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Comment on "Angiotensin-Converting-Enzyme 2 Inhibits Liver Fibrosis in Mice"

To the Editor:

In their article in the September 2009 issue of HEPATOLOGY, Österreicher et al. conclude with a protective role for angiotensin-converting enzyme 2 (ACE2) on liver injury.[1] ACE2 acts to counterbalance up-regulation of the renin-angiotensin system (RAS) through degradation of angiotensin II to angiotensin 1-7. Based on previous reports on other disease models of RAS overactivity, we would like to highlight another potential anti-RAS mechanism. In these models, immunoassay studies have identified the presence of circulating antibodies against ACE and angiotensin II considered to exert a neutralizing effect.[2,3] Currently, no studies evaluating the levels of serum/tissue anti-RAS antibodies in chronic liver disease models are reported in the literature. It is possible that standardization of their titers could prove to be of prognostic significance.

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Carvedilol Versus Variceal Band Ligation for Prevention of the First Variceal Bleed

To the Editor:

We read with great interest the article by Tripathi et al.[1] In this randomized controlled trial, carvedilol, a noncardioselective vasodilating beta-blocker, was compared with variceal banding ligation (VBL) for primary prophylaxis of variceal bleed. The authors found carvedilol to have lower bleeding rates than VBL, with no difference in survival by intention-to-treat (ITT) analyses. In addition, this was the first reporting of drug therapy having an advantage over VBL. Although their results provided important data for primary prophylaxis of variceal bleeding, several issues deserve further discussion.

First, the most important finding was the greater efficacy of carvedilol in the prevention of the first variceal bleed by ITT analyses. However, the significant statistic disappeared after per-protocol analyses. The dropout rates of the two treatment arms were around 30%, suggesting that only 70% of the initial subjects really completed the study protocol. In addition, the relative higher rate of first variceal bleed in the VBL arm could be due to several reasons, such as bleeding before the first endoscopy following randomization in three patients, noncompliance with the VBL protocol in five patients, and the use of propranolol as rescue therapy in patients with discontinued intervention, which was less effective in primary prevention of variceal hemorrhage than VBL, as confirmed by two meta-analyses.[2,3] In contrast, the rescue treatment for patients with discontinued intervention in the carvedilol arm was VBL. Taking these lines of evidence together, we should be very careful to interpret the results from the ITT analyses.

Second, bleeding due to banding ulceration was one important complication of VBL, thus decreasing the efficacy in primary prophylaxis for variceal bleed. Patients with decompensated cirrhosis with bleeding tendency obviously had increased risk of bleeding from banding ulceration. In this study, two-thirds of patients in the VBL arm had decompensated liver reserve and almost 40% of them were classified as having Child C cirrhosis. Therefore, the risk of bleeding from banding ulceration could be higher in this population, which could contribute to the higher rate of first variceal bleed in the VBL arm. Therefore, whether patients with Child C classification, severe coagulopathy, or bleeding tendency could benefit from VBL for primary prophylaxis needs further studies to confirm.

Third, variceal eradication is an important endpoint to prevent variceal bleeding. This study adopted short intervals of 2 weeks between banding sessions, according to the guidelines suggested by

the American Association for the Study of Liver Diseases.[4] A previous report showed that longer interbanding interval (more than 3 weeks) had lower risk of rebleeding in secondary prophylaxis.[5] Therefore, whether short intervals between banding sessions could accelerate eradication of esophageal varices or contradictorily increased the risk of bleeding remained unclear.

In summary, carvedilol and VBL are alternative options for primary prophylaxis of esophageal varices. Defining the optimum banding protocol and benefit-to-risk ratio in patients classified as having Child C cirrhosis are needed to improve the efficacy of VBL.

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Metformin in Chronic Hepatitis C Virus Hepatitis: Caution Needed with Sex-Based Subgroup Analysis

To the Editor:

We read with great interest the study by Romero-Gómez et al.[1] demonstrating that the combination of metformin, peginterferon alfa-2, and ribavirin improved insulin resistance in >50% of patients and increased sustained virological response (SVR) rate in 10% of patients with hepatitis C genotype 1 and homeostasis model assessment (HOMA) >2. Intriguingly, in female participants, the addition of metformin to the standard of care for chronic HCV infection doubled the SVR rate.[1]

Since 1994, the U.S. National Institutes of Health requires that at least half of all clinical trial participants enrolled are females,[2] and increasing interest in women's health and sex-specific outcomes have led to the increase in subgroup analyses stratified by sex. However, improperly conducted sex-based subgroup analysis in clinical trials can yield incorrect conclusions that may result in adverse effects on women's health. It has been therefore suggested that: (1) sex-based subgroup analysis should be planned *a priori* to the study commencement; (2) hypothesis or rationale for the analysis should be provided; (3) a statistical tests for interaction with sex should be performed when analyzing the outcomes; and (4) the overall treatment results should be emphasized more than the findings of the sex-based subgroup analysis.[3] The study by Romero-Gómez et al.[1] clearly had not planned the sex-based subgroup analysis *a priori* because the authors did not mention any adjustment by sex in the Methods section of the article. In addition, there is no clear hypothesis or rationale for a sex-based subgroup analysis in the Introduction or Methods section. The Methods and Results sections were searched for information regarding a statistical test for interaction between sex and the SVR, but no mention was found. In contrast, the authors properly placed equal emphasis on sex-based subgroup results as they did with the overall trial results. Given the frequency with which subgroup analyses by sex are now being performed, it is paramount that investigators should caution the scientific community in their interpretation. Discussion of the sex-specific effects of metformin in chronic HCV infection should be considered proper only when sex-specific analysis are viewed as hypothesis-generating, and further research to confirm these observations is recommended.

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