Fourth, the use of different formulations of doxazosin (short-acting vs. extended-release) may explain, at least in part, the differences of the occurrence of heart failure between our study [1], ALLHAT [4], ASCOT-BPLA [2] and Barrios' study [3]. Although the short acting form of doxazosin reduces blood pressure with a sympathetic stimulation, the extended-release form of doxazosin does not produce any significant sympathetic stimulation [6]. These differential effects on the cardiovascular autonomic system may contribute to the differential cardiac outcome among the four studies [1–4].

Therefore, as suggested by Barrios, there is still an open debate as to whether doxazosin, despite decreasing the blood pressure, may increase the risk of developing heart failure. We should now use doxazosin in hypertension after clarifying the overall benefits and any associated problems.

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Comments on the reproducibility of Ambulatory Arterial Stiffness Index and QKD

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We have read with interest the paper of Dechering *et al.* [1] on the reproducibility of the AASI in the hypertensive recently published in this journal. This study of reproducibility for a new index was needed and supports the data from two of our studies [2,3] indicating a rather modest reproducibility. We are not sure why the authors claim it to be the first study of reproducibility as they cite ours in the discussion. Nonetheless, the main point is that despite studying different populations with different mean values of AASI at different times between the two examinations and using different equipment, their results were comparable to ours.

Our first study [2] was on a small sample of 38 patients with two examinations a fortnight apart. The standard deviation (SD) of the differences between the two measurements was 0.15, which is comparable to the values of 0.16 and 0.20 in the two populations studied by Dechering. From the SD of the differences (SDD) in our report the repeatability coefficient is readily calculated to be 0.30, versus 0.32–0.40 for the study of Dechering. Interestingly, our results show a rather better reproducibility for the AASI than that observed by Dechering. The authors suggest expressing this coefficient as a percentage of the maximal biological variation of the measurement in the studied population, estimated by multiplying the SD of the mean of the measurements on the two occasions by four. They suppose in the discussion that this calculation might alter the results of our comparison of the AASI with the $QKD_{100\text{-}60}$. This method of expression seems debatable as the poorer the reproducibility of a parameter the greater will be the SD of the measurement, tending to reduce this percentage value. Furthermore, although the significance of the repeatability coefficient is clear [4], assigning a rapid confidence interval to the measured value, its expression relative to the 'biological' variability of the measurement has no directly useful significance. Nevertheless, we calculated this percentage as described and found 34% for the $QKD_{100\text{-}60}$ and 58% for the AASI, which still favors the better reproducibility of the $QKD_{100\text{-}60}$ by almost a factor of two.

We found similar results in the PROOF [3] cohort, which included individuals from the general population all aged 65 years on recruitment. These individuals benefited from a second recording 2 years later. Here again the SD of the differences of the $QKD_{100\text{-}60}$ and AASI appeared relatively constant, although arterial stiffness may well have altered over 2 years. The normotensive individuals had a significant fall ($P = 0.02$) in $QKD_{100\text{-}60}$ as expected from normal aging, whereas the AASI was unchanged. Table 1 [5,6] summarizes these data including those of Dechering for the sake of comparison. We have also included the results of two other studies for which the reproducibility values for $QKD_{100\text{-}60}$ were available.

Table 1 Comparison of reproducibility data for Ambulatory Arterial Stiffness Index and $QKD_{100\text{-}60}$ in published studies

Author Method	Pts	*n*	Interval	First	Repeat	SDD	RC	CV	pMV
Gosse [2]									
AASI	NT	38	2 weeks	0.60 ± 12	0.60 ± 13	0.15	0.30	25%	58%
$QKD_{100\text{-}60}$ (ms)	NT	38		224 ± 13	224 ± 13	9	18	4%	34%
Gosse [3]									
AASI	NT	568	2 years	0.62 ± 0.12	0.63 ± 0.13	0.13	0.26	21%	55%
$QKD_{100\text{-}60}$ (ms)		237		205 ± 13	203 ± 13	9	18	4%	34%
Gosse [3]									
AASI	HT	211	2 years	0.65 ± 0.12	0.64 ± 0.12	0.14	0.28	22%	58%
$QKD_{100\text{-}60}$ (ms)		75		200 ± 19	201 ± 18	11	22	5%	30%
Gosse [5]									
$QKD_{100\text{-}60}$ (ms)	NT	28	1 week	200 ± 21	199 ± 17	12	24	6%	
Gosse [6]									
$QKD_{100\text{-}60}$ (ms)	SS	48	1 year	201 ± 16	202 ± 18	13	26	6%	
Dechering [1]									
AASI Nijmegen	HT	152	2 months	0.47 ± 0.16	0.45 ± 0.17	0.16	0.32	35%	55%
AASI Syst-Eur		145		0.52 ± 0.19	0.51 ± 0.20	0.20	0.40	39%	61%

AASI, Ambulatory Arterial Stiffness Index; CV, coefficient of variation; interval, time between first and repeat measurement; HT, hypertensive; NT, normotensive; pMV, RC expressed as a percentage of four times the SD of the mean of the paired recordings; Pts, patients studied; RC, repeatability coefficient; SDD, standard deviation of differences; SS, patients with systemic sclerosis.

We maintain that the $QKD_{100\text{-}60}$ has better reproducibility than the AASI, and in turn a higher sensitivity in the search for alterations in arterial rigidity with time or under treatment.

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Comments on the reproducibility of ambulatory arterial stiffness index and QRS Korotkoff delay index

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We would first like to clarify that when we submitted our manuscript [1], Gosse *et al.* [2] had only published the report on the prediction of cardiovascular complications by the QRS Korotkoff Delay index standardised to a systolic blood pressure of 100 mmHg and a heart rate of 60 bpm ($QKD_{100\text{-}60}$). Gosse *et al.* [2] also studied the short-term (2 weeks) reproducibility of $QKD_{100\text{-}60}$ and the ambulatory arterial stiffness index (AASI) in 38 volunteers who were selected from a cohort of 469 hypertensive patients. In a subsequent article [3], published after ours had been accepted for publication [1], the French researchers investigated the long-term (2 years) reproducibility of $QKD_{100\text{-}60}$ and AASI in a 65-year birth cohort recruited from the municipality Saint Etienne.

We are grateful to the French investigators because they followed our suggestion [1] to express repeatability (twice the standard deviation of the differences between duplicate recordings) as a percentage of nearly maximal variation in the measurement under study (four times the standard deviation). In the PROOF study [3], $QKD_{100\text{-}60}$ ranged from 160 to 280 ms and AASI ranged from 0.27 to 0.97. From the lowest to the highest value, $QKD_{100\text{-}60}$ increased by 1.8-fold and AASI by 3.6-fold. In contrast to the statement of Gosse *et al.* [2], expressing repeatability as a percentage of nearly maximal variation is not debatable, but the only possible way to compare repeatability among

measures of a similar trait that are expressed in different units and/or have a dissimilar range [4].

Gosse *et al.* [2] claim that $QKD_{100\text{-}60}$ has higher reproducibility than AASI. However, the table in the letter by Gosse *et al.* [2] does not include any test statistic or associated *P*-value to substantiate this assertion. The French report only involved 65-year-old patients, whereas, in our study [1], the age range was 20–78 years. Moreover, Gosse *et al.* [2] overlooked that they had standardized $QKD_{100\text{-}60}$ to a systolic blood pressure of 100 mmHg and a heart rate of 60 bpm, whereas we did not standardize AASI for any of these factors. A selected age group and standardizing $QKD_{100\text{-}60}$ removes variability in the measurement, which might increase reproducibility, but at the expense of removing potentially relevant information.

We doubt that 38 patients, selected by unspecified criteria, are sufficient to compare the short-term variability of $QKD_{100\text{-}60}$ and AASI in a reliable fashion [2]. In the report on the long-term reproducibility [3], over a 2-year interval, a significant reduction occurred in $QKD_{100\text{-}60}$ in 237 normotensive subjects (−2 ms; $P = 0.02$), but not in 75 hypertensive patients (+1 ms). AASI did not change in 568 normotensive subjects (+0.01) or in 211 hypertensive patients (−0.01). The 2 ms reduction in $QKD_{100\text{-}60}$ in normotensive subjects is counterintuitive because hypertension, not normotension, accelerates arterial stiffening with age. The physiological meaning of a 2 ms change remains obscure, because the standard deviation of the differences between paired recordings was as high as 9 ms. The number of patients available for analysis of the repeatability of $QKD_{100\text{-}60}$ ($n = 312$) and AASI ($n = 779$) also highlights the technical difficulties in obtaining high-quality estimates of $QKD_{100\text{-}60}$, whereas AASI can be computed from simple 24 h ambulatory blood pressure recordings without the discomfort for patients of wearing ECG electrodes.

Finally, Gosse *et al.* [2] argued that $QKD_{100\text{-}60}$ reflected arterial stiffness better than AASI because, in multivariable-adjusted analyses, $QKD_{100\text{-}60}$ correlated with pulse pressure and the presence of diabetes mellitus, whereas AASI only correlated with blood pressure. We believe that prognostic value prevails over statistical findings. To date, several cross-sectional studies [5,6] and at least four prospective cohort studies [7–10] demonstrated an association of AASI with all-cause mortality in patients referred for ambulatory blood pressure monitoring [10] or with cardiovascular mortality and morbidity in hypertensive patients [7], or in the general population [8,9]. When adjusted for pulse pressure [7–9] or aortic pulse wave velocity [11], AASI remained predictive, in particular of stroke. To our knowledge, the corresponding prognostic information for $QKD_{100\text{-}60}$ rests on a single underpowered study [2].

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Influencing the natural history of hypertension: is it the blood pressure achieved, the drug, or the drug dose?

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In his editorial [1], Dr Hollenberg raises a valuable point regarding the importance of dosing of antihypertensive medications and their effects beyond blood pressure control. He goes further, stating that 'physicians seem to be apathetic on the issue of dosing', thereby exemplifying poor quality of medicine. However, elsewhere he and his colleagues seem to be affected by similar apathy. Fisher *et al.* [2] compared the effects of a direct renin inhibitor, aliskiren, to an angiotensin-converting enzyme (ACE) inhibitor, captopril, on renal vascular response. At the dose of 600 mg (twice the maximal dose approved by the FDA), aliskiren showed superior renal vasodilating response when compared with captopril at 25 mg (1/18 of the maximal FDA approved dose). The authors justify this low dose stating that the maximal renal response was achieved with 25 mg with no incremental gain at higher