“The correlation between blood pressure and kidney function decline in the old: a registry-based retrospective cohort study”

dr. Emilie Beke

Promotoren: dr. Bert Vaes, dr. Gijs Van Pottelbergh

Praktijkopleiders: dr. Michel Polet, dr. Johan Van Pelt.

Masterproef 2013 – 2014

ABSTRACT:

Objectives:

To study the relationship between static and dynamic blood pressure (BP) measurements and the evolution of the kidney function in the old, independent of the presence of multimorbidity.

Design:

Retrospective cohort study during a 10 year time interval (2002–2011) in three age strata of patients aged 60 and older.

Setting: Primary registration network with 97 general practitioners working in 55 practices sending routinely 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. The change in systolic and diastolic BP and the pulse pressure (PP) in the years after 2002 was calculated. The relationship between the evolution of the kidney function 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 $\geq$3ml/min/1.73m^2/year decline.

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 confirmed previous 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.

ABSTRACT

Doel: De correlatie te bestuderen tussen statische en dynamische bloeddruk (BD) metingen en de evolutie van de nierfunctie bij ouderen, onafhankelijk van de aanwezigheid van multimorbiditeit.
Design: Retrospectief cohortonderzoek tijdens een 10-jarig tijdsinterval (2002–2011) in drie leeftijdstrata van patiënten 60 jaar en ouder.
Setting: Registratie van gegevens in 55 huisartsenpraktijken bij 97 huisartsen verspreid over Vlaanderen.
Deelnemers: Inclusie van patiënten met minstens één BD meting in 2002 en minstens 4 serum creatinine waarden na 2002 (n = 8636). Een aangepaste Charlson Comorbidity Index (mCCI) werd geregistreerd op baseline. De verandering van de systolische (SBD), diastolische (DBD) en polsdruk (PD) na 2002 werd berekend. Het verband tussen zowel de baseline BD, als de verandering van de BD, met de evolutie van de nierfunctie werd bestudeerd a.d.h.v. lineaire en logistische regressie analyse.
Uitkomstmaten: De evolutie van de eGFR (estimated glomerular filtration rate, bepaald d.m.v. de MDRD-formule) werd berekend d.m.v. de ordinary least square method. Een snelle jaarlijkse daling van de nierfunctie werd gedefinieerd als een jaarlijkse daling van $\geq$3ml/min/1.73m^2.
Resultaten: Het aantal patiënten met een snelle jaarlijkse achteruitgang van de nierfunctie bedroeg 1,130 (13.1%). Een hoge baseline SBD en PD was een voorspellende factor voor een nierfunctiedaling bij 60–79 jarigen. Bij de 80-plussers werd geen verband aangetoond tussen de baseline BD en een nierfunctiedaling. Een jaarlijkse daling van de SBD en de PD met $\geq$1mmHg was een sterke risicofactor voor een jaarlijkse snelle nierfunctiedaling, onafhankelijk van de baseline BD en mCCI. Een jaarlijkse daling van de DBD voorspelde eveneens een snelle nierfunctiedaling bij patiënten 60–79jaar.
Besluit: Deze studie bevestigde het eerder gevonden verband tussen baseline BD en nierfunctiedaling. Maar bovendien toonde deze studie aan dat een daling van de BD over jaren een aanzienlijke risicofactor betekent voor een snelle achteruitgang van de nierfunctie in alle leeftijdsgroepen, onafhankelijk van de aanwezigheid van multimorbiditeit en de baseline BD.

What this paper adds

What is already known on this subject?

Static blood pressure measurements have been identified as a risk factor for kidney function decline in older persons. However, in patients aged 85 no relationship between baseline blood pressure and kidney function decline was found, but a decline in systolic and diastolic blood pressure in a five year time interval was shown to be associated with an accelerated decline of creatinine clearance over time.

What this study adds

The present study confirmed previous found associations between static BP measurements and decline of kidney function in older persons, but more importantly identified a decline in BP over time 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.

Introduction

Belgium and other western countries are facing a grey epidemic. Furthermore, a "double grey" epidemic is expected, seen the proportional higher increase of persons aged 80 and older. In 2012 17.4% and 5.2% of the total Belgian population was aged respectively 65 or older and 80 or older. These percentages will rise to respectively 24.5% and 9.5% by 2050 (http://statbel.fgov.be). This will lead to an explosion of chronic diseases and generate numerous complicated patients with multiple comorbid conditions.

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[1,2,3]. 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 health budget of the Belgian government is used to cover dialysis costs. Second, CKD increases the risk for cardiovascular events and mortality, and many medications cannot be used or need dose adaptation in patients with CKD[4,5].

Arterial hypertension and cardiovascular disease have been identified both as a cause and as a consequence[6,7,8] of CKD and end-stage renal disease (ESRD)[3]. This has been well studied in the younger population. However, until now, many clinical trials and clinical studies excluded older persons and especially older persons with multiple chronic conditions[9]. Furthermore, studies investigating the relationship between arterial hypertension and the risk for decline in kidney function in older persons are scarce. The Cardiovascular Health study[10] and the SHEP study[7] identified baseline blood pressure (BP) as a risk factor for kidney function decline in older persons. The Leiden 85 Plus-study[11] on the other hand, did not find a relationship between baseline BP and kidney function decline, but found 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. Until now, the relationship between the evolution of BP and the evolution of kidney function over time has not been studied in persons aged 60 and older. Moreover, the impact of concomitant chronic conditions on this relationship has not been evaluated.

Therefore, this retrospective cohort study was done in a large Flemish morbidity registry to study the relationship between static and dynamic BP measurements and the evolution of the kidney function over time in three age strata of persons aged 60 and older, independent of the presence of multimorbidity.

Methodology

Study design and study population

Data were obtained from Intego, a Flemish general practice-based morbidity registration network at the Department of General Practice at the University of Leuven. Ninety-seven general practitioners (GPs), all using the medical software program Medidoc, collaborate in the Intego project. These 97 GPs work in 55 practices evenly spread over Flanders, the northern part of Belgium. GPs applied for inclusion in the registry. Before acceptance of their data, registration performance was audited using a number of algorithms that compared their results with all other applicants. Only the data of the practices with an optimal registration performance were included in the database. The Intego GPs prospectively and routinely registered all new diagnoses together with new drug prescriptions, as well as laboratory test results and some background information (including gender and year of birth), using computer-generated keywords internally linked to codes.

Using specially framed extraction software, new data were coded 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 was a retrospective cohort study that used Intego data of a 10 year time interval from January 1st 2002 to December 31st 2011. First, a selection was made of all patients in the Intego database that had at least one contact with their GP in 2002 and that were aged 60 or older in 2002 (birth year 1942, n = 20,301). Second, of these patients those that had at least one BP measurement that was registered in 2002 were nominated (n =

12,904). Third, only those patients with at least four serum creatinine measurements after 2002 were retained (n = 8,636).

Clinical characteristics

Blood pressure

BP measurements registered by the GP in 2002 (baseline) and yearly thereafter were used. For each year of the study time interval a single SBP and DBP measurement was used in the analyses; when only one BP measurement in a specific year was registered, this measurement was used in the analyses; when two BP measurements were available the average BP was used; when three or more measurements were registered, the average BP of the lowest two values of the last three measurements of that year were used in order to deal with possible 'white coat hypertension'[12]. The 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[10].

The slope of the SBP, the DBP and the PP (mmHg/year) was calculated for every study participant where BP measurements were available for at least four years after 2002 (n = 7,283). The slope was calculated by 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 estimated glomerular filtration rate (eGFR) calculated with the MDRD equation (eGFR (ml/min/1.73 m^2) = 186 × (Serum creatinine)$^{-1.154}$ × (Age)$^{-0.203}$ × (0.742 if female) × (1.212 if black))[13]. Baseline eGFR was calculated based on the average serum creatinine value of the last two measurements in 2002. When no serum creatinine value was available for 2002, the first measurement of 2003 or 2004 was used to

calculate the baseline eGFR. The classification system based on that of the American Kidney Foundation to classify patients based on their baseline eGFR was used: eGFR between 45 and 60 ml/min/1.73 m^2 = stage 3A and eGFR between 30 and 45 ml/min/1.73 m^2 = stage 3B. Patients with an eGFR > 60 ml/min/1.73m^2 with or without signs of kidney damage (stage 1 or 2 or no chronic kidney disease) were analysed as one group. Also patients with an eGFR < 30 ml/min/1.73m^2 (stage 4 and 5 chronic kidney disease) were analysed as one group.

The slope of the eGFR (ml/min/1.73 m^2/year) for every participant was calculated by the ordinal least square method using all (range 4 – 50) available eGFR values starting from 2003. A rapid annual decline of kidney function was defined as $\geq$ 3 ml/min/1.73m^2/year decline.

Comorbidity

The medical history at baseline of every study participant was registered and used in the analyses. The presence of the following diagnoses was collected: hypertension, diabetes mellitus, a history of myocardial infarction, heart failure, a history of transient ischaemic attack or cerebrovascular accident, peripheral arterial illness, chronic pulmonary disease, a history of peptic ulcer, dementia, liver disease, hemiplegia, a history of cancer, a history of leukaemia, a history of lymphoma and AIDS.

The Charlson Comorbidity Index (CCI) includes 19 chronic diseases which are weighted based on their association with mortality[14]. A modified CCI (mCCI) at baseline was calculated for every study participant. Connective tissue disease could not be reliably assessed from the registry and the difference 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 cancers were assigned the same score, all diabetics were assigned the same score and all patients with liver disease were assigned the same score.

The prescription of cardiovascular medication at baseline including beta-blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, calcium antagonists and diuretics was extracted 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 analysis were performed in three strata of age at baseline: 60 – 69 years, 70 – 79 years and ≥ 80 years.

The correlation between baseline BP measurements 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 adjusting for age, gender, mCCI at baseline, cardiovascular medication at baseline, time between the first and last eGFR measurement after 2002 (≥ 5 years) and baseline eGFR. Second, the relationship between categories of baseline BP measurements and a rapid annual decline of kidney function was examined by using bivariate and multivariable logistic regression analysis.

The correlation between the change in SBP, DBP and PP and kidney function decline was first explored using bivariate and multivariable linear regression analysis adjusting for age at baseline, gender, mCCI at baseline, cardiovascular medication at baseline, time between the first and last eGFR measurement after 2002 (≥ 5 years), baseline eGFR, and baseline BP measurements. Second, the relationship between categories of BP change and rapid annual decline of kidney function was calculated by using 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. In case the interaction term was statistically significant ($P < 0.05$) the interaction term was kept in the model. A goodness-of-fit test was performed by means of the ANOVA 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 $P < 0.05$).

The 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 had 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. The prevalence of rapid decline of kidney function increased with increasing baseline SBP and PP on the one hand (χ^2 test, $P < 0.001$), and increased with increasing decline in SBP, DBP and PP on the other hand (χ^2 test, $P < 0.001$).

Correlation between systolic blood pressure and kidney function decline

Baseline systolic blood pressure

An inverse linear relationship 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

In patients aged 60 – 69 years, 70 – 79 years and aged 80 or older a change in SBP ≤ -3mmHg/year was seen in 6.1%, 9.3% and 15.9% respectively, a change > -3 or ≤ -1mmHg/year in 21.9%, 25.9% and 30.9% respectively, a change > -1 or < 1mmHg/year in 49.6%, 46.4% and 38.2% respectively, and a change ≥ 1mmHg/year in 22.3%, 18.4% and 15.0% respectively. A positive and independent linear relationship was found between a change in SBP and a change in kidney function in the oldest two age strata; the more the SBP decreased the more the kidney function decreased in the years after 2002 (Table 3). Categories of decreasing SBP showed an increased risk for rapid decline of kidney function 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 3). 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 relationship 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 old did not fit the observed data ($P < 0.001$).

Change in diastolic blood pressure

In patients aged 60 – 69 years, 70 – 79 years and aged 80 or older a change in DBP ≤ -1mmHg/year was seen in 23.2%, 24.5% and 28.0% respectively, a change > -1 or < 1mmHg/year in 70.8%, 68.9% and 63.5% respectively, and a change ≥ 1mmHg/year in 6.1%, 6.6% and 8.6% respectively. An independent and positive linear relationship 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 the goodness-of-fit test for the adjusted model was 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

In patients aged 60 – 69 years, 70 – 79 years and aged 80 or older a change in PP ≤ -1mmHg/year was seen in 16.1%, 24.0% and 33.0% respectively, a change > -1 or < 1mmHg/year in 59.0%, 54.1% and 51.4% respectively, and a change ≥ 1mmHg/year in 24.9%, 21.9% and 15.6% respectively. 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 for 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 relationship between static and dynamic BP measurements and kidney function over time in older persons was investigated. The present study confirmed previous 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 persons 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 persons aged 70 – 79 years a relationship 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 old no correlation between baseline BP measurements and kidney function decline was found, a decline in SBP and PP in the years after baseline, however, also predicted a rapid annual decline in kidney function in this age group and a trend was seen for a decline in DBP.

To date, no consensus exists about which level of BP causes a higher risk for cardiovascular mortality, morbidity or kidney function decline in the elderly population. In the KDOQI/KDIGO guidelines[15] a strict BP control is advised in older persons for the preservation of the kidney function, both in patients with CKD as in those without. This evidence is based on several studies that mentioned arterial hypertension to be a risk factor for the development of CKD but also for the evolution of CKD to ESRD in the global population. The MDRD-trial[16] studied arterial hypertension as a risk factor for kidney function decline in stage 3 and 4 CKD in a population aged 18 – 70 years old. They studied the impact of baseline and follow-up BP during 2.2 years on the evolution of kidney function in an intervention group (antihypertensive) and a control group. No effect of high blood pressure

on kidney function decline was found except for an important proteinuria >3g/day. Klag et al[17] found in a cohort of 332,544 men aged 35 – 57 years old a 22% higher risk for ESRD in patients with arterial hypertension stage 4, defined as a SBP >210mmHg or a DBP >120mmHg, compared to patients with normal BP. In a large Japanese cohort Tozawa et al[18] included 98,759 patients aged 20 – 98 years old. They found a significant risk of higher baseline SBP and DBP for the development of ESRD. The 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.[19] studied risk factors for ESRD in patients aged 50 years and older in the same Flemish cohort study as the present study. 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)).

In older persons, studies investigating the impact of BP on the evolution of kidney function are extremely rare. Some studied the risk of baseline BP for kidney function decline. Rifkin et al.[10] 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[7] used their placebo-arm to study the relationship between baseline BP and a yearly incident increase of serum creatinine (≥0.4mg/dl). They found a higher baseline SBP increased the relative risk for kidney function decline. A positive trend was found for DBP. However, no correction was made for comorbidity. The relationship 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[11]. In the Leiden 85+ study they found that elevated baseline SBP and DBP did not influence the annual decline in renal function in the oldest individuals. However, a 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 until the age of 80 years old was confirmed with the present study. Furthermore, intervention trials have shown that BP lowering prevents the need for renal replacement therapy up till the age of 70, independent of renal function at baseline[20]. Then, 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 could possibly lead to a chronic hypoperfusion of the kidney, causing the kidney function to deteriorate. Question remains what caused the decline in BP. Possibly underlying heart failure with lowered cardiac output could be a reason[21]. One the other hand, a too strict BP control or the effects of antihypertensive medications like RAAS system inhibitors that 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, no correction was made for possible changes in the medication intake and occurrence of new morbidities in the years after baseline. Furthermore, the results of the present study should be interpreted with caution, since they originate from an observational retrospective cohort study. But they give a realistic reflection of every day practice and future analyses should be done to 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 relationship between dynamic BP measurements and kidney function over time in subjects aged 60 and older. The major strengths of this study are the study population being a large primary care population that is representative of the population of Flanders[22] and the long follow-up period. Because of the large number of persons included in the study we were able to perform the analyses in

different age strata in order to possibly detect different patterns due to age. This study is also the first that included the presence of multimorbidity in the analyses.

However, this study has some limitations. First, we had no mortality data, nor data on the start of renal replacement therapy. Second, the MDRD equation presents several weaknesses as a proxy for the real kidney function. For example, loss of muscle mass in elderly patients 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 persons, a change in equation does not affect the model outcomes. Third, no data related to proteinuria or albuminuria could be used in the analyses, because these data 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 (https://www.wiv-isp.be/QML/index_nl.htm), which diminished the analytical differences among the laboratories. Fifth, blood pressure measurement 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 relationship between static and dynamic BP measurements and the evolution of the kidney function, independent of the presence of multimorbidity. Previous 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.

Funding Intego is funded on a regular basis by the Flemish Government (Ministry of Health and Welfare) and by the Belgian National Institute for Health and Disability Insurance on a contractual basis (ACHIL project). This work would not have been possible without the collaboration of all general practitioners of the Intego network. We hereby state the independence of researchers from funders.

Competing interests None.

Ethics approval The 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).

Provenance and peer review Not commissioned; externally peer reviewed.

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.

References

1. Van Pottelbergh G, Bartholomeeusen S, Buntinx F et al. The prevalence of chronic kidney disease in a Flemish primary care morbidity register. Age Ageing 2012;41:231-233.
2. Coresh J, Selvin E, Stevens LA et al. Prevalence of chronic kidney disease in the United States. JAMA 2007;298:2038-2047.
3. U.S. Renal Data System, USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2013.
4. Go AS, Chertow GM, Fan D et al. Chronic kidney disease and the risk of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296-1305.
5. Shastri S, Katz R, Rifkin DE et al. Kidney function and mortality in octogenarians: Cardiovascular Health Study All Stars. J Am Geriatr Soc 2012;60:1201-1207.
6. National High Blood Pressure Education Program Working Group. 1995 Update of the working group reports on chronic renal failure and renovascular hypertension. Arch Intern Med 156:1938-1947, 1995.
7. Mailloux LU, Levey AS. Hypertension in chronic renal disease. Am J Kidney Dis 32:S120-S141, 1998 (suppl 3)SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA. 1991;265(24):3255-3264.
8. Walker WG: Hypertension-related renal injury: A major contributor to end-stage renal disease. Am J Kidney Dis 22:164-173, 1993 (erratum 22:626, 1993).

9. Crome P, Lally F, Cherubini A et al. Exclusion of older people from clinical trials: professional views from nine European countries participating in the PREDICT study. Drugs Aging 2011;28:667-677.
10. Rifkin D., Katz R.,Chonchol M., Shlipak M.,et al., Blood Pressure Components and Decline in Kidney Function in Community-Living Older Adults: The Cardiovascular Health Study, American Journal of Hypertension 26(8) August 2013, 1034 -1044.
11. Van Bemmel T., Woittiez K., Blauw G., et al, Prospective Study of the Effect of Blood Pressure on Renal Function in Old Age: The Leiden 85-Plus Study J Am Soc Nephrol 17: 2561–2566, 2006.
12. Martin U, Holder R, Hodgkinson J, et al. Inter-arm blood pressure differences compared with ambulatory monitoring: a manifestation of the 'white-coat' effect? Br J Gen Pract 2013;63:e97–103.
13. Levey AS, Greene T, Kusek J, Beck G. A simplified equation to predict glomerular filtration rate from serum creatinine [Abstract]. J Am Soc Nephrol 2000; 11: 155A.
14. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.
15. Inker LA, Astor BC, Fox CH, KDOQI US Commentary on the 2012 KDIGO Clinical Practice Guideline for the Evaluation and Management of CKD, Am J Kidney Dis. 2014 Mar 16. pii: S0272-6386(14)00491-0.
16. Klahr et al., The Effects of Dietary Protein Restriction and Blood-Pressure Control on the Progression of Chronic Renal Disease, N Engl J Med 1994; 330:877-884.
17. Klag etal., Blood pressure and End-Stage Renal Disease in Men, N Engl J Med 1996;334:13-8.

18. Tozawa et al., Blood Pressure Predicts Risk of Developing End-Stage Renal Disease in Men and Women, *Hypertension.* 2003; 41: 1341-1345.
19. Van Pottelbergh et al., The evolution of renal function and the incidence of end-stage renal disease in patients aged ≥50 years. Nephrol Dial Transplant (2012) 27: 2297–2303.
20. Maschio G, Alberti D, Janin G, Locatelli F, Mann JF, Motolese M, Ponticelli C, Ritz E, Zucchelli P: Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group. *N Engl J Med* 334:939 – 945, 1996.
21. Nichols WW, O'Rourke M, eds. Ageing, high blood pressure and disease in humans. In: McDonald's blood flow in arteries, theoretical, experimental and clinical principals.4th edn.London:Edward Arnold, 1998:54–113.
22. Bartholomeeusen S, Truyers C, Buntinx F. ziekten in de huisartsenpraktijk in Vlaanderen (1994–2008). Leuven, Belgium: ACCO, 2010.

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.

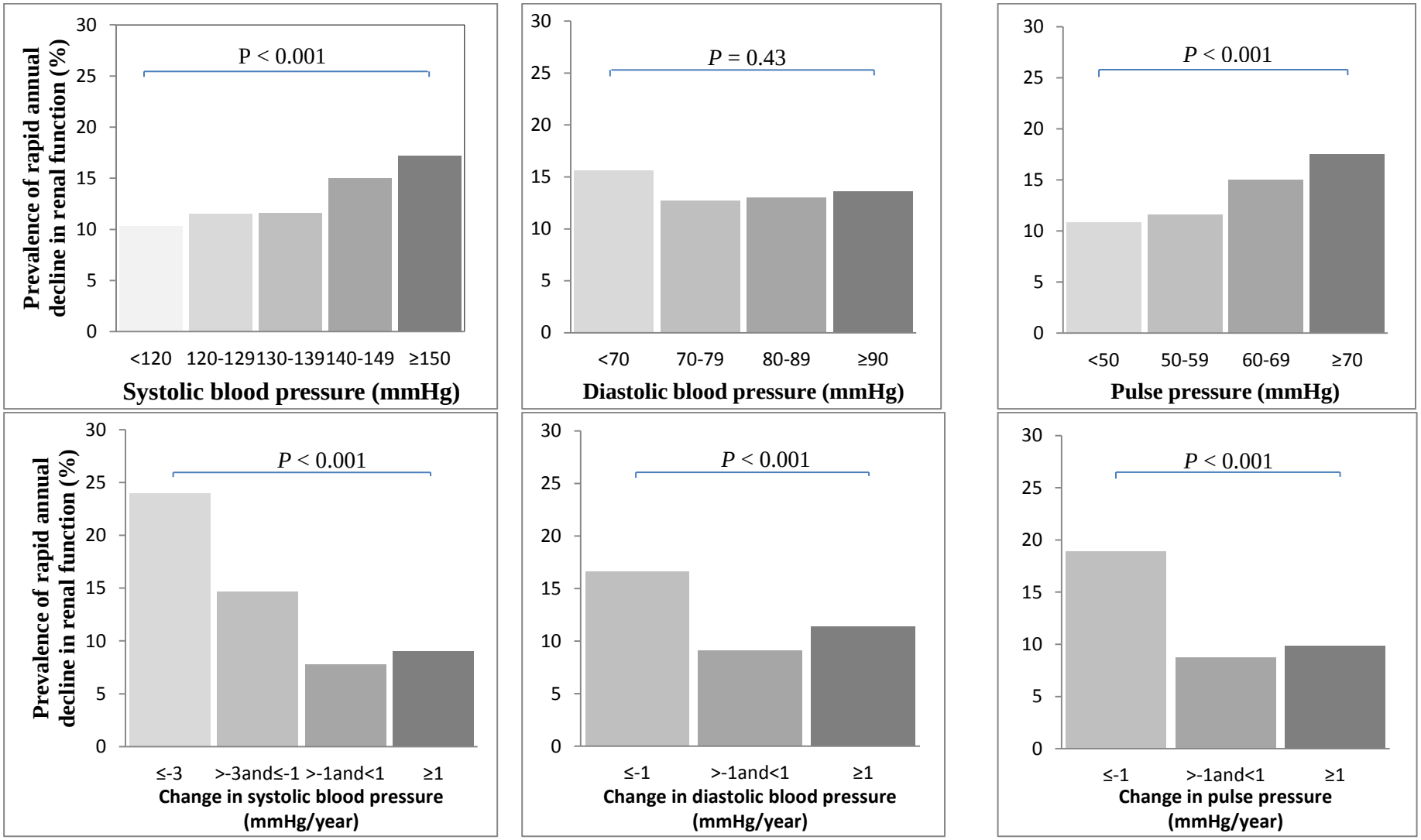
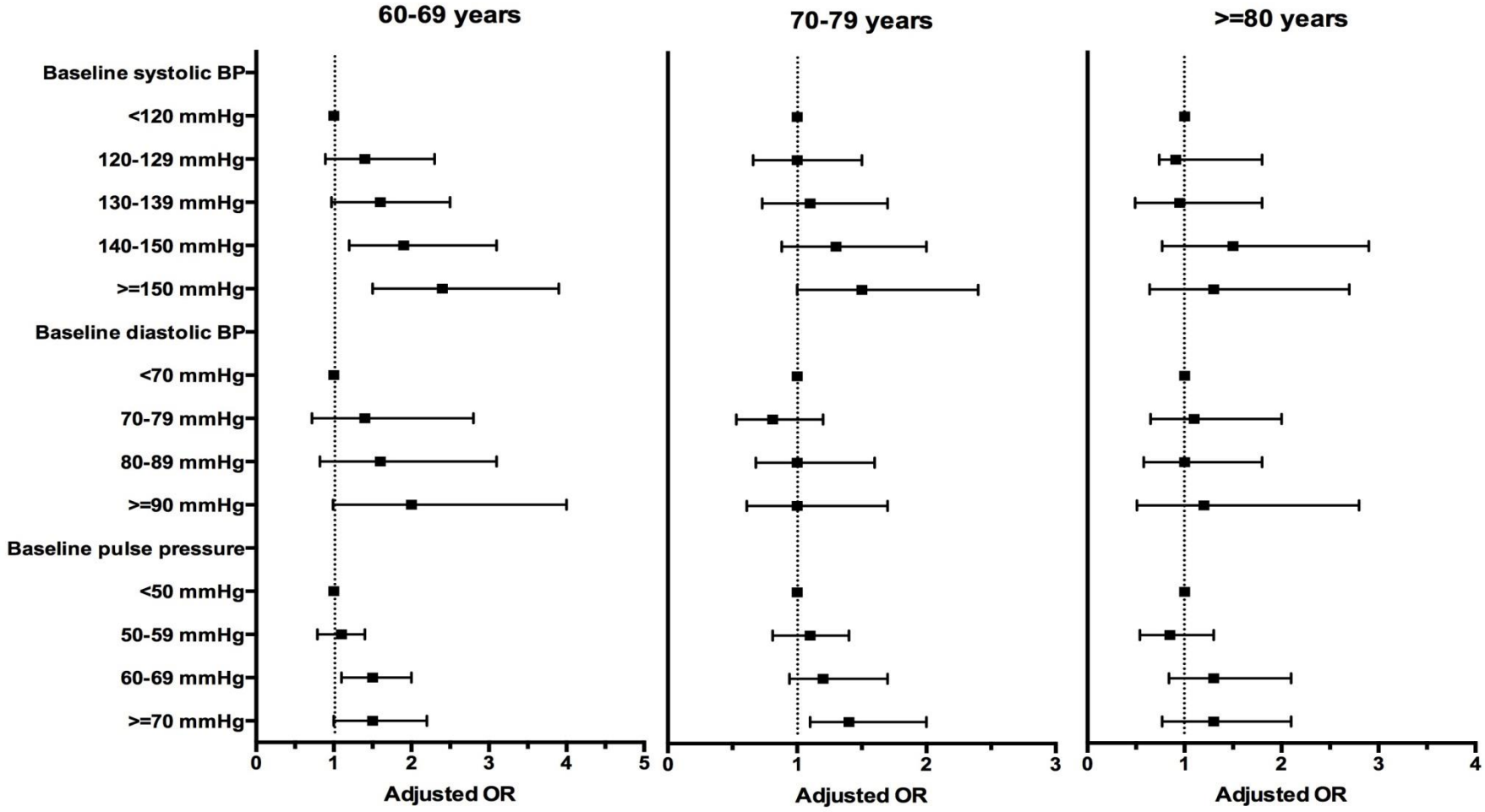
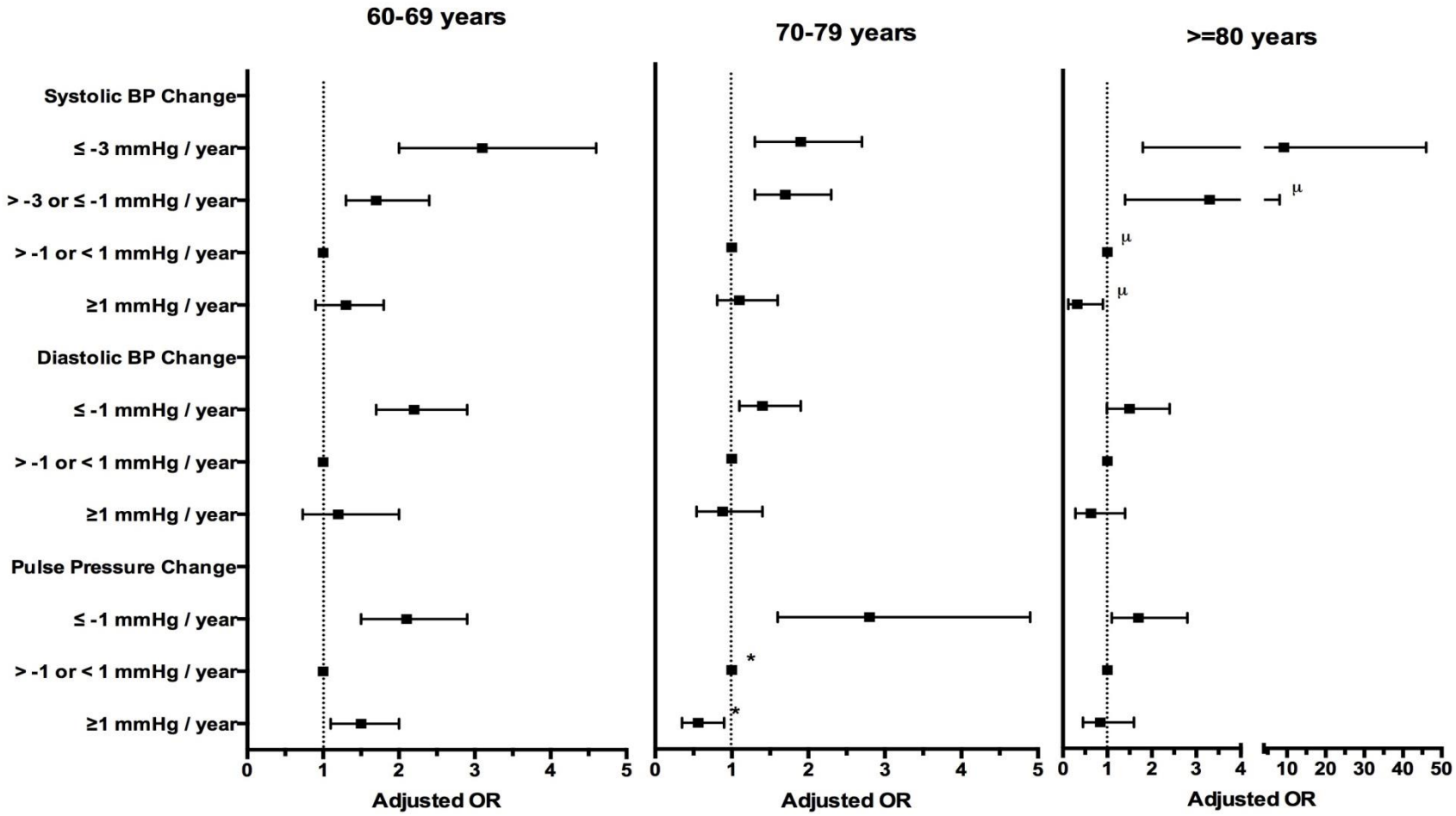


Figure 2. Baseline blood pressure as a predictor of rapid annual decline in kidney function (≥3ml/min/1.73m²/year) (logistic regression) (n = 8636)



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. 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).