The current issue of the European Heart Journal focuses on a novel area of research, i.e. the function of microribonucleic acids (miRNAs). miRNAs are short, usually around 22-nucleotide-long non-coding RNAs involved in the regulation of gene expression (Figure 1). They guide ribonucleoprotein complexes that induce translational repression or messenger RNA degradation to targeted messenger RNAs. miRNAs were first described the development of nematode worms in 1993, but are now recognized to play an important role in human health and disease as well. Since their discovery, an increasing number of miRNAs with a whole array of biological effects have been found. Interestingly, overexpression or underexpression of specific single miRNAs or signatures of several nucleotides has been implicated in the development of several diseases, including those affecting the heart and the circulation. Indeed, the European Heart Journal has published a series of papers suggesting the involvement of microRNAs in resistant hypertension, the progression of vascular disease, neovascularization, aspirin resistance, myocardial fibrosis, myocarditis, myocardial infarction, and heart failure.

In this issue of the European Heart Journal, four papers report new findings on the potential role of microRNAs in experimental and clinical cardiovascular disease. The first paper, ‘MicroRNAs As Non-Invasive Biomarkers of Heart Transplant Rejection’ by Jean-Paul Duong-Van-Huyen et al. from the Hôpital Necker in Paris demonstrates a differential expression of miRNA such as miR-10a, miR-21, miR-31, miR-92a, miR-142-3p, miR-155, and miR-451 in rejecting allograft patients. Since this was not only observed at the tissue level in endomyocardial biopsies, but also in the serum, their findings may be clinically important since they suggest the potential of this microRNA signatures as a non-invasive biomarker of heart transplant rejection. Obviously, this small cohort of 60 patients should be expanded to a larger population in future studies.

The second paper, ‘AntagomiR directed against miR-20a restores functional levels of BMPR2 in pulmonary arteries and prevents vascular remodeling. This sets the basis for future exploratory studies in humans with pulmonary hypertension.’ by Lars Huber et al. from Zurich for the first time reports the effects of miR-20a inhibition using a specific antagonir in an in vivo model for pulmonary hypertension. Recently, the authors have identified the microRNA, miR-20a, with a highly conserved pathway regulating the expression of bone morphogenetic protein receptor type 2 (BMPR2), which is a hallmark of several forms of pulmonary hypertension. Their data obtained in mice with hypoxia-induced pulmonary hypertension reported in this issue suggest that treatment with the antagoniR-20a restores functional levels of BMPR2 in pulmonary arteries and prevents vascular remodeling. This sets the basis for future exploratory studies in humans with pulmonary hypertension.

The third paper, ‘The 106b–25 MicroRNA Cluster is Essential for Neovascularization After Hindlimb Ischaemia in Mice’ by Jacob George et al. from the Kaplan Medical Center in Israel, is based on the observation that several miRNAs control angiogenesis either by increasing or by inhibiting the expression of angiogenic or angiostatic proteins, respectively. They found using a miR-106b–25 knockout mouse model—in which the response to hindlimb ischaemia is impaired as assessed by laser Doppler perfusion imaging—that the miR-106b–25 cluster improves post-ischaemic neovascularization in mice, and that it does so in part by regulating the function of angiogenic bone marrow-derived stromal cells and that of endothelial cells via altering apoptosis, matrigel tube formation capacity, cytokine secretion, and expression of the stem-cell marker Sca-1. Whether the miR-106b–25 cluster might be a promising therapeutic target in patients with peripheral artery disease remains to be seen in future studies.

The fourth paper, ‘Vascular importance of the miR-212/132 cluster’ by Thomas Thum et al. from the Hannover Medical School in Germany, is complementary to the previous one and focuses on the complex crosstalk of microRNAs in regulating certain endothelial functions. Their study shows that the anti-angiogenic stimulation of endothelial cells by transforming growth factor beta activates the miRNA-212/132 cluster by de-repression of their transcriptional co-activator CREB-binding protein which is a novel target of a previously identified pro-angiogenic miRNA miR-30a-3p. This novel miRNA-crosstalk involving miR-30a-3p and miR-212 led to suppression of crucial endothelial genes such as GAB1 and SIRT1, which finally lead to endothelial dysfunction. Importantly, in vivo deletion of the miR-212/132 cluster increased endothelial vasodilatory function and improved angiogenic responses during post-natal development in adult mice.

In a first review article on abnormalities of coronary vasomotion, Hiroaki Shimokawa from Sendai University in Japan discusses to what degree endothelial dysfunction and coronary artery spasm are involved in that process. In particular, he stresses that endothelial vasodilator function and dysfunction with a greater contribution of nitric oxide (NO) in conduit arteries and a predominant role of endothelium-derived hyperpolarizing factor (EDHF) in resistance arteries. The central mechanism of the spasm is hypercontraction of vascular smooth muscle cells in particular activation of Rho-kinase. The importance of vasospasticangina in an Asian population is
documented by the Japanese Coronary Spasm registry which is now expanded to six countries including Europe.

Beyond that, this issue contains a joint ‘Current Opinion’ by the ‘European Society of Cardiology Working Group on Thrombosis’, the ‘European Heart Rhythm Association, the European Association of Percutaneous Cardiovascular Interventions’, and the ‘European Association of Acute Cardiac Care’ led by Gregory Lip7 on ‘Management of Antithrombotic Therapy in Atrial Fibrillation Patients Presenting With Acute Coronary Syndrome and/or Undergoing Percutaneous Coronary or Valve Interventions’. Indeed, the optimal antithrombotic management strategy for patients with atrial fibrillation presenting with an acute coronary syndrome and/or undergoing percutaneous coronary intervention with or without stenting for stable coronary artery disease continues to represent a clinical challenge. They concluded that as with use of any antithrombotic drug, clinicians need to balance the risks of ischaemic stroke and thromboembolism, recurrent cardiac ischaemia and/or stent thrombosis, and bleeding and haemorrhagic stroke. Their joint consensus document provides an update of the published evidence and recommendations for ‘best practice’ antithrombotic therapy in such AF patients. However, while some new data have become available, they are mainly from observational studies and subgroup analyses of small cohorts enrolled in larger clinical trials, there is still an unfortunate lack of dedicated randomized studies. Thus, many of the recommendations are based on expert consensus as we are awaiting results of future dedicated trials.

We sincerely hope that this novel area of research will stimulate our readers to explore microRNAs further in patients with cardiovascular disease, either as biomarkers for diagnosis or as outcome and/or a therapeutic targets.

References

Figure 1 Schematic of microRNA biogenesis and action. The mature microRNA sequence is given in red. TF, transcription factor; Pol, RNA polymerase II or III; Exp5, exportin 5. (From Condorelli et al. 1).