The association of muscle size, strength and exercise capacity with all-cause mortality in non-dialysis-dependent CKD patients

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Abstract

Background/Objective: Patients with chronic kidney disease (CKD) are commonly reported to exhibit skeletal muscle wasting, reduced strength and exercise capacity. Evidence from patients with end-stage renal disease (ESRD) demonstrates these factors are associated with mortality, but it is unclear whether this relationship exists earlier in the illness. Our objective was to determine whether muscle size, strength or exercise capacity was associated with all-cause mortality, unscheduled hospital admissions or time to ESRD in patients not requiring dialysis.

Methods: This is a prospective cohort study of 89 patients with CKD stages 3b-5 not requiring renal replacement therapy with a mean follow-up period of 3.3 years in which the contribution of predictors of rectus femoris muscle size, muscle strength, exercise capacity to all-cause mortality rates, progression to ESRD and time to first hospitalization were investigated.

Results: Unadjusted analysis suggested each 1 cm² increase in quadriceps muscle size (measured by ultrasonography cross-sectional area) was associated with a 38% reduced risk for death ($p = .006$), and a 10 m improvement on the incremental shuttle walk test was associated with a 3% reduced risk for death ($p = .04$). However, this relationship was not present in analysis adjusted for age, gender and eGFR. No association was seen between any factor for the development of ESRD or time to first hospitalization.

Conclusion: These results suggest that in this small cohort, muscle size and exercise capacity are associated with mortality when considered alone, but this relationship was not present in adjusted analyses. Further investigation in a larger patient group is warranted.

Keywords
death, fitness, hospitalization, kidney disease, muscle mass
Chronic kidney disease (CKD) is a global health concern with an estimated worldwide prevalence of 11%–13%, with the majority of patients falling within stage 3 (Coresh et al., 2007; Eckardt et al., 2013; Hill et al., 2016). It is well documented that patients with CKD experience skeletal muscle wasting, reduced exercise capacity and poor levels of physical functioning which can contribute to a downward spiral of physical inactivity and deconditioning (Carrero et al., 2008; Harada et al., 2017; Hiraki et al., 2013; John, Sigrist, Taal, & McIntyre, 2013; Painter, 2005; Roshanravan, Gamboa, & Wilund, 2017; Roshanravan et al., 2013). Though these debilitating consequences are associated with reduced quality of life (Tsai et al., 2017) and impact upon independent living, there is also evidence to show they are clinically important and contribute to poor outcomes (Carrero et al., 2008; Desmeules et al., 2004; Dong et al., 2008; Harada et al., 2017; Isoyama et al., 2014).

Muscle mass has consistently been associated with mortality in patients with end-stage renal disease (ESRD), with a higher muscle mass associated with reduced mortality (Carrero et al., 2008; Desmeules et al., 2004; Dong et al., 2008; Isoyama et al., 2014). However, there is conflicting evidence from the non-dialysis population depending upon the method used to determine muscle mass. Some studies report an association between low muscle mass and poor survival (Di Micco et al., 2013; Pereira et al., 2015; Wilson et al., 2014), but this is not always confirmed using objective measures of muscle mass (Navaneethan, Kirwan, Arrigain, & Schold, 2014).

Likewise, better handgrip strength has been associated with reduced mortality in ESRD (Chang et al., 2011; Vogt, Borges, Goes, & Caramori, 2016). Using an adjusted model, dialysis patients with a low handgrip strength had a 98% greater risk of death irrespective of their level of muscle mass. This suggests that muscular strength potentially has a stronger relationship with mortality than the degree of muscle mass (Isoyama et al., 2014). However, again, there is conflicting evidence from the non-dialysis population with some studies observing a relationship between handgrip strength and renal outcomes (Chang et al., 2011; Pereira et al., 2015), but this is not always replicated (Roshanravan et al., 2013).

In addition to strength, performance in physical function tests has also been associated with clinical outcome (Mackinnon et al., 2018). In patients with CKD stages 2–4, every 0.1 m/s decrement in gait speed was associated with a 26% greater risk of death and every one-second reduction in the “timed-up-and-go” assessment with an 8% increased risk of death; results of both tests were at least 30% below normative values (Roshanravan et al., 2013). Finally, exercise capacity, which is reduced in CKD patients (Faria Rde et al., 2013; Johansen & Painter, 2012), has also been shown to be a good predictor of mortality (Myers et al., 2002; Sietsema, Amato, Adler, & Brass, 2004). Sietsema and colleagues demonstrated a VO$_{2peak}$ > 17.5 ml/kg/min was a powerful predictor of survival in dialysis patients, but data on the association between exercise capacity and mortality in patients at earlier stages of CKD are lacking.

Research has shown that cardiorespiratory fitness, assessed using a Bruce protocol, may modify the association between eGFR and mortality (Gulati, Black, Arnsdorf, Shaw, & Bakris, 2012). Furthermore, muscle mass, strength and physical functioning are all modifiable risk factors that can be easily targeted with relatively low-cost interventions such as exercise. Understanding the contributions these factors make to clinical outcomes in CKD patients not yet requiring dialysis would be vital to identifying patients at greater risk, and whom would benefit from such intervention. However, at the present time this information is lacking. This study provides these additional data on whether such relationships exist at this earlier stage of the illness.

The aim of the current study was to determine whether muscle size, strength or exercise capacity was associated with patient outcomes of all-cause mortality, unscheduled hospital admissions or time to ESRD. We hypothesized that measurements of muscle size, muscular strength and exercise capacity would be associated with all-cause mortality, unscheduled hospital admission and time to ESRD in patients with CKD stages 3b-5.

2 | METHODS

2.1 | Study design and patient recruitment

This is a secondary analysis of baseline data collected as part of two exercise training studies conducted by our group (Watson et al., 2015, 2018). Patients were recruited to ethically approved studies, and all measures and follow-up were performed prospectively. Both studies were approved by a national research ethics committee (approval numbers: 10/H0406/50; 13/EM/0344) and were conducted in accordance with the declaration of Helsinki.

The first cohort of CKD patients (stages 3b-4) were recruited between November 2010 and February 2012. The second cohort (stages 3b-5) were recruited between December 2013 and April 2016. Both cohorts were recruited from nephrology outpatient clinics at Leicester General Hospital, UK. Exclusion criteria included <40 years in cohort 1 (Watson et al., 2015) <18 years in cohort 2 (Watson et al., 2018), myocardial infarction within the last 6 months, any unstable chronic condition, physical impairment that would prevent them from taking part in the intervention, insufficient command of English and/or an inability to give informed consent.

2.2 | Assessments

Upon entry to the study, both cohorts underwent the following baseline assessments of muscle size, strength and exercise capacity.

2.3 | Quadriceps muscle size

Rectus femoris anatomical cross-sectional area (RF-ACSA) was determined using B-mode 2-D ultrasonography (Hitachi EUB-6500; probe frequency 7.5 MHz) (Watson et al., 2015, 2018; Wilkinson, Gould, WATSON ET AL.
Nixon, Watson, & Smith, 2018) which has recently been validated against MRI (Gould et al., 2019). Images were captured at the mid-point between the greater trochanter and the superior aspect of the patella on the midsagittal plane of the thigh. Three images were acquired with <10% variation, and the mean ACSA in cm² was recorded and RF-ACSA index calculated (RF-ACSA corrected to height m²). This is an easy measure to carry out that requires minimal training and can be performed at the patient’s bedside or at a routine clinic appointment. The rectus femoris quadriceps muscle was chosen because of its ease to be measured by ultrasound and involvement in walking and functional tasks, such as rising from a chair. Therefore, decrements in the size and/or function of this muscle could impact upon physical functioning and engagement in physical activity.

2.4 | Exercise capacity

Exercise capacity was assessed using the 10-m progressive incremental shuttle walk test (ISWT) described previously (Watson et al., 2015, 2018; Wilkinson et al., 2019) and has been used in a variety of illnesses (Andersen, Vinther, Poulsen, & Mellemgaard, 2011; Singh, Morgan, Scott, Walters, & Hardman, 1992; Walker et al., 2000). We recently validated the ISWT against VO²peak in non-dialysis CKD (Wilkinson et al., 2019). Following a familiarization, patients were played standardized instructions and asked to walk for as long as possible along the 10-m course keeping up with the externally paced beeps which became progressively quicker. The test was terminated upon failure to maintain the required pace, or when patients reached exhaustion. Total distance covered in metres was recorded.

2.5 | Muscular strength

Patients performed either a 5-repetition maximum (5-RM) (Watson et al., 2018) or 10-repetition maximum tests (10-RM) (Watson et al., 2015) on leg extension equipment (Technogym, Italy) in order to predict maximal strength. This was the weight that patients were unable to lift more than 5 or 10 times with good form. Maximal leg extension strength (e1-RM) was estimated using predication equations (Brzycki, 1993).

2.6 | Patient outcomes

The most recently recorded blood and urine test results prior to the patient’s consent date were extracted from the electronic patient records. This included serum creatinine and urine protein to creatinine ratio (PCR). Estimated glomerular filtration rate (eGFR) was calculated from the serum creatinine using the EPI-CKD formula. Patients were then followed from consent until 4 December 2017 when data relating to death, dialysis initiation (criteria for which was a clinical decision), or transplantation, and the date of first emergency hospitalization following study consent were extracted from hospital records.

2.7 | Statistical analysis

A composite endpoint of either death, hospitalization or progression to ESRD during the follow-up period was used as the primary measure in this study. Data are reported for continuous outcomes as mean ± standard deviation (SD) and for categorical variables as counts and percentage. Spearmann’s correlation coefficient was used to assess the association between muscle size, strength, exercise capacity and age, eGFR and PCR. Unadjusted (Model 1) and adjusted (Model 2) hazard ratios for mortality, time to first hospitalization and development of end-stage renal disease were calculated using Cox proportional hazard models for the available outcomes. Adjusted models included the individual measures of RF-ACSA, e1-RM and ISWT as well as the potential confounders of age, gender and EPI eGFR. The proportional hazards assumption was tested using log–log survival plots, observed Kaplan–Meier survival curves versus Cox predicted curves and Schoenfeld residuals. All statistical analysis was performed using Stata 15.0, with p < .05 considered statistically significant.

3 | RESULTS

3.1 | Cohort characteristics

In total, 89 patients were included in the analysis, 38 from cohort 1 and 51 from cohort 2. The mean age of the entire cohort was 62.8 ± 11.0 years (with only 3 patients in cohort 2 aged between 18–40 years) and 45% were female. The mean eGFR was 23.9 ± 8.4 ml/min/1.73 m², with 25% of patients falling within stage 3b (n = 22), 67% within stage 4 (n = 60) and 8% within stage 5 (n = 7), but not yet requiring dialysis. These small numbers prevented further sub-group analysis. The mean follow-up time was 3.3 ± 1.8 years. There was no loss to follow-up. Full patient characteristics can be found in Table 1.

3.2 | Associations with all-cause mortality

Results from Cox proportional hazard models can be found in Table 2 and Figures 1 and 2. 16 patients (18% of the total cohort) died during the follow-up period. The strongest predictor of death in this cohort was age (HR 1.16, 95% CI 1.08–1.25, p < .001). Model 1 showed every 1 cm² increase in RF-ACSA was associated with a reduced risk of death by approximately 38% (HR 0.62, 95% CI 0.44–0.87, p = .006), an association that strengthened when muscle size was corrected for body surface area. An improved performance in the ISWT by 10 m was also significantly associated with a reduced risk of death by approximately 3% (HR 0.97, 95% CI 0.94–1.00, p = .04). There was an association seen between strength and mortality (HR 0.95, 95% CI 0.89–1.01, p = .09) whereby a 1 kg increase in maximum strength reduced mortality risk by 5%, but this was not significant. These associations were no longer observed when adjusting for confounding variables (Model 2).
TABLE 1 Patient characteristics of the total cohort

| Characteristics                  | Mean/n    | SD/%     |
|----------------------------------|-----------|----------|
| n                                | 89        |          |
| Age (years)                      | 62.8      | 11.0     |
| Female (n)                       | 40        | 44.9%    |
| EPI eGFR (ml/min/1.73 m²)        | 23.9      | 8.4      |
| Median EPI eGFR (ml/min/1.73 m²) | 23.1      | 18.0–29.6|
| Ethnicity (n)                    | 66        | 74.2%    |
| White British (n)                | 20        | 22.5%    |
| South Asian (n)                  | 2         | 2.2%     |
| Black Caribbean (n)              | 1         | 1.1%     |
| Other                            |           |          |
| Median PCR                       | 127.0     | 42.9–242.6|
| Hypertension (n)                 | 55        | 61.8%    |
| Diabetes mellitus (n)            | 22        | 24.7%    |
| Cardiovascular disease (n)       | 20        | 22.5%    |
| Cause of chronic kidney disease  |           |          |
| Glomerulonephritis               | 22        | 23.9%    |
| Interstitial nephritis           | 7         | 7.6%     |
| Cardiovascular disease           | 6         | 6.5%     |
| Polycystic kidney disease        | 6         | 6.5%     |
| Diabetic nephropathy             | 5         | 5.4%     |
| Other                            | 4         | 4.4%     |
| Unknown aetiology                | 39        | 43.8%    |
| Physical function assessment     |           |          |
| ISWT (m)                         | 375       | 193      |
| RF-ACSA (cm²)                    | 7.2       | 2.6      |
| RF-ACSA index (cm²/m²)           | 2.6       | 0.8      |
| e-1RM (kg)                       | 47.0      | 21.7     |
| Outcomes                         |           |          |
| Follow-up (years)                | 3.3       | 1.8      |
| Median follow-up (years)         | 2.8       | 2.0–4.1 |
| Deaths (n)                       | 16        | 18.0%    |
| ESRD (n)                         | 21        | 23.6%    |
| Hospitalization (n)              | 51        | 51.7%    |

Note: Data for categorical variables are presented as n and percentage, and data for continuous variables are presented as mean ± standard deviation unless otherwise stated.

Abbreviations: e-1RM, estimated one-repetition maximum; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; ISWT, incremental shuttle walk test; PCR, protein/creatinine ratio; RF-CSA, rectus femoris cross-sectional area.

3.3 Associations with ESRD and hospitalization rates

Within the follow-up period, 21 patients (24% of the total cohort) reached ESRD. The strongest predictor of ESRD was level of renal function at study consent (HR 0.90, 95% CI 0.85–0.96, p = .001). Other factors that showed an association with ESRD were age (HR 0.96, 95% CI 0.92–1.00, p = .05), presence of cardiovascular disease (HR 0.14, 95% CI 0.02–1.05, p = .05) and hypertension (HR 2.74, 95% CI 0.92–8.2, p = .07).

Neither model showed any associations between muscle size (p = .4), strength (p = .1) or exercise capacity (p = .3; Table 3) and the development of ESRD. The rate of unplanned hospital admissions within this cohort was relatively high, 51 patients (57%) had an unscheduled admission within the follow-up period. There were also no associations between muscle size (p = .2), strength (p = .4) or exercise capacity (p = .5) and time to first admission and either before or after adjustment for confounders (Table 3).

3.4 Association with clinical data

A small, but significant association was seen between age and RF-ACSA index (rho = −0.47; p < .001), and ISWT performance (rho = −0.44, p < .001). A significant association was seen between RF-ACSA index and ISWT performance (rho = 0.40; p < .001) and e-1RM (rho = 0.55; p < .001). No associations were seen between strength and any of the clinical data, or between PCR or eGFR and any measure of physical function (Table 3).

4 DISCUSSION

The aim of the current study was to determine whether quadriceps muscle size, strength or exercise capacity was associated with patient outcomes defined as all-cause mortality, development of ESRD and unscheduled hospital admissions. The results presented here demonstrate that when considered alone, reduced quadriceps size and exercise capacity are both associated with higher mortality rates in patients with CKD stages 3b-5; however, this association is no longer present once adjustments for age, gender and eGFR were made. This suggests that whilst muscle size and exercise capacity may be important contributors to mortality, they are not the predominant factors. These data did show that muscle size and exercise capacity have a profound relationship with age, as would be expected.

Previous evidence suggests that a strong relationship exists between the degree of muscle mass and mortality in dialysis patients (Carrero et al., 2008; Desmeules et al., 2004; Dong et al., 2008; Isoyama et al., 2014), with fewer studies investigating this relationship in patients not yet requiring renal replacement therapy. These earlier stage patients make up a significant proportion of the CKD population and for whom there may be an opportunity for early intervention. Recently, Androga and colleagues (Androga, Sharma, Amodu, & Abramowitz, 2017) have shown in an adjusted analysis, that sarcopenia was associated with increased mortality in predialysis CKD patients, but that this relationship was modified by the presence of obesity. Two studies using urinary creatinine as an approximate of muscle mass have reported an association between a low urinary creatinine level and reduced patient survival in an
adjusted analysis, but questions remain over the validity of using this to accurately predict muscle mass in this population (Di Micco et al., 2013; Wilson et al., 2014). Pereira and colleagues (Pereira et al., 2015) demonstrated that sarcopenia was an independent predictor of mortality in an adjusted model with sarcopenic patients exhibiting a three-fold greater risk of mortality than patients with a greater muscle mass.

However, not all studies report such an association. Navaneethan and colleagues reported an association between lean body mass, measured by DXA and mortality in non-CKD but not CKD patients (Navaneethan et al., 2014). Our data suggest a greater quadriceps cross-sectional area is associated with an increased likelihood of survival, but only when considered alone. We observed that every 1 cm² increase in RF-ACSA conferred a 38% reduction in mortality risk. To put this into context, we have recently reported 12 weeks of combined aerobic and resistance exercise resulted in mean increase in RF-ACSA of 0.7 cm² with a maximum increase of 2.0 cm² observed (Watson et al., 2018). Following adjusted analysis, the magnitude of risk associated with low muscle mass was still large (18% increase in mortality for every 1 cm² reduction in muscle size), albeit not significant. This suggests that in these patients, other factors, such as age, are stronger predictors of mortality, but nevertheless, muscle size may still be an important target for early intervention to reduce mortality in CKD.

### TABLE 2
Unadjusted and adjusted hazard ratios and confidence intervals for the development of ESRD, time to first unscheduled hospitalization and all-cause mortality in relation in muscle size (RF-ACSA, RF-ACSA index), muscular strength (e-1RM) and exercise capacity (ISWT) per unit of measurement

|                      | Model 1: Unadjusted analysis | Model 2: Adjusted analysis |
|----------------------|------------------------------|----------------------------|
|                      | HR (95% CI)                  | p Value                    | HR (95% CI)                  | p Value |
| Development of ESRD  |                              |                            |                            |         |
| RF-ACSA (per cm²)    | 0.92 (0.76–1.10)             | .4                         | 0.90 (0.71–1.14)             | .4      |
| RF-ACSA index (per cm²/m²) | 0.81 (0.44–1.50) | .5                         | 0.66 (0.29–1.48)             | .3      |
| e-1RM (per kg)       | 0.98 (0.95–1.00)             | .1                         | 0.98 (0.95–1.02)             | .4      |
| ISWT (per 10 m)      | 1.01 (0.99–1.03)             | .3                         | 1.02 (1.02–1.05)             | .1      |
| Time to first hospitalization |                   |                            |                            |         |
| RF-ACSA (per cm²)    | 0.92 (0.82–1.05)             | .2                         | 0.92 (0.79–1.08)             | .3      |
| RF-ACSA index (per cm²/m²) | 0.71 (0.47–1.07) | .1                         | 0.75 (0.46–1.23)             | .3      |
| e-1RM (per kg)       | 0.99 (0.98–1.01)             | .4                         | 0.99 (0.97–1.01)             | .2      |
| ISWT (per 10 m)      | 1.00 (0.98–1.01)             | .5                         | 0.99 (0.98–1.01)             | .6      |
| All-cause mortality  |                              |                            |                            |         |
| RF-ACSA (per cm²)    | 0.62 (0.44–0.87)             | .006†                      | 0.82 (0.56–1.20)             | .3      |
| RF-ACSA index (per cm²/m²) | 0.15 (0.05–0.45) | .001†                      | 0.48 (0.15–1.55)             | .2      |
| e-1RM (per kg)       | 0.95 (0.89–1.01)             | .09                        | 0.96 (0.89–1.04)             | .3      |
| ISWT (per 10 m)      | 0.97 (0.94–1.00)             | .04†                       | 1.00 (0.99–1.00)             | .8      |

Abbreviations: 95% CI, 95% confidence interval; e-1RM, estimated one-repetition maximum; HR, hazard ratio; ISWT, incremental shuttle walk test; Model 2: adjusted multivariable analysis adjusted for age, gender and EPI eGFR; RF-ACSA, rectus femoris anatomical cross-sectional area. Model 1: unadjusted analysis.

* Denotes p < .05.
† Denotes p < .001.
previously demonstrated that patients exhibited a 32 m and 28 m improvement ISWT performance following 12 weeks of combined exercise and aerobic-only exercise, respectively (Watson et al., 2018), suggesting that exercise interventions may beneficially impact upon patient outcome. However, this association also disappeared following adjusted analysis, suggesting that while distance walked during this test is a marker of increased mortality risk, there are other factors to consider. Associations between exercise capacity and mortality have been made before. Roshanravan and colleagues (Roshanravan et al., 2013) previously observed in a fully adjusted analysis every 0.1 m/s decrement in gait speed was associated with a 26% increase in mortality risk and for every second longer patients took to complete the “timed-up-and-go” assessment there was an increased risk of 8% in CKD patients’ stages 2–4. Recently Greenwood and colleagues reported an improvement of 50 m in the ISWT was associated with a 40% reduction in the risk of morbidity and mortality (Greenwood et al., 2019).

The relationship between strength and mortality has been investigated previously, but the results are conflicting depending upon patients studied and the method by which muscle strength was assessed, which was largely by handgrip strength. Interestingly, Isoyama and colleagues (Isoyama et al., 2014) found that the association between muscular strength and mortality was stronger than that for muscle mass. Unlike these previous studies, we have measured lower extremity strength. To our knowledge, the relationship between lower extremity strength and mortality has not been investigated previously in CKD. We did not include healthy participants in our analysis, so are unable to comment whether the lack of an observation of a relationship between strength and mortality can be explained by a lack of a decrement of strength in patients at this stage of CKD. This would be an important comparison to make.

This study is limited by a relatively small sample size, meaning it may be underpowered to detect more complex relationships in multivariate analyses. The relationships we have observed here were only seen in unadjusted analysis and are therefore not as strong as those observed in previous studies where relationships have been seen in adjusted analysis. It might be that relationships only emerge when patients are stratified into low and adequate muscle size for example, as previously observed in chronic obstructive pulmonary disease (COPD) (Greening et al., 2015). Diabetes is highly prevalent in CKD and was confirmed in 25% of our cohort. Diabetes is associated with metabolic derangement, which is likely to also impact upon the outcomes we have defined here. Unfortunately, our sample size has prevented us from performing these sub-group analyses, but they remain an important future research question. Our study is also limited by a lack of ethnic diversity. The majority of patients in our cohort were White British which may limit the results’ generalizability.

In conclusion, we have shown that in CKD patients’ stages 3b-5 not requiring dialysis, muscle size and exercise capacity are associated with mortality when considered alone, but in adjusted analysis this relationship was not present. Given our small sample size, we believe the investigation into the role of muscle size and exercise capacity on clinical outcomes in larger cohorts of non-ESRD patients is warranted. Previous studies in dialysis patients clearly show a relationship between muscle size, strength and exercise capacity with patient outcomes and it is therefore reasonable to consider early intervention in a predialysis population to reduce the effects of CKD-associated muscle wasting and decrements in physical functioning.

**FIGURE 2** Kaplan–Meier survival curve for mortality and performance in the ISWT. ISWT, incremental shuttle walk test

**TABLE 3** Spearman’s correlation coefficient to test the association between measures of muscle size corrected for body surface area (RF-ACSA/height²), strength (e-1RM) and exercise capacity (ISWT) with EPI eGFR, age and PCR

| Test       | Age | eGFR | PCR | RF-ACSA index |
|------------|-----|------|-----|---------------|
|            | rho | p    | rho | p      | rho | p     |
| RF-ACSA index | -0.47 | .001 | 0.22 | .5     | -0.11 | .44  |
| e-1RM       | -0.22 | .07  | 0.09 | .5     | -0.25 | .1   |
| ISWT        | -0.44 | .001 | 0.1  | .3     | -0.03 | .8   |

Abbreviations: e-1RM, estimated one-repetition maximum; eGFR, estimated glomerular filtration rate; ISWT, incremental shuttle walk test; PCR, protein/creatinine ratio; RF-ACSA, rectus femoris anatomical cross-sectional area.

Denotes p < .001.
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CONFLICT OF INTEREST

The authors state there are no financial conflicts of interest.

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