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Blood pressure targets and the 2003 WHO/ISH guidelines

As a general practitioner, I have found that hypertension affects about one-quarter of my patients and about half of my elderly patients.

I am constantly being reminded of the joint guidelines published by WHO and ISH (the World Health Organisation and the International Society of Hypertension), and am made to feel guilty if I do not follow them to the letter.

Why did you not mention these guidelines in your 2004 review article (issue 75 of *Prescrire International*, pages 25-33)? Was it because they contained nothing new, or because *Prescrire* overlooked them or did not have time to analyse them in detail?

I really need to know your opinion on these guidelines, and whether you stand by your 1999 position statement.

This is even more important to me from a legal standpoint, because one of the mainstays of my defence against biased medicolegal experts would be an article published in *Prescrire*.

Francis Blanc
General practitioner
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In 1999, WHO and the International Society of Hypertension (ISH) created a joint task force charged with establishing guidelines for the management of hypertension. We examined these guidelines in detail when they were published (1).

Independently of the WHO-ISH guidelines, we published our own suggestions for management of hypertension during the same year. These recommendations were based on a thorough analysis of clinical trial data, in which we gave the most weight to strategies shown to prevent morbidity and mortality (2).

Since 1999, we have continued to address this issue in three principal ways: we have constructively criticised the WHO-ISH guidelines (and WHO also responded to our criticisms) (a); we have continued to provide our subscribers with sound information based on detailed evaluation of new antihypertensive drugs, published results of comparative trials, and significant clinical practice guidelines; and, in 2004, we updated our 1999 review article (3).

New WHO-ISH guidelines were published in 2003 (b) (4). We should have mentioned them in our 2004 review of this question:

whatever our opinion of their quality, they represent a widely disseminated international standard.

Francis Blanc's letter provides us with a new opportunity to examine the 2003 WHO-ISH guidelines.

The 2003 WHO-ISH guidelines

The WHO-ISH guidelines published in 2003 contains little information on the methodology chosen by the task force, or on the nature of the literature search. The task force included a number of international experts. The text was written by two "secretaries" who enlisted the help of two other experts. How exactly these four experts were chosen is not known.

The task force made the following recommendations aimed at improving the management of hypertension (4).

Definition of hypertension. As in 1999, the WHO-ISH task force defined adult hypertension as a blood pressure $\geq 140/90$ mmHg, and classified it in three grades:

Grade 1: systolic pressure (SP) 140-159 mmHg or diastolic pressure (DP) 90-99 mmHg;

Grade 2: SP 160-179 mmHg or DP 100-109 mmHg;

Grade 3: SP > 180 mmHg or DP > 110 mmHg.

The guidelines state that available clinical trials only show a treatment benefit in patients with SP and DP values of > 160 and > 100 mmHg, respectively, and that these thresholds have not been called into question by the results of recent comparative trials. However, they also state that the results of two epidemiological studies support anti-hypertensive drug therapy for all adults with SP and DP values of > 140 mmHg and/or > 90 mmHg, respectively, with the aim of keeping them below these thresholds (c).

It should be noted that the WHO-ISH grading system does not take age or gender into account (even for patients over 80).

Stratification of hypertensive patients according to complications and other risk factors.

As in 1999, the WHO-ISH task force used the dataset of the Framingham epidemiological study to estimate the 10 year risk of myocardial infarction and stroke among hypertensive patients, with and without other cardiovascular risk factors (e.g.

smoking, hypercholesterolemia, obesity, etc.), signs of an impact on "target organs" (ventricular hypertrophy, hypertensive retinopathy, etc.), and a history of cardiovascular events (stroke, heart failure, etc.).

As in 1999, the task force stratified hypertensive subjects according to the three grades of hypertension and presence or absence of the risk factors described above. They consider adults to be at low risk (below 15%) if they have SP values between 140 mmHg and 159 mmHg or DP values between 90 mmHg and 99 mmHg (Grade 1 hypertension) and no other risk factors; at moderate risk (15% to 20%) with Grade 2 hypertension (SP 160-179 mmHg or DP 100-109 mmHg) and one other risk factor, or with Grade 1 hypertension and one or two other risk factors; and finally, all other hypertensive patients are considered to be at high risk (over 20%).

The task force mentions the existence of other stratifications based on other epidemiological data, and recognises that the predictive value of the WHO-ISH stratification is not known for populations outside North America and northern Europe.

Blood pressure targets. According to the 2003 WHO-ISH task force, blood pressure targets depend on the individual degree of risk.

For hypertensive patients who have a low or moderate risk the task force recommends (as in 1999) maintaining blood pressure below 140/90 mmHg. As in 1999, they base this recommendation mainly on the results of the HOT study (5). They recognise that the main protective effect is obtained by keeping blood pressure below 150/90 mmHg, and that the 140/90 threshold is based on the results of two epidemiological studies (c).

For high-risk hypertensive patients the WHO-ISH task force recommends maintaining blood pressure below 130/80 mmHg. This is based on the results of comparative trials: ramipril was tested in patients with coronary heart disease or a high risk of vascular events; perindopril in stroke patients; and irbesartan and losartan in type-2 diabetic patients with diabetic nephropathy (d).

Diuretic monotherapy. The 2003 WHO-ISH guidelines are based mainly on comparative trials with clinical outcomes and on antihypertensive drugs that have

been shown to reduce cardiovascular morbidity and mortality; these recommendations were based on a meta-analysis, published in 2000, including a total of 75 000 hypertensive patients, as well as the ALLHAT, ANBP2 and LIFE trials (e).

The task force stated that a low-dose diuretic was the first-line treatment for most hypertensive adults, unless other antihypertensive drugs were specifically indicated. In contrast, the 1999 WHO-ISH guidelines stated that treatment could start with any category of antihypertensive drug (1).

The 2003 guidelines state that most hypertensive patients participating in clinical trials required at least a two-drug antihypertensive combination to reach their blood pressure target. The task force recommends that treatment should consist primarily of a low-dose diuretic; if needed, a second antihypertensive drug belonging to a different class should be added.

The 2003 WHO/ISH guidelines: some good, some debatable

The 2003 WHO-ISH guidelines are largely in line with our 1999 proposals (1).

Not enough epidemiological data to establish a therapeutic strategy. As in 1999, the 2003 WHO-ISH task force defined hypertension, and stratified the associated risks, on the basis of the Framingham epidemiological study conducted in the United States.

The results of epidemiological studies are clearly useful, but they mainly serve to derive hypotheses that must be tested in comparative clinical trials before being applied to millions of patients worldwide. This has not been the case to date.

In order to avoid exposing patients to adverse effects of unnecessary treatments, it is best to select interventions whose clinical value has been demonstrated in comparative trials. This was the position we adopted when writing our 2004 review article: *"In people with no risk factors an antihypertensive is required when blood pressure at rest is above 160/95 according to several measurements. The goal is to reduce blood pressure below 150/90. Treatment is indicated for blood pressure exceeding 140/80 in patients with diabetes or a history of stroke"* (3).

In the absence of relevant comparative trials, we do not know if the risk-benefit balance of drug-based intervention is also positive in patients with milder hypertension.

Persistent questions on the quality and independence of the 2003 WHO-ISH task force. Given that the 1999 guidelines drew abundant international criti-

cism, one might have expected the new WHO-ISH guidelines to be more transparent (1).

What was needed was a true systematic review based on an explicit methodology and a thorough literature search. We also hoped that, this time, the guidelines would be independent and transparent.

Unfortunately, the nature of the 2003 WHO-ISH literature search is unclear. It appears that the task force simply updated its 1999 data by means of an unspecified search strategy. The task force also failed to provide information on how the draft guidelines were written or verified. A list of "contributors" appears in an annex, but their precise roles and influence are not stated. Several conflicts of interest are also listed in an appendix. It is particularly noteworthy that the two editors nominated by the two "secretaries" of the four-member writing team declared conflicts of interest with the pharmaceutical industry (one had links to 10 companies, several of which market antihypertensive drugs); and that one of the two secretaries also declared conflicts of interest with companies that market antihypertensive drugs.

Physicians need practice guidelines based on robust data

All public health issues attract abundant research, generating a considerable mass of data.

Individual physicians cannot possibly comb through all the available literature in order to select the most significant data. They need reliable review articles and practice guidelines if they are to integrate concrete therapeutic advances into their daily practice.

Such review articles and practice guidelines must be based on exhaustive, up-to-date documentation, and must base their conclusions on the results of comparative clinical trials. They must be written in total independence, using an explicit and transparent methodology.

WHO must require all task forces it organises or collaborates with to follow these simple principles.

Overall, the WHO-ISH guidelines improved between 1999 and 2003. However, they are undermined by a lack of information on the literature search strategy, the lack of transparency, and the important role played by experts with links to the pharmaceutical industry.

The 2003 WHO-ISH guidelines in no way challenge the conclusions of our review article published in 2004.

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a- Most of these exchanges involved the International Society of Drug Bulletins (ISDB), of which Prescrire is a founding member, and have been published in the ISDB Newsletter (ref 6-8).

b- As in 1999, the WHO-ISH task force limited its guidelines to the management of adult hypertension. Quite logically in our opinion, it did not consider the specific problems that arise in children and pregnant women, or during hypertensive emergencies (ref 4).

c- According to the expert group, the references underlying this proposal are: Van en Hoogen PCW et al. "The relation between blood pressure and mortality due to coronary heart disease among men in different parts of the World" *N Engl J Med* 2000; **342**: 1-8; and Vasani RS et al. "Impact of high-normal pressure on the risk of cardiovascular disease" *N Engl J Med* 2001; **345**: 1291-1297.

d- Particularly the HOPE, PROGRESS and LIFE studies (included in our 2004 update), and the VALUE study published in 2004 (refs 3,9-11).

e- We have examined these trials in references 10, 11, 12 and 14.

Selected references from Prescrire's literature search

1- Prescrire Editorial Staff "Flawed WHO recommendations on hypertension" *Prescrire Int* 1999; **8** (42): 121-123.

2- Prescrire Editorial Staff "Antihypertensives drugs" 1999; **8** (41): 90-95.

3- Prescrire Rédaction "Hypertension artérielle de l'adulte. Des repères pour réduire la morbidité et la mortalité cardiovasculaires" *Rev Prescrire* 2004; **24** (253): 601-611 + addendum 2005; **25** (257): front inside cover.

4- World Health Organisation, International Society of Hypertension Writing Group "2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension" *J Hypertension* 2003; **21** (11): 1983-1992.

5- Prescrire Rédaction "Diabétiques de type 2: viser une pression artérielle diastolique = 80 mmHg réduit la mortalité" *Rev Prescrire* 2001; **21** (217): 364.

6- Bardelay G "Beware of the 1999 WHO-ISH Recommendations on hypertension!" *ISDB Newsletter* 1999; **13** (1): 1-2.

7- "Correspondence of la revue Prescrire with the World Health Organization about the hypertension guidelines" *ISDB Newsletter* 1999; **13** (2): 10-12.

8- "Poor Sources" *ISDB Newsletter* 2001; **15** (2): 3.

9- Prescrire Rédaction "Prescrire un diurétique après accident vasculaire cérébral. Des données favorables aussi chez les normotendus" *Rev Prescrire* 2002; **22** (228): 373-375.

10- Prescrire Rédaction "Hypertension artérielle: quelle place pour les antagonistes de l'angiotensine II?" *Rev Prescrire* 2002; **22** (232): 696-698.

11- Prescrire Rédaction "Diabète de type 2 et microalbuminurie - Limiter surtout le risque cardiovasculaire" *Rev Prescrire* 2004; **24** (255): 760-768 + addendum 2005; **25** (257): front inside cover.

12- The ALLHAT officers and coordinators for the ALLHAT collaborative Research group "Major outcomes in high risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic" *JAMA* 2002; **288** (23): 2981-2997. Summarised in: "Hypertension artérielle: diurétique en première ligne. Confirmation par un grand essai" *Rev Prescrire* 2003; **23** (238): 299-301.

13- Psaty BM et al. "Health outcomes associated with various antihypertensive therapies used as first-line agents. A network meta-analysis" *JAMA* 2003; **289** (19): 2534-2544. Summarised in "HTA: diurétique d'abord (suite)" *Rev Prescrire* 2003; **23** (242): 618. Prescrire Rédaction "L'essai ANBP2 est-il réellement à l'avantage des IEC?" *Rev Prescrire* 2003; **23** (242): 636 (full version available on the Prescrire website: www.prescrire.org).

14- Prescrire Rédaction "L'essai ANBP2 est-il réellement à l'avantage des IEC?" *Rev Prescrire* 2003; **23** (242): 636.