

Institution: University of Hertfordshire
Unit of Assessment: Panel A3A: Pharmacy and Pharmacology
Title of case study: Effective Clinical Management of Highly Comorbid Patients with End Stage Kidney Disease
<p>1. Summary of the impact (indicative maximum 100 words)</p> <p>Dialysis has revolutionised the management of End Stage Kidney Disease (ESKD), but the benefits of this invasive, demanding treatment may not be clear-cut for elderly, frail patients with other serious comorbidities. University of Hertfordshire and East and North Hertfordshire NHS Trust researchers have led the development of Conservative Management, an alternative to dialysis for some patients, providing multidisciplinary support and careful symptomatic management until death. The research shows that quality of life is maintained, survival may not be significantly compromised, and preferred place of death is more often achieved than for counterparts on dialysis. Conservative Management programmes have been adopted across the UK and elsewhere, influencing the care of many patients.</p>
<p>2. Underpinning research (indicative maximum 500 words)</p> <p>The Clinical Context</p> <p>Life on dialysis can be arduous, entailing four-hourly haemodialysis sessions thrice weekly, travel to and from dialysis centres, dietary and fluid restrictions, and multiple medications. The impact on quality of life for patients and carers can be huge. As many patients with End Stage Kidney Disease (ESKD) are elderly, frail and have serious co-morbid conditions, there are concerns about whether they necessarily benefit from receiving dialysis, and whether other management options might not offer a better quality of life.</p> <p>The Research Programme</p> <p>Research into the management of patients with advanced kidney disease has been pursued at the university along multiple parallel research strands – clinical, psychosocial, and pharmacological – beginning in the late 1990s. University researchers including Dr Joerg Schultz (Senior Lecturer), Dr David Wellsted (Head, Centre for Lifespan and Chronic Illness Research), and Professor Anwar Baydoun (Pharmacology) have worked in close collaboration with research-active Hertfordshire NHS clinicians including Professor Ken Farrington, Dr Shahid Chandna and Dr Maria Da Silva Gane. Farrington, who was instrumental in setting up the university's R&D Support Unit in 1995, attended as a visiting researcher in the early 2000s, moving to a secondment role in 2010 and a substantive contract in 2013.</p> <p>Initial work by Farrington and Schultz in 1998/9, using routinely collected data, defined a high-risk group of patients (based on age, extra-renal comorbidity, and functional status), comprising about 10% of incident dialysis patients. The survival of these patients was poor (median < 3 months), raising questions about whether dialysis was the appropriate treatment (sect. 3, Ref. 1). Local clinical practice subsequently changed, with efforts made during patient counselling to include prognostic information and, where appropriate, to offer Conservative Management (CM) as a treatment option. It was though important to emphasise that the proposed approach was rational and appropriate rather than resource-led, because until at least the late 1980s dialysis in the UK had been underprovided and effectively rationed. 'Conservative management' traditionally connoted measures – usually dietary – aimed at postponing the need for dialysis; CM, based on palliative, supportive treatment and involving careful symptom control, continued full medical treatment short of dialysis, including use of erythropoietin to manage anaemia, and continuing multidisciplinary support in liaison with community and hospice services.</p> <p>Evaluation of this approach, based on retrospective data in collaboration with university statisticians, demonstrated that survival in patients undergoing CM was not significantly less than</p>

in those offered CM but choosing to dialyse. A significantly higher proportion of patients on CM died at home rather than in hospital (65% v 27%). Subsequent work by our researchers and others has confirmed these findings (Ref. 2).

Further work compared quality of life in patients on dialysis and CM and found that patients on CM tended to maintain quality of life as renal function declined, whilst for those on dialysis, life satisfaction deteriorated following dialysis initiation, with no recovery at least during the following year (Ref. 3). Adjusted survival from recruitment in late stage 4 and stage 5 CKD was 1,317 days in dialysis patients and 913 days in CM, the difference approximating the number of days on which patients actually underwent haemodialysis sessions (mean 326 sessions per patient).

Work has progressed in other related research strands. Psychosocial research has included an ongoing placebo randomised control study on use of SSRIs in treatment of depression in haemodialysis patients. Since 2008, there has been a pharmacological collaboration between Professors Farrington and Baydoun to investigate factors likely to predict evolution of vascular calcification in patients with kidney failure. This attracted funding from the pharma company Genzyme. A model was developed which has shown differences in the potential for calcification in relation to the severity of kidney failure. Further work is now taking place to determine the mechanisms involved, to develop biomarker profiles, and to generate a calcification risk score that that may be useful clinically.

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

Key Publications

1. Chandna S.M., **Schultz J.**, Lawrence C., Greenwood R.N., and Farrington K. (1999). Is there a rationale for rationing chronic dialysis? A hospital based cohort study of factors affecting survival and morbidity. *British Medical Journal*, 318, 217–223. doi: <http://dx.doi.org/10.1136/bmj.318.7178.217>
2. Chandna, S.M., Da Silva-Gane, M., Marshall, C., Warwicker, P., Greenwood, R.N., **Farrington, K.** (2011). Survival of elderly patients with stage 5 CKD: comparison of conservative management and renal replacement therapy. *Nephrology Dialysis Transplantation* 26, 1608–1614. doi:10.1093/ndt/gfq630
– REF2 Output
3. Da Silva-Gane, M., **Wellsted, D.M.**, Greenshields, H., Norton, S., Chandna, S.M., **Farrington, K.** (2012). Quality of life and survival in patients with advanced kidney failure managed conservatively or by dialysis. *Clinical Journal of the American Society of Nephrology* 7(12), 2002–2009. <http://dx.doi.org/10.2215/CJN.01130112>
– REF2 Output
4. **Patidar A.**, Singh D.K., Winocour P., **Farrington K.**, **Baydoun A.** (2013). Human uraemic serum displays calcific potential *in vitro* that increases with advancing chronic kidney disease. *Clinical Science*, 125(5), 237–245. doi: 10.1042/cs20120638.
– REF2 Output

Selected Funding

Baydoun A., Farrington K. Calcification potential of plasma from patients with chronic kidney disease and diabetes. **Genzyme, 2010 (1 year): £32,000.**

Farrington K., Wellsted D.M., Da Silva Gane M. Facilitation of self-management in a haemodialysis unit: An evaluation. **NIHR RfPB, PB-PG-0909-19044. July 2011: £247,164 (SELFMADE).**

Farrington K., Almond M., Day C., Davenport A., Da Silva Gane M., Wellsted D. A pilot RCT of drug treatment for depression in patients undergoing Haemodialysis. **NIHR RfPB PB-PG-0110-21073. October 2011: £249,317 (ASSERTID).**

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

The research relating to Conservative Management has already had a substantial impact on care delivered to patients in the NHS and worldwide. The associated publications have played a major role in persuading clinicians in Renal Services across the UK that CM is a viable treatment option for frail elderly patients with advanced kidney disease, and have contributed to establishing CM programmes within many Renal Services across the UK and other countries.

The initial impact occurred in local Renal Services within Hertfordshire and Bedfordshire. The characterisation of a high-risk haemodialysis patient group, with poor short-term survival, prompted from 2000 onwards a reconfiguration of pre-dialysis pathways. Patients, relatives and carers were counselled about prognosis and about CM as a treatment option. The aims were supportive, focused on symptom control and provision of palliative care. This approach was viewed as groundbreaking by many in the renal community, and the team led by Farrington won the *British Journal of Renal Medicine* Innovations Award in 2001. As a result the approach became more widely known, as team members were invited to give talks in renal units across the country. Team members also contributed to the Kidney Alliance document (Sect. 5, Ref. 5.1), which included putative National Service Standards for Conservative and Supportive Care.

A 2003 publication by the clinicians involved in the research (Ref. 5.2) formally presented and disseminated the findings that survival may not be significantly enhanced by dialysis in comparison to CM in high-risk patients. Widely cited (Google scholar: 155 citations), it has been effective in reaching other clinicians and NHS decision makers. It was quoted in the National Service Framework for Renal Services (2005) (Ref. 5.3), underpinning the Quality Requirement that 'people with established renal failure receive timely evaluation of their prognosis, information about choices available to them, and for those near end of life, a jointly agreed palliative care plan, built around individual needs and preferences'.

The research influenced Health Policy and Clinical Guidelines in other ways. Farrington co-authored both the Department of Health Kidney Care document 'End of Life Care in Advanced Kidney Disease' (Ref. 5.4) and, with the help of staff at the university's Centre for Life Span and Chronic Illness, co-authored the UK Renal Association Guidelines on 'Planning, Initiating and Withdrawal of Renal Replacement Therapy' (Ref. 5.5). Farrington and Da Silva Gane co-authored health information literature for Kidney Care UK (Ref. 5.6). Further dissemination came via Farrington's invitations to speak on the topic at the World Congress of Nephrology, Renal Association of Ireland, and Royal College of Physicians (Edinburgh and London) between 2007 and 2012, and co-chairmanship of the planned European Renal Best Practice (ERBP) clinical practice guideline on the management of CKD in frail and elderly patients, reflecting growing interest in adoption of this management approach.

The establishment of CM Programmes continues to expand in the UK and other parts of the world. A UK Renal Registry survey (Ref. 5.7) revealed a high prevalence of CM programmes across the UK, but with considerable organisational variation between centres. Fifty-four centres (75%) followed patients in a general clinic, 18 (28%) utilising a dedicated CM clinic, and 14 (19%) employing renal palliative nurses for outreach community care. Around 20% of patients with ESKD over 75 years old were considered to be receiving CM. The CKMAPPS UK National Survey (2013) (Ref 5.8) found that 66 of the 67 responding renal units (from a total of 72) had CM patients. A recent survey of European nephrologists estimated that conservative care was provided to up to 15% of their patients (Ref. 5.9). Similarly, in Australia around 15% of units reported having a formal CM programme, with around 65% of ESKD patients being offered the choice of CM and about 14% choosing this option (Ref. 5.10). This translates worldwide into a large number of patients. There is potential for cost saving, although this is difficult to quantify and is not the primary focus, which is to enhance quality of life and end-of-life care.

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

- 5.1 'End Stage Renal Failure – A Framework for Planning and Service Delivery', Kidney Alliance (2001) <www.kidneyalliance.org/docs/k_report.pdf>
- 5.2 Smith C, Da Silva-Gane M, Chandna S, Warwicker P, Greenwood R, Farrington K. (2003). Choosing not to dialyse: evaluation of planned non-dialytic management in a cohort of patients with end-stage renal failure. *Nephron Clinical Practice*, 95, c40–c46. DOI:10.1159/000073708
- 5.3 'National Service Framework for Renal Services, Part Two: Chronic Kidney Disease, Acute Renal Failure and End of Life Care' (2005).
<www.gov.uk/government/uploads/system/uploads/attachment_data/file/199002/National_Service_Framework_for_Renal_Services_Part_Two_-_Chronic_Kidney_Disease__Acute_Renal_Failure_and_End_of_Life_Care.pdf>
- 5.4 'End of Life Care in Advanced Kidney Disease: A Framework for Implementation', NHS Kidney Care, National End of Life Care Programme (2009):
<www.endoflifecare.nhs.uk/search-resources/resources-search/publications/imported-publications/end-of-life-care-in-advanced-kidney-disease.aspx>
- 5.5 'Renal Association Guidelines: Planning, Initiating and Withdrawal of Renal Replacement Therapy' (2009). <www.renal.org/Clinical/GuidelinesSection/RenalReplacementTherapy.aspx>
- 5.6 'Does everyone choose to dialyse?', Kidney Research UK web page:
<www.kidneyresearchuk.org/health/factsheets/ckd-and-issues/choosing-not-to-start-dialysis.php>
- 5.7 UK Renal Registry Survey (2011): Castledine C, Gilg J, Rogers C, Ben-Shlomo Y, Caskey F. UK Renal Registry 13th Annual Report (December 2010), Chapter 15: UK renal centre survey results 2010:RRT incidence and use of home dialysis modalities. *Nephron Clinical Practice*, 119, Suppl. 2, c255–67. doi: 10.1159/000331783
- 5.8 CKMAPPS: Summary of UK National Survey of Conservative Kidney Management (2013), p.1. (Unpublished report; copy available.)
- 5.9 van de Luijtgaarden M.W. et al. (2013). Conservative care in Europe: Nephrologists' experience with the decision not to start renal replacement therapy. *Nephrology Dialysis Transplantation*, 28(10), 2604–2612. doi: 10.1093/ndt/gft287.
- 5.10 National Survey Australia (2012): Morton R.L., Turner R.M., Howard K., Snelling P., Webster A.C. Patients who plan for conservative care rather than dialysis: A national observational study in Australia. *American Journal of Kidney Disease* 59(3), 419–427. doi:10.1053/j.ajkd.2011.08.024