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Will the recent hypertension trials change the guidelines?

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Despite the fact that the treatment of hypertension remains one of the most extensively investigated areas of clinical medicine, there remain a number of important questions, the answers to which would affect guidelines for hypertension management and a change in clinical practice.

Three of these questions were addressed by the PATHWAY Programme of trials conducted under the auspices of the British Hypertension Society (BHS).

The first of these trials, PATHWAY 1,[1] was designed to test the hypothesis that hypertensive patients initially randomised to monotherapy, with subsequent progression to combination drugs, are less likely to achieve optimal blood pressure (BP) reduction when compared with those assigned initially to combination therapy. The "never catch up hypothesis" was suggested by the blood pressure responses reported in two trials,VALUE[2] and ASCOT,[3] and was based on the premise that poor responses to monotherapy are, in part, due to the reflex activation of counter-regulatory responses that may, in the longer term, affect BP control by combination drugs.

PATHWAY 1, was a parallel group, randomised, double-blind trial, carried out in hypertensive patients with untreated home systolic BP > 150 mmHg or diastolic BP > 95 mmHg. Six hundred and five patients were randomised in a double-blind study to sequential monotherapy with either hydrochlorothiazide 12.5 mg, or losartan 50 mg, or combination therapy with the two drugs. After a period of four weeks, doses of the drugs were doubled for a further four weeks. The monotherapy arms then crossed over for a similar time period during which the combination therapy arm continued on optimal dosage (phase 1). At the end of the second monotherapy period all patients continued for a further 16 weeks on combination therapy (phase 2). The primary endpoint was the difference from baseline in home SBP, compared between monotherapy and the combination, first averaged across phases 1 and 2 and then at the end of phase 2. In a third phase of the study, additional drugs could be added openly (amlodipine and doxazosin) in those who failed to reach target blood pressures.

This trial and indeed the other PATHWAY trials were unique in that they were the first trials to use home blood pressure measurements as the basis for patient inclusion and management throughout the trial.

The results of PATHWAY 1 have been presented but await publication. Whilst the underlying hypothesis was rejected by the finding that both arms of the trial achieved identical blood pressure reduction at the time of evaluation of the primary endpoint, the time course for blood pressure reduction in those subject to sequential monotherapy was much slower than in those starting with combination treatment. There was no excess of withdrawals from treatment in the combination treatment group; however, there were more reports of symptoms suggesting hypotension on combination therapy.

The implication of these findings is that new hypertensive patients embarking on treatment with traditional monotherapy will be exposed to higher pressures for longer time periods than those initiated with combination treatment. At a population level this clearly will increase risk of major cardiovascular events.

PATHWAY 2[4] was designed to investigate optimal treatment for patients with resistant hypertension. Guidelines, notably the NICE Guidelines,[5] provide treatment algorithms for hypertensive patients which specify the first three drugs (an angiotensin converting enzyme inhibitor [ACEI], or an angiotensin receptor blocker [ARB], a calcium channel blocker [CCB], and a thiazide-like diuretic) together with recommendations for add-on therapy for those who fail to achieve BP goals on three drugs. There are, however, no trials of additional drug treatment to provide insight into optimal treatment. This is

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particularly important because there remain a substantial number of resistant hypertensive patients at high residual cardiovascular risk for whom there are no clear guidelines for preferred treatment, but an increasing number of costly, invasive interventions, advocated by many, but for which there is doubtful objective evidence of real benefit.

PATHWAY 2 was a double-blind, placebo-controlled, crossover study carried out in 348 hypertensive patients receiving three antihypertensive drugs in optimal or best-tolerated doses, and whose BP was uncontrolled (clinic SBP > 140 mmHg, home SBP > 130 mmHg) following observed drug ingestion and subsequent BP monitoring. Patients received sequential treatment with spironolactone (25−50 mg), bisoprolol (5−10 mg), doxazosin MR (4−8 mg) or placebo, assigned in random order, in addition to their baseline treatment. Each cycle was for 12 weeks duration with dose force titrated at six weeks. The hierarchical primary endpoints were the difference in home SBP between spironolactone and placebo followed by the difference in home SBP between spironolactone and the average of the two other active drugs and finally the difference in home SBP between spironolactone and each of the two other active drugs.

Spironolactone was substantially more effective than placebo (−8.70 mmHg), and significantly more effective than doxazosin (−4.03 mmHg) or bisoprolol (−4.48 mmHg).

A critical finding in this trial was that spironolactone controlled home SBP in almost 60% of patients (and an even greater percentage if clinic pressures were used). In addition, over 75% of patients had a > 10 mmHg reduction in SBP.

These observations, in conjunction with the fact that BP responses to spironolactone were inversely related to plasma renin, confirm the view that sodium retention plays a major role in the pathophysiology of resistant hypertension.

These results should be viewed in the context of the many invasive intervention trials in so-called drug-resistant hypertension, particularly in the light of the fact that many recruits into these trials were not receiving or had not received a trial of spironolactone.

In PATHWAY 2, concerns about hyperkalaemia with spironolactone were not realized. Discontinuations due to renal impairment, hyperkalaemia and gynaecomastia were not increased in those assigned to spironolactone compared with the other drugs.

PATHWAY 3[6] was designed to explore whether the addition or substitution of a potassium-sparing diuretic would prevent the glucose intolerance associated with a thiazide diuretic and improve blood pressure control. Many guidelines have advocated the use of low-dose thiazide diuretics in the treatment of hypertension yet the evidence for cardiovascular event reduction was based on trials of higher doses of thiazides, thiazide-like diuretics (chlorthalidone, indapamide) or combinations of diuretics such as hydrochlorothiazide (HCTZ)/amiloride.

The development of glucose intolerance associated with thiazides appears linked to the development of hypokalaemia, and PATHWAY 3 addressed this issue with a comparison of the metabolic effects of a thiazide, amiloride and the combination.

Four hundred and forty-one hypertensive patients with one component of the metabolic syndrome, on background antihypertensive drugs requiring additional therapy, were randomised to HCTZ 25 mg, amiloride 10 mg or the combination of HCTZ 12.5 mg/amiloride 5 mg. Doses were doubled after 12 weeks of treatment for a further 12 weeks.

The primary endpoint was the difference in blood glucose measured two hours after a 75 g oral glucose load. Secondary endpoints included differences in home SBP, plasma electrolytes and renin.

Two-hour glucose rose on HCTZ, and fell on both amiloride and the combination. A greater fall in home SBP at 24 weeks treatment was seen on the combination (−19 mmHg), than either HCTZ (−14 mmHg) or amiloride (−16 mmHg) despite the combination being used in half the doses of the individual components. Importantly serum potassium fell on HCTZ, rose on amiloride and was unchanged on the combination.

These observations clearly demonstrated that the glucose intolerance associated with thiazides was closely linked to hypokalaemia and could be abolished when the thiazide was combined with amiloride. Given the well-established benefits of the HCTZ/amiloride combination on cardiovascular outcome reported in the Medical Research Trial in Elderly Patients[7] and the International Nifedipine GITS Study Intervention as a Goal in Hypertension Treatment (INSIGHT),[8] PATHWAY 3 provides compelling evidence for this combination to replace thiazide and thiazide-like diuretics in clinical practice, particularly in those patients at increased risk of developing new-onset diabetes (NOD). No doubt some will argue that NOD induced by thiazides does not carry the cardiovascular risk associated with non-drug-induced diabetes;[9] however, this remains a highly controversial issue. Logic surely dictates that if you can prevent major metabolic consequences of a drug treatment by replacement with an alternative that carries no such risk, and for which there is excellent evidence for outcome benefits, a combination of thiazide/amiloride should be the preferred choice diuretic for most hypertensive patients.

These three trials were carried out over a period of five years, in 12 secondary and two primary care centres in the UK. All were part of a framework established by the BHS. The working party was established to address a number of important but unanswered questions in hypertension management at a time when most antihypertensive drug classes were available in generic formulation and there seemed little hope for industry sponsorship. In comparison with industry-funded trials they were carried out at substantially lower cost, despite the requirements for meeting the

demands of the drug regulatory bodies for trial oversight and management. The trials were supported by a grant from the British Heart Foundation and the UK National Institute for Health Research through infrastructure support at regional level to the recruiting centres. The BHS working party is now challenged with the design of and funding for new studies to provide further insight into optimal management of patients with hypertension.

One objective of the PATHWAY Programme of trials was to provide an evidence base for new guidelines for the management of hypertensive patients.

PATHWAY 2 clearly establishes the case for recommending spironolactone as the optimal 4th line drug in the treatment algorithm for patients with resistant hypertensive patients, whilst PATHWAY 3 provides an important insight into the different metabolic effects of the diuretics commonly used in hypertension treatment strategies and evidence for the benefits of a thiazide/amiloride combination. In some respects the outcome of PATHWAY 1 was disappointing in that the "never catch up" hypothesis was refuted. Had it been upheld then the case for initial combination therapy as opposed to the more traditional monotherapy would have been a powerful one. Nevertheless with increasing evidence that failure to get to goal BP exposes patients to continuing hypertensive risk of stroke and coronary heart disease events, PATHWAY 1 provides substantial evidence that initial combination therapy achieves more rapid blood pressure reduction safely and with the vast majority of patients reaching target BP within a few weeks of onset of treatment.

Schematic of PATHWAY trials

PATHWAY 1 and PATHWAY 3 parallel group comparisons. PATHWAY 2 randomised crossover design (Figure 1).

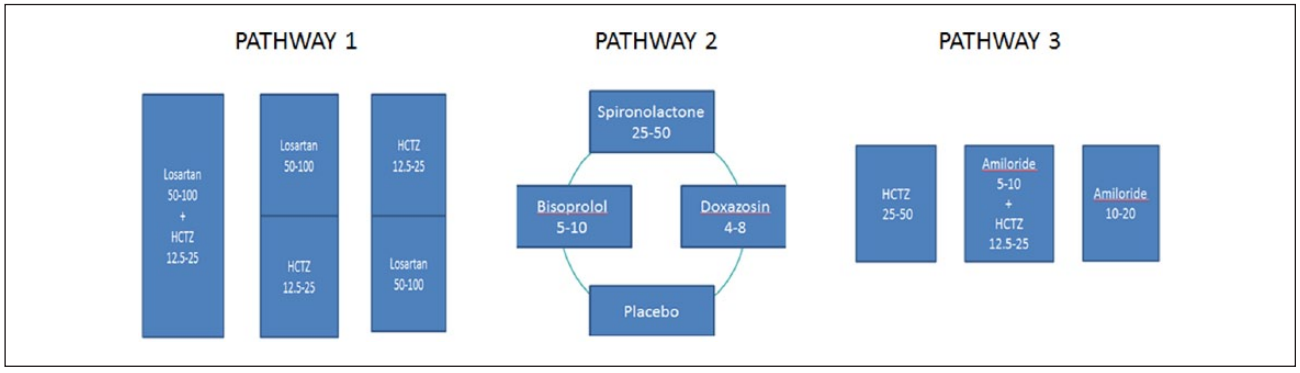

Figure 1. Schematic of PATHWAY trials.

Systolic blood pressure intervention trial: SPRINT

For more than a decade discussions have taken place on the need for a trial designed to determine optimum systolic treatment goals to prevent cardiovascular outcomes. During the 20th century, treatment thresholds and targets were set by diastolic pressure readings, largely dependent on the historical focus of diastolic as the more important of the two blood pressure readings, the fact that older intervention trials in hypertension also used predominantly diastolic thresholds and that guidelines had no hard evidence base on which to recommend optimal systolic blood pressure targets. Treatment trials in the elderly more recently focused on systolic thresholds but there has been no clear evidence that lowering systolic blood pressure below 140−150 mmHg confers additional benefit in the middle-aged and elderly population. Guidelines have, however, consistently advocated a 140 mmHg target, whilst admitting that the evidence base is lacking.

The dearth of new antihypertensive molecules and the withdrawal by major pharma of investment in hypertension research has meant that new trials addressing important unanswered questions about optimal treatment strategies have been lacking. It was perhaps inevitable, therefore, that the only independent funding body with sufficient resources to fund a systolic pressure intervention trial designed to ascertain optimal treatment targets was the US National Heart Lung and Blood Institute and, together with the coordinating committee, they are to be congratulated for designing and conducting this long-awaited trial.

SPRINT[10] was an open label randomised parallel group clinical trial carried out in approximately 100 sites in the USA. Nine thousand, three hundred and sixty-one adults aged 50 years or older with systolic blood pressure >130 mmHg and at least one additional cardiovascular risk factor were randomised to either intensive treatment designed to achieve a systolic pressure of <120 mmHg, or less intensive treatment with a goal of <140 mmHg (Figure 2). The

primary outcome was a combination of non-fatal myocardial infarction, acute coronary syndrome, non-fatal stroke, heart failure and cardiovascular death. Follow-up was planned for a maximum of six years.

Systolic blood pressures at one year were 121.4 mmHg in the intensive group and 136.2 in the standard treatment group. The trial was stopped prematurely after 3.3 years owing to a significant benefit in the primary endpoint (HR 0.75, CI 0.64−0.89, $p<0.001$). All-cause mortality was also significantly reduced (HR 0.73, CI 0.60−0.90, $p=0.003$). Serious adverse events, including hypotension, syncope and renal complications were, however, increased in the intensive treatment group.

These are extraordinary outcomes for a number of reasons, the main reason being that the on-treatment analyses reported by the Blood Pressure Treatment Trialists Collaboration showed that in the non-diabetic hypertensive population there was no additional cardiovascular benefit from lowering systolic pressure below 140−150 mmHg.[11] These data were based on observations on 125,000 trial participants. This raises the question as to whether the SPRINT population was different in any way from the usual hypertensive population within this age group and, more particularly, whether the SPRINT results can be extrapolated to all hypertensives, particularly those with much higher initial pressures, and those with diabetes.

One of the main concerns about the methodology used in SPRINT was that blood pressure was measured in an environment in which there was no doctor or nurse present. This, more basal blood pressure, has been shown to be equivalent to a routine clinic pressure of at least 10−15mm systolic higher − thus reflecting a benefit of achieving a usual clinic blood pressure <140 mmHg, rather than a blood pressure of <120 mmHg systolic !

On average, one additional drug was needed to achieve the lower pressure targets. On the positive side the numbers needed to treat to prevent one primary outcome, death from any cause and death from a cardiovascular cause during the trial were 61, 90 and 172. On the other hand there was a significant excess of hypotension, syncope, electrolyte disturbance and renal impairment in those assigned intensive treatment. The population excluded those with diabetes, who in the ACCORD trial[12] did not benefit from more intensive treatment, although in that trial, in a subgroup analysis, there were some additional benefits of systolic pressure reduction to <120 mmHg.

Many patients in the standard care group in SPRINT had antihypertensive drugs withdrawn in order to prevent the achievement of lower systolic pressures and the consequences of this practice are unknown.

Worldwide control of blood pressure in hypertensive patients is very poor. In many countries more than 50% of treated patients fail to be controlled to <140 mmHg systolic pressure. Whilst there are many reasons for poor control, the results of SPRINT should encourage physicians to focus on systolic targets, rather than diastolic targets, and aim to achieve control to at least 140 mmHg in the majority of their patients using published treatment algorithms and await further evidence of benefits of achieving lower targets.

As the SPRINT investigators advocate, it is vital to assess achieved blood pressure comprehensively by multiple measurements, ideally with home blood pressure measurements or 24-hour ambulatory recordings. Single clinic readings will grossly overestimate usual blood pressure and aggressive therapy based on unrepresentative readings of blood pressure could result in adverse consequences of too low blood pressure.

SPRINT study design

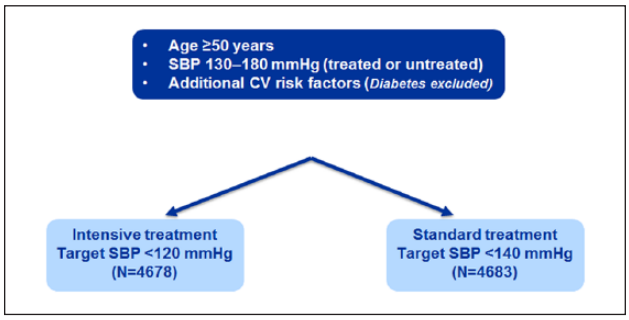

Figure 2. SPRINT study design.

Observations on the "J"-Curve relationship

Several observational studies and updated meta-analyses of the intervention trials in hypertension have been published.[13,14,15] These studies have addressed the issue as to whether low levels of blood pressure, particularly diastolic pressure, are associated with an increase in coronary and other CV events. Most of these studies, both observational and interventional, have failed to show any evidence for a "J"-curve relationship. However, a comprehensive observational study in over 22,000 hypertensive patients with established coronary disease, followed up over a period of seven years, demonstrated that those with low diastolic pressures had an increase in CHD events and all-cause mortality, with a nadir of around 75 mmHg diastolic pressure.[16] Whilst these data are robust, the question is whether the achievement of low diastolic pressures is a treatment effect, or whether it is a phenomenon associated with large artery pathology, an established marker for CVD events, i.e. reverse causation.

Will the results of SPRINT influence new guidelines for the management of hypertension?

The current treatment targets for most hypertensive patients is 140 mmHg systolic pressure − a goal that remains elusive for most patients in clinical practice.

Whilst in North America it is likely that the results of SPRINT will be applied by many physicians to achieve lower targets, it remains to be seen whether the US Guidelines and new European Guidelines will urge caution based on a critical review of the blood pressure assessment technique applied in SPRINT, and remain more conservative in keeping with today's recommendation of a goal of <140 mmHg systolic. For those with diabetes there is evidence that, for stroke, a lower systolic target of 130 mmHg is beneficial, but for other outcomes there is no advantage below 140 mmHg. The recent trials provide no new data for those with chronic renal disease.

There remain many outstanding questions in relation to optimal patient management in hypertension. Several trials and observational studies have confirmed the importance of blood pressure variability, rather than achieved mean blood pressure, as an important determinant of CV outcome, including stroke and myocardial infarction.[17,18,19] Moreover, it is clear that individual drugs have markedly different effects on blood pressure variability and this may be the underlying explanation for the benefits of the calcium channel blocker regimen compared with the beta-blocker regimen reported from ASCOT.[3,20] No trials have been designed prospectively to compare outcomes based on blood pressure variability and, thus, the evidence base required to influence future guidelines on blood pressure variability is limited.

New guidelines should include a section on patient adherence, which is a major problem in hypertension, particularly in those with treatment-resistant hypertension, where as many as two thirds of patients are poorly adherent to drug therapy.[21]

Whilst recent trials have contributed to our better understanding of more optimal treatment strategies for hypertensive patients, the healthcare costs to the community associated with hypertension are largely influenced by under-diagnosis and under-treatment. Unless a major effort is taken to address these problems, hypertension will remain a major contributor to poor health outcomes and a substantial burden on healthcare costs.

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