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The correlation between blood pressure and kidney function decline in older people: a registry-based cohort study

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ABSTRACT

Objectives:

To examine the relation between static and dynamic blood pressure (BP) measurements and the evolution of kidney function in older people, adjusted for the presence of multimorbidity.

Design:

Retrospective cohort study during a 10-year time interval (2002–2012) in three age strata of patients aged 60 and older.

Setting:

Primary care registration network with 97 general practitioners working in 55 practices regularly submitting collected patient data.

Participants:

All patients with at least one BP measurement in 2002 and at least four serum creatinine measurements after 2002 (n=8,636). A modified Charlson Comorbidity Index (mCCI) at baseline was registered. Change in systolic and diastolic BP and pulse pressure (PP) from 2002 onwards was calculated. The relation between kidney function evolution and baseline BP and change in BP was examined using linear and logistic regression analysis.

Main outcome measures:

The slope of the estimated glomerular filtration rate (eGFR, MDRD equation) was calculated by the ordinal least square method. A rapid annual decline of kidney function was defined as ≥3ml/min/1.73m^2/year.

Results:

Rapid annual decline of kidney function occurred in 1,130 patients (13.1%). High baseline SBP and PP predicted kidney function decline in participants aged 60–79 years. No correlation between baseline BP and kidney function decline was found in subjects aged 80 and older. An annual decline of ≥1mmHg in SBP and PP was a strong risk factor for a rapid

annual kidney function decline in all age strata, independent of baseline BP and mCCI. A decline in DBP was also a strong independent predictor in participants aged 60–79 years.

Conclusions:

The present study identified a decline in BP over time as a strong risk factor for kidney function decline in all age strata, independent of the presence of multimorbidity and baseline BP.

Strengths and limitations of this study

- The first study that investigated the relation between dynamic blood pressure measurements and kidney function over time in subjects aged 60 and older.
- Large primary care study population representative of the population of Flanders with a long follow-up period.
- Analyses in various age strata were performed in order to detect possibly different patterns due to age.
- The presence of multimorbidity was included in the analyses.
- Lack of mortality data, data on renal replacement therapy, insufficient data on proteinuria/albuminuria and no standardized measurements of creatinine and blood pressure.
- Weaknesses inherent to a retrospective design and registry data: possible healthy survivor bias, no information about missing data and loss to follow-up.

Introduction

Belgium and other western countries are facing a grey epidemic. Furthermore, a "double grey" epidemic is expected, given the proportionally higher increase of persons aged 80 and older. In 2012, 17.4% and 5.2% of the total Belgian population was aged 65 or older, and 80 or older, respectively. By 2050, these percentages will rise to 24.5% and 9.5%, respectively[1]. This will probably lead to a dramatic increase of chronic diseases and an increased number of patients with multiple comorbidities.

The prevalence of chronic kidney disease (CKD) (estimated glomerular filtration rate (eGFR) <60ml/min/1.73m²) increases with ageing to approximately 10% at the age of 65 years and to 60% in persons aged 80 and older[2-4]. CKD and especially end-stage renal disease is recognized as an important problem in public health. First, the cost of dialysis per patient per year is more than 50,000 euro, and >1% of the public health budget of the Belgian government is used to cover these costs. Second, CKD increases the risk of cardiovascular events and mortality. Moreover, many medications cannot be used or need dose adjustment in patients with CKD[5,6].

Arterial hypertension and cardiovascular disease have been identified both as a cause and as a consequence of CKD[7-9] and end-stage renal disease (ESRD)[4]. This has been well studied in the younger population. However, to date, many clinical trials and clinical studies have excluded older persons and especially older persons with multiple chronic conditions[10]. Furthermore, studies investigating the association between arterial hypertension and the risk of kidney function decline in older persons are scarce. The Cardiovascular Health study[11] and the SHEP study[8] identified baseline blood pressure (BP) as a risk factor for kidney function decline in older persons. The Leiden 85 Plus-study[12] on the other hand, did not find a relation between baseline BP and kidney function decline. It reported a decline in systolic (SBP) and diastolic blood pressure (DBP) between ages 85 and 90 to be related to an accelerated decline

of creatinine clearance over time. To date , the relation between the evolution of BP and that of kidney function over time has not been studied in persons aged 60 years and older. Moreover, the impact of concomitant chronic conditions on this relation has not been examined.

Therefore, the aim of this retrospective cohort study within the framework of a large Flemish morbidity registry was to study the relation between static and dynamic BP measurements and the evolution of kidney function over time in three age strata of subjects aged 60 years and older, adjusted for the presence of multimorbidity.

Methods

Study design and study population

Data were obtained from Intego, a Belgian general practice-based morbidity registration network at the Department of General Practice of the University of Leuven[13]. Intego procedures were approved by the ethical review board of the Medical School of the Catholic University of Leuven (N° ML 1723) and by the Belgian Privacy Commission (no SCSZG/13/079). Ninety-seven general practitioners (GPs) of 55 practices evenly spread throughout Flanders, Belgium, collaborate in the Intego project. GPs applied for inclusion in the registry. Before acceptance of their data, registration performance was audited using algorithms to compare their results with those of all other applicants. Only the data of the practices with optimal registration performance were included in the database. The Intego GPs prospectively and routinely registered all new diagnoses and new drug prescriptions, as well as laboratory test results and patient information, using computer-generated keywords internally linked to codes.

With specially framed extraction software, new data were encrypted and collected from the GPs' personal computers and entered into a central database. Registered data were continuously updated and historically accumulated for each patient. New diagnoses were classified according to a very detailed thesaurus automatically linked to the International Classification of Primary Care (ICPC-2) and International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). Drugs were classified according to the WHO's Anatomical Therapeutic Chemical (ATC) classification system.

The present study used Intego data of a 10-year time period from January 1st 2002 to January 1st 2012. First, patients aged 60 years or older in 2002 with a BP measurement registered in 2002 were selected (n = 12,904). Second, patients with at least four serum creatinine measurements after 2002 were withheld (n = 8,636).

Clinical characteristics

Blood pressure

BP measurements registered by the GP in 2002 (baseline or static BP) and yearly thereafter were used. For each year of the study time interval, a single SBP and DBP value was used in the analyses. The average BP of the two lowest values of that year's last three measurements were used[14]. Pulse pressure (PP) was calculated as the difference between the SBP and the DBP. Categories of baseline BP measurements were based on previously reported categories[11].

The slope of the SBP, DBP and PP (mmHg/year) was calculated for every study participant of whom BP measurements were available for at least four years following 2002 (n = 7,283). The slope, or dynamic BP, was calculated according to the ordinal least square method. Patients were divided in categories based on the slope using predefined subgroups of ≤-3, >-3 or ≤-1, >-1 or <1, and ≥1mmHg/year for the SBP and ≤-1, >-1 or <1 and ≥1mmHg/year for the DBP and the PP.

Kidney function

Kidney function was expressed as the eGFR calculated with the MDRD (Modification of Diet in Renal Disease) equation[15]. Baseline eGFR was calculated based on the average serum creatinine value of the last two measurements in 2002.

The slope of the eGFR (ml/min/1.73m^2/year) for every participant was calculated according to the ordinal least square method using all (range 4–50) available eGFR values. A rapid annual decline of kidney function was defined as ≥3ml/min/1.73m^2/year; this change is known to be associated with clinically deleterious outcomes[11].

Comorbidity

Medical history at baseline of every study participant was registered. The Charlson Comorbidity Index (CCI) includes 19 chronic diseases that are weighted based on their

association with mortality[16]. A modified CCI (mCCI) at baseline was calculated for every study participant[17]. Connective tissue disease could not be reliably assessed from the registry and the differentiation between cancers with or without metastasis, diabetes with or without end organ failure and mild or moderate to severe liver disease could not be made. Consequently all patients with cancers were assigned the same score (=2), as well as all patients with diabetes (=1) and with liver disease (=1).

The prescription of cardiovascular medication at baseline including beta-blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, calcium antagonists and diuretics was extracted from the database for every study participant.

Data analysis

Continuous data are presented as the mean and standard deviation (SD). Categorical data are presented as numbers and frequencies. All further analyses were performed in three age strata at baseline: 60–69 years, 70–79 years and ≥80 years.

The correlation between baseline BP measurements and kidney function decline and change in BP and kidney function decline was first explored by calculating odds ratios (ORs) with the corresponding 95% confidence intervals (CIs) using bivariate and multivariable linear regression analysis and adjusting for age, gender, mCCI at baseline, cardiovascular medication at baseline, time between the first and last eGFR measurement after 2002 (≥ or <5 years) and baseline eGFR (and baseline BP measurements for BP change). Second, the relation between categories of baseline BP measurements or categories of BP change and a rapid annual decline of kidney function was examined with bivariate and multivariable logistic regression analysis.

In order to avoid co-linearity, the correlation coefficients between all covariates were calculated. In case of co-linearity (*r*-value >0.90), only one of the two covariates was considered in the multivariate model. Interaction was checked between the slope of the BP

measurement and the baseline BP measurement, between the slope of the BP measurement and the mCCI, and between the baseline BP measurement and the mCCI. If the interaction term was statistically significant (P <0.05), it was kept in the model. A goodness-of-fit test was performed with the ANOVA (analysis of variance) F test for the linear regression models and the Hosmer-Lemeshow test for the logistic regression models and was reported when the model did not fit the observed data (ANOVA F test $P \geq 0.05$ and Hosmer-Lemeshow test P <0.05).

Statistical analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA) and GraphPad prism 6 (GraphPad Software, San Diego, CA, USA).

Results

In total, 8,636 patients from the Intego registry had at least one BP measurement registered in 2002 and at least four serum creatinine measurements after 2002. The baseline clinical characteristics of the study population according to their age at baseline are presented in Table 1. After baseline, rapid annual decline of kidney function occurred in 1,130 patients (13.1%): in 9.4% (n = 387) of patients aged 60–69 years, in 15.1% (n = 533) of patients aged 70–79 years and in 21.5% (n = 210) of patients aged 80 or older. Figure 1 presents the prevalence of rapid annual decline of kidney function according to categories of baseline BP and categories of change in BP. Prevalence of rapid decline of kidney function increased with higher baseline SBP and PP (χ^2 test, P <0.001), as well as with increased decline in SBP, DBP and PP (χ^2 test, P <0.001).

Correlation between systolic blood pressure and kidney function decline

Baseline systolic blood pressure

An inverse linear relation was found between baseline SBP and kidney function decline in all age strata, also after adjusting for confounders (Table 2). The goodness-of-fit test was not significant in the oldest age stratum (ANOVA F test, P = 0.23). Categories of higher baseline SBP predicted rapid decline of kidney function in patients aged 60–69 years (adjusted OR 1.9 (95% CI 1.2–3.1) and adjusted OR 2.4 (95% CI 1.5–3.9) for 140–150mmHg and ≥150mmHg respectively) (Figure 2). In patients aged 70–79 years a trend was seen for the highest category (adjusted OR 1.5 (95% CI 1.0–2.4), P = 0.052), and no correlation was found in patients aged 80 or older (Hosmer-Lemeshow test (≥80 years), P = 0.005).

Change in systolic blood pressure

Figure 3 presents the prevalence of the change in blood pressure for the various age strata. A positive and independent linear relation was found between a change in SBP and a

change in kidney function in the oldest two age strata; the more SBP decreased, the more the kidney function decreased in the years after 2002 (Table 3). Categories of decreasing SBP showed an increased risk of rapid kidney function decline compared with no change in patients 60–69 years (adjusted OR 1.7 (95% CI 1.3–2.4) and adjusted OR 3.1 (95% CI 2.0–4.6), respectively), in patients 70–79 years (adjusted OR 1.7 (95% CI 1.3–2.3) and adjusted OR 1.9 (95% CI 1.3–2.7), respectively) and in patients aged 80 and older (adjusted OR 3.3 (95% CI 1.4–8.1) and adjusted OR 9.2 (95% CI 1.8–46), respectively) (Figure 4). In the oldest age stratum the model was also corrected for the interaction term between change in SBP and baseline mCCI (adjusted OR 1.2 (95% CI 1.0–1.3), $P = 0.026$).

Correlation between diastolic blood pressure and kidney function decline

Baseline diastolic blood pressure

No linear relation was found between baseline DBP and kidney function decline (Table 2). The goodness-of-fit test for the adjusted model was not significant in the oldest age stratum (ANOVA F test, P = 0.64). A trend of predicting rapid decline of kidney function was only seen in the highest category of baseline DBP in patients aged 60–69 years (adjusted OR 2.0 (95% CI 0.99–4.0)). The Hosmer-Lemeshow test showed the adjusted model in the oldest patients did not fit the observed data (P <0.001).

Change in diastolic blood pressure

An independent and positive linear relation was found between change in DBP and change in kidney function in all age strata (Table 3). A decline in DBP predicted rapid decline of kidney function in patients aged 60–69 years and 70–79 years (adjusted OR 2.2 (95% CI 1.7–2.9) and adjusted OR 1.4 (1.1–1.9), respectively). In the oldest age stratum a trend of higher risk in patients with a decline in DBP was seen (adjusted OR 1.5 (95% CI 0.99–2.4), $P = 0.054$ (Hosmer-Lemeshow test, $P = 0.020$)).

Correlation between pulse pressure and kidney function decline

Baseline pulse pressure

An inverse linear correlation was found between baseline PP and decline in kidney function in all age strata. Only in the oldest age stratum was the goodness-of-fit test for the adjusted model not significant (ANOVA F test, P = 0.29). The highest categories of baseline PP predicted rapid decline of kidney function in patients aged 60–69 years and aged 70–79 years (adjusted OR 1.5 (95% CI 1.0–2.2) and adjusted OR 1.4 (95% CI 1.1–2.0).

Change in pulse pressure

A change in PP was independently correlated with change in kidney function in the youngest age group (Table 3). The goodness-of-fit test for the adjusted model was not significant in the oldest age stratum (ANOVA F test, P = 0.18). Patients in all age strata in the category ≤-1mmHg/year change showed a higher risk of rapid annual decline of kidney function compared with patients without change in PP (adjusted OR 2.1 (95% CI 1.5–2.9), adjusted OR 2.8 (95% CI 1.6–4.9) and adjusted OR 1.7 (95% CI 1.1–2.8), respectively). In patients 70 – 79 years the model was also corrected for the interaction term between change in PP and baseline PP (adjusted OR 1.3 (95% CI 1.1–1.5), *P* = 0.009).

Discussion

In this large retrospective population-based cohort study the relation between static and dynamic BP measurements and kidney function over time in older subjects was investigated. The present study confirmed previously found associations between baseline BP measurements and decline of kidney function, but more importantly identified a decline in BP over time as a strong risk factor for kidney function decline in all age strata, independent of the presence of multimorbidity and baseline BP. In people aged 60–69 years, high baseline SBP and PP predicted kidney function decline and a decline in SBP, DBP and PP in the years after baseline were related to a rapid annual decline in kidney function. In patients aged 70–79 years a relation between high baseline SBP and PP and kidney function decline was confirmed, and an association between a decline in SBP, DBP and PP after baseline and a decline in kidney function was seen. In the oldest age stratum, no correlation between baseline BP measurements and kidney function decline was found. A decline in SBP and PP in the years after baseline, however, predicted a rapid annual decline in kidney function in this age group. Moreover, DBP tended to decline.

To date, there is no consensus about which level of BP causes a higher risk of cardiovascular mortality, morbidity or kidney function decline in the elderly population. In the KDOQI/KDIGO guidelines tailored BP control is advised in older persons for the preservation of the kidney function[18]. This evidence is based on several studies reporting on arterial hypertension as a risk factor for the development of CKD, as well as on the evolution of CKD to ESRD in the global population. The MDRD-trial[19] studied arterial hypertension as a risk factor for kidney function decline in stage 3 and 4 CKD in a population aged 18-70 years. They studied the impact of baseline and follow-up BP during 2.2 years on the evolution of kidney function in an intervention (antihypertensive) and in a control group. No effect of high blood pressure on kidney function decline was found except for severe proteinuria

>3g/day. In a cohort of 332,544 men aged 35–57 years, Klag et al[20] found a 22% higher risk of ESRD in patients with arterial hypertension stage 4, defined as a SBP >210mmHg or a DBP >120mmHg, compared to that of patients with normal BP. In a large Japanese cohort, Tozawa et al[21] included 98,759 patients aged 20–98 years. They found higher baseline SBP and DBP showed a significant risk of development of ESRD. Cumulative incidence for ESRD in patients with severe arterial hypertension was 1.7% vs 0.2% in patients with a normal BP. Finally, Van Pottelbergh et al.[22] studied risk factors for ESRD in patients aged 50 years and older in the same Flemish cohort study as the present study did. Baseline arterial hypertension (BP ≥140/90mmHg) was found to be a significant risk factor for the development of ESRD (adjusted Hazard Ratio 1.25 (95% CI 1.22–1.28)).

Studies investigating the impact of BP on the evolution of kidney function in older persons are extremely rare. Some studied the risk of baseline BP for kidney function decline. Rifkin et al.[11] found baseline SBP to have the strongest association with rapid annual kidney function decline in persons aged 65 years or older, with 14% increased hazard of rapid decline per 10mmHg, independent of other BP measurements. The SHEP-trial[8] used their placebo-arm to study the relation between baseline BP and a yearly incident increase of serum creatinine (≥0.4mg/dl). They found higher baseline SBP increased the relative risk of kidney function decline. A positive trend was found for DBP, however, without correction for comorbidity. The relation between baseline BP and the evolution of SBP, DBP and PP and kidney function decline in a 5-year time interval has only been studied in patients aged 85 and older[12]. The Leiden 85+ study reported that elevated baseline SBP and DBP did not influence the annual decline in renal function in the oldest individuals. However, DBP <70mmHg and a decline in SBP or DBP was related to an accelerated decline of creatinine clearance over time. The present study results are in line with these findings.

The deleterious effect of higher baseline BP measurements on the evolution of the kidney function in persons up to 80 years was confirmed by the present study. Furthermore, intervention trials have shown that BP lowering prevents the need for renal replacement therapy up to the age of 70, independent of renal function at baseline[23]. The question remains how to explain the observations of the present study that identified a decline of ≥1 mmHg/year SBP, DBP or PP as a predictor of kidney function decline, not only in the oldest old, as shown in the Leiden 85+ Study, but also in persons aged 60–79 years old. A decline in BP may lead to chronic hypoperfusion of the kidney, causing the kidney function to deteriorate. The cause of BP decline remains unclear. Underlying heart failure with lowered cardiac output could be a reason[24]. On the other hand, BP control which is too strict or the effects of antihypertensive medications such as RAAS system inhibitors, which influence intra-renal BP and renal perfusion could be responsible. The analyses were corrected for baseline morbidities, including the presence of heart failure and history of myocardial infarction, cardiovascular medication and baseline BP and kidney function. However, possible changes in medication intake and occurrence of new morbidities in the years after baseline could also be underlying the observed relationship. Furthermore, the results of the present study should be interpreted with caution, since they originate from an observational registry-based cohort study. However, they do provide a realistic reflection of every-day practice. Future analyses should further clarify the findings of this study before it could lead to an adaptation or refinement of the current guidelines.

This study is the first that investigated the relation between dynamic BP measurements and kidney function over time in subjects aged 60 and older. The major strengths of this study are its large primary care study population representative of the population of Flanders and the long follow-up period[13]. Because of the large number of patients included in the study we were able to perform the analyses in various age strata in order to detect possibly different

patterns due to age. This study is also the first that included the presence of multimorbidity in the analyses.

However, the study is limited in that we had neither mortality data, nor data on the start of renal replacement therapy. Second, the MDRD equation has several weaknesses as a proxy for the real kidney function. For example, loss of muscle mass in older people may falsely give reduced estimates of renal function. However, this widely used equation to estimate the eGFR corrects for age that can act as a proxy for muscle mass. Since we were interested in the evolution of kidney function in the same population, a change in equation does not affect model outcomes. Third, no data related to proteinuria or albuminuria could be used in the analyses, because they were only available for a limited number of patients. Using these limited albuminuria and proteinuria data would have caused substantial selection bias. Fourth, not all creatinine values were measured by the same laboratory or by the same creatinine assay due to the design of the database, which collects data from practices throughout Flanders. However, all Belgian laboratories are subject to quality control measures[24], which limited the analytical differences among the laboratories. Fifth, blood pressure measurements were not standardized but were reported by the general practitioner as measured with his/her own blood pressure device.

Conclusion

This large retrospective, registry–based cohort study investigated the relation between static and dynamic BP measurements and the evolution of kidney function, independent of the presence of multimorbidity. Previously found associations between baseline BP measurements and decline of kidney function in older persons were confirmed, but more importantly a decline in BP over time was identified as a strong risk factor for kidney function decline in all patients aged 60 and older, independent of the presence of multimorbidity and baseline BP.

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Contributors BV, EB and GVP performed the analyses and wrote the manuscript. CT and SE extracted the data. FB is responsible for the study concept, design and acquisition of subjects and data. All authors participated in the interpretation of the data.

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Competing interests All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethics approval Intego procedures were approved by the ethical review board of the Medical School of the Catholic University of Leuven (N° ML 1723) and by the Belgian Privacy Commission (no SCSZG/13/079).

Data sharing statement All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Transparency declaration The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Table 1. Baseline characteristics of the study population (n = 8636)

	60 – 69 years n = 4128	70 – 79 years n = 3530	≥ 80 years n = 978
Men, n (%)	2011 (48.7)	1505 (42.6)	357 (36.5)
Age (years), mean ± SD	64.7 ± 2.8	74.0 ± 2.8	83.1 ± 3.3
Hypertension, n (%)	1855 (44.9)	1738 (49.2)	451 (46.1)
Systolic blood pressure (mmHg), mean ± SD	134 ± 14	136 ± 14	135 ± 15
Systolic blood pressure categories, n (%)			
<120mmHg	394 (9.5)	264 (7.5)	70 (7.2)
120 – 129mmHg	1001 (24.2)	779 (22.1)	240 (24.5)
130 – 139mmHg	1232 (29.8)	1033 (29.3)	287 (29.3)
140 – 149mmHg	951 (23.0)	872 (24.7)	236 (24.1)
≥150mmHg	550 (13.3)	582 (16.5)	145 (14.8)
Diastolic blood pressure (mmHg), mean ± SD	80 ± 8	78 ± 7	76 ± 7
Diastolic blood pressure categories, n (%)			
<70	143 (3.5)	185 (5.2)	90 (9.2)
70 – 79mmHg	1183 (28.7)	1248 (35.4)	394 (40.3)
80 – 89mmHg	2240 (54.3)	1795 (50.8)	445 (45.5)
≥90mmHg	562 (13.6)	302 (8.6)	49 (5.0)

Pulse pressure (mmHg), mean ± SD	54 ± 11	57 ± 12	59 ± 13
Pulse pressure, n (%)			
<50mmHg	1295 (31.4)	776 (22.0)	194 (19.8)
50 – 59mmHg	1495 (36.2)	1205 (34.1)	308 (31.5)
60 – 69mmHg	940 (22.8)	972 (27.5)	282 (28.8)
≥70mmHg	398 (9.6)	577 (16.3)	194 (19.8)
Baseline eGFR (ml/min/1.73m²), mean ± SD	68.8 ± 13.8	63.2 ± 14.7	55.4 ± 15.3
Baseline eGFR categories, n (%)			
≥60ml/min/1.73m²	3167 (76.7)	2097 (59.4)	356 (36.4)
45 – 59ml/min/1.73m²	850 (20.6)	1119 (31.7)	377 (38.5)
30 – 44ml/min/1.73m²	97 (2.3)	268 (7.6)	204 (20.9)
<30ml/min/1.73m²	14 (0.3)	46 (1.3)	41 (4.2)
Charlson Comorbidity Index, median (IQR)	3 (2 – 4)	4 (3 – 5)	6 (5 – 7)
Diabetes, n (%)	859 (20.8)	800 (22.7)	220 (22.5)
Myocardial infarction, n (%)	231 (5.6)	237 (6.7)	80 (8.2)
Heart failure, n (%)	135 (3.3)	313 (8.9)	201 (20.6)
CVA or TIA, n (%)	318 (7.7)	556 (15.8)	229 (23.4)
Peripheral arterial illness, n (%)	322 (7.8)	404 (11.4)	118 (12.1)
Chronic pulmonary disease, n (%)	144 (3.5)	146 (4.1)	36 (3.7)

History of peptic ulcer disease, n (%)	381 (9.2)	393 (11.1)	108 (11.0)
Dementia, n (%)	49 (1.2)	213 (6.0)	87 (8.9)
Liver disease, n (%)	172 (4.2)	123 (3.5)	26 (2.7)
Hemiplegia, n (%)	40 (1.0)	60 (1.7)	20 (2.0)
History of cancer, n (%)	523 (12.7)	557 (15.8)	148 (15.1)
Leukemia, n (%)	19 (0.5)	24 (0.7)	6 (0.6)
Lymphoma, n (%)	20 (0.5)	27 (0.8)	7 (0.7)
Cardiovascular medication, n (%)	2061 (49.9)	1925 (54.5)	554 (56.6)
Beta-blockers, n (%)	1262 (30.6)	1122 (31.8)	247 (25.3)
ACE inhibitors, n (%)	490 (11.9)	509 (14.4)	150 (15.3)
Angiotensin receptor blocker, n (%)	362 (8.8)	300 (8.5)	79 (8.1)
Calcium antagonist, n (%)	463 (11.2)	553 (15.7)	167 (17.1)
Diuretic, n (%)	905 (21.9)	964 (27.3)	338 (34.6)

SD: standard deviation; IQR: inter-quartile range; eGFR: estimated glomerular filtration rate; CVA : cerebrovascular accident ; TIA : transient ischaemic attack; ACE: angiotensin converting enzyme.

Table 2. Baseline blood pressure as a predictor of change in eGFR in ml/min/1.73m²/year (linear regression) (n = 8636)

	60 – 69 years (n = 4128)		70 – 79 years (n = 3530)		≥ 80 years (n = 978)	
	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value
Systolic BP (per 10 mmHg)						
Unadjusted	-0.14 (-0.21, -0.066)	<0.001	-0.18 (-0.27, -0.083)	<0.001	-0.26 (-0.47, -0.043)	0.018
Adjusted[a]	-0.14 (-0.21, -0.064)	<0.001	-0.19 (-0.29, -0.094)	<0.001	-0.27 (-0.49, -0.055)	0.014
Adjusted[b]	-0.11 (-0.18, -0.034)	0.004	-0.14 (-0.24, -0.048)	0.003	-0.24 (-0.46, -0.024)	0.029
CCI (per point increase)	-0.15 (-0.23, -0.061)	0.001	-0.27 (-0.37, -0.18)	<0.001	0.003 (-0.20, 0.21)	0.97
CV medication	-0.28 (-0.49, -0.073)	0.008	-0.57 (-0.85, -0.29)	<0.001	-0.49 (-1.1, 0.17)	0.14
Baseline eGFR (per ml/min/1.73m²)	-0.014 (-0.021, -0.006)	<0.001	-0.027 (-0.036, -0.017)	<0.001	-0.004 (-0.028, 0.019)	0.73
Diastolic BP (per 10 mmHg)						
Unadjusted	-0.077 (-0.21, 0.059)	0.27	-0.12 (-0.31, 0.069)	0.21	-0.20 (-0.64, 0.24)	0.38
Adjusted[a]	-0.090 (-0.23, 0.045)	0.19	-0.16 (-0.35, 0.032)	0.10	-0.22 (-0.66, 0.23)	0.34
Adjusted[b]	-0.069 (-0.21, 0.068)	0.33	-0.14 (-0.33, 0.056)	0.17	-0.19 (-0.63, 0.26)	0.41
CCI (per point increase)	-0.15 (-0.24, -0.066)	<0.001	-0.28 (-0.38, -0.19)	<0.001	0.001 (-0.20, 0.20)	0.99
CV medication	-0.33 (-0.53, -0.12)	0.002	-0.61 (-0.88, -0.33)	<0.001	-0.58 (-1.2, 0.065)	0.078
Baseline eGFR (per ml/min/1.73m²)	-0.014 (-0.022, -0.007)	<0.001	-0.027 (-0.037, -0.017)	<0.001	-0.004 (-0.028, 0.020)	0.73
Pulse pressure (per 10 mmHg)						

Unadjusted	-0.18 (-0.27, -0.090)	<0.001	-0.20 (-0.31, -0.089)	<0.001	-0.26 (-0.50, -0.025)	0.031
Adjusted[a]	-0.17 (-0.26, -0.081)	<0.001	-0.20 (-0.32, -0.092)	<0.001	-0.27 (-0.51, -0.033)	0.026
Adjusted[b]	-0.14 (-0.23, -0.043)	0.004	-0.15 (-0.26, -0.037)	0.009	-0.25 (-0.49, -0.002)	0.048
CCI (per point increase)	-0.14 (-0.22, -0.055)	0.001	-0.27 (-0.36, -0.18)	<0.001	0.006 (-0.20, 0.21)	0.95
CV medication	-0.30 (-0.51, -0.087)	0.005	-0.59 (-0.86, -0.31)	<0.001	-0.51 (-1.16, 0.14)	0.12
Baseline eGFR (per ml/min/1.73m²)	-0.014 (-0.022, -0.006)	<0.001	-0.027 (-0.037, -0.017)	<0.001	-0.004 (-0.028, 0.019)	0.72

[a], adjusted for age and gender.

[b], adjusted for gender, age, baseline Charlson Comorbidity Index, baseline cardiovascular medication, time between the first and last eGFR measurement after 2002 (≥ 5 years), baseline eGFR.

BP: blood pressure; CI: confidence interval; CCI: Charlson Comorbidity Index; CV: cardiovascular; eGFR: estimated glomerular filtration rate.

Table 3. Correlation between change in blood pressure and change in eGFR in ml/min/1.73m²/year (linear regression) (n = 7283)

	60 – 69 years (n = 3696)		70 – 79 years (n = 2933)		≥ 80 years (n = 654)	
	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value
Systolic BP change (per mmHg/year)						
Unadjusted	0.11 (0.058, 0.16)	<0.001	0.14 (0.080, 0.19)	<0.001	0.17 (0.052, 0.29)	0.005
Adjusted[a]	0.10 (0.052, 0.15)	<0.001	0.13 (0.076, 0.19)	<0.001	0.17 (0.048, 0.29)	0.006
Adjusted[b]	0.030 (-0.025, 0.086)	0.28	0.069 (0.006, 0.13)	0.031	1.2 (0.34, 2.1)	0.007
Baseline BP pressure (per 10mmHg)	-0.15 (-0.22, -0.074)	<0.001	-0.14 (-0.23, -0.042)	0.005	-0.11 (-0.37, 0.15)	0.42
Baseline CCI (per point increase)	-0.21 (-0.28, -0.13)	<0.001	-0.28 (-0.36, -0.19)	<0.001	-0.10 (-0.29, 0.083)	0.28
Baseline CV medication	-0.25 (-0.44, -0.069)	0.007	-0.50 (-0.73, -0.26)	<0.001	-0.61 (-1.2, -0.023)	0.042
Baseline eGFR (per ml/min/1.73m²)	-0.015 (-0.021, -0.008)	<0.001	-0.021 (-0.030, -0.013)	<0.001	-0.013 (-0.035, 0.009)	0.24
Interaction term 'systolic BP change x baseline systolic BP'	NS	NS	NS	NS	-0.079 (-0.14, -0.014)	0.018
Diastolic BP change (per mmHg/year)						
Unadjusted	0.16 (0.072, 0.25)	<0.001	0.18 (0.073, 0.29)	0.001	0.38 (0.15, 0.62)	0.002
Adjusted[a]	0.15 (0.064, 0.24)	0.001	0.18 (0.069, 0.28)	0.001	0.37 (0.14, 0.61)	0.002
Adjusted[b]	0.11 (0.008, 0.21)	0.034	0.14 (0.019, 0.25)	0.023	0.42 (0.16, 0.67)	0.001
Baseline diastolic BP (per 10mmHg)	-0.082 (-0.22, 0.054)	0.24	0.57 (0.048, 1.1)	0.032	0.25 (-0.20, 0.71)	0.27

Baseline CCI (per point increase)	-0.22 (-0.29, -0.14)	<0.001	0.91 (0.029, 1.8)	0.043	-0.13 (-0.32, 0.052)	0.16
Baseline CV medication	-0.31 (-0.50, -0.13)	0.001	-0.55 (-0.78, -0.32)	<0.001	-0.66 (-1.2, -0.080)	0.026
Baseline eGFR (per ml/min/1.73m²)	-0.015 (-0.022, -0.008)	<0.001	-0.021 (-0.030, -0.013)	<0.001	-0.015 (-0.037, 0.007)	0.18
Interaction term 'baseline diastolic BP x baseline CCI'	NS	NS	-0.15 (-0.27, -0.041)	0.008	NS	NS
Pulse pressure change (per mmHg/year)						
Unadjusted	0.092 (0.031, 0.15)	0.003	0.13 (0.062, 0.20)	<0.001	0.11 (-0.038, 0.25)	0.15
Adjusted[a]	0.086 (0.025, 0.15)	0.006	0.12 (0.057, 0.19)	<0.001	0.10 (-0.042, 0.24)	0.17
Adjusted[b]	0.17 (0.015, 0.32)	0.031	0.050 (-0.025, 0.13)	0.19	0.064 (-0.10, 0.23)	0.45
Baseline pulse pressure (per 10mmHg)	-0.19 (-0.28, -0.094)	<0.001	-0.15 (-0.26, -0.043)	0.006	-0.052 (-0.31, 0.20)	0.69
Baseline CCI (per point increase)	-0.20 (-0.27, -0.13)	<0.001	-0.28 (-0.36, -0.19)	<0.001	-0.13 (-0.31, 0.059)	0.18
Baseline CV medication	-0.27 (-0.46, -0.091)	0.003	-0.52 (-0.75, -0.28)	<0.001	-0.62 (-1.2, -0.026)	0.041
Baseline eGFR (per ml/min/1.73m²)	-0.015 (-0.022, -0.008)	<0.001	-0.021 (-0.030, -0.013)	<0.001	-0.014 (-0.036, 0.008)	0.22
Interaction term 'pulse pressure change x baseline CCI'	-0.052 (-0.096, -0.009)	0.018	NS	NS	NS	NS

[a], adjusted for age and gender.

[b], adjusted for gender, age at baseline, baseline Charlson Comorbidity Index, baseline cardiovascular medication, time between the first and last eGFR measurement after 2002, baseline eGFR and baseline blood pressure measurements.

BP: blood pressure; CI: confidence interval; CCI: Charlson Comorbidity Index; CV: cardiovascular; eGFR: estimated glomerular filtration rate.

Figure 1. Prevalence of rapid annual decline in kidney function according to different blood pressure measurements

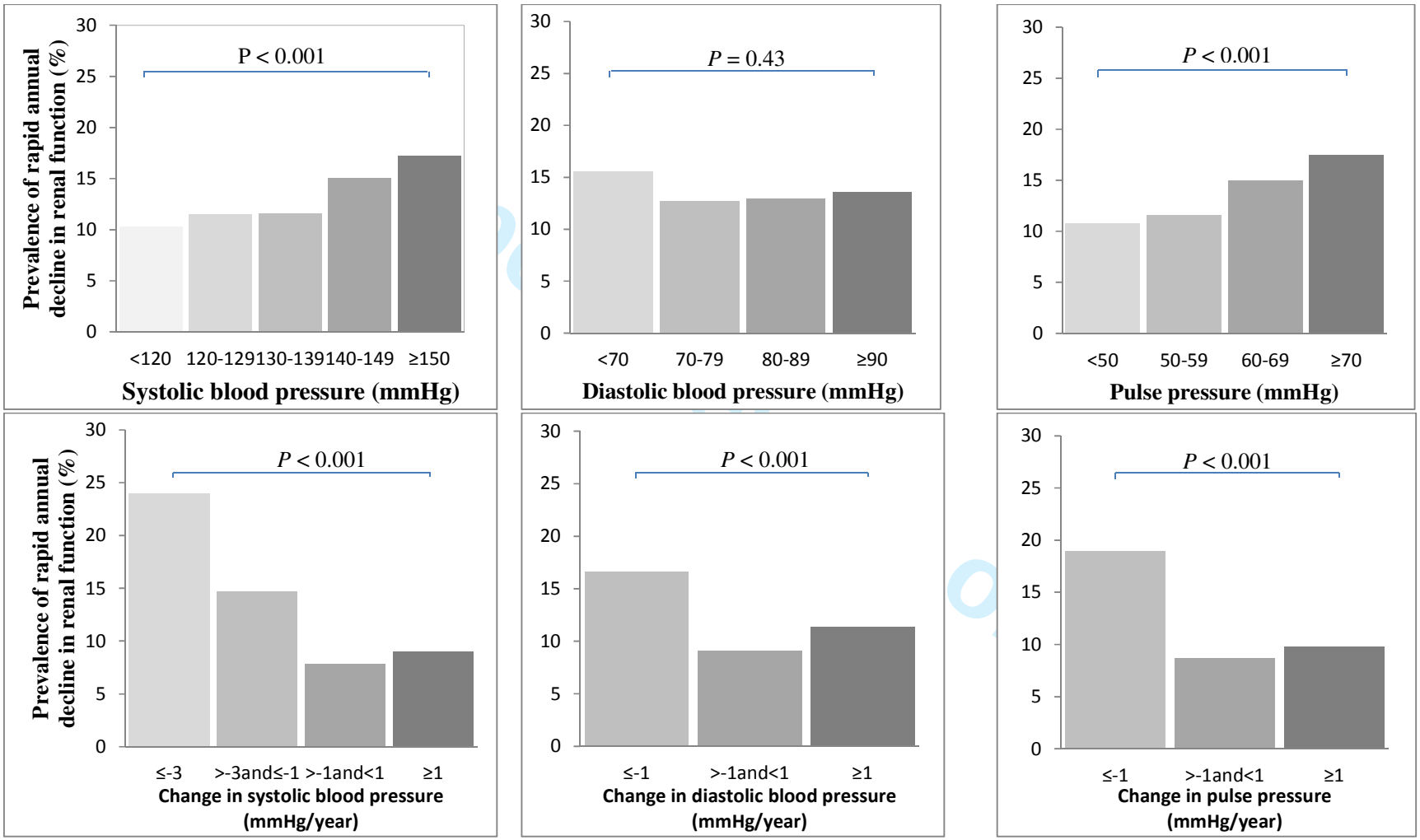
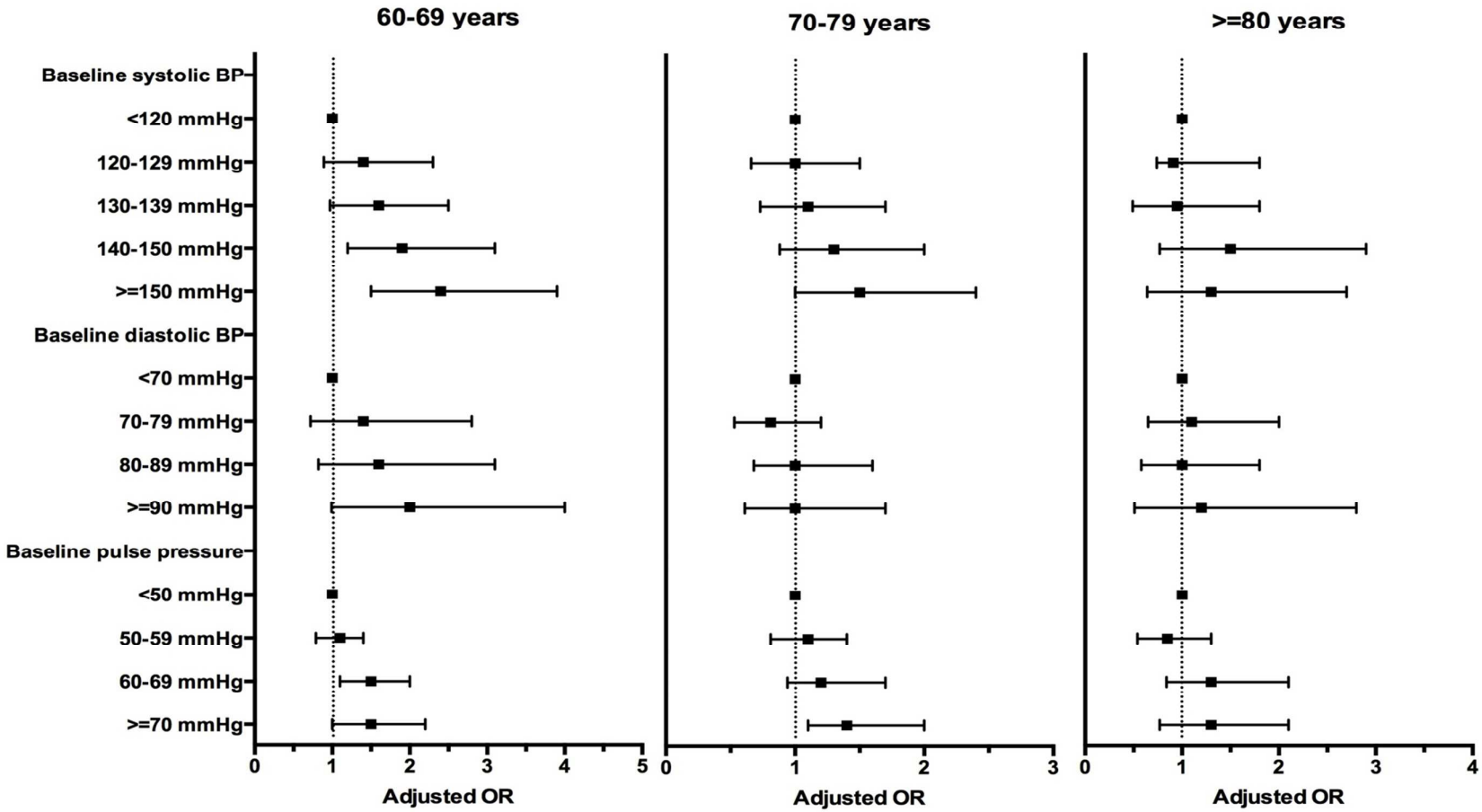
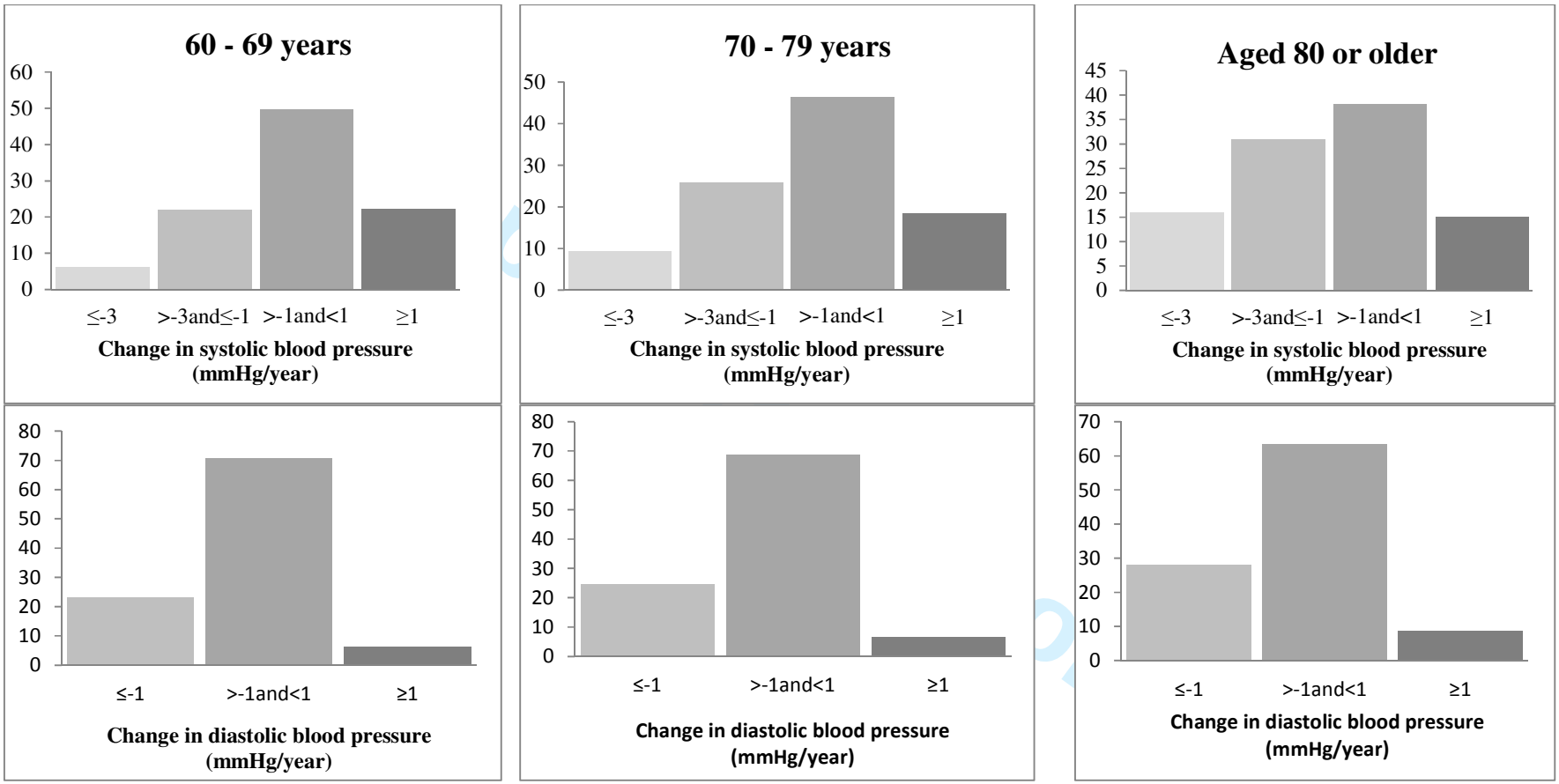


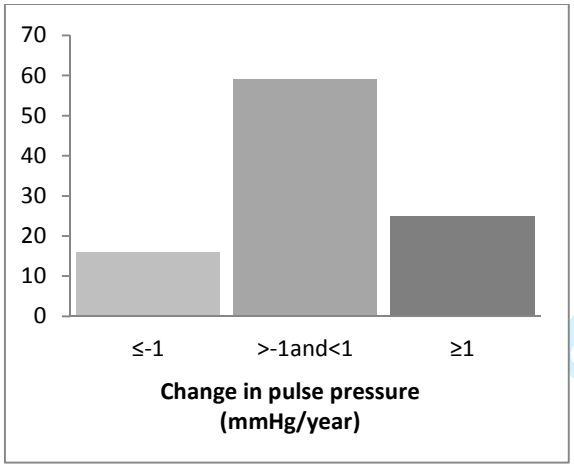
Figure 2. Baseline blood pressure as a predictor of rapid annual decline in kidney function (≥3ml/min/1.73m²/year) (logistic regression) (n = 8636)

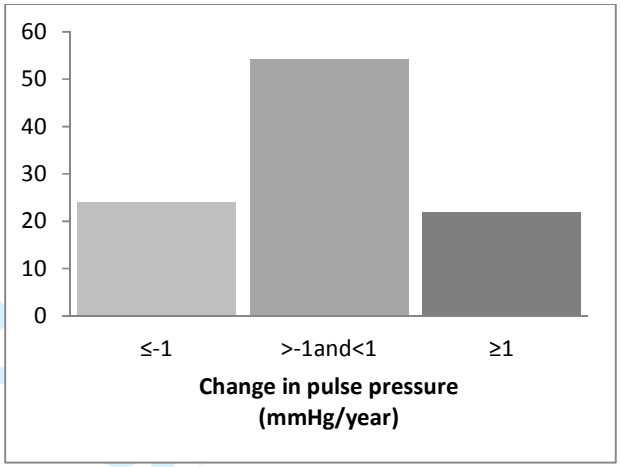


Adjusted for gender, age, baseline Charlson Comorbidity Index, baseline cardiovascular medication, time between the first and last eGFR measurement after 2002, baseline eGFR.

Figure 3. Prevalence (%) of change in systolic and diastolic blood pressure and pulse pressure in different age strata







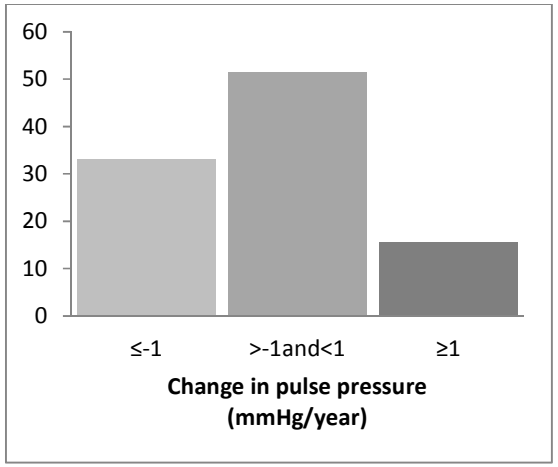
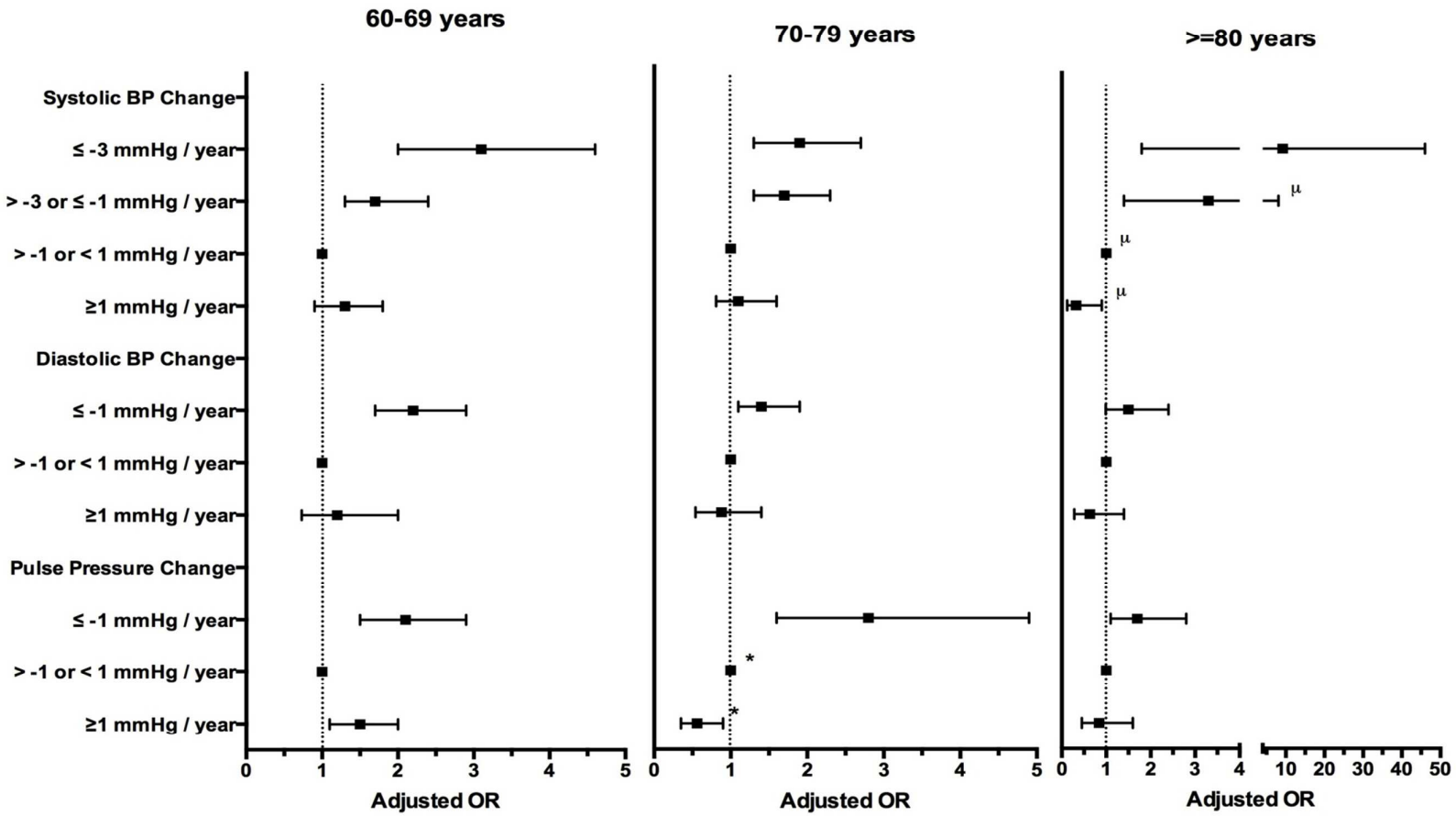


Figure 4. Correlation between change in blood pressure and a rapid annual decline in kidney function (≥3ml/min/1.73m²/year) (logistic regression) (n = 7283)



Adjusted for gender, age at baseline, baseline measurements (systolic blood pressure or diastolic blood pressure or pulse pressure), baseline Charlson Comorbidity Index, baseline cardiovascular medication, time between the first and last eGFR measurement after 2002, baseline eGFR.

[μ], adjusted for interaction term 'systolic BP change x baseline CCI' (adjusted OR of the interaction term 1.2 (95% CI 1.0 – 1.3).

[*], adjusted for interaction term 'pulse pressure change x baseline pulse pressure' (adjusted OR of the interaction term 1.3 (95% CI 1.1 – 1.5).

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	OK
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	OK
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	OK
Objectives	3	State specific objectives, including any prespecified hypotheses	OK
Methods			
Study design	4	Present key elements of study design early in the paper	OK
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	OK
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	OK
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	OK
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	OK
Bias	9	Describe any efforts to address potential sources of bias	OK
Study size	10	Explain how the study size was arrived at	OK
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	OK
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	OK
		(*b*) Describe any methods used to examine subgroups and interactions	OK
		(*c*) Explain how missing data were addressed	OK
		(*d*) If applicable, explain how loss to follow-up was addressed	OK
		(*e*) Describe any sensitivity analyses	OK
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	OK
		(b) Give reasons for non-participation at each stage	OK
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	OK
		(b) Indicate number of participants with missing data for each variable of interest	OK
		(c) Summarise follow-up time (eg, average and total amount)	OK
Outcome data	15*	Report numbers of outcome events or summary measures over time	OK
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which	OK

		confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	OK
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	OK
Discussion			
Key results	18	Summarise key results with reference to study objectives	OK
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	OK
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	OK
Generalisability	21	Discuss the generalisability (external validity) of the study results	OK
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	OK

*Give information separately for exposed and unexposed groups.

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The correlation between blood pressure and kidney function decline in older people: a registry-based cohort study

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The correlation between blood pressure and kidney function decline in older people: a registry-based cohort study

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Number of figures: 4

ABSTRACT

Objectives:

To examine the relation between static and dynamic blood pressure (BP) measurements and the evolution of kidney function in older people, adjusted for the presence of multimorbidity.

Design:

Retrospective cohort study during a 10-year time interval (2002–2012) in three age strata of patients aged 60 and older.

Setting:

Primary care registration network with 97 general practitioners working in 55 practices regularly submitting collected patient data.

Participants:

All patients with at least one BP measurement in 2002 and at least four serum creatinine measurements after 2002 (n=8,636). A modified Charlson Comorbidity Index (mCCI) at baseline was registered. Change in systolic and diastolic BP and pulse pressure (PP) from 2002 onwards was calculated. The relation between kidney function evolution and baseline BP and change in BP was examined using linear and logistic regression analysis.

Main outcome measures:

The slope of the estimated glomerular filtration rate (eGFR, MDRD equation) was calculated by the ordinal least square method. A rapid annual decline of kidney function was defined as ≥3ml/min/1.73m^2/year.

Results:

Rapid annual decline of kidney function occurred in 1,130 patients (13.1%). High baseline SBP and PP predicted kidney function decline in participants aged 60–79 years. No correlation between baseline BP and kidney function decline was found in subjects aged 80 and older. An annual decline of ≥1mmHg in SBP and PP was a strong risk factor for a rapid

annual kidney function decline in all age strata, independent of baseline BP and mCCI. A decline in DBP was also a strong independent predictor in participants aged 60–79 years.

Conclusions:

The present study identified a decline in BP over time as a strong risk factor for kidney function decline in all age strata, independent of the presence of multimorbidity and baseline BP.

Strengths and limitations of this study

- The first study that investigated the relation between dynamic blood pressure measurements and kidney function over time in subjects aged 60 and older.
- Large primary care study population representative of the population of Flanders with a long follow-up period.
- Analyses in various age strata were performed in order to detect possibly different patterns due to age.
- The presence of multimorbidity was included in the analyses.
- Lack of mortality data, data on renal replacement therapy, insufficient data on proteinuria/albuminuria and no standardized measurements of creatinine and blood pressure.
- The results are purely descriptive and were not adjusted for time-dependent changes in medication prescription and incident comorbidity.
- Weaknesses inherent to a retrospective design and registry data: possible healthy survivor bias, no information about missing data and loss to follow-up.

Introduction

Belgium and other western countries are facing a grey epidemic. Furthermore, a "double grey" epidemic is expected, given the proportionally higher increase of persons aged 80 and older. In 2012, 17.4% and 5.2% of the total Belgian population was aged 65 or older, and 80 or older, respectively. By 2050, these percentages will rise to 24.5% and 9.5%, respectively[1]. This will probably lead to a dramatic increase of chronic diseases and an increased number of patients with multiple comorbidities.

The prevalence of chronic kidney disease (CKD) (estimated glomerular filtration rate (eGFR) <60ml/min/1.73m²) increases with ageing to approximately 10% at the age of 65 years and to 60% in persons aged 80 and older[2-4]. CKD and especially end-stage renal disease is recognized as an important problem in public health. First, the cost of dialysis per patient per year is more than 50,000 euro, and >1% of the public health budget of the Belgian government is used to cover these costs. Second, CKD increases the risk of cardiovascular events and mortality. Moreover, many medications cannot be used or need dose adjustment in patients with CKD[5,6].

Arterial hypertension and cardiovascular disease have been identified both as a cause and as a consequence of CKD[7-9] and end-stage renal disease (ESRD)[4]. This has been well studied in the younger population. However, to date, many clinical trials and clinical studies have excluded older persons and especially older persons with multiple chronic conditions[10]. Furthermore, studies investigating the association between arterial hypertension and the risk of kidney function decline in older persons are scarce. The Cardiovascular Health study[11] and the SHEP study[8] identified baseline blood pressure (BP) as a risk factor for kidney function decline in older persons. The Leiden 85 Plus-study[12] on the other hand, did not find a relation between baseline BP and kidney function decline. It reported a decline in systolic (SBP) and diastolic blood pressure (DBP) between ages 85 and 90 to be related to an accelerated decline

of creatinine clearance over time. To date , the relation between the evolution of BP and that of kidney function over time has not been studied in persons aged 60 years and older. Moreover, the impact of concomitant chronic conditions on this relation has not been examined.

Therefore, the aim of this retrospective cohort study within the framework of a large Flemish morbidity registry was to study the relation between static and dynamic BP measurements and the evolution of kidney function over time in three age strata of subjects aged 60 years and older, adjusted for the presence of multimorbidity.

Methods

Study design and study population

Data were obtained from Intego, a Belgian general practice-based morbidity registration network at the Department of General Practice of the University of Leuven[13]. Intego procedures were approved by the ethical review board of the Medical School of the Catholic University of Leuven (N° ML 1723) and by the Belgian Privacy Commission (no SCSZG/13/079). Ninety-seven general practitioners (GPs) of 55 practices evenly spread throughout Flanders, Belgium, collaborate in the Intego project. GPs applied for inclusion in the registry. Before acceptance of their data, registration performance was audited using algorithms to compare their results with those of all other applicants. Only the data of the practices with optimal registration performance were included in the database. The Intego GPs prospectively and routinely registered all new diagnoses and new drug prescriptions, as well as laboratory test results and patient information, using computer-generated keywords internally linked to codes.

With specially framed extraction software, new data were encrypted and collected from the GPs' personal computers and entered into a central database. Registered data were continuously updated and historically accumulated for each patient. New diagnoses were classified according to a very detailed thesaurus automatically linked to the International Classification of Primary Care (ICPC-2) and International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). Drugs were classified according to the WHO's Anatomical Therapeutic Chemical (ATC) classification system.

The present study used Intego data of a 10-year time period from January 1st 2002 to January 1st 2012. First, patients aged 60 years or older in 2002 with a BP measurement registered in 2002 were selected (n = 12,904). Second, patients with at least four serum creatinine measurements after 2002 were withheld (n = 8,636).

Clinical characteristics

Blood pressure

BP measurements registered by the GP in 2002 (baseline or static BP) and yearly thereafter were used. For each year of the study time interval, a single SBP and DBP value was used in the analyses. The average BP of the two lowest values of that year's last three measurements were used[14]. Pulse pressure (PP) was calculated as the difference between the SBP and the DBP. Categories of baseline BP measurements were based on previously reported categories[11].

The slope of the SBP, DBP and PP (mmHg/year) was calculated for every study participant of whom BP measurements were available for at least four years following 2002 (n = 7,283). The slope, or dynamic BP, was calculated according to the ordinal least square method. Patients were divided in categories based on the slope using predefined subgroups of ≤-3, >-3 or ≤-1, >-1 or <1, and ≥1mmHg/year for the SBP and ≤-1, >-1 or <1 and ≥1mmHg/year for the DBP and the PP.

Kidney function

Kidney function was expressed as the eGFR calculated with the MDRD (Modification of Diet in Renal Disease) equation[15]. Baseline eGFR was calculated based on the average serum creatinine value of the last two measurements in 2002.

The slope of the eGFR (ml/min/1.73m^2/year) for every participant was calculated according to the ordinal least square method using all (range 4–50) available eGFR values. A rapid annual decline of kidney function was defined as ≥3ml/min/1.73m^2/year; this change is known to be associated with clinically deleterious outcomes[11].

Comorbidity

Medical history at baseline of every study participant was registered. The Charlson Comorbidity Index (CCI) includes 19 chronic diseases that are weighted based on their

association with mortality[16]. A modified CCI (mCCI) at baseline was calculated for every study participant[17]. Connective tissue disease could not be reliably assessed from the registry and the differentiation between cancers with or without metastasis, diabetes with or without end organ failure and mild or moderate to severe liver disease could not be made. Consequently all patients with cancers were assigned the same score (=2), as well as all patients with diabetes (=1) and with liver disease (=1).

The prescription of cardiovascular medication at baseline including beta-blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, calcium antagonists and diuretics was extracted from the database for every study participant.

Data analysis

Continuous data are presented as the mean and standard deviation (SD). Categorical data are presented as numbers and frequencies. All further analyses were performed in three age strata at baseline: 60–69 years, 70–79 years and ≥80 years.

The correlation between baseline BP measurements and kidney function decline and change in BP and kidney function decline was first explored by calculating odds ratios (ORs) with the corresponding 95% confidence intervals (CIs) using bivariate and multivariable linear regression analysis and adjusting for age, gender, mCCI at baseline, cardiovascular medication at baseline, time between the first and last eGFR measurement after 2002 (≥ or <5 years) and baseline eGFR (and baseline BP measurements for BP change). Second, the relation between categories of baseline BP measurements or categories of BP change and a rapid annual decline of kidney function was examined with bivariate and multivariable logistic regression analysis.

In order to avoid co-linearity, the correlation coefficients between all covariates were calculated. In case of co-linearity (*r*-value >0.90), only one of the two covariates was considered in the multivariate model. Interaction was checked between the slope of the BP

measurement and the baseline BP measurement, between the slope of the BP measurement and the mCCI, and between the baseline BP measurement and the mCCI. If the interaction term was statistically significant (P <0.05), it was kept in the model. A goodness-of-fit test was performed with the ANOVA (analysis of variance) F test for the linear regression models and the Hosmer-Lemeshow test for the logistic regression models and was reported when the model did not fit the observed data (ANOVA F test $P \geq 0.05$ and Hosmer-Lemeshow test P <0.05).

Statistical analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA) and GraphPad prism 6 (GraphPad Software, San Diego, CA, USA).

Results

In total, 8,636 patients from the Intego registry had at least one BP measurement registered in 2002 and at least four serum creatinine measurements after 2002. The baseline clinical characteristics of the study population according to their age at baseline are presented in Table 1. After baseline, rapid annual decline of kidney function occurred in 1,130 patients (13.1%): in 9.4% (n = 387) of patients aged 60–69 years, in 15.1% (n = 533) of patients aged 70–79 years and in 21.5% (n = 210) of patients aged 80 or older. Figure 1 presents the prevalence of rapid annual decline of kidney function according to categories of baseline BP and categories of change in BP. Prevalence of rapid decline of kidney function increased with higher baseline SBP and PP (χ^2 test, P <0.001), as well as with increased decline in SBP, DBP and PP (χ^2 test, P <0.001).

Correlation between systolic blood pressure and kidney function decline

Baseline systolic blood pressure

An inverse linear relation was found between baseline SBP and kidney function decline in all age strata, also after adjusting for confounders (Table 2). The goodness-of-fit test was not significant in the oldest age stratum (ANOVA F test, P = 0.23). Categories of higher baseline SBP predicted rapid decline of kidney function in patients aged 60–69 years (adjusted OR 1.9 (95% CI 1.2–3.1) and adjusted OR 2.4 (95% CI 1.5–3.9) for 140–150mmHg and ≥150mmHg respectively) (Figure 2). In patients aged 70–79 years a trend was seen for the highest category (adjusted OR 1.5 (95% CI 1.0–2.4), P = 0.052), and no correlation was found in patients aged 80 or older (Hosmer-Lemeshow test (≥80 years), P = 0.005).

Change in systolic blood pressure

Figure 3 presents the prevalence of the change in blood pressure for the various age strata. A positive and independent linear relation was found between a change in SBP and a

change in kidney function in the oldest two age strata; the more SBP decreased, the more the kidney function decreased in the years after 2002 (Table 3). Categories of decreasing SBP showed an increased risk of rapid kidney function decline compared with no change in patients 60–69 years (adjusted OR 1.7 (95% CI 1.3–2.4) and adjusted OR 3.1 (95% CI 2.0–4.6), respectively), in patients 70–79 years (adjusted OR 1.7 (95% CI 1.3–2.3) and adjusted OR 1.9 (95% CI 1.3–2.7), respectively) and in patients aged 80 and older (adjusted OR 3.3 (95% CI 1.4–8.1) and adjusted OR 9.2 (95% CI 1.8–46), respectively) (Figure 4). In the oldest age stratum the model was also corrected for the interaction term between change in SBP and baseline mCCI (adjusted OR 1.2 (95% CI 1.0–1.3), $P = 0.026$).

Correlation between diastolic blood pressure and kidney function decline

Baseline diastolic blood pressure

No linear relation was found between baseline DBP and kidney function decline (Table 2). The goodness-of-fit test for the adjusted model was not significant in the oldest age stratum (ANOVA F test, P = 0.64). A trend of predicting rapid decline of kidney function was only seen in the highest category of baseline DBP in patients aged 60–69 years (adjusted OR 2.0 (95% CI 0.99–4.0)). The Hosmer-Lemeshow test showed the adjusted model in the oldest patients did not fit the observed data (P <0.001).

Change in diastolic blood pressure

An independent and positive linear relation was found between change in DBP and change in kidney function in all age strata (Table 3). A decline in DBP predicted rapid decline of kidney function in patients aged 60–69 years and 70–79 years (adjusted OR 2.2 (95% CI 1.7–2.9) and adjusted OR 1.4 (1.1–1.9), respectively). In the oldest age stratum a trend of higher risk in patients with a decline in DBP was seen (adjusted OR 1.5 (95% CI 0.99–2.4), $P = 0.054$ (Hosmer-Lemeshow test, $P = 0.020$)).

Correlation between pulse pressure and kidney function decline

Baseline pulse pressure

An inverse linear correlation was found between baseline PP and decline in kidney function in all age strata. Only in the oldest age stratum was the goodness-of-fit test for the adjusted model not significant (ANOVA F test, P = 0.29). The highest categories of baseline PP predicted rapid decline of kidney function in patients aged 60–69 years and aged 70–79 years (adjusted OR 1.5 (95% CI 1.0–2.2) and adjusted OR 1.4 (95% CI 1.1–2.0).

Change in pulse pressure

A change in PP was independently correlated with change in kidney function in the youngest age group (Table 3). The goodness-of-fit test for the adjusted model was not significant in the oldest age stratum (ANOVA F test, P = 0.18). Patients in all age strata in the category ≤-1mmHg/year change showed a higher risk of rapid annual decline of kidney function compared with patients without change in PP (adjusted OR 2.1 (95% CI 1.5–2.9), adjusted OR 2.8 (95% CI 1.6–4.9) and adjusted OR 1.7 (95% CI 1.1–2.8), respectively). In patients 70 – 79 years the model was also corrected for the interaction term between change in PP and baseline PP (adjusted OR 1.3 (95% CI 1.1–1.5), *P* = 0.009).

Discussion

In this large retrospective population-based cohort study the relation between static and dynamic BP measurements and kidney function over time in older subjects was investigated. The present study confirmed previously found associations between baseline BP measurements and decline of kidney function, but more importantly identified a decline in BP over time as a strong risk factor for kidney function decline in all age strata, independent of the presence of multimorbidity and baseline BP. In people aged 60–69 years, high baseline SBP and PP predicted kidney function decline and a decline in SBP, DBP and PP in the years after baseline were related to a rapid annual decline in kidney function. In patients aged 70–79 years a relation between high baseline SBP and PP and kidney function decline was confirmed, and an association between a decline in SBP, DBP and PP after baseline and a decline in kidney function was seen. In the oldest age stratum, no correlation between baseline BP measurements and kidney function decline was found. A decline in SBP and PP in the years after baseline, however, predicted a rapid annual decline in kidney function in this age group. Moreover, DBP tended to decline.

To date, there is no consensus about which level of BP causes a higher risk of cardiovascular mortality, morbidity or kidney function decline in the elderly population. In the KDOQI/KDIGO guidelines tailored BP control is advised in older persons for the preservation of the kidney function[18]. This evidence is based on several studies reporting on arterial hypertension as a risk factor for the development of CKD, as well as on the evolution of CKD to ESRD in the global population. The MDRD-trial[19] studied arterial hypertension as a risk factor for kidney function decline in stage 3 and 4 CKD in a population aged 18-70 years. They studied the impact of baseline and follow-up BP during 2.2 years on the evolution of kidney function in an intervention (antihypertensive) and in a control group. No effect of high blood pressure on kidney function decline was found except for severe proteinuria

>3g/day. In a cohort of 332,544 men aged 35–57 years, Klag et al[20] found a 22% higher risk of ESRD in patients with arterial hypertension stage 4, defined as a SBP >210mmHg or a DBP >120mmHg, compared to that of patients with normal BP. In a large Japanese cohort, Tozawa et al[21] included 98,759 patients aged 20–98 years. They found higher baseline SBP and DBP showed a significant risk of development of ESRD. Cumulative incidence for ESRD in patients with severe arterial hypertension was 1.7% vs 0.2% in patients with a normal BP. Finally, Van Pottelbergh et al.[22] studied risk factors for ESRD in patients aged 50 years and older in the same Flemish cohort study as the present study did. Baseline arterial hypertension (BP ≥140/90mmHg) was found to be a significant risk factor for the development of ESRD (adjusted Hazard Ratio 1.25 (95% CI 1.22–1.28)).

Studies investigating the impact of BP on the evolution of kidney function in older persons are extremely rare. Some studied the risk of baseline BP for kidney function decline. Rifkin et al.[11] found baseline SBP to have the strongest association with rapid annual kidney function decline in persons aged 65 years or older, with 14% increased hazard of rapid decline per 10mmHg, independent of other BP measurements. The SHEP-trial[8] used their placebo-arm to study the relation between baseline BP and a yearly incident increase of serum creatinine (≥0.4mg/dl). They found higher baseline SBP increased the relative risk of kidney function decline. A positive trend was found for DBP, however, without correction for comorbidity. The relation between baseline BP and the evolution of SBP, DBP and PP and kidney function decline in a 5-year time interval has only been studied in patients aged 85 and older[12]. The Leiden 85+ study reported that elevated baseline SBP and DBP did not influence the annual decline in renal function in the oldest individuals. However, DBP <70mmHg and a decline in SBP or DBP was related to an accelerated decline of creatinine clearance over time. The present study results are in line with these findings.

The deleterious effect of higher baseline BP measurements on the evolution of the kidney function in persons up to 80 years was confirmed by the present study. Furthermore, intervention trials have shown that BP lowering prevents the need for renal replacement therapy up to the age of 70, independent of renal function at baseline[23]. The question remains how to explain the observations of the present study that identified a decline of ≥1 mmHg/year SBP, DBP or PP as a predictor of kidney function decline, not only in the oldest old, as shown in the Leiden 85+ Study, but also in persons aged 60–79 years old. A decline in BP may lead to chronic hypoperfusion of the kidney, causing the kidney function to deteriorate. The cause of BP decline remains unclear. Underlying heart failure with lowered cardiac output could be a reason[24]. On the other hand, BP control which is too strict or the effects of antihypertensive medications such as RAAS system inhibitors, which influence intra-renal BP and renal perfusion could be responsible. The analyses were corrected for baseline morbidities, including the presence of heart failure and history of myocardial infarction, cardiovascular medication and baseline BP and kidney function. However, possible changes in medication intake and occurrence of new morbidities in the years after baseline could also be underlying the observed relationship. Furthermore, the results of the present study should be interpreted with caution, since they originate from an observational registry-based cohort study. However, they do provide a realistic reflection of every-day practice. Future analyses should further clarify the findings of this study before it could lead to an adaptation or refinement of the current guidelines.

This study is the first that investigated the relation between dynamic BP measurements and kidney function over time in subjects aged 60 and older. The major strengths of this study are its large primary care study population representative of the population of Flanders and the long follow-up period[13]. Because of the large number of patients included in the study we were able to perform the analyses in various age strata in order to detect possibly different

patterns due to age. This study is also the first that included the presence of multimorbidity in the analyses.

However, the study is limited in that we had neither mortality data, nor data on the start of renal replacement therapy. Second, the MDRD equation has several weaknesses as a proxy for the real kidney function. For example, loss of muscle mass in older people may falsely give reduced estimates of renal function. However, this widely used equation to estimate the eGFR corrects for age that can act as a proxy for muscle mass. Since we were interested in the evolution of kidney function in the same population, a change in equation does not affect model outcomes. Third, no data related to proteinuria or albuminuria could be used in the analyses, because they were only available for a limited number of patients. Using these limited albuminuria and proteinuria data would have caused substantial selection bias. Fourth, not all creatinine values were measured by the same laboratory or by the same creatinine assay due to the design of the database, which collects data from practices throughout Flanders. However, all Belgian laboratories are subject to quality control measures[25], which limited the analytical differences among the laboratories. Fifth, blood pressure measurements were not standardized but were reported by the general practitioner as measured with his/her own blood pressure device.

Conclusion

This large retrospective, registry–based cohort study investigated the relation between static and dynamic BP measurements and the evolution of kidney function, independent of the presence of multimorbidity. Previously found associations between baseline BP measurements and decline of kidney function in older persons were confirmed, but more importantly a decline in BP over time was identified as a strong risk factor for kidney function decline in all patients aged 60 and older, independent of the presence of multimorbidity and baseline BP.

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Contributors BV, EB and GVP performed the analyses and wrote the manuscript. CT and SE extracted the data. FB is responsible for the study concept, design and acquisition of subjects and data. All authors participated in the interpretation of the data.

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Competing interests All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethics approval Intego procedures were approved by the ethical review board of the Medical School of the Catholic University of Leuven (N° ML 1723) and by the Belgian Privacy Commission (no SCSZG/13/079).

Data sharing statement All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Transparency declaration The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Figure legends

Figure 1. Prevalence of rapid annual decline in kidney function according to different blood pressure measurements

Figure 2. Baseline blood pressure as a predictor of rapid annual decline in kidney function (≥3ml/min/1.73m²/year) (logistic regression) (n = 8636)

Adjusted for gender, age, baseline Charlson Comorbidity Index, baseline cardiovascular medication, time between the first and last eGFR measurement after 2002, baseline eGFR.

Figure 3. Prevalence (%) of change in systolic and diastolic blood pressure and pulse pressure in different age strata

Figure 4. Correlation between change in blood pressure and a rapid annual decline in kidney function (≥3ml/min/1.73m²/year) (logistic regression) (n = 7283)

Adjusted for gender, age at baseline, baseline measurements (systolic blood pressure or diastolic blood pressure or pulse pressure), baseline Charlson Comorbidity Index, baseline cardiovascular medication, time between the first and last eGFR measurement after 2002, baseline eGFR.

[μ], adjusted for interaction term 'systolic BP change x baseline CCI' (adjusted OR of the interaction term 1.2 (95% CI 1.0 – 1.3).

[*], adjusted for interaction term 'pulse pressure change x baseline pulse pressure' (adjusted OR of the interaction term 1.3 (95% CI 1.1 – 1.5).

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Table 1. Baseline characteristics of the study population (n = 8636)

	60 – 69 years n = 4128	70 – 79 years n = 3530	≥ 80 years n = 978
Men, n (%)	2011 (48.7)	1505 (42.6)	357 (36.5)
Age (years), mean ± SD	64.7 ± 2.8	74.0 ± 2.8	83.1 ± 3.3
Hypertension, n (%)	1855 (44.9)	1738 (49.2)	451 (46.1)
Systolic blood pressure (mmHg), mean ± SD	134 ± 14	136 ± 14	135 ± 15
Systolic blood pressure categories, n (%)			
<120mmHg	394 (9.5)	264 (7.5)	70 (7.2)
120 – 129mmHg	1001 (24.2)	779 (22.1)	240 (24.5)
130 – 139mmHg	1232 (29.8)	1033 (29.3)	287 (29.3)
140 – 149mmHg	951 (23.0)	872 (24.7)	236 (24.1)
≥150mmHg	550 (13.3)	582 (16.5)	145 (14.8)
Diastolic blood pressure (mmHg), mean ± SD	80 ± 8	78 ± 7	76 ± 7
Diastolic blood pressure categories, n (%)			
<70	143 (3.5)	185 (5.2)	90 (9.2)
70 – 79mmHg	1183 (28.7)	1248 (35.4)	394 (40.3)
80 – 89mmHg	2240 (54.3)	1795 (50.8)	445 (45.5)
≥90mmHg	562 (13.6)	302 (8.6)	49 (5.0)

Pulse pressure (mmHg), mean ± SD	54 ± 11	57 ± 12	59 ± 13
Pulse pressure, n (%)			
<50mmHg	1295 (31.4)	776 (22.0)	194 (19.8)
50 – 59mmHg	1495 (36.2)	1205 (34.1)	308 (31.5)
60 – 69mmHg	940 (22.8)	972 (27.5)	282 (28.8)
≥70mmHg	398 (9.6)	577 (16.3)	194 (19.8)
Baseline eGFR (ml/min/1.73m²), mean ± SD	68.8 ± 13.8	63.2 ± 14.7	55.4 ± 15.3
Baseline eGFR categories, n (%)			
≥60ml/min/1.73m²	3167 (76.7)	2097 (59.4)	356 (36.4)
45 – 59ml/min/1.73m²	850 (20.6)	1119 (31.7)	377 (38.5)
30 – 44ml/min/1.73m²	97 (2.3)	268 (7.6)	204 (20.9)
<30ml/min/1.73m²	14 (0.3)	46 (1.3)	41 (4.2)
Charlson Comorbidity Index, median (IQR)	3 (2 – 4)	4 (3 – 5)	6 (5 – 7)
Diabetes, n (%)	859 (20.8)	800 (22.7)	220 (22.5)
Myocardial infarction, n (%)	231 (5.6)	237 (6.7)	80 (8.2)
Heart failure, n (%)	135 (3.3)	313 (8.9)	201 (20.6)
CVA or TIA, n (%)	318 (7.7)	556 (15.8)	229 (23.4)
Peripheral arterial illness, n (%)	322 (7.8)	404 (11.4)	118 (12.1)
Chronic pulmonary disease, n (%)	144 (3.5)	146 (4.1)	36 (3.7)

History of peptic ulcer disease, n (%)	381 (9.2)	393 (11.1)	108 (11.0)
Dementia, n (%)	49 (1.2)	213 (6.0)	87 (8.9)
Liver disease, n (%)	172 (4.2)	123 (3.5)	26 (2.7)
Hemiplegia, n (%)	40 (1.0)	60 (1.7)	20 (2.0)
History of cancer, n (%)	523 (12.7)	557 (15.8)	148 (15.1)
Leukemia, n (%)	19 (0.5)	24 (0.7)	6 (0.6)
Lymphoma, n (%)	20 (0.5)	27 (0.8)	7 (0.7)
Cardiovascular medication, n (%)	2061 (49.9)	1925 (54.5)	554 (56.6)
Beta-blockers, n (%)	1262 (30.6)	1122 (31.8)	247 (25.3)
ACE inhibitors, n (%)	490 (11.9)	509 (14.4)	150 (15.3)
Angiotensin receptor blocker, n (%)	362 (8.8)	300 (8.5)	79 (8.1)
Calcium antagonist, n (%)	463 (11.2)	553 (15.7)	167 (17.1)
Diuretic, n (%)	905 (21.9)	964 (27.3)	338 (34.6)

SD: standard deviation; IQR: inter-quartile range; eGFR: estimated glomerular filtration rate; CVA : cerebrovascular accident ; TIA : transient ischaemic attack; ACE: angiotensin converting enzyme.

Table 2. Baseline blood pressure as a predictor of change in eGFR in ml/min/1.73m²/year (linear regression) (n = 8636)

	60 – 69 years (n = 4128)		70 – 79 years (n = 3530)		≥ 80 years (n = 978)	
	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value
Systolic BP (per 10 mmHg)						
Unadjusted	-0.14 (-0.21, -0.066)	<0.001	-0.18 (-0.27, -0.083)	<0.001	-0.26 (-0.47, -0.043)	0.018
Adjusted[a]	-0.14 (-0.21, -0.064)	<0.001	-0.19 (-0.29, -0.094)	<0.001	-0.27 (-0.49, -0.055)	0.014
Adjusted[b]	-0.11 (-0.18, -0.034)	0.004	-0.14 (-0.24, -0.048)	0.003	-0.24 (-0.46, -0.024)	0.029
CCI (per point increase)	-0.15 (-0.23, -0.061)	0.001	-0.27 (-0.37, -0.18)	<0.001	0.003 (-0.20, 0.21)	0.97
CV medication	-0.28 (-0.49, -0.073)	0.008	-0.57 (-0.85, -0.29)	<0.001	-0.49 (-1.1, 0.17)	0.14
Baseline eGFR (per ml/min/1.73m²)	-0.014 (-0.021, -0.006)	<0.001	-0.027 (-0.036, -0.017)	<0.001	-0.004 (-0.028, 0.019)	0.73
Diastolic BP (per 10 mmHg)						
Unadjusted	-0.077 (-0.21, 0.059)	0.27	-0.12 (-0.31, 0.069)	0.21	-0.20 (-0.64, 0.24)	0.38
Adjusted[a]	-0.090 (-0.23, 0.045)	0.19	-0.16 (-0.35, 0.032)	0.10	-0.22 (-0.66, 0.23)	0.34
Adjusted[b]	-0.069 (-0.21, 0.068)	0.33	-0.14 (-0.33, 0.056)	0.17	-0.19 (-0.63, 0.26)	0.41
CCI (per point increase)	-0.15 (-0.24, -0.066)	<0.001	-0.28 (-0.38, -0.19)	<0.001	0.001 (-0.20, 0.20)	0.99
CV medication	-0.33 (-0.53, -0.12)	0.002	-0.61 (-0.88, -0.33)	<0.001	-0.58 (-1.2, 0.065)	0.078
Baseline eGFR (per ml/min/1.73m²)	-0.014 (-0.022, -0.007)	<0.001	-0.027 (-0.037, -0.017)	<0.001	-0.004 (-0.028, 0.020)	0.73
Pulse pressure (per 10 mmHg)						

Unadjusted	-0.18 (-0.27, -0.090)	<0.001	-0.20 (-0.31, -0.089)	<0.001	-0.26 (-0.50, -0.025)	0.031
Adjusted[a]	-0.17 (-0.26, -0.081)	<0.001	-0.20 (-0.32, -0.092)	<0.001	-0.27 (-0.51, -0.033)	0.026
Adjusted[b]	-0.14 (-0.23, -0.043)	0.004	-0.15 (-0.26, -0.037)	0.009	-0.25 (-0.49, -0.002)	0.048
CCI (per point increase)	-0.14 (-0.22, -0.055)	0.001	-0.27 (-0.36, -0.18)	<0.001	0.006 (-0.20, 0.21)	0.95
CV medication	-0.30 (-0.51, -0.087)	0.005	-0.59 (-0.86, -0.31)	<0.001	-0.51 (-1.16, 0.14)	0.12
Baseline eGFR (per ml/min/1.73m²)	-0.014 (-0.022, -0.006)	<0.001	-0.027 (-0.037, -0.017)	<0.001	-0.004 (-0.028, 0.019)	0.72

[a], adjusted for age and gender.

[b], adjusted for gender, age, baseline Charlson Comorbidity Index, baseline cardiovascular medication, time between the first and last eGFR measurement after 2002 (≥ 5 years), baseline eGFR.

BP: blood pressure; CI: confidence interval; CCI: Charlson Comorbidity Index; CV: cardiovascular; eGFR: estimated glomerular filtration rate.

Table 3. Correlation between change in blood pressure and change in eGFR in ml/min/1.73m²/year (linear regression) (n = 7283)

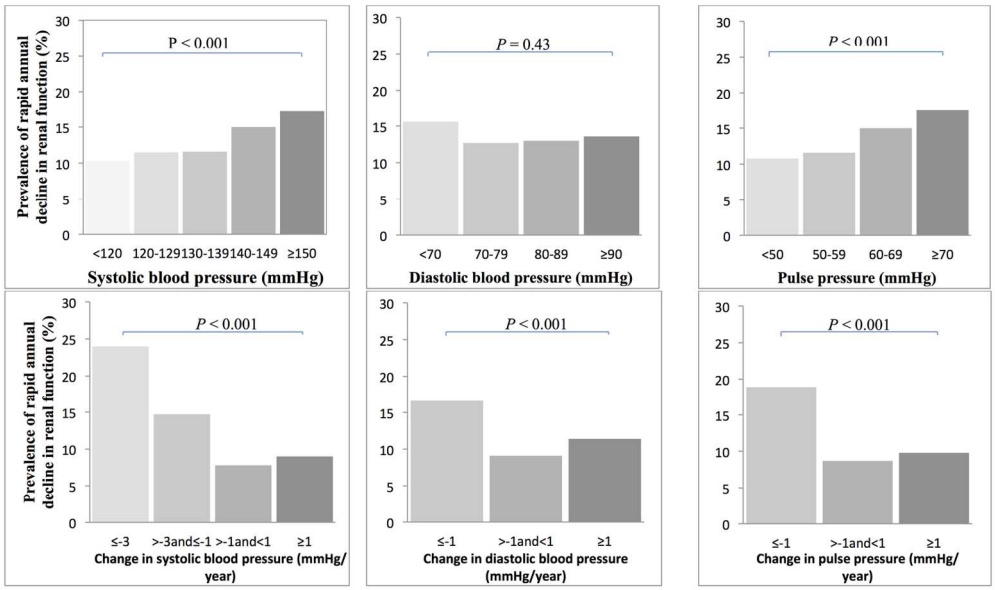
	60 – 69 years (n = 3696)		70 – 79 years (n = 2933)		≥ 80 years (n = 654)	
	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value
Systolic BP change (per mmHg/year)						
Unadjusted	0.11 (0.058, 0.16)	<0.001	0.14 (0.080, 0.19)	<0.001	0.17 (0.052, 0.29)	0.005
Adjusted[a]	0.10 (0.052, 0.15)	<0.001	0.13 (0.076, 0.19)	<0.001	0.17 (0.048, 0.29)	0.006
Adjusted[b]	0.030 (-0.025, 0.086)	0.28	0.069 (0.006, 0.13)	0.031	1.2 (0.34, 2.1)	0.007
Baseline BP pressure (per 10mmHg)	-0.15 (-0.22, -0.074)	<0.001	-0.14 (-0.23, -0.042)	0.005	-0.11 (-0.37, 0.15)	0.42
Baseline CCI (per point increase)	-0.21 (-0.28, -0.13)	<0.001	-0.28 (-0.36, -0.19)	<0.001	-0.10 (-0.29, 0.083)	0.28
Baseline CV medication	-0.25 (-0.44, -0.069)	0.007	-0.50 (-0.73, -0.26)	<0.001	-0.61 (-1.2, -0.023)	0.042
Baseline eGFR (per ml/min/1.73m²)	-0.015 (-0.021, -0.008)	<0.001	-0.021 (-0.030, -0.013)	<0.001	-0.013 (-0.035, 0.009)	0.24
Interaction term 'systolic BP change x baseline systolic BP'	NS	NS	NS	NS	-0.079 (-0.14, -0.014)	0.018
Diastolic BP change (per mmHg/year)						
Unadjusted	0.16 (0.072, 0.25)	<0.001	0.18 (0.073, 0.29)	0.001	0.38 (0.15, 0.62)	0.002
Adjusted[a]	0.15 (0.064, 0.24)	0.001	0.18 (0.069, 0.28)	0.001	0.37 (0.14, 0.61)	0.002
Adjusted[b]	0.11 (0.008, 0.21)	0.034	0.14 (0.019, 0.25)	0.023	0.42 (0.16, 0.67)	0.001
Baseline diastolic BP (per 10mmHg)	-0.082 (-0.22, 0.054)	0.24	0.57 (0.048, 1.1)	0.032	0.25 (-0.20, 0.71)	0.27

Baseline CCI (per point increase)	-0.22 (-0.29, -0.14)	<0.001	0.91 (0.029, 1.8)	0.043	-0.13 (-0.32, 0.052)	0.16
Baseline CV medication	-0.31 (-0.50, -0.13)	0.001	-0.55 (-0.78, -0.32)	<0.001	-0.66 (-1.2, -0.080)	0.026
Baseline eGFR (per ml/min/1.73m²)	-0.015 (-0.022, -0.008)	<0.001	-0.021 (-0.030, -0.013)	<0.001	-0.015 (-0.037, 0.007)	0.18
Interaction term 'baseline diastolic BP x baseline CCI'	NS	NS	-0.15 (-0.27, -0.041)	0.008	NS	NS
Pulse pressure change (per mmHg/year)						
Unadjusted	0.092 (0.031, 0.15)	0.003	0.13 (0.062, 0.20)	<0.001	0.11 (-0.038, 0.25)	0.15
Adjusted[a]	0.086 (0.025, 0.15)	0.006	0.12 (0.057, 0.19)	<0.001	0.10 (-0.042, 0.24)	0.17
Adjusted[b]	0.17 (0.015, 0.32)	0.031	0.050 (-0.025, 0.13)	0.19	0.064 (-0.10, 0.23)	0.45
Baseline pulse pressure (per 10mmHg)	-0.19 (-0.28, -0.094)	<0.001	-0.15 (-0.26, -0.043)	0.006	-0.052 (-0.31, 0.20)	0.69
Baseline CCI (per point increase)	-0.20 (-0.27, -0.13)	<0.001	-0.28 (-0.36, -0.19)	<0.001	-0.13 (-0.31, 0.059)	0.18
Baseline CV medication	-0.27 (-0.46, -0.091)	0.003	-0.52 (-0.75, -0.28)	<0.001	-0.62 (-1.2, -0.026)	0.041
Baseline eGFR (per ml/min/1.73m²)	-0.015 (-0.022, -0.008)	<0.001	-0.021 (-0.030, -0.013)	<0.001	-0.014 (-0.036, 0.008)	0.22
Interaction term 'pulse pressure change x baseline CCI'	-0.052 (-0.096, -0.009)	0.018	NS	NS	NS	NS

[a], adjusted for age and gender.

[b], adjusted for gender, age at baseline, baseline Charlson Comorbidity Index, baseline cardiovascular medication, time between the first and last eGFR measurement after 2002, baseline eGFR and baseline blood pressure measurements.

BP: blood pressure; CI: confidence interval; CCI: Charlson Comorbidity Index; CV: cardiovascular; eGFR: estimated glomerular filtration rate.



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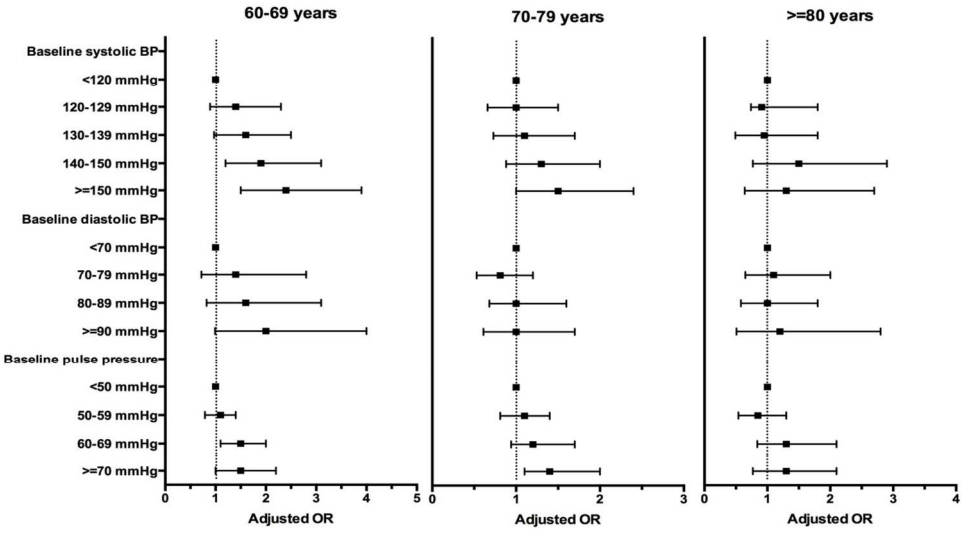

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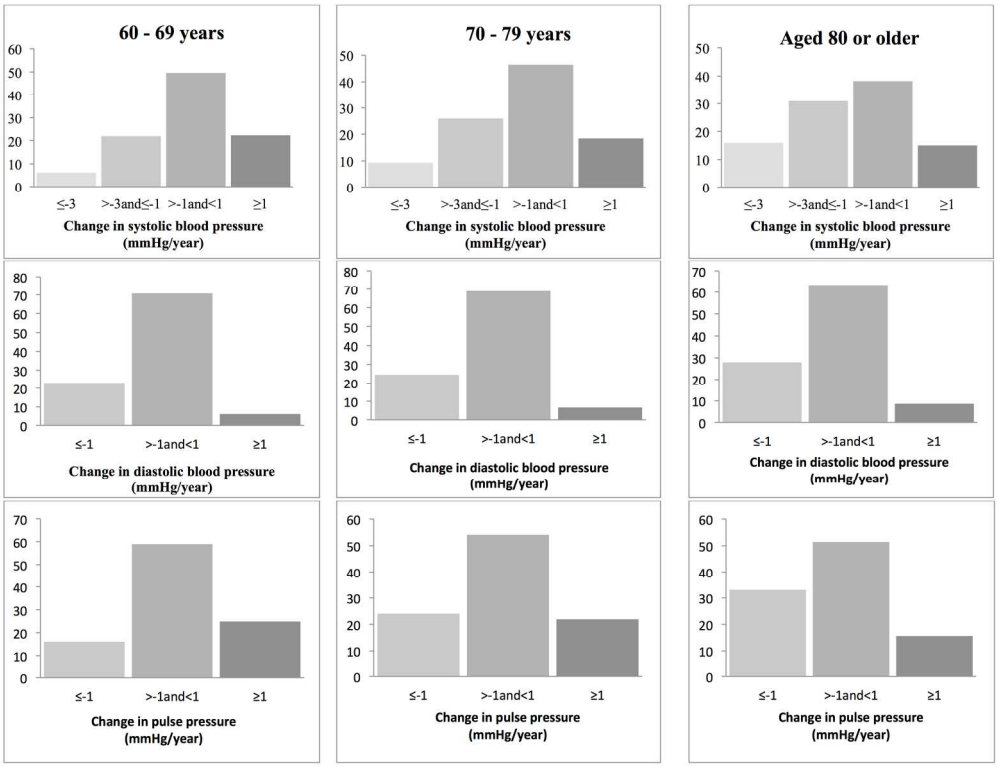

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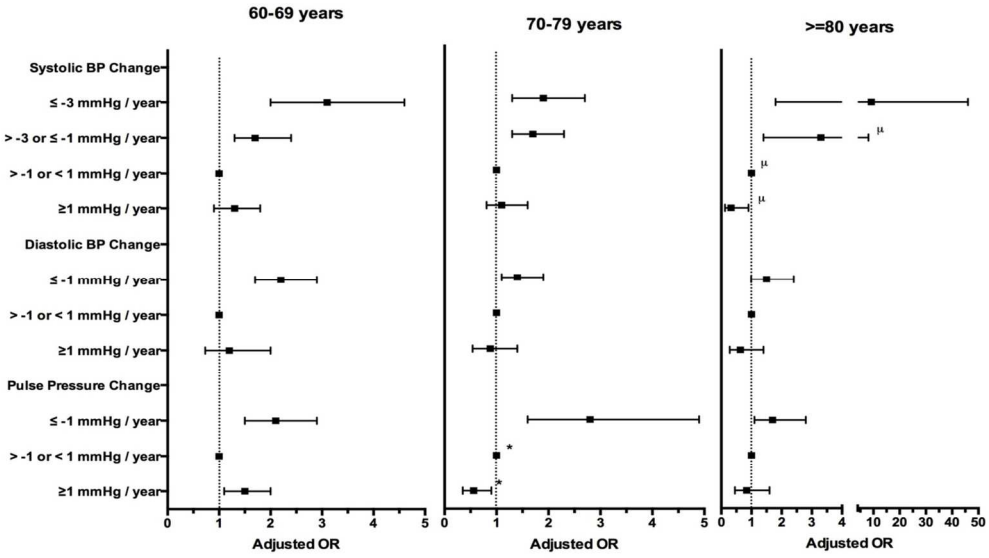

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	OK
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	OK
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	OK
Objectives	3	State specific objectives, including any prespecified hypotheses	OK
Methods			
Study design	4	Present key elements of study design early in the paper	OK
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	OK
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	OK
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	OK
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	OK
Bias	9	Describe any efforts to address potential sources of bias	OK
Study size	10	Explain how the study size was arrived at	OK
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	OK
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	OK
		(*b*) Describe any methods used to examine subgroups and interactions	OK
		(*c*) Explain how missing data were addressed	OK
		(*d*) If applicable, explain how loss to follow-up was addressed	OK
		(*e*) Describe any sensitivity analyses	OK
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	OK
		(b) Give reasons for non-participation at each stage	OK
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	OK
		(b) Indicate number of participants with missing data for each variable of interest	OK
		(c) Summarise follow-up time (eg, average and total amount)	OK
Outcome data	15*	Report numbers of outcome events or summary measures over time	OK
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which	OK

		confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	OK
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	OK
Discussion			
Key results	18	Summarise key results with reference to study objectives	OK
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	OK
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	OK
Generalisability	21	Discuss the generalisability (external validity) of the study results	OK
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	OK

*Give information separately for exposed and unexposed groups.

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The correlation between blood pressure and kidney function decline in older people: a registry-based cohort study

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The correlation between blood pressure and kidney function decline in older people: a registry-based cohort study

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ABSTRACT

Objectives:

To examine the relation between static and dynamic blood pressure (BP) measurements and the evolution of kidney function in older people, adjusted for the presence of multimorbidity.

Design:

Retrospective cohort study during a 10-year time interval (2002–2012) in three age strata of patients aged 60 and older.

Setting:

Primary care registration network with 97 general practitioners working in 55 practices regularly submitting collected patient data.

Participants:

All patients with at least one BP measurement in 2002 and at least four serum creatinine measurements after 2002 (n=8,636). A modified Charlson Comorbidity Index (mCCI) at baseline was registered. Change in systolic and diastolic BP and pulse pressure (PP) from 2002 onwards was calculated. The relation between kidney function evolution and baseline BP and change in BP was examined using linear and logistic regression analysis.

Main outcome measures:

The slope of the estimated glomerular filtration rate (eGFR, MDRD equation) was calculated by the ordinal least square method. A rapid annual decline of kidney function was defined as ≥3ml/min/1.73m^2/year.

Results:

Rapid annual decline of kidney function occurred in 1,130 patients (13.1%). High baseline SBP and PP predicted kidney function decline in participants aged 60–79 years. No correlation between baseline BP and kidney function decline was found in subjects aged 80 and older. An annual decline of ≥1mmHg in SBP and PP was a strong risk factor for a rapid

annual kidney function decline in all age strata, independent of baseline BP and mCCI. A decline in DBP was also a strong independent predictor in participants aged 60–79 years.

Conclusions:

The present study identified a decline in BP over time as a strong risk factor for kidney function decline in all age strata, adjusted for mCCI and baseline kidney function and BP.

Strengths and limitations of this study

- The first study that investigated the relation between dynamic blood pressure measurements and kidney function over time in subjects aged 60 and older.
- Large primary care study population representative of the population of Flanders with a long follow-up period.
- Analyses in various age strata were performed in order to detect possibly different patterns due to age.
- The presence of multimorbidity was included in the analyses.
- Lack of mortality data, data on renal replacement therapy, insufficient data on proteinuria/albuminuria and no standardized measurements of creatinine and blood pressure.
- The results are purely descriptive and were not adjusted for time-dependent changes in medication prescription and incident comorbidity.
- Weaknesses inherent to a retrospective design and registry data: possible healthy survivor bias, no information about missing data and loss to follow-up.

Introduction

Belgium and other western countries are facing a grey epidemic. Furthermore, a "double grey" epidemic is expected, given the proportionally higher increase of persons aged 80 and older. In 2012, 17.4% and 5.2% of the total Belgian population was aged 65 or older, and 80 or older, respectively. By 2050, these percentages will rise to 24.5% and 9.5%, respectively[1]. This will probably lead to a dramatic increase of chronic diseases and an increased number of patients with multiple comorbidities.

The prevalence of chronic kidney disease (CKD) (estimated glomerular filtration rate (eGFR) <60ml/min/1.73m²) increases with ageing to approximately 10% at the age of 65 years and to 60% in persons aged 80 and older[2-4]. CKD and especially end-stage renal disease is recognized as an important problem in public health. First, the cost of dialysis per patient per year is more than 50,000 euro, and >1% of the public health budget of the Belgian government is used to cover these costs. Second, CKD increases the risk of cardiovascular events and mortality. Moreover, many medications cannot be used or need dose adjustment in patients with CKD[5,6].

Arterial hypertension and cardiovascular disease have been identified both as a cause and as a consequence of CKD[7-9] and end-stage renal disease (ESRD)[4]. This has been well studied in the younger population. However, to date, many clinical trials and clinical studies have excluded older persons and especially older persons with multiple chronic conditions[10]. Furthermore, studies investigating the association between arterial hypertension and the risk of kidney function decline in older persons are scarce. The Cardiovascular Health study[11] and the SHEP study[8] identified baseline blood pressure (BP) as a risk factor for kidney function decline in older persons. The Leiden 85 Plus-study[12] on the other hand, did not find a relation between baseline BP and kidney function decline. It reported a decline in systolic (SBP) and diastolic blood pressure (DBP) between ages 85 and 90 to be related to an accelerated decline

of creatinine clearance over time. To date , the relation between the evolution of BP and that of kidney function over time has not been studied in persons aged 60 years and older. Moreover, the impact of concomitant chronic conditions on this relation has not been examined.

Therefore, the aim of this retrospective cohort study within the framework of a large Flemish morbidity registry was to study the relation between static and dynamic BP measurements and the evolution of kidney function over time in three age strata of subjects aged 60 years and older, adjusted for the presence of multimorbidity.

Methods

Study design and study population

Data were obtained from Intego, a Belgian general practice-based morbidity registration network at the Department of General Practice of the University of Leuven[13]. Intego procedures were approved by the ethical review board of the Medical School of the Catholic University of Leuven (N° ML 1723) and by the Belgian Privacy Commission (no SCSZG/13/079). Ninety-seven general practitioners (GPs) of 55 practices evenly spread throughout Flanders, Belgium, collaborate in the Intego project. GPs applied for inclusion in the registry. Before acceptance of their data, registration performance was audited using algorithms to compare their results with those of all other applicants. Only the data of the practices with optimal registration performance were included in the database. The Intego GPs prospectively and routinely registered all new diagnoses and new drug prescriptions, as well as laboratory test results and patient information, using computer-generated keywords internally linked to codes.

With specially framed extraction software, new data were encrypted and collected from the GPs' personal computers and entered into a central database. Registered data were continuously updated and historically accumulated for each patient. New diagnoses were classified according to a very detailed thesaurus automatically linked to the International Classification of Primary Care (ICPC-2) and International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). Drugs were classified according to the WHO's Anatomical Therapeutic Chemical (ATC) classification system.

The present study used Intego data of a 10-year time period from January 1st 2002 to January 1st 2012. First, patients aged 60 years or older in 2002 with a BP measurement registered in 2002 were selected (n = 12,904). Second, patients with at least four serum creatinine measurements after 2002 were withheld (n = 8,636).

Clinical characteristics

Blood pressure

BP measurements registered by the GP in 2002 (baseline or static BP) and yearly thereafter were used. For each year of the study time interval, a single SBP and DBP value was used in the analyses. The average BP of the two lowest values of that year's last three measurements were used[14]. Pulse pressure (PP) was calculated as the difference between the SBP and the DBP. Categories of baseline BP measurements were based on previously reported categories[11].

The slope of the SBP, DBP and PP (mmHg/year) was calculated for every study participant of whom BP measurements were available for at least four years following 2002 (n = 7,283). The slope, or dynamic BP, was calculated according to the ordinal least square method. Patients were divided in categories based on the slope using predefined subgroups of ≤-3, >-3 or ≤-1, >-1 or <1, and ≥1mmHg/year for the SBP and ≤-1, >-1 or <1 and ≥1mmHg/year for the DBP and the PP.

Kidney function

Kidney function was expressed as the eGFR calculated with the MDRD (Modification of Diet in Renal Disease) equation[15]. Baseline eGFR was calculated based on the average serum creatinine value of the last two measurements in 2002.

The slope of the eGFR (ml/min/1.73m^2/year) for every participant was calculated according to the ordinal least square method using all (range 4–50) available eGFR values. A rapid annual decline of kidney function was defined as ≥3ml/min/1.73m^2/year; this change is known to be associated with clinically deleterious outcomes[11].

Comorbidity

Medical history at baseline of every study participant was registered. The Charlson Comorbidity Index (CCI) includes 19 chronic diseases that are weighted based on their

association with mortality[16]. A modified CCI (mCCI) at baseline was calculated for every study participant[17]. Connective tissue disease could not be reliably assessed from the registry and the differentiation between cancers with or without metastasis, diabetes with or without end organ failure and mild or moderate to severe liver disease could not be made. Consequently all patients with cancers were assigned the same score (=2), as well as all patients with diabetes (=1) and with liver disease (=1).

The prescription of cardiovascular medication at baseline including beta-blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, calcium antagonists and diuretics was extracted from the database for every study participant.

Data analysis

Continuous data are presented as the mean and standard deviation (SD). Categorical data are presented as numbers and frequencies. All further analyses were performed in three age strata at baseline: 60–69 years, 70–79 years and ≥80 years.

The correlation between baseline BP measurements and kidney function decline and change in BP and kidney function decline was first explored by calculating odds ratios (ORs) with the corresponding 95% confidence intervals (CIs) using bivariate and multivariable linear regression analysis and adjusting for age, gender, mCCI at baseline, cardiovascular medication at baseline, time between the first and last eGFR measurement after 2002 (≥ or <5 years) and baseline eGFR (and baseline BP measurements for BP change). Second, the relation between categories of baseline BP measurements or categories of BP change and a rapid annual decline of kidney function was examined with bivariate and multivariable logistic regression analysis.

In order to avoid co-linearity, the correlation coefficients between all covariates were calculated. In case of co-linearity (*r*-value >0.90), only one of the two covariates was considered in the multivariate model. Interaction was checked between the slope of the BP

measurement and the baseline BP measurement, between the slope of the BP measurement and the mCCI, and between the baseline BP measurement and the mCCI. If the interaction term was statistically significant (P <0.05), it was kept in the model. A goodness-of-fit test was performed with the ANOVA (analysis of variance) F test for the linear regression models and the Hosmer-Lemeshow test for the logistic regression models and was reported when the model did not fit the observed data (ANOVA F test $P \geq 0.05$ and Hosmer-Lemeshow test P <0.05).

Statistical analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA) and GraphPad prism 6 (GraphPad Software, San Diego, CA, USA).

Results

In total, 8,636 patients from the Intego registry had at least one BP measurement registered in 2002 and at least four serum creatinine measurements after 2002. The baseline clinical characteristics of the study population according to their age at baseline are presented in Table 1. After baseline, rapid annual decline of kidney function occurred in 1,130 patients (13.1%): in 9.4% (n = 387) of patients aged 60–69 years, in 15.1% (n = 533) of patients aged 70–79 years and in 21.5% (n = 210) of patients aged 80 or older. Figure 1 presents the prevalence of rapid annual decline of kidney function according to categories of baseline BP and categories of change in BP. Prevalence of rapid decline of kidney function increased with higher baseline SBP and PP (χ^2 test, P <0.001), as well as with increased decline in SBP, DBP and PP (χ^2 test, P <0.001).

Correlation between systolic blood pressure and kidney function decline

Baseline systolic blood pressure

An inverse linear relation was found between baseline SBP and kidney function decline in all age strata, also after adjusting for confounders (Table 2). The goodness-of-fit test was not significant in the oldest age stratum (ANOVA F test, P = 0.23). Categories of higher baseline SBP predicted rapid decline of kidney function in patients aged 60–69 years (adjusted OR 1.9 (95% CI 1.2–3.1) and adjusted OR 2.4 (95% CI 1.5–3.9) for 140–150mmHg and ≥150mmHg respectively) (Figure 2). In patients aged 70–79 years a trend was seen for the highest category (adjusted OR 1.5 (95% CI 1.0–2.4), P = 0.052), and no correlation was found in patients aged 80 or older (Hosmer-Lemeshow test (≥80 years), P = 0.005).

Change in systolic blood pressure

Figure 3 presents the prevalence of the change in blood pressure for the various age strata. A positive and independent linear relation was found between a change in SBP and a

change in kidney function in the oldest two age strata; the more SBP decreased, the more the kidney function decreased in the years after 2002 (Table 3). Categories of decreasing SBP showed an increased risk of rapid kidney function decline compared with no change in patients 60–69 years (adjusted OR 1.7 (95% CI 1.3–2.4) and adjusted OR 3.1 (95% CI 2.0–4.6), respectively), in patients 70–79 years (adjusted OR 1.7 (95% CI 1.3–2.3) and adjusted OR 1.9 (95% CI 1.3–2.7), respectively) and in patients aged 80 and older (adjusted OR 3.3 (95% CI 1.4–8.1) and adjusted OR 9.2 (95% CI 1.8–46), respectively) (Figure 4). In the oldest age stratum the model was also corrected for the interaction term between change in SBP and baseline mCCI (adjusted OR 1.2 (95% CI 1.0–1.3), $P = 0.026$).

Correlation between diastolic blood pressure and kidney function decline

Baseline diastolic blood pressure

No linear relation was found between baseline DBP and kidney function decline (Table 2). The goodness-of-fit test for the adjusted model was not significant in the oldest age stratum (ANOVA F test, P = 0.64). A trend of predicting rapid decline of kidney function was only seen in the highest category of baseline DBP in patients aged 60–69 years (adjusted OR 2.0 (95% CI 0.99–4.0)). The Hosmer-Lemeshow test showed the adjusted model in the oldest patients did not fit the observed data (P <0.001).

Change in diastolic blood pressure

An independent and positive linear relation was found between change in DBP and change in kidney function in all age strata (Table 3). A decline in DBP predicted rapid decline of kidney function in patients aged 60–69 years and 70–79 years (adjusted OR 2.2 (95% CI 1.7–2.9) and adjusted OR 1.4 (1.1–1.9), respectively). In the oldest age stratum a trend of higher risk in patients with a decline in DBP was seen (adjusted OR 1.5 (95% CI 0.99–2.4), $P = 0.054$ (Hosmer-Lemeshow test, $P = 0.020$)).

Correlation between pulse pressure and kidney function decline

Baseline pulse pressure

An inverse linear correlation was found between baseline PP and decline in kidney function in all age strata. Only in the oldest age stratum was the goodness-of-fit test for the adjusted model not significant (ANOVA F test, P = 0.29). The highest categories of baseline PP predicted rapid decline of kidney function in patients aged 60–69 years and aged 70–79 years (adjusted OR 1.5 (95% CI 1.0–2.2) and adjusted OR 1.4 (95% CI 1.1–2.0).

Change in pulse pressure

A change in PP was independently correlated with change in kidney function in the youngest age group (Table 3). The goodness-of-fit test for the adjusted model was not significant in the oldest age stratum (ANOVA F test, P = 0.18). Patients in all age strata in the category ≤-1mmHg/year change showed a higher risk of rapid annual decline of kidney function compared with patients without change in PP (adjusted OR 2.1 (95% CI 1.5–2.9), adjusted OR 2.8 (95% CI 1.6–4.9) and adjusted OR 1.7 (95% CI 1.1–2.8), respectively). In patients 70 – 79 years the model was also corrected for the interaction term between change in PP and baseline PP (adjusted OR 1.3 (95% CI 1.1–1.5), *P* = 0.009).

Discussion

In this large retrospective population-based cohort study the relation between static and dynamic BP measurements and kidney function over time in older subjects was investigated. The present study confirmed previously found associations between baseline BP measurements and decline of kidney function, but more importantly identified a decline in BP over time as a strong risk factor for kidney function decline in all age strata, independent of the presence of multimorbidity and baseline BP. In people aged 60–69 years, high baseline SBP and PP predicted kidney function decline and a decline in SBP, DBP and PP in the years after baseline were related to a rapid annual decline in kidney function. In patients aged 70–79 years a relation between high baseline SBP and PP and kidney function decline was confirmed, and an association between a decline in SBP, DBP and PP after baseline and a decline in kidney function was seen. In the oldest age stratum, no correlation between baseline BP measurements and kidney function decline was found. A decline in SBP and PP in the years after baseline, however, predicted a rapid annual decline in kidney function in this age group. Moreover, DBP tended to decline.

To date, there is no consensus about which level of BP causes a higher risk of cardiovascular mortality, morbidity or kidney function decline in the elderly population. In the KDOQI/KDIGO guidelines tailored BP control is advised in older persons for the preservation of the kidney function[18]. This evidence is based on several studies reporting on arterial hypertension as a risk factor for the development of CKD, as well as on the evolution of CKD to ESRD in the global population. The MDRD-trial[19] studied arterial hypertension as a risk factor for kidney function decline in stage 3 and 4 CKD in a population aged 18-70 years. They studied the impact of baseline and follow-up BP during 2.2 years on the evolution of kidney function in an intervention (antihypertensive) and in a control group. No effect of high blood pressure on kidney function decline was found except for severe proteinuria

>3g/day. In a cohort of 332,544 men aged 35–57 years, Klag et al[20] found a 22% higher risk of ESRD in patients with arterial hypertension stage 4, defined as a SBP >210mmHg or a DBP >120mmHg, compared to that of patients with normal BP. In a large Japanese cohort, Tozawa et al[21] included 98,759 patients aged 20–98 years. They found higher baseline SBP and DBP showed a significant risk of development of ESRD. Cumulative incidence for ESRD in patients with severe arterial hypertension was 1.7% vs 0.2% in patients with a normal BP. Finally, Van Pottelbergh et al.[22] studied risk factors for ESRD in patients aged 50 years and older in the same Flemish cohort study as the present study did. Baseline arterial hypertension (BP ≥140/90mmHg) was found to be a significant risk factor for the development of ESRD (adjusted Hazard Ratio 1.25 (95% CI 1.22–1.28)).

Studies investigating the impact of BP on the evolution of kidney function in older persons are extremely rare. Some studied the risk of baseline BP for kidney function decline. Rifkin et al.[11] found baseline SBP to have the strongest association with rapid annual kidney function decline in persons aged 65 years or older, with 14% increased hazard of rapid decline per 10mmHg, independent of other BP measurements. The SHEP-trial[8] used their placebo-arm to study the relation between baseline BP and a yearly incident increase of serum creatinine (≥0.4mg/dl). They found higher baseline SBP increased the relative risk of kidney function decline. A positive trend was found for DBP, however, without correction for comorbidity. The relation between baseline BP and the evolution of SBP, DBP and PP and kidney function decline in a 5-year time interval has only been studied in patients aged 85 and older[12]. The Leiden 85+ study reported that elevated baseline SBP and DBP did not influence the annual decline in renal function in the oldest individuals. However, DBP <70mmHg and a decline in SBP or DBP was related to an accelerated decline of creatinine clearance over time. The present study results are in line with these findings.

The deleterious effect of higher baseline BP measurements on the evolution of the kidney function in persons up to 80 years was confirmed by the present study. Furthermore, intervention trials have shown that BP lowering prevents the need for renal replacement therapy up to the age of 70, independent of renal function at baseline[23]. The question remains how to explain the observations of the present study that identified a decline of ≥1 mmHg/year SBP, DBP or PP as a predictor of kidney function decline, not only in the oldest old, as shown in the Leiden 85+ Study, but also in persons aged 60–79 years old. A decline in BP may lead to chronic hypoperfusion of the kidney, causing the kidney function to deteriorate. The cause of BP decline remains unclear. Underlying heart failure with lowered cardiac output could be a reason[24]. On the other hand, BP control which is too strict or the effects of antihypertensive medications such as RAAS system inhibitors, which influence intra-renal BP and renal perfusion could be responsible. The analyses were corrected for baseline morbidities, including the presence of heart failure and history of myocardial infarction, cardiovascular medication and baseline BP and kidney function. However, possible changes in medication intake and occurrence of new morbidities in the years after baseline could also be underlying the observed relationship. Furthermore, the results of the present study should be interpreted with caution, since they originate from an observational registry-based cohort study. However, they do provide a realistic reflection of every-day practice. Future analyses should further clarify the findings of this study before it could lead to an adaptation or refinement of the current guidelines.

This study is the first that investigated the relation between dynamic BP measurements and kidney function over time in subjects aged 60 and older. The major strengths of this study are its large primary care study population representative of the population of Flanders and the long follow-up period[13]. Because of the large number of patients included in the study we were able to perform the analyses in various age strata in order to detect possibly different

patterns due to age. This study is also the first that included the presence of multimorbidity in the analyses.

However, the study is limited in that we had neither mortality data, nor data on the start of renal replacement therapy. Second, the MDRD equation has several weaknesses as a proxy for the real kidney function. For example, loss of muscle mass in older people may falsely give reduced estimates of renal function. However, this widely used equation to estimate the eGFR corrects for age that can act as a proxy for muscle mass. Since we were interested in the evolution of kidney function in the same population, a change in equation does not affect model outcomes. Third, no data related to proteinuria or albuminuria could be used in the analyses, because they were only available for a limited number of patients. Using these limited albuminuria and proteinuria data would have caused substantial selection bias. Fourth, not all creatinine values were measured by the same laboratory or by the same creatinine assay due to the design of the database, which collects data from practices throughout Flanders. However, all Belgian laboratories are subject to quality control measures[25], which limited the analytical differences among the laboratories. Fifth, blood pressure measurements were not standardized but were reported by the general practitioner as measured with his/her own blood pressure device. Furthermore, the variability in blood pressure and creatinine measurements in routine clinical practice may have affected the study findings.

Conclusion

This large retrospective, registry–based cohort study investigated the relation between static and dynamic BP measurements and the evolution of kidney function, independent of the presence of multimorbidity. Previously found associations between baseline BP measurements and decline of kidney function in older persons were confirmed, but more importantly a decline in BP over time was identified as a strong risk factor for kidney function decline in all patients aged 60 and older, independent of the presence of multimorbidity and baseline BP.

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Competing interests All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethics approval Intego procedures were approved by the ethical review board of the Medical School of the Catholic University of Leuven (N° ML 1723) and by the Belgian Privacy Commission (no SCSZG/13/079).

Data sharing statement All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Transparency declaration The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Figure legends

Figure 1. Prevalence of rapid annual decline in kidney function according to different blood pressure measurements

Figure 2. Baseline blood pressure as a predictor of rapid annual decline in kidney function (≥3ml/min/1.73m²/year) (logistic regression) (n = 8636)

Adjusted for gender, age, baseline Charlson Comorbidity Index, baseline cardiovascular medication, time between the first and last eGFR measurement after 2002, baseline eGFR.

Figure 3. Prevalence (%) of change in systolic and diastolic blood pressure and pulse pressure in different age strata

Figure 4. Correlation between change in blood pressure and a rapid annual decline in kidney function (≥3ml/min/1.73m²/year) (logistic regression) (n = 7283)

Adjusted for gender, age at baseline, baseline measurements (systolic blood pressure or diastolic blood pressure or pulse pressure), baseline Charlson Comorbidity Index, baseline cardiovascular medication, time between the first and last eGFR measurement after 2002, baseline eGFR.

[μ], adjusted for interaction term 'systolic BP change x baseline CCI' (adjusted OR of the interaction term 1.2 (95% CI 1.0 – 1.3).

[*], adjusted for interaction term 'pulse pressure change x baseline pulse pressure' (adjusted OR of the interaction term 1.3 (95% CI 1.1 – 1.5).

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Table 1. Baseline characteristics of the study population (n = 8636)

	60 – 69 years n = 4128	70 – 79 years n = 3530	≥ 80 years n = 978
Men, n (%)	2011 (48.7)	1505 (42.6)	357 (36.5)
Age (years), mean ± SD	64.7 ± 2.8	74.0 ± 2.8	83.1 ± 3.3
Hypertension, n (%)	1855 (44.9)	1738 (49.2)	451 (46.1)
Systolic blood pressure (mmHg), mean ± SD	134 ± 14	136 ± 14	135 ± 15
Systolic blood pressure categories, n (%)			
<120mmHg	394 (9.5)	264 (7.5)	70 (7.2)
120 – 129mmHg	1001 (24.2)	779 (22.1)	240 (24.5)
130 – 139mmHg	1232 (29.8)	1033 (29.3)	287 (29.3)
140 – 149mmHg	951 (23.0)	872 (24.7)	236 (24.1)
≥150mmHg	550 (13.3)	582 (16.5)	145 (14.8)
Diastolic blood pressure (mmHg), mean ± SD	80 ± 8	78 ± 7	76 ± 7
Diastolic blood pressure categories, n (%)			
<70	143 (3.5)	185 (5.2)	90 (9.2)
70 – 79mmHg	1183 (28.7)	1248 (35.4)	394 (40.3)
80 – 89mmHg	2240 (54.3)	1795 (50.8)	445 (45.5)
≥90mmHg	562 (13.6)	302 (8.6)	49 (5.0)

Pulse pressure (mmHg), mean ± SD	54 ± 11	57 ± 12	59 ± 13
Pulse pressure, n (%)			
<50mmHg	1295 (31.4)	776 (22.0)	194 (19.8)
50 – 59mmHg	1495 (36.2)	1205 (34.1)	308 (31.5)
60 – 69mmHg	940 (22.8)	972 (27.5)	282 (28.8)
≥70mmHg	398 (9.6)	577 (16.3)	194 (19.8)
Baseline eGFR (ml/min/1.73m²), mean ± SD	68.8 ± 13.8	63.2 ± 14.7	55.4 ± 15.3
Baseline eGFR categories, n (%)			
≥60ml/min/1.73m²	3167 (76.7)	2097 (59.4)	356 (36.4)
45 – 59ml/min/1.73m²	850 (20.6)	1119 (31.7)	377 (38.5)
30 – 44ml/min/1.73m²	97 (2.3)	268 (7.6)	204 (20.9)
<30ml/min/1.73m²	14 (0.3)	46 (1.3)	41 (4.2)
Charlson Comorbidity Index, median (IQR)	3 (2 – 4)	4 (3 – 5)	6 (5 – 7)
Diabetes, n (%)	859 (20.8)	800 (22.7)	220 (22.5)
Myocardial infarction, n (%)	231 (5.6)	237 (6.7)	80 (8.2)
Heart failure, n (%)	135 (3.3)	313 (8.9)	201 (20.6)
CVA or TIA, n (%)	318 (7.7)	556 (15.8)	229 (23.4)
Peripheral arterial illness, n (%)	322 (7.8)	404 (11.4)	118 (12.1)
Chronic pulmonary disease, n (%)	144 (3.5)	146 (4.1)	36 (3.7)

History of peptic ulcer disease, n (%)	381 (9.2)	393 (11.1)	108 (11.0)
Dementia, n (%)	49 (1.2)	213 (6.0)	87 (8.9)
Liver disease, n (%)	172 (4.2)	123 (3.5)	26 (2.7)
Hemiplegia, n (%)	40 (1.0)	60 (1.7)	20 (2.0)
History of cancer, n (%)	523 (12.7)	557 (15.8)	148 (15.1)
Leukemia, n (%)	19 (0.5)	24 (0.7)	6 (0.6)
Lymphoma, n (%)	20 (0.5)	27 (0.8)	7 (0.7)
Cardiovascular medication, n (%)	2061 (49.9)	1925 (54.5)	554 (56.6)
Beta-blockers, n (%)	1262 (30.6)	1122 (31.8)	247 (25.3)
ACE inhibitors, n (%)	490 (11.9)	509 (14.4)	150 (15.3)
Angiotensin receptor blocker, n (%)	362 (8.8)	300 (8.5)	79 (8.1)
Calcium antagonist, n (%)	463 (11.2)	553 (15.7)	167 (17.1)
Diuretic, n (%)	905 (21.9)	964 (27.3)	338 (34.6)

SD: standard deviation; IQR: inter-quartile range; eGFR: estimated glomerular filtration rate; CVA : cerebrovascular accident ; TIA : transient ischaemic attack; ACE: angiotensin converting enzyme.

Table 2. Baseline blood pressure as a predictor of change in eGFR in ml/min/1.73m²/year (linear regression) (n = 8636)

	60 – 69 years (n = 4128)		70 – 79 years (n = 3530)		≥ 80 years (n = 978)	
	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value
Systolic BP (per 10 mmHg)						
Unadjusted	-0.14 (-0.21, -0.066)	<0.001	-0.18 (-0.27, -0.083)	<0.001	-0.26 (-0.47, -0.043)	0.018
Adjusted[a]	-0.14 (-0.21, -0.064)	<0.001	-0.19 (-0.29, -0.094)	<0.001	-0.27 (-0.49, -0.055)	0.014
Adjusted[b]	-0.11 (-0.18, -0.034)	0.004	-0.14 (-0.24, -0.048)	0.003	-0.24 (-0.46, -0.024)	0.029
CCI (per point increase)	-0.15 (-0.23, -0.061)	0.001	-0.27 (-0.37, -0.18)	<0.001	0.003 (-0.20, 0.21)	0.97
CV medication	-0.28 (-0.49, -0.073)	0.008	-0.57 (-0.85, -0.29)	<0.001	-0.49 (-1.1, 0.17)	0.14
Baseline eGFR (per ml/min/1.73m²)	-0.014 (-0.021, -0.006)	<0.001	-0.027 (-0.036, -0.017)	<0.001	-0.004 (-0.028, 0.019)	0.73
Diastolic BP (per 10 mmHg)						
Unadjusted	-0.077 (-0.21, 0.059)	0.27	-0.12 (-0.31, 0.069)	0.21	-0.20 (-0.64, 0.24)	0.38
Adjusted[a]	-0.090 (-0.23, 0.045)	0.19	-0.16 (-0.35, 0.032)	0.10	-0.22 (-0.66, 0.23)	0.34
Adjusted[b]	-0.069 (-0.21, 0.068)	0.33	-0.14 (-0.33, 0.056)	0.17	-0.19 (-0.63, 0.26)	0.41
CCI (per point increase)	-0.15 (-0.24, -0.066)	<0.001	-0.28 (-0.38, -0.19)	<0.001	0.001 (-0.20, 0.20)	0.99
CV medication	-0.33 (-0.53, -0.12)	0.002	-0.61 (-0.88, -0.33)	<0.001	-0.58 (-1.2, 0.065)	0.078
Baseline eGFR (per ml/min/1.73m²)	-0.014 (-0.022, -0.007)	<0.001	-0.027 (-0.037, -0.017)	<0.001	-0.004 (-0.028, 0.020)	0.73
Pulse pressure (per 10 mmHg)						

Unadjusted	-0.18 (-0.27, -0.090)	<0.001	-0.20 (-0.31, -0.089)	<0.001	-0.26 (-0.50, -0.025)	0.031
Adjusted[a]	-0.17 (-0.26, -0.081)	<0.001	-0.20 (-0.32, -0.092)	<0.001	-0.27 (-0.51, -0.033)	0.026
Adjusted[b]	-0.14 (-0.23, -0.043)	0.004	-0.15 (-0.26, -0.037)	0.009	-0.25 (-0.49, -0.002)	0.048
CCI (per point increase)	-0.14 (-0.22, -0.055)	0.001	-0.27 (-0.36, -0.18)	<0.001	0.006 (-0.20, 0.21)	0.95
CV medication	-0.30 (-0.51, -0.087)	0.005	-0.59 (-0.86, -0.31)	<0.001	-0.51 (-1.16, 0.14)	0.12
Baseline eGFR (per ml/min/1.73m²)	-0.014 (-0.022, -0.006)	<0.001	-0.027 (-0.037, -0.017)	<0.001	-0.004 (-0.028, 0.019)	0.72

[a], adjusted for age and gender.

[b], adjusted for gender, age, baseline Charlson Comorbidity Index, baseline cardiovascular medication, time between the first and last eGFR measurement after 2002 (≥ 5 years), baseline eGFR.

BP: blood pressure; CI: confidence interval; CCI: Charlson Comorbidity Index; CV: cardiovascular; eGFR: estimated glomerular filtration rate.

Table 3. Correlation between change in blood pressure and change in eGFR in ml/min/1.73m²/year (linear regression) (n = 7283)

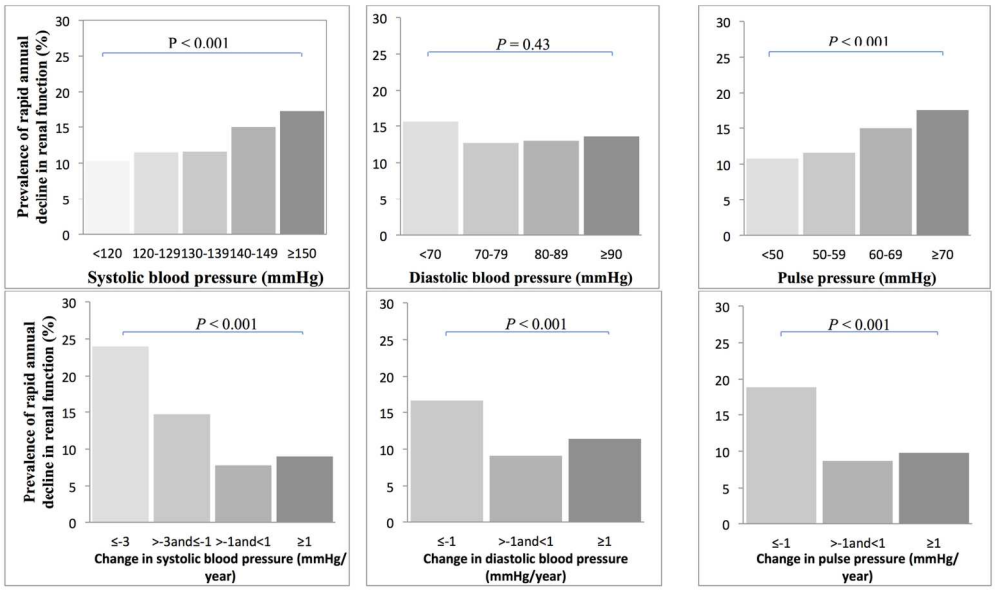
	60 – 69 years (n = 3696)		70 – 79 years (n = 2933)		≥ 80 years (n = 654)	
	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value
Systolic BP change (per mmHg/year)						
Unadjusted	0.11 (0.058, 0.16)	<0.001	0.14 (0.080, 0.19)	<0.001	0.17 (0.052, 0.29)	0.005
Adjusted[a]	0.10 (0.052, 0.15)	<0.001	0.13 (0.076, 0.19)	<0.001	0.17 (0.048, 0.29)	0.006
Adjusted[b]	0.030 (-0.025, 0.086)	0.28	0.069 (0.006, 0.13)	0.031	1.2 (0.34, 2.1)	0.007
Baseline BP pressure (per 10mmHg)	-0.15 (-0.22, -0.074)	<0.001	-0.14 (-0.23, -0.042)	0.005	-0.11 (-0.37, 0.15)	0.42
Baseline CCI (per point increase)	-0.21 (-0.28, -0.13)	<0.001	-0.28 (-0.36, -0.19)	<0.001	-0.10 (-0.29, 0.083)	0.28
Baseline CV medication	-0.25 (-0.44, -0.069)	0.007	-0.50 (-0.73, -0.26)	<0.001	-0.61 (-1.2, -0.023)	0.042
Baseline eGFR (per ml/min/1.73m²)	-0.015 (-0.021, -0.008)	<0.001	-0.021 (-0.030, -0.013)	<0.001	-0.013 (-0.035, 0.009)	0.24
Interaction term 'systolic BP change x baseline systolic BP'	NS	NS	NS	NS	-0.079 (-0.14, -0.014)	0.018
Diastolic BP change (per mmHg/year)						
Unadjusted	0.16 (0.072, 0.25)	<0.001	0.18 (0.073, 0.29)	0.001	0.38 (0.15, 0.62)	0.002
Adjusted[a]	0.15 (0.064, 0.24)	0.001	0.18 (0.069, 0.28)	0.001	0.37 (0.14, 0.61)	0.002
Adjusted[b]	0.11 (0.008, 0.21)	0.034	0.14 (0.019, 0.25)	0.023	0.42 (0.16, 0.67)	0.001
Baseline diastolic BP (per 10mmHg)	-0.082 (-0.22, 0.054)	0.24	0.57 (0.048, 1.1)	0.032	0.25 (-0.20, 0.71)	0.27

Baseline CCI (per point increase)	-0.22 (-0.29, -0.14)	<0.001	0.91 (0.029, 1.8)	0.043	-0.13 (-0.32, 0.052)	0.16
Baseline CV medication	-0.31 (-0.50, -0.13)	0.001	-0.55 (-0.78, -0.32)	<0.001	-0.66 (-1.2, -0.080)	0.026
Baseline eGFR (per ml/min/1.73m²)	-0.015 (-0.022, -0.008)	<0.001	-0.021 (-0.030, -0.013)	<0.001	-0.015 (-0.037, 0.007)	0.18
Interaction term 'baseline diastolic BP x baseline CCI'	NS	NS	-0.15 (-0.27, -0.041)	0.008	NS	NS
Pulse pressure change (per mmHg/year)						
Unadjusted	0.092 (0.031, 0.15)	0.003	0.13 (0.062, 0.20)	<0.001	0.11 (-0.038, 0.25)	0.15
Adjusted[a]	0.086 (0.025, 0.15)	0.006	0.12 (0.057, 0.19)	<0.001	0.10 (-0.042, 0.24)	0.17
Adjusted[b]	0.17 (0.015, 0.32)	0.031	0.050 (-0.025, 0.13)	0.19	0.064 (-0.10, 0.23)	0.45
Baseline pulse pressure (per 10mmHg)	-0.19 (-0.28, -0.094)	<0.001	-0.15 (-0.26, -0.043)	0.006	-0.052 (-0.31, 0.20)	0.69
Baseline CCI (per point increase)	-0.20 (-0.27, -0.13)	<0.001	-0.28 (-0.36, -0.19)	<0.001	-0.13 (-0.31, 0.059)	0.18
Baseline CV medication	-0.27 (-0.46, -0.091)	0.003	-0.52 (-0.75, -0.28)	<0.001	-0.62 (-1.2, -0.026)	0.041
Baseline eGFR (per ml/min/1.73m²)	-0.015 (-0.022, -0.008)	<0.001	-0.021 (-0.030, -0.013)	<0.001	-0.014 (-0.036, 0.008)	0.22
Interaction term 'pulse pressure change x baseline CCI'	-0.052 (-0.096, -0.009)	0.018	NS	NS	NS	NS

[a], adjusted for age and gender.

[b], adjusted for gender, age at baseline, baseline Charlson Comorbidity Index, baseline cardiovascular medication, time between the first and last eGFR measurement after 2002, baseline eGFR and baseline blood pressure measurements.

BP: blood pressure; CI: confidence interval; CCI: Charlson Comorbidity Index; CV: cardiovascular; eGFR: estimated glomerular filtration rate.



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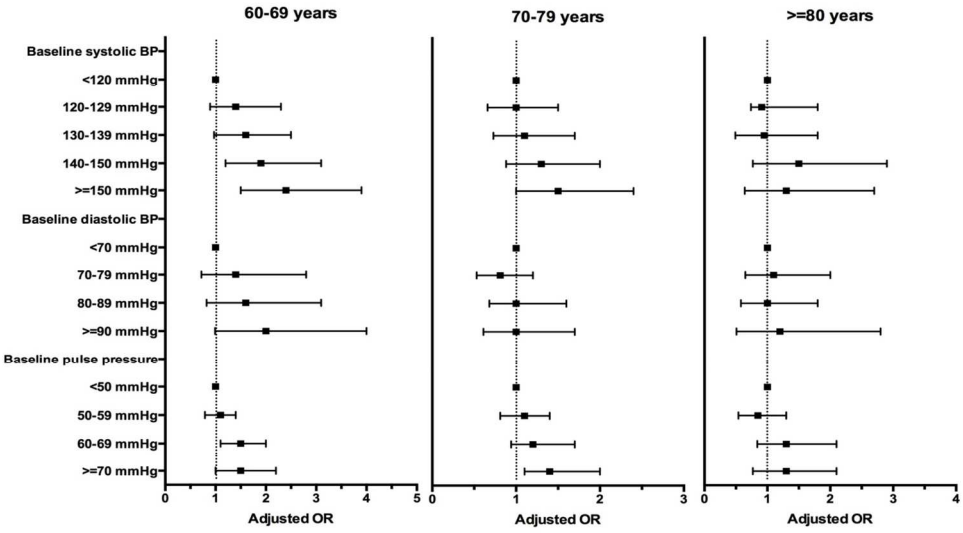

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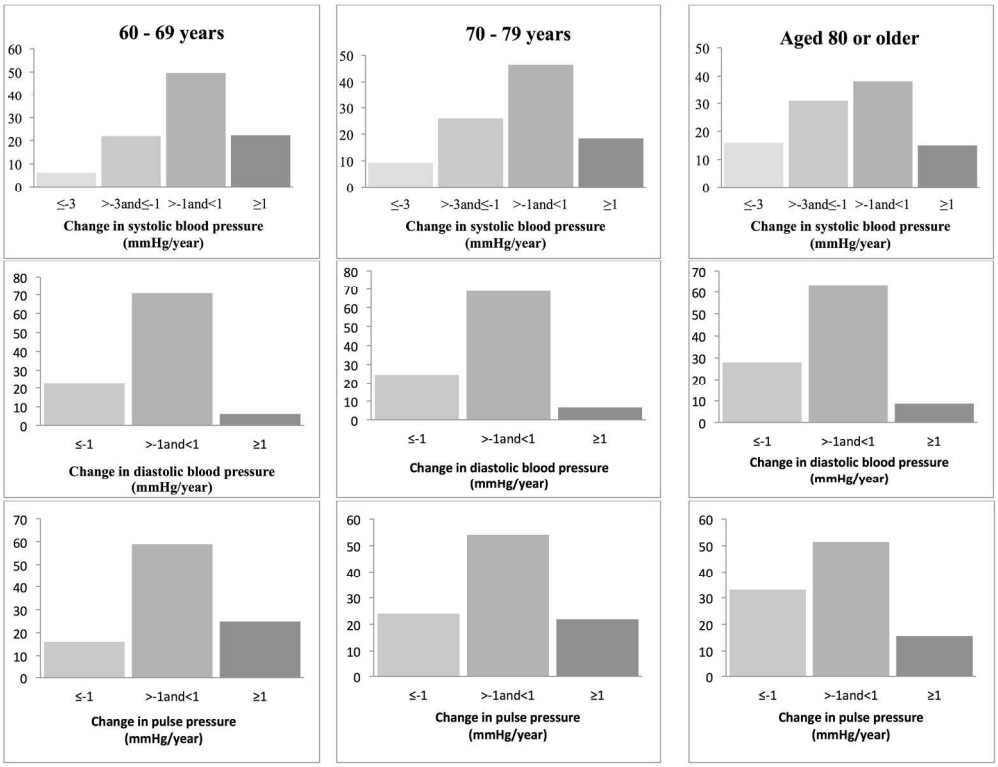

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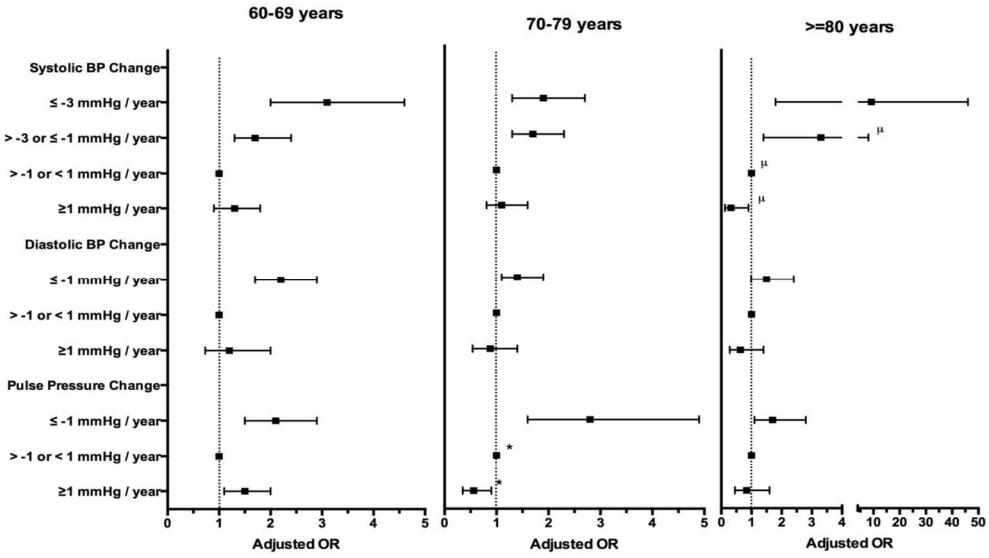

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	OK
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	OK
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	OK
Objectives	3	State specific objectives, including any prespecified hypotheses	OK
Methods			
Study design	4	Present key elements of study design early in the paper	OK
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	OK
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	OK
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	OK
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	OK
Bias	9	Describe any efforts to address potential sources of bias	OK
Study size	10	Explain how the study size was arrived at	OK
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	OK
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	OK
		(*b*) Describe any methods used to examine subgroups and interactions	OK
		(*c*) Explain how missing data were addressed	OK
		(*d*) If applicable, explain how loss to follow-up was addressed	OK
		(*e*) Describe any sensitivity analyses	OK
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	OK
		(b) Give reasons for non-participation at each stage	OK
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	OK
		(b) Indicate number of participants with missing data for each variable of interest	OK
		(c) Summarise follow-up time (eg, average and total amount)	OK
Outcome data	15*	Report numbers of outcome events or summary measures over time	OK
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which	OK

		confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	OK
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	OK
Discussion			
Key results	18	Summarise key results with reference to study objectives	OK
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	OK
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	OK
Generalisability	21	Discuss the generalisability (external validity) of the study results	OK
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	OK

*Give information separately for exposed and unexposed groups.