Institution: University College London		
Unit of Assessment: 1 - Clinical Medicine		
Title of case study: Transforming national and international clinical practice in the treatment of resistant hypertension		
Period when the underpinning research was undertaken: 2009-2019		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Bryan Williams	Chair of Medicine	2012- present
Period when the claimed impact occurred: 2013-2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Resistant hypertension is high blood pressure that cannot be controlled with a combination of three medicines. It affects approximately 100 million people worldwide, increasing their risk of heart disease and stroke. Research at UCL to study the pathophysiology and treatment of resistant hypertension including two randomised controlled clinical trials, demonstrate that a widely available and cheap medicine - spironolactone – can control blood pressure in patients with resistant hypertension. UCL's research has changed clinical guidelines and medical practice ad education across Europe, US and globally and reduced associated healthcare costs for patients at high risk of high blood pressure-related cardiovascular disease.

2. Underpinning research

High blood pressure (HBP) is one of the most common causes of premature cardiovascular disease, stroke and death and affects over a billion people worldwide, with one in ten patients experiencing resistant hypertension. Despite the prevalence of resistant hypertension, its underlying cause is poorly understood and until recently, there was little rationale to underpin treatment recommendations**.** In the last 10 years, UCL-led research has helped explain the underlying pathophysiology of the condition and has demonstrated the effectiveness of the widely used diuretic, spironolactone (and the 'potassium sparing' drug amiloride) to control blood pressure in patients whose blood pressure is not controlled by standard hypertensive medication (**R1**). Professor Williams's research has also demonstrated that spironolactone can be used safely in patients with chronic kidney disease when co-administered with a potassium binding agent to control potassium levels.

Patients with resistant hypertension continue to have uncontrolled high blood pressure, despite being treated with maximally tolerated doses of three drugs: typically, a diuretic, a renin angiotensin system inhibitor and a calcium channel blocker. Professor Williams designed a study, in collaboration with Morris Brown (QMUL), Tom MacDonald (Dundee) and the British Hypertension Society PATHWAY study group, to test whether spironolactone (an aldosterone receptor antagonist) when added to existing therapy, helped reduce blood pressure in these patients (**R2**). This was the first randomised controlled trial (RCT) of the treatment of resistant hypertension (**PATHWAY 2**) which began in May 2009 and completed in June 2015, including 314 patients with uncontrolled high blood pressure. The study unequivocally demonstrated that spironolactone was superior at reducing blood pressure in patients with resistant hypertension when compared to commonly used blood pressure lowering drugs (**R3**).

To explore the mechanisms underlying the pathogenesis of resistant hypertension and the clinical efficacy of spironolactone, three sub-studies were carried out during the PATHWAY2 trial. Patient serum samples were tested for plasma renin and aldosterone levels, and thoracic bioimpedance was monitored to assess fluid shifts in response to various treatments (**R4**). The study showed that one in three patients at baseline had low plasma renin concentrations and

higher than average aldosterone concentrations. These findings demonstrated for the first time that resistant hypertension is most commonly a salt-retaining state (as indicated by suppressed renin levels), in many cases related to inappropriate aldosterone secretion in the context of sodium retention.

Overall, the PATHWAY2 study found that (i) spironolactone was the most effective drug treatment for resistant hypertension and was most effective in patients with supressed renin levels (consistent with sodium excess); (ii) spironolactone was acting predominantly as a diuretic to reduce blood pressure, and (iii) the effect of spironolactone could be replicated by higher than usual doses of amiloride (10-20mg daily) – another diuretic with a similar biological effect (**R4**).

The team went on to explore use of spironolactone in patients with advanced chronic kidney disease (CKD), who are at high risk of resistant hypertension and at much higher risk of fatal and non-fatal cardiovascular events due to elevated blood pressure. These patients are also at higher risk of experiencing high blood potassium levels (hyperkalaemia) with spironolactone (or amiloride), so were excluded from PATHWAY 2. Building on the PATHWAY 2 findings, the UCL team worked with a consortium of clinical academics from Europe and US and Relypsa Inc, a small US-based pharmaceutical company that had developed an orally active potassium-binding agent (Patiromer) to reduce blood potassium levels in patients with CKD. The consortium designed and conducted a Phase II RCT (**AMBER**) in patients with advanced CKD and uncontrolled resistant hypertension. The trial, involving patients from 62 outpatient centres in 10 countries, was the first to demonstrate that spironolactone can be used effectively and safely to reduce blood pressure in patients with advanced CKD with co-administration of patiromer to reduce the likelihood of hyperkalaemia, thus facilitating more extended use of spironolactone in these patients (**R5**).

3. References to the research

R1 Myat A, Redwood SR, Qureshi AC, Spertus JA, **Williams B**. (2012) Resistant hypertension. *BMJ*;345:e7473. doi: 10.1136/bmj.e7473.

R2 Williams B, MacDonald TM, Caulfield M, Cruickshank JK, McInnes G, Sever P, Webb DJ, Salsbury J, Morant S, Ford I, Brown MJ. (2015) Prevention And Treatment of Hypertension With Algorithm-based therapy (PATHWAY) number 2: protocol for a randomised crossover trial to determine optimal treatment for drug-resistant hypertension. *BMJ Open*;5(8):e008951. doi: 10.1136/bmjopen-2015-008951

R3 Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, McInnes G, Ford I, Cruickshank JK, Caulfield MJ, Salsbury J, Mackenzie I, Padmanabhan S, Brown MJ; British Hypertension Society's PATHWAY Studies Group. (2015) Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet*. ;386(10008):2059-2068. doi: 10.1016/S0140-6736(15)00257-3

R4 Williams B, MacDonald TM, Morant SV, Webb DJ, Sever P, McInnes GT, Ford I, Cruickshank JK, Caulfield MJ, Padmanabhan S, Mackenzie IS, Salsbury J, Brown MJ (2018) British Hypertension Society programme of Prevention And Treatment of Hypertension With Algorithm based Therapy (PATHWAY) Study Group. Endocrine and haemodynamic changes in resistant hypertension, and blood pressure responses to spironolactone or amiloride: the PATHWAY-2 mechanisms substudies. *Lancet Diabetes Endocrinol.* Jun;6(6):464-475. doi: 10.1016/S2213-8587(18)30071-8.

R5 Agarwal R, Rossignol P, Romero A, Garza D, Mayo MR, Ma J, White WB, **Williams, B**. (2019) Patiromer versus placebo to enable spironolactone use in the treatment of patients with resistant hypertension and chronic kidney disease (AMBER): a randomised, double blind, placebo-controlled trial. *Lancet* Oct 26;394(10208):1540-1550. doi: 10.1016/S0140-6736(19)32135-X.

4. Details of the impact

Professor Williams' research at UCL to identify the mechanisms underlying the pathogenesis of treatment resistant hypertension and the discovery that spironolactone (a low cost generic medicine) is effective in controlling blood pressure in these patients, have been pivotal in changing treatment guidelines in Europe, US and globally. The treatment recommendations, now also embedded in medical teaching, have led to a five-fold increase in the use of aldosterone inhibitors such as spironolactone, helping to reduce the disease burden of HBP globally and reducing the direct and indirect medical care costs associated with difficult to treat HBP. Once fully implemented, the new treatment regimen could reduce morbidity and mortality due to uncontrolled blood pressure by up to 25% (based on the anticipated reduction in blood pressure).

Changing treatment practice globally

The results of the PATHWAY2 study unequivocally demonstrated that spironolactone (or alternatively amiloride) was the most effective treatment for resistant hypertension when added to existing therapies. Expert commentary on the study results, provided alongside an 'Alert' article published by National Institutes for Health Research, with the explicit purpose of translating research into practice, said: "Doctors often have difficulty selecting a fourth antihypertensive drug in patients who are established on three agents and have yet to achieve an acceptable target of blood pressure control. This study gives unequivocal support to the use of spironolactone in this regard. … The practice point from these data is that if one is faced with a patient apparently refractory to antihypertensive medication, the fourth agent of choice should be an aldosterone antagonist such as spironolactone" (**S1**).

Professor Williams presented the PATHWAY2 findings as a highlight of the European Society of Cardiology Annual Congress (the world's largest cardiovascular disease congress) in London August 2015 and subsequently, the study was reviewed in editorials in leading medical journals including the Lancet which described the research findings and implications for clinical practice as 'groundbreaking' and 'landmark' studies (**S2**). A comment piece linked to the article stated: "PATHWAY2 makes the addition of spironolactone to a three-drug regimen hard to resist in cases of resistant hypertension among overweight patients with stages 1 and 2 kidney disease." Commenting in Lancet Diabetes & Endocrinology, David Calhoun, University of Alabama at Birmingham, US said: "These new findings are important both for advancing our understanding of the mechanisms of resistant hypertension, and also in providing important clinical guidance for choice of drugs for more effective treatment of resistant hypertension." (**S3**). Spironolactone in resistant hypertension (specifically the PATHWAY2 study) was also recognised by NEJM's *Journal Watch* as one of the top ten "most important thematic areas in clinical research" in 2015 (**S4**).

The results of the PATHWAY2 studies were soon recognized as the "gold standard" and in the four years following publication of PATHWAY2, European, US and global treatment guidelines have been updated and cite the PATHWAY2 studies as the key evidence underpinning their treatment recommendations for resistant hypertension (**S5**).

The new treatment regimen is also being applied in low resource settings where the burden of untreated resistant hypertension is highest. The recent International Society of Hypertension (ISH) Guidelines 2020, designed to drive local improvements in standards of care in low- and middle- income countries and other low resource settings, specifically recommend spironolactone as the optimal treatment for resistant hypertension citing the PATHWAY2 study as the key underpinning evidence. (**S5**) The Chair of the International Society of Hypertension said: 'evidence provided by PATHWAY2 Study i.e. that spironolactone is remarkably effective at lowering blood pressure in patients with resistant hypertension has shaped my therapeutic decisions and drug choices when it comes to patients whose blood pressure is not controlled on 3 "basic" antihypertensive medications. Moreover, the results of PATHWAY2 Study have influenced several treatment guidelines globally and have been instrumental to the advice on

treatment of resistant hypertension in our recent ISH guidelines. Thus, the insights from PATHWAY2 have already benefited many patients in my practice and will continue to do so for thousands of hypertensive individuals looked after by my colleagues around the world' (**S6**).

The latest US treatment guidelines for resistant hypertension state: "The other major advance in the clinical management of resistant hypertension is the recent confirmation that resistant hypertension is broadly attributable to excess sodium and fluid retention induced by relative degrees of aldosterone excess, and the definitive demonstration of the superiority of mineralocorticoid receptor antagonists (MRAs), specifically spironolactone, for treating resistant hypertension. These observations were both critical findings of the landmark PATHWAY2 study……Combined, the PATHWAY2 findings clearly implicate aldosterone excess as an important mediator of resistant hypertension that is best overcome by use of an MRA (**S5**).

The research is changing clinical practice in the US, where a study of the American College of Cardiology National Cardiovascular Data Registry – PINNACLE Registry – identified over 7,000 patients in the registry who would benefit from spironolactone treatment and concluded "the potential implications for daily practice are huge" (**S7**).

Reducing health care costs

The cost of treating HBP in the UK accounts for over GBP1bn in drug costs annually and disease attributed to HBP cost the NHS GBP2.1bn per year. As the prevalence of HBP increases with ageing, the impact of hypertension and the potential benefit of more effective treatment will continue to rise. Over 100 million people with resistant hypertension worldwide could benefit. The UCL team's research has demonstrated the effectiveness of repurposing an existing generic medicine at a cost of less than GBP15 a year per treatment. In the UK, in the period from 2009 to 2017 there was a five-fold increase in the use of aldosterone inhibitors such as spironolactone (**S8**).

Improving treatment of high blood pressure in patients with advanced kidney disease

Patients with chronic kidney disease are usually denied drugs such as spironolactone because of their increased risk of developing high blood potassium levels (hyperkalaemia). However, the UCL-led AMBER study demonstrated the effectiveness of a novel strategy including the potassium binding agent patiromer, together with spironolactone to lower BP in these patients (**R5**). These findings are further extending the use of spironolactone to treat resistant hypertension in patients with advanced kidney disease. The AMBER study has attracted global attention. The trial findings were presented at the US National Kidney Foundation Clinical Meeting in March 2019 and Heart Failure Society conference, and via the NephJC Twitter chat, a bimonthly online Journal club with almost 21,000 followers and on Medscape.

Changing medical education

The PATHWAY2 findings have been incorporated into international teaching resources on resistant hypertension via the online medical education platform 'UptoDate' (**S9**) which is accessed by more than 1.9 million clinicians in approximately 190 countries. The "UpToDate" website (accessed on 14 December 2020) states: "The effect of spironolactone in patients with resistant hypertension has been evaluated in multiple randomized trials, each of which found that it was more effective than placebo or other antihypertensive drugs. The most compelling data come from the PATHWAY2 trial, a randomized, double-blind crossover study comparing spironolactone (25 to 50 mg/day) with placebo, doxazosin, or bisoprolol …. It also states: "In a substudy of the PATHWAY2 trial described above, amiloride 10 mg once daily was equally effective in lowering clinic blood pressure, compared with spironolactone 25 once daily. These findings illustrate that amiloride may be an effective alternative as the fourth-line medication in resistant hypertension." Data from the studies is also included in all major medical textbooks addressing the topic of resistant hypertension, including the ESC Textbook of Cardiovascular Medicine (**S10**).

5. Sources to corroborate the impact

S1 NIHR Evidence Alerts: https://discover.dc.nihr.ac.uk/content/signal-000152/spironolactone-is-effective-for-treating-resistant-hypertension

S2 Sternlicht H, Bakris GL (2015) *Lancet*: 386 2032-2034 DOI:https://doi.org/10.1016/S0140-6736(15)00264-0

S3 Calhoun DA (2018) *Lancet Diabetes and Endocrinology* (2018) Vol 6:431-433 https://doi.org/10.1016/S2213-8587(18)30080-9

S4 Soloway B (2015) *New England J Medicine* JournalWatch feature on Pathway2 https://www.jwatch.org/na39809/2015/12/30/spironolactone-resistant-hypertension. With front page stating Sprionolactone in hypertension as one of the year's top ten thematic areas in clinical medicine.

S5 i) US Hypertension guidelines 2017: DOI: 10.1016/j.jacc.2017.11.006
ii) European Hypertension Guidelines 2018: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Arterial-Hypertension-Management-of
iii) US Guidelines on Resistant Hypertension 2018:
Resistant Hypertension: Detection, Evaluation, and Management: A Scientific Statement From the American Heart Association.
iv) 2020 International Society of Hypertension Global Hypertension Practice Guidelines
https://www.ahajournals.org/doi/10.1161/HYPERTENSIONAHA.120.15026

S6 Testimonial letter from Chair of International Society of Hypertension

S7 https://www.mdedge.com/chestphysician/article/163427/hypertension/consider-spironolactone-treatment-resistant-hypertension

S8 Data in personal communication from London School of Hygiene and Tropical Medicine

S9 https://www.uptodate.com/contents/treatment-of-resistant-hypertension

S10 The ESC textbook of cardiovascular medicine 3rd Ed. Oxford Medicine https://oxfordmedicine.com/view/10.1093/med/9780199566990.001.0001/med-9780199566990 Chapter 13.