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Long-term blood pressure variability in patients with rheumatoid arthritis (RA) and its impact on cardiovascular events and all-cause mortality in RA: a population-based comparative cohort study

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Abstract

Objectives—To examine long-term visit-to-visit blood pressure (BP) variability in rheumatoid arthritis (RA) vs non-RA subjects and to assess its impact on cardiovascular events and mortality in RA.

Methods—Clinic BP measures were collected in a population-based incident cohort of RA patients (1987 ACR criteria met between 1/1/1995 and 1/1/2008) and non-RA subjects. BP variability was defined as within-subject standard deviation (SD) in systolic and diastolic BP.

Results—Study included 442 RA patients (mean age 55.5 years, 70% females) and 424 non-RA subjects (mean age 55.7 years, 69% females). RA patients had higher visit-to-visit variability in systolic BP (13.8 ± 4.7 mm Hg), than non-RA subjects (13.0 ± 5.2 mm Hg, $p=0.004$). Systolic BP variability declined after the index date in RA ($p<0.001$), but not in the non-RA cohort ($p=0.73$), adjusting for age, sex and calendar year of RA. During the mean follow-up of 7.1 years, 33 cardiovascular events and 57 deaths occurred in RA cohort. Visit-to-visit systolic BP variability was associated with increased risk of cardiovascular events (hazard ratio [HR] per 1 mm Hg increase in BP variability 1.12, 95% confidence interval [CI] 1.01-1.25); diastolic BP variability was associated with all-cause mortality in RA (HR 1.14, 95% CI 1.03-1.27), adjusting for systolic and diastolic BP, body mass index, smoking, diabetes, dyslipidemia, use of antihypertensives.

Conclusion—Patients with RA had higher visit-to-visit systolic BP variability vs non-RA subjects. There was a significant decline in systolic BP variability after RA incidence. Higher visit-to-visit BP variability was associated with adverse cardiovascular outcomes and all-cause mortality in RA.

Introduction

The evidence for the increased cardiovascular risk in rheumatoid arthritis (RA) compared to the general population is convincing (1-4). The underlying mechanisms of this increased cardiovascular risk in RA are not fully understood, and the relative impact of traditional and non-traditional risk factors and inflammation on cardiovascular disease in RA is actively studied (5). Along with smoking, obesity and dyslipidemia, hypertension is considered one of the most common modifiable cardiovascular risk factors with significant detrimental impact on cardiovascular disease progression, both in the general population and in RA (6-9). While the role of mean estimates of systolic and diastolic blood pressure (BP) in cardiovascular risk has been widely studied in various populations, the concept of BP variability is a much less explored and increasingly growing area of research (10-13).

There are several types of BP variability depending on time intervals of its assessment, including very short term (beat-to-beat) variability, short term (24 hour) variability, mid-term (day-to-day) variability and long-term (visit-to-visit) variability (10). Among these types, visit-to-visit variability has been for a long time disregarded as random BP variation. However, this concept has been recently debated and the findings of several large prospective cohort studies in the general population suggest that long-term visit-to-visit BP variability is a reproducible measure and an important prognostic factor for cardiovascular outcomes (10-16).

The literature regarding BP variability in patients with RA is limited to studies of short-term BP variability as part of assessment of autonomic system dysfunction in RA (17). Studies of long-term BP variability in RA in comparison to the general population are lacking and prognostic significance of changes in BP measures over time on cardiovascular outcomes and mortality in RA is poorly understood. To address this gap in knowledge, we studied long-term visit-to-visit BP variability in RA vs non-RA subjects and examined the impact of BP variability on cardiovascular events and all-cause mortality in RA.

Materials and Methods

Study setting and design

This retrospective longitudinal cohort study was performed using the population-based resources of the Rochester Epidemiology Project (REP) medical record linkage system. This system ensures virtually complete ascertainment of all clinically recognized cases of RA among the residents of Olmsted County, MN. The unique features of the REP and its capabilities for the population-based research have been previously described (18, 19).

The study included a population-based incidence cohort of patients with RA who were Olmsted County, Minnesota residents ≥ 18 years of age and first met the 1987 American College of Rheumatology (ACR) criteria (20) for RA between 1/1/1995 and 1/1/2008. The date when the patient met ≥ 4 ACR criteria was considered the RA incidence date. For each patient with RA, a randomly selected subject without RA with similar characteristics (i.e., age, sex and calendar year) was chosen from the same population. Each non-RA subject was assigned an index date corresponding to the RA incidence date of the designated patient

with RA. All subjects were followed until death, migration from Olmsted county, MN or 7/1/2010.

Information on the following cardiovascular risk factors was collected at baseline as previously described (21, 22): smoking (current/former); alcohol abuse; dyslipidemia (defined according to the Adult Treatment Panel III guidelines (23) as total cholesterol ≥ 240 mg/dl (≥ 6.2 mmol/l), low-density cholesterol ≥ 160 mg/dl (≥ 4.1 mmol/l), triglycerides ≥ 200 mg/dl (≥ 2.3 mmol/l) or high-density cholesterol <40 mg/dl (<1.0 mmol/l), physician diagnosis/documentated use of lipid-lowering medications); body mass index (BMI; kg/m²), hypertension (defined as ≥ 2 BP readings ≥ 140 mm Hg systolic and/or ≥ 90 mm Hg diastolic obtained in the outpatient setting during a 1-year period, physician diagnosis/documentated use of antihypertensive medications) (8), diabetes mellitus (defined as fasting plasma glucose ≥ 126 mg/dl [≥ 7.0 mmol/l]), physician diagnosis/documentated use of insulin and/or oral hypoglycemics) (24, 25), and family history of premature ischemic heart disease (IHD), i.e. IHD in first-degree relatives at age <65 years females and <55 years males). Personal history of cardiovascular disease was defined when one or more of the following were present: IHD (namely angina, hospitalized myocardial infarction [MI], or revascularization procedures, i.e. coronary bypass surgery/angioplasty); and physician diagnosis of heart failure (22). Incident cardiovascular events were identified throughout the follow-up. Data on cardiovascular and all-cause mortality (defined as death from any cause) were also collected.

All systolic and diastolic BP measures obtained routinely during any clinical visit were collected retrospectively from the medical records for all subjects. BP measurements were performed by uniformly trained Mayo Clinic medical professionals using standardized and validated equipment and techniques. After a patient has rested for ≥ 5 min, BP measurement was taken manually using auscultatory method, with appropriately sized cuff, in a sitting position using the left arm with arm supported at heart level. Palpated radial pulse obliteration pressure was used to estimate systolic BP defined as the point at which the first Korotkoff sounds are heard; the disappearance of Korotkoff sounds was used to define diastolic BP. In more recent years, BP measurements were obtained using an automated device. If the BP measurement was $\geq 140/90$ mm Hg, it was repeated after 10 minutes, with the patient sitting. Pulse pressure was calculated as a difference between systolic and diastolic BP. All subjects in the study had at least 2 BP measurements during the study period. This included 442 (95%) of the 464 patients with RA and 424 (91%) of the 464 non-RA subjects.

For patients with RA, information on RA characteristics (i.e. rheumatoid factor [RF] positivity; erythrocyte sedimentation rates [ESR]; joint erosions/destructive changes on radiographs, large joint swelling, rheumatoid nodules, and joint surgery (i.e. arthroplasty/synovectomy) was collected. The data regarding the use of antirheumatic medications, i.e. methotrexate, hydroxychloroquine, other disease-modifying antirheumatic drugs (DMARDs, including sulfasalazine, leflunomide, azathioprine), biologic response modifiers, glucocorticosteroids and non-steroidal antirheumatic drugs (NSAIDs), including Cox-2 inhibitors, were also gathered. Data on the use of acetylsalicylic acid (ASA) for arthritis (the use of >6 tablets/day of ASA [>1950 mg/day] for ≥ 3 months) were recorded. The study

protocol was approved by the Institutional Review Boards from Mayo Clinic and Olmsted Medical Center.

Statistical Methods

Visit-to-visit BP variability was defined as within-subject standard deviation (SD) in systolic and diastolic BP, as well as in pulse pressure between all the visits to any health care provider. SD was divided by the corresponding BP mean to calculate a coefficient of variation of BP. Cox models were used to examine the effect of BP variability on incident cardiovascular events and all-cause mortality, adjusting for age, sex and calendar year of RA incidence/index date. Additional adjustment for traditional risk factors was also performed, and time-dependent covariates were used to represent risk factors that could change over time (e.g., diabetes mellitus, hypertension, use of anti-hypertensives, and dyslipidemia). Patients with a cardiovascular event before RA were excluded from the analyses as they were not at risk of developing that cardiovascular event during follow-up. To assess trends in BP variability, consecutive sets of 7 BP measurements were used to compute BP variability measures over time. Generalized additive models with smoothing splines were used to illustrate trends in BP measurements over time. Mixed models with random intercepts for each patient were used to test for significance of trends. Logistic regression models were used to study the associations between RA characteristics and medications with high BP variability during the first year after RA incidence, adjusting for age, sex, calendar year of RA incidence, hypertension and use of antihypertensives. High BP variability was defined based on the arbitrarily chosen top 25% values (cutoffs were 16.5 mm Hg for systolic and 9.8 mm Hg for diastolic BP variability) because there were no pre-specified cutoffs available in the literature. Linear regression models with the outcomes of continuous systolic and diastolic BP variability were also examined and results were similar to the logistic regression analyses.

Results

Patients' characteristics

The study included 442 patients with RA and 424 non-RA subjects. Table 1 shows baseline characteristics for both cohorts. Although patients with RA tended to have more BP measures than non-RA subjects (13460 BP measures in 3127 person-years of follow-up = 4.3 BP measures per year in RA vs. 9467 BP measures in 3085 person-years = 3.1 BP measures per year in non-RA; $p < 0.001$), the time between consecutive measurements was similar in both cohorts ($p = 0.93$). Patients with RA were more likely to have a diagnosis of hypertension at index date than the non-RA subjects ($p = 0.007$). However, the proportion of hypertensive subjects on antihypertensive drugs was similar in RA and non-RA cohort at index date and during the follow-up. There were no statistically significant differences in the distribution of other cardiovascular risk factors between the cohorts (Table 1).

BP characteristics for RA and non-RA cohorts are shown in Table 2. The mean systolic BP and pulse pressure at RA incidence/index date were higher in RA vs non-RA cohort; the mean diastolic BP was similar in both cohorts. Patients with RA had higher visit-to-visit variability in systolic BP and pulse pressure, but not diastolic BP, than the non-RA subjects.

Similarly, the coefficient of variation for systolic BP and pulse pressure was higher in RA vs non-RA subjects.

Trends in systolic and diastolic BP variability in RA vs non-RA cohort

The analysis of trends in BP variability in RA and non-RA subjects showed a significant decline in systolic BP variability in RA ($p<0.001$), but not in the non-RA cohort ($p=0.73$), after RA incidence/index date, adjusting for age, sex and calendar year of RA (Figure 1, upper panel). The results were similar when smoking, BMI and use of antihypertensive medications were added as adjusters. In contrast to systolic BP variability, diastolic BP variability remained essentially unchanged in both RA ($p=0.56$) and non-RA ($p=0.15$) cohort over the study period (Figure 1, lower panel).

Impact of BP variability on cardiovascular events and all-cause mortality

During the follow-up, 33 cardiovascular events and 57 deaths occurred in the RA cohort. Table 3 shows the associations of BP variability measures with cardiovascular outcomes and mortality in patients with RA. Increased systolic and diastolic BP variability were associated with increased risk of cardiovascular events and all-cause mortality in RA, adjusting for age, sex and calendar year of RA incidence. Increased pulse pressure variability was associated with increased risk of all-cause mortality, adjusting for age, sex and calendar year of RA incidence. The associations of systolic BP variability with the risk of cardiovascular events (HR per 1 mm Hg increase in BP variability 1.12, 95%CI 1.01-1.25) and diastolic BP variability with the risk of all-cause mortality (HR 1.14, 95%CI 1.03-1.27) remained statistically significant, after additional adjusting for systolic and diastolic BP, BMI, smoking at index date, and for time dependent covariates (i.e. diabetes mellitus, dyslipidemia, use of antihypertensives).

In the non-RA subjects, the associations of diastolic BP variability with cardiovascular events (HR 1.28; 95%CI 1.11-1.48 per 1 mmHg BP variability adjusted for systolic and diastolic BP, BMI, smoking at index date, diabetes mellitus, dyslipidemia, and use of antihypertensives) and all-cause mortality (HR 1.11; 95%CI 0.93-1.31) were similar to those in RA, despite the lack of statistical significance for cardiovascular events. However, in the non-RA subjects, there was no evidence of an association of systolic BP variability with cardiovascular events (HR 1.02; 95%CI 0.94-1.11) or all-cause mortality (HR 1.04; 95%CI 0.96-1.12).

Association of RA characteristics and medications with BP variability

To better understand the underlying mechanisms for BP variability and its changes in RA, we examined the association of RA characteristics and antirheumatic drug use with systolic and diastolic BP variability during the first year after RA incidence. Three hundred forty three patients with RA had 2 BP values during the first year after RA incidence for calculation of BP variability and were included in the analysis. The results are summarized in Table 4. The Cox-2 inhibitor users were approximately twice as likely to have high systolic BP variability ($p=0.009$) and 1.7-times more likely to have high diastolic BP variability during the first year after RA incidence than the non-users ($p=0.039$). The associations with other RA characteristics and medications did not reach statistical

significance. The associations between systolic BP variability and the use of methotrexate ($p=0.085$) and hydroxychloroquine ($p=0.09$) approached statistical significance (Table 4).

Discussion

In contrast to the growing number of studies of the unfavorable impact of visit-to-visit BP variability on cardiovascular outcomes in the general population, research on long-term BP variability in patients with RA is scarce. We report, for the first time, increased visit-to-visit systolic BP variability and pulse pressure variability in a large cohort of patients with RA vs non-RA subjects. We have also found a significant decline in visit-to-visit systolic BP variability after RA incidence/index date in RA, but not in the non-RA subjects. Concordant with studies from the general population we report association of BP variability with increased risk of cardiovascular events and all-cause mortality, adjusting for systolic and diastolic BP, BMI, smoking, diabetes, dyslipidemia and use of antihypertensives (10-13).

Among patients with rheumatic diseases, substantial change in BP levels over time was previously reported in a large longitudinal cohort study of 1,240 patients with systemic lupus erythematosus (SLE) from a Toronto lupus cohort followed for a mean of 9.3 years (26). In this study 46.4% SLE patients had their BP measures varying between normal and elevated during the course of the disease, suggesting substantial variation of BP in SLE over time. Unlike our study, there was no comparison cohort. For this reason, the results of our study may provide further insight into the longitudinal dynamics of BP changes in patients with autoimmune rheumatic disease vs general population, by demonstrating predisposition to increased systolic BP variability in RA vs non-RA cohort, and subsequent decline in systolic BP variability over time which was only found in RA, but not in the non-RA cohort.

We also found that the coefficient of variation for systolic BP and pulse pressure was higher in RA vs non-RA subjects. Given that coefficient of variation is a normalized measure of variability which accounts for the mean, this latter observation suggests that the difference in BP variability between RA and non-RA cohorts was not solely due to the difference in mean values. The underlying mechanisms for this increase in systolic BP variability in RA vs non-RA and decline in variability after RA incidence are unclear. Several factors may contribute to this difference in BP variability between RA and the general population, including RA disease activity and medications.

The use of Cox-2 inhibitors was one of the predisposing factors to high systolic and diastolic BP variability during the first year after RA incidence. This is concordant with the previous findings on the association of Cox-2 inhibitor use with increased BP and destabilization of BP management in the general population (27). It can be suggested that decreased production of prostacyclin following the inhibition of Cox-2 in blood vessels may be associated not only with increase in BP but also with increased BP variability, both of which may exert unfavorable impact on cardiovascular outcomes reported in Cox-2 users (28). Alternatively, changes in RA characteristics in Cox-2 users (e.g., improved inflammatory and functional status) could contribute to decreases in BP, which would also increase BP variability. However, the exact mechanisms underlying the association of Cox-2 inhibitor use and increased BP variability in RA are unclear and require further study.

The use of hydroxychloroquine in our study tended to be associated with a lower likelihood of high systolic BP variability, although statistical significance was not achieved for this association. This emerging finding is concordant with the results from the Toronto lupus cohort where the use of antimalarials was negatively correlated with systolic and diastolic BP estimates in females (26).

The associations between high systolic BP variability and methotrexate use approached statistical significance. Considering that methotrexate use is thought to be associated with the overall beneficial cardiovascular risk profile, this trend towards increased BP variability in methotrexate users is difficult to explain and requires further investigation.

There was no apparent association between the use of glucocorticosteroids and BP variability in the first year of RA in our study which was concordant with the findings of others (26). The association of glucocorticoids with increased BP is well-known but poorly understood (29). The effect of glucocorticoid use on long-term BP variability and the impact of changing patterns of glucocorticoid use on BP variability trends is a subject for further investigation.

In our study we did not find any apparent associations between characteristics of RA activity and severity and BP variability. This is in line with the findings of the recent cross-sectional study in RA patients suggesting that generalized systemic inflammation as measured by ESR and CRP may not be a significant contributor to hypertension in RA (30). In Toronto lupus cohort greater SLE activity measured by SLE Disease Activity Index 2000 (SLEDAI 2K) was found to correlate with higher systolic and diastolic BP (26). These findings cannot be directly compared to ours as unlike our study the authors examined associations between disease characteristics and systolic/diastolic BP measures rather than BP variability. More studies are needed to better understand the impact of RA characteristics on BP variability.

We showed unfavorable impact of BP variability on the risk of cardiovascular events and all-cause mortality in RA which is consistent with studies from the general population, in particular those including patients from high cardiovascular risk categories (i.e. elderly, patients with multiple cardiovascular risk factors and comorbidities) (11, 13). Similarly to the general population, one of the relevant and clinically important questions for BP management in patients with RA is whether stabilizing BP variability has a beneficial impact on cardiovascular outcomes in RA. This requires more studies with prospective design.

Our findings should be interpreted in the scope of several potential limitations. First, this retrospective study used only information on clinic BP measures available from medical records. We believe that the use of the comprehensive REP resources likely minimized shortcomings of the retrospective data use. While measurement bias cannot be excluded, this shortcoming may be minimized by the fact that the measurements for both cohorts were taken at similar medical facilities, by similarly trained medical professionals using standardized and validated equipment and techniques. We acknowledge that methodology changes from manual to automatic BP measurement could have an impact on the results. However, all subjects in both the RA and non-RA cohorts received their medical care from

similar healthcare facilities in the area, and any changes in BP measurement during the study time would affect both groups equally. Second, we cannot exclude that the non-RA cohort could have different reasons for visiting health care providers than patients with RA suggesting different patterns of follow-up depending on the nature of their comorbidities. However, BP was uniformly measured at virtually every medical visit in our institution, and there was no statistically significant difference in the time intervals between the BP measurements in the RA and non-RA cohorts suggesting that patients in both cohorts had largely similar patterns of routine outpatient BP monitoring. While we have not compared the full comorbidity profile between the cohorts, the similar distributions of the majority of cardiovascular risk factors in the non-RA and RA cohorts at baseline suggests that their cardiovascular comorbidity profiles were largely similar. Third, we assessed long-term fluctuations of BP from one clinic visit to another, thus the results may not be extrapolated to BP variability assessed by other methods and measured at different time intervals, e.g. short-term 24-hour fluctuations of BP. Fourth, the information on antihypertensive medication dosage and compliance with antihypertensive treatment was not available in this retrospective study. However, the percentage of patients on antihypertensive medications at baseline and during the follow-up was similar in RA vs non-RA cohort. In fact, recent findings from the general population have shown that poor medication adherence explains only a small proportion of visit-to-visit BP variability, suggesting that compliance with antihypertensive drug use does not have a major impact on BP variability and other factors may contribute (31). Fifth, in this study we have not examined the association of C-reactive protein with BP variability as C-reactive protein values were not available. This needs to be addressed in the future studies. Finally, the population of Olmsted County, MN is predominantly white. Thus, the results may not be generalizable to more ethnically diverse populations.

This study had several important strengths. This is a large population-based study using comprehensive medical records linkage system. Further, this is the first longitudinal study with parallel analysis of BP variability in patients with RA and non-RA subjects from the same community during the same calendar period.

In conclusion, patients with RA demonstrated a significantly higher long-term visit-to-visit systolic BP variability and pulse pressure variability than the non-RA subjects. Systolic BP variability declined significantly after the index date in patients with RA, but not in the non-RA subjects. Increased visit-to-visit BP variability was associated with adverse cardiovascular outcomes and all-cause mortality in RA, adjusting for systolic and diastolic BP, BMI, smoking, diabetes, dyslipidemia and use of antihypertensives. The use of some antirheumatic medications, including Cox-2 inhibitors, can potentially increase BP variability in patients with RA. The impact of RA characteristics and medications on BP variability in RA merits further study.

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Figure 1.

Trends in within-subject blood pressure variability in the rheumatoid arthritis (RA) and non-RA cohorts. The upper panel shows trends in systolic BP variability after RA incidence/index date; the lower panel shows trends in diastolic BP variability after RA incidence/index date. In each panel, the solid line shows trends in RA patients and the dotted line shows trends in non-RA subjects. SD = standard deviation.

Table 1
Baseline characteristics of patients with RA and non-RA subjects

Characteristic	RA (n=442)	Non-RA (n=424)
Age at RA incidence/index date, mean $\pm$ SD, years	55.5 $\pm$ 15.6	55.7 $\pm$ 15.6
Female, n (%)	309 (70)	293 (69)
Length of follow-up, mean $\pm$ SD, years	7.1 $\pm$ 2.6	7.3 $\pm$ 2.6
BP measurements		
- Total number	13,460	9,467
- Median, measures per subject	27.0	19.0
Median time between BP measurements, days	30.0	27.0
Hypertension, diagnosis at index date, n (%)	282 (64)	235 (55)
Antihypertensive medications, n (%)		
- At index date	144 (33)	131 (31)
- During the follow-up	216 (49)	193 (46)
Smoking, n (%)		
- Current	72 (16)	61 (14)
- Former	152 (34)	125 (29)
Alcohol abuse	35 (8)	26 (6)
Diabetes mellitus, n (%)	48 (11)	43 (10)
Dyslipidemia, n (%)	266 (60)	248 (58)
BMI, mean $\pm$ SD, kg/m ²	28.6 $\pm$ 6.1	28.8 $\pm$ 6.7
BMI $\geq$ 30 kg/m ² , n (%)	158 (36)	160 (38)
Family history of ischemic heart disease, n (%)	103 (23)	99 (23)
Personal history of cardiovascular disease, n (%)	48 (11)	59 (14)

Abbreviations: RA = rheumatoid arthritis; BMI = body mass index; BP = blood pressure; SD = standard deviation

Table 2
BP characteristics in patients with RA and the non-RA subjects

Variable ^{#X}	RA (n=442)	Non-RA (n=424)	p-value
BP at RA incidence, mm Hg			
- Systolic BP	131.2 ± 18.7	128.2 ± 19.3	0.018
- Diastolic BP	75.1 ± 10.9	75.6 ± 11.0	0.53
- Pulse pressure	56.1 ± 15.4	52.6 ± 15.8	<0.001
BP variability[*], mm Hg			
- Systolic	13.8 ± 4.7	13.0 ± 5.2	0.004
- Diastolic	8.4 ± 2.9	8.0 ± 2.6	0.21
- Pulse pressure	11.7 ± 3.7	10.9 ± 4.3	<0.001
Coefficient of variation of BP^{**}			
- Systolic	0.106 ± 0.032	0.102 ± 0.037	0.034
- Diastolic	0.115 ± 0.039	0.111 ± 0.039	0.28
- Pulse pressure	0.209 ± 0.058	0.203 ± 0.065	0.046

[#] All values are given as mean ± standard deviation;

^X statistically significant differences (p<0.05) are shown in bold.

^{*} Visit-to-visit BP variability was defined as within-subject standard deviation (SD) in systolic and diastolic BP, as well as in pulse pressure levels between the visits to any health care provider.

^{**} Coefficient of variation was calculated as SD divided by the corresponding BP mean.

Abbreviations: RA = rheumatoid arthritis; BP = blood pressure

Table 3
Impact of BP variability on cardiovascular events and all-cause mortality in RA[#]

Variable	Hazard ratio (95% confidence interval [CI]) [*] , adjusted for age, sex, and calendar year of RA incidence		Hazard ratio (95% CI) [*] , adjusted for age, sex, and calendar year of RA incidence, and cardiovascular risk factors ^{**}	
	Cardiovascular events	All-cause mortality	Cardiovascular events	All-cause mortality
Systolic BP variability	1.14 (1.04-1.25)	1.10 (1.03-1.17)	1.12 (1.01-1.25)	1.04 (0.97-1.12)
Diastolic BP variability	1.15 (1.02-1.30)	1.22 (1.11-1.34)	1.11 (0.95-1.28)	1.14 (1.03-1.27)
Pulse pressure variability	1.10 (0.98, 1.24)	1.11 (1.02, 1.22)	1.09 (0.96, 1.23)	1.06 (0.97, 1.17)

^{*} HRs per 1 mm Hg increase in BP variability;

^{**} adjusting for systolic and diastolic BP, BMI, smoking at index date, and for time-dependent covariates (i.e. diabetes, dyslipidemia, use of antihypertensives)

[#] Patients with a cardiovascular event before RA were excluded from the analyses as they were not at risk of developing that cardiovascular event during follow-up.

Abbreviations: RA = rheumatoid arthritis; BP = blood pressure

Table 4
Association of RA disease characteristics and medications with increased BP variability in RA during the first year after RA incidence in 343 patients with RA^{*}, #, ^

RA characteristic	Value ^X	High systolic BP variability ^{**} Odds ratio, OR (95% confidence interval, CI)	High diastolic BP variability ^{**} OR (95% CI)
ESR, mean $\pm$ standard deviation	23.3 $\pm$ 19.5	1.06 [†] (0.93, 1.21)	1.00 [†] (0.87, 1.14)
RF positivity	211 (62)	1.20 (0.70, 2.04)	0.78 (0.46, 1.31)
Rheumatoid nodules	67 (20)	0.95 (0.50, 1.79)	0.96 (0.50, 1.84)
Erosions/destructive changes	96 (28)	0.62 (0.34, 1.13)	0.68 (0.37, 1.22)
Large joint swelling	217 (63)	1.32 (0.76, 2.27)	1.15 (0.67, 1.97)
Joint surgery	28 (8)	0.59 (0.22, 1.57)	1.18 (0.48, 2.88)
<i>Use of antirheumatic medications in the first year</i>			
Methotrexate	183 (53)	1.60 (0.94, 2.73)	1.17 (0.69, 1.98)
Hydroxychloroquine	204 (59)	0.65 (0.39, 1.08)	0.70 (0.42, 1.17)
Other DMARDs	33 (10)	0.94 (0.40, 2.24)	1.16 (0.50, 2.69)
Biologic response modifiers	34 (10)	1.21 (0.51, 2.86)	0.87 (0.37, 2.07)
Glucocorticosteroids	256 (75)	0.92 (0.51, 1.67)	0.95 (0.52, 1.73)
Cox-2 inhibitors	157 (46)	1.99 (1.18, 3.34)	1.74 (1.03, 2.94)
ASA for arthritis ^{##}	54 (16)	0.90 (0.45, 1.82)	1.06 (0.52, 2.16)
NSAIDs	300 (87)	0.70 (0.34, 1.44)	1.21 (0.56, 2.58)

* High BP variability was defined based on the top 25% values (cutoffs were 16.5 mm Hg for systolic BP variability and 9.8 mm Hg for diastolic BP variability).

Statistically significant associations ($p < 0.05$) are shown in bold

^ Three hundred forty three RA patients had BP values sufficient for calculation of BP variability during the first year after RA incidence, and were included in this analysis

^X All values are given as n (%), unless specified otherwise

^{**} adjusted for age, sex, calendar year of RA incidence, hypertension and use of antihypertensive medications

[†] Per 10 mm/hr increase

^{##} the use of >6 tablets/day of acetylsalicylic acid [>1950 mg/day] for 3 months

Abbreviations: ASA = aspirin; DMARDs = disease modifying antirheumatic drugs; ESR = erythrocyte sedimentation rate; NSAIDs = nonsteroidal antiinflammatory drugs; RA = rheumatoid arthritis; RF = rheumatoid factor; BP = blood pressure