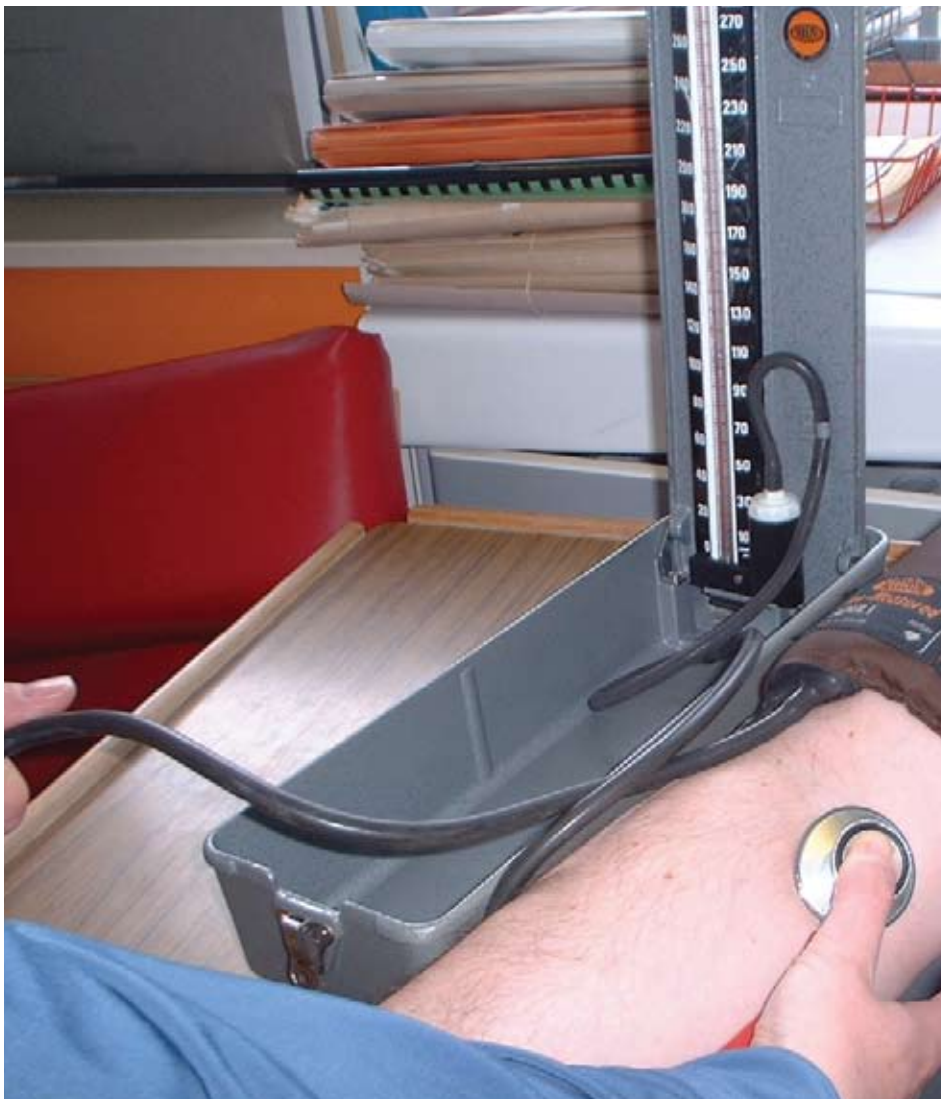
Blood pressure

Blood pressure variability: clarity for clinical practice

Prof Eoin O'Brien focuses on the consequences of blood-pressure fluctuations on cardiovascular outcomes



General practitioner checking the blood pressure of a patient

We have recently seen a virtual deluge of papers (six in all) in two of the world's most prestigious journals – *The Lancet* and *Lancet Neurology* – on an often-neglected aspect of blood pressure, namely its variability and the consequences of fluctuations in blood pressure on cardiovascular outcome, especially stroke. Prof Peter Rothwell, Department of Clinical Neurology, University of Oxford initiated and led the research project that culminated in these papers.

However, these papers, by virtue of their sheer volume (almost 50 pages of printed text and 70 pages of supplementary webappendix data), could overwhelm all but the most stoic readers and misinterpretation of the data could lead to confusion and have an adverse effect on clinical practice. It is important, therefore, to assess the scientific reality and determine how this can benefit patients with hypertension.

The papers can be divided into two groups – three papers give the facts as derived from re-analyses of scientific data in a number of large clinical trials. [1-3], and three papers comment in varying detail on the importance of the analyses. [4-6]

A summary

The three scientific studies show that blood pressure variability whether measured on clinic visits or on ABPM is predictive for stroke and it would appear from a number of analyses that calcium-channel blockers (CCB) and to a lesser extent thiazide diuretics are superior to other drugs in reducing variability and thereby reducing stroke and other vascular events, and that the older beta-blockers increase blood pressure variability and should probably only be used as first-line drugs if there are other compelling clinical indications, such as ischaemic heart disease.

The three commentary papers [4-6] agree that

- Lowering of mean blood pressure, as is common practice, is not in question and should continue.
- However, patients with consistently normal systolic blood pressure have fewer vascular events than patients with normal systolic blood pressure and high blood pressure variability.
- Reductions in variability, rather than reductions in mean blood pressure, might therefore account for some of benefits of antihypertensive drugs.
- Further research is needed to refine understanding of the causes, consequences, and treatment of variability in blood pressure.
- Drugs that bring about the greatest reduction in visit-to-visit blood-pressure variability (calcium antagonists and diuretics) are associated with the best stroke prevention, independently of mean systolic blood pressure.
- β blockers, which increase the variability of blood pressure, are the least effective in stroke prevention. However, in this regard it should be noted that the adverse effect of beta-blockers on blood pressure variability applies to older beta-blockers such as atenolol and the newer generation of beta-blockers may or may not have a similar effect.
- Blood pressure variability must now be given due consideration in clinical practice and in research.

Implications for clinical practice

The body of research led by Rothwell is clearly important and should focus the minds of clinical scientists, the pharmaceutical industry, those interested in blood pressure measurement and doctors who care for patients with hypertension on the need to study the mechanisms of blood pressure variability, its accurate detection and the means to reduce it.

From a research viewpoint we need to obtain a readily applicable measure of variability and this may be best achieved with ABPM, which provides a range of previously unexploited measures of variability in the windows of the 24-hour profile.

Further research is needed to refine understanding of the causes, consequences, and treatment of variability in blood pressure. The pharmaceutical industry needs to provide drugs that not only reduce mean blood pressure but that also reduce variability.

Finally, trials are needed to evaluate drugs and combinations of drug that reduce both mean blood pressure and BP variability.

Not readily done

How then do we take account of blood pressure variability in practice? Detecting variability appears easy in retrospective studies, such as those reported in *The Lancet*, but this is not readily done in practice. Improved methods of collecting data electronically so as to detect trends in blood pressure in the office and home and the increased use of ABPM are methods that should be more widely available.

However, there are more immediate solutions at hand on the therapeutic front. The pharmaceutical industry has recognised the need for flexible dose combinations within one tablet – what I will term the flexipill to differentiate it from its more primitive predecessor the polypill, which only provides fixed-dose combinations in one tablet.

ARBs and CCBs

In this regard, we have flexipill combinations of ARBs and CCBs (olmesartan and amlodipine, valsartan and amlodipine); ACE inhibitors and CCBs (perindopril and amlodipine, ramipril and felodipine, enalapril and lercandipine); ARBs and thiazide diuretics (olmesartan, valsartan, irbesartan, telmesartan, losartan and HCTZ); ACE inhibitors and non-loop diuretics (captopril, lisinopril, ramipril and HCTZ and peridopril and indapamide).

There are also beta-blocker flexipills (nebivolol and HCTZ and Atenolol and HCTZ) and a rennin inhibitor flexipill (aliskiren and HCTZ).

These flexipills allow a prescribing physician to increase the dosage of the component parts in a single tablet, according to blood response. The flexipill allows prescribing of low doses of two drugs in one tablet thereby minimising the adverse effects that might occur with higher doses of the individual components.

This advantage provides a means of overcoming therapeutic inertia and improving patient compliance to treatment by avoiding the occurrence of adverse effects and reducing the daily tablet intake.

But perhaps most importantly the flexipill provides a means of not only lowering mean blood pressure, but of also reducing blood pressure variability, and thereby passing on to our patients the benefits of the scientific research reported in *The Lancet*.

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References:

1. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, Sever PS, Poulter NR. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet* 2010; 375: 895–905
2. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, Poulter NR, Sever PS on behalf of the ASCOT-BPLA and MRC Trial Investigators Effects of Ðblockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. *Lancet Neurology*. www.thelancet.com/neurology Published online March 12, 2010 DOI:10.1016/S1474-4422(10)70066-11
3. Webb AJS, Fischer U, Mehta Z, Rothwell PM. Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis. *Lancet* 2010; 375: 906–15
4. Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. *Lancet* 2010; 375: 938–48
5. Carlberg B, Lindholm LH. Stroke and blood-pressure variation: new permutations on an old theme. *Lancet* 2010;375:867-8
6. Gorelick PB. Reducing blood pressure variability to prevent stroke? *Lancet Neurology*. www.thelancet.com/neurology Published online March 12, 2010 DOI: 10.1016/S0140-6736(08)61345-8.