Alberto Ferrarese
Multivisceral Transplant Unit,
Department of Surgery Oncology and Gastroenterology,
Padua University Hospital,
Padua, Italy

Emmanuel Tsochatzis
Andrew Kenneth Burroughs
Sheila Sherlock Liver Centre,
Royal Free Hospital and UCL Institute of Liver and Digestive Health,
London, UK

Marco Senzolo*
Multivisceral Transplant Unit,
Department of Surgery Oncology and Gastroenterology,
Padua University Hospital,
Padua, Italy
*Corresponding author.
E-mail address: marcosenzolo@hotmail.com

An apology for beta blockers

To the Editor:
We read with interest the recent review on beta-blockers in cirrhosis by Ge and Runyon [1]. This topic is of great importance, as non-selective beta blockers are a pharmacological mainstay in the management of patients with cirrhosis; the amount of evidence has been increasing substantially since the first published trial of their use in the prevention of variceal bleeding [2], particularly in recent years.

In their review, the authors dedicate a sub-heading to "Benefits of beta-blocker therapy". This consists of only two paragraphs, in which some trials of beta blockade for primary prevention of variceal bleeding are discussed. In the last line, the use of beta blockers in secondary prophylaxis of variceal bleeding is just about mentioned, and reference to a table (Table 1) is made. Table 1, titled "Key studies supporting beta-blocker usage", only lists trials of beta blockers for the primary prevention of variceal bleeding. For reasons best known to them (but not to us), the authors chose to completely ignore mountains of evidence for a wide range of non-selective beta blockers in patients with cirrhosis, including such trivialities as effects on mortality, risk of decompensation, development of ascites, renal failure, encephalopathy, and bacterial infections. This includes true landmark studies [3], the results of which have both been replicated [4] and extensively discussed in the literature [5]. Similarly, the vast majority of the wide-ranging pharmacological effects of beta-blockers, particularly non-haemodynamic effects [5,6], are largely ignored, exception made for a single mentioning of bacterial translocation in Fig. 1.

The authors then embark on a lengthy discussion of "adverse effects of beta-blocker therapy". The sub-heading itself spans 5 paragraphs (more than twice the length of the benefits!), but the successive elaboration on the inherent evil of beta blockers (variously termed "The differential effect of beta-blockers in cirrhosis", "Blood pressure and survival", "Beta-blockers in refractory ascites", and "Additional challenges of beta-blocker therapy") cover several pages. In this section, the authors discuss at length the possible adverse effects of beta blockers, quoting studies in patients without liver disease published mainly between 1969 and 1990. It is also rather puzzling that the use of beta blockers in arterial hypertension, cardiac failure, and acute coronary syndromes is discussed, as this debate has little importance to their use in liver disease. Interestingly, had the authors applied a bit more dedication to their "holistic" approach to beta-blockers, they might have stumbled across other rather informative (and much more recent) studies outlining the safety (and significant benefit) of beta blockers in COPD [7,8], peripheral vascular disease [9], and diabetes [10]. Table 2, titled "Key studies suggesting potential harm from beta-blocker usage" clearly is meant to mirror Table 1 in size and importance. It strikes us that of the "key" studies mentioned in this table, the first only shows an increased likelihood of adverse events with beta blockers as compared to placebo (a finding which is hardly surprising), while the second study quite amusingly only investigates the prognostic importance of the cardiac index in cirrhosis without making use of beta blockers. The other two quoted studies are a heavily debated observational study and a cross-over study looking at paracentesis-induced circulatory dysfunction in 10 patients. By contrast, even the completely unrepresentative choice of key studies in Table 1 entirely consists of controlled trials.

At this point it is of little further consequence to mention other surprising findings, such as the space given to the discussion of midodrine and ACE inhibitors in a review on beta blockers, and the fact that studies on midodrine are quoted as evidence "confirming the importance of maintaining cardiac output in patients with advanced cirrhosis" – indeed, midodrine is a vasoconstricting agent and does not increase cardiac output, but has actually been found to decrease it [11].

Finally, in their fervour against beta-blockers, the authors go as far as providing "recommendations" for the use of beta blockers in cirrhosis, the evidence for which is as feeble as the discussion leading up to it. Needless to say, these are to our mind very hazardous statements, which might well lead to a reduction in the use of this class of highly effective and very cheap agents, which have rightly been termed "the Hepatologist's Aspirin" [12].

Sadly, we feel that a great opportunity to discuss this crucial topic in Hepatology has been missed, as this review is ill-conceived and poorly researched, leading to conclusions which might be far more harmful than any effect beta blockers might have in patients with cirrhosis.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References

[1] Ge PS, Runyon BA. The changing role of beta-blocker therapy in patients with cirrhosis. J Hepatol 2014;60:643–653.
[2] Lebrec D, Nouel O, Corbic M, Benhamou JP. Propranolol – a medical treatment for portal hypertension? Lancet 1980;2:180–182.
[3] Abraldes JG, Tarantino I, Turnes J, Garcia-Pagan JC, Rodes J, Bosch J. Hemodynamic response to pharmacological treatment of portal hypertension and long-term prognosis of cirrhosis. Hepatology 2003;37:902–908.
[4] Hernandez-Gea V, Aracil C, Colomo A, Garupera I, Poca M, Torras X, et al. Development of ascites in compensated cirrhosis with severe portal hypertension treated with beta-blockers. Am J Gastroenterol 2012;107:418–427.
[5] Thalheimer U, Bosch J, Burroughs AK. How to prevent varices from bleeding: shades of grey – the case for nonselective beta blockers. Gastroenterology 2007;133:2029–2036.
[6] Thalheimer U, Triantos CK, Samonakis DN, Patch D, Burroughs AK. Infection, coagulation, and variceal bleeding in cirrhosis. Gut 2005;54:556–563.
[7] Farland MZ, Peters CJ, Williams JD, Bielak KM, Heidel RE, Ray SM. Beta-Blocker use and incidence of chronic obstructive pulmonary disease exacerbations. Ann Pharmacother 2013;47:651–656.
[8] Short PM, Lipworth SI, Elder DH, Schembri S, Lipworth BJ. Effect of beta blockers in treatment of chronic obstructive pulmonary disease: a retrospective cohort study. BMJ 2011;342:d2549.
[9] Paravastu SC, Mendonca DA, Da SA. Beta blockers for peripheral arterial disease. Cochrane Database Syst Rev 2013;9:CD005508.
[10] Ryden L, Standl E, Bartnik M, Van den Berghe G, Betteridge J, de Boer MJ, et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). Eur Heart J 2007;28:88–136.
[11] Singh V, Singh A, Singh B, Vijayvergiya R, Sharma N, Ghai A, et al. Midodrine and clonidine in patients with cirrhosis and refractory or recurrent ascites: a randomized pilot study. Am J Gastroenterol 2013;108:560–567.
[12] Triantos C, Samonakis D, Thalheimer U, Patch D, Burroughs A. The relationship between liver function and portal pressure: what comes first, the chicken or the egg? J Hepatol 2005;42:146–147.

Ulrich Thalheimer*
The Exeter Liver Unit,
Royal Devon & Exeter Foundation Trust,
Exeter, UK
*Corresponding author.
E-mail address: uthalheimer@gmx.net

Jaime Bosch
Hepatic Hemodynamic Laboratory,
Hospital Clínic-IDIBAPS and Ciberehd,
University of Barcelona, C.Villarroel 170,
08036 Barcelona,
Spain

Andrew K. Burroughs
Sheila Sherlock Liver Centre,
Royal Free Hospital,
London, UK

CrossMark

Beta-blockers in cirrhosis: Thank you for your attention

To the Editor:

We graciously thank Drs. Ferrarese, Thalheimer, their colleagues, and the editorial board and worldwide readership of the *Journal of Hepatology* for their interest in our article [1]. We are humbled and honored by the international attention that our article has received, and are excited by the debate that it has ignited within the hepatology community. We have received numerous positive correspondences regarding our review [2]. In light of recent studies that have stirred controversy, and in anticipation of future studies that will continue to stir controversy, we believed a fresh objective look at the emerging evidence in the use of beta-blockers in cirrhosis was warranted.

At our institution, our chief executive officer frequently impresses his mantra to "put patients first" upon our entire hospital staff [3]. As physicians, we all believe that what comes first is our relentless and selfless service and dedication to our patients. Sometimes, this involves challenging existing treatments when they are later found to be harmful, such as when the same investigator who first studied the benefits of beta-blockers in patients with cirrhosis no longer found these benefits universally applicable [4].

We have frequently cared for patients with advanced cirrhosis who were seemingly harmed by beta-blockers once they had fallen outside a certain "therapeutic window" (that had only recently been hypothesized) [5]. Once their beta-blockers were discontinued, azotemia, hypotension, and acute kidney injury frequently and convincingly resolved. We were certain other clinicians around the world must have encountered similar experiences, yet the scientific evidence appeared to be lacking. How could we turn our back on 30 years of highly cited landmark studies that promoted the use of beta-blockers? Did we miss something that was actually harming our patients?

Our article was therefore inspired by a need to re-explore the data. We do not dispute that the benefits of beta-blockers have been well-documented in patients with cirrhosis; however, that was not the focus of our article. We acknowledged these existing benefits and set out to more closely examine the studies that had been ignored [6], forgotten [7], or downplayed [8,9]. What we found was evidence – the quality of which can be debated, but nonetheless evidence stemming from astute clinicians making clinical observations – that beta-blockers were perhaps not as universally indicated as even we ourselves had previously believed. Just as the acetylsalicylic acid of cardiology has its limitations, the "aspirin of hepatology" appears to have its own pitfalls and limitations.

Even now, as this debate re-emerges, a new study from Mandorfer and colleagues provides fresh evidence demonstrating the detrimental effect of beta-blocker treatment after the development of spontaneous bacterial peritonitis [10]. More studies and debate are certain to follow.

We are extremely pleased that our review has achieved its intended effect of renewing dialogue and reopening the scrutiny on beta-blockers. We hope that this dialogue, along with new research specifically focusing at studying the end-stages of