Box 5. Choice of antihypertensive drugs

(1) Large-scale meta-analyses of available data confirm that major antihypertensive drug classes, that is, diuretics, ACE inhibitors, calcium antagonists, angiotensin receptor antagonists, and β-blockers do not differ significantly for their overall ability to reduce BP in hypertension.

(2) There is also no undisputable evidence that major drug classes differ in their ability to protect against overall cardiovascular risk or cause-specific cardiovascular events, such as stroke and myocardial infarction. The 2007 ESH/ESC guidelines conclusion that diuretics, ACE inhibitors, calcium antagonists, angiotensin receptor antagonists, and β-blockers can all be considered suitable for initiation of antihypertensive treatment, as well as for its maintenance, can thus be confirmed.

(3) Because the percentage of patients responsive to any drug class is limited and patients responsive to one drug are often not those responsive to another drug, keeping the number of drug options large increases the chance of BP control in a larger fraction of hypertensives. This is of crucial importance because cardiovascular protection by antihypertensive treatment substantially depends on BP lowering *per se*, regardless of how it is obtained.

(4) Each drug class has contraindications as well favorable effects in specific clinical settings. The choice of drug(s) should be made according to this evidence. The traditional ranking of drugs into first, second, third, and subsequent choice, with an average patient as reference, has now little scientific and practical justification and should be avoided.

(5) Drugs acting via direct renin inhibition are the only new classes of antihypertensive agents that have recently become available for clinical use. Several additional new classes are under an early investigational phase. Selective antagonism of endothelin receptors holds some promise to improve rate of BP control in hypertensive patients resistant to multiple drug treatment.

small arteries, and cardiac structure associated with a BP elevation [131]. This appears to be supported by the results of the few trials in which patients were followed for a number of years after termination of randomized treatment. In the SYST-EUR and SHEP trials, for example, the beneficial effects of antihypertensive treatment on the incidence of cardiovascular events remained evident years after termination of the double-blind phase of the trial, despite the fact that antihypertensive treatment was started also in the placebo group [132,133]. A similar phenomenon, which is referred to as the 'legacy effect', has also been reported for the Steno 2 trial [134], which reported a postinterventional benefit on the microvascular and macrovascular complications of type 2 diabetes after 13.3 years of follow-up with an intensive multifactorial therapy that included antihypertensive drugs and in the UKPDS trial [135] during a 10-year follow-up of the effect of a previous 10-year intensive blood glucose control in diabetes.

The most important points related to threshold and target BP values for treatment are summarized in Boxes 3 and 4.

Treatment strategies

Choice of antihypertensive drugs

In their 2003 [136] and 2007 versions [1], the European guidelines reviewed the large number of randomized trials of antihypertensive therapy, both those comparing active treatment versus placebo and those comparing treatment regimens based on different compounds (Box 5). They concluded that the main benefits of antihypertensive treatment are due to lowering of BP *per se*, and are largely independent of the drugs employed. Therefore, thiazide diuretics (as well as chlorthalidone and indapamide), β-blockers, calcium antagonists, ACE inhibitors, and angiotensin receptor antagonists can adequately lower BP and significantly and importantly reduce cardiovascular outcomes. All these drugs are suitable for the initiation and maintenance of antihypertensive treatment either as monotherapy or in some combinations with each other.

The issue of the equivalence of the various classes of antihypertensive agents, and of various agents within a given class, has been a long debated one, heralded in the 1970s by the incautious suspicion of a role played by reserpine in breast cancer [137], and continuing in the 1990s with the campaign against calcium antagonists as responsible for coronary events, bleeding, and cancer [138,139]. After the acquittal of calcium antagonists, even by their prosecutors, attention has been recently focused by different groups of investigators on a possible inferiority of β-blockers and diuretics as well as on the possible inferiority of ACE inhibitors for stroke prevention and of angiotensin receptor antagonists for coronary disease prevention. Obviously, paying careful attention to possible adverse effects or limitations of both new and old drugs is an obligation of physicians and clinical epidemiologists and must be taken seriously by members of guidelines committees. On the contrary, unfounded suspicion should not be used to deprive patients of the benefits of drugs.

β-*Blockers*

The evidence upon which β-blockers have been questioned as first choice antihypertensive drugs [140] and actually downgraded in the British recommendations [141] was discussed in the 2007 European guidelines.