Education in atherothrombosis

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The prevalence of atherothrombosis and the incidence of its various clinical manifestations in Europe and the rest of the world is such that a huge amount of resource is committed to enhancing our understanding of its causes and improving its treatment and prevention. The range and increasing effectiveness of cardiovascular drugs that are available to assist in the prevention and management of atherothrombosis has now provided physicians with an impressive number of options which continues to expand as each year passes. This delivers a challenge to the scientific and clinical communities as to how best to disseminate knowledge in order to direct future research endeavours and maximise the impact of therapeutic advances. We now have a rich variety of media through which such knowledge can be spread, including original research and review articles available in paper and online form, guidelines, updates and position papers of societies such as the European Society of Cardiology, American College of Cardiology and American Heart Association (also available in printed and electronic form), books, conferences (often with presentations available online or through other digital media), websites specialising in cardiovascular research, such as the Heart.org and Cardiosource, and printed materials provided by the pharmaceutical and device industries. The complexity of many of the areas relating to atherothrombosis gives a platform to individuals with expert knowledge who can guide the way to consensus. Yet herein lies a perceived danger that has attracted much attention: the commercial forces behind cardiovascular drug and device development have the potential to influence expert opinion in a way that could bias the presentation of research data for commercial gain (1, 2). Whatever the level of disclosure, the reader of educational materials must identify for themselves the likely bias of an article (3) and be prepared to probe deeper into the literature to form an opinion on the evidence for a particular intervention or else rely on a trusted source.

This supplement was supported by an unrestricted educational grant to an academic institution from the pharmaceutical industry. This type of support can take many guises but in this case the companies have had no part in constructing the articles and have not reviewed or approved the content. This is clearly a prerequisite for minimising the risk of bias. Furthermore the articles have been submitted to a formal peer-review process. The aspiration of this process is that high-quality educational materials can be provided to the scientific and clinical communities, accessible free-of-charge via the internet, to inform scientific and clinical debates and research endeavours as well as support therapeutic decision-making in an increasingly complex world of primary and secondary prevention therapies. We hope that readers of this supplement will judge that the authors have succeeded in meeting this aim.

Numerous animal models are available for studying the roles of different cell types and extracellular molecules in arterial thrombosis and its sequelae. Mouse models have the advantage of the availability and study feasibility of genetic knock-out lines that can characterise the role of platelet receptor pathways and coagulation proteins in thrombosis to complement and substantiate pharmacological studies. For example, P2Y12 receptor knockout mice have confirmed the role of this receptor in thrombus propagation and stability in vivo as well as the importance of this platelet receptor in the vessel wall response to thrombogenic injury, supporting the studies in wild-type mice of P2Y12 inhibitors (4–7). Developing these models to reflect more closely the process of atherothrombosis has led to establishment of models that mimic the atherosclerotic plaque rupture that underlies the majority of cases of acute coronary syndrome and in this issue Hechler and Gachet describe two methods in hyperlipidaemic mice with atherosclerotic disease that may characterise potential new targets for management and prevention of atherothrombotic events (8).

Characterisation of the chemokines present in platelet α-granules and their roles in inflammatory responses has stimulated much research into the potential contribution of platelets to not only atherothrombosis but also a range of other diseases. Here, Nurden gives a broad overview of the pro-inflammatory effects of platelets and the mechanisms by which platelets contribute to tissue healing, angiogenesis and potentially numerous disease processes (9). This article nicely illustrates how platelets are designed to be much more than just the agents that plug breaches in vessel wall integrity. The theme of inflammation is certainly a hot topic in atherothrombosis as well as a complex one that has deserved much research and educational effort. Knowledge of the role of different types of lipid in atherogenesis has continued to identify new potential targets. The increasingly complex interactions between lipids, vessel walls, platelets and the coagulation cascade are here presented by Badimon et al. to advance understanding of the interplay between different molecules and cell types in the pathobiology of atherothrombosis (10). Looking at the impact of glycaemic control on inflammation and atherothrombotic events adds a further fascinating dimension, which is increasingly important as the incidence of type 2 diabetes mellitus continues to rise. Hess and...
Grant here present an overview of the mechanisms for the pro-inflammatory and pro-thrombotic phenotype associated with diabetes (11), which is further complicated by an adverse impact of diabetes on the antithrombotic response to some antiplatelet drugs as described elsewhere (12–15).

Clopidogrel, a prodrug that acts on the platelet P2Y<sub>12</sub> receptor via an active thiol metabolite, has found broad usage either in combination with aspirin, such as in patients undergoing percutaneous coronary intervention or following acute coronary syndrome, or as monotherapy instead of aspirin or aspirin/dipyridamole combination. The finding that poor active metabolite formation underlies many (recurrent) arterial thrombotic events in clopidogrel-treated patients has focused much attention on the genetic and non-genetic factors that lead to poor pharmacodynamic response, as described here by Huber et al. (16, 17). The cost differential in Europe between generic clopidogrel and more effective alternative P2Y<sub>12</sub> inhibitors such as prasugrel and ticagrelor is accentuating the demand to find the most cost-effective strategies for preventing ischaemic events and death in high-risk patients, so understanding the complexities of the pharmacology of clopidogrel is becoming increasingly important. The flip side to efficacy is safety concerns related to the effects of increasing levels of P2Y<sub>12</sub> inhibition on haemostasis and risk of bleeding, as described here by Cattaneo who provides insights from patients with genetic-determined defects of the P2Y<sub>12</sub> receptor that complement pharmacological studies (18). Finally, a wealth of evidence is emerging for drugs with different mechanisms of inhibiting the P2Y<sub>12</sub> receptor, with studies of reversibly-binding inhibitors providing intriguing data that will increasingly impact on management of acute coronary syndromes and other clinical settings (19).

The abundance of basic and clinical scientific data that is now available in the area of atherothrombosis and the devastating effects of this disease process globally provide a great educational challenge and meeting this challenge is fundamental to improving health through pharmacological and other means.

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**References**