Institution:
University of Cambridge

Unit of Assessment:
UoA1

Title of case study:
The AB/CD of treating hypertension

1. Summary of the impact (indicative maximum 100 words)

Research led by Professor Brown has led to widespread changes in clinical practice regarding the management of Hypertension. Following his demonstration that patients' response to drugs for Hypertension is variable (in a systematic manner), subsequent clinical guidelines acknowledged the variability among patients, and changed from recommending the same treatment for all patients, to an algorithm based on the Cambridge AB/CD rule. The simplicity of the AB/CD rule led to popularity among doctors, and adoption by national bodies – British Hypertension Society, NICE, and foreign guidelines, and by textbooks of Medicine. The guidelines arising from his research have contributed to improved health outcomes in the UK. Specifically, NICE's simple and rational guidance how to reach strict targets for blood pressure is credited with changing the UK from the poorest to best performing country in Europe.

2. Underpinning research (indicative maximum 500 words)

The research was led by Professor Brown (Clinical Pharmacology Unit of the Department of Medicine 1985-present), aided by Claire Dickerson, (research nurse), Dr Aroon Hingorani, (MRC Training Fellow, Clinical Pharmacology Unit of the Department of Medicine, 1996-1999) and Dr Chris Palmer, (statistician, Department of Public Health and Primary Care, 1996-present).

From 1997-1999, Brown led his first study into personalised treatments for hypertension. The study aimed to test the hypothesis that four groups of patients could be defined, in whom each of the four drug classes was the most efficacious treatment. The research group designed what Brown called a 'rotation study' in which 56 patients referred to Brown's clinic at Addenbrooke's with untreated hypertension were prescribed each drug for a month, with a month's washout between each treatment. Because this design entailed several months on no treatment, Brown recruited younger patients than in most hypertension studies, aged <50, so as to minimise risks. This decision proved critical, since it was found that the AB drugs (= ACE inhibitors and Beta-blockers) were on average twice as effective as CD drugs (=Calcium Blockers and Diuretics) in lowering blood pressure (BP) in the younger patients. The researchers deduced that this was due to younger patients having a higher blood level of the kidney hormone renin, compared to older patients – and that what AB drugs had in common was their action on various components of 'the renin system'. Conversely, CD drugs work primarily by eliminating salt, which typically plays a greater role in the hypertension of patients older than 50. Although a small number of the younger patients did respond better to CD than AB, tellingly Brown found them all to have a low plasma renin at baseline. The finding reflects the kidneys' ability to detect salt excess in the circulation, and showed these few patients to be the exceptions within a young cohort. The results, and the proposed AB/CD rule emanating from these, was published in the Lancet.[1]

In contrast to the prior hypothesis, of four different patterns of response (best, that is, to one each of A,B,C,D), this study concluded that there are only two main patterns of BP response to therapy, with patients responding better to *either* A and B, *or* to C and D. The findings prompted a further study to test the AB/CD rule, funded by Pfizer. Once again, C and D were less effective on average than A and B drugs in reducing blood pressure in young patients.[2] On this occasion, as well as BP, the group measured a haemodynamic parameter, called augmentation index, and serum biomarker, plasma BNP, which is a measure of heart strain. Although A and B had a similar effect on BP, plasma BNP and augmentation index were elevated several-fold by B (β-blockers), while all other classes (A,C,D) reduced (i.e. improved) these parameters.[3] The results became available at the same time in 2002 as the first outcome comparison – a clinical trial, published in the Lancet, called 'LIFE' – of β-blockade with another class (ARBs); the coincidence allowed Brown to publish a response in the Lancet explaining the inferior protection by β-blockade against strokes.[4] At the time, LIFE received considerable Pharma-promotion that ARBs superiority over β-blockade represented a proprietary 'benefit beyond blood pressure control'. Brown suggested, rather, that it was β-blockade which caused an additional harm – by increasing augmentation index and hence heart strain – and that no class achieved benefits beyond blood pressure control.

Brown's prediction that older subjects would respond better to CD than AB drugs, was confirmed by several large outcome trials conducted around the world, published from 2000 onwards in leading medical journals, such as JAMA and Lancet, and the subject of an authoritative, prospectively designed meta-analysis of which Brown was a part. One of the first of these outcome trials was the INSIGHT study, led by Professor Brown, which compared C with D in 6321 patients aged >55, (published in 2000 in the Lancet.)[5] This reported an average reduction in BP of 32/17 mmHg, almost identical in both arms of the trial and achieved on single therapy in two thirds of patients. This was substantially larger than the reductions in trials using AB drugs in similar patients.

A consequence of identifying two broad types of Hypertension, each with its more effective options for treatment, was the ability to recognise patients where salt excess is the main cause, who often need better treatment with diuretics and sometimes have specific underlying causes – particularly a benign hormone-secreting tumour of the adrenal gland. Brown found that these salt-dependent patients had a level of renin in their blood that was inappropriately low for their age and/or drug treatment (most of which should elevate renin). In 2007, Brown led a study comparing 'low-renin' patients' response to each of 2 doses of 3 different diuretics, showed that two older diuretics, not currently licensed or used for hypertension, were more effective than the UK standard, bendroflumethiazide.[6] The discovery of a specific adrenal tumour in some of these patients led Brown to develop a novel PET CT scan, using the radiotracer ^{11}C-metomidate, which permits non-invasive diagnosis of patients whose hypertension might be cured by keyhole surgery to remove the tumour.[7] Taking Brown's research in a rather beautiful full circle, the PET CT led to the recognition of a common variant of the adrenal tumour caused by somatic mutations of the L-type Ca^{++} channel – the very target of the C drugs used to treatment hypertension[8].

3. References to the research (indicative maximum of six references)

1. Dickerson JEC, Hingorani AD, Ashby MJ, Palmer CR, Brown MJ. Optimisation of anti-hypertensive treatment by crossover rotation of four major classes. Lancet. 1999; 353: 2008-13.
2. Deary A, Schumann A, Murfet H, Haydock S, Foo R, Brown M. Double-blind, placebo-controlled crossover comparison of five classes of antihypertensive drugs. Journal of Hypertension. 2002; 20: 771-7.
3. Deary AJ, Schumann AL, Murfet H, Haydock S, Foo RS, Brown MJ. Influence of drugs and gender on the arterial pulse wave and natriuretic peptide secretion in untreated patients with essential hypertension. Clin Sci (Lond). 2002; 103(5): 493-9.
4. Cockcroft JR, Brown MJ. Losartan for cardiovascular disease in patient's with and without diabetes in the LIFE study. Lancet. 2002; 359(9324): 2202; discussion 3-4.
5. Brown MJ, Palmer CR, Castaigne A, De Leeuw PW, Mancia G, Rosenthal T, Ruilope LM. Morbidity and mortality in patients randomised to double-blind treatment with once-daily calcium channel blockade or diuretic in the International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT). Lancet. 2000; 356: 366-42
6. Hood SJ, Taylor KP, Ashby MJ, Brown MJ. The Spironolactone, Amiloride, Losartan, and Thiazide (SALT) double-blind crossover trial in patients with low-renin hypertension and elevated aldosterone-renin ratio. Circulation. 2007; 116: 268-75.
7. Burton TJ, Mackenzie IS, Balan K, Koo B, Bird N, Soloviev DV, Azizan EA, Aigbirhio F, Gurnell M, Brown MJ. Evaluation of the sensitivity and specificity of (11)C-metomidate positron emission tomography (PET)-CT for lateralizing aldosterone secretion by Conn's adenomas. J Clin Endocrinol Metab. 2012; 97: 100-9.
8. Azizan EA, Poulsen H, Tuluc P, Zhou J, Clausen MV, Lieb A, Maniero C, Garg S, Bochukova EG, Zhao W, Shaikh LH, Brighton CA, Teo AE, Davenport AP, Dekkers T, Tops B, Kusters B, Ceral J, Yeo GS, Neogi SG, McFarlane I, Rosenfeld N, Marass F, Hadfield J, Margas W, Chaggar K, Solar M, Deinum J, Dolphin AC, Farooqi IS, Striessnig J, Nissen P, Brown MJ. Somatic mutations in ATP1A1 and CACNA1D underlie a common subtype of adrenal hypertension. Nat Genet. 2013; 45:1055-1060.

4. Details of the impact (indicative maximum 750 words)

On national guidelines

The clearest impact has been on national guidelines published by the British Hypertension Society,

then NICE and the onward influence of these upon trends in use of antihypertensive drugs.

BHS 2004 and BHS/NICE 2006

In 2004, the BHS published the fourth update of national guidelines, which adopted AB/CD. In the same year NICE published its own guidance[9-12]. Because it became rapidly clear that primary care doctors found BHS-4 much easier to enact than NICE's guidance, NICE decided within a year to revise its own guidance, in conjunction with the relevant specialist society. The resulting NICE/BHS guidance of 2006 was the first time NICE partnered a specialist society. The NICE-BHS guidance of 2006 adopted A(B)/CD, with β-blockade relegated to second-line because of several trials which by then had reported worse outcome on β-blockade than comparator – and explanation for this provided by Brown's crossover studies above (refs. 3&5). With regards to the impact period; both of these were valid from 2008-2011 (when NICE updated the guidance as described below).

NICE 2011

The principle underlying the AB/CD rule that there are but two broad types of hypertension, and two ways in which blood pressure can be lowered, led NICE to retain the rule in its 2011 guidance, simplified to an A/C rule, with B remaining as second-line therapy. (Ref 10, section 5). This simplification was controversial, and NICE took some criticism for the contradiction of relegating D(iuretic) from a 1st to 3rd choice, while at the same time making D the cornerstone of managing patients with resistant hypertension. Here the advice to use spironolactone – the only specific drug mentioned by NICE (rather than an overall class of drugs) – was dependent on Brown's formal 2007 comparison of spironolactone with other diuretics (ref 6 above). Spironolactone is a type of diuretic, different from the class ('thiazides') commonly used in Hypertension. The discovery by Brown of a common group of patients whose blood pressure was not controlled by thiazide diuretics, but was controlled by spironolactone, followed from his 1999 work, of investigations into the causes of salt-dependent (low-renin) hypertension.

Other countries

The NICE version of the AB/CD algorithm has been adopted by other countries; for example in Hong Kong in 2008[12] and in New Zealand in 2010.[13]

Blood Pressure Control Rates

A secondary impact of Brown's research is on blood pressure control rates in England, which used to be among the lowest in Europe, and are now among the highest.[14] Between first publication of AB/CD and the introduction of the GPs' 'Quality Outcomes Framework' in 2004, few other external influences are likely to have impacted on the improvement. Thereafter, payment incentives to GPs clearly contributed, but they still required – and widely acknowledged – a simple and effective guideline for achieving the prescribed targets.

Complications of hypertension (stroke, myocardial infarction)

The most important potential impact, but most difficult to document cause and effect, is a reduction in the complications of hypertension as a consequence of improvements in blood pressure control. The goal for the treatment of hypertension is prevention of stroke and heart disease. Clearly any change in incidence of these multifactorial diseases is multifactorial. It is interesting, according to figures on www.heartstats.org that annual rates for stroke in the UK - the complication of hypertension with the steepest dependence on blood pressure - were static from 2000-3, and then fell progressively from 130 to 100 per 10,000 over just 3 years.

This was before the introduction of 'QOF' – payments to GPs for screening and treatment of hypertension – which are likely to have contributed to further improvements, in concert with the more tailored treatment regimen.

Mainstream Teaching and Clinical Training

AB/CD, and subsequent NICE derivatives, are part of mainstream teaching in Medicine, appearing in textbooks (e.g the Oxford Textbook of Medicine[15]) and Wikipedia.

Public understanding and patient awareness

Patients rarely comment on <u>not</u> suffering a stroke, but are hugely grateful for a cure that may save them 50 years of taking tablets! So the impact of the research on recognition of curable causes of hypertension may be smaller on a population scale, but for individuals affected the impact is more perceptible. The BHF uses a video, which cites Brown's work, in order to illustrate patient satisfaction with the successful use of BHF research funds.[16]

Lay media

The BBC story in 2011, about the development of PET CT for Conn's Syndrome, generally appears on the first page of a Google search on this condition.[17] The population significance of

Brown's 2013 Nature Genetics paper, describing mutations in a common sub-type of adrenal tumours, was recognised by the Times and BBC; both reported that many patients with hypertension will now be found to have a distinct, anatomical cause which can be cured by surgery.[18,19]

5. Sources to corroborate the impact (indicative maximum of 10 references)

9. NICE/BHS. CG34 Hypertension 2006.- NICE guideline (all the recommendations). http://www.nice.org.uk/nicemedia/pdf/cg034niceguideline.pdf
10. Williams B, Poulter NR, Brown MJ, Davies M, McInnes G, Potter J, et al. Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004 . BHS IV. Journal of Human Hypertension. 2004; **18**(3) 139-185.
11. NICE. Hypertension: clinical management of primary hypertension in adults. Clinical guideline CG127. 2011. http://www.nice.org.uk/nicemedia/live/13561/56008/56008.pdf
12. http://www.pdqa.gov.hk/english/primarycare/clinical/files/htguideline2008.pdf
13. http://www.bpac.org.nz/BPJ/2010/October/antihypertensive.aspx
14. Falaschetti E, Chaudhury M, Mindell J, Poulter N. Continued Improvement in Hypertension Management in England: Results From the Health Survey for England 2006. Hypertension. 2009; **53**(3): 480-6.
15. Oxford Textbook of Medicine: Chapter on Hypertension. http://oxfordmedicine.com/view/10.1093/med/9780199204854.001.1/med-9780199204854-chapter-161702#med-9780199204854-figureGroup-161702006
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19. Tiny adrenal tumours 'cause high blood pressure'. http://www.bbc.co.uk/news/health-23534101