Treatment of end-stage kidney failure without renal replacement therapy

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Abstract

For the majority of patients with end-stage kidney failure (ESKF) replacement of excretory renal function by dialysis or transplantation (RRT) can extend life and alleviate symptoms. Historically there has been an insufficiency of provision and this remains the case for much of the world. However, RRT is now widely available in healthcare systems of higher income countries.

Increasing numbers of elderly patients are developing ESKF. RRT in this population is largely by dialysis, comorbidity is high and life expectancy short. Evidence of effectiveness coupled with the burden of treatment amongst these individuals has raised concerns that health services in high-income countries may have moved from an era of unmet need into one of potential over-treatment. Alongside the requirement to make treatment more patient-centred this has driven the development of comprehensive conservative care as an alternative approach for older co-morbid individuals with ESKF, with the potential for acceptable symptom control and reduced treatment burden.

This paper provides a largely UK-perspective on treating ESKF without RRT. Emphasis is on the need for high quality evidence to inform treatment decisions. Complexities of defining, delivering and improving treatment of ESKF without dialysis care are explored. Quantitative and qualitative evidence are summarised and the relationship with palliative and terminal care examined. A framework is suggested for classifying management of ESKF and recommendations made to improve delivery of non-dialysis care in the future.

For patients with a poor prognosis such treatment may not result in significantly different survival or quality of life when compared with dialysis. There is a key need to generate the best possible evidence of person-centred health outcomes associated with the various treatment options for ESKF and to present this to patients in a balanced, personalised way that allows them to make the treatment decision most appropriate for them.

Introduction

Renal replacement therapy (RRT) using dialysis has been available for the treatment of end-stage kidney failure (ESKF) from the 1960s. Early technology and availability meant it was offered only to those with the best prognosis. Infamously, this led to the development of committees responsible for directing limited capacity towards those felt most ‘eligible’(1). RRT remains an expensive therapy largely unavailable to the populations of lower income countries (2, 3). In higher income countries successive health policy changes have seen progressive service expansion, and capacity no longer restricts dialysis provision. Improvement in outcomes from long term dialysis allows patients with ESKF to live longer (4). Despite a plateauing of RRT incidence in many countries, the prevalent population receiving dialysis continues to expand (5). Compounded by the limited supply of transplant organs, the population with ESKF has shifted from largely working-age people with single organ disease to one increasingly comprising older, more comorbid individuals, predominantly treated by in-centre haemodialysis (6). With the United Kingdom (UK) general population aged over 65 predicted to increase by 60%, from 10.3 to 16.9 million by 2035 this trend seems set to continue (7).

As people live longer and die with chronic, non-communicable disease, cultural attitudes towards illness, treatment and death have changed (8). Illness and dying are perceived as preventable, even in an individual's older and last years. In the UK almost half of adults die in a hospital bed (9) and about one in five Americans die during a hospitalisation including intensive care (10). Patients approaching the end of life are frequently in receipt of polypharmacy (11). Revolutionary advances in medicine have been replaced by gradual refinement of practice and development of increasingly expensive, higher-technology treatments with slighter, incremental benefits to the individual. In parallel, there has been a practice shift away from paternalistic medicine towards increasingly holistic and patient-centred care. Shared decision making empowers individuals and their carers to make choices about what care they want based on honest, open disclosure of the known benefits and risks of proposed treatment options (12). The model of 'cumulative complexity' recognises a requirement for individuals to cope with demands of illness and treatment, and that incapacity to cope with these demands can lead to further negative health outcomes (13). So called 'minimally disruptive medicine' advocates a pragmatic approach to therapeutic recommendations in an effort to minimise treatment-burden on patients and their carers, especially those with major comorbidity or approaching the end of life (14).

Preparation for RRT involves planning for in-centre haemodialysis for most older comorbid patients with advanced CKD and guidelines promote education and vascular access well in advance of ESKF (15-17). The benefits of this approach are available only to those who survive to start RRT, whereas every patient is exposed to the burdens and associated risk of harm of preparing for dialysis. Some individuals elect for the symptoms and complications of their kidney disease to be managed without RRT. Terminology for this approach includes 'comprehensive conservative care' (CCC – used in this paper)(18), 'non-dialysis care' and 'conservative kidney management'(19, 20). The comparative effectiveness of dialysis and CCC has been studied in countries which have formally introduced such pathways and is discussed in more detail below.

Historically the UK RRT programme has had lower uptake than many other countries with comparable populations, although rates have increased (21). It is not easy to disentangle the role of rationing (implicit or explicit) in this, as compared with careful and appropriate use of treatment. Nevertheless CCC is more accepted in the UK than in many other developed countries, affording a key perspective from which to examine the evidence base for its appropriate and effective development. In this paper the complexities surrounding definition and identification of ESKF are examined. Pathways of chronic kidney disease (CKD) care are illustrated and a treatment classification advanced. Quantitative and qualitative evidence of outcomes and experiences of CCC and dialysis are summarised. Approaches to the development of higher quality evidence to support clinicians and patients in making better-informed decisions about how to plan for ESKF are proposed.

Incidence and prevalence of ESKF

Robust, population-based data to describe ESKF epidemiology are unavailable (Figure 1). RRT registries only systematically collect individual patient outcomes and describe the natural history of RRT-treated ESKF. RRT receipt is influenced by levels of detection of advanced CKD, referral and acceptance on to RRT. Internationally, RRT treatment has been increasing steadily over the last few decades, although rates in high income countries have stabilised more recently (5). Whilst this increase is substantially due to population ageing, rising prevalence of diabetes and decline in competing mortality risk from cardiovascular disease, it also reflects expansion in dialysis services and changing referral and acceptance rates, highlighting the inadequacy of studying ESKF epidemiology using RRT receipt. Hospitalisation data are an invalid measure of ESKF incidence or prevalence because they relate only to known treated inpatient cases and lack clarity due to insufficiencies in International Classification of Diseases coding. Beyond reach of routinely captured data are those with undiagnosed ESKF who have never had blood tests. Mortality data are unreliable because of under-ascertainment of renal disease on death certificates (22). Cohort studies suggest the incidence of CKD has been relatively stable in comparison with growth in RRT-treated ESKF (23), but CKD registries are not widespread.

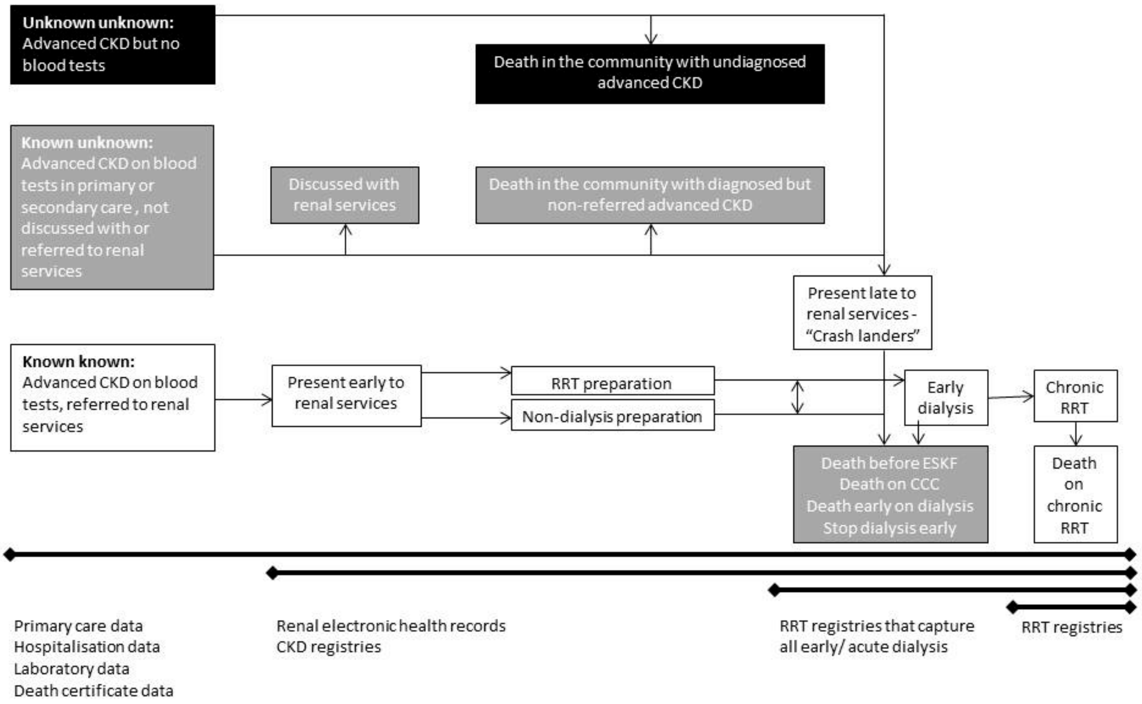

Figure 1 │ *Pathway for people with advanced chronic kidney disease in primary or secondary care with reference to potential data sources on numbers affected and outcomes. Black/ grey shaded boxes represent areas where no/ limited data exist. Abbreviations: CKD chronic kidney disease, CCC comprehensive conservative care, RRT renal replacement therapy*

RRT treatment in the UK has been rising fastest among those aged over 75 years, who now account for almost a quarter of new dialysis patients(21). Comorbidity is prevalent and increases with age(6).

Of patients aged over 65 commencing dialysis, 82% receive haemodialysis (21) and transplantation is not an option for most, especially once aged over 75 (24). Fifty five percent of 65-74 year olds and 40% of those aged 75 or over survive three years. However, 30% of over-85 year olds die within one year of commencing dialysis (4). Early mortality is probably underestimated due to incomplete registry data for patients receiving dialysis following acute decompensation (25) (figure 1) . In the UK, 19% of deaths within one year of commencing dialysis amongst patients aged over 65 are due to withdrawal from treatment and rates are rising (4).

For much of the globe there remains a deficiency of organised data on the incidence and prevalence of ESKF, provision for its treatment and its outcomes (26). Considerable portions of the world population have no access to specialist renal services. Once ESKF develops individuals are likely to either remain undiagnosed, or be diagnosed and unable to access RRT. Reported global incidence rates for RRT-treated ESKF range from 12 to 455 (median 130) per million population (3). This variation reflects factors including population health and demography including disease burden. However, macroeconomic and service factors such as Gross Domestic Product spent per capita, percentage of Gross Domestic Product spent on health care, dialysis reimbursement rate and the private for-profit share of dialysis provision are more strongly associated (3). Work needs to be done to join up these various sources of data on CKD in different settings and gain a full picture of the care of people with CKD and ESKF, though the solutions are likely to have to be specific to the databases and information governance laws in the different countries.

Provision of non-dialysis care

Whilst CCC is recognised and delivered widely (19, 20, 27-29), the international population of individuals receiving CCC has not been evaluated. Scope and practice patterns of CCC in the UK have been systematically recorded (20). A non-dialysis pathway was available in nearly every UK renal unit. Data on the number of older patients on a non-dialysis pathway was available for almost half of units, and varied greatly from 4 to 152, often but not always reflecting the total population of patients in a unit. Data on symptomatic older patients on a non-dialysis pathway, perhaps a better gauge of CCC delivery, also varied widely, ranging from 1 to 50 patients per unit. Approximately one in five units had clinics exclusively for patients on a non-dialysis pathway and this was closely related to whether they had staff primarily responsible, and funding , for non-dialysis care. Unlike RRT preparation and delivery, CCC receives no automatic payment by results within UK healthcare tariffs. Linkage with primary care data was available for a small number of units and suggested that most (94%) individuals with CKD stage 5 were known to renal services. What degree of triage occurred before laboratory testing in primary care was not examined.

The very wide variation in numbers of patients receiving non-dialysis care (20) is likely to reflect, in part, the lack of an agreed definition of the pathway and highlights the need for a uniform terminology (19). Variation also reflects local CKD identification, referral and treatment patterns along with deviation in population demographics. The trend over the past decade has been for increasing investment in such services (30), and some units have shown considerable investment in staff time and dedicated processes to support patients on a non-dialysis pathway.

In 2013 Kidney Disease: Improving Global Outcomes (KDIGO), in partnership with the International Society of Nephrology (ISN), held a conference to develop consensus on the application of palliative care in CKD (18). The lack of clear definitions was felt to have constrained both treatment and research for this population. A definition of CCC was proposed including all aspects of care for individuals with ESKF managed without RRT (Table 1). The conference represented a milestone in the care of patients with or approaching ESKF and prepared the ground for development of an evidence base from which care and outcomes can be improved.

Table 1 | *Definition of comprehensive conservative care following the KDIGO Controversies Conference on Supportive Care in Chronic Kidney Disease(18)*

CCC is planned holistic patient-centred care for patients with CKD stage five including the following

- Interventions to delay progression of kidney disease and minimise adverse events or complications
- Shared decision making
- Active symptom management
- Detailed communication including advance care planning
- Psychological support
- Social and family support
- Cultural and spiritual domains of care

CCC care does not include dialysis

Abbreviations : CCC, comprehensive conservative care; CKD, chronic kidney disease

Treatment of individuals with or approaching ESKF: a proposed terminology

An agreed terminology for treatment of those with or approaching ESKF is necessary to facilitate communication with patients, carers, clinicians and policy makers. In research and policy, evidence, guidance and direction can be developed only once patient populations are defined. The KDIGO/ISN conference defined supportive care and CCC, but did not produce a classification of treatment pathways where both RRT and CCC are available (18). A classification is proposed in Figure 2.

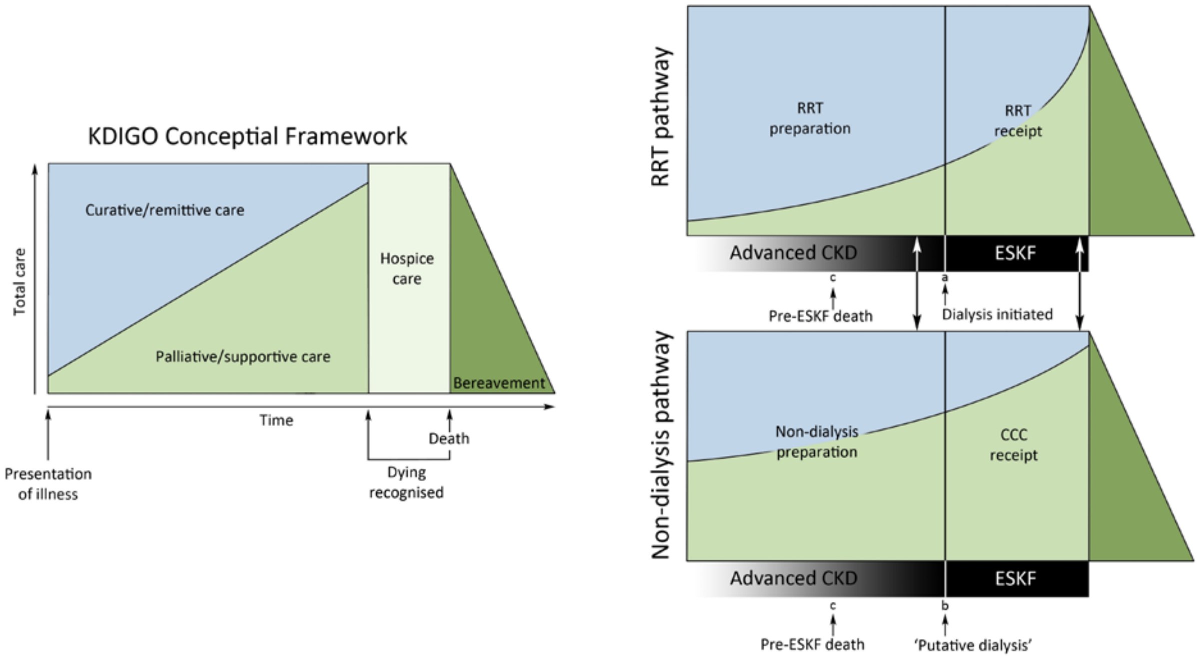

Figure 2 | *Proposed classification of treatment of patients with or approaching ESKF. Left: conceptual framework from the KDIGO Controversies Conference on Supportive Care in Chronic Kidney Disease(18).Right: RRT (upper) and non-dialysis (lower) preparation pathways. Individuals with advanced CKD who anticipate commencing RRT if/when ESKF develops are classified as receiving 'RRT preparation'. Those who opt not to prepare for RRT are classified as receiving 'non-dialysis preparation'. In some, symptoms or biochemical abnormalities trigger RRT initiation (a). From this point such individuals are classified as having ESKF and receiving RRT. At an equivalent point (b) patients who choose not to commence RRT should be classified as having ESKF and receiving CCC, although identifying this 'putative dialysis' point in practice is difficult (see text). Many patients will die before ESKF develops (c). Patients can move freely between the pathways, during both preparatory and ESKF phases (double arrows). All patients are eligible for supportive care as defined by the KDIGO guideline, though supportive needs may be greater amongst the non-dialysis group (curved areas). Abbreviations: CKD, chronic kidney disease; RRT, renal replacement therapy; CCC, comprehensive conservative care; ESKF, end stage kidney failure*

The proposed classification uses 'ESKF' to describe sufficiently impaired kidney function such that individuals are in receipt of either RRT or CCC (after a putative point similar to an indication to start RRT). Estimated glomerular filtration rate (eGFR) associates imperfectly with disease severity and cannot alone identify ESKF (31). Serum creatinine reflects body composition as well as renal function and loses precision as a marker of kidney function in individuals with low muscle mass, malnourishment or at extremes of age (32). Some individuals with an eGFR as high as ≥15 mL/min/1.73m^2 have substantial symptoms or biochemical complications and a small number initiate dialysis at this stage (33). Many patients with eGFR <15 mL/min/1.73m^2 have acceptable fluid balance, biochemistry and symptom control and stability of kidney function.

Initiation of dialysis is not an unambiguous marker of ESKF. Initiating dialysis pre-emptively does not provide benefit over waiting for an indication to commence treatment (34). Symptoms, hyperkalaemia and fluid overload increase with declining kidney function, but are not categorical phenomena – the risk of sudden death, for example, increases progressively with rising serum potassium concentration (35). Individuals (36) and their clinicians (37) weigh potential benefits and burdens of treatment differently depending on personal preferences and values and despite similar disease profiles, may initiate dialysis – thus acquiring a label of treated ESKF – at different times. Some will consider the benefits of dialysis insufficient to outweigh the burdens and choose non-dialysis care(36). The point at which such individuals have progressed from non-dialysis preparation to CCC may be difficult to identify with precision. The proposed classification recognises the difference between individuals who are not planning for RRT if ESKF develops and others receiving CCC who would be undergoing dialysis if that had been the chosen mode of care. However, the dividing lines are indistinct, reflecting gradual progression of disease, plasticity of decision making and the elusiveness of a definition for ESKF.

Decision-making is a process, not an epiphany and this is reflected by the ability for patients to move freely between the pathways, both at preparatory and ESKF phases. Individuals presenting late to renal services (Figure 1) may develop ESKF without being on either pathway and need to elect for RRT or CCC at short notice.

Access to supportive care, advance planning and palliative services should not be influenced by which pathway a patient has chosen. As comorbidities develop and an end of life phase approaches, care may become progressively palliative on either pathway and some patients receiving RRT may choose to withdraw from dialysis. A greater proportion of patients opting for CCC may already be at this stage, but supportive care is a component of both pathways as depicted in Figure 2.

Comparing outcomes between RRT and non-dialysis care

Tables 2 and 3 summarise key studies that have compared the outcomes of patients receiving non-dialysis and RRT care. All have been observational in design, and with only three prospective cohorts (29, 38, 39). Most have been single centre and from the UK, including three from the same unit (38, 40,42). The cohorts are small, with only four including over 100 patients on a non-dialysis pathway. In total, 913 patients receiving non-dialysis care were included. There are methodological issues with the comparisons which include: dealing with selection bias in allocation (treatment by indication) and residual confounding; identification of a start time for survival analysis with long lead times in advanced CKD (and potential for lead time bias); exclusion criteria; uncertain disease progression and prognosis in individuals approaching ESKF; and variation in threshold for RRT initiation between individuals, units and countries; cross over between pathways and failure of intention to treat analysis, and limited outcome data.

Patients on a non-dialysis pathway tended to be older, more comorbid and have poorer functional status (38, 41-43), although this was not found in all studies (39). Selection bias was addressed by restriction or multivariate analysis including propensity scoring (see Table 3). However, residual confounding was a problem given the limited set of routinely available variables in retrospective studies from which adjustments can be made. There was typically no adjustment made for functional status, frailty, malnutrition or cognitive impairment.

Identifying equivalent time points for individuals on RRT and non-dialysis pathways is necessary for survival comparisons. Approaches to start time allocation have included time of recording of decision making (intention to treat), estimating a putative eGFR indicating ESKF and its timing in those on a non-dialysis pathway, and time of reaching a threshold eGFR (see Table 2). Time of decision making fails to distinguish patients in a preparatory phase from those in receipt of CCC and treatment decisions may be made at different times amongst those who choose RRT and non-dialysis pathways. Most studies excluded individuals first presenting to renal services with an eGFR <10-15 mls/min on the grounds there was little time for decision making and high use of RRT in this group. Such patients are often older and more comorbid and are likely to have poor outcomes. The limitations of eGFR as a marker of ESKF have already been outlined. Outcome data available were largely restricted to survival, with a lack of cause of death statistics to inform the role of direct death from ESKF in those treated with CCC. Only three studies investigated quality of life (29, 38, 39).

Compared with patients of the same age receiving dialysis there was a survival disadvantage associated with non-dialysis care, but this diminished and even disappeared when comparison was restricted to patients with high comorbidity or on multivariate analysis (40, 43-46), though this was not found in all studies (38, 47). Patients receiving non-dialysis care were more likely to die out of hospital, with palliative care input, and less likely to have an ‘over-medicalised’ death (42, 43, 45, 48). The patients receiving RRT, who were largely treated with in-centre haemodialysis, had greater hospitalisation rates and longer time spent in hospital compared with those receiving CCC (43, 47, 48), except in one study of patients receiving peritoneal dialysis, where the reverse was found (45). In the three studies that examined changes in quality of life (29, 38, 39), there were some baseline differences with lower scores in patients on a non-dialysis pathway, notably in terms of their physical health. However, quality of life was more stable over time in those receiving non-dialysis care, in contrast to those who started dialysis where an adverse impact on burden of disease and life satisfaction was seen, with no apparent quality of life gained.

Table 2 │ *Characteristics of studies comparing comprehensive conservative care (CCC) and dialysis*

Study	Setting	Design	Conservative care intervention	Primary Outcome	Sample characteristics		Baseline comparison CCC vs RRT
					CCC	**Dialysis**	
Joly, 2003(41)	France Single centre	Retrospective cohort Consecutive referrals Age>80 Creatinine Clearance<10 1989-2000	Palliative care Fluid balance Symptom control Psychological social and spiritual care	Mortality Time 0 = at day started RRT or date decision not to perform dialysis recorded	N=37 Mean age 84	N=107 Mean age 83 HD 6 patients switched to CCC	+Comorbidity +Social isolation, +Late referral, +Diabetes - Karnofsky score
Smith, 2003 (42)	UK Single centre (Lister)	Retrospective cohort All referrals 1996-2000	Ongoing support by multi-disciplinary team in liaison with community and hospice, and full medical care	Mortality Time = 0 at putative dialysis initiation Mean eGFR 9.4ml/mi	N=63 Mean age 71 10 CCC patients switched to RRT	N=258 Mean age 59 6 patients declined RRT	+ Age + Comorbidity - Karnofsky score
Murtagh, 2007(44)	UK Four centres	Retrospective cohort pre-dialysis care clinic referrals Age >75 (excluded late presenters, first presentation eGFR<15, terminal malignancy) 2003-2004	Dedicated multidisciplinary care	Mortality Time = 0 at first date eGFR<15	N=77 Mean age 83	N=52 Mean age 80	+Age No other differences No functional measures

Carson, 2009(48)	UK Single centre	Retrospective cohort Age >/=70, started RRT or CCC Included late referrals 1997-2003	Clinic follow-up Optimised haemoglobin and blood pressure plan same in both groups. In CCC calcium and phosphate control. Diuretic treatment. Dietary restriction only for potassium.	Mortality Time = 0 at start RRT and putative dialysis initiation date in CCC (threshold eGFR in RRT group = first eGFR <10.8ml/min	N=29 Mean age 82	N=173 Mean age 76 All modes	+ Age
Teo, 2010(47)	Singapore Single centre	Retrospective cohort of new ESKD (not defined) 2005	Not reported	Mortality and hospitalisation Time = 0 at ESKF diagnosis Treatment mode defined at 90 days after time = 0	N=16 Mean Age 67	N=152 Mean Age 59 All modes	
Chandna, 2011(40)	UK Single centre (Lister)	Retrospective cohort eGFR <15 (excluded those presenting <10) 1990-2008	Multidisciplinary team liaising with community primary care and hospice services	Mortality Time = 0 at first eGFR <15	N=155 Age at CKD5 Mean 78	N=689 Age at CKD5 Mean 59 All modes	+Age +Comorbidity
Da Silva-Gane, 2012(38)	UK Single centre (Lister)	Prospective cohort Advanced CKD 70% response rate Serial Quality of life assessments	Medical treatment and multidisciplinary support	Mortality Time = 0 at date enrolled in study (eGFR approx. 13) Used propensity	N=30 Mean Age 78	N=124 Mean age 61 All modes	+ Age + Comorbidity + HADs anxiety - Karnofsky - SF36 PCS

		Decisions on mode up to 15 months after 16 patients remained Undecided 2005-06		scoring and multilevel models for quality of life over time			
Hussain, 2013(43)	UK Single centre	Retrospective cohort Age >=70 eGFR <20 Excluded late referrals presenting eGFR <15 2006-11	Multi-disciplinary review Palliative medicine consultant review and care led by them for those with symptomatic uraemia Emphasis on symptoms, advance care planning Fluid, anaemia, renal bone disease management same for CCC and RRT groups	Mortality Time = 0 at eGFR <20 <15 <12	N=172 Age not reported	N=269 Age not reported Modes not reported	+Age +Comorbidity - Performance status + institutionalised
Seow, 2013(39)	Singapore Single centre	Prospective cohort Age >75 or comorbid (Charlson score >=8) And eGFR 8-12 Serial quality of life measurements 2007-9		Quality of life	N=63 Median 78	N=38 Median 71	+ Age (Karnofsky and Charlson comorbidity index same)

Shum, 2014(45)	Hong Kong China Single centre	Retrospective cohort Age >=65 eGFR<15 receiving pre-dialysis assessment 2003-10	Regular clinic follow-up Same medical care as RRT	Mortality Time = 0 at eGFR<15	N=42 Mean 75	N=157 Mean 73 PD	+Age + No helper for PD + stroke + Social assistance
Brown, 2015(29)	Australia Single centre	Prospective cohort Recruited when attended pre-dialysis clinic or renal supportive care clinic Dialysis group included separate late referrals 2009-13	Renal supportive care clinic in addition to usual nephrology care. Address symptoms and advance care planning.	Mortality Time = 0 at time of decision making	N=122 Mean age 82 2 patients planning for CCT started dialysis	N=273 Mean age 67 33 patients planning for RRT started CCC and 72 started a dialysis modality different from planned HD & PD	+age + comorbidity +malnutrition –SF36 PCS +symptoms
Verberne, 2016(46)	Netherlands Single centre 2004-14	Retrospective cohort Age >=70 eGFR<20	Full medical and multidisciplinary care	Mortality Time = 0 at time of mode choice	N=107 Mean age 83 2 pateitnts switched to RRT	N=204 Mean age 76 HD & PD 12 pts switched to CCC	+Age No difference in comorbidity + eGFR at decision

Table 3 | *Outcomes in studies comparing comprehensive conservative care (CCC) and dialysis*

Study	Univariate Survival CCC vs Dialysis	Adjusted survival	Hospitalisation	Quality of life	Other outcomes
Joly, 2003(41)	Median survival 8.9 months vs 28.9 months p <0.001 1year survival 29% vs 74%				
Smith, 2003(42)	Survival significantly worse for CCC group Survived slightly longer (2 months) if switched from CCC to dialysis vs continuing CCC	Cox proportional hazard not significant for CCC intended and then dialysed vs CCC intended and not dialysed			More deaths in CCC group were at home or in a hospice (p<0.001)
Murtagh, 2007(44)	Median time to death or study end 540 days vs 588 days p<0.001 1 year survival 68% vs 84%	No difference in survival if comorbidity grade 2 especially if had ischaemic heart disease Significant predictors: CCC vs dialysis Ischaemic heart disease			
Carson, 2009(48)	Median survival 13.9 vs 37.8 months p<0.01	None	Hospital days 16 CCC vs 25 haemodialysis per patient year		Place of death at home odds ratio for CCC 4.15 (1.67-10.25)
Teo, 2010(47)	1 year survival 69% vs 22% peritoneal dialysis and 20% haemodialysis	Cox proportional hazard CCC HR 2.29 (1.16-4.45) adjusted age sex, race, LV ejection fraction,	Mean number of admissions 2.63 CCC vs 3.45 haemodialysis vs 3.2 peritoneal dialysis		

		therapy centre	(not significant)		
Chandna, 2011(40)	Median survival in those age >75 and low comorbidity 29.4 vs 36.8 (p=0.03) High comorbidity 20.4 vs 25.8 months (not significant)	Cox proportional hazard model in age >75 RRT pathway survive 4 months longer (not significant) Adjusted for age, gender comorbidity, diabetes			
Da Silva- Gane, 2012(38)	Median survival 913 vs 1317 days (vs HD only)	Adjusted hazard ratio for haemodialysis vs CCC 0.47 (0.2-1.1) p=0.08 Adjusted for comorbidity, performance status, age, physical health component of SF-36 and propensity score		Quality of life summary over time: No differences over time in quality of life assessments, depression or anxiety Life satisfaction fell at dialysis initiation below levels in CCC group, which were stable	
Hussain, 2013(43)	Survival at 1 year 58% vs 72% Survival on RRT greater from time of eGFR 20,15 or 12	RRT survival advantage became non-significant in older age (>80) or WHO Performance score >3, and much reduced if more comorbid	RRT group at increased risk of hospitalisation relative risk 1.6 (1-1-2.1) p<0.05		76% CCC accessed community palliative care, 0% RRT CCC group had greater chance of death outside hospital (though high levels of missing data)
Seow, 2013(39)				No difference in CCC or RRT quality of life trajectories (Kidney disease specific Short form 36) after	

				adjustment, except RRT initiation showed benefit to cognitive function score and adverse impact on burden of kidney disease and effects of kidney disease scores	
Shum, 2014(45)	Median survival 2.35 vs 3.79 years P<0.001	Cox proportional hazard ratio for PD 0.46 (0.31-0.68) adjusted for age, comorbidities and impairment in activities of daily living Advantage lost in high comorbidity or if impaired daily living	Greater hospital days and emergency hospitalisation in CCC even after adjustment for age, comorbidity and functional status		Less bothersome intervention at end of life and more renal palliative care P<0.001 No difference in institutionalisation
Brown, 2015(29)	Mean 20 vs 33 months Cause of Death was more commonly renal failure in CCC than RRT group	Various sub-group analyses If Age>75 with >=2 comorbidities including coronary disease or heart failure, hazard ratio for RRT 0.48 (0.21-1.09) [small numbers]		Symptoms and quality of life where reported often stable or improved with no difference between CCC and dialysis	
Verberne, 2016(46)	Median survival 1.5 vs 3.1 years Less difference in age >80, age<70 with Davies comorbidity score >3 or if cardiovascular disease	Age, comorbidity and mode significant Hazard ratio for RRT vs CCC 0.60(0.42-0.92)			

Attitudes of medical staff, patients and their families to CCC

Given the lack of high quality comparative outcome data to guide decision making, it is crucial to understand how clinicians and patients view management options. Different patients may view the same treatment in different ways and it is important for clinicians to understand individual patients' needs and how these may influence decisions. Qualitative research, aimed at exploring people's views of various life experiences, can help to unearth the beliefs and expectations people hold regarding their health, quality of life and medical treatments.

A significant proportion of the qualitative literature has explored patients' perceptions of choosing between types of ESKF treatment, most frequently between dialysis modalities, and living with dialysis. Qualitative syntheses of this type of work have highlighted that patients consider various aspects when deciding what type of treatment is right for them (49, 50). Patients are seen to consider the effect of treatment on their lifestyle and the impact on family members. They can experience great uncertainty when making treatment choices as they are unclear how their CKD is likely to progress and unsure about what different treatment approaches can offer.

More recently researchers have started to explore patients' views of non-dialysis care. Five studies have explored older patients' reasons for choosing non-dialysis care (28, 36, 51-53). These indicate that the perceived burden of dialysis is a common reason why patients may choose non-dialysis care. Patients report that their age and functional ability make attending dialysis sessions demanding and, as a consequence, feel dialysis would negatively affect their quality of life (51-53). Many older adults report difficulties in attending dialysis either because of availability of transport, time taken or cost of travel (51). Patients also feel that choosing dialysis may be a burden on family members; interrupting their lives or causing them emotional stress (28). Such practicalities can outweigh perceived benefit of dialysis and those who feel they have lived a fulfilled life may not want treatment that disrupts their way of living (28, 36, 53).

When choosing non-dialysis care patients most often report feeling that they have made an informed and autonomous decision (28, 36). Patients report having opportunities to discuss their options with clinical staff and feel equipped to make decisions (52). However, patients state that information about dialysis is often given priority by staff and that non-dialysis care may be discussed little or not at all (53). Decision aids and information leaflets are likely to be heavily weighted towards dialysis options, possibly reflecting the amount of evidence in this area.

Interviews with individuals indicate that patients may hold misunderstandings about CKD as a disease and what treatment can offer. Most often patients are uncertain about how their disease will progress and what this will mean for the future. Some patients opting for non-dialysis care report feeling well, reporting no symptoms from their CKD and as a result do not see the need for dialysis (52, 53). Patients can fail to recognise how their CKD may progress and make treatment decisions based on how they feel in the present rather than on how they might feel in the future(51). This could explain why patients change their minds and request dialysis once symptoms develop (53).

A small number of studies have explored clinicians' views on how treatment decisions are made with patients (20, 54, 55). Interviews with health professionals have highlighted the difficulty nephrology staff have in explaining CKD treatment and getting patients to appreciate the severity of the disease

(20, 54, 55). Lack of public awareness of CKD and its treatment are perceived to contribute to this. Clinicians report additional challenges such as tailoring information to the educational level of the patient, eliciting patient concerns about treatment options and discussing options with patients who fear dialysis after hearing the experiences of others (54). Clinicians often report the importance of timing discussions so patients have enough time to understand the information, but also introducing new material to patients gradually to avoid anxiety (55).

Clinicians report that uncertainty about disease progression makes it hard to advise patients on management options and to prepare them for future treatment (20, 55). Uncertainty can lead to clinicians avoiding discussions about the future; fearing that information will be too negative for patients (55). Discussions about prognosis or end of life may be delayed until prompted by the patient or by illness progression.

Only one study to date has specifically sought clinicians' views on non-dialysis care (20). Clinicians generally accepted it as an alternative to dialysis, with most being grateful that they could offer something to patients if they did not choose dialysis. Clinicians reported that discussing non-dialysis options with patients was a difficult task, more suited to experienced professionals because of the complexity and sensitivity of end-of-life issues. Clinicians felt more able to have these discussions when they felt confident in talking about end of life and in eliciting patient expectations. Such open discussions were felt to prevent misunderstandings and patients changing their mind between treatment options when symptoms developed at a later stage (20). Similar qualitative work with clinicians focusing on advanced care planning for patients with CKD has also identified that staff may not view such discussions as part of their role and that clinical teams may not have a shared understanding of advanced care planning (56). Research with patients indicates that timely information regarding ACP can help to support patient's psychological needs when undergoing treatment for ESKF (57).

Components of non-dialysis care

Patients who choose the non-dialysis pathway are generally pursuing a less disruptive approach to their care (49). Balancing minimal therapeutic burden with maximal symptom control requires an enhanced focus on individualised goals, preferences and values. Ascertainment of these must be a routine component of planning treatment. Clinicians who can elicit expectations can correct misconceptions and help individuals understand how treatment options might impact upon their quality and quantity of life. Practicalities of treatment need to be considered alongside clinical benefits in order for patients to frame decisions in relation to their own lives. The organisation of available non-dialysis care is varied (19, 20, 56) and there is no evidence available to identify best practice. Systems that encourage continuity of care and guidance from multidisciplinary teams trained and experienced in communication skills, shared decision making, end of life discussions and advance care planning may be best. Integration with primary and palliative care services is needed.

The components of CCC are summarised in Table 1 (18). However, all individuals with advanced CKD need these components addressed and ultimately it is preparation for and delivery of RRT which delineates the care pathways. Given the evolving nature of disease and personal preferences, regular review is needed to ensure treatment is aligned with achievable goals. For some this will involve movement between the care pathways (Figure 2). Many individuals will wish to concentrate on quality of life over longevity. Others may value life extension more highly and this stance is not discordant with non-dialysis care for those with a poor prognosis. Potential therapeutic benefits are offset by treatment burdens, side effects and the competing risk of death.

The majority of patients in a non-dialysis preparation phase will receive treatment undifferentiated from routine CKD care. Those approaching end of life and those who develop ESKF may choose to reduce or stop treatment such as antihypertensives that offer no immediate symptomatic benefit and a low probability of life prolongation. Others will decide to continue such treatment if they feel the benefits outweigh the burdens. High quality shared decision making is needed to facilitate informed choices. Treatment for patients on a non-dialysis pathway is summarised in Table 4.

Table 4 | *Pharmacological treatment of patients on the non-dialysis pathway. Abbreviations CCC, comprehensive conservative care, ACE, angiotensin converting enzyme; eGFR estimated glomerular filtration rate; ESKF, end stage kidney failure; Hb, haemoglobin*

Goal	Rationale	Approach	Risks/Burdens	Non-dialysis preparation	CCC	Approaching end of life
Symptom control	Manage: • Pruritus • Lethargy • Insomnia • Restless legs • Anorexia • Nausea/vomiting • Pain • Depression	• Non-pharmacological • Pharmacological • See KDIGO report(18)	• Polypharmacy • Sedation • Constipation • Other side effects	Symptomatic benefit likely **Treatment recommended, regular symptom screening using validated tools and stepwise approach(18)**	Symptomatic benefit likely **Treatment recommended, regular symptom screening using validated tools and stepwise approach(18)**	Symptomatic benefit likely **Treatment recommended, regular symptom screening using validated tools and stepwise approach(18)**
Preservation of residual renal function	• Delay/prevent ESKF • Prolong ESKF-free life • Prolong life	• ACE inhibitors/Angiotensin 2 receptor blockers • Blood pressure control • Treating primary disease (e.g. glycaemic control) • ACE inhibitor/Angiotensin 2 receptor blocker withdrawal at low eGFR	• Polypharmacy • Hyperkalaemia and acute kidney injury with ACE inhibitors/ Angiotensin 2 receptor blockers • Postural hypotension and falls • ACE inhibitor /Angiotensin 2 receptor blocker withdrawal may accelerate disease progression	May delay/prevent ESKF and prolong life Symptomatic benefit unlikely **Treatment recommended**	Prevention of ESKF no longer possible. Risks of treatment heightened. Symptomatic benefit unlikely Competing risk of death high **Individualised approach needed**	Prevention of ESKF or life prolongation no longer beneficial Symptomatic benefit unlikely **Treatment not recommended**
Prevent cardiovascular complications	• Prolong life • Prevent disabling comorbidity • Reduce hospital	• ACE inhibitors • Blood pressure control • Statins • Glycaemic control	• Polypharmacy • Hyperkalaemia and acute kidney injury with ACE inhibitors/	May prolong life and prevent comorbidity	May prolong life and prevent comorbidity	Meaningful benefit unlikely

(Primary & Secondary prevention)	admission	• Smoking cessation	Angiotensin 2 receptor blockers • Postural hypotension and falls	Symptomatic benefit unlikely **Treatment recommended**	Symptomatic benefit unlikely Competing risk of death high **Individualised approach needed**	Symptomatic benefit unlikely **Treatment not recommended**
Treat renal bone disease	• Prevent fractures • Prevent bone pain	• Dietary phosphate restriction • Phosphate binders • Vitamin D • Parathyroidectomy • Calcimimetics	• Polypharmacy • Tablet burden • Hypercalcaemia • Hypocalcaemia • Unpleasant diet	May prevent future fractures Symptomatic benefit unlikely **Treatment recommended**	Prevention of future fractures possible Symptomatic benefit unlikely Competing risk of death high **Individualised approach needed**	Unlikely to reduce fractures Symptomatic benefit unlikely **Treatment not recommended**
Manage fluid retention	• Prevent swelling and breathlessness • Treat congestive cardiac failure • Reduce chance of acute pulmonary oedema • Reduce hospital admission	• Dietary salt restriction • Dietary fluid restriction • Diuretics	• Polypharmacy • Worsening renal function • Gout • Electrolyte disturbance • Risk of acute kidney injury • Unpleasant diet	Symptomatic benefit likely **Treatment recommended, adjusted to clinical response and laboratory results**	Symptomatic benefit likely **Treatment recommended, adjusted to clinical response and laboratory results**	Symptomatic benefit likely **Treatment recommended, adjusted to clinical response** **Consider stopping blood tests**

						Lifting dietary restrictions may improve quality of life
Manage anaemia	• Prevent breathlessness • Reduce fatigue • Reduce transfusion • Prevent cardiac failure	• Iron therapy • Erythropoiesis stimulating agents • Transfusion	• Stroke • Hypertension • Transfusion reaction • Anaphylaxis	Symptomatic benefit likely **Treatment recommended as per guidelines**	Symptomatic benefit likely **Treatment recommended – individualised Hb targets may be appropriate**	Symptomatic benefit possible **Treatment recommended Transfusion may be required for rapid effect**
Prevent hyperkalaemia	• Reduce risk of sudden cardiac death	• Dietary potassium restriction • Diuretics • Stopping ACE inhibitors/ angiotensin 2 receptor blockers • Exchange resins	• Polypharmacy • Unpleasant diet • Electrolyte disturbance	May prolong life Symptomatic benefit unlikely **Treatment recommended**	May prolong life Symptomatic benefit unlikely **Treatment recommended**	May prolong dying Symptomatic benefit unlikely **Treatment not recommended** **Consider stopping blood tests** **Lifting dietary restrictions may improve quality of life**

The future of non-dialysis care – conclusion and recommendations

Given the human and economic impact of dialysis, there is a pressing need to establish the comparative effectiveness and cost-effectiveness of RRT and non-dialysis care. It is incumbent on the nephrology community to generate the best possible evidence of person-centred health outcomes associated with each treatment approach and learn how to present this evidence to patients in a way that allows them to make decisions that are most appropriate for them. The following five recommendations are focussed on this aim.

1. Agreed definitions are required that clearly distinguish phases of treatment. A suggested framework is proposed (Figure 2).
2. Non-dialysis care should be discussed early and openly with patients approaching ESKF and should feature more prominently in decision-support materials.
3. Improved observational and organisational research is needed to gain a better understanding of the natural history of advanced CKD and ESKF and to identify the most effective and efficient ways to deliver care and monitor equity of care. This could be achieved through a combination of extending RRT registries to capture earlier stages of CKD and by studying routine hospital and primary care databases. Improved capture of early dialysis outcomes and inclusion of patients with CKD including those on CCC (58) will improve data capture in areas known to be deficient (Figure 1). Auditable standards and quality assurance data could help to coordinate more consistent care at a national level, and ensure equity of delivery.
4. The viability of a trial comparing the effectiveness and cost-effectiveness of non-dialysis and RRT care pathways in individuals where clinical equipoise exists should be investigated. Whilst practical and ethical intricacies make this challenging, observational data may never be able to separate unmeasured confounding by indication from treatment effect.
5. Working with colleagues in primary care and palliative medicine, the renal community must continue to strive to improve dialysis outcomes for older patients and those with multiple comorbidities, including greater use of home and assisted therapies. The benefits and risks of RRT are not fixed and whatever evidence is generated regarding non-dialysis pathways will need to keep pace with advances in practice.

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