Comments on the 2018 ESC/ESH Guidelines for the management of arterial hypertension

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Quick history

The treatment of hypertension is one of Medicine's success stories. Partly because Hypertension is the commonest non-communicable, treatable cause of serious morbidity, partly reflecting clever science and clinical investigation, we have more genuine choice of effective, well-tolerated drugs, and more long-term data proving their efficacy and tolerability, than elsewhere in Medicine. Most of these drugs, off patent, are so cheap, whilst complications of Hypertension are so devastating and expensive, that hypertension treatment is not only cost-effective but cost-saving, and deserves credit for substantial reductions in cardiovascular events, antedating widespread use of statins.

New drugs for hypertension, and the heyday of morbidity-mortality studies, are long past. These studies, and their prospective meta-analysis, provided unconditional negative answers to the big questions of the 1990s: were 'older drugs' failing to prevent CHD by causing adverse metabolic problems; were calcium blockers killing patients; did RAS blockers confer 'benefits beyond blood pressure control'.

Recent challenges

The similar outcomes for the major classes switched focus from comparisons of morbidity-mortality to how best to lower blood pressure (BP); to optimal BP thresholds and targets; and to how BP be best measured. The last is important. But how ironic that a condition which is its measurement, on whose sole basis drugs are registered without proof of long-term efficacy and safety, still cannot agree what should be measured. The tragicomedy of this dilemma is illustrated by SPRINT. This brilliant trial was the highpoint of the last decade, asking how far BP should be reduced. But its translation into guidelines and practice has been bedevilled by use of an unfamiliar measurement device which, sin of sins, removed the placebo effect of treatment. When meta-analysis of RCTs shows the average difference in BP that has translated into long-term benefit (<10 mmHg) to be smaller than the average difference between devices, it is difficult to determine thresholds and targets.

So a 2018 guideline has a challenge to re-kindle enthusiasm, and do justice to its year of preparation by Bryan Williams, Giuseppe Mancia, and colleagues. One justification for quinquennial renewal is that guidelines are imperfect, compromise readings of incomplete data and arguments. There is no single route to consensus, so vive la difference among methodologies. These vary between the extremes of bottom-up, expert-scarce, stakeholder-rich, guidelines of NICE, UK, and top-down, expert-driven guidelines of ESC/ESH, delivered as 10 tableaux to an adulatory audience, with 2 symbolic minutes for discussion.

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What’s new

Bryan and Giuseppe highlighted six recommendations:
- wider use of home BP monitoring to confirm diagnosis
- single pill combination treatment, started as initial therapy in most patients
- simplified treatment algorithms, comprising A+{C or D}
- new target BP ranges (aim for 140/90, then proceed to 130/80, but no lower than 120/70)
- detection of poor adherence

and listed 26 gaps in evidence, needing further studies.

Have they succeeded in giving Hypertension its 2020 vision? To some, it is a puzzle how international guidelines can differ so much from each other. But given the variation in methodology, and acknowledgement that gaps (questions) outnumber recommendations (answers) by >4:1, the agreement is more striking than the discord. Similarly, my impressions are not criticisms, but musings of a triallist unfettered by the collective responsibility of a large committee.

What’s excellent, what’s good

Solution for resistant hypertension

Among the highlights, I expect the treatment algorithm to have greatest impact. As the English Channel widens, it is reassuring to interpret what’s new as a rapprochement of UK and Continental approaches. The UK has long sought to limit the number of first-choice options at each stage of treatment, reflecting both the evidence for long-term benefit (sub-optimal for beta-blockade) and a rational connection between the physiological target of each drug class, and the pathway(s) at fault in the individual patient. It is a law of physics that pressure = force/area, suggesting two fundamental routes to Hypertension and its reversal. That subsets of patients are identifiable, with overwhelmingly superior response to one drug class than another, was substantiated by the British and Irish Hypertension Society (BIHS)’s PATHWAY-2 study, in which spironolactone vanquished conventional antihypertensive therapy as add-on for resistant hypertension. Roland Schmieder paid generous tribute to our PATHWAY programme for validating spironolactone as unconditional first choice in this condition — probably because resistant hypertension is what befalls the 99% of patients with primary aldosteronism who are never diagnosed.2

Single pill combinations

However, in moving from the six-sided diamond of ESH to the language of A+C+D, the 2018 guideline leapfrogs the stratified approach of current UK guidance to an emphasis on single pill combinations. This change illustrates the tightrope which guidelines tread between grand visions that lead doctors across a threshold, and details essential to implementation. Two tripwires may catch the unwary. In the large BIHS trials of initial combination therapy, PATHWAY-1 and ACCELERATE, inclusion required an untreated SBP>150 or DBP>90, and side effects were lower on combination than monotherapy. Excessive hypotension in milder patients could reverse symptom-benefit ratio. The second practicality is cost. Treatment with individual A, C or D costs a euro a month. There are no generic combinations of A+C; those of ACEi + diuretic cost 2-4 times the individual drugs, and use insufficient diuretic; only one ARB+diuretic is cost-neutral. It is hard to recommend triple combination pills without endorsing particular brands costing 8 times as much as component drugs. Treatment of hypertension could cease to be cost-saving. Within the 16-week phases of PATHWAY-1, ARB and diuretic achieved identical average BP readings, home or clinic, whether taken as one or two pills.3

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Initial combination therapy abolishes temptation to find each patient's best drug. Such lumping simplifies practice, but splitting helps patients to surpass average. A constituency not favoured by the guideline is the young, with no mention of using lifetime rather than absolute risk to enfranchise earlier treatment, or of the long-term benefit of recognising secondary hypertension. For a 30-year old with BP of 145/95 mmHg, it seems suboptimal either to start combination therapy or to wait for absolute risk to trigger treatment. A 25-euro measurement of plasma renin can lead to curable causes of hypertension, or predict optimal monotherapy.

A closing recommendation was for head-to-head comparison of thiazide and non-thiazide diuretics, but a more important question may be whether K+-sparing diuretic should supplement or substitute both of these at an earlier stage than resistant hypertension. Observations in registries point to a U-shaped curve relating CV outcomes to plasma K+. PATHWAY-3 showed half-dose HCTZ-amiloride to lower BP by 4 mmHg more than either diuretic alone, with respectively neutral and beneficial effect on plasma K+ and glucose.4

**Legend to Figure**

The new guideline (adapted).

On the right, recommendations mirror presentation by ESC/ESH except that [i] initial monotherapy remains the rule, not the exception, in younger patients, and [ii] K+-neutral combination of diuretics is preferred to K+-lowering sub-classes. Recommendations in red represent changes from NICE 2011.

On the left, 3 stages in the treatment algorithm are suggested as optimal for renin screening. A low value in a young patient may prompt initial therapy with diuretic, and/or investigations for primary aldosteronism.

(A= ACE inhibitor or Angiotensin receptor blocker; C=Calcium Blocker; D2=Diuretic combination)

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The Future

Imagery of the new guideline now enters Purdah until presentation at ESC. Respecting this embargo, I fill the vacuum with a crystal-ball depiction (Figure) of an ideal guideline, amalgamating ESH/ESC with a prediction of NICE 2018. The original AB/CD rule underpinning NICE was in part stimulus to research (eventually the PATHWAY programme), and in part belief that any memorable rule is better than no rule, encouraging escalation rather than inertia. ESH/ESC's 'one pill, many drugs' is a clever evolution, if cheap formulations of optimal dose-combinations ensue. But the long-term vision for chronic, non-communicable disease should, through prevention and cure, be to maximise numbers on 'no pill, no drugs'.

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REFERENCES


