Institution: King's College London

Unit of Assessment: 1- Clinical Medicine

Title of case study: Slowing the progression of diabetic kidney disease

1. Summary of the impact

King's College London (KCL) researchers were the first to identify that an early sign of diabetic kidney disease was the presence of albumin in the urine, a condition known as albuminuria. Building on this finding, the KCL Unit of Metabolic Medicine designed and led in-house, national then international randomised controlled clinical trials with the aim of preserving kidney function in diabetic patients. Ultimately, KCL research established that several drug inhibitors of the renin-angiotensin-aldosterone system (RAAS) can control albuminuria, slow the deterioration of kidney function and significantly extend survival rates in diabetic patients. These drugs are now generically available, and their prescription is recommended by current international clinical guidelines across North America, Europe, Australia and Asia. This shows major impact in terms of reach and significance.

2. Underpinning research

Diabetes and kidney disease: The number of diabetic patients worldwide is estimated to increase to 350 million by 2030. Since over 40% of the current diabetic population experiences kidney pathology (United States Renal Data System 2010 http://www.usrds.org/2010/pdf/V1_01.PDF), this will lead to a dramatic increase in new cases of kidney disease over the next two decades. This may be further aggravated in the developing world, as the risk of kidney disease is higher in patients of Afro-Caribbean and Asian descent. Thus, the current and future prevention and management of diabetic kidney disease is a huge global challenge.

KCL research establishes the mechanisms behind the development of albuminuria in diabetic patients: Microalbuminuria was first described in patients with diabetes in 1969 by KCL researcher Professor Harry Keen (Guy's and St Thomas' Hospitals, 1961–1990). Subsequent KCL research led by Professor Giancarlo Viberti (1975–2009) identified albuminuria as an important risk factor for kidney and cardiovascular disease, and established several factors that contributed to disease progression. In 1993, the Viberti group determined that as diabetes progresses, it leads to the appearance of small amounts of albumin in the urine (micro-albuminuria) (1). Without treatment, albumin concentrations continue to rise (macro-albuminuria), indicative of a steady decline in kidney function towards failure.

KCL scientists translate original research into clinical treatments: In 1994, the KCL group at the Unit for Metabolic Medicine (Cardiovascular Division) led by Professor Viberti ran the first interventional randomised controlled clinical trial into the use of the drug, Captopril, an angiotensin-converting enzyme inhibitor (ACE-I) that acts via the RAAS pathway, to treat diabetes-related albuminuria. In diabetic patients enrolled from 12 centres across Europe and Asia over 2 years, Captopril slowed the progression of microalbuminuria and reduced the transition to macroalbuminuria (2).

ACE inhibitors, such as Captopril, were effective at clinically managing microalbuminuria and protecting kidney function, but were also associated with several side effects. Furthermore, over time, the body compensated for the effects of ACE-I drugs, and bypassed their positive effects. Thus, the KCL group lobbied industry to study the effects of a second class of drugs, the angiotensin receptor-II blockers (ARBs), on controlling albuminuria and preserving kidney function. These studies were designed and led by KCL, and showed that ARBs were at least as effective as ACE-I drugs at reducing albumin levels in urine (3, 4). By comparing ACE-1 and ARB drugs, both of which target the same RAAS pathway, with a similar drug that acts via a different pathway, KCL research performed in 2008 and led by Dr Karalliedde and Professor Viberti (KCL Unit for Metabolic Medicine, 2002–present) established that targeting the RAAS pathway was critical to this anti-albuminuric effect (5).

In 2010, KCL researchers subsequently led an innovative combinatorial approach that paired either an ACE-I or an ARB drug with the novel blood vessel-targeted drug, Avosentan, to determine if this approach could maintain positive effects (i.e. diminished progression of albuminuria) while reducing side effects in diabetic patients. While Avosentan had a pronounced effect on reducing urine albumin levels, substantial adverse events were evident (6) and the drug is therefore not indicated for reduction of albuminuria.

KCL scientists continue to identify new targets to prevent the progression of diabetic kidney disease: In parallel with these seminal randomised-controlled intervention clinical trials, KCL research pioneered by Professor Luigi Gnudi (Guy's Hospital, 1997–present) continues to identify new therapeutic targets that control the progression of diabetic kidney disease. Such work has revealed vascular endothelial growth factor A (VEGF-A), among others, as a promising target for albuminuria treatment in diabetic patients (7).

3. References to the research

1) Yip J, Mattock MB, Morocutti A, Sethi M, Trevisan R, **Viberti G**. Insulin resistance in insulin-dependent diabetic patients with microalbuminuria. *Lancet*. 1993;342:883–87. PMID: 8105164, cited by 161.
2) **Viberti G**, Mogensen CE, Groop LC, Pauls JF. Effect of captopril on progression to clinical proteinuria in patients with insulin-dependent diabetes mellitus and microalbuminuria. European Microalbuminuria Captopril Study Group. *JAMA*. 1994;271:275–79. PMID: 8295285, cited by 462.
3) **Viberti G**, Wheeldon NM; MicroAlbuminuria Reduction with VALsartan (MARVAL) Study Investigators. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure-independent effect. *Circulation*. 2002;106:672–78. PMID: 12163426, cited by 615.
4) Haller H, Ito S, Izzo JL Jr, Januszewicz A, Katayama S, Menne J, Mimran A, Rabelink TJ, Ritz E, Ruilope LM, Rump LC, **Viberti G**; ROADMAP Trial Investigators. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. *N Engl J Med*. 2011;364:907–17. PMID: 21388309, cited by 206.
5) **Karalliedde J**, Smith A, DeAngelis L, **Mirenda V**, Kandra A, Botha J, Ferber P, **Viberti G**. Valsartan improves arterial stiffness in type 2 diabetes independently of blood pressure lowering. *Hypertension*. 2008;51:1617–23. PMID: 18426991, cited by 59.
6) Mann JF, Green D, Jamerson K, Ruilope LM, Kuranoff SJ, Littke T, **Viberti G**; ASCEND Study Group. Avosentan for overt diabetic nephropathy. *J Am Soc Nephrol*. 2010;21:527–35. PMID: 20167702, cited by 81.
7) Ku CH, White KE, Dei Cas A, **Hayward A**, Webster Z, Bilous R, Marshall S, **Viberti G**, **Gnudi L**. Inducible overexpression of sFlt-1 in podocytes ameliorates glomerulopathy in diabetic mice. *Diabetes*. 2008;57:2824–833. PMID: 18647955, cited by 42.

The research above has been supported by substantial competitive charitable and industrial funding, including major awards from the following bodies:

- British Diabetic Association & Department of Health (1993, ~£100,000)
- Novartis Pharmaceuticals Ltd. (1998–2000, ~£100,000)
- European Foundation for the Study of Diabetes (2002-2007, ~£120,000)
- Diabetes UK (2006–2008, £172,263)
- Biotechnology and Biological Sciences Research Council (BBSRC) (2001–2004, £233,484)
- Speedel Pharma Ltd. (2006–2007, £13,682)

4. Details of the impact

Improved survival times for diabetic patients experiencing albuminuria: Increased survival rates for patients experiencing diabetes-related albuminuria must be considered the most significant impact of this KCL research. An EU-based analysis into the effect of prescribing **ACE-I** drugs to diabetic patients experiencing albuminuria estimates an increase in life expectancy of 1.14 quality-adjusted life-years (QALYs) over an individual's lifetime (8). A similar

analysis of the impact of prescribing **ARB** drugs concluded an increase in life expectancy of 0.555 QALYs per patient compared to the next best drug. In real terms, this represents an additional 7 months of survival in full health (9). Both treatment approaches significantly improve survival rates in diabetic patients presenting with albuminuria, and are directly attributable to the original research carried out by KCL researchers and translated into clinical therapies (see [2] and [5] above).

The clinical aspects of KCL research are highlighted by the appointment of Professor Viberti as the co-chair of the steering committee for the ROADMAP (Randomised Olmesartan and Diabetes Microalbuminuria Prevention) study into 2008 (see [4] above), and his full chair of the steering committee for the ASCEND study scheduled into 2009 (see [6] above).

Improved cost-benefits following ACE-I or ARB therapy in diabetic albuminuria patients: In case studies analysing a typical diabetic patient presenting with albuminuria, the use of ACE-I drugs pioneered by Professor Viberti (see [2] above) has been associated with incremental savings of $12,506 compared to the next best drug (8). Since generic versions of ACE inhibitors are now available at a modest cost (approximately $100/year), current cost savings are even higher than this 2011 estimate. A similar study reviewing the economic benefits of prescribing ARB drugs (based on research by Professor Viberti (see [3] above)) to treat diabetic patients newly diagnosed with albuminuria concluded that significant cost savings would be achieved with this approach compared to alternative drugs (9). Thus, KCL research continues to drive economic healthcare improvements worldwide.

KCL research shapes clinical guidelines worldwide: Original research performed at KCL has contributed to clinical practice guidelines both nationally and internationally. The key patient benefits and socio-economic consequences of our research on multiple healthcare systems continue to have long-reaching impact in the current assessment period. Research by Professor Viberti (see [2] above) has informed national governmental policies for the management of chronic kidney disease in patients with type-2 diabetes and diabetes-related high blood pressure for the National Institute for Health and Clinical Excellence (NICE) (10) in the **UK**. The percentage of patients with diabetes, on general practice registers, with a diagnosis of kidney disease (clinical proteinuria) or micro-albuminuria who are currently treated with an ACE-I (or ARBs) [DM06] is embedded in the NICE Quality and Outcomes Framework 2013 (http://bma.org.uk/-/media/Files/PDFs/Practical%20advice%20at%20work/Contracts/gpqofguidance20132014.pdf, thereby incentivising best practice in primary care (11). In **Europe**, this research has influenced the clinical guidelines of the European Society of Cardiology directing the treatment of diabetic patients with kidney disease (12). In **North America**, KCL research has been incorporated into the current US Veterans Affairs/Department of Defence (VA/DoD) clinical practice guidelines for management of chronic kidney disease in primary care version 2.0 (13). KCL findings have also shaped the US Kidney Foundation Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease (14), and the National Kidney Foundation KDOQI™ Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease (15). KCL research has also contributed to the national evidence-based guidelines for diagnosis, prevention and management of chronic kidney disease in type-2 diabetes in **Australia** (16).

KCL research led by Professor Viberti (see [3] above) has also influenced the guidelines of multiple medical societies for the management of chronic kidney disease, including the European Society of Hypertension (17), the Diabetes Australia Guideline Development Consortium (18), the Canadian Diabetes Association (19) and the Taiwan Society of Cardiology (20).

5. Sources to corroborate the impact

Improved survival times and economic cost-benefit analyses based on KCL research:

8) Adarkwah CC, Gandjour A, Akkerman M, Evers SM. Cost-effectiveness of angiotensin-converting enzyme inhibitors for the prevention of diabetic nephropathy in The Netherlands

– A Markov model. *PLoS ONE.* 2011;6:e26139.
9) Theodoratou D, Maniadakis N, Fragoulakis V, Stamouli E. Analysis of published economic evaluations of angiotensin receptor blockers. *Hellenic J Cardiol*. 2009;50:105–18.

National and international disease guidelines based on KCL research:

10) UK NICE Guidelines Update 2008 on Type-2 diabetes http://www.nice.org.uk/nicemedia/live/11983/40803/40803.pdf
11) British Medical Association. 2013. *Quality and Outcomes Framework guidance for GMS contract 2013/14*. http://bma.org.uk/practical-support-at-work/contracts/independent-contractors/qof-guidance.
12) 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, DeBacker G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F. *J Hypertens.* 2013;7:1281–357. PMID 23817082.
13) VA/DoD clinical practice guideline for management of chronic kidney disease in primary care. Department of Veterans Affairs, Department of Defence, Version 2.0, published in 2008 and currently implemented. Prepared by: The Management of CKD Working Group. Support from: The Office of Quality and Performance, VA, Washington, DC & Quality Management Directorate, United States Army MEDCOM. http://www.healthquality.va.gov/ckd/ckd_v478.pdf
14) National Kidney Foundation KDOQI™ Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease (current guidelines, established 2004). http://www.kidney.org/professionals/kdoqi/guidelines_bp/index.htm
15) National Kidney Foundation KDOQI™ Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease. *Am J Kidney Dis.* 49:S1–180, 2007 (suppl 2) (current guidelines, established 2007) http://www.kidney.org/professionals/KDOQI/guideline_diabetes/
16) Chadban S, Howell M, Twigg S, Thomas M, Jerums G, Cass A, Campbell D, Nicholls K, Tong A, Mangos G, Stack A, MacIsaac RJ, Girgis S, Colagiuri R, Colagiuri S, Craig J. The CARI guidelines. Prevention and management of chronic kidney disease in type 2 diabetes – guidelines. *Nephrology*. 2010;15:S162–94. PMID 20591029
17) Mancia G, Laurent S, Agabiti-Rosei E, Ambrosioni E, Burnier M, Caulfield MJ, Cifkova R, Clément D, Coca A, Dominiczak A, Erdine S, Fagard R, Farsang C, Grassi G, Haller H, Heagerty A, Kjeldsen SE, Kiowski W, Mallion JM, Manolis A, Narkiewicz K, Nilsson P, Olsen MH, Rahn KH, Redon J, Rodicio J, Ruilope L, Schmieder RE, Struijker-Boudier HA, van Zwieten PA, Viigimaa M, Zanchetti A; European Society of Hypertension. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. *J Hypertens*. 2009;27:2121–58. PMID 19838131
18) Diabetes Australia Guideline Development Consortium. National evidence-based guidelines for diagnosis, prevention and management of chronic kidney disease in type 2 diabetes (2009). Prepared by: CARI Guidelines, Centre for Kidney Research & NHMRC Centre of Clinical Research Excellence The Children's Hospital at Westmead. In collaboration with: The Diabetes Unit, Menzies Centre for Health Policy, The University of Sydney. ISBN 978-0-9806997-2-2 http://diabetesaustralia.com.au/PageFiles/763/Chronic%20Kidney%20Disease%20Guideline%20August%202009.pdf), 978-0-9806997-3-9 (published).
19) Canadian Diabetes Association 2008 Clinical Practice Guidelines for the Prevention and management of Diabetes in Canada. *Canadian Journal of Diabetes*. 2008;32(Suppl 1): S1–201. http://www.diabetes.ca/files/cpg2008/cpg-2008.pdf
20) Chiang CE, Wang TD, Li YH, Lin TH, Chien KL, Yeh HI, Shyu KG, Tsai WC, Chao TH, Hwang JJ, Chiang FT, Chen JH; Hypertension Committee of the Taiwan Society of Cardiology. 2010 guidelines of the Taiwan Society of Cardiology for the management of hypertension. *J Formos Med Assoc*. 2010;109:740–73. PMID 20970072.