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# Targeted Cardiovascular Therapy Using Nanoparticles: Advances and Perspectives

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## Abstract

Cardiovascular Diseases (CVDs) remain the leading cause of mortality worldwide, posing substantial public health and economic burdens despite remarkable progress in modern medicine. Conventional pharmacological and surgical interventions often lack tissue specificity, resulting in systemic side effects and suboptimal therapeutic efficacy. In recent years, nanotechnology has emerged as a promising platform for the diagnosis and treatment of CVDs, enabling targeted drug delivery, enhanced bioavailability, and controlled release of therapeutic agents. Various classes of nanoparticles, including lipid-based, polymeric, metallic, and biomimetic systems, have been engineered to deliver drugs, genes, or imaging agents directly to diseased cardiovascular tissues. These nanocarriers can be tailored to recognize specific molecular markers or respond to pathological stimuli, thereby improving selectivity and therapeutic precision. Despite encouraging preclinical outcomes, several barriers continue to hinder clinical translation, such as limited biocompatibility data, immune system clearance, manufacturing scalability, and stringent regulatory requirements. This review provides an up-to-date overview of nanoparticle-based targeted therapies in cardiovascular medicine, highlighting current design strategies, therapeutic applications, and remaining challenges. It also discusses future perspectives and translational considerations to advance the development of safe and effective cardiovascular nanotherapeutics.

**Keywords:** Nanoparticles, Targeted therapy, Cardiovascular diseases, Drug delivery, Nanomedicine.

## 1 | Introduction

Cardiovascular Diseases (CVDs) continue to represent the leading cause of mortality worldwide, accounting for more than 17 million deaths annually and imposing an immense global health and socioeconomic burden [1]. Despite substantial advancements in conventional treatment modalities such as pharmacotherapy, angioplasty, and coronary artery bypass grafting, these approaches often fail to achieve optimal therapeutic

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outcomes due to nonspecific drug biodistribution, limited targeting efficiency, and undesirable systemic side effects [2].

In recent decades, the concept of targeted therapy has garnered growing attention in cardiovascular medicine as a means to overcome these limitations. By selectively directing therapeutic agents to diseased tissues or cells, targeted delivery systems aim to enhance pharmacological efficacy, reduce off-target toxicity, and improve overall patient outcomes [3].

Among emerging biomedical technologies, nanotechnology has shown exceptional promise in revolutionizing cardiovascular therapeutics. Nanoparticle-based delivery systems provide nanoscale platforms for encapsulating, stabilizing, and releasing bioactive compounds in a controlled, site-specific manner [4]. These engineered nanocarriers exhibit tunable physicochemical properties, including particle size, surface charge, morphology, and composition that can be precisely modified to optimize blood circulation time, cellular internalization, and accumulation at pathological cardiovascular sites [5].

Furthermore, surface functionalization with specific targeting ligands ,such as monoclonal antibodies, peptides, or nucleic acid aptamers, enables active recognition of molecular markers associated with atherosclerotic plaques, inflamed endothelium, or ischemic myocardium, thereby achieving greater therapeutic selectivity [6]. A growing body of preclinical evidence supports the potential of nanoparticle-mediated strategies for managing primary cardiovascular conditions, including atherosclerosis, myocardial infarction, and ischemia-reperfusion injury [7].

Nevertheless, despite these promising developments, the clinical translation of cardiovascular nanotherapeutics remains limited. Key challenges include biological safety and long-term biocompatibility, recognition and clearance by the immune system, manufacturing scalability, reproducibility, and the lack of standardized evaluation protocols [8].

This review, therefore, aims to provide a comprehensive overview of recent advances in nanoparticle-based targeted cardiovascular therapy. It summarizes the current design principles, therapeutic applications, and biological considerations, while highlighting significant translational barriers and future opportunities for the clinical implementation of next-generation cardiovascular nanomedicines [9].

# 2|Types of Nanoparticles Used in Targeted Cardiovascular Therapy

Nanoparticles are the cornerstone of targeted cardiovascular nanomedicine, providing platforms for precise drug delivery, enhanced bioavailability, and controlled release. Over the past decade, a wide variety of nanoparticle systems have been engineered, each exhibiting distinct physicochemical properties and biomedical functions. The optimal selection of nanoparticle type depends mainly on the therapeutic objective, physicochemical characteristics of the active agent, and the biological microenvironment of the target cardiovascular tissue. The following sections summarize the significant classes of nanoparticles currently under investigation for targeted cardiovascular applications.

## 2.1|Lipid-Based Nanoparticles

Lipid-based nanoparticles, including liposomes, Solid Lipid Nanoparticles (SLNs), and Nanostructured Lipid Carriers (NLCs), are among the most extensively investigated systems owing to their structural similarity to biological membranes and their excellent biocompatibility (*Fig. 1*) [10], [11]. Their amphiphilic nature allows for the encapsulation of both hydrophilic and hydrophobic drugs, while their lipid bilayer structure provides superior protection against premature degradation. Furthermore, the surface of lipid nanoparticles can be functionalized with targeting ligands such as peptides, antibodies, or small molecules to facilitate selective accumulation in atherosclerotic plaques or ischemic myocardium. Recent developments have also focused on stimuli-responsive lipid carriers, capable of releasing therapeutic payloads in response to pH, temperature, or enzymatic changes within diseased cardiovascular tissues.

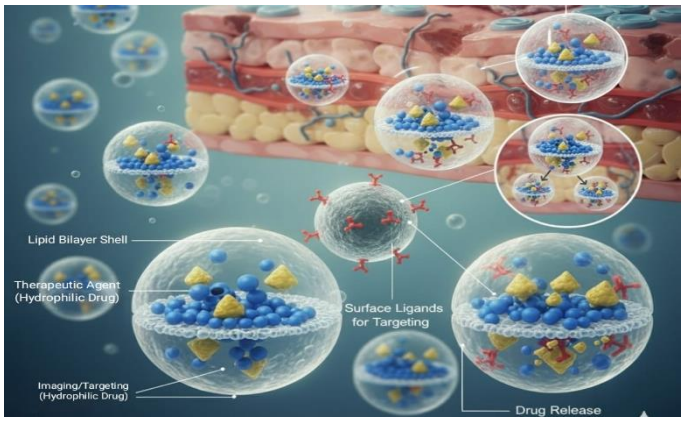


**Fig. 1. Lipid-Based nanoparticles for targeted cardiovascular delivery.**

## 2.2 | Polymeric Nanoparticles

Polymeric nanoparticles, synthesized from natural or synthetic polymers such as Poly(Lactic-co-Glycolic Acid) (PLGA), Polylactic Acid (PLA), Polycaprolactone (PCL), and chitosan, offer high chemical stability and the ability to provide sustained and controlled drug release *Fig. 2* [12], [13]. Their biodegradability and tunable composition make them suitable for long-term therapeutic delivery. Moreover, stimuli-responsive polymeric nanoparticles can alter their structure or release kinetics in response to environmental cues (e.g., pH, redox potential, or enzymatic activity), enabling precise spatiotemporal control over drug delivery at pathological cardiovascular sites.

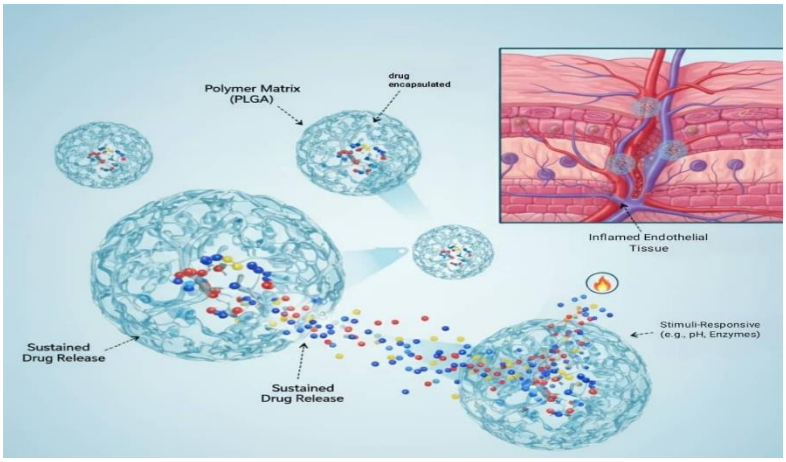


**Fig. 2. Polymeric nanoparticles for controlled and stimuli-responsive cardiovascular delivery.**

## 2.3 | Metallic Nanoparticles

Metallic nanoparticles, such as Gold (AuNPs), Silver (AgNPs), and Iron Oxide nanoparticles ($Fe_3O_4$), exhibit unique optical, magnetic, and plasmonic characteristics that render them multifunctional tools for cardiovascular therapy and diagnostics *Fig. 3* [14], [15]. Their ability to convert electromagnetic energy into heat has led to applications in photothermal and magnetothermal therapy, while their high surface-to-volume ratio enables efficient drug or gene conjugation. Additionally, iron oxide nanoparticles have been used as Magnetic Resonance Imaging (MRI) contrast agents, enabling noninvasive visualization of atherosclerotic lesions and thrombotic regions.

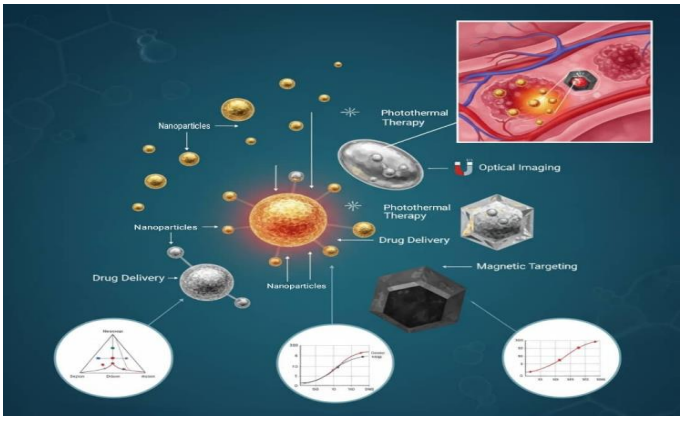


**Fig. 3. Metallic nanoparticles for cardiovascular theragnostic.**

## 2.4 | Biomimetic Nanoparticles

Biomimetic nanoparticles represent a new generation of smart nanocarriers designed to replicate biological behavior through surface coating with cell-derived membranes or biomolecules *Fig. 4* [16], [17]. Examples include nanoparticles camouflaged with Red Blood Cell (RBC), platelet, or leukocyte membranes, which enable immune evasion, prolonged systemic circulation, and enhanced homing to sites of vascular inflammation or myocardial injury. This biomimicry provides an effective strategy to overcome the limitations of synthetic nanomaterials by integrating natural recognition capabilities with engineered drug-delivery functions.

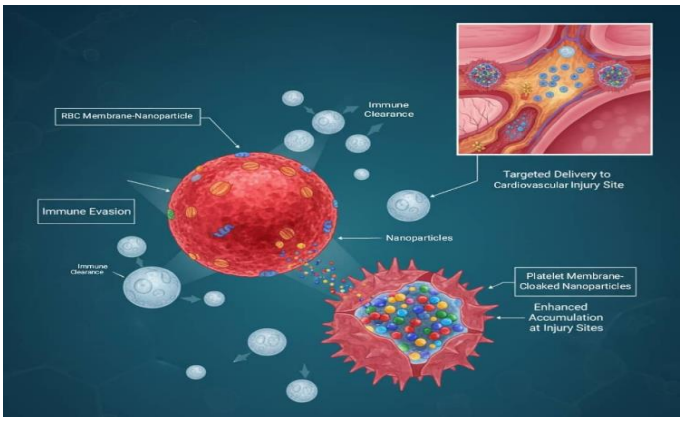


**Fig. 4. Biomimetic nanoparticles for immune evasion and targeted cardiovascular delivery.**

## 2.5 | Hybrid Nanostructures

Hybrid nanostructures combine the advantages of multiple nanomaterial classes into a single multifunctional platform (*Fig. 5*) [18], [19]. Typical examples include polymer lipid hybrid nanoparticles, metal–polymer composites, and biomimetic metallic hybrids. These architectures synergistically integrate biocompatibility, structural stability, and targeting specificity, enabling simultaneous imaging, therapy, and real-time monitoring often referred to as theranostics. Hybrid nanoparticle systems hold tremendous potential for addressing the multifaceted pathophysiology of CVDs by enabling the co-delivery of drugs, genes, or imaging agents within a single nanosystem.

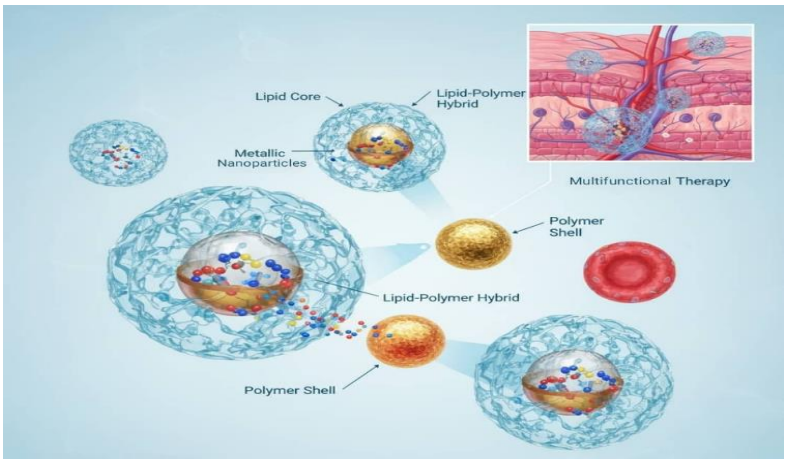


**Fig. 5. Hybrid nanostructures for multifunctional cardiovascular therapies.**

# 3 | Mechanisms of Targeting in Nanotherapeutics for Cardiovascular Diseases

A critical challenge in cardiovascular nanomedicine is achieving precise and efficient delivery of therapeutic agents to the diseased or injured tissue while minimizing systemic exposure and off-target toxicity. Nanoparticles employ diverse targeting strategies to enhance local drug accumulation and improve therapeutic efficacy. These strategies can be broadly classified into passive, active, stimulus-responsive, and magnetic targeting mechanisms.

## 3.1 | Passive Targeting

Passive targeting exploits the inherent pathological features of diseased cardiovascular tissues. Injured or inflamed areas often exhibit enhanced vascular permeability and impaired lymphatic drainage, facilitating the extravasation and retention of nanoparticles, a phenomenon commonly referred to as the Enhanced Permeability and Retention (EPR) effect [20], [21]. The size, shape, and surface chemistry of nanoparticles are critical determinants of their ability to penetrate vessel walls and preferentially accumulate at the target site. This strategy is particularly relevant in atherosclerotic plaques, ischemic myocardium, and regions of vascular injury where microvascular leakage is prominent.

## 3.2 | Active Targeting

Active targeting involves functionalizing nanoparticle surfaces with specific ligands, such as monoclonal antibodies, peptides, aptamers, or small molecules, that selectively bind receptors expressed on target cells [22], [23]. In cardiovascular applications, these receptors are frequently present on endothelial cells, macrophages, or other immune/inflammatory cells residing within the diseased tissue. Such ligand-receptor interactions enhance nanoparticle retention, facilitate cellular internalization, and increase localized therapeutic concentrations, thereby improving treatment efficacy while reducing systemic side effects.

## 3.3 | Stimuli-Responsive Targeting

Stimuli-responsive nanoparticles are engineered to respond to specific microenvironmental cues within pathological tissues, including acidic pH, oxidative stress, enzymatic activity, or hypoxia [24], [25]. Upon encountering these stimuli, nanoparticles undergo conformational or chemical changes that trigger controlled and site-specific drug release, enabling precise delivery of therapeutic agents directly to the lesion site. This strategy effectively minimizes off-target effects and enhances therapeutic selectivity.

## 3.4 | Magnetic Targeting

Magnetic targeting utilizes Magnetic Nanoparticles (MNPs) guided by external magnetic fields to achieve localized drug accumulation [26], [27]. By directing MNPs toward diseased vascular or myocardial tissue, this approach increases nanoparticle retention, enhances cellular uptake, and improves therapeutic outcomes. Magnetic targeting can also be combined with imaging modalities, such as MRI, enabling theranostic applications for simultaneous diagnosis and therapy.

## 3.5 | Integrative Targeting Approaches

Recent advances suggest that combining multiple targeting strategies, for example, passive accumulation with active ligand-mediated recognition or stimuli-responsive release, can synergistically enhance the precision, efficacy, and safety of cardiovascular nanotherapeutics. Such integrative approaches hold significant promise for overcoming current limitations in drug delivery and maximizing clinical outcomes.

# 4 | Cutting-Edge Applications of Targeted Nanoparticle Therapy in Cardiovascular Diseases

Targeted nanoparticle-based therapies have emerged as innovative and transformative strategies for the management of CVDs, enabling precise delivery of therapeutic agents directly to injured or diseased tissues. By concentrating treatment at the site of pathology, these approaches enhance therapeutic efficacy while minimizing systemic exposure and off-target side effects, thereby providing significant advantages over conventional pharmacological and surgical interventions. The primary applications of targeted nanoparticles in cardiovascular medicine are summarized below.

## 4.1 | Atherosclerosis Treatment

Nanoparticles can selectively accumulate in atherosclerotic plaques, facilitating the targeted delivery of anti-inflammatory, antioxidant, and lipid-modulating agents [28], [29]. Localized therapy reduces plaque inflammation, mitigates oxidative stress, and promotes plaque stabilization, ultimately lowering the risk of acute cardiovascular events such as myocardial infarction and ischemic stroke. Functionalization of nanoparticles with ligands targeting macrophages or endothelial cells further enhances therapeutic precision.

## 4.2 | Myocardial Regeneration

In myocardial infarction and other cardiac injuries, nanoparticles act as carriers for drugs, growth factors, or gene therapy constructs that promote tissue repair and regeneration [30], [31]. These nanocarriers can stimulate angiogenesis, enhance cardiomyocyte proliferation, and modulate local inflammatory responses, thereby supporting functional heart recovery and improving post-infarction remodeling.

## 4.3 | Gene and Ribonucleic Acid Therapies

Nanoparticles provide an efficient platform for targeted delivery of genetic material, including DNA, Small Interfering Ribonucleic Acid (siRNA), and micro Ribonucleic Acid (miRNA), to specific cardiac cell populations. This targeted gene modulation enables precise correction of the pathological molecular pathways implicated in CVDs, offering personalized, highly specific therapeutic interventions. Nanoparticle-mediated delivery also protects nucleic acids from degradation and enhances cellular uptake, overcoming significant limitations of conventional gene therapy approaches.

## 4.4 | Theranostics

Theranostic nanoparticles, which combine therapeutic and diagnostic functionalities, enable simultaneous drug delivery and real-time imaging [30], [31]. This dual capability enables clinicians to monitor treatment responses in real time, adjust therapeutic regimens, and optimize patient outcomes. Theranostic strategies are

particularly valuable for tracking plaque regression, myocardial repair, and vascular remodeling, providing a comprehensive approach to precision cardiovascular medicine.

# 5 | Challenges and Limitations in Targeted Nanoparticle Therapy for Cardiovascular Diseases

Despite the promising potential of targeted nanoparticle-based therapies in cardiovascular medicine, several critical challenges must be addressed before widespread clinical translation can be achieved.

## 5.1 | Safety and Nanoparticle Toxicity

A major concern in the clinical implementation of nanoparticle therapies is their safety profile. Depending on their size, composition, and surface characteristics, nanoparticles can elicit unintended toxicological effects. For example, certain biodegradable polymeric nanoparticles have been reported to disrupt endothelial function and provoke inflammatory responses, potentially exacerbating cardiovascular pathology [32]. Additionally, systemic accumulation of nanoparticles in organs such as the liver, kidneys, and spleen raises concerns regarding long-term toxicity and biocompatibility. Therefore, comprehensive in vivo and in vitro evaluations are essential to thoroughly assess safety and ensure patient protection during prolonged treatments [33], [34].

## 5.2 | Stability and Controlled Drug Release

Maintaining nanoparticle stability in the dynamic cardiovascular environment and achieving precise, controlled release of therapeutic agents at the target site remain significant challenges. Fluctuations in blood flow, enzymatic activity, and local pH can affect nanoparticle integrity and drug release kinetics. Development of smart or stimuli-responsive nanoparticles that release their payload exclusively in pathological tissue is a major focus of current research, aiming to maximize therapeutic efficacy while minimizing off-target effects [35], [36].

## 5.3 | Precise Targeting and Tissue Penetration

Achieving selective accumulation of nanoparticles within diseased cardiovascular tissue is impeded by multiple biological barriers. Nanoparticles must evade immune clearance mechanisms and traverse intact endothelial barriers to reach target lesions, such as atherosclerotic plaques or ischemic myocardium. The dense extracellular matrix and fibrotic tissue surrounding pathological sites further restrict nanoparticle penetration, limiting delivery efficiency. Innovative targeting ligands and surface modifications are critical to enhance homing, tissue infiltration, and therapeutic outcomes [37], [38].

## 5.4 | Scalability of Production and Cost

Translating laboratory-scale nanoparticle formulations to industrial-scale production poses technical and economic challenges. Ensuring batch-to-batch reproducibility, stability, and functional consistency is complex, while the use of expensive raw materials and sophisticated synthesis protocols contributes to high manufacturing costs. These factors may hinder the accessibility and affordability of nanoparticle-based therapies for cardiovascular patients [39], [40].

## 5.5 | Ethical and Regulatory Considerations

The novelty of nanomedicine introduces unique ethical and regulatory challenges. Current regulatory frameworks for nanoparticle-based therapies are evolving, and comprehensive guidelines for evaluating safety, efficacy, and long-term outcomes are still lacking. Collaboration among scientists, clinicians, and regulatory authorities is essential to establish standardized testing protocols, ensure responsible clinical implementation, and address public concerns regarding nanotechnology applications [41], [42].

# 6 | Future Perspectives in Targeted Nanoparticle Therapy for Cardiovascular Diseases

Recent advances in nanoparticle technology and their biomedical applications have opened new avenues for treating CVDs. With improvements in targeting specificity, physicochemical stability, and the development of smart nanocarriers, nanoparticle-based therapies are expected to achieve higher efficacy, enhanced safety, and reduced systemic side effects.

## 6.1 | Multifunctional Nanoparticles and Theranostics

A prominent future direction involves multifunctional nanoparticles capable of co-delivering multiple therapeutic agents or integrating diagnostic and therapeutic functionalities, a strategy commonly referred to as theranostics [43], [44]. These advanced platforms enable real-time monitoring of therapeutic responses, facilitating personalized and adaptive treatment regimens tailored to individual patient needs.

## 6.2 | Stimuli-Responsive and Smart Nanoparticles

The development of stimuli-responsive nanoparticles that respond to specific biological cues, such as pH, temperature, oxidative stress, or enzyme activity, is anticipated to enhance further targeting precision [45], [46]. Such smart systems can achieve selective drug release at pathological sites, minimizing off-target toxicity and maximizing therapeutic efficacy

## 6.3 | Integration with Artificial Intelligence and Bioinformatics

The integration of nanoparticle technology with cutting-edge computational tools, including Artificial Intelligence (AI) and bioinformatics, is poised to transform cardiovascular therapeutics [47], [48]. AI-driven algorithms can analyze large datasets derived from patient profiles and nanoparticle behavior to optimize nanoparticle design, predict therapeutic outcomes, and support clinical decision-making, thereby accelerating the translation of nanomedicine into practice.

## 6.4 | Enhancing Biocompatibility and Safety

Ongoing efforts are focused on improving biocompatibility and reducing potential toxicity through surface modifications, the use of biodegradable materials, and precise control over particle size and morphology [49], [50]. Ensuring long-term safety is essential not only for regulatory approval but also for widespread patient acceptance of nanoparticle-based therapies.

## 6.5 | Translational and Collaborative Strategies

Interdisciplinary collaboration among engineers, biologists, clinicians, and regulatory experts is critical to accelerate the translation of nanoparticle therapies from the laboratory to clinical settings. Establishing standardized protocols for preclinical evaluation, scalable manufacturing, and regulatory compliance will support the successful integration of nanomedicine into cardiovascular care [51], [52].

# 7 | Ethical and Regulatory Considerations in Targeted Nanoparticle Therapy for Cardiovascular Diseases

The rapid advancement of nanotechnology in cardiovascular medicine introduces complex ethical and regulatory challenges that must be addressed to ensure the safe, responsible, and equitable implementation of these therapies. Patient safety remains the foremost priority; therefore, comprehensive evaluation of the potential risks and benefits of nanoparticle-based interventions is essential before clinical translation.

## 7.1 | Data Privacy and Informed Consent

The rise of personalized nanomedicine, which often relies on genomic and biomarker data, has heightened concerns about data privacy and patient confidentiality. Robust legal frameworks are required to protect patient information, and informed consent procedures must clearly communicate the potential benefits and risks of nanoparticle-based treatments.

## 7.2 | Regulatory Standards and Global Harmonization

Regulatory requirements for the production, characterization, and clinical evaluation of nanoparticles differ widely across countries, creating challenges for global approval, manufacturing, and adoption. Organizations such as the FDA, EMA, and WHO are actively developing guidelines; however, regulatory frameworks are still evolving and must be continuously updated to keep pace with technological advancements. Standardized protocols for preclinical testing, quality control, and safety assessment are critical for facilitating clinical translation.

## 7.3 | Environmental and Ecological Considerations

Public concerns regarding the environmental impact of nanoparticles, including their long-term persistence and bioaccumulation, necessitate responsible policymaking and transparency from researchers and manufacturers. Integrating environmental risk assessments into the development and production pipeline is essential to mitigate potential ecological hazards and ensure sustainable nanomedicine practices.

## 7.4 | Ethical Dilemmas and Social Equity

Ethical challenges include equitable access to potentially expensive nanoparticle therapies, the risk of misuse of nanotechnologies, and the imperative for clear communication to prevent public misinformation. Collaborative engagement among scientists, clinicians, ethicists, regulatory bodies, and patient advocacy groups is crucial to formulate fair, transparent, and socially responsible policies.

# 8 | Conclusion

Targeted nanoparticle-based therapies represent a revolutionary approach in cardiovascular medicine, offering unprecedented opportunities for precision, efficiency, and multifunctionality in treatment. Throughout this review, we have highlighted the unique physicochemical properties of various nanoparticle platforms, including lipid-based, polymeric, metallic, biomimetic, and hybrid systems that enable site-specific delivery of therapeutic and diagnostic agents to diseased cardiovascular tissues. Such precision enhances therapeutic efficacy, reduces systemic toxicity, and opens the door to personalized treatment strategies tailored to individual patient needs.

The mechanisms of targeting, including passive accumulation, active ligand-mediated targeting, stimuli-responsiveness, and magnetic guidance, have demonstrated the ability to overcome traditional barriers in cardiovascular therapy, such as poor drug bioavailability and off-target effects. Additionally, emerging theranostic and multifunctional nanoparticles allow for simultaneous imaging and therapy, enabling real-time monitoring of treatment responses and adaptive interventions, which are crucial for optimizing patient outcomes.

Despite these promising advancements, several critical challenges remain. Nanoparticle toxicity, immune clearance, limited tissue penetration, production scalability, regulatory hurdles, and ethical considerations pose significant obstacles to clinical translation. Addressing these issues requires comprehensive preclinical evaluation, standardization of manufacturing protocols, and interdisciplinary collaboration among scientists, clinicians, engineers, and regulatory authorities. Moreover, integrating emerging technologies such as AI and bioinformatics could optimize nanoparticle design, predict therapeutic efficacy, and streamline decision-making in clinical practice.

Looking forward, the future of targeted nanoparticle therapy lies in the development of smart, stimuli-responsive, and multifunctional nanoplatforms with enhanced biocompatibility, safety, and adaptability. Such systems are expected not only to improve treatment outcomes for prevalent cardiovascular conditions, including atherosclerosis, myocardial infarction, and ischemia-reperfusion injuries, but also to pave the way for precision cardiovascular medicine that accounts for patient-specific pathophysiology, genetic background, and risk profiles.

In conclusion, while significant progress has been made, realizing the full clinical potential of nanoparticle-based cardiovascular therapies requires continued technological innovation, robust clinical evaluation, ethical oversight, and consideration of global accessibility. By overcoming current limitations and integrating multidisciplinary expertise, targeted nanoparticle therapy is poised to transform cardiovascular care, offering safer, more effective, and highly personalized treatment options that could significantly reduce morbidity and mortality worldwide.

## Conflict of Interest

The authors declare no conflict of interest.

## Data Availability

All data are included in the text.

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## References

[1] Gerhardt, T., Gerhardt, L. M., Ouwerkerk, W., Roth, G. A., Dickstein, K., Collins, S. P., & Angermann, C. E. (2023). Multimorbidity in patients with acute heart failure across world regions and country income levels (report-HF): A prospective, multicentre, global cohort study. *The lancet global health*, *11*(12), e1874-e1884.

[2] Berlowitz, J. B., Xie, W., Harlow, A. F., Hamburg, N. M., Blaha, M. J., Bhatnagar, A., & Stokes, A. C. (2022). E-cigarette use and risk of cardiovascular disease: A longitudinal analysis of the PATH study (2013–2019). *Circulation*, *145*(20), 1557-1559.

[3] Fang, J., Nakamura, H., & Maeda, H. (2011). The EPR effect: Unique features of tumor blood vessels for drug delivery, factors involved, and limitations and augmentation of the effect. *Advanced drug delivery reviews*, *63*(3), 136–151. https://doi.org/10.1016/j.addr.2010.04.009

[4] Omidian, H., Babanejad, N., & Cubeddu, L. X. (2023). Nanosystems in cardiovascular medicine: advancements, applications, and future perspectives. *Pharmaceutics*, *15*(7), 1935. https://doi.org/10.3390/pharmaceutics15071935

[5] Nasir, k., Saba, s., Hussa, in, a., Ramzan, k., & Mushtaq, s. (2023). Nano particle based drug delivery in cancer therapy. *Current studies in health and life sciences*, 169. https://B2n.ir/sp9339

[6] Wang, Y., Wang, J., Gao, R., Liu, X., Feng, Z., Zhang, C., & Wang, W. (2022). Biomimetic glycopeptide hydrogel coated pcl/nha scaffold for enhanced cranial bone regeneration via macrophage m2 polarization-induced osteo-immunomodulation. *Biomaterials*, *285*, 121538. https://doi.org/10.1016/j.biomaterials.2022.121538

[7] Ding, L., Chang, C.J., Liang, M.L., Dong, K. M., & Li, F.R. (2024). Plant derived extracellular vesicles as potential emerging tools for cancer therapeutics. *Advanced therapeutics*, *7*(11), 2400256.

[8] Yu, Y., Jin, H., Li, L., Zhang, X., Zheng, C., Gao, X., Sun, B. (2023). An injectable, activated neutrophil-derived exosome mimetics/extracellular matrix hybrid hydrogel with antibacterial activity and wound

healing promotion effect for diabetic wound therapy. *Journal of nanobiotechnology*, *21*(1), 308. https://doi.org/10.1186/s12951-023-02073-0

[9] Seol, Y., Ganguly, K., Kim, H., Randhawa, A., Patil, T. V, Dutta, S. D., & Lim, K.T. (2024). Stimuli-triggered pollen-inspired micro/nanorobots for advanced therapeutics. *Nano today*, *57*, 102337. https://doi.org/10.1016/j.nantod.2024.102337

[10] Hu, Q., Qian, C., Sun, W., Wang, J., Chen, Z., Bomba, H. N., … & Gu, Z. (2016). Engineered nano-platelets for enhanced treatment of multiple myeloma and thrombus. *Advanced materials (deerfield beach, fla.)*, *28*(43), 9573. https://pmc.ncbi.nlm.nih.gov/articles/PMC5283718/

[11] Li, X., Guan, Q., Zhuang, Z., Zhang, Y., Lin, Y., Wang, J., … & Licheng Ling. (2023). Ordered mesoporous carbon grafted MXene catalytic heterostructure as Li-ion kinetic pump toward high-efficient sulfur/sulfide conversions for Li S battery. *ACS nano, 17*(2), 1653–1662. https://pubs.acs.org/doi/abs/10.1021/acsnano.2c11663

[12] Li, L., Zhang, Q., He, B., Pan, R., Wang, Z., Chen, M., … & Litao Sun. (2022). Advanced multifunctional aqueous rechargeable batteries design: from materials and devices to systems. *Advanced materials*, *34*(5), 2104327. https://doi.org/10.1002/adma.202104327

[13] Zhang, Y., Liu, Q., Zhang, X., Huang, H., Tang, S., Chai, Y., …& Chengbin Yang . (2022). Recent advances in exosome-mediated nucleic acid delivery for cancer therapy. *Journal of nanobiotechnology*, *20*(1), 279. https://doi.org/10.1186/s12951-022-01472-z

[14] Singh, D., & Ray, S. (2023). A short appraisal of nanodiamonds in drug delivery and targeting: recent advancements. *Frontiers in nanotechnology*, *5*, 1259648. https://doi.org/10.3389/fnano.2023.1259648

[15] Dong, Y., Zheng, S., Qin, J., Zhao, X., Shi, H., Wang, X., … & Wu, Z. S. (2018). All-MXene-based integrated electrode constructed by Ti3C2 nanoribbon framework host and nanosheet interlayer for high-energy-density Li--S batteries. *ACS nano*, *12*(3), 2381–2388. https://pubs.acs.org/doi/abs/10.1021/acsnano.7b07672

[16] Zhang, D., Chen, Q., Shi, C., Chen, M., Ma, K., Wan, J., & Liu, R. (2021). Dealing with the foreign-body response to implanted biomaterials: Strategies and applications of new materials. *Advanced functional materials*, *31*(6), 2007226. https://doi.org/10.1002/adfm.202007226

[17] Wang, X., Wang, X., Yue, Q., Xu, H., Zhong, X., Sun, L., & Cheng, L. (2021). Liquid exfoliation of TiN nanodots as novel sonosensitizers for photothermal-enhanced sonodynamic therapy against cancer. *Nano today*, *39*, 101170. https://doi.org/10.1016/j.nantod.2021.101170

[18] Li, N., Sun, C., Jiang, J., Wang, A., Wang, C., Shen, Y., … & Yan Wang. (2021). Advances in controlled-release pesticide formulations with improved efficacy and targetability. *Journal of agricultural and food chemistry*, *69*(43), 12579–12597. https://pubs.acs.org/doi/abs/10.1021/acs.jafc.0c05431

[19] Gupta, A. K., & Gupta, M. (2005). Synthesis and surface engineering of iron oxide nanoparticles for biomedical applications. *Biomaterials*, *26*(18), 3995–4021. https://doi.org/10.1016/j.biomaterials.2004.10.012

[20] Sun, M., Su, X., Ding, B., He, X., Liu, X., Yu, A., & Zhai, G. (2012). Advances in nanotechnology-based delivery systems for curcumin. *Nanomedicine*, *7*(7), 1085–1100. https://doi.org/10.2217/nnm.12.80

[21] Pu, H. L., Chiang, W. L., Maiti, B., Liao, Z. X., Ho, Y. C., Shim, M. S., & Sung, H.W. (2014). Nanoparticles with dual responses to oxidative stress and reduced ph for drug release and anti-inflammatory applications. *ACS nano*, *8*(2), 1213–1221. https://doi.org/10.1021/nn4058787

[22] Wang, J., Tang, W., Yang, M., Yin, Y., Li, H., Hu, F., & Wang, Y. (2021). Inflammatory tumor microenvironment responsive neutrophil exosomes-based drug delivery system for targeted glioma therapy. *Biomaterials*, *273*, 120784. https://doi.org/10.1016/j.biomaterials.2021.120784

[23] Lee, S. W. L., Paoletti, C., Campisi, M., Osaki, T., Adriani, G., Kamm, R. D., … & Chiono, V. (2019). MicroRNA delivery through nanoparticles. *Journal of controlled release*, *313*, 80–95. https://doi.org/10.1016/j.jconrel.2019.10.007

[24] Cheng, Y., Xu, Q., Yu, M., Dang, C., Deng, L., & Chen, H. (2025). Curcumin nanoparticles-related non-invasive tumor therapy, and cardiotoxicity relieve. *Current medicinal chemistry*, *32*(3), 447–467. https://doi.org/10.2174/0109298673305616240610153554

[25] Deng, Y., Zhang, X., Shen, H., He, Q., Wu, Z., Liao, W., & Yuan, M. (2020). Application of the nano-drug delivery system in treatment of cardiovascular diseases. *Frontiers in bioengineering and biotechnology*, *7*, 489. https://doi.org/10.3389/fbioe.2019.00489

[26] Mandal, A. K., & Chakraborty, S. K. (2025). Biogenesis and implication of miRNAs in the development of diseases and their theranostic inhibitions. *Journal of drug delivery & therapeutics*, *15*(8). https://doi.org/10.22270/jddt.v15i8.7336

[27] Swierczewska, M., Han, H. S., Kim, K., Park, J. H., & Lee, S. (2016). Polysaccharide-based nanoparticles for theranostic nanomedicine. *Advanced drug delivery reviews*, *99*(Pt A), 70–84. https://doi.org/10.1016/j.addr.2015.11.015

[28] Liu, Y., Li, C., Yang, X., Yang, B., & Fu, Q. (2024). Stimuli-responsive polymer-based nanosystems for cardiovascular disease theranostics. *Biomaterials science*, *12*(15), 3805–3825. https://doi.org/10.1039/D4BM00415A

[29] Sun, X., Shi, J., Fu, X., Yang, Y., & Zhang, H. (2018). Long-term in vivo biodistribution and toxicity study of functionalized near-infrared persistent luminescence nanoparticles. *Scientific reports*, *8*(1), 10595. https://doi.org/10.1038/s41598-018-29019-z

[30] Bi, J., Mo, C., Li, S., Huang, M., Lin, Y., Yuan, P., & Xu, S. (2023). Immunotoxicity of metal and metal oxide nanoparticles: From toxic mechanisms to metabolism and outcomes. *Biomaterials science*, *11*(12), 4151–4183. https://doi.org/10.1039/d3bm00271c

[31] Pan, L., Zhang, X., Yang, B., He, Z., Sun, M., Sun, J., & Wang, W. (2025). Invasive pulmonary fungal diseases: towards formulation-optimized targeted therapeutic strategies. https://doi.org/10.26599/NR.2025.94908114

[32] Yan, S., Na, J., Liu, X., & Wu, P. (2024). Different targeting ligands-mediated drug delivery systems for tumor therapy. *Pharmaceutics*, *16*(2). https://doi.org/10.3390/pharmaceutics16020248

[33] Das, A., Pathak, K., Saikia, R., Pathak, M. P., Gogoi, U., Das, D., …& Sonowal, S. (2023). *Future perspectives and challenges: Clinical translation and regulatory aspects, scale-up and manufacturing, ethical considerations*, Nanocarriers for nucleic acids and proteins. CRC press. https://doi.org/10.2174/1573406419666221226093311

[34] Arnold, K. E., Brown, A. R., Ankley, G. T., & Sumpter, J. P. (2014). Medicating the environment: Assessing risks of pharmaceuticals to wildlife and ecosystems. *Philosophical transactions of the royal society b: Biological sciences*, *369*(1656), 1-11. https://doi.org/10.1098/rstb.2013.0569

[35] Rajput, D., Dwivedi, A., Derashri, A., Bhandari, D. D., & Kolhe, N. (2024). *Assessment of nanoparticle induced cytotoxicity and safety profile*. Nanoparticles in cancer therapy. CRC press. https://doi.org/10.1201/9781003515630-18

[36] Wasti, S., Lee, I. H., Kim, S., Lee, J. H., & Kim, H. (2023). Ethical and legal challenges in nanomedical innovations: A scoping review. *Frontiers in genetics*, *14*, 1163392. https://doi.org/10.3389/fgene.2023.1163392

[37] Zhang, P., Li, Y., Tang, W., Zhao, J., Jing, L., & Mchugh, K. J. (2022). Theranostic nanoparticles with disease-specific administration strategies. *Nano today*, *42*, 101335. https://doi.org/10.1016/j.nantod.2021.101335

[38] Alhazmi, H. A., Ahsan, W., Mangla, B., Javed, S., Hassan, M. Z., Asmari, M., & Najmi, A. (2022). Graphene-based biosensors for disease theranostics: Development, applications, and recent advancements. *Nanotechnology reviews*, *11*(1), 96–116. https://doi.org/10.1515/ntrev-2022-0009

[39] Li, X., Xie, X., Wu, Y., Zhang, Z., & Liao, J. (2023). Microneedles: Structure, classification, and application in oral cancer theranostics. *Drug delivery and translational research*, *13*(9), 2195–2212. https://doi.org/10.1007/s13346-023-01311-0

[40] Yang, F., Xue, J., Wang, G., & Diao, Q. (2022). Nanoparticle-based drug delivery systems for the treatment of cardiovascular diseases. *Frontiers in pharmacology*, *13*, 999404. https://doi.org/10.3389/fphar.2022.999404

[41] Rajpoot, K. (2025). Role of artificial intelligence in nanomedicine and organ-specific therapy: an updated review. *Current drug targets*, *26*, (3), 921 - 953.https://doi.org/10.2174/0113894501394785250715165404

[42] Khan, A., Barapatre, A. R., Babar, N., Doshi, J., Ghaly, M., Patel, K. G., … & Jamil, U. (2025). Genomic medicine and personalized treatment: A narrative review. *Annals of medicine and surgery (2012)*, *87*(3), 1406–1414. https://doi.org/10.1097/MS9.0000000000002965

[43] Zamay, G. S., Zamay, T. N., Lukyanenko, K. A., & Kichkailo, A. S. (2020). Aptamers increase biocompatibility and reduce the toxicity of magnetic nanoparticles used in biomedicine. *Biomedicines*, *8*(3). https://doi.org/10.3390/biomedicines8030059

[44] Buchete, N. V., Cicha, I., Dutta, S., & Neofytou, P. (2024). Multiscale physics-based in silico modelling of nanocarrier-assisted intravascular drug delivery. *Frontiers in drug delivery*, *4*, 1362660. https://doi.org/10.3389/fddev.2024.1362660

[45] Smith, B. R., & Edelman, E. R. (2023). Nanomedicines for cardiovascular disease. *Nature cardiovascular research*, *2*(4), 351–367. https://www.nature.com/articles/s44161-023-00232-y

[46] Młynarska, E., Bojdo, K., Frankenstein, H., Kustosik, N., Mstowska, W., Przybylak, A., & Franczyk, B. (2025). Nanotechnology and artificial intelligence in dyslipidemia management—cardiovascular disease: Advances challenges and future perspectives. *Journal of clinical medicine*, *14*(3), 887. https://doi.org/10.3390/jcm14030887

[47] Panchpuri, M., Painuli, R., & Kumar, C. (2025). Artificial intelligence in smart drug delivery systems: A step toward personalized medicine. *RSC pharmaceutics, 2025*(2), 882-914. https://doi.org/10.1039/d5pm00089k

[48] Badarinadh, K. S., Shukla, P., Chauhan, S. B., & Singh, I. (2024). A comprehensive exploration of nanomedicine's current landscape and future horizons. In *Lipid based nanocarriers for drug delivery*, (391-433). Nova Science Publishers, Inc. https://B2n.ir/yu2175

[49] Mangla, B., Kumar, P., Javed, S., Pathan, T., Ahsan, W., & Aggarwal, G. (2025). Regulating nanomedicines: challenges, opportunities, and the path forward. *Nanomedicine*, *20*(15), 1911–1927. https://doi.org/10.1080/17435889.2025.2533107

[50] Rodriguez Gómez, F. D., Monferrer, D., Penon, O., & Rivera Gil, P. (2025). Regulatory pathways and guidelines for nanotechnology-enabled health products: A comparative review of EU and US frameworks. *Frontiers in medicine*, *12*, 1544393. https://doi.org/10.3389/fmed.2025.1544393

[51] El-Shafey, S. E., Obada, M. K., El-Shamy, A. M., & Mohamed, W. S. (2024). Silica/klucel nanocomposite as promising durable adsorbent for lead removal from industrial effluents. *Scientific reports*, *14*(1), 26095. https://www.nature.com/articles/s41598-024-74680-2

[52] Zeng, H., Lv, Z., Sun, X., Tong, Y., Wu, W., Dong, S., & Mao, L. (2024). Predicting bioaccumulation of nanomaterials: Modeling approaches with challenges. *Environment health (Washington, D.C.)*, *2*(4), 189–201. https://doi.org/10.1021/envhealth.3c00138

[53] Tawiah, B., Ofori, E. A., & George, S. C. (2024). Nanotechnology in societal development. In *Nanotechnology in societal development* (pp. 1–64). Springer. https://doi.org/10.1007/978-981-97-6184-5_1

[54] Joseph, J. S. (2025). Balancing innovation and biomedical ethics within national institutes of health: Integrative and regulatory reforms for artificial intelligence-driven biotechnology. *Biotechnology law report*, *44*(2), 93–116. https://doi.org/10.1089/blr.2025.360002.jj