Ginseng is an herb that populations have valued as a tonic since 25 A.D.\textsuperscript{1} It is also shown through randomized, controlled trials (RCTs) to improve glycemic control\textsuperscript{2} and cognitive function.\textsuperscript{3} In contrast, however, there is repeated mention in the medical literature that ginseng can elevate blood pressure (BP).\textsuperscript{4–6} This stems from an early observational study by Siegel\textsuperscript{7} that connected the self-reported use of ginseng in 20% of adults to the development of hypertension in 14 individuals after 3 months of use. This possibility could have widespread impact, because ginseng is used by 10% to 20% of adults in Asia\textsuperscript{8–10} and by up to 5% in the United States,\textsuperscript{11} Australia,\textsuperscript{12} and parts of Europe.\textsuperscript{13} Furthermore, given that 20% to 40% of adults in these regions are estimated to have hypertension,\textsuperscript{14} there is potential for overlap between the prevalence of ginseng use and hypertension. Still, there remains no long-term RCT investigation of the effect of ginseng on BP, and until such evaluations are undertaken, physicians will remain greatly limited in the advice they can provide to hypertensive individuals regarding ginseng use.

Although many species of ginseng exist, \textit{Panax quinquefolius}, or North American ginseng (NAG), and \textit{Panax ginseng} together account for the majority of ginseng consumed worldwide. Recently, we demonstrated that single 3-g doses of NAG\textsuperscript{15} and \textit{P.ginseng}\textsuperscript{16} exert neutral and lowering effects on BP, respectively, for 160 minutes after intake. In the former study,\textsuperscript{15} the neutral effect on BP was comprehensively shown with 6 batches of NAG in hypertensive individuals. To add to this finding now, the long-term effect of NAG on BP would be of even greater significance, because long-term BP outcomes are associated with cardiovascular disease events.\textsuperscript{17,18} Also, because long-term BP outcomes might not necessarily be inferable from acute outcomes,\textsuperscript{19} we proceeded to address the effect of NAG on BP after 12 weeks of intake (defined as long-term relative to our acute studies). We measured 24-hour ambulatory BP (ABP), because it is a better determinant of cardiovascular disease risk than office BP, and it allows for an assessment of circadian BP changes.\textsuperscript{20,21} As well, for safety reasons, serum cystatin C was measured as a marker of glomerular filtration rate and an indicator of the effect of NAG on renal function.\textsuperscript{22}

We determined here, through a single-center, randomized, controlled, double-blinded, crossover trial, the effect of 12-
week NAG intake on 24-hour ABP and renal function in hypertensive individuals. We used a single batch of NAG, which was representative of NAG on the world market and which was shown previously to exert a neutral effect on BP for 160 minutes after intake. Thus, this study provided, for the first time, insight into how long-term ginseng intake could affect both BP and renal function in humans.

**Methods**

**Participants**

The research ethics board at St Michael’s Hospital approved the study, and the procedures used were in accordance with institutional guidelines. Individuals were recruited through newspaper advertisements in Toronto and provided written informed consent to participate. Inclusion was an age of 18 to 85 years and defined by the use of antihypertensive drugs or a seated office systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg at each of 3 prestudy visits. Exclusion was secondary hypertension, white-coat hypertension, diabetes, kidney/liver disease, unstable angina, ginseng use for 2 months before or during the study, or any changes in the type/dose of antihypertensive drugs 1 month before or during the study.

Overall, 37 (30 men and 7 women) hypertensive individuals were included in the main analysis. Their ethnicities included European-white (n=26), East-Asian (n=5), South-Asian (n=4), African-Caribbean (n=2), and Native-Canadian (n=1) individuals. At run-in they had a mean ±SEM age of 58.4±1.6 years, body mass index of 28.6±0.9 kg/m², serum creatinin C of 0.97±0.03 mg/dL, office systolic/diastolic BP of 130.2±24/85.8±1.6 mm Hg, and 24-hour systolic/diastolic BP of 131.6±19.8/11.1±1.5 mm Hg. Of the 37 individuals, 32 were taking antihypertensive agents (monotherapy, n=20; ≥2 agents, n=12), including angiotensin-converting enzyme inhibitors (n=16), angiotensin receptor blockers (n=5), β-blockers (n=7), calcium channel blockers (n=12), diuretics (n=8), and α-blockers (n=1). The run-in characteristics of the 37 individuals included in the main analysis did not significantly differ from those who withdrew or were removed from main analysis (n=15; data not shown).

**Treatments and Protocol**

In this single-center, randomized, placebo-controlled, double-blinded trial conducted between April 2001 and October 2003 (recruitment: April 2001 to May 2002; follow-up: May 2002 to October 2003), we sought to determine the effect of 12-week NAG intake on 24-hour BP. To do so, we used an AB/BA 2-treatment, 2-period crossover design with the treatment sequences being NAG-then-placebo and placebo-then-NAG.

We tested a 3-g dose of cornstarch placebo and a single batch of 3-year-old dried NAG root from an Ontario farm. Its acute BP effects were fitted with an ABP monitor (ABPM) that was activated to 12 hours prior) and off their antihypertensives (8 hours prior). Participants refrained from taking NAG or placebo capsules for the period that the ABPM was worn (≥24 hours). Participants were instructed to retire between 10:00 PM and 12:00 AM to awaken between 6:00 AM and 8:00 AM. They also prepared a 24-hour diary detailing activity, sleep, and drug schedules.

**Primary and Secondary Outcomes**

The primary outcome was mean 24-hour ambulatory systolic BP at week 12. Secondary outcomes included mean 24-hour diastolic BP and pulse pressure (PP), as well as mean daytime and night systolic BP, diastolic PP, and ABP at week 12, with daytime defined as 8:00 AM to 8:00 PM and nighttime as 12:00 AM to 6:00 AM. Additional secondary outcomes were serum creatin C (marker of kidney function) and body weight at week 12. To avoid multiplicity, no subgroup analyses or adjusted analyses were performed.

**BP Measurement**

Office BP (at recruitment and run-in) was measured as described previously. Briefly, 3 readings were obtained from the right arm of seated participants while their arm was supported at heart level; 1 trained observer took all of the measures and used a mercury sphygmomanometer (Baumanometer, W.A. Baum). For ABP measurements, participants were fitted with a SpaceLabs 90207 ABPM (SpaceLabs), with the cuff secured on the nondominant arm for the entire 24-hour period (worn on the same arm for all of the visits). ABPM measurements occurred every 15 minutes from 7:00 AM to 9:00 PM inclusive and every 20 minutes from 10:00 PM to 6:00 AM inclusive, with a maximum of 87 successful readings for the 24-hour period. Measurements were automatically repeated if an error occurred. The adult and large adults cuffs were used for arm circumferences of 24 to 31 cm and 32 to 42 cm, respectively.

**Cystatin C**

All of the assays were performed in serum obtained from fasted participants. Specimens were stored at −70°C. Cystatin C was measured by a particle-enhanced immunonephelometric assay (N Latex Cystatin C, Dade Behring) with a nephelometer (BNII, Dade Behring).

**Statistical Analyses**

Based on previous findings, we speculated that the maximum difference in mean 24-hour systolic BP at week 12 between NAG and placebo would be 4.4 mm Hg. Accordingly, with an estimated SD of the between-treatment difference being 7.1 mm Hg and assuming a correlation coefficient of 0.80 between-treatment values at week 12, at a significance level (α) of 0.05 we calculated that 36
individuals were required to achieve the noted difference in mean 24-hour systolic BP compared with placebo with 80% power. Based on previous withdrawal rates of ~10% during study periods of 12 weeks,²⁸ we calculated that the enrollment of 52 participants would yield 36 participants to a 36-week study period.

We conducted a main analysis, a secondary analysis, and an intention-to-treat analysis. The main analysis included participants who: (1) finished both treatment periods, (2) completed 24-hours of ABPM monitoring for all of the visits, and (3) adhered to the study protocol and exclusion criteria (ie, no medication changes). Data from these participants underwent crossover analysis.²³ According to the assumptions of this analysis, each parameter was first tested for a period and carryover effect. Then, for the 24-hour, 8:00 AM to 8:00 PM, and 12:00 AM to 6:00 AM periods, the independent and interactive effects of treatment (NAG versus placebo) and week (0 versus 12) on ABP during the first treatment period. Significant treatment effects were explored at weeks 0 and 12 with repeated-measures GLM-ANOVA. We assessed body weight and compliance by pill count (NAG: 91.7 ± 1.9%; placebo: 93.6 ± 1.9%; P = 0.50). Evaluation of blinding re-

### Results

**Subjects**

Of the screened individuals (n = 67), 52 proceeded through run-in and randomization. Among them, 12 (23%) withdrew: 8 from the NAG-then-placebo sequence (n = 3, period 1; n = 1, washout; n = 4, period 2) and 4 from the placebo-then-NAG sequence (n = 2, period 1; n = 2, washout). Accordingly, 3 withdrew while taking NAG (n = 1, diarrhea; n = 1, headache; n = 1, antihypertensive drug change), 6 while taking placebo (n = 6, work schedule), and 4 during washout (n = 3, work schedule; n = 1, antihypertensive drug change). Also, 3 from the placebo-then-NAG sequence were not included in main analysis because of antihypertensive drug changes (n = 2) and unsuccessful ABPM (n = 1). Overall, 37 participants (71%) proceeded to main analysis.

**Compliance and Blinding**

Compliance was estimated by pill count (NAG: 91.7 ± 2.3%; placebo: 93.6 ± 1.9%; P = 0.50). Evaluation of blinding re-

### Mean 24-Hour, Daytime, and Night Ambulatory Systolic BP, Diastolic BP, and PP Before (Week 0) and After (Week 12) NAG and Placebo Intake in 37 Hypertensive Participants

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment</th>
<th>Week 0 (n=37), mm Hg</th>
<th>P Value*</th>
<th>Week 12 (n=37), mm Hg</th>
<th>P Value*</th>
<th>Difference at Week 12 (NAG–Placebo 95% CI), mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-Hour systolic BP</td>
<td>NAG</td>
<td>129.6 ± 1.8</td>
<td>0.56</td>
<td>130.9 ± 2.0</td>
<td>0.99</td>
<td>(−2.4 to 2.4)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>130.4 ± 1.9</td>
<td></td>
<td>130.9 ± 1.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime systolic BP†</td>
<td>NAG</td>
<td>135.1 ± 2.0</td>
<td>0.83</td>
<td>136.6 ± 2.1</td>
<td>0.64</td>
<td>(−2.0 to 3.3)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>135.9 ± 2.0</td>
<td></td>
<td>136.0 ± 2.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Night systolic BP‡</td>
<td>NAG</td>
<td>118.3 ± 1.7</td>
<td>0.25</td>
<td>120.8 ± 1.9</td>
<td>0.59</td>
<td>(−3.9 to 2.2)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>120.1 ± 2.1</td>
<td></td>
<td>121.6 ± 1.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-Hour diastolic BP</td>
<td>NAG</td>
<td>79.7 ± 1.3</td>
<td>0.91</td>
<td>80.6 ± 1.5</td>
<td>0.99</td>
<td>(−1.6 to 1.7)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>79.9 ± 1.3</td>
<td></td>
<td>80.5 ± 1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime diastolic BP†</td>
<td>NAG</td>
<td>84.6 ± 1.5</td>
<td>0.93</td>
<td>84.9 ± 1.5</td>
<td>0.79</td>
<td>(−1.6 to 2.0)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>84.6 ± 1.5</td>
<td></td>
<td>84.7 ± 1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Night diastolic BP‡</td>
<td>NAG</td>
<td>71.4 ± 1.3</td>
<td>0.63</td>
<td>73.4 ± 1.6</td>
<td>0.94</td>
<td>(−2.3 to 2.2)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>72.4 ± 1.4</td>
<td></td>
<td>73.4 ± 1.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-Hour PP</td>
<td>NAG</td>
<td>49.8 ± 1.6</td>
<td>0.27</td>
<td>50.3 ± 1.6</td>
<td>0.94</td>
<td>(−1.5 to 1.4)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>50.4 ± 1.5</td>
<td></td>
<td>50.4 ± 1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime PP†</td>
<td>NAG</td>
<td>51.1 ± 1.7</td>
<td>0.61</td>
<td>51.6 ± 1.8</td>
<td>0.60</td>
<td>(−1.2 to 1.9)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>51.5 ± 1.6</td>
<td></td>
<td>51.3 ± 1.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Night PP‡</td>
<td>NAG</td>
<td>46.9 ± 1.6</td>
<td>0.21</td>
<td>47.4 ± 1.5</td>
<td>0.35</td>
<td>(−2.5 to 0.9)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>48.1 ± 1.6</td>
<td></td>
<td>48.2 ± 1.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Also shown are the 95% CIs for the treatment differences at week 12. Values are presented as mean ± SEM.

*P values are for between-treatment comparisons at week 0 and at week 12.
†Daytime indicates the mean of the period 8:00 AM to 8:00 PM inclusive.
‡Night indicates the mean of the period 12:00 AM to 6:00 AM inclusive.
vealed that of the 40 participants who completed both treatment periods, only 16 expressed certainty of when (ie, indicated what period) they consumed NAG. Accordingly, 9 of 40 (22.5%) correctly predicted when they were on NAG, whereas 7 of 40 (17.5%) indicated they were on NAG when on placebo ($P=0.58$ for $\chi^2$ analysis).

**Main Analysis of BP, Cystatin C, and Body Weight**

There were no significant period or carryover effects on any of the measured parameters (BP, bodyweight, or cystatin C). For the BP parameters at week 0, mean values did not differ between NAG and placebo (Table). However, at 6:00 AM on week 0, the PP was significantly lower for NAG compared with placebo ($P<0.05$; Figure); there were no other mean hourly differences.

There was no significant effect of treatment on the primary outcome, mean 24-hour systolic BP, or on any secondary outcomes (ie, mean values at week 12 did not differ between NAG and placebo; Table); and there was no significant interaction among treatment, week, and/or hour. At 1:00 PM (13:00 hours), however, diastolic BP was significantly higher at week 12 for NAG compared with placebo (Figure). There were no other mean hourly differences.

Body weight did not differ between NAG and placebo at week 0 (82.8±2.3 versus 82.7±2.3 kg, respectively; $P=0.86$; $n=37$) and at week 12 (82.6±2.3 versus 82.8±2.3 kg, respectively; $P=0.47$; $n=37$). The serum level of cystatin C did not differ between NAG and placebo at week 0 (0.97±0.03 versus 0.98±0.03 mg/L, respectively; $P=0.40$; $n=34$) and at week 12 (1.00±0.03 versus 0.90±0.03 mg/L, respectively; $P=0.32$; $n=34$). A sufficient number of blood samples were obtained from only 34 participants for the measurement of serum cystatin C.

**Secondary Analysis**

The secondary analysis included the 39 participants who completed the entire study plus those who withdrew but completed the first treatment period ($n=7$). When their data were analyzed together in a parallel-design comparison of NAG ($n=25$) versus placebo ($n=21$) on all of the ABP parameters from treatment period 1, NAG showed no signifi-
icant effect versus placebo on any parameter (results not shown).

Intention-to-Treat Analysis
Because 12 of the 52 randomized participants were lost to follow-up, and 1 had incomplete ABPM, the intention-to-treat analysis included 39 individuals. It was only performed for ABP and showed no significant effect of period, carryover, or treatment on any ABP parameter (results not shown).

Discussion
We showed here, for the first time in a long-term RCT, the effect of ginseng on BP and renal function. The ginseng used was NAG, which is a species native to North America that is used predominantly in Canada, the United States, and China.\(^7\) We found that its intake at 3 g/day for 12 weeks relative to placebo was associated with a neutral effect on BP in hypertensive individuals. This was shown in the main analysis by a lack of difference between NAG and placebo at 12 weeks for each of the mean 24-hour, daytime and night ABP parameters (Table), which was supported by an intention-to-treat analysis. Also, although there was an increase in diastolic BP for NAG relative to placebo at the 1:00 PM (13:00 hours) time point of week 12 (Figure), this was considered clinically insignificant, because mean daytime and 24-hour diastolic BP did not differ between treatments. As for cystatin C, NAG intake did not affect its serum level relative to placebo, indicating no influence on renal function. Thus, this study showed that 12-week consumption of NAG had no effect on ABP or renal status in hypertensive individuals.

The BP outcomes here added to our previous finding,\(^15\) which showed an acute neutral effect on BP with 6 batches of NAG differing in quality and profile of ginsenosides, pharmacologically active components of NAG.\(^30\) Importantly, the 6 batches were chosen by the Ginseng Growers Association of Ontario to represent the total crop of NAG from Ontario, which supplies >60% of NAG worldwide.\(^15\) Here, we tested 1 of these batches, and because it was phytochemically similar to the other 5 batches, we speculated that our current findings could be extrapolated to these other 5 and, thus, to a majority of NAG on the world market.

With respect to the form of NAG tested, we administered the whole dried root in its natural form, which is the most consumed form, and the form that cultivators sell to supplement manufacturers. Accordingly, we were able to assess all of the components of NAG within their native matrix. In particular, we avoided using aqueous-alcohol extracts, because they would have contained only the NAG components soluble within the base of the extract,\(^31\) thus precluding a comprehensive investigation of the efficacy of NAG.

As for dosage, in keeping with our acute efficacy trial,\(^15\) we administered 3 g, which is the recommended dose of ginseng in traditional Chinese medicine,\(^32\) and the average intake reported in the study by Siegel,\(^7\) where ginseng intake was associated with elevated BP. As well, the 12-week treatment period represented the time span in which hypertension developed in Siegel’s report.\(^7\)

Although this was the first long-term RCT on ginseng root and BP, it should be emphasized that it evaluated the species of ginseng known as \(P\) \textit{quinquefolius}, or NAG. NAG is unique from \(P\) \textit{ginseng}, which is the species that has been tested in other clinical interventions on ginseng and BP.\(^16,33-35\) After harvest, the root portion of NAG is dried, whereas the root portion of \(P\) \textit{ginseng} is either dried or steamed,\(^1\) with the steamed form being marketed as Korean red ginseng (KRG). Importantly, NAG contains a 3- to 5-times higher content of ginsenosides and different profile of ginsenosides than both forms of \(P\) \textit{ginseng}.\(^2,15,16,24,28\) As well, KRG is the only marketed ginseng to contain ginsenoside R\(_g3\), the most potent vasodilating ginsenoside.\(^36\)

To date, 4 clinical interventions have tested the effect of \(P\) \textit{ginseng} root on BP.\(^16,33-35\) Of these, 1 tested the dried root and showed that an aqueous-alcohol extract of it at 200 mg/day had no effect on BP in a 4-week RCT with young, normotensive adults.\(^33\) In the case of steamed root, KRG, our group found that 3 g of the natural root could lower BP for 160 minutes relative to placebo in an RCT with hypertensive individuals.\(^16\) As well, an 8-week nonrandomized trial demonstrated that 4.5 g/day of the natural KRG root significantly decreased BP in hypertensive individuals.\(^30\) Furthermore, in a nonrandomized trial with young, normotensive adults, an aqueous extract of KRG root at a mean dose of 610 mg significantly decreased BP at 45, 60, and 75 minutes after intake.\(^34\) Thus, although studies on ginseng and BP exist, the use of extracts and nonrandomized designs was common, which precluded an accurate assessment of efficacy. Still, evidence to date indicates that NAG has no effect on BP and that \(P\) \textit{ginseng}, if steamed, could be antihypertensive. Future RCTs will have to determine whether the ginseng species, the steaming process, and the ginsenoside content and/or profile are important factors affecting BP. Importantly, though, contrary to Siegel’s\(^7\) observational finding, no clinical intervention has shown ginseng to elevate BP.

In the current study, 2 participants reported adverse events (headache and diarrhea), and withdrew, and both were taking NAG at the time. Whereas clinical documentation of the adverse events of NAG is lacking, Coon and Ernst\(^37\) systematically reviewed 146 clinical trials representing >8500 individual exposures to \(P\) \textit{ginseng} and found it to have the same adverse event profile as placebo.

The current study had 3 limitations. First, 25% of the participants withdrew, and another 5% had their data removed from main analysis. We did, however, conduct a secondary analysis and intention-to-treat analysis to rectify this, and both showed identical outcomes to the main analysis. Second, whereas the antihypertensive-treated participants in the main analysis (\(n=32\)) held their antihypertensive type(s) and dose(s) constant for the entire study, their use of antihypertensives could have prevented an accurate interpretation of the effect of NAG on BP because of possible NAG–drug interactions. However, an objective here was to determine the effect of NAG on BP in a representative population of hypertensive individuals so that the findings could be extrapolated to such individuals. To add to the current findings, future studies should determine the effect of NAG on BP in untreated hypertensive or prehypertensive individuals to better understand the influence of NAG on BP in the absence of antihypertensive drugs.
Perspectives
The topic of ginseng and BP in humans commenced greater than 25 years ago with an observational study that suggested a link between ginseng use and hypertension. Since then, 2 acute-duration RCTs found that NAG and P. ginseng have neutral and lowering effects on BP, respectively. We showed here that 12-week intake of NAG is associated with a neutral effect on 24-hour BP relative to placebo in a multiethnic, middle-to-older aged, hypertensive population. NAG also had no effect on the serum level of cystatin C, a marker of renal function and cardiovascular mortality. Overall, these findings widen the perspective on ginseng and BP and provide initial insight into the effect of ginseng on renal function. Future RCTs should evaluate additional doses of NAG that represent its range of intake in the general population. As well, the effect of P. ginseng on BP should be determined through similar long-term RCTs, because it shows the potential to lower BP.

Acknowledgments
Funding for this study was provided by the Ontario Ministry of Agriculture and Food, as well as by the Ontario Ginseng Growers Association, who also provided the ginseng.

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Long-Term Intake of North American Ginseng Has No Effect on 24-Hour Blood Pressure and Renal Function

P. Mark Stavro, Minna Woo, Lawrence A. Leiter, Tibor F. Heim, John L. Sievenpiper and Vladimir Vuksan

_Hypertension_. 2006;47:791-796; originally published online March 6, 2006;
doi: 10.1161/01.HYP.0000205150.43169.2c

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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