We examined the prevalence of CVD by AoAC grade and determined the association between AoAC and presence of CVD using binomial regression. CVD prevalence by AoAC grade was 14% (N = 14), 42% (N = 19), 64% (N = 14) and 75% (N = 4) for Grades 0–3, respectively (P for trend < 0.01; Figure 1). Univariate analysis revealed that CVD was associated with AoAC Grades 2 and 3 [versus Grade 0, prevalence difference (PD): 0.50 and 0.61, respectively; Table 1]. After adjustment for age and diabetes as a cause of dialysis, CVD was found to be associated with AoAC Grades 1, 2 and 3 (versus Grade 0, PD: 0.25, 0.43 and 0.62, respectively).

Despite the relatively small population and limited covariates available in our analyses, our results suggest that AoAC grade as assessed by using PA-CXR may be associated with CVD in haemodialysis patients, and CVD prevalence may increase with progression of AoAC. This simple four-grade system has been shown to predict CVD events in the general population [4] and appears applicable in haemodialysis facilities across Japan. A large longitudinal study is needed to clarify whether or not this grading system based on PA-CXR is able to predict CVD outcomes as well as lateral CXR in dialysis patients.

Conflict of interest statement. None declared.

Editorial Note: Dr Noordzij et al. had no further comments on this letter.

1Department of Epidemiology and Healthcare Research, Kyoto University, Kyoto, Japan
2Department of Medicine, Mikamikai Yasu Hospital, Shiga, Japan
3Department of Nephrology, Rakuwakai Otowa Kinen Hospital, Kyoto, Japan
E-mail: kurita_n@opal.plala.or.jp

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Impact of renal impairment on the risk of severe hypoglycaemia associated with the use of insulin and glyburide

Sir,

With great interest, I read the article by Weir et al. [1], which addresses the impact of renal function on the risk of severe hypoglycaemia (SH) among users of insulin versus glyburide. In their large, retrospective nested case–control study, the authors demonstrated that renal function did not significantly modify glyburide’s risk for SH, whereas insulin’s hypoglycaemic risk was significantly attenuated in the setting of renal impairment. These results are unexpected contradicting the complex pharmacokinetics of glyburide, the experience of daily clinical practice and the results from recent studies.

The longacting sulfonylurea glyburide (half-life of 5–10 h) carries a high risk of SH due to its high binding affinity to the beta-cell sulfonylurea receptor with a low exchange rate. The two principal metabolites, which undergo 50% renal elimination, have significant hypoglycaemic activity, too. Thus, the half-life of glyburide as well as of its metabolites are indisputably prolonged by renal impairment. Furthermore, there are numerous potential metabolic drug–drug interactions with other commonly prescribed drugs. Additional medication metabolized through the genetically polymorphic cytochrome enzyme CYP2C9 (among others such as warfarin, torasemid, losartan) might reduce the metabolism of glyburide and potentiate its hypoglycaemic effects [2]. An additional analysis of concomitant medication metabolized as well through CYP2C9 would have been valuable for the present study. Concerning insulin therapy, neither the type of diabetes nor the type of insulin used was disclosed. Thus, also patients with type 1 diabetes had been included. Preliminary data indicate that insulin clearance and/or the metabolic activity of human and analogue insulin differ in the state of renal insufficiency [3].

Nowadays, SH associated with the use of longacting sulfonylureas can be regarded as a problem of uncritical prescription neglecting crucial contraindications—particularly renal insufficiency—and deficiencies of diabetes care in the mainly geriatric patients. Recent prospective population-based studies from Germany [4] and Italy [5] with a restrictive definition of SH—a symptomatic event requiring treatment with intravenous glucose that was confirmed by a blood glucose measurement of <50 mg/dL—demonstrated renal impairment in 73 and 50%, respectively, of patients with sulfonylurea-associated SH. Among other factors such as long duration of diabetes, multimorbidity and polypharmacy, a low HbA1c (6.6 and 5.9%, respectively) was the strongest predictor for the risk of SH indicating recurrent antecedent hypoglycaemic episodes. Unfortunately, the current study by Weir et al. [1] did not provide either the diabetes duration or HbA1c levels indicating the quality of antecedent metabolic control and allowing the evaluation
of the a priori risk for SH. It would have been highly relevant to match initially the two cohorts of hypoglycaemic versus non-hypoglycaemic patients with regard to comparable diabetes durations and HbA1c values. Furthermore, the definition of SH followed numerous ICD-9 and -10 codes, thus probably covering a broad spectrum of hypoglycaemic episodes.

In summary, the heterogeneous definition of hypoglycaemia, the missing profound baseline characteristics, and not accounting for some of the potential risk modifiers could have confounded the results.

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First Department of Medicine, Clinic Lippe-Detmold, Detmold, Germany E-mail: Andreas.Holstein@t-online.de

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Reply

Sir,

On behalf of all the authors, we thank Dr Holstein for his interest in our study. As noted in the paper’s discussion section, we share his surprise at the study’s findings and his interest in the role played by potentially confounding variables. In the analysis of our data, we adjusted for many known predictors of hypoglycaemia; however, the nature of our administrative data did not allow measurement of some potentially influential variables. We could not reliably determine the duration of diabetes in our population of elderly patients nor could we assess their level of glycaemic control. It is possible that the exclusion of these and other variables may have contributed to the lower risk of hypoglycaemia we observed in patients with impaired renal function. However, it should not be forgotten that the effect of impaired renal function on glyburide-induced hypoglycaemia is based largely on pharmacologic data [1,2]. Glyburide can certainly cause hypoglycaemia [3], as can impaired renal function [4], but outside of our study, the clinical interaction between these two variables has not been explored. Our findings support the multifactorial nature of hypoglycaemia in patients with diabetes and impaired renal function and suggest that the delayed clearance of partially active metabolites may not be as important at the population level as previously thought.

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E-mail: matthew.weir@gmail.com
Amit X. Garg


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Targeting FGF23 and phosphorus in CKD: do not forget calcium

Sir,

Isakova et al. [1] examined the impact of dietary phosphorus restriction and phosphorus binder (lanthanum carbonate) on fibroblast growth factor 23 (FGF23) serum levels in patients with chronic kidney disease (CKD). While either intervention significantly reduced 24-h urinary phosphorus excretion and fractional urinary phosphorus excretion over the course of the 2-week study period, FGF23 levels were unaffected. These findings, contrasting with observations made in healthy individuals [2], are intriguing indeed.

First, reducing intestinal phosphorus load short term does not affect FGF23 levels in patients with CKD. The authors speculate that the duration of the intervention was probably too short for a CKD population, in which FGF23 levels are chronically elevated. The reasons for this lag time remain speculative. One aspect that was not touched upon was the role of calcium as determinant of FGF23 production. In vitamin D receptor-null mice, dietary calcium supplementation significantly increased FGF23 messenger RNA abundance [3]. In a recent intervention trial in CKD patients, a 6-week treatment with calcium acetate failed to decrease FGF23 levels, as opposed to sevelamer [4]. These findings indicate that calcium may be part of another feedback loop in bone and mineral homeostasis involving FGF23. Indeed, serum calcium is