Comment on 'Time of administration important? Morning versus evening dosing of valsartan'

Jorie Versmissen, A.H. Jan Danser, and Anton H. van den Meiracker

We read with interest the article by Zappe *et al.* [1] on the influence of time of administration of valsartan on efficacy of treatment of hypertension. A recent Cochrane meta-analysis on this topic showed a beneficial effect of night administration of antihypertensive drugs, but since most earlier studies were small, a larger study was required to fully support this concept [2]. This study now suggests that once-daily dosing of valsartan 320 mg results in equally effective 24-h blood pressure efficacy, regardless of dosing time. Yet, we have some questions on the data on 'nondippers', the group that could potentially benefit most from evening administration as was demonstrated in a previous study [3]. Zappe *et al.* reported no differences in this particular group as well. The proportion of nondippers in this study in patients with grade 1–2 hypertension who could safely discontinue medication, if on any prior medication at all, was high: 49.4–55.2% (see Table 1 of the original paper). Obviously, this is related to the used definition of nondipping, that is, a decline in night-time blood pressure less than 10%. Current guidelines propose to classify persons with a nocturnal decline of blood pressure between 0 and 10% as 'mild dippers', whereas only patients without any nocturnal decline in nocturnal blood pressure are considered 'nondippers' [4]. When comparing Figure 1 and Table 2 of the paper, it appears that, although approximately half of the patients were nondippers, the nocturnal decline in blood pressure compared to daytime values was still substantial, amounting on average 11% for SBP and 15% for DBP. These findings indicate that most patients classified as nondippers still had a substantial nocturnal blood pressure decline at baseline. In this regard, it would be of interest to explore whether the absent difference in nocturnal blood pressure decline related to the time of dosing of valsartan also holds for more severe degrees of nondipping. To investigate this, the authors could perform in their nondippers linear regression analyses on the relation between the percentage nocturnal decline in blood pressure at baseline and the nocturnal decline in blood pressure induced either by the morning or evening dose of valsartan. In addition, when analyzing nondippers, it should be taken into account that 24-h ambulatory blood pressure measurements are highly variable and one single measurement at baseline and follow-up are insufficient [5]. We feel these issues have to be addressed before concluding that timing of administration of valsartan in nondippers does not matter.

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Conflicts of interest

All authors declare that they have no conflicts of interest.

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Reply

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The letter by Versmissen *et al.* [1] suggests that our results might have shown a benefit for night-time dosing of valsartan if we would have used a more stringent definition of 'nondippers' (i.e. persons who have no decline in night-time SBP rather than a decline <10%) to evaluate the night-time BP response [2,3]. We did not conduct the additional analyses, proposed for the nondipper subgroup, because there was no good reason to do so from our results. The reduction in night-time SBP in the patients classified as 'nondippers' at baseline was similar between those receiving valsartan in the morning

TABLE 1. Percentage of nondippers after 12 and 26 weeks of therapy with morning vs. evening dosing of valsartan

	Week 12		Week 26	
	% Nondippers	%Δ	% Nondippers	%Δ
Valsartan morning dosing	51.9%	−6.3%	49.0%	−11.2%
Valsartan evening dosing	44.6%	−9.7%	45.7%	−7.5%

(−12.8, −16.8 mmHg) or valsartan in the evening (−12.0, −14.9 mmHg) after 12 and 26 weeks of treatment, respectively [4]. No further subdividing of the nondipper group was considered justified.

We agree that the definition of 'mild dippers' for that group of patients might be more appropriate, but this is a matter of definition rather than of clinical relevance. On the contrary, the rate of true 'nondippers' or 'reverse dippers' in a hypertensive population is very low, being around 3% in previous studies, and thus of limited clinical relevance at the population level. We also agree with Versmissen *et al.* that the 'nondipper' status has poor reproducibility and that in the individual patient the diagnosis should be confirmed with a second 24-h monitoring. However, the purpose of our analysis was to study the phenomenon within a population, and thus we are confident that our protocol and the size of the sample were appropriate for giving an answer to our original question.

Nonetheless, given the arbitrary classification and poor reproducibility of test results in patients classified as 'nondippers' at baseline, we decided to evaluate the percentage of patients who were still considered 'nondippers' during and at the end of the study [5,6]. Morning or night-time dosing of valsartan resulted in a similar reduction (6–11%) in the percentage of nondippers during and at the end of the study, with no advantage of night-time dosing (see Table 1).

On the basis of these findings, the hypertensive patients with reduced BP-lowering during the night-time period benefited equally with morning or evening dosing. Thus, the use of a long-lasting, once-a-day antihypertensive, such as an angiotensin receptor blocker, night-time dosing was no better than morning dosing to ensure effective 24-h and night-time BP-lowering.

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Potential impact of fetal genotype on maternal blood pressure during pregnancy: the example of EP300

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We read with great interest the review by Petry *et al.* [1] concerning the possible impact of fetal genotype on maternal blood pressure during pregnancy. The article is very detailed, but we think that a very rare but probably underestimated fetal condition deserves to be added: Rubinstein–Taybi syndrome (RSTS) due to mutations in the *EP300* gene.

RSTS (OMIM #180849, #613684) is an ultrarare (1:125 000) autosomal dominant plurimal formative disease characterized by dysmorphic features, intellectual disability, postnatal growth delay, and skeletal anomalies such as broad or duplicated distal phalanges of the thumbs and halluces. It is caused by mutations in two conserved genes: *CREBBP* (RSTS1, 16p13.3, about 50–60% of cases) and *EP300* (RSTS2, 22q13, about 8%), which respectively encode the ubiquitously expressed CREB-binding protein and E1A-associated protein (p300) that regulate gene expression as a result of their histone acetyltransferase function. They are therefore involved in multiple cell pathways of growth control, DNA repair, differentiation, apoptosis, and tumour suppression [2].

Only 14 RSTS2 patients have so far been described [3–9], but an additional 12 *EP300* mutations are listed in the LOVD database (http://chromium.liacs.nl/LOVD2/home.php?select_db=EP300). The effect of all the detected alterations can be attributed to *EP300* gene haploinsufficiency.

In comparison with classic RSTS1, RSTS2 seems to be associated with a milder phenotype characterized by less severe dysmorphic features, better growth, and cognitive function, and no radial deviation or bifid thumbs or halluces, but more severe microcephaly and malformations of facial bone structures [2]. An increased risk of gestational hypertension in pregnancies of children with *EP300* mutations has been suggested [8]: six of the 10 cases with reported pregnancy data were associated with maternal gestosis [5,6,8,9] and, particularly, the mother of the patient described by Foley [6] had three other healthy children from uncomplicated pregnancies. No precise gravidic anamnesis is available for the other four cases, but two were characterized by a preterm caesarean delivery [3,5]. On the contrary, to the best of our knowledge, maternal gestosis has been described in only one patient carrying a *CREBBP* mutation [10], and we have none in our RSTS1 cohort (personal observation).

Interestingly, p300 plays an essential role in modulating the transcription and expression of the *Npr1* gene encoding guanylyl cyclase-A/natriuretic peptide receptor-A (GC-A/NPRA), which binds atrial natriuretic peptide (ANP), mediates natriuresis/diuresis and vasorelaxation, and subsequently decreases arterial blood pressure [11]. Moreover, the natriuretic peptide system plays an important role in pregnancy and fetal development as ANP is synthesized *de novo* in the human placenta, increases during pregnancy (possibly secondarily to hypervolemia and increased preload), and antagonizes the vasoconstriction of maternal and fetal placental vasculature [12]. In addition, alterations in corin (the enzyme that activates pro-ANP) have been described in preeclamptic patients [13], thereby confirming the importance of natriuretic peptide system in correctly setting blood pressure during pregnancy.

Given the deleterious effects of fetal RSTS2 on maternal blood pressure, we think that this rare disease should be considered among the fetal genotypes associated with increased maternal blood pressure during pregnancy. We also wonder whether polymorphic variants of *EP300* that do not lead to RSTS2 in newborns could contribute to maternal gestosis.

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