Aortic stiffness and aortic-brachial stiffness mismatch as markers of renal dysfunction in hypertension

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ABSTRACT

Purpose: The dismal combination of hypertension and chronic kidney disease potentiates both cardiovascular disease and loss of renal function. Research points to the importance of arterial and left ventricular stiffening in this process but few studies have compared aspects of central and peripheral hemodynamics in relation to renal function in hypertension.

Materials and methods: We investigated 107 hypertensive individuals with renal function ranging from normal to severe dysfunction with pulse wave analysis to obtain central blood pressures (BP), augmentation index, carotid-femoral and carotid-radial pulse wave velocity (cfPWV, crPWV), aortic-to-brachial stiffness mismatch (cfPWV/crPWV), endothelial function by forearm flow-mediated vasodilation and myocardial microvascular function by subendocardial viability ratio, and indices of left ventricular structure (left ventricular mass index and relative wall thickness, RWT) and diastolic function (left atrial volume index, E/A, and E/e).

Results: Mean age was 58 years, BP 149/87 mm Hg, 9% had cardiovascular disease, and 31% > 0.001, E/A (r = 0.27, p = 0.01) were related to eGFR in multivariate analyses. Remaining markers of hypertensive heart disease and measures of microvascular function were not related to eGFR.

Conclusion: Increased aortic stiffness and aortic-to-brachial stiffness mismatch are independently related to reduced eGFR in hypertensive patients, suggesting an important role for aortic stiffness in the evolution of hypertension-mediated renal dysfunction. Aortic stiffness and aortic-brachial stiffness mismatch may be useful early markers to find hypertensive patients at risk for decline in renal function.

Introduction

Increased blood pressure is the leading cause of cardiovascular morbidity and premature death, and hypertension is a major cause of chronic kidney disease (CKD) [1,2]. CKD is a condition with markedly increased cardiovascular risk, and the leading cause of death in patients with CKD is indeed cardiovascular disease [3]. Thus, the combination of hypertension and CKD is an alarming situation, which accelerates the progression of both cardiovascular morbidity and renal disease [3,4].

Evidence shows the importance of structural cardiac and vascular alterations with arterial and left ventricular remodelling and stiffening in patients with CKD-related vascular disease [5–8]. Studies in individuals with estimated glomerular filtration rate (eGFR) > 60 ml/min × 1.73 m² and in patients with CKD suggest that aortic stiffness assessed by pulse pressure or by pulse wave velocity (PWV) derived from pulse wave analysis, can predict a decline in renal function, and progression to end stage renal disease and death [5,9–12]. However, an increased aortic stiffness is apparently not accompanied by an increased peripheral arterial stiffness in CKD patients, since previous studies have shown a decrease in carotid-to-radial PWV [13]. This aortic-to peripheral
stiffness mismatch has gained interest as a potential mediator in the development of renal injury [14–16]. This said, there are few studies in hypertensive people with latent or mild CKD comparing aortic stiffness and aortic-brachial stiffness mismatch, myocardial function, and endothelial function in relation to renal function. Thus, we still lack tools to single out hypertensive individuals prone to develop renal dysfunction, which would facilitate preventive efforts.

The feasibility of the assessment of arterial stiffness to reclassify subjects, particularly at intermediate risk of future cardiovascular disease, has been acknowledged [17]. While measures of arterial function are sparsely used in the clinical setting today, as they have been considered time-consuming, operator-dependent, and expensive, the technical development is rapid and these issues are underway to be resolved. Furthermore, the different impacts of antihypertensive medication on arterial stiffness beyond that of blood pressure-lowering have gained interest and are an important part of personalised antihypertensive treatment [18–20]. Thus, this study aimed to provide simultaneously obtained information about several markers of cardiac and vascular function, and to assess their independent associations to renal function. Accordingly, we performed detailed investigations of cardiac structure and function, aortic and peripheral arterial stiffness, and endothelial function in a hypertensive population with renal function ranging from normal to CKD stage 4.

**Materials and methods**

**Study design and setting**

This patient cohort originates from two previously published randomised interventional trials, the Doxazosin-Ramipril Study (DoRa) [21] and the Sympathetic Activation and Inflammation in Moderate Kidney Failure and in Diabetic Nephropathy: Disease Modification with Vitamin-D Receptor Activation – the SOLID Trial (SOLID) [22]. These studies included men and women >18 years, with either hypertension and eGFR >60 ml/min × 1.73 m² (DoRa), or CKD patients with hypertension and eGFR 59–15 ml/min × 1.73 m² (SOLID). Patients were eligible with a mean of 2 or more measurements >140 mm Hg systolic and/or >90 mm Hg diastolic by standard techniques in the clinical setting, or ongoing antihypertensive medication. The primary aims of DoRa were to evaluate the effects of treatment with ramipril or doxazosin on endothelial function and haemostasis [21,23] and for SOLID to examine the effects of paricalcitol on sympathetic activation, endothelial function, arterial stiffness, and inflammatory markers [22]. For the current post hoc analysis only baseline measurements were used. Both studies were approved of by the appropriate Ethics committee, performed in accordance with the Declaration of Helsinki, and all patients provided oral and written informed consent. Both studies are registered at clinicaltrials.gov (NCT02901977 and NCT01204528).

**Procedures**

All investigations were performed at the Cardiovascular research laboratory, within the Clinical research centre, Danderyd University Hospital, Stockholm (Sweden). The procedures were performed in the supine position in a quiet room, after overnight fasting and without the intake of morning medicines. For details, see elsewhere [21,22].

Brachial blood pressure was obtained by an oscillometric device (OMRON 705IT, OMRON Healthcare Co Ltd, Kyoto, Japan) on the right arm with an appropriately sized cuff as a mean of 3 readings. Mean arterial pressure (MAP) was calculated as DBP + 1/3 (SBP–DBP). Pulse wave analysis by applanation tonometry (Millar Instruments, Houston, TX, USA) assessed by the integral software of a SphygmoCor device (AtCor Pty, West Ryde, NSW, Australia) was used to obtain an averaged peripheral and central waveform, from which carotid-radial and carotid-femoral PWV (crPWV and cfPWV, respectively), central systolic and diastolic blood pressure (cSBP and cDBP), and pulse wave augmentation index (Alx) were calculated according to recommendations [24], as described previously [21,22]. Furthermore, cfPWV/crPWV was calculated, as a marker of aortic-brachial stiffness mismatch [14].

Endothelium-dependent flow mediated vasodilation (FMD) was assessed by forearm ischaemia induced reactive hyperaemia and measured as relative change in brachial artery diameter from rest by a Vivid 7 Dimension ultrasound device (GE Medical System, Horten, Norway) according to recommendations [25], as described previously [21,22]. Subendocardial viability ratio (SEVR) was assessed as a marker of coronary microvascular function and derived from a general transfer function using pulse wave analysis, as described elsewhere [26] SEVR is a non-invasive estimate of myocardial oxygen supply and demand, calculated as the ratio (aortic diastolic pressure × time integral)/(aortic systolic blood pressure × time integral), which is taken to represent
subendocardial perfusion capacity relative to myocardial contraction, i.e. myocardial perfusion relative to cardiac workload [27,28].

Transthoracic echocardiography and conventional pulsed Doppler echocardiography (Vivid 7 Dimension, GE Medical System, Horten, Norway) was performed according to current recommendations [29,30], as described elsewhere [31]. Left chamber dimensions were used to calculate left atrial volume and left ventricular mass, both indexed to body surface area to express left atrial volume index (LAVI) and left ventricular mass index (LVMI). Left ventricular relative wall thickness (RWT) was calculated as (interventricular septum thickness + posterior wall thickness)/left ventricular end-diastolic diameter. Left ventricular diastolic function was assessed using E/A, E/e, and LAVI.

Body mass index was calculated as weight/height². Routine biochemistry was analysed by standard procedures from fasting blood samples. eGFR was calculated by the CKD-EPI formula. Low density lipoprotein cholesterol (LDL) values were calculated by the Friedewald formula as total cholesterol – plasma HDL – (0.45 × fasting plasma triglycerides).

**Statistical analyses**

Data are presented as mean values ± SD or n and proportions (percentage), as appropriate. Analysis of variance (ANOVA) was used to compare strata of eGFR, grouped as >90 ml/min × 1.73 m², 89–60 ml/min × 1.73 m², 59–30 ml/min × 1.73 m², and <30 ml/min × 1.73 m². Bivariate correlations were used to investigate the relationship between circulatory variables and eGFR. Bivariate correlations between stiffness indices and MAP were also analysed, to further clarify the roles of each in relation to renal function. In case of correlations with eGFR and p < 0.1, multivariate linear regression analyses were performed, including age, sex, height, heart rate, MAP, previous cardiovascular disease (myocardial infarction, heart failure, atrial fibrillation, transient ischaemic attack, haemorrhagic or ischaemic stroke), and antihypertensive medication as covariates. Separate models with SBP, DBP, and pulse pressure instead of MAP were also performed. The significance level was set to a two-sided probability (p) value of <0.05. SPSS versions 25 and 27 (IBM Corp. IBM SPSS Statistics for Windows. Armonk, NY), were used for the analyses.

**Results**

**General**

The baseline characteristics of the 107 participants are presented in Table 1. Renal function ranged from eGFR 130 to 21 ml/min × 1.73 m². Antihypertensive medication was present in 33 (31%), almost exclusively in patients with eGFR ≤59 ml/min × 1.73 m². Concomitant cardiovascular disease was present in only 10 patients (9%); however, it increased with decline in renal function.

**Pulse wave analysis**

Central blood pressures and indices of aortic and arterial stiffness according to the stage of renal dysfunction are presented in Table 1. Renal function ranged from eGFR 130 to 21 ml/min × 1.73 m². Antihypertensive medication was present in 33 (31%), almost exclusively in patients with eGFR ≤59 ml/min × 1.73 m². Concomitant cardiovascular disease was present in only 10 patients (9%); however, it increased with decline in renal function.

### Table 1. Baseline characteristics according to eGFR group.

|                          | All     | eGFR ≥ 90 ml/min × 1.73 m² | eGFR 89–60 ml/min × 1.73 m² | eGFR 59–30 ml/min × 1.73 m² | eGFR < 30 ml/min × 1.73 m² |
|--------------------------|---------|---------------------------|---------------------------|---------------------------|---------------------------|
| n                        | 107     | 39                        | 31                        | 32                        | 4                         |
| Age, years               | 58 ± 13 | 51 ± 13                   | 59 ± 9.6                  | 65 ± 11.1                 | 74 ± 1.7                  |
| Male sex                 | 73      | 30                        | 14                        | 24                        | 75                        |
| Heigt, cm                | 175.5 ± 8.8 | 156–196                  | 172 ± 8.3                 | 178 ± 9.4                 | 176 ± 9.6                 |
| Body mass index, kg/m²   | 26.8 ± 4.3 | 19–49                    | 27.1 ± 5.7                | 26.4 ± 2.7                | 27.5 ± 5.1                |
| Current smoking          | 6       | 1                         | 2                         | 6.5                       | 7                         |
| CVD                      | 10      | 9                         | 1                         | 7                         | 21                        |
| SBP, mm Hg               | 149.1 ± 16.6 | 119–205                  | 154 ± 14.9                | 143 ± 18.7                | 168 ± 18.1                |
| DBP, mm Hg               | 87.3 ± 10.1 | 67–135                   | 89 ± 11.6                 | 81 ± 6.8                  | 91 ± 2.5                  |
| Heart rate, bpm          | 58.3 ± 7.4 | 43–81                    | 59 ± 6.8                  | 57 ± 7.3                  | 65 ± 15.3                 |
| On going anti-hypotenive | 33      | 31                        | 2                         | 6.5                       | 27                        |
| medication               | ACEI or ARB treatment | 29                        | 2                         | 3                         | 25                        | 78.1 | 3 | 75 |
| eGFR, ml/min × 1.73 m²   | 3.7 ± 24.7 | 21–130                  | 100 ± 9.4                 | 85.8 ± 25                | 41.9 ± 8.8               |
| ACR, mg/mmol             | 13.7 ± 38.8 | 0.2–282.5              | 21 ± 5.6                  | 26 ± 7.5                  | 50.0 ± 5.0               |
| Glucose, mmol/l          | 5.5 ± 6.4 | 4.4–7.5                  | 5.5 ± 0.6                 | 5.5 ± 0.6                 | 6.0 ± 1.1               |
| Total cholesterol, mmol/l| 5.1 ± 1.1 | 0.8–9.6                  | 5.6 ± 1.2                 | 4.6 ± 1.1                 | 5.3 ± 1.2               |
| LDL cholesterol, mmol/l  | 3.3 ± 0.9 | 0.8–6.9                  | 3.6 ± 1.1                 | 2.9 ± 0.8                 | 3.0 ± 1.0               |

Mean values ± SD and range, or n and %; as appropriate. CVD, cardiovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker, ACR, albumin creatinine ratio; LDL, low density lipoprotein.
Echocardiographic indices did not relate to eGFR group (Table 2). Accordingly, eGFR (\(r = 0.40, p < 0.001\)) and cfPWV were independently related to eGFR (\(r = 0.39, p < 0.001\)) related inversely to eGFR, whereas cfPWV did not relate to renal function (\(r = 0.07, p = 0.52\)) (Figures 1–3). Furthermore, cfPWV related to MAP (\(r = 0.33 p < 0.001\)), whereas cfPWV and cfPWV/crPWV did not (\(r = 0.19, p = 0.07, \) and \(r = 0.06, p = 0.59\), respectively). Subsequent multivariate regression analyses confirmed cfPWV and cfPWV/crPWV to be independently correlated with eGFR (\(r = -0.20, p = 0.002, \) and \(r = -0.16, p = 0.01\), respectively). cfPWV was independently related to MAP (\(r = 0.29, p = 0.005\)), whereas the trend for a relation between cfPWV and MAP was attenuated by accounting for the confounding influence of antihypertensive treatment (\(r = 0.19, p = 0.13\)). Multivariate regression analyses where MAP as covariate was replaced by SBP and DBP, or pulse pressure showed similar results (cfPWV with SBP and DBP instead of MAP: \(r = -0.18, p = 0.004\); cfPWV with pulse pressure instead of MAP: \(r = -0.19, p = 0.003\); cfPWV/crPWV with SBP and DBP instead of MAP: \(r = -0.14 p = 0.02\); cfPWV/crPWV with pulse pressure instead of MAP: \(r = -0.15, p = 0.02\)).

Table 2. Circulatory measurements according to the eGFR group.

| eGFR ≥ 90 ml/min × 1.73 m² | eGFR 89–60 ml/min × 1.73 m² | eGFR 59–30 ml/min × 1.73 m² | eGFR < 30 ml/min × 1.73 m² |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| All                         | 107                         | 39                          | 31                          | 32                          | 4                           |
| Central blood pressure      |                             |                             |                             |                             |
| Central SBP, mm Hg          | 140 ± 19                    | 106–200                     | 137 ± 17                    | 107–181                     | 150 ± 14                    | 122–200                     | 134 ± 21                    | 110–189                     | 153 ± 25                    | 138–182                     | ns                           |
| Central DBP, mm Hg          | 88 ± 10                     | 69–133                      | 90 ± 12                     | 69–132                      | 92 ± 8                      | 74–105                      | 82 ± 7                      | 71–98                       | 94 ± 2                       | 92–96                       | 0.04                         |
| Central PP, mm Hg           | 52 ± 14.8                   | 29–99                       | 47 ± 10.8                   | 29–79                       | 58 ± 13.4                   | 32–97                       | 52 ± 17.9                   | 31–99                       | 59 ± 23.0                   | 45–86                       | 0.08                         |
| Pulse wave analysis         |                             |                             |                             |                             |
| cfPWV, m/s                  | 9.4 ± 2.8                   | 4.2–24.5                    | 8.6 ± 1.5                   | 4.2–11.2                    | 9.0 ± 2.5                   | 6.2–15                      | 10.0 ± 2.6                  | 5.5–15.3                    | 14.3 ± 7.3                  | 7.1–24.5                    | <0.001                       |
| crPWV, m/s                  | 9.0 ± 1.2                   | 5.5–11.4                    | 9.0 ± 1.3                   | 5.5–11.4                    | 9.2 ± 1.2                   | 6.8–11.3                    | 8.7 ± 1.1                   | 5.8–10.7                    | 9.7 ± 1.3                   | 8.4–11.1                    | ns                           |
| cfPWV/crPWV                 | 1.0 ± 0.3                   | 0.59–2.8                    | 0.9 ± 0.1                   | 0.7–1.3                     | 1.0 ± 0.3                   | 0.6–1.6                     | 1.2 ± 0.3                   | 0.6–1.6                     | 1.5 ± 0.9                   | 0.9–2.8                     | <0.001                       |
| Aix, mm Hg                  | 30.3 ± 11.5                 | –7.5–54                     | 27.1 ± 13.6                 | –7.5–54                     | 35.5 ± 8.0                  | 15.5–49.5                   | 29.7 ± 10.7                 | 8.0–48.5                    | 28.7 ± 7.6                  | 22.0–37.0                    | ns                           |
| Mean values ± SD, and range; p by bivariate correlation. SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; cfPWV, carotid to femoral pulse wave velocity; crPWV, carotid to radial PWV; Aix, augmentation index; FMD, postischemic forearm flow mediated vasodilation; SEVR, subendocardial viability ratio; LVMI, left ventricular mass index; LAVI, left atrial volume index.

Figure 1. Relations between carotid-femoral pulse wave velocity (cfPWV) and eGFR. The solid regression line shows all 107 patients: bivariate correlation (only four cases had an eGFR ≤ 30 ml/min × 1.73 m²), slope \(r = 0.40, p < 0.001; \) multivariate correlation slope = −0.19, \(R = 0.88, r = -0.20, p = 0.002.\) Broken line shows 74 patients without antihypertensive medication (only four cases had an eGFR ≤ 60 ml/min × 1.73 m²), slope = −2.32, \(R = 0.58, r = -0.28 p = 0.08.\) The broken-dotted line shows 33 patients on antihypertensive medication (only two cases had a eGFR > 60 ml/min × 1.73 m²), slope = −2.10, \(R = 0.63 r = -0.60, p = 0.003.\)
Endothelial function and myocardial microvascular function

Endothelial function (assessed by FMD) and myocardial microvascular function (assessed by SEVR) did not relate to renal function, neither by analyses by eGFR group (data not shown) nor by bivariate regression analyses (Table 2).

Echocardiographic measures

Echocardiographic indices for left ventricular structure and diastolic function according to eGFR group are shown in Table 2. RWT and E/€ increased with groups having lower eGFR. In bivariate regression analyses, RWT was inversely related to eGFR ($r = -0.34$, $p = 0.001$), whereas E/€ was inversely related and E/A directly related to eGFR ($r = -0.39$, $p < 0.001$; and $r = 0.27$, $p = 0.01$, respectively). However, none of these findings were retained significant in the multivariate regression analyses. No other echocardiographic indices of LV structure or diastolic function examined, related to renal function.

Discussion

This cross-sectional study in 107 hypertensive patients with renal function ranging from normal to severe dysfunction demonstrates independent associations between aortic stiffness and aortic-brachial stiffness mismatch, and renal function. However, assessments of forearm endothelial function, cardiac structure and function, and myocardial microvascular function failed to reveal similar associations to renal function.

Our finding of an association between increased cfPWV and impaired renal function is in agreement with reports of an increased aortic stiffness related to a decline in eGFR and to renal microvascular damage with microalbuminuria in hypertensive patients [5,32]. Aortic stiffness is related to blood pressure. However, aortic stiffness provides additional independent information to improve the prediction of CV events [33], and aortic stiffness assessed by cfPWV increases before blood pressure in people with incident hypertension [34]. These and other findings [35,36] suggest that aortic stiffness may serve as an early marker for people at increased risk to develop hypertension-mediated organ damage (such as an impaired renal function) and untoward prognosis.
Patients with CKD develop an aggressive structural vascular disease with inflammation and vascular calcification, with subsequent arterial stiffening [6,37,38]. A greater aortic (cfPWV), as compared to brachial (crPWV) stiffness indicates a mismatch and loss of protection in the periphery for the propagating pulse wave, with increases in renal microvascular flow which induces end-organ damage [39]. This seems to be especially important in CKD [14,40], where pulse wave propagation has been shown of importance to the microcirculation of the kidney [15,41]. In our study, increased aortic stiffness (cfPWV) was independently related to impaired renal function, whereas peripheral stiffness (crPWV) did not show such a relation. Furthermore, crPWV was independently related to blood pressure (MAP), whereas cfPWV and the cfPWV/crPWV ratio were not, in line with previous findings [42]. We suggest that the impact of cfPWV on renal function is beyond central arterial forward wave pressures. A separation analysis of the central arterial waveform would help clarify this [43–45]. Unfortunately the data available did not allow us to perform such an analysis. Thus, whether our findings are related to a pressure effect generated by forward travelling waves or because of a decrease in the impedance mismatch between central and peripheral arteries remains to be clarified.

Our results extend previous observations by revealing a relation of the aortic-to-brachial ratio to renal function independent of MAP, showing an increased stiffness mismatch in the CKD population. In addition, almost all patients with eGFR <60 ml/min × 1.73 m² were on antihypertensive medication (see Figures 1–3), indicating that such therapy has insufficient beneficial effect on aortic stiffness. Studies performed in people with normal renal function indicate that cfPWV, pulse pressure and carotid artery stiffness can predict future decline of renal function [5,12]. Taken together, these and our results imply a central role for aortic stiffness and aortic-to-brachial stiffness mismatch in renal dysfunction, and suggest that these measures may be useful early markers for future risk of CKD in hypertensive patients with no overt renal dysfunction.

We did not find relations between cBP, cPP or AIx, and eGFR. Although these measures seem to predict future CV events in late-stage CKD [46,47], the impact on the decline in renal function in earlier stages of renal dysfunction is inconsistent. However, few of our patients with eGFR >60 ml/min × 1.73 m² were on antihypertensive medications, while nearly all with eGFR <60 ml/min × 1.73 m² were treated. This may, at least in part, confound our findings and explain why no independent relations for these markers to eGFR were observed.

Endothelial function (here assessed by FMD) did not relate to eGFR in this study. This is in line with previous results, where endothelial dysfunction evaluated by FMD seems to be more related to comorbidity with CV disease in late-stage CKD than to declining kidney function [48–50]. These results, together with our findings, imply that endothelial function assessed by FMD is not as useful as measures of arterial stiffness to predict renal dysfunction. Neither did myocardial microvascular function (evaluated by SEVR) relate to renal function. SEVR is an established non-invasive marker of coronary flow reserve [27,28], relates to albuminuria in CKD patients [51,52] and predicts CV prognosis in moderate to late stage CKD [53,54]. However, coronary microvascular function may be more closely related to the development of atherosclerosis, while hypertension mediated changes in renal microvascular function may depend more on arteriosclerotic manifestations, which could contribute to our findings. In addition, there may be confounding influence by antihypertensive medications such as blockers of the renin-angiotensin system (with anti-inflammatory and nitric oxide releasing properties) on endothelial function measurements, as compared to indices of aortic stiffness such as PWV.

Finally, we found that indices of LV structural remodelling (RWT) and of diastolic dysfunction (E/e) related to decline in renal function. This is in agreement with observations in patients with manifest CKD, where LV structural changes and diastolic dysfunction predict CV events and negative renal outcome [7,55]. However, our results were not retained in multivariate analyses, suggesting possible confounding influence by e.g. blood pressure and concomitant medication.

Limitations

This was a cross-sectional study and prospective implications could not be assessed. The study sample was relatively small, and there were few subjects with severe renal dysfunction. There were also differences in antihypertensive treatment, with more medication as eGFR declined. However, statistical models were used to control for BP and ongoing treatment. Lastly, we only used standard echocardiographic measures, and more advanced techniques might have rendered other results.
Conclusions

Aortic stiffness and aortic-to-brachial stiffness mismatch are independently related to eGFR in hypertensive patients, suggesting an important role for aortic stiffness in the evolution of early hypertension mediated renal dysfunction. Furthermore, aortic stiffness remained associated with CKD even after risk factor management, while other measures of organ damage did not relate to CKD. Thus, compared to assessments of endothelial or microvascular function, or cardiac structure or function, aortic PWV may be an earlier and more specific measure for CKD. We suggest aortic stiffness and aortic-to-brachial stiffness mismatch to be potentially useful markers to identify hypertensive patients at risk for progressive decline in renal function, where preventive measures may be of particular value. Properly designed prospective studies are warranted.

Acknowledgements

We thank Ms. E. Andersson, J. Rasck and E. Wallén Nielsen for expert technical assistance.

Disclosure statement

KL declares advisory board honoraria from NovoNordisk and Bayer. JS declares speaker honoraria from AstraZeneca, Bayer, Boehringer-Ingelheim and NovoNordisk, and advisory board honoraria from AstraZeneca and NovoNordisk. TK declares research grants to Karolinska Institutet from Amgen, Medtronic, and ReCor Medical; all outside the submitted work. SJ declares speaker honoraria and advisory board honoraria from AstraZeneca, Astellas, ViforPharma, Baxter and Fresenius Medical Care. LD and AJ, have no conflicts of interest to report.

Funding

The DoRa study was funded by the Swedish Heart-Lung Foundation (20130467), Karolinska Institutet Research Foundations (2018-01758), and an unrestricted grant from Pfizer Inc. Abbvie (former Abbott) supported the SOLID study.

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