Reservoir Pressure Integral is Independently Associated with the Reduction in Renal 1 2 **Function in Older Adults** 3 4 **Authors:** Kunihiko Aizawa, ¹ Alun D Hughes, ² Francesco Casanova, ¹, Phillip E Gates, ¹ David M 5 Mawson, ¹ Kim M Gooding, ¹ Mark Gilchrist, ¹ Isabel Goncalves, ^{3,4} Jan Nilsson, ³ Faisel Khan, ⁵ 6 Helen M Colhoun, ⁶ Carlo Palombo, ⁷ Kim H Parker, ⁸ Angela C Shore. ¹ 7 8 9 **Affiliations:** 10 ¹Diabetes and Vascular Medicine Research Centre, NIHR Exeter Clinical Research Facility, University of Exeter Medical School, Exeter, UK. ²MRC unit for Lifelong Health & Ageing, 11 Institute of Cardiovascular Science, University College London, London, UK. ³Department of 12 Clinical Sciences, Lund University, Malmö, Sweden. ⁴Department of Cardiology, Skåne 13 University Hospital, Malmö, Sweden. 5 Division of Systems Medicine, University of Dundee, 14 Dundee, UK. ⁶Centre for Genomic and Experimental Medicine, University of Edinburgh, 15 Edinburgh, UK. ⁷Department of Surgical, Medical, Molecular and Critical Area Pathology, 16 University of Pisa, Pisa, Italy. ⁸Department of Bioengineering, Imperial College, London, UK. 17 18 19 **Short Title:** Reservoir-excess pressure analysis and kidney 20 21 **Word Count for Manuscript:** 5733 words 22 Word Count for Abstract: 238 words 23 Number of Figures: 3 figures 24 25 **Corresponding author:** 26 Kunihiko Aizawa, PhD 27 Diabetes and Vascular Medicine Research Centre 28 University of Exeter Medical School 29 NIHR Exeter Clinical Research Facility Barrack Road, Exeter 30 31 EX2 5AX, UK 32 +44 1392 403081 (TEL) 33 +44 1392 403027 (FAX) k.aizawa@exeter.ac.uk 34

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ABSTRACT:

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Background: Arterial haemodynamic parameters derived from reservoir-excess pressure analysis exhibit prognostic utility. Reservoir-excess pressure analysis may provide useful information about an influence of altered haemodynamics on target organ such as the kidneys. We determined whether the parameters derived from the reservoir-excess pressure analysis were associated with the reduction in estimated glomerular filtration rate (eGFR) in 542 older adults (69.4±7.9 yrs, 194 females) at baseline and after three years. Methods: Reservoir-excess pressure parameters including reservoir pressure integral (INTPR), excess pressure integral, systolic and diastolic rate constants were obtained by radial artery tonometry. Results: After three years, and in a group of 94 individuals (72.4±7.6 yrs, 26 females), there was an eGFR reduction of more than 5% per year (median reduction of 20.5% over three years). A multivariable logistic regression analysis revealed that higher baseline INTPR was independently associated with a smaller reduction in eGFR after accounting for conventional cardiovascular risk factors and study centres [odds ratio: 0.660 (95% confidence intervals, 0.494-0.883), p=0.005]. The association remained unchanged after further adjustments for potential confounders and baseline renal function [odds ratio: 0.528 (95% confidence intervals, 0.351-0.794), p=0.002]. No other reservoirexcess pressure parameters exhibited associations with the reduction in renal function. Conclusions: This study demonstrates that baseline INTPR was associated with the decline in renal function in older adults at 3-year follow-up, independently of conventional cardiovascular risk factors. This suggests that INTPR may play a role in the functional decline of the kidneys.

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Key Words: Aging; arterial stiffness; blood flow; blood pressure; kidney.

List of abbreviations and acronyms

BP, blood pressure; CKD, chronic kidney disease; DCL, the decline group; DRC, diastolic rate constant; eGFR, estimated glomerular filtration rate; INTPR, reservoir pressure integral; INTXSP, excess pressure integral; MAXPR, peak reservoir pressure; ND, the non-decline group; OR, odds ratio; SRC, systolic rate constant; SUMMIT-VIP, the SUrrogate markers for Micro- and Macrovascular hard endpoints for Innovative diabetes Tools-Vascular Imaging Prediction study.

INTRODUCTION:

The arterial blood pressure (BP) waveform provides valuable information about cardiovascular risk. The peak and trough on a BP waveform, for example, represent systolic and diastolic BP, respectively, which are well-recognised cardiovascular risk factors that have been utilised for risk stratification. Another example is pulse pressure and augmentation index, which are obtained from specific points on the BP waveform and are indicators of BP pulsatility and a pulsatility marker, respectively. Despite the proven usefulness of these BP parameters, there remains a greater residual cardiovascular risk associated with BP that is unaccounted for at present. This may be partly explained by the fact that these BP parameters are derived either from extreme points on the BP waveform or calculated from specific points on the BP waveform, rather than extracting information from the BP waveform as a whole.

Reservoir-excess pressure analysis conceptualises the BP waveform as the summation of 1) the reservoir pressure component that reflects the theoretical minimum hydraulic work

necessary to generate a given stroke volume, and 2) the excess pressure component that is an index of unnecessary work done by the left ventricle in each cardiac cycle. Reservoir-excess pressure analysis derives its parameters by directly extracting them from the BP waveform morphology. This is an advantage of this analysis over other BP parameters because subtle haemodynamic abnormalities, that are not apparent at specific points on the BP waveform, may be identified with the parameters of reservoir-excess pressure analysis. In this regard, the ability of reservoir-excess pressure parameters to predict cardiovascular events has been demonstrated independently of conventional cardiovascular risk factors including BP, 3-10 suggesting a clinical utility of the concept.

A reduction in renal function, expressed as a reduced estimated glomerular filtration rate (eGFR) in clinical practice, occurs with normal ageing, but the age-related loss of renal function is exacerbated by comorbidities such as hypertension and type 2 diabetes.

Progressive renal impairment leads to chronic kidney disease (CKD), a dire consequence of which is the progression to end-stage renal disease that requires dialysis and/or renal transplantation. Patients with CKD have a significantly higher risk for cardiovascular disease than appropriately matched controls.

Clinical care of people with CKD focuses on slowing the decline in renal function, aiming to delay/avoid the need for renal replacement therapy and reducing cardiovascular risk. Identification of those at highest risk of progressive renal disease and cardiovascular disease in this patient group remains an important and unmet clinical need. In this context, reservoir-excess pressure analysis may provide useful information about the influence of altered haemodynamics on target organs, in this case the kidneys, additionally to conventional risk factors like systolic and diastolic BP.

Specifically, because reservoir pressure corresponds to the instantaneous blood volume stored in large

arteries,¹⁴ and diastolic rate constant (DRC) represents the rate of reservoir pressure discharge, alterations in these parameters may be indicative of adverse renal haemodynamics. Therefore, we aimed to test the hypothesis that the parameters derived from reservoir-excess pressure analysis would predict the reduction in eGFR at 3-year follow-up in older adults.

METHODS:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Participants

This is a sub-study of the SUrrogate markers for Micro- and Macrovascular hard endpoints for Innovative diabetes Tools-Vascular Imaging Prediction (SUMMIT-VIP) study. Participants were older adults (n=542) recruited from Exeter, Dundee (both United Kingdom) and Malmö (Sweden) for the SUMMIT-VIP study, for whom raw radial pressure waveform data were available (Supplemental Figure S1). Participants were studied at baseline and at 3-year follow-up. The details of the main study including the criteria for inclusion/exclusion have been described elsewhere 15, 16 and a brief summary is included in the Supplemental Material (Supplemental Methods). Demographic and clinical characteristics data including physical and laboratory analyses were obtained based on the predefined main study protocol at each site. All study procedures were approved by UK National Research Ethics Service South West Committee, East of Scotland Research Ethics Service and the institutional ethics committee at the University of Lund, Sweden. Written informed consent was obtained from all participants.

Acquisition of radial pressure waveform and derivation of reservoir-excess pressure

parameters

The details of our radial pressure waveform acquisition method have been described elsewhere. ¹⁰ Briefly, the participants lay supine on an examining bed and rested for 10 min before the assessment. Right radial artery pressure waveforms were recorded with a high-fidelity micromanometer attached to a SphygmoCor system (Version 8.2, AtCor Medical Pty Ltd, West Ryde, Australia) over 10 sec. Dedicated inbuilt software then processed acquired waveforms to calculate an ensemble-averaged radial pressure waveform calibrated by brachial systolic and diastolic BP (as per the manufacturer's recommendation) using a validated semi-automated oscillometric device (Omron M6, Hoofddorp, Netherlands).

The ensemble-averaged radial pressure waveform was then used to calculate reservoir-excess pressure parameters based on the pressure-alone approach. A review of the method that includes its theoretical basis and validation has been published recently. In the reservoir-excess pressure analysis, the measured pressure waveform can be separated into 1) a reservoir pressure component which varies in magnitude through changes in the resistance to outflow from the reservoir, the reservoir compliance and the asymptotic pressure, and 2) an excess pressure component which is the difference between the measured pressure waveform and reservoir pressure. The calculation of the reservoir pressure depends on determination of two rate constants: the systolic rate constant (SRC) which is the inverse of the product of the constant of proportionality between the excess pressure and the arterial inflow and the total arterial compliance; and DRC which is the inverse of the product of the peripheral vascular resistance and the total arterial

compliance. Reservoir-excess pressure parameters analysed in this study were 1) reservoir pressure integral (INTPR), 2) peak reservoir pressure (MAXPR), 3) excess pressure integral (INTXSP), 4) SRC, and 5) DRC. <u>Figure 1</u> shows a schematic example of the reservoir-excess pressure separation.

Renal function

The reduction of renal function over three years was defined as a reduction of eGFR of more than 5% per year (Decline Group: DCL; taken as a reduction of 15% or more at follow-up), as previously published study described. ¹⁹ eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation ²⁰ at baseline and after 3-year follow-up period. Urinary albumin to creatinine ratio was obtained by a random spot urine sample obtained during the study visit with a detection limit for albumin of 3.0 mg/l. ²¹ Albuminuria (macro-albuminuria) was defined as the urinary albumin to creatinine ratio >25 mg/mmol for men and 35 mg/mmol for women.

Statistical analysis

Data are presented as means±SD, median (interquartile range), means [95% confidence intervals (CI)] or number (%). Skewed data were appropriately transformed for statistical analysis. Independent samples t-tests and analysis of covariance were used to examine the differences in variables between groups. Univariable and multivariable logistic regression analyses were performed to quantify associations between reservoir-excess pressure parameters and the decline in renal function at 3-year follow-up and reported as odds ratio (OR) [95% CI]. For multivariable logistic regression analyses, the following variables were considered and included as covariates: age, sex, baseline eGFR, brachial systolic BP, type 2

diabetes, total and HDL cholesterol, current smoking, pharmacological hypertensive treatment, study centre, body mass index, previous history of cardiovascular disease, presence of albuminuria at baseline and resting heart rate (assigned as above/below median due to collinearity as a continuous variable). Reservoir-excess pressure parameters were standardised before entering into the logistic regression analysis to allow comparisons across the parameters (i.e. 1-standard deviation increase). A sensitivity analysis was performed by changing the cut-off point for a decline in renal function from 5% per year to 10% per year to determine whether different thresholds would influence associations between reservoir-excess pressure parameters and the decline in renal function. Statistical analysis was conducted using IBM SPSS Statistics 26 (IBM, Armonk, NY) and statistical significance was set at p<0.05 (two sided).

RESULTS:

Table 1 shows the selected baseline characteristics of the study participants for the combined group and the DCL and ND groups. The DCL group was older, had lower levels of HDL cholesterol, had a higher concentration of fasting glucose and HbA1c, and had a faster heart rate than the ND group (all p<0.05). The presence of type 2 diabetes was more prevalent in DCL than ND (p<0.05). At 3-year follow-up, changes in eGFR compared with baseline was -16.7 (-21.8 – -13.9) ml/min/1.73m² in DCL and 0.6 (-4.7 – 7.3) ml/min/1.73m² in ND. This corresponded to a percentage change in eGFR of -20.5 (-26.3 – -17.6) % in DCL and 0.8 (-6.3 – 9.6) % in ND (both p<0.001).

The reservoir-excess pressure parameters at baseline between DCL and ND are shown in **Figure 2**. After age and sex were accounted for, INTPR was lower in DCL [84.2 (81.1-87.5)

204 mmHg·s] than ND [90.5 (88.9-92.1) mmHg·s, p=0.001]. There were no differences in MAXPR 205 [107.5 (106.2-108.8) mmHg], INTXSP [7.3 (6.9-7.8) vs 7.2 (7.0-7.4) mmHg·s, p=0.533], SRC 206 [6.6 (6.3-7.0) vs 6.9 (6.7-7.1) 1/s, p=0.159] and DRC [2.3 (2.2-2.5) vs 2.3 (2.2-2.3) 1/s, 207 p=0.491] between DCL and ND after age and sex were taken into account. 208 209 Logistic regression analysis was performed to determine whether baseline reservoir-excess 210 pressure parameters predicted the reduction of renal function (as a dichotomised 211 parameter) at 3-year follow-up (Figure 3). In a minimally adjusted (age and sex) logistic 212 regression model (Figure 3A), INTPR was associated with the reduction of eGFR at follow-up 213 [OR: 0.685 (0.537-0.452), p=0.002]. The association was unattenuated after a multivariable 214 adjustment that included Framingham risk factors and study centre [OR: 0.660 (0.494-215 0.883), p=0.005], as shown in **Figure 3B**. Further, more extensive adjustment for body mass 216 index, previous history of cardiovascular disease, baseline eGFR, presence of albuminuria at 217 baseline and resting heart rate above/below the median value did not alter the association 218 [Figure 3C, OR: 0.528 (0.351-0.794), p=0.002]. Nor was the association altered by the 219 inclusion of haemoglobin A1c, heart rate-corrected aortic augmentation index, carotid-220 femoral pulse wave velocity or by the replacement of brachial systolic BP with other BP 221 variables (aortic BP, aortic pulse pressure and brachial pulse pressure; Supplemental Table 222 <u>S1</u>). 223 224 There was no association between the reduction in eGFR at follow-up and MAXPR [OR: 225 0.827 (0.649-1.055) p=0.126, 0.686 (0.460-1.024) p=0.065, and 0.682 (0.444-1.047) p=0.080], INTXSP [OR: 1.102 (0.865-1.404) p=0.433, 1.142 (0.821-1.587) p=0.430, and 1.102 226 227 (0.770-1.579) p=0.596], SRC [OR: 0.870 (0.646-1.172) p=0.360, 0.948 (0.706-1.274) p=0.724,

and 0.979 (0.720-1.329) p=0.890], DRC [OR: 1.110 (0.877-1.405) p=0.387, 1.248 (0.945-1.649) p=0.118, and 1.274 (0.951-1.706) p=0.105] in the minimally adjusted model, the multivariable adjusted model, or the extensively adjusted multivariable model (**Figure 3**). The association did not change with the inclusion of haemoglobin A1c, heart rate-corrected aortic augmentation index, carotid-femoral pulse wave velocity or when replacing brachial systolic BP with brachial pulse pressure in the model, although 1) the addition of heart rate-corrected augmentation index and carotid-femoral pulse wave velocity in the extensively adjusted model marginally strengthened the association between MAXPR and the reduction in eGFR, and 2) the association between DRC and the reduction in eGFR during the follow-up period was marginally strengthened with the replacement of brachial systolic BP with aortic systolic BP and aortic pulse pressure (**Supplemental Table S1**).

When the threshold for the decline in renal function was changed to a reduction in eGFR of more than 10% per year from 5% per year as a part of a sensitivity analysis, INTPR remained associated with the reduction of renal function at follow-up, and the other reservoir-excess pressure parameters showed no association with the reduction of renal function. That is, results were similar for each threshold of reduction in eGFR (Supplemental Table S2 shows the participants characteristics and Supplemental Table S3 shows detailed results for the sensitivity analysis).

DISCUSSION:

In this longitudinal study of older adults with variable cardiovascular risk factors, we demonstrate an association between baseline INTPR and the decline in renal function at 3-year follow-up independently of conventional cardiovascular risk factors. The association

between baseline INTPR and the decline in renal function persisted after taking other potential confounders into account and after changing the threshold for the decline in renal function. These are novel observations that support the notion that INTPR plays a pivotal role in the functional decline of the kidneys in older adults. It also suggests that INTPR is a marker of adverse systemic haemodynamics.

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The parameters derived from reservoir-excess pressure analysis have already demonstrated prognostic utility by predicting cardiovascular morbidity and mortality in several studies.³⁻¹⁰ In this study, we are able to provide novel evidence that the reservoir-excess pressure parameter, INTPR, possesses additional clinical utility by predicting the decline in renal function in older adults over three years. The observed association was independent of conventionally obtained BP indices, such as brachial and aortic systolic BP, indices of BP pulsatility such as brachial and aortic pulse pressure, and index of pulsatility marker such as aortic augmentation index. This indicates an advantage of reservoir-excess pressure analysis over conventional BP waveform analysis to decipher the information contained in a BP waveform contour. In other words, the capability of parameters derived from conventional BP waveform analysis to extract information from a BP waveform may be inadequate because those parameters are extreme points on the BP waveform or derivatives calculated from those specific points. There remains a greater residual cardiovascular risk associated with BP that is unaccounted for by conventional BP indices, and reservoir-excess pressure analysis may be able to fill the gap by identifying subtle haemodynamic abnormalities apparent in a BP waveform that would be otherwise undetected.

In our cohort, a smaller baseline INTPR was associated with a large decline in eGFR at 3-year follow-up, indicating that INTPR may play a protective role in maintaining and/or slowing a decline in eGFR in older adults. This proposition makes sense because INTPR corresponds to the net volume of blood stored in an artery¹⁴ and the volume of blood stored in central arteries, especially in the aorta, becomes smaller when the buffering function of those arteries become less effective as a consequence of the age-associated increase in central artery stiffness. Considering the premise that the reservoir pressure component makes a major contribution to the diastolic phase of the BP waveform and tissue perfusion in diastole, increased central artery stiffness could lead to impaired renal perfusion and potentially affect eGFR. These assumptions are supported by a previous observation in patients with hypertension showing that an increased aortic stiffness 1) amplifies blood flow reversal in the descending thoracic aorta which in turn reduces a diastolic flow discharge toward the abdominal aorta, and then 2) reduces the blood inflow from the supra-renal abdominal aorta to the renal arteries, which eventually leads to a reduction in eGFR.²² Therefore, the diminished reservoir function could not only increase cardiovascular risk but also deteriorate renal function, potentially creating positive feedback that progressively damages the kidneys. In older adults, this might explain the higher cardiovascular risk and accelerated renal decline in people with CKD. 12, 23

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The smaller INTPR may also indicate a deleterious influence of increased central artery stiffness on the microvasculature of highly-perfused low-resistance organs such as the brain and kidneys. Greater central artery stiffness reduces impedance mismatch between central and peripheral arteries that 1) increases flow pulsatility, and 2) increases the penetration of excessive pulsatile energy into the microcirculation of the organs that may cause adverse

structural changes. In the case of the kidneys, sustained exposure to flow pulsatility and excessive pulsatile energy is considered to damage small arteries and glomeruli in the renal cortex, leading to a loss of arterial volume in that area and/or an increase in renal vascular resistance. ^{24, 25} It is thus plausible that these derangements occurring in the kidneys, separately from or in combination with diminished blood flow to the renal arteries discussed above, may account for the deterioration of renal function observed in this study.

The observed robust association between INTPR and the eGFR reduction at 3-year follow-up independently of conventional haemodynamic indices could potentially be influenced by the underestimation of brachial cuff-measured BP at baseline. ²⁶ A previous study revealed a significant underestimation of brachial cuff-measured BP due to serious vascular irregularities associated with advanced CKD, leading to significant trend for underestimation of aortic systolic BP with declining eGFR. ²⁷ Given the greater burden of cardiovascular risk at baseline in DCL compared to ND in our study, it could be reasonable to speculate that baseline risk assessed from conventional brachial cuff-measured BP and derived central haemodynamic indices could have been underappreciated in our DCL cohort. This, in turn, may provide another advantage of applying the reservoir-excess pressure concept in people with CKD, in whom conventional haemodynamic indices inadequately extract cardiovascular risk embedded in the BP waveform.

A recent pilot study has demonstrated that changes in INTXSP were inversely associated with the changes in eGFR over three years in healthy middle-aged and older adults, ¹³ which is contrary to our null finding of no association between baseline INTXSP and the reduction in eGFR. There are several important differences in study cohorts that could account for the

divergent results between the studies, such as sample size (33 vs 542 participants in this study), age (>10 yrs older in our cohort), health status (far more cardiovascular risk factors in our cohort), and differences in baseline eGFR (~30 ml/min/1.73m² lower baseline eGFR in our cohort). Additionally, the divergent results could also stem from the difference between INTXSP derived from the aorta (previous study) and INTXSP derived from the radial artery (this study). Excess pressure, like the BP waveform, undergoes substantial and variable amplification from the aorta to the radial artery²⁸ due to wave reflections,²⁹ and thus INTXSP measured in the radial artery may not correspond to INTXSP measured in the aorta. In contrast, reservoir pressure is little different between the aorta and radial artery. 28, 30 The implication of this is that, when acquired from peripheral sites, an association of eGFR with reservoir-excess pressure parameters could be more consistently observed with reservoir pressure parameters rather than those from the excess pressure parameters. A recent cross-sectional study has shown that DRC derived from the aorta and brachial artery is consistently associated with eGFR in older adults who underwent elective coronary angiography,³¹ providing additional support for our finding of an association between the reservoir pressure component and preserved renal function in older adults.

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Limitations

eGFR was obtained twice in this study: once at baseline and the other at the 3-year follow-up period. Thus, it is not possible to characterise the temporal pattern of change in eGFR during this period.³² Whether baseline INTPR is associated with different patterns of eGFR change over time is beyond the scope of this study. Additionally, renal haemodynamics data such as renal resistive index by Doppler ultrasound were not available in this study; these could have helped interpret our findings. Finally, our study cohort was older adults with

varied cardiovascular risk factors, and hence, the results found in this study may not be applicable to specific patient cohorts, for example people with hypertension or type 2 diabetes.

Perspectives

This study demonstrates that a smaller baseline INTPR was associated with the decline in renal function in older adults at 3-year follow-up, independently of conventional cardiovascular risk factors. These observations have unveiled a novel prognostic utility of reservoir-excess pressure parameters beyond the ability to predict cardiovascular events. Reservoir-excess pressure analysis has the potential to provide an additional tool for the risk stratification of renal function in at-risk individuals and older adults with CKD.

Novelty and Relevance:

What is new?

 Reservoir pressure integral, a parameter derived from reservoir-excess pressure analysis, was associated with the decline in renal function independently of conventional cardiovascular risk factors.

What is relevant?

- INTPR plays a pivotal role in the functional decline of the kidneys in older adults.
- Reservoir-excess pressure parameters may have a novel prognostic utility beyond the ability to predict cardiovascular events.

Clinical/Pathophysiological Implications?

Reservoir-excess pressure analysis has the potential to provide an additional tool for the risk stratification of renal function in at-risk individuals and older adults with CKD. **ACKNOWLEDGEMENT:** a. Acknowledgements: The authors would like to thank all the participants who participated in the study. b. Sources of Funding: This study was supported by the European Union's Seventh Framework Programme (FP7/2007-2013) for the Innovative Medicine Initiative under grant agreement number IMI/115006 (the SUMMIT consortium) and in part by the National Institute of Health Research (NIHR) Exeter Clinical Research Facility. The views expressed are those of the authors and not necessarily those of the UK National Health Service, the NIHR or the UK Department of Health and Social Care. ADH receives support from the British Heart Foundation, the Economic and Social Research Council (ESRC), the Horizon 2020 Framework Programme of the European Union, the National Institute on Aging, the National Institute for Health Research University College London Hospitals Biomedical Research Centre, the UK Medical Research Council and works in a unit that receives support from the UK Medical Research Council. c. Disclosure: No potential conflicts of interest relevant to this article were reported. **Supplemental Material:** Supplemental Method Supplemental Tables S1-S3

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Supplemental Figure S1

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492 32. Shou H, Hsu JY, Xie D, Yang W, Roy J, Anderson AH, Landis JR, Feldman HI, Parsa A, Jepson C, 493 Chronic Renal Insufficiency Cohort Study I. Analytic considerations for repeated measures of egfr in cohort studies of ckd. Clin J Am Soc Nephrol. 2017;12:1357-1365 494 495 496 FIGURE LEGENDS: 497 Figure 1. A schematic representation of reservoir-excess pressure separation in the radial artery. 10 Total pressure is the acquired radial pressure waveform and reservoir pressure is 498 499 the calculated waveform. INTPR, reservoir pressure integral; MAXPR, peak reservoir 500 pressure; INTXSP, excess pressure integral; SRC, systolic rate constant; DRC, diastolic rate 501 constant. 502 503 Figure 2. Comparisons of reservoir-excess pressure parameters between groups. Data are 504 shown as the means (95% confidence intervals) before the adjustment for age and sex. 505 *different between groups (p=0.001). ND, participants without a decline in renal function; 506 DCL, participants with a decline in renal function; INTPR, reservoir pressure integral; MAXPR, 507 peak reservoir pressure; INTXSP, excess pressure integral; SRC, systolic rate constant; DRC, 508 diastolic rate constant. 509 510 Figure 3. Minimally adjusted (A), multivariable (B) and extensively adjusted (C) logistic 511

Figure 3. Minimally adjusted (A), multivariable (B) and extensively adjusted (C) logistic regression analyses to predict the reduction of estimated glomerular filtration rate at 3-year follow-up. Data are shown as odds ratio (95% confidence interval). The minimally adjusted model includes age and sex as independent variables. The multivariable adjusted model includes age, sex, total and HDL cholesterol, type 2 diabetes, current smoking, systolic blood pressure, pharmacological treatment for hypertension and study centre as independent variables. The extensively adjusted multivariable model further includes body mass index,

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| 517 | history of cardiovascular disease, baseline estimated glomerular filtration rate, albuminuria |
|------------|-----------------------------------------------------------------------------------------------|
| 518 | at baseline and resting heart rate above/below the median value as independent variables. |
| 519 | INTPR, reservoir pressure integral; MAXPR, peak reservoir pressure; INTXSP, excess pressure |
| 520 | integral; SRC, systolic rate constant; DRC, diastolic rate constant. |
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| 523 | |

<u>Table 1.</u> Selected characteristics of the study participants at baseline stratified by groups.

| | ALL (n=542) | ND (n=448) | DCL (n=94) | p (ND v DCL) |
|----------------------------------------|------------------|------------------|-----------------------|--------------|
| Age, yrs | 69.4±7.9 | 68.8±7.8 | 72.4±7.6 | <0.001 |
| Female, n (%) | 194 (35.8) | 168 (37.5) | 26 (27.7) | 0.070 |
| BMI, kg/m ² | 28.6 (25.5-31.9) | 28.5 (25.6-32.1) | 28.9 (25.1-31.2) | 0.644 |
| Total CHOL, mmol/l | 4.2 (3.6-5.0) | 4.2 (3.6-5.1) | 4.1 (3.5-4.6) | 0.102 |
| LDL CHOL, mmol/l | 2.2 (1.7-2.9) | 2. (1.7-3.0) | 2.1 (1.6-2.7) | 0.255 |
| HDL CHOL, mmol/l | 1.3 (1.1-1.6) | 1.3 (1.1-1.6) | 1.2 (1.0-1.5) | 0.024 |
| Creatinine, µmol/l | 85.5±23.9 | 85.4±24.1 | 85.8±22.9 | 0.892 |
| HbA1c, mmol/mol | 47.5 (40.0-59.0) | 46.0 (40.0-57.0) | 53.0 (42.0-67.8) | 0.001 |
| eGFR, ml/min/1.73m ² | 79.0±19.3 | 78.9±19.3 | 79.7±19.2 | 0.706 |
| eGFR change, ml/min/1.73m ² | -1.0 (-9.3–5.4) | 0.6 (-4.7–7.3) | -16.7 (-21.8 – -13.9) | <0.001 |
| Brachial Systolic BP, mmHg | 135±17 | 134±17 | 136±17 | 0.291 |
| Brachial Diastolic BP, mmHg | 75±9 | 75±9 | 73±8 | 0.111 |

| Brachial PP, mmHg | 59.8±13.7 | 59.2±13.5 | 62.7±14.3 | 0.024 |
|--------------------------|-----------------|-----------------|-----------------|--------|
| Aortic systolic BP, mmHg | 126±17 | 126±17 | 127±17 | 0.541 |
| Aortic PP, mmHg | 50±14 | 49±14 | 52±14 | 0.107 |
| Aortic Alx@HR75, % | 24.7±7.8 | 24.6±7.9 | 24.9±7.4 | 0.712 |
| Heart rate, beat/min | 60±10 | 59±9 | 62±10 | 0.018 |
| CVD, n (%) | 233 (43.0) | 185 (41.3) | 48 (51.1) | 0.082 |
| Type 2 diabetes, n (%) | 345 (63.7) | 273 (60.9) | 72 (76.6) | 0.004 |
| Diabetes duration, yrs | 10 (5-15) | 9 (5-14) | 13 (7-18) | <0.001 |
| Albuminuria, n (%) | 13 (2.4) | 3 (0.7) | 10 (10.6) | <0.001 |
| Smoking, n (%) | 34 (6.3) | 27 (6.0) | 7 (7.5) | 0.606 |
| HTRx, n (%) | 384 (70.9) | 310 (69.2) | 74 (78.7) | 0.065 |
| RASRx, n (%) | 305 (56.3) | 245 (54.7) | 61 (64.9) | 0.064 |
| Statin, n (%) | 368 (67.9) | 303 (67.6) | 65 (69.2) | 0.775 |
| CFPWV, m/s* | 10.4 (9.0-12.4) | 10.3 (9.0-12.2) | 11.2 (9.6-13.2) | 0.023† |

Data are shown as means±SD, median (interquartile range) or number (%). *n=454 for ALL, n=379 for DCL and n=75 for ND. †p=0.555 after age, mean arterial pressure and heart rate were taken into account. ALL, combined group; ND, participants without a decline in renal function; DCL, participants with a decline in renal function; BMI, body mass index; CHOL, cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, haemoglobin A1c; eGFR, estimated glomerular filtration rate; BP, blood pressure; PP, pulse pressure; Alx@HR75, augmentation index corrected at heart rate of 75 bpm; CVD, cardiovascular disease; HTRx, pharmacological treatment for hypertension; RASRx, the use of renin-angiotensin system blockers; CFPWV, carotid-femoral pulse wave velocity.





