Review Article

# Application of Nanotechnology in Device Promotion in Cardiology: A Promising Horizon for Nanocardiology toward Personalized Medicine

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## ABSTRACT

Cardiovascular diseases such as coronary artery disease, stroke, and atherosclerosis constitute some of the most challenging problems in the medical field because of their high mortality rates. Nanotechnology in medicine/nanomedicine has several applications in different medical fields, especially in cardiology. Recent advances in nanotechnology and nanomedicine have created many opportunities for cardiovascular diseases, from diagnosis, treatment, and monitoring to drug delivery and nanoscale surgery. We reviewed recent applications of nano-enabled devices in cardiology such as targeted drug delivery, nanocoated drug-eluting stents, injectable peptide nanofibers, anticoagulation applications, and post-surgical monitoring. ***(Iranian Heart Journal 2015; 16(3): 45-53)***

**Keywords:** ■Nanotechnology ■Nanomedicine ■Nanocardiology ■Personalized medicine

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**Received:** July 20, 2015 **Accepted:** September 25, 2015

Cardiovascular disease (CVD) is the largest cause of mortality in the world and includes coronary artery disease, cerebrovascular disease, peripheral disease, angina, arrhythmias, atherosclerosis, stroke, hypertension, myocarditis, cardiomyopathy, and pericarditis. Each year, 18,000,000 people die from CVD, so their treatment should be one of the main priorities of cardiovascular research and governmental health care expenditure.[1,2] Several traditional treatment approaches are used for CVD with different degrees of invasiveness and efficacy. For example, the use of stent prostheses to unblock diseased heart vessels to restore the flow in the vessel is a traditional cardiovascular intervention that can be promoted by nanotechnology and nanomedicine approaches.

Nanotechnology, the manipulation of matter on a molecular and atomic scale, is a useful technology for deconstructing and reconstructing nature at these levels. The nanoscale is exceedingly tiny; it is the world of atoms and molecules. The working mode of nanotechnology involves the nanometer scale, one-billionth of a meter, and can include 1-100 nanometer particle size and further applications.[3] A human hair is huge by comparison, about 60.000 nm thick, and a typical molecule is 2.5 nm.[4] Therefore, nanotechnology, nanomedicine, and nanomaterials can control the behavior and differentiation of cells and interact with both the surface and the inside of cells, leading to new ways for disease detection and drug delivery.[5] For instance, artificial nanodevices can sense and repair the damaged parts of our body and influence the behavior of individual cells. Or artificial antibodies and white and red blood cells as well as antiviral nanorobots have potentially successful applications in diagnosis and therapeutic procedures.[6] The size range of natural biomolecules in terms of nano size is depicted in Figure 1 (http://www.particlesciences.com).

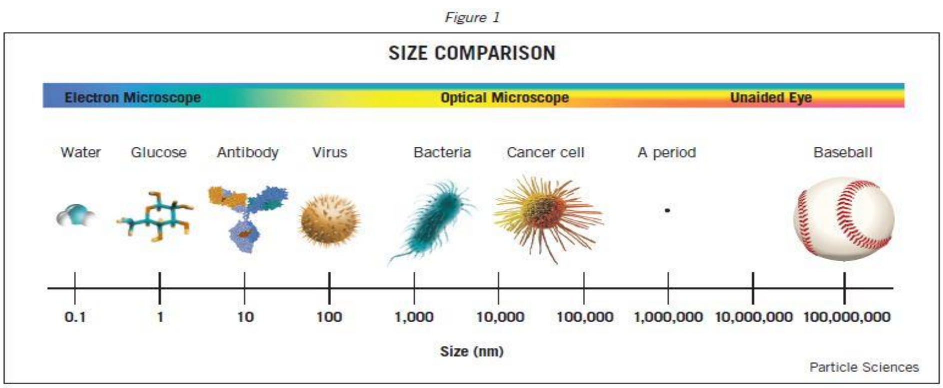


**Figure 1.** Size comparison of nanoparticles is depicted here.

The ability to control materials at such a small scale has conferred nanomedicine a potential advantage in various medical fields from diagnosis, cancer treatment, drug delivery, and monitoring to surgery and control of biological systems.[7,8] The hierarchical relation of nanomedicine approaches in the cardiology field is depicted in Figure 2.

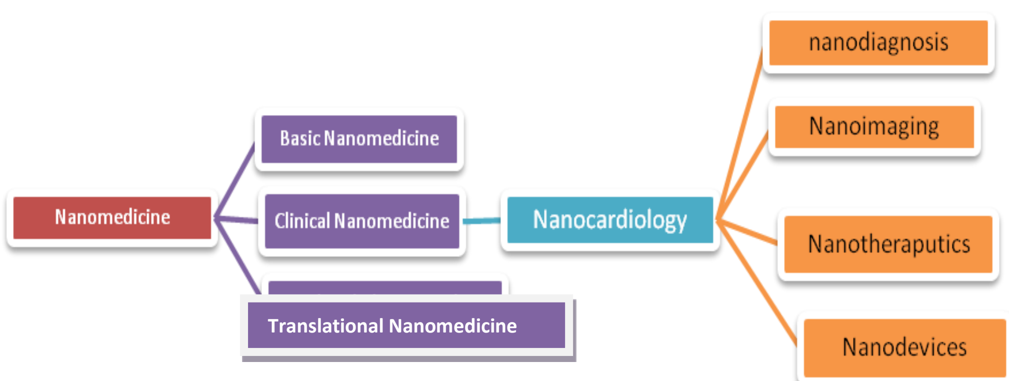


**Figure 2.** Nanomedicine categorization in the field of nanocardiology is illustrated here.

Nanomaterials are not simply smaller; they exhibit very different fundamental physical, chemical, and biological properties than bulk (non-nano) materials.[9] These new properties excite industries and governments. Indeed, governments, universities, and businesses around the world are racing to commercialize nanotechnologies and nanomaterials. Any such particle (e.g., quantum dots, lipid-based nanoparticles such as micelle and liposomes, dendrimers, and polymer-based nanoparticles) not only plays a role in imaging[10] and diagnostic modalities but also could be used as therapeutic options.[11]

Accordingly, nanotechnology can be defined as the science and engineering involved in the design, synthesis, characterization, and application of materials and devices whose smallest functional organization is on a 1-100 nanometer scale. Despite this size restriction, nanotechnology commonly refers to structures that are up to several hundred nanometers in size developed by top-down approach, from bulk material to nanomaterials, or bottom-up engineering, fabrication of nanomaterials by putting together individual atoms.[12] In medical application, nanomaterials and devices are designed for interaction with the human body at submolecular scales. The medical application of nanotechnology is nanomedicine or nanobiomedicine,[6] which includes monitoring, diagnostics, therapeutics, preventative applications, and other medical interventions impacting upon human health.[13] Nanomedicine has the potential to develop medical applications such as cancer treatment, drug delivery systems, molecular manipulation, and clinical applications. The special properties of nanomaterials, however, present challenging facts that should be thoroughly comprehended. A deep understanding of these facts will create novel horizons for research, diagnosis, and therapy of heart, lung, blood, and sleep disorders.[14] In recent years, major efforts have been made to develop nanotechnology for drug delivery systems because they offer suitable tools for delivering small molecular weight drugs as well as macromolecules such as proteins, peptides, and genes.[15]

Nanocardiology is the use of the properties and application of nanobiotechnology in CVD. Recent rapid advances in nanotechnology and nanoscience have created many opportunities for the diagnosis and treatment of cardiovascular and hematological diseases. To review the challenges and opportunities of these growing fields and to focus on the alternative possibilities of nanotechnology with a view to removing clinical problems, scientists should probe into various aspects and applications of nanotechnology in heart, lung, and vascular complications.[16]

Such attempts that will suggest the creation of multidiscipline research centers to develop the applications of nanotechnology and nanoscience for medical research — particularly in the cardiovascular field (e.g., stenting and nanotechnology-based drug delivery systems) — are highlighted below.

### *Nanoliposomes for Targeted Cardiovascular Drug Delivery*

High-tendency ligan/receptor interactions have been used in the design and fabrication of targeted systems which apply liposomal nanostructures for cardiovascular drug delivery applications.[17, 18] The use of anti-integrin/anticoagulant/anti-inflammatory drugs altogether for multifactor pathological thrombogenesis seems to be essential. For this purpose, a nano-tool which can carry this combination specifically to the thrombotic lesion has been designed in Department of Biomedical Engineering of Case Western Reserve University.[16]

### *Anti-Restenosis Drugs Encapsulated in Environmentally Biodegradable Nanoparticles*

The local delivery of anti-proliferative drugs encapsulated in environmentally biodegradable nanoparticles has presented advantages as experimental ways to prevent the developing of restenosis.[19-21] Calbiochem® is a new PDGFR β-specific tyrphostin formulized in a nanoparticle structure which has been applied intraluminally to balloon-injured rat carotid wall and porcine coronary artery stenting.[22]

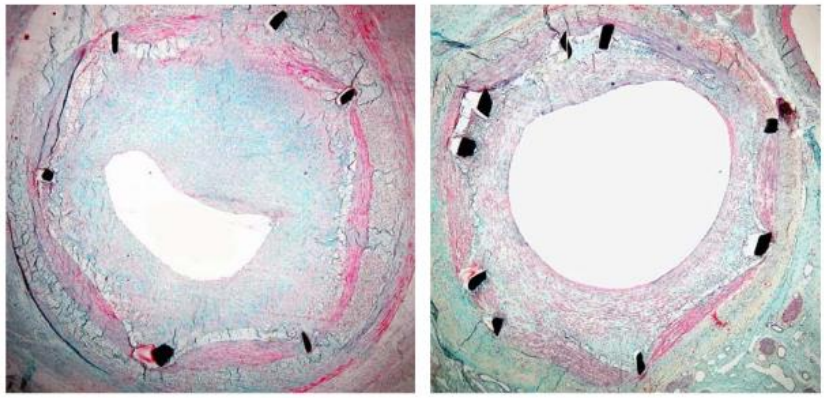

**Figure 3.** Porcine left anterior descending coronary artery bypassing in an empty stented (A) and with AGL 2043-laden NP treated group (B) is depicted.

The anti-multiplication effect of tyrphostin encapsulated in nanostructure has emerged considerably more than surface-absorbed drugs. In a porcine model, it was reported that delivering intramural AGL-2043 reduced the formation of in-stent neointimia in the coronary arteries of the case group in comparison with a control group with similar degrees of wall injury. The results of this study suggested that the local delivery of formulized tyrphostin AGL-2043 in environmentally biodegradable nanoparticles could be used for the treatment of anti-restenosis, independent of the stent model or the type of injury.

***Polymeric Nanoparticles Containing Low-Molecular-Weight Heparin***

Low-molecular-weight heparin (LMWH) nanoparticles have been prepared as oral carriers of heparin.[23, 24] Nanoparticles were formulized through an ultrasound probe via the water-in-oil emulsification and evaporation of a solvent. The average size of the nanoparticles with LMWH was 240 to 290 nm[25, 26] and the highest effect of encapsulation was seen during the application of EUDRAGIT® polymers in matrix composition.[27]

***Injectable Peptide Nanofibers for Myocardial Ischemia***

Endothelial cells can protect cardiomyocytes against injury through platelet-derived growth factor signaling (PDGF)-BB. PDGF-BB induces cardiomyocyte akt/ PDGFR-β phosphorylation in a dose- and time-dependent manner *in vivo* and prevents apoptosis by PI3K/Akt signaling. A separate study showed that PDGF-BB, delivered by nanofibers, decreased the size of infarct after ischemia/reperfusion. The data showed that PDGF-BB signaling and *in vitro* finding could be translated into an effective method for protecting the myocardium after infarction. Therefore, that study showed that injectable nanofibers with slow and precise delivering of proteins to the myocardium contained great therapeutic benefits.[16, 28, 29] Also, another investigation found that self-assembling peptides provided nanofibrous microenvironments in the myocardium and promoted vascular cell recruitment.[30, 31]

***Applications in Atherosclerosis***

***Nanotechnology Approach for Vulnerable Plaques as a Cause of Cardiac Arrest***

Recent studies have shown that there are 2 types of plaques: non-vulnerable and vulnerable. Vulnerable plaques are the probable cause of death in sudden cardiac arrest. The blood passing through an artery induces a shearing force and can cause vulnerable plaque injury, which usually leads to occlusion and myocardial infarction. Approximately, 60 – 80% of sudden cardiac deaths can be assigned to the physical injury of vulnerable plaques. Currently, there is no appropriate solution to the problem of vulnerable plaques, but a solution is expected to emerge courtesy of the “Program of Excellence in Nanotechnology” by the National Heart, Lung, and Blood Institute of The National Institutes of Health (NIH). According to its strategy for speeding up progress in medical research and practical research, the NIH chose cardiac diseases as its goal and recently released the “Program of Excellence in Nanotechnology”. The program will benefit from the cooperation of 25 scientists of the Burnham Institute (La Jolla, CA), University of California Santa Barbara, and the Scripps Research Institute (San Diego, CA) and will use a $13-million reward to design nanotechnologies to detect, monitor, treat, and remove vulnerable plaques. By concentrating on nanodevices and machines at molecular level, the scientists at these institutions will specifically reach vulnerable plaques. It is expected that this work will come up with noninvasive diagnostic and therapeutic strategies for those who suffer from this cardiac disease.

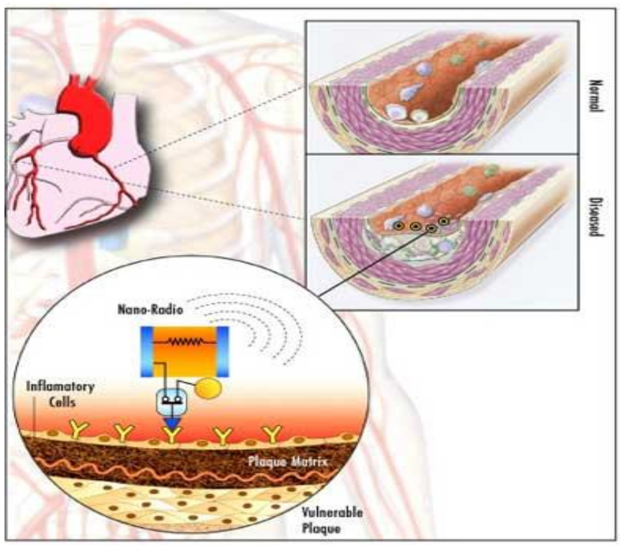


**Figure 4.** Burnham Institute’s idea to mount nano-attack on the atherosclerotic plaque is depicted.

On the other hand, nano-sized particles can be synthetically designed for potential intervention in the inhibition of lipoprotein matrix and lipoprotein uptake in cells-central activities for atherosclerosis. These micelles can contain different degrees of anionic chemistry, which is a primary mechanism to cause differential retentivity of low-density lipoproteins (LDLs). The scientists at Rutgers University have reported lipoprotein interactions of nanomicelles self-arrangement from scorpion-like lauryl chloride based acid macromolecules and polyethylene glycol shell. They used engineered molecules on a nano scale called “nanolipoblockers” (NLBs) to attack atherosclerotic plaques on higher LDL levels.[32, 33]

***Nanocoated Drug-Eluting Stents***

The drug-eluting stent (DES) provides drug release and vessel patency.[34] MIV Therapeutics Inc. developed unmatched covering techniques that use hydroxyapatite (HAp) with application in medical tools and drug delivery systems. A production strategy is developing a coronary stent covered by HAp with a nano film coating. In November 2006, the result of a porcine study at the Department of Cardiology, Thoraxcenter, Erasmus University Medical Center in the Netherlands showed that 3 non-polymer drug-eluting MIV variables were even more effective than cypher ones (Johnson & Johnson). The challenging processes for the production of nanoscale particles by using

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wet milling and super critical fluid inherently limit their ability to produce pure coordinated particles between distribution and range. ElectroNanoSpray™ formulization technology (Nanocopoeia) produces pure and accurate nanoscale particles. The particle scale could be from 2 to 200 nm. These tools have the functionality to cover the particle in one level and produce a drug-contained core.

Debiotech SA in collaboration with the Laboratory of Powder Technology at École polytechnique fédérale de Lausanne (Lausanne, Switzerland) is developing a new type of ceramic coatings for the DES and other implants.[35-37] Ceramics offer unique properties compared to polymers. Polymers over time become insoluble and their remnants stimulate inflammation, while ceramics in contact with the living tissue are stable and neutral. The cover can release the active drug during the first week after the implantation of the ceramic combined with long-term sustainability. Nanostructural ceramics provide the properties of new biomaterials that are not achievable with other materials.

### *Nanoporous Materials for Improving Compatibility of Drug-Eluting Stents*

Nanoporous substrates and coatings are determined by their large surface area. Recently, these substrates have attracted attention thanks to their various applications — including nano-manufacturing, energy harvesting, integrated circuits, bio or chemical sensing, orthopedic implants, and controlled elution systems. Their surfaces can be produced with careful control on the pore size, distribution, and pore density. Furthermore, the surface chemical features can also be manipulated to intended applications.[38] Scientists at the Forschungszentrum Dresden-Rossendorf in Germany have developed a new method for preparing a large number of nanopores on the surface of steel. The bombing of the stent from all directions with a high dose of noble gas ions creates a nanoporous scaffold on the surface. The desired porosity can be precisely designed with the setting of particle energy, flux, and temperature. Large quantities of drugs with high efficacy can be stored on the neutral metal surface of the pored nanostructure with improvement of the biocompatibility of the implants in the human body. This treatment leads to the release of the drug over a longer period of time. The method has been evaluated as a base technology for the next generation of the DES by Scientific Corporation. The product of this research group is about to become industrialized.[16]

### *Restenosis after Percutaneous Coronary Angioplasty*

Restenosis after percutaneous coronary intervention continues to be a serious problem in clinical cardiology. Recent progresses in nanoparticle targeting make the delivery of NK911 to the balloon-injured artery a possibility.[21] NK911 is a PEG-based core-shell nanoparticle with drug doxorubicin encapsulation, which will accumulate in vascular lesions by increasing the penetration. The biomedical engineers at Purdue University (Lafayette, IN) have shown that vascular stents used to treat arteries might perform better if their surface contains "nanobumps", which imitate mini shapes found in the living tissue. The stents that contain titanium and other metals enable the arteries to grow new tissue after vessel-clogging plaque deposits have been removed.

However, the main problem is to identify metal objects as an invader by the body mechanisms and to prevent the connection of endothelial cells to the scaffold, which can be a stimulator for scar tissue formation in the blood vessels.

## CONCLUSIONS

The future of cardiovascular procedures for the treatment of CVD seems to be intertwined with nanosystems capable of rendering pathological diagnosis and treatment by using changeable and controlled targeted systems.[3] The dual capability of nanoparticles in imaging and targeted delivery of therapeutic agents to patients with CVD (also called theranostics) will be a great hope to personalized medicine. Imaging-based treatments with special agents should be able to confirm the arrival of drugs to the target and its molecular impact. The combination of target drug delivery and molecular imaging with magnetic resonance imaging can specify the features of serials by expressing epitope through reading images. Monitoring and treatment confirmation at target site will pave the way for individual treatments. Potentially, nanotechnology-based approaches are very useful and efficient for medical fields, especially in CVD and related diseases. Nanotechnology can be effective for the treatment of complicated dysfunction of the cardiovascular system via its special properties such as high biocompatibility, biodegradability, controllability, specificity, and efficiency.

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