MicroRNAs (miRNAs) are small non-coding regulatory molecules of approximately 22 nucleotides length with the capacity to modify gene expression at the post-transcriptional level by binding to the 3’ untranslated region (UTRs) of their target messenger RNAs (mRNAs) (1). Extracellular miRNA is present in circulating blood after exosome release from certain cells. Remarkably, circulating miRNAs have been associated with the pathogenesis of several cardiovascular disorders including hypertension, coronary artery disease, myocardial infarction, and heart failure (2,3). In contrast to intracellular miRNAs, circulating miRNAs may function as suitable biomarkers due to their stability and easy detectibility. However, for any potential clinical application, quantification of circulating miRNAs will have to be performed with high accuracy and precision (4). Recent advances in the development of innovative technologies aiming for miRNA expression profiling and quantification allow the assessment of patterns of circulating miRNAs with extraordinary sensitivity and specificity. In the current Theme Issue of Thrombosis and Haemostasis, Zampetaki and Mayr highlight the latest technological approaches in this field (5).

Delivered into the blood stream from bone marrow megakaryocytes, circulating blood platelets are central players not only in the maintenance of hemostasis but are also involved in pathophysiological conditions that cause substantial morbidity and mortality including cardiovascular diseases (atherosclerosis), inflammation and cancer (6–8). Platelets lack nucleus and genomic DNA but are nevertheless capable of protein synthesis. They were shown to contain rough endoplasmic reticulum and ribosomes, as well as a small amount of poly(A)-RNA from their progenitor cells (9). Remarkably, these anucleated cells have recently been demonstrated to harbour a gene regulatory pathway based on miRNAs (10). Representing a new class of potential regulatory mediators in platelets, miRNAs lend an additional level of complexity to the control of gene expression, an aspect that is depicted in detail by Dangwal and Thum in this issue (11). A dysfunctional miRNA-based regulatory system leads to the development of serious platelet-related cardiovascular diseases (12). For instance, levels of miR-340 and miR-624 were found to be up-regulated in platelets of patients suffering with premature coronary disease (13). Moreover, overexpression of miR-28 was detected in platelets from patients with myeloproliferative neoplasms (14).

One major haemostatic disorder that involves platelet abnormalities is chronic kidney disease (CKD). Uraemic toxins found in the blood of patients suffering from CKD may deregulate the platelet transcriptome interfering with their function and affecting the haemostatic balance (15). Results from experiments presented by Plé et al. in this issue illustrate new data on the CKD uraemia-related platelet complications and highlight the importance of miRNA-based mRNA regulatory pathway in this context (16). The altered platelet mRNA and miRNA profile found in CKD patients can be elegantly corrected via dialysis. The proteins phosphatidylcholine transfer protein (PCTP) and WD repeat-containing protein 1 (WDR1) involved in the pathophysiology of CKD were found to be regulated through miRNAs. Interestingly, miRNA-19b that targets the expression of WDR1 is strongly up-regulated in uremic platelets and thereby may trigger the bleeding disorders which are typically observed in CKD patients.

Concerning the risk factors associated with the development of atherosclerosis, dysfunction of mechanical forces are known as important mediators in the early stages of the disease. Boon et al. in this issue elegantly survey the different roles of miRNAs in shear stress emphasising the need of clarifying upstream signalling pathways by which these forces regulate the miRNA profile (17). The shear stress-responsive transcription factor Krüppel-like factor 2 (KL2) was identified to critically regulate global endothelial gene expression patterns induced by an atheroprotective flow. Recent studies report that both KL2 and shear stress regulate a number of miRNAs in endothelial cells (ECs). Strikingly, the miR-143/-145 cluster was among the most significantly up-regulated miRNAs under these conditions. These miRNAs have been suggested to be atheroprotective and play a critical role in modulating the phenotype of vascular smooth muscle cells (SMC) by promoting differentiation and repressing proliferation of these cells (18). Moreover atheroprotective communication has been...
demonstrated to exist between ECs and SMCs via miRNA- and vesicle-mediated mechanisms (19–21). Since these vesicles are taken up by atherosclerotic lesions, KLF2-induced vesicle-mediated transfer of miRNAs may comprise a promising strategy to combat atherosclerosis and improve plaque stability.

In conclusion, the identification of circulating stable miRNAs launches a new generation of potentially unrivaled specificity and sensitivity biomarkers in cardiovascular diseases. The role of miRNAs is no longer locally confined but may have also roles distant from the cell which originate from in a miRNA-based versatile messaging system. This second part of the Theme Issue on miRNAs provides state-of-the-art authoritative overviews addressing these topics.

Conflicts of interest
None declared.

References