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EDITORIAL

Cardiovascular pharmacology: a look back and a glimpse into the future

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When I graduated from New York University's School of Medicine in 1952, drugs available for the management of cardiovascular diseases were few and with the exception of nitroglycerine, which was widely used in the treatment of angina, they were relatively ineffective. Digitalis was given universally for heart failure, along with painful, deep i.m. injections of the diuretic mercuhydrin; to augment the latter's potency, it was sometimes preceded by large doses of oral ammonium chloride and followed by i.v. theophylline. The only anti-arrhythmic drug available was quinidine, which was widely used for the treatment of many tachyarrhythmias; its intrinsic pro-arrhythmic properties were not suspected. Bradycardia and heart block were treated with oral ephedrine, and in emergencies epinephrine was administered subcutaneously. While heparin and warfarin were available, the indications for their use were unclear and they were not prescribed frequently. High doses of salicylates were administered for acute rheumatic fever, a condition which was still quite common, and penicillin was life saving in many patients with streptococcal endocarditis.

Anti-hypertensive drugs, adrenergic receptor blockers, antiplatelet agents (other than salicylates), cholesterol-lowering agents, and oral diuretics had not yet been developed. The renin–angiotensin–aldosterone axis had not been defined and drugs that blocked its activity did not exist. The entire subject of drug therapy of cardiovascular diseases was well covered in a 1 hour lecture, with time to spare.

Since then, it has been my privilege to observe extraordinary progress in this field, and in a few instances to have a ringside seat. In the 1950s, the thiazides[1] and mineralocorticoid receptor blockers[2] were introduced by scientists at Merck and Searle, respectively. The 1960s and 1970s witnessed the development of the first beta-blocker by Black and Stephenson,[3] the first angiotensin-converting enzyme inhibitor by Ondetti *et al.*,[4] and the first HMG-CoA reductase inhibitor by Endo *et al.*[5] (*Figure 1*). All three of these groups were employees of the pharmaceutical industry at the time that they made their momentous contributions. Black was appropriately rewarded with a Nobel Prize; while Ondetti, Cushman, and Endo received Lasker Awards (often referred to as 'American Nobels'). Other important drug classes followed, including calcium channel blockers, loop diuretics, platelet inhibitors, angiotensin receptor blockers, and so-called novel oral anticoagulants.

As a consequence of carefully conducted clinical trials on these agents, there has been a transformation in cardiac care and prevention. Most members of the drug classes mentioned above are well tolerated when administered appropriately, and are now generic, inexpensive, and available throughout the world. As a result of their widespread use (along with implanted pacemakers, cardiac defibrillators, and other therapeutic devices), the mortality of cardiovascular diseases has plummeted and the quality of life of millions has improved. Taken together, the developments in cardiovascular therapeutics represent one of the triumphs of modern medicine.

Are the 'golden years' of the discovery of important cardiovascular drugs over as some fear? Most certainly not! Actually, I believe that we are at the cusp of important new developments in this field. Among the numerous promising directions that the field can take, I will mention just four:

'Classical' drug discovery is living and well. For example, there has been interest in combining into a single molecule, a blocker of the renin–angiotensin system and of neprilysin (the endopeptidase responsible for degrading biologically active natriuretic peptides). The combination of an angiotensin receptor blocker with the pro-drug of a potent neutral endopeptidase inhibitor is such a molecule. This drug (LCZ696) developed by Novartis has been shown to be a potent anti-hypertensive agent.[6] A large multicentre, multinational trial in patients with heart failure and reduced ejection fraction has been halted on the recommendation of its Data and Safety Monitoring Committee because of compelling evidence of clinical benefit.[7] The results of a phase 2 trial in patients with heart failure and preserved ejection fraction have been encouraging.[8] A phase 3 trial in this population will begin shortly.

Monoclonal antibodies are widely used as therapeutic agents in many areas of medicine, such as oncology and rheumatology. However, their use for the treatment or prevention of cardiovascular disease has been slower in coming. Pro-protein convertase subtilisin/kexin 9 is a serine protease that degrades low-density lipoprotein (LDL) receptors and thereby raises serum LDL-cholesterol concentrations. Monoclonal antibodies that inhibit PCSK9 have been shown to reduce LDL-cholesterol markedly, even in patients receiving statins.[9] Several of these agents are now in phase 3 trials and if positive we could enter a new era in the prevention of atherosclerosis.

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Figure 1 Discoverers of three of the most important classes of cardiovascular drugs.

Although it has long been appreciated that hereditary factors play a role in the response to drugs, we now know that specific genetic variants—including rare mutations and common polymorphisms—can affect profoundly the actions of these drugs. For example, variants in the hepatic enzymes responsible for drug metabolism have been shown to alter the blood levels, and thereby the dose requirements of a variety of drugs, such as clopidogrel.[10] Gene variants associated with decreased dose requirements for warfarin have been described previously,[11] as have mutations that increase the risk of myopathy, resulting from statin administration.[12] Polymorphisms of beta-adrenergic receptors can modify the response to beta-blockers in patients with heart failure.[13] Although pharmacogenetics is still in its infancy, it is likely to refine profoundly the use of cardiovascular (and other) drugs, and thereby greatly facilitate the development of truly personalized medicine.

MicroRNAs are small, 22 nucleotide long RNAs that can bind to and inactivate messenger RNA and thereby regulate the synthesis of specific proteins. MicroRNAs are becoming important targets of therapy. Chemically synthesized oligonucleotide antagonists of miRNAs, named *antagomirs*, which 'silence' miRNAs and thereby enhance gene expression, are being developed.[14] MicroRNA-25 is strongly up-regulated in the hearts of patients with advanced heart failure as well as in a mouse model of heart failure. The antagomir to this miRNA has been shown to reverse heart failure in this model.[15] Clinical trials with this agent are under consideration.

This is an auspicious time to commence the publication of *European Heart Journal – Cardiovascular Pharmacotherapy* as the latest member of the *European Heart Journal* family of journals. Its pages are likely to report the future advances in this important field and will thereby accelerate their translation to clinical care, benefitting patients with, or at risk for the development of, cardiovascular disease around the globe.

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