

Hypertension – state of the art 2015

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ABSTRACT

A conference organised in conjunction with the British Hypertension Society at the Royal College of Physicians (London) assembled an expert panel to present recent advances in the understanding and management of hypertension – the leading reversible risk factor for global morbidity and mortality. Despite recognised therapeutic approaches, less than half of patients on treatment for hypertension achieve blood pressure control to international guideline-based targets. This failure may, in part, be due to uncertainty into optimum treatment strategies, and the PATHWAY studies reporting later this year will hopefully address some outstanding questions relating to the standardised ABCD approach to drug selection. Targeting degradation of natriuretic peptides by LCZ696 (a combination of valsartan and a neutral endopeptidase inhibitor) has demonstrated potential as a novel therapeutic option, with mortality benefits in heart failure beyond that solely attributable to its blood pressure lowering ability. However, critical to any therapeutic strategy is patient involvement, and it is clear that the delivery of patient-centric treatment options is vital to ensure adherence with medication and to facilitate healthier lifestyle decisions.

KEYWORDS: Hypertension, blood pressure, pathway, salt, LCZ696

Introduction

Hypertension affects one-third of the world's population and is a major preventable risk factor for premature death and disability.¹ Hypertension is a global problem for which there are accepted treatment and prevention strategies, notwithstanding ethnic diversity and its impact on aetiology (presented by Prof F Cappuccio and Prof K Cruickshank). Despite this recognition, the prevalence of hypertension is increasing as populations age and sedentary lifestyles fuelled by nutritionally poor, calorie-rich food lead to its manifestation earlier in life (presented by Dr J Deal).² Despite the linear relationship between blood pressure and cardiovascular events, less than half receiving treatment achieve appropriate blood pressure control.^{3,4}

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Refining the treatment PATHWAY (presented by Prof B Williams)

There are a myriad of antihypertensive medications available for prescription and so it was somewhat fortuitous that the age-based efficacy of certain drug classes enabled the development of the now globally accepted ABCD acronym.⁵ This universal approach to prescribing has left some unresolved questions that have been addressed through the PATHWAY (Prevention And Treatment of resistant Hypertension With Algorithm guided therapy) studies. These three randomised controlled trials (RCTs) are briefly summarised in Table 1.

The potential clinical utility of these studies was highlighted by Prof Brown with a case study of a patient enrolled into PATHWAY 2 who was found to respond optimally to spironolactone. Subsequent investigations revealed a Conn's adenoma that had not been previously identified despite standard investigations for secondary causes of hypertension.

A novel therapeutic approach (presented by Prof B Williams)

Hypertension is the largest single risk factor for heart failure due to its aetiological connection to ischaemic heart disease, left ventricular hypertrophy, atrial fibrillation and renal dysfunction. It is therefore perhaps unsurprising that many of the most effective treatments for heart failure are medications with antihypertensive effects, although paradoxically once

Table 1. Summary of hypotheses investigated in the PATHWAY studies.

| Pathway | Hypothesis |
|---------|---|
| 1 | Patients treated with a single drug never catch-up with the blood pressure control achieved with initial combination therapy, because of compensatory vasoconstriction or sodium retention. |
| 2 | Spironolactone is the best overall treatment for patients at step 4 of the NICE/BHS algorithm, and that the best drug for individual patients can be determined by measurement of plasma renin. |
| 3 | Multiple nephron blockade is more effective than single, and that addition or substitution of a potassium-sparing diuretic or thiazide in patients with features of metabolic syndrome will prevent deterioration of glucose tolerance. |

heart failure is established, achieving normotension can worsen outcomes by driving a maladaptation reflex for higher systemic arterial pressures. Natriuretic peptides counter this drive for salt and water retention, and the ability to impair their degradation may soon be added to a clinician's armamentarium.

LCZ696 is a combination of two antihypertensive drugs: valsartan acts on the angiotensin II receptor (AT₁ subtype) and LCZ696 is a prodrug whose metabolite inhibits neprilysin (neutral endopeptidase), an enzyme responsible for the degradation of atrial and brain natriuretic peptide. LCZ696 has been previously demonstrated in mild-to-moderate hypertensive patients to significantly reduce both systolic and diastolic blood beyond that observed for each compound individually.⁶

The PARADIGM-HF study was a double-blind RCT that compared LCZ696 to enalapril in patients with NYHA II-IV and reduced left ventricular ejection fraction.⁷ A significant blood pressure reduction was again observed (mean difference -2.7 mmHg; 95% confidence interval (CI) $-3.1, -2.3$), but more importantly there was a significant reduction in the primary outcomes of cardiovascular death and hospitalisation for heart failure. The difference in blood pressure did not account for the incremental benefits of LCZ696.

Interventions to facilitate healthier life choices

In the past, the delivery of healthcare has reflected a somewhat paternalistic approach whereby the knowledge imbalance between doctor and patient led to 'best interests' decisions to which compliance was expected. As this knowledge imbalance has been reduced, principally through the ubiquity of online information, the role of healthcare professionals has shifted towards facilitating shared decision-making and providing information to enable healthier life choices. In hypertension management, patient involvement is crucial in three key areas: weight loss, dietary salt reduction and approaches to maximise medication adherence.

Gender-sensitised weight loss programmes for men (presented by Prof A Brady)

Obesity, and the inactivity that either precedes or follows it, is a major risk factor for cardiovascular disease. Weight loss of 5–10% can produce substantial health benefits but, due to poor engagement with the issue, men are under-represented in both clinical trials and clinical weight loss programmes. The Football Fans in Training (FFIT) programme targeted obese men (BMI ≥ 28 kg/m²) and delivered gender-appropriate classroom education and physical activity in association with Scottish Premier League clubs.⁸ The gender-sensitised programme focused on healthy eating rather than dieting and was hosted at football clubs, utilising peer support through group participation. The RCT provided 12 weekly sessions of programmed activities followed by intermittent email reminders over the next 9 months.

Significant weight loss was achieved in the intervention group at 12 weeks (adjusted between-group difference -5.18 kg; 95% CI $-6.00, -4.35$) and maintained at 12 months (-4.96 kg; 95% CI $-5.94, -3.95$). A corresponding decrease was observed at 12 weeks for both systolic (-5.51 mmHg; 95% CI $-6.36,$

-2.67) and diastolic (-2.51 mmHg; 95% CI $-3.71, -1.32$) blood pressure. Attenuation in blood pressure gains were observed at 12 months, but the decrease in both indices remained significant. Improvements were also observed in a plethora of secondary measures including self-reported physical activity, psychological and quality-of-life outcomes.

The initial data suggest that such interventions are cost effective, with an estimated incremental cost of £13,847 per quality-adjusted life year (QALY) gained. This is below the threshold range of £20,000–30,000 per QALY used by the National Institute for Health and Care Excellence (NICE) to assess the affordability of new treatments. Data on the long-term follow-up of these individuals should ascertain the true cost effectiveness of the programme.

Reducing salt consumption both in the UK and globally (presented by Prof G MacGregor)

The consumption of heavily salted food is an anachronism harking back to a time before refrigeration and the abundance of fresh food. The relationship between salt consumption and blood pressure is well understood, with relatively modest reductions in consumption (median reduction 4.6 g/day for 4 weeks) leading to significant blood pressure reduction in both normotensive ($2.03/0.97 \pm 0.27/0.21$ mmHg; $p < 0.001$) and hypertensive individuals ($4.96/2.73 \pm 0.40/0.24$ mmHg; $p < 0.001$).⁹ A corresponding reduction in cardiovascular events has been observed.

The reduction in UK salt consumption represents a major public health achievement as, through a combination of public health campaigns and pressure on the food industry (which is responsible for approximately 80% of salt consumed in developed countries), salt intake has been reduced by 1.4 g/day since 2000 to 8.1 g/day in 2011. This figure remains short of both the UK and World Health Organization targets for salt consumption that are set at 6 and 5 g/day, respectively. Progressive salt reduction targets set by the Food Standards Agency enabled incremental annual reductions of 10–20% in over 80 categories of food, with the gradual reformulation of products not affecting the public's perception of taste. There are however concerns that recent political decisions to make the food agency responsible for self-regulation of targets will attenuate any future gains.

Excessive salt consumption as a driver of adverse cardiovascular events is not a phenomenon limited to developed countries, but rather a global problem spanning the full socio-economic spectrum. In developing countries the major source of salt is added by the consumer during food preparation, and this pattern of consumption provides an opportunity to reduce salt consumption solely through education without the need for industry involvement.

The School-EduSalt study was a cluster RCT involving primary school children in urban Changzhi, China.¹⁰ In the intervention group, a salt-reduction curriculum was delivered to the children by locally trained educators for the duration of one school term (about 3.5 months). The curriculum consisted of both classroom and family component, in an attempt to reduce not just the salt consumption of individual children, but that of their whole family. A significant reduction in salt reduction was measured in both children (adjusted between-group difference -1.9 g; 95% CI $2.6, -1.3$) and adults (-2.9 g; 95% CI $-3.7, -2.2$). A significant

reduction in systolic blood pressure was observed in adults (-2.3 mmHg; 95% CI $-4.5, -0.04$).

Maximising medication adherence (presented by Dr S Antoniou)

Medication adherence is a problem in all chronic diseases, and an individual's beliefs and behaviours are often the rate-limiting step between converting evidence-based treatments into optimum health outcomes. Non-adherence is difficult to predict as it does not appear to be a feature of an individual disease or patient characteristics, as adherence rates both between patients and within the same patient vary over time. Adherence is inversely proportional to medication burden although it appears not to be regimen complexity *per se* that is the limiting factor, but rather how well treatments fit with a patient's routine, expectations and preferences.¹¹

The New Medicines Service (NMS) was launched in 2011 and is an intervention that involves a consultation between a community pharmacist and patient within 7–14 days of starting a new medication for a number of chronic diseases (including hypertension). The primary aim of the consultation is the patient-centred identification of any problems with the treatment and to identify any support or action needed. Similarly to the FITT programme discussed earlier, the NMS looks to provide support in a patient-appropriate context.

The service was evaluated in a RCT with a primary outcome measure of self-reported adherence.¹² At week 10 post-intervention, the NMS significantly increased adherence by approximately 10% (adjusted odds ratio 1.67; 95% CI 1.06–2.62) and had an economic evaluation that was below the cost-per-QALY NICE threshold.

Summary

Hypertension remains a global problem as the leading reversible cause of morbidity and mortality. Established treatments have led to significant health improvements but there remain unanswered questions regarding optimum therapeutic strategies. New medications are on the horizon targeting previous neglected pathways, but it remains to be seen how these may integrate into clinical practice. Critical to all of these approaches is ensuring treatment adherence through patient-centric engagement programmes. ■

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