Consequences of Increased Systolic Blood Pressure in Patients with Osteoarthritis and Rheumatoid Arthritis

GURKIRPAL SINGH, JEFFREY D. MILLER, DANIEL M. HUSE, DAN PETTITT, RALPH B. D'AGOSTINO, and MASON W. RUSSELL

ABSTRACT. ***Objective.*** To estimate the potential effect on cardiovascular event occurrence and treatment costs associated with increases in systolic blood pressure (SBP) among patients with osteoarthritis (OA) and rheumatoid arthritis (RA).

Methods. We used cardiovascular risk prediction models from the Framingham Heart Study and data on risk factors from the Third National Health and Nutrition Examination Survey (NHANES III) to estimate occurrences of ischemic heart disease and stroke over one year among US adults with OA/RA. Separate analyses were conducted for treated hypertensive patients, and untreated hypertensive and normotensive patients, respectively. Published estimates were used to assign costs to these events and to follow care. The effect of incremental increases in SBP on events and costs was then assessed. Monte Carlo simulation was undertaken to assess the range of event occurrence and costs associated with alternative assumptions regarding the distribution of increased SBP in the at-risk population.

Results. Of the estimated 30 million adults in the US aged ≥ 35 years with OA and RA, roughly 11.8 million (39%) receive pharmacologic treatment for hypertension. Increases in SBP of 1–5 mm Hg were associated with 7,100–35,700 additional ischemic heart disease and stroke events over one year, with corresponding costs (year 2000 USD) of $114–569 million. A 20 mm Hg increase in SBP experienced by 15% of the at-risk population (equivalent to a population-average 3 mm Hg increase) is associated with about 21,700 additional events (95% CI 19,120, 24,221) and $346 million (95% CI $305, 387 million) in associated costs.

Conclusion. Relatively small changes in SBP associated with use of common arthritis medications can have a significant effect on the cardiovascular risk profile. It is important that clinicians who treat patients with OA/RA accurately weigh the potential risks of these medications against their benefits. (J Rheumatol 2003;30:714–9)

Key Indexing Terms:
RHEUMATOID ARTHRITIS OSTEOARTHRITIS CARDIOVASCULAR DISEASE
HYPERTENSION COSTS COST ANALYSIS

Arthritis and hypertension are 2 of the most prevalent chronic diseases affecting adults in the US. It is therefore not surprising that the co-prevalence of hypertension and arthritis is considerable. Data from the Third National Health and Nutrition Examination Survey (NHANES III), conducted by the National Center for Health Statistics from 1988 to 1994, suggest that roughly 30 million people aged ≥ 35 years have osteoarthritis (OA) or rheumatoid arthritis (RA) and 11.8 million of these receive pharmacologic treatment for hypertension[1].

The potential effects on blood pressure of many classes of drugs with antiinflammatory properties, particularly corticosteroids and nonsteroidal antiinflammatory drugs (NSAID), are understood by most clinicians. NSAID, for example, are known inhibitors of several commonly used classes of antihypertensive drugs, such as angiotensin-converting enzyme (ACE) inhibitors and beta-blockers[2-4], and can lead to a significant loss of blood pressure control in some patients (e.g., high renin-producing hypertensive patients who use an ACE inhibitor)[5]. Evidence from the Framingham Heart Study, as well as from large clinical trials such as the Systolic Hypertension in the Elderly Program (SHEP), suggests that even small increases in blood pressure are associated with significantly increased frequency of occurrence of cardiovascular events. The potential incremental risk of cardiovascular events associated with increases in blood pressure in patients with RA is of even greater concern since these patients already have a significantly higher baseline risk of fatal and nonfatal

From Medical Research International, Waltham, Massachusetts, USA.

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G. Singh, MD, Senior Research Scholar, Director ARAMIS-PMS Program, Division of Immunology and Rheumatology, Department of Medicine, Stanford University School of Medicine; J.D. Miller, MS, Senior Health Economist, Medical Research International; D.M. Huse, MA, Senior Research Scientist, Innovus Research, Inc.; D. Pettitt, DVM, MSc, Director, Outcomes Research, Pfizer, Inc.; R.B. D'Agostino, PhD, Professor of Mathematics and Statistics, Department of Mathematics, Boston University; M.W. Russell, MAPE, Executive Director, Medical Research International.

Address reprint requests to M.W. Russell, Medical Research International, 1601 Trapelo Road, Waltham, MA 02451-7341, USA.
E-mail: mrussell@cnsmail.com

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serious thrombotic cardiovascular events[6]. The prevalence of use of antiinflammatory agents with potentially adverse effects on blood pressure in the 11.8 million people cited above is not readily ascertainable from the available data. Nevertheless, clinical experience suggests that the proportion of patients taking such medications is not trivial and thus the potential excess cardiovascular burden associated with their use may be substantial.

Many clinicians do not appreciate the extent to which drug-drug interaction can lead to loss of blood pressure control in patients treated concomitantly for hypertension. This may be particularly true among rheumatologists, who typically focus more on controlling pain and joint inflammation, which have immediate implications for patient functioning and quality of life, than on potential drug-drug interaction. While antiinflammatory medications obviously yield important benefits to the patient, appropriate selection of these agents (e.g., those with a less adverse effect on blood pressure), along with routine blood pressure monitoring, can mitigate at least some of the corresponding risks.

We investigated the potential excess burden of ischemic heart disease and stroke occurrence in the OA/RA population associated with increases in systolic blood pressure (SBP). Specifically, we estimated the effect on cardiovascular disease risk and associated treatment costs of a range of potential increases in SBP that might be experienced by the adult population with OA/RA in the US. We based our analyses on patient-level data from national survey data (the NHANES III), published cardiovascular risk prediction models developed from the Framingham Heart Study database, and published estimates of the costs of cardiovascular disease treatment in the US.

MATERIALS AND METHODS

Occurrences of cardiovascular disease attributable to increases in SBP. The current risk profile of men and women in the US with arthritis aged ≥ 35 years by age category (35–44, 45–64, and 65+ years) and hypertension treatment status (i.e., treated hypertensives and untreated hypertensives/normotensives, respectively) was estimated using national survey data from the NHANES III[1]. NHANES is designed to collect information about the health and diet of people in the US, including patients with arthritis. Relevant data on each individual's cardiovascular disease history and risk factors (including use of antihypertensive medications), demographics (i.e., age and sex), and history of OA and RA were obtained from the survey database. Sampling weights required to generate population estimates from sample means also were obtained from the database.

Some risk factor data required in the analysis (see below) as well as information on cardiovascular mortality could not be obtained from the NHANES III database. Specifically, history of left ventricular hypertrophy was estimated using age and sex-specific prevalence data from the Framingham Heart Study, an ongoing epidemiologic study of risk factors for and consequences of cardiovascular disease[7]. History of atrial fibrillation was estimated from prevalence data collected by the Mayo Clinic as part of the Rochester Cardiovascular Disease Survey[8] for people aged 35–39 years, and from Framingham data for people aged ≥ 40 years[9]. Mortality due to ischemic heart disease and stroke was estimated from unpublished Framingham data on the proportions of ischemic heart disease and stroke events that are fatal (written communication, R. D'Agostino).

Probabilities of occurrence over one year of ischemic heart disease and stroke were estimated for each NHANES III participant described above using the demographic and risk factor data described above in conjunction with published Framingham cardiovascular risk prediction models. The ischemic heart disease risk equations used in the analysis are sex-specific Weibull nonproportional hazards specification as described[10]. Risk factors incorporated in each equation include age (in years), the log-ratio of total and HDL cholesterol, SBP, current cigarette smoking status, history of diabetes mellitus, and electrocardiographic evidence of left ventricular hypertrophy. The stroke risk equations are sex-specific Cox proportional hazards models, as described[11,12]. These models include the risk factors described above (with the exception of the lipid measure), as well as history of cardiovascular disease, history of atrial fibrillation, and use of antihypertensive medication among patients with SBP between 110 and 200 mm Hg.

Patient-level estimates of the probability of event occurrence were weighted (using the NHANES III sampling weight assigned to the patient) and then summed across patients to generate national estimates for all people with arthritis in each age/sex/hypertension treatment status category defined above.

Costs of cardiovascular disease treatment. Costs of treating ischemic heart disease and stroke events were derived from an economic model of hypertension treatment and control[13]. Costs reported in that analysis were estimated from public use databases of healthcare resource utilization and cost, as well as published literature. We adjusted these cost estimates to reflect year 2000 US dollars using the Medical Care component of the US Consumer Price Index for All Urban Consumers (CPI-U)[14]. Costs of treating nonfatal coronary heart disease events were estimated at $17,173; corresponding costs of treating fatal coronary heart disease events, nonfatal stroke events, and fatal stroke events, respectively, were $12,328, $16,865, and $11,112.

Distributional effects of a population-average increase in SBP. The results generated by the methods described above reflect the expected incremental clinical and direct medical cost burdens of a given increase in SBP experienced by all people in the at-risk population (i.e., all OA/RA patients). In reality, patients who concomitantly use antihypertensive and antiinflammatory medications are likely to exhibit variable response in SBP. In the extreme, it is even possible that the entire mean effect is concentrated in a small portion of the population (e.g., those with the highest or lowest systolic pressures). while the remainder experience no adverse effect. To illustrate how the distribution of a given mean effect on SBP can affect estimated event occurrence and costs, we conducted a Monte Carlo simulation in which 15% of patients in the weighted NHANES III subsample of adults with OA/RA were assigned a 20 mm Hg increase in SBP and the remaining 85% were assumed to have no change in SBP (which yields a mean population effect on SBP of 3 mm Hg). A total of 100,000 random samples were drawn with replacement to generate sampling distributions for events and costs. From these sampling distributions, mean values and 95% confidence intervals (CI) were estimated.

RESULTS

Prevalence of treated hypertension among adults with arthritis in the US. Of the estimated 24.3 million and 5.7 million US adults aged ≥ 35 years with diagnoses of OA and RA, respectively, roughly 11.8 million (39%) also receive pharmacologic treatment for hypertension. Treatment for hypertension is more prevalent in the OA population than in the RA population (41% vs 34%).

Cardiovascular events attributable to increases in SBP. Based on the age/sex distribution of adults with arthritis in the NHANES III population and the prevalence of other cardiovascular risk factors in that subpopulation, roughly

7100 additional ischemic heart disease and stroke events would be expected to occur, on average, in the OA/RA population over one year as a consequence of a 1 mm Hg increase in SBP (Table 1). By comparison, a mean increase in SBP of 5 mm Hg is associated with roughly 35,700 additional ischemic heart disease and stroke events.

Costs of cardiovascular disease treatment. The direct economic burden associated with treating the ischemic heart

Table 1. Estimated occurrences of ischemic heart disease and stroke events over one year before and after selected increases in SBP among US adults with OA and RA, by hypertension treatment status, sex, and age category.

		Ischemic Heart Disease and Stroke Events							
		Events Attributable to SBP Increase (mm Hg), n							
Sex/Age Group	n	Status Quo	1	3	5	7	10	15	20
OA patients									
Treated hypertensive									
Men									
35–44 yrs	161,212	771	15	51	86	117	170	263	357
45–64 yrs	1,150,531	24,209	367	1,095	1,813	2,537	3,639	5,464	7,298
65+ yrs	1,820,708	83,268	1,028	3,091	5,107	7,150	10,181	15,096	19,910
Total	3,132,451	108,248	1,410	4,237	7,006	9.804	13,990	20,823	27,565
Women									
35–44 yrs	318,084	902	20	64	109	143	208	319	433
45–84 yrs	2,564,315	28,174	446	1,363	2,278	3,206	4,590	6,896	9,219
65+ yrs	3,846,755	83,215	1,181	3,484	5,742	7,991	11,277	16,517	21,447
Total	6,729,154	112,291	1,647	4,911	8,129	11,340	16,075	23,732	31,099
Subtotal	9,861,605	220,539	3,057	9,148	15,135	21,144	30,065	44,555	58,664
Untreated hypertensive/normotensive									
Men									
35–44 yrs	1,237,022	5,406	109	320	528	747	1,083	1,680	2,283
45–64 yrs	2,476,724	36,409	593	1,780	2,996	4,223	6,088	9,292	12,614
65+ yrs	2,169,483	75,464	970	3,009	5,055	7,118	10,263	15,641	21,199
Total	5,883,229	117,279	1,672	5,109	8,579	12,088	17,434	26,613	36,096
Women									
35–44 yrs	1,521,957	1,110	40	87	146	214	308	469	642
45–64 yrs	3,421,913	19,991	365	1,083	1,829	2,583	3,723	5,717	7,787
65+ yrs	3,656,666	44,506	709	2,143	3,607	5,123	7,429	11,436	15,675
Total	8,600,536	65,607	1,114	3,313	5,582	7,920	11,460	17,622	24,104
Subtotal	14,483,765	182,886	2,786	8,422	14,161	20,008	28,894	44,235	60,200
Total OA patients	24,345,370	403,425	5,843	17,570	29,296	41,152	58,959	88,790	118,864
RA patients									
Treated, hypertensive									
Men									
35–44 yrs	10,459	125	2	8	12	16	24	36	47
45–64 yrs	268,135	7,501	104	308	506	716	1,011	1,520	2,004
65+ yrs	160,729	8,635	103	300	504	707	1,002	1,490	1,957
Total	439,323	16,261	209	616	1,022	1,439	2,037	3,046	4,008
Women									
35–44 yrs	27,146	41	1	1	4	6	7	14	22
45–64 yrs	736,062	7,919	143	406	679	943	1,358	2,032	2,727
65+ yrs	762,185	15,855	249	726	1,216	1,698	2,408	3,555	4,646
Total	1,525,373	23,815	393	1,133	1,899	2,647	3,773	5,601	7,395
Subtotal	1,964,898	40,076	602	1,749	2,921	4,086	5,810	8,647	11,403
Untreated hypertensive/normotensive									
Men									
35–44 yrs	298,706	1,151	26	71	121	174	250	388	530
45–64 yrs	487,945	7,240	104	334	547	778	1,118	1,709	2,312
65+ yrs	523,377	19,106	253	775	1,292	1,805	2,601	3,956	5,355
Total	1,310,028	27,497	383	1,180	1,960	2,757	3,967	6,053	8,197
Women									
35–44 yrs	719,586	546	10	42	74	107	157	243	335
45–64 yrs	996,711	7,462	118	372	620	883	1,273	1,947	2,643
65+ yrs	724,066	9,723	161	477	797	1,133	1,633	2,513	3,429
Total	2,440,363	17,731	289	891	1,491	2,123	3,063	4,703	6,407
Subtotal	3,750,391	45,228	672	2,071	3,451	4,880	7,030	10,756	14,604
Total RA patients	5,715,087	85,304	1,274	3,820	6,372	8,966	12,840	19,403	26,007
Grand total	30,060,457	488,729	7,117	21,390	35,668	50,118	71,799	108,193	144,871

SBP: systolic blood pressure; OA: osteoarthritis; RA: rheumatoid arthritis.

disease and stroke events that would be expected to occur over one year in the OA population (with no change in cardiovascular risk factors) is estimated to range from $114 million (year 2000 dollars) for a 1 mm Hg increase in SBP to $569 million for a 5 mm Hg increase (Table 2).

Distributional effects of a population-average increase in SBP. A 3 mm Hg mean increase in SBP achieved by 15% of patients experiencing a 20 mm Hg increase and the remainder experiencing no increase would result in 17,797 additional ischemic heart disease and stroke events (95% CI

Table 2. Associated costs (year 2000 US dollars, in thousands) of treating ischemic heart disease and stroke events over one year attributable to selected increases in SBP among US adults with OA and RA, by hypertension treatment status, sex, and age category.

Sex/Age Group	n	Cost (Thousands, $USD) of Events Attributable to SBP Increase (mm Hg) 1	3	5	7	10	15	20
OA patients								
Treated hypertensive								
Men								
35–44 yrs	161,212	245	838	1,409	1,933	2,791	4,336	5,894
45–64 yrs	1,150,531	5,956	17,838	29,561	41,370	59,294	89,084	118,998
65+ yrs	1,820,708	16,153	48,485	80,142	112,145	159,835	237,163	312,814
Total	3,132,451	22,355	67,161	111,112	155,448	221,920	330,584	437,706
Women								
35–44 yrs	318,084	337	1,068	1,832	2,399	3,473	5,338	7,257
45–64 yrs	2,564,315	7,488	22,771	37,980	53,477	76,520	114,960	153,751
65+ yrs	3,846,755	18,379	54,026	88,983	123,911	175,000	256,410	333,190
Total	6,729,154	26,204	77,865	128,795	179,787	254,992	376,708	494,198
Subtotal	9,861,605	48,559	145,026	239,906	335,235	476,912	707,292	931,903
Untreated hypertensive/normotensive								
Men								
35–44 yrs	1,237,022	1,814	5,326	8,808	12,403	18,001	27,972	38,000
45–64 yrs	2,476,724	9,787	29,177	49,101	69,159	99,652	152,133	206,509
65+ yrs	2,169,483	15,329	47,468	79,649	112,132	161,602	246,128	333,626
Total	5,883,229	26,930	81,971	137,558	193,694	279,258	426,233	578,135
Women								
35–44 yrs	1,521,957	651	1,446	2,446	3,582	5,176	7,887	10,803
45–64 yrs	3,421,913	6,122	18,165	30,729	43,337	62,437	95,869	130,609
65+ yrs	3,656,666	11,066	33,434	56,294	79,876	115,766	178,199	244,380
Total	8,600,536	17,839	53,044	89,469	126,796	183,379	251,955	385,793
Subtotal	14,483,765	44,769	135,015	227,027	320,490	462,634	708,188	963,928
Total OA patients	24,345,370	93,328	280,041	466,934	655,725	939,546	1,415,480	1,895,832
RA Patients								
Treated hypertnesive								
Men								
35–44 yrs	10,459	34	137	205	274	405	599	783
45–64 yrs	266,135	1,687	5,027	8,271	11,695	16,520	24,858	32,763
65+ yrs	160,729	1,602	4,664	7,856	11,001	15,590	23,185	30,451
Total	439,323	3,323	9,828	16,332	22,970	32,515	48,641	63,997
Women								
35–44 yrs	27,146	17	17	68	103	120	239	375
45–64 yrs	736,062	2,379	6,733	11,308	15,683	22,603	33,828	45,420
65+ yrs	762,165	3,882	11,362	19,028	26,605	37,709	55,679	72,812
Total	1,525,373	6,278	18,112	30,403	42,390	60,432	89,746	118,607
Subtotal	1,964,696	9,601	27,940	46,734	65,361	92,947	138,388	182,604
Untreated hypertensive/normotensive								
Men								
35–44 yrs	298,706	429	1,196	2,026	2,891	4,167	6,475	8,825
45–64 yrs	487,945	1,672	5,438	8,921	12,653	18,189	27,893	37,731
65+ yrs	523,377	3,979	12,178	20,288	28,413	40,902	62,159	84,197
Total	1,310,028	6,080	18,809	31,233	43,957	63,258	96,527	130,753
Women								
35–44 yrs	719,586	171	719	1,253	1,807	2,653	4,098	5,647
45–64 yrs	996,711	1,981	6,233	10,398	14,835	21,364	32,669	44,327
65+ yrs	724,066	2,481	7,387	12,353	17,586	25,354	39,015	53,266
Total	2,440,363	4,633	14,339	24,003	34,227	49,371	75,782	103,240
Subtotal	3,750,391	10,713	33,149	55,236	78,184	112,629	172,309	233,993
Total RA patients	5,715,087	20,314	61,089	101,970	143,544	205,576	310,697	416,597
Grand total	30,060,457	113,642	341,130	568,904	799,269	1,145,122	1,726,177	2,312,428

SBP: systolic blood pressure; OA: osteoarthritis; RA; rheumatoid arthritis

16,115, 19,478) in the OA population, and 3874 additional such events (95% CI 3005, 4743) in the RA population (Table 3). Corresponding costs range from $284 million (95% CI $257, $311 million) in the OA population, and $62 million (95% CI $48, $76 million) in the RA population (Table 3). A result at the upper (lower) limit of the CI would occur if the patients experiencing the increase in SBP had much higher (lower) than average SBP at baseline.

DISCUSSION

We used patient-level data from the NHANES III, well accepted cardiovascular risk prediction models derived from Framingham Heart Study data, and current estimates of the costs of cardiovascular disease treatment to estimate the potential effect of a range of increases in SBP on occurrence of cardiovascular events and associated treatment costs among adults with OA/RA. Our findings suggest that the clinical and economic consequences of what may appear to be modest increases in blood pressure are considerable. Indeed, we believe our findings are conservative in light of evidence from several large clinical trials. In the ALLHat trial, increases in SBP of as little as 3 mm Hg were associated with a 10–20% increased frequency of occurrence of congestive heart failure[15], while findings from the Hypertension Detection and Follow-Up Program suggest that a 3 mm Hg increase in SBP is associated with increases in the risk of stroke and angina, respectively, of 15–20% and 12%[16]. In the SHEP[17], a large-scale trial designed to test whether antihypertensive drug therapy reduces the frequency of new strokes in a multiethnic cohort of 4736 men and women aged 60 years or older with isolated systolic hypertension, reductions in SBP of about 20 mm Hg were associated with reductions in the occurrence of cardiovascular events of roughly 34%; by comparison, our findings suggest that 3 and 20 mm Hg increases in SBP would be associated with 4% and 30% increased occurrence in ischemic heart disease and stroke events, respectively.

Some limitations of our study bear mention. For example, we assessed the potential cardiovascular consequences of increased SBP through the use of risk equations derived from the general population of the Framingham Heart Study. While Framingham models have been shown to predict risk well in other populations, actual experience in an OA/RA population may differ. Also, we used patient-reported data from a national survey to ascertain whether or not a participant had arthritis or hypertension. The possibility of faulty recall or other ascertainment bias among NHANES III participants cannot be ruled out. However, the use of NHANES patient data to ascertain prevalence of chronic disease has been commonplace since the 1970s. Finally, we considered only ischemic heart disease and stroke events in our analysis. There is a considerable body of evidence suggesting an association between increased blood pressure and increased clinical burden of other cardiovascular events, most notably congestive heart failure[15].

The use of certain classes of drugs with antiinflammatory properties, namely corticosteroids and NSAID, in patients treated with antihypertensive medication can lead to a significant loss of antihypertensive control. Results from our study should reinforce that relatively small changes in SBP associated with use of common arthritis medications can have a significant effect on the cardiovascular risk profile. The value and importance of routine blood pressure monitoring in patients with arthritis who are receiving

Table 3. Monte Carlo simulation of a 20 mm Hg increase in SBP in 15% of the OA/RA population over one year: effect on ischemic heart disease and stroke events and event costs.

	Events Attributable to SBP Increase (95% CI)	Cost (Thousands, USD) (95% CI)
OA Patients		
Treated hypertensive		
Ischemic heart disease	5,824 (4,725, 6,923)	93,978 (76,250, 111,706)
Stroke	2,964 (2,381, 3,548)	45,624 (36,645, 54,604)
Untreated hypertensive/normotensive		
Ischemic heart disease	6,444 (5,309, 7,579)	104,654 (86,218, 123,090)
Stroke	2,565 (2,140, 2,989)	39,589 (33,033, 46,144)
Totals	17,797 (16,115, 19,478)	283,847(257,034, 310,660)
RA Patients		
Treated hypertensive		
Ischemic heart disease	1,107 (582, 1,633)	18,042 (9,481, 26,603)
Stroke	593 (324, 862)	9,186 (5,020, 13,351)
Untreated hypertensive/normotensive		
Ischemic heart disease	1,572 (1,024, 2,120)	25,547 (16,637, 34,457)
Stroke	602 (390, 814)	9,280 (6,006, 12,553)
Totals	3,874 (3,005, 4,743)	62,056 (48,130, 75,982)

OA: osteoarthritis; RA: rheumatoid arthritis; SBP: systolic blood pressure; USD: US dollars.

medications known to increase blood pressure are thereby underscored.

It is also important that clinicians accurately weigh the potential risks of these medications against their benefits. For example, in cases where 2 medications yield similar clinical benefits but can have different effects on SBP, consideration of incremental cardiovascular risk may be particularly relevant.

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