"Triveram®, the hybrid combination of atorvastatin, perindopril, and amlodipine and a practical translation of the ASCOT results, represents a new concept in the management of cardiovascular disease focused on global cardiovascular protection by combining drugs targeting two different risk factors"

A career spent protecting the hypertensive heart: the future belongs to combination therapy

by K. Narkiewicz, *Poland*

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I have devoted my whole 30-year professional career to hypertension, trying not only to understand the mechanisms underlying its development and progression, but also to become a better clinician managing this complex disease and its associated risk factors.

As always stressed by the late Alberto Zanchetti, research on hypertension and the development of effective and well-tolerated antihypertensive therapies have been among the greatest successes of medicine in the second half of the 20th century. Yet, despite enormous progress, management of the disease remains challenging and hypertension control is far from satisfactory.

Why do we fail to achieve target blood pressure so frequently? First, we tend to underestimate the challenge. We should remember that blood pressure is maintained by multiple pressor systems, inhibition of one system activates another and hypertension-related organ damage is associated with blood pressure–lowering resistance. Second, there is strong evidence that treatment inertia contributes to hypertension-mediated cardiovascular risk, with many patients remaining on monotherapy and/or suboptimal doses, despite inadequate blood pressure control. Third, we are not taking into account a human factor. Almost one-half of patients drop out entirely from treatment within 1 year, and there is a huge discrepancy between the self-reported compliance rates and the data derived from objective measurements.

Factors that may influence compliance include complexity of the treatment regimen, inadequate understanding of the complications of hypertensive disease, as well as the lack of perceived benefit of treatment.

Progress in hypertension management in the second half of the 20th century was related to development of new classes of drugs. It is being followed by the increasing availability of antihypertensive treatments in single-pill combinations (SPCs) in the new millennium.

The 2018 ESC/ESH guidelines presented a new SPC treatment strategy to improve blood pressure control, including: (a) preferred use of two-drug combination therapy for the initial treatment of most people with hypertension; (b) the preferred use of SPC therapy for most patients; and (c) simplified drug treatment algorithms with the preferred use of an ACE inhibitor or ARB combined with a CCB and/or diuretic as the core treatment strategy for most patients, with β-blockers used for specific indications.

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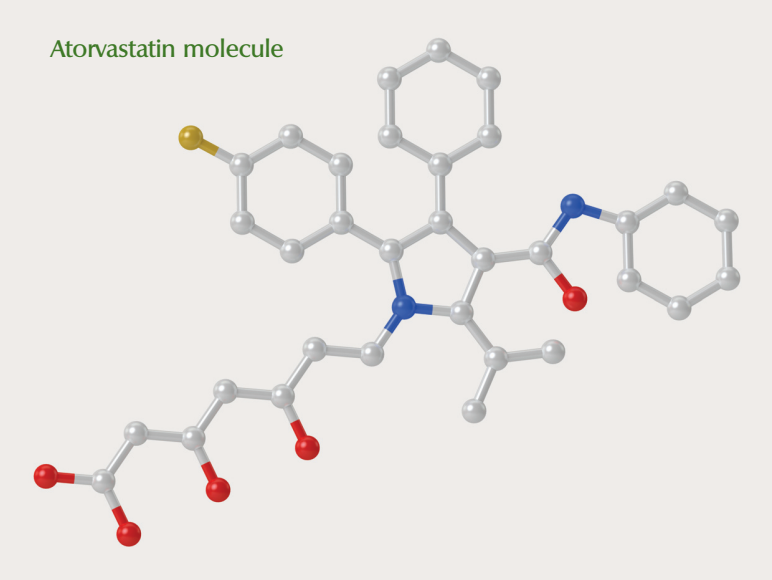
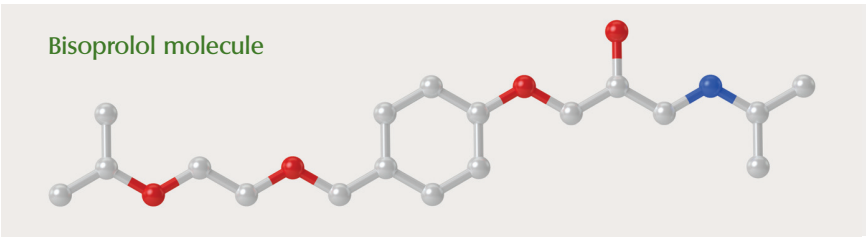
There are several reasons for the strong position of SPCs in the management of hypertension, such as faster and better blood pressure control, less variability in response, safety and better tolerability, and better adherence to therapy. In other words, SPCs in hypertension management meet the challenge, take into account a human factor, minimize the risk of failure, and replace previous strategies, thereby becoming a new standard of treatment.



The ideal core component of an SPC should be useful in various clinical conditions and in different age groups, available in combination with several drugs in double and triple SPCs, and supported by randomized clinical trials (evidence-based medicine). It is clear that the perindopril family of SPCs fulfills these criteria. Among ACE inhibitors, perindopril (used as monotherapy or in combination) probably has the strongest evidence of cardiovascular protection in different clinical high-risk conditions, including coronary artery disease (EUROPA trial[1]), diabetes (ADVANCE[2] and ADVANCE ON[3]), post-stroke patients (PROGRESS[4]), and hypertension in the very elderly (HYVET[5]). Our clinical experience with perindopril-based SPCs was initially based on its combination with indapamide, followed by a double SPC with amlodipine, and consequently a triple SPC of perindopril, indapamide, and amlodipine. The spectrum of treatment options has been expanded by the introduction of a bisoprolol/perindopril SPC, and a "hybrid" combination of atorvastatin, perindopril, and amlodipine. The combinations were launched in Poland a few years ago, allowing myself and other clinicians to gain substantial experience using these novel treatment options.



There is a strong rationale to inhibit the sympathetic nervous system and the renin-angiotensin-aldosterone system, as they are both involved in the pathogenesis of hypertension, coronary artery disease, and congestive heart failure. Their activation might lead to both atherosclerosis (development of plaques) and arteriosclerosis (arterial stiffening), and is associated with a poorer prognosis. There is growing evidence that β-blockers and ACE inhibitors have complementary effects in terms of cardiovascular protection. Therefore, the availability of the first β-blocker/ACE inhibitor SPC, Cosyrel, has the clear-cut potential to improve the management of patients with coronary artery disease, congestive heart failure, and hypertension. Bisoprolol, which has been tested in several hypertension studies and in the landmark CIBIS trials in chronic heart failure, is a highly β_1-selective drug without intrinsic sympathomimetic activity. Its cardioselectivity might be advantageous not only for cardioprotection, but also to avoid side effects, such as bronchoconstriction, vasoconstriction, and metabolic disturbances mediated by the blockade of β_2-receptors.

This might be of particular relevance in the treatment of patients with cardiovascular disease and associated clinical conditions, including chronic obstructive pulmonary disease, peripheral artery disease, and pre-diabetes.

Hypertension and dyslipidemia often coexist. The benefit of adding a statin to antihypertensive treatment was well established in the ASCOT-Lipid-Lowering Arm study.[6] Triveram, the "hybrid" combination of atorvastatin, perindopril, and amlodipine and a practical translation of the ASCOT results, represents a new concept in the management of cardiovascular disease focused on global cardiovascular protection by combining drugs targeting two different risk factors. For the very first time, we can tell our patients: I can fix your "double trouble" with a single tablet.

In summary, Servier is celebrating 50 years of involvement in hypertension pharmacotherapy and has become a global leader in bringing novel SPCs to market. By addressing clinical needs and filling in the pharmacotherapy gaps, Servier has clearly changed our practice and improved the cardiovascular protection of our patients. ■

See references on next page

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