Multimorbidity and risk among patients with established cardiovascular disease: a cohort study

Liam G Glynn, Brian Buckley, Donal Reddan, John Newell, John Hinde, Sean F Dinneen and Andrew W Murphy

Abstract

Background

Most patients managed in primary care have more than one condition. Multimorbidity presents challenges for the patient and the clinician, not only in terms of the process of care, but also in terms of management and risk assessment.

Aim

To examine the effect of the presence of chronic kidney disease and diabetes on mortality and morbidity among patients with established cardiovascular disease.

Design of study

Retrospective cohort study.

Setting

Random selection of 35 general practices in the west of Ireland.

Method

A practice-based sample of 1609 patients with established cardiovascular disease was generated in 2000–2001 and followed for 5 years. The primary endpoint was death from any cause and the secondary endpoint was a cardiovascular composite endpoint that included death from a cardiovascular cause or any of the following cardiovascular events: myocardial infarction, heart failure, peripheral vascular disease, or stroke.

Results

Risk of death from any cause was significantly increased in patients with increased multimorbidity ($P<0.001$), as was the risk of the cardiovascular composite endpoint ($P<0.001$). Patients with cardiovascular disease and diabetes had a similar survival pattern to those with cardiovascular disease and chronic kidney disease, but experienced more cardiovascular events.

Conclusion

Level of multimorbidity is an independent predictor of prognosis among patients with established cardiovascular disease. In such patients, the presence of chronic kidney disease carries a similar mortality risk to diabetes. Multimorbidity may be a useful factor in prioritising management of patients in the community with significant cardiovascular risk.

Keywords

chronic kidney disease; coronary disease; diabetes; mortality; multimorbidity; primary care.

INTRODUCTION

There is a growing recognition in the literature that multimorbidity — the simultaneous coexistence in individuals of more than one disease state — is the rule rather than the exception in primary care.[1] A recent editorial in the *British Journal of General Practice* highlighted the many problems facing patients and clinicians as a result of multimorbidity.[2] Patients with multimorbidity are more likely to die prematurely, be admitted to hospital, have poor quality of life, and experience a loss of physical functioning.[3] With the exception of relatively uncommon conditions, the majority of visits to care for both an indicator condition and any coexisiting conditions are made to primary care physicians, not specialists.[4]

The practice of excluding patients with significant multimorbidity from clinical trials contributes to a lack of evidence with regard to appropriate interventions in this group.[5] The identification of trial participants through acute settings, as well as the lack of reporting of multimorbidity in those patients who are enrolled,[6]

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further limit the applicability of some research findings to the primary care population that is heterogeneous and multimorbid.[7]

Established cardiovascular disease, diabetes, and chronic kidney disease are common and important diagnoses in the community. These three conditions have in common increased prevalence with age; additionally, they often coexist and are responsible for at least 40% of deaths in a developed country such as Ireland. In patients with established cardiovascular disease, diabetes is associated with a significantly increased risk of cardiovascular mortality and morbidity,[8–11] as is chronic kidney disease.[12–16]

Previous reports have highlighted the importance of improving the care of patients with diabetes or chronic kidney disease alongside cardiovascular disease.[11,12] However, there appears to be little evidence regarding the relative and cumulative effect on prognosis of cardiovascular multimorbidity (coexisting cardiovascular disease and diabetes, and/or chronic kidney disease).

Clarification of the extent to which cardiovascular multimorbidity has a cumulative effect on risk, may help to inform the development of cohesive approaches to risk-factor management and improve processes and outcomes of care. The current study used a cohort of patients from a random sample of practices with the full spectrum of cardiovascular disease in the community. The study examined whether a relationship exists between the level of multimorbidity and new cardiovascular morbidity and mortality.

How this fits in

Multimorbidity is the rule, rather than the exception, in primary care. Few studies have compared outcomes for patients with varying levels of cardiovascular multimorbidity. This study demonstrates that the level of multimorbidity is an independent predictor of prognosis among patients with established cardiovascular disease. These data also suggest that, in patients with cardiovascular disease, diabetes carries a similar mortality risk to chronic kidney disease but is associated with a higher incidence of cardiovascular events. Multimorbidity may be a useful indicator when it comes to prioritising the management of patients with chronic disease in the community.

METHOD

Study population

The methods by which the cohort was assembled have been described previously.[17,18] In short, the study sample consisted of a cohort of 1609 patients with cardiovascular disease, who were identified in 2000–2001 from a stratified random sample of 35 general practices in the west of Ireland. To generate this sample, practices were randomly selected, after stratification by practice type (single-handed or group) and location (rural or urban), from the Health Services Executive, Western Area and asked to participate in the study.

After randomisation, 35 practices (60%) chose to take part in the study; these were then asked to generate a list of all their patients with established cardiovascular disease using multiple methods, including practice disease registers, patient database searches, prescribing records, prospective recording of patient attendance, and opportunistic practitioner recall.

Patients were defined as having cardiovascular disease if they had a history of myocardial infarction, angina, or revacularisation by percutaneous coronary intervention or coronary artery bypass grafting. Patients were included in the current study where data were available on diabetic status (written confirmation of diagnosis of type 1 or type 2 diabetes, according to World Health Organisation classification,[19] from primary or secondary care present at baseline in the medical record) and kidney status (serum creatinine sample measurement from the regional laboratory within the study period or up to 30 days before recruitment). Participants with positive and negative status for diabetes and chronic kidney disease were part of the study. However, if the researchers could not determine whether participants were positive or negative, these patients were not included. The first date of measurement of serum creatinine was considered to be the patient's index date for purposes of analysis.

Follow-up data on the cohort were collected after a period of 5 years; patients who had not died or experienced a cardiovascular event were censored at this point. Data on participants were also censored where follow-up data ceased to be available.

Measurement of renal function

Renal function was assessed using estimated glomerular filtration rate (GFR) calculated by the abbreviated Modified Diet in Renal Disease (MDRD) equation.[20] Patients were defined as having chronic kidney disease if they had an estimated GFR of <60 ml/min/1.73 m^2 according to National Kidney Foundation guidelines:[21]

Estimated GFR (ml/min) = 186 × (serum creatinine level in milligrams per deciliter) – 1.154 × (age in years) – 0.203.

Sex and ethnicity data were collected at baseline to determine the women and people of Afro-Caribbean descent; the product of this equation was multiplied by correction factors of 0.742 and 1.21 respectively.[20]

Outcomes

The primary endpoint was death from any cause.

Table 1. Baseline characteristics of patients with cardiovascular disease according to level of cardiovascular multimorbidity.[a]

Characteristic	CVD only (*n* = 718)	CVD and CKD (*n* = 388)	CVD and diabetes (*n* = 81)	CVD and diabetes and CKD (*n* = 69)
Mean age in years	68.6	74.9	68.8	74.8
Female, %	24.5	54.1	25.6	50.7
Current smoker, %	32.4	26.6	28.4	19.0
Previous CVD event, %				
Myocardial infarction	48.0	43.7	46.9	39.7
Angina	84.6	87.6	86.4	85.3
Heart failure	5.3	8.1	3.7	14.5
Previous CVD intervention, %				
Coronary artery bypass graft	19.1	17.8	22.0	24.6
Percutaneous coronary intervention	16.1	10.5	12.2	10.3
Previous comorbidity, %				
Peripheral vascular disease	3.9	5.3	14.6	15.9
Stroke	3.0	5.6	9.8	8.7
Thromboembolism: PE, DVT, TIA	9.3	14.7	7.3	14.5
Baseline clinical status, mean (SD)				
Systolic blood pressure, mmHg	137.5 (18.1)	139.8 (20.2)	142.3 (18.6)	143.9 (22.0)
Diastolic blood pressure, mmHg	80.9 (9.8)	80.3 (8.6)	82.9 (8.1)	80.6 (8.6)
Total cholesterol, mmol/L	5.3 (1.0)	5.5 (1.1)	5.1 (1.2)	5.3 (1.1)
Baseline medication, %				
Aspirin	75.7	71.9	81.7	72.5
Beta-blocker	48.9	46.8	35.4	39.1
Lipid-lowering agent	51.3	44.5	53.7	50.7
ACE inhibitor	23.6	24.3	43.9	43.5

[a]*Total number of patients = 1256. ACE = angiotensin-converting enzyme. CKD = chronic kidney disease. CVD = cardiovascular disease. DVT = deep vein thrombosis. PE = pulmonary embolism. TIA = transient ischemic attack.*

Mortality data were collected from a search of practice records and the General Register Office: the central civil repository for records relating to births, marriages, and deaths in the Republic of Ireland. The secondary endpoint was a cardiovascular composite endpoint that included death from a cardiovascular cause (included as either a primary or a contributing factor according to the death certificate, but not if simply a coexisting morbidity),[22] or any of the following cardiovascular events: myocardial infarction, heart failure, peripheral vascular disease, and stroke.

Statistical analysis

For analysis of baseline characteristics and survival analysis, patients were classified according to level of multimorbidity. Baseline characteristics were analysed with the use of one-way analysis of variance for continuous variables and a χ^2-test for categorical variables. Patient variables included 18 baseline characteristics (Table 1).

To control for the large number of covariates, variable selection techniques were used to identify the most succinct model containing significant explanatory variables, while including the covariate of interest (level of multimorbidity). Cox proportional hazards models (backwards elimination, Wald criterion) were used to evaluate the prognostic effect of level of multimorbidity over the study period, while controlling for all explanatory variables. Adjusted hazard ratios, categorised according to level of multimorbidity in instances of death from any cause and the cardiovascular composite endpoint, were determined while adjusting for all other significant explanatory variables.

Assumptions underlying the final models were checked using suitable residual plots, and the interactions between multimorbidity and the key categorical variables, such as sex, smoking status, and previous myocardial infarction, were investigated. All statistical test values were two-sided, and a *P*-value of less than 0.05 was considered to indicate statistical significance. Analysis was carried out using SPSS (version 14.0) and R statistical software.

RESULTS

Baseline characteristics

Among the original 1609 patients in the study, 42 (2.6%) patients were lost to follow up and 1256 (78.1%) had complete data on level of multimorbidity and follow up. Median follow up was 2.9 years (standard deviation 1.47) and there were no significant differences in age, sex, social status, smoking status, diabetes status, and previous cardiovascular morbidity between patients with and without complete datasets.

Table 1 details the baseline characteristics of the patients according to level of multimorbidity. A total of 718 (57.2%) patients had cardiovascular disease only; 388 (30.9%) had cardiovascular disease and chronic kidney disease; 81 (6.4%) had cardiovascular disease and diabetes; and 69 (5.5%) patients had cardiovascular disease, chronic kidney disease, and diabetes.

Compared with other patients in the study, patients with multimorbidity involving all three conditions had a higher prevalence of heart failure and peripheral vascular disease; and had a higher mean systolic blood pressure.

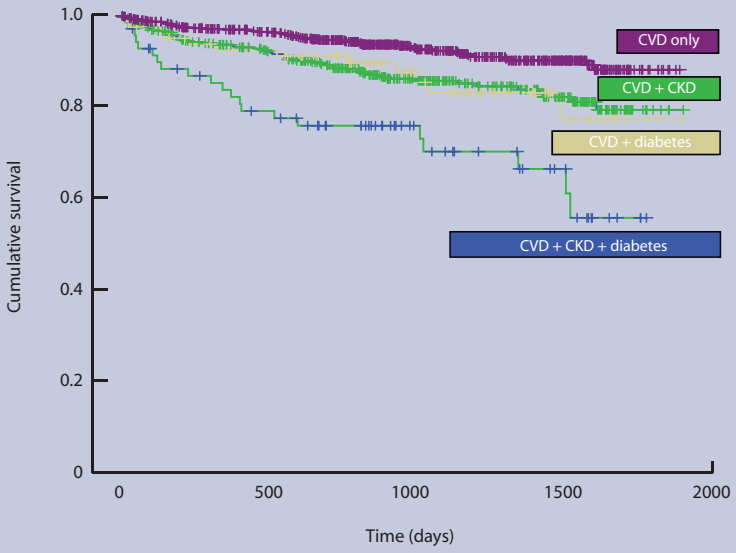
Outcomes

During follow up there were 141 deaths and 167 cardiovascular events. The risk of death from any cause (log-rank/Mantel-Cox 42.24, $P<0.001$) was significantly increased in patients with increased level of multimorbidity (Figure 1) as was the risk of the cardiovascular composite endpoint (log-rank/Mantel-Cox 38.56, $P<0.001$; Figure 2).

In the examination of the relationship between the primary and secondary outcomes and level of multimorbidity while controlling for all significant explanatory variables, patients with cardiovascular disease only were used as the reference group (Table 2). The explanatory variables available for inclusion in the Cox proportional hazards model were age, sex, smoking status, systolic blood pressure, diastolic blood pressure, total cholesterol level, previous myocardial infarction, angina, heart failure, stroke, peripheral vascular disease, thromboembolic events, prior percutaneous coronary intervention, prior coronary artery bypass grafting, and medication use.

The adjusted hazard ratios for both outcomes according to level of multimorbidity are given in Table 2. Estimated risk of death from any cause (primary endpoint), when compared with patients with cardiovascular disease only, was 1.82 (95% confidence interval [CI] = 1.11 to 2.99) for patients with cardiovascular disease and chronic kidney disease; 1.73 (95% CI = 0.79 to 3.78) for patients with cardiovascular disease and diabetes; and 4.73 (95% CI = 2.43 to 9.18) for patients with all three conditions.

Estimated risk of the cardiovascular composite (secondary endpoint), when compared with patients with cardiovascular disease only, was 1.35 (95% CI = 0.88 to 2.07) for patients with cardiovascular disease and chronic kidney disease; as compared with 2.29 (95% CI = 1.25 to 4.17) for patients with cardiovascular disease and diabetes; and 2.72 (95% CI = 1.54 to 4.81) for patients with all three conditions. No significant two-way interactions were identified between multimorbidity and other factors in the model when considering death by any cause.

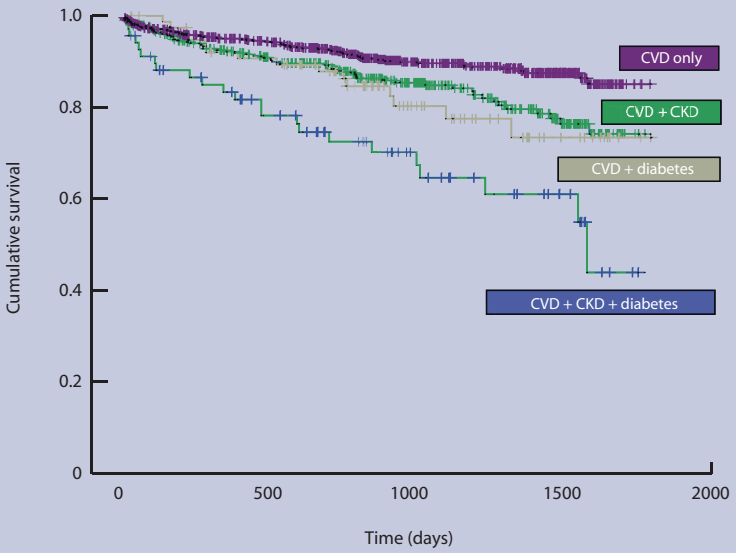


Level of cardiovascular multimorbidity	Total, *n*	Number of events (%)	Censored, *n* (%)
CVD only	718	53 (7.4)	665 (92.6)
CVD and CKD	388	55 (14.2)	333 (85.8)
CVD and diabetes	81	12 (14.8)	69 (85.2)
CVD, CKD, and diabetes	69	21 (30.4)	48 (69.6)
Total	1256	141 (11.2)	1115 (88.8)

CKD = chronic kidney disease. CVD = cardiovascular disease.

Figure 1. Kaplan-Meier survival plots for risk of 'death from any cause' according to level of cardiovascular multimorbidity.

Figure 2. Kaplan-Meier survival plots for risk of composite cardiovascular outcome according to level of cardiovascular multimorbidity.



Level of cardiovascular multimorbidity	Total, *n*	Number of events (%)	Censored, *n* (%)
CVD only	718	68 (9.5)	650 (90.5)
CVD and CKD	388	61 (15.7)	327 (84.3)
CVD and diabetes	81	15 (18.5)	66 (81.5)
CVD, CKD, and diabetes	69	23 (33.3)	46 (66.7)
Total	1256	167 (13.3)	1089 (86.7)

CKD = chronic kidney disease. CVD = cardiovascular disease.

Table 2. Adjusted hazard ratios for primary and secondary endpoints among patients according to level of cardiovascular multimorbidity.[a]

Level of cardiovascular multimorbidity	Primary endpoint: death from any cause		Secondary endpoint: cardiovascular composite	
	$\hat{\beta}$	$\exp\hat{\beta}$ (95% CI)	$\hat{\beta}$	$\exp\hat{\beta}$ (95% CI)
CVD only[b]	–	1.00	–	1.00
CVD and CKD	0.598	1.82 (1.11 to 2.99)	0.299	1.35 (0.88 to 2.07)
CVD and diabetes	0.550	1.73 (0.79 to 3.78)	0.827	2.29 (1.25 to 4.17)
CVD, CKD, and diabetes	1.553	4.73 (2.43 to 9.18)	1.001	2.72 (1.54 to 4.81)

*Total number of patients = 1256. [a]Cox proportional hazards model used in the above analysis adjusted for the following covariates (*denotes covariates kept in the final all-cause mortality model; **denotes covariates kept in the final cardiovascular composite event model): age*,**; sex; smoking status*; systolic blood pressure; diastolic blood pressure; total cholesterol level**; previous myocardial infarction**; angina; heart failure; stroke; peripheral vascular disease**; thromboembolic events; prior percutaneous coronary intervention; prior coronary artery bypass grafting; use of aspirin; beta-blocker; lipid-lowering agent; or ACE (angiotensin converting enzyme) inhibitor*,**.*
[b]This group served as the reference group. CVD = cardiovascular disease. CKD = chronic kidney disease.

There was evidence of a significant interaction between multimorbidity and previous myocardial infarction (P = 0.009) when modeling the cardiovascular composite endpoint. This interaction appears to represent an increased risk of experiencing a composite event for those patients with cardiovascular disease and diabetes who have had a previous myocardial infarction, when compared with the effect of previous myocardial infarction in the other multimorbidity categories.

DISCUSSION

Summary of main findings

Multimorbidity is common in this representative community-based population of patients with cardiovascular disease, with 43% of patients having chronic kidney disease or diabetes or both. Multimorbidity appears to be a significant risk factor for mortality and for new cardiovascular morbidity. Patients with cardiovascular disease and diabetes appear to have a similar risk of death to those with cardiovascular disease and chronic kidney disease but experienced more cardiovascular events. For patients with cardiovascular disease, chronic kidney disease, and diabetes, mortality and morbidity appeared to be significantly and independently increased above the risk associated with the addition of chronic kidney disease or diabetes alone.

The effect of cardiovascular multimorbidity appears more marked on all-cause mortality than the composite cardiovascular endpoint used in this study. It is likely that those patients with increasing cardiovascular multimorbidity also had increasing levels of multimorbidity generally. This, coupled with the increased associated polypharmacy, would contribute to a risk profile that is generally poorer.

Comparison with existing literature

Reported prevalence of cardiovascular multimorbidity in this study population is probably an underestimation, particularly in light of the lower-than-expected proportion of patients with diabetes compared with other populations.[23,24] Population surveys suggest that 30% of adults suffer from more than one chronic health problem.[25] In the US, the prevalence of multimorbidity is estimated at 65% in those over 65 years of age.[26] There is a large discrepancy between the prevalence of multimorbidity in the general population and the number of research studies devoted to it, especially in primary care.[5]

Following myocardial infarction, diabetes and chronic kidney disease appear to predict mortality and increased adverse outcomes. In patients with previous myocardial infarction, the incidence of death from a cardiovascular cause is 42% among those with diabetes compared with 15.9% among those who do not have diabetes.[11] The 1-year mortality of older patients with moderate chronic kidney disease (serum creatinine 220–343 mol/L) after myocardial infarction is nearly tripled compared with those with normal renal function (66% versus 24%).[27] The evidence in this study suggests that this risk is not confined to patients with previous myocardial infarction, but exists in all patients with cardiovascular disease.

Strengths and limitations of the study

This study had a number of limitations. Although the hypothesis was formulated before starting analyses, data collection was retrospective. In addition, the cohort was not formed as a *de novo* population with multimorbidity. Instead, this was a cardiovascular population in which multimorbidity was then identified. Although the level of multimorbidity appears to

discriminate prognosis between patients with established cardiovascular disease, it is difficult to identify the different elements of this association, as chronic kidney disease can have its origin in cardiovascular disease and diabetes.

Another limitation was that the study sample was Caucasian and the prevalence of diabetes and chronic kidney disease in this study may underestimate the prevalence in other ethnic groups. Further, the proportion of patients with diabetes (11.9%) is less than that reported in other relevant studies.[23,24] This study was unable to ascertain cases of impaired glucose tolerance or impaired fasting glucose in the cohort studied — this reflects the current lack of proactive diagnosis of diabetes in primary care in the Republic of Ireland. It is likely that the true impact of diabetes and dysglycemia on mortality in the current cohort has been underestimated.

Finally, lack of availability of serum creatinine data in the community setting excluded some patients from the study and shortened follow up in others. This reflects the limited availability of data, which can restrict chronic-disease management and research in primary care.

To the authors' knowledge, this is the first description of the comparative risks associated with diabetes and chronic kidney disease in a cardiovascular population in primary care. This study describes a nationally representative community-based cohort of patients with cardiovascular disease. To the extent that this was possible, the cohort comprised the total populations with cardiovascular disease of a randomly selected sample of practices. Despite the difficulties of detailed data collection in primary care, very few patients were lost to follow up.

Implications for future research and clinical practice

To date, clinical management and practice guidelines are based on evidence from disease-specific research efforts focusing on a single condition, rather than taking into account multimorbidity which is experienced by most patients.[28,29] Payment for performance in primary care, based on adherence to disease-specific guidelines, is being considered in a number of other countries around the world and has been accepted in the UK with the Quality and Outcomes Framework. There is a method within this system whereby patients who are thought to be unsuitable for application of a disease-specific guideline can be excluded, for example, where there exists a contraindication, a supervening condition, terminal illness, or frailty. It is hoped that such exclusions are limited, appropriate, and have no adverse effect on the care of individual patients. However, the lack of evidence-based guidance on best practice for instances where comorbidity excludes a patient from a guideline is unfortunate, given the overwhelming prevalence of such patients in primary care. This absence of national, or international, guidelines for the management of patients with multimorbidity highlights the gulf that exists between the complexity of disease and the reductionism inherent in disease-specific guideline development.

As chronic-disease management moves increasingly to primary care, there are understandable concerns regarding associated workload. It has been suggested that multimorbidity affects the majority of patients in primary care and the current results suggest that such multimorbidity may become a useful tool to prioritise their disease management. A mortality rate of over 30% over a 3-year period for those with cardiovascular multimorbidity (coexisting cardiovascular disease, diabetes, and chronic kidney disease in this study) is striking, albeit among a small subgroup of 69 patients from 35 practices. It is unfortunate that analysis of comorbidity is not possible using UK Quality and Outcomes Framework data as a result of data being collected at an aggregate level from each practice.

As the number of patients with multimorbidity continues to rise, the need to develop strategies that may improve their survival, physical functioning, and quality of life becomes increasingly important. A paucity of experimental data in this area undermines the development of guidance on management of this complex patient group. The current data suggest that, although those with coexisting cardiovascular disease, diabetes, and chronic kidney disease are clearly a group at high risk of death and cardiovascular events, risk-factor management remains suboptimal. Such results highlight a potentially vital role for primary-care physicians in risk-factor assessment and management decision-making for patients with multimorbidity — whether such a role will lead to improved outcomes requires further experimental work.

Level of multimorbidity appears to discriminate prognosis among patients with established cardiovascular disease. The current data suggest that in patients with cardiovascular disease, diabetes carries a similar mortality risk to chronic kidney disease, but is associated with a higher incidence of cardiovascular disease events.

Multimorbidity may be a useful tool to prioritise the management of patients with chronic disease in the community, a concept that may be of particular interest in light of the planned focus on the prevention and management of chronic disease by the World Health Organisation.[30] To develop effective

management strategies, innovative approaches to the study of this population are required and, because of the diversity of patients and medical conditions encountered, primary care offers an ideal setting for this to take place.

Funding body

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Ethical approval

Ethical approval was granted by the research ethics committee of the Irish College of General Practitioners (Protocol No: REC0904-4)

Competing interests

Andrew W Murphy has received funding from Pfizer to support educational meetings for GPs who teach medical students from the Department of General Practice at the National University of Ireland, Galway. Liam G Glynn and Donal Reddan have received an honorarium from Roche Laboratories for contribution to the development of chronic kidney disease guidelines for primary care. Brian Buckley has received honoraria from Novo Nordisk for participation in meetings aimed at the development of a patient-centred quality-of-life instrument. Sean F Dineen has been reimbursed for attending medical meetings by Novo Nordisk, GSK, and Pfizer; received speaker fees from Novo Nordisk, Sanofi Aventis, and GSK; and has received support for a research study from Novo Nordisk. John Newell and John Hinde declare no competing interests

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