Novel combined management approaches to patients with diabetes, chronic kidney disease and cardiovascular disease

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Abstract

Most patients we care for today suffer from more than one chronic disease, and multimorbidity is a rapidly growing challenge. Concomitant cardiovascular disease, renal dysfunction and diabetes represent a large proportion of all patients in cardiology, nephrology and diabetology. These entities commonly overlap due to their negative effects on vascular function and an accelerated atherosclerosis progression. At the same time, a progressive subspecialisation has caused the cardiologist to treat 'only' the heart, nephrologists 'only' the kidneys and endocrinologists' 'only' diabetes. Studies and guidelines follow the same pattern. This often requires patients to visit specialists for each field, with a risk of both under-diagnosis and under-treatment. From the patient's perspective, there is a great need for coordination and facilitation of the care, not only to reduce disease progression but also to improve quality of life. Person-centred integrated clinics for patients with cardiovascular disease, renal dysfunction and diabetes are a promising approach for complex chronic disease management.

Keywords cardiology, diabetology, HND, multimorbidity, nephrology

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Growing burden of cardiovascular disease

Cardiovascular diseases (CVDs) are the leading cause of death not only in Europe but also globally.[1] Smoking, hyperlipidemia, hypertension and diabetes mellitus are well established as the most powerful modifiable risk factors for CVD. About 20% of the population in developed countries have hypertension, while the prevalence exceeds 50% in those above age 60 years.[1] The prevalence of chronic kidney disease (CKD), defined as reduced glomerular filtration rate (GFR) or albuminuria, range from 10–13% in the general population and exists in about 30% of those aged over 65.[2] The prevalence of diagnosed diabetes mellitus in adults aged over 65 ranges from 10–20% in most European countries, and an additional 50% have pre-diabetes.[3]

These diseases commonly overlap, and the risk of having several at the same time is high. In fact, in patients aged 65 or older, it is more common to have two or more chronic conditions than just one (Figure 1).[4] One of the most common and yet most challenging group of patients with multiple chronic conditions to treat are those with concomitant CVD, CKD, and diabetes mellitus; referred to in this review as HND patients (heart-nephrology-diabetes).[5]

Atherosclerosis and vascular ageing

Our genetic inheritance together with lifestyle predisposes some individuals for early cardiovascular events. The complex interplay between factors that hastens vascular ageing, plaque formation and rupture is today studied in detail (Figure 2). We can very accurately predict individuals at risk, but are poor at predicting the time of events. Due to increased awareness, changes in lifestyle and improved acute medical care, fewer die early from cardiovascular events. As a result, more live longer with existing CVDs. In recent years CKD has emerged as a factor of equal importance as diabetes for future cardiovascular events.[6–10] CKD and diabetes share many of the mechanisms causing accelerated vascular ageing.[11] It has been argued that diabetes should be called a CVD,[12] and similar arguments apply in the case of CKD.[13]

CKD and CVD

The risk of CVD increases dramatically with declining renal function (Figure 3).[14] Consequently, a large proportion of all patients in both inpatient and specialised outpatient clinics have renal dysfunction. In our cardiology and diabetology outpatient clinics, about 40% have an estimated GFR < 60 mL/min/m^2 and 13 % < 30 ml/min/m^2.

The cardiovascular morbidity in patients with renal failure is explained only in part by traditional risk factors such as hypertension, diabetes and dyslipidemia. Several factors associated with the renal impairment in themselves, like anaemia, calcium-phosphate disorders, vascular

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calcification, inflammation and endothelial dysfunction, all contribute to the increased risk.[5,15,16] As renal function declines we also see a paradoxical clinical picture with simultaneous increased risk of both thrombosis and bleeding.[17] The cause is most likely multifactorial and not completely clear, but platelet dysfunction, endothelial dysfunction, anaemia and impaired fibrinolysis have been shown to contribute.[18]

These associations between CKD and CVD are usually called cardiorenal syndrome type 4, or 'chronic renocardiac syndrome'.[5,19]

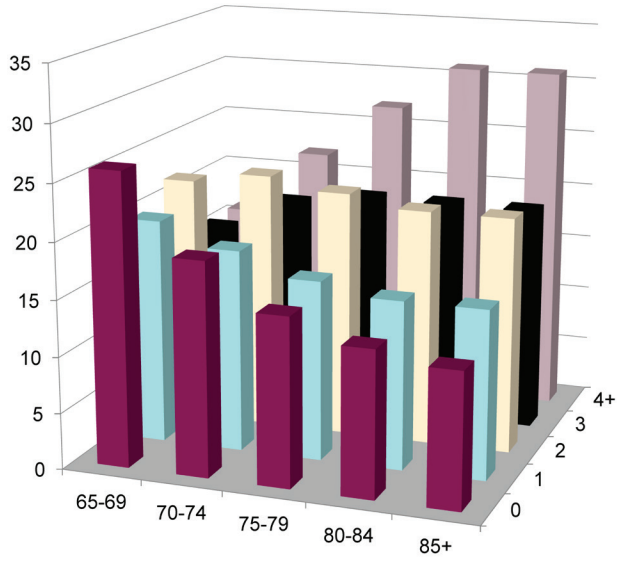
Acute myocardial infarction is the single most common cause of death worldwide.[1] About 40% of these patients have at least moderate kidney dysfunction with an eGFR below 60 mL/min/m^2.[20] The increased mortality in CKD patients after an acute coronary event is directly related to the kidney dysfunction,6 and in patients with eGFR < 60 the 1-year mortality is about 25%, compared to 5% in patients with normal renal function.[20] This may in part be due to the fact that patients with impaired kidney function receive less active treatment, such as early revascularisation, often of concern for contrast induced nephrotoxicity.[21] However, those that receive early revascularisation do appear to have a better outcome in registry follow up data after adjustments for co-morbidities.[21] The increased cardiovascular risk may also be caused by a range of disturbances in, for instance, haemostasis and vascular function.[11] It appears that some drugs, despite correct dose adjustments, do not have the same beneficial effects in patients with renal impairment. For instance, clopidogrel during coronary interventions does not provide the same protection against death, new myocardial infarction or stroke.[22]

CKD, CVD and diabetes

The strong link between CVD and diabetes is more commonly recognised. Patients with diabetes have a nearly 40% incidence of early CVD, including coronary artery disease, stroke and vascular disease.[23] It is also all too common with undiagnosed type 2 diabetes, and it is often first diagnosed when the patient is suffering a heart attack or stroke. Patients with diabetes live an average of 8.5–10 years less than non-diabetics, and it is CVDs that lead to premature death.[23]

Diabetes is also the fastest growing cause of end-stage renal failure worldwide. Between 1995 and 2009 the initiation of renal replacement therapy in diabetes patients increased from 12.3 to 27.6 patients per million in UK, although these rates still are about five times less than those in the USA.[24] Despite their high risk, treatment control of simple but effective measures to reduce CVD risk, such as blood pressure and blood glucose levels are poor in diabetes-CKD patients.[23,25] Also, treatment studies in diabetes have traditionally focused primarily on blood sugar control, and secondarily on the common risk factors like high blood pressure or lipids. However, it is clear that a multifactorial approach is required to achieve clinically relevant treatment effects.[23,26]

Figure 1. Older patients have a very high probability to suffer from several chronic conditions at the same time. Figures based on MEDICARE data by Wolff et al.[4]



Preventing CVD in diabetes mellitus and CKD

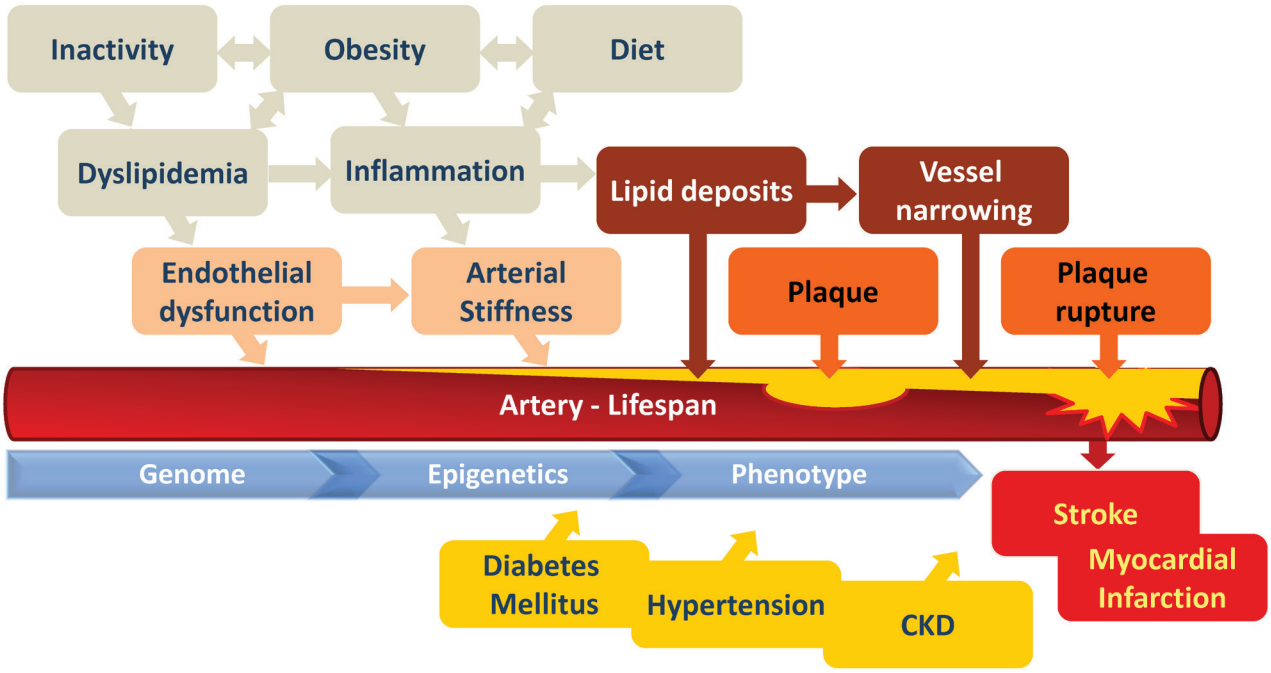
More than 80% of all cardiovascular deaths can be delayed by changes in lifestyle and commonly prescribed drugs.[27] Hyperlipidemia, smoking, hypertension and diabetes mellitus are well-established as the most powerful modifiable risk factors for CVD. If not prevented or treated optimally, the result is increased morbidity, impaired quality of life, and premature death.[1] Despite this, many patients never receive the full benefits from these interventions because of frequent under-diagnosis, late presentation, and subsequent under-treatment.[28,29] This suggests that patients need interventions that are more holistic in nature than the medically-oriented treatment plans that many subspecialised clinics tend to offer.

Under-treatment despite high healthcare consumption

Our current healthcare system is poorly equipped to meet the needs of patients with multiple comorbidities such as HND patients. As described in Figure 1, diseases commonly overlap, and the risk of having several chronic conditions is high. At the same time, healthcare utilisation and cost more than doubles by each additional chronic condition.[4] Diagnosis, prognosis, and treatment are complex due to interactions between the diseases, and care coordination is a challenge.[14] Despite using a remarkable amount of healthcare recourses, no one is coordinating these interventions, and patients often experience low levels of control in a daily life filled with pills, injections, measurements, blood-work ups, and doctor and nurse appointments.[14]

In general, current guidelines recommend the same treatment for patients with multiple morbidities as for patients with only one.[30–32] However, evidence is limited particularly in CKD patients as reduced renal function remains a common exclusion criterion in clinical trials.[33] The interrelationships between HND suggest that an integrated and coordinated approach to treatment is needed, but frequently these

Figure 2. The complex interplay between lifestyle factors and inherited predispositions contribute to the development of vascular dysfunction, plaque formation and rupture, all hastened by concomitant diabetes, hypertension and CKD

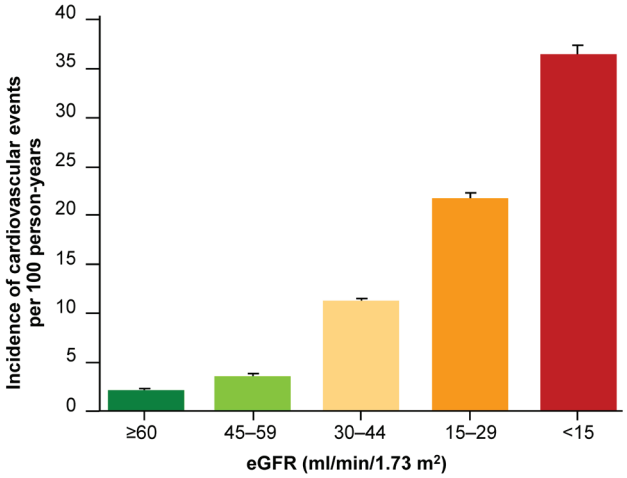


conditions are managed in silos and patients risk receiving suboptimal care.[13] Lack of care coordination and poor design of care processes contribute to ineffectiveness and inefficiency, and, on average, one third of all healthcare resources do not produce any value; and risk causing harm.[4]

Combined management

The chronic nature of CKD, diabetes and heart failure has led these specialties to recognise the importance of multidisciplinary intervention. Multidisciplinary in this setting refers to collaborations within medical specialties but between professions, i.e. physicians, nurses and paramedics. For instance, nurse practitioners have taken a large active part in dialysis treatment since the early days. In heart failure, nurse-directed, multidisciplinary intervention improves quality of life, reduces hospital use and improves survival.[34,35] In type 2 diabetes, the STENO trials have firmly established that a multidisciplinary, intensive treatment approach can not only reduce the risk of nephropathy and retinopathy, but also reduce the absolute risk of death by 50%.[26] Cohort studies suggest that similar integrated, multidisciplinary clinics based on a nephrologist and a team with other professions are associated with improvements in metabolic and blood pressure control.[36,37] Multidisciplinary clinics are also associated with a slower decline in GFR than usual care,[38] and a significant reduction in the risk for all-cause mortality.[37,39] Results from randomised trials are less clear but likely slow the decline in GFR.[40] Taking these data into consideration, nephrology guidelines state that people with progressive CKD should be managed in a multidisciplinary care setting, with access to dietary advice, education and counselling.[30] 'Holistic management' is currently a class IA recommendation by the European Society of Cardiology. The guidelines specify

Figure 3. Age-standardised incidence of cardiovascular events (death, hospitalised coronary artery disease, heart failure, stroke, or peripheral arterial disease) in relation to renal function. Data from the Kaiser Permanente Northern California database during 1996–2000 (n = 1,120,295). GFR was calculated with the MDRD formula. Mean follow-up was 2.8 years. Adapted from Go et al.[14]



that the management should include not only optimised medical treatment but also patient education, social support, exercise training, patient monitoring, and palliative care in a multidisciplinary management programme.[41]

Many institutions are developing chronic disease management programmes. However, the majority focus on a single disease

and may not recognise the extent of comorbidities and the complexity of the diseases in many of these individuals.[42,43]

Integrated care units are a new way of conducting healthcare.[44] Pilot studies using this approach have shown potential benefits, but also highlighted many difficulties with changing traditional organisations and physicians' way of working.[45] The first multidisciplinary clinic in the HND area, meaning integrating several specialities, is the Integrated Care Clinic at St Paul's Hospital in Vancouver.[46] This clinic brings together medical specialists in nephrology, cardiology and endocrinology, as well as a team of nurses, pharmacists, dieticians and social workers. This clinic has focused on patients already attending a nephrology clinic and one or two cardiology or endocrinology patients, and is not aimed at those with unrecognised CVD or undiagnosed diabetes.[46] In this setting, patients were randomised (n = 150) to either standard care or to the integrated clinic. Mortality, hospitalisation rates and progression to end-stage renal disease did not differ and a similar proportions in each group achieved clinical and laboratory targets.[46] Their conclusion was that medical care of complex patients may be delivered in a single combined specialty clinic as compared to multiple disease specific clinics without compromising patient care or important health outcomes, with demonstrable outpatient costs savings.[46,47]

Person-centred healthcare

Chronic diseases require a different approach to care compared to acute diseases, since almost all the actual care is done by the patient themselves through changes in lifestyle and diet, actively taking medications and following self-measured glucose levels, body weight and sometimes blood pressure. This requires a well-informed and involved patient; informed at a level which the patient can take in. Person-centred care is a model that in recent years has also been shown to produce very positive results in chronic CVD.[48–50] Person-centred care can be described as a partnership between patients and professional caregivers, where the patient is seen as a person with resources and abilities to participate in their own care.[48] The prerequisite for being able to provide person-centred care is that health professionals thoroughly understand not only the patient's illness but also the patient's situation in life, personal goals and abilities. Only after establishing this can a plan with goals and realistic strategies for implementation and short- and long-term follow-up be made. It is important to focus on not too many issues at once, and set small, realistic sequential goals, and to document not only the medical aspects but also the 'softer' issues concerning the patient-healthcare providers.[48–50]

HND-Centrum

Our current healthcare structure with increased subspecialisation is a systematic barrier to multidisciplinary intervention. In November 2013, Danderyd University Hospital and Karolinska Institutet, Stockholm, opened a new integrated outpatient clinic, as Sweden's first, and the second in the world after Vancouver.[46]

The outpatient clinic accepts patients with newly diagnosed or established CVD, diabetes mellitus type 1 or 2 and CKD (eGFR < 60 mL/min/m^2 or macroalbuminuria). HND-Centrum is staffed by specialists in cardiology, nephrology and endocrinology, and by nurses and paramedics. Previous contacts within these specialist areas are replaced by one of the HND specialists and one of the specialist nurses. All patients are discussed at therapy conferences with senior specialists from all three specialities. From the start, the HND-Centrum implements person-centred healthcare, with a large focus on lifestyle followed up by the specialist nurses and paramedics. Our main hypothesis is that HND-Centrum results in better care, from many aspects, at a lower overall cost, which is currently being tested in a randomised clinical trial.

Future directions

From a patient's perspective, many things in life matter more than morbidity and mortality, while many physicians think of diseases in terms of GFR, HbA1C or blood pressure. The average patient does not. We need to change how we talk to patients about their diseases, and also include their health in those conversations. The objective of a multidisciplinary integrated clinic should not only focus on disease progression and mortality, but also on health and quality of life.

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References

1 World Health Organization. World Health Statistics 2011. http://www.who.int/whosis/whostat/2011/en
2 Coresh J, Selvin E, Stevens LA et al. Prevalence of chronic kidney disease in the United States. *JAMA* 2007; 298: 2038–47.
3 Go AS, Mozaffarian D, Roger VL et al. Heart disease and stroke statistics – 2013 update: A report from the American Heart Association. *Circulation* 2013; 127: e6–e245.
4 Wolff JL, Starfield B, Anderson G. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. *Arch Intern Med* 2002; 162: 2269–76.
5 Goldsmith DJA, Spaak J, Covic A. *Cardiorenal Clinical Challenges*. Germany: Springer Verlag; 2014.
6 Anavekar NS, McMurray JJ, Velazquez EJ et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med* 2004; 351: 1285–95.
7 Wright RS, Reeder GS, Herzog CA et al. Acute myocardial infarction and renal dysfunction: A high-risk combination. *Ann Intern Med* 2002; 137: 563–70.
8 McCullough PA, Soman SS, Shah SS et al. Risks associated with renal dysfunction in patients in the coronary care unit. *J Am Coll*

Cardiol 2000; 36: 679–84.
9 Santopinto JJ, Fox KA, Goldberg RJ et al. Creatinine clearance and adverse hospital outcomes in patients with acute coronary syndromes: Findings from the global registry of acute coronary events (grace). *Heart* 2003; 89: 1003–8.
10 Rashidi A, Sehgal AR, Rahman M et al. The case for chronic kidney disease, diabetes mellitus, and myocardial infarction being equivalent risk factors for cardiovascular mortality in patients older than 65 years. *Am J Cardiol* 2008; 102: 1668–73.
11 Izquierdo MC, Perez-Gomez MV, Sanchez-Nino MD et al. Phosphate and inflammation/ageing in chronic kidney disease. *Nephrol Dial Transplant* 2012; 27 (Suppl 4): iv6–10.
12 Grundy SM, Benjamin IJ, Burke GL et al. Diabetes and cardiovascular disease: A statement for healthcare professionals from the American Heart Association. *Circulation* 1999; 100: 1134–46.
13 Suckling R, Gallagher H. Chronic kidney disease, diabetes mellitus and cardiovascular disease: Risks and commonalities. *J Ren Care* 2012; 38 (Suppl 1): 4–11.
14 Go AS, Chertow GM, Fan D et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; 351: 1296–1305.
15 Ohman K, Larsson T, Spaak J. [Vitamin d deficiency in kidney failure. Risk factor for cardiovascular disease]. *Lakartidningen* 2010; 107: 2884–7.
16 Leonard O, Spaak J, Goldsmith D. Regression of vascular calcification in chronic kidney disease – feasible or fantasy – a review of the clinical evidence. *Br J Clin Pharmacol* 2013; 76: 560–72.
17 Wattanakit K, Cushman M, Stehman-Breen C et al. Chronic kidney disease increases risk for venous thromboembolism. *J Am Soc Nephrol* 2008; 19: 135–40.
18 Mortberg J, Blomback M, Wallen A et al. Increased fibrin formation and impaired fibrinolytic capacity in severe chronic kidney disease. *Blood Coagul Fibrinolysis* 2016; 27: 401–7.
19 Ronco C, Haapio M, House AA et al. Cardiorenal syndrome. *J Am Coll Cardiol* 2008; 52: 1527–39.
20 Szummer K, Lundman P, Jacobson SH et al. Cockcroft-Gault is better than the Modification of Diet in Renal Disease study formula at predicting outcome after a myocardial infarction: Data from the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART). *Am Heart J* 2010; 159: 979–86.
21 Szummer K, Lundman P, Jacobson SH et al. Influence of renal function on the effects of early revascularization in non-ST-elevation myocardial infarction: data from the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART). *Circulation* 2009; 120: 851–8.
22 Best PJ, Steinhubl SR, Berger PB et al. The efficacy and safety of short- and long-term dual antiplatelet therapy in patients with mild or moderate chronic kidney disease: results from the Clopidogrel for the Reduction of Events During Observation (CREDO) trial. *Am Heart J* 2008; 155: 687–93.
23 Wang CCL, Reusch JEB. Diabetes and cardiovascular disease: Changing the focus from glycemic control to improving long-term survival. *Am J Cardiol* 2012; 110: 58B–68B.
24 Hill CJ, Fogarty DG. Changing trends in end-stage renal disease due to diabetes in the United Kingdom. *J Ren Care* 2012; 38 (Suppl 1): 12–22.
25 Hill CJ, Cardwell CR, Patterson CC et al. Chronic kidney disease and diabetes in the National Health Service: A cross-sectional survey of the UK National Diabetes Audit. *Diabet Med* 2014; 31: 448–54.
26 Gaede P, Lund-Andersen H, Parving HH et al. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 2008; 358: 580–91.
27 Emberson JR, Whincup PH, Morris RW et al. Re-assessing the contribution of serum total cholesterol, blood pressure and cigarette smoking to the aetiology of coronary heart disease: Impact of regression dilution bias. *Eur Heart J* 2003; 24: 1719–26.
28 Qvarnstrom M, Wettermark B, Ljungman C et al. Antihypertensive treatment and control in a large primary care population of 21,167 patients. *J Hum Hypertens* 2011; 25: 484–91.
29 SWEDEHEART. Annual report for 2016, published 2017.
30 KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney disease. Kidney Int 2013; 3(Suppl): 1–150.
31 Smith SC Jr, Benjamin EJ, Bonow RO et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update. *J Am Coll Cardiol* 2011; 58: 2432–46.
32 Piepoli MF, Hoes AW, Agewall S et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2016; 37: 2315–81.
33 Konstantinidis I, Nadkarni GN, Yacoub R et al. Representation of patients with kidney disease in trials of cardiovascular interventions: An updated systematic review. *JAMA Intern Med* 2016; 176: 121–4.
34 Rich MW, Beckham V, Wittenberg C et al. A multidisciplinary intervention to prevent the readmission of elderly patients with congestive heart failure. *N Engl J Med* 1995; 333: 1190–5.
35 Stewart S, Marley JE, Horowitz JD. Effects of a multidisciplinary, home-based intervention on unplanned readmissions and survival among patients with chronic congestive heart failure: a randomised controlled study. *Lancet* 1999; 354: 1077–83.
36 Thanamayooran S, Rose C, Hirsch DJ. Effectiveness of a multidisciplinary kidney disease clinic in achieving treatment guideline targets. *Nephrol Dial Transplant* 2005; 20: 2385–93.
37 Chen YR, Yang Y, Wang SC et al. Effectiveness of multidisciplinary care for chronic kidney disease in Taiwan: a 3-year prospective cohort study. *Nephrol Dial Transplant* 2013; 28: 671–82.
38 Bayliss EA, Bhardwaja B, Ross C et al. Multidisciplinary team care may slow the rate of decline in renal function. *Clin J Am Soc Nephrol* 2011; 6: 704–10.
39 Hemmelgarn BR, Manns BJ, Zhang J et al. Association between multidisciplinary care and survival for elderly patients with chronic kidney disease. *J Am Soc Nephrol* 2007; 18: 993–9.
40 Barrett BJ, Garg AX, Goeree R et al. A nurse-coordinated model of care versus usual care for stage 3/4 chronic kidney disease in the community: a randomized controlled trial. *Clin J Am Soc Nephrol* 2011; 6: 1241–7.
41 McMurray JJ, Adamopoulos S, Anker SD et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. *Eur Heart J* 2012; 33: 1787–847.
42 Levin A, Chaudhry MR, Djurdjev O et al. Diabetes, kidney disease and cardiovascular disease patients. Assessing care of complex patients using outpatient testing and visits: additional metrics by which to evaluate health care system functioning. *Nephrol Dial Transplant* 2009; 24: 2714–20.
43 Ovretveit J, Gillies R, Rundall TG et al. Quality of care for chronic illnesses. *Int J Health Care Qual Assur* 2008; 21: 190–202.
44 Maslin-Prothero SE, Bennion AE. Integrated team working: A literature review. *Int J Integr Care* 2010; 10: e043.
45 Curry N, Harris M, Gunn LH et al. Integrated care pilot in north-west london: A mixed methods evaluation. *Int J Integr Care* 2013; 13: e027.
46 Weber C, Beaulieu M, Djurdjev O et al. Towards rational approaches of health care utilization in complex patients: An exploratory randomized trial comparing a novel combined clinic to multiple specialty clinics in patients with renal disease-cardiovascular disease-diabetes. *Nephrol Dial Transplant* 2012; 27 (Suppl 3): iii104–10.
47 Hopkins RB, Garg AX, Levin A et al. Cost-effectiveness analysis of a randomized trial comparing care models for chronic kidney disease. *Clin J Am Soc Nephrol* 2011; 6: 1248–57.
48 Ekman I, Swedberg K, Taft C et al. Person-centered care – ready for prime time. *Eur J Cardiovasc Nurs* 2011; 10: 248–51.
49 Olsson LE, Jakobsson Ung E et al. Efficacy of person-centred care as an intervention in controlled trials – a systematic review. *J Clin Nurs* 2013; 22: 456–65.
50 Henbest RJ, Stewart M. Patient-centredness in the consultation. 2: Does it really make a difference? *Fam Pract* 1990; 7: 28–33.