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## Letter to the Editor

**Reply to So-Ryoung Lee, Byoung-Won Park, and Jae Heon Kim's Letter to the Editor re: Christian Gratzke, Rob van Maanen, Christopher Chapple, et al. Long-term Safety and Efficacy of Combined Mirabegron and Solifenacin Compared with Monotherapy in Patients with Overactive Bladder: A Randomised, Multicentre Phase 3 Study (SYNERGY II). Eur Urol 2018;74:501–9**

We welcome the important comments raised by Lee et al and would like to take this opportunity to provide further context about the investigations conducted to evaluate the cardiovascular safety of mirabegron in patients with overactive bladder (OAB) [1].

The use of mirabegron for treating OAB symptoms has been extensively investigated and the positive findings from these studies have culminated in the clinical approval of both monotherapy and a combination therapy with the antimuscarinic solifenacin [2]. The overall safety of mirabegron, including the cardiovascular safety profile, has been confirmed through interventional clinical trials and real-world evidence generation. Furthermore, cardiovascular safety is also monitored through post-marketing pharmacovigilance.

Three large-scale, 12-wk phase 3 trials have demonstrated the safety and superior efficacy of mirabegron versus placebo for the treatment of OAB symptoms [3–5]. Although a pooled analysis of these trials found that hypertension was the most commonly reported treatment-emergent adverse event (TEAE), similar incidences were observed for placebo, mirabegron, and tolterodine extended-release (ER) [6]. This analysis also highlighted negligible differences between the active groups and placebo in terms of vital signs. Hypertension-related TEAEs were also commonly reported in an active-controlled, 12-mo phase 3 trial, although comparable rates were again observed for mirabegron and tolterodine ER [7].

Using data from 12-wk trials, a literature analysis showed that there was no evidence of a higher risk of cardiovascular events with mirabegron versus placebo (relative risk 0.24, 95% confidence interval 0.02–1.69) [8]. Similarly, there was no higher risk with mirabegron versus tolterodine in the above 12-mo study.

The combination therapy clinical trial programme included SYNERGY, a 12-wk phase 3 trial that evaluated the potential of solifenacin plus mirabegron to deliver superior efficacy versus the individual monotherapies [9]. A cardiovascular subanalysis found that there were no clinically meaningful differences between combination therapy and the monotherapies in terms of change from baseline in QT interval corrected for heart rate using Fridericia's formula [10]. Although an increase in heart rate of approximately 1 bpm was noted with mirabegron and combination therapy, very few major cardiovascular events were reported. A further blood pressure safety evaluation from this trial showed that combination therapy produced no meaningful changes in blood pressure or heart rate in comparison with either placebo or the monotherapies [11].

In terms of real-world data, a Japanese post-marketing study found that 13 patients (5.5%) experienced nonserious cardiovascular adverse drug reactions with mirabegron [12]. However, the majority of the patients enrolled had coexisting cardiovascular disease and no unexpected cardiovascular safety concerns were observed in the study.

Overall, the available clinical evidence shows that mirabegron has an acceptable cardiovascular safety profile that is similar to that of antimuscarinics. It is also important to note that many of the patients enrolled in these mirabegron studies had underlying cardiovascular conditions. As mentioned by Lee and colleagues, there are initial studies that indicate that mirabegron may have a positive effect on the treatment of structural heart disease [13,14]. Large randomised clinical trials are therefore required to confirm any cardiovascular benefit associated with mirabegron in structural heart disease and we will follow this research with interest.

***Conflicts of interest:*** Christian Gratzke was a global Principal Investigator for the Synergy II study and has received honoraria from Astellas, Bayer, GSK, Lilly, Pfizer, Recordati, Steba, Ipsen, Allergan, and Janssen. Emad Siddiqui is an employee of Astellas.

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Christian Gratzke[a,c*]
Emad Siddiqui[b]

[a]*University of Munich, Munich, Germany*
[b]*Astellas Pharma Inc., Chertsey, UK*
[c]*Department of Urology, University of Freiburg, Germany*

*Corresponding author. University-Hospital Grosshadern, Ludwig-Maximilians-University Munich, Marchioninistr., 81377 Munich, Bavaria, Germany. Tel. +49 89 440073529; Fax. +49 89 440078890.
E-mail address: christian.gratzke@med.uni-muenchen.de (C. Gratzke).


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