Longterm Blood Pressure Variability in Patients with Rheumatoid Arthritis and Its Effect on Cardiovascular Events and All-cause Mortality in RA: A Population-based Comparative Cohort Study

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ABSTRACT. ***Objective.*** To examine longterm visit-to-visit blood pressure (BP) variability in patients with rheumatoid arthritis (RA) versus non-RA subjects and to assess its effect on cardiovascular (CV) events and mortality in RA.

Methods. Clinic BP measures were collected in a population-based incident cohort of patients with RA (1987 American College of Rheumatology criteria met between January 1, 1995, and January 1, 2008) and non-RA subjects. BP variability was defined as within-subject SD in systolic and diastolic BP.

Results. The study included 442 patients with RA (mean age 55.5 yrs, 70% females) and 424 non-RA subjects (mean age 55.7 yrs, 69% females). Patients with RA had higher visit-to-visit variability in systolic BP (13.8 ± 4.7 mm Hg) than did 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 followup of 7.1 years, 33 CV events and 57 deaths occurred in the RA cohort. Visit-to-visit systolic BP variability was associated with increased risk of CV events (HR per 1 mm Hg increase in BP variability 1.12, 95% 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, and use of antihypertensives.

Conclusion. Patients with RA had higher visit-to-visit systolic BP variability than did 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 CV outcomes and all-cause mortality in RA. (First Release July 1 2014; J Rheumatol 2014;41:1638–44; doi:10.3899/jrheum.131170)

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The evidence for the increased cardiovascular (CV) risk in rheumatoid arthritis (RA) compared to the general population is convincing[1,2,3,4]. The underlying mechanisms of this increased CV risk in RA are not fully understood, and the relative effect of traditional and nontraditional risk factors and inflammation on CV disease in RA is actively studied[5]. Along with smoking, obesity, and dyslipidemia, hypertension (HTN) is considered one of the most common modifiable CV risk factors with significant detrimental effect on CV disease progression, both in the general population and in RA[6,7,8,9]. While the role of mean estimates of systolic and diastolic blood pressure (BP) in CV risk has been widely studied in various populations, the concept of BP variability is a much less explored and increasingly growing area of research[10,11,12,13].

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 h), midterm (day-to-day), and longterm (visit-to-visit)[10]. Among these types, visit-to-visit variability has long been 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

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that longterm visit-to-visit BP variability is a reproducible measure and an important prognostic factor for CV outcomes[10,11,12,13,14,15,16].

The literature regarding BP variability in patients with RA is limited to studies of short-term BP variability as part of an assessment of autonomic system dysfunction in RA[17]. Studies of longterm BP variability in RA in comparison to the general population are lacking, and prognostic significance of changes in BP measures over time on CV outcomes and mortality in RA is poorly understood. To address this gap in knowledge, we studied longterm visit-to-visit BP variability in patients with RA versus non-RA subjects and examined the effect of BP variability on CV 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 gathering of all clinically recognized cases of RA among the residents of Olmsted County, Minnesota, USA. The unique features of the REP and its capabilities for the population-based research have been 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 January 1, 1995, and January 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 of RA incidence/index date) 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, or July 1, 2010.

Information on the following CV risk factors was collected at baseline as 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/documented use of lipid-lowering medications]; body mass index (BMI; kg/m^2); HTN (defined as ≥ 2 BP readings ≥ 140 mm Hg systolic and/or ≥ 90 mm Hg diastolic obtained in the outpatient setting during a 1-yr period, physician diagnosis/documented use of antihypertensive medications)[8]; diabetes mellitus [defined as fasting plasma glucose ≥ 126 mg/dl (≥ 7.0 mmol/l), physician diagnosis/documented 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 in females and < 55 years in males. Personal history of CV disease was defined when 1 or more of the following were present: IHD (angina, hospitalized myocardial infarction, or revascularization procedures, i.e., coronary bypass surgery/angioplasty), and physician diagnosis of heart failure[22]. Incident CV events were identified throughout the followup. Data on CV 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 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 ≥ 140/90 mm Hg, it was repeated after 10 min, 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 was collected [i.e., rheumatoid factor positivity; erythrocyte sedimentation rates (ESR); joint erosions/destructive changes on radiographs, large joint swelling, rheumatoid nodules, and joint surgery (arthroplasty/synovectomy)]. Data were also gathered regarding the use of antirheumatic medications, i.e., methotrexate (MTX), hydroxychloroquine (HCQ), other disease-modifying antirheumatic drugs (including sulfasalazine, leflunomide, azathioprine), biologic response modifiers, glucocorticosteroids and nonsteroidal antirheumatic drugs including cyclooxygenase inhibitors (Cox-2). Data on the use of acetylsalicylic acid (ASA) for arthritis were recorded [the use of > 6 tablets/day of ASA (> 1950 mg/day) for ≥ 3 months]. The study protocol was approved by the institutional review boards from the Mayo Clinic and Olmsted Medical Center.

Statistical methods. Visit-to-visit BP variability was defined as within-subject SD in systolic and diastolic BP, as well as in pulse pressure between all the visits to any healthcare 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 CV 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, HTN, use of antihypertensives, and dyslipidemia). Patients with a CV event before RA were excluded from the analyses because they were not at risk of developing that CV event during followup. 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, HTN, 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 prespecified 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 (13,460 BP measures in 3127 person-yrs of followup = 4.3 BP measures per yr in RA vs 9467 BP measures in 3085 person-yrs = 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 HTN at index date than the non-RA subjects ($p = 0.007$). However, the proportion of hypertensive subjects taking antihypertensive drugs was

Table 1. Baseline characteristics of patients with rheumatoid arthritis (RA) and non-RA subjects.

Characteristic	RA, n = 442	Non-RA, n = 424
Age at RA incidence/index date, mean ± SD, yrs	55.5 ± 15.6	55.7 ± 15.6
Female, n (%)	309 (70)	293 (69)
Length of followup, mean ± SD, yrs	7.1 ± 2.6	7.3 ± 2.6
BP measurements		
Total number	13,460	9467
Median, measures per subject	27.0	19.0
Median time between BP measurements, days	30.0	27.0
HTN, diagnosis at index date, n (%)	282 (64)	235 (55)
Antihypertensive medications, n (%)		
At index date	144 (33)	131 (31)
During the followup	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 ± SD, kg/m^2	28.6 ± 6.1	28.8 ± 6.7
BMI ≥ 30 kg/m^2, n (%)	158 (36)	160 (38)
Family history of ischemic heart disease, n (%)	103 (23)	99 (23)
Personal history of CV disease, n (%)	48 (11)	59 (14)

BMI: body mass index; BP: blood pressure; HTN: hypertension; CV: cardiovascular.

similar in the RA and non-RA cohorts at index date and during the followup. There were no statistically significant differences in the distribution of other CV 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 versus 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 adjustors. In contrast to systolic BP variability, diastolic BP variability remained essentially unchanged in both the RA ($p = 0.56$) and non-RA ($p = 0.15$) cohorts over the study period (Figure 1, lower panel).

Effect of BP variability on CV events and all-cause mortality. During the followup, 33 CV events and 57 deaths

Table 2. BP characteristics in patients with rheumatoid arthritis (RA) and the non-RA subjects.

Variable	RA, n = 442	Non-RA, n = 424	p
BP at RA incidence/index date, 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 ± SD. Statistically significant differences ($p < 0.05$) are shown in bold. * Visit-to-visit BP variability was defined as within-subject SD in systolic and diastolic BP, as well as in pulse pressure levels between the visits to any healthcare provider. ** Coefficient of variation was calculated as SD divided by the corresponding BP mean. BP: blood pressure.

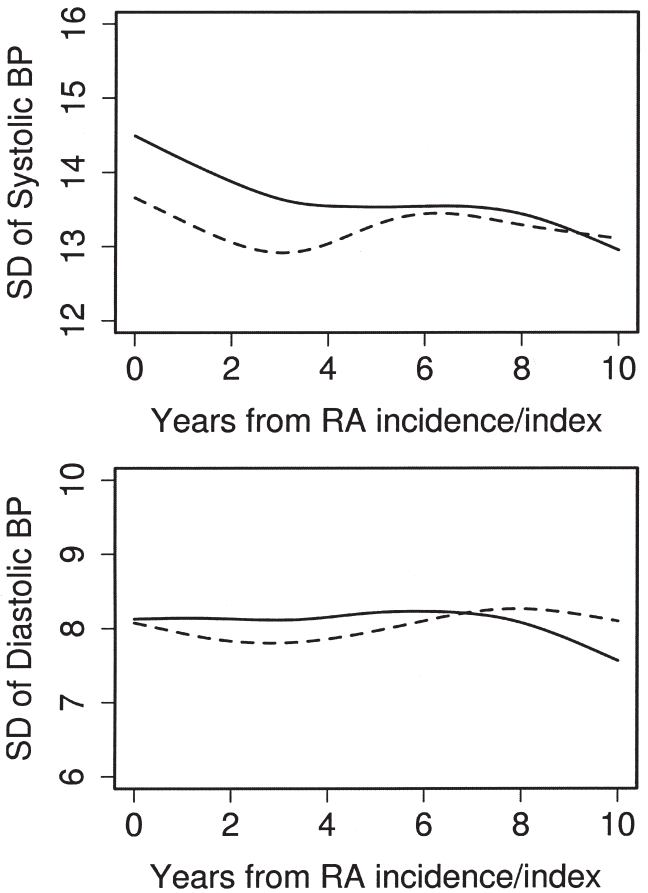

Figure 1. Trends in within-subject blood pressure (BP) variability in the rheumatoid arthritis (RA) and non-RA cohorts. The upper panel shows trends in systolic BP variability after RA incidence/index date. The lower panel shows trends in diastolic BP variability after RA incidence/index date. In each panel, the solid line shows trends in patients with RA and the dotted line shows trends in non-RA subjects.

Table 3. Effect of BP variability on cardiovascular (CV) events and all-cause mortality in rheumatoid arthritis (RA). Patients with a CV event before RA were excluded from the analyses because they were not at risk of developing that CV event during followup.

Variable	HR (95% CI)*, Adjusted for Age, Sex, and Calendar Year of RA Incidence		HR (95% CI)*, Adjusted for Age, Sex, and Calendar Year of RA Incidence, and CV Risk Factors**	
	CV events	All-cause Mortality	CV 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)

* HR 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). BP: blood pressure.

Table 4. Association of rheumatoid arthritis (RA) disease characteristics and medications with increased BP variability during the first year after RA incidence in 343 patients with RA. 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). Three hundred forty-three patients with RA had BP values sufficient for calculation of BP variability during the first year after RA incidence, and were included in this analysis. All values are given as n (%), unless specified otherwise.

RA Characteristic	Value	High Systolic BP Variability*, OR (95% CI)	High Diastolic BP Variability*, OR (95% CI)
ESR, mean ± SD	23.3 ± 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)
Use of antirheumatic medications in the first year			
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 DMARD	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)
NSAID	300 (87)	0.70 (0.34, 1.44)	1.21 (0.56, 2.58)

* Adjusted for age, sex, calendar year of RA incidence, hypertension, and use of antihypertensive medications. † Per 10 mm/h increase. ## The use of > 6 tablets/day of acetylsalicylic acid (> 1950 mg/day) for ≥ 3 months. ASA: aspirin; DMARD: disease-modifying antirheumatic drugs; ESR: erythrocyte sedimentation rate; NSAID: nonsteroidal antiinflammatory drugs; RF: rheumatoid factor; BP: blood pressure; Cox-2: cyclooxygenase.

occurred in the RA cohort. Table 3 shows the associations of BP variability measures with CV outcomes and mortality in patients with RA. Increased systolic and diastolic BP variability were associated with increased risk of CV 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 CV 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 CV events (HR 1.28; 95% CI 1.11–1.48 per 1 mm Hg 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 CV events. However, in the non-RA subjects, there was no

evidence of an association of systolic BP variability with CV 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 and 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 about 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 were 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 MTX (p = 0.085) and HCQ (p = 0.09) approached statistical significance (Table 4).

DISCUSSION

In contrast to the growing number of studies of the detriment of visit-to-visit BP variability on CV 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 CV events and all-cause mortality, adjusting for systolic and diastolic BP, BMI, smoking, diabetes, dyslipidemia, and use of antihypertensives[10,11,12,13].

Among patients with rheumatic diseases, substantial change in BP levels over time was previously reported in a large longitudinal cohort study of 1240 patients with systemic lupus erythematosus (SLE) from a Toronto cohort followed for a mean of 9.3 years[26]. In that study, 46.4% patients with SLE 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 versus the general population, by demonstrating predisposition to increased systolic BP variability in the RA versus the non-RA cohort, and subsequent decline in systolic BP variability over time, which was only found in the 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 patients with RA than in non-RA subjects. Given that coefficient of variation is a normalized measure of variability that 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 are unclear for this increase in systolic BP variability in RA vs non-RA and decline in variability after RA incidence. 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 an increase in BP but also with increased BP variability, both of which may unfavorably influence CV 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 HCQ 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 SLE 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 MTX use approached statistical significance. Considering that MTX use is thought to be associated with the overall beneficial CV risk profile, this trend toward increased BP variability in MTX 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, a finding concordant with those of others[26]. The association of glucocorticoids with increased BP is well known but poorly understood[29]. The effect of glucocorticoid use on longterm BP variability and the effect 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 a recent cross-sectional study in patients with RA, suggesting that

generalized systemic inflammation as measured by ESR and C-reactive protein (CRP) may not be a significant contributor to HTN in RA[30]. In the Toronto SLE cohort, greater SLE activity measured by SLE Disease Activity Index 2000 was found to correlate with higher systolic and diastolic BP[26]. These findings cannot be directly compared to ours because 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 effect of RA characteristics on BP variability.

We showed unfavorable influence of BP variability on the risk of CV events and all-cause mortality in RA, which is consistent with studies from the general population, in particular those including patients from high CV risk categories (i.e., elderly, and patients with multiple CV 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 effect on CV 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 effect 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 healthcare providers than patients with RA, suggesting different patterns of followup 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 CV risk factors in the non-RA and RA cohorts at baseline suggest that their CV comorbidity profiles were largely similar. Third, we assessed longterm 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-h 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 taking antihypertensive medications at baseline and during the followup was similar in both cohorts. 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 effect on BP variability and that other factors may contribute[31]. Fifth, in this study we have not examined the association of CRP with BP variability because CRP values were not available. This needs to be addressed in the future studies. Finally, the population of Olmsted County 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 a 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.

Patients with RA demonstrated a significantly higher longterm visit-to-visit systolic BP variability and pulse pressure variability than did 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 CV 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 effect of RA characteristics and medications on BP variability in RA merits further study.

REFERENCES

1. Solomon DH, Goodson NJ, Katz JN, Weinblatt ME, Avorn J, Setoguchi S, et al. Patterns of cardiovascular risk in rheumatoid arthritis. Ann Rheum Dis 2006;65:1608-12.
2. Maradit-Kremers H, Crowson CS, Nicola PJ, Ballman KV, Roger VL, Jacobsen SJ, et al. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study. Arthritis Rheum 2005;52:402-11.
3. Symmons DP, Gabriel SE. Epidemiology of CVD in rheumatic disease, with a focus on RA and SLE. Nat Rev Rheumatol 2011;7:399-408.
4. Avina-Zubieta JA, Thomas J, Sadatsafavi M, Lehman AJ, Lacaille D. Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis 2012;71:1524-9.
5. Crowson CS, Liao KP, Davis JM 3rd, Solomon DH, Matteson EL, Knutson KL, et al. Rheumatoid arthritis and cardiovascular disease. Am Heart J 2013;166:622-8 e1.
6. Panoulas VF, Metsios GS, Pace AV, John H, Treharne GJ, Banks MJ, et al. Hypertension in rheumatoid arthritis. Rheumatology

2008;47:1286-98.
7. van den Meiracker AH. A global approach to hypertension. EuroIntervention 2013;9 Suppl R:R16-20.
8. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr., et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206-52.
9. Sarmiento-Monroy JC, Amaya-Amaya J, Espinosa-Serna JS, Herrera-Diaz C, Anaya JM, Rojas-Villarraga A. Cardiovascular disease in rheumatoid arthritis: a systematic literature review in Latin America. Arthritis 2012;2012:371909.
10. Parati G, Ochoa JE, Lombardi C, Bilo G. Assessment and management of blood-pressure variability. Nat Rev Cardiol 2013;10:143-55.
11. Hsieh YT, Tu ST, Cho TJ, Chang SJ, Chen JF, Hsieh MC. Visit-to-visit variability in blood pressure strongly predicts all-cause mortality in patients with type 2 diabetes: a 5.5-year prospective analysis. Eur J Clin Invest 2012;42:245-53.
12. Muntner P, Shimbo D, Tonelli M, Reynolds K, Arnett DK, Oparil S. The relationship between visit-to-visit variability in systolic blood pressure and all-cause mortality in the general population: findings from NHANES III, 1988 to 1994. Hypertension 2011;57:160-6.
13. Poortvliet RK, Ford I, Lloyd SM, Sattar N, Mooijaart SP, de Craen AJ, et al. Blood pressure variability and cardiovascular risk in the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). PLoS One 2012;7:e52438.
14. Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. Lancet 2010;375:938-48.
15. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlof B, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet 2010;375:895-905.
16. Muntner P, Joyce C, Levitan EB, Holt E, Shimbo D, Webber LS, et al. Reproducibility of visit-to-visit variability of blood pressure measured as part of routine clinical care. J Hypertens 2011;29:2332-8.
17. Milovanovic B, Stojanovic L, Milicevik N, Vasic K, Bjelakovic B, Krotin M. Cardiac autonomic dysfunction in patients with systemic lupus, rheumatoid arthritis and sudden death risk. Srp Arh Celok Lek 2010;138:26-32.
18. Maradit-Kremers H, Crowson CS, Gabriel SE. Rochester Epidemiology Project: a unique resource for research in the rheumatic diseases. Rheum Dis Clin North Am 2004;30:819-34, vii.
19. Maradit-Kremers H, Myasoedova E, Crowson CS, Savova G, Gabriel SE, Matteson EL. The Rochester Epidemiology Project: exploiting the capabilities for population-based research in rheumatic diseases. Rheumatology 2011;50:6-15.
20. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
21. Nicola PJ, Maradit-Kremers H, Roger VL, Jacobsen SJ, Crowson CS, Ballman KV, et al. The risk of congestive heart failure in rheumatoid arthritis: a population-based study over 46 years. Arthritis Rheum 2005;52:412-20.
22. Myasoedova E, Crowson CS, Nicola PJ, Maradit-Kremers H, Davis JM 3rd, Roger VL, et al. The influence of rheumatoid arthritis disease characteristics on heart failure. J Rheumatol 2011; 38:1601-6.
23. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143-421.
24. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 2003;26 Suppl 1:S5-20.
25. Diagnosis and classification of diabetes mellitus. Diabetes Care 2005;28 Suppl 1:S37-42.
26. Nikpour M, Gladman DD, Ibanez D, Harvey PJ, Urowitz MB. Variability over time and correlates of cholesterol and blood pressure in systemic lupus erythematosus: a longitudinal cohort study. Arthritis Res Ther 2010;12:R125.
27. Sowers JR, White WB, Pitt B, Whelton A, Simon LS, Winer N, et al. The effects of cyclooxygenase-2 inhibitors and nonsteroidal anti-inflammatory therapy on 24-hour blood pressure in patients with hypertension, osteoarthritis, and type 2 diabetes mellitus. Arch Intern Med 2005;165:161-8.
28. Cannon CP, Cannon PJ. Physiology. COX-2 inhibitors and cardiovascular risk. Science 2012;336:1386-7.
29. Goodwin JE, Geller DS. Glucocorticoid-induced hypertension. Pediatr Nephrol 2012;27:1059-66.
30. Manavathongchai S, Bian A, Rho YH, Oeser A, Solus JF, Gebretsadik T, et al. Inflammation and hypertension in rheumatoid arthritis. J Rheumatol 2013;40:1806-11.
31. Muntner P, Levitan EB, Joyce C, Holt E, Mann D, Oparil S, et al. Association between antihypertensive medication adherence and visit-to-visit variability of blood pressure. J Clin Hypertens 2013;15:112-7.