Brief Report

Effects of Warfarin on Blood Pressure in Men With Diabetes and Hypertension—A Longitudinal Study

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Warfarin causes extensive vascular calcification leading to increased systolic blood pressure and pulse pressure in rats, may be associated with increased valvular and coronary calcifications in man, and possibly worsens hypertension in high-risk patients, particularly in those with diabetes mellitus or uncontrolled hypertension. The authors evaluated blood pressure and intensity of antihypertensive therapy over 36 months in a cohort of 58 patients with diabetes and hypertension on warfarin and 58 control subjects with diabetes and hypertension not on warfarin. The results demonstrate that warfarin therapy at conventional doses does not increase systolic blood pressure or pulse pressure in patients with diabetes and hypertension. (J Clin Hypertens. 2007;9:256–258) ©2007 Le Jacq

Isolated systolic hypertension is prevalent in 55% to 80% of Americans older than 60 years and is associated with substantial cardiovascular morbidity and mortality.[1] The pathogenesis of isolated systolic hypertension is closely linked to arterial stiffness,[1] which is associated with calcification of the arterial media.[2] One of the most potent inhibitors of vascular calcification in vivo is matrix Gla protein (MGP).[3] Vascular calcification and systolic hypertension occur in rats given high doses of warfarin—a process presumed to be related to warfarin's inhibition of vitamin K regeneration and thus low levels of active MGP.[3,4]

In humans, long-term warfarin therapy is associated with increased valvular and coronary calcification seen on computed tomography[5] and increased calcium deposition on histopathologic examination of aortic valves.[6] It is therefore possible that warfarin-induced arterial calcification may lead to systolic hypertension in humans as well. We recently performed a post hoc analysis of a randomized clinical trial of warfarin in atrial fibrillation and demonstrated that there was no effect on blood pressure (BP) or pulse pressure (PP) after 24 months of warfarin therapy in all trial participants.[7] A subgroup analysis suggested, however, that patients with underlying hypertension or diabetes mellitus (DM) receiving warfarin might have increased systolic BP and PP compared with controls.[7] In the present study, we tested these subgroups separately and hypothesized that long-term warfarin therapy leads to increased systolic BP and PP in older men with DM and hypertension.

METHODS

We performed an historical cohort study of male patients with a diagnosis of DM and hypertension who were on warfarin therapy for 3 years or longer. Patients on dialysis or receiving anticoagulation for

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a prosthetic valve were excluded. Fifty-eight warfarin patients were matched by age (identical year) to 58 control patients with DM and HTN but who were not receiving warfarin. The indications for warfarin therapy were atrial fibrillation (75%), deep venous thrombosis and pulmonary embolism (8%), and cardiomyopathy with poor ejection fraction (3%).

The primary end point was the change in BP at follow-up; a secondary end point was the change in antihypertensive medications at follow-up based on the World Health Organization's (WHO) "defined daily doses" (DDD) guidelines (available at: http://www.whocc.no/atcddd).

RESULTS

Results are summarized in the Table. The subjects were 74±8 years of age in both groups and were followed for 24 to 36 months. Baseline characteristics were comparable for both groups, with the exception of a higher prevalence of heart failure, coronary disease, and cerebrovascular disease in the warfarin group. Warfarin doses were not obtained; international normalized ratios (INRs) ranged between 2 and 3. As shown in the Table, results indicate that BP parameters were actually lower in the warfarin group at baseline, presumably due to the higher doses of antihypertensive therapy (higher DDD). These lower levels remained throughout the follow-up period of 36 months. No BP difference was observed between the 2 groups (change in systolic BP –8.2±23 mm Hg in the warfarin group vs –3.6±21 mm Hg in controls [*P*=.29]; change in diastolic BP –5.5±12 mm Hg in the warfarin group vs –1.4±13 mm Hg controls [*P*=.09]; change in PP –2.6±18 mm Hg in the warfarin group vs –2.2±17 mm Hg in controls [*P*=.9]; change in DDD 1.1±2 in the warfarin group vs 1±1.6 in controls, [*P*=.79]). When changes in systolic BP or PP at follow-up were analyzed in a multiple regression model adjusting for the variables that differed at baseline, the only variable that predicted the change was baseline systolic BP (data not shown). In other words, warfarin therapy did not result in progressive changes in BP or in the need for more aggressive BP-lowering therapy during the 3-year follow-up.

DISCUSSION

Our results indicate that warfarin does not have any significant effect on BP in this group of older men with DM and hypertension. There are several possible explanations for the disparity between our hypothesis and the study results. First, MGP might not be as important in human vascular calcification

Table. Blood Pressure Levels and Intensity of Antihypertensive Therapy (DDD) During Follow-Up

	No. of Patients		SBP, mm Hg		DBP, mm Hg		PP, mm Hg		DDD, Total Per Day	
	Warfarin	Control	Warfarin	Control	Warfarin	Control	Warfarin	Control	Warfarin	Control
Baseline	58	58	136±17	145±19*	77±10	77±11	59±13	67±16	3.2±2.5	1.8±1.6†
12 months	56	57	136±14	141±15*	75±10	77±10	61±13	64±12	4.2±2.7	2.4±2.1†
24 months	54	57	131±15	139±16†	74±10	76±10	57±14	63±16	4±2.4	2.6±2.1†
36 months	48	57	128±14	141±15†	71±9	76±9	56±12	65±13	4.3±2.7	2.8±2.1†

Data are presented as mean ± SD. *P<.05 vs warfarin. †P<.01 vs warfarin. DDD indicates defined daily doses of antihypertensive agents according to the World Health Organization Collaborating Centre for Drug Statistics Methodology; SBP, systolic blood pressure; DBP, diastolic blood pressure; and PP, pulse pressure.

as it is in rats. Second, rats studied in the warfarin model of systolic hypertension received 15 mg of warfarin per 100 g of body weight (10.5 g/d in a 70-kg man), a significantly higher dose than what our patients received. Lastly, the 4 weeks of warfarin therapy required to produce calcification in rats with a normal life expectancy of 2 to 3.5 years could represent a significantly longer time than our follow-up period of 36 months. More significant BP changes might have been detected with longer follow-up.

There are limitations to this study. Because this was a retrospective study, BP measurements were not performed under standardized conditions. This could have led to both type I and type II errors. Confounding factors such as data on serum calcium and phosphorus levels and supplementation with vitamin D and calcium were not readily available in all patients and were thus not considered. These factors are known to mediate calcification. Our population was limited predominantly to Caucasian older men; thus, these results might not be applicable to the general population. Finally, we did not measure arterial calcification or arterial stiffness, only its surrogate, PP. These pathophysiologic changes could have occurred, but may not have resulted in measurable BP changes.

In summary, we failed to confirm previous observations[7] that warfarin leads to worsened systolic hypertension and increased PP in patients with DM and hypertension. In this cohort study, warfarin therapy in conventional doses for 3 years did not result in increased BP or a greater need for antihypertensive therapy.

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