Randomized, Open-Label, Cross-Over Comparison of the Effects of Benzbrromarone and Febuxostat on Endothelial Function in Patients with Hyperuricemia

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Summary

Uric acid is generated with reactive oxygen species via xanthine oxidase (XO), and hyperuricemia, which is identified as the excess of uric acid in the blood, has been associated with vascular endothelial dysfunction. However, the effects of urate-lowering medicines on endothelial function have not been fully elucidated. Thus this study determined and compared the effects of benzbrromarone (urate transporter 1 inhibitor) and febuxostat (XO inhibitor) on endothelial function.

This randomized, cross-over, open-label study initially recruited 30 patients with hyperuricemia. They were divided into two groups, treated initially with benzbrromarone or febuxostat for three months and then were switched for the next three months. Endothelial function was defined as reactive hyperemia indexes (RHI) determined using Endo-PAT 2000 before and at three and six months after medication using the two agents. Blood levels of asymmetric dimethylarginine (ADMA) and high-molecular-weight (HMW) adiponectin were also compared. We finally analyzed data from 24 patients whose endothelial function was assessed as described above.

Our findings show that levels of uric acid significantly decreased, whereas those of HMW adiponectin and the RHI have significantly increased after treatment with benzbrromarone. Meanwhile, in patients administered with febuxostat, uric acid levels tended to decrease and RHI significantly decreased. Neither of the two agents altered ADMA levels. The changes in RHI ($P = 0.026$) and HMW adiponectin levels ($P = 0.001$) were found to be significantly greater in patients treated with benzbrromarone than febuxostat. Changes in the levels of HMW adiponectin and of uric acid were significantly correlated ($r = -0.424, P = 0.039$).

Benzbrromarone has increased adiponectin besides reducing uric acid levels, and thus, this might confer more benefits on endothelial function than febuxostat.

Key words: Uric acid, Reactive oxygen species, Adiponectin, Asymmetric dimethylarginine

Recent epidemiological studies have associated high uric acid levels with the development of hypertension, dyslipidemia, diabetes mellitus, chronic kidney disease, and cardiovascular diseases. En- dothelial dysfunction has been determined as key to the development and progression of the diseases based on atherosclerosis. Endothelial dysfunction is mediated in part by reactive oxygen species (ROS) that can be generated by several mechanisms, one of which involves the reaction of xanthine oxidase (XO) with xanthine in generating superoxide anions and uric acid. Xanthine oxidase readily donates electrons to molecular oxygen, resulting in the generation of $O_2^-$ and hydrogen peroxide. The inhibition of XO by oxypurinol is seen to reduce $O_2^-$ production and improve endothelium-dependent vascular relaxa-
Patients with hyperuricemia

\[ n = 30 \]

\[ \text{Benzbromarone} \]
\[ n = 15 \]
\[ (n = 1) \]
\[ \text{Measurement (RHI, blood tests)} \]
\[ (n = 2) \]
\[ \text{Febuxostat} \]
\[ n = 14 \]
\[ \text{Benzbromarone} \]
\[ n = 13 \]
\[ (n = 1) \]
\[ \text{Measurement (RHI, blood tests)} \]
\[ (n = 2) \]
\[ \text{Analysis} \]
\[ \text{Benzbromarone} \rightarrow \text{Febuxostat} \]
\[ n = 13 \]
\[ \text{Febuxostat} \rightarrow \text{Benzbromarone} \]
\[ n = 11 \]

3 months

\[ R \]

Figure 1. Study flow chart. Thirty patients with hyperuricemia were recruited and randomized to two groups that were initially treated with either benzbromarone or febuxostat for three months and then switched to either febuxostat or benzbromarone for another three months. Reactive hyperemia index (RHI), a marker of endothelial function, was measured, and blood samples were tested before and at three and at six months after treatment. Finally, 13 and 11 patients who initially started on benzbromarone and febuxostat, respectively, were included in the analyses. The numbers in parentheses indicate the number of patients who did not undergo RHI measurement. R indicates randomization.

control hyperuricemia, in addition to inhibiting urate synthesis. The urate transporter 1 (URAT1) is encoded by the SLC22A12 gene, and it facilitates urate reabsorption in proximal tubules and helps regulate serum uric acid.\(^{11}\) Experimental studies have shown that uric acid transporters are expressed not only in renal tubular cells, but also in other cell types, such as vascular endothelial cells.\(^{12-15}\) Uric acid absorbed into endothelial cells via urate transporters can cause inflammation or oxidative stress, which both contribute to endothelial dysfunction. Benzbro-
marone, a uricosuric agent, is an URAT1 inhibitor that regulates hyperuricemia and might have beneficial effects on endothelial function. However, this remains to be investigated in detail.

This present cross-over study compared the effects of febuxostat and benzbromarone on endothelial function in patients with hyperuricemia.

**Methods**

**Patients:** This randomized, open-label, cross-over interventional study (UMIN ID: UMIN000009468) included patients with hyperuricemia (serum uric acid > 8.0 mg/dL) and hypertension, ischemic heart disease, diabetes mellitus or metabolic syndrome, or serum uric acid > 9.0 mg/dL. They were randomized using an envelope method and were further assigned to groups treated with either benzbromarone or febuxostat for three months. Thereafter, these agents were switched for the next three months. Endothelial function was assessed using an Endo-PAT 2000 device (Itamar Medical, Caesarea, Israel), and blood tests included asymmetric dimethylarginine (ADMA) and high-molecular-weight (HMW) adiponectin before and at three and at six months after treatment. The exclusion criteria were as follows: inability to comply with urate-lowering medications for three months; high probability of frequent changes in concomitant medications; severe renal dysfunction and/or on hemodialysis; pregnancy; clinically problematic allergies; hypersensitivity to, or adversely affected by, benzbromarone and febuxostat; or judged ineligible for the study by a physician. We initially recruited 30 (\( n = 15 \) per group) patients; however, six were excluded whose endothelial function was not assessed after treatment. Thus, 24 patients were included for analysis (male, \( n = 19 \)), of whom 13 were initially started on benzbromarone (Figure 1).
The definitions of underlying diseases or conditions were as follows. Hypertension was defined as either being treated with antihypertensive agents or having systolic blood pressure of ≥ 140 mmHg and/or diastolic blood pressure of ≥ 90 mmHg. Diabetes mellitus was defined as having fasting blood glucose ≥ 126 mg/dL, HbA1c ≥ 6.5% or being under medication with anti-diabetic drugs. Dyslipidemia was defined as being medicated with lipid lowering agents or as having low-density lipoprotein cholesterol (LDL-C) ≥ 140 mg/dL, triglycerides ≥ 150 mg/dL, and/or high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL. Lastly, ischemic heart diseases included old myocardial infarction and stable angina pectoris after coronary intervention.

This study is in accordance with the Declaration of Helsinki, and the Ethics Committee of Nagasaki University Hospital has approved the protocol. All patients provided written, informed consent to participate in the study before enrollment.

**Measurement of endothelial function:** Endothelial function was evaluated by peripheral artery tonometry (PAT) using an Endo-PAT 2000 device (Itamar Medical, Caesarea, Israel) as described by the manufacturer. After an overnight fast, a PAT finger probe was placed on both index fingers of supine patients while resting in a quiet, temperature-controlled environment. Pressure alterations in the finger cuff reportedly induced by pulsatile volume changes in the distal digits sensed by a pressure transducer were transmitted to and recorded by the Endo-PAT 2000 device. The reactive hyperemia index (RHI) was taken as an indicator of endothelial function. Reactive hyperemia consisted of a 5-minute baseline measurement, after which a blood pressure cuff on the test arm was inflated to 60 mmHg above a baseline systolic blood pressure or at least 200 mmHg for 5 minutes. Thereafter, the cuff was deflated, and the PAT tracing was recorded for a further 6 minutes. The contralateral arm served as a control, and the Endo-PAT 2000 software automatically calculated the RHI from differences between the two arms.

**Blood tests:** Venous blood samples were withdrawn from the forearms of all patients after an overnight fast. Serum HMW adiponectin and ADMA were measured at a commercial laboratory (SRL Inc., Tokyo, Japan) using latex 144 turbidimetric immunoassays and high-performance liquid chromatography, respectively. All other parameters were measured at our hospital using routine laboratory protocols.

**Statistical analyses:** The normal distribution of continuous values was tested using Shapiro-Wilk tests and is expressed as means ± SD for parametric data or as medians (first to third quartile) for nonparametric data. Continuous data at baseline were compared using unpaired t-tests or Mann-Whitney U-tests. Categorical data at baseline are presented as numbers (%) and were compared using chi-square test. Values before and after treatment were compared using paired t-tests or Wilcoxon signed-rank tests. Correlations between changes in ADMA or HMW adiponectin and those in other variables were evaluated using Spearman rank correlation coefficients. Values with P < 0.05 were considered statistically significant. All data were statistically analyzed using IBM SPSS version 23 (IBM Corp., Armonk, NY, USA).

**Results**

The demographics of the patients before treatment are summarized in Table I. Laboratory findings of liver/renal function, lipid/glucose profiles, serum ADMA, HMW adiponectin, uric acid values, and the RHI were determined to have not significantly differ between patients initially treated by benzbromarone and febuxostat. Among the underlying diseases, the number of patients with ischemic heart disease was greater in the group initially treated with febuxostat than with benzbromarone.

Table II shows the changes in parameters before and after three months of benzbromarone or febuxostat administration. In patients administered with benzbromarone, uric acid levels have significantly decreased, whereas LDL-C, creatinine, HMW adiponectin, and the RHI significantly increased. Meanwhile, in patients treated with febuxostat, levels of LDL-C and the RHI as well as uric acid have significantly decreased, while a significant increase in HDL-C levels was noted. The changes in RHI and HMW adiponectin levels were significantly greater in patients treated with benzbromarone than febuxostat (Figure 2A and B, respectively). Levels of ADMA did not significantly change before and after either of the treatment. Figures 3, 4, respectively, show the entire course of RHI and HMW adiponectin. Benzbromarone tended to increase RHI and significantly increase HMW adiponectin levels. The changes in parameters during the treatment phases of benzbromarone and febuxostat are shown in Tables III, IV, respectively. The benzbromarone-induced increase in creatinine and decrease in uric acid levels were determined to be significant during the first, but not the second phase. In contrast, HMW adiponectin levels were significantly increased during both phases. The RHI did not significantly increase in either phase. Febuxostat significantly decreased LDL-C levels during the second phase and significantly decreased uric acid levels during the first phase but the latter increased during the second phase. Median HMW adiponectin values and the median RHI increased and decreased, respectively, during each phase, but the differences were not significant. In terms of the correlations among uric acid, HMW adiponectin, and RHI, the changes in uric acid and HMW adiponectin significantly correlated in patients treated with febuxostat, but not with benzbromarone (Figure 5). Changes in RHI did not correlate with those in the other two parameters during both therapies (data not shown).

**Discussion**

The main results of this present study were as follows: benzbromarone has significantly increased RHI levels, whereas febuxostat decreased the total change in RHI. Thus, the changes between the two groups have differed significantly. Benzbromarone significantly increased HMW adiponectin levels, whereas febuxostat did not. In contrast, changes in uric acid and in HMW adiponectin significantly correlated in patients treated with febuxostat, but not benzbromarone.
increases in NADPH oxidase-derived ROS production in
ically produced along with ROS through XO, it stimulates
results in the inhibition of intracellular NADPH oxidase-

| Parameters Before and After Benzbromarone or Febuxostat Administration throughout the Study |
|------------------------------------|------------------|------------------|------------------|
| Duration, days                     | Before           | After            | Before           | After            |
| LDL-C, mg/dL                       | 98.2 ± 26.1      | 108.8 ± 29.9     | 0.018            | 107.1 ± 32.9     | 100.0 ± 31.3     | 0.035 |
| TG, mg/dL                          | 108.0 (84.5-145.5) | 114.5 (89.5-14.0) | 0.607           | 108.5 (79.5-126.8) | 114.5 (89.5-134.0) | 0.068 |
| HDL-C, mg/dL                       | 51.9 ± 13.2      | 52.5 ± 17.7      | 0.667            | 51.7 ± 17.3      | 54.3 ± 19.6      | 0.027 |
| FBS, mg/dL                         | 99.5 (93.0-104.8) | 97.0 (92.5-104.5) | 0.112            | 97.5 (94.0-105.0) | 96.5 (92.3-110.8) | 0.867 |
| HbA1c, %                           | 5.84 ± 0.77      | 5.85 ± 0.61      | 0.841            | 5.86 ± 0.58      | 5.85 ± 0.75      | 0.896 |
| Cre, mg/dL                         | 1.15 ± 0.30      | 1.27 ± 0.47      | 0.017            | 1.17 ± 0.33      | 1.16 ± 0.29      | 0.669 |
| BUN, mg/dL                         | 20.1 ± 6.5       | 21.6 ± 7.2       | 0.088            | 20.1 ± 6.7       | 20.7 ± 8.0       | 0.619 |
| Uric acid, mg/dL                   | 7.00 (5.2-8.65)  | 4.80 (4.23-5.60) | < 0.001          | 6.35 (4.50-8.20) | 5.20 (4.73-5.88) | 0.089 |
| ADMA, μmol/L                      | 0.486 ± 0.071    | 0.501 ± 0.051    | 0.096            | 0.489 ± 0.062    | 0.482 ± 0.061    | 0.489 |
| HMW-A, ng/mL                       | 3.35 (1.85-8.15) | 4.42 (2.27-9.96) | < 0.001          | 3.34 (1.98-9.63) | 3.49 (1.77-8.50) | 0.230 |
| RHI                                | 1.60 (1.33-1.86) | 1.83 (1.42-2.21) | 0.037            | 1.73 (1.48-2.0)  | 1.62 (1.33-1.85) | 0.033 |

Benzbromarone not only suppresses uric acid reab-
sorption via inhibition of the uric URAT1 in renal tubular
cells, but it also interferes with uric acid uptake via URAT
1 in adipocytes and vascular smooth muscle cells, which
results in the inhibition of intracellular NADPH oxidase-
derived ROS production. Although uric acid is basic-
ally produced along with ROS through XO, it stimu-
lates increases in NADPH oxidase-derived ROS production in
adipocytes, vascular smooth muscle cells, and vascular en-
dotheial cells. Furthermore, uric acid can activate the
local renin-angiotensin system, in which angiotensin II
increases intracellular oxidative stress by stimulating
NADPH oxidase. These findings suggest that ROS pro-
duction through enzymes other than XO might play im-
portant roles in uric acid-induced endothelial dysfunction.
Benzbromarone has a phenolic hydroxy group that might
be involved in its radical trapping action. Kadowaki, et al.
have identified benzbroxarone as having the ability to

ADMA indicates asymmetric dimethylarginine; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Benz, benzbroxarone; BMI, body mass index; BUN, blood urea nitrogen; Cre, creatinine; DM, diabetes mellitus; Feb, febuxos-
stat; FBS, fasting blood sugar; Hb, hemoglobin; HbA1c, hemoglobin A1C; HDL-C, high density lipoprotein cholesterol; HMW-A, high molecular weight adiponectin; IHD, ischemic heart disease; LDL-C, low-density lipoprotein cholesterol; RHI, reactive hyperemia index; TG, triglyceride; and WBC, white blood cells.
Figure 2. Comparison of changes in RHI (A) and HMW adiponectin (B) between patients treated with benz bromarone and febuxostat. HMW indicates high molecular weight; and RHI, reactive hyperemia index.

Figure 3. Changes in RHI during the study period. Patients administered with benz bromarone followed by febuxostat (left) and with febuxostat followed by benz bromarone (right). RHI indicates reactive hyperemia index.

We found that HMW adiponectin levels significantly increased in patients with hyperuricemia treated by benz bromarone. Adipose tissues synthesize and release adiponectin, which is considered an endocrine factor that increases nitric oxide production through the AMPK-dependent activation of eNOS. Adiponectin also increased cyclooxygenase-2 expression in cultured endothelial cells, and deleting it inhibits adiponectin-mediated growth and the migration, differentiation, and survival of endothelial cells. These findings indicate that adiponectin improves endothelial function. Adiponectin secreted into the bloodstream forms oligomeric, trimers (67 kDa), hexamers (140 kDa), and HMW (300 kDa) multimeric complexes comprising at least 18 monomers.

We possess direct scavenging ability against $O_2^-$ and LOO$^-$ and suppress ROS production induced by uric acid and angiotensin II in vascular endothelial cells. These findings suggested that benz bromarone reduces ROS production directly and indirectly by acting as both a URAT1 inhibitor and a radical scavenger, respectively. On the other hand, allopurinol inhibits ROS production via XO inhibition, but it does not act as a radical scavenger. Given that a recent study claimed that febuxostat had higher cardiovascular mortality than allopurinol, benz bromarone reduces ROS generation more potently than febuxostat, which might explain the difference between the two medicines in improving endothelial function in this present study.
Among them, HMW oligomeric adiponectin is the major bioactive isoform that contributes to its cardiovascular protective effects. Therefore, we measured HMW adiponectin as a marker of endothelial function. Several studies have investigated associations between uric acid and adiponectin. Ferreira, et al. reported that serum uric acid and adiponectin levels negatively correlate; meanwhile, Park, et al. found an inverse relationship between these levels in 841 postmenopausal women aged ≥50 years. The mechanisms responsible for this relationship might be that uric acid uptake by adipocytes induces oxidative stress, generates inflammatory mediators, and inhibits adiponectin synthesis, resulting in endothelial dysfunction by reducing nitric oxide bioavailability.

We then considered why serum adiponectin levels were increased more by benzbromarone than febuxostat in the present study. Inokuchi, et al. showed that benzbromarone treatment for one year increased serum adiponectin concentrations in patients with gout, whereas allopurinol did not. Furthermore, their findings in vitro showed that benzbromarone increased adiponectin mRNA levels partly via PPAR-γ activation. Given that benzbromarone reduced ROS generation, it might increase adiponectin more potently than febuxostat. We found a significant correlation between the changes in HMW adiponectin and in uric acid in patients treated with febuxostat followed by benzbromarone (right). HMW indicates high molecular weight.

Table III. Changes in Parameters Before and After Benzbromarone Administration

|                        | Benzbromarone 1st phase |                | p     | Benzbromarone 2nd phase |                | p     |
|------------------------|-------------------------|----------------|-------|-------------------------|----------------|-------|
|                        | Before                  | After          |       | Before                  | After          |       |
| Duration, days         | 91.0 (84.5-101.5)        | 84.0 (84.0-97.0) | 0.052 | 86.7 ± 21.3             | 95.3 ± 14.8    | 0.202 |
| LDL-C, mg/dL           | 107.8 ± 26.5            | 120.2 ± 35.0   | 0.861 | 113.0 (83.0-147.0)      | 123.0 (106.0-162.0) | 0.423 |
| TG, mg/dL              | 99.0 (86.0-144.5)       | 110.0 (82.0-129.0) | 0.289 | 48.5 ± 12.9             | 46.7 ± 13.1    | 0.141 |
| HDL-C, mg/dL           | 54.8 ± 13.2             | 57.4 ± 20.1    | 0.052 | 1.17 ± 0.28             | 1.37 ± 0.58    | 0.093 |
| Cre, mg/dL             | 1.12 ± 0.33             | 1.19 ± 0.36    | 0.273 | 20.0 ± 5.7              | 22.5 ± 8.3     | 0.177 |
| BUN, mg/dL             | 20.2 ± 7.3              | 20.8 ± 6.4     | 0.001 | 5.10 (4.80-6.20)        | 5.10 (4.30-5.80) | 0.201 |
| Uric acid, mg/dL       | 8.50 (7.65-8.95)        | 4.80 (4.05-5.05) | 0.575 | 0.468 ± 0.070           | 0.502 ± 0.062  | 0.061 |
| ADMA, μmol/L           | 0.493 ± 0.075           | 0.500 ± 0.058  | 0.001 | 2.16 (2.15-14.30)       | 4.36 (2.49-5.23) | 0.004 |
| HMW-A, ng/mL           | 4.41 (1.80-11.2)        | 5.16 (2.15-14.30) | 0.152 | 1.86 (1.65-2.31)        | 1.62 (1.29-2.14) | 0.153 |
| RHI                    | 1.62 (1.51-1.98)        | 1.86 (1.65-2.31) |      | 1.48 (1.30-1.69)        | 1.62 (1.29-2.14) |      |

ADMA indicates asymmetric dimethylarginine; BUN, blood urea nitrogen; Cre, creatinine; HDL-C, high-density lipoprotein cholesterol; HMW-A, high molecular weight adiponectin; LDL-C, low-density lipoprotein cholesterol; RHI, reactive hyperemia index; and TG, triglyceride.
buxostat, but not benzbromarone (Figure 5). This also suggests that benzbromarone affects adiponectin levels via pathways other than reducing uric acid, because the amount of adiponectin increased more in patients treated with benzbromarone.

The endogenous inhibitor of nitric oxide synthase, ADMA, is also considered as a marker and mediator of endothelial dysfunction. Decreased NO bioavailability is considered to mediate uric acid-induced endothelial dysfunction. Thus, we considered that ADMA levels would be altered by agents that reduce uric acid. However, ADMA levels did not significantly change in patients treated by both agents in the present study. Fliser, et al. showed that treating type 2 diabetes mellitus with an angiotensin II receptor antagonist reduces oxidative stress, but does not alter plasma ADMA concentrations. Hypercholesterolemia increases ADMA levels, but endothelial dysfunction in the setting of hypertension or diabetes is not accompanied by such an increase. These findings suggested that the ADMA response is altered under different conditions and/or by different medicines. However, the exact mechanisms remain unknown.

**Limitations:** The small patient cohort from a single center imposed inherent limitations. However, the cross-over design of this study required fewer participants than other designs and further reduced the effects of the confounding factors. A carry-over effect might have affected the results, because the wash-out period for benzbromarone and febuxostat might have been insufficient. Although benzbromarone tended to increase RHI values in each phase, the difference was not significant, whereas an increase in HMW adiponectin levels was significant in both phases. Adiponectin has a protective effect on endothelial function mediated through the activation of endothelial nitric oxide synthase and the suppressed generation of ROS and proinflammatory cytokines. Therefore, benzbromarone might need more time to improve endothelial function; otherwise, more patients might be required for analysis due to the small changes in RHI values. The febuxostat dose required titration; therefore, the dose might not have been

**Table IV. Changes in Parameters Before and After Administration of Febuxostat**

|                      | Febuxostat 1st phase | Febuxostat 2nd phase |
|----------------------|----------------------|----------------------|
|                      | Before | After | Before | After |
| Duration, days       | 92.0 (84.0-105.0)    | 91.0 (84.0-119.0)    |
| LDL-C, mg/dL         | 91.6 ± 23.1 | 86.7 ± 21.3 | 120.2 ± 35.0 | 111.2 ± 34.7 |
| TG, mg/dL            | 102.0 (74.0-126.0) | 113.0 (83.0-147.0) | 110.0 (82.0-129.0) | 116.0 (80.5-141.0) |
| HDL-C, mg/dL         | 44.9 ± 10.6 | 48.5 ± 12.9 | 57.4 ± 20.1 | 59.2 ± 23.2 |
| Cre, mg/dL           | 1.15 ± 0.31 | 1.18 ± 0.28 | 1.19 ± 0.36 | 1.14 ± 0.30 |
| BUN, mg/dL           | 19.2 ± 7.2  | 20.0 ± 5.7  | 20.8 ± 6.4  | 21.2 ± 9.8  |
| Uric acid, mg/dL     | 8.20 (8.10-9.8)   | 5.10 (4.80-6.20)   | 4.80 (4.05-5.05) | 5.20 (4.50-5.85) |
| ADMA, μmol/L         | 0.476 ± 0.066 | 0.468 ± 0.070 | 0.500 ± 0.058 | 0.493 ± 0.053 |
| HMW-A, ng/mL         | 2.45 (1.43-5.14) | 3.04 (1.84-4.68) | 5.16 (2.15-14.3) | 5.60 (1.70-12.5) |
| RHI                   | 1.60 (1.39-1.84) | 1.48 (1.30-1.69) | 1.86 (1.65-2.31) | 1.75 (1.50-1.90) |

ADMA indicates asymmetric dimethylarginine; BUN, blood urea nitrogen; Cre, creatinine; HDL-C, high-density lipoprotein cholesterol; HMW-A, high molecular weight adiponectin; LDL-C, low-density lipoprotein cholesterol; RHI, reactive hyperemia index; and TG, triglyceride.

**Figure 5. Correlations between changes in uric acid and HMW adiponectin in patients treated with benzbromarone (A) and febuxostat (B). HMW indicates high molecular weight.**
escalated sufficiently over three months to exert beneficial effects on endothelial function. Change in lipid profiles was also found to differ between the two medicines. This might have been due to dietary issues, but the reason(s) remains unclear. Regardless, the increase in LDL-C levels after benzbromarone treatment was determined within the normal range, and the RHI values improved even under this circumstance.

Conclusions

Benzbromarone increased adiponectin in addition to reducing uric acid levels, and thus, this might confer more benefits on endothelial function than febuxostat. These results warrant further randomized control studies to investigate the effects of urate-lowering therapies such as XO and URAT-1 inhibitors on endothelial function in a larger patient cohort.

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Disclosure

Conflicts of interest: None.

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