REVIEW ARTICLE

Reappraisal of the European guidelines on hypertension management

The European Society of Hypertension Task Force document: a short review

Robert Fagard

Hypertension and Cardiovascular Rehabilitation Unit, Department of Cardiovascular Diseases, Faculty of Medicine, KU Leuven University, Leuven, Belgium

KEY WORDS

antihypertensive treatment, cardiovascular risk, elderly, guidelines, hypertension

ABSTRACT

The European Society of Hypertension Task Force document on reappraisal of the 2007 European guidelines on hypertension addresses a number of studies published in the last 2 years to estimate their contribution to the expanding knowledge on hypertension. The importance of total cardiovascular risk with inclusion of subclinical cardiac, vascular, and renal organ damage was reemphasized, followed by a critical reappraisal of recommendations for the initiation of antihypertensive drug treatment in patients with high normal blood pressure (BP) and grade 1 hypertension. Whereas there is sufficient evidence for reducing BP below 140/90 mmHg in most hypertensives, the recommendation of previous guidelines to aim at a lower BP in diabetics and in patients at very high cardiovascular risk is not consistently supported by trial evidence. Moreover, the J-curve phenomenon may occur in patients at high cardiovascular risk. With regard to the choice of antihypertensive drugs, the conclusions of the 2007 guidelines that diuretics, angiotensin-converting enzyme inhibitors, calcium antagonists, angiotensin receptor antagonists, and β-blockers are suitable for initiation and maintenance of antihypertensive treatment are reinforced. Furthermore, apart from starting with combination therapy in certain conditions, adding a drug from another class to the initially prescribed one is preferred to increasing the dose of the first one. Some of the drug combinations recommended in 2007 are now regarded as more recommendable. In addition to the benefits of antihypertensive treatment in the elderly, the HYVET (Hypertension in the Very Elderly Trial) has shown that antihypertensive treatment also has benefits in octogenarians. The document ends with a number of issues in urgent need to be approached by new trials.

Correspondence to:
Prof. Robert Fagard, MD, PhD, Hypertension and Cardiovascular Rehabilitation Unit, Department of Cardiovascular Diseases, Faculty of Medicine, KU Leuven University, Leuven, Belgium, phone: +32-16-34-87-07, fax: +32-16-34-37-66, e-mail: robert.fagard@uz.kuleuven.ac.be
Received: December 1, 2009.
Accepted: December 1, 2009.
Conflict of interests: none declared.
Pol Arch Med Wewn. 2010; 120 (1-2): 31-36

In the 2 years since the publication of the 2007 guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC),[1] research on hypertension has further advanced and the results of new important studies have been published. Some of these studies have reinforced the evidence on which the recommendations of the 2007 ESH/ESC guidelines were based. Other studies, however, have widened the information available in 2007, modifying some of the previous concepts and suggesting that new evidence-based recommendations could be appropriate. The purpose of the recently published document by the ESH task force on reappraisal of the European guidelines on hypertension management was to address a number of studies on hypertension published in the last 2 years in order to estimate their contribution to the expanding knowledge on hypertension.[2] The aim of the current manuscript is to briefly review the main issues addressed in this document.

Assessment of subclinical organ damage for the stratification of total cardiovascular risk The importance of the assessment of total cardiovascular risk in patients with hypertension in order to optimize decisions about treatment initiation, intensity, and goals has been reinforced. In hypertension,

the quantification of total cardiovascular risk must include a search for subclinical organ damage. The evidence on the important prognostic role of subclinical organ damage is constantly increasing. The presence of electrocardiographic or echocardiographic left ventricular hypertrophy, a carotid plaque or carotid intima-media thickening, an increased arterial stiffness, a reduced estimated glomerular filtration rate (eGFR), or microalbuminuria or proteinuria substantially increase total cardiovascular risk, usually moving hypertensive patients into the high absolute risk range. Subclinical organ damage alone may not be sufficient for the normotensive subjects to be placed in the high risk category, although this may occur with multiple organ damage or in the presence of metabolic syndrome.

Several measures of cardiac, vascular, and renal damage can be considered for routine total cardiovascular risk quantification. Because of their simplicity, wide availability, and limited cost, measures based on electrocardiography, urinary protein excretion, and eGFR (the Modification of Diet in Renal Disease – MDRD formula) are suitable for routine use. Cardiac and vascular ultrasound examinations are more and more easily available in Europe, and their use in the evaluation of the hypertensive patient can be encouraged. Subclinical organ damage should be assessed both at screening and during treatment, because the number of treatment-induced changes in organ damage, including the changes in electrocardiographically or echocardiographically detected left ventricular hypertrophy or changes in urinary protein excretion, relate to cardiovascular and renal outcomes, thereby offering information on whether the selected treatment is protecting patients from organ damage progression.

Several other measures of subclinical organ damage, such as nuclear magnetic resonance and structural alterations in small subcutaneous arteries, have been shown to have prognostic significance; however, their complexity, low availability, and high cost prevent their routine clinical use. The importance of endothelial dysfunction and inflammatory markers is currently inconsistent. It is likely that technological progress will make use of some of these measurements more common in the future. Any measure, however, should be considered only if it adds to the overall accuracy of cardiovascular risk quantification.

Initiation of antihypertensive treatment A critical reappraisal of the recommendations for the initiation of antihypertensive drugs in patients with hypertension has recently been undertaken in the light of further information provided by recent trials,[3] with the following conclusions: in subjects with high normal blood pressure (BP) (systolic BP 130–139 or diastolic BP 85–89 mmHg) uncomplicated by diabetes or previous cardiovascular events, no trial evidence is available for treatment benefits, except for a delayed onset of hypertension that is crossing the 140/90 mmHg cut-off. In addition, prospective trial evidence is scant for the guideline recommendations to initiate drug treatment in the high normal BP range in patients with diabetes. For the time being, it appears reasonable to recommend treatment initiation in diabetics with high normal BP, if subclinical organ damage, particularly microalbuminuria or proteinuria, is present.

Although trial evidence is limited, it seems reasonable to recommend that, in patients with grade 1 hypertension (systolic BP ≥140–159 or diastolic BP ≥90–94 mmHg) at low and moderate risk, drug therapy should be started, if BP is 140/90 mmHg or higher after a suitable period of time with appropriate lifestyle changes, with the goal to bring BP below this cut-off value. Prompter initiation of treatment is advisable, if grade 1 hypertension is associated with a high level of risk, or in grade 2 or 3 hypertension. Similar cautious recommendations can be given to patients with previous cardiovascular events, for whom current trial evidence is controversial concerning both the initiation of antihypertensive drug treatment when BP is in the high normal range, and the benefit of aiming at a BP target of less than 130/80 mmHg. Further trials must be completed before firm recommendations can be given.

In general, early introduction of BP lowering treatments, before organ damage develops or becomes irreversible or before cardiovascular events occur, appears a prudent recommendation. This is because in high-risk hypertensive patients even intense cardiovascular drug therapy, though beneficial, is nonetheless unable to lower total cardiovascular risk below the high-risk threshold.

Blood pressure treatment goals On the whole, there is sufficient evidence to recommend that systolic BP be reduced to less than 140 mmHg and diastolic BP to less than 90 mmHg in the general population of patients with grade 1 or 2 hypertension and low or moderate total cardiovascular risk, as well as in those at high risk. Evidence is only missing for elderly hypertensive patients, in whom the benefit of lowering systolic BP below 140 mmHg has never been tested in randomized trials.[3] The recommendation of previous guidelines to aim at a lower systolic BP goal (<130 mmHg) in diabetics and in patients at a very high cardiovascular risk because of previous cerebrovascular or coronary disease may be wise, but is not consistently supported by trial evidence. In none of the randomized trials performed in diabetic patients has systolic BP been brought below 130 mmHg with proven benefits. Moreover, trials in which systolic BP was lowered to less than 130 mmHg in patients with previous cardiovascular events have provided controversial results. Despite their obvious limitations and a lower strength of evidence, post-hoc analyses of trial data indicate a progressive reduction of cardiovascular event incidence with progressive lowering of systolic BP down to about 120–125 mmHg

and diastolic BP down to about 70–75 mmHg, although the additional benefit at lower BP values becomes rather small. The J-curve phenomenon is unlikely to occur below these values, except perhaps in patients at high cardiovascular risk in whom antihypertensive treatment regimens that reduce BP to values close to or below these levels may be accompanied by an increase rather than a further reduction in the incidence of cardiovascular events.[4,5]

On the basis of the current data, it may be advisable to recommend lowering systolic/diastolic BP to values within the range 130–139/80–85 mmHg, and possibly close to the lower values in this range, in all hypertensive patients. However, more critical evidence from specific randomized trials is desirable.

The choice of antihypertensive drugs In previous versions of the European guidelines, it was concluded that the main benefits of antihypertensive treatment are due to lowering of BP per se, and that they are largely independent of the drugs employed. Large scale meta-analyses of the available data do not confirm the contention that major antihypertensive drug classes, that is diuretics, angiotensin-converting enzyme (ACE) inhibitors, calcium antagonists, angiotensin receptor antagonists, and β-blockers differ significantly in their overall ability to reduce BP in hypertension. In addition, there is no undisputable evidence that major drug classes differ in their ability to protect against overall cardiovascular risk or cause-specific cardiovascular events, e.g., stroke and myocardial infarction.[6] The effects on cause-specific outcomes of the various agents are similar or differ only to a minor degree, and, in addition, the type of outcome to occur in a given patient is unpredictable. This confirms the conclusion of the 2007 ESH/ESC guidelines that diuretics, ACE inhibitors, calcium antagonists, angiotensin receptor antagonists and β-blockers can all be considered suitable for the initiation and maintenance of antihypertensive treatment. No single agent is generally prescribed, but each agent can be preferentially prescribed in specific conditions.

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 numerous drug options, increases the chance of BP control in a larger fraction of patients with hypertension. This is of crucial importance because cardiovascular protection by antihypertensive treatment substantially depends on BP lowering per se, regardless of how it is obtained. Each drug class has contraindications as well as 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.

Drugs acting via direct renin inhibition are the only new class of antihypertensive agents that has recently become available for clinical use.[7] Several additional new classes are in an early investigational phase. Selective antagonism of endothelin receptors holds some promise to improve the rate of BP control in hypertensives resistant to multiple drug treatment.[8]

Monotherapy and combination therapy Evidence has continued to grow that in the vast majority of hypertensive patients effective BP control can only be achieved by combination of at least 2 antihypertensive drugs. In addition, a recent meta-analysis has shown that combining 2 agents from any 2 classes of antihypertensive drugs increases the BP reduction much more than doubling the dose of 1 agent.[9] Adding a drug from another class to the initially prescribed one should thus be regarded as a recommendable treatment strategy, unless the initial drug needs to be withdrawn because of the appearance of side effects or the absence of any BP lowering effect. The combination of 2 antihypertensive drugs may offer advantages also for treatment initiation, particularly in hypertensive patients having a high initial BP or classified as being at high/very high cardiovascular risk because of the presence of organ damage, diabetes, renal disease, or a history of cardiovascular disease, in whom early BP control may be desirable. Whenever possible, the use of a fixed dose or single pill combinations should be preferred, because of the advantages brought about by simplification of treatment regimen. However, it should be recognized that it is possible that the use of 2 drugs together as initial therapy may imply the administration of a futile one.

As mentioned by the 2007 ESH/ESC guidelines, several two-drug combinations are suitable for clinical use. Some of the large-scale trials published in the last 2 years importantly expanded information on the advantages and disadvantages of several two-drug combinations in hypertension. Older and new trial evidence of outcome reduction has been obtained particularly for the combination of a diuretic with an ACE inhibitor[10,11] or an angiotensin receptor antagonist, or a calcium antagonist, and in a recent large-scale trial for the ACE inhibitor/calcium antagonist combination.[12] These combinations can thus be recommended for priority use. Despite trial evidence of outcome reduction, the β-blocker/diuretic combination favors the development of diabetes and should thus be avoided, unless required for other reasons, in predisposed subjects. Use of an ACE inhibitor/angiotensin receptor antagonist combination presents a dubious potentiation of benefits with a consistent increase of serious side effects.[13] Specific benefits in nephropathic patients with proteinuria because of a superior antiproteinuric effect expect confirmation in event-based trials.

Finally, it is important to remember that no less than 15% to 20% of hypertensive patients

need more than 2 antihypertensive drugs to achieve an effective BP reduction. When 3 drugs are required, the most rational combination appears to be a blocker of the renin-angiotensin system, a calcium antagonist and a thiazide diuretic at effective doses, although other drugs, such as a β-blocker or an α-blocker may be included in a multiple approach depending on clinical circumstances.

Antihypertensive treatment in the elderly Since the publication of the last guidelines, evidence from large meta-analyses of published trials has confirmed that antihypertensive treatment is highly beneficial in elderly patients. The proportional benefit in patients over 65 years is no less than that in younger patients.[14] Data from meta-analyses do not support the claim that antihypertensive drug classes significantly differ in their ability to lower BP and to exert cardiovascular protection, both in younger and in elderly patients.[14] Thus, the choice of drugs to employ should not be guided by age. Thiazide diuretics, ACE inhibitors, calcium antagonists, angiotensin receptor antagonists, and β-blockers can be considered for the initiation and maintenance of treatment also in the elderly. For isolated systolic hypertension in this population, there are 3 older trials that used a diuretic and a calcium antagonist as first-line treatment.

No single trial on elderly hypertensive patients recruited subjects with a systolic BP in grade 1 hypertension range, and in none of the trials in which a benefit was shown, the systolic BP lowering was below 140 mmHg.[3] Evidence from the outcome trials addressing lower entry and achieving lower on-treatment values is thus needed, but common sense considerations suggest that also in the elderly drug treatment can be initiated when systolic BP is higher than 140 mmHg, and that systolic BP can be brought to less than 140 mmHg, provided that the treatment is conducted with particular attention to adverse responses, potentially more frequent in the elderly.

As mentioned in the previous versions of the European guidelines, evidence of the benefits of BP lowering was inconclusive for patients aged 80 years or older. For this population, only a meta-analysis of a limited number of patients from various trials and data from the pilot HYVET (Hypertension in the Very Elderly Trial) were available, suggesting beneficial effects for morbidity but not mortality. This gap in the evidence has been filled with the publication of the results from the main HYVET outcome trial, which showed that antihypertensive treatment has benefits also in octogenarians, at least in those with systolic BP higher than 160 mmHg.[10] Beneficial effects included a 30% reduction in stroke and a significant reduction in congestive heart failure, major cardiovascular events, and all-cause mortality. BP lowering drugs should thus be continued or initiated when patients turn 80, starting with monotherapy and adding a second drug, if needed. Because HYVET patients were generally in good condition, the extent to which the HYVET results can be extrapolated to more fragile octogenarians is uncertain. The decision to treat should thus be made on an individual basis, and patients should always be carefully monitored during and beyond the treatment titration phase.

Antihypertensive treatment in diabetes mellitus In diabetic patients antihypertensive treatment should always be initiated when BP is at the level of 140/90 mmHg or higher. However, there is scant evidence in favor of initiating BP lowering therapy in diabetic patients with high normal BP. It can nevertheless be recommended, based on the evidence of its favorable effect on prevention of progression or enhancement of organ damage regression, particularly microalbuminuria. The BP goal traditionally recommended in diabetes, i.e., <130/80 mmHg, is also not supported by outcome evidence from trials,[3] and has also been very difficult to achieve in the majority of patients. Thus, it appears realistic to recommend only to pursue a sizeable BP reduction without indicating a goal that is unproven. The meta-analyses of available trials show that in diabetes all major antihypertensive drug classes protect against cardiovascular complications, probably because of the protective effect of BP lowering per se. Thus, they can all be considered for treatment. In diabetes, combination treatment is commonly needed to effectively lower BP. A renin angiotensin receptor blocker should be included because of the evidence of its superior protective effect against initiation or progression of nephropathy. Microvascular complications of diabetes in organs are differently affected by treatment in different organs; antihypertensive treatment exerts a major protective effect against renal complications, while evidence of a similar effect on eye and neural complications is less consistent.

In hypertensive diabetic patients tight blood glucose control (HbA_{1c} to 6.5%) is beneficial, particularly on microvascular complications. Recent evidence suggests that combining effective blood glucose and BP control increases protection, particularly of the kidney. Tight blood glucose control should not be pursued abruptly and patients should be monitored closely because of the increased risk of severe hypoglycemic episodes.

New trials needed Despite the availability of many trials of antihypertensive therapy, some major important decisions on hypertension management must currently be taken without the support of evidence from large randomized controlled trials. The document on the reappraisal of the European guidelines on hypertension management ends with a number of issues that need to be urgently addressed by simply designed trials.

1 Should antihypertensive drugs be prescribed to all subjects with grade 1 hypertension, even when total cardiovascular risk is relatively low or moderate? Because of the very low rate of

cardiovascular events expected in these subjects, a placebo-controlled trial using intermediate endpoints, such as signs of organ damage of recognized prognostic importance, would be feasible, ethical, and clinically relevant.

2 Should antihypertensive drugs be prescribed to the elderly with grade 1 hypertension, and should antihypertensive treatment achieve the goal of BP below 140/90 mmHg also in the elderly? These trials could make use of hard cardiovascular outcomes and could be placebo--controlled.

3 Should antihypertensive drug treatment be started in diabetics or in patients with previous cerebrovascular or cardiovascular disease when BP is still in the high normal level, and should BP goal be below 130/80 mmHg in these patients? These issues can be approached by placebo-controlled trials because no trial evidence is still available on the benefit of lowering high normal BP or of achieving BP goals below 130/80.

4 What are the lowest safe BP values to achieve by treatment in different clinical conditions? This issue should be approached by trials comparing more or less intense BP lowering treatment strategies in patients with different cardiovascular risk levels.

5 Are lifestyle measures known to reduce BP also capable of reducing morbidity and mortality in hypertension? A controlled randomized trial using intermediate endpoints (organ damage) would be feasible and desirable in subjects with high normal BP or grade 1 hypertension.

REFERENCES

1 Mancia G, De Backer G, Dominiczak A, et al.; Management of Arterial Hypertension of the European Society of Hypertension; European Society of Cardiology. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens. 2007; 25: 1105-1187.

2 Mancia G, Laurent S, Agabiti-Rosei E, et al. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. J Hypertens. 2009 Oct 15. [Epub ahead of print].

3 Zanchetti A, Grassi G, Mancia G. When should antihypertensive drug treatment be initiated and to what levels should systolic blood pressure be lowered? A critical reappraisal. J Hypertens. 2009; 27: 923-934.

4 Fagard RH, Staessen JA, Thijs L, et al. On-treatment diastolic blood pressure and prognosis in systolic hypertension. Arch Intern Med. 2007; 167: 1884-1891.

5 Sleight P, Redon J, Verdecchia P, et al.; ONTARGET investigators. Prognostic value of blood pressure in patients with high vascular risk in the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial study. J Hypertens. 2009; 27: 1360-1369.

6 Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ. 2009; 338: 1665-1683.

7 Stanton A. Therapeutic potential of renin inhibitors in the management of cardiovascular disorders. Am J Cardiovasc Drugs. 2003; 3: 389-394.

8 Weber MA, Black H, Bakris G, et al. A selective endothelin-receptor antagonist to reduce blood pressure in patients with treatment-resistant hypertension: a randomized double-blind placebo-controlled trial. Lancet. 2009; 374: 1423-1431.

9 Wald DS, Law M, Morris JK, et al. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. Am J Med. 2009; 122: 290-300.

10 Beckett NS, Peters R, Fletcher AE, et al.; HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. N Engl J Med. 2008; 358: 1887-1898.

11 Patel A; ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet. 2007; 370: 829-840.

12 Turnbull F, Neal B, Algert C, et al.; Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. Arch Intern Med. 2005; 165: 1410-1419.

13 Yusuf S, Teo KK, Pogue J, et al.; ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med. 2008; 358: 1547-1559.

14 Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. BMJ. 2008; 336: 1121-1123.

ARTYKUŁ POGLĄDOWY

Aktualizacja europejskich wytycznych postępowania w nadciśnieniu tętniczym

Krótki przegląd dokumentu Grupy Roboczej European Society of Hypertension

Robert Fagard

Hypertension and Cardiovascular Rehabilitation Unit, Department of Cardiovascular Diseases, Faculty of Medicine, KU Leuven University, Leuven, Belgia

SŁOWA KLUCZOWE

leczenie hipotensyjne, nadciśnienie tętnicze, podeszły wiek, ryzyko sercowo-naczyniowe, wytyczne

STRESZCZENIE

Dokument Grupy Roboczej ESH dotyczący uaktualnienia europejskich wytycznych na temat nadciśnienia tętniczego z 2007 r. odnosi się do szeregu badań opublikowanych w ciągu ostatnich dwóch lat, oceniając ich wkład w poszerzenie wiedzy na temat tej choroby. Ponownie podkreślono znaczenie całkowitego ryzyka sercowo-naczyniowego, z uwzględnieniem subklinicznych sercowych, naczyniowych i nerkowych uszkodzeń narządowych. Dokonano także krytycznego przeglądu zaleceń dotyczących rozpoczęcia farmakologicznego leczenia hipotensyjnego u pacjentów z wysokim normalnym ciśnieniem tętniczym i nadciśnieniem w stopniu 1. Istnieją wystarczające dowody na temat słuszności obniżania ciśnienia tętniczego $<140/90$ mm Hg u większości pacjentów z nadciśnieniem tętniczym, jednak zalecenia poprzednich wytycznych na temat dążenia do niższych wartości ciśnienia tętniczego u pacjentów z cukrzycą lub bardzo wysokim ryzykiem sercowo-naczyniowym nie zostały jednoznacznie potwierdzone w badaniach klinicznych. Co więcej, u pacjentów z bardzo wysokim ryzykiem sercowo-naczyniowym może wystąpić zjawisko krzywej J, wskazujące, że nadmierne obniżanie ciśnienia tętniczego jest szkodliwe. W odniesieniu do wyboru leku hipotensyjnego potwierdzono wnioski podane w wytycznych z 2007 r. – leki moczopędne, inhibitory konwertazy angiotensyny, antagoniści wapnia, antagoniści receptora angiotensynowego i β-blokery mają podstawowe znaczenie w leczeniu hipotensyjnym, zarówno w czasie rozpoczynania terapii, jak i podczas jej kontynuacji. Jeśli kontrola ciśnienia tętniczego nie jest wystarczająca, dodanie leku z innej klasy do pierwotnie stosowanego ma przewagę nad zwiększaniem dawki pierwszego leku. Niektóre z połączeń lekowych zalecanych w 2007 r. uważane są obecnie za szczególnie polecane. Badanie HYVET (Hypertension in the Very Elderly Trial) wykazało, że leczenie hipotensyjne jest korzystne również u osób >80. roku życia. Dokument kończy się listą zagadnień wymagających pilnego wyjaśnienia w nowych badaniach klinicznych.

Adres do korespondencji:
prof. Robert Fagard, MD, PhD, Hypertension and Cardiovascular Rehabilitation Unit, Department of Cardiovascular Diseases, Faculty of Medicine, KU Leuven University, Leuven, Belgium, tel.: +32-16-34-87-07, fax: +32-16-34-37-66, e-mail: robert.fagard@uz.kuleuven.ac.be

Praca wpłynęła: 01.12.2009.
Przyjęta do druku: 01.12.2009.
Nie zgłoszono sprzeczności interesów.
Pol Arch Med Wewn. 2010; 120 (1-2): 31-36
Tłumaczył lek. Krzysztof Rewiuk