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Fixed Combinations in Antihypertensive Therapy

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As we stand in the early years of the 21st century, with hundreds of antihypertensive drugs at our disposal, it is difficult to believe that 60 years ago there was absolutely nothing available for the treatment of hypertension. In fact, it was not even universally accepted that the "benign" or "essential" hypertension needed to be treated, unless it entered the malignant phase. At that point, it was treated with desperate measures, such as pyrogens or poisons causing circulatory shock or with radical surgical procedures, such as severance of sympathetic tracts or bilateral adrenalectomy.

Throughout the 1950s and 1960s several classes of antihypertensive agents became available and were tested in clinical trials. The results indicated not only that lowering elevated blood (BP) was beneficial, but also that the optimal BP target was much lower than the initial target of 160/95, which was later set at 140/90 and more recently at 130/80, whereas normal BP is now considered to be 120/80 or less. Indeed, several studies have now confirmed that average differences of 10/5 mmHg may translate into decreases of 20-40% in the rate of cardiovascular and cerebrovascular complications. However, it also became apparent that optimal targets could rarely be reached by monotherapy and indeed required multiple drugs in various combinations, leading patients to confusion, expense, denial. This led to the idea that the best way to overcome patient resistance may be fixed combinations of two or more drugs in a single pill or capsule. The earliest such two- or three-drug combinations appeared in the 1950s and consisted mostly of a diuretic, a sympatholytic and a vasodilator—whatever was available at the time.

With further research into mechanisms of action and development of new drugs, it became evident that the most effective combinations were those, whose mechanisms are complementary or synergistic. An example of this is rendering the BP renin-dependent by removing salt with diuretics, so that angiotensin-inhibiting agents become greatly potentiated. Others have simply additive, or even less than additive effect, but may prevent each other's adverse effects, such as combination of a kaliuretic with a potassium-sparing diuretic. Others yet, have the capacity to treat frequently coexisting conditions, such as high BP and dyslipidemia, with a single pill. Thus, the pills containing a fixed drug combination have evolved from random (whatever happens to be available), to rational (complementary or synergistic) and expedient (concurrent treatment of co-morbidities). And the use of these combinations is gaining ground not only for treatment of hypertension, but also for related disorders, such as coronary artery disease, where initial treatment of acute coronary syndrome or chronic preventive treatment of coronary risk factors was proposed with the "tetrapill" or "polypill," i.e., various fixed combinations containing a diuretic, an ACE inhibitor, a beta-adrenoceptor blocker, a statin and low-dose aspirin. Even if the more distant future may promise personalized therapy based on pharmacogenetics, the current

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availability of rational fixed drug combinations is a practical and convenient approach for today's clinical practice.

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