Assoc. (2016) 5:e003188.
22. Marino R, Magrini L, Orsini F, Russo V, Cardelli P, Salerno G, et al. Comparison between soluble ST2 and high-sensitivity troponin i in predicting short-term mortality for patients presenting to the emergency department with chest pain. Ann Lab Med. (2017) 37:137– 46.
23. Dudek M, Kałuzna-Oleksy M, Migaj J, Straburzyn ska-Migaj E. Clinical value of soluble ST2 in cardiology. Adv Clin Exp Med. (2020) 29:1205– 10.
24. Emdin M, Aimo A, Vergaro G, Bayes-Genis A, Lupón J, Latini R, et al. sST2 Predicts outcome in chronic heart failure beyond NT-proBNP and high-sensitivity troponin T. J Am Coll Cardiol. (2018) 72:2309– 20.
25. McCarthy CP, Januzzi JL, Jr. Soluble ST2 in Heart Failure. Heart Fail Clin. (2018) 14:41–8.
26. Schmitz J, Owyang A, Oldham E, Song Y, Murphy E, McClanahan TK, et al. IL-33, an interleukin-1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines. Immunity. (2005) 23:479–90.
27. Villacorta H, Maisel AS. Soluble ST2 testing: a promising biomarker in the management of heart failure. Arq Bras Cardiol. (2016) 106:145– 52.
28. Yao HC, Li XY, Han QF, Wang LH, Lou T, Zhou YH, et al. Elevated serum soluble ST2 levels may predict the fatal outcomes in patients with chronic heart failure. Int J Cardiol. (2015) 186:303–4.
29. Díez J, González A, López B, Querejeta R. Mechanisms of disease: pathologic structural remodeling is more than adaptive hypertrophy in hypertensive heart disease. Nat Clin Pract Cardiovasc Med. (2005) 2:209– 16.
30. Sadoshima J, Izumo S. The cellular and molecular response of cardiac myocytes to mechanical stress. Annu Rev Physiol. (1997) 59:551–71.
31. McKinsey TA, Olson EN. Toward transcriptional therapies for the failing heart: chemical screens to modulate genes. J Clin Invest. (2005) 115:538– 46.
32. Dattagupta A, Immaneni S. ST2: Current status. Indian Heart J. (2018) 70:S96–101.
33. Shah RV, Januzzi JL. ST2: a novel remodeling biomarker in acute and chronic heart failure. Curr Heart Fail Rep. 2010 Mar;7(1):9–14.
34. Brint, E.K.; Fitzgerald, K.A.; Smith, P.; Coyle, A.J.; Gutierrez-Ramos, J.C.; Fallon, P.G.; O'Neill, L.A. Characterization of signaling pathways activated by the interleukin 1 (IL-1) receptor homologue T1/ST2. A role for Jun N-terminal kinase in IL-4 induction. J. Biol. Chem. 2002, 277, 49205–49211.

35. De la Fuente M, MacDonald TT, Hermoso MA. The IL-33/ST2 axis: Role in health and disease. Cytokine Growth Factor Rev. (2015) 26:615– 23.
36. Seki K, Sanada S, Kudinova AY, Steinhauser ML, Handa V, Gannon J, et al. Interleukin-33 prevents apoptosis and improves survival after experimental myocardial infarction through ST2 signaling. Circ Heart Fail. (2009) 2:684– 91.
37. Homsak E, Gruson D. Soluble ST2: A complex and diverse role in several diseases. Clinica Chimica Acta. (2020) 507:75– 87.
38. Boisot S, Beede J, Isakson S, Chiu A, Clopton P, Januzzi J, et al. Serial sampling of ST2 predicts 90-day mortality following destabilized heart failure. J Card Fail. (2008) 14:732–8.
39. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. (2013) 128:e240– 327.
40. Kakkar R, Lee RT. The IL-33/ST2 pathway: therapeutic target and novel biomarker. Nat Rev Drug Discov. 2008 Oct;7(10):827–40.
41. Zhang T, Xu C, Zhao R, Cao Z. Diagnostic Value of sST2 in Cardiovascular Diseases: A Systematic Review and Meta-Analysis. Front Cardiovasc Med. 2021 Jul 23;8:697837.
42. Perez-Alday et al. Dynamic predictive accuracy of electrocardiographic biomarkers of sudden cardiac death within a survival framework:the Atherosclerosis Risk in Communities(ARIC) study: BMC Cardiovascular Disorders (2019) 19:255
43. Lepojärvi ES, Huikuri HV, Piira O-P, Kiviniemi AM, Miettinen JA, Kentta T, et al. (2018) Biomarkers as predictors of sudden cardiac death in coronary artery disease patients with preserved left ventricular function (ARTEMIS study). PLoS ONE 13(9): e0203363.
44. Wong TC, Piehler K, Meier CG, Testa SM, Klock AM, Aneizi AA et al. Association Between Extracellular Matrix Expansion Quantified by Cardiovascular Magnetic Resonance and Short-Term Mortality. Circu- lation 2012; 126:1206–1216.
45. Dumic,J.;Dabelic,S.;Flogel,M.Galectin-3:Anopen-endedstory.Biochim.Biophys.Acta2006,1760,616–635.
46. de Boer RA, van Veldhuisen DJ, Gansevoort RT, Muller Kobold AC, van Gilst WH, Hillege HL, et al. The fibrosis marker galectin-3 and outcome in the general population. J Intern Med. 2012 Jul;272(1):55–64.
47. Gehlken C, Suthahar N, Meijers WC, de Boer RA. Galectin-3 in Heart Failure: An Update of the Last 3 Years. Heart Fail Clin. 2018 Jan;14(1):75–92.
48. Emet, S.; Dadashov, M.; Sonsoz, M.R.; Cakir, M.O.; Yilmaz, M.; Elitok, A.; Bilge, A.K.; Mercanoglu, F.; Oncul, A.; Adalet, K.; et al. Galectin-3: A Novel Biomarker Predicts Sudden Cardiac Death in Hypertrophic Cardiomyopathy. Am. J. Med. Sci. 2018, 356, 537–543.
49. Haudek,K.C.;Spronk,K.J.;Voss,P.G.;Patterson,R.J.;Wang,J.L.;Arnoys,E.J.Dynamicsofgalectin-3inthe nucleus and cytoplasm. Biochim. Biophys. Acta 2010, 1800, 181–189.
50. Waks JW, Sitlani CM, Soliman EZ, Kabir M, Ghafoori E, Biggs ML, et al. Global electric heterogeneity risk score for prediction of sudden cardiac death in the general population: the atherosclerosis risk in communities (ARIC) and cardiovascular health (CHS) studies. Circulation. 2016;133(23):2222–34.
51. Tereshchenko LG, Sotoodehnia N, Sitlani CM, Ashar FN, Kabir M, Biggs ML, et al. Genome-wide associations of global electrical heterogeneity ECG phenotype: the ARIC (atherosclerosis risk in communities) study and CHS (cardiovascular health study). J Am Heart Assoc. 2018;7(8):e008160.
52. The ARIC Investigators. The atherosclerosis risk in community (ARIC) study: design and objectives. Am J Epidemiol. 1989;129(4):687–702.
53. Glatz JF, van Bilsen M, Paulussen RJ, Veerkamp JH, van der Vusse GJ, Reneman RS. Release of fatty acid-binding protein from isolated rat heart subjected to ischemia and reperfusion or to the calcium paradox. Biochim Biophys Acta. 1988 Jul 1;961(1):148–52.
54. Kleine AH, Glatz JF, Van Nieuwenhoven FA, Van der Vusse GJ. Release of heart fatty acid-binding protein into plasma after acute myocardial infarction in man. Mol Cell Biochem. 1992 Oct 21;116(1–2):155–62.
55. Otaki Y, Watanabe T, Takahashi H, Hirayama A, Narumi T, Kadowaki S, et al. Association of Heart-Type Fatty Acid-Binding Protein with Cardiovascular Risk Factors and All-Cause Mortality in the General Population: The Takahata Study. PLoS One. 2014 May 21;9(5):e94834.
56. Lindsey ML, Iyer RP, Jung M, DeLeon-Pennell KY, Ma Y. Matrix Metalloproteinases as Input and Output Signals for Post-Myocardial Infarction Remodeling. J Mol Cell Cardiol. 2016 Feb;91:134–40.
57. Zachariah JP, Colan SD, Lang P, Triedman JK, Alexander ME, Walsh EP, et al. Circulating matrix metalloproteinases in adolescents with hypertrophic cardiomyopathy and ventricular arrhythmia. Circ Heart Fail. 2012 Jul 1;5(4):462–6.
58. Yanagisawa, M.; Kurihara, H.; Kimura, S.; Tomobe, Y.; Kobayashi, M.; Mitsui, Y.; Yazaki, Y.; Goto, K.; Masaki, T. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. Nature 1988, 332, 411–415.
59. Abebe W, Agrawal DK. Role of tyrosine kinases in norepinephrine-induced contraction of vascular smooth muscle. J Cardiovasc Pharmacol. 1995 Jul;26(1):153–9.
60. Szokodi I, Horkay F, Merkely B, Solti F, Gellér L, Kiss P, et al. Intrapericardial infusion of endothelin-1 induces ventricular arrhythmias in dogs. Cardiovasc Res. 1998 May;38(2):356–64.
61. Salvati P, Chierchia S, Dho L, Ferrario RG, Parenti P, Vicedomini G, et al. Proarrhythmic activity of intracoronary endothelin in dogs: relation to the site of administration and to changes in regional flow. J Cardiovasc Pharmacol. 1991 Jun;17(6):1007–14.
62. Yorikane R, Shiga H, Miyake S, Koike H. Evidence for direct arrhythmogenic action of endothelin. Biochem Biophys Res Commun. 1990 Nov 30;173(1):457–62.
63. Yorikane R, Koike H, Miyake S. Electrophysiological effects of endothelin-1 on canine myocardial cells. J Cardiovasc Pharmacol. 1991;17 Suppl 7:S159-162.
64. Muiesan ML, Agabiti-Rosei C, Paini A, Salvetti M. Uric Acid and Cardiovascular Disease: An Update. Eur Cardiol. 2016 Aug;11(1):54–9.
65. Anker SD, Doehner W, Rauchhaus M, Sharma R, Francis D, Knosalla C, et al. Uric acid and survival in chronic heart failure: validation and application in metabolic, functional, and hemodynamic staging. Circulation. 2003 Apr 22;107(15):1991–7.
66. Pieters M, Wolberg AS. Fibrinogen and fibrin: An illustrated review. Res Pract Thromb Haemost. 2019 Apr;3(2):161–72.
67. Stec JJ, Silbershatz H, Tofler GH, Matheney TH, Sutherland P, Lipinska I, et al. Association of fibrinogen with cardiovascular risk factors and cardiovascular disease in the Framingham Offspring Population. Circulation. 2000 Oct 3;102(14):1634–8.
68. Zhang K, Zhang XC Mi YH, Liu J. Predicting value of serum soluble ST2 and interleukin-33 for risk stratification and prognosis in patients with acute myocardial infarction. Chin Med J (Engl). (2013) 126:3628–31.
69. Weir RA, Miller AM, Murphy GE, Clements S, Steedman T, Connell JM, et al. Serum soluble ST2: a potential novel mediator in left ventricular and infarct remodeling after acute myocardial infarction. J Am Coll Cardiol. (2010) 55:243–50.
70. Weinberg EO, Shimpo M, Hurwitz S, Tominaga S, Rouleau JL, Lee RT. Identification of serum soluble ST2 receptor as a novel heart failure biomarker. Circulation. (2003) 107:721–6.