

Cardiovascular Imaging and Theranostics in Cardiovascular Pharmacotherapy

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Abstract

Imaging plays a pivotal role in the diagnostic and prognostic assessment of cardiovascular diseases. During the past two decades, there has been an expansion of the available imaging techniques, some of which are now part of routine clinical practice. Cardiovascular imaging of atherosclerosis is a useful instrument, and it can corroborate and expand pathophysiological evidence on cardiovascular disease, providing proof of concept for medical therapy and can predict its responsiveness, and it may be able to be used as surrogate endpoints for clinical trials. Theranostics is an emerging therapy that combines imaging and therapeutic functions, using imaging-based therapeutic delivery systems. Theranostics could partially overcome current imaging limitations and translate experimental evidence and large-scale trials assessing clinical endpoints, rationalising cardiovascular drug development and paving the way to personalised medicine. The medical community cannot overlook the use of cardiovascular imaging as a complementary and supportive adjunct to trials investigating clinical endpoints, which remain the mainstay for investigating the efficacy and safety of cardiovascular pharmacotherapy.

Keywords

Atherosclerosis, imaging, theranostic, cardiovascular pharmacotherapy

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Imaging has played an instrumental role in the diagnostic and prognostic assessment of cardiovascular diseases. Arterial Doppler ultrasound, echocardiography, myocardial perfusion imaging tests and angiography are now part of everyday clinical practice and represent a cornerstone of atherosclerosis management.¹ During the past two decades, there has been an expansion of the available imaging techniques, some of which give us greater understanding of atherosclerosis in both coronary and peripheral arteries. This article summarises the current and potential role and limitations of emerging imaging techniques in demonstrating mechanisms of atherosclerosis, focusing on the potential translational role of theranostics in cardiovascular drug design and personalised cardiovascular medicine.

Cardiovascular Imaging: A Growing Field

Acute cardiovascular events result from the multifaceted relationship between a patient's atherosclerotic risk factors and local factors, such as the location, burden, metabolic and functional characteristics of atherosclerotic disease that go beyond simple lumen stenosis.^{2–4} Consequently, scientific interest has moved from the degree of the lumen stenosis to investigating vessel wall structure, haemodynamic features, and the molecular and cellular mechanisms underlying atherogenesis, progression and thrombosis. Optical coherence tomography (OCT); coronary intravascular ultrasound (IVUS); coronary CT angiography; high-resolution MRI; nuclear imaging such as PET and spectroscopy; molecular imaging by contrast media for OCT,

ultrasound and MRI; and fusion imaging have the potential to broaden our structural, functional and biological understanding of plaque.^{5–9} Likewise, computational flow dynamics allows the appraisal of the biomechanical factors of atherosclerosis.¹⁰

These invasive and non-invasive techniques are shedding light on the identification of vulnerable plaque, which is one of the greatest challenges in cardiovascular medicine. Cardiovascular imaging has provided the proof of concept for medical therapy such as the stabilisation and regression of atherosclerosis with statins and, more recently, by the use of the PKSK9 inhibitors.^{11,12} Notably, cardiovascular imaging may be able to anticipate the beneficial effect of pharmacological agents on clinical endpoints and patients' potential responsiveness to these agents.¹³ However, this may not provide sufficient evidence to change clinical practice, since it should be supported by large-scale trials possibly assessing both imaging and clinical endpoints. This would allow a rationalisation of cardiovascular drug development.

Limitations and Perspectives

Currently, there is no consensus on the specific roles of different imaging modalities or the best targets for imaging in the clinical setting. Despite the expectations for being able to phenotype atherosclerosis by distinct features, imaging cannot predict clinical outcome with sufficient accuracy as a standalone technique. This is exemplified by

a randomised clinical trial of dalcetrapid, which failed to demonstrate a reduction in major cardiovascular events, despite initial encouraging results in MRI and PET/CT primary endpoints.^{14,15}

An explanation may reside in the inability of the imaging's surrogate endpoints to detect either the ancillary and/or systemic mechanisms of action of the drug being investigated or any genetic differences among patients that may affect the clinical outcome. The concept of the risk continuum in atherosclerosis is progressively taking over from the categorical classification of vulnerable plaque, and the vulnerable plaque (rupture- and erosion-prone) concept is being integrated with the vulnerable patient concept.^{16–19} Naghavi et al. have suggested a cumulative vulnerability index to assess total vulnerability burden and strengthening traditional risk assessment strategies with imaging and biological findings. This should include the consideration of local, systemic and haematic features and myocardial vulnerability.¹⁶ The scientific community must also consider the setbacks that hinder the translatability of the existing imaging techniques, particularly for radiation, contrast media exposure and high costs.²⁰

Theranostics

Considering the complexity, rationalising cardiovascular drug development and moving towards personalised, preventive and therapeutic medicine should be a mainstay of future research. Theranostics could be used to help bridge the gap between experimental evidence and large-scale trials.

Theranostics combines imaging and therapeutic functions by using imaging-based therapeutic delivery systems. Studies have employed nanoparticles for contrast agent-assisted diagnostic imaging, therapeutic delivery and subsequent evaluation of therapeutic efficacy. Theranostics is a result of advances in multiple natural and material sciences, particularly nanotechnology. Primarily used in oncology, it has been gradually applied to early and late atherosclerotic lesions with encouraging results.²¹ In theranostics, drug delivery and subsequent action in a region of interest is controlled by an external energy field – mostly ultrasound, light, or a magnetic field – in an attempt to minimise systemic and local effects.²²

Ultrasound's intrinsic technical characteristics, including real-time imaging to avoid radiation, allowed its early implementation in theranostic. The Combined Lysis of Thrombus in Brain Ischemia using

Transcranial Ultrasound and Systemic tPA (CLOTBUST) trial and a later meta-analysis demonstrated the efficacy of ultrasound-enhanced fibrinolysis.^{23,24} However, this was not supported by a recent multicentre randomised controlled trial, showing no benefit in sonothrombolysis delivered within 3 hours of symptom onset over classical thrombolysis by alteplase.²⁵ Contrast-enhanced ultrasound-targeted microbubbles have been used to promote angiogenesis in a model of critical limb ischaemia, to attenuated arterial neointimal formation and reduce microvascular dysfunction after acute MI in a large animal model.^{26–29}

Based on a similar principle, MRI has been used for site-specific vascular intervention. A magnetic field attracts and activates metallic nanoparticles with a protective coating to detect and inhibit inflammatory processes in atherosclerosis.^{30,31} In another study, gold nanorods were synthesised to diagnose and attenuate macrophage activity and release by delivering photodynamic therapy.^{32,33}

Similarly, paramagnetic nanoparticles have delivered anti-proliferative drugs and micro-RNA to inhibit either proliferation of smooth muscle cells or angiogenesis.^{34,35} In the past 5 years, a variety of new nanoparticles targeting lipids, inflammation signalling, vascular growth factors, endothelial function, oxidative stress, platelets function and apoptosis signalling have been delivered in pre-clinical studies using MRI, nuclear imaging and novel technical advances such as photoacoustic imaging.^{36,37}

The development of imaging systems specifically designed for theranostic use will improve its potential. However, unsolved issues related to potential harmful exposures and costs need to be addressed before application of theranostics in extended human research and clinical practice could be feasible.

Conclusion

Cardiovascular imaging of atherosclerosis is a useful instrument, which corroborates and expands pathophysiological evidence on cardiovascular disease, and provides proof of concepts for medical therapy. It might also be used to anticipate the beneficial effect on clinical endpoints and the responsiveness to medical therapy and can represent surrogate endpoints in clinical trials. Theranostics could further translate experimental evidence and large-scale trials assessing clinical endpoints, rationalising cardiovascular drug development and paving the way to more personalised medicine. ■

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