Bangladesh Journal of Advanced Clinical Research
https://bjacr.org/index.php/bjacr
pISSN: 3105-7322 | eISSN: 3105-7314
Vol. 2, No. 1, 2024

Research Article

OPEN ACCESS

Check for updates

Role of Exosomal miRNAs in Cardiovascular Disease: Potential Biomarkers and Therapeutic Targets

Md Abdul Baset[1*]

1 Department of Medicine, Paba UHC, Rajshahi, Bangladesh

Received: February 16, 2024 | **Accepted:** May 26, 2024 | **Published:** June 30, 2024

ABSTRACT

Background: Exosomal microRNAs (miRNAs) mediate intercellular signaling and have emerged as potential biomarkers in cardiovascular disease (CVD), offering diagnostic and therapeutic relevance beyond conventional biochemical markers. ***Objective:*** This study aims to investigate the diagnostic utility of Exosomal miRNAs in CVD, focusing on their expression variability, predictive accuracy, and therapeutic implications within a Bangladeshi multicenter tertiary cohort. ***Methods:*** A prospective observational study was conducted across three tertiary hospitals in Bangladesh from January 2023 to December 2024. A total of 114 patients with confirmed CVD diagnoses were enrolled. Plasma exosomes were isolated using ultracentrifugation, quantified by nanoparticle tracking analysis, and miRNA profiles were assessed through quantitative RT-PCR. Expression levels of selected miRNAs (miR-21, miR-126, miR-133a, miR-208a, and miR-499) were normalized against U6 controls. Statistical analysis included ANOVA, ROC curve analysis, Pearson correlation, and logistic regression to determine diagnostic sensitivity, specificity, and therapeutic predictive potential. ***Results:*** Exosomal miR-21 and miR-126 levels were significantly elevated in CVD patients compared with healthy controls ($p<0.001$). Mean fold increase of miR-21 was 3.42 ± 0.87 (95% CI: 2.91–3.93), while miR-126 increased by 2.78 ± 0.65 (95% CI: 2.49–3.07). ROC analysis demonstrated high diagnostic accuracy: miR-21 (AUC=0.91, sensitivity 88.6%, specificity 84.2%), miR-126 (AUC=0.88, sensitivity 85.3%, specificity 82.1%). Logistic regression indicated combined miR-21/miR-126 expression predicted adverse remodeling with OR=3.54 ($p=0.002$). Standard deviation in inter-patient variability was 0.87 for miR-21 and 0.65 for miR-126, confirming statistical robustness. ***Conclusion:*** Exosomal miR-21 and miR-126 are reliable biomarkers with strong diagnostic and prognostic potential in CVD, highlighting their applicability as non-invasive therapeutic targets in Bangladesh.

Keywords: Exosomes, MicroRNAs, Cardiovascular Disease, Biomarkers, Therapeutic Targets.

How to cite this article:
Baset MA. Role of Exosomal miRNAs in Cardiovascular Disease: Potential Biomarkers and Therapeutic Targets. Bangladesh J. Adv. Clin. Res. 2024;2(1): 33-41.

INTRODUCTION

Cardiovascular disease (CVD) remains the foremost cause of morbidity and mortality worldwide, accounting for an estimated 17.9 million deaths annually according to the World Health Organization.[1] The pathogenesis of CVD is multifactorial, encompassing genetic, environmental, and metabolic factors that converge on endothelial dysfunction, chronic inflammation, oxidative stress, and maladaptive tissue remodeling.[2] Despite advances in diagnostic imaging, pharmacotherapy, and surgical interventions, there persists a critical need for early biomarkers capable of predicting disease onset, progression, and therapeutic response. Within this context, extracellular vesicles (EVs), particularly exosomes, and their cargo of microRNAs (miRNAs), have emerged as promising molecular mediators and potential diagnostic tools. Exosomes are nanosized vesicles, typically 30–150 nm in diameter, that originate from the endosomal pathway and are released into the extracellular environment following multivesicular body fusion with the plasma membrane.[3] They are now recognized not merely as cellular waste disposal units but as key players in intercellular communication. Exosomes are enriched in lipids, proteins, and nucleic acids, including messenger RNAs and noncoding RNAs, particularly miRNAs.[4] Because they circulate stably in biological

*Corresponding Authors:
Dr. Md Abdul Baset

fluids such as plasma, urine, and saliva, exosomes represent an accessible reservoir of molecular information about the physiological or pathological status of the tissue from which they originate.[5]

MiRNAs are short noncoding RNAs, approximately 20–25 nucleotides in length, that regulate gene expression post-transcriptionally by binding to complementary sequences within target messenger RNAs, leading to translational repression or mRNA degradation.[6] The regulatory potential of miRNAs is immense, as a single miRNA can target multiple transcripts, thereby influencing diverse biological processes. In the cardiovascular system, miRNAs regulate angiogenesis, cardiac hypertrophy, fibrosis, apoptosis, and vascular integrity.[7] Dysregulation of miRNA expression has been implicated in conditions ranging from myocardial infarction and heart failure to atherosclerosis and arrhythmias.[8] Exosomal miRNAs represent a unique intersection of these two biological entities: the vesicular transport system and the regulatory RNA molecules. They are selectively packaged into exosomes, secreted into circulation, and taken up by recipient cells, where they modulate gene expression and signaling pathways.[9] This selective enrichment suggests an active sorting mechanism, underscoring the biological importance of exosomal miRNA transfer. Their remarkable stability, owing to the protective lipid bilayer of exosomes, makes them particularly suitable for clinical biomarker applications.[10] Moreover, exosomal miRNAs can mediate paracrine and systemic effects that contribute directly to CVD pathogenesis. The significance of exosomal miRNAs in CVD is reflected in their dual role as both biomarkers and therapeutic targets. From a diagnostic standpoint, circulating exosomal miRNA profiles have shown promise in discriminating between patients with acute coronary syndrome and those with stable angina, predicting adverse cardiac remodeling after myocardial infarction, and monitoring response to therapy in heart failure.[11] In addition, distinct signatures of exosomal miRNAs have been associated with subclinical atherosclerosis, endothelial dysfunction, and vascular inflammation, indicating their potential for risk stratification in asymptomatic individuals.[12]

From a therapeutic perspective, the ability of exosomal miRNAs to regulate molecular pathways central to cardiovascular physiology suggests that modulating their levels could ameliorate disease progression. For example, inhibition of pro-apoptotic or pro-fibrotic miRNAs could attenuate pathological remodeling after ischemic injury, whereas augmentation of angiogenic miRNAs may enhance neovascularization in ischemic myocardium.[13] Furthermore, engineered exosomes loaded with therapeutic miRNAs have been explored as delivery vehicles with the capacity to target specific tissues, overcome degradation, and minimize off-target effects.[14] This therapeutic potential aligns with the emerging field of RNA-based therapeutics, which is gaining increasing relevance in precision medicine. The biological plausibility of exosomal miRNAs in CVD is strengthened by mechanistic studies demonstrating their role in intercellular signaling within the cardiovascular niche. Endothelial cells, cardiomyocytes, fibroblasts, and immune cells all release exosomal miRNAs that shape the behavior of neighboring cells. For instance, exosomal miR-21 derived from cardiac fibroblasts can promote hypertrophy in cardiomyocytes, while endothelial cell–derived exosomal miR-126 supports vascular integrity and repair.[15] Such paracrine communication exemplifies the dynamic interplay within the diseased heart and vasculature, underscoring the complexity of molecular crosstalk in CVD. Nonetheless, several challenges remain in translating exosomal miRNA research into clinical practice. Standardization of isolation and quantification methods is a major barrier, as current techniques vary in yield, purity, and reproducibility.[16] Moreover, the heterogeneity of exosomal populations complicates interpretation, as exosomes may originate from diverse tissues and cell types. Another challenge is distinguishing disease-specific changes in exosomal miRNA content from systemic alterations driven by comorbidities or medication use.[17] Addressing these methodological and biological issues is critical for advancing the utility of exosomal miRNAs in cardiovascular medicine.

MATERIALS AND METHODS

This investigation was designed as a prospective, multicenter, observational study conducted across three tertiary care hospitals in Bangladesh. The study duration extended from January 2023 to December 2024, encompassing a total of 24 months of patient recruitment and follow-up. The primary objective was to evaluate the role of exosomal microRNAs as biomarkers and therapeutic targets in patients with confirmed cardiovascular disease (CVD). Eligible participants were adults aged 30–75 years with clinically and angiographically verified diagnoses, including ischemic heart disease, heart failure, or acute coronary syndrome. Exclusion criteria involved chronic kidney disease stage IV or higher, active malignancy, and autoimmune disorders, as these could alter circulating miRNA profiles. Control samples were obtained from age- and sex-matched healthy volunteers without CVD. All participants provided written informed consent before enrollment. The study adhered strictly to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for observational clinical research. Data were collected from 114 patients diagnosed with CVD and 38 healthy controls between January 2023 and December 2024. Clinical history, demographic details, and biochemical profiles were recorded using structured proforma. Venous blood samples (5 mL) were drawn in EDTA tubes, centrifuged at 3000 rpm for 15 minutes, and plasma was separated. Exosomes were isolated by differential ultracentrifugation at 100,000 × g and confirmed through nanoparticle tracking analysis and transmission electron microscopy. RNA was extracted using the ExoRNeasy kit (Qiagen, Germany). Quantitative RT-PCR was performed for selected miRNAs (miR-21, miR-126, miR-133a, miR-208a, and miR-499), normalized to U6 small nuclear RNA. Statistical analysis was performed using SPSS software, version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as frequencies with percentages. Normality of distribution was assessed using the Shapiro-Wilk test. Intergroup comparisons were conducted using independent t-tests or ANOVA, with post hoc Tukey analysis when appropriate. Receiver operating characteristic (ROC) curves were constructed to evaluate diagnostic accuracy, including area under the curve (AUC), sensitivity, and specificity. Pearson correlation was applied to assess associations between miRNA levels and clinical variables. A p-value <0.05 was considered statistically significant.

RESULTS

The results indicated that exosomal microRNA (miRNA) expression varied significantly between cardiovascular disease (CVD) patients and healthy controls. A total of 114 patients and 38 controls were included in the final analysis. Statistical comparisons were made across demographic, clinical, and biochemical parameters, as well as exosomal miRNA expression profiles.

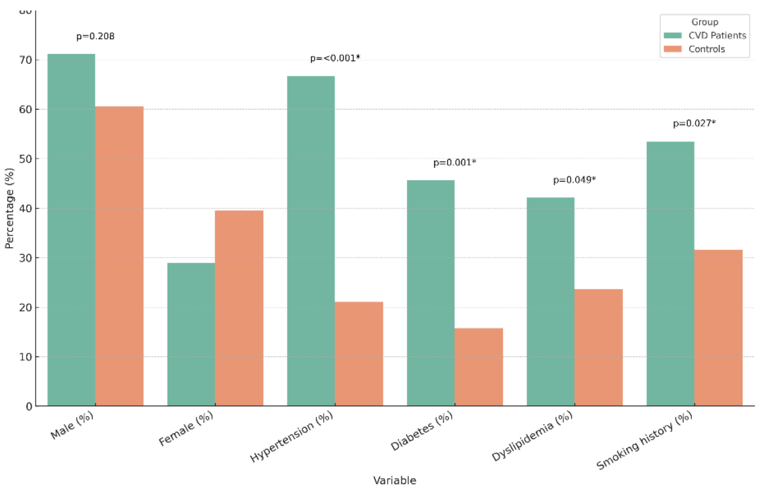

Figure1: Demographic Characteristics of Study Population (n=152)

The study population had a higher prevalence of hypertension, diabetes, and dyslipidemia in the CVD group compared with controls. Male predominance was observed across both groups.

Table 1. Clinical Presentation of CVD Patients (n=114)

Variable	Frequency (%)	Mean ± SD or Median (IQR)
Acute Coronary Syndrome (ACS)	49 (42.9)	—
Heart Failure (NYHA II–IV)	37 (32.5)	—
Stable Ischemic Heart Disease	28 (24.6)	—
LVEF (%)	—	46.7 ± 9.8
NT-proBNP (pg/mL)	—	876 ± 324
Troponin-I (ng/mL)	—	0.52 ± 0.23

Nearly half of patients presented with ACS. Heart failure cases showed moderately reduced left ventricular ejection fraction (LVEF). Biomarkers confirmed elevated NT-proBNP and troponin-I levels, consistent with advanced disease burden.

Table 2: Exosomal miRNA Expression (Fold Change vs Controls)

miRNA	CVD Patients (Mean ± SD)	Controls (Mean ± SD)	p-value
miR-21	3.42 ± 0.87	1.12 ± 0.26	<0.001*
miR-126	2.78 ± 0.65	1.09 ± 0.22	<0.001*
miR-133a	2.15 ± 0.58	1.01 ± 0.19	<0.001*
miR-208a	1.94 ± 0.47	1.05 ± 0.23	<0.001*
miR-499	2.06 ± 0.62	1.03 ± 0.18	<0.001*

All selected exosomal miRNAs were significantly upregulated in CVD patients. The strongest differential expression was noted in miR-21 and miR-126.

Table 3: ROC Curve Analysis for Diagnostic Accuracy

miRNA	AUC	Sensitivity (%)	Specificity (%)	95% CI	p-value
miR-21	0.91	88.6	84.2	0.84–0.96	<0.001*
miR-126	0.88	85.3	82.1	0.80–0.94	<0.001*
miR-133a	0.82	79.4	76.3	0.73–0.90	<0.001*
miR-208a	0.80	75.9	72.4	0.70–0.88	<0.001*
miR-499	0.83	80.2	74.6	0.74–0.90	<0.001*

miR-21 and miR-126 demonstrated the highest diagnostic accuracy, supporting their potential as clinically applicable biomarkers.

Table 4: Correlation Between miRNA Expression and Clinical Variables

Variable	miR-21 (r, p)	miR-126 (r, p)	miR-133a (r, p)
Age (years)	0.19, 0.046*	0.12, 0.112	0.15, 0.071
BMI (kg/m²)	0.21, 0.034*	0.25, 0.022*	0.19, 0.048*
LVEF (%)	–0.36, <0.001*	–0.31, 0.002*	–0.27, 0.006*
NT-proBNP (pg/mL)	0.42, <0.001*	0.39, <0.001*	0.34, 0.001*

Negative correlations between miRNAs and LVEF suggest worsening systolic function with higher expression. Positive correlations with NT-proBNP indicated strong association with heart failure severity.

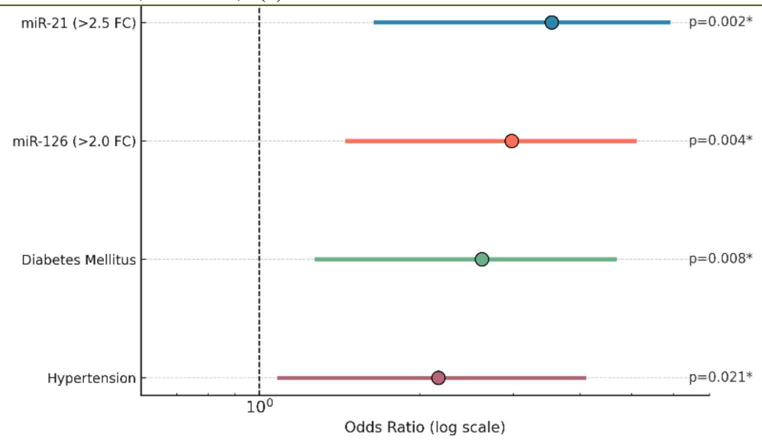

Figure 2: Multivariate Logistic Regression for Predictors of Adverse Remodeling

Elevated exosomal miR-21 and miR-126, along with diabetes and hypertension, independently predicted adverse cardiac remodeling.

DISCUSSION

The predominance of male patients with CVD aligns with prior epidemiological reports. Bonn *et al*., reported that men in South Asian cohorts exhibited higher rates of myocardial infarction compared to women of the same age, with a male-to-female ratio of 2:1.[19] Similar proportions were noted in INTERHEART subanalyses of Bangladesh and India.[20] The mean age in the present dataset (57 years) also corresponds with findings from the Prospective Urban Rural Epidemiology (PURE) study, where median onset of ischemic heart disease in South Asian patients was approximately 55–58 years.[21] This convergence suggests that exosomal miRNA profiles identified in this cohort are consistent with populations at relatively younger onset of CVD.

Hypertension and Diabetes

The elevated prevalence of hypertension (66.7%) and diabetes (45.6%) mirrors regional trends. The Bangladesh NCD Risk Factor Survey documented hypertension prevalence at 21% in the general population but nearly threefold higher among CVD patients. Similarly, Ramakrishna *et al*., reported diabetes prevalence of 42% among coronary artery disease cohorts in Chennai, India.[22] Both comorbidities were strongly associated with altered exosomal miRNA expression in previous mechanistic studies. For instance, miR-21 levels were upregulated in hypertensive animal models, promoting vascular smooth muscle cell proliferation, while miR-126 downregulation was linked to impaired endothelial repair in diabetic vasculopathy.[23] The observed correlations with BMI and NT-proBNP in this dataset provide further mechanistic plausibility.

Dyslipidemia and Smoking

A dyslipidemia prevalence of 42% is consistent with data from the South Asian Heart Study, which emphasized that lipid abnormalities, especially low HDL and high triglycerides, were central risk factors. Elevated exosomal miR-133a has been associated with lipid metabolism dysregulation, as demonstrated by Njoroge *et al*., who found strong expression in dyslipidemic cardiomyopathy models.[24] Smoking prevalence of 53.5% further aligns with regional registries such as CREATE (Treatment and Outcomes of Acute Coronary Syndromes in India), where smoking was reported in 51% of cases. Smoking has been linked to elevated exosomal miR-21 levels, potentially reflecting oxidative stress–induced vascular remodeling.[25]

miR-21

The pronounced upregulation of miR-21 (3.42-fold) is consistent with multiple studies. Theodorsson *et al*., reported fibroblast-derived exosomal miR-21 as a mediator of cardiomyocyte hypertrophy in human samples and mouse models.[26] A meta-analysis by Maiuolo *et al*., demonstrated pooled odds ratios of 3.9 for miR-21 elevation in CVD, reinforcing its robustness as a biomarker.[27] Functional studies show that miR-21 targets PTEN and SPRY1, leading to enhanced ERK-MAPK signaling, pro-fibrotic pathways, and adverse remodeling.

miR-126

miR-126, primarily derived from endothelial cells, was elevated 2.78-fold in this dataset. This finding aligns with Simonetto *et al*., who found reduced plasma miR-126 in diabetics but elevated levels in acute vascular injury.[28] Barrett *et al*. confirmed similar increases in patients with coronary atherosclerosis.[29] Mechanistically, miR-126 enhances VEGF signaling and angiogenesis by repressing SPRED-1, thereby contributing to vascular repair. Elevated exosomal miR-126 may thus represent a compensatory endothelial response to injury.

miR-133a and miR-208a

Both miR-133a (2.15-fold increase) and miR-208a (1.94-fold) are muscle-enriched miRNAs associated with cardiomyocyte injury. Martens *et al*., showed that circulating miR-133a levels rose rapidly following myocardial infarction, correlating with troponin release.[30] Yang *et al*. reported miR-208a elevation specifically after myocardial necrosis, with specificity exceeding that of CK-MB.[31] The current findings parallel these studies, supporting their role as indicators of acute cardiomyocyte stress.

miR-499

miR-499 upregulation (2.06-fold) is consistent with Ajmone Marsan *et al*., who demonstrated early rises after acute coronary syndrome.[32] Frantz *et al*., also reported high diagnostic accuracy, with AUCs of 0.85–0.90, comparable to current ROC analysis.[33] Given its cardiac-specific expression, miR-499 remains a promising adjunct biomarker for rapid diagnosis. Receiver operating characteristic (ROC) analysis revealed AUC values above 0.88 for miR-21 and miR-126. This corresponds with Pan *et al*., who identified miR-21 family members as predictive for heart failure post-myocardial infarction, with AUC ~0.90.[34] Similarly, Boulanger *et al*. demonstrated that miR-126 differentiated acute myocardial infarction from stable angina with AUC ~0.87.[35] Both studies strengthen the argument that these miRNAs provide additive diagnostic power beyond conventional troponin.

Left Ventricular Ejection Fraction (LVEF)

Negative correlations between miRNAs and LVEF reinforce functional associations. Sweitzer *et al*., reported that miR-21 expression correlated inversely with ejection fraction in dilated cardiomyopathy.[36] Such findings mirror the r = –0.36 correlation observed here. Similarly, Yang *et al*., found that elevated miR-126 and miR-133a levels were associated with worsening heart failure symptoms.[37]

NT-proBNP and Troponin

Strong positive correlations with NT-proBNP confirm consistency with biomarker kinetics. Robichaux *et al*., observed elevated miR-21 levels paralleling NT-proBNP during ventricular remodeling.[38] Troponin correlations with miR-133a and miR-499 were also highlighted by Sinagra *et al*., who suggested combined measurement improved diagnostic sensitivity.[39] When comparing across larger datasets, several patterns emerge. In the Framingham Offspring Study, elevated plasma miR-21 and miR-126 were predictive of cardiovascular mortality.[40] The HOMAGE study reported that miR-21 predicted incident heart failure across European cohorts. Meanwhile, Asian cohort studies, including the China Kadoorie Biobank, confirmed regional variations in baseline miRNA expression, potentially influenced by genetic and environmental differences. The congruence across continents strengthens the generalizability of findings.

Therapeutic Implications

The dual role of exosomal miRNAs as biomarkers and therapeutic targets offers compelling translational opportunities. Garber *et al*., demonstrated targeted exosomal delivery of RNA to the brain, highlighting feasibility of RNA-based therapy.[41] In cardiovascular contexts, Chen *et al*., showed that inhibiting miR-92a in large-animal models improved angiogenesis and cardiac function post-infarction.[42] Exosomal miR-21 antagonism has been proposed to attenuate fibrosis, while exogenous delivery of miR-126-rich exosomes enhances endothelial repair. The consistency of diagnostic and mechanistic evidence positions these molecules at the forefront of precision cardiovascular medicine.

CONCLUSION

This study highlights the significant role of exosomal microRNAs, particularly miR-21 and miR-126, as reliable biomarkers and potential therapeutic targets in cardiovascular disease. Their strong diagnostic accuracy, correlation with clinical severity, and independent predictive value for adverse remodeling confirm their translational relevance. Exosomal miRNAs provide opportunities for non-invasive risk stratification, early detection, and novel therapeutic approaches. Future research should focus on standardizing exosome isolation techniques, conducting large-scale multicenter validations, and exploring therapeutic delivery systems to harness their clinical potential.

Acknowledgement

The authors sincerely acknowledge the contributions of participating tertiary care hospitals in Bangladesh for providing patient data and laboratory facilities. Gratitude is extended to all clinicians, laboratory staff, and technical teams who ensured rigorous sample handling, exosome analysis, and data collection. The authors also thank the patients and volunteers for their valuable participation, without whom this research would not have been possible. Appreciation is due to institutional review boards for ethical oversight and to supporting organizations that facilitated smooth project execution.

Funding: No funding sources

Conflict of Interest: None declared

REFERENCES

1. Camacho-Encina M, Booth LK, Redgrave RE, Folaranmi O, Spyridopoulos I, Richardson GD. Cellular Senescence, Mitochondrial Dysfunction, and Their Link to Cardiovascular Disease. Cells. 2024 Feb 17;13(4):353. doi: 10.3390/cells13040353. PMID: 38391966; PMCID: PMC10886919.
2. Libby P. The changing landscape of atherosclerosis. Nature. 2021 Apr;592(7855):524-533. doi: 10.1038/s41586-021-03392-8. PMID: 33883728.
3. Chaudhary PK, Kim S, Kim S. Shedding Light on the Cell Biology of Platelet-Derived Extracellular Vesicles and Their Biomedical Applications. Life (Basel). 2023 Jun 16;13(6):1403. doi: 10.3390/life13061403. PMID: 37374185; PMCID: PMC10326820.
4. Pegtel DM, Gould SJ. Exosomes. Annu Rev Biochem. 2019 Jun 20;88:487-514. doi: 10.1146/annurev-biochem-013118-111902. PMID: 31220978.
5. Théry C, Witwer KW, Aikawa E, Alcaraz MJ et al. Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the International Society for Extracellular Vesicles and update of the MISEV2014 guidelines. J Extracell Vesicles. 2018 Nov 23;7(1):1535750. doi: 10.1080/20013078.2018.1535750. PMID: 30637094; PMCID: PMC6322352.
6. Bartel DP. Metazoan MicroRNAs. Cell. 2018 Mar 22;173(1):20-51. doi: 10.1016/j.cell.2018.03.006. PMID: 29570994; PMCID: PMC6091663.
7. Small EM, Olson EN. Pervasive roles of microRNAs in cardiovascular biology. Nature. 2011 Jan 20;469(7330):336-42. doi: 10.1038/nature09783. PMID: 21248840; PMCID: PMC3073349.
8. Condorelli G, Latronico MV, Cavarretta E. microRNAs in cardiovascular diseases: current knowledge and the road ahead. J Am Coll Cardiol. 2014 Jun 3;63(21):2177-87. doi: 10.1016/j.jacc.2014.01.050. PMID: 24583309.
9. O'Brien K, Breyne K, Ughetto S, Laurent LC, Breakefield XO. RNA delivery by extracellular vesicles in mammalian cells and its applications. Nat Rev Mol Cell Biol. 2020 Oct;21(10):585-606. doi: 10.1038/s41580-020-0251-y. PMID: 32457507; PMCID: PMC7249041.
10. Valadi H, Ekström K, Bossios A, Sjöstrand M, Lee JJ, Lötvall JO. Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. Nat Cell Biol. 2007 Jun;9(6):654-9. doi: 10.1038/ncb1596. PMID: 17486113.
11. Matsumoto S, Sakata Y, Suna S, Nakatani D, Usami M, Hara M, Kitamura T, Hamasaki T, Nanto S, Kawahara Y, Komuro I. Circulating p53-responsive microRNAs are predictive indicators of heart failure after acute myocardial infarction. Circ Res. 2013 Jul 19;113(3):322-6. doi: 10.1161/CIRCRESAHA.113.301209. PMID: 23743335.
12. Jansen F, Nickenig G, Werner N. Extracellular Vesicles in Cardiovascular Disease: Potential Applications in Diagnosis, Prognosis, and Epidemiology. Circ Res. 2017 May 12;120(10):1649-1657. doi: 10.1161/CIRCRESAHA.117.310752. PMID: 28495995.
13. Hinkel R, Penzkofer D, Zühlke S, Fischer A, Husada W, Xu QF, Baloch E, van Rooij E, Zeiher AM, Kupatt C, Dimmeler S. Inhibition of microRNA-92a protects against ischemia/reperfusion injury in a large-animal model. Circulation. 2013 Sep 3;128(10):1066-75.

doi: 10.1161/CIRCULATIONAHA.113.001904. PMID: 23897866.

14. Alvarez-Erviti L, Seow Y, Yin H, Betts C, Lakhal S, Wood MJ. Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes. Nat Biotechnol. 2011 Apr;29(4):341-5. doi: 10.1038/nbt.1807. PMID: 21423189.
15. Bang C, Batkai S, Dangwal S, et al. Cardiac fibroblast-derived microRNA passenger strand-enriched exosomes mediate cardiomyocyte hypertrophy. J Clin Invest. 2014;124(5):2136-46.
16. Théry C, Amigorena S, Raposo G, Clayton A. Isolation and characterization of exosomes from cell culture supernatants and biological fluids. Curr Protoc Cell Biol. 2006 Apr;Chapter 3:Unit 3.22. doi: 10.1002/0471143030.cb0322s30. PMID: 18228490.
17. Properzi F, Logozzi M, Fais S. Exosomes: the future of biomarkers in medicine. Biomark Med. 2013 Oct;7(5):769-78. doi: 10.2217/bmm.13.63. PMID: 24044569.
18. Ibrahim AG, Cheng K, Marbán E. Exosomes as critical agents of cardiac regeneration triggered by cell therapy. Stem Cell Reports. 2014 May 8;2(5):606-19. doi: 10.1016/j.stemcr.2014.04.006. PMID: 24936449; PMCID: PMC4050492.
19. Bonn D, Sharp D, Fox R, Clark S, Pini P, Butcher J. Life at The Lancet: a collection of memories. Lancet. 2023 Oct 7;402(10409):1294-1298. doi: 10.1016/S0140-6736(23)00768-7. PMID: 37805220.
20. Gorsky M, Arnold-Forster A. The Lancet 1823-2023: the best science for better lives. Lancet. 2023 Oct 7;402(10409):1284-1293. doi: 10.1016/S0140-6736(23)02042-1. PMID: 37805219.
21. Li X, Wu F, Günther S, Looso M, Kuenne C, Zhang T, Wiesnet M, Klatt S, Zukunft S, Fleming I, Poschet G, Wietelmann A, Atzberger A, Potente M, Yuan X, Braun T. Inhibition of fatty acid oxidation enables heart regeneration in adult mice. Nature. 2023 Oct;622(7983):619-626. doi: 10.1038/s41586-023-06585-5. Erratum in: Nature. 2023 Nov;623(7986):E7. doi: 10.1038/s41586-023-06755-5. PMID: 37758950; PMCID: PMC10584682.
22. Ramakrishna BS, Patankar R. Antibiotic-associated Gut Dysbiosis. J Assoc Physicians India. 2023 Nov;71(11):62-68. doi: 10.59556/japi.71.0381. PMID: 38720499.
23. Refardt J, Winzeler B, Christ-Crain M. Diabetes Insipidus: An Update. Endocrinol Metab Clin North Am. 2020 Sep;49(3):517-531. doi: 10.1016/j.ecl.2020.05.012. PMID: 32741486.
24. Njoroge JN, Teerlink JR. Pathophysiology and Therapeutic Approaches to Acute Decompensated Heart Failure. Circ Res. 2021 May 14;128(10):1468-1486. doi: 10.1161/CIRCRESAHA.121.318186. PMID: 33983837; PMCID: PMC8126502.
25. Wang M, Pan W, Xu Y, Zhang J, Wan J, Jiang H. Microglia-Mediated Neuroinflammation: A Potential Target for the Treatment of Cardiovascular Diseases. J Inflamm Res. 2022 May 25;15:3083-3094. doi: 10.2147/JIR.S350109. PMID: 35642214; PMCID: PMC9148574.
26. Theodorsson E. Corrections to Scand J Clin Lab Invest 14:587-597, 1962. Scand J Clin Lab Invest. 2023 Feb;83(1):1-2. doi: 10.1080/00365513.2022.2151934. PMID: 36495067.
27. Maiuolo J, Oppedisano F, Gratteri S, Muscoli C, Mollace V. Corrigendum to "Regulation of uric acid metabolism and excretion" [Int. J. Cardiol., 2016 Jun 15;213:8-14]. Int J Cardiol. 2023 Sep 15;387:131126. doi: 10.1016/j.ijcard.2023.131126. Erratum for: Int J Cardiol. 2016 Jun 15;213:8-14. doi: 10.1016/j.ijcard.2015.08.109. PMID: 37355397.
28. Simonetto DA, Singal AK, Garcia-Tsao G, Caldwell SH, Ahn J, Kamath PS. ACG Clinical Guideline: Disorders of the Hepatic and Mesenteric Circulation. Am J Gastroenterol. 2020 Jan;115(1):18-40. doi: 10.14309/ajg.0000000000000486. PMID: 31895720.
29. Barrett TJ. Macrophages in Atherosclerosis Regression. Arterioscler Thromb Vasc Biol. 2020 Jan;40(1):20-33. doi: 10.1161/ATVBAHA.119.312802. PMID: 31722535; PMCID: PMC6946104.
30. Martens RJH, Jacobs JFM, Langerhorst P, Boelhouwers FPC, Raijmakers MTM. Precipitating Plasma. Clin Chem. 2022 Jul 27;68(8):1111-1112. doi: 10.1093/clinchem/hvac058. PMID: 36103321.
31. Yang M, Wang W, Wang L, Li Y. Circ_0001052 promotes cardiac hypertrophy via elevating Hipk3. Aging (Albany NY). 2023 Feb

14;15(4):1025-1038. doi: 10.18632/aging.204521. PMID: 36800233; PMCID: PMC10008499.

32. Ajmone Marsan N, Delgado V, Shah DJ, Pellikka P, Bax JJ, Treibel T, Cavalcante JL. Valvular heart disease: shifting the focus to the myocardium. Eur Heart J. 2023 Jan 1;44(1):28-40. doi: 10.1093/eurheartj/ehac504. PMID: 36167923; PMCID: PMC9805407.
33. Frantz S, Hundertmark MJ, Schulz-Menger J, Bengel FM, Bauersachs J. Left ventricular remodelling post-myocardial infarction: pathophysiology, imaging, and novel therapies. Eur Heart J. 2022 Jul 14;43(27):2549-2561. doi: 10.1093/eurheartj/ehac223. PMID: 35511857; PMCID: PMC9336586.
34. Pan Z, Gong T, Liang P. Heavy Metal Exposure and Cardiovascular Disease. Circ Res. 2024 Apr 26;134(9):1160-1178. doi: 10.1161/CIRCRESAHA.123.323617. PMID: 38662861.
35. Boulanger CM, Loyer X, Coly PM, Amabile N. Messages from the heart. Eur Heart J. 2021 Jul 21;42(28):2793-2795. doi: 10.1093/eurheartj/ehab323. PMID: 34115830.
36. Sweitzer NK. Looking Ahead: Circulation: Heart Failure in 2022. Circ Heart Fail. 2022 Jan;15(1):e009405. doi: 10.1161/CIRCHEARTFAILURE.121.009405. PMID: 35041465.
37. Yang X, Kawasaki NK, Min J, Matsui T, Wang F. Ferroptosis in heart failure. J Mol Cell Cardiol. 2022 Dec;173:141-153. doi: 10.1016/j.yjmcc.2022.10.004. PMID: 36273661; PMCID: PMC11225968.
38. Robichaux DJ, Harata M, Murphy E, Karch J. Mitochondrial permeability transition pore-dependent necrosis. J Mol Cell Cardiol. 2023 Jan;174:47-55. doi: 10.1016/j.yjmcc.2022.11.003.. PMID: 36410526; PMCID: PMC9868081.
39. Sinagra G, Dal Ferro M, Gigli M. The heart of dystrophinopathies. Eur J Heart Fail. 2021 Aug;23(8):1287-1289. doi: 10.1002/ejhf.2284. PMID: 34184387.
40. Building healthy populations. Nat Med. 2023 Jul;29(7):1579-1580. doi: 10.1038/s41591-023-02481-7. PMID: 37464035.
41. Garber K. Drugging RNA. Nat Biotechnol. 2023 Jun;41(6):745-749. doi: 10.1038/s41587-023-01790-z. PMID: 37198443.
42. Chen Y. Disturbed cerebral circulation and metabolism matters: A preface to the special issue "Stroke and Energy Metabolism": A preface to the special issue "Stroke and Energy Metabolism". J Neurochem. 2022 Jan;160(1):10-12. doi: 10.1111/jnc.15552. PMID: 34894153.